M1 BBS - EM8BBSEM

Simulation de Systèmes Biologiques

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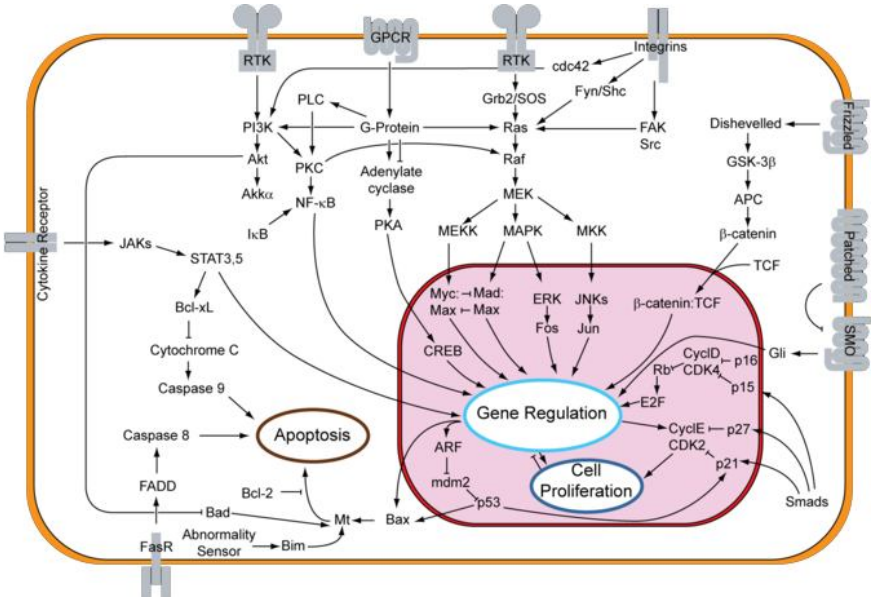
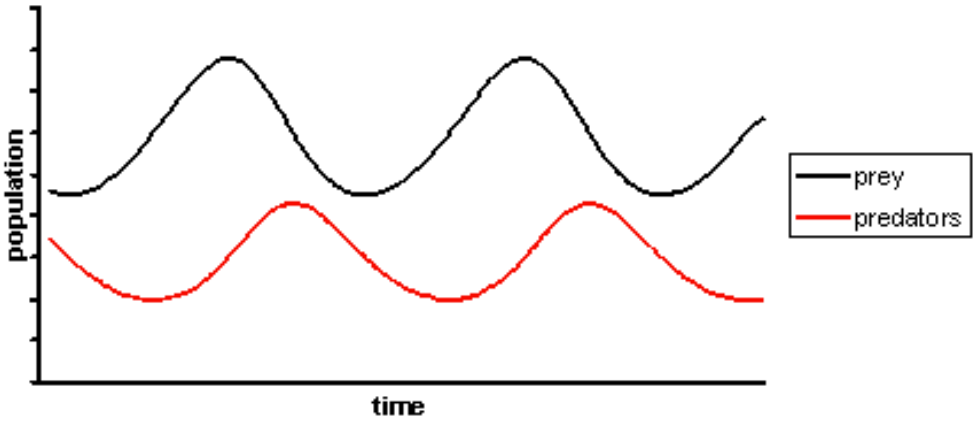
Modélisation dans la biologie des systèmes

La biologie systémique s'appuie lourdement sur l'utilisation d'outils mathématiques et de ressources bioinformatiques pour la modélisation et la simulation de systèmes biologiques complexes et dynamiques.

Les méthodes d'analyse développées pour les besoins de la simulation couvrent beaucoup de domaines différents et sont valides à des niveaux différents de l'organisation de systèmes biologiques. Les approches pareilles peuvent être utilisées pour analyser les processus dynamiques au niveau de molécules ou de cellules, mais aussi au niveau de populations entières.





Complexe, dynamique, difficile à comprendre

Système biologique

Simple, avec les paramètres permettant l'analyse efficace des résultats

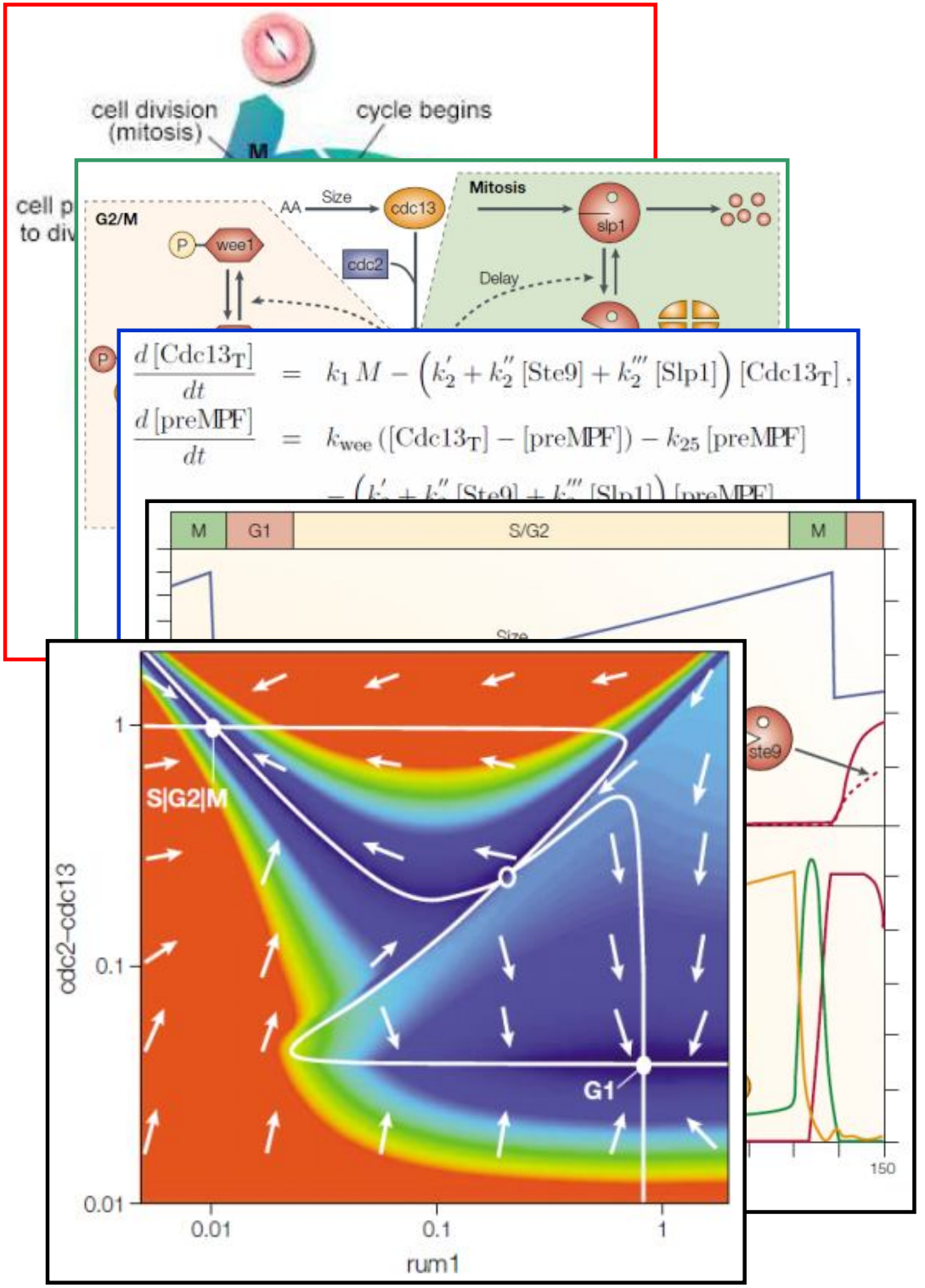
Modèle du système

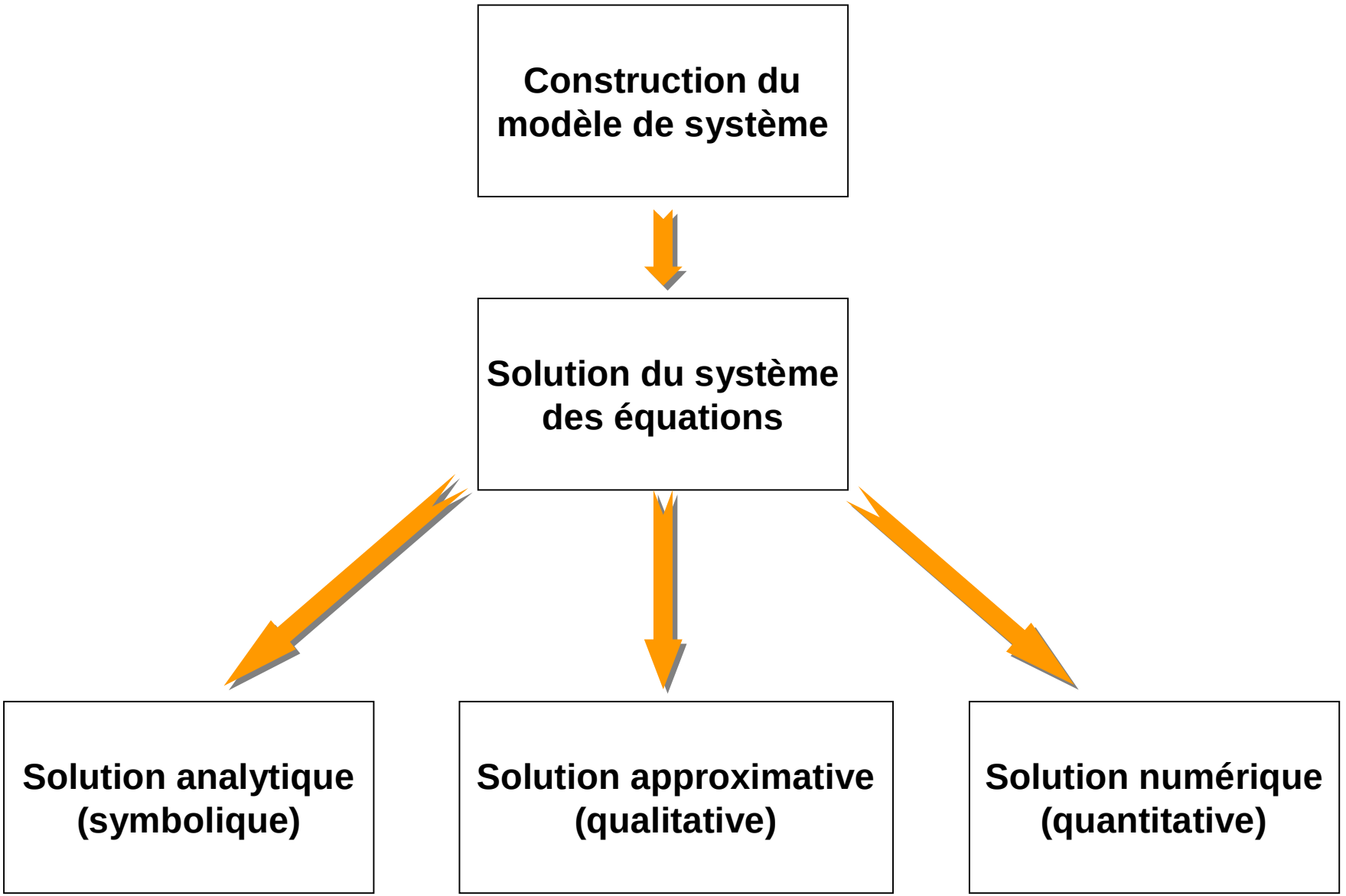
Fiable, robuste, adaptative, évolutive

Simulation du système

Nécessite une validation expérimentale

Analyse de résultats




Construction du modèle de système
Solution du système des équations
Solution analytique (symbolique)
Solution approximative (qualitative)
Solution numérique (quantitative)

Objectif :

Apprendre les bases de la modélisation de processus biologiques.

Contenu :

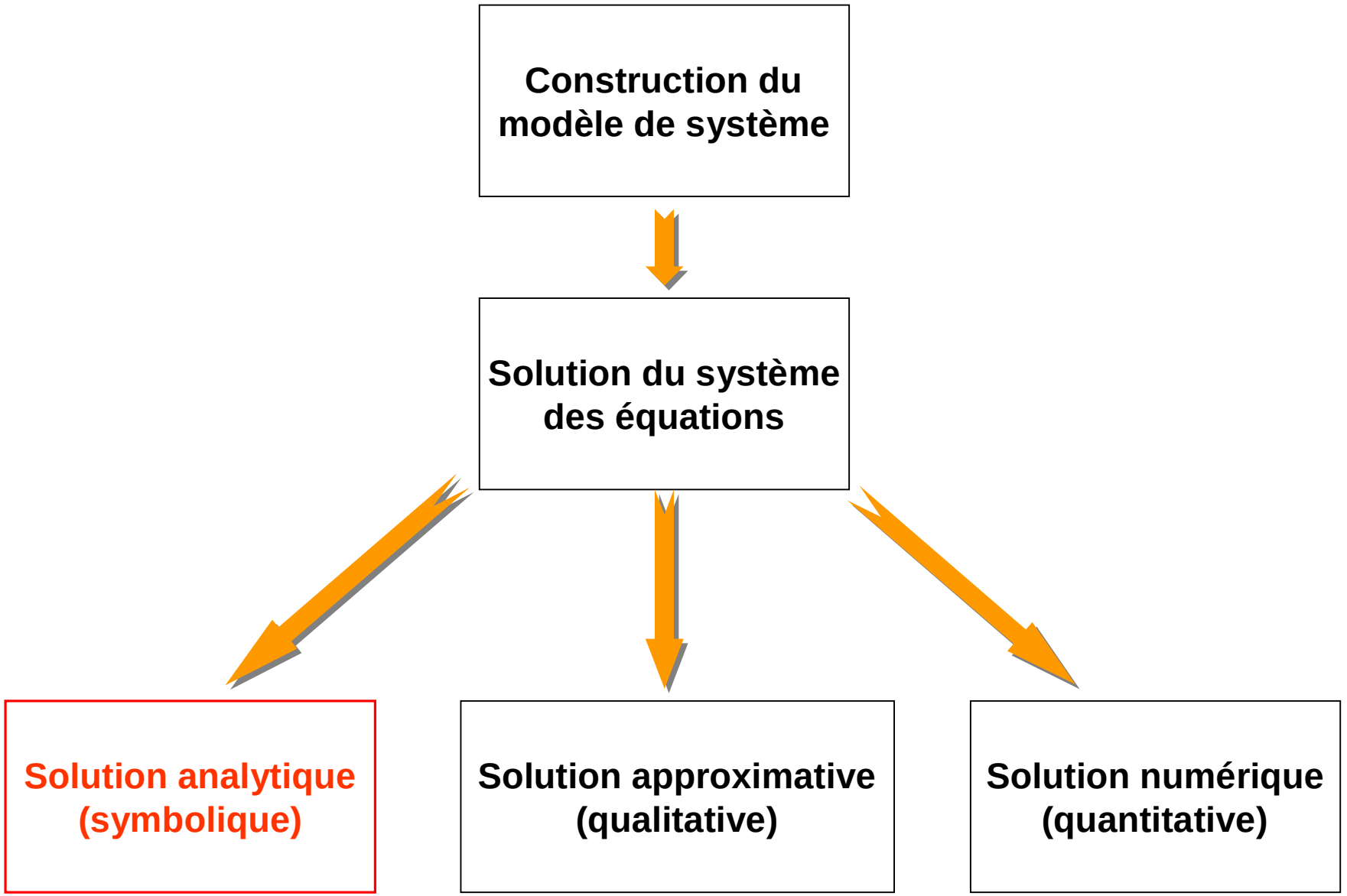
- **Principes de construction de modèles dynamiques dans biologie**

- **Recherche de solutions analytiques**
  - **présentation des équations différentielles**
  - **méthodes d'obtention de solutions analytiques**

- **Théorie qualitative de systèmes dynamiques**
  - **simplification de systèmes d'équations**
  - **points stationnaires et leur stabilité**
  - **portrait de phase et trajectoires**

- **Approches numériques**
  - **introduction au calcul numérique et au langage Matlab**
  - **intégration de jeux d'équations différentielles**

- **Sélection des applications pratiques**
  - **cinétique enzymatique (réactions chimiques)**
  - **modélisation de la croissance de la biomasse**
  - **processus périodiques et systèmes prédateur-proie**
  - **sélection d'un des espèces équivalents**
  - **les *triggers* génétiques (biosynthèse)**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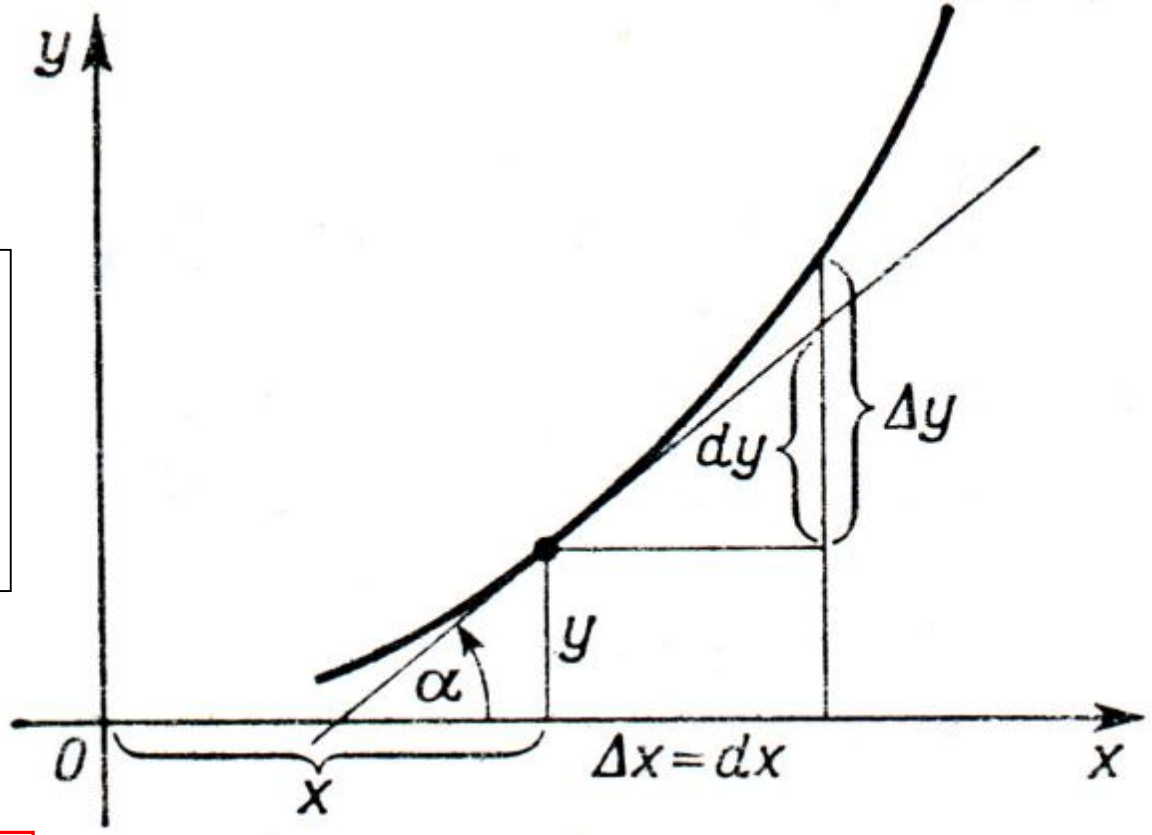
Définition de la dérivée d'une fonction

Afin de faciliter l'analyse de fonctions, on introduit la notion de la dérivée. La dérivée *y'(x)* d'une fonction *y=f(x)* qui dépend d'une seule variable *x*, est définie comme suit :

$$y' = \frac{dy}{dx} = \lim_{\Delta x \to 0} \frac{y(x+\Delta x) - y(x)}{\Delta x}$$

La dérivée montre la variation de la fonction *y=f(x)* quand on varie son argument x. Voici l'interprétation géométrique de la dérivée :

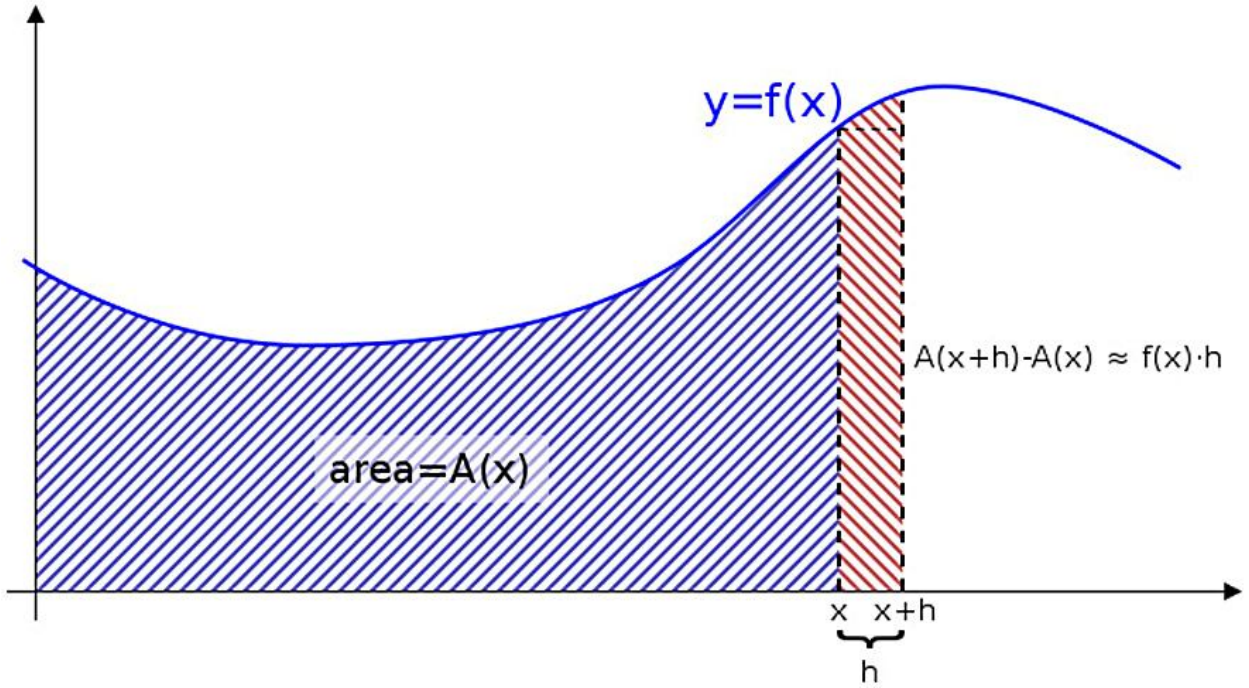


$$\tan(\alpha) = \frac{\Delta y}{\Delta x} \xrightarrow{\Delta x \to 0} \frac{dy}{dx} = y'(x)$$

Définition de l'intégrale d'une fonction

$$A(x) = \int f(x)\,dx$$

A = l'aire sous la courbe f(x)
(ici, entre 0 et la coordonnée x)



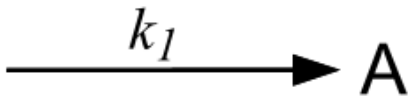
L'aire entre x et x+h =
A(x+h) – A(x)

L'aire entre x et x+h =
h · f(x)

$$h \cdot f(x) \approx A(x+h) - A(x)$$

$$f(x) \approx \frac{A(x+h) - A(x)}{h} \quad \Rightarrow \quad f(x) = \frac{dA}{dx}$$

Réactions élémentaires : production constante

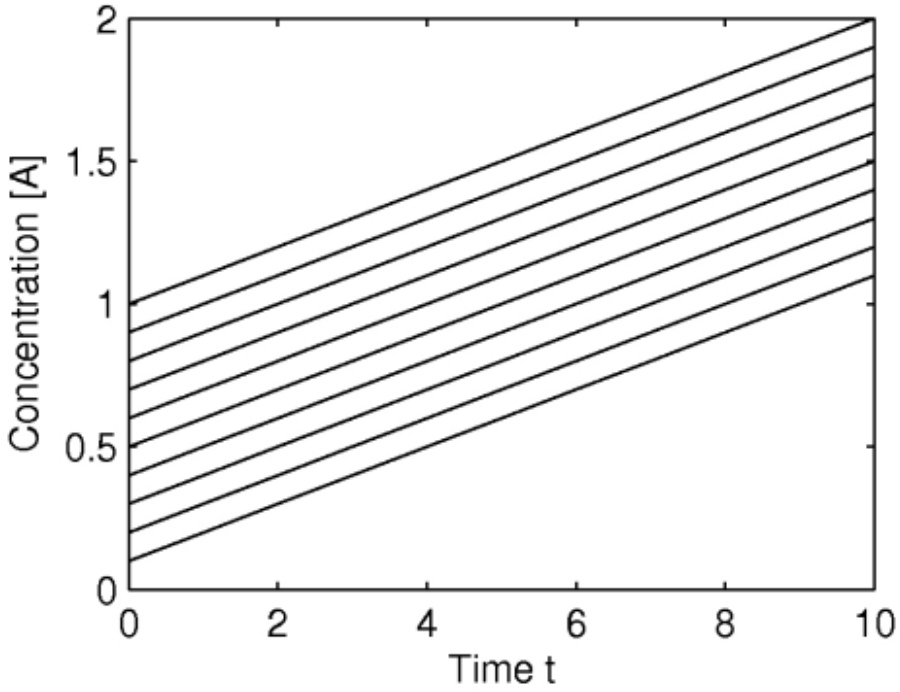


$$\frac{dA}{dt} = k_1$$

$$dA = k_1 dt$$

$$A = \int dA = \int k_1 dt$$

$$A = k_1 \int dt = k_1 t + A_0$$



(Synthèse constante, e.g. expression génique, sans dégradation mARN/protéine)

Réactions élémentaires : dégradation linéaire

$$A \xrightarrow{k_1}$$

$$\frac{dA}{dt} = -k_1 A$$

$$\frac{dA}{A} = -k_1 dt$$

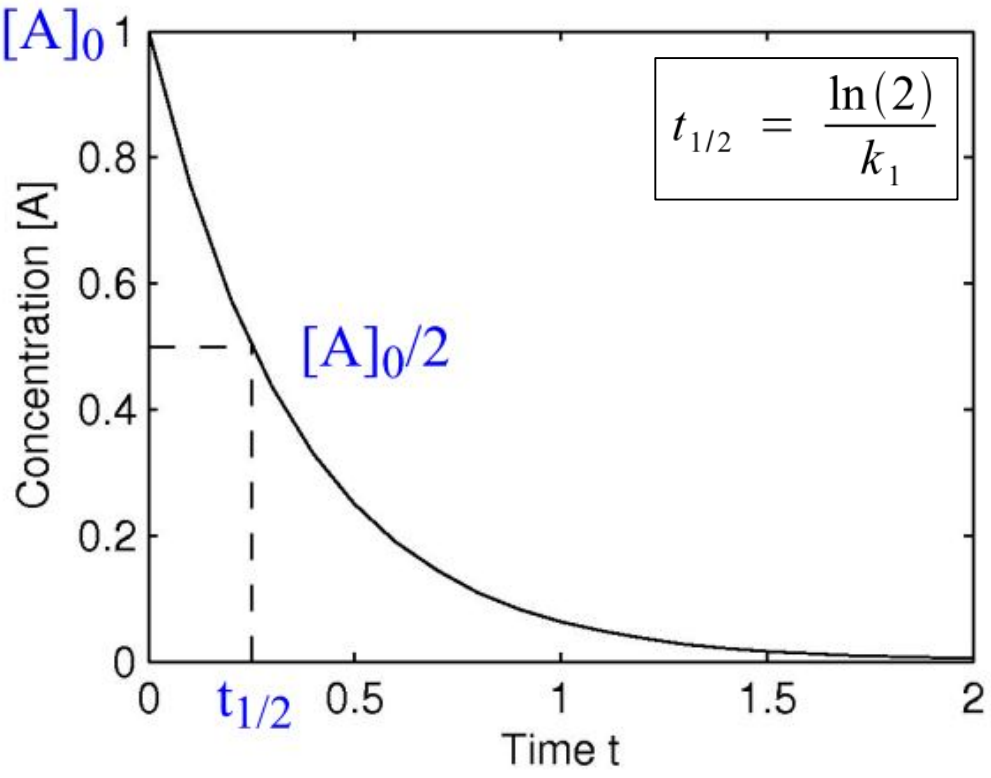
$$\int \frac{dA}{A} = -\int k_1 dt$$

$$\ln(A) = -k_1 \int dt = -k_1 t + C$$

$$A(t) = \exp\left(-k_1 t + C\right) = e^{-k_1 t} \cdot e^{C}$$

$$A(t=0) = A_0$$

$$A_0 = e^{C} \quad \Rightarrow \quad A(t) = A_0 e^{-k_1 t}$$



Réactions élémentaires : autocatalyse

$$\xrightarrow{k_1 \cdot [A]} A \qquad \boxed{\frac{dA}{dt} = +k_1 A}$$

$$\frac{dA}{A} = k_1 dt$$

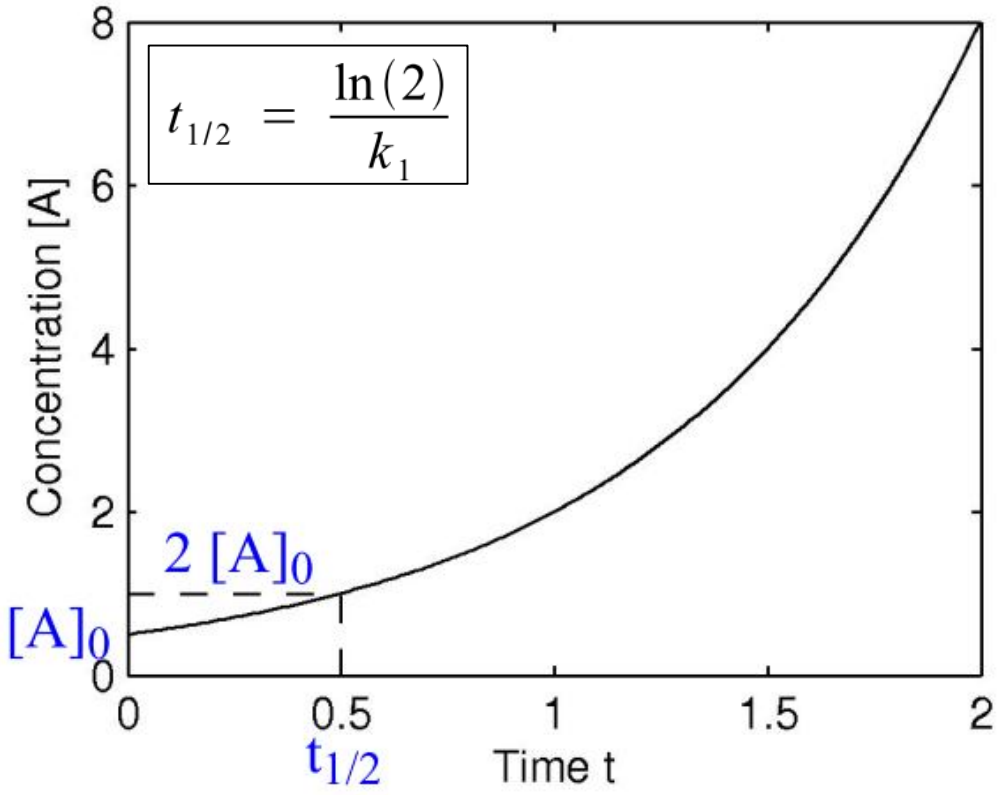
$$\int \frac{dA}{A} = \int k_1 dt$$

$$\ln(A) = k_1 \int dt = k_1 t + C$$

$$A(t) = \exp(k_1 t + C) = e^{k_1 t} \cdot e^{C}$$

$$A(t = 0) = A_0$$

$$A_0 = e^{C} \quad \Rightarrow \quad A(t) = A_0 e^{k_1 t}$$

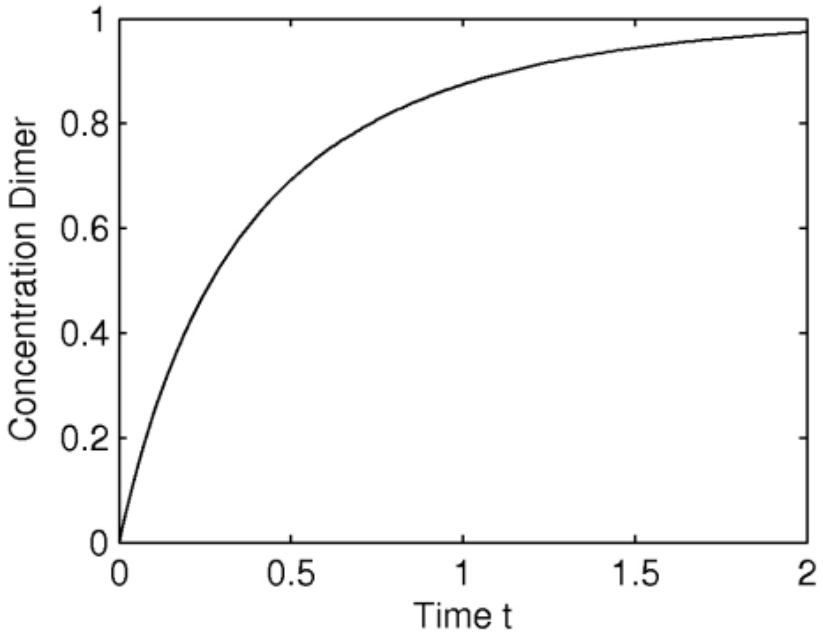


Réactions élémentaires : dimérisation

$$A + B \xrightarrow{k_1} AB$$

$$\begin{cases} \dfrac{d[A]}{dt} = -k_1[A]\cdot[B] \\ \dfrac{d[B]}{dt} = -k_1[A]\cdot[B] \\ \dfrac{d[AB]}{dt} = k_1[A]\cdot[B] \end{cases}$$

$$[AB] = \frac{A_0 B_0 \left[1 - e^{-(A_0 - B_0)k_1 t}\right]}{A_0 - B_0 e^{-(A_0 - B_0)k_1 t}}$$



Dimérisation : solution

$$\frac{d[AB]}{dt} = k_1[A]\cdot[B] \quad \begin{matrix}[A] = A_0 - [AB] \\ [B] = B_0 - [AB]\end{matrix} \quad \boxed{\frac{d[AB]}{dt} = k_1(A_0 - [AB])\cdot(B_0 - [AB])}$$

$$\frac{d[AB]}{(A_0 - [AB])\cdot(B_0 - [AB])} = k_1 dt \quad \Rightarrow \quad \int \frac{d[AB]}{(A_0 - [AB])\cdot(B_0 - [AB])} = \int k_1 dt = k_1 t + C$$

$$\int \frac{d[AB]}{(A_0 - [AB])\cdot(B_0 - [AB])} = \frac{1}{B_0 - A_0}\left[\int \frac{d[AB]}{(A_0 - [AB])} - \int \frac{d[AB]}{(B_0 - [AB])}\right]$$

$$\frac{1}{B_0 - A_0}\ln\left(\frac{B_0 - [AB]}{A_0 - [AB]}\right) = k_1 t + C$$

$$\boxed{[AB] = \frac{B_0 - A_0 \cdot Ce^{-(A_0 - B_0)k_1 t}}{1 - Ce^{-(A_0 - B_0)k_1 t}}} \qquad (A_0 > B_0)$$

Solution : conditions initiales

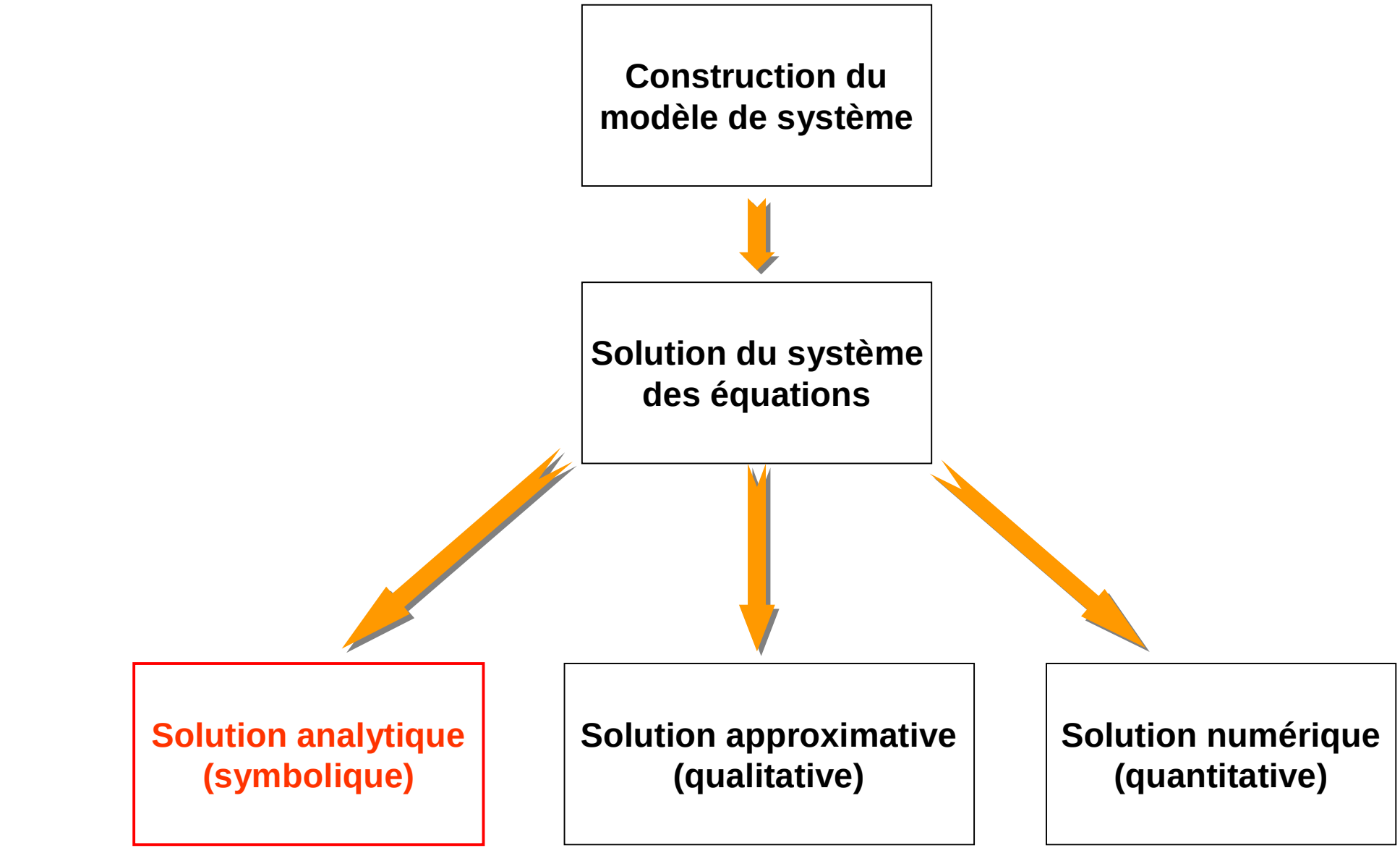
$$[AB] = \frac{B_0 - A_0 \cdot Ce^{-(A_0 - B_0)k_1 t}}{1 - Ce^{-(A_0 - B_0)k_1 t}}$$

$$[AB]_{t=0} = 0 \quad \Rightarrow \quad 0 = \frac{B_0 - A_0 \cdot C}{1 - C} \quad \Rightarrow \quad C = \frac{B_0}{A_0}$$

$$[AB] = \frac{A_0 B_0 \left[1 - e^{-(A_0 - B_0)k_1 t}\right]}{A_0 - B_0 e^{-(A_0 - B_0)k_1 t}}$$

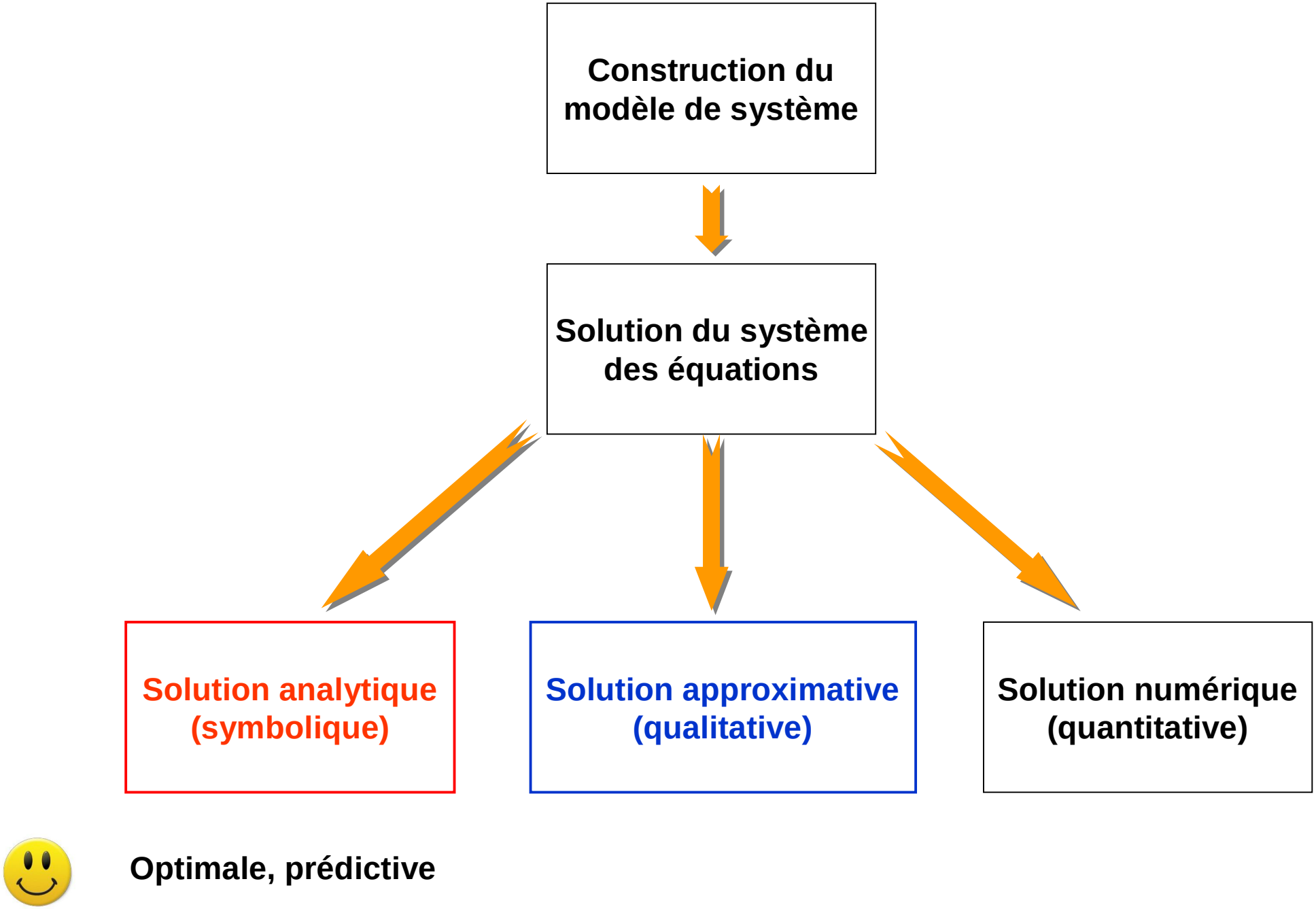
Qu'est-ce qui se passe après un temps très long ?

$$[AB]_{t=\infty} = \frac{A_0 B_0 [1 - 0]}{A_0 - B_0 \cdot 0} = B_0 \qquad (A_0 > B_0)$$



Optimale, prédictive

Rarement disponible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Rarement disponible

In enzymatic catalysis, a molecule of **S**ubstrate binds to **E**nzyme, forming a **Michaelis complex**. As a result of this interaction a molecule of **P**roduct is released:

$$S + E \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} [ES] \xrightarrow{k_{+2}} P + E$$

Complex synthesis is a **second order** reaction while that of its dissociation is a **first order** reaction. Evolution of concentrations of all components can be described by the following set of equations:

$$\begin{cases} \dfrac{dS}{dt} = -k_{+1}SE + k_{-1}[ES] & \text{(a)} \\ \dfrac{dE}{dt} = -k_{+1}SE + k_{-1}[ES] + k_{+2}[ES] & \text{(b)} \\ \dfrac{d[ES]}{dt} = k_{+1}SE - k_{-1}[ES] - k_{+2}[ES] & \text{(c)} \\ \dfrac{dP}{dt} = k_{+2}[ES] & \text{(d)} \end{cases}$$

By adding **(b)** to **(c)** we find that the total enzyme concentration is constant:

$$\frac{dE}{dt}+\frac{d[ES]}{dt}=\frac{d}{dt}(E+[ES])=0$$

$$E+[ES]=const=E_0$$

We simplify the equations by substituting ***E = E₀ – [ES]*** into **(c)**:

$$\frac{d[ES]}{dt}=k_{+1}S\,(E_0-[ES])-k_{-1}[ES]-k_{+2}[ES]$$

$$\Downarrow$$

$$\frac{d[ES]}{dt}=-(k_{-1}+k_{+2}+k_{+1}S)[ES]+k_{+1}SE_0$$

Typically, S ≈ P ≈ 1 ÷ 10 mM, while E ≈ 1 ÷ 10 μM. Hence, enzymatic activity (particularly *in vitro*) usually takes place in the limit of constant substrate concentration. The stationary solution of the above equation can be obtained by setting ***d[ES]/dt = 0***:

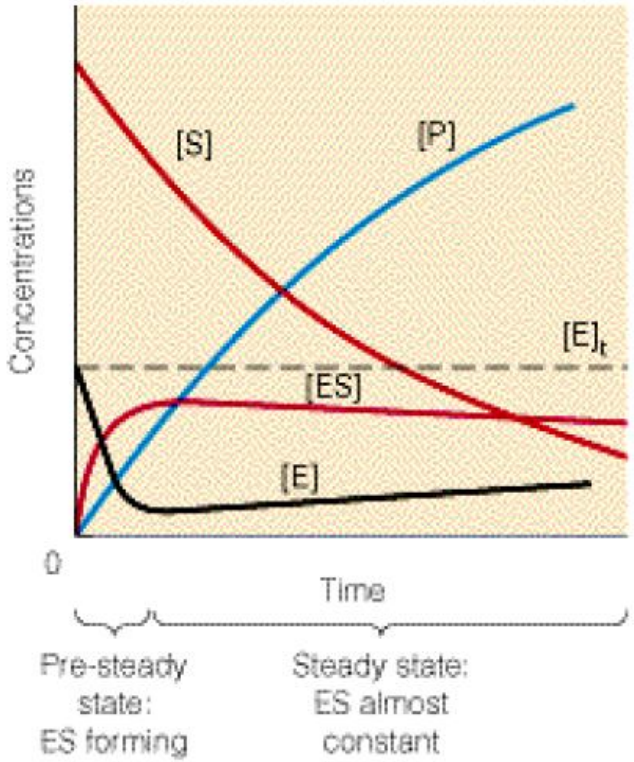
$$\left[\overline{ES}\right] = \frac{E_0 S}{K_M + S}$$

$$K_M = \frac{k_{-1} + k_{+2}}{k_{+1}}$$

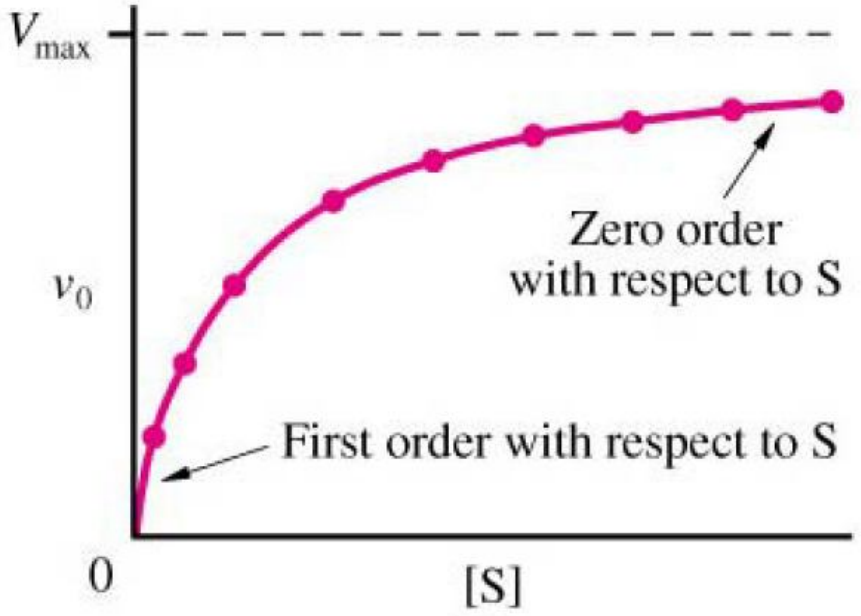
K_M is the Michaelis constant, corresponding to the substrate concentration at which half of the enzyme molecules are complexed. The other two equations can be written as:

$$\frac{dS}{dt} = -k_{+1} S E + k_{-1}\left[\overline{ES}\right] = -k_{+2}\left[\overline{ES}\right]$$

$$\frac{dP}{dt} = k_{+2}\left[\overline{ES}\right] = -\frac{dS}{dt} = \frac{k_{+2} S E_0}{K_M + S}$$



The more ES present, the faster ES will dissociate into E + P or E + S. Therefore, when the reaction is started by mixing enzymes and substrates, the [ES] builds up at first, but quickly reaches a STEADY STATE, in which [ES] remains constant. This steady state will persist until almost all of the substrate has been consumed.



For large substrate concentrations the enzymatic reaction rate reaches a constant value, called the ***maximal enzymatic reaction rate***:

$$\frac{dP}{dt} = -\frac{dS}{dt} = \frac{k_{+2} S E_0}{K_M + S} \xrightarrow{S \to \infty} k_{+2} E_0$$

It describes the number of catalytic reactions per unit of time performed by enzyme when it is fully saturated with substrate.

In reality, reactions may be much more complex than the above equations, and yet it is possible to describe a system accurately with a relatively simple approach. Think of the chemical reaction:

$$2H_2 + O_2 \rightarrow 2H_2O$$

Many of the intermediate states are not reflected at all, since only the initial conditions and final results are taken into account. Similarly, in biology it is quite sufficient to monitor the substrate and product concentrations, describing the complex network of intermediate reactions by the simple concept of the enzyme.

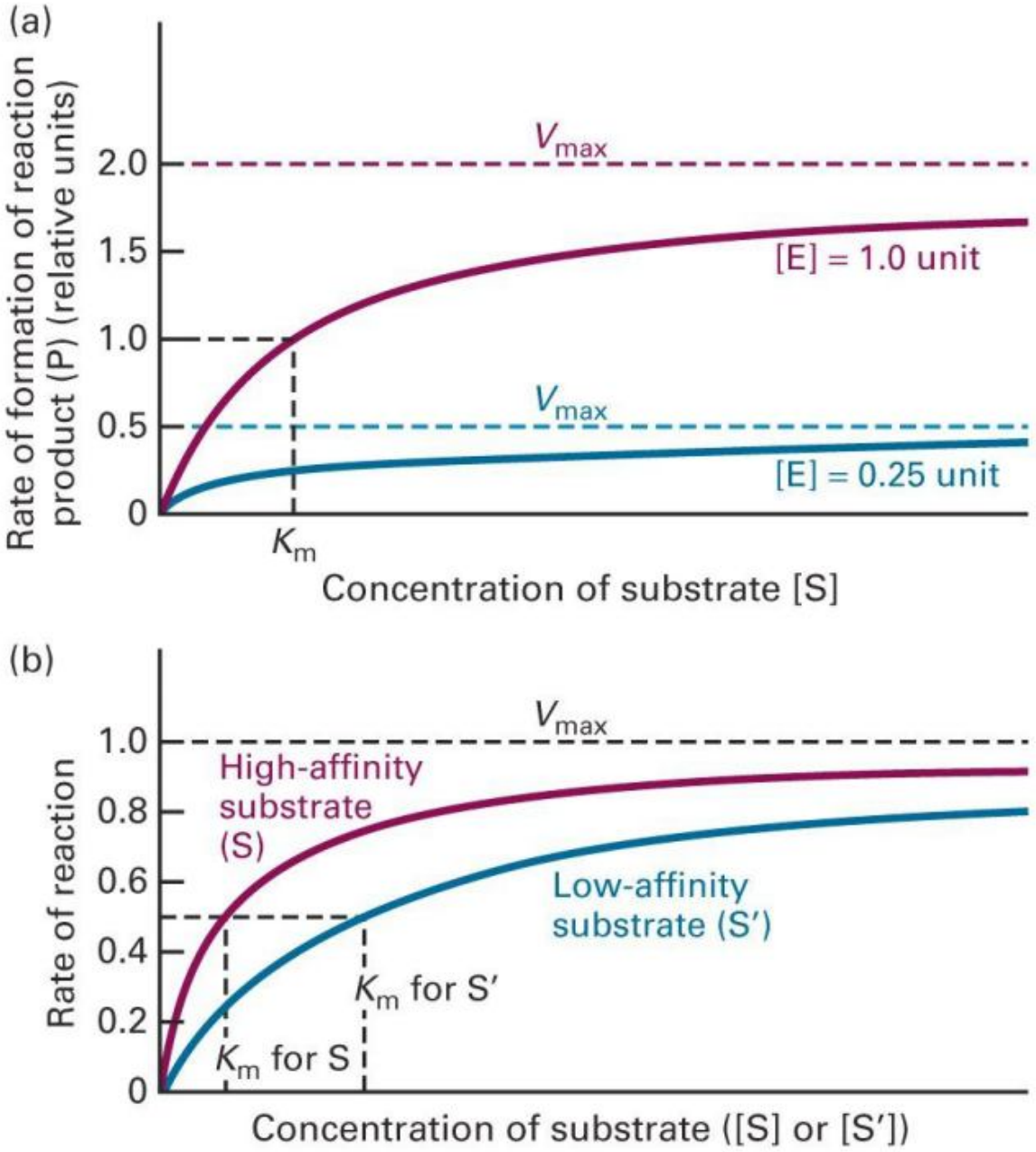
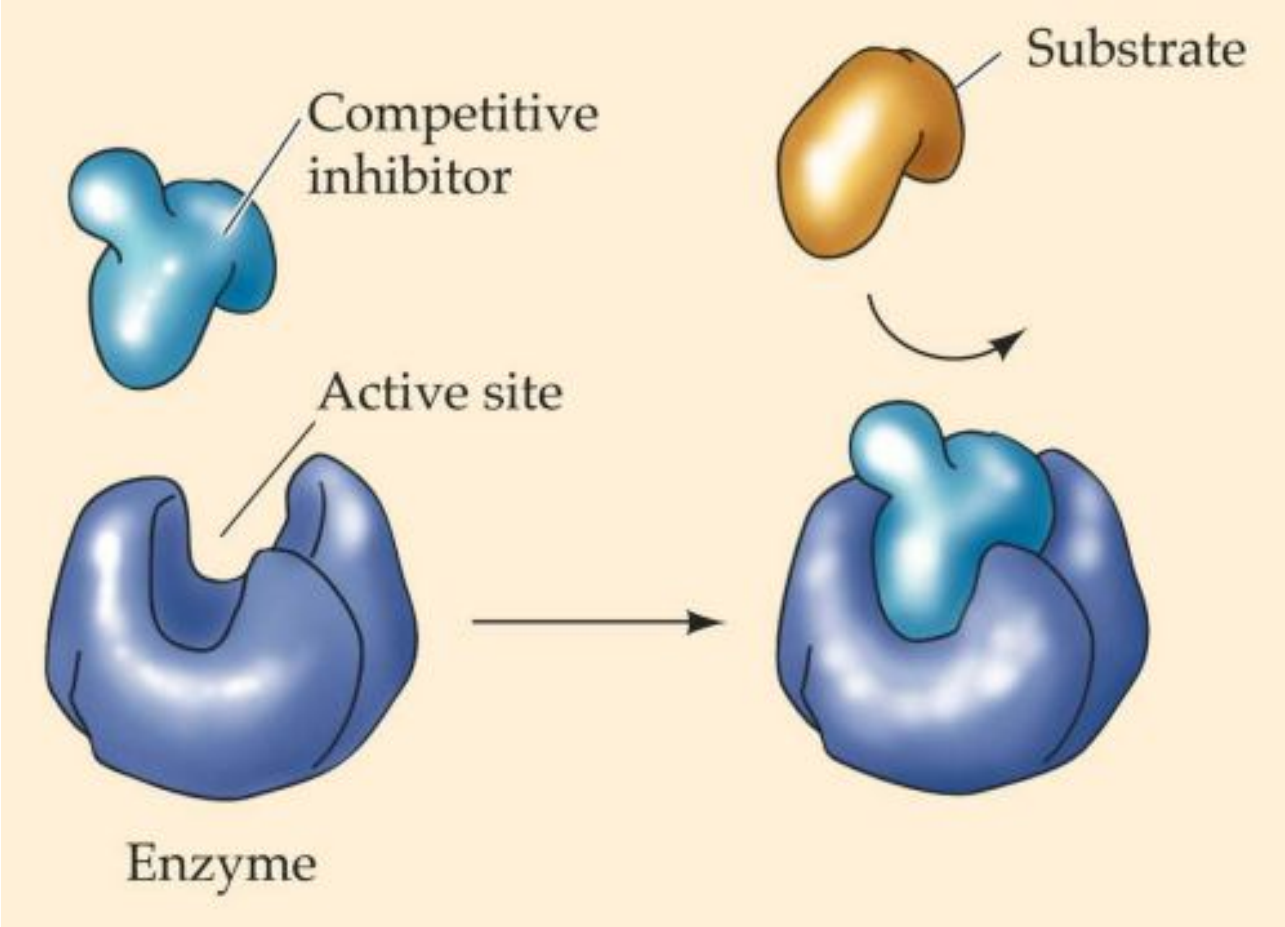


Figure from: H. Lodish et al., *Molecular Cell Biology*, 5th ed., 2004.

$$v = \frac{v_{max}[S]_0}{[S]_0 + K_M}$$

- v_{max} : Maximal reaction velocity.
- K_M: Affinity enzyme-substrate (subtrate conc. at half-maximal rate).

Inhibition compétitive (isostérique)



$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

$$EI + S \underset{k_3}{\overset{k_{-3}}{\rightleftharpoons}} E + S + I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES + I \xrightarrow{k_2} E + P + I$$

Steady state: $$\frac{d[E]}{dt} = \frac{d[ES]}{dt} = \frac{d[EI]}{dt} = 0$$

$$[E]_0 = [E] + [ES] + [EI] \quad \textbf{(1)}$$

$$\frac{d[E]}{dt} = 0 = -k_1[E][S] + k_{-1}[ES] + k_2[ES] - k_3[E][I] + k_{-3}[EI] \quad \textbf{(2)}$$

$$\frac{d[ES]}{dt} = 0 = k_1[E][S] - k_{-1}[ES] - k_2[ES] \quad \textbf{(3)}$$

$$\frac{d[EI]}{dt} = 0 = k_3[E][I] - k_{-3}[EI] \quad \textbf{(4)}$$

From equation (**3**), we can define *E* in terms of *ES* by rearranging to

$$[E] = \frac{(k_{-1} + k_2)[ES]}{k_1[S]} \quad \textbf{(5)}$$

Substituting equation (**5**) into equation (**4**), we have

$$[EI] = \frac{K_m k_3[I][ES]}{k_{-3}[S]}$$

At this point, we can define the dissociation constant for the inhibitor as $K_i = k_{-3}/k_3$, giving

$$[EI] = \frac{K_m[I][ES]}{K_i[S]} \tag{6}$$

substitute equation (**5**) and equation (**6**) into equation (**1**):

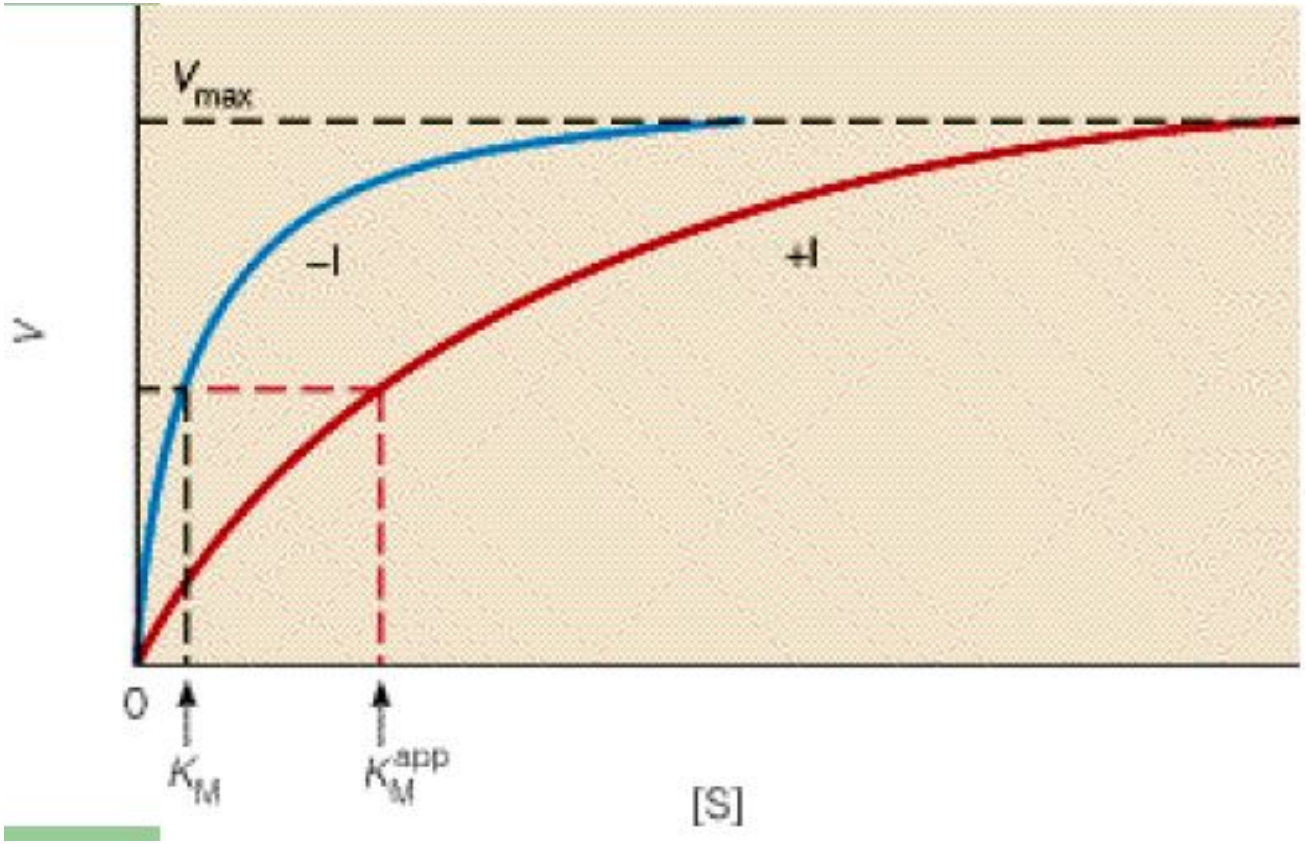
$$[E]_0 = [ES]\left(\frac{K_m}{[S]} + 1 + \frac{K_m[I]}{K_i[S]}\right) = [ES]\frac{K_mK_i + K_i[S] + K_m[I]}{K_i[S]}$$

$$[ES] = \frac{K_i[S][E]_0}{K_mK_i + K_i[S] + K_m[I]} \tag{7}$$

Returning to our expression for V_0, we now have:

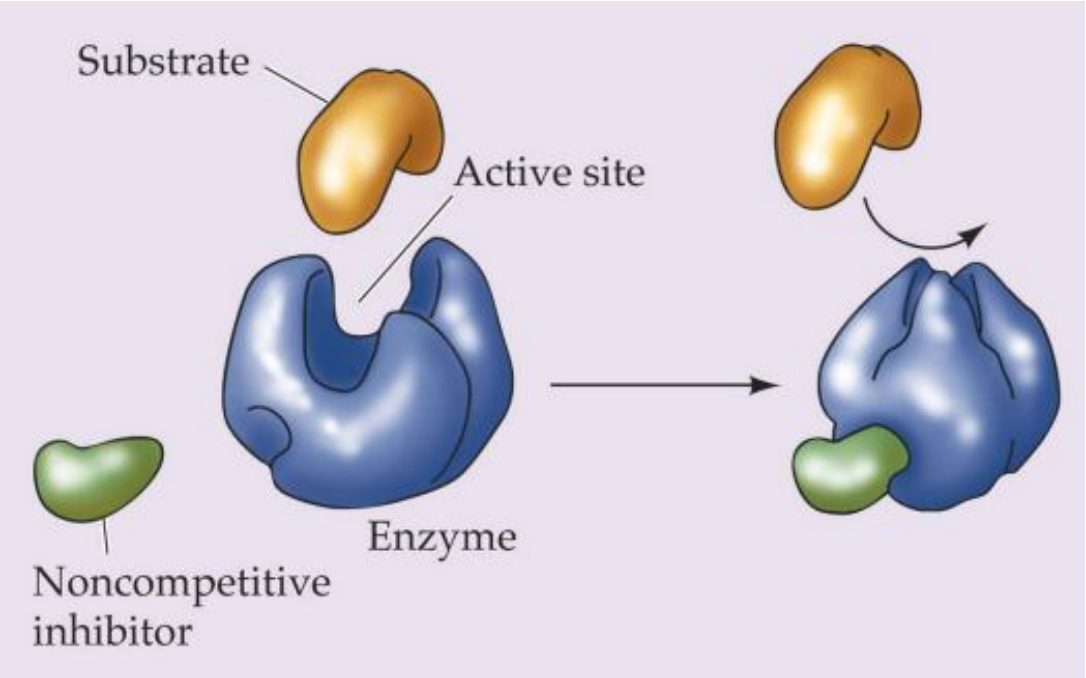
$$V_0 = k_2[ES] = \frac{k_2K_i[S][E]_0}{K_mK_i + K_i[S] + K_m[I]}$$

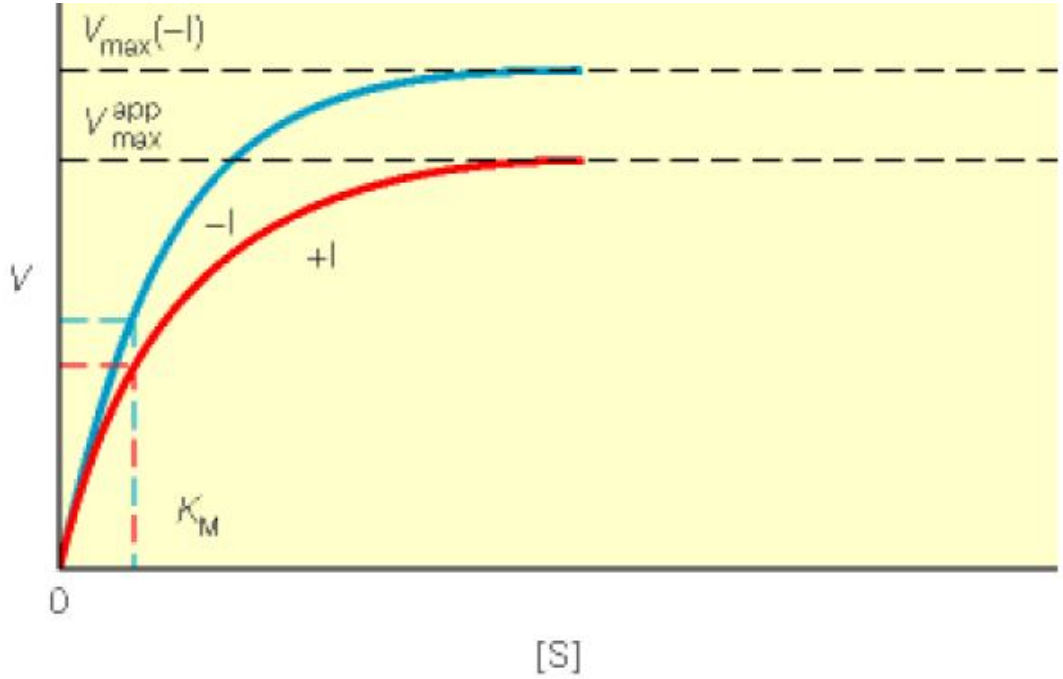
$$= \frac{k_2[E]_0[S]}{K_m + [S] + K_m\frac{[I]}{K_i}} \quad \Rightarrow \quad \boxed{V_0 = \frac{V_{\max}[S]}{K_m(1 + \frac{[I]}{K_i}) + [S]}}$$



Reduced apparent affinity enzyme-substrate

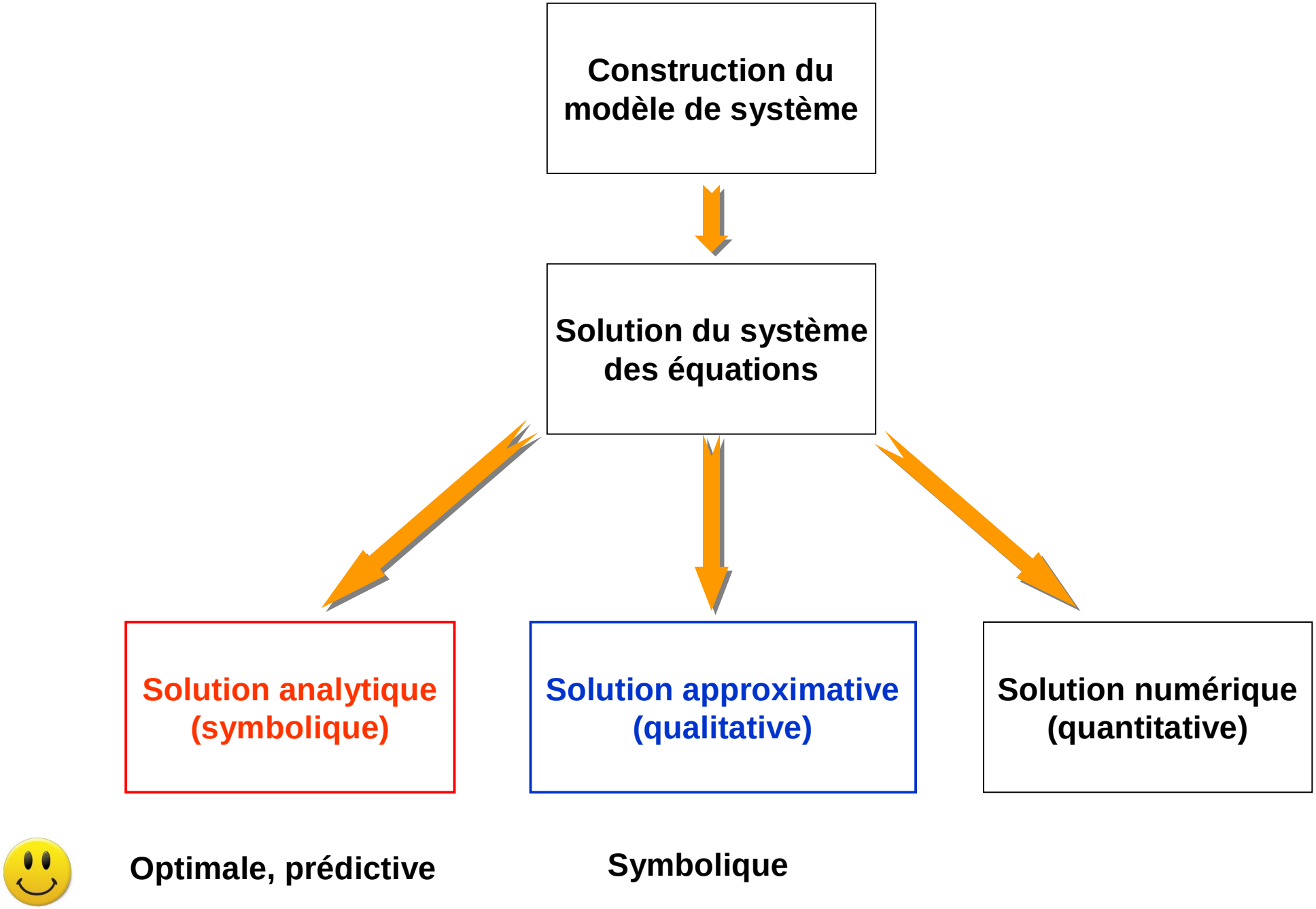
Inhibition non-compétitive (allostérique)





$$\frac{dP}{dt} = k_{+2}\frac{SE_0 \Big/ \left(1+\frac{I_0}{K_I}\right)}{K_M + S}$$

Reduced maximal reaction velocity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Optimale, prédictive
Symbolique
Rarement disponible
Validité limitée

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Optimale, prédictive

Symbolique

Rarement disponible

Validité limitée

Closed Form Solution for Time-dependent Enzyme Kinetics

S. SCHNELL*,† AND C. MENDOZA‡,§

J. theor. Biol. (1997) **187,** 207–212

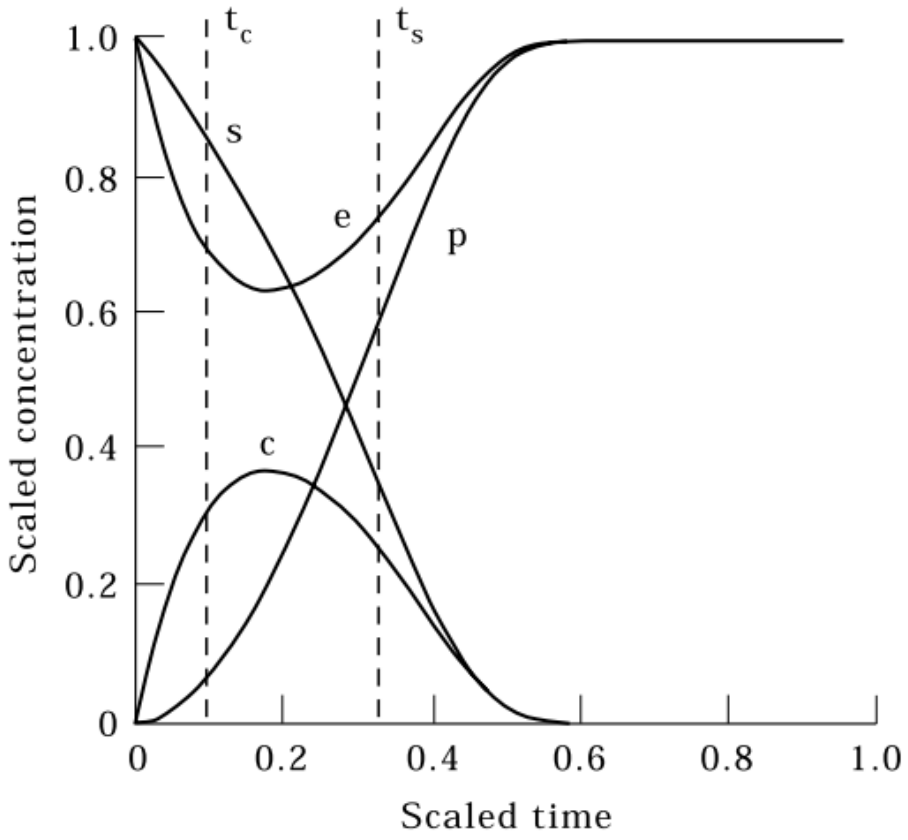


FIG. 1. Time-dependent behaviour of the reactant concentrations in an enzyme–substrate reaction. The infinite time range has been mapped onto the interval (0, 1) with the aid of the exponential time scale $\tau = 1 - 1/\ln(t + e)$, and the reactant concentrations have been non-dimensionally scaled as follows: free substrate $s = [S]/[S_0]$; free enzyme $e = [E]/[E_0]$; complex $c = [ES]/[E_0]$ and product $p = [P]/[S_0]$. The fast, t_C, and slow, t_S, time-scales are also shown.

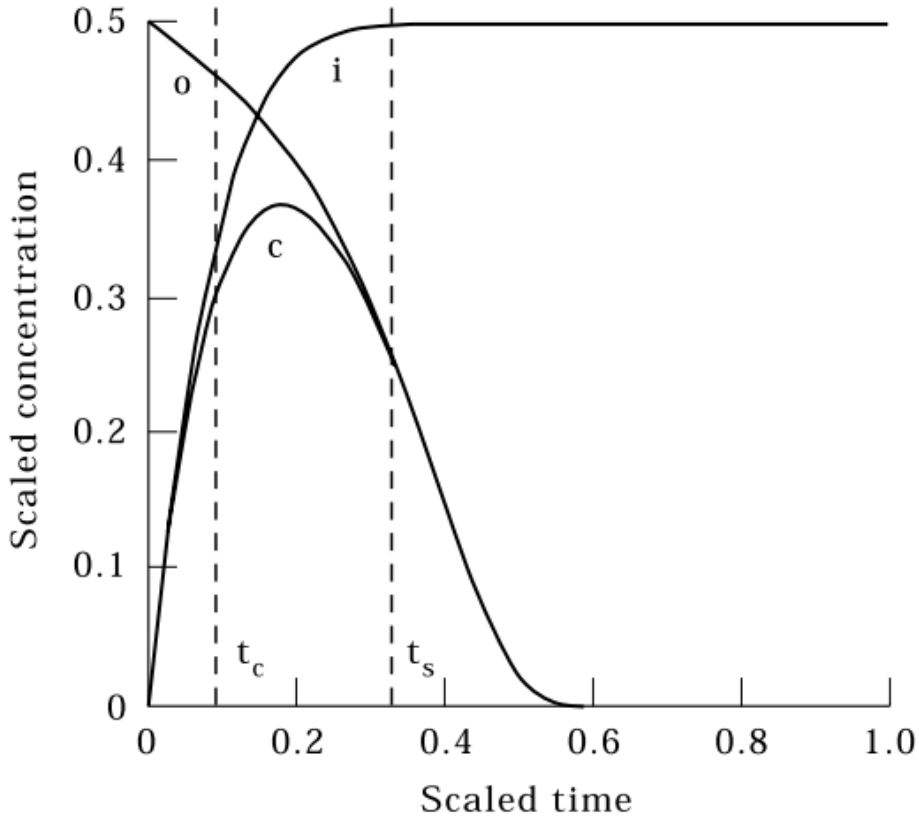
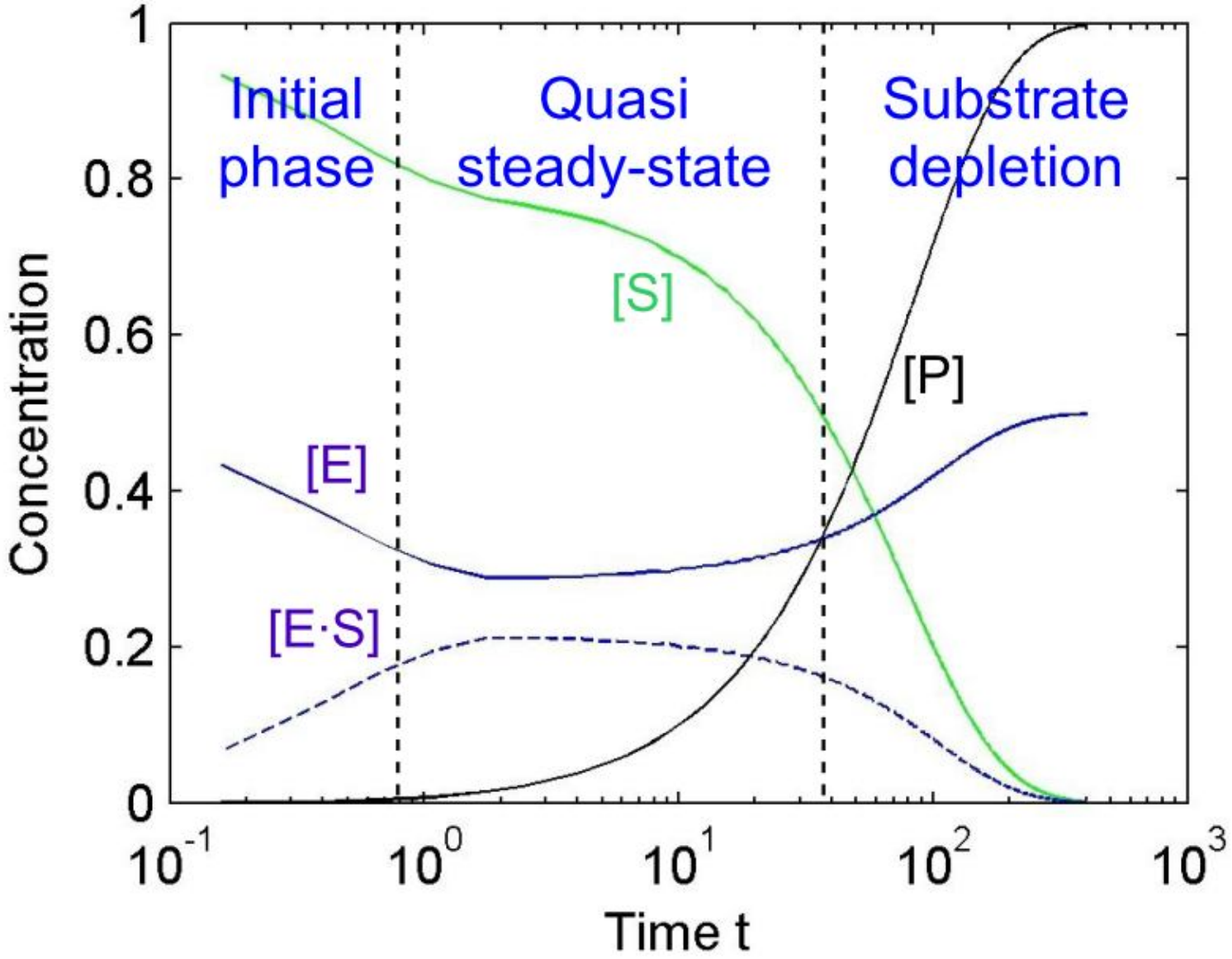


FIG. 3. Comparison of the present closed-form solution for the complex concentration (curve c) with those obtained by singular perturbation methods to order $[E_0]/[S_0]$. It may be appreciated that the agreement with the inner solution (curve i) during the fast transient ($t < t_C$) and with the outer solution (curve o) for $t > t_S$ is very good. However, data from the perturbation methods are noticeably different in the important transition interval $t_C < t < t_S$.

Enzyme Kinetics: Michaelis-Menten



Intégration numérique des équations différentielles

Equation différentielle typique :

$$\begin{cases} y' = f(x, y(x)) \\ y(x_0) = y_0 \end{cases}$$

Méthode d'Euler :

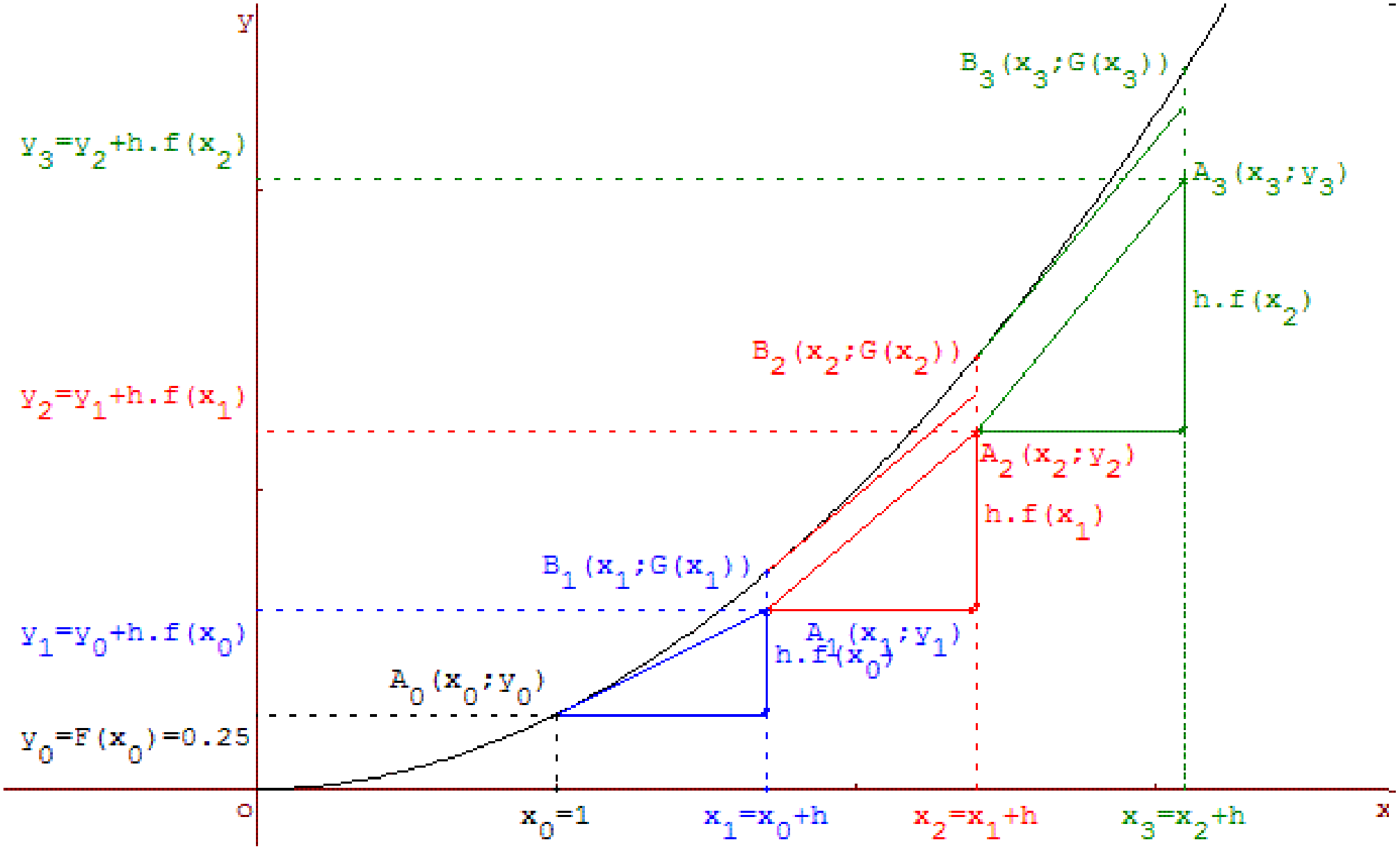
$$y' \approx \frac{y(x+\Delta x) - y(x)}{\Delta x} \quad \Rightarrow \quad y' \cdot \Delta x \approx y(x+\Delta x) - y(x)$$

$$y(x+\Delta x) = y(x) + y' \cdot \Delta x$$

$$y(x+\Delta x) = y(x) + f(x, y(x)) \cdot \Delta x$$

$$y(x_1) = y(x_0) + f(x_0, y(x_0)) \cdot \Delta x$$

$$y(x_{k+1}) = y(x_k) + f(x_k, y(x_k)) \cdot \Delta x$$


y
$y_3=y_2+h.f(x_2)$
$y_2=y_1+h.f(x_1)$
$y_1=y_0+h.f(x_0)$
$y_0=F(x_0)=0.25$
o
$x_0=1$
$x_1=x_0+h$
$x_2=x_1+h$
$x_3=x_2+h$
x
$B_3(x_3;G(x_3))$
$A_3(x_3;y_3)$
$h.f(x_2)$
$B_2(x_2;G(x_2))$
$A_2(x_2;y_2)$
$h.f(x_1)$
$B_1(x_1;G(x_1))$
$A_1(x_1;y_1)$
$h.f(x_0)$
$A_0(x_0;y_0)$

$$y' = y, y(0) = 1.$$

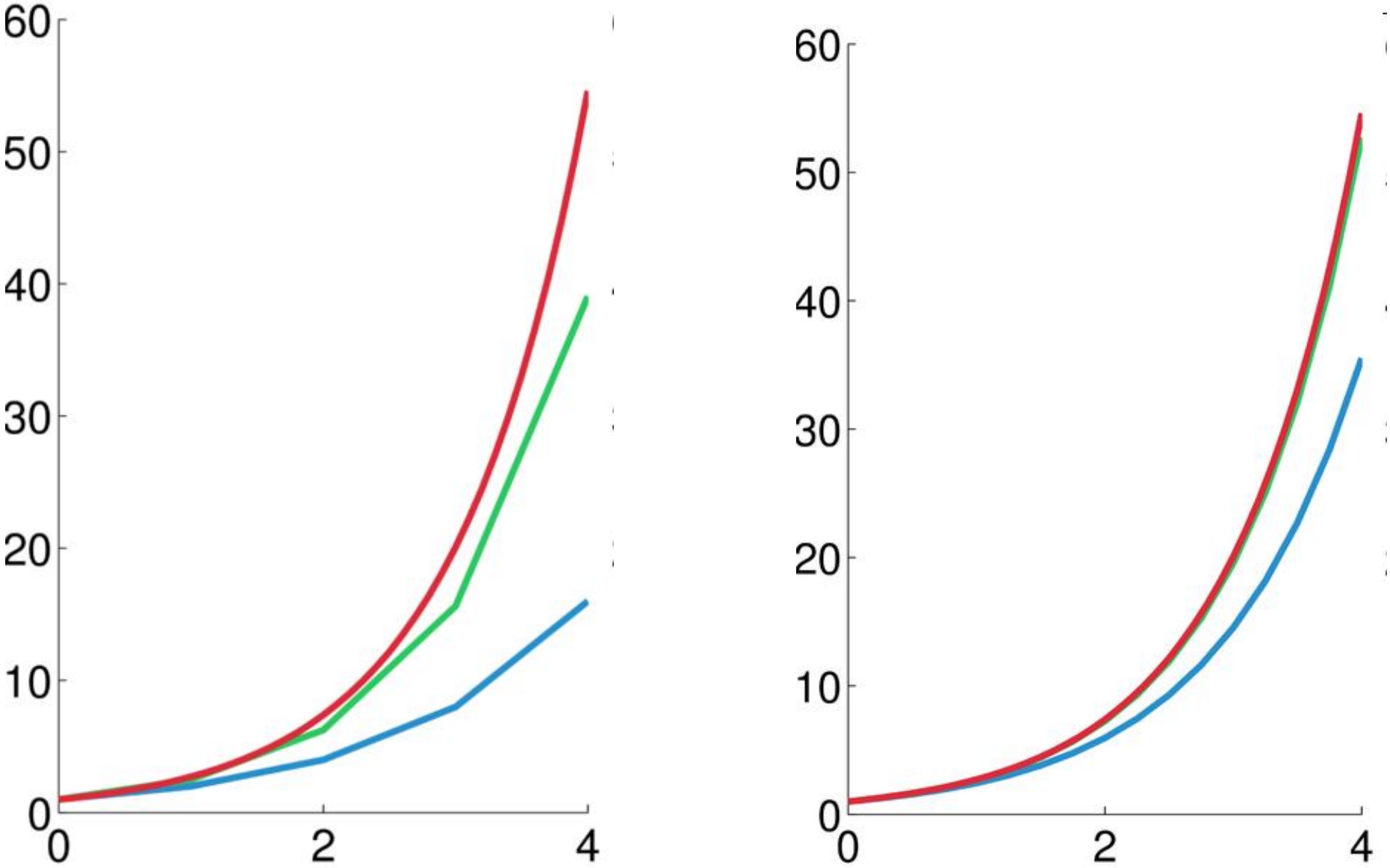
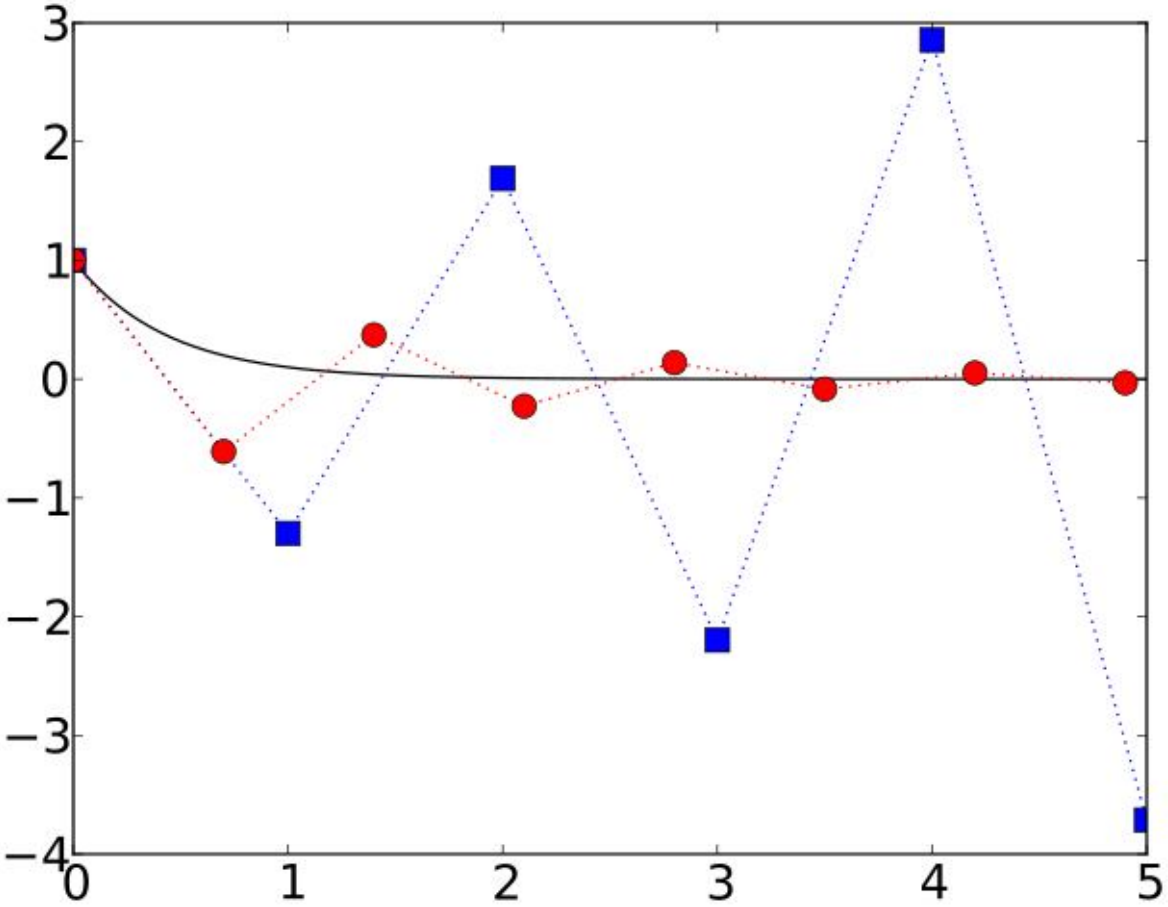


Illustration of several different methods of numerical integration:
Blue is the Euler method, **green**, the midpoint method, **red**, the exact solution.
The step size is *h* = 1.0 (left) and 0.25 (right).

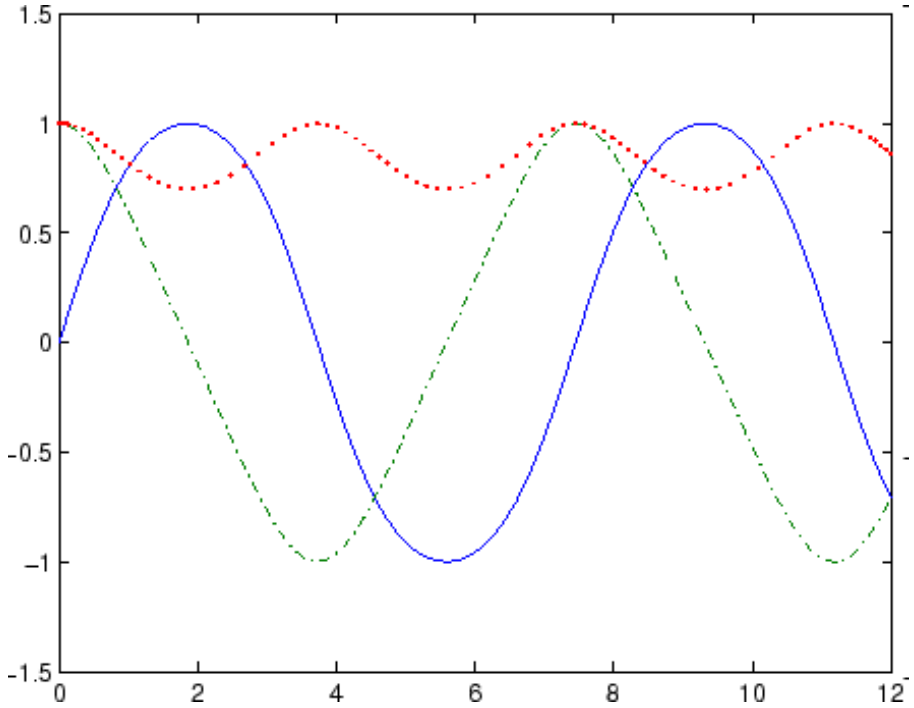
Précision, convergence, stabilité…

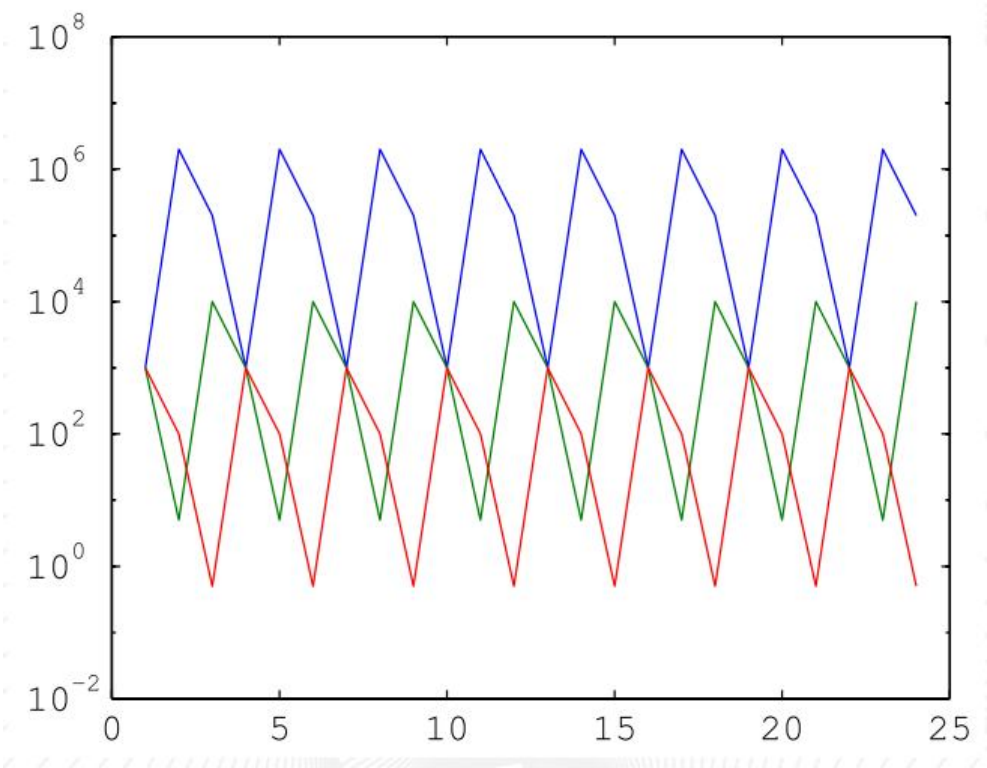
$$y' = -2.3y$$

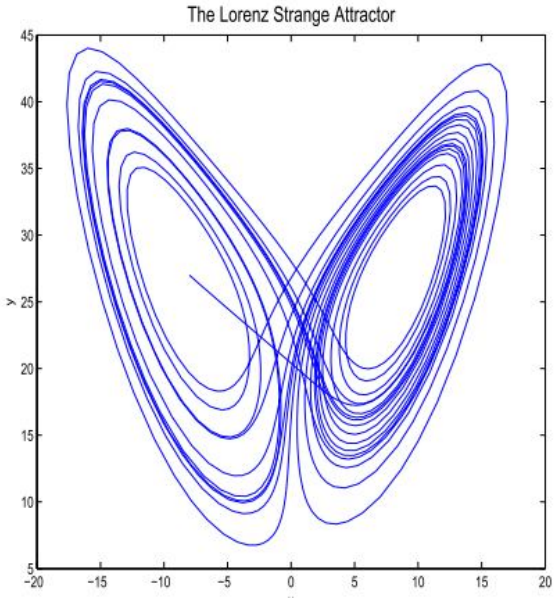


Solution computed with the Euler method with step size *h=1* (blue squares) and *h=0.7* (red circles). The black curve shows the exact solution.

Matlab et les solutions numériques







Construction du modèle de système

Solution du système des équations

Solution analytique (symbolique)	**Solution approximative (qualitative)**	**Solution numérique (quantitative)**
 **Optimale, prédictive**	**Symbolique**	**Toutes les équations**
 **Rarement disponible**	**Validité limitée**	**Performance, résultats partiels**