Molecular Recognition in Membrane Adhesion

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Cells adhere to other cells via adhesion molecules located on their membrane surfaces. Each adhesion molecule on one cell binds to a "partner molecule" on the other cell. The two binding partners can be identical molecules, like two hands holding each other, or distinct molecules that fit together like a lock and a key. Cadherins, for example, are adhesion molecules that often bind to identical cadherins, holding together cells of the same type in the development and maintenance of body tissues. Integrins and selectins, on the other hand, bind to distinct adhesion partners, for example during adhesion of white blood cells in an immune defense.

The adhesion of two cells involves a subtle balance between the attractive binding energies of the adhesion molecules and repulsive energies, which result from cell shape fluctuations or from large non-adhesive proteins that impede adhesion. In a healthy organism, cells have to control this balance between attraction and repulsion. For some cancers, mutations of adhesion molecules shift the balance and lead to abnormal cell-cell adhesion events and tumor growth.

Active Switching of Adhesion Molecules

Via gene expression, cells can regulate the numbers and types of adhesion molecules at their surfaces and, thus, the strength and specifity of their adhesiveness. But some cells are known to change their adhesiveness rather quickly, much more quickly than gene expression allows. These cells have adhesion molecules that can be switched between different states. Integrins, for example, are adhesion molecules that have at least two different conformational states. In a "stretched" conformational state, the integrins are active and can bind to their partners on an apposing cell surface. In a "bent" state, the integrins are inactive and can't bind (see **Fig. 1**).

The numbers of active integrins are crucial for the adhesiveness of these cells. But besides mere numbers, other effects may count as well. We have shown that the characteristic switching rates of adhesion molecules can strongly affect the adhesiveness. The switching of an adhesion molecule between an active and an inactive conformation is a stochastic process, i.e. a process that occurs with a certain probability at a certain time. The process typically requires the input of "chemical energy", e.g., from ATP molecules, at least in one direction.

We have thus studied the adhesion of membranes via switchable adhesion molecules **[1, 2, 3]**. The two opposing forces in the adhesion balance of the membranes are the attractive forces of the adhesion molecules, and repulsive forces from membrane shape fluctuations. Both forces have characteristic times scales. These time scales are the switching times of the adhesion molecules, and the relaxation times of the membrane shape fluctuations. A resonance effect occurs if the characteristic times are similar (see **Fig. 1**). The resonance leads to an increase in membrane fluctuations, and to a decrease of the adhesiveness of the membranes **[1, 3]**.

This resonance effect may also be used to control cell adhesion. During the last decade, synthetic molecules have been developed that can be switched by light between different conformations. The switching times of such molecules depend on the light intensity. Anchored at a substrate, the molecules can be used to switch the adhesive substrate properties and, thus, to manipulate and study cell adhesion.

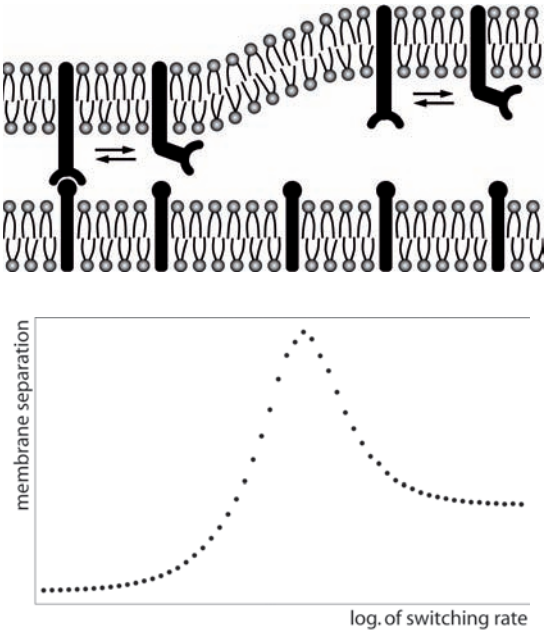

Fig. 1: (Top) A membrane with switchable adhesion molecules adhering to a second membrane. The adhesion molecules are switched between a stretched, active conformation and a bent, inactive conformation. In the stretched conformation, the adhesion molecules can bind to their ligands in the other membrane. (Bottom) Membrane separation as a function of the receptor switching rate. The active switching leads to a stochastic resonance with increased membrane separations at intermediate switching rates.

Long and Short Adhesion Molecules

The adhesion of biological membranes often involves various types of adhesion molecules. These adhesion molecules can have different lengths. The adhesion molecule complexes that mediate the adhesion of T cells, for example, have characteristic lengths of 15 or 40 nm. During T cell adhesion, a lateral phase separation into domains that are either rich in short or long adhesion molecules occurs. The domain formation is presumably caused by the length mismatch of the adhesion molecules **[4]**. The domains may play a central role for T cell signaling in immune responses.

We have developed a statistical-mechanical model for membranes interacting via various types of adhesion molecules **[4, 5]**. In our model, the membranes are discretized into small patches that can contain single adhesion molecules. The conformations of the membranes are characterized by the local separation of apposing membrane patches, and by the distribution of adhesion molecules in the membranes.

The equilibrium phase behavior of the membranes can be derived from the partition function of our model. The partition function is the sum over all possible membrane conformations, weighted by their Boltzmann factors. In our model, the summation over all possible distributions of the adhesion molecules in the partition function leads to an effective double-well potential (see **Fig. 2**). The depths of the wells depend on the concentrations and binding energies of the molecules.

The membranes exhibit two characteristic phase transitions. The first transition is the unbinding transition of the membranes, which is driven by an entropic membrane repulsion arising from thermal shape fluctuations. The second transition is lateral phase separation within the membranes, driven by the length mismatch of the adhesion molecules. The length mismatch leads to a membrane-mediated repulsion between long and short adhesion molecules, because the membranes have to be bent to compensate this mismatch, which costs elastic energy. This repulsion leads to a lateral phase separation for sufficiently large concentrations of the molecules and, thus, sufficiently deep wells of the effective potential (see **Fig. 3**).

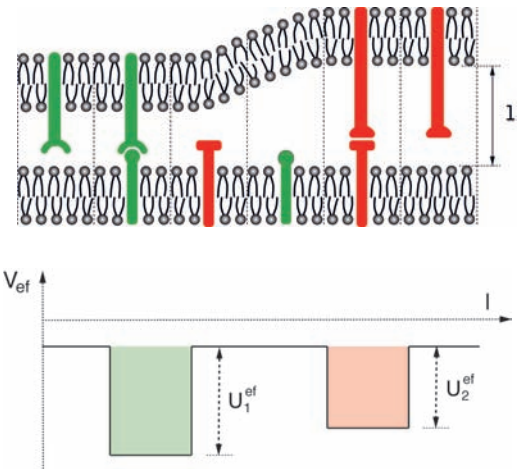

Fig. 2: (Top) A membrane containing long and short receptor molecules (upper membrane) adhering to a membrane with complementary ligands. (Bottom) The effective adhesion potential V_{ef} of the membranes is a double-well potential. The potential well at short separations l reflects the interactions of the short receptor/ligand bonds, the well at larger separations reflects the interactions of the long receptor/ligand bonds.

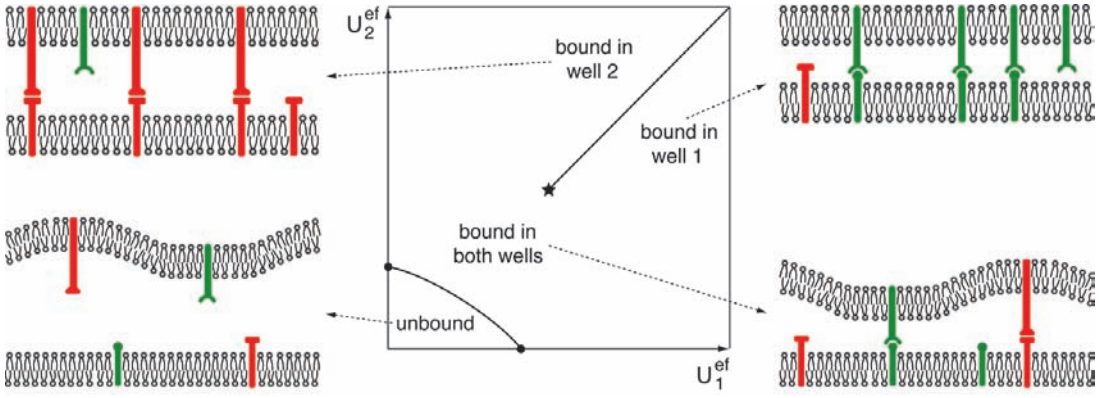

Fig. 3: Phase diagram of membranes adhering via long and short adhesion molecules. The membranes are unbound for small well depths U_1^{ef} and U_2^{ef} of the effective interaction potential shown in Fig. 2, i.e. for small concentrations or binding energies of receptors and ligands. At large values of U_1^{ef} and U_2^{ef}, the membranes are either bound in well 1 or well 2. At intermediate well depths, the membranes are bound in both potential wells.

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