Self-Gating of Ion Channels in Cell Adhesion

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(Received 13 November 1996)

When a cell membrane is attached to an inert surface, ionic current may flow from the bath along the narrow cleft between membrane and surface into the cell kept at constant potential. This current modifies the voltage across the membrane due to the voltage drop in the cleft. As a result, the conductance of voltage-gated ion channels is affected. By positive feedback, smooth gating is transformed into switching with bistability, hysteresis, and memory as shown by cable theory. Self-gating in cell adhesion is triggered by minute modulations of the attachment or of the intracellular potential. [S0031-9007(97)03253-5]

PACS numbers: 87.22.Bt, 87.22.Jb

The electrical features of excitable biomembranes are discussed usually in the context of isolated cells embedded in an electrolyte on ground potential [1,2]. In a tissue such as a brain, however, nerve cells and glia cells are in close contact with each other. There the flow of current along the narrow extracellular space can affect the local extracellular electrical potential. As a consequence, voltage-dependent processes may be triggered in the adjacent membranes. Similar effects may occur in cell adhesion on an inert surface; e.g., mobile ion channels may undergo self-focusing by lateral electrophoresis and self-assemble to periodic patterns [3,4].

In this paper, a process of self-gating in cell adhesion is described: The current through weakly open channels affects the electrical potential in the extracellular space such that voltage-dependent gating of the channels is enhanced by positive feedback. Below a critical width of the extracellular cleft, a transition occurs between states of low and high conductance with features of a phase transition of the first kind.

We consider the situation of cell adhesion with the membrane attached to a planar inert surface as illustrated in Fig. 1(a). Such a system is particularly adequate with respect to an experimental test: The voltage in the cell can be controlled through a fused patch pipette, and the voltage profile in the narrow cleft can be observed by transistors integrated in a substrate of oxidized silicon [5,6]. First we describe a nonlinear cable equation for the adhesion region and the approximation of a point contact. Then we use the latter model to discuss the conditions of self-gating. Finally, some examples of the full-fledged cable theory are computed numerically.

Nonlinear sandwich cable.—The junction of a cell membrane with an inert surface forms a two-dimensional core-coat conductor [3,4]: A thin sheet of extracellular electrolyte is separated from the intracellular electrolyte by the insulating membrane. The edge of this sandwich cable is kept on bath potential. The voltage in the extracellular cleft is determined by the current flow along the cleft and across the membrane. Kirchhoff's law applied to each infinitesimal area element leads to a two-dimensional Kelvin equation for the voltage $V_J(x,y,t)$ in the junction as a function of the coordinates x, y and of time t [3]. We consider here only the stationary state and omit capacitive currents. If the junction is homogeneous with a distance d_J of membrane and surface and with a specific resistance ρ_J (resistance times unit length) in the cleft, we obtain Eq. (1) with the Laplace operator Δ, the specific conductance g_{JM} of the membrane (conductance per unit area), the reversal voltage V_0 of ion-selective channels, and the intracellular voltage V_M,

$$\frac{d_J}{\rho_J}\Delta V_J + g_{JM}(V_M - V_J - V_0) = 0\,. \qquad (1)$$

The conductance g_{JM} is assigned to voltage-gated ion channels. It depends on the voltage drop $V_M - V_J$ across the membrane. We describe the gating by a Fermi-type function according to Eq. (2) [2,7] with a maximum conductance g_0 and a gating voltage V_G. The slope is controlled by the gating charge q_G at a thermal energy k_BT,

$$g_{JM} = \frac{g_0}{1 + \exp\left[-\frac{q_G}{k_BT}(V_M - V_J - V_G)\right]}\,. \qquad (2)$$

When we insert Eq. (2) into Eq. (1), we obtain a nonlinear cable equation.

Gated point-contact model.—We approximate the two-dimensional cable by the model of a "point contact" described by the circuit of Fig. 1(b) [8]. The state of the junction is given by the voltage V_J in the junction, a global conductance G_{JM} of the membrane, and a global resistance R_J of the cleft. Kirchhoff's law leads to Eq. (3) which replaces the cable equation Eq. (1). The global parameters G_{JM} and R_J are given by Eq. (4) for a circular shape of the junction with radius a_J [8], taking into account the voltage-dependent gating of Eq. (2),

$$-\frac{1}{R_J}V_J + G_{JM}(V_M - V_J - V_0) = 0\,, \qquad (3)$$

$$R_J = \frac{\rho_J}{5\pi d_J}\,, \qquad G_{JM} = g_{JM}a_J^2\pi\,. \qquad (4)$$

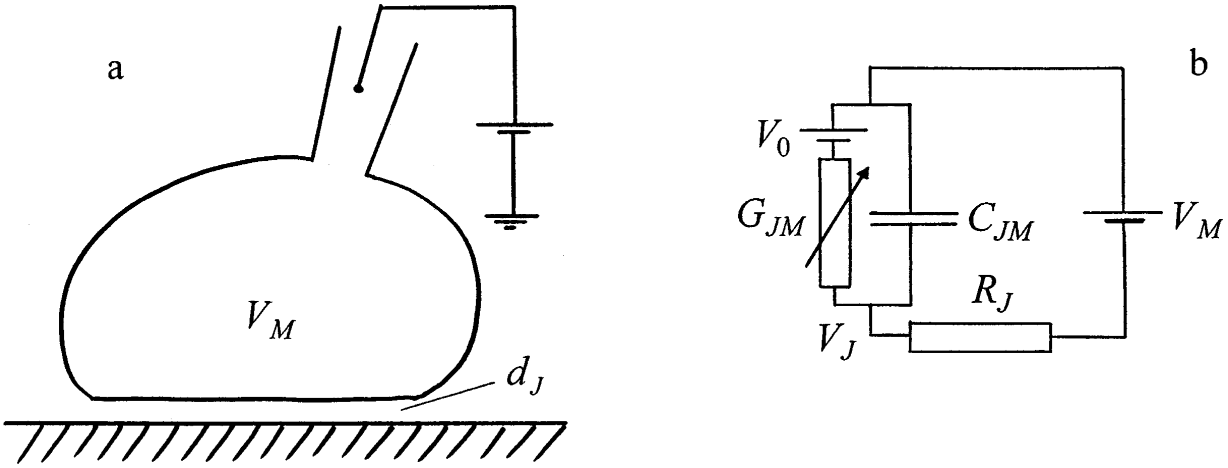


FIG. 1. Cell adhesion. (a) Cell attached to an inert surface: The width of the narrow cleft between membrane and surface is d_J. The interior of the cell is kept at a constant voltage V_M with respect to the bath using a fused electrode. (b) Point-contact model: The parameters are a capacitance C_{JM} and a conductance G_{JM} of the membrane, a reversal voltage V_0 of the conductance, and a resistance R_J of the cleft. The cell is kept at a voltage V_M. The voltage in the junction is V_J. The conductance G_{JM} depends on the voltage drop $V_M - V_J$ across the membrane.

We introduce dimensionless variables v, θ, δ, and y according to Eqs. (5): The membrane voltage V_M is referred to the reversal voltage and scaled by the difference of gating voltage and reversal voltage. The gating charge q_G is scaled by a reference charge q_0, the distance d_J is scaled by a reference distance d_0, and the conductance G_{JM} is scaled by the maximum conductance G_0,

$$v = \frac{V_M - V_0}{V_G - V_0}, \tag{5a}$$

$$\theta = \frac{q_G}{q_0}, \qquad q_0 = \frac{k_B T}{V_G - V_0}, \tag{5b}$$

$$\delta = \frac{d_J}{d_0}, \qquad d_0 = \frac{\rho_J g_0 a_J^2}{5}, \tag{5c}$$

$$y = \frac{G_{JM}}{G_0}, \qquad G_0 = g_0 a_J^2 \pi . \tag{5d}$$

Using Eq. (3) with Eqs. (4) and (2), we obtain the conductance $y = y(v, \theta, \delta)$ as a function of voltage, gating charge, and distance. It is expressed implicitly by the roots of Eq. (6),

$$f(y) = 1 + \frac{1}{\theta} \ln \frac{y}{1 - y} - \frac{v}{1 + y/\delta} . \tag{6}$$

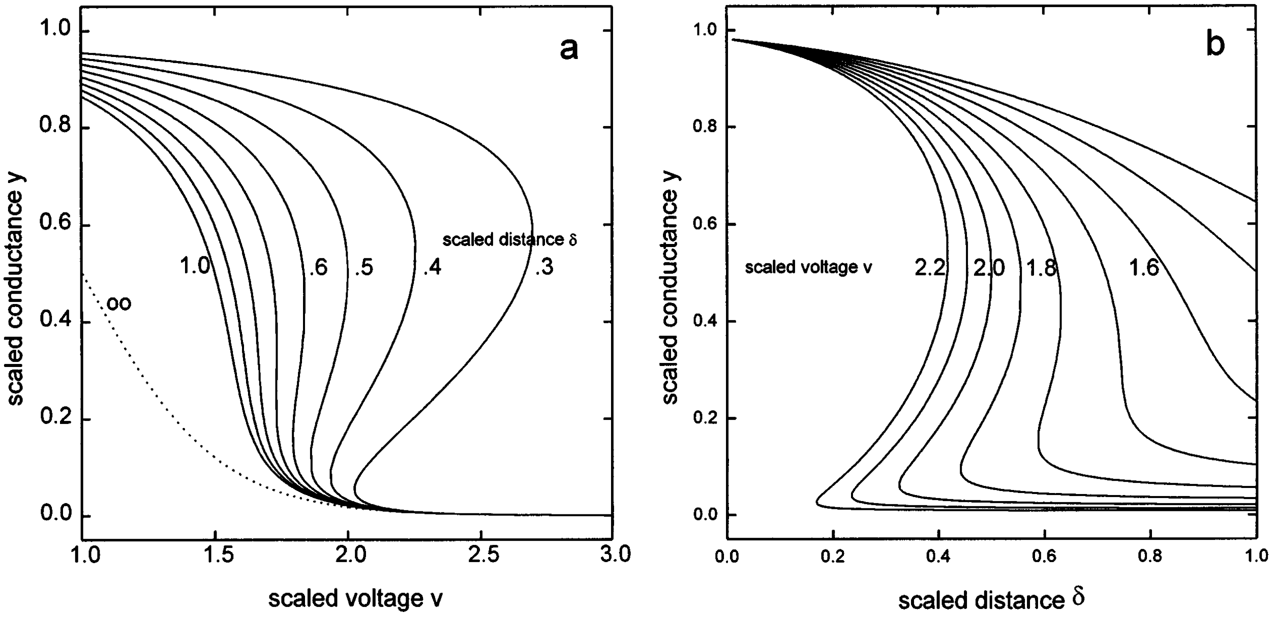


FIG. 2. Self-gating in the point-contact model. (a) Scaled conductance y plotted versus the scaled voltage v for scaled distances $\delta = 0.3-1.0$. The scaled gating charge is $\theta = -4$. The gating relation of a free cell with $\delta = \infty$ is marked as a dotted line. (b) Scaled conductance y versus scaled distance δ for scaled voltages $v = 1.4-2.2$.

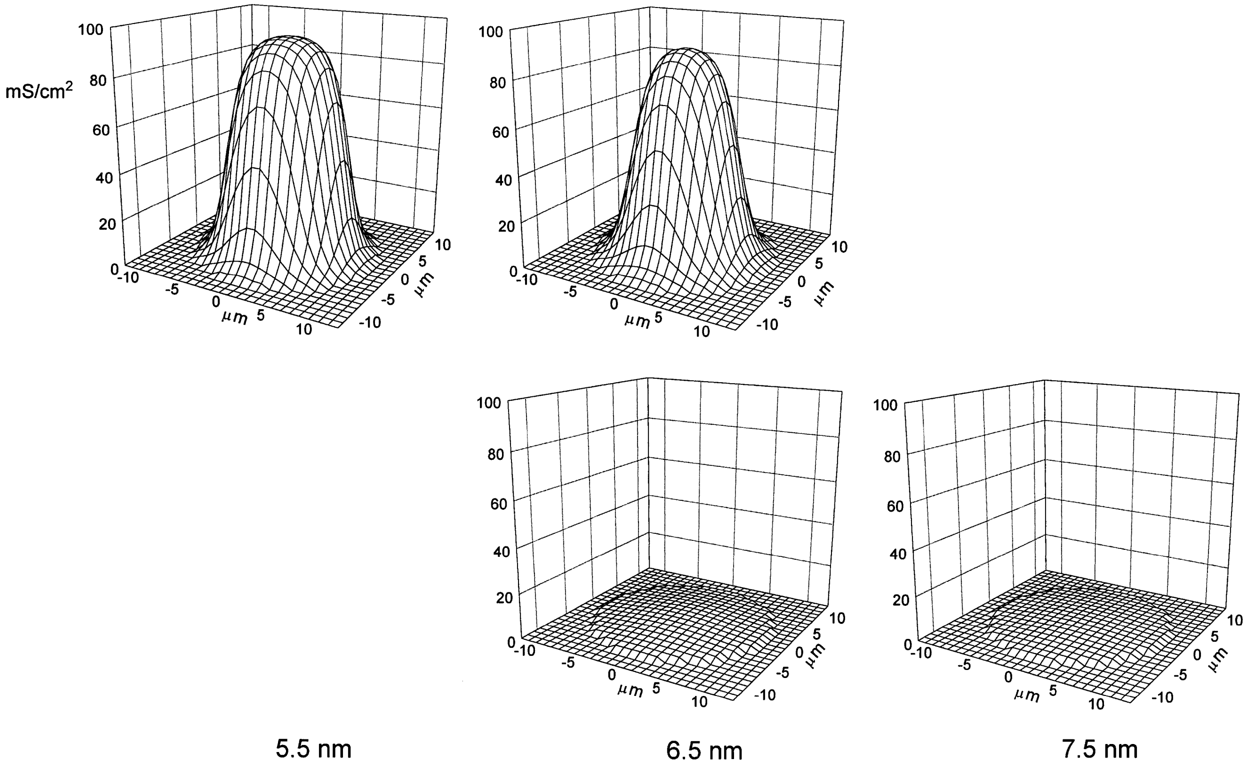
Isotherms.—We consider how the membrane conductance changes with the membrane voltage at constant distance and how the conductance is affected by the distance at constant voltage. We evaluate Eq. (6) using a Newton-Raphson algorithm [9].

(i) Voltage-triggered switch: The conductance y is shown in Fig. 2(a) as a function of the voltage v for various distances δ. We choose a gating charge $\theta = -4$. The relation $y(v)$ for a free membrane at infinite distance is marked as a reference: There the conductance increases smoothly with $y = 0.5$ at $v = 1$. When the distance becomes small, however, the conductance increases with a steeper slope at a higher voltage. Part of the applied voltage drops then in the cleft due to the flow of current. The remaining voltage drop across the membrane is closer to the gating voltage than in a free membrane. Below a critical distance the function $y(v)$ is S shaped. It resembles a van der Waals isotherm. When we lower the voltage—starting from a high value—the junction stays in a state of low conductance until we reach the left quasispinodal. Then the conductance jumps to a high value. When we enhance the voltage again, the system keeps its high conductance until we reach the right quasispinodal. Then the conductance jumps downwards. Adhesion transforms smooth gating into switching with hysteresis and memory.

(ii) Mechanoelectrical switch: Switching of conductance with hysteresis and memory is triggered also at constant voltage by an attachment and a detachment of the membrane. The function $y(\delta)$ is also S shaped, as shown in Fig. 2(b).

(iii) Parameters: Switching appears near a scaled voltage $v = 2$ and a scaled distance $\delta = 0.5$ for a scaled charge $\theta = -4$, as shown in Fig. 2. Let us consider ion channels with a reversal voltage $V_0 = +50$ mV and a gating voltage $V_G = 0$ mV. Switching becomes effective then at a membrane potential $V_M = -50$ mV [Eq. (5a)]. The gating charge is $q_G = +2e_0$ (e_0 elementary charge) at a temperature $T = 300$ K [Eq. (5b)]. At a maximum conductance $g_0 = 100\ \mathrm{mS/cm^2}$, a specific resistance $\rho_J = 100\ \Omega$ cm, and a radius $a_J = 10\ \mu$m, mechanoelectric switching occurs at a distance $d_J = 10$ nm [Eq. (5c)]. A higher extracellular resistance ρ_J caused by a protein matrix would enhance the critical distance. It is a crucial issue of the proposed theory that all parameters are in a range with can be attained in cell adhesion or in a biological tissue.

Profile of conductance.—We check the validity of the point-contact model by solving the nonlinear cable equation [Eqs. (1) and (2)] using an algorithm of simultaneous over-relaxation [9]. We consider the example mentioned in the previous section with a membrane



5.5 nm 6.5 nm 7.5 nm

FIG. 3. Profile of the membrane conductance g_{JM} in a circular junction with a radius $a_J = 10\ \mu$m for three distances between membrane and surface. At $d_J = 5.5$ nm the membrane is in a state of high conductance. At $d_J = 6.5$ nm there are two stable stationary states. At $d_J = 7.5$ nm the membrane is in a state of low conductance. The parameters are maximum conductance $g_0 = 100\ \mathrm{mS/cm^2}$, gating charge $q_G = 2e_0$, reversal voltage $V_0 = +50$ mV, gating voltage $V_G = 0$ mV, intracellular voltage $V_M = -50$ mV, and specific resistance $\rho_J = 100\ \Omega$ cm.

potential $V_M = -50$ mV. The stationary profiles of the conductance $g_{JM}(x,y)$ are shown in Fig. 3 for three different distances d_J. At $d_J = 7.5$ nm the conductance is rather low. At $d_J = 6.5$ nm we find a low conductance when we start the integration at a low conductance, but we find a high conductance when we start at a high conductance. The system is bistable. At $d_J = 5.5$ nm the conductance is high, independent on the starting conditions. The switching of the point-contact model is reproduced. We may compare the result of Fig. 3 with the isotherms of Fig. 2(b) at a scaled voltage $v = 2.0$. There the range of bistability extends from $\delta = 0.325$ to 0.5. The scaled distances of the example in Fig. 3 are $\delta = 0.275$ (high conductance), 0.325 (bistability), and 0.375 (low conductance). Thus the actual range of bistability in the two-dimensional cable is fairly close to that predicted by the simple point-contact model.

In conclusion, an instability may occur in cell adhesion if the membrane contains voltage-gated ion channels. The membrane conductance changes by orders of magnitude as triggered by minute changes of the intracellular voltage or of the distance to the surface. It is the purpose of the present paper to point out that the common physics of biomembranes implies such a transition with hysteresis and memory in the situation of cell adhesion. It has to be studied carefully whether the conditions for such a transition—with respect to the gating of ion channels and their reversal voltage—are given in a real tissue with nerve cells, glia cells, muscle cells or sensory cells, or in a real cell culture. It may well be that the spontaneous inactivation of voltage-gated channels [2,7] and the level of the reversal voltages in biological systems suppress this kind of self-gating. On the other hand, it is suggestive to study experimentally the physics of self-gating in adhesion. A genetically transfected cell may be adequate when it expresses an ion channel with appropriate gating voltage and reversal voltage.

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