# Steady-State Diffusion in Complex Amphiphilic Films

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# Steady-State Diffusion in Complex Amphiphilic Films

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LUND UNIVERSITY

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Abstract

The relation between structure and diffusive transport at steady-state is investigated theoretically for amphiphilic systems. Amphiphilic systems typically show a large response to moderate changes in control parameters, such as temperature, osmotic pressure, and the presence of cosolvents and cosolutes. Such systems is therefore expected to show a local response in structure due to the transport process. The structure of the system is analysed in terms of a local equilibrium description. The main focus is on systems with the propensity of undergoing an internal phase separation. In this case there is a particularly strong coupling between the diffusion process(es) and the local structure of the system, which can lead to non-linear behaviour.

Specific applications include diffusive transport through the outermost layer of human skin, the stratum corneum, where the possibility of a phase change of the stratum corneum lipids could explain experimental observations of a non-linear behaviour of the water transport. A model for the formation of a gradient in pH over the stratum corneum is also presented in terms of the diffusive transport of water and carbon dioxide. Another application is film formation at the air-liquid interface of surfactant-water systems undergoing evaporation. A study showing that the structure of the surfactant layer lining the alveoli is functionally beneficial for the diffusive transport of oxygen is also presented.



Key words
diffusive transport, phase transition, responding membrane, stratum corneum, skin surface pH, film formation, lung surfactant

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# List of Papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I Diffusional Transport in Lung Alveoli
Christoffer Åberg, Emma Sparr, Marcus Larsson, Håkan Wennerström
Manuscript

II Transport Processes in Responding Lipid Membranes: A Possible Mechanism for the pH Gradient in the Stratum Corneum
Christoffer Åberg, Håkan Wennerström, Emma Sparr
*Langmuir*, 24 8061-8070. **2008**

III Drug Transport in Responding Lipid Membranes Can Be Regulated by an External Osmotic Gradient
Fátima O. Costa-Balogh, Christoffer Åberg, João J. S. Sousa, Emma Sparr
*Langmuir*, 21 10307-10310. **2005**

IV Responding Double-Porous Lipid Membrane: Lyotropic Phases in a Polymer Scaffold
Christoffer Åberg, Cécile Pairin, Fátima O. Costa-Balogh, Emma Sparr
*Biochimica et Biophysica Acta Biomembranes*, 1778 549-558. **2008**

V Non-Equilibrium Phase Transformations at the Air-Liquid Interface
Christoffer Åberg, Emma Sparr, Karen J. Edler, Håkan Wennerström
Submitted to *Langmuir*

VI Coupled Transport Processes in Responding Membranes: The Case of a Single Gradient
Christoffer Åberg, Håkan Wennerström
Manuscript

## List of Contributions

I I was responsible for the theoretical model, and performed the analysis and wrote the paper together with my coauthors.

II I performed the study, and was responsible for writing the paper.

III I was responsible for the theoretical part of the study, and took part in the writing of the paper.

IV I was responsible for the theoretical part of the study, took part in the analyis of the experimental data, and was responsible for writing the paper.

V I performed the study, and was responsible for writing the paper.

VI I performed the study, and was responsible for writing the paper.

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# Contents

# Chapter 1

# Introduction

A basic assumption of classical transport theory is that the flux is proportional to the driving force for transport. This is reflected in Fourier's law of heat conduction, Ohm's law of electric conduction, or — more important for the present subject matter — Fick's law of diffusion. This assumption has been formulated in a systematic fashion within the framework of the theory of irreversible thermodynamics.[1–3] It also emerges from kinetic theory based on the Boltzmann equation,[4–6] or (at least for the case of diffusion) from considerations based upon the theory of stochastic processes.[7,8]

Classical transport theory is well established and has, from an application point of view, found a solid existence as part of chemical engineering.[9] Within science the development, in contrast, has focused on abstract mathematical models, describing e.g. self-organization and pattern formation.[10,11]

The work described in this thesis concerns theoretical studies of molecular transport due to diffusion. As such, it is also based upon the classical assumption of a proportionality between flux and driving force. The novelty rather is to be found in the analysis of how the structure of the system reacts to the presence of the transported molecular species. This is included within the framework of the theory of irreversible thermodynamics, with its assumption of a local thermodynamic equilibrium. However, the classical examples are often (implicitly) systems with a static structure. In contrast, amphiphilic systems show an amazing diversity in structure as a function of control parameters such as temperature, solvent concentration and the presence of cosolvents or cosolutes.[12–15] It is therefore expected that diffusive transport in amphiphilic systems can have significant effects on the local structure. Furthermore, following a structural change, the transport properties typically also changes.

This provides a feedback mechanism, and effectively couples the local structure with the diffusion process.

A case that can have particular striking effects is when the system has a propensity of undergoing an internal phase separation. A phase transformation can then be driven by the diffusion process, providing a rather extreme example of structural changes due to transport. As the transport properties often change dramatically with a phase change, structure and transport is particularly strongly coupled for these systems.

The focus of the work described in this thesis is precisely on the interplay between structure and transport, as exemplified by a number of different amphiphilic systems. A background to, and discussion of, this work is given in the following chapters. The exposition is incremental, going from the simpler cases to the more complex, and involves some specific applications. The appendices, finally, collect the papers on which this thesis is based.

# Chapter 2

# Diffusion

This chapter starts the main text with a discussion of what is actually meant with the term diffusion. For the expert reader we note that the subject matter of this thesis concerns diffusive *transport*, rather than the related concepts of self-diffusion and intradiffusion. The physical picture is most transparent in the case of gases, and we illustrate the mechanism with an example of gaseous diffusion. However, we have to be a bit careful to distinguish the diffusive mode of transport from other mechanisms, e.g. bulk flow.

We continue with the more complicated case of diffusion in liquids. In contrast to the case of gaseous diffusion, there is as of yet no satisfactory microscopic theory of liquid diffusion. This has implications for how we formulate the basic laws of diffusion for the strongly heterogeneous systems discussed in this thesis. Fortunately, it is possible to make an educated *ansatz* on how to describe diffusion that covers the cases we are interested in. We also spend some time discussing the concept of permeability that will prove useful in the following.

This chapters finishes with a discussion of diffusion through the complex structure found at the alveolar interface in the human lung (paper I). This example illustrates many of the points in this chapter: the difference between diffusion and bulk flow, the diffusion law and permeabilities in heterogeneous systems.

## 2.1 The Physical Mechanism

### 2.1.1 Qualitative Picture

A classical example of a diffusion process is the spreading of perfume in a room where the air is still. For the purpose of our discussion it is

not important whether the perfume emanates from an open bottle or a person, but in the name of visualisation the reader is asked to imagine the perfume spreading from the skin of a person of prefered gender.

Close to the skin, at the place of application of the perfume, there are a certain amount of 'perfume molecules' present in the air. Like all molecules in the room, they are in constant motion. Due to this motion, they collide with each other and change direction often. A reasonabe first description is that they change direction so often that the motion of a molecule is essentially random. Therefore, every now and then a molecule close to the skin moves a bit further away. The opposite process also occurs, i.e. every now and then a molecule that happens to be a bit further away from the person moves a bit closer. In many cases it is reasonable to assume that it is equally likely for a given molecule to be heading in either direction. However, there is a clear assymmetry in the sense that there are initially many more perfume molecules close to the skin than further away. The result is — even though all directions are equally likely for a *single* molecule — a net transport of perfume molecules away from the skin. Eventually the perfume molecules fill upp the whole room with a uniform concentration. At this point, molecules still move equally likely in either direction, but since the concentration is uniform, no net transport occurs.

The net transport of molecules that occurs due to an assymmetrical concentration distribution, exemplified above with the spreading of perfume, is what one refers to as *diffusion*. We emphasise the point that there is no inherent 'desire' of a single molecule to move in the direction of transport. Rather individual molecules move in either direction equally likely. It is simply the net effect of having more molecules in a certain place initially that brings about a net transport.

### 2.1.2 Quantitative Picture

The picture of diffusion given above is essentially a description of a *random walk*[7,8] performed by an individual molecule. We can make this description quantitative by dividing the room into small cubes and considering the probability, $P(n,t)$, that a given molecule is within a certain cube $n$ at time $t$. For simplicity we only consider one dimension. The probability that a molecule is found in cube $n$ then changes due to four processes: a molecule entering cube $n$ from the left or the right, or a molecule that already is in cube $n$ exiting in either direction. The probability of entering cube $n$ is proportional to the probability that there

is a molecule in the neighbouring cube. Similarly, the probability of exiting cube $n$ is proportional to the probability that there is a molecule in cube $n$. The assumption that a molecule moves equally likely in either direction then implies that the change in probability during a small time-interval $\mathrm{d}t$ is

$$\mathrm{d}P(n, t+\mathrm{d}t) = w\mathrm{d}t\big(P(n-1,t) - 2P(n,t) + P(n+1,t)\big) \tag{2.1}$$

where $w\mathrm{d}t$ is the probability of moving. The factor 2 in Eq. (2.1) comes about since a molecule in cube $n$ can either exit to the left or to the right. Equation (2.1) can be rewritten

$$\frac{\mathrm{d}P(n,t+\mathrm{d}t)}{\mathrm{d}t} = w(\Delta z)^2 \frac{P(n-1,t) - 2P(n,t) + P(n+1,t)}{(\Delta z)^2}.$$

where $\Delta z$ is the size of the cubes. If the cubes are made sufficiently small, the fraction in the right-hand side becomes an approximation of the second order derivative $\partial^2 P(z,t)/\partial z^2$, and we find

$$\frac{\partial P}{\partial t} = w(\Delta z)^2 \frac{\partial^2 P}{\partial z^2} \tag{2.2}$$

Equation (2.2) describes how the probability of finding a *single* molecule at position $z$ at time $t$ evolves in space-time. We are more interested in the *concentration*, $c_i(z,t)$, of the molecular species $i$ at position $z$ and time $t$. We assume that the concentration is proportional to the probability of finding a single molecule, and Eq. (2.2) therefore implies

$$\frac{\partial c_i}{\partial t} = D_i \frac{\partial^2 c_i}{\partial z^2}. \tag{2.3}$$

Equation (2.3) is called the *diffusion equation*, and $D_i = w(\Delta z)^2$ the *diffusion coefficient*.

A classical solution of the diffusion equation is for the case when the diffusing substance is initially present within a very small region around the origin, $z = 0$, and subsequently spreads throughout all space. This solution is[16]

$$c_i(z,t) = \frac{\text{const}}{\sqrt{D_i t}} \exp\left(-z^2/4D_i t\right). \tag{2.4}$$

To return to our earlier example, this could describe the rather idealised case of perfume spreading around an infinitely thin man seated at the origin of an infinitely large room.

A characteristic of the diffusion equation, Eq. (2.3), is the first-order temporal and second-order spatial dependence. This is also reflected

in the argument to the exponential of the solution in Eq. (2.4). A characteristic feature of diffusion is therefore that molecules spread such that the distance is proportional to the square root of time

$$z \propto \sqrt{D_i t} \tag{2.5}$$

in contrast to classical applications of Newton's second law to linear motion or free fall due to gravity. Though being based on the idealised solution in Eq. (2.4), Eq. (2.5) provides a good rule of thumb to estimate the effect of diffusion. We will exemplify this in the next section.

## 2.2 Diffusion and Bulk Flow

Though there was no major emphasis on it, a fundamental assumption in the discussion of perfume spreading, is that the air in the room is still. In practice, it is utterly impossible to prevent small winds of air blowing through a room of reasonable size. In fact, the major mode of molecular transport for the case of perfume is *via bulk flow*, i.e. these air winds, and diffusion is negligible. We reach this conclusion by using numerical values in Eq. (2.5). The diffusion coefficient in gases at atmospheric pressures is of the order of $D_i = 10^{-5}\,\mathrm{m}^2/\mathrm{s}$.[17] Therefore the characteristic time for a perfume molecule to reach a nose but one decimeter away from the skin is of the order of $t = 10^3\,\mathrm{s}$, or around 15 min! This time-scale is clearly in opposition to practical experience, and we conclude that diffusion cannot be the main mode of transport for this example.

This conclusion begs the question: when *is* diffusion important? One example is respiration in small organisms.[18] If the organism is sufficiently small, $O_2$ taken up from the air is transported within the organism sufficiently rapid *via* diffusion. The same conclusion holds for $CO_2$ being transported in the opposite direction. We will get back to this in section 2.4.3, when discussing diffusion across the alveolar interface in the human lung.

The papers included in this thesis serve as other examples where diffusion is important. In general, diffusion is an important mode of transport at mesoscopic length-scales and below. We furthermore note that even in the presence of bulk flow, *mixing* of two molecular species, by definition (see below), occurs as a result of diffusion.

### 2.2.1 The Equation of Continuity

In order to make the considerations quantitative, we have to be able to separate transport due to diffusion from transport due to bulk flow. The basis of such a separation is the *equation of continuity* (here in one dimension) for the total mass density $\rho$

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial z}(\rho v) = 0. \tag{2.6}$$

Here both $\rho$ and $v$ are, in general, functions of both position, $z$, and time, $t$. The velocity $v$ that enters Eq. (2.6) is the total momentum per unit mass at the position $z$, and can be interpreted as the local velocity of the system.[19]

An equation of continuity can also be written down for the mass density, $\rho_i$, of each molecular species

$$\frac{\partial \rho_i}{\partial t} + \frac{\partial J_i^{\mathrm{Tot}}}{\partial z} = 0. \tag{2.7}$$

where $J_i^{\mathrm{Tot}}$ is the total mass flux of component $i$, composed of contributions due to bulk flow as well as diffusion. From the condition that there is no mixing of the components in the absence of diffusion, the only possible separation of bulk and diffusive flux is to write[19]

$$J_i^{\mathrm{Tot}} = \rho_i v + J_i \tag{2.8}$$

where $J_i$ denotes the diffusive flux. Equation (2.7) then becomes

$$\frac{\partial \rho_i}{\partial t} + \frac{\partial}{\partial z}(\rho_i v + J_i) = 0. \tag{2.9}$$

We note that since the total mass flux, $\rho v$, must be equal to the sum of the total mass fluxes of the individual components, $J_i^{\mathrm{Tot}}$, it follows that the diffusive fluxes sum to zero

$$\sum_i J_i = 0.$$

It is obvious that an equation of continuity can equally well be written down for a concentration (in, say, number of moles of a molecular species per volume), rather than a mass density, *viz*

$$\frac{\partial c_i}{\partial t} + \frac{\partial}{\partial z}(c_i v + J_i) = 0 \tag{2.10}$$

where $J_i$ in Eq. (2.10) is the molecular flux, rather than mass flux, per unit area and time.

Equation (2.9) represents the separation of bulk flow and diffusive transport that we sought. This separation is also apparent in Eq. (2.9) and (2.10), which provides the starting point for considerations of combined diffusive transport and bulk flow.

### 2.2.2 On Different Definitions of the Bulk Velocity

The separation between bulk flow and diffusion presented in the preceeding section is, actually, often not the unique choice. The considerations above are based on the equation of continuity, Eq. (2.6), for the total mass density. The reason for this choice is that an equation of motion for the total momentum per unit mass, $v$, can be derived as a continuum generalization of Newton's second law. Depending on auxiliary assumptions the resulting equation of motion could be the Euler equation for ideal fluids, the Navier-Stokes equation for viscous fluids, or a more general equation.[19]

In practical considerations it is instead not uncommon to define the diffusive flux with respect to a different reference velocity, like e.g. the total number of particles per unit volume, rather than the total momentum per unit mass, $v$.[9,17] A theorem, originally due to Prigogine, states that such a redefinition does not cause any problem for many cases of practical interest.[1]

## 2.3 The Driving Force for Diffusion

### 2.3.1 Fick's First Law

In section 2.1.2 we derived an equation for the how the concentration profile of a molecular species changes with time due to diffusion. Comparing this with the equation of continuity, Eq. (2.10), in the absence of bulk flow (i.e. $v = 0$) we can identify the diffusive flux as

$$J_i = D_i \frac{\partial c_i}{\partial z}. \tag{2.11}$$

Equation (2.11) was originally proposed by Fick,[20] in analogy with Fourier's law of heat conduction, and is known as *Fick's first law*[16,17] (the diffusion equation, Eq. (2.3), is sometimes referred to as *Fick's second law*). It states that the diffusive flux is proportional to a gradient in

concentration. The concentration gradient thus acts as a *driving force* for diffusion, which in many cases is a reasonable first approximation.

In this text we have given a *derivation* of Fick's first law, Eq. (2.11), rather than postulating it. A derivation has the advantage that it might easier to investigate its validity. The main assumptions used in the derivation of Eq. (2.11) were that a molecule moves on the average equally often in either direction, and that the concentration of a molecular species can be found by studying the probability distribution of a single molecule. It is clear that bulk flow is one occasion when molecules has a bias to move in a particular direction, i.e. in the direction of the bulk flow. This can actually be incorporated into the derivation, and leads to an equation with the exact form of Fick's first law, Eq. (2.11), inserted into the equation of continuity, Eq. (2.10).

A more serious problem has to do with correctly accounting for interactions among molecules. The random walk picture is based on collisions, i.e. a form of intermolecular interaction, in order for a stochastic treatment to be valid at all. However, both assumptions on which the derivation was based breaks down in the presence of strong intermolecular interactions: a single molecule could potentially have a bias to move in a particular direction, and the individual molecules do not move independently. It is not clear how to generalize the analysis for this case.

In a phenomenological approach, one can account for interactions simply by letting the diffusion coefficient in Fick's first law, Eq. (2.11), depend on concentration, and using experimental data. Such a procedure, however, obviously lacks some predictive power. The ideal situation would be a theory which can relate the diffusion coefficient to more fundamental parameters. For gases, kinetic theory[4–6] provides a such a theory. At least for dilute gases it is possible to calculate diffusion coefficients from the interaction potential between molecules.[4] For complicated potentials this likely has to be done numerically, but, at least in principle, the diffusion coefficients can thereby be written in terms of more fundamental interaction parameters. For liquids the situation is worse. Reference 21 reviews numerous attempts at relating the diffusion coefficient to more fundamental parameters, or to other parameters like e.g. the viscosity or the self-diffusion or intradiffusion coefficients[22] (see section 2.3.3 below). However, no clear answer has emerged from these studies.

In spite of the described difficulties, there exists limiting cases where one can make reasonable assumptions. An important example is the dilute solution limit, when one component, the solute, is present in small

amounts compared to another, the solvent. In that case, there are certainly interactions among molecules. However, due to the high dilution solute-solute interactions are negligible, and the solute-solvent interactions are essentially equal everywhere. It is therefore reasonable that Eq. (2.11), with a constant diffusion coefficient, will prove valid in this limit. On the other hand, we expect that the diffusion coefficient will be significantly altered due to solute-solvent interactions. Indeed, the diffusion coefficient in liquids is around four orders of magnitude smaller than in gases.[17]

### 2.3.2 A Generalised Fick's First Law

A common theme of the work presented in this thesis is diffusive transport between regions of profoundly different characteristics, like from a gas phase to a liquid phase (paper I,II,V), or an aqueous phase to a surfactant (or lipid) bilayer (paper I-V). One quickly realises that Fick's first law of the form given in Eq. (2.11) is inadequate for these cases. As an example, take the case of air and an aqueous solution. At equilibrium the air is saturated with water. However, in terms of concentrations it is clear that the water concentration in the gas phase is orders of magnitude lower than the concentration of water in pure water. According to Fick's first law, Eq. (2.11), there would therefore be driving force for diffusion of water from solution to a gas phase — even at equilibrium!

One possible solution to this problem is to explicitly deal with the discontinuity of the concentration at an interface, and otherwise assume the validity of Fick's first law within each phase. At the interface one assumes that the concentration in, say, a gas phase is related to the concentration in a liquid phase by a solubility parameter/partition coefficient, $K_i$

$$c_i(\text{gas}) = K_i c_i(\text{aq}). \tag{2.12}$$

Another possibility is the recognition that the driving force for diffusion is a gradient in chemical potential rather than a gradient in concentration. This is also the approach taken within the theory of irreversible thermodynamics.[1–3] Within a phase, there is a gradient in chemical potential if and only if there is a gradient in concentration, so for this case a redefinition of the driving force does not matter. In contrast, the chemical potentials in two phases are equal at equilibrium, so formulating the driving force as a gradient in chemical potential correctly predicts the absence of diffusion across an interface at equilibrium.

In the majority of the work presented in this thesis, a generalised Fick's first law on the form[23]

$$J_i = -\frac{D_i}{RT} c_i \frac{\partial \mu_i}{\partial z} \tag{2.13}$$

was used. The motivation for Eq. (2.13) is that the molecular flux ought to depend on three factors: i) a driving force, the chemical potential gradient $\partial\mu/\partial z$ ii) the number of molecules able to diffusive, the local concentration $c$ iii) a molecular mobility, the diffusion coefficent $D$ (the denominator $RT$ has to be added for reasons of dimensional consistency). In the dilute solution limit, the chemical potential of the solute can be approximated by the ideal solution contribution

$$\mu_i = \mu_i^\theta + RT \ln c_i \tag{2.14}$$

which inserted into the generalised Fick's first law, Eq. (2.13)

$$J_i = \frac{D_i}{RT} c_i \frac{\partial}{\partial z} \left( RT \ln c_i \right) = \frac{D_i}{RT} c_i \frac{RT}{c_i} \frac{\partial c_i}{\partial z} = D_i \frac{\partial c_i}{\partial z},$$

shows that the generalised Fick's first law, Eq. (2.13), reduces to the classical Fick's first law, Eq. (2.11), in the limit where we expect the latter to be correct.

Formulating Fick's first law in terms of a chemical potential gradient, also makes the analogy between heat conduction and diffusion more clear. Fourier's law of heat conduction states that the heat flux is proportional to a gradient in temperature. Just like chemical potential, temperature is an intensive thermodynamic variable, and it is also continuous across an interface at equilibrium (an intensive thermodynamic variable with these properties is sometimes called a *field variable*,[24] in contrast to intensive variables like density or concentration). The fact that the concept of chemical potential seems more elusive than temperature in everyday life might be a factor behind this historical inconsistency.

### 2.3.3 Self-Diffusion and Intradiffusion

A somewhat particular case of diffusion is a single-component solution containing a small amount of labelled, but otherwise identical, molecules. It is possible to setup a concentration gradient in the labelled molecules. The system can then be at thermodynamical equilibrium, but still show a diffusive flux in the labelled molecules. (Following the nomenclature of Albright and Mills[21,25]) this is refered to as the *self-diffusion* of that

molecular species. The generalisation to multi-component systems, with a concentration gradient in labelled molecules of one of the components, is called *intradiffusion*.

In the dilute solution limit, the diffusion coefficient and the intradiffusion coefficient of the solute approaches the same value.[21] Intradiffusion coefficients are therefore useful as estimates of the diffusion coefficient for dilute solutions.

## 2.4 Steady-State Diffusion in Composite Systems

### 2.4.1 The Steady State

The concept of steady state prevails throughout the work described in this thesis (and is consequently included in the title). The canonical example is a membrane separating two solutions, as in Fig. 2.1. The concentration (or, more generally, the chemical potential) of a solute is different in the two solutions, and the solutions are mechanically stirred so as to ensure a uniform concentration in each solution. The gradient drives diffusive transport across the membrane. Eventually transport of the solute results in the concentration being equal in the two solutions. However, if the two solutions are sufficiently large (in mathematical terms: infinite) compared to the membrane, asymptotically a well-defined state is reached in which the concentration within the membrane is constant in time. In this state, solute is continuously being transported through the membrane, but as long as the same amount enters that exits, the local concentration is constant. This state is referred to as *steady*. A neccessary condition for its appearance is that the two solutions are much larger than the membrane, and that the concentration is kept uniform within them; these properties are commonly implied by usage of the word *reservoir*.

In mathematical terms, the steady state is characterized by a vanishing of the time-derivative. In the simplest case the diffusion equation, Eq. (2.3), holds, and the steady state reads

$$0 = \frac{\partial c_i}{\partial t} = D_i \frac{\partial^2 c_i}{\partial z^2} \tag{2.15}$$

i.e. the concentration profile within the membrane is linear at steady state

$$c_i(z) = c_{i0} + (c_{iL} - c_{i0})z/L$$


Figure 2.1: A membrane separating two reservoirs of constant concentration $c_{i0}$ and $c_{iL}$, respectively. The direction of diffusive transport is along the $z$ direction, and $L$ denotes the thickness of the membrane.

where $c_{i0}$ and $c_{iL}$ are the concentrations at either side of the membrane, and $L$ the membrane thickness. Clearly, a more complicated behaviour is expected for a diffusion process not described by Fick's first law, Eq. (2.11), or if the diffusion constant depends on concentration. Either way, the assumption of steady-state is an enormous simplification in that the diffusion equation, Eq. (2.3), which is a partial differential equation, is converted to an ordinary differential equation.

Of course, assumption of a steady state should not be done purely of mathematical convenience, if the physical situation does not justify it. In many cases, however, this assumption *is* justified. Reference 16 discusses this in more detail. However, already Eq. (2.5) provides a simple estimate of the time-scale, by using the size of the membrane for $z$. We also note that one can explicitly ensure steady-state conditions in an experimental setup (as done in the experimental work reported in paper III and IV).

### 2.4.2 The Permeability

For steady-state transport, the concept of permeability proves particularly advantageous. In the simplest case, the permeability of a membrane to a diffusing component is defined as the diffusive flux divided by the concentration difference[17]

$$J_i = -P_i(c_{iL} - c_{i0}). \tag{2.16}$$

From Fick's first law, Eq. (2.11), the permeability of the diffusion process described in the preceeding section therefore is

$$P_i = D_i/L$$

The advantage of utilizing the concept of permeability is that for a composite membrane made up of different layers of permeability $P_i$, the total permeability can be written[16]

$$\frac{1}{P_i} = \sum_j \frac{1}{P_{ij}} \tag{2.17}$$

as is easily shown from its definition.

Above we discussed how Fick's first law in its classical form, Eq. (2.11), is inadequate in many cases, as e.g. for diffusion across two phases, or for diffusion between an aqueous phase and a surfactant (or lipid) bilayer. In particular, Eq. (2.16) is formulated in terms of a concentration difference, rather than the real driving force, the chemical potential gradient. In spite of this, it is often convenient to keep a description in terms of concentrations. This is possible if one is a bit careful, as we will now exemplify.

We consider for definiteness diffusion across a surfactant bilayer and an aqueous film, as in Fig. 2.2. This case does not only serve as an illustration, but will also be important for us in the following. In defining the permeability we have to make a definite choice of a reference concentration. We choose to use aqueous concentrations, which is an actual concentration within the aqueous film, $b < z < b + w$. This is not case within the bilayer region, $0 < z < b$. However, there exists a well-defined *hypothetical* aqueous concentration, related to the actual concentration by a partition coefficient (cf. Eq. (2.12))

$$c_i(\text{bilayer}) = K_i(\text{bilayer,aq})c_i(\text{aq}). \tag{2.18}$$

For a dilute solution the partition coefficient is given in terms of the standard chemical potentials $\mu_i^\theta$ by

$$RT \ln K_i(\text{bilayer,aq}) = \mu_i^\theta(\text{aq}) - \mu_i^\theta(\text{bilayer}).$$

The permeability is then defined in terms of aqueous concentrations, *viz*

$$J_i = -P_i \Delta c_i(\text{aq}).$$

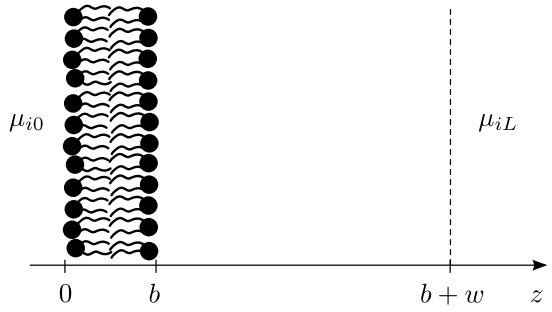


Figure 2.2: A bilayer and an aqueous film, of thickness $b$ and $w$, respectively. This could be the repeat unit of a lamellar phase, but for now we view it simply as it is.

From the generalised Fick's first law, Eq. (2.13), it then follows in the dilute solution limit that the permeability can be written

$$\frac{1}{P_i} = \frac{w}{D_i(\text{aq})} + \frac{b}{K_i(\text{bilayer,aq})D_i(\text{bilayer})}. \tag{2.19}$$

in analogy with Eq. (2.17). Equation (2.19) has a simple interpretation in the limit when the diffusing molecule is strongly hydrophilic, $K_i(\text{bilayer,aq}) \ll 1$, and prefers the aqueous region. In that case the first term of the right-hand side of Eq. (2.19) is negligible in comparison with the second, and the total permeability is dominated by the effect of the bilayer. An analogous conclusion can be reached for the opposite case when the diffusing molecule is strongly lipophilic, $K_i(\text{bilayer,aq}) \gg 1$, and prefers the bilayer.

For a general composite system, the permeability of an individual layer is given by $P_i = K_i D_i/l$, with respect to a certain reference concentration. The total permeability then conveniently fulfills Eq. (2.17). However, it should be obvious that the permeabilities of individual layers has to be defined with respect to the *same* reference system.

### 2.4.3 Diffusion in the Human Lung

In section 2.2 we discussed how the metabolic gases $O_2$ and $CO_2$ can be transported efficiently enough by diffusion in smaller organisms. In contrast, for a larger organism, diffusion is inadequate and a system, like e.g. the human cardiovascular system, has to be developed in order to

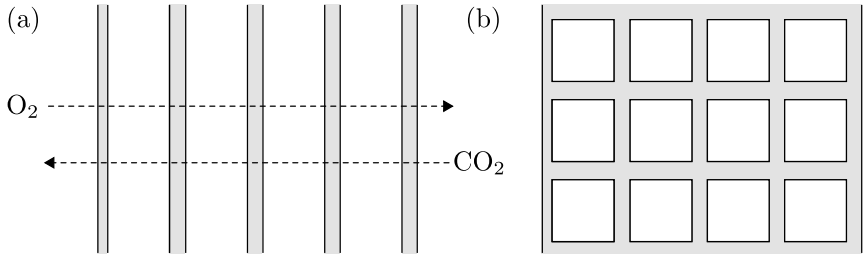


Figure 2.3: A comparison of two structures for the lipid region of the alveolar interface. In both cases, the left side represents the gas phase in the lungs. $O_2$ is transported from the gas phase towards the capillaries, whereas $CO_2$ follows the opposite direction. (a) Lamellar arrangement of stacked bilayers, with a monolayer facing the gas phase. (b) Tubular network, where the monolayer is connected to a bilayer reservoir.

transport the metabolic gases to and from all cells.[18] In humans, $O_2$ and $CO_2$ are transported by bulk flow in both the lungs and the blood vessels. However, across the thin interface between the gas phase in the lungs and the liquid phase in the blood vessels, transport occurs *via* diffusion. This interface is located in the smallest constituents of the lung, the alveoli. The smallest blood vessels, the capillaries, intersperse around the alveoli, more in the form of a net than individual tubes.[26]

The alveolar interface in contact with the gas phase is covered by a fluid layer composed mainly of lipids, but also some proteins.[27] Closest to the gas phase a lipid monolayer is found,[27] whose main function is the reduction of the surface tension of the alveolar interface. This is physiologically beneficial since it reduces the work of changing the alveolar volume during respiration.[26,28] There are also other benefits of the lipid monolayer (see paper I).

Beneath the lipid monolayer, there is a reservoir of lipids that serves as a depot for the lipid monolayer. The structure of this lipid reservoir is refered to as *tubular myelin*.[27,29] A recent suggestion, based on observations using electron microscopy, is that the lipid reservoir forms a structure where the bilayers are draped on a tetragonal minimal surface.[30] Paper I describes a calculation of the permeability of this structure, as well as a comparison with the permeability of a stack of bilayers. Figure 2.3 shows a schematic of the two cases.

It turns out that the major part of the gradient in the chemical potential of $CO_2$ from the atmospheric air to the blood vessels is in the gas

phase of the lung. In contrast, for $O_2$ the major part of the gradient is located across the alveolar interface.[26] Therefore a structure that facilitates transport of $O_2$ across the interface would potentially constitute a physiological advantage.

The oil/water partition coefficient for $O_2$ is $K_i = 4.41$,[31] which means that $O_2$ is slightly lipophilic. The hydrocarbon chains of the lipids are likely in a melted state with low order, refered to as a *liquid-crystalline* phase. For this case the diffusion coefficient in the bilayer and the aqueous film are similar. From the discussion following Eq. (2.19), we therefore reach the conclusion that the structure shown in Fig. 2.3a slows down diffusive transport of $O_2$, and increasingly so for each aqueous film. The structure in Fig. 2.3a also slows diffusive transport of a *hydrophilic* molecule, but in this case the bilayers provide the main resistance.

The structure in Fig. 2.3b, however, facilitates transport of lipophilic molecules, due to a continuous diffusion path within the bilayers throughout the structure. In contrast, for a hydrophilic molecule diffusive transport through the structure shown in Fig. 2.3b is even slower than through the structure shown in Fig. 2.3a.

The conclusion therefore is that both structures provide a protection against diffusive transport of hydrophilic molecules. The structure in Fig. 2.3b, however, facilitates transport of lipophilic compounds compared to the structure in Fig. 2.3a. In this sense, the structure could play a functional role for respiration.

# Chapter 3

# Diffusion in Responding Membranes

At the end of the previous chapter we discussed and exemplified diffusion in systems with a complex structure. It is clear that the local structure within the system affects transport, and that it can have important practical consequences. An example of this was given in section 2.4.3 for diffusion across the alveolar interface. The analysis of how the structure of a specific system affects transport is complicated by the fact that for all but the most simple cases, it is (in general) impossible to find an analytical solution. In other words, one has to resort to approximations and/or numerical solutions. Fortunately, nowadays there exists powerful numerical techniques, like e.g. the finite element method,[32,33] and software packages that aid such computations.

A different aspect of the relationship between structure and diffusional transport is when the membrane is able to respond by structural changes due to the presence of the diffusing component. A gradient in concentration (chemical potential) then implies a gradient in the structure of the membrane. In the example of section 2.4.3, the structure was assumed static, and the diffusion equation was solved in order to find how the flux of the diffusing molecule(s) reacted to this structure. In many cases this is a relevant model. However, amphiphilic systems show an amazing diversity in structure, and, furthermore, the particular structure can be quite sensitive to variations in thermodynamic variables such as temperature, the chemical potential of the solvent, and the presence of cosolvents or cosolutes.[12–15] One therefore expects the possibility of an interplay between structure and diffusive transport in such systems. We call a membrane that is able to react with structural changes to the

diffusion process a *responding membrane*.[34,35] The current chapter aims to provide, by example, a rather general discussion of such systems.

## 3.1 The Responding Lamellar Phase

A rather simple example of a responding membrane is a lamellar phase that is exposed to a gradient in the chemical potential of water. The responding lamellar phase is not only interesting for illustrative purposes, but also as a crude model of diffusive transport through human skin (paper II). This will application will be discussed in more detail in section 4.2. The gradient in the chemical potential of water drives diffusive transport of water across the lamellar phase. It also affects the local structure, as we will shortly describe.

### 3.1.1 Osmotic Pressure and Interbilayer Forces

It is customary and convenient to phrase a theoretical discussion of the structure of a lamellar phase in terms of the osmotic pressure, $\Pi_{\text{osm}}$, rather than the chemical potential of water, $\mu_w$. The concept of osmotic pressure comes from a discussion of *osmosis*, which is the transport of the solvent from a dilute solution separated from a concentrated solution by a membrane permeable only to the solvent. The transport of the solvent can be prevented by increasing the pressure on the concentrated solution; an increase in pressure increases the chemical potential of the solvent, and a change in pressure is therefore one way of reducing the driving force for transport of the solvent. This is another example where it is crucial to formulate the driving force for diffusion in terms of the chemical potential rather than the concentration (cf. section 2.3.2). If the pressure is large enough, the driving force is completely eliminated. For this case, the osmotic pressure of the concentrated solution is defined as the difference in pressure between the concentrated solution and the pure solvent. For an incompressible fluid this definition implies for an aqueous solution

$$\Pi_{\text{osm}}\bar{V}_w = \mu_w^0 - \mu_w \tag{3.1}$$

where $\bar{V}_w$ is the (molar) volume, and $\mu_w^0$ the chemical potential, of pure water.

An advantage with using the osmotic pressure, rather than the chemical potential, is that the osmotic pressure can be identified with the force per area between two interacting bilayers,[23] and so lends a direct physical interpretation. With this physical picture in mind, the osmotic pressure

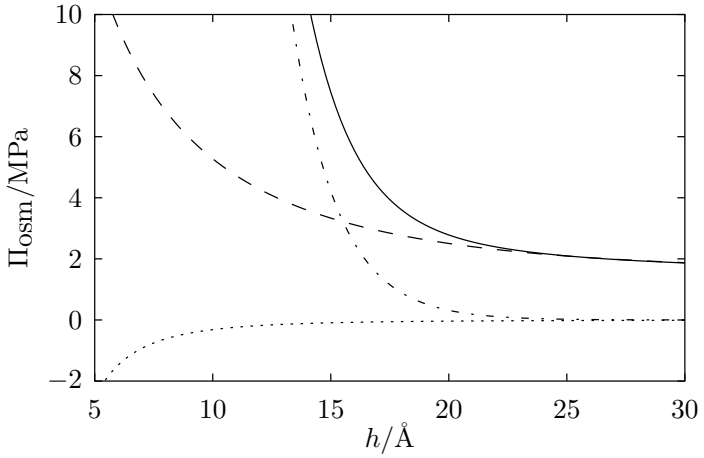


Figure 3.1: The contribution to the osmotic pressure from electrostatic interactions (dashed line), the dispersion interaction (dotted line) and short-range repulsive force (dot-dashed line) for a given model (see paper II for details). The total osmotic pressure (solid line) is clearly dominated by the short-range repulsive force at short range.

is written as a sum of forces (per area) due to different mechanisms (in the hope that the latter are separable and additative). The most general case that has been relevant for the work described in this thesis is a sum of three contributions

$$\Pi_{\mathrm{osm}} = \Pi_{\mathrm{el}} + \Pi_{\mathrm{disp}} + \Pi_{\mathrm{rep}}. \tag{3.2}$$

$\Pi_{\mathrm{el}}$ is the contribution from electrostatic interactions if the bilayers of the lamellar phase are charged, $\Pi_{\mathrm{disp}}$ is an attractive dispersion interaction and $\Pi_{\mathrm{rep}}$ is a short-ranged repulsive force.[23,36] The quantitative expressions are not important for us at the moment (though we will come back to the electrostatic interaction in section 4.2.2). Instead the main point is the dependence on the interbilayer separation. This is illustrated in Fig. 3.1, which shows the forces for the particular model used in paper II. In this way, one can predict the interbilayer separation corresponding to a given osmotic pressure, and gain a quantitative description of the effect of osmotic pressure (chemical potential of water) on the structure of a lamellar phase.

In our discussion of the responding lamellar phase in the current section, we will assume that the bilayers are in a liquid crystalline state,

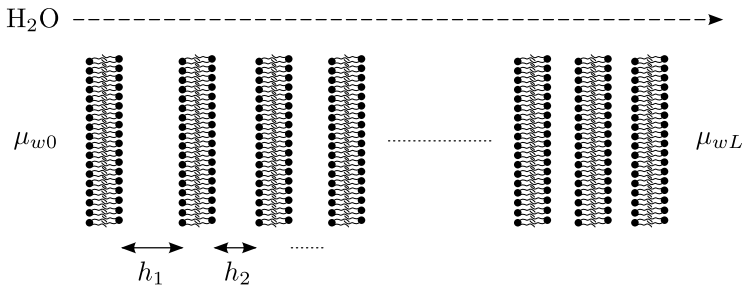


Figure 3.2: A membrane composed of a lamellar phase exposed to a gradient in the chemical potential of water. The gradient drives diffusive transport of water across the lamellar phase. It also causes the lamellar phase to respond by a heterogeneous swelling (a decreasing interbilayer distance) in the direction of the gradient.

and that the structure within the bilayer does not change due to a change in osmotic pressure. There is the possibility of a phase change from a liquid crystalline state to a gel state, in which the conformational state of the hydrocarbon chains of the surfactant changes.[23] However, we delay a discussion of the effect of a phase change until section 3.2.

### 3.1.2 The Swelling of a Lamellar Phase

When a membrane composed of a lamellar phase is exposed to a gradient in the chemical potential of water, or equivalently a gradient in osmotic pressure, water diffuses through it. At steady state, the spatial variation of the osmotic pressure along the gradient is constant in time. The actual variation is dependent on the details of the interplay between structure and diffusive transport of water, as we will discuss shortly. However, already now we can anticipate the qualitative trend. The assumption that the structure within each bilayer is independent of the local osmotic pressure allows a great simplification. It implies that the lamellar phase simply responds by a variation in the interbilayer distance due to the local osmotic pressure, according to Eq. (3.2). In this way, there will be a heterogeneous swelling of the lamellar phase, in the sense that the interbilayer distance varies along the gradient. With the osmotic pressure at the boundaries given, the interbilayer distance at either boundary is known. If we assume a monotonic variation we already have a fair idea of the structure, and expect something similar to what is depicted in Fig. 3.2.

A quantitative analysis of the swelling of a lamellar phase has been given previously,[35] and shows that the picture in Fig. 3.2 is qualitatively correct. Furthermore, as the gradient is increased the heterogeneity in swelling also increases. An interesting feature is that the variation in swelling is most pronounced for the part of the lamellar phase at the boundary corresponding to a lower value of osmotic pressure. The interbilayer distance plateaus quickly. This result can be explained by the fact that for lower values of the osmotic pressure, a small increase in osmotic pressure corresponds to a rather large increase in the interbilayer separation, as seen in Fig. 3.1. In contrast, for higher values of the osmotic pressure, a finite change in interbilayer separation corresponds to a large change in osmotic pressure, due to the steep force curve at smaller separations. As we will see in section 4.2, this effect has interesting consequences for a model of the pH gradient across human skin.

### 3.1.3 Transport Properties

For a strongly hydrophilic molecule, the total permeability of a bilayer followed by an aqueous film is dominated by the permeability of the bilayer (see section 2.4.2) Water is (of course) a hydrophilic molecule, and the bilayer/water partition coefficient in Eq. (2.18) is very low,[37] and, indeed, the permeability of a lipid bilayer is only of the order of $10^{-5}\,\mathrm{m/s}$.[38,39] It is therefore clear that water transport across a lamellar phase in the direction perpendicular to the bilayer normal is significantly hindered by the bilayers. On the other hand, for bilayers in a liquid-crystalline state, the local diffusion coefficient is not significantly different from that in water. The low permeability is therefore due to the low solubility — there are simply not enough water molecules within the bilayer to give an efficient transport. We encountered a similar situation (though in the opposite direction, and not as extreme) for the transport of $O_2$ in the lipid structure of the alveoli in section 2.4.3.

The very low solubility of water in a bilayer implies that it is an excellent approximation to neglect the gradient in the chemical potential of water across the aqueous films of the lamellar phase. In this limit, transport through the lamellar phase is therefore independent of the swelling, and exactly equivalent to transport through a lipid phase with the same thickness as the total thickness of the bilayers in the lamellar phase. Therefore, even though there is a clear response of the lamellar phase due to the gradient in the chemical potential of water, this does not affect the transport of water. In other words, there is no interplay

between structure and transport, and transport remains linear. This is obviously due to the low solubility of water in the bilayers. A different scenario would occur if the partition coefficient would be more moderate.

## 3.2 Phase Changes in Responding Membranes

A membrane that has the propensity of undergoing an internal phase separation can give rise to a more intimate coupling between structure and transport. The phase change can give rise to a strongly non-linear response in the membrane, as we will exemplify with a monoolein membrane responding to a gradient in water chemical potential (paper III and IV). This work was carried out in close contact with experimental work on the same system.

### 3.2.1 The Responding Monoolein Membrane

The reason for studying a monoolein membrane is that the monoolein-water system has a well-characterized phase behaviour and structure.[40–44] In particular, it is known to form an inverted bicontinuous cubic Ia3d phase at lower osmotic pressures, followed by a liquid-crystalline lamellar phase at higher osmotic pressures. The water permeability of the lamellar phase is low, as was discussed above. In contrast, water transport is not significantly hindered through the cubic phase, since there are continuous water channels through it.[45]

In the experimental setup, the monoolein membrane was exposed to a gradient in osmotic pressure. The osmotic pressure in one of the reservoirs was kept constant throughout all experiments. This osmotic pressure was chosen such that it corresponds to the cubic phase of the monoolein-water system. The osmotic pressure of the other reservoir was increased in successive experiments, from being equal to the osmotic pressure in the first reservoir, to being well past the cubic to lamellar phase transition.

### 3.2.2 Structure and Phase Behaviour

Due to the large body of reference literature available, it is possible to theoretically model the structure of the responding monoolein membrane explictly. The description is physical rather than analytical, and follows the experimental setup closely. The interested reader can find the full mathematical model stated in paper IV.

We start by considering the monoolein membrane equilibrated between the two reservoirs of the same osmotic pressure. In other words, there is no gradient, and hence no diffusive transport of water. Under these conditions the membrane forms a homogeneous cubic phase.

We now imagine increasing the osmotic pressure in the second reservoir, but not enough to cross the cubic to lamellar phase transition. In a similar fashion as the responding lamellar phase, the cubic phase responds by a heterogeneous swelling. An increase in osmotic pressure has the effect that the unit cell size of the cubic phase decreases. As the thickness of the lipid bilayers of the cubic phase are essentially determined by the size of the monoolein molecule, the effect of an increase in osmotic pressure is mainly a decrease in the size of the aqueous channels. This is analogous to the responding lamellar phase, though in this case the swelling occurs in three dimensions rather than just one. The steady-state structure therefore has more, but smaller, unit cells of the cubic phase close to the reservoir with a higher value of the osmotic pressure. The quantitative analysis has to deal with both the redistribution of the lipids as well as the water.

For even higher values of the osmotic pressure in the second reservoir, eventually the cubic to lamellar phase transition is crossed. We then expect that the part of the membrane exposed to the higher osmotic pressure will form the lamellar phase. In the opposite end of the membrane, the membrane is still in a cubic phase. If the gradient is increased even further, the part of the membrane that is in the lamellar phase grows. Due to the osmotic gradient, the lamellar phase in itself also responds by a heterogeneous swelling. The thickness of the lamellar phase is determined by the gradient in osmotic pressure, but is also strongly dependent on the respective transport properties of the two phases. The theoretical model shows that the higher permeability of a phase, the thicker it is at steady state. Since the permeability of the lamellar phase is very low compared to the cubic phase, in actuality only a few bilayers of the lamellar phase forms.

We note that this analysis has neglected the free-energy cost of creating the new interface when the lamellar phase is induced. This is likely negligible for this particular system (and is not seen in the experiments), but in general would have to be taken into account. See paper V for a discussion of this effect for a slightly different case.

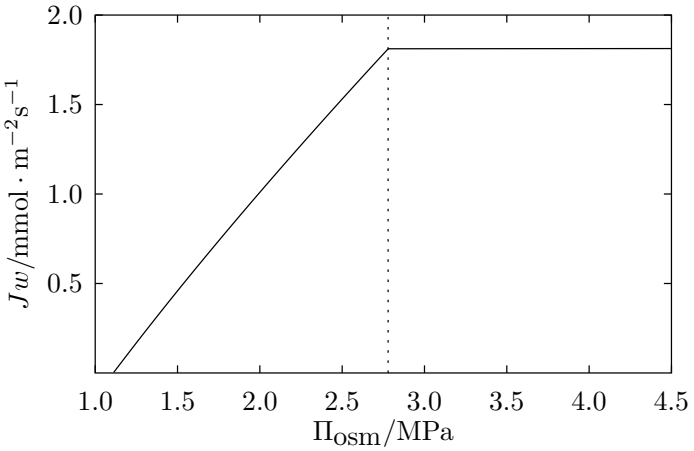


Figure 3.3: The water flux through a monoolein membrane exposed to an osmotic gradient as a function of gradient. The osmotic pressure in one of the reservoirs is kept constant at 1.11MPa. In the second reservoir the osmotic pressure, shown on the $x$-axis, is progressively increased from 1.11MPa upto 4.5MPa. For lower gradients, the whole membrane forms the cubic phase, but at 2.78MPa, the lamellar phase is induced.

### 3.2.3 Coupling between Transport and Structure

Above we have described how the monoolein membrane responds to the osmotic gradient in terms of structural changes as well as phase changes. We have taken the liberty of describing the structure of the membrane before discussing transport. This was done only for ease of presentation; in actuality the two are intimately coupled, and one cannot be separated from the other.

Figure 3.3 shows the water flux as a function of the osmotic gradient. For lower osmotic pressures, when the whole membrane is in the cubic phase, there is an essentially linear relation between driving force and flux. It is not completely linear, due to the heterogeneous swelling of the cubic phase, but very nearly so. As soon as the cubic to lamellar phase transition is crossed, there is a dramatic change in the water flux. This is due to the introduction of the lamellar phase with its significantly lower permeability. It is amazing that this large change is due to only a handful of bilayers.

The same qualitative behaviour as seen in Fig. 3.3 is also seen in a theoretical model for water transport in a two-component DLPC (di-

lauroyl phosphatidyle choline)-DMPC (dimyristoyl phosphatidyl choline) responding lamellar phase.[46] It has been shown experimentally that the liquid-crystalline phases of the DLPC-water and DMPC-water systems undergoe a phase transformation to a gel phase at higher values of the osmotic pressure.[47] This phase transformation gives rise to qualitatively similar results as the cubic to lamellar phase transformation in the monoolein-water system.

The responding monoolein membrane has demonstrated how a coupling between transport and structure can give rise to strongly non-linear effects. These effects does not arise from a complicated transport process. Rather, it is how the local thermodynamics depends on the local chemical potential of the diffusing component (water in this case) that gives rise to the non-linear effects. This leads to a fascinating interplay between diffusive transport and structure, which is particularly strong when the membrane has the propensity of undergoing an internal phase separation.

## 3.3 Spontaneously-Formed Membranes

The examples of systems given so far have been explicit *membranes*, in the sense that they have been created — by nature (paper I and II), or the experimental setup (paper III and IV) — to separate two environments (cf. Fig. 2.1). We here consider a related case of film formation at the air-liquid interface. There are numerous observations of such films forming at the air-liquid interfaces of water-amphiphile,[48–55] or water-amphiphile-polymer systems.[56–62] It is possible that these films form due to diffusive transport across the interface, thereby spontaneously creating, in some sense, a membrane. In the studies performed by Edler *et al.*, a key observation is that film formation is prevented by an increase of the relative humidity in the gas phase.[56–59] A possible explanantion for this effect can be given within the conceptual framework of phase changes in responding membranes.

### 3.3.1 Steady-State Diffusive Transport with Evaporation

We study evaporation of the solvent from a water-amphiphile solution that is exposed to the ambient atmosphere. Due to the evaporation, the solute concentration in the solution continuously increases, and the location of the air-liquid interface changes with time. A steady-state in the sense of section 2.4.1 does not exist for this case.

In terms of a coordinate system in which the moving interface is fixed, however, it is possible to define a steady state. As shown in paper V, this results in the equation

$$-D\frac{\mathrm{d}X_s}{\mathrm{d}z} = \dot{s}X_s \tag{3.3}$$

where $s$ denotes the solute, and $\dot{s}$ the interface speed, which is constant at steady-state. The formulation is done in terms of mass fractions for a solution where the density of solvent and solute are equal. Furthermore, Fick's first law in its classical form, Eq. (2.11), (reformulated in terms of mass fractions) has been used for simplicity. Equation (3.3) should be compared with Eq. (2.15) for a 'true' steady state. An integration of Eq. (3.3) yields

$$\dot{s} = \frac{D}{L}\ln\left(X_s(0)/X_s(L)\right) \tag{3.4}$$

from which we can identify the permeability of $D/L$ of section 2.4.2. The other factors are, however, radically different, and the concept of permeability does not seem very useful for the problem at hand.

To complete the analysis we have to determine the boundary conditions $X_s(0)$ and $X_s(L)$. In practice it is extremely difficult to prevent bulk flow in a container of reasonable size (cf. the discussion of diffusive flux and bulk flow in section 2.2). However, close to the air-liquid interface there is boundary layer, refered to as an *unstirred layer*, where bulk flow is not efficient, and transport occurs *via* diffusion. We therefore assume that the concentration (chemical potential) is constant within the solution, apart from the unstirred layer where the gradient is located. $X_s(L)$ in Eq. (3.4) is then equal to the bulk concentation, if the location of the unstirred layer is $z = L$. The remaining boundary condition is found by matching the solute concentration at the air-water interface to the relative humidity

$$\mathrm{RH} = \frac{1 - X_s(0)}{1 - (1 - M_w/M_s)X_s(0)} \tag{3.5}$$

according to Raoult's law. $M_w/M_s$ in Eq. (3.5) is the ratio of molecular weight of solvent and solute.

### 3.3.2 The Formation of an Interfacial Phase

The analysis of the preceeding section presupposes a homogeneous environment along the direction of diffusive transport. If conditions are

such that the bulk concentration of the solution, $X_s(L)$, and the concentration in (local) equilibrium with the atmosphere, $X_s(0)$, correspond to different phases, there is the possibility of forming a separate interfacial phase at the air-liquid interface.

Assuming the existence of two phases, $\alpha$ and $\beta$, we can write down the equation analogous to (3.4) for each phase. As shown in paper V, this implies that the interface position, $z_{\text{int}}$, is given by

$$\frac{z_{\text{int}}}{L} = \frac{D(\beta)\ln\left(X_s(0)/X_s(\beta)\right)}{D(\alpha)\ln\left(X_s(\alpha)/X_s(L)\right) + D(\beta)\ln\left(X_s(0)/X_s(\beta)\right)}. \tag{3.6}$$

where $D(\alpha)$ and $D(\beta)$ are the diffusion coefficients in the $\alpha$ and $\beta$ phase, respectively. Furthermore, $X_s(\alpha)$ and $X_s(\beta)$ denote the composition of the $\alpha$ and $\beta$ phase, respectively, on either side of the two-phase region of the equilibrium phase diagram.

From Eq. (3.6) it is possible to predict the thickness of the interfacial phase $\beta$ as a function of the bulk concentration, ambient conditions or the parameters of the system. The qualitative conclusions are that the interfacial phase is more likely to form for lower relative humidities, for a bulk solution close to phase separation, and when diffusion through the interfacial phase is fast. The conclusion that no interfacial phase is formed for more humid conditions is consistent with the observation of Edler *et al.*, that film formation in their systems was prevented by increasing relative humidity.[56–59]

The effect of the interfacial energy, due to the creation of the new $\alpha$-$\beta$ interface, has been neglected in the deriviation of Eq. (3.6). This could make appearance of the interfacial phase less likely. See paper V for details.

### 3.3.3 Film Formation in the AOT-Water System

To arrive at Eq. (3.6), we used a rather crude model for the diffusional process. A more realistic description is found in paper V for the specific case of an aqueous AOT (sodium bis(2-ethylhexyl)sulfosuccinate) solution. The AOT-water system provides a good example, and ties in nicely with the presentation here. AOT is a bit particular in the sense that it readily forms a lamellar phase from an isotropic micellar solution at low surfactant concentrations.[63] Thus there is the possibility of forming a lamellar interfacial phase at the air-liquid interface. The situation is therefore similar to the responding lamellar phase described above, and the conceptual understanding gained from this example proves beneficial in the theoretical analysis. Furthermore, the swelling of the lamellar

phase is well described by electrostatic theory,[64,65] so modelling of the interbilayer force is possible.

The theoretical analysis shows that film formation is not a likely event for a bulk micellar solution. When the bulk solution instead is in the micellar-lamellar coexistence region, the lamellar phase sinks to the bottom of the container since AOT is heavier than water.[66] In this case, the formation of an interfacial film is most likely, and the film thickness depends strongly on the ambient relative humidity. An interesting feature is that the evaporation rate, $\dot{s}$, shows a strong dependence on the gradient for high values of the relative humidity (before film formation). As soon as the film is formed, however, the evaporation rate is essentially constant regardless of the gradient. This is a similar behaviour to the one noted for the responding monoolein membrane (see Fig. 3.3).

# Chapter 4

# Multi-Component Diffusion in Responding Membranes

So far we have treated the diffusion of a *single* component across 'static' (chapter 2) as well as responding membranes (chapter 3). We now proceed by considering multi-component diffusion. The effects vary depending upon if the membrane responds to the presence of the other component(s) or not, and if the diffusional fluxes are coupled. We will treat these different cases separately, starting with the simplest one of a second component diffusing through a responding membrane whose structure and phase behaviour only depends on the chemical potential of the first component. Next we extend the study of the responding lamellar phase by considering the case when the swelling depends on the chemical potentials of two components. This has a clear relevance for the pH gradient over human skin. Finally we discuss some aspects of the analysis of a responding membrane with the propensity of a phase change when exposed to gradients in two chemical potentials.

We have previously noted the similarity between diffusion and heat conduction. It is therefore not surprising that the analysis made here for diffusion of two components could, in many cases, be directly translated by a mere change of notation into a corresponding statement about diffusion together with heat conduction. We will point this out specifically in some cases, but the reader should keep in mind that it might be more generally applicable.

## 4.1 Diffusion of an 'Inert' Solute

Consider a membrane that responds to the gradient in the chemical potential of one component. In the previous examples, this has been the gradient in the chemical potential of water. In the general discussion we will refer to this component as component 1. We now consider also the diffusive transport of a second component, component 2, through the same membrane. The simplest case is if component 2 is present in very low concentrations, or if the structure and phase behaviour of the membrane for other reasons is rather insensitive to variations in the concentration of component 2. In this case it is a good approximation to view the structure of the membrane as solely determined by the gradient in the chemical potential of component 1. Through this structure component 2 then diffuses, as if through a 'static' membrane (cf. section 2.4).

As an example, we consider the diffusion of a second component through the responding monoolein membrane. A theoretical model for how the monoolein membrane reacts to the gradient in the chemical potential of water was described in section 3.2. The diffusion of a second component, that does not affect the structure and phase behaviour of the monoolein membrane, can easily be included in this model. As a result one finds a theoretical expression for the permeability of the second component as a function of the gradient in the chemical potential of water. See paper III and IV for the detailed analysis.

There is a practical reason for discussing the diffusion of a second component through the monoolein membrane. If this second component has a low partition coefficient between an aqueous phase and the lipid bilayer, then we expect that the flux shows a strong decrease as the lamellar phase is induced. Experimentally, a second component can therefore serve as indirect indicator of the internal structure of the membrane. This was used in the studies reported in paper III and IV, where the flux of a dye, present in low concentration, through the monoolein membrane was measured. There is a good agreement between the theoretical description and the experimental results. We emphasise in particular, not only the quantitative agreement, but the experimental verification that a phase change can affect transport.

## 4.2 The Responding Lamellar Phase Revisited

We now consider diffusion of two components through a membrane which is sensitive to the local chemical potential of *both* components. This case is somewhat more complicated to describe, and we start by disregarding the possibility of phase changes along the membrane. We return to the example of the responding lamellar phase. In this context, we discuss diffusion of the two components water and $CO_2$ across the responding lamellar phase as a crude model for the pH gradient across human skin.

### 4.2.1 Relevance as a Model of the *Stratum Corneum*

The main function of the human skin is to serve as a barrier, keeping unwanted substances out of the body, and wanted substances inside. One of the most important roles is to prevent uncontrolled water loss. The chemical potential of water inside the body corresponds to a 150 mM NaCl solution, which implies an osmotic pressure of 0.8 MPa. In the surrounding gas phase, on the other hand, the relative humidity is commonly in the range of $30 - 90\%$, corresponding to an osmotic pressure of $170 - 15$ MPa. There is therefore a rather extreme gradient in osmotic pressure over the skin, driving transport of water out of the body. Even more amazing is the fact that almost the full gradient in osmotic pressure is located across the outermost part of the human skin, the *stratum corneum*, which is only $10 - 20\,\mu$m thick.[67] This very thin structure therefore provides the main protection against uncontrolled water loss.[68]

The *stratum corneum* is composed of dead keratin-filled cells, called corneocytes, embedded in a multilamellar lipid matrix.[69] Since the lipid matrix is continuous throughout the structure, a molecule diffusing across the *stratum corneum* by neccessity passes the lipid structure.[70–72] A simplified picture of diffusive transport across the *stratum corneum* is then to view it as diffusion across a lamellar phase. This is obviously a crude simplification that neglects the presence of the corneocytes. However, the advantage is that it is possible to make a quantitative modelling. In this way the responding lamellar phase is relevant for diffusive transport across the *stratum corneum*.[35,46]

A case which is particularly relevant is the possibility of a phase change within the responding lamellar phase, as we discussed briefly at the end of section 3.2. It has been shown that water transport through the *stratum corneum* is a linearly dependent on the water gradient for high values of the relative humidity (low values of osmotic pressure), but levels off at lower values of the relative humidity (high values of osmotic

pressure).[73] In other words, the water flux shows the same qualitative behaviour as that shown in Fig. 3.3. It has been observed that extracted *stratum corneum* lipids can undergo phase transformations in the same region of relative humidities as where the water transport becomes non-linear.[74] It is therefore tempting to explain the non-linear behaviour of transport through the *stratum corneum* with a phase transformation within the lipid matrix.[35,46]

A second important case is the diffusion not only of water, but also of $CO_2$, across the responding lamellar phase. $CO_2$ can react with water to form ions. At the relevant conditions this is dominated by the reaction equilibrium

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+. \tag{4.1}$$

With a source of ions, the electrostatic interaction between two bilayers change. Therefore we have a situation where both water and $CO_2$ affects the local structure in the responding lamellar phase. This is interesting as a model for the pH gradient across the *stratum corneum*.

The gradient in pH across human skin is likely common knowledge due to its appearance in many commercials for soaps and shampoos. In spite of this, there is little consensus on the actual mechanism behind it. The experimental observation is that the skin surface is acidic, with a pH varying between 4 and 6.[75] In contrast, the pH in the body has a regulated value of about 7.4, close to neutral conditions. Also in this case, the gradient is considered to be located across the *stratum corneum*.[76] Physiological conditions correspond to a partial pressure of around $p_{CO_2} = 6\,\mathrm{kPa}$, whereas in the ambient atmosphere the partial pressure is only around $p_{CO_2} = 40\,\mathrm{Pa}$.[26] In other words, there is a gradient in $CO_2$ across the *stratum corneum* of more than two orders of magnitude. The gradient drives transport of $CO_2$ out of the body. In the lung the gradient is equally large, but in this case the major part is located in the gas phase in the lung, rather than in the condensed phase (see section 2.4.3).

Due to the reaction described by Eq. (4.1), it is clear that the large gradient in $CO_2$ could potentially have a significant effect on the local proton concentration between bilayers. It is perhaps less clear that also the osmotic gradient plays a role. To understand this, we need to discuss the electrostatic force between two charged bilayers in more detail.

### 4.2.2 Electrostatic Interactions

The conventional (and easiest) way to describe the electrostatical interaction between two charged surfaces is to consider the *Poisson-Boltzmann equation*[23,36] for the electrostatic potential, $\Phi$; in one dimension

$$\epsilon_r \epsilon_0 \frac{\mathrm{d}^2\Phi}{\mathrm{d}z^2} = \sum_i (Z_i e) c_{i0} \exp\left(Z_i e \Phi(z)/kT\right)$$

where summation runs over all ions present. Here $Z_i$ is the valency and $c_{i0}$ the concentration where $\Phi = 0$ for the ionic species $i$, respectively. Furthermore, $e$ is the (absolute) electron charge, $k$ the Boltzmann constant, $T$ the absolute temperature, $\epsilon$ the dielectric constant of water and $\epsilon_0$ the vacuum permittivity. The Poisson-Boltzmann includes interactions among the ions, and a mean-field description of the ion distribution. The interactions with the charges of the bilayer surface can be included by the boundary condition

$$\epsilon_r \epsilon_0 \left.\frac{\mathrm{d}\Phi}{\mathrm{d}z}\right|_{\text{bilayer surface}} = -\sigma$$

where $\sigma$ is the bilayer surface charge. For two bilayers with the same charge, the electrostatic potential has to be symmetric around the midplane between the surfaces, so a second boundary condition is

$$\left.\frac{\mathrm{d}\Phi}{\mathrm{d}z}\right|_{\text{midplane}} = 0.$$

The lipid matrix of the *stratum corneum* contains titrating fatty acids, so the surface charge is determined by a chemical equilibrium. This is referred to as *charge regulation*.[77] We furthermore assume the presence of only monovalent ions. In this case the mean-field description inherent in the Poisson-Boltzmann equation is a good approximation.[23]

The presence of $CO_2$ implies an additional source of ions from the reaction equilibrium in Eq. (4.1). Therefore there is an indirect effect of $CO_2$ on the local electrostatics. This can rather easily be included in the Poisson-Boltzmann description, though the resulting equations are rather intricate to solve numerically (see paper II for details).

As the interbilayer distance decreases (due to an increase in osmotic pressure), the ions are pushed closer together. The *mean* concentration of the different ionic species within the aqueous film therefore increases. However, the local concentration of an ionic species between the charged

bilayers is not uniform; rather positive ions are attracted to the negative surface, and negative ions expelled. To get the full quantitative result we have to consider the actual solution of the Poisson-Boltzmann equation.

For the case when the partial pressure of $CO_2$ corresponds to atmospheric conditions, the result of such an analysis is the following: The local concentration of protons at the bilayer surface is, to a very good approximation, constant around $-^{10}\log c_{H^+}(\text{surface}) = 6.0$, irregardless of osmotic pressure. In contrast, the concentration of protons at the midplane between the bilayer surfaces varies between $-^{10}\log c_{H^+}(\text{midplane}) = 7.4$ and 6.4, due to a variation in osmotic pressure between 0.8 MPa and 50 MPa (corresponding to a variation in relative humidity between 100 and 70%). The variation follows the description of the swelling given in section 3.1.2, with a strong variation for low osmotic pressures, and then a plateau region for higher osmotic pressures. The cause is the strong variation in the force between bilayers at short distances (cf. Fig. 3.1).

### 4.2.3 The $H^+$ Profile

Let us now consider the actual gradient in proton concentration along the responding lamellar phase. The permeability of a bilayer to ions is very low.[38,78] A reasonable (and simple) limit is therefore to consider the case when the ions do not pass the individual bilayers. As a model of the lipid matrix of the *stratum corneum*, we imagine that the aqueous film that is closest to being in contact with the physiological environment is open to equilibrate with a solution containing 150mM NaCl and having a pH of 7.4. This equilibrium provides a given number of ions, that can be modelled within the Poisson-Boltzmann formalism. Due to the continuous ageing of the skin, each repeat unit travels towards the surface, loosing the contact with the bulk. In the limit when the ions do not diffuse through the bilayers, the number of ions within an aqueous film is constant, apart from those produced by the gradient in $CO_2$ due to the reaction described by Eq. (4.1).

When chemical reactions are possible, the equation of continuity, Eq. (2.10), has to be generalised to include a term that describes the local production (per unit volume), $s_i$, of species $i$

$$\frac{\partial c_i}{\partial t} + \frac{\partial J_i}{\partial z} + s_i = 0. \tag{4.2}$$

The reaction equilibrium described by Eq. (4.1) implies that these pro-

duction terms satisfies the relations

$$s_{CO_2} = s_{H_2O} = -s_{HCO_3^-} = -s_{H^+}.$$

At steady state this means that the fluxes of $CO_2$ and water must fullfill

$$\frac{d}{dz}(J_w + J_i) = 0 \quad \frac{d}{dz}(J_{CO_2} + J_i) = 0. \tag{4.3}$$

where $i = HCO_3^-, H^+$. Hence the fluxes of water and $CO_2$ are directly coupled, even in the absence of the coupling to the local structure. In principle, such a coupling complicates the analysis. However, for the particular case described by Eq. (4.1), the equilibrium constant is small (of the order of $10^{-7}$ M), and it is an excellent approximation to neglect the direct transport of the ions, so that Eq. (4.3) reads

$$\frac{dJ_w}{dz} = 0 \quad \frac{dJ_{CO_2}}{dz} = 0. \tag{4.4}$$

Within the approximation that the transport of ions can be neglected, Eq. (4.4) shows a certain uncoupling of the fluxes of water and $CO_2$. This is not completely true, since the local structure still depends on the chemical potential of both components. However, Eq. (4.4) relates directly to the permeabilities as described in section 2.4. The main advantage of Eq. (4.4) is therefore that we can use the concept of permeability as before.

The result of the model is that there is hardly any variation in the proton concentration at the bilayer surface along the lamellar phase, and ${}^{10}\log c_{H^+}(\text{surface}) \approx 6$. In contrast, there can be a substantial gradient in the proton concentration at the midplane between the bilayers. The actual gradient is strongly dependent on the ambient humidity conditions; for a very humid environment there is essentially no gradient at all, and $-{}^{10}\log c_{H^+}(\text{midplane}) = 7.4$ throughout. On the other hand, already for an atmospheric relative humidity of 90%, the part of the lamellar phase that corresponds to the skin surface has ${}^{10}\log c_{H^+}(\text{midplane}) = 6.6$. For a relative humidity of 60%, this value reaches ${}^{10}\log c_{H^+}(\text{midplane}) = 6.4$.

The conclusion is therefore that the combined effect of the gradient in osmotic pressure and $CO_2$ show a substantial effect on the proton concentration at the midplane along the lamellar phase. The midplane concentration close to what in the model corresponds to the skin surface, is strongly dependent on the relative humidity. For humid conditions, it is the same as physiological pH, whereas for dry conditions it is acidic. This is consistent with experimental investigations that have shown an

increase in skin surface pH after occlusion (covering of the skin),[79,80] or rinsing with tap water.[81]

We have deliberately been careful to phrase the results described above in terms of (local) proton concentrations, rather than pH. The reason for this is that it is not obvious how pH should be defined for a system that is not at equilibrium, and, furthermore, is locally heterogeneous both when it comes to concentrations and charge distributions. A natural definition can be given that takes these effects into account within the given model. See paper II for details.

## 4.3 Phase Changes and Multi-Component Diffusion

We proceed with the case of a responding membrane with a propensity of an internal phase transformation. The analysis for the case of gradients in two chemical potentials is somewhat mathematically complicated — even with substantial simplifying assumptions. In order to cope with this technicality we introduce a description based on generalised permeabilities.

### 4.3.1 Coupled Transport

If two components are involved in a reaction equilibrium, then the corresponding diffusive fluxes are coupled, as was exemplified in section 4.2.3 above. In more general terms, the theory of irreversible thermodynamics[1–3] includes the coupling of two transport processes from the start, by making the *ansatz*

$$\begin{aligned} J_1 &= -L_{11}\frac{\partial \mu_1}{\partial z} - L_{12}\frac{\partial \mu_2}{\partial z} \\ J_2 &= -L_{21}\frac{\partial \mu_1}{\partial z} - L_{22}\frac{\partial \mu_2}{\partial z} \end{aligned} \tag{4.5}$$

for the case of two diffusion processes. Here $L_{ij}$ are transport coefficients describing how the $i$th flow depends on the $j$th gradient. In the more general case, one writes down all possible transport processes coupled to the corresponding gradients. Sometimes one can infer from symmetry arguments, within the theory of irreversible thermodynamics known as the Curie principle, that a certain off-diagonal transport coefficient (i.e. an $L_{ij}$ for which $i \neq j$) must vanish; e.g. for an isotropic system vectorial flows cannot couple to a tensor flow,[1] so that diffusion and viscous flow

are uncoupled. However, in the general case all transport coefficients are non-zero.

There is a celebrated theorem due to Onsager[82,83] that relates the off-diagonal coefficients to each other, if the fundamental laws of nature obey time-reversibility. In its simplest form, it states that the matrix of transport coefficients is symmetric, i.e. $L_{ij} = L_{ji}$. This form is not applicable in the presence of forces that depends on the velocity of a particle, such as magnetic and centrifugal forces. In the latter case Onsager's theorem instead relates $L_{ij}$ to $L_{ji}$ with reversal of the velocity-dependent force(s).[1] Strictly speaking there *are* forces that do not obey time-reversibility, but this is completely negligible when dealing with molecular systems.

It might not be readily apparent that the *ansatz* in Eq. (4.5) covers the case when transport of two components are coupled *via* a reaction equilibrium, as e.g. that described by Eq. (4.1). To demonstrate this, we take for convenience the simpler example of two components, A and B, that can form the product AB

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{AB}. \tag{4.6}$$

In the limit that the reaction proceeds sufficiently fast compared to diffusion, it is a good approximation to assume local chemical equilibrium with respect to the reaction described by Eq. (4.6). Under that assumption, the corresponding chemical potentials fullfill

$$\mu_{\mathrm{A}} + \mu_{\mathrm{B}} = \mu_{\mathrm{AB}}. \tag{4.7}$$

We relate the transport of each of the three components individually by a transport coefficient $l$

$$J_i = -l_i \frac{\partial \mu_i}{\partial z} \qquad\qquad i = \mathrm{A}, \mathrm{B}, \mathrm{AB}.$$

Then due to Eq. (4.7)

$$J_{\mathrm{AB}} = -l_{\mathrm{AB}} \frac{\partial \mu_{\mathrm{AB}}}{\partial z} = -l_{\mathrm{AB}} \frac{\partial (\mu_{\mathrm{A}} + \mu_{\mathrm{B}})}{\partial z}$$

so that the total flux of A and B are given by

$$\begin{aligned} J_{\mathrm{A}}^{\mathrm{Tot}} &= J_{\mathrm{A}} + J_{\mathrm{AB}} = -(l_{\mathrm{A}} + l_{\mathrm{AB}}) \frac{\partial \mu_{\mathrm{A}}}{\partial z} - l_{\mathrm{AB}} \frac{\partial \mu_{\mathrm{B}}}{\partial z} \\ J_{\mathrm{B}}^{\mathrm{Tot}} &= J_{\mathrm{B}} + J_{\mathrm{AB}} = -l_{\mathrm{AB}} \frac{\partial \mu_{\mathrm{A}}}{\partial z} - (l_{\mathrm{AB}} + l_{\mathrm{B}}) \frac{\partial \mu_{\mathrm{B}}}{\partial z}. \end{aligned}$$

This has the same form as Eq. (4.5), so that coupling of two diffusion processes due to a reaction equilibrium like Eq. (4.6) fits well into the formalism of the theory of irreversible thermodynamics. Also note that Onsager's theorem is explicitly satisfied in this simple model (though it is not obvious that it is a result of time-reversibility).

If the diffusion of, say, component A is slow in a membrane, then the transport of A can be significantly increased due to a chemical reaction within the membrane. This happens if the equilibrium constant of the reaction described by Eq. (4.6) is large, and if the diffusion of component AB is faster than the diffusion of component A by itself. In that case, A mainly exists as AB within the membrane, and is transported more efficiently in this form. AB act as *carrier* for A.[84]

### 4.3.2 Generalised Permeabilities

Before we consider the full problem with a responding membrane, we discuss a generalisation of the concept of permeability for a composite membrane in the presence of two gradients. The main convenience of the concept of permeability is that the permeability of a composite membrane satisfies the simple relation in Eq. (2.17). It is not *a priori* obvious that this relation remains valid in the presence of two gradients.

To generalise the concept of permeability, we consider a composite membrane made up of two layers, denoted $\alpha$ and $\beta$. The two layers occupies the regions $z = 0$ to $z_{\text{int}}$ and $z = z_{\text{int}}$ to $L$, respectively (cf. Fig. 2.2). For simplicity we assume that the transport coefficients in Eq. (4.5) are independent of the chemical potentials, but possibly different in the two layers. As usual we assume steady-state conditions and that the flux of either component is constant throughout the system. We then have

$$-L_{i1}^{\alpha}\frac{(\Delta\mu_1)^{\alpha}}{z_{\text{int}}} - L_{i2}^{\alpha}\frac{(\Delta\mu_2)^{\alpha}}{z_{\text{int}}} = J_i = -L_{i1}^{\beta}\frac{(\Delta\mu_1)^{\beta}}{L - z_{\text{int}}} - L_{i2}^{\beta}\frac{(\Delta\mu_2)^{\beta}}{L - z_{\text{int}}} \tag{4.8}$$

in terms of

$$(\Delta\mu_i)^{\alpha} = \mu_{i\text{int}} - \mu_{i0} \qquad\qquad (\Delta\mu_i)^{\beta} = \mu_{iL} - \mu_{i\text{int}}$$

where $\mu_{i\text{int}}$ are the chemical potentials at the interface between $\alpha$ and $\beta$, and $\mu_{i0}$ and $\mu_{iL}$ the chemical potentials at $z = 0$ and $L$, respectively.

One can show that Eq. (4.8) implies

$$\begin{aligned}(\Delta\mu_1)^\alpha &= \frac{(P^\beta + P^{\beta\alpha})(\mu_{1L} - \mu_{10}) + P^{(2)}(\mu_{2L} - \mu_{20})}{P^\alpha + P^{\alpha\beta} + P^{\beta\alpha} + P^\beta} \\ (\Delta\mu_2)^\alpha &= \frac{P^{(1)}(\mu_{1L} - \mu_{10}) + (P^\beta + P^{\alpha\beta})(\mu_{2L} - \mu_{20})}{P^\alpha + P^{\alpha\beta} + P^{\beta\alpha} + P^\beta}\end{aligned} \tag{4.9}$$

in terms of

$$\begin{aligned} P^\alpha &= \frac{L_{11}^\alpha L_{22}^\alpha - L_{12}^\alpha L_{21}^\alpha}{{z_{\text{int}}}^2} \qquad P^\beta = \frac{L_{11}^\beta L_{22}^\beta - L_{12}^\beta L_{21}^\beta}{(L - z_{\text{int}})^2} \\ P^{\alpha\beta} &= \frac{L_{11}^\alpha L_{22}^\beta - L_{12}^\beta L_{21}^\alpha}{z_{\text{int}}(L - z_{\text{int}})} \quad P^{\beta\alpha} = \frac{L_{11}^\beta L_{22}^\alpha - L_{12}^\alpha L_{21}^\beta}{z_{\text{int}}(L - z_{\text{int}})} \\ P^{(1)} &= \frac{L_{11}^\alpha L_{21}^\beta - L_{11}^\beta L_{21}^\alpha}{z_{\text{int}}(L - z_{\text{int}})} \quad P^{(2)} = \frac{L_{22}^\alpha L_{12}^\beta - L_{12}^\alpha L_{22}^\beta}{z_{\text{int}}(L - z_{\text{int}})}. \end{aligned} \tag{4.10}$$

Equation (4.10) shows that $P^\alpha$ and $P^\beta$ remain the same under an interchange of the two components. $P^{\alpha\beta}$ and $P^{(1)}$ are interchanged with $P^{\beta\alpha}$ and $P^{(2)}$, respectively. According to Eq. (4.9), $(\Delta\mu_1)^\alpha$ is then interchanged with $(\Delta\mu_2)^\alpha$, as it should. Similarly, Eq. (4.9) and (4.10) show the correct symmetry with respect to an interchange of $\alpha$ and $\beta$.

By inserting Eq. (4.9) and (4.10) into Eq. (4.8) one can finally show that

$$J_i = -P_{i1}(\mu_{1L} - \mu_{10}) - P_{i2}(\mu_{2L} - \mu_{20})$$

in terms of

$$P_{ij} = \frac{\frac{L_{ij}^\alpha}{z_{\text{int}}} P^\beta + \frac{L_{ij}^\beta}{L - z_{\text{int}}} P^\alpha}{P^\alpha + P^{\alpha\beta} + P^{\beta\alpha} + P^\beta}. \tag{4.11}$$

$P_{ij}$ in Eq. (4.11) are the generalised permeabilities we aimed to find.

### 4.3.3 Phase Changes in the Presence of Two Gradients

We are now ready to tackle how the possibility of phase changes affect a responding membrane in the presence of two gradients. In contrast to the case of a single component, the chemical potential(s) at which the phase change takes place are not known *a priori*, but rather have to be determined as part of the solution.

For this purpose we have to consider the equilibrium phase diagram corresponding to the membrane. Fig. 4.1 shows an examplar phase

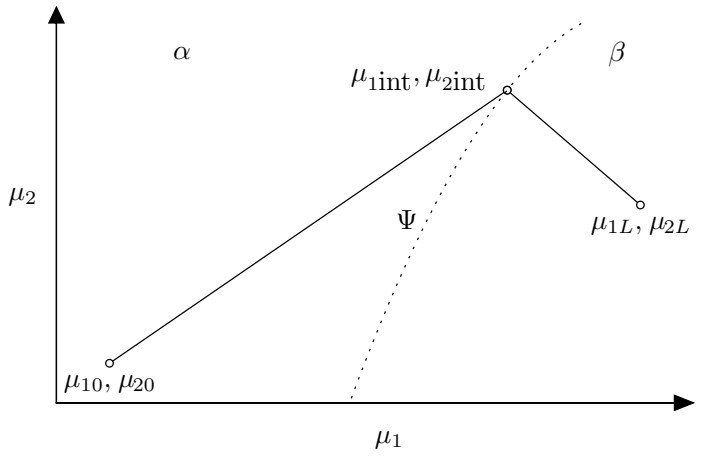


Figure 4.1: A schematic phase diagram of two phases, $\alpha$ and $\beta$, separated by a two-phase coexistence line, $\Psi$ (dotted line). The boundary values, $\mu_{i0}$ and $\mu_{iL}$, on either side of the membrane correspond to different phases. The projection (see text) of the chemical potential profiles within the membrane is also shown (solid line).

diagram, upon which our discussion will be based. In terms of chemical potentials, one- and two-phase regions of the phase diagram are areas and lines, respectively. The advantage of using chemical potentials rather than concentrations, is therefore even more apparent for multi-component diffusion. This is also true for the case of heat conduction and diffusion, since temperature is also a thermodynamical 'field variable'.[24] The example in Fig. 4.1 has two one-phase regions, $\alpha$ and $\beta$, separated by a two-phase line, $\Psi$. For the case we are interested in, the boundary values are on opposite sides of the two-phase line. We therefore expect that the membrane will be made up of two phases.

Even though the case of two gradients is complicated by the fact that the chemical potentials at the $\alpha$-$\beta$ interface are unknown, there is a fortunate simplification: by solving for the gradients in Eq. (4.5), and dividing one by the other, we find

$$\frac{\mathrm{d}\mu_2}{\mathrm{d}\mu_1} = \frac{-L_{21}J_1 + L_{11}J_2}{L_{22}J_1 - L_{12}J_2} = \frac{L_{11} - L_{21}J_1/J_2}{L_{22}J_1/J_2 - L_{12}} \tag{4.12}$$

The great simplification inherent in Eq. (4.12) is that the dependence on the spatial coordinate, $z$, does not appear. This means that we do

not have to find both the position of, and the chemical potentials at, the interface simultaneously. This fact comes about since $J_i$ are constant throughout the membrane. Therefore Eq. (4.12) is a differential equation for $\mu_2$ as a function of $\mu_1$, with one unknown $J_2/J_1$. The equation is different for the two phases, but the two boundary conditions and the condition that the chemical potentials at the interface must lie on the two-phase line, ensures a solution. This solution, i.e. $\mu_2$ as a function of $\mu_1$, can be interpreted as a projection of the 'full solution' $\mu_i(z)$ onto the phase diagram.

Under the simplifying assumption that the transport coefficients are independent of the chemical potentials, Eq. (4.12) shows that $\mu_2$ is a linear function of $\mu_1$. The solution projected onto the phase diagram is therefore a straight line with, in general, different slopes within the two phases. Such a projection is shown in Fig. 4.1.

We note that even for transport coefficients $L_{ij}$ that *do* depend on the chemical potentials, Eq. (4.12) implies an independence on the spatial coordinate. However, for this more general case, the projected solution is not a straight line in the phase diagram, and most probably a numerical solution has to be employed.

For transport coefficients independent of chemical potential, Eq. (4.12) can readily be integrated

$$\frac{(\Delta\mu_2)^\alpha}{(\Delta\mu_1)^\alpha} = \frac{L_{11}^\alpha - L_{21}^\alpha J_1/J_2}{L_{22}^\alpha J_1/J_2 - L_{12}^\alpha} \qquad \frac{(\Delta\mu_2)^\beta}{(\Delta\mu_1)^\beta} = \frac{L_{11}^\beta - L_{21}^\beta J_1/J_2}{L_{22}^\beta J_1/J_2 - L_{12}^\beta}.$$

Solving for $J_1/J_2$ one finds

$$\frac{L_{11}^\alpha(\Delta\mu_1)^\alpha + L_{12}^\alpha(\Delta\mu_2)^\alpha}{L_{21}^\alpha(\Delta\mu_1)^\alpha + L_{22}^\alpha(\Delta\mu_2)^\alpha} = \frac{J_1}{J_2} = \frac{L_{11}^\beta(\Delta\mu_1)^\beta + L_{12}^\beta(\Delta\mu_2)^\beta}{L_{21}^\beta(\Delta\mu_1)^\beta + L_{22}^\beta(\Delta\mu_2)^\beta}$$

so that

$$\begin{aligned} &P^{(2)}\big(\Psi(\mu_{1\mathrm{int}}) - \mu_{20}\big)^2 - \\ &- \big(P^{\alpha\beta}(\mu_{1\mathrm{int}} - \mu_{10}) + P^{\beta\alpha}(\mu_{1L} - \mu_{1\mathrm{int}})\big)\big(\Psi(\mu_{1\mathrm{int}}) - \mu_{20}\big) + \\ &+ P^{(1)}(\mu_{1\mathrm{int}} - \mu_{10})(\mu_{1L} - \mu_{1\mathrm{int}}) = 0 \end{aligned} \tag{4.13}$$

in terms of the parameters defined by Eq. (4.10).

Equation (4.13) is an equation for the chemical potential at the interface, $\mu_{1\mathrm{int}}$. Depending on the two-phase line $\Psi$, it generally has to be solved numerically. Once solved, the chemical potentials at the interface, $\mu_{1\mathrm{int}}$ and $\mu_{2\mathrm{int}} = \Psi(\mu_{1\mathrm{int}})$ are known. From $\mu_{i\mathrm{int}}$, the position of the interface, $z_{\mathrm{int}}$, easily follows from Eq. (4.8).

We briefly note that once again we have neglected the effect of the surface free energy of the new interface. See paper V for a discussion of this for a slightly different case.

### 4.3.4 The Case of a Single Gradient

Instead of illustrating the solution of Eq. (4.13) and (4.8) in some generality, we consider the particular case when the chemical potential gradient for component 2 vanishes. One might expect that this corresponds to the case treated already (chapter 3, in particular section 3.2). However, if one considers the possibility that transport of component 2 can be driven by the gradient in the chemical potential of component 1, this is not true.

To justify this statement, consider the indirect transport of component 2, i.e. transport due to a gradient in the chemical potental of component 1, before the steady state is attained. If the indirect transport of component 2 through, say, the $\alpha$ phase is faster than through the $\beta$ phase, there will be an accumulation of component 2 at the $\alpha$-$\beta$ interface. In the opposite case, there will instead be a depletion at the interface. This will help drive the phase change. The result is that, at steady state, there can be opposing gradients in the chemical potential of component 2 in phase $\alpha$ and $\beta$, such that they add up to the vanishing of an overall gradient. Furthermore, there will also be a shift in coexistence along the two-phase line.

This reasoning leads us to conclude that whenever there is coupling between two transport processes, the vanishing of an overall gradient does not imply that the case can be treated as a single transport process. However, this is only true for a membrane composed of two phases, and when transport is different in the two phases. For some numerical examples, see paper VI.

This effect also has corresponding consequences for coupled diffusive transport and heat conduction through a responding membrane. For example, even though the temperature on either side of the membrane are kept equal, there can still be a different temperature within the membrane. Therefore, the phase change within the membrane can be at a different temperature compared to the (equal) temperature at the boundaries.

# Chapter 5

# Conclusions and Outlook

## 5.1 Diffusion through the Alveolar Interface

The main resistance to transport of $O_2$ in the human lung, from the inhaled air to the capillary vessels, is located across the alveolar interface. A structure that facilitates the diffusion of $O_2$ is therefore physiologically beneficial. The structure depicted in Fig. 2.3b has previously been proposed as a model for lipid reservoir covering the alveolar interface. In paper I it was shown how diffusive transport of $O_2$ is faster through this structure than through a bilayer arrangement (Fig. 2.3a).

## 5.2 Phase Changes in Responding Membranes

A significant part of the work presented in this thesis (paper III-VI) concerns diffusive transport through a membrane with the propensity of an internal phase transformation. Even a diffusion process that in itself is uncomplicated then becomes highly non-linear. This is especially the case if the transport properties of the two phases differ significantly. In this case, the general qualitative behaviour for diffusion of a single component is similar to what is shown in Fig. 3.3.

There is a concomitant change in the transport of a second component that itself does not change the structure of the membrane material. In this way, the membrane can act as a 'switch' for diffusion, regulated by a primary transport process that determines the structure.

In the work presented in paper III and IV a specific model system was investigated, experimentally as well as theoretically. A good agreement was found, lending support to the proposed mechanism.

The behaviour shown in Fig. 3.3 is not the only possibility in the

presence of two diffusional processes that both affect the local phase behaviour. An interesting special case is when the gradient in chemical potential of one of the two components vanishes (paper VI). Due to coupling of the two processes, there might still be a gradient within the membrane. This also affects the position of the interface between the two phases, as well as the flux. Interestingly, this effect is rather general, and implies that one must take into account all possible transport processes, even the onces for which there is no (direct) driving force.

Apart from a basic interest in how a phase change affects diffusional transport, the studies have implications for diffusive transport through the outmost layer of human skin, the *stratum corneum* (see below). Another example with similarities to the *stratum corneum* from the point of view of this thesis, is the plant cuticle, which is the outmost part of the membrane that separates the aerial parts of all higher plants.[85–87]

A related application is for film formation at a non-equilibrium interface. The case of water evaporation from an open aqueous surfactant solution was treated in paper V. The evaporation of water is due to a diffusive transport of water from the bulk solution to the gas phase. Hence there is also a gradient in the chemical potential of water, and the possibility of a phase transformation close to the interface. Compared to a membrane the film forms spontaneously, but the general concepts are very similar.

## 5.3 Implications for the *Stratum Corneum*

The outmost part of the human skin, the *stratum corneum*, is main barrier against uncontrolled water loss. The response in water flux through the *stratum corneum* is a non-linear function of the driving force, with the same general behaviour as that shown in Fig. 3.3. Furthermore, it has been shown that extracted *stratum corneum* lipids can undergo phase transformations due to variations in the chemical potential of water.[74] It is possible that the non-linear response of the *stratum corneum* is due to phase changes among the *stratum corneum* lipids, in a similar fashion as the response shown for a model system in paper III and IV.

The gradient in pH across the *stratum corneum* is well-established, but its origin remains obscure. A very simple model for the lipid matrix found in the *stratum corneum* is in terms of a stack of bilayers. The response of the stack to diffusion of water and $CO_2$ has been calculated (paper II). In particular, the local proton concentration between bilayers was investigated along the stack, and as a function of relative humidity.

A main result is that the transport of water and $CO_2$ can give rise to a significant gradient in proton concentration along the bilayer stack. Furthermore, the experimental observation that the skin surface pH depends on the relative humidity could be correlated with the model.

## 5.4 Outlook

The study presented in paper V drew inspiration from the studies of Edler *et al.* concerning film formation in surfactant-polymer-water systems, but for simplicity only treated the case of a binary system. The work reported in paper VI, on the other hand, concerns the effect of multi-component transport on the phase behaviour of a membrane. It is intriguing to combine these studies, and treat film formation in a ternary system. There are also several other phenomena that are possibly related to the problem of film formation, e.g. the formation of liquid crystalline phases when spin or dip coating surfactant solutions,[88–90] or surfactant dissolution in water.[91,92]

Furthermore, a study of the effect of two coupled transport processes on a specific system would be interesting. Preferably such a study would be combined with experimental work on the same system.

All the analysis reported in this thesis has been based on an assumption of local equilibrium, in the sense that it presupposes the existence of a local entropy which is the same function of the local extensive variables as at equilibrium. This is the approach taken within the theory of irreversible thermodynamics, and leads to the introduction of a local temperature, local temperature and local chemical potentials. Within this framework, the phase change within a membrane with a propensity for phase transformations occurs at the same chemical potential as it does at equilibrium. However, there exists several thermodynamical formalism that go beyond the local equilibrium formulation.[93,94] It is conceivable that such an approach can predict a change in the phase coexistence.

# Populärvetenskaplig sammanfattning på svenska

Huden är vårt största organ, och utgör den barriär som avgränsar oss från vår omgivning. En av dess främsta uppgifter är att skydda oss från giftiga ämnen, bakterier och virus, men minst lika viktigt är att den förhindrar att önskade ämnen *lämnar* kroppen. Ett ämne som måste behållas inom kroppen är naturligtvis vatten. I regnskogen eller något annat fuktigt klimat är detta kanske inget större problem, eftersom omgivningen då kan vara nästan lika 'blöt' som kroppens inre. I torrare miljöer är en väl fungerande barriär däremot livsnödvändig.

Vi kan se luftens torrhet som en kraft som får vattnet att lämna kroppen. Desto torrare luft, desto större kraft. I experiment har man visat att mängden vatten som förloras genom huden inte beror på denna kraft riktigt som man förväntar sig. Vi kan jämföra med att dra en kärra med muskelkraft. I detta fall gäller att ju kraftigare vi drar i kärran, desto snabbare går den. Detsamma gäller för huden om kraften är relativt liten; om vi ökar kraften, så ökar vattenförlusten. Vid en viss kraft upphör dock detta enkla samband att gälla. Även om vi ökar kraften, så ökar inte vattenförlusten. Man skulle kunna säga att huden beter sig som om en illmarig unge sitter på kärran och bromsar med fötterna så fort en viss hastighet uppnåtts.

Fördelen med ett sådant uppförande är uppenbar: Oavsett hur torr luften är (d v s oavsett hur stor kraften är), så finns det en maximal vattenförlust. På så sätt kan huden undvika att vi torkar ut. Men hur lyckats huden med detta konststycke?

En möjlig förklaring till detta är en s k fasövergång hos (en del av) molekylerna som huden består av. Ett exempel på en fasövergång är när flytande vatten fryser till fast is. Till skillnad från vatten som fryser då temperaturen sänks, så övergår istället molekylerna i huden i en fast fas då det blir torrt. Vår hypotes är att när luften blir för torr, så bildas en tät hinna av fasta molekyler ytterst på huden. Denna täta hinna gör det

svårare för en vattenmolekyl att ta sig igenom huden. När hinnan väl bildats så ökar inte vattenförlusten genom huden längre, även om luften blir torrare. Desto torrare luft, desto tjockare hinna. Detta kompenserar för den ökande kraften.

I denna avhandling har vi inspirerats av hur huden (eventuellt) lyckas förhindra vatten att lämna kroppen med en fasövergång. Dock är huden väldigt komplicerad, och det kan vara svårt att utföra välkontrollerade experiment. Vi har därför istället studerat enklare system. En annan anledning till att studera enklare system är att vi varit intresserade av själva mekanismen i sig. Från denna synvinkel är huden ett specifikt fall där ett mer allmänt uppförande exemplifieras.

Mer konkret så påvisar vi att den allmänna mekanism vi beskrivit verkligen *kan* ge ett uppförande som liknar hudens. Vi kombinerar experiment på ett enklare system än huden, med en teoretisk analys av samma system. Den goda överenstämmelsen tyder på att mekanismen verkligen existerar. Vi diskuterar även en teoretisk modell för varför en hinna ibland bildas på ytan av lösningar av en viss grupp molekyler i vatten. Det är troligt att samma allmänna mekanism exempliferas i detta fall, och att idén med en fasövergång kan förklara även detta fenomen. Vi behandlar också möjliga uppförande då det finns fler ämnen än vatten som kan påverka ett system och dess fasövergångar.

I denna avhandling diskuteras även en annan aspekt hos huden, nämligen dess pH-värde, som i reklam för hudprodukter brukar anges som $5,5$. Just själva värdet är kanske inte så vetenskapligt väletablerat, men det är ett experimentellt faktum att pH vid hudens yta skiljer sig från kroppens inre där pH-värdet är $7,4$. Trots många förslag finns det å andra sidan ingen allmänt accepterad förklaring till detta. En intressant observation är att hudens pH faktiskt varierar med luftens torrhet. För väldigt torr luft ligger värdet runt $4-6$, medan det i väldigt fuktig luft närmar sig kroppens inre. Vi visar här i en enkel teoretiskt modell att vattenförlusten genom huden kan ge upphov till ett liknande uppförande och till liknande värden.

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