Information-Geometric Selection in T-Cell Receptor Cascades: How Noise Shapes Ligand Discrimination

Mario Castro
Instituto de Investigación Tecnológica (IIT), and Grupo Interdisciplinar de Sistemas Complejos (GISC)
Universidad Pontificia Comillas, E28015, Madrid, Spain

T cell recognition requires rapid, precise discrimination of scarce antigens in a noisy environment. To understand why physiological responses peak at specific ligand dwell times and doses, we reframe T cell receptor signaling using a universal model that contains proposed phenotypic models in the literature as particular cases [1] as a physical implementation of Bayesian inference under strict time constraints. Rather than relying on specific kinetic proofreading schemes, we employ a universal unifying model of Lever [2] mechanisms to analyze the stochastic duration of cell-to-cell encounters.

We demonstrate that antigen discrimination is fundamentally governed by the interplay between ligand dwell time, limited signaling windows, and stochastic encounter termination rates. Mutual information between ligand identity and the final signaling state correlate with the encounter timescale matches the receptor's internal decision-making kinetics. Furthermore, our approach shows that signaling architectures featuring an irreversible commitment step act as informational filters. By preventing the accumulation of ambiguous evidence, this mechanism sharply enhances the discrimination between agonists and antagonists. Ultimately, this framework connects stochastic contact dynamics to cellular information processing, explaining how physical time constraints shape the design of immune receptor architectures. Overall the immune system behaves, effectively, as a Bayesian filtering device.

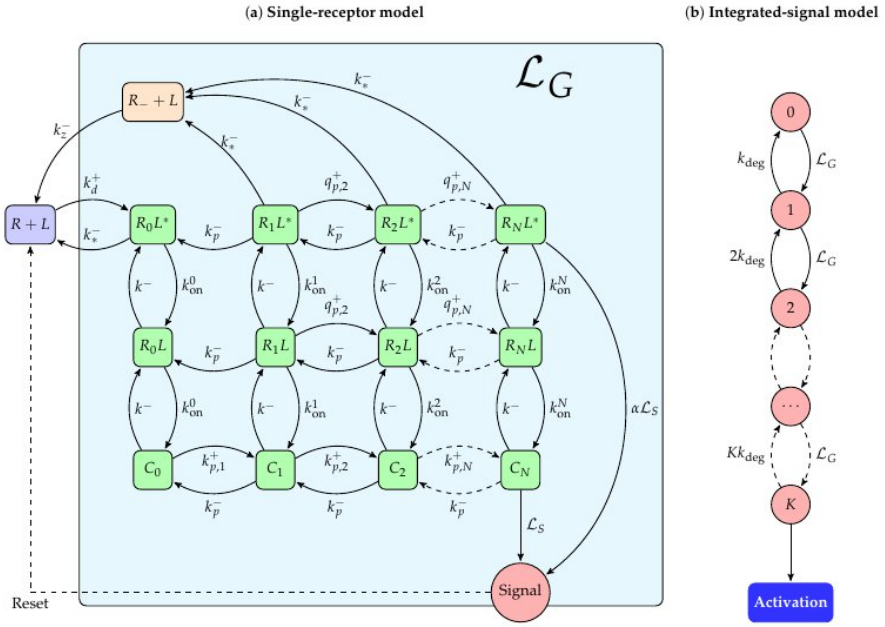

Fig. 1 Universal model of T-cell activation (a) Model states at the single-receptor level. (b) Integrated-signal model: Receptors act independently and each time one is internalized and reached the Signal state (with overall waiting-time distribution summarized in the function $\mathcal{L}_G$), this signal is accumulated or, if time is longenough, degradated at a rate, k_{deg}. Effectively, this mechanism can be understood as a Bayesian filtering machine processing weak signals in a noisy environment, exploiting exquisite differences in kinetic rates [3]

References

[1] J. Gálvez, et al., "Is TCR/pMHC affinity a good estimate of the T-cell response?" Front. Immunol. 10, 349 (2019).
[2] M. Lever, et al., "Phenotypic models of T cell activation," Nat. Rev. Immunol. 14, 619 (2014).
[3] M. García-Sánchez, M. Castro, M., and J. Faro, (2023). B cell receptors and free antibodies have different antigen-binding kinetics. Proceedings of the National Academy of Sciences, 120(35), e2220669120.