Stochastic reaction and diffusion on growing domains: Understanding the breakdown of robust pattern formation

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Many biological patterns, from population densities to animal coat markings, can be thought of as heterogeneous spatiotemporal distributions of mobile agents. Many mathematical models have been proposed to account for the emergence of this complexity, but, in general, they have consisted of deterministic systems of differential equations, which do not take into account the stochastic nature of population interactions. One particular, pertinent criticism of these deterministic systems is that the exhibited patterns can often be highly sensitive to changes in initial conditions, domain geometry, parameter values, etc. Due to this sensitivity, we seek to understand the effects of stochasticity and growth on paradigm biological patterning models. In this paper, we extend spatial Fourier analysis and growing domain mapping techniques to encompass stochastic Turing systems. Through this we find that the stochastic systems are able to realize much richer dynamics than their deterministic counterparts, in that patterns are able to exist outside the standard Turing parameter range. Further, it is seen that the inherent stochasticity in the reactions appears to be more important than the noise generated by growth, when considering which wave modes are excited. Finally, although growth is able to generate robust pattern sequences in the deterministic case, we see that stochastic effects destroy this mechanism for conferring robustness. However, through Fourier analysis we are able to suggest a reason behind this lack of robustness and identify possible mechanisms by which to reclaim it.

I. INTRODUCTION

Mathematical modeling is of fundamental importance in developmental biology due to its ability to suggest and test mechanisms by which complex biological patterns can arise. Although many mechanisms have been proposed, we focus on the Turing system as a model of morphogenesis as it has been postulated to be the key mechanism behind feather bud, limb bud, and hair follicle development. In most cases these models have been constructed in a deterministic framework and the effects of intrinsic noise on pattern formation have only recently been considered. Indeed, due to the sensitivity of the Turing model to perturbations in parameter values, domain geometry, etc., it has been seen that stochastic effects are able to influence the evolving patterns in ways not seen through deterministic simulations.

Previous research in the area of stochastic reaction-diffusion systems has focused on analyzing and simulating the effects of external noise. External noise is modeled as an additional effect that is controlled by the user, thus its properties are known a priori. Here, we focus on the role of intrinsic stochasticity by modeling diffusion of the chemical constituents as a space-jump process, i.e., the individual particles of the chemical populations undergo unbiased random walks on a domain which has been discretized into boxes. Reactions between constituent populations are assumed to act within each box, thus reagents in box i can only react with other reagents in box i. For each stochastic system, a chemical master equation (CME) can be generated as an exact description of the evolution of the system. Linear noise expansions allow derivation of Fokker-Plank equations that characterise the properties of the noise, which can then be converted into ordinary differential equations (ODEs) that define the covariances. Recently developed spatial Fourier transform techniques can also be applied in order to gain an insight into the potential spatial dynamics that are possible in such systems.

Primarily, we can consider which wave modes are stochastically excited inside and outside of the deterministic Turing domain. Within the parameter region that allows deterministic systems to realize Turing patterns, we analytically demonstrate that the stochastically excited wave modes correspond exactly to their deterministic analogues. It is found that these stochastically excited wave modes grow exponentially with time and, since the noise perturbs the populations away from the uniform steady state, patterning is able to form much earlier in a stochastic system than in its deterministic counterpart. Outside of this region, deterministic systems are unable to sustain viable patterns, whereas the noise inherent in a stochastic system is able to produce a state that is consistently far removed from the homogeneous steady state, a result that was previously noted by Biancalani et al.

Having considered the stationary domain case, we use a recently developed mapping technique to explore stochastic reaction-diffusion systems on growing domains. We are interested in the effects of stochasticity in such systems, as, in the deterministic setting, it has been shown that domain growth is able to support robust pattern doubling sequences. Barrass et al. further illuminated this mechanism by producing bifurcation diagrams showing the observed pattern doubling occurs by the mth wave mode destabilizing and
the solution trajectory moving onto the stabilized $2m$ wave mode. During the jump from one stable mode to the other, the trajectory moves through a window where wave modes $k$, $m < k < 2m$, may also be stable, thus, if the growth is too slow, period doubling will break down. Alternatively, if growth is too fast, period doubling breaks down because the system does not reside for sufficiently long in a specific range of pattern stability to allow that pattern to establish [31]. Furthermore, in the case that domain length has a more complex dependence on concentration, growth can cause a number of interesting pathological phenomena [31].

We cast the Turing models onto growing domains in order to consider the possible transition sequences. Since robustness in a deterministic Turing system is achieved through domain growth, we may naively suspect that robustness may also exist in the stochastic formulation, since the excited wave modes are identical in both systems. However, it is quickly realized that stochasticity inhibits pattern-doubling robustness. Even in the limit of large populations, stochasticity is able to cause a breakdown in the doubling, eventually. Although we lose period doubling as a mechanism of robustness, stochastic systems appear to excite consecutive modes, and thus we investigate the robustness of this mechanism through simulation.

With the aim of analyzing robustness, or lack thereof, in mind, we start in Sec. II by creating the stochastic framework in which we will construct the models. In Sec. III we justify the mapping from the Eulerian domain, which is time-dependent, to the Lagrangian domain, which is time-independent, and then recapitulate the application of spatial Fourier transforms on growing domains in Sec. IV. The effects of stochasticity on a specific Turing system, both inside and outside of the Turing unstable parameter region, are then considered in Sec. V, and these results are then extended to the case of deterministically and stochastically growing domains. Finally, in Sec. VI, we show that the stochastically excited wave modes are exactly equivalent to their deterministic analogues and derive an inequality for the discretization needed to generate noise appropriately.

II. STOCHASTIC FORMALISM

For a detailed discussion of the following ideas see Refs. [28,29], where we considered a general system containing a single stochastic biochemical population. In order to examine Turing systems, we need to consider at least two spatially extended populations that interact through nonlinear reactions. Thus, in this section, we briefly recapture the weak noise expansion, applied to a system of two diffusing populations, $U(x,t)$ and $V(x,t)$, that are coupled through nondelayed reactions, on a one-dimensional domain.

Although other descriptions of diffusion are possible [33], we model diffusion as a space-jump process; see Fig. 1 [20]. The domain is partitioned into one-dimensional boxes of size $\Delta x$, where each box, $i$, contains the indexed populations, $U_i$ and $V_i$. Higher dimensional domains can be considered by replacing the one-dimensional boxes with appropriate analogues [34]. Thus, for two particle types that have been discretized into $K$ compartments in a one-dimensional domain of length $L$, with Neumann boundary conditions and stochastic diffusion coefficients $d_u$ and $d_v$, respectively, the diffusion reactions are:

$$U_1 \xleftarrow{d_u} U_2 \xleftarrow{d_u} \cdots \xleftarrow{d_u} U_K, \quad (1)$$

$$V_1 \xleftarrow{d_v} V_2 \xleftarrow{d_v} \cdots \xleftarrow{d_v} V_K. \quad (2)$$

We use $U_i$ and $V_i$ to stand for both respective species and populations and this abuse of notation should not cause confusion. Since a space-jump process gives rise to first-order reactions, the equations governing mean particle numbers are equivalent to the equations derived using the Law of Mass Action [35]. Thus, if $d_u = D_u / \Delta x^2$ and $d_v = D_v / \Delta x^2$, where $D_u$ and $D_v$ are the macroscopic rates of diffusion [36], then the mean-field equations are seen to be second-order, finite difference approximations of the one-dimensional Laplacian, which is derived through a Taylor expansion of the continuous formulation [37,38].

In addition to diffusion, suppose these populations undergo $J$ reactions, $[R_1, \ldots, R_J]$. For simplicity, we use the convention that bold variables stand for the vector of spatially extended variables, e.g. $U(t) = [U_1(t), \ldots, U_K(t)]$ and $V(t) = [V_1(t), \ldots, V_K(t)]$ are the state vectors of the system at time $t$. Each reaction, $R_j$, is specified by the propensity function, $a_j(u, v)$, where $u$ and $v$ are single realizations of $U$ and $V$ and the stoichiometric vector $v_j = (v_{1j}, \ldots, v_{Kj})$. Explicitly, for the $j$th reaction, $v_{ij}$ is the change in population $U_i$ for $1 \leq i \leq K$ and $V_{i-k}$ for $K+1 \leq i \leq 2K$. From these definitions and the Laws of Probability [39], we can construct the CME. By defining $P(W, t) = P(u, v)$ to be the probability of being in state $W = (u, v)$ at time $t$, then, given an initial state, $W_0 = (U_0, V_0)$, $W_0 = (U(t_0), V(t_0)) = (u_0, v_0)$,

$$\frac{\partial}{\partial t} P(W, t | W_0, t_0) = \sum_{j=1}^{J} \left[ P(W - v_j, t | W_0, t_0) a_j(W - v_j) \right. \left. - P(W, t | W_0, t_0) a_j(W) \right]. \quad (3)$$

Due to the CME usually being nonlinear it is generally not solvable, except in certain, special, circumstances [37, 40]. Thus, we derive a weak noise expansion of the CME using a suitable system parameter, denoted $\Omega$. This expansion allows us to consider the deterministic and stochastic effects separately.

FIG. 1. Diagram illustrating the stochastic description of diffusion. Each particle has equal probability of moving left as of moving right. If, for example, the right diffusion reaction, $R_j$, occurs one molecule from box $j$ moves to box $j + 1$. Reproduced from Ref. [28]. “Copyright 2011 by the American Physical Society.”
We define new random variables, \( \eta_{ai} \) and \( \eta_{ei} \) (which are of order one as \( \Omega \to \infty \), for \( i = 1, \ldots, K \)), through the relations,

\[
U_i = \phi_i \Omega + \eta_{ai} \sqrt{\Omega},
\]

\[
V_i = \psi_i \Omega + \eta_{ei} \sqrt{\Omega},
\]

where \( \Omega \) is the magnitude of the smallest homogeneous steady state of the populations \( U \) or \( V \). \( \phi_i \) and \( \psi_i \) are the expected ratios of the populations at time \( t \) to the order of magnitude, \( \Omega \), and are dimensionless “macroscopic” variables. The statistics of \( U_i \) and \( V_i \) are linked to \( \eta_{ai} \) and \( \eta_{ei} \), respectively, through the identification [22]

\[
P(U, V, t) = \Pi(\eta_u, \eta_v, t).
\]

By using this form of expansion the fluctuations are treated as Gaussian perturbations about the deterministic solution and, as such, this approximation only works in the case of large \( \Omega \). Note that, if considering a monotonically increasing process, such as exponential growth, this approximation suggests that, although the mean population undergoes a net exponential growth, the domain length in the Gaussian approximation is able to shrink instantaneously. The final piece of terminology we need is the macroscopic rate of reaction, \( a_j \), which is used to define the macroscopic variables, \( \phi_i \) and \( \psi_i \), as solutions of

\[
\frac{d\phi_i}{dt} = \sum_{j=1}^{J} a_j(\phi_i, \psi_i) v_{ij},
\]

\[
\frac{d\psi_i}{dt} = \sum_{j=1}^{J} a_j(\phi_i, \psi_i) v_{K+i,j}.
\]

Through using the relationships between \( P, \Pi, a_j, \) and \( a_i \), we are able to expand and separate Eq. (3) in terms of decreasing orders of \( \Omega \) [28,29]. The leading order terms are of size \( \mathcal{O}(\sqrt{\Omega}) \) and define the deterministic dynamics of the macroscopic equations,

\[
\sum_{i=1}^{K} \left[ \frac{d\phi_i}{dt} \frac{\partial \Pi}{\partial \eta_{ai}} + \frac{d\psi_i}{dt} \frac{\partial \Pi}{\partial \eta_{ei}} \right] = \left[ \sum_{i=1}^{K} \sum_{k=1}^{K} a_j(\phi_i, \psi_i) v_{ij} \frac{\partial \Pi}{\partial \eta_{ai}} + \sum_{i=1}^{K} a_j(\phi_i, \psi_i) v_{K+i,j} \frac{\partial \Pi}{\partial \eta_{ei}} \right].
\]

This is satisfied by the definitions of \( \phi_i \) and \( \psi_i \) in Eqs. (7) and (8).

The second-order term in the expansion is of size \( \mathcal{O}(1) \) and gives rise to a Fokker-Planck equation [41], which defines the dynamics of the probability density,

\[
\frac{\partial \Pi}{\partial t} = -\sum_{i=1}^{2K} A_{ii} \frac{\partial [\eta_i \Pi]}{\partial \eta_i} + \frac{1}{2} \sum_{i,j=1}^{2K} B_{ij} \frac{\partial^2 \Pi}{\partial \eta_i \partial \eta_j},
\]

where \( \eta_i = \eta_{ai} \) for \( i = 1, \ldots, K \) and \( \eta_i = \eta_{ei} - K \) for \( i = K + 1, \ldots, 2K \). The coefficients \( A_{ii} \) and \( B_{ij} \) are defined through the matrix equations [42]

\[
A = \{ A_{ii} \} = \{ \partial [\mathbf{a} \mathbf{v}] / \partial \phi_i \},
\]

\[
B = \{ B_{ij} \} = \mathbf{v} \text{diag}(\mathbf{a}) \mathbf{v}^T,
\]

\[
\mathbf{v} = \{ v_{ij} \}_{j=1}^{J},
\]

and \( \mathbf{a}^T = (a_1, \ldots, a_J) \).

III. LAGRANGIAN COORDINATES

As discussed in Sec. I, growth has been used theoretically to ensure robustness in deterministic Turing patterning systems [30]. Because growth is so important in biology [43], there has recently been interest in producing a stochastic description of growth [20] that is consistent with continuum theory [44].

In previous work [28,29], we developed a rigorous analytic framework that allows the consideration of stochastic and deterministic domain growth by mapping the growing Eulerian domain to a static Lagrangian domain. This consists of discretizing a domain into \( K \) boxes, as usual, but each box, \( i \), is now identified as a Lagrangian compartment of size \( \Delta_L \), containing \( N_i(t) \) Eulerian subdivisions of size \( \Delta_E \) (see Fig. 2). This microscopic variable, \( N_i(t) \), is governed by a stochastic process and is linked to a macroscopic variable, \( n_i(t) \), which defines the average ratio of Lagrangian box size, \( \Delta_L \), to the total size of the corresponding Eulerian sub compartments, \( N_i(t) \Delta_E \), at time \( t \). Further, similar to Sec. II, a new random variable, \( \epsilon_i(t) \), is defined through

\[
N_i = n_i \theta + \epsilon_i \sqrt{\theta},
\]

where

\[
\theta \overset{\text{def}}{=} \frac{\Delta_L}{\Delta_E}.
\]

is the scaling of Eulerian box length to Lagrangian box length. Initially, the \( N_i(0) \) are taken to be equal for all \( i \), thus

\[
\Delta_L n_i(0) = \theta \Delta_E = N_i(0) \Delta_E,
\]

(see Fig. 2) and hence, \( n_i(0) = 1 \) for all \( i \). The intrinsic noise in the domain length arises through probabilistic changes in the number of microscopic compartments, which are biologically motivated by the stochastic processes of cell division and cell death. Thus, similar to the case of reactions, the noise forms an integral part of the domain’s dynamics.

In the Appendix we use the specific example of Schnakenberg reaction kinetics to illustrate the effect of this spatial mapping. Since the mean-field behaviour of the CME is given by the deterministic system shown in Eqs. (A6) and (A7) we use the deterministic reaction rates to produce stochastic
analogue by substituting $n_i(t)$ for $N_i/\theta$ and noting that,
\begin{equation}
\lim_{\theta \to \infty} \frac{N_i(t)}{\theta} = n_i(t).
\end{equation}

Using the weak noise expansion [22,42] discussed in Sec. II, we can separate the leading order equations of $\Omega$ and $\theta$ to obtain the deterministic behavior, and then consider the lower-order terms to explore the stochastic behavior. Note that not only do we obtain terms of order one, but there will be new terms of order $\sqrt{\Omega}/\theta$. Thus, the general Fokker-Planck equation for stochastic reactions on a stochastically growing domain is
\begin{equation}
\frac{\partial \Pi}{\partial t} = - \sum_{i,j} A_{ij} \frac{\partial}{\partial \phi_i} (\phi_i \Pi) + \frac{1}{2} \sum_{i,j} B_{ij} \frac{\partial^2 \Pi}{\partial \phi_i \partial \phi_j},
\end{equation}
where $\Theta_i$ is the scaling for the variable $\phi_i$. In the current case, $\phi_i = \eta_{ui}$ for $i = 1, \ldots, K$; $\phi_i = \eta_{vi} - K$ for $i = K + 1, \ldots, 2K$; $\phi_i = \epsilon_{i-2K}$ for $i = 2K + 1, \ldots, 3K$; $\Theta_i = \Omega$ for $i = 1, \ldots, 2K$; and $\Theta_i = \theta$ for $i = 2K + 1, \ldots, 3K$. Note that, for simplicity, whenever we consider stochastic growth we fix the scaling parameters to be equal, i.e., $\theta = \Omega$. If $\theta \ll \Omega$, it would be possible to assume that the reactions were deterministic on a stochastically growing domain. However, since we are interested in small number numbers this is not considered here. Similarly, if $\theta \gg \Omega$, the domain would effectively be growing deterministically. This assumption is used later, once we have compared deterministic and stochastic growth in Sec. V B and shown that the noise generated from growth is much less significant than that generated from reactions. Furthermore, we see that the pattern evolution of a Turing system on a stochastically growing domain is sufficiently similar to one undergoing deterministic growth so that it is appropriate to investigate only deterministic growth. Finally, we fix the form of Lagrangian diffusion to be approximate midpoint to midpoint diffusion [29]. This defines the transition rates left and right to be equal to
\begin{equation}
\frac{d \epsilon_i}{\pi N_i^2},
\end{equation}
where $d \epsilon = d_a$ or $d_r$ depending on the population. For a derivation of this rate from Dynkin’s formula see Refs. [29,45].

In general, a system of non-delayed, coupled reaction–diffusion equations on a deterministically growing domain can be rescaled to remove dilution and projected onto the stationary domain thus giving the form (see the Appendix) [30,43,44]:
\begin{equation}
\frac{\partial \phi}{\partial t} = \frac{D_u}{n(t)^2} \nabla^2 \phi(x,t) + f(\phi(x,t), \psi(x,t), t),
\end{equation}
\begin{equation}
\frac{\partial \psi}{\partial t} = \frac{D_v}{n(t)^2} \nabla^2 \psi(x,t) + g(\phi(x,t), \psi(x,t), t),
\end{equation}
where $\phi(t), \psi(t)$, and $n(t)$ are the spatially continuous forms of the discretized populations $\phi_i(t), \psi_i(t), and n_i(t)$, respectively. Also, due to the rescaling of the reaction kinetics using $n(t)$ (see the Appendix), the kinetic functions of the reactions, $f$ and $g$, will normally be time-dependent. Thus, except for the diffusion term (which uses a three-point stencil in one dimension), the discretized system will contain only terms evaluated at the same spatial and temporal points. Further, since we are dealing with a regular grid of points in the discretized domain, the diffusive operator stencil only includes two neighboring spatial terms. These are identical at all points across the domain, excluding the end points, which are accounted for by the form of the Fourier cosine expansion. Thus, the matrices $A$ and $B$, defined in Eqs. (11) and (12), can be split into symmetric tridiagonal submatrices, where the terms along each diagonal are identical. This allows the equations to be Fourier-transformed analytically, even where we have time-dependent coefficients. If instead an irregular discretization is used, the Fourier transform can be calculated, but only numerically. Although, by considering different stochastic descriptions of diffusion the number of nonzero super- and subdiagonals may change, the matrices will always be symmetric and so spatial Fourier transforms will always be applicable.

For stochastic growth, the matrices $A$ and $B$ will be $3K \times 3K$ in size, as we have three distinct, spatially discretized populations, $U, V$, and $N = (N_1, N_2, \ldots, N_K)$. In the case that the growth rate is independent of the chemical concentrations, $A$ and $B$ will have sparse forms. These matrices can be split up into nine $K \times K$ submatrices of the form
\begin{equation}
A = \begin{bmatrix}
a & b & e \\
c & d & f \\
0 & 0 & 0 \\
\end{bmatrix},
B = \begin{bmatrix}
\alpha & \beta & 0 \\
\beta & \gamma & 0 \\
0 & 0 & \delta \\
\end{bmatrix},
\end{equation}
where $b$ and $c$ are diagonal and the zeros exist because a change in the number of Eulerian subdivisions, $N_i$, only affects the chemical species $U_i$ and $V_i$ through the diffusion coefficient. Since we would like to consider stochastic growth the submatrices $a, d, e,$ and $f$ have nonunique forms due to different possible spatial dependencies in the definition of diffusion on a Lagrangian domain [29]. However, as mentioned, in the present case we fix the definition of diffusion to be approximate midpoint to midpoint diffusion, so that the matrices $a, d, e,$ and $f$ will be tridiagonal and symmetric.

For the matrix $B$, we first note that, by definition, it is symmetric and the submatrices $a, \beta, \gamma$, and $\delta$ are of the same structure as the corresponding submatrices of $A$. The submatrix $\delta$ is diagonal since each growth “reaction” only affects a single Lagrangian box. For a specific worked example of the derivation of $A$ and $B$, see the Appendix.

Using matrices $A$ and $B$, we are able to derive the corresponding general Fokker-Planck equation for the variables $\eta_{ui}, \eta_{vi},$ and $\epsilon_i$:
\begin{equation}
\frac{\partial \Pi}{\partial t} = - \sum_{i,j} A_{ij} \frac{\partial}{\partial \eta_{ui}} [\eta_{ui}] \Pi - \sum_{i,j} B_{ij} \frac{\partial}{\partial \eta_{ui}} [\eta_{ui}] \Pi - \sum_{i,j} c_{ij} \frac{\partial}{\partial \eta_{vi}} [\eta_{vi}] \Pi - \sum_{i,j} d_{ij} \frac{\partial}{\partial \eta_{vi}} [\eta_{vi}] \Pi
\end{equation}
\begin{equation}
- \sum_{i,j} f_{ij} \frac{\partial}{\partial \eta_{vi}} [\epsilon_i] \Pi + \frac{1}{2} \sum_{i,j} a_{ij} \frac{\partial^2 \Pi}{\partial \eta_{ui} \partial \eta_{ui}} + \sum_{i,j} b_{ij} \frac{\partial^2 \Pi}{\partial \eta_{ui} \partial \eta_{vi}} + \frac{1}{2} \sum_{i,j} \gamma_{ij} \frac{\partial^2 \Pi}{\partial \eta_{vi} \partial \eta_{vi}} + \frac{1}{2} \sum_{i,j} \delta_{ij} \frac{\partial^2 \Pi}{\partial \epsilon_i \partial \epsilon_j},
\end{equation}

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From this we can immediately derive the covariances as [22]

\[
\langle \eta_{ul} \rangle = \sum_j a_{ij} \langle \eta_{uj} \rangle + \sum_j a_{mj} \langle \eta_{ul} \rangle + \sum_j b_{ij} \langle \eta_{uj} \rangle + \sum_j b_{mj} \langle \eta_{ul} \rangle + \sum_j c_{ij} \langle \eta_{ul} \rangle + \sum_j e_{ij} \langle \epsilon_j \rangle + \sum_j e_{mj} \langle \eta_{ul} \epsilon_j \rangle + a_{lm}.
\]

(24)

\[
\langle \eta_{ul} \rangle = \sum_j a_{ij} \langle \eta_{uj} \rangle + \sum_j b_{ij} \langle \eta_{uj} \rangle + \sum_j c_{ij} \langle \eta_{ul} \rangle + \sum_j d_{ij} \langle \eta_{uj} \rangle + \sum j d_{mj} \langle \eta_{ul} \rangle + \sum_j e_{ij} \langle \epsilon_j \rangle + \sum_j f_{ij} \langle \epsilon_j \rangle + \sum j f_{mj} \langle \eta_{ul} \epsilon_j \rangle + \beta_{lm}.
\]

(25)

\[
\langle \eta_{ul} \rangle = \sum_j c_{ij} \langle \eta_{uj} \rangle + \sum_j d_{ij} \langle \eta_{uj} \rangle + \sum j d_{mj} \langle \eta_{ul} \rangle + \sum j e_{ij} \langle \epsilon_j \rangle + \sum j f_{ij} \langle \epsilon_j \rangle + \sum j f_{mj} \langle \eta_{ul} \epsilon_j \rangle + \gamma_{lm}.
\]

(26)

where \(\dot{\cdots} = \partial / \partial t\) and \(\langle ab \rangle\) denotes the covariance of \(a\) and \(b\). Partial differential equations governing the covariances of \(\langle \eta_{ul} \epsilon_m \rangle\), \(\langle \epsilon_j \rangle \), and \(\langle \epsilon_j \epsilon_m \rangle\) can be found similarly.

IV. SPATIAL FOURIER TRANSFORM

We now introduce the discrete spatial Fourier transform. We choose to use the discrete Fourier cosine expansion [14, 25, 46], since, by setting \(k = m \pi / L\), \(m = 0, 1, \ldots, K - 1\), we can incorporate the boundary terms as the cosine function naturally encapsulates the Neumann boundary conditions [28]. The transform has the explicit form

\[
\hat{f}(k) = \Delta_x \sum_{j=1}^{K} \cos(k \Delta_x (j - 1)) f(x_j).
\]

(27)

Note that the factor of \((j - 1)\) in the cosine function is simply to correct for the fact that, spatially, we have defined our populations to start with an index one, instead of zero. Hence, the differential equations governing the spatial power spectrum of the system are specified by

\[
\langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle = [4a_1 \cos(kDelta_x) + 2a_0 \langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle + 2b_0 \langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle + \Delta_x^2 K/2 \langle \eta_{ul} \rangle \alpha_1].
\]

(28)

\[
\langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle = [2(a_1 + d_1) \cos(kDelta_x) + a_0 + d_0 \langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle + b_0 \langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle + c_0 \langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle + \Delta_x^2 K/2 \beta_0].
\]

(29)

\[
\langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle = [4d_1 \cos(kDelta_x) + 2d_0 \langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle + 2c_0 \langle \hat{\eta}_{ul} \hat{\eta}_{uk} \rangle + \Delta_x^2 K/2 \gamma_0].
\]

(30)

where, for \(w \in \{a, b, c, d, e, f, \alpha, \beta, \gamma, \delta\}\), \(w_0\) and \(w_1\) are the diagonal and off-diagonal elements of the submatrix \(w\), respectively. ODEs governing the Fourier transforms of the covariances for \(\langle \hat{\eta}_{ul} \epsilon_k \rangle\), \(\langle \epsilon_k \hat{\eta}_{uk} \rangle\), and \(\langle \epsilon_k \epsilon_k \rangle\) can be found similarly. Hence, we have reduced the system from \(6K \times 6K\) to six ODEs, which define the dynamics of the spatial power spectra of the stochastic variables. These equations tell us which spatial wave modes are activated and, thus, give us insights into the patterns we should expect. However, it should be noted that we have lost information concerning the cross correlations. This is not a problem, since we are only concerned with the activated wave modes predicted by the power spectra.

V. SIMULATION COMPARISON

We now face the problem of comparing theory with simulation. The derived theory is only applicable at the spatially homogeneous steady state. However, in the Turing unstable parameter region, the system will try to evolve into a patterned state, making the conclusions drawn from the theory invalid. Thus, we are in exactly the same situation as with deterministic Turing linear analysis; we can only predict to which modes a spatially uniform steady state is unstable and not which mode (or supposition of modes) will be finally displayed at steady state. Thus, the theory has two applications. First, it can be used to suggest which wave modes are being initially excited and question whether they correspond to the modes available in the deterministic system. Second, we can explore the parameter region outside the Turing unstable regime. In the deterministic regime we would obtain no patterns. However, it has been shown that, in this regime, the stochastic description of the problem may be able to support structures which have been referred to as “stochastic Turing patterns” [14, 47].

A. Stationary domain

As an initial illustration, we simulate a deterministic system and compare it to its stochastic analog. To complement this, we investigate the stochastic and deterministic wave modes to which the uniform steady state is linearly unstable, both inside and outside of the deterministic Turing patterning parameter domain.

1. Inside the Turing parameter domain

Turing systems on stationary domains normally do not exhibit pattern selection robustness because the homogeneous steady state is generally unstable to multiple wave modes, as illustrated in Fig. 3. This figure shows that, as the length of the domain, \(L\), increases, the number of possible final patterns...
FIG. 3. Linearly growing wave modes of the Schnakenberg kinetics for varying domain lengths. The two solid lines delineate the region of possible linearly growing wave modes. The dotted line denotes the maximum eigenvalue of the dispersion relation, i.e., the fastest growing Fourier mode in the continuous system. The inset magnifies the region [0,0.1]. Parameters used: $D_u = 1 \times 10^{-4}$, $D_v = 1 \times 10^{-2}$, $\kappa_1 = 10$, $\kappa_2 = 0.2$, $\kappa_{-1} = 30$, and $\kappa_3 = 1 \times 10^{-3}$. This is comparable to the standard Turing analysis [10,35,48].

2. Outside the Turing parameter domain

To illustrate the second use of our theory, we now extend our investigation to parameter regions that do not allow deterministic systems to pattern. For $L = 0.1$, the inset of Fig. 3 suggests that no deterministic Turing patterns exist, which is confirmed by deterministic simulation (not shown). Contrarily, Fig. 5(a) clearly shows that the inclusion of noise promotes patterning. However, although stochastic Turing patterns are able to exist outside of the deterministic parameter domain, they are unable to stabilize over the entire simulation time. Due to the instability of these “stochastic Turing patterns,” the structures are able to undergo polarity switching. Note that polarity switching is also possible within the normal Turing parameter region if noise levels are sufficiently high. However, it is realized more easily outside this region because of the competing effects that are occurring; the noise tends to pattern the domain, whereas the mean-field dynamics tend to homogenize the system.

In Fig. 5(c) we see that, since we are not inside the Turing unstable parameter region, the stochastically excited wave modes no longer continuously grow without bound and instead tend to a constant value of power. This compares well to the averaged power spectrum of the simulated data shown in Fig. 5(b). Here, we see the theory works far better than we would expect it to. As mentioned previously, we only expect a good comparison when the population is near its steady-state value, yet Fig. 5 clearly shows that the theory may hold even in situations where the stochastic kinetics are such that a spatial mode is being activated to move the system away from the steady state. Currently, there is a debate as to how the noise is able to act constructively over such long time scales. However, by considering Eqs. (28)–(30), we can be sure that the wave
modes are excited due to the second-order moments of our Gaussian approximation to the noise.

B. Comparing deterministic and stochastic growth

Having seen that the intrinsic noise of reactions can affect the patterning properties of a Turing system on a stationary domain, we now include growth to see how this influences mode selection.

In Fig. 6 we compare not only the deterministic evolution of Schnakenberg kinetics to their stochastic analogues but we also illustrate the difference between stochastic and deterministic descriptions of growth. Starting from an initial length of \( L = 0.4 \) the domain was allowed to grow uniformly linearly as \( n = 1 + rt/\theta \) at a rate of \( r/\theta = 1 \times 10^{-4} \). Thus after \( 10^4 \) time steps the domain doubles in size, to \( L = 0.8 \). By comparing Fig. 3 we can see that, for a domain of length \( L = 0.4 \), the system can evolve to a final pattern of wave mode two or three, whereas when the length of the domain is \( L = 0.8 \), the system can evolve to a final pattern of any integer wave mode between three and seven, inclusive. This evolution of activated modes is captured in Figs. 6(d) and 6(e) where, initially, mode two has the highest power but as time increases further wave modes are activated. As the simulation reaches \( t = 2220 \) the growth of the second mode begins to slow down and eventually reduces, whilst the third mode overtakes it as the most strongly excited mode. This transition can be linked to the breakdown of period doubling that occurs in the transition from deterministic kinetics to stochastic kinetics, as seen in Figs. 6(a)–6(c), although the realization of the transition occurs much later in the simulated system than estimated from the covariance ODEs.

From comparing Figs. 6(b), 6(c), 6(d), and 6(e) we can conclude that the inherent noise of the reactions far outweighs the noise generated from the stochastic description of growth, since qualitatively the figures are the same. However, it should be noted that the stochastic growth spectrum has a higher power. The only noticeable difference in the simulations being that, as expected, the stochastic growing domain simulation is noisier; the maximum range of the solution is larger than the deterministic growth simulation and the transition from mode two to three occurs earlier. Practically, this implies that it is sufficient to consider deterministic growth.

In both the situations of growing and static domains, whenever we are inside the Turing unstable parameter region the noise excites the same modes as the deterministic Turing analysis. Particularly, due to consecutive wave mode excitation, the primary effect of growth is seen to remove peak-splitting as the mechanism of transition and replace it with consecutive increasing of the wave mode of the solution. This correspondence of activated wave modes is proved in Sec. VI.

C. Mechanisms of robustness

In the previous section we saw that stochasticity caused a breakdown of robustness via mode doubling. Although this loss of robustness may not be surprising, it does lead us to question the sensitivity of the pattern doubling mechanism, i.e., will arbitrarily small noise lead to a breakdown of pattern doubling? Furthermore, is this new mechanism of consecutive mode excitation robust?

Theoretically, as the population scale, \( \Omega \), becomes larger, the stochastic simulations should approximate their deterministic counterparts better. The effect of increasing \( \Omega \) can be seen in Fig. 7, where, for values of \( \Omega \ll 10^4 \), the pattern doubling mechanism breaks down as the system undergoes the transition from wave mode two to three. Although \( \Omega = 10^8 \) is nowhere near the number of molecules in a mole (10^{23}), numerically we are at the limit of our computational power using single particle interactions. Thus, to consider stochastic effects within larger populations, we use a Langevin framework in which the noise is correctly scaled (Fig. 8) [49–51]. Although this is only an approximation of the system under consideration, as we have moved from a discrete case description to a continuous description, it will at least suggest if the transitions are stable against any form of noise, or whether stochasticity singularly perturbs the deterministic system. From Fig. 8 we see the first signs of robust doubling reappearing, as the transition 2 \( \rightarrow \) 4 stabilizes for \( \Omega \geq 10^6 \) and, further, the transition 2 \( \rightarrow \) 4 \( \rightarrow \) 8 is observed in Fig. 8(b). Thus, we conjecture that as the
FIG. 6. (a) Deterministic evolution of the Schnakenberg equations on a linearly growing domain. (b) Stochastic Schnakenberg kinetics on a deterministically, linearly growing domain. (c) Stochastic Schnakenberg kinetics on a stochastically, linearly growing domain. (d, e) Evolution of the corresponding theoretical power spectra, $\langle \hat{\eta}_u \hat{\eta}_u \rangle$, on deterministically and stochastically growing domains, respectively. Note that the plots have a log scale. Parameters used: $D_u = 1 \times 10^{-4}$, $D_v = 1 \times 10^{-2}$, $\kappa_1 = 10$, $\kappa_{-1} = 0.2$, $\kappa_2 = 30$, $\kappa_3 = 1 \times 10^{-5}$, $\Omega = 100$, $\vartheta = 100$, and $r/\vartheta = 10^{-4}$. The initial length of the domain is $L = 0.4$ and there are $K = 50$ compartments.

As the parameter $\Omega$ increases, the doubling transitions will become more and more common. However, for any finite value of $\Omega$ there will come a time point at which the stochastic transitions diverge from the deterministic transitions. This is because, as the system evolves to higher and higher wave modes, the bifurcation diagram increases in complexity and therefore it is more likely that the simulations will exhibit one of the other possible modes [32]. This breakdown of period doubling is also compounded by the fact that we are using linearly growing domains, as has been shown analytically that only exponentially growing domains can support period doubling in the deterministic case. Hence, for all subexponential growth rates, there will come a point at which even the deterministic system is unable to maintain a pattern doubling transition.
FIG. 7. Stochastic simulations with increasing value of $\Omega$, noted beneath each figure. Parameters are $D_u = 1 \times 10^{-4}$, $D_x = 1 \times 10^{-2}$, $\kappa_1 = 10$, $\kappa_{-1} = 0.2$, $\kappa_2 = 30$, $\kappa_3 = 1 \times 10^{-5}$, and $r/\theta = 10^{-4}$. Initially the length of the domain was $L = 0.4$ and the domains in (a) and (b) were discretized into $K = 50$ compartments, whereas the domains in (c) and (d) were discretized into $K = 100$ boxes.

Since our primary concern is with low copy number systems, we must return to the hypothesis that, although pattern doubling is not robust, it may be possible to use consecutive wave number increase as a mechanism of robustness, as suggested by Fig. 6. In Fig. 9 we show the results of repeated simulation of the stochastic system for cases with $K = 50$ Lagrangian boxes (top row) and $K = 100$ Lagrangian boxes (bottom row) to demonstrate that the domain discretization was not affecting the simulations. The simulations show that the phenomenon of sequentially increasing wave numbers is not completely robust as, although the majority of simulations do show transitions $2 \rightarrow 3 \rightarrow 4$, after this transitions $4 \rightarrow 5$ and $4 \rightarrow 6$ are both seen and, furthermore, the transition $2 \rightarrow 4$ is also possible. Also note that we have no control over the polarity of the solution. Thus, we conclude that, for systems that contain only a small number of active particles, uniformly growing domains may be able to support robust sequences of the lower wave modes. For further evidence of this claim, see Fig. 10. Here, we have simulated the evolution of 100 stochastic systems and calculated the dominant wave mode at each time point. Clearly we see that the most likely transition sequence is a consecutively increasing one, since the wave mode with the highest probability increases consecutively. However, this probability reduces with increasing number of active wave modes. For example, the probability that the system will exhibit a wave mode two pattern during the first 5000 time units is 0.98. Similarly, the probability the system will exhibit a mode three pattern during the next 5000 time units is 0.96. Interestingly, although we can see that the probability of being in a particular state decreases over time, due to more wave modes becoming available, this decrease is not monotonic. Indeed, over the regions where the probability of being in an even mode is highest, this probability is higher than the probability of the preceding odd mode. For example, the probability of being in a mode six pattern during $t \approx 25000−30000$ time units is 0.87, whereas the probability
FIG. 8. Langevin simulations with increasing value of $\Omega$, noted beneath each figure. Parameters are $D_u = 1 \times 10^{-4}$, $D_v = 1 \times 10^{-2}$, $\kappa_1 = 10$, $\kappa_{-1} = 0.2$, $\kappa_2 = 1 \times 10^{-5}$, and $r/\theta = 10^{-4}$. Initially the length of the domain was $L = 0.4$ and the domains were discretized into $K = 100$ boxes.

of being in a mode five pattern during $t \approx 20000-25000$ is 0.81. This can be explained by reasoning that it is an artefact of the mean-field causing the system to exhibit mode-doubling. Hence, although small transition sequences of consecutive increasing modes are likely, they are not certain. This was also commented upon by Arcuri and Murray [52], who studied deterministic Turing systems on growing domains. They incorporated growth through a simple scaling argument rather than a derivation from first principles, and noticed that their systems would often miss certain wave modes during their evolution. Hence, they concluded that patterns must form sequentially as any mechanism that acts over the whole domain is subject to too many sources of error to be capable of robust pattern formation at high wave modes. Although they did not include a dilution term, which we can now account for if the growth is isotropic, in the stochastic setting we are unable to generate robustness successfully on uniformly growing domains.

VI. ANALYSIS OF THE COVARIANCE ODES

Simulations seem to suggest that, inside the parameter region that realizes deterministic Turing patterns, the excited wave modes of the stochastic Schnakenberg system correspond to its deterministic analog, although the transition sequences may not. From considering a general reaction-diffusion system on a deterministic, uniformly growing domain that has been mapped onto a Lagrangian domain,

$$\frac{\partial \phi}{\partial t} = D_u \frac{\partial^2 \phi}{\partial x^2} + f(\phi, \psi, t),$$  \hspace{1cm} (31)

$$\frac{\partial \psi}{\partial t} = D_v \frac{\partial^2 \psi}{\partial x^2} + g(\phi, \psi, t),$$  \hspace{1cm} (32)

we intend to show that this is true for all Turing systems. As we are assuming slow growth, we use a quasi-steady-state hypothesis and, thus, fix $n = 1$. 

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Exponential functions with exponents analytically yielding a solution that is the linear sum of three

\[ L \]

Eq. (33) is linear and autonomous, we can solve the ODEs in Eqs. (7) and (8), we can calculate the matrices and stoichiometric matrix (see the Appendix). Then, using from the definitions in Eqs. (11) and (12), which allows us to construct the ODE system of Fourier-transformed covariances in Eqs. (28)–(30). Rewriting this as a matrix ODE equation we obtain
\[
\dot{X} = MX - V,
\]
where \( X^T = [\langle \tilde{\eta}_{uk} \tilde{\eta}_{vk} \rangle, \langle \tilde{\eta}_{uk} \tilde{\eta}_{vk} \rangle, \langle \tilde{\eta}_{uk} \tilde{\eta}_{vk} \rangle] \), the explicit form of \( M \) is

\[
M = \begin{bmatrix}
4a_1 \cos(k \Delta_L) + 2a_0 & 2b_0 & 0 \\
2a_1 \cos(k \Delta_L) + a_0 + 2d_1 \cos(k \Delta_L) + d_0 & b_0 & 0 \\
0 & 2c_0 & 4d_1 \cos(k \Delta_L) + 2d_0
\end{bmatrix},
\]

and \( V \) is defined appropriately from Eqs. (28)–(30). Since Eq. (33) is linear and autonomous, we can solve the ODEs analytically yielding a solution that is the linear sum of three exponential functions with exponents
\[
\lambda_1 = 2a_1 \cos(k \Delta_L) + a_0 + 2d_1 \cos(k \Delta_L) + d_0,
\]
\[
\lambda_{\pm} = 2a_1 \cos(k \Delta_L) + a_0 + 2d_1 \cos(k \Delta_L) + d_0 \\
\pm [4(a_1 - d_1)^2 \cos(k \Delta_L) - 1]^2 \\
+ 4(a_1 - d_1)[2a_1 + a_0 - d_0 - 2d_1] \cos(k \Delta_L) \\
+ (a_0 - d_0)^2 - 4(d_1 - a_1)^2 + 4b_0c_0]^2.
\]

The existence of such a solution also depends on these three values not being zero, which is always satisfied inside the Turing domain, as shown below.

Since we are only interested in the coefficients matrix, \( M \), of the Fourier-transformed covariances, we only need to consider the matrix \( A \). This can be split up into four \( K \times K \) submatrices,
\[
A = \begin{bmatrix}
a & b \\
c & d
\end{bmatrix},
\]
where \( a \) and \( d \) are symmetric and tridiagonal and \( b \) and \( c \) are diagonal. From their definitions Eq. (11) we can show that \( b = \partial f/\partial \psi \mid I = b_0 I \) and \( c = \partial g/\partial \phi \mid I = c_0 I \), where \( I \) is the...
FIG. 10. Exhibited wave modes of 100 simulations using the same parameters as described in the legend of Fig. 9. The domain was discretized into 100 Lagrangian compartments.

$K \times K$ identity matrix. The diagonal and off-diagonal values of $a$ are

$$a_0 = \frac{-2D_{\phi} K^2}{L^2} \quad \text{and} \quad a_1 = \frac{D_{\phi} K^2}{L^2},$$

respectively, whereas

$$d_0 = \frac{-2D_{\psi} K^2}{L^2} \quad \text{and} \quad d_1 = \frac{D_{\psi} K^2}{L^2},$$

are the diagonal and off-diagonal elements, respectively, of $d$. Each term is evaluated at the homogeneous steady state, $\phi_i = \phi^*$ and $\psi_i = \psi^*$, for all values of $i$.

Substituting these values into Eqs. (35) and (36), we obtain

$$\lambda_1 = 2 \frac{D_{\phi} K^2}{L^2} \left[ \cos(k \Delta L) - 1 \right] + 2 \frac{D_{\psi} K^2}{L^2} \left[ \cos(k \Delta L) - 1 \right] + f_{\phi} + g_{\phi}.$$  

$$\lambda_{\pm} = \lambda_1 \pm \frac{4 \left[ D_{\phi} \frac{K^2}{L^2} - D_{\psi} \frac{K^2}{L^2} \right]^2 \left[ \cos(k \Delta L) - 1 \right]^2 + 4 \left( f_{\phi} D_{\psi} - g_{\phi} D_{\psi} \right) \left[ D_{\phi} \frac{K^2}{L^2} - D_{\psi} \frac{K^2}{L^2} \right] \left[ \cos(k \Delta L) - 1 \right] + 4 \left( g_{\phi} f_{\phi} - f_{\phi} g_{\phi} \right) + \left( f_{\phi} + g_{\phi} \right)^2 \right]^{1/2}.  

$$

Since $\left[ \cos(k \Delta L) - 1 \right] \leq 0$ and inside the Turing region we know that $f_{\phi} + g_{\phi} < 0$ \cite{48}, it follows that $\lambda_1$ and Re($\lambda_-\lambda_+$) are negative. Hence, the only way to obtain an excited mode in the Turing region is if $\text{Re}(\lambda_+) > 0$. In order to satisfy this condition the following inequality for $y = \left[ \cos(k \Delta L) - 1 \right]$ must be satisfied:

$$4D_{\phi} D_{\psi} K^4 L^4 y^2 + 2K^2 L^2 (f_{\phi} D_{\psi} + D_{\phi} g_{\phi}) y + f_{\phi} g_{\phi} - g_{\phi} f_{\phi} < 0.$$  

Thus, excited modes will exist for

$$- \frac{L^2}{K^2} y_+ < y < - \frac{L^2}{K^2} y_-,$$

where

$$y_+ = \frac{f_{\phi} D_{\phi} + g_{\phi} D_{\psi} \pm \sqrt{(f_{\phi} D_{\psi} + D_{\phi} g_{\psi})^2 - 4D_{\phi} D_{\psi}(f_{\phi} g_{\psi} - f_{\psi} g_{\phi})}}{4D_{\phi} D_{\psi}}.$$
Note that inside the Turing unstable domain \( y_\pm \) are real and so the steady state is unstable whenever
\[
1 - \frac{L^2}{K^2} y_+ \cos(k\Delta_L) < 1 - \frac{L^2}{K^2} y_-.
\]
(47)
Thus, whenever the two limits of this range are within \([-1, 1]\) we can invert the cosine function to obtain:
\[
\frac{\arccos \left(1 - \frac{L^2}{K^2} y_+ \right)}{\Delta_L} < k < \frac{\arccos \left(1 - \frac{L^2}{K^2} y_- \right)}{\Delta_L}.
\]
(48)
Since \( K \) is the number of compartments then to make sure the domain discretization does not interfere with the simulations we make \( K \) large and, hence, we are able to expand the arccos operator in terms of large \( K \):
\[
\sqrt{2} y_\pm \left[1 + \frac{1}{12} y_\pm \left(\frac{L}{K}\right)^2\right] \lesssim k \lesssim \sqrt{2} y_\pm \left[1 + \frac{1}{12} y_\pm \left(\frac{L}{K}\right)^2\right].
\]
(49)
Letting \( K \to \infty \), or \( \Delta_L \to 0 \), in such a way that \( L = K \Delta_L \) remains constant, space becomes a continuum and, thus, using \( k = m\pi/L \),
\[
\frac{\sqrt{2} y_-}{\pi} L = m_- < m_+ < m_+ = \sqrt{2} y_+ L.
\]
(50)
Using Eq. (46), inequality Eq. (50) can be compared exactly with the activated modes derived from the deterministic Turing analysis [48]. Hence, we can see that inside the deterministically unstable Turing parameter region, the stochastically excited modes are exactly the same as the Turing excited modes.

However, this is only true in the limit \( K \to \infty \). In a discretized domain of \( K \) boxes there can be, at most, \( K \) active wave modes and, as the domain grows, higher wave modes also have the possibility of growing. As the activated wave modes tend to the number of boxes, the noise is able to excite higher wave modes than otherwise expected. For example, consider the dotted line in Fig. 11. This shows the stochastically excited modes when the domain is discretized into 25 boxes. As the number of modes increases, the line begins to distort until its tangent becomes infinite at wave mode 25. In terms of inequality Eq. (47), the lower root has reduced to below \(-1\), implying that the equation no longer has two, real solutions.

For a given length, \( L \), we are able to use the upper boundary of inequality Eq. (49) to define a lower bound on \( K \),
\[
m = \frac{kL}{\pi},
\]
\[
\approx \frac{L}{\pi} \sqrt{2} y_+ \left[1 + \frac{1}{12} y_+ \left(\frac{L}{K}\right)^2\right],
\]
\[
= m_+ + \frac{\sqrt{2}}{12\pi} y_+^{3/2} \left(\frac{L^3}{K^2}\right).
\]
(51)
The discretization of the space will become inadequate when it allows higher wave modes to be amplified than would be expected by the deterministic Turing analysis. From Eq. (51), we see that we need to choose \( K \) satisfying
\[
\frac{\sqrt{2}}{12\pi} \frac{L^3}{K^2} < 1, \quad \Rightarrow \frac{1}{\sqrt{\pi}} L \frac{L}{\sqrt{6\sqrt{2}K}} < K.
\]
(52)
However, although we were able to suggest which wave modes were excited, we were unable to predict which mode the final pattern would adopt. This is similar to the standard Turing analysis, which, due to the linearization process, suggests that all excited modes tend to grow exponentially and ignores higher-order terms that become important as the solution evolves. In the stochastic case, due to our use of a linear noise expansion, we also lose the higher-order effects and, thus, our analysis is only valid around the homogeneous steady state.

Although we are unable to predict exactly to which mode the system is going to evolve, if the number of excited modes is small then the power spectrum suggests which mode grows most quickly. This, in turn, suggests to which mode the system will tend. This was demonstrated in Fig. 4, where the power spectrum suggests that both modes two and three are excited, although wave mode two grows more quickly. This correlates with the fact that, out of 100 stochastic simulations, 93 yielded a stable mode two pattern, whereas only seven exhibited a stable wave mode three pattern. This correlation between highest power mode and realized stable pattern was also seen in the growing domain simulations (Fig. 6). Here, the power spectrum shows that, although wave mode two is initially the highest power mode, during growth wave mode three surpasses mode two to become the dominant mode. This can then be linked to the exact same transition in the simulated systems.

Parameters outside the deterministic Turing unstable region were then considered. Although such stochastic Turing patterns have been noted before [14], our simulations are, to our knowledge, the first numerical evidence of their actual existence. Further, we have discovered that, due to stochastic effects, polarity switching is possible (Fig. 5). Using this knowledge we focused simply on deterministic growth, which further reduced the system of Fourier covariance ODEs. Using general reaction-diffusion equations we were able to show that the stochastic Turing modes were able to grow exponentially and, further, that these excited modes exactly correspond to their analogous deterministic Turing modes. This has allowed us to suggest that the reason that the peak doubling sequences break down is that the simulations simply switch to the highest power mode, which increases consecutively.

In Sec. VC we investigated this breakdown further and questioned whether stochasticity was a singular perturbation of the deterministic system. Since the noise scales as $1/\sqrt{\Omega}$, we increased $\Omega$ to our computational limit and saw that for sufficiently large populations, $\Omega = 10^p - 10^{p+2}$, period doubling can be realized, at least for the first couple of transitions. If we now compare these particle numbers to a physical system of Turing patterns over a single cell [54], we see that a Dictyostelium cell has a volume of order $10^{-12}$ m$^3$ and, thus, it could contain on the order of $10^7$ particles. As seen in Fig. 8(a), by this point the stochastic effects in the system are incredibly small. Hence, systems of this size and larger could be justified to act as a continuum. However, there are many biological systems that depend on very low copy numbers of active proteins, e.g., the genome of the bacterium *Escherichia coli*, where there are only 10–30 molecules of the lac repressor, which is involved in the regulation of gene expression [55]. Thus, our focus on small population numbers is fully justified.

Furthermore, in this low copy number regime, even the consecutive inclusion of wave modes is not robust on uniformly growing domains when the homogeneous steady state is unstable to large numbers of wave modes. In this case, predicting the evolution of the pattern is incredibly difficult. Thus, our results support those of Arcuri and Murray [52], who concluded that patterns must form sequentially as any mechanism that acts over the whole domain is subject to too many sources of error to be capable of robust pattern formation at high wave modes. Hence, to generate robustness, in a stochastic environment, we suggest apical growth as a plausible mechanism that can robustly support consecutive wave mode increasing pattern sequences (see Fig. 12). Thus, if apical domain growth and wave number were connected in some form of feedback loop then, once the desired wave
number is reached, growth would stop, leaving a stable pattern of exactly the desired wave mode.

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APPENDIX: SCHNACKENBERG EXAMPLE

Letting $\kappa_i$ be the stochastic rate of reaction, the Schnakenberg system [56,57] consists of the chemical reactions

$$\emptyset \leftrightarrow U, \quad U \leftrightarrow \emptyset, \quad \emptyset \leftrightarrow V, \quad 2U + V \leftrightarrow 3U,$$  \hspace{1cm} (A1)

plus diffusion of the two reacting species. We consider the Schnakenberg system on a uniformly growing domain, which causes the Eulerian coordinates, $x_E$, to behave like $x_E = x_L n(t)$, where $x_L$ is the fixed Lagrangian coordinate and $n(t)$ encapsulates the definition of growth [noting $n(0) = 1$]. The mean-field equations take the form [30,43,44]

$$\frac{\partial \phi}{\partial t} + \frac{d\phi}{d t} = D_u \frac{\partial^2 \phi}{\partial x_L^2} + \frac{\kappa_1}{\Omega} - \phi \kappa_{-1} + \phi^2 \psi \kappa_3 \Omega^2,$$  \hspace{1cm} (A2)

$$\frac{\partial \psi}{\partial t} + \frac{d\psi}{d t} = D_v \frac{\partial^2 \psi}{\partial x_L^2} + \frac{\kappa_2}{\Omega} - \phi^2 \psi \kappa_3 \Omega^2,$$  \hspace{1cm} (A3)

where $\phi$ and $\psi$ are defined in equations (4) and (5). Converting to Lagrangian coordinates and dropping the $L$ yields

$$\frac{\partial \phi}{\partial t} + \frac{\dot{n}}{n} \frac{\partial \phi}{\partial n} = D_u \frac{\partial^2 \phi}{\partial x_L^2} + \frac{\kappa_1}{\Omega} - \phi \kappa_{-1} + \phi^2 \psi \kappa_3 \Omega^2,$$  \hspace{1cm} (A4)

$$\frac{\partial \psi}{\partial t} + \frac{\dot{n}}{n} \frac{\partial \psi}{\partial n} = D_v \frac{\partial^2 \psi}{\partial x_L^2} + \frac{\kappa_2}{\Omega} - \phi^2 \psi \kappa_3 \Omega^2.$$  \hspace{1cm} (A5)

Finally, by rescaling $\Phi = \phi n$ and $\Psi = \psi n$, we remove the dilution terms and, upon ignoring the subscript, $L$, again, we obtain

$$\frac{\partial \Phi}{\partial t} = D_u \frac{\partial^2 \Phi}{\partial x_L^2} + \frac{\kappa_1 n}{\Omega} - \Phi \kappa_{-1} + \Phi^2 \Psi \kappa_3 \Omega^2,$$  \hspace{1cm} (A6)

$$\frac{\partial \Psi}{\partial t} = D_v \frac{\partial^2 \Psi}{\partial x_L^2} + \frac{\kappa_2 n}{\Omega} - \Phi^2 \Psi \kappa_3 \Omega^2.$$  \hspace{1cm} (A7)

Using this as a template, we redefine the stochastic rates of reaction so as to simulate the reactions on a Lagrangian domain:

$$\emptyset \rightarrow U, \quad U \rightarrow \emptyset, \quad \emptyset \rightarrow V, \quad 2U + V \rightarrow 3U.$$  \hspace{1cm} (A8)

Thus, the mean-field equations of these reactions (plus diffusion scaled similarly) are exactly Eqs. (A6) and (A7).

Assuming deterministic growth, the stoichiometric matrix is

$$\mathbf{v} = \begin{bmatrix} R & L & 0 & 0 & I & -I & 0 & I \\ 0 & R & L & 0 & 0 & I & -I \end{bmatrix},$$  \hspace{1cm} (A9)

where $L$ and $R$ are the $K \times K$ stoichiometric matrices for diffusion left and right, respectively [see Eqs. (1) and (2)], and $I$ is the $K \times K$ identity matrix. The corresponding vector of macroscopic transition rates, $\mathbf{a}$, is

$$\mathbf{a}^T = \begin{bmatrix} d_1 \phi_1 \\ \vdots \\ d_n \phi_n \end{bmatrix}, \quad \mathbf{b} = \begin{bmatrix} -\kappa_1 + 2\phi^* \kappa_3 \Omega^2/n^2 \\ \vdots \end{bmatrix},$$

$$\mathbf{c} = \begin{bmatrix} 2\phi^* \kappa_3 \Omega^2/n^2 \\ \vdots \end{bmatrix},$$

$$\mathbf{d} = \begin{bmatrix} -\kappa_1 \phi \kappa_1 \Omega^2/n^2 \\ \vdots \end{bmatrix}, \quad \mathbf{a} = \begin{bmatrix} 4\phi_1 \phi \kappa_1 \Omega^2/n^2 \\ \vdots \end{bmatrix}, \quad \mathbf{b} = \begin{bmatrix} -\kappa_1 \phi \kappa_1 \Omega^2/n^2 \\ \vdots \end{bmatrix},$$

$$\mathbf{c} = \begin{bmatrix} -\kappa_1 \phi \kappa_1 \Omega^2/n^2 \\ \vdots \end{bmatrix},$$

These then determine the desired matrices $\mathbf{A}$ and $\mathbf{B}$, which have the forms shown in Eqs. (11) and (12). Noting that we are interested in the homogeneous state, $\phi_i = \phi^*$ and $\psi_i = \psi^*$ for all $i$, we can write down the elements of the matrices $\mathbf{A}$ and $\mathbf{B}$ as

$$a_1 = \frac{d_1}{n^2}, \quad a_2 = 2\phi^* \kappa_3 \Omega^2/n^2, \quad b_0 = 2\phi^* \kappa_3 \Omega^2/n^2, \quad c_0 = 2\phi^* \kappa_3 \Omega^2/n^2,$$

$$d_1 = \frac{d_2}{n^2}, \quad d_2 = -\frac{d_2}{n^2}, \quad b_1 = \frac{d_2}{n^2} + \frac{n \kappa_1}{\Omega} + \frac{\kappa_1 \phi \kappa_1 \Omega^2/n^2}, \quad c_1 = \frac{d_2}{n^2} + \frac{n \kappa_1}{\Omega} + \frac{\kappa_1 \phi \kappa_1 \Omega^2/n^2},$$

where, for $w \in \{a,b,c,d,e,f,a_1,a_2,b_0,c_0,d_1,d_2,b_1,c_1\}$, $w_0$ and $w_1$ are the diagonal elements and off-diagonal elements of the submatrix $w$, respectively.

In the case that growth is stochastic, the stoichiometric matrix and the macroscopic transition rate vector in Eqs. (A9) and (A10), respectively, will need to be extended in the obvious way. From these we can then calculate the final elements needed to completely define the matrices Eq. (22),

$$e_1 = -2\phi \kappa \Omega^2/n^2, \quad e_0 = \frac{4\phi \kappa \Omega^2/n^2}{\kappa_3 \Omega^2/n^2}, \quad f_1 = -2\phi \kappa \Omega^2/n^2, \quad f_0 = \frac{4\phi \kappa \Omega^2/n^2}{\kappa_3 \Omega^2/n^2},$$

$$\delta_0 = \frac{r}{\Omega},$$  \hspace{1cm} (A11)