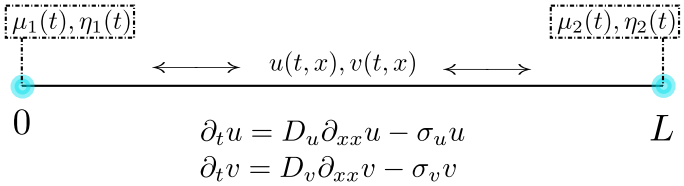
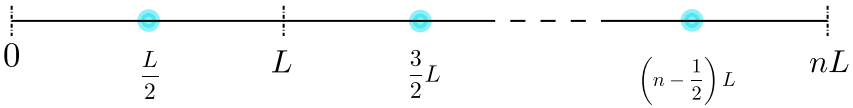
The Emergence of Spatial Patterns for Diffusion-Coupled Compartments with Activator-Inhibitor Kinetics in 1-D and 2-D

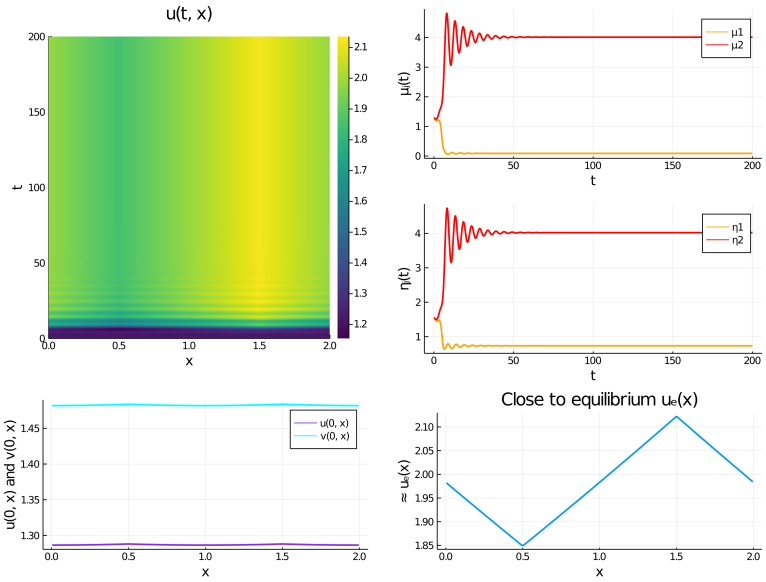
UBC Math Bio Seminar Talk

Merlin Pelz
Ph.D. candidate at the University of British Columbia
January 10, 2023

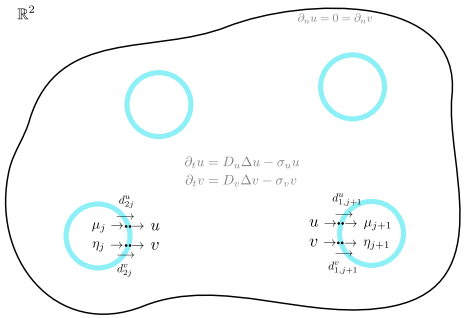
1-D

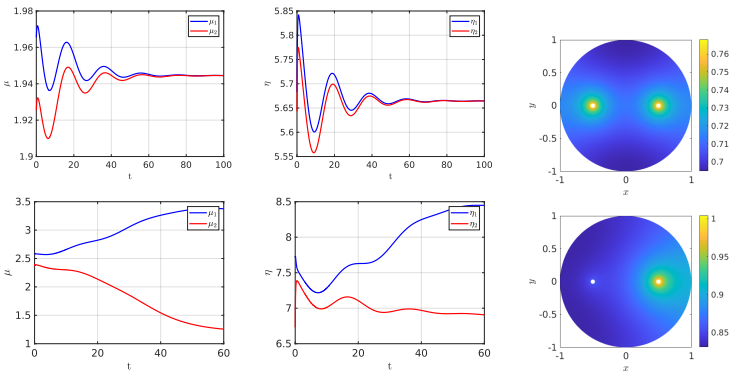


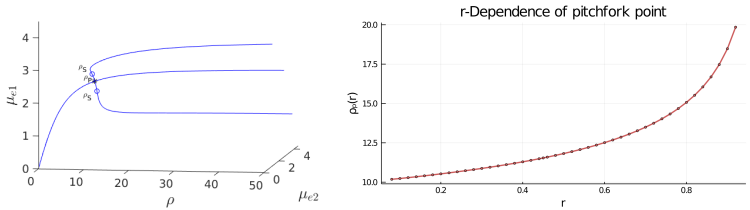




2-D







Merlin Pelz
Ph.D. candidate at the University of British Columbia

Motivation

- 1952: Alan Turing and reaction-diffusion (RD) systems [44]:

$$\begin{aligned} \partial_t u(t,x) &= D_u \Delta u + f(u,v), \qquad (t,x) \in (0,\infty) \times (0,L) \\ \partial_t v(t,x) &= D_v \Delta v + g(u,v) \end{aligned}$$

with certain boundary conditions, e.g.,

$$\partial_x u(t,0) = 0 = \partial_x v(t,0), \quad \partial_x u(t,L) = 0 = \partial_x v(t,L).$$

For $D_u = 0 = D_v$, one obtains the uniform (uncoupled) steady-state (u_e, v_e) through $f(u_e, v_e) = 0 = g(u_e, v_e)$; should be linearly stable.

With $D_u > 0, D_v > 0$, assuming separation of variables, general eigenperturbations of the linearized system about $(u_e, v_e)^T$ are

$$\begin{pmatrix} \zeta \\ \eta \end{pmatrix} e^{\lambda t} \cos(xk\pi/L), \quad k \in \mathbb{N}_0.$$

Searching for when $\mathrm{Re}(\lambda) > 0$, one concludes that

$$\frac{D_v}{D_u} \partial_u f(u_e, v_e) + \partial_v g(u_e, v_e) > 2\sqrt{\frac{D_v}{D_u} \det(J_0)} \text{ with } J_0 := \begin{pmatrix} \partial_u f(u_e, v_e) & \partial_v f(u_e, v_e) \\ \partial_u g(u_e, v_e) & \partial_v g(u_e, v_e) \end{pmatrix}$$

has to be satisfied for exponentially growing non-uniform perturbations.

- 1952: Alan Turing and reaction-diffusion (RD) systems [44]:

$$\begin{aligned} \partial_t u(t,x) &= D_u \Delta u + f(u,v), \qquad (t,x) \in (0,\infty) \times (0,L) \\ \partial_t v(t,x) &= D_v \Delta v + g(u,v) \end{aligned}$$

with certain boundary conditions, e.g.,

$$\partial_x u(t,0) = 0 = \partial_x v(t,0), \quad \partial_x u(t,L) = 0 = \partial_x v(t,L).$$

For $D_u = 0 = D_v$, one obtains the uniform (uncoupled) steady-state (u_e, v_e) through $f(u_e, v_e) = 0 = g(u_e, v_e)$; should be linearly stable.
With $D_u > 0, D_v > 0$, assuming separation of variables, general eigenperturbations of the linearized system about $(u_e, v_e)^T$ are

$$\begin{pmatrix} \zeta \\ \eta \end{pmatrix} e^{\lambda t} \cos(xk\pi/L), \quad k \in \mathbb{N}_0.$$

Searching for when $\mathrm{Re}(\lambda) > 0$, one concludes that

$$\frac{D_v}{D_u} \partial_u f(u_e, v_e) + \partial_v g(u_e, v_e) > 2\sqrt{\frac{D_v}{D_u} \det(J_0)} \text{ with } J_0 := \begin{pmatrix} \partial_u f(u_e, v_e) & \partial_v f(u_e, v_e) \\ \partial_u g(u_e, v_e) & \partial_v g(u_e, v_e) \end{pmatrix}$$

has to be satisfied for exponentially growing non-uniform perturbations.

Requirement of $D_v \gg D_u$ unless finely tuned

When $\uparrow$ *reasonable*, it has been shown (cf. [45], [46], [21], [22]) that two-component RD systems admit wide range of spatially localized patterns and instabilities that occur in "far-from-equilibrium" regime, far from where a Turing linear stability analysis will provide any insight into pattern-forming properties.

- FitzHugh-Nagumo neuronal kinetics, Brusselator and Gray-Scott model (glycolysis cycle)[45][46],
- Intracellular pattern formation via Min protein system [21][22].

However, *often unrealistic* in cell systems as signalling molecules diffuse on comparable time scales

- Nodal/Lefty morphogen system patterns germ layers during early embryogenesis [33] (activator Nodal has same local diffusivity as Lefty but $\sim$ 90% lower effective diffusivity; only this makes Turing theory applicable)
- Scientists trying to make Turing instability range bigger by adding new model features & fine tuning [7] [2]

Requirement of $D_v \gg D_u$ unless finely tuned

When ↑ reasonable, it has been shown (cf. [45], [46], [21], [22]) that two-component RD systems admit wide range of spatially localized patterns and instabilities that occur in "far-from-equilibrium" regime, far from where a Turing linear stability analysis will provide any insight into pattern-forming properties.

- FitzHugh-Nagumo neuronal kinetics, Brusselator and Gray-Scott model (glycolysis cycle)[45][46],
- Intracellular pattern formation via Min protein system [21][22].

However, *often unrealistic* in cell systems as signalling molecules diffuse on comparable time scales

- Nodal/Lefty morphogen system patterns germ layers during early embryogenesis [33] (activator Nodal has same local diffusivity as Lefty but $\sim$ 90% lower effective diffusivity; only this makes Turing theory applicable)
- Scientists trying to make Turing instability range bigger by adding new model features & fine tuning [7] [2]

Work on overcoming the diffusivity ratio condition

- *Fine-tuning* allows for not vastly different diffusivities [37]: tuned reaction kinetics lead to almost neutrally stable steady-state (has evolution created organisms fine-tuned throughout yet?),
- *Adding immobile species* to system ("2+1") allows for equal diffusivities [28] [29]: reaction kinetics everywhere? Also, can lead to discontinuities,
- Incorporation of *randomness* in RD systems makes diffusivity ranges for instability much wider [20]: no rigorous analytical theory yet and continuous in space.

Our approach

- Inspired by (active membrane)-(bulk diffusion field) articles (FN kinetics 1-D [15], GM kinetics 2-D [31])
- We diffusively couple intra-compartmental reactions, all with two species (one extrac. species: [19] [17] [18] [34] (1-D) [16] [27] [40] [14] (2-D)) and build the corresponding theory,
- We show that the *ratio of inhibitor membrane reaction rate to activator membrane reaction rate* is key bifurcation parameter ρ.

Possible scenarios:

- Collective behaviour occurring for microemulsion consisting of Belousov-Zhabotinsky (BZ) chemical reactants that are confined within small *aqueous droplets* that are dispersed in oil [43] (see also [9], [5])
- Membrane attachment mechanism, which reduces the effective diffusivity of one of the morphogens; referred to in [33] as a *binding-mediated hindrance* diffusion process.

Our approach

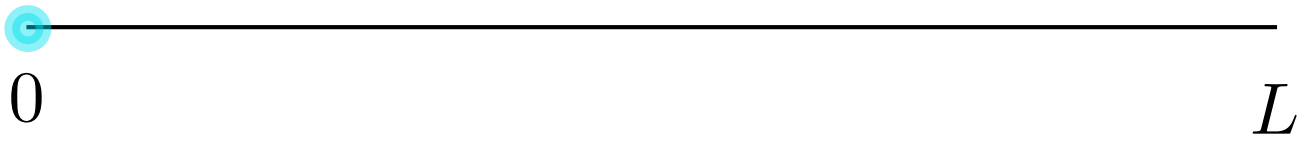
- Inspired by (active membrane)-(bulk diffusion field) articles (FN kinetics 1-D [15], GM kinetics 2-D [31])
- We diffusively couple intra-compartmental reactions, all with two species (one extrac. species: [19] [17] [18] [34] (1-D) [16] [27] [40] [14] (2-D)) and build the corresponding theory,
- We show that the *ratio of inhibitor membrane reaction rate to activator membrane reaction rate* is key bifurcation parameter ρ.

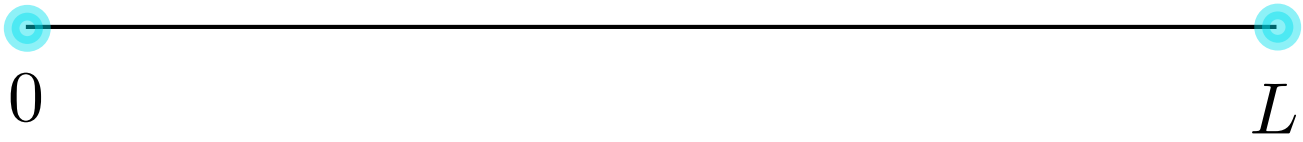
Possible scenarios:

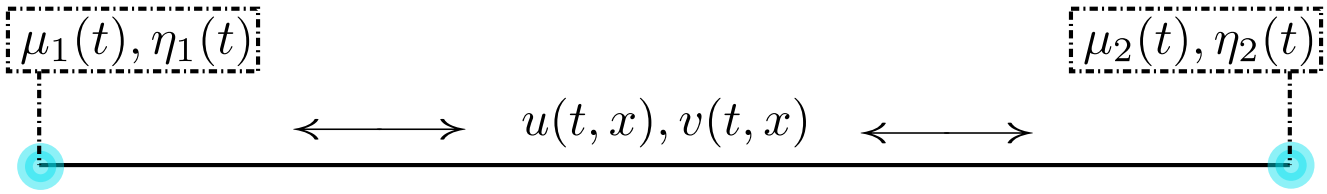
- Collective behaviour occurring for microemulsion consisting of Belousov-Zhabotinsky (BZ) chemical reactants that are confined within small *aqueous droplets* that are dispersed in oil [43] (see also [9], [5])
- Membrane attachment mechanism, which reduces the effective diffusivity of one of the morphogens; referred to in [33] as a *binding-mediated hindrance* diffusion process.

1-D setting: atomic domain


0
L


0
L


0
L



$$\partial_t u = D_u \partial_{xx} u - \sigma_u u$$
$$\partial_t v = D_v \partial_{xx} v - \sigma_v v$$

Consider intra-compartmental reaction kinetics coupled through a linear diffusion field on $(0, L)$ with two compartments on the boundary:

$$\text{bulk} \quad \begin{cases} \partial_t u(t,x) = D_u\, \partial_{xx} u - \sigma_u u, & x \in (0,L) \\ \partial_t v(t,x) = D_v\, \partial_{xx} v - \sigma_v v, & x \in (0,L) \end{cases}$$

$$\text{fluxes} \quad \begin{cases} D_u \partial_x u(t,0) = \beta_u\, (u(t,0) - \mu_1(t)) & \text{(boundary conditions)} \\ D_v \partial_x v(t,0) = \beta_v\, (v(t,0) - \eta_1(t)) \\ -D_u \partial_x u(t,L) = \beta_u\, (u(t,L) - \mu_2(t)) \\ -D_v \partial_x v(t,L) = \beta_v\, (v(t,L) - \eta_2(t)) \end{cases}$$

$$\text{intracellular} \quad \begin{cases} \dot{\mu}_1 = f(\mu_1, \eta_1) + D_u\, \partial_x u(t,0) & \text{(reaction kinetics at } x = 0) \\ \dot{\eta}_1 = g(\mu_1, \eta_1) + D_v\, \partial_x v(t,0) \\ \dot{\mu}_2 = f(\mu_2, \eta_2) - D_u\, \partial_x u(t,L) & \text{(reaction kinetics at } x = L) \\ \dot{\eta}_2 = g(\mu_2, \eta_2) - D_v\, \partial_x v(t,L) \end{cases}$$

with, e.g., identical intracellular FN kinetics ($q > 0, z > 0, \delta > 0$) [15]:

$$\begin{aligned} f(\mu, \eta) &:= \mu - q(\mu - 2)^3 + 4 - \eta, \\ g(\mu, \eta) &:= \delta\mu z - \delta\eta. \end{aligned}$$

Important properties of the compartmental-reaction diffusion system:

- Does not admit nontrivial spatially uniform state
  $\Rightarrow$ No Turing analysis possible
- Instead, when compartments are identical, we can construct spatially *non-uniform* steady-state solution that is *symmetric*. This solution is the *base-state* for our analysis.
- We are interested in bifurcations from base state leading to *asymmetric structures*
  $\Rightarrow$ More sophisticated steady-state construction and linear stability analysis needed
- Emergence of such asymmetry is important in the sciences (e.g., embryogenesis [41])

Solving for the *global region* equilibrium yields through the fluxes a nonlinear algebraic system (NAS) for all coupled cellular equilibria:

$$0 = \begin{pmatrix} g(\mu_1^e, \eta_1^e) \\ g(\mu_2^e, \eta_2^e) \end{pmatrix} - \frac{\beta_v}{\gamma_v^2 - 1} \widetilde{A} \begin{pmatrix} \eta_1^e \\ \eta_2^e \end{pmatrix}$$

$$\text{where } \widetilde{A} := \begin{pmatrix} \gamma_v \cosh(\omega_v L) - 1 & \cosh(\omega_v L) - \gamma_v \\ \cosh(\omega_v L) - \gamma_v & \gamma_v \cosh(\omega_v L) - 1 \end{pmatrix}$$

and

$$0 = \begin{pmatrix} f(\mu_1^e, \eta_1^e) \\ f(\mu_2^e, \eta_2^e) \end{pmatrix} - \frac{\beta_u}{\gamma_u^2 - 1} B \begin{pmatrix} \mu_1^e \\ \mu_2^e \end{pmatrix}$$

$$\text{where } B := \begin{pmatrix} \gamma_u \cosh(\omega_u L) - 1 & \cosh(\omega_u L) - \gamma_u \\ \cosh(\omega_u L) - \gamma_u & \gamma_u \cosh(\omega_u L) - 1 \end{pmatrix}$$

with $\gamma_\square := \cosh(\omega_\square L) + \frac{\beta_\square}{D_\square \omega_\square} \sinh(\omega_\square L)$ and freq. $\omega_\square := \sqrt{\sigma_\square / D_\square}$, leads with linear inhibitor-dependence in $g(\mu, \eta) = g_1(\mu) - g_2 \eta$ to

$$\begin{pmatrix} f(\mu_1^e, (1,0)(\frac{\beta_v}{\gamma_v^2-1}\widetilde{A} + g_2 I)^{-1}(g_1(\mu_1^e), g_1(\mu_2^e))^T) \\ f(\mu_2^e, (0,1)(\frac{\beta_v}{\gamma_v^2-1}\widetilde{A} + g_2 I)^{-1}(g_1(\mu_1^e), g_1(\mu_2^e))^T) \end{pmatrix} - \frac{\beta_u}{\gamma_u^2 - 1} B \begin{pmatrix} \mu_1^e \\ \mu_2^e \end{pmatrix} = 0\,. \quad (1)$$

Solving for the *global region* equilibrium yields through the fluxes a nonlinear algebraic system (NAS) for all coupled cellular equilibria:

$$0 = \begin{pmatrix} g(\mu_1^e, \eta_1^e) \\ g(\mu_2^e, \eta_2^e) \end{pmatrix} - \frac{\beta_v}{\gamma_v^2 - 1} \widetilde{A} \begin{pmatrix} \eta_1^e \\ \eta_2^e \end{pmatrix}$$

$$\text{where } \widetilde{A} := \begin{pmatrix} \gamma_v \cosh(\omega_v L) - 1 & \cosh(\omega_v L) - \gamma_v \\ \cosh(\omega_v L) - \gamma_v & \gamma_v \cosh(\omega_v L) - 1 \end{pmatrix}$$

and

$$0 = \begin{pmatrix} f(\mu_1^e, \eta_1^e) \\ f(\mu_2^e, \eta_2^e) \end{pmatrix} - \frac{\beta_u}{\gamma_u^2 - 1} B \begin{pmatrix} \mu_1^e \\ \mu_2^e \end{pmatrix}$$

$$\text{where } B := \begin{pmatrix} \gamma_u \cosh(\omega_u L) - 1 & \cosh(\omega_u L) - \gamma_u \\ \cosh(\omega_u L) - \gamma_u & \gamma_u \cosh(\omega_u L) - 1 \end{pmatrix}$$

with $\gamma_\square := \cosh(\omega_\square L) + \frac{\beta_\square}{D_\square \omega_\square} \sinh(\omega_\square L)$ and freq. $\omega_\square := \sqrt{\sigma_\square / D_\square}$, leads with linear inhibitor-dependence in $g(\mu, \eta) = g_1(\mu) - g_2 \eta$ to

$$\begin{pmatrix} f(\mu_1^e, (1,0)(\frac{\beta_v}{\gamma_v^2-1}\widetilde{A} + g_2 I)^{-1}(g_1(\mu_1^e), g_1(\mu_2^e))^T) \\ f(\mu_2^e, (0,1)(\frac{\beta_v}{\gamma_v^2-1}\widetilde{A} + g_2 I)^{-1}(g_1(\mu_1^e), g_1(\mu_2^e))^T) \end{pmatrix} - \frac{\beta_u}{\gamma_u^2 - 1} B \begin{pmatrix} \mu_1^e \\ \mu_2^e \end{pmatrix} = 0\,. \quad (1)$$

Now the symmetric equilibrium $(\mu_1^e, \mu_2^e)^T = \mu_e(1,1)^T$ is easily obtained through

$$f(\mu_e, \frac{g_1(\mu_e)}{a_1}) - \frac{\beta_u}{\gamma_u^2 - 1} b_1 \mu_e = 0\,,$$

and, perturbing about it by ϕ using (1) gives, to first order,

$$\begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{pmatrix} \phi - \frac{\beta_u}{\gamma_u^2 - 1} B\phi = 0\,.$$

Since the coupling matrices $\widetilde{A}$ and B are circulant, the eigenperturbations are $\phi = c(1,1)^T$ and $\phi = c(1,-1)^T$, $|c| \ll 1$, hence, we are landing on the bifurcation point (μ_e, ρ_p, z) solving

$$\begin{aligned} \partial_\mu f(\mu_e, \tfrac{g_1(\mu_e)}{a_1}) + \partial_\eta f(\mu_e, \tfrac{g_1(\mu_e)}{a_1}) \tfrac{g_1'(\mu_e)}{a_1} - \tfrac{\beta_u}{\gamma_u^2 - 1} b_1 &= 0 \qquad \text{(symmetric)} \\ \partial_\mu f(\mu_e, \tfrac{g_1(\mu_e)}{a_1}) + \partial_\eta f(\mu_e, \tfrac{g_1(\mu_e)}{a_1}) \tfrac{g_1'(\mu_e)}{a_2} - \tfrac{\beta_u}{\gamma_u^2 - 1} b_2 &= 0 \qquad \text{(asymmetric)} \end{aligned}$$

with bifurcation parameter $\rho = \beta_v/\beta_u$ and possibly, in case of FN kinetics, another one (here z).

Solution continuation from the bifurcation point with MatCont [6] gives

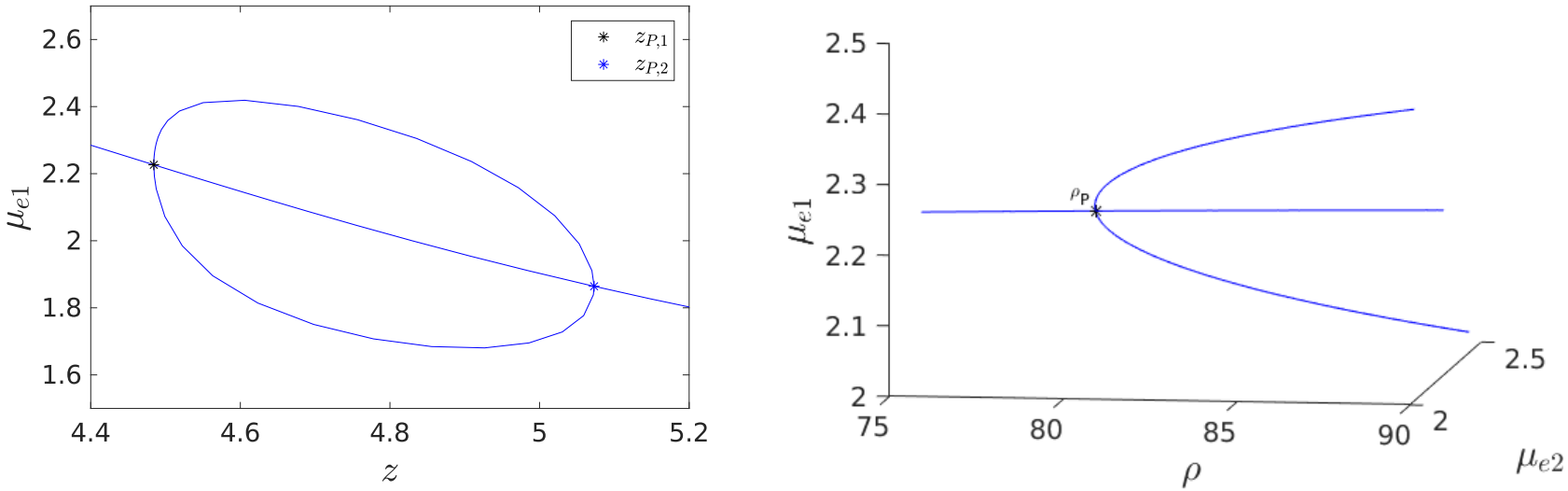
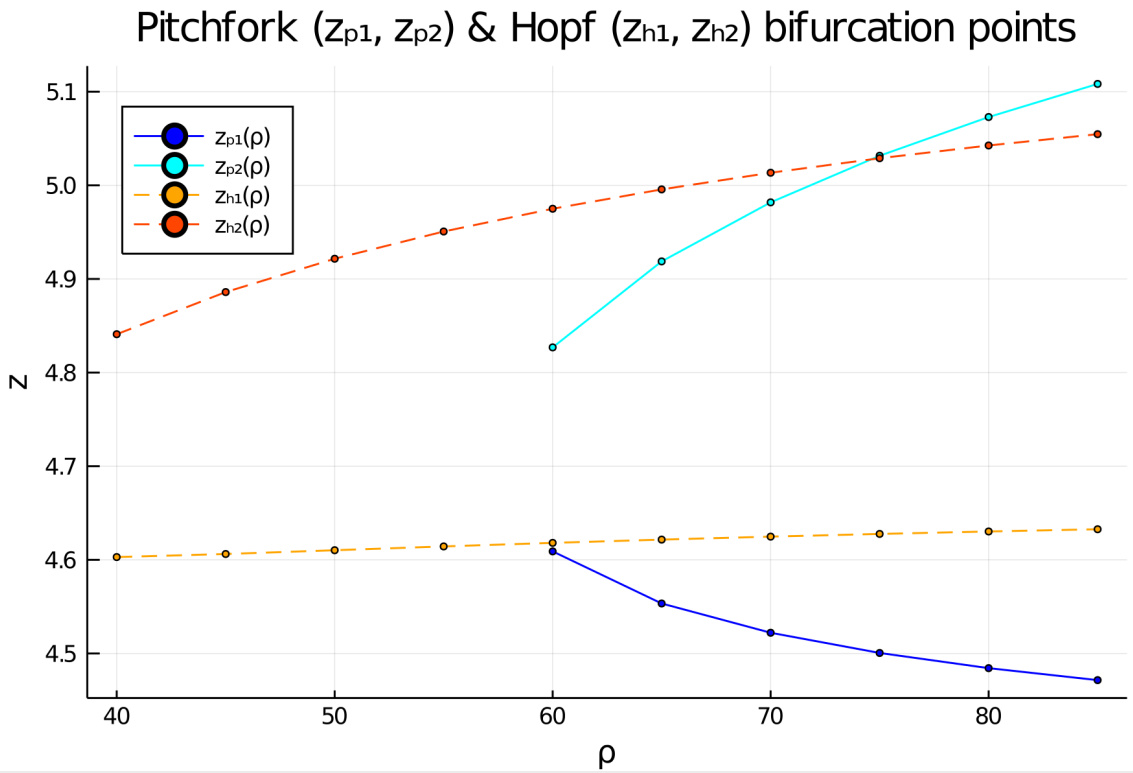


Figure: Left: μ_1^e versus z showing that asymmetric equilibria exist inside a pitchfork bubble delimited by $z_{P,1} \approx 4.48430$ and $z_{P,2} \approx 5.07294$ when $\rho = \beta_v/\beta_u = 80$. Right: For $z = z_{P,1}$, there is a symmetry-breaking bifurcation of the symmetric steady-state as ρ increases past the critical value $\rho_p \approx 80$. Parameters: $D_u = 1, D_v = 3, \sigma_u = \sigma_v = 1, \varepsilon = 0.7, q = 1, L = 1$, and $\beta_u = 0.1$.

A partially overlapping Hopf bubble also exists, found by

- introducing into PDE-ODE system the general perturbations $u(t,x) = u_e(x) + \phi(x)e^{\lambda t}, v(t,x) = v_e(x) + \psi(x)e^{\lambda t}, \mu_j(t) = \mu_e + \xi_j e^{\lambda t}, \eta = \eta_e + \zeta_j e^{\lambda t}$, where $|\phi| \ll 1, |\psi| \ll 1, |\xi_j| \ll 1$ and $|\zeta_j| \ll 1$ for $j \in \{1,2\}$,
- linearizing to obtain globally coupled matrix eigenvalue problem (GCEP) $\det(\mathcal{M}(\lambda)) = 0$ for the (complex) growth rates λ.



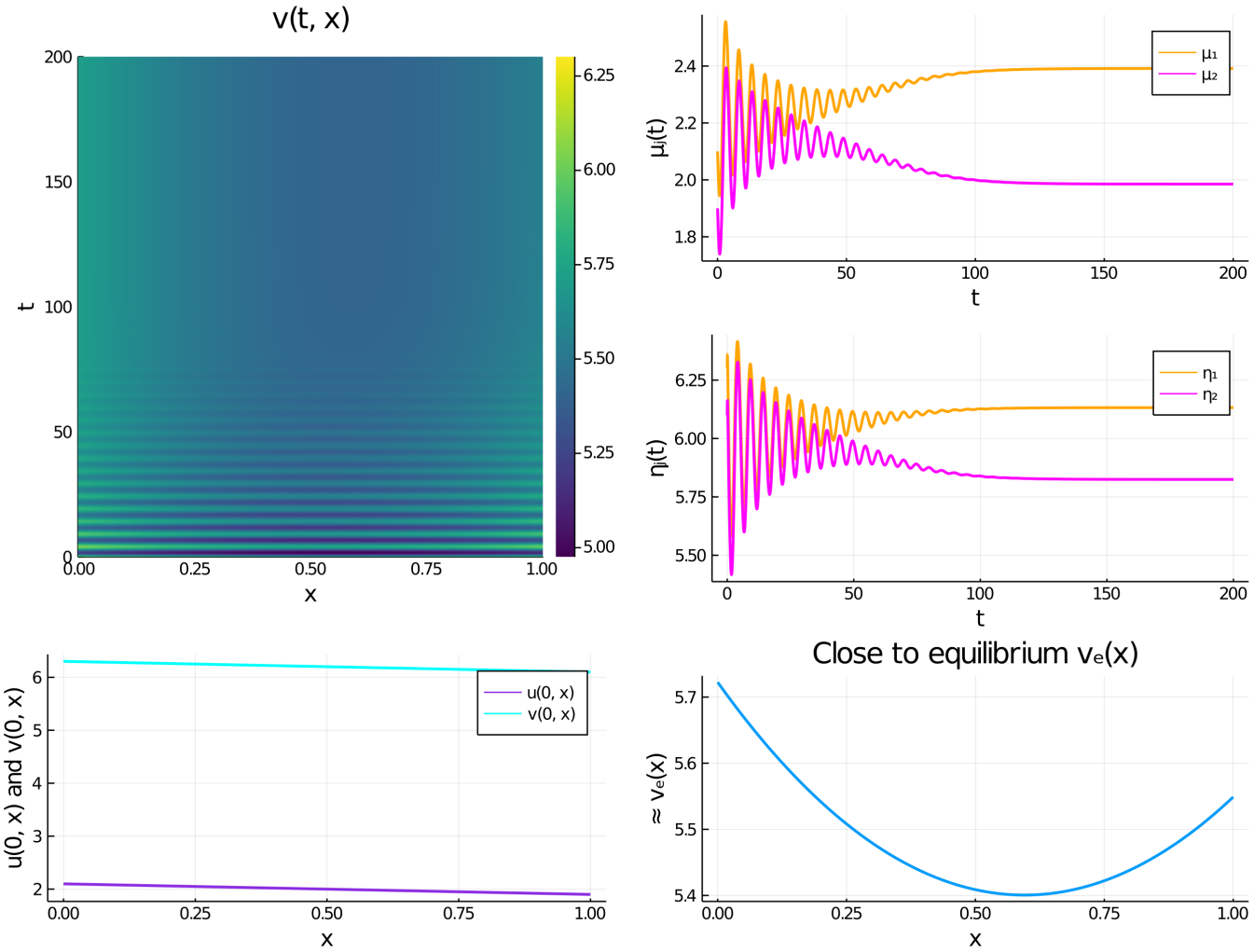
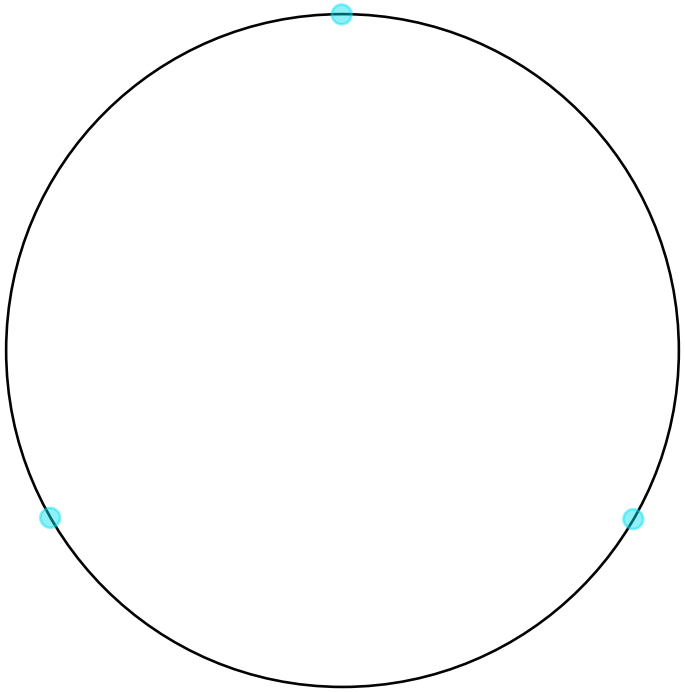


Figure: For initial condition near unstable symmetric branch, and for $z \approx 4.52211$ and $\rho = 80$, we predict that asymmetric solution branch is linearly stable since $z_{P,1} < z < z_{H,1}$. Numerically solved with our CN-RK4 IMEX method in Julia [4].

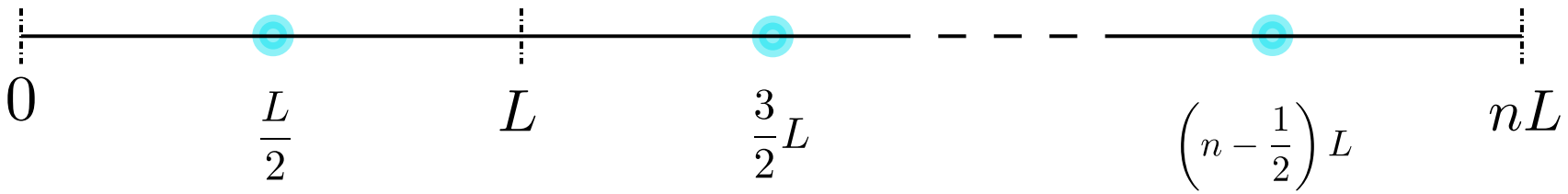
1-D setting: cells on ring



The system now reads

$$
\begin{aligned}
&\text{bulk} && \begin{cases} \partial_t u = D_u\, \partial_{xx} u - \sigma_u u\,, & t \in (0,\infty)\,,\ x \in (0, nL)\backslash \bigcup_{j=1}^{n} \{x_j\} \\ \partial_t v = D_v\, \partial_{xx} v - \sigma_v v, & t \in (0,\infty),\ x \in (0, nL)\backslash \bigcup_{j=1}^{n} \{x_j\} \end{cases} \\
&\text{bulk boundary} && \begin{cases} u(t,0) = u(t,nL)\,, & v(t,0) = v(t,nL) \\ \partial_x u(t,0) = \partial_x u(t,nL)\,, & \partial_x v(t,0) = \partial_x v(t,nL) \end{cases} \quad \text{(periodic BC)} \\
&\text{reaction fluxes} && \begin{cases} [D_u \partial_x u]|_{x=x_j} &= \beta_u\, (u(t,x_j) - \mu_j(t)) \\ [D_v \partial_x v]|_{x=x_j} &= \beta_v\, (v(t,x_j) - \eta_j(t)) \end{cases} \quad \text{(cell jump conditions)} \\
&\text{compartments} && \begin{cases} \dot{\mu}_j = f(\mu_j, \eta_j) + [D_u \partial_x u]|_{x=x_j} \\ \dot{\eta}_j = g(\mu_j, \eta_j) + [D_v \partial_x v]|_{x=x_j}\,, \end{cases} \quad \text{(reaction kinetics at } x = x_j\text{)}
\end{aligned}
$$

for $j = \{1, \ldots, n\}$. Here for any function $\mathcal{F}$ we have defined $[\mathcal{F}]|_{x=\tilde{x}} := \mathcal{F}(\tilde{x}^+) - \mathcal{F}(\tilde{x}^-)$.



NAS for all equilibria similarly obtained as above, with $g(\mu, \eta) = g_1(\mu) - g_2\eta$,

$$\begin{pmatrix} f(\mu_1^e, (1,0)A^{-1}(g_1(\mu_1^e), g_1(\mu_2^e))^T) \\ f(\mu_2^e, (0,1)A^{-1}(g_1(\mu_1^e), g_1(\mu_2^e))^T) \end{pmatrix} - \frac{\beta_u}{\gamma_u^2 - 4} B \begin{pmatrix} \mu_1^e \\ \mu_2^e \end{pmatrix} = 0\,,$$

where the coupling matrices A and B are now

$$A := \frac{\beta_v}{\gamma_v^2 - 4}\widetilde{A} + g_2 I\,, \qquad \widetilde{A} := \begin{pmatrix} 2\gamma_v \cosh(\omega_v L) - 4 & 4\cosh(\omega_v L) - 2\gamma_v \\ 4\cosh(\omega_v L) - 2\gamma_v & 2\gamma_v \cosh(\omega_v L) - 4 \end{pmatrix},$$

$$B := \begin{pmatrix} 2\gamma_u \cosh(\omega_u L) - 4 & 4\cosh(\omega_u L) - 2\gamma_u \\ 4\cosh(\omega_u L) - 2\gamma_u & 2\gamma_u \cosh(\omega_u L) - 4 \end{pmatrix}.$$

Perturbing about the symmetric equilibrium with $u(t,x) = u_e(x) + \phi(x)e^{\lambda t}$, $v(t,x) = v_e(x) + \psi(x)e^{\lambda t}$, $\mu_j(t) = \mu_e + \xi_j e^{\lambda t}$, $\eta = \eta_e + \zeta_j e^{\lambda t}$, where $|\phi| \ll 1$, $|\psi| \ll 1$, $|\xi_j| \ll 1$ and $|\zeta_j| \ll 1$ for $j \in \{1,2\}$, we solve on *fundamental domain* $[0,L]$ with $0 \sim L$ and a Floquet-type boundary condition:

$$\text{bulk} \quad \begin{cases} \partial_{xx}\phi - \Omega_u^2\phi = 0\,, & x \in (0,L)\backslash\{\frac{L}{2}\} \\ \partial_{xx}\psi - \Omega_v^2\psi = 0\,, & x \in (0,L)\backslash\{\frac{L}{2}\} \end{cases}$$

$$\text{bulk boundary} \quad \begin{cases} \phi(0) = Z\phi(L), & \psi(0) = Z\psi(L) \\ \partial_x\phi(0) = Z\partial_x\phi(L)\,, & \partial_x\psi(0) = Z\partial_x\psi(L) \end{cases} \qquad \text{(Floquet BC)}$$

$$\text{reaction fluxes} \quad \begin{cases} [D_u\partial_x\phi]|_{x=\frac{L}{2}} = \beta_u\,(\phi(\frac{L}{2}) - \xi) \\ [D_v\partial_x\psi]|_{x=\frac{L}{2}} = \beta_v\,(\psi(\frac{L}{2}) - \zeta) \end{cases} \qquad \text{(cell jump conditions)}$$

$$\text{intracellular} \quad \begin{cases} \lambda\xi = \partial_\mu f_e\xi + \partial_\eta f_e\zeta + [D_u\partial_x\phi]|_{x=\frac{L}{2}} \\ \lambda\zeta = \partial_\mu g_e\xi + \partial_\eta g_e\zeta + [D_v\partial_x\psi]|_{x=\frac{L}{2}}\,. \end{cases} \qquad \text{(reaction kinetics at } x = \tfrac{L}{2}\text{)}$$

Hence, using translational invariance,

$$Z^n = 1 \quad \Leftrightarrow \quad Z_k = e^{2\pi ik/n}\,, \quad \text{for } k \in \{0,\ldots,n-1\}\,.$$

With $\Omega_u = \sqrt{(\lambda + \sigma_u)/D_u}$, $\Omega_v = \sqrt{(\lambda + \sigma_v)/D_v}$ and $G_{\Omega_u,Z}(L/2)$, $G_{\Omega_v,Z}(L/2)$ of quasi-periodic Green function,

- GCEP $\det(M_{Z_k}(\lambda)) = 0$ for each perturbation mode Z_k (compare with eigenperturbations)
- Special case $\lambda = 0$

Now for generic intracellular reaction (Rauch-Millonas) kinetics to universal signal transduction system proposed in [39]

$$\begin{aligned} \dot{\mu} &= f(\mu,\eta) := c_u - q_u\mu + \frac{\alpha_1^u \mu}{\gamma_1^u + \mu} - \frac{\alpha_2^u \mu \eta}{\gamma_2^u + \mu} \\ \dot{\eta} &= g(\mu,\eta) := c_v + w_v\mu - q_v\eta\,, \end{aligned}$$

we identify $g_1(\mu) = c_v + w_v\mu$ and $g_2 = q_v$.

With $\Omega_u = \sqrt{(\lambda + \sigma_u)/D_u}$, $\Omega_v = \sqrt{(\lambda + \sigma_v)/D_v}$ and $G_{\Omega_u,Z}(L/2)$, $G_{\Omega_v,Z}(L/2)$ of quasi-periodic Green function,

- GCEP $\det(M_{Z_k}(\lambda)) = 0$ for each perturbation mode Z_k (compare with eigenperturbations)
- Special case $\lambda = 0$

Now for generic intracellular reaction (Rauch-Millonas) kinetics to universal signal transduction system proposed in [39]

$$\begin{aligned} \dot{\mu} &= f(\mu,\eta) := c_u - q_u\mu + \frac{\alpha_1^u\mu}{\gamma_1^u+\mu} - \frac{\alpha_2^u\mu\eta}{\gamma_2^u+\mu} \\ \dot{\eta} &= g(\mu,\eta) := c_v + w_v\mu - q_v\eta\,, \end{aligned}$$

we identify $g_1(\mu) = c_v + w_v\mu$ and $g_2 = q_v$.

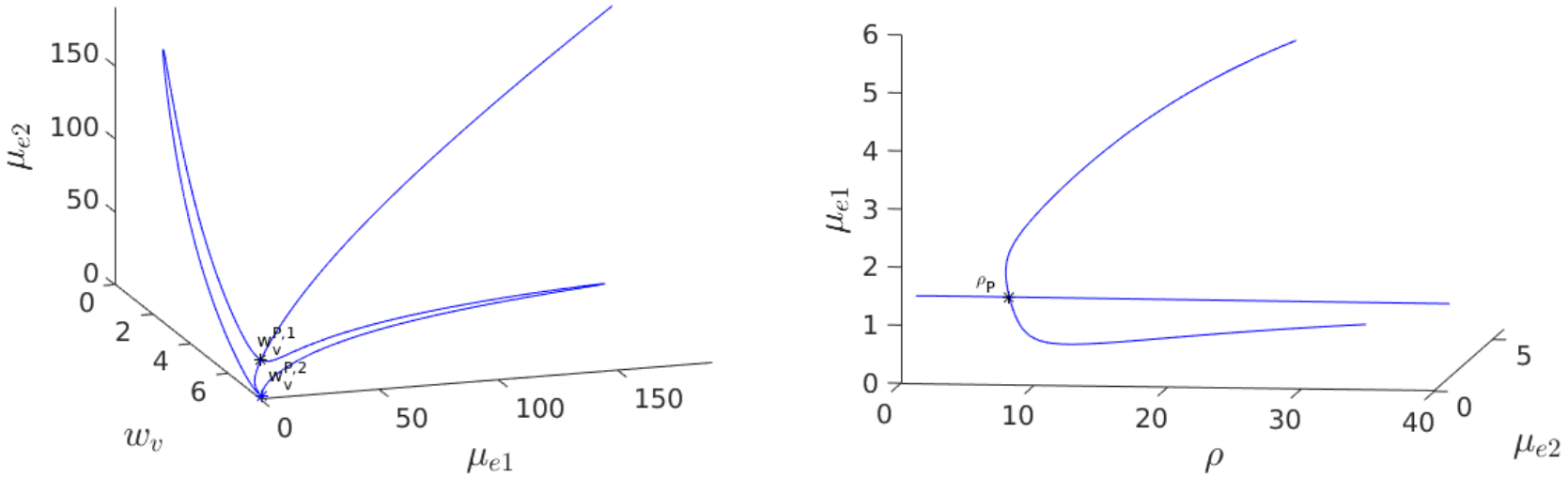


Figure: Bifurcation diagrams for Rauch-Millonas kinetics (24) with $n = 2$ computed from (22) using MatCont [6]. Left: Plot of μ_1^e showing that asymmetric steady-states occur inside a degenerate pitchfork bubble bounded by $w_v^{P,1} \approx 6.34518$ and $w_v^{P,2} \approx 7.64062$ when $\rho = \beta_v/\beta_u = 7$. Right: Supercritical pitchfork bifurcation in ρ from the symmetric branch occurs when $w_v = w_v^{P,2}$. Stable asymmetric branches occur past this threshold in ρ. Parameters: $D_u = D_v = 1, \sigma_u = \sigma_v = 0.01, c_u = c_v = 1, q_u = 1/100, q_v = 7, \alpha_1^u = 600, \alpha_2^u = 6, \gamma_1^u = 100, \gamma_2^u = 1/10$, and $\beta_u = 0.3$.

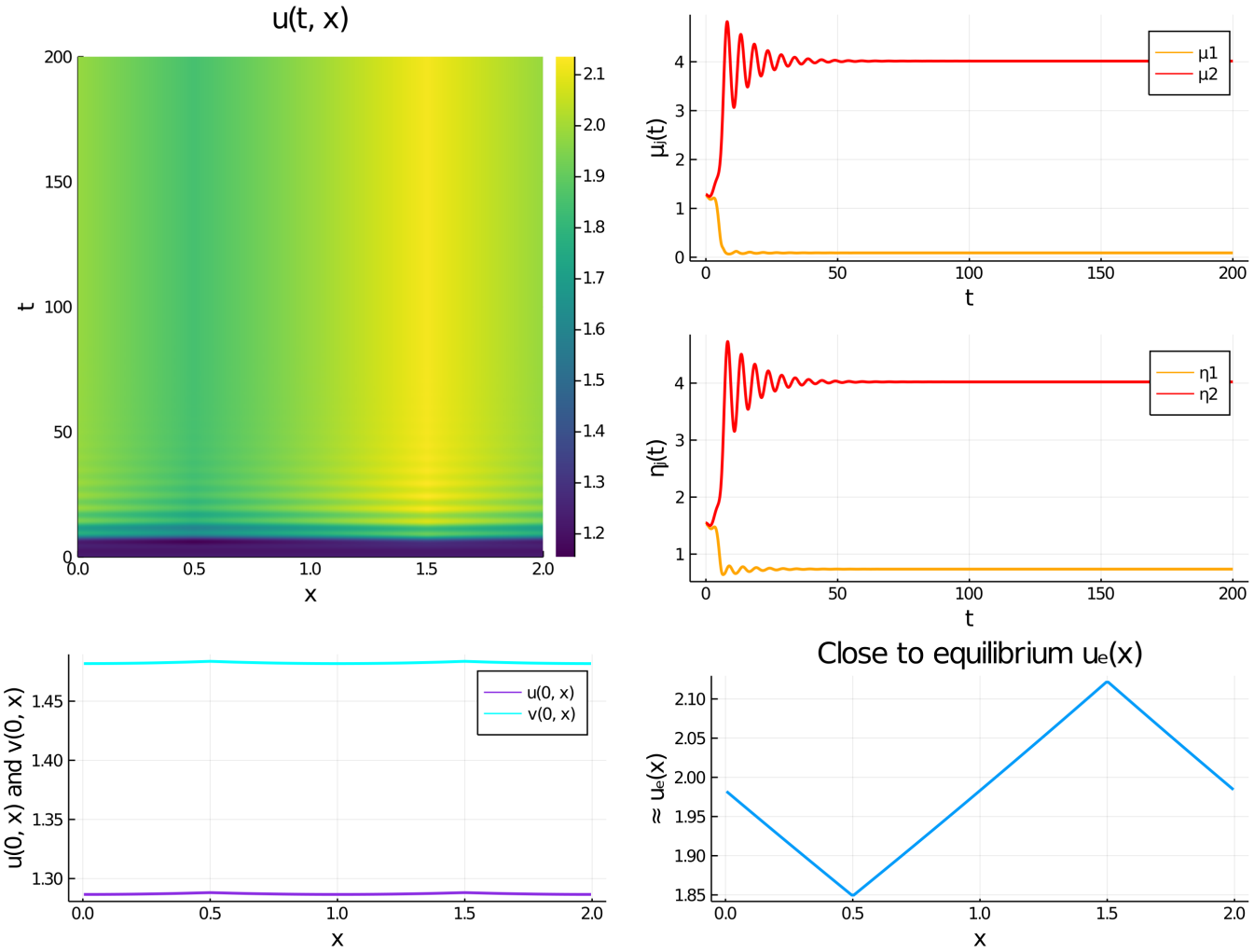
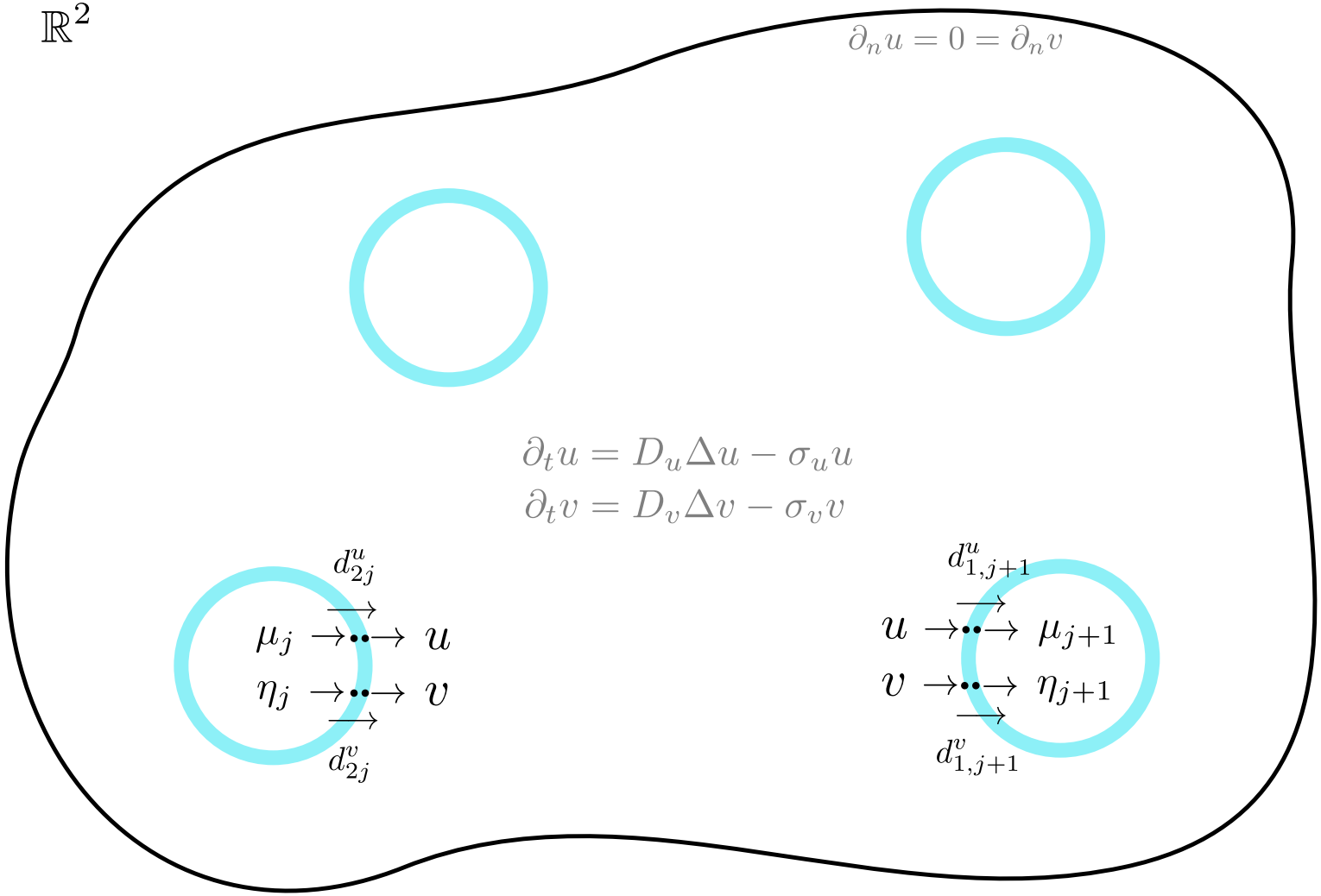


Figure: Rauch-Millonas kinetics with $n = 2$. For an initial condition near the unstable symmetric branch, and for $\rho = 15$ and $w_V = w_V^{P,2}$, the full time-dependent solution computed using the BE-RK4-IMEX scheme of [38] converges to a stable asymmetric steady-state.

2-D setting

Instead of an infinite 1-D consideration, it may be a step towards reality to consider a finite domain in 2-D.



Instead of an infinite 1-D consideration, it may be a step towards reality to consider a finite domain in 2-D.

$$\text{bulk} \quad \begin{cases} \partial_t u = D_u \Delta u - \sigma_u u\,, & \mathbf{x} \in \Omega \setminus \bigcup_{j=1}^m \Omega_j\,, \\ \partial_t v = D_v \Delta v - \sigma_v v\,, & \mathbf{x} \in \Omega \setminus \bigcup_{j=1}^m \Omega_j\,, \\ \partial_{\tilde{n}} u = \partial_{\tilde{n}} v = 0\,, & \mathbf{x} \in \partial\Omega\,, \end{cases}$$

$$\text{reaction fluxes} \quad \begin{cases} \varepsilon D_u \partial_{n_j} u = d_1^u u - d_2^u \mu_j\,, & \mathbf{x} \in \partial\Omega_j\,, \\ \varepsilon D_v \partial_{n_j} v = d_1^v v - d_2^v \eta_j\,, & \mathbf{x} \in \partial\Omega_j\,, \end{cases}$$

$$\text{compartments} \quad \begin{cases} \frac{d\mu_j}{dt} = f(\mu_j, \eta_j) + \frac{1}{\varepsilon} \int_{\partial\Omega_j} (d_1^u u - d_2^u \mu_j)\, dS\,, \\ \frac{d\eta_j}{dt} = g(\mu_j, \eta_j) + \frac{1}{\varepsilon} \int_{\partial\Omega_j} (d_1^v v - d_2^v \eta_j)\, dS\,, \end{cases}$$

for $j \in \{1, \ldots, m\}$, with outward normal vectors n_j to Ω_j.

In the j^{th} *local region*, within $\mathcal{O}(\varepsilon)$ of boundary of j^{th} cell,

- local coordinates $\mathbf{y}_j = \varepsilon^{-1}(\mathbf{x} - \mathbf{x}_j)$, $p_j := |\mathbf{y}_j|$
- local variables $U_j(\mathbf{x}) = U_j(\varepsilon \mathbf{y}_j + \mathbf{x}_j)$, and $V_j(\mathbf{x}) = V_j(\varepsilon \mathbf{y}_j + \mathbf{x}_j)$
-

$$\begin{array}{rclcrcll} \Delta U_j & = & 0 & & \Delta V_j & = & 0 & \text{for } p_j \geq 1 \\ D_u\, \partial_{p_j} U_j & = & d_1^u U_j - d_2^u \mu_j & \text{and} & D_v\, \partial_{p_j} V_j & = & d_1^v V_j - d_2^v \eta_j & \text{on } p_j = 1 \end{array}$$

- radially symmetric solutions to these problems are

$$U_j(p_j) = A_j^u \ln p_j + \frac{1}{d_1^u}\left(D_u A_j^u + d_2^u \mu_j\right), \qquad V_j(p_j) = A_j^v \ln p_j + \frac{1}{d_1^v}\left(D_v A_j^v + d_2^v \eta_j\right),$$

  for $j \in \{1, \ldots, m\}$, where A_j^u and A_j^v for $j \in \{1, \ldots, m\}$ are constants to be determined

- substituting into the steady-state problem

$$f(\mu_j, \eta_j) + 2\pi D_u A_j^u = 0, \qquad g(\mu_j, \eta_j) + 2\pi D_v A_j^v = 0, \qquad j \in \{1, \ldots, m\}.$$

In the *global region*

$$\Delta U - \omega_u^2 U = 0\,, \quad \mathbf{x} \in \Omega \setminus \{\mathbf{x}_1, \ldots, \mathbf{x}_m\}\,; \qquad \partial_n U = 0\,, \quad \mathbf{x} \in \partial\Omega\,;$$
$$U \sim A_j^u \log|\mathbf{x} - \mathbf{x}_j| + \frac{A_j^u}{\nu} + \frac{1}{d_1^u}(D_u A_j^u + d_2^u \mu_j)\,, \quad \text{as} \quad \mathbf{x} \to \mathbf{x}_j\,,\ j \in \{1, \ldots, m\}\,,$$

where $\nu := -1/\log\varepsilon \ll 1$ and $\omega_u := \sqrt{\sigma_u/D_u}$. Similarly, for V.

- With the reduced-wave Green function G_ω solving

$$\Delta G_\omega - \omega^2 G_\omega = -\delta(\mathbf{x} - \mathbf{x}_j)\,, \quad \mathbf{x} \in \Omega\,; \qquad \partial_n G_\omega = 0\,, \quad \mathbf{x} \in \partial\Omega\,;$$
$$G_\omega \sim -\frac{1}{2\pi}\log|\mathbf{x} - \mathbf{x}_j| + R_\omega(\mathbf{x}_j) + o(1)\,, \quad \text{as} \quad \mathbf{x} \to \mathbf{x}_j\,.$$

we get

$$U(\mathbf{x}) = -2\pi \sum_{i=1}^{m} A_i^u G_{\omega_u}(\mathbf{x}; \mathbf{x}_i)\,, \qquad V(\mathbf{x}) = -2\pi \sum_{i=1}^{m} A_i^v G_{\omega_v}(\mathbf{x}; \mathbf{x}_i)\,.$$

The singularity behaviours of U, V, G_{ω_u} and G_{ω_v} directly yield linear algebraic systems for $\mathcal{A}^u := (A_1^u, \ldots, A_m^u)^T$ and $\mathcal{A}^v := (A_1^v, \ldots, A_m^v)^T$, given in matrix form by

$$\left(\left(1 + \frac{\nu D_u}{d_1^u}\right) I + 2\pi\nu\mathcal{G}_{\omega_u}\right)\mathcal{A}^u = -\frac{\nu d_2^u}{d_1^u}\,\mu\,, \qquad \left(\left(1 + \frac{\nu D_v}{d_1^v}\right) I + 2\pi\nu\mathcal{G}_{\omega_v}\right)\mathcal{A}^v = -\frac{\nu d_2^v}{d_1^v}\,\eta\,.$$

Substituting into the intracellular equilibrium equations, we obtain a $2m$-dimensional nonlinear algebraic system for μ_j and η_j, for $j \in \{1, \ldots, m\}$, given by

$$f(\mu_j, \eta_j) - \mathbf{e}_j^T \Theta_u \mu = 0\,, \qquad g(\mu_j, \eta_j) - \mathbf{e}_j^T \Theta_v \eta = 0\,, \quad \text{for} \quad j \in \{1, \ldots, m\}\,,$$

with coupling matrices

$$\Theta_u := 2\pi\nu D_u \frac{d_2^u}{d_1^u}\left[\left(1 + \frac{\nu D_u}{d_1^u}\right) I + 2\pi\nu\mathcal{G}_{\omega_u}\right]^{-1}\,, \quad \Theta_v := 2\pi\nu D_v \frac{d_2^v}{d_1^v}\left[\left(1 + \frac{\nu D_v}{d_1^v}\right) I + 2\pi\nu\mathcal{G}_{\omega_v}\right]^{-1}$$

Again, for linear inhibitor dependence in $g(\mu, \eta) = g_1(\mu) - g_2\eta$, we simply obtain

$$f\left(\mu_j, \mathbf{e}_j^T (g_2 I + \Theta_v)^{-1} \mathbf{g}_1\right) - \mathbf{e}_j^T \Theta_u \mu = 0\,, \qquad j \in \{1, \ldots, m\}\,.$$

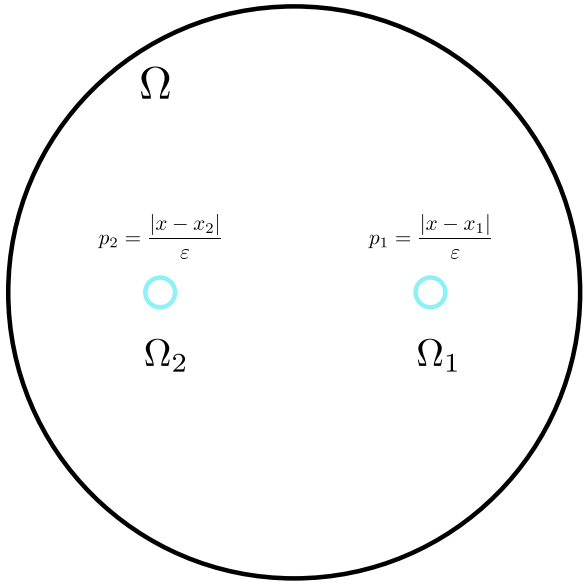
- We now focus on cell arrangement for which $\mathbf{e} := (1, \ldots, 1)^T$ is an eigenvector of $\mathcal{G}_\omega \; \forall\, \omega > 0$ and the eigenspace of $\mathcal{G}_\omega$ orthogonal to $\mathbf{e}$ is independent of ω.
- Then, with eigenvalues α_u of Θ_u and α_v of Θ_v to $\mathbf{e}$, the symmetric equilibrium is recovered from

$$f\left(\mu_c, \frac{g_1(\mu_c)}{g_2 + \alpha_v}\right) - \alpha_u \mu_c = 0\,.$$

- Perturbing about it with perturbations $\tilde{\mu}$ and $\tilde{\eta}$ setting $\lambda = 0$,

$$\begin{pmatrix} f_\mu^c I - \Theta_u & f_\eta^c I \\ g_\mu^c I & g_\eta^c I - \Theta_v \end{pmatrix} \begin{pmatrix} \tilde{\mu} \\ \tilde{\eta} \end{pmatrix} = \begin{pmatrix} \mathbf{0} \\ \mathbf{0} \end{pmatrix}\,,$$

letting us recover the bifurcation points



$m = 2$
$d_v = \rho\, d_u$
$\rho > 1, d_u > 0$
$D_u = D_v$

Figure: A schematic plot of a ring arrangement in the unit disk with two cells. The bifurcation parameter for symmetry-breaking is ρ, while the diffusivities satisfy $D_u = D_v$.

Consider this time intracellular tissue kinetics of the Gierer-Meinhardt model

$$\dot{\mu}(t) = f(\mu, \eta) := \frac{\mu^2}{\eta}\,, \qquad \dot{\eta}(t) = g(\mu, \eta) := \mu^2\,.$$

The uncoupled equilibrium given by $\mu_e = 0$, and where η_e is an arbitrary constant, is non-hyberbolic in all directions.

- Decreasing cell separation decreases symmetry-breaking threshold ρ_p
- There exists hysteresis for lower d_u with bigger extent as D_v/D_u decreases

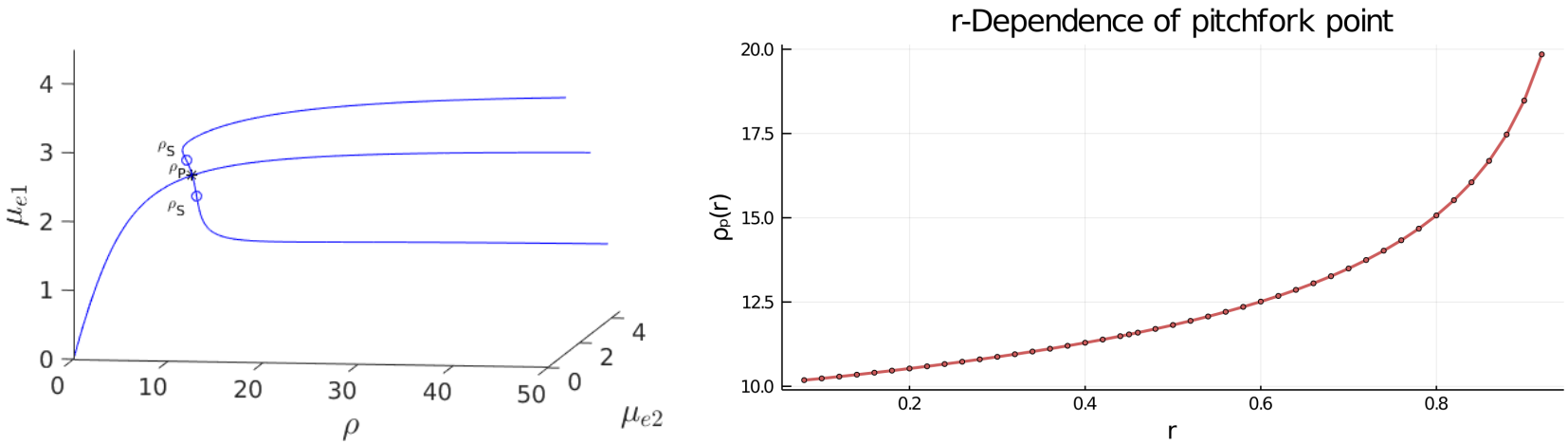


Figure: Left: 3-D Bifurcation diagram for $d_u = 0.08$ directly after hysteresis has emerged when decreasing from $d_u = 0.09$. Here the cell ring radius is $r = 0.5$. Right: The pitchfork bifurcation value of ρ increases rapidly as the ring radius r, and consequently the distance between the cells, increases. Here $d_u = 0.09$ (supercritical ρ_p case). Remaining parameters: $D_u = D_v = 5, \sigma_u = \sigma_v = 0.6$, and $\varepsilon = 0.03$.

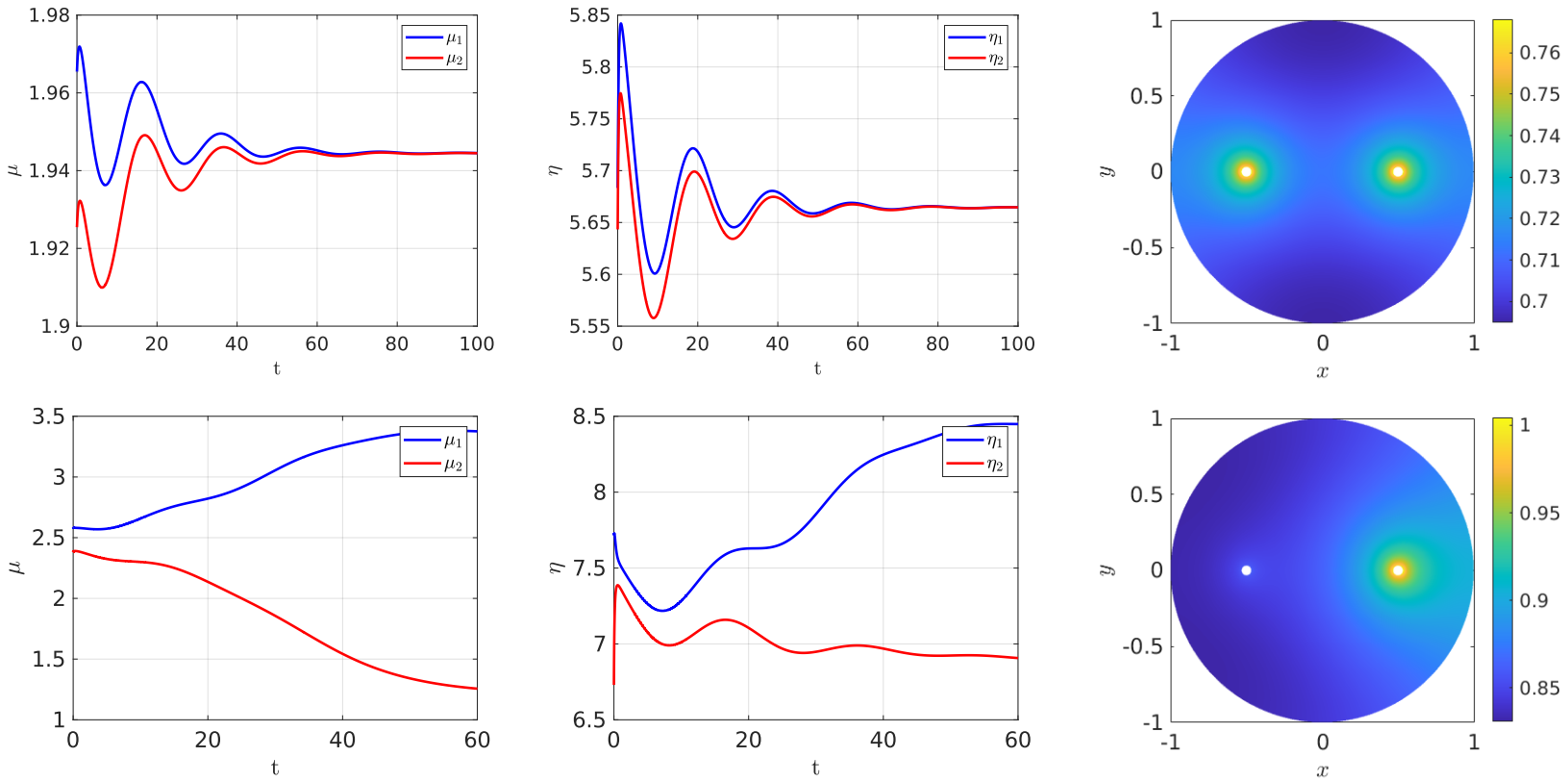


Figure: PDE simulation results with FlexPDE [11] for GM kinetics. Left: convergence to symmetric branch for $\rho = 5$ before supercritical pitchfork point $\rho_p \approx 9.79168$, for an initial condition close to the symmetric branch. Right: convergence to the asymmetric branch selected by eigenperturbation direction $\mathbf{q}_2 = (1, -1)^T$ for $\rho = 15$ and starting near symmetric branch. Parameters: $D_u = D_v = 5, \sigma_u = \sigma_v = 0.6, d_u = 0.09, \varepsilon = 0.03$ and $r = 0.5$.

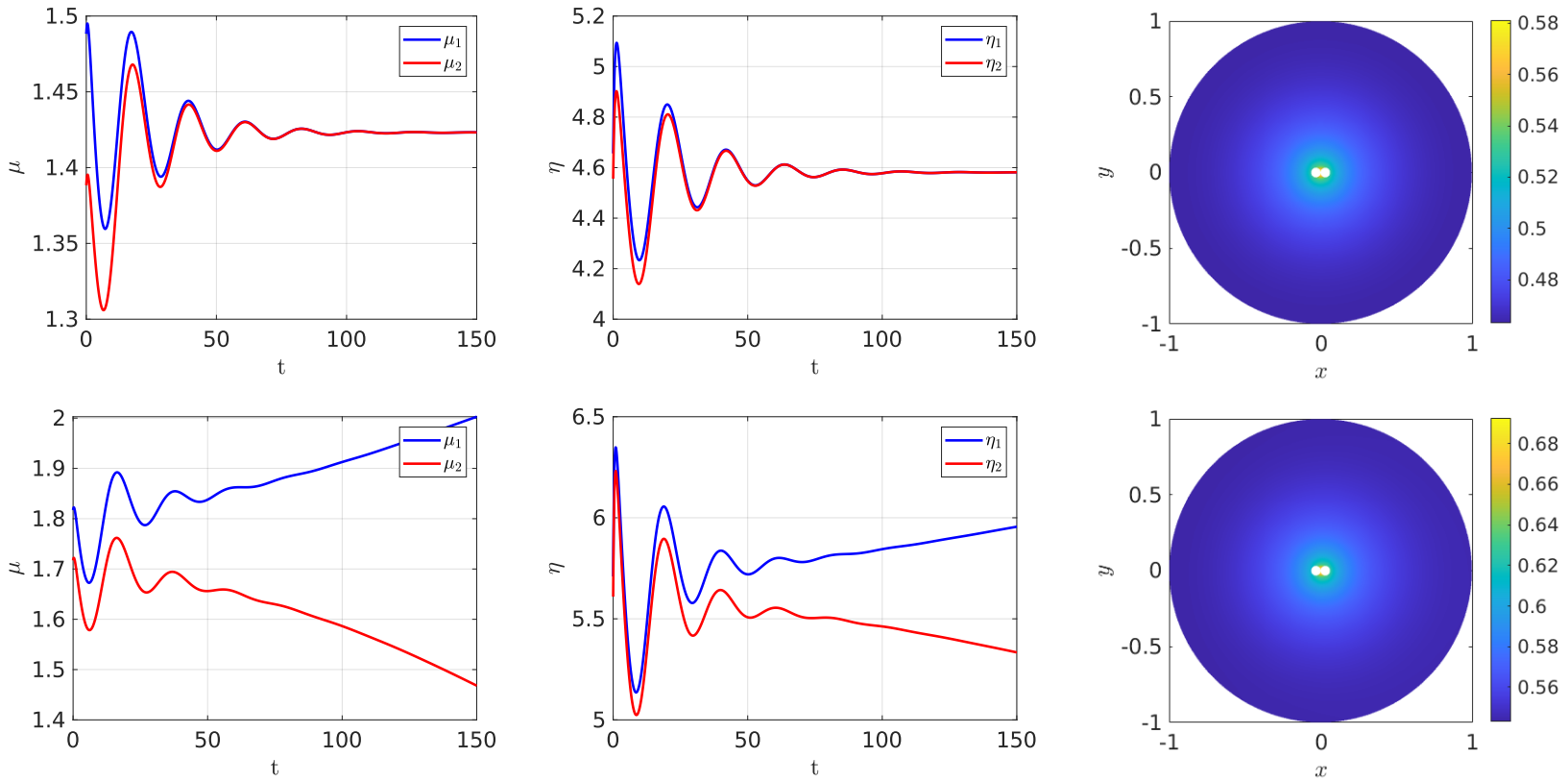


Figure: Simulation results with FlexPDE [11] for GM kinetics (34) with two closely spaced cells centered on a ring of radius $r = 0.031$ and with minimum cell separation of 0.002. Left: convergence to a stable symmetric steady-state solution when $\rho = 3$. Right: convergence to a stable asymmetric steady-state solution for $\rho = 8$ when starting with a symmetric initial condition. Parameters: $D_u = 5$, $D_v = 1.5$, $\sigma_u = \sigma_v = 0.6$, $d_u = 0.08$ and $\varepsilon = 0.03$.

Discussion & Next steps

- We derived NAS for all equilibria, equations determining pitchfork bifurcation points and GCEP for general perturbation growth rates λ for finite & periodic 1-D domain and finite no-flux bc 2-D domain
- Space of symmetry-destabilizing perturbations spanned by the ones with $\mathrm{Re}(\lambda) > 0$ anywhere on symmetric equilibrium branch
- Needed for NAS was $g(\mu, \eta) = g_1(\mu) - g_2\eta$ (Lengyel-Epstein?)
- Collective behaviour that occurs for a microemulsion consisting of Belousov-Zhabotinsky chemical reactants confined within small aqueous droplets dispersed in oil [43] ([9] [5])

- We derived NAS for all equilibria, equations determining pitchfork bifurcation points and GCEP for general perturbation growth rates λ for finite & periodic 1-D domain and finite no-flux bc 2-D domain
- Space of symmetry-destabilizing perturbations spanned by the ones with $\mathrm{Re}(\lambda) > 0$ anywhere on symmetric equilibrium branch
- Needed for NAS was $g(\mu, \eta) = g_1(\mu) - g_2\eta$ (Lengyel-Epstein?)
- Collective behaviour that occurs for a microemulsion consisting of Belousov-Zhabotinsky chemical reactants confined within small aqueous droplets dispersed in oil [43] ([9] [5])

- We derived NAS for all equilibria, equations determining pitchfork bifurcation points and GCEP for general perturbation growth rates λ for finite & periodic 1-D domain and finite no-flux bc 2-D domain
- Space of symmetry-destabilizing perturbations spanned by the ones with $\mathrm{Re}(\lambda) > 0$ anywhere on symmetric equilibrium branch
- Needed for NAS was $g(\mu, \eta) = g_1(\mu) - g_2\eta$ (Lengyel-Epstein?)
- Collective behaviour that occurs for a microemulsion consisting of Belousov-Zhabotinsky chemical reactants confined within small aqueous droplets dispersed in oil [43] ([9] [5])

- We derived NAS for all equilibria, equations determining pitchfork bifurcation points and GCEP for general perturbation growth rates λ for finite & periodic 1-D domain and finite no-flux bc 2-D domain
- Space of symmetry-destabilizing perturbations spanned by the ones with $\mathrm{Re}(\lambda) > 0$ anywhere on symmetric equilibrium branch
- Needed for NAS was $g(\mu, \eta) = g_1(\mu) - g_2\eta$ (Lengyel-Epstein?)
- Collective behaviour that occurs for a microemulsion consisting of Belousov-Zhabotinsky chemical reactants confined within small aqueous droplets dispersed in oil [43] ([9] [5])

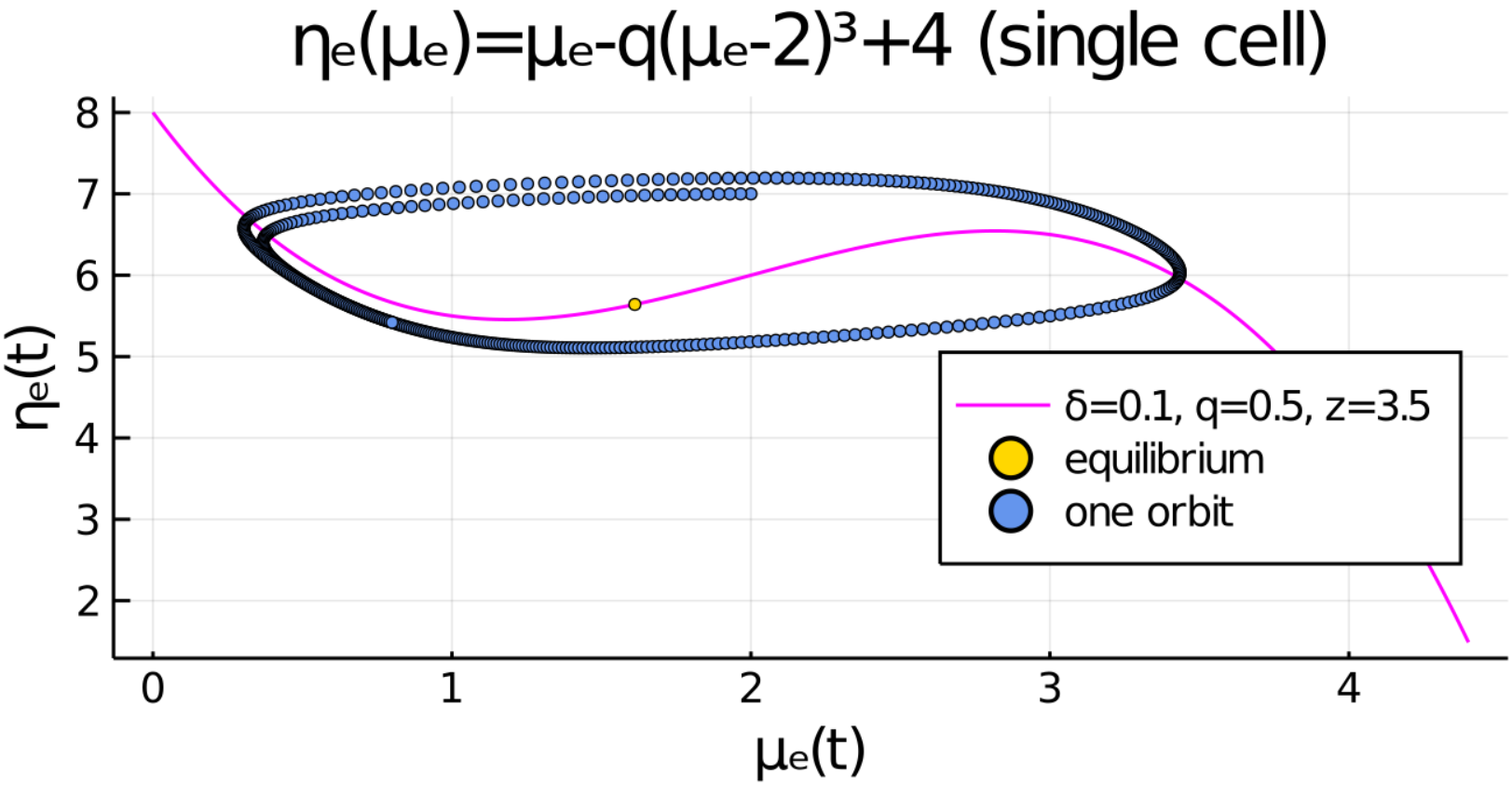
- Amplitude equations remain to be derived as in [34]
- On $\mathbb{R}^2$: small identical cells of centered at lattice points of arbitrary Bravais lattice (Floquet-Bloch theory, reduced-wave Bloch Green function [25])
- Developing extension of our asymptotic approach to treat closely-spaced cell configurations (biological tissues): extension of approach developed in [26] to analyze the mean first passage time for a cluster of small traps may be fruitful
- 1-D setting: geometric graphs with diffusion on edges (e.g., [3])

- Amplitude equations remain to be derived as in [34]
- On $\mathbb{R}^2$: small identical cells of centered at lattice points of arbitrary Bravais lattice (Floquet-Bloch theory, reduced-wave Bloch Green function [25])
- Developing extension of our asymptotic approach to treat closely-spaced cell configurations (biological tissues): extension of approach developed in [26] to analyze the mean first passage time for a cluster of small traps may be fruitful
- 1-D setting: geometric graphs with diffusion on edges (e.g., [3])

- Amplitude equations remain to be derived as in [34]
- On $\mathbb{R}^2$: small identical cells of centered at lattice points of arbitrary Bravais lattice (Floquet-Bloch theory, reduced-wave Bloch Green function [25])
- Developing extension of our asymptotic approach to treat closely-spaced cell configurations (biological tissues): extension of approach developed in [26] to analyze the mean first passage time for a cluster of small traps may be fruitful
- 1-D setting: geometric graphs with diffusion on edges (e.g., [3])

- Amplitude equations remain to be derived as in [34]
- On $\mathbb{R}^2$: small identical cells of centered at lattice points of arbitrary Bravais lattice (Floquet-Bloch theory, reduced-wave Bloch Green function [25])
- Developing extension of our asymptotic approach to treat closely-spaced cell configurations (biological tissues): extension of approach developed in [26] to analyze the mean first passage time for a cluster of small traps may be fruitful
- 1-D setting: geometric graphs with diffusion on edges (e.g., [3])

- Perturbing about stable limit cycle in contrast to uniform or symmetric steady-state. Time-dependence of limit cycle will lead to time-dependent Green matrices



- Chemical reactions happen randomly [42] [47] [23]. Assuming they are Markovian, analyzing their effect could yield novel behaviour [10]

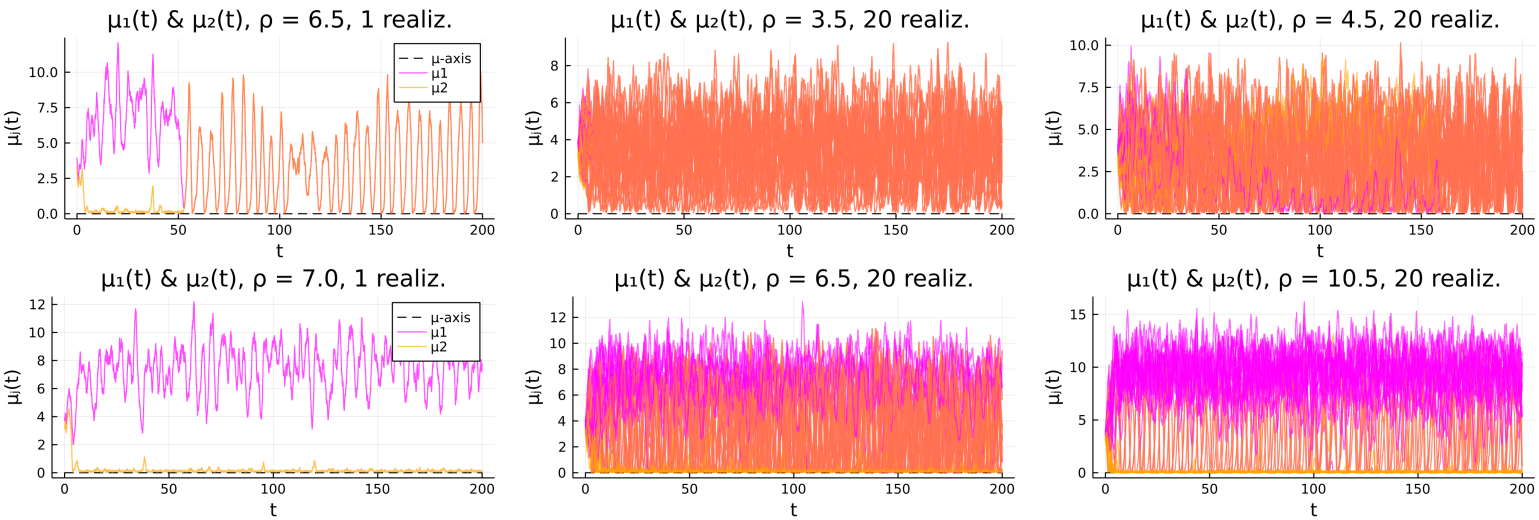


Figure: Simulations of RM kinetics for two cells on periodic 1-D domain. RM kinetics are randomly nonlinearly perturbed with square rooted propensities multiplied by independent Wiener processes.

- Notion of stochastic P-bifurcation point versus D-bifurcation point may be interesting [1]
- Approximate Fokker-Planck equation for stationary distribution (using bulk equilibrium):

$$\begin{aligned} 0 \quad = \quad \partial_t p_s(\nu) \quad &= \quad \nabla \cdot ((-\mathrm{F}(\nu) + C\nu)p_s + \tfrac{1}{2}\nabla \cdot (D(\nu)p_s) \\ &= \quad -\sum_{l=1}^{2n} \partial_{\nu_l}(\mathbf{e}_l^T(\mathrm{F}(\nu) - C\nu)p_s) + \tfrac{1}{2}\sum_{l=1}^{2n} \partial_{\nu_l}^2(\mathbf{e}_l^T D\,\mathbf{e}_l\, p_s). \end{aligned}$$

supplied with the mass-conserving reflecting boundary condition $\mathbf{j} \cdot \mathbf{n} = 0$ at zero boundaries for which $\exists\, l \in \{1, ..., 2n\} : \nu_l = 0$ [24] [35]. Here $\mathbf{j}$ is the flux

$$\mathbf{j} = (\mathrm{F}(\nu) - C\nu)p_s - \frac{1}{2}(\partial_{\nu_1}(\mathbf{e}_1^T D\,\mathbf{e}_1\, p_s), ..., \partial_{\nu_{2n}}(\mathbf{e}_{2n}^T D\,\mathbf{e}_{2n}\, p_s))^T.$$

Questions? ☺

References I

[1] Ludwig Arnold. "Random dynamical systems". In: *Dynamical systems* (1995), pp. 1–43.

[2] R. E. Baker, E. A. Gaffney, and P. K. Maini. "Partial differential equations for self-organization in cellular and developmental biology". In: *Nonlinearity* 21.11 (2008), R251.

[3] C. Besse and G. Faye. "Dynamics of epidemic spreading on graphs". In: *J. Math. Bio.* 82.6 (2021), pp. 1–52.

[4] J. Bezanson et al. "Julia: A fast dynamic language for technical computing". In: *arXiv preprint arXiv:1209.5145* (2012).

[5] M. A. Budroni et al. "Membrane structure drives synchronization patterns in arrays of diffusively coupled self-oscillating droplets". In: *J. Phys. Chem. Lett* 11.6 (2020), pp. 2014–2020.

References II

[6] A. Dhooge, W. Govaerts, and Y. A Kuznetsov. "MatCont: a MATLAB package for numerical bifurcation analysis of ODEs". In: *ACM Trans. Math. Software (TOMS)* 29.2 (2003), pp. 141–164.

[7] L. Diambra et al. "Cooperativity to increase Turing pattern space for synthetic biology". In: *AVS Synthetic Biology* 4 (2015), pp. 177–186.

[8] X. Diego et al. "Key features of Turing systems are determined purely by network topology". In: *Phys. Rev. X* 8 (2018), p. 021071.

[9] I. Epstein and B. Xu. "Reaction-diffusion processes at the nano- and microscales". In: *Nature Technology* 11 (2016), pp. 312–319.

[10] R. Erban and J. Chapman. *Stochastic modeling of reaction-diffusion processes*. Cambridge Texts in Applied Mathematics, Cambridge U. Press, 2020, p. 380.

[11] PDE FlexPDE. "Solutions inc". In: *URL http://www. pdesolutions. com* (2015).

References III

[12] A. Gierer. “Generation of biological patterns and form: some physical, mathematical, and logical aspects”. In: *Progress in biophysics and molecular biology* 37 (1981), pp. 1–47.

[13] A. Gierer and H. Meinhardt. “A theory of biological pattern formation”. In: *Kybernetik* 12.1 (1972), pp. 30–39.

[14] D. Gomez et al. “Pattern forming systems coupling linear bulk diffusion to dynamically active membranes or cells”. In: *Phil. Trans. Roy. Soc. A.* 379 (2021), p. 20200276.

[15] A. Gomez-Marin, J. Garcia-Ojalvo, and J. M. Sancho. “Self-sustained spatiotemporal oscillations induced by membrane-bulk coupling”. In: *Phys. Rev. Lett.* 98 (16 2007), p. 168303.

[16] J. Gou and M. J. Ward. “An asymptotic analysis of a 2-D model of dynamically active compartments coupled by bulk diffusion”. In: *J. Nonlin. Sci.* 26.4 (2016), pp. 979–1029.

References IV

[17] J. Gou and M. J. Ward. “Oscillatory dynamics for a coupled membrane-bulk diffusion model with Fitzhugh-Nagumo kinetics”. In: *SIAM J. Appl. Math.* 76.2 (2016), pp. 776–804.

[18] J. Gou et al. “A theory of synchrony by coupling through a diffusive chemical signal”. In: *Physica D* 339 (2017), pp. 1–17.

[19] J. Gou et al. “Synchronized oscillatory dynamics for a 1-D model of membrane kinetics coupled by linear bulk diffusion”. In: *SIAM J. Appl. Dyn. Sys.* 14.4 (2015), pp. 2096–2137.

[20] P. Haas and R. Goldstein. “Turing’s diffusive threshold in random reaction-diffusion systems”. In: *Phys. Rev. Lett.* 126 (2021), p. 238101.

[21] J. Halatek, F. Brauns, and E. Frey. “Self-organization principles of intracellular pattern formation”. In: *Phil. Trans. R. Soc. B* 373.1747 (2018), p. 20170107.

References V

[22] J. Halatek and E. Frey. “Rethinking pattern formation in reaction–diffusion systems”. In: *Nature Physics* 14.5 (2018), p. 507.

[23] Desmond J Higham. “Modeling and simulating chemical reactions”. In: *SIAM review* 50.2 (2008), pp. 347–368.

[24] Miranda Holmes-Cerfon. *Applied Stochastic Analysis*. In preparation.

[25] S. Iyaniwura, J. Gou, and M. J. Ward. “Synchronous oscillations for a coupled cell-bulk PDE-ODE model with localized cells on $\mathbb{R}^2$”. In: *J. Eng. Math.* 127.18 (2021), 24 pp.

[26] S. Iyaniwura and M. J. Ward. “Asymptotic analysis for the mean first passage time in finite or spatially periodic 2-D domains with a cluster of small traps”. In: *ANZIAM* 63.1 (2021), pp. 1–22.

References VI

[27] S. Iyaniwura and M. J. Ward. “Synchrony and oscillatory dynamics for a 2-D PDE-ODE model of diffusion-mediated communication between small signalling compartments”. In: *SIAM J. Appl. Dyn. Sys.* 20.1 (2021), pp. 438–499.

[28] V. Klika et al. “The influence of receptor-mediated interactions on reaction-diffusion mechanisms of cellular self-organization”. In: *Bull. Math. Bio.* 74 (2012), pp. 935–957.

[29] K. Korvasová et al. “Investigating the Turing conditions for diffusion-driven instability in the presence of a binding immobile substrate”. In: *J. Theor. Biol.* 367 (2015), pp. 286–295.

[30] A. Landge et al. “Pattern formation mechanisms of self-organizing reaction-diffusion systems”. In: *Dev Biol.* 460.1 (2020), pp. 2–11.

[31] H. Levine and W. J. Rappel. “Membrane-bound Turing patterns”. In: *Phys. Rev. E* 72 (6 2005), p. 061912.

References VII

[32] L. Marcon et al. “High throughput mathematical analysis identifies Turing networks for patterning with equal diffusing signals”. In: *eLife* 5 (2016), e14022.

[33] P. Müller et al. “Morphogen transport”. In: *Development* 140.8 (2013), pp. 1621–1639.

[34] F. Paquin-Lefebvre, W. Nagata, and M. J. Ward. “Weakly nonlinear theory for oscillatory dynamics in a one-dimensional PDE-ODE model of membrane dynamics coupled by a bulk diffusion field”. In: *SIAM J. Appl. Math.* 80.3 (2020), pp. 1520–1545.

[35] Grigorios A Pavliotis. *Stochastic processes and applications: diffusion processes, the Fokker-Planck and Langevin equations*. Vol. 60. Springer, 2014.

[36] J. Pearson. “Pattern formation in a (2+1)-species activator-inhibitor immobilizer system”. In: *Physica A* 188.1-3 (1992), pp. 178–189.

References VIII

[37] J. Pearson and W. Horsthemke. “Turing instabilities with nearly equal diffusivities”. In: *J. Chem. Phys.* 90 (1989), p. 1588.

[38] M. Pelz and M. J. Ward. “The emergence of spatial patterns for compartmental reaction kinetics coupled by two bulk diffusing species with comparable diffusivities”. In: *Phil. Trans. Roy. Soc. A (38 pages, submitted)* (2022).

[39] E. M. Rauch and M. M. Millonas. “The role of trans-membrane signal transduction in Turing-type cellular pattern formation”. In: *J. Theor. Biol.* 226.4 (2004), pp. 401–407.

[40] W. Ridgway, M. J. Ward, and B. T. Wetton. “Quorum-sensing induced transitions between bistable steady-states for a cell-bulk ODE-PDE model with Lux intracellular kinetics”. In: *J. Math. Bio.* 84.1-2 (2021).

References IX

[41] B. Sozen, J. Cornwall-Scoones, and M. Zernicka-Goetz. "The dynamics of morphogenesis in stem cell-based embryology: Novel insights for symmetry breaking". In: *Development* 474 (2021), pp. 82–90.

[42] Peter S Swain and André Longtin. "Noise in genetic and neural networks". In: *Chaos: An Interdisciplinary Journal of Nonlinear Science* 16.2 (2006), p. 026101.

[43] N. Tompkins et al. "Testing Turing's theory of morphogenesis in chemical cells". In: *PNAS* 111.12 (2014), pp. 4397–4402.

[44] A. M. Turing. "The chemical basis of morphogenesis". In: *Phil. Trans. Roy. Soc., Series B* 237.641 (1952), pp. 37–72.

[45] V. K. Vanag and I. R. Epstein. "Localized patterns in reaction-diffusion systems". In: *Chaos* 17.3 (2007), p. 037110.

References X

[46] M. J. Ward. “Spots, traps, and patches: Asymptotic analysis of localized solutions to some linear and nonlinear diffusive processes”. In: *Nonlinearity* 31.8 (2018), R189.

[47] Darren J Wilkinson. “Stochastic modelling for quantitative description of heterogeneous biological systems”. In: *Nature Reviews Genetics* 10.2 (2009), pp. 122–133.