THE NEED FOR A KINETICS FOR BIOLOGICAL TRANSPORT

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ABSTRACT The traditional theory of transport across capillary membranes via a laminar Poiseuille flow is shown to be invalid. It is demonstrated that the random, diffusive nature of the molecular flow and interactions with the "pore" walls play an important role in the transport process. Neither the continuum Navier-Stokes theory nor the equivalent theory of irreversible thermodynamics is adequate to treat the problem. Combination of near-continuum hydrodynamic theory, noncontinuum kinetic theory, and the theory of fluctuations provides a first step toward modeling both liquid processes in general and membrane transport processes as a specific application.

In a current critical reexamination of the theory of biological membrane transport, we have been concerned primarily with the passage of small molecules through the pores presumed to exist in capillary walls. The traditional approach to this problem treats that passage as if it took place by a simple laminar Poiseuille flow. It is easy to show that such a model cannot be correct.

The traditional modeling assumes that cylindrical pores of diameter d penetrate the capillary membrane and the volume flow is given by Poiseuille's law and Starling's hypothesis that there is no flow when osmotic and hydrostatic pressures are equal (1):

$$Q = \frac{A_p d^2}{32\mu} \frac{(\Delta p - \Delta\pi)}{\Delta x}, \qquad (1)$$

where A_p equals the total are of pores equal to fA_0; A_0 equals the total surface area ($\approx$ 70 cm²/g in muscle); f equals the fraction of area covered by pores (0.001–0.004 estimated); μ equals the viscosity (0.01 g/cm-s for water); Δp equals the hydrostatic pressure drive; $\Delta\pi$ equals the osmotic pressure difference; $\Delta p - \Delta\pi$ equals the net pressure drive, about 10 mm Hg; and Δx equals the pore length. Δx equal to 250 Å to 1 μm are reported, here we use $\Delta x = 0.1$ μm. From this expression the pore diameter can be calculated; it is found to be about 80 Å in a variety of muscle capillaries.

From van't Hoff's relation for osmotic pressure, Fick's law for diffusive flow, and the Starling hypothesis the flow by diffusion can be derived:

$$Q = \frac{DA_pV_0}{RT\Delta x}(\Delta p - \Delta\pi), \tag{2}$$

where D equals the diffusion coefficient (2×10^{-5} cm^2/s for water); V_0 equals the molar volume (18 cm^3/mol for water); R equals the gas constant (8.3×10^7 erg/°K per mol); and T equals the absolute temperature (about 300°K).

The importance of diffusion through capillary membranes is generally discounted by computing the pore diameter for which diffusive and Poiseuille flows are equal. Thus, by equating Eqs. 1 and 2,

$$d = \left[\frac{32\mu DV_0}{RT}\right]^{1/2} \approx 7 \text{ Å}.$$

However, at the same time that the molecules are "flowing" through the pore, they are diffusing with respect to each other. Their random diffusive motions can be nearly described by a modified Stokes-Einstein relation

$$\overline{x^2} = \frac{2kT}{3\pi\mu r}t, \tag{3}$$

where k equals the Boltzmann constant (1.38×10^{-16} erg/°K), and r equals the molecular radius (about 1.5 Å for water). (The factor of 2 is a correction required because all the molecules have the same size.)

If a molecule flowing through a pore diffuses a distance greater than the pore diameter, then interactions with the pore walls becomes a dominating feature of the transport. To test this, compute the transit time t of a molecule being transported by Poiseuille flow

$$Q = A_p\frac{\Delta x}{t} = \frac{A_pd^2}{32\mu}\frac{(\Delta p - \Delta\pi)}{\Delta x},$$

where t equals the mean transit time. Then

$$t = \frac{32\mu(\Delta x)^2}{d^2(\Delta p - \Delta\pi)},$$

and, using $d \approx 80$ Å, $\Delta x \approx 0.1$ μm, $t \approx 5 \times 10^{-3}$ s so that, from Eq. 3, $(\overline{x^2})^{1/2} \approx 5 \times 10^{+4}$ Å. This diffusive spread is more than 500 times larger than the pore diameter and so the transport cannot be validly described by a simple laminar flow.

Others have suggested that the transport must be treated as a diffusive flow (2), but the course of research in this field has turned mainly to the application of irreversible thermodynamics to this problem (3). However, it can be shown (4) that the same limitations apply to the ranges of validity of both Poiseuille flow (based on the Navier-Stokes equations) and irreversible thermodynamics. The essence of the argument is that irreversible thermodynamics is derivable from the Navier-Stokes equations and thus cannot solve problems which the Navier-Stokes equations cannot solve.

The failure of Navier-Stokes theory to treat adequately the membrane transport problem can be attributed to its being a continuum theory. That is, for its consequences to be valid, a sufficiently large space (or number of molecules) *and* time must be available. For a 80 Å pore, the space is too small by about a factor of 3 (4). At best, a near-continuum theory can be used, with properly formulated boundary conditions. The foundations for such a theory exist. The classical kinetic theory of Maxwell and Boltzmann is adequate for gas flows. An extension of that theory is needed which will be applicable to the flow of liquids through narrow channels. By combining classical kinetic theory with classical fluctuation theory, we have begun that extension and have developed useful models for the transport coefficients in liquids and the boundary conditions at liquid-solid interfaces. The important role of ever-present fluctuations in producing transport coefficients and the related transport (diffusive, incoherent) processes and propagative (coherent) processes is becoming clearer. General liquid properties, equations of state, begin to emerge. The details of these investigations are the subject of a forthcoming monograph (4).

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