Membrane Adhesion

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In the classic fluid-mosaic model of Singer and Nicolson, biological membranes are envisioned as lipid bilayers with embedded or adsorbed proteins. Recent research on membranes emphasizes two important 'updates' of this picture: First, biological membranes contain *domains* of different composition, and second, *active processes* play a central role for many membrane functions. Our theoretical models of membranes and membrane adhesion are focused on these two novel aspects.

In principle, the formation of membrane domains can be driven by a demixing of the lipid bilayer, or by the aggregation of membrane proteins. Our research here focuses on protein aggregation, in particular during membrane adhesion. The adhesion of biological membranes is mediated by various types of receptors and ligands, also called 'stickers'. These stickers often differ in their characteristic binding lengths. The length difference leads to an indirect, membrane-mediated repulsion between long and short stickers, simply because the lipid membranes have to be curved to compensate the length mismatch, which costs bending energy. The membrane-mediated repulsion causes a lateral phase separation into domains containing short and domains containing long stickers (see **Fig. 1**). In general, the lateral phase behavior depends on the sticker concentrations. Lateral phase separation can only occur if the sticker concentrations exceed a critical threshold. An additional driving force for phase separation comes from large, repulsive glycoproteins, which form a steric barrier for the binding of short stickers. The rich equilibrium phase behavior of such membranes can be characterized using scaling estimates and Monte Carlo simulations.

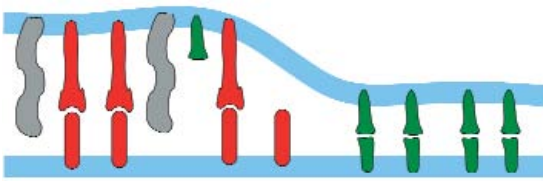

Fig. 1: Domain formation in membranes adhering via short (green) and long (red) receptor-ligand complexes, or 'stickers'. The domains are caused by the length mismatch between the complexes. Repulsive glycoproteins (grey) pose a steric barrier for the short sticker complexes and constitute an additional driving force for the domain formation.

The protein domains in biological membranes are often highly dynamic. Intriguing examples are the domain patterns formed during T cell adhesion. The patterns are composed of domains which either contain short TCR/MHCp receptor-ligand complexes or the longer LFA-1/ICAM-1 complexes. The domain formation is driven by the length difference between the TCR/MHCp and the LFA-1/ICAM-1 complexes. During T cell adhesion, the domains evolve in a characteristic pattern inversion: The final pattern consists of a central TCR/MHCp domain surrounded by a ring-shaped LFA-1/ICAM-1 domain, whereas the characteristic pattern formed at intermediate times is inverted with TCR/MHCp complexes at the periphery of the contact zone and LFA-1/ICAM-1 complexes in the center.

We have studied the pattern formation dynamics in a statistical-mechanical model for the adhesion of multicomponent membranes [**1,3**]. In this model, the adhesion geometry of the cells is taken into account by dividing the membranes into a contact zone and a non-adhering membrane region (see **Fig. 2**).

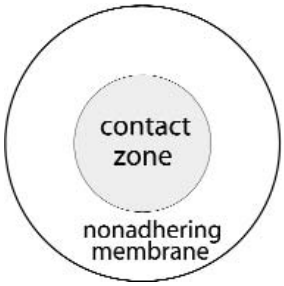

Fig. 2: Cell adhesion geometry. The circular contact zone is surrounded by a nonadhering membrane ring. Receptors, ligands, and glycoproteins diffuse around in the whole membrane, but interact with the apposing membrane only within the contact zone.

We consider the pattern formation in Monte Carlo simulations (see **Fig. 3**) and propose a novel self-assembly mechanism for the formation of the intermediate inverted T-cell pattern. This mechanism is based (i) on the initial nucleation of numerous TCR/MHCp microdomains, and (ii) on the diffusion of free receptors and ligands into the cell contact zone. The diffusion of receptors and ligands into the contact zone leads to the faster growth of peripheral TCR/MHCp microdomains and to a closed ring for sufficiently large TCR/MHCp concentrations. At smaller TCR/MHCp concentrations, we observe a second regime of pattern formation with characteristic multifocal intermediates, which resemble patterns observed during adhesion of immature T cells or thymozytes. The formation of the final T-cell pattern requires active cytoskeletal transport processes in our model, in agreement with experimental findings **[3]**.

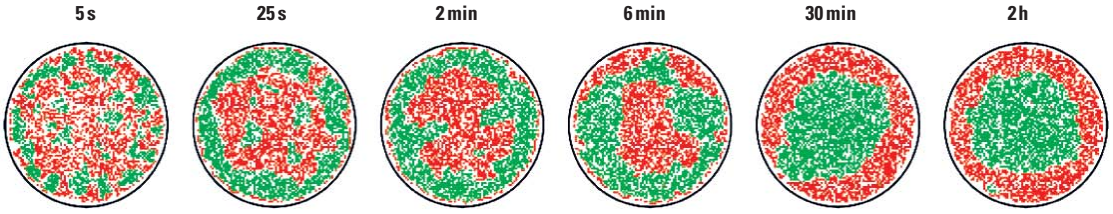

Fig. 3: Simulated pattern formation during T cell adhesion. Within the first minute of adhesion, a peripheral ring of short TCR/MHCp complexes (green) is formed, surrounding a central domain of long ICAM-1/LFA-1 complexes (red). After 30 minutes, this pattern is inverted and a central TCR/MHCp domain emerges.

Active processes also play a role in controlling the adhesiveness of biological membranes. We have considered a simple theoretical model of membranes with active adhesion molecules, or 'stickers' **[4]**. The stickers are actively switched 'on' or 'off', which keeps the system out of thermal equilibrium. We find that the phase behavior of the membranes depends rather sensitively on the switching rates of the stickers and not only on the fraction of 'on'-stickers. In asymptotic regimes of 'slow' and 'fast' switching, we obtain exact results that relate the unbinding behavior of the active membranes to well-studied properties of equilibrium membranes. At intermediate switching rates, we observe resonance and weak binding in Monte Carlo simulations. These results may provide insights into novel mechanisms for the controlled adhesion of biological or biomimetic membranes.

Membranes elastically mediate interactions also between curved objects adhering to them **[2]**. These membrane-mediated interactions are related to those between long and short stickers. The adhesion of curved objects such as rods or beads causes a local perturbation of the equilibrium membrane shape, which leads to the indirect, membrane-mediated interactions. For a planar membrane under a lateral tension, the interaction between two parallel rods is repulsive if the rods adhere to the same side of the membrane, and attractive if the rods adhere at opposite membrane sides. For a membrane in an external potential, the membrane-mediated interactions between adsorbed rods are always attractive and increase if forces perpendicular to the membrane act on the rods.

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References:

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