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Demonstration of the Developed Meta- and Hyper-Multiscale Models and Repositories

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COVER AND CONTROL PAGE OF DOCUMENT	
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ABSTRACT

This document demonstrates the highly innovative cancer meta- and hyper-multiscale models and repositories developed by the CHIC project in the context of their envisaged clinical use, following completion of their prospective clinical validation. Till that point in the future, the presented hypermodel utilization workflows can be used for research and educational purposes. The demonstration is extensively achieved through the use of screenshots produced by the Clinically Relevant Application Framework (CRAF) in conjunction with descriptive and explanatory text. The hypermodels developed by the cancer modelling partners of the consortium concern nephroblastoma, non small cell lung cancer, glioblastoma and prostate cancer. These four paradigmatic cancer types are treated with a variety of modalities including chemotherapy, radiation therapy, immunotherapy and hormone therapy. Three out of the four developed multiscale hypermodels i.e the nephroblastoma, the non small cell lung cancer and the prostate cancer ones have been collectively developed by three up to six geographically distributed modelling partners each, in both EU and US using the technological infrastructure developed by CHIC. The (hyper)model annotation strategy, the composition of a new hypermodel through the Hypermodelling Editor and the storage of a new hypermodel in the Model Repository are also outlined. All hypermodels demonstrated in this document have successfully undergone the processes of verification, clinical adaptation and partial clinical validation as described among other CHIC deliverables in D6.4. Successful testing and validation of the relevant repositories has been reported *inter alia* in D8.4.

KEYWORD LIST

cancer modelling, multiscale cancer modelling, hypermodelling, CHIC project, hypermodel,

¹ R=Report, P=Prototype, D=Demonstrator, O=Other

² 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)

hypomodel, component model, tumour growth, angiogenesis, cancer biomechanics, cancer metabolism, molecular cancer modelling, integrated cancer model, Oncosimulator, hypermodel based oncosimulator, *in silico* oncology, *in silico* medicine, systems medicine, computational oncology, computational medicine, systems oncology, finite element method, discrete event, discrete entity, partial differential equation, ordinary differential equation, semantics, model repository, clinical research application framework, CRAF, hypermodelling editor, hypermodel execution, nephroblastoma, non small cell lung cancer, glioblastoma multiforme, prostate cancer

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EXECUTIVE SUMMARY

This deliverable demonstrates the highly innovative cancer meta- and hyper-multiscale models and repositories developed by the CHIC project in the context of their envisaged clinical use, following completion of their prospective clinical validation. Till that expected time point in the future, the presented hypermodel utilization workflows can be used for research and educational purposes. The demonstration is extensively achieved through the use of screenshots generated through the Clinically Relevant Application Framework (CRAF) in conjunction with descriptive and explanatory text. The hypermodels developed by the cancer modelling partners of the consortium concern nephroblastoma, non small cell lung cancer, glioblastoma and prostate cancer. These four paradigmatic cancer types are treated with a variety of modalities including chemotherapy, radiation therapy, immunotherapy and hormone therapy. Three out of the four developed multiscale hypermodels i.e. the nephroblastoma, the non small cell lung cancer and the prostate cancer ones have been collectively developed by three up to six geographically distributed modelling partners each in both EU and US using the technological infrastructure developed by CHIC. There are two workflow options regarding the utilization of hypermodels. According to the first one CRAF is launched through the cancer domain specific wizzard whereas according to the second one CRAF is launched through the patient specific wizzard. As an example, the major steps pertaining to the domain specific initiated workflow are the following: selection of the clinical question of interest out of the available ones, selection of a patient out of a list of patients, selection of a hypermodel out of the available ones, introduction of the input parameter values, execution of the hypermodel, selection of the output files, generation of the execution report. The (hyper)model annotation strategy, the composition of a new hypermodel using the Hypermodelling Editor and the storage of a new hypermodel in the Model Repository are also outlined. In this context, the following aspects are addressed *inter alia*: the role of metadata in the creation of hypermodels, the scope of the CHIC RDF annotation schema, the process of defining a parameter, the process of querying around parameters by meaning and the model and parameter annotation procedure in the Model Repository. All hypermodels demonstrated in this document have successfully undergone the processes of verification, clinical adaptation and partial clinical validation as described among other CHIC deliverables in D6.4.

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CHAPTER IN: INTRODUCTION

(NOTE: Numbering of sections, subsections, equations, figures and references within this chapter refers exclusively to the latter and is not applicable to other chapters of the document, If any of the above entities of another chapter is to be referred to, the chapter under consideration should also be mentioned through its two capital letter code)

This document demonstrates the innovative cancer meta- and hyper-multiscale models and repositories developed by the CHIC project in the context of their envisaged clinical use. The latter is expected to take place following completion of hypermodel prospective clinical validation. It is noted that in the meantime, the presented hypermodel utilization workflows can be used for research and educational purposes.

The demonstration is extensively achieved through the use of screenshots generated using the Clinically Relevant Application Framework (CRAF). Pertinent descriptive and explanatory text completes the demonstration.

The hypermodels developed by the cancer modelling partners of the CHIC consortium concern nephroblastoma (Chapter NB), non small cell lung cancer (Chapter LC), glioblastoma (Chapter GB) and prostate cancer (Chapter PC). These four paradigmatic cancer types are treated with a variety of modalities including chemotherapy, radiation therapy, immunotherapy and hormone therapy. Three out of the four developed multiscale hypermodels i.e. the nephroblastoma, the non small cell lung cancer and the prostate cancer ones have been collectively developed by three up to six geographically distributed modelling partners each, in both EU and US using the technological infrastructure developed by CHIC.

There are two workflow options regarding the utilization of hypermodels. According to the first one, CRAF is launched through the cancer domain specific wizard, whereas according to the second one, CRAF is launched through the patient specific wizard. As an example, the major steps pertaining to the domain specific initiated workflow are the following: selection of the clinical question of interest out of the available ones, selection of a patient out of a list of patients, selection of a hypermodel out of list of the available ones, introduction of the input parameter values, execution of the hypermodel, selection of the output files, generation of the execution report.

The (hyper)model annotation strategy, the composition of a new hypermodel using the Hypermodelling Editor and the storage of a new hypermodel in the Model Repository are also outlined (Chapter TE). In this context, the following aspects are *inter alia* addressed: the role of metadata in the creation of hypermodels, the scope of the CHIC RDF annotation schema, the process of defining a parameter, the process of querying around parameters by meaning and the model and parameter annotation procedure in the Model Repository.

It is noted that all hypermodels demonstrated in this document have successfully undergone the processes of verification, clinical adaptation and partial clinical validation as described among other CHIC documents in deliverable D6.4.

CHAPTER NB: THE NEPHROBLASTOMA HYPERMODEL

(NOTE: Numbering of sections, subsections, equations, figures and references within this chapter refers exclusively to the latter and is not applicable to other chapters of the document, If any of the above entities of another chapter is to be referred to, the chapter under consideration should also be mentioned through its two capital letter code)

I. The Nephroblastoma Demonstrator

I.1 Execution through CRAF

Step 0: The clinician enters the initial CRAF page and can launch the Nephroblastoma hypermodels either by selecting "Domain specific" or "Patient specific" wizard (Fig 1).



Fig 1. Home page of CRAF

I.1.1 Configuring Lung Hypermodels Starting with the Domain Selection

Step I: When the clinician launches CRAF through the 'Domain Specific' wizard the four cancer domains (Nephroblastoma, Non Small Cell Lung Cancer, Glioblastoma and Prostate Cancer) considered in CHIC project appear (Fig 2).

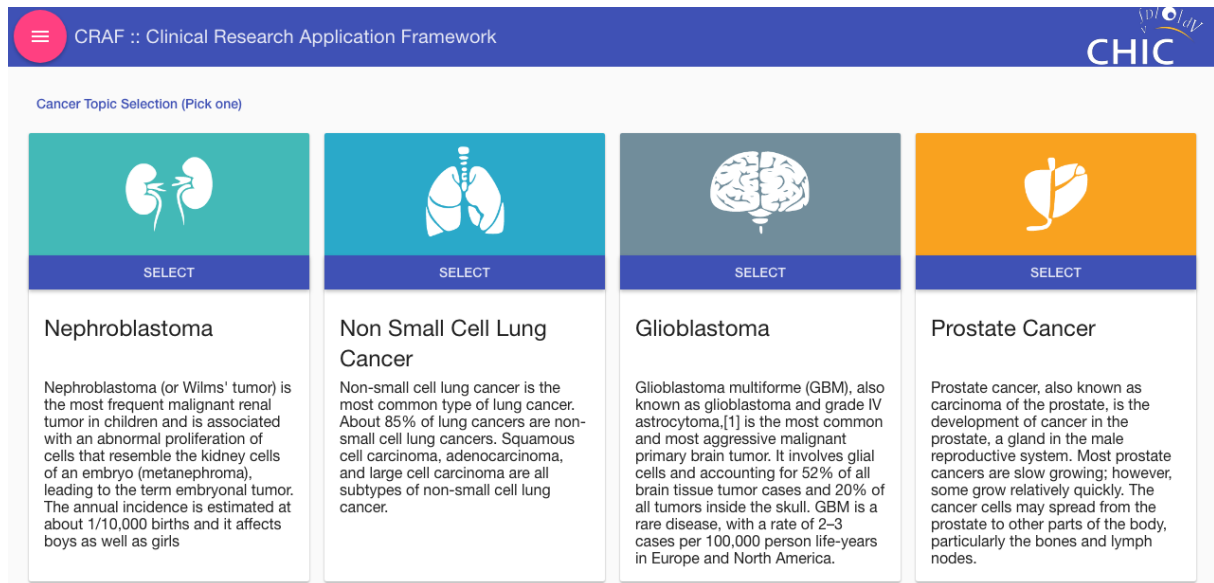


Fig 2. CHIC Cancer domains

Step2: By selecting the 'Nephroblastoma' option, three clinical questions of interest that have been set by clinicians appear (Fig 3). Clinical questions which have been already addressed by an available hypermodel appear enabled. The clinical question "Will a given nephroblastoma in a patient respond to pre-operative chemotherapy by tumour shrinkage, yes or not?" is chosen here for demonstration purposes.

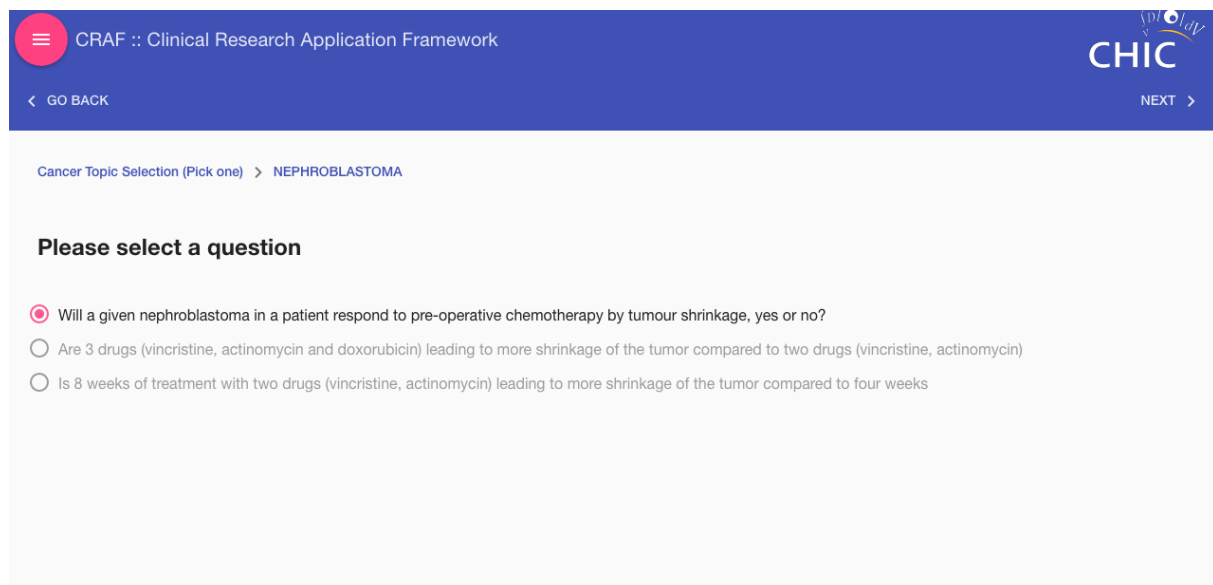


Fig 3. Clinical questions for Nephroblastoma [(I) Will a given nephroblastoma in a patient respond to pre-operative chemotherapy by tumour shrinkage, yes or no? (II) Are 3 drugs (vincristine, actinomycin and doxorubicin) leading to more shrinkage of the tumor compared to two drugs (vincristine, actinomycin) (III) Is 8 weeks of treatment with two drugs (vincristine, actinomycin) leading to more shrinkage of the tumor compared to four weeks]

Step 3: After clicking on the ‘NEXT’ button, a list of patients uploaded on the clinical data repository is presented in CRAF (Fig 4). However, only the patients of the preselected tumour type (nephroblastoma) are enabled. By turning ‘show all patients’ switch off, the disabled patients can be hidden (Fig 5). On the left panel of the screen the available info and clinical data of the selected patient can be previewed (Fig 4, Fig 5).

The screenshot shows the CRAF interface with the following components:

- Header:** CRAF :: Clinical Research Application Framework, CHIC logo, and navigation buttons (GO BACK, NEXT).
- Breadcrumbs:** Cancer Topic Selection (Pick one) > NEPHROBLASTOMA > Select a Patient
- Left Panel:** "Please select a patient" with a "Show all patients" toggle. A list of patients is shown, with Hans Fischer selected.
- Main Panel:**
 - Patient Card:** Fischer, Hans
 - Patient's Information:**
 - Demographics:** First Name: Hans, Last Name: Fischer, Gender: Not Provided, Date Of Birth: Not Provided, E-MAIL: Not Provided.
 - Clinical Data:** A grid of data items including CDR.Kidney.XX.XX.CDISC_ODM.6831.000.xml, CDR.Kidney.XX.XX.MINI.ML.7691.000.xml, CDR.Kidney.XX.FMR.7829.000.dom, CDR.Kidney.XX.FMR.7830.000.dom, CDR.Kidney.XX.XX.CDISC_ODM.8043.000.xml, and CDR.XX.BSEY.O.MR.17659.000.dom.

Fig 4. List of patients registered on the clinical data repository

The screenshot shows the CRAF interface with the following components:

- Header:** CRAF :: Clinical Research Application Framework, CHIC logo, and navigation buttons (GO BACK, NEXT).
- Breadcrumbs:** Cancer Topic Selection (Pick one) > NEPHROBLASTOMA > Select a Patient
- Left Panel:** "Please select a patient" with a "Show all patients" toggle. A list of patients is shown, with Hans Fischer selected.
- Main Panel:**
 - Patient Card:** Fischer, Hans
 - Patient's Information:**
 - Demographics:** First Name: Hans, Last Name: Fischer, Gender: Not Provided, Date Of Birth: Not Provided, E-MAIL: Not Provided.
 - Clinical Data:** A grid of data items including CDR.Kidney.XX.XX.CDISC_ODM.6831.000.xml and CDR.Kidney.XX.XX.CDISC_ODM.8043.000.xml.

Fig 5. List of patients registered as nephroblastoma patients.

Step 4: The clinician selects a patient and clicks on the ‘NEXT’ button. The associated list of hypermodels which address the pre-specified clinical question appears (Fig 6) along with a short description. Three models are currently uploaded on CRAF. For demonstration purposes at this section the Nephroblastoma multimodeller hypermodel_v1_0 is selected.

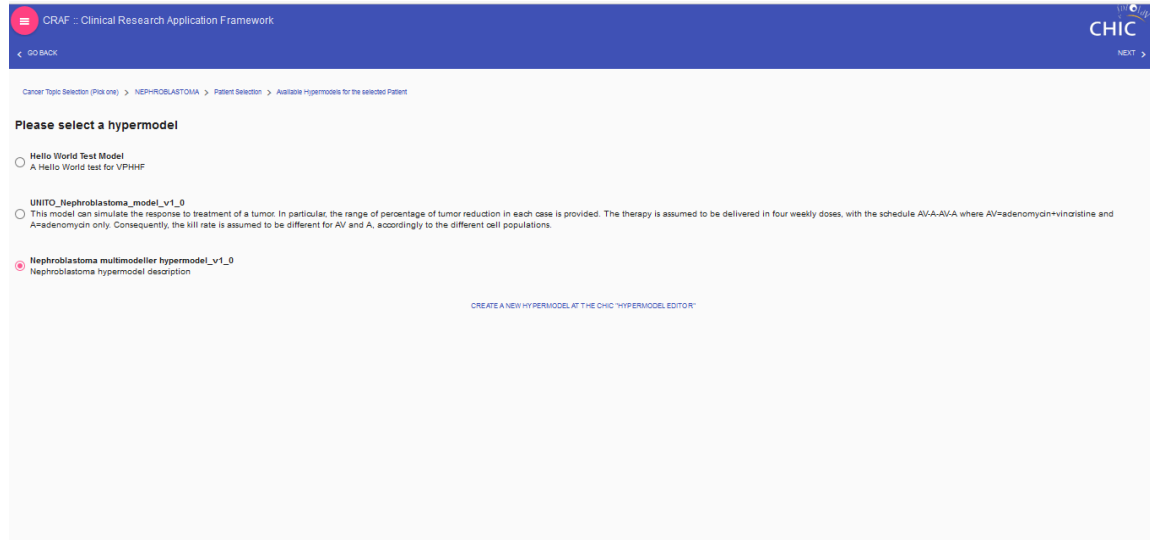


Fig 6. Available nephroblastoma hypermodels for the chosen cancer domain, clinical question and patient. the Nephroblastoma multimodeller hypermodel_v1_0 is selected.

Step 5: By clicking on the ‘NEXT’ button, the clinician can view the input (Fig 7, 8) and output (Fig. 9) parameters of the selected hypermodel and, if necessary, can make corrections/changes to the input arguments before starting the execution of this hypermodel. In order not to distract the clinician with excess information, only the required input arguments is shown (Fig 7). However the complete list of input arguments can appear using the corresponding switches (Fig 8).

CRAF :: Clinical Research Application Framework

GO BACK

EXECUTE

Cancer Topic Selection (Pick one) > NEPHROBLASTOMA > Patient Selection > Hypermodel for the selected Patient

Nephroblastoma multimodeller hypermodel_v1_0

INPUT OUTPUT

Input parameters

Show required Show editable

vor_time_A*	vor_time_B*	vor_time_C*
7	14	21
Units: d, Default: 7, Range: 0-...	Units: d, Default: 14, Range: 0-...	Units: d, Default: 21, Range: 0-...
vor_time_D*	dt_posttreatment_scan*	act_time_A*
28	1	7
Units: d, Default: 28, Range: 0-...	Units: d, Default: 1, Range: 0-...	Default: 7
act_time_B*	miRNA_expression_data*	input_metainage*
0.4		

Fig 7. Required input parameters of the selected hypermodel.

CRAF :: Clinical Research Application Framework

GO BACK

EXECUTE

Cancer Topic Selection (Pick one) > NEPHROBLASTOMA > Patient Selection > Hypermodel for the selected Patient

Nephroblastoma multimodeller hypermodel_v1_0

INPUT OUTPUT

Input parameters

Show required Show editable

sim_ancillaries	sim_ancillaries_timestep	sim_ancillaries_timestep	vor_time_A*
0.05	0.01	0.01	7
Default: 0.05, Range: 0-1	Default: 0.01, Range: 0-1	Default: 0.01, Range: 0-1	Units: d, Default: 7, Range: 0-...
vor_time_B*	vor_time_C*	vor_time_D*	dt_posttreatment_scan*
14	21	28	1
Units: d, Default: 14, Range: 0-...	Units: d, Default: 21, Range: 0-...	Units: d, Default: 28, Range: 0-...	Units: d, Default: 1, Range: 0-...
output_dir	act_time_A*	seed_timestep_multiplier	act_time_B*
./wills_oncosimulator/output_files	7	0.31	21
Default: ./wills_oncosimulator/output_files	Default: 7	Default: 0.31, Range: 0-1	Units: d, Default: 21, Range: 0-...
sim_direction_multiplier	sim_direction_multiplier	model_time_multiplier	model_time_multiplier
0.54	0.54	20	20
Default: 0.54, Range: 0-1	Default: 0.54, Range: 0-1	Default: 20, Range: 10-30	Default: 20, Range: 10-30
approx_time_multiplier	approx_time_multiplier	n_cells_per_cell	sim_ancillaries_timestep
6	6	7	96
Default: 6, Range: 1-15	Default: 6, Range: 1-15	Default: 7, Range: 1-10	Units: d, Default: 96, Range: 20-150

Fig 8. All input parameters of the selected hypermodel.

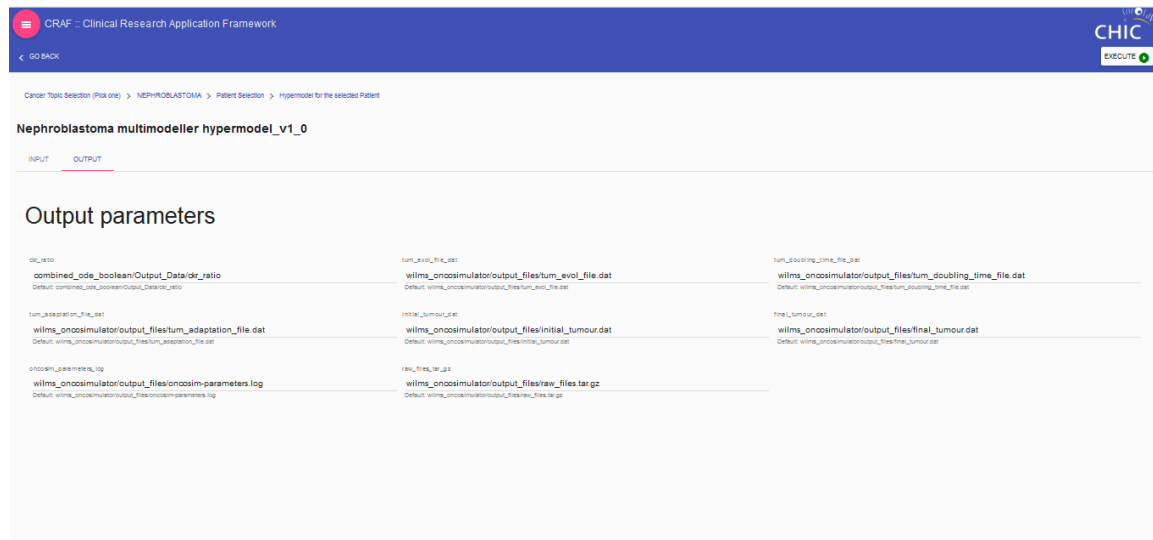


Fig 9. Output files of the selected hypermodel.

Step 6: The user can proceed to the execution of the model by clicking the "Execute" button on the right side of the screen. A pop-up window notifies the user about the status of the submitted execution (successful initialization of the execution of the hypermodel or failure to start) (Fig 10).

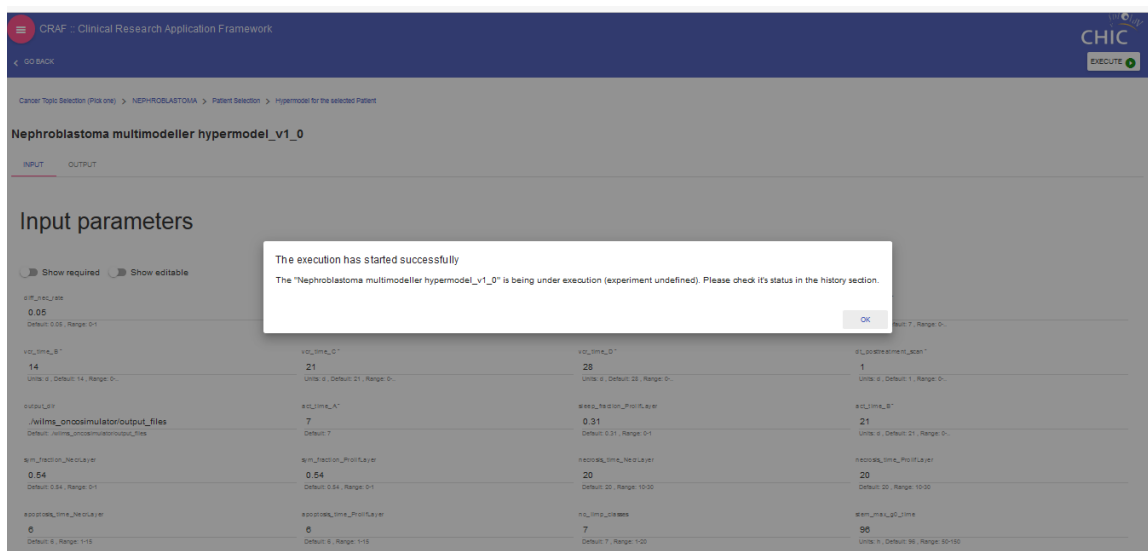


Fig 10. Pop up window with the status of the execution

Step 7: After the user clicks OK the dialog window, the execution history appears with the list of previous and current executions (Fig 11) performed by the logged in user. The status of each execution (failure to start, currently running, failed, successful) is depicted by the use of a corresponding symbol.

Id	Started	End	Model	Patient	Description	Status
900	2017/04/20 22:53	23:07	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
905	2017/04/20 22:40	22:51	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
904	2017/04/20 22:28	22:38	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
903	2017/04/20 22:18	22:20	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
902	2017/04/20 22:03	22:12	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
901	2017/04/20 21:53	22:03	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
900	2017/04/20 21:40	21:48	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
909	2017/04/20 21:32	21:39	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
908	2017/04/20 21:13	21:21	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
906	2017/04/20 21:05	21:12	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
905	2017/04/20 20:51	21:01	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓

Fig 11. List of executions (History).

Step 8: Once an execution is completed and its status is updated to completed, the user can launch the “Create Report” and “Output” tabs which are now enabled (Fig 12). Upon clicking the “Outputs” button, a window appears which displays information regarding the selected execution (Fig 13) and provides the ability to the user to download the output files of the hypermodel by clicking the download button (Fig 14, 15).

Id	Started	End	Model	Patient	Description	Status
900	2017/04/20 22:53	23:07	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
905	2017/04/20 22:40	22:51	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
904	2017/04/20 22:28	22:38	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
903	2017/04/20 22:18	22:20	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
902	2017/04/20 22:03	22:12	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
901	2017/04/20 21:53	22:03	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
900	2017/04/20 21:40	21:48	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
909	2017/04/20 21:32	21:39	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
908	2017/04/20 21:13	21:21	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
906	2017/04/20 21:05	21:12	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓
905	2017/04/20 20:51	21:01	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	✓

Fig 12: Tabs for launching outputs of completed executions.

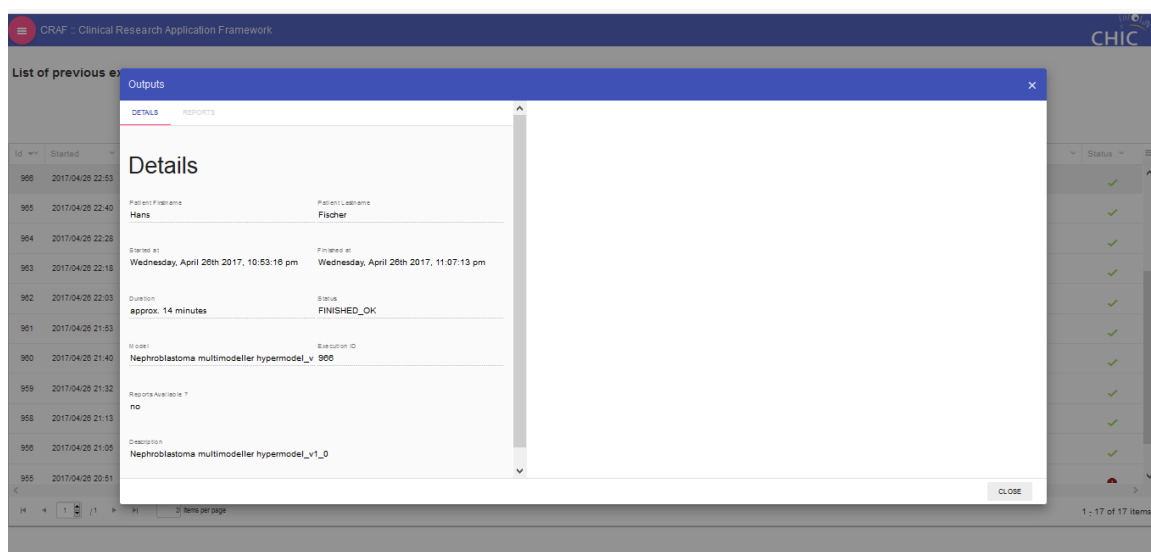


Fig 13. Outputs window: Details tab

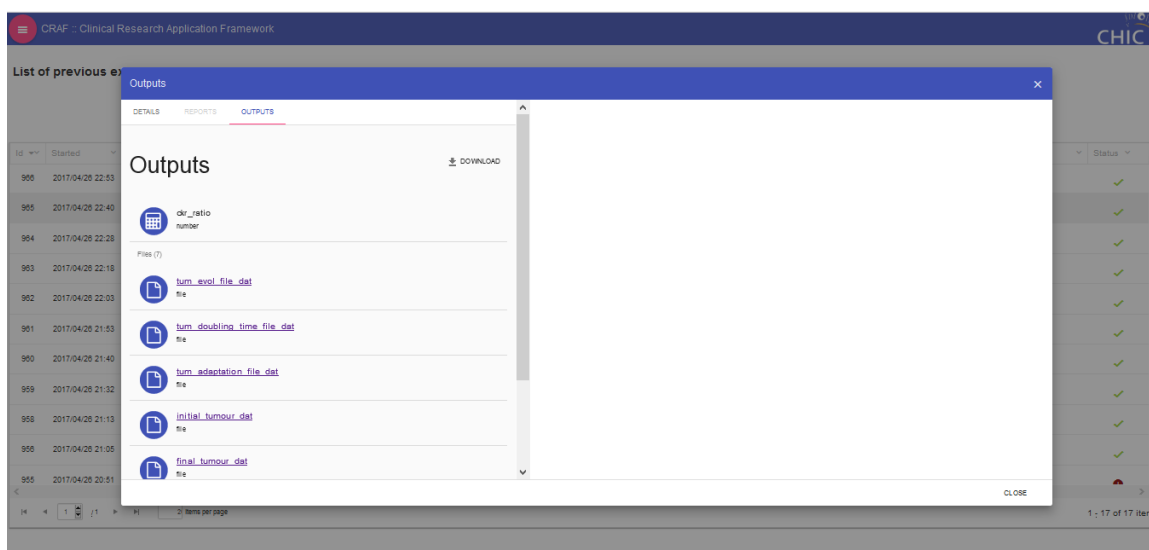


Fig 14. Outputs window: Outputs tab

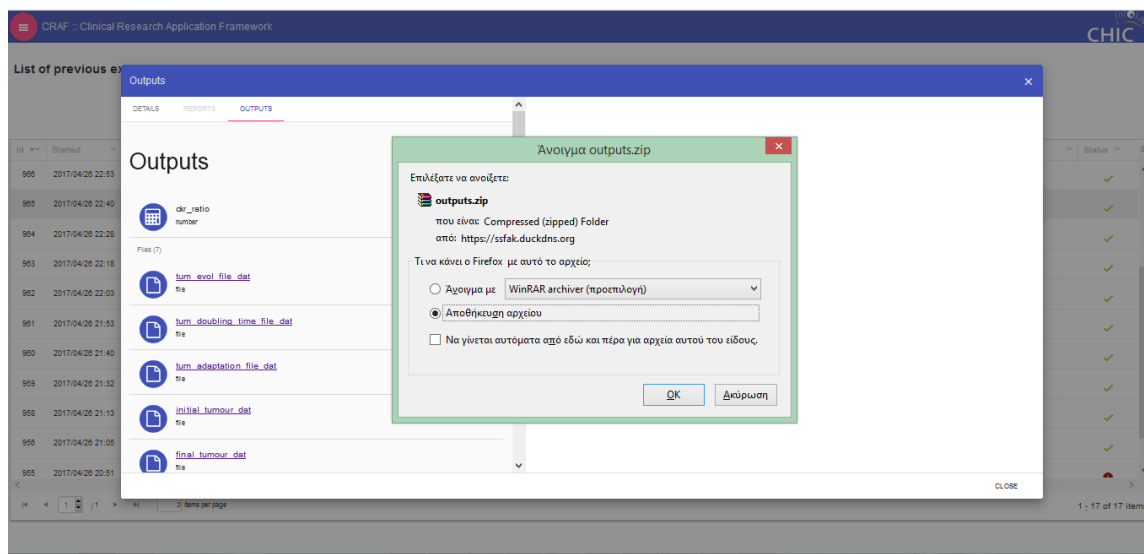


Fig I5. Downloading of output files

Step 9: The user can select the “Create report” tab and open or download it in a pdf format. The outline of the multipage report is depicted in Fig I6.

In silico study of cancer response to treatment

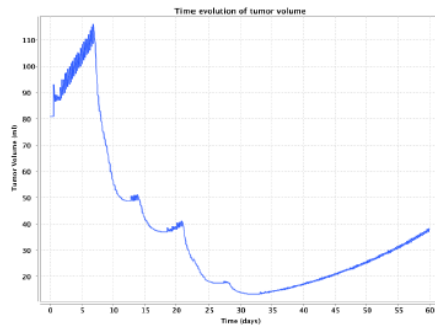
Patient Name: Fischer, Hans
Date of birth: [Not available]
Started at: 2017-04-26 19:53 Finished at: 2017-04-26 20:07

Clinical question:

Will a given nephroblastoma in a patient respond to pre-operative chemotherapy by tumour shrinkage, yes or no?
Simulated Tumour Volume reduction percentage: 53.02 %

Simulation predictions

Time evolution of simulated tumor volume:

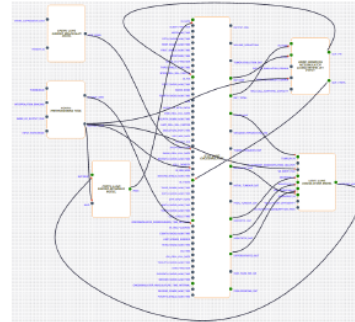


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Hypermodel Description

Nephroblastoma hypermodel description



The CHIC project

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Input values of hypermodel parameters

Fraction of differentiated cells dying through necrosis, per unit time.: 0.05
Fraction of the stem cells having just left dormant phase (G0) that re-enter active cell cycle at G1 phase: 0.01
Fraction of the limp cells having just left dormant phase (G0) that re-enter active cell cycle at G1 phase: 0.01
Time point of 1st administration of vincristine: 7
Time point of 2nd administration of vincristine: 14
Time point of 3rd administration of vincristine: 21
Time point of 4th administration of vincristine: 28
Time interval between the last administration and the end of simulation: 32
Path (including name) to the directory where the output files are stored: / wllms_oncosimulator/output_files
Time point of 1st administration of actinomycin: 7
Fraction of cells that enter G0 phase following mitosis, in the proliferative regions of the tumor: 0.31
: 21
Fraction of the stem cells that divide symmetrically, i.e. gives birth to two stem cells, in the necrotic regions of the tumor: 0.54
Fraction of the stem cells that divide symmetrically, i.e. gives birth to two stem cells, in the proliferative regions of the tumor: 0.54
Time needed for necrosis to be completed and its lysis products to be eliminated from the necrotic regions of the tumor: 20
Time needed for necrosis to be completed and its lysis products to be eliminated from the proliferating regions of the tumor: 20
Time needed for apoptosis to be completed and its products to be eliminated from the necrotic regions of the tumor: 6
Time needed for apoptosis to be completed and its products to be eliminated from the proliferative regions of the tumor: 6

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The maximum number of mitoses that a LIMP cell can perform before becoming terminally differentiated: 7

Maximum G0 (dormant) phase duration before stem cells enters necrosis or re-enters G1: 96

Maximum G0 (dormant) phase duration before stem cells enters necrosis or re-enters G1: 96

This parameter belongs to UPENN Nephroblastoma molecular model. This parameter is about a MinML file which contains the miRNA expression data.: [https:// cdr.chic-vph.eu/ api/ files/ 4557/ download](https://cdr.chic-vph.eu/api/files/4557/download)

This parameter belongs to the preprocessing tool. A valid metainage which contains the segmentations with the tumor value to be 255: [https:// cdr.chic-vph.eu/ api/ files/ 18280/ download](https://cdr.chic-vph.eu/api/files/18280/download)

This parameter belongs to the preprocessing tool. Name of output file which will contain the interpolated and cropped result: output

This parameter belongs to the preprocessing tool. Defines the threshold for the cropping (float between 0 and 1): 0.6

This parameter belongs to the preprocessing tool The spacing to be used for the isotropic interpolation.: 2

This parameter belongs to biomechanical hypomodel. Vtk-readable segmentation file with organ labels. Labels for Nephroblastoma scenario 1: healthy kidney 2: spine 3: surrounding organs 255: tumour (valid file system path relative to execution directory) : [https:// cdr.chic-vph.eu/ api/ files/ 18280/ download](https://cdr.chic-vph.eu/api/files/18280/download)

This parameter belongs to biomechanical hypomodel. Tumour cell concentration used for pressure computation. : 1000000

Cell cycle duration of cells through the phases of the active cell cycle (G1, S, G2, M-not including G0 phase) : 6

Fraction of cells that enter G0 phase following mitosis in the necrotic regions of the tumor: 0.31


This parameter belongs to nephroblastoma vasculature model. Diffusion coefficient for glucose. Default value 0.396 mm²/2hr from A HYBRID MODEL FOR TUMOR SPHEROID GROWTH IN VITRO I: THEORETICAL DEVELOPMENT AND EARLY RESULTS, Kim et al. 2007.: 0.396

This parameter belongs to nephroblastoma vasculature model. Rate of glucose consumption per cell per hour.: 7.6e-9

Spontaneous apoptosis rate of proliferating cells: 0.008

The CHIC project

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This parameter belongs to nephroblastoma vasculature model. Glucose concentration in non tumour regions. Output is normalized by this value. : 0.9

Apoptosis rate of differentiated tumor cells per unit time : 0.03

This parameter belongs to nephroblastoma molecular model. Anonymized ids of patients selected for the trial. In the model demo run precomputed results are available for only these patients: 4L3VB6HMD3LK52ZVLCF, SXIHGGQZ2GDYMITSSKON, 6Z34IQAMEQG2YZTU3S0E, ECCOAH3MWROQXV6BQOFH, SXIHGGQZ2GDYMITSSKON

Fig I6. Output report of the simulation results.

1.1.2 Configuring Nephroblastoma Hypermodels By with the Patient Selection

Step1: When the clinician selects the ‘Patient Specific’ option the full list of patients registered in CRAF appears (Fig 17). The clinician can select any patient and preview his/her info and available clinical/genomics/dicom series and timeline data (Fig 17).

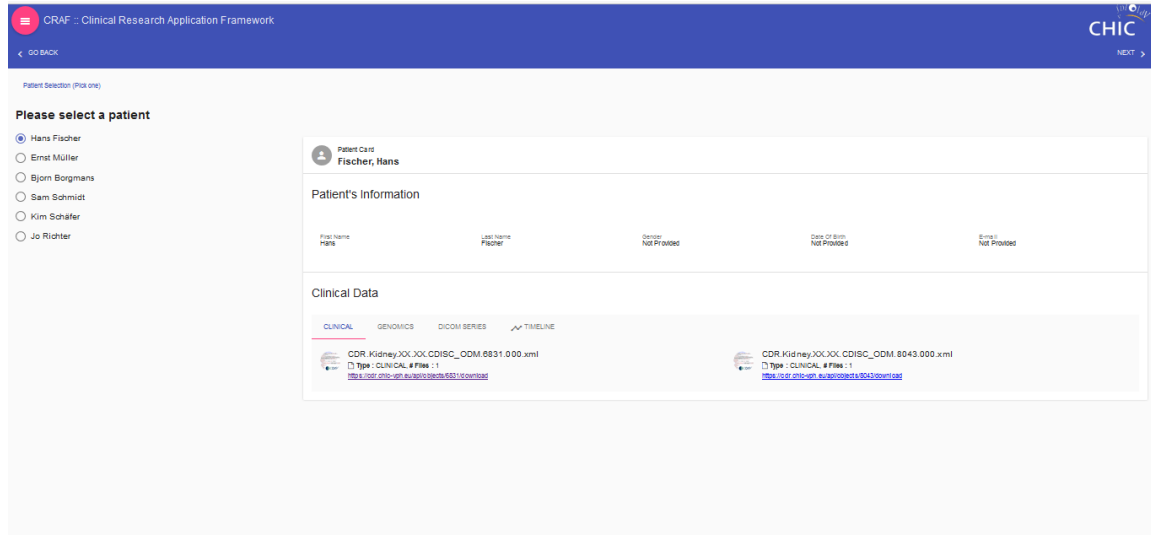


Fig 17. Viewing the dicom series of a selected patient

Step2: After selecting the patient of interest and clicking the ‘NEXT’ button, the available clinical questions relative to the patient and his/her cancer type are displayed (Fig 18). The clinical question ‘Will a given nephroblastoma in a patient respond to pre-operative chemotherapy by tumour shrinkage, yes or no?’ is chosen here for demonstration purposes.

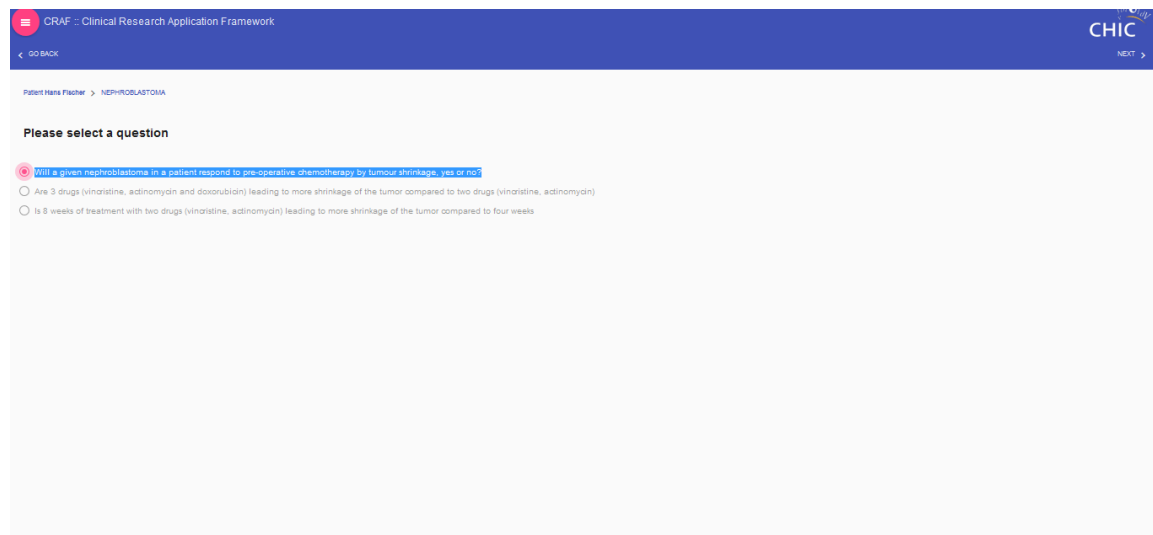


Fig 18. List of clinical questions considered related to the selected patient

Step 3: By clicking on the 'NEXT' button, the list of hypermodels addressing the cancer type of the selected patient for the specific clinical question are presented (Fig 19). The UNITO Nephroblastoma model is chosen this time and 'NEXT' is clicked.

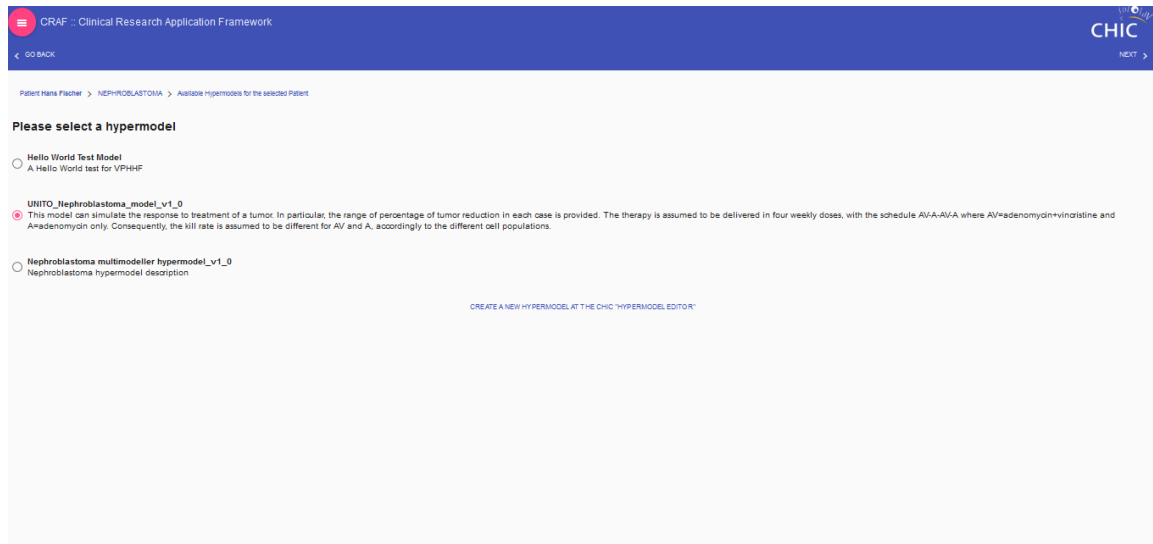


Fig. 19 Available nephroblastoma hypermodels for the chosen patient, cancer domain and clinical question. The UNITO_Nephroblastoma_model_v1_0 is selected

Step4: The clinician can view the inputs/outputs of the hypermodel (Fig 20, 21) and, if necessary, make corrections/changes to the input arguments before starting the execution of this hypermodel.

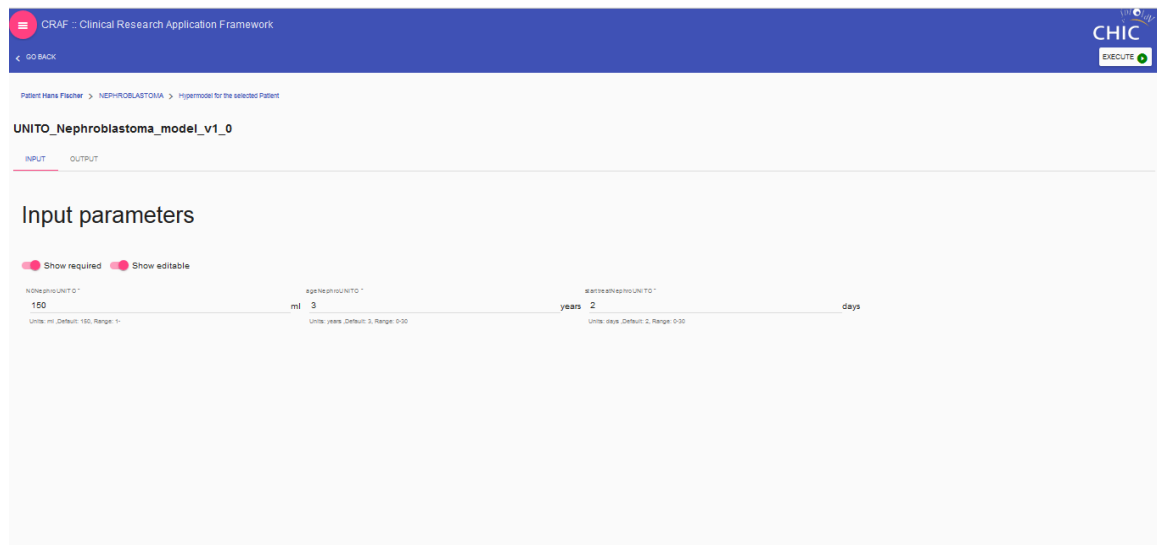


Fig 20. Input parameters of selected hypermodel

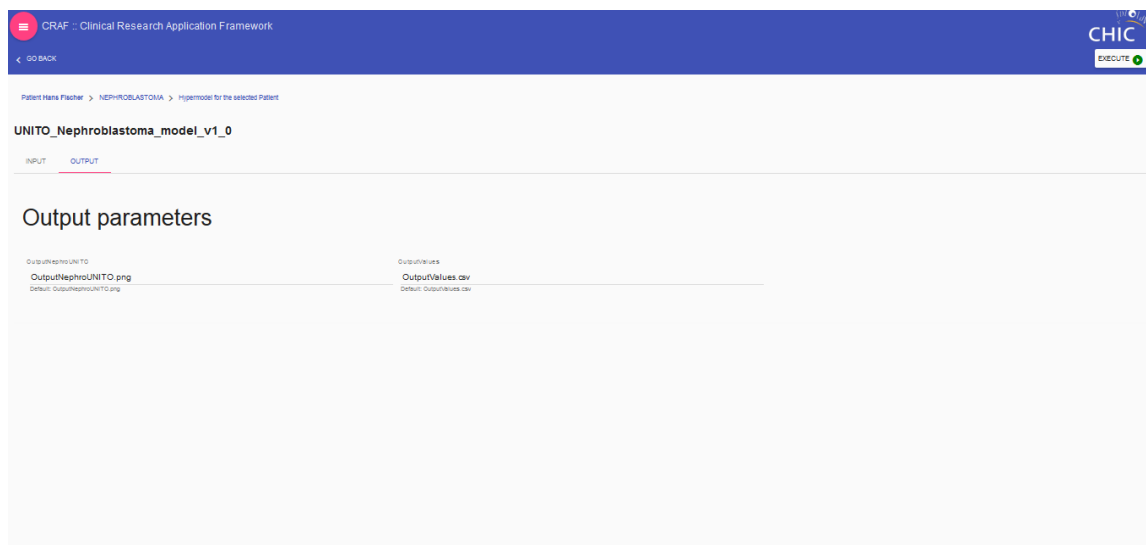


Fig 21. Output parameters of selected hypermodel

Step 5: The user can proceed to the execution of the model by clicking the "Execute" button on the right side of the screen. A pop-up window notifies the user about the status of the submitted execution (successful initialization of the execution of the hypermodel or failure to start) (Fig 22).

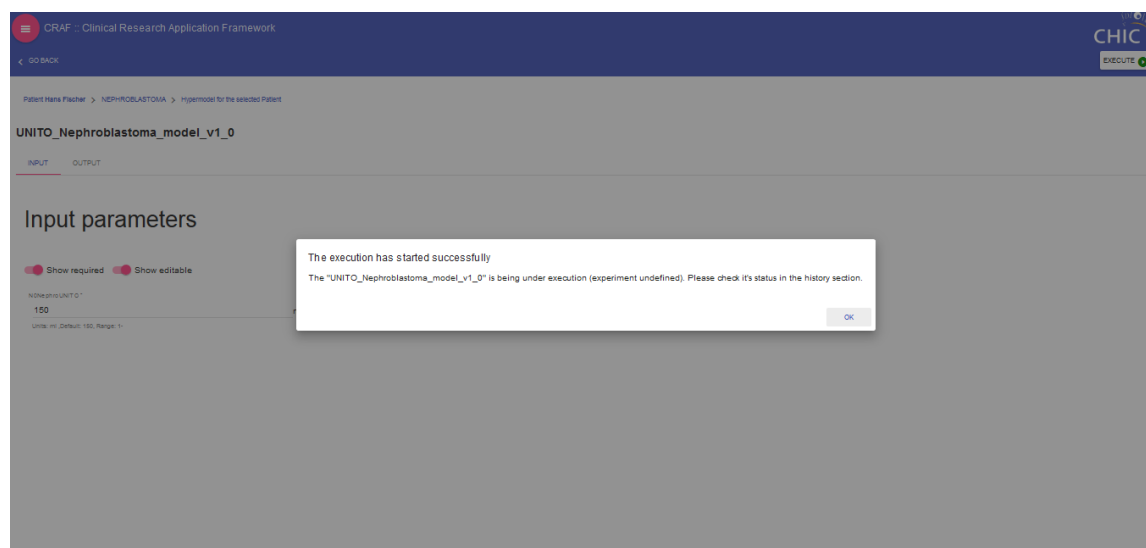


Fig 22. Pop up window with the status of the execution

Step 6: Upon execution completion, the user can view the details of the execution (Fig 23), download the produced output files (Fig 24, 25), as previously described, create, download and viewing the outcome report by clicking the create report button (Fig 26, 27).

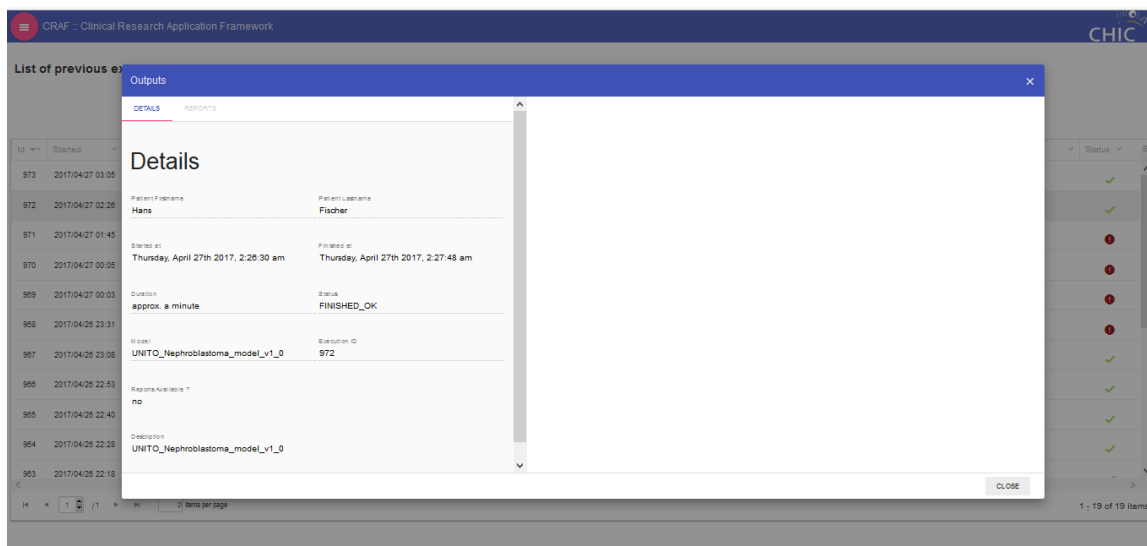


Fig 23. Viewing the details of the execution

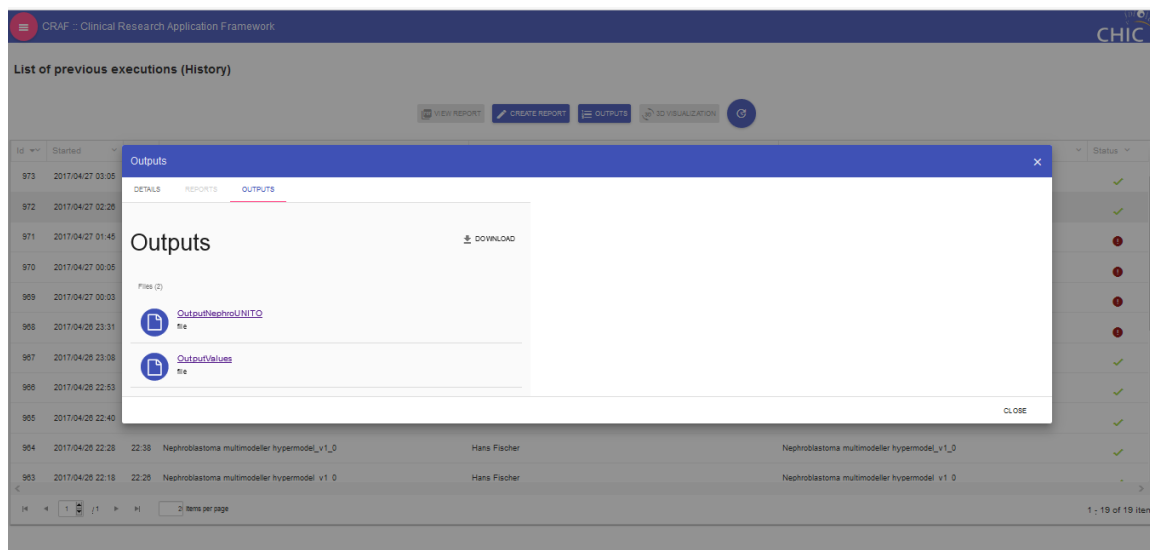


Fig 24. Viewing the output files of the execution

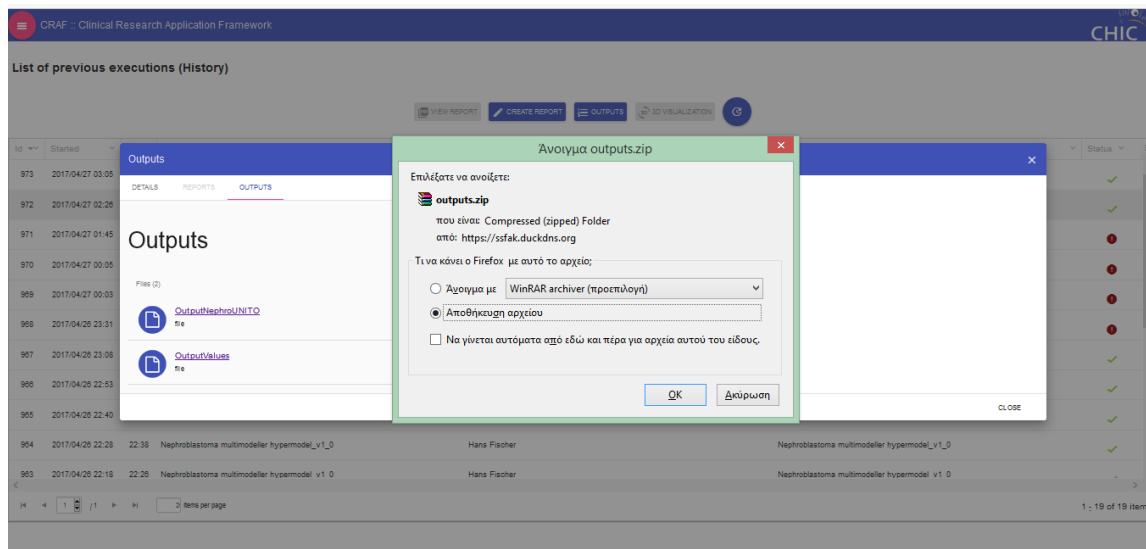


Fig. 25 Downloading the output files of the execution

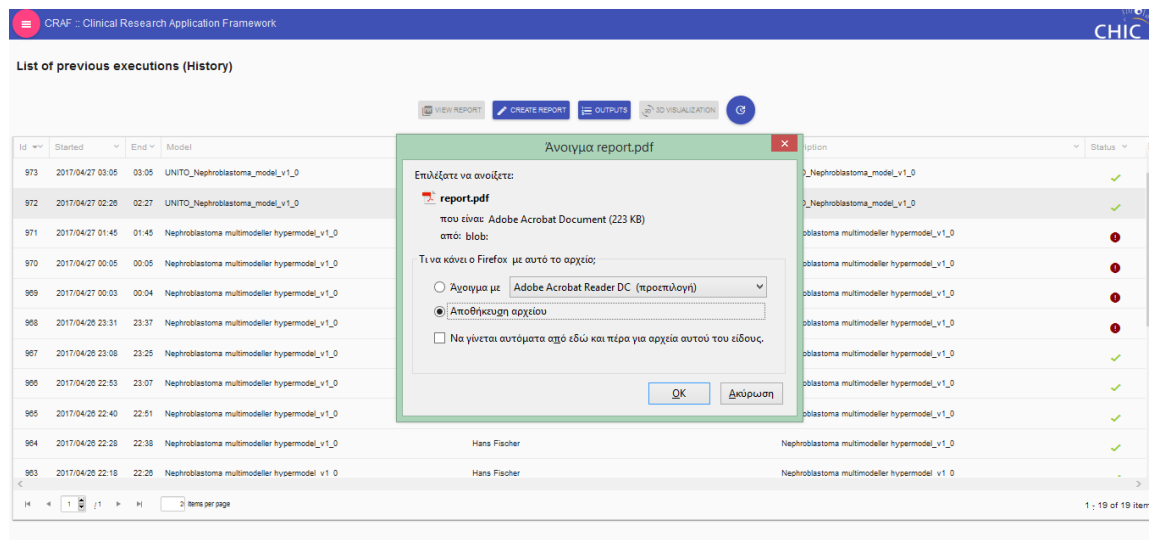


Fig. 26 Opening or download the report of the execution

In silico study of cancer response to treatment

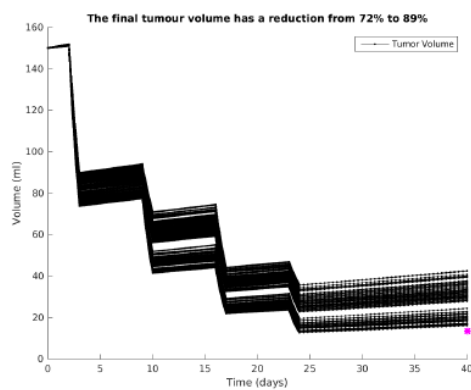
Patient Name: Fischer, Hans
Date of birth: [Not available]
Started at: 2017-04-26 23:26

Finished at: 2017-04-26 23:27

Clinical question:

Will a given nephroblastoma in a patient respond to pre-operative chemotherapy by tumour shrinkage, yes or no?

Simulation predictions

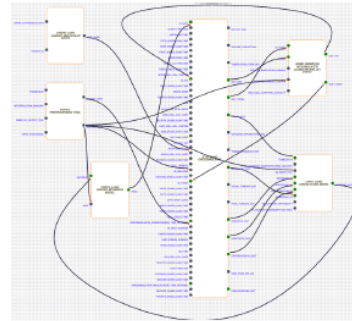


The CHIC project

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Hypermodel Description

This model can simulate the response to treatment of a tumor. In particular, the range of percentage of tumor reduction in each case is provided. The therapy is assumed to be delivered in four weekly doses, with the schedule AV-A-AV-A where AV=adenomycin+vincristine and A=adenomycin only. Consequently, the kill rate is assumed to be different for AV and A, accordingly to the different cell populations.



The CHIC project

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Input values of hypermodel parameters

Initial tumor volume (in ml): 150
age of the patient (in years) – mandatory: 3
number of days after which the treatment is started – optional: default value = 2 days: 2
the model provides the simulations of treatment changing the percentage of the three cell populations (epithelial, stromal and blastemal) with a step between 0 and 1 – optional: default value = 0.05: 0.05
If the clinician knows the type of the tumor (epithelial – 1, stromal – 2 or blastemal – 3), he/she can insert the value directly. In this case, the model will provide only one PDF file with only one simulation – optional: default value = 0 (all simulations): 0
If it is available, the final tumor volume after treatment (in ml) – optional: 13.422364
Number of days of treatment (more than 21) – optional: 40
Cell kill ratio using only 1 drug: 0.47
Cell kill ratio using 2 drugs: 0.63

The CHIC project

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Fig. 27 Viewing the report of the execution in pdf format

CHAPTER LC: THE NON SMALL CELL LUNG CANCER HYPERMODEL

(Please note that the numbering of sections, subsections, equations, figures and references within this chapter refers exclusively to the latter and is not applicable to other chapters of the document, If any of the above entities of another chapter is to be referred to, the chapter under consideration should also be mentioned through its two capital letter code)

I. The Non-Small Cell Lung Cancer Demonstrator

I.1 Execution through CRAF

Step 0: The clinician can configure and initiate Lung hypermodels' execution either by selecting "Domain specific" or "Patient specific" wizard (Fig I).

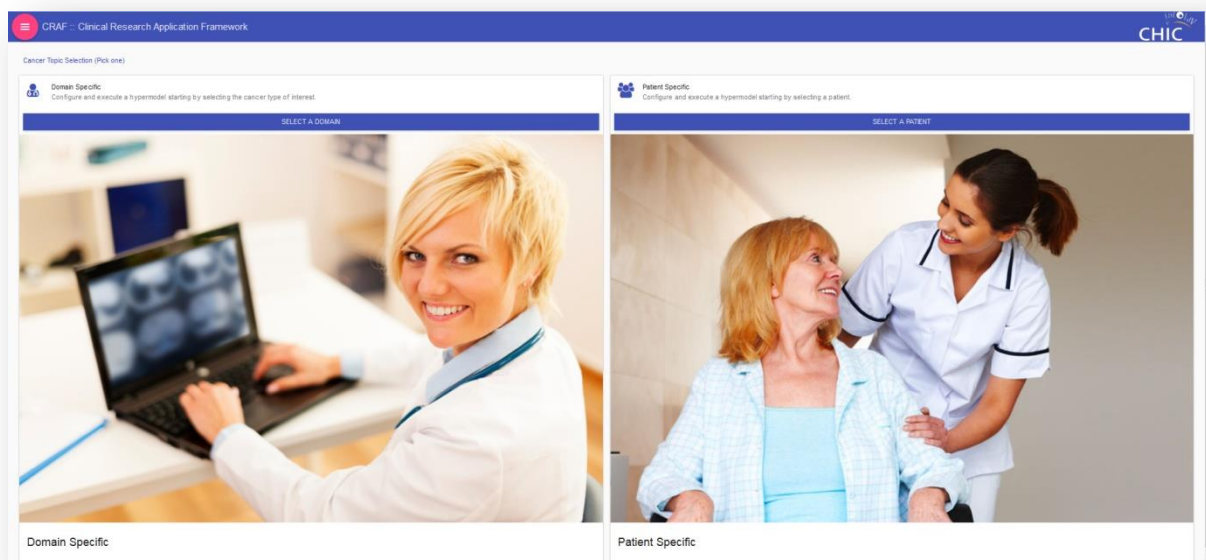


Fig I. Home page of CRAF

1.1.1 Configuring Lung Hypermodels Starting with the Domain Selection

Step1: When the clinician selects the ‘Domain Specific’ option the four cancer domains considered in CHIC appear (Fig 2).

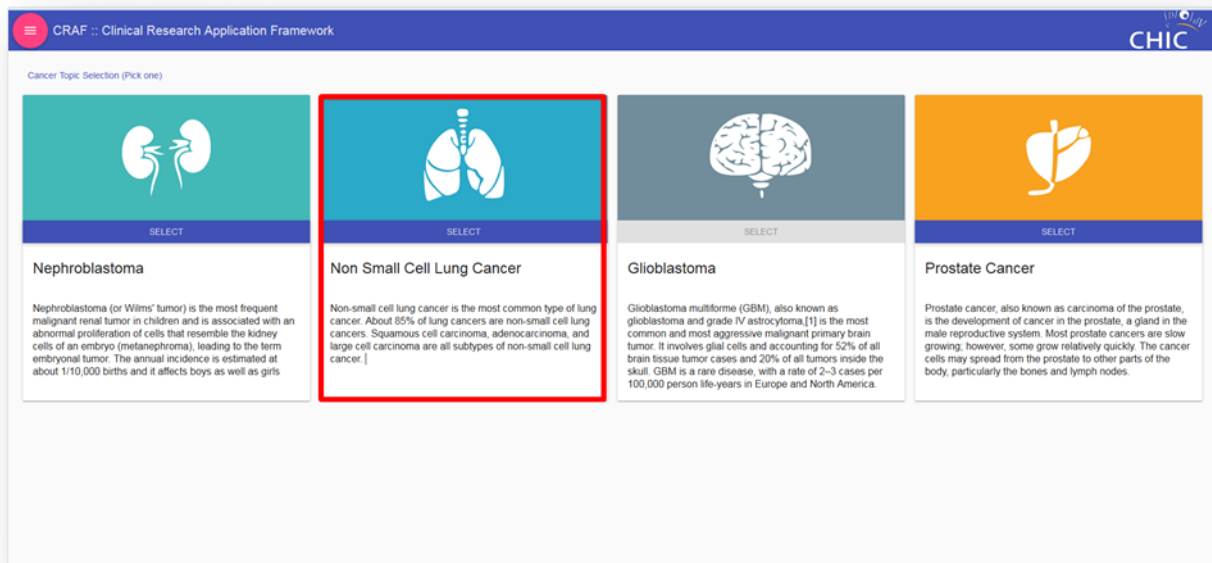


Fig 2. CHIC Cancer domains

Step2: By clicking on the ‘Non Small Cell Lung Cancer’ option two clinical questions appear (Fig 3). The clinical question ‘Will a Lung Cancer patient with NSCLC adenocarcinoma suffer from tumor recurrence after surgical resection?’ is chosen here for demonstration purposes.

The screenshot shows the CRAF (Clinical Research Application Framework) interface. At the top, there is a blue header bar with the CRAF logo on the left and the CHIC logo on the right. Below the header, there is a navigation bar with a 'GO BACK' button on the left and a 'NEXT' button on the right. The main content area is white and contains the text 'Cancer Topic Selection (Pick one) > LUNG'. Below this, there is a section titled 'Please select a question'. There are two radio button options: the first is 'Will a Lung Cancer patient with NSCLC adenocarcinoma suffer from tumor recurrence after surgical resection?' and the second is 'How much will be the imageable volume reduction of the tumor one year following the completion of tumor irradiation?'. The first option is selected.

Fig 3. Clinical questions for non-small cell lung cancer [(I) Will a Lung Cancer patient with NSCLC adenocarcinoma suffer from tumor recurrence after surgical resection? (II) How much will be the imageable volume reduction of the tumor one year following the completion of tumor irradiation?]

Step 3: After clicking on the 'NEXT' button, the list of all patients registered in CRAF is shown (Fig 4). However, only the non-small lung cancer patients are enabled, i.e. their info/clinical data can be viewed and they can be chosen for the next step. By using 'show all patients' switch, the disabled patients can be hidden (Fig 5).

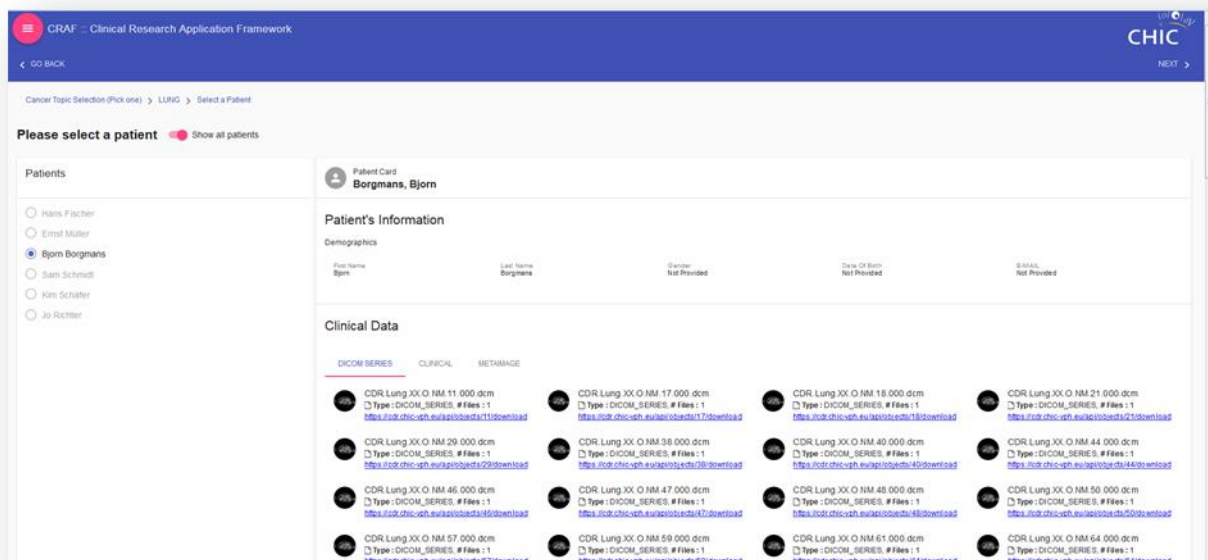


Fig 4. List of patients registered to non-small cell lung cancer domain

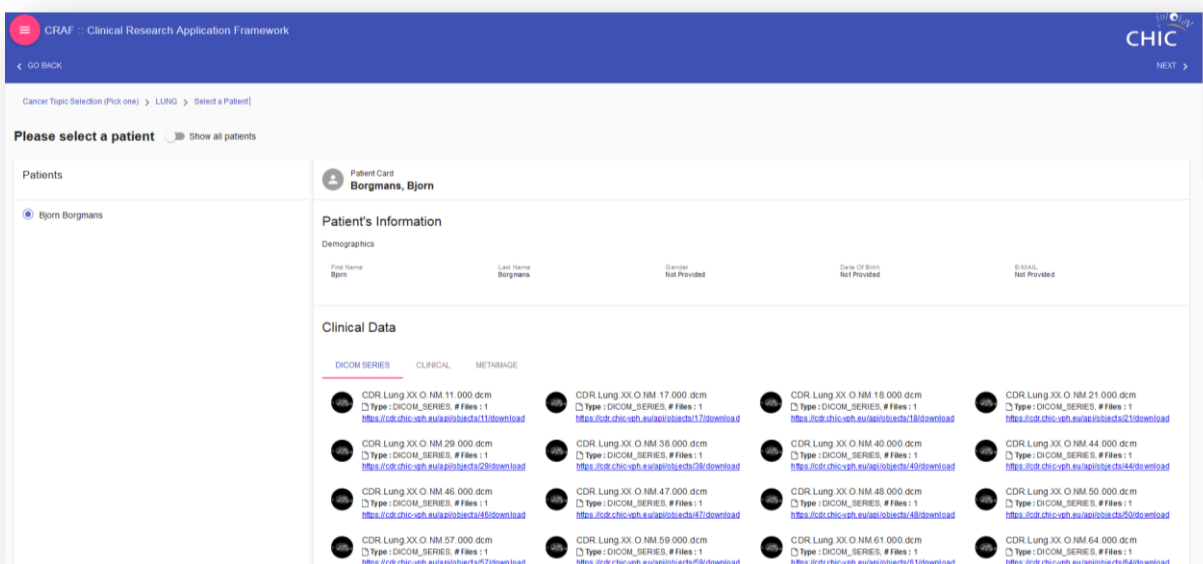


Fig 5. List of patients with 'show all patients' switch disabled.

Step4: As the clinician picks up a patient and clicks on the ‘NEXT’ button, the associated list of hypermodels appears (Fig 6). Only one statistical hypermodel associated with the selected clinical question and patient is currently uploaded on CRAF.

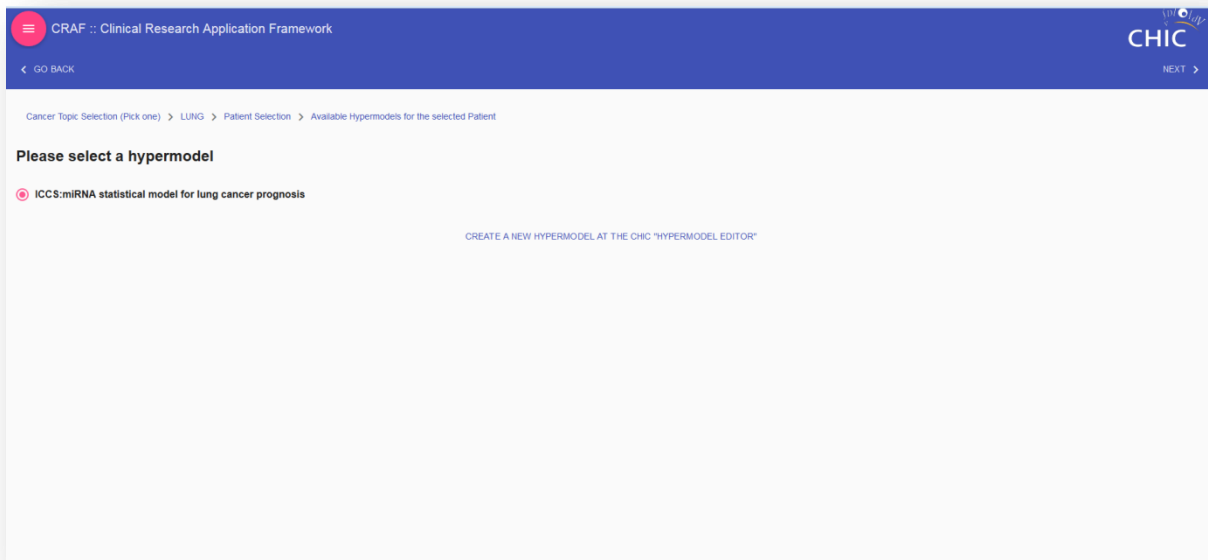


Fig 6. Available lung hypermodels for the chosen cancer domain, question and patient: miRNA statistical model for lung cancer prognosis

Step5: After clicking on the ‘NEXT’ button, the clinician can view the input and output parameters of the selected hypermodel (Fig 7, 8, 9) and, if necessary, can make corrections/changes to the input arguments before starting the execution of this hypermodel. In order not to distract the clinician with excess information, only the required input arguments is shown (Fig 7). However the complete list of input arguments can appear using the corresponding switches (Fig 8).

CRAF :: Clinical Research Application Framework

GO BACK

Cancer Topic Selection (Pick one) > LUNG > Patient Selection > Hypermodel for the selected Patient

ICCS:miRNA statistical model for lung cancer prognosis

INPUT OUTPUT

Input parameters

Show required Show editable

in_miRNA_file*

<https://cdr.chic-vph.eu/api/files/18268/download>

Default: <https://cdr.chic-vph.eu/api/files/18268/download>

Fig 7. Required input parameters of the miRNA statistical model for lung cancer prognosis

CRAF :: Clinical Research Application Framework

GO BACK

Cancer Topic Selection (Pick one) > LUNG > Patient Selection > Hypermodel for the selected Patient

ICCS:miRNA statistical model for lung cancer prognosis

INPUT OUTPUT

Input parameters

Show required Show editable

in_miRNA_file*	outfolder	classifier
https://cdr.chic-vph.eu/api/files/18268/download	/	/ICCS_LungStatisticalModel/config/BayesianClassifier.mat
Default: https://cdr.chic-vph.eu/api/files/18268/download	Default: /	Default: /ICCS_LungStatisticalModel/config/BayesianClassifier.mat

Fig 8. All input parameters of the miRNA statistical model for lung cancer prognosis

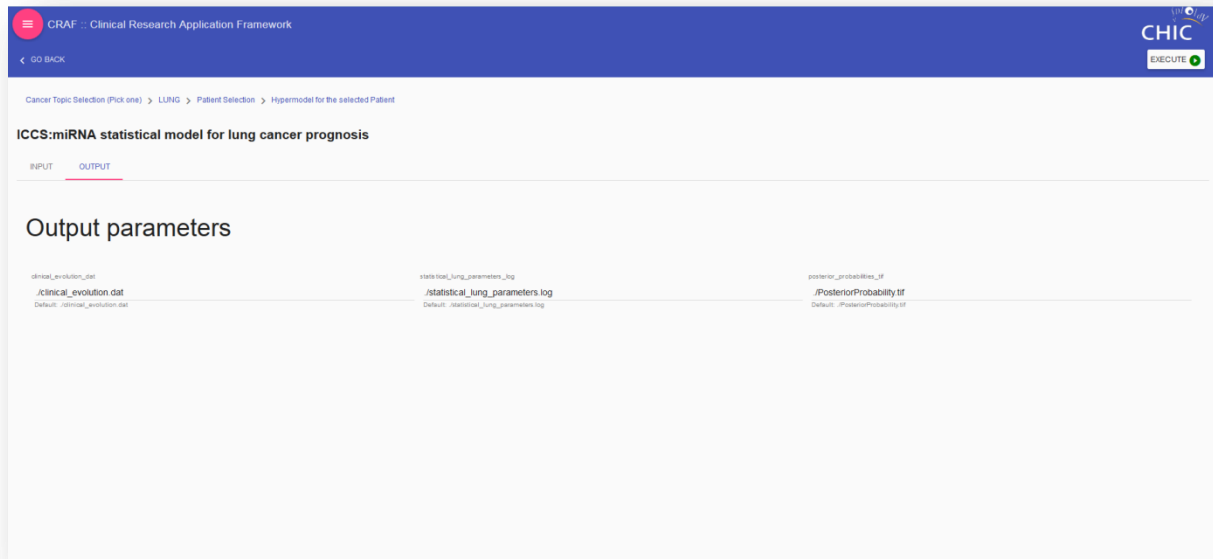


Fig 9. Output files of the miRNA statistical model for lung cancer prognosis

Step 6: The user can proceed to the execution of the model by clicking the "Execute" button (Fig 10). A window appears which notifies the user about the status of its execution (successful initialization of the execution of the hypermodel or failure to start) (Fig 11). After the user closes the dialog window, the execution history appears with the list of previous and current execution (Fig 12) performed by the logged in user. The status of each execution (failure to start, currently running, failed, successful) is evident by the use of the appropriate mark.

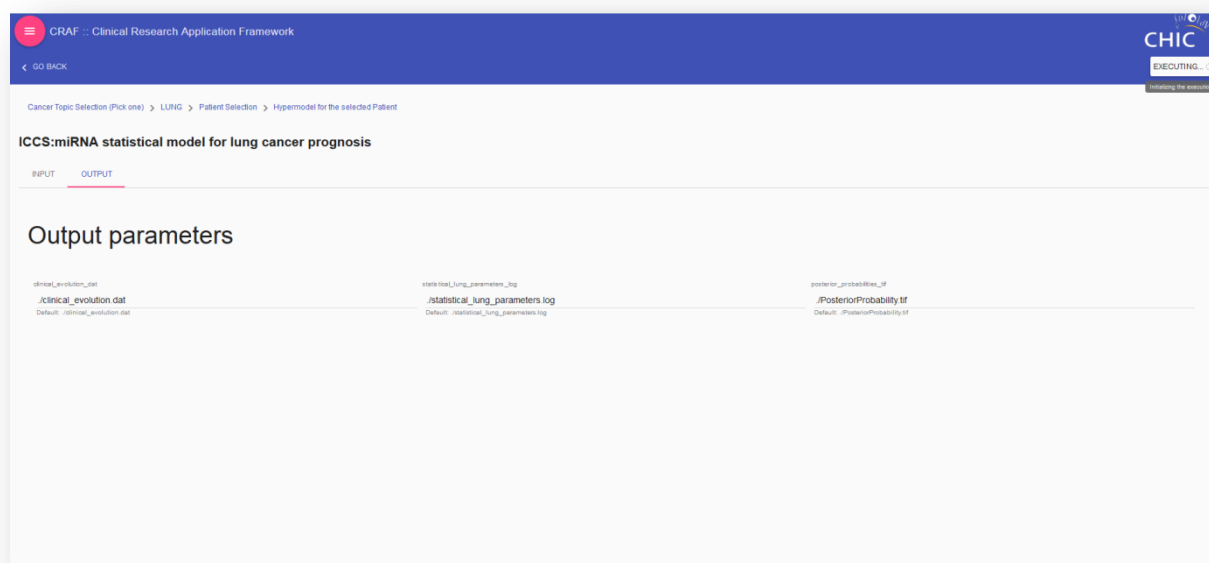


Fig 10. Execution of the hypermodel by clicking the "Execute" button

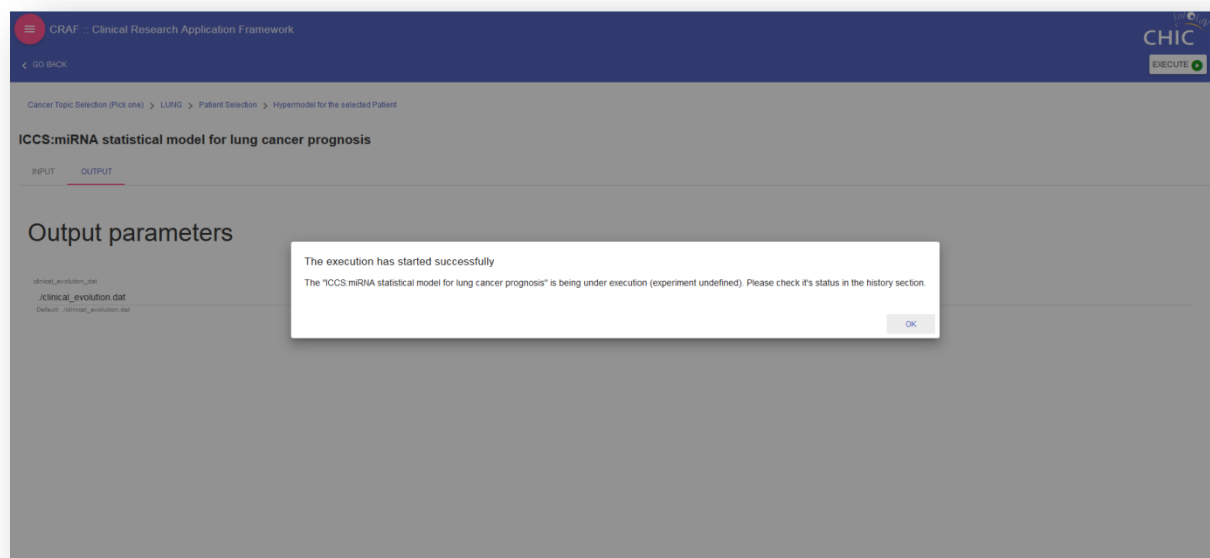


Fig 11. Pop up window with the status of the execution

ID	Started	End	Model	Patient	Description	Cancer Type	Status
1054	2017/05/05 10:22		ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	
1053	2017/05/05 09:59	10:00	ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1052	2017/05/05 08:51	08:52	ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1051	2017/05/05 02:35		Prostate Cancer Hypermodel	Sam Schmidt	Prostate Cancer Hypermodel	Prostate Cancer	⚠
1050	2017/05/05 02:23	02:23	ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1049	2017/05/04 18:38	18:42	Lung Cancer multimodeller hypermodel_v1_0	Bjorn Borgmans	Lung Cancer multimodeller hypermodel_v1_0	Non Small Lung Cancer	✓
1047	2017/05/04 18:24	18:25	ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	❌
1014	2017/05/01 01:11	02:07	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	Nephroblastoma	✓
1013	2017/04/30 12:20	12:21	Lung Cancer multimodeller hypermodel_v1_0	Bjorn Borgmans	Lung Cancer multimodeller hypermodel_v1_0	Non Small Lung Cancer	❌

Fig 12. List of executions (History) while an execution is running

Step 7: Once the execution is completed, its status is updated (Fig 13). Upon clicking the Outputs button, a dialog window appears which displays information regarding the selected execution (Fig 14) and gives the possibility to the user to download the output files of the hypermodel by clicking the download button (Fig 15, 16).

CHIC Clinical Research Application Framework

LIST OF PREVIOUS EXECUTIONS STATISTICS

VIEW REPORT CREATE REPORT OUTPUTS ADD TO COMPARE

Check for new results (force update)

ID	Started	End	Model	Patient	Description	Cancer Type	Status
1054	2017/05/05 10:22		ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1053	2017/05/05 09:59	10:00	ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1052	2017/05/05 08:51	08:52	ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1051	2017/05/05 02:35		Prostate Cancer Hypermodel	Sam Schmidt	Prostate Cancer Hypermodel	Prostate Cancer	⚠
1050	2017/05/05 02:23	02:23	ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1049	2017/05/04 18:38	18:42	Lung Cancer multimodeller hypermodel_v1_0	Bjorn Borgmans	Lung Cancer multimodeller hypermodel_v1_0	Non Small Lung Cancer	✓
1047	2017/05/04 18:24	18:25	ICCS miRNA statistical model for lung cancer prognosis	Bjorn Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✗
1014	2017/05/01 01:11	02:07	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	Nephroblastoma	✓
1013	2017/04/30 12:20	12:21	Lung Cancer multimodeller hypermodel_v1_0	Bjorn Borgmans	Lung Cancer multimodeller hypermodel_v1_0	Non Small Lung Cancer	✗

1 - 20 of 72 items

Fig I3. List of previous executions (History)

CHIC Clinical Research Application Framework

LIST OF PREVIOUS EXECUTIONS

DETAILS REPORTS OUTPUTS

Details

Patient Firstname	Bjorn	Patient Lastname	Borgmans
Started at	Friday, May 5th 2017, 10:22:02 am	Finished at	Friday, May 5th 2017, 10:22:53 am
Duration	approx. a minute	Status	FINISHED_OK
Model	ICCS miRNA statistical model for lung cancer prognosis	Execution ID	1054
Reports Available ?	no		
Description	ICCS miRNA statistical model for lung cancer prognosis		

CLOSE

1 - 20 of 72 items

Fig I4. Outputs window: Details tab

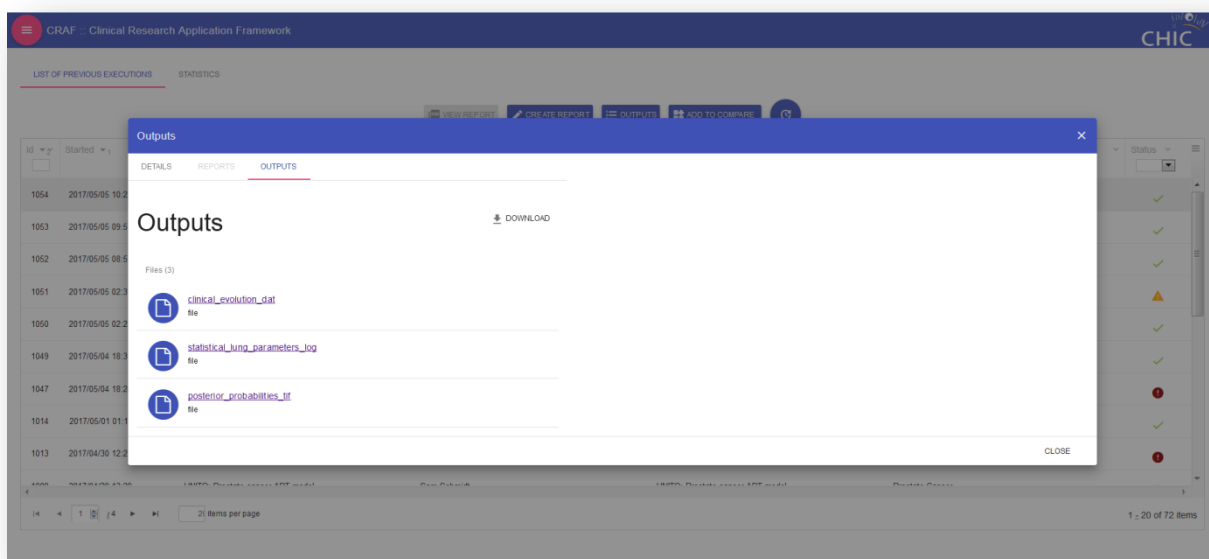


Fig 15. Outputs window: Outputs tab

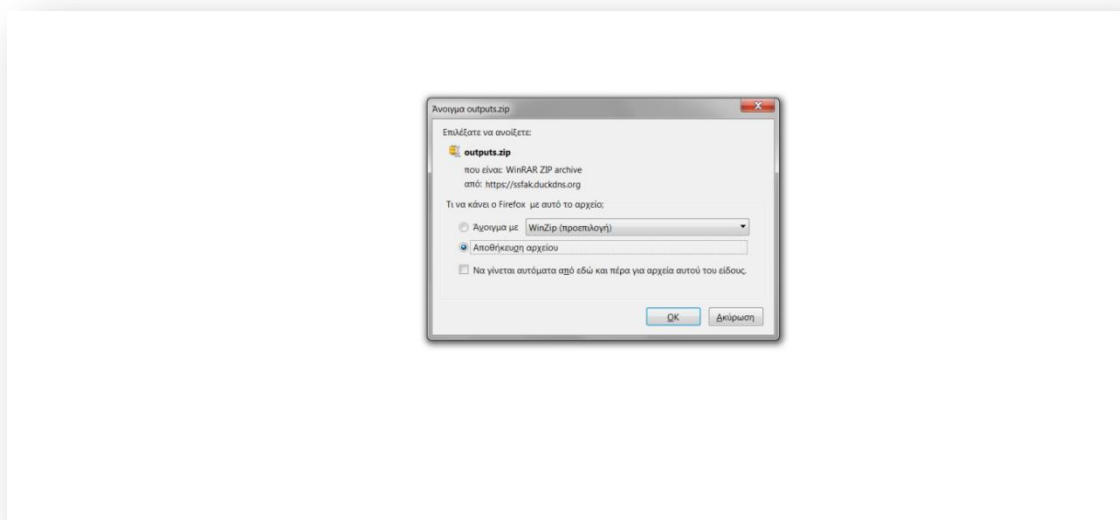


Fig 16. Downloading of output files

I.1.2 Configuring Lung Hypermodels Starting with the Patient Selection

Step I: When the clinician selects the ‘Patient Specific’ option the full list of patients registered in CRAF appears (Fig I7). The clinician can select any patient and view his/her data (Fig I7, I8).

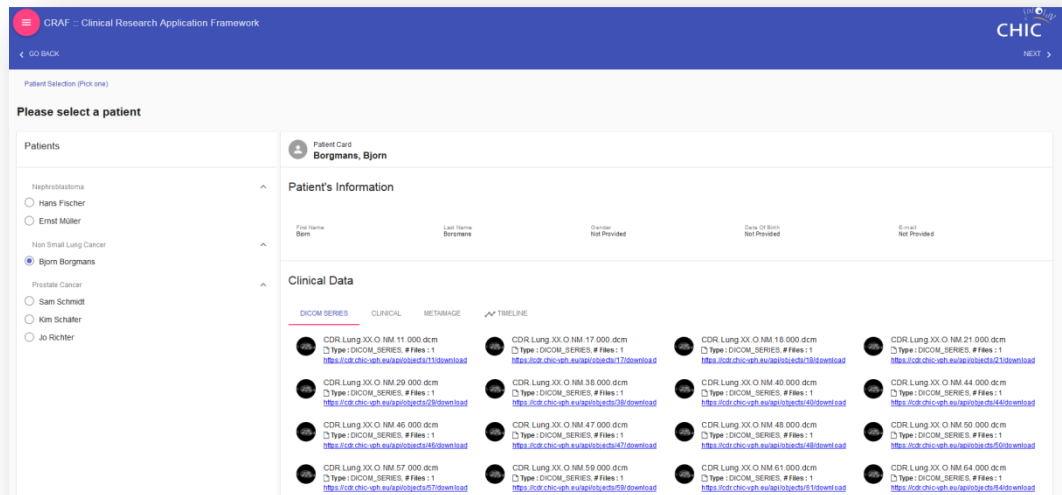


Fig I7. Viewing the dicom series of a selected patient

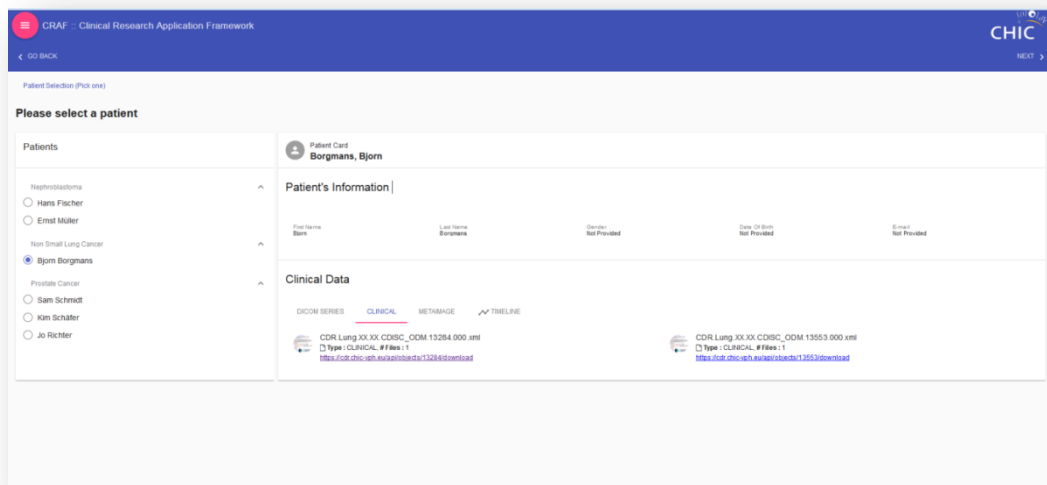
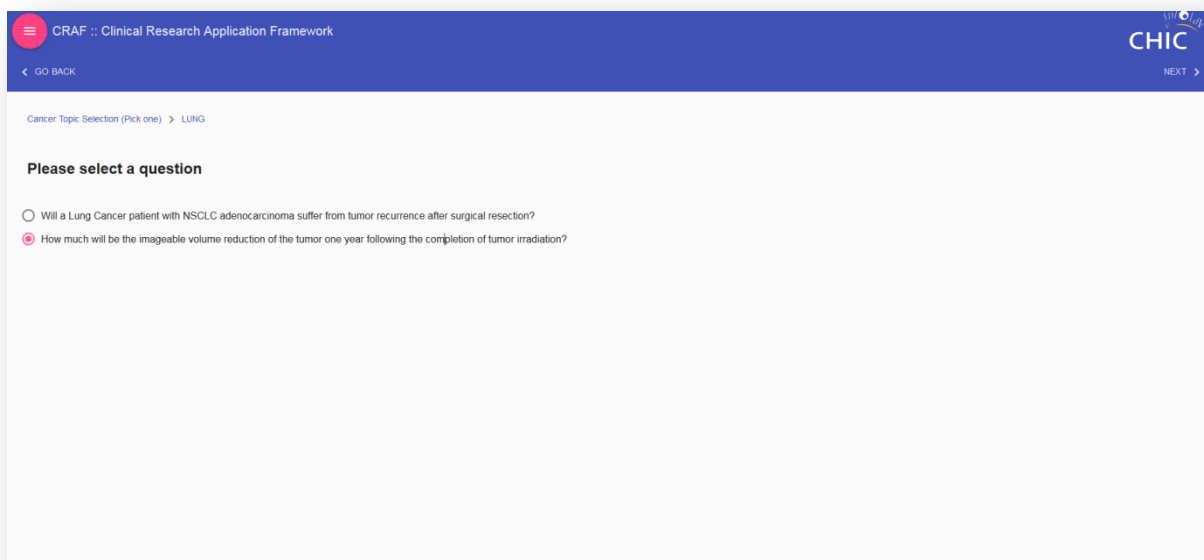


Fig I8. Viewing the clinical data of a selected patient

Step2: After selecting the non small cell lung cancer patient and clicking the ‘NEXT’ button, the clinical questions relative the patient and his/her cancer type are displayed (Fig 19). The clinical question ‘How much will be the imageable volume reduction of the tumor one year following the completion of tumor irradiation?’ is chosen here for demonstration purposes.



The screenshot shows the CRAF (Clinical Research Application Framework) interface. At the top, there is a blue header bar with the CRAF logo on the left and the CHIC logo on the right. Below the header, there is a breadcrumb trail: "Cancer Topic Selection (Pick one) > LUNG". The main content area is titled "Please select a question" and contains two radio button options. The first option is "Will a Lung Cancer patient with NSCLC adenocarcinoma suffer from tumor recurrence after surgical resection?". The second option is "How much will be the imageable volume reduction of the tumor one year following the completion of tumor irradiation?", which is selected with a red radio button.

Fig 19. List of clinical questions related to the selected patient

Step 3: By clicking on the ‘NEXT’ button, the list of hypermodels related to the selected patient and clinical question is shown (Fig 20).

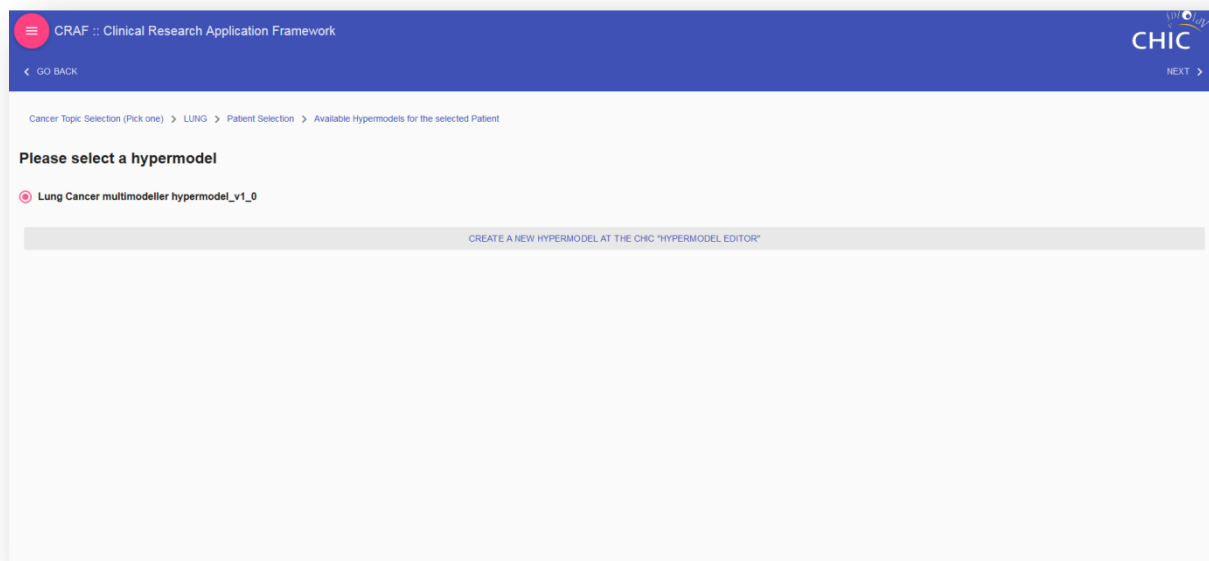
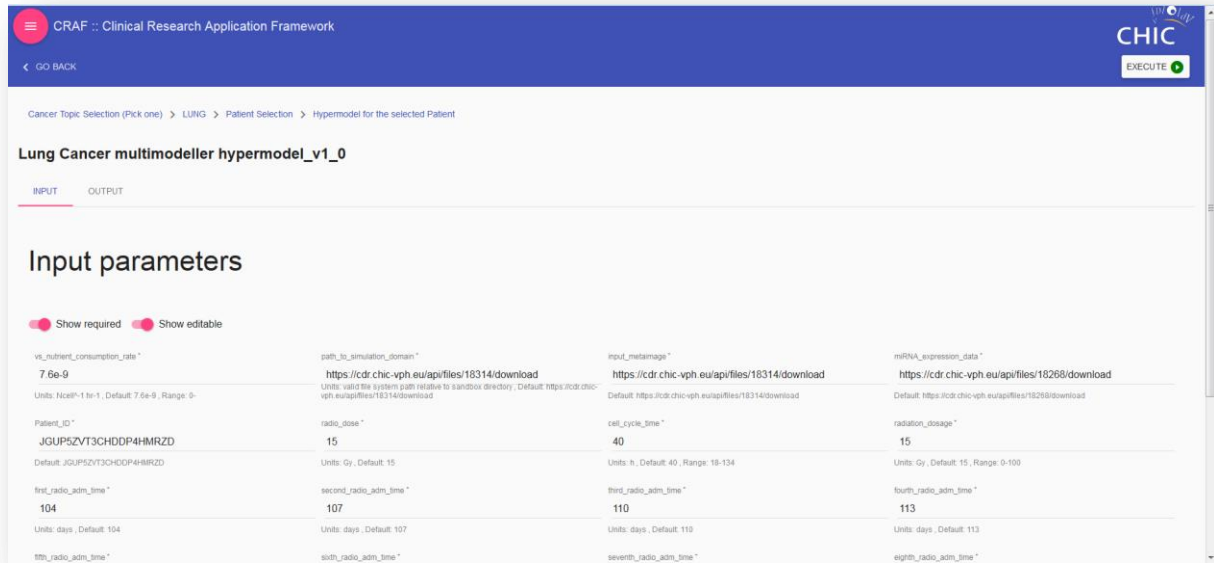


Fig 20. Selection of the available hypermodels for the chosen patient and the chosen question

Step4: After selecting the Lung cancer multimodeller hypermodel and clicking on the 'NEXT' button, the clinician can view the inputs/outputs of the hypermodel (Fig 21, 22, 23), the inputs' description (Fig 24) and, if necessary, make corrections/changes to the input arguments before starting the execution of this hypermodel.



CRAF :: Clinical Research Application Framework

GO BACK

Cancer Topic Selection (Pick one) > LUNG > Patient Selection > Hypermodel for the selected Patient

Lung Cancer multimodeller hypermodel_v1_0

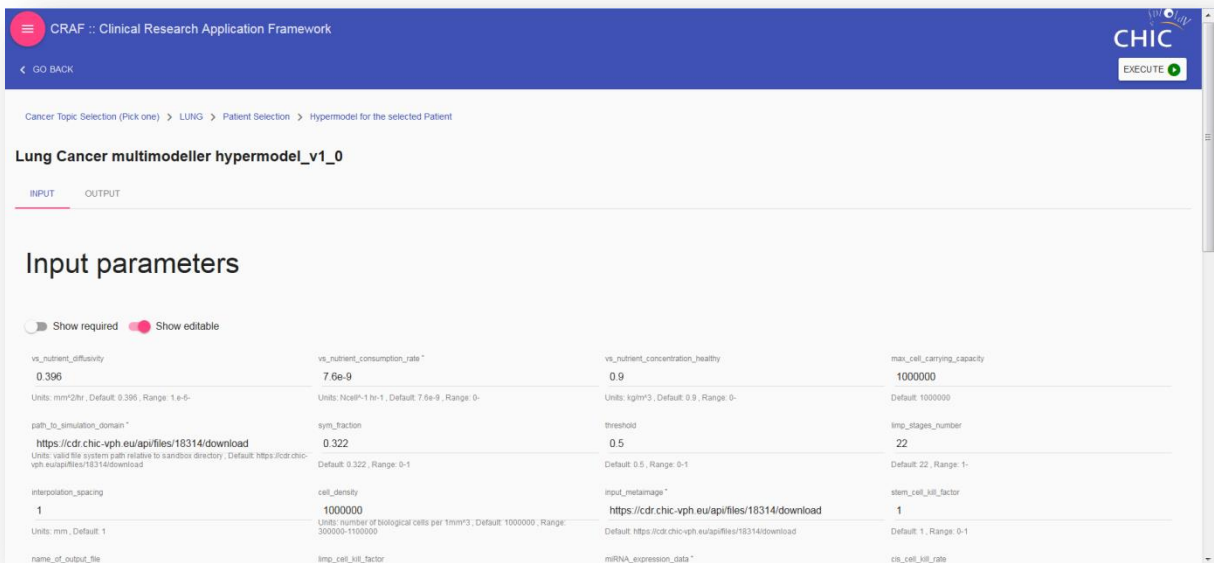
INPUT OUTPUT

Input parameters

Show required Show editable

vs_nutrient_consumption_rate * 7.6e-9 Units: NcicP-1 to-1, Default: 7.6e-9, Range: 0-	path_to_simulation_domain * https://cdr.chic-vph.eu/api/files/18314/download Units: valid file system path relative to a sandbox directory, Default: https://cdr.chic-vph.eu/api/files/18314/download	input_metastage * https://cdr.chic-vph.eu/api/files/18314/download Default: https://cdr.chic-vph.eu/api/files/18314/download	miRNA_expression_data * https://cdr.chic-vph.eu/api/files/18268/download Default: https://cdr.chic-vph.eu/api/files/18268/download
Patient_ID * JGUP5ZVT3CHDDP4HMRZD Default: JGUP5ZVT3CHDDP4HMRZD	radio_dose * 15 Units: Gy, Default: 15	cell_cycle_time * 40 Units: h, Default: 40, Range: 18-134	radiation_dosage * 15 Units: Gy, Default: 15, Range: 0-100
first_radio_adm_time * 104 Units: days, Default: 104	second_radio_adm_time * 107 Units: days, Default: 107	third_radio_adm_time * 110 Units: days, Default: 110	fourth_radio_adm_time * 113 Units: days, Default: 113
fifth_radio_adm_time *	sixth_radio_adm_time *	seventh_radio_adm_time *	eighth_radio_adm_time *

Fig 21. Required input arguments of Lung Cancer multimodeller hypermodel



CRAF :: Clinical Research Application Framework

GO BACK

Cancer Topic Selection (Pick one) > LUNG > Patient Selection > Hypermodel for the selected Patient

Lung Cancer multimodeller hypermodel_v1_0

INPUT OUTPUT

Input parameters

Show required Show editable

vs_nutrient_diffusivity 0.396 Units: mm ² /hr, Default: 0.396, Range: 1.e-6-	vs_nutrient_consumption_rate * 7.6e-9 Units: NcicP-1 to-1, Default: 7.6e-9, Range: 0-	vs_nutrient_concentration_healthy 0.9 Units: kg/m ³ , Default: 0.9, Range: 0-	max_cell_carrying_capacity 1000000 Default: 1000000
path_to_simulation_domain * https://cdr.chic-vph.eu/api/files/18314/download Units: valid file system path relative to a sandbox directory, Default: https://cdr.chic-vph.eu/api/files/18314/download	sym_fraction 0.322 Default: 0.322, Range: 0-1	threshold 0.5 Default: 0.5, Range: 0-1	limp_stages_number 22 Default: 22, Range: 1-
interpolation_spacing 1 Units: mm, Default: 1	cell_density 1000000 Units: number of biological cells per mm ³ , Default: 1000000, Range: 300000-1100000	input_metastage * https://cdr.chic-vph.eu/api/files/18314/download Default: https://cdr.chic-vph.eu/api/files/18314/download	stem_cell_factor 1 Default: 1, Range: 0-1
name_of_output_file	limp_cell_factor	miRNA_expression_data *	cell_factor

Fig 22. Complete list of input arguments of Lung Cancer multimodeller hypermodel

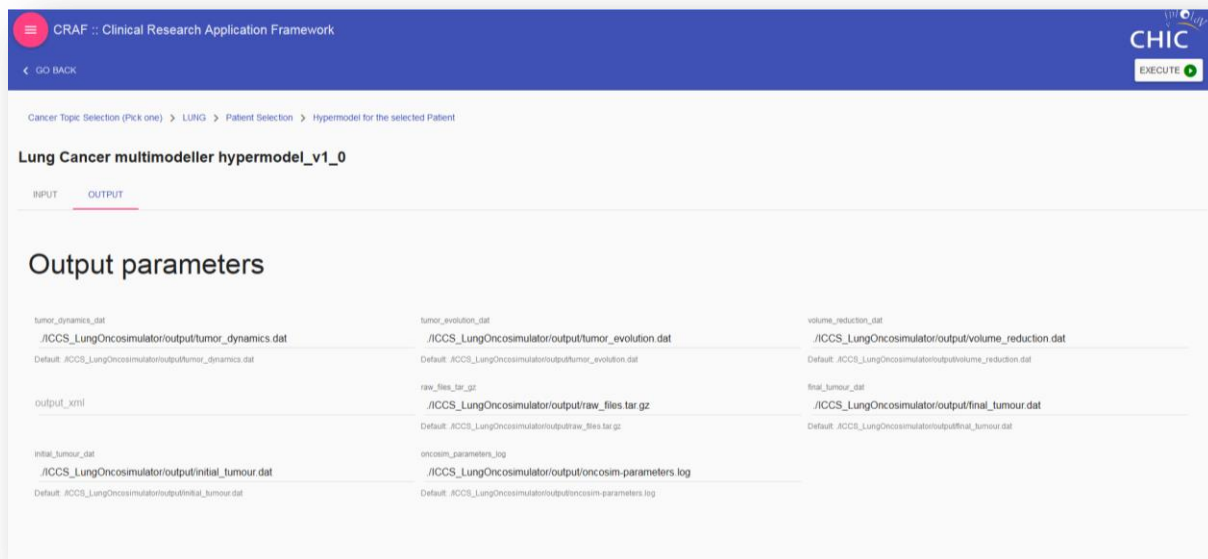


Fig 23. Output files of Lung Cancer multimodeller hypermodel

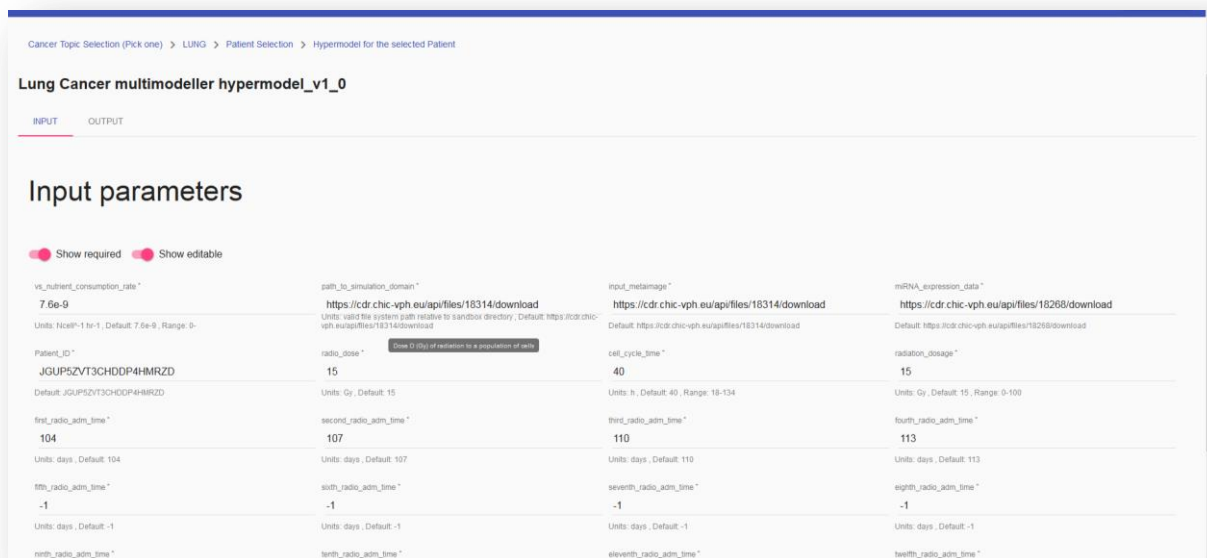


Fig 24. Viewing input parameters' description

Step 5: The user can proceed to the execution of the model by clicking the "Execute" button. If, by mistake, no value is passed to an input argument, the specific argument is highlighted red (Fig. 25). After filling in the missing value, a window appears which notifies the user about the status of its execution (successful initialization of the execution of the hypermodel or failure to start) (Fig 26). After the dialog window is closed, the execution history of the logged in user appears (Fig 27).

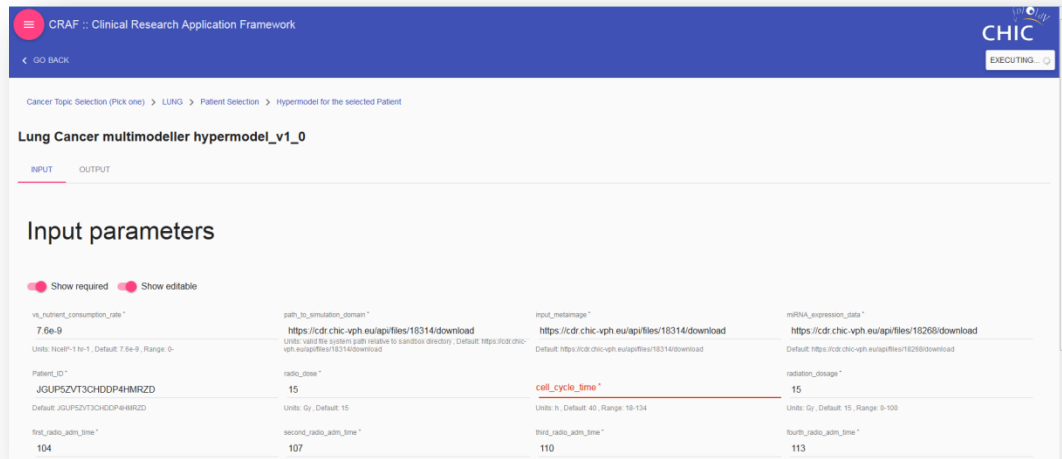


Fig 25. User notification in case of missing input value

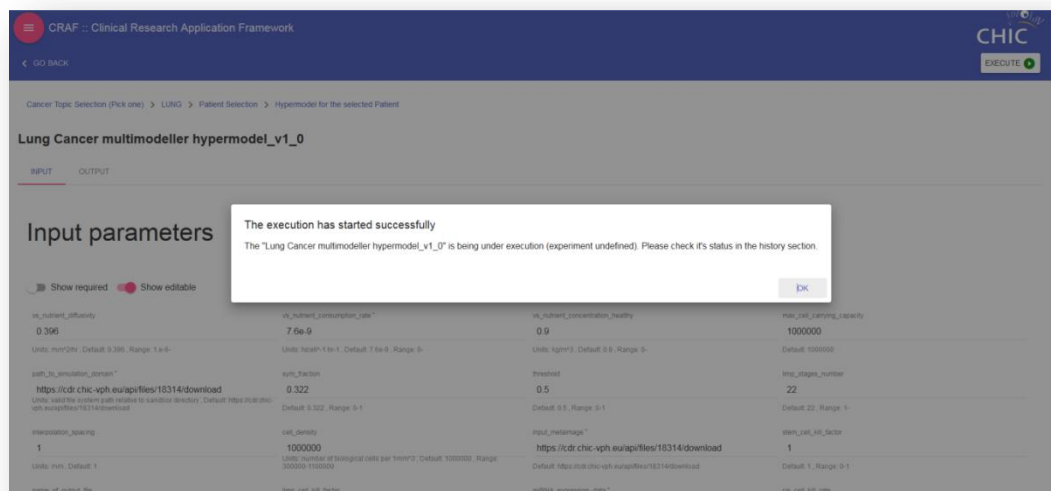


Fig 26. Pop up window with the status of the execution

Id	Started	End	Model	Patient	Description	Cancer Type	Status
1055	2017/05/05 10:33		Lung Cancer multimodeller hypermodel_v1_0	Byron Borgmans	Lung Cancer multimodeller hypermodel_v1_0	Non Small Lung Cancer	⚙️
1054	2017/05/05 10:22	10:22	ICCS miRNA statistical model for lung cancer prognosis	Byron Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✅
1053	2017/05/05 09:59	10:00	ICCS miRNA statistical model for lung cancer prognosis	Byron Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✅
1052	2017/05/05 08:51	08:52	ICCS miRNA statistical model for lung cancer prognosis	Byron Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✅
1051	2017/05/05 02:35		Prostate Cancer Hypermodel	Sam Schmidt	Prostate Cancer Hypermodel	Prostate Cancer	⚠️
1050	2017/05/05 02:23	02:23	ICCS miRNA statistical model for lung cancer prognosis	Byron Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✅
1049	2017/05/04 18:38	18:42	Lung Cancer multimodeller hypermodel_v1_0	Byron Borgmans	Lung Cancer multimodeller hypermodel_v1_0	Non Small Lung Cancer	✅
1047	2017/05/04 18:24	18:25	ICCS miRNA statistical model for lung cancer prognosis	Byron Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✅
1014	2017/05/01 01:11	02:07	Nephroblastoma multimodeller hypermodel_v1_0	Hans Fischer	Nephroblastoma multimodeller hypermodel_v1_0	Nephroblastoma	✅
1048	2017/05/04 15:06	15:06	Lung Cancer multimodeller hypermodel_v1_0	Byron Borgmans	Lung Cancer multimodeller hypermodel_v1_0	Non Small Lung Cancer	❗

Fig 27. History list of logged in user

Step 6: Upon execution completion, the user can view the details of the execution (Fig 28), download the produced output files (Fig 29, 30), as previously described, and create the outcome report by clicking the create report button (Fig 31, 32).

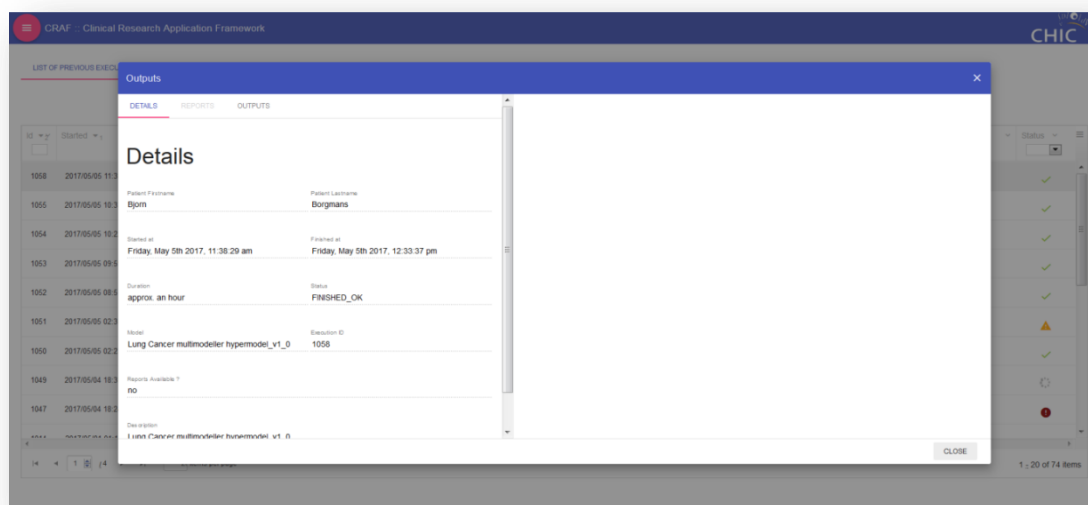


Fig 28. Viewing the details of an execution

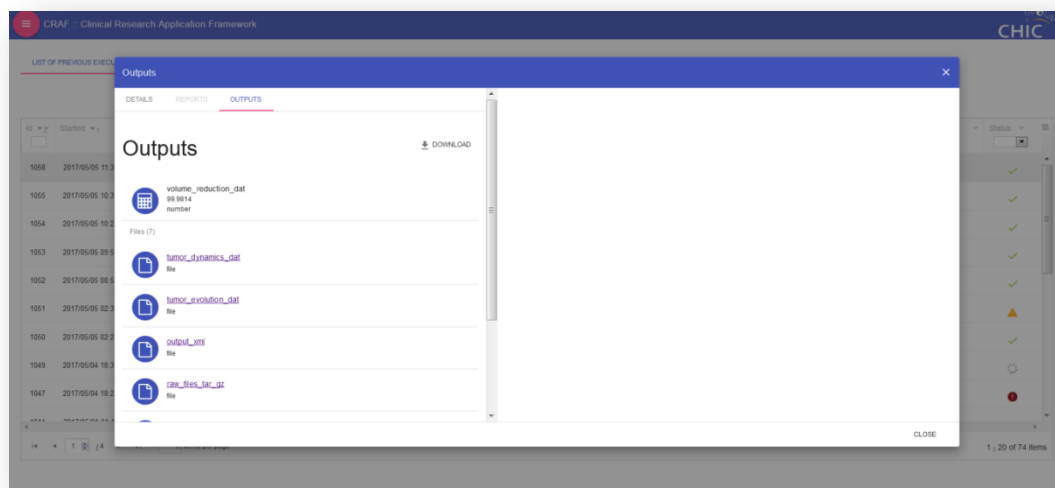


Fig 29. Viewing the output files of an execution

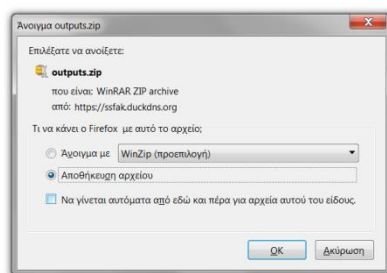


Fig 30. Downloading the output files of the execution

CRAF :: Clinical Research Application Framework

CHIC

LIST OF PREVIOUS EXECUTIONS STATISTICS

VIEW REPORT CREATE REPORT OUTPUTS ADD TO COMPARE

ID	Started	End	Model	Patient	Description	Cancer Type	Status
1058	2017/05/05 11:38	12:33	Lung Cancer multimodeler hypermodel_v1_0	Ejzen Borgmans	Lung Cancer multimodeler hypermodel_v1_0	Non Small Lung Cancer	✓
1055	2017/05/05 10:33	10:40	Lung Cancer multimodeler hypermodel_v1_0	Ejzen Borgmans	Lung Cancer multimodeler hypermodel_v1_0	Non Small Lung Cancer	✓
1054	2017/05/05 10:22	10:40	ICCS miRNA statistical model for lung cancer prognosis	Ejzen Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1053	2017/05/05 09:59	10:40	ICCS miRNA statistical model for lung cancer prognosis	Ejzen Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1052	2017/05/05 08:51	10:40	ICCS miRNA statistical model for lung cancer prognosis	Ejzen Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1051	2017/05/05 02:35		Prostate Cancer Hypermodel	Sam Schmidt	Prostate Cancer Hypermodel	Prostate Cancer	⚠
1050	2017/05/05 02:23	10:40	ICCS miRNA statistical model for lung cancer prognosis	Ejzen Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✓
1049	2017/05/04 19:38		Lung Cancer multimodeler hypermodel_v1_0	Ejzen Borgmans	Lung Cancer multimodeler hypermodel_v1_0	Non Small Lung Cancer	⌛
1047	2017/05/04 19:24	10:40	ICCS miRNA statistical model for lung cancer prognosis	Ejzen Borgmans	ICCS miRNA statistical model for lung cancer prognosis	Non Small Lung Cancer	✖

1 - 20 of 74 items

Fig 31. Creating the outcome report of the execution

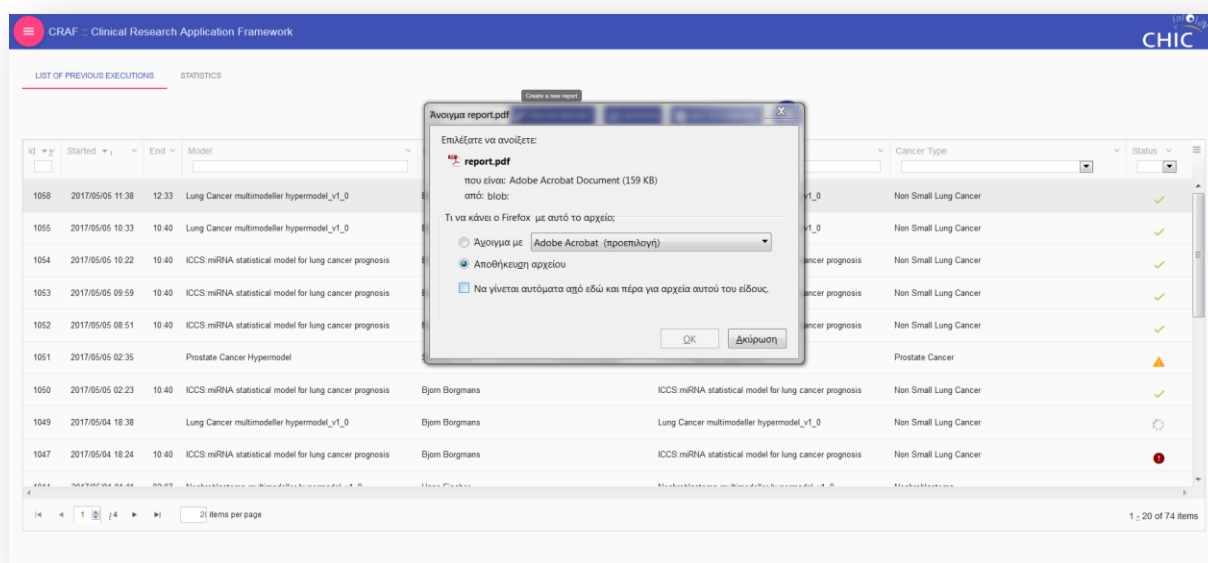
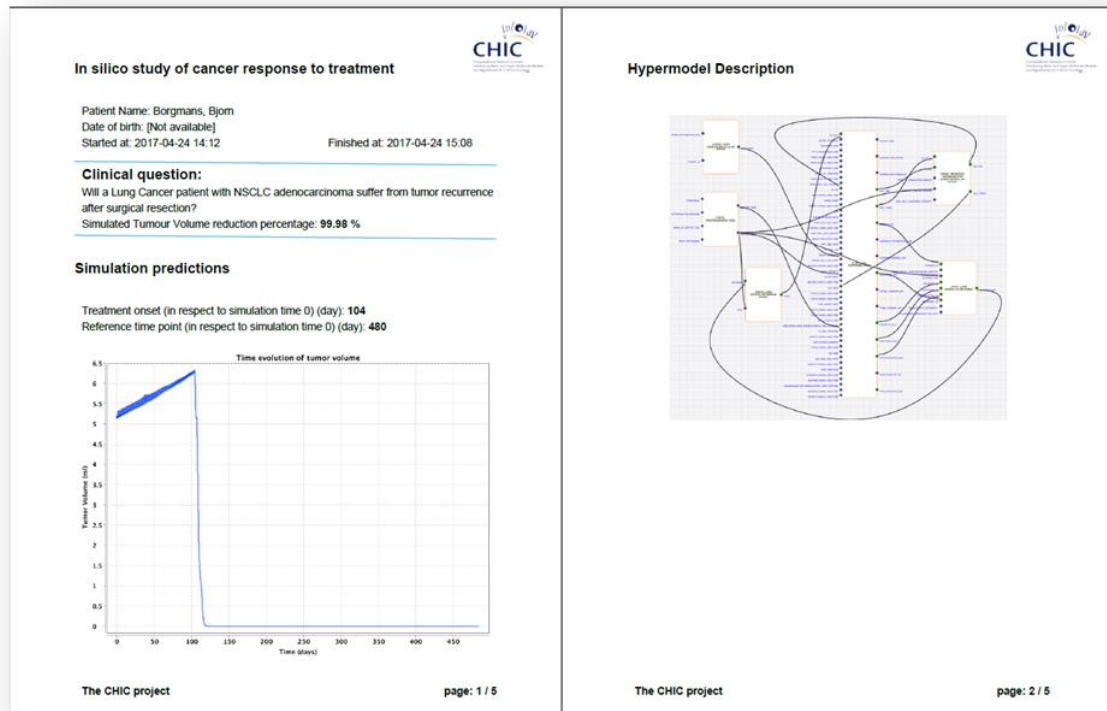


Fig 32. Opening/saving the outcome report of the execution

Step 7: The user can select any execution from the history list, view its details, and download/view its output files and outcome report.

I.2 Example of outcome report (is following)



<p>Input values of hypermodel parameters</p> <p>Default value 0.396 mm²/hr from A HYBRID MODEL FOR TUMOR SPHEROID GROWTH IN VITRO I: THEORETICAL DEVELOPMENT AND EARLY RESULTS, Kim et al. 2007.: 0.396</p> <p>Rate of glucose consumption per cell per hour.: 7.6e-9</p> <p>Glucose concentration in non tumour regions. Output is normalized by this value.: 0.9</p> <p>Tumour cell concentration used for pressure computation.: 1000000</p> <p>Vtk-readable segmentation file with organ labels. Labels for Lung scenario 1: right lung 2: left lung 3: bone 4: soft tissue outside 5: other internal organs 6: bronchi 255: tumour: https://cdr.chic-vph.eu/api/files/18314/download</p> <p>Fraction of stem cells that divide symmetrically in necrotic regions: 0.322</p> <p>Defines the threshold for the cropping (float between 0 and 1): 0.55</p> <p>Number of limited mitotic potential (LIMP) cell stages before differentiation occurs = number of LIMP cell mitoses before differentiation occur: 22</p> <p>The spacing to be used for the isotropic interpolation.: 1</p> <p>Tumor cell density in number of biological cells per 1mm³.: 1000000</p> <p>A valid metainage which contains the segmentations with the tumor value to be 255: https://cdr.chic-vph.eu/api/files/18314/download</p> <p>: 1</p> <p>Name of output file which will contain the interpolated and cropped result: output</p> <p>: 1</p> <p>Csv or mirnmi file which contains the miRNA expression data.: https://cdr.chic-vph.eu/api/files/18268/download</p> <p>Cell kill rate of cisplatin: 0</p> <p>Anonymized ids of patients selected for the trial. In the model demo run precomputed results are available for only patient JGUP5ZVT3CHDDP4HMRZD: JGUP5ZVT3CHDDP4HMRZD</p> <p>Cell kill rate of vinorelbine: 0</p> <p>alpha/beta ratio, where alpha: radiosensitivity parameter of the Linear Quadratic model in Gy⁻¹ beta: radiosensitivity parameter of the Linear Quadratic model in Gy⁻²: 10</p> <p>The CHIC project page: 3 / 5</p>	<p>Enhancement of therapeutic or detrimental effect of ionizing radiation due to the presence of oxygen: 1</p> <p>Dose D (Gy) of radiation to a population of cells: 15</p> <p>Cell cycle duration of stem and LIMP cells (G0 phase not included): 40</p> <p>Dormant (G0) phase duration of stem and LIMP cells : 168</p> <p>Time before necrosis products are eliminated: 23</p> <p>Time before apoptosis products are eliminated in necrotic regions: 4</p> <p>Spontaneous apoptosis rate corresponding to transition to apoptosis from any of the G1, S, G2, M, G0 phases of the stem and LIMP cells : 0.0001</p> <p>Spontaneous apoptosis rate corresponding to transition to apoptosis from the differentiated cell state: 0.017</p> <p>Rate to enter necrosis for differentiated cells : 0.025</p> <p>Fraction of dormant cancer stem cells re-entering the G1 phase after a time interval equal to the G0 duration in necrotic regions: 0.1</p> <p>Fraction of cells that will enter G0 following mitosis in necrotic regions: 0.263</p> <p>radiation dosage for the UPENN lung molecular model: 15</p> <p>Time point after initialization (in days) when the 1st combination chemotherapy takes place: -1</p> <p>Time point after initialization (in days) when the 2nd combination chemotherapy takes place (= -1 if total cycles less than 2): -1</p> <p>Time point after initialization (in days) when the 3rd combination chemotherapy takes place (= -1 if total cycles less than 3): -1</p> <p>Time point after initialization (in days) when the 4th combination chemotherapy takes place (= -1 if total cycles less than 4): -1</p> <p>Time point after initialization (in days) when the 1st single chemotherapy takes place: -1</p> <p>Time point after initialization (in days) when the 2nd single chemotherapy takes place (= -1 if total cycles less than 2): -1</p> <p>Time point after initialization (in days) when the 3rd single chemotherapy takes place (= -1 if total cycles less than 3): -1</p> <p>Time point after initialization (in days) when the 4th single chemotherapy takes place (= -1 if total cycles less than 4): -1</p> <p>The CHIC project page: 4 / 5</p>
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Time point after initialization (in days) when the 1st irradiation takes place:	104
Time point after initialization (in days) when the 2nd irradiation takes place (= the last administration time point if total irradiations less than 2):	107
Time point after initialization (in days) when the 3rd irradiation takes place (= the last administration time point if total irradiations less than 3):	110
Time point after initialization (in days) when the 4th irradiation takes place (= the last administration time point if total irradiations less than 4):	113
Time point after initialization (in days) when the 5th irradiation takes place (= the last administration time point if total irradiations less than 5):	-1
Time point after initialization (in days) when the 6th irradiation takes place (= the last administration time point if total irradiations less than 6):	-1
Time point after initialization (in days) when the 7th irradiation takes place (= the last administration time point if total irradiations less than 7):	-1
Time point after initialization (in days) when the 8th irradiation takes place (= the last administration time point if total irradiations less than 8):	-1
Time point after initialization (in days) when the 9th irradiation takes place (= the last administration time point if total irradiations less than 9):	-1
Time point after initialization (in days) when the 10th irradiation takes place (= the last administration time point if total irradiations less than 10):	-1
Time point after initialization (in days) when the 11th irradiation takes place (= the last administration time point if total irradiations less than 11):	-1
Time point after initialization (in days) when the 12th irradiation takes place (= the last administration time point if total irradiations less than 12):	-1
Execution stop time after initialization:	480

CHAPTER GB: THE GLIOBLASTOMA HYPERMODEL

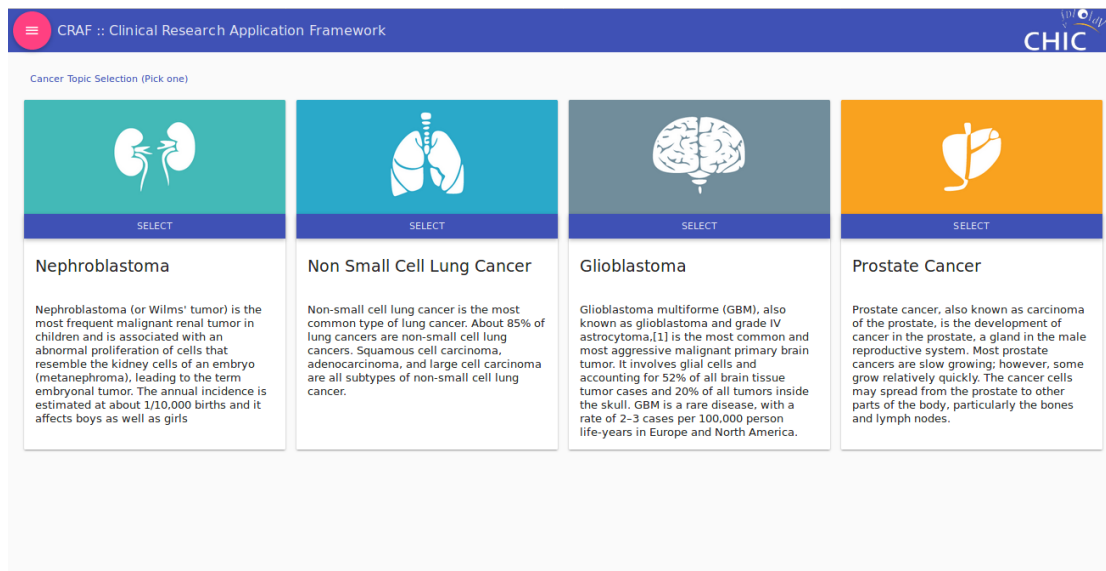


Figure 1. Initial screen, GBM is selected.

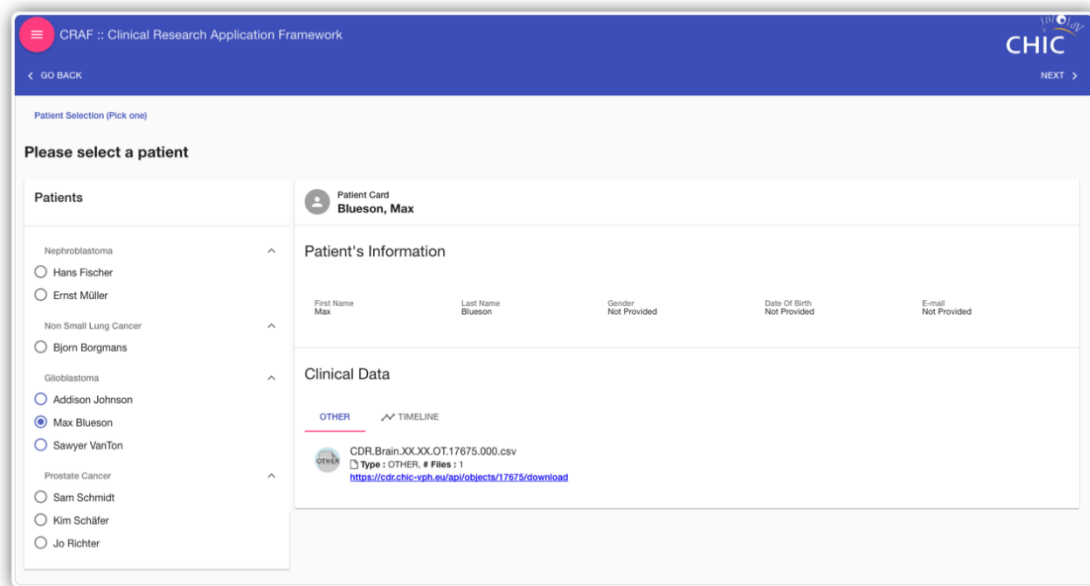
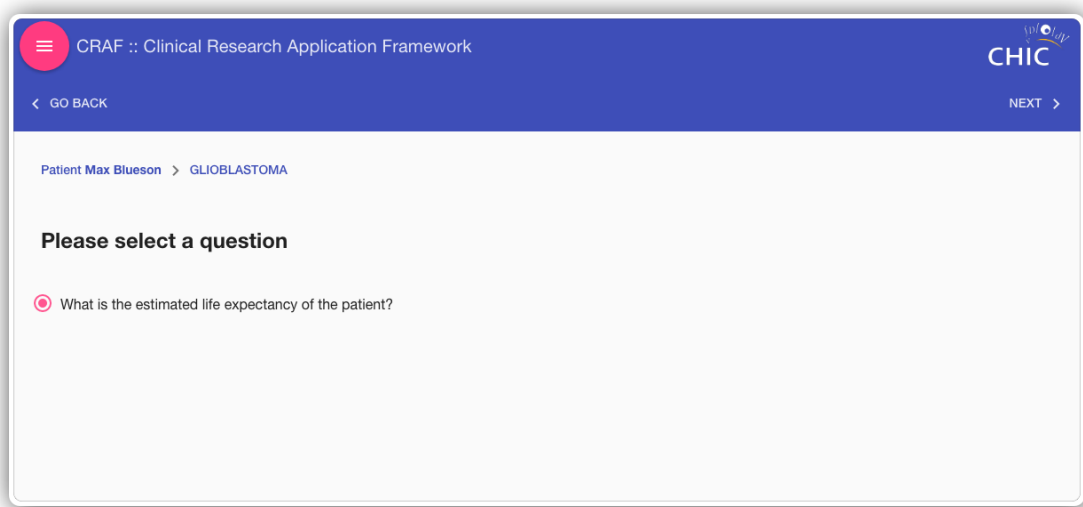
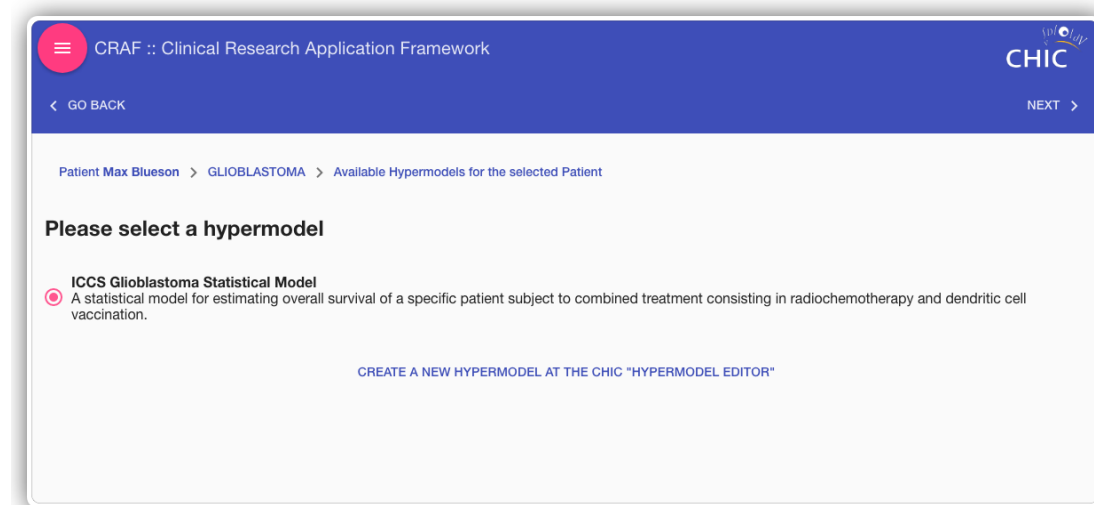


Figure 2. GBM Patients and patient selection.



The screenshot shows the CRAF interface with a blue header. The title bar reads "CRAF :: Clinical Research Application Framework". On the left is a "GO BACK" button, and on the right is a "NEXT" button. The breadcrumb trail is "Patient Max Blueson > GLIOBLASTOMA". The main content area has the heading "Please select a question" and a single radio button option: "What is the estimated life expectancy of the patient?".

Figure 3. The basic clinical question [What is the estimated life expectancy of the patient? The clinician is expected to run this question twice for the same patient, one for early vaccination and one for late vaccination and compare the results.



The screenshot shows the CRAF interface with a blue header. The title bar reads "CRAF :: Clinical Research Application Framework". On the left is a "GO BACK" button, and on the right is a "NEXT" button. The breadcrumb trail is "Patient Max Blueson > GLIOBLASTOMA > Available Hypermodels for the selected Patient". The main content area has the heading "Please select a hypermodel" and a single radio button option: "ICCS Glioblastoma Statistical Model". Below this option is a description: "A statistical model for estimating overall survival of a specific patient subject to combined treatment consisting in radiochemotherapy and dendritic cell vaccination." At the bottom of the content area is a link: "CREATE A NEW HYPERMODEL AT THE CHIC 'HYPERMODEL EDITOR'".

Figure 4. Hypermodel selection. The model essentially is the one dictated by the basic stratification $RTV=0$ or >0 and Vaccination = Early or Late, as described in detail in D6.4

The screenshot shows the CRAF web interface. The header includes the CRAF logo, a hamburger menu, the text "CRAF :: Clinical Research Application Framework", a "GO BACK" button, the CHIC logo, and an "EXECUTE" button. The breadcrumb trail is "Patient Max Blueson > GLIOBLASTOMA > Hypermodel for the selected Patient". The main heading is "ICCS Glioblastoma Statistical Model". Below this are two tabs: "INPUT" (active) and "OUTPUT". The "INPUT" tab displays "Input parameters" with two toggle switches: "Show required" (checked) and "Show editable" (unchecked). A text input field labeled "filepatient *" contains the URL "https://cdr.chic-vph.eu/api/files/76417". Below the input field, it says "Default: https://cdr.chic-vph.eu/api/files/76417".

Figure 5. (Automated) input file for the model. Essentially a txt file containing all FACS data of the patient at the time points of Leukapheresis and PI/VI (first vaccine) as real numbers, plus the RTV and Vaccination Schedule values for the specific patient as integers. (RTV=0, RTV>0 correspond to integer values 0 and 1, respectively. Early or Late Vaccination correspond to integer values 0 and 1, respectively)

The screenshot shows the CRAF web interface. The header is identical to Figure 5. The breadcrumb trail is "Cancer Topic Selection (Pick one) > GLIOBLASTOMA > Patient Selection > Hypermodel for the selected Patient". The main heading is "ICCS Glioblastoma Statistical Model". Below this are two tabs: "INPUT" and "OUTPUT" (active). The "OUTPUT" tab displays "Output parameters". A text input field labeled "output_file" contains the path "/out/result.dat". Below the input field, it says "Default: ./out/result.dat".

Figure 6

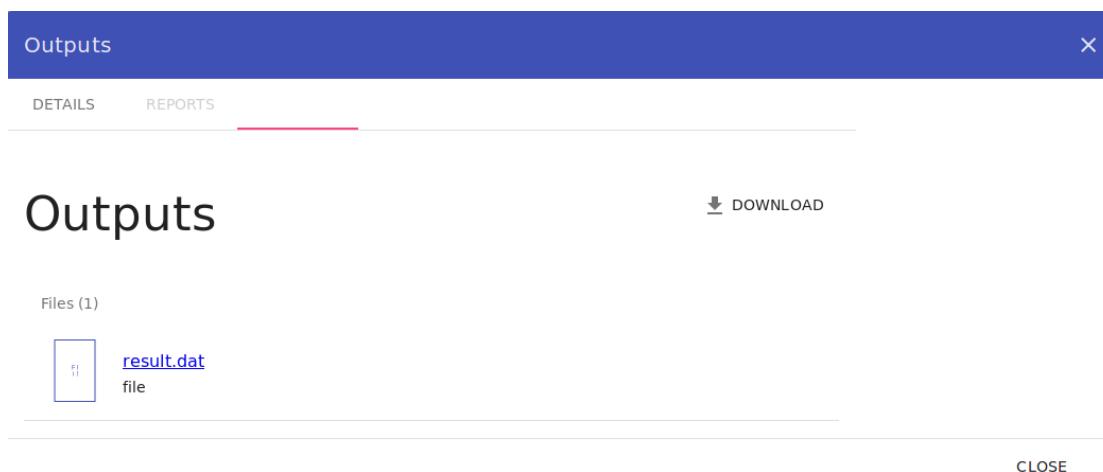


Figure 7.

Figures 6,7. Output screenshots. The output is essentially a txt file containing a real number, corresponding to the estimated by the model overall survival in months.

Average execution time for the model in the platform is 7-8 seconds.

In the following three pages a typical report generated by CRAF during the execution of the glioblastoma hypermodel is presented.



In silico study of cancer response to treatment

Patient Name: Blueson, Max

Date of birth: [Not available]

Started at: 2017-05-05 14:00

Finished at: 2017-05-05 14:02

Clinical question:

What is the estimated life expectancy of the patient?

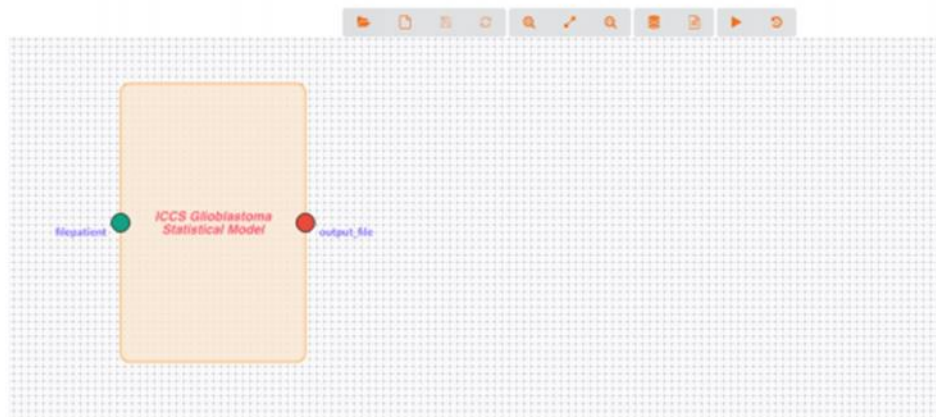
Simulation predictions

Estimated life expectancy of the patient: 18.2624 months

Hypermodel Description

Glioblastoma Hypermodel description

CHIC Hypermodeling Editor: Glioblastoma "hypermodel" (version: 367)



Input values of hypermodel parameters

Txt file containing 22 real and 2 integer patient specific values: https://istr.chic-vph.eu/trial_app/getTrFileById/?id=2918

CHAPTER PC: THE PROSTATE CANCER HYPERMODEL

I. Prostate cancer hypermodel execution through CRAF

CRAF environment enables the user to configure and initiate the execution of prostate cancer hypermodels using either a ‘cancer domain – based’ wizard or a ‘patient – based wizard’ (see figure P1).

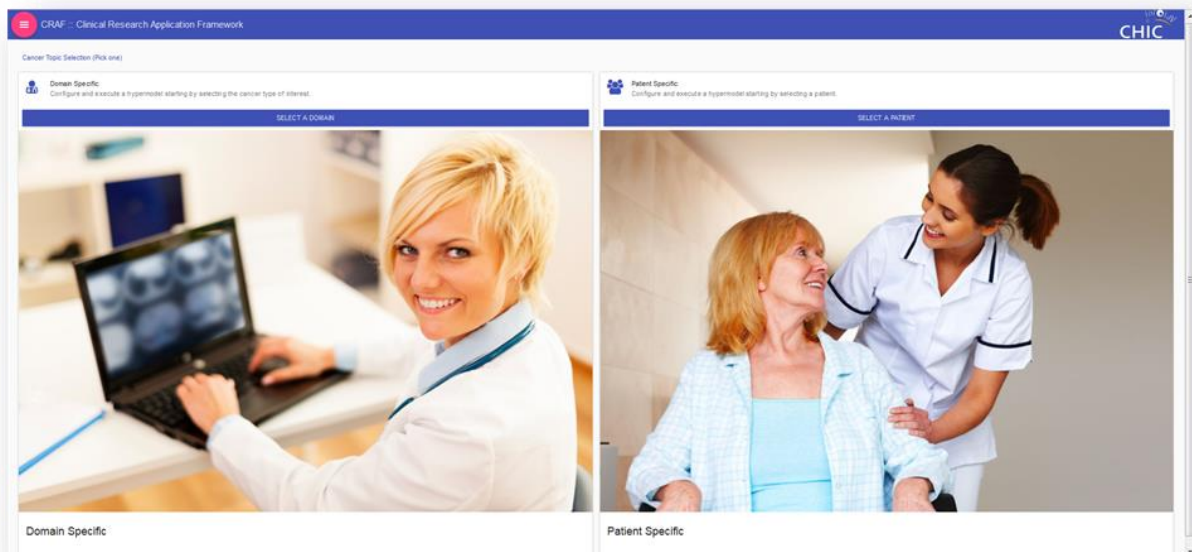


Figure P1: Home page of CRAF. On the left, the cancer domain-specific wizard while on the right, the patient-specific wizard.

Upon clicking the domain-specific wizard, the four cancer domains considered in CHIC appear (figure P2).

This is the welcome page that includes the Prostate Cancer “domain”:

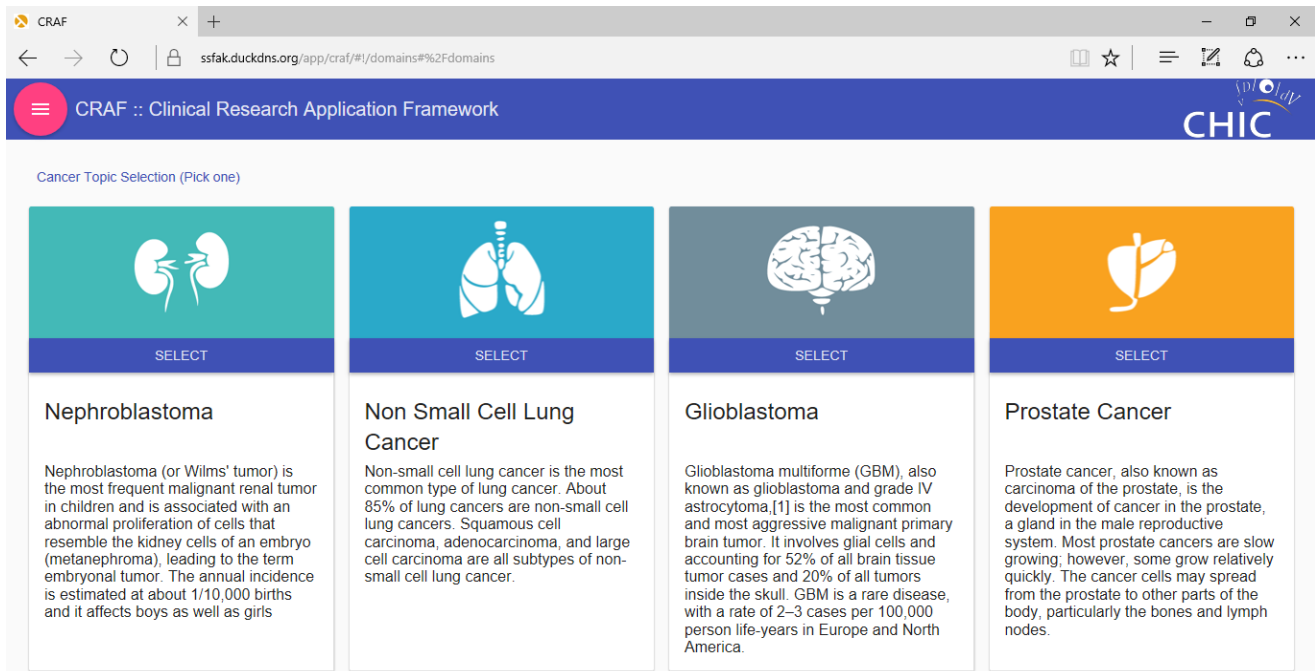


Figure P2: Cancer domains considered in CHIC along with a shorth description for each one of them.

By clicking on the prostate cancer domain, the respective clinical question that has been selected for demonstration purposes appears (*Will the patient have any advantage from adjuvant Androgen Deprivation Therapy?*) (Figure P3).

The screenshot shows the CRAF web application. The header includes the CRAF logo and navigation links. The main content area displays the breadcrumb 'Cancer Topic Selection (Pick one) > PROSTATE'. Below this, a heading 'Please select a question' is followed by a single radio button option: 'Will the patient have any advantage from adjuvant Androgen Deprivation Therapy?'. A 'NEXT' button is visible in the top right corner.

Figure P3: Clinical question investigated through CRAF for the case of prostate cancer. [Will the patient have any advantage from adjuvant Androgen Deprivation Therapy?]

Clicking on the NEXT button, the list of all patients registered in CRAF appears (figure P4). Since the user currently navigates in prostate cancer, only the prostate cancer patients are enabled. Thus the clinician can select whoever prostate cancer patient he/she desires and view their data. By using 'show all patients' switch, the disabled patients can be hidden (figure P5).

The screenshot shows the CRAF web application with the 'Select a Patient' screen. On the left, a list of patients is shown with radio buttons: Hans Fischer, Ernst Müller, Björn Borgmans, Sam Schmidt (selected), Kim Schäfer, and Jo Richter. On the right, a detailed view for 'Sam Schmidt' is displayed. This view includes 'Patient's Information' (Demographics) with fields for First Name, Last Name, Gender, Date Of Birth, and E-MAIL. Below this is the 'Clinical Data' section, which has tabs for CLINICAL, GENOMICS, DICOM SERIES, and METAIMAGE. The CLINICAL tab is active, showing a file named 'CDR.Prostate.XX.XX.OT.17670.000.csv' with a download link.

Figure P4: List of patients that are registered in CRAF

The screenshot shows the CRAF web application interface. The browser address bar displays 'ssfak.duckdns.org/app/craf/#1/patients#%2Fdomains'. The application header includes the CRAF logo and navigation links like 'GO BACK' and 'NEXT'. The main content area is titled 'Please select a patient' and includes a toggle for 'Show all patients'. A list of patients is shown on the left, with 'Sam Schmidt' selected. On the right, a 'Patient Card' for 'Schmidt, Sam' is displayed, showing demographic information in a table and a section for clinical data.

Patient's Information				
Demographics				
First Name	Last Name	Gender	Date Of Birth	E-MAIL
Sam	Schmidt	Not Provided	Not Provided	Not Provided

Clinical Data

Figure P5: List of prostate cancer patients that are registered in CRAF

Upon selecting a patient and clicking on 'NEXT' button, the associated list of hypermodels appears (figure P6). Only one hypermodel, Prostate Cancer Hypermodel, is currently associated with the selected clinical question and patient.



Figure P6: Available hypermodel given the cancer domain (prostate), clinical question and patient: Prostate Cancer Hypermodel

The following step is for the clinician to click once more on the 'NEXT' button so that he/she views the input and output parameters of the selected hypermodel (Figure P7) and, modify input arguments before starting the execution of this hypermodel. In order not to distract the clinician with excess information, only the required input arguments are shown (Figure P7). However the complete list of input arguments appear using the corresponding switches.

The screenshot shows the CRAF Clinical Research Application Framework interface. At the top, there is a blue header bar with the CRAF logo and a navigation menu. Below the header, there is a breadcrumb trail: Cancer Topic Selection (Pick one) > PROSTATE > Patient Selection > Hypermodel for the selected Patient. The main content area is titled "Prostate Cancer Hypermodel" and has two tabs: "INPUT" and "OUTPUT". The "INPUT" tab is active, showing a section titled "Input parameters". Below this, there are two toggle buttons: "Show required" (active) and "Show editable". The input parameters are displayed in a grid format:

I1 number of administrations 3 Default: 3	I1 first administration timepoint 0 Units: day, Default: 0	I1 time interval between administrations 28 Units: day, Default: 28
I1 end of simulation 84 Units: day, Default: 84	I3 PSA patient file https://istr.chic-vph.eu/trial_app/getTrFileById?id=2998 Default: https://istr.chic-vph.eu/trial_app/getTrFileById?id=2998	I4 Patient ID Control Default: Control

Figure P7: Required input parameters of the prostate cancer hypermodel.

At this point, the clinician can proceed with the hyper-model execution by clicking on the upper right 'Execute' button. Once he/she does, a window appears in order to notify the user about the execution status (successful initialization of the execution of the hyper-model or failure to start) (Figure P8).

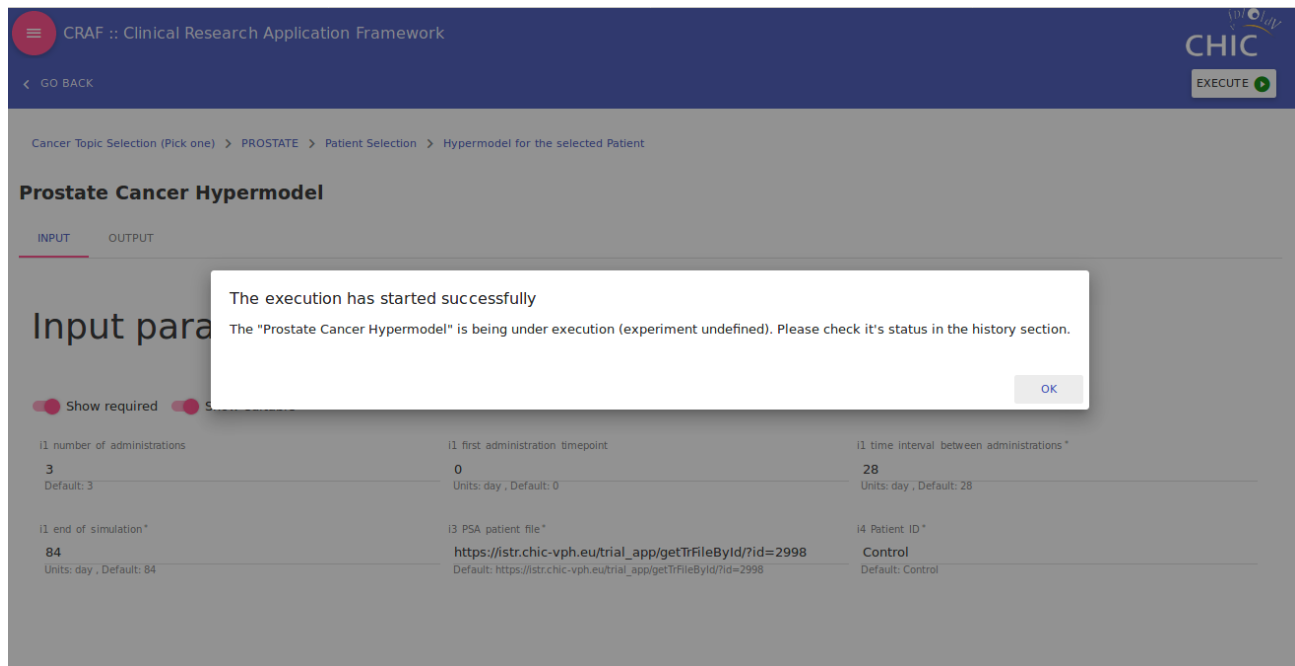


Figure P8: Pop up window with the status of the execution

Once the user closes the dialog window, the execution history appears with the list of previous and current execution performed by the logged in us. The status of each execution is stated (failure to start, currently running, failed, successful) with the use of the appropriate mark. When the execution is completed, its status is updated (Figure P9).

CRAF :: Clinical Research Application Framework

CHIC

LIST OF PREVIOUS EXECUTIONS STATISTICS

VIEW REPORT CREATE REPORT OUTPUTS ADD TO COMPARE ↻

Id	Started	End	Model	Patient	Description	Cancer Type	Status
1051	2017/05/05 02...	02:53	Prostate Cancer Hypermodel	Sam Schmidt	Prostate Cancer Hypermodel	Prostate Cancer	✓
1050	2017/05/05 02...	02:23	ICCS:miRNA statistical model for L...	Bjorn Borgmans	ICCS:miRNA statistical model for L...	Non Small Lung Cancer	✓
1049	2017/05/04 18...	18:42	Lung Cancer multimodeller hyper...	Bjorn Borgmans	Lung Cancer multimodeller hyper...	Non Small Lung Cancer	✓
1047	2017/05/04 18...	18:25	ICCS:miRNA statistical model for L...	Bjorn Borgmans	ICCS:miRNA statistical model for L...	Non Small Lung Cancer	❗
1014	2017/05/01 01...	02:07	Nephroblastoma multimodeller h...	Hans Fischer	Nephroblastoma multimodeller hy...	Nephroblastoma	✓
1013	2017/04/30 12...	12:21	Lung Cancer multimodeller hyper...	Bjorn Borgmans	Lung Cancer multimodeller hyper...	Non Small Lung Cancer	❗
1009	2017/04/29 13...		UNITO: Prostate cancer ADT model	Sam Schmidt	UNITO: Prostate cancer ADT model	Prostate Cancer	⚠
1008	2017/04/28 22...	22:37	Lung Cancer multimodeller hyper...	Bjorn Borgmans	Lung Cancer multimodeller hyper...	Non Small Lung Cancer	❗

1 - 20 of 68 items

Figure P9: List of previous executions (History)

Upon clicking the Outputs button, a dialog window appears which displays information regarding the selected execution (Figure P10) and gives the possibility to the user to download the output files of the hyper-model by clicking the download button (Figure P11).

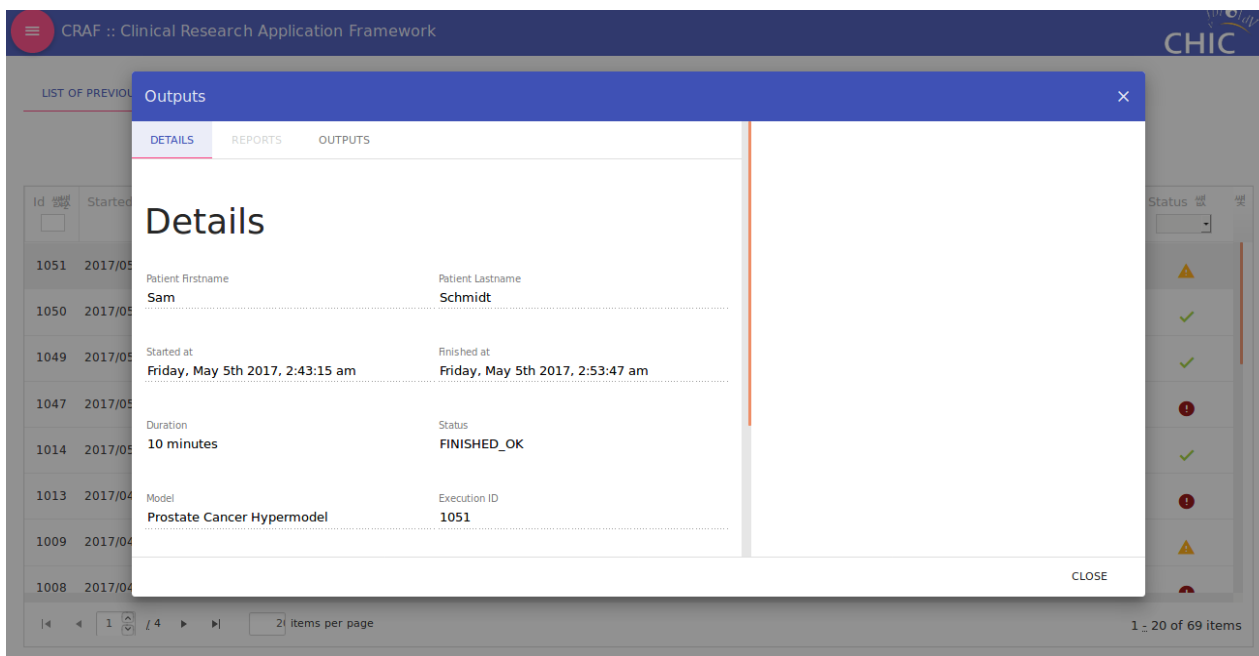


Figure P10: Outputs window (Details tab)

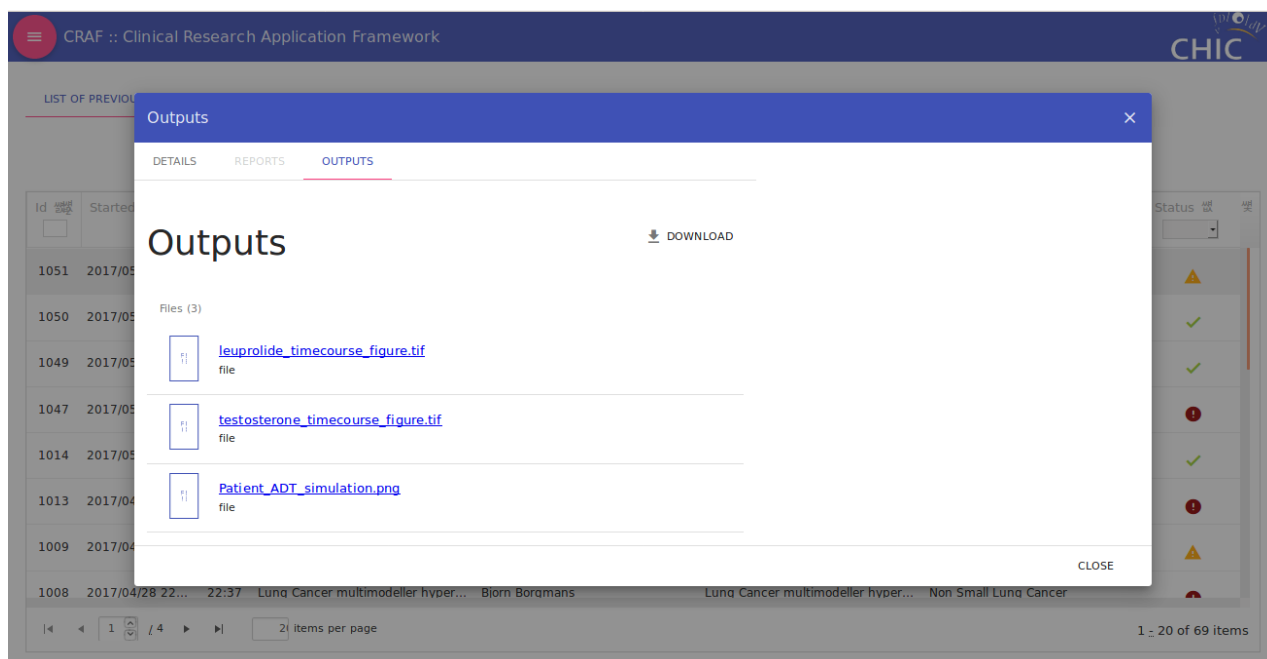
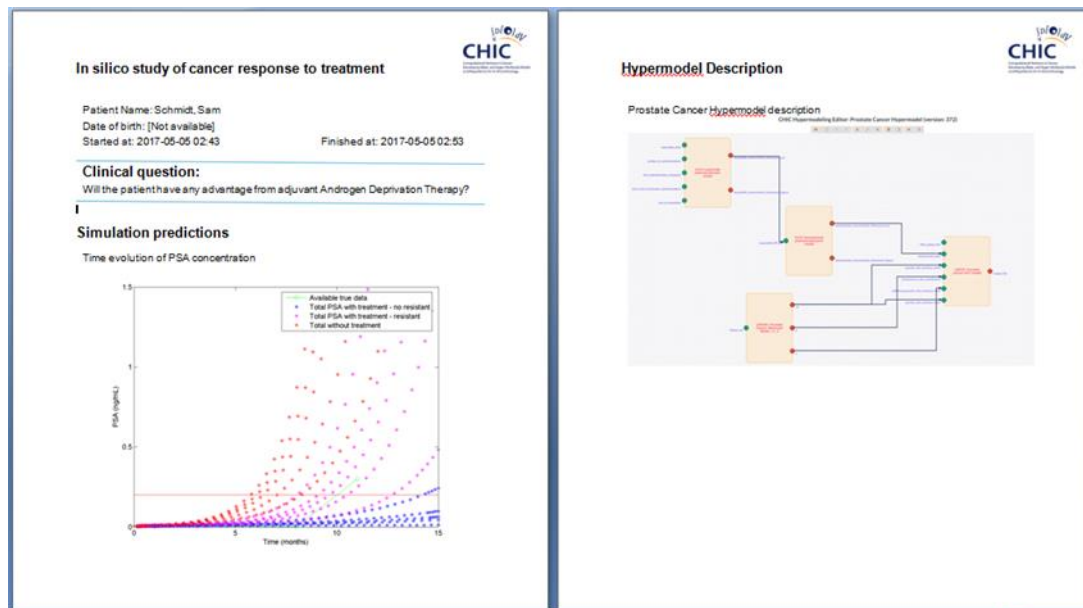


Figure P11: Outputs window (Download of output files)

2. Example of Outcome Report



Input values of **hypermodel parameters**

Dose of leuprolide: 3.75

Number of Leuprolide administrations: 3

Timepoint of first leuprolide administration: 0

Time interval between two consecutive administrations of Leuprolide: 28

End of simulation: 84

A .csv file which contains the 'name' of the patient (first column), at least the first PSA value after surgery (second column) and when it is sampled in number of months after surgery (third column): https://istr.chic-vph.eu/trial_app/getTrFileById/?id=2998

Id of patients for which model is to be run. In demo mode the data for following patients are available AA65, CC87, Z59, AA69, L12, B17, A3, W25, A5, G70, B11, C25 and Control: Control

CHAPTER TE: TECHNOLOGICAL ISSUES – ANNOTATION OF THE CHIC MODELS. THE COMPOSITION AND STORAGE OF A NEW HYPERMODEL

(Please note that the numbering of sections, subsections, equations, figures and references within this chapter refers exclusively to the latter and is not applicable to other chapters of the document, If any of the above entities of another chapter is to be referred to, the chapter under consideration should also be mentioned through its two capital letter code)

I. Annotation of CHIC Models

I.1 The role of metadata in the creation of hypermodels.

We adopt an approach which refines the one described in D6.3 for the initial cancer hypermodels. In that deliverable, we used D7.3 “Hypermodels annotation services” as a foundation for our work. D7.3 reviews the requirements relating to the use of semantic technologies within the CHIC infrastructure and CHIC tools. The deliverable also elaborates on the scope, content and structure of the formal solution used in order to describe models through semantic annotation. In the present deliverable we demonstrate how the semantic framework is used in order to support the construction of hypermodels from annotated hypomodels. Using the term “meta-models” in the present context we describe the result of applying semantic metadata to the description of models in CHIC.

In CHIC, the formalisation of metadata descriptions for models uses the Resource Description Framework (RDF) as a formal language. We created by term aggregation a series of supporting vocabularies (called an ‘RDF schema’ or sometimes an ‘ontology’) designed for the CHIC resources, which is named CHIC Resource Ontology (CHICRO):

<https://github.com/open-physiology/chic/tree/master/ontologies/internal>.

In this approach, models are considered resources, which are described using CHICRO. CHICRO provides what is sometimes referred to as “application ontology”, a knowledge engineering artefact designed and tailored to specific application needs. The essence of this application context is to support the annotation of models and parameters according to requirements elicited by modellers so as:

- i) to allow annotations to be performed and managed within the model repository
- ii) to allow the annotation data to be used for searches against the model repository, also in the context of end-user applications (e.g., CRAF).
- iii) to allow the annotation data to be used in certain workflows and processes leading to the creation of hypermodels (in the model editor).

Further to CHICRO, we use a dedicated (RDF) schema for the record of the relevant metadata about models and their parameters: <https://github.com/open-physiology/chic/tree/master/rdfschema>. This schema provides a skeletal schematic for the designation of hypomodels and hypermodels and their constituent parameters. Furthermore, it provides the means to ascribe metadata to the resulting resources (models and parameters).

In many instances, we found it useful to explicitly control terms available for annotations. This has been embedded into the schema so it could also be used to configure the Graphical User Interface in the Model Repository. Some excerpts can be found in the following link:

<https://github.com/open-physiology/chic/tree/master/controlled-terms>

We relied on a convention defined by the Model Repository in order to refer to a) models and b) model parameters according to which they are given a globally unique identifier. For example, <https://mr.chic-vph.eu/metadata#04e3c5aa-ad45-11e5-bd32-fa163e092aac> is the identifier of the ICCS Wilms Oncosimulator hypomodel.

I.2 Scope of CHIC RDF and Annotation Schema

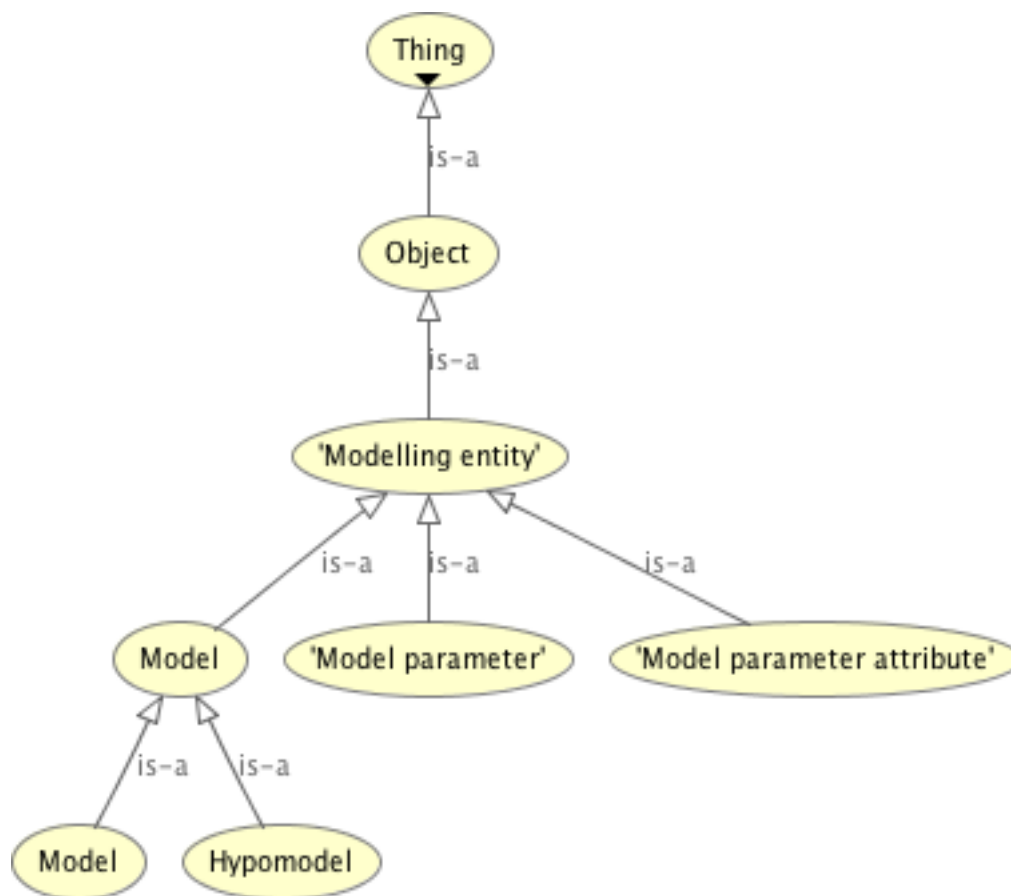


Figure I: High level CHIC RDF Schema constituting a baseline ontology of models and parameters.

CHIC models and parameters in CHIC models are resources that can be described using ontological terms in a series of domains (see, in particular, D7.3).

Metadata for models are essentially made from the following aspects:

- Name (not an ontological object, but a string of text)
- Human readable description (not an ontological object, but a string of text)
- Ascription to one or more of the hypomodel Perspectives (ontological terms, see below and D6.1, 6.3, 7.3).

Metadata for parameters are essentially made from:

- Name (not an ontological object, but a string of text)
- Human readable description (not an ontological object, but a string of text)
- Types of parameters (ontological terms from the CHICRO application ontology, see below)
- Input/output Roles (in relation to models and formally encoded using the CHIC schema, see below)
- Datatype (optional but provisioned with ontological terms from a controlled list, see below)
- Units of measurements (ontological terms from the CHICRO application ontology)
- Biological Meaning of parameter (“interpreted type”, ontological terms from the CHICRO application ontology)

Ruled out of metadata encoding for parameters:

- Type of file
- Default values (encoded into the repository directly)

Categories

Modelling objects: A class of objects. An instance of the class `ModellingObject` is a model or a part (logical or conceptual) of a model, in particular a parameter.

Mathematical models: A subclass of the class of modelling objects. An instance of the class `MathematicalModel` is a model.

Hypermodels: A subclass of the class of mathematical models. An instance of the class `Hypermodel` is a hypermodel in the sense of CHIC technical specifications.

Hypomodels: A subclass of the class of mathematical models. An instance of the class `Hypomodel` is a hypomodel in the sense of CHIC technical specifications.

Parameter of a mathematical model: A subclass of the class of modelling objects such that an instance of this class is a parameter of a mathematical model.

Input parameter of a mathematical model: A subclass of the class of parameter of a mathematical model such that an instance of this class is an input parameter of some mathematical model.

Output parameter of a mathematical model: A subclass of the class of parameter of a mathematical model such that an instance of this class is an output parameter of a mathematical model.

Model Parameter Attribute: An instance of `ModelParameterAttribute` is an attribute of a parameter in a model.

Structural Relations

`parameterOfModel`: Links generically a model to one of its parameters, or its converse

`input-parameter-of`: Links a parameter to a model when the parameter is an input parameter of the model.

output-parameter-of: Links a parameter to a model when the parameter is an output parameter of the model.

Annotation Relations

hasFileByFilename: Links a parameter to the filename in which the parameter is specified.

parameterhasUnits: Link between a parameter and a unit (an object in an ontology).

parameterhasUnits-string: Link between a parameter and a unit (string name).

parameterhasDatatype: Link between a parameter and a datatype, for example an xsd datatype or other.

parameterHasDefaultValue: Link between a parameter and a value recorded as its default.

modelParameterHasAttribute: Link between a model parameter and one of its attributes. Examples are given in the following list.

Instances: Model parameter types

ModelParameterAttribute-IsMandatory: An attribute of model parameters which are mandatory for the execution of the model which they refer to.

ModelParameterAttribute-IsOutput: An attribute of model parameters that are output parameters of the model which they refer to. See also outputParameterOfModel.

ModelParameterAttribute-IsStatic: An attribute of model parameters that are static parameters of the model which they refer to.

Modelling logic: A model parameter which is used by the software environment in the model execution. Such a parameter lacks a biological meaning related to the modelled phenomenon .

Domain logic: A model parameter which is used to describe aspects of the biological phenomenon modelled.

Patient specific: A parameter that varies depending on the context of application of a model to a specific subject

Population specific: A parameter that varies depending on the context of application of a model to a specific group of subjects

Patient agnostic: A parameter that does not vary across a subject or a population but is generic. It can be considered as a limited case of a population specific parameter for the most encompassing population.

Aggregate data: A parameter that encodes source of data that may be implicitly contained in the target, typically archives or files.

Discrete data: A parameter that provides qualitative or quantitative values that are directly linked to the model execution rather than included in a larger file or archive.

Data types

Table 1: Mapping between data types as presented in the model repository for parameters and external controlled vocabulary (NCI Thesaurus).

Type	NCIT mapping	URI used
File	C42883	<http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C42883>
Integer	C45255	<http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C45255>
Float	C48150	<http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C48150>
Double	C48870	<http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C48870>
String	C45253	<http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C45253>

Units of measurements

Empirical evidence was extracted from the model repository in order to guide an informal analysis based on a sample dataset (**Table 2**).

Brief analysis: The large majority of parameters do not have unit strings attached to them. A brief look at them shows that a large majority are non-quantity parameters (example, reference to a file, flags, etc.). A number of parameters that could be given a unit are not. This is a data acquisition issue; the model was not annotated fully. There is anecdotal evidence that the string based annotation allows ambiguity, for example “days” or “d” is used. There are overall few units used. Some of the units are rather atypical (especially count and rates related to cell numbers).

Solution: Use an ad hoc assembly of unit terms with one preferred name to be displayed in the annotation tools of the repository. The ID used for the representation of units can be tied together via relations if reasoning is needed to establish commensurability between parameters in applications (e.g. CRAFT).

Table 2: Frequency of occurrence of the values for the unit string attribute of annotated models in the sample. The users of the repository who uploaded the model entered these strings. Most parameters had no annotation.

	Var1	Frequency
1	(no units)	114
2	l/h	2
3	d	7
4	days	27
5	fraction of cell per hour	3
6	Gy	3
7	h	7
8	h-l	2
9	Kg/m ³	2
10	ml	2
11	mm	1
12	mm ² /hr	2
13	months	6
14	Ncell ⁻¹ hr ⁻¹	2
15	non-dimensional	2
16	none	3
17	number of biological cells per 1mm ³	1
18	percentage	1
19	valid system path relative to sandbox directory	4
20	years	1

Table 3: Current set of controlled terms for units of measurement (RDF Schema 1.0.1).

"valueURI"	"valueLabel"
"http://www.chic-vph.eu/ontologies#chic_0002115"	"second (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002113"	"hour (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002203"	"per cent (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002131"	"millimeter (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002201"	"square millimeter per hour (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002111"	"year (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002202"	"kilogram per cubic meter (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002112"	"day (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002153"	"cubic centimeter (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002116"	"month (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002171"	"per hour (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002151"	"liter (unit)"
"http://www.chic-vph.eu/ontologies#chic_0002152"	"milliliter (unit)"

Interpreted type

We used a minimalistic strategy (D6.3) in which a selected number of standardised identifiers for biological interpretation of model parameters is used. These standardised terms are useful in order to facilitate semantic integration and also in order to benefit from the formalised meaning associated with the terms. However, as indicated in the illustrative queries below, we do not support complex reasoning over these terms. In practice, tool support for the on-the-fly creation of well-defined ontological term was not feasible. Instead our strategy consisted in providing a range of generic reusable terms belonging to well articulate ontologies. While this strategy may not allow the annotation of a parameter with its most specific and detailed meaning, despite this apparent limitation, the trade-off is a gain in applicability of the approach. Also, this approach allows for further development and refinement.

The current set of controlled terms is as follows and abstracts at the highest level of generality from a number of models annotated in the model repository:

Table 4: Current set of controlled terms for biological meanings (RDF Schema 1.0.1).

"valueURI"	"valueLabel"
"http://www.chic-vph.eu/ontologies#chic_0001024"	"rate of proliferation of cell population"
"http://purl.org/obo/owlapi/quality#PATO_0000070"	"count"
"http://purl.org/obo/owlapi/quality#PATO_0000918"	"volume"
"http://www.chic-vph.eu/ontologies#chic_0001021"	"doubling time (duration)"
"http://purl.org/obo/owlapi/quality#PATO_0000011"	"age"
"http://www.chic-vph.eu/ontologies#chic_0001022"	"percentage (ratio)"
"http://www.chic-vph.eu/ontologies#chic_0001020"	"timepoint (duration to)"
"http://purl.org/obo/owlapi/quality#PATO_0000161"	"rate"
"http://purl.org/obo/owlapi/quality#PATO_0001309"	"duration"
"http://purl.org/obo/owlapi/quality#PATO_0001745"	"radiation absorbed dose"
"http://www.chic-vph.eu/ontologies#chic_0001023"	"probability (ratio)"
"http://www.chic-vph.eu/ontologies#chic_0001025"	"cell kill rate (probability)"
"http://purl.org/obo/owlapi/quality#PATO_0000033"	"concentration"
"http://www.chic-vph.eu/ontologies#chic_0001026"	"count of cells in population"
"http://purl.org/obo/owlapi/quality#PATO_0002326"	"angle"
"http://purl.org/obo/owlapi/quality#PATO_0001470"	"ratio"

This list is extensible, although extensions are to be managed so as to preserve the trade-off between usability and adequacy.

1.1 Example of the WILMS model parameters

		Full name as presented in the Editor	Description	Type (Int, float, double, string, file etc.)	Units or file extension	Value range ("from"-"to") or Discrete possible values (value1,value2,value3)	If the Input parameter is included in a file state the name of the file	Default value to appear in Editor	Comment
wilms	input	Cell cycle duration of stem cells	Cell cycle duration of stem cells through the phases of the active cell cycle (G1, S, G2, M-not including G0 phase)	int	hours	10-40	input.xml	23	

Figure 2: XLS description of modeller provided input

```
<https://mr.chic-vph.eu/metadata#test-vmp1>

a: <http://www.chic-vph.eu/ontologies/resource#ModelParameter> ;

<http://www.chic-vph.eu/ontologies/resource#inputParameterOfModel>
<https://mr.chic-vph.eu/metadata#04e3c5aa-ad45-11e5-bd32-fa163e092aac> ;

<http://www.chic-vph.eu/ontologies/resource#hasName> "Cell cycle duration of
stem cells" ;

<http://www.chic-vph.eu/ontologies/resource#parameterHasDatatype>
<http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C45255> ;

<http://www.chic-vph.eu/ontologies/resource#parameterHasUnits-string> "hours" ;

<http://www.chic-vph.eu/ontologies/resource#modelParameterHasAttribute>
<http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-
IsAggregateData> ;

<http://www.chic-vph.eu/ontologies/resource#hasFileByFilename> "input.xml" ;

<http://www.chic-vph.eu/ontologies/resource#parameterHasDefaultValue> "23" .
```

Figure 3: RDF encoding, describing the contents of Figure 2

SPARQL query interface showing a query and its results.

```
1 PREFIX rdf: <http://www.w3.org/1999/02/22-rdf-syntax-ns#>
2
3 SELECT ?subject ?model ?name ?dtype ?nunit ?type ?file ?default
4 WHERE {
5   ?subject <http://www.chic-vph.eu/ontologies/resource#inputParameterOfModel> ?model
6   . ?subject <http://www.chic-vph.eu/ontologies/resource#hasName> ?name
7   . ?subject <http://www.chic-vph.eu/ontologies/resource#parameterHasDatatype> ?dtype
8   . ?subject <http://www.chic-vph.eu/ontologies/resource#parameterHasUnits-string> ?nunit
9   . ?subject <http://www.chic-vph.eu/ontologies/resource#modelParameterHasAttribute> ?type
10  . ?subject <http://www.chic-vph.eu/ontologies/resource#hasFileByFilename> ?file
11  . ?subject <http://www.chic-vph.eu/ontologies/resource#parameterHasDefaultValue> ?default
12 }
13 LIMIT 250
```

QUERY RESULTS

Raw Response Table

subject	model	name	dtype	nunit	type	file	default
1 <https://mr.chic-vph.eu/metadata#test-vmp1>	<https://mr.chic-vph.eu/metadata#04e3c5aa-ad45-11e5-bd32-fa163e092aac>	"Cell cycle duration of stem cells"	<http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C45255>	"hours"	<http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsAggregateData>	"input.xml"	"23"

Figure 4: SPARQL query against the CHIC triple store for the RDF metadata described in figure 3 (top part) and tabled-formed response (bottom part)

I.4 Defining a parameter

For a hypothetical parameter with an ID: <https://mr.chic-vph.eu/metadata#test-vmpI>, the following metadata are formulated:

Definition as a parameter:

Subject	Parameter URI
Predicate	a:
Object	<http://www.chic-vph.eu/ontologies/resource#ModelParameter>
Example:	
RDF code	<https://mr.chic-vph.eu/metadata#test-vmpI> a: <http://www.chic-vph.eu/ontologies/resource#ModelParameter> .
Paraphrase	VmpI is a parameter.

Associate to model as input or output parameter:

Subject	Parameter URI
Predicate	One of: <http://www.chic-vph.eu/ontologies/resource#inputParameterOfModel> <http://www.chic-vph.eu/ontologies/resource#outputParameterOfModel>
Object	Model URI
Example:	
RDF code	<https://mr.chic-vph.eu/metadata#test-vmpI> <http://www.chic-vph.eu/ontologies/resource#inputParameterOfModel> <https://mr.chic-vph.eu/metadata#04e3c5aa-ad45-11e5-bd32-fa163e092aac> .
Paraphrase	VmpI is an input parameter of the Wilms model.

Ascribe name:

Subject	Parameter URI
Predicate	<http://www.chic-vph.eu/ontologies/resource#hasName>
Object	RDF literal (string)
Example:	
RDF code	<https://mr.chic-vph.eu/metadata#test-vmpI> <http://www.chic-vph.eu/ontologies/resource#hasName> "Cell cycle duration of stem cells"
Paraphrase	VmpI is named "Cell cycle duration of stem cells"

Ascribe datatype from controlled vocabulary:

Subject	Parameter URI
Predicate	<http://www.chic-vph.eu/ontologies/resource#parameterHasDatatype>
Object	RDF resource, one of: File <http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C42883> Integer <http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C45255> Float <http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C48150> Double <http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C48870>

	String <http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C45253>
Example:	
RDF code	<https://mr.chic-vph.eu/metadata#test-vmpI> <http://www.chic-vph.eu/ontologies/resource#parameterHasDatatype> <http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#C45253>
Paraphrase	VmpI has the datatype integer.

Ascribe string name of units:

Subject	Parameter URI
Predicate	<http://www.chic-vph.eu/ontologies/resource#parameterhasUnits-string>
Object	RDF literal (string)
Example:	
RDF code	<https://mr.chic-vph.eu/metadata#test-vmpI> <http://www.chic-vph.eu/ontologies/resource#parameterhasUnits-string> "hours".
Paraphrase	The unit for the values of vmpI is hours.

Ascribe string name of units:

Subject	Parameter URI
Predicate	<http://www.chic-vph.eu/ontologies/resource#parameterhasUnits>
Object	RDF resource, one of: Hour (unit) <http://www.chic-vph.eu/ontologies#chic_0002113> Per cent (unit) <http://www.chic-vph.eu/ontologies#chic_0002203> Millimeter (unit) <http://www.chic-vph.eu/ontologies#chic_0002131> Square millimeter per hour (unit) <http://www.chic-vph.eu/ontologies#chic_0002201> Year (unit) <http://www.chic-vph.eu/ontologies#chic_0002111> Kilogram per cubic meter (unit) <http://www.chic-vph.eu/ontologies#chic_0002202> Day (unit) <http://www.chic-vph.eu/ontologies#chic_0002112> Cubic centimeter (unit) <http://www.chic-vph.eu/ontologies#chic_0002153> Month (unit) <http://www.chic-vph.eu/ontologies#chic_0002116> Per hour (unit)

	<http://www.chic-vph.eu/ontologies#chic_0002171> Liter (unit) <http://www.chic-vph.eu/ontologies#chic_0002151> Milliliter (unit) <http://www.chic-vph.eu/ontologies#chic_0002152>
--	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Example:

RDF code	<https://mr.chic-vph.eu/metadata#test-vmpI> vph.eu/ontologies/resource#parameterhasUnits> vph.eu/ontologies#chic_0002152>	<http://www.chic-vph.eu/ontologies#chic_0002151> <http://www.chic-vph.eu/ontologies#chic_0002152>
Paraphrase	The unit for the values of vmpI is milliliter	

Ascribe parameter attribute:

Subject	Parameter URI
Predicate	<http://www.chic-vph.eu/ontologies/resource#modelParameterHasAttribute>
Object	RDF resource, one of: is modelling logic <http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsModellingLogic> is domain logic <http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsDomainLogic> is aggregate data <http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsAggregateData> is discrete data <http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsDiscreteData> is patient specific <http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsPatientSpecific> is population specific <http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsPopulationSpecific> is generic <http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsGeneric>

Example:

RDF code	<code><https://mr.chic-vph.eu/metadata#test-vmpI></code> <code><http://www.chic-vph.eu/ontologies/resource#modelParameterHasAttribute></code> <code><http://www.chic-vph.eu/ontologies/resource#ModelParameterAttribute-IsAggregateData></code> .
Paraphrase	VmpI is of type aggregated data parameter.

Ascribe associated filename:

Subject	Parameter URI
Predicate	<code><http://www.chic-vph.eu/ontologies/resource#hasFileByFilename></code>
Object	RDF Literal (string)
Example:	
RDF code	<code><https://mr.chic-vph.eu/metadata#test-vmpI></code> <code><http://www.chic-vph.eu/ontologies/resource#hasFileByFilename></code> "input.xml".
Paraphrase	The name of the file in which values are found for vmpI is "input.xml".

Ascribe default value:

Subject	Parameter URI
Predicate	<code><http://www.chic-vph.eu/ontologies/resource#parameterHasDefaultValue></code>
Object	RDF Literal (string)
Example:	
RDF code	<code><https://mr.chic-vph.eu/metadata#test-vmpI></code> <code><http://www.chic-vph.eu/ontologies/resource#parameterHasDefaultValue></code> "23".
Paraphrase	The default value for vmpI is 23. (Assumes knowledge of unit independently recorded.)

Ascribe interpretation:

Subject	Parameter URI
Predicate	<code><http://www.chic-vph.eu/ontologies/resource#interpreted-type></code>
Object	RDF resource, one of: Rate of proliferation of cell population <code><http://www.chic-vph.eu/ontologies#chic_0001024></code> Count (Quantity) <code><http://purl.org/obo/owlapi/quality#PATO_0000070></code> Volume <code><http://purl.org/obo/owlapi/quality#PATO_0000918></code> Doubling time (duration) <code><http://www.chic-vph.eu/ontologies#chic_0001021></code> Age <code><http://purl.org/obo/owlapi/quality#PATO_0000011></code> Percentage (ratio) <code><http://www.chic-vph.eu/ontologies#chic_0001022></code>

	<p>Timepoint (duration to) <http://www.chic-vph.eu/ontologies#chic_0001020></p> <p>Rate <http://purl.org/obo/owlapi/quality#PATO_0000161></p> <p>Duration <http://purl.org/obo/owlapi/quality#PATO_0001309></p> <p>Radiation absorbed dose <http://purl.org/obo/owlapi/quality#PATO_0001745></p> <p>Probability(ratio) <http://www.chic-vph.eu/ontologies#chic_0001023></p> <p>Cell kill rate (probability) <http://www.chic-vph.eu/ontologies#chic_0001025></p> <p>Concentration <http://purl.org/obo/owlapi/quality#PATO_0000033></p> <p>Count of cells in population <http://www.chic-vph.eu/ontologies#chic_0001026></p> <p>Angle <http://purl.org/obo/owlapi/quality#PATO_0002326></p> <p>Ratio <http://purl.org/obo/owlapi/quality#PATO_0001470></p>
--	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Example:

RDF code	<https://mr.chic-vph.eu/metadata#test-vmp1> <http://www.chic-vph.eu/ontologies/resource#interpreted-type> <http://purl.org/obo/owlapi/quality#PATO_0000161>
Paraphrase	The parameter vmp1 is a rate.

Ascribe units

Subject	Parameter URI
Predicate	<http://www.chic-vph.eu/ontologies/resource#parameterhasUnits>
Object	RDF resource:
Example:	
RDF code	<https://mr.chic-vph.eu/metadata#test-vmp1> <http://www.chic-vph.eu/ontologies/resource#parameterhasUnits> <>
Paraphrase	The unit for the values of vmp1 is <>.

I.5 Querying around parameters by meaning

No reasoning is applied on the hierarchy of meanings. For example, there is no query to retrieve a parameter with a meaning that is a specialisation of the meaning of another parameter (e.g., retrieving a glucose concentration when starting the query from a parameter annotated to concentration in general). The abstraction mechanism over parameter meanings renders such a mechanism vain, finer granularity of the annotations would be needed. Thus, for example, all biological phenomena rates are considered simply as “rates” and cell kill rate can be associated to tumour growth rate by the type of under-specification allowed here. This means that the queries supported are at best contributing to a pre-selection workflow intended to help a prospective user filter through possible associations. ‘

Two illustrative queries around managing parameters through their meaning are provided using an ad hoc dataset:

Files used are:

Schema version 1.0.1 [https://github.com/open-](https://github.com/open-physiology/chic/blob/master/rdfs/schema/chicrdfs/schema-1.0.1.ttl)

[physiology/chic/blob/master/rdfs/schema/chicrdfs/schema-1.0.1.ttl](https://github.com/open-physiology/chic/blob/master/rdfs/schema/chicrdfs/schema-1.0.1.ttl)

Input parameter data (random) [https://github.com/open-](https://github.com/open-physiology/chic/blob/master/data/randomly/testparam-inter1-input2.ttl)

[physiology/chic/blob/master/data/randomly/testparam-inter1-input2.ttl](https://github.com/open-physiology/chic/blob/master/data/randomly/testparam-inter1-input2.ttl)

Output parameter data (random) [https://github.com/open-](https://github.com/open-physiology/chic/blob/master/data/randomly/testparam-inter1-output2.ttl)

[physiology/chic/blob/master/data/randomly/testparam-inter1-output2.ttl](https://github.com/open-physiology/chic/blob/master/data/randomly/testparam-inter1-output2.ttl)

I.5.1 Retrieve all controlled values and their preferred name

Template:

Get_ControlledValues_InterpretedType

Template definition:

PREFIX rdf: <http://www.w3.org/1999/02/22-rdf-syntax-ns#>

select ?valueURI ?valueLabel where {

<http://www.chic-vph.eu/ontologies/resource#interpreted-type>

<http://www.chic-

vph.eu/ontologies/resource#designatedValueWithPreferredLabel> ?pair .

?pair rdf:first ?valueURI .

?pair rdf:rest ?rest .

?rest rdf:first ?valueLabel

}

Results in JSON format:

```
{
  "head": {
    "vars": [ "valueURI" , "valueLabel" ]
  },
  "results": {
```

```
"bindings": [
  {
    "valueURI": { "type": "uri" , "value": "http://www.chic-vph.eu/ontologies#chic_0001024" } ,
    "valueLabel": { "type": "literal" , "value": "rate of proliferation of cell population" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0000070" } ,
    "valueLabel": { "type": "literal" , "value": "count" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0000918" } ,
    "valueLabel": { "type": "literal" , "value": "volume" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://www.chic-vph.eu/ontologies#chic_0001021" } ,
    "valueLabel": { "type": "literal" , "value": "doubling time (duration)" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0000011" } ,
    "valueLabel": { "type": "literal" , "value": "age" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://www.chic-vph.eu/ontologies#chic_0001022" } ,
    "valueLabel": { "type": "literal" , "value": "percentage (ratio)" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://www.chic-vph.eu/ontologies#chic_0001020" } ,
    "valueLabel": { "type": "literal" , "value": "timepoint (duration to)" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0000161" } ,
    "valueLabel": { "type": "literal" , "value": "rate" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0001309" } ,
    "valueLabel": { "type": "literal" , "value": "duration" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0001745" } ,
    "valueLabel": { "type": "literal" , "value": "radiation absorbed dose" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://www.chic-vph.eu/ontologies#chic_0001023" } ,
    "valueLabel": { "type": "literal" , "value": "probability (ratio)" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://www.chic-vph.eu/ontologies#chic_0001025" } ,
    "valueLabel": { "type": "literal" , "value": "cell kill rate (probability)" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0000033" } ,
```

```

    "valueLabel": { "type": "literal" , "value": "concentration" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://www.chic-vph.eu/ontologies#chic_0001026" } ,
    "valueLabel": { "type": "literal" , "value": "count of cells in population" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0002326" } ,
    "valueLabel": { "type": "literal" , "value": "angle" }
  },
  {
    "valueURI": { "type": "uri" , "value": "http://purl.org/obo/owlapi/quality#PATO_0001470" } ,
    "valueLabel": { "type": "literal" , "value": "ratio" }
  },
]
}
}

```

Results (human readable “table”):

"valueURI"	"valueLabel"
"http://www.chic-vph.eu/ontologies#chic_0001024"	"rate of proliferation of cell population"
"http://purl.org/obo/owlapi/quality#PATO_0000070"	"count"
"http://purl.org/obo/owlapi/quality#PATO_0000918"	"volume"
"http://www.chic-vph.eu/ontologies#chic_0001021"	"doubling time (duration)"
"http://purl.org/obo/owlapi/quality#PATO_0000011"	"age"
"http://www.chic-vph.eu/ontologies#chic_0001022"	"percentage (ratio)"
"http://www.chic-vph.eu/ontologies#chic_0001020"	"timepoint (duration to)"
"http://purl.org/obo/owlapi/quality#PATO_0000161"	"rate"
"http://purl.org/obo/owlapi/quality#PATO_0001309"	"duration"
"http://purl.org/obo/owlapi/quality#PATO_0001745"	"radiation absorbed dose"
"http://www.chic-vph.eu/ontologies#chic_0001023"	"probability (ratio)"
"http://www.chic-vph.eu/ontologies#chic_0001025"	"cell kill rate (probability)"
"http://purl.org/obo/owlapi/quality#PATO_0000033"	"concentration"
"http://www.chic-vph.eu/ontologies#chic_0001026"	"count of cells in population"
"http://purl.org/obo/owlapi/quality#PATO_0002326"	"angle"
"http://purl.org/obo/owlapi/quality#PATO_0001470"	"ratio"

1.5.2 Defined query – Retrieve all parameters with a specified meaning.

Template

Get_Parameters_With_InterpretedType

Example input: http://purl.obolibrary.org/obo/PATO_0000161

<http://purl.obolibrary.org/obo/PATO_0000161>

Template definition:

0 Meaning

PREFIX chicro: <<http://www.chic-vph.eu/ontologies/resource#>>

SELECT ?PARAMETER

```
WHERE {
?PARAMETER chicro:interpreted-type <[0]> }
```

SPARQL Example

```
PREFIX chicro: <http://www.chic-vph.eu/ontologies/resource#>
PREFIX quant: <http://purl.obolibrary.org/obo/>
SELECT ?PARAMETER
WHERE {
?PARAMETER chicro:interpreted-type quant:PATO_0000161 }
LIMIT 3
```

Results in JSON format:

```
{
  "head": {
    "vars": [ "PARAMETER" ]
  },
  "results": {
    "bindings": [
      {
        "PARAMETER": { "type": "uri" , "value": "http://www.chic-vph.eu/data/testeditor#2" }
      },
      {
        "PARAMETER": { "type": "uri" , "value": "http://www.chic-vph.eu/data/testeditor#4" }
      },
      {
        "PARAMETER": { "type": "uri" , "value": "http://www.chic-vph.eu/data/testeditor#31" }
      }
    ]
  }
}
```

1.6 Model and parameter annotation procedure in the Model Repository

The initial point for creating model and parameter metadata is the Model Repository. During the uploading procedure of a model and its parameters, a set of metadata is produced and sent via web services to the CHIC triplestore. The procedure and some indicative results are described in D8.4. This automated way of metadata production is beneficiary for elements that can be annotated by a finite number of terms or URL's (such as the assignment of a unique URL to each new model/parameter or a model's perspectives and corresponding values). The existence, however of elements that are annotated from domains with a significantly high amount of terms, dictates a slightly different approach, which requires the user's (in this case, the modeller's) involvement.

The key idea for the aforementioned approach requires the user to initially upload their model along with their parameters, using the model repository wizard, and proceed at a later point in time to specifically annotate any existing elements "by hand", from proper sets of available values. These values correspond to terms located in ontologies which reside within the CHIC metadata

infrastructure (including CHICRO). The sets of values are considered to be more changeable than others (e.g. the perspective value sets), thus evolving constantly. Currently this method is utilized for the annotation of a parameter's unit and biological meaning (interpreted type). The next figures demonstrate the envisioned high level workflow diagram of the suggested procedure, the corresponding sequential diagram and implementation details from the model repository.

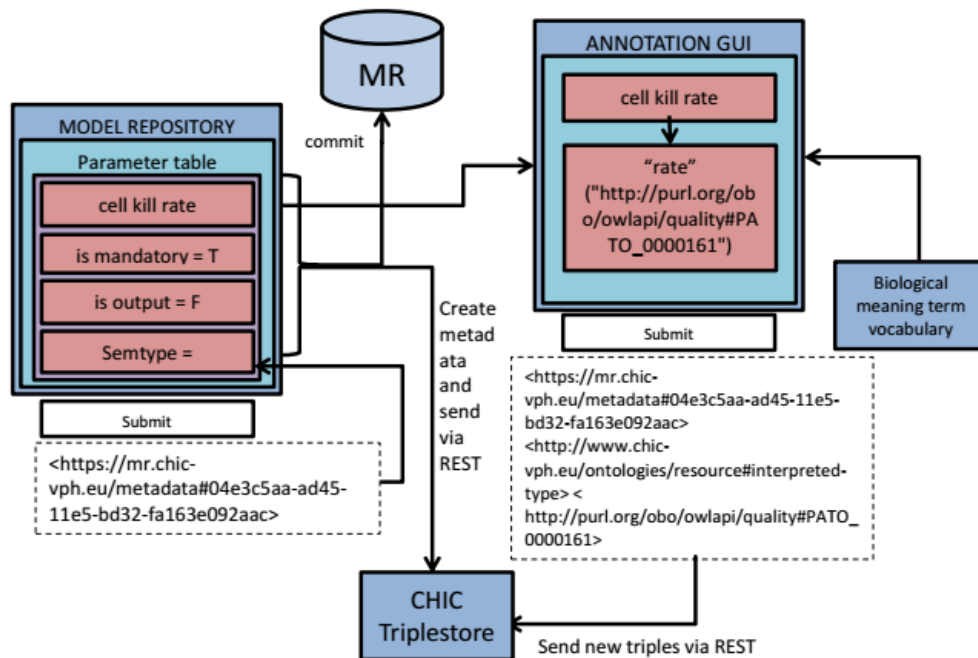


Figure 5: Workflow diagram for annotating the biological meaning of a parameter. The same principle applies to all non-automatically annotated model parameters.

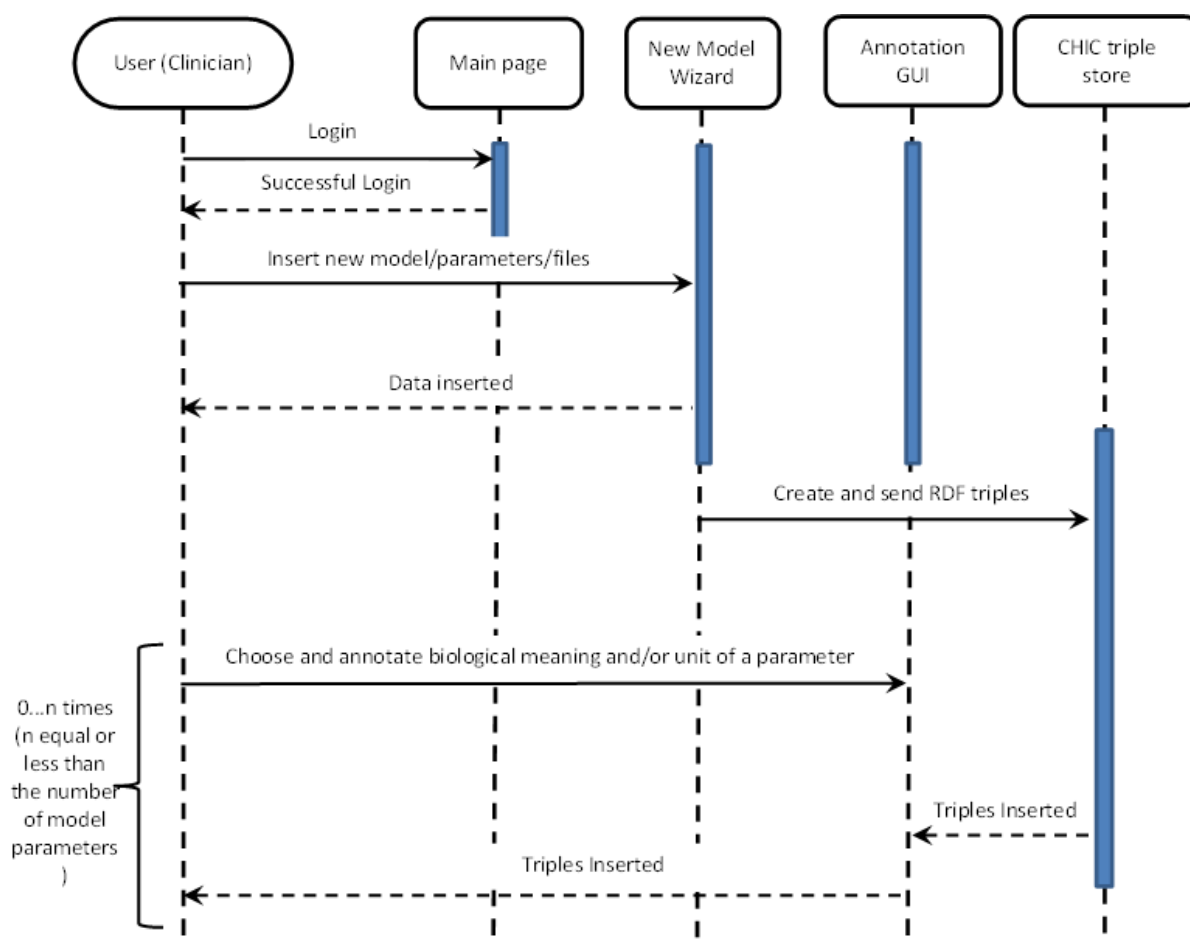


Figure 6: Sequential diagram for annotating the biological meaning and/or the unit of a parameter.

Annotating procedure

The annotation of the model parameters is currently conducted through the user interface of the Model Repository. The user has to select the their model, pick the desired parameter and then press the button “Annotate this parameter”. Afterwards the user is redirected to a new page where they can select the appropriate semantic meaning of the parameter and the semantic description of the parameter’s unit. The following figures depict the aforementioned workflow for the parameter annotation through the Model Repository. More specifically, figure 7 presents the page where the user intends to annotate the parameter cell cycle duration of the model ICCS Wilms Oncosimulator whereas figure 8 presents the form where the user is going to select the appropriate semantic meanings for the definition of the parameter and its unit.

The user is going to annotate the parameter “cell cycle duration” which belongs to the model ICCS Wilms Oncosimulator

Parameters of the model: ICCS Wilms Oncosimulator									
Add one more parameter for this model									
Action	ID	UUID	Name	Description	Data type	Unit	Flag used to read static input parameter	Data range	Default value
<div>Action ▾</div> <div> Update this parameter Delete this parameter Annotate this parameter </div>	416	58eda828-ad45-11e5-9207-92aac	cell_cycle_duration	Cell cycle duration of cells through the phases of the active cell cycle (G1, S, G2, M-not including G0 phase)	number	h	-Tc	10-40	6
<div>Action ▾</div>	419	165b40aa-ad46-11e5-8313-fa163e092aac	cell_kill_rate	Factor to adjust and personalize cell kill rate derived from bibliography	number		-CKR_FACTOR	0-1	0.53
<div>Action ▾</div>	420	328b20b0-ad46-11e5-934a-fa163e092aac	sleep_fraction_NecrLayer	Fraction of cells that enter G0 phase following mitosis in the necrotic regions of the	number		-Psleep_Nec	0-1	0.31

Figure 7: The user is going to annotate the parameter “cell cycle duration” which belongs to the model ICCS Wilms Oncosimulator



Annotation of the parameter "cell cycle duration" of model ICCS: Wilms Oncosimulator:

Choose the semantic meaning for this parameter:

Choose the semantic description of the parameter's unit:

Annotate parameter

Figure 8: The users selects the appropriate semantic meanings with respect to the parameter and its unit.

2. The composition of a new hypermodel through the editor and the storage of the hypermodel in the Model Repository

The Model and Tool Repository is the CHIC component which persistently stores the hypermodels which that have been developed in the context of the CHIC project. The hypermodels are stored in the form of xMML descriptive language . The latter defines the topology of the hypermodel and it is produced automatically by the Editor whenever the modeller needs to design a new hypermodel through the graphical user interface of the editor. The Editor, allows the composition of existing hypomodels into complex hypermodels that can be used in the clinical setting. Figure 9 outlines the integration and the collaboration between the Model Repository and the Editor.

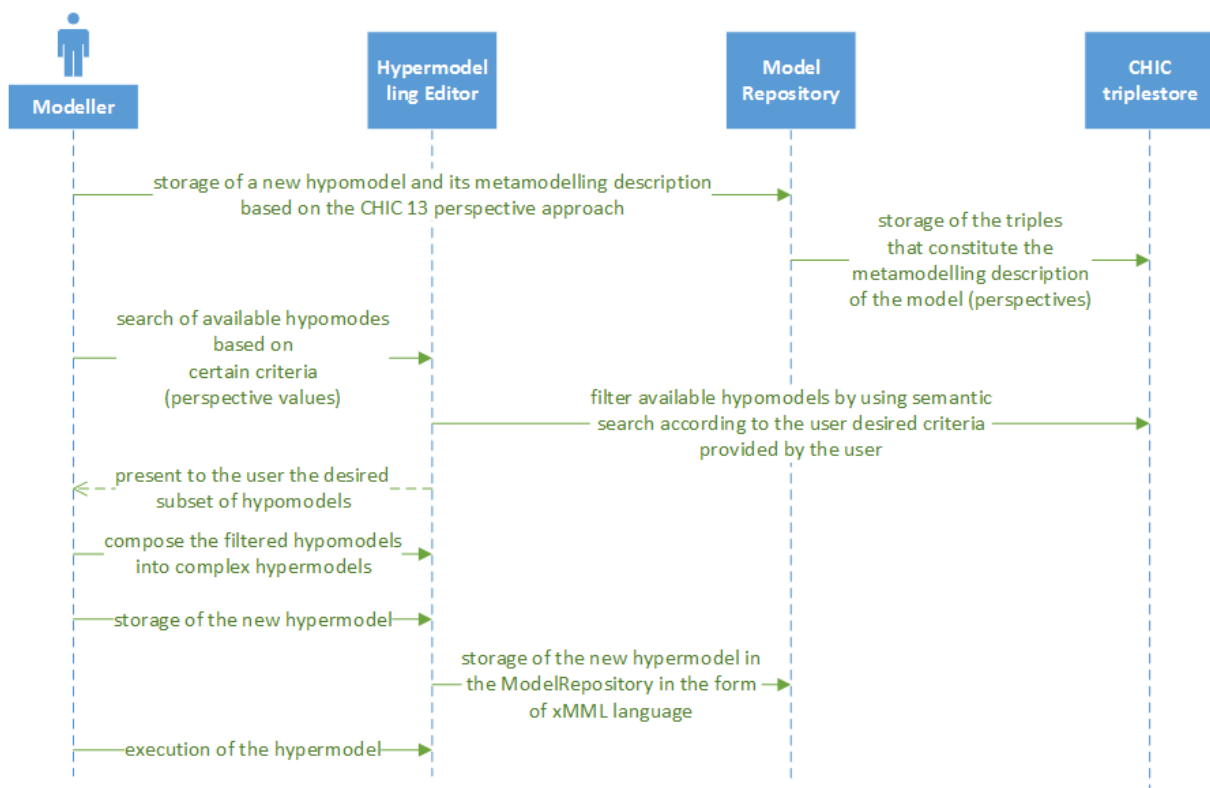


Figure 9: The sequential diagram which depicts the collaboration between the Editor, the Model Repository and the CHIC triplestore with respect to the composition of a new hypermodel, its storage in the Model Repository in the form of xMML and its execution

As shown in figure 9, the following steps are needed for the composition of a new hypermodel:

- **Step one:** The modeller stores in the Model Repository the full information of the new hypomodel along with its metamodeling description based on the CHIC 13 perspective approach.
- **Step two:** The Model Repository stores in the CHIC triplestore the triples that constitute the metamodeling description of the model (perspectives).
- **Step three:** The modeller searches for available hypomodels based on certain criteria (perspective values).
- **Step four:** The Hypermodelling Editor connects to the CHIC triplestore through the RICORDO web services. Afterwards it filters the available hypomodels by conducting semantic search according to the user desired criteria.
- **Step five:** The Hypermodelling editor presents to the user the filtered hypomodels.
- **Step six:** The user having available the filtered hypomodels, proceeds to the composition of the new hypermodel.
- **Step seven:** The user chooses to store the new hypermodel into the Model Repository.
- **Step eight:** The Hypermodelling Editor stores the new hypermodel into the Model Repository in the form of xMML language.
- **Step nine:** The user is now able to run the new hypermodel.

As described previously, some of the meta-information related to models is converted to RDF triples so as to be stored in the CHIC triplestore. The aforementioned meta-information is something valuable for the Hypermodelling Editor in order to perform sophisticated queries through semantic reasoning. A part of the models meta-information is related to the categorization of the models. As stated in the Deliverable 6.1 “Cancer hypomodelling and hypermodelling strategies and initial component models”, mathematical and computational cancer models can be categorized depending on the perspective from which they are viewed in the basic science context. The definition of the thirteen perspectives and their indicative values is included in the aforementioned deliverable. Consequently, both the Model Repository and the Hypermodelling Editor have been integrated into the CHIC semantics infrastructure for different reasons. The Model Repository connects to the semantics infrastructure for storing semantic description of the models, whereas the Hypermodelling Editor mainly connects to the semantics infrastructure in order to elicit the needed information for filtering the available hypomodels or for checking the validity when connecting the different hypomodel parameters.

Regarding the integration of the Model Repository with the CHIC semantics infrastructure, both components make use of a common RDF mapping configuration file so as to produce a model (a set of RDF triples) based also on the already locally stored relational data. The aforementioned configuration file maps some of the Model Repository’s database tables and columns to specific CHIC ontology terms. This mapping defines the virtual RDF graph that contains some of the information from the Model and Tool repository’s MySQL database which is related to the categorization of the models. With this kind of integration between the Model Repository and the CHIC triplestore, the user is able to categorize their model by visiting only a single CHIC component. After the submission of the user’s data, it is the Model Repository’s responsibility to store the information related to the categorization of the model both to the repository’s relational database and to the CHIC triplestore. It has to be noted, that as shown in figure 10, the user is able to categorize their new model based on the 13 perspectives defined within CHIC through the fourth step of the Model Repository wizard. After the storage of the new model, the semantic description of the categorization of the new model is automatically stored in the form of triples into the CHIC semantics infrastructure. The topology of the CHIC components that handle the semantic annotation of the models with respect to perspective categorization is presented in figure 11. According to figure 11, the following modules are used for the use case of the semantic annotation of the models categorization:

- **Controller:** The controller is the central module of the model repository that consists of many other submodules. It opens the local relational database connection and it handles web requests and presentation details that the user will see. It also calls the Loader module.
- **Loader:** The Loader is in charge of converting MySQL data into RDF property values that will be provided to the CHIC semantics infrastructure web services. It also loads the RDF mapping configuration file and calls the application programming interfaces of the CHIC metadata store.
- **RDF mapping configuration file:** This file includes the necessary information for mapping MySQL table and columns of the CHIC model repository to RDF properties, vocabularies and OWL ontologies of the CHIC metadata store.
- **API:** This module consists of all the web annotation services that are exposed from the CHIC metadata store and are being used, among others, for the semantic annotation of the models' categorization.

Wizard for storing a new model

Model
Parameters
Files
Model categorization
References

In this step you can categorize your new model based on the 13 perspectives that have been defined within CHIC. One or more categories can be selected for each perspective. The categorization of your new model will be stored both in the relational database of the model repository and in the CHIC semantics infrastructure in the form of triples.

■ Skip this step

Heads up! The categorization of your model could be skipped for now. Furthermore, you can categorize your new model only for a few perspectives and ✕ not for all.

Perspective I is about the Tumour-affected normal tissue modelling.
☐ I want right now to categorize my new model based on Perspective I.

Perspective II is about the spatial scale(s) of the manifestation of life.
☐ I want right now to categorize my new model based on Perspective II.

Perspective III is about the temporal scale(s) of the manifestation of life.
☐ I want right now to categorize my new model based on Perspective III.

Figure 10: The fourth step of the Model Repository wizard for storing a new model. Through this step the modeller is able to categorize their new model. The semantic description of the categorization of the new model based on the perspectives is automatically stored in the form of triples into the CHIC semantics infrastructure

Table 4 presents the result of the semantic annotation of the categorization of the model named “Nephroblastoma Molecular Model” for perspective V, in the form of subject-predicate-object expressions. The subject denotes the resource, and the predicate denotes traits or aspects of the resource and expresses a relationship between the subject and the object. The RDF statements that are included in table 4 represent the following knowledge base:

- The CHIC resource with the URI <https://mr.chic-vph.eu/metadata#c4a42066-a4fc-11e5-a252-fa163e092aac> represents a CHIC hypomodel.
- The aforementioned CHIC hypomodel has the name “Nephroblastoma Molecular Model”
- The aforementioned CHIC hypomodel has the unique identifier “c4a42066-a4fc-11e5-a252-fa163e092aac”
- The aforementioned CHIC hypomodel addresses the tumour type named “Nephroblastoma”. As stated in the fifth row and third column of Table 4, the “Nephroblastoma” term has the URI “http://purl.obolibrary.org/obo/HP_0002667” which has been derived from the human phenotype ontology.

Table 4: The RDF statements that represent the semantic annotation of the categorization of the model entitled “Nephroblastoma Molecular Model” for perspective V

Subject	Predicate	Object
< https://mr.chic-vph.eu/metadata#c4a42066-a4fc-11e5-a252-fa163e092aac >	< http://www.chic-vph.eu/ontologies/resource#hasCHICuid >	“c4a42066-a4fc-11e5-a252-fa163e092aac”
< https://mr.chic-vph.eu/metadata#c4a42066-a4fc-11e5-a252-fa163e092aac >	< http://www.w3.org/1999/02/22-rdf-syntax-ns#type >	< http://www.chic-vph.eu/ontologies/resource#Model-ChicHypomodel >
< https://mr.chic-vph.eu/metadata#c4a42066-a4fc-11e5-a252-fa163e092aac >	< http://www.chic-vph.eu/ontologies/resource#hasName >	“Nephroblastoma Molecular Model”
< https://mr.chic-vph.eu/metadata#c4a42066-a4fc-11e5-a252-fa163e092aac >	< http://www.chic-vph.eu/ontologies/resource#hasPositionIn-5 >	< http://purl.obolibrary.org/obo/HP_0002667 >

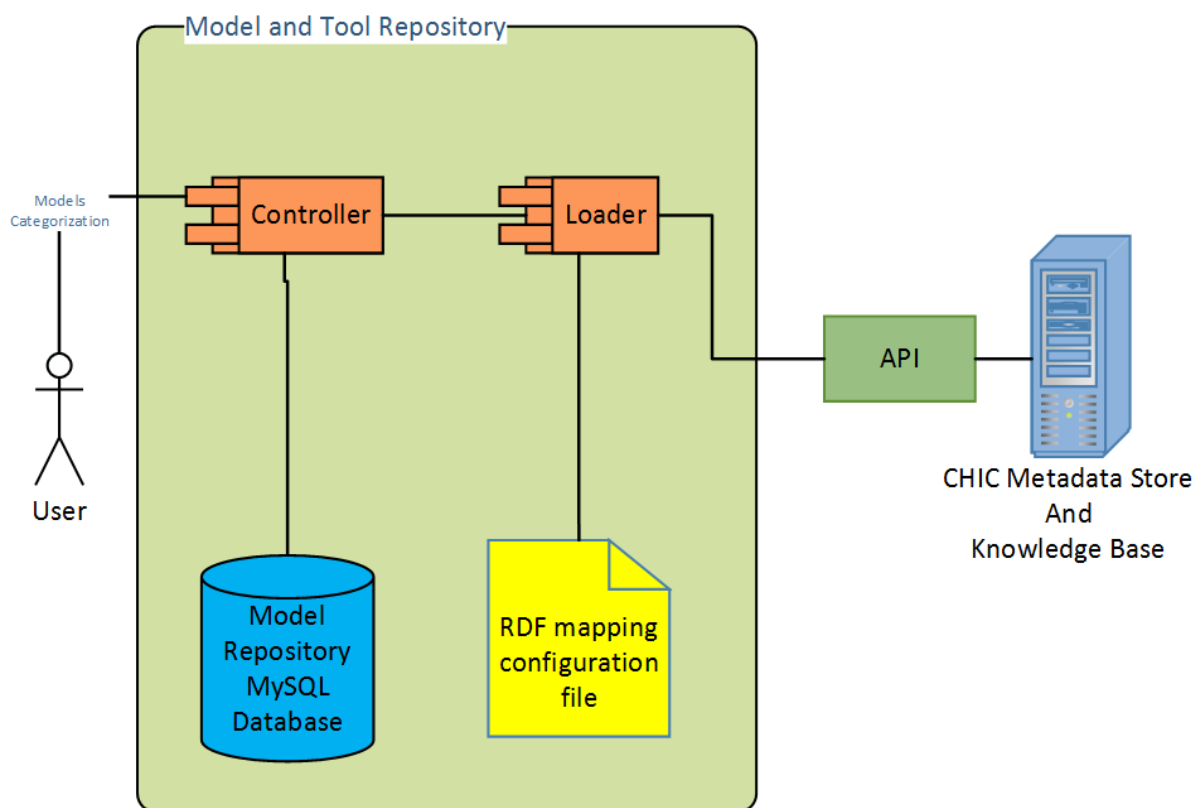


Figure 11: Integration of the Model Repository with the CHIC metadata store

As stated earlier in the current chapter, after the composition of the new hypermodel, the Hypermodelling Editor stores through the web services the xMML file of the hypermodel into the Model Repository. This xMML file defines the topology of the hypermodel and is required by the Hypermodelling Execution Framework for the execution of the hypermodel. Figure 12 presents the screenshot where the modeller downloads the descriptive language of the nephroblastoma multimodeller hypermodel through the user interface of the Model Repository whereas figure 13 presents a part of the aforementioned language. The part of the language for the nephroblastoma multimodeller hypermodel which is depicted in figure 13 includes the static input parameters of the hypermodel.

Nephroblastoma multimodeller hypermodel_v1_0

Choose action for this model ▾

ID	UUID	Description	Comments	Version	String consisted of flag-value pairs	Name of the executable	Strongly coupled	Composite model
109	24925fc0-75d5-11e6-b20b-fa163e092aac	Nephroblastoma hypermodel description		2		muscle_configuration_file/muscle_coupled_simulator_2mm_adaptation_test.cxa.rb	No	No

Files of the model: Nephroblastoma multimodeller hypermodel_v1_0

+ Add one more file for this model

Action	ID	Title	Description	Kind of file	License	sha1sum	comment	engine	Created on	Modified on
Action ▾ Download this file Update this file Delete this file	170	Nephroblastoma multimodeller hypermodel t2flow description file	Nephroblastoma multimodeller hypermodel t2flow description file	t2flow		c69bc05b7f431b1c31a854dea0071f030026060c			Sept. 9, 2016, 5:51 p.m.	None

Figure 12: The modeller is going to download the descriptive language of the nephroblastoma multimodeller hypermodel. The aforementioned descriptive language had been previously created by the Hypermodelling Editor

```

28 <static_inputs />
29 <inputs>
30 <entry>
31 <string>sym_fraction_NecrLayer</string>
32 <de.uni_luebeck.inb.knowarc.usecases.ScriptInputUser>
33 <tag>sym_fraction_NecrLayer</tag>
34 <file>true</file>
35 <tempFile>false</tempFile>
36 <binary>false</binary>
37 <charsetName>UTF-8</charsetName>
38 <forceCopy>false</forceCopy>
39 <list>false</list>
40 <concatenate>false</concatenate>
41 <mime />
42 </de.uni_luebeck.inb.knowarc.usecases.ScriptInputUser>
43 </entry>
44 <entry>
45 <string>apoptosis_time_NecrLayer</string>
46 <de.uni_luebeck.inb.knowarc.usecases.ScriptInputUser>
47 <tag>apoptosis_time_NecrLayer</tag>
48 <file>true</file>
49 <tempFile>false</tempFile>
50 <binary>false</binary>
51 <charsetName>UTF-8</charsetName>
52 <forceCopy>false</forceCopy>
53 <list>false</list>
54 <concatenate>false</concatenate>
55 <mime />
56 </de.uni_luebeck.inb.knowarc.usecases.ScriptInputUser>
57 </entry>
58 <entry>
59 <string>output_dir</string>
60 <de.uni_luebeck.inb.knowarc.usecases.ScriptInputUser>
61 <tag>output_dir</tag>
62 <file>true</file>
63 <tempFile>false</tempFile>
64 <binary>false</binary>
65 <charsetName>UTF-8</charsetName>

```

Figure 13: A part of the descriptive language for the nephroblastoma multimodeller hypermodel. The static input parameters of the aforementioned hypermodel are depicted in this screenshot

In case the new hypermodel has already composed and its descriptive language already exists in the Model Repository, the user is able to run the new hypermodel through the Hypermodelling Editor. After applying the needed criteria for fetching the desired hypermodel, the representation of the hypermodel along with its parameter definition is being displayed to the user. Figure 14 depicts the representation of the ICCS: miRNA Simple Hypermodel through the editor.

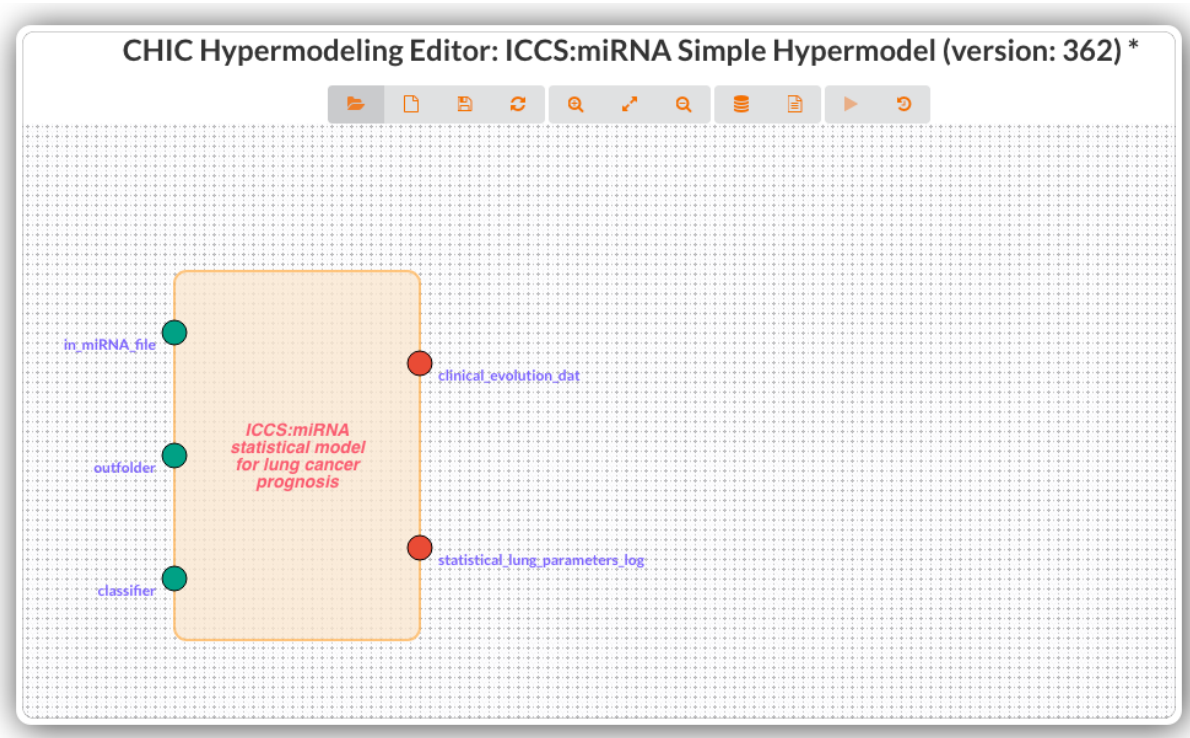


Figure 14: Representation of the ICCS:miRNA Simple Hypermodel through the editor

In order for ICCS:miRNA Simple Hypermodel to run, the user has to provide some input values. Figure 15 presents the form in the editor where the user inserts values for the input parameters of the hypermodel.

Execution Inputs (only models with non-connected inputs are shown)

▾ ICCS:miRNA statistical model for lung cancer prognosis (1)

in_miRNA_file

outfolder

classifier

☒ Use caching

Figure 15: The form in the Hypermodelling Editor where the user is able to provide values for the input parameters of the hypermodel in order to run.

After pressing the “Run!” button shown in figure 15, the hypermodelling Editor sends a message to the Execution Framework in order for the latter to initiate the execution. As shown in figure 16, the user gets informed for the progress of the execution.

Experiments			
#	Hypermodel	Status	
852	ICCS:miRNA Simple Hypermodel (ver. 363)	Running	○
847	ICCS:miRNA Simple Hypermodel (ver. 362)	Finished	⬇
845	ICCS:miRNA Simple Hypermodel (ver. 362)	Finished	⬇
844	ICCS:miRNA Simple Hypermodel (ver. 360)	Finished	⬇
843	ICCS:miRNA Simple Hypermodel (ver. 360)	Finished	⬇
842	ICCS:miRNA Simple Hypermodel (ver. 360)	Finished	⬇
			OK

Figure 16: The Hypermodelling Editor notifies the user with respect to the progress of the execution of the ICCS:miRNA Simple Hypermodel

And finally, when the simulation has ended, the user is informed accordingly as shown in the following figure.

Experiments			
#	Hypermodel	Status	
852	ICCS:miRNA Simple Hypermodel (ver. 363)	Finished	⬇
847	ICCS:miRNA Simple Hypermodel (ver. 362)	Finished	⬇
845	ICCS:miRNA Simple Hypermodel (ver. 362)	Finished	⬇
844	ICCS:miRNA Simple Hypermodel (ver. 360)	Finished	⬇
843	ICCS:miRNA Simple Hypermodel (ver. 360)	Finished	⬇
842	ICCS:miRNA Simple Hypermodel (ver. 360)	Finished	⬇
			OK

Figure 17: The user is being notified about the completion of the simulation

This chapter demonstrated all the steps of the workflow which consists of the storage of new hypomodels in the Model Repository, the semantic annotation of the aforementioned hypomodels with respect to the perspective categorization, the retrieval of the available hypomodels by the

editor through semantic querying, the composition of a new hypermodel and finally, its execution. Three main components participate in this workflow. The Model Repository which stores the descriptive language of the hypermodels in the form of xMML and semantically annotates the models based on their perspective values, the Hypermodelling Editor through which new hypermodels are composed, and the CHIC triplestore which holds the semantic representation of all the CHIC resources. All the aforementioned CHIC components interact with each other through RESTful web services. The end result is a user friendly environment for the modeller in order to compose and evaluate new hypermodels. For the semantic annotation of the model perspectives we demonstrated as an example the nephroblastoma molecular model, for the demonstration of the descriptive language we used the nephroblastoma multimodeller hypermodel and for the execution of the hypermodel through the editor we demonstrated the ICCS:miRNA Simple Hypermodel.

CHAPTER DI: DISCUSSION

In this document the innovative cancer meta- and hyper-multiscale models and repositories developed by the CHIC project in the context of their envisaged clinical use have been demonstrated. All developed hypemodells and repositories are in working order and will be demonstrated “live” during the CHIC final review. The demonstration workflows presented (Scenario I: starting with the cancer domain and Scenario II: starting with the patient domain) cover efficiently the needs of both clinical research and clinical practice.

All hypermodels demonstrated have successfully undergone the processes of verification, clinical adaptation and partial clinical validation as described among other CHIC deliverables in D6.4. All repositories have also been successfully tested as has been reported *inter alia* in deliverable D8.4.

CHAPTER CO: CONCLUSIONS

The highly innovative cancer meta- and hyper-multiscale models and repositories developed by the CHIC project in the context of their envisaged clinical use have been demonstrated in this document. Clinical translation of the models is expected to take place following completion of their prospective clinical validation. Till that expected time point in the future, the presented hypermodel utilization workflows can be used for research and educational purposes.

The hypermodels developed by the cancer modelling partners of the consortium concern nephroblastoma, non small cell lung cancer, glioblastoma and prostate cancer. These four paradigmatic cancer types are treated with a variety of modalities including chemotherapy, radiation therapy, immunotherapy and hormone therapy. Three out of the four developed multiscale hypermodels i.e the nephroblastoma, the non small cell lung cancer and the prostate cancer ones have been collectively developed by three up to six geographically distributed modelling partners each in both EU and US using the technological infrastructure developed by CHIC.

The (hyper)model annotation strategy, the composition of a new hypermodel through the Hypermodelling Editor and the storage of a new hypermodel in the Model Repository have also been outlined. All hypermodels demonstrated in this document have successfully undergone the processes of verification, clinical adaptation and partial clinical validation as described among other CHIC deliverables in D6.4. Successful testing and validation of the relevant repositories has been reported inter alia in D8.4.

APPENDIX I: FREQUENT CHIC RELATED ABBREVIATIONS AND ACRONYMS

IMPORTANT NOTE Abbreviations and acronyms that are not included in this table may be deciphered using the “Find” facility which is provided by current pdf document readers. By locating the first instance of an abbreviation or an acronym in the document, the reader can also see its full name

AD	Androgen Dependent
ADC	Adenocarcinoma
ADSCC	Adenosquamous Cell Carcinoma
ADT	Androgen Deprivation Therapy
AJCC	American Joint Committee on Cancer
Akt	Protein kinase B (PKB)
ALK	Anaplastic Lymphoma Kinase
AMD	Advanced Microdevices
ANSI	American National Standards Institute
API	Application Program Interface
ATP	Adenosine Triphosphate
AUC	Area Under Curve
BED	University of Bedfordshire
bGS	biopsy Gleason Score
BMS	Bio-Mechanical Simulator
BS	Biomechanics Simulator
CGAL	Computational Geometry Algorithms Library
CHIC	Computational Horizons in Cancer
CINECA	Consorzio Interuniversitario del Nord Est Italiano Per il Calcolo Automatico (Interuniversity Consortium for High Performance Systems)
CKP	Cell Kill Probability
CKR	Cell Kill Rate
CNS	Central Nervous System
COSMIC	Catalog of Somatic Mutations in Cancer
CRAF	Clinical Research Application Framework (CRAF)
CS	Cell Simulator
CSF	Cerebrospinal Fluid
CSS	Cancer Stem Cell
CSV	Comma Separated Values
CT	Computed Tomography
DC	Dendritic Cell
DGM	Diffusion Coefficient of Grey Matter
DICOM	Digital Imaging and Communications in Medicine
DIFF	Terminally Differentiated Cell
DRE	Digital Rectal Examination
DWM	Diffusion Coefficient of White Matter
EAU	European Association of Urology
EBRT	External Beam Radiation Therapy

ED	Equivalent Dose
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
ERBB2	erb-b2 Receptor Tyrosine Kinase 2
ERK	Extracellular Signal-Regulated Kinases
FEM	Finite Element Method
FORTH	Foundation for Research and Technology Hellas
GBM	Glioblastoma Multiforme
GF	Growth Fraction
GC	Geometrical Cell
GPSM	Gleason, PSA, Seminal Vesicle and Margin Status
GS	Gleason Score
GUI	Graphical User Interface
HE	Hypermodelling Editor
HER3	Human Epidermal Growth Factor Receptor 3
HTML	Hypertext Markup Language
ICCS or ICCS- NTUA	Institute of Communication and Computer Systems – National Technical University of Athens
IMRT	Intensity Modulated Radiation Therapy
ISO	International Organization for Standardization
KUL	Catholic University of Leuven
LADC	Lung Adenocarcinoma
LCC	Large Cell Carcinoma
LIMP	Limited Mitotic Potential
LQ	Linear Quadratic
LSCC	Lung Squamous Cell Carcinoma
MAPK	Mitogen-Activated Protein Kinase
MD	Molecular Dynamics
MRI	Magnetic Resonance Imaging
MUSCLE	Multiscale Coupling Library and Environment
MUT	Mutant
NBC	Number of Biological Cells
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGCT	Neighbour Geometrical Cells belonging to the Tumour
NIH	National Institutes of Health
NK	Natural Killer
NSCLC	Non Small Cell Lung Cancer
NSG	NOD- <i>scid</i> <i>IL2ry^{null}</i> Mouse Model of Human Skin
OER	Oxygen Enhancement Ratio
OFAT	One Factor at A Time
OS	Oncosimulator
OWL	Web Ontology Language
pAKT	phospho-AKT
PCa	Prostate Cancer
PDE	Partial Differential Equation
PSA	Prostate Specific Antigen
PUN	Phenomenological Universalities (Approach)
RDF	Resource Description Framework

RP	Radical Prostatectomy
RT	Radiotherapy
RTK	Receptor Tyrosine Kinase
SASA	Solvent Accessible Surface Area
SBML	Systems Biology Markup Language
SCC	Squamous Cell Carcinoma
SCID	Severe Combined ImmunoDeficient
SCLC	Small Cell Lung Cancer
SQL	Structured Query Language
STAT	Signal Transducer and Activator of Transcription or Signal Transduction And transcription
SVM	Support Vector Machines
TCGA	The Cancer Genome Atlas
TKI	Tyrosine Kinase Inhibitors
TRUS	Trans-Rectal Ultrasound
UBERN	University of Bern
UCL	University College London
ULC	Undifferentiated Large Cell Carcinoma
UML	Unified Modeling Language
UNITO	University of Turin
UOXF	University of Oxford
UPENN	University of Pennsylvania
USAAR	University of Saarland
USFD	University of Sheffield
VEGF	Vascular Endothelial Growth Factor
VPH	Virtual Physiological Human
VTk	Visualization ToolKit
WT	Wild Type
WT	Wilms Tumour = Nephroblastoma
XML	EXtensible Markup Language