

L'équipe BioComputing

Cristian Versari
cristian.versari@univ-lille.fr

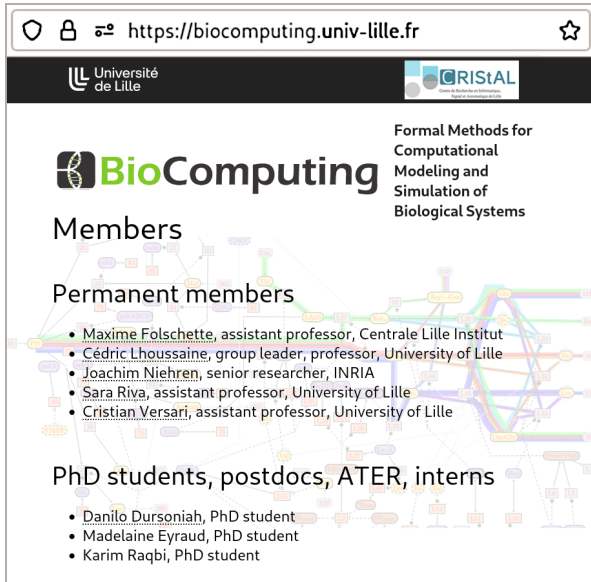
BioComputing - CRIStAL

JOLIBIO

—

9 Novembre 2023





The image is a screenshot of a web browser displaying the BioComputing website. The browser's address bar shows the URL <https://biocomputing.univ-lille.fr>. The website header features the logos of the University of Lille and CRIStAL (Centre de Recherche en Informatique et Simulation de Systèmes). The main content area has a large 'BioComputing' logo on the left and a descriptive text on the right: 'Formal Methods for Computational Modeling and Simulation of Biological Systems'. Below this, the 'Members' section is titled, followed by 'Permanent members' and a list of five individuals. At the bottom, the 'PhD students, postdocs, ATER, interns' section is titled, followed by a list of three individuals. The background of the page is a complex network diagram with various colored nodes and connecting lines.

Universit  de Lille

CRIStAL
Centre de Recherche en Informatique et Simulation de Syst mes

BioComputing

Formal Methods for
Computational
Modeling and
Simulation of
Biological Systems

Members

Permanent members

- Maxime Folschette, assistant professor, Centrale Lille Institut
- C dric Lhoussaine, group leader, professor, University of Lille
- Joachim Niehren, senior researcher, INRIA
- Sara Riva, assistant professor, University of Lille
- Cristian Versari, assistant professor, University of Lille

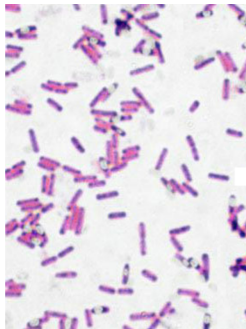
PhD students, postdocs, ATER, interns

- Danilo Dursoniah, PhD student
- Madelaine Eyraud, PhD student
- Karim Raqbi, PhD student

Systèmes biologiques

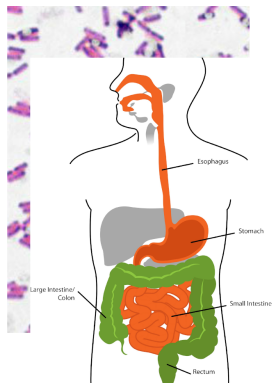
Systèmes biologiques

- micro-organismes



Systèmes biologiques

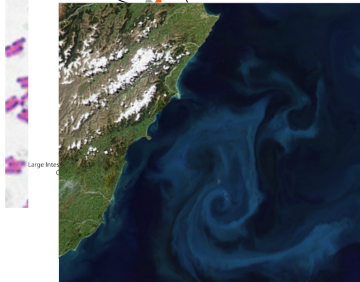
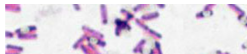
- micro-organismes
- systèmes multicellulaires



Comportement des systèmes biologiques

Systèmes biologiques

- micro-organismes
- systèmes multicellulaires
- écosystèmes



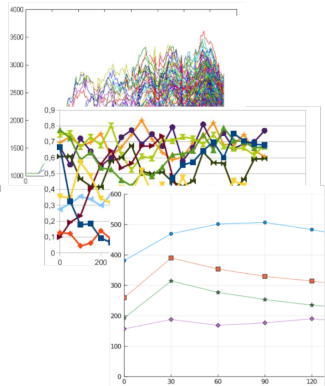
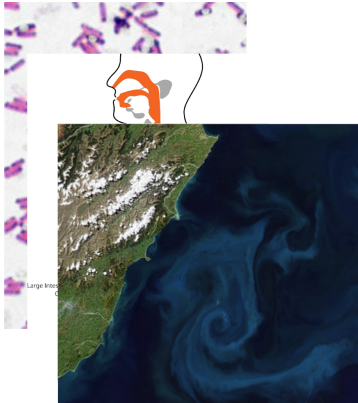
Comportement des systèmes biologiques

Systèmes biologiques

- micro-organismes
- systèmes multicellulaires
- écosystèmes

Comportement au cours du temps

- expression de gènes
- flux/concentration de métabolites
- dynamique des populations

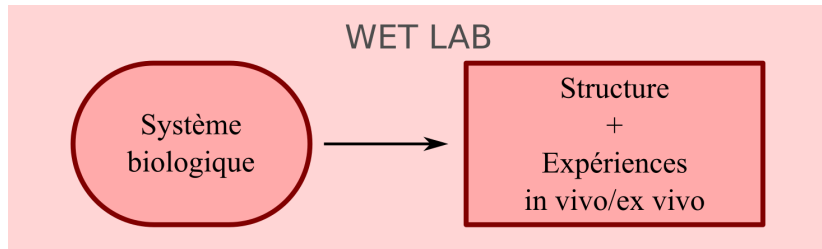


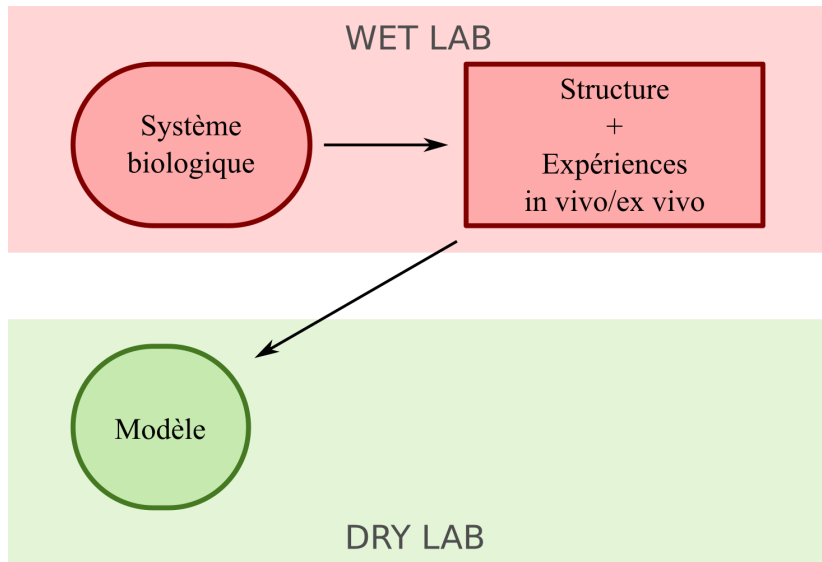
WET LAB

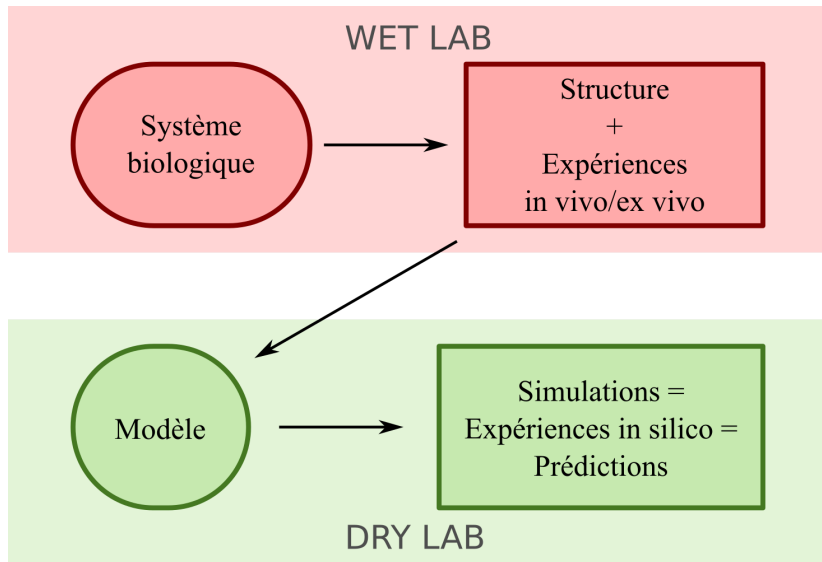
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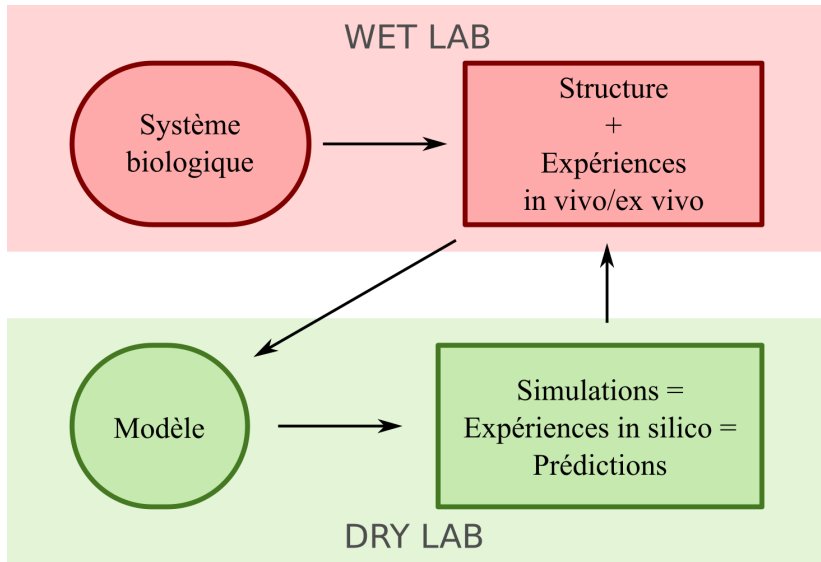


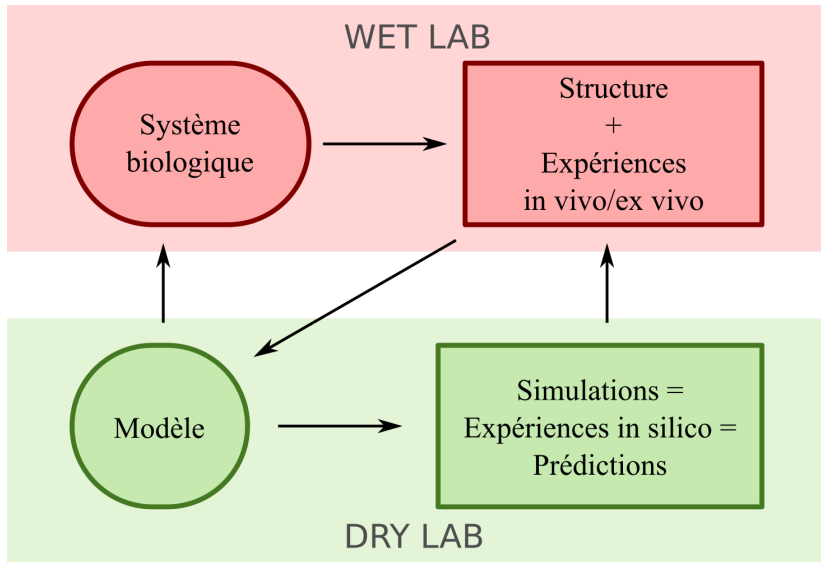
Système
biologique











Systèmes de réactions chimiques

Réaction chimique

réactifs → *produits*

Systèmes de réactions chimiques

Réaction chimique

réactifs → *produits*

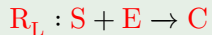
Exemple de
système de réactions :
réaction enzymatique

Systèmes de réactions chimiques

Réaction chimique

réactifs $\rightarrow$ *produits*

Exemple de
système de réactions :
réaction enzymatique

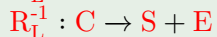
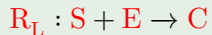


Systèmes de réactions chimiques

Réaction chimique

réactifs $\rightarrow$ *produits*

Exemple de
système de réactions :
réaction enzymatique

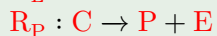
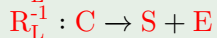
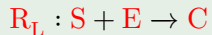


Systèmes de réactions chimiques

Réaction chimique

réactifs $\rightarrow$ *produits*

Exemple de
système de réactions :
réaction enzymatique

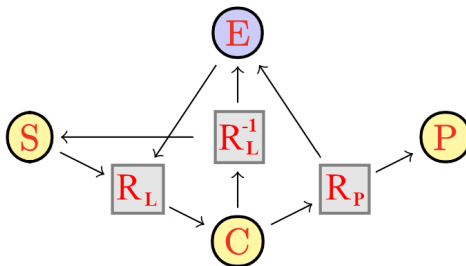
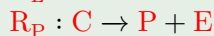
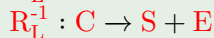
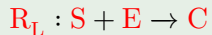


Systèmes de réactions chimiques

Réaction chimique

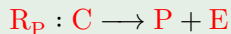
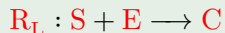
réactifs $\rightarrow$ *produits*

Exemple de
système de réactions :
réaction enzymatique



Connaissances requises

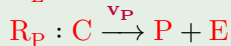
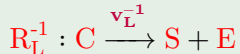
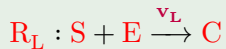
Réaction enzymatique



Connaissances requises

Vitesse des réactions

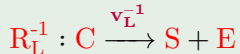
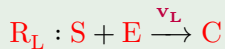
Réaction enzymatique



Connaissances requises

Vitesse des réactions $\Rightarrow$ fonctions cinétiques et leurs constantes numériques

Réaction enzymatique



$$v_L = 10000 \cdot S \cdot E$$

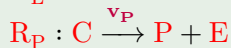
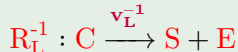
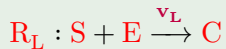
$$v_L^{-1} = 0.2 \cdot C$$

$$v_P = 0.1 \cdot C$$

Connaissances requises

Vitesse des réactions $\Rightarrow$ fonctions cinétiques et leurs constantes numériques

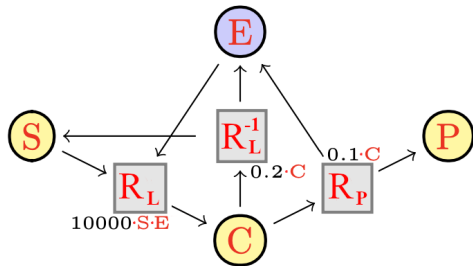
Réaction enzymatique



$$v_L = 10000 \cdot S \cdot E$$

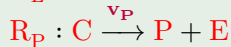
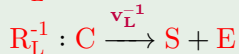
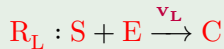
$$v_L^{-1} = 0.2 \cdot C$$

$$v_P = 0.1 \cdot C$$



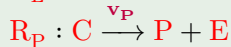
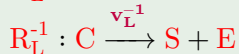
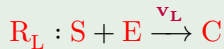
Équations différentielles ordinaires (EDOs)

Reaction enzymatique



Équations différentielles ordinaires (EDOs)

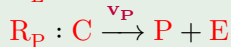
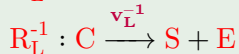
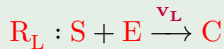
Reaction enzymatique



Changement au cours du temps

Équations différentielles ordinaires (EDOs)

Reaction enzymatique

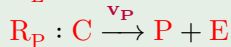
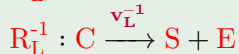
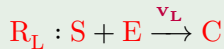


Changement au cours du temps

$$S(t = 0.1)$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique

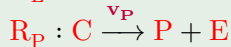
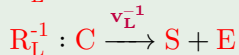
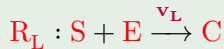


Changement au cours du temps

$$S(t = 0.1) \approx S(t = 0)$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique

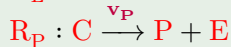
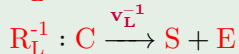
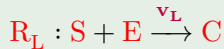


Changement au cours du temps

$$S(t = 0.1) \approx S(t = 0) - v_L$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique

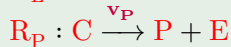
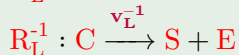
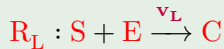


Changement au cours du temps

$$S(t = 0.1) \approx S(t = 0) - v_L \cdot 0.1$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique

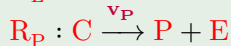
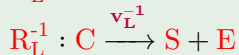
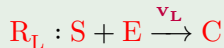


Changement au cours du temps

$$S(t = 0.1) \approx S(t = 0) - v_L \cdot 0.1 + v_L^{-1} \cdot 0.1$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique



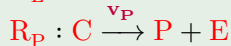
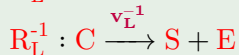
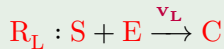
Changement au cours du temps

$$S(t = 0.1) \approx S(t = 0) - v_L \cdot 0.1 + v_L^{-1} \cdot 0.1$$

$$S(t = 0.1) - S(t = 0)$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique



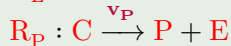
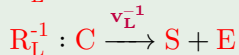
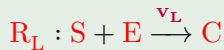
Changement au cours du temps

$$S(t = 0.1) \approx S(t = 0) - v_L \cdot 0.1 + v_L^{-1} \cdot 0.1$$

$$S(t = 0.1) - S(t = 0) \approx (-v_L + v_L^{-1}) \cdot 0.1$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique



Changement au cours du temps

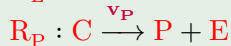
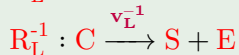
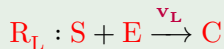
$$S(t = 0.1) \approx S(t = 0) - v_L \cdot 0.1 + v_L^{-1} \cdot 0.1$$

$$S(t = 0.1) - S(t = 0) \approx (-v_L + v_L^{-1}) \cdot 0.1$$

$$\Delta S(t)$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique



Changement au cours du temps

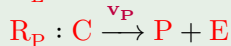
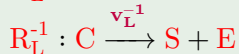
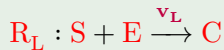
$$S(t = 0.1) \approx S(t = 0) - v_L \cdot 0.1 + v_L^{-1} \cdot 0.1$$

$$S(t = 0.1) - S(t = 0) \approx (-v_L + v_L^{-1}) \cdot 0.1$$

$$\Delta S(t) \approx (-v_L + v_L^{-1}) \cdot \Delta t$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique



Changement au cours du temps

$$S(t = 0.1) \approx S(t = 0) - v_L \cdot 0.1 + v_L^{-1} \cdot 0.1$$

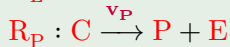
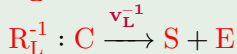
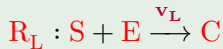
$$S(t = 0.1) - S(t = 0) \approx (-v_L + v_L^{-1}) \cdot 0.1$$

$$\Delta S(t) \approx (-v_L + v_L^{-1}) \cdot \Delta t$$

$$\frac{\Delta S(t)}{\Delta t} \approx -v_L + v_L^{-1}$$

Équations différentielles ordinaires (EDOs)

Reaction enzymatique



Changement au cours du temps

$$S(t = 0.1) \approx S(t = 0) - v_L \cdot 0.1 + v_L^{-1} \cdot 0.1$$

$$S(t = 0.1) - S(t = 0) \approx (-v_L + v_L^{-1}) \cdot 0.1$$

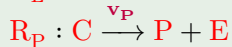
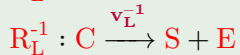
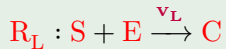
$$\Delta S(t) \approx (-v_L + v_L^{-1}) \cdot \Delta t$$

$$\frac{\Delta S(t)}{\Delta t} \approx -v_L + v_L^{-1}$$

$$\xrightarrow[\Delta t \rightarrow 0]{\lim}$$

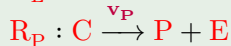
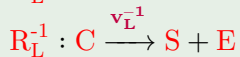
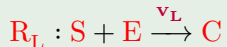
$$\frac{dS(t)}{dt} = -v_L + v_L^{-1}$$

R. enzymatique



Expérience *in silico* : simulation numérique via EDOs

R. enzymatique



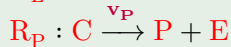
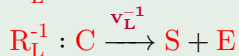
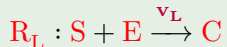
Équations différentielles ordinaires

$$\frac{dS(t)}{dt} = -v_L + v_L^{-1} \quad \frac{dE(t)}{dt} = -v_L + v_L^{-1} + v_P$$

$$\frac{dP(t)}{dt} = +v_P \quad \frac{dC(t)}{dt} = +v_L - v_L^{-1} - v_P$$

Expérience *in silico* : simulation numérique via EDOs

R. enzymatique



Équations différentielles ordinaires

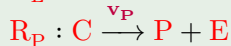
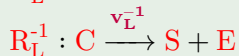
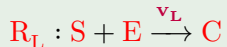
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$$\frac{dP(t)}{dt} = +v_P \quad \frac{dC(t)}{dt} = +v_L - v_L^{-1} - v_P$$

Simulation numérique

Expérience *in silico* : simulation numérique via EDOs

R. enzymatique



Équations différentielles ordinaires

$$\frac{dS(t)}{dt} = -v_L + v_L^{-1} \quad \frac{dE(t)}{dt} = -v_L + v_L^{-1} + v_P$$

$$\frac{dP(t)}{dt} = +v_P \quad \frac{dC(t)}{dt} = +v_L - v_L^{-1} - v_P$$

Simulation numérique

Vitesses :

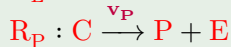
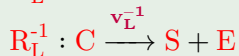
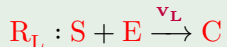
$$v_L = 10000 \cdot S \cdot E$$

$$v_L^{-1} = 0.2 \cdot C$$

$$v_P = 0.1 \cdot C$$

Expérience *in silico* : simulation numérique via EDOs

R. enzymatique



Équations différentielles ordinaires

$$\frac{dS(t)}{dt} = -v_L + v_L^{-1} \quad \frac{dE(t)}{dt} = -v_L + v_L^{-1} + v_P$$

$$\frac{dP(t)}{dt} = +v_P \quad \frac{dC(t)}{dt} = +v_L - v_L^{-1} - v_P$$

Simulation numérique

Vitesses :

$$v_L = 10000 \cdot S \cdot E$$

$$v_L^{-1} = 0.2 \cdot C$$

$$v_P = 0.1 \cdot C$$

État initial :

$$S(t=0) = 5$$

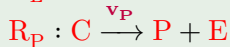
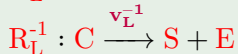
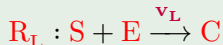
$$E(t=0) = 0.2$$

$$C(t=0) = 0$$

$$P(t=0) = 0$$

Expérience *in silico* : simulation numérique via EDOs

R. enzymatique



Équations différentielles ordinaires

$$\frac{dS(t)}{dt} = -v_L + v_L^{-1} \quad \frac{dE(t)}{dt} = -v_L + v_L^{-1} + v_P$$

$$\frac{dP(t)}{dt} = +v_P \quad \frac{dC(t)}{dt} = +v_L - v_L^{-1} - v_P$$

Simulation numérique

Vitesses :

$$v_L = 10000 \cdot S \cdot E$$

$$v_L^{-1} = 0.2 \cdot C$$

$$v_P = 0.1 \cdot C$$

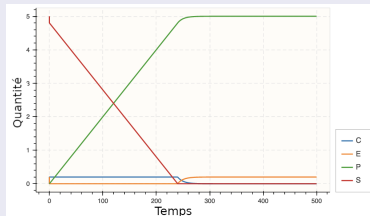
État initial :

$$S(t=0) = 5$$

$$E(t=0) = 0.2$$

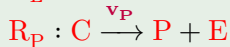
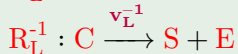
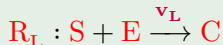
$$C(t=0) = 0$$

$$P(t=0) = 0$$



Expérience *in silico* : simulation numérique via EDOs

R. enzymatique



Équations différentielles ordinaires

$$\frac{dS(t)}{dt} = -v_L + v_L^{-1} \quad \frac{dE(t)}{dt} = -v_L + v_L^{-1} + v_P$$

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Simulation numérique

Vitesses :

$$v_L = 10000 \cdot S \cdot E$$

$$v_L^{-1} = 0.2 \cdot C$$

$$v_P = 0.1 \cdot C$$

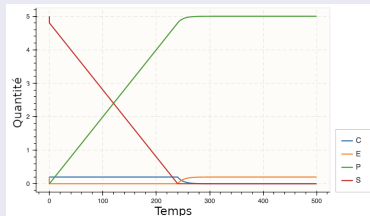
État initial :

$$S(t=0) = 5$$

$$E(t=0) = 0.2$$

$$C(t=0) = 0$$

$$P(t=0) = 0$$



Choix du “bon” jeu de paramètres $\Rightarrow$ *optimisation des paramètres*

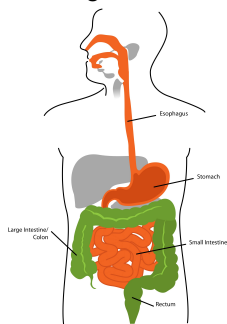
Diabète de type 2

- hyperglycémie chronique
- résistance à l'insuline

Diabète de type 2

- hyperglycémie chronique
- résistance à l'insuline

Anatomie gastro-intestinale

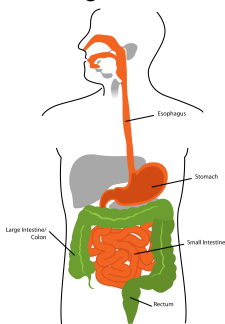


[<https://foodandhealth.com/digestive-diseases-awareness/>]

Diabète de type 2

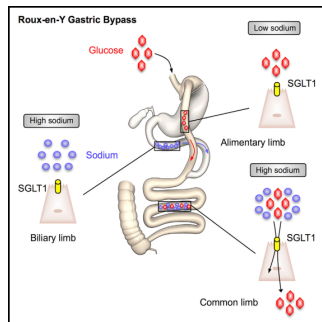
- hyperglycémie chronique
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Anatomie gastro-intestinale



[<https://foodandhealth.com/digestive-diseases-awareness/>]

Bypass gastrique roux-en-y

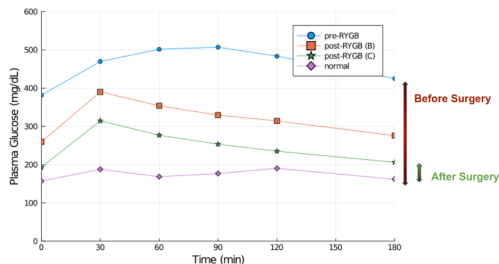


[Baud et al., Cell Metabolism, 2016]

Diabète de type 2

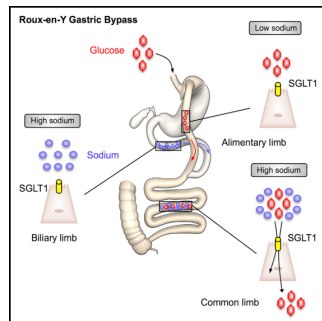
- hyperglycémie chronique
- résistance à l'insuline

Homeostasie du glucose restaurée



[Courtesy of Pattou et coll.]

Bypass gastrique roux-en-y

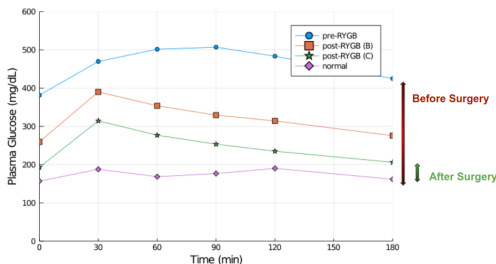


[Baud et al., Cell Metabolism, 2016]

Diabète de type 2

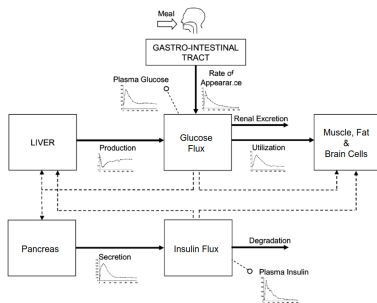
- hyperglycémie chronique
- résistance à l'insuline

Homeostasie du glucose restaurée



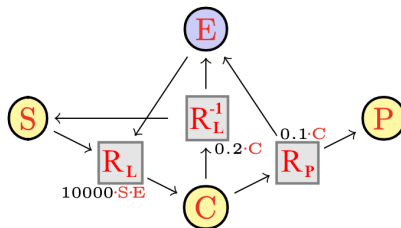
[Courtesy of Pattou et coll.]

Modèle à EDOs du flux de glucose



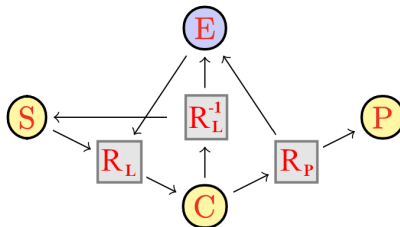
[Dalla Man et al., IEEE Trans. on Biom. Eng., 2007]

Information partielle



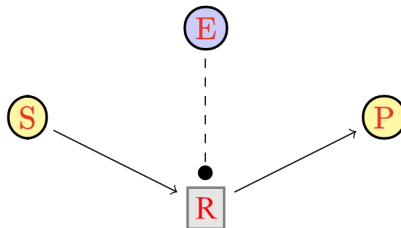
Information partielle

- manque de données quantitatives $\implies$ estimation des paramètres

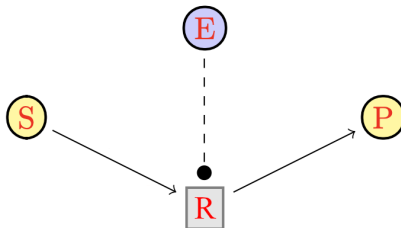


Information partielle

- manque de données quantitatives $\Rightarrow$ estimation des paramètres
- cinétiques/réactions partiellement connues
 $\Rightarrow$ informations structurelles et cinétiques *qualitatives*

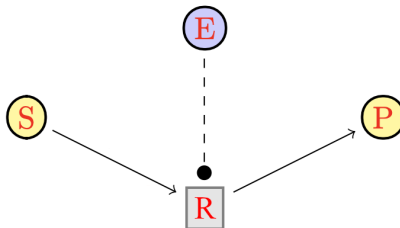


Modélisation *différentielle qualitative*



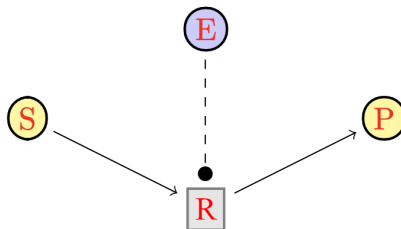
Modélisation *différentielle qualitative*

- description discrète / logique



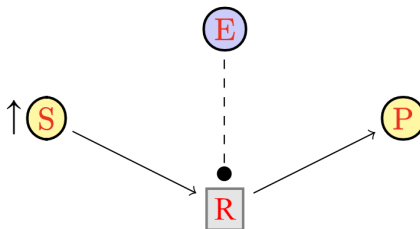
Modélisation *différentielle qualitative*

- description discrète / logique
- modélise *augmentations* $\uparrow\uparrow$ et *diminutions* $\downarrow\downarrow$



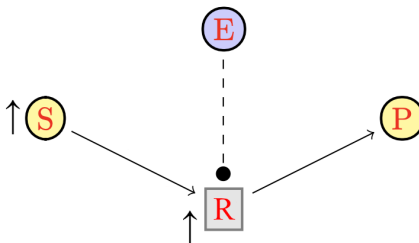
Modélisation *différentielle qualitative*

- description discrète / logique
- modélise *augmentations* $\uparrow\uparrow$ et *diminutions* $\downarrow\downarrow$



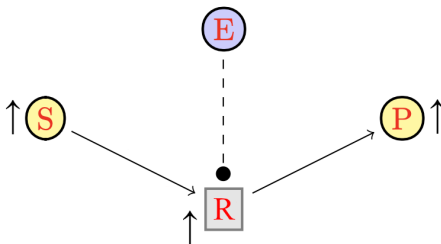
Modélisation *différentielle qualitative*

- description discrète / logique
- modélise *augmentations* $\uparrow\uparrow$ et *diminutions* $\downarrow\downarrow$



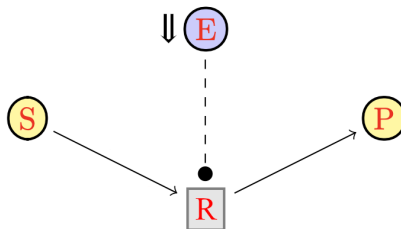
Modélisation *différentielle qualitative*

- description discrète / logique
- modélise *augmentations* $\uparrow\uparrow$ et *diminutions* $\downarrow\downarrow$



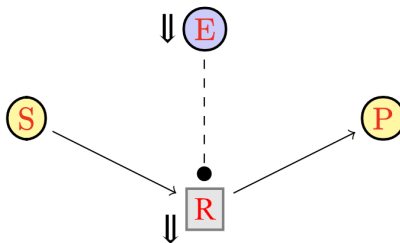
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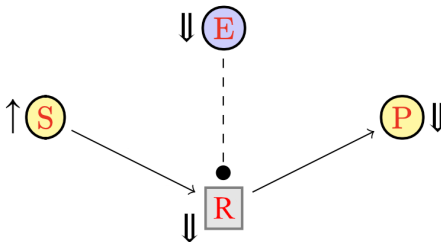
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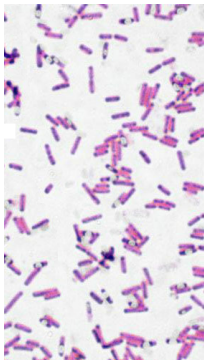


Modélisation *différentielle qualitative*

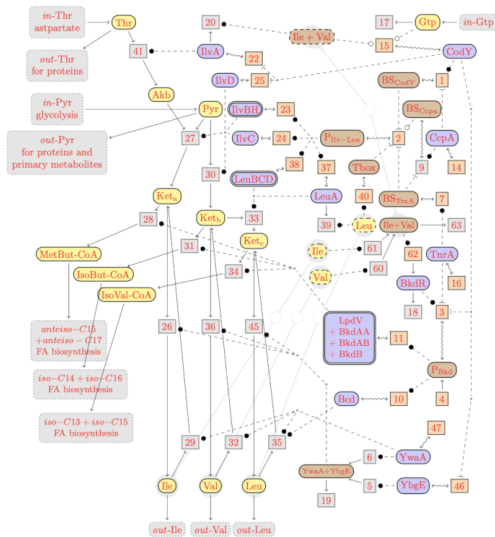
- description discrète / logique
- modélise *augmentations* $\uparrow\uparrow$ et *diminutions* $\downarrow\downarrow$



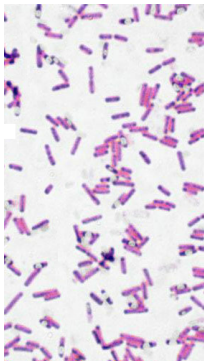
Application : *b. subtilis* | F. Coutte @ BioEcoAgro



B. subtilis [source: Wikipedia]



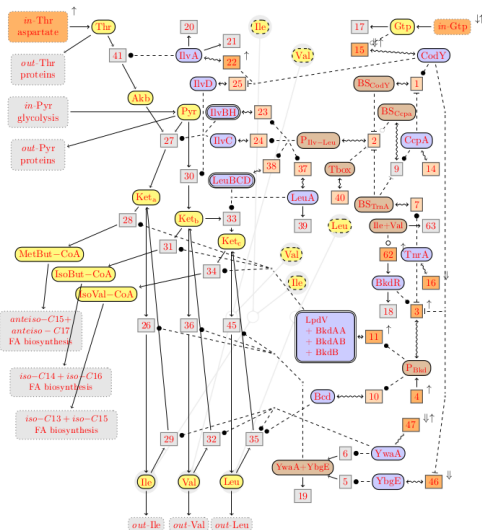
Modèle du métabolisme du *b. subtilis*



B. subtilis [source: Wikipedia]

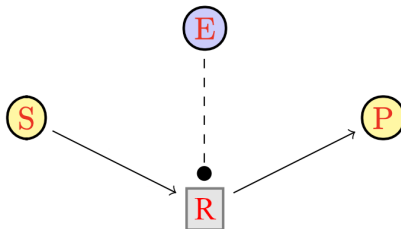
Surproduction de surfactine

- prédiction de knock-out de gènes
- optimisation du milieu



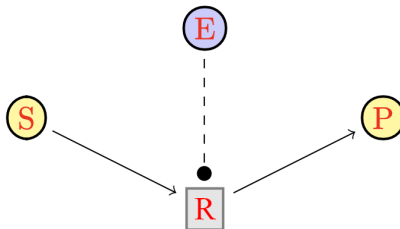
Prédiction de knock-out de gènes et changement de milieu

Modélisation *booléenne*



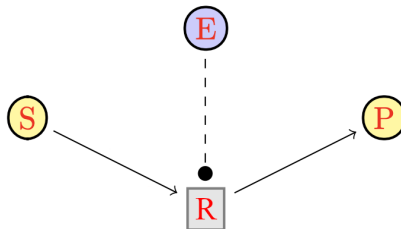
Modélisation *booléenne*

- description discrète / logique



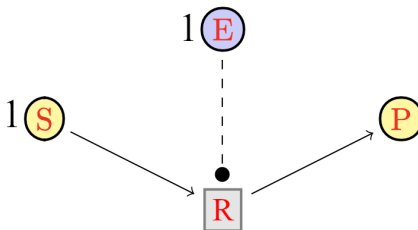
Modélisation *booléenne*

- description discrète / logique
- état booléen des espèces : 0 ou 1



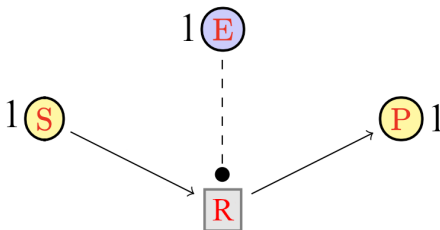
Modélisation *booléenne*

- description discrète / logique
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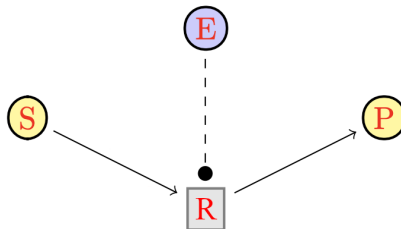
Modélisation *booléenne*

- description discrète / logique
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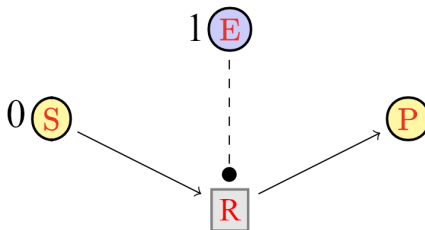
Modélisation *booléenne*

- description discrète / logique
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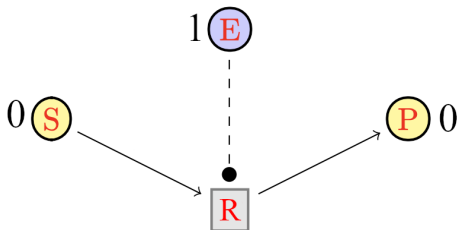
Modélisation *booléenne*

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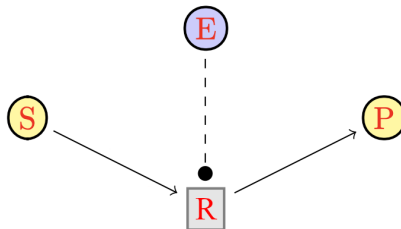
Modélisation *booléenne*

- description discrète / logique
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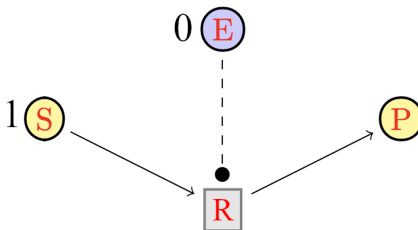
Modélisation *booléenne*

- description discrète / logique
- état booléen des espèces : 0 ou 1



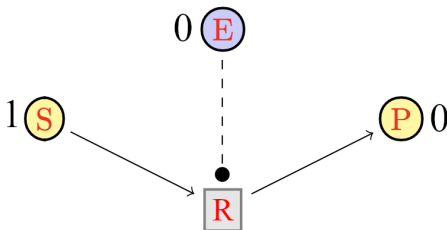
Modélisation *booléenne*

- description discrète / logique
- état booléen des espèces : 0 ou 1



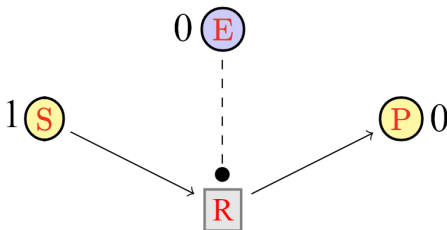
Modélisation *booléenne*

- description discrète / logique
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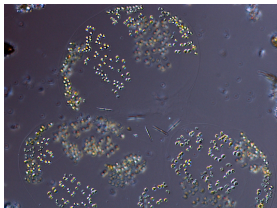


Modélisation *booléenne*

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- état booléen des espèces : 0 ou 1

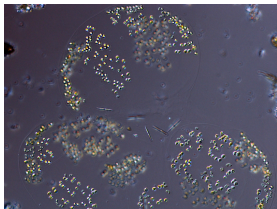


R = opérateur de multiplication arithmétique = opérateur “et” logique



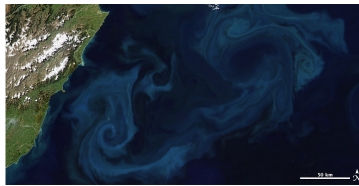
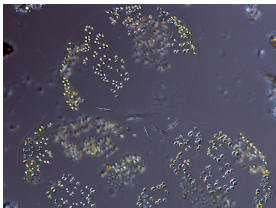
Dynamique du phytoplancton marin

- colonies de phytoplancton



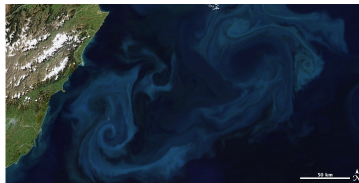
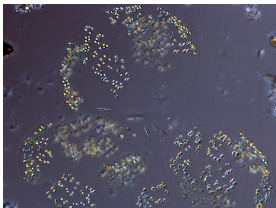
Dynamique du phytoplancton marin

- colonies de phytoplancton
- bloom phytoplanktonique



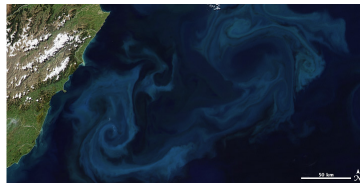
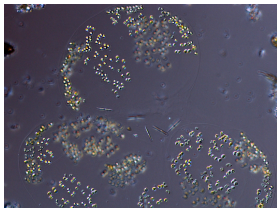
Dynamique du phytoplancton marin

- colonies de phytoplancton
- bloom phytoplanctonique



Dynamique du phytoplankton marin

- colonies de phytoplankton
- bloom phytoplanktonique
- interactions biotiques ?



Dynamique du phytoplancton marin

- colonies de phytoplancton
- bloom phytoplanktonique
- interactions biotiques ? $\Rightarrow$ inférence

