Consolidated requirements (including information flows) of the *in silico* simulation models

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ABSTRACT:

The present deliverable outlines the requirements of the *in silico* oncology simulation models to be developed within the frame of workpackage WP8 of ACGT. An introduction to the notion of the "Oncosimulator" along with a number of high-level information flow diagrams and a brief description of the corresponding clinical trials constitute the core of the document.

The basic actions to be implemented are the following: **1.** Development of the "Oncosimulator". The constituent simulation models will be based on the novel, essentially "top-down" modeling approach developed by the In Silico Oncolog Group, ICCS, National Technical University of Athens. **2.** Provision of pertinent clinical data for the two cases to be addressed, namely nephroblastoma (Wilm's tumour) and breast cancer. The *in silico* oncology trial will be based on the two clinical trials (nephroblastoma SIOP 2001/GPOH and breast cancer TOP trial) following their considerable enhancement in terms of data collection. It is pointed out that the design and implementation of clinical trials in order to validate, adapt and optimize tumour behaviour models is a worldwide novelty. **3.** Technical requirements (data handling, parallelization and grid architecture usage, image processing, visualization).

Indicative references delineating the basis of the overall modeling philosophy to be adopted are also provided.

KEYWORD LIST: *in silico* oncology, Oncosimulator, cancer, treatment optimization, clinical trials, models

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Executive Summary

In Silico Oncology is a complex and multiscale combination of sciences and technologies in order to simulate malignant tumour growth and tumour and normal tissue response to therapeutic modalities at all levels of biocomplexity.

The aim is to better understand cancer and related phenomena and to optimize therapeutic interventions by performing in silico (on the computer) experiments based on the individual data (clinical, imaging, histopathologic, molecular) of the patient.

Within the framework of ACGT Workpackage 8 is entirely devoted to *in silico* oncology. The objective of this WP is to develop a technologically advanced and user friendly system able to spatiotemporally simulate *within well defined reliability limits* tumour growth and tumour and to a lesser extent normal tissue response to chemotherapy for the cases of breast cancer and nephroblastoma in the patient's individualized context. Pertinent clinical, imaging, histopathologic and molecular data in conjunction with the *ACGT* clinical trials will be exploited in order to validate the model both prospectively and retrospectively.

The present deliverable outlines the requirements of the *in silico* oncology simulation models to be developed and constitute the "Oncosimulator". The "*Oncosimulator*" will be an advanced information system able to simulate the response of tumours and affected normal tissues to therapeutic schemes based on clinical, imaging, histopathologic and molecular data of a given cancer patient. It aims at optimizing cancer treatment on a *patient-individualized* basis by performing *in silico* (on the computer) experiments of candidate therapeutic schemes.

The document provides a number of high-level information flow diagrams and a brief description of the corresponding clinical trials constitute the core of the document.

The basic actions to be implemented are the following:

1. Development of the "Oncosimulator".

   The constituent simulation models will be based on the novel, essentially "top-down" modeling approach developed by the In Silico Oncolog Group, ICCS, National Technical University of Athens.

2. Provision of pertinent clinical data for the two cases to be addressed, namely nephroblastoma (Wilm's tumour) and breast cancer.

   The *in silico* oncology trial will be based on the two clinical trials (nephroblastoma SIOP 2001/GPOH and breast cancer TOP trial) following their considerable enhancement in terms of data collection. It is pointed out that the design and implementation of clinical

trials in order to validate, adapt and optimize tumour behaviour models is a worldwide novelty.

3. Technical requirements (data handling, parallelization and grid architecture usage, image processing, visualization).

Indicative references delineating the basis of the overall modeling philosophy to be adopted are also provided.

1 Introduction

This document describes the requirements of the "Oncosimulator" to be developed within the framework of ACGT workpackage 8 (WP8) and provides simple diagrams depicting the flow of information through the various gross blocks of the system. Indicative references mainly indicating the overall modelling philosophy to be adopted have been appended at the end of the document.

It is worth noting that within the broader framework of the ACGT project the Second International Advanced Research Workshop on *In Silico* Oncology (**http://www.ics.forth.gr/bmi/2nd-iarwiso/**) was coorganized by ICCS and FORTH, two ACGT partner institutes, at Kolympari, Chania, Greece on September 25 and 26, 2006. This event proved to be a unique opportunity for the exchange of ideas and suggestions aiming at bringing computational biology and medicine closer to the clinical reality in the area of oncology. The proceedings of the workshop appearing on its website contain **9 papers** produced by ACGT partners within the framework of WP8 and reflect to some extent the work already produced by this workpackage.

2 Development of the "Oncosimulator" (ICCS)

The aim of this WP is to develop technologically advanced and user friendly computer simulation models of tumour growth and tumour and normal tissue response to therapeutic schemes based on the patient's individual imaging, histopathologic, clinical and molecular data. The composite system is to be called "Oncosimulator".

From the mathematical point of view the "Oncosimulator" will be primarily based on cellular automata, the generic Monte Carlo technique and differential equations. Although for the cases of tumour growth and response to therapeutic modalities there will be a rather detailed mathematical treatment, for the case of normal tissues only a gross adverse effect prediction-estimate will be provided due to the substantially higher complexity of normal tissue behaviour and the difficulties in side effects quantification. The constituent simulation models will be based on the novel, essentially "top-down" modeling approach developed by *the In Silico* Oncolog Group, ICCS, National Technical University of Athens [1-14].

Processed molecular data will be used in order to *perturb* the (radiobiological or) pharmacodynamic cell kill parameters about their population based mean values. A prototype system of quantizing cell clusters included within each geometrical cell of a discretizing mesh covering the anatomic area of interest lies at the heart of the proposed simulation approach. Cell cycle phase durations and imaging based metabolism distribution define i.a. the quantization equivalence classes considered. Several algorithms will be developed or adapted so as to simulate i.a. various macroscopic mechanisms such as tumour expansion/shrinkage and mechanical boundary conditions as well as the effects of particular drugs (or radiation) on the tumor under consideration.

The testing and validation of the models will be performed by applying several numerical validation techniques and using pertinent clinical, imaging, histopathologic and molecular data.

The ultimate goal is to contribute to the optimization of the therapeutic strategy through conducting *in silico* experiments on a patient-specific setting (*in silico* oncology trial). The cases of breast cancer (IJB) and nephroblastoma (Wilms' tumour) (USAAR) will be considered. To this end, the clinical, imaging and molecular data of the patient for the case of nephroblastoma and the clinical, imaging, histopathologic and molecular data of the patient for the case of breast cancer, following preprocessing, will be introduced into the "Oncosimulator" along with the description of the therapeutic scheme (temporal drug administration scheme) to be simulated. The prediction of the "Oncosimulator" regarding the tumour response as a function of time will be compared with the imaging data at various instants during and after the chemotherapeutic scheme. The outcome of the comparison will be used as an adaptation/optimization feedback for the "Oncosimulator". The reliability limitations of the predictions will be clearly defined.

In the following figure a synoptic flow diagram of the Oncosimulator is presented.

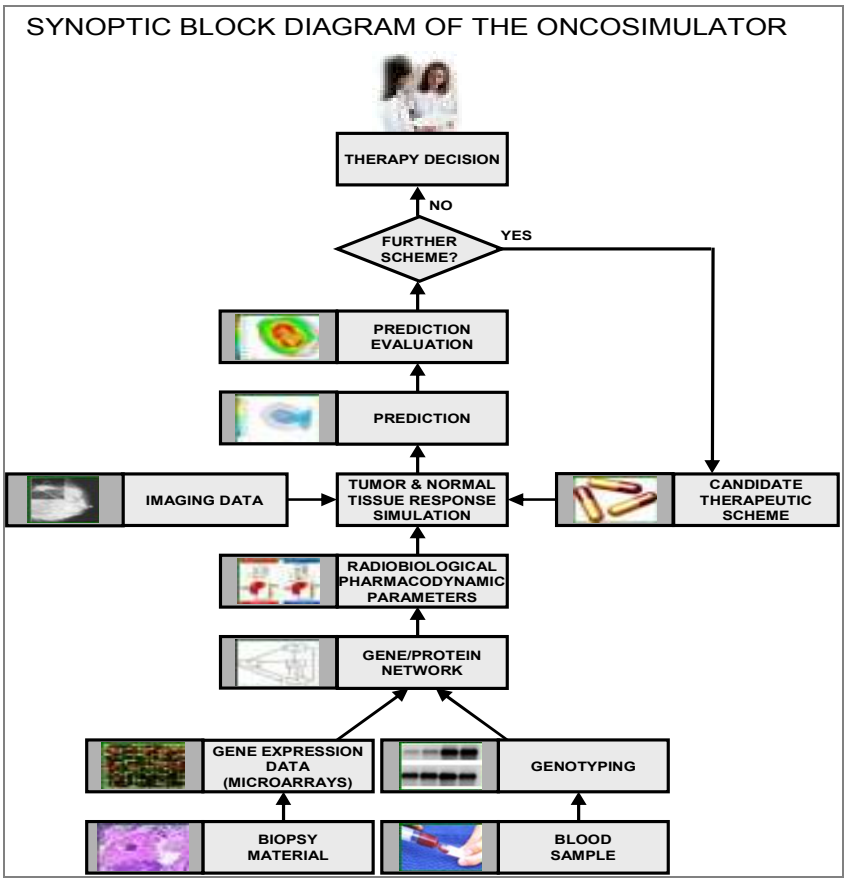


Figure 1 An oversimplified block diagram of the "Oncosimulator".

The information flow within the entire Oncosimulator is briefly described as follows (see Figure 1 from bottom to top).

I. The biopsy material and/or the blood sample is/are collected and the molecular expressions (e.g. gene expression, specific serum antibodies etc.) are obtained.

II. The molecular expressions in combination with the therapeutic agent(s) to be administered (e.g. epirubicin, vincristin etc.) are analysed through the use of gene protein networks. The output of this process is an estimate of the change of cell death probability following interaction with the drug(s).

III. This estimate will be used in order to perturb the population based mean values of tumour cell survival (e.g. pharmacodynamic parameters) for the agent(s) under consideration based on pertinent literature.

IV. The imaging data (e.g. ultrasoung, MRI etc.) before start of treatment are collected, preprocessed and introduced into the "Tumour and Normal Tissue Response Simulation" block of the "Oncosimulator"

V. A candidate treatment administration scheme is described by the clinician and introduced into the previously mentioned block.

VI. The simulation is executed

VII. The prediction of the simulation is obtained

VIII. The simulation prediction is evaluated by the clinician based on his or her logic, intuition etc.

IX. If the clinician judges that a further candidate scheme needs to be simulated then he or she formulates its description and a new simulation run takes place.

X. When the clinician feels that all the most promising schedules have been simulated he or she makes his or her final decision on the schedule to be adopted for the particular patient based on the patient's individualized computer prediction but also on the clinician's formal medical knowledge.

XI. The treatment schedule is applied on the patient. Obviously the real outcome will be registered for continuous model optimization purposes.

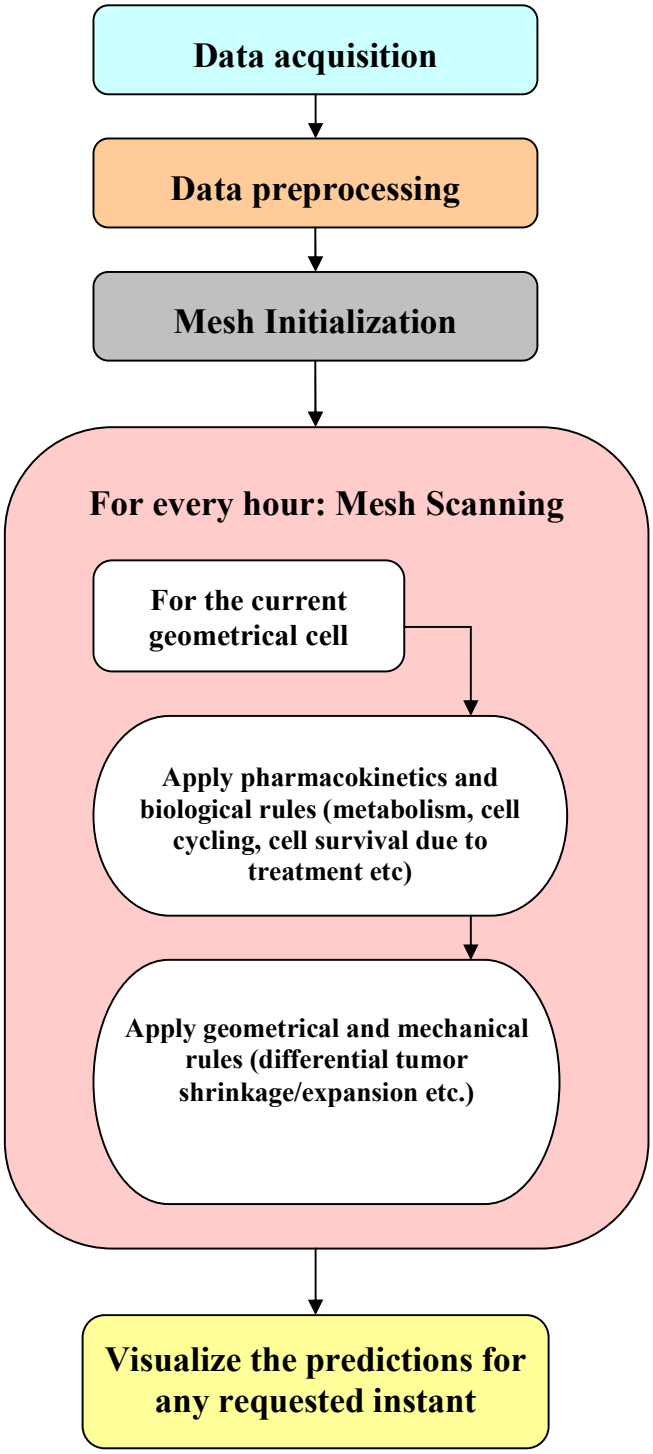


Figure 2 A high level flow diagram of the "Tumour and Normal Tissue Response Simulation" block of the "Oncosimulator"

3 Clinical data provision (USAAR, IJB)

The clinical validation of the "Oncosimulator" will be based on the two clinical trials incorporated in ACGT (nephroblastoma SIOP 2001/GPOH and breast cancer TOP trial). Below a rather *generic* description of the validation procedure is given which nevertheless is *modified* and *adapted* in the two cases to be considered. A more detailed description of the related clinical trials may be found in the ACGT deliverable D12.1. It is pointed out that the systematic prospective clinical validation of the Oncosimulator, a system of tumour response to therapy simulation models, is a worldwide novelty.

The tumour biopsy material and blood samples *when feasible* will be collected and transported to the DNA microarray facility where the gene expression will be obtained. Subsequently, a cancer- and patient specific "gene-protein network" of the tumour will be identified based on the gene expression of the particular specimen and the gene clustering, classification and gene selection for each subtype of the tumour considered. Perturbations suggested by molecular data sets are introduced and an estimation of the radiobiological (LQ α and β) and pharmacodynamic (cell survival constant for particular drugs) parameters takes place based on the identified gene-protein network.

Concerning e.g. breast cancer, the pharmacodynamic parameters are evaluated depending on the status and expression of critical genes such as topo II α, p53 etc. More generally, if a sequence of molecular events leads to e.g. apoptosis as a response to irradiation or chemotherapy, a rough semi-quantitative estimation of the radiobiological/ pharmacodynamic parameters as variations about their mean values reported in literature can be made. A more quantitative evaluation can be achieved using the patient data to be collected and applying multiple parameter adaptation methods such as genetic algorithms or neural networks.

The following paragraphs present in detail the requirements for the two cases considered.

3.1 The nephroblastoma case

A nephroblastoma (Wilm's) tumour consists generally of a mixture of the histological subtypes *blastemal*, *epithelial* and *stromal predominant* in varying proportions. The tumour responsiveness to chemotherapeutic regimens (combinations of *vincristine*, *dactinomycin* and eventually *doxorubicin*) is highly dependent on the relative contribution of each one of the subtypes and obviously on their genetic characteristics [15-45]. Furthermore *anaplasia* (which may be focal or diffuse) is another factor significant for the prediction of therapeutic outcome. The histology of nephroblastoma (Wilm's tumour) at the time of presentation is unknown, because no biopsy takes place [as is the case in the SIOP 2001/GPOH clinical trial]. An indirect way of determining would be of paramount importance in order for the clinician to judge whether or not a particular patient would benefit from chemotherapy. N.

Graf has suggested that serum antibody profiling [46] (termed "the antibody scenario") may be used as a surrogate indicator of the actual cell type composition of the tumour.

Based on the previous reasoning the following **clinical scenario** will be implemented within the frame of both ACGT workpackages WP8 and WP12. It is pointed out that for reasons of simplicity and better control only unilateral tumours without nephrogenic rests and metastasis will be considered.

After presentation of the patient to the clinical institution, collection of the following data takes place (see also the attached SIOP 2001/GPOH case report form). These data will be used by the oncosimulator. The most important prediction of the oncosimulator for the clinician will be the amount of shrinkage of the given tumour in % of the initial volume.

3.1.1 Clinical Data

- Age
- Sex
- Weight
- Height
- Syndromes (WAGR, Denys-Drash, Beckwith-Wiedermann, and others)
- Family history

3.1.2 Imaging Data

(baseline: just before chemotherapy start)

- CT (DICOM) and/or MRI (DICOM) and/or ultrasound (DICOM)]
- Three ellipsoidal axes of the tumour.
- Delineation of the necrotic, cystic, hemorrhagic and solid tumour regions on the tomograhic slices.

3.1.3 Molecular Data

- Profiling of antibodies to tumour antigens (antigen scenario)

↓

- Estimated cell type composition of the tumour

↓

- Estimated tumour cell responsiveness to the drugs under consideration

3.1.4 Recommended Treatment Scheme(s) Data

- Description of the recommended scheduling of drugs dose administration

Based on the "Oncosimulator" prediction (mainly the expected tumour shrinkage in percentage of the initial volume), the following two situations arise:

1. Prediction of a reduction of the tumour volume of more than 10 %

   In this situation the clinician would judge that preoperative chemotherapy is beneficial for the patient.

2. Prediction of less than 10 % or no reduction of the tumour or even increase in tumour volume.

   In this situation the clinician would judge that preoperative chemotherapy is not beneficial for the patient.

Independent of this judgement the patient will always receive preoperative chemotherapy.

The actual chemotherapy administration schedule is registered.

The following examinations are carried out during and after treatment:

3.1.5 Actual CT Outcome and Histology Recording

3.1.5.1 During chemotherapy

- Ultrasound imaging every week (if possible)
- Recording of the 3 tumour ellipsoidal axes

3.1.5.2 After completion of chemotherapy

- Profiling of serum antibodies against tumour antigens
- CT (DICOM) and/or MRI (DICOM) and/or ultrasound (DICOM)
- Three ellipsoidal axes of the tumour.

- Delineation of the necrotic, cystic, hemorrhagic and solid tumour regions on the tomograhic slices.
- Serious Adverse Effects (SAE) concerning hematologic reactions

3.1.5.3 After surgery

- Histology (types)

3.1.6 The Oncosimulator as a learning system

A "perfect correlation" between the oncosimulator and the in vivo situation for the nephroblastoma case is defined by getting the same result of more or less than 10 % tumour volume reduction by both methods in all patients and by predicting the correct histological subtype. Tumour volume response and histological outcome have to be evaluated independendly. For the clinical situation the prediction of the correct tumour volume reduction before starting treatment is most important. This will help to choose the best treatment for an individual patient upfront. The correct prediction of the histological subtype will add only little by choosing starting with preoperative chemotherapy or primary surgery. For surgical complications will be less in a shrunken tumour, the stage distribution better and postoperative treatment minimized.

Table 1. Correlation of the tumour volume reduction between the in vivo situation and the oncosimulator

		In vivo	
		< 10 %	**> 10 %**
Oncosimulator	**< 10 %**	**good correlation** *no preoperative chemotherapy is indicated*	**bad correlation** *Oncosimulator has to be improved*
	> 10 %	**bad correlation** *Oncosimulator has to be improved*	**good correlation** *preoperative chemotherapy is indicated*

During the evaluation of the oncosimulator the number of patients (A, B, C, D) are to be used for statistical analysis (table 2).

In order to estimate the *statistical significance* of the in silico model predictions and therefore the model's reliability the following correlation and best fitting approach [47,48] will be implemented.

If on a two dimensional Cartesian system one axis (e.g. the abcissa) represents the real treatment outcome (e.g. imageable tumour volume) and the other axis (ordinate) represents the corresponding simulation prediction, then the points determined by the pairs: (real treatment outcome, corresponding simulation prediction) would *ideally* lie on a straight line with slope 1 (non dimensional slope) or at an angle of 45 deg with the horizontal axis, passing through the point (0,0) and being exactly the bisector of the first Cartesian quadrant. Therefore, the only reasonable form of the curve to fit the previously mentioned points (pairs) would be a straight line passing through the origin of the Cartesian axes with slope=1.

Concerning the necessary number of sets of data (number of time points for which complete series of imaging data are available for a given patient as well as number of patients whose data are available) to obtain statistically significant validation results, it would be unrealistic to give a fairly accurate estimate at this stage. Obviously the more data sets are available for each patient and the more patients are available, the higher the significance of the validation process would be. Nevertheless, as the tables of the critical values for the Pearson correlation [47, p.A-33] have 3 as the minimum number of points (or n-2=1), at least 3 complete sets of data are needed for each patient [for the statistical approach under consideration]. Furthermore, apart from treating each patient separately and trying to fit a straight line into his/her data, data sets (e.g. tumour volumes) from different patients can also be mixed together in random combinations. The rationale behind this is that we know a priori all the properties of the ideal fitting line (a straight line passing through (0,0) with slope 1) which should hold true for *all* patients. This remark is expected to enhance the exploitation degree of the data to be collected and lead to statistically significant validation results with even a rather moderate number of patients. Obviously in the latter way the histological and molecular specificity of the model could not be evaluated in a very refined way.

Nevertheless, as even the acquisition of 3 datapoints per patient might still not be practically feasible for all patients, careful use of two data points (before initiation of chemotherapy and before surgery) per patient will also be exploited. In that case the data will be viewed primarily as categorical ones [perfect or non perfect matching] rather than as continuous data.

Therefore, for each patient at least 2 or better *many more* follow up imaging data sets will be used. It is noted that the clinical, histological and molecular data of each patient will be provided generally once. As many patients as possible will be recruited. It is also pointed out that a number of patients will be assigned to the optimization procedure of the model whereas another number will be assigned to the pure validation procedure.

Table 2. Numbers (A, B, C, D) of patients in the different categories during the trial period.

		In vivo	
		< 10 %	**> 10 %**
Oncosimulator	**< 10 %**	***A***	***B***
	> 10 %	***C***	***D***

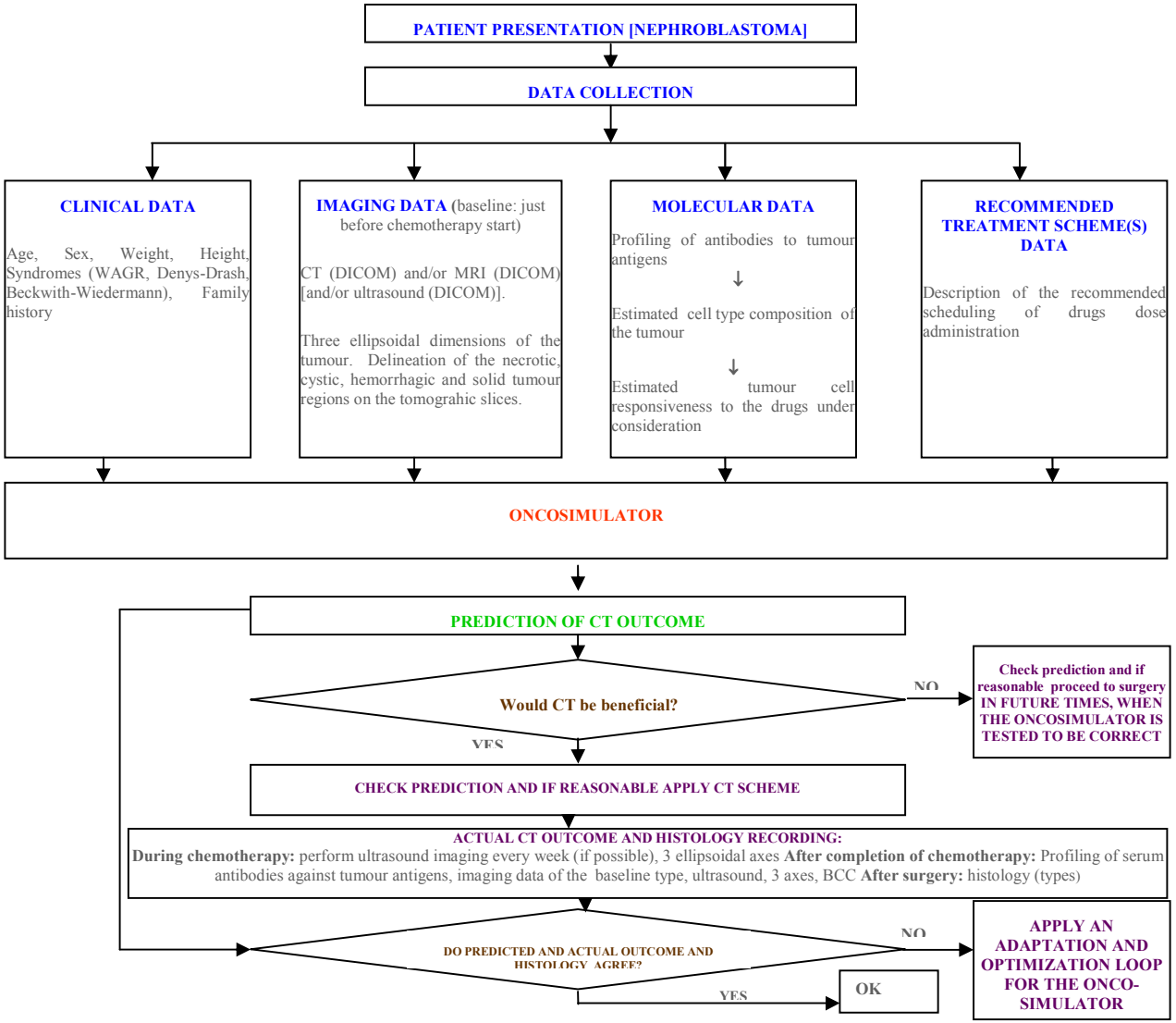
To accept the oncosimulator as a tool in the real clinical setting, numbers B and C have to be zero. The predicted and the actual tumour volume are compared in every patient. In case of a discrepancy an optimization and adaptation loop for the "Oncosimulator" is carried out, otherwise the current checking of the "Oncosimulator" is judged as favourable.

The same process of optimization of the oncosimulator will be done for histology.

If there is a perfect correlation between the prediction of tumor response regarding tumour volume by the oncosimulator and the clinical response to preoperative chemotherapy, in future trials the result of the oncosimulator may be used for stratification of treatment. Meaning that in a patient, where the expected outcome is not judged as beneficial, the patient may proceed directly to surgery without receiving preoperative chemotherapy. Otherwise, the chemotherapeutic scheme is applied on the real patient. In a second step the kind of preoperative chemotherapy can be evaluated in those patients showing no response to the current chemotherapeutic regimen. For these patients the oncosimulator may be used to find an optimal combination of cytostatic drugs.

Figure 3 presents a flow diagram of the nephroblastoma scenario.

Figure 3 (next page). Flow diagram of the nephroblastoma branch of the *in silico* oncology trial


PATIENT PRESENTATION [NEPHROBLASTOMA]
DATA COLLECTION
CLINICAL DATA
Age, Sex, Weight, Height, Syndromes (WAGR, Denys-Drash, Beckwith-Wiedermann), Family history
IMAGING DATA (baseline: just before chemotherapy start)
CT (DICOM) and/or MRI (DICOM) [and/or ultrasound (DICOM)].
Three ellipsoidal dimensions of the tumour. Delineation of the necrotic, cystic, hemorrhagic and solid tumour regions on the tomograhic slices.
MOLECULAR DATA
Profiling of antibodies to tumour antigens
↓
Estimated cell type composition of the tumour
↓
Estimated tumour cell responsiveness to the drugs under consideration
RECOMMENDED TREATMENT SCHEME(S) DATA
Description of the recommended scheduling of drugs dose administration
ONCOSIMULATOR
PREDICTION OF CT OUTCOME
Would CT be beneficial?
NO
Check prediction and if reasonable proceed to surgery IN FUTURE TIMES, WHEN THE ONCOSIMULATOR IS TESTED TO BE CORRECT
YES
CHECK PREDICTION AND IF REASONABLE APPLY CT SCHEME
ACTUAL CT OUTCOME AND HISTOLOGY RECORDING:
During chemotherapy: perform ultrasound imaging every week (if possible), 3 ellipsoidal axes After completion of chemotherapy: Profiling of serum antibodies against tumour antigens, imaging data of the baseline type, ultrasound, 3 axes, BCC After surgery: histology (types)
DO PREDICTED AND ACTUAL OUTCOME AND HISTOLOGY AGREE?
NO
APPLY AN ADAPTATION AND OPTIMIZATION LOOP FOR THE ONCO-SIMULATOR
YES
OK

3.2 The breast cancer case (IJB)

The number of effective treatments for breast cancer is on the rise; however, the benefit from specific treatments to individual patients and the adverse events they experience vary considerably [49-50]. Concerning the enhanced TOP trial which will be used for the optimization and validation of the "Oncosimulator", the following data collection procedure will take place. After presentation of the patient to the clinical institution collection of the following data takes place:

3.2.1 Clinical Data

- Age
- Sex
- Weight
- Height
- Blood cell counts (BCC) or eventual or no haematological side effects as reported in CRFs {to monitor adverse effects on normal tissues}

ACCESS TO ***THE NECESSARY*** DATA RECORDED IN THE TOP TRIAL DATA BASES DURING THE PATIENT'S TREATMENT (IJB data)

3.2.2 Imaging Data

(baseline: just before chemotherapy start)

- Ultrasound (DICOM)
- Prospectively Somo-vu 3D US images
- Digital mammography (DICOM) for some cases
- PET and CT or MRI for certain cases (DICOM)
- **Three ellipsoidal axes of the tumour** i.e. length, breadth and depth (obligatory).
- Delineation of the necrotic, cystic, hemorrhagic and solid tumour regions on the tomograhic slices.

3.2.3 Histopathological And Molecular Data

- Histopathological profile (tumour cell types etc.) if the patient is not metastatic
- Photographs of HE histopathology slides (MIRAX scan system)
- Topo IIα (gene and protein), HER-2 (gene and protein), p53 (protein)
- ***DNA array*** based gene expression profiling of the bioptic material

↓

- Estimated tumour cell responsiveness to the drugs under consideration

3.2.4 Recommended Treatment Scheme(S) Data

- Description of the recommended scheduling of drug dose administration. The agent *epirubicin* will be considered.

Based on the oncosimulator prediction (mainly the expected tumour shrinkage), the clinician judges whether or not the chemotherapy outcome would be beneficial to the patient under consideration by also taking into account his or her logic, expertise and even intuition.

ONLY AFTER THE ONCOSIMULATOR HAS BEEN CHECKED: In case that the expected outcome is not judged as beneficial, the patient may undergo other therapeutic interventions.

ONLY AFTER THE ONCOSIMULATOR HAS BEEN CHECKED: Otherwise, the chemotherapeutic scheme is applied to the real patient.

The actual chemotherapy administration schedule is registered.

The following examinations are carried out during and after treatment:

3.2.4.1 During chemotherapy (prospectively)

- Ultrasound imaging *after every other CT cycle (and preferably on the 1st day of the week corresponding to every other chemotherapeutic cycle).* More frequent ultrasound examinations will also be exploitable.
- Recording of the tumour 3 ellipsoidal axes

3.2.4.2 After completion of chemotherapy

- Ultrasound (DICOM)
- Prospectively Somo-vu 3D US images
- Digital mammography (DICOM) for some cases
- PET and CT or MRI for certain cases (DICOM)
- **Three ellipsoidal axes of the tumour** (obligatory).
- Delineation of the necrotic, cystic, hemorrhagic and solid tumour regions on the tomograhic slices.
- Blood Cell Counts (BCC) or eventual or no haematological side effects as reported in CRFs {to monitor adverse effects on normal tissues}

The predicted and the actual **outcome** are compared and if they are in significant contradiction an optimization and adaptation loop for the “Oncosimulator” is carried out, otherwise the current checking of the “Oncosimulator” is judged as favourable.

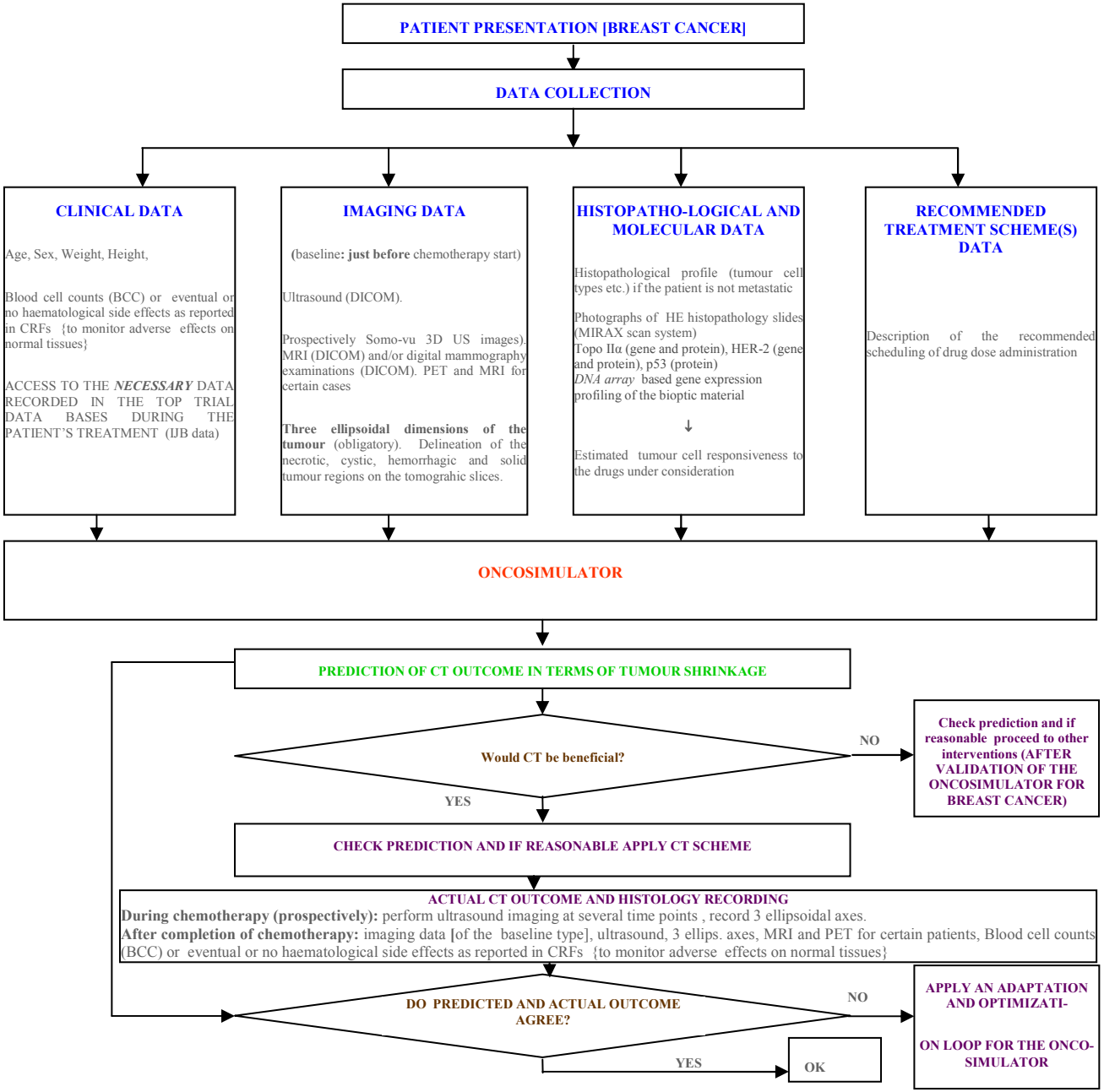
Figure 4 presents a flow diagram of the breast cancer scenario.

3.2.5 The Oncosimulator as a learning system

A “perfect correlation” between the oncosimulator and the in vivo situation for the breast cancer case is defined by getting the same result of more or less than 10 % tumour volume reduction by both methods in all patients.

In order to optimize and statistically validate the oncosimulator for the breast cancer case a process similar to the one developed for nephroblastoma will be followed.

Figure 4 (next page) Flow diagram of the breast cancer branch of the *in silico* oncology trial


PATIENT PRESENTATION [BREAST CANCER]
DATA COLLECTION
CLINICAL DATA
Age, Sex, Weight, Height,
Blood cell counts (BCC) or eventual or no haematological side effects as reported in CRFs {to monitor adverse effects on normal tissues}
ACCESS TO THE NECESSARY DATA RECORDED IN THE TOP TRIAL DATA BASES DURING THE PATIENT'S TREATMENT (IJB data)
IMAGING DATA
(baseline: just before chemotherapy start)
Ultrasound (DICOM).
Prospectively Somo-vu 3D US images). MRI (DICOM) and/or digital mammography examinations (DICOM). PET and MRI for certain cases
Three ellipsoidal dimensions of the tumour (obligatory). Delineation of the necrotic, cystic, hemorrhagic and solid tumour regions on the tomograhic slices.
HISTOPATHO-LOGICAL AND MOLECULAR DATA
Histopathological profile (tumour cell types etc.) if the patient is not metastatic
Photographs of HE histopathology slides (MIRAX scan system)
Topo IIα (gene and protein), HER-2 (gene and protein), p53 (protein)
DNA array based gene expression profiling of the bioptic material
↓
Estimated tumour cell responsiveness to the drugs under consideration
RECOMMENDED TREATMENT SCHEME(S) DATA
Description of the recommended scheduling of drug dose administration
ONCOSIMULATOR
PREDICTION OF CT OUTCOME IN TERMS OF TUMOUR SHRINKAGE
Would CT be beneficial?
NO
Check prediction and if reasonable proceed to other interventions (AFTER VALIDATION OF THE ONCOSIMULATOR FOR BREAST CANCER)
YES
CHECK PREDICTION AND IF REASONABLE APPLY CT SCHEME
ACTUAL CT OUTCOME AND HISTOLOGY RECORDING
During chemotherapy (prospectively): perform ultrasound imaging at several time points , record 3 ellipsoidal axes.
After completion of chemotherapy: imaging data [of the baseline type], ultrasound, 3 ellips. axes, MRI and PET for certain patients, Blood cell counts (BCC) or eventual or no haematological side effects as reported in CRFs {to monitor adverse effects on normal tissues}
DO PREDICTED AND ACTUAL OUTCOME AGREE?
NO
APPLY AN ADAPTATION AND OPTIMIZATI-
ON LOOP FOR THE ONCO-SIMULATOR
YES
OK

4 Technical requirements (FHG, FORTH, ICCS, IJB, USAAR)

4.1 Data handling (FHG etc)

Information flows have the following characteristics:

I. Multimodal, multilevel and heterogeneous data are used

II. Access to many data sources is needed

III. A variety of tools must be orchestrated into complex workflows

IV. There is need for intermediate data storage and reuse

As far as *primarily* imaging data storage and handling is concerned the following depositories will exist:

a. Main repository (*only for the initial "Oncosimulator" development period*) : FHG

b. Technical local repositories: FORTH, ICCS.

c. Clinical source repositories: IJB, USAAR.

Especially the FHG depository will consist of a highly inhomogeneous database on which pseudonymized clinical, imaging, histopathological and molecular data will be stored will be accessible when needed to run the simulation.

4.2 Parallelization and grid architecture usage (INRIA/IRISA)

The computational needs of the simulation models are expected to dramatically increase as the discretizing mesh density and therefore the simulation resolution increase. Furthermore, the need for in parallel simulation of several candidate therapeutic schemes dictates parallel code execution. In order to cope with these demands both INRIA-IRISA and the overall ACGT grid infrastructures have been planned to be used. In fact the "Oncosimulator" running will make use of most of the technological infrastructure to be developed within ACGT (including the solution of legal issues, use of the ontologies infrastructure etc.).

Concerning the use of already available infrastructure of the IRISA the following resources will be used:

- Grid 5000
- A 32-node bi-processor cluster
- Reconfigurable platform (ReMIX)

4.3 Image processing (FORTH)

The image processing component of WP8 aims to utilise (or develop tools) for the optimal information extraction concerning the geometry as well as the properties of cancerous tissue from medical images. It is important to stress that there are inherent limitations due to either the image acquisition process (e.g. resolution, artefacts) or the clinical protocols (e.g. due to the large radiation dose CT isn't routinely used in children although it can provide detailed information). However, the work in this WP is mostly an optimisation process for the Oncosimulator since it aims only to improve the accuracy of the temporal data (geometry and composition of a tumour before and after therapy) and thus improve the results. To this end, and based on the extensive experience of the consortium ([54-62]) the aim is to work on the following image analysis scenarios. It is noted that the exact solutions to them that will finally be adopted for the needs of the *in silico* oncology trial will have been provided by Month 12. References [51-62] will serve as a basis for their formulation.

Scenario 1: Geometrical normalisation.

This scenario is concerned with establishing correspondences in temporal imaging data in order to better assess changes (this is potentially a crucial point in validating the oncosimulator). Geometrical changes occur in soft tissue imaging (e.g. in the case of breast imaging owing to the differences in breast shape/compression) but also in newer applications such as molecular imaging and microarray imaging. Non-rigid alignment or registration is required to compensate for such differences. This problem does not only pertain to the multi-modal scenaria, as a temporal acquisition of the same modality will still likely involve registration in order to facilitate comparison. Figure 5 isllustrates the changes in geometry in the case of pre and post therapy imaging (a nephroblastoma is present).

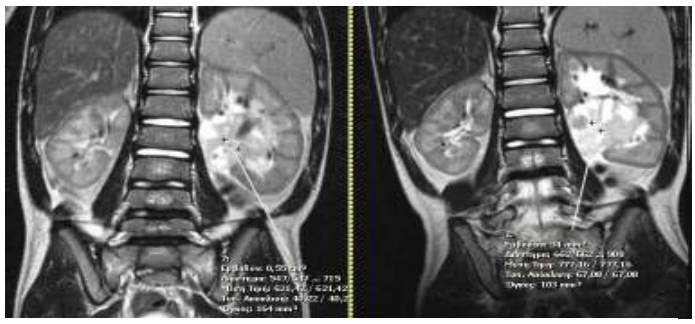


Figure 5. Conventional T2 weighted images acquired prior (A) and post (B) tumor treatment. The tumour is shown with an arrow.

To solve this problem we will consider the various registration algorithms which can be classified as being either frame based, point landmark based, surface based, or voxel based. Stereotactic frame-based registration is very accurate, but inconvenient, and cannot be applied retrospectively, as with any external point landmark-based method, while anatomical point landmark-based methods are usually very intensive and their accuracy depends on the accurate indication of corresponding landmarks in all modalities. Surface-based registration requires delineation of corresponding surfaces in each of the images separately. Voxel similarity based (VSB) registration methods optimise a functional measuring the similarity of all geometrically corresponding voxel pairs for some feature. The main advantage of VSB methods is that feature calculation is straightforward or even absent when only grey-values

are used, such that the accuracy of these methods is not limited by segmentation errors as in surface based methods. Based on prior experience of the consortium the consortium will investigate the possible use of such methods for alighning the data. However, this isn't a crucial step for the Oncosimulator to work, since the most important aspect is the assessment of global changes (i.e. if and how much a tumour will shrink under a therapeutical regime) and not on a local basis (e.g. how much the tumour shrank at a specific coordinate (x,y)). Most likely, image matching will be used as a tool for finding the best match in slices of different acquisitions. This would be helpful for both the clinician and the modeller in order to 'confront' the actual temporal data with the predictions of the simulator and more importantly, to measure the change in volume after therapy.

Scenario 2: Extraction of relevant information.

This is in fact the most crucial step for WP8 from the image analysis perspective. Essentially, it implies the use of some kind of process (e.g. segmentation) to identify important structures and features in the images (e.g. tumours can be segmented using a pharmacokinetic model of gadolinium uptake with contrast-enhanced MRI). In order to produce a 4D prediction of tumour responmse to therapy it is essential to identify the region of interest (i.e. segment the tumour from the background tissue) and if possible, estimate different prorerties or tissue sub-categories within the tumour (e.g. differentiate necrotic from proliferating tissue, dense/highly vascularised tissue from fat, etc.). For conventional imaging studies, we will use existing algorithms for differentiating the tumour on the basis of image contrast. Such tools are well known and therefore there is no necessity to describe them herein.

For contrast enhanced data (e.g. CE MRI), we will expoit the fact that malignant tumours exhibit an increased vascularity, since they begin to grow their own blood supply network. For this reason when the contrast agent is distributed, malignant masses enhance faster. This has led to the development of models of contrast uptake as is illustrated in Figure 6, based on which we can extract the region of the cancer.

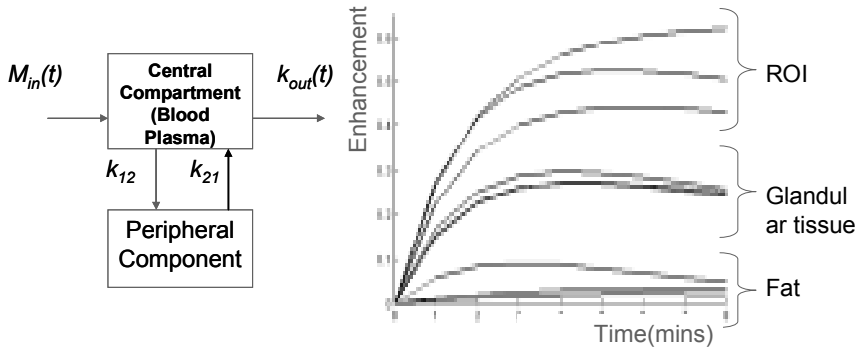


Figure 6: A two-compartment pharmacokinetic model with typical contrast curves for fat, parenchymal (glandular) tissue and enhancing regions of interest. Min is the mass of contrast injected into the blood stream with respect to time. k12 and k21 are inter-compartment exchange rates and kout is the leaving contrast rate.

Scenario 3: Quantification.

This scenario will provide the tools to estimate the actual change in tumour volume after a specific therapy regime. This in turn, will be compared with the simulation results. A basic problem in quantification is that in each imaging modality the representation has different parametric properties. For example, the active volume of a tumour detected with X-ray mammography is less accurate than that using with MRI. However, both the simulation and the ground truth will be based on data of the same modality and for this reason the effect of the abovementioned problem will be minimised. Nevertheless, the consortium will provide a short account with all the issues related to volume quantification from the imaging data.

Scenario 4: Visualisation.

This is a fundamental aspect of biomedical data information fusion that is typically less well addressed in the literature, but which can dramatically increase the clinical utility of a solution if implemented intelligently. The effectiveness of visualisation depends very strongly on how clearly different indicators can be extracted from data and therefore segmentation is of utmost importance. For the specific application (In Silico Oncology) the visualisation requirements are discussed in the next session.

4.4 Visualization of the "Oncosimulator" predictions (UvA)

Dedicated 2D, 3D and 4D visualization techniques will permit detailed and intuitive representations of the tumours under study. The visualization of the region of interest can provide the clinician, the researcher and even the interested patient with an enhanced 3D/4D picture of the biological problem. Virtual cuts of the tumour and the adjacent anatomic area can reveal the inner structure of the tumour and normal tissue under consideration as well as their cytokinetic activity distribution. To this end various interactive visualization tools will be developed and adapted to the input / output of the simulation software. The visualization tools will use virtual reality technology (including technology used in CAVE ®) for stereoscopic rendering and intuitive interaction. In order to be intuitive, the models have to be displayed together with the actual imaging data of the patient, thus creating a visualization environment where both the imaging data of the patient and the in silico simulation results of cancer response are displayed. This will allow the clinician to interact with the data and have a patient-specific view of the in silico models.

The simultaneous visualization of imaging data and *in silico* simulation results requires a high-performance computing architecture. For this, and to ensure responsive interaction on a wide range of graphical devices, a distributed infrastructure will be developed that will be able to match the capabilities of graphics devices with computational devices available on the grid. In addition, facilities will be provided to support collaborative visualization on geographically distributed locations.

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6 APPENDIX (GLOSSARY)

ACGT: Advancing ClinicoGenomic Trials on Cancer

CAVE: a recursive acronym that stands for CAVE Automatic Virtual Environment

CE: Contrast Enhanced

CT: Computed Tomography

DICOM: Digital Imaging and Communications in Medicine. A standard developed by the American College of Radiology Manufacturers Association to define the connectivity and communication protocols of medical imaging devices.

GPOH: German Society for Paediatric Oncology and Haematology

HE: Haematoxylin and Eosin

HER: Human Estrogen Receptor

IARWISO: International Advanced Research Workshop on In Silico Oncology

MRI: Magnetic Reasonance Imaging

PET: Positron Emission Tomography

SAE: Serious Adverse Effects

SIOP: International Society of Paediatric Oncology

TOP (clinical trial): Trial of Principle. Prospective evaluation of topoisomerase II alpha gene amplification and protein overexpression as markers predicting the efficacy of epirubicin in the primary treatment of breast cancer patients.

US: UltraSound

VSB: Voxel Similarity Based