M2 internship: The physics of T-cell spreading and activation

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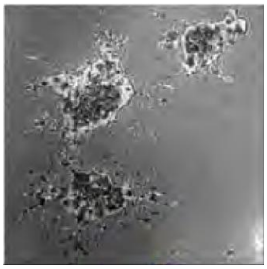
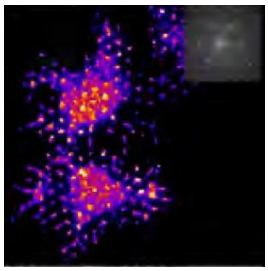
Context and motivation

The adaptive immune system relies on T lymphocytes to detect and eliminate infected or cancerous cells. A T cell recognizes a molecular signal on the surface of another cell and becomes activated, switching on a response program leading to division or target killing. A crucial early step is spreading over the presenting cell to create a broad contact zone [1]. The geometry and mechanics of this spreading strongly influence activation, which in turn feeds back on spreading. Spreading is a hallmark of T-cell activation [2] and can lead to formation of the immune synapse [3]. Three protein families shape this process: recognition receptors (TCR-CD3) that bind the signal, adhesion molecules such as integrins that stabilize contact, and bulky glycocalyx proteins that must be excluded for signaling [4]. These molecules differ not only in function but also in geometry, dynamics, and interaction strength, and their contribution is shaped by the mechanics of the contact, through the forces and constraints generated as cells spread, deform and pull on one another. How these elements combine to link spreading with the all-or-nothing decision of activation remains unclear. Here we will combine tools from statistical physics (nucleation, segregation, phase transitions) and soft matter (fluid-like spreading, wetting analogies) to gain novel insight into the physical coupling between spreading and activation.

This M2 internship is theoretical and funded by the ANR CriticaliTy. It will run in close connection with three experimental PhD projects in the consortium: at LAI Marseille (microscopy and traction force of T-cell spreading), Ecole Polytechnique/LadHyX (mechanical response under controlled forces), and Institut Cochin (extension to B-cell synapses). Regular exchanges will ensure that experimental results directly guide model building. For a motivated student, the internship may lead to a PhD in theoretical biophysics.





Experimental techniques used by project collaborators to characterize the immune synapse. RICM (left) to visualize T-cell spreading and TIRF (right) to visualize receptor distribution [5].

Scientific objectives and methodology

This internship aims to develop a minimal theoretical framework linking early nucleation of TCR-rich domains to the long-time, fluid-like spreading of the T-cell footprint. Key questions include how spreading and activation couple at different timescales, how receptor size and binding energetics control segregation, and which parameters govern transitions from transient contacts to stable synapses. To address these points, we will extend nucleation theory of receptor domains [6] to mixed receptors of different sizes, and treat the spreading phase as a soft-matter problem using analogies with liquid films and active gels [7], coupled to receptor segregation dynamics. Deliverables include scaling laws for contact growth $R(t)$, predicted nucleation thresholds, and segregation phase diagrams, to be compared with experimental data from consortium partners.

Candidate

Physicist or engineer with background in statistical physics, continuum mechanics and/or soft matter. Comfortable with analytical calculations and numerical work. Interest in biology and in interacting with experimental teams.

[1] Sengupta K et al., *Biophys J* 123, 2224 (2024).
[2] Cretel E et al., *J Phys Condens Matter* 22, 194107 (2010).
[3] Jin W et al., *PNAS* 116, 19835 (2019).
[4] Dustin ML & Groves JT, *Annu Rev Biophys* 41, 543 (2012).
[5] Dillard P et al., *Integr Biol* 8, 287 (2016).
[6] Bihr T et al., *Phys Rev Lett* 109, 258101 (2012).
[7] Gonzalez-Rodriguez D et al., *Science* 338, 910 (2012).