Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2020-2021

Personal Information

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Project

Computational systems biology

Project Title:

Simulation of drug interactions in multiscale model tailored to prostate cell-lines

Keywords:

multiscale modelling, drug simulations, gastric cancer, parameter databases

Summary:

General context The candidate will join the area of Precision Medicine in Alfonso Valencia's Computational Biology group within the Life Sciences Department at the Barcelona Supercomputing Center. This research line encompasses the development of different strategies and approaches to improved personalized diagnosis of disease, as well as treatment selection for particular patients, based on their individual characteristics. Computational systems biomedicine relies on the development of in silico models to integrate different sources of experimental information and produce patient-specific mechanistic explanations of cellular behaviour used to design new targeted therapies. In the context of cancer, cell signalling as well as metabolic models have been reconstructed for different cancer types and healthy tissues. Simulation of these models using different computational approaches (e.g. Boolean formalism, Constraint-Based Modelling) have supported the development of targeted therapies that attack specific biological pathways in the cell. The candidate will focus on using and further developing a set of tools aimed for the simulation drug inhibitions of different cell lines. These simulations will explore varying concentrations of single drug inhibition and combinations of them. Scientific context Discovery of efficient anti-cancer drug combinations is a major challenge, since experimental testing of all possible combinations is clearly impossible. Recent efforts to computationally predict drug combination responses retain this experimental search space, as model definitions typically rely on extensive drug perturbation data1,2. Relying on background knowledge extracted from literature and databases, patient-specific dynamical models were developed3 previously tailoring a general cancer model4 to breast-cancer patients. In this work, the study of solutions of the Boolean model led to identifications of particularities among patients and their clinical stratifications3. Currently, we have used this same framework to obtain prostate-cell-line-specific dynamical models and are starting to perform drug perturbation studies. Nevertheless, due to the limitations of the simulation tools used5,6, this study neither identifies sets of concentrations where this synergy is maximal nor it considers population-level constraints and behaviours. In present project, the candidate will simulate varying concentration of inhibitors in the different cell lines model using a multiscale modelling framework, PhysiBoSS7, that that combines agent-based8, Boolean5,6 and environmental dynamics9 modelling. The candidate will first gather from databases and literature biophysical information on parameters that allows for the tailoring of the multiscale simulation to each cell-line such as uptake rates, growth rates, etc. Then, the use of scripts already in place (in python, bash, perl, R) and new ones developed by the student will allow exploring different concentrations of drugs to find maximal synergies specific for each cell-line that would help identifying drug responses potentially relevant in the clinic.

References:

1. Flobak, Å. et al. Discovery of Drug Synergies in Gastric Cancer Cells Predicted by Logical Modeling. PLOS Comput. Biol. 11, e1004426 (2015). 2. Flobak, Å., Vazquez, M., Lægreid, A. & Valencia, A. CImbinator: a web-based tool for drug synergy analysis in small- and large-scale datasets. Bioinformatics 33, 2410–2412 (2017). 3. Béal, J., Montagud, A., Traynard, P., Barillot, E. & Calzone, L. Personalization of logical models with multi-omics data allows clinical stratification of patients. Front. Physiol. 9, 1965 (2019). 4. Fumia, H. F. & Martins, M. L. Boolean Network Model for Cancer Pathways: Predicting Carcinogenesis and Targeted Therapy Outcomes. PLoS ONE 8, e69008 (2013). 5. Stoll, G., Viara, E., Barillot, E. & Calzone, L. Continuous time Boolean modeling for biological signaling: application of Gillespie algorithm. BMC Syst. Biol. 6, 116 (2012). 6. Stoll, G. et al. MaBoSS 2.0: an environment for stochastic Boolean modeling. Bioinformatics 33, 2226–2228 (2017). 7. Letort, G. et al. PhysiBoSS: a multi-scale agent-based modelling framework integrating physical dimension and cell signalling. Bioinformatics bty766 (2018) doi:10.1093/bioinformatics/bty766. 8. Ghaffarizadeh, A., Heiland, R., Friedman, S. H., Mumenthaler, S. M. & Macklin, P. PhysiCell: An open source physics-based cell simulator for 3-D multicellular systems. PLOS Comput. Biol. 14, e1005991 (2018). 9. Ghaffarizadeh, A., Friedman, S. H. & Macklin, P. BioFVM: an efficient, parallelized diffusive transport solver for 3-D biological simulations. Bioinformatics 32, 1256–1258 (2016).

Expected skills::

Knowledge of molecular and cell biology // Strong interest in the information gathering, analysis, modelling and simulation of biological systems. // Programming skills (python, R, bash and perl for the scripts and software tools are written in C++). // Ability to access and evaluate scientific literature.

Possibility of funding::

Yes

Possible continuity with PhD: :

Yes

Comments:

The project will be supervised by Arnau Montagud, co-supervised by Miguel Ponce de León and Alfonso Valencia.