Redesigning the response of T cell signaling networks using *in silico* evolution

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***Short Abstract* — The T cell receptor (TCR) signal transduction pathway allows T cells to activate upon binding molecular signatures of pathogens. To gain insight into the T cell signaling network, we utilize *in silico* evolutionary algorithms to produce a variety of signaling profiles as a function of TCR-antigen binding strength. Repeated, independent *in silico* trials produce a variety of potential solutions for a given target signaling profile, and analysis of the data provides insight into relations between various reaction rates that produce the profile.**

I. Introduction

CELLS have evolved an array of signal transduction pathways that allow them to detect and respond to their environments. T lymphocytes use the T cell receptor (TCR) signal transduction network to identify molecular signatures of pathogens. The pathway exhibits a sharp activation threshold as a function of the binding strength of the TCR with peptide-MHC (pMHC) ligands presented on other cells. Following pMHC binding, the cytoplasmic region of the TCR complex is phosphorylated by a kinase associated with coreceptors that also bind to the pMHC complex [1]. It has been shown that coreceptor-mediated recruitment of the kinase has a dramatic effect on the rate of TCR phosphorylation [2]. TCR phosphorylation is an important early signaling event that results in the recruitment of other proteins that promote downstream signaling.

The TCR network topology is the result of natural evolution. Novel signal transduction network topologies have also been produced through the use of *in silico* evolutionary algorithms (EA) [3-5]. EAs are a class of heuristic optimization techniques that utilize a selective pressure in order to discover a system that produces a desired output. In this work, we consider a fixed-topology network and allow kinetic rates to vary. The parameters are screened by evaluating them with a fitness function that measures the deviation of the actual output from the target output. Parameter sets with improved performance are selected for and then mutated and/or recombined with other desirable parameter sets to produce new networks. This process is repeated until a desired level of fitness is reached [6].

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II. Model and Methods

We consider a deterministic, well-mixed model of the TCR signaling network [2] and utilize an *in silico* evolutionary algorithm to search for sets of kinetic parameters that give a variety of altered output responses as a function of the off rate between pMHC and TCR. With fixed network topology, we allow variation in all reaction rates in the model. The evolutionary algorithm can produce sets of reaction rates that shift the activation threshold typically observed for the TCR network to both higher and lower values of the TCR-pMHC off rate. Interestingly, we find that the TCR signaling network topology can achieve even more dramatic output profiles, such as an inversion of the activation pattern in which weak TCR-pMHC binding achieves activation and strong binding does not.

By running multiple independent instances of the evolutionary algorithm for each desired output, we find many different sets of reaction rates consistent with the desired output. Distinct patterns of solutions become apparent when analyzing the resulting data sets using techniques such as k-means cluster analysis.

III. Conclusion

In silico evolutionary algorithms can be applied to existing biochemical network topologies to produce novel outputs not seen in nature. We demonstrate that through moderate adjustments of kinetic parameters, the TCR signal transduction network has the potential to produce a wide array of input-output relations. Such studies can help to shed insight into T cell signaling and may provide a means for designing artificial networks with desired signaling properties.

References

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