Multi-Protease Queueing

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***Short Abstract* — Cells depend on proteases to prevent the harmful accumulation of extraneous proteins and their unstable constituents, though degradation resources such as proteases are often limited. We employ queueing theory, a mathematical formalism describing systems of servers and customers, in characterizing the behavior of a multi-protease, multi-protein system, explicitly assuming limited degradation resources. We find that despite strong enzymatic preference of substrates, a correlation resonance phenomenon previously observed in single enzyme systems is also observed in some regimes. This may play a key role in scalability of synthetic systems where orthogonality of degradation pathways is often not plausible.**

Keywords — **synthetic biology, queueing theory, multi-protease, coupled degradation, correlation resonance**

I. Introduction

Queueing theory is a mathematical formalism first used to describe telecommunication networks where finite processing resources naturally lead to bottlenecks and waiting lines [1]. It typically employs both discrete and stochastic methods to effectively model the traffic of general server networks. This makes queueing theory a natural language for describing biochemical networks where resources are often limited, and where low copy number effects and natural noise play important roles in chemical processing.

Queueing theory has successfully characterized several biological systems in the past, in particular for systems involving enzyme kinetics [2,3]. In systems where enzymatic processing resources are limited, queueing theory predicts several regimes that systems may occupy. These regimes depict drastically different behaviors, each of which is relevant in cellular processing. For instance, it has been shown that the buildup of sigma factors consequent of enzymatic overload increases the expression of housekeeping genes, which help the cell cope with an unforgiving environment. This overload occurs as stress in the environment such as nutritional starvation causes misfolded or partially constructed proteins to accumulate. Thus the cell uses a bottleneck in degradation processing to trigger a stress response within the cell, which aids in coping with environmental stress. Such mechanisms would be essential in the construction of robust synthetic systems.

II. Multienzyme, multisubstrate kinetics

While many proteins, or protein constituents, exhibit strong enzymatic preference in the form of non-equal affinities for a host of enzymes found in cells, there are often multiple enzymes capable of degrading any one substrate. Queueing theory predicts that as resources such as enzymes become limited, substrates may more readily be degraded by other enzymes for which they have a relatively low affinity. Understanding how secondary degradation pathways affect a system experiencing a bottleneck in processing is likely essential in designing synthetic systems effectively. Many such systems would require components not to interact with one another to attain scalability. On the other hand, having a set of components that behaves in several fundamentally different ways based on some set of environmental controls could become a key design principle for efficient synthetic circuits.

III. Conclusion

It has been shown that the sharing of processing resources alone is sufficient to couple otherwise non-interacting subsystems operating within cells. Such coupling can drastically change the way a system evolves. For instance, in the context of a single enzyme that degrades two substrates, it has been shown that as the total rate of production of substrates approaches the degradation rate of the enzyme, coupling of substrate counts results in a phenomenon known as correlation resonance. Such coupling may also become an essential design principle for flexible, multi-functional circuits. As limitations on processing resources is a ubiquitous problem faced by organisms, a biological perspective rooted in queueing theory should have a wide range of applicability to different systems.

IV. References

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