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The CHIC Clinical Research integrated platform

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ABSTRACT:

This deliverable presents the Clinical Research Application Framework (CRAF) that aims to bridge the gap between the research done on the CHIC platform and the clinical setting. Its primary objective is to provide a “packaged” clinically relevant representation of the CHIC environment that allows the clinicians to get patient specific insights and findings based on the CHIC research outcomes. CRAF in fact comprises a suite of tools and end-user applications for accessing, in an intuitive and user friendly way, the results of CHIC for clinical research in the clinical domain. The development of this environment requires interactions and support from the main components of the CHIC platform, especially the CHIC hypermodelling framework, the data and model repositories.

KEYWORD LIST:

translational research, clinical decision making

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

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Table of Contents

1. Executive Summary	6
2. Introduction	7
2.1. Purpose of this document	7
2.2. Structure of this document	7
3. Motivation and basic functionality	8
3.1. High level requirements and functionality	9
4. Architecture	12
4.1. Security	13
4.2. Patient Data management	14
4.3. Implementation	15
4.3.1. Backend server	15
4.3.2. User Interface	15
5. A tour in the user interface	18
5.1. Basic usage	18
5.1.1. Login	18
5.1.2. Main dashboard & side menu	18
5.1.3. Create a New Patient	20
5.1.4. Data Upload	21
5.1.5. List of Patients	22
5.1.6. List of executions	23
5.1.7. Settings	25
5.2. Model Execution	26
5.2.1. Execution workflows	26
Cancer Domain based	26
Patient Based	29
5.2.2. Execution Overview and Report Generation	31
Example of a generated Report	33
6. Discussion	38
6.1. Handling incomplete data	38
6.2. Handling conflicting results	39

Table of Figures

Figure 1 CRAF as the bridge of between the research and clinical domains.....	8
Figure 2 The main flow of user interactions in CRAF	10
Figure 3 3D parallel comparison of real and simulated nephroblastoma tumours in CCGVis (Deliverable 9.2)	11
Figure 4 The interactions of CRAF with the backend services.....	13
Figure 5 Clinical versus Research Domains	15
Figure 6 The Traditional Page Lifecycle versus. the SPA Lifecycle.....	16
Figure 7 The login screen	18
Figure 8 Main dashboard / Home screen	19
Figure 9 Side menu	20
Figure 10 the new patient demographics form.....	21
Figure 11 Data upload form	22
Figure 12 The list of available patients.....	23
Figure 13 The list of executions.....	24
Figure 14 Overview of the execution details.....	24
Figure 15 Overview of the execution outputs.....	25
Figure 16 The settings screen.....	26
Figure 17 Available Cancer Domains	27
Figure 18 Available questions for the selected domain	27
Figure 19 Patient selection	28
Figure 20 (Hyper)model selection	28
Figure 21 Selected models' input parameters.....	29
Figure 22 Selected models' output parameters	29
Figure 23 Patient selection	30
Figure 24 Available questions for the selected patient.....	30
Figure 25 Hypermodel selection	31
Figure 26 Selected models' input/output parameters	31
Figure 27 List of reports for a selected completed hypermodel execution.	32

1. Executive Summary

The main objective of the CHIC project is to offer a computational platform for the biomedical researchers and computational biologists to build complex integrative models which address the challenges in cancer research and treatment using a multilevel and multiscale approach. At the same time, the findings and outcomes of this research in the CHIC computational environment is of high relevance to the needs in the clinical practice and decision support in the clinical setting. The challenge is therefore to provide the means for harnessing the knowledge acquired in the CHIC research platform into clinically useful applications for the best treatment of cancer patients.

The Clinical Research Application Framework (“CRAF”) aims to support this transfer of knowledge from “bench-to-bedside” in the context of CHIC. In particular, CRAF is the central component to support the clinicians for performing CHIC-enabled clinical research in their premises. To this end, its user interface should be simple and smooth by hiding the complexity of the CHIC platform. Furthermore, CRAF incorporates and coordinates the functionality of other CHIC components and repositories that are highly important for the clinicians to gain access to the CHIC services, such the data upload tool for uploading patient data to the CHIC cloud, the hypermodel execution infrastructure, and the visualization and image processing tools.

This functionality is offered to the clinical researchers and the clinicians via a simple and intuitive user interface. CRAF is accessible through the Web allowing ubiquitous, user-friendly, secure, and efficient access to the managed data and computational infrastructure.

2. Introduction

2.1. Purpose of this document

The aim of this document is to describe the provisions that the CHIC consortium has put in place in order to support the clinical adaptation and exploitation of the computational models that are designed and implemented in the research platform. Nevertheless, this endeavour was not really the main focus of the project at its initial stages, when the effort was mainly on the design of the hypermodelling strategies to use for integrating hypomodels of different time and space scales and the development of the infrastructure for the needs of the computational modellers. It was the urge of the external experts to deliver “a clinically relevant, validated and evaluated CHIC environment for clinicians working in the cancer domain” that highlighted this important challenge. The experts had also pointed out the lack of “a ‘packaged’ clinically oriented demonstration” and the adaptation of the user interface to be usable by research clinicians.

In Work Package 10, we have taken full notice of these remarks and recommendations and there were many rounds of discussions at the consortium level to address these new requirements. The culmination of these interactions between the technical partners, the modellers, and the clinicians was the Clinical Research Application Framework (hereinafter “CRAF”) to provide a “*CHIC-in-a-box*” abstraction for the clinicians to use in clinical research. The vision is for CRAF to comprise a suite of tools and end-user applications that provide an “one-stop” solution for accessing the results of CHIC for clinical research in the clinical domain. This vision is in line with the “bench-to-bedside” enterprise of harnessing knowledge from basic sciences to produce new drugs, devices, and treatment options for patients, what is also called “translational medicine”.³

In the present document, therefore, we present the design of CRAF, its functionality, and user interface. We also document its relation and interactions with the core of the CHIC platform, where the main modelling work is performed. Finally, we also present the general context and the design choices we have made, and we discuss the challenges and the areas of future work.

2.2. Structure of this document

The document is organized as follows:

- Section 3 describes the concept of CRAF and the motivation for its introduction,
- Section 4 presents the position of CRAF in the CHIC architecture and how CRAF integrates with it,
- Section 5 presents its features and the main functionality offered through a tour in its user interface,
- Finally, Section 6 provides discussion on general and important issues, and how the CRAF tries to address them.

³ Cohrs, Randall J., Tyler Martin, Parviz Ghahramani, Luc Bidaut, Paul J. Higgins, and Aamir Shahzad. "Translational medicine definition by the European Society for Translational Medicine." (2015): 86-88.

3. Motivation and basic functionality

The personalized treatment of cancer patients requires access to a multitude of patient specific data but also the availability of the computational tools that are able to exploit these data and provide actionable knowledge. These tools need to follow a multidisciplinary and holistic approach that considers in parallel multiple levels of information and organizational aspects of the biological processes in the disease state.

In this endeavour, the CHIC hypermodels can be instrumental for the better understanding of the cancer dynamics and ultimately for the effective and economical treatment of the patients. Of course, before the CHIC hypermodels are dedicated to this cause and be used, for example, for clinical decision support in the clinical domain, an important validation process should be in place to explore their efficacy and safety guarantees. Nevertheless, even before such a validation process is established, the CHIC models can be of great interest to clinicians since they can be an additional source of information for the progress of the disease or the proper treatment plan, should the right disclaimers be in place so that the clinicians are well aware of the potential uncertainty in predictions. On the other hand, feedback from the clinicians can also be useful for the further adaptation and fine tuning of the models in the research environment. For the CHIC project as a whole and its objectives, it means that the computational modelling work is not cut off from its clinical relevance and practical use.

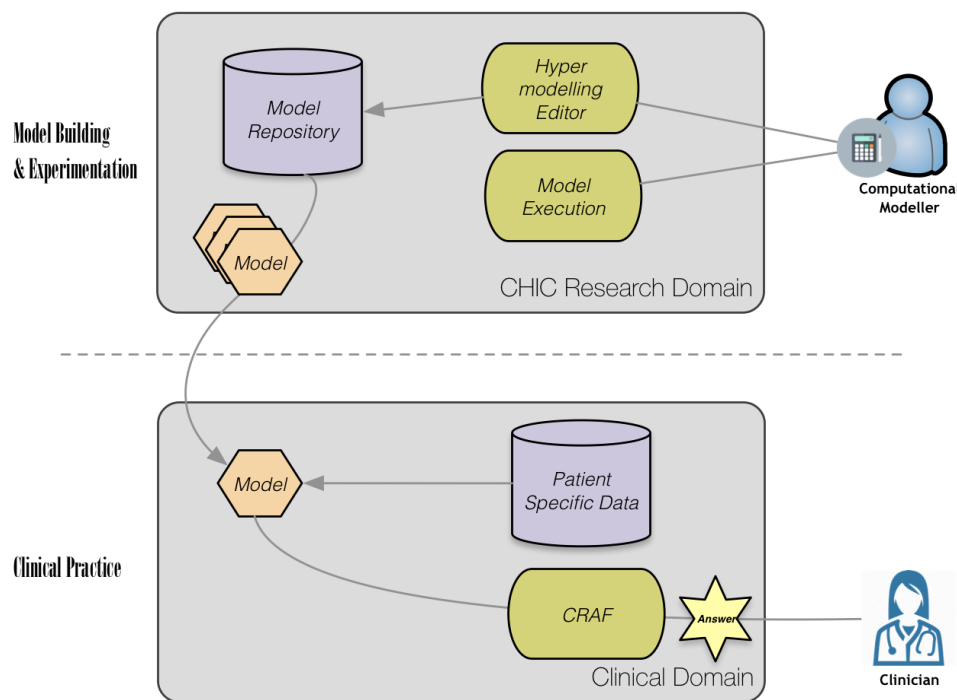


Figure 1 CRAF as the bridge of between the research and clinical domains

In order to realize this concept, a technical infrastructure should be available to facilitate the “transfer” of models from the CHIC research domain where they are built to the clinical domain where they are used by clinicians and other healthcare professionals (Figure 1). This is the role of the Clinical Research Application Framework (CRAF), that is, to provide the bridge between the research and clinical domains and make sure that these two “worlds” are not isolated from each other. In more practical terms, this means that CRAF should be able to launch the execution of the CHIC models using patient specific data that reside in the clinical domain and show their results to the clinical user. CRAF was first introduced in Deliverable 2.5 (“Clinical Relevance of the CHIC Project -

Describing the integrated workflows of the scenarios from a clinical perspective”). That deliverable describes the scenarios for the use of the CHIC hypermodels as tools for clinical decision support in three main cancer types (nephroblastoma, glioblastoma, non-small cell lung cancer) and prostate cancer as an additional one. As described in D2.5, the clinician interacts only with CRAF and CRAF communicates with other CHIC components in order to deliver to the clinician the desired output. This includes the user authentication (login to the system), selection of the cancer type (e.g. nephroblastoma), selection of the clinical question and the hypermodel that could answer the question, selection of the patient, running the selected hypermodel based on the provided inputs, and visualization of the results. This is a straightforward user interaction that was designed based on the guidance and supervision of the clinicians participating in CHIC.

3.1. High level requirements and functionality

CRAF operates in a clinical setting, or, to be more precise, on the edge between the clinical and the research platform. In the context of the clinical decision process for the patients’ individualized treatment, it’s imperative that clinicians have access to the personal (not fully anonymized) data of a given patient. Therefore, CRAF is the enabling technology for the secure handling of patient data during the invocation of the CHIC hypermodelling infrastructure, operating as a “security policy enforcement point” for the authentication and authorization of the users.

Being a tool used primarily by clinicians, CRAF aims to be simple and “smooth” by hiding the complexity of the underlying CHIC platform behind an intuitive and user friendly graphical interface. It should be accessible in the local premises of the clinicians with minimal requirements in terms of required software or hardware infrastructure.

Deliverable 2.5 presents the interaction between the end-user (clinician) and the developed integrated tools in a step by step manner for the four cancer types that are considered in CHIC. The following are the relevant steps:

- Data upload to the CHIC data repository: CRAF supports the upload of the different data types, for guaranteeing data safety and security, to handle semantic interoperability
- Data post-processing: Tumour segmentation using DrEye (Deliverable 9.4) needs to be done and the segmented data needs to be uploaded
- Selection of hypomodels or a hypermodel: The clinician is able to select a hypermodel composed of different hypomodels.
- Execution of the hypermodel:
 - After the selection of the hypermodel, CRAF checks if all data are available
 - If not all data are available the missing data needs to be uploaded to the CHIC data repository or missing data can be inserted manually
 - If all data are available the hypermodel will be automatically executed
- Visualization, reporting and storage of the results: Results of the hypermodel will be visualized, reported, and stored in the CHIC platform linked to the specific patient
- Validation of the results in single patients and fine-tuning of the hypermodel. After the end of the pre-operative chemotherapy new data are uploaded to the CHIC data repository to allow the validation and fine tuning of the hypermodel

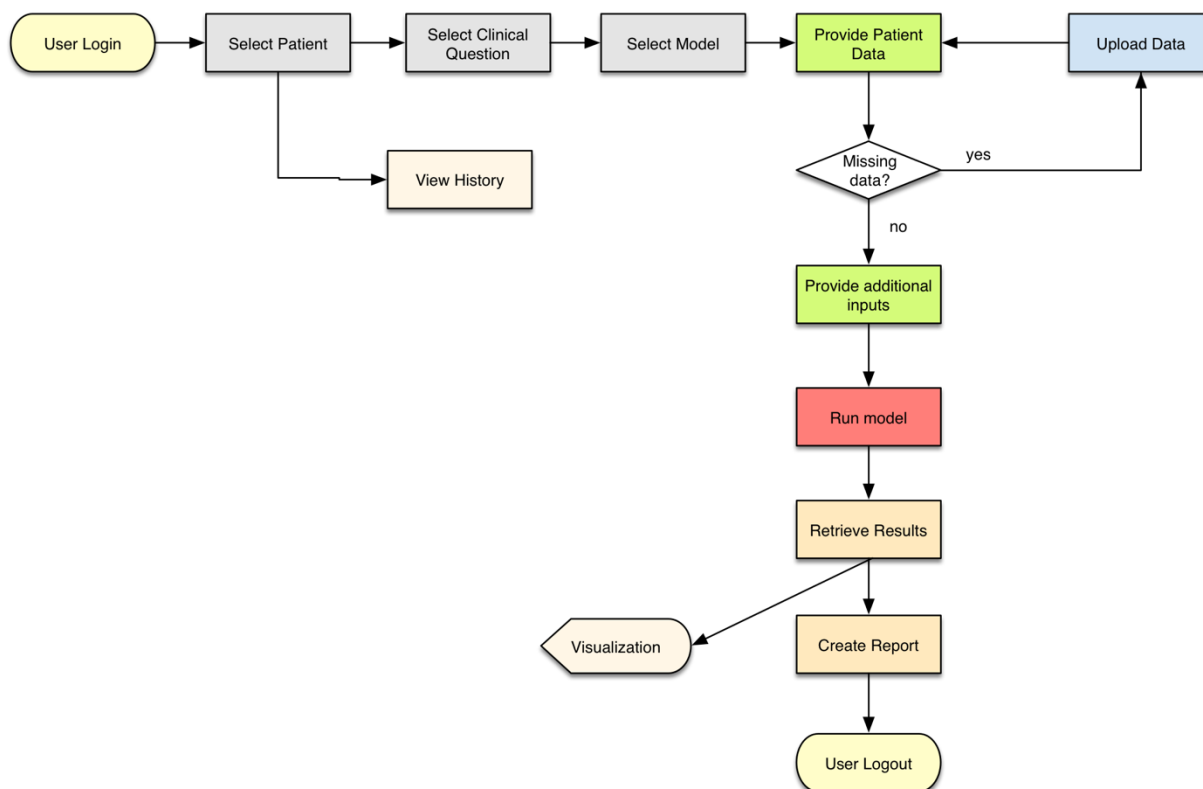


Figure 2 The main flow of user interactions in CRAF

These steps are shown in more detail in the flow chart of Figure 2:

- The user logs into CRAF by providing her/his user credentials in order for the system to authenticate her/him.
- There may be already a number of patients that have been registered with CRAF and the user is then able to select one of them. It may also be the case that the patient the user is interested in is not known to the system and therefore the user can create a new record for him/her (not shown in the figure).
- After the selection of a given patient the user could either see the history of previous models runs, or proceed to a new execution of a model. In the latter case, the user should first select a *clinical question*. The set of available clinical questions depend on the selected patient, or, more accurately, to the type of cancer of the patient. A typical clinical question is, for example, whether a specific treatment plan e.g. with three drugs (vincristine, actinomycin and doxorubicin) results in increased tumour shrinkage compared to two drugs (vincristine, actinomycin) in the selected nephroblastoma patient. The range of possible clinical questions are limited of course based on the availability of CHIC models that could possibly answer them.
- The selection of a clinical question immediately filters out models that cannot provide answers to it, so the next step is the selection of the specific model, amongst the applicable ones, to run.
- The selected model could answer the question chosen but it may be still the case that additional patient data are required for the execution. If so, CRAF asks the user to upload the missing patient data. In some cases, the user should use a specialized tool, such as DrEye (Deliverable 9.4), to perform some post-processing on the available data, e.g. to get the

tumour volume and the tumour composition, and the upload the result. The new data can then be reused in the future executions of the selected model or similar ones that need them.

- Prior to the actual execution, the user may need to provide some additional input values, for example the dosage of a drug in the selected treatment plan or other simulation parameters.
- When everything is ready and all needed model inputs have values, the execution of the model starts. The actual run of the model takes place in the CHIC server side infrastructure and therefore the user can logout if the execution takes too long.
- When the model has completed its execution, the user can download its results. A tool like CCGVis (Deliverable 9.2, see also Figure 3) can then be used for visualizing and comparing tumours and simulations.
- After the download of results and their visualization, CRAF can also produce a *report* that contains the full details of the execution, its inputs, outputs, and more importantly the answer to the initially selected clinical question. The user can also download this report and print it or import it to the electronic health record of the patient that is kept in the clinical environment.

The steps above represent the main sequence of interactions between the clinicians and CRAF but it's certainly non-exhaustive. First, there are alternative flows, such as starting from a specific cancer type, for example glioblastoma, that the clinical researcher may be interested in, and then proceeding to the selection of the patient or set of patients of this cancer type and the relevant clinical question. Secondly, CRAF is meant to serve as a platform for additional functionality: for example, more visualization capabilities can be provided in the future, or better collaboration with the existing infrastructure in the clinical domain (e.g. Picture Archiving and Communication Systems - PACS, Electronic Health Records). The vision for CRAF is to become a “framework” indeed, providing a domain specific functionality but in a generic way, so that other more specialized components can be plugged into it and enrich its capabilities.

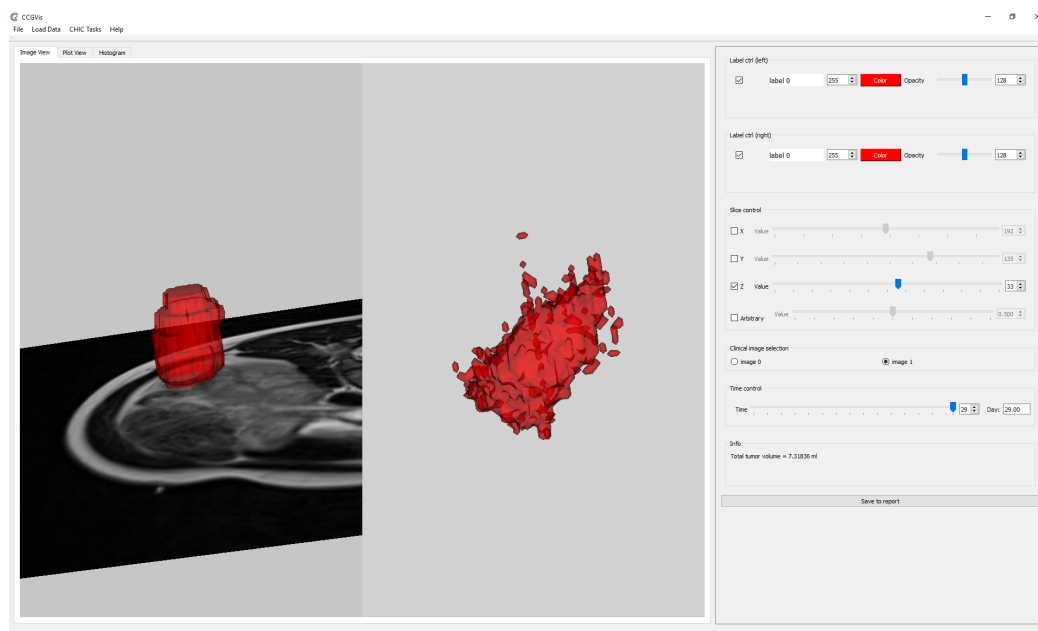


Figure 3 3D parallel comparison of real and simulated nephroblastoma tumours in CCGVis (Deliverable 9.2)

4. Architecture

The objective of CRAF is to provide a suite of tools in the clinical domain for the clinicians to run the CHIC models that have been verified for clinical use in order to gain potentially valuable information for the best treatment or diagnosis of their patients. Its main responsibility therefore is to request the execution of the CHIC hypermodels for the given patient data and to present their results to the clinical users. In addition to that, CRAF is also responsible for the upload of the patient data to the clinical domain of CHIC and their proper categorization and indexing, and in general for the provision of a unified interface to the whole CHIC platform for the clinical purposes. The CRAF application is therefore the frontend to important components of the CHIC research platform in order to support the following exemplary functionality:

- Allow the enrolment of patients by the authorized clinical stuff and the upload of the relevant clinical data. This means that there's a tight integration of CRAF with the CHIC security services (Deliverable 5.2.2) and the Clinical Data Repository (CDR) for the authentication and authorization of the users and the management of patient data.
- Support the selection of the most relevant hypermodels to run based on the profile and characteristics of a given patient. CRAF should integrate with the Model Repository, the Semantics Repository, and, of course, CDR in order to match the capabilities of the CHIC models with the profiles and the data of the patients
- Support the execution of the selected hypermodels for a specific patient based on a relevant clinical question and the presentation of their results. CRAF communicates with the CHIC VPH Hypermodelling Framework (VPH-HF) that provides the execution engine for the CHIC hypermodels (Deliverable 7.4) and the inSilico Trial Repository for the management of the inputs of the runs and their results (Deliverable 8.4).

The complete list of backend services that CRAF interacts with can be visualized as shown in Figure 4 and includes the following:

- The Model Repository, which is the model registry of CHIC. CRAF retrieves the list of the available, clinically relevant, hyper models from this repository and presents them to the user to be selected.
- The VPH-HF execution framework that is responsible for the actual model execution using the user supplied patient data.
- The inSilico Trial Repository, which stores the results of the executions alongside with the input data used and any other relevant information, such as starting and ending time, the identity of the users that triggered the execution, etc.
- The Clinical Data Repository for the storage and the indexing of the patient data that the users upload through CRAF. These sets of data are subsequently used for the execution of the CHIC hypermodels, so CRAF also keeps enough information about what have been uploaded, by whom, etc.
- The Semantic services and the semantic infrastructure are the curator of rich metadata annotations using domain specific ontologies for the models, their parameters, and their outputs. CRAF contacts the semantic infrastructure to retrieve these annotations and make intelligent decisions on the values of the parameters of the hypermodels or the specific patient data that should be used for each execution.

- The security related set of services, such as the Identity Provider/Secure Token Service, the Authorization Service, the Personal Information Management Service (PIMS), and the Distributed Audit Service (XDAS) are vital for providing the security layer in the CHIC clinical domain.

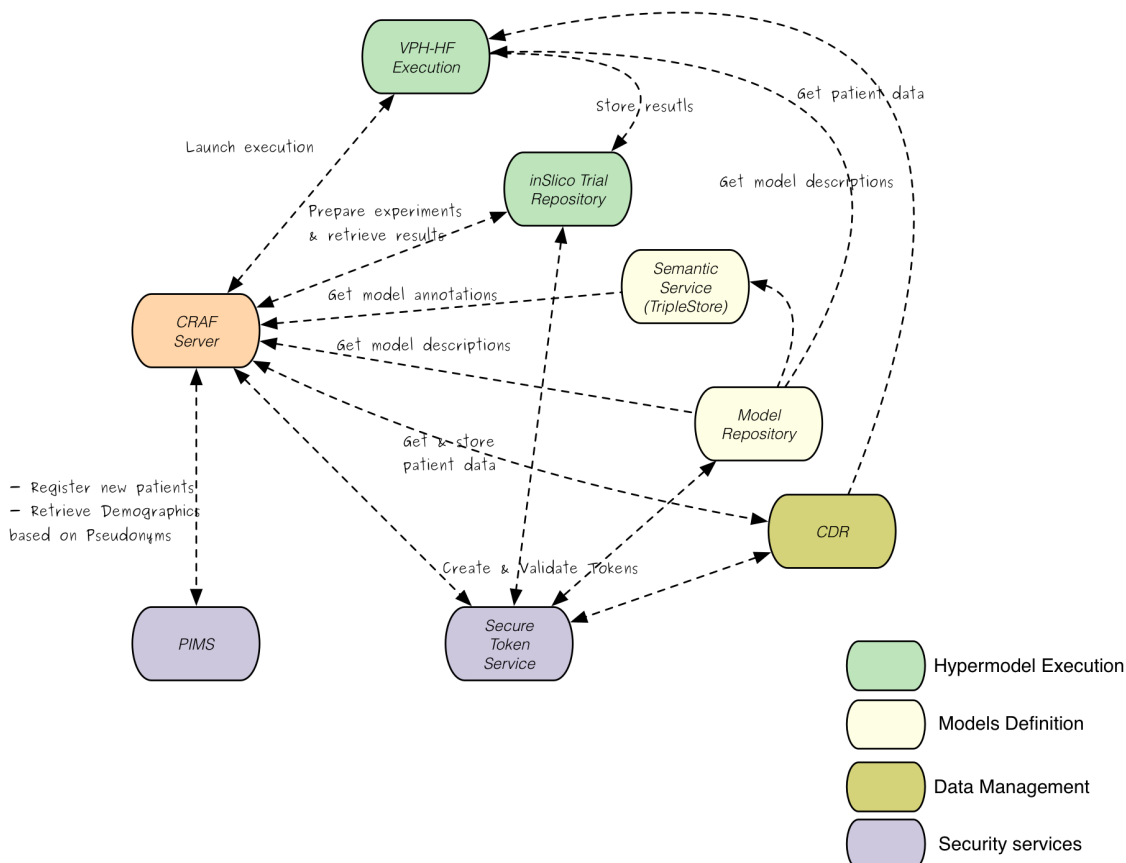


Figure 4 The interactions of CRAF with the backend services

4.1. Security

CRAF leverages the security infrastructure of the CHIC research platform for user authentication, authorization, and auditing. The CHIC Identity Provider (IdP) is used for the authentication of the users but proper provisions are in place to make sure that the two security domains, clinical and research, remain separate in terms of their users and access rights despite the fact that they are sharing a common deployment.

CRAF operates also as a Policy Enforcement Point (PEP, see Deliverable 5.2.2, “Final version of security tools and guidelines”) for authorizing the user access to the patient data. CRAF contacts the Authorization Service in order to make authorization decisions based on the users’ identity and roles before any access or modification to the sensitive patient data and prior to any model execution. In fact, no patient specific (identifying) information is stored in CRAF. Instead, during the registration of a new patient, it forwards patient demographics and identifiers to PIMS and gets back the patient pseudonym. All data managed by CRAF are tagged with the patient pseudonyms. Whenever, for usability purposes, it needs to present the patients’ demographics to the user, CRAF contacts PIMS again to do the reverse mapping, from the pseudonym to the real patient identity and names. Also, the integration of the security services and CRAF allows for separate “virtual organizations”. For

example, CRAF can be setup in the context of multiple hospitals so that each is independent and isolated in terms of the users and patients from each other.

Every user action is registered with the XDASv2 auditing server of CHIC (Deliverable 5.2.2), from the login to the platform, to the data access, and the execution of the hypermodels. The auditing is of paramount importance for CRAF since it handles, even indirectly, personal patient data. As described in the next paragraph, this is in direct contrast with the CHIC components in the research platform, which they handle “*de facto*” anonymous data after the two stage pseudonymization procedure.

4.2. Patient Data management

CRAF is built to cooperate with the CHIC research platform and therefore the actual patient data are stored in the central CHIC data repository which is CDR. Nevertheless, there is a big difference between the research and clinical domains: In the research domain, the data are made *de facto* anonymous, subject to two rounds of de-identification (Deliverable 4.3.2). Instead, in the clinical research domain, the patient data need not go through the whole anonymization process and, in fact, this would be against the purpose of CRAF to be used for the individualized treatment of patients. But still, the data need to be pseudonymized and only authorized personnel can, through CRAF, identify the patient or retrieve the data of a specific patient. Therefore, CRAF, before the upload of patient data to the CDR, performs a de-identification process to remove any patient identifiers. For example, for the medical images in the DICOM format, CRAF applies the DICOM de-identification profile⁴, effectively removing all names, replacing patient ids with the patient pseudonym, etc.

Prior to the upload of a new data set for a given patient, it's evident that the system should have already information about this patient. The patients' enrolment would entail the availability of the patient's consent. An authorized clinician will then use CRAF to create a new patient registration providing the complete set of demographics and identifying information. CRAF will not store this information, as explained in the previous paragraph, but instead it will forward it to PIMS and get back a patient pseudonym. The patient pseudonym is the only information that CRAF keeps in its database for a given patient. Then, when a clinical user provides data for an existing patient, CRAF uses the patient pseudonym as the only identifier to associate the data that are sent to CDR with the patient.

CRAF, being the only tool accessible to the clinicians for clinical research, is also responsible for the reverse action, that is the complete removal of the patients' data. For example, this could be the case when a patient (or their proxy) retracts the consent. CRAF will then do the following:

- instruct CDR to remove all the data linked to the patient's pseudonym,
- ask the in Silico Trial repository and the Execution Framework to delete all experiments (runs of the models) of the patient,
- ask PIMS to remove the patient's pseudonym, and finally
- remove all entries in its database for this patient

To close the loop of interactions between the research and the clinical domains, CRAF can also release the patient data in the CHIC research domain, as shown in the (updated) Figure 5 below. This again can only happen after a new consent is given by the patient, specifically for this purpose, and

⁴ See Annex E (ATTRIBUTE CONFIDENTIALITY PROFILES) of part 15 (“Security and System Management Profiles”) of the DICOM standard, http://dicom.nema.org/dicom/2011/11_15pu.pdf

the second stage of de-identification is performed by the CHIC's Centre for Data Protection (CDP) or equivalent data controller.

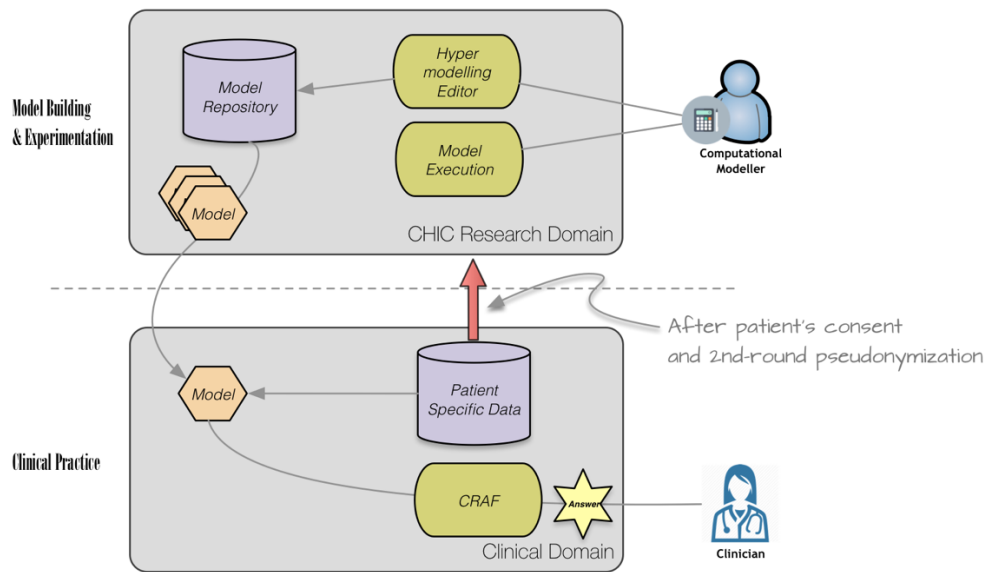


Figure 5 Clinical versus Research Domains

4.3. Implementation

CRAF follows a “two-tier” architecture, similar to the one of the Hypermodelling Editor (see Deliverable 10.4): at the backend, deployed in the private cloud of CHIC, there is the server side of CRAF that plays the role of a “Gateway server”⁵ that handles the connections with the other CHIC components using the specific programming interface (API) of each. In the frontend, the CRAF user interface is web-based, which means that it can be accessed with any modern web browser.

4.3.1. Backend server

The server side of CRAF consists of an HTTP-accessible application server written in Java using the lightweight, performant Undertow⁶ web server, and a PostgreSQL database server⁷ for its persistence needs. The CRAF server is reusing the event-based architecture of the CHIC execution environment in order to get (almost) real time messages about the status of the running hypermodels (see Deliverable 10.4). The introduction of a RabbitMQ message broker⁸ provisions of great deal of autonomy to the CRAF server as the execution status and model change events are delivered asynchronously.

4.3.2. User Interface

The end-user facing application of CRAF is accessible through a web browser, although a desktop version of it is also available but it's considered deprecated. CRAF does not expose any programmatic interface (API) apart from the one used for its own purposes, i.e. the communication between the

⁵ See the Gateway pattern in page 466 of Fowler, Martin. Patterns of enterprise application architecture. Addison-Wesley Longman Publishing Co., Inc., 2002.

⁶ <http://undertow.io/>

⁷ <https://www.postgresql.org/>

⁸ <https://www.rabbitmq.com/>

HTML and Javascript based client interface and the server side.

The user interface (UI) of the CRAF application is implemented using the state of the art in hybrid application development. CRAF's UI is designed based on the guidelines of the Material Design language⁹ as defined by Google. The application is built using open source components following the Single-Page Application (SPAs¹⁰) architecture based on the AngularJS¹¹ Javascript framework.

Single-Page Applications (SPAs) are Web apps that load a single HTML page and dynamically update that page as the user interacts with the app. As shown in Figure 6, in a traditional Web app, every time the app calls the server, the server renders a new HTML page. This triggers a page refresh in the browser (top of figure). In an SPA, after the first page loads, all interaction with the server happens through AJAX calls. These AJAX calls return data—not markup—usually in JSON format. The app uses the JSON data to update the page dynamically, without reloading the page (bottom of figure).

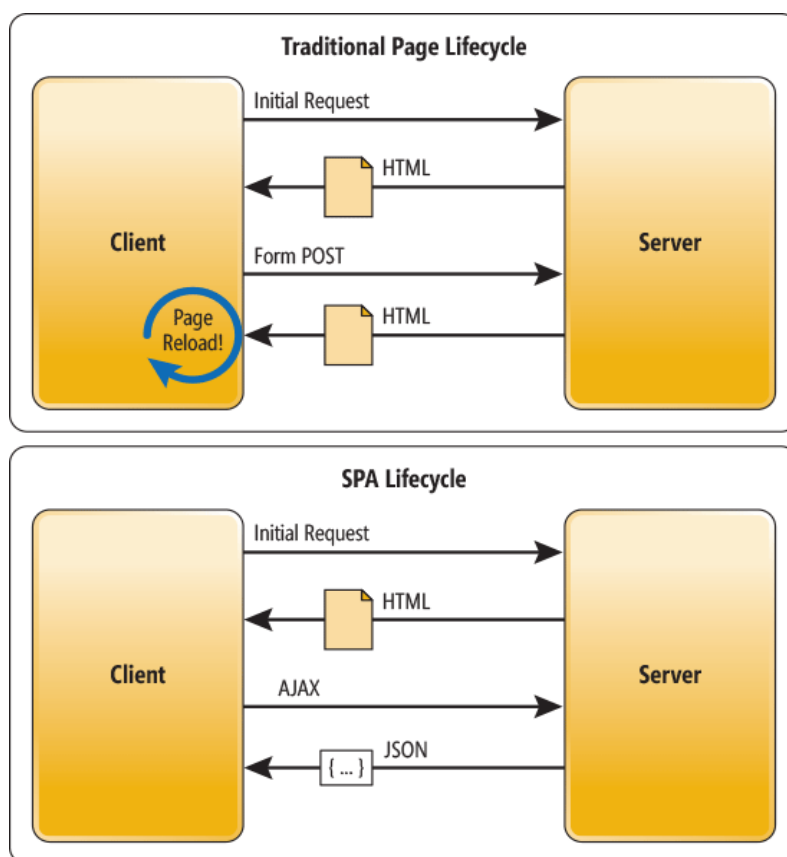


Figure 6 The Traditional Page Lifecycle versus. the SPA Lifecycle

SPAs, therefore, use AJAX and HTML5 to create fluid and responsive Web apps, without constant page reloads, as much of the work happens on the client side, in JavaScript. Single-Page Applications are the de facto standard to make Responsive Websites which support all the major display factors: mobile, tablet, and desktop. The advantages of SPAs are:

- No extra queries to the server to download pages.

⁹ Google. (n.d.). Material Design. Retrieved from <https://material.io/>

¹⁰ Birdeau, Lucas, et al. "Delivery of data and formatting information to allow client-side manipulation." U.S. Patent No. 8,136,109. 13 Mar. 2012

¹¹ Google. (n.d.). AngularJS — Superheroic JavaScript MVW Framework. Retrieved from <https://angularjs.org/>

- User friendly.
- Performance Improvement, Single Page Application can improve performance in many ways, Single time file load each of HTML, CSS, JS.

In the next chapter, we present some of the CRAF's functionality and the user interface it supports.

5. A tour in the user interface

5.1. Basic usage

5.1.1. Login

By accessing the web address (URL) where the CRAF application is available, the first and required step that the user has to make is to login. By providing the proper credentials to the login controls, the user is authenticated using the CHIC Identity Provider service and is granted the permission to continue to the private area of the application. If the credentials are not correct or if the user does not exist then a notification message appears and the application remains to the login screen (Figure 7).

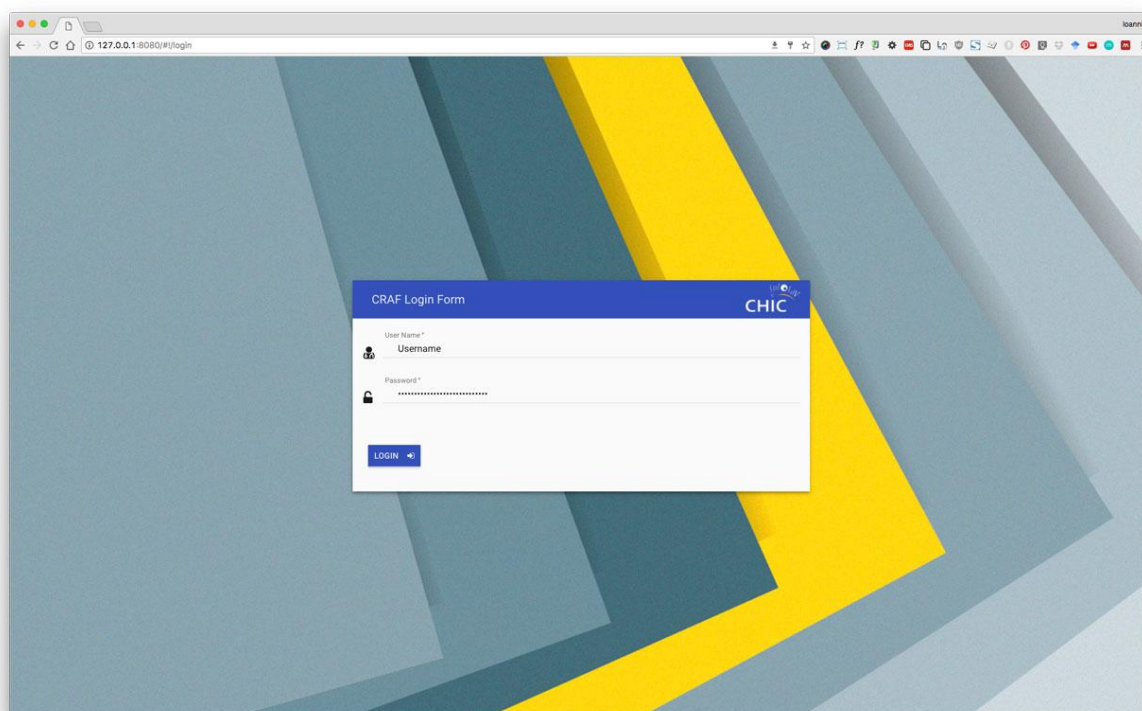


Figure 7 The login screen

5.1.2. Main dashboard & side menu

Once the clinician has successfully authenticated and logged in the CRAF app, is presented with the main dashboard. The main dashboard or Home screen (Figure 8) provides two options to the clinician, each initializing the corresponding workflow to configure and execute a hypermodel which will answer a significant question. The two choices are either to select a cancer domain or a patient, as a start of the wizard which will conclude to the execution of a hypermodel.

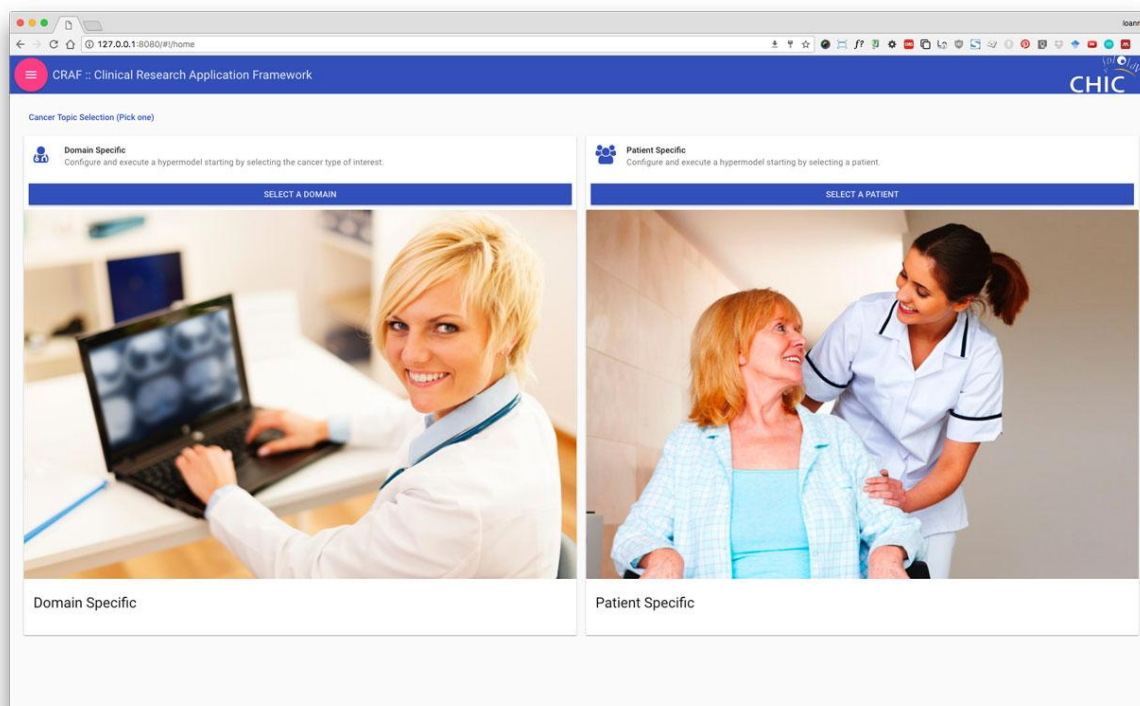


Figure 8 Main dashboard / Home screen

All the available functionalities of CRAF are available from its main menu. The menu is accessible by the "hamburger" button¹² (the round button at the top right side of the screen which displays an icon that consists of three parallel horizontal lines). Once the clinician clicks the button, a menu appears at the left side of the display (Figure 9), with the following options:

- Home, to navigate to the initial welcome page
- History, to get the previous runs (experiments)
- Patient List, to retrieve the list of available patients
- New Patient, to create a new patient entry in the system
- Upload, to upload a new data set for a given patient
- Settings, to change various user preferences
- About,
- Sign Out

¹² Xerox Corporation. (2015). Xerox Connect – The Juicy Story of the “Hamburger Symbol.” Retrieved from <https://connect.blogs.xerox.com/2015/07/02/the-juicy-story-of-the-hamburger-icon-for-web-design/>

In the following sections detailed information is provided regarding each functionality of the side menu.

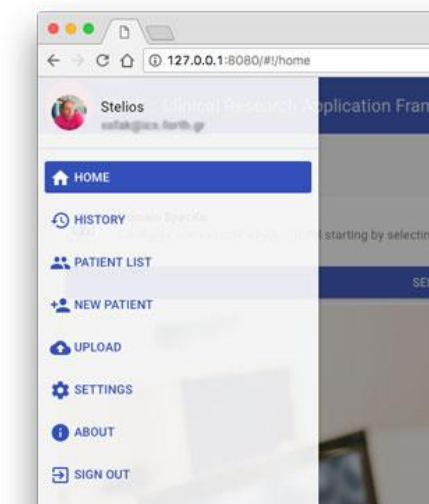


Figure 9 Side menu

5.1.3. Create a New Patient

Using the Create Patient option from the side menu, the user can enrol a new patient in the platform. The process requires to enter the demographics of the patient in a form (Figure 7). Patient demographic information provided to CRAF by an authorised healthcare professional during patient enrolment is not stored in the CHIC clinical data repository. Instead all demographic information is stored in a Patient Identity Management System (PIMS). PIMS securely stores demographic information and assigns a pseudonym to the patient or return an existing one if the patient has already been registered with PIMS (Deliverable 5.2.2, Final version of security tools and guidelines - Section 5.1.3, Data upload and de-identification).

The screenshot shows a web browser window displaying the 'CRAF - Clinical Research Application Framework' interface. The page title is 'New Patient'. Below the title, there is a section for 'Patient's Information'. This section is divided into four sub-sections: 'GENERAL INFORMATION', 'NATIONAL HEALTH SYSTEM', 'CONTACT', and 'ADDRESS'. Each sub-section contains several input fields for patient data. The 'GENERAL INFORMATION' section includes fields for First Name (Required), Last Name (Required), Middle Name, Gender (Required), and Date of Birth. The 'NATIONAL HEALTH SYSTEM' section includes a field for National ID Number. The 'CONTACT' section includes fields for Phone and E-mail. The 'ADDRESS' section includes fields for City, Region, Country, Street, and House Number. The form is designed with a clean, modern layout and includes validation markers (asterisks) for required fields.

Figure 10 the new patient demographics form

5.1.4. Data Upload

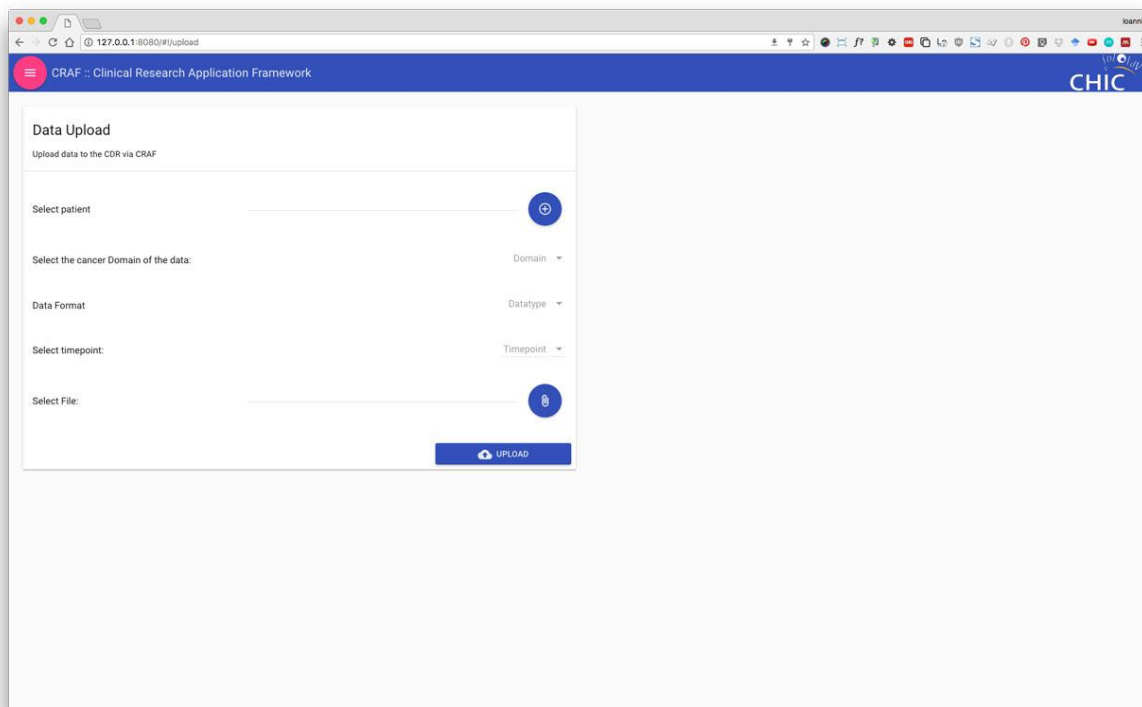
Clinical data uploaded through CRAF using the Upload Data option, are stored in the clinical data repository (CDR) and assigned the pseudonym issued by PIMS. Because of the separation of clinical and demographic information users and system administrators with access to the clinical data repository cannot easily or by accident re-identity a patient through his/her demographics.

CRAF supports “resumable”¹³ uploads with validation check for the file types of the content to be uploaded. The clinician can upload any of the following data types:

- Clinical study data in the form of CDISC-ODM files, supporting the following extensions (txt, xml, odm, soft).
- Genomics data in textual files, supporting the following extensions (xml, txt).
- Imaging data in DICOM files, supporting the following extensions (dcm, dicom, zip). Specifically, for the case of the imaging data, the files must be compressed (in zip format) prior to their uploading. This is because compression reduces the time to upload the data and also it groups all the files of a DICOM Series in a single upload (when the series is not a single multi frame DICOM file).
- Segmentation data as labeled metaimages in a single file (mha format, where the header of the metaimage is contained in the same file with the raw data), supporting the following extensions (mha, zip). These metaimages can be the result of the segmentation done by clinicians or more specialized personnel using DrEye (see Deliverable 9.4).

To conclude the uploading process, the user has to select the patient of interest, to define the data type format of the file to upload, to associate the file to a specific *timepoint* and finally to pick the file. The uploading form is depicted in Figure 8.

¹³ In case of a connection or other error, the upload can resume from the point it stopped.



The screenshot shows a web browser window with the address bar displaying '127.0.0.1:8080/#/upload'. The page title is 'CRAF - Clinical Research Application Framework'. The main content area is titled 'Data Upload' and includes the instruction 'Upload data to the CDR via CRAF'. The form contains several input fields and dropdown menus: 'Select patient' with a plus icon, 'Select the cancer Domain of the data:' with a 'Domain' dropdown, 'Data Format' with a 'Datatype' dropdown, 'Select timepoint:' with a 'Timepoint' dropdown, and 'Select File:' with a file selection icon. A blue 'UPLOAD' button is located at the bottom right of the form.

Figure 11 Data upload form

The timepoint information is cancer type specific annotation of the data, and could be, for example, “at the time of diagnosis” or “after chemotherapy”. This is an important information that will allow CRAF to propose a specific data set for a given model execution.

5.1.5. List of Patients

This section provides an overview of the available patients for the logged user (Figure 12), based on his/her specific permission criteria. Upon selecting a patient, the user can select to view their clinical data or other available information.

	Name	MiddleName	BirthDate	Gender	Cancer Type
<input type="checkbox"/>	Hans Fischer				NEPHROBLASTOMA
<input type="checkbox"/>	Ernst Müller				NEPHROBLASTOMA
<input type="checkbox"/>	Bjorn Borgmann				LUNG
<input type="checkbox"/>	Sam Schmidt				PROSTATE
<input type="checkbox"/>	Kim Schäfer				PROSTATE
<input type="checkbox"/>	Jo Richter				PROSTATE

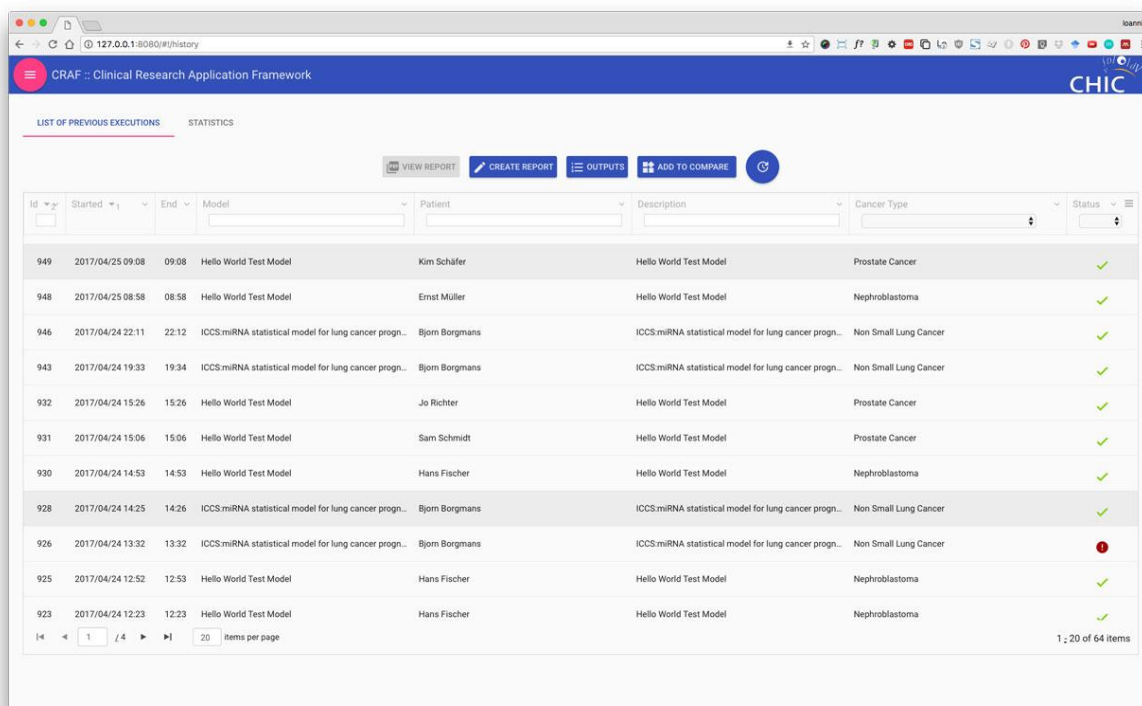
Figure 12 The list of available patients

5.1.6. List of executions

In the History section, there is a tabular control with the list of all the executions that have been performed by the logged in clinician (Figure 13). Each row in the table represents a hypermodel execution, providing information regarding the initialization and completion times of the execution, the model, the patient and the status. The table is interactive and allows the user to filter the presented executions and also to select a specific execution.

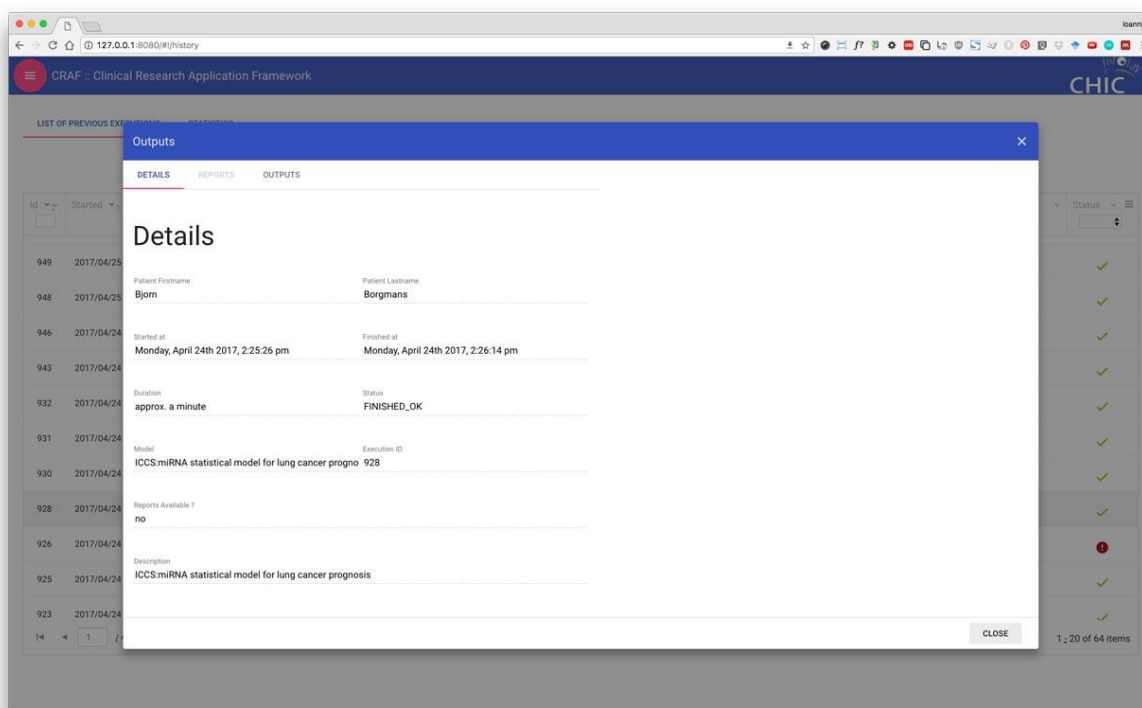
For a selected application, the user can perform the following actions:

- Create and download a report
- View the last report of the execution
- View the outputs of the execution (details, reports, output files, etc.), from where they can be downloaded (Figure 14 and Figure 15).
- Perform simple comparisons among executions
- Check for a new execution (manual request to update the results of the execution list)



Id	Started	End	Model	Patient	Description	Cancer Type	Status
949	2017/04/25 09:08	09:08	Hello World Test Model	Kim Schäfer	Hello World Test Model	Prostate Cancer	✓
948	2017/04/25 08:58	08:58	Hello World Test Model	Ernst Müller	Hello World Test Model	Nephroblastoma	✓
946	2017/04/24 22:11	22:12	ICCS.miRNA statistical model for lung cancer progn...	Bjorn Borgmans	ICCS.miRNA statistical model for lung cancer progn...	Non Small Lung Cancer	✓
943	2017/04/24 19:33	19:34	ICCS.miRNA statistical model for lung cancer progn...	Bjorn Borgmans	ICCS.miRNA statistical model for lung cancer progn...	Non Small Lung Cancer	✓
932	2017/04/24 15:26	15:26	Hello World Test Model	Jo Richter	Hello World Test Model	Prostate Cancer	✓
931	2017/04/24 15:06	15:06	Hello World Test Model	Sam Schmidt	Hello World Test Model	Prostate Cancer	✓
930	2017/04/24 14:53	14:53	Hello World Test Model	Hans Fischer	Hello World Test Model	Nephroblastoma	✓
928	2017/04/24 14:25	14:26	ICCS.miRNA statistical model for lung cancer progn...	Bjorn Borgmans	ICCS.miRNA statistical model for lung cancer progn...	Non Small Lung Cancer	✓
926	2017/04/24 13:32	13:32	ICCS.miRNA statistical model for lung cancer progn...	Bjorn Borgmans	ICCS.miRNA statistical model for lung cancer progn...	Non Small Lung Cancer	✗
925	2017/04/24 12:52	12:53	Hello World Test Model	Hans Fischer	Hello World Test Model	Nephroblastoma	✓
923	2017/04/24 12:23	12:23	Hello World Test Model	Hans Fischer	Hello World Test Model	Nephroblastoma	✓

Figure 13 The list of executions



Details	
Patient Firstname	Patient Lastname
Bjorn	Borgmans
Started at	Finished at
Monday, April 24th 2017, 2:25:26 pm	Monday, April 24th 2017, 2:26:14 pm
Duration	Status
approx. a minute	FINISHED_OK
Model	Execution ID
ICCS.miRNA statistical model for lung cancer progn...	928
Reports Available ?	
no	
Description	
ICCS.miRNA statistical model for lung cancer prognosis	

Figure 14 Overview of the execution details.

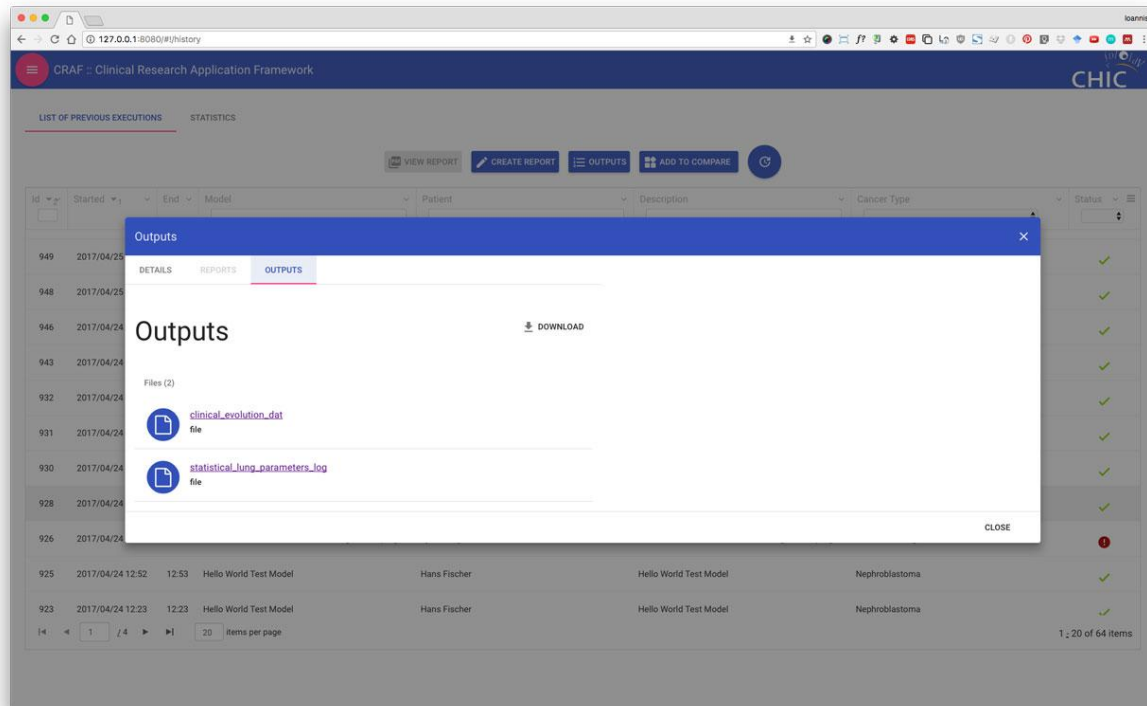


Figure 15 Overview of the execution outputs

5.1.7. Settings

From the settings screen (Figure 16) several configuration options can be adjusted, such as the default language of the CRAF application. The application currently supports the following 3 languages, Greek, German and English, and it is easy to add more as it is using dedicated language files. From this screen, the user may choose to enable reminders of the platform or change the colour scheme of the UI.

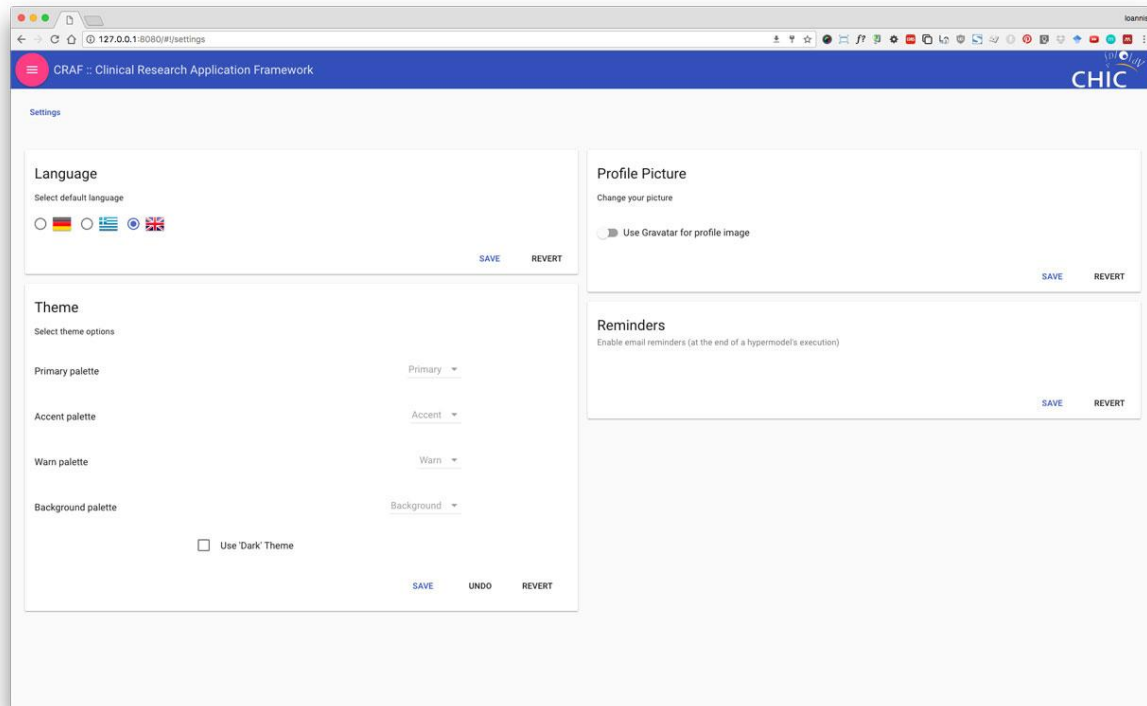


Figure 16 The settings screen

5.2. Model Execution

5.2.1. Execution workflows

CRAF provides a wizard procedure which guides the clinician using sequential steps to intuitively configure and execute a model (hyper-model or other). The wizard provides two ways of initialization which correspond to two different workflows. The clinician either picks a cancer domain and carries on the procedure, or a patient registered in the CHIC platform. Although the two workflows can produce the same results, there is a differentiation in the interaction with the user, which is described in the next subsections.

Cancer Domain based

In the domain based workflow, the expert has to select from the four available cancer domains of CRAF, Nephroblastoma, Non Small Lung Cancer, Glioblastoma and Prostate. This step is displayed in Figure 17.

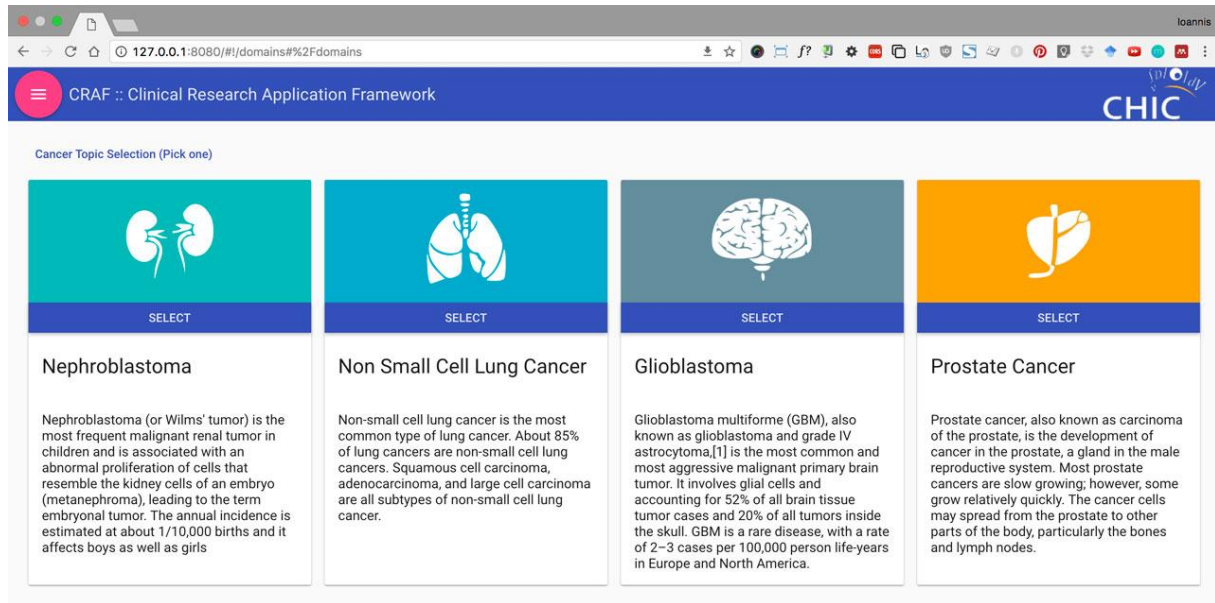


Figure 17 Available Cancer Domains

Once the user has selected a domain then the corresponding questions appear in the form of a radio button list. The user picks the question of interest and proceeds to the next step, by clicking the NEXT button at the right side of the main toolbar (Figure 18).

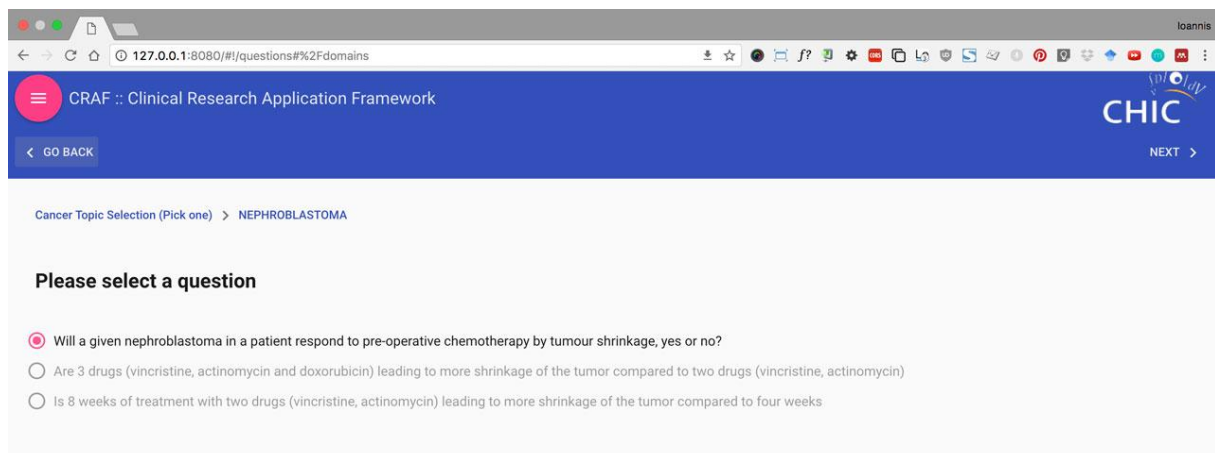


Figure 18 Available questions for the selected domain

At this step, a list of the available patients is showing. The list is filtered, disabling the ones that do not fulfil the criteria (proper domain or incomplete data). The unsuitable patients appear in a grey hue, and they cannot be selected. There is also a switch that can hide them in order to keep the UI simple, reducing the clutter. By changing the selected patient, the Patient card at the right side, updates to show any available information and data. The data are grouped automatically based on their datatype. A screenshot of the patient selection interface is presented in Figure 19.

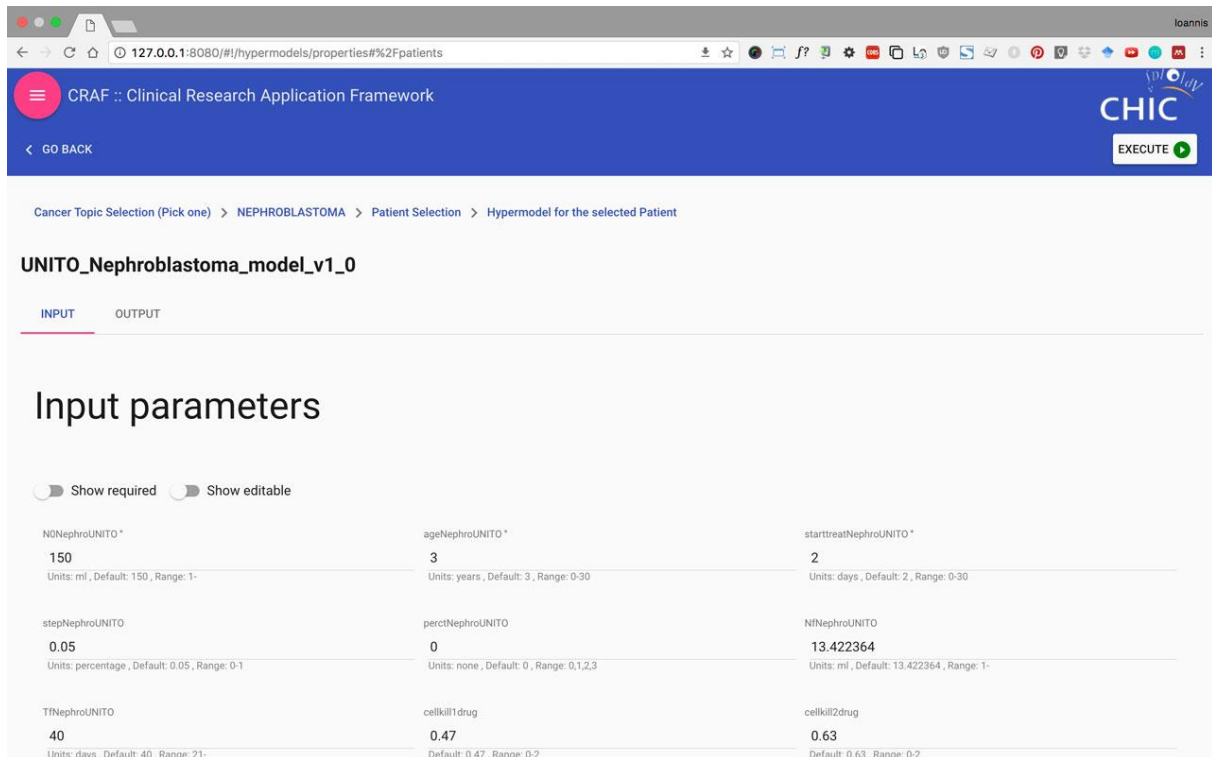
Figure 19 Patient selection

After the selection of the question and the patient of interest, the user is guided to this step where the available (hyper)models appear (Figure 20).

Figure 20 (Hyper)model selection

The final step is to configure the selected (hyper)model for the selected patient. All the parameters of the model are presented in two tabs, one for the input parameters (Figure 21) and one for the

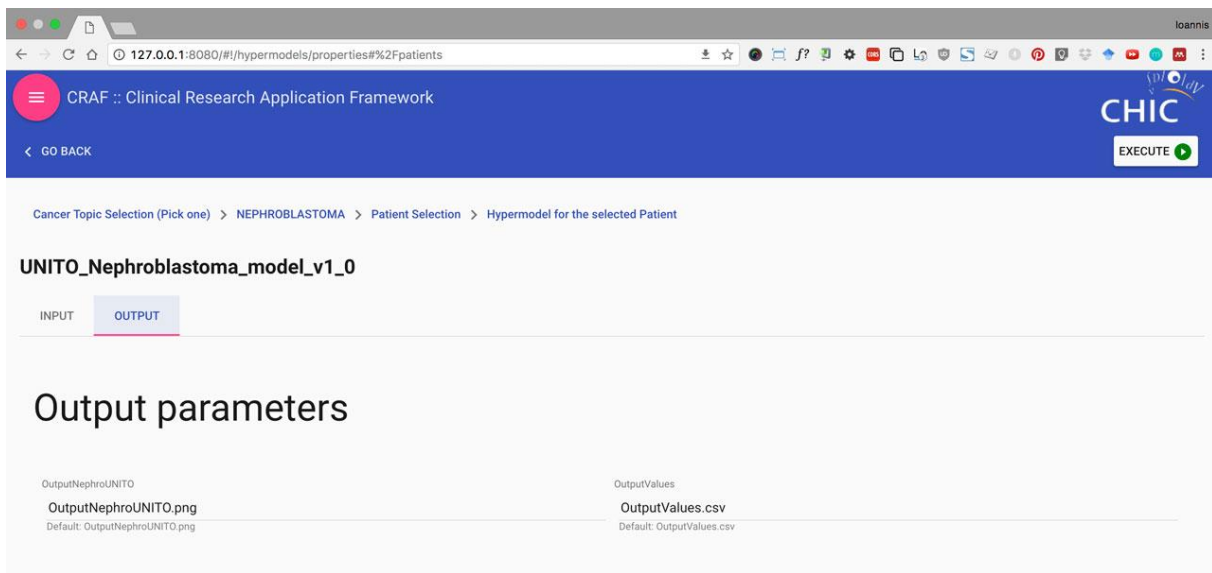
output parameters (Figure 22). The input parameters can be filtered using the appropriate switch in order to show only the required and/or the editable ones.



The screenshot shows the CHIC Clinical Research Application Framework interface. The breadcrumb trail is: Cancer Topic Selection (Pick one) > NEPHROBLASTOMA > Patient Selection > Hypermodel for the selected Patient. The model selected is UNITO_Nephroblastoma_model_v1_0. The 'INPUT' tab is active, showing a list of input parameters with their current values and units. The 'Show required' and 'Show editable' filters are both selected.

Parameter	Value	Units	Default	Range
ageNephroUNITO *	3	years	3	0-30
starttreatNephroUNITO *	2	days	2	0-30
stepNephroUNITO	0.05	percentage	0.05	0-1
perctNephroUNITO	0	none	0	0,1,2,3
NINephroUNITO	13.422364	ml	13.422364	1-
TINephroUNITO	40	days	40	21-
cellkill1drug	0.47		0.47	0-2
cellkill2drug	0.63		0.63	0-2

Figure 21 Selected models' input parameters



The screenshot shows the CHIC Clinical Research Application Framework interface. The breadcrumb trail is: Cancer Topic Selection (Pick one) > NEPHROBLASTOMA > Patient Selection > Hypermodel for the selected Patient. The model selected is UNITO_Nephroblastoma_model_v1_0. The 'OUTPUT' tab is active, showing a list of output parameters with their default values and units.

Parameter	Value	Units	Default
OutputNephroUNITO	OutputNephroUNITO.png		OutputNephroUNITO.png
OutputValues	OutputValues.csv		OutputValues.csv

Figure 22 Selected models' output parameters

Patient Based

In the patient based workflow the process starts with the expert to have to select one of the available patients in order to initialize the wizard. As in the domain based workflow by changing

patients their corresponding information and data appear in the patient card that lies beside (Figure 23). Any patient can be selected in this stage. As each patient has been associated with only one cancer type, their separation in domain based groups greatly assists the clinician to locate the patient of interest.

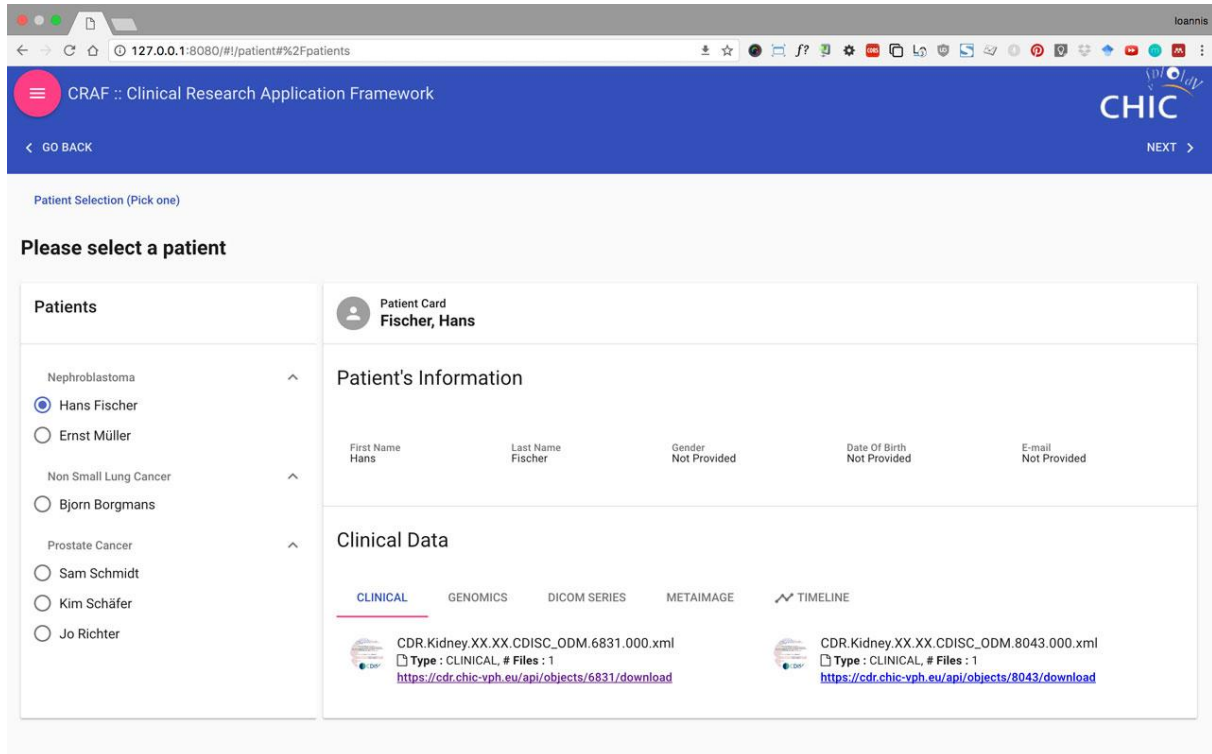


Figure 23 Patient selection

After the selection of the patient, a list with the available questions for the associated cancer type appears (Figure 24).

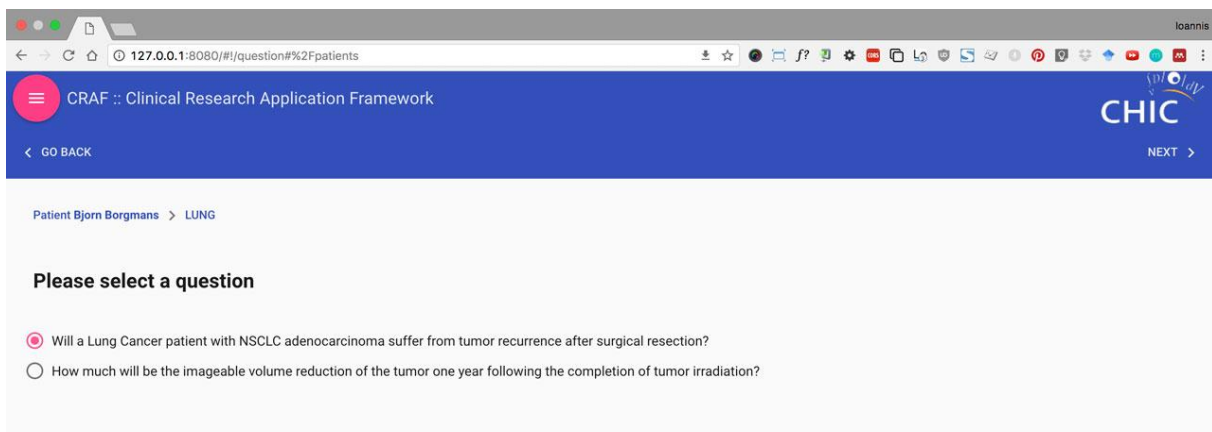


Figure 24 Available questions for the selected patient.

In the third step a hyper-model has to be selected (Figure 25).

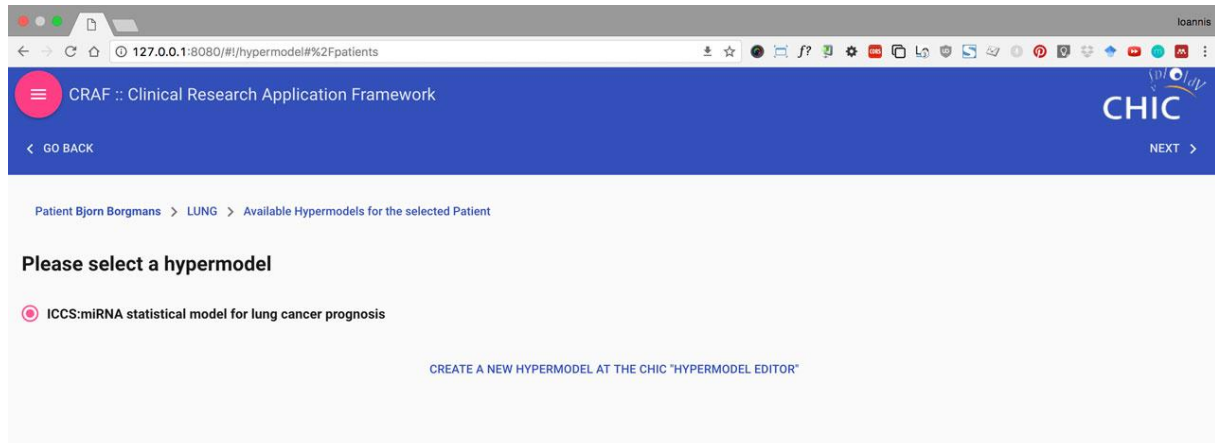


Figure 25 Hypermodel selection

In the fourth and final step, the clinician has to configure all the available parameters of the selected model for the patient of interest (or just accept the default values). The parameters are separated in input and output parameters, in two corresponding tabs. The input parameters can be further filtered in two groups, the required and/or the editable (Figure 26).

When all the parameters are set, the clinician launches the execution of the model. If the execution of the model initiates successfully in the back-end then a short notification message appears and the user is transferred in the history section where he/she can view the status of the models' execution and, upon its completion, the results.

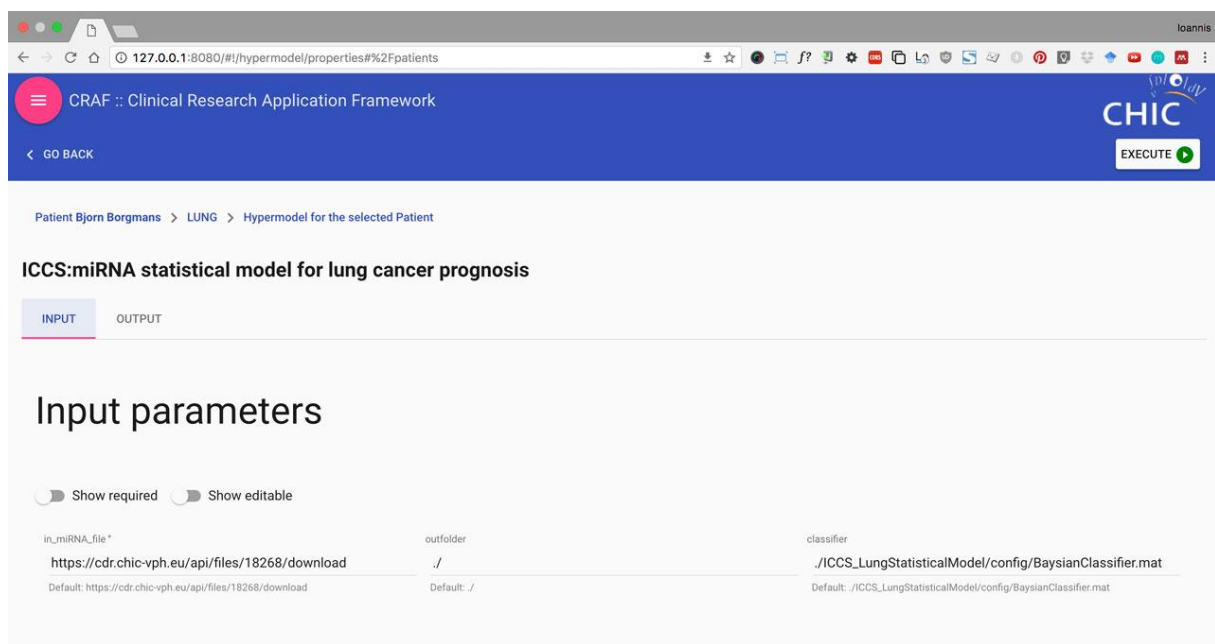


Figure 26 Selected models' input/output parameters

5.2.2. Execution Overview and Report Generation

In the list of executions section (history section), a complete list of all the models' executions of the user (both running and previous) appears in tabular way. For the successfully completed executions,

the clinician can generate a report which can be downloaded locally as a pdf document. In the report the following information is included: The clinical question and the model's answer for the patient under investigation, escorting graphs (if any), the hypermodel description plot and finally a list with the input parameters of the hypermodel. An example of a report is provided in the next subsection.

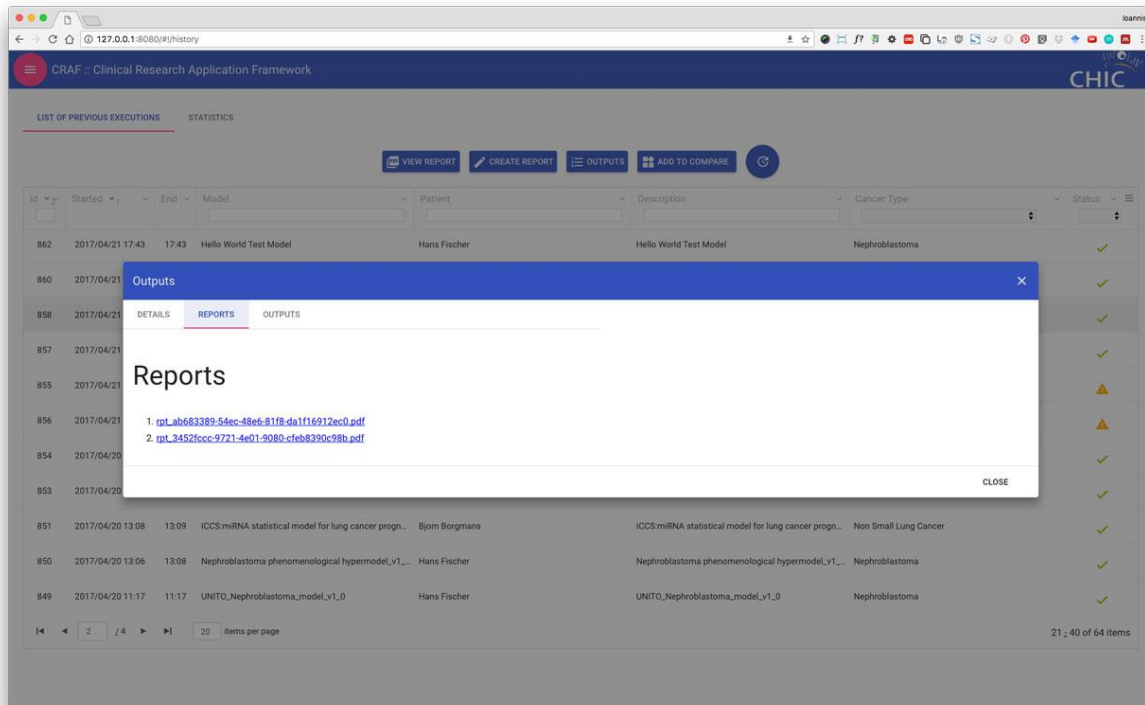


Figure 27 List of reports for a selected completed hypermodel execution.

Example of a generated Report

In silico study of cancer response to treatment

Patient Name: Borgmans, Bjorn

Date of birth: [Not available]

Started at: 2017-04-21 14:00

Finished at: 2017-04-21 14:06

Clinical question:

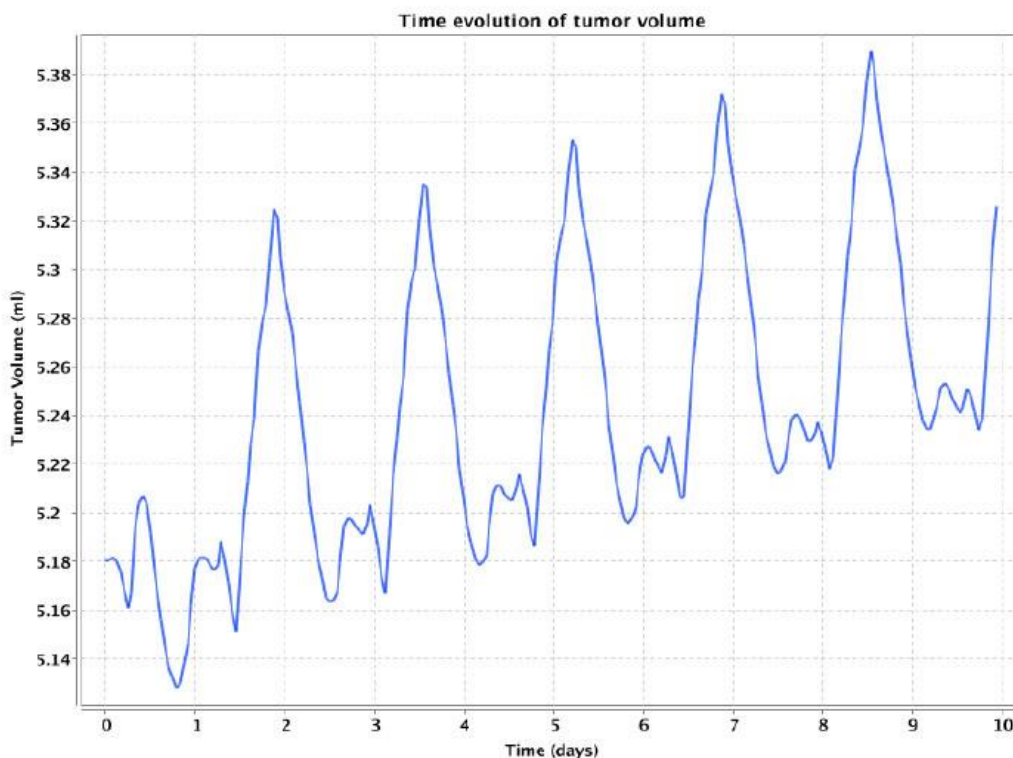
How much will be the imageable volume reduction of the tumor one year following the completion of tumor irradiation?

Simulated Tumour Volume reduction percentage: **-2.83 %**

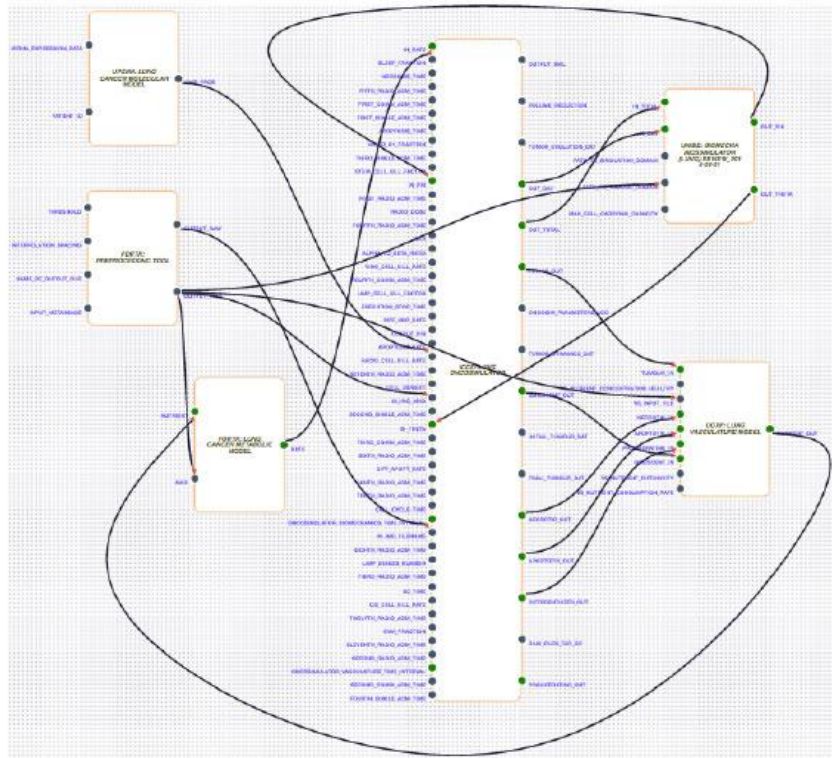
Simulation predictions

Treatment onset (in respect to simulation time 0) (day): **104**

Reference time point (in respect to simulation time 0) (day): **10**



Hypermodel Description



Input values of hypermodel parameters

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

Rate of glucose consumption per cell per hour.: 7.6e-9

Glucose concentration in non tumour regions. Output is normalized by this value.: 0.9

Tumour cell concentration used for pressure computation.: 1000000

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](https://cdr.chic-vph.eu/api/files/18314/download)

Fraction of stem cells that divide symmetrically in necrotic regions: 0.322

Defines the threshold for the cropping (float between 0 and 1): 0.5

Number of limited mitotic potential (LIMP) cell stages before differentiation occurs = number of LIMP cell mitoses before differentiation occur: 22

The spacing to be used for the isotropic interpolation.: 1

Tumor cell density in number of biological cells per 1mm³.: 1000000

A valid metaimage which contains the segmentations with the tumor value to be 255: [https:// cdr.chic-vph.eu/ api/ files/ 18314/ download](https://cdr.chic-vph.eu/api/files/18314/download)

: 1

Name of output file which will contain the interpolated and cropped result: output

: 1

Csv or minml file which contains the miRNA expression data.: [https:// cdr.chic-vph.eu/ api/ files/ 18268/ download](https://cdr.chic-vph.eu/api/files/18268/download)

Cell kill rate of cisplatin: 0

Anonymized ids of patients selected for the trial. In the model demo run precomputed results are available for only patient JGUP5ZVT3CHDDP4HMRZD: JGUP5ZVT3CHDDP4HMRZD

Cell kill rate of vinorelbine: 0

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

Enhancement of therapeutic or detrimental effect of ionizing radiation due to the presence of oxygen: 3

Dose D (Gy) of radiation to a population of cells: 15

Cell cycle duration of stem and LIMP cells (G0 phase not included): 40

Dormant (G0) phase duration of stem and LIMP cells : 168

Time before necrosis products are eliminated: 23

Time before apoptosis products are eliminated in necrotic regions: 4

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

Spontaneous apoptosis rate corresponding to transition to apoptosis from the differentiated cell state: 0.017

Rate to enter necrosis for differentiated cells : 0.025

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

Fraction of cells that will enter G0 following mitosis in necrotic regions: 0.263

radiation dosage for the UPENN lung molecular model: 15

Time point after initialization (in days) when the 1st combination chemotherapy takes place: -1

Time point after initialization (in days) when the 2nd combination chemotherapy takes place (= -1 if total cycles less than 2): -1

Time point after initialization (in days) when the 3rd combination chemotherapy takes place (= -1 if total cycles less than 3): -1

Time point after initialization (in days) when the 4th combination chemotherapy takes place (= -1 if total cycles less than 4): -1

Time point after initialization (in days) when the 1st single chemotherapy takes place: -1

Time point after initialization (in days) when the 2nd single chemotherapy takes place (= -1 if total cycles less than 2): -1

Time point after initialization (in days) when the 3rd single chemotherapy takes place (= -1 if total cycles less than 3): -1

Time point after initialization (in days) when the 4th single chemotherapy takes place (= -1 if total cycles less than 4): -1

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

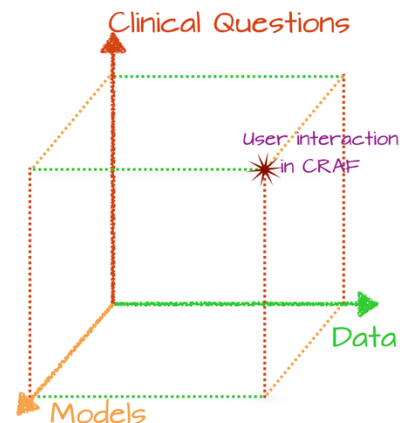
Time point after initialization (in days) when the 12th irradiation takes place(= the last administration time point if total irradiations less than 12): -1

Execution stop time after initialization: 10

6. Discussion

The clinical research platform requires tools such as CRAF in order to facilitate health care provisioning and planning. We can identify three main pillars for CRAF, as the graphic on the right tries to convey:

- The CHIC research platform provides a set of integrative *models* that provide some insight on the physiology of the cancer or its treatment.
- On the clinical practice, *questions* about the disease progression or the best cancer treatment arise every day.
- A multitude of heterogeneous and multilevel *data* are generated during the hospitalization or follow up of patients.



Therefore, in a typical user interaction in CRAF, we try to combine the available models with the patients' data in order to answer important clinical questions or research hypotheses. Due to the complexity in managing of each of these aspects on its own, it's a lot more difficult task to handle their combination in a user-friendly, generic, and scalable way.

First of all, these three dimensions shown in the figure (models, data, and "questions") are not truly independent. There are certainly important clinical questions for which no models exist and therefore cannot be answered, or there may exist models that only partially answer a question. Also, some models may require rich input data sets that are not usually available.

Another aspect is the "protocol" for the association of questions with models and how generic and independent of these choices CRAF may be. Currently, the set of available models for the four exemplary cancer types in CHIC determines the questions that can be posed and answered in CRAF. A feature that may be interesting would be for the clinicians submitting their (unanswered) questions so that the computational modellers could start building the (hyper)models that respond to them. CRAF could therefore act also as a facilitator for this discussion between clinicians and modellers. In terms of the implementation, the code is quite generic and independent of the models and questions. The incorporation of a new model and possibly a new question only requires a change in the configuration for the mapping between questions and models. The only modification that is needed is in the code of the report generator since the outputs differ between models and for this some interaction between the users, the modellers, and the developers is usually required.

With respect to the availability of data and the results of the model executions we take heed of the following issues:

6.1. Handling incomplete data

What if the hypermodel selected by the user cannot be applied to a given patient because important data are currently missing and cannot be found or it's too costly or time consuming to collect? Depending on the type of information needed we can address this issue as follows:

- In the case of simple scalar parameters (i.e. numbers) CRAF uses any default values assuming the model provides them. For example, the "cell-cycle duration" parameter can be annotated with a default value to be used if the user does not supply a patient-specific or other concrete value. Such handling of missing input can be extended even to non-numeric data, if some generic information can be used. For example, if we had some "virtual

patients" population we could use some of their data (e.g. generic gene expression information) to run the model. The selection of "virtual data" to be used could be more "guided" if the selection of the specific instances of the data to be used is based on the "similarity" of the real to the virtual patient based on known information (e.g. patient age and gender).

- If the missing data are absolutely vital for the hypermodel to run, then, apparently, the model cannot be used. In such a case, a simpler version of the model could be employed, i.e. a model that does not require this type of data, possibly at the cost of being less accurate. CRAF locates a (possibly) simpler model looking into the set of the models that can answer the selected question. If all of them require additional data that the user does not have (yet) then no progress is made and the user should select another patient and/or model.

6.2. Handling conflicting results

Conflicting results in the execution of different models for the same patient and the same clinical question can also appear in practice. For example, a user, for a given clinical question, runs two models for the same patient and they produce "different" answers. What can be conflicting about their answers?

- The two models could respond with totally different outputs, e.g. whether a given treatment plan is or is not beneficial for the patient
- Or their responses could differ in their *estimations*: e.g. the tumour shrinkage will be 50% or 70%

There are two cases can be handled differently. The 1st case corresponds to **qualitative answers** (yes/no answers, or selecting one of several categories) while the 2nd case can be observed in **quantitative answers**. For example, in the quantitative case we can devise ways to integrate the two answers (the two numbers or ranges of values) e.g. take their average, unless they differ so much that we are cast to the first case (for example, imagine that the first model predicts "shrinkage" of -30% while the second predicts 50%).

When the conflicting answers cannot be merged then the only thing left is to try to prioritise (rank) the answers and select the most "credible". The credibility of a model's answer can be based in the **credibility the response itself** or in the **credibility ("trustworthiness") of the model**. For example, if the response of the model is accompanied with some level of "certainty" we can choose the most plausible answer. So far, the models in CHIC do not provide such certainty information in their results. So, the other case is to rank the models and then select the answer of the highest ranked model, according to the following criteria:

- Based on the data they use to make their predictions, i.e. models that use genomic in addition to clinical information could be considered more credible compared to the ones that use only the clinical data. Another example: does the model uses default (generic) values instead of the actual data corresponding to the given patient? (see the previous paragraph about this in the case of "incomplete data")
- Based on their structure and other domain specific characteristics, e.g. if they try to model important pathways and molecular processes in cancer
- Based on their past performance, *if* CRAF has their previous predictions and the **actual** outcome
- Based on the uncertainty the predictions are accompanied with
- Based on who built them, the publications (citations of hypotheses), etc.

Appendix 1 – Abbreviations and acronyms

<i>API</i>	Application Programming Interface
<i>CDISC</i>	Clinical Data Interchange Standards Consortium
<i>CDISC-ODM</i>	Operational Data Model from the Clinical Data Interchange Standards Consortium
<i>CDP</i>	Center for Data Protection
<i>CDR</i>	Clinical Data Repository
<i>CRAF</i>	Clinical Research Application Framework
<i>DICOM</i>	Digital Imaging and Communications in Medicine
<i>EHR</i>	Electronic Health Record
<i>PACS</i>	Picture Archiving and Communication System
<i>PIMS</i>	Personal Identification Management System
<i>SOA</i>	Service Oriented Architecture
<i>STS</i>	Secure Token Service
<i>UI</i>	User Interface
<i>URI</i>	Uniform Resource Identifier
<i>UUID</i>	Universally Unique Identifier
<i>SPA</i>	Single Page Application
<i>XDAS</i>	Distributed Audit Service