Specificity and First Passage Times of Common Biochemical Processes

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***Short Abstract* — Biological processes usually involve huge number of individual steps, each with its own dynamical rate constants. For example kinetic proofreading [1] requires many steps to achieve high specificity. In this work we study the properties of first passage (completion) times of the kinetic proofreading scheme as well as the specificity achieved by it. We fully characterize the completion time distribution and provide explicit expressions for the mean and the variance of the completion time. We find that for a wide range of parameters, as the system size grows, the character of the escape time simplifies: it becomes either exponentially distributed or deterministic with very narrow transition between the two regimes. In both regimes dynamics of input-output process through the system is trivial compared to the system complexity. The qualitative explanation of this behavior suggests that similar simplicity will arise in the dynamics of other, more complicated, biochemical processes. In addition we show that there is a non-trivial interplay between the completion time and the specificity of the process.**

***Keywords* — kinetic proofreading, completion time.**

Considering the ever increasing quantity of known biochemical reactions, one cannot help but be amazed and daunted by the incredible complexity of the implied cellular networks. For example, just a handful of different proteins can form a large number of interacting molecular species, such as in the case of immune signaling [2], where multiple receptor modification sites result in a model with 354 distinct chemical species. The natural questions are: When do all details of this incomprehensible complexity actually matter, and when is there a smaller set of coarse-grained dynamical variables and parameters that approximate the salient features of the system's dynamics? And if the networks have a simple equivalent dynamics, did nature choose to make them so complex in order to fulfill a specific biological function? Or alternatively, does the unnecessary complexity provide a ``fossil network" which may reveal some information about the system's evolutionary heritage?

In this work, we begin investigation of these questions in the context of specific biochemical kinetic network, namely a general kinetic proofreading scheme. In particular the dynamics of molecules with different proofreading/backward rates is treated as a kinetic process with multiple pathways between the initial point and the final state. The analytical solution of the equations describing the dynamics of the system leads to the full description of the system, namely we obtain both the specificity and the distribution of completion times. The interplay between the completion time and the specification of the process is non-trivial.

We find that over a broad range of parameters, the kinetic proofreading schemes exhibit the behavior of either a deterministic or a single–step exponential –waiting-time process. We provide an intuitive argument for the result, which leads us to believe that similar simplifications of complex behavior may appear for other kinetic diagrams. We also show that two simplified versions of the general kinetic proofreading, the directed kinetic proofreading and a random walk yield higher specificity for different regimes of the parameters. The fact that the KPR process, as well as many others, has such simple limiting behaviors has important consequences for the modeling of biochemical systems. The bad news is that it is unreasonable to hope to characterize individual molecular reactions with observations of the input-to-output responses many different internal organizations will result in equivalent observable behaviors. The good news is that, when attempting to understand such processes in a wider cellular context, it is often unnecessary to explicitly treat every individual step; a coarse-grained model with only a handful of parameters may be sufficient.

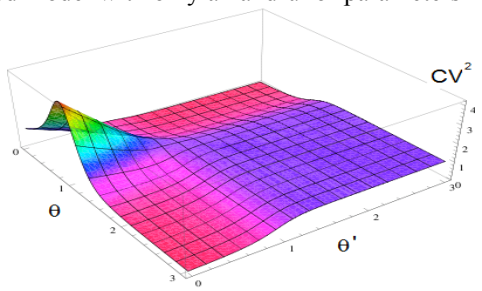

Figure. The coefficient of variation (CV) of the completion time for two pathways of random walk (no proofreading) between the initial point and the final state. The length of each branch is 16 and the forward rates on the branches denoted by θ, θ' are 1, 6 correspondingly. The ratios between the backward and forward rates are given by θ and θ'. When both branches are strongly backward biased we obtain an exponential distribution (CV=1), while over most of the regime in which one of the branches is forward biased we obtain a deterministic behavior (CV=0).

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