Mechanism for the formation of density gradients through semipermeable membranes

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We describe and theoretically analyze here a phenomenon which can take place in a system with two different compartments, each containing the same chemicals, which undergo reactions on the surface of both sides of the membrane which separates the two compartments, in the case where the membrane permeabilities to the various chemicals are different and diffusion is fast. There are two main reasons of interest for this kind of system. First, if the overall system is isolated, starting from the case where the initial concentrations of the chemicals are the same in the two phases, one observes the formation of a transient concentration difference. This difference eventually vanishes, although it might last for a long time, depending upon the value of the relevant parameters. The second reason of interest is that, in the case of an open system, one can achieve a steady-state value of the concentration of some chemicals in the smaller compartment which is higher than that in the external one. These results may prove important, *inter alia*, to understand the behavior of lipid vesicles in water, a topic which is important for studies on the origin of life as well as for possible future applications.

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I. INTRODUCTION

It is generally believed that the approach to thermodynamic equilibrium in isolated systems leads to a monotonic decrease of the inhomogeneities which may be present in the initial conditions of a system, at least when gravitational effects can be neglected. However, it has recently been shown, both by theoretical analysis and experimental test, that a transient onset or increase of concentration differences can be achieved in a two-compartment system when the pores of the separating membrane are asymmetric [1].

We will describe below a different kind of isolated system where concentration differences may transiently increase in time without violating the second law of thermodynamics. Moreover, when this system is allowed to exchange matter with the environment, some chemicals are concentrated in a part of it, a phenomenon that might have interesting applications.

Let us consider a system composed of two compartments with different volumes separated by a semipermeable membrane (Fig. 1). There are chemicals on both sides, and the permeabilities of the membrane to the various chemicals may be very different. We will suppose that the volumes of the two compartments do not change, and that chemical reactions may take place in both compartments, in a region very close to the membrane surface: For example, the reactions may be catalyzed by some molecules which are bound to the membrane [2].

The treatment below applies equally well to the case where the two phases in the two compartments are both gaseous or both liquid, provided that in the latter case both compartments are filled with solvent and that the two volumes cannot change. We will refer to the number of moles of chemical A per unit volume as the *density* of A (ρ_A), if A is either a gas or a solute (in the latter case, provided that the whole compartment is filled with solvent, ρ_A coincides with the molar concentration of A).

In Sec. II we present a specific model of a simple system of this kind, which will be used to investigate its possible behaviors. However, as it will be apparent from the analysis, the phenomenon described below is independent from the details of the model. The main results of the analysis of Sec. II are the following.

Let us consider a closed system and an initial state with equal densities of each chemical on both sides of the membrane. If the densities are exactly those corresponding to the values at chemical equilibrium, they of course remain unchanged. But if they differ from those values (while being equal for each chemical on both sides) and if the volumes of the two compartments are different, then an interesting phenomenon takes place, i.e., a transient density difference is established across the membrane. This difference eventually vanishes but, depending upon the values of the parameters, it may last for a relatively long time. While the buildup of a concentration difference in a previously homogeneous situation might seem at odds with the second law, it actually is not so, since the initial concentrations of the chemical reactions in the bulk are initially not at equilibrium. Therefore the entropy increase associated with the advancement of the reactions allows compliance with the second law.

If the larger compartment is not isolated, but there is a mass flow, then the density difference does not vanish but it rather persists in the steady state. The density of nonpermeating chemicals is higher within the smaller compartment, therefore providing a means to concentrate them, which may lead to relevant applications.

Applications to chemical reactors are quite straightforward, but we will briefly comment here on a possible nonobvious application to the problem of the origin of life (briefly, OoL). Vesicles in water are composed by a lipid bilayer which surrounds an aqueous interior: They display interesting physical phenomena [2,4] and, since they can spontaneously fission, they are believed to be important for the study of

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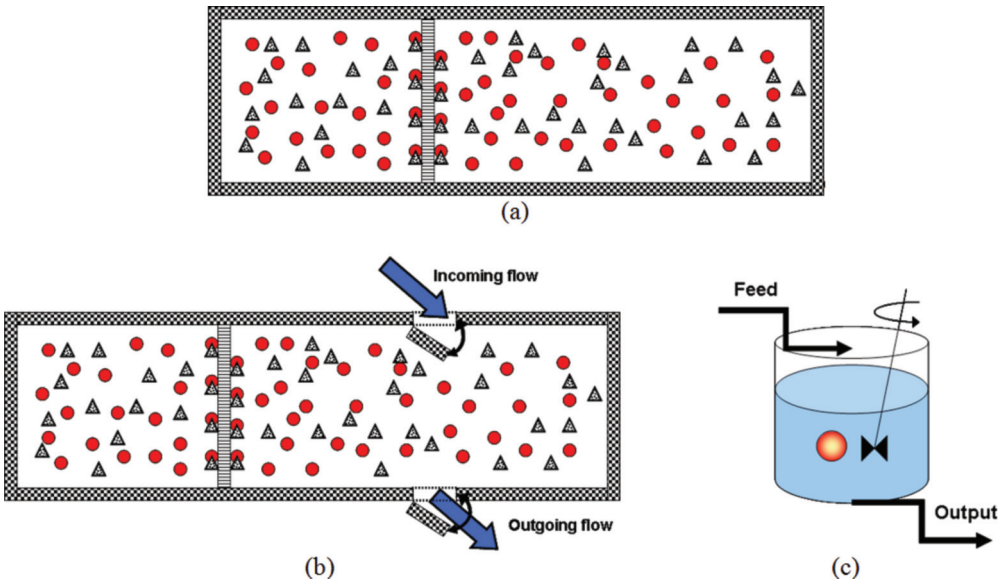

FIG. 1. (Color online) (a) A schematic view of the two-compartment system, where it is possible to observe the presence of two different chemicals (represented by circles and triangles), interacting near the semipermeable membrane; the triangles cannot pass through the membrane. (b) The same, where one of the two compartments can exchange matter with the environment. (c) A particularly interesting two-compartment open system: a vesicle inside a continuously stirred tank reactor.

the origin of life [5,6] as well as for possible applications of protocells [3,7–10].

It would be important to be able to concentrate chemicals in vesicles with respect to the external phase [11]: Indeed, the presence of a concentration difference across the membrane corresponds to a high energy state [12], which may be coupled to other chemical reactions (as it happens, e.g., in photosynthesis [13]). If the concentration of some chemicals is higher within the vesicle, then one may achieve very effective chemical processing (synthesis, degradation, removal). Moreover, a more speculative possibility is that the high inner concentration of chemicals might allow the formation of large autocatalytic reaction sets. There are indeed theoretical arguments in favor of the spontaneous development of such cycles [14], but they are very difficult to achieve experimentally: A possible explanation for this difference between theory and experiments might be that the concentrations of some key components in the bulk are too low, but this problem might be mitigated in a vesicle.

In Sec. II we will introduce the model, and show its behavior. In Sec. III we will comment on the generality and relevance of the phenomenon.

II. THE MODEL

Let us consider a two-compartment system like that of Fig. 1, and let V' and V be the volumes of the two compartments ($V \gg V'$). Let S be the surface of the membrane which separates the two compartments. We consider below two cases, one where the system is isolated and one where the larger compartment can be crossed by a constant mass flow.

Let us suppose that a chemical reaction takes place on both sides of the membrane surface, both inside and outside: For the sake of simplicity let us initially consider a unimolecular reaction $A \leftrightarrow X$. Therefore, all the reactions take place in a small "effective volume" $V_r \approx S\delta$ near the surface. The direct and reverse kinetic constants are such that formation of X is favored. Reactant A can cross the membrane—φ being its flow rate and D its diffusion coefficient across the membrane—while X cannot (it would be easy to introduce a small diffusion coefficient of X as well).

Let ρ and Q denote, respectively, the densities (moles/liter) and the quantities (moles) of A and X, using a superscript to indicate the chemical species and a subscript the compartment (i denoting the smaller one, e the other one), so, for example, Q_i^A is the number of moles of A in the smaller compartment. Diffusion time both in V and V' is supposed to be negligible, so the densities equal the ratios of the quantities to the corresponding volumes; therefore

$$\begin{aligned} \rho_i^A &= \frac{Q_i^A}{V'}, \quad \rho_e^A = \frac{Q_e^A}{V}, \\ \rho_i^X &= \frac{Q_i^X}{V'}, \quad \rho_e^X = \frac{Q_e^X}{V}. \end{aligned} \tag{1}$$

In order to ease the exposition we will often refer to the smaller and larger volumes as the internal and external one, respectively (this is reminiscent of the vesicle case but, at an abstract level, internal just means smaller).

We also allow A (not X) to enter the external compartment: If F denotes the constant volume flow, the quantity of A which enters the external compartment is $F\rho_{ext}^A$, while the quantities of A and X which leave it are, respectively, $F\rho_e^A$ and $F\rho_e^X$. If the system is closed, of course $F = 0$.

Using the above notations, the flow of A across the vesicle membrane is

$$\varphi = DS\left(\rho_i^A - \rho_e^A\right), \tag{2}$$

where D is the diffusion coefficient of chemical A across the membrane whose surface area is S.

Assuming that the reaction is first order, by imposing mass conservation one obtains the following rate equations for the internal and external quantities of A and X:

$$\begin{aligned}\frac{dQ_e^A}{dt} &= -(kV_r + F)\rho_e^A + k'V_r\rho_e^X + \varphi + F\rho_{ext}^A \\ \frac{dQ_e^X}{dt} &= kV_r\rho_e^A - (k'V_r + F)\rho_e^X \\ \frac{dQ_i^A}{dt} &= -kV_r\rho_i^A + k'V_r\rho_i^X - \varphi \\ \frac{dQ_i^X}{dt} &= kV_r\rho_i^A - k'V_r\rho_i^X\end{aligned} \tag{3}$$

In the case of a closed system ($F = 0$) one can compute the equilibrium values and, if the initial conditions coincide with those values, no change is of course observed. Suppose now that the initial densities of A and X are the same in the two compartments but that they do not coincide with the equilibrium values,

$$\frac{\rho_i^X}{\rho_i^A} = \frac{\rho_e^X}{\rho_e^A} \neq \frac{\rho_{eq}^X}{\rho_{eq}^A}. \tag{4}$$

In this case one observes (Fig. 2) an increase in the inner density of X which, depending upon the parameters, may be high, and may also last long.

Simulations show that the value of the ratio $\frac{\rho_i^X}{\rho_e^X}$ at the peak of ρ_i^X is inversely proportional to V'/V: If the "small" compartment were a vesicle, this would allow a possible independent estimate of its volume. If we assume spherical vesicles also the surface S is thus determined. It has also been observed that the duration of the transient (defined, e.g., as the time elapsed from the beginning of the simulation until the moment when the two curves showing the values of ρ_i^X and ρ_e^X versus time embrace 95% of the total area between them) depends upon the value of DS. This remark, combined with the previous one, provides a way to estimate the value of the diffusion coefficient D.

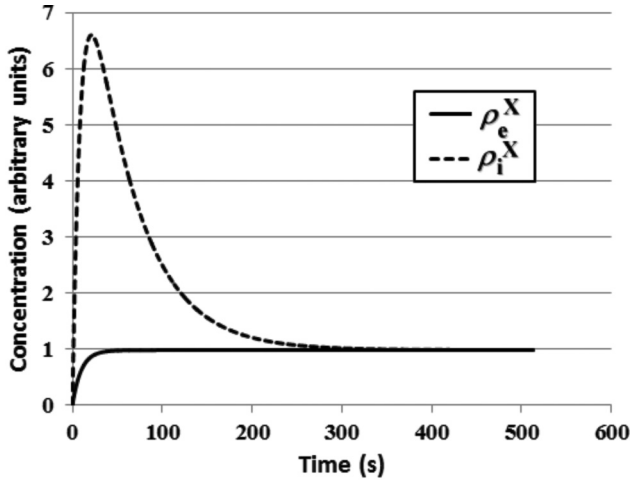

FIG. 2. Internal and external densities of X versus time, closed system. The curves represent the outcome of a numerical integration of Eq. (3), using a Euler method with step size control.

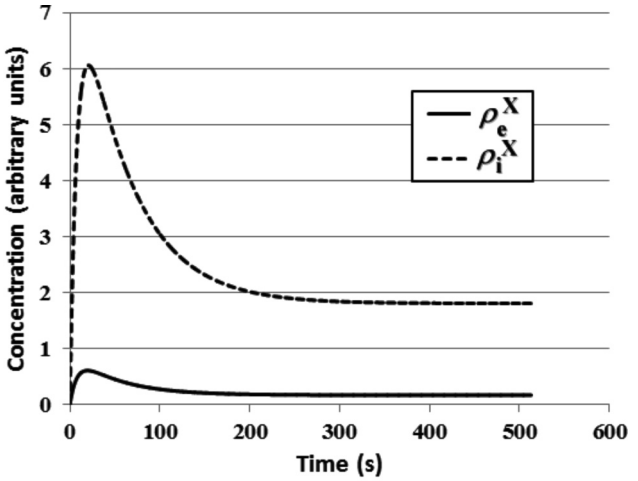

FIG. 3. Internal and external concentration of X versus time, open system. The curves represent the outcome of a numerical integration of Eq. (3), using a Euler method with step size control.

Let us now consider the case of a nonisolated system, where $F \neq 0$. In this case it can be analytically proven that at steady state the internal concentration of X is larger than the external one, and in particular that

$$\begin{aligned}\bar{\rho}_i^A &= \bar{\rho}_e^A, \\ \bar{\rho}_e^X &= \frac{kV_r}{(k'V_r + F)}\bar{\rho}_e^A < \bar{\rho}_i^X = \frac{k}{k'}\bar{\rho}_e^A,\end{aligned} \tag{5}$$

where a bar denotes asymptotic (steady-state) values. A simulation is shown in Fig. 3.

Note that the ratio of the asymptotic values of the two concentrations depends only upon the kinetic constants, the incoming flow rate, and the effective reaction volume V_r:

$$\frac{\bar{\rho}_i^X}{\bar{\rho}_e^X} = \frac{(k'V_r + F)}{k'V_r}. \tag{6}$$

From Eq. (5) we also obtain

$$V_r = \frac{F}{k'}\left(\bar{\rho}_e^A\frac{k}{k'\bar{\Delta}_\rho} - 1\right), \tag{7}$$

where $\bar{\Delta}_\rho \equiv \bar{\rho}_e^X - \bar{\rho}_i^X$.

In a proper experiment it would therefore be possible to determine the effective reaction volume V_r from the measurement of the asymptotic concentration difference.

III. CONCLUSIONS

The fact that a membrane is permeable to one chemical but not to the other might be due to different chemical properties, but it might also be related to the size of the molecule (if the membrane has pores). Since it might be questionable to consider only a unimolecular reaction where A "becomes larger" when it is converted to X, we have also analyzed the case of a bimolecular reaction $A + A \leftrightarrow X$. The behaviors observed in this case are closely similar to those of the previous one, described in Sec. II.

We have also analyzed in a similar way the case of a reaction $A + B \leftrightarrow X + Y$, considering different hypotheses about the permeability of reactants and products, again confirming

the behaviors observed in the simpler model. It is worth noting that the concentration effect at steady state ($F \neq 0$) of nonpermeable products may be indeed very large.

A perhaps surprising remark is that the model described by Eq. (2) is actually linear: Therefore the onset of a concentration difference cannot be considered a nonlinear effect (although it is observed also when nonlinear kinetic equations are considered).

While the phenomenon has been discussed here in a model, it is likely to be real and experimentally verifiable. Indeed, the mechanism which leads to the breaking of the initial equality of internal and external concentrations is that, since reactions take place on the vesicle surface, the same quantities of chemicals per unit time react on both sides of the membrane. But the internal and external volumes are different, and therefore the internal and external concentrations become different. This is essentially independent from the details of the specific kinetic model used.

The equations in our system (3) are based on Fick's law, so they are essentially those of classical irreversible thermodynamics, that is known to be valid on a suitable space and time scale, that excludes very fast phenomena and very small distances [15]. Moreover, note that we assume instantaneous diffusion in the bulk in both the small and the large volumes. Therefore our analysis can be applied provided that there exists a time scale that is long with respect to the diffusion time (of chemicals in the water), long enough for classical irreversible thermodynamics to apply, and short with respect to the relaxation time of the transmembrane concentration difference (see, e.g., Fig. 3). The existence of such a time scale seems plausible in the case of vesicles, whose linear dimensions are in the range 0.1–10 μm.

It would be extremely interesting to investigate the phenomena involved in the process we describe on a shorter time scale. In order to do so we would need to resort to a different approach, such as, e.g., the one of extended irreversible thermodynamics.

The assumption of instantaneous diffusion of the chemicals in the bulk of the two compartments is certainly a simplification, but behaviors similar to those of Sec. II are to be expected even if finite diffusion times are considered and have been observed in a cellular automata model [16], provided that they are faster than transmembrane diffusion.

In a multiphase system, increased concentration of a chemical in a particular phase according to its partition coefficient is of course a well-known phenomenon [17], but here it arises between two phases with the same physic-chemical properties. It should also be noticed that it is not due to active transport. Therefore the appearance of concentration gradients seems surprising, although, as we have seen, it does not violate the second law due to the coupling with chemical reactions and diffusion. In these systems concentration gradients may lead to transient interesting effects, while in a flow reactor the gradients are stable and therefore they can provide an energy source driving chemical reactions which might have been otherwise impossible.

It is also interesting to notice that the system described above should be amenable to experimental testing; in this case, as has been discussed in Sec. II, experimental measures of the values of the internal and external density of X could allow an independent estimate of the vesicle geometrical properties, of the diffusion coefficient, and of the effective reaction volume.

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