CPIB SUMMER SCHOOL 2011: INTRODUCTION TO BIOLOGICAL MODELLING

Lecture 2.2
Analysing multi-variable differential equation models

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Recap...

- We have introduced simple ordinary differential equation (ODE) models for a single state variable.
- **Steady states** and their **stability** are crucial determinants of system dynamics.
- Changes in number or stability of steady states are called **bifurcations**.
- For 1st order **autonomous** ODEs, the **phase-line diagram** can tell us most of the qualitative information we'd like to know about the system dynamics:
  - if you can sketch the graph, you can sketch the dynamics...
  - steady states, stability AND qualitative solution behaviour (fast, slow, increasing, decreasing, etc), bifurcations.
  - solutions cannot oscillate
- We used CellDesigner to build and simulate simple one variable models.
- **We introduced models with more than one state variable:** more complex dynamics possible, analysis more difficult, often resort to computer simulation
- Here we introduce **phase-plane** techniques for ODE models with two variables.

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Toggle switch: two-gene repressor network

Rate of change of ***u***	=	production repressed by ***v***	-	degradation
Rate of change of ***v***	=	production repressed by ***u***	-	degradation

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^\beta} - u, \qquad \frac{dv}{dt} = \frac{\alpha_2}{1+u^\gamma} - v$$

- Can behave as a bistable switch, depending on parameters
- **Phase-plane analysis** very useful
- Nullclines are curves on which one variable is not changing
  - u-nullcline: $du/dt = 0$, here $u = \frac{\alpha_1}{1+v^\beta}$
  - v-nullcline: $dv/dt = 0$, here $v = \frac{\alpha_2}{1+u^\gamma}$
  - Steady states where nullclines cross
  - Stability requires more maths - linear algebra, eigenvalues, etc ...

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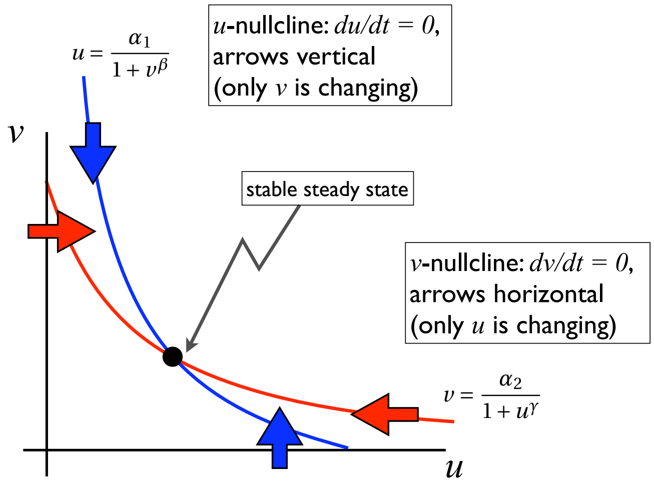
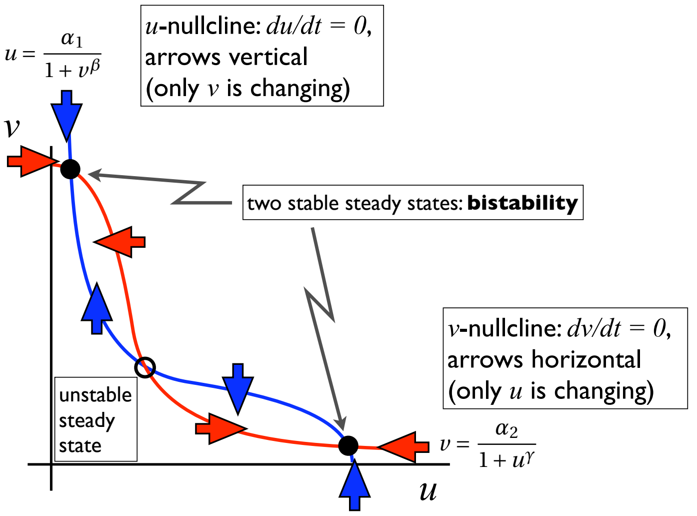
Two-gene repressor network: $\beta = \gamma = 1$

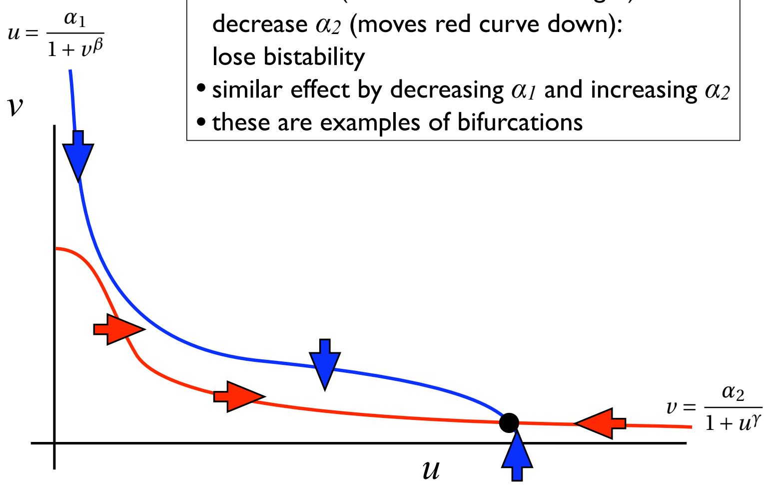


Two-gene repressor network: $\beta, \gamma > 1$

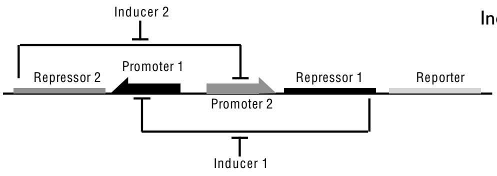


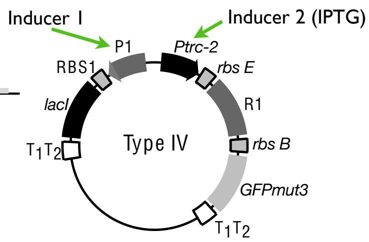
Two-gene repressor network: $\beta, \gamma > 1$

- increase α_1 (moves blue curve to right) and decrease α_2 (moves red curve down): lose bistability
- similar effect by decreasing α_1 and increasing α_2
- these are examples of bifurcations

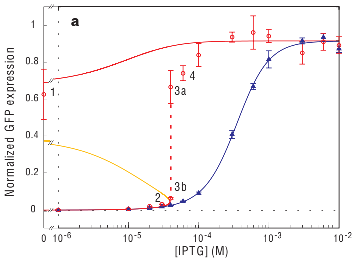


Toggle switch: implementation

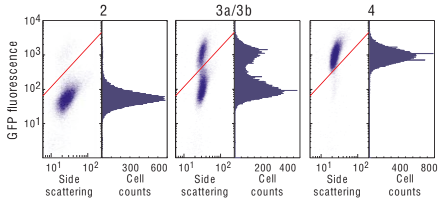




Transitions as predicted by model

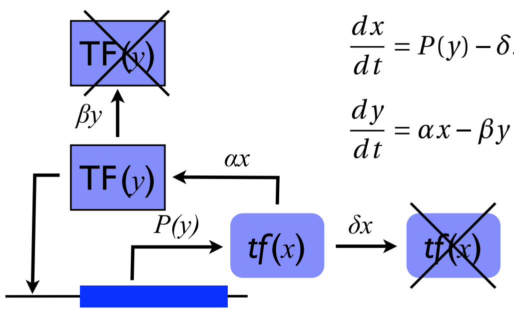


Close to bifurcation, bimodal distribution of cells



Gardner, T.S., Cantor, C.R. & Collins, J.J. (2000). *Nature* **403**, 339–342.

Transcriptional regulation revisited



$$\frac{dx}{dt} = P(y) - \delta x$$

$$\frac{dy}{dt} = \alpha x - \beta y$$

- Protein synthesis requires transcription and translation.
- Phase plane analysis quite straightforward.

Transcriptional regulation revisited

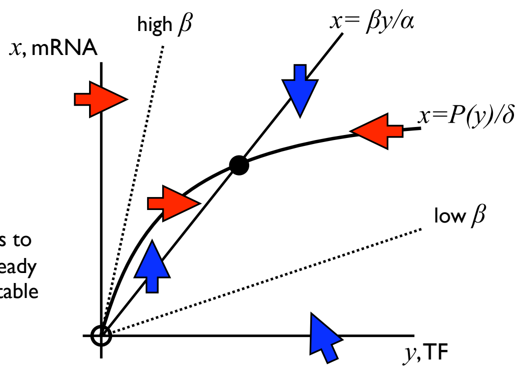
$$\frac{dx}{dt} = P(y) - \delta x$$

$$\frac{dy}{dt} = \alpha x - \beta y$$

- x-Nullcline is: $x = P(y)/\delta$ and y-nullcline is $x = \beta y/\alpha$
- Easier to think of x as a function of y, otherwise we have $y = P^{-1}(\delta x)$ where P^{-1} is the inverse function...

$$P(y)=Ay/(h+y)$$

- Increasing β or δ leads to loss of the nonzero steady state, $(0,0)$ becomes stable



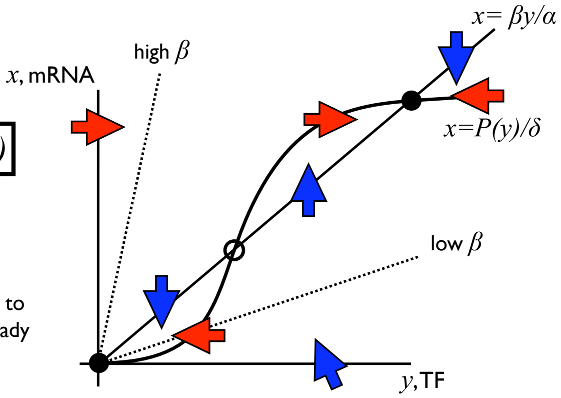
Transcriptional regulation revisited

$$\frac{dx}{dt} = P(y) - \delta x$$

$$\frac{dy}{dt} = \alpha x - \beta y$$

- x-Nullcline is: $x = P(y)/\delta$ and y-nullcline is $x = \beta y/\alpha$
- Easier to think of y as a function of y, otherwise we have $y = P^{-1}(\delta x)$ where P^{-1} is the inverse function...

$$P(y)=Ay^2/(h^2+y^2)$$



- Bistability again ...
- Increasing β or δ leads to loss of the nonzero steady states.

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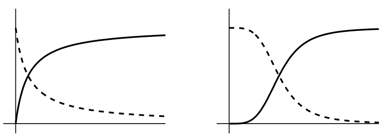
Gene network modelling

- Variables: mRNAs and proteins.
- ODE models: mass action, sigmoidal transcriptional activation and repression, linear decay and translation.



$$\frac{dx}{dt} = \text{synthesis} - \text{decay} \pm \text{transformation} \pm \text{transport}$$

- Parameters:
  - Thresholds for the sigmoidal functions;
  - effective co-operativities, can be high for indirect pathways;
  - half-lives;
  - relative contributions of multiple transcriptional regulators;
  - transfer rates, e.g. cytosol to cell surface;
  - transformation rates, e.g. cleavage, phosphorylation, binding.
- intracellular species: single equation per cell
- cell-surface: multiple equations per cell (e.g. six if we assume hexagonal cells).

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Epidemiology

Simplest model: SIR model.

- Closed population. Individuals do not enter, and leave only by death due to disease.
- Population in 3 compartments: Susceptible, Infective, or Removed (cured and now immune, or dead).
- No spatial effects (uniform mixing), and no heterogeneity in activity (important in, e.g., STDs such as AIDS).
- Negligible incubation time.
- Susceptibles move into Infective class at rate proportional to number of contacts between Susceptibles and Infectives (like law of mass action).
- Infectives removed at some rate into Removed class (*which decouples*).
- An EPIDEMIC if $I(t)>I(0)$ for some $t>0$ (i.e. if the number of infectives goes up)

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

- Constant total population

$$S + I + R = N$$

$$S + I \le N$$

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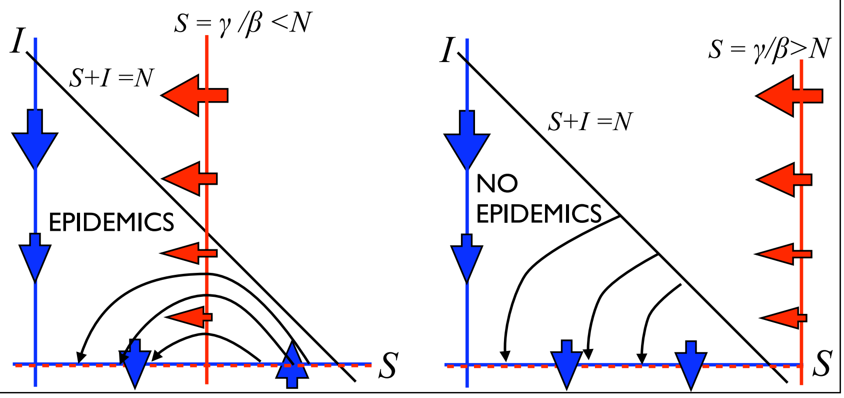
Epidemiology $\frac{dS}{dt} = -\beta SI, \quad \frac{dI}{dt} = \beta SI - \gamma I$

S-nullcline: $dS/dt = 0$.	I-nullcline: $dI/dt = 0$.
$S = 0$ and $I = 0$.	$I = 0$ or $S = \gamma/\beta$, but $S <= N$, so only relevant if $\gamma/\beta < N$.
Arrows vertical (only I is changing)	Arrows horizontal (only S is changing)



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Brusselator model

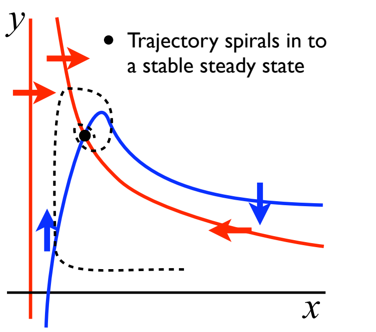
- This system is a famous example which can have oscillatory solutions.

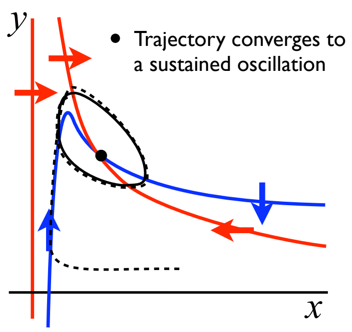
$$\frac{dx}{dt} = k_1 A - (k_2 B + k_4)x + k_3 x^2 y,$$
$$\frac{dy}{dt} = k_2 B x - k_3 x^2 y.$$

Nullclines

$$\frac{dx}{dt} = 0: \quad y = \frac{(k_2 B + k_4)x - k_1 A}{k_3 x^2}$$

$$\frac{dy}{dt} = 0: \quad y = \frac{k_2 B}{k_3 x} \quad \text{or} \quad x = 0$$





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Summary

- Mathematical analysis of relatively simple models (with two state variables) can be done using **phase-plane** methods.
  - the **phase-plane** represents the state of a two-variable system by points on the plane.
  - each point has associated rates of change for each variable, which define a **direction** in the phase-plane (often represented by an **arrow**).
  - sketch the nullclines - curves where one variable is not changing (so there are **two** nullclines if there are **two** variables)
  - steady states are where nullclines cross
- Mutual repression can lead to bistability - but we have also seen that cooperative positive autoregulation can lead to bistability.
- Other simple motifs can be analysed in considerable detail.
- No analogous approach to phase-planes for systems with more than two variables - we rely on more advanced maths (not here!), or computer simulation.
- Network topology *may* be more important than parameter values.

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