Limit Cycles II

Prof. Ned Wingreen

MOL 410/510

How to prove a closed orbit exists?

- numerically
- Poincaré-Bendixson Theorem: If
  1. R is a closed, bounded subset of the plane
  2. $\dot{\vec{x}} = \vec{f}(\vec{x})$ is a continuously differentiable vector field on an open set containing R
  3. R *does not* contain any fixed points
  4. There exists a trajectory C that is "confined" in R

  Then either C is a closed orbit or it spirals towards a closed orbit as $t \to \infty$. Either way, R *contains a closed orbit.*

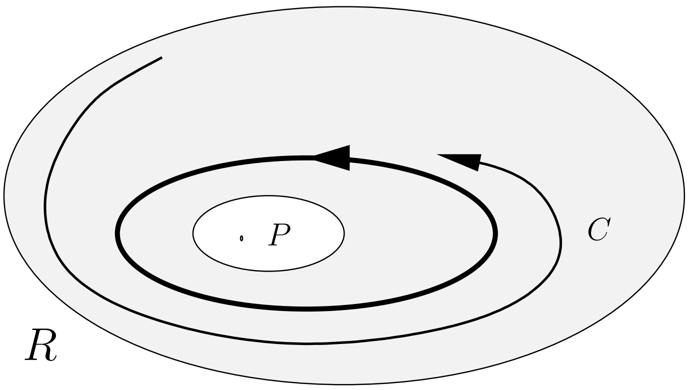


Figure 1: Poincaré-Bendixson Theorem

Example — Glycolytic oscillations

Background

Organisms may obtain energy by breaking down sugar. Glycolysis can proceed in an oscillatory fashion. In a simple model with

$$x = \text{concentration of ADP (adenosine diphosphate)}$$
$$y = \text{concentration of F6P (fructose-6-phosphate)}$$

we have

$$\dot{x} = -x + ay + x^2 y$$
$$\dot{y} = b - ay - x^2 y$$

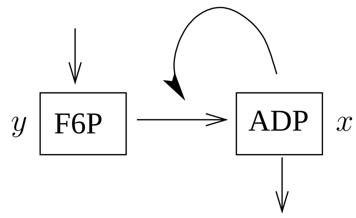


Figure 2: Glycolysis model

Starting from Kinetic Equations

A brief aside on deriving dimensionless equations from kinetic equations - by rescaling chemical concentrations and time by appropriate units, one can generally reduce the number of parameters. In our case, the underlying kinetic equations are

$$\frac{\mathrm{d[A]}}{\mathrm{d}t} = -\mu[\mathrm{A}] + \alpha[\mathrm{F}] + \gamma[\mathrm{A}]^2[\mathrm{F}]$$
$$\frac{\mathrm{d[F]}}{\mathrm{d}t} = \beta - \alpha[\mathrm{F}] - \gamma[\mathrm{A}]^2[\mathrm{F}]$$

which has four (dimensionful) parameters, α, β, γ, and μ. We'll start by rescaling time. Divide by μ, which is a rate, to give

$$\frac{\mathrm{d[A]}}{\mathrm{d}(\mu t)} = \frac{\mathrm{d[A]}}{\mathrm{d}t'} = -[\mathrm{A}] + (\alpha/\mu)[\mathrm{F}] + (\gamma/\mu)[\mathrm{A}]^2[\mathrm{F}]$$
$$\frac{\mathrm{d[F]}}{\mathrm{d}(\mu t)} = \frac{\mathrm{d[F]}}{\mathrm{d}t'} = \beta/\mu - (\alpha/\mu)[\mathrm{F}] - (\gamma/\mu)[\mathrm{A}]^2[\mathrm{F}],$$

where we have defined $t' = \mu t$. Now, to eliminate the parameter γ/μ in front of the last term in each equation, while continuing to measure [A] and [F] in the same units, we'll rescale the concentrations [A] and [F] as

$$[\mathrm{A}] = (\mu/\gamma)^{1/2} x$$
$$[\mathrm{F}] = (\mu/\gamma)^{1/2} y,$$

which yields

$$(\mu/\gamma)^{1/2} \frac{\mathrm{d}x}{\mathrm{d}t'} = -(\mu/\gamma)^{1/2} x + (\alpha/\mu)(\mu/\gamma)^{1/2} y + (\gamma/\mu)(\mu/\gamma)^{3/2} x^2 y$$
$$(\mu/\gamma)^{1/2} \frac{\mathrm{d}y}{\mathrm{d}t'} = \beta/\mu - (\alpha/\mu)(\mu/\gamma)^{1/2} y - (\gamma/\mu)(\mu/\gamma)^{3/2} x^2 y,$$

and simplifies to

$$\dot{x} = -x + (\alpha/\mu)y + x^2 y$$
$$\dot{y} = (\gamma/\mu)^{1/2}(\beta/\mu) - (\alpha/\mu)y - x^2 y.$$

These are our original, dimensionless equations, and now we can see exactly how the two remaining dimensionless constants a and b depend on the underlying rates in the kinetic equations: $a = \alpha/\mu$ and $b = (\gamma/\mu)^{1/2}(\beta/\mu)$.

Intuition

Since rate of F6P→ADP increases with ADP, we can get "overshooting," i.e. F6P gets depleted, ADP has no source so it also gets depleted, followed by slow recovery of F6P. This is a possible oscillator, but how can we prove a limit cycle?

Find the nullclines

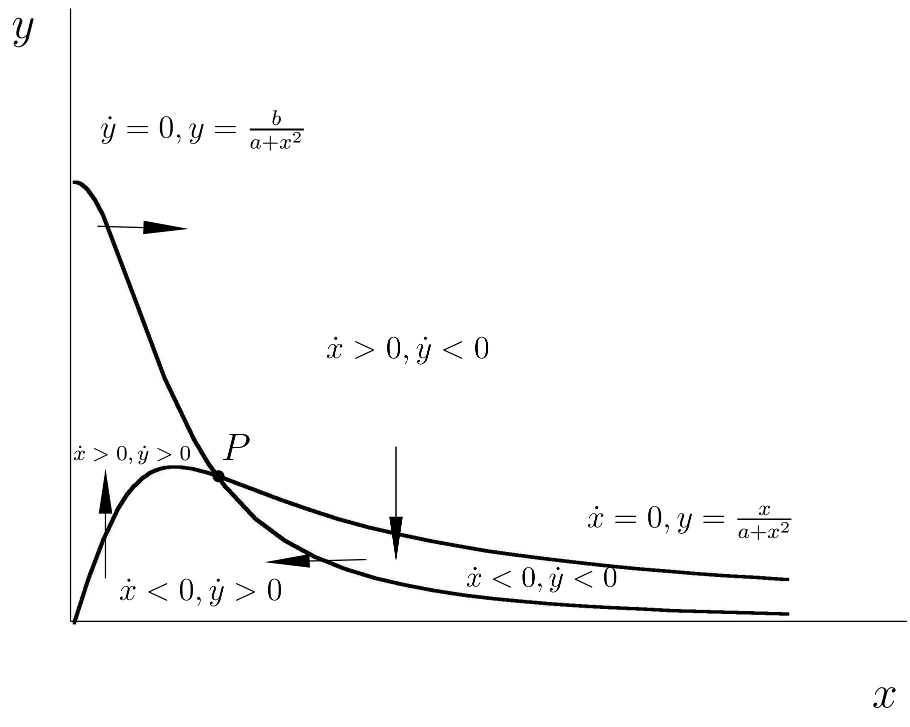


Figure 3: Nullclines sketch

$$\begin{aligned}
\dot{x} = 0 \qquad & \implies -x + ay + x^2 y = 0 \\
& \implies y = \frac{x}{a + x^2} \\
\dot{y} = 0 \qquad & \implies b - ay - x^2 y = 0 \\
& \implies y = \frac{b}{a + x^2}
\end{aligned}$$

Solve for fixed point: $x = b$, $y = \frac{b}{a+b^2}$.

Does this prove a limit cycle? *NO!* We could have a stable fixed point at P, or trajectories could spiral out to ∞. Indeed, at the intersection of the nullclines $\dot{x} = \dot{y} = 0$, so P is a fixed point.

Fixed point

We can't apply Poincaré-Bendixson yet because of the fixed point. We *can* use P-B, though, if the fixed point is a repeller, because then our trapping region is just $R \setminus P$. Analyze stability of fixed point P by linearizing the differential equations around the fixed point:

$$\text{Jacobian } A = \begin{pmatrix} \frac{\partial \dot{x}}{\partial x} & \frac{\partial \dot{x}}{\partial y} \\ \frac{\partial \dot{y}}{\partial x} & \frac{\partial \dot{y}}{\partial y} \end{pmatrix} = \begin{pmatrix} -1 + 2xy & a + x^2 \\ -2xy & -(a + x^2) \end{pmatrix}$$

$$\text{Fixed point } P\colon x^* = b, y^* = \frac{b}{a+b^2}$$

$$A(P) = \begin{pmatrix} -1 + 2\frac{b^2}{a+b^2} & a + b^2 \\ -\frac{2b^2}{a+b^2} & -(a + b^2) \end{pmatrix}$$

$$\Delta = \det A(P) = a + b^2 > 0$$

$$\tau = \operatorname{tr} A(P) = -1 + 2\frac{b^2}{a+b^2} - (a + b^2) = -\frac{b^4 + (2a-1)b^2 + (a + a^2)}{a + b^2}$$

In general, we can quickly determine the stability of a fixed point if we know Δ and τ, i.e. the determinant and trace of the Jacobian at the fixed point, because the eigenvalues are given by

$$\lambda_J = \frac{1}{2}(\tau \pm \sqrt{\tau^2 - 4\Delta}).$$

(It's worth remembering that for any square matrix $\Delta = \Pi_i \lambda_i$ and $\tau = \Sigma_i \lambda_i$.)

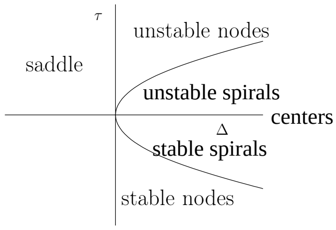


Figure 4: Stability and types of fixed points

The fixed point P is unstable for $\tau > 0$, stable for $\tau < 0$. The dividing line $\tau = 0$ is at

$$b^2 = \frac{1}{2}(1 - 2a \pm \sqrt{1 - 8a})$$

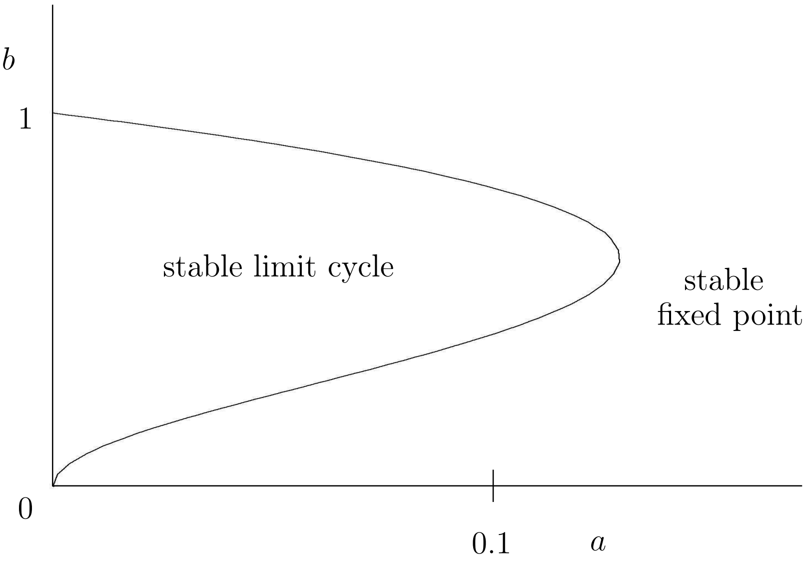


Figure 5: Glycolysis analysis

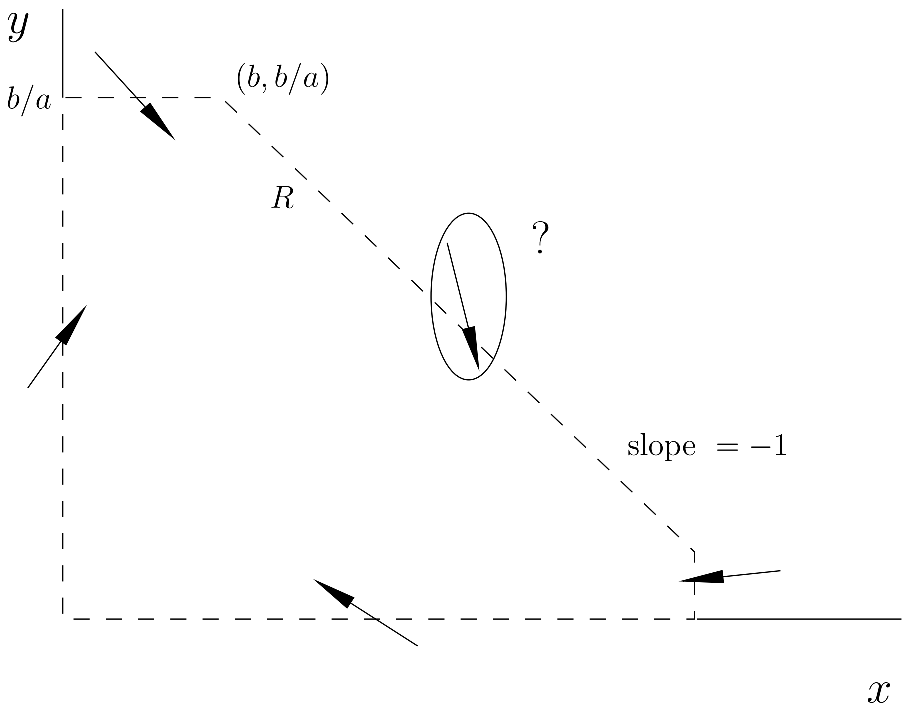


Figure 6: Trapping region

Find a trapping region

Examine Figure 6 (page 6). The vectors for $\dot{x} = 0$ or $\dot{y} = 0$ follow from the last figure. But what about the circled vector?

Circled vector is trapping if $\dot{y} < -\dot{x}$ (i.e. $\dot{x} + \dot{y} < 0$) along the boundary:

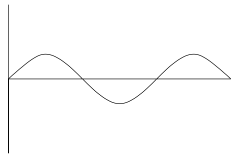
$$\dot{x} + \dot{y} = -x + b \implies \dot{x} + \dot{y} < 0 \text{ if } x > b,$$

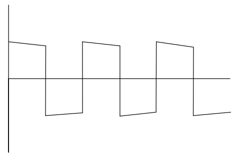
so the dashed lines do define a trapping region.

A model for glycolysis

We can conclude that our glycolytic model functions as in Figure 5 (page 5).Does this make sense? If a is too big, then F6P→ADP even for low levels of ADP, so there's no chance for a pool of F6P to accumulate. At a fixed a, if b is too small then new F6P will "instantly" turn into ADP and get used up, so the system is locked in a low flux state. If b is too big, ADP will never be low enough, so the system is locked into a high flux state.

How to characterize a limit cycle?





- (nearly) harmonic oscillator vs relaxation oscillator
- period
- amplitude

Example - van der Pol oscillator

$$\ddot{x} + \mu(x^2 - 1)\dot{x} + x = 0$$

Damped harmonic oscillator: ordinary damping for $|x| > 1$,"negative" damping for $|x| < 1$. Large amplitude oscillations will decay, but small amplitude oscillations will get pumped up. Like a parent pushing a child on a swing...

It can be proven that the van der Pol oscillator has a single, stable limit cycle for each $\mu > 0$.

van der Pol as a relaxation oscillator ($\mu >> 1$)

$$\ddot{x} + \mu(x^2 - 1)\dot{x} = \frac{\mathrm{d}}{\mathrm{d}t}\left[\dot{x} + \mu(\frac{1}{3}x^3 - x)\right]$$

$$\text{Let } F(x) = \frac{1}{3}x^3 - x, \omega = \dot{x} + \mu F(x).$$

The van der Pol equation implies

$$\dot{\omega} = -x, \quad \dot{x} = \omega - \mu F(x),$$

and if we let $y = \omega/\mu$,

$$\dot{x} = \mu[y - F(x)] \qquad \leftarrow \text{fast}$$

$$\dot{y} = -\frac{1}{\mu}x \qquad \leftarrow \text{slow}$$

Nullclines

So there are two separated timescales:

"crawls"	$\Delta t \sim \mu$
"jumps"	$\Delta t \sim 1/\mu$

Period

The period of relaxation oscillator is dominated by crawls. For van der Pol, by symmetry $T \approx 2\int_{t_A}^{t_B} \mathrm{d}t$.

On the slow branches:

$$\frac{\mathrm{d}y}{\mathrm{d}t} \approx \left.\frac{\mathrm{d}y}{\mathrm{d}x}\right|_{\text{Nullcline}} \frac{\mathrm{d}x}{\mathrm{d}t} = \frac{\mathrm{d}F(x)}{\mathrm{d}x}\frac{\mathrm{d}x}{\mathrm{d}t} = (x^2 - 1)\frac{\mathrm{d}x}{\mathrm{d}t}.$$

But

$$\frac{\mathrm{d}y}{\mathrm{d}t} = -\frac{1}{\mu}x,$$

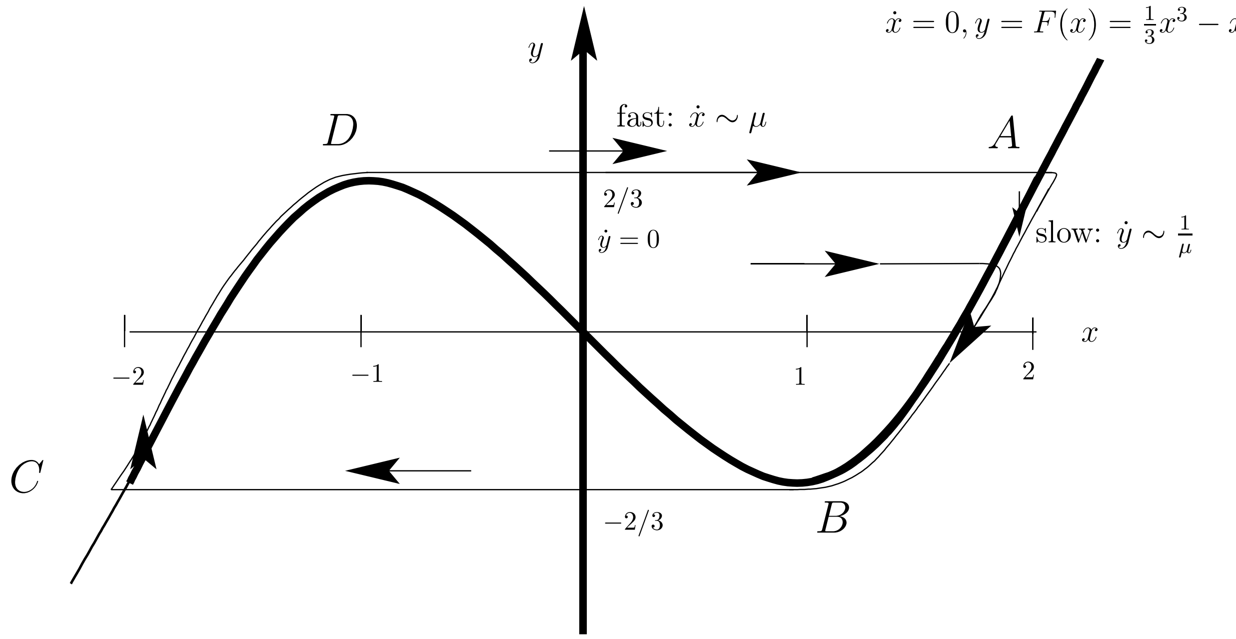


Figure 7: van der Pol nullclines

so

$$-\frac{1}{\mu}x \approx (x^2 - 1)\frac{\mathrm{d}x}{\mathrm{d}t}$$

and

$$\mathrm{d}t \approx -\frac{\mu(x^2-1)}{x}\mathrm{d}x.$$

Therefore:

$$\begin{aligned} T &= 2\int_{t_A}^{t_B} \mathrm{d}t \approx 2\int_{x_A}^{x_B} -\frac{\mu(x^2-1)}{x}\,\mathrm{d}x \\ &= 2\mu\left[\frac{x^2}{2} - \ln x\right]\Bigg|_1^2 && \text{since } (x_A = 2,\, x_B = 1) \\ &= \mu(3 - 2\ln 2) \sim \mu && \checkmark \end{aligned}$$