2017-00189 - Biochemical computing (research internship)

Level of qualifications required: Bachelor's degree or equivalent
Fonction: Internship Research

About Inria
Inria, the French National Institute for computer science and applied mathematics, promotes “scientific excellence for technology transfer and society”. Graduates from the world’s top universities, Inria's 2,700 employees rise to the challenges of digital sciences. With its open, agile model, Inria is able to explore original approaches with its partners in industry and academia and provide an efficient response to the multidisciplinary and application challenges of the digital transformation. Inria is the source of many innovations that add value and create jobs.

About the research centre or Inria department
Located at the heart of the main national research and higher education cluster, member of the Université Paris Saclay, a major actor in the French Investments for the Future Programme (Idex, LabEx, IRT, Equipex) and partner of the main establishments present on the plateau, the centre is particularly active in three major areas: data and knowledge; safety, security and reliability; modelling, simulation and optimisation (with priority given to energy).

The 500 researchers and engineers from Inria and its partners who work in the research centre’s 31 teams, the 100 research support staff members, the high-level equipment at their disposal (image walls, high-performance computing clusters, sensor networks), and the privileged relationships with prestigious industrial partners, all make Inria Saclay Île-de-France a key research centre in the local landscape and one that is oriented towards Europe and the world.

Context
This research internship position is offered at Inria Saclay IdF (https://www.inria.fr/en/centre/saclay) in the LIFEWARE project-team, in the framework of the ANR-MOST project BIOPSY “Biochemical Programming System” in partnership with Franck Molina's lab Sys2diag in Montpellier, France and Prof. Jieh-Hong Jiang, Dept. electrical engineering, National Taiwan University.

The LIFEWARE team (http://lifeware.inria.fr) develops the Biochemical Abstract Machine (BIOCHAM http://lifeware.inria.fr/biocham4) software for modeling, analyzing and now synthesizing biochemical reaction networks (CRNs), using methods from fundamental Computer Science and mathematics. The software developments are expected to be integrated in BIOCHAM.

The internship will be supervised by François Fages who has supervised 29 Ph.D. theses in his career, the last defended in May 2016, and who currently is 100% available with no Ph.D. student.

Assignment
General introduction: Cells compute, they process signals they receive from and emit to their environment, regulate their metabolism, and take decisions such as cell division, differentiation or migration. Understanding these processes is a central

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difficulty in many applications in medicine, health and agriculture, and the ultimate goal of molecular cell biology which we see as a grand challenge for computer science. Unlike digital programs, biochemical computation involves state transitions that are stochastic rather than deterministic, continuous-time rather than discrete-time, poorly localized instead of well-separated in modules, and created by evolution instead of by rational design. Based on recent results in computability, complexity and computable analysis, we are developing novel synthesis methods for compiling mixed analog-digital programs into enzymatic reactions, comparing the generated code to natural evolved reaction networks, and making experiments with extensive validation in non-living vesicles created by microfluidic devices at Sys2diag lab.

**Objective of the research internship:**

The objective of this internship is to develop robust design principles for biochemical reaction networks (CRNs) and gain insights on natural biochemical networks through synthesis of artificial biochemical circuits with the same function. The state-of-the-art in synthesis is to measure parameter sensitivity indices and optimize robustness after the design. Depending on the skills of the candidate, the work will focus more on

- the computational theory of dynamical systems,
- the definition of low computational complexity classes for CRNs,
- robust design patterns for CRNs,
- high-level specifications of the function of natural CRNs (e.g. from the BioModels repository [http://biomodels.org](http://biomodels.org)) with comparison between natural and synthesized CRNs for the same function,
- or realization of novel designs for biosensors with *in vitro* evaluation.

In all cases, *in silico* experiments and developments will be preferably done in the BIOCHAM modeling environment, and some *in vitro* experiments will be possibly done in tight collaboration with our Sys2diag partner.

**Main activities**

Our first compilation principles are described in the following paper


We believe that these preliminary results have opened an whole avenue of research with very nice results in several directions. The candidate will benefit from an exceptional environment to develop his/her research among the points mentioned above.

**Skills**

This subject requires common and basic knowledge on ordinary differential equations, computability theory and complexity. The candidate will have to be fluent in English.

There is no specific prerequisite for this Thesis. However, some specific knowledge on either analog computing, differential dynamical systems, circuit verification, circuit synthesis, VHDL-AMS, Prolog, systems biology, synthetic biology, or chemistry will be a plus.

**Benefits package**

- Subsidised catering service
- Partially-reimbursed public transport
- Social security
- Paid leave
- Flexible working hours
- Sports facilities

**Remuneration**

500 euros/month + living compensation for foreigners