



# **Deliverable D6.1**

## **Cancer hypomodelling and hypermodelling strategies and initial component models**

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D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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<b>PU</b>	Public	
<b>PP</b>	Restricted to other programme participants (including the Commission Services)	
<b>RE</b>	Restricted to a group specified by the consortium (including the Commission Services)	
<b>CO</b>	Confidential, only for members of the consortium (including the Commission Services)	<b>X</b>

## D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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**ABSTRACT:**

This deliverable provides an outline of the strategies proposed for the development of hypomodels (or component models) and hypermodels (or composite or integrative models) of cancer progression and response to treatment. The suggested strategies will be exploited by the large scale integrating project CHIC. Hypomodels that address fewer biological mechanisms than their corresponding hypermodels are to be appropriately annotated using pertinent ontology based descriptions of their input, output and content. A cancer model categorization and annotation framework is also proposed. The standardized model annotations that will be developed and serve as metamodels will be used by the prospective users of the CHIC platform in order to substantially facilitate the development of customized hypermodels suitable for the particular biomedical problems they address. The document provides an extensive list of categorized and appropriately described models that have already been developed or are under development, refinement or adaptation by the consortium modellers. The models will serve as the starting point and the basis for the creation of several CHIC hypomodels and hypermodels through metamodeling. Specific examples of initial component models or hypomodels are provided in a tabular format. The hypomodelling and hypermodelling strategies presented in this document will serve as the overall architectural framework of the CHIC project.

**KEYWORD LIST:** VPH, multiscale model, repository, hypomodel, metamodel, hypermodel, cancer, in silico oncology, computational oncology, oncosimulator, hypomodelling, hypermodelling, strategy

<sup>1</sup> R=Report, P=Prototype, D=Demonstrator, O=Other

<sup>2</sup> PU=Public, PP=Restricted to other programme participants (including the Commission Services), RE=Restricted to a group specified by the consortium (including the Commission Services), CO=Confidential, only for members of the consortium (including the Commission Services)

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## 1 Executive Summary

The purpose of this document is to provide an outline of the strategies for the development of hypomodels (or component models) and hypermodels (or composite or integrative models) of cancer progression and response to treatment. The suggested strategies will be exploited by the large scale integrating project CHIC. Hypomodels that address fewer biological mechanisms than their corresponding hypermodels are to be appropriately annotated using pertinent ontology based descriptions of their input, output and content. A cancer model categorization and annotation framework is also proposed. The standardized model annotations that will be developed and serve as metamodels will be used by the prospective users of the CHIC platform in order to substantially facilitate the creation of customized hypermodels suitable for the particular biomedical problems they may address. Hypermodels are in turn annotated using a similar ontology based approach. All kinds of models and metamodels are to be stored in the CHIC repositories for further utilization. For those models that address concrete clinical scenarios, clinical adaptation and validation is to be performed before they are eventually translated into clinical practice.

The document provides an extensive list of models already developed or being under development by the consortium modellers. These models will provide the starting point and the basis for the creation of several CHIC hypomodels and hypermodels through metamodeling. The basic science related descriptive data provided for each model include *inter alia* the following descriptors: model title, brief model description, biological scale, input parameters and their symbols, input parameter units, input parameter types, input parameter ranges, output parameters and their symbols, output parameter units and output parameter types. The technology related descriptive data provided for most models include the following technical characteristics and software and hardware requirements: software code language, operating systems and architecture, external library dependencies, cores, disk memory, RAM memory and typical execution time.

Typical hypomodels or component models include models of cell cycling at the cellular level, molecular interactions or networks affecting cell cycle and/or the cell phase durations, cell survival probability during radiotherapy for a given radiation dose, molecular interactions or networks affecting cell survival probability during radiotherapy, cell cycle survival probability during chemotherapy for a given area under curve AUC and molecular interactions or networks affecting cell survival probability during chemotherapy. Typical hypermodels include models of tumour response to treatment for assumed metabolic activity regions and models of angiogenesis and neovasculature distribution. A higher level hypermodel can simulate in vivo tumour growth and response to treatment in which an explicit modelling of angiogenesis and neovasculature distribution is included.

The main strategies for both hypomodeling and hypermodelling are outlined using a number of elucidating diagrams. Specific examples of initial component model or hypomodel are provided in a tabular format. The hypomodelling and hypermodelling strategies presented so far are to serve as the overall architectural framework of the CHIC project.

## 2. Introduction [INT]

### 2.1 Purpose of the document

The purpose of this document is to provide an outline of the strategies for the development of hypomodels (or component models) and hypermodels (or composite or integrative models) of cancer development and response to treatment. The suggested strategies will be exploited by the large scale integrating project CHIC. Hypomodels that address fewer biological mechanisms than their corresponding hypermodels are to be appropriately annotated using pertinent ontology based descriptions of their input, output and content. A cancer model categorization and annotation framework is also proposed. The standardized model annotations that will be developed and serve as metamodels will be used by the prospective users of the CHIC platform in order to substantially facilitate the development of customized hypermodels suitable for the particular biomedical problems they address. Hypermodels are in turn annotated using a similar ontology based approach. All sorts of models and metamodels are to be stored in the CHIC repositories for further utilization. For those models that address concrete clinical scenarios, clinical adaptation and validation is to be performed before they are eventually translated into clinical practice.

### 2.2 The hyper-complexity of the natural phenomenon of cancer and its treatment strategies

The impressive rate of generation of human biological data during the last decades has dictated the development of numerous statistical, computational and mathematical methods, in order to extract, analyze and exploit the hidden wealth of information. Unquestionably, systems biology has been established as a key player in this arena. However, despite its maturation over the last decade a number of obstacles render it difficult for systems biology to be directly exploitable by clinical practice [INT1]. Recognizing that in most medical conditions crucial biological phenomena are manifested at several spatiotemporal scales, including scales lying far above the subcellular level - which is traditionally addressed by systems biology- researchers have proposed a number of ways to integrate super-cellular levels into systems biology approaches. Such initiatives have taken various forms and names such as systems physiology [INT2], systems medicine, multiscale modeling and Virtual Physiological Human (VPH). Despite the differences in each one's emphasis, they all essentially try to reach and serve the clinic, since the latter appears to be the ultimate goal of the main bulk of biological research. In the specific paradigmatic VPH domain of cancer, where the multiscale character of the disease is exceptionally pronounced, there is particularly demanding need for biomodels to address several organizational levels and scales *concurrently*. If one takes into account the additional complexity which is due to the large number of involved elementary bioprocesses (biomechanisms) including angiogenesis, the numerous cancer types and subtypes and the clinically available treatments which may be rather complicated (Fig. 2.1), one can readily realize that the requirements for a cancer model to be comprehensive and versatile so as to potentially be of use to the clinic are tremendous.



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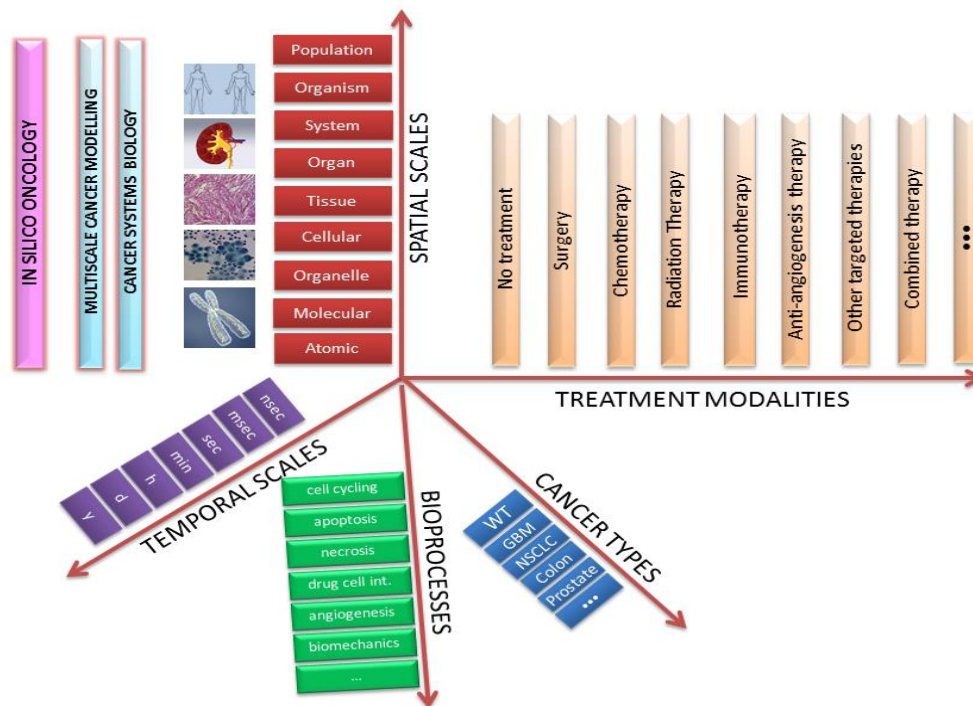


Fig. 2.1 Dimensions of cancer manifestation and treatment

This remark suggests that cancer in the clinical context dictates the development of integrative hypermodels consisting of simpler and more manageable constituent component models which may already be available. Nevertheless, in order for models generally developed by different modellers or modelling groups to be reusable, there are a number of prerequisites that have to be satisfied. Models should be robust, reproduceable and interoperable. This implies that standardization of model description and operation is a sine qua non necessity if rational, coherent and comprehensive exploitation of the invaluable information hidden within human multiscale biological data is envisaged.

Responding to this imperative in the context of both the broad (VPH) initiative and the paradigmatic cancer domain, CHIC proposes the development of a suite of tools and services in a secure infrastructure that will support accessibility and reusability of VPH mathematical and computational hypermodels. The proposed objective is primarily centered around the development of a hypermodelling environment which, although will be applicable to the broad VPH space, it will be driven by and originally tested in the cancer domain. In order to ensure clinical relevance and foster clinical acceptance of hypermodelling in the future, the whole endeavour will in practice be driven by the clinical partners of the consortium. Cancer hypermodels to be collaboratively developed by the consortium cancer modellers will provide the framework and the testbed for the development of the CHIC technologies. Clinical adaptation and partial clinical validation of hypermodels and hypermodel oncosimulators will be undertaken. The VPH hypermodelling environment that will be developed in CHIC, starting from an advanced prototype developed in the VPHOP project, will expose by the end of the CHIC project a set of features so advanced and sophisticated to be easily identified as the leading solution worldwide for this specific problem. CHIC is expected to foster the further

development of the VPH initiative, as it transits towards its second stage of maturity, the vision of the so-called *in silico* medicine that will be the primary target of Horizon 2020. CHIC already includes fundamental elements in its design anticipating this vision in particular and will provide a testbed for some of the most challenging concepts. *In silico* oncology addressed by CHIC is to serve as a concrete messenger of this vision. Fig. 2.2 depicts the positioning of the hypermodelling environment to be developed in the current phase of VPH, in the emergent *in silico* oncology context and ultimately in the vision of general *in silico* medicine.

CHIC will actually be deployed on the transatlantic research environment, since one of the key consortium partners is from the US. In this context the concrete outcome of previous joint EU-US initiatives such as the First Transatlantic Workshop on Multiscale Cancer Modelling [INT3], [INT4] will be exploited to the full.

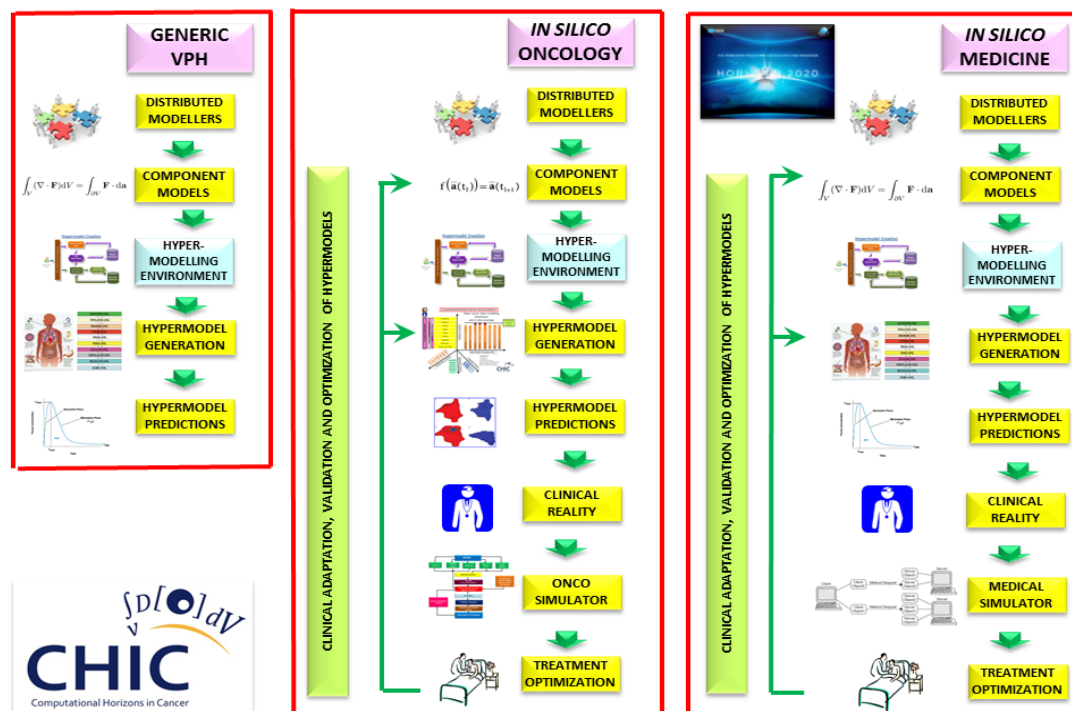


Fig. 2.2 The niche of the hypermodelling environment to be developed within the framework of VPH, in silico oncology and in silico medicine in general

## 2.3 The Hypermodel Oncosimulator

The Hypermodel Oncosimulator is an extension of the notion and the system of the original Oncosimulator [INT5] so as to make use of cancer and normal tissue hypermodels. The (hypermodel) Oncosimulator is at the same time a concept of multilevel integrative cancer biology, a complex algorithmic construct, a biomedical engineering system and eventually in the future a clinical tool which primarily aims at supporting the clinician in the process of optimizing cancer treatment in the patient individualized context through conducting experiments *in silico* i.e. on the computer. Additionally it is a platform for simulating, investigating, better understanding and exploring the *natural phenomenon* of cancer, supporting the design and interpretation of clinicogenomic trials and

finally training doctors, researchers and interested patients alike<sup>17,18,19</sup>. A synoptic outline of the clinical utilization of a specific version of the *Oncosimulator*, as envisaged to take place following an eventually successful completion of its clinical adaptation, optimization and validation process is provided in the form of steps (Fig.2.3).

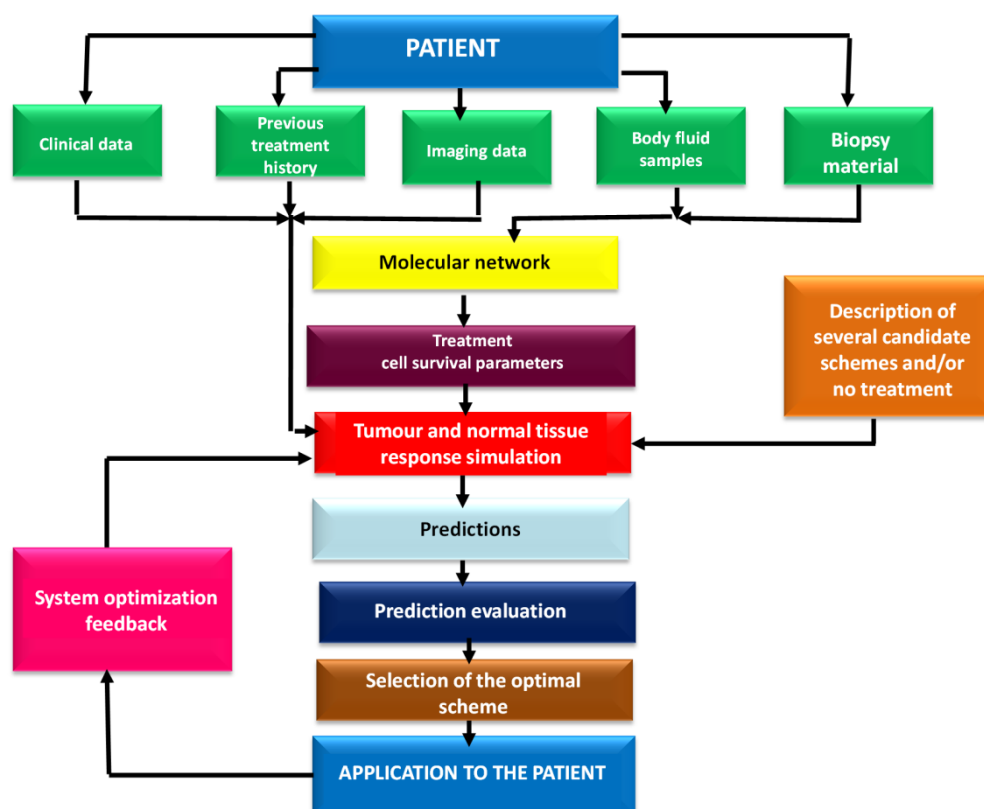


Fig. 2.3 A synoptic diagram of the hypermodel based oncosimulator

## 2.4 Multiscale cancer modelling: A general overview

### State of the art

The extreme complexity of the *natural phenomenon* of cancer in conjunction with the seriousness of the *disease* have dictated the development of highly demanding mathematical and computational cancer models aiming at promoting both biological insight and clinical medicine. In the last decade it became clear that cancer modeling should become explicitly multi-scale, so as to address several levels of biocomplexity concurrently [INT6]. Already a great diversity of cancer related models exist, focusing on various aspects of this complex phenomenon at different scale levels. Several mathematical techniques [INT7] and approaches have been proposed. These include continuous, discretized continuous and discrete [INT8] methods as well as hybrid approaches. Hybrid approaches combine the benefits of continuous and discrete mathematics and offer the possibility of integrating phenomena of different time and length scales. Within this context and in order to address concrete clinical questions the idea of the “oncosimulator” has emerged [INT9], [INT10]. Efforts on an international and even intercontinental level have been initiated, in order to both promote the multi-scale character of cancer modeling and intensify the interaction among modelers, experimentalists,

clinicians and other specialists so as to develop advanced mutually hybridized models of cancer development and response to treatment. Within this framework the European Commission, in collaboration with the National Cancer Institute, National Institute of Health of the United States, funded the 1<sup>st</sup> Transatlantic Workshop on Multiscale Cancer Modeling as a component of the ICT 2008 event [INT11]. Research group leaders from both coasts of the Atlantic presented their modeling approaches and an important intercontinental interaction was established and subsequently a transatlantic book was published [INT12]. Although in order to understand cancer and optimize its treatment in the patient individualized context all its aspects are important, it appears that models that are directly driven from actual clinical problems and questions, preferably formulated by clinicians, may lie more closely to the clinical translation path. Therefore, if the utilization of a model as a decision support tool is envisaged, then a direct involvement of clinicians in the model development and validation process should be considered.

### **Expected contribution of CHIC**

Due to the hypercomplexity of cancer it appears that no single modeler or modeling research group has developed models that optimally describe every single aspect of the cancer phenomenon and its interactions with a vast number of particular medical treatment schemes. Additionally, despite the progress made so far, there have not been any standards regarding both the description of each model and its internal architecture. This renders the eventual hybridization of different models extremely difficult. Therefore, in order to facilitate the development of composite and “custom” made comprehensive models (hypermodels) aiming at addressing concrete medical and biological questions and eventually leading to their transformation into patient individualized decision support and treatment design systems, a model description standardization through a metalanguage will be developed and proposed to the broader cancer modeling community. Generic strategies and hypermodelling infrastructure that will enable the mutual fitting together of elementary models will be developed by CHIC. The special tumour types considered by the project (i.e. nephroblastoma, glioblastoma, lung cancer, colon cancer and prostate cancer) will serve as guiding paradigms. A number of exemplary hypermodels based on the previous paradigms will be developed and validated. Subsequently, a more generic version of the Oncosimulator [INT13], a multiscale cancer modelling concept and system will emerge. The new Hypermodel Oncosimulator will be clinically adapted by exploiting the clinical studies and multiscale data to be provided by the CHIC clinical partners (concerning nephroblastoma, glioblastoma and non-small cell lung cancer). A new multiscale and continuum model of early colorectal cancer and vascular tumour growth will also be developed and validated against data obtained by experimental and clinical partners. Regarding prostate cancer, ‘traditional’ growth models will be enhanced by assuming that the tumour carrying capacity may vary throughout development, promoting organ invasion, near (and far) metastasis, etc. Hybrid biomechanical-biological models of glioblastoma will undergo further hybridization with additional small spatial scale biomechanisms. A model, a data and an *in silico* trials repository will be developed, in order to store both the standardized models (hypomodels, models and hypermodels) and relevant data for their validation. These repositories will be made accessible to the wider cancer modeling community under the legal constraints applicable. It is pointed out that the hypemodelling infrastructure/software tools will be fairly generic so as to be usable for other multiscale domains of the VPH initiative apart from cancer.

## **2.5 Multiscale cancer modelling: Systems biology**

### **State of the art**

Human genome-sequencing has enabled the creation of an exhaustive parts-list in mammalian cellular systems. The primary challenge has now shifted towards functional relationships between

the parts and mechanistic description of how the parts function as modules and as a whole. Systems biology lies at the heart of addressing this grand challenge and focuses mainly on synthesizing these relationships when they are considered together. Pathways have long represented a convenient way of summarizing the results of many hundreds of experiments. The past decade has prompted the creation of several databases of metabolic and signaling pathways (e.g Kyoto Encyclopedia of Genes and Genomes, BioCarta, Signal Transduction Knowledge Environment). In general, these resources represent the relationships between molecules in a cell either as reactions or as activation or inhibition events. The specificity of cellular responses is decoded by spatial and temporal signals propagating through intracellular signaling pathways. Computational models [INT14], [INT15] and network analysis tools continue to provide insights into the complex relationships between the stimuli, cellular responses, and cell fate.

### **Expected contribution of CHIC**

CHIC will be engaged in multiscale modeling of altered functional interactions in oncogenic signaling networks through multiscale hybrid physical/systems approaches relevant to non-small-cell lung cancer, glioblastoma, and neuroblastoma. The aims include: (1) an in-house developed multiscale strategy for constructing models of intracellular signaling networks with the ability to encode molecular resolution of key nodes; (2) extensive molecular modeling of the effect of mutations on protein function in order to differentiate driver mutations from passenger mutations; (3) physical biology approaches to study sub-cellular localization and trafficking using mesoscale models and linking altered trafficking to signaling and cell fates.

## ***2.6 Proposed categories of mathematical and computational cancer models in the basic science context***

Mathematical and computational cancer models can be categorized depending on the perspective from which they are viewed in the basic science context. The following thirteen perspectives are proposed:

**PERSPECTIVE I: TUMOUR-AFFECTED NORMAL TISSUE MODELLING**

**PERSPECTIVE II: SPATIAL SCALE(S) OF THE MANIFESTATION OF LIFE**

**PERSPECTIVE III: TEMPORAL SCALE(S) OF THE MANIFESTATION OF LIFE**

**PERSPECTIVE IV: BIOMECHANISM(S) ADDRESSED**

**PERSPECTIVE V: TUMOUR TYPE(S) ADDRESSED**

**PERSPECTIVE VI: TREATMENT MODALITY(-IES) ADDRESSED**

**PERSPECTIVE VII: GENERIC CANCER BIOLOGY – CLINICALLY DRIVEN CHARACTER OF THE MODELLING APPROACH**

**PERSPECTIVE VIII: ORDER OF ADDRESSING DIFFERENT SPATIAL SCALES**

**PERSPECTIVE IX: ORDER OF ADDRESSING DIFFERENT TEMPORAL SCALES**

**PERSPECTIVE X: MECHANISTIC-STATISTICAL CHARACTER OF THE MODELLING APPROACH**

**PERSPECTIVE XI: DETERMINISTIC-STOCHASTIC CHARACTER OF THE MODELLING APPROACH**

**PERSPECTIVE XII: CONTINUOUS-FINITE-DISCRETE CHARACTER OF THE MATHEMATICS INVOLVED**

**PERSPECTIVE XIII: CLOSED FORM SOLUTION – ALGORITHMIC SIMULATION MODELLING APPROACH**

Table INT1 provides examples of possible categories for each given perspective.

TABLE INT1 ( FIRST PART)		
PERSPECTIVE CODE NUMBER	PERSPECTIVE TITLE	EXAMPLES OF POSSIBLE CATEGORIES PER PERSPECTIVE
I	TUMOUR-AFFECTED NORMAL TISSUE MODELLING	tumour, tumour or treatment affected normal tissue, oedema, ... <i>combinations</i>
II	SPATIAL SCALE(S) OF THE MANIFESTATION OF LIFE	atomic, molecular, cellular, tissue, organ, body system, organism, population, ... <i>combinations</i>
III	TEMPORAL SCALE(S) OF THE MANIFESTATION OF LIFE	nsec, msec, sec, min, h, d, y, ... <i>combinations</i>
IV	BIOMECHANISM(S) ADDRESSED	cell cycling, apoptosis, necrosis, metabolism, ... <i>combinations</i>
V	TUMOUR TYPE(S) ADDRESSED	lung cancer, glioblastoma, nephroblastoma, colon cancer, prostate cancer, ... <i>combinations</i>
VI	TREATMENT MODALITY(-IES) ADDRESSED	Chemotherapy, Radiotherapy, Immunotherapy, ... <i>combinations</i>

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TABLE INT1 ( SECOND PART)		
PERSPECTIVE CODE NUMBER	PERSPECTIVE TITLE	EXAMPLES OF POSSIBLE CATEGORIES PER PERSPECTIVE
VII	GENERIC CANCER BIOLOGY – CLINICALLY DRIVEN CHARACTER OF THE MODELLING APPROACH	generic cancer biology, clinically driven, <i>mixed</i>
VIII	ORDER OF ADDRESSING DIFFERENT SPATIAL SCALES	Bottom-up, middle-out, top-down <i>combinations</i>
IX	ORDER OF ADDRESSING DIFFERENT TEMPORAL SCALES	short periods → longer periods, long periods → shorter periods, <i>combinations</i>
X	MECHANISTIC-STATISTICAL CHARACTER OF THE MODELLING APPROACH	explicit biological mechanism modeling (e.g. using cytokinetic diagrams), neural networks based “black box” statistical modeling, ... <i>combinations</i>
XI	DETERMINISTIC-STOCHASTIC CHARACTER OF THE MODELLING APPROACH	deterministic, stochastic, <i>hybrid</i>
XII	CONTINUOUS-FINITE-DISCRETE CHARACTER OF THE MATHEMATICS INVOLVED	continuous, finite (finitized continuous), discrete, <i>combinations</i>
XIII	CLOSED FORM SOLUTION – ALGORITHMIC SIMULATION MODELLING APPROACH	closed form solution based modelling, algorithmic simulation, <i>combinations</i>

The above proposed system will serve as the starting point for the ontology based annotation of cancer models to be developed during the CHIC lifetime.

## ***2.7 Structure of the document***

The rest of the document is structured as follows. Chapter 3 presents a list of models developed by the CHIC modelling partners along with several important model characteristics including all input and output parameters for each model. Chapter 4 outlines the major hypomodelling and hypermodelling strategies proposed and adopted within the framework of the CHIC project. Chapter 5 presents a number of initial component models that are under development, refinement or adaptation by various CHIC cancer modellers. Chapter 6 summarizes the conclusions of the work. A list of references and an abbreviation and acronym appendix are provided at the end of the document.



### **3. Models developed by the CHIC consortium modellers in a tabular format [MOD]**

#### **3.1 Introduction**

This chapter provides an extensive list of models already developed or under development by the consortium modellers. These models will provide the starting point and the basis for the development of several CHIC hypomodels and hypermodels through metamodelling. Hypomodels can be obtained “by appropriately breaking down” composite models, whereas hypermodels can be obtained “by appropriately linking together” elementary models or hypomodels. The basic science related descriptive data provided for each model include inter alia the following kinds of information: model title, brief model description, biological scale, input parameters and their symbols, input parameter units, input parameter types, input parameter ranges, output parameters and their symbols, output parameter units and output parameter types. The technology related descriptive data provided for most models include the following technical characteristics as well as the following software and hardware requirements: software code language, operating systems and architecture, external library dependencies, cores, disk memory, RAM memory and typical execution time. It should be noted however, that the model lists included in this document are under continuous completion, extension and improvement. New updated versions are expected to be prepared during the CHIC lifetime for internal use by the consortium.

#### **3.2 Basic science related description of existing models**

Section 3.2 provides a tabulated description of existing (“e”) models of tumour growth and/or normal tissue response to treatment from the basic science perspective. All models presented have been developed by CHIC consortium partners. In order to render the code names of the models as informative as possible the following symbols and abbreviations have been proposed and adopted:

#### **CATEGORIZATION SYMBOLS**

**A:** atomic scale  
**M:** molecular scale  
**C:** cell scale  
**T:** tissue scale  
**O:** organ scale  
**S:** body system scale  
**C+T:** cell and tissue scales  
**C+T+S:** cell and tissue and body system scales  
 etc.

**e:** existing ( model or model implementation)

**d:** (model or model implementation) under development or refinement or adaptation

#### **ABBREVIATIONS**

**# :** particle number

**LIMP:** Limited Mitotic Potential



# **BASIC SCIENCE RELATED DESCRIPTION OF EXISTING MODELS**



# Ae1

Model information	
Model number	Ae1.
Reference partner	UPENN
Model title	Molecular Dynamics of clinical mutations in oncogenic receptors
Brief model description	All-atom molecular dynamics simulations are performed and analyzed for 30 mutations found in neuroblastoma patients to determine potential of kinase activation
Biological scale	ATOMIC
Core mathematical methods utilized	NAMD molecular dynamics package VMD molecular visualization package Carma molecular dynamics analysis package
References	<a href="http://www.ks.uiuc.edu/Research/namd/">http://www.ks.uiuc.edu/Research/namd/</a> <a href="http://www.ks.uiuc.edu/Research/vmd/">http://www.ks.uiuc.edu/Research/vmd/</a> <a href="http://utopia.duth.gr/~glykos/Carma.html">http://utopia.duth.gr/~glykos/Carma.html</a>
COMMENTS	40ns of MD trajectory is simulated and analyzed for each mutant to determine the oncogenic relevance.

# Ae1

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Parameter file	-	CHARMM FF parameters (*.prm)	file	-	.prm
Topology file	-	CHARMM FF topologies (*.top)	file	-	.top
PSF	-	Protein Structure File (*.psf)	file	-	.psf
PDB	-	Protein Data Bank file (*.pdb)	file	-	.pdb
Temp		Temperature of simulation			kelvins
Dimensions		Dimensions of periodic box			angstroms
Timestep		Integration timestep			femtoseconds

# Ae1

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
HBonds		Hydrogen bond occupancies		% simulation
SASA		Solvent Accessible Surface Area		angstroms squared
RMSD		Root Mean Squared Deviations		angstroms
PCA		Principal Component Analysis eigenvalues		angstroms squared
Free Energy				

# Ae2

Model information	
Model number	Ae2.
Reference partner	UPENN
Model title	Autodock
Brief model description	AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. <a href="http://autodock.scripps.edu">http://autodock.scripps.edu</a>
Biological scale	ATOMIC
Core mathematical methods utilized	Computational Small Molecule Docking Algorithm. Generates a score that attempts to distinguish between molecules binding ability, as well as their optimal placement in the binding pocket.
References	J.Computational Chemistry 2009, 16: 2785-91. J.Computational Chemistry, 28: 1145-1152.
COMMENTS	GNU General Public License

# Ae2

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
PDBQT	-	(PDB) The Protein Data Bank (pdb) file format is a textual file format describing the three dimensional structures of molecules held in the Protein Data Bank. Describes the three dimensional structures of molecules.	File	-	.pdb
PDB	-	(PDBQT) atomic coordinates, partial charges and AutoDock atom types, for both the receptor and the ligand) . Describes the three dimensional structures of molecules.	File	-	.pdbqt



# Ae2

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
PDBQT (File)	-	(PDBQT) atomic coordinates, partial charges and AutoDock atom types, for both the receptor and the ligand	file	.pdb
HBonds		Hydrogen bond occupancies		% simulation
RMSD		Root Mean Squared Deviations		angstroms
Free Energy				Kcal/mol

# Ae3

Model information	
Model number	Ae3.
Reference partner	UPENN
Model title	Glide
Brief model description	<p>Glide offers the full spectrum of speed and accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level.</p> <p><a href="http://www.schrodinger.com/productpage/14/5/">http://www.schrodinger.com/productpage/14/5/</a></p>
Biological scale	ATOMIC
Core mathematical methods utilized	<p>Computational Small Molecule Docking Algorithm.</p> <p>Generates a score that attempts to distinguish between molecules binding ability, as well as their optimal placement in the binding pocket.</p>
References	<p>J. Med. Chem., 2006, 49, 6177–6196</p> <p>J. Med. Chem., 2004, 47, 1750–1759</p> <p>J. Med. Chem., 2004, 47, 1739–1749</p>
COMMENTS	Schrödinger, Inc proprietary

# Ae3

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
DICE	-			-	
PDB	-	(PDB) The Protein Data Bank (pdb) file format is a textual file format describing the three dimensional structures of molecules held in the Protein Data Bank.	file	-	.pdb
MOL2	-	(MOL2) Sybyl/Tripes- Used in cheminformatics applications and on the web for storing and exchanging 3D molecule models.	file	-	.mol2

# Ae3

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
SDF	-	(SDF) structure-data file. Has the ability to include associated data.	file	
MOL2 (files)	-	(MOL2) Sybyl/Tripes- Used in cheminformatics applications and on the web for storing and exchanging 3D molecule models.	file	.mol2
HBonds		Hydrogen bond occupancies		% simulation
RMSD		Root Mean Squared Deviations		angstroms
Free Energy				Kcal/mol

# Ae4

Model information	
Model number	Ae4.
Reference partner	UPENN
Model title	Shape Signatures
Brief model description	Computer-aided ligand- and receptor-based drug design.
Biological scale	ATOMIC
Core mathematical methods utilized	Ray-tracing to explore the volume enclosed by a ligand molecule, or the volume exterior to the active site of a protein. Probability distributions are derived from the ray-trace, and can be based solely on the geometry of the reflecting ray, or may include joint dependence on properties, such as the molecular electrostatic potential, computed over the surface.
References	J Med Chem. 2003 Dec 18;46(26):5674-90
COMMENTS	Open to Public

# Ae4

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
MOL2	-	(MOL2) Sybyl/Tripes- Used in cheminformatics applications and on the web for storing and exchanging 3D molecule models. Describes the three dimensional structures of molecules.	file	-	.mol2

# Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
MOL2	-	(MOL2) Sybyl/Tripes- Used in cheminformatics applications and on the web for storing and exchanging 3D molecule models. *description of molecular shape only. Describes the three dimensional structures of molecules.	file	.mol2

# Me1

Model information	
Model number	Me1.
Reference partner	UOXF
Model title	Cell cycle model
Brief model description	ODE model of cell cycle at subcellular level; focus on influence of local oxygen concentration on cell cycle progression; distinguish between normal and cancer cells
Biological scale	MOLECULAR
Core mathematical methods utilized	
References	
COMMENTS	



# Me1

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
B3					
b4					
J3		Michaelis-Menten constant $\ll 1$			
J4		Michaelis-Menten constant $\ll 1$			
A4		Rate at which [CycCdk] produced			
a1		Decay rate of y			
a2		Rate at which x degrades y			
a3		Rate at which z degrades y			
Eta		Growth rate of cell mass, m			
m*		Carrying capacity of cell mass = cell mass when cell divides			
C1		Constant of proportionality relating rate at which p27 (=z) is produced to $(1-m/m^*)$			
c2		Max rate at which z degraded (when oxygen levels high)			
P		Oxygen tension			
B		Michaelis-menten coefficient			
D1		Constant/basal rate at which u produced			
D2		Rate at which u decays naturally			

# Me1

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension

# Me2

Model information	
Model number	Me2.
Reference partner	UOXF
Model title	Wnt signalling pathway
Brief model description	Ode model for wnt signalling pathway at subcellular level; model accounts for competition for beta-catenin between nucleus and cell membrane.
Biological scale	MOLECULAR
Core mathematical methods utilized	
References	Van Leeuwen et al (2007). J Theor Biol, 247: 77-102
COMMENTS	Again, more details are needed here – parameter values, governing odes and specification of functional forms of reaction rates.

# Me2

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
R1		Rate of assembly of active destruction complexes			
R2		Rate of dissociation of active destruction complexes			
R3		Rate of de novo b-cat synthesis			
R4		Rate of APC-dependent degradation of open-form b-cat			
R5		Rate of de novo synthesis of adhesion molecules			
R6		Rate of elimination of adhesion molecules			
R7		Rate at which open-form b-cat is phosphorylated			
R8		Rate at which phosphorylated b-cat is eliminated			
R9		Rate at which adhesion complexes form			
R10		Rate at which adhesion complexes dissociate;			
R11		Rate at which [CoT] complexes form			
R12		Rate at which [CoT] complexes dissociate			
R13		Rate of synthesis of target protein			
R14		Rate at which target gene eliminated			
R15		Rate at which open-form b-cat, [Co], changes to closed form, [Cc]			
R16		Rate at which closed form, [Cc], becomes ubiquitinated			
R17		Rate of degradation of closed form b-cat			

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R18		Rate of association of [CcT] complexes			
R19		Rate of dissociation of [CcT] complexes			
R20		Rate of de novo synthesis of transcription molecules			

# Me2

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
R21		Rate at which transcription molecules eliminated			
R22		Rate of de novo synthesis of axin			
R23		Rate at which axin eliminated			
R24		Wnt-dependent rate at which active destruction complex, [D], is degraded			

# Me2

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
[A]		Free adhesion molecules		
[CA]		Adhesion complex (C0 bound to A)		
[Cc]		Closed form beta-catenin		
[CcT]		Closed form b-cat in transcription complex		
[Cu]		B-cat marked for ubiquitination		
[CF]		Total free b-cat = [Cc] + [Co]		
[Co]		Open form (unphosphorylated) b-cat		
[CoT]		Open form b-cat in transcription complex		
[CT]		Transcription complex = [CcT]+[CoT]		
[D]		Destruction complex		
[T]		Free transcription molecules		
[X]		Axin		
[Y]		Wnt target protein		

# C+Te1

Model information (I)	
Model number	C+Te1.
Reference partner	ICCS
Model title	Untreated Tumor Growth. Spatial code
Brief model description	<p>The model simulates the spatiotemporal growth of untreated clinical tumors. It is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid of “geometrical cells” (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transition between these states, as well as cell movement throughout the tumor volume; the aim is a realistic, conformal to the initial shape of the tumor, simulation of spatial evolution.</p> <p>The adopted cytokinetic model incorporates the biological mechanisms of cell cycling, quiescence, differentiation and loss. Stem, LIMP, DIFF, apoptotic and necrotic cells represent the distinct cell categories of the model. More specifically, tumor sustenance is attributed to the presence of a cell population that exhibits stem cell like properties. Specifically, cancer stem cells have the ability to preserve their own population, as well as give birth to cells of limited mitotic potential (LIMP cells) that follow the path towards terminal differentiation (DIFF cells). A proliferating tumor cell (stem or LIMP) passes through the successive cell cycle phases. Phases within or out of the cell cycle (G1, S, G2, M, G0) constitute different states in which cells may be found. After the completion of mitosis a fraction of newborn cells will enter the dormant phase, whereas the rest will continue to cycle. Transition to quiescence (dormant, G0, phase) and “awakening” of dormant cells are regulated by local metabolic conditions. All cell categories may die through spontaneous apoptosis. However, for dormant and differentiated cells necrosis is the main cell loss mechanism caused by inadequate nutrients’ and oxygen supply.</p>
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Based on discrete time and space stochastic cellular automata



# C+Te1

## Model information (II)

References	<p>Eleni A. Kolokotroni, Dimitra D. Dionysiou, Nikolaos K. Uzunoglu, Georgios S. Stamatakis, Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model, Mathematical and Computer Modelling, volume 54, issues 9–10, pages 1989-2006, November 2011. DOI:10.1016/j.mcm.2011.05.007.</p> <p>G. S. Stamatakis, E. Ch. Georgiadi, N. Graf, E. A. Kolokotroni, and D. D. Dionysiou, "Exploiting Clinical Trial Data Drastically Narrows the Window of Possible Solutions to the Problem of Clinical Adaptation of a Multiscale Cancer Model", PLoS ONE 6(3), e17594, 2011</p> <p>"D.D.Dionysiou, G.S. Stamatakis, N.K.Uzunoglu, K.S.Nikita, A. Marioli , "A Four Dimensional In Vivo Model of Tumour Response to Radiotherapy: Parametric Validation Considering Radiosensitivity, Genetic Profile and Fractionation," Journal of Theoretical Biology , 230 , 1-20 , 2004"</p>
COMMENTS	<p>Programming language: C++</p> <p><b>Input:</b> All Input parameters are fed into the model in the form of an xml file</p> <p><b>Output:</b></p> <ul style="list-style-type: none"> <li>- <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file</li> <li>- <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file</li> </ul> <p>Initial and final tumor images are given as dat and raw files</p> <ul style="list-style-type: none"> <li>- Tumor images every 24h are given as raw files</li> <li>- Furthermore the model gives as an output</li> </ul> <ol style="list-style-type: none"> <li>a) a dat file containing the values assigned to the model input parameters and</li> <li>b) an xml document listing the output files and the parameter <math>\Delta V/V</math></li> </ol>

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# C+Te1

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	
Cell density	input.xml	Tumor cell density	int	300000-1100000	Number of biological cells

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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					/mm <sup>3</sup> .
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# C+Te1

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Voxel dimension	input.xml	Voxel/GC acne dimension	int	1-2	mm
$N_{LIMP}$	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
$x_{dim}$	input.xml	Image (grid) width	int		voxels
$y_{dim}$	input.xml	Image (grid) depth	int		voxels
$z_{dim}$	input.xml	Image (grid) height	int		voxels
tumor_length	input.xml	Tumor length (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_breadth	input.xml	Tumor breadth (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_width	input.xml	Tumor width (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
$T_{stop}$	input.xml	Execution stop time after initialization	int	0-25	days
Spatial evolution?	input.xml	Inclusion of spatial evolution algorithms	boolean		
Input image?	input.xml	Input image existence	boolean		
Image filename	input.xml	Name of the input image file	string		

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Output directory	input.xml	Name of the directory where the output files are stored	string		
input.xml		A .xml file containing parameters (see comments for format).	file		.xml

# C+Te1

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\hat{I}$ {stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP) ,G0 (stem + LIMP), living, dead and total}	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	voxels
$\Delta V/V$	output.xml	Relative Volume reduction	double	
tumor_day_#.raw		Tumor image every 24h	file	.raw
final_tumor.raw		Final tumor image	file	.raw
initial_tumor.raw		Initial tumor image	file	.raw
$T_d$	tumor_dynamics.dat	Tumor doubling time	int	days

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<b>F<sub>cell class</sub></b>	<b>tumor_dynamics.dat</b>	<b>Fraction of the various cell categories cell class <math>\hat{I}</math> {stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic}</b>	<b>double (array)</b>	
<b>output.xml</b>		<b>A .xml file containing output parameters.</b>	<b>file</b>	<b>.xml</b>



# C+Te1

Output specifications (II)				
All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
final_tumour.dat		Final tumor occupied voxels	file	.dat
initial_tumour.dat		Initial tumor occupied voxels	file	.dat
tumor_dynamics.dat		Cell composition and Td	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te2

Model information (I)	
Model number	C+Te2.
Reference partner	ICCS
Model title	Untreated Tumor Growth. Non Spatial code
Brief model description	The non-spatial model constitutes a variation/simplification of the previous model (Untreated Tumor Growth. Spatial code). Its crucial new features consist in a. omitting the simulation of the spatial evolution of the tumor and b. considering more compartments that the proliferating cells can be found. The omission of the simulation of the three dimensional expansion of the tumor allows a more realistic modeling of the cell cycle, in terms of available computational resources. The exclusion of the spatial evolution of the tumor does not affect the temporal evolution of the various cancerous cell categories and the total cell population. Subsequently, the time course of the tumor volume can be easily derived assuming typical cell densities, e.g. $10^9$ biological cells/cm <sup>3</sup> (Steel, 1997). In the non-spatial model the cycling and dormant cancerous cells are distributed in a number of classes/compartments that equals the duration of the relevant phase (see paragraph 1.2). Each compartment corresponds to an hour-long interval.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Based on discrete cellular automata

## D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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# C+Te2

## Model information (II)

References	<p>Eleni A. Kolokotroni, Dimitra D. Dionysiou, Nikolaos K. Uzunoglu, Georgios S. Stamatakis, Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model, Mathematical and Computer Modelling, volume 54, issues 9–10, pages 1989-2006, November 2011. DOI:10.1016/j.mcm.2011.05.007.</p> <p>G. S. Stamatakis, E. Ch. Georgiadi, N. Graf, E. A. Kolokotroni, and D. D. Dionysiou, "Exploiting Clinical Trial Data Drastically Narrows the Window of Possible Solutions to the Problem of Clinical Adaptation of a Multiscale Cancer Model", PLoS ONE 6(3), e17594, 2011</p> <p>D.D.Dionysiou, G.S. Stamatakis, N.K.Uzunoglu, K.S.Nikita, A. Marioli , "A Four Dimensional In Vivo Model of Tumour Response to Radiotherapy: Parametric Validation Considering Radiosensitivity, Genetic Profile and Fractionation," Journal of Theoretical Biology , 230 , 1-20 , 2004</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output:</p> <ul style="list-style-type: none"> <li>- <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file</li> <li>- <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file</li> <li>- Furthermore the model gives as an output <ul style="list-style-type: none"> <li>a) a dat file containing the values assigned to the model input parameters and</li> <li>b) an xml document listing the output files and the parameter <math>\Delta V/V</math></li> </ul> </li> </ul>

# C+Te2

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	

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$N_{\text{LIMP}}$	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
$V_{\text{initial}}$	input.xml	Initial tumor volume	int		$\text{mm}^3$
$T_{\text{stop}}$	input.xml	Execution stop time after initialization	int	0-	days

# C+Te2

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Output directory	input.xml	Name of the directory where the output files are stored	string	0-	
input.xml		A .xml file containing parameters (see comments for format).	file		.xml

# C+Te2

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in$ {stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP), G0 (stem + LIMP), living, dead and total}	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$\Delta V/V$	output.xml	Relative Volume reduction	double	
$T_d$	tumor_dynamics.dat	Tumor doubling time	int	days
$F_{\text{cell class}}$	tumor_dynamics.dat	Fraction of the various cell categories cell class $\in$ {stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic}	double (array)	
output.xml		A .xml file containing output parameters.	file	.xml
tumor_dynamics.dat		Cell composition and Td	file	.dat



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tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te3

## Model information (I)

Model number	C+Te3.
Reference partner	ICCS
Model title	Single Agent Chemotherapy. Spatial code
Brief model description	<p>The model simulates the spatiotemporal response of clinical tumors to chemotherapeutic treatment. It is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid of “geometrical cells” (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transition between these states, as well as cell movement throughout the tumor volume; the aim is a realistic, conformal to the initial shape of the tumor, simulation of spatial evolution.</p> <p><b>Free Growth:</b> The adopted cytokinetic model incorporates the biological mechanisms of cell cycling, quiescence, differentiation and loss. Stem, LIMP, DIFF, apoptotic and necrotic cells represent the distinct cell categories of the model. More specifically, tumor sustenance is attributed to the presence of a cell population that exhibits stem cell like properties. Specifically, cancer stem cells have the ability to preserve their own population, as well as give birth to cells of limited mitotic potential (LIMP cells) that follow the path towards terminal differentiation (DIFF cells). A proliferating tumor cell (stem or LIMP) passes through the successive cell cycle phases. Phases within or out of the cell cycle (G1, S, G2, M, G0) constitute different states in which cells may be found. After the completion of mitosis a fraction of newborn cells will enter the dormant phase, whereas the rest will continue to cycle. Transition to quiescence (dormant, G0, phase) and “awakening” of dormant cells are regulated by local metabolic conditions. All cell categories may die through spontaneous apoptosis. However, for dormant and differentiated cells necrosis is the main cell loss mechanism caused by inadequate nutrients’ and oxygen supply.</p> <p><b>Treatment:</b> The model addresses the case of cell-cycle non-specific chemotherapeutic agents. When a tumor is chemotherapeutically treated, a fraction of cancerous proliferating cells are lethally hit by the drug. These cells enter a rudimentary cell cycle that leads to apoptotic death through a cell cycle phase depending each time on the specific chemotherapeutic agent. In the simulation model the case of drugs that primarily inhibit the DNA synthesis and lead to apoptotic death at the end of the S phase is addressed. The effect of</p>

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	<b>the drug is considered instantaneous at the time of its administration.</b>
<b>Biological scale</b>	<b>CELL AND TISSUE</b>

# C+Te3

## Model information (II)

Core mathematical methods utilized	Based on discrete time and space stochastic cellular automata
References	G.S. Stamatakis, E.A. Kolokotroni, D.D. Dionysiou, E.Ch. Georgiadi, C. Desmedt, An advanced discrete state - discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study, Journal of Theoretical Biology volume 266, issue 1, pages 124-139, September 2010. DOI:10.1016/j.jtbi.2010.05.019.
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output:</p> <ul style="list-style-type: none"> <li>- <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file</li> <li>- <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file</li> <li>- Initial and final tumor images are given as dat and raw files</li> <li>- Tumor images every 24h are given as raw files</li> <li>- Furthermore the model gives as an output <ul style="list-style-type: none"> <li>a) a dat file containing the values assigned to the model input parameters and</li> <li>b) an xml document listing the output files and the parameter <math>\Delta V/V</math></li> </ul> </li> </ul>

# C+Te3

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	

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<b>CKR</b>	<b>input.xml</b>	<b>Cell kill rate of the drug</b>	<b>double</b>	<b>0-1</b>	
<b>CKF[stem]</b>	<b>input.xml</b>	<b>Cell kill factor of stem tumor cells</b>	<b>double</b>	<b>0-1</b>	
<b>CKF[LIMP]</b>	<b>input.xml</b>	<b>Cell kill factor of LIMP tumor cells</b>	<b>double</b>	<b>0-1</b>	

# C+Te3

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Cell density	input.xml	Tumor cell density	int	300000-1100000	Number of biological cells /mm <sup>3</sup> .
Voxel dimension	input.xml	Voxel/GC acne dimension	int	1-2	mm
N <sub>LIMP</sub>	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
x <sub>dim</sub>	input.xml	Image (grid) width	int		voxels
y <sub>dim</sub>	input.xml	Image (grid) depth	int		voxels
z <sub>dim</sub>	input.xml	Image (grid) height	int		voxels
tumor_length	input.xml	Tumor length (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_breadth	input.xml	Tumor breadth (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_width	input.xml	Tumor width (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
T <sub>stop</sub>	input.xml	Execution stop time after initialization	int	0-25	days

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<b>Spatial evolution?</b>	<b>input.xml</b>	<b>Inclusion of spatial evolution algorithms</b>	<b>boolean</b>		
<b>Input image?</b>	<b>input.xml</b>	<b>Input image existence</b>	<b>boolean</b>		
<b>Image filename</b>	<b>input.xml</b>	<b>Name of the input image file</b>	<b>string</b>		



# C+Te3

## Input specifications (III)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Output directory	input.xml	Name of the directory where the output files are stored	string		
T <sub>1st,adm</sub>	input.xml	First administration time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second administration time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third administration time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth administration time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth administration time point	int	0-	days
T <sub>6th,adm</sub>	input.xml	Sixth administration time point	int	0-	days
input.xml		A .xml file containing parameters (see comments for format).	file		.xml

# C+Te3

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in \{ \text{stem proliferating, stem G0, stem proliferating hit by chemotherapy, stem G0 hit by chemotherapy, LIMP proliferating, LIMP G0, LIMP proliferating hit by chemotherapy, LIMP G0 hit by chemotherapy, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP), G0 (stem + LIMP), living, hit by chemotherapy, dead and total} \}$	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	voxels
$\Delta V/V$	output.xml	Relative Volume reduction	double	
tumor_day_#.raw		Tumor image every 24h	file	.raw
final_tumor.raw		Final tumor image	file	.raw

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<b>initial_tumor.raw</b>		<b>Initial tumor image</b>	<b>file</b>	<b>.raw</b>
<b>T<sub>d</sub></b>	<b>tumor_dynamics.dat</b>	<b>Tumor doubling time</b>	<b>int</b>	<b>days</b>

# C+Te3

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$F_{\text{cell class}}$	tumor_dynamics.dat	Initial fraction of the various cell categories cell class $\in \{\text{stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic}\}$	double (array)	
output.xml		A .xml file containing output parameters.	file	.xml
initial_tumour.dat		Initial tumor occupied voxels	file	.dat
final_tumour.dat		Final tumor occupied voxels	file	.dat
tumor_dynamics.dat		Cell composition and Td	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te4

## Model information

Model number	C+Te4.
Reference partner	ICCS
Model title	Single Agent Chemotherapy. Non Spatial code
Brief model description	The non-spatial model constitutes a variation/simplification of the previous model (Single Agent Chemotherapy. Spatial code). Its crucial new features consist in a. omitting the simulation of the spatial evolution of the tumor and b. considering more compartments that the proliferating cells can be found. The omission of the simulation of the three dimensional expansion of the tumor, in the case of free growth, or shrinkage, in the case of therapy, allows a more realistic modeling of the cell cycle, in terms of available computational resources. The exclusion of the spatial evolution of the tumor does not affect the temporal evolution of the various cancerous cell categories and the total cell population. Subsequently, the time course of the tumor volume can be easily derived assuming typical cell densities, e.g. $10^9$ biological cells/cm <sup>3</sup> (Steel, 1997). In the non-spatial model the cycling and dormant cancerous cells are distributed in a number of classes/compartments that equals the duration of the relevant phase (see paragraph 1.2). Each compartment corresponds to an hour-long interval.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Based on discrete cellular automata
References	G.S. Stamatakis, E.A. Kolokotroni, D.D. Dionysiou, E.Ch. Georgiadi, C. Desmedt, An advanced discrete state - discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study, Journal of Theoretical Biology volume 266, issue 1, pages 124-139, September 2010. DOI:10.1016/j.jtbi.2010.05.019.
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output: - <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file</p>

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- $T_d$  and  $F_{\text{cell class}}$  are given as a dat file
- Furthermore the model gives as an output
  - a) a dat file containing the values assigned to the model input parameters and
  - b) an xml document listing the output files and the parameter  $\Delta V/V$

# C+Te4

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	

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CKR	input.xml	Cell kill rate of the drug	double	0-1	
CKF[stem]	input.xml	Cell kill factor of stem tumor cells	double	0-1	
CKF[LIMP]	input.xml	Cell kill factor of LIMP tumor cells	double	0-1	



# C+Te4

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$N_{LIMP}$	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	300000-1100000	
$V_{initial}$	input.xml	Initial tumor volume	int		mm <sup>3</sup>
$T_{stop}$	input.xml	Execution stop time after initialization	int	0-	days
Output directory	input.xml	Name of the directory where the output files are stored	string	0-	
$T_{1st,adm}$	input.xml	First administration time point	int	0-	days
$T_{2nd,adm}$	input.xml	Second administration time point	int	0-	days
$T_{3rd,adm}$	input.xml	Third administration time point	int	0-	days
$T_{4th,adm}$	input.xml	Fourth administration time point	int	0-	days
$T_{5th,adm}$	input.xml	Fifth administration time point	int	0-	days
$T_{6th,adm}$	input.xml	Sixth administration time point	int	0-	days
input.xml		A .xml file containing parameters (see comments for format).	file		.xml

# C+Te4

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in \{\text{stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP), G0 (stem + LIMP), living, dead and total}\}$	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$\Delta V/V$	output.xml	Relative Volume reduction	double (array)	
$T_d$	tumor_dynamics.dat	Tumor doubling time	double	days
$F_{\text{cell class}}$	tumor_dynamics.dat	Fraction of the various cell categories	double (array)	
output.xml		A .xml file containing output parameters.	file	.xml
tumor_dynamics.dat		Cell composition and $T_d$	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat

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<b>oncosim- parameters.log</b>		<b>Parameters log file</b>	<b>file</b>	<b>.log</b>
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D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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# C+Te5

## Model information (I)

Model number	C+Te5.
Reference partner	ICCS
Model title	Radiotherapy. Spatial code
Brief model description	<p>The model simulates the spatiotemporal response of clinical tumors to chemotherapeutic treatment. It is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid of “geometrical cells” (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transition between these states, as well as cell movement throughout the tumor volume; the aim is a realistic, conformal to the initial shape of the tumor, simulation of spatial evolution.</p> <p><b>Free Growth:</b> The adopted cytokinetic model incorporates the biological mechanisms of cell cycling, quiescence, differentiation and loss. Stem, LIMP, DIFF, apoptotic and necrotic cells represent the distinct cell categories of the model. More specifically, tumor sustenance is attributed to the presence of a cell population that exhibits stem cell like properties. Specifically, cancer stem cells have the ability to preserve their own population, as well as give birth to cells of limited mitotic potential (LIMP cells) that follow the path towards terminal differentiation (DIFF cells). A proliferating tumor cell (stem or LIMP) passes through the successive cell cycle phases. Phases within or out of the cell cycle (G1, S, G2, M, G0) constitute different states in which cells may be found. After the completion of mitosis a fraction of newborn cells will enter the dormant phase, whereas the rest will continue to cycle. Transition to quiescence (dormant, G0, phase) and “awakening” of dormant cells are regulated by local metabolic conditions. All cell categories may die through spontaneous apoptosis. However, for dormant and differentiated cells necrosis is the main cell loss mechanism caused by inadequate nutrients’ and oxygen supply.</p> <p><b>Treatment:</b> In the case of radiation therapy lethally damaged cells die through a radiation-induced mitotic necrotic mechanism. These cells enter a rudimentary cell cycle and die after undergoing a few mitotic divisions. The probability of cells to be hit by irradiation depends primarily on the phase they reside. Cell killing by irradiation is described by the Linear Quadratic or LQ Model.</p>
Biological scale	CELL AND TISSUE

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<b>Core mathematical methods utilized</b>	<b>Based on discrete time and space stochastic cellular automata</b>
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# C+Te5

## Model information (II)

References	<p>G.S. Stamatakis, E.A. Kolokotroni, D.D. Dionysiou, E.Ch. Georgiadi, C. Desmedt, An advanced discrete state - discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study, Journal of Theoretical Biology volume 266, issue 1, pages 124-139, September 2010. DOI:10.1016/j.jtbi.2010.05.019.</p> <p>D.D. Dionysiou, G.S. Stamatakis, D. Gintides, N. Uzunoglu, K. Kyriaki, “ Critical Parameters Determining Standard Radiotherapy Treatment Outcome for Glioblastoma Multiforme: A Computer Simulation,” The Open Biomedical Engineering Journal 2, 43-51, 2008</p> <p>G.S. Stamatakis, D.D. Dionysiou, E.I. Zacharaki, N.A. Mouravliansky, K.S.Nikita, N.K. Uzunoglu , “In silico radiation oncology: combining novel simulation algorithms with current visualization techniques,” Proceedings of the IEEE, Special Issue on Bioinformatics: Advances and Challenges , 90(11) , 1764-1777 , 2002</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output:</p> <ul style="list-style-type: none"> <li>- <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file</li> <li>- <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file</li> <li>- Initial and final tumor images are given as dat and raw files</li> <li>- Tumor images every 24h are given as raw files</li> <li>- Furthermore the model gives as an output             <ol style="list-style-type: none"> <li>a dat file containing the values assigned to the model input parameters and</li> <li>an xml document listing the output files and the parameter <math>\Delta V/V</math></li> </ol> </li> </ul>

# C+Te5

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	



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<b>a</b>	<b>input.xml</b>	<b>Alpha parameter of LQ model</b>	<b>double</b>	<b>0.017-0.61</b>	<b>Gy<sup>-1</sup></b>
<b>b</b>	<b>input.xml</b>	<b>Beta parameter of LQ model</b>	<b>double</b>	<b>0.003-0.06</b>	<b>Gy<sup>-2</sup></b>
<b>OER</b>	<b>input.xml</b>	<b>Oxygen Enhancement Ratio</b>	<b>double</b>	<b>2.5-3</b>	
<b>D</b>	<b>input.xml</b>	<b>Radiation dose</b>	<b>double</b>		<b>Gy</b>

# C+Te5

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Cell density	input.xml	Tumor cell density	int	300000-1100000	Number of biological cells /mm <sup>3</sup> .
Voxel dimension	input.xml	Voxel/GC acne dimension	int	1-2	mm
N <sub>LIMP</sub>	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
x <sub>dim</sub>	input.xml	Image (grid) width	int		voxels
y <sub>dim</sub>	input.xml	Image (grid) depth	int		voxels
z <sub>dim</sub>	input.xml	Image (grid) height	int		voxels
tumor_length	input.xml	Tumor length(in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_breadth	input.xml	Tumor breadth (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_width	input.xml	Tumor width (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
T <sub>stop</sub>	input.xml	Execution stop time after initialization	int	0-25	days

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<b>Spatial evolution?</b>	<b>input.xml</b>	<b>Inclusion of spatial evolution algorithms</b>	<b>boolean</b>		
<b>Input image?</b>	<b>input.xml</b>	<b>Input image existence</b>	<b>boolean</b>		
<b>Image filename</b>	<b>input.xml</b>	<b>Name of the input image file</b>	<b>string</b>		

# C+Te5

## Input specifications (III)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Output directory	input.xml	Name of the directory where the output files are stored	string		
T <sub>1st,adm</sub>	input.xml	First irradiation time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second irradiation time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third irradiation time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth irradiation time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth irradiation time point	int	0-	days
T <sub>6th,adm</sub>	input.xml	Sixth irradiation time point	int	0-	days
T <sub>7th,adm</sub>	input.xml	Seventh irradiation time point	int	0-	days
T <sub>8th,adm</sub>	input.xml	Eighth irradiation time point	int	0-	days
T <sub>9th,adm</sub>	input.xml	Ninth irradiation time point	int	0-	days
T <sub>10th,adm</sub>	input.xml	Tenth irradiation time point	int	0-	days
input.xml		A .xml file containing parameters (see comments for format).	file		.xml

# C+Te5

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in \{ \text{stem proliferating, stem G0, stem proliferating hit by irradiation, stem G0 hit by irradiation, LIMP proliferating, LIMP G0, LIMP proliferating hit by irradiation, LIMP G0 hit by irradiation, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP), G0 (stem+ LIMP), living, hit by irradiation, dead and total} \}$	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	voxels
$\Delta V/V$	output.xml	Relative Volume reduction	double	
tumor_day_#.raw		Tumor image every 24h	file	.raw
final_tumor.raw		Final tumor image	file	.raw

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>initial_tumor.raw</b>		<b>Initial tumor image</b>	<b>file</b>	<b>.raw</b>
<b>T<sub>d</sub></b>	<b>tumor_dynamics.dat</b>	<b>Tumor doubling time</b>	<b>int</b>	<b>days</b>

# C+Te5

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$F_{\text{cell class}}$	tumor_dynamics.dat	Initial fraction of the various cell categories cell class $\in \{\text{stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic}\}$	double (array)	
output.xml		A .xml file containing output parameters.	file	.xml
initial_tumour.dat		Initial tumor occupied voxels	file	.dat
final_tumour.dat		Final tumor occupied voxels	file	.dat
tumor_dynamics.dat		Cell composition and Td	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te6

## Model information (I)

Model number	C+Te6.
Reference partner	ICCS
Model title	Radiotherapy. Non Spatial code
Brief model description	The non-spatial model constitutes a variation/simplification of the previous model (Radiotherapy. Spatial code). Its crucial new features consist in a. omitting the simulation of the spatial evolution of the tumor and b. considering more compartments that the proliferating cells can be found. The omission of the simulation of the three dimensional expansion of the tumor, in the case of free growth, or shrinkage, in the case of therapy, allows a more realistic modeling of the cell cycle, in terms of available computational resources. The exclusion of the spatial evolution of the tumor does not affect the temporal evolution of the various cancerous cell categories and the total cell population. Subsequently, the time course of the tumor volume can be easily derived assuming typical cell densities, e.g. $10^9$ biological cells/cm <sup>3</sup> (Steel, 1997). In the non-spatial model the cycling and dormant cancerous cells are distributed in a number of classes/compartments that equals the duration of the relevant phase (see paragraph 1.2). Each compartment corresponds to an hour-long interval.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Based on discrete cellular automata
References	<p>G.S. Stamatakis, E.A. Kolokotroni, D.D. Dionysiou, E.Ch. Georgiadi, C. Desmedt, An advanced discrete state - discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study, Journal of Theoretical Biology volume 266, issue 1, pages 124-139, September 2010. DOI:10.1016/j.jtbi.2010.05.019.</p> <p>D.D. Dionysiou, G.S. Stamatakis, D. Gintides, N. Uzunoglu, K. Kyriaki, “ Critical Parameters Determining Standard Radiotherapy Treatment Outcome for Glioblastoma Multiforme: A Computer Simulation,” The Open Biomedical Engineering Journal 2, 43-51, 2008</p> <p>G.S. Stamatakis, D.D. Dionysiou, E.I. Zacharaki, N.A. Mouravliansky, K.S.Nikita, N.K. Uzunoglu , “In silico radiation oncology:</p>



	<b>combining novel simulation algorithms with current visualization techniques,” Proceedings of the IEEE, Special Issue on Bioinformatics: Advances and Challenges , 90(11) , 1764-1777 , 2002</b>
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# C+Te6

## Model information (II)

### COMMENTS

Programming language: C++

#### Input:

- All Input parameters are fed into the model in the form of an xml file

#### Output:

- $N_{\text{cell class}}(t)$  and  $V_{\text{tumor}}(t)$  are given as a dat file
- $T_d$  and  $F_{\text{cell class}}$  are given as a dat file
- Furthermore the model gives as an output
  - a dat file containing the values assigned to the model input parameters and
  - an xml document listing the output files and the parameter  $\Delta V/V$

# C+Te6

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>a</b>	<b>input.xml</b>	<b>Alpha parameter of LQ model</b>	<b>double</b>	<b>0.017-0.61</b>	<b>Gy<sup>-1</sup></b>
<b>b</b>	<b>input.xml</b>	<b>Beta parameter of LQ model</b>	<b>double</b>	<b>0.003-0.06</b>	<b>Gy<sup>-2</sup></b>
<b>OER</b>	<b>input.xml</b>	<b>Oxygen Enhancement Ratio</b>	<b>double</b>	<b>2.5-3</b>	
<b>D</b>	<b>input.xml</b>	<b>Radiation dose</b>	<b>double</b>		<b>Gy</b>

# C+Te6

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$N_{LIMP}$	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
$V_{initial}$	input.xml	Initial tumor volume	int		mm <sup>3</sup>
$T_{stop}$	input.xml	Execution stop time after initialization	int	0-25	days
Output directory	input.xml	Name of the directory where the output files are stored	string		
$T_{1st,adm}$	input.xml	First irradiation time point	int	0-	days
$T_{2nd,adm}$	input.xml	Second irradiation time point	int	0-	days
$T_{3rd,adm}$	input.xml	Third irradiation time point	int	0-	days
$T_{4th,adm}$	input.xml	Fourth irradiation time point	int	0-	days
$T_{5th,adm}$	input.xml	Fifth irradiation time point	int	0-	days
$T_{6th,adm}$	input.xml	Sixth irradiation time point	int	0-	days
$T_{7th,adm}$	input.xml	Seventh irradiation time point	int	0-	days
$T_{8th,adm}$	input.xml	Eighth irradiation time point	int	0-	days

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<b>T<sub>9th,adm</sub></b>	<b>input.xml</b>	<b>Ninth irradiation time point</b>	<b>int</b>	<b>0-</b>	<b>days</b>
<b>T<sub>10th,adm</sub></b>	<b>input.xml</b>	<b>Tenth irradiation time point</b>	<b>int</b>	<b>0-</b>	<b>days</b>
<b>input.xml</b>		<b>A .xml file containing parameters (see comments for format).</b>	<b>file</b>		<b>.xml</b>

# C+Te6

Output specifications				
All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in$ {stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP) ,G0 (stem + LIMP), living, dead and total}	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$\Delta V/V$	output.xml	Relative Volume reduction	double (array)	
$T_d$	tumor_dynamics.dat	Tumor doubling time	double	days
$F_{\text{cell class}}$	tumor_dynamics.dat	Fraction of the various cell categories cell class $\in$ {stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic}	double (array)	
output.xml		A .xml file containing output parameters.	file	.xml
tumor_dynamics.dat		Cell composition and $T_d$	file	.dat

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tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log



# C+Te7

## Model information (I)

Model number	C+Te7.
Reference partner	ICCS
Model title	Breast Cancer Therapy: Epirubicin
Brief model description	<p>The model simulates the spatiotemporal response of breast cancer clinical tumors to chemotherapeutic treatment with single agent Epirubicin. It is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid of “geometrical cells” (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transition between these states, as well as cell movement throughout the tumor volume; the aim is a realistic, conformal to the initial shape of the tumor, simulation of spatial evolution.</p> <p><b>Free Growth:</b> The adopted cytokinetic model incorporates the biological mechanisms of cell cycling, quiescence, differentiation and loss. Stem, LIMP, DIFF, apoptotic and necrotic cells represent the distinct cell categories of the model. More specifically, tumor sustenance is attributed to the presence of a cell population that exhibits stem cell like properties. Specifically, cancer stem cells have the ability to preserve their own population, as well as give birth to cells of limited mitotic potential (LIMP cells) that follow the path towards terminal differentiation (DIFF cells). A proliferating tumor cell (stem or LIMP) passes through the successive cell cycle phases. Phases within or out of the cell cycle (G1, S, G2, M, G0) constitute different states in which cells may be found. After the completion of mitosis a fraction of newborn cells will enter the dormant phase, whereas the rest will continue to cycle. Transition to quiescence (dormant, G0, phase) and “awakening” of dormant cells are regulated by local metabolic conditions. All cell categories may die through spontaneous apoptosis. However, for dormant and differentiated cells necrosis is the main cell loss mechanism caused by inadequate nutrients’ and oxygen supply.</p> <p><b>Treatment:</b> The model addresses the case of Epirubicin agent. When a tumor is chemotherapeutically treated, a fraction of cancerous proliferating cells are lethally hit by the drug. These cells enter a rudimentary cell cycle that leads to apoptotic death through a cell cycle phase depending each time on the specific chemotherapeutic agent. In the simulation model the case of Epirubicin agent that</p>

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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	primarily inhibits the DNA synthesis and lead to apoptotic death at the end of the S phase is addressed. The effect of the drug is considered instantaneous at the time of its administration.
Biological scale	CELL AND TISSUE

# C+Te7

## Model information (II)

Core mathematical methods utilized	Based on discrete time and space stochastic cellular automata
References	<p>G.S. Stamatakos, E.A. Kolokotroni, D.D. Dionysiou, E.Ch. Georgiadi, C. Desmedt, An advanced discrete state - discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study, Journal of Theoretical Biology volume 266, issue 1, pages 124-139, September 2010. DOI:10.1016/j.jtbi.2010.05.019.</p> <p>Eleni A. Kolokotroni, Dimitra D. Dionysiou, Nikolaos K. Uzunoglu, Georgios S. Stamatakos, Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model, Mathematical and Computer Modelling, volume 54, issues 9–10, pages 1989-2006, November 2011. DOI:10.1016/j.mcm.2011.05.007.</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output:</p> <ul style="list-style-type: none"> <li>- <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file</li> <li>- <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file</li> </ul> <p>Initial and final tumor images are given as dat and raw files</p> <ul style="list-style-type: none"> <li>- Tumor images every 24h are given as raw files</li> <li>- Furthermore the model gives as an output               <ol style="list-style-type: none"> <li>a dat file containing the values assigned to the model input parameters and</li> <li>an xml document listing the output files and the parameter <math>\Delta V/V</math></li> </ol> </li> </ul>

# C+Te7

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	

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CKR	input.xml	Cell kill rate of epirubicin	double	0-1	
CKF[stem]	input.xml	Cell kill factor of stem tumor cells	double	0-1	
CKF[LIMP]	input.xml	Cell kill factor of LIMP tumor cells	double	0-1	

# C+Te7

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Cell density	input.xml	Tumor cell density	int	300000-1100000	Number of biological cells /mm <sup>3</sup> .
Voxel dimension	input.xml	Voxel/GC acne dimension	int	1-2	mm
N <sub>LIMP</sub>	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
x <sub>dim</sub>	input.xml	Image (grid) width	int		voxels
y <sub>dim</sub>	input.xml	Image (grid) depth	int		voxels
z <sub>dim</sub>	input.xml	Image (grid) height	int		voxels
tumor_length	input.xml	Tumor length (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_breadth	input.xml	Tumor breadth (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_width	input.xml	Tumor width (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
T <sub>stop</sub>	input.xml	Execution stop time after initialization	int	0-25	days

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<b>Spatial evolution?</b>	<b>input.xml</b>	<b>Inclusion of spatial evolution algorithms</b>	<b>boolean</b>		
<b>Input image?</b>	<b>input.xml</b>	<b>Input image existence</b>	<b>boolean</b>		
<b>Image filename</b>	<b>input.xml</b>	<b>Name of the input image file</b>	<b>string</b>		

# C+Te7

## Input specifications (III)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Output directory	input.xml	Name of the directory where the output files are stored	string		
T <sub>1st,adm</sub>	input.xml	First administration time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second administration time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third administration time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth administration time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth administration time point	int	0-	days
T <sub>6th,adm</sub>	input.xml	Sixth administration time point	int	0-	days
input.xml		A .xml file containing parameters (see comments for format).	file		.xml



# C+Te7

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in \{ \text{stem proliferating, stem G0, stem proliferating hit by chemotherapy, stem G0 hit by chemotherapy, LIMP proliferating, LIMP G0, LIMP proliferating hit by chemotherapy, LIMP G0 hit by chemotherapy, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP), G0 (stem + LIMP), living, hit by chemotherapy, dead and total} \}$	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	voxels
$\Delta V/V$	output.xml	Relative Volume reduction	double	
tumor_day_#.raw		Tumor image every 24h	file	
final_tumor.raw		Final tumor image	file	

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<b>initial_tumor.raw</b>		<b>Initial tumor image</b>	<b>file</b>	
<b>T<sub>d</sub></b>	<b>tumor_dynamics.dat</b>	<b>Tumor doubling time</b>	<b>int</b>	<b>days</b>
<b>F<sub>cell class</sub></b>	<b>tumor_dynamics.dat</b>	<b>Initial fraction of the various cell categories</b>	<b>double (array)</b>	
<b>output.xml</b>		<b>A .xml file containing output parameters.</b>	<b>file</b>	<b>.xml</b>

# C+Te7

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
initial_tumour.dat		Initial tumor occupied voxels	file	.dat
final_tumour.dat		Final tumor occupied voxels	file	.dat
tumor_dynamics.dat		Cell composition and Td	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te8

## Model information (I)

Model number	C+Te8.
Reference partner	ICCS
Model title	Lung Cancer Therapy: Cisplatin and Docetaxel
Brief model description	<p>The model simulates the spatiotemporal response of lung cancer to combination chemotherapy treatment with the regimens Cisplatin and Docetaxel. In accordance to clinical practice the cisplatin/docetaxel regimen is given as a three-week cycle and is administrated usually three times. On the first day of each cycle the patient is given both the docetaxel and cisplatin.</p> <p>It is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid of “geometrical cells” (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transition between these states, as well as cell movement throughout the tumor volume; the aim is a realistic, conformal to the initial shape of the tumor, simulation of spatial evolution.</p> <p>Free Growth: The adopted cytokinetic model incorporates the biological mechanisms of cell cycling, quiescence, differentiation and loss. Stem, LIMP, DIFF, apoptotic and necrotic cells represent the distinct cell categories of the model. More specifically, tumor sustenance is attributed to the presence of a cell population that exhibits stem cell like properties. Specifically, cancer stem cells have the ability to preserve their own population, as well as give birth to cells of limited mitotic potential (LIMP cells) that follow the path towards terminal differentiation (DIFF cells). A proliferating tumor cell (stem or LIMP) passes through the successive cell cycle phases. Phases within or out of the cell cycle (G1, S, G2, M, G0) constitute different states in which cells may be found. After the completion of mitosis a fraction of newborn cells will enter the dormant phase, whereas the rest will continue to cycle. Transition to quiescence (dormant, G0, phase) and “awakening” of dormant cells are regulated by local metabolic conditions. All cell categories may die through spontaneous apoptosis. However, for dormant and differentiated cells necrosis is the main cell loss mechanism caused by inadequate nutrients’ and oxygen supply.</p>

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	<b>Treatment: When a tumor is chemotherapeutically treated, a fraction of cancerous proliferating cells are lethally hit by the drug. These cells enter a rudimentary cell cycle that leads to apoptotic death through a cell cycle phase depending each time on the specific chemotherapeutic agent. The effect of the drug is considered instantaneous at the time of its administration.</b>
<b>Biological scale</b>	<b>CELL AND TISSUE</b>

# C+Te8

Model information (II)	
Core mathematical methods utilized	Based on discrete time and space stochastic cellular automata
References	<p>G. S.Stamatakos, E. Kolokotroni, D. Dionysiou, C. Veith, Yoo-Jin Kim, A. Franz, K. Marias, J. Sabczynski, R. Bohle, N.Graf, "In Silico Oncology: Exploiting Clinical Studies to Clinically Adapt and Validate Multiscale Oncosimulators," accepted in Proc. EMBC 2013 (35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Osaka, Japan)</p> <p>Eleni A. Kolokotroni, Dimitra D. Dionysiou, Nikolaos K. Uzunoglu, Georgios S. Stamatakos, Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model, Mathematical and Computer Modelling, volume 54, issues 9–10, pages 1989-2006, November 2011. DOI:10.1016/j.mcm.2011.05.007.</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output:            - <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file            - <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file            Initial and final tumor images are given as dat and raw files            - Tumor images every 24h are given as raw files            - Furthermore the model gives as an output            a) a dat file containing the values assigned to the model input parameters and            b) an xml document listing the output files and the parameter <math>\Delta V/V</math> </p>

# C+Te8

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>CKR[cis]</b>	<b>input.xml</b>	<b>Cell kill rate of cisplatin</b>	<b>double</b>	<b>0-1</b>	
<b>CKR[doc]</b>	<b>input.xml</b>	<b>Cell kill rate of docetaxel</b>	<b>double</b>	<b>0-1</b>	
<b>CKF[stem]</b>	<b>input.xml</b>	<b>Cell kill factor of stem tumor cells</b>	<b>double</b>	<b>0-1</b>	
<b>CKF[LIMP]</b>	<b>input.xml</b>	<b>Cell kill factor of LIMP tumor cells</b>	<b>double</b>	<b>0-1</b>	



# C+Te8

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Cell density	input.xml	Tumor cell density	int	300000-1100000	Number of biological cells /mm <sup>3</sup> .
Voxel dimension	input.xml	Voxel/GC acne dimension	int	1-2	mm
N <sub>LIMP</sub>	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
x <sub>dim</sub>	input.xml	Image (grid) width	int		voxels
y <sub>dim</sub>	input.xml	Image (grid) depth	int		voxels
z <sub>dim</sub>	input.xml	Image (grid) height	int		voxels
tumor_length	input.xml	Tumor length (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_breadth	input.xml	Tumor breadth (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_width	input.xml	Tumor width (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
T <sub>stop</sub>	input.xml	Execution stop time after initialization	int	0-25	days

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>Spatial evolution?</b>	<b>input.xml</b>	<b>Inclusion of spatial evolution algorithms</b>	<b>boolean</b>		
<b>Input image?</b>	<b>input.xml</b>	<b>Input image existence</b>	<b>boolean</b>		
<b>Image filename</b>	<b>input.xml</b>	<b>Name of the input image file</b>	<b>string</b>		

# C+Te8

## Input specifications (III)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Output directory	input.xml	Name of the directory where the output files are stored	string		
T <sub>1st,adm</sub>	input.xml	First combination drug administration time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second combination drug administration time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third combination drug administration time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth combination drug administration time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth combination drug administration time point	int	0-	days
T <sub>6th,adm</sub>	input.xml	Sixth combination drug administration time point	int	0-	days
input.xml		A .xml file containing parameters (see comments for format).	file		.xml

# C+Te8

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in$ { stem proliferating, stem G0, stem proliferating hit by chemotherapy, stem G0 hit by chemotherapy, LIMP proliferating, LIMP G0, LIMP proliferating hit by chemotherapy, LIMP G0 hit by chemotherapy, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP), G0 (stem + LIMP), living, hit by chemotherapy, dead and total }	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	voxels
$\Delta V/V$	output.xml	Relative Volume reduction	double	
tumor_day_#.raw		Tumor image every 24h	file	
final_tumor.raw		Final tumor image	file	

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>initial_tumor.raw</b>		<b>Initial tumor image</b>	<b>file</b>	
<b>T<sub>d</sub></b>	<b>tumor_dynamics.dat</b>	<b>Tumor doubling time</b>	<b>double</b>	<b>days</b>

# C+Te8

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$F_{\text{cell class}}$	tumor_dynamics.dat	Initial fraction of the various cell categories cell class $\in \{\text{stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic}\}$	double (array)	
output.xml		A .xml file containing output parameters.	file	.xml
initial_tumour.dat		Initial tumor occupied voxels	file	.dat
final_tumour.dat		Final tumor occupied voxels	file	.dat
tumor_dynamics.dat		Cell composition and Td	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te9

## Model information (I)

Model number	C+Te9.
Reference partner	ICCS
Model title	Lung Cancer Therapy: Cisplatin and Gemcitabine
Brief model description	<p>The model simulates the spatiotemporal response of lung cancer to combination chemotherapy treatment with the regimens Cisplatin and Gemcitabine. In accordance to clinical practice the cisplatin/ gemcitabine regimen is given as a three-week cycle and is administrated usually two or three times. On the first day of treatment the patient is given both the gemcitabine and cisplatin. On the same day of the following week (day eight) only gemcitabine is adminstrated.</p> <p>It is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid of “geometrical cells” (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transition between these states, as well as cell movement throughout the tumor volume; the aim is a realistic, conformal to the initial shape of the tumor, simulation of spatial evolution.</p> <p>Free Growth: The adopted cytokinetic model incorporates the biological mechanisms of cell cycling, quiescence, differentiation and loss. Stem, LIMP, DIFF, apoptotic and necrotic cells represent the distinct cell categories of the model. More specifically, tumor sustenance is attributed to the presence of a cell population that exhibits stem cell like properties. Specifically, cancer stem cells have the ability to preserve their own population, as well as give birth to cells of limited mitotic potential (LIMP cells) that follow the path towards terminal differentiation (DIFF cells). A proliferating tumor cell (stem or LIMP) passes through the successive cell cycle phases. Phases within or out of the cell cycle (G1, S, G2, M, G0) constitute different states in which cells may be found. After the completion of mitosis a fraction of newborn cells will enter the dormant phase, whereas the rest will continue to cycle. Transition to quiescence (dormant, G0, phase) and “awakening” of dormant cells are regulated by local metabolic conditions. All cell categories may die through spontaneous apoptosis. However, for dormant and differentiated cells necrosis is the main cell loss mechanism caused by inadequate nutrients’ and oxygen supply.</p>

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D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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	<p><b>Treatment: When a tumor is chemotherapeutically treated, a fraction of cancerous proliferating cells are lethally hit by the drug. These cells enter a rudimentary cell cycle that leads to apoptotic death through a cell cycle phase depending each time on the specific chemotherapeutic agent. The effect of the drug is considered instantaneous at the time of its administration.</b></p>
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# C+Te9

Model information (II)	
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Based on discrete time and space stochastic cellular automata
References	<p>G. S.Stamatakos, E. Kolokotroni, D. Dionysiou, C. Veith, Yoo-Jin Kim, A. Franz, K. Marias, J. Sabczynski, R. Bohle, N.Graf, "In Silico Oncology: Exploiting Clinical Studies to Clinically Adapt and Validate Multiscale Oncosimulators," accepted in Proc. EMBC 2013 (35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Osaka, Japan)</p> <p>Eleni A. Kolokotroni, Dimitra D. Dionysiou, Nikolaos K. Uzunoglu, Georgios S. Stamatakos, Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model, Mathematical and Computer Modelling, volume 54, issues 9–10, pages 1989-2006, November 2011. DOI:10.1016/j.mcm.2011.05.007.</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output:            - <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file            - <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file            Initial and final tumor images are given as dat and raw files            - Tumor images every 24h are given as raw files            - Furthermore the model gives as an output            a) a dat file containing the values assigned to the model input parameters and            b) an xml document listing the output files and the parameter <math>\Delta V/V</math> </p>

# C+Te9

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{sleep}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{sym}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	
$CKR[\text{cis}]$	input.xml	Cell kill rate of cisplatin	double	0-1	
$CKR[\text{gem}]$	input.xml	Cell kill rate of gemcitabine	double	0-1	

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

CKF[stem]	input.xml	Cell kill factor of stem tumor cells	double	0-1	
CKF[LIMP]	input.xml	Cell kill factor of LIMP tumor cells	double	0-1	

# C+Te9

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Cell density	input.xml	Tumor cell density	int	300000-1100000	Number of biological cells /mm <sup>3</sup> .
Voxel dimension	input.xml	Voxel/GC acne dimension	int	1-2	mm
NLIMP	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
x <sub>dim</sub>	input.xml	Image (grid) width	int		voxels
y <sub>dim</sub>	input.xml	Image (grid) depth	int		voxels
z <sub>dim</sub>	input.xml	Image (grid) height	int		voxels
tumor_length	input.xml	Tumor length (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_breadth	input.xml	Tumor breadth (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_width	input.xml	Tumor width (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
T <sub>stop</sub>	input.xml	Execution stop time after initialization	int	0-25	days
Spatial evolution?	input.xml	Inclusion of spatial evolution algorithms	boolean		

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>Input image?</b>	<b>input.xml</b>	<b>Input image existence</b>	<b>boolean</b>		
<b>Image filename</b>	<b>input.xml</b>	<b>Name of the input image file</b>	<b>string</b>		
<b>Output directory</b>	<b>input.xml</b>	<b>Name of the directory where the output files are stored</b>	<b>string</b>		

# C+Te9

## Input specifications (III)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
T <sub>1st,adm</sub>	input.xml	First combination drug administration time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second combination drug administration time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third combination drug administration time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth combination drug administration time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth combination drug administration time point	int	0-	days
T <sub>6th,adm</sub>	input.xml	Sixth combination drug administration time point	int	0-	days
T <sub>1st,adm</sub>	input.xml	First single drug administration time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second single drug administration time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third single drug administration time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth single drug administration time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth single drug administration time point	int	0-	days
T <sub>6th,adm</sub>	input.xml	Sixth single drug administration time point	int	0-	days
input.xml		A .xml file containing parameters (see comments for format).	file		.xml

# C+Te9

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in$ { stem proliferating, stem G0, stem proliferating hit by chemotherapy, stem G0 hit by chemotherapy, LIMP proliferating, LIMP G0, LIMP proliferating hit by chemotherapy, LIMP G0 hit by chemotherapy, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP), G0 (stem + LIMP), living, hit by chemotherapy, dead and total }	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	voxels
$\Delta V/V$	output.xml	Relative Volume reduction	double	
tumor_day_#.raw		Tumor image every 24h	file	
final_tumor.raw		Final tumor image	file	

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>initial_tumor.raw</b>		<b>Initial tumor image</b>	<b>file</b>	
<b>T<sub>d</sub></b>	<b>tumor_dynamics.dat</b>	<b>Tumor doubling time</b>	<b>double</b>	<b>days</b>
<b>F<sub>cell class</sub></b>	<b>tumor_dynamics.dat</b>	<b>Initial fraction of the various cell categories</b>	<b>double (array)</b>	



# C+Te9

Output specifications (II)				
All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
output.xml		A .xml file containing output parameters.	file	.xml
initial_tumour.dat		Initial tumor occupied voxels	file	.dat
final_tumour.dat		Final tumor occupied voxels	file	.dat
tumor_dynamics.dat		Cell composition and $T_d$	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te10

## Model information (I)

Model number	C+Te10.
Reference partner	ICCS
Model title	Lung Cancer Therapy: Cisplatin and Vinorelbine
Brief model description	<p>The model simulates the spatiotemporal response of lung cancer to combination chemotherapy treatment with the regimens Cisplatin and Vinorelbine. In accordance to clinical practice the cisplatin/vinorelbine regimen is given as a three-week cycle and is administrated usually two or three times. On the first day of treatment the patient is given both the vinorelbine and cisplatin. On the same day of the following week (day eight) only vinorelbine is adminstrated.</p> <p>It is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid of “geometrical cells” (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transition between these states, as well as cell movement throughout the tumor volume; the aim is a realistic, conformal to the initial shape of the tumor, simulation of spatial evolution.</p> <p>Free Growth: The adopted cytokinetic model incorporates the biological mechanisms of cell cycling, quiescence, differentiation and loss. Stem, LIMP, DIFF, apoptotic and necrotic cells represent the distinct cell categories of the model. More specifically, tumor sustenance is attributed to the presence of a cell population that exhibits stem cell like properties. Specifically, cancer stem cells have the ability to preserve their own population, as well as give birth to cells of limited mitotic potential (LIMP cells) that follow the path towards terminal differentiation (DIFF cells). A proliferating tumor cell (stem or LIMP) passes through the successive cell cycle phases. Phases within or out of the cell cycle (G1, S, G2, M, G0) constitute different states in which cells may be found. After the completion of mitosis a fraction of newborn cells will enter the dormant phase, whereas the rest will continue to cycle. Transition to quiescence (dormant, G0, phase) and “awakening” of dormant cells are regulated by local metabolic conditions. All cell categories may die through spontaneous apoptosis. However, for dormant and differentiated cells necrosis is the main cell loss mechanism caused by inadequate nutrients’ and oxygen supply.</p>

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D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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	<p><b>Treatment: When a tumor is chemotherapeutically treated, a fraction of cancerous proliferating cells are lethally hit by the drug. These cells enter a rudimentary cell cycle that leads to apoptotic death through a cell cycle phase depending each time on the specific chemotherapeutic agent. The effect of the drug is considered instantaneous at the time of its administration.</b></p>
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# C+Te10

## Model information (II)

Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Based on discrete time and space stochastic cellular automata
References	<p>G. S.Stamatakis, E. Kolokotroni, D. Dionysiou, C. Veith, Yoo-Jin Kim, A. Franz, K. Marias, J. Sabczynski, R. Bohle, N.Graf, "In Silico Oncology: Exploiting Clinical Studies to Clinically Adapt and Validate Multiscale Oncosimulators," accepted in Proc. EMBC 2013 (35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Osaka, Japan)</p> <p>Eleni A. Kolokotroni, Dimitra D. Dionysiou, Nikolaos K. Uzunoglu, Georgios S. Stamatakis, Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model, Mathematical and Computer Modelling, volume 54, issues 9–10, pages 1989-2006, November 2011. DOI:10.1016/j.mcm.2011.05.007.</p> <p>K. Marias, D. Dionysiou, V. Sakalis, N. Graf, R.M. Bohle, P.V. Coveney, S. Wan, A. Folarin, P. Bóchler, M. Reyes, G. Clapworthy, E. Liu, J. Sabczynski, T. Bily, A. Roniotis, M. Tsiknakis, E. Kolokotroni, S. Giatili, C. Veith, E. Messe, H. Stenzhorn, Yoo-Jin Kim, S. Zasada, A.N. Haidar, C. May, S. Bauer, T. Wang, Y. Zhao, M. Karasek, R. Grewer, A. Franz, G. Stamatakis, Clinically driven design of multi-scale cancer models: the ContraCancrum project paradigm, Interface Focus volume 1, number 3, pages 450–461, June 2011. DOI:10.1098/rsfs.2010.0037.</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output: - <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file - <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file</p>

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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|--|---|
|  | <ul style="list-style-type: none"><li>- Initial and final tumor images are given as <b>dat</b> and <b>raw</b> files</li><li>- Tumor images every 24h are given as <b>raw</b> files</li><li>- Furthermore the model gives as an output<ul style="list-style-type: none"><li>a) a <b>dat</b> file containing the values assigned to the model input parameters and</li><li>b) an <b>xml</b> document listing the output files and the parameter <math>\Delta V/V</math></li></ul></li></ul> |
|--|---|

# C+Te10

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>CKR[cis]</b>	<b>input.xml</b>	<b>Cell kill rate of cisplatin</b>	<b>double</b>	<b>0-1</b>	
<b>CKR[vin]</b>	<b>input.xml</b>	<b>Cell kill rate of vinorelbine</b>	<b>double</b>	<b>0-1</b>	
<b>CKF[stem]</b>	<b>input.xml</b>	<b>Cell kill factor of stem tumor cells</b>	<b>double</b>	<b>0-1</b>	
<b>CKF[LIMP]</b>	<b>input.xml</b>	<b>Cell kill factor of LIMP tumor cells</b>	<b>double</b>	<b>0-1</b>	

# C+Te10

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Cell density	input.xml	Tumor cell density	int	300000-1100000	Number of biological cells /mm <sup>3</sup> .
Voxel dimension	input.xml	Voxel/GC acne dimension	int	1-2	mm
N <sub>LIMP</sub>	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
x <sub>dim</sub>	input.xml	Image (grid) width	int		voxels
y <sub>dim</sub>	input.xml	Image (grid) depth	int		voxels
z <sub>dim</sub>	input.xml	Image (grid) height	int		voxels
tumor_length	input.xml	Tumor length (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_breadth	input.xml	Tumor breadth (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_width	input.xml	Tumor width (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
T <sub>stop</sub>	input.xml	Execution stop time after initialization	int	0-25	days



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<b>Spatial evolution?</b>	<b>input.xml</b>	<b>Inclusion of spatial evolution algorithms</b>	<b>boolean</b>		
<b>Input image?</b>	<b>input.xml</b>	<b>Input image existence</b>	<b>boolean</b>		
<b>Image filename</b>	<b>input.xml</b>	<b>Name of the input image file</b>	<b>string</b>		

# C+Te10

## Input specifications (III)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Output directory	input.xml	Name of the directory where the output files are stored	string		
T <sub>1st,adm</sub>	input.xml	First combination drug administration time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second combination drug administration time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third combination drug administration time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth combination drug administration time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth combination drug administration time point	int	0-	days
T <sub>6th,adm</sub>	input.xml	Sixth combination drug administration time point	int	0-	days
T <sub>1st,adm</sub>	input.xml	First single drug administration time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second single drug administration time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third single drug administration time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth single drug administration time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth single drug administration time point	int	0-	days

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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input.xml		A .xml file containing parameters (see comments for format).	file		.xml
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# C+Te10

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in$ { stem proliferating, stem G0, stem proliferating hit by chemotherapy, stem G0 hit by chemotherapy, LIMP proliferating, LIMP G0, LIMP proliferating hit by chemotherapy, LIMP G0 hit by chemotherapy, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + LIMP), G0 (stem + LIMP), living, hit by chemotherapy, dead and total }	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	voxels
$\Delta V/V$	output.xml	Relative Volume reduction	double	
tumor_day_#.raw		Tumor image every 24h	file	
final_tumor.raw		Final tumor image	file	

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<b>initial_tumor.raw</b>		<b>Initial tumor image</b>	<b>file</b>	
<b>T<sub>d</sub></b>	<b>tumor_dynamics.dat</b>	<b>Tumor doubling time</b>	<b>double</b>	<b>days</b>
<b>F<sub>cell class</sub></b>	<b>tumor_dynamics.dat</b>	<b>Initial fraction of the various cell categories</b>	<b>double (array)</b>	
<b>output.xml</b>		<b>A .xml file containing output parameters.</b>	<b>file</b>	<b>.xml</b>

# C+Te10

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
initial_tumour.dat		Initial tumor occupied voxels	file	.dat
final_tumour.dat		Final tumor occupied voxels	file	.dat
tumor_dynamics.dat		Cell composition and Td	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te11

## Model information (I)

Model number	C+Te11.
Reference partner	ICCS
Model title	Glioblastoma Therapy: Temozolomide and Radiation
Brief model description	<p>The model simulates the spatiotemporal response of glioblastoma multiforme to combined modality treatment using radiation and chemotherapy with temozolomide agent. It is based on the consideration of a discrete time and space stochastic cellular automaton, representing the tumor region. More specifically, the tumor region can be considered as a grid of “geometrical cells” (GCs, the elementary volume of the grid). Each GC corresponds to a cluster of heterogeneous cells found in various states. Specific rules regulate the transition between these states, as well as cell movement throughout the tumor volume; the aim is a realistic, conformal to the initial shape of the tumor, simulation of spatial evolution.</p> <p><b>Free Growth:</b> The adopted cytokinetic model incorporates the biological mechanisms of cell cycling, quiescence, differentiation and loss. Stem, LIMP, DIFF, apoptotic and necrotic cells represent the distinct cell categories of the model. More specifically, tumor sustenance is attributed to the presence of a cell population that exhibits stem cell like properties. Specifically, cancer stem cells have the ability to preserve their own population, as well as give birth to cells of limited mitotic potential (LIMP cells) that follow the path towards terminal differentiation (DIFF cells). A proliferating tumor cell (stem or LIMP) passes through the successive cell cycle phases. Phases within or out of the cell cycle (G1, S, G2, M, G0) constitute different states in which cells may be found. After the completion of mitosis a fraction of newborn cells will enter the dormant phase, whereas the rest will continue to cycle. Transition to quiescence (dormant, G0, phase) and “awakening” of dormant cells are regulated by local metabolic conditions. All cell categories may die through spontaneous apoptosis. However, for dormant and differentiated cells necrosis is the main cell loss mechanism caused by inadequate nutrients’ and oxygen supply.</p> <p><b>Treatment:</b> The model addresses the case of temozolomide chemotherapeutic agent. When a tumor is chemotherapeutically treated, a fraction of cancerous proliferating cells are lethally hit by the drug. These cells enter a rudimentary cell cycle that leads to apoptotic death through a cell cycle phase depending each time on the specific chemotherapeutic agent. The effect of the drug is considered</p>

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**instantaneous at the time of its administration.**

**In the case of radiation therapy, lethally damaged cells die through a radiation-induced mitotic necrotic mechanism after undergoing a few mitotic divisions. The probability of cells to be hit by irradiation depends primarily on the phase they reside.**



# C+Te11

Model information (II)	
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Based on discrete time and space stochastic cellular automata
References	<p>G.S.Stamatakis, V.P.Antipas, and N.K. Uzunoglu , “A spatiotemporal, patient individualized simulation model of solid tumor response to chemotherapy in vivo: the paradigm of glioblastoma multiforme treated by temozolomide,” IEEE Transactions on Biomedical Engineering , 53(8) , 1467-1477 , 2006</p> <p>Eleni A. Kolokotroni, Dimitra D. Dionysiou, Nikolaos K. Uzunoglu, Georgios S. Stamatakis, Studying the growth kinetics of untreated clinical tumors by using an advanced discrete simulation model, Mathematical and Computer Modelling, volume 54, issues 9–10, pages 1989-2006, November 2011. DOI:10.1016/j.mcm.2011.05.007.</p> <p>K. Marias, D. Dionysiou, V. Sakkalis, N. Graf, R.M. Bohle, P.V. Coveney, S. Wan, A. Folarin, P. Bóchler, M. Reyes, G. Clapworthy, E. Liu, J. Sabczynski, T. Bily, A. Roniotis, M. Tsiknakis, E. Kolokotroni, S. Giatili, C. Veith, E. Messe, H. Stenzhorn, Yoo-Jin Kim, S. Zasada, A.N. Haidar, C. May, S. Bauer, T. Wang, Y. Zhao, M. Karasek, R. Grewer, A. Franz, G. Stamatakis, Clinically driven design of multi-scale cancer models: the ContraCancrum project paradigm, Interface Focus volume 1, number 3, pages 450–461, June 2011. DOI:10.1098/rsfs.2010.0037.</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output: - <math>N_{\text{cell class}}(t)</math> and <math>V_{\text{tumor}}(t)</math> are given as a dat file - <math>T_d</math> and <math>F_{\text{cell class}}</math> are given as a dat file</p>

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	<p><b>Initial and final tumor images are given as dat and raw files</b></p> <ul style="list-style-type: none"><li>- Tumor images every 24h are given as raw files</li><li>- Furthermore the model gives as an output</li></ul> <p>a) a dat file containing the values assigned to the model input parameters and</p> <p>b) an xml document listing the output files and the parameter <math>\Delta V/V</math></p>
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# C+Te11

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c[\text{stem}]$	input.xml	Stem cell cycle duration	int	20-120	hours
$T_c[\text{LIMP}]$	input.xml	LIMP cell cycle duration	int	20-120	hours
$T_{G0}[\text{stem}]$	input.xml	Stem G0 phase duration	int	96-240	hours
$T_{G0}[\text{LIMP}]$	input.xml	LIMP G0 phase duration	int	96-240	hours
$T_N$	input.xml	Necrosis duration	int	0-500	hours
$T_A$	input.xml	Apoptosis duration	int	0-25	hours
$R_A$	input.xml	Apoptosis rate of stem and LIMP tumor cells	double	0-1	hour <sup>-1</sup>
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells	double	0-1	hour <sup>-1</sup>
$P_{G0toG1}[\text{stem}]$	input.xml	Fraction of dormant stem cells re-entering cell cycle	double	0-1	
$P_{G0toG1}[\text{LIMP}]$	input.xml	Fraction of dormant LIMP cells re-entering cell cycle	double	0-1	
$P_{\text{sleep}}$	input.xml	Fraction of newborn cells entering G0 phase	double	0-1	
$P_{\text{sym}}$	input.xml	Fraction of stem cells that perform symmetric division	double	0-1	

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CKF[stem]	input.xml	Cell kill factor of stem tumor cells	double	0-1	
CKF[LIMP]	input.xml	Cell kill factor of LIMP tumor cells	double	0-1	

# C+Te11

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Cell density	input.xml	Tumor cell density	int	300000-1100000	Number of biological cells /mm <sup>3</sup> .
Voxel dimension	input.xml	Voxel/GC acne dimension	int	1-2	mm
N <sub>LIMP</sub>	input.xml	Number of mitoses performed by LIMP cells before becoming differentiated	int	0-	
x <sub>dim</sub>	input.xml	Image (grid) width	int		voxels
y <sub>dim</sub>	input.xml	Image (grid) depth	int		voxels
z <sub>dim</sub>	input.xml	Image (grid) height	int		voxels
tumor_length	input.xml	Tumor length (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_breadth	input.xml	Tumor breadth (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
tumor_width	input.xml	Tumor width (in case a triaxial ellipsoidal tumor is considered)	int	1-	mm
T <sub>stop</sub>	input.xml	Execution stop time after initialization	int	0-25	days

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<b>Spatial evolution?</b>	<b>input.xml</b>	<b>Inclusion of spatial evolution algorithms</b>	<b>boolean</b>		
<b>Input image?</b>	<b>input.xml</b>	<b>Input image existence</b>	<b>boolean</b>		
<b>Image filename</b>	<b>input.xml</b>	<b>Name of the input image file</b>	<b>string</b>		

# C+Te11

## Input specifications (III)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Output directory	input.xml	Name of the directory where the output files are stored	string		
T <sub>1st,adm</sub>	input.xml	First drug administration time point	int	0-	days
T <sub>2nd,adm</sub>	input.xml	Second drug administration time point	int	0-	days
T <sub>3rd,adm</sub>	input.xml	Third drug administration time point	int	0-	days
T <sub>4th,adm</sub>	input.xml	Fourth drug administration time point	int	0-	days
T <sub>5th,adm</sub>	input.xml	Fifth drug administration time point	int	0-	days
T <sub>6th,adm</sub>	input.xml	Sixth drug administration time point	int	0-	days
T <sub>7th,adm</sub>	input.xml	Seventh drug administration time point	int	0-	days
T <sub>8th,adm</sub>	input.xml	Eighth drug administration time point	int	0-	days
T <sub>9th,adm</sub>	input.xml	Ninth drug administration time point	int	0-	days
T <sub>10th,adm</sub>	input.xml	Tenth drug administration time point	int	0-	days
V <sub>d</sub>	input.xml	Volume of distribution	double		L/m <sup>2</sup>

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	input.xml	Bioavailability	double		
$k_a$	input.xml	Absorption rate constant	double		$h^{-1}$
$k_{el}$	input.xml	Elimination rate constant	double		$h^{-1}$
$S_F$	input.xml	Survival fraction constant	double		$(h * mg/L)^{-1}$



# C+Te11

## Input specifications (IV)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
<b>D<sub>Drug</sub></b>	input.xml	Drug dose	double		mg/m <sup>2</sup>
<b>T<sub>1st,radio</sub></b>	input.xml	First irradiation time point	int	0-	days
<b>T<sub>2nd,radio</sub></b>	input.xml	Second irradiation time point	int	0-	days
<b>T<sub>3rd, radio</sub></b>	input.xml	Third irradiation time point	int	0-	days
<b>T<sub>4th,radio</sub></b>	input.xml	Fourth irradiation time point	int	0-	days
<b>T<sub>5th, radio</sub></b>	input.xml	Fifth irradiation time point	int	0-	days
<b>T<sub>6th, radio</sub></b>	input.xml	Sixth irradiation time point	int	0-	days
<b>T<sub>7th, radio</sub></b>	input.xml	Seventh irradiation time point	int	0-	days
<b>T<sub>8th, radio</sub></b>	input.xml	Eighth irradiation time point	int	0-	days
<b>T<sub>9th, radio</sub></b>	input.xml	Ninth irradiation time point	int	0-	days
<b>T<sub>10th, radio</sub></b>	input.xml	Tenth irradiation time point	int	0-	days
<b>a</b>	input.xml	Alpha parameter of LQ model	double	0.017-0.61	Gy <sup>-1</sup>
<b>b</b>	input.xml	Beta parameter of LQ model	double	0.003-0.06	Gy <sup>-2</sup>

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<b>OER</b>	<b>input.xml</b>	<b>Oxygen Enhancement Ratio</b>	<b>double</b>	<b>2.5-3</b>	
<b>D<sub>radio</sub></b>	<b>input.xml</b>	<b>Radiation dose</b>	<b>double</b>		<b>Gy</b>
<b>input.xml</b>		<b>A .xml file containing parameters (see comments for format).</b>	<b>file</b>		<b>.xml</b>

# C+Te11

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$N_{\text{cell class}}(t)$	tumor_evolution.dat	Time evolution of the various cell categories populations cell class $\in$ { stem proliferating, stem G0, stem proliferating hit by chemotherapy, stem proliferating hit by irradiation, stem G0 hit by chemotherapy, stem G0 hit by irradiation, LIMP proliferating, LIMP G0, LIMP proliferating hit by chemotherapy, LIMP proliferating hit by irradiation, LIMP G0 hit by chemotherapy, LIMP G0 hit by irradiation, differentiated, apoptotic, necrotic, stem (proliferating + G0), LIMP (proliferating + G0), proliferating (stem + limp), G0 (stem + LIMP), living, hit (chemotherapy + irradiation), dead and total }	double (array)	
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	mm <sup>3</sup>
$V_{\text{tumor}}(t)$	tumor_evolution.dat	Time evolution of tumor volume	double (array)	voxels
$\Delta V/V$	output.xml	Relative Volume reduction	double	
tumor_day_#.raw		Tumor image every 24h	file	

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<b>final_tumor.raw</b>		<b>Final tumor image</b>	<b>file</b>	
<b>initial_tumor.raw</b>		<b>Initial tumor image</b>	<b>file</b>	
<b>T<sub>d</sub></b>	<b>tumor_dynamics.dat</b>	<b>Tumor doubling time</b>	<b>double</b>	<b>days</b>

# C+Te11

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
$F_{\text{cell class}}$	tumor_dynamics.dat	Initial fraction of the various cell categories cell class $\hat{I}$ {stem proliferating, stem G0, LIMP proliferating, LIMP G0, differentiated, apoptotic, necrotic}	double (array)	
output.xml		A .xml file containing output parameters.	file	.xml
initial_tumour.dat		Initial tumor occupied voxels	file	.dat
final_tumour.dat		Final tumor occupied voxels	file	.dat
tumor_dynamics.dat		Cell composition and $T_d$	file	.dat
tumor_evolution.dat		Tumor temporal evolution	file	.dat
oncosim-parameters.log		Parameters log file	file	.log

# C+Te12

## Model information (I)

Model number	C+Te12.
Reference partner	ICCS
Model title	Free Growth of homogeneous solid tumors simulation model
Brief model description	A four-dimensional discrete simulation model of solid homogeneous tumor free growth.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Hybrid method (primarily discrete event based).
References	<p>E.C.Georgiadi, D.D.Dionysiou, N.Graf, G.Stamatakis, "Towards In Silico Oncology: Adapting a Four Dimensional Nephroblastoma Treatment Model to a Clinical Trial Case Based on Multi-Method Sensitivity Analysis.", Comput Biol Med. 2012 Nov;42(11):1064-78. doi: 10.1016/j.compbimed.2012.08.008. Epub 2012 Oct 10</p> <p>N. Graf, A. Hoppe , E. Georgiadi, R. Belleman, C. Desmedt, D. Dionysiou, M. Erdt , J. Jacques, E. Kolokotroni, A. Lunzer, M. Tsiknakis and G. Stamatakis, “ "In Silico Oncology" for Clinical Decision Making in the Context of Nephroblastoma. [Die Bedeutung von ,in silico Onkologie` zur klinischen Entscheidungsfindung am Beispiel des Nephroblastoms],” Klin. Paediatr. (Klinische Paediatric) 221, 141-149, 2009</p> <p>Eleni Ch. Georgiadi, Dimitra D. Dionysiou, Norbert Graf and Georgios S. Stamatakis, “Modeling nephroblastoma treatment response cases with in-silico scenarios”, 10/2012; In proceeding of: 2012 5 th Int. Adv. Res. Workshop on In Silico Oncology and Cancer</p>

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	<b>Investigation – The TUMOR Project Workshop (IARWISOCI), At Athens, Greece, Volume: ISBN: 978-618-80348-0-8 (open-access version) , <a href="http://www.5th-iarwisoci.iccs.ntua.gr">www.5th-iarwisoci.iccs.ntua.gr</a>, Edited by G. Stamatakos and D. Dionysiou, pages 35-28.</b>
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# C+Te12

## Model information (II)

References	<p>E. Ch. Georgiadi, G. S. Stamatakos, N. M. Graf, E. A. Kolokotroni, D. D. Dionysiou, A. Hoppe, N. K. Uzunoglu, "Multilevel Cancer Modeling in the Clinical Environment: Simulating the Behavior of Wilms Tumor in the Context of the SIOP 2001/GPOH Clinical Trial and the ACGT Project," Proc. 8th IEEE International Conference on Bioinformatics and Bioengineering (BIBE 2008), Athens, Greece, 8-10 Oct. 2008. IEEE Catalog Number: CFP08266, ISBN: 978-1-4244-2845-8, Library of Congress: 2008907441, Paper No. BE-2.1.2, length: 8 pages (in electronic format). 2008</p> <p>D.D.Dionysiou, G.S. Stamatakos, N.K.Uzunoglu, K.S.Nikita, A. Marioli , "A Four Dimensional In Vivo Model of Tumour Response to Radiotherapy: Parametric Validation Considering Radiosensitivity, Genetic Profile and Fractionation," Journal of Theoretical Biology , 230 , 1-20 , 2004</p> <p>G.S. Stamatakos, D.D. Dionysiou, E.I. Zacharaki, N.A. Mouravliansky, K.S.Nikita, N.K. Uzunoglu , "In silico radiation oncology: combining novel simulation algorithms with current visualization techniques," Proceedings of the IEEE, Special Issue on Bioinformatics: Advances and Chalenges , 90(11) , 1764-1777 , 2002</p>
COMMENTS	*Able to set different values for STEM and LIMP cells



# C+Te12

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c$	input.xml	Cell cycle duration of cells (G0 phase not included)	int	20-50	
$T_{G0}^*$	input.xml	Maximum G0 (dormant) phase duration before stem cell enters necrosis or re-enters G1	int	0-200	
$T_N^{**}$	input.xml	Time needed for necrosis to be completed and its lysis products to be eliminated from the tumor	int	0-500	
$T_A^{**}$	input.xml	Time needed for apoptosis to be completed and its products to be eliminated from the tumor	int	0-50	
$R_A^{**}$	input.xml	Apoptosis rate of living stem and LIMP tumor cells (fraction of non-differentiated cells dying through apoptosis per hour)	double	0.0-1.0	$h^{-1}$
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells per hour	double	0.0-1.0	$h^{-1}$
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells per hour	double	0.0-1.0	$h^{-1}$
$P_{G0toG1}^*$	input.xml	The fraction of stem or LIMP cells having just left the G0 compartment that re-enter the cell cycle	double	0.0-1.0	
$N_{LIMP}$	input.xml	The maximum number of mitoses that a LIMP cell can perform before becoming terminally differentiated	int	1-10	

# C+Te12

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$P_{sym}^{**}$	input.xml	Fraction of stem cells that perform symmetric division.	double	0.0-1.0	
$P_{sleep}^{**}$	input.xml	Fraction of cells that enter G0 phase following mitosis	double	0.0-1.0	
$l_{GC}$ (cm)	input.xml	length of voxel's side	int	1-5	mm
x_dim	input.xml	Dimension of the mesh along x direction	int	1-200	GC
y_dim	input.xml	Dimension of the mesh along y direction	int	1-200	GC
z_dim	input.xml	Dimension of the mesh along z direction	int	1-200	GC
NBC	input.xml	Number of biological cells typically contained within a GC of the mesh (assigned in relation to the GC's volume)	int	300000-1100000	cells
input.xml		A .xml file containing parameters.	file		.xml

# C+Te12

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
V(t)	tum_evol_file.dat	Time evolution of tumor volume	double (array)	mm(h) or GCs (h)
P <sub>op</sub> (t)	tum_evol_file.dat	Time evolution of several cell populations (stem, LIMP, diff, dead, dormant, hit, necrotic, apoptotic, etc)	double (array)	Cells (h)
P <sub>pop</sub> (t)	tum_evol_file.dat	Time evolution of relative percentages of populations out of the total population	double (array)	Cells(h)
T <sub>1/2</sub>	tum_doubling_time_file.dat	The doubling time of the tumor	double	
DV	tum_evol_file.dat	The relative percentage of tumor volume change	double	
Mesh(t)	tumor_day_*.raw	Arrays with the size of the discretization mesh of the anatomic region of interest and values that indicate the state of the GC (eg. Occupied) for a series of time points.	int (array)	

# C+Te12

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
tum_evol_file.dat		Contains the time evolutions of : various cell type populations , the whole tumor volume, the relative percentage of populations over whole cell population	file	
tum_doubling_time_file.dat		Contains the estimated doubling time of the simulated tumor.	file	
tumor_day_[day#].raw		Arrays with the size of the discretization mesh of the anatomic region of interest and values that indicate the state of the GC (eg. Occupied) for a series of time points.	file	
oncosim-parameters.log		Contains input parameter values per execution	file	
initial_tumour.dat		At t=0, (x, y, z) of each GC occupied by the tumor	file	

# C+Te13

## Model information (I)

Model number	C+Te13.
Reference partner	ICCS
Model title	Actinomycin Chemotherapy Simulation model
Brief model description	A generic four-dimensional simulation model of tumor response to actinomycin chemotherapy. The model is based on the consideration of a discrete time and space stochastic cellular automata.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Hybrid method (primarily discrete event based).
References	<p>E.C.Georgiadi, D.D.Dionysiou, N.Graf, G.Stamatakis, "Towards In Silico Oncology: Adapting a Four Dimensional Nephroblastoma Treatment Model to a Clinical Trial Case Based on Multi-Method Sensitivity Analysis.", Comput Biol Med. 2012 Nov;42(11):1064-78. doi: 10.1016/j.combiomed.2012.08.008. Epub 2012 Oct 10</p> <p>G.S. Stamatakis, E.C. Georgiadi, N. Graf, E.A. Kolokotroni, D.D. Dionysiou, Exploiting Clinical Trial Data Drastically Narrows the Window of Possible Solutions to the Problem of Clinical Adaptation of a Multiscale Cancer Model, Plos One, 6 (2011).</p> <p>N. Graf, A. Hoppe , E. Georgiadi, R. Belleman, C. Desmedt, D. Dionysiou, M. Erdt , J. Jacques, E. Kolokotroni, A. Lunzer, M. Tsiknakis and G. Stamatakis, “ "In Silico Oncology" for Clinical Decision Making in the Context of Nephroblastoma. [Die Bedeutung von ,in silico Onkologie` zur klinischen Entscheidungsfindung am Beispiel des Nephroblastoms],” Klin. Paediatr. (Klinische Paediatric) 221, 141-149, 2009</p> <p>Eleni Ch. Georgiadi, Dimitra D. Dionysiou, Norbert Graf and Georgios S. Stamatakis, “Modeling nephroblastoma treatment response cases with in-silico scenarios”, 10/2012; In proceeding of: 2012 5 th Int. Adv. Res. Workshop on In Silico Oncology and Cancer</p>

	<b>Investigation – The TUMOR Project Workshop (IARWISOCI), At Athens, Greece, Volume: ISBN: 978-618-80348-0-8 (open-access version) , <a href="http://www.5th-iarwisoci.iccs.ntua.gr">www.5th-iarwisoci.iccs.ntua.gr</a>, Edited by G. Stamatakos and D. Dionysiou, pages 35-28.</b>
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# C+Te13

## Model information (II)

References	<p>E. Ch. Georgiadi, G. S. Stamatakos, N. M. Graf, E. A. Kolokotroni, D. D. Dionysiou, A. Hoppe, N. K. Uzunoglu, "Multilevel Cancer Modeling in the Clinical Environment: Simulating the Behavior of Wilms Tumor in the Context of the SIOP 2001/GPOH Clinical Trial and the ACGT Project," Proc. 8th IEEE International Conference on Bioinformatics and Bioengineering (BIBE 2008), Athens, Greece, 8-10 Oct. 2008. IEEE Catalog Number: CFP08266, ISBN: 978-1-4244-2845-8, Library of Congress: 2008907441, Paper No. BE-2.1.2, length: 8 pages (in electronic format). 2008</p> <p>D.D.Dionysiou, G.S. Stamatakos, N.K.Uzunoglu, K.S.Nikita, A. Marioli , "A Four Dimensional In Vivo Model of Tumour Response to Radiotherapy: Parametric Validation Considering Radiosensitivity, Genetic Profile and Fractionation," Journal of Theoretical Biology , 230 , 1-20 , 2004</p> <p>G.S. Stamatakos, D.D. Dionysiou, E.I. Zacharaki, N.A. Mouravliansky, K.S.Nikita, N.K. Uzunoglu , "In silico radiation oncology: combining novel simulation algorithms with current visualization techniques," Proceedings of the IEEE, Special Issue on Bioinformatics: Advances and Chalenges , 90(11) , 1764-1777 , 2002</p>
COMMENTS	<p>*Able to set different values for STEM and LIMP cells</p> <p>** Able to set different values for necrotic and proliferating layer</p> <p>***The drug's administration instants might be defined separately and not as a scheme</p>

# C+Te13

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c$	input.xml	Cell cycle duration of cells (G0 phase not included)	int	20-50	
$T_{G0}^*$	input.xml	Maximum G0 (dormant) phase duration before stem cell enters necrosis or re-enters G1	int	0-200	
$T_N^{**}$	input.xml	Time needed for necrosis to be completed and its lysis products to be eliminated from the tumor	int	0-500	
$T_A^{**}$	input.xml	Time needed for apoptosis to be completed and its products to be eliminated from the tumor	int	0-50	
$R_A^{**}$	input.xml	Apoptosis rate of living stem and LIMP tumor cells (fraction of non-differentiated cells dying through apoptosis per hour)	double	0.0-1.0	$h^{-1}$
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells per hour	double	0.0-1.0	$h^{-1}$
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells per hour	double	0.0-1.0	$h^{-1}$
$P_{G0toG1}^*$	input.xml	The fraction of stem or LIMP cells having just left the G0 compartment that re-enter the cell cycle	double	0.0-1.0	
$N_{LIMP}$	input.xml	The maximum number of mitoses that a LIMP cell can perform before becoming terminally differentiated	double	0.0-1.0	



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$P_{sym}^{**}$	input.xml	Fraction of stem cells that perform symmetric division.	double	0.0-1.0	
$P_{sleep}^{**}$	input.xml	Fraction of cells that enter G0 phase following mitosis	double	0.0-1.0	
$l_{GC}$ (cm)	input.xml	length of voxel's side	int	1-5	mm
$x_{dim}$	input.xml	Dimension of the mesh along x direction	int	1-200	GC

# C+Te13

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
y_dim	input.xml	Dimension of the mesh along y direction	int	1-200	GC
z_dim	input.xml	Dimension of the mesh along z direction	int	1-200	GC
NBC	input.xml	Number of biological cells typically contained within a GC of the mesh (assigned in relation to the GC's volume)	int	300000-1100000	cells
CKR <sub>ACT</sub> *	input.xml	Cell kill ratio of cells for a specific dose of actinomycin	double	0-0,99	
T <sub>init</sub>	input.xml	Time interval between the pre-treatment imaging data acquisition and the first drugs' administration	int	0-	
T <sub>pt_scan</sub>	input.xml	Time interval between the last drug administration and the post-treatment imaging data acquisition	int	0-	
ACT_time[n]***	input.xml	Actinomycin administration instants	int	0-	
distance_factor**	input.xml	Factor to adjust the rate of cell killing effects of chemotherapy in the corresponding tumor metabolic layer	double	0-0,99	
input.xml		A .xml file containing parameters.	file		.xml

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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# C+Te13

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
V(t)	tum_evol_file.dat	Time evolution of tumor volume	double (array)	Mm(h) Or GCs (h)
P <sub>op</sub> (t)	tum_evol_file.dat	Time evolution of several cell populations (stem, LIMP, diff, dead, dormant, hit, necrotic, apoptotic, etc)	double (array)	Cells (h)
P <sub>pop</sub> (t)	tum_evol_file.dat	Time evolution of relative percentages of populations out of the total population	double (array)	Cells(h)
T <sub>1/2</sub>	tum_doubling_time_file.dat	The doubling time of the tumor	double	
DV	tum_evol_file.dat	The relative percentage of tumor volume change	double	
Mesh(t)	tumor_day_*.raw	Arrays with the size of the discretization mesh of the anatomic region of interest and values that indicate the state of the GC (eg. Occupied) for a series of time points.	int (array)	

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tum_evol_file.dat		Contains the time evolutions of : various cell type populations , the whole tumor volume, the relative percentage of populations over whole cell population	file	
tum_doubling_time_file.dat		Contains the estimated doubling time of the simulated tumor.	file	

# C+Te13

Output specifications (II)				
All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
tumor_day_[day#].raw		Arrays with the size of the discretization mesh of the anatomic region of interest and values that indicate the state of the GC (eg. Occupied) for a series of time points.	file	
oncosim-parameters.log		Contains input parameter values per execution	file	
initial_tumour.dat		At t=0, (x, y, z) of each GC occupied by the tumor	file	

# C+Te14

Model information (I)	
Model number	C+Te14.
Reference partner	ICCS
Model title	Vincristine Chemotherapy Simulation model
Brief model description	A generic four-dimensional simulation model of tumor response to vincristine chemotherapy. The model is based on the consideration of a discrete time and space stochastic cellular automata.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Hybrid method (primarily discrete event based).
References	<p>E.C.Georgiadi, D.D.Dionysiou, N.Graf, G.Stamatakis, "Towards In Silico Oncology: Adapting a Four Dimensional Nephroblastoma Treatment Model to a Clinical Trial Case Based on Multi-Method Sensitivity Analysis.", Comput Biol Med. 2012 Nov;42(11):1064-78. doi: 10.1016/j.compbimed.2012.08.008. Epub 2012 Oct 10</p> <p>G.S. Stamatakis, E.C. Georgiadi, N. Graf, E.A. Kolokotroni, D.D. Dionysiou, Exploiting Clinical Trial Data Drastically Narrows the Window of Possible Solutions to the Problem of Clinical Adaptation of a Multiscale Cancer Model, Plos One, 6 (2011).</p> <p>N. Graf, A. Hoppe , E. Georgiadi, R. Belleman, C. Desmedt, D. Dionysiou, M. Erdt , J. Jacques, E. Kolokotroni, A. Lunzer, M. Tsiknakis and G. Stamatakis, “ "In Silico Oncology" for Clinical Decision Making in the Context of Nephroblastoma. [Die Bedeutung von ‚in silico Onkologie` zur klinischen Entscheidungsfindung am Beispiel des Nephroblastoms],” Klin. Paediatr. (Klinische Paediatric) 221, 141-149, 2009</p>

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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	<p><b>Eleni Ch. Georgiadi, Dimitra D. Dionysiou, Norbert Graf and Georgios S. Stamatakos, “Modeling nephroblastoma treatment response cases with in-silico scenarios”, 10/2012; In proceeding of: 2012 5 th Int. Adv. Res. Workshop on In Silico Oncology and Cancer Investigation – The TUMOR Project Workshop (IARWISOCI), At Athens, Greece, Volume: ISBN: 978-618-80348-0-8 (open-access version) , <a href="http://www.5th-iarwisoci.iccs.ntua.gr">www.5th-iarwisoci.iccs.ntua.gr</a>, Edited by G. Stamatakos and D. Dionysiou, pages 35-28.</b></p>
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# C+Te14

## Model information (II)

References	<p>E. Ch. Georgiadi, G. S. Stamatakos, N. M. Graf, E. A. Kolokotroni, D. D. Dionysiou, A. Hoppe, N. K. Uzunoglu, "Multilevel Cancer Modeling in the Clinical Environment: Simulating the Behavior of Wilms Tumor in the Context of the SIOP 2001/GPOH Clinical Trial and the ACGT Project," Proc. 8th IEEE International Conference on Bioinformatics and Bioengineering (BIBE 2008), Athens, Greece, 8-10 Oct. 2008. IEEE Catalog Number: CFP08266, ISBN: 978-1-4244-2845-8, Library of Congress: 2008907441, Paper No. BE-2.1.2, length: 8 pages (in electronic format). 2008</p> <p>D.D.Dionysiou, G.S. Stamatakos, N.K.Uzunoglu, K.S.Nikita, A. Marioli , "A Four Dimensional In Vivo Model of Tumour Response to Radiotherapy: Parametric Validation Considering Radiosensitivity, Genetic Profile and Fractionation," Journal of Theoretical Biology , 230 , 1-20 , 2004</p>
COMMENTS	<p>Able to set different values for STEM and LIMP cells</p> <p>** Able to set different values for necrotic and proliferating layer</p> <p>***The drug's administration instants might be defined separately and not as a scheme</p>

# C+Te14

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c$	input.xml	Cell cycle duration of cells (G0 phase not included)	int	20-50	
$T_{G0}^*$	input.xml	Maximum G0 (dormant) phase duration before stem cell enters necrosis or re-enters G1	int	0-200	
$T_N^{**}$	input.xml	Time needed for necrosis to be completed and its lysis products to be eliminated from the tumor	int	0-500	
$T_A^{**}$	input.xml	Time needed for apoptosis to be completed and its products to be eliminated from the tumor	int	0-50	
$R_A^{**}$	input.xml	Apoptosis rate of living stem and LIMP tumor cells (fraction of non-differentiated cells dying through apoptosis per hour)	double	0.0-1.0	$h^{-1}$
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells per hour	double	0.0-1.0	$h^{-1}$
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells per hour	double	0.0-1.0	$h^{-1}$
$P_{G0toG1}^*$	input.xml	The fraction of stem or LIMP cells having just left the G0 compartment that re-enter the cell cycle	double	0.0-1.0	
$N_{LIMP}$	input.xml	The maximum number of mitoses that a LIMP cell can perform before becoming terminally differentiated	double	0.0-1.0	

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$P_{sym}^{**}$	input.xml	Fraction of stem cells that perform symmetric division.	double	0.0-1.0	
$P_{sleep}^{**}$	input.xml	Fraction of cells that enter G0 phase following mitosis	double	0.0-1.0	
$l_{GC}$ (cm)	input.xml	length of voxel's side	int	1-5	mm
$x_{dim}$	input.xml	Dimension of the mesh along x direction	int	1-200	GC

# C+Te14

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$CKR_{ACT}^*$	input.xml	Cell kill ratio of cells for a specific dose of actinomycin	double	0-0,99	
$T_{init}$	input.xml	Time interval between the pre-treatment imaging data acquisition and the first drugs' administration	int	0-	
$T_{pt\_scan}$	input.xml	Time interval between the last drug administration and the post-treatment imaging data acquisition	int	0-	
$ACT\_time[n]^{***}$	input.xml	Actinomycin administration instants	int	0-	
$distance\_factor^{**}$	input.xml	Factor to adjust the rate of cell killing effects of chemotherapy in the corresponding tumor metabolic layer	double	0-0,99	
input.xml		A .xml file containing parameters.	file		.xml

# C+Te14

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
V(t)	tum_evol_file.dat	Time evolution of tumor volume	double (array)	mm(h) or GCs (h)
P <sub>op</sub> (t)	tum_evol_file.dat	Time evolution of several cell populations (stem, limp, diff, dead, dormant, hit, necrotic, apoptotic, etc)	double (array)	Cells (h)
P <sub>pop</sub> (t)	tum_evol_file.dat	Time evolution of relative percentages of populations out of the total population	double (array)	Cells(h)
T <sub>1/2</sub>	tum_doubling_time_file.dat	The doubling time of the tumor	double	
DV	tum_evol_file.dat	The relative percentage of tumor volume change	double	
Mesh(t)	tumor_day_*.raw	Arrays with the size of the discretization mesh of the anatomic region of interest and values that indicate the state of the GC (eg. Occupied) for a series of time points.	int (array)	

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

tum_evol_file.dat		Contains the time evolutions of : various cell type populations , the whole tumor volume, the relative percentage of populations over whole cell population	file	
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# C+Te14

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
tum_doubling_time_file.dat		Contains the estimated doubling time of the simulated tumor.	file	
tumor_day_[day#].raw		Arrays with the size of the discretization mesh of the anatomic region of interest and values that indicate the state of the GC (eg. Occupied) for a series of time points.	file	
oncosim-parameters.log		Contains input parameter values per execution	file	
initial_tumour.dat		At t=0, (x, y, z) of each GC occupied by the tumor	file	

# C+Te15

## Model information (I)

Model number	C+Te15.
Reference partner	ICCS
Model title	Actinomycin-Vincristine Combined Chemotherapy Simulation model
Brief model description	A generic four-dimensional simulation model of tumor response to combined therapy of vincristine and actinomycin. The model is based on the consideration of a discrete time and space stochastic cellular automata
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Hybrid method (primarily discrete event based).
References	<p>E.C.Georgiadi, D.D.Dionysiou, N.Graf, G.Stamatakis, "Towards In Silico Oncology: Adapting a Four Dimensional Nephroblastoma Treatment Model to a Clinical Trial Case Based on Multi-Method Sensitivity Analysis.", Comput Biol Med. 2012 Nov;42(11):1064-78. doi: 10.1016/j.compbio.2012.08.008. Epub 2012 Oct 10</p> <p>G.S. Stamatakis, E.C. Georgiadi, N. Graf, E.A. Kolokotroni, D.D. Dionysiou, Exploiting Clinical Trial Data Drastically Narrows the Window of Possible Solutions to the Problem of Clinical Adaptation of a Multiscale Cancer Model, Plos One, 6 (2011).</p> <p>N. Graf, A. Hoppe , E. Georgiadi, R. Belleman, C. Desmedt, D. Dionysiou, M. Erdt , J. Jacques, E. Kolokotroni, A. Lunzer, M. Tsiknakis and G. Stamatakis, " "In Silico Oncology" for Clinical Decision Making in the Context of Nephroblastoma. [Die Bedeutung von ,in silico Onkologie` zur klinischen Entscheidungsfindung am Beispiel des Nephroblastoms], " Klin. Paediatr. (Klinische Paediatric) 221, 141-149, 2009</p>



D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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	<p><b>Eleni Ch. Georgiadi, Dimitra D. Dionysiou, Norbert Graf and Georgios S. Stamatakos, “Modeling nephroblastoma treatment response cases with in-silico scenarios”, 10/2012; In proceeding of: 2012 5 th Int. Adv. Res. Workshop on In Silico Oncology and Cancer Investigation – The TUMOR Project Workshop (IARWISOCI), At Athens, Greece, Volume: ISBN: 978-618-80348-0-8 (open-access version) , <a href="http://www.5th-iarwisoci.iccs.ntua.gr">www.5th-iarwisoci.iccs.ntua.gr</a>, Edited by G. Stamatakos and D. Dionysiou, pages 35-28.</b></p>
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# C+Te15

## Model information (II)

References	<p>E. Ch. Georgiadi, G. S. Stamatakis, N. M. Graf, E. A. Kolokotroni, D. D. Dionysiou, A. Hoppe, N. K. Uzunoglu, "Multilevel Cancer Modeling in the Clinical Environment: Simulating the Behavior of Wilms Tumor in the Context of the SIOP 2001/GPOH Clinical Trial and the ACGT Project," Proc. 8th IEEE International Conference on Bioinformatics and Bioengineering (BIBE 2008), Athens, Greece, 8-10 Oct. 2008. IEEE Catalog Number: CFP08266, ISBN: 978-1-4244-2845-8, Library of Congress: 2008907441, Paper No. BE-2.1.2, length: 8 pages (in electronic format). 2008</p> <p>D.D.Dionysiou, G.S. Stamatakis, N.K.Uzunoglu, K.S.Nikita, A. Marioli , "A Four Dimensional In Vivo Model of Tumour Response to Radiotherapy: Parametric Validation Considering Radiosensitivity, Genetic Profile and Fractionation," Journal of Theoretical Biology , 230 , 1-20 , 2004</p> <p>G.S. Stamatakis, D.D. Dionysiou, E.I. Zacharaki, N.A. Mouravliansky, K.S.Nikita, N.K. Uzunoglu , "In silico radiation oncology: combining novel simulation algorithms with current visualization techniques," Proceedings of the IEEE, Special Issue on Bioinformatics: Advances and Chalenges , 90(11) , 1764-1777 , 2002</p>
COMMENTS	<p>Able to set different values for STEM and LIMP cells</p> <p>** Able to set different values for necrotic and proliferating layer</p> <p>***The drugs' administration instants might be defined separately and not as a scheme</p>

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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# C+Te15

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$T_c$	input.xml	Cell cycle duration of cells (G0 phase not included)	int	20-50	
$T_{G0}^*$	input.xml	Maximum G0 (dormant) phase duration before stem cell enters necrosis or re-enters G1	int	0-200	
$T_N^{**}$	input.xml	Time needed for necrosis to be completed and its lysis products to be eliminated from the tumor	int	0-500	
$T_A^{**}$	input.xml	Time needed for apoptosis to be completed and its products to be eliminated from the tumor	int	0-50	
$R_A^{**}$	input.xml	Apoptosis rate of living stem and LIMP tumor cells (fraction of non-differentiated cells dying through apoptosis per hour)	double	0.0-1.0	$h^{-1}$
$R_{ADiff}$	input.xml	Apoptosis rate of differentiated tumor cells per hour	double	0.0-1.0	$h^{-1}$
$R_{NDiff}$	input.xml	Necrosis rate of differentiated tumor cells per hour	double	0.0-1.0	$h^{-1}$
$P_{G0toG1}^*$	input.xml	The fraction of stem or LIMP cells having just left the G0 compartment that re-enter the cell cycle	double	0.0-1.0	
$N_{LIMP}$	input.xml	The maximum number of mitoses that a LIMP cell can perform before becoming terminally differentiated	double	0.0-1.0	

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

$P_{sym}^{**}$	input.xml	Fraction of stem cells that perform symmetric division.	double	0.0-1.0	
$P_{sleep}^{**}$	input.xml	Fraction of cells that enter G0 phase following mitosis	double	0.0-1.0	
$l_{GC}$ (cm)	input.xml	length of voxel's side	int	1-5	mm
$x_{dim}$	input.xml	Dimension of the mesh along x direction	int	1-200	GC

# C+Te15

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
<b>y_dim</b>	input.xml	Dimension of the mesh along y direction	int	1-200	GC
<b>z_dim</b>	input.xml	Dimension of the mesh along z direction	int	1-200	GC
<b>NBC</b>	input.xml	Number of biological cells typically contained within a GC of the mesh (assigned in relation to the GC's volume)	int	300000-1100000	cells
<b>CKR<sub>VCR</sub>*</b>	input.xml	Cell kill ratio of cells for a specific dose of vincristine	double	0-0.99	
<b>CKR<sub>ACT</sub>*</b>	input.xml	Cell kill ratio of cells for a specific dose of actinomycin	double	0-0.99	
<b>T<sub>init</sub></b>	input.xml	Time interval between the pre-treatment imaging data acquisition and the first drugs' administration	int	0-	
<b>T<sub>pt_scan</sub></b>	input.xml	Time interval between the last drug administration and the post-treatment imaging data acquisition	int	0-	
<b>ACT_time[n]***</b>	input.xml	Actinomycin administration instants	int	0-	
<b>VCR_time[n]***</b>	input.xml	Vincristine administration instants	int	0-	
<b>distance_factor**</b>	input.xml	Factor to adjust the rate of cell killing effects of chemotherapy in the corresponding tumor metabolic layer	double		
<b>input.xml</b>		A .xml file containing parameters.	file		.xml

# C+Te15

## Output specifications (I)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
V(t)	tum_evol_file.dat	Time evolution of tumor volume	double (array)	mm(h) or GCs (h)
P <sub>op</sub> (t)	tum_evol_file.dat	Time evolution of several cell populations (stem, LIMP, diff, dead, dormant, hit, necrotic, apoptotic, etc)	double (array)	Cells (h)
P <sub>pop</sub> (t)	tum_evol_file.dat	Time evolution of relative percentages of populations out of the total population	double (array)	Cells(h)
T <sub>1/2</sub>	tum_doubling_time_file.dat	The doubling time of the tumor	double	
DV	tum_evol_file.dat	The relative percentage of tumor volume change	double	
Mesh(t)	tumor_day_*.raw	Arrays with the size of the discretization mesh of the anatomic region of interest and values that indicate the state of the GC (eg. Occupied) for a series of time points.	int (array)	

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tum_evol_file.dat		Contains the time evolutions of : various cell type populations , the whole tumor volume, the relative percentage of populations over whole cell population	file	
tum_doubling_time_file.dat		Contains the estimated doubling time of the simulated tumor.	file	



# C+Te15

## Output specifications (II)

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
tumor_day_[day#].raw		Arrays with the size of the discretization mesh of the anatomic region of interest and values that indicate the state of the GC (eg. Occupied) for a series of time points.	file	
oncosim-parameters.log		Contains input parameter values per execution	file	
initial_tumour.dat		At t=0, (x, y, z) of each GC occupied by the tumor	file	

# C+Te16

Model information	
Model number	C+Te16.
Reference partner	UOXF
Model title	Angiogenesis
Brief model description	PDE model for tumour angiogenesis
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	
References	Byrne and Chaplain (1995). Bull Math Biol, 57: 461-486
COMMENTS	<ul style="list-style-type: none"> <li>- Model formulated as system of nonlinear pdes in 1D Cartesian geometry</li> <li>- Boundary and initial conditions need to be included, along with statement of governing PDEs</li> </ul>

# C+Te16

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Mu		Random motility coefficient for capillary tips			
Chi		Chemotaxis coefficient for capillary tip cells			
Dc		Diffusion coefficient of chemoattractant			
Lambda		Decay rate of chemoattractant			
Alpha_1_bar		Rate at which capillary tips consume chemoattractant			
Alpha_0		Rate at which capillary tips emerge from vessels per unit concentration of chemoattractant			
Alpha_1		Rate at which capillary tips emerge from existing capillary tips			
Beta		Rate at which capillary tips fuse with existing vessels			

# C+Te16

Output specifications				
All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
N		Capillary tip density		
Rho		Vessel density		
C		Chemoattractant concentration		

# C+Te17

Model information	
Model number	C+Te17.
Reference partner	UOXF
Model title	Angiogenesis and vasculogenesis
Brief model description	ODE model that investigates how contribution from angiogenesis and vasculogenesis changes during tumour growth
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	
References	
COMMENTS	

# C+Te17

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension

# C+Te18

Model information	
Model number	C+Te18.
Reference partner	UOXF
Model title	Ascular tumour growth and chemotherapy
Brief model description	PDE model that investigates how interplay between vascular remodelling and tumour growth and resulting spatio-temporal dynamics influence tumour's response to chemotherapy
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	
References	Stamper, Owen, Maini and Byrne (2009). Biol Direct 5: 27
COMMENTS	

# C+Te18

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension



# C+Te19

Model information	
Model number	C+Te19.
Reference partner	UOXF
Model title	Vascular tumour growth
Brief model description	PDE model of vascular tumour growth based on the theory of mixtures
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	
References	Hubbard and Byrne (2013). J theor Biol 316: 70-89
COMMENTS	

# C+Te19

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension

# C+Te20

Model information	
Model number	C+Te20.
Reference partner	ICCS
Model title	Untreated vascular tumour growth
Brief model description	This model describes the interplay between pathological angiogenesis and solid tumour growth.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Ordinary Differential Equations
References	<p>P. Hahnfeldt, D. Panigrahy, J. Folkman and L. Hlatky, "Tumour development under angiogenic signaling: A dynamical theory of tumour growth, treatment response and postvascular dormancy", Cancer Res., vol. 59, pp. 4770-4775, 1999.</p> <p>J. Poleszczuk, M. Bodnar, U. Foryś, "New approach to modelling of antiangiogenic treatment on the basis of Hahnfeldt et al. model", Math Biosci Eng., vol. 8, no. 2, pp. 591-603, April. 2011</p> <p>Argyri, K.D.; Dionysiou, D.D.; Stamatakis, G.S., "Modeling the interplay between pathological angiogenesis and solid tumor growth: The anti-angiogenic treatment effect," Advanced Research Workshop on In Silico Oncology and Cancer Investigation - The TUMOR Project Workshop (IARWISOCI), 2012 5th International , vol., no., pp.1,4, 22-23 Oct. 2012</p>
COMMENTS	<ul style="list-style-type: none"> <li>- Continuum model</li> <li>- Implemented in Matlab</li> </ul>

# C+Te20

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
lamda1	input_VTG.csv	Gompertzian growth constant	double	0-	day <sup>-1</sup>
lamda2	input_VTG.csv	Proportionality constant related to the term reflecting the spontaneous loss of functional vasculature	double	0-	day <sup>-1</sup>
c	input_VTG.csv	Proportionality constant related to the term reflecting endogenous stimulation of the tumour upon the vasculature	double	0-	day <sup>-1</sup>
d	input_VTG.csv	Proportionality constant related to the term reflecting endogenous inhibition of tumour vasculature	double	0-	1/(day · mm <sup>2</sup> )
t_initial	input_VTG.csv	Initial time-point	double	0-	day
t_final	input_VTG.csv	Final time-point	double	0-	day
V0	input_VTG.csv	Initial value of tumour volume	double	0-	mm <sup>3</sup>
K0	input_VTG.csv	Initial value of carrying capacity	double	0-	mm <sup>3</sup>
input_VTG.csv		A .csv file (comma delimiter) containing input parameters.	file		.csv

# C+Te20

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
tumour_volume	tumor_evolution.csv	Time evolution of tumour volume	double	mm <sup>3</sup>
carrying_capacity	tumor_evolution.csv	Time evolution of tumour carrying capacity	double	mm <sup>3</sup>
tumor_evolution.csv		A .csv file (comma delimiter) containing output parameters.	file	.csv
tumor_evolution_plot.tiff		A file presenting a figure plotting the time course of tumor volume and tumor capacity in common system of axes.	file	.tiff

# C+Te21

Model information	
Model number	C+Te21.
Reference partner	ICCS
Model title	Vascular tumour growth under bevacizumab monotherapy
Brief model description	This model describes the response of a solid tumour to bevacizumab monotherapy
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Ordinary Differential Equations
References	<p>J. Poleszczuk, M. Bodnar, U. Foryś, "New approach to modelling of antiangiogenic treatment on the basis of Hahnfeldt et al. model", Math Biosci Eng., vol. 8, no. 2, pp. 591-603, April. 2011</p> <p>Argyri, K.D.; Dionysiou, D.D.; Stamatakis, G.S., "Modeling the interplay between pathological angiogenesis and solid tumor growth: The anti-angiogenic treatment effect," Advanced Research Workshop on In Silico Oncology and Cancer Investigation - The TUMOR Project Workshop (IARWISOCI), 2012 5th International , vol., no., pp.1,4, 22-23 Oct. 2012</p>
COMMENTS	<ul style="list-style-type: none"> <li>- Continuum model</li> <li>- Implemented in Matlab</li> </ul>

# C+Te21

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"-"to")	Input parameter unit or file extension
lamda1	input_VTG.csv	Gompertzian growth constant	double	0-	day <sup>-1</sup>
lamda2	input_VTG.csv	Proportionality constant related to the term reflecting the spontaneous loss of functional vasculature	double	0-	day <sup>-1</sup>
c	input_VTG.csv	Proportionality constant related to the term reflecting endogenous stimulation of the tumour upon the vasculature	double	0-	mg/(ml·day·mm <sup>3p</sup> )
d	input_VTG.csv	Proportionality constant related to the term reflecting endogenous inhibition of tumour vasculature	double	0-	1/(day · mm <sup>2</sup> )
alpha	input_VTG.csv	Constant related to the total amount of stimulators inside the tumor	double	0-	mg/(mm <sup>3p</sup> ·ml)
beta	input_VTG.csv	Constant related to the total amount of stimulators inside the tumor	double	0-	mm <sup>3p</sup>
	input_VTG.csv	Hill coefficient	double	0-	
tinitial	input_VTG.csv	Initial time-point	double	0-	day
tfinal	input_VTG.csv	Final time-point	double	0-	day
V0	input_VTG.csv	Tumour volume at the initial time-point	double	0-	mm <sup>3</sup>

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K0	input_VTG.csv	Carrying capacity at the initial time-point	double	0-	mm <sup>3</sup>
	input_therapy.csv	Bevacizumab concentration	double	0-	mg/ml
input_VTG.csv		A .csv file (comma delimiter) containing input parameters.	file		.csv
input_therapy.csv		A .csv file (comma delimiter) containing input parameters.	file		.csv



# C+Te21

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
tumour_volume	tumor_evolution.csv	Time evolution of tumour volume	double	mm <sup>3</sup>
carrying_capacity	tumor_evolution.csv	Time evolution of tumour carrying capacity	double	mm <sup>3</sup>
tumor_evolution.csv		A .csv file (comma delimiter) containing output parameters.	file	.csv
tumor_evolution_plot.tiff		A file presenting a figure plotting the time course of tumor volume and tumor capacity in common system of axes.	file	.tiff

# C+Te22

Model information	
Model number	C+Te22.
Reference partner	ICCS
Model title	Time-course of bevacizumab concentration in plasma
Brief model description	This model describes the time-course of bevacizumab concentration in plasma
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Ordinary Differential Equations
References	Bertrand J, Mentré F. Mathematical Expressions of the Pharmacokinetic and Pharmacodynamic Models implemented in the MONOLIX software ( <a href="http://www.monolix.org">http://www.monolix.org</a> ). 2008
COMMENTS	<ul style="list-style-type: none"> <li>- Continuum model</li> <li>- Two – compartmental pharmacokinetic model</li> <li>- Implemented in Matlab</li> </ul>

# C+Te22

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"-"to")	Input parameter unit or file extension
dosage	input_therapy.csv	Bevacizumab administered dosage	double	0-	mg/kg
n	input_therapy.csv	Number of infusions to be administered	int	0-	
inf_dur	input_therapy.csv	Infusion duration	double	0-	day
ke	input_therapy.csv	Rate of elimination	double	0-	day <sup>-1</sup>
V	input_therapy.csv	Volume of distribution of central compartment	double	0-	mm <sup>3</sup>
k12	input_therapy.csv	Transfer constant from central to peripheral compartment	double	0-	day <sup>-1</sup>
k21	input_therapy.csv	Transfer constant from peripheral to central compartment	double	0-	day <sup>-1</sup>
w	input_therapy.csv	Patient's weight	double	0-	kg
T1	input_therapy.csv	Time-point of 1 <sup>st</sup> drug administration	double	0-	day
adm_int	input_therapy.csv	Administration interval	double	0-	day
t_init	input_therapy.csv	Initial time-point	double	0-	day
t_fin	input_therapy.csv	Final time-point	double	0-	day
time_step	input_therapy.csv	Time step of the execution	double	0-	day
input_therapy.csv		A .csv file (comma delimiter) containing parameters.	file		.csv

# C+Te22

## Output specifications

<u>All</u> model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
bev_conc	drug_concentration_timecourse.csv	Time evolution of bevacizumab concentration in plasma	double	mg/ml
drug_concentration_timecourse.csv		A .csv file (comma delimiter) containing output parameters.	file	.csv
drug_concentration_timecourse_plot.tiff		A file presenting a figure plotting the time course of bevacizumab concentration in plasma.	file	.tiff

# C+Te23

Model information	
Model number	C+Te23.
Reference partner	ICCS
Model title	Bevacizumab concentration in plasma in a given time-point
Brief model description	Given a specific time-point, this model computes the concentration of bevacizumab in plasma
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Ordinary Differential Equations
References	Bertrand J, Mentré F. Mathematical Expressions of the Pharmacokinetic and Pharmacodynamic Models implemented in the MONOLIX software ( <a href="http://www.monolix.org">http://www.monolix.org</a> ). 2008
COMMENTS	<ul style="list-style-type: none"> <li>- Continuum model</li> <li>- Two – compartmental pharmacokinetic model</li> <li>- Implemented in Matlab</li> </ul>

# C+Te23

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
t	input_therapy.csv	Time-point	float	0-	day
dosage	input_therapy.csv	Bevacizumab administered dosage	float	0-	mg/kg
n	input_therapy.csv	Number of infusions to be administered	int	0-	
inf_dur	input_therapy.csv	Infusion duration	float	0-	day
ke	input_therapy.csv	Rate of elimination	float	0-	day <sup>-1</sup>
V	input_therapy.csv	Volume of distribution of central compartment	float	0-	ml
k12	input_therapy.csv	Transfer constant from central to peripheral compartment	float	0-	day <sup>-1</sup>
k21	input_therapy.csv	Transfer constant from peripheral to central compartment	float	0-	day <sup>-1</sup>
w	input_therapy.csv	Patient's weight	float	0-	kg
T1	input_therapy.csv	Time-point of 1 <sup>st</sup> drug administration	float	0-	day
adm_int	input_therapy.csv	Administration interval	float	0-	day
input_therapy.csv		A .csv file (comma delimiter) containing parameters.	file		.csv

# C+Te23

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
bev_conc_t	drug_concentration.csv	Bevacizumab concentration in plasma at time-point t	double	mg/ml
drug_concentration.csv		A .csv file (comma delimiter) containing output parameters.	file	.csv

# C+Te24

Model information	
Model number	C+Te24.
Reference partner	ICCS
Model title	Time-course of vinorelbine concentration in plasma
Brief model description	This model describes the time-course of vinorelbine concentration in plasma
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Ordinary Differential Equations
References	Bertrand J, Mentré F. Mathematical Expressions of the Pharmacokinetic and Pharmacodynamic Models implemented in the MONOLIX software ( <a href="http://www.monolix.org">http://www.monolix.org</a> ). 2008
COMMENTS	<ul style="list-style-type: none"> <li>- Continuum model</li> <li>- Three – compartmental pharmacokinetic model</li> <li>- Implemented in Matlab</li> </ul>



# C+Te24

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"-"to")	Input parameter unit or file extension
dosage	input_therapy.csv	Vinorelbine administered dosage	float	0-	mg/kg
n	input_therapy.csv	Number of infusions to be administered	float	0-	
inf_dur	input_therapy.csv	Infusion duration	float	0-	day
ke	input_therapy.csv	Rate of elimination	float	0-	day <sup>-1</sup>
V	input_therapy.csv	Volume of distribution of central compartment	float	0-	ml
k12	input_therapy.csv	Inter-compartmental rate constant	float	0-	day <sup>-1</sup>
k21	input_therapy.csv	Inter-compartmental rate constant	float	0-	day <sup>-1</sup>
k13	input_therapy.csv	Inter-compartmental rate constant	float	0-	day <sup>-1</sup>
k31	input_therapy.csv	Inter-compartmental rate constant	float	0-	day <sup>-1</sup>
w	input_therapy.csv	Patient's weight	float	0-	kg
T1	input_therapy.csv	Time-point of 1 <sup>st</sup> drug administration	float	0-	day
adm_int	input_therapy.csv	Administration interval	float	0-	day
t_init	input_therapy.csv	Initial time-point	float	0-	day
t_fin	input_therapy.csv	Final time-point	float	0-	day
time_step	input_therapy.csv	Time step of the execution	float	0-	day

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input_therapy.csv		A .csv file (comma delimiter) containing parameters.	file		.csv
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# C+Te24

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
bev_conc_t	drug_concentration.csv	Bevacizumab concentration in plasma at time-point t	double	mg/ml
drug_concentration.csv		A .csv file (comma delimiter) containing output parameters.	file	.csv

# C+Te25

Model information	
Model number	C+Te25.
Reference partner	ICCS
Model title	Vinorelbine concentration in plasma in a given time-point
Brief model description	Given a specific time-point, this model computes the concentration of vinorelbine in plasma
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Ordinary Differential Equations
References	Bertrand J, Mentré F. Mathematical Expressions of the Pharmacokinetic and Pharmacodynamic Models implemented in the MONOLIX software ( <a href="http://www.monolix.org">http://www.monolix.org</a> ). 2008
COMMENTS	<ul style="list-style-type: none"> <li>- Continuum model</li> <li>- Three – compartmental pharmacokinetic model</li> <li>- Implemented in Matlab</li> </ul>

# C+Te25

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
t	input_therapy.csv	Time-point	double	0-	day
dosage	input_therapy.csv	Vinorelbine administered dosage	double	0-	mg/kg
n	input_therapy.csv	Number of infusions to be administered	double	0-	-
inf_dur	input_therapy.csv	Infusion duration	double	0-	day
ke	input_therapy.csv	Rate of elimination	double	0-	day <sup>-1</sup>
V	input_therapy.csv	Volume of distribution of central compartment	double	0-	ml
k12	input_therapy.csv	Inter-compartmental rate constant	double	0-	day <sup>-1</sup>
k21	input_therapy.csv	Inter-compartmental rate constant	double	0-	day <sup>-1</sup>
k13	input_therapy.csv	Inter-compartmental rate constant	double	0-	day <sup>-1</sup>
k31	input_therapy.csv	Inter-compartmental rate constant	double	0-	day <sup>-1</sup>
w	input_therapy.csv	Patient's weight	double	0-	kg
T1	input_therapy.csv	Time-point of 1 <sup>st</sup> drug administration	double	0-	day
adm_int	input_therapy.csv	Administration interval	double	0-	day
input_therapy.csv		A .csv file (comma delimiter) containing parameters.	file		. csv

# C+Te25

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
vin_conc_t	drug_concentration_timecourse.csv	Vinorelbine concentration in plasma at time-point t	double	mg/ml
drug_concentration.csv		A .csv file (comma delimiter) containing output parameters.	file	.csv

# C+Te26

Model information	
Model number	C+Te26.
Reference partner	ICCS
Model title	Diffusion-Reaction Based Glioblastoma multiforme (GBM) Invasion and Response to Treatment Model with Boundary Conditions
Brief model description	The purpose of the model is to demonstrate in real time the spatiotemporal predictions of the continuous mathematics based Oncosimulator built around a multiscale model of the evolution of a highly diffusive solid tumor. The modelling approach is based on the numerical solution for a homogeneous approximation of the diffusive growth of gliomas and in particular glioblastoma multiforme (GBM). According to the diffusion based approach the tumor is considered a spatiotemporal distribution of continuous cell density which follows the general diffusion law. The crucial component is the numerical handling of the adiabatic Neumann boundary conditions since the physical processes is taking place in the vicinity of the anatomic boundaries imposed by the of the skull.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Exploitation of the Generic Diffusion Phenomenon, Partial Differential Equations (PDEs), Finite Difference Time Domain Numerical Method (FDTD), Crank Nicolson Method, Non - Stationary Iterative Conjugate Gradient Method, Neumann Boundaries, A Novel Numerical Treatment of the Neumann Boundary Conditions.

# C+Te26

## Model information

References	<p>Stavroula G. Giatili, Georgios S. Stamatakos , “A detailed numerical treatment of the boundary conditions imposed by the skull on a diffusion–reaction model of glioma tumor growth. Clinical validation aspects.” Applied Mathematics and Computation 05/2012; 218(17):8779-8799.</p> <p>(Georgios S. Stamatakos, Stavroula Giatili, “In Silico Oncology: a Novel and Explicit Numerical Treatment of the Neumann Boundary Conditions Imposed by the Skull on a Multiscale Diffusion-Reaction Model of Glioblastoma Growth. Clinical Validation Aspects.”Proc. VPH2012 Integrative Approaches to Computational Biomedicine, A VPH NoE Conference <a href="http://www.vph-noe.eu/vph2012">www.vph-noe.eu/vph2012</a>, London, UK; 09/2012</p> <p>S.Giatili, G.Stamatakos, “The Continuous Mathematics Based Glioblastoma Oncosimulator: Application of an Explicit Three Dimensional Numerical Treatment of the Skull-Glioblastoma Neumann Boundary Condition on Real Anatomical Data.” Proc. 2012 5th Int. Adv. Res. Workshop on In Silico Oncology and Cancer Investigation – The TUMOR Project Workshop, Athens, Greece; <a href="http://www.5th-iarwisoci.iccs.ntua.gr">http://www.5th-iarwisoci.iccs.ntua.gr</a></p>
COMMENTS	<p>Programming language: C++</p> <p>Input:</p> <p>All Input parameters are fed into the model in the form of an .csv file.</p>



# C+Te26

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
dt	parameters.csv	Time step size (For the time discretization)	double	0-	days
dx	parameters.csv	Space step size (For the space discretization)	double	0-	cm
t	parameters.csv	Time of simulation	int	0-	days
D	parameters.csv	Diffusion Coefficient	double	0-	cm <sup>2</sup> /day
net_tumor_growth_rate	parameters.csv	Net tumor growth rate (Represents the net rate of tumor growth including proliferation, loss and death)	double	0-	units per day
loss_rate_due_to_treatment	parameters.csv	Loss rate of tumor cell density due to treatment (The temporal profile of treatment such as radiotherapy and/or chemotherapy and as a first approximation is constant. It is a measure of the effectiveness of the treatment.)	double	0-	units per day
mesh_edge_length	parameters.csv	Mesh edge length (The edge dimension of the computational cubic mesh)	double	0-	cm
C	parameters.csv	Cell concentration (The variable c denotes the cell concentration at any spatial point x and time t)	int	0-	cells/cm <sup>3</sup>

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

tumor_image	parameters.csv	The name of the .raw file which depicts the initial tumor with white color.	string		
skull_image	parameters.csv	The name of the .raw file which depicts the boundary shape with black color.	string		

# C+Te26

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
parameters.csv		A .csv file containing the input parameters.	file		.csv
InitialTumor.raw		A .raw file (8-bit) which depicts the initial tumor with white color.	file		.raw
skull.raw		A .raw file (8-bit) which depicts the boundary shape with black color.	file		.raw

# C+Te27

Model information	
Model number	C+Te27.
Reference partner	UNITO
Model title	Phenomenological universality in cancer growth
Brief model description	Series expansion $U_n$ of the solution of the growth equation: exact solutions of $U_0$ , $U_1$ and $U_2$
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Analytical
References	<p>P. Castorina, P.P. Delsanto, C. Guiot, "Classification scheme for phenomenological universalities in growth problems in physics and other sciences.", Phys Rev Lett 96,188701 (2006).</p> <p>Delsanto PP, Gliozzi A, Iordache DA, Guiot C. Universal features in the laws of growth. J of Design &amp; Nature and Ecodynamics, 2010, 5 (4): 1-12.</p> <p>Guiot C., Delsanto PP., Gliozzi A. Computer simulation and modelling in oncology: methods and applications. In: Modelling in Medicine and Biology VIII, Ed. C.A. Brebbia, Witpress, Southampton, 2009, Pages. 267-275. WIT Transactions on Biomedicine and Health, 13.</p>
COMMENTS	

# C+Te27

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
a	command line	Growth rate	float		s <sup>-1</sup>
a0	command line	Initial growth rate	float		s <sup>-1</sup>
b	command line	Growth acceleration	float		s <sup>-2</sup>
beta	command line	Carrying capacity	float		t <sup>-1</sup>
gamma	command line	Weat-law parameter	float		t <sup>-1</sup>

# Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
N (t)	console output	Number of cells	float	

# C+Te28

Model information	
Model number	C+Te28.
Reference partner	UNITO
Model title	Cancer growth & radiotherapy
Brief model description	Comparison between the predictions of U1 and U2 in different clinical schedules
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Analytical, numeric
References	P. Castorina, T.S. Deisboeck, P. Gabriele, C Guiot, "Growth laws in cancer: implications for radiotherapy", Radiation Res ,168:349-356,2007.
COMMENTS	

# C+Te28

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
a	command line	Growth rate	float	0-	s <sup>-1</sup>
a0	command line	Initial growth rate	float	0-	s <sup>-1</sup>
b	command line	Growth acceleration	float	0-	s <sup>-2</sup>
beta	command line	Carrying capacity	float	0-	t <sup>-1</sup>
gamma	command line	Weat-law parameter	float	0-	t <sup>-1</sup>
c	command line	Clonogen number	float	0-	
schedule	command line	Schedule (standard, hyper, hypo, CHART)	float		string
d	command line	Dose	float	0-	Gy
linear-quadratic parameter	command line	Radiosensitivity	float		Gy



# C+Te28

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
	console output	Surviving fraction	float	dimensionless
	console output	Control probability	float	dimensionless

# C+Te29

Model information	
Model number	C+Te29.
Reference partner	UNITO
Model title	Multipassage tumor growth
Brief model description	U1 application to tumor regrowth
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	
References	Gliozzi AS, Guiot C, Delsanto PP (2009), "A New Computational Tool for the Phenomenological Analysis of Multipassage Tumor Growth Curves. ", PLoS ONE 4(4): e5358. doi:10.1371/journal.pone.0005358
COMMENTS	

# C+Te29

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
a	command line	Growth rate	float		s <sup>-1</sup>
a0	command line	Initial growth rate	float		s <sup>-1</sup>
b	command line	Growth acceleration	float		s <sup>-2</sup>
beta	command line	Carrying capacity	float		t <sup>-1</sup>
gamma	command line	Weat-law parameter	float		t <sup>-1</sup>
N	command line	Number of serial transplant	float		

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
N (t)	console output	Number of cells	float	

# C+Te30

Model information	
Model number	C+Te30.
Reference partner	UNITO
Model title	Cancer growth and chemotherapy
Brief model description	U1 & U2 predictions for chemotherapy dosage
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	
References	Castorina P., Carcò D., Guiot C., TS Deisboeck, "Tumor growth instability and its implications for chemotherapy", Cancer Res. 2009 Nov 1;69(21):8507-15, Epub 2009 Oct 27.
COMMENTS	

# C+Te30

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
a	command line	Growth rate	float		s <sup>-1</sup>
a0	command line	Initial growth rate	float		s <sup>-1</sup>
b	command line	Growth acceleration	float		s <sup>-2</sup>
beta	command line	Carrying capacity	float		t <sup>-1</sup>
gamma	command line	Weat-law parameter	float		t <sup>-1</sup>
C	command line	Dose	float		m
t*	command line	Time at therapy	float		day

# C+Te30

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
N1 (t)	console output	Number of cells of the various populations sensible to drug	float	
N2 (t)	console output	Number of cells of the various populations unsensitive to drug	float	

# C+Te31

## Model information

Model number	C+Te31.
Reference partner	FORTH
Model title	PIHNA-ECM-LQ
Brief model description	The PIHNA-ECM-LQ mathematical model describes the vascular and invasive phases of tumor growth considering the complex interactions between cancer cells and the host-tissue microenvironment. Specifically, the tumor microenvironment consists of the vasculature that provides oxygen to cancer cells, tumor-induced angiogenic factors (e.g., VEGF) as well as the macromolecules of the extracellular matrix (ECM) and matrix degrading enzymes (e.g., Matrix Metalloproteinases), which degrade the ECM locally. Depending on oxygen supply, cancer cells can be proliferative, hypoxic or necrotic. Furthermore, cancer cell populations can invade the surrounding tissue driven by chemotaxis towards higher oxygen or haptotaxis towards higher ECM concentrations. The model can also accommodate the effect of radiotherapy on cancer population, which is based on the Linear Quadratic Model (LQ) approximation.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Deterministic approach consisting of a system of coupled reaction-diffusion equations
References	<p>K. R. Swanson, et al., "Quantifying the role of angiogenesis in malignant progression of gliomas: In Silico modeling integrates imaging and histology, " Cancer Res, vol. 71, pp. 7366-7375, 2011</p> <p>P. Hinow, et al., "A spatial model of tumor-host interaction: application of chemotherapy, " Math Biosci Eng, vol. 6, no. 3, pp. 521-46, 2009</p> <p>A. Roniotis, et al., "Solving the PIHNA model while accounting for radiotherapy," 5th Int. Adv. Research Workshop on In Silico</p>



D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

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	Oncology and Cancer Investigation (IARWISOCI 2012), Oct 22-23, Athens, Greece, 2012
COMMENTS	

# C+Te31

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
			double		
L	input_continuum.xml	Grid size	int	1-	cm
N	input_continuum.xml	Number of grid cells	int	100-	ND
TIME	input_continuum.xml	Total simulation time	double	8-	h
c <sub>0</sub>	input_continuum.xml	Initial Normoxic cell concentration	double	0-1	ND
h <sub>0</sub>	input_continuum.xml	Initial Hypoxic cell concentration	double	0-1	ND
n <sub>0</sub>	input_continuum.xml	Initial Necrotic cell concentration	double	0-1	ND
v <sub>0</sub>	input_continuum.xml	Initial vasculature	double	0-1	ND or

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

					cells/cm <sup>3</sup>
<b><math>o_0</math></b>	input_continuum.xml	Initial oxygen	double	0-1	ND or moles/cm <sup>3</sup>
<b><math>a_0</math></b>	input_continuum.xml	Initial angiogenic concentrations	double	0-1	ND or moles/cm <sup>3</sup>
<b><math>f_0</math></b>	input_continuum.xml	Initial ECM	double	0-1	ND or M
<b><math>m_0</math></b>	input_continuum.xml	Initial MDEs	double	0-1	ND
<b><math>D_c</math></b>	input_continuum.xml	Diffusion coefficient of normoxic cells	double	0.0000000001-0.000000001	cm <sup>2</sup> s <sup>-1</sup>
<b><math>D_h</math></b>	input_continuum.xml	Diffusion coefficient of hypoxic cells	double	0.0000000001-0.000000001	cm <sup>2</sup> s <sup>-1</sup>
<b><math>D_v</math></b>	input_continuum.xml	Diffusion coefficient of endothelial cells	double	1E-11	cm <sup>2</sup> s <sup>-1</sup>
<b><math>D_a</math></b>	input_continuum.xml	Diffusion coefficient of angiogenic factors	double	0.00000029	cm <sup>2</sup> s <sup>-1</sup>
<b><math>D_o</math></b>	input_continuum.xml	Diffusion coefficient of oxygen	double	0.00001	cm <sup>2</sup> s <sup>-1</sup>
<b><math>\chi_{\text{hapt}}</math></b>	input_continuum.xml	Haptotactic coefficient	double	2600	cm <sup>2</sup> s <sup>-1</sup> M <sup>-1</sup>
<b><math>\chi_m</math></b>	input_continuum.xml	Chemotaxis coefficient	double	2600	cm <sup>2</sup> s <sup>-1</sup> M <sup>-1</sup>
<b>ti_cycle</b>	input_continuum.xml	Proliferation time	double	4-24	h
<b>gamma</b>	input_continuum.xml	Hypoxic to normoxic conversion rate	double	0.002-0.2	h <sup>-1</sup>

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<b>beta</b>	input_continuum.xml	Normoxic to hypoxic conversion rate	double	0.002-0.2	$h^{-1}$
<b><math>\alpha_h</math></b>	input_continuum.xml	Hypoxic to necrotic conversion rate	double	0.0002-0.002	$h^{-1}$
<b><math>\alpha_n</math></b>	input_continuum.xml	Death rate	double	0.0002-0.002	$h^{-1}$
<b><math>m_v</math></b>	input_continuum.xml	Proliferation rate of endothelial cells	double	0.0019	$h^{-1}$
<b>deltac/deltah</b>	input_continuum.xml	Production rate of angiogenic factors by normoxic/hypoxic	double	3E-17	$mmol\ cell^{-1}h^{-1}$
<b>w</b>	input_continuum.xml	Consumption rate of angiogenic factors	double	0.00000217	$cell^{-1}h^{-1}$
<b>lamda</b>	input_continuum.xml	Decay rate of angiogenic factors	double	0.64	$h^{-1}$
<b>d</b>	input_continuum.xml	Degradation rate of ECM	double	0.1-50	ND
<b>mic/mih</b>	input_continuum.xml	Production rate of MDE by normoxic/hypoxic	double	0.01-0.5	ND
<b>lm</b>	input_continuum.xml	Decay rate of MDE	double	0-1	ND
<b>bo</b>	input_continuum.xml	Production rate of oxygen	double	0-1	ND
<b>goc/goh</b>	input_continuum.xml	Consumption rate of oxygen by normoxic/hypoxic	double	1-50	ND
<b><math>a_o</math></b>	input_continuum.xml	Decay rate of oxygen	double	0.025	ND
<b>a</b>	input_continuum.xml	Radiobiology parameter	double	0-0.2	$Gy^{-1}$
<b>b</b>	input_continuum.xml	Radiobiology parameter	double	0-0.02	$Gy^{-2}$
<b>D</b>	input_continuum.xml	Dose	double	40-60	Gy

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

OER	input_continuum.xml	Oxygen Enhancement Ratio	double	1-3	ND
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# C+Te31

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
c (t)	Normoxic_temp.pdf	Total Normoxic cell concentration over time	file	.pdf
h (t)	Hypoxic_temp.pdf	Total Hypoxic cell concentration over time	file	.pdf
n (t)	Necrotic_temp.pdf	Total Necrotic cell concentration over time	file	.pdf
v (x,y)	Vasculature.pdf	Endpoint spatial distribution of vasculature	file	.pdf
o (x,y)	Oxygen.pdf	Endpoint spatial distribution of oxygen	file	.pdf
a (x,y)	Angiogenic.pdf	Endpoint spatial distribution of angiogenic factors	file	.pdf
f (x,y)	Movement_Filter.pdf	Endpoint spatial distribution of ECM	file	.pdf
m (x,y)	MDE.pdf	Endpoint spatial distribution of MDEs	file	.pdf
c (x,y)	Normoxic.pdf	Endpoint spatial distribution of normoxic cells	file	.pdf

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>h (x,y)</b>	<b>Hypoxic.pdf</b>	<b>Endpoint spatial distribution of hypoxic cells</b>	<b>file</b>	<b>.pdf</b>
<b>n (x,y)</b>	<b>Necrotic.pdf</b>	<b>Endpoint spatial distribution of necrotic cells</b>	<b>file</b>	<b>.pdf</b>

# C+Te32

Model information	
Model number	C+Te32.
Reference partner	FORTH
Model title	Cell-level tumor invasion
Brief model description	This mathematical model describes tumor growth invasion at cell-level linking genotypes with phenotypes and their interactions with the extracellular space. Specifically, cells are discrete entities that follow specific rules in response to their microenvironment and in accordance to their genotype-phenotype characteristics while the components of the extracellular space are treated as continuous variables.
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Cellular automata linked with a system of partial differential equations of reaction-diffusion type.
References	A.R.A. Anderson, "A hybrid mathematical model of solid tumour invasion: the importance of cell adhesion, " Math. Med. Biol, 2005.  G. Tzedakis, et al., " Hybrid Model for Tumor Spheroids with Intratumoral Oxygen Supply Heterogeneity," 5th Int. Adv. Research Workshop on In Silico Oncology and Cancer Investigation (IARWISOCI 2012), Oct 22-23, Athens, Greece, 2012
COMMENTS	



# C+Te32

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
L	input_hybrid.xml	Grid size	double	0.5-4	cm
N	input_hybrid.xml	Number of grid cells	double	200-1600	ND
TIME	input_hybrid.xml	Total simulation time	double	8-320	h
$v_0$	input_hybrid.xml	Initial vasculature	double	0-1	ND
$o_0$	input_hybrid.xml	Initial oxygen	double	0-1	ND
$a_0$	input_hybrid.xml	Initial angiogenic concentrations	double	0-1	ND
$f_0$	input_hybrid.xml	Initial ECM	double	0-1	ND
$m_0$	input_hybrid.xml	Initial MDEs	double	0-1	ND
$D_c$	input_hybrid.xml	Diffusion coefficient of normoxic cells	double	0.0000000001-0.000000001	$\text{cm}^2\text{s}^{-1}$
$D_h$	input_hybrid.xml	Diffusion coefficient of hypoxic cells	double	0.0000000001-0.000000001	$\text{cm}^2\text{s}^{-1}$
$D_v$	input_hybrid.xml	Diffusion coefficient of endothelial cells	double	1,00E-11	$\text{cm}^2\text{s}^{-1}$
$D_a$	input_hybrid.xml	Diffusion coefficient of angiogenic factors	double	2,90E-07	$\text{cm}^2\text{s}^{-1}$

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

$D_o$	input_hybrid.xml	Diffusion coefficient of oxygen	double	0,00001	$\text{cm}^2\text{s}^{-1}$
$\chi_i$	input_hybrid.xml	Haptotactic coefficient (for each phenotype)	double	2600-10400	$\text{cm}^2\text{s}^{-1}\text{M}^{-1}$
$\chi_m$	input_hybrid.xml	Chemotaxis coefficient	double	2600-10400	$\text{cm}^2\text{s}^{-1}\text{M}^{-1}$
$ti\_cycle_i$	input_hybrid.xml	Proliferation time (for each phenotype)	double	8-24	h

# C+Te32

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$m_v$	input_hybrid.xml	Proliferation rate of endothelial cells	double	0,0019	$h^{-1}$
deltac/deltah	input_hybrid.xml	Production rate of angiogenic factors by normoxic/hypoxic	double	3E-17	$mmol\ cell^{-1}h^{-1}$
w	input_hybrid.xml	Consumption rate of angiogenic factors	double	0,00000217	$cell^{-1}h^{-1}$
lamda	input_hybrid.xml	Decay rate of angiogenic factors	double	0.64	$h^{-1}$
d	input_hybrid.xml	Degradation rate of ECM	double	50	ND
mic/mih	input_hybrid.xml	Production rate of MDE by normoxic/hypoxic	double	1-4	ND
lm	input_hybrid.xml	Decay rate of MDE	double	0-1	ND
bo	input_hybrid.xml	Production rate of oxygen	double	0-1	ND
goci/goh	input_hybrid.xml	Consumption rate of oxygen by normoxic (for each phenotype)/hypoxic	double	1-4	ND
ao	input_hybrid.xml	Decay rate of oxygen	double	0,025	ND
Thres_n	input_hybrid.xml	Oxygen level for cell death	double	0-1	ND
Thres_h	input_hybrid.xml	Oxygen level for cell hypoxia	double	0-1	ND
$A_i$	input_hybrid.xml	Adhesion coefficient (for each phenotype)	int	1-4	ND
$P_{mut}$	input_hybrid.xml	Mutation probability	double	0-1	ND

# C+Te32

Output specifications (I)				
All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
pqn_cells (x,y)	ProlifQuiesNec.pdf	Endpoint spatial distribution of proliferative, quiescent and dead cells	file	.pdf
chn_cells (x,y)	NormHypoNec.pdf	Endpoint spatial distribution of normoxic, hypoxic and dead cells	file	.pdf
v (x,y)	Vasculature.pdf	Endpoint spatial distribution of vasculature	file	.pdf
o (x,y)	Oxygen.pdf	Endpoint spatial distribution of oxygen	file	.pdf
a (x,y)	Angiogenic.pdf	Endpoint spatial distribution of angiogenic factors	file	.pdf
f (x,y)	ECM.pdf	Endpoint spatial distribution of ECM	file	.pdf
m (x,y)	MDE.pdf	Endpoint spatial distribution of MDEs	file	.pdf

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

<b>phenotypes_properties</b>	<b>phenotypes_properties.txt</b>	<b>List of all phenotypes and their characteristics</b>	<b>file</b>	<b>.txt</b>
<b>phenotypes (x,y)</b>	<b>phenotypes.txt</b>	<b>Endpoint spatial distribution of phenotypes</b>	<b>file</b>	<b>.txt</b>
<b>v (x,y)</b>	<b>Vasculature.txt</b>	<b>Endpoint spatial distribution of vasculature</b>	<b>file</b>	<b>.txt</b>
<b>o (x,y)</b>	<b>Oxygen.txt</b>	<b>Endpoint spatial distribution of oxygen</b>	<b>file</b>	<b>.txt</b>
<b>a (x,y)</b>	<b>Angiogenic.txt</b>	<b>Endpoint spatial distribution of angiogenic factors</b>	<b>file</b>	<b>.txt</b>
<b>f (x,y)</b>	<b>ECM.txt</b>	<b>Endpoint spatial distribution of ECM</b>		<b>.txt</b>
<b>m (x,y)</b>	<b>MDE.txt</b>	<b>Endpoint spatial distribution of MDEs</b>		<b>.txt</b>
<b>chl_cells (t)</b>	<b>NormHypoLive_temp.pdf</b>	<b>Hypoxic, Normoxic and total Live cells growth curves</b>	<b>file</b>	<b>.pdf</b>
<b>pql_cells (t)</b>	<b>ProlifQuiesLive_temp.pdf</b>	<b>Proliferative, Quiescent and total Live cells growth curves</b>	<b>file</b>	<b>.pdf</b>
<b>nl_cells (t)</b>	<b>NecLive_temp.pdf</b>	<b>Necrotic and total Live cells growth curves</b>	<b>file</b>	<b>.pdf</b>

# C+Te33

Model information	
Model number	C+Te33.
Reference partner	UBERN
Model title	Brain Biomechanics
Brief model description	Calculates strain/stresses in the brain tissues
Biological scale	CELL AND TISSUE
Core mathematical methods utilized	Finite Element Analysis
References	PMID: 21740923
COMMENTS	

# C+Te33

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Images		Segmented images			mm
		Concentration of biological cells			cells/mm <sup>-3</sup>

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
		Direction of propagation of tumor cells		

### ***3.3 Technology related description of existing (e) models***

Section 3.3 provides a tabulated description of existing (“e”) models of tumour growth and/or normal tissue response to treatment from the technological perspective. Each technological model description corresponds to the basic science description of the model with the same code name (see the previous list of the basic science model descriptions). All models presented have been developed by CHIC consortium partners. In order to render the code names of the models as informative as possible the following symbols and abbreviations have been proposed and adopted:

#### **CATEGORIZATION SYMBOLS**

**A:** atomic scale

**M:** molecular scale

**C:** cell scale

**T:** tissue scale

**O:** organ scale

**S:** body system scale

**C+T:** cell and tissue scales

**C+T+S:** cell and tissue and body system scales

etc.

**e:** existing ( model or model implementation)

**d:** (model or model implementation) under development or refinement or adaptation

#### **ABBREVIATIONS**

**# :** particle number

**LIMP:** Limited Mitotic Potential





# **TECHNOLOGY RELATED DESCRIPTION OF EXISTING MODELS**

# Ae1

## Model information

Model number	Ae1.
Reference partner	UPENN
Model title	Molecular Dynamics of clinical mutations in oncogenic receptors

## Software requirements

Code language	
Command line or GUI	command line and GUI
Operating systems and architecture (x86 or x64)	x86,x64
External libraries dependencies	VMD, NAMD, GROMACS

## Hardware requirements

Cores	Multicore
Disk memory	
RAM memory	
Typical execution time	24-48 hours per mutatnt when run in parallel on 16 cores

# Ae2

## Model information

Model number	Ae2.
Reference partner	UPENN
Model title	Autodock

## Software requirements

Code language	
Command line or GUI	Command line & GUI
Operating systems and architecture (x86 or x64)	Linux x64
External libraries dependencies	-

## Hardware requirements

Cores	Multicore
Disk memory	
RAM memory	
Typical execution time	Less than 5 minutes per ligand

# Ae3

## Model information

Model number	Ae3.
Reference partner	UPENN
Model title	Glide

## Software requirements

Code language	Proprietary
Command line or GUI	Command line & GUI
Operating systems and architecture (x86 or x64)	Linux x64
External libraries dependencies	-

## Hardware requirements

Cores	Multicore
Disk memory	
RAM memory	
Typical execution time	Less than 5 minutes per ligand

# Ae4

## Model information

Model number	Ae4.
Reference partner	UPENN
Model title	Shape Signatures

## Software requirements

Code language	C++
Command line or GUI	GUI (webserver)
Operating systems and architecture (x86 or x64)	Windows x86 & x64, Linux x86 & x64
External libraries dependencies	-

## Hardware requirements

Cores	Not core dependent
Disk memory	
RAM memory	
Typical execution time	5 minutes per ligand

# Me1

## Model information

Model number	Me1.
Reference partner	UOXF
Model title	Cell cycle model

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# Me2

## Model information

Model number	Me2.
Reference partner	UOXF
Model title	Wnt signalling pathwa

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# C+Te1

## Model information

Model number	C+Te1.
Reference partner	ICCS
Model title	Untreated Tumor Growth. Spatial code

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes



# C+Te2

## Model information

Model number	C+Te2.
Reference partner	ICCS
Model title	Untreated Tumor Growth. Non Spatial code

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te3

## Model information

Model number	C+Te3.
Reference partner	ICCS
Model title	Single Agent Chemotherapy. Spatial code

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te4

## Model information

Model number	C+Te4.
Reference partner	ICCS
Model title	Single Agent Chemotherapy. Non Spatial code

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te5

## Model information

Model number	C+Te5.
Reference partner	ICCS
Model title	Radiotherapy. Spatial code

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te6

## Model information

Model number	C+Te6.
Reference partner	ICCS
Model title	Radiotherapy. Non Spatial code

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te7

## Model information

Model number	C+Te7.
Reference partner	ICCS
Model title	Breast Cancer Therapy: Epirubicin

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te8

## Model information

Model number	C+Te8.
Reference partner	ICCS
Model title	Lung Cancer Therapy: Cisplatin and Docetaxel

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te9

## Model information

Model number	C+Te9.
Reference partner	ICCS
Model title	Lung Cancer Therapy: Cisplatin and Gemcitabine

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes



# C+Te10

## Model information

Model number	C+Te10.
Reference partner	ICCS
Model title	Lung Cancer Therapy: Cisplatin and Vinorelbine

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te11

## Model information

Model number	C+Te11.
Reference partner	ICCS
Model title	Glioblastoma Therapy: Temozolomide and Radiation

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te12

## Model information

Model number	C+Te12.
Reference partner	ICCS
Model title	Free Growth of homogeneous solid tumors simulation model

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te13

## Model information

Model number	C+Te13.
Reference partner	ICCS
Model title	Actinomycin Chemotherapy Simulation model

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te14

## Model information

Model number	C+Te14.
Reference partner	ICCS
Model title	Vincristine Chemotherapy Simulation model

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te15

## Model information

Model number	C+Te15.
Reference partner	ICCS
Model title	Actinomycin-Vincristine Combined Chemotherapy Simulation model

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# C+Te16

## Model information

Model number	C+Te16.
Reference partner	UOXF
Model title	Angiogenesis

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# C+Te17

## Model information

Model number	C+Te17.
Reference partner	UOXF
Model title	Angiogenesis and vasculogenesis

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	



# C+Te18

## Model information

Model number	C+Te18.
Reference partner	UOXF
Model title	Ascular tumour growth and chemotherapy

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# C+Te19

## Model information

Model number	C+Te19.
Reference partner	UOXF
Model title	Vascular tumour growth

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# C+Te20

## Model information

Model number	C+Te20.
Reference partner	ICCS
Model title	Untreated vascular tumour growth

## Software requirements

Code language	Matlab
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 GB
Typical execution time	1 seconds

# C+Te21

## Model information

Model number	C+Te21.
Reference partner	ICCS
Model title	Vascular tumour growth under bevacizumab monotherapy

## Software requirements

Code language	Matlab
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 GB
Typical execution time	1 seconds

# C+Te22

## Model information

Model number	C+Te22.
Reference partner	ICCS
Model title	Time-course of bevacizumab concentration in plasma

## Software requirements

Code language	Matlab
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 GB
Typical execution time	1 seconds

# C+Te23

## Model information

Model number	C+Te23.
Reference partner	ICCS
Model title	Bevacizumab concentration in plasma in a given time-point

## Software requirements

Code language	Matlab
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 GB
Typical execution time	1 seconds

# C+Te24

## Model information

Model number	C+Te24.
Reference partner	ICCS
Model title	Time-course of vinorelbine concentration in plasma

## Software requirements

Code language	Matlab
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 GB
Typical execution time	1 seconds

# C+Te25

## Model information

Model number	C+Te25.
Reference partner	ICCS
Model title	Vinorelbine concentration in plasma in a given time-point

## Software requirements

Code language	Matlab
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 GB
Typical execution time	1 seconds



# C+Te26

## Model information

Model number	C+Te26.
Reference partner	ICCS
Model title	Diffusion-Reaction Based Glioblastoma multiforme (GBM) Invasion and Response to Treatment Model with Boundary Conditions

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 GB
RAM memory	4 GB
Typical execution time	5 minutes

# C+Te27

## Model information

Model number	C+Te27.
Reference partner	UNITO
Model title	Phenomenological universality in cancer growth

## Software requirements

Code language	matlab
Command line or GUI	command line
Operating systems and architecture (x86 or x64)	windowsx64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 MB
Typical execution time	10 min

# C+Te28

## Model information

Model number	C+Te28.
Reference partner	UNITO
Model title	Cancer growth & radiotherapy

## Software requirements

Code language	matlab
Command line or GUI	command line
Operating systems and architecture (x86 or x64)	windowsx64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 MB
Typical execution time	10 min

# C+Te29

## Model information

Model number	C+Te29.
Reference partner	UNITO
Model title	Multipassage tumor growth

## Software requirements

Code language	matlab
Command line or GUI	command line
Operating systems and architecture (x86 or x64)	windowsx64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8 MB
Typical execution time	15 min

# C+Te30

## Model information

Model number	C+Te30.
Reference partner	UNITO
Model title	Cancer growth and chemotherapy

## Software requirements

Code language	matlab
Command line or GUI	command line
Operating systems and architecture (x86 or x64)	windowsx64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8MB
Typical execution time	10 min

# C+Te31

## Model information

Model number	C+Te31.
Reference partner	FORTH
Model title	PIHNA-ECM-LQ

## Software requirements

Code language	matlab
Command line or GUI	command line
Operating systems and architecture (x86 or x64)	windowsx64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	10 MB
RAM memory	8MB
Typical execution time	10 min

# C+Te32

## Model information

Model number	C+Te32.
Reference partner	FORTH
Model title	Cell-level tumor invasion

## Software requirements

Code language	MATLAB, C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# C+Te33

## Model information

Model number	C+Te33.
Reference partner	UBERN
Model title	Brain Biomechanics

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	



## 4. Cancer hypomodelling and hypermodelling strategies [STR]

### 4.1 Introduction

Typical hypomodels or component models include models of cell cycling at the cellular level, molecular interactions / networks affecting cell cycle and/or cell phase durations, cell survival probability during radiotherapy for a given radiation dose, molecular interactions / networks affecting cell survival probability during radiotherapy, cell cycle survival probability during chemotherapy for a given area under curve, AUC, and molecular interactions / networks affecting cell survival probability during chemotherapy.

Typical hypermodels include models of tumour response to treatment for assumed metabolic activity regions and models of angiogenesis and neovasculature distribution. A higher level hypermodel can simulate in vivo tumour growth and response to treatment in which an explicit modelling of angiogenesis and neovasculature distribution is included.

The main strategies for both hypomodelling and hypermodelling are outlined using a number of elucidating diagrams.

### 4.2 Hypomodelling and hypermodelling strategies

#### 4.2.1 Generic hypomodelling and hypermodelling strategy

Fig.4.1 depicts the generic hypomodelling and hypermodelling strategy to be adopted. Moving in the bottom-up direction on the figure corresponds to the basic hypermodelling strategy, whereas moving top-down corresponds to the basic hypomodelling strategy. Hypermodels can be obtained “by appropriately linking together” elementary models or hypomodels. Hypomodels can inversely be obtained “by appropriately breaking down” composite models or hypermodels. Both hypermodelling and hypomodelling can take place at several aggregation or disaggregation levels. For example, Fig. 4.1 shows hypermodels at two levels, i.e. hypermodels 1-2-3, 4-5 and 6-7-8 belong to the same level of aggregation, whereas hypermodel 1-2-3-4-5-6-7-8 belongs to a higher aggregation level.

Referring to the example shown on Fig. 4.1, COMPONENT MODEL 1 is appropriately annotated by META-MODEL 1 through the use of pertinent ontologies. In an analogous way, COMPONENT MODEL 2 to COMPONENT MODEL 8 are annotated by META-MODEL 2 to META-MODEL 8 respectively. The software module “ONTOLOGY BASED LINKER” facilitates the linking of COMPONENT MODEL 1 to COMPONENT MODEL 3 by exploiting the METAMODEL 1 TO METAMODEL 3 annotations and descriptions. The emerging hypermodel 1-2-3 is in turn annotated so that META-HYPERMODEL 1-2-3 is obtained. A similar procedure is applied to the rest of the clusters of component models. Thus HYPERMODEL 1-2-3, HYPERMODEL 4-5 and HYPERMODEL 6-7-8 have emerged. META-HYPER-MODEL 1-2-3 TO METAHYPERMODEL 6-7-8 annotations and descriptions are exploited by the ONTOLOGY BASED LINKER, in order to facilitate the construction of HYPERMODEL 1-2-3-4-5-6-7-8 in a clearly *recursive way*.

A reverse way of action could lead to the disaggregation of HYPERMODEL 1-2-3-4-5-6-7-8 to its constituent “hypomodels” (in relation to the hypermodel under consideration) HYPERMODEL 1-2-3, HYPERMODEL 4-5 and HYPERMODEL 6-7-8. A further disaggregation could lead to the more elementary hypomodels or component models COMPONENT MODEL 1 to COMPONENT MODEL 8.

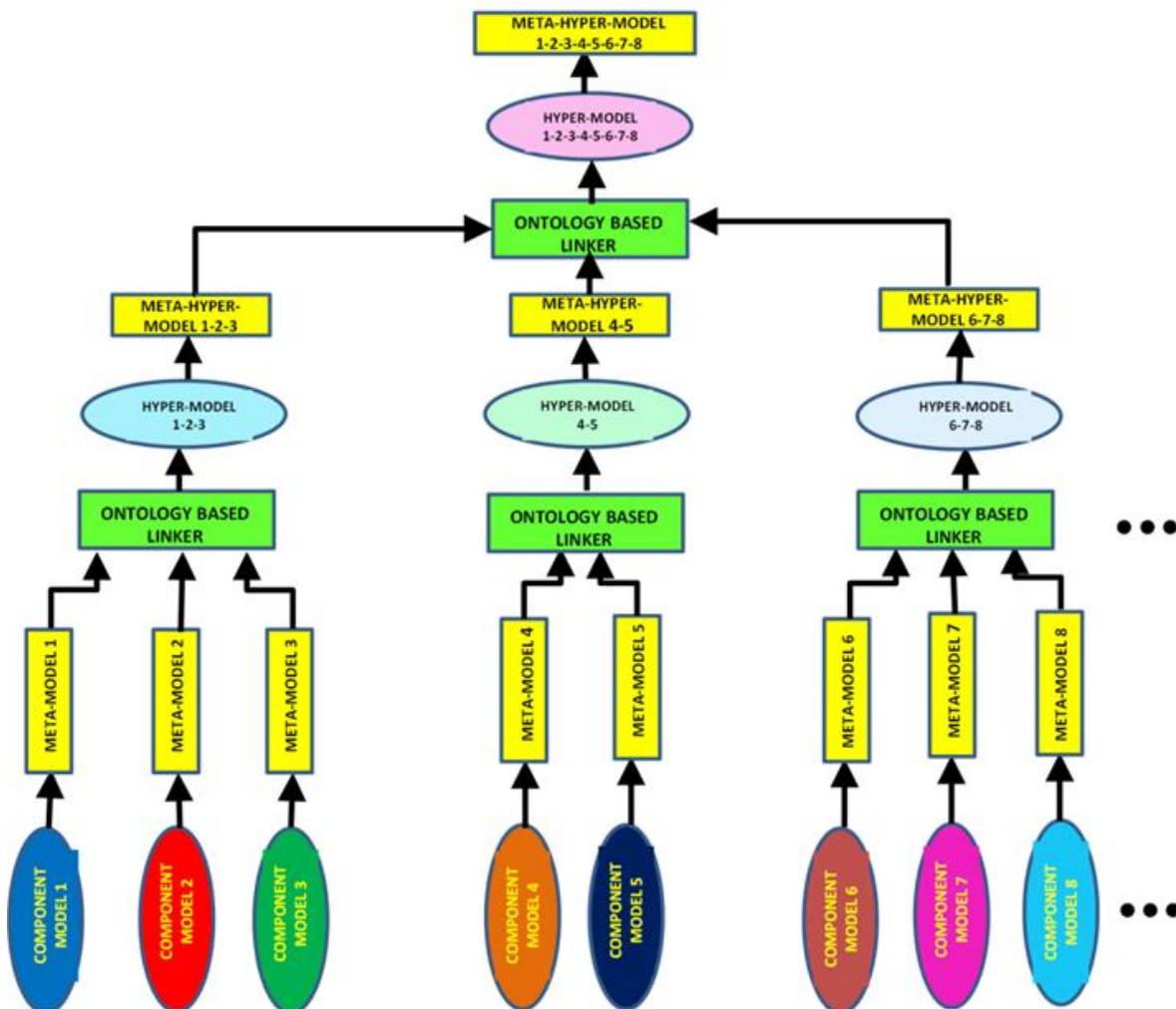


Fig. 4.1

#### 4.2.2 Cancer domain hypomodelling and hypermodelling strategy

Fig. 4.2 provides an illustrative example of how the generic strategy outlined in the previous section can be applied specifically to the cancer domain.

HYPO-MODEL 1A1b is a model of molecular interactions / networks affecting cell cycle and/or cell phase durations. A pertinent metamodel is produced for the specific model. HYPO-MODEL 1A1a is a model of cell cycling at the cellular level. A pertinent metamodel is produced for the second model too. The ontology based linker facilitates the linking of HYPO-MODEL 1A1b and HYPO-MODEL 1A1a by exploiting the metamodel annotations and descriptions. HYPO-MODEL 1A1 emerges. A metamodel for the latter is created.

HYPO-MODEL 1A2b is a model of molecular interactions / networks affecting cell survival probability during radiotherapy. A pertinent metamodel is produced for the specific model. HYPO-MODEL 1A2a is a model of cell survival probability during radiotherapy for a given radiation dose. A pertinent metamodel is produced for this model too. The ontology based linker facilitates the linking of HYPO-MODEL 1A2b and HYPO-MODEL 1A2a by exploiting the metamodel annotations and descriptions. HYPO-MODEL 1A2 emerges. A metamodel for the latter is created.

The HYPO-MODEL 1A3b is a model of molecular interactions / networks affecting cell survival probability during chemotherapy. A pertinent metamodel is produced for the specific model. HYPO-MODEL 1A3a is a model of cell cycle survival probability during chemotherapy for a given area under curve, AUC. A pertinent metamodel is produced for this model too. The ontology based linker facilitates the linking of HYPO-MODEL 1A3b and HYPO-MODEL 1A3a by exploiting the metamodel annotations and descriptions. HYPO-MODEL 1A3 emerges. A metamodel for the latter is created.

Other hypomodels could also be present.

An ontology based linker facilitates the linking of HYPO-MODEL 1A1, HYPO-MODEL 1A2 and HYPO-MODEL 1A3 by exploiting the corresponding metamodels. HYPO-MODEL 1A emerges. This is a model of tumour response to treatment for assumed metabolic activity regions. A metamodel for the latter is created.

In parallel, similar work leads to the creation of HYPER-MODEL 1B. This is a model of angiogenesis and neovasculature distribution within the tumour region. A metamodel for the latter is created.

An ontology based linker facilitates the linking of HYPER-MODEL 1A and HYPER-MODEL 1B by exploiting the corresponding metamodels. HYPER-MODEL 1 emerges. This is a model of in vivo tumour growth and response to treatment. Last but not least, a metamodel for the latter is also created (not shown in Fig. 4.2).

A reverse way of action could lead to the disaggregation of HYPERMODEL 1 to its constituent “hypomodels” (in relation to the hypermodel under consideration) HYPERMODEL 1A and HYPERMODEL 1B. A further disaggregation could lead to the more elementary hypomodels or component models HYPO-MODEL 1A1a, HYPO-MODEL 1A1b, HYPO-MODEL 1A2a, HYPO-MODEL 1A2b, HYPO-MODEL 1A3a and HYPO-MODEL 1A3b as well as to the component models of HYPER-MODEL 1B (not shown in Fig. 4.2).

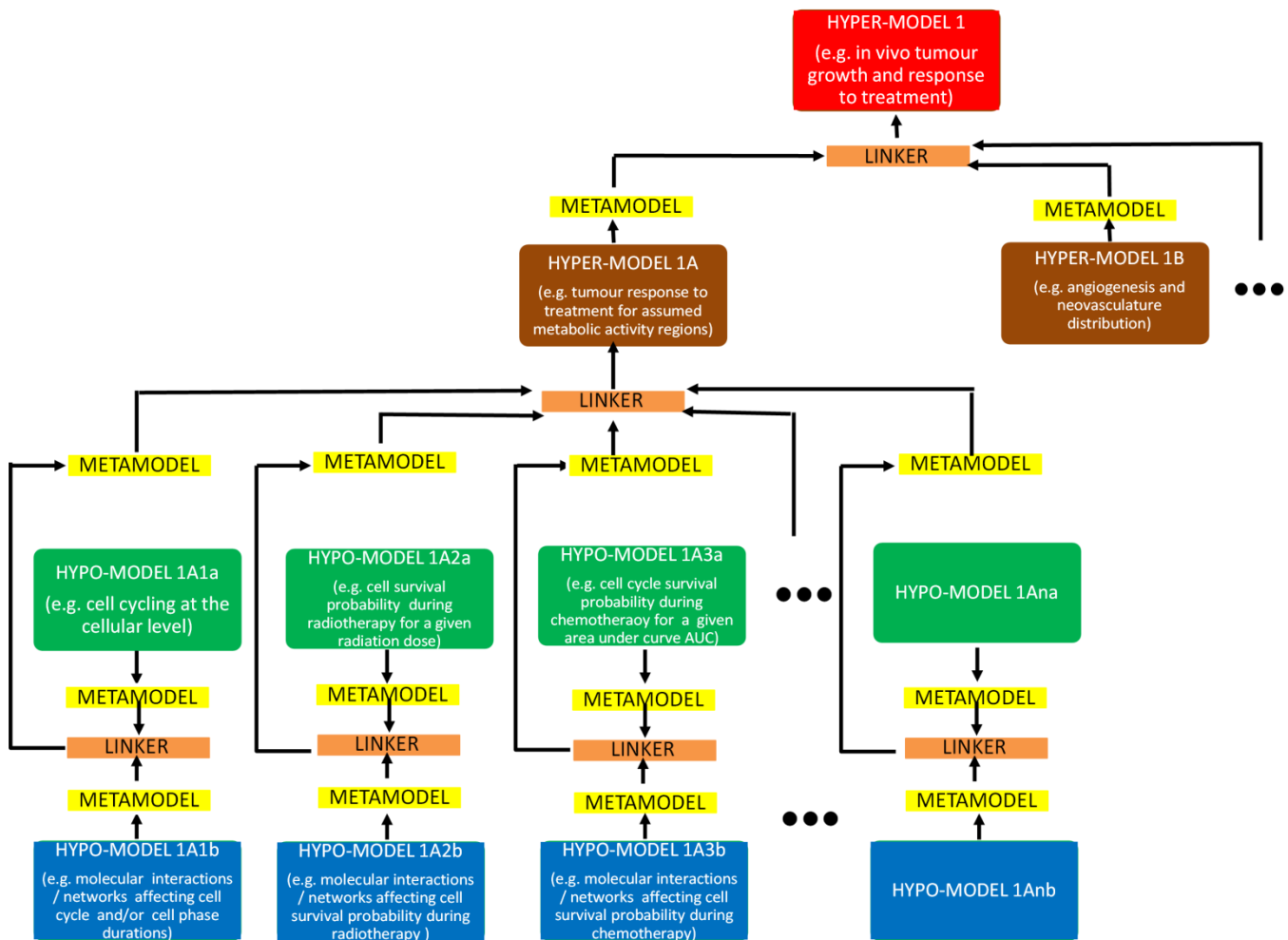


Fig.4.2 An application example of the cancer domain hypomodelling and hypermodelling strategy

### 4.2.3 The “summarize and jump” strategy

An efficient method for the biological linking of different scales of the manifestation of life into a single multiscale hypermodel that will be adopted by CHIC is the “*summarize and jump*” strategy [STR1],[STR2]. This is to be used in conjunction with the hypomodelling and hypermodelling strategy presented in the previous subsections. An illustrative example of the method is provided by Fig. 4.3. The overarching idea is to summarize what is happening in a lower scale of the manifestation of life (e.g. the molecular scale) by appropriately calculating or estimating the value(s) of one or a small number of parameters common in the scale under consideration and the next upper scale e.g. the cellular scale). In this way simulations at the upper scale are affected by the lower scale interactions. This method can be used in a top-down sense as well.

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

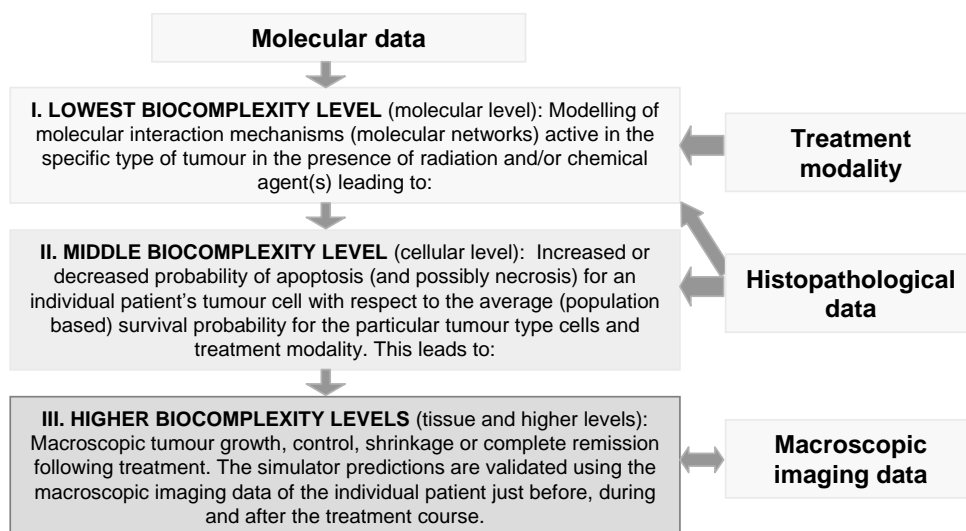


Fig.4.3 An example of the “*summarize and jump*” strategy as applied to the case of tumour response to treatment modelling in the clinical setting. Only three (clusters of) levels are depicted for simplification purposes.

## 5. Initial component models [COM]

### 5.1 Introduction

In this chapter specific examples of initial component models are provided. A more comprehensive list and description of component models will be included in subsequent deliverables. Fig. 5.1 and Fig. 5.2 [COM1], [COM2] provide two indicative examples of elementary component models. The former one presents a generic cytokinetic model of a tumour cell under free tumour growth conditions. The latter shows a generic cytokinetic model of a tumour cell under chemotherapeutic treatment. Numerous other elementary or component or hypomodels are described in the lists of the sections 5.2 and 5.3.

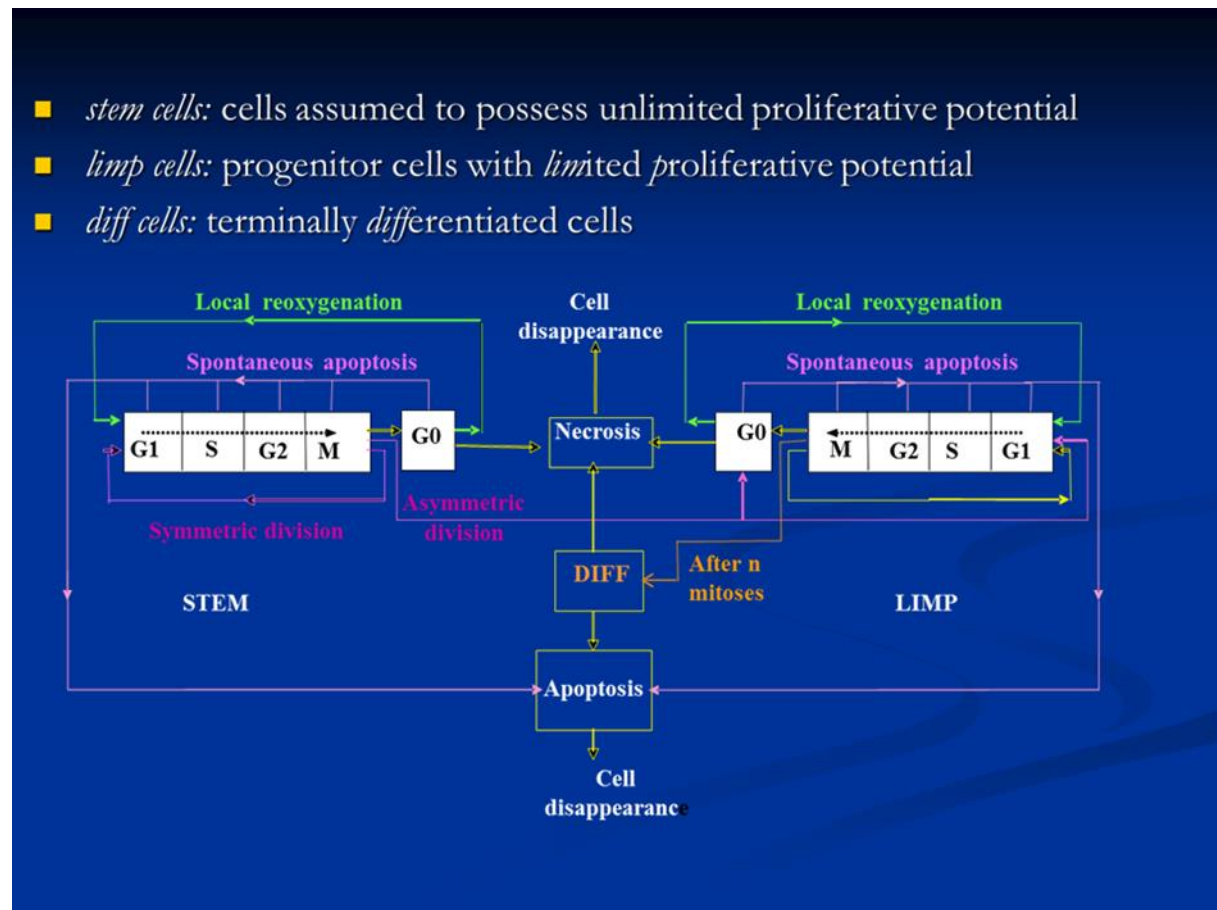


Fig.5.1 A generic cytokinetic model of a tumour cell under free tumour growth conditions. LIMP: Limited Mitotic Potential (committed progenitor) cell, G1: Gap 1 phase, S: DNA synthesis phase, G2: Gap 2 phase, M: mitosis, G0: dormant phase.

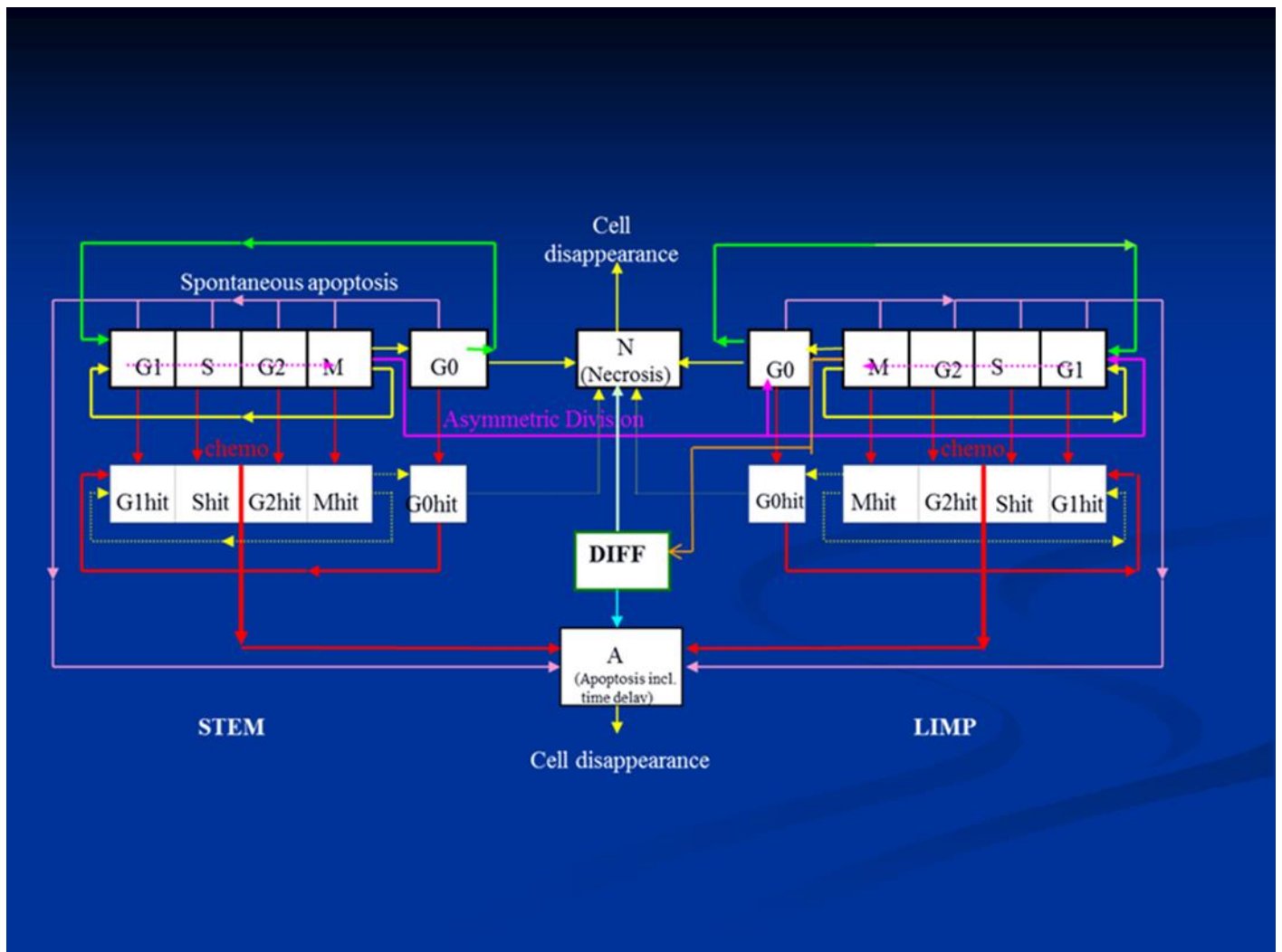


Fig. 5.2 A generic cytokinetic model of a tumour cell under chemotherapeutic treatment. LIMP: Limited Mitotic Potential (committed progenitor) cell, G1: Gap 1 phase, S: DNA synthesis phase, G2: Gap 2 phase, M: mitosis, G0: dormant phase, hit: cell lethally hit by chemotherapy.

## 5.2 Basic science related description of initial component models (under development, refinement or adaptation)

Section 5.2 provides a tabulated description of initial component models of tumour growth and/or normal tissue response to treatment from the basic science perspective. These models are under development, refinement or adaptation. All models presented have been developed or are being

developed by CHIC consortium partners. In order to render the code names of the models as informative as possible, the following symbols and abbreviations have been proposed and adopted:

## **CATEGORIZATION SYMBOLS**

**A:** atomic scale

**M:** molecular scale

**C:** cell scale

**T:** tissue scale

**O:** organ scale

**S:** body system scale

**C+T:** cell and tissue scales

**C+T+S:** cell and tissue and body system scales  
etc.

**e:** existing ( model or model implementation)

**d:** (model or model implementation) under development or refinement or adaptation

## **ABBREVIATIONS**

**# :** particle number

**LIMP:** Limited Mitotic Potential



# **BASIC SCIENCE RELATED DESCRIPTION OF INITIAL COMPONENT MODELS**

**(BEING UNDER DEVELOPMENT, REFINEMENT OR ADAPTATION)**



# Ad1

Model information	
Model number	Ad1.
Reference partner	UPENN
Model title	Bioinformatics analysis of somatic cancer mutations
Brief model description	This model seeks to classify cancer mutations as driver or passenger using machine learning
Biological scale	ATOMIC
Core mathematical methods utilized	Support vector machines, covariance matrix calculation
References	
COMMENTS	

# Ad1

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Cosmic		Catalog of somatic mutations in cancer	Text file		
TCGA		the cancer genome atlas	text file		
Uniprote		UniProt knowledge base	database		
SVM lite		Support vector machine lite	program		

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
PD		Probability that a mutation is a Driver mutations	float	

# Md1

Model information	
Model number	Md1.
Reference partner	UPENN
Model title	Modeling signal transduction in cancer signaling pathways.
Brief model description	Signal transduction in the signaling pathways will be studied using a set of coupled ode/pde equations. The code will be primarily written MATLAB with the information about the network provided using the SMBL framework.
Biological scale	MOLECULAR
Core mathematical methods utilized	Numerical methods for solving coupled ode/pdes
References	
COMMENTS	

# Md1

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Topology	input-parameter.in	Topology	int	0-infintiy	-
Ca	input-parameter.in	Concentration	float	0.0-1.0	Mol/litre
Kab	input-parameter.in	Transition rate constants	float	0-10 <sup>15</sup>	1/time
Di	input-parameter.in	Diffusion coefficients	float	0-10 <sup>9</sup>	m <sup>2</sup> /sec

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
Ca*	parameter-state.out	Steady state Concentration	float	mol/liter
Kab*	parameter-state.out	Steady state transition rates	float	1/time
Di*	parameter-state.out	Diffusion constant	float	m <sup>2</sup> /sec

# Md2

Model information	
Model number	Md2.
Reference partner	UPENN
Model title	Modelling endocytosis
Brief model description	We use phenomenological model based numerical modelling to understand the process of endocytosis in membranes. For this purpose we will be using a custom code based on Dynamically triangulated Monte carlo, written in Fortran and C++ .
Biological scale	MOLECULAR
Core mathematical methods utilized	
References	
COMMENTS	

# Md2

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
$\kappa$	input-parameter.in	Bending rigidity	float	0-100	k_B T
C_0	input-paramteter.in	Spontaneous curvature	float	0.0-1.0	1/length
$\varphi$	input-paramteter.in	Concentration of receptor	float	0.0-1.0	-
T	input-paramteter.in	Temperature	float	0.01-10	k_B T

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extention	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
Membrane conformation	membrane-conf.vtu	Vtu files	file	.vtu
Thermodynamic distributions	distribution.dat	One data file corresponding to each quantity of interest	file	.dat

# Md3

Model information	
Model number	Md3.
Reference partner	ICCS
Model title	Molecular models formulated in General SBML
Brief model description	The General Case of an SBML model
Biological scale	MOLECULAR
Core mathematical methods utilized	
References	
COMMENTS	SBML at the same time includes the description (structure) of the model and the default values for the input parameters (more specifically the parameters that define the Initial conditions of the system). The values of the input parameters can be changed only using a tool that supports SBML (are not read from an external file or from command line) or by using SED-ML files and a tool that supports both SBML and SED-ML.



# Md3

## Input specifications (I)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Simulation Method		Depends on the simulation tool to be used. There are three main categories of Simulation Methods (Deterministic, Stochastic, and Hybrid). The choice must be done by the user or described in a SED-ML file (or tool specific file)			
Simulation Duration		Should be given by the user or should be defined in a SED-ML file (or tool specific file).			
Compartment's X Initial Volume		As many compartments as needed could be defined			A unit that describes Volume (e.g. l)
Species' X Initial Concentration		As many species as needed could be defined			A unit that describes Concentration (e.g. nmol/l) or Amount (e.g. Particle Numbers)

# Md3

## Input specifications (II)

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Reaction's X ky parameter (Ky Parameter of reaction X (e.g. A+B->C))		As many reactions as needed (X) could be defined. Every reactions, depending on the kinetic rate law chosen, may have more than one parameters (y).			A unit that describes rate (e.g. 1/s). It depends on the kinetic rate law chosen.
Constant Global Quantity Value		A constant number used either as a parameter (species levels or kinetic constant) or as a value in the calculation of an assignment.			Any unit defined in the model or derived based on the units defined in the model

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Non-Constant Global Quantity Initial Value		A variable that is calculated during the simulation of the model based on a mathematical assignment			Any unit defined in the model or derived based on the units defined in the model
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# Md3

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extention	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
Species' X Transient Concentration		The transient Concentration of species X (calculated during the simulation procedure)		A unit that describes Concentration (e.g. ) or Amount (e.g. Particle Numbers)
Non-Constant Global Quantity Transient Value		The transient value of a Non-Constant Global Quantity (calculated during the simulation procedure)		Any unit defined in the model or derived based on the units defined in the model

# Md4

Model information	
Model number	Md4.
Reference partner	ICCS
Model title	Differentially Expressed Genes
Brief model description	A Statistical Model that identifies the differentially expressed genes between two phenotypes (e.g. patient groups)
Biological scale	MOLECULAR
Core mathematical methods utilized	Statistical Tests
References	
COMMENTS	Programming Languages: R, MATLAB, C/C++

# Md4

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
		Gene Expression Levels for a number of Genes (Matrix as txt, csv, cel, ArrayExpress etc. file)			Intensity (either transformed or not)
		Parameters of the Statistical Method (e.g. p-value, False Discovery Rate etc.)			

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
List of differentially expressed Genes				

# Md5

Model information	
Model number	Md5.
Reference partner	ICCS
Model title	Differentially Expressed Pathways
Brief model description	A Statistical Model that identifies the differentially expressed pathways between two phenotypes (e.g patient groups)
Biological scale	MOLECULAR
Core mathematical methods utilized	Statistical Tests
References	
COMMENTS	Programming Languages: R. MATLAB, C/C++

# Md5

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
		Gene Expression Levels for a number of Genes (Matrix as txt, csv, cel, ArrayExpress etc. file)			
		Prior External Knowledge (Gene Lists/Genes with similar functions, Genes participating in the same pathway, Pathway Structure) (KGML files, BIOPAX files, XML files with gene lists etc.)			
		Parameters of the Statistical Method (e.g. p-value, False Discovery Rate etc.)			



# Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extention	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
		List of differentially expressed Pathways		

# Md6

## Model information

Model number	Md6.
Reference partner	ICCS
Model title	Phenotype Prediction Based on Gene Expression
Brief model description	
Biological scale	MOLECULAR
Core mathematical methods utilized	Machine Learning Methods (Classifiers like SVM, BayesNet etc.)
References	
COMMENTS	Programming Languages: R, MATLAB, C/C++ Specific tools (e.g.WEKA)

# Md6

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
		Gene Expression Levels of Differentially expressed Genes between phenotypes or Pathway Activity levels of Differentially expressed Pathways between phenotypes for a number of samples that the phenotype is known (training and test sets) (Matrix as txt, csv, cel, ArrayExpress etc. file)			
		Possibly: Gene Expression Levels of Differentially expressed Genes between phenotypes or Pathway Activity levels of Differentially expressed Pathways between phenotypes for a number of samples that the phenotype is unknown and has to be predicted (Matrix as txt, csv, cel, ArrayExpress etc. file)			

# Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
		Classification of new samples (patients) into phenotypes		

# Md7

Model information	
Model number	Md7.
Reference partner	ICCS
Model title	Drug Sensitivity Prediction based on Gene Expression
Brief model description	
Biological scale	MOLECULAR
Core mathematical methods utilized	Statistical Tests Correlation Tests Machine Learning Methods
References	
COMMENTS	Programming Languages: R, MATLAB, C/C++

# Md7

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
		Gene Expression Levels for a number of Genes (Matrix as txt, csv, cel, ArrayExpress etc. file) coupled with Drug Sensitivity (e.g. LC50 values) measurements (usually in vitro) for the same cell lines, animal models or patients (Matrix as txt, csv, cel, ArrayExpress etc. file)			
		Gene Expression Levels for a number of Genes (Matrix as txt, csv, cel, ArrayExpress etc. file) for patients with unknown drug sensitivity			

# Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension

# Md8

## Model information

Model number	Md8.
Reference partner	ICCS
Model title	A molecular pathway based model of the cell cycle [for the case of Acute Lymphoblastic Leukemia (ALL)]
Brief model description	A kinetic Systems Biology oriented model that simulates the biochemical dynamics of the G1 phase of the cell cycle in precursor-B ALL cells. The model is based
Biological scale	MOLECULAR
Core mathematical methods utilized	
References	<p>Haberichter et al. A systems biology dynamical model of mammalian G1 cell cycle progression. Mol. Syst. Biol. 2007; 3: 84</p> <p>Modifications are described in p-medicine deliverable D12.3</p>
COMMENTS	<p>Described in SBML. SBML at the same time includes the description (structure) of the model and the default values for the input parameters (more specifically the parameters that define the Initial conditions of the system). The values of the input parameters can be changed only using a tool that supports SBML (are not read from an external file or from command line) or by using SED-ML files and a tool that supports both SBML and SED-ML.</p>



# Md8

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Simulation Method		Depends on the simulation tool to be used. There are three main categories of Simulation Methods (Deterministic, Stochastic, and Hybrid). The choice must be done by the user or described in a SED-ML file (or tool specific file)			
Simulation Duration		Should be given by the user or should be defined in a SED-ML file (or tool specific file).			
Cell		Cell Compartment Initial Volume			Dimensionless
Initial Amounts (Species)					
CyclinD		Cyclin D			Particle Number (#)
Cdk4[00]		Cdk 4			Particle Number (#)
Cdk4[10]		p27:Cdk 4			Particle Number (#)

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Cdk4[01]		Cyclin D:Cdk 4			Particle Number (#)
Cdk4[11]		p27:Cyclin D:Cdk 4			Particle Number (#)
p27		p27			Particle Number (#)
CyclinE		Cyclin E			Particle Number (#)
CyclinA		Cyclin A			Particle Number (#)
Cdk2[000]		Cdk 2			Particle Number (#)
Cdk2[100]		p27:Cdk2			Particle Number (#)
Cdk2[010]		Cdk2(M)			Particle Number (#)
Cdk2[110]		p27:Cdk2(M)			Particle Number (#)
Cdk2[001]		Cyclin E:Cdk2			Particle Number (#)
Cdk2[101]		p27:Cyclin E:Cdk2			Particle Number (#)
Cdk2[011]		Cyclin E:Cdk2(M)			Particle Number (#)
Cdk2[111]		p27:Cyclin E:Cdk2(M)			Particle Number (#)
Cdk2[002]		Cyclin A:Cdk2			Particle Number (#)

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<b>Cdk2[102]</b>		<b>p27:Cyclin A:Cdk2</b>			<b>Particle Number (#)</b>
<b>Cdk2[012]</b>		<b>Cyclin A:Cdk2(M)</b>			<b>Particle Number (#)</b>
<b>Cdk2[112]</b>		<b>p27:Cyclin A:Cdk2(M)</b>			<b>Particle Number (#)</b>
<b>Cdk1[00]</b>		<b>Cdk1</b>			<b>Particle Number (#)</b>
<b>Cdk1[10]</b>		<b>Cdk1(M)</b>			<b>Particle Number (#)</b>
<b>Cdk1[01]</b>		<b>Cyclin A:Cdk1</b>			<b>Particle Number (#)</b>
<b>Cdk1[11]</b>		<b>Cyclin A:Cdk1(M)</b>			<b>Particle Number (#)</b>
<b>pRb[00]</b>		<b>pRb</b>			<b>Particle Number (#)</b>
<b>pRb[10]</b>		<b>pRb-P</b>			<b>Particle Number (#)</b>
<b>pRb[20]</b>		<b>pRb-PP</b>			<b>Particle Number (#)</b>
<b>pRb[20]cdk4</b>		<b>pRb-PP (hyper-phosphorylated by Cdk4)</b>			<b>Particle Number (#)</b>
<b>pRb[01]</b>		<b>E2F:pRb</b>			<b>Particle Number (#)</b>
<b>pRb[11]</b>		<b>E2F:pRb-P</b>			<b>Particle Number (#)</b>
<b>pRb[21]</b>		<b>E2F:pRb-PP</b>			<b>Particle Number (#)</b>

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pRb[21]cdk4		E2F:pRb-PP (hyper-phosphorylated by Cdk4)			Particle Number (#)
E2F		E2F			Particle Number (#)
Emi1		Emi1			Particle Number (#)
APC/C		APC/C			Particle Number (#)
APC/C:Emi1		APC/C:Emi1			Particle Number (#)
Cdk4[01]_pRb[00]_pRb[10]_Int					Particle Number (#)
Cdk4[01]_pRb[01]_pRb[11]_Int					Particle Number (#)
Cdk4[01]pRb[10]pRb[20]Int					Particle Number (#)
Cdk4[01]pRb[11]pRb[21]Int					Particle Number (#)
Cdk2[011]_pRb[10]_pRb[20]_Int					Particle Number (#)
Cdk2[011]_pRb[11]_pRb[21]_Int					Particle Number (#)
Cdk2[012]_pRb[10]_pRb[20]_Int					Particle Number (#)
Cdk2[012]_pRb[11]_pRb[21]_Int					Particle Number (#)
Cdk1[11]_pRb[10]_pRb[20]_Int					Particle Number (#)

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Cdk1[11]_pRb[11]_pRb[21]_Int					Particle Number (#)
APC/C_CyclinA_Int					Particle Number (#)
APC/C_Cdk2[000]_Cdk2[002]_Int					Particle Number (#)
APC/C_Cdk2[100]_Cdk2[102]_Int					Particle Number (#)
APC/C_Cdk2[010]_Cdk2[012]_Int					Particle Number (#)
APC/C_Cdk2[110]_Cdk2[112]_Int					Particle Number (#)
APC/C_Cdk1[00]_Cdk1[01]_Int					Particle Number (#)
APC/C_Cdk1[10]_Cdk1[11]_Int					Particle Number (#)
Total_CyclinYD					Particle Number (#)
Total_CyclinYE					Particle Number (#)
Total_CyclinYA					Particle Number (#)
Total_p27					Particle Number (#)
Hypophosphorylated_pRb					Particle Number (#)
Hyperphosphorylated_pRb					Particle Number (#)

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<b>Total_Emi1</b>					<b>Particle Number (#)</b>
<b>Initial Values (Global Quantities)</b>					
<b>ksYE2F</b>					<b>Absolute Number</b>
<b>ksYEmi1</b>					<b>Absolute Number</b>
<b>ksYCyclinA</b>					<b>Absolute Number</b>
<b>ksYCyclinE</b>					<b>Absolute Number</b>
<b>kYact</b>					<b>Absolute Number</b>
<b>ksYCyclinD</b>					<b>Absolute Number</b>
<b>ksYp27</b>					<b>Absolute Number</b>
<b>kdYp27</b>					<b>Absolute Number</b>
<b>kd1Yp27</b>					<b>Absolute Number</b>
<b>ks0YCyclinE</b>					<b>Absolute Number</b>
<b>ks1YCyclinE</b>					<b>Absolute Number</b>

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ksMYCyclinE					Absolute Number
ks0YCyclinA					Absolute Number
ks1YCyclinA					Absolute Number
ksMYCyclinA					Absolute Number
ks0YE2F					Absolute Number
ks1YE2F					Absolute Number
ksMYE2F					Absolute Number
kdYE2F					Absolute Number
kd0YE2F					Absolute Number
ks0YEmi1					Absolute Number
ks1YEmi1					Absolute Number
ksMYEmi1					Absolute Number
kdYEmi1					Absolute Number
kbYCyclinDYCdk4					Absolute Number

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kbYp27YYCdk4					Absolute Number
kbYp27YYCdk2					Absolute Number
k1Yact					Absolute Number
timeYModifier					Absolute Number
kbYCyclinEYYCdk2					Absolute Number
kbYCyclinAYYCdk2					Absolute Number
kbYCyclinAYYCdk1					Absolute Number
kbYD4YYpRb					Absolute Number
kupYD4YYpRb					Absolute Number
kbYE2YYpRb					Absolute Number
kupYE2YYpRb					Absolute Number
kbYA2YYpRb					Absolute Number
kupYA2YYpRb					Absolute Number
kbYA1YYpRb					Absolute Number



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<b>kupYA1YYpRb</b>					<b>Absolute Number</b>
<b>ktYpRbYYDephos</b>					<b>Absolute Number</b>
<b>kbYE2FYYpRb</b>					<b>Absolute Number</b>
<b>kbYEmi1YYAPCC</b>					<b>Absolute Number</b>
<b>kbYAPCCYYCyclinA</b>					<b>Absolute Number</b>
<b>kudYAPCCYYCyclinA</b>					<b>Absolute Number</b>
<b>kdYCyclinD</b>					<b>Absolute Number</b>
<b>kdYCyclinE</b>					<b>Absolute Number</b>
<b>kdYCyclinA</b>					<b>Absolute Number</b>
<b>kuYCyclinDYYCdk4</b>					<b>Absolute Number</b>
<b>kuYp27YYCdk4</b>					<b>Absolute Number</b>
<b>kuYCyclinEYYCdk2</b>					<b>Absolute Number</b>
<b>kuYp27YYCdk2</b>					<b>Absolute Number</b>
<b>kuYCyclinAYYCdk2</b>					<b>Absolute Number</b>

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kuYCyclinAYYCdk1					Absolute Number
kuYD4YYpRb					Absolute Number
kuYE2YYpRb					Absolute Number
kuYA2YYpRb					Absolute Number
kuYA1YYpRb					Absolute Number
kuYE2FYYpRb					Absolute Number
kuYEmi1YYAPCC					Absolute Number
kuYAPCCYYCyclinA					Absolute Number
kspRb0001CyclinA					Absolute Number
ksMpRb0001CyclinA					Absolute Number
kspRb11CyclinA					Absolute Number
ksMpRb11CyclinA					Absolute Number
pRbpp_all					Particle Number #
Transition_time					min

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Kinetic Rate Constants					
v		(constant flux) parameter of reaction rxnY001			(#/min)
k1		(mass action constant) parameter of reaction rxnY002			(1/min)
k1		(mass action constant) parameter of reaction rxnY003			(1/min)
k1		(mass action constant) parameter of reaction rxnY004			(1/min)
v		(constant flux) parameter of reaction rxnY005			(#/min)
k1		(mass action constant) parameter of reaction rxnY006			(1/min)
k1		(mass action constant) parameter of reaction rxnY007			(1/min)
k1		(mass action constant) parameter of reaction rxnY008			(1/min)
k1		(mass action constant) parameter of reaction rxnY009			(1/min)
k1		(mass action constant) parameter of reaction rxnY010			(1/min)
k1		(mass action constant) parameter of reaction rxnY011			(1/min)
k1		(mass action constant) parameter of reaction rxnY012			(1/min)
k1		(mass action constant) parameter of reaction rxnY013			(1/min)
k1		(mass action constant) parameter of reaction rxnY014			(1/min)
v		(constant flux) parameter of reaction rxnY015			(#/min)
k1		(mass action constant) parameter of reaction rxnY016			(1/min)

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k1		(mass action constant) parameter of reaction rxnY017			(1/min)
k1		(mass action constant) parameter of reaction rxnY018			(1/min)
k1		(mass action constant) parameter of reaction rxnY019			(1/min)
k1		(mass action constant) parameter of reaction rxnY020			(1/min)
v		(constant flux) parameter of reaction rxnY021			(#/min)
k1		(mass action constant) parameter of reaction rxnY022			(1/min)
k1		(mass action constant) parameter of reaction rxnY023			(1/min)
k1		(mass action constant) parameter of reaction rxnY024			(1/min)
k1		(mass action constant) parameter of reaction rxnY025			(1/min)
k1		(mass action constant) parameter of reaction rxnY026			(1/min)
k1		(mass action constant) parameter of reaction rxnY027			(1/min)
k1		(mass action constant) parameter of reaction rxnY028			(1/min)
v		(constant flux) parameter of reaction rxnY029			(#/min)
k1		(mass action constant) parameter of reaction rxnY030			(1/min)
k1		(mass action constant) parameter of reaction rxnY031			(1/min)
k1		(mass action constant) parameter of reaction rxnY032			(1/min)
k1		(mass action constant) parameter of reaction			(1/min)

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		<b>rxnY033</b>			
<b>v</b>		<b>(constant flux) parameter of reaction rxnY034</b>			<b>(#/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY035</b>			<b>(1/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY036</b>			<b>(1/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY037</b>			<b>(1/(#*min))</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY038</b>			<b>(1/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY039</b>			<b>(1/(#*min))</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY040</b>			<b>(1/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY041</b>			<b>(1/(#*min))</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY042</b>			<b>(1/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY043</b>			<b>(1/(#*min))</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY044</b>			<b>(1/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY045</b>			<b>(1/(#*min))</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY046</b>			<b>(1/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY047</b>			<b>(1/(#*min))</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction rxnY048</b>			<b>(1/min)</b>
<b>k1</b>		<b>(mass action constant) parameter of reaction</b>			<b>(1/(#*min))</b>

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		rxnY049			
k1		(mass action constant) parameter of reaction rxnY050			(1/min)
k1		(mass action constant) parameter of reaction rxnY051			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY052			(1/min)
k1		(mass action constant) parameter of reaction rxnY053			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY054			(1/min)
k1		(mass action constant) parameter of reaction rxnY055			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY056			(1/min)
k1		(mass action constant) parameter of reaction rxnY057			(1/min)
k1		(mass action constant) parameter of reaction rxnY058			(1/min)
k1		(mass action constant) parameter of reaction rxnY059			(1/min)
k1		(mass action constant) parameter of reaction rxnY060			(1/min)
k1		(mass action constant) parameter of reaction rxnY061			(1/min)
k1		(mass action constant) parameter of reaction rxnY062			(1/min)
k1		(mass action constant) parameter of reaction rxnY063			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY064			(1/min)

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

k1		(mass action constant) parameter of reaction rxnY065			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY066			(1/min)
k1		(mass action constant) parameter of reaction rxnY067			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY068			(1/min)
k1		(mass action constant) parameter of reaction rxnY069			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY070			(1/min)
k1		(mass action constant) parameter of reaction rxnY071			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY072			(1/min)
k1		(mass action constant) parameter of reaction rxnY073			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY074			(1/min)
k1		(mass action constant) parameter of reaction rxnY075			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY076			(1/min)
k1		(mass action constant) parameter of reaction rxnY077			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY078			(1/min)
k1		(mass action constant) parameter of reaction rxnY079			(1/min)
k1		(mass action constant) parameter of reaction rxnY080			(1/min)

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k1		(mass action constant) parameter of reaction rxnY081			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY082			(1/min)
k1		(mass action constant) parameter of reaction rxnY083			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY084			(1/min)
k1		(mass action constant) parameter of reaction rxnY085			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY086			(1/min)
k1		(mass action constant) parameter of reaction rxnY087			(1/min)
k1		(mass action constant) parameter of reaction rxnY088			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY089			(1/min)
k1		(mass action constant) parameter of reaction rxnY090			(1/min)
k1		(mass action constant) parameter of reaction rxnY091			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY092			(1/min)
k1		(mass action constant) parameter of reaction rxnY093			(1/min)
k1		(mass action constant) parameter of reaction rxnY094			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY095			(1/min)
k1		(mass action constant) parameter of reaction			(1/min)



D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

		rxnY096			
k1		(mass action constant) parameter of reaction rxnY097			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY098			(1/min)
k1		(mass action constant) parameter of reaction rxnY099			(1/min)
k1		(mass action constant) parameter of reaction rxnY100			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY101			(1/min)
k1		(mass action constant) parameter of reaction rxnY102			(1/min)
k1		(mass action constant) parameter of reaction rxnY103			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY104			(1/min)
k1		(mass action constant) parameter of reaction rxnY105			(1/min)
k1		(mass action constant) parameter of reaction rxnY106			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY107			(1/min)
k1		(mass action constant) parameter of reaction rxnY108			(1/min)
k1		(mass action constant) parameter of reaction rxnY109			(1/min)
k1		(mass action constant) parameter of reaction rxnY110			(1/min)
k1		(mass action constant) parameter of reaction rxnY111			(1/(#*min))

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

k1		(mass action constant) parameter of reaction rxnY112			(1/min)
k1		(mass action constant) parameter of reaction rxnY113			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY114			(1/min)
k1		(mass action constant) parameter of reaction rxnY115			0.07 1/min
k1		(mass action constant) parameter of reaction rxnY116			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY117			(1/min)
k1		(mass action constant) parameter of reaction rxnY118			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY119			(1/min)
k1		(mass action constant) parameter of reaction rxnY120			(1/min)
k1		(mass action constant) parameter of reaction rxnY121			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY122			(1/min)
k1		(mass action constant) parameter of reaction rxnY123			(1/min)
k1		(mass action constant) parameter of reaction rxnY124			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY125			(1/min)
k1		(mass action constant) parameter of reaction rxnY126			(1/min)
k1		(mass action constant) parameter of reaction rxnY127			(1/(#*min))

D6.1 – Cancer hypomodelling and hypermodelling strategies and initial component models

k1		(mass action constant) parameter of reaction rxnY128			(1/min)
k1		(mass action constant) parameter of reaction rxnY129			(1/min)
k1		(mass action constant) parameter of reaction rxnY130			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY131			(1/min)
k1		(mass action constant) parameter of reaction rxnY132			(1/min)
k1		(mass action constant) parameter of reaction rxnY133			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY134			(1/min)
k1		(mass action constant) parameter of reaction rxnY135			(1/min)
k1		(mass action constant) parameter of reaction rxnY136			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY137			(1/min)
k1		(mass action constant) parameter of reaction rxnY138			(1/min)
k1		(mass action constant) parameter of reaction rxnY085_for_PP			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY087_for_PP			(1/min)
k1		(mass action constant) parameter of reaction rxnY085_for_E2F_PP			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY087_for_E2F_PP			(1/min)

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k1		(mass action constant) parameter of reaction rxnY115_re (constant flux)erse			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY086_for_PP			(1/min)
k1		(mass action constant) parameter of reaction rxnY086_for_E2F_PP			(1/min)
k1		(mass action constant) parameter of reaction rxnY087_for_E2F_PP			(1/min)
k1		(mass action constant) parameter of reaction rxnY115_re (constant flux)erse			(1/(#*min))
k1		(mass action constant) parameter of reaction rxnY086_for_PP			(1/min)
k1		(mass action constant) parameter of reaction rxnY086_for_E2F_PP			(1/min)

# Md8

Output specifications				
All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
Transient Amounts (Species)				
CyclinD		Cyclin D		Particle Number (#)
Cdk4[00]		Cdk 4		Particle Number (#)
Cdk4[10]		p27:Cdk 4		Particle Number (#)
Cdk4[01]		Cyclin D:Cdk 4		Particle Number (#)
Cdk4[11]		p27:Cyclin D:Cdk 4		Particle Number (#)
p27		p27		Particle Number (#)

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CyclinE		Cyclin E		Particle Number (#)
CyclinA		Cyclin A		Particle Number (#)
Cdk2[000]		Cdk 2		Particle Number (#)
Cdk2[100]		p27:Cdk2		Particle Number (#)
Cdk2[010]		Cdk2(M)		Particle Number (#)
Cdk2[110]		p27:Cdk2(M)		Particle Number (#)
Cdk2[001]		Cyclin E:Cdk2		Particle Number (#)
Cdk2[101]		p27:Cyclin E:Cdk2		Particle Number (#)
Cdk2[011]		Cyclin E:Cdk2(M)		Particle Number (#)
Cdk2[111]		p27:Cyclin E:Cdk2(M)		Particle Number (#)
Cdk2[002]		Cyclin A:Cdk2		Particle Number (#)
Cdk2[102]		p27:Cyclin A:Cdk2		Particle Number (#)
Cdk2[012]		Cyclin A:Cdk2(M)		Particle Number (#)
Cdk2[112]		p27:Cyclin A:Cdk2(M)		Particle Number (#)

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<b>Cdk1[00]</b>		<b>Cdk1</b>		<b>Particle Number (#)</b>
<b>Cdk1[10]</b>		<b>Cdk1(M)</b>		<b>Particle Number (#)</b>
<b>Cdk1[01]</b>		<b>Cyclin A:Cdk1</b>		<b>Particle Number (#)</b>
<b>Cdk1[11]</b>		<b>Cyclin A:Cdk1(M)</b>		<b>Particle Number (#)</b>
<b>pRb[00]</b>		<b>pRb</b>		<b>Particle Number (#)</b>
<b>pRb[10]</b>		<b>pRb-P</b>		<b>Particle Number (#)</b>
<b>pRb[20]</b>		<b>pRb-PP</b>		<b>Particle Number (#)</b>
<b>pRb[20]cdk4</b>		<b>pRb-PP (hyper-phosphorylated by Cdk4)</b>		<b>Particle Number (#)</b>
<b>pRb[01]</b>		<b>E2F:pRb</b>		<b>Particle Number (#)</b>
<b>pRb[11]</b>		<b>E2F:pRb-P</b>		<b>Particle Number (#)</b>
<b>pRb[21]</b>		<b>E2F:pRb-PP</b>		<b>Particle Number (#)</b>
<b>pRb[21]cdk4</b>		<b>E2F:pRb-PP (hyper-phosphorylated by Cdk4)</b>		<b>Particle Number (#)</b>
<b>E2F</b>		<b>E2F</b>		<b>Particle Number (#)</b>
<b>Emi1</b>		<b>Emi1</b>		<b>Particle Number (#)</b>

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<b>APC/C</b>		<b>APC/C</b>		<b>Particle Number (#)</b>
<b>APC/C:Emi1</b>		<b>APC/C:Emi1</b>		<b>Particle Number (#)</b>
<b>Cdk4[01]_pRb[00]_pRb[10]_Int</b>				<b>Particle Number (#)</b>
<b>Cdk4[01]_pRb[01]_pRb[11]_Int</b>				<b>Particle Number (#)</b>
<b>Cdk4[01]pRb[10]pRb[20]Int</b>				<b>Particle Number (#)</b>
<b>Cdk4[01]pRb[11]pRb[21]Int</b>				<b>Particle Number (#)</b>
<b>Cdk2[011]_pRb[10]_pRb[20]_Int</b>				<b>Particle Number (#)</b>
<b>Cdk2[011]_pRb[11]_pRb[21]_Int</b>				<b>Particle Number (#)</b>
<b>Cdk2[012]_pRb[10]_pRb[20]_Int</b>				<b>Particle Number (#)</b>
<b>Cdk2[012]_pRb[11]_pRb[21]_Int</b>				<b>Particle Number (#)</b>
<b>Cdk1[11]_pRb[10]_pRb[20]_Int</b>				<b>Particle Number (#)</b>
<b>Cdk1[11]_pRb[11]_pRb[21]_Int</b>				<b>Particle Number (#)</b>
<b>APC/C_CyclinA_Int</b>				<b>Particle Number (#)</b>
<b>APC/C_Cdk2[000]_Cdk2[002]_Int</b>				<b>Particle Number (#)</b>



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APC/C_Cdk2[100]_Cdk2[102]_Int				Particle Number (#)
APC/C_Cdk2[010]_Cdk2[012]_Int				Particle Number (#)
APC/C_Cdk2[110]_Cdk2[112]_Int				Particle Number (#)
APC/C_Cdk1[00]_Cdk1[01]_Int				Particle Number (#)
APC/C_Cdk1[10]_Cdk1[11]_Int				Particle Number (#)
Total_CyclinYD				Particle Number (#)
Total_CyclinYE				Particle Number (#)
Total_CyclinYA				Particle Number (#)
Total_p27				Particle Number (#)
Hypophosphorylated_pRb				Particle Number (#)
Hyperphosphorylated_pRb				Particle Number (#)
Total_Emi1				Particle Number (#)
Global Quantities				
Transition_time		Stores the time point that the transition to S-phase is predicted to happen		min

# Cd1

Model information	
Model number	Cd1.
Reference partner	ICCS (code developer)
Model title	Radiation cell killing
Brief model description	The models aims at estimating the cell killing by irradiation based on the Linear Quadratic or LQ Model
Biological scale	CELL
Core mathematical methods utilized	
References	
COMMENTS	<p>Programming language: C++Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p> <p>Output: The code gives as an output: a) a log file containing the values assigned to the model input parameters and b) a xml file containing the path of the above file and the calculated CKR</p>

# Cd1

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
a		Alpha parameter of LQ model			Gy <sup>-1</sup>
b		Beta parameter of LQ model			Gy <sup>-2</sup>
OER		Oxygen Enhancement Ratio			
Dradio		Radiation dose			Gy

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
CKR[phase]		Cell kill rate of the considered phase phase ∈ [G0, S, rest proliferating(G1, G2, M)]		

# Cd2

## Model information

Model number	Cd2.
Reference partner	ICCS
Model title	Epirubicin pharmacodynamics
Brief model description	The model simulates epirubicin pharmacodynamics assuming an exponential law
Biological scale	CELL
Core mathematical methods utilized	
References	<p>G.S. Stamatakis, E.A. Kolokotroni, D.D. Dionysiou, E.Ch. Georgiadi, C. Desmedt, An advanced discrete state - discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study, Journal of Theoretical Biology volume 266, issue 1, pages 124-139, September 2010. DOI:10.1016/j.jtbi.2010.05.019.</p> <p>E. A. Kolokotroni, G. S. Stamatakis, D. D. Dionysiou, E. Ch. Georgiadi, Ch. Desmedt, N. M. Graf, "Translating Multiscale Cancer Models into Clinical Trials: Simulating Breast Cancer Tumor Dynamics within the Framework of the "Trial of Principle" Clinical Trial and the ACGT Project.," Proc. 8th IEEE International Conference on Bioinformatics and Bioengineering (BIBE 2008), Athens, Greece, 8-10 Oct. 2008. IEEE Catalog Number: CFP08266, ISBN: 978-1-4244-2845-8, Library of Congress: 2008907441, Paper No. BE-2.1.1, length: 8 pages (in electronic format). 2008</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p>

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**Output:**

**The code gives as an output:**

- a) a log file containing the values assigned to the model input parameters and**
- b) a xml file containing the path of the above file and the calculated CKR**

# Cd2

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
AUC		Area Under Curve			mg*h/L
KSF		Survival fraction constant.			(mg*h)-1L

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
CKR		Cell kill rate of epirubicin		

# Sd1

## Model information

Model number	Sd1.
Reference partner	ICCS
Model title	Epirubicin pharmacokinetics
Brief model description	The model simulates epirubicin pharmacokinetics assuming a three compartment open model with elimination from the central compartment
Biological scale	BODY SYSTEM
Core mathematical methods utilized	Compartmental analysis
References	<p>G.S. Stamatakis, E.A. Kolokotroni, D.D. Dionysiou, E.Ch. Georgiadi, C. Desmedt, An advanced discrete state - discrete event multiscale simulation model of the response of a solid tumor to chemotherapy: Mimicking a clinical study, Journal of Theoretical Biology volume 266, issue 1, pages 124-139, September 2010. DOI:10.1016/j.jtbi.2010.05.019.</p> <p>E. A. Kolokotroni, G. S. Stamatakis, D. D. Dionysiou, E. Ch. Georgiadi, Ch. Desmedt, N. M. Graf, "Translating Multiscale Cancer Models into Clinical Trials: Simulating Breast Cancer Tumor Dynamics within the Framework of the "Trial of Principle" Clinical Trial and the ACGT Project.," Proc. 8th IEEE International Conference on Bioinformatics and Bioengineering (BIBE 2008), Athens, Greece, 8-10 Oct. 2008. IEEE Catalog Number: CFP08266, ISBN: 978-1-4244-2845-8, Library of Congress: 2008907441, Paper No. BE-2.1.1, length: 8 pages (in electronic format). 2008</p>
COMMENTS	<p>Programming language: C++</p> <p>Input: All Input parameters are fed into the model in the form of an xml file</p>

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**Output:**

**The code gives as an output:**

- a) a dat file containing the  $C=f(t)$ ,**
- b) a log file containing the values assigned to the model input parameters and**
- c) a xml file containing the path of the above files and the calculated AUC**



# Sd1

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
k12		Inter-compartmental rate constant			hours <sup>-1</sup>
k21		Inter-compartmental rate constant			hours <sup>-1</sup>
k13		Inter-compartmental rate constant			hours <sup>-1</sup>
k31		Inter-compartmental rate constant			hours <sup>-1</sup>
kel		Elimination rate constant			hours <sup>-1</sup>
Vc		Volume of central compartment			L
D		Epirubicin dose			mg m <sup>-2</sup>
Tstop		Execution stop time for concentration=f(t) plot (h)			hours
Output directory		Directory where the output files are stored			

# Sd1

Output specifications				
All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extention	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
CKR[phase]		Cell kill rate of the considered phase phase $\in$ [G0, S, rest proliferating(G1, G2, M)]		

# Sd2

## Model information

Model number	Md2.
Reference partner	ICCS
Model title	Modelling endocytosis
Brief model description	We use phenomenological model based numerical modelling to understand the process of endocytosis in membranes. For this purpose we will be using a custom code based on Dynamically triangulated Monte carlo, written in Fortran and C++ .
Biological scale	MOLECULAR
Core mathematical methods utilized	
References	
COMMENTS	<p>Could be implemented in many programming languages including C/C++, MATLAB.</p> <p>The model has five internal parameters that their values were estimated using clinical data from children with ALL.</p>

# Sd2

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extention	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
BSA		Body Surface Area			
WT		Weight			

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extention	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
CL		Clearance		l/h
V_c		Central Compartment Volume		l
V_p		Peripheral Compartment Volume		l

# Sd3

Model information	
Model number	Sd3.
Reference partner	ICCS
Model title	Oral Prednisone PK model
Brief model description	A model that simulates the Pharmacokinetics of orally administrated Prednisone
Biological scale	BODY SYSTEM
Core mathematical methods utilized	
References	Eleftherios N. Ouzounoglou, Dimitra D. Dionysiou, Martin Stanulla and Georgios S.Stamatakis,. Towards patient personalization of an Acute Lymphoblastic Leukemia Model during the oral administration of prednisone in children: Initiating the ALL Oncosimulator, Advanced Research Workshop on In Silico Oncology and Cancer Investigation - The TUMOR Project Workshop (IARWISOCI), 2012 5th International
COMMENTS	

# Sd3

## Input specifications

All model input parameters (symbols)	File that includes the input parameter (if the input parameter is included in a file)	Full name of each model input parameter or/and files format and extension	Input parameter type (int,float,double, string, file etc.)	Input parameter range ("from"- "to")	Input parameter unit or file extension
Central		Central Compartment Volume			liter
Peripheral		Peripheral Compartment Volume			liter
Depot_compartment		Depot Compartment Volume			liter
Dose		The dose of the drug			milligram
Bioavailability		The oral bioavailability of the drug			Percentage
PREDNL_fraction		The fraction of the drug absorbed at the metabolized form in the Central Compartment from depot Compartment			Percentage
Ka_from_depot		Absorption rate from Depot to Central Compartment			1/hour
CL_Central		The Clearance rate of the drug from the Central Compartment			liter/hour
CL_Central_Peripheral		The drug transport rate constant from Central Compartment to Peripheral compartment and vice versa			liter/hour

# Sd3

## Output specifications

All model output parameters (symbols)	File that includes the output parameter (all output parameters, except files, must be included in a file)	Full name of each model output parameter or/and files format and extension	Output parameter type (int,float,double, string, file etc.)	Output parameter unit or file extension
Drug_Central		Concentration of drug in the Central Compartment		ng/milliliter
Drug_Peripheral		Concentration of drug in the Peripheral Compartment		ng/milliliter

## ***5.2 Technology related description of initial component models (under development, refinement or adaptation)***

Section 5.2 provides a tabulated description of the component models of tumour growth and/or normal tissue response to treatment that are under development, refinement or adaptation from the technological perspective. Each technological model description corresponds to the basic science description of the model with the same code name (see the previous list of the basic science model descriptions.) All models presented have been developed or are being developed by CHIC consortium partners. In order to render the code names of the models as informative as possible the following symbols and abbreviations have been proposed and adopted:

### **CATEGORIZATION SYMBOLS**

**A:** atomic scale

**M:** molecular scale

**C:** cell scale

**T:** tissue scale

**O:** organ scale

**S:** body system scale

**C+T:** cell and tissue scales

**C+T+S:** cell and tissue and body system scales

etc.

**e:** existing ( model or model implementation)

**d:** (model or model implementation) under development or refinement or adaptation

### **ABBREVIATIONS**

**# :** particle number

**LIMP:** Limited Mitotic Potential





# **TECHNOLOGY RELATED DESCRIPTION OF INITIAL COMPONENT MODELS**

**(BEING UNDER DEVELOPMENT, REFINEMENT OR  
ADAPTATION)**

# Ad1

## Model information

Model number	Ad1.
Reference partner	UPENN
Model title	Bioinformatics analysis of somatic cancer mutations

## Software requirements

Code language	perl and python
Command line or GUI	command line and GUI
Operating systems and architecture (x86 or x64)	x86,x64
External libraries dependencies	

## Hardware requirements

Cores	Multicore
Disk memory	
RAM memory	
Typical execution time	10-60mins
Technical contact person	Joe Jordan

# Md1

## Model information

Model number	Md1.
Reference partner	UPENN
Model title	Modeling signal transduction in cancer signaling pathways.

## Software requirements

Code language	MATLAB and SBML
Command line or GUI	command line and GUI
Operating systems and architecture (x86 or x64)	x86 and x64
External libraries dependencies	SBML and matlab base engine

## Hardware requirements

Cores	1
Disk memory	20GB
RAM memory	200MB
Typical execution time	2-3hours

# Md2

## Model information

Model number	Md2.
Reference partner	UPENN
Model title	Modelling endocytosis

## Software requirements

Code language	C++ and Fortran (>gcc4.4)
Command line or GUI	command line
Operating systems and architecture (x86 or x64)	x86,x64
External libraries dependencies	none

## Hardware requirements

Cores	1
Disk memory	20GB
RAM memory	1GB
Typical execution time	4-6hours

# Md3

## Model information

Model number	Md3.
Reference partner	ICCS
Model title	Molecular models formulated in General SBML

## Software requirements

Code language	SBML and SED-ML.
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# Md4

## Model information

Model number	Md4.
Reference partner	ICCS
Model title	Differentially Expressed Genes

## Software requirements

Code language	R, MATLAB, C/C+
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# Md5

## Model information

Model number	Md5.
Reference partner	ICCS
Model title	Differentially Expressed Pathways

## Software requirements

Code language	R. MATLAB, C/C+
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# Md6

## Model information

Model number	Md6.
Reference partner	ICCS
Model title	Phenotype Prediction Based on Gene Expression

## Software requirements

Code language	R, MATLAB, C/C++
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	Specific tools (e.g. WEKA)

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	



# Md7

## Model information

Model number	Md7.
Reference partner	ICCS
Model title	Drug Sensitivity Prediction based on Gene Expression

## Software requirements

Code language	R, MATLAB, C/C++
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# Md8

## Model information

Model number	Md8.
Reference partner	ICCS
Model title	A molecular pathway based model of the cell cycle [for the case of Acute Lymphoblastic Leukemia (ALL)]

## Software requirements

Code language	SBML and SED-ML.
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# Cd1

## Model information

Model number	Cd1.
Reference partner	ICCS
Model title	Radiation cell killing

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# Cd2

## Model information

Model number	Cd2.
Reference partner	ICCS
Model title	Epirubicin pharmacodynamics

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# Sd1

## Model information

Model number	Sd1.
Reference partner	ICCS
Model title	Epirubicin pharmacokinetics

## Software requirements

Code language	C++
Command line or GUI	Command line
Operating systems and architecture (x86 or x64)	Windows x64, Linux x64
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	1 MB
RAM memory	8 MB
Typical execution time	5 minutes

# Sd2

## Model information

Model number	Md2.
Reference partner	ICCS
Model title	Modelling endocytosis

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

# Sd3

## Model information

Model number	Sd3.
Reference partner	ICCS
Model title	Oral Prednisone PK model

## Software requirements

Code language	
Command line or GUI	
Operating systems and architecture (x86 or x64)	
External libraries dependencies	

## Hardware requirements

Cores	
Disk memory	
RAM memory	
Typical execution time	

## 6. Conclusion [CON]

This document has outlined a considerable number (50+) of cancer models already developed or being under development, refinement or adaptation by the CHIC cancer modelling partners. A basic cancer model annotation framework has also been suggested. Fundamental cancer hypomodelling and hypermodelling strategies have been proposed and delineated. The latter will be exploited for the needs of the CHIC project throughout its lifetime. A series of initial component models or hypomodels that can be used as building blocks for several CHIC hypermodels have also been presented.

The hypomodelling and hypermodelling strategies presented so far are to serve as the overall project architectural framework. The latter also dictates the main specifications of the technological platform architecture to be developed. Since at this early stage only high level strategic descriptions are possible, an evaluation of the actual efficiency of the suggested approach remains to be made. This will take place during the subsequent steps of the project implementation. Nevertheless, the facts that the strategies proposed are based on the actual biology of the *natural phenomenon* of cancer and at the same time are highly straightforward provide a rational and promising basis for a successful deployment of the project.



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**NOTE** Numerous other references are included in the tabulated description of the models developed or under development by the CHIC consortium cancer modelling partners.

## Appendix 1 – Abbreviations and acronyms

ABBREVIATION/ACRONYM	FULL TITLES/NAMES/TERMS
FORTH	FOUNDATION FOR RESEARCH AND TECHNOLOGY HELLAS
ICCS or ICCS-NTUA	INSTITUTE OF COMMUNICATION AND COMPUTER SYSTEMS – NATIONAL TECHNICAL UNIVERSITY OF ATHENS
UBERN	UNIVERSITAET BERN
UNITO	UNIVERSITA DEGLI STUDI DI TORINO
UOXF	THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD
UPENN	THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA
USFD	THE UNIVERSITY OF SHEFFIELD