GSTDMB 2012: DYNAMICAL MODELLING FOR BIOLOGY AND MEDICINE

Lecture 2
Introduction to modelling with differential equations

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Key ideas about dynamic models

- **Dynamic models** describe the change in the **state** of a system with time.
- **Solution/trajectory:** the set of future states given a particular initial state.
- **Steady state:** a solution which is steady/constant/not changing in time.
- **Periodic solution/limit cycle:** an oscillatory solution, i.e. one that repeats exactly the same values at an interval known as the **period**.
- The **stability** of a **steady state** describes what happens to the system if it starts close to that steady state:
  - **stable:** if we start close to the steady state, the system converges to that steady state
  - **unstable:** if we start close to the steady state, the system diverges from that steady state
- **Bifurcation:** the number or stability of steady states (or periodic solutions) changes as a parameter varies.
- **Qualitative analysis:** determines information about qualitative properties of solutions and bifurcations. Steady states and stability are important here.
- **Quantitative analysis:** determines numerical values for solutions, bifurcations, etc, usually via computer simulation (except for special cases).

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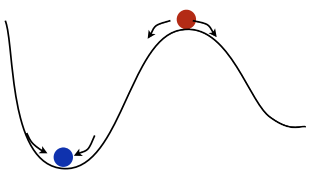
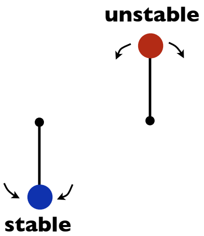
Stability: examples

- Consider a ball rolling on a smooth landscape.
- The ball can be placed at the top of a hill and will stay there for all time - this is a **steady state**.
  In practice, any small disturbance will lead to the ball rolling down one side or the other.
  This is an example of an **unstable steady state**.
- Another **steady state** is at the bottom of a valley.
  After any small disturbance the ball will roll back to the bottom.
  This is an example of a **stable steady state**.



- Another example is a rigid pendulum:



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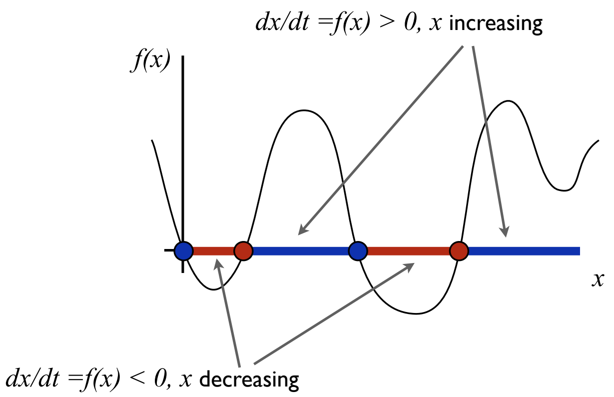
1^{st} order Ordinary Differential Equations

- Dynamic models for the dependence of single state variable, x on the **independent variable** t. The **solution** is $x(t)$
- Describe the rate of change of x, written $\dfrac{dx}{dt}$
- In general, this may depend on x itself and on time, t: (e.g. time dependent parameters in circadian models) $\dfrac{dx}{dt} = f(x,t)$
- We will consider the **autonomous** case, when the rate of change of x does not depend on t, but only on the state variable x itself. $\dfrac{dx}{dt} = f(x)$
- In this case qualitative analysis is reasonably straightforward
- Steady states are where $f(x)=0$.
- The **phase-line diagram** shows us where x is increasing, where it is decreasing, and where any **steady states** lie.
- Relies on being able to sketch or plot the graph of $f(x)$

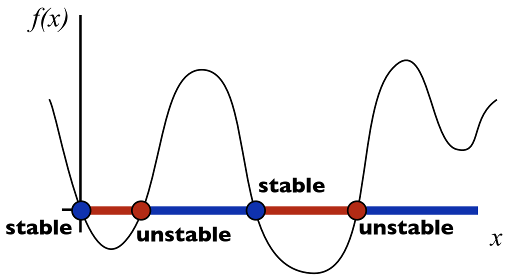
Phase-line diagrams (1)

- Enable qualitative analysis of 1^{st} order autonomous ODEs.
- Given $dx/dt=f(x)$, sketch $f(x)$
- Remember that $f(x)$ **is** the rate of change of x



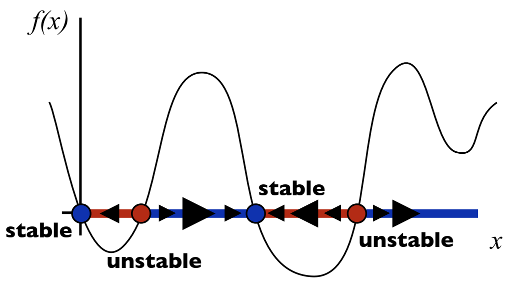
Phase-line diagrams (2)

- **Steady states** where $f(x)$ crosses the horizontal axis ($dx/dt=f(x)=0$)
- **Stable** if $f(x)$ crosses from positive to negative
- **Unstable** if $f(x)$ crosses from negative to positive



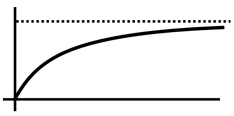
Phase-line diagrams (3)

- Also tells you how fast x is increasing or decreasing
- Easiest to indicate graphically with arrows
- Arrows to right (left) for x increasing (decreasing)
- This reinforces our understanding of (in)stability

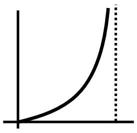


Sketching the graph of a function f(x)

- $f(0)$ - where the graph crosses the vertical axis
- $f'(0)$ - slope at $x=0$ (f' is shorthand for df/dx, the gradient of $f(x)$)
- anywhere else obvious where $f(x)=0$?
- is $f(x)$ polynomial ($ax^n + bx^{n-1} + cx^{n-2} + ... + dx + e$)?
  - quadratic (highest power is 2), $ax^2 + bx + c$ - always one max or min
  - cubic (highest power is 3) - one inflection, or one max and one min
  - In general, at most n-1 turning points
- what about $f(x)$ as x get very large positive (negative)? Does it go up, down, or become flat (i.e. approach a *horizontal asymptote*)?

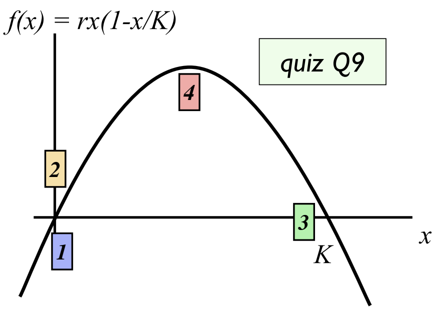


- Any *vertical asymptotes*?



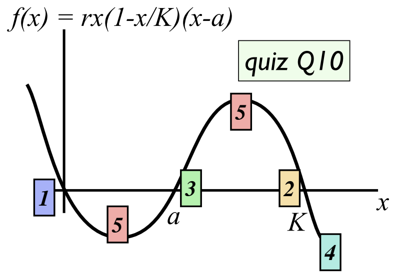
Sketching the graph of a function f(x)

- **Example:** $f(x) = rx(1-x/K) = rx - rx^2/K$
  1. $f(0)=0$
  2. $f'(x)=r-2rx/K$, so $f'(0)=r$, $f(x)$ is increasing through the origin
  3. clearly $f(K)=rK(1-1)=rK(0)=0$ so crosses at $x=K$
  4. $f(x)$ is quadratic, so one turning point.



Sketching the graph of a function f(x)

- **Example:** $f(x) = rx(1-x/K)(x-a)$
  1. $f(0)=0$, $f'(x)$ is harder to work out
  2. clearly $f(K)=rK(1-1)(K-a)=1(0)(K-a)=0$ so crosses at $x=K$
  3. clearly $f(a)=ra(1-a/K)(a-a)=ra(1-a/K)(0)=0$ so crosses at $x=a$
  4. As x gets very large, $f(x)$ gets very large negative...
     $r.(large).(-large/K).(large) = -r(large)^3/K$
     could also see this by expanding brackets...
  5. $f(x)$ is cubic, so one max and one min (or one inflection).



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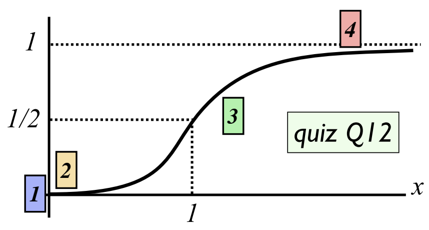
Sketching the graph of a function f(x)

- **Example:** $f(x) = x^2/(1+x^2)$
  1. $f(0)=0$
  2. $f'(x)=2x/(1+x^2)^2$, so $f'(0)=0$, and as x gets large, $f'(x)$ goes to zero (horizontal asymptote).
     Another way to see $f'(0)=0$, for small x, $f(x)$ looks like x^2).
  3. clearly $f(0) \geq 0$
  4. As x gets large, $f(x)$ approaches one (the 1 on the bottom is insignificant).
     If you're not convinced, consider x=10, 100, ...
     $10^2/(1+10^2) = 100/101 = 0.99$
     $100^2/(1+100^2) = 10000/10001 = 0.9999$



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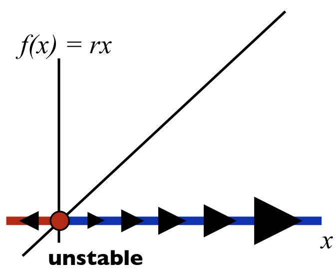
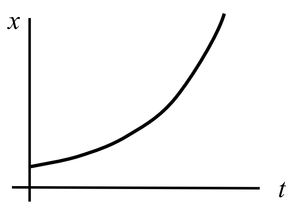
Exponential population growth $\frac{dx}{dt} = rx$

- Examples from Population growth illustrate many key points

- x is the **number** of individuals
- r is a parameter, the **rate** of growth *per capita*.
  It has dimensions of $1/$(time)
- **Steady state**: any steady solution has $dx/dt = 0$
- Hence $rx = 0$. Assuming $r > 0$, this must mean $x = 0$
- Can see this, and more, from phase-line diagram:



- for small values of x, x grows slowly
- as x increases, its rate of growth increases
- this gives characteristic exponential growth:



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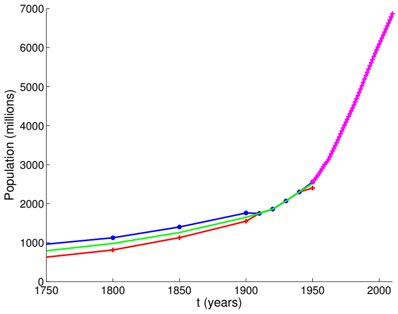
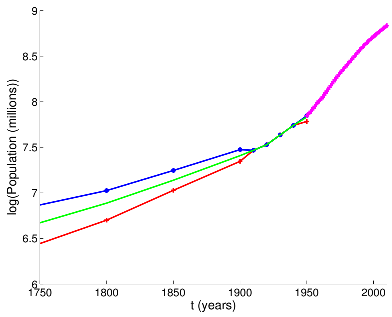
Exponential population growth? $\frac{dx}{dt} = rx$

- Solution is $x(t) = x(0)e^{rt}$ (quiz Q16). Take logs of both sides: $ln(x(t)) = rt + x(0)$
- Log of population data should be straight line...
- Here we show global human population data
  http://www.census.gov/ipc/www/idb/worldpop.html
  http://www.census.gov/ipc/www/worldhis.html





- Growth rate is slowing (after a period of acceleration)

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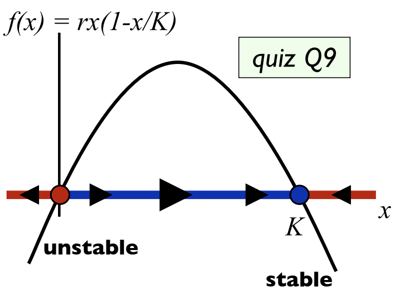
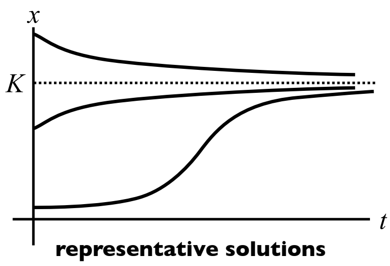
Logistic growth $\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right)$

- r measures the **maximum** rate of growth. It has dimensions of $1/$(time).
- K measures the **carrying capacity** for the population.
  It has dimensions of **number** of individuals.
- Effectively, we have replaced a constant *per capita* growth rate r, with a rate that *decreases as the population size increases*. This models the depletion of resources as a population grows.
- Steady states are where $dx/dt = 0$, which is where $x = 0$ or $x = K$





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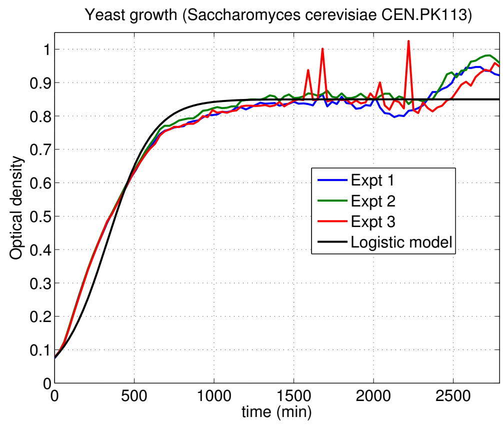
Logistic growth? $\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right)$

- Consider experimental data on the growth of yeast.
- Dynamics look a bit like logistic growth ...



- But logistic growth is too slow at first, and too fast later.

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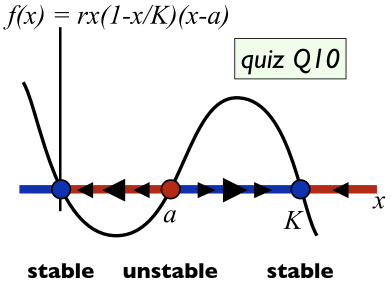
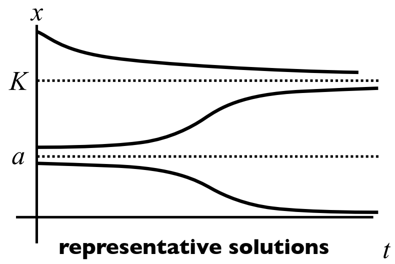
Allee effect $\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right)(x-a)$

- Many species exhibit lower or even negative growth rates at low numbers.
- Here, the *per capita* growth rate is: $r\left(1 - \frac{x}{K}\right)(x-a)$
- This is negative if $x < a$, i.e. if the population is too small (NB: $0<a<K$)



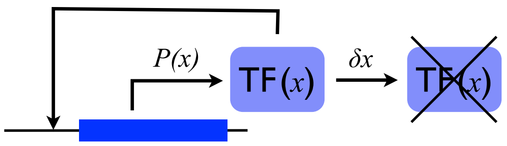


- **Bistability**: two stable steady states. Final state depends on initial value, $x(0)$.

Production & degradation models

- In each of the preceding cases, the form of $f(x)$ (straight line, quadratic, cubic) makes it easy to sketch the phase-line diagram (**and there is no qualitative dependence on parameter values**)
- Next we will consider models for simple feedback loops, such as may arise with transcriptional autoregulation

$$\begin{pmatrix}\text{Rate of} \\ \text{change of } x\end{pmatrix} = (\text{ production }) - (\text{ decay })$$

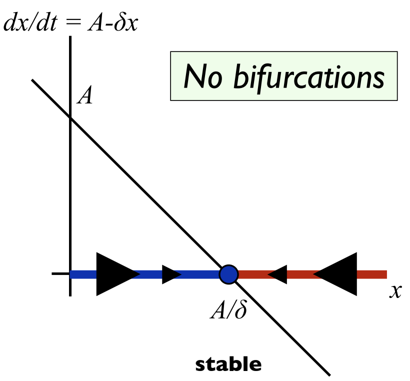


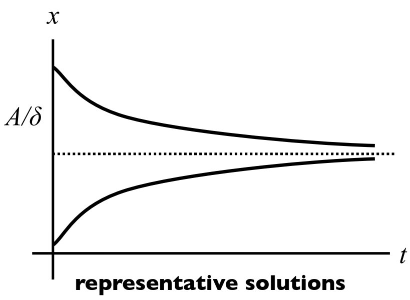
$$\frac{dx}{dt} = P(x) - \delta x$$

- $P(x)$ represents the effect of a Transcription Factor x on its own synthesis
- We will consider various common forms for $P(x)$
- What are we interested in?
  - Steady states: production and turnover of x are balanced
  - How fast are steady states reached? Any bifurcations (ideal for exp'tal validation)?

Constant production $\frac{dx}{dt} = A - \delta x$

- $P(x) = A$, a constant. This could model constitutive transcription
- As usual, steady states satisfy $dx/dt = 0$, hence $A = \delta x$
- So the steady state TF level is $x = A/\delta$
- Does this fit with our biological understanding and intuition?





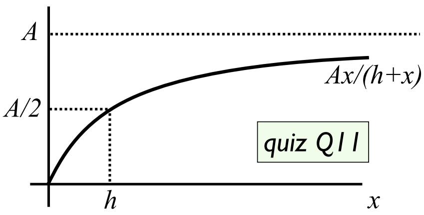
Larger δ ➔ faster decay to steady state

Saturating positive feedback $P(x) = \dfrac{Ax}{h+x}$

- Transcription rate increases with TF, x, but saturates to a maximum rate A
- e.g. TF binds to its own promoter
- This is an example of a Hill function:

$$P(x) = \frac{Ax^n}{h^n + x^n}$$

- Half maximal response at $x = h$



- Model equation becomes: $\dfrac{dx}{dt} = \dfrac{Ax}{h+x} - \delta x$
- How to sketch the phase-line diagram and find steady states?

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Saturating positive feedback $P(x) = \dfrac{Ax}{h+x}$

$$\boxed{\frac{dx}{dt} = \frac{Ax}{h+x} - \delta x}$$

- It turns out there are two qualitatively different phase-line diagrams
- Algebra: steady states satisfy $Ax/(h+x) = \delta x$

  One obvious solution is $x=0$ the other has $A/(h+x) = \delta$, hence
  $A = \delta h + \delta x$, hence
  $\delta x = A - \delta h$, hence
  $x = (A-\delta h)/\delta$
- If $A < \delta h$ then this steady state is negative and not biologically relevant
- Interpretation: if TF turnover rate too large, TF level decays to zero
- There is a **bifurcation** at $A = \delta h$,
  (i.e. change in number or stability of steady states)

- **Graphically**, dx/dt is the difference between the curve $P(x)$ and the line δx

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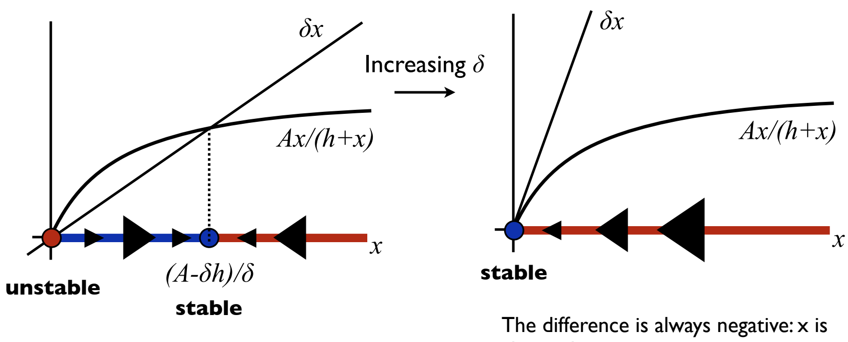
Saturating positive feedback $P(x) = \dfrac{Ax}{h+x}$

$$\boxed{\frac{dx}{dt} = \frac{Ax}{h+x} - \delta x}$$

- **Graphically**, dx/dt is the difference between the curve $P(x)$ and the line δx
- It is easy to see the effect of increasing δ which is the slope of the line



The difference is always negative: x is always decreasing to zero

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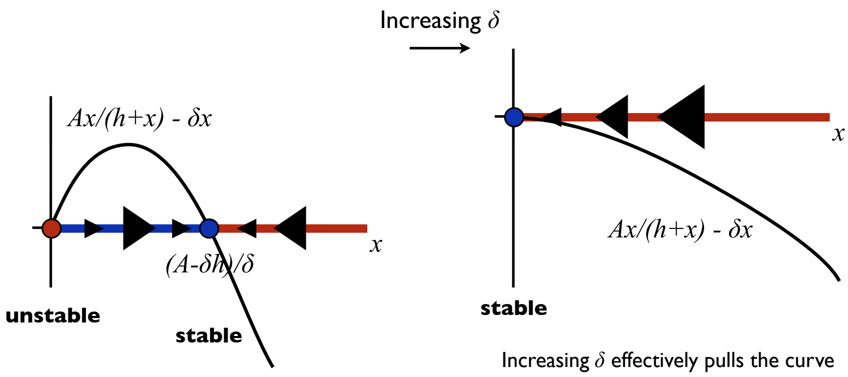
Saturating positive feedback $P(x) = \dfrac{Ax}{h+x}$

- **Graphically**, dx/dt is the difference between the curve $P(x)$ and the line δx
- It is easy to see the effect of increasing δ which is the slope of the line



Increasing δ effectively pulls the curve of dx/dt down through the axis

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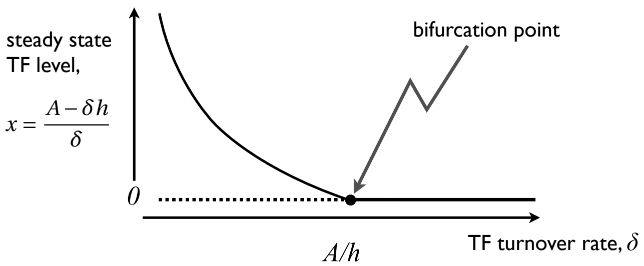
Saturating positive feedback $P(x) = \dfrac{Ax}{h+x}$

- We see that as δ increases, the steady state TF level decreases, until it reaches zero. Beyond this point TF production cannot be sustained.
- We can summarise this information in a **Bifurcation diagram**, which shows steady states and their stability as a parameter varies
- Solid lines indicate stable steady states, dashed lines unstable steady states



- **Could test this structure against experiment...**
- **... but bifurcation will be at TF levels below detection threshold.**

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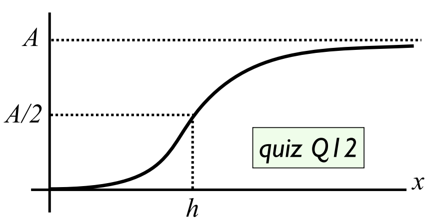
Sigmoidal positive feedback $P(x) = \dfrac{Ax^n}{h^n+x^n}$

- Transcription rate increases with TF, x, but saturates to a maximum rate A
- A Hill function with order > 1 is an example of a *sigmoid curve*
- Half maximal response at $x = h$



- Model equation becomes: $$\frac{dx}{dt} = \frac{Ax^n}{h^n+x^n} - \delta x$$

- How to sketch the phase-line diagram and find steady states?

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Sigmoidal positive feedback $P(x) = \dfrac{Ax^n}{h^n + x^n}$

$$\boxed{\frac{dx}{dt} = \frac{Ax^n}{h^n + x^n} - \delta x}$$

- Again there are two qualitatively different phase-line diagrams
- Algebra: steady states satisfy $Ax^n/(h^n+x^n) = \delta x$

  One obvious solution is $x=0$ the other has $Ax^{n-1}/(h^n+x^n) = \delta$ ...
  ... hard to solve in general.

- We resort to **graphical analysis**.

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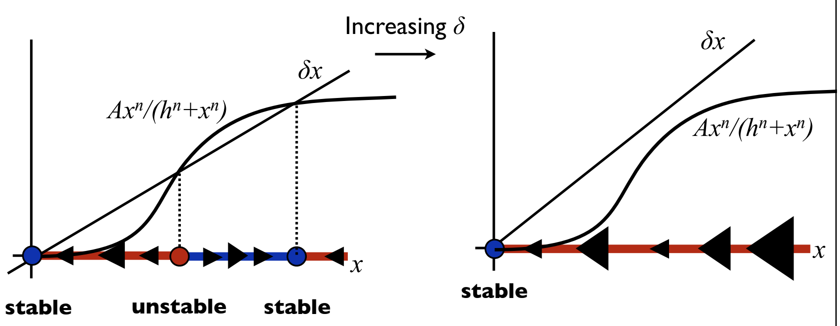
Sigmoidal positive feedback $P(x) = \dfrac{Ax^n}{h^n + x^n}$

$$\boxed{\frac{dx}{dt} = \frac{Ax^n}{h^n + x^n} - \delta x}$$

- **Graphically**, dx/dt is the difference between the curve $P(x)$ and the line δx
- It is easy to see the effect of increasing δ which is the slope of the line



Three steady states - BISTABILITY

The difference is always negative: x is always decreasing to zero

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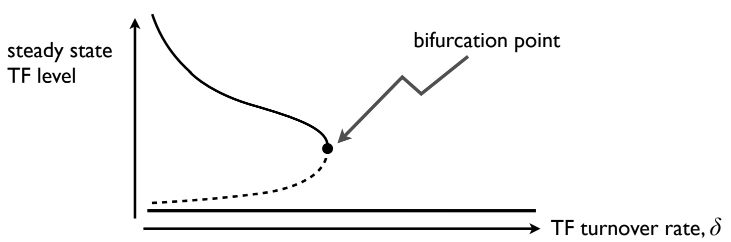
Sigmoidal positive feedback $P(x) = \dfrac{Ax^n}{h^n + x^n}$

- We see that the zero steady state is always stable.
- As δ increases, the nonzero stable steady state TF level decreases, until it disappears in a bifurcation. Beyond this point TF production cannot be sustained.
- We can summarise this information in a **Bifurcation diagram**, which shows steady states and their stability as a parameter varies.
- Solid lines indicate stable steady states, dashed lines unstable steady states.



- **Could test this structure against experiment...**
- **... at bifurcation TF levels could be above detection threshold.**

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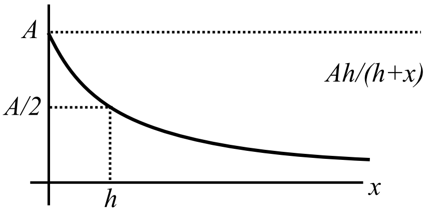
Negative feedback $P(x) = \frac{Ah}{h+x}$

- Transcription rate decreases with TF, x.
- Maximum rate A, minimum zero
- A decreasing Hill function:

$$P(x) = \frac{Ah^n}{h^n + x^n}$$

- Half maximal response at $x = h$



- Model equation becomes: $\frac{dx}{dt} = \frac{Ah}{h+x} - \delta x$
- How to sketch the phase-line diagram and find steady states?

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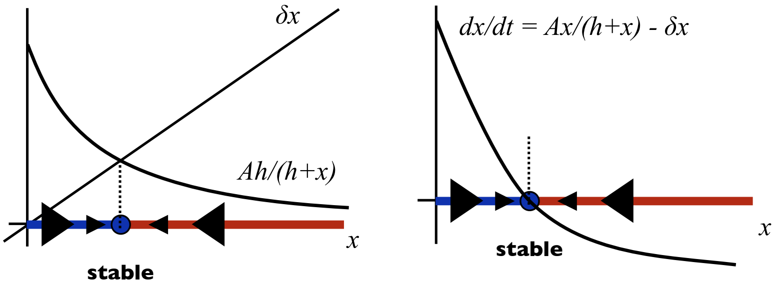
Negative feedback $P(x) = \frac{Ah}{h+x}$

- Algebra: steady states satisfy $Ah/(h+x) = \delta x$
  No obvious solutions - need to cross multiply and solve a quadratic ....
- **Graphically**, dx/dt is the difference between the curve $P(x)$ and the line δx



- The pictures are **qualitatively** the same whatever the parameters
- Always just one stable steady state TF level
- As δ increases the TF level falls

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Discussion

- We have introduced simple ordinary differential equation (ODE) models for single state variables.
- **Steady states** and their **stability** are crucial determinant 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
- For 1st order **non-autonomous** ODEs (e.g. circadian models with time dependent parameters) solutions can oscillate (driven by e.g. day-night cycle)
- Next:
  - Using CellDesigner to build and simulate single variable models
  - models with >1 state variable - more complex dynamics possible, analysis more difficult, often resort to computer simulation

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