Systembiologi
Biologiska system, TEK292

September 2013

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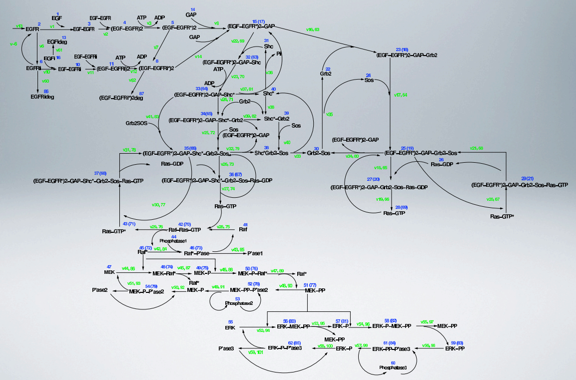
http://www.thep.lu.se/~henrik/tek292/

Hur skulle du göra en modell?



THE SAINSBURY LABORATORY
UNIVERSITY OF CAMBRIDGE

The study of plant development is being transformed by the new scientific and technical resources becoming available to biologists, including high-throughput DNA sequencing, new imaging methods, increasingly sophisticated genetic tools, and refined chemical interventions. The data derived from these approaches has opened the way for predictive computational models, which are essential for understanding the dynamic, self-organising properties of plants.

LUND UNIVERSITY
Faculty of Science

Computational Biology & Biological Physics

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The Computational Biology & Biological Physics Group at Lund University pursues a very broad spectrum of research activities. In particular, the group builds models of macromolecules and living systems, and investigates biological processes by applying machine learning and statistical techniques. It also hosts the Lund Swegene Bioinformatics Facility. More...

Forskningsöversikt

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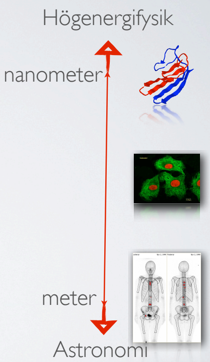
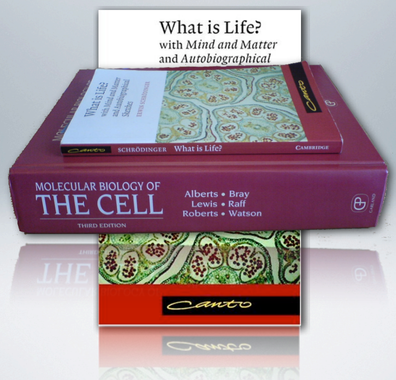
- Proteindynamik
- Bio-nanofysik
- Systembiologi
- Bioinformatik
- Datoriserat beslutsstöd för kliniken

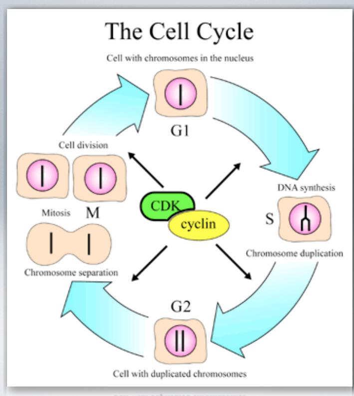


What is life?

What is life?



Hur går det till?



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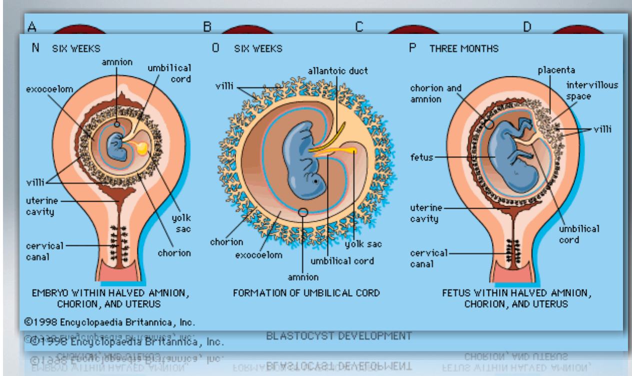
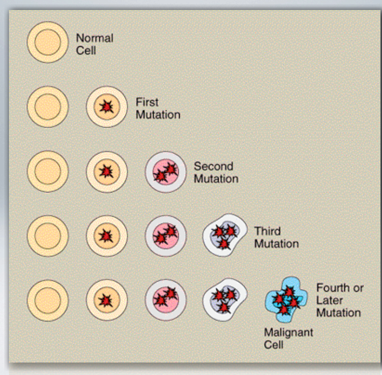
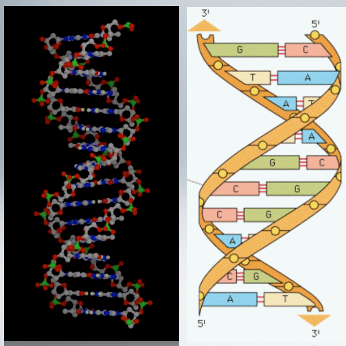


Varför går det fel?

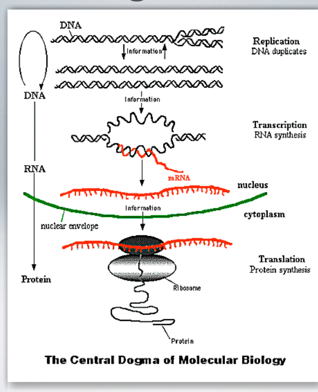


DNA

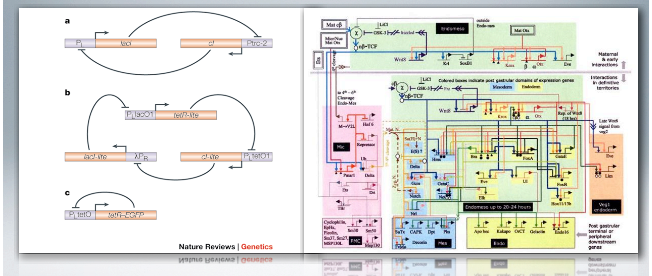


30000 gener
5 miljarder bp
2 meter

Molekylärbiologins centrala dogma

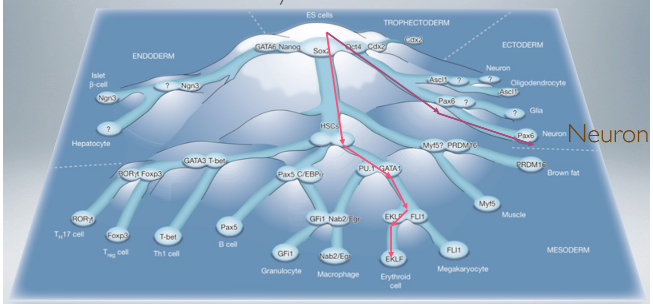


Reglering av gener



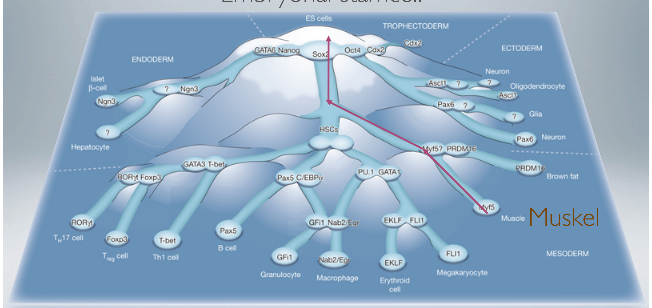
Vad bestämmer en stamcells öde ....

Embryonal stamcell

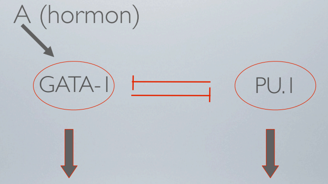


…och hur omprogrammerar man en mogen cell till något annat?

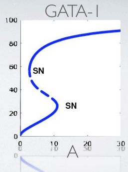
Embryonal stamcell

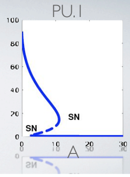


Vad bestämmer en stamcells öde…
och hur omprogrammerar man en mogen cell till något annat?

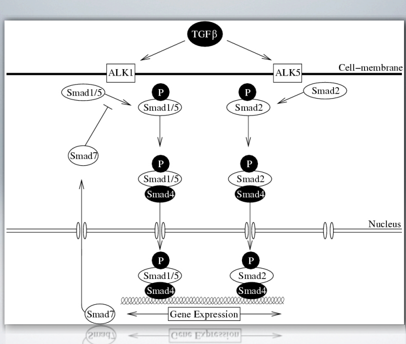


Matematiska modeller av biokemiska reaktioner samarbete med experiment

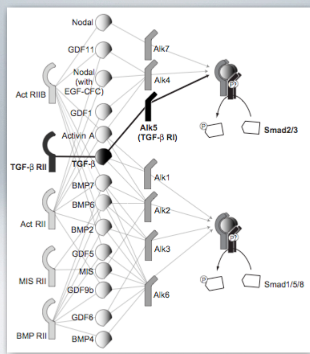




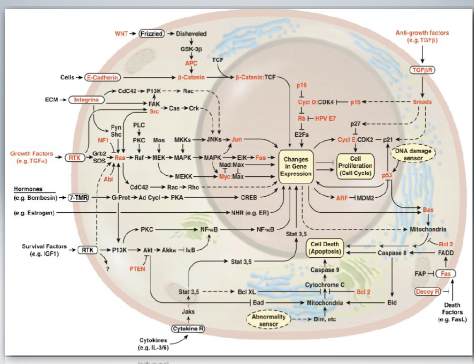
Signalering mellan celler



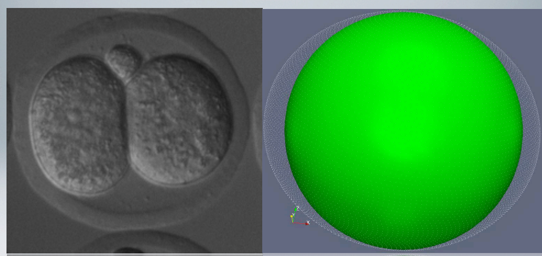
Signalering mellan celler



Signalering mellan celler

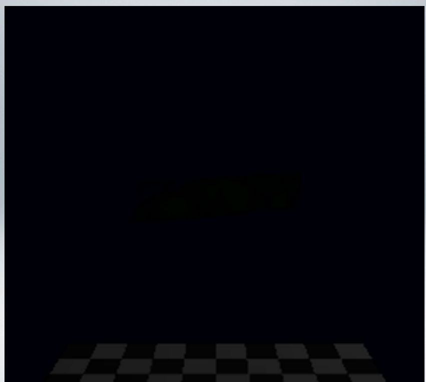


Embryoutveckling



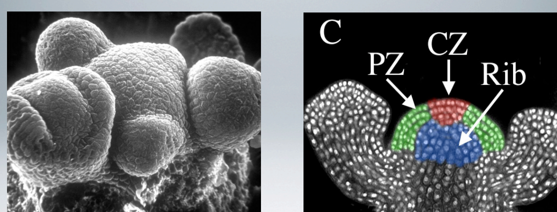
Motosugi et al (2005) P Krupinski

Hur ett växtskott växer



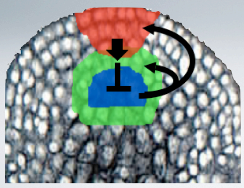
M Heisler, Caltech

Skottets stamcellsniche



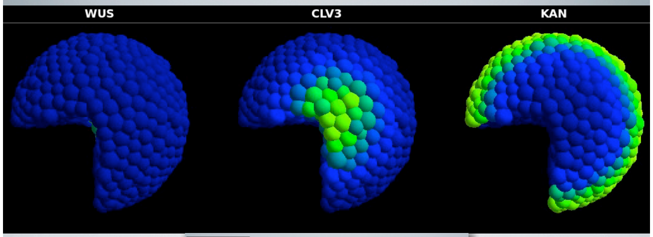
Stamcellsreglering i skottet

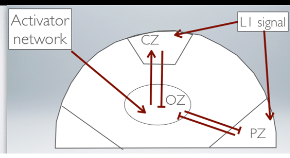
- CLV3 marks stem cells and WUS ‘defines’ an organizing center
- WUS activates CLV3 (stem cells)
- CLV3/CLV1 network repress WUS



- CLV3 extracellular peptid
- CLV1 receptor
- WUS transkriptionsfaktor

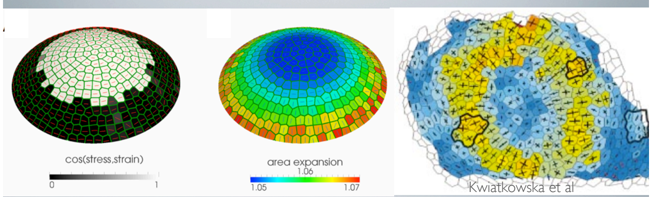
on growing template





J Gruel

pure mechanical model

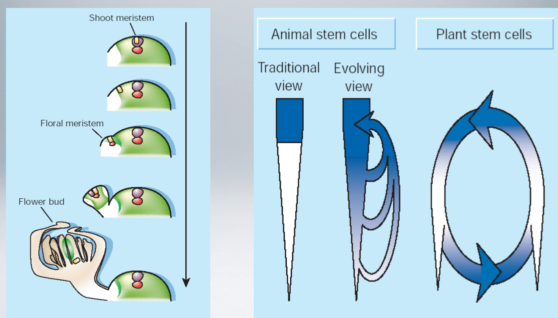


Can explain growth dynamics

Creates a central zone!

Bozorg et al (submitted)

Växtceller mycket kapabla



Nature 415, 751-754, (2002)

Morotscell + kokosnötsmjölk

Sammanfattning, organismer styrs av

- Gener som reglerar varandra
- Signalmolekyler som transporteras mellan celler
- Komplicerade växelverkningar

Ingenjörsperpektiv

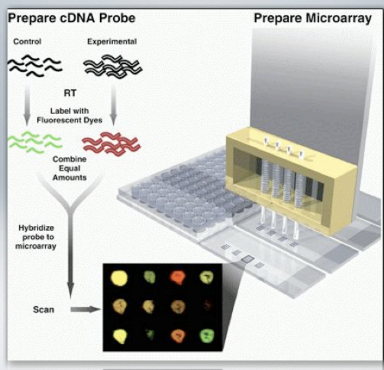
The Wright brothers
$O(100)$ components

Boeing B747
$O(10^7)$ components

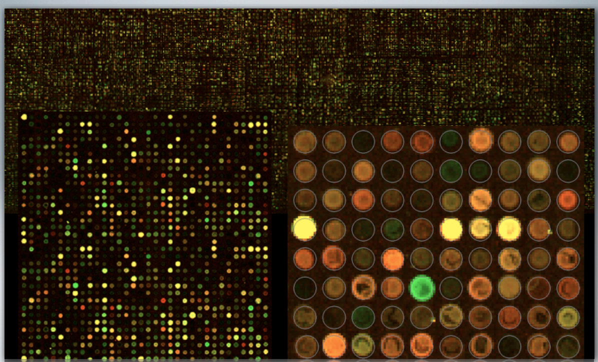
- System Control (feedback loops)
- Modularity
- Redundancy

Cells are wired according to similar principles

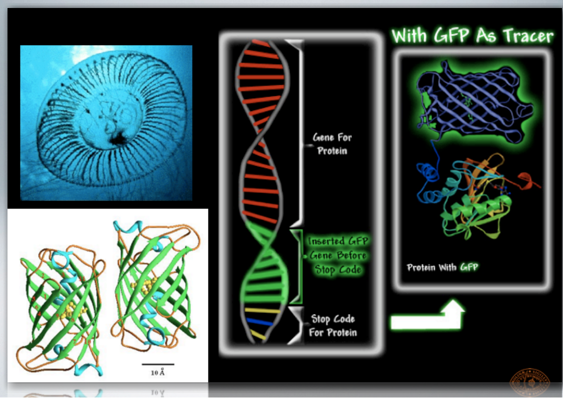
Experimentell revolution, del I:omics



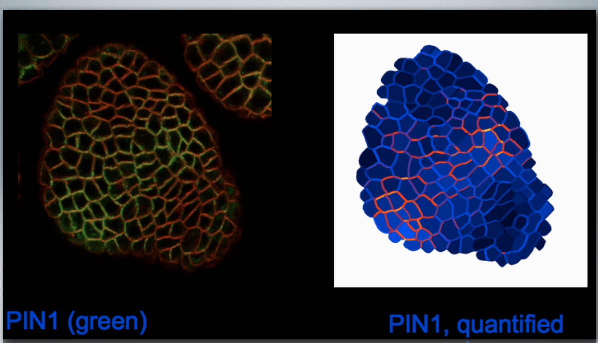
Experimentell revolution, del I:omics



Experimentell revolution, del2:GFP



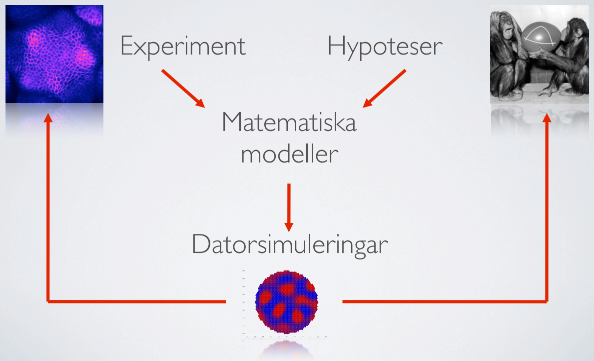
Experimentell revolution, del2:GFP



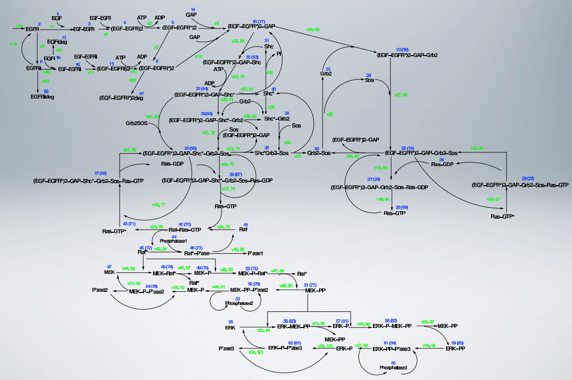
Why systems biology?

- Complexity too great to intuitively understand the behavior
- Mathematical model leads to formalization of hypotheses and boundary conditions
- Easier to test things in model compared to in experiments
- Always compare with experiments

Systembiologi, metoden



Hur skulle du göra en modell?



Några val för våra modeller

- Upplösningsnivå
- MOLEKYLER
- Variabler, kontinuerliga vs diskreta
- KONTINUERLIGA
- Uppdateringar, deterministisk vs stochastisk
- DETERMINISTISK

Ordinära differentialekvationer

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

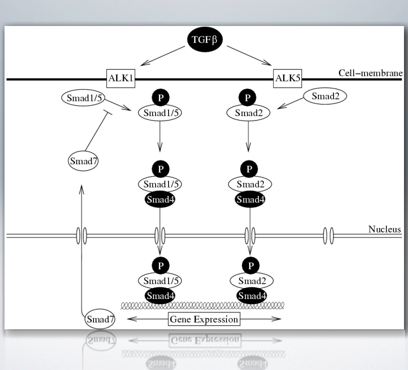
x - tillståndsvariabler
t - tid
f(x) - definierade uppdateringsfunktioner

x(t) kan beräknas om f(x) och $x(t_0)$ är kända

Typiskt används numerisk integration:

$$x(t + \Delta t) \approx x(t) + \Delta t f(x)$$

Exempel, TGF-beta



Exempel, TGF-beta

$$\emptyset \underset{p_0 p_1}{\overset{p_0}{\rightleftharpoons}} \mathrm{ALK1} \quad (1)$$

$$\emptyset \underset{p_4 p_5}{\overset{p_4}{\rightleftharpoons}} \mathrm{Smad4} \quad (2)$$

$$\emptyset \underset{p_8 p_9}{\overset{p_8}{\rightleftharpoons}} \mathrm{ALK5} \quad (3)$$

$$\mathrm{TGF}\beta + \mathrm{ALK1} \underset{p_{14}}{\overset{p_{13}}{\rightleftharpoons}} \mathrm{TA1} \quad (4)$$

$$\mathrm{PSmad1} + \mathrm{Smad4} \underset{p_{19}}{\overset{p_{18}}{\rightleftharpoons}} \mathrm{PS14} \quad (5)$$

$$\mathrm{TGF}\beta + \mathrm{ALK5} \underset{p_{21}}{\overset{p_{20}}{\rightleftharpoons}} \mathrm{TA5} \quad (6)$$

$$\mathrm{P_A} + \mathrm{TA1} \underset{p_{28}}{\overset{\mathrm{Smad7}\; p_{27}}{\rightleftharpoons}} \mathrm{TA1P} \quad (7)$$

$$\mathrm{P_B} + \mathrm{TA5} \underset{p_{32}}{\overset{\mathrm{Smad7}\; p_{31}}{\rightleftharpoons}} \mathrm{TA2P} \quad (8)$$

$$\emptyset \underset{p_2 p_3}{\overset{p_2}{\rightleftharpoons}} \mathrm{Smad1} \quad (9)$$

$$\emptyset \underset{p_6 p_7}{\overset{p_6}{\rightleftharpoons}} \mathrm{Smad2} \quad (10)$$

$$\emptyset \underset{p_{10}}{\overset{PS14N\;(p_{11}, p_{12})}{\rightleftharpoons}} \mathrm{Smad7} \quad (11)$$

$$\mathrm{Smad1} \underset{p_{17}}{\overset{TA1\;(p_{15}, p_{16})}{\rightleftharpoons}} \mathrm{PSmad1} \quad (12)$$

$$\mathrm{Smad2} \underset{p_{24}}{\overset{TA5\;(p_{22}, p_{23})}{\rightleftharpoons}} \mathrm{PSmad2} \quad (13)$$

$$\mathrm{PSmad2} + \mathrm{Smad4} \underset{p_{26}}{\overset{p_{25}}{\rightleftharpoons}} \mathrm{PS24} \quad (14)$$

$$\mathrm{PS14} \underset{k_{30}}{\overset{p_{29}}{\rightleftharpoons}} \mathrm{PS14N} \quad (15)$$

Exempel, TGF-beta

$$\frac{dA_1}{dt} = p_0(1 - p_1 A_1) - p_{13} T_\beta A_1 + p_{14} T_1$$

$$\frac{dS_1}{dt} = p_2(1 - p_3 S_1) - \frac{p_{15} T_1 S_1}{p_{16} + S_1} + p_{17} P_1$$

$$\frac{dS_4}{dt} = p_4(1 - p_5 S_4) - p_{18} P_1 S_4 + p_{19} P_{14} - p_{25} P_2 S_4 + p_{26} P_{24}$$

$$\frac{dS_2}{dt} = p_6(1 - p_7 S_2) - \frac{p_{22} T_1 S_2}{p_{23} + S_2} + p_{24} P_2$$

$$\frac{dA_5}{dt} = p_8(1 - p_9 A_5) - p_{20} T_\beta A_5 + p_{21} T_5$$

$$\frac{dS_7}{dt} = \frac{p_{11} P_{14}}{p_{12} + P_{14}} - p_{10} S_7$$

$$\frac{dP_1}{dt} = \frac{p_{15} T_1 S_1}{p_{16} + S_1} - p_{17} P_1 - p_{18} P_1 S_4 + p_{19} P_{14}$$

$$\frac{dP_{14}}{dt} = p_{18} P_1 S_4 - p_{19} P_{14} - p_{29} P_{14} + p_{30} P_{14N}$$

$$\frac{dP_{14N}}{dt} = p_{29} P_{14} - p_{30} P_{14N}$$

$$\frac{dP_2}{dt} = \frac{p_{22} T_1 S_2}{p_{23} + S_2} - p_{24} P_2 - p_{25} P_2 S_4 + k_{17} P_{26}$$

$$\frac{dP_{24}}{dt} = p_{25} P_2 S_4 - p_{26} P_{24}$$

$$\frac{dT_1}{dt} = p_{13} T_\beta A_1 - p_{14} T_1 - p_{27} S_7 P_{P1} T_1 + p_{28} T_{1P}$$

$$\frac{dT_5}{dt} = p_{20} T_\beta A_5 - p_{21} T_5 - p_{31} S_7 P_{P2} T_5 + p_{32} T_{5P}$$

$$\frac{dP_A}{dt} = -p_{27} S_7 P_A T_1 + p_{28} T_{1P}$$

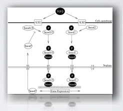
$$\frac{dP_B}{dt} = -p_{31} S_7 P_B T_1 + p_{32} T_{1P}$$

$$\frac{dT_{1P}}{dt} = p_{27} S_7 P_A T_1 - p_{28} T_{1P}$$

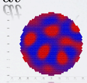
$$\frac{dT_{5P}}{dt} = p_{31} S_7 P_B T_5 - p_{32} T_{5P}$$

'Typiskt' systembiologiprojekt

- Definiera det biokemiska nätverket
- Beskriv växelverkningar matematiskt (ODE)
- Simulera på dator
- Hitta modellparametrar
- Analysera dynamiken



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

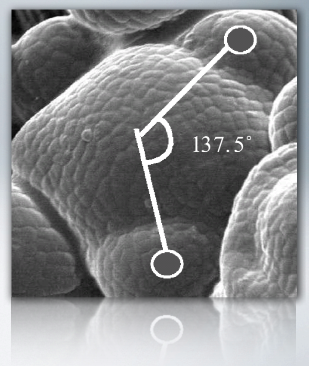


Outline

- Analys av dynamiska system (ODE) (se lectureNotes.pdf)
- Byggstenar för biokemiska modeller
- Kombinera till hela modeller
- Diffusion och molekyltransport
- Parameteruppskattningar (kortfattat, jmf LH)

För komplicerat för att lösa?

- Växtceller organiserar sig efter gyllene snittet...
- Växten har löst det genom molekylväxelverkningar...
- FINNS LÖSNING!



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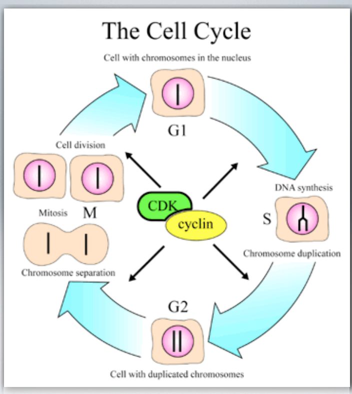
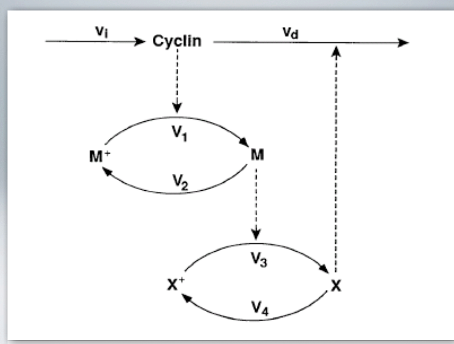
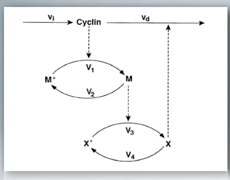


Exempel, cellcykel

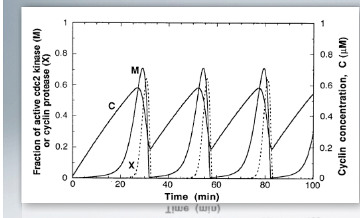


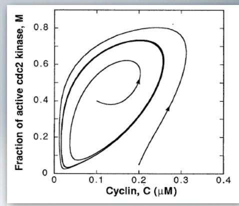
Exempel, cellcykel



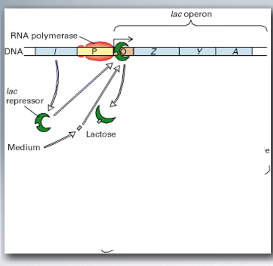
$$
\begin{aligned}
\frac{dC}{dt} &= v_i - v_d X \frac{C}{K_d + C} - k_d C \\
\frac{dM}{dt} &= V_1 C \frac{(1-M)}{K_1 + (1-M)} - V_2 \frac{M}{K_2 + M} \\
\frac{dX}{dt} &= V_3 M \frac{(1-X)}{K_3 + (1-X)} - V_4 \frac{X}{K_4 + X}
\end{aligned}
$$

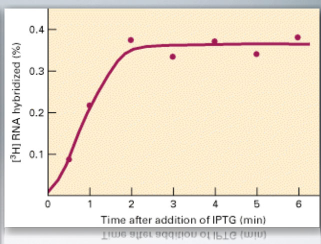
Exempel, cellcykel



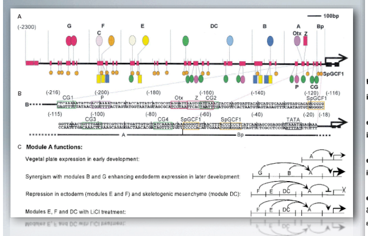


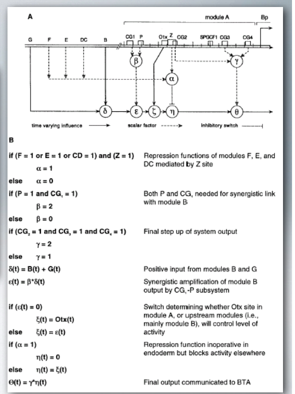
Exempel, Lac operon



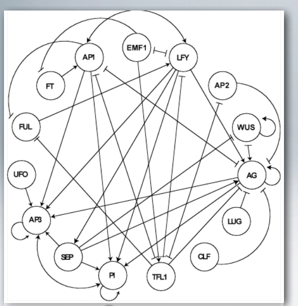


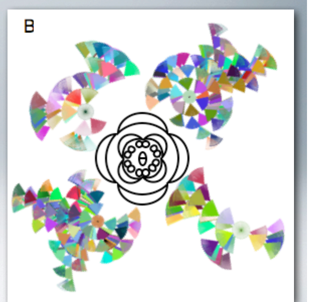
Exempel, Sea urchin



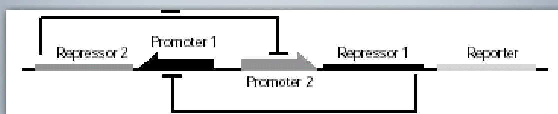


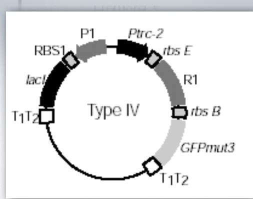
Exempel, Boolean plant flower



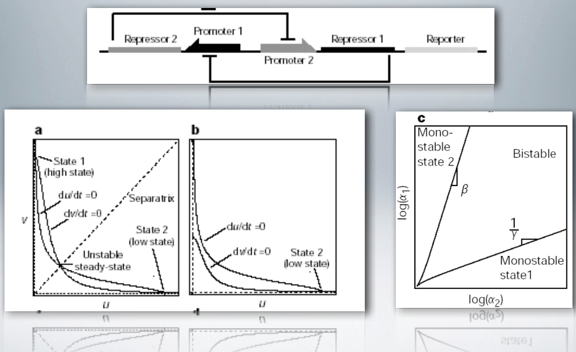


Bistable switch

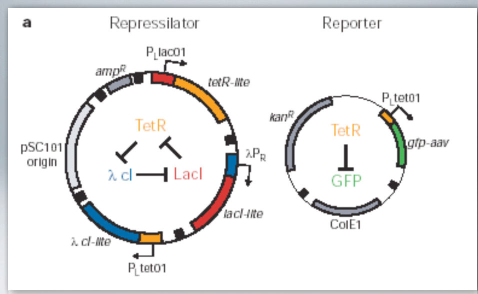




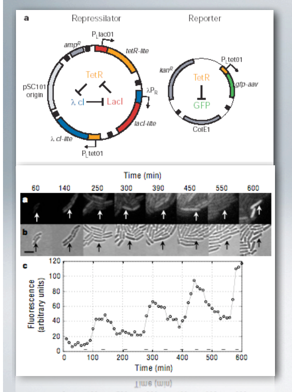
Bistable switch



Repressilator

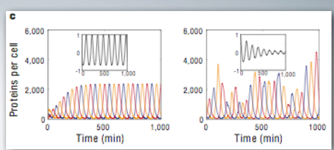


Repressilator



$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{(1+p_j^n)} + \alpha_0 \qquad \left(\begin{array}{l} i = lacI, tetR, cI \\ j = cI, lacI, tetR \end{array}\right)$$

$$\frac{dp_i}{dt} = -\beta(p_i - m_i)$$



Transkription

$$\text{TF} \rightleftarrows \text{DNA} \rightarrow X$$

$$\text{Prob(TF bunden)} = P_1 = \frac{TF}{K+TF}$$

$$\text{Prob(TF inte bunden)} = P_2 = \frac{K}{K+TF}$$

Aktivator: transkription om TF bunden

$$\frac{d[X]}{dt} = VP_1 = \frac{V[TF]}{K+[TF]}$$

Repressor: transkription om TF inte bunden

$$\frac{d[X]}{dt} = VP_2 = \frac{VK}{K+[TF]}$$

Flera transkriptionsfaktorer

A B → X

$$\text{Prob(A bunden)} = P_1 = \frac{A}{K_1+A}$$

$$\text{Prob(B inte bunden)} = P_2 = \frac{K_2}{K_2+B}$$

Transkription om A bunden, B inte bunden

$$\frac{dX}{dt} = VP_1P_2 = \frac{VAK_2}{(K_1+A)(K_2+B)}$$

Flera transkriptionsfaktorer

A B → X

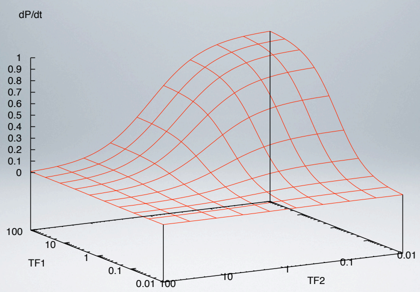
$$\text{Prob(A bunden)} = P_1 = \frac{A}{K_1+A}$$

$$\text{Prob(B inte bunden)} = P_2 = \frac{K_2}{K_2+B}$$

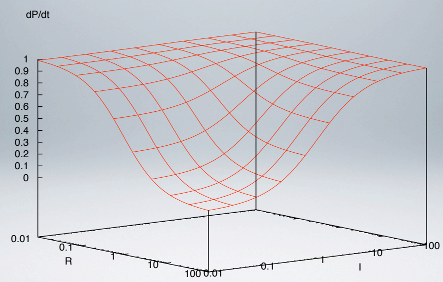
Transkription om A bunden, B inte bunden
och lite om A och B bundna

$$\frac{dX}{dt} = V_1P_1P_2 + V_2 = \frac{V_1AK_2 + V_2AB}{(K_1+A)(K_2+B)}$$

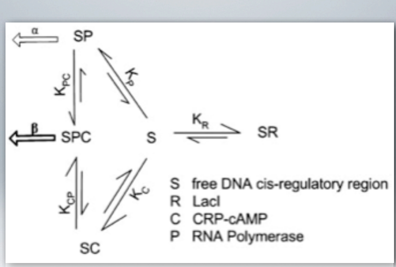
activator-repressor, MM



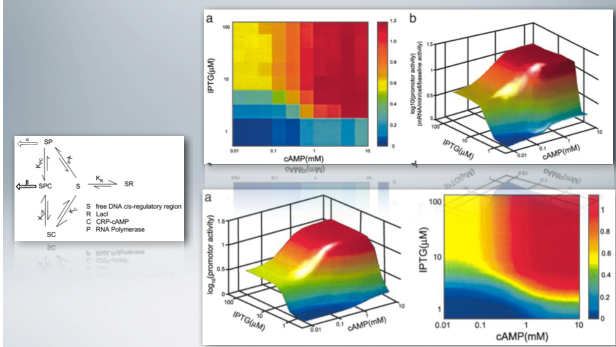
Lac operon, MM



Lac operon, experiment



Lac operon, experiment



Shea Ackers

Alternative derivation of transcription rates derived from statistical physics

Statistical weight given for each configuration of bound sigma=1 and unbound sigma=0 configuration

$$Z = \sum_{\sigma_1 \ldots \sigma_n} \prod_i^n [TF_i]^{\sigma_i} e^{-\Delta G_\sigma / RT}$$

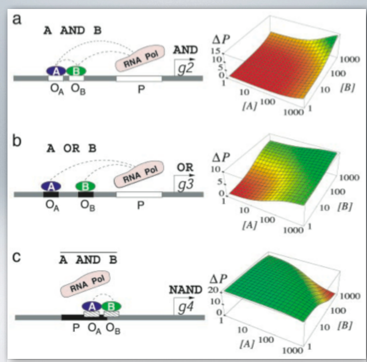
Rate of transcription proportional to

$$P = \frac{Z_{active}}{Z_{inactive} + Z_{active}}$$

Shea and Ackers (1985)

Can be mapped to Hill description

Transkriptionslogik



Competitive inhibition

One substrate S, one 'inhibitor' I, one binding site

$$
\begin{array}{ccccc}
E+S & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & E\cdot S & \xrightarrow{k_2} & E+P \\
+ & & & & \\
I & & & & \\
{\scriptstyle k_{-3}}\uparrow\downarrow{\scriptstyle k_3} & & & & \\
E\cdot I & & & &
\end{array}
$$

Competitive inhibition

One substrate S, one inhibitor I, one binding site

$$\frac{dp}{dt} = \frac{V_{max}s}{s + K_m(1 + i/K_i)} \quad \text{where } K_i = \frac{k_{-3}}{k_3}$$

inhibitor 'alters' K parameter

Non-competitive inhibition

One substrate S, one inhibitor I, two binding sites

$$
\begin{array}{ccccc}
E+S & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & E\cdot S & \xrightarrow{k_2} & E+P \\
+ & & + & & \\
I & & I & & \\
{\scriptstyle k_{-3}}\uparrow\downarrow{\scriptstyle k_3} & & {\scriptstyle k_{-3}}\uparrow\downarrow{\scriptstyle k_3} & & \\
E\cdot I+S & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & E\cdot I\cdot S & &
\end{array}
$$

Non-competitive inhibition

One substrate S, one inhibitor I, two binding sites

$$\frac{dp}{dt} = \frac{V_{max}}{1 + i/K_i} \frac{s}{K_s + s} \quad \text{where } \begin{cases} K_s = \frac{k_{-1}}{K_1} \\ K_i = \frac{k_{-3}}{k_3} \end{cases}$$

inhibitor 'alters' V_{max} parameter

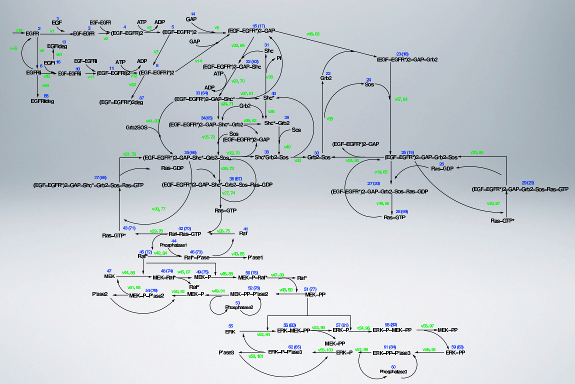
Post transcriptional regulation, miRNA

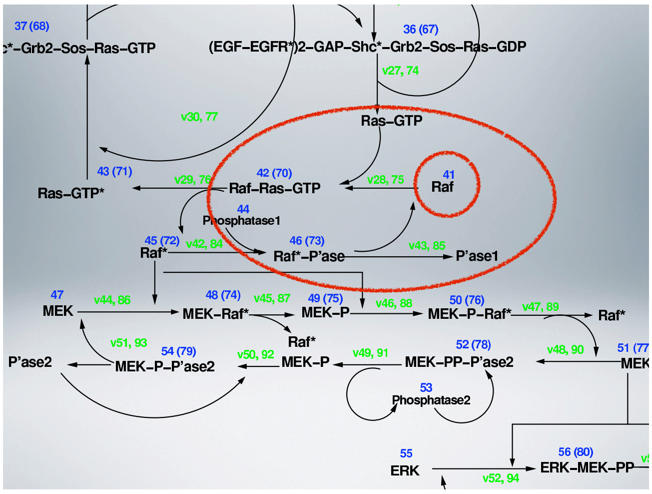
How would you model regulation by miRNA/siRNA?

$$mRNA + siRNA \rightleftharpoons C \longrightarrow siRNA$$

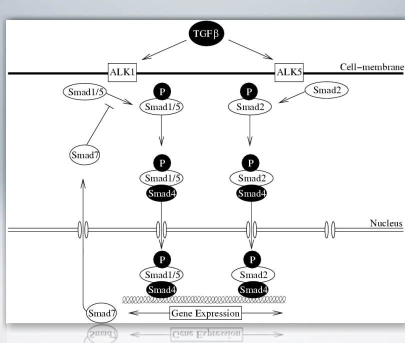
$$\frac{d[mRNA]}{dt} = -\frac{V_{max}[mRNA]}{K + [mRNA]} + \ldots$$

Hur skulle du göra en modell?





Exempel, TGF-beta



Exempel, TGF-beta

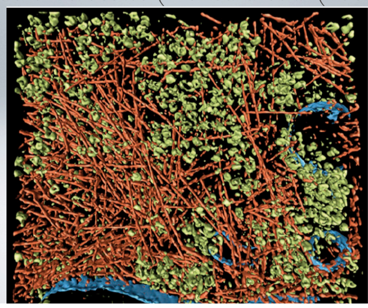
$\emptyset$	$\underset{P_0P_1}{\rightleftharpoons}$	ALK1	(1)	$\emptyset$	$\underset{P_2P_3}{\rightleftharpoons}$	Smad1	(9)
$\emptyset$	$\underset{P_4P_5}{\rightleftharpoons}$	Smad4	(2)	$\emptyset$	$\underset{P_6P_7}{\rightleftharpoons}$	Smad2	(10)
$\emptyset$	$\underset{P_8P_9}{\rightleftharpoons}$	ALK5	(3)	$\emptyset$	$\overset{PS14N}{\underset{P_{10}}{(P_{11},P_{12})\rightleftharpoons}}$	Smad7	(11)
TGFβ + ALK1	$\overset{P_{13}}{\underset{P_{14}}{\rightleftharpoons}}$	TA1	(4)	Smad1	$\overset{TA1}{\underset{P_{17}}{(P_{15},P_{16})\rightleftharpoons}}$	PSmad1	(12)
PSmad1 + Smad4	$\overset{P_{18}}{\underset{P_{19}}{\rightleftharpoons}}$	PS14	(5)	Smad2	$\overset{TA5}{\underset{P_{24}}{(P_{22},P_{23})\rightleftharpoons}}$	PSmad2	(13)
TGFβ + ALK5	$\overset{P_{20}}{\underset{P_{21}}{\rightleftharpoons}}$	TA5	(6)	PSmad2 + Smad4	$\overset{P_{25}}{\underset{P_{26}}{\rightleftharpoons}}$	PS24	(14)
P_A + TA1	$\overset{Smad7}{\overset{P_{27}}{\underset{P_{28}}{\rightleftharpoons}}}$	TA1P	(7)	PS14	$\overset{P_{29}}{\underset{k_{30}}{\rightleftharpoons}}$	PS14N	(15)
P_B + TA5	$\overset{Smad7}{\overset{P_{31}}{\underset{P_{32}}{\rightleftharpoons}}}$	TA2P	(8)				

Law of mass action

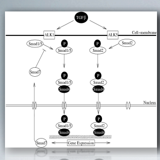
Caveats

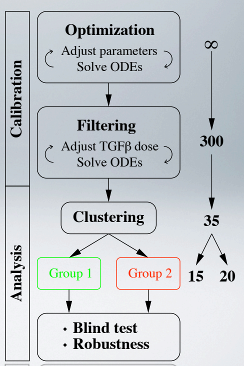
Also assumes well-stirred low concentration environment

A cell environment with actin, membranes and macromolecules (Mendalia et al (2002))



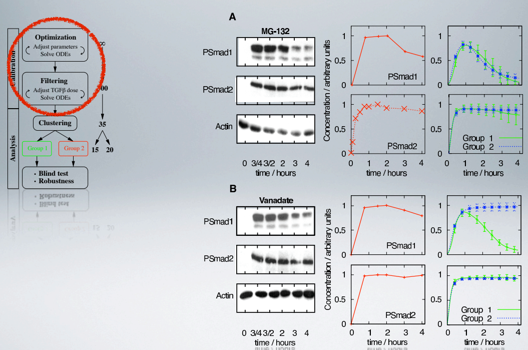
Exempel, TGFbeta



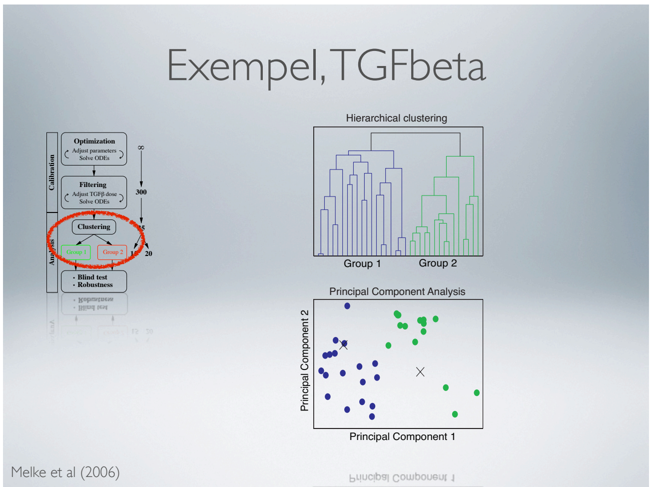


Melke et al (2006)

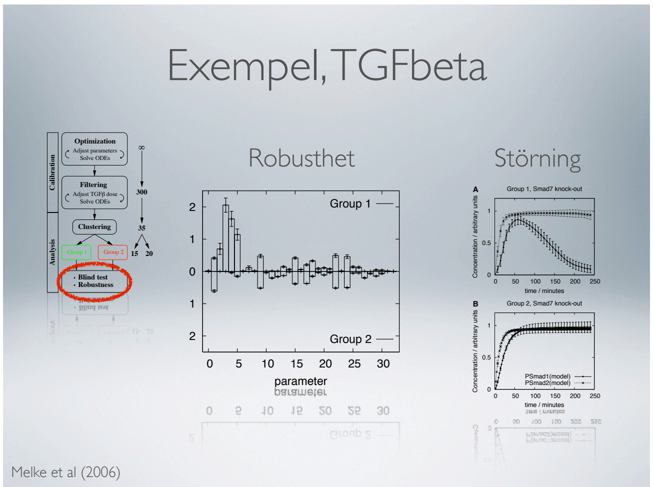
Exempel, TGFbeta



Melke et al (2006)



Exempel, TGFbeta
Hierarchical clustering
Group 1
Group 2
Principal Component Analysis
Principal Component 2
Principal Component 1
Optimization
Filtering
Clustering
Blind test
Robustness
Calibration
Analysis
Melke et al (2006)



Exempel, TGFbeta
Robusthet
Störning
Group 1
Group 2
parameter
Group 1, Smad7 knock-out
Group 2, Smad7 knock-out
time / minutes
Optimization
Filtering
Clustering
Blind test
Robustness
Melke et al (2006)