

# CPIB SUMMER SCHOOL 2011: INTRODUCTION TO BIOLOGICAL MODELLING

## Lecture 1.2 Introduction to modelling with differential equations

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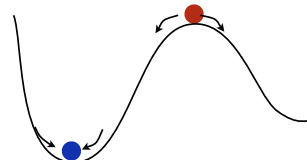
### Key ideas about dynamic models

- **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).

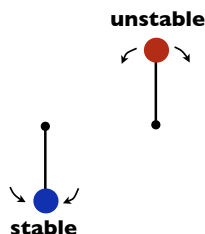
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### Stability: examples

- 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:

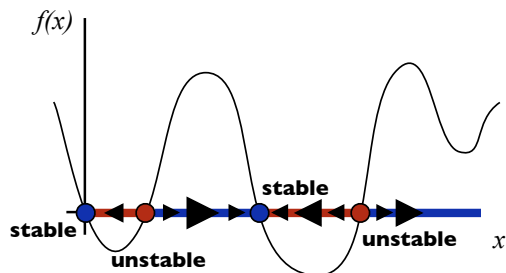


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## Phase-line diagrams (3)

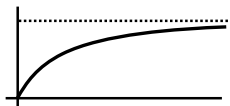
- Also tells you how fast  $x$  is increasing or decreasing
- Easiest to indicate graphically with arrows
- Arrows to right (left) for  $x$  increasing (decreasing)
- This reinforces our understanding of (in)stability



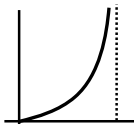
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## Sketching the graph of a function $f(x)$

- $f(0)$  - 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 ( $ax^n + bx^{n-1} + cx^{n-2} + \dots + dx + e$ )?
  - 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)?



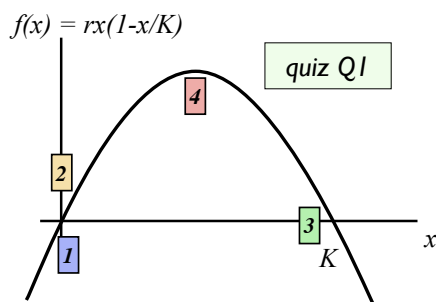
- Any vertical asymptotes?



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## Sketching the graph of a function $f(x)$

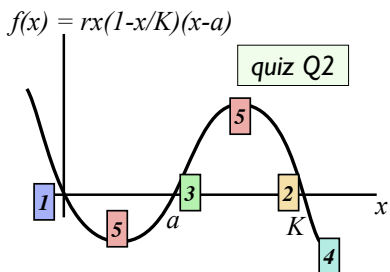
- **Example:**  $f(x) = rx(1-x/K) = rx - rx^2/K$ 
  1.  $f(0)=0$
  2.  $f'(x)=r-2rx/K$ , so  $f'(0)=r$ ,  $f(x)$  is increasing through the origin
  3. clearly  $f(K)=rK(1-1)=rK(0)=0$  so crosses at  $x=K$
  4.  $f(x)$  is quadratic, so one turning point.



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## Sketching the graph of a function $f(x)$

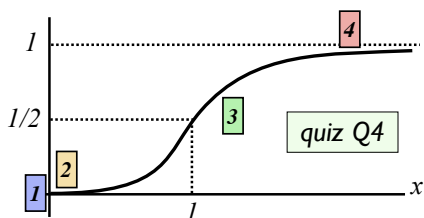
- **Example:**  $f(x) = rx(1-x/K)(x-a)$ 
  1.  $f(0)=0$ ,  $f'(x)$  is harder to work out
  2. clearly  $f(K)=rK(1-1)(K-a)=1(0)(K-a)=0$  so crosses at  $x=K$
  3. clearly  $f(a)=ra(1-a/K)(a-a)=ra(1-a/K)(0)=0$  so crosses at  $x=a$
  4. As  $x$  gets very large,  $f(x)$  gets very large negative...  
 $r(\text{large}) \cdot (-\text{large}/K) \cdot (\text{large}) = -r(\text{large})^3/K$   
 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  $f(x) \geq 0$
  4. As  $x$  gets large,  $f(x)$  approaches one (the 1 on the bottom is insignificant).  
 If you're not convinced, consider  $x=10, 100, \dots$   
 $10^2/(1+10^2) = 100/101 = 0.99$   
 $100^2/(1+100^2) = 10000/10001 = 0.9999$

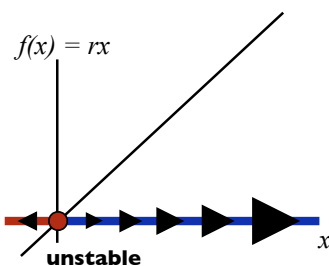


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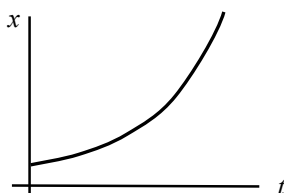
## Exponential population growth $\frac{dx}{dt} = rx$

- 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  $1/(\text{time})$
- **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:



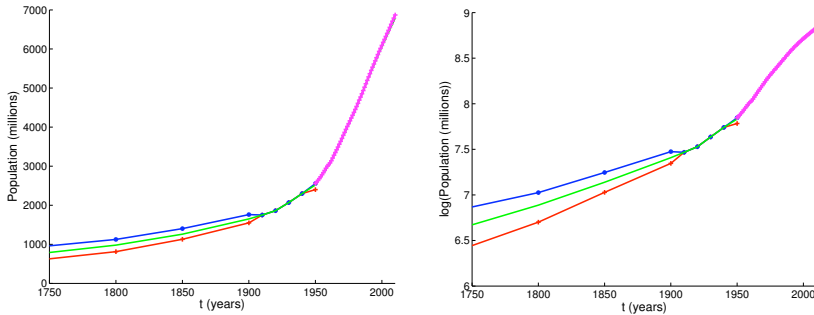
- for small values of  $x$ ,  $x$  grows slowly
- as  $x$  increases, its rate of growth increases
- this gives characteristic exponential growth:



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

- Solution is  $x(t) = x(0)e^{rt}$ . Take logs of both sides:  $\ln(x(t)) = rt + \ln(x(0))$
- 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>

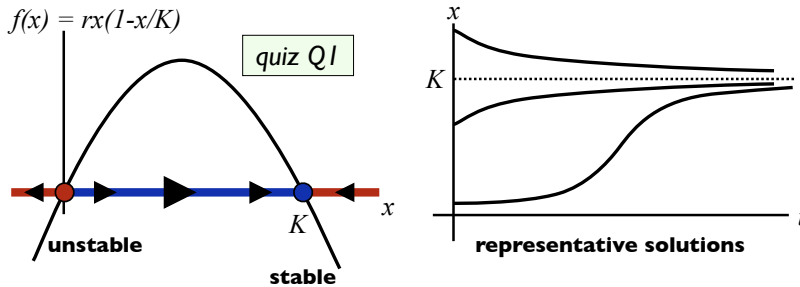


- Growth rate is slowing (after a period of acceleration)

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

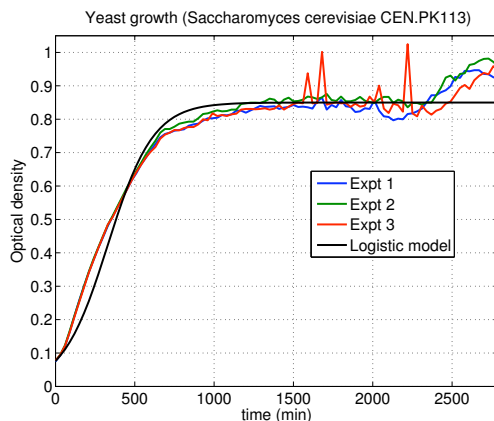
- $r$  measures the **maximum** rate of growth. It has dimensions of  $1/(\text{time})$ .
- $K$  measures the **carrying capacity** for the population. It has dimensions of **number** of individuals.
- Effectively, we have replaced a constant *per capita* growth rate  $r$ , with a rate that *decreases* 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 ...



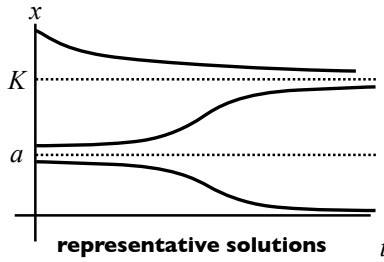
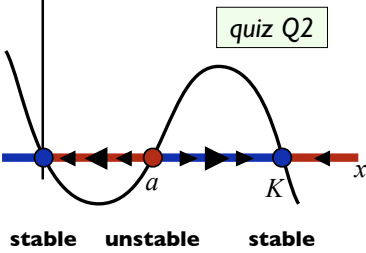
- But logistic growth is too slow at first, and too fast later.

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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:  $0 < a < K$ )

$$f(x) = rx\left(1 - \frac{x}{K}\right)(x - a)$$



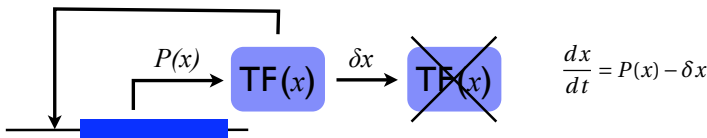
- **Bistability:** two stable steady states. Final state depends on initial value,  $x(0)$ .

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## 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

$$\left( \begin{array}{l} \text{Rate of} \\ \text{change of } x \end{array} \right) = ( \text{production} ) - ( \text{decay} )$$



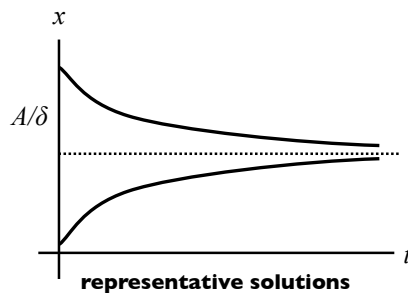
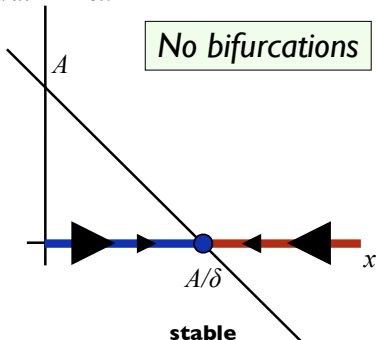
- $P(x)$  represents the effect of a Transcription Factor  $x$  on its own synthesis
- We will consider various common forms for  $P(x)$
- What are we interested in?
  - Steady states: production and turnover of  $x$  are balanced
  - How fast are steady states reached? Any bifurcations (ideal for exp'tal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

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## 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?

$$dx/dt = A - \delta x$$



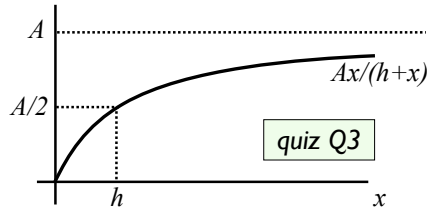
Larger  $\delta \rightarrow$  faster decay to steady state

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

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

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

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

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

- 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

$$A = \delta h + \delta x, \text{ hence}$$

$$\delta x = A - \delta h, \text{ hence}$$

$$x = (A - \delta h) / \delta$$

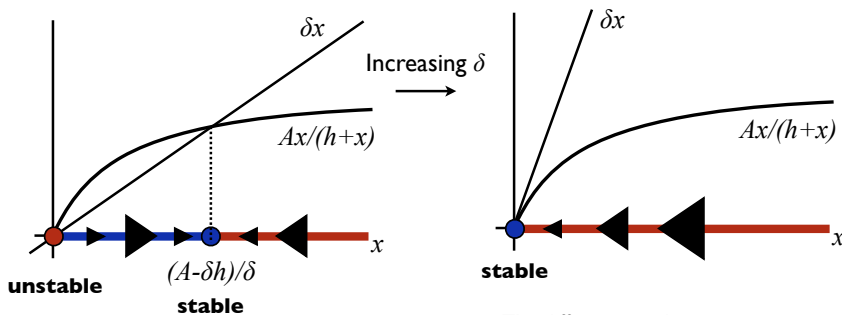
- If  $A < \delta h$  then this steady state is negative and not biologically relevant
- Interpretation: if TF turnover rate too large, TF level decays to zero
- There is a **bifurcation** at  $A = \delta h$ , (i.e. change in number or stability of steady states)
- **Graphically**,  $dx/dt$  is the difference between the curve  $P(x)$  and the line  $\delta x$

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

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

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



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

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

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

- 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  $Ax^{n-1}/(h^n+x^n) = \delta \dots$   
 ... hard to solve in general.

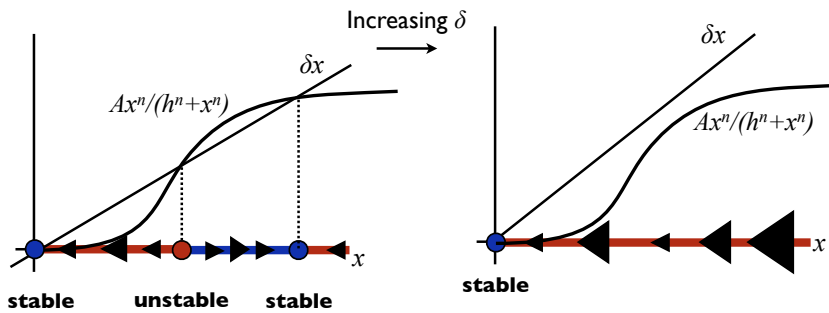
- We resort to **graphical analysis**.

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

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

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



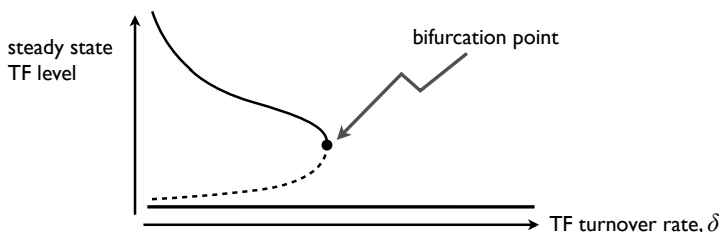
**Three steady states - BISTABILITY**

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

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

- We see that the zero steady state is always stable.
- As  $\delta$  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.



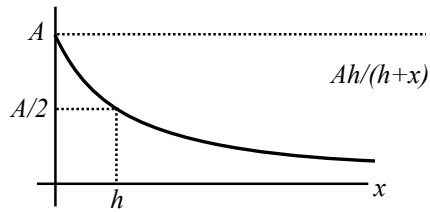
- **Could test this structure against experiment...**
- **... at bifurcation TF levels could be above detection threshold.**

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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  $x = h$

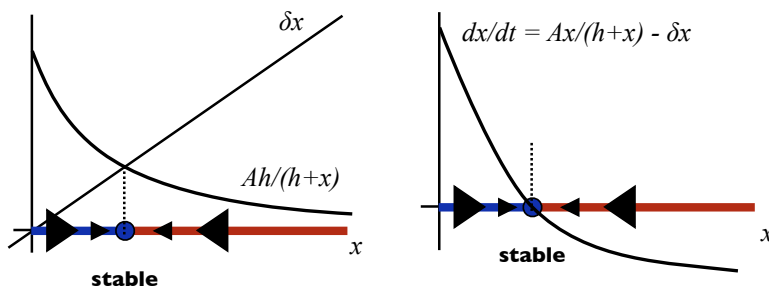
- Model equation becomes:  $\frac{dx}{dt} = \frac{Ah}{h+x} - \delta x$

- 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  $\delta x$



- The pictures are **qualitatively** the same whatever the parameters
- Always just one stable steady state TF level
- As  $\delta$  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 1<sup>st</sup> 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 1<sup>st</sup> 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 simple one variable models.
  - models with >1 state variable - more complex dynamics possible, analysis more difficult, often resort to computer simulation

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