Proposition de sujet de Post-Doc

Model of tumor damage heterogeneity in radiation therapies

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Mots-clés : modeling, estimation, probability, Markov chain, cancer, radiotherapy

Subject

In 2010, cancer has become the leading cause of death worldwide. In all anti-cancer therapies, one major issue is to choose the suited dose of radiation or drug to be applied to the patient. The appropriate dose is the one that both maximizes the therapeutic response (eliminating all the cancer cells) and minimizes the side effects (death or mutation of normal cells). A well calibrated mathematical model of the tumor response can help the clinicians to determine the optimal dose to be applied [1]. Current models implemented in clinical treatment planning systems have two main disadvantages. They do not account for (1) the dynamic response of the tumor and (2) the heterogeneity of cell phenotypes and damages. Indeed, cancer cells within individual tumors often exist in distinct phenotypic states that differ in functional attributes. Because anticancer therapies preferentially kill specific cancer cell states, treatment can result in selective changes in phenotypic proportions within tumors. Therefore, understanding how cancer cell states coexist and evolve within tumors is of fundamental interest and could facilitate the development of more effective therapies [2].
The first cause of damage heterogeneity in a treated tumor comes from a nonuniform spatial distri- bution of the radiation dose. The second one is due to the differences between the cell types (necrotic, quiescent, proliferating, stem cells, etc.) and the nonuniform concentration of oxygen and nutrients. A third factor is the cell-to-cell DNA variability of damages and the variation of the cell sensitivity to radiation. To account for the damage heterogeneity in tumors, we have proposed in [3] a bi-scale mo- del (cell-tumor), which is a generalization of the Linear-Quadratic model. It is based on a discrete-time Markov chain at the cell scale. This model is based on the hit-modeling paradigm of the target theory, which were introduced in the 1920s when biologists were beginning to develop quantum approaches to inactivation phenomena in irradiated biological tissue. In target theory, a cell has different vital sites called targets, which must be all inactivated to kill the cell. Each target is deactivated when it is hit by a number of radiation particles. The multi-hit modeling of cancer is a way to outline the progression of cancer as the accumulation of mutations in the genome of cells. Our model is composed of three main parameters : the number of targets, the probability for a given dose fraction to hit a target and the probability for a damaged target to be repaired in a surviving cell. More recently, we have also proposed another original model of the tumor lifespan and we have shown that the mean value of the tumor lifespan can be approached by a logarithmic function of the initial cancer cell number [4]. This model evolution also accounts for the proliferation rate of living cells.

In both papers, we have shown that the two models were able to compute in the one hand the Tumor Control Probability (TCP) and on the other hand the Normal Tissue Complication Probability (NTCP). These two statistics estimate the therapeutic efficiency and complication respectively and are gathered in a ROC curve, entitled ECT (Efficiency-Complication Trade-off), suited to the selection by clinicians of the appropriate treatment planning.

National & international context

- ANR PCV Nano-VTP Nanoparticles for Imaging and Vascular Photodynamic Treatment of Brain Tumors (2008-2011) ;
- ANR P2N PDTX Active Nanoplatforms for Photodynamic Therapy (2011-2013) ;

- ANR EMED Target-PDT Photodynamic Therapy using photosensitizer-doped targeted organic nanoparticles (2009-2012) ;
- PEPS CNRS-INSIS MOCOBIO MOdeling and COntrol of heterogeneous systems in systems BIO- logy (2010-2011) ;
- UGR I-DERBI Infrastructure Distribuée d ?Enseignement et de Recherche en Biologie Intégrative (2010-2012), Université de la Grande Région (U. Li`ege, U. Lorraine, U. Luxembourg, U. Sarrebruck), Eric Bullinger (Université de Li`ege) & Thierry Bastogne (Université de Lorraine).
- CPER MINS-AOC EMC2 Experimental design, Modeling and Control in Cancerology, (2009-2013).

Missions

This work was partially supported by Contrat de Projet Etat-Région 2007-2013, Région Lorraine.
The main objectives of this post-doc internship are to

- propose an extension of our stochastic model able to account for by-standing effect and time delays of the treatment response due to the propagation of DNA damages in daughter cells after several cell cycles;
- test its relevance to explain in vitro responses obtained from real-time cell-impedance sensing assay ;
- examine how this model could be used or transformed in order to account for the DNA damage measurement obtained from molecular markers like γH2AX [5].

This work will be carried out in collaboration with biologists of the Centre Alexis Vautrin (Lorraine Cancer Research Center). A potential application of this model could be the development of an adaptive anti-cancer treatment. Subsequently, the postdoc student should also collaborate with system control researchers.

4 Skills and profile

Required qualification : PhD in mathematics and specialized in probability and/or statistics. Any experience of applications in biology or biomedicine and programming skills in Matlab/R would be appreciated.

5 Contacts

Supervision and contact: T. Bastogne (thierry.bastogne@inria.fr), P. Vallois (pierre.vallois@iecn.u-nancy.fr),

Duration: 1 year (possibly extendable)
Starting date : between Sept. 1st 2012 and Jan. 1st 2013
Salary: about 1600 euros net /month

The required documents for an INRIA postdoc application are the following:
- CV, including a description of your research activities (2 pages max) and a short description of what you consider to be your best contributions and why (1 page max and 3 contributions max); the contributions could be theoretical, implementation, or industry transfer. Include also a brief description of your scientific and carreer projects.
- The report(s) from your PhD external reviewer(s), if applicable.
- If you haven't defended yet, the list of expected members of your PhD committee (if known) and the expected date of defense (the defense, not the manuscript submission).
- Your best publications, up to 3.
- At least one recommendation letter from your PhD advisor, and possibly up to two other letters.

All these documents should be sent to thierry.bastogne@cran.uhp-nancy.fr.

References

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