Offre n°2024-08500

Master 2 Internship : Stochastic modelling and estimation for the distribution of lengthening and abrupt shortening of ALT cells in yeasts

Le descriptif de l'offre ci-dessous est en Anglais

Niveau de diplôme exigé : Bac + 4 ou équivalent

Fonction : Stagiaire de la recherche

Contexte et atouts du poste

Internship context : The internship will take place in the Probability and Statistics team of the Institut E□lie Cartan de Lorraine (IECL) and in the SIMBA (Statistical Inference and Modeling for Biological Applications) team of Inria Nancy. The trainee will be involved in discussions with Marie-Noe□lle Simon (CRCM, Aix-Marseille University) on the biological and data aspects of the project. During the internship, the trainee will have the opportunity to discover the world of mathematical research through the life of a dynamic mathematics laboratory, and to attend seminars and working groups in probability and statistics. The trainee will receive the standard stipend (around 600€/month).

Keywords : applied probability, stochastic modelling of population processes, branching processes, statistical modeling for biology, estimation, telomere length dynamics

Skills : The candidate should have skills in statistics and/or stochastic modeling. R, Python or Matlab programming skills are also required. An affinity or experience with biological applications will be highly appreciated.

Supervision : The internship will be supervised by Nicolas Champagnat, Coralie Fritsch (IECL and INRIA Nancy) and Denis Villemonais (University of Strasbourg).

Follow up with a PhD thesis : At the end of the internship, the intern can apply for a PhD thesis on the continuation of this research project, funded by PEPR Maths VivES. This application will be given priority if the results of the internship are satisfactory.

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Full Internship subject: https://bul.univ-lorraine.fr/index.php/s/yLn2DpGL8CJfLjp

Mission confiée

Biological context

Telomeres are nucleoprotein structures located at the ends of chromosomes, which they protect from degradation. During the cell division, the DNA is not entirely replicated leading to a loss of telomere sequences. Without any mechanism of telomere lengthening, telomeres progressively shorten until they reach a critical length (roughly at 70 bp in yeasts). Below this critical threshold, shortened telomeres trigger a permanent cell division cycle arrest, leading to a replicative senescence. This phenomenon is known as the end replication problem.

In the yeast Saccharomyces cerevisiae, telomere length homeostasis is the result of a balance between the action of the enzyme telomerase reverse transcriptase (TERT), which adds telomere sequences on short telomeres, and losses of telomere sequences due to the replication of DNA ends at cell divisions. As a result, telomere length varies from cell to cell and from telomere to telomere within a given cell, but stay of the order of 300 bp. When TERT activity is repressed, telomeres progressively shorten following the end replication problem until the replicative senescence. However, most often, in cultures of TERT-inactivated yeasts, rare "survivors" (roughly 1 among 100 000 individuals) escape senescence thanks to other telomerase-independent telomere maintenance mechanisms (called ALT for Alternative Lengthening of Telomeres), based in particular on homologous recombination.

ALT cells are characterized by very heterogeneous distribution of telomere lengths up to 10 kb. In ALT cells, telomeres are confronted with the end replication problem and therefore shorten with each cycle of cell division. Furthermore, as with natural telomeres, replication of ALT telomeres is a challenge to the cell's replication machinery and therefore a source of stochastic replicative damage leading to abrupt shortening in the absence of telomerase. Finally, like natural telomeres, ALT telomeres are considered to be the preferential target of oxidative stress, which could be another source of abrupt telomere attrition.

Project description

The internship takes place in a larger project aiming to develop a comprehensive model at the level of a population of lengthening and shortening of telomeres in ALT yeasts and to validate it on data of culture, giving the time evolution of the distribution of telomere lengths in the population.

The aim of the internship is to get familiar with the data of the project and to propose and analyse a first stochastic model at the level of a single lineage. Other tasks listed below could also be considered during the internship, depending on the interests of the trainee, and will be part of a PhD thesis in the continuity of the internship.

Principales activités

Tasks

The first task of the trainee will be to get familiar with the various types of ALT telomere data of the project. Our biologist collaborator, Marie-Noe□lle Simon (CRCM, Aix-Marseille University), will provide us with data of telomere length distributions at the population level, for all the telomeres or for a single telomere selected using a specific probe. These are temporal data, obtained from samples regularly collected in cultures. Due to the exponential growth of the population, subpopulations are selected on a daily basis either on Petri dishes with successive transplantations of a single colony, or on liquid experiments with successive dilutions. Most of the data are collected using the Southern blot, but we will also study data obtained with other types of methods, including the TeSLA method, which provides measurements of few telomeres selected in the population.

Then, the intern will design a stochastic model of telomere evolution at the level of a single lineage, including mechanisms of abrupt telomere shortening and lengthening. The parameters of this model will be estimated from the data of evolution of the length of single telomeres. We can take our inspiration from the work [1,2] for the modeling part and from [3] for the estimation part.

The third step of the project is to construct a stochastic model of telomere evolution at the level of the population, including the individual mechanisms developed earlier. This will take the form of a branching process, where the progeny of different individuals follow independent processes, structured by the vector of individual telomere lengths. Such infinite-dimensional branching processes will be represented as measure-valued Markov processes following the formalism of [4,5]. In particular, the intern will prove that the many-to-one formula holds true for this process, as in [6,7] where the authors study telomere length dynamics, and provide numerical simulations in order to illustrate its main property.

The last step of the project will consist in building from the previous model another model for the successive transplantations or dilutions experiments described above, able to account for the collected data of telomere length distribution at the level of the population. The goal is here to estimate the main parameters of the model, namely the rates of abrupt attrition and lengthening of telomeres and their range and the rate of progressive telomere shortening due to the end replication problem, from the data. Due to the complexity of the model, it is particularly difficult to design model-specific methods and we will thus use classical optimisation methods, such as least-square estimates, combined with expert opinion on the biological relevance of the obtained parameters values. One of the biological questions we would like to answer is the following: is the rate of progressive telomere shortening due to the end replication problem the same for ALT yeasts than for normal yeasts (with active telomerase)?

The Master 2 project will be continued in a PhD thesis, funded by PEPR Maths VivES, where the last questions will be further investigated, and also other modeling questions regarding the proliferative capacity and the competitivity of ALT cells in populations with multiple non-attrition strategies.

Bibliography

[1] Thibault Bourgeron, Zhou Xu, Marie Doumic, Maria Teresa Teixeira, The asymmetry of telomere replication contributes to replicative senescence heterogeneity, Scientific Reports, vol 5, 2015.

[2] Hugo Martin, Marie Doumic, Maria Teresa Teixeira, Zhou Xu, Telomere shortening causes distinct cell division regimes during replicative senescence in Saccharomyces cerevisiae, Cell & Bioscience, vol. 11, 2021.

[3] Christoph Zimmer and Sven Sahle. Comparison of approaches for parameter esti- mation on stochastic models: Generic least squares versus specialized approaches. Computational Biology and Chemistry, vol. 61, 2016.

[4] Vincent Bansaye and Sylvie Me□le□ard. Stochastic Models for Structured Populations, Scaling Limits and Long Time Behavior, Springer, 2015.

[5] Emma Horton and Andreas Kyprianou. Stochastic Neutron Transport And Non-Local Branching Markov Processes, Springer, 2023.

[6] Athanase Benetos, Coralie Fritsch, Emma Horton, Lionel Lenotre, Simon Toupance, Denis Villemonais. Stochastic branching models for the telomeres dynamics in a model including telomerase activity, arXiv:2407.11453, 2024.

[7] Jules Olaye and Milica Tomasevic. Long-time behaviour of a multidimensional age- dependent branching process with a singular jump kernel, arXiv:2408.02476, 2024.

[8] Simon Toupance, Denis Villemonais, Daphne Germain, Anne Gegout-Petit, Anne and Eliane Albuisson, Athanase Benetos. The individual's signature of telomere length distribution, Scientific reports, vol 9(1), 2019.

Compétences

The candidate should have skills in statistics and/or stochastic modeling. R, Python or Matlab programming skills are also required. An affinity or experience with biological applications will be highly appreciated.

Avantages

- Subsidized meals
- Partial reimbursement of public transport costs
- Leave: 7 weeks of annual leave + 10 extra days off due to RTT (statutory reduction in working hours) + possibility of exceptional leave (sick children, moving home, etc.)
- Possibility of teleworking (after 6 months of employment) and flexible organization of working hours
- Professional equipment available (videoconferencing, loan of computer equipment, etc.)
- Social, cultural and sports events and activities
- Access to vocational training
- Social security coverage

Rémunération

€4.35/hour

Informations générales

- **Thème/Domaine :** Approches stochastiques
  Biologie et santé, Sciences de la vie et de la terre (BAP A)
- **Ville :** Villers lès Nancy
- **Centre Inria :** Centre Inria de l'Université de Lorraine
- **Date de prise de fonction souhaitée :** 2025-04-01
- **Durée de contrat :** 6 mois
- **Date limite pour postuler :** 2025-01-19

Contacts

- **Équipe Inria :** SIMBA
- **Recruteur :**
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A propos d'Inria

Inria est l'institut national de recherche dédié aux sciences et technologies du numérique. Il emploie 2600 personnes. Ses 215 équipes-projets agiles, en général communes avec des partenaires académiques, impliquent plus de 3900 scientifiques pour relever les défis du numérique, souvent à l'interface d'autres disciplines. L'institut fait appel à de nombreux talents dans plus d'une quarantaine de métiers différents. 900 personnels d'appui à la recherche et à l'innovation contribuent à faire émerger et grandir des projets scientifiques ou entrepreneuriaux qui impactent le monde. Inria travaille avec de nombreuses entreprises et a accompagné la création de plus de 200 start-up. L'institut s'efforce ainsi de répondre aux enjeux de la transformation numérique de la science, de la société et de l'économie.

Attention: Les candidatures doivent être déposées en ligne sur le site Inria. Le traitement des candidatures adressées par d'autres canaux n'est pas garanti.

Consignes pour postuler

Sécurité défense :
Ce poste est susceptible d'être affecté dans une zone à régime restrictif (ZRR), telle que définie dans le décret n°2011-1425 relatif à la protection du potentiel scientifique et technique de la nation (PPST). L'autorisation d'accès à une zone est délivrée par le chef d'établissement, après avis ministériel favorable, tel que défini dans l'arrêté du 03 juillet 2012, relatif à la PPST. Un avis ministériel défavorable pour un poste affecté dans une ZRR aurait pour conséquence l'annulation du recrutement.

Politique de recrutement :
Dans le cadre de sa politique diversité, tous les postes Inria sont accessibles aux personnes en situation de handicap.