A Queueing Approach to Multisite Enzyme Kinetics

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***Short Abstract* — All biological cells must cope with limited resources. We are becoming increasingly aware of the fundamental importance of finite processing resources that are behind a myriad of tasks, including not only metabolism but also protein production, degradation, and modification. I will discuss the experimental and theoretical development of a biological queueing theory, which fundamentally assumes limited processing resources. In particular, I will describe developments in multisite enzyme theory, where a low latency "waiting line" of substrate to an enzyme's catalytic core can continue to collect substrate even when the catalytic core is occupied.**

***Keywords* — synthetic biology, queueing, protease, SspB**

I. Introduction

QUEUEING theory, which treats the routing of individual "customers" between different "stations" of "servers," was historically developed to establish a mathematical understanding of telecommunication networks and service centers [1]. A major strength of queueing theory is that it incorporates foundationally the discrete and stochastic nature of many real world processing networks, while also including equally important concepts such as the priority of customers. The enormous utility of queueing theory in a variety of disciplines is evident by the immense collection of associated literature that has been and continues to be generated on rigorous and applied queueing theory research.

Recently, the value of queueing theory in the context of biological systems has been established by a number of researchers. The rationale behind this trend is that every catalyzed reaction within the cell necessarily has finite bandwidth imposed on the reaction velocity, due to either limited catalyst or limited reactants. Truly, the study of finite bandwidth enzyme kinetics is itself not new and has a long history, with early representative works being that of Michaelis and Menten [2] and Monod [3], and more recent works in this field extending the discussion to discrete and stochastic systems [4]. The value that a biological queueing theory adds to these existing works is manifold, such as providing powerful quantitative tools in the situation where multiple substrate "classes" (with generally different affinities) compete for common processing.

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II. Multisite Enzyme Kinetics

In this talk, we extend a prior investigation of ClpXP proteolytic kinetics [5]. ClpXP is a well-studied protease in E. coli that is responsible for degrading mistranslated proteins and (in healthy conditions) certain stress response factors. ClpXP's function is greatly enhanced by the presence of multiple binding sites for substrate via interaction with a molecular chaperone, SspB. Absence or dysfunction of the SspB molecule is strongly associated with reduced substrate affinity, since SspB bound to ClpX binding sites forms a "waiting line" of substrate for the ClpXP catalytic core, thus preventing the catalytic core of ClpXP from being unoccupied by substrate for any appreciable duration of time.

An appropriate queueing analogy for a single ClpXP molecule is then a server (catalytic core) that selects customers (protein substrate) at random from a finite capacity waiting line (SspB-substrate complex associated with ClpX binding sites) and processes (degrades) the customers (substrate). In this talk, we analyze this model in some detail, and we argue that the multisite nature of the enzyme drives the model into a regime well-approximated by traditional queueing models [6]. It is also worth mentioning that this investigation of multisite enzyme kinetics is multiclass, i.e. exactly treating the dynamics of multiple types of substrate competing for the same enzyme. This analysis is assisted by a new result, independent departure symmetry, which generalizes results originally derived for quasireversible queues. These multiclass results rely on the assumption that different classes of substrate are distinguishable but otherwise identical, but we will comment on why we anticipate that our results are not particularly sensitive to weakly breaking this assumption.

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