

Post-doc subject in Probability and Statistics

Title: Modeling and estimation of ctDNA dynamics for detecting targeted therapy resistance

Location: INRIA Nancy Grand Est research center --- IECL Laboratory, Vandoeuvre-lès-Nancy, France

Supervision

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Duration: 18 months starting from January 2018, with possible extension.

Scientific context

Development of targeted therapies has been a real progress for the treatment of patients with cancer. Most of these therapies are kinase inhibitors, also called targeted therapies, and require assessing somatic mutations on DNA tumor to ensure the absence of resistance. It is now described that solid tumors are heterogeneous and contain a large number of different subclones. Their detection is rarely possible with common techniques like PCR or NGS and only with one tumor sample. During their development, cancer cells may undergo apoptosis or necrosis and their DNA is then released in blood in the form of circulating tumor DNA (ctDNA). It is a mirror of cancer heterogeneity and improvements of molecular assays sensitivity allows its detection with high precision.

The post-doc is funded from an ITMO Cancer project involving IECL (Institut Elie Cartan de Lorraine, Mathematics laboratory of Université de Lorraine), Inria (Institut National de Recherche en Informatique et Automatique), ICL (Institut de Cancérologie de Lorraine) and Strasbourg's CHRU (Centre Hospitalier Régional Universitaire). The goal of this collaboration is to develop mathematical models for the dynamics of ctDNA to predict response to targeted therapies for patients with non-small cells lungs cancer (NSCLC) and metastatic melanoma.

Missions

The post-doc project has two main objectives. First, to propose several models accounting for the dynamics of the concentration of resistant and sensitive ctDNA in a patient's blood. The dynamics of the different types of cancer cells is governed by local interactions, hence the models should account for (ecological) interactions between them. Second, to design appropriate statistical estimation methods of the parameters of the models, and apply them to data of repeated ctDNA NGS and ddPCR from patients with metastatic melanoma or NSCLC and treated with targeted therapies. The estimated models will be used to quantify the probability of occurrence of a resistance during a given time-window. The consistency between the predicted probability and the observed data will be used to select the best model and the statistical method. Parallel to this, the post doc will also develop other statistical methods not directly based on models, but rather trying to detect global trends in temporal data

Methods

The modeling part of the project will be based on standard stochastic Markov models, either discrete (multitype birth-death processes [1], branching processes [2]) or continuous (multidimensional diffusion processes, such as Feller diffusions [3] or logistic diffusions [4,5]). The statistical part consists in parametric estimation for these models. Any appropriate method for this may be used (likelihood maximization, Bayesian methods, MCMC for density estimation...). Finally, the direct statistical study (not based on models) can involve different methods (machine learning, curve clustering, random forests, discriminant analysis...). The statistical study in this project will be based at the beginning on data available from the literature and on simulated data, and later from data collected by the medical partners of the project.

Environment

The Post-doc will take place in [IECL](#) Nancy under the supervision of Nicolas Champagnat, Anne Gégout-Petit and Pierre Vallois. The Institut Élie Cartan de Lorraine (IECL) is the laboratory of Mathematics of Université de Lorraine. The Probability and Statistics group, composed of more than 30 permanent members, is the largest one in east part of the France. Two Inria projects belong to this group: the first one called [BIGS](#) (BIology, Genetics and Statistics) works on statistics and stochastic modeling for Biology and Medicine; [TOSCA](#) (TO Simulate and CALibrate stochastic models) is the second one, with field of research stochastic modeling, control and stochastic numerical methods. The Post-doc takes part of a collaboration with [ICL](#) (Institut de Cancérologie de Lorraine) and CHRU Strasbourg. Regular meetings are planned between the different partners of the project.

Skills and profile

Required qualification: Ph.D. thesis in probability or statistics. Specific knowledge on estimation of Markov processes is desirable. A strong interest in biological applications is also important.

Funding

ITMO 2017 (INSERM). Net salary: 2132,97 euros per months.

Bibliography

- [1] M. Baar, L. Coquille, H. Mayer, M. Hölzel, M. Rogava, T. Tüting, and A. Bovier. A stochastic model for immunotherapy of cancer. *Sci. Rep.*, **6**, 24169 (2016).
- [2] Haeno H., Gonen M., Davis M.B., Herman J.M., Iacobuzio-Donahue C.A., Michor F. Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. *Cell* **148(1-2)**, 362-75 (2012).
- [3] Cattiaux, P., Méléard, S. Competitive or weak cooperative stochastic lotka-volterra systems conditioned to non-extinction. *J. Math. Biol.*, **6**, 797-829 (2010).
- [4] Sun X., Bao J., Shao Y. Mathematical modeling of therapy-induced cancer drug resistance. *Sci Rep.*, **6**, 22498 (2016).
- [5] Giet, J.-S., Vallois, P., Wantz-Mézières, S. The logistic S.D.E. *Theory Stoch. Process.* **20(1)**, 28-62 (2015).
- [6] Sène, M., Bellera, C.A. and Proust-Lima, C., 2014. Shared random-effect models for the joint analysis of longitudinal and time-to-event data: application to the prediction of prostate cancer recurrence. *Journal de la Société Française de Statistique*, 155(1), 134-155.