Post-doc subject in Probability and Statistics

Title: Modeling of heterogeneity in ctDNA dynamics for detecting targeted therapies resistance

Location: IECL Laboratory, Vandoeuvre-lès-Nancy, France

Supervision
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Duration: 12 months starting either from September or October or November 2019.

Scientific context
Targeted therapies are a real progress for the treatment of patients with cancer. Most of these therapies are kinase inhibitors and require somatic mutations assessment on DNA extracted from tumor tissue to ensure the absence of primary resistance. Solid tumors are heterogeneous and contain a large number of different subclones whose detection is rarely possible with common techniques like PCR or NGS and only with one tumor sample. During their growth, circulating tumor DNA (cfDNA) is shed by cancer cells by apoptosis, necrosis and active mechanisms. ctDNA is known as a mirror of cancer heterogeneity and improvements of molecular assays sensitivity allow its detection with high sensitivity.
The post-doc is part of a scientific project funded by ITMO cancer. This project involves 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 CHRU (Centre Hospitalier Régional Universitaire). This project aims at developing mathematical models for the dynamics of ctDNA and predicting response to targeted therapies for patients with non-small cells lungs cancer (NSCLC) and metastatic melanoma.

Missions
The first objective of the post-doctoral project is to introduce mathematical models accounting for the temporal evolution of the concentrations of heterogeneous ctDNA in patient with cancer's blood. The models should account for interactions between the different cells involved in the cancer, which may be either sensitive or resistant to the targeted therapy. Theoretical and statistical estimates of the models parameters play a central role and constitute the second task of the project. The statistical study will be done from data of repeated ctDNA NGS and ddPCR from patients with metastatic melanoma or NSCLC currently collected by the medical partners of the project. Once the project is fully implemented, it will permit the estimation of the probability of occurrence of a resistance during a given time-window. Other questions can also be studied, such as the inference of the genealogy of mutations in the tumor and the improvement of therapy protocols using optimal control.

Methods
The mathematical modeling part of the project will be based on standard stochastic Markov models, either discrete (multitype birth-death processes, as in [1], or branching

processes, as in [2]) or continuous (logistic diffusions, as in [4,5]), with potential mixed-effects to account for possible heterogeneity between patients (for example in diffusion models as in [3]).
The statistical part can consist in parametric estimation for these models. Any appropriate method for this may be used (likelihood maximization, Bayesian methods, MCMC…). The statistical study will be based at the beginning on data available from the literature and on simulated data, and later from data of the project.
Depending of her or his expertise and desires, the candidate will also develop models accounting for the ancestry of mutations and the associated ancestral inference methods, and study questions of stochastic control to design optimal therapies.

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 team: 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 in an existing collaboration with ICL (Institut de Cancérologie de Lorraine) and CHRU of Strasbourg. Regular meetings are planned between the different partners of the project. The post-doctoral project will build on works already completed within this collaboration.

Skills and profile
Required qualification: Ph.D. thesis in probability or statistics. A strong interest in biological applications is important. Specific knowledge on Markov processes, mixed-effect models, stochastic control, parametric estimation or ancestral inference is desirable.

Funding
ITMO cancer 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] Samson A., Lavielle M., Mentré F. The SAEM algorithm for group comparison tests in longitudinal data analysis based on non-linear mixed-effects model**. Statistics in Medicine**, 26(27):4860-4875 (2007).
- [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.