New direct dynamic models of protein interactions coupled to photosynthetic electron transport reactions

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Abstract This review covers the methods of computer simulation of protein interactions taking part in photosynthetic electron transport reactions. A direct multiparticle simulation method that simulates reactions describing interactions of ensembles of molecules in the heterogeneous interior of a cell is developed. In the models, protein molecules move according to the laws of Brownian dynamics, mutually orient themselves in the electrical field, and form complexes in the 3D scene. The method allows us to visualize the processes of molecule interactions and to calculate the rate constants for protein complex formation reactions in the solution and in the photosynthetic membrane. Three-dimensional multiparticle computer models for simulating the complex formation kinetics for plastocyanin with photosystem I and cytochrome *bf* complex, and ferredoxin with photosystem I and ferredoxin:NADP⁺-reductase are considered. Effects of ionic strength are featured for wild type and mutant proteins. The computer multiparticle models describe nonmonotonic dependences of complex formation rates on the ionic strength as the result of long-range electrostatic interactions.

Keywords Protein interaction · Photosynthesis · Electrostatic interaction · Computer model · Complex formation

Introduction

Protein-protein complex formation is a basis for the electron transport in a cell in photosynthetic and mitochondrial membranes where electron transfer proceeds in protein multienzyme complexes and via mobile carriers (Malkin and Niyogi 2000; Mathews et al. 2000). For the general kinetic description of these reactions, mathematical models have been developed where some modifications of the mass action law are used. The rate constants of biochemical reactions of protein-protein association and concentrations of donor and acceptor protein molecules serve as parameters in these kinetic models. The values of rate constants of protein-protein association under different conditions (different pH, ionic strength values, etc.) are evaluated according to the experimental dependence of the reaction rate constants on the reagent concentrations in solution. These constructed kinetic models are essentially phenomenological, hence their rate constants have effective values.

Electron transfer between proteins includes the following steps: (1) protein diffusion to the docking point (or diffusion of the mobile protein to another protein embedded in the membrane multienzyme complex); (2) mutual orientation of proteins under the effect of electrostatic interactions; (3) formation of the preliminary complex; (4) conformational changes and final complex formation, where the reaction centers come close to each other; (5) charge transfer (tunneling) from one protein carrier to another; (6) complex decomposition. In recent papers models simulating separate stages of the process have been presented where modern structural and kinetic data were taken into account. The most advanced are kinetic models of electron transfer between components within multienzyme complexes (Stirbet et al. 1998; Riznichenko et al. 1999; Lazar 2003; Strasser et al. 2004; Zhu et al. 2005; Belyaeva et al. 2008) and the models of formation of the preliminary complex between two mobile proteins based on the Brownian dynamics (BD) approach

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(Ullmann et al. 1997; Pearson and Gross 1998; Rienzo et al. 2001; Gross and Pearson 2003; Gross and Rosenberg 2006).

When following the BD approach, it is possible to predict the complex structure and estimate the rate constant values of protein complex formation calculated from the probability values of protein binding obtained in computer experiments (Gabdouline and Wade 1997, 1998). However following the BD approach, interactions of only two individual protein molecules can be simulated.

In subcellular energy-transforming systems, chloroplasts and mitochondria redox reactions occur in limited space, constrained by membranes, and involve a number of molecules. To simulate the behavior of such complex subcellular systems in vivo, it is necessary to consider not only a single pair of molecules but rather a great number of them interacting in the constrained reaction volumes of cell organelles. Below we shall briefly describe the “direct” multiparticle simulation method (DMSM) we developed to solve this problem (Kovalenko et al. 2003, 2006, 2007, 2008a, b, 2009; Kovalenko and Riznichenko 2007; Riznichenko et al. 2009; Rubin and Riznichenko 2009).

As an object for the simulation, we analyzed the system of photosynthetic electron transport, which has been investigated thoroughly in the literature (Malkin and Niyogi 2000). A photosynthetic electron transport chain is a traditional object for mathematical modeling. Systems of differential equations serve here as a main mathematical tool (Laisk et al. 2009). For this system, structural data on protein components of photosynthetic chain, rate constants of protein interactions in solution at different ionic strengths as well as rate constants of electron transfer in chloroplast thylakoids are well known (Hope 2000; Fromme et al. 2001; Zhu et al. 2005).

The scheme of a photosynthetic energy-transforming membrane is presented in Fig. 1. Light-induced charge separation and stabilization of separated charges occur in the transmembrane multienzyme photosystem I (PSI) and PSII complexes, whereas the cytochrome (cyt) bf complex is responsible for the coupling of electron and proton transmembrane transport.

To describe electron transport at different steps, different types of equations are used. Inside of multienzyme complexes, PSI, PSII, cyt bf electron transport proceeds via “electron pathways,” where the order of carriers in every single multienzyme complex is fixed. This type of electron transport is traditionally described by master equations for the probabilities of certain complex states. The fundamentals of this approach are described in detail in Rubin and Riznichenko (2009). The electron transport between the complexes PSII, cyt bf, and PSI via mobile carriers is usually described by equations of mass action law (Karavaev and Kukushkin 1993; Kuznetsova and Kukushkin 1999; Kukushkin et al. 2002).

Some modern kinetic and structural data show that the basic assumption of kinetic modeling by differential equa-

Fig. 1 Schematic view of photosynthetic electron transport. Two thylakoid membranes and the luminal space between them are shown. Multiprotein complexes photosystem 1 (PSI), photosystem 2 (PSII), and cytochrome bf (cyt bf) are embedded in the membrane. Mobile electron carrier protein plastocyanin (Pc) diffuses in the lumen. The arrows denote electron transport. The connection with the Calvin cycle is carried out by mobile carriers Fd or Fld via FNR. Inside the multienzyme complexes of PSI, PSII, and cyt bf complex, the electron follows the “electron pathway” via a fixed sequence of carriers in the multienzyme complexes

tions—free diffusion of mobile carriers and homogeneous structure of the photosynthetic reaction system—is far from the reality. Electron microscopy data demonstrate that the multienzyme complexes are distributed heterogeneously in the membrane (Albertsson 2001; Nelson and Yocum 2006).

The mobility of plastocyanin (Pc) molecules is restricted by the membrane complexes protruding from the membrane into the lumen space (Fig. 1). In native chloroplasts, the luminal space is narrow (40–100 Å), and since the size of the Pc molecule (40×28×30 Å) is about the thickness of the lumen, the diffusion of Pc in the lumen is obviously hindered by the membrane protein complexes (Hope 2000; Dekker and Boekema 2005). It is not clear how Pc can rapidly diffuse over a distance of hundreds of nanometers. To take into account these and other peculiarities of the photosynthetic electron transport system, we use DMSM for the simulation, which directly describes motions of ensembles of mobile carriers in the lumen, stroma, and intramembrane space of the photosynthetic membrane.

Direct multiparticle computer models

DMSM models simulate diffusion of protein molecules approaching each other and their mutual orientation due to the effect of electrostatic forces. We studied the effects of (1) charge distribution on the surface of protein molecules, (2) the number of molecules in the ensemble, (3) geometrical

Fig. 2 Ellipsoid of revolution

parameters of the reaction volume on the kinetic characteristics of the reactions, and (4) ionic strength.

Mobile carriers as well as multienzyme complexes embedded in the membrane are considered as individual objects in 3D space. Every object is characterized by a set of parameters such as coordinates, geometrical shape and dimensions, reduced and oxidized states, and parameters of interactions with other objects. For the simulation of the ensembles of molecules (containing hundreds of molecules of each type), we take into account geometrical restrictions of the reaction volume. The states of multienzyme complexes, mechanisms of complex-protein interactions, and laws of electron carrier movements were defined by special rules.

In the process of protein diffusion, two or more protein molecules can approach each other, and the electrostatic fields generated by different proteins can overlap in the simulation space. Hence the total electrostatic field at any point in the reaction volume is the result of the contribution of each charge of protein particles. The distance between interacting parts of the moving proteins may become less than the value of the critical parameter of the model, which we call the docking distance r . In this case, the two proteins form the preliminary encounter complex, which then forms the final complex with the probability p . The accidental nature of this final complex formation is implemented in the computer algorithm by generating a random number, which is compared to the given p value.

To a good approximation, the complexes form by rigid-body associations (Janin 2000). However, hydrophobic

Fig. 3 Description of plastocyanin (Pc) and cytochrome f ($cyt f$) by ellipsoids of revolution for the calculation of the viscous friction coefficients of the molecules. Reprinted from (Kovalenko et al. 2006) with permission from IOP Publishing

Fig. 4 Approximation of the cytochrome f (a) and plastocyanin (b) molecules by sets of spheres (shown in blue)

interactions, possible complex rearrangements, and conformational changes of proteins may be important for the transformation of the encounter complex into the final complex. Our method explicitly simulates encounter complex formation and does not simulate the transformation of the encounter complex into the final complex. Instead, this transformation is taken into account implicitly by introducing the probability p of the final complex formation. This approach is suitable for simulation of diffusion-controlled reactions and the reactions in which the reaction rate is influenced by diffusion and some other processes.

To estimate the parameters of the computer model (docking distance and probability), first we simulate protein

Fig. 5 Approximation of the multisubunit complex photosystem I by sets of spheres. The spheres are shown in blue, the atoms are red. The surface of the parts of PSI protruding from the membrane are approximated in high detail (Abaturova et al. 2008)

Fig. 6 Equipotential surfaces, -6.5 mV (red) and $+6.5$ mV (blue), for the reduced cytochrome f (*Cyt f*) and oxidized plastocyanin [*Pc*, wild-type (*WT*) and mutant *E59K/E60Q*], calculated using Poisson-Boltzmann equation. Ionic strength is 100 mM, $\text{pH}=7$, $\epsilon_{\text{sol}}=80$, $\epsilon_{\text{prot}}=2$. Reprinted from (Kovalenko et al. 2006) with permission from IOP Publishing. The lines connect the amino acids on *Pc* and *cyt f* used in the simulation to calculate the distance between the proteins. For mutant *Pc*, the blue points represent atoms with charges changed as compared to the wild-type. The values for distances between contacting amino acid residues are given in Table 1 in (Kovalenko et al. 2006)

interactions in a solution and compare the results with corresponding experimental data.

Protein interactions in solution

To verify the results of the DMSM, we need to compare the kinetic curves obtained in real and computer experiments.

To investigate the effects of the protein shape, geometry of the reaction volume, and electrostatic interactions on the observed kinetic characteristics—in particular on the rate constant values—we simulate protein interactions in a solution. On the basis of experimental data on the kinetics of the process in a solution, we evaluated the parameters introduced in the multiparticle model, i.e., probabilities and distances characterizing protein interactions.

Fig. 7 Equipotential surfaces, -6.5 mV (red) and $+6.5$ mV (blue), for the reduced wild-type Fd (**a**) and oxidized wild-type FNR (**b**), calculated by the Poisson-Boltzmann equation. Ionic strength is

100 mM, $\text{pH}=7$, $\epsilon_{\text{sol}}=80$, $\epsilon_{\text{prot}}=2$ (Kovalenko et al. 2008b). As the docking distance r we chose the distance between Fe1 atom of the [2Fe-2 S] cluster on Fd and C8M atom of FAD on FNR

The interacting molecules were considered as Brownian particles, performing the translational and rotational motions in viscous media due to the collisions of proteins with the surrounding molecules. Electrostatic forces were considered only when the distance between the surfaces of the molecules was less than 35 Å (the distance of electrostatic interactions), whereas at higher distances electrostatic interactions become negligible.

Protein diffusion and approximation with ellipsoids of revolution

In the DSMS model, protein molecules perform translational and rotational motion due to random and electrostatic forces. In physics, the Langevin equation is used to describe the motion of Brownian particles under the action of electrostatic force. Molecules of the solvent serve as a source of random Brownian and friction forces. But in the DSMS model due to small acceleration of molecules in viscous media and therefore small relaxation times of inertia compared to the target time scale, inertia is neglected. It means that total force, which consists of Brownian, random, and external (electrostatic) forces, is zero. Therefore the Langevin equation for translational motion without inertia term has the following form:

$$\xi_t^x \frac{dx}{dt} = f_x(t) + F_x, \quad \langle f_x(t) \rangle = 0, \quad \langle f_x(t)^2 \rangle = \frac{2kT\xi_t^x}{\Delta t}. \quad (1)$$

where k is the Boltzmann constant, T is the temperature, x is the coordinate, ξ_t^x is the viscous friction coefficient at x , and $f_x(t)$ and F_x are the projections of the random Brownian force and electrostatic force onto the x axis, respectively. $F_x = -q \cdot \frac{d\varphi}{dx}$, q is the charge, and φ the electrostatic potential.

The Langevin equation for the rotational motion is as follows:

$$\xi_{rot}^x \frac{d\alpha}{dt} = m_x(t) + M_x \quad (2)$$

where α is the angle of rotation, ξ_{rot}^x is the viscous friction coefficient for the rotational motion around the x axis, and $m_x(t)$ and M_x are the moments of the random Brownian force and electrostatic force with respect to the x axis, respectively.

To simplify the calculation of viscous friction coefficients, protein molecules are represented as ellipsoids of revolution with axes $2a$, $2b$, and $2c$ ($2a$ is the axis of revolution, $b=c$, Fig. 2).

The 3D molecular models were constructed based on Protein Data Bank (PDB) data. The axes and sizes of the ellipsoids were chosen in such a way that the moment of inertia relative to the axis of revolution (axis a , Fig. 2) was minimal and equal to the moment of inertia of the protein molecule.

The procedure described above was used to simulate in a solution individual interactions of spinach Pc with turnip

cyt f, PDB ID 2PCF (Kovalenko et al. 2006); interactions of ferredoxin (Fd) and ferredoxin-NADP-reductase (FNR) taken from the cyanobacterium *Anabaena*, PDB ID 1EWY (Kovalenko et al. 2008b); and also interactions of a multienzyme complex PSI from higher plant with light harvesting complex I (LHCI), PDB ID 2O01, with mobile stromal protein flavodoxin from *Anabaena*, PDB ID 1RCF (Abaturva et al. 2008). The ellipsoids of revolution for Pc and cyt f molecules calculated by the procedure described above are presented in Fig. 3 (Kovalenko et al. 2006).

Fig. 8 The logarithm of second-order protein binding rate constant k dependence on the root square of the ionic strength I for the wild-type and mutant Pc and cytochrome f. **a** Experimental data from (Kannt et al. 1996 and Crowley et al. 2004). **b** Simulation results (Kovalenko et al. 2006). k is in $(M \cdot s)^{-1}$, the ionic strength I is in M. Reprinted from (Kovalenko et al. 2006) with permission from IOP Publishing

Simulation of the initial complex formation and description of protein surface by a set of spheres

To calculate the protein collisions, we need to take into account the complex shape of the proteins' molecular surfaces. We approximated the surface of the proteins by a set of spheres (Figs. 4 and 5). With this approximation, two molecules overlap if the respective sets of spheres overlap. This approach ensures a realistic representation of the molecular surface for simulation kinetics of preliminary complex formation and is less time consuming than calculations based on the overlap of each atom because the number of constructed spheres is less than the number of atoms by an order of magnitude. The coordinates of the centers of the spheres and their radii for a given protein are calculated by a special procedure in such a way that the deviation of the protein surface represented by the calculated spheres from the real protein atomic surface is less than 2 Å.

Simulation of the electrostatic interactions; equipotential surfaces of proteins

As two molecules approach each other under the effect of an electrostatic field they may occupy the position favorable for the formation of a precomplex. Our calculations showed that the process of their "electrostatic" orientation enhances the binding rate constant greatly (up to three orders of magnitude) compared to the pure accidental collisions of proteins without the effect of electrostatic forces.

Poisson-Boltzmann calculation is used to determine the electrostatic potential grid around each type of object (Ullmann and Knapp 1999; Fogolari et al. 2002). As a result of the calculation of the potential grid we know the value of the electrostatic potential around each type of object in the model scene where proteins are in the oxidized and the reduced states. Figure 6 demonstrates the equipo-

tential surfaces of cyt f and Pc proteins (Kovalenko et al. 2006), and Fig. 7 shows the equipotential surfaces of Fd and FNR proteins (Kovalenko et al. 2008b).

To evaluate the parameter values of multiparticle models, the results of the simulation were compared with the experimental data obtained for several mutant proteins with different local charges and therefore have different shapes of equipotential surfaces. The equipotential surfaces of the wild type and a mutant Pc are presented in Fig. 6 (left).

Rate constant dependence on the ionic strength

Using the DMSM, we calculated dependences of the protein binding rate constants on the ionic strength for the reaction between Pc and cyt f (Kovalenko et al. 2006), PSI complex with its donor reaction partner Pc and acceptor component Fld (Abaturova et al. 2008), and also Fd with FNR (Kovalenko et al. 2008b) for different mutants. Qualitatively the calculated curves agree with the experimental data. In Fig. 8, experimental and calculated curves for the Pc-cyt f interaction are presented.

The nonlinear dependence of the protein binding rate constant on the ionic strength observed experimentally is realized in the model at certain values of parameters. Such dependences were calculated for the reactions Pc-cyt f, Pc-PSI, PSI-Fld, and Fd-FNR. Obviously this dependence is the result of the great differences between electrostatic potential surfaces of proteins at different ionic strength values. Figures 9 and 10 demonstrate equipotential surfaces for the protein electron acceptor Fld and PSI complex at different ionic strength values.

The calculated rate constant dependence on the ionic strength for the PSI-Fld complex formation at the docking distance 22 Å and docking probability 0.025 is presented in Fig. 11b. As the docking distance we chose the distance between FMN on Fd and F_B cofactor on PSI. Qualitatively the calculated curve is in agreement with the experimental

Fig. 9 Equipotential surfaces, -6.5 mV (red) and +6.5 mV (blue), for flavodoxin. Green points are atoms of the molecule; the arrow points to the FMN cofactor. **a** Ionic strength is 0 mM. **b** Ionic strength is 80 mM (Abaturova et al. 2008)

Fig. 10 Equipotential surfaces, -6.5 mV (red) and $+6.5$ mV (blue), for PSI. The luminal side is on the bottom, the stromal side is on the top. **a** Ionic strength is 0 mM. **b** Ionic strength is 80 mM (Abaturova et al. 2008)

dependence of the observed rate constant k_{obs} upon the ionic strength for Fd binding with PSI (Medina et al. 1992) (Fig. 11a). Generally the calculated second-order and observed rate constants can not be compared directly because k_{obs} includes both association and electron transfer steps. However the electron transport step is considered to be faster than the protein binding.

The sloping portion of the curve in Fig. 11 at ionic strength values greater than 40 mM is due to the decrease in the electrostatic attractive forces at high ionic strength values. Similar sloping experimental dependences are represented in Fig. 8. Noteworthy is the nonmonotonic character of the experimental and calculated dependences, manifested as the drop in the observed rate constant at ionic strength below 40 mM (Fig. 11a,b).

Medina et al. (1992) and Ubbink et al. (1998) suggested that such a drop in the rate constant at low ionic strength

values is due to the shift in the equilibrium between protein complex substates to the fast-exchanging electrostatically favorable orientations of flavodoxin and PSI. These orientations are not optimal for the final complex formation capable of electron transfer. Our model shows a similar drop in the rate constant of the preliminary complex formation at ionic strength values below the optimal value. Thus the direct multiparticle simulation supports the conclusion that such nonmonotonic dependence is due mainly to electrostatic effects.

Modeling of protein interactions in a photosynthetic membrane

The values of parameters, obtained by the DMSM analysis of protein interactions in solution, with the account of electrostatic interactions were further used to simulate

Fig. 11 a Experimental dependence of the observed rate constant for PSI-Fd reaction on the solution ionic strength. Reprinted from (Medina et al. 1992) with permission from Elsevier and the author. **b** Calculated dependence of the second-order rate constant at docking distance $r=22$ Å and docking probability $p=0.025$ (Abaturova et al. 2008)

Fig. 12 The model scene visualization (the thylakoid lumen bounded by the thylakoid membranes) with proteins plastocyanin (Pc) and cytochrome f (Cyt f)

interactions of mobile carrier Pc and cyt f as part of the cytochrome complex protruding into the lumen space (see Fig. 12) (Kovalenko et al. 2008a). The model scene of the luminal space was presented as a rectangular parallelepiped, bounded by membranes at the top and bottom, while at the butt ends, the mirror boundary conditions were assumed (Fig. 12).

The spaces of the membranes, the distance between the membranes, the density of cytochrome complexes in the membranes, and mobile Pc molecule concentrations were evaluated according to the literature data. The diameter of the granal membrane ranges from 300 to 600 nm (Staehelin and van der Staay 1996), the density of cyt bf complexes in the membrane is about 2.55 per 1,000 nm² (Albertsson 2001), and the number of Pc molecules is considered to be equal to the number of cyt bf complexes (at the span of the lumen 100 Å it corresponds to Pc concentration 430 μM).

By means of the DMSM we studied the dependence of the reaction rate constant on the distance between the membranes (the width of the lumen). It was shown (Fig. 13) that the rate constant value has a maximum at the distance of 8 nm, which is the distance between thylakoid membranes under physiological conditions in natural photosynthesis (Dekker and Boekema 2005). The increase in the distance over the optimum leads to the rate decrease because of the drop in the concentration of Pc molecules taking part in the reaction. The distance decrease below the optimal value also leads to the rate constant decrease because Pc diffusion in the luminal space becomes difficult and even impossible at the small lumen width. This conclusion corresponds to the known effect of hyperosmotic stress, changing the lumen volume and inhibiting the Pc-cyt reaction, which is observed experimentally (Cruz et al. 2001).

Conclusions and perspectives

DMSM simulates reactions describing interactions of ensembles of molecules in the heterogeneous interior of a cell. The adequacy of the model is verified by comparing the simulated kinetics with the experimental data. The advantage of the method is the capability to take directly into account shapes and dimensions of interacting molecules and structural elements within the reaction volume.

By modifying the shape and geometric parameters of the reaction volume, the number and arrangement of the interacting molecules and other characteristics, it is possible to study their effects on the rate of the reaction under consideration. Using PDB data one can “directly” calculate the distribution of the electrical potential around the interacting protein molecules and study the effect of electrostatic interactions on the docking and formation of the supercomplex, where the redox reaction occurs.

The Brownian dynamics method known from the literature, which can be used for predicting the structure of protein complexes, considers the interaction of only two molecules in solution (Ullmann et al. 1997; Pearson and Gross 1998; Rienzo et al. 2001; Gross and Pearson 2003; Gross and Rosenberg 2006). A characteristic feature and novelty of our method is the capability to use it for studying the interactions of several protein molecules simultaneously. This makes it possible to simulate the formation of a large number of complexes, as takes place in solution or cell compartments, and to monitor the real-time kinetics of this process.

In DMSM, as in the BD approach, the proteins are considered as rigid bodies. This prevents simulation of conformational changes and molecular flexibility at the protein-protein interface, which are important in the process of final complex formation and dissociation processes. In

Fig. 13 Dependence of the protein binding rate constant of the Pc-cyt f reaction divided by cyt f concentration in the thylakoid lumen on the distance z between the membranes at constant number of molecules (Kovalenko et al. 2008a)

the current version of DMSM, these processes are included implicitly with the parameter of probability of interaction. To solve this problem, we need to combine DMSM with molecular dynamics methods. We will address this problem in the future.

A possible application of DMSM is the prediction of protein binding sites. It can be useful in detecting common arrangements of functional amino acid residues when it is possible to assume that their conformation is well-conserved (Kovalenko et al. 2009). Electrostatics is a very important scoring parameter that can reduce the number of possible locations of the binding surface. DMSM allows us to study the way physical mechanisms of molecular interactions (diffusion, electrostatics, etc.) determine general dynamics of the processes occurring in a cell.

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