Dynamics of protein-protein encounter: a Langevin equation approach with reaction patches

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***Short Abstract* — We study formation of protein-protein encounter complexes for three model systems of different degrees of coarse-graining with a Langevin equation approach. The encounter of model proteins is defined by the overlap of reaction patches placed on their surfaces. For all three models, association rates are obtained within one order of magnitude within the experimentally measured association rates. The number of unsuccessful contacts before encounter is inversely correlated with association rate. Our study shows that the computational efficiency of modeling protein-protein encounter can be dramatically increased by using coarse-grained approaches if reaction patches are appropriately defined. In the future, this will allow us to study the dynamics of larger protein complexes.**

***Keywords* — Mean First Passage Time, Encounter Complex, Protein Association, Langevin Equation.**

I. Motivation

PROTEIN-PROTEIN interactions play key roles in many cellular processes such as signal transduction, bioenergetics, immune response and the formation of larger protein complexes like cell-matrix adhesions or cytoskeletal structures. Conceptually, protein-protein association can be divided into two main steps [1]. First, an initial *encounter complex* is formed by the separated proteins due to a transport process including mainly diffusion but also drift on small length scales. To form the final complex, the system then has to overcome a free energy barrier due to many specific effects like dehydration, constraints due to van der Waals repulsions and others. From the viewpoint of stochastic dynamics, protein-protein association can be considered to be a first passage time (FPT) problem, which can be addressed mathematically in the framework of Langevin equations, see e.g. [2, 3].

II. Description of the Model

In our study, proteins are modeled either as spherical particles (*M* 1), as dipolar spheres (*M* 2) or as collection of several small beads with one dipole (*M* 3). In all variants, the diffusion of the model particles is determined by a full anisotropic 6x6 diffusion matrix [4]. The effective dielectric interaction is incorporated in *M* 2 and *M* 3 via the dipolar sphere model [5]. As three model systems with distinctly different properties we consider the pairs barnase:barstar, cytochrome c:cytochrome c peroxidase and p53:MDM2.

III. Results

We find that encounter frequency scales linearly with protein concentration, thus proving that our microscopic model results in a well-defined macroscopic association rate. The number of unsuccessful contacts is inverse correlated with association rate and range from 100-1000, except for Cytc:CCP, which proofs to be systematically different, as found before [3]. For all three models, association rates are obtained within one order of magnitude within the experimentally measured association rates. Electrostatic steering enhances association up to 50-fold. If diffusional encounter is dominant (p53:MDM2) or similarly important as electrostatic steering (barnase:barstar), then association rate decreases with decreasing patch radius. More detailed modelling of protein shapes (M3) decreases association rates by 5-40 percent.

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