A PROPOSAL FOR A FORCE ESSENTIAL TO BIOLOGICAL ORGANIZATION

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A recent monograph on the kinetics of the liquid state as applied to transport [1] and an application of that monograph to hydrodynamic and diffuse flow in small channels (down to 15 Å) [2] have led my colleagues and me to some new ideas on the nature of the forces organizing the living state. In this highly speculative note, we would like to outline our view of the total reach of these ideas. While the outline may be wrong in some of its details, we believe the theme rich enough to deserve a hearing.

Thesis 1.—There are three simple well-known states of matter and a number of complex correlated states. The three simple states are the gaseous, liquid, and solid states. The complex states may be the vitreous, the living, the geochemical, and the plastic-elastic state. We wish to focus on the living state, which we believe to be a complex liquid-plastic state.

Thesis 2.—Within a current outlook, interaction in physics is limited to not more than four basic forces: the gravitational, electromagnetic, strong nuclear, and weak. Of these, possibly only two, the gravitational and electromagnetic, may be fundamental. A fundamental question of concern to the origin and character of life is whether these forces are sufficient to account for life and its self-organizing capability or whether new themes must be developed to deal with that state. We opt for the belief that life processes can be described by the known forces of physics and propose now to give that belief particular form.

Thesis 3.—Both the deviations from the ideal gas state (that is, descriptions that are immediately true for all real gases) and the transport properties of fluids are intimately tied up with the nature and spatial range of intermolecular forces. The forces are fairly well known (electrostatic and quantum mechanical exchange), being repulsive at a few tenths to 1 Å and attractive at levels greater than 1 Å. Nuclear forces, not interactive with intermolecular chemical forces, are expressed as

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form—they keep electrons and nuclei organized as discrete, slightly deformable bodies.

Chemically, these intermolecular forces relate to ionic and valence force bindings. They have the competence to organize structures as complex as organic biochemical molecules, for example, proteins and polynucleotides.

But physically, what are the forces that lead to biological organization? Can one travel the chain that bridges nonideal gas laws of state, to transport coefficients, to dynamic chemical moieties, to biological system dynamics?

Thesis 4.—Flow processes in liquids must be developed on an enriched kinetic base beyond gas kinetic theory [1]. We have proposed such a basis for processes of the order of a few atomic diameters (not one, but perhaps three diameters). Because of high-bulk modulus (low compressibility, e.g., $[\partial p/\partial \ln v]_T \approx 15{,}000$ atm), a molecule in the liquid phase is surrounded by a cage of about 20 neighbors. The escape of a molecule from that cage is somewhat more difficult than has heretofore been depicted. Loosely speaking, fluctuational interaction with all of its neighbors has to occur before an "escape" exchange can take place. But conversely, when that exchange does take place (i.e., as a Stokes-Einstein diffusional step), the ensemble process is near equilibrium. Thus, spacewise, a $3 \times 3 \times 3$ molecular array is near enough to thermodynamic equilibrium to be describable as a continuum hydrodynamic field. Timewise, near-equilibrium equations of state and of change will hold for macroscopic processes longer than these 20-odd fluctuations.

Thesis 5.—But there is a dilemma in describing flow boundary conditions at solid walls. It is already encountered in gas flow. In gases, Knudsen proved that boundary conditions required "slip" at the wall in a flow field rather than a vanishing relative velocity. The theory ties in and relates to studies, dating back to Maxwell, relative to momentum and energy boundary exchange between the incoming gas molecules and the wall. Energy and momentum are not conserved on each collision. Instead, there is a nonequipartition of energy that can be represented by a nonclassical statistical mechanical transport coefficient, the bulk viscosity. In general, collisions of liquid molecules with liquid molecules are marked by a nonzero bulk viscosity (expressed better as the bulk to shear viscosity ratio; this ratio is represented roughly by the *action* tied up in internal degrees of freedom relative to that tied up in translational degrees of freedom). On the other hand, the ratio of bulk to shear viscosity of a molecule striking the wall is likely of much greater magnitude. Since this is true for molecules striking the wall for both the gas and liquid state (the issue of equipartition being decided during the collision), there must be a similarity in boundary conditions in both cases. In the gas state, the boundary condition is now known to be the Knudsen slip.

We have "proved" an analogous process in liquids. There is a single molecular layer near the wall which essentially rolls along the wall. Thus, we have succeeded in developing a near-continuum fluid mechanics, as an extension of continuum fluid mechanics, analogous to Knudsen near-continuum slip flow but consisting of a near-continuum rolling boundary condition. This theory is thus good to cross sections that will admit five molecules (e.g., 15 Å nominally), namely, three molecules side by side to produce a continuum cell and two bordering molecules to match the solid boundary.

Thesis 6.—But this model only establishes an interesting fluid mechanics for liquids, analogous to near-continuum gas flow, and provides some commentary on the significance of bulk viscosity in describing intermolecular exchange, particularly with solid walls. It does not immediately establish its significance for biology.

However, we now add the tertiary structure of molecules in biology (see, e.g., [3]). First, atoms bond to form molecular chains. Second, there are polymeric chains formed in the polypeptide links of the so-called globular proteins. They can be reproduced, by translation, from helically wound and coded polynucleotides. Third, when expressed in watery milieu, these fibrous proteins ball up into globular form. We submit that this gets us on toward a dynamic mechanism, a Turing machine structure for life processes. (We offer no mechanism for the reproductive capability of nucleotide segments of DNA, although we suspect it may also be related to the rolling boundary conditions.)

In particular, we will consider those globular proteins that are incorporated into lipid bilayers are mosaic proteins.

Our particular postulate is that the living system is a state (as exhibited by the watery milieu bounding a lipid bilayer with its incorporated enabling protein mechanisms) *between the liquid and plastic which dynamically controls, in self-regulatory manner, the ratio of the bulk to shear viscosity of the boundary, and thereby provides a variable dynamic gate for major physical-chemical processes of life* (e.g., chemical reaction, admission, transmission, catalysis). A basic, if not the basic, organizing force for the living system is its self-regulatory control of the admission characteristics to cellularized structures. This systems principle, one level beyond local chemical reactivity, we believe is used over and over again to establish major operative processes of the living system.

Thesis 7.—We start by providing one illustration of such a process, transport out of capillaries (i.e., resulting in protein regulation of colloidal osmotic pressure and metabolite and electrolyte transports). We submit, first, that a calcium pump [4] bonds endothelial cells together against the hydrostatic pressure developed by virtue of an osmotic pressure difference (e.g., approximately 25 mm Hg due to protein production into the interior of the vascular circulation) to maintain a dynami-

cally critical separation (40 Å nominal) which acts as an appropriate diffusional gate for outborne and inborne fluxes. The significance of this critical separation between endothelial cells is that an appropriate fraction of the flow is brought with suitable diffusional velocity into rolling contact with the membrane walls. In particular, we ask that attention be paid to the character of small molecules 3 Å in diameter rolling along highly surface coded 100-Å patches of globular proteins. We submit that those patches, analogous to IBM typewriter balls, act as "pinball machine" factories to make, break, and exchange bonds, that is, to perform chemical transformations. The protein patches, thus, can act as catalyst surfaces (see discussions of catalysis in [5, p. 83] and the conditions for catalysis in [6]). The significance of this thesis is that, whereas 1-atm gas molecular relaxation times are of the order of 10^{-10} sec with 10^{-12}-sec collision times, and liquid collision times are of the order of 10^{-12} sec, the rolling contact time is of the order of appreciable fractions of a second (i.e., 10^{-3} to 1 sec). It is dubious that the short interval relaxation time of gas and liquid near equilibria of the order of 10^{-10} sec is sufficient to permit the processes of surface catalysis needed for life. Chemists have learned a considerable amount about catalytic reactions at solid surfaces, but they require extended contact periods. What we postulate here is that living systems have developed evolutionarily a rich capability of controlling their surface catalysis around the liquid-solid property of a controlled bulk-to-shear viscosity ratio which releases or ties up internal degrees of freedom as required in the local tissue.

There is nothing physically mysterious about this process. Basically, it is achieved by electrical forces that control the gating. At this point we do not wish to detail the interactions but simply point out the significance of the rolling contact to provide the time and space scale for such dynamic processes to take place.

Thesis 8.—Thus far, we have established that rolling contact (within a fraction of 1 Å) brings the catalytic and catalyzable molecule within electric range for appreciable periods of time to make chemoelectric processes associated with passage near membranes occur. Examples are binding, passive transport, active transport, electrical streaming, coupling for systems flow process effects, as well as systems piezo- and pyroelectric effects. Further, we have proposed that $3 \times 3 \times 3$ molecules form a sufficiently aggregated continuum to "talk" to a cell as an equal (i.e., to electrochemically communicate both ways). The insulating layer (e.g., of lipid membranes, of Schwann cells, of glia) provides a medium that acts as a near-plastic-elastic surface (that is, surface tension provides the minimum near-elastic property; the polar nature of the lipid bilayer provides the electrical and mobile fluid properties).

Thesis 9.—Now we would like to propose an additional possibility. A

similar nature for transmembrane exchange through the cell wall, as well as membrane passage along the cell wall, can be suspected from this rolling contact boundary condition. We cannot offer a full kinetic theory of flow, since we are limited to five molecules (15 Å) and now wish to look at one molecular diameter (3 Å). Clearly, small molecules passing through membranes, if their motion is seriously impeded by the lipid layer, can only get through near the mosaic protein molecule. The process must involve a significant rolling through a specially designed hole. Thus again, the imprinting character is present. Thus again, transfer depends on osmotic and electrical gradients across the membrane in the vicinity of the surface of the 100-Å globular protein passage. The movement, except for the specific detailed "flow" process, is essentially like the rolling process in the passage between capillary cells. The "diffusional" velocity likely is similar (for appropriate gradients). Thus, the process is similar except for the probability factor (i.e., the specific flux).

The variety of electrical and chemical pinball processes feasible makes a considerable number of thermodynamic engine processes possible (see, e.g., a new proposal on the sodium pump [7]).

Thesis 10.—Besides offering such a case for a variety of well-known facilitated diffusions (i.e., thermodynamic engine or "pump" processes, including one little-known systems one we have proposed, namely, that a streaming zeta potential governed by muscle fiber metabolism controls the admittance characteristics of red cells into nutrient capillaries [8, 9]), we believe that a case can be made for the character of memory. Consider the "memory" model in which genetic material elaborates its code as a result of memory conditioning, that is, imagine that the DNA increases its surface coding. As a result of that little added chemical complexity [10] (also see [11]), the effect on nearby rolling molecules is to slightly change the nature of the metabolic, electrolytic readout; that is, the changed coding affects the state of the catalytic tabula rasa that governs electrical and chemical fluxes—it changes the state of the system. Such a change in state, whether external or internal, represents the communicational nature of informational fluxes.

Thesis 11.—Thus, in toto, the rolling process at the 0.1-Å unit level makes a control of genetic coding, control of reproduction and expression of the genetic code, control of catalysis and of metabolic and electrolytic processes, and control of information processes, including memory, possible. Now it becomes a matter for chemical design of the molecular surface details. The chemist can claim that these controls always were possible, but he had no beaker chemical forces that could make life spring out of the beaker. We now provide chemical engineering unit processes, that is, flow processes (rolling), and a time and space scale that can make the chemical processes occur. Reading this proposed

mechanism in this sense shows that we have provided some preliminary answers to uncertainties that we could only raise as questions 4 years ago [12].

Summary

Careful examination of the kinetics of liquids provides a new view of near-equilibrium status in liquids. Near equilibrium is achieved within a cell of about $3 \times 3 \times 3$ molecules. New boundary conditions are proposed for such near-equilibrium cellular arrays when urged by gradient forces into fluid motion. The surface layer of molecules at rigid walls roll. Such rolling contact along membranes (e.g., through the interstitial space between capillary cells), or through membranes, of small molecules passing alongside globular proteins provides catalytic conditions for the making, breaking, and exchanging of bonds. Such rolling contact represents a specific systems form of physical forces for organizing function in the living system. Because of this rolling contact, further encoding of these globular proteins through experience also furnishes a possible dynamic basis for memory storage.

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