Mixed Analog-Digital Programs in the Cell

**Scientist offers:**
Position type: PhD  
Functional area: Palaiseau  
Research theme: Digital health, biology and earth  
Project: LIFEWARE  
Scientific advisor: François Fages

**About Inria and the job:**

Inria

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.

Lifeware is a project-team of the Inria Saclay – Île de France center, located in Palaiseau on the Campus of Ecole Polytechnique in Alan Turing Building. Created in January 2014 as a follow-up of the Contraintes project-team on constraint logic programming, Lifeware aims at developing formal methods and experimental settings for understanding the cell machinery and establishing computational paradigms in cell biology. It is based on the vision of cells as machines, biochemical reaction systems as programs, and on the use of concepts and tools from computer science to master the complexity of cell processes.

The Thesis will be supervised by François Fages, head of Lifeware.

**Mission:**

The computational viewpoint at cell biology leads to the analysis of biochemical reaction systems as programs, and to the use of formal methods to reason about their behaviours. This is the foundation of our modeling environment Biocham. Furthermore, advancements in synthetic biology have resulted in the implementation of biochemical systems of increasing complexity within either living cells or DNA-free vesicles. For instance, oscillators, toggle switches, logic gates, band pass filters, and analog circuits have been designed and implemented in living cells, while digital circuits, neural networks, and switchable memories have been demonstrated in cell-free systems. In these developments, computer-aided design, simulation, verification and robustness analysis, are crucial steps before any implementation with either real enzymes or DNA.

One major difficulty in this enterprise of deciphering the biochemical interaction networks is the importance of analog computation in the cell. While gene activation can be well approximated by all-or-nothing Boolean transitions, this is not the case for many activation of protein complexes and the...
The time taken by these transformations is important for many signalling and control tasks. Recent results in the theory of computability over the reals, and the algorithmic complexity of analog computation, provide novel concepts to speak of the algorithmic complexity of natural biochemical reaction systems and compare it to engineered circuits. Along these lines, we have started the implementation, in Biocham, of a biochemical compiler which takes as input a specification of the input-output relation, given by a mathematical function, polynomial differential equation or mixed analog digital programs, and generates a set of elementary reactions that implement the specification. Our first experiments on the MAPK signaling network and its specification by sigmoid functions show a better computational complexity for the natural MAPK circuit than our compiler-generated reaction systems.

The purpose of this thesis is to investigate the specifications of natural circuits in the cell by mathematical functions and mixed analog-digital programs, compare the complexity and robustness of natural and synthesized circuits, and improve the principles of reaction code generation in our compiler. In course, we expect fundamental advances on the theory of biochemical programming, on our understanding of the cell biochemical machinery and on the design of artificial biosensors.

The Thesis will be done in the context of the ANR-MOST project BIOPSY with our partners at Sys2Diag Lab, Montpellier, and NTU, Taiwan.

Job offer description:

The doctoral project will consist in making advances in the following topics:
- Formal specifications of the input/output function of natural biochemical circuits for cell signaling, cell cycle, regulation, decision making
- Theory of biochemical programming, robustness and computational complexity
- Principles of compilation of mixed analog-digital programs in reaction systems (in interaction with NTU, Taiwan)
- Design of artificial biosensors in microfluidic vesicles (in interaction with Sys2diag, Montpellier).

Skills and profile:

The applicant should have a very strong background in fundamental computer science and differential analysis, together with a real interest for cell biology and the idea of programming with enzymatic reactions.

Benefits:
- Immersion in a cutting edge research team in computational systems biology;
- Wonderful environment of Inria project-teams and CNRS groups in Computer Science and Applied Mathematics within Alan Turing building;
- Canteen of Ecole Polytechnique;
- Sports equipment of Ecole Polytechnique;
- Transport reimbursement.

Additional information:

Security and Defense procedure:
In the interests of protecting its scientific and technological assets, Inria is a restricted-access establishment. Consequently, it observes special regulations for welcoming foreign visitors from outside of the Schengen area. The final acceptance of each candidate thus depends on applying this security and defense procedure.

**Duration of the contract:** 36 months from October 1st 2017

**Salary:**

**Contact(s):** François Fages