

# W2-Note

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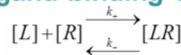
2023-08-08

## W2. Intro to Dynamical Systems

Systems of ODE:

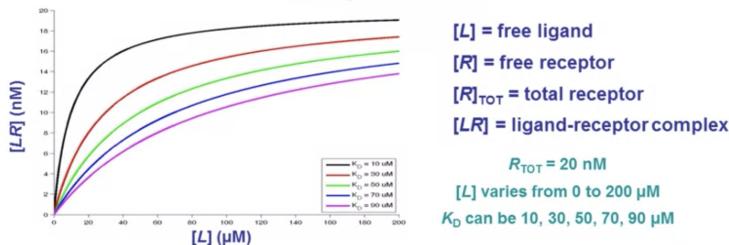
### Systems of Ordinary Differential Equations

Consider ligand binding to a receptor



In the steady-state, bound receptor can be calculated as:

$$[LR] = \frac{R_{TOT} [L]}{K_D + [L]} \quad K_D = \frac{k_-}{k_+}$$



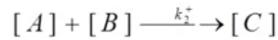
What about non-steady-state solutions?

## Law of mass action

The rate of an elementary reaction (a reaction that proceeds through only one transition state, that is one mechanistic step) is proportional to the product of the concentrations of the participating molecules. (source: Wikipedia)



$$\text{Forward rate (concentration/time)} = k_1^+ [A]$$



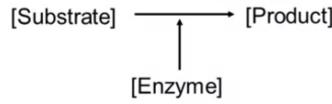
$$\text{Forward rate} = k_2^+ [A][B]$$

[A], [B], [C] = generic chemical species

Law of mass action

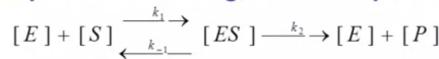
## Enzyme-catalyzed reactions

Frequently shorthand is used



$[S]$  = free substrate  
 $[E]$  = free enzyme  
 $[E]_{\text{TOT}}$  = total enzyme  
 $[P]$  = product

This shorthand implies the following, more complete reaction scheme:



Michaelis-Menten kinetics are usually assumed

$$V_0 = \frac{dP}{dt} = \frac{V_{\max} [S]}{K_M + [S]}$$

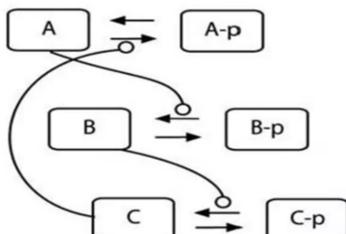
with variable definitions:  
 $V_{\max} = k_2 [E]_{\text{TOT}}$      $K_M = \frac{k_{-1} + k_2}{k_1}$

### Enzyme-catalyzed reactions

### More complicated biochemical reactions

#### More complicated biochemical reactions

The full set of equations underlying this scheme



$$\begin{aligned} \frac{d[A]}{dt} &= \frac{k_{p1}([A]_T - [A])}{[A]_T + K_{p1}} - \frac{k_{k1}[A][C]}{[A] + K_{k1}} \\ \frac{d[B]}{dt} &= \frac{k_{p2}([B]_T - [B])[A]}{[B]_T + [B] + K_{p2}} - \frac{k_{k2}[B]}{[B] + K_{k2}} \\ \frac{d[C]}{dt} &= \frac{k_{p3}([C]_T - [C])[B]}{[C]_T + [C] + K_{p3}} - \frac{k_{k3}[C]}{[C] + K_{k3}} \end{aligned}$$

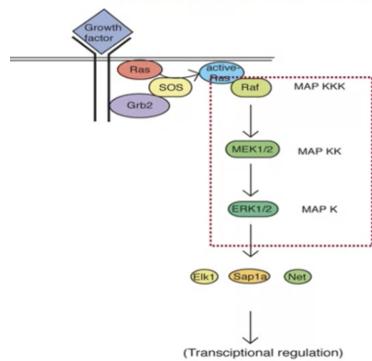
Mogilner et al., *Developmental Cell* 11:279–287, 2006

Two questions we need to address:

- (1) Why only 3 equations rather than 6?
- (2) Why do the 3 equations share a characteristic structure?

#### More complicated biochemical reactions

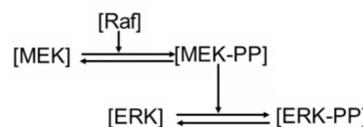
Sometimes the shorthand is even more extreme



Summary of Map kinase pathway

Diagram from the RIKEN BioResource Center:  
<http://www.brc.riken.jp/>

What this really means is:



Equations can be derived from this scheme, not from scheme on the left

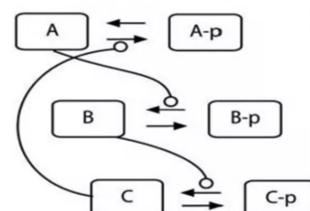
$[\text{Raf}]$ ,  $[\text{MEK}]$ ,  $[\text{ERK}]$  = proteins involved in mitogen-activated protein kinase signaling  
 $[-\text{PP}]$  = doubly phosphorylated form

Sometimes considerable prior biological knowledge is required to derive equations from cartoons describing mechanisms.

#### More complicated biochemical

Example: a generic three-component representation

Equations just for  $[A]$  a



$$\frac{d[A]}{dt} = \frac{k_{p1}[AP]}{[AP] + K_{p1}} - \frac{k_{k1}[A][C]}{[A] + K_{k1}}$$

$$\frac{d[AP]}{dt} = \frac{k_{k1}[A][C]}{[A] + K_{k1}} - \frac{d[AP]}{dt}$$

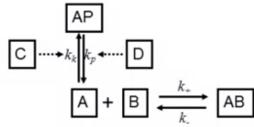
Mogilner et al., *Developmental Cell* 11:279–287, 2006

Notice that:  
 $\frac{d[A]}{dt} = -\frac{d[AP]}{dt}$  Sa

One equation can be eliminated, substitute: [A]

$$\frac{d[A]}{dt} = \frac{k_{p1}([A]_T - [A])}{[A]_T - [A] + K_{p1}} - \frac{k_{k1}[A][C]}{[A] + K_{k1}}$$

## Self-assessment question



$$\frac{d[A]}{dt} = -\frac{k_k[C][A]}{[A] + K_k} + \frac{k_p[D][AP]}{[AP] + K_p} - k_+[A][B] + k_-[AB]$$

(1) Decrease due to phosphorylation  
 (2) Increase due to dephosphorylation  
 (3) decrease due to binding to B  
 (4) increase due to AB dissociation

(B)  $\frac{d[A]}{dt} = \frac{k_k[C][A]}{[A] + K_k} - \frac{k_p[D][AP]}{[AP] + K_p}$  actually the ODE for [AP]

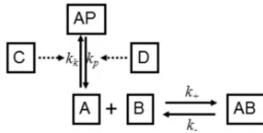
(D)  $\frac{d[A]}{dt} = k_+[A][B] - k_-[AB]$  actually the ODE for [AB]

(A)  $\frac{d[A]}{dt} = -\frac{k_k[D][A]}{[A] + K_k} + \frac{k_k[D][A]}{[A] + K_k} - k_+[A][B] + k_-[AB]$  this one just has mistakes

Example question

## Self-assessment question

Consider the reaction scheme below. Proteins A and B can bind to form complex AB. When it is free, but r when it is bound to B, protein A can be phosphorylated. Phosphorylated A, A-P, can be dephosphorylated. Phosphorylation and dephosphorylation reactions, respectively, are catalyzed by proteins C and D. These two proteins, respectively, have K\_M's K\_k and K\_p (for kinase and phosphatase). Rate constants are listed. Which is the correct ODE for A, the unbound, dephosphorylated form of the protein?



(A)  $\frac{d[A]}{dt} = -\frac{k_k[D][A]}{[A] + K_k} + \frac{k_k[D][A]}{[A] + K_k} - k_+[A][B] + k_-[AB]$

(B)  $\frac{d[A]}{dt} = \frac{k_k[C][A]}{[A] + K_k} - \frac{k_p[D][AP]}{[AP] + K_p}$

**(C)**  $\frac{d[A]}{dt} = -\frac{k_k[C][A]}{[A] + K_k} + \frac{k_p[D][AP]}{[AP] + K_p} - k_+[A][B] + k_-[AB]$

(D)  $\frac{d[A]}{dt} = -k_+[A][B] + k_-[AB]$

## Euler's method

$$\frac{dx}{dt} = f(x) \quad x(t=0) = x_0$$

$$\frac{dx}{dt} \approx \frac{x(t + \Delta t) - x(t)}{\Delta t} \quad \frac{x(t + \Delta t) - x(t)}{\Delta t} = f(x)$$

$$x(t + \Delta t) = x(t) + f(x) \cdot \Delta t$$

So, we start with  $x(0)$ , which is known

$$x(\Delta t) = x(0) + f(x(0)) \cdot \Delta t$$

Now  $x(\Delta t)$  is known

$$x(2\Delta t) = x(\Delta t) + f(x(\Delta t)) \cdot \Delta t$$

$$x(3\Delta t) = x(2\Delta t) + f(x(2\Delta t)) \cdot \Delta t$$

Euler's method for solving ODE systems:

# Summary

Euler's method is the simplest and most straightforward algorithm for solving ODEs numerically

Euler's method is based on approximating the derivative for small values of  $\Delta t$

$$\frac{dx}{dt} = \lim_{\Delta t \rightarrow 0} \frac{x(t + \Delta t) - x(t)}{\Delta t} \quad \frac{dx}{dt} \approx \frac{x(t + \Delta t) - x(t)}{\Delta t} \text{ for small } \Delta t$$

Because Euler's method sometimes fails, more complex numerical algorithms are preferred for most models of biological interest

**Analyzing stability of ODE systems**

Example: a generic three-component repressive network

The scheme implies a set of differential equations

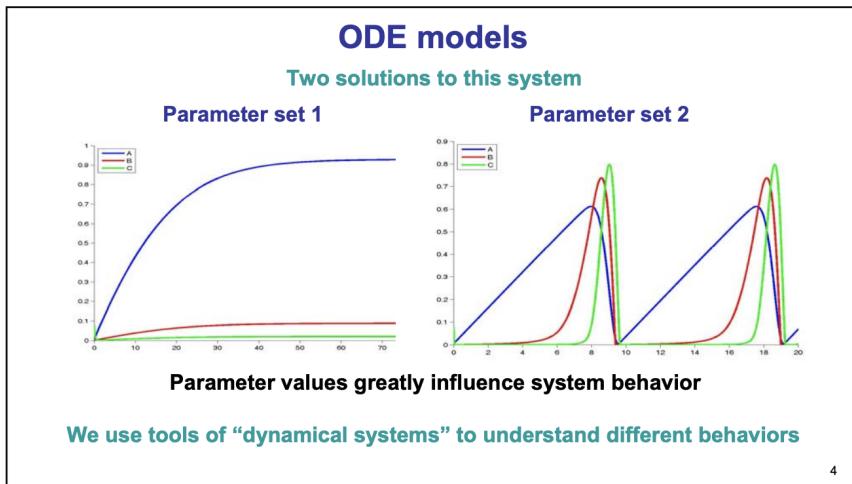
$$\frac{d[A]}{dt} = \frac{k_{p1}([A]_T - [A]) - k_{k1}[A][C]}{[A]_T - [A] + K_{p1}} \quad \frac{d[B]}{dt} = \frac{k_{p2}([B]_T - [B])[A] - k_{k2}[B]}{[B]_T - [B] + K_{p2}} \quad \frac{d[C]}{dt} = \frac{k_{p3}([C]_T - [C])[B] - k_{k3}[C]}{[C]_T - [C] + K_{p3}}$$

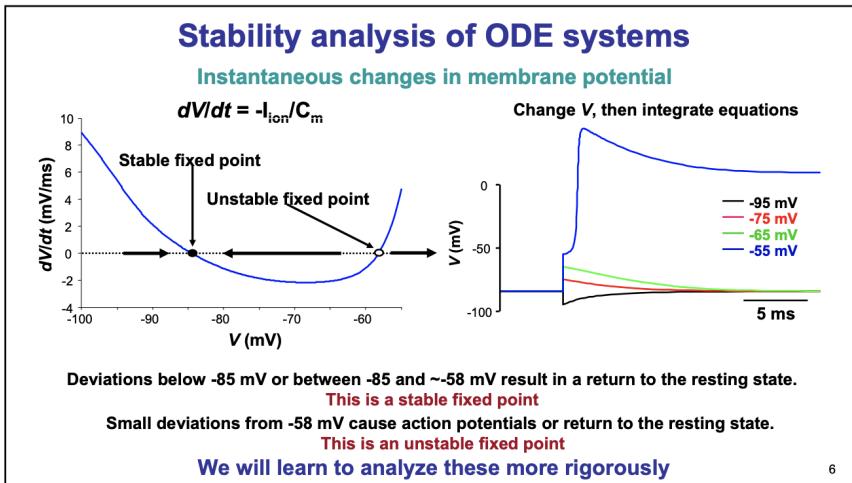
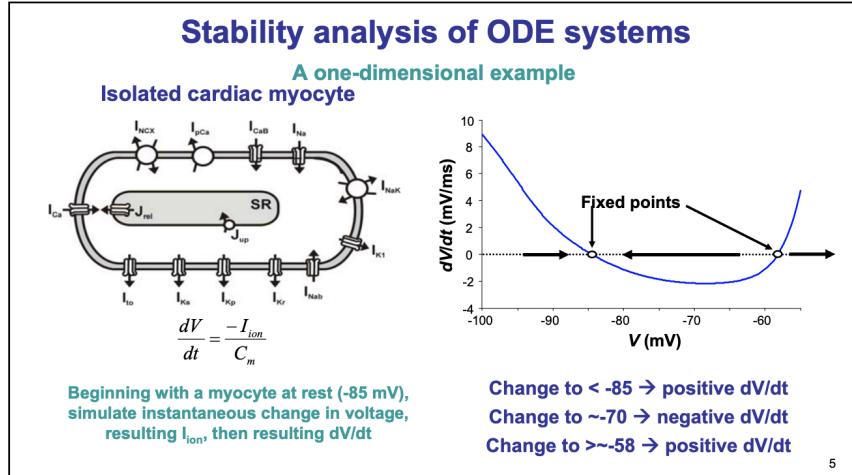
Mogilner et al., *Developmental Cell* 11:279–287, 2006

**Model parameters:**  
 $k_{cat}$ 's and  $K_m$ 's for phosphorylation reactions  
 $k_{cat}$ 's and  $K_m$ 's for dephosphorylations  
total amounts of [A], [B], and [C]

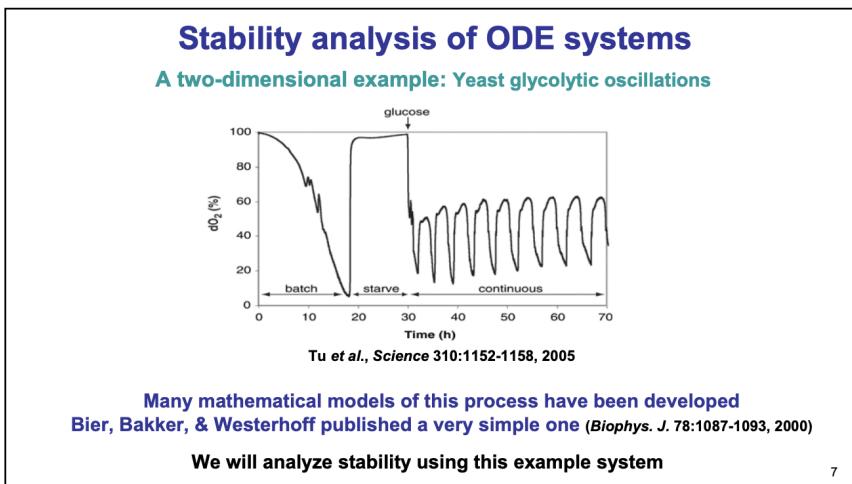
The equations are solved using standard numerical techniques

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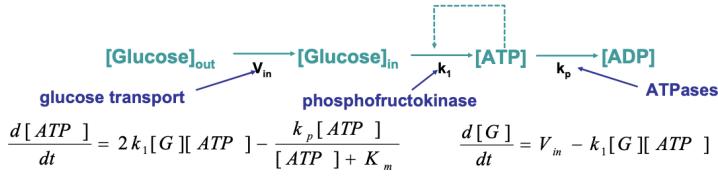


## 2D Example

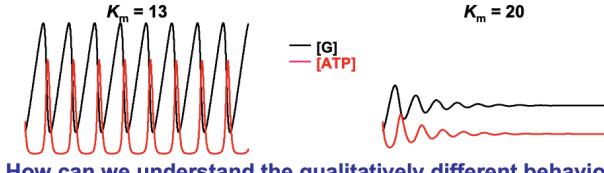


## Stability analysis of ODE systems

Bier model of yeast glycolytic oscillations



Default parameter values:  $V_{in} = 0.36$ ,  $k_1 = 0.02$ ,  $k_p = 6$



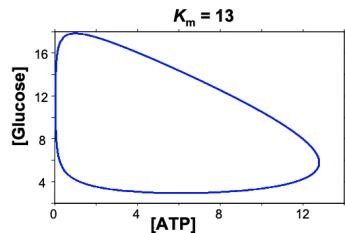
How can we understand the qualitatively different behavior?

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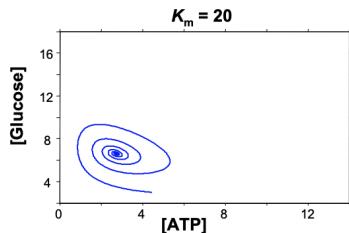
## Stability analysis of ODE systems

Phase-plane techniques for 2D systems

Instead of plotting  $[G]$  and  $[ATP]$  vs. time, plot  $[G]$  vs.  $[ATP]$



$[G]$  and  $[ATP]$  oscillate indefinitely in a "stable limit cycle"



$[G]$  and  $[ATP]$  converge to a "stable fixed point"

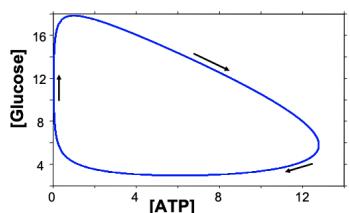
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## Stability analysis of ODE systems

In 2D phase plane, direction determined by:

$$\begin{bmatrix} \frac{d[ATP]}{dt} \\ \frac{d[G]}{dt} \end{bmatrix}$$

At any given location, the derivatives define a vector in the phase plane



$$\frac{d[G]}{dt} = V_{in} - k_1[G][ATP]$$

$$\frac{d[ATP]}{dt} = 2k_1[G][ATP] - \frac{k_p[ATP]}{[ATP] + K_m}$$

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## Summary

A "fixed point" of a dynamical system is a set of variables where all derivatives are equal to zero.

A fixed point can be stable, meaning that after a small perturbation away from the fixed point, the system will return to that fixed point.

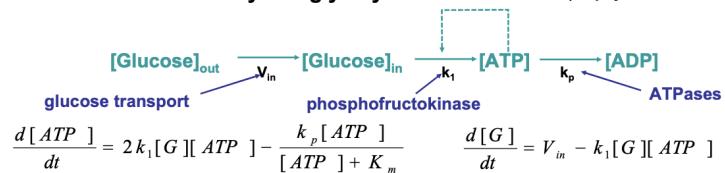
With two-variable systems, it can be helpful to plot one variable versus the other, in the "phase-plane."

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## Stability analysis of ODE systems

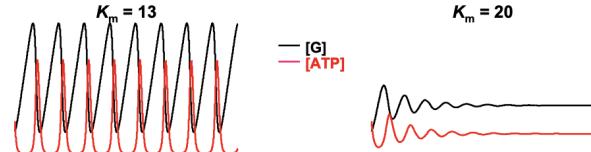
Bier et al. model of yeast glycolytic oscillations

(Biophys. J. 78:1087-1093, 2000)



Default parameter values:  $V_{in} = 0.36$ ,  $k_1 = 0.02$ ,  $k_p = 6$

$K_m = 20$



How can we understand the qualitatively different behavior?

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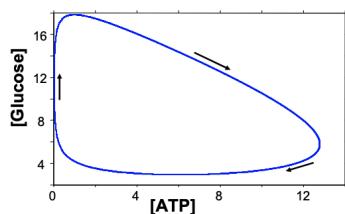
Stability Analysis of ODE systems

## Stability analysis of ODE systems

In 2D phase plane, direction determined by:

$$\begin{bmatrix} \frac{d[ATP]}{dt} \\ \frac{d[G]}{dt} \end{bmatrix}$$

At any given location, the derivatives define a vector in the phase plane



$$\frac{d[G]}{dt} = V_{in} - k_1[G][ATP]$$

$$\frac{d[ATP]}{dt} = 2k_1[G][ATP] - \frac{k_p[ATP]}{[ATP] + K_m}$$

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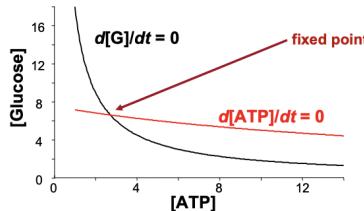
## Stability analysis of ODE systems

It is useful to plot “nullclines”

This is the set of points for which  $d[G]/dt = 0$ ;  $d[ATP]/dt = 0$   
These can usually be calculated analytically

$$\frac{d[ATP]}{dt} = 2k_1[G][ATP] - \frac{k_p[ATP]}{[ATP] + K_m} = 0 \quad \frac{d[G]}{dt} = V_{in} - k_1[G][ATP] = 0$$

$$[G] = \frac{k_p}{2k_1([ATP] + K_m)} \quad [G] = \frac{V_{in}}{k_1[ATP]}$$



Where the nullclines intersect, both derivatives are zero.

This is a “fixed point”

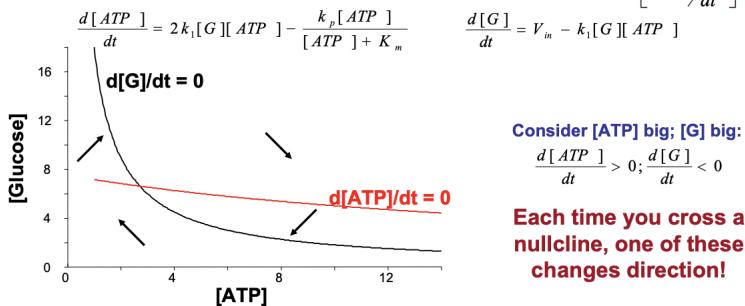
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## Direction arrows in the phase plane

In 2D phase plane, direction determined by:

Plot direction vectors in the Bier model

$$\begin{bmatrix} \frac{d[ATP]}{dt} \\ \frac{d[G]}{dt} \end{bmatrix}$$



Consider [ATP] big; [G] big:

$$\frac{d[ATP]}{dt} > 0; \frac{d[G]}{dt} < 0$$

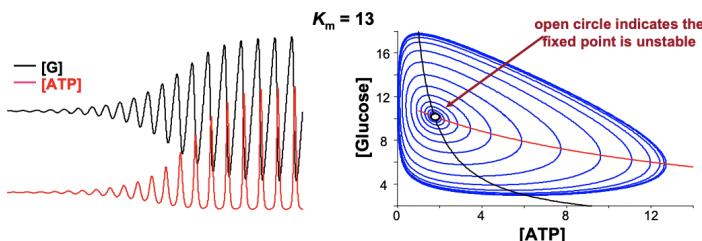
Each time you cross a nullcline, one of these changes direction!

The system will proceed in a clockwise direction (stability is unclear)  
Nullclines divide the phase space into discrete regions

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## Stability analysis of ODE systems

What if we start the oscillating system close to the fixed point?



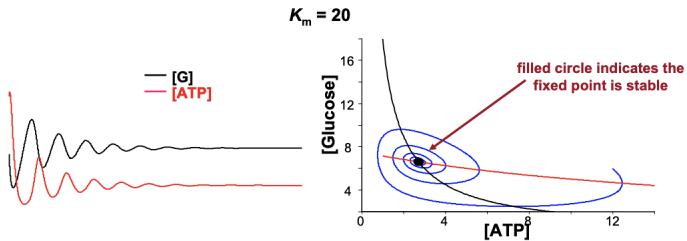
This system moves away from the fixed point, then will oscillate forever

The fixed point is “unstable.” The oscillation is a “stable-limit cycle.”

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## Stability analysis of ODE systems

What if we start the non-oscillating system away from the fixed point?



No matter the initial conditions, this system moves towards the fixed point

This fixed point is “stable.”

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## Stability analysis of ODE systems

How can we understand stable and unstable fixed points mathematically?

$$\frac{d[ATP]}{dt} = 2k_1[G][ATP] - \frac{k_p[ATP]}{[ATP] + K_m} = f$$

$$\frac{d[G]}{dt} = V_{in} - k_1[G][ATP] = g$$

Compute the “Jacobian” matrix:

$$J = \begin{bmatrix} \frac{\partial f}{\partial [ATP]} & \frac{\partial f}{\partial [G]} \\ \frac{\partial g}{\partial [ATP]} & \frac{\partial g}{\partial [G]} \end{bmatrix} = \begin{bmatrix} 2k_1[G] - \frac{k_pK_m}{([ATP] + K_m)^2} & 2k_1[ATP] \\ -k_1[G] & -k_1[ATP] \end{bmatrix}$$

Evaluate this at the fixed point defined by  $[G]^*$ ,  $[ATP]^*$

(This is where analytical computations can become difficult.)

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## Stability analysis of ODE systems

Evaluate Jacobian matrix at the fixed point defined by  $[G]^*$ ,  $[ATP]^*$

$$J = \begin{bmatrix} 2k_1[G]^* - \frac{k_pK_m}{([ATP]^* + K_m)^2} & 2k_1[ATP]^* \\ -k_1[G]^* & -k_1[ATP]^* \end{bmatrix}$$

The eigenvalues of the Jacobian (at the fixed point) determine stability

Eigenvalues can be real or complex numbers

Real parts of both are positive: the fixed point is unstable

Real parts of both are negative: the fixed point is stable

Complex eigenvalues have positive real parts: a limit cycle is stable

Other possibilities are encountered less frequently

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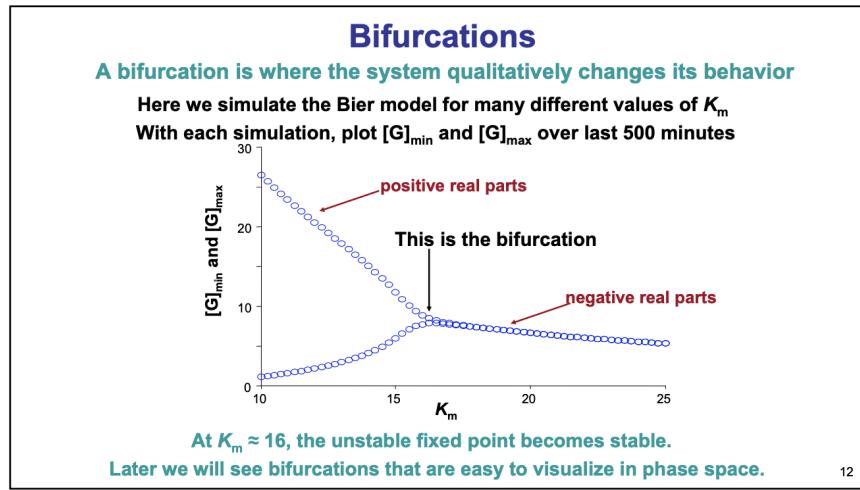
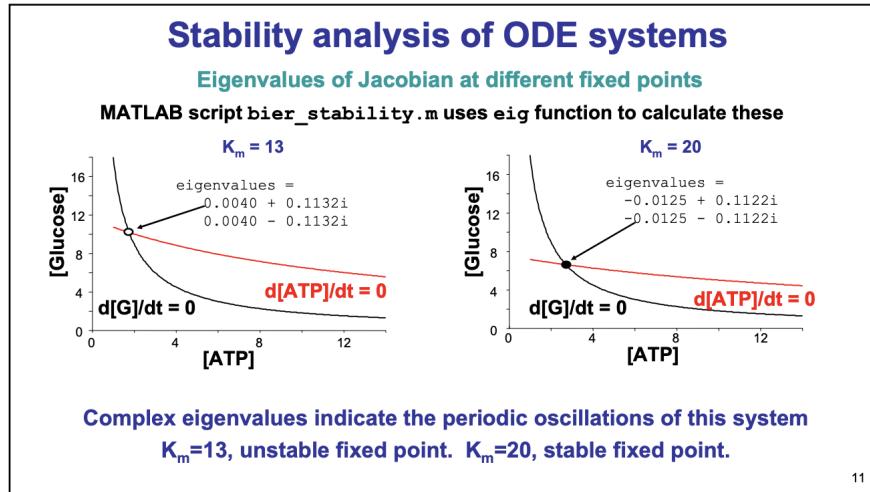


Figure 1:

## Summary

A "nullcline" of a dynamical system is a set points where one of the derivatives is equal to zero. Fixed points are therefore defined by intersections of nullclines.

In phase space, each time a nullcline is crossed, one of the directions of the system changes.

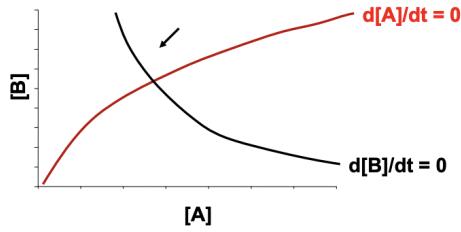
Fixed point stability can be determined by calculating the eigenvalues of the Jacobian matrix, evaluated at the fixed point.

Bifurcations are locations where dynamical systems exhibit qualitative changes in behavior.

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## Self-assessment question

Let's consider a system of two variables, **A** and **B**. In the phase space, with **A** on the x-axis and **B** on the y-axis, we plot the **A** and **B** nullclines as shown. We deduce that in one region of the phase space, the system is travelling in the approximate direction shown. Determine which directions the system will be traveling in the other regions of phase space.



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