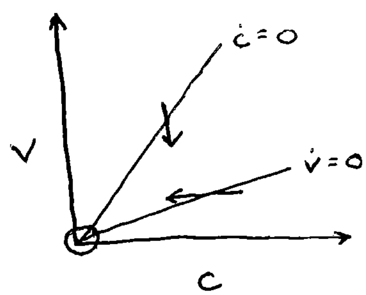
Lecture 3 : Multistability

- Null clines and cooperativity
- multiple steady-states
- positive feedback revisited
- irreversible transitions
- bistability and noise
- cross repression

Recap: the intersection of null clines are the steady-states of the system

HIV:

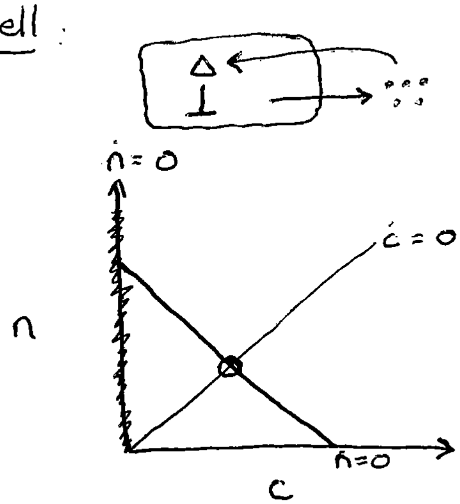
$$T + HIV \longrightarrow T^*$$



$$\frac{dc}{d\tau} = \theta v - c$$

$$\frac{dv}{d\tau} = Nc - Kv$$

cell-cell:

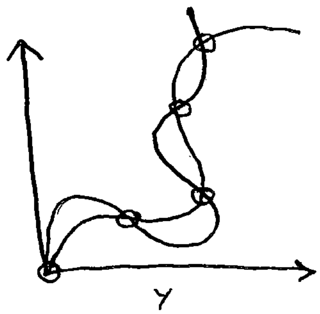


$$\frac{dn}{d\tau} = Kn(1-n) - \delta cn$$

$$\frac{dc}{d\tau} = \theta n - c$$

What has to happen to have multiple steady-states?

Null clines have to intersect ~~at~~ multiple points



Each intersection is
a steady state (stable or unstable)

Multistability usually ~~refers~~ refers
to multiple steady states

What types of equations curve? $\Longrightarrow$ polynomials
(or when there is a null cline @ $x=0$ or $y=0$)

In biology, polynomial null clines usually arise from cooperativity

examples:

(4 binding sites)

$$\frac{K_4 X^4}{1 + K_4 X^4 + K_3 X^3 + K_2 X^2 + K_1 X}$$

(Ken: binding polynomials)

cascades:

$X^n \rightarrow S^n \rightarrow R^N$

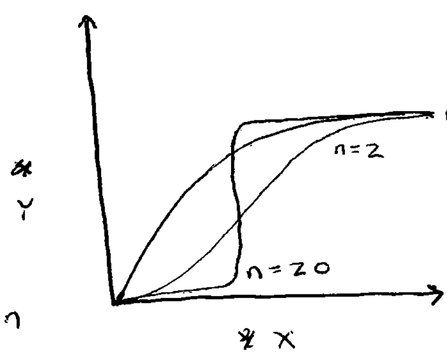
m steps

cooperativity

$n \times m$

multi-site phosphorylation

$O \xrightarrow{E} O_p \xrightarrow{E} O_p^p$



$$Y = \frac{x^n}{1+x^n}$$

Competition Models:

eg, sheep/rabbits, lions/hyenas, etc

two competing species for limited resources

$$\frac{dX}{dt} = \underbrace{k_x X}_{\text{growth}} \Big(1 - \underbrace{\frac{X}{N_1} - \overset{\text{competitive edge}}{a} \frac{Y}{N_1}}_{\text{carrying capacity}}\Big)$$

$$\frac{dY}{dt} = k_Y Y \left(1 - \frac{Y}{N_2} - b\frac{X}{N_2}\right)$$

$$\tau \equiv t \cdot k_x \qquad x \equiv \frac{X}{N_1} \qquad y = \frac{Y}{N_2} \qquad K \equiv \frac{k_Y}{k_x} \qquad \alpha \equiv a\frac{N_2}{N_1} \qquad \beta \equiv b\frac{N_1}{N_2}$$

$$\boxed{\begin{aligned} \frac{dx}{d\tau} &= x(1 - x - \alpha y) \\ \frac{dy}{d\tau} &= y(1 - y - \beta x) \end{aligned}}$$

$K = 1$

$\alpha = 2$

$\beta = 2$

@ steady-state,

$$0 = x(1 - x - \alpha y)$$

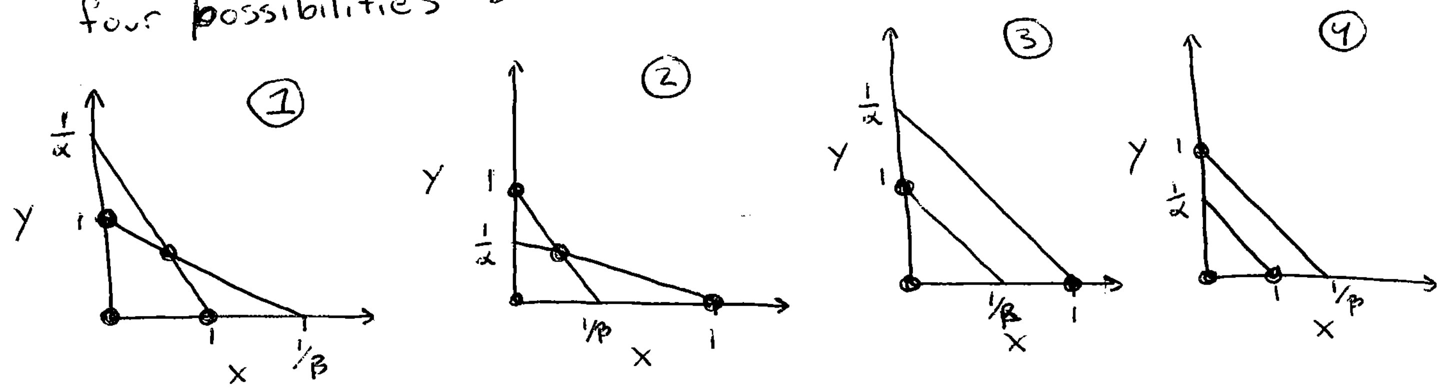
$$0 = Ky(1 - y - \beta x)$$

null clines at $x = 0$ and $y = 0$

$$0 = 1 - x - \alpha y \qquad y_1 = \frac{1-x}{\alpha}$$

$$0 = 1 - y - \beta x \qquad y_2 = 1 - \beta x$$

four possibilities based on the values of x and y



4 steady-states

$(0,0) \quad (1,0) \quad (0,1)$

$y_1 = y_2$

$$\frac{1-x}{\alpha} = 1 - \beta x$$

$$1 - x = \alpha - \alpha\beta x$$

$$1 - \alpha = x - \alpha\beta x \qquad \left(x = \frac{1-\alpha}{1-\alpha\beta} \qquad y = \frac{1-\beta}{1-\alpha\beta} \right)$$

Stabilities

$$J = \begin{bmatrix} 1 - 2x - \alpha y & -\alpha x \\ -\beta y & 1 - 2y - \beta x \end{bmatrix}$$

@ $(0,0)$ $\quad J = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$ $\quad \tau = 1 + 1 > 0$ always unstable

@ $(1,0)$ $\quad J = \begin{bmatrix} \cancel{1-2}\ -1 & -\alpha \\ 0 & 1-\beta \end{bmatrix}$ $\quad \tau = \cancel{1} - \beta$

$\Delta = \beta - 1 > 0$

stable when $\beta > 1$

@ $(0,1)$ $\quad J = \begin{bmatrix} 1-\alpha & 0 \\ -\beta & -1 \end{bmatrix}$ $\quad \tau = -\alpha$

$\Delta = \alpha - 1 > 0$

stable when $\alpha > 1$

@ $\left(x = \frac{1-\alpha}{1-\alpha\beta},\ y = \frac{1-\beta}{1-\alpha\beta} \right)$

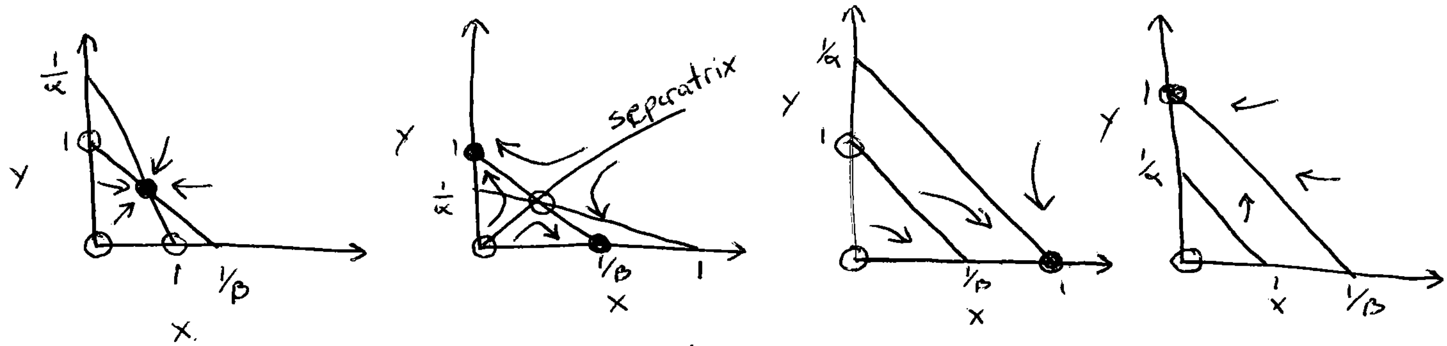
$$\tau = 1 - 2\left(\frac{1-\alpha}{1-\alpha\beta}\right) - \alpha\left(\frac{1-\beta}{1-\alpha\beta}\right) + 1 - 2\left(\frac{1-\beta}{1-\alpha\beta}\right) - \beta\left(\frac{1-\alpha}{1-\alpha\beta}\right)$$

$$= \frac{1 - \alpha\beta - 2 + 2\alpha - \alpha + \alpha\beta + 1 - \alpha\beta - 2 + 2\beta - \beta + \alpha\beta}{1 - \alpha\beta}$$

$$= \frac{\alpha + \beta - 2}{1 - \alpha\beta} < 0 \qquad \text{stable when } \alpha + \beta > 2$$

Complete phase plane

● = stable ○ = unstable



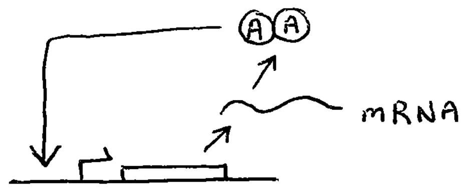
multistability (initial condition matters)

- A change in parameters or a random perturbation can ~~ch~~ cause the system to switch between states

- ~~Hcely~~ Two species sharing same resources are unlikely to coexist

- stable ⇒ 1 goes extinct ⇒ climate change ⇒ other species walks in on the system switches to a new state

Positive feedback revisited



$$\frac{dM}{dt} = \beta_M \frac{KA^2}{1+KA^2} - \gamma_M M$$

$$\frac{dA}{dt} = \beta_A M - \gamma_A A$$

$\tau \equiv t \cdot \beta_A$ $\quad m \equiv M\sqrt{K}$ $\quad a \equiv A\sqrt{K}$

$$\boxed{\begin{aligned} \frac{dm}{d\tau} &= \frac{ba^2}{1+a^2} - gm \\ \frac{da}{d\tau} &= m - \theta a \end{aligned}}$$

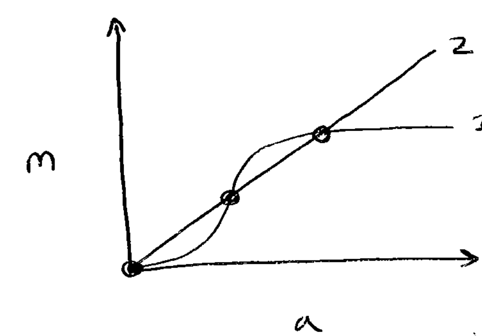
$b \equiv \frac{\beta_M \sqrt{K}}{\beta_A}$

$g \equiv \frac{\gamma_M}{\beta_A}$

$\theta \equiv \frac{\gamma_A}{\beta_A}$

null cline 1 : $m = \left(\frac{b}{g}\right)\left(\frac{a^2}{1+a^2}\right)$

null cline 2 : $m = \theta a$



3 intersections = 3 steady states

Steady - state solutions

$$\theta a = \left(\frac{b}{g}\right)\left(\frac{a^2}{1+a^2}\right)$$

$$g\theta a(1+a^2) = ba^2$$

$$g\theta a^3 - ba^2 + g\theta a = 0$$

(the math in this business is often a polynomial root solving game)

$$a_1 = 0$$

$$g\theta a^2 - ba + g\theta = 0$$

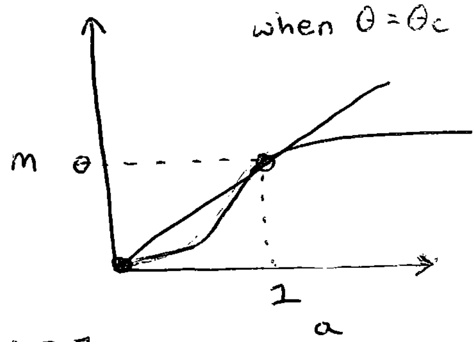
$$a_2 = \frac{b - \sqrt{b^2 - 4g^2\theta^2}}{2g\theta} \qquad a_3 = \frac{b + \sqrt{b^2 - 4g^2\theta^2}}{2g\theta}$$

roots a_2 and a_3 are equal when:

$$b^2 - 4g^2\theta^2 = 0$$

$$b = 2g\theta$$

$$\boxed{\theta_c = \frac{b}{2g}}$$



$$a_1 = a_2 = \frac{b}{2g\theta} = \frac{b}{2g\left(\frac{b}{2g}\right)} = 1$$

$$m_1 = m_2 = \theta$$

calculate stabilities

$$J = \begin{bmatrix} -g & \frac{2ba}{(1+a^2)^2} \\ 1 & -\theta \end{bmatrix}$$

$\tau = -g - \theta$ (always negative

stability determined by

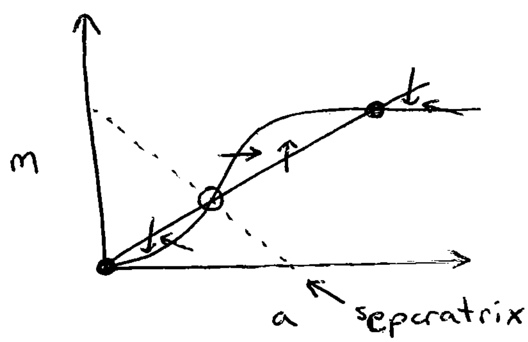
$$\Delta = g\theta - \frac{2ba}{(1+a^2)^2}$$

when $\theta = \theta_c$

$$\Delta = \frac{b}{2} - \frac{2b}{(1+1)^2} = 0$$

$a > 1 \quad \Delta > 0$ (stable)

$a < 1 \quad \Delta < 0$ (saddle-unstable)

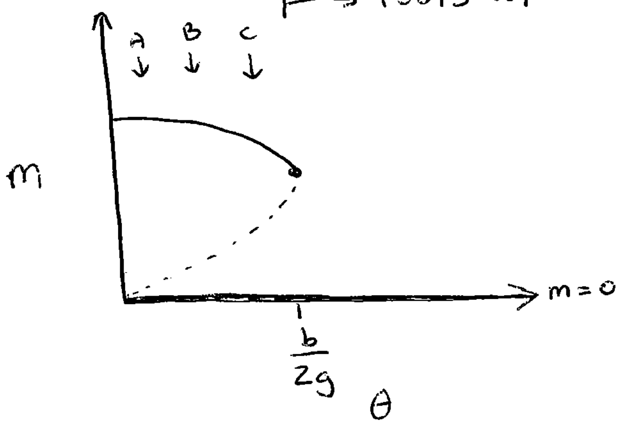


~~Can redraw this~~ as a ~~bifurcation~~ :

Can redraw as bifurcation diagram

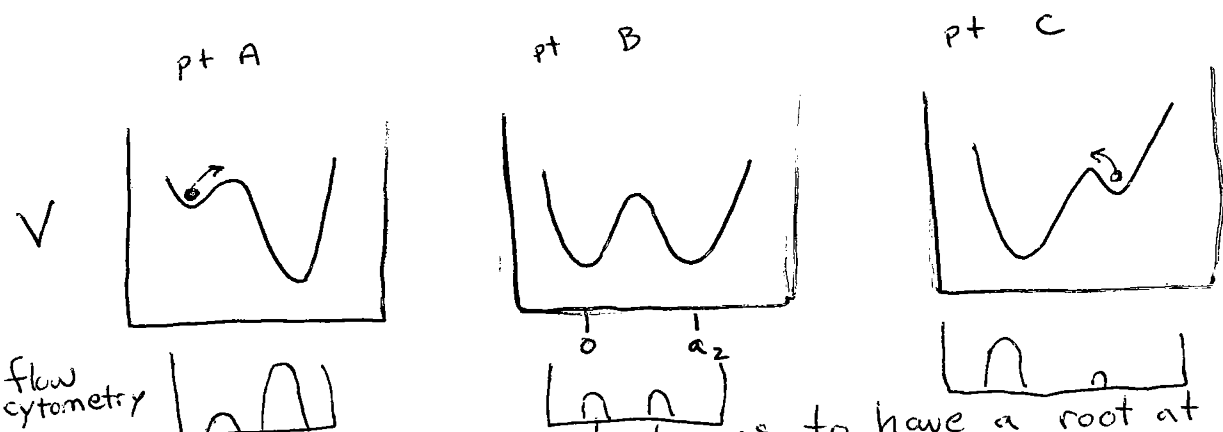
(changes in stability or behavior as a function of a parameter)

⟼ roots a_1 and a_2 become imaginary and vanish

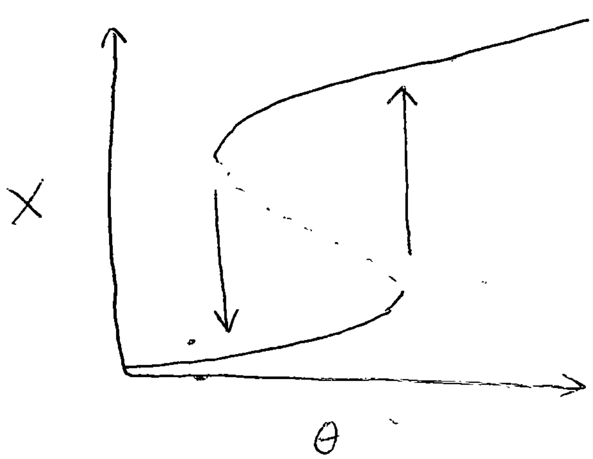


- discontinuous transition
- hysteresis
- stability to noise

Energy diagrams



when you are not so lucky as to have a root at 0



2 more ways to get bistability

cross repression

$A \rightleftarrows B$

intuition: 2 steady-states
HIGH A, LOW B , HIGH B, LOW A

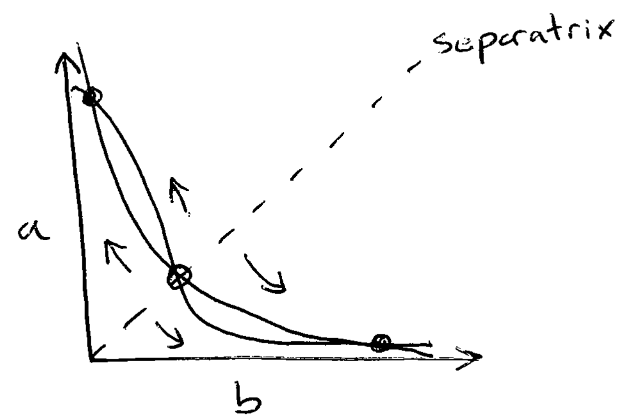
$$\frac{da}{d\tau} = \frac{1}{1+Kb^2} - a$$

$$\frac{db}{d\tau} = \frac{\beta}{1+Ka^2} - b$$

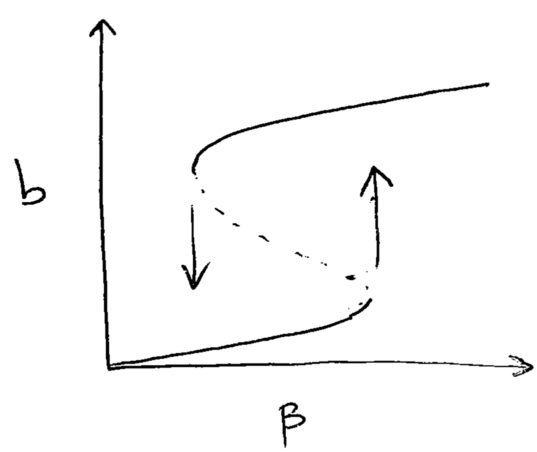
NOTE: still need cooperativity

null clines:

$$a = \frac{1}{1+Kb^2} \qquad b = \frac{\beta}{1+Ka^2}$$

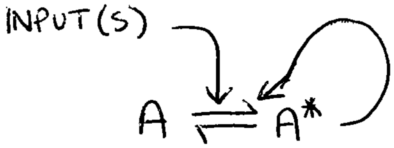


bifurcation diagram



Bistability w/ perfect Irreversibility

phosphorylation w/ feedback



$$\frac{dA^*}{dt} = S\left(A_{TOTAL} - A^*\right) + f\,\frac{A^{*n}}{K^n + A^{*n}} - \gamma A^*$$

when $n > 4$ f large

null cline: