Kinetic proofreading by Hopfield and Ninio

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Kinetic proofreading was independently proposed by John Hopfield and Jacques Ninio. We will focus on the paper by Hopfield:

"Kinetic Proofreading: A New Mechanism for Reducing Errors in Biosynthetic Processes Requiring High Specificity". Proc. Nat. Acad. Sci. USA. Vol. 71, No. 10, pp. 4135-4139.

The paper by Ninio was published pretty much at the same time and represents an independent discovery of the same mechanism.

When answering these questions, please prepare such that you can present the answer to your peers using screen sharing. This could be scanned notes, slides, ipython notebooks, or similar.

Question 1 – the problem

- What is the problem that kinetic proofreading is supposed to solve?
- Why are low error rates important in each of the canonical examples?
- What would the consequences of high error rates in each case?

Question 2 – error rates in Michaelis-Menten reactions

- What is the "energy of discrimination"?
- How is it related to the population of the transition state?
- Why do the off-rates matter, rather than the on-rates?
- How is equation 3 related to the energy of discrimination?
- What is the approximation involved?

Question 3 – irreversible proof-reading step

- In equations 4 to 6, Hopfield shows that adding simple reversible intermediate steps does not help. Why not?

- Why is a coupled side reaction necessary?
- At least one step as to be coupled to an irreversible reaction. Why? What would happen if there simply was another entry point into the final intermediate?

Question 4 – interpretation as delay

- Correct and wrong intermediates decay with rates k_C and k_D, respectively. If there was a way to delay formation of the product, how would the discrimination increase with the duration of the delay?
- Hopfield discusses a time dependent rate $W(t) \sim t$. How could this be implemented?
- Write down a system of equations that describe Eq. 9 and solve it.
- What is the rate of product accumulation in such a two-step reaction?
- How does this generalize to more than two intermediates?

Question 5 – molecular implementations

Hopfield discusses possible implementations of kinetic proof reading during peptide extension by the ribosome, rRNA charging and DNA replication. Each of these examples is coupled to an irreversible hydrolysis step. In which step does this happen? How does proofreading reduce errors?

Bonus Question – Immunology

The concept of kinetic proofreading is important to achieve sensitivity and specificity in immune system activation and signaling.

- Why are T-cell or B-cell activation by foreign antigens problems that require high sensitivity and specificity?
- How is proof-reading implemented in T-cell activation? What are the irreversible steps?
- What are the specific predictions of the model?

Outlook

- Can you think of other biological contexts where kinetic proofreading is used?
- How do humans achieve high-fidelity communication in noisy environments?