2021-03668 - PhD Position F/M [Cordi-S Campaign 2021 Grenoble] Computational analysis of metabolic strategies in pathogenic bacteria

Type de contrat: CDD
Niveau de diplôme exigé: Bac + 5 ou équivalent
Fonction: Doctorant
Niveau d'expérience souhaité: Jeune diplômé

A propos du centre ou de la direction fonctionnelle

Grenoble Rhône-Alpes Research Center groups together a few less than 650 people in 37 research teams and 8 research support departments.

Staff is localized on 5 campuses in Grenoble and Lyon, in close collaboration with labs, research and higher education institutions in Grenoble and Lyon, but also with the economic players in these areas.

Present in the fields of software, high-performance computing, Internet of things, image and data, but also simulation in oceanography and biology, it participates at the best level at international scientific achievements and collaborations in both Europe and the rest of the world.

Contexte et atouts du poste

The PhD student will carry out the project in the context of IBIS, an interdisciplinary research group involving researchers from Inria Grenoble – Rhône-Alpes and the Laboratoire Interdisciplinaire de Physique (CNRS/Université Grenoble Alpes), in close collaboration with the experimental group of Luz Pedro Carvalho at the Francis Crick Institute (associated with UCL, Imperial College and King's College) in London. This group is a world-leading expert on mycobacterial biochemistry, metabolism and antibiotic research.

Mission confiée

The growth of heterotrophic microorganisms consists in the conversion of nutrients available in the environment into biomass. At the molecular level, this process involves a complex network of biochemical reactions involved in the uptake of the nutrients, their degradation into metabolic precursors, and the assembly of the latter into macromolecules that constitute the biomass of the cell (proteins, DNA, RNA, lipids...). In recent years, constraint-based models have been developed that describe the above reaction networks in a simplified manner as a linear system of balanced metabolic fluxes with additional flux inequalities expressing fundamental thermodynamic and biochemical constraints as well as experimental observations [3]. Constraint-based modeling of microbial growth has become a very effective tool for the analysis of the metabolic strategies of microorganisms as well as the redesign of these strategies for biotechnological or environmental purposes [2]. In particular, they provide an excellent framework for integrating heterogeneous, genome-scale datasets in a principled and efficient manner [3,4].

While constraint-based models have been mostly used for model organisms like the gut bacterium Escherichia coli or yeast, the formalism is also very well suited for the analysis of microorganisms that have been less well-studied but that are of large societal or economic interest. One example consists in the genus of mycobacteria, which includes Mycobacterium tuberculosis, the causative agent of tuberculosis [5]. Whereas different mycobacteria species have very similar metabolic capacities, they nevertheless show a bewildering variety of metabolic strategies, resulting in growth rates that vary over an order of magnitude (doubling times between 1 and 24 hours) [6]. In recent years, laboratories over the world have accumulated experimental datasets quantifying the physiology of different mycobacteria [7], but a fundamental understanding of the underlying metabolic strategies and their relation with pathogenicity is still in its infancy. Constraint-based modeling of mycobacterial metabolism is a promising approach for making sense of these data and gaining a better understanding of the relation between metabolism and pathogenicity.

The above considerations motivate a PhD proposal consisting of (i) the development of constraint-based models of a dozen of mycobacteria species, (ii) the integration of various high-throughput datasets for these mycobacteria available in the literature and in the laboratory of our experimental collaborator, and (iii) the computational and statistical analysis of the models to identify different metabolic strategies as well as their connection to pathogenicity.

Informations générales

- Thème/Domaine: Biologie numérique
- Ville: Montbonnot
- Centre Inria: CRI Grenoble - Rhône-Alpes
- Date de prise de fonction souhaitée: 2021-10-01
- Durée de contrat: 3 ans
- Date limite pour postuler: 2021-05-10

Contacts

- Equipe Inria: IBIS
- Directeur de thèse : Ropers Delphine
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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 200 équipes-projets agiles, en général communiques avec des partenaires académiques, impliquent plus de 3500 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 quinzaine 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 impacteront le monde. Inria travaille avec de nombreuses entreprises et a accompagné la création de plus de 180 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.

Consignes pour postuler

Important information concerning the COVID-19 epidemic: in case the rules by the French government and Inria related to the epidemic make it impossible for the candidate to physically start the position at Inria Grenoble, the position will start with teleworking.

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.

Attention: Les candidatures doivent être déposées en ligne sur le site Inria.
Principales activités
The activities that the PhD student will carry out include the following:

1. Reconstruct constraint-based models for a dozen of different mycobacteria species, starting from available models for some species, the genome sequence of others, and the biomass composition (proteins, lipids, RNA, ...) experimentally determined by the group of Luiz Carvalho at the Francis Crick Institute.
2. Using measured growth rates, metabolite uptake and secretion rates, as well as information on metabolite concentrations, apply metabolic flux analysis, flux variability analysis, and Monte Carlo sampling to estimate flux distributions compatible with the experimental observations.
3. Cluster the inferred flux distributions and cross-relate fluxes with experimentally determined protein concentrations. This will allow the formulation of hypotheses on regulatory mechanisms that could explain the large metabolic variability across species, as input for further testing by the group of Luiz Carvalho.

Compétences
Applicants may come from different disciplinary backgrounds – bioinformatics, mathematical biology, microbiology, bioengineering, or biophysics. We expect them to be strongly motivated by interdisciplinary work combining the mathematical modeling of biological systems with the (statistical and computational) analysis of high-throughput experimental datasets. Basic knowledge in microbiology and previous experience with methods for data analysis and data integration would be appreciated. Good relational skills are very important for the project, as it will be carried out in an interdisciplinary and international environment.

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 two days per week 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

Monthly salary after taxes: around 1596,05€ for 1st and 2nd year. 1678,99€ for 3rd year. (medical insurance included, income tax excluded).