Thermal Diffusion as a Mechanism for Biological Transport

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Accumulated experimental information is used to assess the possible significance of thermal diffusion to mass transport in living matter. Possible thermal gradients across membranes, a single living cell, and an ensemble of such cells (*e.g.* an organ, tumor, etc.) are estimated. The corresponding model calculations, although not describing the biological process in detail, lead to conclusions about the possibilities for thermal diffusion as follows. Adequate thermal gradients to support substantial thermal diffusion could exist across biological membranes. Thermal diffusive flow would become significant when ordinary Fickian diffusion is sufficiently suppressed, *e.g.* in more concentrated systems near critical points of solution (*i.e.* near incipient phase separations). Conditions favorable to thermal diffusion functioning as a mechanism for active transport appear possible. Thermal diffusion appears much more important for transport into and out of an ensemble of cells than into or out of a single cell. Such mass transport by thermal diffusion could assume a sizable magnitude for an ensemble of cells with the dimensions of an organ or a tumor.

Background

Noting that early experiments evidenced unusual precipitation and transport phenomena in protein solutions subjected to temperature gradients [1], the present work is an attempt to assess the significance of thermal diffusion to mass transport in living matter.

On the one hand, it is well known that a temperature gradient operating over a physical system (solid, liquid, or gaseous) generally tends to cause a flow of matter. This phenomenon, termed thermal diffusion or the Soret effect [2], can cause a concentration gradient to build up in an initially uniform mixture. If the temperature gradient acts for a sufficiently long time, a steady state concentration distribution may be established, *viz.* the so-called Soret equilibrium. Both Soret equilibriums and moving boundaries, *i.e.* interfaces between solvent and solution and between solutions of different concentrations, have been used to determine thermal diffusion coefficients [3]. Thermal diffusion has been applied to practical problems, *e.g.* the gas phase separation of isotopes [4] and the liquid phase separation of macromolecules [5, 6]. Concomitant convection, an essential factor in some separation schemes as for example in Clusius-Dickel type columns [4], often remains a significant factor even in so-called convectionless thermal diffusion cells [7–9].

On the other hand, it is well known that the production and removal of heat are important to the functioning of any living organism. A special and rather dramatic example is the case of an overstressed marathon runner where rectal temperatures can rise from a normal 38 °C to 40 °C and even 45 °C (before death) with large changes in body chemistry and organ damage [10]. Some living organisms adjust to the temperature of their surroundings; others maintain a characteristic temperature within narrow limits independent of their surroundings. Irrespective of this, however, there are known to be local temperature differences in the interior of the organism. Local temperature gradients could exist in the interior of a cell or an ensemble of cells and across membranes of various types and in connective tissues, all being situations in which the viscosity is high and hence where convective flow is impeded. One could also expect temperature gradients on the surface of various organs, *e.g.* heart, liver, etc., and where there is

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extensive exposure to the surroundings as in the case of eyes and lungs. The local spatial variation in temperature is probably primarily caused by metabolic reactions but other chemical and physical processes could contribute. The circulation of blood introduces certain temperature differences between the moving liquid and the surrounding structures. Mechanical energy is dissipated as heat in the vicinity of moving joints. Local infections, inflammations, and other disorders produce locally exaggerated temperature variations. Tumors, for example, are known to have elevated temperatures and to cause temperature perturbations in their surroundings [11].

Proximity to phase separation often exists in living matter, *e.g.* inside a living cell. With this in mind, it is worth noting that considerable enhancement of the thermal diffusion effect has been observed under conditions of incipient phase separation in the vicinity of a critical point of mixing [6, 12–17]. This can be seen in the accompanying Figures 1a–c. There has been some discussion about the possible reasons for such enhanced thermal diffusion. Some experiments showed a tendency for the apparent magnitude of the thermal diffusion coefficient, D', to increase considerably when a critical point of mixing was approached [12, 14, 18]. On the other hand, some more recent experiments [16, 17, 19] seem to indicate that D' does not vary very much and that the increased thermal diffusion effects, *e.g.* solute redistribution when approaching Soret equilibrium, are mostly due to an increase in the Soret coefficient, *viz.* $\sigma = D'/D$, caused by a decrease in the Fickian diffusion coefficient, D (*cf.* Fig. 1a–c). Thus, this Soret coefficient would increase considerably in the vicinity of a critical point, even if D' stays almost constant, since for thermodynamic reasons D tends to zero at a critical point [14, 16, 20–23].

The flow equation for undirectional, non-convective mass flow in the presence of a temperature gradient for a two component system under quite general conditions can be written [3]

$$J = -D\frac{\partial c}{\partial x} - D'c\frac{\partial T}{\partial x}. \qquad (1)$$

Here J is the solute flux (*i.e.* mass of solute transported through unit cross-sectional area in unit time), c is the solute concentration (*i.e.* mass per unit volume), T is the temperature, x is the positional coordinate, and D and D' are the already mentioned Fickian and thermal diffusion coefficients, respectively. In general J is a function of both position, x, and time, t. With J everywhere equal to zero, *i.e.* under steady state (Soret equilibrium) conditions, integrating equation 1 between the positional limits x_a and x_b (which could correspond to the positions of the inner and outer interfaces of a membrane along a coordinate normal to its surface), while assuming a constant temperature gradient $\tau = dT/dx$ and constant coefficients D and D', gives

$$\frac{c_b}{c_a} = e^{-\sigma\tau(x_b - x_a)}. \qquad (2)$$

Whether solute accumulates at the lower or the higher temperature depends on the system through the sign of σ [24, 25]. Macromolecular solutes usually accumulate at the lower temperature [6, 7, 15], *i.e.* $c_b > c_a$ if $T_b < T_a$ (where T_a and T_b correspond to the positional coordinates x_a and x_b, respectively). This direction of solute redistribution implies $D' > 0$ since $D > 0$.

Assessment

In order to assess to what extent biological systems can maintain conditions required for significant thermal diffusion, a single living cell with heat removal at the surface by conduction only and an ensemble of cells, *e.g.* an organ of a tumor, again with heat removal at the surface by conduction only will be considered. The following calculations based on these models are not intended to describe the biological processes in detail but rather to give some numerical basis for estimating if conditions could exist under which thermal diffusion might play a role in biological transport.

The magnitudes of local temperature differences in living organisms are not known in much detail, but the total variation of temperature inside the human body, for instance, is to the order of 1 °C. Temperature differences of 0.5 to 1.0 °C have been measured in and around tumors [26]. Normal local temperature differences generally would probably be much smaller. In some recent measurements on enzyme systems of physically small dimensions by means of thermistors [27, 28] temperature variations circa 0.01 °C have been measured. The local temperature variations in a living cell could well be even less. Even though these temperature differences

are very small, they could, if operative over short enough distances, give rise to *temperature gradients* of sufficient magnitude to support significant thermal diffusive transport. A temperature difference of only 0.0001 °C across a 100 Å thick membrane, *e.g.* a bimolecular, "black", lipid type membrane, could cause a temperature gradient as high as 100 °C cm^{-1}. From laboratory experiments on thermal diffusion of electrolytes [24, 29], nonelectrolytes [12, 13, 21], and macromolecules [7, 15] in solution, one knows that even temperature gradients of only 1 to 10 °C cm^{-1} can cause measurable mass transport (or a redistribution of solute in the Soret equilibrium case). Thus, even allowing for the possibility that some convection within the membrane would lower the effective temperature gradient, it seems reasonable to conclude that vanishingly small temperature differences across biological membranes could still produce sufficient temperature gradients to support substantial thermal diffusion.

The possibility that thermal diffusion could function as a general mechanism for active biological transport, *i.e.* transport across a membrane from lower to higher concentration, is especially intriguing. To assess this possibility in terms of Eq. (2), T_a and T_b are selected so that $c_b > c_a$. The primary task is then to investigate under what conditions and to what extent the ratio c_b/c_a might be greater than unity. Substituting

$$\xi = -\sigma\tau(x_b - x_a) \tag{3}$$

in Eq. (2) gives

$$\frac{c_b}{c_a} = e^{\xi}. \tag{4}$$

Three parameters determine ξ and thereby also the ratio c_b/c_a, *viz.* σ, relating to the chemical and physical properties of the system; τ, the temperature gradient imposed externally or by internally generated heat; $\Delta x = x_b - x_a$, expressing the dimensional size of the heat and mass transfer path. The last two quantities can be combined for a not too extended system where, with $\Delta T = T_b - T_a$, $\tau = \Delta T/\Delta x$ is a good approximation. Then

$$\xi = \sigma\Delta T, \tag{5}$$

which leads to

$$\frac{c_b}{c_a} = e^{-\sigma\Delta T}. \tag{6}$$

Thus, as $|\sigma\tau(x_b - x_a)|$ or $|\sigma\Delta T|$ varies from 0.001 to 10, c_b/c_a will vary from 1.001 to 2.2×10^4 and the corresponding indications of possible active transport would vary from negligible to very large. The assessment now devolves to determining the maximum accessible values of $|\sigma\tau(x_b - x_a)|$ or $|\sigma\Delta T|$.

The Soret coefficient, σ, is usually much less than unity [7, 12, 13, 17, 29]. As already mentioned, however, it increases in the vicinity of the critical point of mixing; and so, values of the order of unity have been measured in solutions under these conditions [12, 17]. It could therefore be expected that in a set of experiments where the temperature is kept near the critical solution temperature, the Soret coefficient would show a marked increase as the concentration is increased towards the value corresponding to the critical point of mixing. There is some experimental evidence for this, *viz.* data for polystyrene in cyclohexane at 30 °C (Fig. 1a) indicate the Soret coefficient to be small at lower concentrations but to approximate 1.6 at higher concentrations where the system is almost in a state of incipient phase separation [17]. This observation could be fairly general, *i.e.* one could expect the magnitude of the thermal diffusion effect to be quite different in dilute and in concentrated systems, the more so the closer the critical conditions are approached. In this way, even assuming that the thermal diffusion coefficient does not increase, it is possible to calculate a value of the Soret coefficient around 10 in the immediate vicinity of the critical point temperature, T_c, for the system nitrobenzene/*n*-hexane [12, 14] as follows (with even higher values suggested for biological membranes).

Combining the thermodynamic observation that $D=0$ at $T=T_c$ with the finding from experimental data that dD/dT approximates $10^{-6}\,cm^2\,s^{-1}\,°C^{-1}$ in the vicinity of T_c gives $D = 10^{-8}\,cm^2\,s^{-1}$ for a temperature 0.01 °C above the critical. Further assuming that $D' = 10^{-7}\,cm^2\,s^{-1}\,°C^{-1}$, which seems a rather conservative lower limit [16, 19], then gives a Soret coefficient, *viz.* $\sigma = D'/D$, equal to $10\,°C^{-1}$. Values for D one and two orders of magnitude less than the just considered $10^{-8}\,cm^2\,s^{-1}$ have been determined for solutes in biological membranes [30–32], which is consistent with biological membranes being systems near phase separation and which also would increase σ to 100 and 1000, respectively. Assuming a rather small ΔT of 0.001 °C and applying equation 5, values for σ of 100 and

1000 give ξ equal to 0.1 and 1.0, which by equation 4 and 6 then give c_b/c_a equal to 1.1 and 2.7. This assessment thus indicates that c_b/c_a around 2 could be accessible and therefore that thermal diffusion could be a significant mechanism for active biological transport. If higher values of D' were operative, *e.g.* if D' increases in the vicinity of T_c, much larger values for c_b/c_a would become accessible. For instance, if the decrease in two orders of magnitude for D described above were matched by D' increasing one order of magnitude, c_b/c_a would grow to 2.2×10^4.

Now consider a single living cell with a temperature gradient across its surrounding membrane, this gradient being maintained by a balance between (a) the rate of heat production within the cell and (b) the rate of heat removal from the outer surface of the cell by conduction only. An estimate for the rate of heat production can be made from data on the bacterial cells *Escherichia coli* [36]. Production of protein constitutes about 90% of the energy balance of the cell. The average rate of production of protein molecules of 500 peptide bonds each is 1000 per second. With a bond energy of 174 kcal mol^{-1} and assuming a reaction efficiency of 50%, the maximum average rate of energy production in one cell is then to the order of 10^{-13} cal s^{-1}. If the volume of the cell is taken to be 10^{-12} cm^3, the energy source strength in the cell interior is 0.1 cal s^{-1} cm^{-3}, *i.e.* $10^{-13}/10^{-12}$. (If the entire energy production is assumed to occur in the mitochondria, the energy source strength there will be a thousand times greater or 100 cal s^{-1} cm^{-3}.)

In order to give a simplified assessment of the temperature gradient that could result from the above heat production combined with heat removal by conduction, the living cell will be approximated by a sphere of radius R with a homogeneous source strength A_0. This sphere is in contact with a surrounding medium having an energy source strength equal to zero and a heat conductivity K. Assuming spherical symmetry and no conductivity resistance at

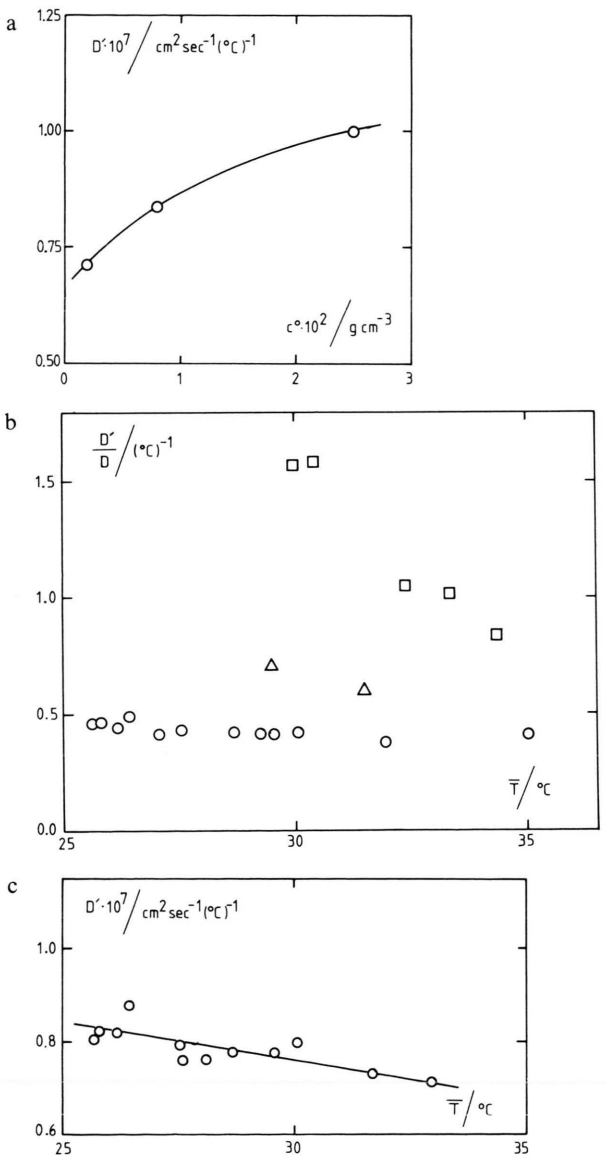

Fig. 1a–c. Fig. 1a shows experimental determinations [17] of the Soret coefficient, D'/D, for a sharp fraction of polystyrene, PS ($M \approx 400\,000$) in cyclohexane at various temperatures ($\bar{T}$ = average experimental temperature) in a 10 °C interval below the theta-temperature ($\theta \approx 34$ °C) for three different concentrations: ○ ~ 0.002 g cm^{-3}, △ ~ 0.008 g cm^{-3}, and □ ~ 0.025 g cm^{-3}. In separate diffusion experiments the ordinary free diffusion coefficient, D, was determined which allowed the thermal diffusion coefficient, D', to be calculated. Fig. 1b shows D' as a function of $\bar{T}$ for the lowest concentration (~ 0.002 g cm^{-3}). Fig. 1c shows D' as a function of initial (approximately average) experimental concentration for a temperature around 30 °C.

For the PS-fraction used, the critical point of mixing (maximum of phase equilibrium curve) in cyclohexane would be in the vicinity of 27 °C and probably located at a concentration 0.03–0.04 g cm^{-3}. Although the data shown must be considered preliminary they seem to indicate that (1°) the Soret effect increases considerably in the vicinity of a critical point and that (2°) the thermal diffusion coefficient shows similar tendencies but much less pronounced.

the surface of the sphere, the Fourier heat conduction equation can be integrated [37]. Giving the solution in terms of the radius vector, r, from the center of the sphere, one has for $r > R$, *i.e.* in the surrounding medium:

$$\tau = \frac{dT}{dr} = -\frac{A_0 R^3}{3K} \cdot \frac{1}{r^2} . \tag{10}$$

It follows from Eq. (10) that τ attains its largest value on the spherical surface, *i.e.*

$$\tau_{surface} = -\frac{A_0}{3K} \cdot R . \tag{11}$$

For a given energy source strength, $\tau_{surface}$ thus depends critically on the numerical values of K (the heat conductivity in the surrounding medium) and R (the size of the sphere). If the sphere, *i.e.* the cell, were surrounded by material, *e.g.* fat, with a heat conductivity similar to that of wax, which is very low, one finds for $A_0 = 10^{-1}$ cal s^{-1} cm^{-3} and $R = 10^{-4}$ cm (*viz.* the approximate size of an *Escherichia coli* cell) $\tau_{surface} \approx 0.3$ deg cm^{-1}. Considering a mitochondrion inside the cell, approximately the same value results if $A_0 = 100$ cal s^{-1} cm^{-3} and $R = 10^{-5}$ cm with water as the surrounding medium.

If structures larger than a single cell are considered much more favorable temperature gradients are obtained. Consider instead of a single cell an agglomerate of cells, *e.g.* an organ in the human body, a tumor, etc., surrounded by a medium having the same low heat conductivity as wax. Retaining the energy source strength of the single cell for the whole agglomerate, *i.e.* $A_0 = 10^{-1}$ cal s^{-1} cm^{-3},

$$|\tau_{surface}| \approx 300\, R . \tag{12}$$

For a sphere, *i.e.* an organ or a tumor, with a radius $R = 3$ cm one obtains $|\tau_{surface}| \approx 1000$ °C cm^{-1}, which is more than a thousand times greater than for a single cell. A conservative assumption that the effective wall thickness of such a cell ensemble is several orders of magnitude greater than the 10^{-6} cm thickness of bimolecular lipid membranes, *e.g.* 10^{-2} cm, produces a very favorable result in terms of the Soret equilibrium concentration redistribution. Putting $\sigma = 1$, $\tau = 100$, and $(x_b - x_a) = 0.01$ cm in Eq. (3) gives $\xi = 1$ and therefore $c_b/c_a = 2.7$ from Eq. (4). If σ increases to only 2.3 while the other parameters remain constant, c_b/c_a becomes 10, and with $\sigma = 10$, c_b/c_a grows to 2.2×10^4. Thus, this assessment indicates that cell ensembles such as organs and tumors could produce a physical situation favorable to significant mass transport, and even active mass transport, by thermal diffusion.

Concluding Remarks

From the simple models considered and from the present general knowledge about thermal diffusion this assessment indicates that at least in certain structures thermal diffusion could be an important mechanism for transport in biological systems. Under conditions where the ordinary Fickian diffusive flow is sufficiently suppressed thermal diffusion could even be a mechanism for active mass transport, *i.e.* transport from a low to a high concentration. As such, it could act as regulator and "lock in" or "lock out" specific substances relative to certain organs or regions, thus causing a redistribution of solutes across membranes at various levels of organization, and it could couple reactions occurring on opposite sides of such boundaries.

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