

Folding kinetics and dynamics – September 14, 2015

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1 2D

1.1 Stability

We calculate average and median number of contacts in native sequences, according to HP-model. It is measured in the units of hydrophobic energy per kT . From [1] it follows that

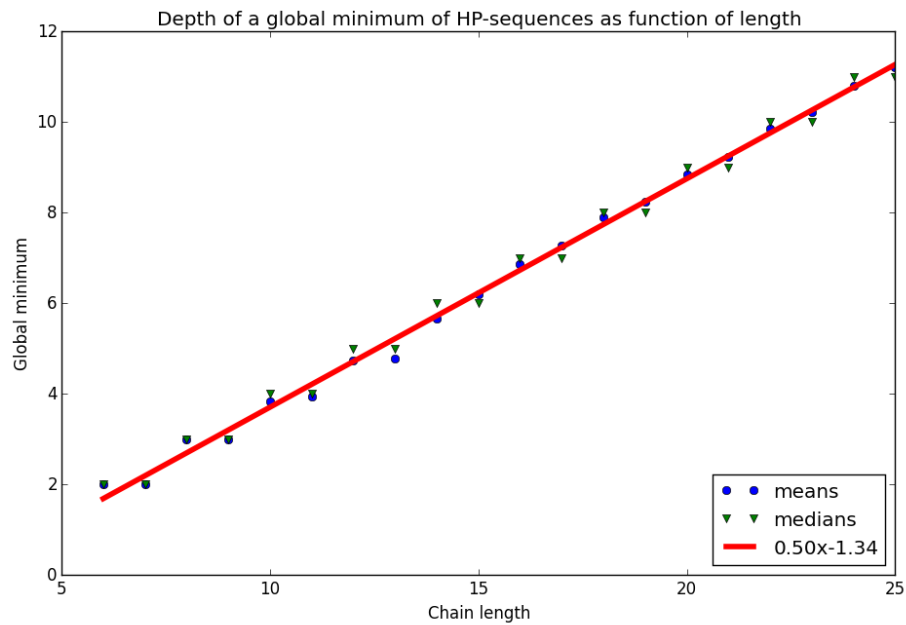


Fig. 1: Depth of the energy well is measured in the units of $e_h = E_h/kT$, where e_h is an energy of one hydrophobic contact per $1kT$.

free energy is composed of two terms: the enthalpy and entropy of the molecular interactions

and $\Delta G_0 = \Delta H_0 - T\Delta S_0$ and conformational entropy $\Delta G_c = -T\Delta S_c = kTN \ln z$. N here is a chain length and z is a number of rotational freedoms.

Fitting a line on a figure 1 to the HP-model minimums yields the following dependency for the energy well depth (per $1kT$):

$$\Delta G_0 = -kNe_h - be_h = -0.5Ne_h + 1.34e_h \quad (1)$$

where N is a chain length and e_h is an absolute value of the energy of one hydrophobic contact. And full free energy of folding will be (per $1kT$):

$$\Delta G = -kNe_h - be_h + N \ln z \quad (2)$$

1.2 Kinetics

There's a theory of protein folding introduced by Ghosh and Dill in a series of papers [2, 3] and more. It is based on simple equilibrium thermodynamics and leads to the following conclusion regarding chain length distribution:

$$\ln k_f = 16.15 - 1.28\sqrt{N} \quad (3)$$

Which in turn predicts the following dependency of the rate constants: While it is likely that

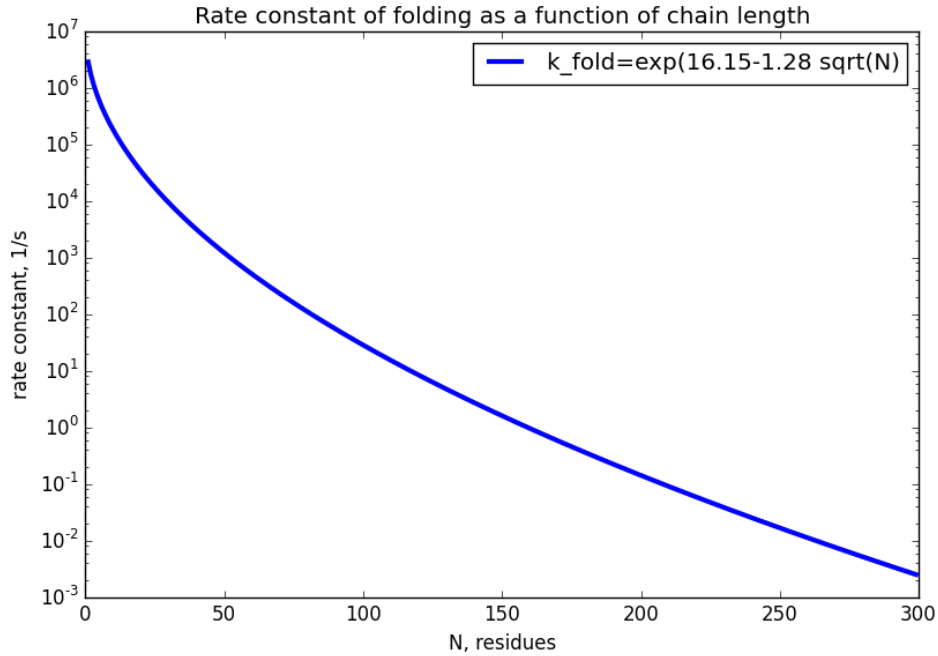


Fig. 2:

model fails at the short sequences, we can use it for a crude estimation of the folding and unfolding rates of the short HP-polymers. Though there's no real way to test if our results are true. This model suggests that the *folding* rate constants would be the following for some short chains:

- $k_f(10) = 2 \cdot 10^5$
- $k_f(20) = 3 \cdot 10^4$
- $k_f(30) = 0.9 \cdot 10^4$

Folding and unfolding rate constants relate to each other and free energy of folding.

$$\ln \left(\frac{k_f}{k_u} \right) = \ln K = -\Delta G/kT \quad (4)$$

From the section 1.1, if ΔG_0 follows law from fig.1 it follows that:

$$\ln k_f - \ln k_u = \Delta G_0/kT - N \ln z \quad (5)$$

which gives

$$\ln k_u = \ln k_f - \Delta G_0/kT + N \ln z \quad (6)$$

Substituting $\ln k_f$ from equation (3) and fitted ΔG_0 we get:

$$\ln k_u = 16.15 - 1.28\sqrt{N} - kNe_h - be_h + N \ln z \quad (7)$$

Therefore

$$k_u = \frac{1}{z^N} \exp(16.15 - 1.28\sqrt{N} - kNe_h - be_h) \quad (8)$$

This gives the following dependencies for k_u and k_f : see fig.4

2 3D

Let's repeat the procedure for 3-dimensional proteins. From [3] we can take a figure 1D, which has a fitted curve for $\Delta G(N)$ at 37°C. Determine parameters from it returns:

$$\Delta G(N) = 0.067N + 7.012kJ/mol \quad (9)$$

Adding to it folding rate constant from (3)

$$\ln k_f = 16.15 - 1.28\sqrt{N}$$

will get

$$\ln k_f - \ln k_u = \Delta G/kT \quad (10)$$

or for k_u

$$\ln k_u = \ln k_f - \Delta G/kT = 16.15 - 1.28\sqrt{N} - (0.067N + 7.012)/2.5775 \quad (11)$$

so

$$k_u = \exp(13.43 - 0.026N - 1.28\sqrt{N}) \quad (12)$$

This leads to the following folding and unfolding rate constants (see fig 5)

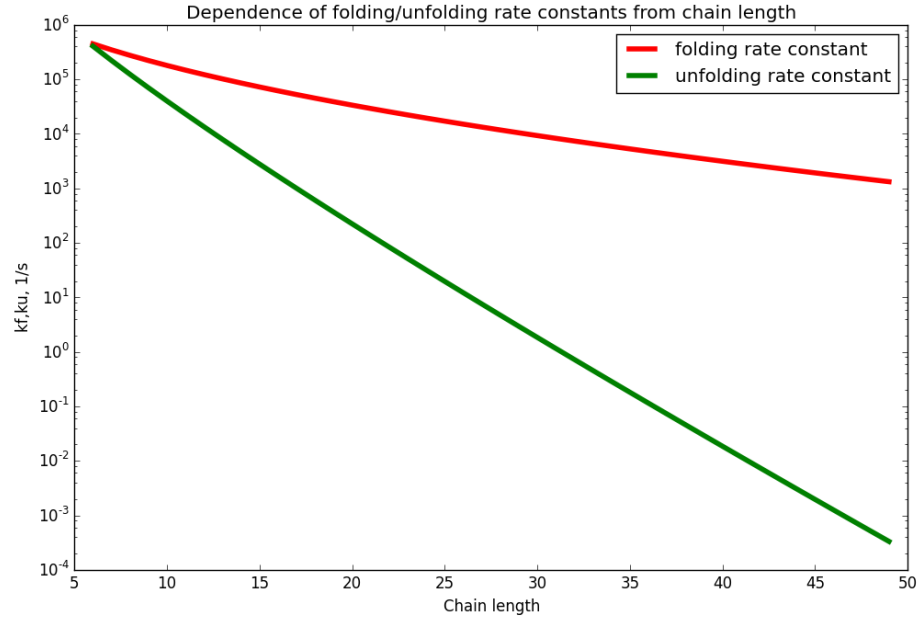


Fig. 3: Folding and unfolding rates as a function of chain length. $e_h = 1.5, z = 1.5$ These numbers are chosen so that equilibrium constant is around $10^2 - 10^4$ when chain lengths are short (around 15-30), see figure ??

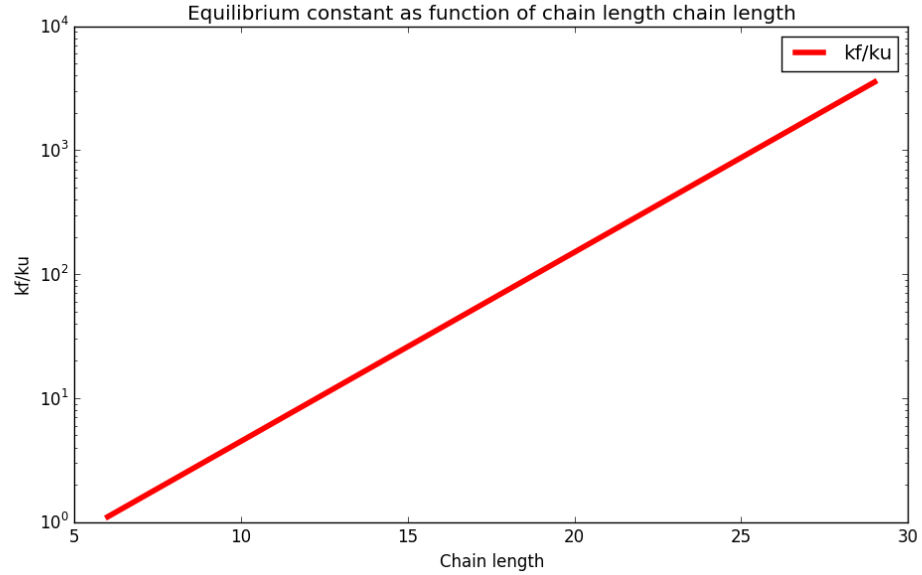


Fig. 4: Equilibrium constant as a function of chain length. $e_h = 1.5, z = 1.5$ These numbers are chosen so that equilibrium constant is around $10^2 - 10^4$ when chain lengths are short (around 15-30)

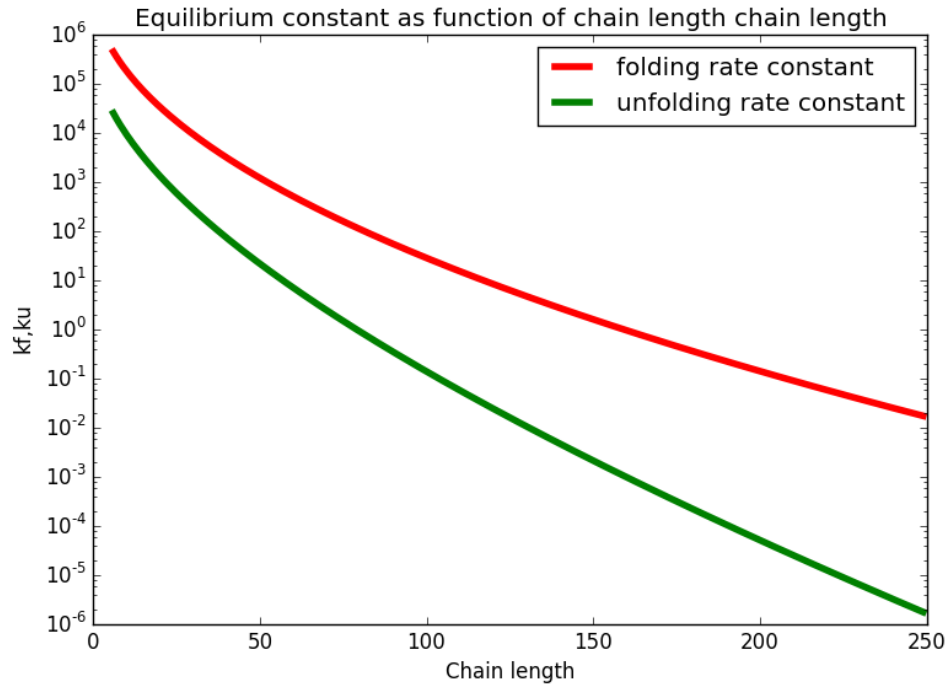


Fig. 5: Folding and unfolding rates as a function of chain length for 3D proteins. Data taken from [3]

References

- [1] Kingshuk Ghosh and Ken A Dill. Computing protein stabilities from their chain lengths. *Proceedings of the National Academy of Sciences of the United States of America*, 106(26):10649–54, June 2009.
- [2] Kingshuk Ghosh and Ken A Dill. Cellular proteomes have broad distributions of protein stability. *Biophysical Journal*, 99(12):3996–4002, 2010.
- [3] Ken A Dill, Kingshuk Ghosh, and Jeremy D Schmit. Physical limits of cells and proteomes. *Proceedings of the National Academy of Sciences of the United States of America*, 108(44):17876–82, November 2011.