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Multiscale Simulation of Protein Cluster Dynamics – the Encounter Complex

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Most proteins in the cell are active in complexes with two to several hundreds of components. As only very small assemblies can be studied in an all-atom framework, coarse-grained approaches are required to model the association and dissociation dynamics of larger protein assemblies. We approach this problem by using Langevin equations, which allow us to simulate the cluster dynamics in a very efficient way. In order to make contact to specific systems of interest, we use the concept of an encounter complex and extract the relevant association and dissociation rates from biomolecular simulations.

Today proteomics provides us with almost complete lists of proteins in different biological systems of interest. In order to further advance our quantitative understanding of these biological systems, we now have to address the interactions of their proteins in space and time. Indeed most proteins are biologically active in complexes and thus it is crucial to understand their association and dissociation dynamics.

Although very complex if investigated in detail, conceptually the dynamics of protein association can be viewed as a sequence of different steps (see Fig. 1). Initially the binding partners undergo pure diffusion. After reaching a certain proximity, the proteins are steered towards each other, usually by electrostatic forces. This leads to the formation of the encounter complex, which can be viewed as a local minimum on an effective free energy landscape. This minimum results often from the electrostatic and hydrophobic attraction on the one hand and from the final barrier of desolvation on the other hand. This view immediately suggests two important measures to speed up the simulation of protein association: first the diffusion step can be described by a simple Langevin simulation of a particle with the respective shape. Second, overcoming the final energy barrier can be described by an effective rate of association which in principle can be extracted from an effective free energy landscape with the help of transition state theory. In order to scale the system to larger complexes, one then has to simulate many cycles of association and dissociation using appropriate Langevin equations.

Although the notion of an encounter complex has been successfully used before to describe association reactions in chemistry and physics, for specific biological systems it has to be validated by biomolecular simulation. Moreover, biomolecular simulations are required to provide detailed values for the association and dissociation rates for specific systems of interest. In the following we review some of the work regarding the encounter complex, with an eye towards the question how it can be used to provide a bridge between Langevin and biomolecular simulations.

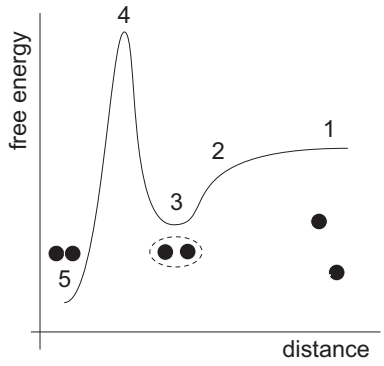

Figure 1. Schematic effective free energy landscape of protein association. 1) free diffusion, 2) electrostatic steering region, 3) encounter complex, 4) barrier due to desolvation and other effects, 5) final complex.

Analytical considerations with respect to the encounter complex have a long tradition. Early works attempted to find mathematical descriptions for the encounter step, i.e. for the transport part of the reaction. One prominent result is the rate of encounter between a colloid of finite size and an ensemble of small colloids derived by Smoluchowski (Z. Phys. Chem. 1916). Later, Debye (Trans. Electrochem. Soc. 1942) calculated reaction rates in ionic solutions. Eigen did the first step towards the consideration of the encounter complex in a biological context, particularly enzyme physics (Quant. Stat. Mech. 1974). He discussed the classic work by Debye and the two limits of pure electrostatics (Langevin 1903, Onsager 1924) and pure geometry (Smoluchowski). Berg and Purcell introduced the standard model for this field: ligands diffuse to a sphere coated with receptor patches (in this case disc like) and are immediately captured upon encounter. Interestingly, for typical values from cell receptor applications, already a very low surface coverage ($\sim 10^{-3}$) leads to nearly optimal outcome. Later, Zwanzig discussed cooperative effects between the receptor patches (PNAS 1990) and derived a correction to the Berg and Purcell result, which perfectly matched simulations by Northrup (JPC 1988).

Bell first connected considerations about the formation of the encounter and the final complex with the additional possibility of dissociation in a model for cell adhesion clusters (Science 1978). Describing both by using stochastic on- and off-rates, he derived basic expressions for the rate of the total reaction, which were discussed both in the diffusion-limited and the reaction-limited case. DeLisi and Wiegel discussed the Berg-Purcell model with a finite reaction rate as introduced by Bell and including electrostatic interactions (PNAS 1981). They claim that, although the particular kinetics of association and dissociation can be affected, the equilibrium properties remain the same. Shoup and Szabo used the concept of a radiation boundary condition to model the formation of the final complex from the encounter state in a mathematically rigorous way (BPJ 1982). Their treatment implied electrostatic interactions and was not restricted to the diffusion-limited case. For the latter, however, they were able to reproduce the results of Berg and Purcell. In the following years, Goldstein and Thompson worked out more details.

In many cases, experimental rates were found to be larger than predicted by the theoretical work. As a consequence, more specific properties like the particular geometry of

the receptor patches were considered in the modelling work. Shoup and Szabo discussed the influence of rotational diffusion and orientation constraints and found that these effects can strongly shorten the mean first passage times for a reaction between a ligand and a receptor patch like in the Berg-Purcell model (BPJ 1981). By using computer simulations, Northrup (PNAS 1992) showed that the rate enhancement seems to be caused by an entrapment of the encounter complex by surrounding water, which makes it possible for the two reacting molecules to test a large number of alignments without leaving the encounter state. Barzykin and Sushin claimed that disk like patches used in the Berg-Purcell model lead to substantially lower reaction rates than the use of hemispherical patches (BPJ 2001). In another paper by the same authors, they suggest that anisotropic diffusion can enhance the reaction rate (BPJ 2001). Recently Korn and Schwarz[1] used the purely geometrical interpretation of the encounter complex to study the efficiency of cell adhesion in hydrodynamic flow, where convection competes with diffusion. Erdmann and Schwarz[2] used the concept of a position-dependent rebinding rate to study the role of cell-substrate distance in cell adhesion.

Schlosshauer and Baker extended the work of Shoup and derived the binding rate for two spherical molecules which both can only bind with hemispherical reactive patches at a finite reaction rate (JPC B 2002). In a recent study, Alsallaq and Zhou (BPJ 2007) again extended this 'hemisphere' model by introducing a 'crater' model consisting of a spherical protein with a crater to which another spherical protein fits snugly. There the formation of a stereospecific complex was disfavored by the loss of translational and rotational freedom, and small translations and rotations between the protein subunits destroyed the interactions, leading to a sharp transition between the bound and the unbound state. The energy lanscape was described as funnel-like, with the deep well of the bound state surrounded by a broad shallow basin.

Miyashita et al. (PNAS 2004) investigated the effect of electrostatic interactions on the binding reaction between cytochrome c2 and a bacterial reaction center. The mechanism involved an encounter complex stabilized by electrostatic interactions, followed by a transition state similar to those found by Zhou, leading to the bound complex active in electron transfer. The study involved determination of a set of transition state structures by fitting experimental kinetic data over a wide range of protein-protein configurations. The transition state ensemble, obtained from structures having the highest correlation coefficients in comparison with the experimental data, had the cytochrome displaced by about 10 Å from its position in the x-ray crystal structure. The observed similarity between the structures of the encounter state, transition state, and bound complex accounted for the rapid rate of association responsible for fast diffusion-controlled electron transfer.

Subsequently, Spaar and Helms[3] used Brownian Dynamics simulations in order to study the association of barnase and barstar. The individual positions and orientations of one protein relative to the other were interpreted as a probability distribution allowing the calculation of the entropy landscape. The free energy landscape was obtained by summing the electrostatic, desolvation, and entropy contributions. A characteristic minimum at about 10 Å distance between the two binding patches denoted the position of the encounter complex.

In summary, biomolecular simulations have identified two systems (cytochrome c : reaction center and barnase : barstar) in which the electrostatic attraction in combination with the desolvation barrier leads to a well-pronounced funnel-shaped free energy surface with a

final transition state barrier between encounter and final complexes. Other protein-protein pairs may have less pronounced features of this kind. This poses the challenge to biomolecular simulations to identify which effective model may apply to particular protein:protein pairs. Yet if a system of this kind has been identified, then methods from stochastic dynamics (like transition state theory and Langevin simulations) can be employed to scale up the system. Only if biomolecular and stochastic simulations are combined, we will be able to model the association and dissociation kinetics of large macromolecular complexes.

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