PhD PROJECT PROPOSAL

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Multiscale killer-target dynamics in an immunotherapy assay

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Abstract (10 lines)*

Antibody-based immunotherapy holds great promises for fighting cancer, but the understanding of fundamental mechanisms of action of existing or potential drugs is often lacking, therefore limiting broader or more efficient applications. A central challenge is to quantitatively bridge scales between molecular design, cell response and collective multicellular behaviour. Our biophysics team has developed in vitro microscopy assays where human immune cells interact with model surfaces or cancerous target co-cultures. They serve to study the effect of original engagers molecules dedicated to recruit and boost killing activity of immune cells onto cancer targets. Building on a powerful home-made image analysis software, we have been characterizing the interactions from molecular to multicellular scales. We plan now to develop theoretical and numerical approaches to model these dynamic multiscale behaviours. Their deciphering will help designing and optimizing new molecules for maximizing their therapeutic function, while minimizing drug amounts and side effects.

Keywords*
statistical physics; image analysis; predator-prey dynamics; first-passage time; molecular and cellular interactions

Scientific question and Objectives (10 lines)*

Immune cell surveillance relies on transient cell-cell contacts mediated by highly specific molecular bonds. Understanding how molecular recognition develops into cell response and further to global cell population behaviour is posing a formidable scientific challenge. Our strategy to adress this question is to harness molecular engineering to design efficient engagers which can control cell interactions, that we carefully monitor *in vitro*. The goal of the project is to develop statistical methods and image analysis tools in a coherent theoretical framework, in order to analyze and interpret the dynamics of interactions between immune and target cells. A multiscale modelling would encompass the localisation and binding of antibodies, the time and density threshold for cells response as well as the population spatio-temporal dynamics. It will rely on analytical tools, numerical simulations, in close comparison with the experiments analyzed with state-of-the art AI based methods.

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

The main dataset concerns bispecific mediated killing of tumour cell lines by Natural-Killer cells and T lymphocytes recorded in videomicroscopy. Multichannel data provide dynamic information at the cell and subcellular scale on populations of thousands of cells simultaneously (see figure). Higher space-resolution data of synapse formation on mimetic target surfaces are also available. Both datasets will be further extended within an on-going collaborative project lead by L. Limozin and testing new molecular designs. Developed by a former Centuri PhD student, a python package and graphical user interface will be used to perform single-cell analysis for two interacting populations on multimodal time lapse microscopy images (https://github.com/celldetective/celldetective). Adaptation and further development of the software will be expected, in collaboration with the Centuri Multi engineering platform (https://centuri-livingsystems.org/multi-engineering-platform/).

The different tasks of the project will involve: (1) identify a minimal set of parameters to describe natural and antibody-induced behaviour (kinetic parameters, effective interactions, etc.) and infer it from data (2) design numerical simulations using Generalized Langevin Dynamics to test and reproduce experimental data (3) Adapt analysis to new image contents to support biologist expert analysis and be force of proposition for new experimental measurements (4) *propose a functional back and forth pipeline between experiment and theory to accelerate the development of new diagnosis and molecules.*

Interdisciplinarity and Implication of the two labs (15 lines)*
(In this section the collaboration of the two laboratories will be explained in details to explain why the project cannot be conducted by one team alone)

The project is interdisciplinary because original physics and computational tools will be developed to address quantitatively a biological system. Laboratory Adhesion Inflammation will provide the expertise in immunobiophysics approaches and image analysis, as well as a close collaboration with biologists performing the experiments. CINAM will provide the theoretical and numerical expertise to elaborate the statistical analysis and physical modelling. If needed, HPC facility of CINaM will be used to either accelerate image analysis or generate stochastic simulations. The analysis and modelling will be performed hand in hand with new experimental developments as previously experienced by the supervisors. Finally, the system is aimed to provide interesting physics as well as paving the way for more rational and efficient approaches in drug design.

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

The person will collaborate with L. Limozin, an engineer and a PhD student in LAI and with N. Levernier in CINAM.

PhD student's expected profile*

The student will have preferentially a degree in physics or biophysics, ideally with an experience in quantitative biology modelling. Basic knowledge on stochastic processes would be preferable.

A previous experience in using computational methods for image analysis would be appreciated. The candidate should be willing to work closely with experimentalists, both physicists and biologists. The candidate will work in a multidisciplinary and international environment, and will share his/her time between a biophysics lab and a physics institute.

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

The theoretical modelling is a new project and a new collaboration. It is based on the recent experimental developments in LAI, including advanced image analysis (articles in preparation)

Two to five references related to the project*

1. Alieva, M., Wezenaar, A. K. L., Wehrens, E. J. & Rios, A. C. Bridging live-cell imaging and next-generation cancer treatment. Nat Rev Cancer (2023) doi:10.1038/s41568-023-00610-5.
2. Hamilton, P. T., Anholt, B. R. & Nelson, B. H. Tumour immunotherapy: lessons from predator–prey theory. Nat Rev Immunol 22, 765–775 (2022).
3. J. F. Dekkers, M. Alieva, A. Cleven et al. Uncovering the mode of action of engineered T Cells in patient cancer organoids, Nat. Biotechnology (2022).
4. A. Frishman, P. Ronceray, Learning force fields from Stochastic Trajectories, Phys Rev X (2020)
5. G. Aguadé-Gorgorio, A. Anderson, R. Solé, Modeling tumors as complex ecosystems, iScience (2024)

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

1 . R Torro*, B Dìaz-Bello, D El Arawi, K . Dervanova, L Ammer, F. Dupuy, P Chames, K Sengupta, L

*: Mandatory

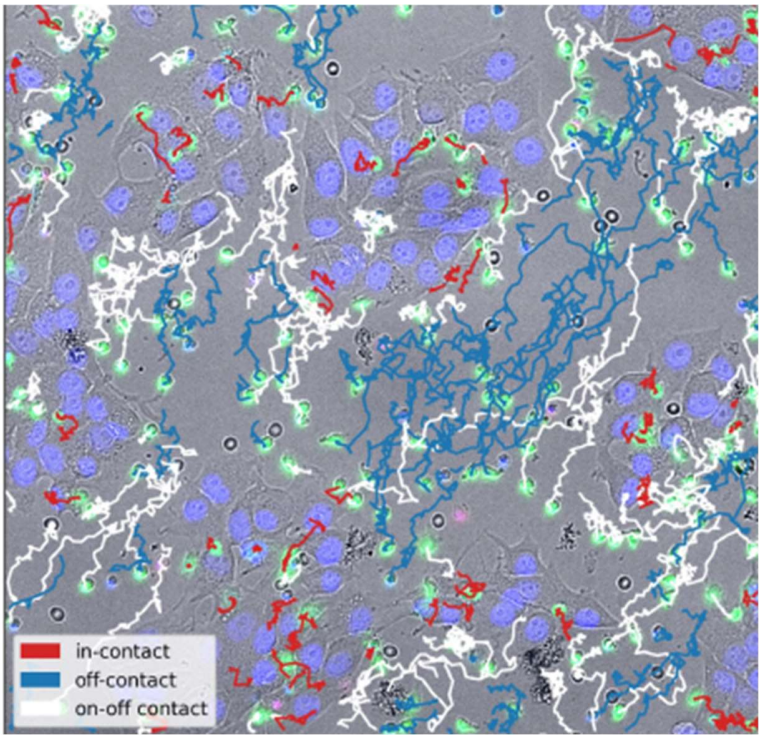
Limozin*. Celldetective: an AI-enhanced image analysis tool for unraveling dynamic cell interactions. Submitted. BiorXiv (2024).

2. C Gonzalez Gutierrez, A Aimard, M Biarnes-Pélicot, B Kerfelec, P-H Puech, P Robert, F Piazza*, P Chames*, L Limozin* . Decoupling individual host response and immune cell engager cytotoxic potency. Accepted to ACS Nano. BiorXiv (2024).

1. N. Levernier, T. Mendès, O. Bénichou, R. Voituriez, T. Guérin, Everlasting impact of initial perturbations on first-passage times of non-Markovian random walks, Nat Comm 13 (2022)

2. N.Levernier, J. Textor, O. Bénichou, T. Guérin, R. Voituriez, Inverse square Levy walks are not optimal search strategies for $d \geq 2$, PRL 124 (2020)

Project's illustrating image



Multitracking of Natural-Killer cells (green cells and colored trajectories) interacting with target cancer cells (nucleii in blue). The trajectory color encodes for NK cells having different contact history with the targets.

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