Modelling the dynamics of GTPase activity

Yue Liu

University of British Columbia

Supervisor: Leah Edelstein-Keshet

Mathematical Biology Seminar, PIMS & UBC Math
November 7, 2018

Overview

Motivation

Cells exhibit a variety of interesting behaviors:

- Cell motility (video)
- Filopodia formation (video)
- Actin wave (video)

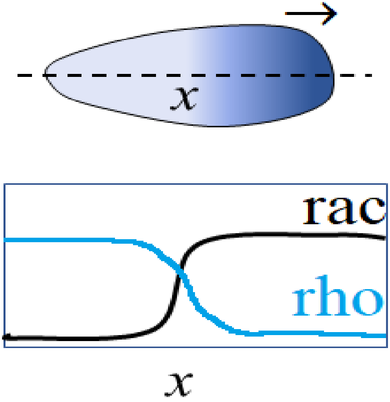
Small GTPases: a family of signalling proteins that controls cell shape by regulating F-actin and myosin. 3 members:

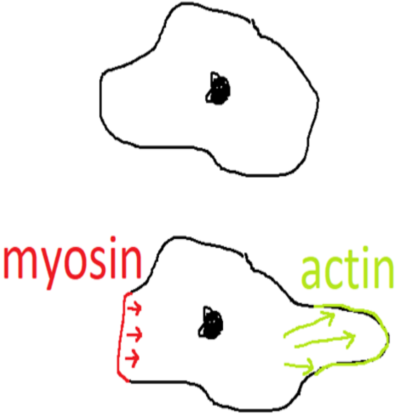
- Rho (makes cell contract)
- Rac, Cdc42 (expand)

Important characteristic: fast-diffusing inactive form vs slow diffusing active form

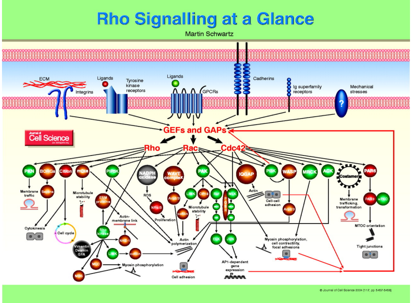
Goal: model the spatio-temporal dynamics of GTPase

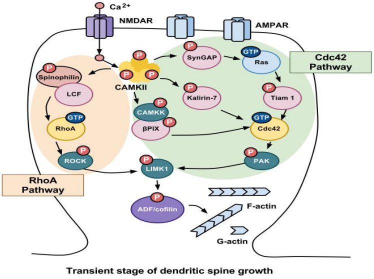
Cell motility





Biology is complicated...





(Schwartz 2004, J Cell Sci 117: 5457-5458)

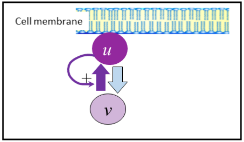
(Wikipedia)

Idea: build *minimalistic* model that can still capture the behaviors of interest to uncover the essential mechanisms

Wave-pinning model

Proposed by Mori et al (2008), considers one type of GTPase by itself. $u(x,t), v(x,t)$ =concentration of active/inactive GTPase

$$\frac{\partial u}{\partial t} = \delta \nabla^2 u + f(u,v), \delta \ll 1$$
$$\frac{\partial v}{\partial t} = \nabla^2 v - f(u,v)$$
$$f(u,v) = \underbrace{(k_0 + \gamma \frac{u^n}{1+u^n})}_{\text{activation rate}} v - \underbrace{\eta}_{\text{deactivation}} u$$



Boundary condition: no flux, $\therefore$ total GTPase $\int (u+v)dx$ conserved

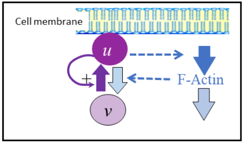
Has 2 homogeneous stable steady states

Able to produce robust polarization in response to external signal

Actin feedback model

Proposed by Holmes et al (2012), adds feedback effect from slow-reacting F-actin.

$$\frac{\partial u}{\partial t} = \delta\nabla^2 u + f(u,v,F)$$
$$\frac{\partial v}{\partial t} = \nabla^2 v - f(u,v,F)$$
$$\frac{\partial F}{\partial t} = \epsilon(k_n u - k_s F), \epsilon \ll 1$$
$$f(u,v,F) = (k_0 + \gamma\frac{u^n}{1+u^n})v - (\eta + s\frac{F}{1+F})u$$

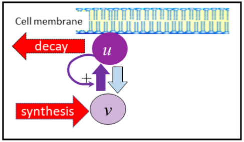


Able to produce pulses and wave trains

Source & sink model

Proposed by Verschueren & Champneys (2017), adds effect of production and degradation of GTPases

$$\frac{\partial u}{\partial t} = \delta \nabla^2 u + f(u,v) - \epsilon_c \theta u$$
$$\frac{\partial v}{\partial t} = \nabla^2 v - f(u,v) + \epsilon_c \alpha$$
$$f(u,v) = (k_0 + \gamma \frac{u^2}{1+u^2})v - \eta u$$

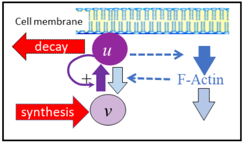


Mass no longer conserved. Able to produce pulses and wave trains
Only 1 stable homogeneous steady state

Combined model

Why not put them together?

$$\frac{\partial u}{\partial t} = \delta\nabla^2 u + f(u,v,F) - \epsilon_c\theta u$$
$$\frac{\partial v}{\partial t} = \nabla^2 v - f(u,v,F) + \epsilon_c\alpha$$
$$\frac{\partial F}{\partial t} = \epsilon(k_n u - k_s F)$$
$$f(u,v) = (k_0 + \gamma\frac{u^2}{1+u^2})v - (\eta + s\frac{F}{1+F})u$$



Other models

- Holmes, Lin, Levchenko & E-Keshet 2012: complex model involving Rac, Rho, Cdc42 and more intermediate proteins. Found change in cell shape can stablize certain patterns
- Diekers et al 2014: ODE model for force-producing molecules (eg. actin, myosin), Found regimes of random and synchronized oscillations in array if coupled cells
- Holmes & E-Keshet 2016: mutual inhibition between Rac and Rho, found bistable regime enveloped inside a polarizable regime
- Zmurchok 2018: coupled cell tension to activation of GTPase. Found periodic behavior in single cells, and waves of contraction in array of coupled cells.
- and many others...

Well-mixed case

Assuming GTPases are well-mixed reduces the PDEs to ODEs. Assume 1D domain with length L. And consider the case where total GTPases (T) is conserved. Then,

$$T = \int_0^L (u+v)dx = L(u+v), \ v = \frac{T}{L} - u$$

Substitute to original PDE:

$$\begin{aligned} \frac{\partial u}{\partial t} &= f(u,v) \\ &= (k_0 + \gamma \frac{u^n}{1+u^n})(\frac{T}{L} - u) - \eta u \end{aligned}$$

1D Well-mixed case, fixed length

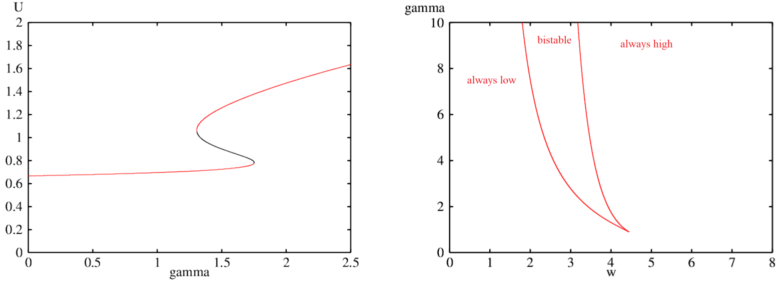


Figure: Bifurcation diagram with respect to γ and $T = 4$, and two-parameter bifurcation wrt γ, T

1D Well-mixed case, changing length

We can make the model more interesting by allowing L to change according to the level of u. In this case, we have

$$\frac{\partial(uL)}{\partial t} = Lf(u)$$

expanding results in a term describing dilution effect:

$$\frac{\partial u}{\partial t} = f(u) - \frac{u}{L}\frac{\partial L}{\partial t}$$

Assume a spring-like dynamic for L to close the system:

$$\frac{\partial L}{\partial t} = -\kappa(L - L_0(u))$$

$$L_0(u) = \begin{cases} L_b + L_d(1 - \frac{u^n}{u_c^n + u^n}) & \text{for Rho (contraction)} \\ L_b + L_d\frac{u^n}{u_c^n + u^n} & \text{for Rac/Cdc42 (expansion)} \end{cases}$$

Rho (contraction) case

In certain parameter regimes, tri-stability is possible. Parameter selection is aided with sharp-switch approximation.

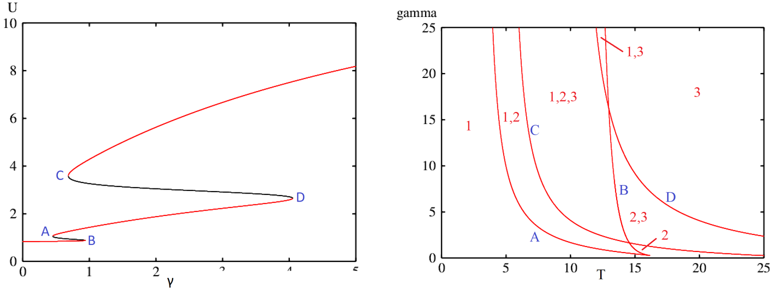
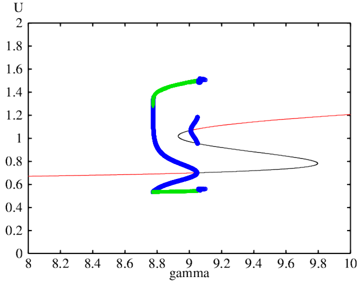


Figure: Bifurcation diagram with respect to γ with $T = 15$, and two-parameter bifurcation wrt γ, T. Notice the extra pair of fold points

Rac (expansion) case

Limit cycles exist in certain parameter regimes.



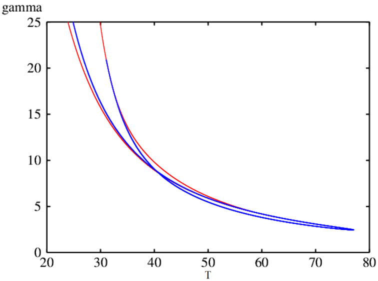
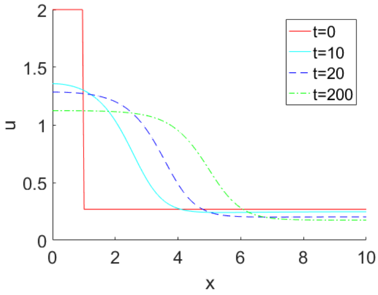


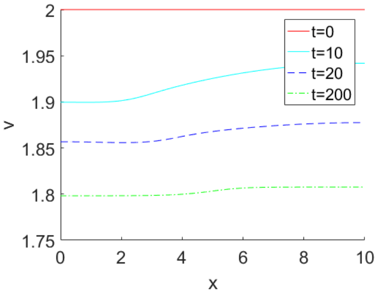
Figure: Bifurcation diagram with respect to γ and $T = 40$, and two-parameter γ, T. Notice the pair of Hopf points, which forms a cusp in the two-parameter plot similar to the fold points.

Numerical simulations

Wave pinning in 1D:



(a) u

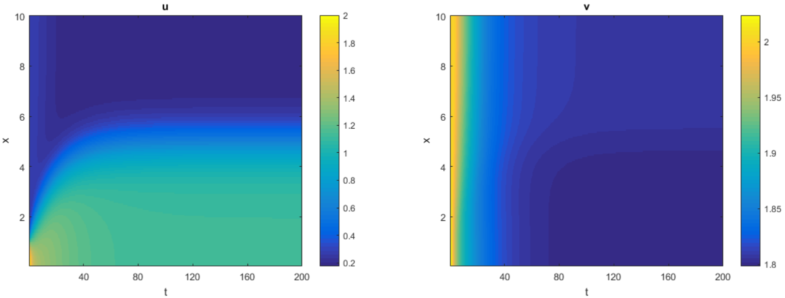


(b) v

Initial excitation leads to a propagating wave front which eventually stalls, hence "wave pinning"

Numerical simulations

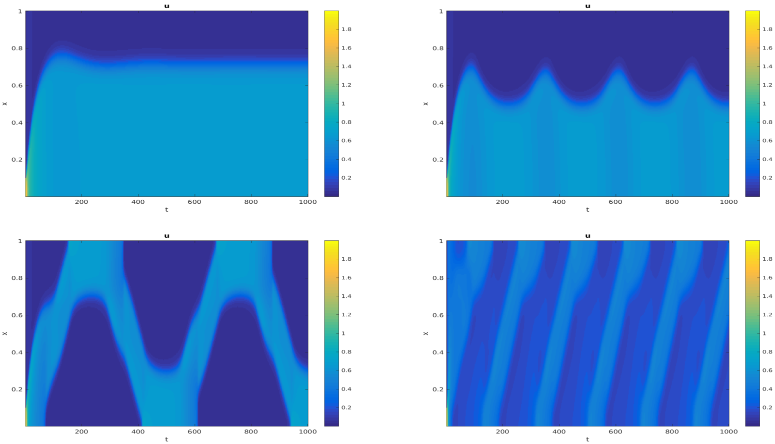
Kymographs makes visualization easier



Later plots will only show u

Numerical simulations

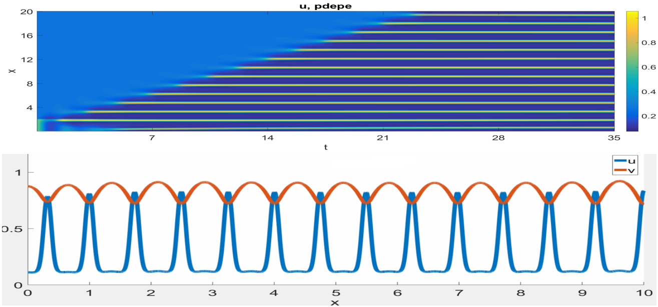
Actin wave in 1D:



Depends on parameters, a variety of dynamic behaviors are possible

Numerical simulations

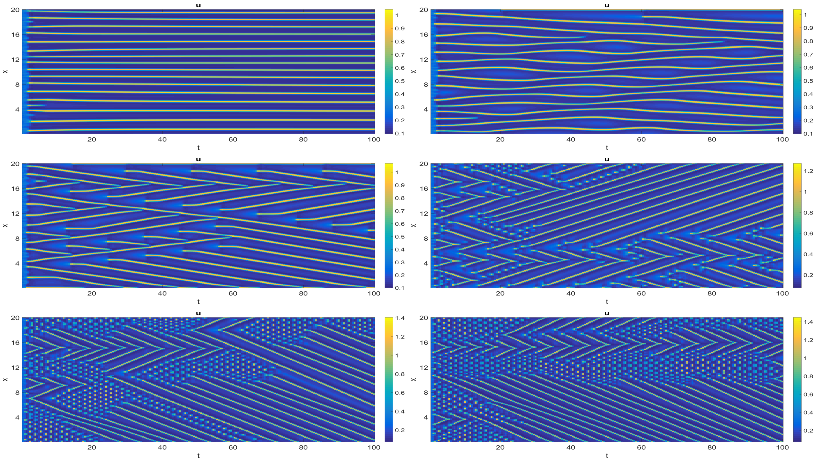
Source & sink in 1D:



Static, spatially periodic solution consisting of a series of spikes

Numerical simulations

Combined model in 1D:

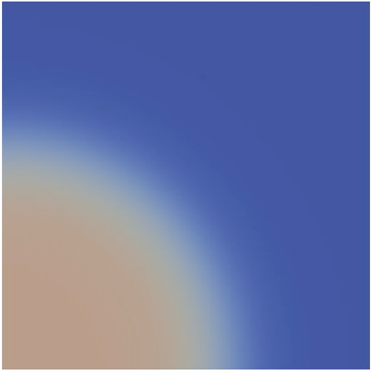


Series of travelling, colliding spikes. Exotic patterns at higher s

Numerical simulations

Wave pinning in 2D:

(a) Initial condition



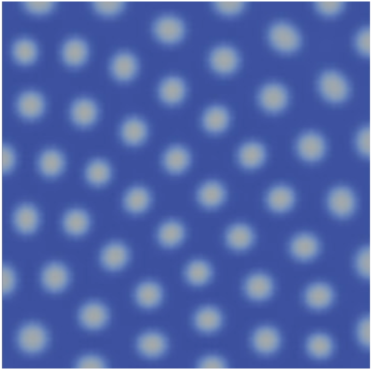
(b) Final static pattern

No surprises

Numerical simulations

Source & sink in 2D:

(a) Intermediate pattern

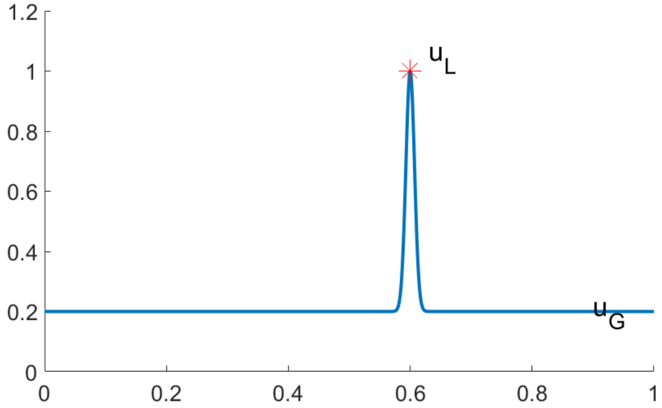


(b) Final static pattern

Many spots of high GTPase activity. Stripes forms but unstable

Local perturbation analysis (LPA)

Starting at a homogeneous steady state, we want to know how would a localized spike evolve.



(Detailed description: see Keshet et al, 2013)

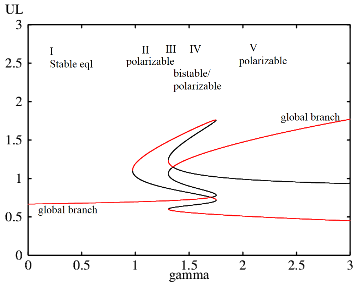
Local perturbation analysis (LPA)

Assume the fast diffusing quantities (v) diffuse infinitely fast, and the others (u, F) do not diffuse at all. Create a local copy of the slow-diffusing quantities to track the height of the spike.
In essence, "zeroth-order approximation" in δ

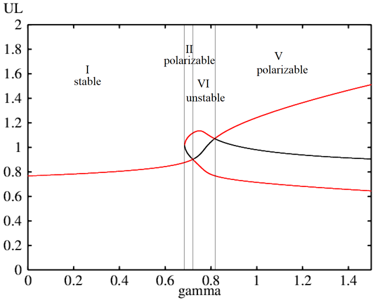
$$\begin{cases} \frac{\partial u}{\partial t} &= \delta \nabla^2 u + f(u,v,F) - \epsilon_c \theta u \\ \frac{\partial v}{\partial t} &= \nabla^2 v - f(u,v,F) + \epsilon_c \alpha \\ \frac{\partial F}{\partial t} &= \epsilon(k_n u - k_s F) \end{cases} \Rightarrow \begin{cases} \frac{\partial u_G}{\partial t} &= f(u_G, v, F_G) - \epsilon_c \theta u_G \\ \frac{\partial u_L}{\partial t} &= f(u_L, v, F_L) - \epsilon_c \theta u_L \\ \frac{\partial v}{\partial t} &= -f(u_G, v, F_G) + \epsilon_c \alpha \\ \frac{\partial F_G}{\partial t} &= \epsilon(k_n u_G - k_s F_G) \\ \frac{\partial F_L}{\partial t} &= \epsilon(k_n u_L - k_s F_L) \end{cases}$$

Bifurcation diagrams for u_L will consists of "global branches" (branches for u_G), and additional "local branches", since $u_L = u_G$ reduces system to well-mixed case.

LPA for wave pinning model



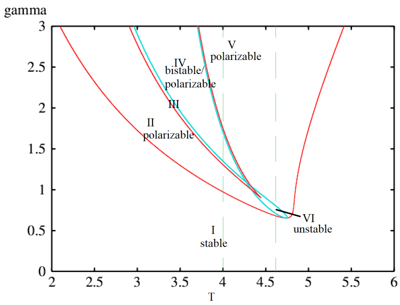
(a)



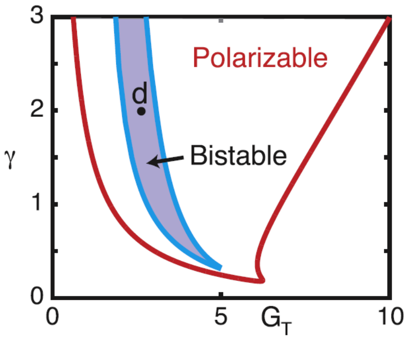
(b)

Figure: LPA bifurcation diagram for wave pinning model with respect to γ. (a) $T = 4$. 5 distinct regimes identified. (b) $T = 4.6$, one additional regime present

LPA for wave pinning model



(a)



(b) (from Holmes & Keshet 2016)

Figure: LPA two-parameter bifurcation diagram for wave pinning model with respect to T and γ. (a) My result, with vertical dashed line corresponding to the two figures on previous slide. (b) from (Holmes & Keshet 2016) which do not distinguish between II, III, V and VI

LPA for source & loss model

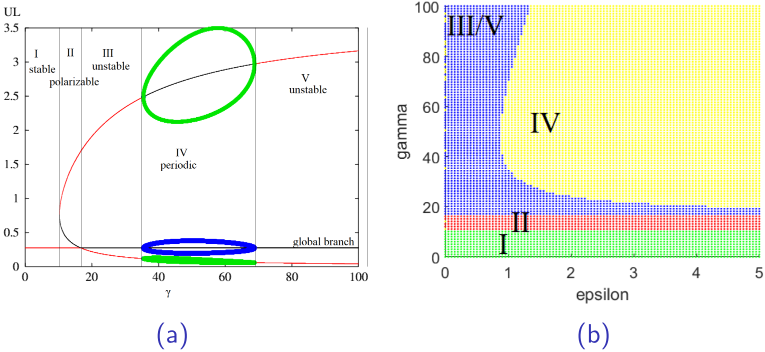
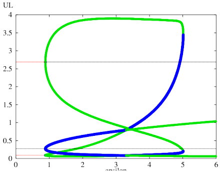
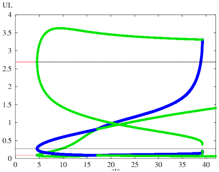


Figure: LPA Bifurcation diagram for source & loss model. (a) with respect to γ, and $\epsilon = 1$. 5 distinct regimes identified. (b) two parameter wrt ϵ and γ

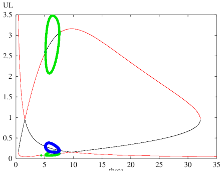
LPA for source & loss model



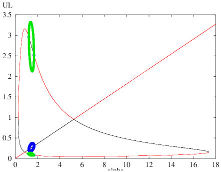
(a) ϵ_c



(b) η



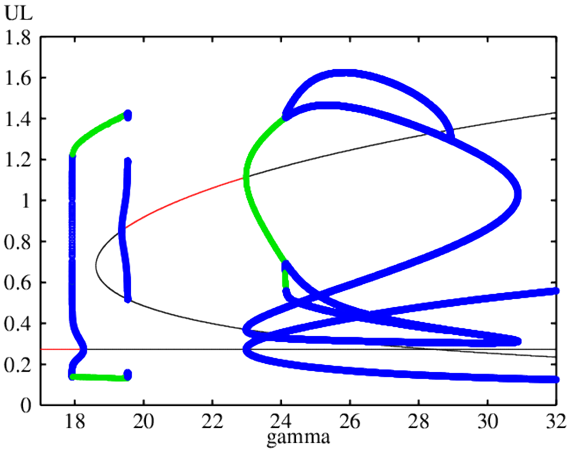
(c) θ



(d) α

Figure: Bifurcation wrt other parameters

LPA for the combined model



Unfortunately, it is hard to interpret this mess

Linear stability

We want to know whether a homogeneous state state is stable. For the source & loss model, linearize around unique equilibrium (u_*, v_*) and use normal form ansatz:

$$\begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix} = \begin{bmatrix} u \\ v \end{bmatrix} - \begin{bmatrix} u_* \\ v_* \end{bmatrix} = \begin{bmatrix} \alpha_u \\ \alpha_v \end{bmatrix} \cos(qx) e^{\sigma t}$$

The mode $cos(qx)$ will $\begin{cases} \text{grow} \\ \text{shrink} \end{cases}$ if $\Re(\sigma) \begin{cases} > 0 \\ < 0 \end{cases}$

Turing analysis

Following Turing (1952), let J =Jacobian of well-mixed system at equilibrium, $D = \begin{bmatrix} \delta & 0 \\ 0 & 1 \end{bmatrix}$, the PDE can be written as

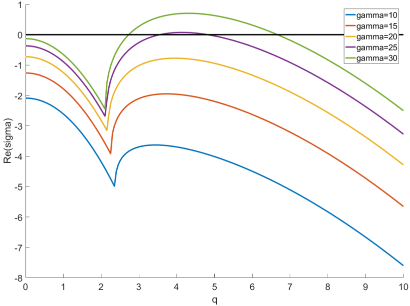
$$\frac{\partial}{\partial t} \begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix} = D \frac{\partial^2}{\partial x^2} \begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix} + J \begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix}$$

Sub in normal form:

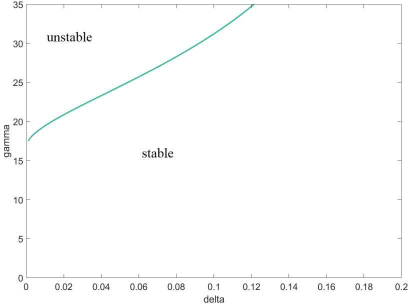
$$(\sigma I + q^2 D - M) \begin{bmatrix} \alpha_u \\ \alpha_v \end{bmatrix} = 0$$

For non-trivial solution, σ must be eigenvalues of $J - q^2 D$.

Turing analysis



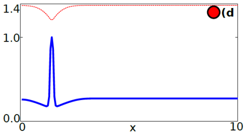
(a) dispersion relation: plotting $\Re(\sigma)$ against q shows which modes are excited. If only one mode excited, this can predict the wave length of pattern. Otherwise they may interact non-linearly and require more involved analysis.



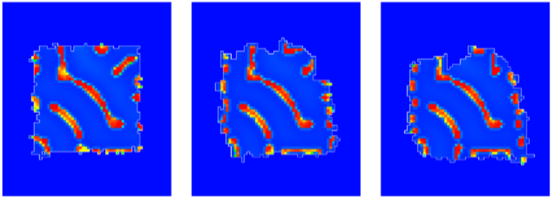
(b) The curve separating linearly stable ($\Re(\sigma) < 0 \ \forall q$) and unstable regimes (spontaneous pattern formation with infinitesimal perturbation)

Future directions

- Explore the well-mixed system with changing cell size more thoroughly
- Asymptotic analysis of soliton solutions
- Moving boundary simulations



(a) Soliton solution from V&C (2017) Fig.5. They obtained it numerically



(b) Simulation with deforming cell shape (Figure from Zachary Pellegrin)

References

Mori, Jilkine & E-Keshet, 2008
Wave-Pinning and Cell Polarity from a Bistable Reaction-Diffusion System
Biophysics J 94(9), 3684 – 3697

Mori, Jilkine & E-Keshet, 2008
From simple to detailed models for cell polarization
Philos T Roy Soc B 368(1629):20130003

Holmes & E-Keshet, 2016
Analysis of a minimal Rho-GTPase circuit regulating cell shape
Phys Biol 13(4):046001

Holmes, Carlsson & E-Keshet, 2012
Regimes of wave type patterning driven by refractory actin feedback: transition from static polarization to dynamic wave behaviour
Phys Biol 9(4):046005

Verschueren & Champneys, 2017
A Model for Cell Polarization Without Mass Conservation
SIAM J Appl Dyn Sys 16(4):1797-1830

Acknowledgement: Thank NSERC for funding. Thank Cole Zmurchok for suggestions on numerical methods and modelling approaches. Thank the math-bio group for comments and support.

Thank you!