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Modelling of Binding Free Energy of Targeted Nanocarriers to Cell Surface

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Abstract

We have developed a numerical model based on Metropolis Monte Carlo (MC) and the weighted histogram analysis method (WHAM) that enables the calculation of the absolute binding free energy between functionalized nanocarriers (NC) and endothelial cell (EC) surfaces. The binding affinities are calculated according to the free energy landscapes. The model predictions quantitatively agree with the analogous measurements of specific antibody coated NCs (100~nm in diameter) to intracellular adhesion molecule-1 (ICAM-1) expressing EC surface in *in vitro* cell culture experiments. The model also enables an investigation of the effects of a broad range of parameters that include antibody surface coverage of NC, glycocalyx in both *in vivo* and *in vitro* conditions, shear flow and NC size. Using our model we explore the effects of shear flow and reproduce the shear-enhanced binding observed in equilibrium measurements in collagen-coated tube. Furthermore, our results indicate that the bond stiffness, representing the specific antibody-antigen interaction, significantly impacts the binding affinities. The predictive success of our computational protocol represents a sound quantitative approach for model driven design and optimization of functionalized nanocarriers in targeted vascular drug delivery.

Introduction

Targeted drug delivery using functionalized nanocarriers (i.e., NCs coated with specific targeting ligands) has been recognized and clinically proven as a promising technique in both therapeutic and diagnostic applications in cancer treatments [1]. The use of functionalized NCs instead of direct injection of drugs has the advantages of better efficiency and less toxicity to normal tissues. However, this procedure also introduces a

wide range of tunable design parameters (size, shape, type, method of functionalization, etc.). In principle, very many experiments are required to reach the optimal treatment in drug delivery [2]. Therefore a unified model, which can characterize and identify the important components, is very useful to the design of the drug delivery using functionalized NCs.

An important feature of this problem is that the local hydrodynamic flow and associated shear play important roles in both NC transportation inside blood vessel and subsequent binding to cell surfaces. Shear-enhanced binding has been observed in a variety of systems in recent years [3-6]. The shear-enhanced binding is characterized by a threshold flow rate. Below that threshold, the rolling velocity decreases with shear rate, while it increases with shear rate above that value. The initial decrease is physiologically important but conceptually counterintuitive. Also, the shear-enhanced binding is commonly attributed to the formation of catch bonds, which dictates a protein structural change under the application of a sufficiently strong tensile force. Catch bonds for different interactions have been directly observed in recent (atomic force microscopy) AFM experiments [7-9]. However, there is still no conclusive evidence that only the catch bond phenomenon can lead to enhanced binding in flow experiments.

Recently, we have numerically investigated the shear-enhanced binding in the context of drug delivery to endothelial cells using a nanocarrier [10]. Without invoking the catch bonds, we were able to reproduce the phenomenon of shear-enhanced binding. This suggests that an alternative mechanism involving an interplay among the multivalent interactions, shear flow, and bond compliance may also lead to shear-enhanced binding. In our model, we numerically compute the binding affinities (association constants) based on the free energy landscapes between the NC and EC surface. The free energy landscapes (or potential of mean force PMFs) are calculated using Metropolis Monte Carlo (MC) and the weighted histogram analysis method (WHAM). This model has been rigorously validated through comparison with *in vitro*, *in vivo* and AFM experiments [11]. In an important extension of this approach described in Ref. [10], we showed that the functional dependence of the binding affinity of NC versus shear force conforms to shear-enhanced binding; that is, for shear rates less than a threshold value, the binding affinity increases with increase in shear, and for those above the threshold, the binding affinity decreases with increase in shear. This biphasic trend in binding affinity versus shear is in contrast to the behavior of rolling velocities versus shear (for which experimental data have been reported). Based on the similarities in the biphasic trend versus shear rate, we propose that binding affinity can prove to be an important indicator of shear-enhanced binding. In this paper, we compare our computational predictions of binding affinity versus shear with experimental data reported in the literature [12], in which the authors measured the equilibrium binding of antibody coated red blood cells (RBC) to a collagen-coated surface under flow conditions. Furthermore, we investigate the effect of bond stiffness (compliance) on binding, which can be potentially applied to rationalize the discrepancies observed between modeling results and experimental measurements.

Methodology

Model Implementation

A detailed description of the numerical methods can be found in our previous publications [10,11,13]. Here we only provide a brief outline. As shown in Fig. 1, the NC is modeled as a rigid sphere with radius a and its surface is decorated with uniformly distributed antibodies. The binding between the NC and cell surface is through the interactions between antibodies and antigens (ICAM-1s), which are allowed to freely diffuse on a flat surface. The interactions are considered through the Bell model [14], in which the interacting complex is treated as a spring, $G_r(d) = G_0 + 0.5kd^2$. Here d represents the distance between the reaction sites of the antibody and antigen, G_0 is the free energy change at equilibrium state ($d = 0$) and k is the interaction bond stiffness.

We also account for the antigens' flexure by allowing them to bend and rotate in θ and φ space (see Fig. 1). Under the assumption of small flexural deformations, the flexure of an antigen can be treated as bending a beam from equilibrium (upright) position. The bending energy can be calculated as (see Ref. [15] for details):

$$\Delta G_f = (2EI/L^3)y_L^2, \quad (1)$$

where EI is the flexural rigidity of antigens, L represents the antigen length and y_L is the distance of the antigen tip from its equilibrium upright position. For small deformations, $y_L \approx L\theta$, therefore the bending energy can be expressed as:

$$\Delta G_f(\theta) = (2EI/L)\theta^2. \quad (2)$$

Clearly the antigen flexural movement is highly orientation dependent. Hence, a configurational-biased sampling technique [16], which obeys the detailed balance, is implemented in our model to improve the sampling efficiency. Detailed implementation can be found in Ref. [13].

To include the effect of flow, as shown in Fig. 1, a simple one-dimensional shear flow with shear rate of S is considered. The flow induced drag F_x and torque T_y are calculated by solving the steady-state Stokes equation for the shear flow past a sphere located near a surface:

$$\begin{cases} \nabla p = \mu \nabla^2 \mathbf{u} \\ \nabla \cdot \mathbf{u} = 0 \end{cases}, \quad (3)$$

with the no-slip boundary conditions and inlet flow condition of $u = Sz$, where μ is the dynamic viscosity of the fluid and S is the shear rate. At the outlet we assume a fully developed flow. In our simulations, we set $\mu = 0.001 \text{ kg m}^{-1} \text{ s}^{-1}$ (dynamic viscosity of water). The Stokes equations are solved using the commercial software COMSOL and the flow induced drag F_x and torque T_y at discrete vertical points z_i are computed through integration

of the force and torque on NC surface. The calculated drag and torque are found to be consistent with theoretical data from Goldmann *et al.* [17] when the sphere is close to the surface. Functions $F_x(z)$ and $T_y(z)$ are then obtained by fitting the numerical data through a cubic approximation [10]. In our Monte Carlo simulations, $F_x(z)$ and $T_y(z)$ will affect the Metropolis acceptance by introducing additional energies during NC translation and rotation steps.

Regular Metropolis Monte Carlo steps are employed for: (i) bond formation/breaking, (ii) NC translation and rotation, and (iii) antigen translation. Step (i) is selected randomly with a probability of 50%, and in the remaining 50%, the NC translation, rotation, and antigen translation are selected randomly with probability of $0.5N_{ab}/N_t$, $0.5N_{ab}/N_t$ and $(N_t - N_{ab})/N_t$ respectively; N_t is the combined total number of antibodies (N_{ab}) and antigen molecules. The simulations are run in parallel on four processors with different realizations of the same physical system. An adaptive step size for NC translation/rotation and antigen diffusion is implemented to ensure a Metropolis acceptance rate of 50%.

Calculation of Binding Affinity

Following the procedures described in Ref. [18], we developed a methodology to compute the binding affinities (K_a) between NCs and cell surfaces. Briefly, for a general interaction between ligands (**L**) (or NC) and receptors (**R**), the binding process can be described as: **L** + **R** $\leftrightarrow$ **LR**, where **LR** is the ligand and receptor in binding state. At thermodynamic equilibrium for a dilute solution, K_a is defined as:

$$K_a = \frac{[\mathbf{LR}]}{[\mathbf{L}][\mathbf{R}]} = \frac{p_1[\mathbf{R}]_{tot}}{[\mathbf{L}]p_0[\mathbf{R}]_{tot}} = \frac{1}{[\mathbf{L}]} \times \frac{p_1}{p_0}. \quad (4)$$

Here **[L]**, **[R]** and **[LR]** are concentrations of each species, p_0 and p_1 are the fractions of receptors with no ligand and one ligand bound respectively, therefore **[R]** and **[LR]** can be expressed as **[R]** = $p_0[\mathbf{R}]_{tot}$ and **[LR]** = $p_1[\mathbf{R}]_{tot}$, where **[R]_{tot}** is the total receptor concentration in the whole system. We relate the fraction in Eq. (4) to the ratio of the integral of configurational degrees of freedoms in the bound state to the unbound state:

$$K_a = \frac{1}{[\mathbf{L}]} \times \frac{\int_{bound} d\mathbf{1}d\mathbf{X} e^{-\beta U_{bound}}}{\int_{unbound} d\mathbf{1}d\mathbf{X} e^{-\beta U_{unbound}}}, \quad (5)$$

where U_{bound} and $U_{unbound}$ are the total potential energies of the system at bound and unbound states, $\beta = 1/k_B T$ in which k_B is the Boltzmann constant and T is the absolute temperature. Here **1** represents all the degrees of freedom associated with the ligand (NC) and **X** is the degrees of freedom for the remaining molecules (receptors). On a per ligand basis, the ligand concentration is **[L]** = $1/V_{unbound}$, where the denominator is the volume accessible to an unbound ligand. The integral associated with the unbound state ($U_{unbound} = 0$) in Eq. (5) is determined over translational degrees of freedom (yielding the volume $V_{unbound}$), and rotational degrees of freedom (yielding a factor of $8\pi^2$ in 3-dimensions).

The final form of the binding affinity for interactions between NC and cell surface can be expressed as:

$$K_a = \frac{1}{[\mathbf{L}]} \times T_1 \times T_2 \times T_3, \quad (6)$$

where T_1 represents the entropy loss from the bounded receptors and it can be calculated as:

$$T_1 = \frac{A_{R,b}^{(1)} \times A_{R,b}^{(2)} \times \dots \times A_{R,b}^{(N_b)}}{A_{R,ub}^{(1)} \times A_{R,ub}^{(2)} \times \dots \times A_{R,ub}^{(N_b)}}. \quad (7)$$

Here $A_{R,b}^{(n)}$ is the accessible surface area to the n th receptor in the bound state and $A_{R,ub}^{(n)}$ is the area in the unbound state. Term T_2 accounts for the NC rotational entropy loss due to binding:

$$T_2 = \frac{(N_{ab}/N_b)\Delta\omega}{8\pi^2}, \quad (8)$$

where N_{ab} is the number of antibodies per NC, N_b is the total number of bonds in equilibrium state, ω is the rotational volume of the NC in the bound state which can be determined from the distributions of Euler angles as described in Ref. [19]. The term T_3 accounts for NC translational entropy loss,

$$T_3 = \frac{A_{NC,b} \int e^{-\beta W(z)} dz}{A_{NC,ub} l_z}, \quad (9)$$

where $A_{NC,b}$ is the area for the NC translational movement in the bound state, $A_{NC,ub}$ and $A_{NC,ub} l_z$ are the area and volume accessible to the NC in the unbound state, and $W(z)$ is the potential of mean force (PMF).

To calculate the PMF, $W(z)$, we define the distance between the center of the NC and cell surface as the reaction coordinate z , along which we perform umbrella sampling with harmonic biasing potentials. The umbrella sampling is performed with window size of Δz and the harmonic biasing potential in each window is chosen to be $0.5k_u(z-z_{0,i})^2$, where $0.5k_u(\Delta z)^2 = 1.0 \times 10^{-20}$ J, k_u is the harmonic force constant and $z_{0,i}$ is the location of the center of window i . In our calculations the value for $\Delta z = 0.05$ nm which results in the value of $k_u = 8$ N/m. The NC is slowly moved to the cell surface by updating $z_{0,i}$. A total of 200 million Monte Carlo steps are performed in each window and the histogram is stored only when there exists at least one bond. All the relevant parameters including the window size Δz , strength of the biasing potential k_u and the sampling size in each window have been tested to ensure convergence. The WHAM algorithm is used to unbias and combine the histograms in different windows to form a complete PMF profile using a tolerance factor of 10^{-6} . PMF profiles for each system are averaged over four independent realizations.

Simulation Parameters

To make direct comparison with available experiment [20], the receptor (antigen) parameters are chosen to mimic ICAM-1, the ligand (antibody) parameters are chosen to mimic the murine anti-ICAM-1 antibody which binds specifically to ICAM-1. For the interactions between antibody and ICAM-1, Muro *et al.* [20] reported the equilibrium free energy change between antibody and ICAM-1 to be -7.98×10^{-20} J at 4°C, which we set as G_0 in the Bell model of our simulations. We estimate the bond stiffness $k = 1.0$ N/m (1000 dyn/cm) by fitting rupture force distribution data reported from single-molecule force spectroscopy [15,21]. Both G_0 and k are assumed to be temperature independent based on which we derive the value of the reactive compliance γ (distance along the reaction coordinate to reach the transition state or point of rupture) to be ~ 0.4 nm, which agrees very well with experimental measurements [21,22]. The saturation antibody coverage has been experimentally determined to be 220 per NC with a diameter of 100 nm (or 7000 Ab/ μm^2) [20]. The ICAM-1 surface density on endothelial cell is set at 2000 ICAM-1 molecules/ μm^2 to be consistent with experimental report of the available binding sites per endothelial cell. Finally, the flexural rigidity of ICAM-1 (see Fig. 1) EI is set at 7000 pN $\cdot\text{nm}^2$, which lies in between that of glyco-proteins (700 pN $\cdot\text{nm}^2$) and actin filaments ($15\text{--}70 \times 10^3$ pN $\cdot\text{nm}^2$) [23].

Results

In our earlier work, Ref. [10], we investigated the effects of particle size and glycocalyx, and we showed that while the binding affinities were only moderately affected by the particle size, the glycocalyx thickness exponentially impacted the binding. We further studied the flow effect and were able to reproduce the shear-enhanced binding, similar to rolling velocity measurements in experiments. However, the rolling velocity is a non-equilibrium quantity, which is not directly related to binding affinity. Here we present a more relevant comparison between model predictions and equilibrium measurements. In the simulations we have neglected the effects of glycocalyx, cell membrane deformation, and cellular processes such as nanocarrier uptake for simplicity. Strategies for implementing such effects have recently been discussed in a recent review [24].

Flow Enhanced Binding

In Ref. [12], the authors have measured the effect of flow rate on RBC targeting to collagen-coated surfaces. The experiments were performed in a plastic tube having an inner diameter of 3 mm and an inner surface coated with collagen. Antibodies, which bind specifically to collagens, were attached to the RBC surface. Then the tube was perfused with the RBC solution at different flow rates. The final binding of RBCs to the tube was determined by γ -counting. Interestingly, they observed a threshold flow rate below which the binding was enhanced (see Fig. 4 in Ref. [12]). Since the data consist of equilibrium measurements of the binding and directly related to the binding affinities calculated in our model, we re-analyzed the data and compared that with our flow results in Ref. [10]. Here, we assume the RBCs to be rigid spheres having a diameter of 8 μm , the fluid dynamic viscosity is $0.001 \text{ kg}\cdot\text{m}^{-1}\text{s}^{-1}$ and the flow inside the tube is laminar Poiseuille flow. We then estimate the shear force (F_x) on the RBCs (which is the characteristic force transmitted to the individual bond) and re-plot the data in Figure 2 as a function of shear force.

In Fig. 2, the left y-axis shows our numerical calculation of binding affinities (K_d) at different shear forces for two NC sizes (100 and 200 nm) and the right y-axis shows the experimental data from. The antibody surface coverage is kept at 74% in our simulations. As shown, the threshold shear force, at which the binding is maximum, is around 20 pN and is relatively insensitive to the particle size (this is consistent with experimental observations in Ref. [25]). Interestingly, the threshold shear force is about 10 pN in experiments. There is only a factor of two difference between our calculations and the experimental measurement. Considering the assumptions we have made in calculating the shear force (mainly the deformability and shape of the RBC), this agreement is surprisingly remarkable.

Effect of Spring Bond Stiffness in Bell Model

Many factors other than the above-mentioned assumptions may contribute to the difference in the threshold shear force between our modeling results and those of experiments. In an earlier paper [13], we have investigated the sensitivity of the antigen flexure on the binding affinity and showed that the results are a weak function of the flexural rigidity in the range of physiological variation of flexure. However, one of the most important parameters, as stated in Ref. [10], is the bond stiffness (compliance) k used in our model. In principle, this parameter characterizes the interaction between specific antibody-antigen pair. To demonstrate the sensitivity of our results to k , we keep the equilibrium free energy G_0 fixed and calculate the PMF profiles for two more cases with $k = 1.25$ and 0.75 N/m, which correspond to 25% larger and smaller than the original value (1.0 N/m). As a result, the values of the reactive compliance are 0.36 and 0.46 nm respectively.

Fig. 3 shows the PMF profiles at different bond stiffness. All three cases are characterized by three firm bonds; however, the free energy changes at equilibrium are significantly different. Decreasing the bond stiffness (increasing the reactive compliance) by 25% enhances the magnitude of the free energy well by $\sim 2k_B T$. Following the procedures described above, based on the PMF profiles and bond distribution (data not shown), we can calculate the binding affinities (dissociation constants shown in the right part of Fig. 3). As clearly shown, the bond stiffness (compliance) indeed significantly impacts the binding. Moreover, it is highly likely this parameter also influences the shear threshold value and therefore can be used to rationalize the difference between model results and experimental data. The value of the bond compliance is experimentally measurable through single molecule force induced detachment experiments [11]. The significance of the sensitivity is that the precise threshold shear force for shear-enhanced binding can be dependent on the bond compliance, which in turn depends on the specific receptor-ligand pair. The physiological impact of bond stiffness in shear flow is currently under investigation and will be explored in future studies.

Conclusions

A versatile yet powerful numerical model has been developed for simulations of drug delivery using nanocarriers. By accurately taking account all the entropy changes during binding, we are able to quantitatively reproduce a variety of experimental measurements. Using this model, we investigated the shear-enhanced binding and compared with

measurements of RBC binding in collagen-coated tube under different flow rates. The distinctive feature of the experiments referred here [12] is that, unlike the rolling velocities measured in Ref. [25], the RBC binding was an equilibrium measurement while the particle (cell) rolling under flow is a non-equilibrium process, although they both show similar shear-enhanced binding. The measurement in Ref. [12] is directly related to the binding affinities calculated in our model. We further studied the effect of bond stiffness (compliance) on binding and found the binding is substantially affected by this parameter. This finding can be exploited to rationalize the discrepancies observed in different experiments involving different interacting antibody-antigen pairs. In summary, the numerical protocol has been validated and employed to help us understand the fundamental mechanisms at play. Therefore, our numerical model represents a quantitative and predictive tool in aiding the design and optimization of targeted drug delivery using nanocarriers.

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Figure 1.
Schematic of model implementation.

Figure 2.

A comparison between simulations and experiments in shear-enhanced binding. The left y-axis represents the simulation results of binding affinities at two different sizes (open circles), the right y-axis shows the experimental measurement of RBC binding (filled triangles). The vertical axes are rescaled for better comparison.

Figure 3.

The PMF profiles at different bond stiffness (left) and the corresponding dissociation constants (right) calculated based on the PMF profiles.