Effect of random environments on clone size distributions of the immune repertoire

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Short Abstract — The adaptive immune system is an essential part of the pathogen-specific immune response. Its efficiency relies on a balance between diversity and selected potency of cell lineages. Different cell types' (B cells, T cells, naïve, memory) growth is governed by a variety of signals, yet the observed clone sizes follow a universal power law distribution. Using methods from statistical mechanics, we explore biologically relevant mechanisms that could explain the observed distributions. We show that only clone-specific multiplicative noise in a *fast varying environment*, or alternatively *highly heritable* cell specific variability are consistent with data. We express the power law exponent in terms of the biological parameters.

Keywords — immune repertoire diversity, clone size distribution, population dynamics, evolution and selection

I. INTRODUCTION

The adaptive immune response is triggered by the recognition of pathogens via specific receptors on the membrane of B and T cells. Those receptors are key players in the immune response to specific pathogens but also influence the homeostasis of the naïve pool : division and death of naïve cells have been shown to rely on frequent receptor specific short binding events to self proteins [1]. Cytokines also act as growth inducers for clones. The propensity of the cell to bind them is not clone-specific but depends on the inner state and number of cytokine receptor on the membrane. Those features are only partially heritable and their memory is slowly lost over generations.

Receptor sequencing experiments suggest that B and T cell clones (cells sharing a common receptor) have size distributions that share a common "Zipf" behavior : the probability of seeing a given clone size scales as a power law of the size [2,3]. Different signals with different time and response scales generate similar clone distributions. Understanding the mechanism underlying lymphocyte homeostasis and fixing parameter ranges for these processes is a major issue in quantitative immunology.

II. METHODS

We study Langevin equations with a minimum number of parameters to represent the dynamics of a clone. For clonespecific growth factors, we model the dynamics as multiplicative colored noise that integrates different interaction scales (self and pathogenic) or cell level noise to model cytokine binding. Both include relaxation parameters quantifying the speed of variation of the environment, or the heritability of the traits. All clones die in the long run and the out of equilibrium system is maintained at steady state by thymic output, which provides a constant source of new clones. In the Fokker-Planck representation, we solve the models analytically in the limits of fast varying environment or low heritability. Using numerical methods we solve the general equation and simulate more realistic biological systems to check the consistency of the models.



III. RESULTS

We find that multiplicative noise models lead to power laws, valid for a larger range of clone sizes when the environment varies quickly. We show that the inverse of the exponent is the product of the average lifetime of a clone

with the square of the relaxation time of the environment times the typical amplitude of environmental variations. We show that a continuum of lymphocyte stimulation strengths is consistent with realistic simulations and state of the art data. On the other hand cytokine models with a



cell-specific partially heritable fitness give short tail distributions that reduce to a neutral model when heritability is low and to a power law with a cut-off when heritability is high.

IV. CONCLUSIONS

We divide models of repertoire dynamics into two classes : cell-specific and clone-specific noise models. We show that the latter can only explain data if fitness is highly heritable. On the other hand, receptor based growth requires fast varying environments to be consistent.

References

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