Onsager's variational principle in soft matter: introduction and application to the dynamics of adsorption of proteins onto fluid membranes

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1 Introduction

Lipid bilayers are unique soft materials operating in general in the low Reynolds limit. While their shape is predominantly dominated by curvature elasticity as in a solid shell, their in-plane behavior is that of a largely inextensible viscous fluid. These two behaviors, however, are tightly coupled through the membrane geometry. Indeed, shape transformations necessarily induce lipid flows that bring material from one part of the membrane to another (Evans and Yeung, 1994). On the other hand, fluid flows in the presence of curvature generate out-of-plane forces, which modify the shape of the membrane and elicit elastic forces (Rahimi et al., 2013). This mechanical duality provides structural stability and adaptability, allowing membranes to build relatively stable structures that can nevertheless undergo dynamic shape transformations. These transformations are critical for the cell function; they are required in vesicular and cellular trafficking (Sprong et al., 2001; Rustom et al., 2004), cell motility and migration (Arroyo et al., 2012; Yamaguchi et al., 2015), or in the mechano-adaptation of cells to stretch and osmotic stress (Kosmalska et al., 2015).

In addition to this solid-fluid duality, lipid membranes are extremely responsive to chemical stimuli. They transiently respond for instance to pH gradients by developing tubules and pearled protrusions (Khalifat et al., 2014, 2008; Fournier et al., 2009). Furthermore, a myriad of proteins interact with lipid bilayers through curvature, either to generate it or to sense it (McMahon and Gallop, 2005; Zimmerberg and Kozlov, 2006; Sens et al., 2008; Shibata et al., 2009; Antonny, 2011). A number of quantitative experiments on synthetic reconstituted systems have examined this interaction,

notably using tethers pulled out of vesicles and exposed to curvature-active proteins delivered from either the bulk solution or a membrane reservoir (Sorre et al., 2009; Heinrich et al., 2010a,b; Sorre et al., 2012). More recently, the interplay between membrane tension and curvature generation by adsorbed curving proteins has been examined, with implications in cell mechanosensing and mechanoadaptation (Sinha et al., 2011; Shi and Baumgart, 2015).

While there is a very large body of theoretical and computational literature covering different aspects of bilayer mechanics, current models and simulation techniques fail to capture the dynamical and chemically responsive nature of bilayer membranes. We highlight below some of the requirements of a sufficiently general modeling framework that can quantify and predict the behavior of lipid bilayer membranes:

Capture the out-of-equilibrium response. Indeed, bilayers are highly dynamical, but due to the complexity of the chemical and hydrodynamical effects involved, theory and experiments have focused on equilibrium. For instance, the classical bending model of Helfrich (Helfrich, 1973; Lipowsky, 1991; Jülicher and Lipowsky, 1993; Staykova et al., 2013) has been very successful in understanding equilibrium conformations (Steigmann, 1999; Capovilla and Guven, 2002; Tu and Ou-Yang, 2004; Feng and Klug, 2006; Rangarajan and Gao, 2015; Sauer et al., 2017), but is insufficient to understand the reconfigurations of membranes when subjected to transient stimuli. To address this challenge, models and simulations coupling membrane hydrodynamics and elasticity (Arroyo and DeSimone, 2009; Arroyo et al., 2010; Rahimi and Arroyo, 2012; Rahimi et al., 2013; Rangamani et al., 2013; Rodrigues et al., 2013; Barrett et al., 2016) or elasticity and the phase-separation of chemical species (Embar et al., 2013; Elliott and Stinner, 2013) are emerging in recent years, but only provide initial steps towards a general dynamical framework.

Capture the bilayer architecture. The classical Helfrich model treats bilayer membranes as simple surfaces. Subsequent refinements in equilibrium, such as the Area Difference Elasticity (ADE) model (Seifert, 1997), acknowledge the bilayer architecture, by which bending compresses one monolayer and stretches the other but, since monolayers can slip relative to each other, this mechanism of elastic energy storage can be released to a certain degree in a nonlocal manner. In real biological membranes, however, the ADE effect is though to play a minor role because of fast cholesterol translocation between monolayers. Beyond equilibrium, the work of Seifert and Langer (1993) and Evans and Yeung (1994) demonstrated that the bilayer architec-

ture is crucial to understand the dynamics of lipid membranes. In particular, these works highlighted the role of inter-monolayer friction as a "hidden" but significant dissipative effect. When it comes to the interaction of bilayers with proteins, the bilayer architecture is bound to play an important role since proteins can merely scaffold the membrane, shallowly insert into one monolayer, or pierce through the entire bilayer. Elasto-hydrodynamical models capturing the bilayer architecture have been developed under the assumption of linearized perturbations (Seifert and Langer, 1993; Fournier et al., 2009; Callan-Jones et al., 2016), or in a fully nonlinear albeit axisymmetric setting (Rahimi and Arroyo, 2012). In the present Chapter, we will not focus on this aspect.

Capture mechanical and chemical nonlinearity. Nonlinearity is essential to understand many soft matter systems such as lipid membranes. On the mechanics side, these systems experience very large deformations that elicit geometric nonlinearity. On the chemical side, bilayers exhibit nonlinear chemical effects as a result of molecular crowding, such as nonlinear adsorption (Sorre et al., 2012) or nonlinear sorting of proteins between vesicles and tubules (Zhu et al., 2012; Aimon et al., 2014; Prévost et al., 2015). Thus, linearized chemo-mechanical models can only provide information about the onset of transitions (Shi and Baumgart, 2015), about dilute concentrations of protein on the surface (Góźdź, 2011), or about the response under very small perturbations (Callan-Jones et al., 2016).

Consistently treat multiple physics. As argued above, the function of lipid bilayers is mediated by the tight interplay between elasticity, hydrodynamics, molecular diffusion, and chemical reactions. All these phenomena act in concert and depend on each other. For instance, the concentration of adsorbed proteins modifies the preferred curvature of the membrane and conversely curvature modulates the adsorption reaction. Application of a force may change the shape, inducing lipid flows that advect proteins, drive diffusion and feedback into shape. Although several models have coupled mechanical and chemical phenomena resulting from the interaction between membranes and proteins, these focus on equilibrium (Zhu et al., 2012; Singh et al., 2012; Lipowsky, 2013), on the linearized setting (Callan-Jones et al., 2016), or consider simplistic models for the mechanical relaxation dynamics (Liu et al., 2009).

In this Chapter, we do not attempt to address all these requirements. Instead, we will focus on the last point. More specifically, our main objective is to introduce an emerging variational modeling framework for the

dissipative dynamics of soft-matter and biological systems, which provides a systematic and transparent approach to generate complex models coupling multiple physics. This approach is founded on Onsager's variational principle, by which the dynamics result from the interplay between energetic driving forces and dissipative drag forces, each of them deriving from potentials that are the sum of individual contributions for each physical mechanism. Models coupling different physics can be assembled by just adding more terms to the energy and dissipation potentials, and encoding in them the interactions between the different physical mechanisms. In this way, this framework provides a flexible and thermodynamically consistent method to generate complex models. The goal of the Chapter is to convey Onsager's variational principle through examples. Some of these examples are directly relevant to bilayer mechanics. In the second part of the Chapter, we emphasize models relevant to the adsorption of proteins on membranes. We avoid, however, the general formulation of a complete model for bilayers coupling elasticity, bulk and interfacial hydrodynamics, bulk and interfacial diffusion, and adsorption in a deformable membrane, which requires many pages and extensive use of differential geometry, but does not significantly contribute to our goal here.

While going through the Chapter, some readers may find some of the material close to trivial or irrelevant. We encourage them to read further because the beauty and importance of Onsager's principle manifests itself when confronted with systems involving multiple physics. We also note that much of the material presented here is standard textbook material or can be found scattered in the recent and not so recent literature. The unified view of Onsager's principle as a powerful and general approach to model nonlinear dissipative systems, however, is an emerging idea. Furthermore, we present some original applications of this principle to model nonlinear adsorption phenomena, and curvature sensing and generation by proteins. The interested reader may find recent applications of Onsager's principle to lipid membranes elsewhere (Arroyo and DeSimone, 2009; Rahimi and Arroyo, 2012; Rahimi et al., 2013; Fournier, 2015; Callan-Jones et al., 2016).

The Chapter is organized as follows. In Section 2 we introduce Onsager's variational principle by way of elementary mechanical models. We also revisit common models such as Stokes incompressible flow, linear diffusion, diffusion coupled with hydrodynamics in the presence of a rigid semipermeable membrane, or a linear reaction-diffusion system involving two species. See Peletier (2014) for a related pedagogical work. By deriving all these problems using Onsager's principle, we frame them into a unified framework and provide the elements to build more complex models. In Section 3, we focus on the adsorption and diffusion of a chemical species

from the bulk onto a surface of fixed shape. This allows us to identify the variational structure behind common linear and nonlinear adsorption models including Langmuir model. Finally, in Section 4, we provide a minimal model to examine curvature sensing and generation, by introducing a coupling between protein concentration and spontaneous curvature.

2   Onsager's variational principle

2.1   Background

Variational principles underly many mechanical and thermodynamic theories. These principles provide a systematic procedure to generate governing equations, and provide an additional mathematical structure that highlights qualitative properties of the solutions not apparent from the Euler-Lagrange equations. For instance, the principle of minimum potential energy provides information about the stability of equilibria, not accessible from the mere equilibrium equations. Hamilton's principle for the inertial mechanics of particles and continua characterizes variationally trajectories otherwise satisfying "$F = mA$". This variational principle provides a natural framework to Noether's theorem and to derive variational time-integrators (Lew et al., 2004).

Towards an analogous framework to model soft-matter and biological systems, we introduce here Onsager's variational principle (Onsager, 1931a,b), in a terminology introduced by Doi (2011). This variational framework describes the dynamics of dissipative systems and is an extension of the principle of least energy dissipation, first introduced by Rayleigh (1873) (Goldstein, 1980). Onsager's relations are generally invoked in the context of linear irreversible thermodynamics (Prigogine, 1967). As argued earlier, however, nonlinearity is essential in many soft matter systems. Importantly, as noted by Doi (2011), Onsager's relations emerge from a more general variational principle applicable in fully nonlinear settings. This fact was exploited to derive the geometrically nonlinear equations for an inextensible interfacial fluid with bending rigidity coupled to a bulk viscous fluid (Arroyo and DeSimone, 2009), or to derive the governing equations for a phase-field model of membranes coupled to a viscous bulk fluid (Peco et al., 2013). This formalism assumes that inertial forces are negligible (see Öttinger (2005) for an extension), but otherwise encompasses the classes of problems encountered in soft matter and biological physics, tightly coupling chemistry, hydrodynamics and nonlinear solid mechanics.

Besides soft matter physics, variational principles of the Onsager type were introduced in solid mechanics, in particular invoking time-incremental discretized principles to generate algorithms (Ortiz and Repetto, 1999) or to

develop mathematical analysis (Mielke, 2011a,b, 2012). Along similar lines, Jordan et al. (1998); Otto (2001) identified a variational formulation for diffusion equations as gradient flows of entropy functionals, providing mathematical and physical insight and highlighting the importance of adequately parametrizing the *processes* that modify the state of the system. This led to a further formalization of Onsager's variational principle by Peletier (2014) introducing the so-called process operators, which were independently used by Doi (2011) to model viscoelastic fluids and by Rahimi and Arroyo (2012) to derive the equations of a nonlinear dynamical model for lipid bilayers. More recently, the gradient structure of reaction-diffusion systems has been identified (Mielke, 2011a), allowing us to couple such problems with other phenomena through Onsager's principle.

We introduce next Onsager's principle through simple mechanical and chemical models. Our goal is to emphasize that this principle provides a systematic way to derive the governing equations for complex systems starting from elementary energetic and dissipative ingredients, which act as building blocks of the theory. Here, we do not address an additional important benefit of Onsager's principle: the fact that it provides a privileged starting point for time and space discretization of the resulting systems of partial differential equations.

2.2   Onsager's principle for elementary systems

We consider a spring of elastic constant k coupled in parallel with a dashpot of drag coefficient η and under the action of a force F (see Fig. 1A). It may seem an overkill to invoke Onsager's principle to describe such an elementary model. However, we shall see that the treatment of more complex systems follows the same rationale, and therefore this and subsequent examples provide a simple physical picture to understand the essential ideas.

The state of the system is characterized by the displacement of the spring with respect to its natural elongation, x. The force generated by the spring is

$$F_{\mathrm{cons}} = -kx, \tag{1}$$

where the label "cons" identifies that this force is conservative. The system is also experiencing a viscous force opposing its motion

$$F_{\mathrm{visc}} = -\mu v, \tag{2}$$

where $v = \dot{x}$. If the drag is sufficiently large, inertia can be neglected. Then, balance of forces reads

$$F_{\mathrm{cons}} + F_{\mathrm{visc}} + F = 0, \tag{3}$$

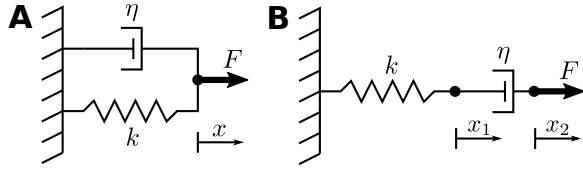**Figure 1.** Diagrams of two elementary mechanical systems. (A) A spring with constant k is in parallel with a dashpot with drag coefficient η and a force F is applied. The system is characterized by the displacement of the point of application of the force from its equilibrium position, x. (B) The spring is now in series with the dashpot and the force is applied to the dashpot; the system in this case is characterized by x_1, the displacement of the spring relative to its equilibrium position, and x_2, the relative displacement of the dashpot with respect to the spring.

leading to

$$\eta \dot{x} + kx = F. \tag{4}$$

This is an ordinary differential equation that can be easily integrated in time to obtain $x(t)$ given an initial condition. But let us focus on the structure of this equation rather than on its solution; this equation follows from a variational principle. Indeed, on the one hand, the spring and external forces derive from a potential, which includes the stored elastic energy in the spring and the potential for the external force

$$F_{\text{cons}} + F = -\frac{d\mathcal{F}}{dx} \quad \text{where} \quad \mathcal{F}(x) = \frac{k}{2}x^2 - Fx. \tag{5}$$

On the other hand, the viscous force also derives from a potential, usually referred to as the dissipation potential or as the Rayleigh dissipation function, depending on v

$$F_{\text{visc}} = -\frac{\partial \mathcal{D}}{\partial v} \quad \text{where} \quad \mathcal{D}(v) = \frac{\eta}{2}v^2. \tag{6}$$

The rate of change of the energy can be written, using the chain rule, as

$$\frac{d}{dt}\left[\mathcal{F}(x(t))\right] = \frac{d\mathcal{F}}{dx}(x(t))\,\dot{x}(t) = (kx - F)\,v, \tag{7}$$

and therefore $\dot{\mathcal{F}}$ depends on the state of the system x and on the rate of change of the state v. Now, let us define the function

$$\mathcal{R}(x, v) = \dot{\mathcal{F}}(x, v) + \mathcal{D}(v) = (kx - F)\,v + \frac{1}{2}\eta v^2. \tag{8}$$

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It is clear that the governing equation for this system (4) follows from $0 = \partial \mathcal{R} / \partial v$. Furthermore, because $\eta > 0$, $\mathcal{R}$ is a convex function of v. Thus, we conclude that the governing equation follows from the variational principle

$$v = \underset{w}{\mathrm{argmin}}\ \mathcal{R}(x, w). \tag{9}$$

This is Onsager's variational principle and the function $\mathcal{R}(x, v)$ is called the *Rayleighian* of the system. The minimization is performed over the rate of change of the state of the system, v, rather than on the state of the system, x, in contrast with the classical equilibrium principle of minimum potential energy. *This is a genuinely dynamical principle establishing a competition between the energy release rate and dissipation* (Onsager, 1931a; Doi, 2011). Focusing on linear response theory, Onsager showed that this principle holds for general irreversible processes, where *the key assumptions are that (i) dissipation dominates over inertia and (ii) viscous forces are derived from a dissipation potential*. This principle, however, is still valid if $\mathcal{F}$ or $\mathcal{D}$ are general non-harmonic potentials for the spring or for the dashpot.

Before showing the application of Onsager's variational principle to continuous systems, we consider another discrete example consisting of a spring in series with a dashpot loaded with a force (see Fig. 1B). The system is characterized by the displacement of the spring from its equilibrium position, x_1, and by the displacement of the dashpot with respect to the spring, x_2. We denote the rate of change of these coordinates by $v_i = dx_i/dt$. Let us proceed directly following Onsager's variational principle. The energy of this system is just the energy stored by the spring and the potential energy of the load, whose application point is displaced by $x_1 + x_2$

$$\mathcal{F}(x_1, x_2) = \frac{k}{2}x_1^2 - F(x_1 + x_2). \tag{10}$$

The rate of change of the energy is

$$\dot{\mathcal{F}}(x_1; v_1, v_2) = kx_1 v_1 - F(v_1 + v_2), \tag{11}$$

which here happens not to depend on x_2. On the other hand, the dissipation potential can be written in terms of v_2 only

$$\mathcal{D}(v_2) = \frac{\eta}{2}v_2^2. \tag{12}$$

Thus, the Rayleighian is

$$\mathcal{R}(x_1; v_1, v_2) = kx_1 v_1 - F(v_1 + v_2) + \frac{\eta}{2}v_2^2 \tag{13}$$

and Onsager's variational principle states that

$$v_1, v_2 = \underset{w_1, w_2}{\operatorname{argmin}} \ \mathcal{R}(x_1; w_1, w_2). \tag{14}$$

The stationarity necessary conditions for the minimizer, $0 = \partial \mathcal{R} / \partial v_i$, lead to

$$F = kx_1 = \eta v_2, \tag{15}$$

which coincides with the result obtained from direct force balance for this system.

We end this Section with a variation of the model in Fig. 1B, in which we have two dashpots in series with constants η_1 and η_2. This example is intended to make a more subtle point and may be skipped in a first reading. In this case, $\mathcal{F} = -F(x_1 + x_2)$ and we simply add the dissipation potentials of each of the dashpots to form

$$\mathcal{D} = \frac{\eta_1}{2} v_1^2 + \frac{\eta_2}{2} v_2^2. \tag{16}$$

Applying Onsager's principle, we immediately find $v_i = F/\eta_i$. Now, let us define the total displacement of the right-end of the system $x = x_1 + x_2$ and its velocity $v = v_1 + v_2$. A simple manipulation shows that the following relation holds

$$v = \frac{\eta_1 + \eta_2}{\eta_1 \eta_2} F, \tag{17}$$

and therefore, the viscous force of the composite system consisting of two dashpots in series derives from the following dissipation potential

$$\hat{\mathcal{D}}(v) = \frac{1}{2} \frac{\eta_1 \eta_2}{\eta_1 + \eta_2} v^2. \tag{18}$$

This potential exhibits a non-additive structure in that the effective drag coefficient is not the sum of the individual drag coefficients. In contrast, the corresponding dual dissipation potential obtained through a Legendre transform

$$\hat{\mathcal{D}}^*(F) = \min_v \left[Fv - \hat{\mathcal{D}}(v) \right] = \frac{1}{2} \left(\frac{1}{\eta_1} + \frac{1}{\eta_2} \right) F^2 \tag{19}$$

does exhibit an additive structure for this model. This point has been raised in a different but related context (Mielke, 2012) to favor a formalism relying on the dual dissipation potential. This simple example shows, however, that the dissipation potential retains an additive structure, see Eq. (16), provided sufficient detail is kept in the formulation describing the rate of change of the system and how these changes dissipate energy.

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2.3 Incompressible Stokes flow

We formulate next the governing equations for a Newtonian incompressible fluid in the low Reynolds limit, the familiar Stokes equations, within the framework of Onsager's principle. This formalization will be useful later, when coupling low Re hydrodynamics with different physics. We consider a fluid in a fixed volume Ω with boundary $\partial\Omega$. The motion of material particles in the fluid is characterized by a velocity field $\boldsymbol{v}(\boldsymbol{x})$. The field $\boldsymbol{v}(\boldsymbol{x})$ is the continuous equivalent to v in the previous example. The dissipation potential characterizes the energy dissipated as the fluid deforms. For an incompressible Newtonian fluid, it takes the form

$$\mathcal{D}[\boldsymbol{v}] = \eta \int_\Omega \boldsymbol{d} : \boldsymbol{d} \; dV, \tag{20}$$

where $\boldsymbol{d}$ is the rate-of-deformation tensor $\boldsymbol{d} = \frac{1}{2}\left(\nabla\boldsymbol{v} + (\nabla\boldsymbol{v})^T\right)$ and η is the shear viscosity of the fluid. Recalling that the viscous shear stress is $2\eta\boldsymbol{d}$ for a Newtonian fluid, then $\eta\,\boldsymbol{d}:\boldsymbol{d}$ can be identified as half of the rate of dissipation per unit volume.

We split $\partial\Omega = \Gamma_D \cup \Gamma_N$ into two disjoint subdomains, the Dirichlet boundary Γ_D, where a velocity field is prescribed $\boldsymbol{v}(x) = \bar{\boldsymbol{v}}(\boldsymbol{x})$, and the Neumann boundary Γ_N, where a traction $\boldsymbol{t}(\boldsymbol{x})$ is applied. The traction at the Neumann boundary is supplying power to the system. This power supply can be introduced through a potential of the form

$$\mathcal{P}[\boldsymbol{v}] = -\int_{\Gamma_N} \boldsymbol{t} \cdot \boldsymbol{v} dS. \tag{21}$$

In this problem there is no energetic ingredient, and therefore the system is oblivious to any variable encoding the state system. Thus the Rayleghian accounting for internal dissipation and power supply through boundary traction is simply $\mathcal{R}[\boldsymbol{v}] = \mathcal{D}[\boldsymbol{v}] + \mathcal{P}[\boldsymbol{v}]$.

Onsager's principle states that the system evolves in such a way that the Rayleghian is minimized with respect to $\boldsymbol{v}$. However, it is important to realize that the velocity field is subjected to constraints. On the one hand, it should satisfy the Dirichlet boundary conditions. On the other hand, since the fluid is incompressible, it should satisfy $\nabla \cdot \boldsymbol{v} = 0$ in Ω. The variational principle allows us to easily incorporate constraints, for instance using a field of Lagrange multipliers and forming the Lagrangian

$$\begin{aligned}
\mathcal{L}[\boldsymbol{v}, p] &= \mathcal{R}[\boldsymbol{v}] - \int_\Omega p\, \nabla \cdot \boldsymbol{v} \; dV \\
&= \eta \int_\Omega \boldsymbol{d} : \boldsymbol{d} \; dV - \int_{\Gamma_N} \boldsymbol{t} \cdot \boldsymbol{v} dS - \int_\Omega p\, \nabla \cdot \boldsymbol{v} \; dV,
\end{aligned} \tag{22}$$

where p can be interpreted as the pressure in the fluid. Now, the constrained Onsager's principle can be stated as a saddle problem

$$\boldsymbol{v}, p = \operatorname*{argmax}_{q} \operatorname*{argmin}_{\boldsymbol{w}} \left\{ \mathcal{L}[\boldsymbol{w}, q] \right\}. \tag{23}$$

The variation of the Lagrangian with respect to the velocity field along $\delta \boldsymbol{v}$ consistent with Dirichlet boundary conditions, i.e. $\delta \boldsymbol{v} = \boldsymbol{0}$ at Γ_D, leads to the stationarity condition

$$2\eta \int_{\Omega} \boldsymbol{d} : \nabla \delta \boldsymbol{v} \, dV - \int_{\Gamma_N} \boldsymbol{t} \cdot \delta \boldsymbol{v} \, dS - \int_{\Omega} p \, \nabla \cdot \delta \boldsymbol{v} \, dV = 0. \tag{24}$$

Variations with respect to p lead to

$$\int_{\Omega} \delta p \, \nabla \cdot \boldsymbol{v} \, dV = 0. \tag{25}$$

Eqs. (24) and (25) are the weak form of the problem. The strong form follows after integration by parts and taking into account the arbitrariness in $\delta \boldsymbol{v}$ and δp,

$$\begin{aligned} \nabla \cdot \boldsymbol{\sigma} &= \boldsymbol{0} & &\text{in } \Omega, \\ \nabla \cdot \boldsymbol{v} &= 0 & &\text{in } \Omega, \\ \boldsymbol{v} &= \bar{\boldsymbol{v}} & &\text{on } \Gamma_D, \\ \boldsymbol{\sigma} \cdot \boldsymbol{n} &= \boldsymbol{t} & &\text{on } \Gamma_N, \end{aligned} \tag{26}$$

where $\boldsymbol{\sigma} = 2\eta \boldsymbol{d} - p\boldsymbol{I}$ is the stress tensor of the fluid, $\boldsymbol{I}$ is the identity tensor, and $\boldsymbol{n}$ is the unit outward normal to $\partial\Omega$. Thus, the equations characterizing an incompressible Newtonian fluid in the low Re limit can be obtained from Onsager's variational principle. This example also illustrates the treatment of constraints in this formalism.

Note that by replacing $\boldsymbol{v}$ by a displacement field $\boldsymbol{u}$ (now a state variable), $\boldsymbol{d}$ by the linearized strain tensor $\boldsymbol{\varepsilon} = (\nabla \boldsymbol{u} + \nabla \boldsymbol{u}^T)/2$, and η by the shear modulus μ, these equations are those of linear isotropic elasticity for an incompressible material. These equations also follow from Onsager's principle, starting from the free energy

$$\mathcal{F}[\boldsymbol{u}] = \mu \int_{\Omega} \boldsymbol{\varepsilon} : \boldsymbol{\varepsilon} \, dV - \int_{\Gamma_N} \boldsymbol{t} \cdot \boldsymbol{u} \, dS. \tag{27}$$

Since we do not have a dissipation source, and noting that $\boldsymbol{v} = \partial_t \boldsymbol{u}$, the constrained Rayleighian becomes

$$\mathcal{L}[\boldsymbol{u}; \boldsymbol{v}, p] = 2\mu \int_{\Omega} \boldsymbol{\varepsilon} : \nabla \boldsymbol{v} \, dV - \int_{\Gamma_N} \boldsymbol{t} \cdot \boldsymbol{v} \, dS - \int_{\Omega} p \, \nabla \cdot \boldsymbol{v} \, dV. \tag{28}$$

2.4 Diffusion of a solute in a fluid

Further building our catalog of models amenable to Onsager's principle, we consider now the diffusion equation. Let Ω be a region of space occupied by a quiescent fluid with a dilute distribution of non-interacting and neutrally buoyant solute molecules. This region is delimited by an impermeable container. We denote by $c(\boldsymbol{x}, t)$ the molar concentration field of this substance at time t. A classical model to describe the time-evolution of this field is based on the diffusion equation, $\partial_t c = D\Delta c$, where D is the diffusion coefficient and Δ is the Laplacian, supplemented by appropriate boundary and initial conditions. Furthermore, the Stokes-Einstein equation provides a microscopic expression for the diffusion coefficient as

$$D = \frac{k_B T}{f} \tag{29}$$

where k_B is the Boltzmann constant, T is the absolute temperature, and f is the hydrodynamic drag coefficient, that is the proportionality coefficient between the drag force experienced by a solute molecule and the speed at which it is moving relative to the fluid. For an incompressible Newtonian fluid at low Re and a spherical solute or radius a,

$$f = 6\pi\eta a \tag{30}$$

where η is the shear viscosity of the fluid (Happel and Brenner, 2012).

As discussed by Jordan et al. (1998), a direct calculation shows that the diffusion equation can be formally derived from Onsager's principle using as free energy

$$\mathcal{F}[c] = \frac{D}{2}\int_\Omega |\nabla c|^2 dV, \tag{31}$$

characterizing the changes of state of the system simply by $\partial_t c$, and considering as dissipation potential

$$\mathcal{D}[\partial_t c] = \frac{1}{2}\int_\Omega (\partial_t c)^2 dV. \tag{32}$$

This approach, however, is not satisfactory for several reasons. First, these potentials do not admit a compelling physical interpretation, nor provide a connection with the microscopic physics. Second, and this cannot be fully appreciated yet, these potentials are not meaningful building blocks that can be combined with elasticity, chemistry or hydrodynamics.

Instead, the main driving force for molecular diffusion is mixing entropy maximization (or minimization of entropic free energy). For a dilute solution

at concentration c, it can be motivated from various points of view (Peletier, 2014; Pauli and Enz, 2000) that the entropy density per unit volume due to mixing between the solute and the solvent is given by $-RTc\log(c/c_0)$, where c_0 is an arbitrary normalization constant and R is the universal gas constant. Therefore, the free energy of the system will be given by the so-called ideal gas mixing entropy

$$\mathcal{F}[c] = RT \int_\Omega c \log \frac{c}{c_0} dV. \tag{33}$$

It is easy to see that c_0 is an arbitrary constant. Indeed, using the properties of the logarithm, the free energy can be written as $\cdots - RT \log c_0 \int_\Omega c\, dV$. Because the container is impermeable, conservation of solute molecules implies that this integral is a constant, and therefore c_0 only modifies an additive constant in the energy. If part of the boundary was capable of exchanging solute molecules with a reservoir at fixed chemical potential, then the constant c_0 would not be arbitrary. We leave this as an exercise. An alternative way to express the normalization constant common in the literature is

$$\mathcal{F}[c] = RT \int_\Omega c \left(\log c - 1\right) dV + \int_\Omega c\mu_0 dV, \tag{34}$$

where μ_0 is called standard chemical potential. As we shall see later, the governing equations will not depend on this arbitrary normalization constant.

The state of the system, and hence its free energy, is characterized at time t by the field $c(\cdot, t)$. Then, the free energy functional evaluated at this time-dependent field $\mathcal{F}[c(\cdot, t)]$ generates a function that depends only on time. Its rate of change, noting that the boundary of Ω is impermeable and therefore Reynolds transport theorem only involves a bulk term, can then be computed as

$$\frac{d}{dt}\left(\mathcal{F}[c(\cdot, t)]\right) = \int_\Omega \left(\mu_0 + RT \log c\right) \partial_t c \; dV, \tag{35}$$

where

$$\mu(c) = \frac{\delta \mathcal{F}}{\delta c} = \mu_0 + RT \log c \tag{36}$$

is the chemical potential at concentration c, defined as the functional derivative of the free energy with respect to the concentration (here it is simply the partial derivative of the free energy density). The chemical potential $\mu(c)$ locally measures the free energy cost of adding one mole of solutes per unit volume at a given concentration. Therefore, it is natural that gradients

in the chemical potential will drive migration of the solutes to reduce the free energy. From this expression we see that μ_0 is the chemical potential at a reference concentration, here $c = 1$.

Now, let's think about the dissipation involved in the diffusive migration of the solutes. Imagining a single solute molecule moving a velocity $\boldsymbol{w}$ relative to the quiescent fluid, we have seen that the drag force is given by $\boldsymbol{F} = -f\boldsymbol{w}$, and therefore the dissipation potential for this single solute would be $(f/2)|\boldsymbol{w}|^2$. Now, in a unit of volume we have $N_A c$ of such molecules, where N_A is Avogadro's number. Let us think of $\boldsymbol{w}$ as an effective collective velocity of the solutes relative to the quiescent fluid–a *diffusive velocity*–in a given region in space. Then, assuming that the solution is dilute, and therefore the drag on a solute molecule is not affected by the presence of other solute molecules, it is reasonable to write the dissipation potential per unit volume as $(fN_A/2)c|\boldsymbol{w}|^2$ and therefore

$$\mathcal{D}[\boldsymbol{w}] = \frac{fN_A}{2} \int_\Omega c|\boldsymbol{w}|^2 dV. \tag{37}$$

Towards applying Onsager's principle, we can combine Eqs. (35) and (37) to form the Rayleighian. However, we immediately note that $\dot{\mathcal{F}}$ is expressed as a functional of $\partial_t c$, but $\mathcal{D}$ is instead a functional of $\boldsymbol{w}$, and therefore it is not clear what should we minimize with respect to. How to proceed?

The first important observation is that not only $\partial_t c$ but also $\boldsymbol{w}$ characterize the rate of change of the state of the system. Indeed, if solutes move with diffusive velocity $\boldsymbol{w}$, they will rearrange in space and the concentration field will be modified. The second observation is that these two ways of expressing the rate of change of the state are not independent. Indeed, they are related by the continuity equation

$$\partial_t c + \nabla \cdot (c\boldsymbol{w}) = 0 \tag{38}$$

expressing locally the conservation of solute molecules (Landau and Lifshitz, 2013). The product $\boldsymbol{j}_D = c\boldsymbol{w}$ is the molar diffusive flux of solute molecules. We will call $\boldsymbol{w}$ the process variable for this system because it describes the rate of change of the system, and allows us to express the dissipation. Plugging this equation into Eq. (35), we can express the rate of change of the energy, after integration by parts, as

$$\dot{\mathcal{F}}[c; \boldsymbol{w}] = -\int_\Omega \mu(c)\nabla \cdot (c\boldsymbol{w}) \ dV$$
$$= -\int_{\partial\Omega} \mu(c)c\boldsymbol{w} \cdot \boldsymbol{n} \ dS + \int_\Omega c\nabla\mu(c) \cdot \boldsymbol{w} \ dV. \tag{39}$$

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Since we have assumed that the solute molecules cannot cross the boundary of the container, and therefore $\boldsymbol{j}_D \cdot \boldsymbol{n} = 0$ over $\partial\Omega$, the boundary integral term vanishes and the Rayleighian takes the form

$$\mathcal{R}[c; \boldsymbol{w}] = \int_\Omega c\nabla\mu(c) \cdot \boldsymbol{w} \ dV + \frac{fN_A}{2} \int_\Omega c|\boldsymbol{w}|^2 dV. \tag{40}$$

Recalling Eq. (36) and minimizing this functional with respect to $\boldsymbol{w}$ we obtain the stationarity condition

$$0 = \int_\Omega RT\nabla c \cdot \delta\boldsymbol{w} \ dV + fN_A \int_\Omega c\boldsymbol{w} \cdot \delta\boldsymbol{w} \ dV, \tag{41}$$

which should hold for all admissible variations $\delta\boldsymbol{w}$. This allows us to localize the relation

$$\boldsymbol{j}_D = c\boldsymbol{w} = -\frac{RT}{fN_A}\nabla c = -\frac{k_B T}{f}\nabla c. \tag{42}$$

Thus, not only do we identify Fick's law of diffusion. We also recover the Stokes-Einstein equation for the diffusion coefficient, see Eq. (29). Plugging this expression into the continuity equation, we recover the classical diffusion equation

$$\partial_t c = \frac{k_B T}{f}\Delta c \quad \text{in} \ \ \Omega, \tag{43}$$

with homogeneous Neumann boundary conditions $\partial c/\partial n = 0$ in $\partial\Omega$. Thus, we have seen that Fick's law, the Stokes-Einstein equation, and the diffusion equation can be derived using Onsager's principle from physically motivated expressions for the free energy and the dissipation potential. We also see that the resulting governing equations are independent of the normalization constant μ_0.

2.5 Abstract statement of Onsager's principle

The previous example has shown that the rate of change of the energy and the dissipation potential may be expressed in terms of different descriptions of the rate of change of the system. $\dot{\mathcal{F}}$ was a functional of $\partial_t c$ while $\mathcal{D}$ was a functional of the diffusive velocity $\boldsymbol{w}$. To place the rate of change of the energy and the dissipation potential on an equal footing in the Rayleighian, we needed a relation between these two quantities (the continuity equation), termed *process operator* in the terminology of Peletier (2014). We follow this reference in this Section to formalize an abstract statement of Onsager's principle. The objective of this formal exercise is to conceptualize the procedure and guide our formulation of more complex problems.

It remains a nontrivial task, however, to map a particular physical model into this formalism.

In the examples examined so far, we have seen that the main ingredients in Onsager's modeling framework are (1) the state variables, such as x or c, which identify the state of the system, (2) the free energy $\mathcal{F}$, which depends on the state variables, (3) the process variables, such as v, $\boldsymbol{v}$ or $\boldsymbol{w}$, which describe how the system changes its state and generates dissipation, (4) the process operator P, which relates the rate of change of the state variables and the process variables, (5) the dissipation potential $\mathcal{D}$, measuring the energy dissipated by the process variables, and possibly (6) potentials accounting for the externally supplied power $\mathcal{P}$ and (7) constraints such as the incompressibility condition. Constraints may be formulated on the state or on the process variables, but the former can always be linearized and expressed as constraints on the process variables. Collecting all these ingredients, we can abstractly state Onsager's variational principle as follows.

Let us describe a dissipative system through some state variables $X(t)$ evolving in a suitable space (possibly a nonlinear manifold), a free energy $\mathcal{F}(X)$, some process variables V (living in a vector bundle and therefore with a clear notion of 0), a dissipation potential $\mathcal{D}(X;V)$, and a potential for the external power supply $\mathcal{P}(X;V)$. Suppose also that the process variables are linearly constrained by $0 = \mathbb{C}(X)V$ during the time-evolution of the system. $\mathcal{F}$ is often a nonlinear function of X, $\mathcal{D}$ may be a nonlinear function of X but is generally quadratic in V, and $\mathcal{P}$ is generally linear in V. However, $\mathcal{D}$ does not need to be quadratic in V in Onsager's formalism as described here. As motivated below, *the thermodynamic requirements we will need on $\mathcal{D}$ are (1) that it is nonnegative, (2) that $\mathcal{D}(X,0) = 0$ and (3) that it is convex as a function of V.* We will also assume here that the dissipation potential is differentiable. This is not necessarily the case, for instance in rate-independent dissipative processes such as dry friction, which can nevertheless be framed in Onsager's principle. The differentiability assumption is justified here because soft and biological matter is generally wet and rate-dependent.

To form the Rayleighian, we need to evaluate the rate of change of the energy, which can most of the times be obtained by the chain rule

$$\dot{\mathcal{F}}(X;\partial_t X) = \frac{d}{dt}\left[\mathcal{F}(X(t))\right] = D\mathcal{F}(X) \cdot \partial_t X, \qquad (44)$$

where $D\mathcal{F}(X)$ denotes the derivative of the free energy. The situations is slightly complicated when considering free energy integrals over non-material domains (open systems), where Reynolds transport theorem pro-

duces an explicit dependence of $\dot{\mathcal{F}}$ on the process variables V. This is the case in the example in Section 2.6. This dependence, however, does not complicate the application of Onsager's principle in any way.

In general, the process variable V ($\boldsymbol{w}$ in the previous example) will not be simply the time-derivative of the state variable $\partial_t X$ ($\partial_t c$ in the previous example), although this was the case in the examples of Section 2.2. To relate these two descriptions of the evolution of the state of the system, we need a process operator, which we consider here to be linear

$$\partial_t X = P(X)V. \tag{45}$$

This operator will often be either trivial, i.e. $\partial_t X = V$, or a statement of conservation of mass. Importantly, as noted by Otto (2001); Peletier (2014), V often contains redundant information to describe $\partial_t X$, which is however required to properly model dissipation. This is the case in the previous example, where $\partial_t c$ is a scalar field but $\boldsymbol{w}$ is a vector field.

The process operator allows us to express the rate of change of the system in terms of the process variable V, and thus form the Rayleighian as

$$\mathcal{R}(X;V) = D\mathcal{F}(X) \cdot P(X)V + \mathcal{D}(X;V) + \mathcal{P}(X;V). \tag{46}$$

Onsager's variational principle then states that the system evolves such that

$$V = \underset{W}{\operatorname{argmin}} \; \mathcal{R}(X;W) \tag{47}$$

subject to the constraints on W

$$\mathbb{C}(X)W = 0. \tag{48}$$

The constrained dynamics can be equivalently characterized as stationary (saddle) points of the Lagrangian

$$\mathcal{L}(X;V,\Lambda) = D\mathcal{F}(X) \cdot P(X)V + \mathcal{D}(X;V) + \mathcal{P}(X;V) + \Lambda \cdot \mathbb{C}(X)V, \tag{49}$$

where Λ are the Lagrange multipliers. Once V is obtained from this variational principle, we can then integrate $\partial_t X$ in time recalling Eq. (45).

Let us now formally examine an important qualitative property of the resulting dissipative dynamics. For this, we will consider a "homogeneous" system with $\mathcal{P}(X;V) = 0$. The stationarity condition $0 = \delta_\Lambda \mathcal{L}$ simply leads to $0 = \mathbb{C}(X)V$. The stationarity condition $0 = \delta_V \mathcal{L}$ results in the dynamical equilibrium equation

$$0 = D_X \mathcal{F}(X) \cdot P(X) + D_V \mathcal{D}(X;V) + \Lambda \cdot \mathbb{C}(X). \tag{50}$$

Multiplying this equation by the actual V along the dissipative dynamics and rearranging terms, we obtain

$$\underbrace{D_X\mathcal{F}(X)\cdot P(X)V}_{\dot{\mathcal{F}}} = -D_V\mathcal{D}(X;V)V - \Lambda\cdot\underbrace{\mathbb{C}(X)V}_{0}. \qquad (51)$$

Now, since $\mathcal{D}$ is convex and differentiable in V and we have required that $\mathcal{D}(X;0) = 0$, we conclude that

$$0 = \mathcal{D}(X;0) \geq \mathcal{D}(X;V) + D_V\mathcal{D}(X;V)(0 - V). \qquad (52)$$

Since we have required $\mathcal{D}(X;V) \geq 0$, we conclude from this equation that

$$0 \geq -\mathcal{D}(X;V) \geq -D_V\mathcal{D}(X;V)V. \qquad (53)$$

This equation, together with Eq. (51), show that during the dynamics

$$\dot{\mathcal{F}} \leq 0, \qquad (54)$$

and $D_V\mathcal{D}(X;V)V$ is the rate of dissipation. For quadratic dissipation potentials, it is easily checked that $D_V\mathcal{D}(X;V)V = 2\mathcal{D}(X;V)$. Therefore, the free energy $\mathcal{F}$ is a Lyapunov function of the dynamics. This also shows that Onsager's principle complies with the second law of thermodynamics by construction, as long as $\mathcal{D}$ satisfies a set of minimal requirements. Finally, we note that this notion of stability is fully nonlinear and does not assume a quadratic form for the dissipation or free energy potentials.

2.6 Diffusion, low Re hydrodynamics and osmosis in a fluid with a solute interacting with a semipermeable membrane

We consider now a simple problem coupling diffusion, hydrodynamics, and mechanics. This problem also exemplifies the treatment of moving interfaces. The physical model is described in Figure 2. Because of the presence of a semipermeable membrane, that selectively blocks the passage of solute molecules (red dots in the figure) but lets solvent molecules go through (blue background medium), this model will allow us to examine osmotic effects. The semipermeable membrane is rigid, but can move laterally at the expense of storing elastic energy in a spring. Thus, this model conceptually recapitulates a number the ingredients relevant to membrane physics. Indeed, lipid bilayers are semipermeable membranes embedded in a solution at high osmolar strength, and their deformation stores elastic energy. Because the impermeable barrier does not allow solute molecules to pass, the concentration of these molecules may be discontinuous across
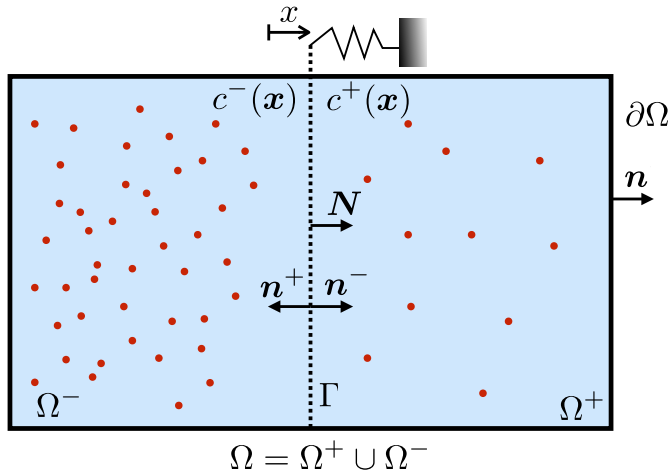
Figure 2. Impermeable fluid container Ω with a semipermeable membrane dividing the container in two sub-domains. The semipermeable membrane is rigid but can move laterally and is connected to a spring. The fluid contains solute molecules.

Γ. On the other hand, the solvent can cross the semipermeable barrier, but this passage involves some friction characterized by a permeation coefficient (Staykova et al., 2013).

Let us address this problem using Onsager's principle, and let us try to follow the systematic procedure outlined in the previous Section. First, we need to identify suitable state variables, which in this case are the concentration field c of solute molecules, which can be discontinuous across Γ (and for this reason we distinguish between c^+ and c^- on the membrane), and the position of the moving semipermeable membrane x. Combining ingredients introduced in the previous examples, we can form the free energy depending on $X = \{c, x\}$ as

$$\mathcal{F}(X) = RT \int_\Omega c \left(\log c - 1\right) dV + \int_\Omega c\mu_0 dV + \frac{k}{2}x^2. \tag{55}$$

Let us discuss the process variables. These include the diffusive velocity $\boldsymbol{w}$ characterizing changes in c and the velocity of the semipermeable membrane $v_m = \dot{x}$. Furthermore, it is clear that the motion of this membrane will displace the fluid, which cannot be assumed to be quiescent as in Section 2.4. Therefore, the velocity of the fluid $\boldsymbol{v}$ will also be part of the process

variables. Now, since the background fluid is moving, we need to decide whether $\boldsymbol{w}$ describes the absolute velocity of the solutes or their velocity relative to the fluid. We choose the latter, since this relative velocity is the one that is meaningful to describe dissipation during diffusion. Thus, the process variables are $V = \{\boldsymbol{w}, v_m, \boldsymbol{v}\}$.

Let us discuss now the constraints affecting the process variables. We shall assume that the solution is dilute, and therefore the solute molecules occupy a negligible volume fraction. The condition of molecular incompressibility then leads to the common condition for an incompressible fluid (here the solvent) $\nabla \cdot \boldsymbol{v} = 0$ in Ω. For the fluid, we adopt no slip boundary conditions at the boundary of the container, $\boldsymbol{v} = \boldsymbol{0}$ on $\partial\Omega$. The fluid can cross the membrane, but tangentially, we impose a no-slip condition $\boldsymbol{v} - (\boldsymbol{v} \cdot \boldsymbol{N})\boldsymbol{N} = 0$ on Γ. By conservation of mass of solvent $\boldsymbol{v} \cdot \boldsymbol{N}$ must be continuous across Γ. Since its normal and tangential components are continuous, $\boldsymbol{v}$ is continuous across Γ. Since the container is impermeable to the solute molecules, we have $\boldsymbol{w} \cdot \boldsymbol{n} = 0$ on $\partial\Omega$.

The two dissipation potentials in Eq. (20) for viscous flow and in Eq. (37) for diffusion are relevant to the present situation. There is an additional source of dissipation associated to solvent permeation through the semipermeable membrane. In agreement with commonly used models for permeation, we postulate that the dissipation potential density per unit area is quadratic in the normal component of the velocity of fluid across the interface $\boldsymbol{v} \cdot \boldsymbol{N} - v_m$. Thus, the dissipation potential for this problem can be written as

$$\mathcal{D}(X; V) = \eta \int_\Omega \boldsymbol{d} : \boldsymbol{d}\, dV + \frac{f N_A}{2} \int_\Omega c|\boldsymbol{w}|^2 dV + \frac{\bar{\eta}}{2} \int_\Gamma (\boldsymbol{v} \cdot \boldsymbol{N} - v_m)^2\, dS, \quad (56)$$

where $\bar{\eta}$ is a permeation coefficient.

Following the systematic procedure outlined in the previous Section, we now turn to the process operator. This operator relating $\partial_t X$ and V contains the trivial component $\dot{x} = v_m$, and another component stating the conservation of solute molecules, which now takes the form

$$0 = \partial_t c + \nabla \cdot (\boldsymbol{j}_D + c\boldsymbol{v}) = \partial_t c + \nabla \cdot [c(\boldsymbol{w} + \boldsymbol{v})], \quad (57)$$

since the solute molecules can be transported either diffusively or by advection. In addition to these two equations, there is another important process relation at the semipermeable membrane. Because the solutes cannot cross the membrane, their diffusive velocity needs to coincide with the membrane velocity on either side of the domain

$$v_m = (\boldsymbol{w}^\pm + \boldsymbol{v}) \cdot \boldsymbol{N}. \quad (58)$$

Since $\boldsymbol{v} \cdot \boldsymbol{N}$ is continuous across the interface, we conclude that $\boldsymbol{w} \cdot \boldsymbol{N}$ is continuous across the interface. Therefore, the process operator can be summarized by the three relations

$$\dot{x} = v_m, \qquad 0 = \partial_t c + \nabla \cdot [c(\boldsymbol{w} + \boldsymbol{v})] \quad \text{in } \Omega, \qquad v_m = (\boldsymbol{w} + \boldsymbol{v}) \cdot \boldsymbol{N} \quad \text{on } \Gamma. \quad (59)$$

Now, we are in a position to compute the rate of change of the free energy, a key point in the theory. Recalling the definition of the chemical potential in Eq. (36) and applying Reynolds transport theorem in Ω^- and Ω^+ separately to account for the internal moving boundary, we obtain

$$\begin{aligned}
\dot{\mathcal{F}} &= \frac{d}{dt} \int_{\Omega^-} [RTc(\log c - 1) + c\mu_0] \, dV + \frac{d}{dt} \int_{\Omega^+} [RTc(\log c - 1) + c\mu_0] \, dV + kx\dot{x} \\
&= \int_{\Omega^-} \mu \partial_t c \, dV + v_m \int_\Gamma \left[RTc^-(\log c^- - 1) + c^- \mu_0 \right] dS + \\
&\qquad \int_{\Omega^+} \mu \partial_t c \, dV - v_m \int_\Gamma \left[RTc^+(\log c^+ - 1) + c^+ \mu_0 \right] dS + kx\dot{x} \\
&= \int_{\Omega^-} \mu \partial_t c \, dV + \int_{\Omega^+} \mu \partial_t c \, dV - v_m \int_\Gamma [\![RTc(\log c - 1) + c\mu_0]\!] \, dS + kx\dot{x} \\
&= \int_{\Omega^-} \mu \partial_t c \, dV + \int_{\Omega^+} \mu \partial_t c \, dV - v_m \int_\Gamma ([\![c\mu]\!] - RT [\![c]\!]) \, dS + kx\dot{x}, \quad (60)
\end{aligned}$$

where $[\![f]\!]$ denotes the jump of a function f across an interface $f^+ - f^-$. Now, using the first and second process equations in Eq. (59), the divergence theorem, the boundary conditions on $\partial\Omega$, and the fact that $\boldsymbol{n}^- = -\boldsymbol{n}^+ = \boldsymbol{N}$ on Γ, we have

$$\begin{aligned}
\dot{\mathcal{F}} &= -\int_{\Omega^-} \mu \nabla \cdot [c(\boldsymbol{w} + \boldsymbol{v})] \, dV - \int_{\Omega^+} \mu \nabla \cdot [c(\boldsymbol{w} + \boldsymbol{v})] \, dV \\
&\quad - v_m \int_\Gamma ([\![c\mu]\!] - RT [\![c]\!]) \, dS + kxv_m \\
&= \int_\Omega c\nabla\mu \cdot (\boldsymbol{w} + \boldsymbol{v}) dV + \int_\Gamma [\![c\mu]\!] (\boldsymbol{w} + \boldsymbol{v}) \cdot \boldsymbol{N} dS \\
&\quad - v_m \int_\Gamma ([\![c\mu]\!] - RT [\![c]\!]) \, dS + kxv_m \quad (61)
\end{aligned}$$

Finally, using the third process equation in Eq. (59), we obtain

$$\dot{\mathcal{F}} = RT \int_\Omega \nabla c \cdot (\boldsymbol{w} + \boldsymbol{v}) dV + v_m \left(RT \int_\Gamma [\![c]\!] \, dS + kx \right). \quad (62)$$

In the abstract formalism of the previous Section, the equation above is a workable expression of $D\mathcal{F}(X) \cdot P(X)V$. The second term already shows

that, in addition to the elastic force kx, the semipermeable membrane experiences an osmotic force that agrees with the classical van't Hoff formula, which naturally follows from the present formalism.

We can now form the constrained Rayleighian (accounting for solvent incompressibility), which takes the form

$$\mathcal{L}[c, x; \boldsymbol{w}, v_m, \boldsymbol{v}, p] = RT \int_\Omega \nabla c \cdot (\boldsymbol{w} + \boldsymbol{v}) dV + v_m \left(RT \int_\Gamma [\![c]\!] \, dS + kx \right)$$
$$+ \eta \int_\Omega \boldsymbol{d} : \boldsymbol{d} \, dV + \frac{f N_A}{2} \int_\Omega c|\boldsymbol{w}|^2 dV$$
$$+ \frac{\bar{\eta}}{2} \int_\Gamma (\boldsymbol{v} \cdot \boldsymbol{N} - v_m)^2 \, dS - \int_\Omega p \, \nabla \cdot \boldsymbol{v} \, dV. \qquad (63)$$

Making this functional stationary with respect to $\boldsymbol{w}$ leads, as in the pure diffusion example, to Fick's law

$$c\boldsymbol{w} = -\frac{k_B T}{f} \nabla c \quad \text{in} \ \ \Omega. \qquad (64)$$

The variation with respect to v_m leads to balance of forces acting on the semipermeable membrane

$$0 = RT \int_\Gamma [\![c]\!] \, dS + kx + \bar{\eta} \int_\Gamma (v_m - \boldsymbol{v} \cdot \boldsymbol{N}) dS. \qquad (65)$$

Variation with respect to p recovers the incompressibility condition $0 = \nabla \cdot \boldsymbol{v}$. Finally, variation with respect to $\boldsymbol{v}$ leads to

$$0 = RT \int_\Omega \nabla c \cdot \delta \boldsymbol{v} dV + 2\eta \int_\Omega \boldsymbol{d} : \nabla \delta \boldsymbol{v} \, dV - \int_\Omega p \, \nabla \cdot \delta \boldsymbol{v} \, dV$$
$$+ \bar{\eta} \int_\Gamma (\boldsymbol{v} \cdot \boldsymbol{N} - v_m) \delta \boldsymbol{v} \cdot \boldsymbol{N} dS. \qquad (66)$$

Performing integration by parts carefully over the two subdomains, and recalling the homogeneous boundary conditions on $\partial \Omega$ and the fact that $\boldsymbol{v}$ (and hence $\delta \boldsymbol{v}$) is continuous across Γ, we find

$$0 = \int_\Omega (RT \nabla c - 2\eta \nabla \cdot \boldsymbol{d} + \nabla p) \cdot \delta \boldsymbol{v} \, dV - \int_\Gamma \boldsymbol{N} \cdot [\![2\eta \boldsymbol{d} - p\boldsymbol{I}]\!] \cdot \delta \boldsymbol{v} \, dS$$
$$+ \bar{\eta} \int_\Gamma (\boldsymbol{v} \cdot \boldsymbol{N} - v_m) \delta \boldsymbol{v} \cdot \boldsymbol{N} dS. \qquad (67)$$

Thus, identifying the stress tensor as $\boldsymbol{\sigma} = 2\eta \boldsymbol{d} - p\boldsymbol{I}$, the above equation leads to

$$0 = \nabla \cdot \boldsymbol{\sigma} - RT \nabla c \quad \text{in} \ \ \Omega \qquad (68)$$

and to

$$\boldsymbol{N} \cdot [\![\boldsymbol{\sigma}]\!] = \bar{\eta}(\boldsymbol{v} \cdot \boldsymbol{N} - v_m)\boldsymbol{N} \quad \text{on} \ \ \Gamma. \tag{69}$$

Finally, we can eliminate $\boldsymbol{w}$ from the formulation by plugging Fick's law in Eq. (64) into the two process relations in Eq. (59) encoding mass conservation to obtain

$$\partial_t c - \frac{k_B T}{f}\Delta c + \boldsymbol{v} \cdot \nabla c = 0 \quad \text{in} \ \ \Omega, \tag{70}$$

and the two equations

$$\frac{k_B T}{f} \frac{\partial c}{\partial N}^{\pm} = c^{\pm}(\boldsymbol{v} \cdot \boldsymbol{N} - v_m) \quad \text{on} \ \ \Gamma. \tag{71}$$

In summary, we have deduced using Onsager's principle the governing equations for the system depicted in Figure 2. These equations are a *Stokes/advection-diffusion system* in the bulk reflecting conservation of mass of solutes and solvent and balance of linear momentum in the fluid, together with Fick's law and the constitutive relation for a Newtonian fluid:

$$\left.\begin{aligned}
0 &= \partial_t c - \frac{k_B T}{f}\Delta c + \boldsymbol{v} \cdot \nabla c \\
0 &= \nabla \cdot \boldsymbol{v} \\
0 &= \nabla \cdot \boldsymbol{\sigma} - RT\nabla c
\end{aligned}\right\} \quad \text{in} \ \ \Omega,$$

where $\boldsymbol{\sigma} = 2\eta\boldsymbol{d} - p\boldsymbol{I}$ with boundary conditions

$$\boldsymbol{v} = \boldsymbol{0} \quad \text{and} \quad \frac{\partial c}{\partial n} = 0 \quad \text{on} \ \ \partial\Omega. \tag{72}$$

These equations are supplemented with conditions at the moving semipermeable membrane. These conditions are a no-slip condition in the tangential direction

$$\boldsymbol{v} - (\boldsymbol{v} \cdot \boldsymbol{N})\boldsymbol{N} = 0 \quad \text{on} \ \ \Gamma, \tag{73}$$

a *global force balance on the membrane* involving permeation, osmotic and elastic forces

$$\bar{\eta}\int_{\Gamma}(\boldsymbol{v} \cdot \boldsymbol{N} - v_m)dS = RT\int_{\Gamma}[\![c]\!]\,dS + kx. \tag{74}$$

a *local force balance in the fluid at the interface* involving the jump of fluid tractions and the permeation tractions

$$\bar{\eta}(\boldsymbol{v} \cdot \boldsymbol{N} - v_m)\boldsymbol{N} = \boldsymbol{N} \cdot [\![\boldsymbol{\sigma}]\!] \quad \text{on} \ \ \Gamma, \tag{75}$$

and *interface conditions resulting from conservation of solute and solvent*

$$[\![\boldsymbol{v}]\!] = \boldsymbol{0}, \quad [\![\boldsymbol{w}]\!] \cdot \boldsymbol{N} = 0, \quad \text{and} \quad \frac{k_B T}{f} \frac{\partial c}{\partial N}^{\pm} = c^{\pm}(\boldsymbol{v} \cdot \boldsymbol{N} - v_m) \quad \text{on} \ \ \Gamma. \tag{76}$$

We note that, at the interface, we impose simultaneously Dirichlet and Neumann-like jump conditions for $\boldsymbol{v}$, and Dirichlet and Robin-like jump conditions for c. This is possible because the interface is moving.

We could have directly arrived at this set of equations with sufficient physical insight and invoking constitutive relations such as Fick's law, van't Hoff's relation, or that of a Newtonian fluid. It is also clear that one can easily make errors in such a direct derivation. Instead, all these relations have followed systematically from the rather simple modeling assumptions behind $\mathcal{F}$ and $\mathcal{D}$, the use of conservation of mass for solvent and solute to define the process operator, and Reynolds transport theorem. Furthermore, just by looking at the final equations, it is not easy to see how is $\mathcal{F}$ driving this system and decreasing during the dynamics or how is energy being dissipated. Finally, Onsager's principle allows us to systematically construct more complex models by adding additional building blocks. For instance, the membrane could be made flexible and endowed with tension or curvature elasticity. Or, using the elementary models presented in the next Sections, the solute molecules could be chemically active and react with other species, adsorb to surfaces, or preferentially react while adsorbed on a catalyzer.

We would like to make a final point regarding this example. We discussed earlier that the diffusion equation can be formally derived from Onsager's principle starting from the energy and dissipation potentials in Eqs. (31) and (32), not founded on the microscopic physics of diffusion. The reader can easily become convinced that these functionals, however, dramatically fail when diffusion acts in concert with other physics. Indeed, they cannot be meaningfully combined in a Rayleighian with the functionals encoding additional ingredients such as hydrodynamics or permeation through a semipermeable membrane. Instead, the approach described above naturally produces, for instance, entropic effects such as osmotic forces.

2.7 Reaction-diffusion of two species in a quiescent fluid

We introduce next a new item into our catalog of phenomena amenable to Onsager's principle: chemical reactions. As a minimal model system, we want to identify the variational structure of a system of two coupled linear reaction-diffusion equations for two chemical species. We consider a domain Ω, whose boundary is assumed for simplicity to be impermeable to both substances.

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Let us first describe this simple model. The state of the system is described by two molar concentration fields c_1 and c_2, one for each one of the species X_1 and X_2, which transform through the simple reaction

$$X_1 \xrightleftharpoons[k_b]{k_f} X_2. \tag{77}$$

We assume that this reaction follows the law of mass action, by which in this simple example the molar rate per unit volume of transformation of species X_1 to species X_2, the forward rate r_f, is proportional to the concentration of the reactant, $r_f = k_f c_1$. Conversely, the backward rate is given by $r_b = k_b c_2$, and thus the net forward rate is $r = k_f c_1 - k_b c_2$. Then, the dynamics of this system can be modeled through the linear system of reaction-diffusion equations

$$\left.\begin{aligned} \partial_t c_1 &= D_1 \Delta c_1 - k_f c_1 + k_b c_2 \\ \partial_t c_2 &= D_2 \Delta c_2 + k_f c_1 - k_b c_2 \end{aligned}\right\} \quad \text{in } \Omega, \tag{78}$$

where D_1 and D_2 are the diffusion coefficient of each chemical species, supplemented by initial and boundary conditions. In equilibrium, the concentrations will be uniform and $r = 0$, and thus $c_1^{eq}/c_2^{eq} = k_b/k_f = K$ is a constant called equilibrium constant of the reaction.

In the previous Sections, we showed that molecular diffusion can be understood as a process of entropic free-energy minimization, dragged by the resistance exerted by the solvent. Can we integrate this phenomenology with that of chemical reactions between the diffusing species? In other words, can we find the appropriate dissipation and free energy potentials so that the diffusion-reaction dynamics emerge from Onsager's principle? The answer is yes and due to Mielke (2012). Let us develop such a model.

We first model the free energy of the system. Assuming that the concentrations are dilute, we write the chemical free energy of the system building on that of an ideal gas in Eq. (34) as a function of $X = \{c_1, c_2\}$

$$\begin{aligned} \mathcal{F}(X) =& RT \int_\Omega c_1 \left(\log c_1 - 1\right) dV + \int_\Omega c_1 \mu_{0,1} dV \\ &+ RT \int_\Omega c_2 \left(\log c_2 - 1\right) dV + \int_\Omega c_2 \mu_{0,2} dV, \end{aligned} \tag{79}$$

where $\mu_{0,i}$ are the standard chemical potentials for each species. In the single-species diffusion case, this was an irrelevant constant. We shall see that for two reacting species, the difference between these two constants determines the equilibrium constant of the reaction.

Now, in addition to the diffusive velocities $\boldsymbol{w}_1$ and $\boldsymbol{w}_2$ for each substance, the concentrations can evolve as a result of chemical reactions quantified for

instance by the net forward reaction rate r. Thus, the process variables are now $V = \{\boldsymbol{w}_1, \boldsymbol{w}_2, r\}$. Note that, in 3D, we need only two scalar fields to describe the state of the system and as many as 7 (two vector fields and a scalar field) to describe the rate of change of the system. As we show later, we do need that many degrees of freedom in V to properly model dissipation.

Accounting for chemical reactions, the process operator is then given by the equations

$$
\begin{aligned}
\partial_t c_1 + \nabla \cdot (c_1 \boldsymbol{w}_1) + r &= 0, \\
\partial_t c_2 + \nabla \cdot (c_2 \boldsymbol{w}_2) - r &= 0,
\end{aligned} \tag{80}
$$

encoding balance of mass for the dissolved species. The conditions $0 = \boldsymbol{w}_i \cdot \boldsymbol{n}$ in $\partial\Omega$, reflecting the fact that $\partial\Omega$ is impermeable, can also be viewed as part of the process operator. With the free energy and the process operator at hand, and following a similar calculation as in Section 2.4, we can write the rate of change of the energy as

$$
\begin{aligned}
\dot{\mathcal{F}}(X; V) = &- \int_\Omega \mu_1 \nabla \cdot (c_1 \boldsymbol{w}_1) \; dV - \int_\Omega \mu_2 \nabla \cdot (c_2 \boldsymbol{w}_2) \; dV \\
&+ \int_\Omega (\mu_2 - \mu_1) r \, dV
\end{aligned} \tag{81}
$$

with the chemical potentials given by

$$
\mu_i(c) = \mu_{0,i} + RT \log c_i. \tag{82}
$$

After integration by parts using the fact that $\partial\Omega$ is impermeable, we obtain

$$
\begin{aligned}
\dot{\mathcal{F}}(X; V) = &RT \int_\Omega \nabla c_1 \cdot \boldsymbol{w}_1 \; dV + RT \int_\Omega \nabla c_2 \cdot \boldsymbol{w}_2 \; dV \\
&+ \int_\Omega (\mu_2 - \mu_1) \, r \, dV.
\end{aligned} \tag{83}
$$

This expression already contains interesting information about equilibrium. Indeed, the equilibrium state should minimize the free energy, and from the expression above three stationary conditions can be extracted. Stationarity with respect to diffusive velocities $\boldsymbol{w}_i$ implies that in equilibrium both concentrations are uniform. Stationarity with respect to the reaction rate r implies that $\mu_2 = \mu_1$, and thus

$$
K = \frac{c_1^{eq}}{c_2^{eq}} = \exp \frac{\Delta \mu_0}{RT}, \tag{84}
$$

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where $\Delta\mu_0 = \mu_{0,2} - \mu_{0,1}$ is the difference of reference chemical potentials. Thus, $K = k_b/k_f$ is a purely thermodynamic quantity (although both k_b and k_f contain kinetic information).

Having examined equilibrium, we introduce the dissipation potential, which accounts for the dissipation during diffusion and reaction. Recalling Eq. (37), we consider

$$\mathcal{D}(X;V) = \frac{f_1 N_A}{2}\int_\Omega c_1|\boldsymbol{w}_1|^2 dV + \frac{f_2 N_A}{2}\int_\Omega c_2|\boldsymbol{w}_2|^2 dV + \frac{1}{2}\int_\Omega \frac{1}{\bar{k}}r^2 dV, \quad (85)$$

where f_i are the molecular drag coefficients of the two species. We postulate that the dissipation potential is quadratic in the rate r (all the dissipation potentials examined so far have been quadratic), and leave the coefficient $\bar{k}$ unspecified for the moment. This parameter should be non-negative for consistency with the second law of thermodynamics, as discussed in Section 2.5.

Forming the Rayleighian $\mathcal{R} = \dot{\mathcal{F}} + \mathcal{D}$ and minimizing it with respect to $\boldsymbol{w}_i$, we recover Fick's law for each species

$$c_i\boldsymbol{w}_i = -\frac{k_B T}{f_i}\nabla c_i \quad \text{in} \ \ \Omega. \quad (86)$$

Minimization with respect to r leads to

$$r = \bar{k}(\mu_1 - \mu_2). \quad (87)$$

Now, let's remember that our goal here was to identify Onsager's variational structure for the reaction-diffusion system in Eq. (78). We can directly established the diffusion part by introducing Eq. (86) into the process equations in (80). To establish the reaction part, we need to express the reaction rate in Eq. (87) in the form $r = k_f c_1 - k_b c_2$. Examining the expression of the chemical potentials in Eq. (82), it is clear that $\bar{k}$ will need to be a complicated function of the concentrations.

Consider now the following choice for the concentration-dependent kinetic coefficient

$$\begin{aligned}\bar{k}(c_1, c_2) =& k\frac{c_1 - e^{\Delta\mu_0/(RT)}c_2}{\mu_1 - \mu_2} \\ =& \frac{ke^{-\mu_{0,1}/(RT)}}{RT}\frac{e^{\mu_1/(RT)} - e^{\mu_2/(RT)}}{\mu_1/(RT) - \mu_2/(RT)},\end{aligned} \quad (88)$$

where $k > 0$ is a kinetic constant not depending on the concentrations. Using Eq. (82) it is easily shown that these two expressions for $\bar{k}$ are equivalent.

The first form is useful because when plugged into Eq. (87), we immediately find the sought after expression

$$r = \underbrace{k}_{k_f} c_1 - \underbrace{ke^{\Delta\mu_0/(RT)}}_{k_b} c_2, \qquad (89)$$

which furthermore shows that we recover Arrhenius equation. The second form of the kinetic coefficient in Eq. (88) is important because, since the exponential function is monotonically increasing, it clearly shows that $\bar{k} \geq 0$ for any choice of concentrations.

Thus, we have recovered the reaction diffusion system in Eq. (78) using Onsager's principle. This derivation has showed that both reaction and diffusion are driven by the same chemical energy in Eq. (79), which decreases during the dynamics. This free energy contains an entropic component, but also an enthalpic one given by the difference of reference chemical potentials between the reacting species $\Delta\mu_0$. The newest and maybe surprising ingredient in this model has been the form of the coefficient encoding dissipation during the chemical reaction in Eq. (88). In the numerator, we have "Δc" measuring the deviation from the equilibrium condition in Eq. (84), and in the denominator we have $\Delta\mu$. This expression can be generalized to more complex chemical reactions obeying the law of mass action (Mielke, 2012). By understanding the basic structure of the reaction dissipation potential, we have a new building block for modeling that can be easily adapted to different settings and combined with different physics, as shown in subsequent Sections. We are not aware of a compelling microscopic interpretation of Eq. (88).

During the derivation of the equations, we have identified the diffusion constants as $D_i = k_B T / f_i$. Furthermore, we have understood that the forward and backward rates contain not only kinetic information, but also thermodynamic information in that their ratio depends on $\Delta\mu_0$. Onsager's principle has allowed us to untangle the kinetic and thermodynamic components of the reaction dynamics. Thus, this example further exemplifies two benefits of Onsager's principle: (1) it provides a systematic method to derive models for dissipative systems from a library of building blocks, and (2) it highlights the energetic-dissipative structure of such systems, providing physical insight into the model parameters.

3 Surface sorption and diffusion

Having considered reaction-diffusion systems in the bulk, we are in a position to examine chemical adsorption. We consider diffusing solutes in a bulk fluid adsorbing or desorbing on the surface enclosing it and also diffusing

on it. For simplicity, we assume that the surface has a fixed shape and the fluid is quiescent. The bulk fluid is represented by Ω and the surface by $\Gamma = \partial\Omega$ as shown in Fig. 3. The bulk fluid can exchange solutes with the surrounding surface through sorption–the process encompassing adsorption and desorption.
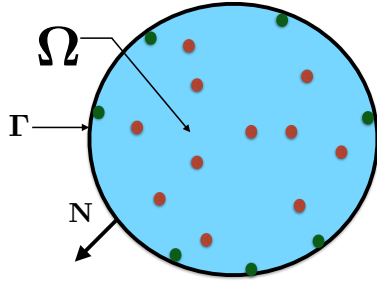

Figure 3. Elementary model for sorption-diffusion. The solutes and adsorbates are labeled with red and green dots respectively. The bulk domain representing quiescent fluid is Ω and the surface of fixed geometry is $\Gamma = \partial\Omega$.

In the context of biological membranes, adsorption from the bulk is a possible mechanism for protein incorporation. Another important mechanism involves fusion with vesicles loaded with membrane proteins. Proteins may adsorb by weakly scaffolding the membrane or by inserting amphiphilic domains into one leaflet or the entire bilayer. Irrespective of whether the process of adsorption induces a conformational change or not, we consider that the chemical reaction is the transformation from a molecule in solution to one bound to the surface. Thus, we treat the solute molecules in the bulk X_B and those on the surface X_S–the adsorbate–as two different species transforming through the elementary reaction

$$X_B \rightleftharpoons X_S. \tag{90}$$

We will denote by c the molar concentration of solute molecules in the bulk. To adhere with the literature, we will express the concentration of adsorbates on the surface through the area fraction of surface covered by adsorbed molecules ϕ. Thus, the state variables are the bulk and surface fields $X = \{c, \phi\}$. The molar surface concentration can then be recovered as ϕ/a_0, where a_0 is the molar area of the adsorbate.

In this Section, we will assume that c is small, which allows us to safely consider the ideal gas mixing entropy introduced earlier. However, we will consider the possibility that the area fraction is finite, and even large. Large area coverage of membrane proteins is common in synthetic systems (Sorre et al., 2012; Zhu et al., 2012) and in cell organelles (Shibata et al., 2009; Terasaki et al., 2013). Molecular crowding of proteins on the membrane can then lead to nonlinear chemical effects as discussed in the introduction. If the adsorbates modify the preferred curvature of the bilayer by any of the proposed mechanisms such as scaffolding, wedging, or crowding (Shibata et al., 2009; Stachowiak et al., 2012), then adsorption may induce significant shape transformations. In the present Section, however, we ignore such a coupling between chemistry and mechanics, which we only examine in a simple model in Section 4, and focus here on the sorption/diffusion system.

3.1 Onsager's principle for linear sorption-diffusion

First, we assume that adsorbates are very dilute. This situation is very similar to that in Section 2.7, and therefore we will provide a concise presentation highlighting the main differences. In close analogy with that Section, we write the chemical energy in the surface and the bulk as

$$
\begin{aligned}
\mathcal{F} = &\frac{RT}{a_0} \int_\Gamma \phi(\log \phi - 1)\, dS + \frac{1}{a_0} \int_\Gamma \mu_{0,a} \phi \, dS \\
&+ RT \int_\Omega c \left(\log \frac{c}{c_0} - 1 \right) dV + \int_\Omega \mu_{0,s} c \, dV,
\end{aligned}
\tag{91}
$$

where the molar area of adsorbate a_0 is introduced in the first line because the standard form of the chemical energy is for a concentration, not an area fraction. To maintain dimensional consistency of the formulation, we have explicitly introduced a reference concentration c_0 at which the chemical potential of the solute is precisely $\mu_{0,s}$. This does not involve a real additional parameter in the model because $\mu_{0,s}$ is defined relative to c_0.

The state of the system in the bulk can change due to the solute diffusive velocity $\boldsymbol{w}_s$ according to the continuity equation

$$
\partial_t c + \nabla \cdot (c\boldsymbol{w}_s) = 0 \quad \text{in } \Omega.
\tag{92}
$$

In the surface, the surface fraction can change due to the adsorbate diffusive velocity $\boldsymbol{w}_a$, a vector field *tangent* to the surface Γ, and also due to the rate of adsorption r, which we express as a rate of change of area fraction. Therefore, the statement of conservation of adsorbate becomes

$$
\partial_t \phi + \nabla_s \cdot (\phi \boldsymbol{w}_a) = r \quad \text{on } \Gamma,
\tag{93}
$$

where ∇_s denotes here the covariant derivative on the surface. Besides these two equations, we need an additional equation expressing the fact that the rate of adsorbed molecules is balanced by a flux of molecules in solution exiting Ω:

$$c\,\boldsymbol{w}_s \cdot \boldsymbol{N} = \frac{r}{a_0} \quad \text{on } \Gamma, \tag{94}$$

where a_0 is required to convert r into rate of change of molar areal concentration. Equations (92-94) are the process equations relating the state variables $X = \{c, \phi\}$ and the process variables $V = \{\boldsymbol{w}_s, \boldsymbol{w}_a, r\}$.

Since the surface does not have boundary and the fluid is quiescent, the rate of change of the free energy takes the form

$$\dot{\mathcal{F}}(X; V) = \frac{1}{a_0} \int_\Gamma \mu_a \partial_t \phi \, dS + \int_\Omega \mu_s \partial_t c \, dV, \tag{95}$$

where the chemical potentials for adsorbate and solute resulting from this calculation are

$$\begin{aligned}
\mu_a(\phi) &= \mu_{0,a} + RT \log \phi, \\
\mu_s(c) &= \mu_{0,s} + RT \log \frac{c}{c_0}.
\end{aligned} \tag{96}$$

Using the process equations and the divergence theorem, we obtain

$$\begin{aligned}
\dot{\mathcal{F}}(X; V) = &\frac{RT}{a_0} \int_\Gamma \nabla_s \phi \cdot \boldsymbol{w}_a \, dS + RT \int_\Omega \nabla c \cdot \boldsymbol{w}_s \, dV \\
&+ \frac{1}{a_0} \int_\Gamma r(\mu_a - \mu_s) \, dS
\end{aligned} \tag{97}$$

We note from this expression that the chemical potential of the solute plays a role only at the interface, where it undergoes a reaction. Making the free energy stationary, we conclude that in equilibrium $\mu_a = \mu_s$, and therefore the equilibrium constant of the reaction is

$$\frac{c^{eq}}{\phi^{eq} c_0} = \exp \frac{\Delta \mu_0}{RT}, \tag{98}$$

where $\Delta \mu_0 = \mu_{0,a} - \mu_{0,s}$.

Similar to the previous Section, the dissipation potential accounting for diffusion of solute, of adsorbate and the sorption reaction is given by

$$\mathcal{D}(X; V) = \frac{f_s N_A}{2} \int_\Omega c |\boldsymbol{w}_s|^2 \, dV + \frac{f_a N_A}{2a_0} \int_\Gamma \phi |\boldsymbol{w}_a|^2 \, dS + \frac{1}{2a_0} \int_\Gamma \frac{1}{k} r^2 \, dS, \tag{99}$$

where f_a, the drag coefficient of an adsorbed molecule on the membrane, will depend strongly on the membrane interfacial viscosity and weakly on the

molecule size according to the theory by Saffman and Delbruck (1975). We consider now a concentration-dependent kinetic coefficient with the same structure as in the previous Section and taking the form

$$\bar{k} = k \frac{c/c_0 - e^{\Delta\mu_0/(RT)}\phi}{\mu_s(c) - \mu_a(\phi)} \tag{100}$$

To prove that, as thermodynamically required, $\bar{k} \geq 0$, we recall Eqs. (96) and (98). Then, a direct calculation shows that

$$\bar{k} = \frac{ke^{-\mu_{0,s}/(RT)}}{RT} \frac{e^{\mu_s/(RT)} - e^{\mu_a/(RT)}}{\mu_s/(RT) - \mu_a/(RT)}, \tag{101}$$

which is manifestly non-negative because the exponential function is strictly increasing.

Forming the Rayleighian combining Eqs. (97) and (99), and making it stationary with respect to r, Onsager's principle leads to

$$r = \bar{k}(\mu_s - \mu_a). \tag{102}$$

Recalling our choice for kinetic coefficient in Eq. (100), we immediately conclude that

$$r = \underbrace{\frac{k}{c_0}}_{k_A} c - \underbrace{ke^{\Delta\mu_0/(RT)}}_{k_D} \phi, \tag{103}$$

which allows us to identify the adsorption and desorption rates k_A and k_D for a model obeying the law of mass action. As in the previous example, we recognize that their ratio is a thermodynamic quantity, while the purely kinetic information about the reaction is given by the rate constant k.

Stationarity of the Rayleighian with respect to the surface and bulk diffusive velocities leads to Fick's law in the bulk and the surface. Finally, replacing these relations in the process equations we obtain the diffusion-sorption equation on the surface

$$\partial_t \phi = \frac{k_B T}{f_a} \Delta_s \phi + k_A c - k_D \phi \qquad \text{on } \Gamma, \tag{104}$$

where Δ_s is the surface Laplacian, the diffusion equation in the bulk

$$\partial_t c = \frac{k_B T}{f_s} \Delta c \qquad \text{in } \Omega, \tag{105}$$

and a condition on the surface matching bulk flux and surface reaction

$$\frac{k_B T}{f_s} \frac{\partial c}{\partial N} = \frac{1}{a_0} (k_D \phi - k_A c) \qquad \text{on } \Gamma. \tag{106}$$

These are the equations that we could have postulated a priori, but now we have a clear understanding of the free energy driving the system and of the dissipative mechanisms dragging the dynamics. This example shows that Onsager's principle naturally deals with interfacial phenomena coupled to bulk phenomena.

While this linear sorption-diffusion model is reasonable in a dilute limit, that is for small values of c and ϕ, an obvious conceptual drawback apparent from Eq. (98) is that ϕ^{eq} can be made arbitrarily large by either increasing c^{eq} at fixed $\Delta\mu_0$, or by considering a negative $\Delta\mu_0$ of increasing the magnitude at fixed c^{eq}. However, the area fraction of adsorbates cannot be larger than 1.

3.2 Onsager's principle for Langmuir sorption-diffusion

The above limitations of the linear sorption model can be overcome with the classical Langmuir model (Masel, 1996). In a nutshell, this model introduces the notion that, for a molecule in solution X_B to become adsorbed, X_S, it needs to react with a free site on the surface X_F, which is thus viewed as an additional reactant/product in the adsorption/desorption reaction

$$X_B + X_F \rightleftharpoons X_S. \tag{107}$$

In this way, as the area coverage of adsorbate increases, fewer free sites become available, which slows down the adsorption reaction and fixes the issue of unbounded area coverage in the linear sorption model. In a continuum model, if ϕ is the area fraction of adsorbates, then the free area fraction is $1 - \phi$. Because in some systems the maximum area fraction of adsorbates ϕ_m saturates before reaching unity, we can slightly generalize the area fraction of free sites as $\phi_m - \phi$. Then, from the reaction above and the law of mass action, we can postulate the following form of the adsorption reaction rate

$$r = k_A c(\phi_m - \phi) - k_D \phi, \tag{108}$$

where k_A and k_D are adsorption/desorption rate coefficients. It is clear that in a dilute limit $\phi_m - \phi \approx \phi_m$ and we essentially recover the reaction rate in Eq. (103). In equilibrium, $r = 0$, which leads to the following expression for the equilibrium area fraction of adsorbates

$$\phi^{eq} = \frac{k_A \phi_m c^{eq}}{k_A c^{eq} + k_D}. \tag{109}$$

It is now clear that as the bulk concentration becomes larger, $c^{eq} \to +\infty$, the area fraction tends to the saturation value $\phi^{eq} \to \phi_m$ as expected. To

couple this adsorption model with diffusion in the bulk and the surface, it seems reasonable to replace the reaction rate in Eq. (103) by that in Eq. (108), which results in simply replacing $k_A c$ by $k_A c(\phi_m - \phi)$ in Eqs. (104) and (106). The reaction-diffusion system that follows from this reasonable modeling approach is nonlinear in the reaction terms.

Our question now is whether Langmuir's sorption model can be derived from Onsager's principle, and if so, what is the appropriate notion of free energy and dissipation potential. If this is the case, Onsager's principle provides a natural way to couple the sorption reaction with diffusion. Then, a second question is whether the resulting sorption-diffusion system is indeed that discussed in the previous paragraph.

Let us focus on the mixing entropy on the surface. In the ideal gas model in Eq. (91), we accounted for the entropy of the adsorbates with a term of the form $\phi \log \phi$ (up to normalization factors). Now, since we view empty sites as a new reacting species, it makes sense to consider also their entropic contribution, which will be of the form $(\phi_m - \phi) \log(\phi_m - \phi)$. Since the empty sites are immaterial, it does not make sense to include an enthalpic term analogous to $\mu_{0,a}\phi$. This argument leads to following expression for the free energy of the system

$$
\begin{aligned}
\mathcal{F}[c, \phi] = & \frac{RT}{a_0} \int_\Gamma \left[\phi \log \phi + (\phi_m - \phi) \log(\phi_m - \phi)\right] dS + \frac{1}{a_0} \int_\Gamma \mu_{0,a}\phi \, dS \\
& + RT \int_\Omega c \left(\log \frac{c}{c_0} - 1\right) dV + \int_\Omega \mu_{0,s} c \, dV.
\end{aligned}
\tag{110}
$$

The first term is in fact the well-known Flory-Huggins expression for the entropy of mixing (Huggins, 1941; Flory, 1942), introduced originally in the context of polymer blends. In the Flory-Huggins theory, an additional enthalpic term is added to the free energy density to account for the interaction between the mixing species of the form $(RT/a_0)\chi\phi(\phi_m - \phi)$, where χ is a dimensionless parameter. In the present context, it makes more sense to interpret this term as a self-interaction term of adsorbate molecules of the form $-(RT/a_0)\chi\phi^2$ plus a term proportional to ϕ that can be included in $\mu_{0,a}$. Such a free energy has been invoked to examine equilibrium in the context of adsorption of curving proteins on lipid membranes (Sorre et al., 2012; Singh et al., 2012).

Let us examine next the consequences of considering this free energy in the framework of Onsager's principle. The process equations of the previous Section remain unchanged. Likewise, a direct calculation shows that the rate

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of change of the free energy adopts the form

$$\dot{\mathcal{F}}(X;V) = \frac{1}{a_0} \int_\Gamma \nabla_s \mu_a \cdot (\phi \boldsymbol{w}_a) \, dS + \int_\Omega \nabla \mu_s \cdot (c \boldsymbol{w}_s) \, dV \\ + \frac{1}{a_0} \int_\Gamma r(\mu_a - \mu_s) \, dS, \tag{111}$$

where now the chemical potentials of the adsorbate in the surface and of the solute in the bulk are

$$\mu_a(\phi) = \mu_{0,a} + RT \log \frac{\phi}{\phi_m - \phi}, \\ \mu_s(c) = \mu_{0,s} + RT \log \frac{c}{c_0}. \tag{112}$$

From the first expression, we recognize that $\mu_{0,a}$ is the chemical potential of the adsorbate when the area fractions of adsorbate and free sites are equal. Noting that now

$$\nabla_s \mu_a = RT \frac{\phi_m}{\phi_m - \phi} \frac{\nabla_s \phi}{\phi} \tag{113}$$

we find that

$$\dot{\mathcal{F}}(X;V) = \frac{RT}{a_0} \int_\Gamma \frac{\phi_m}{\phi_m - \phi} \nabla_s \phi \cdot \boldsymbol{w}_a \, dS + RT \int_\Omega \nabla c \cdot \boldsymbol{w}_s \, dV \\ + \frac{1}{a_0} \int_\Gamma r(\mu_a - \mu_s) \, dS \tag{114}$$

In equilibrium, $\mu_a = \mu_s$ and therefore, similarly to earlier, we find that

$$\frac{\phi_m - \phi^{eq}}{\phi^{eq}} \frac{c^{eq}}{c_0} = e^{\Delta \mu_0 / (RT)}, \tag{115}$$

where $\Delta \mu_0 = \mu_{0,a} - \mu_{0,s}$.

We adopt the same structure of dissipation potential as in Eq. (99) with the following natural choice for the kinetic coefficient

$$\bar{k} = k \frac{\frac{1}{c_0} c(\phi_m - \phi) - e^{\Delta \mu_0 / (RT)} \phi}{\mu_s(c) - \mu_a(\phi)}, \tag{116}$$

which can be shown to be nonnegative with analogous arguments to those leading to Eq. (101). Invoking Onsager's principle and making the Rayleighian stationary with respect to r, we recover Langmuir's adsorption model and identify the thermodynamic/kinetic components behind the reaction rates

$$r = \underbrace{\frac{k}{c_0}}_{k_A} c(\phi_m - \phi) - \underbrace{k e^{\Delta \mu_0 / (RT)}}_{k_D} \phi. \tag{117}$$

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Therefore, this derivation establishes that the Langmuir's adsorption model can be viewed as a consequence of the Flory-Huggins form of the mixing entropy. Now, making the Rayleighian stationary with respect to $\boldsymbol{w}_a$, we find that the adsorbates undergo non-Fickian transport in that

$$\boldsymbol{j}_a = \phi \boldsymbol{w}_a = -\frac{k_B T}{f_a} \frac{\phi_m}{\phi_m - \phi} \nabla_s \phi. \tag{118}$$

The term multiplying $\nabla_s \phi$ can be interpreted as a diffusion coefficient dependent on area fraction. When plugged into the corresponding process operator, this relation leads to the nonlinear diffusion equation on the surface

$$\partial_t \phi = \frac{k_B T}{f_a} \nabla_s \cdot \left(\frac{\phi_m}{\phi_m - \phi} \nabla_s \phi \right) + k_A c(\phi_m - \phi) - k_D \phi \quad \text{on } \Gamma. \tag{119}$$

Thus, according to this derivation, the nonlinear Langmuir adsorption model would be paired with a nonlinear diffusion of adsorbates, both following from the Flory-Huggins entropy of mixing.

It is instructive to note that we can recover Fickian diffusion on the surface by defining the surface contribution to the dissipation potential as

$$\frac{f_a N_A \phi_m}{2 a_0} \int_\Gamma \frac{\phi}{\phi_m - \phi} |\boldsymbol{w}_a|^2 \, dS. \tag{120}$$

Without a compelling physical interpretation, however, this remains nothing but a mathematical trick. As we argue next, removing the nonlinearity with such a trick is artificial and does not seem justified from a physical point of view.

Indeed, something unsettling about the nonlinear diffusion equation in (119) is that it has been obtained from a free energy that tries to account for the finite area coverage of the adsorbates to deal with inconsistencies in the dilute limit. However, the dissipation contribution due to adsorbates has the structure

$$\frac{N_a \phi}{a_0} \cdot \frac{f_a}{2} |\boldsymbol{w}_a|^2 \tag{121}$$

where the first factor represents the number of molecules per unit area and the second factor is the dissipation potential for a single molecule. Thus, it is the superposition of the effect of an isolated molecule, which can be expected to be valid only in a dilute limit. A more pertinent modeling approach would be to couple the Flory-Huggins entropy to a better approximation of dissipation in a crowded solution of adsorbates. It is natural to expect that accounting for crowding will introduce an additional source

of nonlinearity in the dissipation, which will not be in general of the form of that in Eq. (120). For instance, in a bulk solution and accounting for first-order interaction effects, the hydrodynamic drag coefficient of spherical solutes of radius a can be approximated as

$$f_s(c) = 6\pi\eta a \left(1 + Bv_0^{1/3}c^{1/3}\right),\qquad(122)$$

where v_0 is the molar volume of solute molecules and B is a non-dimensional positive constant (Happel and Brenner, 2012). Such a concentration dependent drag will introduce additional nonlinear effects and lead to non-Fickian diffusion. We are not aware of similar approximations capturing the influence of area coverage and applicable to molecules moving on a two-dimensional fluid, that is an expression for $f_a(\phi)$ extending the theory by Saffman and Delbruck (1975) to crowded membranes.

Thus, Onsager's approach vividly shows that a concentration-dependent diffusion coefficient (Ramadurai et al., 2009) can have its origin in both the free energy driving diffusion and in the dissipation dragging it. Furthermore, *Onsager's approach provides a framework to model systems at multiple scales*, in that it connects effective coefficients such as diffusivity or reaction rates to microscopic thermodynamic and kinetic quantities, which can in principle be estimated with microscopic theories or experiments.

4 A minimal model for curvature sensing and generation in a membrane tube

Having established the Onsager variational structure behind the Langmuir adsorption model, in this Section we study the coupling between adsorption and mechanics. Rather that consider a general model with concentration gradients and general shapes, we focus on a uniform tubular lipid membrane to highlight how this coupling allows us to understand curvature sensing and generation by membrane proteins.

We consider membrane tube of length ℓ and radius ρ, subjected to a longitudinal force F. We will assume that the membrane is inextensible, and therefore the product $\ell\rho$ is constant. We will consider two different ensembles, one in which the length (and therefore the radius) is fixed and the force can adjust, and another in which the force is fixed and the length and radius are allowed to adjust. In neither of these situations the membrane tension is constant. A constant membrane tension ensemble would require changes in membrane area and therefore lipid flows from a reservoir, which is at odds with a simple uniform dynamical model. Zhu et al. (2012); Prévost et al. (2015) have developed models that allow for exchange of lipids and

proteins with a reservoir, albeit in equilibrium. We further assume that both the osmolarity and the hydraulic pressure are the same inside and outside of the tube. Therefore there is no pressure difference across the membrane.

When proteins are dissolved in the bulk fluid, only those closest to the membrane will adsorb, thereby creating a gradient in concentration followed by diffusion of dissolved proteins towards the membrane. Thus, if we assume that the concentration of proteins in bulk is uniform, we are assuming that the timescale associated with equilibration of bulk protein gradients by diffusion is much smaller than the timescale of the adsorption reaction. Let's check if this is reasonable. The typical diffusion coefficient for proteins in the bulk is in the range of $D \approx 1 - 10 \ \mu\text{m}^2/\text{s}$, (Elowitz et al., 1999). Therefore the timescale for radial diffusion can be estimated as $\tau_d = \rho^2/D$. The timescale associated with protein adsorption on membranes is typically of a few tens of minutes, $\tau_a \approx 600$ s (Sorre et al., 2012). Requiring that $\tau_d \ll \tau_a$ is then tantamount to requiring that $\rho \ll 25 - 80 \ \mu\text{m}$, which is the case in most situations of interest where tubules have radii of tens of nanometers. Therefore, it is reasonable to assuming a uniform concentration in the bulk.

The state of the system is hence characterized by the area fraction of proteins on the surface, the radius of the cylinder and the length of the cylinder, $X = \{\phi, \rho, \ell\}$. We will model the bending elasticity of the membrane using Helfrich's curvature model (Helfrich, 1973; Lipowsky, 1991). According to this classical model, the free energy density takes the form $\frac{\kappa}{2}(H - C_0)^2$ where κ is the bending rigidity, H is the mean curvature (here $H = 1/\rho$), and C_0 is the spontaneous curvature. Thus, it penalizes deviations of the mean curvature from the spontaneous curvature. As discussed earlier, membrane proteins can change the preferred curvature of the bilayer in various ways (McMahon and Gallop, 2005; Zimmerberg and Kozlov, 2006; Sens et al., 2008; Shibata et al., 2009; Antonny, 2011). This effect is generally modeled by considering that C_0 is a function of the area coverage of proteins, the simplest model being that it is proportional to ϕ (see Breidenich et al. (2000) for a microscopic justification). Thus, the free energy of the system considering the elastic and chemical contributions and the potential of the longitudinal force is

$$
\begin{aligned}
\mathcal{F}(X) = & 2\pi\ell\rho \left\{ \frac{\kappa}{2} \left(\frac{1}{\rho} - C_0\phi \right)^2 + \frac{RT}{a_0} \left[\phi \log \phi + (\phi_m - \phi) \log (\phi_m - \phi) \right] \right. \\
& \left. + \frac{\mu_{0,a}\phi}{a_0} \right\} - F\ell.
\end{aligned}
$$
(123)

Note that in this simple uniform example, $\mathcal{F}$ is an algebraic function of the state variables. We chose to impose the inextensibility constraint $\ell\rho$ =constant,

or equivalently $\dot{\ell}\rho + \ell\dot{\rho} = 0$, later using a Lagrange multiplier, which will allow us to identify the membrane tension. The nontrivial process equation is the balance of adsorbed molecules analogous to Eq. (93). Because the system is uniform, this equation does not involve diffusive fluxes. However, because we are not imposing yet the inextensibility condition of the surface, this equation includes a second term involving the rate of change of area (Rahimi et al., 2013):

$$\dot{\phi} = r - \phi \frac{\dot{\ell}\rho + \ell\dot{\rho}}{\ell\rho}. \tag{124}$$

Following a lengthy but direct calculation that uses the process equation above, the rate of change of the free energy can be computed as

$$\begin{aligned}
\dot{\mathcal{F}} = &\frac{2\pi\rho\ell}{a_0} \left\{ \mu_{0,a} + RT \log \frac{\phi}{\phi_m - \phi} - a_0\kappa \left(\frac{1}{\rho} - C_0\phi \right) C_0 \right\} r \\
&+ 2\pi\ell \left\{ \frac{RT}{a_0} \phi_m \log(\phi_m - \phi) - \frac{\kappa}{2} \left(\frac{1}{\rho} - C_0\phi \right)^2 \right\} \dot{\rho} \\
&+ 2\pi\rho \left\{ \frac{RT}{a_0} \phi_m \log(\phi_m - \phi) + \frac{\kappa}{2} \left(\frac{1}{\rho^2} - C_0^2\phi^2 \right) \right\} \dot{\ell} - F\dot{\ell}.
\end{aligned} \tag{125}$$

During this calculation, we identify the chemical potential of adsorbates as

$$\mu_a = \underbrace{\mu_{0,a} + RT \log \frac{\phi}{\phi_m - \phi}}_{\mu_a^{chem}} \underbrace{-a_0\kappa \left(\frac{1}{\rho} - C_0\phi \right) C_0}_{\mu_a^{mech}}, \tag{126}$$

involving a chemical component, but also a mechanical component.

To model the effect of the fixed bulk concentration of proteins $\bar{c}$, which are thus at a fixed chemical potential $\bar{\mu}_s = \mu_{0,s} + RT \log(\bar{c}/c_0)$, we introduce the external chemical power

$$\mathcal{P} = -\frac{2\pi\ell\rho\bar{\mu}_s}{a_0} r, \tag{127}$$

where we recall that a_0 allows us to dimensionally reconcile a chemical potential per unit mole with a reaction rate measuring the rate of change of adsorbate area fraction. Finally, the only dissipative mechanism operative here is the sorption reaction, and therefore

$$\mathcal{D} = \frac{\pi\ell\rho}{a_0\bar{k}} r^2. \tag{128}$$

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With these ingredients, we can form the constrained Rayleighian as

$$\mathcal{L} = \dot{\mathcal{F}} + \mathcal{D} + \mathcal{P} + 2\pi\sigma\left(\dot{\ell}\rho + \ell\dot{\rho}\right). \tag{129}$$

Let us focus first on adsorption. The optimality condition $\partial\mathcal{L}/\partial r = 0$ resulting from Onsager's principle leads to

$$r = \bar{k}(\bar{\mu}_s - \mu_a). \tag{130}$$

Now, we are confronted with the modeling choice of defining the coefficient $\bar{k}$ characterizing dissipation during reaction. A direct analogy with the previous Section would suggest

$$\bar{k} = k\frac{\frac{\bar{c}}{c_0}(\phi_m - \phi) - e^{\Delta\mu_0/(RT)}\phi}{\bar{\mu}_s - \mu_a}, \tag{131}$$

where as before $\Delta\mu_0 = \mu_{0,a} - \mu_{0,s}$. Combining the two equations above, a direct calculation shows that this leads to an adsorption rate of the Langmuir form $r = k_A\bar{c}(\phi_m - \phi) - k_D\phi$. However, the choice in Eq. (131) has at least two important drawbacks. First, such a model does not capture the phenomenology by which curving proteins bind at a higher rate to curved membranes–*curvature sensing*. Second, because μ_a depends also on the curvature of the membrane, see Eq. (126), it is not possible to express $\bar{k}$ as defined in Eq. (131) as a positive coefficient times a term of the form $(e^a - e^b)/(a - b)$, and therefore, in general, we will not be able to guarantee that $\bar{k} \geq 0$ as thermodynamically required. Therefore, a standard Langmuir adsorption model insensitive to curvature $r = k_A\bar{c}(\phi_m - \phi) - k_D\phi$ is thermodynamically inconsistent with our form of free energy in Eq. (123). Therefore, we discard Eq. (131).

One way around thermodynamic inconsistency is to define the reaction-dissipation coefficient as

$$\bar{k} = k\frac{\frac{\bar{c}}{c_0}(\phi_m - \phi) - e^{\Delta\mu_0/(RT)}\phi}{\bar{\mu}_s - \mu_a^{chem}} \tag{132}$$

$$= \frac{ke^{-\mu_{0,s}/(RT)}(\phi_m - \phi)}{RT}\frac{e^{\bar{\mu}_s/(RT)} - e^{\mu_a^{chem}/(RT)}}{\bar{\mu}_s/(RT) - \mu_a^{chem}/(RT)}, \tag{133}$$

which has the right structure to guarantee its non-negativity. Importantly, with Eq. (132) we are postulating that dissipation due to the adsorption reaction does not depend on membrane curvature. This choice for $\bar{k}$ does lead to a reaction rate sensitive to curvature because, when combined with

Eq. (130), we find

$$r = [k_A \bar{c}(\phi_m - \phi) - k_D \phi] \left[1 + \frac{a_0 \kappa \left(\frac{1}{\rho} - C_0 \phi \right) C_0}{\bar{\mu}_s - \mu_a^{chem}(\phi)} \right]$$

$$= [k_A \bar{c}(\phi_m - \phi) - k_D \phi] \left[1 + \frac{a_0 \kappa \left(\frac{1}{\rho} - C_0 \phi \right) C_0}{RT \log \frac{k_A \bar{c}(\phi_m - \phi)}{k_D \phi}} \right] \tag{134}$$

with k_A and k_D defined as in Eq. (117). We recover the Langmuir equation when $C_0 = 0$. In the dilute limit, the second term between brackets becomes 1, $\phi_m - \phi \approx \phi_m$, and we recover the linear adsorption model.

Therefore, we conclude that the model emanating from Eq. (132) is thermodynamically acceptable and physically meaningful. Of course, there are other possible choices. One could be replacing the two instances of μ_a^{chem} in Eq. (133) by μ_a, which leads to positive dissipation, introduces an explicit curvature dependence in $\bar{k}$, but strangely, this dependence has a structure dictated by thermodynamics. Therefore, it would be a rather artificial choice. A more realistic model accounting for the curvature sensitivity in the dissipation could consider k to be a function of curvature. To our knowledge, none of these issues have been examined before. Again, we see how Onsager's principle provides a systematic framework to think about modeling.

Variations of the constrained Rayleighian with respect to $\dot{\rho}$ and $\dot{\ell}$ lead to the radial and longitudinal equilibrium equations

$$0 = \frac{RT}{a_0} \phi_m \log(\phi_m - \phi) - \frac{\kappa}{2} \left(\frac{1}{\rho} - C_0 \phi \right)^2 + \sigma, \tag{135}$$

$$0 = \frac{RT}{a_0} \phi_m \log(\phi_m - \phi) + \frac{\kappa}{2} \left(\frac{1}{\rho^2} - C_0^2 \phi^2 \right) - \frac{F}{2\pi\rho} + \sigma. \tag{136}$$

Not being dragged by any dissipative mechanism, these equations are instantaneously satisfied by the system at any value of ϕ by adjusting σ and F in the first ensemble, or σ, ℓ and ρ in the second ensemble. Subtracting these two equations, we can relate the applied force to the shape and area fraction of protein as

$$F = 2\pi\kappa \left(\frac{1}{\rho} - C_0 \phi \right). \tag{137}$$

4.1 Protein sorption at fixed shape of the tube

Suppose that the length of the tube is held fixed. As a result of the inextensibility of the membrane, the radius is also fixed, However, the force

required to maintain the fixed length will depend on protein area coverage. Recalling the expression for the sorption rate, we have

$$\dot{\phi} = [k_A \bar{c}(\phi_m - \phi) - k_D \phi] \left[1 + \frac{a_0 \kappa \left(\frac{1}{\rho} - C_0 \phi \right) C_0}{RT \log \frac{k_A \bar{c}(\phi_m - \phi)}{k_D \phi}} \right]. \qquad (138)$$

We consider the parameters reported in (Sorre et al., 2012) for amphiphysins interacting with a model lipid membrane: $C_0 = 10$ nm^{-1}, $\bar{c} = 100$ nMolar, $k_D/k_A = 35$ nMolar. This is a first order nonlinear differential equation, which can be solved numerically.

Figure 4 (top) shows the results for $\phi(t)$ assuming no initial area coverage of protein, $\phi(0) = 0$ for tubes of varying curvature between 0.001 C_0 and 1.5 C_0. The figure shows that the adsorption dynamics strongly depends on curvature. Both the initial adsorption rate and the saturation area fraction in equilibrium increase with increasing curvature. This curvature-dependent adsorption of proteins is generally referred to as *curvature sensing*, and generally quantified by ratios of the equilibrium area coverage for various curvatures. Curvature sensing may provide a mechanism for the chemical organization of membrane organelles.

Even though shape is fixed in the present Section, the adsorbing proteins have a mechanical manifestation in the force required to maintain the tubule shape, see Fig. 4 (bottom). Force is computed using Eq. (137). The decrease of required force needed to maintain a tube as adsorption proceeds is an expected consequence of the scaffolding effect of the curving proteins and is consistent with experiments in tethers pulled out of vesicles. Along with this, our simple model provides an explanation for observations of no retraction of membrane tubules covered with proteins upon removal of the applied force (Sorre et al., 2012). Beyond equilibrium, the model can also predict the time and area fraction of protein at which we can observe no retraction upon force removal or even compressive buckling.

Figure 5 represents the adsorption isotherms for tubes of various curvatures. These curves represent the equilibrium area coverage–the horizontal asymptotes in Figure 4 (top)– as a function of the bulk concentration. In equilibrium, $\dot{\phi} = 0$, and therefore the right-hand-side in Eq. (138) is equal to zero. In the Langmuir model, recovered when $C_0 = 0$, the first factor is zero and the isotherm is given by $\phi^{eq}(\bar{c}) = \phi_m/[1 + (k_D/k_A\bar{c})]$. If the adsorbed molecules are mechanically active, however, the isotherm $\phi^{eq}(\bar{c})$ is implicitly defined by the relation

$$0 = RT \log \frac{k_A \bar{c}(\phi_m - \phi^{eq})}{k_D \phi^{eq}} + a_0 \kappa \left(\frac{1}{\rho} - C_0 \phi^{eq} \right) C_0. \qquad (139)$$
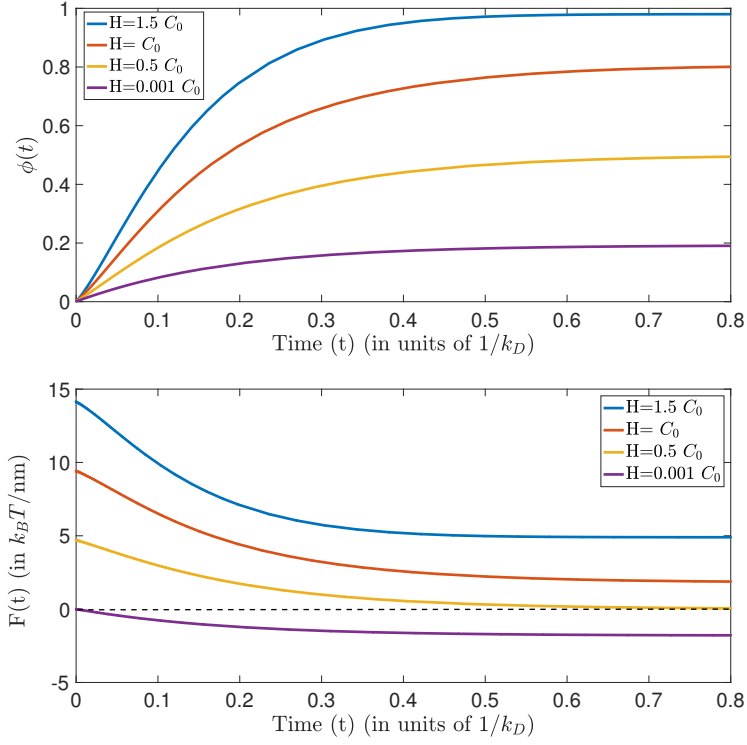
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Figure 4. (Top) Area fraction of adsorbed proteins as a function of time for various fixed curvatures of the membrane. We observe a curvature-dependent adsorption response: both the initial rate of change of ϕ (slope of the curve at $t \sim 0$) and the equilibrium area coverage increase with increasing curvature of tube $(1/\rho)$. (Bottom) Tube longitudinal force F as a function of time. The force decreases with time due to increased area fraction of the protein. The unit of force is in $k_B T/\text{nm} \approx 4.1$ pN

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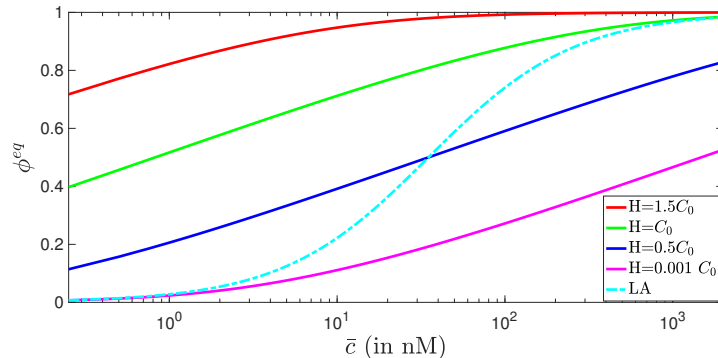
Figure 5. Adsorption isotherms in tubules of different curvature, i.e. equilibrium values ϕ^{eq} as a function of concentration of proteins in the bulk in a semi-log scale. The legend 'LA' stands for the Langmuir adsorption model.

The figure shows how, for proteins with preferred curvature ($C_0 \neq 0$), the isotherms significantly deviate from the Langmuir model. Notably, when the membrane is nearly planar (a similar model can be derived for spherical shapes more pertinent to tense vesicles, yielding similar results), the behavior closely follows the Langmuir model at very small concentrations, but strongly deviates from it at large concentrations. Yet, Langmuir's model is still used to interpret adsorption experiments onto large vesicles of proteins with preferred curvature (Sorre et al., 2012). The present model suggests a methodology to interpret similar experiments, where in addition to the parameters k_D/k_A and ϕ_m present in the Langmuir isotherm, the additional parameters a_0, κ, and C_0 could be fit from equilibrium or dynamical observations at different bulk concentration and curvature.

4.2 Protein sorption at fixed force

While the fixed shape ensemble of the previous Section allowed us to examine the curvature sensing capability of proteins with preferred curvature, it did not provide insight about their ability to generate curvature. Towards an elementary model for shape generation, we consider now a membrane tube at fixed force, which can adapt its radius and length to meet the mechanical equilibrium equations and the inextensibility constraint during adsorption.

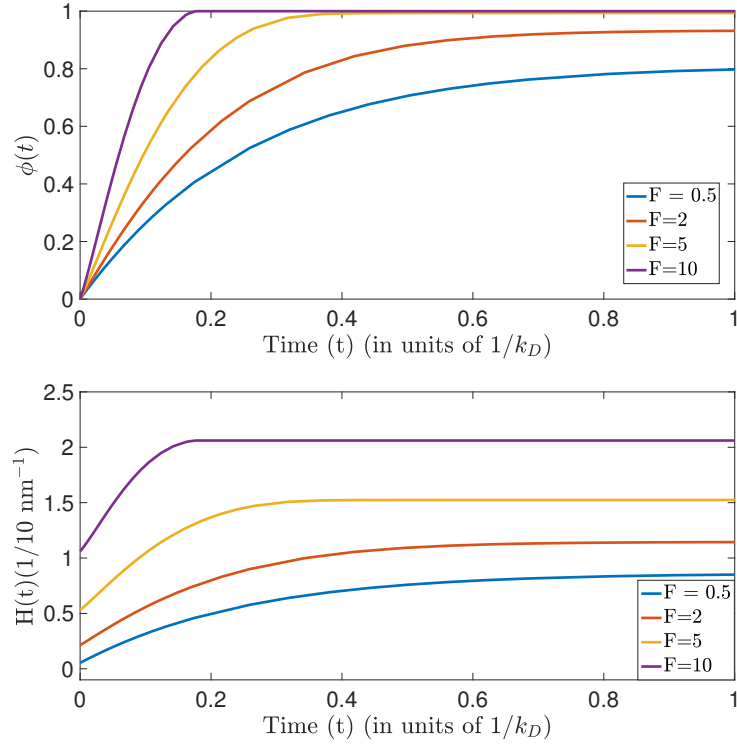Now, we integrate in time the differential-algebraic system for ϕ and ρ

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Figure 6. Area fraction of proteins on the membrane (top) and mean curvature $1/\rho$ (bottom) as a function of time. The bulk concentration of proteins is $\bar{c} = 100$ nM and the unit of force is $k_B T / nm \approx 4.11$ pN.

given by Eqs. (137) and (138). Equation (135) allows us to compute the tension σ. By plugging Eq. (137) into (138), we find that

$$\dot{\phi} = [k_A \bar{c}(\phi_m - \phi) - k_D \phi] \left[1 + \frac{a_0 C_0 F/(2\pi)}{RT \log \frac{k_A \bar{c}(\phi_m - \phi)}{k_D \phi}} \right], \qquad (140)$$
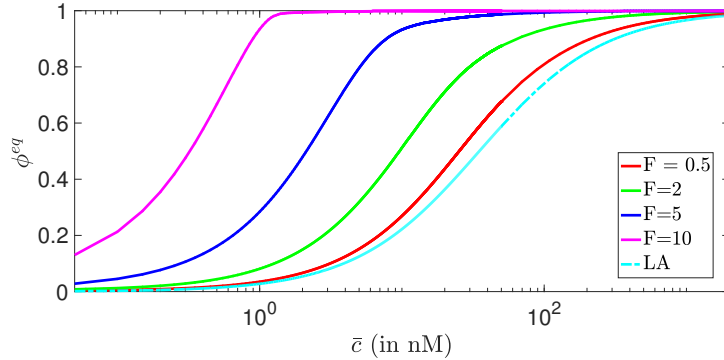
and therefore the Langmuir model is recovered for $F = 0$.

Figure 7. Adsorption isotherms for fixed force adsorption of proteins. The isotherms deviate from the Langmuir isotherm with increase in area fraction as a function of concentration. The unit of force is $k_B T/nm \approx 4.11$ pN.

Figure 6 shows the dynamics of area coverage and of tube curvature. We observe that both quantities increase in time up to an equilibrium value. Thus, as molecules adsorb, they modify the shape of the membrane. The rate of increase and magnitude of area coverage and curvature increase with the magnitude of the applied load, consistent with experiments. The adsorption isotherms are shown in Fig. 7. As predicted theoretically, the low force limit approaches the Langmuir model. The figure also shows a very large sensitivity of the equilibrium area coverage to the applied force, particularly at intermediate bulk concentrations.

To highlight the chemo-mechanical coupling captured by our simple model, we consider that during adsorption, and close to the equilibrium plateau, the force F is suddenly increased (decreased), see Fig. 8. It can be observed how, to adapt to such a disturbance, the protein coverage, tube curvature and tension increase (decrease). Interestingly, the mechanical quantities F and σ adjust discontinuously but the area fraction adjusts
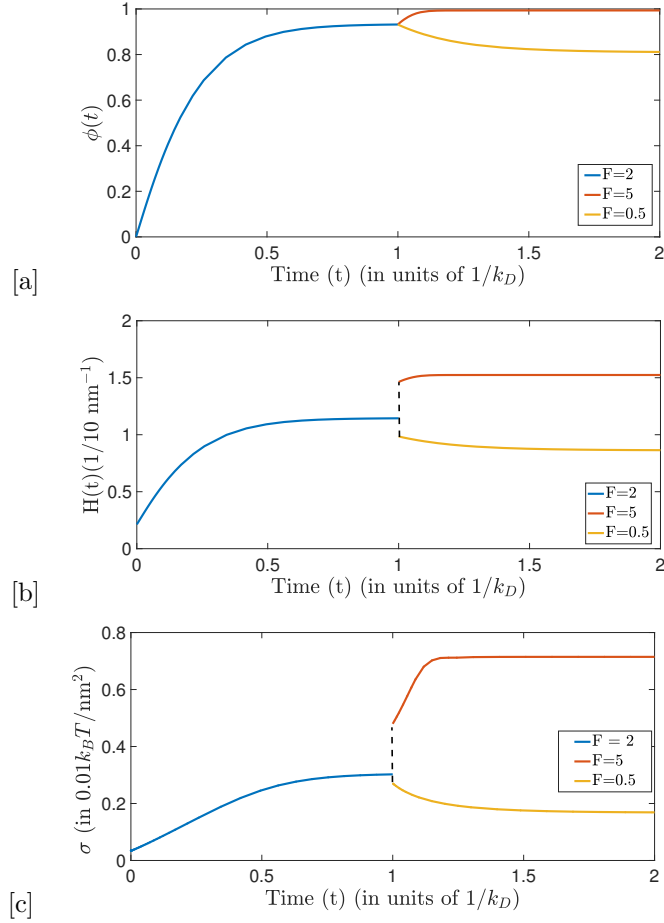
[a]

[b]

[c]

Figure 8. Dynamics of a tubule during adsorption in response to a sudden increase (decrease) of the applied force. (a) Area fraction, (b) mean curvature and (c) surface tension as a function time. The bulk concentration of proteins is $\bar{c} = 100$ nM and the unit of force is $k_B T/nm \approx 4.11$ pN.

continuously, since the rate of adsorption/desorption is penalized by the dissipation potential.

Bibliography

Sophie Aimon, Andrew Callan-Jones, Alice Berthaud, Mathieu Pinot, Gilman E S Toombes, and Patricia Bassereau. Membrane Shape Modulates Transmembrane Protein Distribution. *Developmental Cell*, 28(2): 212–218, 2014.

Bruno Antonny. Mechanisms of membrane curvature sensing. *Annu. Rev. Biochem.*, 80(March):101–23, jan 2011.

Marino Arroyo and Antonio DeSimone. Relaxation dynamics of fluid membranes. *Physical Review E*, 79:031915, 2009.

Marino Arroyo, Antonio DeSimone, and Luca Heltai. The role of membrane viscosity in the dynamics of fluid membranes. *arXiv*, (2007):1–21, 2010.

Marino Arroyo, Luca Heltai, Daniel Millán, and Antonio DeSimone. Reverse engineering the euglenoid movement. *Proceedings of the National Academy of Sciences of the United States of America*, (44):17874–9, 2012.

John W. Barrett, Harald Garcke, and Robert Nürnberg. *A stable numerical method for the dynamics of fluidic membranes*, volume 134. Springer Berlin Heidelberg, 2016.

M Breidenich, R R Netz, and R Lipowsky. The shape of polymer-decorated membranes. 49(February):431–437, 2000.

A Callan-Jones, M Durand, and J-B Fournier. Hydrodynamics of bilayer membranes with diffusing transmembrane proteins. *Soft Matter*, 12(6): 1791–800, 2016.

R Capovilla and J Guven. Stresses in lipid membranes. *Journal of Physics A: Mathematical and General*, 35(30):6233–6247, 2002.

Masao Doi. Onsager's variational principle in soft matter. *Journal of Physics: Condensed Matter*, 23(28):284118, 2011.

Charles M. Elliott and Björn Stinner. Computation of two-phase biomembranes with phase dependent material parameters using surface finite elements. *Communications in Computational Physics*, 13(2):325–360, 2013.

Michael B. Elowitz, Michael G. Surette, Pierre Etienne Wolf, Jeffry B. Stock, and Stanislas Leibler. Protein mobility in the cytoplasm of Escherichia coli. *Journal of Bacteriology*, 181(1):197–203, 1999.

Anand Embar, John Dolbow, and Eliot Fried. Microdomain evolution on giant unilamellar vesicles. *Biomechanics and Modeling in Mechanobiology*, 12(3):597–615, 2013.

E. Evans and A. Yeung. Hidden dynamics in rapid changes of bilayer shape. *Chemistry and Physics of Lipids*, 73(1-2):39–56, 1994.

Feng Feng and William S. Klug. Finite element modeling of lipid bilayer membranes. *Journal of Computational Physics*, 220(1):394–408, 2006.

Paul J Flory. Thermodynamics of high polymer solutions. *The Journal of chemical physics*, 10(1):51–61, 1942.

J.-B. Fournier, N. Khalifat, N. Puff, and M. I. Angelova. Chemically Triggered Ejection of Membrane Tubules Controlled by Intermonolayer Friction. *Phys. Rev. Lett.*, 102(1):018102, jan 2009.

Jean Baptiste Fournier. On the hydrodynamics of bilayer membranes. *International Journal of Non-Linear Mechanics*, 75:67–76, 2015.

Herbert Goldstein. *Classical mechanics*. World student series. Addison-Wesley, Reading (Mass.), Menlo Park (Calif.), Amsterdam, 1980.

W. T. Góźdź. Shape transformation of lipid vesicles induced by diffusing macromolecules. *Journal of Chemical Physics*, 134(2), 2011.

John Happel and Howard Brenner. *Low Reynolds number hydrodynamics: with special applications to particulate media*, volume 1. Springer Science & Business Media, 2012.

Michael Heinrich, Aiwei Tian, Cinzia Esposito, and Tobias Baumgart. Dynamic sorting of lipids and proteins in membrane tubes with a moving phase boundary. *Proc. Natl. Acad. Sci. U. S. A.*, 107(16):7208–13, apr 2010a.

Michael C Heinrich, Benjamin R Capraro, Aiwei Tian, Jose M Isas, Ralf Langen, and Tobias Baumgart. Quantifying Membrane Curvature Generation of Drosophila Amphiphysin N-BAR Domains. *J. Phys. Chem. Lett.*, 1(23):3401–3406, nov 2010b.

W Helfrich. Elastic properties of lipid bilayers: theory and possible experiments. *Z. Naturforsch.*, 28c:693–703, 1973.

Maurice L Huggins. Solutions of long chain compounds. *The Journal of chemical physics*, 9(5):440–440, 1941.

Richard Jordan, David Kinderlehrer, and Felix Otto. The Variational Formulation of the Fokker–Planck Equation. *SIAM Journal on Mathematical Analysis*, 29(1):1–17, 1998.

F Jülicher and R Lipowsky. Domain-induced budding of vesicles. *Phys. Rev. Lett.*, 70(19):2964–2967, 1993.

Nada Khalifat, Nicolas Puff, Stéphanie Bonneau, Jean-Baptiste Fournier, and Miglena I Angelova. Membrane deformation under local pH gradient: mimicking mitochondrial cristae dynamics. *Biophys. J.*, 95(10):4924–33, nov 2008.

Nada Khalifat, Mohammad Rahimi, Anne-Florence Bitbol, Michel Seigneuret, Jean-Baptiste Fournier, Nicolas Puff, Marino Arroyo, and Miglena I. Angelova. Interplay of Packing and Flip-flop in Local Bilayer Deformation. How Phosphatidylglycerol Could Rescue Mitochondrial Function in a Cardiolipin-deficient Yeast Mutant. *Biophys. J.*, 107 (4):879–890, 2014.

Anita Joanna Kosmalska, Laura Casares, Alberto Elosegui-Artola, Joseph Jose Thottacherry, Roberto Moreno-Vicente, Víctor González-Tarragó, Miguel Ángel del Pozo, Satyajit Mayor, Marino Arroyo, Daniel Navajas, Xavier Trepat, Nils C Gauthier, and Pere Roca-Cusachs. Physical principles of membrane remodelling during cell mechanoadaptation. *Nature communications*, 6:7292, 2015.

LD Landau and EM Lifshitz. *Fluid mechanics: Landau and Lifshitz: course of theoretical physics*, volume 6. Elsevier, 2013.

A. Lew, J. E. Marsden, M. Ortiz, and M. West. Variational time integrators. *International Journal for Numerical Methods in Engineering*, 60(1):153–212, 2004.

R. Lipowsky. The conformation of membranes. *Nature*, 349(6309):475–481, 1991.

Reinhard Lipowsky. Spontaneous tubulation of membranes and vesicles reveals membrane tension generated by spontaneous curvature. *Faraday Discuss*, 161:305–331, 2013.

Jian Liu, Yidi Sun, David G Drubin, and George F Oster. The mechanochemistry of endocytosis. *PLoS Biol*, 7(9):e1000204, 2009.

Richard I Masel. *Principles of adsorption and reaction on solid surfaces*, volume 3. John Wiley & Sons, 1996.

Harvey T McMahon and Jennifer L Gallop. Membrane curvature and mechanisms of dynamic cell membrane remodelling. *Nature*, 438(7068):590–596, 2005.

Alexander Mielke. A gradient structure for reactiondiffusion systems and for energy-drift-diffusion systems. *Nonlinearity*, 24(4):1329–1346, 2011a. ISSN 0951-7715. doi: 10.1088/0951-7715/24/4/016.

Alexander Mielke. On thermodynamically consistent models and gradient structures for thermoplasticity. *GAMM Mitteilungen*, 34(1):51–58, 2011b.

Alexander Mielke. Thermomechanical modeling of energy-reaction-diffusion systems, including bulk-interface interactions. *Discrete and Continuous Dynamical Systems - Series S*, 6(2):479–499, nov 2012.

L. Onsager. Irreversible processes. *Phys. Rev.*, 37:237–241, 1931a.

Lars Onsager. Reciprocal relations in irreversible processes. I. *Phys. Rev.*, 37(4):405–426, 1931b.

M. Ortiz and E.a. Repetto. Nonconvex energy minimization and dislocation structures in ductile single crystals. *Journal of the Mechanics and Physics of Solids*, 47(2):397–462, 1999.

Hans Christian Öttinger. *Beyond Equilibrium Thermodynamics*. John Wiley & Sons, Inc., 2005.

Felix Otto. The geometry of dissipative evolution equations: The porous medium equation. *Communications in Partial Differential Equations*, 26 (1-2):101–174, 2001.

Wolfgang Pauli and Charles P Enz. *Thermodynamics and the kinetic theory of gases*, volume 3. Courier Corporation, 2000.

C. Peco, A. Rosolen, and M. Arroyo. An adaptive meshfree method for phase-field models of biomembranes. Part II: A Lagrangian approach for membranes in viscous fluids. *Journal of Computational Physics*, 249: 320–336, 2013.

Mark A. Peletier. Variational Modelling: Energies, gradient flows, and large deviations. feb 2014.

Coline Prévost, Hongxia Zhao, John Manzi, Emmanuel Lemichez, Pekka Lappalainen, Andrew Callan-Jones, and Patricia Bassereau. IRSp53 senses negative membrane curvature and phase separates along membrane tubules. *Nature communications*, 6:8529, 2015.

I Prigogine. *Introduction to thermodynamics of irreversible processes.* Interscience Publishers, 1967.

Mohammad Rahimi and Marino Arroyo. Shape dynamics, lipid hydrodynamics, and the complex viscoelasticity of bilayer membranes. *Physical Review E*, 86(1):011932, jul 2012.

Mohammad Rahimi, Antonio DeSimone, and Marino Arroyo. Curved fluid membranes behave laterally as effective viscoelastic media. *Soft Matter*, 9(46):11033, 2013.

Sivaramakrishnan Ramadurai, Andrea Holt, Victor Krasnikov, Geert van den Bogaart, J Antoinette Killian, and Bert Poolman. Lateral Diffusion of Membrane Proteins. *J. Am. Chem. Soc.*, 131(35):12650–12656, 2009.

Padmini Rangamani, Ashutosh Agrawal, Kranthi K. Mandadapu, George Oster, and David J. Steigmann. Interaction between surface shape and intra-surface viscous flow on lipid membranes. *Biomechanics and Modeling in Mechanobiology*, 12(4):833–845, 2013.

Ramsharan Rangarajan and Huajian Gao. A finite element method to compute three-dimensional equilibrium configurations of fluid membranes: Optimal parameterization, variational formulation and applications. *Journal of Computational Physics*, 297:266–294, 2015.

Rayleigh. *Proc. Math. Soc. London*, 363:357, 1873.

Diego S Rodrigues, Roberto F Ausas, Fernando Mut, and Gustavo C Buscaglia. Numerical Modeling of Tether Formation in Viscous. XXXII: 19–22, 2013.

Amin Rustom, Rainer Saffrich, Ivanka Markovic, Paul Walther, and Hans-Hermann Gerdes. Nanotubular highways for intercellular organelle transport. *Science (New York, N.Y.)*, 303(5660):1007–1010, 2004.

P. G. Saffman and M Delbruck. Brownian motion in biological membranes. *Proc Natl Acad Sci USA*, 72(8):3111–3113, 1975.

Roger A Sauer, Thang X Duong, Kranthi Mandadapu, and David Steigmann. A stabilized finite element formulation for liquid shells and its application to lipid bilayers Summary of liquid shell theory. *Journal of Computational Physics*, 330:1–19, 2017.

U. Seifert and S. A. Langer. Viscous Modes of Fluid Bilayer Membranes. *Europhysics Letters (EPL)*, 23(1):71–76, 1993.

Udo Seifert. *Advances in Physics Configurations of fluid membranes and vesicles*. Number July 2011. 1997.

Pierre Sens, Ludger Johannes, and Patricia Bassereau. Biophysical approaches to protein-induced membrane deformations in trafficking. *Current Opinion in Cell Biology*, 20(4):476–482, 2008.

Zheng Shi and Tobias Baumgart. Membrane tension and peripheral protein density mediate membrane shape transitions. *Nat. Commun.*, 6(May 2014):5974, 2015.

Yoko Shibata, Junjie Hu, Michael M Kozlov, and Tom a Rapoport. Mechanisms shaping the membranes of cellular organelles. *Annu. Rev. Cell Dev. Biol.*, 25:329–54, jan 2009.

Pankaj Singh, Paritosh Mahata, Tobias Baumgart, and Sovan Lal Das. Curvature sorting of proteins on a cylindrical lipid membrane tether connected to a reservoir. *Physical Review E - Statistical, Nonlinear, and Soft Matter Physics*, 85(5):1–10, 2012.

Bidisha Sinha, Darius Köster, Richard Ruez, Pauline Gonnord, Michele Bastiani, Daniel Abankwa, Radu V. Stan, Gillian Butler-Browne, Benoit Vedie, Ludger Johannes, Nobuhiro Morone, Robert G. Parton, Graa Raposo, Pierre Sens, Christophe Lamaze, and Pierre Nassoy. Cells respond to mechanical stress by rapid disassembly of caveolae. *Cell*, 144(3):402–413, 2011.

Benoit Sorre, Andrew Callan-Jones, Jean-Baptiste Manneville, Pierre Nassoy, Jean-François Joanny, Jacques Prost, Bruno Goud, and Patricia Bassereau. Curvature-driven lipid sorting needs proximity to a demixing point and is aided by proteins. *Proc. Natl. Acad. Sci. U. S. A.*, 106(14):5622–6, apr 2009.

Benoît Sorre, Andrew Callan-Jones, John Manzi, Bruno Goud, Jacques Prost, Patricia Bassereau, and Aurélien Roux. Nature of curvature coupling of amphiphysin with membranes depends on its bound density. *Proc. Natl. Acad. Sci. U. S. A.*, 109(1):173–8, 2012.

Hein Sprong, P van der Sluijs, and G van Meer. How proteins move lipids and lipids move proteins. *Nature reviews. Molecular cell biology*, 2(7):504–13, 2001.

Jeanne C. Stachowiak, Eva M. Schmid, Christopher J. Ryan, Hyoung Sook Ann, Darryl Y. Sasaki, Michael B. Sherman, Phillip L. Geissler, Daniel a. Fletcher, and Carl C. Hayden. Membrane bending by proteinprotein crowding. *Nature Cell Biology*, 14(9):944–949, 2012.

Margarita Staykova, Marino Arroyo, Mohammad Rahimi, and Howard A. Stone. Confined bilayers passively regulate shape and stress. *Phys. Rev. Lett.*, 110:028101, 2013.

D. J. Steigmann. On the Relationship between the Cosserat and Kirchhoff-Love Theories of Elastic Shells. *Mathematics and Mechanics of Solids*, 4 (May):275–288, 1999.

Mark Terasaki, Tom Shemesh, Narayanan Kasthuri, Robin W Klemm, Richard Schalek, Kenneth J Hayworth, Arthur R Hand, Maya Yankova, Greg Huber, Jeff W Lichtman, Tom a Rapoport, and Michael M Kozlov. Stacked endoplasmic reticulum sheets are connected by helicoidal membrane motifs. *Cell*, 154(2):285–96, jul 2013.

Z C Tu and Z C Ou-Yang. A geometric theory on the elasticity of biomembranes. *Journal of Physics A: Mathematical and General*, 37(47): 11407–11429, nov 2004.

Naoya Yamaguchi, Takeomi Mizutani, Kazushige Kawabata, and Hisashi Haga. Leader cells regulate collective cell migration via Rac activation in the downstream signaling of integrin $\beta 1$ and PI3K. *Scientific Reports*, 5:7656, 2015.

Chen Zhu, Sovan L. Das, and Tobias Baumgart. Nonlinear sorting, curvature generation, and crowding of endophilin N-BAR on tubular membranes. *Biophysical Journal*, 102(8):1837–1845, 2012.

Joshua Zimmerberg and Michael M Kozlov. How proteins produce cellular membrane curvature. *Nat. Rev. Mol. Cell Biol.*, 7(1):9–19, jan 2006.