Current Opinion in Colloid & Interface Science 18 (2013) 432–439

Contents lists available at ScienceDirect

Current Opinion in Colloid & Interface Science

journal homepage: www.elsevier.com/locate/cocis

Physics of interactions at biological and biomaterial interfaces ☆

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ARTICLE INFO

Article history:
Received 28 May 2013
Received in revised form 1 July 2013
Accepted 2 July 2013
Available online 10 July 2013

Keywords:
Supported membrane
Grazing incidence
X-ray fluorescence
Offspecular scattering
Cell adhesion
Cell migration

ABSTRACT

Soft interlayers based on membranes and biopolymers define the spatial boundaries between different phases in biological systems. Physical interactions of soft matter under biologically relevant conditions (in aqueous media containing various ions) are governed by complex interplays of generic and specific interfacial interactions, which are clearly different from those acting at the interface between hard matter. This review aims at providing a comprehensive overview on: (a) models of cell–cell and cell–tissue interfaces with aid of defined building blocks, (b) new X-ray and neutron scattering techniques to probe fine structures, electrostatics, and mechanics of soft interfaces, and (c) control of dynamic cell morphology and migration of cells using tailor-made, soft interfaces.

1. Introduction

In biological systems, boundaries between many phases are defined by "soft interlayers", such as membranes and biopolymers, which are immersed in physiological electrolytes. For example, biological membranes are vital components that define the outer boundary of living cells to the surrounding environments as well as that of cell compartments (organelles) in cytoplasmic space. Their main constituent is a bilayer lipid membrane that sustains lateral fluidity, and a variety of membrane-associated proteins facilitate communication and transport on/across the membrane. From the view point of material science, membranes serve as smart filters that confine many processes in the compartments (organelles). Here, toxic substances are kept out of the cell, while specific nutrients, wastes and metabolites can pass across the membranes to reach their destinations. On the other hand, if one sheds light on membranes from a biochemical point of view, many important biological processes are regulated at membrane surfaces, through interactions between peripheral and integral membrane proteins.

1.1. Importance of interfaces in biological systems

Why does nature need/use interfaces? In the 70's, Hardt [1] showed a relatively simple answer to the question by extending the steady state of diffusion-limited reactions described by Smoluchowski, and represented the mean diffusion time τ for three body collision in two- and three-dimensions:

$$\langle \tau_{2D} \rangle = \frac{x^2}{2D} \ln\left(\frac{x}{r}\right) \text{ and } \langle \tau_{3D} \rangle = \frac{x^3}{3Dr}. \quad (1)$$

D is the diffusion coefficient, r the radius of diffusing particles, and x the separation distance between two particles. The dependence of mean diffusion time on the particle radius r is $\langle \tau_{2D} \rangle \propto -\ln(r)$ for two-dimensional systems, while $\langle \tau_{3D} \rangle \propto r^{-1}$ in three-dimensional systems. A clear difference in the dependence of τ on r indicates the energetic and thus economic reasons why many biochemical reactions are confined in 2D membranes.

1.2. Free energy minimization by soft interfaces

As a general starting point, let us consider interactions between two biological interfaces (e.g. two neighboring cell membranes) as those between two planes that keep a finite separation distance via a thin spacer. When a separation distance is large, the interlayer retains its intrinsic bulk properties. Here, a change in the interlayer thickness at a constant phase volume does not cost any energy penalty, as all individual interfaces follow the classical Gibbs capillary theory. In contrast, any change in the interlayer thickness costs energy if the long-range force fields overlap within interlayers.

In order to analytically describe the thermodynamics of thin liquid films, Derjaguin introduced a simple measure, called disjoining pressure [2]. Disjoining pressure Π is defined as the excess of the external pressure that must be applied to the fluid interlayer between the plates

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http://dx.doi.org/10.1016/j.cocis.2013.07.002

in order to keep a finite distance. Practically, Π is nothing but the sum of the all individual forces acting per unit area, which can experimentally be determined by measuring the external pressures to keep the separation distance constant. The disjoining pressure can be defined in terms of the lateral density of Gibbs free energy at constant temperature T: $\Pi(d) = -(\partial G/\partial d)_T$, where d is the interlayer thickness (Fig. 1).

In order to keep a finite separation distance d between two planes, the free energy minimization coincides with the condition of $\Pi = 0$. When the interaction is weak, the interfacial interaction potential $V(d)$ can be approximated by a harmonic potential according to the inverse work functional theory as the probability function of the spacing distance follows the Boltzmann distribution: $V(d) \propto -kT \ln P(d)$.

On the other hand, the continuous thinning of the interlayer results in collapse/dewetting of the interlayer. Typical examples in material science are the rupturing of polymer and surfactant films [3,4].

2. Model cell membranes on soft surfaces: "polymer-supported membranes"

As experimental models of cell surfaces, phospholipid bilayers deposited onto planar solid substrates (so-called "solid-supported membranes") have commonly been used for almost 30 years [5••,6••,7]. Supported membranes retain both the lateral fluidity and excellent mechanical stability. They do not only enable one to probe the structural and dynamic properties of membranes with various surface-sensitive techniques, but also allow for in vitro modeling of cell–cell recognition. Solid-supported membranes have the drawback of being confined in the close proximity of solid substrates. Here, the separation via a very thin water reservoir (thickness: 5–20 Å) is not sufficient to prevent large transmembrane proteins from coming into direct contact with the bare substrate.

This problem can be avoided by separating membranes and solid substrates using soft interlayers based on hydrated polymers [8••,9]. In nature, interactions between cells and tissues are mediated by complex interplays of short-range and long-range forces across hydrated layers of carbohydrate-based biopolymers, such as extracellular matrix and cell surface glycocalyx. They keep a finite distance (typically in the range of 10–100 nm) between neighboring cells to avoid direct, non-specific cell–cell contacts as well as to create hydrodynamic pathways for solute transport.

2.1. Roles of soft interfaces (1): wetting, lateral fluidity

The deposition of a lipid bilayer onto a hydrated polymer support can energetically be favored only if the presence of a membrane results in the gain of Gibbs free energy of the whole system. For example, the stability of a liquid film on a surface can be characterized by a spreading coefficient S within the basic framework of wetting physics: [10] $S = \gamma_{SV} - (\gamma_{SL} + \gamma_{LV})$. Here, γ_{SV} is the free energy of the solid/vapor interface, γ_{SL} at solid/liquid interface, and γ_{LV} liquid/vapor interface. Compared to solid-supported membranes, the presence of polymer supports assists the self-healing of local defects in the membrane to cover macroscopically large substrates (~cm^2) [11].

Within the framework of Saffman and Delbrück's approach [12••], the translational diffusion coefficient of a cylindrical particle (radius R_p) immersed in a quasi-2D continuum is written as:

$$D \sim \frac{k_B T}{4\pi\eta_m h} \ln\left(\frac{\eta_m h}{\eta_w R_p} - \gamma\right). \tag{2}$$

η_w and η_m are the viscosities of medium (water) and membrane given in [Pa s], h the thickness of membrane and hence the height of a particle, and γ Euler's constant $\gamma = 0.5772$. Such a logarithmic law suggests a relatively little dependence of D on the particle radius R_p, which agrees well with experimental findings [13].

To model the lateral diffusion lipids and proteins in contact with viscous, asymmetric environments (e.g. glycocalyx and cytoskeleton), it is necessary to consider asymmetric boundary conditions (Fig. 2). Evans and Sackmann [14] expressed the diffusion coefficient D as a function of the dimensionless particle radius of diffusing particle ε:

$$D = \frac{kT}{4\pi\eta_m h}\left(\frac{1}{4}\varepsilon^2 + \frac{\varepsilon K_1(\varepsilon)}{K_0(\varepsilon)}\right)^{-1}. \tag{3}$$

K_0 and K_1 are modified zero and first order Bessel functions of the second kind. In contrast to the description in Eq. (2), the diffusion constant is much more strongly dependent on the particle size. It should be noted that ε can analytically be obtained from the dimensionless particle mobility $m = 4\pi\eta_m D/k_B T$, which can be determined from the diffusion coefficient D. The frictional coefficient b_s can be given by the membrane viscosity η_m, membrane thickness h, and the ratio between ε and the radius of transmembrane domain R_p: $b_s = \eta_m h(\varepsilon/R_p)^2$. Namely, once R_p is known, one can determine the significance of frictional stress exerted on proteins. This enables one to nail down how the thickness and density of polymer interlayers influence the friction exerted on transmembrane receptor proteins in a quantitative manner [15•].

2.2. Roles of soft interfaces (2): modulation of interfacial forces

If one takes lipids and polymers that carry no net charges (e.g. zwitter-ionic lipids and neutral polymer chains, Fig. 3a), one can identify the three major long-range forces (pressures) that dominate

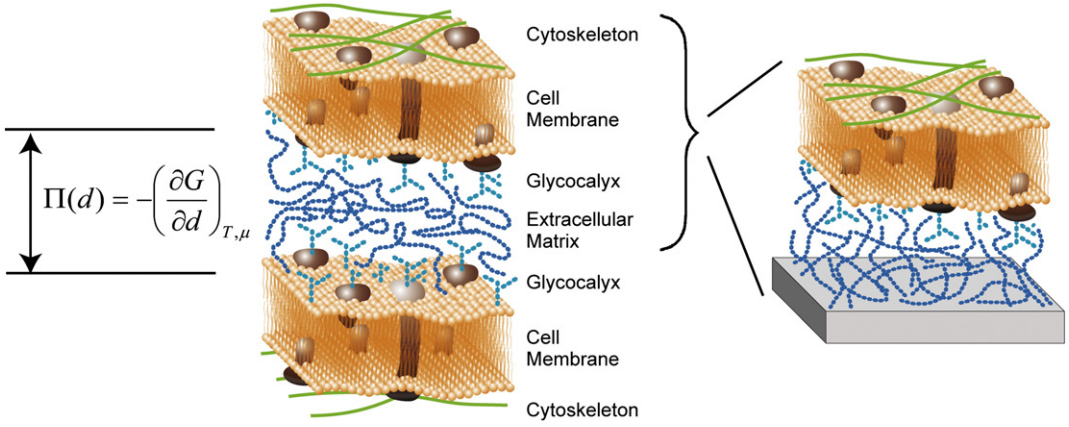

Fig. 1. Models of cell–extracellular matrix contacts by the deposition of a two-dimensional cell membrane on a polymer support (polymer-supported membrane). The net force acting per unit area (disjoining pressure) coincides with the excess pressure to maintain the finite distance between two planes.