Offer #2023-06315

Post-Doctoral Research Visit F/M Post-Doctoral Research Visit F/M [Campagne POSTDOC DRI - programme Inria Londres] Genome-wide metabolic network reconstruction of a whole genus: Application to mycobacteria species

Contract type : Fixed-term contract

Level of qualifications required : PhD or equivalent

Fonction : Post-Doctoral Research Visit

About the research centre or Inria department

The Centre Inria de l'Université de Grenoble groups together almost 600 people in 22 research teams and 7 research support departments.

Staff is present on three campuses in Grenoble, in close collaboration with other research and higher education institutions (Université Grenoble Alpes, CNRS, CEA, INRAE, …), but also with key economic players in the area.

The Centre Inria de l'Université Grenoble Alpe is active in the fields of high-performance computing, verification and embedded systems, modeling of the environment at multiple levels, and data science and artificial intelligence. The center is a top-level scientific institute with an extensive network of international collaborations in Europe and the rest of the world.

Context

The post-doctoral researcher will carry out the project in the context of MICROCOSME, an interdisciplinary research group involving researchers from the Inria research centre at Univ. Grenoble Alpes and the Laboratoire Interdisciplinaire de Physique (CNRS/Université Grenoble Alpes), in close collaboration with the Mycobacterial Metabolism and Antibiotic Research Laboratory from the Francis Crick Institute in London (UK), within the framework of the Inria London programme. Regular visits to the London laboratory are planned. Travel expenses will be covered within the limits of the scale in force.

Assignment

Candidates for postdoctoral positions are recruited after completing their Ph.D. or after a first postdoctoral period: for the candidates who obtained their Ph.D. in the Northern hemisphere, the date of the Ph.D. defence shall be later than 1 September 2021; in the Southern hemisphere, later than 1 April 2021.

In order to encourage mobility, the postdoctoral position must be in a scientific environment that is truly different from that of the doctoral studies (and, if applicable, from the position held since the doctoral studies); particular attention will therefore be given to French or international candidates who obtained their doctorate abroad.

The duration of the post-doctoral position will be a maximum of two years.

Contact for application details: Delphine.Ropers@inria.fr (MICROCOSME website: https://team.inria.fr/microcosme/)

Deadline for application June, 18, 2023.

Main activities

Keywords: Bioinformatics, genome-scale modelling of metabolic networks, health, microbiology

Context and motivation: Mathematical models that can reproduce *in silico* the growth phenotype of a dozen of species from the *Mycobacterium* genus are promising avenues to uncover metabolic bottlenecks explaining the growth-rate variability observed across the genus. These species are indeed at the heart of a mystery of microbiology: some of them, such as the causative agent of tuberculosis, are

slow growers living in association with a host, while environmental and inoffensive species are often fast growers.

Description: Genome-scale metabolic networks are useful to understand the complex network of chemical transformations happening inside cells [1]. These networks typically consist of thousands of reactions and small compounds, the metabolites, involved in vital biological processes, such as the transport of molecules into cells or the degradation of nutrients into precursors fuelling cellular growth. Metabolic networks are commonly formalized as graphs describing the relations between the metabolites, the chemical reactions transforming one metabolite to another, the enzymes (proteins) catalysing these reactions, and their corresponding genes [2]. Metabolic network reconstruction is nowadays a partially automated process, which starts from genomics data (the DNA sequence of the organism) and knowledge on metabolic reactions stored in databases. It subsequently assigns a function to the genes, such as the metabolic reactions they are involved in, and assembles the corresponding metabolic reactions into large networks. These reconstructions at the genome-scale level allow to investigate systems-level metabolic properties and functions by different methods [3]: graph-theory approaches to analyse the structure of the network, stoichiometric modelling representing the metabolic network as a large system of linear equations to analyse metabolic fluxes at steady state (e.g. [4]), or kinetic modelling for the dynamical analysis of the network behaviour in changing conditions.

Metabolic networks are well understood in some species, including the model organism *Escherichia coli*. Lesser known microorganisms are of great societal or economic interest. Examples include the case of the genus *Mycobacterium*. Numerous mycobacteria species pose serious threats to human and animal health. *Mycobacteria tuberculosis* (Mtb) strains are notably known to withstand several of the antibiotics used to treat the infection. However, mycobacteria still need to be understood in terms of how they assimilate nutrients, grow and become pathogenic: most pathogenic strains in this genus are slow growers replicating in their host, while fast growers are environmental with only a few opportunistic pathogens. In recent years, laboratories across the world have accumulated experimental datasets quantifying the physiology of different mycobacteria, including our colleagues at the Mycobacterial Metabolism and Antibiotic Research Laboratory from the Francis Crick Institute [5]. Combining their datasets with genome-scale models of mycobacterial metabolism can help to understand growth-rate variability. Such knowledge would be useful, in the long term, for the development of new treatments for curing tuberculosis and other mycobacterial infections.

The reconstruction of metabolic networks is a difficult problem for the poorly characterized mycobacteria species [3]. While an existing reconstruction of Mtb metabolism [6] has been improved and manually curated in our team, there is a need to reconstruct the metabolic networks of other mycobacteria species, including slow and fast growers, pathogenic and environmental species. In collaboration with the Francis Crick Institute, we propose to automate the approach used for the Mtb model in order to produce metabolic network reconstructions for a dozen of mycobacteria that allow to produce experimentally-testable hypotheses on the relation between growth-rate variability and mycobacterial metabolism. This will require dealing with a number of issues related to the poor knowledge about most mycobacteria species: 1) the incompleteness of their genome annotations, 2) the knowledge gaps in their metabolic networks, 3) the incompleteness of metabolic databases of these less-well studied microorganisms, 4) the greedy inclusion of metabolic reactions during the automated reconstruction process, leading to imprecise growth-rate predictions.

References:

[1] Bordbar, Monk, King & Palsson (2014). Constraint-based models predict metabolic and associated cellular functions. *Nature Review Genetics*, 15,2.

[2] Lacroix, Cottret, Thébault & Sagot (2008). An introduction to metabolic networks and their structural analysis. *IEEE/ACM transactions on computational biology and bioinformatics*, 5(4), 594-617.

[3] Thiele & Palsson (2010). A protocol for generating a high-quality genome-scale metabolic reconstruction. *Nature protocols*, 5:1.

[4] Morin, Ropers, Letisse, Laguerre, Portais, Cocaign Bousquet & Enjalbert (2016). The post transcriptional regulatory system CSR controls the balance of metabolic pools in upper glycolysis of *Escherichia coli*. *Molecular Microbiology*, 100(4), 686-700.

[5] Agapova, Petridis, Hunt, Garza-Garcia, Sohaskey & de Carvalho (2019). Flexible nitrogen utilization by the metabolic generalist *Mycobacterium tuberculosis* reveals a highly adapted metabolic network. *Elife* 8, e41129.

[6] López-Agudelo, Mendum, Laing, Wu, Baena, Barrera, ... & Rios-Estepa (2020). A systematic evaluation of *Mycobacterium tuberculosis* genome-scale metabolic networks. *PLOS Computational Biology*, 16(6), e1007533.

Skills

The candidate is expected to hold a PhD thesis in bioinformatics or in computer science, or biology with a strong computational background, with a working knowledge of metabolic network modelling. Programming skills (such as in Python) are required as the reconstruction of multiple models will need automatization. Good relational skills and English skills are also important for the project.

Benefits package

- 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 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

Remuneration

- 2 746 euros gross salary/month

General Information

- **Theme/Domain** : Computational Biology
- **Town/city** : Montbonnot
- **Inria Center** : Centre Inria de l'Université Grenoble Alpes
- **Starting date** : 2023-11-01
- **Duration of contract** : 2 years
- **Deadline to apply** : 2023-09-30

Contacts

- **Inria Team** : MICROCOSME
- **Recruiter** :
  Ropers Delphine / delphine.ropers@inria.fr

About Inria

Inria is the French national research institute dedicated to digital science and technology. It employs 2,600 people. Its 200 agile project teams, generally run jointly with academic partners, include more than 3,500 scientists and engineers working to meet the challenges of digital technology, often at the interface with other disciplines. The Institute also employs numerous talents in over forty different professions. 900 research support staff contribute to the preparation and development of scientific and entrepreneurial projects that have a worldwide impact.

The keys to success

The candidate is expected to be proactive and open to collaboration in an interdisciplinary and international environment.

> **Warning** : you must enter your e-mail address in order to save your application to Inria. Applications must be submitted online on the Inria website. Processing of applications sent from other channels is not guaranteed.

Instruction to apply

Defence Security :
This position is likely to be situated in a restricted area (ZRR), as defined in Decree No. 2011-1425 relating to the protection of national scientific and technical potential (PPST).Authorisation to enter an area is granted by the director of the unit, following a favourable Ministerial decision, as defined in the decree of 3 July 2012 relating to the PPST. An unfavourable Ministerial decision in respect of a position situated in a ZRR would result in the cancellation of the appointment.

Recruitment Policy :
As part of its diversity policy, all Inria positions are accessible to people with disabilities.