

Stable spatially periodic patterns of ion channels in biomembranes

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Ion flow through channels in a membrane may cause lateral gradients of the electrical potential which give rise to electrophoresis of charged channels. Coupled dynamics of the channel density and of the voltage across the membrane together with a binding-release reaction for the proteins leads via a pattern forming instability into a spatially periodic channel density. We derive near the onset of the spatial periodic pattern a Ginzburg-Landau equation and determine the parameter ranges with continuous transitions to periodic patterns. Above such a continuous transition the periodic patterns are stable within a wave-number band and within a finite range of the control parameter.

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I. INTRODUCTION

Spatiotemporal pattern formation is ubiquitous in systems driven away from thermal equilibrium [1,2]. Many of those structures are of universal character. Membranes represent a main structural component for the complex architecture of biological systems. A basic question of biophysics is how far they contribute to the pattern formation in cells in early development and in learning processes of adult organisms. This aspect has been neglected in the extensive discussion of biological morphogenesis [3].

Two central physical ideas in the field of biomembranes are the fluid-mosaic concept [4], which assumes that protein molecules are free to diffuse along the fluid bimolecular layer of lipid, and the channel concept [5], which implies that the conductance of membranes is made up of discrete ion channels formed by protein molecules. It was found that a fluid-mosaic of ion channels has an intrinsic propensity for self-organization [6]. When a concentration gradient of salt across the membrane exceeds a certain threshold, a conserved number of freely movable ion channels may organize into metastable periodic patterns which finally evolve into global clusters [7-9].

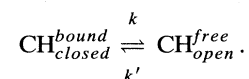
The model of a fluid-mosaic of ion channels neglects two important properties of real biomembranes: (a) An interaction with signal molecules may induce a reversible molecular transition which opens or closes an ion channel [5], and (b) an interaction with the cell skeleton may immobilize ion channels [10]. As a first step towards a more complete treatment of self-organization in membranes we consider here an extension of the original model which accounts for immobilization and for closing of ion channels. For the sake of simplicity we choose a model which integrates the two processes: We take into account a reversible binding-release reaction of ion channels with the cell skeleton and assume that this interaction induces a closing of the channels. We find that the mobile molecules may self-organize again, however, with qualitatively new features: (a) stable periodic patterns are formed above threshold; (b) this formation of stationary periodic patterns belongs to the same universality class as, for example, convection rolls in hydrodynamic sys-

tems; (c) the transition into the periodic pattern is of first or second order depending on the equilibrium constant and the relaxation time of the binding-release reaction.

II. SYSTEM

We consider a membrane which separates a thin layer of electrolyte from the electrolytic bath as in a planar cable (Fig. 1) [11]. This geometry may refer to two biological situations. (i) A cell membrane is in close contact to another cell. The thin layer is given by the extracellular cleft and the bath is the cytoplasm. A particular important example of this case is the post-synaptic membrane of a neuronal synapse. (ii) A membrane cable occurs in the dendrites and axons of neurons. In that case the narrow cylindrical cytoplasm plays the role of a one-dimensional cleft and the extracellular space plays the role of the bath.

Ion channels are embedded in the membrane. We assume that they interact with the cell skeleton in a reversible binding-release (BR) reaction (Fig. 1) and that binding closes the channels by a conformational change. We describe the reaction by a simple scheme with the two rate constants k and k' , i.e., by an equilibrium constant $K_{BR} = k/k'$ and a relaxation time $\tau_{BR} = (k + k')^{-1}$.



The free channels undergo Brownian motion along the membrane with a diffusion coefficient D . They have an electrical conductance Λ . The channels are selective for ions with an unequal distribution across the membrane described by a Nernst-type potential E . The proteins bear an electrophoretic charge q such that they move in a lateral electrical field. The current through the mobile channels and through a homogeneous leak conductance of the membrane affects the local voltage in the cleft. An inhomogeneous distribution of the channels gives rise to lateral gradients of the voltage. The mobile channels move in those fields by electrophoresis.

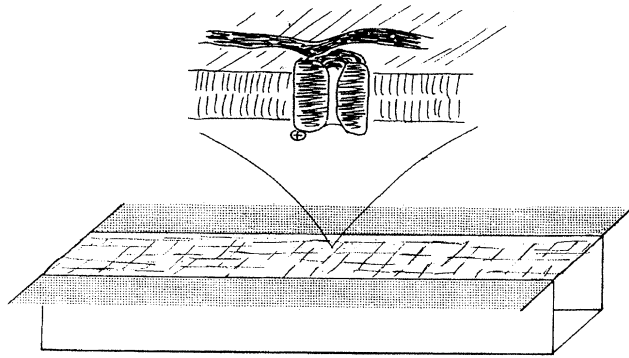


FIG. 1. One-dimensional membrane model. The fluid membrane separates a narrow cleft of electrolyte (in a groove) from a bulk electrolytic phase. Membrane proteins are embedded in the lipid bilayer (inset). They are mobile along the membrane (diffusion coefficient D), they form selective ion channels across the membrane (conductance Λ), they bear an electrophoretic charge q , and they interact with a filamentous substrate of the membrane (cell skeleton) in a binding-release reaction with rate constants k and k' . Binding closes the channels by a conformational change. The system is driven by a concentration gradient of those ions which are conducted by the channels (Nernst-type potential E). The geometry of the model refers to the biological situations of a cell-cell-contact (post-synaptic membrane of a synapse) and of a cylindrical cellular cable (neuron dendrite). The cleft of the model corresponds to the extracellular space in the first case, whereas it corresponds to the narrow cytoplasm in the second case. The structure of the model is described by the density of mobile channels $n(x,t)$ and by the voltage in the cleft $v(x,t)$ as a function of space x and time t .

A. Basic equations

The local density $n(x,t)$ of free open channels (particles per unit length) depends on the diffusion, on electrophoretic drift, and on the dynamics of the binding-release reaction. Assuming that the equilibrium density \bar{n} is kept constant by a homogeneous reservoir $\bar{n}_B = \text{const}$ of bound channels with $\bar{n} = K_{BR}\bar{n}_B$ we obtain

$$\partial_t n = D \partial_x \left(\partial_x n + \frac{q}{k_B T} n \partial_x v \right) - \frac{1}{\tau_{BR}} (n - \bar{n}). \quad (1)$$

The voltage v in the cleft is obtained from Kirchhoff's law for each element of the cable. Taking into account the current across the membrane and along the core of the cable we obtain the Kelvin equation with the membrane capacitance per unit length C , the resistance of the cleft per unit length R , and the leak conductance of the membrane per unit length G .

$$C \partial_t v = \frac{1}{R} \partial_x^2 v - G v - \Lambda n (v - E). \quad (2)$$

B. Scaled equations

We scale Eqs. (1) and (2) by introducing dimensionless coordinates for space $x' = x/\lambda$ and time $t' = t/\tau$ with the average range of an electrical perturbation $\lambda = [R(\Lambda\bar{n} + G)]^{-1/2}$ and the time constant of displacement $\tau = \lambda^2/D$. We use normalized variables for the particle den-

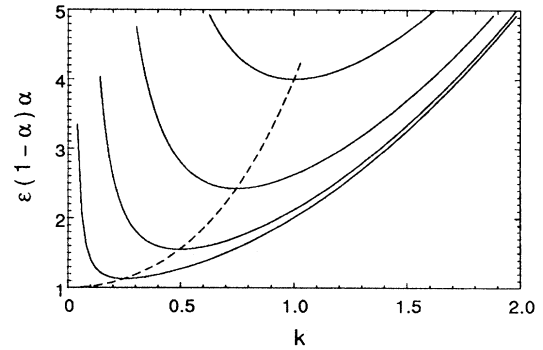


FIG. 2. The solid lines are the neutral curves $\alpha(1-\alpha)\epsilon_0(k)$ for different values of the rate parameter β and the dashed curve is the location of the minimum of these neutral curves as a function of β : $(k_c, \epsilon_c)(\beta)$.

sity $N = (n - \bar{n})/\bar{n}$ and voltage $V = (v - v_R)q/k_B T$ with the resting voltage $v_R = E\Lambda\bar{n}/(\Lambda\bar{n} + G)$. Introducing the normalized relaxation time $\tau_V = RCD$ we obtain the normalized reactive Smoluchowski-Kelvin equations

$$\partial_{t'} N = \partial_{x'} [\partial_{x'} N + (1 + N) \partial_{x'} V] - \beta N, \quad (3)$$

$$\tau_V \partial_{t'} V = [\partial_{x'}^2 - 1] V - \alpha(1-\alpha) \epsilon N - \alpha V N. \quad (4)$$

The dynamics of the system is controlled by three parameters: (i) the density parameter $\alpha = \Lambda\bar{n}/(\Lambda\bar{n} + G)$ which characterizes the equilibrium of the binding-release reaction; (ii) the rate parameter $\beta = \tau/\tau_{BR}$ which characterizes the dynamics of the reaction; (iii) the control parameter $\epsilon = -qE/(k_B T)$ which characterizes the distance from thermal equilibrium. Since the spread of the voltage is fast compared to the diffusion of ion channels we take $\tau_V = 0$ in the following. For simplicity the primes of the new coordinates x' and t' are suppressed in the following.

III. ONSET OF PERIODIC PATTERNS

We test the stability of the homogeneous equilibrium density $n = \bar{n}$ of the mobile channels ($N = 0$) against small perturbations. Therefore we transform the linear part of Eqs. (3) and (4) with the ansatz $(N, V) = (\delta N, \delta V) e^{\omega t} e^{ikx}$ and obtain a dispersion relation

$$\omega = -k^2 \left(1 - \frac{\alpha(1-\alpha)\epsilon}{1+k^2} \right) - \beta. \quad (5)$$

The homogeneous state becomes unstable against periodic perturbations of a wave number k when the real part of ω passes zero as a function of the control parameter ϵ . From the condition of vanishing real part $\text{Re}(\omega) = 0$ one obtains the neutral curve [1,2]

$$\epsilon_0 = \frac{1+k^2}{\alpha(1-\alpha)} \left(1 + \frac{\beta}{k^2} \right). \quad (6)$$

A set of curves $\epsilon_0(k, \beta)$ is shown in Fig. 2 for various values of the rate parameter β . The minimum of the neutral curve

defines the most unstable wave number $k_c(\beta)$ and the critical value of the control parameter $\epsilon_c(\alpha, \beta)$

$$k_c = \beta^{1/4}, \quad \epsilon_c = (1 + \sqrt{\beta})^2 / [\alpha(1 - \alpha)]. \quad (7)$$

For ϵ values above the curve $\epsilon_0(k, \alpha, \beta)$ the growth rate $\text{Re}(\omega)$ is positive and the homogeneous channel distribution becomes unstable against growing periodic perturbations with wave numbers lying inside the neutral curve. For $\beta > 0$ the pattern sets in with a finite wave number. This is in contrast to the earlier work [6–8], where the β parameter was neglected and the mode $k=0$ was most unstable. This difference is due to the fact that there exists now no conservation of the number of mobile ion channels due to the exchange with the reservoir of bound channel proteins.

IV. AMPLITUDE EQUATION

The properties of the structural transition may be evaluated in the neighborhood of the critical point (k_c, ϵ_c) via a perturbation expansion. It leads for the complex amplitude $A(x, t)$ of the critical mode

$$\begin{pmatrix} N \\ V \end{pmatrix} = \begin{pmatrix} 1 \\ E_0 \end{pmatrix} (A e^{ik_c x} + A^* e^{-ik_c x}) \quad (8)$$

with $E_0 = -(1 + \sqrt{\beta})$ to an equation, the so called amplitude or Ginzburg-Landau equation [12,1,2]

$$\tau_0 \partial_t A = [\eta + \xi_0^2 \partial_x^2 - \gamma |A|^2] A. \quad (9)$$

The small parameter η is the difference between the control parameter ϵ and its critical value ϵ_c : $\eta = (\epsilon - \epsilon_c) / \epsilon_c$. The relaxation time τ_0 and the coherence length ξ_0 can be derived by a Taylor expansion of the dispersion relation (5) around the critical point (k_c, ϵ_c) : $\tau_0^{-1} = (\partial \omega / \partial \epsilon)_c \epsilon_c$ and $\xi_0^2 = (1/2\epsilon_c)(\partial^2 \epsilon_0 / \partial k^2)$. The nonlinear coefficient γ determines the transition behavior into the periodic state (8) and can be calculated by an approach which is discussed, e.g., in Refs. [2,12,13]. This amplitude equation is rather universal and holds for stationary and continuous bifurcations with a critical wave number $k_c > 0$ as they arise, e.g., in thermal or electroconvection [1,2,14].

Stationary patterns on membranes

For the coefficients of the amplitude equation we obtain for the reactive Smoluchowski-Kelvin equation

$$\tau_0 = \frac{1}{(1 + \sqrt{\beta})\sqrt{\beta}}, \quad \xi_0^2 = \frac{4}{(1 + \sqrt{\beta})^2}, \quad (10)$$

$$\gamma = -\frac{1}{3} \left[\frac{6\alpha^2 - (2 + 2\sqrt{\beta} - \alpha)^2}{1 + \sqrt{\beta}} + \frac{2}{3\sqrt{\beta}} (4\sqrt{\beta} - 2\alpha + 1)(\sqrt{\beta} - 2\alpha + 1) \right]. \quad (11)$$

The linear coefficients depend on the rate parameter β only. For faster binding-release reactions the relaxation time and also the correlation length become smaller. The nonlinear

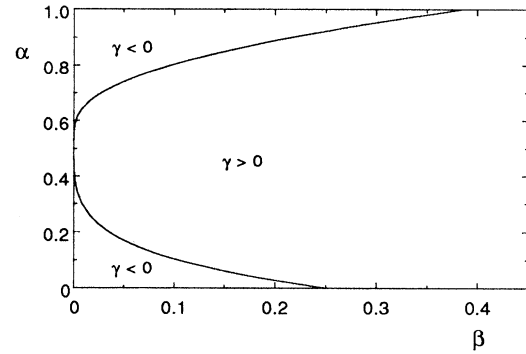


FIG. 3. The line separates in the β - α plane the areas where the bifurcation into the periodic state is of second order ($\gamma > 0$, supercritical) or of first order ($\gamma < 0$, subcritical).

coefficient depends on the rate parameter β and on the density parameter α . It is quite remarkable that the relaxation time of the pattern as well as the nonlinear coefficient γ both diverge for a frozen binding-release reaction ($\beta \rightarrow 0$).

In the regime $\gamma > 0$ the Ginzburg-Landau equation has stationary solutions for $\eta > 0$ with $Q = k - k_c$

$$A = F e^{iQx} \quad \text{with} \quad F^2 = (\eta - \xi_0^2 Q^2) / \gamma, \quad (12)$$

The amplitude is maximal in the center of the band of the instability and vanishes at the edges of the band $Q^2 = \eta / \xi_0^2$. This solution (12) exists for $\gamma > 0$ above threshold ($\eta > 0$), whereas it exists for $\gamma < 0$ only for $\eta < 0$. The latter can only happen in the case of a first order transition where the finite amplitude F^2 below threshold belongs to the unstable branch [1,2].

Supercritical and subcritical bifurcations are separated by the tricritical line $\gamma(\alpha, \beta) = 0$, which is plotted in Fig. 3. It is apparent that a phase transition of second order occurs only for nonzero values of the rate parameter β , while the transition is of first order for the frozen reaction $\beta = 0$ [8]. The type of phase transition for $\beta > 0$ and $\gamma > 0$ in the membrane belongs to the same universality class as the formation of rolls in thermal convection (see, e.g., [1,2]) or in electroconvection in nematic liquid crystals [14] where the amplitude equation (9) has the same form with different expressions for the coefficients, of course.

V. SECONDARY BIFURCATION

In order to test the solution given in Eq. (12) against small perturbations with arbitrary wave numbers (up to $q \sim k_c$), one has to start with the following ansatz into Eqs. (3) and (4):

$$\begin{pmatrix} N \\ V \end{pmatrix} = \begin{pmatrix} 1 \\ E_0 \end{pmatrix} 2A \cos[(k_c + Q)x] + \begin{pmatrix} N_p \\ V_p \end{pmatrix}. \quad (13)$$

The explicit form of the perturbation is $(N_p, V_p) = \exp[\omega t + iqx] \sum_{l=-M}^M (N_l, V_l) \exp[ik_c l x]$. Linearizing Eqs. (3) and (4) with respect to the small perturbations N_l and V_l and calculating $\omega(\eta, q, F, Q)$, one will recover by varying Q and keeping q small the Eckhaus instability

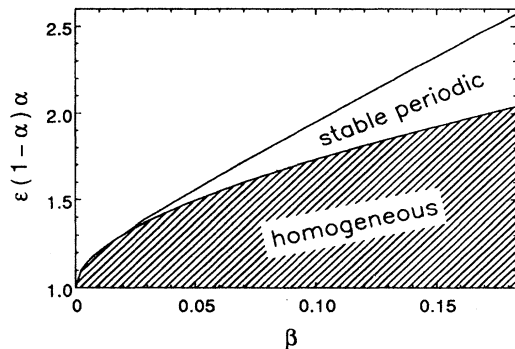


FIG. 4. At the upper curve $\epsilon_{sec}(\beta)$ the solution (12) taken at the bandcenter $Q=0$ becomes unstable against short wavelength perturbations. The β values, where $\epsilon_{sec}(\beta)$ meets the lower curve (threshold) and the nonlinear coefficient $\gamma=0$ vanishes ($\alpha=0.683$).

boundary (see, e.g., Refs. [1,2]). Keeping, e.g., $Q=0$ at the band center, for increasing values of η the dispersion relation $\omega(\eta, q, F, Q)$ exhibits a maximum at $q_m \sim k_c$ which becomes at some $\eta_{sec}(\alpha, \beta)$ positive. The curve $\epsilon_{sec}(\beta) = \epsilon_c(\beta)(1 + \eta_{sec})$ restricts the stability range for the periodic pattern and is plotted in Fig. 4. The instability occurring above $\eta_{sec}(\alpha, \beta)$ may lead to clustering or other complex spatial distributions of the ion channels (these details will be discussed in [15]). The stable η range of the periodic state (8) shrinks to zero at the line $\gamma=0$ in Fig. 3, where the bifurcation changes from a supercritical to a subcritical one.

VI. DISCUSSION AND CONCLUSION

Driven by a concentration gradient of ions across the membrane, mobile charged ion channels in membranes may

form patterns far from equilibrium. The gating of the ion channels by signal molecules and the immobilization caused by the cell skeleton leads to the formation of a periodic channel-density pattern, instead of channel-clustering discussed in previous investigations [8,9]. (While we have discussed for the sake of simplicity the integrated version of both interactions, patterns may also occur in the presence of one interaction alone.) The onset of the pattern may be of first or second order depending on the actual parameters, and in the range of second order transition there exists a sub-gime with stable periodic patterns. In two spatial dimensions the pattern formation is even richer, because competitions between various possible patterns may arise, such as between stripes, squares, or hexagons [15]. A structured cell skeleton and/or two different types of ion channels can lead to an even richer dynamics of the pattern, indicating that biomembranes may exhibit a rich manifold of patterns, depending on details of the biochemical interactions [15–17].

Considering the complicated interactions in biological systems, it might be difficult to distinguish patterns induced by our mechanism from conservative mechanisms of aggregation which are operative in a biological system. At a first step, well defined model membrane systems are needed, such as in Ref. [11], to verify these patterns. It seems worthwhile to accept the challenges of further investigations, especially with regard to the prospects of getting a biological membrane system available for quantitative investigations, which offers possibly alternative aspects of pattern formation as well.

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