Internship in machine learning of mechanistic signaling pathways for oncology

A 6 months internship (starting February 2020) is available in the ANR/DFG project SYMBIONT "Symbolic Methods for Biological Networks" at the **University of Montpellier**. We are looking for master or engineering students with excellent skills in mathematical modeling (differential equations, machine learning) and in programming (Matlab and/or Python); knowledge in the biology of signaling pathways will be appreciated.

Context: Signalling cascades with complex dynamic regulation and plasticity are deregulated in human cancers. The dynamic cross-talks in these pathways are determinant of the rapid adaptation and long-term acquired resistance to targeted therapies in cancer. In order to understand the mechanisms of resistance and to optimize therapies one needs mathematical models. At the highest level of abstraction, these models are directed graphs in which the nodes are molecular species and the edges are repressive or activating interactions between species. At a lower level, pathway interactions are represented as chemical reaction networks (CRNs) whose dynamics is defined by systems of non-linear differential equations. The analysis of how CRNs are affected by node inhibitions (representing treatment) is difficult in networks containing tens and hundreds of nodes and parameters. Furthermore, machine learning methods suffer from the curse of dimensionality that leads to parametric indeterminacy. In our team we use model reduction to cope with these problems. Model reduction replaces a complex problem with a simpler and tractable one (see [1] for a review).
Problem: Develop a fully parametrized reduced dynamical model of MAPK-PI3K signalling important in melanoma resistance to targeted therapy.
Solution: The model will be generated automatically using unsupervised learning. Static interaction graphs will be generated from phospho-proteomic data using the tool Phos2Net developed in our team [3]. Given a static interaction graph, candidate dynamical ODE models of signaling pathways will be generated using a collection of mechanisms within the Python platform PySB. As the resulting models are typically too big for parametric machine learning they will be reduced using tropical geometry methods developed by our team [3]. We will retain smaller models approximating the data as well as more complex models and having reduced parametric indeterminacy. The resulting models will be used for predicting the effects of drugs, individually or in combinations.

References

[1] O.Radulescu, A.N.Gorban, A.Zinovyev, V.Noel. Reduction of dynamical biochemical reaction networks in computational biology. Frontiers in Bioinformatics and Computational Biology (2012) 3: 131.
[2] Marion Buffard, Aurélien Naldi, Ovidiu Radulescu, Peter J. Coopman, Romain M. Larive, Gilles Freiss. Network Reconstruction and Significant Pathway Extraction Using Phosphoproteomic Data from Cancer Cells. Proteomics, in press 2019, E-pub ahead of print 31 August 2019
[3] O.Radulescu, S.Vakulenko, D.Grigoriev. Model Reduction of Biochemical Reactions Networks by Tropical Analysis Methods. Mathematical Modelling of Natural Phenomena (2015) 10: 124-138.

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