3. Incorporation of Domain Growth

In this chapter the evolution equations describing reaction and diffusion of chemicals within a growing domain are derived and developed to consider several different examples of domain growth. These examples are examined in detail in the remainder of this thesis.

Several assumptions will be made about the growing domain. The domain is not treated as a realistic biological tissue: rather, we consider a general framework which will allow for subsequent inclusion of a detailed description of the properties of any specific tissue. Consequently the derivation of the governing equation is considered as a problem in kinematics, and no constitutive equations are proposed. Specifically, it is assumed that the domain undergoes deformation and expansion with no accompanying change in density. Growth consists of local directional volume expansion (possibly nonuniform) resulting in convection of material. Firstly we look at previous attempts to investigate reaction and diffusion on growing domains.

3.1 Previous Models and Results

Previously several studies have incorporated some form of parameter time dependence into reaction-diffusion equations and their numerical simulation to model pattern formation on a growing domain. This has been done by a variety of *ad hoc* means. In their paper on fish skin patterns, Kondo and Asai [64] do not model growth as such but increase the numerical grid mesh spacing during a computation. Bunow *et al.* [10] investigate pattern formation on two-dimensional geometries for the imaginal wing disk of *Drosophila* using a similar technique in a finite element calculation. Several other authors have performed similar numerical computations. Varea *et al.* [127] argue that domain growth simply reduces the effective diffusion and assume $D(t) = D_0/(\alpha t)^2$, where domain length L is proportional to time t.

In their influential paper, which seems to be the standard reference for reaction-diffusion on growing domains, Arcuri and Murray [3] propose a similar approach, suggesting that the domain growth changes the relative strengths of reaction and diffusion, as described by the dimensionless scaling parameter γ (see also the book by Murray [88]). The authors choose to scale the time variable with γ so that it appears explicitly in the reaction-diffusion equation multiplying the reaction term. The scaling parameter is then assigned a specific time dependence and the equation subsequently studied is

$$\frac{\partial \mathbf{c}}{\partial t} = \mathcal{D}\frac{\partial^2 \mathbf{c}}{\partial x^2} + \gamma(t)\mathbf{R}(\mathbf{c}, p) \tag{3.1}$$

with appropriate boundary and initial conditions. Discussing the results of their simulations the authors note a 'strong tendency towards frequency-doubling', however,

this behaviour seems by no means universal in their model. Eilbeck [35] studied the same model, finding that it produced a succession of patterns with no missing modes. Jenkins [55] has also studied this equation for the two-species Schnakenberg kinetics, imposing time-dependence $\gamma(t) = \gamma_0(1+\rho t)$. He found that for small ρ (~ 0.005) with $d \sim 0.1$, and under various alternative growth functions (quadratic and exponential), a sequence of pattern modes was generated with no missing modes. Larger values for ρ (~ 100) served to delay the onset of patterning to large amplitude, after which the same incremental sequence was generated. No dependence of the sequence on the initial data was observed. However, Jenkins also found that moving d further from its critical value precipitated the omission of modes from the sequence of patterns. For extreme values an initial window of frequency-doubling behaviour was generated.

3.1.1 Domain Growth in a Model for Alligator Dentition. In a paper addressing the spatio-temporal positioning of teeth primordia in the alligator *Alligator mississippiensis*, Kulesa *et al.* [65] consider the problem of modelling an exponentially growing domain. The lower jaw of the alligator is modelled as a one-dimensional entity, with symmetry about the frontal midpoint (thus only half the jaw is considered), and with growth due to a constant strain rate σ. They argued as follows: for a domain of length $\ell(t)$ growing under constant strain,

$$\frac{\mathrm{d}\ell}{\mathrm{d}t} = \sigma\ell, \quad \ell(t) \propto \exp(\sigma t). \tag{3.2}$$

Kinetic terms are considered on a small segment of the domain of length y, ignoring the effects of diffusion. If Q is the quantity of reactant in length segment y then the concentration $c = Q/y$. The change in concentration at each location over a small time interval $(t, t+\Delta t)$, $\Delta t \ll 1$, is due to dilution from the growth ($y \to y + \Delta y$) and to the action of the kinetic terms over this time interval ($Q \to Q + \Delta Q$). Hence

$$\frac{\Delta Q}{y} = R(c)\Delta t \tag{3.3}$$

where $R(c)$ is the function describing production and degradation of the reactant. Growth at constant strain rate gives that $\Delta y = \sigma y \Delta t$ and so

$$\begin{aligned} \Delta c &= \frac{Q+\Delta Q}{y+\Delta y} - \frac{Q}{y} \\ &= \frac{1}{y}\left(\frac{Q + yR(c)\Delta t}{1+\sigma\Delta t} - Q\right). \end{aligned} \tag{3.4}$$

For $\sigma\Delta t \ll 1$ we have $(1+\sigma\Delta t)^{-1} = 1 - \sigma\Delta t + \mathcal{O}(\Delta t)^2$ and so

$$\begin{aligned} \Delta c &= \frac{1}{y}\left(yR(c)\Delta t - \sigma Q\Delta t + \mathcal{O}(\Delta t)^2\right) \\ &\approx (R(c) - \sigma c)\Delta t, \end{aligned} \tag{3.5}$$

which leads us, ignoring the diffusion term, to

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \lim_{\Delta t \to 0} \frac{\Delta c}{\Delta t} = R(c) - \sigma c. \tag{3.6}$$

The diffusion coefficient, it is then supposed, scales with the square of the domain length, in the same manner as for Varea *et al.*, and the equation on the unit interval is then

$$\frac{\partial c}{\partial t} = \frac{d}{\gamma} \exp\left(-2\sigma t\right) \frac{\partial^2 c}{\partial x^2} + R(c) - \sigma c \tag{3.7}$$

Painter *et al.* [107] have used this approach to model the chemotactic response of cells to a reaction-diffusion prepattern on a growing domain.

Now we look at a general derivation for reaction and diffusion on a growing domain.

3.2 Kinematic Derivation

The equation for reaction and diffusion of a chemical C through a growing domain $\Omega(t)$ with boundary $\partial\Omega(t)$ may be derived from first principles. Considerations of conservation of matter in an elemental volume $V(t)$, which moves with the flow due to domain growth, give the equation for concentration $c(\mathbf{x}, t)$ at position $\mathbf{x}$ and time t as

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{V(t)} c(\mathbf{x}, t)\, \mathrm{d}\mathbf{x} = \int_{V(t)} \Big[-\nabla \cdot \mathbf{j} + R(c, p) \Big]\, \mathrm{d}\mathbf{x}. \tag{3.8}$$

where the integrals are over any (time-varying) elemental volume. The effect of other chemicals or factors in the tissue on the reaction rates are represented in the reaction term R by the variable $p(\mathbf{x}, t)$. Application of the divergence theorem is consistent, being instantaneously valid at all time. The Reynolds Transport theorem of elementary fluid mechanics (reproduced in Appendix B.1) gives

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{V(t)} c(\mathbf{x}, t)\, \mathrm{d}\mathbf{x} = \int_{V(t)} \left[\frac{\partial c}{\partial t} + \nabla \cdot (\mathbf{a}\, c) \right] \mathrm{d}\mathbf{x} \tag{3.9}$$

where $\mathbf{a}$ is the velocity field of the flow generated by the domain growth and

$$\frac{d\mathbf{x}}{dt} = \mathbf{a}(\mathbf{x}, t). \tag{3.10}$$

The usual argument as to the arbitrariness of the elemental volume requires that the equation hold everywhere on the growing domain $\Omega(t)$. The instantaneous flux $\mathbf{j}$ is taken to be due to Fickian diffusion, $\mathbf{j} = -D\nabla c$ where D is the diffusivity at constant density. The equations may be nondimensionalised as before, introducing no new dimensionless parameters. However, it is useful to point out that the incorporation of domain growth introduces (several) new timescales into the problem. This is discussed further below.

We introduce nondimensional variables $\bar{c}$ for the concentration and position $\bar{\mathbf{x}} = \mathbf{x}/L$, where L is a length scale. As before the reaction term is characterised by reaction rate ω and time is scaled according to $\bar{t} = \omega t$. Taking $\bar{\mathbf{a}} = \mathbf{a}/\omega L$, and dropping the

over-bars for notational convenience we recover the nondimensional evolution equation for $c(\mathbf{x}, t)$

$$\frac{\partial c}{\partial t} + \nabla \cdot (\mathbf{a}\, c) = \frac{d}{\gamma}\nabla^2 c + R(c, p) \tag{3.11}$$

$$\mathbf{x} \in \Omega(t), \quad t \in [0, \infty) \tag{3.12}$$

where $d = D/D_*$ for reference diffusivity D_* and $\gamma = \omega L^2/D_*$ is the dimensionless scaling parameter. For a system of reaction-diffusion equations D_* will be taken to be the diffusivity of the fastest diffusing species. Boundary conditions are imposed on

$$\mathbf{x} \in \partial\Omega(t) \tag{3.13}$$

and prescription of initial conditions on the domain closes the problem.

The derivation on the growing domain introduces two new terms to the standard reaction-diffusion equation. These terms will be discussed in more detail below, however, it will be intuitively clear that material is transported around the domain by the term $\mathbf{a} \cdot \nabla c$, and that $c\nabla \cdot \mathbf{a}$ represents a dilution due to local volume increase.

3.2.1 Determination of the Flow. The flow $\mathbf{a}$ may be specified directly for certain simple cases, however, in general it is expected that $\mathbf{a}(\mathbf{x}, t)$ will be determined by some extended system of constitutive equations describing the properties of the tissue. Here we will assume that growth properties are determined locally in the tissue, due to factors that are not modelled but which might include prepatterns in growth factors and cellular and sub-cellular structures influencing the direction of growth. Such properties will be specified on an initial domain and will be displaced, following the flow due to subsequent tissue growth.

The movement of tissue as a result of growth can be described in terms of the trajectories of elements of the tissue, i.e. the paths followed in time by elemental volumes. This Lagrangian description is particularly apt as the factors determining local growth characteristics move with the tissue as it grows. Therefore, a very natural coordinate system in which to work is Lagrangian coordinates, $(\mathbf{X}, t)$ where $\mathbf{X} = (X_1, X_2, X_3)$ is the initial position of a tissue element moving with the flow $\mathbf{a}$. The movement of tissue as a result of growth can be described in terms of the trajectories $\mathbf{\Gamma}$ of elements of the tissue such that

$$\mathbf{x} = \mathbf{\Gamma}(\mathbf{X}, t) = \big(\Gamma_1(\mathbf{X}, t), \Gamma_2(\mathbf{X}, t), \Gamma_3(\mathbf{X}, t)\big) \tag{3.14}$$

where $\mathbf{\Gamma}(\mathbf{X}, t)$ describes the trajectory[1] of a tissue element initially at position $\mathbf{X}$. The inverse of $\mathbf{\Gamma}$ is given by

$$\mathbf{X} = \mathbf{\Lambda}(\mathbf{x}, t) = \big(\Lambda_1(\mathbf{x}, t), \Lambda_2(\mathbf{x}, t), \Lambda_3(\mathbf{x}, t)\big) \tag{3.15}$$

which gives the initial location of a particle at position $\mathbf{x}$ at time t.

[1]Conventionally one writes $\mathbf{x} = \mathbf{x}(\mathbf{X}, t)$, representing the dependent variable and functional dependence by the same letter, but for clarity we will make the functional dependence explicit.

For the purposes of examining the effect of growth on pattern formation we will not be interested in solid body translations and rotations of the domain, which leave the pattern generated by reaction and diffusion within the tissue unaffected. The coordinates for the domain are chosen such that there is a reference point which is initially at the origin of the coordinate system and which remains at the origin. Some general conditions must then be observed for the components of $\mathbf{\Gamma}$. The initial condition is, by the definition of $\mathbf{\Gamma}$, that

$$\mathbf{\Gamma}(\mathbf{X}, 0) = \mathbf{X}. \tag{3.16}$$

In the absence of solid body translations we also have the boundary condition that for the reference point, $\mathbf{X}_r$, we require that $\mathbf{\Gamma}(\mathbf{X}_r, t) = \mathbf{X}_r$ and choosing the coordinate system such that $\mathbf{X}_r = \mathbf{0}$ leads to the condition

$$\mathbf{\Gamma}(\mathbf{0}, t) = \mathbf{0}. \tag{3.17}$$

Furthermore the domain is supposed to remain simply connected, which requires in one dimension (for example) that if

$$0 \leq X_p < X_q \leq 1, \tag{3.18}$$

then

$$\Gamma(X_p, t) < \Gamma(X_q, t), \qquad \forall t > 0. \tag{3.19}$$

This will be ensured by the approach taken here, where growth is specified locally and then integrated up to find the global form for the domain growth, as will be shown below.

3.2.2 Local Specification of the Growth. The deformation of the tissue due to growth is described by the rate-of-deformation tensor $\mathcal{L}_{ij}$ which can be decomposed into symmetric and antisymmetric parts $\mathcal{D}_{ij}$ and $\mathcal{W}_{ij}$ respectively. The antisymmetric part is associated with rigid body rotation, which is not relevant to pattern formation, and so in what follows we will consider only the symmetric component of $\mathcal{L}_{ij}$, the rate-of strain tensor $\mathcal{D}_{ij}$. Components of $\mathcal{D}_{ij}$ correspond to

- $\mathcal{D}_{ij}$ $(i = j)$: the rate of extension along the axis x_i
- $\mathcal{D}_{ij}$ $(i \neq j)$: the rate of (pure) shear along between axes x_i and x_j (with no accompanying volume change).

The trace of $\mathcal{D}_{ij}$

$$\mathcal{D}_{ii} = \nabla \cdot \mathbf{a} = S(\mathbf{X}, t) \tag{3.20}$$

(summation implied) gives the rate of volumetric change per unit volume (the rate of volume expansion) and so, for domain *growth*, $S(\mathbf{X}, t) > 0$. The antisymmetric part of $\mathcal{L}_{ij}$ corresponds to angular velocity $\frac{1}{2}\boldsymbol{\omega}$

$$\nabla \times \mathbf{a} = \boldsymbol{\omega} \tag{3.21}$$

for $\boldsymbol{\omega} = (\omega_1, \omega_2, \omega_3)$ and so we set $\boldsymbol{\omega} = \mathbf{0}$.

The components of the rate of strain tensor $\mathcal{D}_{ij}$ are determined by the local properties of the tissue, and thus we consider $\mathcal{D}_{ij}(\mathbf{X}, t)$, where

$$\mathcal{D}_{ij} = \frac{\partial a_i}{\partial x_j} \tag{3.22}$$

which is related to coordinates $(\mathbf{X}, t)$ via

$$\frac{\partial^2 \Gamma_i}{\partial t \, \partial X_k} = \frac{\partial a_i}{\partial x_j} \frac{\partial \Gamma_j}{\partial X_k} \tag{3.23}$$

(summation implied) from which in general we can calculate the function $\boldsymbol{\Gamma}(\mathbf{X}, t)$ and thus $\mathbf{a}$, the flow due to the domain growth.

Now we reconsider the terms introduced into the reaction-diffusion equation by the incorporation of domain growth. As $\nabla \cdot \mathbf{a} = S(\mathbf{X}, t)$ gives the local rate of volume expansion we recognise $c\nabla \cdot \mathbf{a} = Sc$ as a dilution term where (ignoring production terms in the kinetics) the local concentration is decreasing as the containing volume increases. The convection term $\mathbf{a} \cdot \nabla c$ represents the transport of chemical within the tissue as the tissue moves due to the growth (such that there is no movement of the chemical relative to the tissue). Then we can rewrite equation (3.11) as

$$\frac{\partial c}{\partial t} + \mathbf{a} \cdot \nabla c = \frac{d}{\gamma} \nabla^2 c + R(c, p) - Sc \tag{3.24}$$

In the following sections we consider several specific cases, where we assume the form of the components of $\mathcal{D}_{ij}$ and from them derive the trajectories, $\boldsymbol{\Gamma}$, and the flow, $\mathbf{a}$. Firstly we consider the general form taken for the evolution equation for one spatial dimension under a generalised local growth.

3.3 One-dimensional Growth

In one spatial dimension the specification of the local growth characteristics reduces to specifying the sole component of $\mathcal{D}_{ij}$. We wish to determine the trajectories given by

$$x = \Gamma(X, t) \tag{3.25}$$

with inverse $X = \Lambda(x, t)$. Equation (3.23) becomes

$$\frac{\partial^2 \Gamma}{\partial t \, \partial X} = S(X, t) \frac{\partial \Gamma}{\partial X} \tag{3.26}$$

where growth is now fully determined by the local expansion rate

$$\mathcal{D}_{11} = \frac{\partial a}{\partial x} = S(X, t) = S\big(\Lambda(x, t), t\big). \tag{3.27}$$

The boundary conditions on Γ are

$$\Gamma(0, t) = 0, \quad \Gamma(X, 0) = X \tag{3.28}$$

and then Γ may be computed directly by integrating (3.26) twice

$$\Gamma(X,t) = \int_0^X \left[\exp \int_0^t S\left(\bar{X},\bar{t}\right)\, \mathrm{d}\bar{t}\right] \mathrm{d}\bar{X}. \tag{3.29}$$

Then the flow is determined by

$$a = \frac{\mathrm{d}x}{\mathrm{d}t} = \frac{\partial \Gamma}{\partial t} \tag{3.30}$$

which fully determines the domain growth. In one dimension the evolution equation for $c(x,t)$ is

$$\frac{\partial c}{\partial t} + a\frac{\partial c}{\partial x} = \frac{d}{\gamma}\frac{\partial^2 c}{\partial x^2} + R(c) - Sc \tag{3.31}$$

where $S = S(\Lambda(x,t),t)$ and $a = a(\Lambda(x,t),t)$ so that each term in equation (3.31) is written in coordinates (x,t). The solution is defined on

$$x \in [0,\ell(t)]\,, \quad t \in [0,\infty) \tag{3.32}$$

where $\ell(t)$ is the time-dependent domain length. Following spatial nondimensionalisation using the initial domain length as reference lengthscale, such that $\ell(0) = 1$, then

$$\ell(t) = \Gamma(1,t). \tag{3.33}$$

3.3.1 Uniform Scaling. For the investigation of pattern formation phenomena it is natural to transform to a time-independent domain. Here we take a uniform spatial scaling to transform spatial coordinates to the unit interval, under

$$(x,t) \to (\xi,\tau) = \left(\frac{x}{\ell(t)}, t\right) \tag{3.34}$$

such that ξ is defined on

$$\xi \in [0,1]\,. \tag{3.35}$$

Under this transformation we have

$$\frac{\partial c}{\partial t} = -\xi\frac{\dot{\ell}}{\ell}\frac{\partial c}{\partial \xi} + \frac{\partial c}{\partial \tau}, \quad \frac{\partial c}{\partial x} = \frac{1}{\ell}\frac{\partial c}{\partial \xi} \tag{3.36}$$

and the transformed evolution equation is

$$\frac{\partial c}{\partial t} = \frac{d}{\gamma}\frac{1}{[\ell(t)]^2}\frac{\partial^2 c}{\partial \xi^2} + \left[\xi\frac{\dot{\ell}(t)}{\ell(t)} - \frac{a(\xi,t)}{\ell(t)}\right]\frac{\partial c}{\partial \xi} + R(c) - Sc \tag{3.37}$$

where the dot implies differentiation with respect to time.

3.4 Lagrangian Formulation

An inherent difficulty with the formulation for the evolution equation that we have derived for reaction and diffusion on the growing domain in coordinates $(\mathbf{x},t)$ is that for the purposes of numerical computation the form of $\mathbf{\Lambda}(\mathbf{x},t)$ must be known explicitly

(we are required to perform the inversion of $\mathbf{\Gamma}(\mathbf{X},t)$). This may not be possible for anything but simple functional forms for $\mathbf{\Gamma}$ (although of course the inversion may be computed numerically, this will prove computationally expensive) and will certainly not be possible if S is determined from some other data, or indeed if S has time and space dependence through the chemical species themselves,

$$S(\mathbf{x},t) = S\big(c_1(\mathbf{x},t),\dots c_n(\mathbf{x},t)\big). \tag{3.38}$$

which is called *reactant-controlled* domain growth. Thus it is useful to write the variables as functions of the Lagrangian position and to derive the evolution equation for $c(\mathbf{X},t)$. In one dimension this is done below. For the flow, and using subscripts to denote partial differentiation,

$$a(X,t) = \Gamma_t \tag{3.39}$$

$$a_x(X,t) = \frac{\Gamma_{Xt}}{\Gamma_X} = S(X,t) \tag{3.40}$$

and the derivatives in the evolution equation are transformed as

$$\frac{\partial c}{\partial t} = -\frac{\Gamma_t}{\Gamma_X}\frac{\partial c}{\partial X} + \frac{\partial c}{\partial t}, \quad \frac{\partial c}{\partial x} = \frac{1}{\Gamma_X}\frac{\partial c}{\partial X}, \quad \frac{\partial^2 c}{\partial x^2} = -\frac{\Gamma_{XX}}{{\Gamma_X}^3}\frac{\partial c}{\partial X} + \frac{1}{{\Gamma_X}^2}\frac{\partial^2 c}{\partial X^2}. \tag{3.41}$$

Hence equation (3.31) for $c(X,t)$ becomes

$$c_t = \frac{d}{\gamma}\left(\frac{1}{{\Gamma_X}^2}c_{XX} - \frac{\Gamma_{XX}}{{\Gamma_X}^3}c_X\right) + R(c) - Sc \tag{3.42}$$

$$\Gamma_{Xt} = S(X,t)\,\Gamma_X \tag{3.43}$$

where we have made the coupling to the equation for $\Gamma(X,t)$ explicit, and where of course Γ may be found explicitly by integrating as in equation (3.29). The coupled evolution equations for $c(X,t)$ and $\Gamma_X(X,t)$ are in a form which is much more amenable to numerical solution, and this is discussed later in Chapter 6. We have initial and boundary conditions for $c(X,t)$

$$c(X,0) = c_0(X) \tag{3.44}$$

$$c_X(0,t) = c_X(1,t) = 0 \tag{3.45}$$

and also for $\Gamma(X,t)$

$$\Gamma(X,0) = X \tag{3.46}$$

$$\Gamma(0,t) = 0. \tag{3.47}$$

To recover the form of the pattern on the dimensional domain (x,t) the solution must be scaled with the (time and space-dependent) trajectories $\Gamma(X,t)$ to determine $c(x,t)$. We have presented the Lagrangian formulation in one dimension, however, the analogous transformation to Lagrangian coordinates may be performed in higher spatial dimensions (W. W. Hackborn, *pers. comm.*).

3.5 Uniform Domain Growth in N-Dimensions

Now we turn to discussion of the simple case when the domain growth is determined by local expansion rates which are independent of spatial position,

$$\mathcal{D}_{ij} = \delta_{ij}\sigma(t) \tag{3.48}$$

where δ_{ij} is the Kronecker delta. Then the total volume expansion rate is

$$\mathcal{D}_{ii} = S(\mathbf{X}, t) = 3\sigma(t). \tag{3.49}$$

Direct integration with initial condition (3.16) and boundary condition (3.17) gives

$$\mathbf{\Gamma}(\mathbf{X}, t) = \mathbf{X} \exp\left[\int_0^t \sigma(\bar{t})\, \mathrm{d}\bar{t}\right] \equiv \mathbf{X} r(t) \tag{3.50}$$

which defines $r(t)$, and by differentiation the flow is easily determined as

$$\mathbf{a} = \mathbf{X} r(t)\sigma(t) = \mathbf{x}\sigma(t), \tag{3.51}$$

which is consistent with $S = \nabla \cdot \mathbf{a} = 3\sigma(t)$. The essential feature of uniform growth is that any two points move apart with a (relative) velocity which depends only on their separation. Thus for two points $\mathbf{x}_p$ and $\mathbf{x}_q$ with separation $\Delta\mathbf{x}$ then from the above we have that their relative velocity $\Delta\mathbf{a}$ is given by

$$\Delta\mathbf{a} = \mathbf{a}(\mathbf{x}_p, t) - \mathbf{a}(\mathbf{x}_q, t) = (\mathbf{x}_p - \mathbf{x}_q)\sigma(t) = \Delta\mathbf{x}\sigma(t). \tag{3.52}$$

Now we consider the evolution equation under uniform growth. The convection term in equation (3.24) corresponds only to uniform transport, and is expected to vanish under a uniform spatial scaling, as given for one dimension in section 3.3. In general the nondimensional domain length in the i^{th} direction is given by

$$\ell_i(t) = \Gamma_i(\mathbf{1}, t) = r(t) \tag{3.53}$$

and so we take the scaling

$$(\mathbf{x}, t) \to (\boldsymbol{\xi}, t) = \left(\frac{\mathbf{x}}{r(t)}, t\right) \tag{3.54}$$

where $\boldsymbol{\xi} = (\xi_1, \xi_2, \xi_3)$. Then the flow $\mathbf{a} = \mathbf{x}\dot{r}/r = \boldsymbol{\xi}\dot{r}(t)$ and the i^{th} component of the convection

$$\frac{1}{\ell(t)}\left[\xi_i \dot{\ell}(t) - a_i(\xi, t)\right] = 0. \tag{3.55}$$

It is straightforward to see that this is in fact the only possible domain growth for which the convection term disappears under uniform scaling. Using the definitions of $\boldsymbol{\xi}$, $\mathbf{a}$ and $\mathbf{\Gamma}$, and rearranging, the components of (3.55) can be written as

$$\frac{\partial \Gamma_i}{\partial t}(\mathbf{X}, t) - \frac{\dot{r}(t)}{r(t)}\Gamma_i(\mathbf{X}, t) = 0. \tag{3.56}$$

This implies that the components of $\mathbf{\Gamma}(\mathbf{X}, t)$ are separable functions of $\mathbf{X}$ and t, but the conditions (3.16) and (3.17) require that $\mathbf{\Gamma}$ take the form given in equation (3.50).

Another similar case considers anisotropic domain growth for which the axial expansion rates differ, but each are uniform (having no space dependence)

$$\mathcal{D}_{ij} = \delta_{ij}\sigma_i(t) \tag{3.57}$$

(no summation). Direct integration gives

$$\mathbf{\Gamma}(\mathbf{X},t) = \big(X_1 r_1(t), X_2 r_2(t), X_3 r_3(t)\big) \tag{3.58}$$

where the time dependences are given by

$$r_i(t) = \exp \int_0^t \sigma_i(\bar{t})\, d\bar{t}. \tag{3.59}$$

In this case the local rate of volume increase is given by

$$S = \nabla \cdot \mathbf{a} = \sigma_1(t) + \sigma_2(t) + \sigma_3(t). \tag{3.60}$$

For general non-uniform domain growth $\mathbf{\Gamma}(\mathbf{X},t)$ is a non-separable function of $\mathbf{X}$ and t. Thus in general the convection terms are not removed under a uniform transformation such as (3.54) and so may play a role in the formation of pattern in the system. In order to investigate pattern formation under non-uniform domain growth we must consider specific examples. In Chapter 6 we consider the one-dimensional problem comprising two sub-domains each with uniform but different growth rates, the *piece-wise uniform* case, to gain some insight into the complexities of pattern sequence generation under more general growth functions.

3.5.1 Slow Uniform Growth. The evolution equations in the previous section are derived for local expansion rates which are functions of time but not position. The introduction of domain growth necessarily introduces a new timescale to the problem. We denote this explicitly for the uniform case (see equation (3.49)) by writing

$$S(\mathbf{X},t) = 3\rho\sigma(t) \tag{3.61}$$

where $\sigma(t) \sim \mathcal{O}(1)$, which introduces the timescale $1/\rho$.[2] The effect of growth on pattern formation is expected to depend on the relative magnitudes of the timescales for domain growth and for pattern formation. One specific timescale for pattern formation that emerges from the linear analysis was presented in Chapter 2. Having nondimensionalised the equations appropriately, the spatial patterns are established on a time of $\mathcal{O}(1)$, and hence $1/\rho$ measures the timescale for domain growth relative to that for pattern formation.

In the following chapters we consider the effect of domain growth on pattern formation when the domain changes size and shape over a much longer timescale than that for pattern formation. This must be the relevant case for biological systems where

[2]The growth rate-determining parameter ρ introduces a timescale for domain growth, however, the rate at which the domain grows must be calculated from $\mathrm{d}\mathbf{\Gamma}(\mathbf{1},t)/\mathrm{d}t$ which is in general a function of ρ and time t.

reaction and diffusion of chemicals will be much faster than the timescales over which the cellular machinery involved in growth will operate. Thus we study slow domain growth, for which

$$0 < \rho \ll 1 \tag{3.62}$$

and initially we will concentrate on uniform growth on the one-dimensional domain. Then the evolution equation is given by

$$\frac{\partial c}{\partial t} = \frac{d}{\gamma(t)}\frac{\partial^2 c}{\partial \xi^2} + R(c) - \rho\sigma(t)c \tag{3.63}$$

where $\gamma(t)$ is the time-dependent scaling parameter defined by

$$\gamma(t) = \gamma_0 \big(r(t)\big)^2 = \gamma_0 \exp\left[2\rho \int_0^t \sigma\left(\bar{t}\right) \mathrm{d}\bar{t}\right] \tag{3.64}$$

and $\gamma_0 = \gamma(0)$ is the scaling parameter for the static domain problem when $\rho = 0$.

When $\rho \ll 1$ the dilution term is small, and in particular it is small compared to any $\mathcal{O}(1)$ linear terms in the kinetic function. Pattern formation in this nonautonomous equation is studied in the following chapter.

3.5.2 Modified Reaction Term. We examine the way in which the dilution term may modify the kinetics. The extra term is in general time and space-dependent. A modified reaction term $\hat{\mathbf{R}}$ may be defined for $S(\mathbf{x}, t)$, where

$$\hat{\mathbf{R}}\left(\mathbf{x}, t\right) = \mathbf{R}\left(\mathbf{c}\right) - S(\mathbf{x}, t)\,\mathbf{c}. \tag{3.65}$$

The obvious consequence is that there may be no *homogeneous* steady state for kinetics $\hat{\mathbf{R}}$, due to spatial dependence. The dilution term is independent of $\mathbf{x}$ when the local expansion is uniform. Furthermore, the dilution term is time-independent when the local expansion is constant (the domain grows under a constant strain rate) in each direction, $\sigma_i(t) = \rho_i$, for which

$$\Gamma_i(\mathbf{X}, t) = X_i \exp \rho_i t. \tag{3.66}$$

For uniform growth, where $\hat{\mathbf{R}}$ is independent of $\mathbf{x}$, at the initial time the kinetics do not have the same steady state as for the static problem. The new steady state must be calculated according to the form and parameters of the growth function, and perturbations taken about these values to produce the initial data.

The modification to the reaction kinetics necessarily changes the dispersion relation and the Turing space for the onset of the instability (although standard linear analysis cannot be performed for the nonautonomous problem). This raises the possibility that the dilution contribution will move the Turing space so as to allow the onset of instability where the original parameters on a static domain were incompatible, or indeed to move the system out of the Turing space.

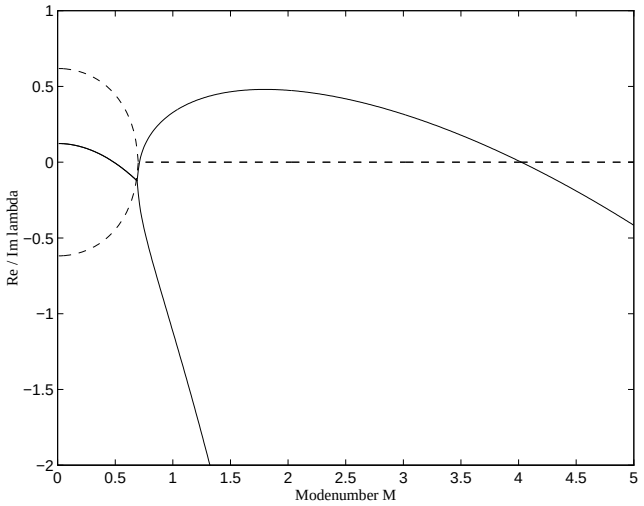


FIGURE 3.1 Dispersion relation for modified kinetic scheme, with $a = 0.1$, $b = 0.9$, $d = 0.05$, $\rho = 0.15$ and $\gamma = 10.0$ (remembering that γ scales the wavenumber). The real part of λ is shown as a solid line, and the imaginary part as a dashed line. The wavenumber is represented by a continuous mode number m where $k = m\pi$.

We now examine the modified kinetics for exponential growth, taking as an example Schnakenberg kinetics, for which, writing $\hat{\mathbf{R}} = (\hat{f}, \hat{g})$, we have

$$\hat{f}(u, v; \rho) = b - \rho u - uv^2 \tag{3.67}$$

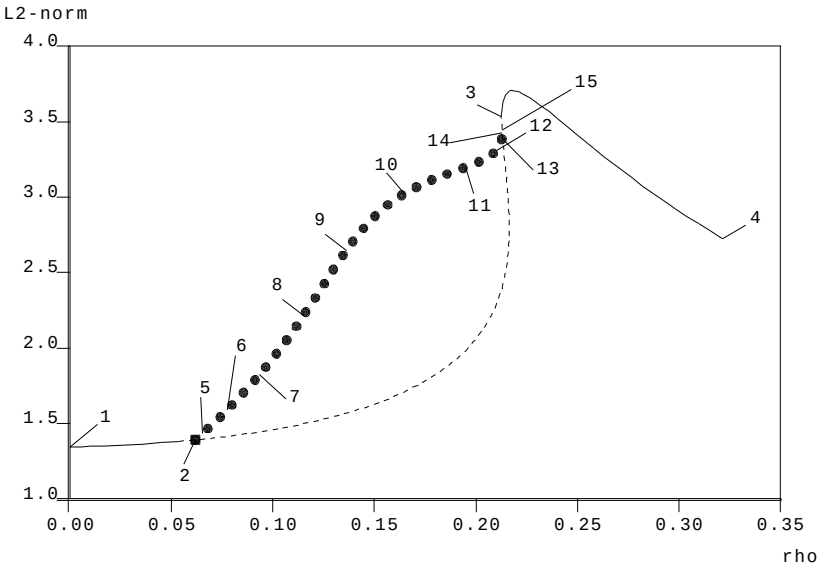
$$\hat{g}(u, v; \rho) = a - (1 + \rho)v + uv^2. \tag{3.68}$$

The dispersion relation for these modified kinetics, for a particular parameter set, is shown in Figure 3.1. Here we see that the zeroth mode has $\mathcal{R}e\,\lambda > 0$ and also that $\mathcal{I}m\,\lambda \neq 0$, allowing temporal oscillation when the system is subject to spatially homogeneous perturbation, i.e. to perturbation in the absence of diffusion. Thus the modified kinetics are no longer in the Turing space, for which the steady state must be stable (and not oscillating) in the absence of diffusion. Numerical simulation has verified the presence of such a Hopf bifurcation for sufficiently large ρ. Using the numerical bifurcation and continuation package `AUTO97` [30, 31, 28, 29] we have performed a numerical bifurcation analysis on the ordinary differential equation system given by

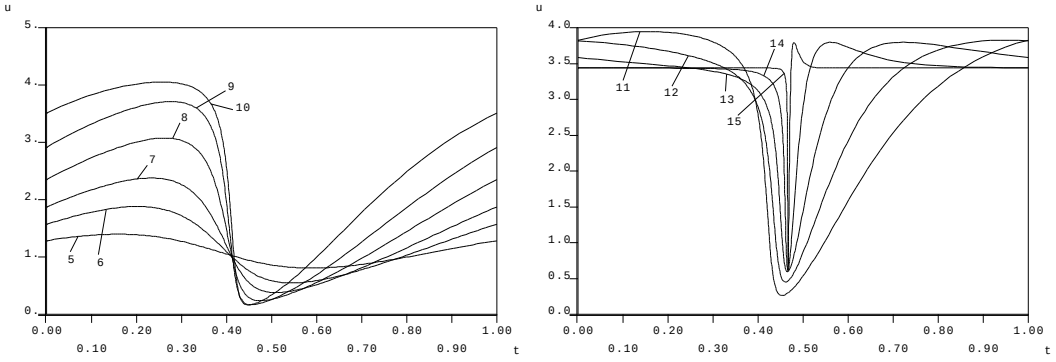
$$\frac{\mathrm{d}u}{\mathrm{d}t} = \hat{f}\,(u, v; \rho) \tag{3.69}$$

$$\frac{\mathrm{d}u}{\mathrm{d}t} = \hat{g}\,(u, v; \rho)\,. \tag{3.70}$$

The bifurcation diagram is shown in Figure 3.2(a) and the waveforms for the variable u are shown in Figures 3.2(b) and 3.2(c). It should be noted, however, that the values of ρ at which these phenomena occur are large in relation to those for which the generation of interesting spatial pattern sequences are observed.



(a)



(b) (c)

FIGURE 3.2 Bifurcation diagram (a) and waveforms (b)–(c) for the modified kinetic scheme with no diffusion: equation (3.69) with $a = 0.1$, $b = 0.9$ and ρ as bifurcation parameter. In (a) the filled square represents a Hopf bifurcation point and the filled circles show stable periodic orbits. Stable (non-oscillatory) solutions for are shown by the solid line, and unstable solutions by the dashed line. Labels refer to the waveforms shown in (b) and (c) for the inhibitor u, where the periods of the waves are normalised to unit time. Similar waveforms are recovered for v.

3.6 Discussion

In this chapter we have considered the evolution equation derived for conservation of matter undergoing reaction and diffusion on a growing domain. The domain growth is specified in terms of local strain and shear rates, supposed to represent underlying tissue growth and movement. Several simplified cases have been identified and these 'reduced systems' will be studied in the remainder of this thesis.

We have considered only very simple geometries for the domain, the interval and the plane. Recently Varea *et al.* [128] have considered pattern formation on spherical surfaces, and Chaplain *et al.* [14] investigate patterns on the radially growing sphere. Clearly the formalism that we have described can be adapted to encompass these and other geometries.

Before we turn to investigate pattern formation in our equations, we briefly reconsider the previous attempts in the literature to model reaction-diffusion and growth. It is apparent from the equations derived from first principles that all of the models discussed earlier consider only the effects of *uniform* domain growth on pattern formation. The model we have derived is much more general and allows for the inclusion of *any* space and time dependence on the growth. The equation derived by Kulesa *et al.* [65] and by Painter *et al.* [107] corresponds to domain growth in one dimension under a constant strain rate and includes the dilution term. However, our equations for uniform growth differ significantly from the model studied by Arcuri and Murray [3] in that the time-dependent scaling parameter appears in a different position in their equation (also the dilution term is absent in Arcuri and Murray's work). The significance of this difference will be discussed in the following chapter in light of the pattern formation properties of our equation, however, it is apparent that the difference arises as Arcuri and Murray adopt a different procedure for nondimensionalisation, which fails to keep separate the timescales for the distinct processes of pattern formation and domain growth.