Systems Biology: A Personal View
XX. Biological oscillators: Hopf Bifurcation & Glycolysis

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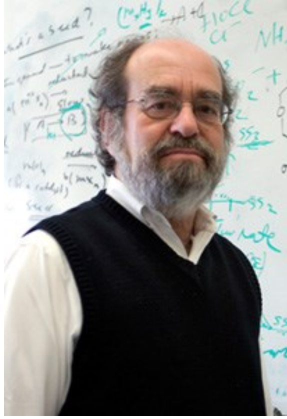
Oscillations in the Chlorine dioxide-Iodine-Malonic Acid (ClO_2-I_2-MA) reaction



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Irv Epstein

$$\mathrm{MA} + \mathrm{I}_2 \rightarrow \mathrm{IMA} + \mathrm{I}^- + \mathrm{H}^+; \qquad \frac{d[\mathrm{I}_2]}{dt} = -\frac{k_{1a}[\mathrm{MA}][\mathrm{I}_2]}{k_{1b} + [\mathrm{I}_2]}$$

$$\mathrm{ClO}_2 + \mathrm{I}^- \rightarrow \mathrm{ClO}_2^{\ -} + \tfrac{1}{2}\mathrm{I}_2; \qquad \frac{d[\mathrm{ClO}_2]}{dt} = -k_2[\mathrm{ClO}_2][\mathrm{I}^-]$$

$$\mathrm{ClO}_2^{\ -} + 4\mathrm{I}^- + 4\mathrm{H}^+ \rightarrow \mathrm{Cl}^- + 2\mathrm{I}_2 + 2\mathrm{H}_2\mathrm{O};$$

$$\frac{d[\mathrm{ClO}_2^{\ -}]}{dt} = -k_{3a}[\mathrm{ClO}_2^{\ -}][\mathrm{I}^-][\mathrm{H}^+] - k_{3b}[\mathrm{ClO}_2^{\ -}][\mathrm{I}_2]\frac{[\mathrm{I}^-]}{u + [\mathrm{I}^-]^2}$$

Strogatz, 1994

MA, I_2 and ClO_2 vary much more slowly than the intermediate I^- and ClO_2^- which change by several orders of magnitude during an oscillation period

ClO_2-I_2-MA reaction oscillations

Approximating the concentrations of the slow reactants as constants the system can be reduced to the two-variable model (in non-dimensional form)

For I^-

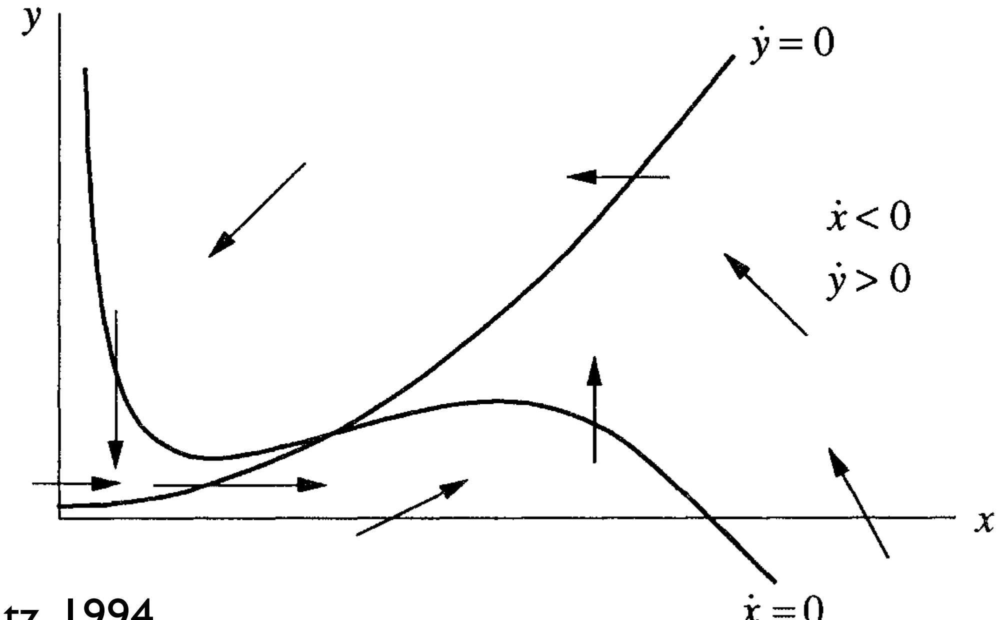
$$\dot{x} = a - x - \frac{4xy}{1+x^2}$$

For ClO_2^-

$$\dot{y} = bx\left(1 - \frac{y}{1+x^2}\right)$$

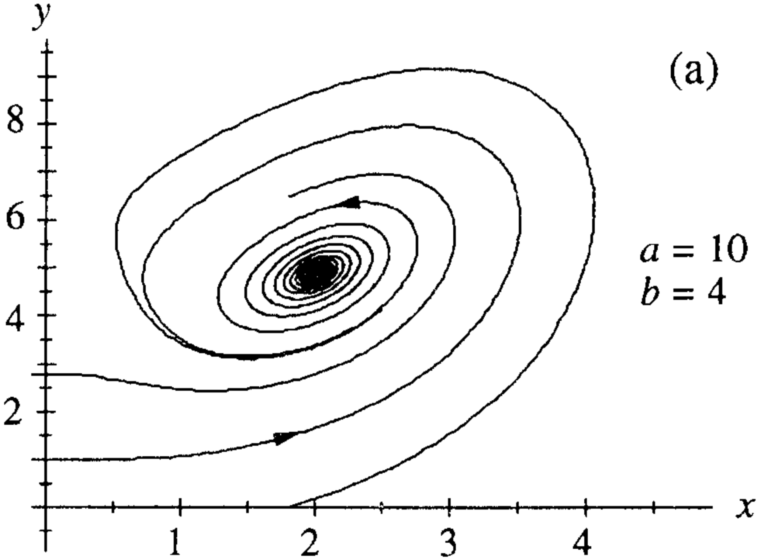
[Note: the approxn neglects the slow consumption of the reactants – so unable to show the eventual approach to equilibrium]

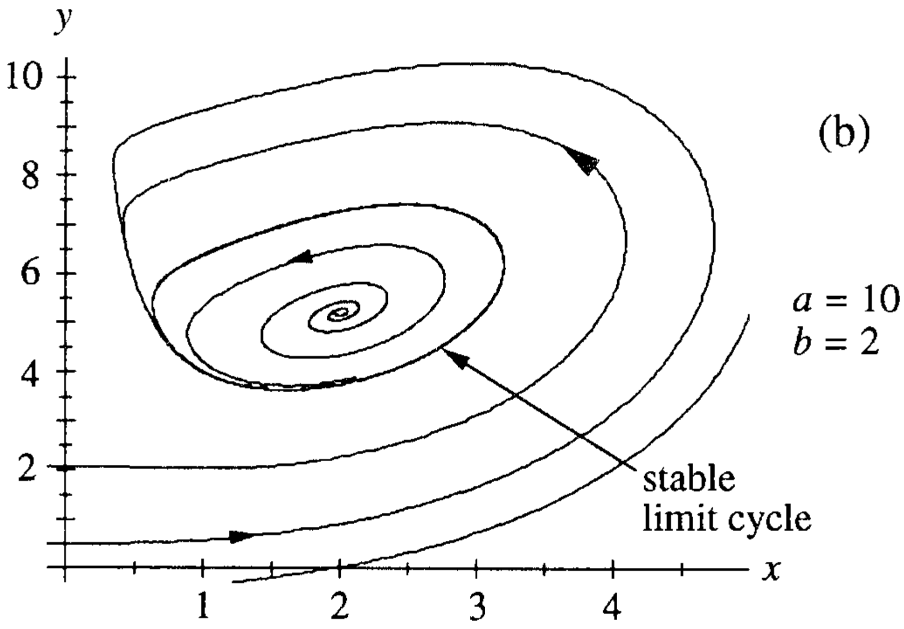
The nullclines give a general idea of the overall flow properties of the system

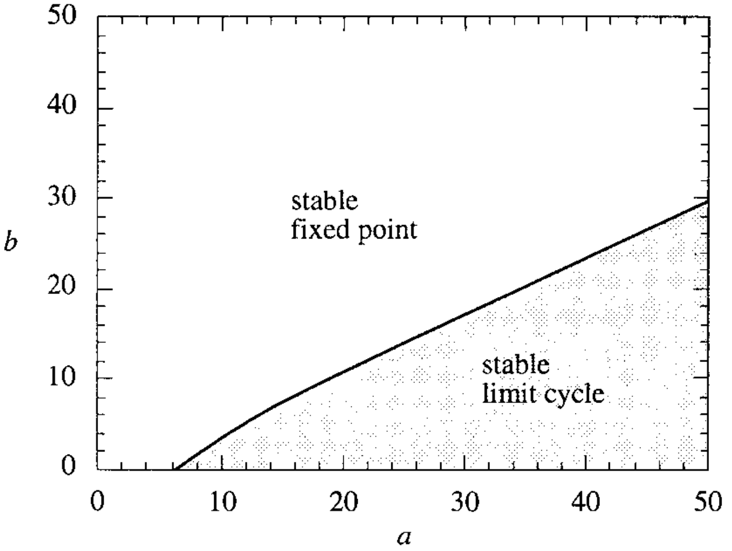


Strogatz, 1994

Hopf bifurcation in ClO_2-I_2-MA reaction





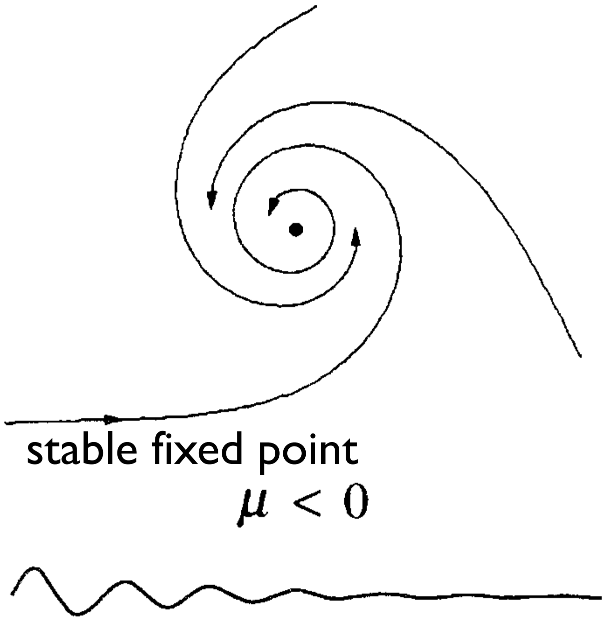


As b is decreased below a critical value $b_c = (3a/5) – (25/a)$
The fixed point $x^* = a/5, y^* = 1 + (a/5)^2$ is destabilized – changes from a stable spiral to an unstable spiral – giving rise to a limit cycle through supercritical Hopf bifurcation

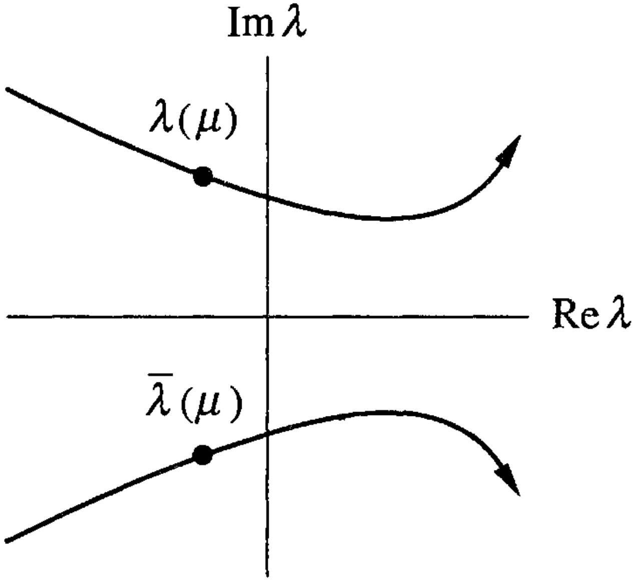
Hopf bifurcation

Bifurcation in which a fixed point and a periodic solution changes stability

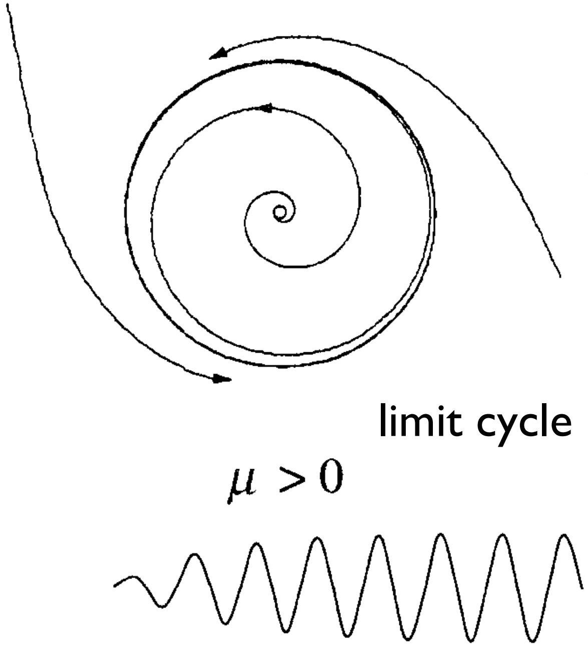
Supercritical Hopf Bifurcation: As a parameter μ is varied, a stable fixed point loses stability at a critical value μ_c and a stable oscillatory solution (limit cycle) comes into existence whose amplitude increases as μ is changed further



stable fixed point



The complex eigenvalues change sign of the real part at the Hopf bifurcation



limit cycle

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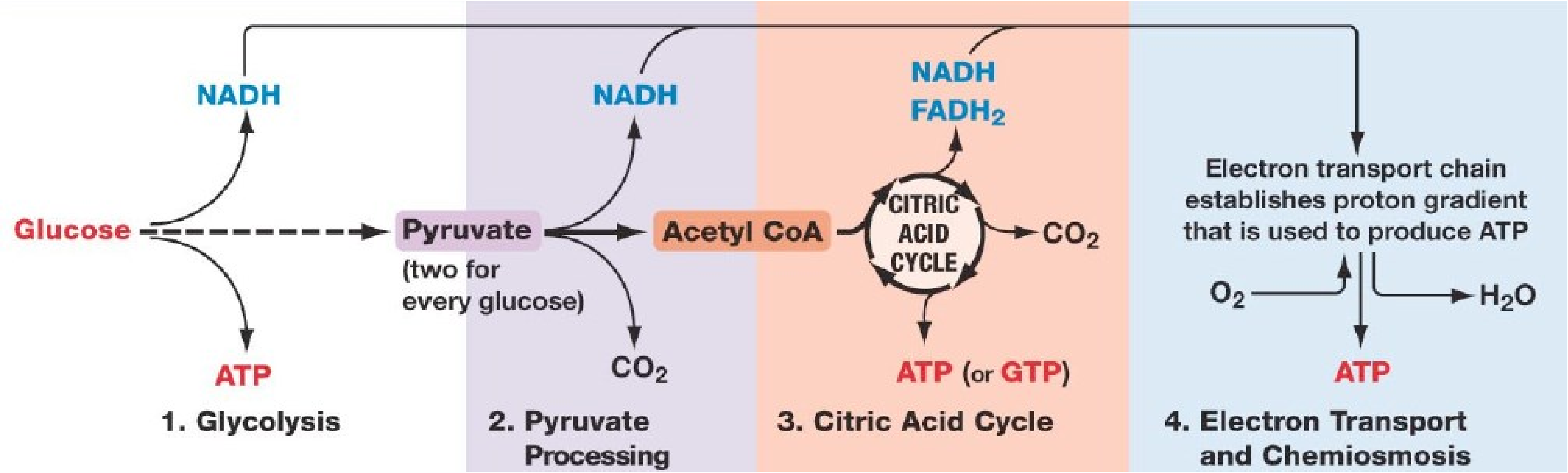
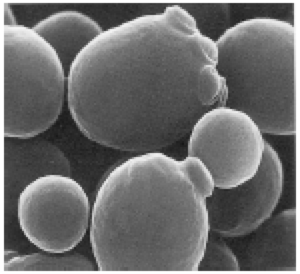
Example of biological oscillations: Glycolysis

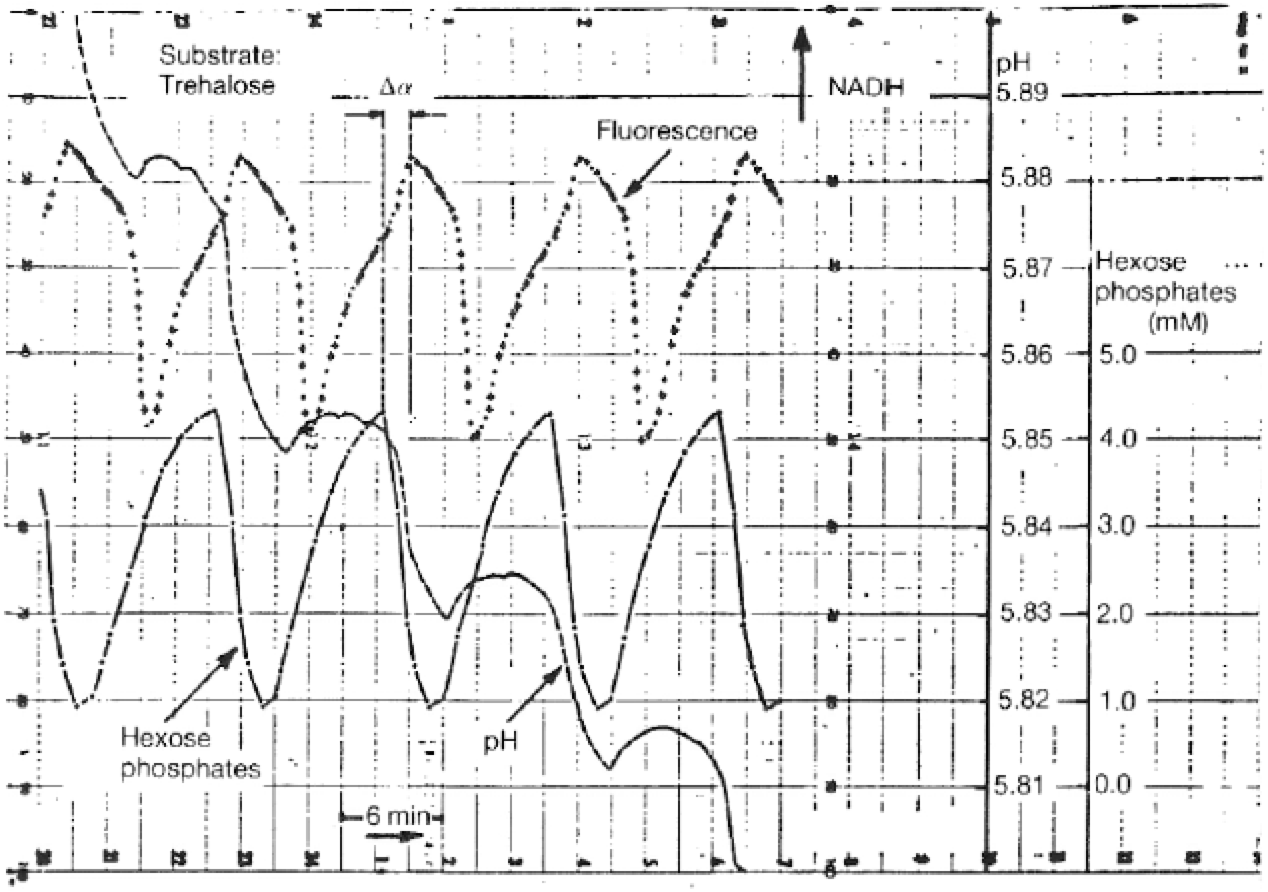


- Glycolysis ("splitting sugars") takes place in cytoplasm
- Metabolic process in which a molecule of glucose is converted to 2 molecules of pyruvate, yielding 2 molecules of ATP and 2 molecules of NADH.
- Pyruvate is then used in the Kreb cycle.

Glycolytic oscillations in Yeast



S. cerevisiae
(yeast)



Glycolytic oscillations in a yeast extract subjected to constant injection of the substrate (trehalose).

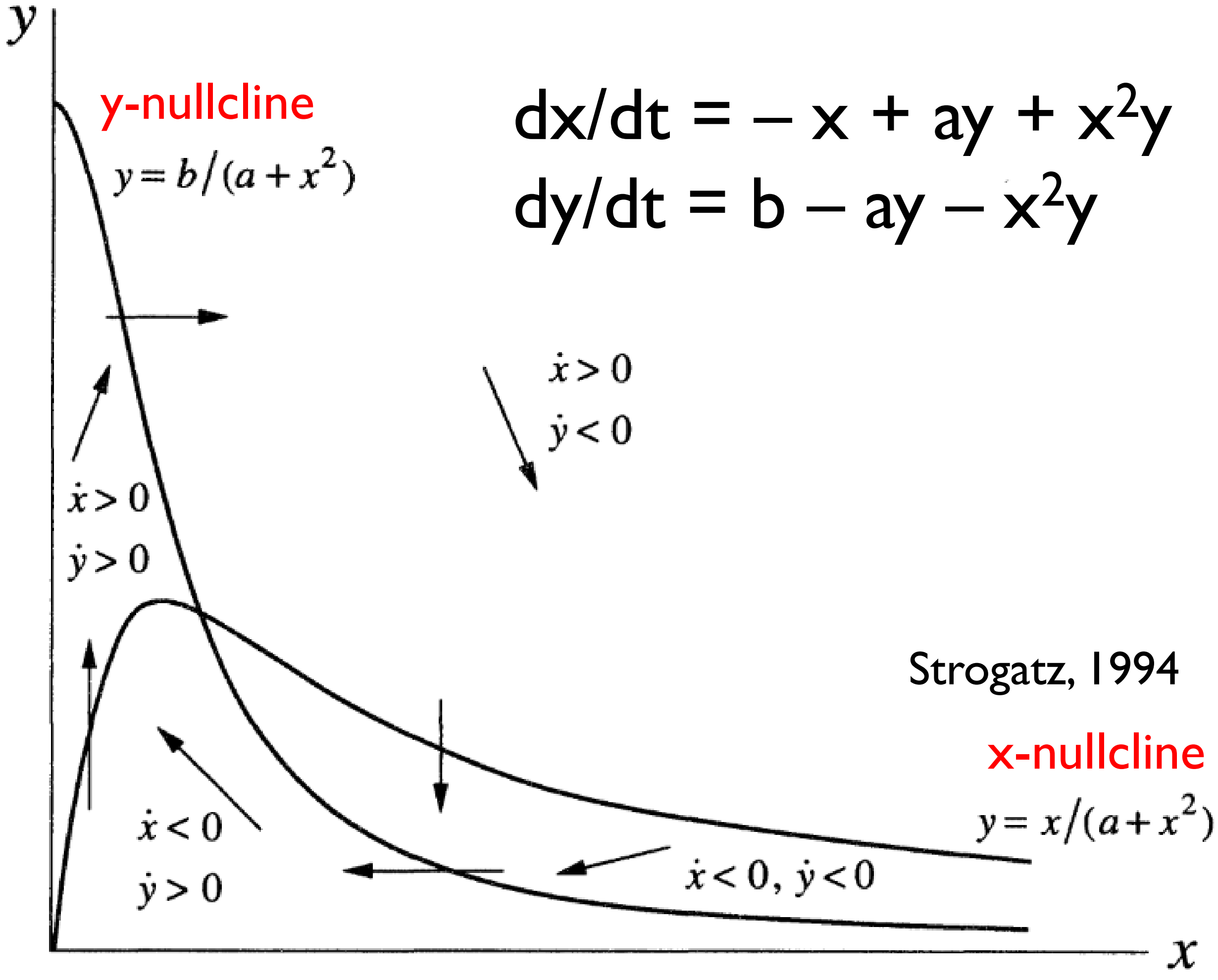
Hess & Boiteux (1968) In Regulatory Functions of Biological Membranes. Ed. J. Jarnefelt, Elsevier.
Hess B, Boiteux A, Krüger J (1969) Cooperation of glycolytic enzymes. Adv Enzyme Regul. 7:149-67

Modeling Glycolytic oscillations

Sel'kov's dimensionless equations (1968)

x: concentration of ADP (adenosine diphosphate)

y: concentration of F6P (fructose-6-phosphate)



$$dx/dt = -x + ay + x^2y$$

$$dy/dt = b - ay - x^2y$$

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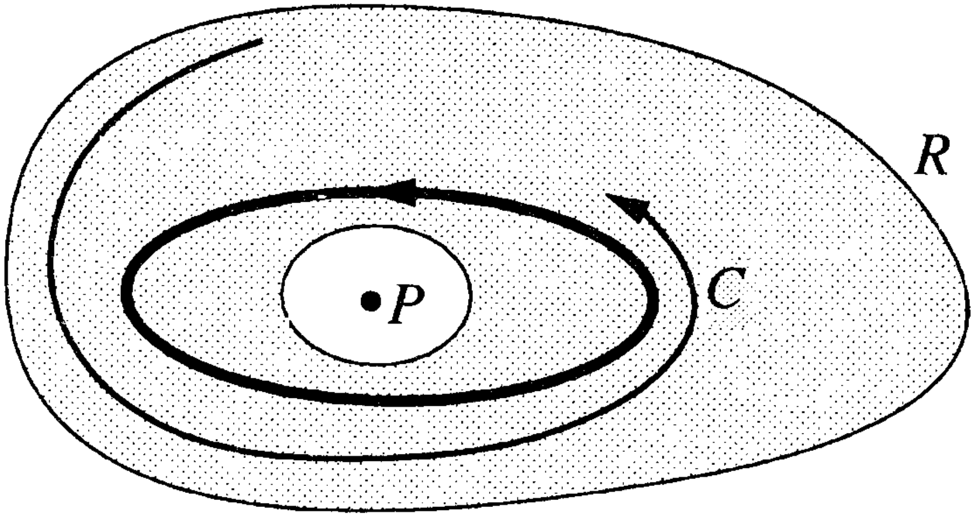
How to show that periodic solutions (closed orbits in phase space) exist in particular systems ?

Poincare-Bendixson Theorem

Suppose that:
(1) R is a closed, bounded subset of the plane;
(2) dx/dt = f (x) is a continuously differentiable vector field on an open set containing R;
(3) R does not contain any fixed points; and
(4) There exists a trajectory C that is “confined” in R, in the sense that it starts in R and stays in R for all future time.



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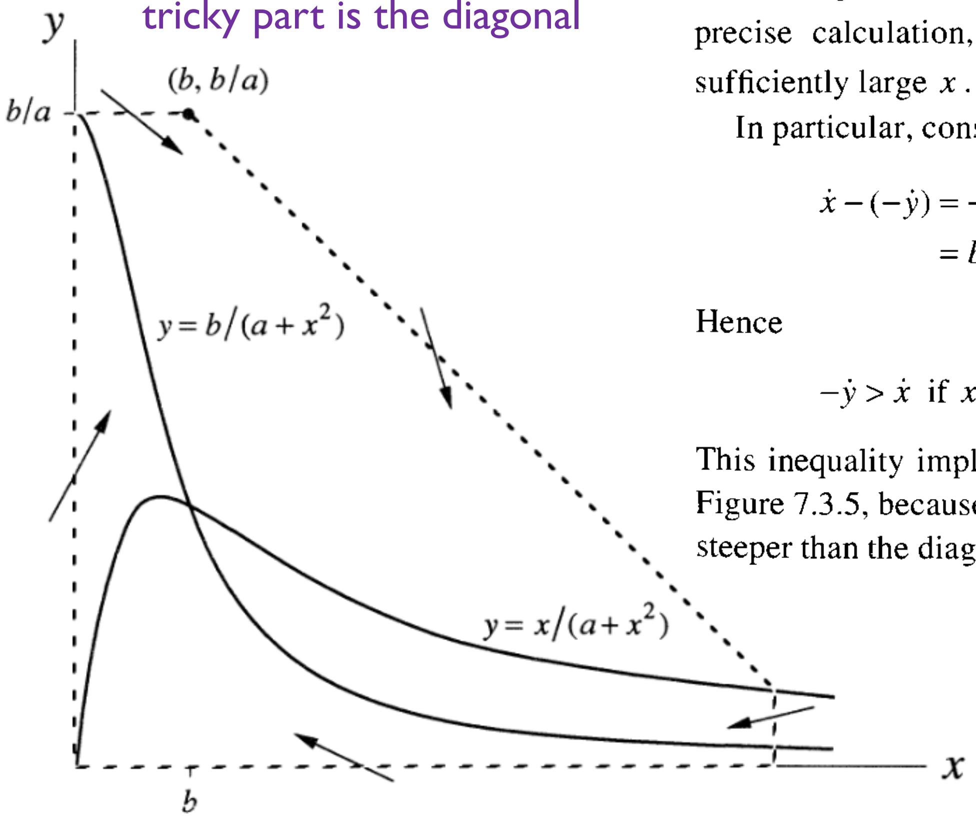
Then either C is a closed orbit, or it spirals toward a closed orbit asymptotically (i.e., $t \to \infty$). In either case, R contains a closed orbit.

To apply the Poincare-Bendixson Theorem

construct a trapping region R

i.e., a closed connected set such that the vector field points "inward" everywhere on boundary of R such that all trajectories in R are confined

On the horizontal & vertical sides, there's no problem – tricky part is the diagonal



Consider dx/dt and dy/dt in the limit of very large x, such that

$\dot{x} \approx x^2 y$ and $\dot{y} \approx -x^2 y$, so $\dot{y}/\dot{x} = dy/dx \approx -1$ along trajectories. Hence the vector field at large x is roughly parallel to the diagonal line. This suggests that in a more precise calculation, we should compare the sizes of $\dot{x}$ and $-\dot{y}$, for some sufficiently large x.

In particular, consider $\dot{x} - (-\dot{y})$. We find

$$\begin{aligned} \dot{x} - (-\dot{y}) &= -x + ay + x^2 y + (b - ay - x^2 y) \\ &= b - x. \end{aligned}$$

Hence

$$-\dot{y} > \dot{x} \text{ if } x > b.$$

This inequality implies that the vector field points inward on the diagonal line in Figure 7.3.5, because dy/dx is more negative than -1, and therefore the vectors are steeper than the diagonal line. Thus the region is a trapping region, as claimed. ■

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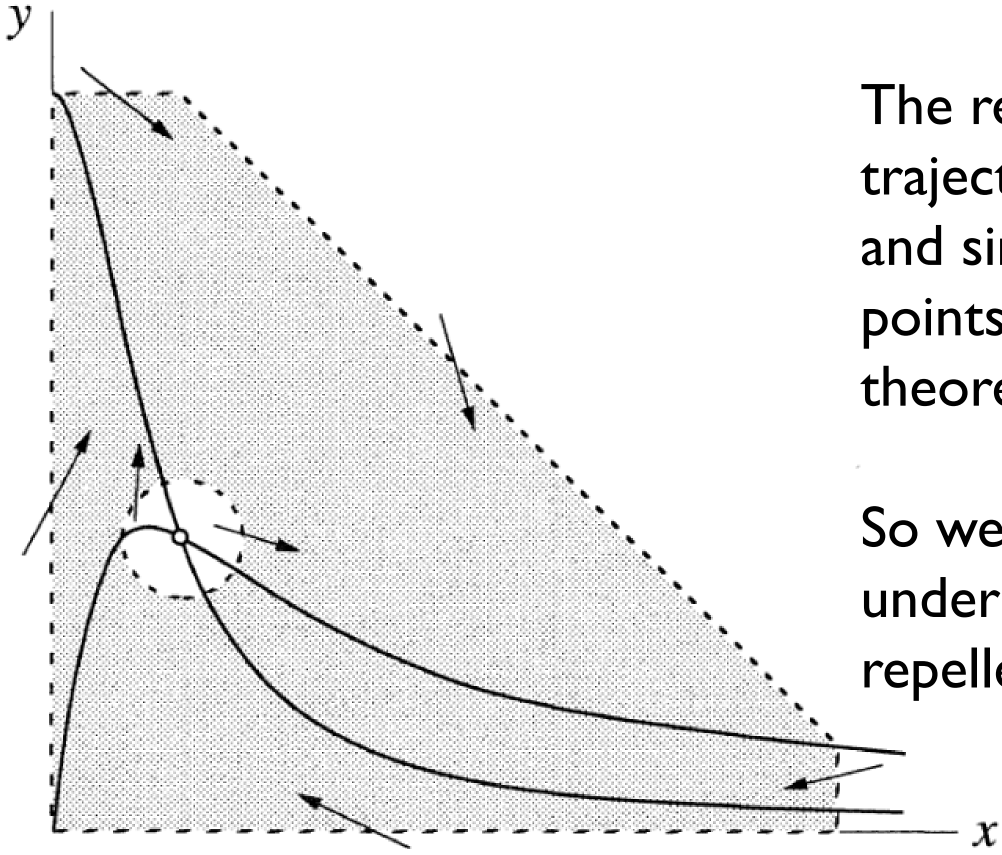
There is a fixed point in the region (at the intersection of the nullclines), and so the conditions of the Poincare-Bendixson theorem are not satisfied.
But if this fixed point is a repeller, then we can prove the existence of a closed orbit by considering the modified "punctured" region (an infintesimal hole around the fixed point)



The repeller drives all neighboring trajectories into the shaded region, and since this region is free of fixed points, the Poincare-Bendixson theorem applies.

So we only need to find the conditions under which the fixed point is a repeller.

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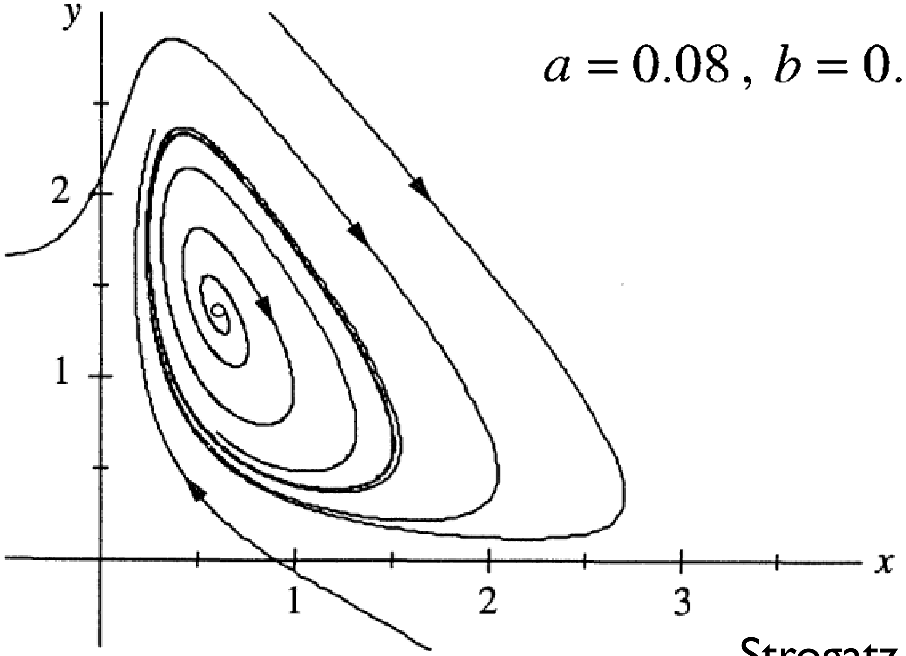
Oscillations in Glycolysis

To find the stability of the fixed point evaluate the Jacobian

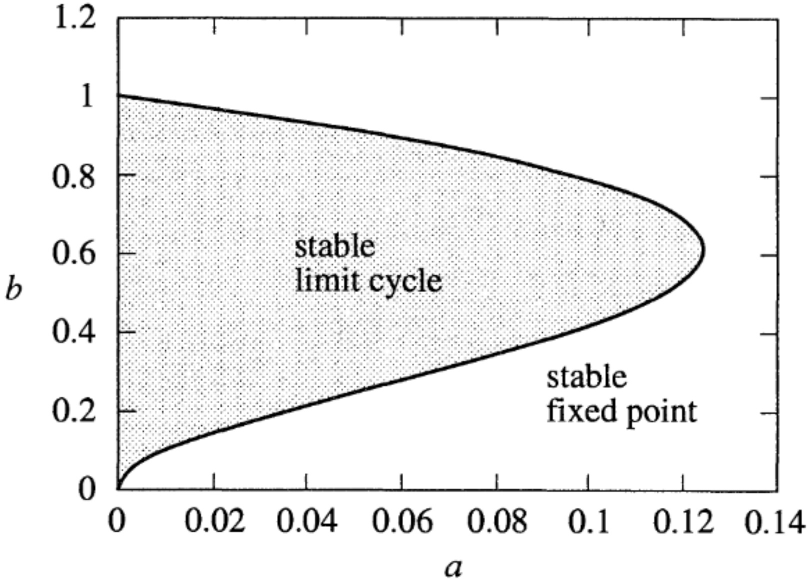
$$A = \begin{pmatrix} -1 + 2xy & a + x^2 \\ -2xy & -(a + x^2) \end{pmatrix}.$$

about the fixed point $x^* = b\,, \qquad y^* = \dfrac{b}{a + b^2}$

The stability-instability boundary is $b^2 = \tfrac{1}{2}\left(1 - 2a \pm \sqrt{1 - 8a}\right)$



$a = 0.08\,,\ b = 0.6$



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