PhD proposal 2021: Computational dynamical modeling of Tumor response to radiation therapy to find a precise and accurate treatment for glioblastoma using logic programming

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Application should consist in: a detailed CV, a cover letter, master 1 and master 2 transcripts

Context.

External beam radiation therapy is one of the most common techniques of therapy against cancer using exposure to ionizing radiation (essentially photon from X-rays) to control tumor growth. The advance of high precision radiotherapy techniques has opened doors to innovative treatments with either modulation of physical parameters of irradiation devices, such as radiation dose, dose rate and energy of the rays, or the combination with chemical drugs radiosensitizing the tumor. These protocols may reduce biochemical recurrence percentages after radiotherapy. However, numerous uncertainties concerning the optimal schedule in terms of tumor control and toxicity risk still exist and cannot be estimated by pricey and long-term clinical trials because of the high number of modulated parameters.

Aim.

Computational models may help unravel the complexity of these dose effect relationships. Especially hybrid modeling as developped in the MeForBio team at LS2N consists in discrete models capturing not only chronological but also chronometrical information (i.e., durations) about the evolution of interacting biological entities. Such models will allow to create, at a limited cost, infinite virtual tumors on which different irradiations protocols can be simulated. Nevertheless, *in silico* modeling faces several challenges. The variety of complex biological mechanisms characterizing cancer and the response to radiotherapy i) may be described with different formalisms involving multiple parameters, ii) take place at different spatiotemporal scales and iii) have an high level of interdependence.

The goal of this PhD thesis is the development of an integrative* in silico *dynamical model of glioblastoma (GBM) tumor growth and response to various modalities of radiotherapy, which is the core of interest of Team PETRY of CRCINA. Inductive logic programming methods, like the Learning From Interpretation Transition (LFIT) framework developed in the MeForBio team at LS2N, will help us to design an explainable model of such a complex biological system.

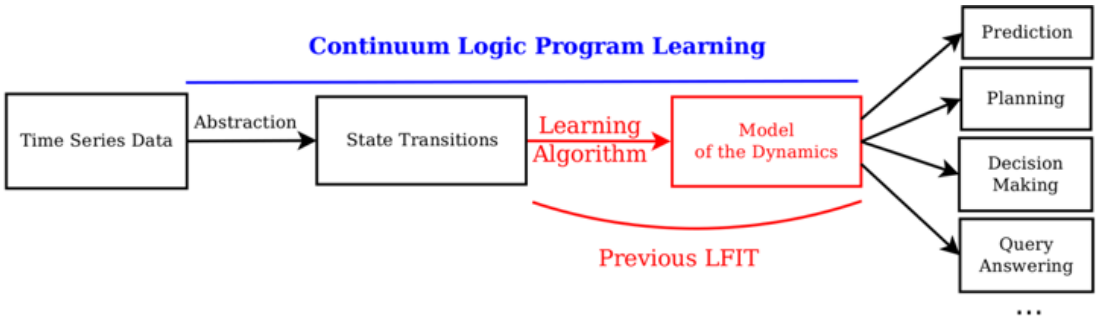
Previous works.

Team PETRY, expert in radiobiology, already experimented the benefits of computational models for the understanding of cell behaviors. It previously proposed in collaboration with Berkeley University (Berkeley, CA, USA), a 2D and 3D cellular automaton [Pau2017] integrating O_2 diffusion and radiation effect on both endothelial and tumor cells. In addition, it introduced mitotic catastrophe instead of arbitrary delayed cell-death. It was validated on human prostate tumors transplanted in mice and then used to generate tumor control probability (TCP) curves for different radiotherapy protocols (2, 3, 4, 6, 8 and 10 Gy per fraction). Furthermore, Team PETRY in collaboration with LTSI (Rennes University, France), developed a multiscale *in silico* approach was implemented in C++ using the Multi-formalism Models and Simulation Library (M2SL) [Sos2021] which integrated the following mechanisms taking place at different temporal and spatial scales: (i) dynamic oxygenation, (ii) angiogenesis, division of (iii) tumor cells (iv) healthy cells, implementing their cycle, and (v) cycle-phase-and-oxygen dependent response to irradiation, considering mitotic death.

These previous works, based on discrete automata, were developed by hand, meaning that the models were developed using human expertise. A major challenge resides now in being able to process the large amount of

data generated by radiotherapy experiments to build an understandable dynamic model of the underlying system. That is where inductive logic programming, and especially the Learning From Interpretation Transition (LFIT) framework, seems promising.

Learning the dynamics of systems with many interactive components becomes more and more important due to many applications, e.g., multi-agent systems, robotics and bioinformatics. In bioinformatics, learning the dynamics of biological systems can correspond to the identification of the influence of genes and can help to understand their interactions. To tackle this problem, we rely on a framework that is the core of a collaboration between the MeForBio team at Centrale Nantes/LS2N and the Inoue Lab at National Institute of Informatics (Tôkyô, Japan) since 2014: learning from interpretation transition (**LFIT**), which automatically constructs a model of the dynamics of a system from the observation of its state transitions. The following figure shows this learning process.



Given some raw data, like time-series data of gene expression, a discretization of those data in the form of state transitions is assumed. From those state transitions, according to the semantics of the system dynamics, different inference algorithms that model the system as a logic program have been proposed. The semantics of system dynamics can indeed differ with regard to the synchronism of its variables, the determinism of its evolution and the influence of its history. In the LFIT framework we propose several modeling and learning algorithms to tackle those different semantics. To date, the following systems have been tackled: memory-less consistent systems with Boolean variables [Ino2013], systems with memory [Rib2015b], non-consistent systems [Mar2015] and their multi-valued extensions [Rib2015c, Mar2016]. All those methods are dedicated to discrete systems or assume an abstraction of time series data as discrete transitions. In [Rib2017], we proposed a method that allows to deal with continuous time series data, the abstraction itself being learned by the algorithm. It allows, for example, to learn the gene expressions levels of expression alongside their interactions.

Until recently, the systems that LFIT handles were restricted to synchronous deterministic dynamics, i.e., all variables update their values at the same time and, for each state of the system, there is only one possible next state. However, many other dynamics exist in the field of logical modeling, in particular the asynchronous and generalized semantics which are of deep interest to model biological systems. In [Rib2018], we propose a method that learns the dynamics of the system independently of its dynamics semantics. Here, we model discrete multi-valued systems as logic programs in which each rule represents that a variable possibly takes some value at the next state, extending the formalism introduced in [Mar2015, Rib2015c, Mar2016]. The multi-valued logic representation used in [Rib2018] is based on annotated logics. Here, to each variable corresponds a domain of discrete values. In a rule, a literal is an atom annotated with one of these values. It allows us to represent annotated atoms simply as classical atoms and thus to remain in the normal logic program semantics. This modeling allows us to represent non-determinism and to propose an extension of LFIT in the form of a semantics free algorithm to learn from discrete multi-valued transitions, regardless of their update schemes. We showed from theoretical results that our new algorithm can learn systems dynamics from both synchronous (deterministic or not), asynchronous and general semantics transitions.

The current project will invite us to extend the LFIT framework in such a way that we can process dynamical data like the evolution of cells (including the information about the division and parent-child relations). This appears to be doable by choosing carefully the litterals that allow us to model the problem.

Research subject and workplan.

Task 1: In vitro time lapse imaging of GBM primoculture

In order to characterize cell dynamics and screening phenotypes after irradiation, relevant GBM primocultures will be irradiated in 24 well dishes 2D culture or in 96 well dishes in 3D tumoroid. The 2 culture models will provide us different radiobiological information. Each well will be separately irradiated at different doses using our experimental X-Rad Image guide irradiator (X-Rad Cx225, PXI). Phenotype induced during radiation response will be tracked by videomicroscopy (Nikon Eclipse owned by PETRY team) for a long period of time (5 days) after defined schemes of radiation therapies (single dose: 0, 2, 4, 8, 10, 15 Gy and fractioned dose; 2 Gy daily, 4 Gy every 2 days, 8 Gy every 3 days). When nuclei are tracked under far-red fluorescent microscopy after adding SirDNA (Spirochrome), the whole cell will be observed under light microscopy and cell death is monitored by DVED-GFP (Thermo). Pictures will be taken every 10 min for 5 days after irradiation and the 3 channels will be merged to a single movie. At least, 9 movies per condition from 3 different experiments will be assessed allowing the monitoring of more than 100 cells and 30 tumoroids.
Recent addition of hypoxia module to the videomicroscopy apparatus allows the monitoring of oxygen rate in the cell dishes. This unique opportunity will allow us to precisely decipher tumor radiosensitivity in function of anoxia rate. For this specific subtask, hypoxia stain (Thermo), a hypoxic marker in alive cells will be added to the cell medium to monitor hypoxia. Team Petry already handled all technologies and equipment necessary for the Task1.

Task 2: Dynamic cell analysis methods aimed at characterizing phenotypic patterns from microscopy video

Aim of task 2 is to characterize dynamics of all the events arising to irradiated cells from the large library of movies gathered in task 1. From 2D culture, monitoring will permit to assess the proliferation and death of tumor cell at the single cell level in time and dose dependent manner. The 3D integrated tumoroid will allow the tracking of overall tumor growth. This unique strategy using videomicroscopy on 2D and 3D cultures is original and will provide new and complementary information to correlate radiosensitivity and the radioresistance outcomes from single cell to integrated multicellular level. Cell tracking and image segmentation techniques will be employed using already developed software (Image J and Job). Furthermore, new tracking algorithms is resulting from a joint collaboration with an international partner (Arrate Munoz, Universidad Carlos III), with high and long-term expertise on cell tracking. She is organizing the Cell Tracking Challenge (ISBI'13-15, ISBI'19) (http://celltrackingchallenge.net/organizers/) and developed cell tracking algorithms already tested in different contexts [Ulm2017]. Several challenges arise particularly to the type of images and events characterized in this PhD proposal (cycle arrest, cell division, death, mitotic catastrophe,) for irradiated cells.

Task 3: development of an integrative in silico dynamical algorithm to model of glioblastoma (GBM) tumor growth and response to various modalities of radiotherapy,

Those biological outputs will serve as input to our inductive logic framework, Learning From Interpretation Transition (LFIT). Using LFIT, we will obtain an explainable dynamical model of the system behavior (expressed as logic rules). This will capture the behaviors of cells submitted to diverse radiation protocols from the observation of time-lapses of the evolution of such cells. With regard to the existing LFIT framework, the novelty of the approach will be to model cell division (i.e., mitosis implying to capture the phylogenetic information of the cells) and spatial interactions between cells. Observations about the dynamic changes of the cells will feed the learning algorithms. Compared to previous works [Mar2016, Rib2018], we will improve the predictive power of the model by, on one hand, capturing probabilistic dynamical events and, on the other hand, refining the modeling by augmenting the number of states defining a cell (for now dose fractionation and cell type) and the number and characterization of the biological cascade of events (cell death, cell mitosis, cell cycle arrest). The goal of such a modeling is to predict the output at the tumor level by considering the fate of each individual cells based on probabilities of state. These probabilities of state will then be fed by the dynamical prediction done by the stochastic model. After validation of the computational approaches, we will then be able to predict future cellular behaviors in the context of different radiation therapy protocols and suggest an optimal dose fractionation to better tumor control. Secondly, at a macroscopic level, an integrated dynamical logical model will be developed to capture and to simulate overall tumor response to radiation exposure. Mouse's observable after irradiation (tumor regression, hypoxia, vessel density) obtained by the

consortium linked with the different simulations from the inductive model mentioned above will bring an integrated GBM response of the new modalities of radiotherapies.

Conclusions and perspectives.

Integration and simulation of the tumor cell response to innovative treatments of radiotherapy represent a challenge to better estimate the numerous uncertainties concerning the optimal schedule in terms of tumor control. The thesis will design computational models that will allow to build the most accurate propositions of the most efficient radiotherapy protocols. Using this model, we intend to propose an optimized and personalized treatment to allow the best anti-tumor efficiency, which cannot be tested by translational or clinical studies.

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