



ELSEVIER

Physics Letters A 304 (2002) 149–156

---

---

PHYSICS LETTERS A

---

---

[www.elsevier.com/locate/pla](http://www.elsevier.com/locate/pla)

# A general mechanism for “inexact” phase differences in reaction–diffusion–advection systems

Razvan A. Satnoianu<sup>a,\*</sup>, Michael Menzinger<sup>b</sup>

<sup>a</sup> *Department of Mathematics, City University, London EC1V 0HB, UK*

<sup>b</sup> *Department of Chemistry, University of Toronto, Toronto, ON, M5S 3H6, Canada*

Received 3 May 2002; accepted 30 September 2002

Communicated by A.P. Fordy

---

## Abstract

‘Inexact’ phase differences that may take any value in the range  $[0, \pi]$ , between the chemical morphogens diffusing in an embryo, have been proposed [M.A. Russell, *Dev. Biol.* 108 (1985) 269] to improve the positional information theory [L. Wolpert, *J. Theor. Biol.* 25 (1969) 1] by encoding this information with higher resolution than that provided by other mechanisms. Reaction–diffusion systems, including Turing systems, show only ‘exact’ phase differences 0 and/or  $\pi$ . We demonstrate here that inexact phase differences arise naturally in reactive flows described by reaction–diffusion–advection equations and illustrate them by the stationary waves in open flows (flow- and diffusion-distributed structures FDS [R.A. Satnoianu, M. Menzinger, *Phys. Rev. E* 62 (2000) 113; R.A. Satnoianu, P.K. Maini, M. Menzinger, *Physica D* 160 (2001) 79] and travelling waves in differential-induced flow systems (DIFI) [A.B. Rovinsky, M. Menzinger, *Phys. Rev. Lett.* 70 (1993) 778; R.A. Satnoianu, J.H. Merkin, S.K. Scott, *Physica D* 124 (1998) 345]. The ability of cells in a developing organism to read phase differences in addition to morphogen concentrations would endow them with a robust mechanism for producing segmentation patterns that is richer, shows higher spatial resolution and is more stable than Turing’s and Wolpert’s positional information mechanisms.

© 2002 Elsevier Science B.V. All rights reserved.

PACS: 82.39.-k; 82.40.Ck; 82.45.-h; 83.60.Wc; 89.75.Kd

*Keywords:* Reaction–diffusion–advection systems; Phase differences; Flow and diffusion structures (FDS); Turing and DIFI patterns; Cellular positional information

---

## 1. Introduction

Different theories have been advanced over the past decades to account for biological morphogenesis and

formation of patterns. Half a century ago Turing [1] conceived the idea that spontaneous symmetry breaking of the homogeneous steady state of certain dynamical systems may give rise to prepatterns which can be read out by competent cells that proceed to develop accordingly. A conceptually simpler idea was introduced by Wolpert [2]. It is based on the monotonic gradi-

---

\* Corresponding author.

*E-mail address:* [r.a.satnoianu@city.ac.uk](mailto:r.a.satnoianu@city.ac.uk) (R.A. Satnoianu).

ent of a passively diffusing morphogen, which may encode positional information for cells that are competent to respond to threshold concentrations. Russell proposed [3] that the classical positional information mechanism [2] could be improved if the monotonic gradient of passively diffusing morphogens were replaced by a spatially periodic field of morphogen species, say  $M(x)$  and  $N(x)$ , between which there exists a so-called *inexact phase shift*  $\Delta\beta$  which may take any value between 0 and  $\pi$ . He showed that this mechanism can accurately encode positional information with higher resolution and in a more robust manner than could other [1,2] mechanisms. He used this idea to account for the abnormal segmentation patterns in the *Drosophila* larvae, which cannot be explained by the classical positional information theory [2]. Until recently one obstacle to Russell's theory was the fact that reaction–diffusion systems (see [18,19] for reviews), including Turing systems for two or more species [4], generate only “in phase” and/or “out of phase” morphogen prepatterns. This makes it difficult to see how Russell's conditions can be met in practice.

Recently, Perumpanani et al. [5] showed that the addition of differential advection terms to a system of reacting and diffusing chemicals, similar to the differential-flow instability DIFI [6,7], may result in travelling waves characterised by an inexact phase shift. However, their realisation of steady patterns is very sensitive to parameter values. When Andresen et al. [9] predicted formation of stationary waves in open flows of oscillatory media they noted the existence of inexact phase shifts, without advancing an explanation for their presence. Recently we have proposed a general pattern formation mechanism which generalises all the above known results which was termed FDS or flow and diffusion distributed structures [8,11]. Turing patterns, DIFI patterns and Andresen's FDO mechanism are all particular instances of FDS [11]. Moreover, FDS waves play a significant role in developmental biology. By realizing that axial growth is equivalent to an open flow, and that the patterns arising in open reactive flows of oscillatory media are very robust indeed, Kaern et al. [20,21] made open reactive flows relevant to biological segmentation.

Here we analyse the mechanism that generates stable, inexact phase differences generally in systems of reaction–advection–diffusion equations with or with-

out differential transport and derive a general expression for the phase shift  $\Delta\beta$ . This mechanism for phase differences is general, encompassing both the mechanism of flow and diffusion distributed structures FDS [8,11] that generates stationary waves, and the DIFI mechanism that generates travelling waves [6,7]. All that is required is that diffusive transport be accompanied by a mechanism that breaks the  $x \rightarrow -x$  axial symmetry. Clearly the advection transport satisfies this requirement but there are other possibilities to achieve this symmetry breaking. We illustrate these ideas here for the case of transport through diffusion coupled to advection. In this case the resulting wave solutions may be stationary, travelling or, as a novel feature, a combination of both. The latter case will be presented elsewhere [12]. Our interest in these situations has been motivated by the recently proposed flow and diffusion-distributed structure (FDS) mechanism for pattern formation [8,11]. Given its robustness to parameter variation the FDS mechanism seems to represent one of the simplest means for robustly generating stationary and/or travelling, space-periodic patterns through inexact phase shifts.

An asymptotic analysis of the solutions of the resulting reaction–diffusion–advection equations is performed for a generic cubic autocatalator kinetic model. This leads to the phase difference function  $\Delta\beta$ . In particular, we establish that nontrivial phase differences require in an essential way the presence of *advection*. We shall show that the mechanism for phase differences based on flow differs fundamentally from that of Turing, with the latter being recovered exactly in the limit of vanishing flow transport. For example, phase differences appear in flow transport systems even if the inhibitory species is immobile. Possible settings are the FDS [8,11] and DIFI mechanisms [6,7]. Our method applies to both FDS and DIFI mechanisms and is not restricted on the number of reacting species.

To illustrate these ideas we shall establish that the FDS waves can be phase shifted to any angle between 0 and  $\pi$  and we shall explicitly illustrate how the phase shift depends on the nonlinearity in the kinetics and the parameter values. Similar conclusions hold for the DIFI mechanism. The results explain also why Turing systems exhibit only in-phase and out-of-phase solutions. Our results may have important consequences for explaining pattern formation in biological systems [20,21].

## 2. Flow and diffusion mechanism for phase differences

When the inflow boundary condition of an open reactive flow (reaction–diffusion–advection system) is kept fixed and the flow exceeds a threshold value, stationary waves may arise to which we refer as flow and diffusion distributed structures (FDS) [8,11], regardless of whether differential transport is present or not [9,10]. When the inflow boundary is forced periodically, the resulting patterns are travelling waves [13,16].

To understand analytically the behaviour of FDS solutions we construct a model posed for a semi-infinite domain. The dimensionless system is

$$\frac{\partial a}{\partial t} = \delta \frac{\partial^2 a}{\partial x^2} - p\phi \frac{\partial a}{\partial x} + f(a, b), \quad (2.1)$$

$$\frac{\partial b}{\partial t} = \frac{\partial^2 b}{\partial x^2} - \phi \frac{\partial b}{\partial x} + g(a, b), \quad (2.2)$$

with Dirichlet boundary conditions at  $x = 0$ .

If the kinetics part has a uniform, steady state solution  $a = a_s$ ,  $b = b_s$  then we take

$$a(0, t) = a_s + \varepsilon_1, \quad b(0, t) = b_s + \varepsilon_2, \quad (2.3)$$

where  $0 < |\varepsilon_1|, |\varepsilon_2| \ll 1$  are small, constant perturbations. Here  $p, \delta, \phi > 0$  are, respectively, the ratios of advection rates terms, diffusion terms and the flow rate of the  $b$  species. Physically differential transport may be achieved by selective immobilization [6], chromatography or application of an external electric field to an ionic system (charged particles  $a$  and  $b$ ) [14]. In the latter case, modelling has shown that  $p = \delta$  for the case of high ionic strength [15]. In the following we derive the phase shift function for the general case  $p \neq \delta$  and will illustrate the results by detailed calculations for the special  $p = \delta$  case for different types of nonlinear kinetics schemes. This special case was the model used in [8] to introduce the FDS mechanism. Biologically, the use of differential-flow in a reaction-diffusion setup may approximate the movement of cells in a growing tissue [20,21], for example, as a model for galvanotaxis [22] or cell movement with respect to the extracellular matrix.

The general necessary conditions [11] for bifurcation to stationary FDS solutions are that  $a, b$  form an activator/inhibitor system. A key feature of the results in [11] is that the FDS parameter domain is very robust

to parameter variation and that it is much bigger than the corresponding Turing domain to which it adjoins.

The sufficient conditions for FDS patterning (not discussed in [11]) cannot be established on the basis of linear analysis alone and one has to do full nonlinear calculations to assess the nature of the bifurcation. However, a simple asymptotic expansion uncovers at first order the nature of the phase differences of the solutions. The results are general, for example, they do not depend on the form of the kinetics used. We first illustrate the method on hand for a generic cubic autocatalator kinetics model and then show that these results can be generalised to any other kinetics nonlinearity with activator–inhibitor competition.

### 2.1. Phase differences for the cubic autocatalator model

The dimensionless cubic autocatalator kinetics (or Gray–Scott) model is [17]

$$f(a, b) = \mu - ab^2, \quad g(a, b) = ab^2 - b. \quad (2.4)$$

Its homogeneous steady state solution is  $(a_s, b_s) = (1/\mu, \mu)$ . Using linear theory it was shown in [8,11] that stationary, space periodic solutions for the system (2.1)–(2.4) appear generically above the critical bifurcation value  $\phi_c = \phi_c(\delta, \mu) \geq 0$ . Previous work has focused on understanding the mechanism for amplitude growth in the solutions. Here we are interested in the phase differences between the two components of the solution. Let  $k_c$  be the critical wavenumber and take  $\phi$  as our bifurcation parameter. Consider an asymptotic solution by setting

$$\phi = \phi_c + \gamma \varepsilon^2 \quad (\gamma \in \{-1, 1\}),$$

$$\begin{pmatrix} a \\ b \end{pmatrix} = \begin{pmatrix} a_s \\ b_s \end{pmatrix} + \sum_{n=1}^{\infty} \varepsilon^n \begin{pmatrix} a_n \\ b_n \end{pmatrix}. \quad (2.5)$$

Saturation in the amplitude of the FDS solution requires use of two new space and time scales

$$s = \varepsilon(x - v_g t), \quad \tau = \varepsilon^2 t, \quad (2.6)$$

where  $v_g$  is the group velocity of the dispersion relation, and we consider that  $a, b$  depend on  $x, s$  and  $\tau$ . We then expand the nonlinear parts  $f, g$  in a Taylor series in power of  $\varepsilon$ . To first order in  $\varepsilon$  the

solution is

$$\begin{pmatrix} a_1 \\ b_1 \end{pmatrix} = A(s, \tau) e^{ik_c x} \begin{pmatrix} d_1 \\ d_2 \end{pmatrix} + \text{c.c.} \quad (2.7)$$

Here  $(d_1, d_2)^T$  is an eigenvector parallel to

$$(c_1, c_2) = (-2, \delta k_c^2 + i\delta\phi_c k_c + \mu^2), \quad (2.8)$$

and  $A(s, \tau)$  is a function depending on  $s, \tau$  only. The complete behaviour of  $A$  is determined at the cubic order in  $\varepsilon$  with  $A$  satisfying the FDS complex Ginzburg–Landau PDE. The character of the bifurcation (whether it is subcritical or supercritical) is given by studying its coefficients (for the linear and cubic term). We found that for this kinetic scheme both stable (supercritical) and unstable (subcritical) FDS solutions are possible depending on the value of the parameters. They will be presented elsewhere. Here we are concerned with the behaviour of the phase component of the solutions.

From (2.5) and (2.7) by putting  $A = Re^{i\Theta}$  we have, to first order in  $\varepsilon$ :

$$a = a_s + 2\sqrt{\phi - \phi_c} R(s, \tau) d_1 \cos(kx + \Theta(s, \tau)) + O(\varepsilon^2), \quad (2.9)$$

$$b = b_s + 2\sqrt{\phi - \phi_c} R(s, \tau) d_2 \cos(kx + \Theta(s, \tau)) + O(\varepsilon^2). \quad (2.10)$$

This shows that the phase difference between the solutions  $a, b$  is determined by the components of the vector (2.8). Representing them in polar coordinates and noting that  $c_1 = -2$ , the shift in their arguments is given by

$$\Delta\beta = \arctan\left(\frac{pk_c\phi_c}{\delta k_c^2 + \mu^2}\right). \quad (2.11)$$

Relations (2.9) and (2.10) show that the *nonlinear phase dynamics of the solutions to reaction–diffusion–advection systems is determined, up to order  $\varepsilon$ , by the separation in the exponential growth phases with the nonlinear saturation contributing the same modulation in their phases*. Relation (2.11) uncovers a fundamental difference between patterning mechanisms based on flow to those based on diffusion alone (Turing). Namely, flow-driven solutions exist and consequently their phase shift  $\Delta\beta$  remains inexact even for no diffusible inhibitor ( $\delta = 0$ ) or for no differential diffusion transport ( $\delta = 1$ ). The first case corresponds to the DIFICI waves [6,7] and the second

one to the flow-distributed structures oscillator waves [9–11]. This adds to the robustness features of the patterning based on flow as a morphogenetic mechanism with respect to parameter variation [11]. Furthermore, the general expression  $\Delta\beta$  given by Eq. (2.11) shows that the existence of the phase shift property necessarily requires that advection transport is present in the system (i.e.,  $p > 0$ ) irrespective of the presence or not of the diffusion. This is consistent with the fact that Turing patterns (i.e., when only differential diffusion is present) are “exactly” in or out of phase solutions. Finally we note that the case  $p = 1$  is of particular relevance in the applications of FDS to modelling axial segmentation patterns during embryological growth [20,21].

It is clear that the same method works for DIFI-induced waves giving the same phase difference  $\Delta\beta$  (2.11) (though with different values for  $\phi_c$  and  $k_c$ ). This shows the universal character of the result. In the case of FDS waves the solutions are stationary [8,11] and for the DIFI case they are periodic travelling waves [7]. This result applies, for example, when periodic perturbations are applied at the inflow boundary [13,16]. Furthermore, it is clear that the method works for more than two interacting species. If one starts with  $n \geq 2$  species, analogous calculations establish the existence of  $n(n-1)/2$  phase shifts between the  $n$  species.

Eq. (2.11) shows that the phase difference is a pure property of the spatio-temporal dynamics of the FDS or DIFI system and that it depends only on the kinetic and transport parameters of the model and not on the form of the boundary conditions. In particular, the phase shift  $\Delta\beta$  does not arise simply from advection of the fixed phase shift imposed by the dynamics at the inflow boundary as was suggested in [9]. The form of the inflow boundary condition does not play any role (other than introducing a transient feature) in the final outcome of the spatio-temporal dynamics in the flow domain. In other words the basin of attraction for the FDS stationary space periodic solution is not equal with the basin of attraction of the limit cycle (if there is one) of the corresponding pure temporal dynamics evolution, i.e., the ODE system. Rather their spatio-temporal evolution is the result of the interplay between flow, diffusion and reaction.

To illustrate our results we show in Fig. 1 the variation of  $\Delta\beta$  as function of  $\mu$ , for the fixed value of

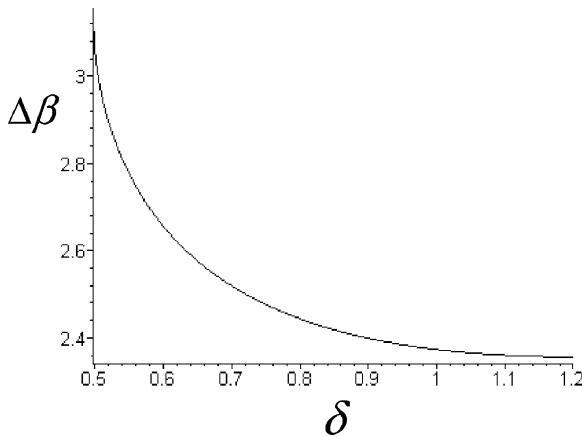


Fig. 1. Phase difference  $\Delta\beta$  as a function of the kinetics parameter  $\mu$  for the cubic autocatalator scheme with  $\delta = 1.44$ . This plot shows that  $\Delta\beta$  is  $\pi$  (out of phase) at the Turing value  $\mu = 1.2(\sqrt{2} - 1) = 0.497$  and is minimum at the FDS boundary  $\mu = \sqrt{\delta} = 1.2$ . The minimum angle in radians is  $3\pi/4$ .

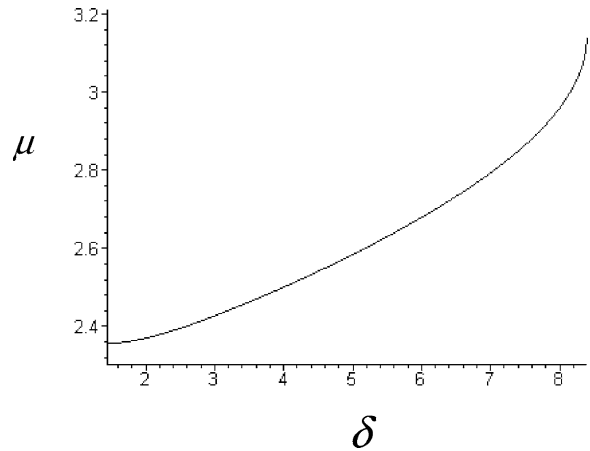


Fig. 2. Phase difference  $\Delta\beta$  as a function of  $\delta$  for the cubic autocatalator model with  $\mu = 1.2$ . The two solutions are out of phase at the Turing boundary  $\delta = 8.393$ .

$\delta = 1.44$ , whereas Fig. 2 gives a plot of  $\Delta\beta$  showing its dependence as a function of  $\delta$  for  $\mu = 1.2$  (see also Fig. 3 for the phase difference behaviour between the two species in a generic case) for the case  $p = \delta$ . From Fig. 2 we predict that the maximum phase difference occurs when the inhibitor species is immobilised. The limit from the left of the derivative of  $\Delta\beta$  at  $\delta = (3 + 2\sqrt{2})\mu^2$  is  $+\infty$  with the function being zero there (the Turing boundary). Therefore, large phase differences can be obtained just by slightly decreasing the diffusion ratio (and consequently increasing the flow rate according to (2.5)) away from the Turing boundary into the FDS domain. This property attests for the versatility of the new FDS mechanism.

Our calculations hold for parameter values near the bifurcation threshold (DIFI or FDS). However, we expect that the property of the phase differences in the solutions in such mechanisms remains true for values far inside the nonlinear patterning domain. We have tested this through a large number of numerical simulations for the dynamics of system (2.1), (2.2), (2.4). In all the cases we found that the two solutions displayed phase differences between the maximums of their amplitudes. We also found that the predictions of the weakly nonlinear analysis hold true far beyond the instability threshold. A typical case for the solutions in the FDS case is illustrated in Fig. 3. The method for

numerical solution is the same as that used in [11] and uses an implicit scheme with finite differences.

### Generalisation to other kinetic schemes

The above method of analysis carries over to other nonlinear kinetic schemes. To illustrate the universality of the phase difference mechanism introduced above we have analysed several nonlinear models, including the quadratic–cubic interpolation and Gierer–Meinhardt models as representative cases. They have been widely used in modelling biological pattern formation. For details of these schemes see [11,18,19].

### 2.2. The quadratic–cubic interpolation model

The quadratic–cubic interpolation model is a generalisation of the cubic autocatalator model from the previous section. The nonlinearity in (2.1), (2.2) is given by

$$\begin{aligned} f(a, b) &= \mu - qab - (1 - q)ab^2, \\ g(a, b) &= qab + (1 - q)ab^2 - b, \end{aligned} \tag{2.12}$$

where  $\mu, q > 0$  and  $0 \leq q \leq 1$ . For  $q = 1$  we have pure quadratic autocatalysis and for  $q = 0$  we have pure cubic case. System (2.12) has a unique uniform steady state given by

$$S = \left\{ (a_s, b_s) = \left( \frac{1}{\mu + q - q\mu}, \mu \right) \right\},$$

that exists for all  $0 \leq q \leq 1$ . Using the procedure above one can easily show that  $S$  is predicted to become FDS unstable at a critical flow rate  $\phi_c$  which is a function with a complicated dependence on  $\mu$ ,  $q$  and  $\delta$ . In this case one finds that the phase difference function for the reaction–diffusion–advection system with linear interpolation quadratic-cubic nonlinearity is

$$\Delta\beta_1 = \arctan\left(\frac{\delta k\phi_c}{\delta k^2 + q\mu + (1-q)\mu^2}\right), \quad (2.13)$$

$\beta_1$  depends on two kinetics parameters  $\mu$  and  $q$  and becomes singular as  $q \rightarrow 1^-$  due to the fact that the FDS bifurcation exists only for  $0 \leq q < 1$  [11]. We find that  $\Delta\beta_1 \rightarrow \pi/2$  as  $q \rightarrow 1^-$ . In comparison for the pure cubic case maximum phase difference angle is  $\pi/4$ . Therefore, nonlinearities that are predominantly quadratic are more favourable to produce bigger phase shifts between the amplitudes of the solutions.

In both above models the solutions were exactly “in phase” as  $\delta \rightarrow \delta_{T^-}$  (see Fig. 2). In the next model kinetics the nonlinearity is such that the solutions exhibit a phase difference of  $\pi$  radians (they are “out of phase”) as  $\delta \rightarrow \delta_{T^-}$ .

### 2.3. The Gierer–Meinhardt kinetics nonlinearity

The Gierer–Meinhardt kinetics nonlinearity is

$$\begin{aligned} f(a, b) &= b^2 - a, \\ g(a, b) &= \sigma - \rho b + \frac{b^2}{a}, \end{aligned} \quad (2.14)$$

where  $a$ ,  $b$  play the role of inhibitor and activator species, respectively, with  $0 < \sigma < 1$ ,  $\rho > 0$ . It is well-known that this system generates “out of phase” Turing patterns [18]. The uniform steady state is given by

$$S = \left( (a_s, b_s) = \left( \frac{(\sigma + 1)^2}{\rho^2}, \frac{(\sigma + 1)}{\rho} \right) \right).$$

The Gierer–Meinhardt can sustain in a robust way FDS patterns, which are a direct generalisation of the Turing patterns [11]. Regarding the phase difference function similar computations as above give the form of it as

$$\Delta\beta_2 = \arctan\left(\frac{\delta k\phi_c}{1 + \delta k^2}\right). \quad (2.15)$$

This depends on the kinetics parameters  $\sigma$ ,  $\rho$  through the critical value of the FDS flow value  $\phi_c$ .

### 3. Conclusions and discussion

We analysed here the phase behaviour of a simple, universal mechanism for pattern formation which is based on the combined action of flow, diffusion and nonlinear kinetics to generate stationary and/or travelling waves with stable, inexact phase differences. We found that the range of the phase difference function depends on the type of nonlinear kinetics, the maximum difference  $\Delta\beta$  ranging between  $0 \leq \Delta\beta \leq \pi$ , and that the phase difference depends monotonically on the system parameters. This puts into perspective the Turing result for which only strictly “in phase” or “out of phase” solutions are possible. As a corollary we found that quadratic kinetics favours larger phase differences than does cubic kinetics.

Russell proposed [3] the idea that phase differences between periodic morphogen distributions can explain the known segmentation patterns in insects (e.g., *Drosophila* larvae). His discussion was abstract and assumed that there exist two morphogens,  $M$  and  $N$ , whose concentrations vary along the embryonic axis sinusoidally:

$$M = m_1 + n_1 \sin x, \quad N = m_2 + n_2 \sin(x + \Delta),$$

where  $m_{1,2}$  are their average values and  $\Delta$  is the phase difference. He then proposed that the relative concentration of  $M$ ,  $N$  generates an angle variable

$$\alpha = \arcsin \frac{-M}{\sqrt{M^2 + N^2}}. \quad (3.1)$$

Russell further proposed that cells read off the local concentrations of the two morphogens and then translate them into the angular variable  $\alpha$ . The latter encodes the positional information for a series of homologous segments. Given the periodicity of the phase difference function each cell in a segment would have a different positional value but all these values will be repeated in all the segments. This works well to explain also abnormal patterns such as segment polarity mutations (when in each segment a certain portion of the normal pattern is deleted and the remainder appears as a mirror image duplication) or growth expansion/contraction variations.

When Russell proposed his theory there was no known mechanism that produced chemical waves with inexact amplitude and phase difference between the key morphogen species. With the discovery of the FDS waves they now serve as good candidates for Russell’s scenario. However, there still remains the question of how cells translate concentration information into the angular variable  $\alpha$ . This is a complex problem but the results in this Letter can offer some steps towards its solution. The recent discovery of diffusible morphogens *in vivo* [23–25] confirms that the spatiotemporal cellular response is a direct consequence of local interaction and spatial fluxes. As an alternative to the specific sensing function  $\alpha$  proposed by Russell, the phase shift mechanism given at Eq. (2.11) could, for instance, be realized also by computing two “sensing functions”: the reaction rate  $\alpha_1 = R = ab^2$  (proportional to the reaction rate of two protein products) and the spatial sensing function

$$\alpha_2 = \frac{\partial a}{\partial x} \frac{\partial b}{\partial x}$$

(the product of the gradients of the two species). Both functions are in principle ‘computable’ by cells. For example, bacteria are known to exhibit chemotaxis whereby they are able to find and follow spatial gradients of increasing (or respectively decreasing) concentration in the various effector cues. They do so by translating the local concentration in the signal (akin to  $\alpha_1$ ) through a series of temporal comparisons into information about the spatial gradient  $\alpha_2$ . Numerical solutions of our model show that these two sensing functions are sufficient for the cells to read their relative position with high precision. Figs. 3 and 4 show typical FDS and Turing solutions to system (2.1), (2.2), (2.4), respectively, for the case  $p = \delta$ . In the FDS case, the sensing functions are spatial functions that always have their local extrema between those of the morphogen species. In both the FDS and Turing cases there are multiple peaks inside any domain between two activator peak concentrations but with a marked difference between the two cases. In the FDS case (Fig. 3) the sensing function  $\alpha_2$  shows higher spatial variation with peaks of higher amplitude than in the Turing case (Fig. 4). The Turing case, on the other hand, shows only regular, symmetric behaviour and patterns with smaller amplitude and with morphogen

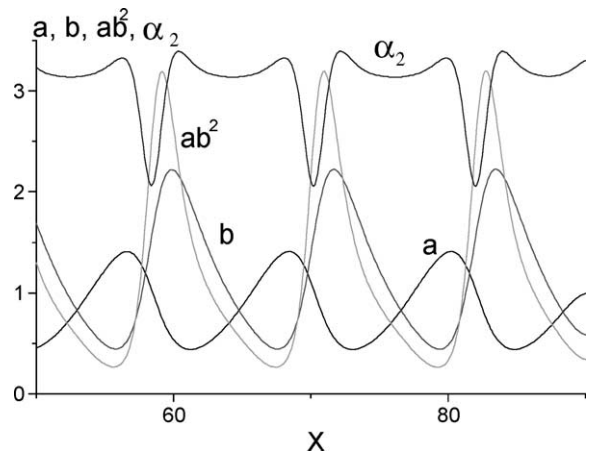


Fig. 3. Snapshot of the morphogen concentrations  $a, b$  for the FDS system (2.1)–(2.4). Also plotted are the sensing functions  $\alpha_1 = ab^2$  and the scaled value of  $\alpha_2$  (the value plotted is  $4\alpha_2 + 3.3$ ). The parameter values are:  $\mu = 1.2, \phi = 1.0, \delta = 4.0$ . Note that  $\alpha_2$  has two peaks with different heights, situated less than one wavelength apart. Also the amplitude of  $\alpha_2$  is many times greater than that in Fig. 4 (Turing case). This higher-dynamical range is directly related to the higher-resolution of the phase shift FDS mechanism.

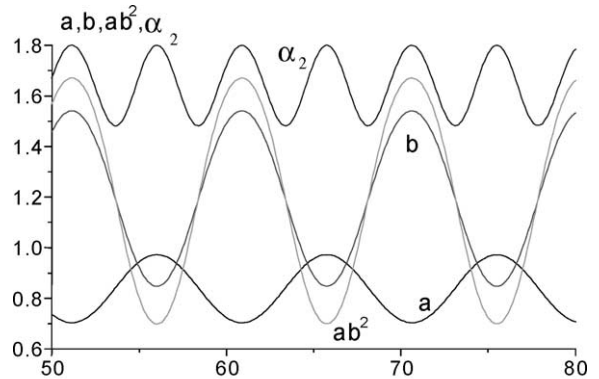


Fig. 4. A snapshot of the morphogen concentrations for the Turing system (2.1)–(2.4). Also plotted are the reaction rate  $\alpha_1 = ab^2$  and the scaled value of the gradient based sensing function  $\alpha_2$  (the value plotted is  $16\alpha_2 + 2.0$ ). Parameter values are:  $\mu = 1.2, \phi = 0, \delta = 8.8$ .

concentrations whose turning points are localised at the same positions in space (Fig. 4).

The key implications of this work is that it offers a viable mechanism for pattern formation through which the classical positional information theory [2] may be extended to accommodate cellular responses in terms of thresholds in both amplitudes and the phases be-

tween the different signalling cues. This would endow target cells with an enhanced repertoire of responses by enabling them to interpret not only morphogen concentrations but also the values and shapes of their gradients. Recent experimental evidence seems to support such a scenario [23–25].

## Acknowledgements

We thank Nick Monk, Mads Kaern and Philip Maini for helpful discussions.

## References

- [1] A.M. Turing, *Philos. Trans. R. Soc. London B* 237 (1952) 37.
- [2] L. Wolpert, *J. Theor. Biol.* 25 (1969) 1;  
L. Wolpert, *Principles of Development*, Oxford Univ. Press, Oxford, 1998.
- [3] M.A. Russell, *Dev. Biol.* 108 (1985) 269.
- [4] R.A. Satnoianu, M. Menzinger, P.K. Maini, *J. Math. Biol.* 41 (2000) 493.
- [5] A.J. Perumpanani, J.A. Sherratt, P.K. Maini, *IMA J. Appl. Math.* 55 (1995) 19.
- [6] A.B. Rovinsky, M. Menzinger, *Phys. Rev. Lett.* 70 (1993) 778.
- [7] R.A. Satnoianu, J.H. Merkin, S.K. Scott, *Physica D* 124 (1998) 345.
- [8] R.A. Satnoianu, M. Menzinger, *Phys. Rev. E* 62 (2000) 113.
- [9] P. Andresen, M. Bache, E. Mosekilde, G. Dewel, P. Borckmans, *Phys. Rev. E* 60 (1999) 297.
- [10] M. Kaern, M. Menzinger, *Phys. Rev. E* 60 (1999) 3471.
- [11] R.A. Satnoianu, P.K. Maini, M. Menzinger, *Physica D* 160 (2001) 79.
- [12] R.A. Satnoianu, M. Menzinger, submitted to *Phys. Rev. E* (2002).
- [13] R.A. Satnoianu, J.H. Merkin, S.K. Scott, *Dynam. Stabil. Syst.* 14 (1999) 275.
- [14] H. Sevcikova, M. Marek, S.C. Muller, *Science* 257 (1992) 951.
- [15] J.H. Merkin, R.A. Satnoianu, S.K. Scott, *Dynam. Stabil. Syst.* 15 (2000) 209.
- [16] M. Kaern, M. Menzinger, *Phys. Rev. E* 61 (2000) 3334.
- [17] P. Gray, S.K. Scott, *Chemical Oscillations and Instabilities*, Oxford Univ. Press, 1994.
- [18] H. Meinhardt, *Models of Biological Pattern Formation*, Academic Press, New York, 1982.
- [19] J.D. Murray, *Mathematical Biology*, Springer, Berlin, 1993.
- [20] M. Kaern, M. Menzinger, A. Hunding, *J. Theor. Biol.* 207 (2000) 473.
- [21] M. Menzinger, M. Kaern, R.A. Satnoianu, A. Hunding, *Faraday Discuss.* 120 (2001) 295.
- [22] L.F. Jaffe, *Nature* 265 (5595) (1977) 600;  
K.Y. Nishiura, R.R. Isseroff, R. Nuccitelli, *J. Cell Sci.* 109 (1996) 199.
- [23] E.V. Entchev, A. Schwabedissen, M. Gonzales-Gaitan, *Cell* 103 (2000) 981.
- [24] S. Vincent, N. Perrimon, *Nature* 411 (2001) 533.
- [25] Yu. Chen, A.F. Schier, *Nature* 411 (2001) 607.