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Design Principles of an Optimal Adaptive Immune System

Short Abstract **— The repertoire of lymphocyte receptors in the adaptive immune system is tailored to collectively provide protection against attacks by diverse pathogens. How should this repertoire adapt to a given pathogenic environment for best protection? Here we propose a theoretical framework for addressing this question in terms of an optimization problem defined on the repertoire as a whole. We then derive features of optimal repertoires. Although the optimization problem is defined at a system-wide level, we show that its solution can be reached through a biologically plausible self-organized population dynamics based on resource competition.**

Keywords **— immunology, mathematical modeling, adaptation, resource competition**

I. Introduction

THE adaptive immune system consists of a large, but limited number of lymphocytes [1,2]. Lymphocyte receptors recognize antigenic peptides by binding. The receptors are specific allowing for a targeted immune response. Specificity is not complete, however, since one receptor is able to bind different antigens, a process known as cross-reactivity. The ensemble of lymphocytes, the immune repertoire, has been widely studied, because it determines immune responses. Reciprocally, the past infection history is known to influence the repertoire composition [3]. The pathogenic environment and the immune repertoire are thus thought to be tightly linked [4]. In this work we investigate this link using mathematical modeling.

II. Model and Methods

We introduce a statistical model of the recognition of pathogens by random encounters of lymphocyte receptors. We make simplifying assumptions about the cross-reactivity of receptors and the frequency distribution of pathogens in the environment. The size of the repertoire is assumed to be fixed, modeling the finite number of lymphocytes. The pathogenic environment is considered to be static. Adaptation is then investigated by analytically and numerically optimizing repertoires to minimize the time to recognition of a pathogen. The time to recognition is chosen as a proxy for the fitness effects of having different immune repertoires. We discuss the influence of different fitness functions on the resulting optimal receptor distribution. Last, we investigate if a biologically plausible lymphocyte population dynamics could allow for optimal adaptation.

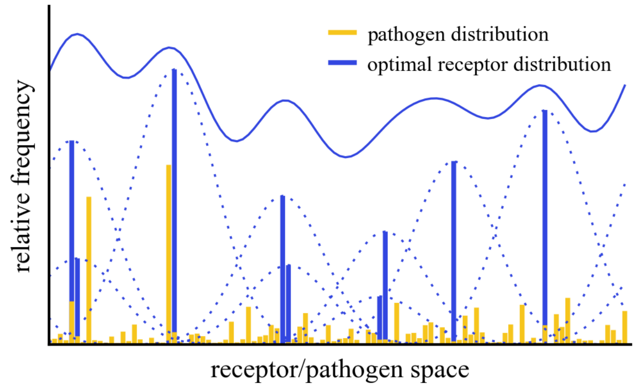

Figure: The optimal distribution of lymphocyte receptors is often found to be highly peaked. As every cross-reactive receptor also detects similar pathogens with some probability (dotted lines) the ensemble of receptors covers the whole pathogen space (solid line).

III. Results and Discussion

We find that recognition is accelerated by biasing the repertoire towards common pathogens. Optimal repertoires often consist of small numbers of distinct receptors (figure). The resource constraint imposed by the limited number of lymphocytes together with cross-reactivity seem to favor this focusing of resources on highly abundant clones. Thanks to cross-reactivity, protection against all pathogens can be maintained with this repertoire of limited diversity. Differences in relative frequencies of pathogens are reflected, yet downplayed in the distribution of receptors. This is due to the need to still detect infrequent pathogens reasonably fast. We describe a population dynamics, in which lymphocytes compete for pathogens, that converges towards the optimal repertoire. The dynamics thus allows the repertoire to self-organize into a state of high protection.

IV. Conclusion

By studying a model of an optimal adaptive immune system we propose three design principles: bias repertoire moderately towards common pathogens, exploit cross-reactivity to focus resources, and let lymphocytes compete for pathogens.

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Acknowledgements: A. Mayer was funded by a DAAD Promos stipend for a part of this work.

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