Project acronym:	CHIC
Project full title:	Computational Horizons in Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories for *In-Silico* Oncology
Grant agreement:	600841 (7th EU Programme)
Duration:	1 April 13 – 31 March 2017
Coordinator:	Georgios Stamatakos Research Professor Director, *In Silico* Oncology Group Institute of Communication and Computer Systems National Technical University of Athens E-Mail: gestam@central.ntua.gr Web: in-silico-oncology.iccs.ntua.gr
Project website:	http://www.chic-vph.eu

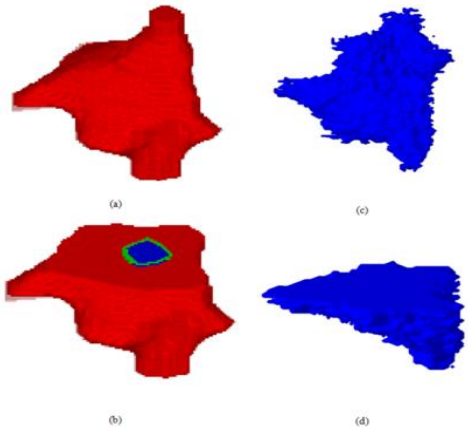
EDITORIAL

Each cancer type is different in many ways, requiring different diagnostic and treatment approaches. On top of this each cancer patient has their own cancer type signature based on their own multiscale data i.e. molecular, histological, imaging and clinical data. This usually leads to markedly differing outcomes when the same treatment is applied to different patients with the same cancer type. Therefore, oncology is a predominant clinical domain where individualized treatment is mandatory. The complexity of cancer, not only as a disease but also as a natural (biological) phenomenon, increasingly dictates the development of highly demanding mathematical and computational cancer models. These models aim at providing biological as well as medical quantifiable insight into the hypercomplex problems addressed.

IN SILICO MEDICINE, an emergent scientific and technological discipline based on clinically driven and oriented multiscale biomodelling, appears to be the latest trend regarding the translation of mathematical and computational biological science to clinical practice through massive exploitation of information technology. *In silico* (i.e. on the computer) experimentation for each individual patient, using their own multiscale biomedical data, including imaging, histological and molecular data, is expected

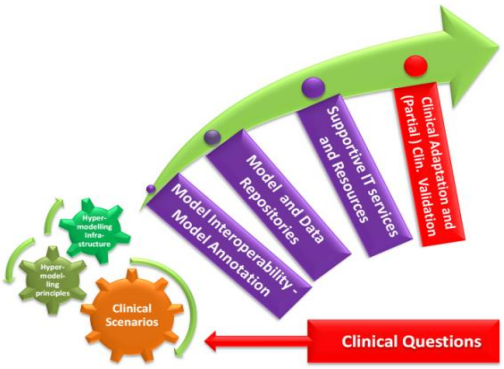
to significantly improve the effectiveness of treatment in the future, since reliable computer predictions could suggest the optimal treatment scheme(s) and schedules(s) for each separate case.

In this context developing robust, reproducible, interoperable and collaborative hyper-models of diseases and normal physiology 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 Virtual Physiological Human (VPH) initiative and the paradigmatic cancer domain, the transatlantic (EU-US) large scale integrating project CHIC has proposed the development of a suite of tools, services and secure infrastructure that will support accessibility and reusability of VPH multiscale mathematical and computational hypermodels. These include a hypermodelling infrastructure consisting primarily of a hypermodelling editor and a hypermodelling execution environment, an infra-structure for semantic metadata management, a hypermodel repository, a hypermodel-driven clinical data repository, a distributed metadata repository and an in silico trial repository for the storage of executed simulation scenarios.



A three dimensional visualization of the computer simulated response of the imageable component of a clinical glioblastoma multiform tumour (left panels) to one cycle of the standard temozolomide chemotherapeutic scheme (right panels)

Multiscale models and data are being semantically annotated using the ontological and annotating tools that are being developed. An image processing and visualization toolkit, and cloud and virtualization services are also being developed.



Clinically driven and clinically oriented cancer hypermodel development

The CHIC tools, services, infrastructure and repositories will provide the community with a collaborative interface for exchanging knowledge and sharing work in an effective and standardized way. A number of open source features and tools will enhance usability and accessibility. In order to ensure clinical relevance and foster clinical acceptance of hypermodelling in the future, the whole endeavour is driven by the clinical partners of the consortium.

Cancer hypermodels being collaboratively developed by the consortium cancer modellers provide the framework and the test-bed for the development of the CHIC technologies.

Following a successful clinical adaptation and validation of hypermodel oncosimulators, exper-imentation *in silico* is expected to serve as both a patient individualized treatment optimizer by exploiting the patient's own multiscale data and a fundamental science based suggestion generator in designing the branches of new prospective clinical trials.

CHIC is funded by the European Commission and co-ordinated by the Institute of Communication and Computer Systems – National Technical University of Athens. Seventeen partner organizations of world acclaim participate in the project.

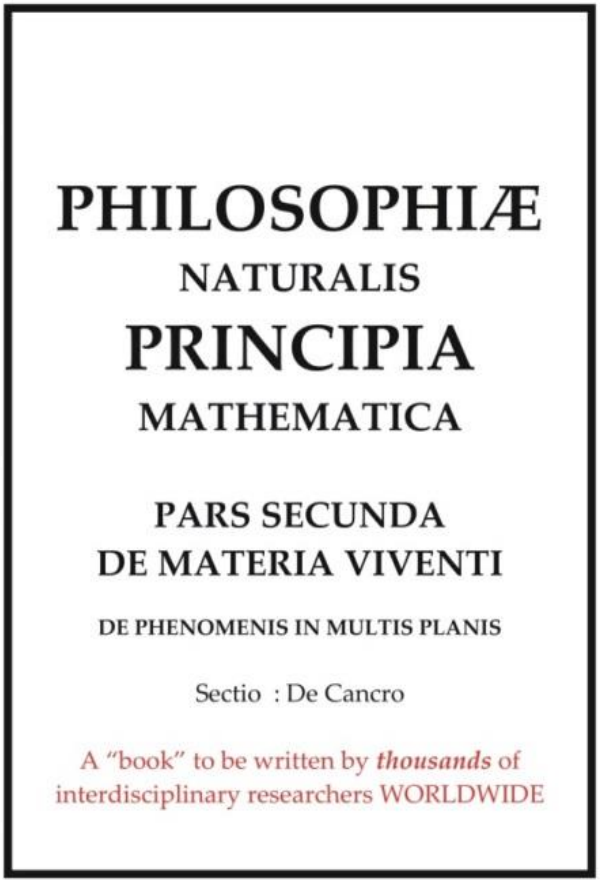
Georgios Stamatakos – CHIC Coordinator

IN SILICO ONCOLOGY: A PHILOSOPHICAL APPROACH

- by Georgios Stamatakos, CHIC Coordinator -

Understanding and effectively modelling the dynamics of cancer and involved normal tissues at all biocomplexity scales by using any efficient combination of mathematical and computer modelling approaches (discrete, continuous, deterministic, stochastic, statistical, analytical, numerical etc.) is a fundamental research challenge in oncology. Obviously this target presupposes success in understanding and modelling numerous critical mechanisms involved in the development and treatment response of cancer and related normal tissue, as well as the subsequent *integration* of all those modelling modules. As the demands of such an endeavour are especially high, a parallelism with the history of Newtonian physics might serve as a source of guidance and inspiration. It has been suggested that cancer epitomizes the entire biology i.e. the multiscale "physics" of living matter. In this context a title like: "Philosophiae Naturalis Principia Mathematica: Pars Secunda, De Materia Viventi, De Phenomenis in Multis Planis – Sectio x : De Cancro" (Mathematical Principles of Natural Philosophy: Second Part, on Living Matter, on Multilevel Phenomena – Section x: on Cancer) might to some extent describe the collaborative and heavily multidisciplinary efforts on a worldwide scale to apply the analytical and mechanistic way of thinking on the description of natural phenomena (mechanisms) involving living matter and especially on those related to cancer.

However, stochastic models may also be needed as supportive players in such an approach due to the extreme complexity of the problems addressed and the ever present gaps of mechanistic knowledge.



A thorough, quantitative, rigorously clinically validated and exploitable understanding of such multi-scale phenomena is expected to dramatically improve the outcome of treatment on a patient individualized basis through experimentation *in silico* (on the computer) by utilizing the multiscale data of the patient (imaging, histological, molecular, clinical etc.). In this context, the term *In Silico* Oncology has been proposed to denote a new scientific, technological and clinical discipline aiming at both understanding the multiscale cancer and related biological phenomena and optimize treatment in the patient individualized context. Simulating and optimizing the design of clinical trials is another crucial field of application of *in silico* oncology.

Reference

G. Stamatakos, "Spotlight on Cancer Informatics," Cancer Informatics 2006:2 83-86 (http://www.la-press.com/spotlight-on-cancer-informatics-georgios-s-stamatakos-phd-article-a120)

WHAT'S IN A WORD…

Science, albeit fascinating, can be tough to follow, especially because of the predominantly technical language. To help you understand what exactly lies behind the research done in CHIC, we present you a glossary of the most important terms in our project with each annual newsletter.

Metamodel

A metamodel is the semantic description of a computer model. In CHIC we define that, at a minimal level, the "metamodel" description should include some descriptive information, such as:

- Model title
- Description
- Creator(s)/Author(s)
- Publication information
- "See also"/"More info" references
- Important dates (e.g. publication date)
- Validation information (verification, pre-clinical accuracy, etc.)
- License and terms of use information

Hypermodel

We observe nature, and we notice recurrences. We develop causal knowledge, first by induction, associating the current observable states to predict future states, and then by inferring why such causal relation exists, recognising some fundamental principles, and then by deduction derive from these principles mechanistic explanations of the observations.

In this context, a hypermodel is the composition and orchestration of multiple hypomodels:

- Component hypomodels capture the existing knowledge about a portion of the process, typically at a characteristic space-time scale.
- Relation hypomodels define how certain properties predicted by one hypomodel transform within the set of idealisations used to build another hypomodel that takes such properties as input.

It should be noted that a hypermodel could be re-used as a hypomodel in another, more complex, hypermodel.

GET TO KNOW US!

As a large scale European collaborative project with a transatlantic arm, CHIC consists of a very diverse consortium of experts in cancer research. In each of the 4 annual CHIC newsletters, we introduce you to individual members of our consortium, their institution, research and tasks in the CHIC project.

Institute of Communication and Computer Systems, National Technical University of Athens, In-Silico Oncology Group, Greece

The Institute of Communication and Computer Systems (ICCS) is an academic research body affiliated with the National Technical University of Athens (NTUA), Greece.

As coordinating institution of the CHIC project, the In-Silico Oncology Group (ISOG) at the Institute of Communication and Computer Systems (ICCS-NTUA) in Athens, Greece, leads the technological and scientific work in the project.

ICCS premises at the National Technical University of Athens

ISOG is a world leading research entity in the field of multiscale cancer modelling and the emerging discipline of *in silico* oncology. A number of novel, primary 'top-down' clinically-driven simulation models have been developed, tested and disseminated by the

group. Moreover, ISOG founded the workshop series 'International Advanced Research Workshops on In Silico Oncology' and will host the 6th workshop in this series this fall.

Even before CHIC, ISOG has been a very active participant in many research projects dealing with *in silico* oncology, VPH research and eHealth. Prominent examples are the EC funded IP projects p-medicine (http://www.p-medicine.eu/), DRTHERAPAT (http://drtherapat.eu/) and MyHealthAvatar (http://www.myhealthavatar.eu/). ISOG has also led in silico oncology related actions in the concluded EC funded projects ACGT (Advancing Clinicogenomic Trials on Cancer), ContraCancrum and TUMOUR.

Besides the overall scientific coordination of CHIC, the *In-Silico* Oncology Group works on a variety of tasks including a) leading the design and development of clinically driven cancer models and integrative hypermodels consisting of simpler and more manageable constituent component models and b) driving the development of hypermodel and data repositories. Another important task of ISOG is its contribution to the clinical adaptation and validation of the CHIC infrastructure as well as the development of the hypermodelling infrastructure.

The most vivid example of the research conducted at ISOG is the development of the Hypermodelling Oncosimulator. As its name already suggests, the Hyper-modelling Oncosimulator is an information technology system simulating in vivo tumour responses to therapeutic treatment such as chemotherapy.

In order to ensure that the entire project will be clinically driven and clinically oriented, three concrete clinical trials/studies will be adopted and addressed. They concern nephroblastoma treated by combined chemotherapy, glioblastoma treated by immunotherapy in combination with chemotherapy and radiotherapy and non-small cell lung cancer treated by a combination of chemotherapy and radiotherapy. In addition, the design of the repositories will be tailored to the clinical scenarios of the project, while being at the same time generic enough to be reusable by several different medical scenarios.

CHIC Coordinator, Georgios S. Stamatakos received his Diploma degree in electrical engineering from the National Technical University of Athens (NTUA), Athens, Greece, the M.Sc. degree in bioengineering from the University of Strathclyde, Glasgow, Scotland, U.K., and the Ph.D. degree in physics (biophysics) from NTUA. He is a Research Professor of *Analysis and Simulation of Biological Systems and their Interaction with Electromagnetic Radiation* at the Institute of Communication and Computer Systems, NTUA where he has founded and leads the *In Silico* Oncology Group. He is also a member of the teaching staff of the School of Electrical and Computer Engineering, NTUA. The focus of his research group is on *in silico* oncology, *in silico* medicine, systems medicine and multiscale cancer modelling. He has also worked as a researcher in bioinformatics, systems biology, biooptics, bioelectromagnetics and computational electromagnetics. He has proposed the notion and the system of *Oncosimulator*. He has led the development of the Oncosimulator of the European Commission (EC) and Japan co-funded ACGT integrated project as well as of the Oncosimulators of several other EC funded and international projects mostly centred around the initiative of the Virtual Physiological Human (VPH). He is the scientific coordinator of the EC funded EU-US large scale integrating research project entitled "CHIC: Computational Horizons in Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories forIn Silico Oncology" FP7-ICT-2011-9, Grant Agreement no

600841. He has also proposed the term and the notion of *in silico* oncology denoting a new clinical trial driven scientific and technological discipline. He is the author or co-author of more than 120 international peer-reviewed publications. He has coinitiated and coorganized a number of international research workshops, including the series of International Advanced Research Workshops on *In Silico* Oncology and Cancer Investigation and the First Transatlantic (EU-US) Workshop on Multiscale Cancer Modelling (ICT 2008, Brussels 2008). The latter was cofunded by the European Commission and the National Cancer Institute, US. G. Stamatakos has been a co-editor, contributor, and reviewer of the transatlantic multiauthor textbook entitled Multiscale Cancer Modelling published by CRC Press (2010/2011). He is a member of IEEE, CViT, the VPH Institute, and the Technical Chamber of Greece.

Katholeike Universiteit Leuven, Belgium

KU Leuven, founded in 1425 and formerly known as Katholieke Universiteit Leuven, is a center of learning and research with the tradition of excellence, situated right in the heart of Europe. World-famous scientists such as Vesalius, Mercator, Rega and Erasmus called Leuven and its university a home at one point of their career and today the town is a second home to more than 40.000 students. KU Leuven is a research-intensive, internationally oriented university that carries out both fundamental and applied research and it is a member of the League of European Research Universities (LERU). It is strongly inter- and multidisciplinary in focus and strives for international excellence. To this end, KU Leuven works together actively with its research partners at home and abroad.

KU Leuven from above

From a basis of social responsibility and scientific expertise, KU Leuven provides high-quality, comprehensive health care in its University Hospitals. KULeuven is considered topnotch in Europe, not only because of its size but also due to its high quality combination of clinical care, high level scientific research and state of the art technical equipment. It fulfills 3 distinctive but complementary tasks. It is a regional hospital for Leuven and its surroundings, but it plays a key role in the national and European context for severe pathology. Moreover, the hospital is a crucial training center for the education and training of new doctors and specialists. Finally, KULeuven in its function of an academic hospital is an extremely important site for scientific and translational clinical and fundamental research.

Professor Stefaan Van Gool leads the ImmunoTherapy Platform Leuven (ITPL), which tries to create a novel treatment for patients with high-grade glioma. These malignant brain tumours are difficult to treat despite

all possibilities of surgery, radiotherapy and chemotherapy. By adding tumour vaccination as a 4th treatment approach, the team aims to extend the survival for relapsed as well as primary diagnosed patients in an experimental setting. Through the years, the ITPL-team has gained deep knowledge in pre-clinical research with cells, cell lines, and mouse models, which can be translated in the clinical practice. Prof. Van Gool discovered that the immune system can be stimulated by a therapeutic vaccine against the tumour and by this, tumour growth can be inhibited. The clinical team possesses the particular expertise to prepare these autologous therapeutic vaccines for patients with malignant brain tumours in a GMP (Good Manufacturing Practice) facilit. Specific blood cells, obtained during leukapheresis, are treated in order to differentiate them into dendritic cells. Afterwards, these cells are loaded with proteins extracted from the patient's tumour tissue. The resulting autologous cell product is then injected in the skin of the patient. Experience in this process has been acquired in the last ten years with hundreds of brain tumour patients, who come from over 25 countries inside and outside Europe to the ITPL research group for this treatment, representing the biggest cohort of patients treated by immunotherapy.

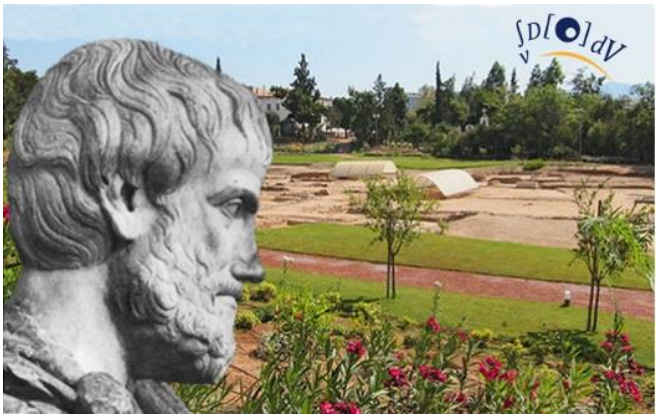
Prof. Stefaan Van Gool and his team from KULeuven

Prof. Van Gool and his organization allow the direct transfer of innovative immunomodulations of the vaccine therapy from pre-clinical research to experimental clinical practice. It represents a unique but achievable model to afford the patients a tailored innovative therapy developed from our own academic scientific research, with the aim to prolong patient survival in a good quality of life.

By Lien Solie, KULeuven

ANNOUNCEMENT: 6th IARWISOCI Workshop

Part of the work in CHIC is devoted to teaching activities and scientific exchange. Within the four years of the project, two larger workshops will be organized which address the larger Virtual Physiological Human (VPH) Community, biologists, clinicians, (tumour) modellers, IT specialists, etc. The first of this series of events is the upcoming 6th International Advanced Research Workshop on In Silico Oncology and Cancer Investigation (IARWISOCI), which will focus almost exclusively on research relevant for or research generated within the CHIC project.



The workshop takes place from 3-4 November 2014 at the Crowne Plaza Hotel in Athens, Greece. A one hour session has been planned to take place in the newly opened to the public original Lyceum of Aristotle.

Further information about the workshop, the venue and the workshop programme are available at http://6th-iarwisoci.iccs.ntua.gr/index.php/.

Stay tuned

Stay up to date and sign up for our bi-monthly CHIC e-mail newsletters!

http://chic-vph.eu/newsletter/

The bi-monthly newsletter includes the latest news from the CHIC project and the wider VPH-community as well as up to date information on conferences and workshops in the field of computational medicine.

Please visit us at **www.chic-vph.eu**

Disclaimer

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The CHIC consortium is not responsible and may not be held accountable for any loss suffered as a result of reliance upon the content of this newsletter.

Newsletter team

Julia Petry
European Research and Project Office GmbH (Eurice)
j.petry@eurice.eu

Corinna Hahn
European Research and Project Office GmbH (Eurice)
c.hahn@eurice.eu

Georgios Stamatakos
Institute of Communication and Computer Systems (ICCS), National Technical University of Athens – In Silico Oncology Group
gestam@central-ntua.gr

Debora Testi
CINECA – SuperComputing Centre
d.testi@cineca.it