

Estimation of the dynamics of protein folding processes from free energy computations

Juan M. Bello-Rivas*, Benjamin Ivorra*, Ángel M. Ramos*, Antonio Rey†

The passage of proteins from a denatured state to a biologically functional (native) state is often modeled as a diffusion process along a reaction coordinate[5]. The usual approach of modeling proteins as mechanical systems and conducting Monte Carlo simulations to sample their phase space yields spatial conformations and free energy profiles[3] but not the phase space trajectories corresponding to the folding process. We present an approach to reconstruct the dynamics from the free energy profiles resulting from Monte Carlo simulations. This approach consists in choosing a suitable diffusivity profile and numerically solving the one-dimensional Smoluchowski equation[4]

$$\begin{cases} \frac{\partial f}{\partial t}(x, t) = \frac{\partial}{\partial x} \left(D(x) p(x) \frac{\partial}{\partial x} \left(\frac{f(x, t)}{p(x)} \right) \right), & (x, t) \in [a, b] \times \mathbb{R}_{>0}, \\ f(x, 0) = f_0(x), & x \in [a, b], \\ \frac{\partial f}{\partial x}(x, t) = \frac{p'(x)}{p(x)} f(x, t), & x \in \{a, b\}. \end{cases} \quad (1)$$

where $f(x, t)$ is the probability density function of the distribution of states with reaction coordinate x at time t , $D(x)$ is the diffusivity profile, $p(x)$ is the (temperature-dependent) equilibrium probability, and $f_0(x)$ is the initial probability. From the solution of this equation for a wide array of temperatures, it is possible to extract folding rates that can be matched against experimentally observed rates. We have used global optimization techniques[2] to find the diffusivity profiles (initially assuming $D(x) = \text{constant}$) that, when substituted in (1), yield folding rates that are closest to those obtained in laboratory experiments. Also, our numerical scheme for solving (1) is significantly faster than the most popular one appearing in the Chemical Physics literature[1] while being of the same order of accuracy.

References

- [1] D. J. Bicout and A. Szabo. Electron transfer reaction dynamics in non-Debye solvents. *The Journal of Chemical Physics*, 109:2325, Aug 1998.
- [2] Ivorra, B., Mohammadi, B. and Ramos, A.M. Optimization strategies in credit portfolio management. *J. Of Glob. Optim.* **43**(2):415–427, 2009
- [3] T. Lelièvre, M. Rousset, and G. Stoltz. *Free energy computations. A mathematical perspective*. Imperial College Press, London, 2010.
- [4] H. Risken. *The Fokker-Planck equation*, volume 18 of *Springer Series in Synergetics*. Springer-Verlag, Berlin, second edition, 1989.
- [5] N. D. Socci, J. N. Onuchic, and P. G. Wolynes. Diffusive dynamics of the reaction coordinate for protein folding funnels. Preprint <http://arxiv.org/abs/cond-mat/9601091>, Jan 1996.

*Departamento de Matematica Aplicada, Universidad Complutense de Madrid, Spain: jmberi@mat.ucm.es; ivorra@mat.ucm.es; angel@mat.ucm.es

†Departamento de Química Física I, Universidad Complutense de Madrid, Spain: jsbach@quim.ucm.es