Thermodynamics of biological copying systems

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Copying information is a fundamental task of biological systems. Examples range from DNA duplication and transcription to translation into a protein. All these operations are performed on the molecular scale and at a finite temperature, so that a finite rate of errors is unavoidable because of thermal fluctuations. Tipical error rates η range from $\eta \sim 10^{-4}$ in protein transcription and translation, to $\eta \sim 10^{-10}$ in DNA duplication. What is the lower bound dictated by thermal fluctuations on the error rate? A naive estimate would suggest $\eta \sim \exp(-\Delta F/kT)$ where ΔE is the binding energy difference between a correct monomer and a wrong one. However, the general picture is slightly more complex.

We consider a case in which the copying bio-machine can be modeled as a three-state system: a blank state $\emptyset$ where no monomer is bound, and two states r/w where the right or wrong monomers are attached. The free-energy landscape is sketched in Fig. 1a. We can see that discrimination can occur in two different ways: via a different energy of the two bound state (γ in the figure) or via different kinetic barriers δ to reach these states.

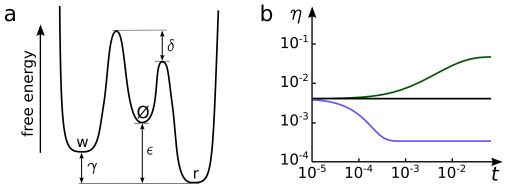

FIG. 1. a) Energy landscape of the three-state model b) error as a function of time in three different cases (green: $\gamma > \delta$, blue: $\gamma < \delta$, black: $\gamma = \delta$.

We study the dynamics of the error $\eta = p_w/(p_r + p_w)$. The short-time error is determined by the barrier δ, while the error at large times is determined by the enrgy difference γ. This means that if the barrier δ is large, a small error can be achieved by terminating the reaction before it reaches thermal equilibrium. As shown in Fig. 1b, the error is always a monotonic function, so that it reaches its minimum either at very short or very large times.

What happens if instead of a single base, a long chain has to be copied? We consider a copolymerization model in which a polymerase adds and removes monomers from the copied strand, trying to match a given template. The parameters are the same as in Fig. 1a, only that $\emptyset$ now represent a generic state of the chain, and r/w represent an addition of a right/wrong monomer at the tip.

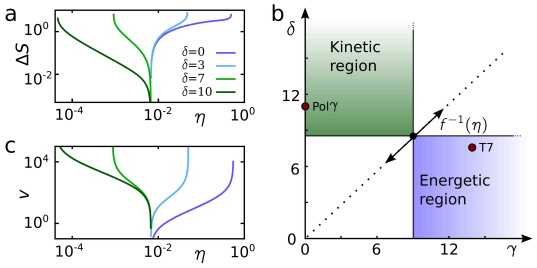

FIG. 2. a) Entropy production per copied base in the copolymerization model as a function of the error η. In all curves $\gamma = 5$. b) Regions in the $\gamma - \delta$ plane compatible with a given error rate η c) Copying velocity.

We calculated the entropy production per copied base (fig. 2a) and copying velocity (fig 2c) of the model as a function of the error rate η, for different parameter values. For a given choice of the two energies δ and γ, the possible values of the error rate are bound from

$$\min\left(\frac{e^{-\delta}}{1+e^{-\delta}}, \frac{e^{-\gamma}}{1+e^{-\gamma}}\right) < \eta < \max\left(\frac{e^{-\delta}}{1+e^{-\delta}}, \frac{e^{-\gamma}}{1+e^{-\gamma}}\right)$$

where energies are in units of kT. The above equation naturally defines two disconnected regions (fig. 2b): one where the error is determined by the energy difference γ (*energetic discrimination region*) and one where it is defined by the barrier δ (*kinetic discrimination region*). These two regions correspond to very different biological tradeoffs: in the kinetic region, the minimum error is achieved in a highly dissipative regime where entropy production and velocity both diverge. In the energetic region this limit is adiabatic, and both dissipation and velocity tend to zero.

Comparing this theory with experimentally measured rates of DNA duplication polymerases, we find that a human polymerase, polγ, adopts a kinetic strategy, while a phage, T7, adopts an energetic one. Their estimated values of γ and δ are shown in Fig. 3b. This proves that both strategies can be actually used by biological copying systems. Finally, we discuss how these strategies can be combined in multi-step reactions involving error-correcting steps such as kinetic proofreading.

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[1] `http://www.nbi.dk/ pigo/`
[2] P. Sartori and S. Pigolotti, arxiv/1209.4566.