Adaptive Sorting Revealed by *In Silico* Evolution

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***Short Abstract* — Many biological networks have to filter out useful information from a vast excess of spurious interactions. We used computational evolution to predict design features of networks processing ligand categorization. The important problem of early immune response is considered as a case-study. Rounds of evolution with different constraints uncover elaborations of the same network motif we name "adaptive sorting". Corresponding network substructures can be identified in current models of immune recognition. Our work draws a deep analogy between immune recognition and biochemical adaptation.**

***Keywords* — Immune recognition, computational evolution, ligand categorization, biochemical adaptation.**

An important instance of cellular information processing is immune recognition by T cells. T cells scan antigen presenting cells (APCs) in their environment, via the binding of their T cell receptors to the presented pMHC ligands. T cells perform a sorting process based on interaction with self (non-agonist) or foreign (agonist) ligands at the surface of APCs: if foreign ligands are detected, then the immune response is triggered. Following the "life-time" dogma [1], one of the main determinants for distinguishing self from foreign is the unbinding time of the pMHC ligand to the TCR. Ligands with up to a critical binding time of $\tau_c \approx 3$ s do not elicit response while foreign ligands bound for a longer time ($\tau_f > \tau_c$) do. Self ligands dissociate rapidly (typically for $\tau_s < 0.1$ s).

The sorting process is sensitive: response is triggered in the presence of minute concentrations of foreign ligands (of the order of 1-10 ligands per cell [2]). Sorting is specific: although foreign (τ_f) and critical ligands (τ_c) have similar binding times, an arbitrary concentration of critical ligands does not elicit response [3]. The idealization of these requirements is schematically shown in Fig. 1. McKeithan [4] proposed that T cells harness the amplifying properties of kinetic proof-reading to solve the recognition problem between few foreign ligands and vastly numerous self ligands. However, this model does not account for sharp thresholding required for sensitivity and specificity as noticed in [3]. Other control structures must exist.

We use computational evolution [5] to address the related "inverse problem" question: how can a network categorize sharply two ligands with similar affinity irrespective of their concentrations?

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Our focus is on the signaling cascade immediately downstream of the receptor ligand complex, as shown in Fig. 1 (a) and (b). We assume that a single species triggers response via a thresholding mechanism. We exhibit networks performing ligand recognition with the help of a new network module that we name "adaptive sorting", which we study analytically. We use extensive evolutionary simulations to show how this solution is improved to solve the related recognition problem of parallel sorting of foreign ligands within a sea of self ligands. Numerical stochastic simulations and linear noise approximations indicate that our results are robust to fluctuations, in spite of the low number of molecules considered. Components of our minimal model can be identified in exhaustive networks responsible for early immune recognition [3,6].

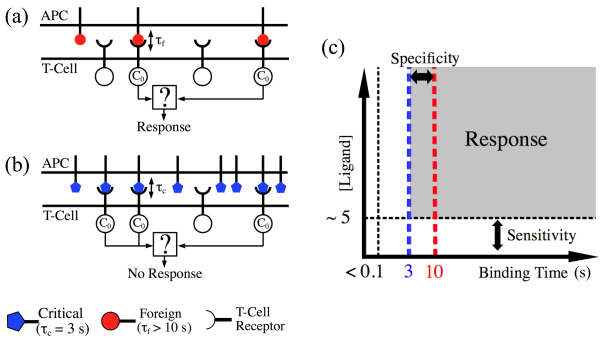

Figure 1. Schematic illustration of the problem setup. (a) Few foreign ligand (τ > 10 s) trigger response. (b) Arbitrary large concentrations of critical agonist (τ_c = 3 s) ligands do not trigger response. (c) Idealization of the number of pMHC ligand required to trigger response as a function of pMHC-TCR binding time.

We expect these principles to have broader relevance for biological recognition systems where specific signals must be extracted from a high number of weak spurious interactions.

References

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