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Nonlinear Wave Propagation in Reacting Systems

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Summary

A "two-phase" continuum model of a developing tissue is formulated and some limiting cases are analyzed. In this "raisin-pudding" model, exchange occurs between cytoplasm and the immobilized cell organelles, and transport within the cytoplasm is via an active or directed mechanism as well as by diffusion. The limit of rapid interphase exchange leads to several distinct cases depending on the rate of reaction in the organelles and the storage capacity of the organelles. For a certain class of systems, marginally stable states are always oscillatory and small amplitude chemical waves can be propagated. Analysis of a one-component system shows that several distinct types of finite-amplitude waves can propagate unattenuated, each at a characteristic velocity. Thus a very simple reaction-transport system can lead to a very flexible chemical transmission line.

1. Introduction

Intercellular communication undoubtedly plays an important role in the control of spatial differentiation in developing systems, and the simplest mode for such communication is exchange of cellular constituents. Diffusion can transmit local concentration changes over distances comparable to a cell diameter in a few seconds, but because the characteristic time for diffusion is proportional to the square of the distance, it takes 10^4 times as long to transmit the same change over a distance of 100 cell diameters. Consequently, diffusive transport alone is inadequate for rapid, long distance signal transmission; if diffusion is involved it must be coupled with some spatially-distributed mechanism for regenerating the signal. Chemical reaction can function as this meachanism, for it is known that when reaction is properly coupled with diffusion, small-amplitude composition changes can propagate throughout a system as unattenuated travelling waves, often at speeds far greater than the rate of advance of a diffusion front (Gmitro and Scriven, 1966). Such travelling waves, the most dramatic examples of which arise in the Zhabotinskii-Belousov reaction (Zaiken and Zhabotinskii, 1970; Winfree, 1972), are potentially important as a mechanism for communication and control in developing systems. Indeed, Goodwin and Cohen (1969) have proposed an elaborate theoretical model for developmental control, in which the phase shifts in several propagating waves provide a global spatio-temporal reference frame for cellular events (Cohen, 1972).

To discover the properties of coupled reaction and transport that lead to unattenuated wave propagation, and thereby, to identify equivalence classes of

reaction-transport schemes that can function as chemical transmission lines, the dynamics of concrete models or classes of models must be analyzed. When the governing conservation equations of a reaction-diffusion system are linear or when nonlinear conservation equations are linearized, undamped travelling waves exist only in oscillatory, marginally-stable systems (Gmitro and Scriven, 1966, Othmer and Scriven, 1969; Ortoleva and Ross, 1972). Such systems are "structurally unstable" in the sense that small parameter changes lead to either growing or decaying waves, and further analysis is required to determine the fate of growing waves. Kopell and Howard (1973, 1974) have studied finite amplitude periodic waves and transition layers for a special class of kinetic mechanisms, while Ortoleva and Ross (1974) constructed such periodic waves by perturbation expansions valid in the small-amplitude, long-wavelength limit. Some numerical results have been reported by Herschkowitz-Kaufmann and Nicolis (1972) and Winfree (1974). Here we begin a study of wave propagation in a broader class of continuum models, a class more relevant to developmental biology because other modes of transport are incorporated and some aspects of internal cell structure are included.

A developing tissue consists of discrete cells, often directly-coupled by junctions of low resistance to diffusion of small molecules, separated from their external environment by high-resistance, non-junctional membrane (Caveney, 1974; Furshpan and Potter, 1968; Lowenstein, 1968). Within each cell there occur the complex networks of chemical reactions involved in respiration, protein synthesis, DNA replication, etc. At the first level of description in a mathematical model, a tissue is regarded either as a collection of discrete, internally-uniform cells connected by zero capacity diffusion pathways (Othmer and Scriven, 1971, 1974) or as a homogeneous entity describable by spatially-averaged values of chemical concentrations and reaction and transport parameters (Turing, 1952). In either case, all internal cell structure is ignored and the choice of discrete or continuum model determined by the relative magnitude of internal transport resistance compared to junctional resistance.

However, cell organelles such as ribosomes, nuclei and mitochondria are more than just dispersed catalysts or inert blobs. At the next level of complexity in a continuum model, these organelles are recognized as distinct from the cytoplasm and the possibility of finite relaxation times for the interactions between cytoplasm and organelles is incorporated. When junctional resistances between cells are comparatively low, such a "two-phase" continuum model, for which we develop the governing equations in the following section, should provide the appropriate level of description of a developing tissue. With such a model, both the effect of blocking reactions within the organelles and the role of transport between cytoplasm and organelles can be studied and conditions that lead to oscillations, such as those observed in mitochondria (Hess and Boiteux, 1971), can be investigated. Moreover, simpler "single-phase" continuum descriptions can be recovered as limiting cases when exchange between organelles and cytoplasm is rapid. However, the analysis done in Section 3 shows that different single-phase descriptions are needed, depending on the rates of the other processes involved.

The first step in analyzing the equations for a new model is a stability analysis of the steady states; this is done in Section 4. In certain special cases, it happens that marginally-stable states are always oscillatory when active or directed transport occurs. Under certain additional conditions, this result implies that an unstable, uniform steady state always evolves to a time-dependent state, never to another steady state. Therefore, steady finite-amplitude waves may exixt in such systems. Such waves are studied in Section 5 where, for reasons of mathematical simplicity, we restrict attention to one component systems. Even such simple systems are capable of supporting a wide variety of finite-amplitude waves for different values of the parameters in the governing equations. It remains to be determined which kinds of waves are excited in real systems and how their shape and velocity depend on the reaction and transport parameters. The results of analytical and numerical computations aimed at answering these questions will be reported in a sequel to this paper.

2. Mathematical Formulation

In the continuum description adopted here, a one-dimensional array of cells is regarded as a two-phase mixture consisting of an immobile phase that comprises such cell organelles as the nucleus, ribosomes and mitochondria, uniformly dispersed throughout the mobile cytoplasm or fluid phase. The mixture is bounded laterally by a membrane outside of which is a uniform constant-composition bath. The thickness of the system is much smaller than its length, and fluid phase concentrations are considered uniform at any cross section. Chemical reaction occurs within both the fluid and dispersed phases, there is mass transfer between the fluid and dispersed phases, and transport in the fluid phase by diffusion, electrical migration, convection or other active processes occur along one dimension only. Concentration gradients within the dispersed phase are assumed to be negligible, *i.e.*, the effectiveness factor for the dispersed phase is set equal to one (Weisz, 1973).

Let c denote the concentration vector $(c_1, \ldots, c_n)$, let J and R represent n-component flux and reaction vectors, respectively, and let ω be the volume fraction of fluid phase. Further, denote by a^i (a^0) the interfacial area per unit volume between fluid and immobile phase (fluid and bath), let t and z be the time and space variables, and let superscripts f, i and o denote quantities in the fluid phase, the immobile phase, and the bath, respectively. The time-dependent conservation equations for chemical species in the two phases are

$$\begin{aligned} \frac{\partial c^f}{\partial t} &= -\frac{\partial J^f}{\partial z} + \frac{a^o}{\omega} J_o^f + \frac{a^i}{\omega} J_i^f + R^f(c^f) \\ \frac{\partial c^i}{\partial t} &= \frac{-a^i}{1-\omega} J_i^f + R^i(c^i). \end{aligned} \tag{1}$$

Here J^f is the flux within the fluid phase while J_o^f and J_i^f represent interphase fluxes. It is postulated that the latter fluxes are given by the constitutive

relations [1]

$$J_o^f = H^o (c^o - c^f)$$
$$J_i^f = H^i (c^i - c^*), \tag{2}$$

where H^o and H^i are $n \times n$ matrices of mass transfer coefficients. The vector c^* is the immobile phase concentration in equilibrium with the local fluid phase concentration when $R^i(c^i) \equiv o$. The relation between these concentrations at equilibrium will be written $c^* = F(c^f)$; this could, for example, represent a Langmuir adsorption isotherm.

The axial flux in the fluid phase consists of a random diffusive component proportional to the local concentration gradient and a directed component that is assumed to be proportional to the local concentration. Accordingly, the total flux is

$$J^f = -\mathscr{D} \frac{\partial c^f}{\partial z} + A(c^f) c^f \tag{3}$$

where $\mathscr{D}$ is an $n \times n$ matrix of binary diffusitivities and $A(c)$ is an $n \times n$ matrix of generalized "velocities". The directed component of the total flux can represent the convective portion due to protoplasmic streaming, the drift flux that arises from an externally-imposed or internally-generated electrical field, or the flux resulting from active transport.

If convection is the only mechanism for directed transport, then $A(c)$ has the form $A = v I$ where v is the convective velocity and I the identity matrix. When two or more of the chemical species are ions, an electric field can be generated if the two species diffuse at different rates or if one species is actively transported. In this case, or the similar case where the field is externally-imposed, the components of $A(c)$ are (Plonsey, 1969)

$$A_{ij} = \begin{cases} 0 & i \neq j \\ -u_j \dfrac{z_j}{|z_j|} E & i = j \end{cases} \tag{4}$$

where u_j is the mobility of, and z_j the charge on, the j-th ion, and E is the axial component of the electric field. In the absence of net space charges, E is a constant, but any of the mobilities may be a function of concentration. Finally, if active transport proceeds via a carrier-mediated mechanism that involves formation of a complex between carrier and transported species, it is reasonable to assume that the flux can be expressed in the form $A(c)c$. At low concentrations of the transported species, the flux should increase with increasing concentration and hence $A(c)$ should be non-decreasing in c for small c. At high concentrations such a mechanism would saturate and therefore $A(c)$ should vary as $1/c$ when c is large. More specific information on $A(c)$ is not required here.

With these constitutive relations, the conservation equations can be written

[1] By definition, the bath has infinite capacity whereas the immobile phase may saturate and equilibrate with the fluid. This accounts for the form chosen for the two constitutive relations.

$$\frac{\partial c^f}{\partial t}=\frac{\partial}{\partial z}\left(\mathscr{D}\frac{\partial c^f}{\partial z}\right)-\frac{\partial}{\partial z}\left(A\left(c^f\right)c^f\right)+\frac{a^o}{\omega}H^o\left(c^o-c^f\right)$$
$$+\frac{a^i}{\omega}H^i\left(c^i-c^*\right)+R^f\left(c^f\right) \tag{5}$$
$$\frac{\partial c^i}{\partial t}=\frac{-a^i}{1-\omega}\left(c^i-c^*\right)+R^i\left(c^i\right).$$

These equations are difficult to analyze when the reaction rates are nonlinear or when the transport coefficients are concentration dependent, but they simplify somewhat when exchange between the fluid and immobile phases is rapid compared with diffusive transport in the fluid phase. For the purpose of deriving the simplification, we assume that there is only one reactive species of interest in each phase and that $\mathscr{D}$, H^o and H^i are concentration independent. This simplifies the notation; the final results are readily translated to the general multi-component case. As usual, analysis of the equations hinges on the appropriate non-dimensionalization of all variables.

Let L be a characteristic length, for example, the cross-sectional thickness of the system. Define the dimensionless variables

$$\zeta=\frac{z}{L}\qquad \tau=\frac{\mathscr{D}t}{L^2}$$
$$u=\frac{c^f}{c^o}\qquad v=\frac{c^i}{F\left(c^o\right)} \tag{6}$$

and the dimensionless parameters and functions

$$\varepsilon=\frac{(1-\omega)\mathscr{D}}{a^i H^i L^2}\qquad \lambda=\frac{(1-\omega)R^i\left(F\left(c^o\right)\right)}{a^i H^i F\left(c^o\right)}$$
$$\mu=\left(\frac{1-\omega}{\omega}\right)\frac{F\left(c^o\right)}{c^o}\qquad \Omega_1=\frac{A\left(c^o\right)L}{\mathscr{D}}$$
$$\Omega_2=\frac{a^o H^o L^2}{\omega\mathscr{D}}\qquad \Omega_3=\frac{L^2 R^f\left(c^o\right)}{c^o\mathscr{D}}$$
$$\tilde{A}(u)=\frac{A\left(c^o u\right)}{A\left(c^o\right)}\qquad \tilde{F}(u)=\frac{F\left(c^o u\right)}{F\left(c^o\right)}$$
$$\tilde{R}^f(u)=\frac{R^f\left(c^o u\right)}{R^f\left(c^o\right)}\qquad \tilde{R}^i(v)=\frac{R^i\left(F\left(c^o\right)v\right)}{R^i\left(F\left(c^o\right)\right)}. \tag{7}$$

The conservation equations can now be written in the dimensionless form

$$\frac{\partial u}{\partial\tau}+\Omega_1\frac{\partial}{\partial\zeta}\left(\tilde{A}(u)u\right)=\frac{\partial^2 u}{\partial\zeta^2}+\Omega_2(1-u)+\frac{\mu}{\varepsilon}\left(v-\tilde{F}(u)\right)+\Omega_3\tilde{R}^f(u)$$
$$\varepsilon\frac{\partial v}{\partial\tau}=-\left(v-\tilde{F}(u)\right)+\lambda\tilde{R}^i(v). \tag{8}$$

When interphase exchange is rapid, $\varepsilon \ll 1$, and physical intuition suggests that the immobile phase concentrations rapidly equilibrate with fluid phase concentrations. However, the exact nature of this equilibration and its effect on the time evolution of the fluid phase concentrations depends on the relative magnitudes of the other parameters. Because we are primarily interested in determining how the presence of the immobile phase affects the dynamics in the fluid phase, we consider only cases for which Ω_1, Ω_2 and $\Omega_3 \sim \mathcal{O}(1)$. The different limiting cases then depend on the relative magnitudes of ε, μ and p.

3. Cases of Rapid Interphase Exchange

When $\varepsilon \ll 1$, one or both concentrations vary rapidly during the time interval $o < \tau < \bar{\mathcal{O}}(\varepsilon)$ and more slowly thereafter. Using standard techniques of singular perturbation theory (Cole, 1968), two asymptotic expansions of the solution of (8), each valid in one of these regimes, can be constructed and the "long-time" ($\tau \gg \varepsilon$) effect of the immobile phase can be determined. The "inner" expansions, valid for $o \leq \tau < \mathcal{O}(\varepsilon)$, are written in terms of the rescaled variable $T = \tau/\varepsilon$ as follows:

$$\begin{aligned} u(\zeta, \varepsilon T, \varepsilon) &\equiv U(\zeta, T, \varepsilon) \sim \sum_{k=0}^{\infty} U_k(\zeta, T)\, \varepsilon^k \\ v(\zeta, \varepsilon T, \varepsilon) &\equiv V(\zeta, T, \varepsilon) \sim \sum_{k=0}^{\infty} V_k(\zeta, T)\, \varepsilon^k. \end{aligned} \tag{9}$$

The "outer" expansions, valid when the solution varies on an $\mathcal{O}(1)$ time scale, are written

$$\begin{aligned} u(\zeta, \tau, \varepsilon) &\sim \sum_{k=0}^{\infty} u_k(\zeta, \tau)\, \varepsilon^k \\ v(\zeta, \tau, \varepsilon) &\sim \sum_{k=0}^{\infty} v_k(\zeta, \tau)\, \varepsilon^k \end{aligned} \tag{10}$$

and the inner and outer expansions are matched by requiring that

$$\begin{aligned} \lim_{T \to \infty} U(\zeta, T, \varepsilon) &= \lim_{\tau \to o} u(\zeta, \tau, \varepsilon) \\ \lim_{T \to \infty} V(\zeta, T, \varepsilon) &= \lim_{\tau \to o} v(\zeta, \tau, \varepsilon). \end{aligned} \tag{11}$$

There are three cases of interest, depending on the relative magnitude of ε, λ and μ.[2]

[2] The results that follow apply to either the interior of the unit interval [0, 1] with u or the flux specified at the end points or the infinite interval with the condition that u be bounded at $\pm\infty$. On the finite interval, the inner solution cannot satisfy the boundary conditions unless compatibility conditions on the initial data are specified. In general, a boundary-layer analysis near the end points is also required.

(a) Slow Immobile Phase Reaction and Low Saturation Concentration: $\lambda \sim \mathcal{O}(\varepsilon)$, $\mu \sim \mathcal{O}(\varepsilon)$

By substituting the series (10) and (11) into (8) and comparing coefficients of like powers of ε, the zero order terms are found to satisfy

$$\begin{aligned} &\frac{\partial U_o}{\partial T}=0 \\ &\frac{\partial V_o}{\partial T}=-(V_o-F(U_o)) \end{aligned} \tag{12}$$

$$\frac{\partial u_o}{\partial \tau}+\Omega_1 \frac{\partial}{\partial \zeta}(A(u_o)u_o)=\frac{\partial^2 u_o}{\partial \zeta^2}+\Omega_2(1-u_o)+\Omega_3 R^f(u_o)$$

$$v_o=F(u_o).$$

Therefore $U_o(\zeta, T)=$constant; the initial distribution in the fluid phase, whereas

$$V_o(\zeta, T)=e^{-T}V_o(\zeta, 0)+F(U_o)[1-e^{-T}].$$

and

$$\lim_{T\to\infty} V_o(\zeta, T)=F(U_o). \tag{13}$$

It follows from (12) and (13) that, within terms of $\mathcal{O}(\varepsilon)$, the immobile phase has no effect on the fluid phase concentration.

(b) Moderate Reaction Rate in the Immobile Phase and Low Saturation Concentration[3]: $\lambda \sim \mathcal{O}(1)$, $\mu \sim \mathcal{O}(\varepsilon)$

The zero order terms satisfy

$$\begin{aligned} &\frac{\partial U_o}{\partial T}=0 \\ &\frac{\partial V_o}{\partial T}=-(V_o-F(U_o))+\lambda R^i(V_o) \end{aligned} \tag{14}$$

$$\frac{\partial u_o}{\partial \tau}+\Omega_1 \frac{\partial}{\partial \zeta}(A(u_o)u_o)=\frac{\partial^2 u_o}{\partial \zeta^2}+\Omega_2(1-u_o)+\frac{\mu}{\varepsilon}(v_o-F(u_o))+\Omega_3 R^f(u_o)$$

$$0=-(v_o-F(u_o))+\lambda R^i(v_o).$$

Again, $U_o(\zeta, T)=$constant, but now $\lim_{T\to\infty} V_o(\zeta, T)$ depends on the nature of $R^i(V_o)$. Suppose that for all positive u

$$F(u)+R^i(0)>0$$

and that the equation

$$v-F(u)=\lambda R^i(v) \tag{15}$$

[3] Here and in the following case moderate reaction rate means that the magnitude of the reference rate $R^i(F(c^o))$ is ~ 1. Moderate saturation concentration means that $F(c^o)\sim c^o$. We do not consider cases for which λ or μ are $\mathcal{O}(1/\varepsilon)$.

has a single positive root for fixed u. Call this root $V_o^*(U_o)\,[v_o^*(u_o)]$ when $(U_o, V_o)\,[(u_o, v_o)]$ is substituted for (u, v) in (15); then

$$\lim_{T\to\infty} V_o(\zeta, T) = V_o^*(U_o) = v_o(\zeta, 0). \tag{16}$$

Furthermore,

$$\frac{\partial u_o}{\partial \tau} + \Omega_1 \frac{\partial}{\partial \zeta}(A(u_o)\,u_o) = \frac{\partial^2 u_o}{\partial \zeta^2} + \Omega_2(1-u_o) + \Omega_3 R^f(u_o) + \frac{\lambda\mu}{\varepsilon} R^i(v_o^*(u_o)), \tag{17}$$

and so the zero order effect of the immobile phase is simply to modify the homogeneous reaction rate. Equation (17) is usually assumed *a priori* as the equation for the exact solution in such cases as those involving a dispersed catalyst. The reaction term $\Omega_3 R^f(u_o) + \frac{\lambda\mu}{\varepsilon} R^i(v_o^*(u_o))$ is then called the pseudo-homogeneous rate. However, neglecting the inner solution entirely and computing only the outer solution is not generally valid; it is appropriate only when $v_o^*(u_o)$ is unique.

When (15) has more than one positive, asymptotically stable root for fixed u, the nature of the outer solution depends critically on the initial distribution of u and v. If the initial values lie in the domain of attraction of the same root for every value of ζ, the problem is similar to the single root case, with the exception that different initial distributions can lead to different roots v_o^* and hence different equations for the outer solution u. However, if the initial conditions lie within the region of multiple roots in $u-v$ space for some values of ζ, a discontinuity in v can develop.

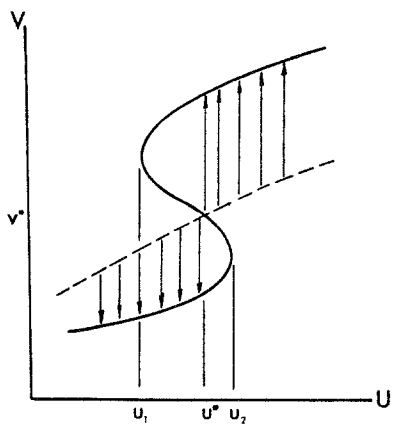

Fig. 1. Relaxation of the initial distribution when (15) has multiple roots

Suppose, for example, that the graph of the solution of (15) is as shown in Fig. 1 and that the initial values lie along the dotted curve, with ζ varying monotonically on that curve. Clearly the immobile phase concentration relaxes to different values at different points in space (cf. Fig. 1), but these values vary slowly with ζ

except at ζ^*, the point at which the initial values are (u^*, v^*). At this point in space, the immobile phase concentration switches from one branch of the curve to the other and the resulting initial condition $v_o(\zeta, o)$ for the outer solution is discontinuous. However, $u_o(\zeta, o)$ varys smoothly with ζ and so there is no shock layer in the fluid phase. Moreover, if the outer solution in the fluid phase is such that the concentration never falls below U_1 nor rises above U_2 at all points in a neighborhood of the discontinuity, the discontinuity persists in time. In a sense, it is dynamically imprinted. Such a mechanism, whereby a smoothly varying distribution in one phase can generate a sharp discontinuity in the other, may be useful for spatial differentiation in developing systems.

(c) *Moderate Immobile Phase Reaction Rate and Moderate Saturation Concentration*: $\lambda \sim \mathcal{O}(\varepsilon)$, $\mu \sim \mathcal{O}(1)$

The zero order terms satisfy

$$\begin{aligned}
\frac{\partial U_o}{\partial T} &= \mu\left(V_o - F(U_o)\right) \\
\frac{\partial V_o}{\partial T} &= -\mu\left(V_o - F(U_o)\right) \\
v_o &= F(u_o) \\
\left(1+\mu F'(u_o)\right)\frac{\partial u_o}{\partial \tau} + \Omega_1 \frac{\partial}{\partial \zeta}\left(A(u_o)\, u_o\right) &= \frac{\partial^2 u_o}{\partial \zeta^2} + \Omega_2(1-u_o) + \Omega_3 R^f(u_o) \\
&\quad + \frac{\lambda \mu}{\varepsilon} R^i\left(F(u_o)\right).
\end{aligned} \tag{18}$$

The first pair of equations imply that

$$U_o(\zeta, T) + V_o(\zeta, T) = C_1 = U^o(\zeta) + V^o(\zeta),$$

where U^o and V^o are the initial values, and therefore

$$\frac{\partial U_o}{\partial T} = \mu\left[C_1 - U_o - F(U_o)\right]. \tag{19}$$

Since $F(u) \geq 0$ for $u \geq 0$, $\lim_{T\to\infty} U_o > 0$. If, in addition, $F'(u) > -1$ for $u > 0$, the limit is independent of the starting point on the line $U_o + V_o = C_1$, and is given by the single positive root U_o^∞ of

$$C_1 - U_o = F(U_o). \tag{20}$$

Corresponding to this is the limiting value of V_o:

$$\lim_{T\to\infty} V_o = V_o^\infty = F(U_o^\infty), \tag{21}$$

and therefore the initial values for the outer solution are

$$\begin{aligned}
u_o(\zeta, o) &= U_o^\infty(\zeta) \\
v_o(\zeta, o) &= V_o^\infty(\zeta).
\end{aligned} \tag{22}$$

Under most circumstances $F'(u)>0$, i.e., the saturation concentration increases with increasing external concentration, so the above covers all cases likely to be of physical interest.

It is significant that under the conditions on reaction rate and saturation concentration applicable here, the presence of the immobile phase is reflected both in the pseudo-homogeneous rate and in the capacity term $\mu F'(u_o)$. If $F'(u_o)$ is a constant, the effect is to simply modify the time scale in the fluid phase, for by defining $\tau^* = \tau/(1+\mu F'(u_o))$, the factor $1+\mu F'(u_o)$ can be absorbed. When $F(u_o)$ is nonlinear, the capacity varies with u_o and in effect, the time scale is different for each concentration. If $F'(u_o)$ is monotone increasing, high concentrations vary on a longer time scale than low concentrations and vice-versa if $F'(u_o)$ is monotone decreasing. In a spatially-homogeneous system, where u is independent of ζ, this difference in time scales plays no essential role for any monotone increasing F, because the capacity term can be absorbed by defining a cumulative time

$$\tau^* = \int_0^\tau \frac{dt}{1+F'(u_o(t))}. \tag{23}$$

However, such a simple rescaling cannot be done in a nonuniform system and the nonlinearity of F has interesting consequences.

Suppose for example, that diffusion is very small and that the space and time variables in the conservation equations are scaled to reflect this. If $A(u_o)=A_o$, a constant, then a rescaled version of (17) reads

$$\frac{\partial u_o}{\partial \tau}+\frac{\Omega_1 A_o}{1+F'(u_o)}\frac{\partial u_o}{\partial \zeta}=\frac{\Omega_2(1-u_o)}{1+F'(u_o)}+\frac{\Omega_3 R^f(u_o)}{1+F'(u_o)} + \frac{\lambda\mu R^i(F(u_o))}{1+F'(u_o)} \tag{24}$$

If $F'(u)$ is decreasing ($F''<0$), the concentration-dependent "velocity" $A_o/(1+F'(u_o))$ increases with u_o and an initially-smooth distribution of u_o can give rise to sharp transition regions or shock layers that propagate through the system. Indeed, such concentration dependence of the velocity is the basis for chromatographic separations, and equations like (24) with Ω_2, Ω_3 and μ equal to zero have been thoroughly studied in that context (Aris and Amundson, 1973; Rhee and Amundson, 1974). The more general case with non-zero reaction has been touched upon by Murray (1970).

Analysis of multicomponent systems governed by equation (5) is complicated by the fact that there are n relaxation times in a n-component system and by the possibility that the kinetics in the immobile phase may by oscillatory. However, with suitable restrictions on the reaction rate functions and the initial conditions, equations for the outer solution can be derived. To this end, assume that the matrices $\mathscr{D}$, H^i and H^0 are constant and define

$$\alpha=\max_{i,j}|A_{ij}(c^o)| \qquad \beta=\max_j|F_j(c^o)|, \qquad \gamma=\max_j c_j^o$$

$$\delta=\max_{i,j}|\mathscr{D}_{ij}|, \qquad \varepsilon=\frac{\delta(1-\omega)}{L^2\theta^i a^i}, \qquad \zeta=\frac{z}{L},$$

$$\theta^i=\max_{i,j}|H^i_{ij}|, \qquad \theta^o=\max_{i,j}|H^o_{ij}|, \qquad \lambda=\frac{\rho^i(1-\omega)}{a^i\theta^i\beta},$$

$$\mu=\left(\frac{1-\omega}{\omega}\right)\frac{\beta}{\gamma}, \qquad \rho^f=\max_{j}|R^f(c^o)|, \qquad \rho^i=\max_{j}|R^i_j(F(c^o))|,$$

$$\tau=\frac{\delta t}{L^2}, \qquad u_j=\frac{c^f_j}{\gamma}, \qquad v_j=\frac{c^i_j}{\beta}, \qquad w_j=\frac{c^0_j}{\gamma}$$

$$\tilde{A}_{ij}=\frac{A_{ij}}{\alpha}, \quad \tilde{\mathscr{D}}_{ij}=\frac{\mathscr{D}_{ij}}{\delta}, \quad \tilde{F}_j=\frac{F_j}{\beta}, \quad \tilde{H}^i_{ij}=\frac{H^i_{ij}}{\theta^i}, \quad \tilde{H}^o_{ij}=\frac{H^o_{ij}}{\theta^o}, \quad \tilde{R}^f_j=\frac{R^f_j}{\rho^f},$$

$$\tilde{R}^i=\frac{R^i}{\rho^i}, \quad \Omega_1=\frac{\alpha L}{\delta}, \quad \Omega_2=\frac{a^o\theta^o L^2}{\omega\delta}, \quad \Omega_3=\frac{\rho^f L^2}{\gamma\delta}.$$

The dimensionless form of (5) is

$$\begin{aligned}\frac{\partial u}{\partial\tau}+\Omega_1\frac{\partial}{\partial\zeta}\left(\tilde{A}(u)u\right)&=\tilde{\mathscr{D}}\frac{\partial^2 u}{\partial\zeta^2}+\Omega_2\tilde{H}^o(w-u)\\&+\frac{\mu}{\varepsilon}\tilde{H}^i\left(v-\tilde{F}(u)\right)+\Omega_3\tilde{R}^f(u)\\\varepsilon\frac{\partial v}{\partial\tau}&=-H^i\left(v-\tilde{F}(u)\right)+\lambda\tilde{R}^i(v).\end{aligned}\tag{25}$$

By virtue of the definitions of the scale factors, the entries in $\tilde{A}$, $\tilde{\mathscr{D}}$, $\tilde{H}^i$, $\tilde{R}^f$ and $\tilde{R}^i$ are $\mathcal{O}(1)$ quantities, and the relative importance of any term in these equations is determined by the corresponding dimensionless group. As in the preceding analysis, Ω_1, Ω_2 and Ω_3 are assumed to be $\mathcal{O}(1)$.

When $\lambda\sim\mathcal{O}(1)$ and $\mu\sim\mathcal{O}(\varepsilon)$, the initial values for the outer solution depend on the asymptotic behaviour, as $T\to\infty$, of the solution of

$$\begin{aligned}\frac{\partial U_o}{\partial T}&=0\\\frac{\partial V_o}{\partial T}&=-H^i\left(V_o-\tilde{F}(U_o)\right)+\lambda\tilde{R}^i(V_o).\end{aligned}\tag{26}$$

where here and hereafter tildas are dropped. If the vector equation

$$H^i\left(V_o-\tilde{F}(U_o)\right)=\lambda\tilde{R}^i(V_o)\tag{27}$$

has a unique, positive, asymptotically-stable solution for fixed U_o, then the first term of the outer solution satisfies an equation analogous to (17),

$$\begin{aligned}\frac{\partial u_o}{\partial\tau}+\Omega_1\frac{\partial}{\partial\zeta}\left(A(u_o)u_o\right)&=\mathscr{D}\frac{\partial^2 u_o}{\partial\zeta^2}+\Omega_2 H^o(w-u)+\Omega_3 R^f(u_o)\\&+\frac{\lambda\mu}{c}R^i\left(v_o^*(u_o)\right)\end{aligned}\tag{28}$$

with smooth initial conditions. If (27) has more than one stable root, initial conditions determine the asympotic behaviour of V_o, and discontinuous profiles are possible when initial conditions lie within the region of multiple roots. It can also happen that (27) has no stable solutions and that (26) has a stable periodic solution, but this case requires a more detailed analysis and will not be treated here.

Case (*c*), in which $\lambda \sim \mathcal{O}(\varepsilon)$ and $\mu \sim \mathcal{O}(1)$, goes through essentially without change for a multicomponent system. As before, $U_o + V_o = \text{constant}$, and the first term of the outer solution satisfies the vector analog of 18 (*d*). However, even if the equilibrium relation $\tilde{F}(u)$ is linear for each species, the capacity term cannot be absorbed by defining a new time scale unless the Jacobian $F'(u)$ is proportional to the identity matrix.

In either of the single- or multi-component cases, the equation for the zero-order outer solution can rarely be solved explicitly, but some information about the dynamics can be gotten by studying the stability of stationary states. This is done in the following section.

4. Stability Analysis of Steady States

The steady state concentrations, which we denote by $(\bar{u}, \bar{v})$, are positive solutions of the equations

$$\mathcal{D}\frac{\partial^2 \bar{u}}{\partial \zeta^2} - \Omega_1 \frac{\partial}{\partial \zeta}\left(A(\bar{u})\bar{u}\right) + \Omega_2 H^o(w-\bar{u}) + \frac{\mu}{\varepsilon} H^i\left(\bar{v} - F(\bar{u})\right) + \Omega_3 R^f(\bar{u}) = 0$$

$$H^i\left(\bar{v} - F(\bar{u})\right) = \lambda R^i(\bar{v}) \tag{29}$$

$$(\bar{u}, \bar{v}) \text{ bounded on } -\infty < \zeta < \infty.$$

We assume hereafter that at least one such solution exists, and investigate the temporal evolution of small disturbances of this steady state. For this purpose, define (ξ, η) by

$$\begin{aligned} u(\zeta, \tau) &= \bar{u}(\zeta) + \xi(\zeta, \tau), \\ v(\zeta, \tau) &= \bar{v}(\zeta) + \eta(\zeta, \tau), \end{aligned} \tag{30}$$

substitute these into (26), and retain only first order terms in the small quantities (ξ, η). The result is the linear vector equation

$$\begin{aligned} &\frac{\partial \psi}{\partial \tau} = \mathcal{L}\psi, \\ &\psi(\pm\infty, \tau) \text{ bounded}, \\ &\psi(\zeta, 0) = \psi_o(\zeta), \end{aligned} \tag{31}$$

in the vector $\psi \equiv \begin{pmatrix} \xi \\ \eta \end{pmatrix}$. The operator $\mathcal{L}$ is defined as

$$\mathscr{L} = \left[\begin{array}{c|c} \dfrac{\partial^2}{\partial \zeta^2} - i A_1 \dfrac{\partial}{\partial \zeta} + K^f - \dfrac{\mu}{\varepsilon} H^i F' + \dfrac{\partial A_1}{\partial \zeta} & \dfrac{\mu}{\varepsilon} H^i \\ \hline \dfrac{H^i F'}{\varepsilon} & \dfrac{\lambda K^i}{\varepsilon} - \dfrac{H^i}{\varepsilon} \end{array}\right],$$

the quantities A_1, F', K and K^i are given by

$$\begin{aligned} (A_1)_{ij} &\equiv \Omega_1 \left[A_{ij}(\bar{u}) + \sum_k \left. \frac{\partial A_{ik}}{\partial u_j} \right|_{u_j = \bar{u}_j} \cdot \bar{u}_k \right], \\ (F')_{ij} &\equiv \left. \frac{\partial F_i}{\partial u_j} \right|_{u_j = \bar{u}_j} \qquad (K^i)_{ij} = \lambda \left. \frac{\partial R_i^i}{\partial v_j} \right|_{v_j = \bar{v}_j}, \\ (K^f)_{ij} &\equiv -\Omega_2 H^o_{ij} + \Omega_3 \left. \frac{\partial R_i^f}{\partial u_j} \right|_{u_j = \underline{u}j}, \end{aligned} \tag{32}$$

and $\mathscr{D}$, H^i, and H^o are assumed to be independent of concentration.

Since $\mathscr{L}$ is time-independent, solutions of (31) have the form $\psi = e^{s\tau}\bar{\psi}$, where $\bar{\psi}$ and s are related through the eigenvalue problem

$$\begin{gathered} (\mathscr{L} - s)\bar{\psi} = 0 \\ \bar{\psi}(\pm\infty, s) \text{ bounded.} \end{gathered} \tag{33}$$

If the largest real part of the eigenvalues s is zero, the solution $(\bar{u}, \bar{v})$ is marginally stable; stationary when the dominant eigenvalue is real and simple, and oscillatory when the dominant eigenvalues are a simple pair of complex conjugates[4]. If $\mathscr{L}$ has any eigenvalues with a positive real part, disturbances grow with time and the steady state $(\bar{u}, \bar{v})$ is said to be unstable. As some parameter, such as a kinetic coefficient or a permeability, in $\mathscr{L}$ varies, the dominant eigenvalue may cross the locus of marginal stability in parameter space and become positive. Another solution of the equations may bifurcate at the critical parameter value; whether it is stable or unstable requires a detailed analysis[5]. Furthermore, whether the bifurcating solution is steady or periodic in time is dictated by whether the dominant eigenvalue is real or complex, respectively. In any case, the first step is to study the character of the eigenvalues of $\mathscr{L}$ to determine the critical loci in parameter space.

When the steady state is uniform, $\mathscr{L}$ has constant coefficients and (33) has solutions of the form

$$\bar{\psi} = e^{ik\zeta}\Phi, \tag{34}$$

where k is a real constant. The determinantal condition for existence of a non-trivial Φ gives the dispersion relation

[4] By which is meant that (31) has only two periodic solutions $\psi_1 = e^{s\tau}\bar{\psi}_1$ and $\psi_2 = \bar{\psi}_1$ when $\mathrm{Re}\, s = 0$ (Joseph and Sattinger, 1972).

[5] For precise statements of some results applicable here see e.g. Aris (1971), Chafee and Infante (1973), Kopell and Howard (1972), Joseph and Sattinger (1972), or Marsden (1973).

$$\det \left[\begin{array}{c|c} -k^2 - ik A_1 + K^f - \dfrac{\mu}{\varepsilon} H^i F' - sI & \dfrac{\mu}{\varepsilon} H^i \\ \hline \dfrac{H^i F'}{\varepsilon} & \dfrac{\lambda K^i}{\varepsilon} - \dfrac{H^i}{\varepsilon} - sI \end{array} \right] = 0 \qquad (35)$$

or the alternate form, valid when $\dfrac{\lambda K^i}{\varepsilon} - \dfrac{H^i}{\varepsilon} - sI$ is non-singular,

$$\det \left[K^f - k^2 \mathscr{D} - ik A_1 - \frac{\mu}{\varepsilon} H^i F' - sI - \frac{\mu}{\varepsilon} H^i (\lambda K^i - H^i - \varepsilon s I)^{-1} H^i F' \right] = 0. \qquad (36)$$

The single-phase version ($K^i = H^i = 0$) with $A_1 = 0$ has been studied elsewhere (Othmer and Scriven, 1969). The general case of (35) is too unwieldy too analyze, even if there are only two components in each phase, so we restrict attention to two of the cases treated in the preceding section.

When $\varepsilon \ll 1$, and when the uniform steady state $(\bar{u}, \bar{v})$ is such that $\bar{v}$ is an asymptotically-stable solution of 26 (*b*) for fixed $\bar{u}$, the linear equations at (31) comprise n "fast" modes that relax to interphase equilibrium within a time interval of order ε, and n "slow" modes that grow or decay on a longer time scale. To find the eigenvalues for these modes, suppose first that $\lambda \sim \mathscr{O}(1)$, $\mu \sim \mathscr{O}(\varepsilon)$, and set $\hat{\mu} = \mu/\varepsilon$. The eigenvalues for the n fast modes are gotten by setting $s = \tilde{s}/\varepsilon$ in (35) and expanding the determinant; the result, to first order in ε, is that $\tilde{s}$ satisfies

$$\det (\lambda K^i - H^i - \tilde{s} I) = 0. \qquad (37)$$

In order that $\bar{v}$ be an asymptotically stable root, $\lambda K^i - H^i$ must have eigenvalues all of whose real parts are negative.

The zero order term for the eigenvalues of the slow modes are gotten from (36) by replacing μ/ε by $\hat{\mu}$ and setting $\varepsilon = 0$; they satisfy

$$\det [K^f - k^2 \mathscr{D} - ik A_1 - \hat{\mu} (I + H^i (\lambda K^i - H^i)^{-1}) H^i F' - sI] = 0. \qquad (38)$$

The first three terms pertain solely to the fluid phase while the term multiplied by $\hat{\mu}$ reflects the interaction between the two phases. Evidently, if $\hat{\mu}$, H^i or F' is zero, the interaction vanishes. That (38) can alternatively be derived by linearizing the equations for the first term in the outer solution may be verified directly from (27) and (28). Moreover, by defining a pseudo-homogeneous reaction-exchange matrix

$$K = K^f - \hat{\mu} (I + H^i (\lambda K^i - H^i)^{-1}) H^i F', \qquad (39)$$

(38) can be written

$$\det [K - k^2 \mathscr{D} - ik A_1 - sI] = 0 \qquad (40)$$

and this is indistinguishable from the equation for a single phase system described by a kinetic-exchange matrix K.

In the other case of interest, namely $\lambda \sim \mathscr{O}(\varepsilon)$, $\mu \sim \mathscr{O}(1)$, it follows from (35) that the zero order term for $\tilde{s}$ solves the equation

$$\det [H^i + \tilde{s} I] = 0. \qquad (41)$$

Consequently, for $\bar{v}$ to be asymptotically stable, it is necessary and sufficient that H^i have eigenvalues all with positive real part. In order to obtain the zero order term in the eigenvalues of the slow modes, the resolvent $(\lambda K^i - H^i - \varepsilon s I)^{-1}$ in (36) must be expanded in powers of ε,

$$(\lambda K^i - H^i - \varepsilon s I)^{-1} = -(H^i)^{-1} \sum_{n=o}^{\infty} \varepsilon^n [\hat{\lambda} K^i - I)(H^i)^{-1}]^n, \tag{42}$$

where $\hat{\lambda} \equiv \lambda/\varepsilon$, $\hat{\lambda} \sim \mathcal{O}(1)$. The series is convergent when $\varepsilon < \| (\hat{\lambda} K^i - s I)(H^i)^{-1} \|$ (Kato, 1966). After inserting (42) into (36) and collecting terms, one finds that the zero order term satisfies

$$\det [K^f - k^2 \mathscr{D} - i k A_1 + \hat{\lambda} \mu K^i F' - s(I + \mu F')] = 0. \tag{43}$$

A pseudo-homogeneous rate K can now be defined by

$$K = K^f + \hat{\lambda} \mu K^i F' \tag{44}$$

and (43) written

$$\det [K - k^2 \mathscr{D} - i k A_1 - s(I + F')] = 0. \tag{45}$$

Evidently this equation differs from (30) in the appearance of the capacity term $I + F'$ and in the different definition of the pseudo-homogeneous reaction-exchange matrix K. Both differences stem from the different order of magnitude of λ and μ in the two cases.

If the conditions on K^i and H^i given after (37) and (41) are satisfied in the respective cases, the fast modes decay, and to first order in ε, stability of the steady state is governed by the real parts of the roots of (40) or (45). A multiplicity of cases arise, depending on the properties of $\mathscr{D}$, A_1, F' and K, but in the following we restrict attention to those features of the stability behaviour that arise from non-zero active or directed transport. We first consider the characteristic equation (40).

Complete information on stability can be derived directly from the properties of the two matrices $K - k^2 \mathscr{D}$ and A_1 when these matrices are simultaneously triangularizable, for then the eigenvalues s_j of $K = k^2 \mathscr{D} - i k A_1$ have the simple form $s_j^{K - k^2 \mathscr{D}} - i k s_j^{A_1}$ for the appropriate pairing of $s_j^{K - k^2 \mathscr{D}}$ and $s_j^{A_1}$, the eigenvalues of $K - k^2 \mathscr{D}$ and A_1, respectively (Othmer and Scriven, 1969). In particular, this simple form pertains if $K - k^2 \mathscr{D}$ and A_1 commute or if A_1 is diagonal; $A_1 = a_1 I$. Since it is always true that

$$\begin{aligned} (s_r)_j &\equiv \operatorname{Re} \{s_j^{K - k^2 \mathscr{D} - ikA_1}\} = \operatorname{Re} \{s_j^{K - k^2 \mathscr{D}}\} + k \operatorname{Im} \{s_j^{A_1}\} \\ (s_i)_j &\equiv \operatorname{Im} \{s_j^{K - k^2 \mathscr{D} - ikA_1}\} = \operatorname{Im} \{s_j^{K - k^2 \mathscr{D}}\} + k \operatorname{Re} \{s_j^{A_1}\}, \end{aligned} \tag{46}$$

it follows that whenever A_1 has only real eigenvalues, stability is determined solely by the reaction-diffusion matrix. If in addition, $K - k^2 \mathscr{D}$ has only real eigenvalues and A_1 is non-singular, the growth or decay of all slow modes is oscillatory with frequency proportional to the eigenvalues of A_1.

In the general case, we require the following

Lemma: Let $\Omega = \Omega_r + i\,\Omega_i$ be a complex $n \times n$ matrix with eigenvalue $s = s_r + i\,s_i$; Ω_r, Ω_i, s_r, s_i real. Let $\lambda_1 \leq \lambda_2 \leq \ldots \leq \lambda_n$, $\mu_1 \leq \mu_2 \leq \ldots \leq \mu_n$ be the eigenvalues of the matrices $A = \dfrac{\Omega_r + \Omega_r^T}{2} + \dfrac{i}{2}(\Omega_i - \Omega_i^T)$ and $B = \dfrac{\Omega_r - \Omega_r^T}{2i} + \dfrac{(\Omega_i - \Omega_i^T)}{2}$, respectively. Then

$$\lambda_1 \leq s_r \leq \lambda_n$$

and (47)

$$\mu_1 \leq s_i \leq \mu_n.$$

Proof: Let x be an eigenvector of Ω and x^* the Hermitian transpose of x. Then

$$\Omega x = s x$$

$$s = \frac{x^* \Omega x}{x^* x}$$

and

$$s_r = \mathrm{Re}\left\{\frac{x^*(\Omega_r + i\,\Omega_i)\,x}{x^* x}\right\}$$

$$= x^* \frac{\left\{\dfrac{(\Omega_r + \Omega_r^T)}{2} + i\,\dfrac{(\Omega_i - \Omega_i^T)}{2}\right\} x}{x^* x} \tag{48}$$

$$= \frac{x^* A x}{x^* x}.$$

Similarly

$$s_i = \frac{x^* B x}{x^* x}.$$

The result follows by first noting that A and B are Hermitian, and then using the fact that for any Hermitian matrix A and vector x, the Rayleigh quotient $x^* A x / x^* x$ lies between the smallest and largest eigenvalues of A (Barnett and Storey, 1970).

The lemma implies that the real part s_r and the imaginary part s_i of $s^{K - k^2 \mathscr{D} - ikA_1}$ lie between the largest and smallest eigenvalues of

$$\frac{K - k^2 \mathscr{D} + (K - k^2 \mathscr{D})^T}{2} - \frac{i\,k}{2}(A_1 - A_1^T)$$

and (49)

$$\frac{K - k^2 \mathscr{D} - (K - k^2 \mathscr{D})^T}{2i} - k\,\frac{A_1 + A_1^T}{2}$$

respectively. When both $K - k^2 \mathscr{D}$ and A_1 are symmetric, these bounds reduce to

$$\min(s_j^{K - k^2 \mathscr{D}}) \leq s_r \leq \max(s_j^{K - k^2 \mathscr{D}})$$

$$\min(s_j^{A_1}) \leq \frac{-s_i}{k} \leq \max(s_j^{A_1}). \tag{50}$$

Therefore if $K - k^2 \mathscr{D}$ has only negative eigenvalues, $K - k^2 \mathscr{D} - i\,k\,A_1$ has eigenvalues, all of whose real parts are negative, and the system is stable. Consequently,

if $K-k^2\mathscr{D}$ and A_1 are symmetric, active or directed transport can never destabilize a system that is stable in its absence. If A_1 is definite, a marginally stable state is always oscillatory.

If only A_1 is symmetric, the bounds on the growth or decay rate depend only on the reaction and diffusion matrices. When $K-k^2\mathscr{D}+(K-k^2\mathscr{D})^T$ has only negative eigenvalues, the s_r are all negative and the system is stable. However, it is not sufficient for this that $K-k^2\mathscr{D}$ have only eigenvalues with negative real parts; this can be seen from a two-component system that has complex conjugate eigenvalues. Conversely, even if $K-k^2\mathscr{D}$ has an eigenvalue with a positive real part, it cannot be concluded that any of the s_r is positive. Thus the only cases in which any conclusive statements on stability can be made are those for which $K-k^2\mathscr{D}$ and A_1 are symmetric; in other cases the eigenvalues must simply be computed. For example, Jorne (1974) has shown that in two-component systems, oscillatory instabilities can exist in a bounded k interval that does not include 0. Such synergistic oscillatory instabilities are impossible with two components in the absence of some form of directed transport; at least three components are necessary when $A_1=0$ (Othmer and Scriven, 1969).

Next consider the characteristic equation (45). If F' is symmetric and has all eigenvalues greater than $-1/\mu$, then $I+\mu F'$ is positive definite and (48) is replaced with

$$s_r=\frac{x^* A x}{x^*(I+\mu F')x}$$

and (51)

$$s_i=\frac{x^* B x}{x^*(I+\mu F')x}.$$

Let $\omega_1\geq\omega_2\geq\ldots\geq\omega_n$ be the eigenvalues of $I+\mu F'$. Then it follows from (51) that

$$\frac{\lambda_1}{\omega_1}\leq s_r\leq\frac{\lambda_n}{\omega_n}$$

$$\frac{\mu_1}{\omega_1}\leq\frac{-s_i}{k}\leq\frac{\mu_n}{\omega_n}. \tag{52}$$

If both $K-k^2\mathscr{D}$ and A_1 are symmetric and $K-k^2\mathscr{D}$ has only negative eigenvalues, it follows as before that neither directed transport nor a non-zero capacity can destabilize a system that is stable when $A_1=F'=0$. Moreover, when A_1 is definite a marginally stable state is always oscillatory. Again as before, other cases must be considered individually to determine their stability.

It is noteworthy that either with or without the capacity term, there is an important class of systems for which the marginally stable state is always oscillatory and undamped waves can be propagated through the system. If the dominant eigenvalue crosses the locus of marginal stability and a bifurcating solution exists, it is always periodic, never stationary. This is one of the major consequences of non-zero directed transport; another will be seen in the following section.

Heretofore we have assumed that the steady state $(\bar{u},\bar{v})$ is uniform. If it is nonuniform, the coefficients of $\mathscr{L}$ are space dependent and the dispersion relation (35)

no longer obtains. It can happen in such cases that instabilities develop in localized regions of space and that the bifurcating solution is also highly localized. Herschkowitz-Kaufman and Nicolis (1972) give a very pretty example of this. When the nonuniform solution is slowly varying in space, the linear analysis can be done by deriving asymptotic dispersion relations valid when the wavelength of a disturbance is much smaller than the scale of the nonuniform solution. However, this aspect is not pursued here. Instead, we determine the kinds of finite amplitude propagating waves that can arise in one component systems.

5. Finite Amplitude Waves

Consider a single-component system, described by (8), on the infinite interval $-\infty<\zeta<\infty$. Suppose that $\lambda\sim\mathcal{O}(1)$, $\mu/\varepsilon=\hat{\mu}\sim\mathcal{O}(1)$ and that the steady state equation for the immobile phase concentration,

$$v-F(u)=\lambda R^i(v), \tag{53}$$

has a single positive, asymptotically-stable root $v=v^*(u)$ for every positive u. Hereafter we set $\varepsilon\equiv 0$ and then can write

$$\frac{\partial u}{\partial \tau}+f(u)\frac{\partial u}{\partial \zeta}=\frac{\partial^2 u}{\partial \zeta^2}+g(u) \tag{54}$$

where

$$f(u)\equiv\Omega_1\left(A(u)+A'(u)u\right)$$

$$g(u)\equiv\Omega_2(1-u)+\Omega_3 R^f(u)+\lambda\hat{\mu}R^i\left(v^*(u)\right).$$

We assume that f and g are smooth functions and that $R^f(0)=R^i(v^*(0))=0$; then $g(0)>0$.

Permanent wave solutions of (54) are bounded functions $u(\zeta,\tau)=U(\zeta-\theta\tau)$ that depend on space and time only through the variable $\phi=\zeta-\theta\tau$, $-\infty<\phi<\infty$. The nonnegative parameter θ is the wave velocity; it is to be determined. By substitution into (54), one finds that a permanent wave $U(\phi)$ is a nonconstant solution of the ordinary differential equation

$$\frac{d^2U}{d\phi^2}+\left(\theta-f(U)\right)\frac{dU}{d\phi}+g(U)=0. \tag{55}$$

This equation is equivalent to the two-dimensional system

$$\begin{aligned}\frac{dU}{d\phi}&=V\\ \frac{dV}{d\phi}&=-g(U)+\left(f(U)-\theta\right)V.\end{aligned} \tag{56}$$

The critical points $(U_k,0)=(g^{-1}(0),0)$ of this system are the identically constant solutions. When permanent wave solutions exist, they are one of the three types:

(i) periodic waves: $U(\phi+T)=U(\phi)$, T the period

(ii) solitary waves: $U(\pm\infty)=U_1$ $U'(\pm\infty)=0$, $U(\phi)\not\equiv U_1$ and

(iii) transition waves: $U(-\infty)=U_1$, $U(+\infty)=U_2$, $U'(\pm\infty)=0$.

Any of the constant solutions U_k is a uniform steady state solution of the partial differential equation (54). As such, it is stable by linear analysis if $g'(U_k)<0$, and unstable to long-wavelength disturbances if $g'(U_k)>0$.

Various special cases of (54) have been studied previously. Firstly, when $f(U)\equiv 0$, $g(U)=U(1-U)$, the equation reduces to that studied by Kolmogorov, Petrovskii, and Piskunov (1937) as a model for the spread of an advantageous gene. The only non-constant solutions are a one-parameter family of transition waves for which $U(-\infty)=0$ and $U(+\infty)=1$. Secondly, if $f(U)=U$ and $g(U)\equiv 0$, the result is Burger's equation, which has the explicit solution (Jeffrey and Kakutani, 1972)

$$U=\tfrac{1}{2}[U(-\infty)+U(+\infty)]-\tfrac{1}{2}[U(-\infty)-U(+\infty)]\tanh\left[\frac{U(-\infty)-U(+\infty)}{4}\phi\right]. \tag{57}$$

This is a two-parameter family of transition waves, parameterized by the velocity $\frac{1}{2}[U(-\infty)+U(+\infty)]$ and the amplitude $\frac{1}{2}[U(-\infty)-U(+\infty)]$. Lastly, when $f(U)\equiv 0$ and $g(U)=U(1-U)(U-a)$, $0<a<1/2$, a limiting form of Nagumo's equation results (McKean, 1970). At fixed a, this equation has a propagating transition wave solution, a nonpropagating solitary wave solution, and a one-parameter family of non-propagating periodic waves (McKean, 1970). It will be shown in the following that for certain $f(U)\not\equiv 0$ and "cubic" $g(U)$, solutions that represent *propagating* solitary and periodic waves also exist.

The nature of a critical point and the qualitative behaviour of trajectories near the critical point are governed by the eigenvalues of the linearized version of (57). Set $\xi=U-U_k$, $\eta=V$; then the linear equations are

$$\frac{d}{d\phi}\begin{bmatrix}\xi\\ \eta\end{bmatrix}=\begin{bmatrix}0 & 1\\ -g'(U_k) & f(U_k)-\theta\end{bmatrix}\begin{bmatrix}\xi\\ \eta\end{bmatrix}. \tag{58}$$

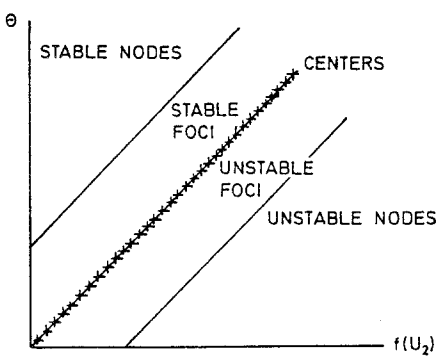

Fig. 2. Character of the critical point $(U_2, 0)$ as a function of $f(U_2)$ and θ

The eigenvalues of this matrix are

$$s_{\pm} = \frac{f(U_k)-\theta}{2} \pm \sqrt{\left(\frac{f(U_k)-\theta}{2}\right)^2 - g'(U_k)} \tag{59}$$

and so are real when the discriminant $\left(\frac{f(U_k)-\theta}{2}\right)^2 - g'(U_k) \geq 0$ and complex conjugates otherwise. If $g'(U_k) < 0$, the eigenvalues have opposite signs and the critical point is a saddle point. When $g'(U_k) > 0$, $(U_k, 0)$ is a node or focus, according as the discriminant is positive or negative, and is stable or unstable according as $\theta - f(U_k)$ is positive or negative. On the boundary between the stable and unstable foci, $f(U_k) = \theta$ and the critical point $(U_k, 0)$ is a center of the linearized system. These conclusions are summarized in Fig. 2.

Since $g(0) > 0$ by hypothesis, $g'(U)$ is always negative at the first positive zero of g and the corresponding critical point is always a saddle point. Moreover, the critical points are always in the sequence saddle point; node, focus or center; saddle point, etc. Therefore, when $g = 0$ has only one root, the critical point is a saddle point and analysis of the phase plane shows that there are no nonconstant bounded solutions, and hence no travelling waves. Any g that has two positive zeroes leads to travelling waves, but they are contained in the case where g has three zeroes. Accordingly, we consider only smooth functions $g(U)$ whose qualitative behaviour is similar to that shown in Fig. 3. An example of such U dependence arises in substrate-inhibited enzyme kinetics wherein U represents the substrate concentration (Haldane, 1965). Hereafter g will be regarded as fixed; bifurcation of steady state solutions will not be considered. For reasons that will be apparent shortly, we assume that the zeroes U_1, U_2 and U_3 are spaced so that

$$\left| \int_{U_1}^{U_2} g(U)\, dU \right| < \int_{U_2}^{U_3} g(U)\, dU. \tag{60}$$

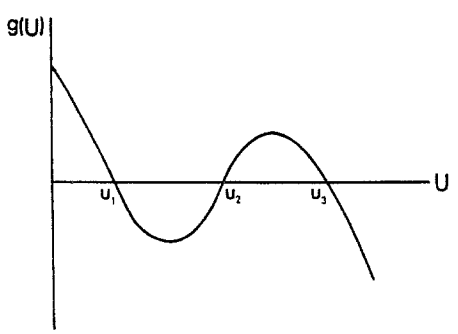

Fig. 3. Qualitative behaviour of the reaction and exchange function $g(U)$

The direction of the separatrices of either of the saddle points U_1 or U_3 are determined by the eigenvectors of the matrix in (58). These eigenvectors are

$$z_+ = \begin{bmatrix} 1 \\ s_+ \end{bmatrix}, \quad z_- = \begin{bmatrix} 1 \\ s_- \end{bmatrix} \tag{61}$$

and therefore the separatrices are arranged as shown in Fig. 4. The local analysis will be complete after we determine the phase portrait near U_2 when $|f(U_2)-\theta|$ is small.

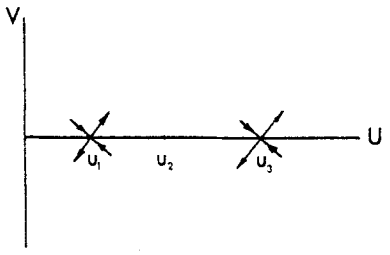

Fig. 4. The phase portrait of (56) near the critical point

It follows from (59) that when U_2 is a focus,

$$\frac{\partial \operatorname{Re}}{\partial \theta}\{s_\pm\} = -1/2, \tag{62}$$

and therefore the real part of the eigenvalues decreases monotonically as θ crosses the line $\theta = f(U_2)$. The real part is zero on this line and consequently the Hopf bifurcation theorem (Ruelle and Takens, 1971) guarantees that a periodic solution bifurcates at $\theta = f(U_2)$. However, further analysis is required to determine the direction of bifurcation and the stability of the bifurcating solution.

To determine these properties, expand $f(U)$ and $g(U)$ in (56) around $U = U_2$, and retain third order terms in the differences (ξ, η). The result is the system

$$\begin{aligned} \frac{d\xi}{d\phi} &= \eta \\ \frac{d\eta}{d\phi} &= -g'\xi + (f-\theta)\eta - \frac{g''}{2}\xi^2 + f'\xi\eta - \frac{g'''}{6}\xi^3 + \frac{f''}{2}\xi^2\eta + \mathcal{O}(\xi^4+\xi^4) \end{aligned} \tag{63}$$

where $f(U), g(U)$ and all their derivatives are evaluated at $U = U_2$. The direction of bifurcation and the stability of the periodic solution are governed by the sign of $\partial \operatorname{Re}\{s_\pm\}/\partial\theta$ and the sign of the third focal value a_3 (Andronov, Leontovich, Gordon and Maier, 1971). For (63), the focal value is given by

$$a_3 = \frac{\pi}{8(g')^{3/2}}[f''g' - f'g'']. \tag{64}$$

Since the partial derivative in (62) is always negative, there are only two possibilities for the direction and stability (Andronov, et al. 1971):

(i) $a_3 > 0$: an *unstable* periodic solution appears as θ increases across $\theta = f(U_2)$, and,

(ii) $a_3 < 0$: a *stable* periodic solution disappears as θ increases across $\theta = f(U_2)$.

The first and second derivatives of f and g determine which of these cases obtain. In the following, we assume that $f(U) = f_0 + f_1 U$, $f_1 > 0$, and that $g''(U_2) > 0$;

the assumption on $f(U)$ means that $A(u)=f_0+f_1\,U/2$. The physical significance of the assumption that $g''>0$ is not clear.[6] Since a nonzero f_0 can always be incorporated into θ, we can set $f_0=0$ without loss of generality. Then the second case obtains, and for $\theta-f_1\,U_2$ small and negative, the local features of the phase portrait are as shown in Fig. 4.

This choice for $f(U)$ implies that f_1 and θ are the only variable parameters in (56) because the kinetic and exchange function $g(U)$ is held fixed. The phase portrait of (56) changes qualitatively only when parameter values cross bifurcation loci in parameter space; once these loci are known, the complete phase portraits can be sketched for any values of f_1 and θ. The phase portraits then show directly the kinds of travelling waves that are possible. One such locus is already known, namely $\theta=f_1\,U_2$; to find the remainder we begin with $(f_1, \theta)=(0, 0)$.

When $(f_1, \theta)=(0, 0)$, (56) is a Hamiltonian system with Hamilton function

$$H(U, V)=\frac{V^2}{2}+\int g(U)\,dU. \tag{65}$$

The level curves are $H(U, V)=$constant, and along the curve through $(U_1, 0)$

$$\frac{V^2}{2}+\int_{U_1}^{U} g(U)\,dU=0. \tag{66}$$

By hypothesis, $\left|\int_{U_1}^{U_2} g(U)\,dU\right|<\int_{U_2}^{U_3} g(U)\,dU$ and consequently, there exists a $U^*\in(U_2, U_3)$ for which $\int_{U_1}^{U^*} g(U)\,dU=0$. This curve cuts the U axis at $U=U^*$ and since $H(U, V)$ is even in V, it forms a closed saddle-to-saddle loop that begins and ends at $(U_1, 0)$. For any point $(\tilde{U}, 0)$, $\tilde{U}\in(U_1, U_2)$, there exists a point $(\tilde{\tilde{U}}, 0)$, $\tilde{\tilde{U}}\in(U_2, U^*)$, such that $\int_{\tilde{U}}^{\tilde{\tilde{U}}} g(U)\,dU=0$: thus there is a one parameter family of closed orbits contained within the saddle-to-saddle loop. Moreover, it is easy to see that these are the only closed orbits that lie in the right half plane. These standing periodic and solitary waves are analogous to those that arise in Nagumo's equation (McKean, 1970).

The slope of the trajectories in the $U-V$ plane is

$$\frac{dV}{dU}=(f_1\,U-\theta)-\frac{g(U)}{V} \tag{67}$$

and when $f_1=\theta=0$,

$$\frac{dV}{dU}=-\frac{g(U)}{V}. \tag{68}$$

Whenever $U>U_3$ $\frac{dV}{dU}\lesseqgtr 0$ according as $V\lesseqgtr 0$ and therefore one outgoing separatrix tends to infinity as $U\to+\infty$ and one incoming separatrix originates

[6] If, for example, $g(U)=(U-U_1)(U-U_2)(U_3-U)$, then $g''(U_2)>0$ provided $U_1+U_3>2U_2$.

at infinity. If $g(U)>0$ for $U<0$, the other separatrices must also begin or terminate at infinity.[7] Consequently, the complete phase portrait for $f_1=\theta=0$ is as shown in Fig. 5.[8]

The first step in the analysis for f_1 and θ nonzero is to show that when periodic solutions exist, they necessarily lie within the vertical strip defined by

$$\{(U, V) \mid U_1<U<U_3, -\infty<V<\infty\}. \tag{69}$$

By differentiating (67) with respect to θ and f_1, one gets

$$\frac{\partial}{\partial \theta}\left\{\frac{dV}{dU}\right\}=-1 \quad \frac{\partial}{\partial f_1}\left\{\frac{dV}{dU}\right\}=U. \tag{70}$$

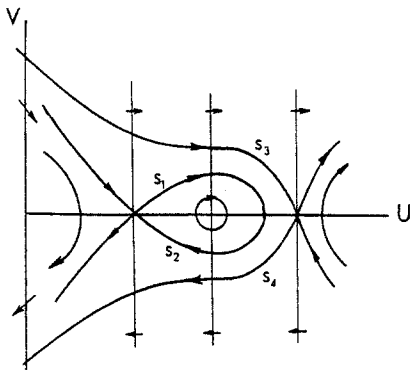

Fig. 5. The phase portrait of (56) when $f_1=\theta=0$. The loop $S_1 S_2$ corresponds to the standing pulse: the closed orbits to the standing periodic waves

Therefore, as θ increases the slope decreases and the vector field of (56) rotates clockwise. Similarly as f_1 increases the slope increases and the field rotates counterclockwise. If $f_1>0$ and $\theta>0$, the field along the vertical lines $U=U_1$ and $U=U_3$ is rotated from that shown in Fig. 5, but always by less than $\pm\pi/2$ radians. Since a closed orbit must have index $+1$, it can never encircle all three critical points. At most, it can encircle $(U_2, 0)$ and leave the strip by crossing one of the lines $U=U_1$ or $U=U_3$. Now if a closed orbit crosses one of the four half lines

$$\begin{aligned} L_1&=\{(U, V) \mid U=U_1 \ \ V\geq 0\} \\ L_2&=\{(U, V) \mid U=U_1, V\leq 0\} \\ L_3&=\{(U, V) \mid U=U_3 \ \ V\geq 0\} \\ L_4&=\{(U, V) \mid U=U_3 \ \ V\leq 0\} \end{aligned} \tag{71}$$

[7] The details of the behaviour "at infinity" depend on the particular choice of $g(U)$ but this behaviour is of no interest here.

[8] Had we chosen $g(U)$ such that $\int_{U_1}^{U_3} g(U)\,dU=0$, two stationary transition waves between U_1 and U_3 would have resulted. If $\left|\int_{U_1}^{U_2} g(U)\,dU\right|>\int_{U_2}^{U_3} g(U)\,dU$, the solitary pulse would begin and end at U_3.

once, it must cross it again, but this is impossible because the field never reverses direction on a half-line. Thus, when periodic solutions exist, they are confined to the vertical strip (69).

This result can be used to rule out the existence of periodic solutions in a large portion of the $f_1-\theta$ plane. Bendixson's theorem asserts that if the divergence of the vector field is of one sign in a region of the $U-V$ plane, there are no periodic solutions completely contained in that region (Andronov, Leontovich, Gordon and Maier, 1973). The divergence of (56) is $f_1\, U-\theta$, which is negative in the strip given by (69) when $\theta > f_1\, U_3$ and positive there when $\theta < f_1\, U_1$. Consequently, periodic solutions can be ruled out for parameters in the regions of Fig. 6, bounded by the θ-axis and line 'a' and by the f_1-axis and line 'f'.

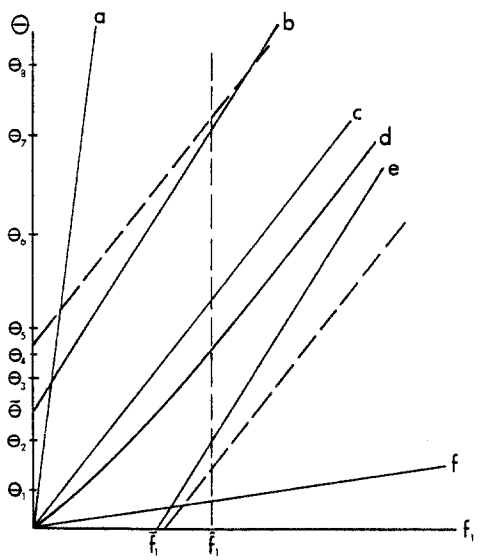

Fig. 6. The bifurcation diagram for (56) when $f(U)=f_1\, U$. a) $\theta=f_1\, U_3$; b) Locus of $U_3\, U_1$ transitions; c) $\theta=f_1\, U_2$; d) Locus of solitary waves; e) Locus of $U_1\, U_3$ transitions; f) $\theta=f_1\, U_1$.

Now suppose that θ is held at zero and f_1 is increased. The vector field rotates counterclockwise and the point at which the separatrix S_1 (Fig. 5) crosses $U=U_2$ moves monotonically upward while the corresponding point for S_3 moves monotonically downward. Thus there exists an $\tilde{f}_1$ at which S_1 and S_3 coincide; this orbit corresponds to a non-propagating transition wave between U_1 and U_3. Because θ and f_1 rotate the field in opposite directions, it is clear that if f_1 is increased beyond $\tilde{f}_1$, θ must be increased to maintain the saddle-to-saddle orbit. An analytic relation between θ and f_1 on this locus of saddle-to-saddle orbits is derived as follows.

If U is any solution for which $U'(\pm\infty)=0$, integration of (55) between $-\infty$ and $+\infty$ gives

$$\theta=f_1\,\frac{[U(+\infty)+U(-\infty)]}{2}-\frac{1}{U(+\infty)-U(-\infty)}\left[\int_{-\infty}^{\infty} g(U)\,d\phi\right]. \quad (72)$$

From the first equation of (56)

$$d\phi = \frac{dU}{V} \tag{73}$$

and if $\bar{V}(U)$ is that solution of (67) for which $\bar{V}(U(-\infty))=0$, then

$$\int_{-\infty}^{\infty} g(U)\, d\phi = \int_{U(-\infty)}^{U(+\infty)} \frac{g(U)\, dU}{\bar{V}(U)} = G(f_1, \theta). \tag{74}$$

The locus of transition waves is now given implicitly by

$$\theta = \frac{[U(+\infty)+U(-\infty)]}{2} f_1 - \frac{G(f_1, \theta)}{U(+\infty)-U(-\infty)} \tag{75}$$

Since θ and f_1 rotate the field in opposite directions, θ is monotone in f_1 and (75) is in principle, solvable for $\theta = \Theta(f_1)$. However, the solution of (56) must be known to do so.

The same procedure can be repeated starting with $f_1=0$ and allowing θ to increase. It can be seen that there is a $\tilde{\theta}$ at which a transition wave between U_3 and U_1 for $f_1=0$ and that θ increases monotonically with f_1 along the locus emanating from this point. Hence at fixed $f_1 > \tilde{f}_1$, there are two distinct transition waves of different speeds; a slow one from U_1 to U_3 and a fast one from U_3 to U_1. When $f_1 < \tilde{f}_1$, only the fast wave exists. The two curves along which these bifurcations occur are denoted by b and e in Fig. 6. Inasmuch as θ increases monotonically with f_1 on either curve, increasing the rate of active transport will increase the speed of both transition waves.

To complete the bifurcation analysis, it must be determined whether a saddle-to-saddle loop exists for $(f_1, \theta) > (0, 0)$ and whether there are loci other than $\theta = f_1 U_2$ along which periodic solution bifurcate. Such a loop exists at $(f_1, \theta)=(0, 0)$ (cf. Fig. 5) and by analyzing the rotation of the field as f_1 and θ vary near (0, 0), it is easy to see that there is a curve d through the origin along which the loop exists. In general, it cannot be determined *a priori* whether d lies above or below the line $\theta = f_1 U_2$. However, if we assume that periodic solutions only bifurcate from a multiple focus or from a saddle-to-saddle loop, the location of d is fixed by the following lemma (Andronov et al., 1971).

Let (x_1, y_1) be a saddle point of

$$\begin{aligned} \dot{x} &= P(x, y) \\ \dot{y} &= Q(x, y) \end{aligned} \tag{76}$$

and suppose that a separatrix forms a saddle-to-saddle loop. Then if $\sigma_1 = P_x(x_1, y_1) + Q_x(x_1, y_1)$ is positive (negative) the loop is unstable (stable).

For (56), $\sigma_1 = f_1 U_1 - \theta < 0$ for $\theta \in (f_1 U_1, f_1 U_3]$ and therefore all trajectories that originate near the loop on the interior side tend to the loop as $\phi \to \infty$. If the curve d lies above $\theta = f_1 U_2$, the critical point $(U_2, 0)$ is a stable focus or node and consequently there must be an unstable cycle in the interior of the loop. This is ruled out by our assumption and hence the curve d lies below the line $\theta = f_1 U_2$, as shown in Fig. 6.

The origin of the periodic solution that disappears at $\theta = f_1\, U_2$ is now determined by the following

Theorem (Andronov, et al., 1971): If a separatrix of (76) forms a saddle-to-saddle loop, and if $\sigma_1 \neq 0$, there exist systems close to (76) that have exactly one limit cycle of the same stability as the loop.

From this it follows that a periodic solution bifurcates from the saddle-to-saddle loop as d is crossed in the upward direction. As θ increases, the amplitude of this periodic solution decreases monotonically until, at $\theta = f_1\, U_2$, it coalesces with the unstable focus and a stable focus emerges. By assumption, this is the only periodic solution that exists and thus the bifurcation diagram (Fig. 6) is complete. The assumption made leads to the simplest possible bifurcation diagram; if it is relaxed one or more pairs of periodic solutions can arise for θ lying between the curves d and c. There is no way to test the assumption in general; specific systems must be examined case by case. With Fig. 6 at hand, all the types of qualitatively different phase portraits can be determined and all possible kinds of travelling waves can be found.

Suppose that f_1 is held fixed at $\hat{f}_1$. At $(\hat{f}_1, \theta_1)$, two distinct transition waves of equal velocity exist; one corresponds to a downward transition from U_2 to U_1 while the other is an upward transition from U_2 to U_3 (Fig. 7 a). The upward transition wave is analogous to the transition waves found in the KPP equation while both waves exist in Nagumo's equation (Nagumo, Yoshizawa and Armito, 1965). As θ increases, the field rotates clockwise, $(U_2, 0)$ changes into a focus, and at $\theta = \theta_2$ the separatrices S_1 and S_3 merge. At this point a transition wave from U_1 to U_3 bifurcates (Fig. 7 b). When θ lies between θ_1 and θ_4, the only bounded, nonconstant solution unwinds from the unstable focus and tends to U_1 as $\phi \to \infty$. This gives rise to a "transition-like" wave that has an oscillatory tail.

As θ increases further, the points at which the separatrices S_1 and S_2 cross the U axis approach each other and at $\theta = \theta_4$ a saddle-to-saddle loop exists. In the $\phi - U$ plane, this loop corresponds to a single pulse that travels at a velocity θ_4 (Fig. 7 d). If $(\bar{U}, 0)$ represents the point at which the loop crosses the U axis, the amplitude of the pulse is $\bar{U} - U_1$. By integrating (55) and rearranging, one finds that

$$\bar{U} - U_1 = \frac{-\int_{U_1}^{U} \frac{g(U)\,dU}{\bar{V}(U)}}{f_1\left[\frac{\bar{U}+U_1}{2}\right] - \theta} \tag{77}$$

which shows how the amplitude is related to f_1 θ and $g(U)$. However, this cannot be solved explicitly, even for relatively simple $g(U)$; to find the amplitude one must integrate (56) numerically.

As θ crosses θ_4 a periodic solution bifurcates from the saddle-to-saddle loop. Each periodic solution corresponds to a travelling periodic wave and since the periodic solution exists for all $\theta \in (\theta_4, f_1\, U_2)$, there is a one-parameter family of

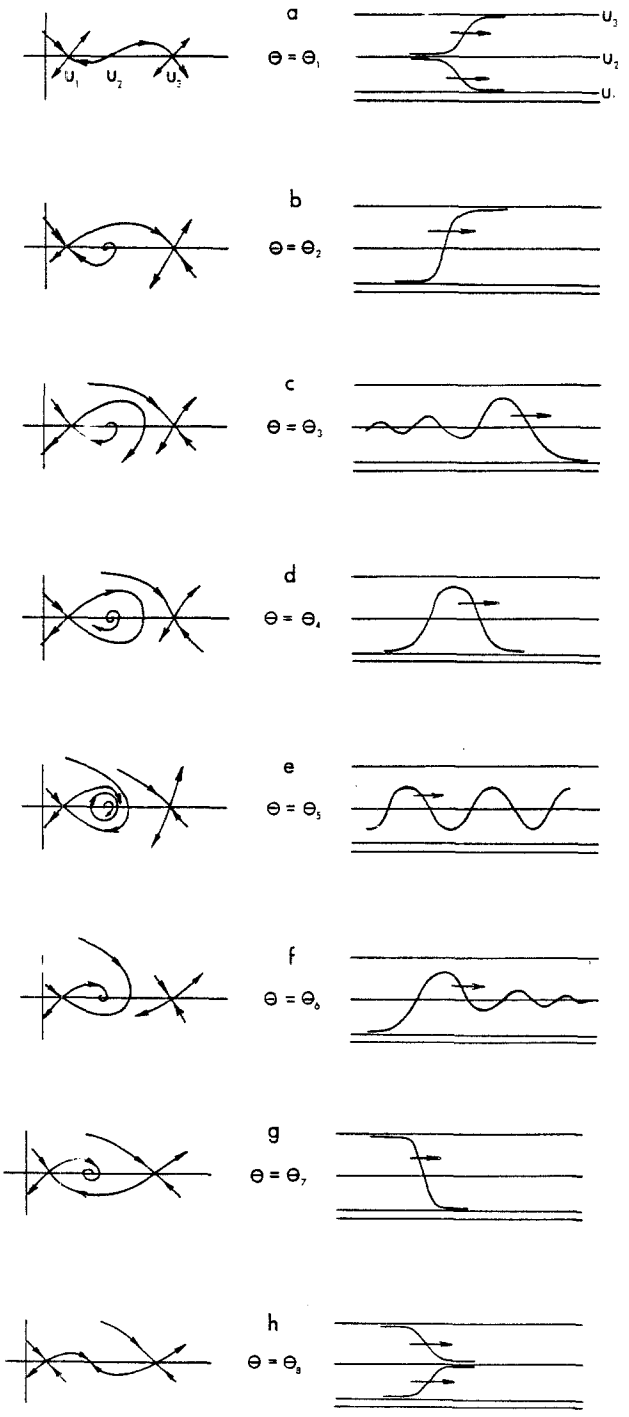

Fig. 7. The phase portrait (left) and the $\phi - U$ plane (right) for the θ-values indicated in Fig. 6

such waves, parameterized either by their velocity or amplitude. The amplitude ranges between $\bar{U}-U_1$ at $\theta=\theta_4$ and 0 at $\theta=f_1\ U_2$.

The remaining distinct types of phase portraits, given in Fig. 7 f, g, and k, can be obtained by reversing the direction of transition in 7 c, b, and a respectively. However, the corresponding pairs of waves travel at entirely different velocities.

It is evident from the foregoing that in the presence of any form of directed transport for which the "mobility" $A(u)$ increases with concentration, a simple one-component system can propagate a number of permanent waves of different velocity and waveform. Moreover, *most of these waves persist, no matter how small* f_1. Indeed, only the transition waves shown in Figs. 7 a and 7 b are precluded when $0<f_1<\tilde{f}_1$. Furthermore, the existence of this variety of waves is not peculiar to the chosen form of f. A case that may be of greater biological significance is the following.

Suppose that active transport occurs via a mechanism that saturates at high concentration, i.e., the flux approaches a constant. A function $A(u)$ that reflects such saturation is

$$A(U)=\frac{f_1}{K_1+U} \tag{78}$$

where K_1 is a fixed positive constant and f_1 is the bifurcation parameter. Corresponding to this $A(U)$ is

$$f(U)=\frac{f_1 K_1}{(K_1+U)^2} \tag{79}$$

To get a bifurcation diagram analogous to Fig. 6, it is necessary that $a_3<0$ and this requires that

$$g''<\frac{f'' g'}{f'}<0 \tag{80}$$

at $(U_2, 0)$.

By repeating the analysis that led to (75), one finds that

$$\theta=\frac{1}{U(-\infty)-U(+\infty)}\left[f_1 K_1\left(\frac{1}{K_1+U(+\infty)}-\frac{1}{K_1+U(-\infty)}\right)+G(f_1,\theta)\right] \tag{81}$$

and that there are two monotone increasing loci $\theta=\Theta(f_1)$ of transition wave bifurcations. Analysis of the vector field rotation near $(f_1,\theta)=(0,0)$ shows that the bifurcation loci for pulses and periodic waves are analogous to those shown in Fig. 6. Thus the same kinds of waves as shown in Fig. 7 exist for the monotone decreasing $A(U)$ given by (78).

6. Conclusion

That active transport may be important in developmental processes is suggested by several experimental observations. For example, it has recently been reported that certain eggs maintain an ionic current through themselves, presumbably by actively pumping ions out of the cell (Robinson and Jaffe, 1975). Such currents

produce electric fields that could set up gradients of morphogens by electrophoretically segregating cellular material. At the multicellular level, ionic gradients are known to exist in the plasmodium of *Dictyostelium discoideum* (Maeda and Maeda, 1973) and gradients of an inhibitory agent have often been invoked in explanations of *Hydra* development (Shostak, 1973). Active transport is one mechanism for maintaining such gradients in the face of diffusion (Cohen, 1972).

The results reported here show that active or directed transport, occurring in conjunction with diffusion and reaction, leads to a chemical transmission line capable of transmitting a variety of "messages" encoded by their waveform. Different waveforms can be used to initiate different cellular events at a location far from the origin of the signal. A transition wave can function as a travelling metabolic switch that activates a chain of reactions by switching the concentration of some control substance from a low to a high steady state. Since either high to low or low to high transition waves can propagate, the switching is reversible. A pulse, by contrast, provides a transitory signal that can be used to nudge a poised system down a particular developmental pathway by momentarily activating or inhibiting some cellular process. In all cases, the desired wave can be initiated by providing the proper input to the end cell or line of cells in a one- or two-dimensional array. In this way, events throughout an entire tissue can be brought under external control of the humoral system, simply by signalling the end cells. In a sense, our reaction-transport system can function as a distributed analog of the homogeneous chemical automata studied by Rössler (1974).

A number of questions remain unresolved. From a mathematical standpoint one would like to know for which of the travelling waves small disturbances in the waveform decay in time and what kinds of initial conditions produce travelling waves. Furthermore, the questions of whether any of these travelling waves persist for $\epsilon \neq 0$ is open. In the biological signalling problem, a more relevant question is to ask whether disturbances of the travelling waves grow or decay in space. As Rinzel (1975) has found, the results for the latter question on spatial stability are not necessarily identical with those for the question of *temporal* stability. More generally, one would like to know how close to the desired wave the signal at the boundary must be in shape and speed in order to stimulate this wave. In a few cases where exact solutions are available, this question can be answered analytically (Montroll and West, 1973). However, in general it requires numerical computations of the sort done by Scribner, Segel and Rogers (1974) in a somewhat similar context.

Having proved that a certain class of differential equations which model chemical reactions coupled with active and diffusive transport can support permanent-form travelling waves, it is necessary to connect these results with a realistic biological system. Analysis of a class of enzyme-catalyzed reactions that can show some of the behaviour reported here is in progress; the results will be reported in a future communication.

References

[1] Andronov, A. A., Leontovich, E. A., Gordon, I. I., Maier, A. G.: Theory of Bifurcations of Dynamic Systems on a Plane. Jerusalem: Israel Program for Scientific Translations 1971.
[2] Andronov, A. A., Leontovich, E. A., Gordon, I. I., Maier, A. G.: Qualitative Theory of Second-Order Dynamic Systems. Jerusalem: Israel Program for Scientific Translations 1973.
[3] Aris, R.: On stability criteria of chemical reaction engineering. Chem. Eng. Sci. *24*, 149—169 (1969).
[4] Aris, R., Amundson, N. R.: Mathematical Methods in Chemical Engineering, Vol. 2. Englewood Cliffs, N. J.: Prentice-Hall 1973.
[5] Barnett, S., Storey, C.: Matrix Methods in Stability Theory. New York: Barnes & Noble 1970.
[6] Caveney, S.: Intercellular communication in a positional field: movement of small ions between insect epidermal cells. Devel. Biol. *40*, 311—322 (1974).
[7] Chafee, N., Infante, E. F.: A bifurcation problem for a nonlinear partial differential equation of parabolic type. Applicable Anal. (to appear).
[8] Cohen, M. H.: Models of clocks and maps in developing organisms, in: Lectures on Mathematics in the Life Sciences (Cowan, J., ed.). Providence: American Mathematical Society 1972.
[9] Cole, J. D.: Perturbation Methods in Applied Mathematics. New York: Blaisdell 1968.
[10] Furshpan, E. J., Potter, D. D.: Low resistance junctions between cells and embryos and tissue culture. Curr. Top. Develop. Biol. *3*, 95—127 (1968).
[11] Gmitro, J. I., Scriven, L. E.: A physicochemical basis for pattern and rhythm, in: Intracellular Transport (Warren, K. B., ed.). New York: Academic Press 1966.
[12] Goodwin, B. C., Cohen, M. H.: A phase-shift model for the spatial and temporal organization of developing systems. J. Theor. Biol. *25*, 49—107 (1969).
[13] Haldane, J. B. S.: Enzymes. Cambridge: M.I.T. Press 1965.
[14] Herschkowitz-Kaufman, M., Nicolis, G.: Localized spatial structures and nonlinear chemical waves in dissipative systems. J. Chem. Phys. *56*, 1890—1895 (1972).
[15] Hess, B., Boiteux, A.: Oscillatory phenomena in biochemistry. Ann. Rev. Biochem. *40*, 237—258 (1971).
[16] Jeffrey, A., Kakutani, T.: Weak nonlinear dispersive waves: a discussion centered around the Korteweg-de Vries equation. SIAM Review *14*, 582—643 (1972).
[17] Jorné, J.: The effects of ionic migration on oscillations and pattern formation in chemical systems. J. Theor. Biol. *43*, 375—380 (1974).
[18] Joseph, D. D., Sattinger, D. H.: Bifurcating time periodic solutions and their stability. Arch. Ration. Mech. Anal. *45*, 79—109 (1972).
[19] Kato, T.: Perturbation Theory for Linear Operators. Berlin-Heidelberg-New York: Springer 1966.
[20] Kolmogorov, A. N., Petrovski, I. G., Piskunov, N. S.: Analysis of the diffusion equation connected with the increase of matter, and its application to one biological problem. Byul. Moskov. Go sud. Univ. section A, *1*, 6 (1937).
[21] Kopell, N., Howard, L. N.: Plane wave solutions to reaction-diffusion equations. Studies Appl. Math. *52*, 291—328 (1973).
[22] Kopell, N., Howard, L. N.: Wave trains, shock structures, and transition layers in reaction-diffusion equations. To appear in Proc. AMS-SIAM Symposium (New York, 1974) on "Mathematical Aspects of Chemical and Biochemical Problems and Quantum Chemistry".
[23] Loewenstein, W. R.: Emergence of order in tissues and organs: Communication through cell junctions. Implications in growth control and differentiation. Dev. Biol. Supp. *2*, 151—183 (1968).
[24] Maeda, Y., Maeda, M.: Exp. Cell Res. *82*, 125 (1973).
[25] McKean, H. P., Jr.: Nagumo's Equation. Adv. in Math. *4*, 209—223 (1970).
[26] Marsden, J.: The Hopf bifurcation for nonlinear semigroups. Bull. AMS *79*, 537—541 (1973).
[27] Montroll, E. W., West, B. J.: Models of population growth, diffusion, competition and rearrangement, in: Synergetics: Cooperative Phenomena in Multi-Component Systems. Proc. Symp. Synergetics, 1972 (Haken, H., ed.), pp. 143—156. 1972.
[28] Murray, J. D.: Perturbation effects on the decay of discontinuous solutions of nonlinear first order wave equations. SIAM J. Appl. Math. *19*, 273—298 (1970).

[29] Nagumo, J., Yoshizawa, S., Arimoto, S.: Bistable transmission lines. IEEE Trans. Circ. Theo. *12*, 400—412 (1965).
[30] Ortoleva, P. J., Ross, J.: Penetration of boundary perturbations in unstable chemical systems. J. Chem. Phys. *56*, 287—292 (1972).
[31] Ortoleva, P., Ross, J.: "On a variety of wave phenomena in chemical reactions" (to appear J. Chem. Phys.).
[32] Othmer, H. G., Scriven, L. E.: Interactions of reaction and diffusion in open systems. Ind. & Eng. Fund. *8*, 302—315 (1969).
[33] Othmer, H. G., Scriven, L. E.: Instability and dynamic pattern in cellular networks. J. Theor. Biol. *32*, 507—537 (1971).
[34] Othmer, H. G., Scriven, L. E.: Nonlinear aspects of dynamic pattern in cellular networks. J. Theor. Biol. *43*, 87—112 (1974).
[35] Plonsey, R.: Bioelectric Phenomena. New York: McGraw-Hill 1969.
[36] Rhee, H. K., Amundson, N. R.: Shock layer in two solute chromatography: effect of axial dispersion and mass transfer. Chem. Eng. Sci. *29*, 2049—2060 (1974).
[37] Rinzel, J.: Spatial stability of travelling wave solutions of a nerve conduction equation. Preprint (1975).
[38] Robinson, K. R., Jaffe, L. F.: Polarizing fucoid eggs drive a calcium current through themselves. Science *187*, 70—72 (1974).
[39] Rössler, O. E.: Chemical automata in homogeneous and reaction-diffusion kinetics, to appear in: Summer School on the Physics and Mathematics of the Nervous System (Conrad, M., Guttinger, W., eds.). New York: Springer.
[40] Ruelle, D., Takens, F.: On the nature of turbulence. Comm. Math. Phys. *20*, 167—192 (1971).
[41] Scribner, T. L., Segel, L. A., Rogers, E. H.: A numerical study of the formation and propagation of traveling bands of chemotactic bacteria. J. Theor. Biol. *46*, 189—219 (1974).
[42] Shostak, S.: Evidence of morphogenetically significant diffusion gradients in *Hydra viridis* lengthened by grafting. J. Embry. exp. Morph. *29*, 311—330 (1973).
[43] Turing, A. M.: The chemical basis for morphogenesis. Phil. Trans. Roy Soc. (London) *B237*, 37 (1952).
[44] Weisz, P. B.: Diffusion and chemical transformation. Science *179*, 433—440 (1973).
[45] Winfree, A. T.: Spiral waves of chemical acitivity. Science *175*, 634—636 (1972).
[46] Winfree, A. T.: Rotating solutions to reaction/diffusion equations in simply-connected media. SIAM-AMS Proc. *8*, 13—31 (1974).
[47] Zaikin, A. N., Zhabotinsky, A. M.: Concentration wave propagation in two-dimensional liquid-phase self-oscillating system. Nature *225*, 535—537 (1970).

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