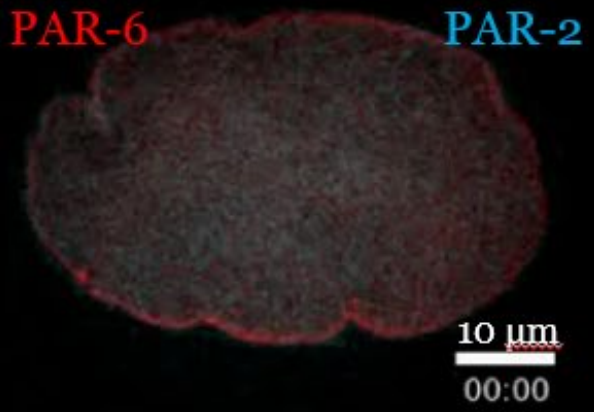
Modeling Biological Waves and Oscillations

QLS Breakfast Seminar

9 October 2024

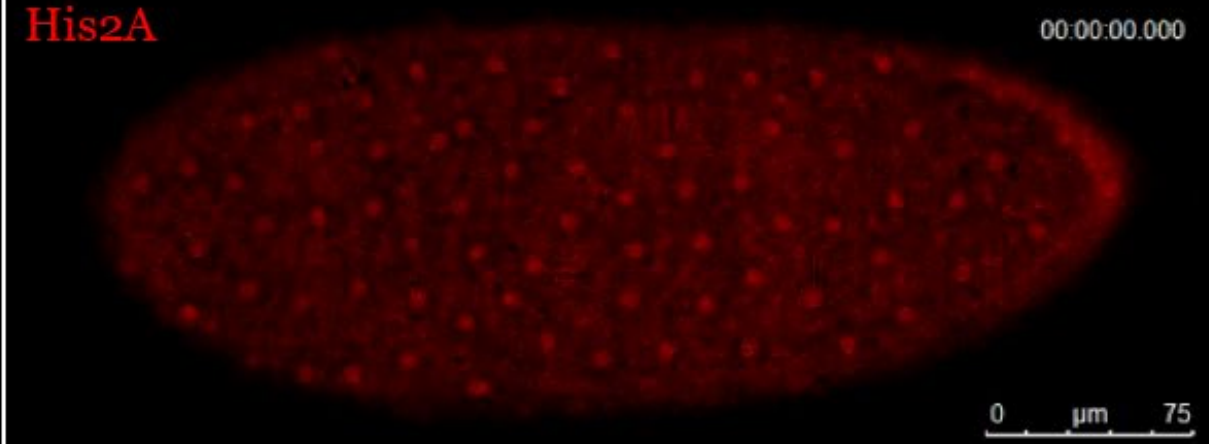
Rocky Diegmiller

cell polarization



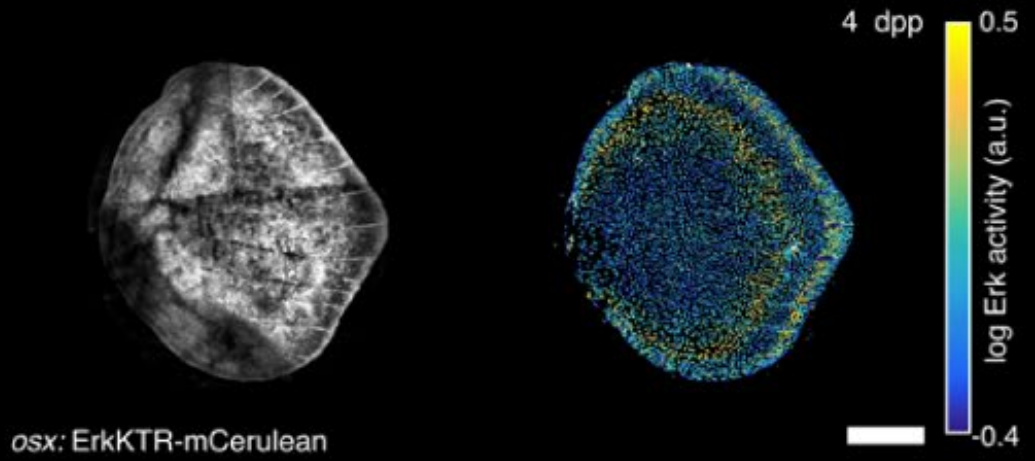
C. elegans embryo

waves of coordinated cell behavior



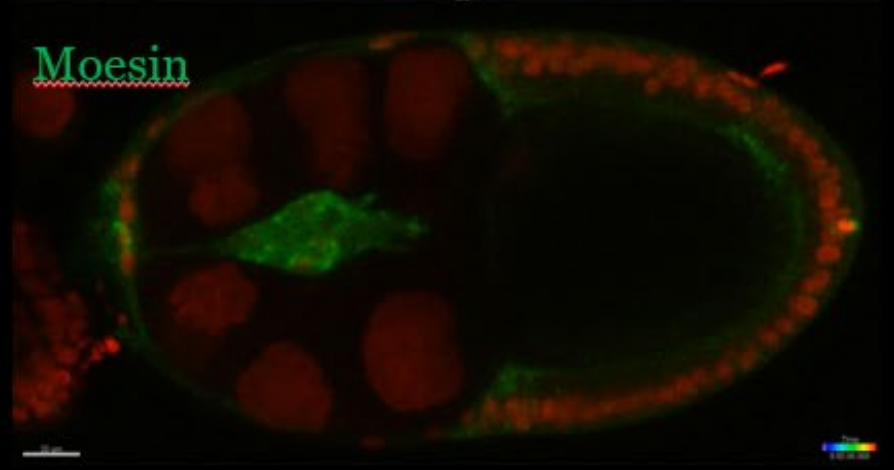
D. melanogaster embryo

appendage regeneration

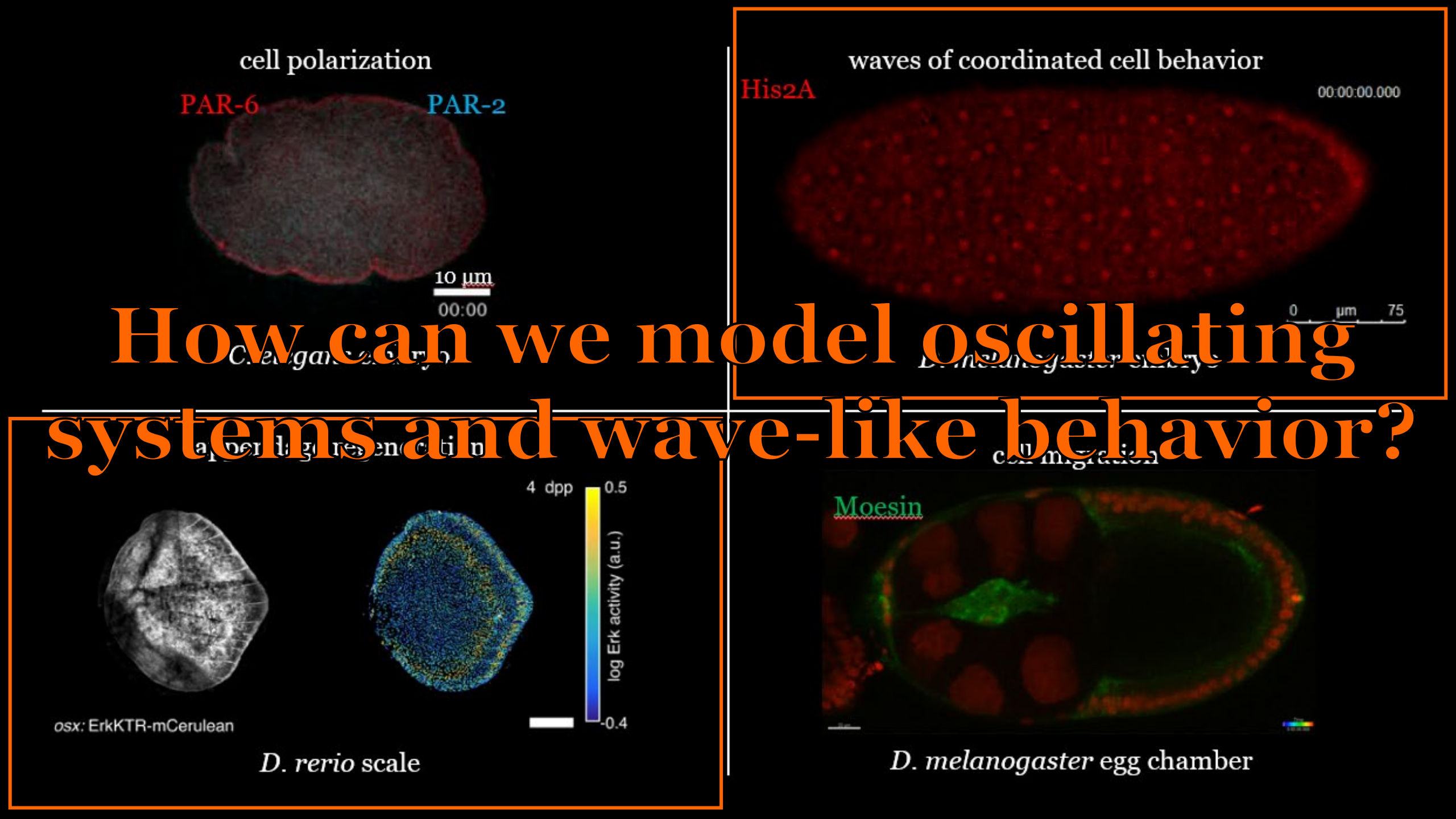


D. rerio scale

cell migration



D. melanogaster egg chamber



How can we model oscillating systems and wave-like behavior?

Some definitions and terms for periodic systems

- Consider a set of concentrations/states of a system, $\underline{\boldsymbol{x}} = \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix}$

  and that the time evolution of the system can be given by the following:

$$\frac{d\underline{\boldsymbol{x}}}{dt} = \underline{\boldsymbol{f}}(\underline{\boldsymbol{x}}), \qquad \text{where} \quad \underline{\boldsymbol{f}}(\underline{\boldsymbol{x}}) = \begin{pmatrix} f_1(x_1, x_2, \dots, x_n) \\ f_2(x_1, x_2, \dots, x_n) \\ \vdots \\ f_n(x_1, x_2, \dots, x_n) \end{pmatrix}$$

- For a solution to this system of ODEs $\underline{\boldsymbol{y}}(t)$, we say that this solution is periodic with period T if $\underline{\boldsymbol{y}}(t + T) = \underline{\boldsymbol{y}}(t)$

Some definitions and terms for periodic systems

- For a solution to this system of ODEs $\underline{\boldsymbol{y}}(t)$, we say that this solution is periodic with period T if $\underline{\boldsymbol{y}}(t+T) = \underline{\boldsymbol{y}}(t)$

- This means that our concentration profile takes on the same values at an interval T (appears to travel the same closed curve over time)

- (Unless neutrally stable) this trajectory is said to be a stable limit cycle – its behavior will oscillate periodically, instead of blowing up indefinitely (unstable) or relaxing to a single point (stable)

Oscillations in biology

Phenomenon	Period
neuron firing	~0.01 – 10 s
heartbeat	~1 s
biochemical oscillations	~1-10 min
cell cycle	~10 min – 1 day
circadian rhythm	~1 day
ovarian cycle	~28 days
ecological patterns	~years – centuries

Biochemical Oscillations and Cellular Rhythms, Goldbeter, 1996

Types of oscillators

- harmonic = when perturbed from rest, experiences a restoring force proportional to the perturbation

  TRANSLATION: response is linear and opposite to displacement

  EXAMPLES: free/damped pendulums, RLC (resistor-inductor-capacitor) circuits, mass-spring system

- relaxation = nonlinear oscillations characterized by rapid firing and slow buildup of signal

  EXAMPLES: nerve cell firing, thermostat regulation, gene activation systems, beating of the heart

Harmonic oscillators – undamped pendulum

- Let's think about the following description for a swinging pendulum:

$$\frac{d^2x}{dt^2} + k^2x = 0, \qquad x(0) = D \qquad \left.\frac{dx}{dt}\right|_{t=0} = 0$$

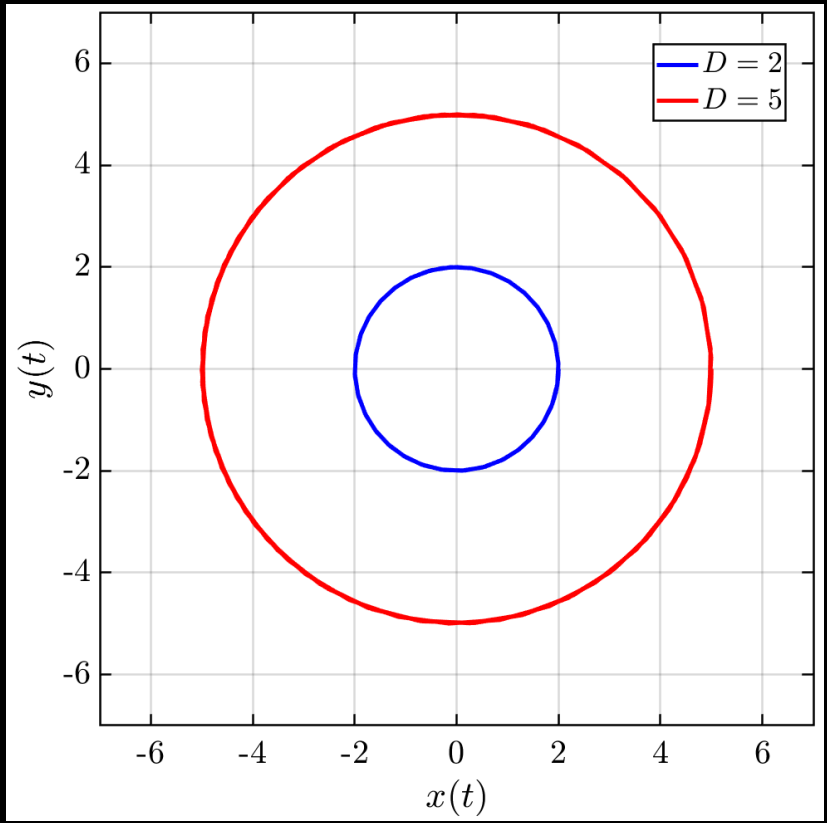
- Remembering our old trick to turn this into a system of ODEs:

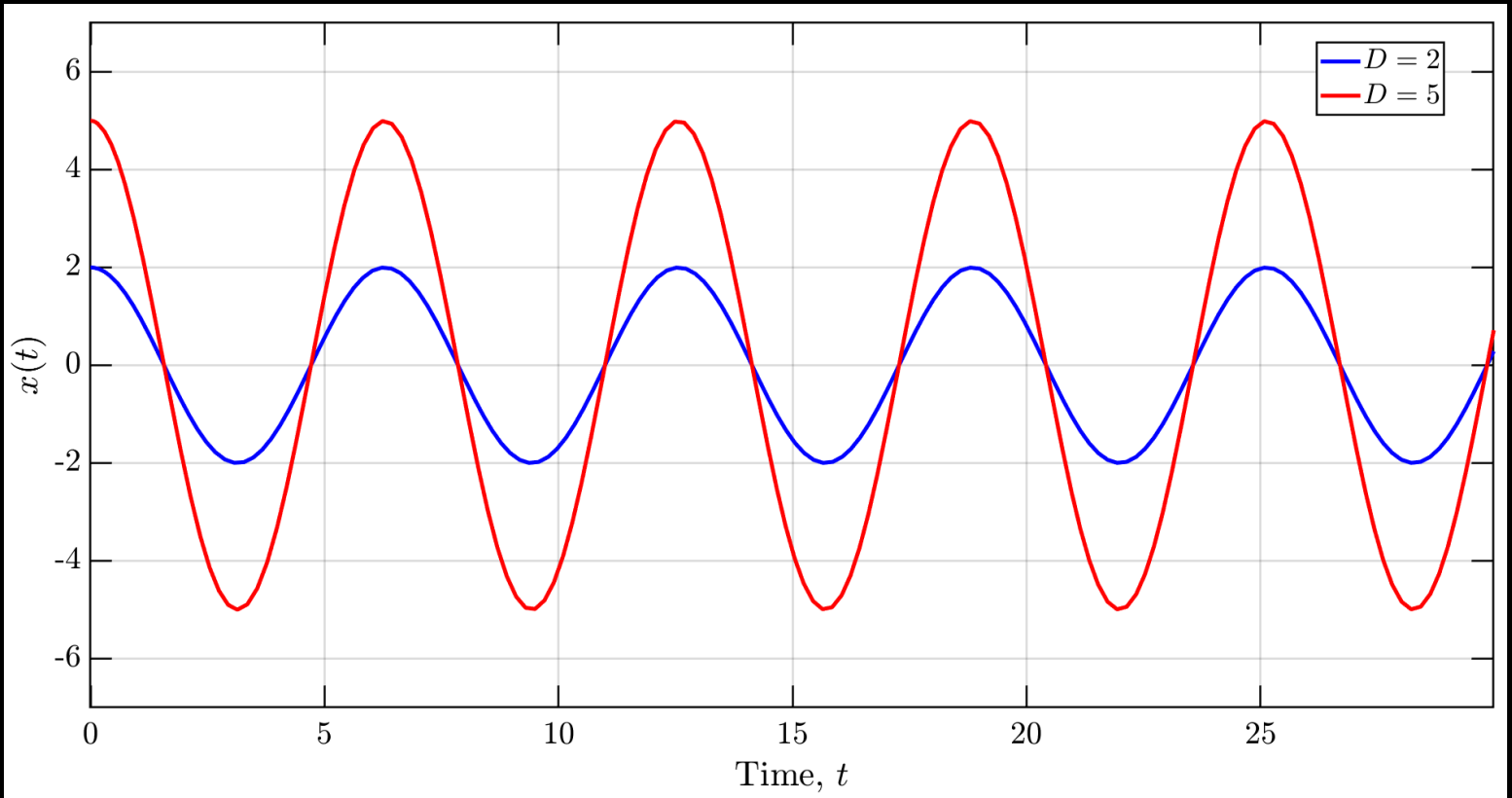
$$y = \frac{dx}{dt}, \quad \frac{dy}{dt} = \frac{d^2x}{dt^2} = -k^2x, \quad \Rightarrow \quad \frac{dx}{dt} = y, \quad \frac{dy}{dt} = -k^2x, \quad \Rightarrow \quad \frac{d}{dt}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -k^2 & 0 \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix}$$

Harmonic oscillators – undamped pendulum

```
A = [0 1; -k.^2 0];
[t,y] = ode45(@(t,y)) A*y, [0 30], [D 0]);
```

$k = 1$





Relaxation oscillators – FitzHugh-Nagumo and van der Pol

- In 1952, Hodgkin and Huxley outlined a (somewhat complicated) model for the initiation and propagation of action potentials in the squid giant axon

- A decade later, FitzHugh described a simpler system (1961) and Nagumo generated (1962) the equivalent circuit, which could be represented as:

$$\frac{dx}{dt} = x - \frac{x^3}{3} - y + I$$

$$\frac{dy}{dt} = \frac{1}{\mu}(x + a - by)$$

x ≔ membrane voltage
y ≔ Na+ activation, K+ deactivation
I ≔ external stimulus (forcing)
μ ≔ timescale separation

Relaxation oscillators – FitzHugh-Nagumo and van der Pol

- Setting $a, b, I = 0$ yields:

$$\frac{dx}{dt} = x - \frac{x^3}{3} - y$$

$$\frac{dy}{dt} = \frac{1}{\mu} x$$

- This is very close to one representation of the van der Pol oscillator, developed in 1927, to describe an irregular noise in a circuit with a vacuum tube:

$$\frac{dx}{dt} = \mu \left(x - \frac{x^3}{3} - y \right)$$

$$\frac{dy}{dt} = \frac{1}{\mu} x$$

Relaxation oscillators – FitzHugh-Nagumo and van der Pol

- An alternate representation (you can verify this is true) is the following:

$$\frac{dx}{dt} = y$$

$$\frac{dy}{dt} = \mu(1 - x^2)y - x$$

- Both the van der Pol and FitzHugh-Nagumo models are commonly used in biological contexts, especially as a stand in for action potentials and neuronal behavior

Relaxation oscillators – van der Pol

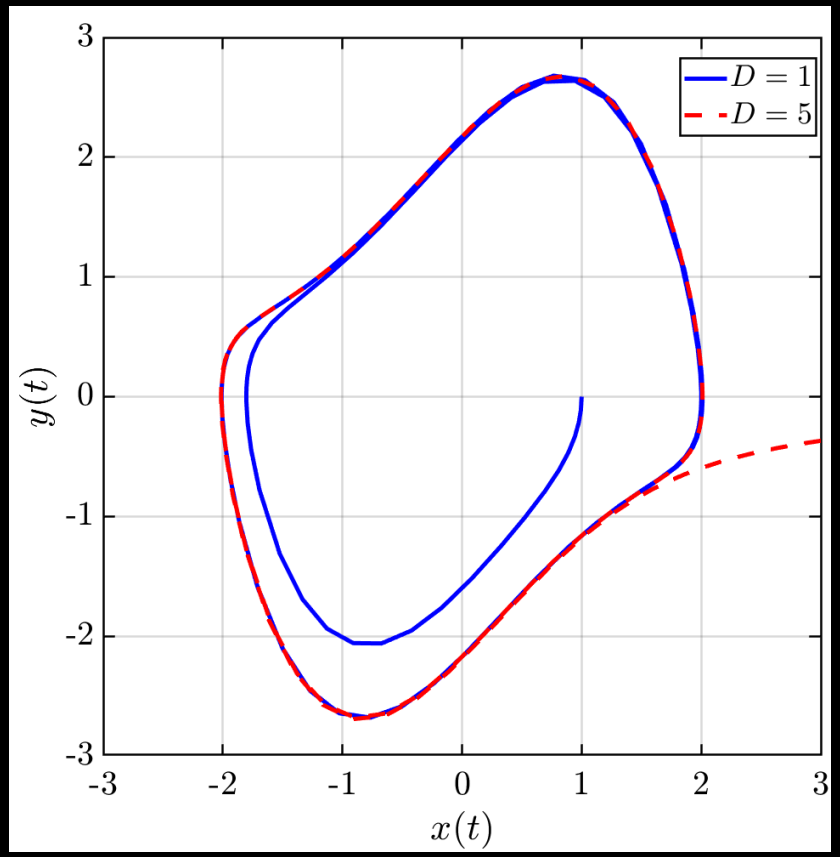
- Let's take a look at the vdP oscillator in this form with $\mu = 1$:

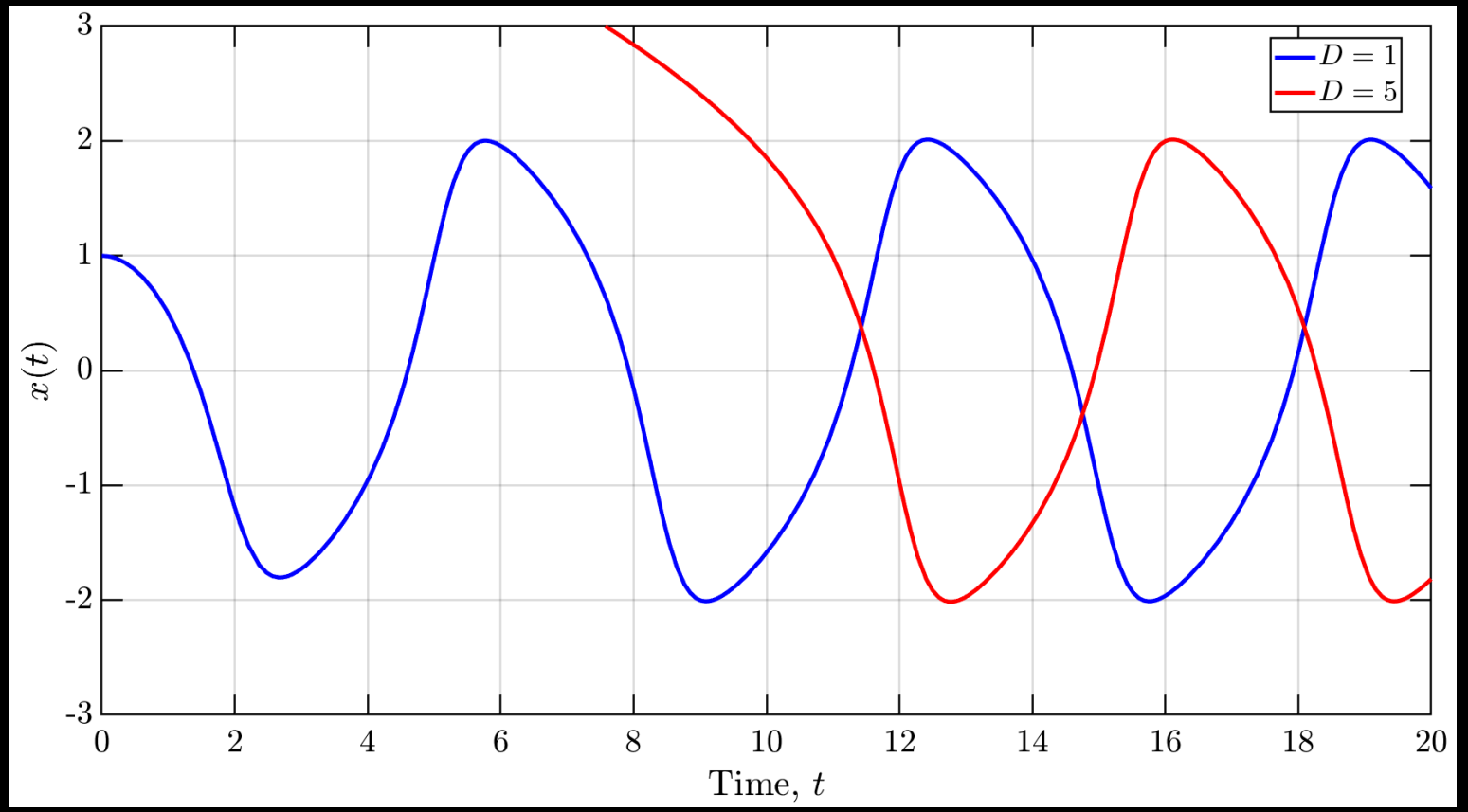
$$\frac{dx}{dt} = y, \qquad x(0) = D$$

$$\frac{dy}{dt} = (1 - x^2)y - x, \qquad y(0) = 0$$

Relaxation oscillators – van der Pol

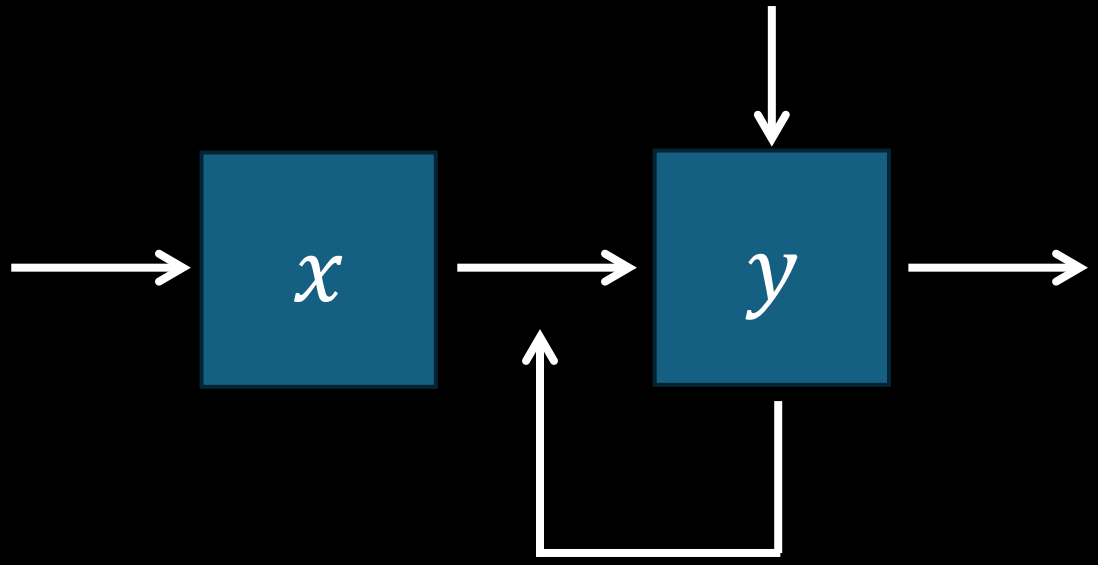
```
[t,y] = ode23s(@(t,y)) [y(2); (1-y(1).^2).*y(2)-y(1)], [0 10], [D 0]);
```





Relaxation oscillators – glycolytic model

- Organisms can break down sugar in a way that generates oscillatory behavior:



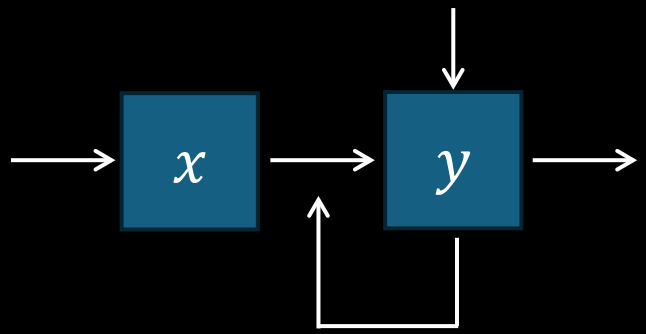
$$\frac{dx}{dt} = a - xy^2,$$

$$\frac{dy}{dt} = b + xy^2 - cy,$$

- x and y represent F6P (fructose-6-phosphate) + ATP and FBP (fructose-1,6-biphosphate)+ ADP, respectively
- This model is adapted from an earlier work by Sel'kov (1967) that showed these interactions could generate limit cycles
- This type of system is known as a "substrate depletion" model

Computational Cell Biology, Fall *et al.*, 2002

Relaxation oscillators – glycolytic model



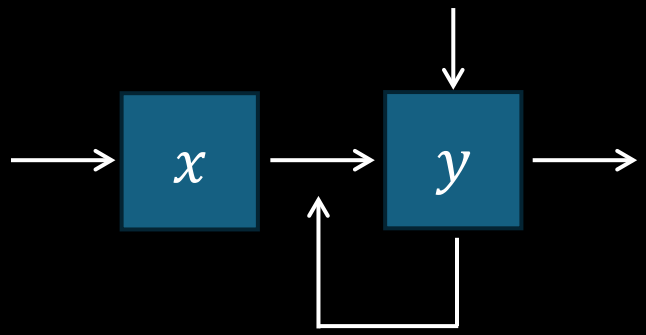
- Pick $a = 0.5, b = 0.05\ c = 1$:

$$\frac{dx}{dt} = 0.5 - xy^2, \qquad x(0) = D$$

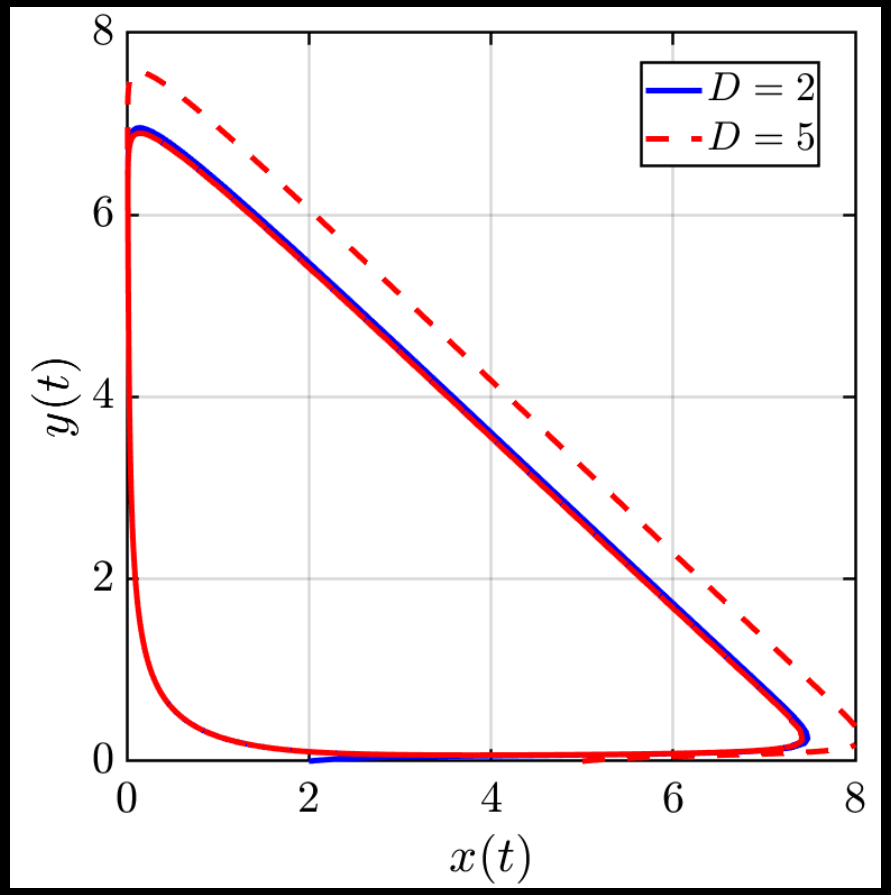
$$\frac{dy}{dt} = 0.05 + xy^2 - y, \qquad y(0) = 0$$

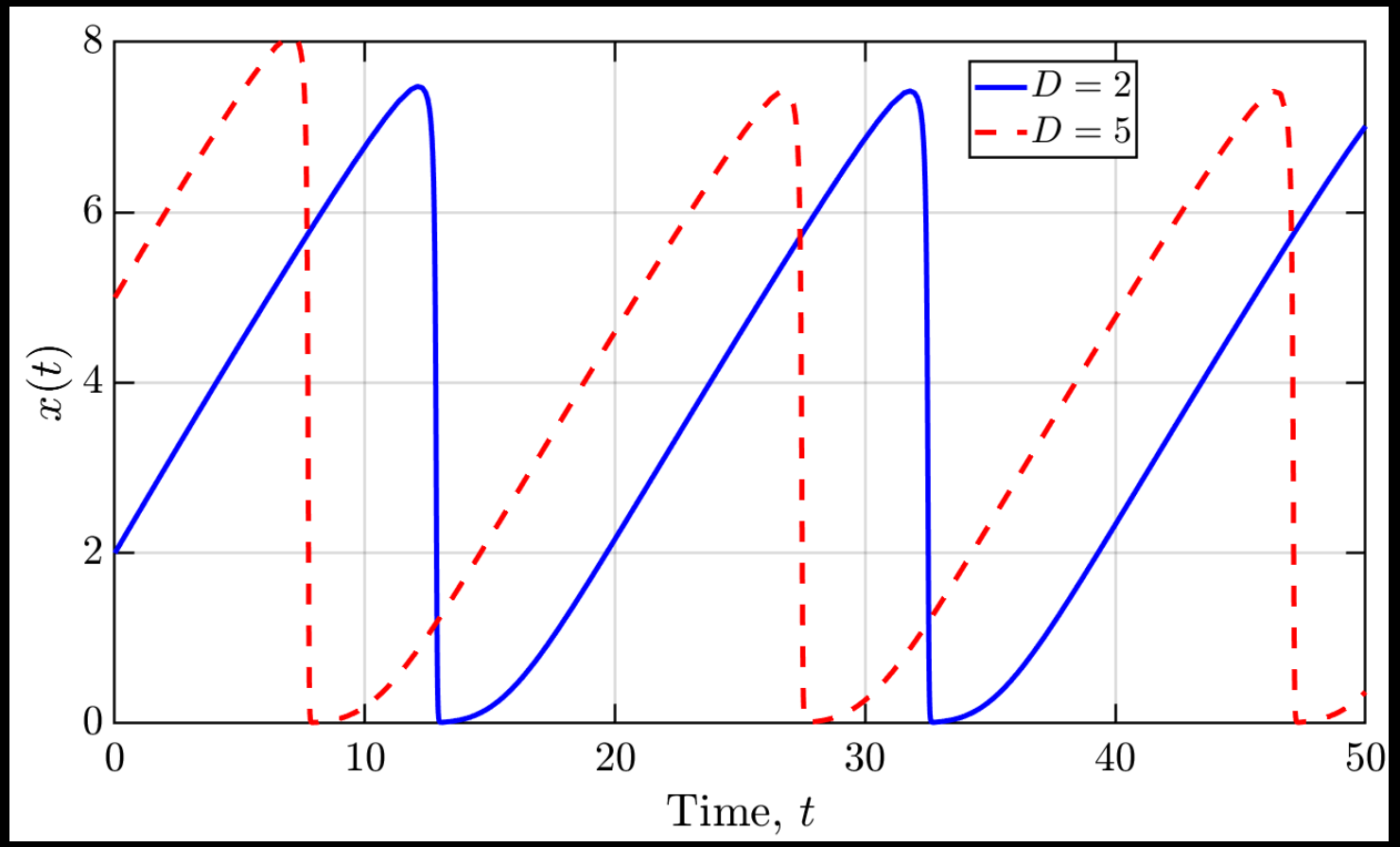
Computational Cell Biology, Fall *et al.*, 2002

Relaxation oscillators – glycolytic model



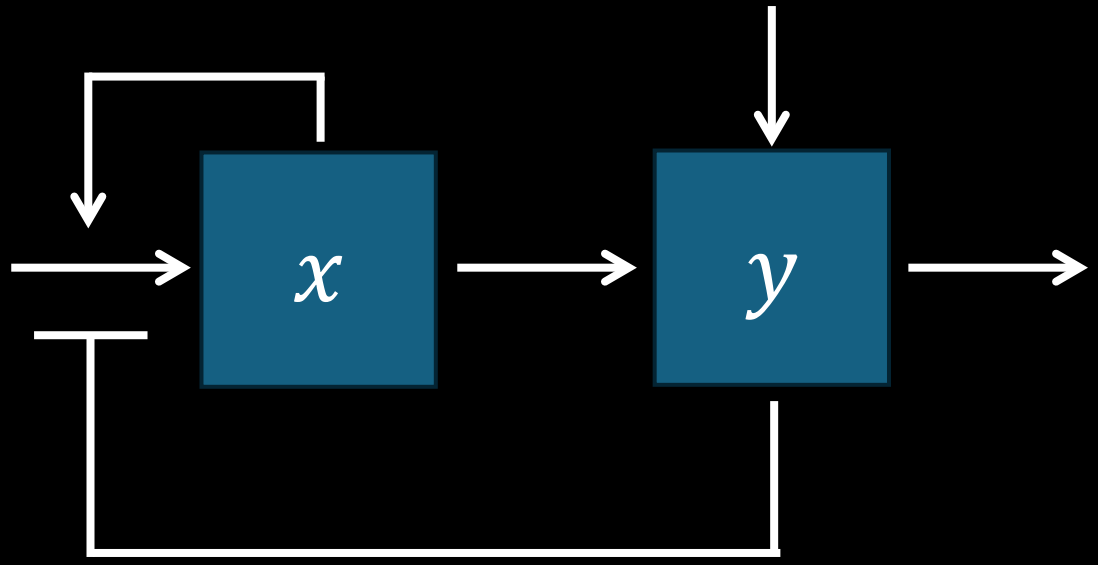

```
[t,y] = ode23s(@(t,y)) [0.5-y(1).*y(2).^2; 0.05+y(1).*y(2).^2-y(2)], [0 50], [D 0]);
```





Relaxation oscillators – cell cycle

- Cyclins can fluctuate within a cell and interact to generate oscillatory behavior:



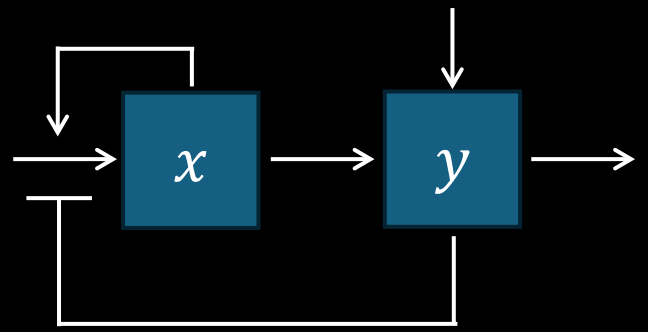
$$\frac{dx}{dt} = \left(\frac{a + x^2}{1 + x^2}\right)\left(\frac{1}{1 + y}\right) - bx,$$

$$\frac{dy}{dt} = c - \frac{dy}{1 + ex^2},$$

- x represents somewhat generic CLN (or G1) cyclins, while y is for CLB (B-type) cyclins, both of which are complexed with their corresponding cyclin-dependent kinases (CDKs)
- Here, the model is meant to depict oscillations in the context of the budding yeast cell cycle
- This type of system is known as an "activator-inhibitor" model

Computational Cell Biology, Fall *et al.*, 2002

Relaxation oscillators – cell cycle



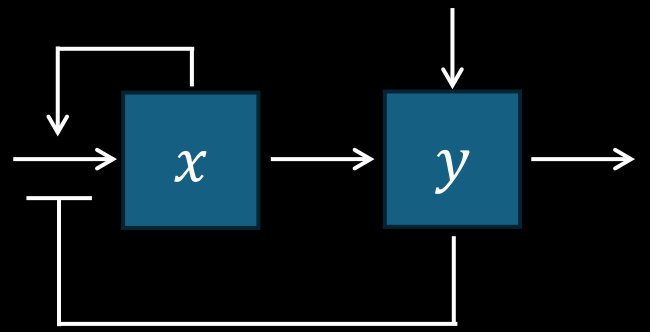
- Pick $a = 0.01, b = 0.1, c = 0.01, d = 0.1, e = 100$:

$$\frac{dx}{dt} = \left(\frac{0.01 + x^2}{1 + x^2}\right)\left(\frac{1}{1 + y}\right) - 0.1x, \qquad x(0) = D$$

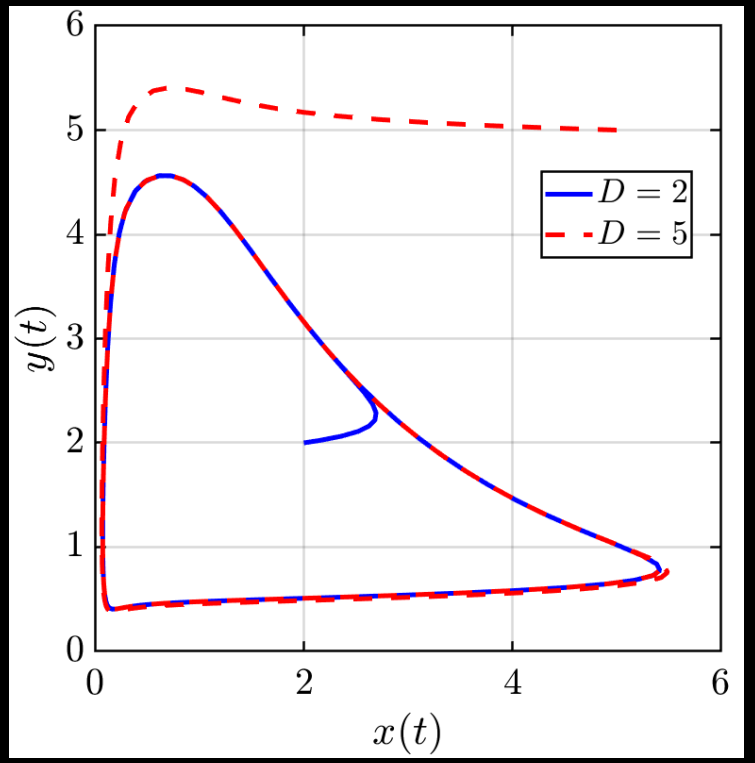
$$\frac{dy}{dt} = 0.01 - \frac{0.1y}{1 + 100x^2}, \qquad y(0) = D$$

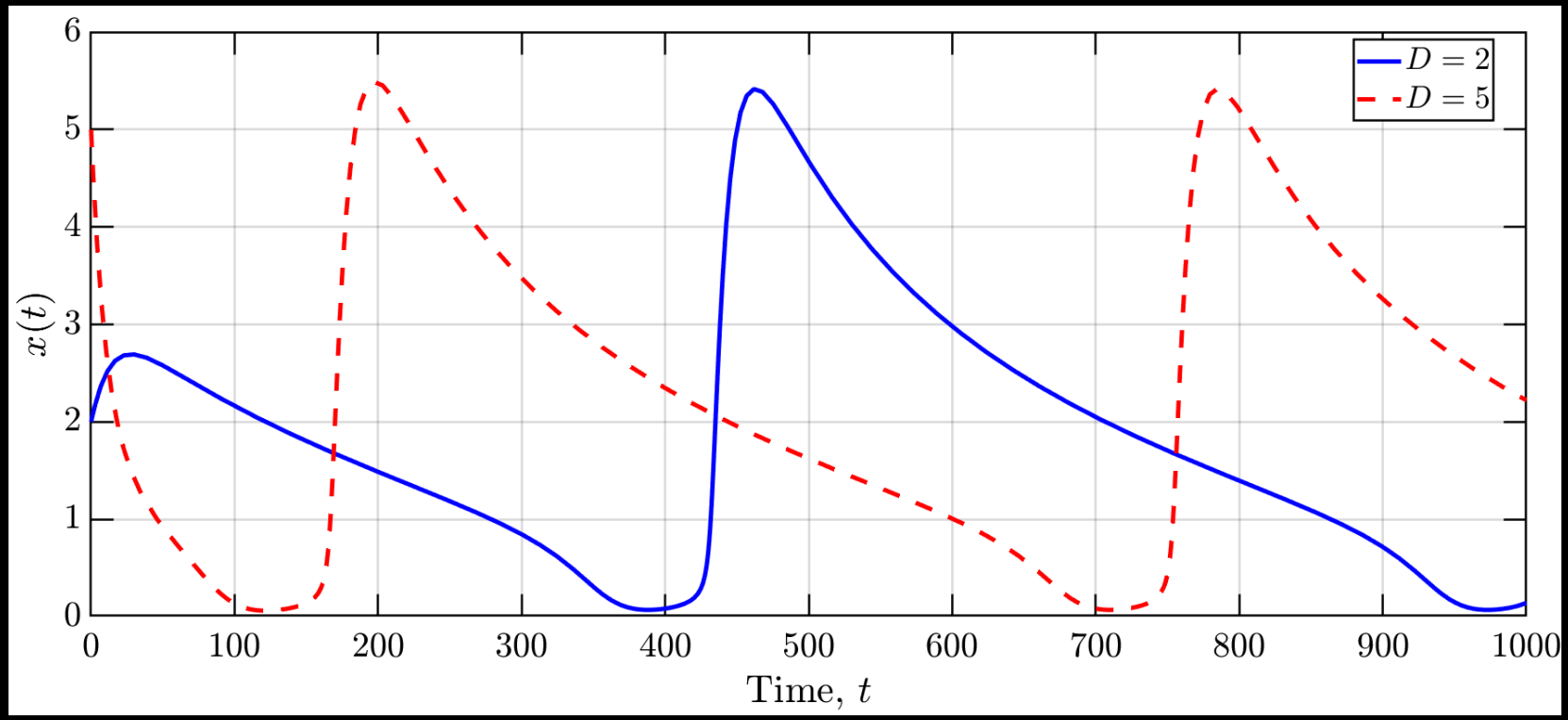
Computational Cell Biology, Fall *et al.*, 2002

Relaxation oscillators – cell cycle



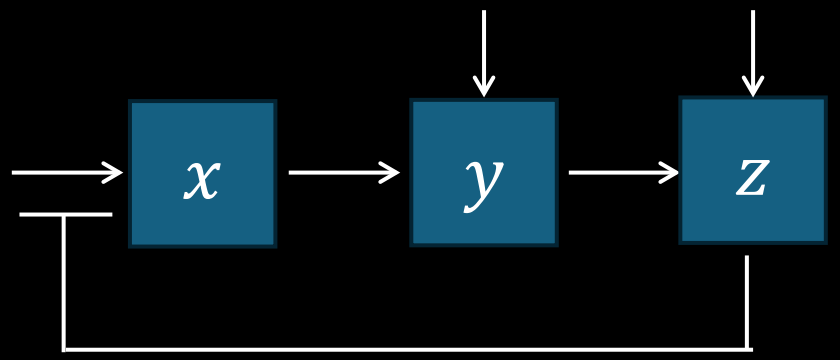

```
[t,y] = ode23s(@(t,y)) [(0.01+y(1).^2)./(1+y(1).^2)./(1+y(2))-0.1.*y(1); 0.01-(0.1.*y(2))./(1+100.*y(1).^2)], [0 1000], [D D]);
```



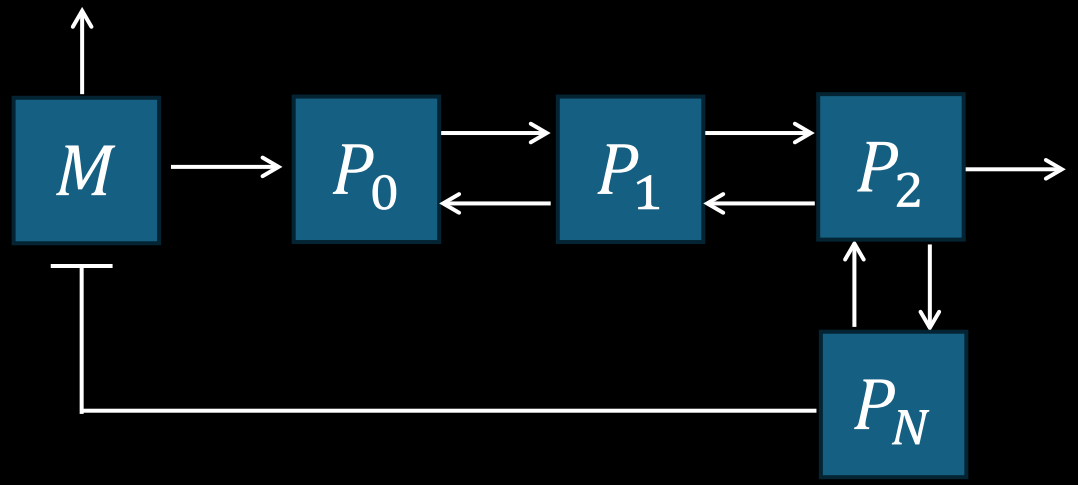


Beyond two species: time-delayed negative feedback

Goodwin model (1965):



Circadian rhythm (Goldbeter, 1995):



Summary

- Many biological systems oscillate over time and a large set of models (both simple and complex) have been formulated to depict their behaviors
- Harmonic oscillators can be modeled by linear systems of ODEs, while relaxation oscillators are nonlinear
- FitzHugh-Nagumo (FHN) and van der Pol (vdP) oscillators have been used as toy models for neural firing for decades
- Other mechanistic models for oscillations in biology include substrate-depletion and activator-inhibitor systems

Spreading the message

- So far, we have considered oscillations that happen within a confined domain, like a single population, an organism, a cell, etc.
- What if the oscillatory behavior of this individual could affect others?

  EXAMPLES: intercellular communication for signaling, infectious disease spreading, fire spreading within a forest
- Under certain conditions, we might expect one system firing could influence areas nearby to also fire and so on, creating a propagating wave
- To understand how this happens, we will again need to consider changes in both space and time

Excitable systems and bistability

- Let's look back at a version of the FitzHugh-Nagumo system:

$$\frac{du}{dt} = u - u^3 - v$$

$$\frac{dv}{dt} = \frac{1}{\mu}(u + a - bv)$$

- We will show that sweeping over different values for the parameter b enables various interesting behaviors

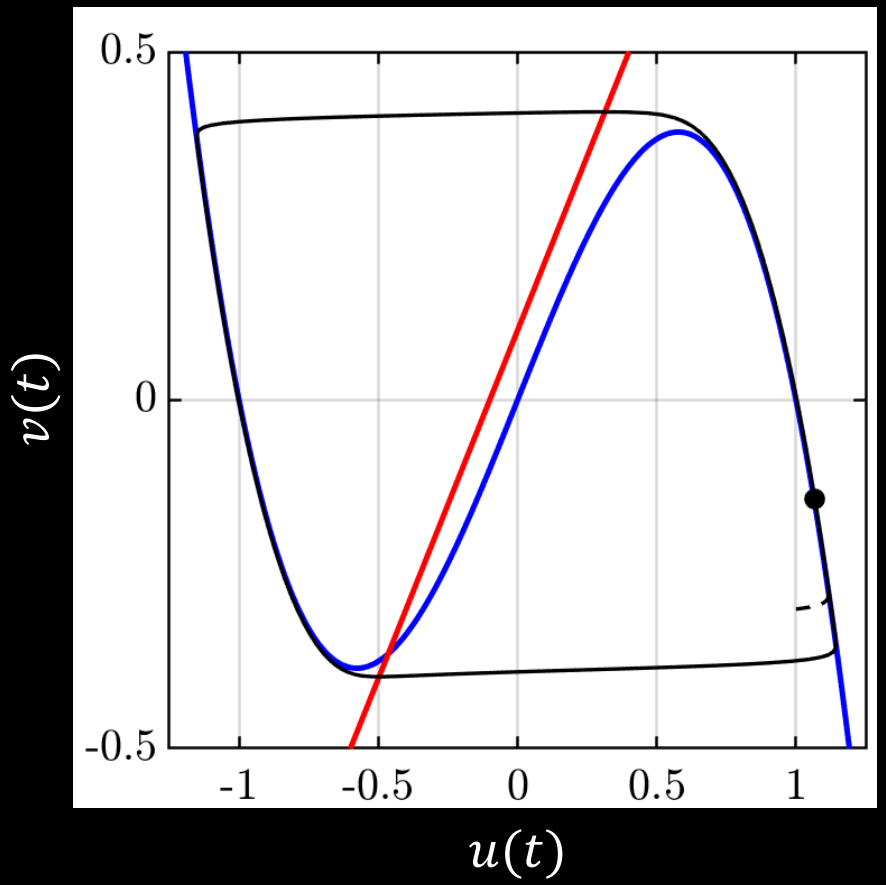
Gelens *et al.*, *MBoC,* 2014

Excitable systems and bistability

- In all cases, let $\mu = 100, a = 0.1$
- For $b = 1$, we get oscillatory behavior:

$$\frac{du}{dt} = u - u^3 - v$$

$$\frac{dv}{dt} = 0.01(u - v + 0.1)$$



Gelens *et al.*, *MBoC*, 2014

Excitable systems and bistability

- If we add diffusion of each component into our system, we get:

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + u - u^3 - v$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + 0.01(u - v + 0.1)$$

- Let's consider some cases where we add an initial pulse into an otherwise homogeneous system…

Gelens *et al.*, *MBoC,* 2014

Excitable systems and bistability

- We can use MATLAB to also simulate systems of PDEs:

$$\underbrace{c\left(x,t,u,\frac{\partial u}{\partial x}\right)}_{\text{coupling}}\frac{\partial u}{\partial t}=x^{-m}\frac{\partial}{\partial x}\left(x^{m}\underbrace{f\left(x,t,u\frac{\partial u}{\partial x}\right)}_{\text{flux}}\right)+\underbrace{s\left(x,t,u,\frac{\partial u}{\partial x}\right)}_{\text{source}}$$

$$a\le x\le b,\qquad t_i\le t\le t_f$$

- Let's look at our equations and pick a domain and some BCs/IC:

$$\frac{\partial u}{\partial t}=D_u\frac{\partial^2 u}{\partial x^2}+u-u^3-v \qquad \Rightarrow c_u=1, f_u=D_u\frac{\partial u}{\partial x}, s_u=u-u^3-v$$

$$\frac{\partial v}{\partial t}=D_v\frac{\partial^2 v}{\partial x^2}+0.01(u-v+0.1) \qquad \Rightarrow c_v=1, f_v=D_v\frac{\partial u}{\partial x}, s_v=0.01(u-v+0.1)$$

$$-200\le x\le 200,\quad 0\le t\le T$$

Excitable systems and bistability

- If we pick no flux boundary conditions for each component, then we can write:

$$p(x,t,u) + q(x,t)f\left(x,t,u,\frac{\partial u}{\partial x}\right) = 0$$

$$p_u(-200,t,u) = p_v(-200,t,v) = 0$$

$$p_u(200,t,u) = p_v(200,t,v) = 0$$

$$q_u(-200,t,u) = q_v(-200,t,v) = 1$$

$$q_u(200,t,u) = q_v(200,t,v) = 1$$

Coding it all up in MATLAB

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + u - u^3 - v,$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + 0.01(u - v + 0.1),$$

$$u(x,0) = -2.2 + 1.6\big(H(x+30) + H(30-x)\big)$$

$$v(x,0) = -0.3$$

```
function [c,f,s] = pdefun(x,t,u,dudx)
Du = 1;
Dv = 1;
a = 0.1;
e = 0.01;
b = 1;
c = [1;1];
f = [Du;Dv].*dudx;
f1 = u(1)-u(1).^3-u(2);
f2 = e*(u(1)-b*u(2)+a);
s = [f1; f2];
end
```

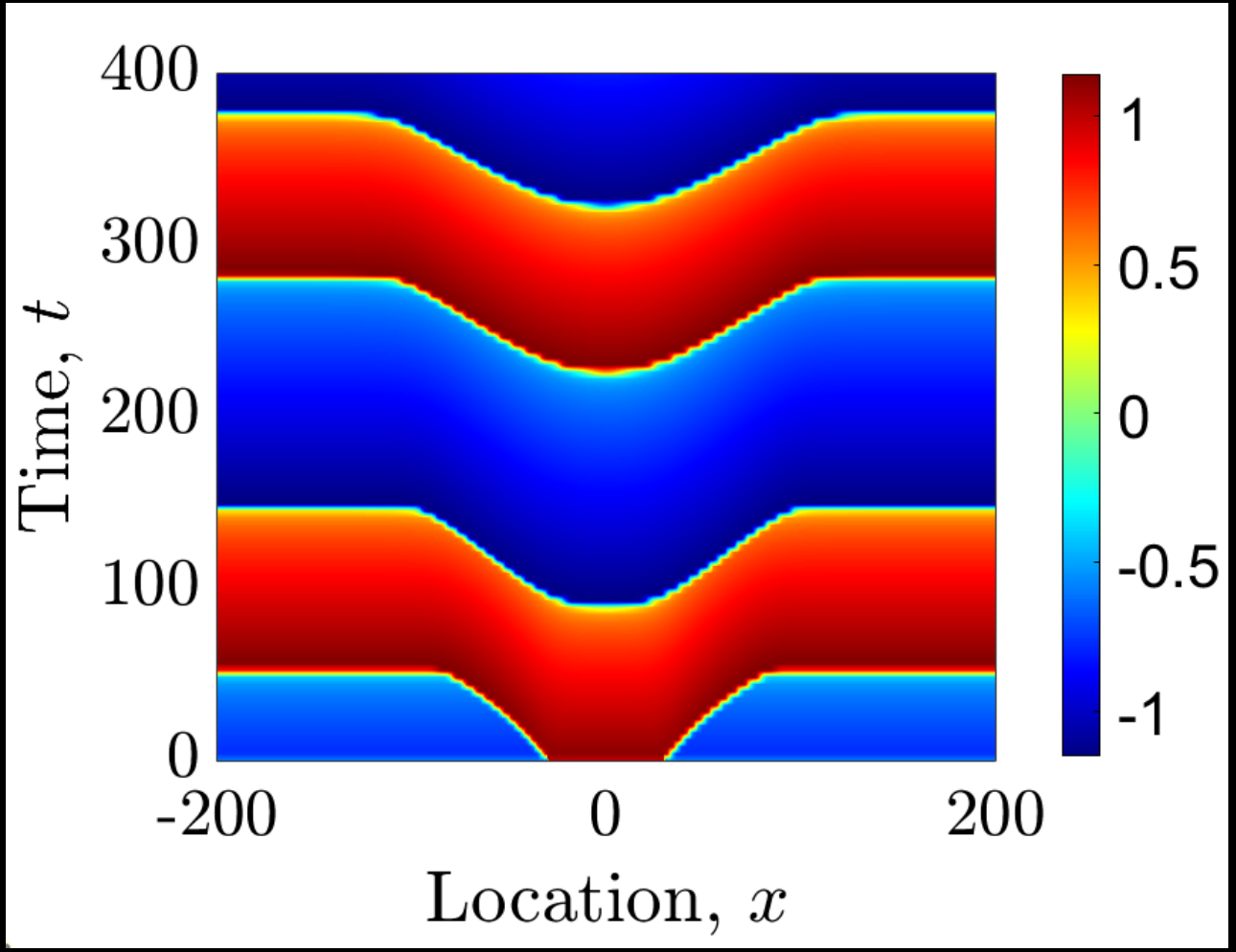
```
function u0 = pdeic(x)
u0 = [-2.2+1.6*(heaviside(x+30)+heaviside(30-
x)); -0.3];
end

function [pl,ql,pr,qr] = pdebc(xl,ul,xr,ur,t)
pl = [0; 0];
ql = [1; 1];
pr = [0; 0];
qr = [1; 1];
end
```

Gelens *et al.*, *MBoC*, 2014

Excitable systems and bistability

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + u - u^3 - v$$

$$\frac{\partial v}{\partial t} = \frac{\partial^2 v}{\partial x^2} + 0.01(u - v + 0.1)$$



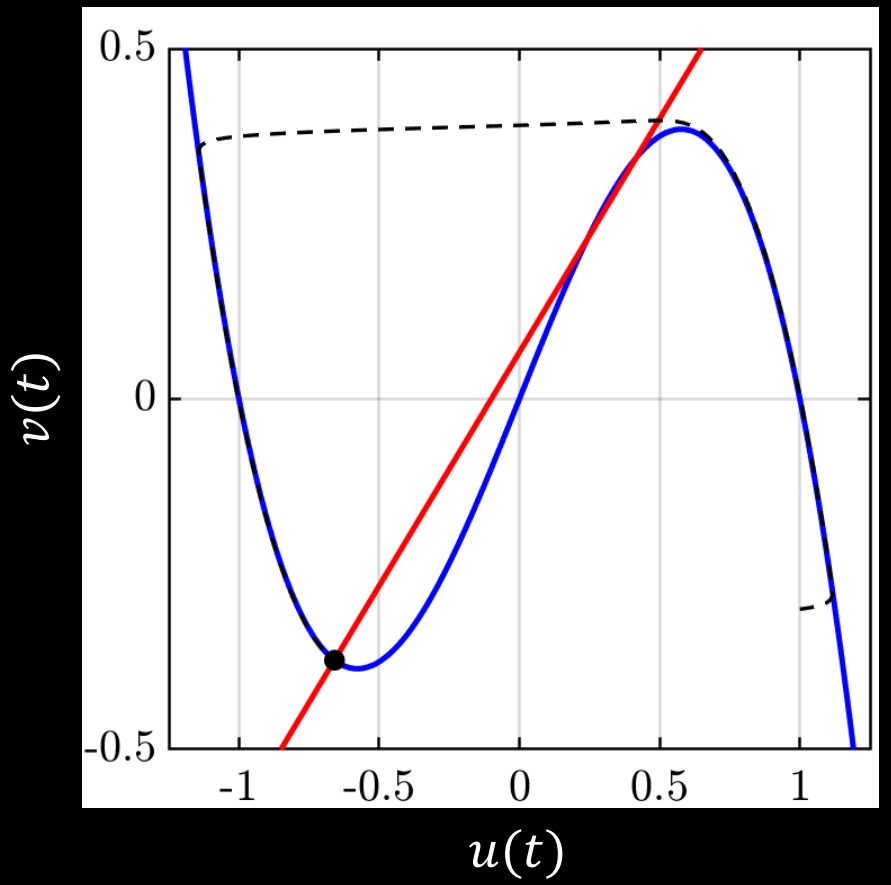
Gelens *et al.*, *MBoC*, 2014

Excitable systems and bistability

- For $b = 1.5$, we get "excitable" behavior:

$$\frac{du}{dt} = u - u^3 - v$$

$$\frac{dv}{dt} = 0.01(u - 1.5v + 0.1)$$



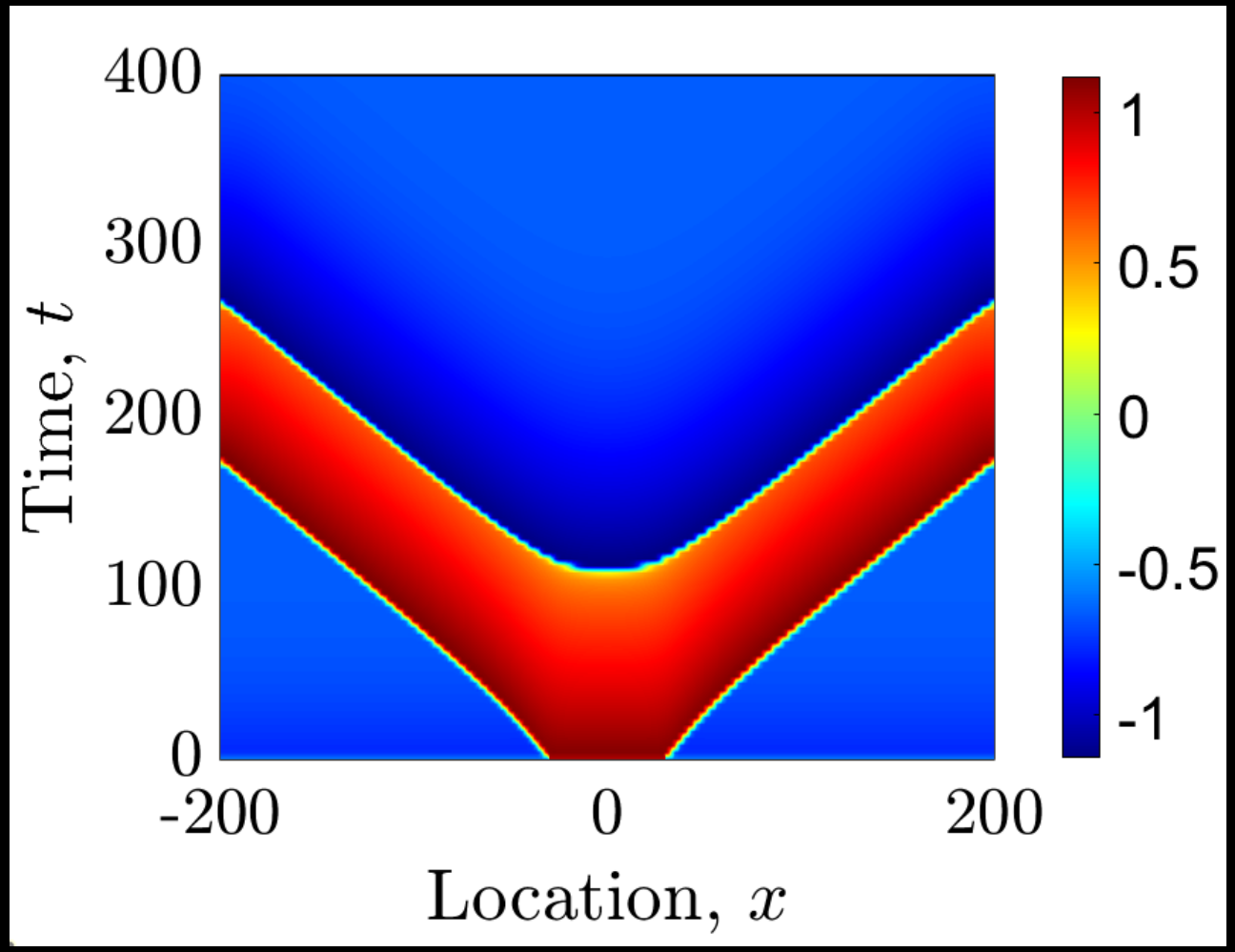
Gelens *et al.*, *MBoC*, 2014

Excitable systems and bistability

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + u - u^3 - v$$

$$\frac{\partial v}{\partial t} = \frac{\partial^2 v}{\partial x^2} + 0.01(u - 1.5v + 0.1)$$

- Adding in diffusion now gives us a single firing before reaching a steady state:



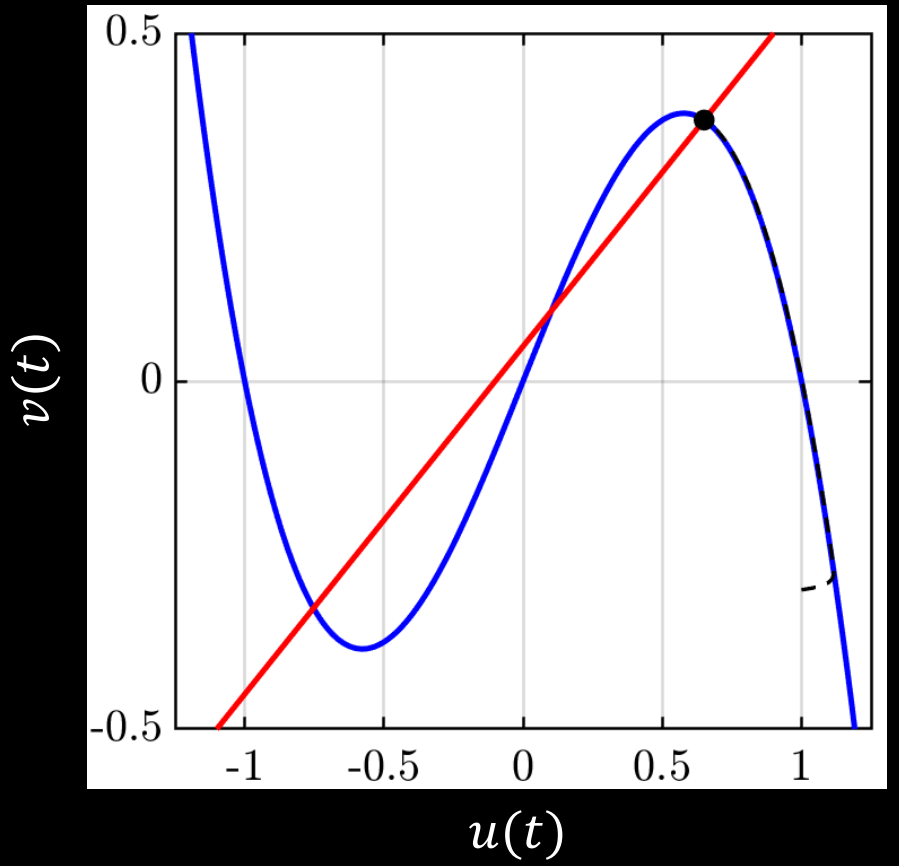
Gelens *et al.*, *MBoC*, 2014

Excitable systems and bistability

- For $b = 2$, we get bistable behavior:

$$\frac{du}{dt} = u - u^3 - v$$

$$\frac{dv}{dt} = 0.01(u - 2v + 0.1)$$



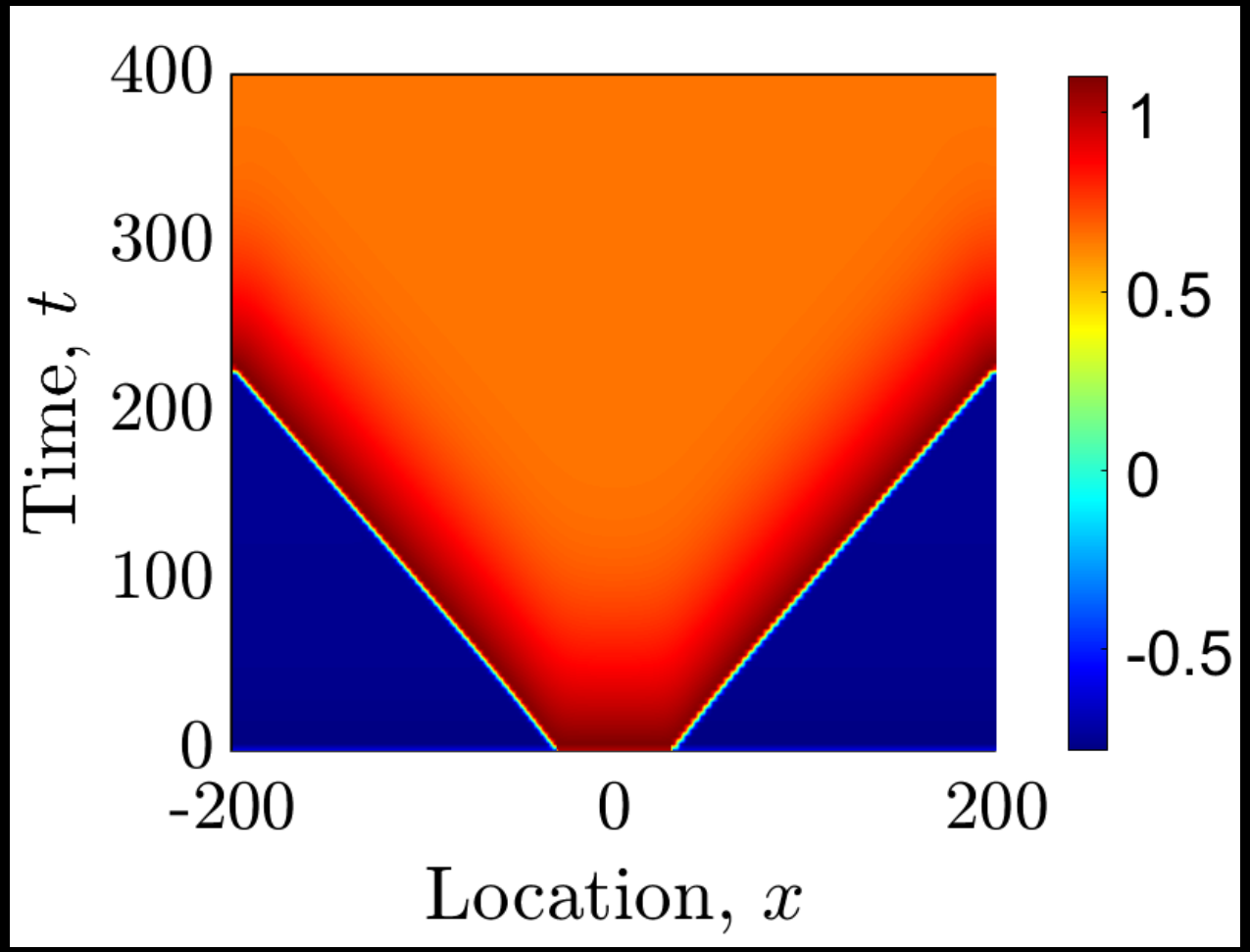
Gelens *et al.*, *MBoC*, 2014

Excitable systems and bistability

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + u - u^3 - v$$

$$\frac{\partial v}{\partial t} = \frac{\partial^2 v}{\partial x^2} + 0.01(u - 2v + 0.1)$$

- Adding in diffusion now just produces a traveling wave where everything stays in a high u state:



Gelens *et al.*, *MBoC*, 2014

Turing patterns and diffusion-driven instabilities

- Let's now look at a generalized reaction-diffusion system:

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + f(u, v)$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + g(u, v)$$

Turing patterns and diffusion-driven instabilities

- Alan Turing (1952) derived the following conditions that need to be satisfied to observe diffusion-driven instabilities (DDI):

just means you can end up with (stable) nonhomogeneous patterns

(1) $$\frac{\partial f(u,v)}{\partial u} + \frac{\partial g(u,v)}{\partial v} < 0$$

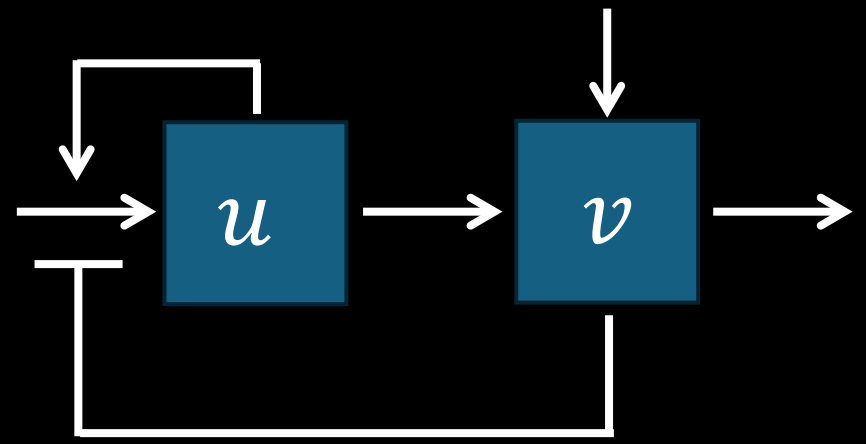
(2) $$\left(\frac{\partial f(u,v)}{\partial u}\right)\left(\frac{\partial g(u,v)}{\partial v}\right) - \left(\frac{\partial f(u,v)}{\partial v}\right)\left(\frac{\partial g(u,v)}{\partial u}\right) > 0$$

(3) $$D_u\left(\frac{\partial g(u,v)}{\partial v}\right) + D_v\left(\frac{\partial f(u,v)}{\partial u}\right) > 2\sqrt{D_u D_v}\sqrt{\left(\frac{\partial f(u,v)}{\partial u}\right)\left(\frac{\partial g(u,v)}{\partial v}\right) - \left(\frac{\partial f(u,v)}{\partial v}\right)\left(\frac{\partial g(u,v)}{\partial u}\right)}$$

Turing, *Phil. Trans. Royal Soc. London B*, 1952
Maini *et al.*, *Interface Focus*, 2012

Gierer-Meinhardt system

- Here is a very common version of a model generated by Gierer and Meinhardt that generates spots/stripes (in 2D) based on differences in diffusion and the value of b



$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + \frac{u^2}{v} - bu$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + u^2 - v$$

Gierer and Meinhardt, *Kybernetik*, 1972

Gierer-Meinhardt system

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + \frac{u^2}{v} - bu,$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + u^2 - v,$$

random values between 0 and 1

$$u(x,0) = 3 * U(0,1) \text{ for all } x$$

$$v(x,0) = 10$$

```
function [c,f,s] = pdefun(x,t,u,dudx)
Du = 1;
Dv = 20;
b = 0.5;
c = [1;1];
f = [Du;Dv].*dudx;
f1 = u(1).^2./u(2)-b*u(1);
f2 = u(1).^2-u(2);
s = [f1; f2];
end
```

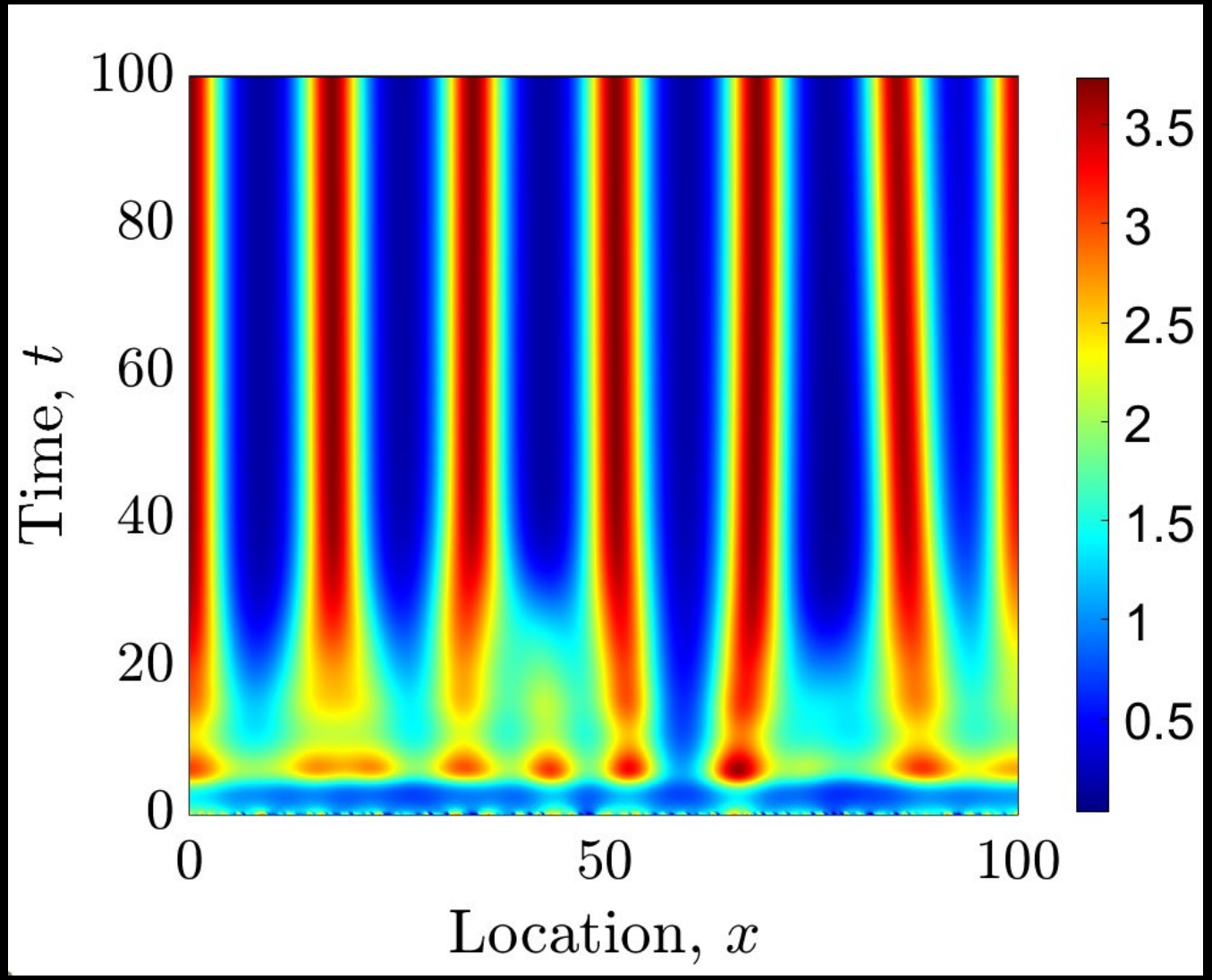
```
function u0 = pdeic(x)
u0 = [3*rand(size(x,2),1); 10];
end
```

```
function [pl,ql,pr,qr] = pdebc(xl,ul,xr,ur,t)
pl = [0; 0];
ql = [1; 1];
pr = [0; 0];
qr = [1; 1];
end
```

Gierer-Meinhardt system

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} + \frac{u^2}{v} - bu$$

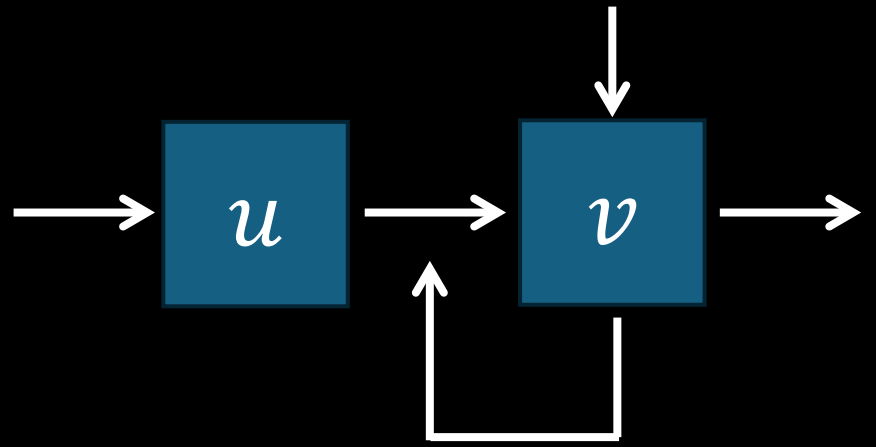
$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + u^2 - v$$



$D_u = 1, D_v = 20, b = 0.5$

Gray-Scott system

- Another pattern-forming model based on Sel'kov's model for glycolysis was generated by Gray and Scott. Here, v interacts with u nonlinearly to produce more v, all while u is being pumped into the system



$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} - uv^2 + F(1-u)$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + uv^2 - (F+k)v$$

Ueyama, *Hokkaido Math. J.*, 1999
Gray and Scott, *Chem. Eng. Sci.*, 1983

Gray-Scott system

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} - uv^2 + F(1-u),$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + uv^2 - (F+k)v,$$

$$u(x,0) = H(x-0.4) + H(0.8-x)$$

$$v(x,0) = 0.1$$

```
function [c,f,s] = pdefun(x,t,u,dudx)
Du = 2e-5;
Dv = 1e-5;
b = 0.06075;
F = 0.04;
c = [1;1];
f = [Du;Dv].*dudx;
f1 = -u(1).*u(2).^2 + F*(1-u(1));
f2 = u(1).*u(2).^2 - (F+b).*u(2);
s = [f1; f2];
end
```

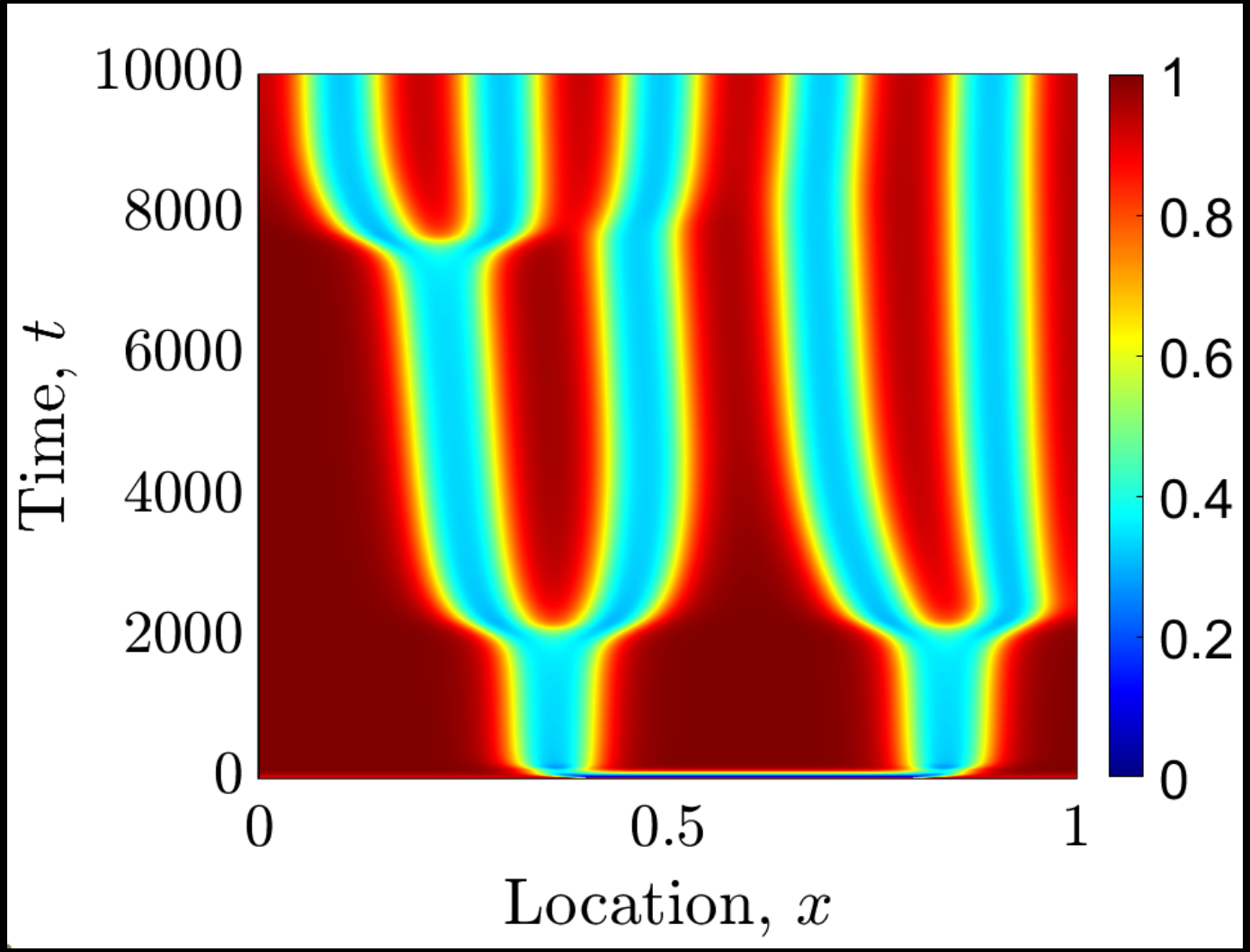
```
function u0 = pdeic(x)
u0 = [(heaviside(x-0.4)+heaviside(0.8-x));0.1];
end
```

```
function [pl,ql,pr,qr] = pdebc(xl,ul,xr,ur,t)
pl = [0; 0];
ql = [1; 1];
pr = [0; 0];
qr = [1; 1];
end
```

Gray-Scott system

$$\frac{\partial u}{\partial t} = D_u \frac{\partial^2 u}{\partial x^2} - uv^2 + F(1-u)$$

$$\frac{\partial v}{\partial t} = D_v \frac{\partial^2 v}{\partial x^2} + uv^2 - (F+k)v$$



$D_u = 2 * 10^{-5}, D_v = 10^{-5}, F = 0.04, k = 0.06075$

Summary

- Local excitation can kickstart a traveling wave, where diffusion/advection and/or the governing reactions between interacting species can all dictate properties of the wave(s)
- Based on parameters of the system, one can have oscillatory waves, excitable waves, or bistable wave behavior
- Activator-inhibitor systems are a well-studied class of reaction-diffusion systems that can produce stable areas of high activity/concentrations in the forms of spots/stripes
- Large areas of mathematical biology research have been devoted to understanding various aspects of patterning and wave propagation, especially within the context of developmental (and regeneration) biology