7. Summary

It has been our aim in this thesis to characterise the effect of domain growth on pattern formation in reaction-diffusion systems. While motivated by the recent paper by Kondo and Asai concerning dynamic patterns in fish skin [64] (discussed in section 1.4) we have sought to explore general features of pattern formation on growing domains, rather than to discuss any specific patterning events from the biological realm. We have found, in particular for uniform domain growth, that the set of possible behaviours is severely limited. Such results may prove useful when trying to identify which biological pattern formation events might arise as a consequence of the reaction-diffusion mechanism, and where it may be more prudent to seek alternative explanations.

One key finding is the role of the various timescales in the problem. We have argued that slow domain growth (where growth is on a long timescale relative to pattern formation) is the appropriate model for biological scenarios, and this turns out to be the case for which a sequence of recognisable patterns is generated. For three-species reaction schemes exhibiting oscillatory patterns a third timescale is introduced and the evolution of solutions on the growing domain is found to be disorganised, even for slow domain growth. The interaction of the third timescale destroys the regular behaviour found previously.

Our investigation of the symmetry between different time-independent solutions on domains of fixed size found that a scaling law in the parameter γ (and hence in the domain length L) relates the different pattern modes. We have been able to extend this idea to the full time-dependent problem with domain growth to predict frequency-doubling and the novel frequency-tripling behaviour. Transitions between patterns are driven by the domain growth. Pearson's discovery of splitting and replication of structures in the bistable Gray-Scott model [109] (discussed in section 2.5.3) is all the more remarkable in that there is no such process driving the system. The kinetic schemes admitting the diffusion-driven instability that we have studied do not show this splitting behaviour without domain growth. However, the mechanism of peak (or spot) splitting in either class of kinetic schemes is not well understood and lacks satisfactory explanation.

One as yet unexplained feature of the simple two-species solutions on the uniformly growing domain is the effect of reducing the growth rate ρ through a lower critical value, below which the regular frequency-doubling breaks down. Corroborating evidence for this phenomenon is provided by the study of the linear growth case, where the breakdown of the regular sequence after several successful frequency-doubling events was shown to be consistent with the lower critical ρ. The implication of this result

is that if a domain grows too slowly then there is not sufficient coupling between domain growth and the pattern formation mechanism to produce the regular sequence. This runs counter to the intuitive idea that for slow domain growth the transitions between patterns are triggered simply by the peak separation exceeding some critical value. Nishiura *et al.* [95] have found that pattern for Gray-Scott kinetics close to the bistable regime develops, on a domain of fixed size, by splitting of the outermost peaks only (see Figure 2.8(a)) presumably for the reason that internal peaks do not achieve a minimum critical separation. For our system, however, peak separation is driven by the domain growth and it seems that the rate at which peaks move apart is important in determining the transitions between patterns, rather than just their instantaneous separation. For the uniform case all peaks on the domain separate at the same rate. With constant strain rate the time dependence is exponential and in one dimension the rate of expansion of any interval, $\mathrm{d}\,\Delta x/\mathrm{d}t = (X_2 - X_1)\rho\exp(\rho t) = \rho\,\Delta x$, is independent of time t. Evenly spaced peaks separate at the same rate, independent of time. Thus it seems that if peak separation is not fast enough then frequency-doubling does not result. For linear domain growth, peak separation $\mathrm{d}\,\Delta x/\mathrm{d}t = \rho\,\Delta x/(1+\rho t)$ is a decreasing function of t and frequency-doubling breaks down when peaks are separating at what was found to be the minimum separation rate for the exponential case.

In this thesis we have focused on patterns on one-dimensional growing domains. The extension of these results to higher dimensions is non-trivial. The two-dimensional patterns on the angelfish undergo transitions by insertion of stripes as the domain length perpendicular to the stripe orientation doubles, in a manner similar to the simulations shown in Figure 6.15(d)–(g). This is seemingly good circumstantial evidence that a mechanism such as reaction-diffusion is at work, however, the experimental observations may also be consistent with any other mechanism which has an intrinsic pattern wavelength. We have found that domain growth can stabilise parallel stripes in two dimensions, as well as giving rise to stripe splitting or insertion. Many more phenomena have been observed in the experimental system, including the formation and movement of Y-shaped branching points where one stripe divides into two. A wider range of behaviours may be possible in two dimensions under nonuniform domain growth. Frequency-doubling generates an even number of repeating elements and we found in one dimension that a low odd number of peaks could be generated with nonuniform growth, where peak splitting or insertion is restricted to one part of the domain. It would be of great interest to explore what further pattern behaviours are possible under nonuniform growth in two dimensions.

The rectangular lattice of spots would seem to be the only planform that can be selected by domain growth for kinetics containing quadratic terms. Thus hexagonal structures occurring in biology, for example the arrangement of feather primordia in the chick [57], are unlikely to be generated in this way. However, in many such

patterns robustness is not a requisite, and hexagonal patterns are favoured on the static domain.

One important feature of growth and form that we have overlooked in this thesis is curvature of the domain. The bowing and folding of sheets of tissue is as important in developmental systems as their migration and expansion. Translation without changing geometry (curvature or size) has no influence on the reaction-diffusion mechanism within a tissue, however, curved surfaces and in particular curvature changing with growth may be an important factor in pattern formation. To our knowledge there is, at present, little work discussing the interaction of curvature and domain growth in pattern formation. One notable exception is the paper by Chaplain *et al.* [14] in which the results of a simulation of reaction-diffusion on the surface of a radially growing sphere are reported, however, there are not sufficient data presented to ascertain whether or not similar phenomena are observed in their system.

We have been able to address the robustness problem, one of the major criticisms of reaction-diffusion theory [6, 10], having found that the incorporation of domain growth into the reaction-diffusion model drives the system to generate sequences of patterns [19]. Component patterns of the frequency-doubling sequence display semi-scale invariance, remaining established while the domain doubles in length, an important feature in the context of regulation. The frequency-doubling mechanism is an efficient manner in which to reliably generate patterns containing even numbers of elements.

The implication of this result is that arguments dismissing reaction-diffusion theory because of its perceived robustness failure must be reconsidered. Saunders and Ho [118] conclude that for reliable segmentation a sequential mechanism is required, in which the domain is successively divided into separate subdomains which are patterned independently. This relies on the result that small domains are patterned more reliably than large ones. We use this same result to select an initial pattern on a small domain, which then determines the modes in the ensuing frequency-doubling sequence. Pattern formation through frequency-doubling is a sequential process, whereby increasingly complicated patterns develop from simpler ones within a single dynamical system. This mechanism has already been proposed in the context of segmentation by Nagorka [91] for the early development of *Drosophila* (however, see earlier comments on current state of knowledge of molecular regulation in this system [2]). Our results support the view of Murray and coauthors [43], who have proposed that if several mechanisms are coupled together in hierarchical systems, whereby the steady state output of one pattern formation mechanism serves as the input or locally determines parameters for the next, then robustness with respect to initial data may be achieved.

Below we restate our results on the various ways in which pattern selection via domain growth can be said to be robust. Once an initial pattern is generated the

frequency-doubling sequence is insensitive to initial conditions. For exponential domain growth the mode composition of the sequence does not change over several orders of magnitude of the domain growth rate ρ, while for linear growth a number of frequency-doubling events is observed unless ρ is very much smaller than the characteristic linear growth rate of the patterns. Under logistic domain growth one of these patterns persists except when the final domain size lies in a small interval of values for which some other pattern mode is admitted. We have also shown that the precise form of the boundary conditions is unimportant (however, the symmetric choice of zero flux conditions greatly simplifies the analysis). These properties are due to the fact, shown in Chapter 5, that sequences are generated because of the dynamics of each element of the pattern, which for the exponential case are all equivalent. Transitions between patterns are dynamically driven and are not induced by fluctuations (as is the Turing bifurcation) and so the mechanism is robust to the presence of noise in the system. Finally, we have shown that the precise form of the kinetic functions for systems admitting the diffusion-driven instability determines the transition mechanism. The sequence, however, seems generic, except for some cases which we have highlighted.

This last point raises the question as to whether the behaviour we have described is particular to reaction-diffusion systems or is generic to all global pattern generation mechanisms, such as chemotaxis and mechanochemical models. In terms of the phenomenology of patterns generated on fixed domains, such mechanisms are difficult to distinguish, all having a range of destabilising modes which present the same pattern selection issues and similar robustness problems. As is discussed by Oster and Murray [99], the underlying mathematical structure of these biologically distinct models may be very similar indeed. If such mechanisms are found to differ then the predicted behaviour on the growing domain will provide a useful means to distinguish between them. Whether these other models exhibit qualitatively different behaviour in response to domain growth is the subject of current investigation.