# Turing's Theory of Morphogenesis: Where We Started, Where We Are and Where We Want to Go

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**Abstract** Over 60 years have passed since Alan Turing first postulated a mechanism for biological pattern formation. Although Turing did not have the chance to extend his theories before his unfortunate death two years later, his work has not gone unnoticed. Indeed, many researchers have since taken up the gauntlet and extended his revolutionary and counter-intuitive ideas. Here, we reproduce the basics of his theory as well as review some of the recent generalisations and applications that have led our mathematical models to be closer representations of the biology than ever before. Finally, we take a look to the future and discuss open questions that not only show that there is still much life in the theory, but also that the best may be yet to come.

## 1 Introduction

The initiation and maintenance of biological heterogeneity, known as morphogenesis, is an incredibly broad and complex issue. In particular, the mechanisms by which biological systems maintain robustness, despite being subject to numerous sources of noise, are shrouded in mystery. Although molecular genetic studies have led to many advances in determining the active species involved in patterning, simply identifying genes alone does not help our understanding of the mechanisms by which structures form. This is where the strengths of mathematical modelling lie. Not only are models able to complement experimental results by testing hypothetical relationships, they are also able to predict mechanisms by which populations interact, thus suggesting further experiments [1].

The patterns we are considering are thought to arise as the consequence of an observable population, e.g. skin cells, responding to diffusing signalling populations, known as morphogens, e.g. proteins. Specifically, the morphogens we consider are simply chemical reactants that do not sense their surroundings and freely diffuse. Through morphogen diffusion and interactions, non-uniform

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S.B. Cooper, M.I. Soskova (eds.), *The Incomputable*, Theory and Applications of Computability, DOI 10.1007/978-3-319-43669-2_13

patterns in concentration can emerge. The observable population is then thought to undergo concentration-dependent differentiation based on this heterogeneous morphogen distribution, thereby producing a corresponding heterogeneous pattern in the observable population [2, 3].

Many mathematical frameworks have been postulated to explain how such patterns arise. Here, we focus on one such paradigm mechanism: Alan Turing's diffusion-driven instability [4]. Turing conjectured that diffusion, normally known as a homogenising process, could destabilise a spatially homogeneous stable steady state of morphogen concentration. At its simplest, the instability can be characterised by interactions between two diffusing morphogen populations. There are two possible types of kinetics that can lead to instability, the better studied being the type where one of the species acts as an activator and the other behaves as an inhibitor [5, 6]. These names are derived from the fact that the activator promotes its own production in a positive feedback loop, which, in turn, is controlled by an inhibitor in a negative feedback loop. If the reaction domain is small enough such that the populations are well-mixed everywhere diffusion dominates the system, i.e. the product of the diffusion rate and reaction time scale is much greater than the domain size squared, the reactions will simply tend to a homogeneous stable steady state of concentration. However, as the domain size increases, diffusion can destabilise the homogeneous steady state. Explicitly, if the inhibitor diffuses faster than the activator, local growth in the activator is able to occur whilst the inhibitor prevents activator spreading [7]; thus, once the domain is large enough, spatial heterogeneity will arise.

Although we will be specifically thinking about Turing's theory in terms of biological pattern formation, the mathematical formalism is quite general and can be used to discuss any situation where the morphogen populations can be considered to be randomly moving reactive agents. Thus, the ideas of diffusion-driven instability are not restricted to biology. Indeed, the idea has been applied to such diverse areas as semiconductor physics [8], hydrodynamics [9] and even astrophysics [10].

## 2 Where We Started

We will be primarily concerned with multiple biochemical populations, $U_i$, where $i = 1, \ldots, n$, which are collectively denoted by the vector $\boldsymbol{U} = (U_1, \ldots, U_n)$. Further, the populations are identified with chemical concentrations $\boldsymbol{\phi} = (\phi_1, \ldots, \phi_n)$. These populations are able to diffuse in a spatial domain $\mathcal{V}$ with boundary surface $\partial\mathcal{V}$. As the populations diffuse around the domain, individual particles will often collide with each other, allowing reactions to occur. The reactions that occur are either motivated through biological observations or are of mathematical interest, proposed to reflect general aspects of the underlying biology.

The system could be completely described deterministically by Newton's laws of motion, treating individual morphogen particles as point masses that can collide and bounce off one another. In this framework, reactions are defined to occur when

particles collide with sufficient force. However, due to our ignorance of the initial positions and velocities of the active and solvent particles and our inability to cope computationally with the large number of particles involved (which can easily be of the order of $10^7$ particles and higher [11]), we instead choose to assume that the discrete populations, $U_i$, are large enough to be approximated by the continuous chemical concentrations, $\phi_i$, which are described using deterministic differential equations. Immediately, we see that this assumption has produced an error as the populations can only physically take integer values, whereas, once we take the continuum limit, the concentrations can take any continuous value. However, it has been shown that stochastic influences that arise due to the discrete nature of the particles scale as the reciprocal of the square root of the population size [12]. Thus, if in a specific biological application the chemical population of interest can be justified to be large, then a deterministic description is, in general, valid [13].

Since we are dealing with biochemical species, the populations will not be able to sense their surroundings and, thus, in the absence of some external force producing directionality, e.g. an electric field, their movement will be a simple random walk down concentration gradients, deterministically modelled by Fick's Law of Diffusion [14]. This law postulates that the chemicals move from regions of high concentration to regions of low concentration, with a magnitude that is proportional to the size of the concentration gradient. Although the framework is described in the context of molecular particles, it is in fact more general and can be applied to any system where motility is considered to be governed by an unbiased random walk [15–17].

The evolution of the concentrations $\phi_i$ at position $\boldsymbol{x} \in \mathcal{V}$ and time $t \geq 0$ is defined by the coupled system of partial differential equations (PDEs)

$$\frac{\partial \boldsymbol{\phi}(\boldsymbol{x}, t)}{\partial t} = \boldsymbol{D}\nabla^2 \boldsymbol{\phi}(\boldsymbol{x}, t) + \boldsymbol{F}(\boldsymbol{\phi}(\boldsymbol{x}, t)), \tag{1}$$

$$\boldsymbol{\phi}(\boldsymbol{x}, 0) = \boldsymbol{\phi}_0(\boldsymbol{x}) \quad \forall \boldsymbol{x} \in \mathcal{V},$$

$$\boldsymbol{G}(\boldsymbol{\phi}(\boldsymbol{x}, t)) = 0 \quad \forall \boldsymbol{x} \in \partial\mathcal{V} \text{ and } t > 0,$$

where $\nabla^2$ denotes the Laplacian operator and represents diffusion. The term

$$\boldsymbol{F} = (F_1(\boldsymbol{\phi}), \ldots, F_n(\boldsymbol{\phi})) \tag{2}$$

defines the (usually non-linear and highly coupled) interactions between the populations whilst $\boldsymbol{D} = [d_{ii}]$ is a diagonal matrix of diffusivities that is generally constant in space and time. The diffusivity constants control how quickly the chemicals spread throughout the domain. Finally, the functional form of $\boldsymbol{G}$ specifies how the chemicals behave on the boundary of the spatial domain that we are considering and $\boldsymbol{\phi}_0(\boldsymbol{x})$ is the initial concentrations of the chemicals [18].

Numerous different types of boundary conditions are possible: for example, homogeneous Neumann, or zero-flux boundary conditions, i.e.

$$\boldsymbol{G} = \frac{\partial \boldsymbol{\phi}}{\partial \boldsymbol{n}} = \boldsymbol{0}, \tag{3}$$

where $\boldsymbol{n}$ is the outward pointing normal of $\partial\mathcal{V}$. This simply states that no material may leave the domain; effectively, the domain is insulated. An alternative type of boundary condition is known as Dirichlet, or fixed concentration boundary condition, which, as the name suggests, simply fixes the concentration of the chemical on the boundary,

$$\boldsymbol{G} = \boldsymbol{\phi} - \boldsymbol{C} = \boldsymbol{0}, \tag{4}$$

where $\boldsymbol{C}$ is normally a constant. Other boundary conditions, e.g. reactive boundary conditions [19] or periodic boundary conditions [20, 21], also can be used although they are not considered here.

Systems such as Eq. (1) are known as 'reaction-diffusion' equations. They are able to produce a large variety of stationary and temporally varying patterns, such as stationary gradients, travelling waves and moving fronts [22], even without the Turing instability. Thus, unless biologically motivated to add further components to capture relevant dynamics, we concentrate on capturing the maximum amount of complexity through the simplest forms of reaction-diffusion equations.

## *2.1 Turing Instability*

For clarity the current formulae are quoted for reaction-diffusion systems of two concentrations $(\phi, \psi)$, with Neumann (zero flux) boundary conditions in a one-dimensional domain, $[0, L]$. Extensions to higher dimensions and various other boundary conditions are possible [18, 23]. In full generality the equations are

$$\phi_t = D_\phi \phi_{xx} + f(\phi, \psi), \tag{5}$$

$$\psi_t = D_\psi \psi_{xx} + g(\phi, \psi), \tag{6}$$

where the subscripts $x$ and $t$ denote partial derivatives, and suitable initial conditions are defined to close the system. Usually the initial conditions are taken simply to be random perturbations around a spatially uniform steady state, as it is the final pattern that is evolved that is important, not the initialisation of the system.

The first requirement of a diffusion-driven instability is that there exists a spatially homogeneous, linearly stable steady state, i.e. there exists $(\phi_0, \psi_0)$ such that $f(\phi_0, \psi_0) = g(\phi_0, \psi_0) = 0$ and all eigenvalues of the Jacobian (evaluated at the homogeneous steady state),

$$J(\phi_0, \psi_0) = \begin{pmatrix} \frac{\partial f}{\partial \phi}(\phi_0, \psi_0) & \frac{\partial f}{\partial \psi}(\phi_0, \psi_0) \\ \frac{\partial g}{\partial \phi}(\phi_0, \psi_0) & \frac{\partial g}{\partial \psi}(\phi_0, \psi_0) \end{pmatrix}, \tag{7}$$

have a negative real part. The second requirement is that the steady state becomes linearly unstable in the presence of diffusion. Note that although we derive conditions that will allow a reaction-diffusion system to realise a Turing pattern, as we will see in the biological applications section, the solution domain also has to be bigger than a critical size in order for the patterns to exist.

To derive necessary conditions for pattern formation to occur, the steady state is perturbed using functions that also satisfy the boundary conditions. Since we are using zero flux boundary conditions, we use a Fourier cosine expansion of the form $(\phi(x,t), \psi(x,t)) = (\phi_0 + \hat{\phi}(x,t), \psi_0 + \hat{\psi}(x,t))$, where

$$\begin{pmatrix} \hat{\phi} \\ \hat{\psi} \end{pmatrix} = \sum_{m=0}^{\infty} \begin{pmatrix} a_m \\ b_m \end{pmatrix} e^{\lambda_m t} \cos(k_m x), \tag{8}$$

and $k_m = m\pi/L$, $m = 0, 1, 2, \ldots$. Explicitly, the cosine function allows us to satisfy the zero flux boundary conditions since at the boundaries of the solution domain its spatial derivative will take the form of a sine function, which evaluates to zero when $x = 0$ or $L$. Moreover, because the cosine functions, $\{\cos(k_m x)\}_{m=0}^{\infty}$, form a complete orthogonal set, any solution of the linearised equation system can be decomposed into a series solution of superpositions.

The growth rate $\lambda_m$ informs us about the stability of the homogeneous steady state with respect to the wave mode, $k_m$. If the real part of $\lambda_m$ is negative for all $m$, then any perturbations will tend to decay exponentially quickly. However, in the case that the real part of $\lambda_m$ is positive for any non-zero value of $m$, our expansion solution suggests that the amplitude of these modes will grow exponentially quickly and so the homogeneous steady state is now linearly unstable. Moreover, in the case where there are multiple $\cos(k_m x)$ terms growing, small alterations in the initial conditions (which are bound to occur, since we are assuming that initial conditions are random perturbations around the homogeneous steady state) can lead to completely different final outcomes. Critically, the integer values of $m$ for which $\lambda_m$ has a positive real part then indicate how many pattern peaks we will see in the final solution. For example, if $\lambda_5$ is the only growth rate with positive real part, then we expect that the system will tend to a solution in which a $\cos(5\pi x/L)$ function is dominant, so the final pattern will have the corresponding number of peaks. However, if a range of growth rates is positive, then multiple cosine modes will fight for dominance and we will be unable to predict with certainty which mode will dominate in the final solution, because of the initial random perturbations and nonlinear interactions. This is the robustness problem. When dealing with animal pigmentation patterns, this dependence on initial conditions can be a useful property; for example zebra stripes are as individual as fingerprints [24]. However, such variability is problematic when we apply Turing's theory to more robust forms of biological development. Fortunately, as we will see later, this robustness problem is surmountable.

Substituting Eq. (8) into the linearised form of Eqs. (5) and (6), we obtain

$$\mathbf{0} = \begin{pmatrix} \lambda_m + D_\phi k_m^2 - f_\phi & -f_\psi \\ -g_\phi & \lambda_m + D_\psi k_m^2 - g_\psi \end{pmatrix} \begin{pmatrix} a_m \\ b_m \end{pmatrix}. \tag{9}$$

This matrix equation has a non-trivial solution ($(a_m, b_m) \neq (0,0)$) if and only if the determinant is zero:

$$\lambda_m^2 + \lambda_m((D_\phi + D_\psi)k_m^2 - f_\phi - g_\psi) + D_\phi D_\psi k_m^4 - k_m^2(D_\phi g_\psi + D_\psi f_\phi) + f_\phi g_\psi - f_\psi g_\phi = 0. \tag{10}$$

Letting $h(k^2) = D_\phi D_\psi k^4 - k^2(D_\phi g_\psi + D_\psi f_\phi) + f_\phi g_\psi - f_\psi g_\phi$, the linear stability of the homogeneous steady state is now governed by the signs of the real parts of

$$\lambda_{m\pm} = \frac{f_\phi + g_\psi - (D_\phi + D_\psi)k_m^2 \pm \sqrt{(f_\phi + g_\psi - (D_\phi + D_\psi)k_m^2)^2 - 4h(k_m^2)}}{2}. \tag{11}$$

First, we consider the linear stability in the case where there is no diffusion, $D_\phi = D_\psi = k_m = 0$. For the homogeneous steady state to be linearly stable, the real parts of both eigenvalues need to be negative. Thus

$$f_\phi + g_\psi < 0, \tag{12}$$

and

$$h(0) = f_\phi g_\psi - f_\psi g_\phi > 0. \tag{13}$$

Diffusion is now included and we derive conditions to ensure that at least one of the eigenvalues has positive real part. Since $f_\phi + g_\psi < 0$ by inequality (12), it follows that $f_\phi + g_\psi - (D_\phi + D_\psi)k_m^2 < 0$; thus the real part of $\lambda_{m-}$ is always negative. The only way to obtain an instability is if the real part of $\lambda_{m+}$ is positive. From (11), this occurs if $h(k_m^2) < 0$. Explicitly,

$$D_\phi D_\psi k_m^4 - k_m^2(D_\phi g_\psi + D_\psi f_\phi) + f_\phi g_\psi - f_\psi g_\phi < 0, \tag{14}$$

$$\Rightarrow k_-^2 < k_m^2 < k_+^2, \tag{15}$$

where

$$2D_\phi D_\psi k_\pm^2 = D_\phi g_\psi + D_\psi f_\phi \pm \sqrt{(D_\phi g_\psi + D_\psi f_\phi)^2 - 4D_\phi D_\psi (f_\phi g_\psi - f_\psi g_\phi)}. \tag{16}$$

For inequality (15) to be realised, $k_+^2$ needs to be real and positive, implying

$$D_\phi g_\psi + D_\psi f_\phi > 0, \tag{17}$$

$$(D_\phi g_\psi + D_\psi f_\phi)^2 - 4D_\phi D_\psi (f_\phi g_\psi - f_\psi g_\phi) > 0. \tag{18}$$

Since $f_\phi g_\psi - f_\psi g_\phi > 0$, from inequality (13), these two inequalities yield one condition,

$$D_\phi g_\psi + D_\psi f_\phi > 2\sqrt{D_\phi D_\psi}\sqrt{(f_\phi g_\psi - f_\psi g_\phi)} > 0. \tag{19}$$

Thus inequalities (12), (13), (15) and (19) form the conditions needed for a Turing instability in a reaction-diffusion system.

$$f_\phi + g_\psi < 0,$$

$$f_\phi g_\psi - f_\psi g_\phi > 0,$$

$$D_\phi g_\psi + D_\psi f_\phi > 2\sqrt{D_\phi D_\psi}\sqrt{(f_\phi g_\psi - f_\psi g_\phi)} > 0,$$

$$k_-^2 < \left(\frac{m\pi}{L}\right)^2 < k_+^2.$$

Turing's computer science background ideally suited this problem, as not only did he possess the mathematical skills to create the theoretical framework, but he was perfectly situated to numerically simulate the equations and, hence, visualise coarse-grained versions of the patterns (Fig. 1a, b). Due to the dramatic increase in computational speed and numerical algorithms, we are able to revisit the calculations (Fig. 1c, d) and see just how good Turing's first simulations were. Clearly, although his simulations were very coarse approximations to the equations,

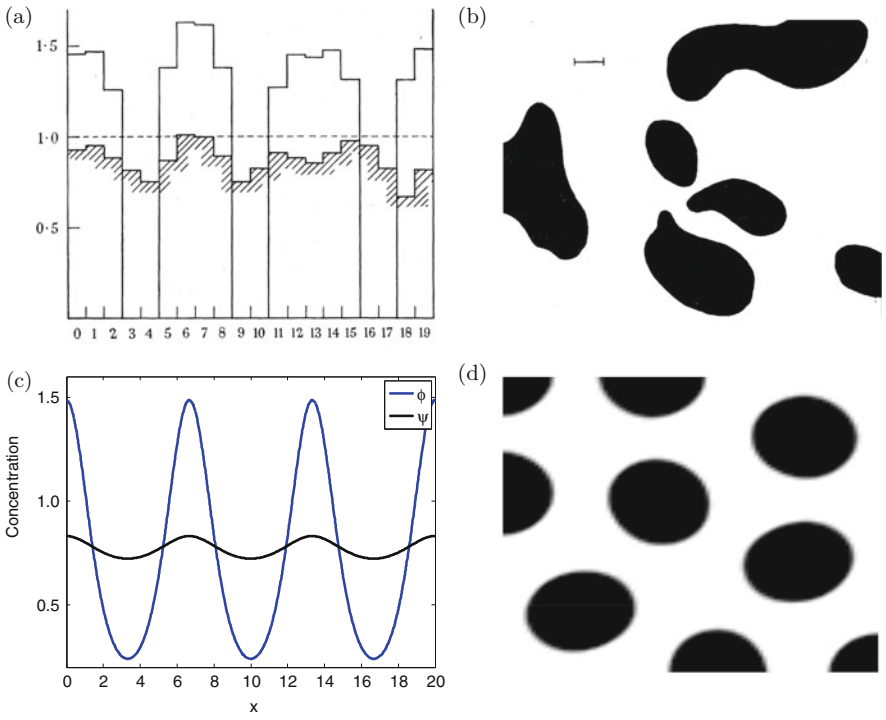


**Fig. 1** Heterogeneous patterns visualised in (**a**) one and (**b**) two dimensions, originally created by Turing himself. Modern versions of the Turing pattern in (**c**) one and (**d**) two dimensions. Figures (**a**) and (**b**) is reproduced from [4] by permission of the Royal Society

the basic patterns are still visible and very close to those we are now able to generate, illustrating his impressive computational abilities.

## 3 Where We Are

Turing's research was ahead of its time and so, for a while, his ideas lay dormant. However, the fast pace of theoretical, numerical and biological development that occurred towards the end of the twentieth century meant that it was the perfect time for Turing's theory to enjoy a successful renaissance [25, 26]. Here, we review just a few of the convincing biological applications, as well as some of the theoretical extensions, illustrating the richness of the original theory.

### *3.1 Biological Applications*

Perhaps the most colourful application is to pigmentation patterns. Importantly, this is not restricted to coat markings and animal skin. The Turing instability has also been suggested to be the mechanism behind the patterns on many seashells [27].

One prediction that immediately springs from the theory concerns tapered domains, for example a tail. By rearranging inequality (15), we obtain a bound on $m$,

$$\frac{Lk_-}{\pi} < m < \frac{Lk_+}{\pi}. \tag{20}$$

Since $k_+$ and $k_-$ are constants, this means that as the domain size, $L$, decreases, the window of viable wave modes shrinks, eventually disappearing. This means that as a domain becomes smaller, we should see a simplification of the pattern, e.g. from peak patterns to homogeneity. This result can be extended to the second dimension, where spot and stripe patterns are available. Once again, as the domain shrinks, we would expect a transition from spots to stripes, and finally to homogeneity, if the domain is small enough (Fig. 2a). This is excellently exemplified on the tail of the cheetah (Fig. 2b). However, the biological world does not always have respect for mathematics, as illustrated in Fig. 2c, where we observe that the lemur's pattern transition goes from a simple homogeneous colour on the body to a more complex striped pattern on the tail. Potentially, this means that Turing's theory does hold for the lemur's skin. Alternatively, if Turing's theory is used to account for the lemur's patterns, then we have to postulate either that the parameter values for the body and the tail are different, causing the difference in pattern, or that the patterns arise from the highly nonlinear regime of the kinetics, where our linear theory breaks down and, hence, we can no longer use the above predictions.

Importantly, we are not restricted to stationary domains, and these predictions were extended by Kondo and Asai [28] to pattern transitions on growing angelfish. As angelfish age, their bodies grow in size and more stripes are included in the pattern. Critically, the evolving patterns maintain a near-constant stripe spacing, which is one of the crucial features of a Turing pattern.

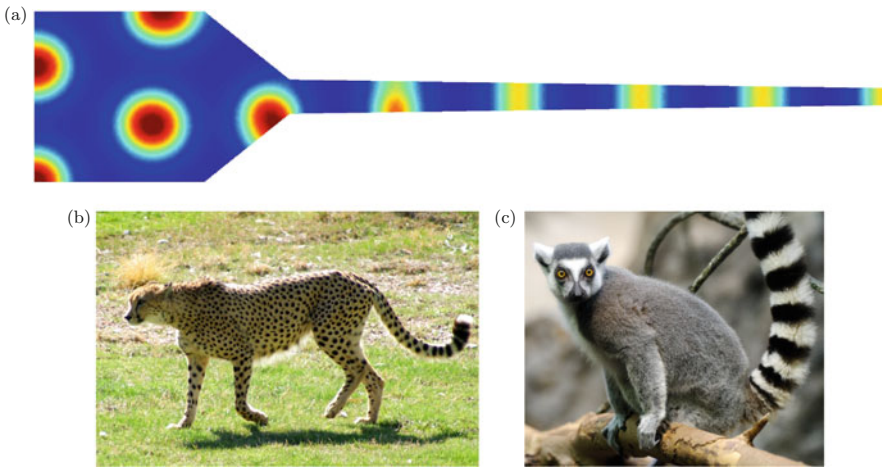


**Fig. 2** (**a**) Turing pattern on a tapered domain. Pattern transitions on (**b**) a cheetah and (**c**) a lemur

Turing patterns have also been postulated to underlie formation of the precursor patterns of many developmental systems, for example in mice, where it has been suggested that molar placement can be described by a diffusion-driven instability. Critically, not only can the normal molar placement be predicted by the model, but, by altering the model parameters to mimic biological perturbations, fused molar prepatterns are predicted, thereby reproducing experimental results [29]. Sheth et al. [30] further showed that Turing systems could underlie mouse digit development. In particular, experimental perturbations produced paws that did not change in size, but the number of digits did increase, leading to a reduction in digit spacing. Like the stripes on the angelfish, this new digit spacing in the treated mice was constant, consistent with a Turing-like mechanism. Critically, the reduction in wavelength could be linked to changes of parameters in a general Turing model.

## *3.2 Theoretical Extensions*

As already discussed, growth is an essential and readily observed process in development that has been identified as an important factor in the production of spatial heterogeneity since it can fundamentally change the observed dynamics of patterning mechanisms. Although growth had previously been included in an ad hoc manner [31], Crampin et al. [32] were the first to rigorously incorporate the effects of domain growth into the reaction-diffusion framework. This led to the discovery that uniform exponential domain growth can robustly generate persistent pattern doubling, even in the face of random initial conditions (Fig. 3a). This insensitivity to initial conditions is particularly significant in the context of biological development,

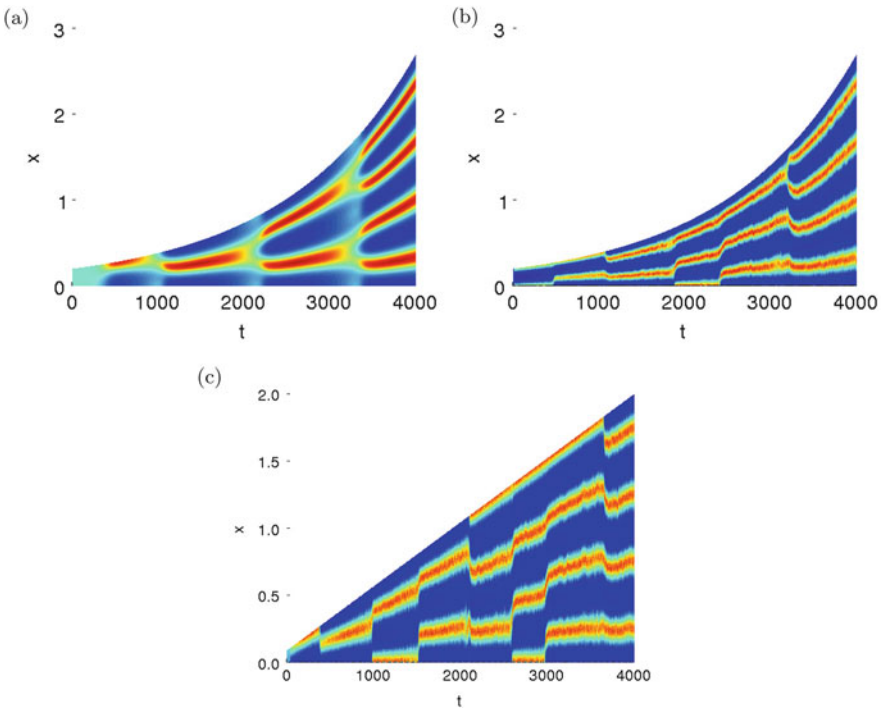


**Fig. 3** (**a**) Deterministic Turing kinetics on an exponentially growing domain. (**b**) Stochastic Turing kinetics on an exponentially growing domain. (**c**) Stochastic Turing kinetics on an linearly, apically growing domain. Figure (**c**) is reproduced with permission from [35]. Copyright 2011 American Physical Society

as not only does heterogeneity need to form, but also, in many cases, it is imperative that the final pattern be reliably reproducible.

Continuing this idea of robustness, we note that biological systems are frequently subject to noisy environments, inputs and signalling, not to mention that important proteins may only appear in very small quantities. Fundamentally, we based the derived partial differential equation (PDE) framework on the assumption that each species was present in high concentration, which allowed us to use a continuous approximation of the chemical concentrations. In order to investigate the Turing mechanism's sensitivity to noise, stochastic formulations have been created and even extended to encompass descriptions of domain growth [33–35]. Although it is clear that the Turing instability is able to exist (Fig. 3b), even in the face of intrinsic randomness, we see that uniform domain growth is no longer able to support the robust peak splitting that Crampin et al. [32] demonstrated in the deterministic system. However, if growth is localized to one of the boundaries (known as apical growth), then we see that pattern peaks appear in the domain one at a time, creating a consistent consecutive increase in the pattern wavenumber (Fig. 3c). If apical domain growth and wavenumber were connected in some form of feedback loop,

then, once the desired wavenumber was reached, growth would stop, leaving a stable pattern of exactly the desired wave mode. Thus, robust pattern generation can be recovered. It should be noted that noise does not need to be generated explicitly through stochastic reactions. Turing systems can also be chaotic, thus producing a deterministic form of noise [36].

A further relaxation of the fundamental assumptions behind the PDE formulation concerns the reaction rates as being defined by the Law of Mass Action. As originally stated, the law assumes that reactant products are created at the same moment that the reaction occurs. However, this may not always be the case. Reaction delays are particularly important when dealing with the production of important proteins as a cascade of time-consuming biological processes must occur in order for a single protein to be produced. Firstly, a linear polymeric ribonucleic acid (RNA) molecule is produced in a cell nucleus. This RNA molecule is an exact copy of the relevant gene sequence and is modified into a form called messenger RNA (mRNA). The mRNA is then transported into the nuclear membrane, where it is used as a blueprint for protein synthesis. In particular, the process of mRNA translation involves the polymerization of thousands to millions of amino acids. Given the complexity of this mechanism, it should not be surprising that a delay occurs between the initiation of protein translation and the point at which mature proteins are observed. The exact delay depends both on the length of the sequence being read and the sequence being created. However, typically the delay ranges from tens of minutes to as long as several hours [37]. Work has been done on including these gene-expression delays into both the deterministic and stochastic PDE formulations of the Turing instability, leading to observations of wildly different outcomes when compared to the non-delayed equations [38–40]. The potentially most worrying case is that of kinetic delays causing a catastrophic collapse of the pattern formation mechanism. Furthermore, such pathological dynamics occur consistently, regardless of domain growth profiles [41].

## 4 Computational Extensions

Of course, our simulations on one-dimensional lines and two-dimensional flat surfaces should always be questioned as to their accuracy in reproducing the effects of a real surface, which may have high curvatures. For example, pigmentation patterns are produced on skin surfaces that are stretched over skeletons that have highly non-trivial geometries. Turing mechanisms have been studied on simple regular surfaces, e.g. spheres, cones, etc. [42]. However, recent developments in numerical algorithms have allowed us to push our studies even further, allowing us to greatly generalise the geometries on which we numerically simulate the reaction-diffusion systems.

PDEs on surfaces are normally solved using finite element discretisations on a triangulation of the surface [43] or some other discretisation based on a suitable parameterisation of the surface [42]. An alternative approach to parameterizing the surface is to embed it in a higher-dimensional space [44]. The PDEs are then

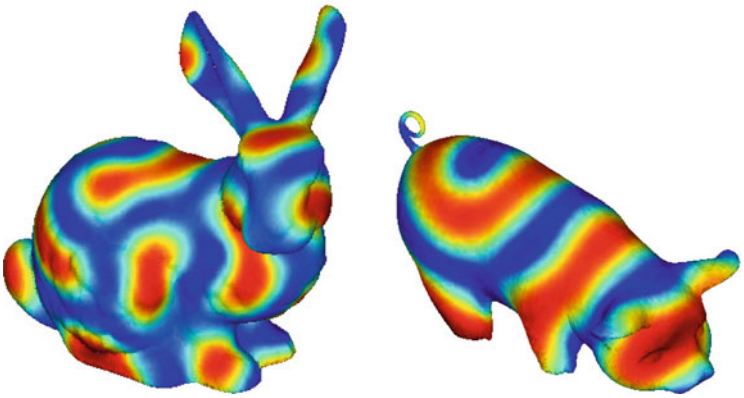

**Fig. 4** Examples of Turing patterns on general surfaces, computed using the closest point method [44]

solved in the embedding space, rather than just on the lower dimensional surface. Embedding methods have the attractive feature of being able to work using standard Cartesian coordinates and Cartesian grid methods [44]. Thus, it is within this class that the Closest Point Method was developed and analyzed [45]. Although we will not go into full details concerning the technique here, we do present the simple central idea of the embedding, which, as the name suggests, is the construction of the closest point function.

**Definition 1** For a given surface $\mathcal{S}$, the closest point function $cp : R^d \to R^d$ takes a point $\boldsymbol{x} \in R^d$ and returns a unique point $cp(\boldsymbol{x}) \in \mathcal{S} \subset R^d$ which is closest in Euclidean distance to $\boldsymbol{x}$. Namely,

$$cp(\boldsymbol{x}) = \min_{\boldsymbol{q} \in \mathcal{S}} ||\boldsymbol{x} - \boldsymbol{q}||_2. \tag{21}$$

If more than one $\boldsymbol{q}$ should fit this property, a single one is chosen arbitrarily.

From this definition, equations governing quantities on the surface can be extended to the embedding space. The equations are then solved more easily in the regular grid of the embedding space. This solution in the embedded space evaluated on the original surface will then agree with the solution that would have been generated if we had simply tried to solve the equation on just the surface. Examples of the impressive generality of this technique are given in Fig. 4.

## 5 Where We Want to Go

Now that we better understand the formation of Turing patterns on general two-dimensional surfaces, it is natural to want to extend to three and higher dimensions. Indeed, theoretical, experimental and computational work does exist heading in

this direction [46–49]. However, by going to higher dimensions we start having problems of pattern degeneracy. In one dimension, we are guaranteed only discrete peaks. The only degeneracy is in the choice of polarity, i.e. for any pattern mode that is based on a $\cos(kx)$ form, $-\cos(kx)$ is also a possible solution with opposite polarity. In two dimensions, not only can we obtain stripes, spots and labrythine patterns, but the orientation of these patterns is also variable, because any wave vector $\boldsymbol{k}$, which is associated with a critical wave number $|\boldsymbol{k}| = \sqrt{k_{xm}^2 + k_{yn}^2} = k_c$, such that $Re(\lambda_m(k_c)) > 0$, defines a growing mode. This means that in the spatially bounded two-dimensional case a finite number of Fourier modes can have wave vectors that lie on the critical circle [50]. Thus, spots can be arranged in rectangular, hexagonal, or rhombic patterns amongst other, more varied templates. This degeneracy problem becomes even more complex in three dimensions, where lamellae, prisms, and various other cubic structures all exist, making prediction even more difficult [51]. Weakly nonlinear theory and equivariant bifurcation theory [7, 51–53] can be used to derive amplitude equations near a critical bifurcation point that separate the homogeneous and patterned stationary stable states.

However, analysis will only get us so far and thus we are depending more and more on numerical simulation in order to explore patterning parameter space. This illustrates the great need for three-dimensional PDE solvers that are not only able to efficiently approximate the solutions of stiff PDEs with fine spatial resolution, but also are flexible enough to incorporate various boundary conditions, geometries and spatial heterogeneities. Further, analogously to the above work, changing from continuous descriptions of the populations to individual-based stochastic simulations in three dimensions poses another computationally intensive task. There has been work done on speeding up stochastic simulation algorithms [54–56]; however, work has only just begun to consider the potential powerful use of parallel computing, which is a much underexplored territory [57].

Equally, the computational visualisation of Turing patterns in higher dimensions needs consideration, as the basic planiforms, discussed above, are much more complicated. Moreover, the ability to compare such visualisations with actual data is still in its infancy and there are, as yet, few metrics by which a simulation can be compared to an experiment. Currently, we depend on simply matching the general pattern and the ability of the kinetics to reproduce experimental perturbations. However, to rigorously compare such patterns we must be able to develop image segmentation software that is capable of extracting dominant features of numerical and experimental results and comparing them using statistical methods.

Importantly, we do not need to extend to a third spatial dimension to find new problems. There are many still unanswered questions in lower spatial dimensions, but with more than two chemical species [58]. To suggest that many complex biological phenomena occur because of the interactions of two chemical species is misguided, at best. In reality, a single developmental pathway can depend on many hundreds of gene products interacting through a complex network of non-linear kinetics. Moreover, living systems have numerous fail-safe mechanisms, such as multiple redundant pathways, that only activate when there is a problem with the main network. This means that even if we are able to produce a complete gene

product interaction map for a given biological phenomenon, the phenomenon may still occur if the network is disrupted, making conclusions difficult.

Once again, analysis of such large systems can only lead us so far, before numerical simulations are required [59]. However, we are starting to see new branches of mathematical biology that seek to deal with these large networks, either through mass computer parallelisation of data processing [60, 61] or through rigorously and consistently identifying key features and time scales that allow the full system to be greatly reduced to a much smaller number of important species [62–66]. In either approach, efficient numerical algorithms are of paramount importance, and we hope to see more development in this direction in the future.

A rapidly growing research area is that of synthetic biology [67, 68]. In the future, no longer will we use mathematics to mimic a natural system's ability to produce patterns; instead, we will design tissues and cells that are able to reproduce mathematical predictions. Further, by utilising the large knowledge base surrounding the numerous extensions of Turing's theory, we may be able to customise such designs in order to produce patterns with specific properties.

## 6 Discussion

As can be clearly seen, Turing's theory for the chemical basis of morphogenesis has been applied to a wide range of patterning phenomena in developmental biology. The incredible richness in behaviour of the diffusion-driven instability has also allowed the theory to be extended dramatically from its humble beginnings of two chemicals deterministically reacting in a simple domain. Indeed, it is testament to Turing's genius that, not only did he discover such a counter-intuitive mechanism, it is still generating new ideas, even after 60 years of research. Importantly, our progress has significantly benefited from the recent rapid developments in computational software and hardware. Indeed, with the continued development of the biological techniques and computational visualisation abilities discussed in the last section, we could be at the dawn of a new age of Turing's theory, enabling us to further strengthen the links between experimental and theoretical researchers.

**Acknowledgements** TEW would like to thank St John's College Oxford for its financial support. This publication is based on work supported by Award No. KUK-C1-013-04, made by King Abdullah University of Science and Technology (KAUST). The cheetah and lemur photos were used under the Attribution-ShareAlike 2.0 license and were downloaded from http://www.flickr.com/photos/53936799@N05/ and http://www.flickr.com/photos/ekilby/.

## References


1. C.J. Tomlin, J.D. Axelrod, Biology by numbers: mathematical modelling in developmental biology. Nat. Rev. Genet. **8**(5), 331–340 (2007)
2. L. Wolpert, Positional information and the spatial pattern of cellular differentiation. J. Theor. Biol. **25**(1), 1–47 (1969)
3. L. Wolpert, Positional information revisited. Development **107**(Suppl.), 3–12 (1989)
4. A.M. Turing, The chemical basis of morphogenesis. Philos. Trans. R. Soc. Lond. B **237**, 37–72 (1952)
5. A. Gierer, H. Meinhardt, A theory of biological pattern formation. Biol. Cybern. **12**(1), 30–39 (1972)
6. R. Kapral, K. Showalter, *Chemical Waves and Patterns* (Kluwer, Dordrecht, 1995)
7. P. Borckmans, G. Dewell, A. De wit, D. Walgraef, Turing bifurcations and pattern selection, in *Chemical Waves and Patterns*, Chap. 10 (Kluwer, Dordrecht, 1995), pp. 325–363
8. Y.I. Balkarei, A.V. Grigor'yants, Y.A. Rzhanov, M.I. Elinson, Regenerative oscillations, spatial-temporal single pulses and static inhomogeneous structures in optically bistable semiconductors. Opt. Commun. **66**(2–3), 161–166 (1988)
9. D.B. White, The planforms and onset of convection with a temperature-dependent viscosity. J. Fluid Mech. **191**(1), 247–286 (1988)
10. T. Nozakura, S. Ikeuchi, Formation of dissipative structures in galaxies. Astrophys. J. **279**, 40–52 (1984)
11. B. Futcher, G.I. Latter, P. Monardo, C.S. McLaughlin, J.I. Garrels, A sampling of the yeast proteome. Mol. Cell. Biol. **19**(11), 7357 (1999)
12. N.G. van Kampen, *Stochastic Processes in Physics and Chemistry*, 3rd edn. (North Holland, Amsterdam, 2007)
13. S. Cornell, M. Droz, B. Chopard, Role of fluctuations for inhomogeneous reaction-diffusion phenomena. Phys. Rev. A **44**, 4826–4832 (1991)
14. A. Fick, On liquid diffusion. Philos. Mag. J. Sci. **10**(1), 31–39 (1855)
15. J.D. Murray, E.A. Stanley, D.L. Brown, On the spatial spread of rabies among foxes. Proc. R. Soc. Lond. B. Biol. **229**(1255), 111–150 (1986)
16. A. Okubo, P.K. Maini, M.H. Williamson, J.D. Murray, On the spatial spread of the grey squirrel in Britain. Proc. R. Soc. Lond. B. Biol. **238**(1291), 113 (1989)
17. T.E. Woolley, R.E. Baker, E.A. Gaffney, P.K. Maini, How long can we survive? in *Mathematical Modelling of Zombies*, Chap. 6 (University of Ottawa Press, Ottawa, 2014)
18. J.D. Murray, *Mathematical Biology I: An Introduction*, vol. 1, 3rd edn. (Springer, Heidelberg, 2003)
19. R. Erban, S.J. Chapman, Reactive boundary conditions for stochastic simulations of reaction–diffusion processes. Phys. Biol. **4**, 16 (2007)
20. T.E. Woolley, R.E. Baker, P.K. Maini, J.L. Aragón, R.A. Barrio, Analysis of stationary droplets in a generic Turing reaction-diffusion system. Phys. Rev. E **82**(5), 051929 (2010)
21. T.E. Woolley, Spatiotemporal behaviour of stochastic and continuum models for biological signalling on stationary and growing domains. Ph.D. thesis, University of Oxford, 2011
22. R.A. Barrio, R.E. Baker, B. Vaughan Jr, K. Tribuzy, M.R. de Carvalho, R. Bassanezi, P.K. Maini, Modeling the skin pattern of fishes. Phys. Rev. E **79**(3), 31908 (2009)
23. R. Dillon, P.K. Maini, H.G. Othmer, Pattern formation in generalized Turing systems. J. Math. Biol. **32**(4), 345–393 (1994)
24. J.C.B. Petersen, An identification system for zebra (Equus burchelli, Gray). Afr. J. Ecol. **10**(1), 59–63 (1972)
25. P.K. Maini, T.E. Woolley, R.E. Baker, E.A. Gaffney, S.S. Lee, Turing's model for biological pattern formation and the robustness problem. Interface Focus **2**(4), 487–496 (2012)
26. T.E. Woolley, Mighty morphogenesis, in *50 Visions of Mathematics*, Chap. 48 (Oxford University Press, Oxford, 2014)

27. H. Meinhardt, P. Prusinkiewicz, D.R. Fowler, *The Algorithmic Beauty of Sea Shells* (Springer, Heidelberg, 2003)
28. S. Kondo, R. Asai, A reaction-diffusion wave on the skin of the marine angelfish Pomacanthus. Nature **376**, 765–768 (1995)
29. S.W. Cho, S. Kwak, T.E. Woolley, M.J. Lee, E.J. Kim, R.E. Baker, H.J. Kim, J.S. Shin, C. Tickle, P.K. Maini, H.S. Jung, Interactions between Shh, Sostdc1 and Wnt signaling and a new feedback loop for spatial patterning of the teeth. Development **138**, 1807–1816 (2011)
30. R. Sheth, L. Marcon, M.F. Bastida, M. Junco, L. Quintana, R. Dahn, M. Kmita, J. Sharpe, M.A. Ros, How genes regulate digit patterning by controlling the wavelength of a Turing-type mechanism. Science **338**(6113), 1476–1480 (2012)
31. P. Arcuri, J.D. Murray, Pattern sensitivity to boundary and initial conditions in reaction-diffusion models. J. Math. Biol. **24**(2), 141–165 (1986)
32. E.J. Crampin, E.A. Gaffney, P.K. Maini, Reaction and diffusion on growing domains: scenarios for robust pattern formation. Bull. Math. Biol. **61**(6), 1093–1120 (1999)
33. T.E. Woolley, R.E. Baker, E.A. Gaffney, P.K. Maini, Power spectra methods for a stochastic description of diffusion on deterministically growing domains. Phys. Rev. E **84**(2), 021915 (2011)
34. T.E. Woolley, R.E. Baker, E.A. Gaffney, P.K. Maini, Influence of stochastic domain growth on pattern nucleation for diffusive systems with internal noise. Phys. Rev. E **84**(4), 041905 (2011)
35. T.E. Woolley, R.E. Baker, E.A. Gaffney, P.K. Maini, Stochastic reaction and diffusion on growing domains: understanding the breakdown of robust pattern formation. Phys. Rev. E **84**(4), 046216 (2011)
36. J.L. Aragón, R.A. Barrio, T.E. Woolley, R.E. Baker, P.K. Maini, Nonlinear effects on Turing patterns: time oscillations and chaos. Phys. Rev. E **86**(2), 026201 (2012)
37. C.N. Tennyson, H.J. Klamut, R.G. Worton, The human dystrophin gene requires 16 hours to be transcribed and is cotranscriptionally spliced. Nat. Genet. **9**(2), 184–190 (1995)
38. T.E. Woolley, R.E. Baker, E.A. Gaffney, P.K. Maini, S. Seirin-Lee, Effects of intrinsic stochasticity on delayed reaction-diffusion patterning systems. Phys. Rev. E **85**(5), 051914 (2012)
39. E.A. Gaffney, N.A.M. Monk, Gene expression time delays and Turing pattern formation systems. Bull. Math. Biol. **68**(1), 99–130 (2006)
40. S.S. Lee, E.A. Gaffney, Aberrant behaviours of reaction diffusion self-organisation models on growing domains in the presence of gene expression time delays. Bull. Math. Biol. **72**, 2161–2179 (2010)
41. S.S. Lee, E.A. Gaffney, R.E. Baker, The dynamics of Turing patterns for morphogen-regulated growing domains with cellular response delays. Bull. Math. Biol. **73**(11), 2527–2551 (2011)
42. R.G. Plaza, F. Sanchez-Garduno, P. Padilla, R.A. Barrio, P.K. Maini, The effect of growth and curvature on pattern formation. J. Dyn. Differ. Equ. **16**(4), 1093–1121 (2004)
43. K.W. Morton, D.F. Mayers, *Numerical Solution of Partial Differential Equations: An Introduction* (Cambridge University Press, Cambridge, 2005)
44. C.B. Macdonald, S.J. Ruuth, The implicit closest point method for the numerical solution of partial differential equations on surfaces. SIAM J. Sci. Comput. **31**(6), 4330–4350 (2009)
45. S.J. Ruuth, B. Merriman, A simple embedding method for solving partial differential equations on surfaces. J. Comput. Phys. **227**(3), 1943–1961 (2008)
46. T.K. Callahan, E. Knobloch, Bifurcations on the fcc lattice. Phys. Rev. E **53**(4), 3559–3562 (1996)
47. T. Leppänen, M. Karttunen, K. Kaski, R.A. Barrio, L. Zhang, A new dimension to Turing patterns. Physica D **168**, 35–44 (2002)
48. E. Dulos, P. Davies, B. Rudovics, P. De Kepper, From quasi-2D to 3D Turing patterns in ramped systems. Physica D **98**(1), 53–66 (1996)
49. S. Muraki, E.B. Lum, K.-L. Ma, M. Ogata, X. Liu, A PC cluster system for simultaneous interactive volumetric modeling and visualization, in *Proceedings of the 2003 IEEE Symposium on Parallel and Large-Data Visualization and Graphics* (2003), p. 13

50. S.L. Judd, M. Silber, Simple and superlattice Turing patterns in reaction-diffusion systems: bifurcation, bistability, and parameter collapse. Physica D **136**(1–2), 45–65 (2000)
51. T.K. Callahan, E. Knobloch, Pattern formation in three-dimensional reaction–diffusion systems. Physica D **132**(3), 339–362 (1999)
52. T.K. Callahan, E. Knobloch, Symmetry-breaking bifurcations on cubic lattices. Nonlinearity **10**(5), 1179–1216 (1997)
53. T. Leppänen, M. Karttunen, R.A. Barrio, K. Kaski, Morphological transitions and bistability in Turing systems. Phys. Rev. E. **70**, 066202 (2004)
54. D.T. Gillespie, Approximate accelerated stochastic simulation of chemically reacting systems. J. Chem. Phys. **115**, 1716 (2001)
55. M. Rathinam, L.R. Petzold, Y. Cao, D.T. Gillespie, Stiffness in stochastic chemically reacting systems: the implicit tau-leaping method. J. Chem. Phys. **119**(24), 12784–12794 (2003)
56. Y. Yang, M. Rathinam, Tau leaping of stiff stochastic chemical systems via local central limit approximation. J. Comput. Phys. **242**, 581–606 (2013)
57. G. Klingbeil, R. Erban, M. Giles, P.K. Maini, STOCHSIMGPU: parallel stochastic simulation for the Systems Biology Toolbox 2 for Matlab. Bioinformatics **27**(8), 1170–1171 (2011)
58. R.A. Satnoianu, M. Menzinger, P.K. Maini, Turing instabilities in general systems. J. Math. Biol. **41**(6), 493–512 (2000)
59. V. Klika, R.E. Baker, D. Headon, E.A. Gaffney, The influence of receptor-mediated interactions on reaction-diffusion mechanisms of cellular self-organisation. B. Math. Biol. **74**(4), 935–957 (2012)
60. J. Dean, S. Ghemawat, MapReduce: simplified data processing on large clusters. Commun. ACM **51**(1), 107–113 (2008)
61. T. Ideker, T. Galitski, L. Hood, A new approach to decoding life: systems biology. Annu. Rev. Genomics Hum. Genet. **2**(1), 343–372 (2001)
62. M.W. Covert, B.O. Palsson, Constraints-based models: regulation of gene expression reduces the steady-state solution space. J. Theor. Biol. **221**(3), 309–325 (2003)
63. O. Cominetti, A. Matzavinos, S. Samarasinghe, D. Kulasiri, S. Liu, P.K. Maini, R. Erban, DifFUZZY: a fuzzy clustering algorithm for complex datasets. Int. J. Comput. Intel. Bioinf. Syst. Biol. **1**(4), 402–417 (2010)
64. H. Conzelmann, J. Saez-Rodriguez, T. Sauter, E. Bullinger, F. Allgöwer, E.D. Gilles, Reduction of mathematical models of signal transduction networks: simulation-based approach applied to EGF receptor signalling. Syst. Biol. **1**(1), 159–169 (2004)
65. O. Radulescu, A.N. Gorban, A. Zinovyev, A. Lilienbaum, Robust simplifications of multiscale biochemical networks. BMC Syst. Biol. **2**(1), 86 (2008)
66. L. Marcon, X. Diego, J. Sharpe, P. Muller, High-throughput mathematical analysis identifies Turing networks for patterning with equally diffusing signals. eLife **5**, e14022 (2016)
67. W. Weber, J. Stelling, M. Rimann, B. Keller, M. Daoud-El Baba, C.C. Weber, D. Aubel, M. Fussenegger, A synthetic time-delay circuit in mammalian cells and mice. Proc. Natl. Acad. Sci. **104**(8), 2643–2648 (2007)
68. E. Fung, W.W. Wong, J.K. Suen, T. Bulter, S. Lee, J.C. Liao, A synthetic gene–metabolic oscillator. Nature **435**(7038), 118–122 (2005)