CCBS. 2025 Fall. Lecture 2. Biochemical reaction networks and its dynamics.

(2.1) Notations of (Bio) chemical reactions

(2.2) Estimates of enzymatic reaction rates

(2.3) Dynamics of chemical reaction networks (CRN)

(2.4) Analysis of 1D, 2D dynamics by phase portrait

(2.5) Local stability analysis

(2.6) Building blocks of bioregulation

(2) Biochemical reactions in cells

- Changes in cells happen via chemical reactions.
  (which are in turn kinetically governed by diffusion.)
- Chemical reactions in cells tend to happen in <u>constant temperature and pressure</u>. (Bio vs Chem)

So whether and when a reaction happens is governed by <u>enzymes</u> i.e. catalysts.

— Thermodynamically favorable reactions can take years.
  e.g. spontaneous degradation of glucose.
  spontaneous breaking of peptide bonds.
  spontaneous hydrolysis of ATP.

But enzymes speed up reactions by 10^{10} or more!

(2.1) Notations of (Bio) chemical reactions

- There are two ways we write chemical reactions.

Reaction types	Notation	Meaning	Examples
Elementary 基元反应	Straight Arrows	Implies reaction mechanism. Key = "all players included"	$E+S \rightleftharpoons C \rightarrow E+P$ $gene + RNAP \rightleftharpoons C_0 \rightarrow C_1 \leftarrow C_2 \leftarrow \cdots \leftarrow C_N \rightarrow gene + RNAP + mRNA$
Composite 复合反应	Squigly arrows or Net change notation	May have hidden mechanisms, reactions, species.	$S \rightsquigarrow P$ $gene \rightsquigarrow gene + mRNA$ $(S,P) \rightsquigarrow (S-1, P+1)$ $mRNA \rightsquigarrow mRNA+1$

— Elementary. — meaning it's an irreducible reaction step.
(implies reaction mechanism) you can't break it down further, or it's useless to do so for your concern.

Straight arrows. $E+S \rightleftharpoons C \rightarrow E+P$.

$gene + RNAP \rightleftharpoons C_0 \rightarrow C_1 \rightarrow C_2 \cdots \rightarrow C_N \rightarrow gene + RNAP + mRNA$

— Composite — it only describes the net change of several steps of reactions.
(may have hidden mechanism).

Squigly arrows. $S \rightsquigarrow P$.

$gene \rightsquigarrow gene + mRNA$.

(could have hidden reactants ...)

Another notation for composite. — focus on change of molecule numbers.

$(S, P) \rightsquigarrow (S-1, P+1)$.

$mRNA \rightsquigarrow mRNA+1$.

— Example: — cell replicating, N becomes 2N.

$\Rightarrow$. Composite. $N \rightsquigarrow 2N$.

or. $N \rightsquigarrow N+1$.

— Photon doubles in a laser.

photon + atom (activated) $\boxed{\longrightarrow}$ 2 photon + atom ground.

— Diffusion into a cell through a passive channel on membrane

$A_{out} \boxed{\longrightarrow} A_{in}$

— ATPase pumping H^+ out of the cell.

$H^+_{in} \boxed{\rightsquigarrow} H^+_{out}$

(2.2) Estimates of Reaction rates.

- Enzymatic reactions happen by Enzyme – substrate collide, then bind, then enzyme's atoms shape substrate in particular ways, s.t. eventually substrate is transformed into product. (with atoms in different locations.)

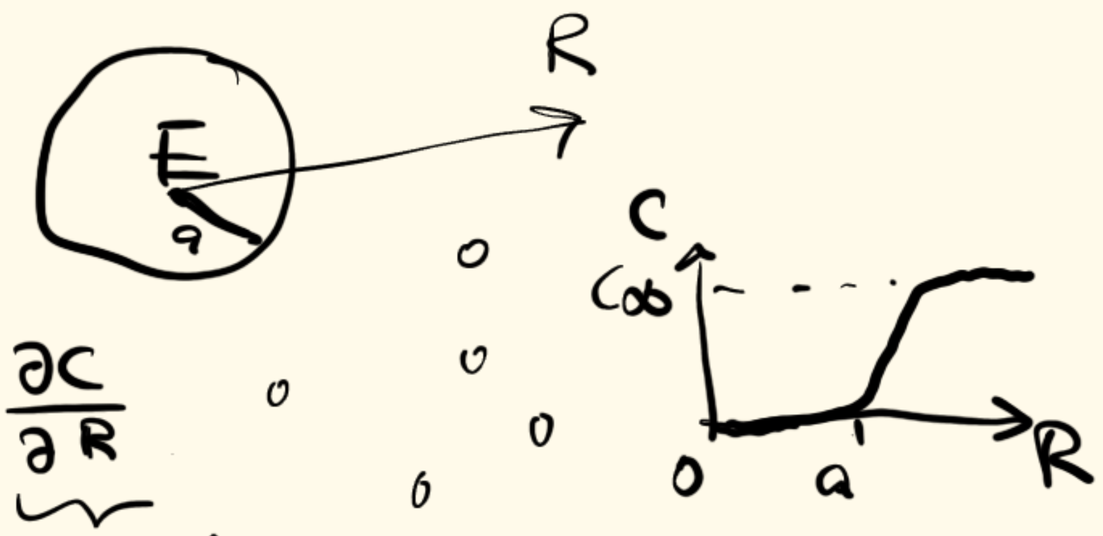
- So. two steps. bind. then. catalysis (with possibly complicated kinetics.)

$$E + S \rightleftharpoons C \rightsquigarrow E + P$$

- The fastest reaction rate is limited by association rate. (react immediately after association.) which is governed by diffusion.

so-called "diffusion limited on rate".

- Like in heat diffusion.



flux at a point on E surface $= j(a) = D \frac{\partial C}{\partial R}$ (gradient)

Roughly. $\frac{\partial C}{\partial R}\Big|_a \sim \frac{C_\infty}{a} \Rightarrow j = D\frac{C_\infty}{a}$ — conc. in the solution away from E.

(More detail: Cons. of mass $\Rightarrow$ $4\pi R^2 j$ is const. $\Rightarrow$ $j \propto \frac{1}{R^2}$.
$\Rightarrow \frac{dC}{dR} = j \propto \frac{1}{R^2} \Rightarrow C(R) = \frac{A}{R} + B$. A, B const.
Boundary condition: $C(a)=0$. $C(\infty)=C_\infty$. So $B=C_\infty$. $A=-aC_\infty$.
$\Rightarrow C(R) = C_\infty(1-\frac{a}{R}) \Rightarrow j = \frac{\partial C}{\partial R}|_a = \frac{C_\infty a}{R^2}|_a = \frac{C_\infty}{a}$.)

$\Rightarrow J = j 4\pi a^2 = 4\pi D a C_\infty := k_{on} C_\infty$

$\Rightarrow k_{on} = 4\pi D a \sim 10 \cdot 10^2\ \mu m^2/s \cdot 1\ nm \cdot \frac{6\times10^{23}}{mol} \cdot \frac{1L}{10^{15}\mu m^3}$

$\sim 10^{24+3-3-15}\ s^{-1} M^{-1}$

$\sim 10^9\ s^{-1} M^{-1}$:

(protein $a \sim 1nm$. metabolite $D \sim 10^2 \mu m^2/s$ to $10^3 \mu m^2/s$).

So. if $C \sim 1mM$. (metabolites) then it's 10^6 reactions/s per enzyme.

- Most enzymes are much slower. bottle-necked by the catalysis step., typically around $10 - 10^2$ reactions/s.

- Note that. for elementary reactions. (i.e. once collide, react.) we have the flux of $E+S \to C$ is $k_{on} E S$. (conc. of E, S.)
  Since each E reacts at rate $k_{on} S$.

This is called the law of mass action.

It gives how the flux scales with reactant concentrations!

(2.3). Rate equation of CRN.

- A generic chemical reaction. (elementary or composite)

$$\alpha_1 X_1 + \alpha_2 X_2 + \cdots + \alpha_n X_n \longrightarrow \beta_1 X_1 + \cdots + \beta_n X_n$$

↑ reactant stoichiometry ⇝ ↑ product stoichiometry

Reaction stoichiometry: $\gamma_j = \beta_j - \alpha_j$ (net change) $j=1,\dots,n$.

Net change notation:

$$(X_1, \dots, X_n) \longrightarrow (X_1+\gamma_1, \dots, X_n+\gamma_n)$$

- every time this reaction happens, x_j change by γ_j number of molecules.
- v is reaction rate / flux. ⇒ x_j flux caused by this reaction is $\gamma_j v$.

- Several reactions form a <u>network</u> (CRN).

m reactions. $i=1,\dots,m$.

n species. $j=1,\dots,n$.

$$\alpha_{i1} X_1 + \cdots + \alpha_{in} X_n \longrightarrow \beta_{i1} X_1 + \cdots + \beta_{in} X_n$$

$$\frac{d}{dt} x_j = \sum_i \gamma_{ij} v_i$$

$$= \sum_{i:\, \gamma_{ij}>0} \gamma_{ij} v_i - \sum_{i:\, \gamma_{ij}<0} |\gamma_{ij}| v_i$$

$$= f_j^+ - f_j^- = f_j$$ production, degradation.

$$\frac{dx}{dt} = \Gamma v = f^+ - f^-$$

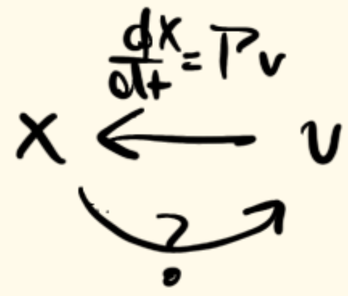
$x \in \mathbb{R}^n_{\geq 0}$, $\alpha_i \in \mathbb{Z}^n_{\geq 0}$

$x \longleftarrow v$.

- Note that this holds <u>always</u>, for both elementary and composite.
  Since all we've done is "accounting" for where molecules went.
- Only depends on γ, not α or β. so "net change notation" is enough

- We can write this even if we don't know the regulatory mechanism!

- But to have a full description of the dynamics.



how does v depend on x?

i.e. reaction kinetics.

- Kinetics. — Law of Mass Action.

— Elementary reactions' kinetics follow the law of mass action. (mechanism!)

k — reaction rate constant.

$$\alpha_1 X_1 + \alpha_2 X_2 + \cdots + \alpha_n X_n \xrightarrow{k} \beta_1 X_1 + \cdots + \beta_n X_n$$

$$v(x) = \text{reaction rate} = \text{flux} = k\, x_1^{\alpha_1} x_2^{\alpha_2} \cdots x_n^{\alpha_n}.$$

e.g. $E + S \xrightarrow{k_{on}} C$. rate $= k_{on} E S$.

— Now with several reactions forming a network.

$$\alpha_{i1} X_1 + \cdots + \alpha_{in} X_n \xrightarrow{(k_i)} \beta_{i1} X_1 + \cdots + \beta_{in} X_n.$$

$$v_i = k_i x_1^{\alpha_{i1}} \cdots x_n^{\alpha_{in}} = k_i x^{\alpha_i} \qquad x \in \mathbb{R}^n_{>0}, \quad \alpha_i \in \mathbb{Z}^n_{\geq 0}$$

$$\frac{d}{dt} x_j = \sum_i \nu_{ij} v_i = \sum \nu_{ij} k_i x^{\alpha_i}$$

$$= \sum_{i:\, \nu_{ij} > 0} \nu_{ij} v_i - \sum_{i:\, \nu_{ij} < 0} |\nu_{ij}| v_i$$

$$= f_j^+(x) - f_j^-(x). \qquad \text{production, degradation}$$

$$\frac{dx}{dt} = \Gamma v(x) = \Gamma \Lambda_k x^{\alpha} \qquad \Lambda_k = \text{diag}(k), \quad \alpha \in \mathbb{Z}^{m \times n}_{\geq 0}$$

$$= f(x)$$

$$= f^+(x) - f^-(x).$$

Exp 1. $\phi \underset{\lambda}{\overset{k}{\rightleftharpoons}} P$ production and degradation of a molecule.

$$\frac{dP}{dt} = k - \lambda P.$$

Exp 2. TxTl. $G \xrightarrow{k_{tx}} G + M$. $M \xrightarrow{k_{tl}} M + P$.

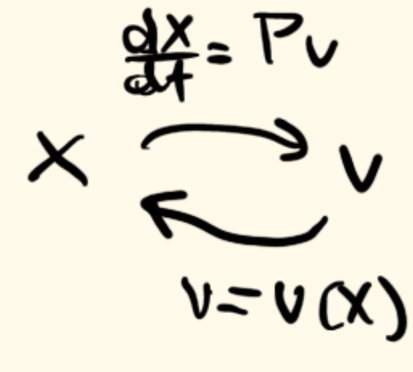
$M \xrightarrow{\gamma_m} \phi$ $P \xrightarrow{\gamma_p} \phi$.

G is conserved. a constant.

$$\frac{dM}{dt} = k_{tx} G - \gamma_m M.$$
$$\frac{dP}{dt} = k_{tl} M - \gamma_p P.$$

These are (autonomous) dynamical systems

$$\frac{dx}{dt} = f(x).$$



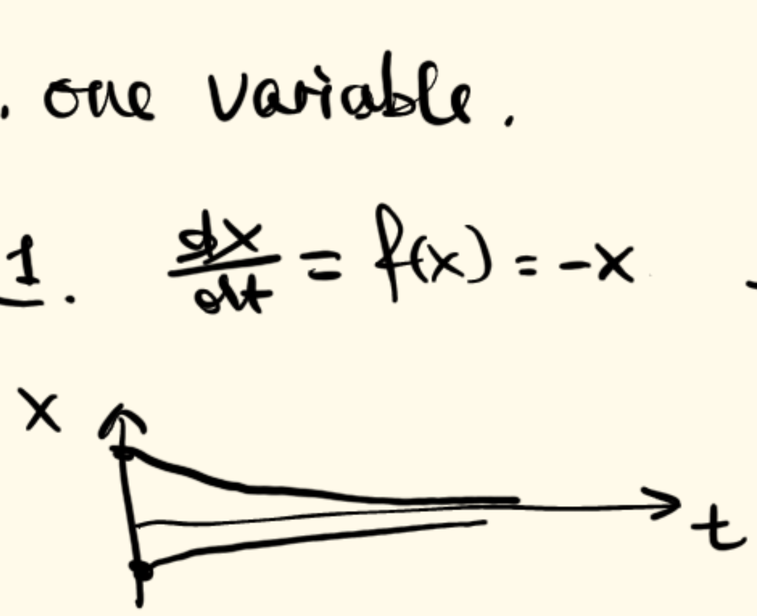
How to understand their dynamics?

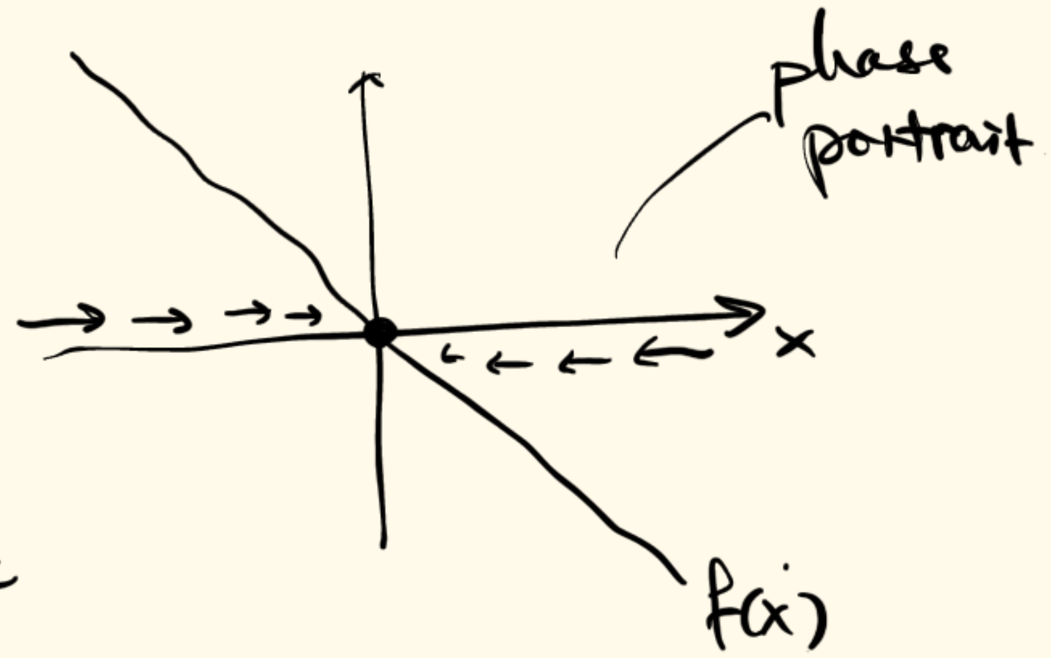
We start simple. — what kind of simple? low dim.

(2.1) Dynamics of 1D and 2D systems.

- 1D. one variable.

Exp 1. $\frac{dx}{dt} = f(x) = -x$





Fixed pt: x^* s.t. $f(x^*) = 0$. Don't change if you starts there.

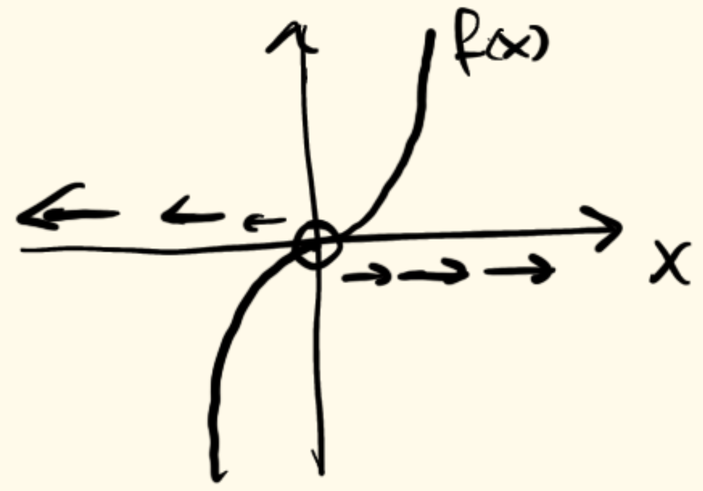
Starting at different initial condition,

all goes to $x = 0$. ← Stable fixed pt.

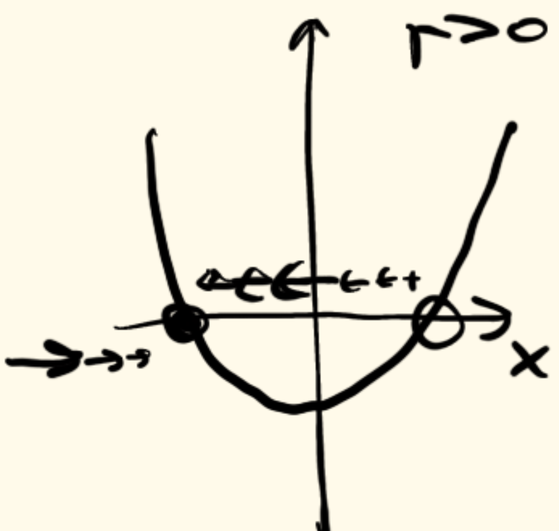
Exp 2. $\frac{dx}{dt} = x^3$.

$x^* = 0$ is also a fixed pt.

but unstable.

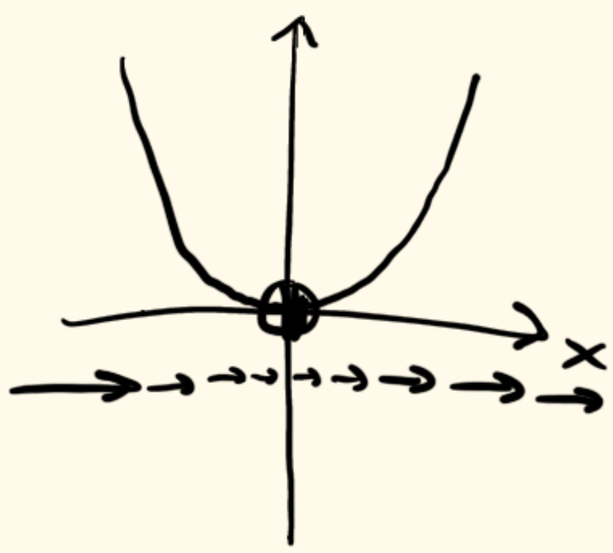


Exp 3. $\frac{dx}{dt} = x^2 + r$



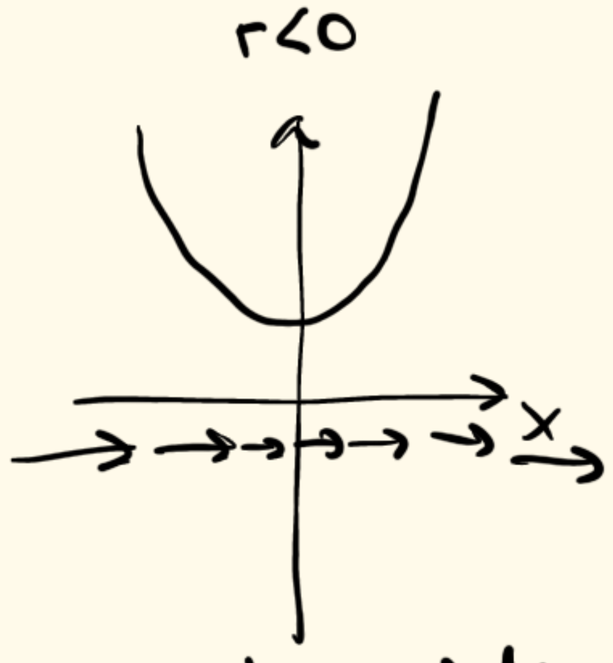
Locally stable.

Stable in a region.



$x^* = 0$ is a fixed pt.

= Half stable".



nowhere stable.

1D can only do this. Stable or unstable.

= go away". or = converge"

because traj is 1D as well. can't go back

Exp 4. Bio. prod minus deg. $\dot{x} = \mu - x$. $\phi \overset{\mu}{\underset{1}{\rightleftarrows}} x$

positive.

* what's the difference?

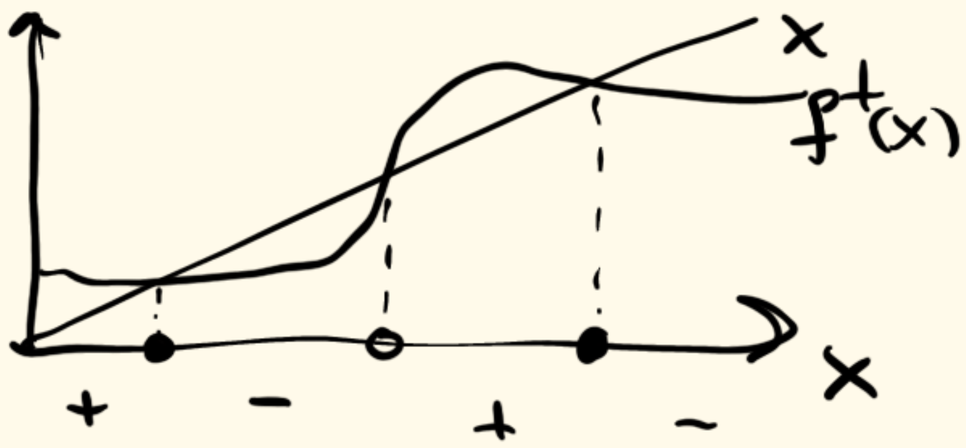
- $f(x)$ in bio is $f^+(x) - f^-(x)$.

No fine tuning! e.g. no = half stable".

* A "Geometric" way of thinking
  - only the rough shape of $f(x)$ is needed to determine the dynamics
  - Intuitive to design / construct dynamics.

• Exp 5. Bistable.

How to create a 1D (bio) bistable system?



$$\dot{x} = f^+(x) - x$$

• 2D system. $\dot{x}_1 = f_1(x)$, $\dot{x}_2 = f_2(x)$

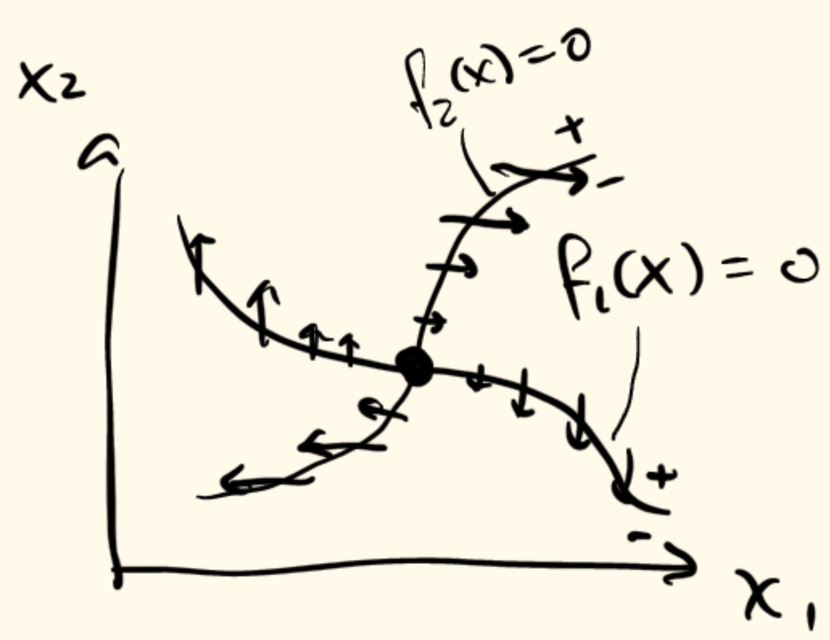
  - In 2D, trajectories can "go back" along any axis.

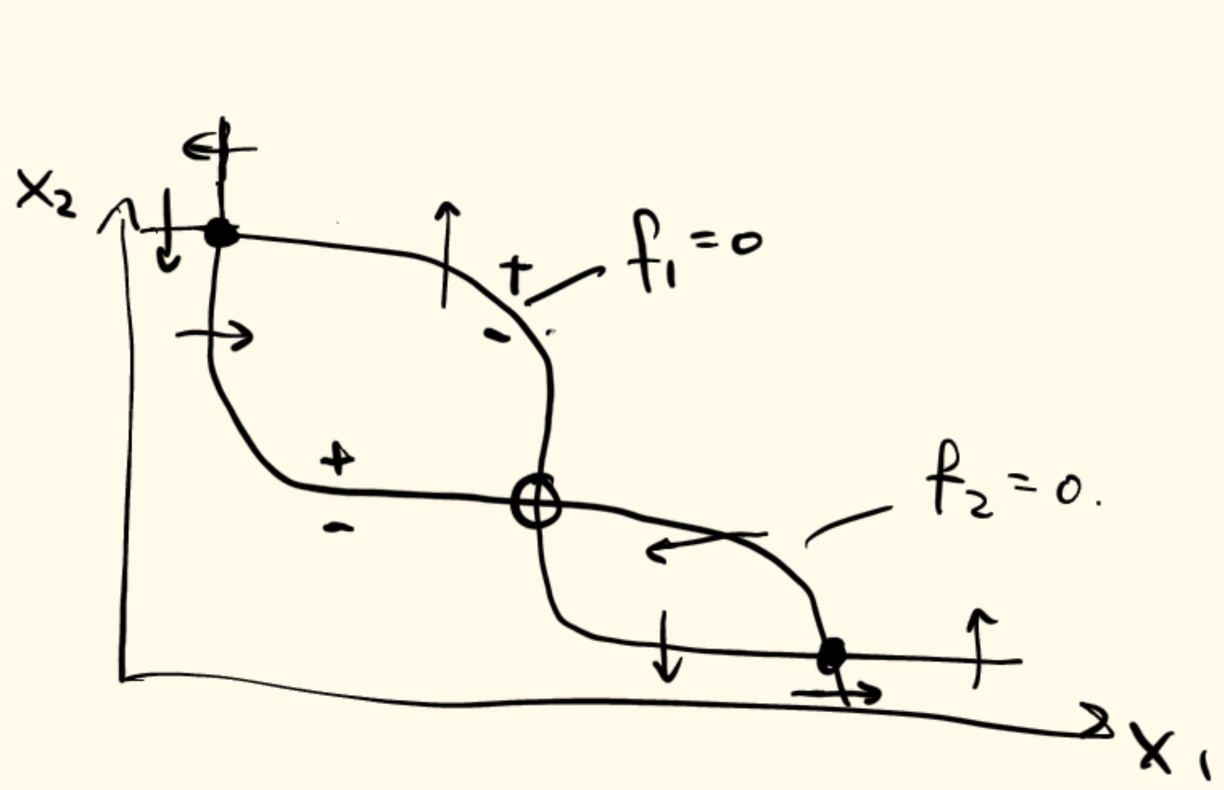
but trajectories <u>can't overlap</u> itself.

  - On top of <u>fixed points</u>. $f_1(x^*) = f_2(x^*) = 0$

    Also <u>nullclines</u> $f_1(x) = 0$. | $f_2(x) = 0$. (only one var can change on nullclines.)

  - These are enough to determine dynamics.



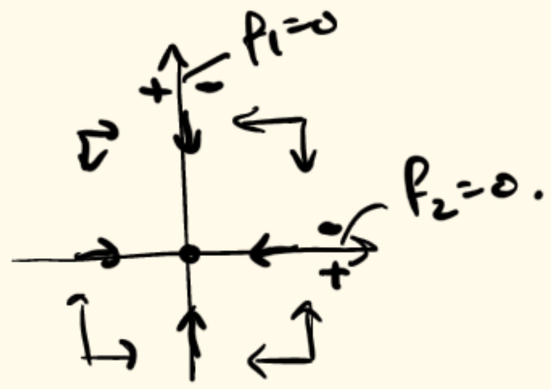


- Types of dynamics in 2D:

— Dynamics about a fixed point

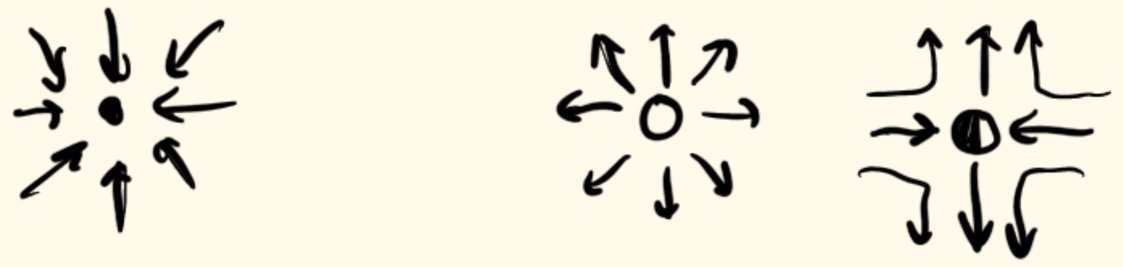
$\dot{x}_1 = -x_1$

$\dot{x}_2 = -x_2$



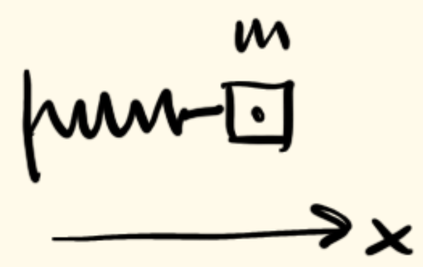
others.

$\frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} -1 & -1 \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$



— New in 2D: center.

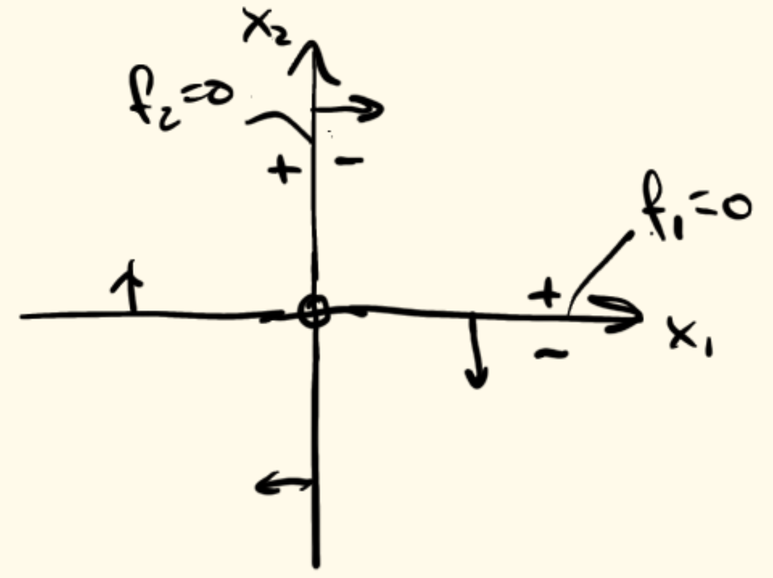
$F = m\ddot{x}$ $\quad F = -kx$.



$\Rightarrow \quad m\ddot{x} + kx = 0$

$\Rightarrow \quad x_1 = x, \quad x_2 = \dot{x}$. so $\quad m\dot{x}_2 + kx_1 = 0$.

$\frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\frac{k}{m} & 0 \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$



Does traj. spiral in or out?

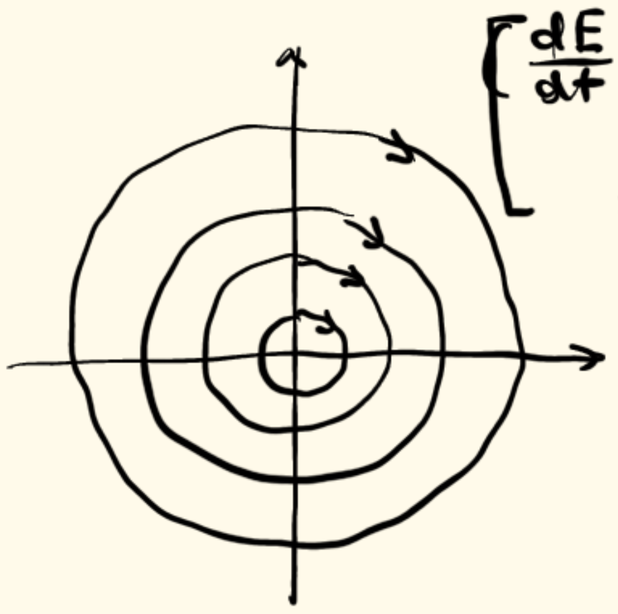
Neither.

$x=0$ is a <u>center</u>. not stable. (traj. doesn't converge to it.)

How to see this? In this case. we can look at energy.

Energy $\frac{1}{2}mx_2^2 + \frac{1}{2}kx_1^2 = E$

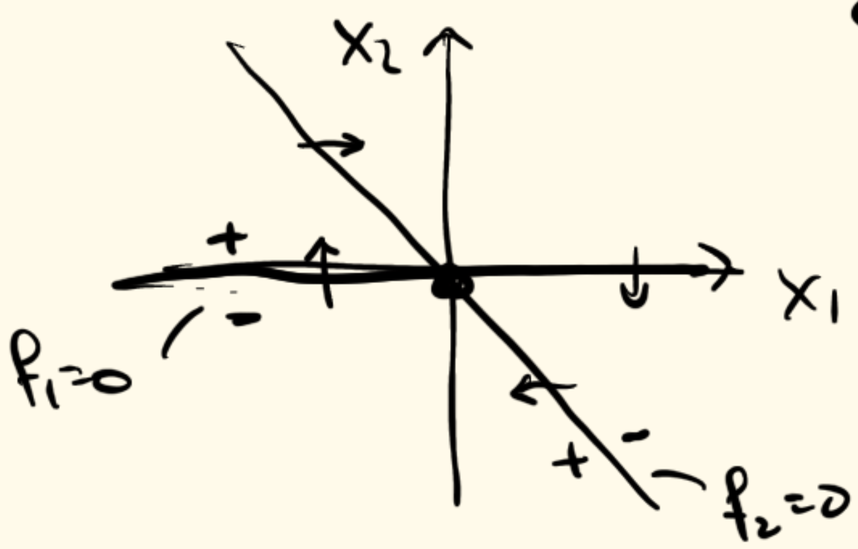
is conserved.



$$\left[\begin{aligned} \frac{dE}{dt} &= mx_2\dot{x}_2 + kx_1\dot{x}_1 \\ &= -mx_2\frac{k}{m}x_1 + kx_1x_2 \\ &= -kx_1x_2 + kx_1x_2 \\ &= 0 \end{aligned}\right]$$

— Add friction. $m\ddot{x} + k_f\dot{x} + k_s x = 0$

$$\Rightarrow \frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\frac{k_s}{m} & -\frac{k_f}{m} \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$



Spiral in or out? $\Rightarrow$.

$$E = \frac{1}{2}mx_2^2 + \frac{1}{2}k_s x_1^2$$

$$\frac{dE}{dt} = m x_2\left(-\frac{k_s}{m}x_1 - \frac{k_f}{m}x_2\right) + k_s x_1 x_2$$

$$= -k_f x_2^2 \leq 0 \text{ unless } x_2 = 0.$$

= Circle shrinks over time..."

$\Rightarrow$.

— New in 2D : limit cycles. (a "fixed orbit").

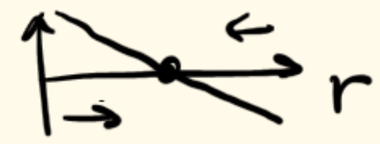
Stable

Unstable

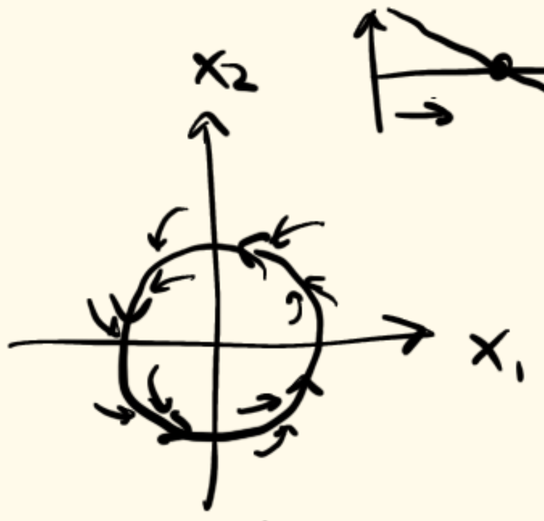
e.g. compose two 1D systems in polar coordinates.

$$\dot{\theta} = k.$$

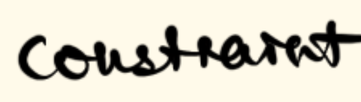
$$\dot{r} = 1 - r.$$



$\Rightarrow$.



To analyze such. usually it's easier to just simulate:

- 3D and beyond.
  - Traj can roam freely. no constraint due to dimensions anymore. e.g. 
  - Chaos, etc... Nothing very useful can be said.

— Best to just simulate and look.

— "Lack of structure" is not a structure.
Not useful.

— To say something for ≥3 dim. still by dimension reduction.

⟶. Reduce to 0-d : fixed point.
Reduce to 1-d : fixed point, limit cycles.
Reduce to 2-d : then analyze on 2d ~

- Fixed point <u>local</u> dynamics in general. ⇒ Local is always Linear.

$\frac{dx}{dt} = f(x)$. ⇒. consider small perturbation. Δx. around x.

$\frac{d}{dt}(x+\Delta x) = \frac{d}{dt}\Delta x = f(x+\Delta x) \approx f(x) + \frac{\partial f}{\partial x}(x)\Delta x$.

At $x = x^*$, a fixed point. so $f(x^*)=0$.

⇒. $\frac{d\Delta x}{dt} = A\Delta x$. $A = \frac{\partial f}{\partial x}(x^*)$.

— Linear dynamics $\frac{dx}{dt} = Ax$. fixed pt. $x=0$.

• Scalar $\frac{dx}{dt} = ax$. ⇒ $x(t) = x(0)e^{at}$.

• Eigenvector. (λ, v) s.t. $Av = \lambda v$.

⇒. let $x(0) = y(0)\,v$. then.

$\frac{1}{\Delta t}(x(\Delta t) - x(0)) = Ax(0)$

$\frac{y(\Delta t) - y(0)}{\Delta t} v = Av\,y(0) = \lambda v\,y(0)$

⇒. $\frac{dy}{dt} = \lambda y$ ⇒. $y(t) = y(0)e^{\lambda t}$.

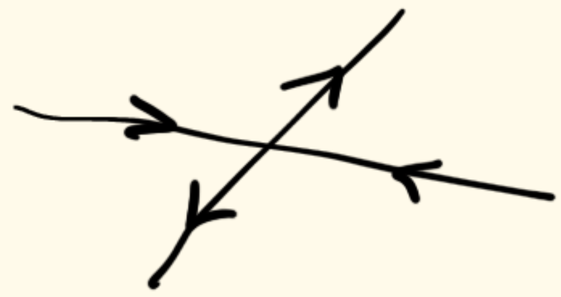
⇒. $x(t) = y(0)e^{\lambda t}\,v$.

- So behaviors can be decomposed in terms of eigenvectors

(Start on an eigenvector. Stay on the eigenvector.)

real part. — $Re(\lambda) > 0$. — unstable

$Re(\lambda) < 0$. — stable.



- Imaginary eigenvalue?

— Rotations. (pairs of eigenvectors.)

↳ Rotation on the plane.

A is Hurwitz: $Re(\lambda) < 0$. for all $\lambda \in$ Eigenvalue(A).

This guarantees $x=0$ is stable.

— 2D. $A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$.

$\lambda_1 + \lambda_2 = \operatorname{tr} A = a_{11} + a_{22} < 0$.

$\lambda_1 \lambda_2 = \det A = a_{11}a_{22} - a_{12}a_{21} > 0$.

This is necessary and suff.

Such rules in general are called. Hurwitz criterion.