Clinically Oriented Translational Cancer Multilevel Modelling

D 10.3 FINAL EXPLOITATION AND DISSEMINATION PLAN

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Executive summary:

This Final Dissemination and Exploitation Plan describes ContraCancrum's planned efforts to disseminate the projects results. An analysis of potential dissemination target groups is given as well as the planned dissemination actions by the consortium and the individual partners after the end of the project.

Deliverable D10.3 was originally designed to be submitted in the end of the project only. The consortium decided that it would be beneficial to submit preliminary versions in PM12 and PM24 in order to better design and implement the dissemination strategy throughout the course of the project. This Final Dissemination and Exploitation Plan builds upon the preliminary versions.

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1 Introduction

The ContraCancrum: Clinically Oriented Translational Cancer Multilevel Modelling project aims to develop a composite multilevel platform for simulating malignant tumour development and the tumour and normal tissue response to therapeutic modalities and treatment schedules.

The project will have an impact primarily in (a) a better understanding of the natural phenomenon of cancer at different levels of biocomplexity and most importantly (b) disease treatment optimization procedures in the patient's individualized context by simulating the response to various therapeutic regimens.

The crucial validation work will be based on comparing the multi-level therapy simulation predictions with the actual medical data (including medical images), acquired before and after therapy. ContraCancrum aims to pave the way for translating clinically validated multilevel cancer models into clinical practice.

The main final result is the integrated multiscale oncosimulator partly adapted, optimized and validated within the clinical environment. The major expected potential impact is a substantial contribution to the personalized optimization of cancer treatment strategies. Furthermore, European biomedical industry is expected to be strengthened through the development of new decision support systems. Obviously, the central socio-economic and societal impact is the alleviation of the multidimensional societal burden of the cancer disease.

From these aims, three different dissemination target groups can be deduced and these are described in detail in Section 3.

2 Purpose of this document

The purpose of this document is to give an overview over the plans for using and disseminating the knowledge in the acquired in ContraCancrum. It describes ContraCancrum's actions and plans how to:

- disseminate information about ContraCancrum, its objectives, its approaches and results
- exchange information with other initiatives and projects relevant for tumour modelling
- promote the use of tools and methods created by ContraCancrum in clinical practice
- establish communication with stakeholders, clinicians, industry, and academic groups for dissemination of ContraCancrum results.
- allow for and promote the commercialisation of ContraCancrum results.

This document includes information from the preliminary versions of the dissemination and exploitation plan, which have been created in PM 12 and PM 24. In addition, the final vision on dissemination as developed in ContraCancrum up to PM 24 is included.

This final document also includes past activities for dissemination of ContraCancrum results.

3 Dissemination target groups (adapted from D10.3-PM24)

ContraCancrum aims to develop a composite multilevel platform for cancer modelling and to perform the clinical validation of cancer models, so the scientific and clinical communities can both be considered primary target groups for dissemination actions. Further, since industrial exploitation of ContraCancrum's results is also of special interest, European industry is a third main target group.

3.1 Scientific community

As defined in the D2.1 *Requirements and specification for the ContraCancrum integrated technological platform* the relevant scientific community can be divided into three parts:

Scientific researchers, including biologists, biophysicists, biomathematicians, biostatisticians, etc., are interested in the fundamental processes that are associated with tumour development and seek to improve an understanding of these. Their main goal is to gain insight into, and an understanding of, the spatiotemporal natural phenomenon of cancer in not just a qualitative, but also a quantitative, manner. As cancer recapitulates to some extent the entire biology, knowledge of more generic biological phenomena such as cell cycling at several levels of biocomplexity may assist in-depth understanding of tumour behaviour and vice versa.

Engineers, including bioengineers, biomedical engineers, information engineers, etc., have a primary target of developing and testing integrated treatment planning systems by bringing together various simulation, image processing, visualisation and other components related to tumour growth and response to treatment.

Clinical researchers seek to improve knowledge of the effects of treatment by the retrospective evaluation of existing patients and treatments, using access to documented archives and results of parametric simulations.

The scientific community has been targeted by ContraCancrum's dissemination actions mainly by the standard methods, i.e. publications as well as contributions to workshops, conferences, and a summer school.

3.2 Clinical community

The clinical community consists of potential users for ContraCancrum's results in the form of software systems.

Clinical users are those users who will use the outcome from ContraCancrum for treating patients. It is fundamental for the dissemination of ContraCancrum's results into the clinical community and the adoption of simulation tools that the validity of the multi-level model to be integrated in ContraCancrum is shown.

Therefore, the clinical community has been targeted by ContraCancrum's dissemination actions mainly by the standard methods, i.e. publications in clinical journals and contributions to clinical conferences. At several of these occasions DoctorEye was demonstrated showing the benefit in rendering tumours and creating histograms of signal intensities. Several students are working on doctoral theses at the Medical School of the Saarland University using DoctorEye in different cancers domains.

3.3 European industry

ContraCancrum's results will be of interest to European industry for product development when ContraCancrum's approach has been embraced by a sufficiently large proportion of the progressive clinical community. Dissemination actions into the clinical community are therefore of primary importance also for dissemination into European industry.

Since ContraCancrum's results can be implemented in software especially as part of decision support systems, the medical informatics industry will be the first to be targeted.

4 Standardisation

The ContraCancrum project made use of de-facto standards, such as DICOM/PACS for the storage of imaging data, and Web Services standards to expose operations on the data warehouse to external tools such as DrEye. In addition, two tools currently contained in the VPH Toolkit promoted by the VPH-NoE have been used, namely, the Application Hosting Environment and the GSEngine.

The Application Hosting Environment (AHE), a light weight grid middleware, provides access to High Performance Computing (HPC) resources from within the ContraCancrum Web portal to run simulations and workflows in a seamless way. This tool meets the usability requirements set by the VPH Toolkit Guideline. The GSEngine is a workflow tool that provides the ability to create, manage and share workflows amongst a community of users developed in the FP6 ViroLab project and currently part of VPH-NoE Toolkit. GSEngine is interfaced through ContraCancrum Web portal to allow users to execute workflows on HPC resources, such as the ones provided by DEISA/PRACE. For example, such workflows allow users to automatically retrieve datasets from the data warehouse, upload the data to a computational resource, execute a simulation based on the data, and then download the results and store them back into the data environment. Through the use of these tools in the ContraCancrum project, we have identified new requirements that need to be met in order to have wider adoption among clinicians. These requirements are relevant to two new VPH project: P-Medicine and VPH-SHARE. As a result, new versions of the above tools are being developed to be used in the above two projects and distributed via the VPH-NoE Toolkit.

The current data warehouse developed in the ContraCancrum will be part of the VPH-NoE Toolkit because of its novelty in storing heterogeneous data (imaging, clinical, and genetic data) and its ease of use. The design of the data warehouse meets the usability and characterisation guidelines set by the VPH Toolkit for adopting new tools. Moreover, the design of the warehouse will be extended in the P-Medicine project (WP7) to accommodate various types of tumours and become more generic.

These toolkit components will be used to establish standards (usability, characterisation, ontologies), through the NoE, as VPH research develops in the future. This is essential if the VPH is to build a critical mass of tools and capabilities on which future research can be constructed.

5 Commercial exploitation

Commercial exploitation is possible on different levels. On the one hand, ContraCancrum aimed at developing a composite multilevel platform for simulating malignant tumour development and tumour and normal tissue response to therapeutic modalities and treatment schedules. This platform could be commercially exploited as a whole. On the other hand, ContraCancrum results on individual levels can commercially be exploited as well. Therefore, there exists a set of opportunities for commercialising ContraCancrum results other than the complete platform.

In the following we describe several scenarios for commercial exploitation of ContraCancrum results.

5.1 Drug binding affinity calculator

ContraCancrum's drug binding affinity calculator is one of the modules, which can be used in the drug discovery process by pharmaceutical industry. The binding affinity calculator could thus be marketed in the global *in silico* drug discovery market. It is estimated that a range between 10% to 15% of the total drug discovery costs are driven towards applications of *in silico* tools (see Frost&Sullivan: *Bioinformatics in drug discovery*, D1FC, 2010). Based on this estimation, the current market for global *in silico* drug discovery applications could be pegged at about $75 billion as of 2010, which has a potential to grow upto $140 billion by 2015 at a CAGR of 14.5%.

Our binding affinity calculator (BAC) is a decision support software to reliably predict binding affinities of compounds with their target protein, therefore identify the compounds which are most likely to bind to the protein. The calculator can perform high throughput binding affinity ranking effectively and automatically, thanks to the development of massively parallel MD codes, the speed of individual computer processors, and the advent of grid computing. This module can be commercially exploited for pharmaceutical industry to accelerate the pace in which lead compounds are identified, and modification of existing drugs predicted.

The development of a new drug is extremely time consuming and expensive. There is a very large number of chemical compounds, from which some early stage molecules are selected, followed by downstream development work. Even with the availability of state-of-the-art methods, such as High-Throughput Screening, the screened compounds are only a drop in the ocean to the chemical universe. The calculator can be used as a virtual screening tool to evaluate large number of compounds automatically, and to reduce the selected candidates to a manageable number that can be synthesized and tested.

Most drugs have unpleasant side-effect, show resistance during or after treatments, or have low efficiency. Drug-protein binding is one of the reasons for these problems. Drug may bind with off-target molecules, which changes their normal functions; target molecule may mutate so the drugs won't bind so well; or drug only has weak binding to its desired target. The calculator can be used to study differences of one drug to wide-type and mutant proteins, or original and modified drugs to same protein. Hence it can help us to understand atomistic details of drug binding strength and specificity, and to predict drug modifications to improve its efficacy.

The binding affinity calculator has potential to support clinical decisions by ranking drug candidates to a specific patient. Doctors have limited ways of matching a drug to the unique genetic profile of a given patient. A drug treatment regimen is usually prescribed using knowledge-based clinical decision support software, which attempts to determine optimal inhibitors using existing clinical records. At the molecular level, it is the drug binding affinity that determines its efficacy. Using patient-specific data, BAC can be used to rank the binding affinities, and therefore the effectiveness of various drug treatments against a patient-specific case. The application of high performance computing provides turnaround times on a clinically-relevant timescale. The binding affinity calculator hence has potential to enhance the efficacy of clinical decision support software by assessing drug efficacy and resistance at the molecular level. Although BAC has been included as an essential module of clinical decision support system for infectious diseases, extended validations are needed before the methodology can be put to widespread use.

BAC can be used by scientific researchers as a work-flow tool to perform molecular simulations on a routine basis. BAC is designed for the rapid and automated molecular simulations, distributed across multiple grid-based resources. It makes the application of molecular simulations much easier and effective by hiding the complexity of grid details from the scientific end use. It has been used recently in our laboratory to perform simulations of key molecules involved in cancer development, such as

KRAS and JAK2. The automatic tools will aid a wider research community in performing rapid constructions, simulations and post processing analyses across multiple supercomputing grid-based resources.

5.2 Workflow system infrastructure as service

Multi-scale modelling initiatives such as ContraCancrum share the need for an IT infrastructure for data collection, result distribution, and workflow management with other clinically oriented initiatives such as large scale clinical trials or other VPH projects.

At the heart of the ContraCancrum technical environment is the data warehouse, used to store a range of different types of clinical data, from images to genetic sequences in a secure yet easily accessible way. While the motivation of the ContraCancrum project is the treatment of lung cancer and gliomas, in fact this data environment is reasonably generic and could be applied in a wide range of scenarios where medical simulation is required to support the clinical decision making process. The design of the data warehouse will be extended to meet the requirements of the P-Medicine project and to become generic and not tied to a specific type of tumors. The associated workflows will be used in P-Medicine and VPH-SHARE without modification since they only rely on genetic sequences that will remain a feature of the extended data warehouse. Currently, the Binding Affinity Calculator (BAC) and Microarray Analysis workflows can be wrapped up as stand-alone service that can be integrated in any environment that supports Web Services. The overall design of the ContraCancrum IT environment uses a Service Oriented Architecture (SOA) and this means that the workflows can be ultimately be packaged as stand-alone product and hence find commercial uptake.

5.3 Biomechanics

In ContraCancrum biomechanics is part of the modelling chain, predicting the mechanical interaction of a growing or shrinking tumour with the surrounding tissue. Methods developed in ContraCancrum can be used in different scenarios ranging from surgical planning to image processing.

Including mechanical information during planning is expected to improve surgical interventions and decrease associated risks for the patients. In this context, the methods developed in ContraCancrum have an important potential to improve the treatment of osteoporotic fractures. Osteoporosis is responsible for millions of fractures annually - mostly involving vertebras, hip, and wrist – with very high associated socio-economical costs. Bone augmentation is a common treatment strategy to remove pain and prevent further collapse of the vertebra. The techniques and tools developed to model tumour growth in ContracCancrum, could provide solutions that enable surgeons to improve the planning and execution of the surgical intervention. Characterization of the cement flow through bone is crucial for the success of the augmentation process. Cement flow characteristics determine the final shape of the filling, which is important not only for the post-operative mechanical loading but also for determining the risk of intra-operative extraosseous leakage. The mechanical effect of the flow of cement in the bone has many similarities with the of tumour expansion. Therefore the numerical model developed within this project could be applied to optimize patient-specific treatments and provide the most effective strengthening of bone structures while simultaneously minimizing the potential of inducing subsequent fractures around the augmentation site and in neighbouring regions. Other applications of the biomechanical models for image-guided surgery include the prediction of craniotomy-induced brain-shift using patient-specific models of the brain or the optimization of deep brain stimulation for the treatment of Parkinson's disease. In this case, some additional adaptations would be required such as the development of a specific solver for the Maxwell's equations.

The biomechanical model developed for ContraCancrum can be used in combination with image analysis to provide physiologically driven image registration methods, motion tracking tools or for the construction of statistical shape models. Biomechanics is an attractive approach to constrain registration algorithms with realistic model describing soft tissue deformations. A possible direct outcome of the work performed in this project concerns atlas-based registration of the brain. Biomechanical models can be used to grow tumour in the brain atlas prior to the registration procedure. Similarly, biomechanical models of the lung could be used to improve breathing compensation, which is important for image reconstruction or radiotherapy treatments. Biomechanically accurate deformation of the soft tissues should significantly increase registration accuracy, which could be integrated in commercial image processing or navigation platforms.

5.4 Brain image processing

MR imaging is the key imaging method in neuro-oncology. MRI image processing methods, especially registration of image series (diagnostic, pre-op, post-op, follow-up) and automatic image segmentation can be used in a variety of products for diagnostic radiology.

Registration tools, which are easy to be handled by clinicians are a much needed tool to be integrated into the clinical workflow. Indeed, several groups evaluating different available tools have shown the necessity of improving the developed techniques to increase their robustness, accuracy and speed. Another point of importance relies on evaluation of registration techniques on patient data. The non-rigid registration techniques employed in this project feature higher speed and robustness than other well-established method. In addition, own developments have enabled cross-contrast multimodality non-rigid image registration, opening a much broader application into multimodality image fusion. These advancements have a clear potential of integration into commercial packages and thus, into clinical practice. Automatic robust and accurate registration tools are also of utmost important for longitudinal intra-patient studies, where follow-up analysis of tumor progression or regression is required.

The segmentation procedures developed within the Contracancrum project are not limited to the case of assistance for tumor-modeling. Without large modifications, similar techniques as the ones under current development, could be used for delineating structures of interest for surgical planning and visualization tasks. The method currently being developed for segmentation of healthy tissues can easily be extended to segment important functional subcortical structures in case of tissue-deforming tumors. These functional structures are of great interest for surgical planning or radiotherapy planning. A commercial product applying segmentation for one of these tasks is likely to be launched sooner than a completely integrated tumor-modeling software.

Additionally, an automatic tumor segmentation tool, estimating tumor volume and delineating different tumor sub-regions could be marketed as a software for initial analysis of tumor progression. This can support clinicians when evaluating time-series analysis of MRI images. Currently, preliminary discussions with an industrial partner are ongoing, how the segmentation algorithms developed within the ContraCancrum project can be incorporated into their commercial tumor segmentation software product.

5.5 Lung image processing

Response assessment of cancer therapy is a crucial component towards a more effective and patient individualized cancer therapy. Integrated PET/CT systems like the Philips GEMINI product line provide the opportunity to combine morphologic with functional information. Change of tumour volume on the one hand and change of maximum SUV on the other hand are important clinical parameters for response assessment. Therefore, software applications supporting the evaluation and response assessment process are valuable tools. The lung cancer specific methods developed in WP7 could be used in the Philips tumour tracking application. This application aims to provide enhanced tools to assist clinicians in diagnosis, staging, treatment planning and monitoring tumour progression or response to therapy using sequential PET or PET/CT scans. It can perform quantitative measurements to track changes in tumour volume and metabolic activity with up to six time points, helping to simplify patient data management.

The lung registration algorithms developed in WP7 could also be used in the Philips Fusion Viewer, which is a powerful yet simple image review and analysis environment for routine clinical evaluation of PET/CT examinations.

5.6 Biology-based Radiotherapy Planning

Radiotherapy (or radiation therapy) is administered to most patients with solid tumours today, often in conjunction with surgery for removing residual tumour or in conjunction with systemic chemo- or endocrine therapy for reducing the distant disease risk. It is estimated that half of all cancer patients in Europe and two thirds in the US receive radiation therapy during their initial therapy, either for salvage or palliation. A normal treatment protocol contains daily doses of radiation (5 days a week) over the course of several weeks.

The efficacy of radiotherapy depends on the delivery of sufficient dose to the tumor in order to eradicate it. Unfortunately, ionizing radiation also has an effect on the normal tissue surrounding the

tumor. Therefore the goal of research in radiation therapy is to increase the chance of tumor control while simultaneously reducing the chance of normal tissue complications. Intensity-modulated radiotherapy (IMRT) can deliver radiation to a target volume of complex shape with high accuracy and precision, minimizing collateral damage.

However, increasing the ability to accurately execute a pre-defined therapeutic plan has led (or will lead) to the situation, where no longer the therapeutic procedure itself is the precision limiting factor, but the underlying therapy plan. In this situation, the best possible definition of the clinical target volume (CTV) becomes more and more important.

Therefore, the understanding of the individual patient's tumor biology, the tumor's response to treatment, and the side-effects induced in the normal tissue is of high importance for the future increase of the therapeutic efficacy as well as for the decrease of normal tissue complications. While in oncologic surgery this is a binary decision (excise or not excise), in radiotherapy the therapeutic options are much more complex.

An approach to solve this problem is to create a radiobiological model and adapt it to an individual patient based upon the available clinical and (functional) imaging data. This model could be based upon ContraCancrum's WP4 and could be integrated into products like the Philips Pinnacle^3 radiation therapy planning system (for details see Philips Radiation Oncology Systems website).

5.7 Clinical Decision Support based upon OncoSimulator

Clinical Decision Support Systems (CDSS) are software tools that support clinicians in more informed clinical decision making by

- integrating available clinical data on an individual patient,
- connect this patient data to a clinical knowledge base,
- allow with a the help of a proper inference engine.

The output of a CDSS can vary substantially. Depending on the clinical application and the systems' maturity it can be

- diagnosis recommendations,
- treatment recommendations, or
- intelligent alerts and reminders.

In-silico models of tumour development, tumour and normal tissue response to treatment integrate the available knowledge on the patient's anatomy, physiology, and pathology. They have the potential of predicting an individual patient's response to a planned therapy. Therefore, the ultimate goal of ContraCancrum is a model-based clinical decision support system, which incorporates the OncoSimulator simulation packages, which have been developed in WP4, WP5, and WP6

The potential market for clinical decision support systems in oncology is large. According to market studies e.g. by Frost&Sullivan (see Frost&Sullivan, *Clinical Decision Support Systems Markets in North America and Europe*, M532-48, December 2009) the total CDSS market in North America and Europe was valued ag 137.7 M$ in 2009 with an expected compound annual growth rate (CAGR) of 14.9% from 2009 to 2016.

Driven by the ongoing digitalisation of hospital processes and archives, the information necessary for the OncoSimulator will be accessible in a few years also in smaller hospitals. Collaborative platforms aimed at supporting the multi-disciplinary decision process during diagnosis and therapy planning will become available commercially as well. The OncoSimulator can be a predictive module of such a system.However, until ContraCancrum results can end up in a clinical decision support system further research, validation, and integration into the clinical hospital infrastructure is necessary.

Several challenges have to be overcome (see Figure 1), before methods of *in-silico oncology* can be commercially exploited in the framework of a comprehensive cancer decision support system.

1. A clinical use of simulation based CDS systems in a foreseeable future is a necessary condition for successful commercial exploitation. However, the clinical community traditionally has a conservative approach to new methods, especially if they involve major paradigm shifts such as *in-silico* oncology. This conservatism is justified with the necessity for thorough testing of medical hypothesis in pre-clinical and clinical trials. Before a new method can be used in

clinical practice, it must be rigorously evaluated. A possibility would be to regard a developed tool like a new drug and test this tool within clinical trials in the same setting as for drugs.

2. Therefore, the biggest challenge for commercial exploitation currently is the lack of validation of tumour simulation methods. Although the interest in tumour simulation is steadily growing in the research community, the majority of simulations are still not validated on real clinical data. Further research is necessary not only in the mathematical foundations of tumour modelling, but also in the methods of validation itself. It should be considered to start using animal models for the foundations of multi-level cancer modelling, to incorporate more real patient data into the model development and validation, and finally to work towards prospective clinical trials in future, so called in silico clinical trials (see point 1).
3. Since the beginning of routine clinical use of *in-silico oncology* as a decision support tool for real clinical problems is not yet expected on a time scale relevant for European industry, a lack of investment of industrial research and development is observed. Although single-level components of the multi-level work of ContraCancrum already have a sound commercial exploitation perspective (see 5.1-5.6) this is more difficult for tumour simulation as a clinical decision support tool, which unavoidably contains all levels of complexity of tumour simulation. Therefore, it is suggested that the gap between basic research on the one hand and clinical application and commercial exploitation on the other hand is bridged by application oriented collaborative projects supporting the cooperation of academic researchers and European industry in the further development of clinically relevant knowledge in *in-silico oncology.* System biology and VPH need to join efforts in this setting. It is important to realise, that a potential lack of interest and investment of industry might not be due to a lack of trust in *in-silico oncology* methods, but in a shorter time-scale of the industrial product creation process in comparison to the time scale of basic science. Therefore, the creation of vicious circle of a lack of industry investment, in consequence a lack of public funding for *in-silico oncology*, thus a lack of clinically relevant validation, thus delayed clinical use, and thus again a lack of industry investment must be avoided. This difference in time-scales is also the reason why a reliable market analysis of clinical decision support tools based on the *in-silico oncology* methods is not possible at the moment. Without at least a first clinical use, any market analysis would only be speculation.
4. One of the most important lessons learned during ContraCancrum is that data integration is not only necessary for clinical decision making, but also for model development and even more for model validation. The ContraCancrum data integration platform (see 5.2 Workflow system infrastructure as service) is a first step towards creating the necessary infra-structure for *in-silico oncology* research. It lies at the heart of the complex interplay of data, researchers, and multi-level models, which made ContraCancrum a successful project.
5. Cancer is a complex multi-level disease. Therefore, cancer models must be multi-level as well. Modelling efforts in ContraCancrum thus reach from cancer genetics to biomechanics over several levels of complexity. Unfortunately, the complexity of cancer has a direct influence on challenges 1-4: It renders clinical validation more complex, makes clinical adoption slower, delays industry investment, and hampers data integration.
6. Last but not least, ContraCancrum has shown that the interplay of researchers from different faculties is the most important success factor. *In-silico* oncology is not only a multi-level problem, it can only be solved in a multi-disciplinary way. Without the constant interaction of clinicians, chemists, bio-physicists, computer scientists with each other. ContraCancrum would not have been successful. However, this constant interaction requires the willingness and the training to understand the heterogeneous scientific approaches and methods. Scientists skilled in this new inter-disciplinary way of working are still rare. Dedicated training programs for *in-silico oncology* do not exist yet in Europe. Therefore, it is suggested to support the education of inter-disciplinary researchers with the methods available on a European level.

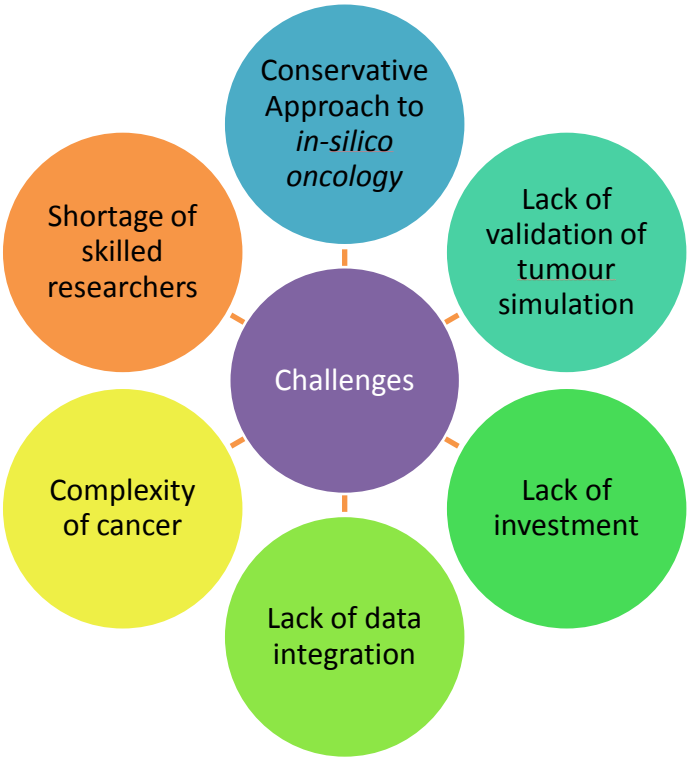


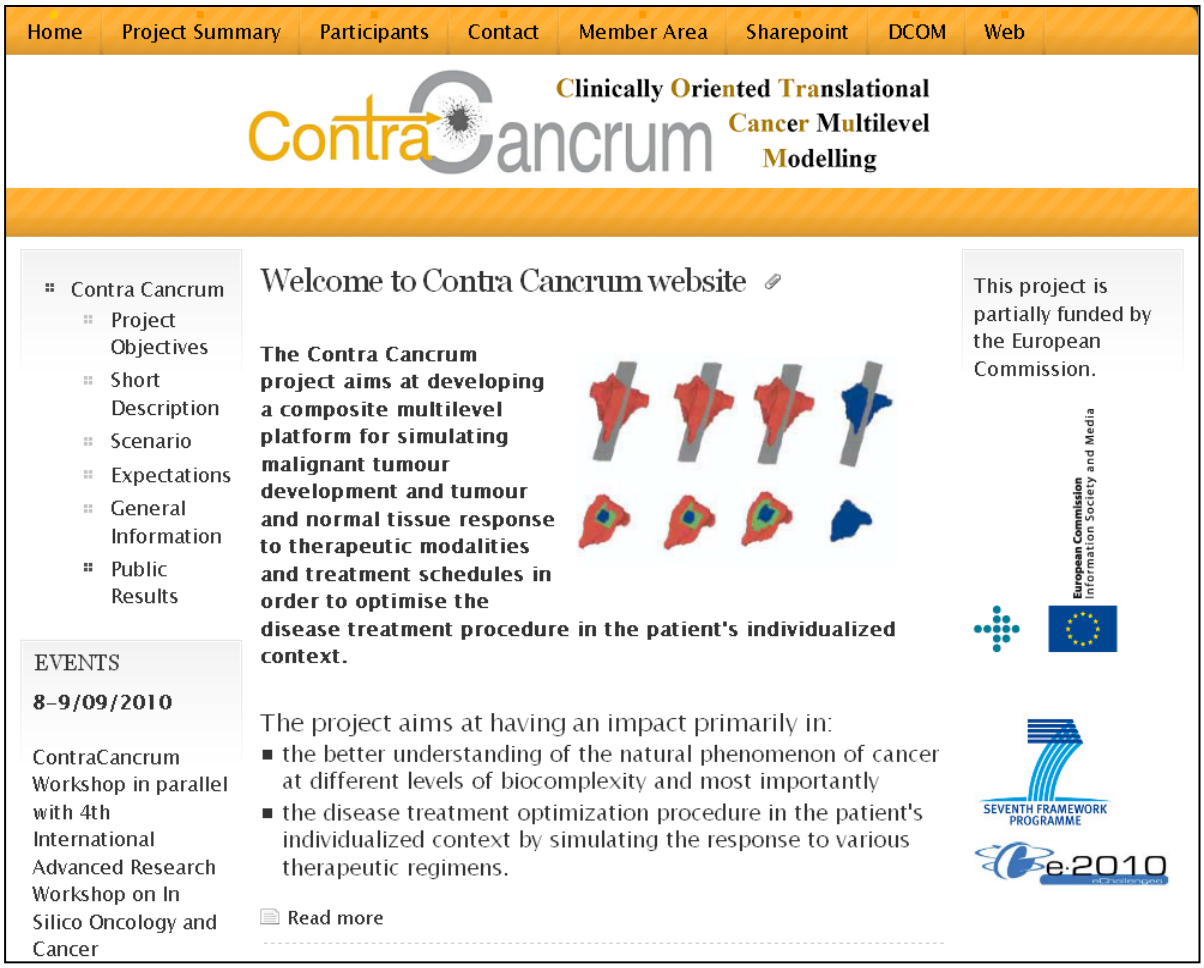
Figure 1: Challenges of Clinical Decision Support based upon OncoSimulator

6 Dissemination actions

6.1 ContraCancrum web page

A public ContraCancrum web site has already been installed at http://www.contracancrum.eu. This web site informs the scientific public about ContraCancrum's goals and achievements.

Furthermore, a ContraCancrum page has been added to the VPH-NoE website at http://www.vph-noe.eu/vph-projects/74-eu-fp7-vph-projects/48-contracancrum-strep. This page allows persons interested in VPH in general to be informed about ContraCancrum. The page is linked to the ContraCancrum web site.



Since May a ContraCancrum page has been added to the ePractice website under ehealth Cases (http://epractice.eu/en/cases/contracancrum) linked to the ContraCancrum web site.

6.2 Promotional material and presentations

Promotional material includes flyers and brochures. The goal is to make scientists, clinicians, as well as the general public, aware of the project's aims, the novelty of its techniques, the home page and the results. This material is used to describe the project's aims, its agenda, and results. Promotional material will be distributed by ContraCancrum partners and during events the project organises or takes part in.

During important conferences project ContraCancrum has shown presentations of the project and its goals.

- ContraCancrum was presented during the VPH consolidation day 2008.
- During ICT BIO 2008 ContraCancrum flyers have been distributed.

- ContraCancrum was presented during V-Tissues 2009.
- ContraCancrum was presented during WC 2009
- ContraCancrum was presented in the VPH-I meeting in Brussels
- ContraCancrum was presented in ICT 2010 in Brussels
- ContraCancrum was presented in WC 2010 Engineering in Medicine and Biology SocietyContraCancrum was presented in the UK e-science All Hands Meeting 2009, 2010, (and in 2011), VPH Symposium 2010, and the Computational Life and Medical Sciences Network (CLMS) Symposium 2011.
- ContraCancrum was presented and flyers were distributed at the 4th **International Advanced Research Workshop on *In Silico Oncology* and Cancer Investigation,** which was held in parallel with the ContraCancrum Workshop

Medical Education - AMEE

In late 2010 the VPH NoE and the Association of Medical Educators in Europe (AMEE) established a relationship to develop jointly initiatives in support of Featured medical education in the field of computational modelling. The core AMEE contributors are the Karolinska Institute, St George's University of London, the University of Heidelberg, and the Aristotle University of Thessaloniki. The goal is to develop educational content for AMEE members and VPHNoE ToolKit. The ContraCancrum project was selected as an exemplar to develop a demonstrator and educational content for AMEE members and VPH NoE ToolKit as well as to help foster integration between theoretical knowledge and practice. A prototype of this demonstrator was presented during the summer school in the talk entitled "Individualised MEdiciNe Simulation Environment (IMENSE): hosting data and providing tools for cancer research and clinical practise" which was well received by the audience who also provided feedback on improving the demo.

6.3 Workshops and tutorials

6.3.1 ContraCancrum Workshop

ContraCancrum has organized the scientific workshop of the project on topics related to ContraCancrum in 2010 (T10.2). The workshop was organised in parallel with the **International Advanced Research Workshop on *In Silico Oncology* and Cancer Investigation**. The workshop took place in Athens on September 8-9,2010 and was hosted by ICCS. Apart from the sponsoring of the European Commission Directorate-General for Information Society and Media Virtual Physiological Human initiative through the ContraCancrum project, the workshop was also endorsed by the International Federation for Medical and Biological Engineering (IFMBE) and technically co-sponsored by the Institute of Electrical and Electronics Engineers (IEEE), Engineering in Medicine and Biology Society (EMBS). For more information see http://www.4th-iarwisoci.iccs.ntua.gr/index.html

The workshop proved an excellent opportunity for researchers working in the field of in silico oncology or in the broader area of cancer research yet with an interest in mathematical and computational oncology to constructively interact, to share experiences and ideas and to contribute to the shaping and advancement of this emergent scientific, technological and medical discipline. Papers from three continents i.e. Europe, America (US) and Asia (Japan) were presented and extensively discussed, as the Workshop was attended by fourty outstanding researchers including clinicians, basic scientists and engineers.

6.3.2 ContraCancrum Summer School

After taking into consideration the 2nd Technical Review Report outcome and the proposals of the Reviewers, the consortium decided to organise a Summer School at FORTH in June 2011. The aim was to disseminate the ContraCancrum technological advances primarily to young clinicians and biomedical researchers and at the same time to provide the basic principles of computational oncology.

The First Summer School in Computational Oncology was organised at FORTH at 13-18 June by FORTH with the aim to provide basic training on the new research dimension of computational oncology based on the experience of four European collaborative projects in this direction (ACGT, ContraCancrum, TUMOR and p-medicine). To this end there was an open invitation (through announcements (like VPH NoE), postings, relevant mailing lists etc) for both clinicians/medical students and engineers/basic scientists/engineering students who wish to learn the principles of computational oncology from pioneers in the field.

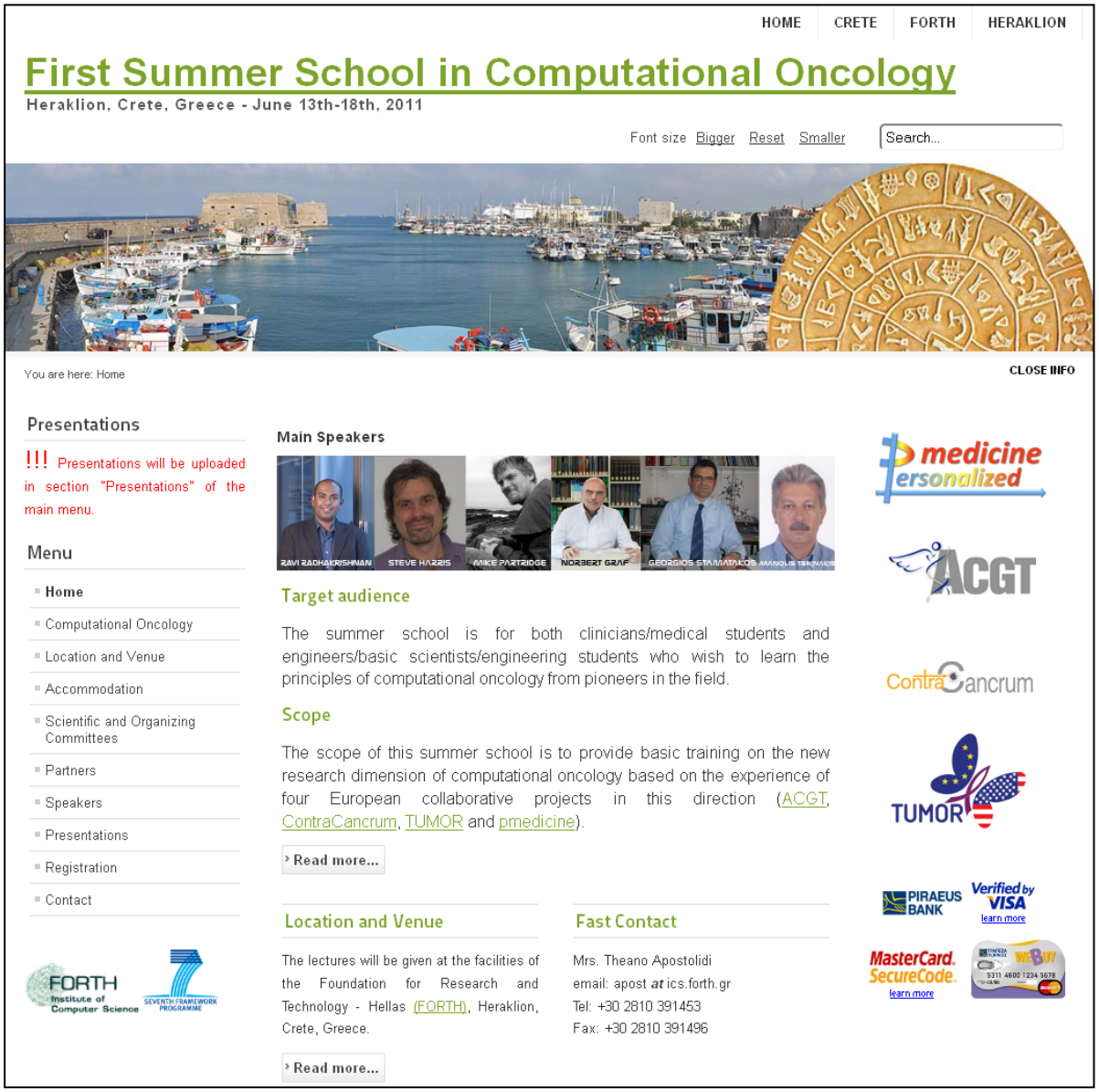
It was organised in daily sessions of specific themes so that it could be even attended for a few hours or days by interested participants. Tutors were mostly researchers that participate at the ContraCancrum project and other strongly interacting projects, like ACGT, TUMOR, and p-medicine. FORTH managed to have also 3 Invited Speakers (not relevant to the abovementioned projects) highly experienced in their domains, namely Ravi Radhakistan, Steve Harris and Mike Partridge. The whole concept of the Summer School made it attractive not only for students but also for researchers (from FORTH, Cyprus and co-tutors) from other or closely related domains who were participating actively in the Summer School even as guests. In this colladorated also the fact that in order to support the Summer School but also following the principles of economy, efficiency and effectiveness, the project meetings of three European funded projects TUMOR, ContraCancrum and p-Medicine were held at FORTH in parallel with the Summer School.

It was attended by 21 participants, mostly MSc and phD students from various disciplines and interdisciplinary courses, like medicine, Computer Science etc. The participants were from Greece, Germany and Cyprus. All participants received informational material on the Summer School and flyers on the ContraCancrum and TUMOR projects

The Summer School was very interesting not only from the scientific point of view but also from the social point of view. FORTH organised the Summer School in a way that there was a strong interaction between all participants and guests, during the Sessions but also during the afternoon Social Program

For the Summer School a special website (www.computationaloncology.com) was setup, hosted at FORTH, through which all the necessary information before and after the event could be found by all the interested parties. Most of the presentations (in Powerpoint) can be found at the site, and soon some of the videorecorded presentations, will also be uploaded. All the presentations will be freely downloadable for maximum dissemination purposes.

The organisation was held mainly by FORTH, assisted and supported by the Scientific Committee.



6.4 Scientific Conferences and Publications

ContraCancrum partners took part in international scientific conferences and presented the result of the work done in ContraCancrum. The main Conferences ContraCancrum partners took part were:

- Data Mining in Biomedicine (DMINBIO)
- Medical Image Computing and Computer Assisted Interventions (MICCAI)
- IEEE Engineering in Medicine and Biology Society, "Merging Medical Humanism and Technology"
- IEEE International Symposium on Biomedical Imaging (ISBI)
- International Advanced Research Workshop on *In Silico* Ongology and Cancer Investigation (IARWISOCI)
- 6th International Conference on Information Assurance and Security (IAS), Atlanta
- VPH Conference
- IITM conference,
- IEEE International Conference on Bioinformatics and Bioengineering (BIBE)Transatlantic Workshop on Multi-scale Cancer Modeling
- eHealth Conference
- International Conference on Biomedical Visualisation
- Computer Methods in Biomechanics and Biomechanical Engineering
- Information Technology Applications in Biomedicine (ITAB)
- International Conference on Intelligent Systems Design and Applications (ISDA)

As planned ContraCancrum partners have been publishing their scientific results in appropriate scientific journals. Some indicative publications can be found below. But, all such activities are reported in the project's periodic reports and in the Appendix at the end of the present report

1. Influence of Smoothing on Voxel-Based Mesh Accuracy in Micro-Finite Element, Journal of Biomechanics
2. Emmanouil Skounakis, Vangelis Sakkalis, Kostas Marias, Konstantinos Banitsas, Graf N: DoctorEye: A Multifunctional Open Platform for Fast Annotation and Visualization of Tumors in Medical Images. Conference: 31st Annual International IEEE EMBS Conference Schedule Code: FrDPo04.44. Conf Proc IEEE Eng Med Biol Soc. 2009;1:3759-3762

3. Georgios S Stamatakos, Eleni Ch Georgiadi, Graf N, Eleni A Kolokotroni, Dimitra D Dionysiou: Exploiting clinical trial data drastically narrows the window of possible solutions to the problem of clinical adaptation of a multiscale cancer model. PLOS one 6:e17594, 2011

4. Ludwig, Nicole ; Keller, Andreas ; Heisel, Sabrina ; Leidinger, Petra ; Klein, Veronika ; Rheinheimer, Stefanie ; Andres, Claudia ; Stephan, Bernhard ; Steudel, Wolf-Ingo ; Graf N, Burgeth, Bernhard ; Weickert, Joachim ; Lenhof, Hans-Peter ; Meese, Eckart: Novel immunogenic antigens increase classification accuracy in meningioma to 93,84 %. Int J Cancer 128:1493-1501, 2011

5. Ludwig N, Keller A, Heisel S, Leidinger P, Klein V, Rheinheimer S, Andres CU, Stephan B, Steudel WI, Graf NM, Burgeth B, Weickert J, Lenhof HP, Meese E: Improving seroreactivity based detection of glioma. Neoplasia 11:1383-1389, 2009

6. Graf N: Glioblastoma in Children with NF1: The need for basic research. Pediatr Blood Cancer 54:870-871, 2010

7. Fischer U, Leidinger P, Keller A, Folarin A, Ketter R, Graf N, Lenhof HP, Meese E. Amplicons on chromosome 12q13-21 in glioblastoma recurrences. Int J Cancer 126:2594-2602, 2010

8. Farmaki C, Marias K, Sakkalis V, Graf N: Spatially adaptive active contours: a semi-automatic tumor segmentation framework. Int J Comput Assist Radiol Surg 5:369-384, 2010

9. Graf N**:** *In silico oncology. - Part II : Clinical requirements regarding in silico oncology* In: Hrsg.: Deisboeck, Thomas S. ; Stamatakos, Georgios S.: Multiscale cancer modeling. - Boca Raton, Fla. : CRC ; London : Taylor & Francis, 2011. - (Chapman & Hall/CRC mathematical and computational biology series ; 34) , S. 437-446

10. S. J. Zasada, T. Wang, A. N. Haidar, E. Liu, N. Graf, G. Clapworthy, S. Manos, and P. V. Coveney, " IMENSE: An e-Infrastructure Environment for Patient specific Multiscale Modelling and Treatment". Journal of Computational Science, (2011), In press.

11. S. J. Zasada, A. N. Haidar, and P. V. Coveney, "On the Usability of Grid Middleware and Security Mechanisms", Accepted for publication in the UK e-Science AHM 2010 theme issue of Philosophical Transactions of the Royal Society A, (2011), 369, 3413-3428, DOI: 10.1098/rsta.2011.0131

12. Ali N. Haidar, Stefan J. Zasada, Peter V. Coveney, Ali E. Abdallah, Bruce Beckles, and Mike A. S. Jones. Audited credential delegation: a usable security solution for the virtual physiological human toolkit Interface Focus 2011 : rsfs.2010.0026v1-rsfs20100026.

13. S. Wan and P. V. Coveney, "Molecular Dynamics Simulation Reveals Structural and Thermodynamic Features of Kinase Activation by Cancer Mutations within the Epidermal Growth Factor Receptor", J. Comput. Chem., (2011), Published Online, DOI:10.1002/jcc.21866

14. K. Marias, D. Dionysiou, V. Sakkalis, N. Graf, R. M. Bohle, P. V. Coveney, S. Wan, A. Folarin, P. Büchler, M. Reyes, G. Clapworthy, E. Liu, J. Sabczynski, T. Bily, A. Roniotis, M. Tsiknakis, E. Kolokotroni, S. Giatili, C. Veith, E. Messe, H. Stenzhorn, Yoo-Jin Kim, S. Zasada, A. N. Haidar, C. May, S. Bauer, T. Wang, Y. Zhao, M. Karasek, R. Grewer, A. Franz, and G. Stamatakos Clinically driven design of multi-scale cancer models: the ContraCancrum project paradigm Interface Focus 2011 : rsfs.2010.0037v1-rsfs20100037.

15. S. Wan, P. V. Coveney, "Rapid and accurate ranking of binding affinities of epidermal growth factor receptor sequences with selected lung cancer drugs", J. R. Soc. Interface, published online Jan 12, (2011), DOI: 10.1098/rsif.2010.0609.

16. S. Bauer, C. May, D. Dionysiou, G. Stamatakos, P. Büchler, M. Reyes. Multi-Scale Modeling for Image Analysis of Brain Tumor Studies, IEEE Transactions on Biomedical Engineering (in revision)

6.5 Cooperation with other projects

ContraCancrum partners are active in other VPH related FP6 and FP7 projects. Therefore, implicit collaboration between the projects exists in a natural way by reusing results from these projects.

The most important collaboration project is ACGT *Advancing Clinico-Genomic Clinical Trials on Cancer* (Project FP6-IST-026996), in which FORTH, ICCS, USAAR, and Philips are participating.

Another collaboration project is the TUMOR project), in which FORTH, ICCS and USAAR are participating.

The TUMOR project aims at developing a European clinically oriented semantic-layered cancer digital model repository from existing EU projects that will be interoperable with the US grid enabled semantic-layered digital model repository platform at CViT.org (Center for the Development of a Virtual Tumor, Massachusetts General Hospital (MGH), Boston, USA) which is NIH/NCI-caGRID compatible.

To achieve these goals, multiscale models/tools developed and data collected within the framework of three ongoing EC funded research projects namely ACGT [Advancing Clinicogenomic Trials on Cancer], ContraCancrum [Clinically Oriented Cancer Multilevel Modeling] and the VPH NoE [Virtual

Physiological Human Network of Excellence], in conjunction with models and data from the NIH supported ICBP Program CViT.org will drive the development, optimization and validation of the integrated system.

This interoperable, CViT interfaced, environment will offer a range of services to international cancer modelers, bio-researchers and eventually clinicians aimed at supporting both basic cancer quantitative research and individualized optimization of cancer treatment. This 'Transatlantic' project will therefore be the starting point for an international validation environment which will support joint applications, verification and validation of the clinical relevance of cancer models.

Figure 1 shows the envisaged architecture of the TUMOR environment. The EU cancer model repository API is integrated with the MGH-CViT DMR API and relevant data sources for deploying specific transatlantic scenarios. VPH model markup language descriptions of employed models will guarantee interoperability. The TUMOR environment will be used to deploy a transatlantic clinical scenario(s) which will be based on combining 'top down' approaches (developed mainly by ICCS), that have been used so far to simulate tumor response to treatment, with 'bottom up' MGH approaches in CViT.

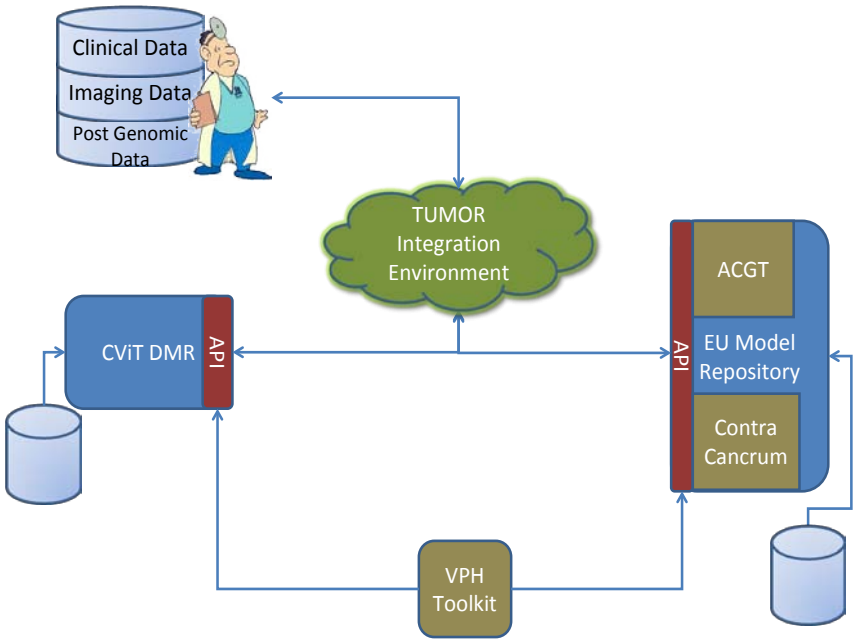


Figure 2. **High level architecture of the TUMOR environment: Multi-level cancer models/data/tools will be shared within a fully interoperable environment for specific transatlantic scenarios.**

Another collaboration project is the p-medicine project), in which FORTH, ICCS and USAAR are participating. P-medicine brings together international leaders in their fields to create an infrastructure that will facilitate the translation from current practice to personalized medicine. In achieving this objective p-medicine has formulated a coherent, integrated workplan for the design, development, integration and validation of technologically challenging areas of today.

Their emphasis is on formulating an open, modular framework of tools and services, so that p-medicine can be adopted gradually, including efficient secure sharing and handling of large personalized data sets, enabling demanding Virtual Physiological Human (VPH) multiscale simulations (in silico oncology), building standards-compliant tools and models for VPH research, drawing on the VPH Toolkit and providing tools for large-scale, privacy-preserving data and literature mining, a key component of VPH research. We will ensure that privacy, non-discrimination, and access policies are aligned to maximize protection of and benefit to patients. The p-medicine tools and technologies will be validated within the concrete setting of advanced clinical research. Pilot cancer trials have been selected based on clear research objectives, emphasising the need to integrate multilevel datasets, in the domains of Wilms tumour, breast cancer and leukaemia. To sustain a self-supporting infrastructure realistic use cases will be built that will demonstrate tangible results for clinicians.The project is clinically driven and promotes the principle of open source and open standards. Tools developed within ContraCancrum, like the data warehouse or DoctorEye will be further developed and used in p-

medicine in clinical trials with real patients data. The data warehouse will be built in a more general way for different kinds of cancers and DoctorEye will be exploited in Wilms Tumour to render tumours, calculate the tumour volume under preoperative chemotherapy and analyse signal intensities of tumours trying to get new insides in the heterogeneity of Wilms tumours (see 7.3).

7 Exploitation plans of ContraCancrum partners

7.1 Exploitation by FORTH

FORTH contributes to the economic, social and technological development of the country and is therefore interested to exploit the results of the project and disseminate VPH research culture in Greece. In this effort, FORTH-ICS has placed special emphasis on education and training related to the outcome of the project, by providing a significant number of scholarships to undergraduate and postgraduate students and by training numerous professionals in cancer modelling technologies.

Within ContraCancrum FORTH has developed a visualization, annotation, segmentation and simulation tools that have been unified in a single user-friendly application, called “DoctorEye”. The tool is freely available and is extensible by adding plug-ins from http://biomodeling.ics.forth.gr/. DrEye is a clinical user-friendly platform that allows the user a number of tasks ranging from cancer annotation to 3D visualisation and simulation of cancer growth. DrEye is a dynamic platform that is constantly being enhanced with new functionalities from CC research and always in close collaboration with the main clinical partner of the project USAAR. We therefore envision that the benefits offered by DrEye guarantee its sustainability and future enhancement and evolution beyond the end of the ContraCancrum project.

The plan for its exploitation includes the following:

- Use of DrEye by the wider VPH community as an integrated clinical collaboration research tool that offers a Powerful DICOM Viewer and Editor, is compatible with all modalities (CT, MRI, NM, US, XA, MG, CR etc.), has measurement tools (Ruler Tool) and DICOM Tags viewer, allows multiple user environment using user accounts and simultaneous editing/annotations of multiple datasets (sessions) using tabbed windows.

- In addition DrEye can be exploited as an image analysis tool for intuitive and powerful segmentation using either manual tools(Pencil, Eraser, Rectangular Marquee, Elliptical Marquee, Invert Selection), fast semi-automatic segmentation tools (Magic Wand, Selection refinement using histogram) or even intelligent semi-automatic segmentation tools based on active contour algorithms (Greedy & Snake). Additionally for the brain imaging case the tool can be used for the automatic extraction of Gray/White Matter areas.

- Another exploitation scenario for DrEye is to use it as a clinical experimentation/educational tool for visualization and evaluation tool for predictive oncology experiments. It offers traditional interpolated (smooth) zoom and advanced zoom options (Stretch Mode), image adjustments (brightness-contrast) customizable interface (support of high contrast themes provides ease of access to the visually impaired) and a number of 3D visualization modules of the dataset slices and the segmented volumes. A Simulation mechanism, based on diffusive models, allows the simulation of glioma growth in space and in time and a comparison mechanism between a couple of annotations can help the clinicians to validate the simulation results with the actual clinical outcome segmentations/annotations that were made by the clinicians.

- Future research in VPH projects exploitation. As a complex open access and fully extensible image analysis and simulation platform the ContraCancrum DrEye offers a large array of possibilities for state of the art research in practically any VPH endeavour that requires a ‘one-stop shop’ for analysing, annotating, modelling and validating of human pathophysiology based on medical data. It is important to stress that an advanced and powerful plugin mechanism based on the .NET Reflection mechanism, allows to third party developers to create and implement their algorithms to the platform. Already the use of DrEye has been

decided in the context of new European VPH projects such as the TUMOR and the p-medicine.

7.2 Exploitation by ICCS

ICCS will use ContraCancrum's intermediate and end results as a basis for further contributing to the shaping and advancement of the emerging discipline of *in silico* oncology in a coherent and systematic way. ICCS is interested in all three aspects of *in silico* oncology i.e. basic science, engineering and medicine and therefore the process of developing the ContraCancrum simulators will be an excellent opportunity for it to capitalize onto the extremely fruitful interactions among the members of the unique consortium.

7.3 Exploitation by USAAR

USAAR (University of Saarland) who is the clinical partner of the consortium is committed to the advancement of *in silico* oncology through the ab initio clinical orientation and thorough clinical validation of the simulators. Therefore, following clinical validation/optimization, it will make a multifaceted exploitation of both the ContraCancrum end results/product and the process of its implementation. Its plans are to use the ContraCancrum platform as a clinical decision support and treatment planning system, an educational tool and a research environment.

The plan for exploitation includes the following:

- With the help of DrEye segmentations of tumours are possible to do in an easy way. Together with statistical analysis of histograms of signal intensities of the tumours better descriptions of tumours can be done at diagnosis and follow-up. It is intended to use DrEye in upcoming clinical trials, like the Nephroblastoma trial to analyse these tumours in a standardised way at the reference centre for radiology of the SIOP/GPOH trial. As USAAR is heading this trial and 90% of all nephroblastomas in Germany are reviewed by the reference radiology the results will be presented at upcoming clinical workshops and conferences. It can be awaited that other hospitals and study groups will use the tool after evaluation by the Nephroblastoma Study group. For the upcoming SIOP Nephroblastoma trial DrEye will be used by reference radiologists around Europe as agreed at the Annual Consortium Meeting of the SIOP Renal Tumour Study Group (SIOP-RTSG) in Lyon on the 30th of June and 1st July 2011.
- DrEye will be used in p-medicine, a FP7 large integrated project, that started in February 2011 (Proposal: 270089). Coordinator of the project is a member of ContraCancrum (NG). This guarantees ongoing and clinically driven refinement of the tool.
- The concept of the data warehouse in ContraCancrum will be further developed in p-medicine.
- Insilico oncology simulations of glioma and lung cancer will primarily be validated with clinical data. If the prediction of the models are precise enough their exploitation in clinical trials will be promoted. At the moment two medical students are writing their doctoral thesis under the supervision of USAAR to further evaluate the analysis of signal intensity histograms in glioblastoma and in other brain cancers. Depending on the evaluation DrEye will be used in the routine diagnosis of brain tumors at the neuroradiology department of USAAR.

7.4 Exploitation by UCL

UCL, along with several other ContraCancrum partners, is involved in the recently funded P-Medicine proposal, which will use several components of the ContraCancrum data environment. Many of the tools developed may also be employed within internal UCL projects, in order to share data between clinical users. The workflows developed in this project will be contributed to the VPH NoE toolkit to act as exemplars to other toolkit users.

The binding affinity calculator (BAC) developed in WP5 uses molecular level simulation to study small molecule - protein interactions where the molecules bind non-covalently. It is used in this project to rank binding affinity of drugs to a specific cancer patient, and hence aid clinician to choose a personalized treatment. The method can be extend to more general cases, and reach the widest possible audience, especially the audiences that will use and benefit from the calculator.

The process of exploiting project outcome will be continuing development, endeavouring to utilise the calculator and incorporate it into researches and practices. The calculator could be used by scientific researchers to understand the reasons of drug efficacy/resistance, by clinicians as a decision support system to choose the best drug for a specific patient, by pharmaceutical industry to virtual screen chemical components for evaluation of potential drugs, and to predict modifications for exist drugs.

UCL is involved in the MAPPER (Multiscale APPlications on European e-InfRastructures) project, which is responding to the challenge of modelling, predicting and controlling multiscale systems which

cross scientific disciplines and where several processes acting at different scales coexist and interact. The MAPPER project will develop computational strategies, software and services for distributed multiscale simulations across disciplines, exploiting existing and evolving European e-infrastructure. Targeting a small number of application domains, two of the five being the VPH and computational biology, allows the development of the methodologies to be driven by the requirements of concrete projects, one of which will be ContraCancrum. Moreover, a major new initiative, Computational Life and Medical Sciences (CLMS), has launched at UCL, which is in part inspired by this project and VPH initiative as a whole.

UCL is involved in two recently funded EU projects: CRESTA (Collaborative Research into Exascale Systemware, Tools and Applications) and EUDAT (EUropean DATa). CRESTA brings together four of Europe's leading supercomputing centres, with one of the world's major equipment vendors, two of Europe's leading programming tools providers and six application and problem owners to explore how the exaflop challenge can be met. CRESTA focuses on the use of six applications with exascale potential and uses them as co-design vehicles to develop: the development environment, algorithms and libraries, user tools, and the underpinning and cross-cutting technologies required to support the execution of applications at the exascale. The applications represented in CRESTA have been chosen as a representative sample from across the supercomputing domain including: biomolecular systems, fusion energy, the virtual physiological human, numerical weather prediction and engineering. In the CRESTA project, we'll be involved with GROMACS developers in scaling to exascale for bio-MD applications. This capability should further enhance sampling of conformational space and convergence of thermodynamic properties. EUDAT is our proposal for the next stage in the realisation of the vision of "data as infrastructure". It will deliver a Collaborative Data Infrastructure (CDI) with the capacity and capability for meeting future researchers' needs in a sustainable way. This will become increasingly important over the next decade as we face the challenges of massive expansion in the volume of data being generated and preserved (the so-called 'data tsunami') and in the complexity of that data and the systems required to provide access to it. EUDAT provides the opportunity for data-sharing between disciplines and cross-fertilisation of ideas. UCL will bring expertise in medical and biological data storage, sharing and access in the EUDAT, and expertise in ICT environment development and biomolecular simulations in the CRESTA project.

7.5 Exploitation by UBERN

The Division of Surgical Technology at UBERN has an interest in clinical integration of Computer Assisted Surgery (CAS) techniques and therefore will exploit the results of the project in the direction of advancing surgical procedures using enabling technologies. Recently a stronger focus has been put on navigation for soft tissue interventions. Within this scope, the developed tools for segmentation and registration could be used for surgical planning and navigation in case of brain tumours.

The current plan to exploit results of the biomechanical model developed by **UBERN** during the ContraCancrum project follow four main directions, i) improve atlas-based image registration, ii) further develop brain tumor segmentation method iii) model vertebroplasty caused by osteoporosis and iiii) optimize deep brain stimulation for the treatment of Parkinson's disease.

Atlas-based segmentation of different tissue types like grey matter, white matter and cerebrospinal fluid is an established way to classify different tissues in MR images of healthy humans. The respective atlas tissue labels are propagated to the patient image through warping with a deformation field obtained by non-rigid registration techniques. However, this strategy fails in case of brain tumor images because of the missing tumour prior in the atlas. It was suggested to circumvent this problem by introducing a tumour seed into the atlas. The tumour can be grown to its approximate shape using different methods. The plan here is to compare a biomechanical approach to the approach based on Markov Random Fields developed within ContraCancrum. The objective of this work will be to determine the method with best registration accuracy, while finding solutions to limit the calculation time. In the end this line of research could lead to segmentation methods used for surgical planning or radiotherapy planning.

Brain Tumor Segmentation: During the course of the ContraCancrum project, a very promising method for segmenting brain tumors including its subregions from multimodal MR images has been developed. We plan to explore how this method can be exploited as a commercial product for technology transfer. Additionally, we would like to evaluate if a similar approach can be used for tumor segmentation in MR images of mouse brains.

Vertebroplasty is a treatment for vertebral compression fractures. This technique is used to stabilize fractured vertebra with the injection of cement in the vertebral body. Cement flow characteristics determine the final shape of the filling, which is important not only for the post-operative mechanical loading but also for determining the risk of intra-operative leakage. The mechanical effect of the flow of cement in the bone has many similarities with the of tumour expansion. Therefore the numerical model developed within this project could be applied to optimize patient-specific treatments and provide the most effective strengthening of bone structures while simultaneously minimizing the potential of inducing subsequent fractures around the augmentation site and in neighbouring regions.

Deep brain stimulation (DBS) is a surgical procedure used to treat neurological symptoms known as Parkinson's diseases at an advanced stage at which drug therapy is no longer efficient. Parkinson's disease is one of the most common neurodegenerative disorders with an estimated prevalence of 0.3% in the whole population, increasing drastically with age to 4% among the age group of over 80. Along with medication, DBS has been established as an effective treatment of Parkinson's disease in the last decades. However, important aspects of the mechanism and the underlying fundamentals of the treatment's effectiveness are still under investigation. High temporal and spatial resolution electromagnetic simulation of the effect of electrode stimulation in the brain offers the potential to improve the understanding of treatment mechanisms and can guide clinicians to adjust treatment parameters on a patient-specific basis in a way to optimize the effect in desired regions while leaving other areas unaffected.

Additionally, results and outcomes will be used in teaching. For example the Medical Image Analysis or finite element lectures are reviewed and remade every year. In order to motivate students and help them get in touch with current research, recent scientific outcomes from this project will be used in teaching. This also forms a good basis to offer thesis projects in an emerging and exciting field of research.

Exploitation by BED

Exploitation of the results by Partner **BED** will have two aspects. In academic terms, BED aims to incorporate any work into the software systems it has developed over recent years, to expand their range of application, and to publish the scientific results achieved in appropriate journals and conferences.

As well as supporting the open source Doctor Eye software developed during the project, which is specific to the area of tumour modelling, BED has been involved for many years in the development of the MAF open source software framework, which has a much broader focus and provides a general computational environment for biomedical software. The 3rd release version of MAF will appear in 2011 and it already has a significant user base. Particular techniques developed by BED within ContraCancrum and incorporated into Doctor Eye will be migrated into MAF to supplement the existing facilities, where considered appropriate.

BED has a good record of working closely with local industry, particularly small niche-market SMEs, having been awarded 8 projects for such collaboration by EPSRC, the national scientific research council, in the last 4 years.

The web services work being developed by BED should provide a basis for future application in research projects and in collaborations with local industry.

The continued development of the GPU, the ready availability of inexpensive of-the-shelf GPU clusters, and the ever-broadening gulf between the computational performance of the latest-generation GPUs and their CPU counterparts will make the uptake of GPUs increasingly attractive in the biomedical sector. Future exploitation of the GPU-based work in "mainstream" academic research projects is envisaged, and BED is active within the VPH community in trying to identify suitable application areas. There are also possibilities in specific programmes targeting SMEs, where there may be considerable commercial benefits to be gained by accelerating computation-hungry software applications or allowing the use of more accurate algorithms or higher resolution computation while maintaining interactive speeds.

7.6 Exploitation by MFF CUNI

MFF CUNI is interested to continue its current work in angiogenesis modelling and exploit the results of the project by expanding their research on all levels of cancer modelling. The project will also have a major impact on the number of students funded for PhD research on cancer modelling at Charles University.

7.7 Exploitation by PFLH

The industrial partner (**PFLH**) is conducting research on behalf of Philips Healthcare (PH), one of the three largest medical imaging systems vendors and leaders in medical workstations. The prototypical technology developed in the framework of this project can be absorbed by the development departments of PH (in the Netherlands and in the USA) and further optimized to serve as a part or a commercial product, e.g. a decision support system for oncology, a medical image analysis workstation or a radiotherapy planning workstation. Since *in silico* oncology has the potential to create a completely new market for “Modeling aided‘ therapy planning and decision support systems it is also conceivable that a therapy simulation workstation as such can be a commercial product. In detail Philips investigates the possibilities of commercialisation of several of ContraCancrum results:

- Brain image processing: The results of WP7 in this area are mainly applicable to MR images. Since Philips is among the leading MRI vendors, it is obvious that ContraCancrum results could be used in MR post processing applications.
- Lung image processing: The results of WP7 can extent Philips products in radiology and nuclear medicine, especially the fusion viewer and the tumour tracking application.
- In the long term and after a successful clinical validation, an integration of *in-silico* modelling results from WP4 into Philips radiation oncology products seems feasible.
- The integration of *in-silico* modelling into potential clinical decision support systems is also investigated.

Appendix: List of Publications

Type	Details
Journal Publication	D.D.Dionysiou, G. S.Stamatakos, D. Gintides, N. Uzunoglou, K. Kyriaki. “Critical parameters determining standard radiotherapy treatment outcome for glioblastoma multiforme: a computer simulation”, Open Biomedical Engineering 2, 43-51, 2008.
Conference Proceedings	D.D.Dionysiou, G.S.Stamatakos, T.Athanaileas, A.Menyxtas, D.Kaklamani, T.Varvarigou, N.K.Uzunoglu “In silico simulation of a clinical trial concerning tumour response to radiotherapy”, in American Institute of Physics Conference Proceedings 1060, pp.94-97, 2008
Conference paper.	K. Marias, “The role of multi-level clinically oriented modelling in cancer research”, v-Tissues 2009, April 21st-23rd in North Carolina, USA.
Conference paper.	Sakkalis, K. Marias, and G. Stamatakos “Clinical data driven in silico tumor growth and therapy modeling”, Data Mining in Biomedicine (DMINBIO ’09) workshop, Athens, 7-8 May, 2009
Conference paper.	K. Marias, “Multi-level image analysis for extracting pathophysiological parameters related to cancer modelling”, 3rd International Advanced Research Workshop on In Silico Oncology: Advances and Challenges, September 23- 24, 2008, Istanbul, Turkey
Conference paper	Georgios S. Stamatakos, "In Silico Oncology: a Paradigm for Clinically Oriented Living Matter Engineering," Proceedings of the 3rd International Advanced Research Workshop on In Silico Oncology, Istanbul, Turkey, Sept. 23-24, 2008. Edited by G. Stamatakos and D. Dionysiou, pp.7-9, 2008
Conference paper	Dimitra D. Dionysiou and Georgios S. Stamatakos, "Glioblastoma Multiforme Response to Radiotherapy: Critical Parameters and In Silico Trials," Proceedings of the 3rd International Advanced Research Workshop on In Silico Oncology, Istanbul, Turkey, Sept. 23-24, 2008.Edited by G. Stamatakos and D. Dionysiou, pp.13-16, 2008
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