

## PARAMETRIC PUMPING A MODEL FOR ACTIVE TRANSPORT

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As a contribution to this interdisciplinary conference, I am presenting the elements of parametric pumping [12], a means for separating liquid mixtures currently under study in our laboratory. The subject involves transport considerations, and hence is suggested to lie within the scope of the meeting. It provides a handy illustration of minimum-essential mathematical model-building procedures that underlie the engineering design of large-scale chemical plants. Perhaps more relevant to biological interest is the observation that parametric pumping is a form of active transport, a process by which a mass flux against an apparently adverse fluid-phase concentration gradient is developed in a localized structure at the expense of some form of energy. Furthermore, because of the mathematical nature of the model description, generalizations are possible, and applicability of the model may be explored beyond the immediate macroscopic separation process for which it presently is written. Speculation thus is invited regarding the relevance (or lack of it) of the model to cellular transport by the usual procedure of comparing system responses of the model with those in nature. This comparison is made in the latter part of the paper between ion transport characteristics of giant squid axon cells, as determined experimentally by Hodgkin and Huxley, and system properties of parametric pumping.

By parametric pumping, generally, is meant coupled action of one oscillatory field upon another to give a desired result. For example, two pendulums, whose weights are connected through a spring, exercise complex parametrically induced motions on each other. Laser action depends upon coupling of electromagnetic waves (light) with quantum mechanical electronic fields of atoms. In the present instance, solid-liquid adsorptive equilibria are caused to be displaced in a cyclic fashion by a "pump" which itself is an oscillatory thermal field. The net consequence of temperature changes acting parametrically on the

solid-fluid composition fields is the formation of a limiting-value, time-average, fluid-phase, spatial concentration gradient in a fixed bed of adsorptive particles. Such a gradient comprises the basis of a solute separation scheme at the ultimate expense of thermal energy. A significant separation by this procedure has been achieved experimentally for NaCl in water, for example.

The subject is developed in what follows through these topics. First, parametric pumping is described operationally and is formulated mathematically for the macroscopic adsorption-separation system. Certain qualitative and quantitative properties of the system are discussed. Next, generalizations of the parametric pumping principle are suggested for possible application to structured systems regardless of ultimate component dimensions, number of variables, or kinds of thermodynamic driving forces. Third and finally, numerical solutions of the system of coupled equations are presented as gross analogs of classic voltage-clamp nerve cell experiments. Some points of possible consistency between the cited experiments and a parametric pumping model for active diffusion are discussed. Results encourage suggestions for experimental work to detect the presence or absence of fine-scale oscillatory phenomena during the course of active transport, together with suggestions for further theoretical development.

## PARAMETRIC PUMPING

### *Operational Description*

Application of dynamic adsorption principles for separating the components of a homogeneous binary liquid mixture is illustrated by means of the experimental elements depicted in Fig. 1. A column containing a bed of porous, particulate, adsorptive material and a charge of the mixture is equipped at its ends by driving and driven pistons acting in tandem. The pistons cause relative position displacements to take place between the column of particles and the column of ambient fluid. As portrayed, the system is closed and its total volume is constant. Initially, let each phase be uniform in solute concentration, let the temperature be uniform throughout the column and permit a solute concentration equilibrium to become established between liquid and solid phases. Thereupon at a starting time,  $t_0$ , a thermodynamic gradient is imposed on the column, as, for example, by bringing fluid temperatures at the column ends to different constant values through the use of heat sources and sinks. It has been shown

experimentally and theoretically that after the above nonsymmetrical process arrangement has been initiated and continued to limiting conditions (i.e., until time-averaged values of all properties have become constant), an axial fluid-phase, time-average, solute composition gradient will have developed. The resulting difference in interparticle solute concentration at the column ends, which arises from coupled

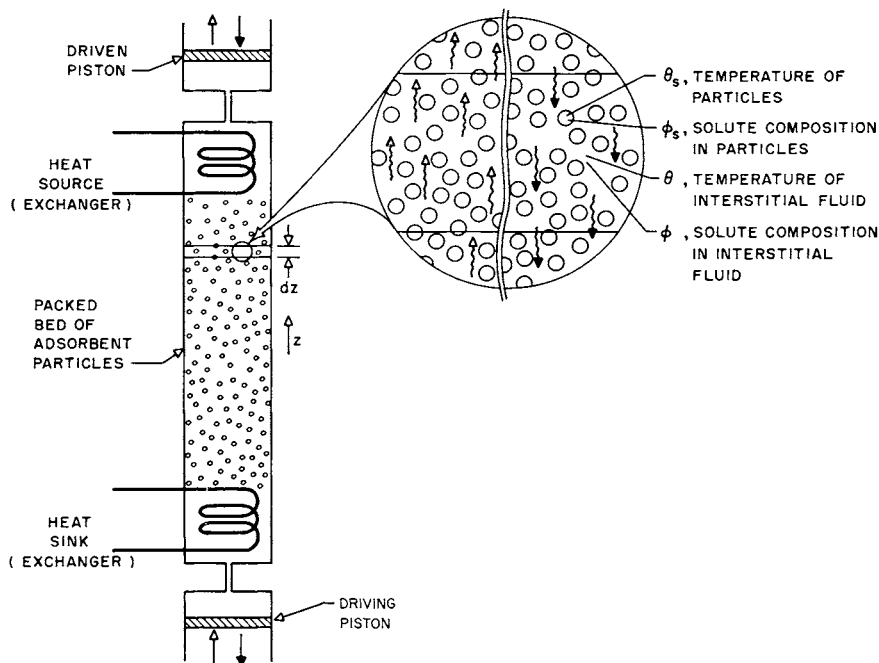


FIG. 1. Experimental arrangement for closed-system separation by means of thermal parametric pumping.

heat and mass transfer processes within the bed, is the separation in question.

In common with other separation processes, individual columns may be used as batch separators with total reflux, as shown in Fig. 1, as continuous-flow, open-system, single columns with various arrangements for feed introduction and product withdrawal and finally as elements in multicolumn arrays; different system arrangements lead to a range of separation potentials and thermal efficiencies.

By way of further amplification, consider the following cycle:

a fluid volume arrives at a stroke-end level, raising the temperature of the adjacent adsorbent. As a result of temperature change, the adsorbent transfers solute to the fluid. Enriched (and cooled) fluid next is displaced axially to contact warmer adsorbent. The fluid cools the adsorbent now adjacent and loses solute to it. Transport of fluid back to the point of origin completes the cycle. The difference between the fluxes of solute in the two flow directions is the net flux due to parametric pumping. In closed systems the net flux approaches zero as limiting conditions are reached.

A central concept of parametric pumping thus comprises designed alternating displacements from equilibrium of the solid-fluid compositions coupled with judicious timing of the axial flow displacements.

### *Mathematical Model*

In this section, the differential equations and initial and boundary conditions for material separation by thermal parametric pumping are presented. The physical meaning of each term and its characteristic dimensionless coefficient are identified. (Dimensional nomenclature is presented elsewhere [12].) Essential features that cause the equations to have parametric pumping characteristics also are noted briefly.

The following five equations taken together with initial and boundary conditions comprise a system description:

#### *Heat Balances*

$$\alpha f(t) \frac{\partial \theta_f}{\partial z} + \frac{\partial \theta_f}{\partial t} + \beta \frac{\partial \theta_s}{\partial t} - \psi \frac{\partial^2 \theta_f}{\partial z^2} = 0 \quad (1)$$

$$\frac{\partial \theta_s}{\partial t} + \gamma(\theta_s - \theta_f) = 0 \quad (2)$$

#### *Mass Balances*

$$\alpha f(t) \frac{\partial \phi_f}{\partial z} + \frac{\partial \phi_f}{\partial t} + \kappa \frac{\partial \phi_s}{\partial t} - \eta \frac{\partial^2 \phi_f}{\partial z^2} = 0 \quad (3)$$

$$\frac{\partial \phi_s}{\partial t} + \lambda(\phi_f^* - \phi_f) = 0 \quad (4)$$

#### *Equilibrium*

$$\phi_f^* = B + D\theta_s + Q\phi_s + R\phi_s\theta_s + S\phi_s^2 + U\theta_s^2 + \dots \quad (5)$$

Equations (1) and (2) are dimensionless heat balances in time and position for interparticle and intraparticle space, corresponding dimensionless temperatures being  $\theta_f$  and  $\theta_s$  (see Fig. 1). Dimension-

less temperatures are defined to vary between 0 and 1 within the temperature limits of the system;  $t$  and  $z$  are dimensionless time and axial position variables.

Equations (3) and (4) are dimensionless mass balances, interparticle and intraparticle concentrations being  $\phi_f$  and  $\phi_s$  respectively. The fact that the mass balances are here written for only one component assumes that solute is present in dilute concentration. In general, there would be  $n$  mass balances for  $n$  components.

The first term of Eq. (1) is the axial fluid-phase convective heat-transfer rate, the second term is the fluid-phase transient, the third, the solid-phase transient, and the fourth, an effective axial thermal diffusivity. The two temperature variables are linked through Eq. (2), which is a simplified rate equation for transfer of heat to and from particles. Terms in Eqs. (3) and (4) have meanings analogous to those in Eqs. (1) and (2).

Both thermal and compositional field equations are "driven" by the periodic velocity,  $\alpha f(t)$ . It is essential that this driving coefficient of the derivative  $\partial/\partial z$  change in sign periodically.

Coupling between the set of thermal fields [Eqs. (1) and (2)] and the set of compositional fields [Eqs. (3) and (4)] is accomplished through the equilibrium relationship [Eq. (5)]. Note that the equilibrium fluid-phase composition,  $\phi_f^*$ , is a function of *both*  $\phi_s$  and  $\theta_s$ , the composition and temperature, respectively, of the local solid phase. The "pump" is identified as the oscillatory thermal field. The larger the positive contribution to the equilibrium fluid composition,  $\phi_f^*$ , of the terms containing the solids temperature,  $\theta_s$ , the larger will be the potential separation. Nonlinearity in the equilibrium relation may contribute positively to the extent of separation but the fact of separation does not seem to depend on it. However, in parametric processes a nonlinearity developed through the coupling action between fields can lead to amplifications in the system output. In the present instance the generation of nonlinearity (higher harmonics) through the first terms of Eqs. (1) and (3) can lead, for selected combinations of system parameters, to very substantial amplifications of concentration ratios over a column length.

Separation as well as thermal efficiencies depend upon these dimensionless coefficients:

$\alpha f(t)$       Velocity of fluid. For a given  $f(t)$ ,  $\alpha$  determines the displacement amplitude, which may be larger or smaller than the column length.

$\beta$	Ratio of the average volumetric heat capacity of the adsorbent phase to that of the fluid phase.
$\kappa$	Ratio of volume within the solid adsorptive phase to that of the fluid phase.
$1/\gamma$	Time constant for thermal response of adsorptive particles relative to the characteristic time of displacement.
$1/\lambda$	Time constant for mass transfer response of adsorptive particles compared to the characteristic time of displacement.
$\psi$	Dissipative axial diffusivity of heat.
$\eta$	Dissipative axial diffusivity of solute mass.
$B, D, Q, R,$ $S, U$	Empirical constants in equilibrium Eq. (5).

Boundary and initial conditions for various column and cascade arrangements differ in detail. Flux of mass entering a column during one half cycle generally will depend upon the output during the previous half cycle. Flux of heat, in turn, depends upon the constant temperature imposed at a column end and the inward flow of fluid at that end. Conditions applicable to the closed system illustrated in Fig. 1, and used in solving the differential equations to secure figures presented in the last section of the paper, are these:

*Boundary Conditions*

$$\xi_H(t,0) = 0 \quad (6)$$

$$\text{for } \nu\pi \leq t \leq (\nu + 1)\pi, \quad \nu = 0, 2, 4 \dots$$

$$\xi_H(t,1) = \alpha \sin t \quad (7)$$

$$\text{for } \nu\pi \leq t \leq (\nu + 1)\pi, \quad \nu = 1, 3, 5 \dots$$

$$\xi_M(t,0) = \left[ \frac{\int \phi^0 \sin t'' dt''}{\int \sin t'' dt''} \right] \alpha \sin t \quad (8)$$

$$\text{for } \nu\pi \leq t \leq (\nu + 1)\pi$$

$$(\nu - 1)\pi \leq t'' \leq \nu\pi, \quad \nu = 0, 2, 4, 6 \dots$$

$$\xi_M(t,1) = \left[ \frac{\int \phi^1 \sin t'' dt''}{\int \sin t'' dt''} \right] \alpha \sin t \quad (9)$$

$$\text{for } \nu\pi \leq t \leq (\nu + 1)\pi$$

$$(\nu - 1)\pi \leq t'' \leq \nu\pi, \quad \nu = 1, 3, 5 \dots$$

*Initial Conditions (Typical)*

$$\theta_f(0,z) = \theta_s(0,z) = \theta_{f_0} = \theta_{s_0} \quad (10)$$

$$\phi_f(0,z) = B + D\theta_{s_0} + Q\phi_{s_0} + R\phi_{s_0}\theta_{s_0} + S\phi_{s_0}^2 + U\theta_{s_0}^2 + \dots \quad (11)$$

$$\phi_s(0,z) = \phi_{s_0} \quad (12)$$

The dimensionless symbols have these meanings:

$\xi_H, \xi_M$	Heat and mass fluxes, respectively, into column ends; $(t,0)$ for all times and cold end, $(t,1)$ for all times and warm end.
$\nu$	Positioning index for sine wave fluid velocity.
$\pi$	Mathematical pi.
$\phi^0$	$\phi(t'',0)$
$\phi^1$	$\phi(t'',1)$

#### *Some System Properties*

Experimental separations of NaCl solutions have been achieved with mixed-bed, ion-exchange resin in beds of the order of 18 inches high with a temperature difference of 50°C over the columns. Open- and closed-system operation has been performed; separation ratios at column ends were of the order of 1.1 to 1.2; cycle times were of the order of minutes.

Analog and digital solutions have been performed in support of experimentation and for exploration of model characteristics. As a result of these numerical solutions the following statements may be made:

In a program of model verification, initial agreement between experiment and theory is close.

Assuming only a previously measured equilibrium relationship [Eq. (5)] for NaCl-resin, other system constants also being in the experimental range, digital calculations yielded column-end separation ratios of the order of 1.1 to 3.0. However, when the values of  $\gamma$  and  $\lambda$ , especially, were placed within a selected range, concentration multiplication was computed to take place, separation ratios substantially larger than two orders of magnitude being indicated as possibilities.

In still other explorations with a different equilibrium relationship, separations of as much as 28 were encountered computationally.

Parametric pumping exhibits the response time characteristic of parametric processes generally. Starting from some initial condition the mean values of the dependent variables change deliberately until a long-time limiting condition has been achieved. Such a system transient is illustrated in Fig. 2, which presents a composition readout on an analog computer simulation of the present process. The location for the readout was chosen arbitrarily to be near one end of the column. Maintenance of separation depends upon maintenance of

oscillations everywhere continuously within the domain described by the differential equations.

It is essential that separation at limiting conditions be finite. That such is the case has been verified by computation for several alternate open and closed process arrangements. Alternate initial conditions were arranged such that the trajectory of approach to the limiting

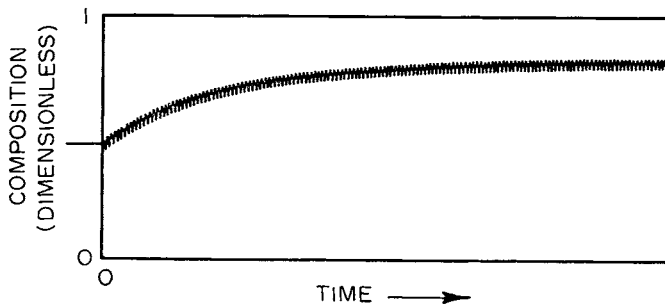


Fig. 2. Dependent variable-time trace characteristic of parametric pumping operation after process initiation or change in conditions. Curve secured at arbitrarily selected system site during analog simulation of Eqs. (1-5).

separation factor (as in Fig. 2) was approached from above and below its final value.

#### GENERALIZATIONS

The general idea of coupling may be summarized in the following equations:

$$\frac{dx}{dt} = ay + b \quad (13)$$

$$\frac{dy}{dt} = mx + n \quad (14)$$

$x$  and  $y$  are variables and  $a$ ,  $b$ ,  $m$ , and  $n$  are coefficients, some of which are driven in an oscillatory fashion. Cross coupling between the variables in both directions is noted in this instance. Numerous examples of coupled processes with a single dependent variable (time or position) are extant [10] in electrical engineering or physics. Generally, energetic processes involving electricity or movement of masses are involved and the conservation equations of motion and energy are called for. In the present instance, the equations are mass and heat conservation balances and the corresponding fields are "driven" simultaneously in alternating fashion in time by means of the  $f(t)$ .



The  $f(t)$  in question plays the same part as an alternating current source in an electrical coupled process but here the velocity alternations serve, through flow displacements between fluid and solid phases, simply to keep the system in a state of disequilibrium. Per se,  $f(t)$  is not a direct energy source; this is supplied by placement of heat sources and sinks at the column ends. In contrast to the set of coupled equations [Eqs. (13) and (14)], the present set [Eqs. (1-5)] are coupled only in one direction; the oscillatory thermal field (in  $\theta$ ) serves to "pump" the mass field (in  $\phi$ ) but the mass field does not affect the thermal field.

A virtue of a system of equations that comprise a model describing one physical situation is that such a system, or a modification of it, may at times be applied to completely different physical situations. In such analogous uses, it is essential only that the basic structure or idea behind the system in the first place be retained; in present work, the idea is that a diffusion-flow system, driven in an oscillatory manner, and to which an energy source is applied, may lead to compositional separation. The following comments are offered regarding generalized application of Eqs. (1-5) and their extensions.

The equations are independent of the scale of action. In adsorber-separation, particle-structure dimensions are of the order of a millimeter, system dimensions are of the order of a foot, and time constants, of a minute. With a new set of coefficients appropriate to the situation, the equations could be applied equally well to a system having independent variables of the order, say of a hundred Ångstroms and small fractions of a second.

The number of dependent variables may be two or more and the physical interpretations placed upon them may differ widely from application to application. Thus, currently there are two types of dependent variables,  $\theta$  and  $\phi$ , representing temperature and composition fields. The number of such types of fields may be increased indefinitely as long as there are coupling relations, such as Eq. (5), operative between them. Dependent relations might include electrical, magnetic, chemical potential such as pH and similar fields, a field also being added for each component in a multicomponent system.

An essential requirement for parametric pumping to occur is that the operation represented by  $f(t)$ , which drives the system, alternate about zero, thereby changing sign in the process. Thus, in thermal parametric pumping, liquid flows back and forth relative to a bed of particles, and in electrical applications, an alternating current is

applied. Parenthetically, dependent variables such as  $\theta_f$ ,  $\theta_s$ ,  $\phi_f$ ,  $\phi_s$ ) will oscillate about mean, finite values of the variable; the  $f(t)$  driving variable, by contrast, must alternate about a mean value of zero. Also, in present equations, note that the driving  $f(t)$ 's are identical for thermal and mass fields. This means simply that flow displacements act simultaneously to affect the processes by which heat and mass are conveyed back and forth axially. In general,  $f(t)$ 's for different fields may be functions of each other, i.e., they may be phase (in an electrical sense) displaced, provided that net phase

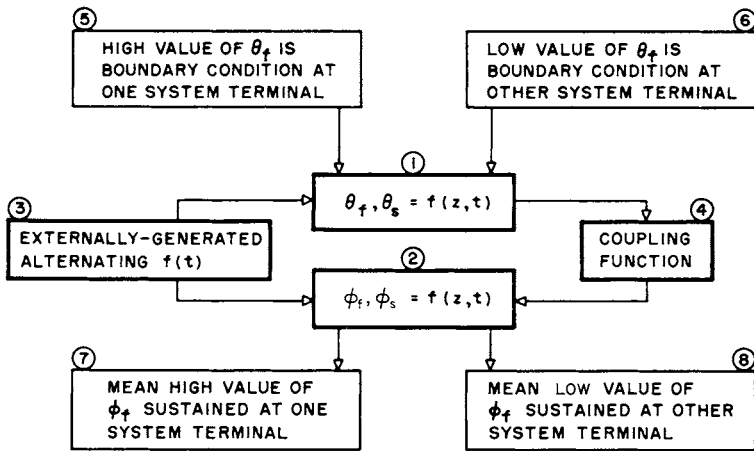


Fig. 3. Generalized function flow sheet showing the essential elements (differential equations, coupling function, driving function) of the model described by Eqs. (1-5).

relations between all system variables still permit desirable parametric results to occur.

The alternating function,  $f(t)$ , describes an action (flow) of one phase (liquid) relative to another (bed of particles). Although our experimental work has been with columns of particles which are fixed in laboratory space, there is nothing in the differential equations that requires the solid phase to be stationary; all that is required is that there be a relative displacement between fluid and solid phases.

Finally, coefficients on terms (such as  $\gamma$ ,  $\lambda$ ) which are now considered to be constant may be the driven coefficients. Boundary conditions also may be oscillatory.

Figure 3 presents a generalized function flow sheet for the para-

metric pumping equations given earlier in the paper. The boxes show the relations between differential equations (boxes 1 and 2), the coupling function (4), the driving  $f(t)$  (3), the boundary conditions (5, 6), and the results of solving the set of equations, i.e., the development of a sustained separation in the dependent variable,  $\phi_t$ , at the terminals of the system (boxes 7 and 8).

### ACTIVE TRANSPORT

In this section we speculate on the system structure of parametric pumping, a macroscopic type of active transport, and its possible relevance to active transport in biological cells. First a tentative flowsheet for a parametric active transport model is presented and its components are discussed. Second, comparison is made between experimental findings of Hodgkin and Huxley on giant squid axon cells and responses typical of a system of parametric pump equations. Specifically, several curve shapes secured by numerical solutions of Eqs. (1-5) are compared with experimental curves. Voltage clamp experiments as well as direct active diffusion experiments and their time constants are touched upon. Finally, certain new biological experiments are suggested which might serve to determine whether an oscillatory transport process, such as is being discussed here, may or may not be involved in transport at the cellular level.

#### *Parametric Pumping—Active Transport Model*

Figure 4 presents in flow sheet form three types of mathematical elements that are essential to parametric pumping; differential equations (boxes 1, 2, 3, 4), coupling functions (boxes 6, 7, 8), and an alternating driving function (box 5). The number of such boxes is chosen to permit inclusion in the framework of ideas frequently associated with biological active diffusion; degrees of freedom in a physicochemical sense may require more differential equations than those suggested to close any mathematical formulation. In contrast to Fig. 3, no boundary conditions are here indicated because the statement of such conditions is possible only after the appropriate differential equations have been expressed in detail.

Consider the set of differential equations first. Box 1 refers to differential equations of metabolism chemistry, and hence to the ultimate source of energy; box 2 refers to developed electrical potentials such as have been measured across the membranes; and finally, boxes 3 and 4 describe the adsorptive interactions of  $\text{Na}^+$  and  $\text{K}^+$  in struc-

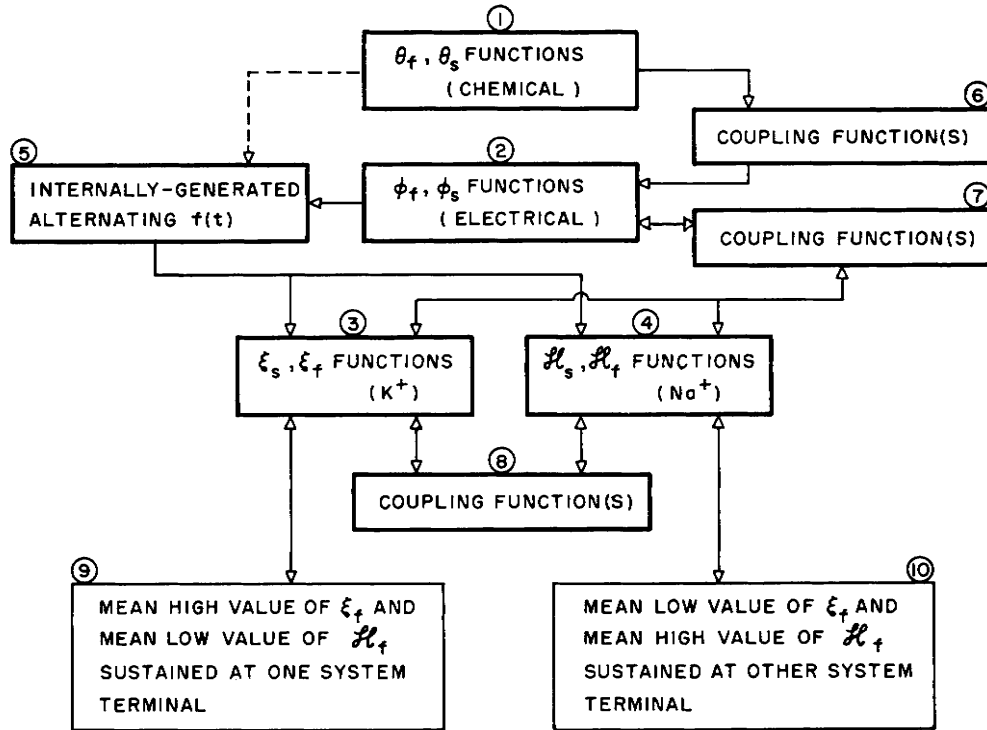


FIG. 4. Tentative generalized function flow sheet for active transport showing relationships between the essential elements: differential equations, coupling functions and driving function.

tured media such as cell walls, mitochondria and the like. A general statement regarding the differential equations seems appropriate at this point. Chemical reactions and the energy released from them, electrical potential and composition ( $\text{Na}^+$ ,  $\text{K}^+$ ), all are scalar quantities. Transport, on the other hand, is a vector quantity. To permit the desired coupling between the vector and scalar quantities to occur requires (from the formulations of irreversible thermodynamics) that the latter quantities have a directional (anisotropic) sense. This means simply that the differential equations should contain space derivatives, whether these apply to an adsorption column or to a cell wall.

Returning now to individual dependent variables one at a time, and starting with the differential equations (boxes 1, 2, 3, 4; chemical reaction, electrical-potential, chemical composition variables), let us proceed toward placement of biological ideas into the framework. Box 1 is intended to include all metabolism-associated enzymatic chemical steps which, according to recent concepts [1] supply energy for  $\text{Na}^+$  and  $\text{K}^+$  separation through an energy-rich phosphate or phosphagen. The over-all rate of a queue of sequential reaction steps is likely to be dynamically of very high order if the substrates must travel from one enzyme site to the next by diffusion, i.e., by a linear, irreversible process. For example, the oxidative pathway for glucose to oxaloacetate is commonly represented by thirteen direct steps (neglecting side paths). Considering the diffusive steps alone, the principles of control theory teach that in such a set of coupled steps the over-all rate by which glucose is converted to oxaloacetate is a thirteenth-order equation. To the extent that the enzymatic reactions that occur between successive diffusive steps are not at equilibrium, the over-all order would be raised even more.

Chemical potential  $\theta_f, \theta_s$  functions (such as pH) may couple directly with the  $\text{Na}^+$ - $\text{K}^+$  separation functions (electrical potential in this instance being merely an evidence of separation accomplishment). Alternatively, the chemical driving forces may act through electrical potentials as intermediates to cause separation; the latter course has quite arbitrarily been depicted in Fig. 4.

Although measured electrical potentials across cell membranes are only of the order of 50 mv, structure thicknesses are small and local voltage gradients may be of the order of 100,000 to 150,000 volts

per centimeter. The influence of such a gradient on adsorptive equilibria of charged species may be large; box 2 is included in the flow sheet to represent the differential equations that control the spatial and temporal distribution of electrical charges.

Boxes 3 and 4 represent material balance equations for charged  $\text{Na}^+$  and  $\text{K}^+$  species in counterpart to Eqs. (3) and (4) of this paper. The number of such sets of balances may be more than the two represented in Fig. 4. For example, balances on other species such as anions and water also must be included in principle if the concentrations of these substances enter the local equilibria and their values oscillate significantly with time.

Coupling functions indicated in boxes 6, 7, 8 are suggested to be counterparts to Eq. 5 of thermal parametric pumping. The chemical-electrical coupling of box 6 appears to have received little direct biological experimental attention. However, for purposes of numerical exploration, mathematical statements regarding some elementary mechanism ideas may be introduced at this point without destroying the over-all nature of the system responses. On the other hand, for a sense of possible structure of the next coupling function, i.e., between electrical and compositional fields (box 7) one may draw upon the work of Hodgkin and Katz [6], who related ionic composition in nerve cells and measured membrane voltages to the Nernst equation, of Eisenman [2], who theoretically investigated the adsorptive selectivity of ionic species as affected by local, internal electrical field strengths, and of Kurella [9], who measured voltages in ion-exchange resin model systems.

Regarding couplings between composition fields (box 8), the work of Helfferich [3] is suggested as relevant. He has dealt with the complex exchange equilibria of ionized species on ionized resins. The couplings must of course allow for opposed  $\text{Na}^+$  and  $\text{K}^+$  transport flux directions such as occur in cells. In this connection it is interesting to note that in the single-component parametric pumping of  $\text{NaCl}$  on monobed ion exchange resins, the higher concentration of  $\text{NaCl}$  is found experimentally to congregate at the upper, hotter end of the column. By changing values of coefficients in the equilibrium relation [Eq. (5)], and hence, in principle, changing the adsorber characteristics, it is found theoretically, through a numerical solution of

the model equations, that NaCl can be caused to migrate toward the opposite, colder end of the column.

Centrally important to separation by parametric operation is the alternating driving function,  $f(t)$ , located in box 5 of the flow sheet. Recall from earlier discussion that  $f(t)$  must alternate about zero, changing sign periodically. In thermal parametric pumping [Eqs. (1-5)] and its generalization (Fig. 3), note that the driving function is externally generated by alternating flows of liquid back and forth relative to a bed of resin particles. In the tentative active transport structure (Fig. 4), the driving function is indicated to be internally generated as indeed it must be if parametric pumping plays a part in such transport in biological cells. The provocative and highly interesting studies of Teorell [11] on alternating liquid flows induced by a membrane-electrolyte system under a dc voltage gradient would seem to provide a natural, mathematically expressed candidate mechanism for  $f(t)$  of box 5. Although the time constant for flow alternation in Teorell's macroscopic model experiments are of the order of 30 minutes, scaling to the dimensions of cell membranes is likely to give time constants of very small fractions of a second, as probably would be called for if parametric pumping were operative.

A parametric pumping model, such as is suggested in Fig. 4, has some interesting over-all response properties that, qualitatively at least, do not depend upon the details of the functions in the boxes but rather on the fact of the coupling of the several layers of differential equations and the driving of them, externally or internally, by an  $f(t)$ . Thus, a change induced in one part of the structure makes itself felt "downstream" in the flow sheet of the coupled system. In this sense parametric pumping would seem to be consistent with three major types of transport-related biological experiments. Interference with cellular metabolism through temporary or permanent metabolic poisons, or widely varying the oxygen supply (box 1) induces changes in electrical potential and in  $\text{Na}^+$  and  $\text{K}^+$  concentration differences. In voltage-clamp experiments, the system is perturbed at the position of box 2 and the consequences are felt in changed ion concentration differences. Finally, in a classic type of experiment, ion concentration of the same or alternate species is changed inside or outside of cells or across membranes, and the consequences are observed through changes in ion concentrations elsewhere in the system or through changes in Nernst voltage across the system.

*Comparison of Parametric Pump Solutions with Squid  
Axon Experiments*

Classic voltage clamp and active ion diffusion experiments of Hodgkin, Huxley, Keynes, and Katz serve as a basis of comparison for theory. Consider first the data (Fig. 5) of Hodgkin [4] and Hodgkin and Huxley [5, 8] for potassium conductance against time computed from alternating step-up and step-down voltage clamp experiments. The authors interpret the results in terms of membrane permeability change and fit an empirical function to the curves as part of the larger development of the ionic basis of nerve conduction.

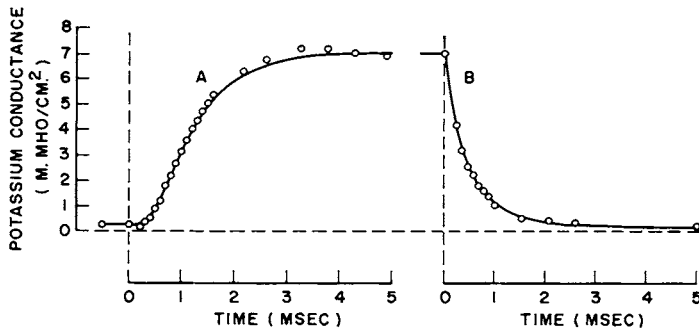


Fig. 5. Voltage clamp experiments on squid axon cells by Hodgkin and Huxley [5] expressed as potassium conductance versus time.

Equations and boundary conditions (1-9) were solved using coefficients conveniently at hand from our macroscopic separation studies. (It is assumed that the basic structure of the equations give qualitative curve forms that do not differ in general shape as coefficients are changed from one kind of problem to another.) Figure 6 presents results of one such calculation; separation ratio over the column is related to number of cycles (time) as axial diffusivities,  $\psi$  and  $\eta$ , are varied simultaneously fourfold up and down in a step-function fashion (actually accomplished by changing the number of axial computer stages in the calculations). Final distributions of values of all dependent variables at the end of one computation are taken as the initial conditions for the next jump calculation. (The initial conditions that are arbitrarily imposed to get started on calculation are wiped out after one such step-function calculation.) Also, changing system



coefficients such as  $\gamma$  and  $\lambda$ , for example, between computation cycles served to change only the magnitude of abscissa and ordinate values, but not the characteristic curve shapes.

Comparison of Figs. 5 and 6 reveals a gross similarity in the time course between experiment and model. Computed results display the slowly rising, deliberate transients characteristic of parametric processes and previously shown in Fig. 2. In the present calculations the local oscillations, which are always present, were purposely averaged out to save machine time. Also of interest is the fact that rising and falling curves are superimposable, a necessary outcome of the fact that Eqs. (1-4) are linear and Eq. 5 was linearized locally for purposes of the calculation. By contrast, the squid axon data are,

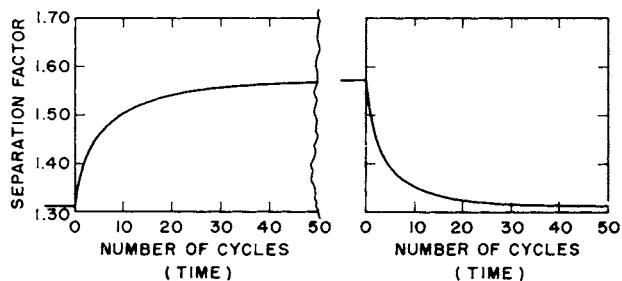


FIG. 6. Computed transient response in separation factor to alternating step function changes in axial diffusivity [ $\psi$  and  $\eta$  in Eqs. (1 and 3)].

as the authors pointed out, not superimposable and are highly nonlinear. It is clear that the mathematical formulation would call for introduction of nonlinear components to describe the data. Such might, for example, be a previously suggested nonlinear dynamic response of the long sequence of first-order steps comprising the glycolysis chain. The nonsymmetry in the rising and falling curves of Hodgkin and Huxley would probably also require the path between chemical and electrical potential mechanisms, as is indicated in the coupling between boxes 1 and 2 in Fig. 4, to be one directional, as shown.

An interesting feature of parametric pumping behavior is the achievement of a definite long-term, limiting value of all dependent, time-averaged variables. Limiting values of separation were explored computationally for a range of stage numbers (i.e., inverse axial conductance), and Fig. 7 presents the results. As noted in Fig. 8, potassium conductance [5] in axon cells also reaches limiting values as

some essential system coefficient is changed experimentally from one value to another; depolarization is the case in point. Again the qualitative similarity between experiment and computation is noted. The fact that one curve has a positive slope and the other a negative

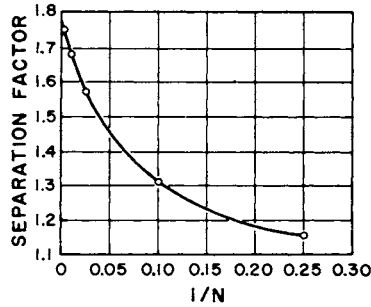


FIG. 7. Long-time limiting values of separation factor versus axial diffusivities computation by numerical integration of Eqs. (1-5) (axial diffusivities  $\psi$  and  $\eta$  are proportional to the variable  $1/N$ ).

one is not relevant here, but the fact that both systems tend to reach finite limiting conditions is suggested to be relevant.

Total ionic nerve cell currents, [4] after a change in bias voltage show a minimum in the transient curve. Figure 9 shows that computa-

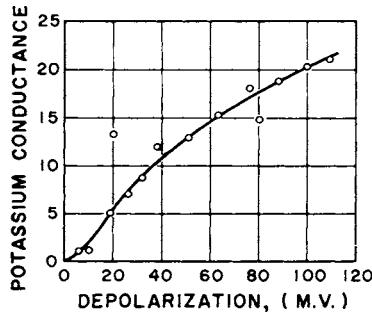


FIG. 8. Long-time limiting values of potassium conductance versus depolarization from Hodgkin and Huxley [5] on squid axon cells.

tional integrations also can lead to curves with minima (or maxima) with parametric pumping. The curve in question is the mean separation transient as the system boundary conditions in  $\theta_f$  are changed in a step fashion. After initial conditions have been wiped out, here

also a succession of superimposable curves are obtained only one of which is presented. In the case of thermal parametric pumping, the curve minima or maxima arise because of rapid changes in local adsorptive equilibria which occur before longer-time axial column compositional rearrangements can take place; both actions occur in response to newly imposed temperature boundary conditions.

In making the assumption that a parametric active-transport pump is associated with the experimental responses of axon cells as given in Fig. 5, one is confronted with a problem of characteristic time constants. The time constant in question is of the order of a

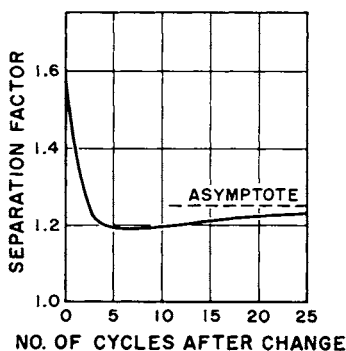


Fig. 9. Mean separation factor versus time (number of cycles after change) computed by integration of Eqs. (1-5) for step function alternations in the value of the system boundary condition in  $\theta$ , (response to only one-step change is depicted). Total ionic nerve cell currents have been observed [4] to show minimum in transient curve after change in bias voltage.

millisecond; by contrast, time constants in the work of Caldwell *et al.* [1] and of Hodgkin and Keynes [7] on direct ion diffusion measurements when metabolism is disturbed by the presence of temporary or permanent poisons is of the order of  $10^3$  seconds. The apparent discrepancy may perhaps be rationalized by a conceptual model extension within the framework of parametric pumping. Consider each end of the pump system (i.e., membrane or similar structure) to be surmounted by a receiver (intra- or extracellular space) which receives solute substance only by the processes of diffusion. In effect the pump locally becomes an open system with a Fickian receiver at its two boundaries. In such an assembly there can be a quick initial response, such as in Figs. 5 and 6 in which a rapid boundary layer gradient

is established, a high, (almost) limiting-value solute concentration being built up at the boundary between pump and diffusion systems. This high, locally pumped-up solute concentration can then serve as a source for "filling up" by diffusion the relatively large total volume of the biological organ, such as an axon cell, this last process having a relatively long over-all time constant.

Order of magnitude figures may be of interest in connection with the time constants under discussion.  $L^2/2t = D$ , the Einstein equation characteristic of diffusion, is employed for this purpose. ( $L$  is the mean diffusion distance,  $t$  is the duration time of diffusion, and  $D$  is the diffusion constant.) Take the squid axon radius (0.05 cm) to be the diffusion path length characteristic of the organ and let the response time be  $10^3$  seconds. A computed diffusion constant thus is about  $10^{-6}$  cm<sup>2</sup>/sec. Diffusion constants in water ordinarily range between  $10^{-4}$  and  $10^{-5}$  cm<sup>2</sup>/sec. Presumably diffusion in colloidal axoplasm is smaller than in water and to this extent the estimate seems to be self consistent. Unfortunately there is little work on direct diffusion measurements in cell fluids with which to make comparison. Turning now to short-time penetration and accepting for the moment the figure for  $D$  of  $10^{-6}$  cm<sup>2</sup>/sec, one may calculate the mean diffusion distance in 1 millisecond to be about  $10^{-4.5}$  cm (5000 Å).

#### *Possible Model Discrimination through Experiment*

If some form of parametric pumping is involved in active transport, then all dependent variables would be expected to oscillate about a mean, which itself can be a transient or be stationary in the limit of large elapsed times, as illustrated in Fig. 2. Thus, in experiments of the type that underlie the data of Fig. 3, one should seek to determine by direct measurement whether oscillations are superimposed on mean values. Electrical outputs are particularly convenient in this connection because, with present instrumentation, frequencies as high as  $5 \times 10^{10}$  cps may be detected. If in such measurements oscillations were found to persist over a long period of time, coordinated behavior in the entire structural unit might well be presumed. On the other hand, if pulsations were to decay after being initiated by step changes in voltage clamp experiments, the presence of synchronous behavior, which subsequently becomes randomized, might be hypothesized.

A second type of experiment is related to chemical perturbations. Effects of adding metabolic inhibitors, of adenosine triphosphate (ATP), and other substances, have been studied in relation to the

energy source for active diffusion, and generally experiments have involved direct measurement of ion transfer rates. Such additives might well be applied in studying rapid-acting electrical outputs, such as are illustrated in Fig. 5, both with regard to influence on the transient response of mean potential values and on the superimposed oscillations, if any. Furthermore, if water transfer through membranes should be involved, the study of hormones and diuretics on the electrical outputs might be instructive.

### CONCLUSIONS

1. Parametric pumping, an oscillation-driven separation process, is described. Experimental separations have been achieved for NaCl-water and a mathematical model has been written and solved numerically. Parametric pumping is suggested to be a form of active diffusion; as presently performed a spatial mean concentration difference is caused to develop in a column of adsorbent particles at the expense of thermal energy.
2. Parametric pumping concepts are generalized and extended as a possible model for active transport in biological cells.
3. Responses of numerical solutions of a minimum-essential set of parametric pumping equations are compared with classic squid axon, voltage clamp, ion transport experiments. It is concluded that curve shapes, somewhat similar to those generated experimentally, can be developed by the mathematical model in question.
4. Experiments are suggested which might serve as a basis for verification, rejection or modification of parametric pumping as a candidate model for active biological transport.

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