Bionanotubes: the ultimate units of the physiology of life

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The cell membrane is the ultimate unit of the physiology of life. Its task is to confine ions and molecules on one side of the membrane and exchange them with others on the opposite side.

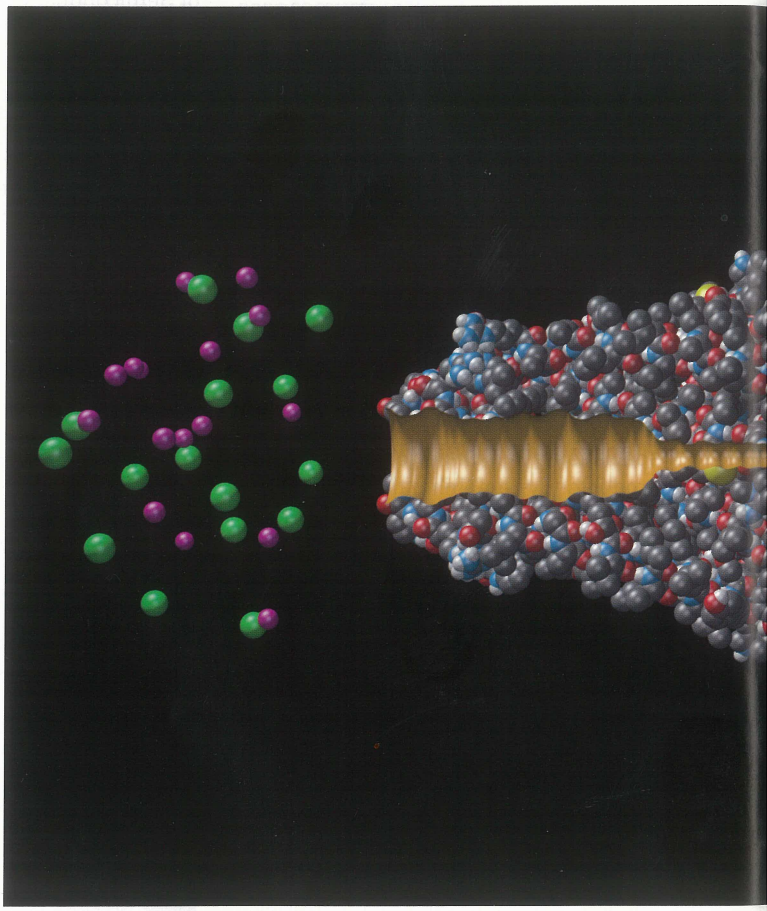
This delicate task of regulating the transport of ions across the membrane is carried out by biological nanotubes known as 'ion channels.' These channels are water-filled, angstrom-unit-sized pores formed by large protein molecules embedded in the cell membrane. They play crucial roles in the existence of living organisms. All electrical activity in the nervous system, including communication between cells and the effects of hormones and drugs, are regulated by the opening and closing of ion channels.

Because ion channels are elementary blocks of brain function, understanding their molecular workings represents a fundamental problem in biological physics. We now know that many inherited neurological, muscular, and renal disorders arise from the malfunctioning of ion channels. Among them are epilepsy, migraine, cystic fibrosis, and diabetes. Thus, elucidation of how ion channels work will ultimately help find the causes of, and potentially cures for, a wide range of inherited disorders.

In recent years, enormous strides have been made in our understanding of channels. These advances have come about by the combined efforts of experimental and computational biological physicists. In recent breakthroughs, the x-ray structures of several different types of ion channels have been determined. It is expected that crystal structures of many other ion channels will follow, ushering in a new era in ion channel research in which the main quest will be predicting the electrical function of channels from their atomic structures. Parallel to these landmark experimental findings, there have also been important advances in computational biophysics. Improved analytical methods have been matched by greater computational power, and theoretical models of ion permeation have become increasingly sophisticated.

We are now at the point where the atomic structure of an ion channel can be related to its function through the fundamental laws of physics governing electrolyte solutions. Macroscopically observable channel properties can be seen to emerge from simulations of the stochastic dynamics of aggregated molecules. Quantitative statements based on rigorous physical laws are replacing qualitative explanations of how ions permeate through the membrane's narrow pores.

Here at the Research School of Biological Sciences, we are making use of a powerful supercomputer to work out how ion channels operate. We are attempting to follow the motion of ions as they move through a channel, trying to understand how a channel can select only the correct type of ion to traverse it. How many ions can a single channel process per second, and how is the channel switched from closed to open?



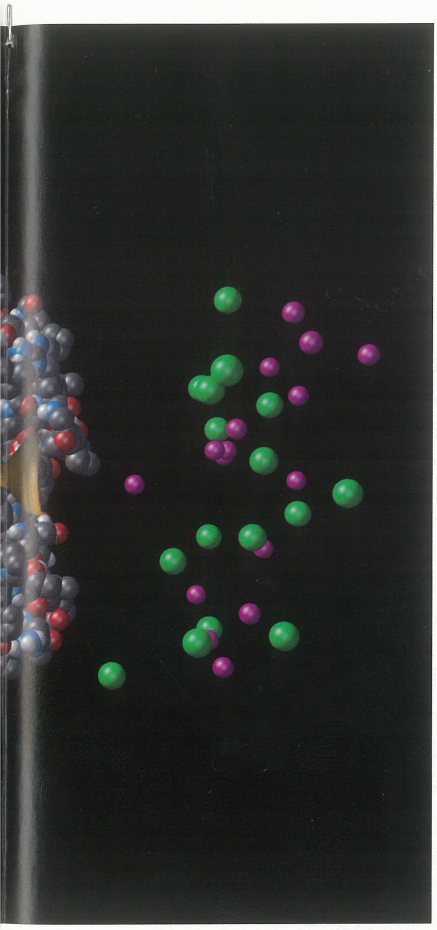
Structure of a potassium channel in a cell membrane, with the intracellular end to the left and the extracellular to the right. K^+ ions are shown as purple, and Cl^- ions as green. The narrowest segment of the conduit is known as the selectivity filter, and is only wide enough for water molecules and K^+ ions to form a single file. Dipoles formed from charged amino acid residues guard the inner and other channel gates.

In providing a comprehensive physical description of biological ion channels, theoretical biophysicists are using a judicious combination of molecular dynamics and stochastic dynamics. In classical molecular dynamics, trajectories of N particles – ions, water molecules and atoms forming the channel – interact via a many-body potential $U(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_N)$ and are followed using Newton's equation of motion,

$$m_i \frac{d^2\boldsymbol{r}_i}{dt^2} = -\nabla_i U(\boldsymbol{r}_1,\ldots,\boldsymbol{r}_N), \qquad i = 1, \ldots, N \qquad (1)$$

where m_i and $\mathbf{r}_i$ denote the mass and position of the i-th particle and where the force on it is given by the gradient of the potential U.

At every time-step, the potential function is recalculated using the new position of the particles and this determines their positions a short time later. This process is iterated over a large number of steps until a statistically satisfactory data set is generated. Although it is not tractable to simulate, through molecular dynamics, the current flowing across the model channel, we can use this technique to see how the ions and protein of the ion channel interact over small segments of the ion channel.



To compare measured channel conductances with those determined experimentally, we make use of Brownian dynamics. Here water molecules that form the bulk of the system are integrated out and only the ions themselves are explicitly simulated. The algorithm for performing Brownian dynamics simulations is conceptually simple. The position and velocity of each individual ion evolves according to a continuous-time stochastic dynamical system. The velocity of an ion with mass m and charge q located at a given position is determined by the force acting on it at time t. This velocity is computed by integrating the equation of motion, known as the Langevin equation:

$$m_i \frac{dv_t^{(i)}}{dt} = -m_i \gamma v_t + F_R + qE \qquad (2)$$

The first two terms on the right-hand side of the equation, the friction force and the random force, represent the effects of collisions with the surrounding water molecules. The last term denotes the total electric field arising from other ions, fixed charges in the protein, the membrane potential, and induced surface charges.

Together, these two computational tools play important roles in understanding ion channel permeation. They have proven to give a good picture of the relationships between the atomic structure of a channel and its experimentally measured properties. The figure shows the structure of an ion channel that selectively allows the passage of K^+ ions across the cell membrane. This is the first biological channel whose high-resolution x-ray structure has been determined.

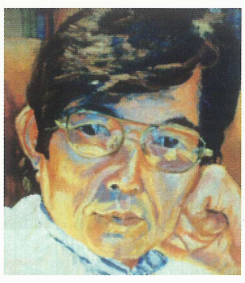
The channel is composed of 396 amino acid residues, or 3504 atoms excluding polar hydrogens. Making use of this structural information, we have used Brownian dynamics to determine how ions permeate through the conduit formed by the protein wall. We have also able to calculate the currents flowing through the channel under various conditions.

Because many negatively charged residues line the ion-conducting pathway, an attractive potential well for K^+ ions is created. Two K^+ ions are attracted by the energy well and form a stable equilibrium. When a third ion enters the pore under the influence of the membrane potential, the equilibrium of the resident ions is disrupted and the outermost ion is expelled from the channel through a rapid multi-ion shuttling process within the narrow segment of the pore. The magnitude of the currents flowing through the model channel, which we calculate from our Brownian dynamics, are directly comparable to the physiological measurements, giving some indication of the reliability and predictive power of the method.

Molecular dynamics calculations also have uncovered important aspects of ion permeation through the K^+ channel. They have shown (i) how the properties of water and ions change when they enter narrow channels from bulk; (ii) the way in which small molecules and toxins interact with ions channels; and (iii) how the channel allows K^+ ions to pass across while preventing smaller Na^+ ions from entering the pore.

The calculations reveal that the energetic cost of dehydrating K^+ ions is repaid by ion–protein interactions, whereas these interactions are too weak to balance the cost of dehydrating Na^+ ions. Molecular dynamics also provides the numerical values of the parameters that can be used for coarse-grained simulation techniques, such as Brownian dynamics and Poisson–Nernst–Planck theory.

As we attempt to further understand membrane channels in terms of fundamental molecular physics, we are finding that there is an increasing interplay between experiment and theory, the former providing hints and clues for building and refining models and the latter making testable predictions.



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