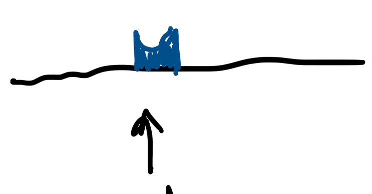
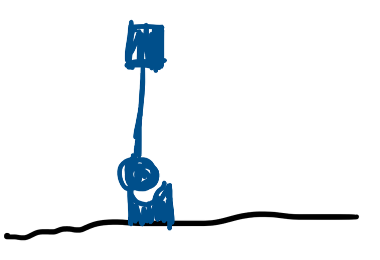
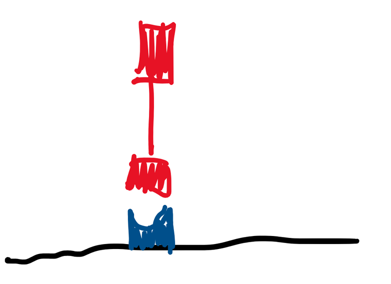
In-class Lecture 18 - Kinetic Proofreading

Thursday, March 17, 2022 11:04 AM

Calculating prob. of right/wrong tRNA binding

STATES	ENERGIES	MULTIPLICITIES
 codon	$\varepsilon_{sol} N_c + \varepsilon_{sol} N_w$	$\frac{\Omega^{N_c}}{N_c!}\ \frac{\Omega^{N_w}}{N_w!}$
	$\varepsilon_{sol}(N_c-1) + \underset{\text{correct binding energy}}{\varepsilon_c} + \varepsilon_{sol} N_w$	$\frac{\Omega^{N_c-1}}{(N_c-1)!}\ \frac{\Omega^{N_w}}{N_w!}$
	$\varepsilon_{sol} N_c + (N_w-1)\varepsilon_{sol} + \underset{\text{wrong binding energy}}{\varepsilon_w}$	$\frac{\Omega^{N_c}}{N_c!}\ \frac{\Omega^{N_w-1}}{(N_w-1)!}$

BOLTZMANN WEIGHTS

$$\text{multipicity} \cdot e^{-\beta \cdot \text{Energy}}, \quad \beta = 1/k_B T$$

$$P_c = \frac{\frac{N_c}{\Omega} e^{-\beta(\overbrace{\varepsilon_c-\varepsilon_{sol}}^{E_c})}}{1+\frac{N_c}{\Omega} e^{-\beta(\underbrace{\varepsilon_c-\varepsilon_{sol}}_{E_c})}+\frac{N_w}{\Omega} e^{-\beta(\underbrace{\varepsilon_w-\varepsilon_{sol}}_{E_w})}}$$

$$P_w = \frac{\frac{N_w}{\Omega} e^{-\beta E_w}}{1+\frac{N_c}{\Omega} e^{-\beta(\underbrace{\varepsilon_c-\varepsilon_{sol}}_{E_c})}+\frac{N_w}{\Omega} e^{-\beta(\underbrace{\varepsilon_w-\varepsilon_{sol}}_{E_w})}}$$

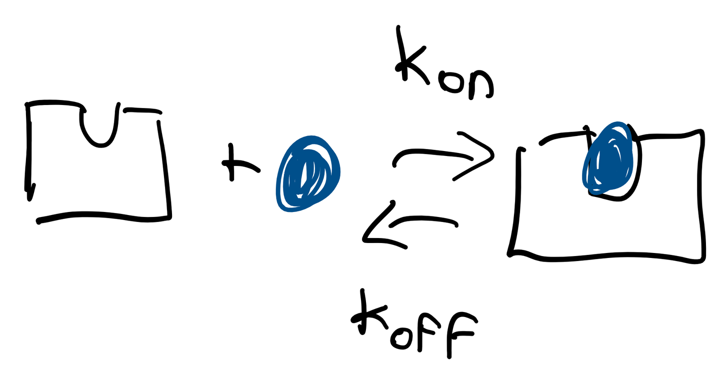
calculate the error rate as

$$\frac{P_w}{P_c} = \frac{\cancel{\frac{N_w}{\Omega}} e^{-\beta E_w}}{\cancel{\frac{N_c}{\Omega}} e^{-\beta E_c}} = e^{-\beta(E_w - E_c)} = e^{-2} \approx \frac{1}{10}$$

assume H-bond w/ $2 k_B T$

assume that $N_c = N_w$

Thinking about binding kinetics



$k_{on}^c = k_{on}^w$

$k_{off}^c < k_{off}^w$

$$K_d = \frac{k_{off}}{k_{on}}$$

simple ligand-receptor problem

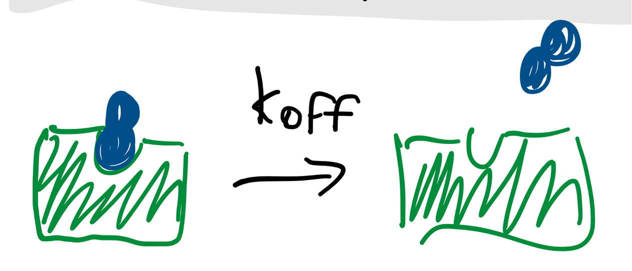
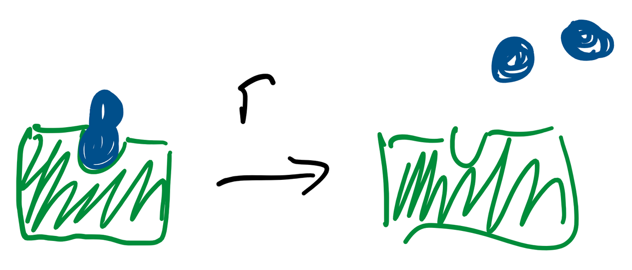
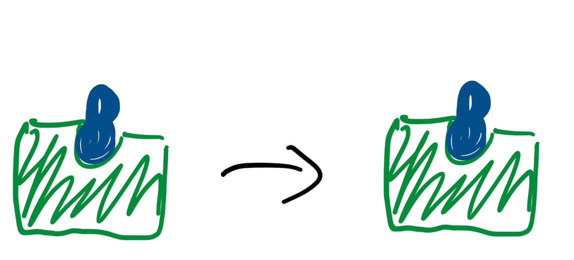
$$P_{bound} = \frac{\frac{c}{c_0} e^{-\beta\Delta E}}{1+\frac{c}{c_0} e^{-\beta\Delta E}} = \frac{c/K_d}{1+c/K_d}$$

$$\Rightarrow K_d = c_0 e^{\beta\Delta E}$$

$$\frac{P_w}{P_c} = e^{-\beta(E_w-E_c)} = \frac{K_d^c}{K_d^w} = \frac{k_{off}^c\, k_{on}^w}{k_{on}^c\, k_{off}^w} = \frac{k_{off}^c}{k_{off}^w} = \frac{1}{10}$$

assume to be the same

I have one more chance a discrimination!

TRAJECTORIES	PROB
	$k_{off} \cdot \Delta t$
	$r \cdot \Delta t$
	$1 - k_{off}\Delta t - r\Delta t$

Prob of cleavage event (given that something happens)

$$= \frac{r\cancel{\Delta t}}{r\cancel{\Delta t} + k_{off}\cancel{\Delta t}} = \frac{r}{r+k_{off}}$$

error in the second stage

$$\approx \frac{P_w^{(2)}}{P_c^{(2)}} = \frac{\frac{r}{r+k_{off}^w}}{\frac{r}{r+k_{off}^c}} = \frac{r+k_{off}^c}{r+k_{off}^w}$$

total error

$$= \frac{P_w^{(1)}}{P_c^{(1)}} \cdot \frac{P_w^{(2)}}{P_c^{(2)}} = \frac{k_{off}^c}{k_{off}^w} \cdot \frac{r+k_{off}^c}{r+k_{off}^w} = \left(\frac{k_{off}^c}{k_{off}^w}\right)^2$$

$r \ll k_{off}^c, k_{off}^w$