EDITORIAL

Prioritizing Clinical Relevance

by Research Professor Georgios Stamatakos,

CHIC Project Coordinator

Dear Reader,

The latest developments in the CHIC project implementation are much encouraging. Having designated *clinical relevance* as the overarching driver of the project implementation - as had been suggested by the independent reviewers - has contributed to the assessment of the progress made by the project as "excellent" (Review of January 2016). In particular Professor Norbert Graf, the Assistant Clinical Coordinator of the project, showed how the CHIC integrated system would work within the clinical environment from the clinical perspective. An excellent assessment is an important indicator of the innovative and the clinical potential of the project.

According to the "Innovation Radar Questionnaire" recently formulated by the European Commission services and filled in by the CHIC consortium, the innovation of the project is briefly described as follows: "*Cancer multiscale hypermodelling* is an innovative modular approach to the modelling of cancer and its response to treatment. Hypomodels simulating crucial biological mechanisms, possibly developed by different cancer modellers, are integrated into hypermodels. The latter, following clinical validation, predict the response of a given patient to candidate therapeutic schemes. Hypermodels in conjunction with the supportive technologies developed so far are to serve as clinical deci-

sion support systems." The types of project innovation include a new product, a new service and a new process. The following tags represent the strongest elements of the project: *basic science* (multiscale cancer hypermodelling, in silico oncology), *clinically relevant hypermodelling technologies*, *clinical decision support systems*.

In this issue of the CHIC Newsletter a number of interesting articles will inform and update you on important aspects of the project implementation. Of special interest is the feedback letter sent by Metin Akay, Professor of Biomedical Engineering, University of Houston, USA and Member of the CHIC External Advisory Board. I hope that you will find the Newsletter both interesting and informative.

PROGRESS ASSESSMENT OF THE CHIC RESEARCH PROJECT BY A MEMBER OF THE EXTERNAL ADVISORY BOARD

by Professor Metin Akay

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21 January 2016

Dear Georgios,

It was a real pleasure for me to participate as a Member of the External Advisory Board of the CHIC Project in the CHIC plenary meeting that took place in Bologna, Italy from 21 October to 23 October 2015. The purpose of this letter is to provide you in writing with the major comments I made orally during the same event, according to your request.

First, I must confess that I was highly impressed by the ideal blend of the clinical, the basic science and the technological aspects of the project that were presented in a comprehensive and substantiated way, extensively supported by helpful visualization aids.

The discussions that followed each presentation were illuminating and did in fact provide an in depth understanding of many critical project implementation issues.

Of particular importance were the components and the integration of the nephroblastoma demonstrator. I absolutely agree with the clear prioritization of the clinical relevance of the CHIC project at the current and next stage(s) of its implementation. I was indeed impressed by the unquestionable clinical focus of literally all presentations and discussions throughout the three days of the meeting. In this context the presence of three distinguished academic

clinicians who are active in clinical research during the entire meeting was of great importance.

Another remarkable characteristic of the meeting was the cross-pollination between the CHIC consortium research activities and the experimental and clinical oncological research undertaken by my research group, represented in the event by Dr Yasemin M Akay and myself. Inspired by emerging tissue- and organ-on-chip platforms, we developed a novel three- dimensional (3D) brain cancer chip for drug screening. This chip is composed of photo-polymerizable poly(ethylene) glycol diacrylate (PEGDA) hydrogel. Our recent data indicated that that this chip is capable of high-throughput glioblastoma multiforme (GBM) cancer spheroids formation, multiple-simultaneous drug administration, and massive-parallel testing of drug response.

Furthermore, during the CHIC consortium meeting, several research issues of mutual interest, including EU and US research policies in cancer and oncological research such as data collection, data transfer and data exploitation were extensively discussed. Potential ways of joining our research efforts in the future were also explored. I do believe that there is plenty of room for further cooperation between EU and US in the broad exciting domain of the CHIC project.

I do encourage the CHIC consortium to stick to the precise clinical goals presented, analysed and agreed during the Bologna plenary meeting. Clinical questions should definitely serve as the central driving force for the entire project.

In summary, having taken into account the reviewers' recommendations which were carefully addressed and extensively discussed during the meeting, I feel that the project implementation is fully in track. I am, therefore, very optimistic about its final outcome.

I wish you and the entire CHIC consortium a great final outcome.

If you have any further questions, please do not hesitate to contact me.

Yours sincerely,

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Metin Akay received his B.S. and M.S. in Electrical Engineering from the Bogazici University, Istanbul, Turkey in 1981 and 1984, respectively and a Ph.D. degree from Rutgers University in 1990. He is the founding chair of the Annual International Summer School on *Biocomplexity from System to Gene* sponsored by the NSF and Dartmouth College and technically co-sponsored by the IEEE EMBS, of the Satellite Conference on Emerging Technologies in Biomedical Engineering. He is also the Founding Chair of the International IEEE Conference on Neural Engineering, in 2003. These activities were sponsored by the NSF and largely attended by the women and minorities. Metin Akay is Founding Chair and John S Dunn Endowed Chair Professor in the Department of Biomedical Engineering, Cullen College of Engineering, University of Houston, Houston, TX, USA

CHIC and MyHealthAvatar

by Feng Dong

As an EC FP7 funded research project, MyHealthAvatar is a proof of concept for the digital representation of the patient health status. It is designed as a lifetime companion for individual citizens that facilitates the collection of, and access to long-term health-status information by utilising the latest ICT technology with an aim of engaging public interest to achieve its targeted outcomes. In addition to data access, it is also an interface to access integrative models and analysis tools, utilizing resources already created by the Virtual Physiological Human (VPH) community.

The MyHealthAvatar platform and app (Figure 1) has now been released for free access by the public at https://myhealthavatar.org and the Google Play Store. It is a non-profit research project to study how technologies are able to help patients and citizens look after their own health and wellbeing. It offers you a place to keep records of your medical information as well as your daily activities and lifestyles. It promotes self-care of patients and citizens for healthy lifestyle and well-being. It remembers your activities of daily living, including your movements, locations, food intake, mood, sleep quality and photos; records your health status such as heart rate, blood pressure and glucose; identifies and highlights important events in your life; summarizes your lifestyle and assess the quality of your life; helps you enter your health records (e.g. conditions, medication, immunization, allergy), indicates your risks of developing diseases, such as cardiovascular, diabetes, hypertension and stroke, and allows you to share information among friends through social media.

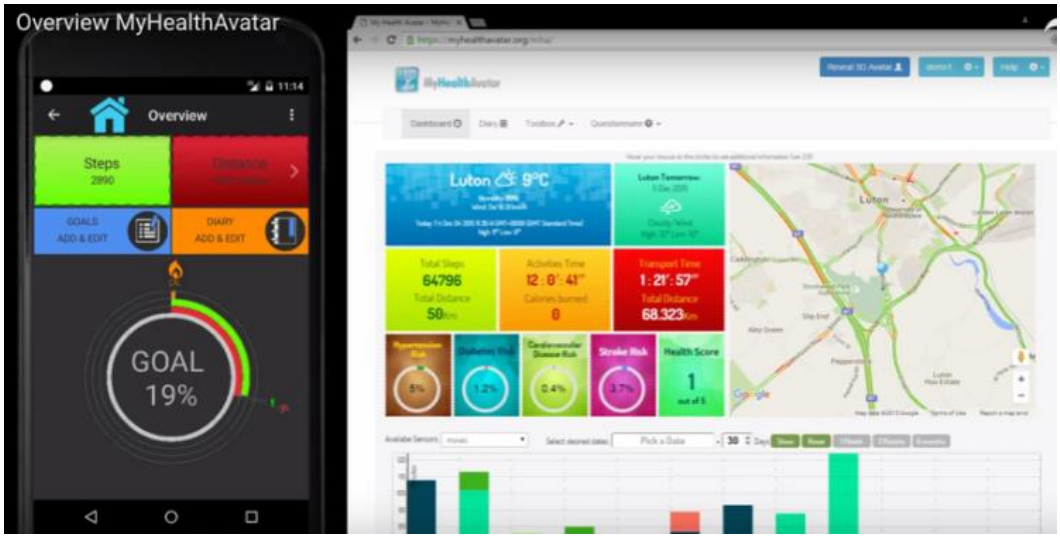

Figure 1 MHA app (left) and the web-based platform (right)

The CHIC project has developed a data repository that provides for a secure storage of clinical data, imaging data, histological data, therapy, etc. CHIC grants access to its data repository to host the medical data of a synthetic patient, generated by MHA. The medical data of the synthetic patient allows MyHealthAvatar to demonstrate the utility of its platform by allowing execution of oncosimulations using the medical data.

This collaboration is beneficial for both projects. MyHeathAvatar is able to demonstrate that amongst other external sources, many of which could be clinically oriented in a commercial way (e.g. HIS), tools and resources can be provided, so that collected data from research resources (clinical, modelling, trials etc.) can be used for educational, research (model adaptation and validation) and clinical purposes (executions of validated models with real data) either from within the platform (depending on the number and kind of stored models), or by bringing together the third part resources and applications that are connected to the platform, the latter thereby acting as a “transit” centre for data and authorization. On the other hand, the CHIC project proves true one of its initial assertions, pertaining to the storage and use of collected and created data not only for its own purposes, but instead to make them accessible after the end of the project to other projects as well.

The CHIC Model and Tool Repository

by Nikolaos Tousert (photo), Dimitra Dionysiou and Georgios Stamatakos,
ICCS- National Technical University of Athens

The CHIC model and tool repository is a web application that permanently hosts the models that have been developed in the context of the CHIC project. It also hosts tools such as linkers and data transformation tools necessary for the construction of hyper-models. For each model, the CHIC model and tool repository contains all the related information including:

- Descriptive information, (abstract and detailed description, references, etc.)
- Input and output parameters (for proper linking with other models and tools)
- Categorization of the models depending on the perspective from which they are viewed in the basic science context
- Direct or indirect links to additional material (journal articles, conference proceedings, etc.)

Users may browse, change and delete the content of the model and tool repository through a graphical user interface. More specifically, users can store a new model, define and then link new input/output parameters to their models, upload files (executables, documentation), categorize their model according to the 13 perspectives that have been defined within the CHIC project, etc. The main page of the model and tool repository is presented in Figure 2.

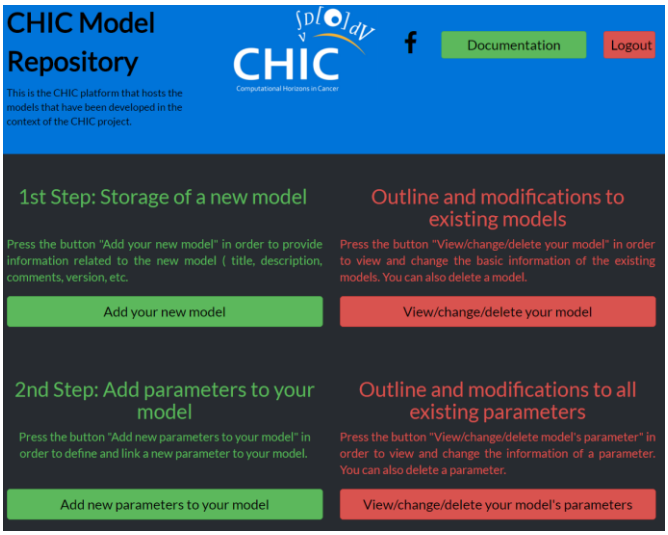

Figure 2: The main page of the CHIC model and tool repository

Each model stored in the model and tool repository may be associated with a set of references, which provide direct or indirect links to additional material, extending in this way the knowledge base related to the specific model/tool. The user interface through which the user is able to provide links to additional material for their model, is presented in Figure 3.

A web page has also been designed for the categorization of mathematical and computational cancer models according to the thirteen perspectives that have been defined within the CHIC project. As shown in Figure 4, the user can easily perform this categorization just by selecting their model and one or more categories for the given perspective. It is worth mentioning that the user is also able to include their own categories for some perspectives.

Apart from the user interface, the contents of the model and tool repository are exposed to other CHIC components through RESTful web services. CHIC model and tool repository web services are consumed by non-browser CHIC clients like the hypermodelling execution framework and the Clinically Relevant Application Framework (CRAF). Consequently, the model repository is not an isolated component, but it has been integrated into the whole CHIC platform.

Regarding the security, the model and tool repository makes use of the brokered authentication mechanism.

Thereafter the users are not directly authenticated by the model and tool repository, but rather by the CHIC authentication broker (identity provider) to support single sign on (SSO).

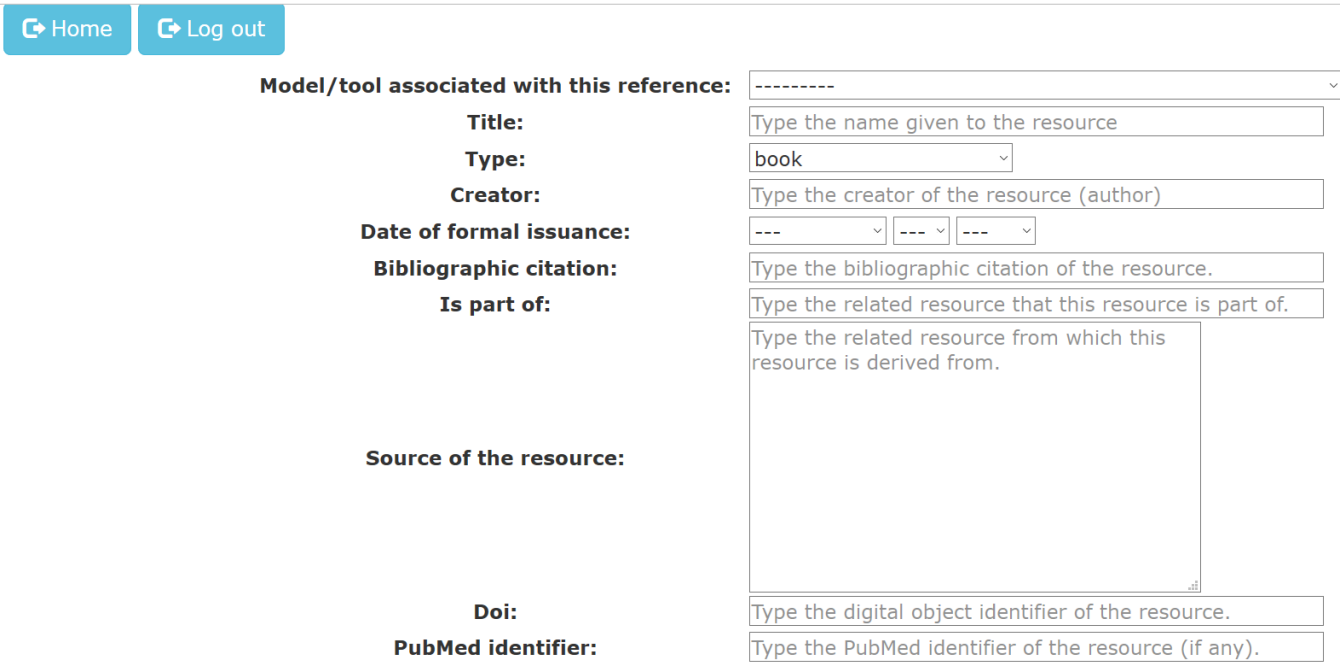

Figure 3: Page for providing links to additional material for an existing model

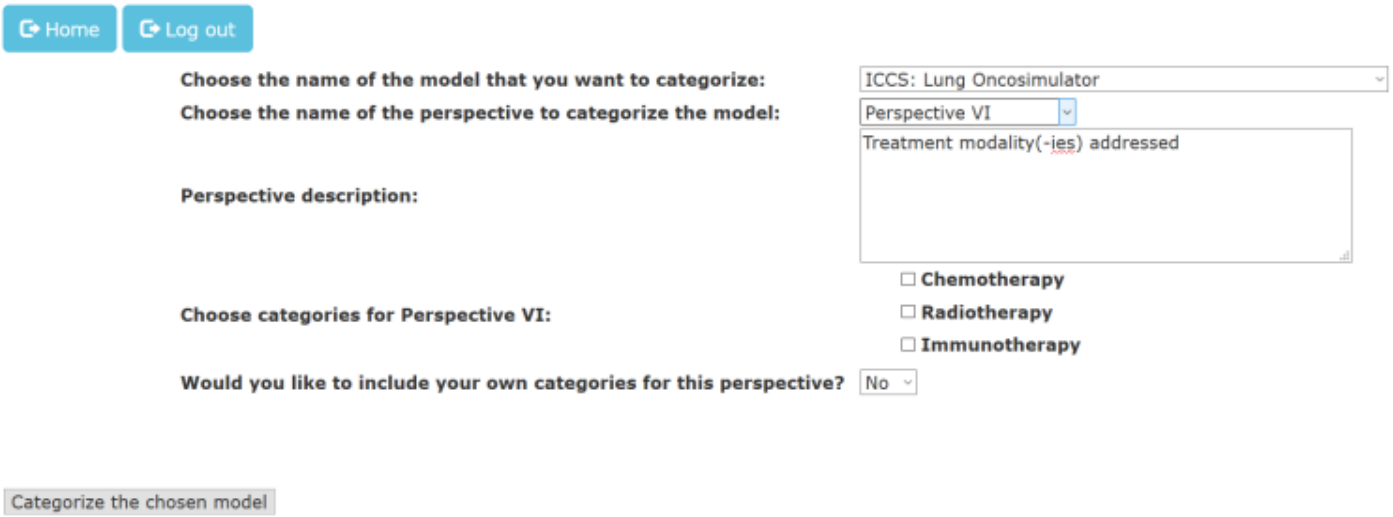

Figure 4: The web page where the user categorizes the lung Oncosimulator model according to "perspective VI

The CHIC In Silico Trial Repository

by Nikolaos Tousert, Dimitra Dionysiou and Georgios Stamatakos,
ICCS-National Technical University of Athens

The *in silico* trial repository is used for the persistent storage of the simulation scenarios and the *in silico* predictions. The input data (the original state of the patient), the simulation scenario (the *in silico* treatment) and the output data (the state of the patient after *in silico* treatment) are stored persistently after the completion of the simulation scenario. More specifically, the *in silico* trial repository contains for each *in silico* trial all the related information, including:

- original input (medical data without any processing)
- model input (processed medical data that can be used as input to the specific model or hypermodel used in the simulation)
- model output (output data of the simulation)
- model or hypermodel (not the actual model/hypermodel code used in the simulation, but information about it)

By storing in one place the complete information concerning the input data, the output data and the modules which participate in the *in silico* experiments and the *in silico* trials, the *in silico* trial repository can advance *in silico* medicine in general, by facilitating the validation of the current *in silico* medicine discoveries.

The *in silico* trial repository consists of three main entities, the subjects, the experiments and the trials. Thereafter, the basic principles of the *in silico* trial repository are the following:

- In a real clinical trial the hypotheses and the scientific method are tested. In case of *in silico* trials, the *in silico* (hyper)model takes the place of the hypotheses and the scientific method. Consequently, the (hyper)model that is being used (and the location where it is stored) is defined in the *in silico* trial entity.
- The *in silico* experiments are organized in *in silico* trials. All *in silico* experiments that are part of the same *in silico* trial use the same *in silico* (hyper)model.
- The *in silico* experiment entity consists of triples of "initial state of the subject" – "*in silico* hypermodel" – "final state of the subject". The *in silico* (hyper)model that is used in an *in silico* experiment is not stated in the experiment entity, but in the *in silico* trial entity in which the experiment belongs.
- The subject entity represents an instance of a subject. The subject may be a person, healthy or not, an animal etc. The subject can be linked to another data repository, such as the CHIC clinical data repository, a clinical trial management system, a hospital record management system, etc. Every instance of a subject can be accompanied by a set of files.

Based on the aforementioned basic principles, a web-based user interface has been implemented in order to allow users to interact with the *in silico* trial repository. The user is able to store and retrieve all the data concerning a complete *in silico* trial (i.e. a set of simulation runs). The user interface through which the user is able to download data of an already conducted experiment, is presented in Figure 5.

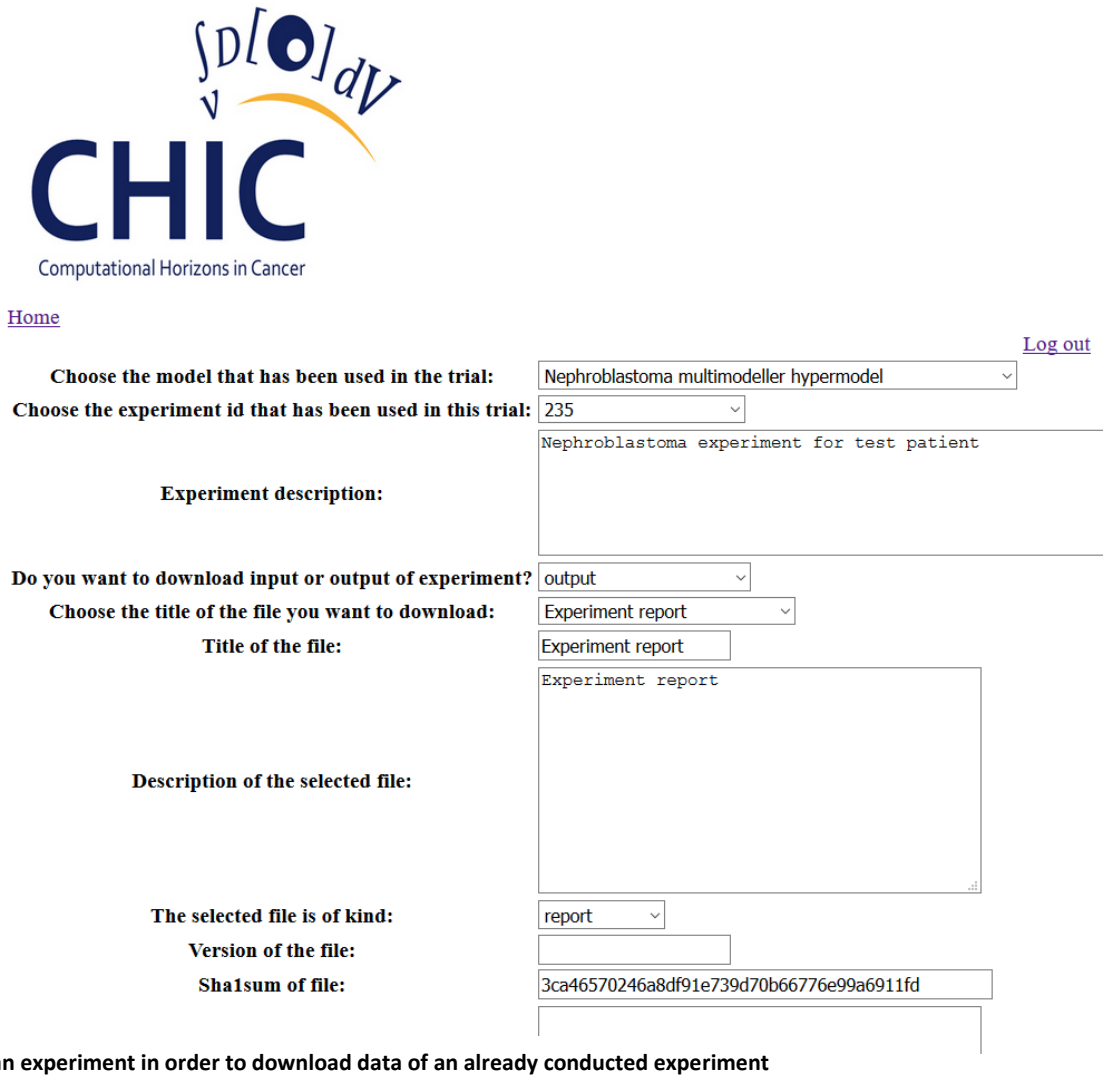

Figure 5: The user selects an experiment in order to download data of an already conducted experiment

Apart from the user interface, the contents of the *in silico* trial repository are exposed to other CHIC components through RESTful web services. By using the aforementioned web services, many CHIC components can interact with the *in silico* trial repository, like the hypermodelling executional environment which is now able to automatically store the outcome of a simulation. The integration of the *in silico* trial repository into the CHIC platform is presented in Figure 6.

Last but not least, authentication and authorization mechanisms have been developed for *in silico* trial repository in order to restrict access to the simulation results. Users are able to interact with the user interface of the *in silico* trial repository only by using their single sign on account.

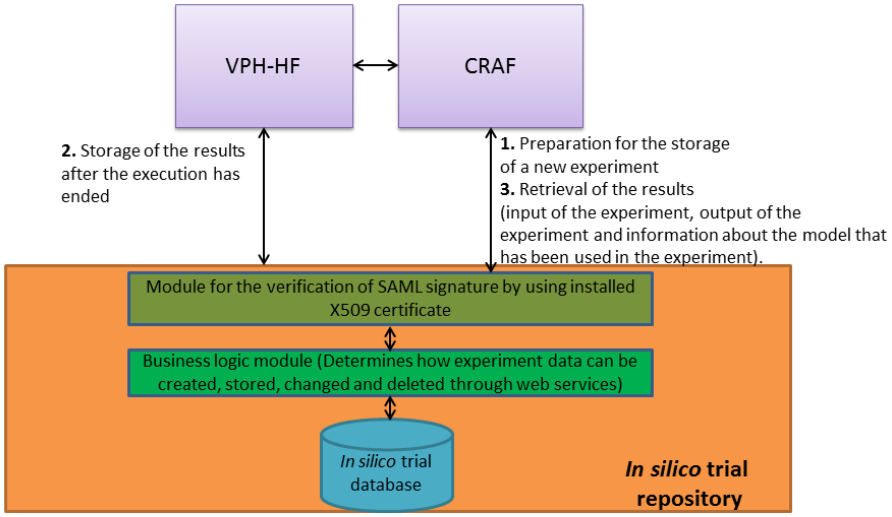

Figure 6: The *in silico* trial repository has been integrated into the CHIC platform

CHIC – Representative Recent Publications

1. E. Ouzounoglou, D. Dionysiou, and G. Stamatakos, "*Differentiation resistance through altered retinoblastoma protein function in acute lymphoblastic leukemia: in silico modelling of the deregulations in the G1/S restriction point pathway*." BMC Systems Biology 10:23(1) DOI: 10.1186/s12918-016-0264-5

2. G. Stamatakos, "*The Oncosimulator - Combining Clinically Driven and Clinically Oriented Multiscale Cancer Modelling with Information Technology in the In Silico Oncology Context,"* Invited and accepted to be presented in the International Conference and Exhibition on Pediatric OncologyAugust 11-13, 2016 Toronto, Ontario, Canada http://pediatriconcology.conferenceseries.com/

3. G. Stamatakos, D. Dionysiou, R. Bohle, S. Gool, L. Solie, F. Dong, N. Mcfarlane, M. Viceconti, D. Tartarini, K. Marias, V. Sakkalis, N. Forgo, I. Lishchuk, R. Radhakrishnan, A. Ghosh, H. Byrne, J. Grogan, C. Guiot, I. Stura, P. Buechler, M. Reyes, E. Neri, A. Bucur, B. de Bono, S. Alexander, G. Erbacci, D. Testi, M. Tsiknakis, E. Kolokotroni, E. Georgiadi, N. Tousert, S. De Vleeshouwer, D. Walker, S. Sfakianakis, I. Karatzanis, S. Bnà and N. Graf on behalf of the CHIC consortium, " *Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology – Strategies, Systems and Results*," Invited and accepted to be presented in the International Conference and Exhibition on Pediatric OncologyAugust 11-13, 2016 Toronto, Ontario, Canada http://pediatriconcology.conferenceseries.com/

4. N. Graf and G. Stamatakos for the CHIC consortium, "*A multiscale hypermodel to predict the nephroblastoma response to preoperative chemotherapy*," accepted to be presented in the 9th International Renal Tumour Biology Conference, Toronto, Ontario, Canada April 2-3, 2016. http://www.cvent.com/events/9th-international-conference-on-pediatric-renal-tumour-biology/event-summary-448a7f212a9a44488984d5239667e75a.aspx

5. K.Argyri, D.Dionysiou, F. Misichroni and G. Stamatakos, "Numerical simulation of vascular tumour growth under antiangiogenic treatment: addressing the paradigm of single-agent bevacizumab therapy with the use of experimental data," Biology Direct 11(1), DOI: 10.1186/s13062-016-0114-9

Events / Announcements

International Conference and Exhibition on Pediatric Oncology to be organised by CHIC partners

CHIC partners Dr. Georgios Stamatakos and Dr. Norbert Graf are members of the Organizing Committee of the International Conference and Exhibition on Pediatric Oncology. The conference will be in August 11th – 13th, 2016 and is to be held in Toronto, Canada.

This year's conference is expected to attract over 250 international participants and offers an excellent opportunity to get and keep in touch with eminent scientists of the field and their research.

CHIC Coordinator Dr. Stamatakos and Dr Graf, Assistant Clinical Coordinator will organize a workshop on the CHIC project within the framework of the Toronto Conference.

Stay tuned

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

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

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

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

Disclaimer

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