# Introduction to Dynamical Systems

## Part 4

Icahn School of Medicine at Mount Sinai

SBCNY



## Outline

### Analyzing stability of ODE systems

**Example: yeast glycolytic oscillations**

**Nullclines, stable and unstable fixed points**

**Bifurcations: abrupt changes in system behavior**

# Stability analysis of ODE systems

**Bier et al. model of yeast glycolytic oscillations** (*Biophys. J.* 78:1087-1093, 2000)

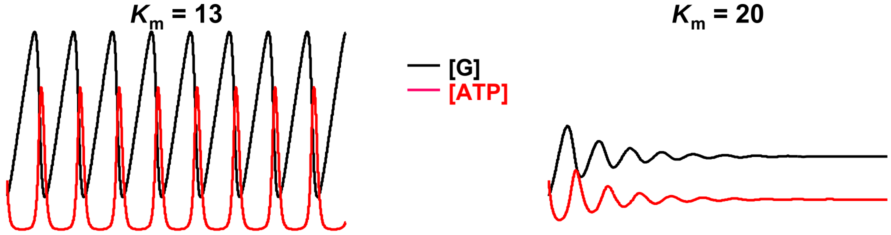
$[\text{Glucose}]_{out} \xrightarrow{V_{in}} [\text{Glucose}]_{in} \xrightarrow{k_1} [\text{ATP}] \xrightarrow{k_p} [\text{ADP}]$

glucose transport ($V_{in}$); phosphofructokinase ($k_1$); ATPases ($k_p$)

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

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

$K_m$ = 13 $\qquad$ $K_m$ = 20



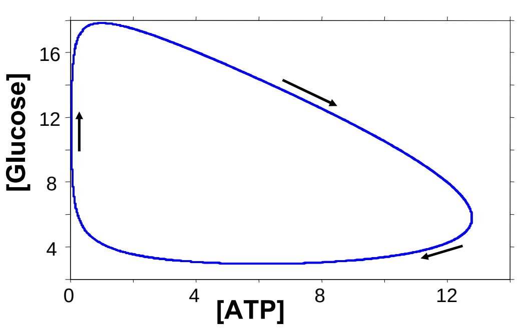

**How can we understand the qualitatively different behavior?**



# Stability analysis of ODE systems

**In 2D phase plane, direction determined by:** $\begin{bmatrix} d[ATP]/dt \\ d[G]/dt \end{bmatrix}$

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




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

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

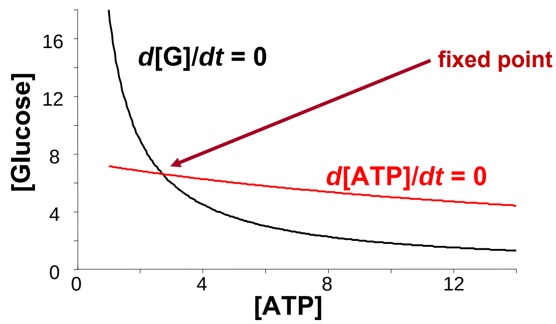
# Stability analysis of ODE systems

## 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**

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

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




**Where the nullclines intersect, both derivatives are zero.**
**This is a "fixed point"**



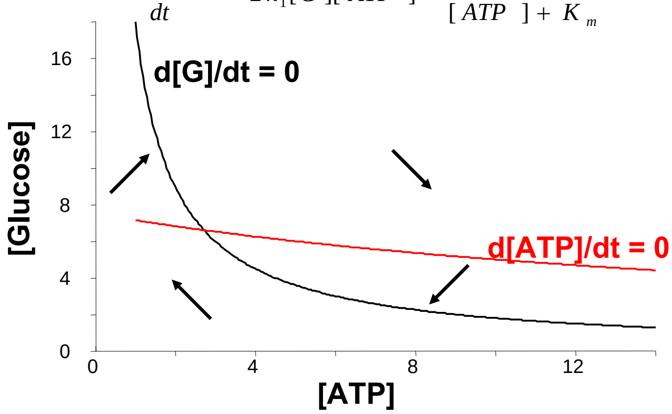
# Direction arrows in the phase plane

## In 2D phase plane, direction determined by:

**Plot direction vectors in the Bier model**

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

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




**Consider [ATP] big; [G] big:**

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

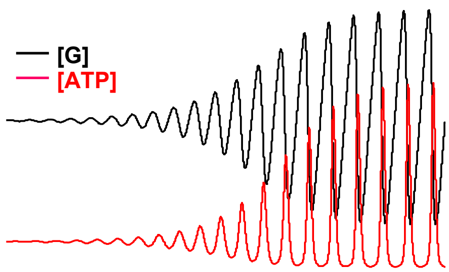
**Each time you cross a nullcline, one of these changes direction!**

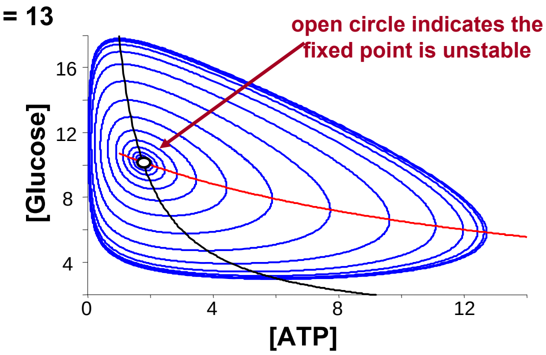
**The system will proceed in a clockwise direction (stability is unclear)**
**Nullclines divide the phase space into discrete regions**

## Stability analysis of ODE systems

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

$K_m = 13$




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

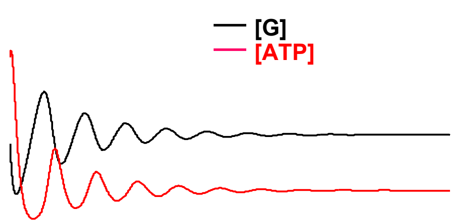
**The fixed point is "unstable." The oscillation is a "stable-limit cycle."**

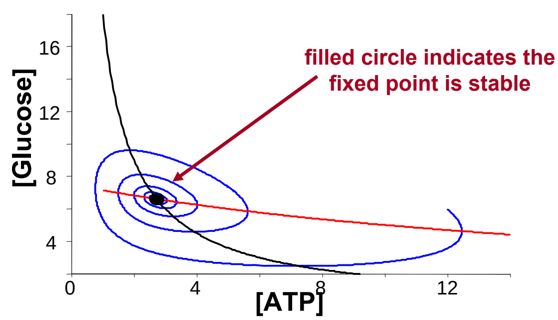


## Stability analysis of ODE systems

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

$K_m = 20$




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

**This fixed point is "stable."**

## 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:**

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

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

**(This is where analytical computations can become difficult.)**



## Stability analysis of ODE systems

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

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

**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**

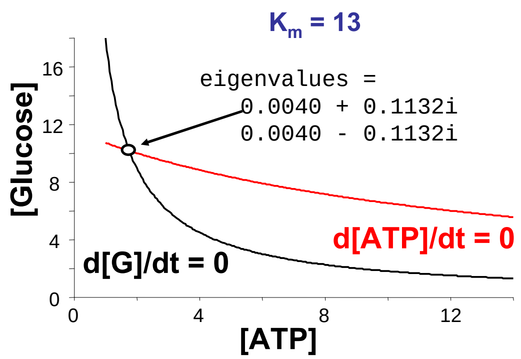
**Complex eigenvalues have positive real parts: a limit cycle is stable**

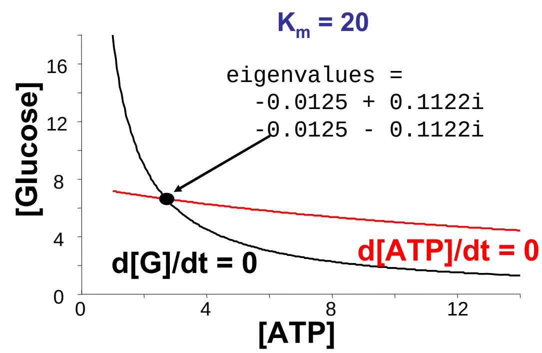
**Other possibilities are encountered less frequently**

# Stability analysis of ODE systems

## Eigenvalues of Jacobian at different fixed points

**MATLAB script `bier_stability.m` uses `eig` function to calculate these**




**Complex eigenvalues indicate the periodic oscillations of this system**

**$K_m$=13, unstable fixed point. $K_m$=20, stable fixed point.**

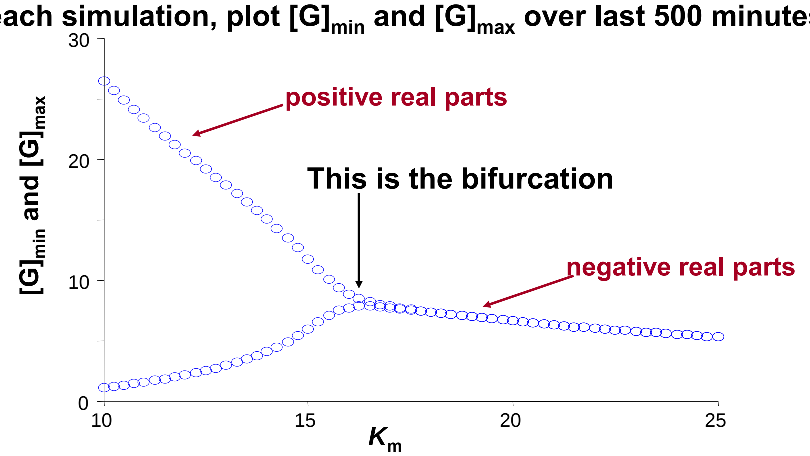


# Bifurcations

## A bifurcation is where the system qualitatively changes its behavior

**Here we simulate the Bier model for many different values of $K_m$**

**With each simulation, plot $[G]_{min}$ and $[G]_{max}$ over last 500 minutes**




**At $K_m$ ≈ 16, the unstable fixed point becomes stable.**

**Later we will see bifurcations that are easy to visualize in phase space.**

## 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.



## 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.