Pattern Formation in Chemical and Biological Systems

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CSUMS Lecture, College of William and Mary
February 18th, 2009

Reaction-Diffusion Equations

Many biological processes can be simulated by mathematical models involving temporal and spatial variables.

Example:

a video of cell division

a video of simulation of a reaction-diffusion system

Reaction-diffusion systems are mathematical models that describe how the concentration of one or more substances distributed in space changes under the influence of two processes: local chemical reactions in which the substances are converted into each other, and diffusion which causes the substances to spread out in space.

Mathematical Models

$$\frac{\partial u(x,t)}{\partial t} = D_1 \Delta u(x,t) + f(u(x,t), v(x,t)),$$
$$\frac{\partial v(x,t)}{\partial t} = D_2 \Delta v(x,t) + g(u(x,t), v(x,t)).$$

t: time variable, $x = (x_1, x_2)$: spatial variable

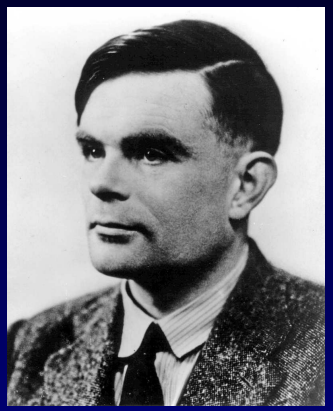
$u(x,t)$, $v(x,t)$: density of substances at time t and location x

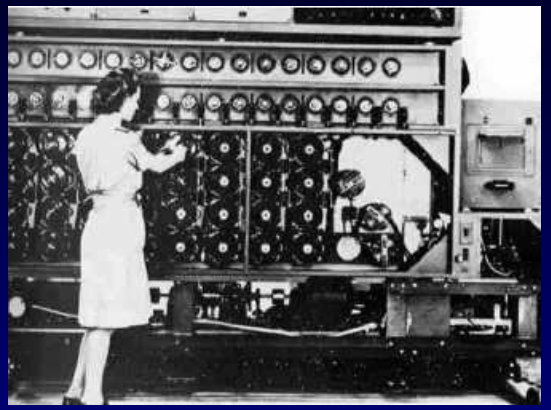
$$\Delta u(x,t) = div(\nabla u(x,t)) = \frac{\partial^2 u(x,t)}{\partial x_1^2} + \frac{\partial^2 u(x,t)}{\partial x_2^2}$$

Δu, Δv are Diffusion: transport of molecules from a region of higher concentration to one of lower concentration by random molecular motion.

$f(u,v)$, $g(u,v)$ are Reaction: death/birth, chemical reaction/generation

Alan Turing (1912-1954)





- One of greatest scientists in 20th century
- Designer of Turing machine (a theoretical computer) in 1930s
- Designing electromechanical machine which breaks German U-boat Enigma, helping the battle of the Atlantic
- Initiate nonlinear theory of biological growth
  [Turing, 1952] The Chemical Basis of Morphogenesis.
  Philosophical transaction Royal Society of London Series B, **237**

http://www.turing.org.uk/

Turing's idea

ODE (1): $u' = f(u, v)$, $v' = g(u, v)$

Reaction-diffusion system (2): $u_t = d_1 \Delta u + f(u, v)$, $v_t = d_2 \Delta v + g(u, v)$

Here $u(x, t)$ and $v(x, t)$ are the density functions of two chemicals (morphogen) or species which interact or react

- A constant solution $u(t, x) = u_0$, $v(t, x) = v_0$ can be a stable solution of (1), but an unstable solution of (2). Thus the instability is induced by diffusion.
- On the other hand, there must be stable non-constant equilibrium solutions, or stable non-equilibrium behavior, which have more complicated spatial-temporal structure.

`http://en.wikipedia.org/wiki/Morphogen`

Oscillatory Chemical Reactions

An example of oscillatory chemical reaction (don’t do this in home though ...)

Chemical reactions were believed to always reach equilibrium states even when the reactions are reversible. But the discoveries since 1960s confirm the existence of chemical oscillations. It is now believed that every living system contains hundreds of chemical oscillators.

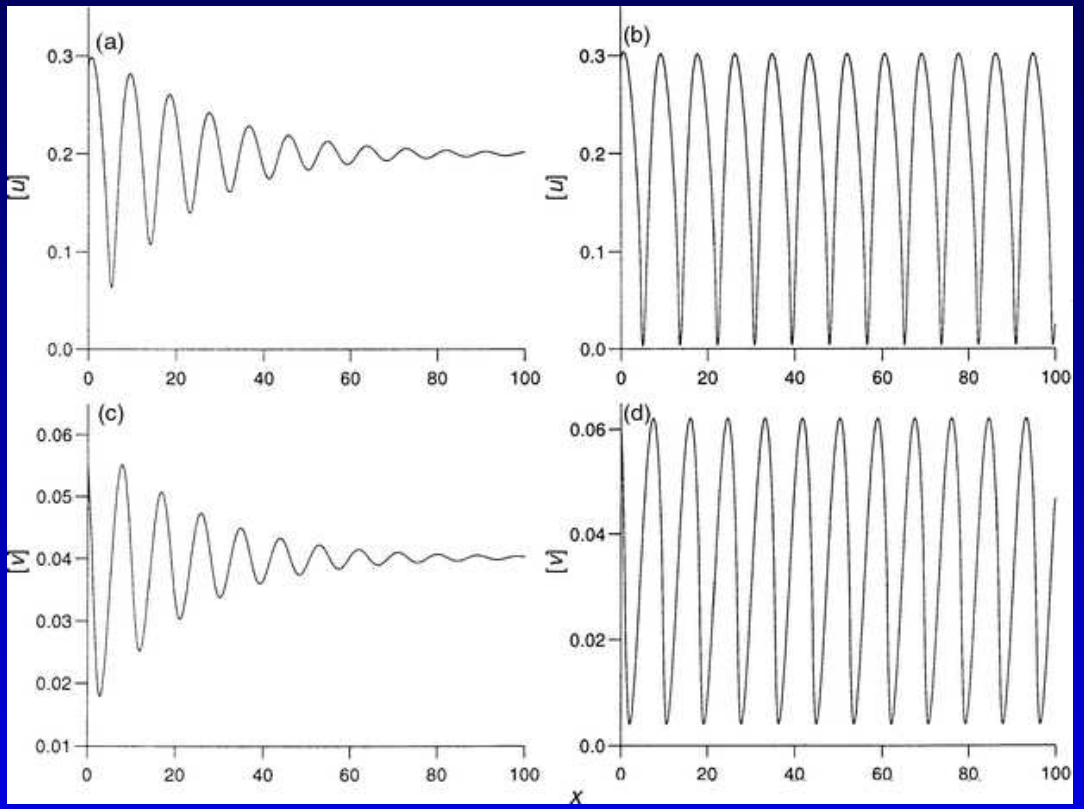
Equilibrium solutions and Periodic solutions

For a dynamical system (ODE, reaction-diffusion model, etc)

Equilibrium solutions are the ones independent of time

Periodic solutions are the ones which repeats itself in time.

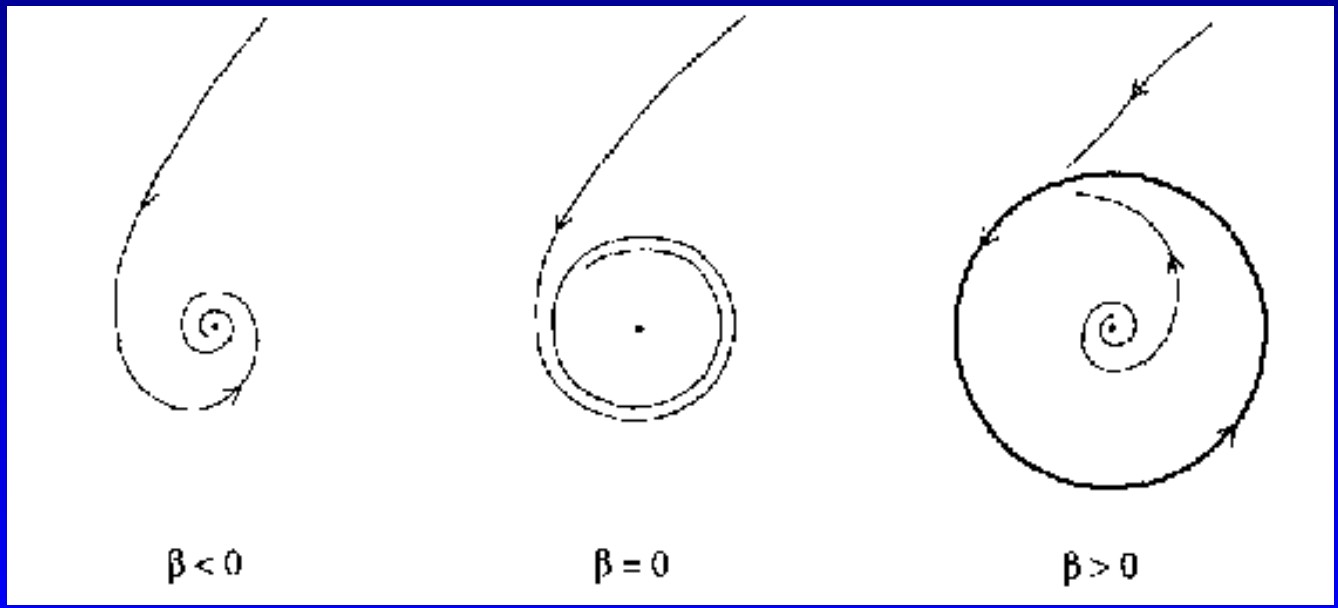
They usually dominate the long time behavior of the dynamical system



Hopf Bifurcation Theorem

Consider ODE $x' = f(\lambda, x)$, $\lambda \in \mathbf{R}$, $x \in \mathbf{R}^n$, and f is smooth.
(i) Suppose that for λ near λ_0 the system has a family of equilibria $x^0(\lambda)$.
(ii) Assume that its Jacobian matrix $A(\lambda) = f_x(\lambda, x^0(\lambda))$ has one pair of complex eigenvalues $\mu(\lambda) \pm i\omega(\lambda)$, $\mu(\lambda_0) = 0$, $\omega(\lambda_0) > 0$, and all other eigenvalues of $A(\lambda)$ have non-zero real parts for all λ near λ_0.

If $\mu'(\lambda_0) \neq 0$, then the system has a family of periodic solutions $(\lambda(s), x(s))$ for $s \in (0, \delta)$ with period $T(s)$, such that $\lambda(s) \to \lambda_0$, $T(s) \to 2\pi/\omega(\lambda_0)$, and $||x(s) - x^0(\lambda_0)|| \to 0$ as $s \to 0^+$.

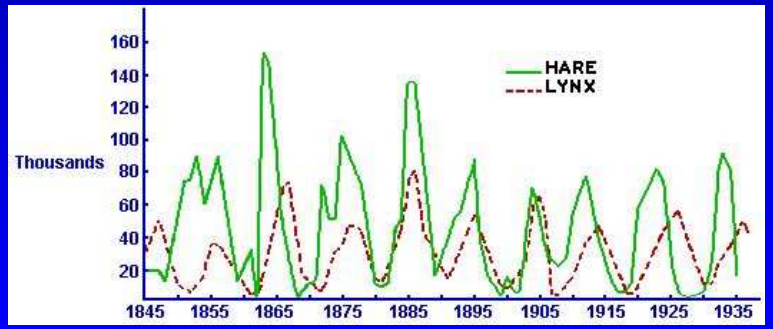


Lotka-Volterra model

Alfred Lotka (1880-1949) Vito Volterra (1860-1940)

$$\frac{du}{dt} = u(a - bu) - cuv,$$
$$\frac{dv}{dt} = -dv + fuv.$$

$a, b, c, d > 0$



Functional response

$$\begin{cases} \dfrac{du}{dt} = u(a - bu) - c\phi(u)v, \\ \dfrac{dv}{dt} = -dv + f\phi(u)v. \end{cases}$$

$\phi(u)$: predator functional response

$\phi(u) = u$ (Lotka-Volterra)

$\phi(u) = \dfrac{u}{1 + mu}$ (Holling type II, m: the handling time of prey)

[Holling, 1959](Michaelis-Menton biochemical kinetics)

Biological work:

[Rosenzweig-MacArthur, *American Naturalist* 1963]

[Rosenzweig, *Science*, 1971] (Paradox of enrichment)

[May, *Science*, 1972] (Existence and uniqueness of limit cycle)

Basic analysis of the model

$$\frac{du}{dt} = u\,(1-u) - \frac{muv}{a+u}, \quad \frac{dv}{dt} = -dv + \frac{muv}{a+u}$$

Nullcline(isocline): $u = 0$, $v = \dfrac{(1-u)(a+u)}{m}$; $v = 0$, $d = \dfrac{mu}{a+u}$.

Solving $d = \dfrac{mu}{a+u}$, one have $u = \lambda \equiv \dfrac{ad}{m-d}$.

Equilibrium points: $(0,0)$, $(1,0)$, (λ, v_λ) where $v_\lambda = \dfrac{(1-\lambda)(a+\lambda)}{m}$

We take λ as a bifurcation parameter

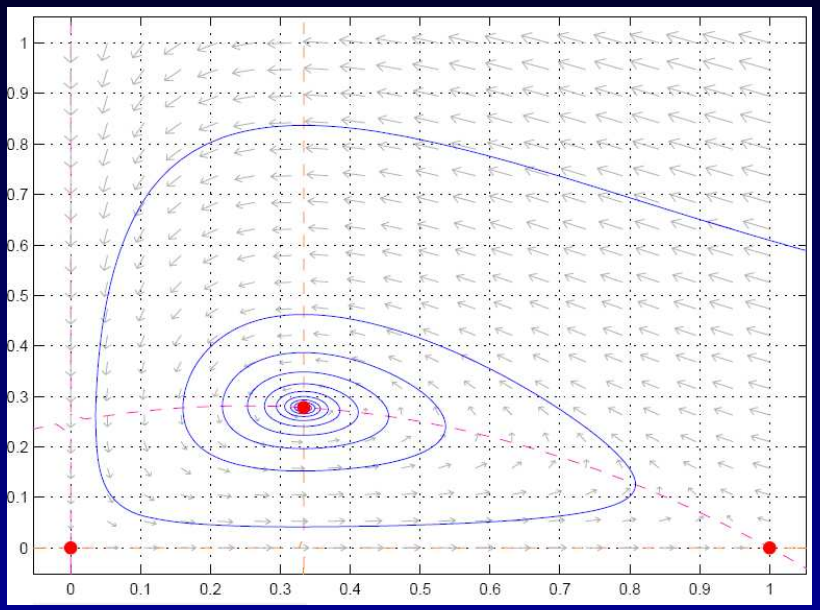
Case 1: $\lambda \geq 1$: $(1,0)$ is globally asymptotically stable

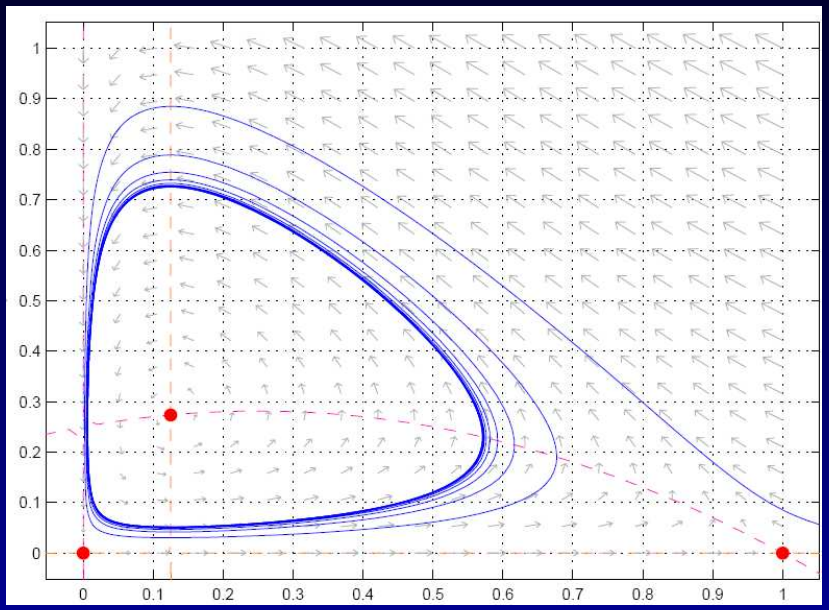
Case 2: $(1-a)/2 < \lambda < 1$: $(1,0)$ is a saddle, and (λ, v_λ) is a locally stable equilibrium

Case 3: $0 < \lambda < (1-a)/2$: $(1,0)$ is a saddle, and (λ, v_λ) is a locally unstable equilibrium

($\lambda = (1-a)/2$ is a Hopf bifurcation point)

Phase portrait





Left: $(1-a)/2 < \lambda < 1$: $(1,0)$ is a saddle, and (λ, v_λ) is a locally stable equilibrium

Right: $0 < \lambda < (1-a)/2$: $(1,0)$ is a saddle, and (λ, v_λ) is a locally unstable equilibrium; there exists a limit cycle

Summary

$$\frac{du}{dt} = u\,(1-u) - \frac{muv}{a+u}, \quad \frac{dv}{dt} = -dv + \frac{muv}{a+u}$$

Nullcline(isocline): $u = 0$, $v = \dfrac{(1-u)(a+u)}{m}$; $v = 0$, $d = \dfrac{mu}{a+u}$.

Solving $d = \dfrac{mu}{a+u}$, one have $u = \lambda \equiv \dfrac{ad}{m-d}$.

Equilibrium points: $(0,0)$, $(1,0)$, (λ, v_λ) where $v_\lambda = \dfrac{(1-\lambda)(a+\lambda)}{m}$

We take λ as a bifurcation parameter

Case 1: $\lambda \geq 1$: $(1,0)$ is globally asymptotically stable

Case 2: $(1-a)/2 < \lambda < 1$: (λ, v_λ) is a globally asymptotically stable

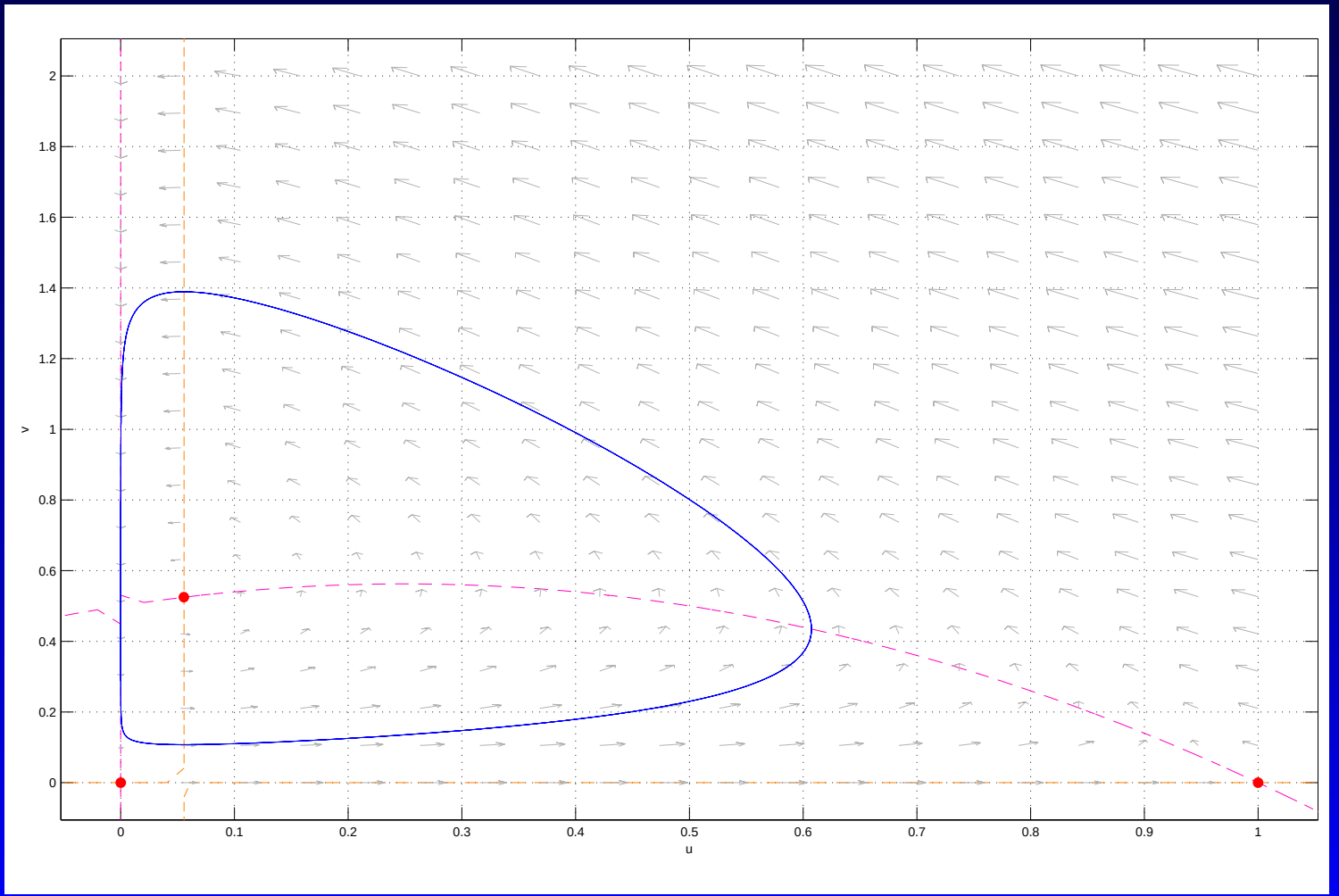
Case 3: $0 < \lambda < (1-a)/2$: the unique limit cycle is globally asymptotically stable

($\lambda = (1-a)/2$ is a Hopf bifurcation point)

New result of this ODE

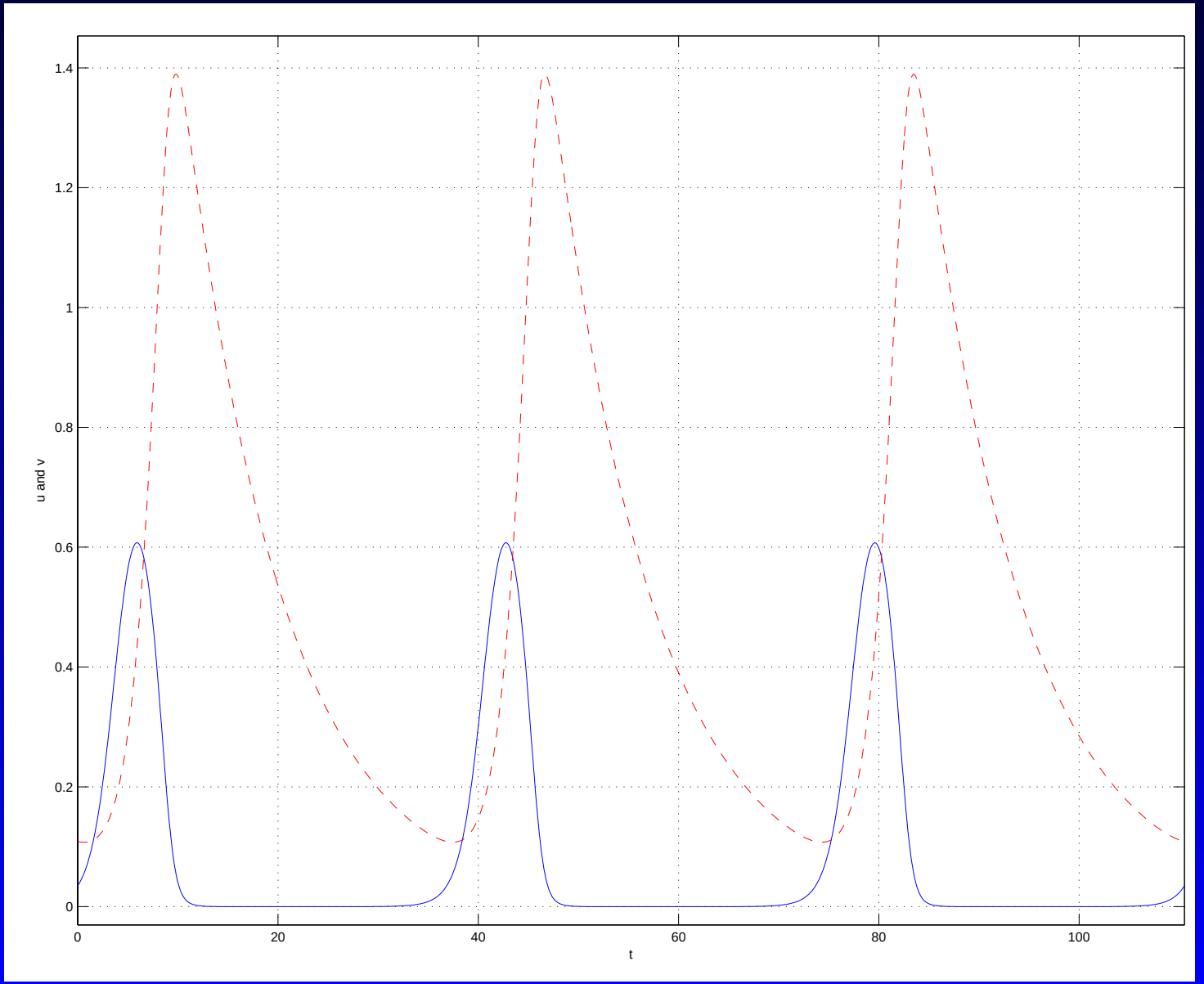
[Hsu-Shi, 2009] Hsu, Sze-Bi; Shi, Junping, Relaxation oscillator profile of limit cycle in predator-prey system. Disc. Cont. Dyna. Syst.-B

(Motivated by numerical observation)



Graph of limit cycle

Parameters: $a = 0.5$, $m = 1$, $d = 0.1$, $\lambda = 1/18 \approx 0.056$, period $T \approx 37$.



More on limit cycles

limit cycle in physiology: neuron,
FitzHugh-Nagumo model
FitzHugh-Nagumo simulation calcium signaling

limit cycle for PDE: CIMA reaction (next lecture),
Twinkling eyes pattern (spatial limit cycle) simulation
More simulation by Lingfa Yang (Brandeis University)

pattern formation: interaction of Turing instability and Hopf instability