Modelisation des reseaux biologiques

Madalena Chaves madalena.chaves@inria.fr (INRIA, Macbes)

Travaux diriges ---> projet computationnel, **scilab**

Jean-Luc Gouze jean-luc.gouze@inria.fr (INRIA, Macbes)

Cours

Modalites : examen (70%), projet (30%)

Useful references :

Mathematical models in biology, Edelstein-Keshet, SIAM classics 2004

Systems Biology in practice, Klipp, Herwig et al , Wiley 2005

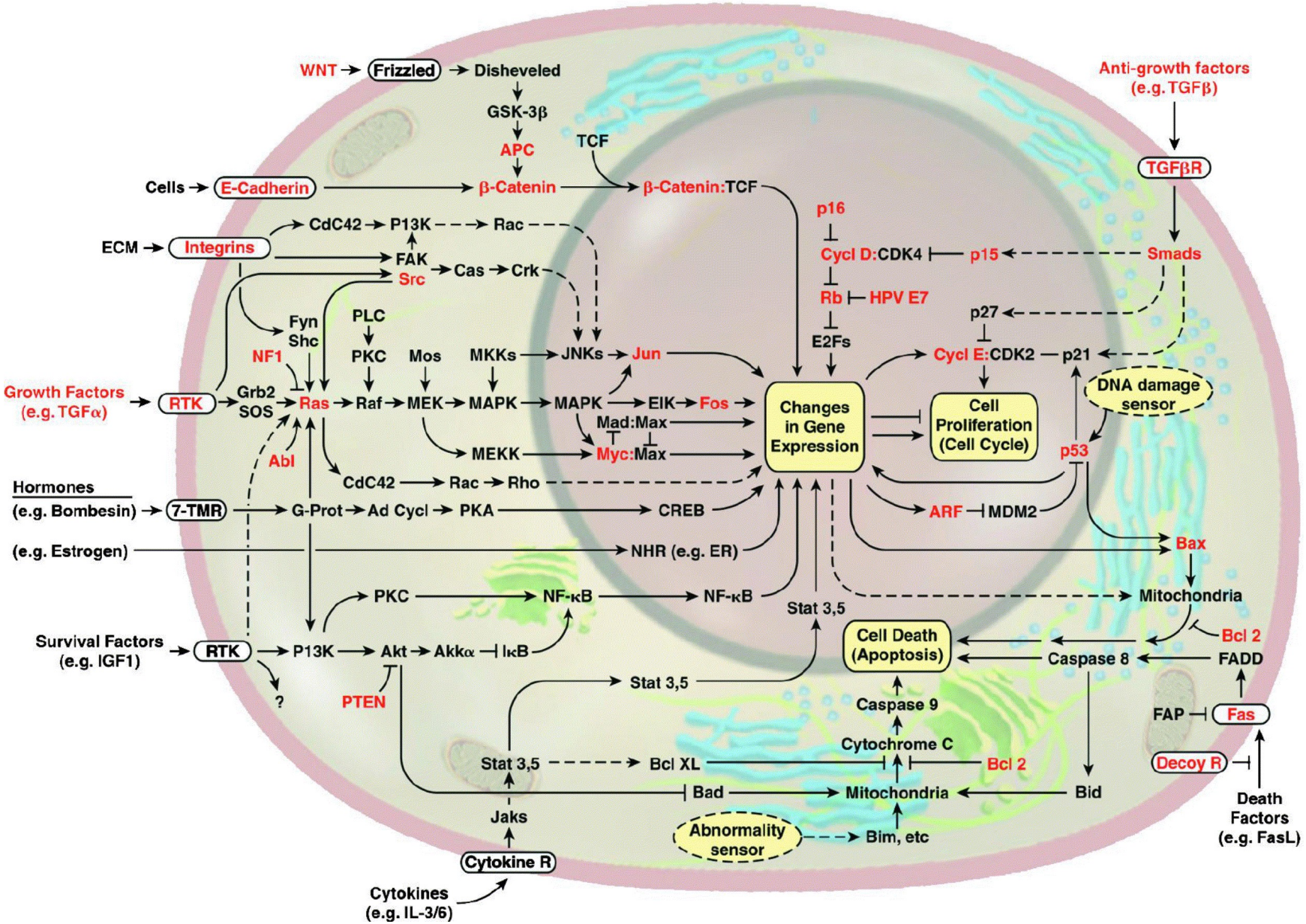
H. de Jong and D. Thieffry. Modelisation, analyse et simulation des reseaux genetiques. Medecine/Sciences, 18:492–502, 2002.

L. Segel. Modeling dynamic phenomena in molecular and cellular biology. Cambridge University Press, New York, 1984.

S.I. Rubinow. Introduction to Mathematical Biology.

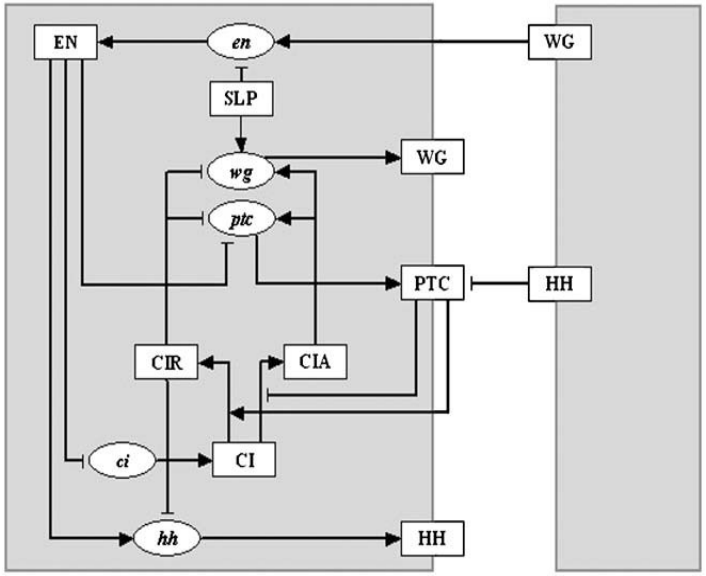
E.D. Sontag. Lecture notes in mathematical biology http://www.math.rutgers.edu/ sontag/613.html.

Cell and cellular signalling

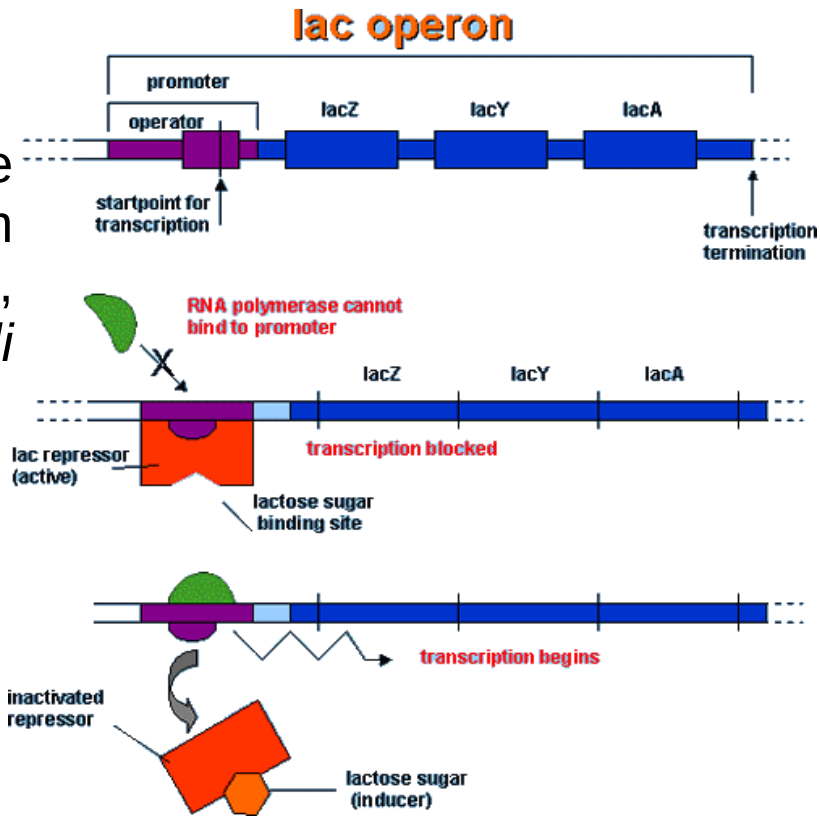


Examples of biological systems and data

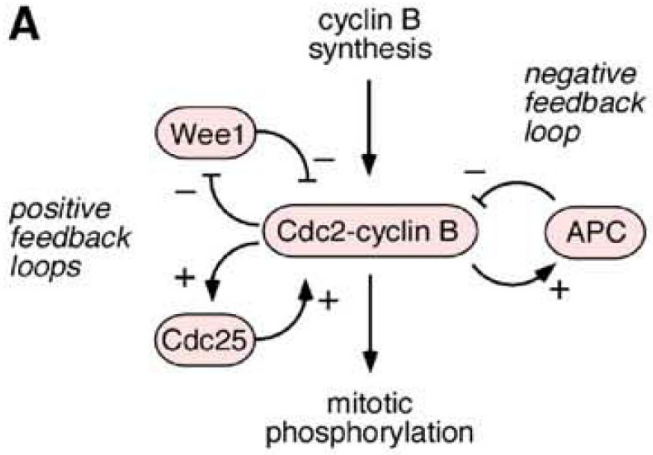
Pattern formation, fly embryo



Lactose metabolism network, *E. coli*



Cell cycle oscillator, eukaryotes

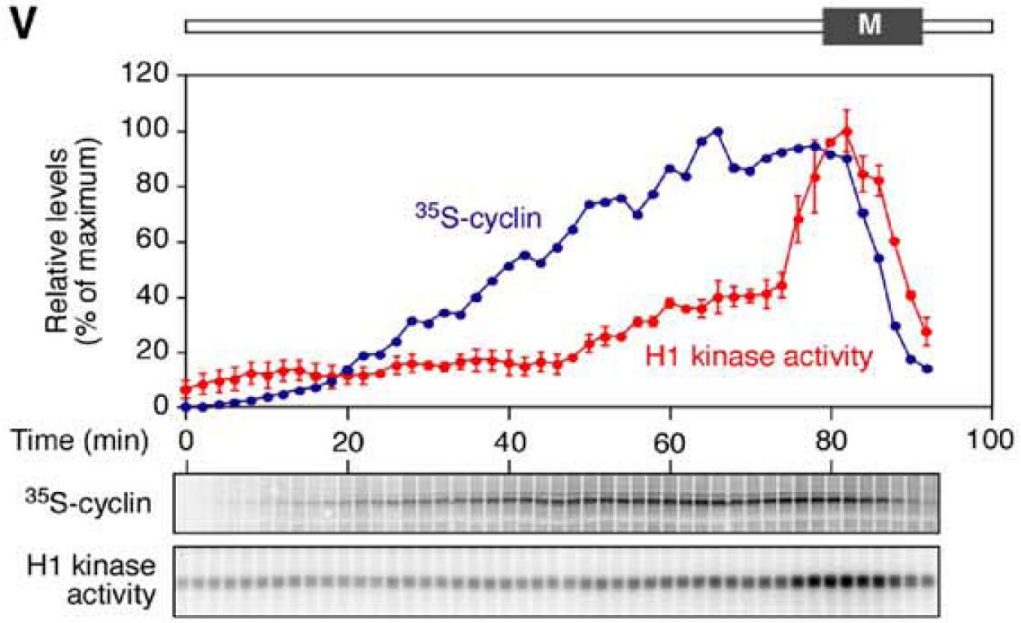


Experimental data available

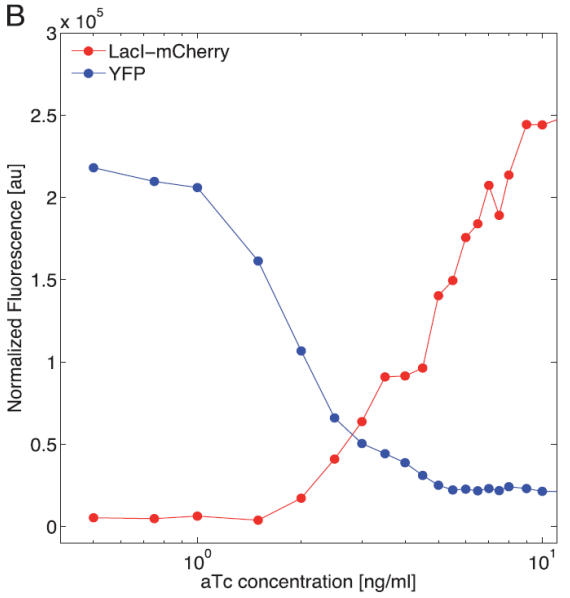
Expression of gene *wingless,* fly embryo (dark: highly expressed)

Microarray relative changes (red: expression increased)

Cdc2, cyclin B,
Pomerening et al. Cell 2005



Lac gene expression,
Brewster et al. Cell 2014



Construct a model : why ?

1. **Not all molecules can be measured simultaneously**

2. **Understand the underlying mechanisms of the system and its dynamics or behavior along time:**
   - → dose-response curves, steady states, oscillations
   - → numerically, by computer simulations,
   - → or by “pencil and paper” to be sure (prove mathematically) that some (desired or) dynamical behavior does happen

3. **Predict the response of a system to given stimuli**

4. **Control, regulate or act on the system:**
   - → add a certain quantity of a ligand
   - → schedule a therapeutic treatment

5. **Which quantities to model?**
   - → concentrations – protein, messenger RNA
   - → quantities you can measure – through GFP, western blots, micro-arrays,...
   - → interactions – how the different proteins affect each other

Mathematical analysis

System of equations: with $x=(x_{1,}\,x_{2,}\ldots,x_N)$

$$\frac{dx}{dt}=f(x) \quad <=> \quad \begin{cases} \dfrac{dx_1}{dt} = f_1(x_{1,}\,x_{2,}\ldots,x_N) \\ \dfrac{dx_2}{dt} = f_2(x_{1,}\,x_{2,}\ldots,x_N) \\ \qquad\ldots \\ \dfrac{dx_N}{dt} = f_N(x_{1,}\,x_{2,}\ldots,x_N) \end{cases}$$

Solutions for a given initial condition:

a vector function $x(t)$ satisfying $\frac{dx}{dt}=f(x), \quad x(0)=x_0$

Equilibrium points (or steady states): $f(\bar{x})=0$

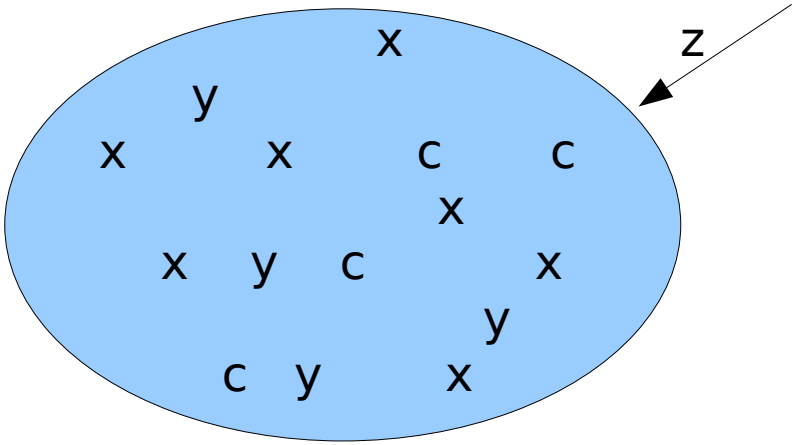
Questions: stability of equilibrium points, oscillatory behaviour, ...

Some hypotheses:

- homogeneously distributed molecules
- a sufficiently large number of molecules

Molecules of type X, Y

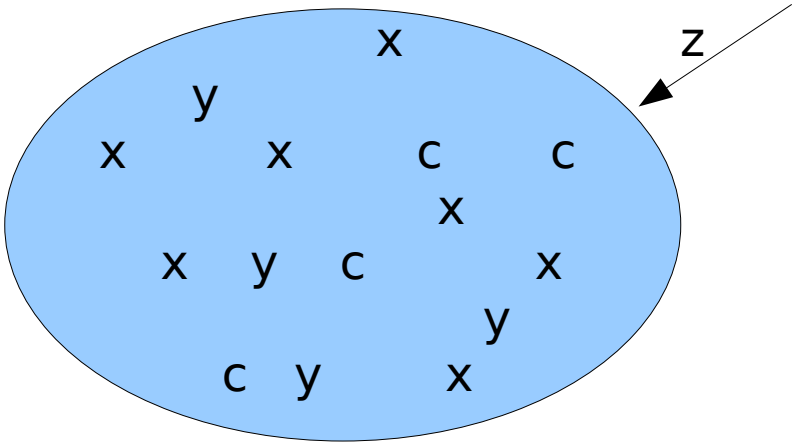
Combine/bind to generate C



Some hypotheses:

- homogeneously distributed molecules
- a sufficiently large number of molecules

Concentration of molecules of type X

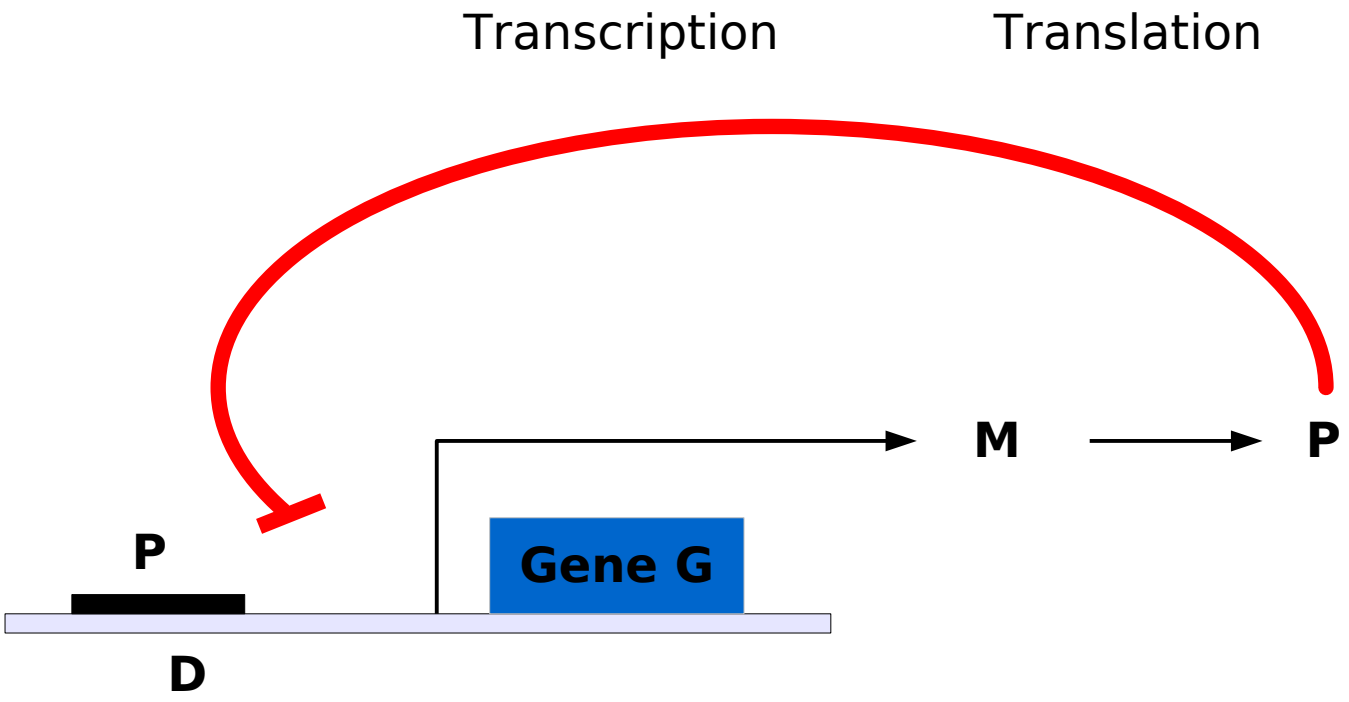


Describe by a **continuous ordinary differential equation** (ODE)

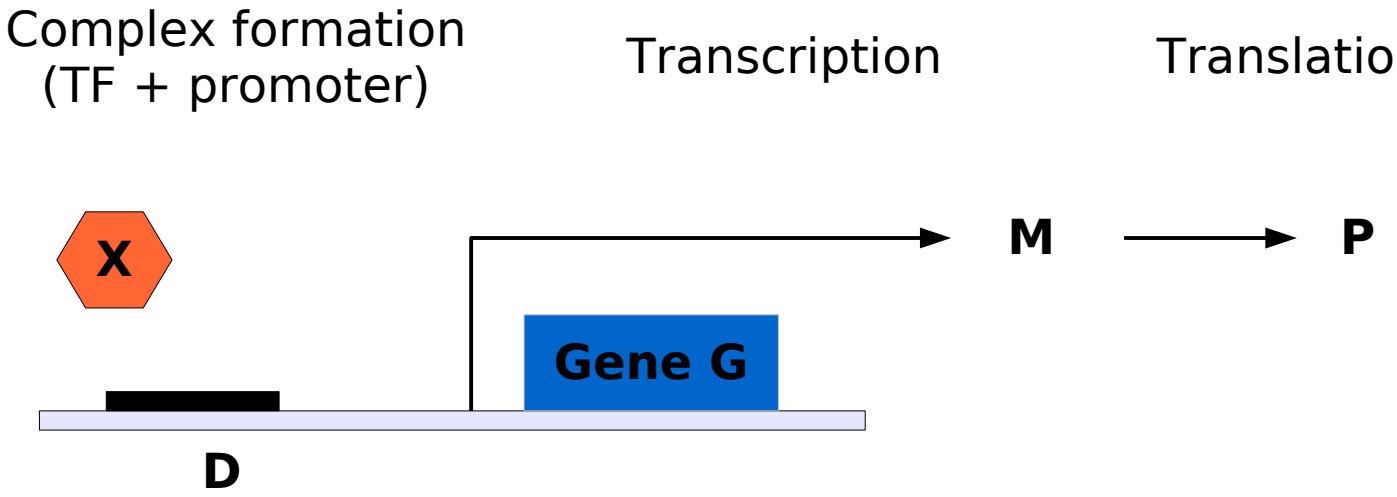
rate of change = production − degradation

$$\frac{dx}{dt} = f(x, y, c, z) - g(x, y, c, z)$$

Example : an auto-repressed gene



Genetic networks: transcription and translation

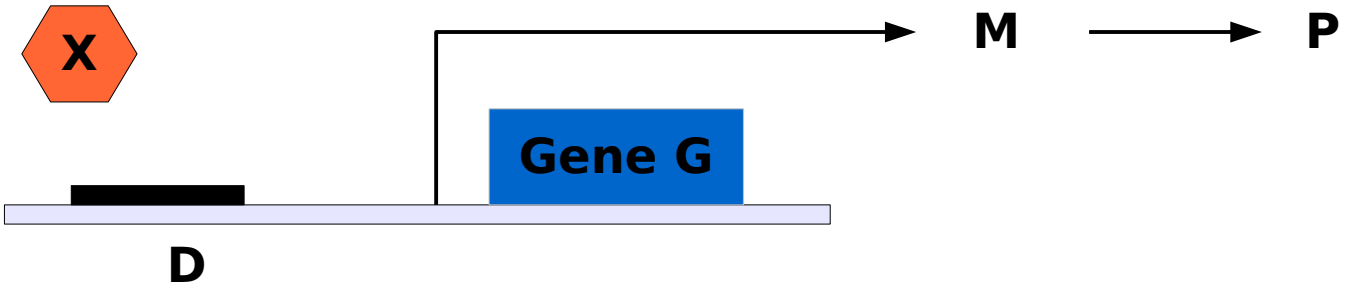


Genetic networks: transcription and translation

Complex formation (TF + promoter)

Transcription

Translation



$$X + D \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C \overset{\alpha_1, \alpha_2}{\rightsquigarrow} M \overset{\beta}{\rightarrow} P$$

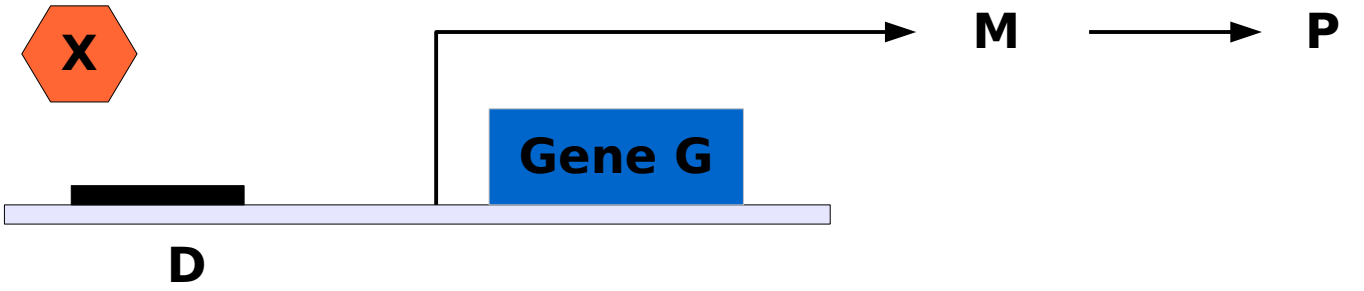
A basic Mathematical model

Genetic networks: transcription and translation

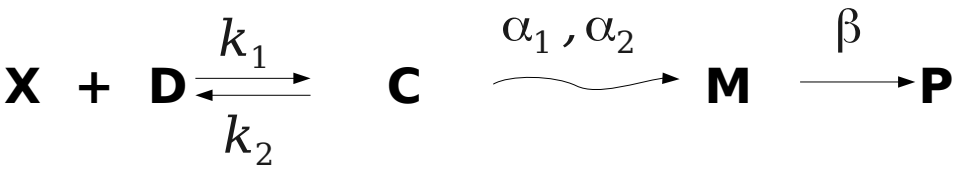
Complex formation (TF + promoter)

Transcription

Translation



A basic Mathematical model



$$\frac{dX}{dt} = -k_1 X D + k_2 C$$

$$\frac{dD}{dt} = -k_1 X D + k_2 C$$

$$\frac{dC}{dt} = k_1 X D - k_2 C$$

$$\frac{dM}{dt} = \alpha_1 C + \alpha_2 D - \gamma_M M$$

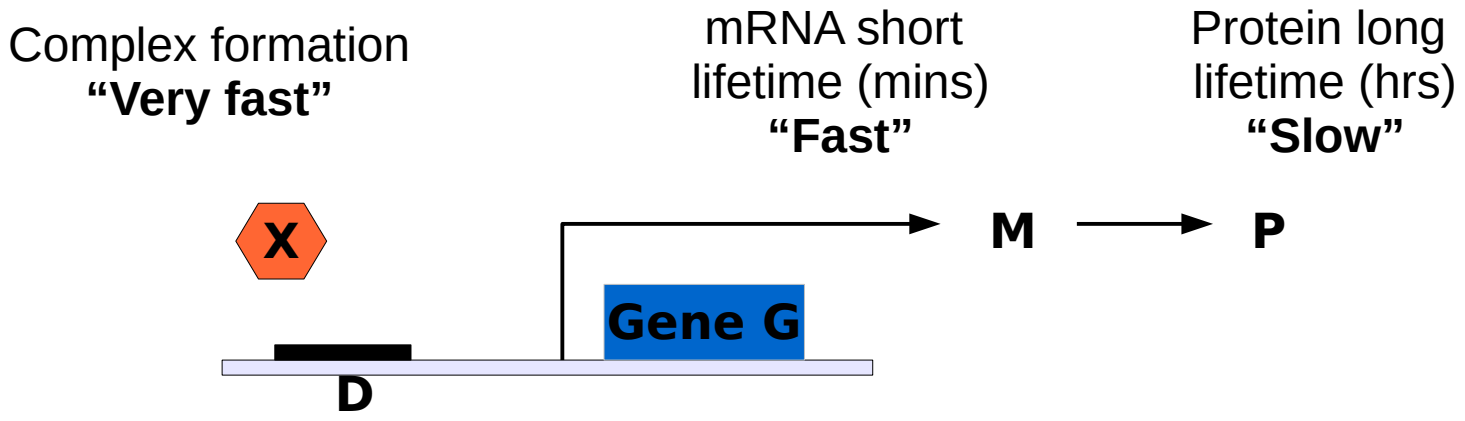
$$\frac{dP}{dt} = \beta M - \gamma_P P$$

Model reduction and simplification

1. **Conservation laws:** X, D or C are not “consumed” during transcription/translation

$$X + C = X_{total}$$
$$D + C = D_{total}$$

2. **Three Timescales** for biological processes



Binding interactions are fast compared with transcription, translation:

$$\frac{dC}{dt} \approx 0 \quad \Leftrightarrow \quad k_1 D X - k_2 C = 0$$

Total [D] (bound+free DNA) is constant:

$$D_T = D + C \quad \Leftrightarrow \quad D = D_T - C$$

Binding interactions are fast compared with transcription, translation:

$$\frac{dC}{dt} \approx 0 \quad \Leftrightarrow \quad k_1 D X - k_2 C = 0$$

Total [D] (bound+free DNA) is constant:

$$D_T = D + C \quad \Leftrightarrow \quad D = D_T - C$$

Substitute into the [C] equation:

$$k_1 \left(D_T - C \right) X - k_2 C \; = \; 0$$

$$\Leftrightarrow \quad k_1 D_T X - \left(k_2 + k_1 X \right) C \; = \; 0$$

Solve with respect to [C] to obtain:

$$k_1 D_T X - \left(k_2 + k_1 X\right) C = 0$$

$$\Rightarrow \quad C = k_1 D_T \frac{X}{k_2 + k_1 X} = \boxed{D_T \frac{X}{\frac{k_2}{k_1} + X}}$$

Michaelis-Menten equation

If ***n molecules of X*** are involved in binding D:

$$\frac{dC}{dt} \approx 0 \quad \Leftrightarrow \quad k_1 X^n D - k_2 C = 0$$

$$D_T = D + C \quad \Leftrightarrow \quad D = D_T - C$$

Obtain the **Hill equation**:

$$\Rightarrow \quad C = D_T \frac{X^n}{\frac{k_2}{k_1} + X^n} \equiv \boxed{D_T \frac{X^n}{k_X^n + X^n}}$$

n is called the Hill exponent

The system of 5 variables is reduced to 2 variables:

$$\frac{dM}{dt} = \alpha_1 C + \alpha_2 D - \gamma_M M$$

$$\frac{dP}{dt} = \beta M - \gamma_P P$$

With:

$$C = D_T \frac{X^n}{k_X^n + X^n}$$

$$D = D_T - C = D_T - D_T \frac{X^n}{k_X^n + X^n} = D_T \frac{k_X^n}{k_X^n + X^n}$$

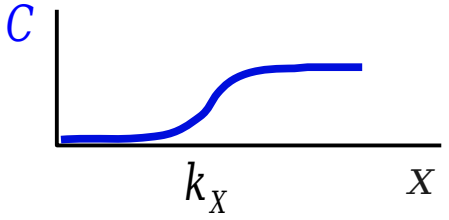
The system of 5 variables is reduced to 2 variables:

$$\frac{dM}{dt} = \alpha_1 C + \alpha_2 D - \gamma_M M$$

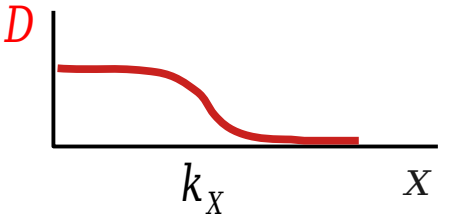
$$\frac{dP}{dt} = \beta M - \gamma_P P$$

With:

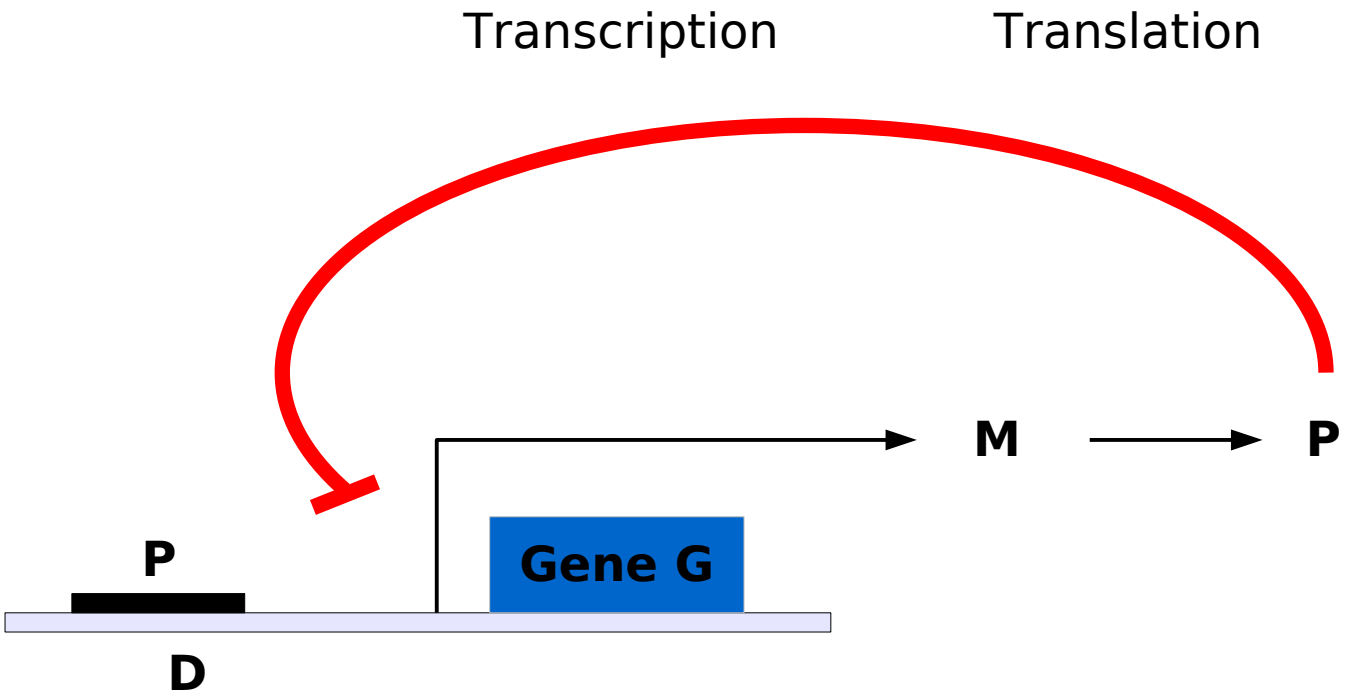
$$C = D_T \frac{X^n}{k_X^n + X^n}$$



$$D = D_T - C = D_T - D_T \frac{X^n}{k_X^n + X^n} = D_T \frac{k_X^n}{k_X^n + X^n}$$



Example : an auto-repressed gene



In the case of a **repression**

TRANSCRIPTION is proportional to the amount of FREE PROMOTER, **D**

System equations? Equilibria ?

Model reduction, continued

Timescales: lifetime(mRNA)<lifetime(protein)

so the **mRNA dynamics is faster** than the protein dynamics:

$$\frac{dM}{dt} = 0 \quad \Leftrightarrow \quad \alpha_1 C + \alpha_2 D - \gamma_M M = 0$$

$$\frac{dP}{dt} = \beta M - \gamma_P P$$

Model reduction, continued

Obtain the following expression for *M*:

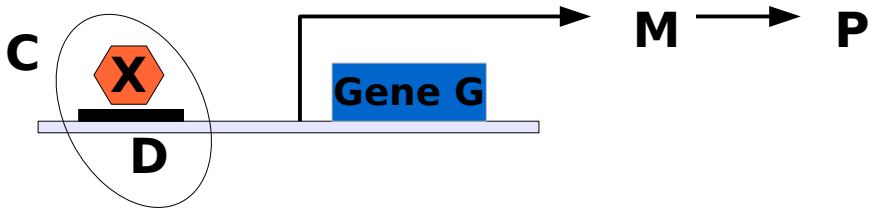
$$M = \frac{\alpha_1}{\gamma_M} D_T \frac{X^n}{k_X^n + X^n} + \frac{\alpha_2}{\gamma_M} D_T \frac{k_X^n}{k_X^n + X^n}$$

Finally, substitute this expression into *P* equation:

$$\frac{dP}{dt} = \beta \frac{\alpha_1}{\gamma_M} D_T \frac{X^n}{k_X^n + X^n} + \beta \frac{\alpha_2}{\gamma_M} D_T \frac{k_X^n}{k_X^n + X^n} - \gamma_p P$$

Modeling **activation**

X is an activator
(helps promote transcription)

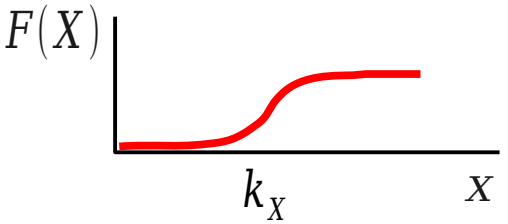


Bound **complex C strongly** contributes to **protein production:** $\alpha_1 \gg \alpha_2$

Rename parameters: $\beta_1 = \frac{\alpha_1}{\gamma_M} D_T$

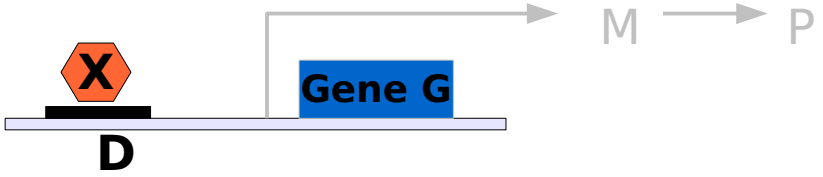
$$\frac{dP}{dt} = \beta_0 + \beta_1 \frac{X^n}{X^n + k_X^n} - \gamma_P P$$

Synthesis of protein is *Increasingly* proportional to amount of X



Modeling **repression**

X is an inhibitor
(represses transcription)

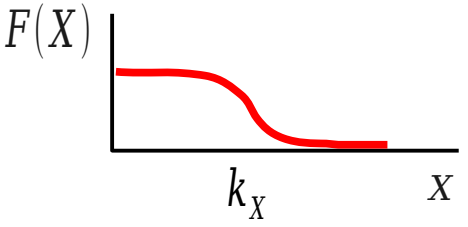


Unbound **sites D strongly** contribute to **protein production:** $\alpha_1 \ll \alpha_2$

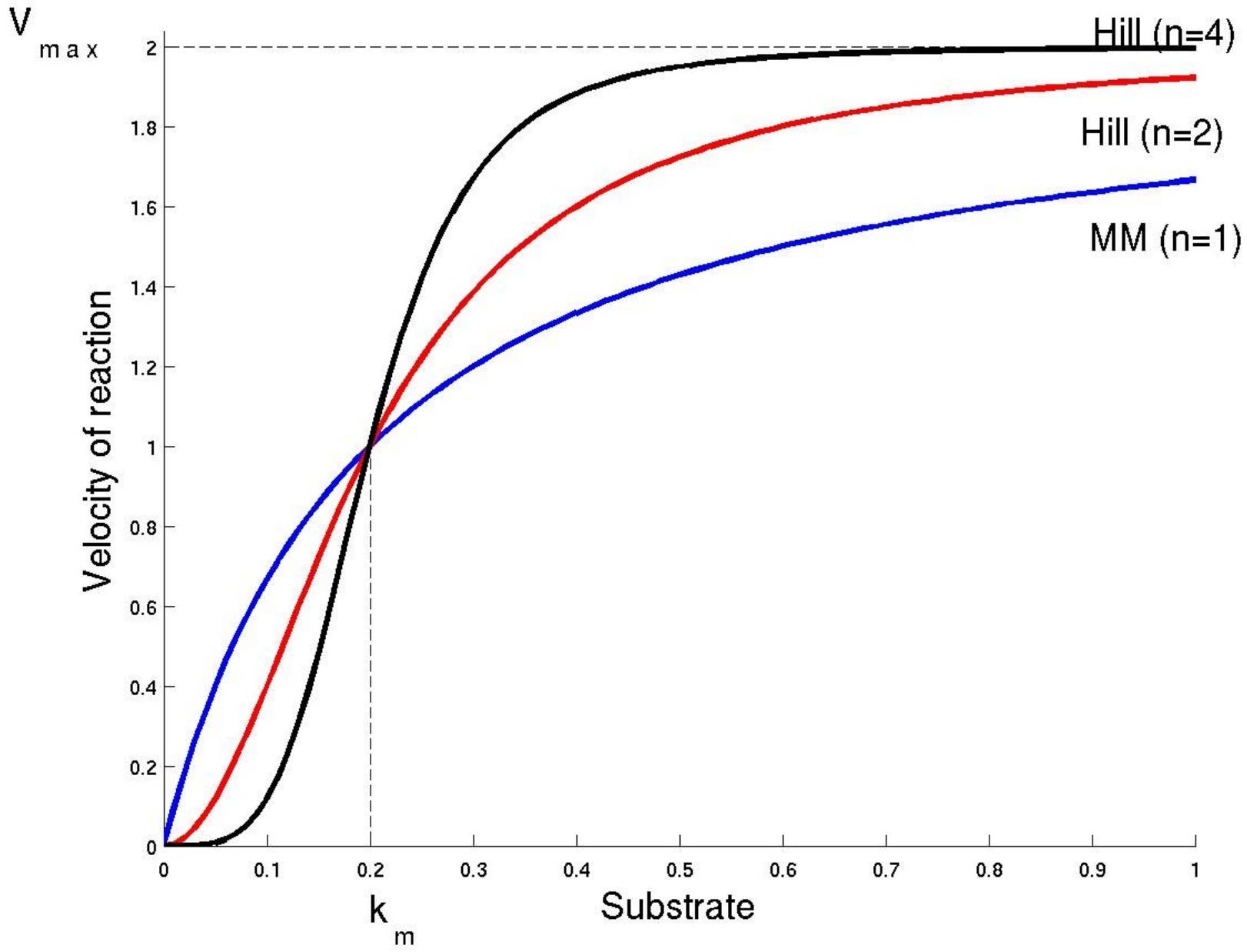
Rename parameters: $\beta_2 = \frac{\alpha_2}{\gamma_M} D_T$

$$\frac{dP}{dt} = \beta_0 + \beta_2 \frac{k_X^n}{X^n + k_X^n} - \gamma_P P$$

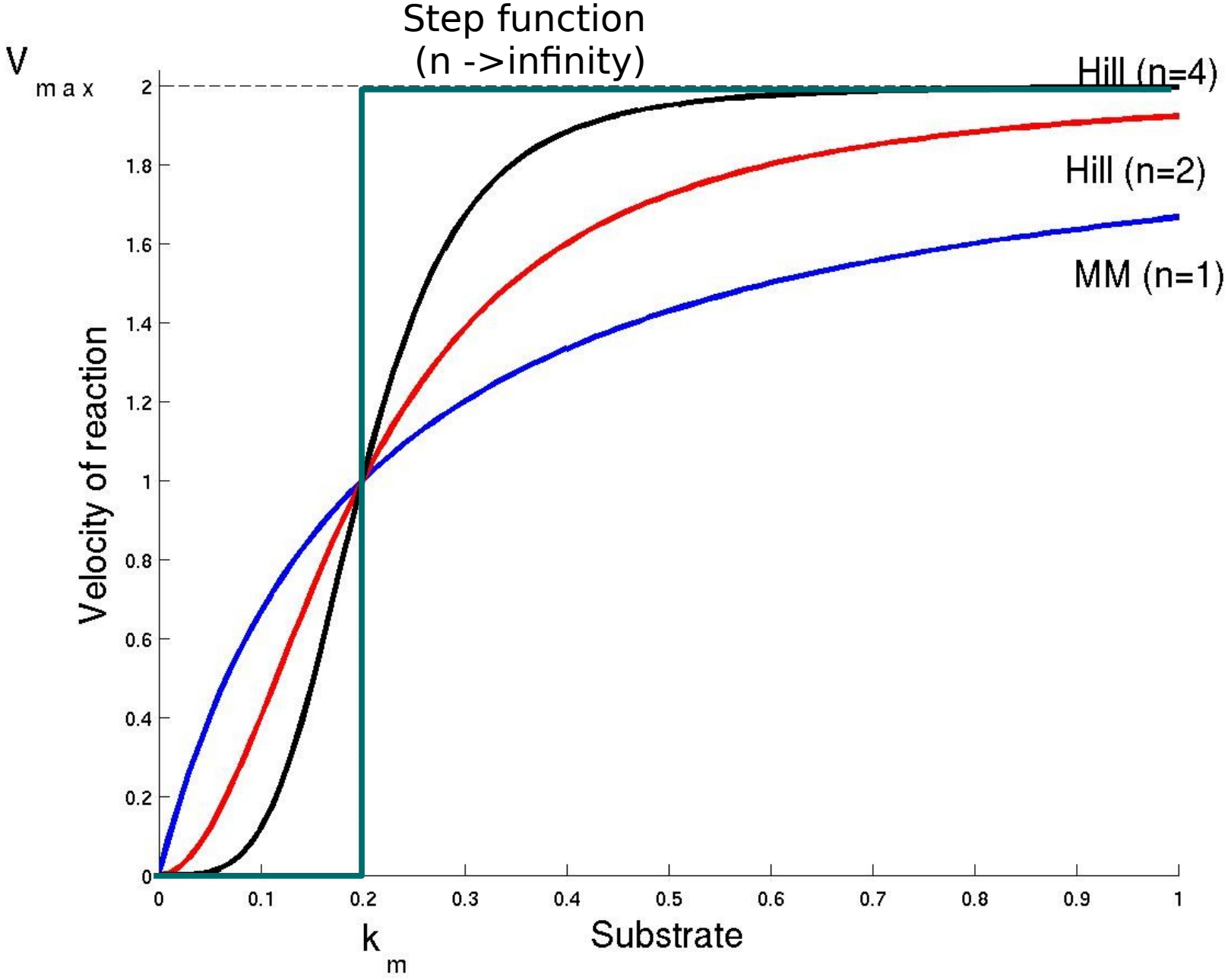
Synthesis of protein is *decreasingly* proportional to amount of X



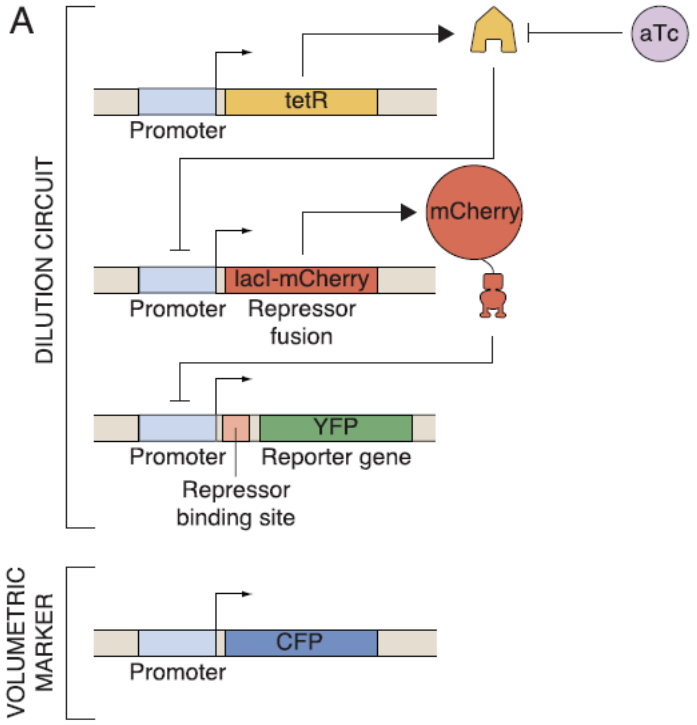
Michaelis-Menten and Hill functions



Michaelis-Menten and Hill functions



Evidence for sigmoidal functions *F(X)*



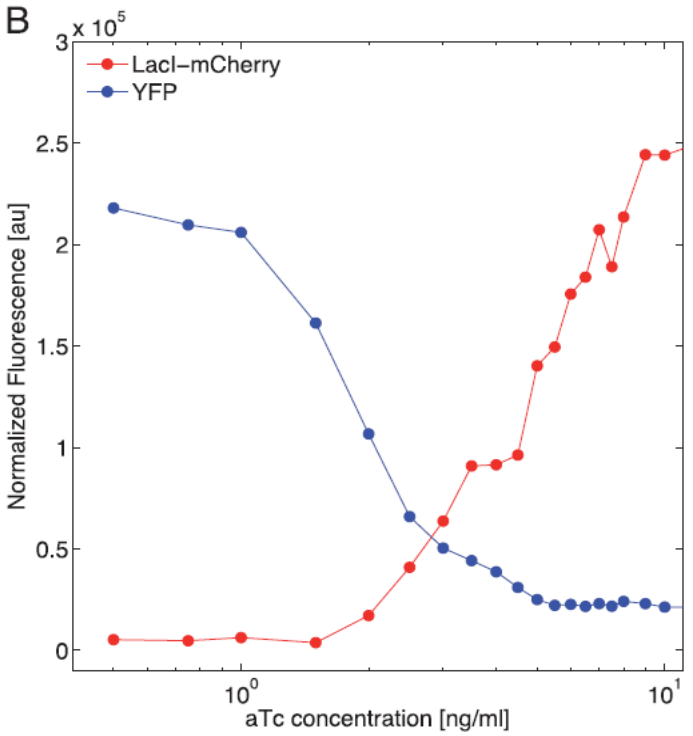
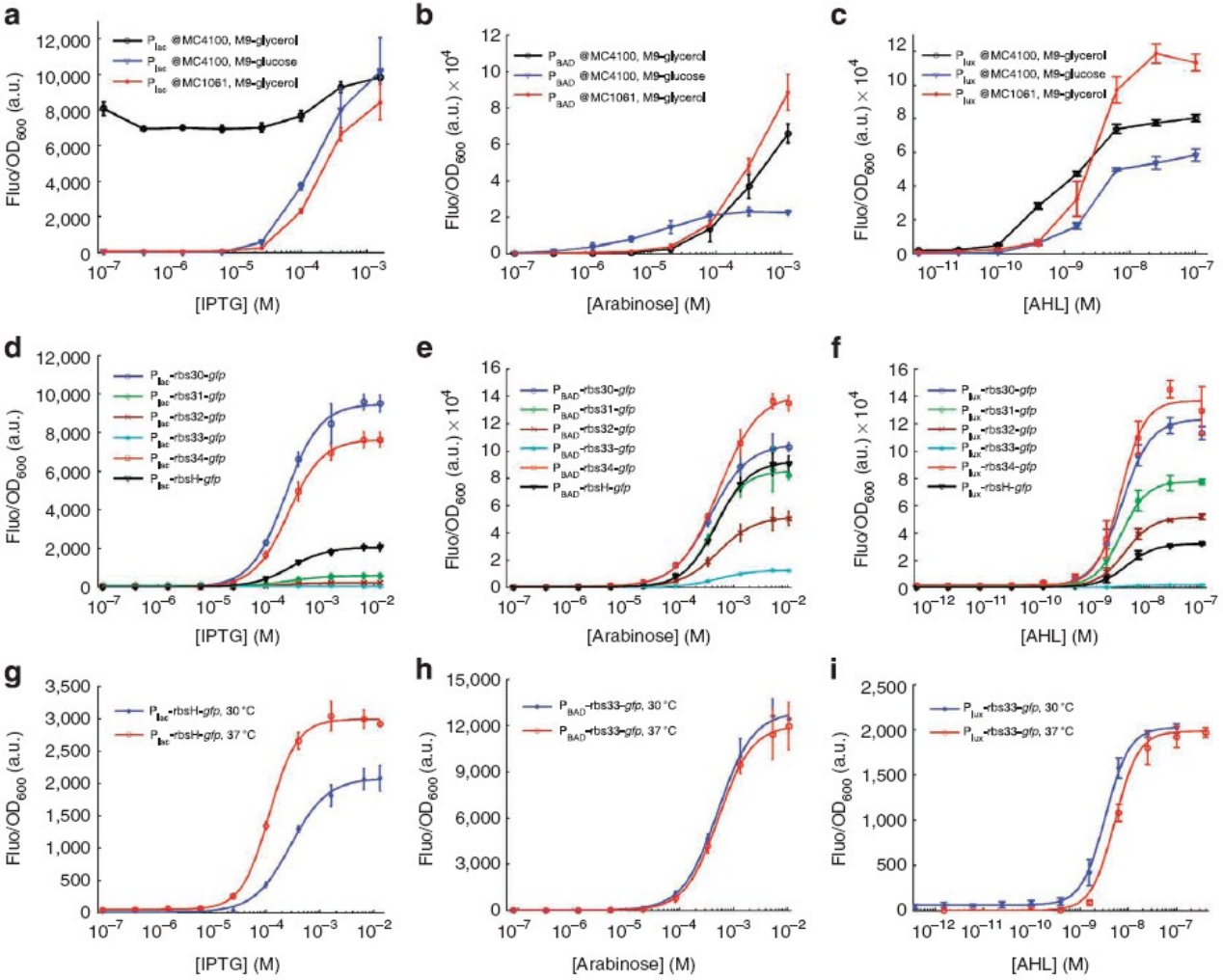


Figure from: Brewster et al. Cell 156 (2014)

Evidence for sigmoidal functions *F(X)*



Wang et al. Nature Communications 2011 (engineering synthetic gates)

Systèmes aux equations différentielles

SOLUTIONS NUMERIQUES avec SCILAB

Telecharger et installer Scilab :

www.scilab.org

Telecharger un exemple :

www-sop.inria.fr/members/Madalena.Chaves/teaching

Ecrire un code en Scilab : basiques

Definitions:

Equations,

Autres fonctions

Partie Principale:

Commandes our la Resolution, Visualisation, Analyse, etc

```
//Creer fichier texte, eg. :   mon_systeme.sci


function [v] = circuit_rhs(t,x,pr)
   .......
endfunction

function  r = autre(x,s,n)
   .......
 endfunction


 //Partie principale

  ..............

 x1=ode(......);

 plot(......);

   ..............
```

```
//Definition du systeme d'equations differentielles, au debut fichier

function [v] = auto_repressor_rhs(t,x,pr)

//t: instant de temps
//x: variables d'etat
//pr: parametres du systeme; reprendre depuis la definition

//Renommer les parametres et les variables
alpha = pr(1);
beta = pr(2);
kP = pr(3);
gM = pr(4);
gP = pr(5);
n = pr(6);

M=x(1);
P=x(2);

//Initialisation du vecteur des derivees
v = [];

v(1) = alpha*(kP^n) / (kP^n + P^n) - gM * M;
v(2) = beta*M – gP * P;

endfunction;
```

```
//Partie principale

//Definition de parametres; vecteur de parametres;
//BIEN RESPECTER L'ORDRE DE DEFINITION DE pr
alpha = 3.1;   beta = 2.3;
kP = 10;
gM = 0.1;   gP = 0.01;
n = 2;

par = [alpha,beta,kP,gM,gP,n];

//Definition de condition(s) initiale(s),
//instant initial et vecteur de temps de simulation
x0 = [10;1];
t0 = 0;
dt = 0.05;
tvec = t0:dt:30;

//Commande de resolution du systeme d'equations differentielles
//methodes numeriques disponibles: "rk", "stiff",...
sol=ode("stiff",x0,t0,tvec, list(auto_repressor_rhs,par) );

//Faire le graphe de la solution au cour du temps, dans la figure 1
//Options: couleur (r=red, b=blue,k=black,...), forme de ligne (-,--,:,-.)
figure(1);
plot(tvec,sol(1,:),'b-',tvec,sol(2,:),'r-');
```