Master 2 Internship in Systems Biology –6 months from January 2018 in Paris

Investigation and Computer Modelling of Cell Dynamics: Establishing a workflow from the quantification to the simulation of lymphocyte dynamics in physiology and immunotherapies

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The project is designed for 2 students, a biologist and a computer scientist.
Each part can be developed independently but a coordinated interdisciplinary collaboration between the students will improve the system biology approach.

-Master 2 in biology: *A biologist/immunologist to produce and analyse new biological data, while developing in parallel competencies in flow cytometry, cell culture and in vivo mouse model analysis.*

-Master 2 in computer science/modelling/simulation: *A computer scientist to develop an integrated and automatized computer workflow from existing data and codes and to develop an interface, usable by biologists, to run simulations and to fit models to experimental data.*

Cell proliferation and cell mortality are common features of all living systems and their analysis is of considerable importance in physiopathology. Quantitative analysis of cell population dynamics can prove valuable in multiple biological and medical fields, such as immunology, stem cell biology or oncology. However, proliferating cell populations are complex ecosystems in which quiescent, cycling, and dead cells of different generations and of different cell types coexist with emergence of a global population behaviour. Therefore, quantification of cell population dynamics is an arduous task. Indeed, our immune system insures at a global level the maintenance of body integrity on the basis of a continuous adaptive production and turnover of diversified lymphocytes at lower scales. This involves processes of differentiation, proliferation, selection, death and migration of lymphocyte populations to peripheral tissues, where clonal expansion/contraction also occurs upon antigen recognition during evolutive immune responses that occur during natural infection, autoimmunity or vaccinations.
Quantification of cell proliferation dynamics requires specific experimental methods to investigate cell dynamics from *in vivo* to *in vitro* approaches and requires mathematical and computer modelling (1, 2). We have recently demonstrated from *in vivo* approaches, investigating the active labelling of dividing cells in mice with EdU, that T cell proliferation is heterogeneous, constrained by genetic influences, declines with age, and is specific to cell differentiation stage, evolving from early thymocytes to mature lymphocyte in the spleen, revealing the multi-scale sensibility of cell proliferation. Specific "signatures" of cell proliferation reveal the state and dynamic biomarkers of individuals, tissues and cell populations, allowing to cluster them (3).
We have also designed an innovative approach for in-depth analysis of cell population dynamics that can be applied ex vivo or in vitro, allowing further potential investigations in humans. "Cell-state transition tracking" allows for single cell multi-parameter flow cytometry analysis, quantification of live and dead cell numbers, quiescent and cycling cell proportions (based on nuclear antigen expression and on DNA content) and of cell generation number (based on fluorescent dye dilution), throughout time. Then, parameter values describing cell population dynamics such as transition rates between G0, G1, S, G2/M cell cycle phases, death, leading to quantitative estimation of cell phase

durations, proliferation and death rates, are estimated with a mathematical model comprehensible by biologists: The ODE model is conceptualized and made understandable by means of a UML state-transition diagram (4). We have demonstrated the feasibility and the efficiency of our method for the quantification of dynamics of heterogeneous populations of primary lymphocytes such as CD4 helper, CD4 regulatory, and CD8 T lymphocytes in vitro, after various culture conditions (5). Our estimates of proliferation and death rates and mean cell cycle phase duration between the lymphocyte lineages and subpopulations and the simulation of population proliferation with agent based model may prove useful in various biological and biomedical fields where precise and standardized quantification of cell population dynamics is of importance, such as in immunology, haematology and oncology and for tracking cell state transition in humans during physiology, pathologies or treatments that affect cell dynamics.

On the basis of these earlier developments as proof of concept, the two master projects will share inter-disciplinary complementary approaches displayed in our collaborative consortium. The project involve (i) A biologist/immunologist to produce and analyse new biological data from *in vivo*, *ex vivo* and *in vitro* experimental design to quantify lymphocyte proliferation from mice (young/aged mice, diabetic mice) and from human donor samples, using multi-parameter flow cytometry single cell analysis for quantifying cell populations according to their phenotype and dynamics. (ii) A computer scientist to provide an automatized computer workflow, integrating the experimental data as input of variables to run the codes (currently in R, Python, Mathematica) of mathematical/computer models, up to the output of parameter value estimates. Various fitting methods (annealing, resolution of equations, evolutive algorithms) should also be tested as proposed by our mathematicians/computer scientist collaborators. The integration of this workflow and interface will be helped by the use of the OpenMole platform[1] designed by ISC-PIF, to integrate heterogeneous codes, up to parallel processing of the simulations and the use of the Easea platform[2] at Unistra to implement evolutionary algorithms and parallel computing.

The two master projects will be coordinated and co-supervised by immunologists, mathematicians and computer scientists and should allow to draw and test a new platform usable by biologists to quantify and model cell proliferative rules of lymphocytes allowing to extension of these protocols from physiology or perturbations (6), vaccination (7), (8) up to diagnostic and therapies.

Related publications

1. Thomas-Vaslin V, Six A, Bellier B, Klatzmann D. Lymphocyte Dynamics and Repertoires, Biological Methods. In: Dubitzky W, Wolkenhauer O, Cho K-H, Yokota H, editors. Encyclopedia of Systems Biology: Springer New York; 2013. p. 1145-9.
2. Thomas-Vaslin V, Six A, Bellier B, Klatzmann D. Lymphocyte Dynamics and Repertoires, Modeling. In: Dubitzky W, Wolkenhauer O, Cho K-H, Yokota H, editors. Encyclopedia of Systems Biology. New York, NY: Springer New York; 2013. p. 1149-52.
3. Vibert J, Thomas-Vaslin V. Modelling T Cell Proliferation: Dynamics Heterogeneity, Depending on Cell Differentiation, Age, and Genetic Background. PLos Comput Biol 2017;13 (3):e1005417.
4. Thomas-Vaslin V, Six A, Ganascia JG, Bersini H. Dynamical and Mechanistic Reconstructive Approaches of T Lymphocyte Dynamics: Using Visual Modeling Languages to Bridge the Gap between Immunologists, Theoreticians, and Programmers. Front Immunol. 2013;4:300.
5. Loap P, Pascalie J, Witten TM, Bersini H, Thomas-Vaslin V. Cell-State Transition Tracking : Multi-Parameter Flow Cytometry and Modelling for Lymphocyte Population Dynamics Quantification. in preparation.
6. Thomas-Vaslin V, Altes HK, de Boer RJ, Klatzmann D. Comprehensive assessment and mathematical modeling of T cell population dynamics and homeostasis. J Immunol. 2008;180(4):2240-50.
7. Bellier B, Thomas-Vaslin V, Saron MF, Klatzmann D. Turning immunological memory into amnesia by depletion of dividing T cells. Proc Natl Acad Sci U S A. 2003;100(25):15017-22.
8. Six A, Bellier B, Thomas-Vaslin V, Klatzmann D. Systems biology in vaccine design. Microb Biotechnol. 2012;5(2):295-304.

[1] https://www.openmole.org/ https://iscpif.fr/

[2] http://easea.unistra.fr/index.php/EASEA_platform

French description:

https://iscpif.fr/2017/07/stage-de-master-2-en-immunologie-annee-2017-2018-duree-6-mois/

https://iscpif.fr/2017/07/stage-de-master-2-bio-informatique-et-modelisation-annee-2017-2018-duree-6-mois/