Restricted energy dissipation induces glass-like kinetics in high precision responses

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Short Abstract — **Cell signaling events usually occur in the absence of the detailed balance condition and continuously dissipate energy. Consequently, when energy supply is limited, specific chemical modification steps might not occur due to the lack of energy to support those reactions. How does the absence of such modification steps, that are intrinsically stochastic in nature, affect single cell signaling kinetics? I address this question in the context of a kinetic proofreading scheme used in a simple model of early time T cell signaling. I show using exact analytical calculations and numerical simulations that restricting energy dissipation leads to poorer discrimination in single cells for weak and low affinity ligands. Furthermore, restricting energy dissipation produced substantially larger intrinsic cell-to-cell variations of proteins with qualitatively different glass-like signaling kinetics in single cells marked by ergodicity breaking, dynamic facilitation, and, non-exponential waiting time distribution.**

Keywords — **Entropy Production, Kinetic Proofreading, Dynamic Facilitation, Energy Dissipation.**

I. Introduction

Living systems function in noisy environments and yet are capable of generating surprisingly precise responses. These responses are observed in scales ranging from the molecular to single cells to cell populations. A common feature of such high precision responses is involvement of non-equilibrium processes that requires constant supply of energy to execute the responses. How does the limitation in the available energy resources affect these responses? We address this question here in the context of a widely accepted kinetic proofreading mechanism describing ligand discrimination in single cells.

The concept of kinetic proofreading was proposed by Hopfield[1] and Ninio[2] in the 1970s to explain low error-rates in protein translation. This concept was applied to explain the remarkably sensitive antigen discrimination property of immune cells[3] which are able to distinguish between ligands, close enough to produce complexes of half-lives that differ only by few seconds. A key element in a kinetic proofreading scheme is the presence of a biochemical step that resets any activated state of the receptor to the original state. While this step increases sensitivity of the response it also requires a constant supply of energy that is dissipated away to sustain a non-vanishing probability current in the system. Usually intercellular sources or nutrients absorbed from the microenvironment provide sources for generating ATP, e.g., metabolism of glucose in T cells or tumor cells.

The dissipation of energy in systems functioning outside equilibrium can be quantified by the rate of entropy production in the system[4]. The relation between entropy production and sensitivity of responses has been recently investigated in populations of cells[5]. However, the discrimination is executed by individual cells where the involved biochemical processes is subject to stochastic fluctuations arising from the intrinsic random nature of biochemical reactions and cell-to-cell variations of protein abundances. Therefore, the amount of energy dissipated as the cells execute the discrimination program will vary from cell-to-cell and the results obtained by averaging over cell populations are not guaranteed to generalize at the level of single cells.

II. Results and Conclusion

I addressed the above issue by calculating energy dissipation in single cells and study the role of limiting dissipation by imposing boundary conditions in the Master Equation or by simulating the stochastic kinetics using a continuous time Monte Carlo simulation. I specifically investigated two cases: (1) a constant pool of energy is available, (2) energy is produced at a rate lower than the required energy. Limiting dissipation in the kinetic proofreading program changed the kinetics of the response qualitatively marked by slow kinetics, substantially large cell-to-cell variations, and, more importantly, by the presence of dynamic facilitation [6] and ergodicity breaking in single cell kinetics. Emergence of the last property points to a fundamental disconnect between the activation kinetics in single cells and the cell population averages. The results are likely to generalize in a large variety of systems working in non-equilibrium.

References

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