MODELING T CELL ACTIVATION MECHANISMS TO ELUCIDATE THE PROCESSING OF DYNAMIC STIMULI

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Abstract (10 lines)*

T cells decode the dynamic features of stimuli, such as frequency and duration, to determine activation outcomes. *In vivo*, transient and sequential interactions with antigen-presenting cells trigger T cell receptor (TCR) signaling. The dynamics of these interactions influence the activation outcome through unknow mechanisms. Our project combines precise optogenetic control of TCR stimulation with advanced mathematical modeling. By varying the duration and frequency of TCR stimulation, we will provide a comprehensive characterization the T cell responses at the signaling and transcriptional levels. These data will be confronted to an integrated mathematical model of the TCR signaling cascade and downstream transcriptional network. An iterative experimental-computational approach will allow the identification of key mechanisms that govern the decoding of stimulation dynamics by T cells.

Keywords*

T cell, optogenetics, dynamic biological processes, signaling pathways, transcriptional networks, mathematical modeling, logical formalism, discrete time formalism

Scientific question and Objectives (10 lines)*

In addition to intensity, the dynamic features of a stimulus (frequency, duration) constitute a layer of information that is decoded by cells and translated into specific outcomes. In vivo, T cells activation is initiated through transient and sequential interactions with different APCs. At each interaction, signaling through the TCR is triggered and T cells appear to be able to integrate signals perceived during discontinuous TCR stimulation events, whose dynamics is reported to influence the outcome of T cell activation. The mechanisms by which T cells integrate and interpret the dynamic properties of stimuli remain poorly understood. This project aims to address this fundamental issue by combining a comprehensive analysis of T cell responses to the dynamics of TCR triggering, with advanced mathematical modeling. The goal is to identify the key signaling nodes and mechanisms that enable T cells to decode the information conveyed by the dynamic properties of these stimuli.

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Proposed approach (experimental / theoretical / computational) and research plan (20 lines)*

Deciphering how cells respond to dynamic stimulation requires precise temporal control of the stimulation process. We have recently developed an innovative optogenetic technology, LiTE (Light-induced T cell Engager), which enables precise spatiotemporal control of TCR (T cell receptor) triggering in primary T cells. Using this technology, we will apply a broad range of TCR stimulation modalities, varying in duration and frequency, to comprehensively characterize T cell responses both at the signaling level and at the transcriptional level (coll with Drs. Milpied and Roncagalli at the CIML). We hypothesize that signal integration occurs: i) at the signaling level: Biochemical reaction kinetics, feedback loops, and activation thresholds introduce specific temporal delays that shape TCR signaling in response to stimulation dynamics; and ii) at the transcriptional level: The timing and coordination of the activity of key transcription factors influence the transcriptional program of T cells.
To test these hypotheses and to identify critical signaling nodes, we will use advanced mathematical modeling approaches. Specifically, we will develop two models: one that captures TCR signaling from the TCR to transcription factor activation, and another that links transcription factor activity to the resulting transcriptome. First, using the logical modeling approach, a comprehensive model will be developed, encompassing the relevant signaling effectors and transcriptional network. Analyses of this model will seek to characterize the relationship between model states during TCR engagement phases (triggering or release), and the associated cell activation outcomes. Core modules (signaling nodes) responsible for this behavior will then be abstracted to define a quantitative dynamical model relying on discrete time modeling, with the intend to better assess delay ranges of TCR activation associated to activation modulation.
Using LiTE-driven TCR triggering, we will Iteratively refine these models through a back-and-forth experimental and computational approach, allowing robust validation and implementation of the insights they provide.

Interdisciplinarity and Implication of the two labs (15 lines)*

This highly interdisciplinary project combines advanced biological techniques with mathematical modeling to unravel the mechanisms of signal integration in T cells and identify the key signaling nodes involved.
The R. Lasserre group in the ATI team at the CRCM will be responsible for generating the biological data sets needed to build and refine the numerical models. R. Lasserre will play an active role in the design of the models, ensuring that they are consistent with biological observations and the current understanding of T cell activation mechanisms. He will also supervise the PhD student in all biological aspects of the project.
C. Chaouiya from the MaBioS team at the I2M will be responsible for building and analysing the logical model of the TCR signaling pathways and downstream transcriptional network. S. Jaeger, head of the CB2M at CIML, is theorical physicist specialized in dynamical modeling. He will be responsible for the analysis of the transcriptomic and phospho-proteomic data generated in R. Lasserre's group, in addition to the establishment and analysis of the discrete time model. The PhD student will receive strong support from the team's biologists for the biological aspects, he/she will also be directly involved in the generation of biological data (the "wet lab" work), giving him/her hands-on experience in the experimental side of the research. The mathematical modeling work will be mainly developed in the I2M team, in close collaboration with S. Jaeger, both being located at Luminy.

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Specify with whom the person recruited will collaborate and on what aspects *

The PhD student will work closely with R. Lasserre and his team on the biological aspects of the project. For the mathematical modeling, which is the main component of this project, the student will be supervised by C. Chaouiya and S. Jaeger. This collaborative framework ensures comprehensive expertise in both the biological and mathematical/computational dimensions of the research program.

PhD student's expected profile*

We are seeking a PhD candidate with strong expertise in mathematical and computational methods for model development, complemented by a solid understanding of cell biology. The ideal candidate will have excellent teamwork skills and the ability to collaborate effectively with colleagues across disciplines.

Is this project the continuation of an existing project or an entirely new one?

This project builds on previous research that developed the LiTE technology and demonstrated the critical role of TCR stimulation dynamics in shaping T cell activation outcomes. The acquisition of the experimental dataset required for this PhD research program is supported by an ANR grant.

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

This new PhD project will develop numerical approaches to improve the interpretation of the results of the biological study. It will also allow the formulation of new hypotheses on the molecular mechanisms underlying the integration of TCR triggering dynamics, which will be tested experimentally in the group of R. Lasserre.

Two to five references related to the project*

- **Encoding and decoding cellular information through signaling dynamics.** Jeremy E Purvis, Galit Lahav. Cell 2013 Feb 28;152(5):945-56.
doi: 10.1016/j.cell.2013.02.005.

- **Light-inducible T cell engagers trigger, tune and shape the activation of primary T cells.** Morgane Jaeger, Amandine Anastasio, Léa Chamy, Sophie Brustlein, Renaud Vincentelli, Fabien Durbesson, Julien Gigan, Morgane Thépaut, Rémy Char, Maud Boussand, Mathias Lechelon, Rafael J. Argüello, Didier Marguet, Hai-Tao He, and **Rémi Lasserre**. PNAS; 2023 Sept 18: https://doi.org/10.1073/pnas.2302500120

- **Dynamics of T-helper cell differentiation and plasticity: How have computational models improved our understanding?** Pradyumna Harlapur, Atchuta Srinivas Duddu and Mohit Kumar Jolly. Current Opinion in Systems Biology, 2024, 37:100508. https://doi.org/10.1016/j.coisb.2024.100508

- **Logical modeling and dynamical analysis of cellular networks. Wassim Abou-Jaoudé, Pauline Traynard, Pedro T Monteiro, Julio Saez-Rodriguez, Tomáš Helikar, Denis Thieffry, and Claudine Chaouiya. *Front Genet*, 7:94, 2016. http://dx.doi.org/10.3389/fgene.2016.00094**

*: Mandatory

– **Dynamic causal modelling of immune heterogeneity.** Thomas Parr, Anjali Bhat, Peter Zeidman, Aimee Goel, Alexander J. Billig, Rosalyn Moran & Karl J. Friston. Sci Rep 11, 11400 (2021). https://doi.org/10.1038/s41598-021-91011-x

Two main publications from each PI over the last 5 years*

Rémi Lasserre:

- Light-inducible T cell engagers trigger, tune and shape the activation of primary T cells
Morgane Jaeger, Amandine Anastasio, Léa Chamy, Sophie Brustlein, Renaud Vincentelli, Fabien Durbesson, Julien Gigan, Morgane Thépaut, Rémy Char, Maud Boussand, Mathias Lechelon, Rafael J. Argüello, Didier Marguet, Hai-Tao He, and **Rémi Lasserre**. PNAS; 2023 Sept 18: https://doi.org/10.1073/pnas.2302500120

-Assessment of coupled bilayer–cytoskeleton modelling strategy for red blood cell dynamics in flow. V. Puthumana, P.G. Chen, M. Leonetti[†], **R. Lasserre**[†] and M. Jaeger[†]. [†] co-coresponding. J. Fluid Mech. (2024), vol. 979, A44, doi:10.1017/jfm.2023.1092

Claudine Chaouiya

-Gianluca Selvaggio, Sara Canato, Archana Pawar, Pedro T. Monteiro, Patrícia S. Guerreiro, M. Manuela Brás, Florence Janody, Claudine Chaouiya; Hybrid Epithelial–Mesenchymal Phenotypes Are Controlled by Microenvironmental Factors. *Cancer Res* 1 June 2020; 80 (11): 2407–2420. https://doi.org/10.1158/0008-5472.CAN-19-3147

-Miguel Cacho Teixeira, Romeu Viana, Margarida Palma, Jorge Oliveira, Mónica Galocha, Marta Neves Mota, Diogo Couceiro, Maria Galhardas Pereira, Miguel Antunes, Inês V Costa, Pedro Pais, Carolina Parada, Claudine Chaouiya, Isabel Sá-Correia, Pedro Tiago Monteiro, YEASTRACT+: a portal for the exploitation of global transcription regulation and metabolic model data in yeast biotechnology and pathogenesis, *Nucleic Acids Research*, Volume 51, Issue D1, 6 January 2023, Pages D785–D791, https://doi.org/10.1093/nar/gkac1041

Sébastien Jaeger :

-Pernelle Outters, Sébastien Jaeger, Nancy Zaarour, Pierre Ferrier ; Long-Range Control of V(D)J Recombination & Allelic Exclusion: Modeling Views. Adv Immunol; 2015 Sep 19; 2015:128:363-413. https://doi.org/10.1016/bs.ai.2015.08.002.

-Crinier A, Milpied P, Escalière B, Piperoglou C, Galluso J, Balsamo A, Spinelli L, Cervera-Marzal I, Ebbo M, Girard-Madoux M, Jaeger S, Bollon E, Hamed S, Hardwigsen J, Ugolini S, Vély F, Narni-Mancinelli E, Vivier E. High-Dimensional Single-Cell Analysis Identifies Organ-Specific Signatures and Conserved NK Cell Subsets in Humans and Mice. Immunity. 2018 Nov 20;49(5):971-986.e5.
https://doi.org/10.1016/j.immuni.2018.09.009

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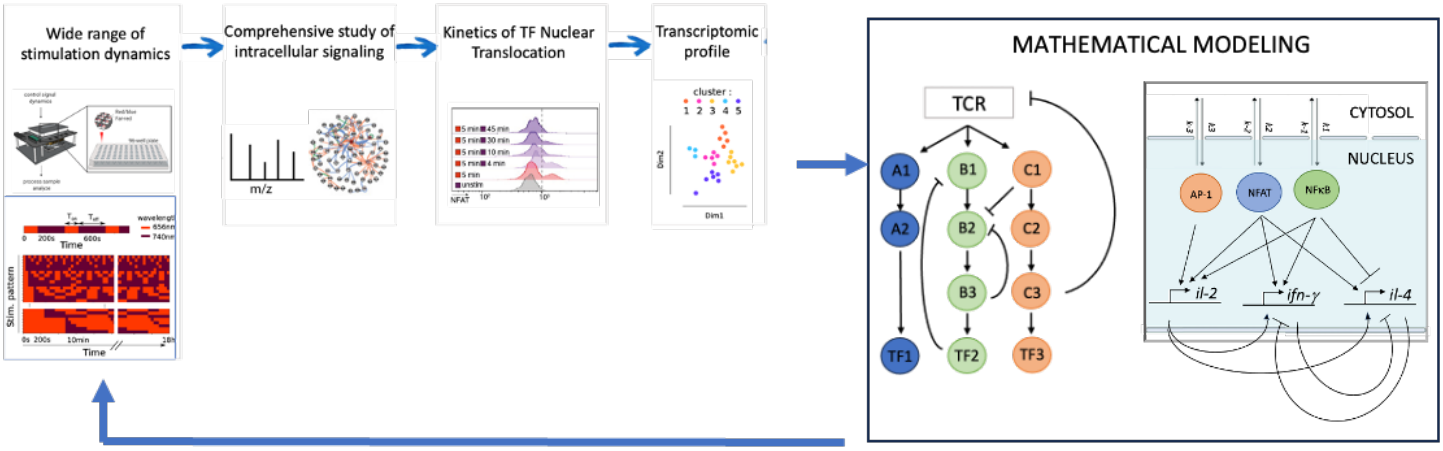
Project's illustrating image



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