

AnnouncementsOffice hours this week:

4-5 pm (right after section) on Tuesday the 25th

No Wednesday office hours this week.

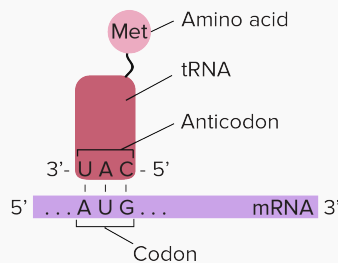
or by appointment.

Section next week:

In-person on November 1st at 3 pm in M217.

Problem 1: Kinetic proofreading

In protein translation, an anticodon on tRNA (bound to an amino acid) binds to its respective codon on mRNA. This occurs on a ribosome.



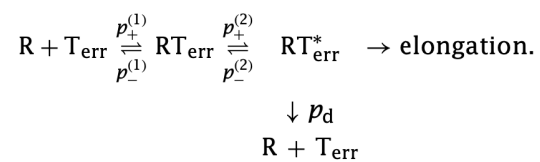
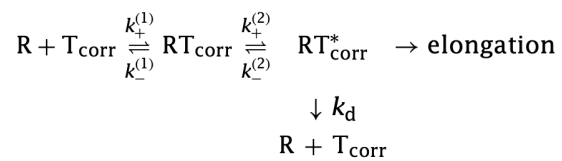
a) Consider a very simplified model of translation and tRNA binding, with just two kinds of amino acids and codons. What is $\frac{p_{error}}{p_{correct}}$, given the binding energies of the correct and incorrect pairs? In this simplified model, we can assume that the concentrations of both species of tRNA are the same. Plug in $\Delta\epsilon = 2K_B T$. What is the error rate from thermodynamics?



If you consider the kinetic description with reaction rates, one gets the same thing – the error rate is a ratio of equilibrium constants for the correct and incorrect binding reactions.

(For translation, ribosomes have an error rate of 10^{-4} , which is surprisingly low!)

b) Consider a reaction scheme where there is an additional step before elongation. k_d and p_d are generally different: the error pairing has a faster "off" rate.



Write the system of differential equations for $\frac{d[\text{R}]}{dt}$, $\frac{d[\text{RT}]}{dt}$, and $\frac{d[\text{RT}^*]}{dt}$.

c) Solving these expressions at steady state, one finds that the error rate is

$$p_{err} = \frac{[RT_{err}^*]}{[RT_{corr}^*]} = \frac{k_-^{(1)}k_-^{(2)} + k_-^{(1)}k_d + k_+^{(2)}k_d}{p_-^{(1)}p_-^{(2)} + p_-^{(1)}p_d + p_+^{(2)}p_d}. \quad (3)$$

Assume that $k_-^{(2)} \ll k_d$, and $k_+^{(2)} \ll k_-^{(1)}$ (and likewise for the p reaction rates). Simplify the expression for p_{err} . We can see that for each intermediate step, we get another chance to improve our selectivity! Kinetic proofreading was first discussed in (Hopfield, 1974) and remains an important concept in models of biological systems today.

Problem 2: Selection and mutation

Consider a very large population of individuals characterized by a fitness parameter f , which is assumed to be Gaussian distributed with a mean m and variance σ^2 . The population undergoes cyclic evolution, such that at each cycle: (i) one half of the population with lower fitness f is removed without creating progeny; (ii) the remaining half (with f values in the upper half) reproduces before dying; (iii) because of mutations that are on average neutral the f values of the new generation is again Gaussian distributed, with mean value and variance reflecting the parents (i.e. coming from the upper half of the original Gaussian distribution).

a) Relate the original mean m_n and variance σ_n of fitness values at the n th generation to those of the previous ones (m_{n-1} and σ_{n-1}).

b) What happens to the distribution of fitness after many generations?

c) Most mutations are deleterious, while at the same time increasing the diversity of the population. To study these effects, assume that at each generation the distribution obtained in (a) above is convoluted with a Gaussian of mean $-\mu$ (thus reducing the mean fitness) and variance s^2 (acting to increase the variance in fitness). Find the recursion relations for m_n and σ_n in this case.

d) What happens to the fitness distribution at long times in this case?

This question was originally written by Mehran Kardar at MIT.