Title of the project

Symbolic and continuous approaches to study attractors and their dynamics during tissue homeostasis destabilization at the root of tumorigenesis

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Lead supervisor: **Belaïd Benhamou** (laboratoire LIS, équipe LIRICA)
LIS participant: Amine Hamri (laboratoire LIS, équipe MOFED)
LIS participant: Mohammed Zerrougui (laboratoire LIS, équipe équipe PECASE)
Co-supervisor: **Flavio Maina** (Institut IBDM, équipe Signalisation dans les cellules souches et tumorales)
INP participant: Philippe Benech (Institut INP, équipe BHE et Neuroinflammation)

Abstract (10 lines)
We apply approaches from the field of artificial intelligence (Answer Set Programming) to represent gene networks, model gene regulatory circuits, and study their dynamics. We explore the reachability of states and attractors, calculating their forces and robustness, to predict stability of biological states versus preferences of their evolution. These approaches allow interrogating biological and molecular events at the root of diseases, to uncover the influence of multi-factorial events, some of which act as strong attractors in tissue perturbation while others play no or limited attraction effects. We will explore reachability of states and attractors, their robustness and dynamics, operating during tissue homeostasis destabilization. We will apply symbolic and continuous approaches on available transcriptomics data from mouse models faithfully recapitulating: 1) healthy tissues, 2) sensitized tissues towards neoplasia, 3) preneoplastic lesions. The uniqueness of these data relay on their power to reflect spontaneous events at the root of tumorigenesis, matching with those occurring in human diseases.

Keywords: Artificial Intelligence, Answer Set programming, Non-monotonic reasoning, Gene and regulatory networks, Reachability and attractor detection in gene networks, mouse models of tissue homeostasis alterations, Transcriptomics.

Objectives (5 lines)

Aim 1) Use AI approaches to deal with state reachability, then focus on the identification of attractors at distinct phases of tissue destabilisation and quantify potency.
Aim 2) Compare attractors operating during spontaneous homeostasis perturbation in two distinct tissues (liver and breast) to identify robustness and specificity.
Aim 3) Experimentally validate identified attractors and their potency in vivo using a CRISPR-based genetic screen.

Expected profile (5 lines)
The candidate should have strong knowledge on the field of Answer Set Programming in logic programming. He should also master constraint programming (SAT Solvers) and Integer Linear Programming (ILP or MILP) in combinatorial optimization. Knowledge of Boolean networks used in bioinformatics to model biological systems, and to bioinformatically process transcriptomic data is desirable. An interdisciplinary experience previously acquired during trainings will be particularly considered. Knowledge on biology are desirable.

Is this project the continuation of an existing project or an entirely new one? This is an entirely new collaborative project, defined mainly between Benhamou and Maina teams and other teams (MOFED, PECASE, INP) as potential participants. This project is based on our mutual interest to study attractors through artificial intelligence and mathematical modelling approaches in biological events operating at the root of human diseases like cancer, exploiting the uniqueness of mouse models generated by Maina team. These models have been used by Maina team to performed several -omics studies, illustrating how they faithfully recapitulate molecular and biological events occurring as well in human patients. Additionally, these screen approaches have been essential to highlight new mechanisms and new signalling components, as exemplify by recent publications. While the proposal is based on transcriptomic outcomes from RNA-seq analyses (using liver or mammary gland tissue and tumours), the proposal will further benefit of ongoing single cell RNA-seq studies aimed at uncovering early events during tissue destabilisation and preneoplastic formations.

In the case of an existing project, please explain the links between the two projects (5 lines)

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2 to 5 references related to the project

- Thomas, René, and Richard d'Ari. Biological feedback. CRC press, 1990.

- De Jong, Hidde. *Modeling and simulation of genetic regulatory systems: a literature review*. **Journal of computational biology** 9, no. 1 (2002): 67-103.

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- Fan Y., Bazai S.K., Daian F., Arechederra M., Richelme S., Temiz N.A., Yim A., Habermann B.H., Dono R., Largaespada D.A., Maina F. *Evaluating the landscape of gene cooperativity with RTKs in liver tumorigenesis.* **J. of Hepatology,** 70(3): 470-482 (2019). PMID: 30529386.

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3 main publications from each PI over the last 5 years

B. Benhamou:

- Tarek Khaled and Belaid Benhamou. *An ASP-based Approach for Boolean Networks Representation and Attractor Detection*. **23nd International Conference on Logic for Programming, Artificial Intelligence and Reasoning** (LPAR-23), pages 317-333, 2020 (https://doi.org/10.29007/fb4f)

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- M. Touat, S. Bouzidi-Hassini, F. Benbouzid-Si Tayeb, B. Benhamou. *A hybridization of genetic algorithms and fuzzy logic for the single-machine scheduling with flexible maintenance problem under human resource constraints*. **Journal of Applied Soft Computing** 59: 556-573 (2017).

F. Maina:

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- Lamballe F., Ahmad F., Vinik Y., Castellanet O., Daian F., Müller A.K., Köhler U.A., Bailly A.L., Josselin E., Castellano R. Cayrou C., Charafe-Jauffret E., Mills G.B., Géli V., Borg J.P., Lev S., Maina F. *Modeling Heterogeneity of Triple-Negative Breast Cancer Uncovers a Novel Combinatorial Treatment Overcoming Primary Drug Resistance.* **Advanced Science,** Dec 16;8(3):2003049 (2020). PMID: 33552868.

- Cassol F., Portal L., Richelme S., Dupont M., Boursier Y., Arechederra M., Auphan-Anezin N., Chasson L., Laprie C., Fernandez S., Balasse L., Lamballe F., Dono R., Guillet B., Lawrence T., Morel C.*, Maina F*. *Tracking dynamics of spontaneous tumours in mice using Photon Counting Computed Tomography.* **iScience,** Nov 22;21:68-83 (2019). PMID: 31655257.