Dynamical modeling of reaction networks. Application to biased signaling

Romain Yvinec

Dynamical modeling of reaction networks

Application to biased signaling

Romain Yvinec

BIOS team, Physiologie de la Reproduction et des Comportements, INRAE Tours,
MUSCA team, INRIA Saclay,
France

Systems Biology and Networks

Reaction network formalism

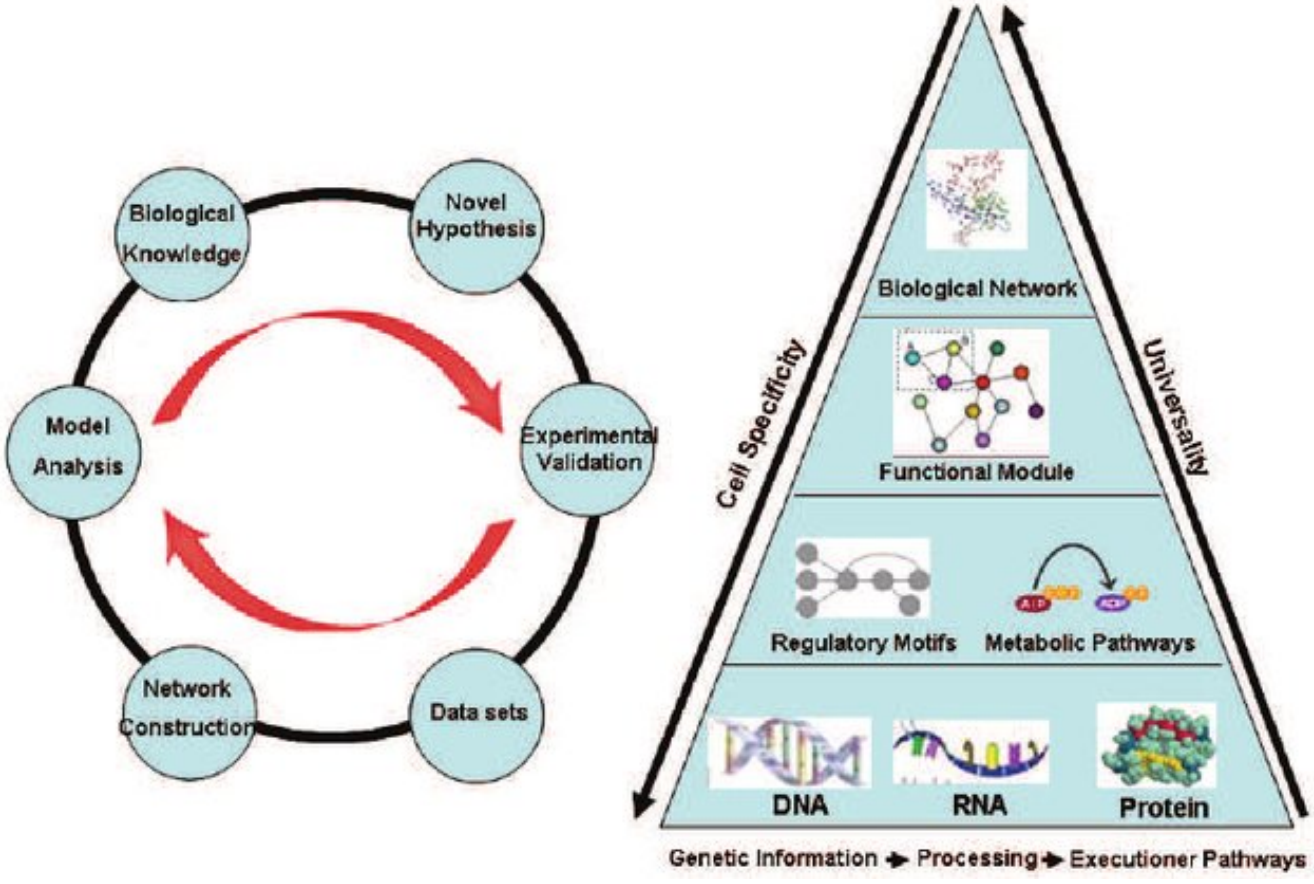
Viewing reaction network and Databases

Dynamics model with reaction network

Parameter estimation

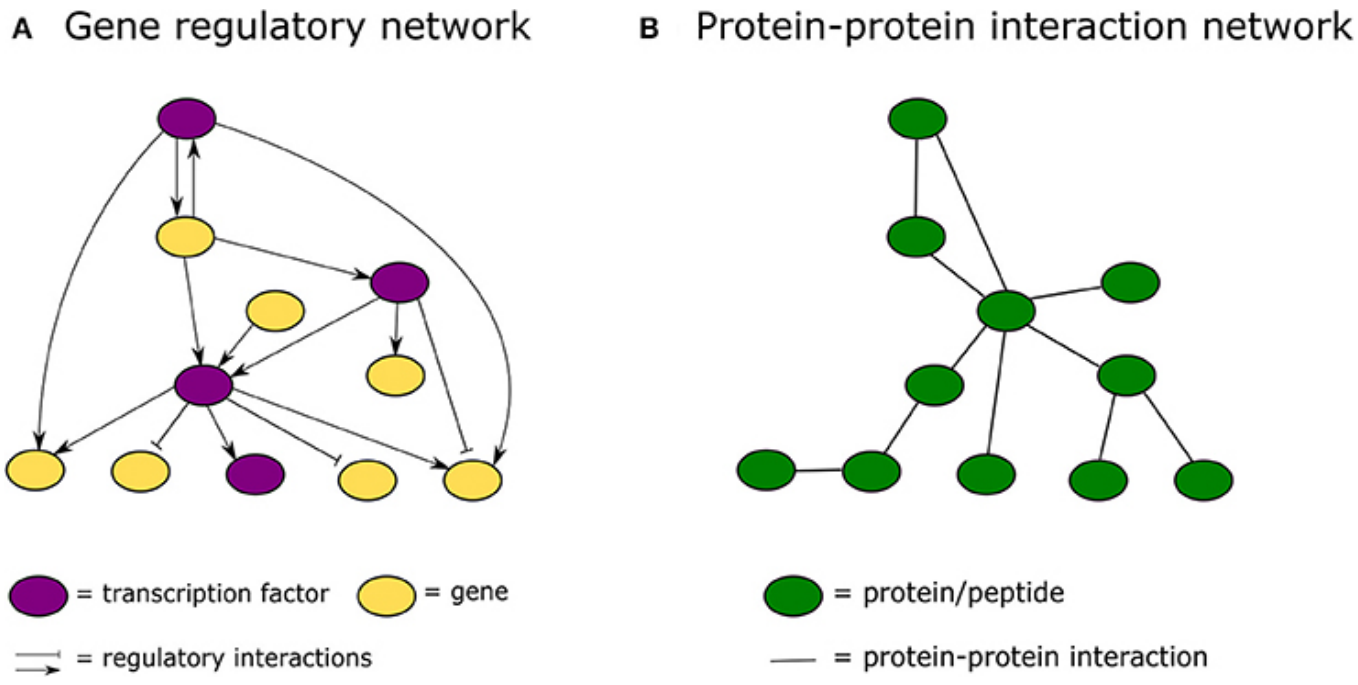
Applications

Outline



Oltvai and Barabasi, Science 25 :763-764, 2002.

What is a network ? Which network are we talking about ?

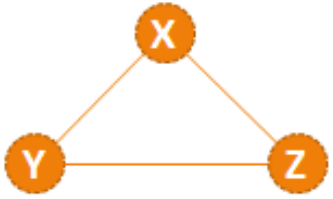


Vandereyken et al., Front. Plant Sci., 2018.

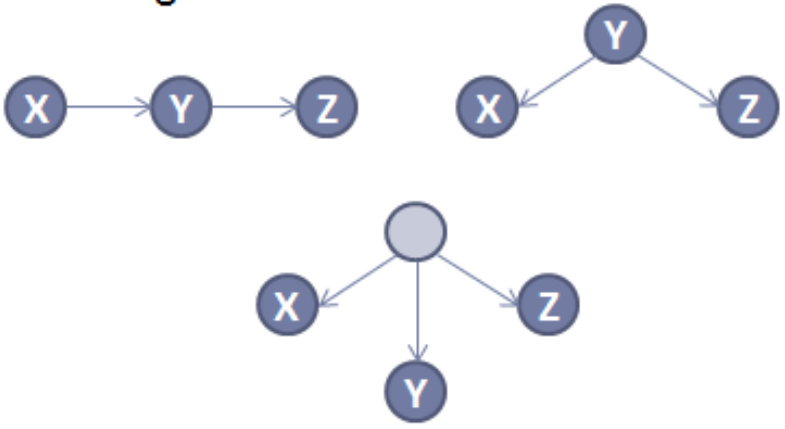
What is a network ? Which network are we talking about ?

Small motifs

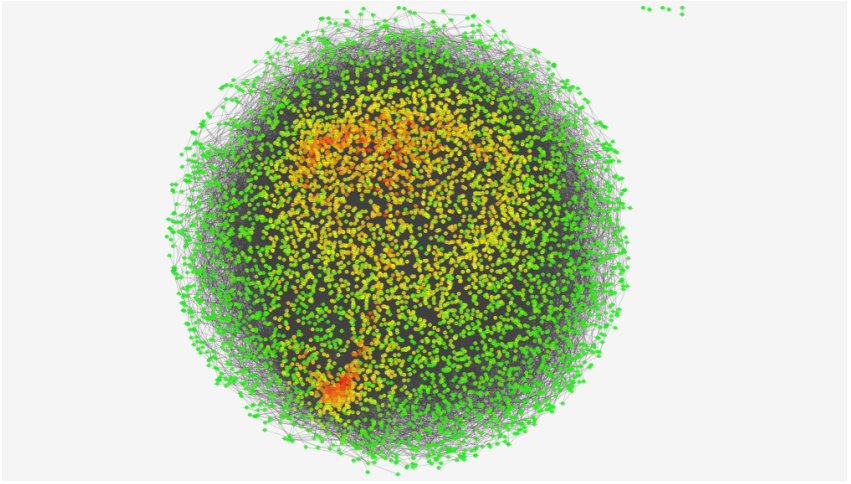
Gene Co-expression



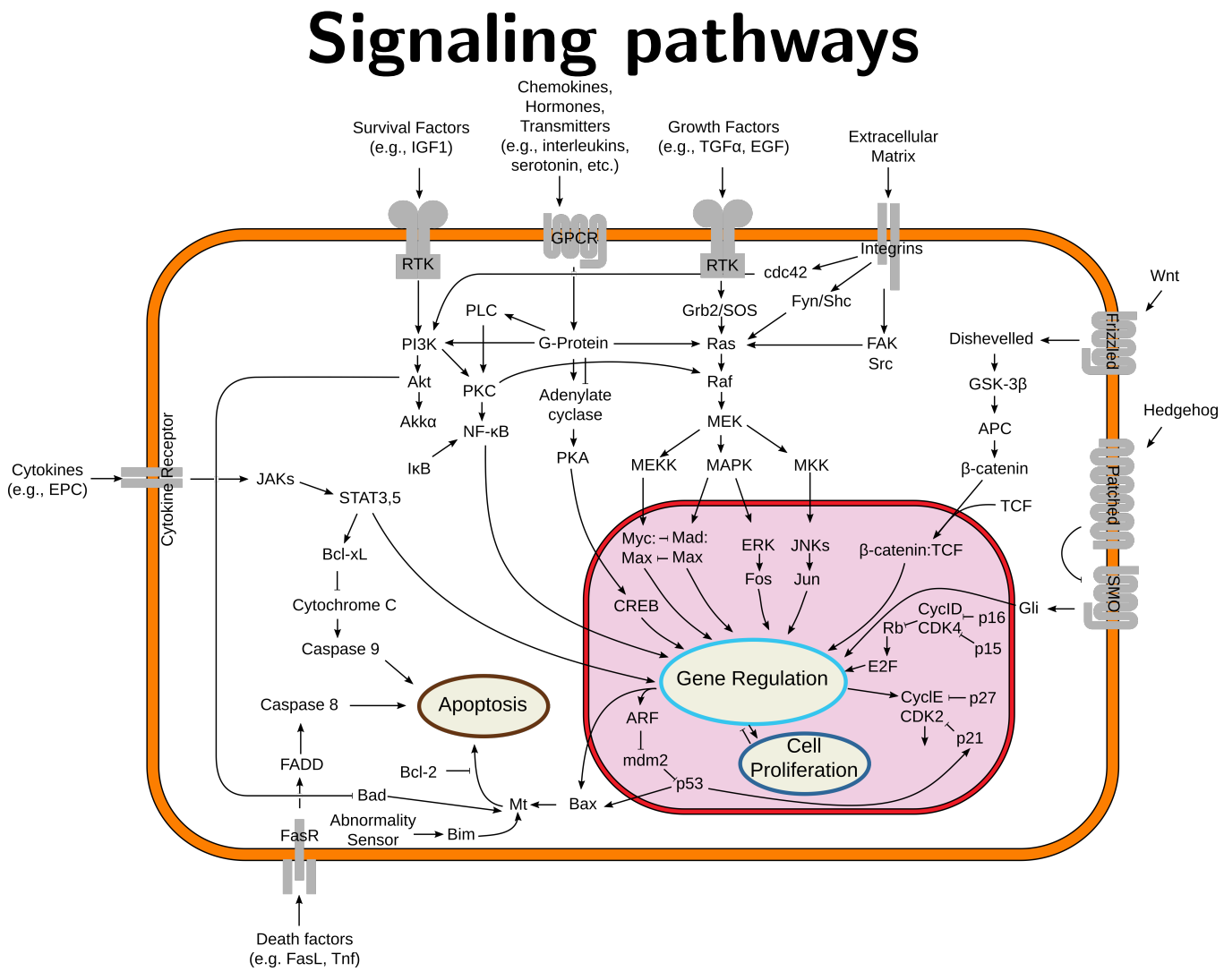
Gene Regulation



Large networks



What is a network ? Which network are we talking about ?



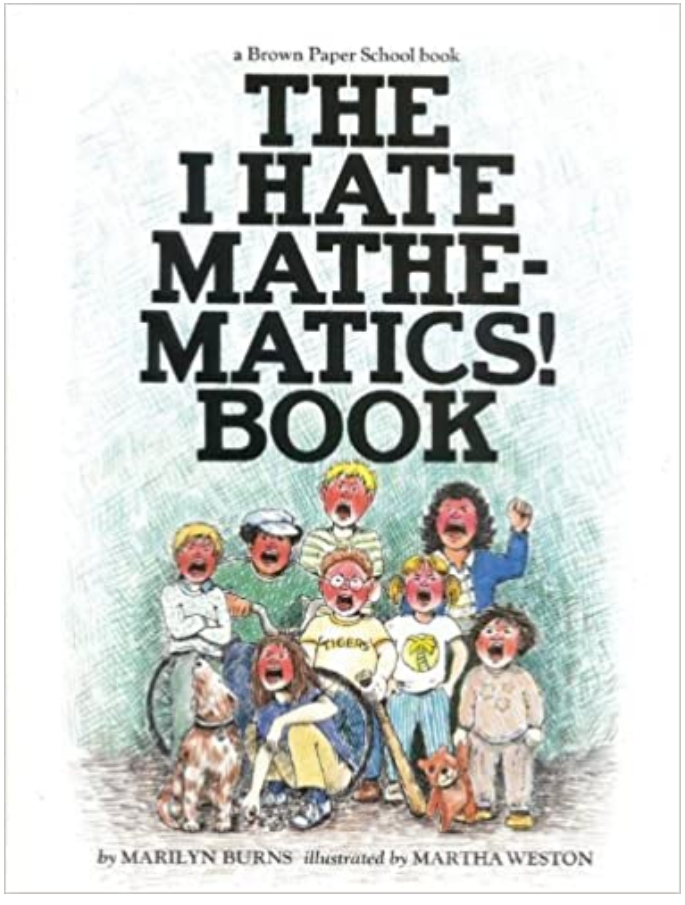
What is a network ? Which network are we talking about ?

Network, graph and reaction network

Today : We will deal with a specific kind of network, that have a higher degree of structure :

- Petri Nets, Species-Reaction graph, Reaction Network...
- It contains **entities** (proteins, genes, metabolites...) and **processes** that modifies the entities **abundances through time**

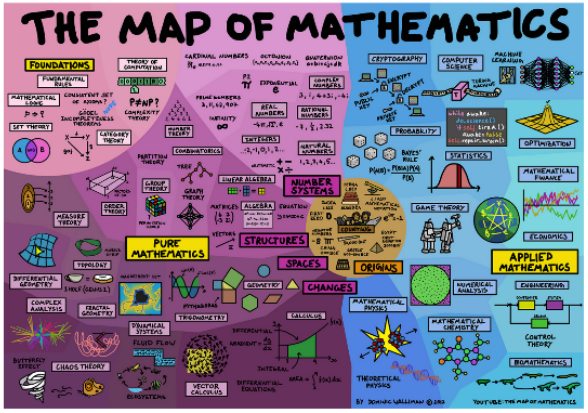
Warning !



#Ihatemathematics

The following couples of slides contain some abstract notions...
Why that ?

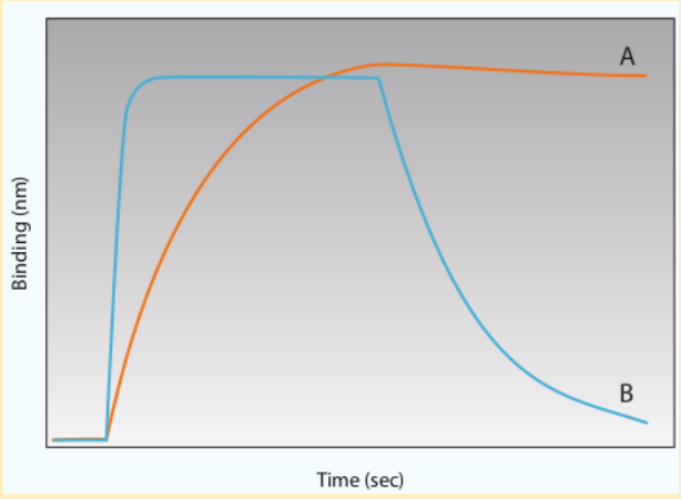
Maths is about structures...and is generic !



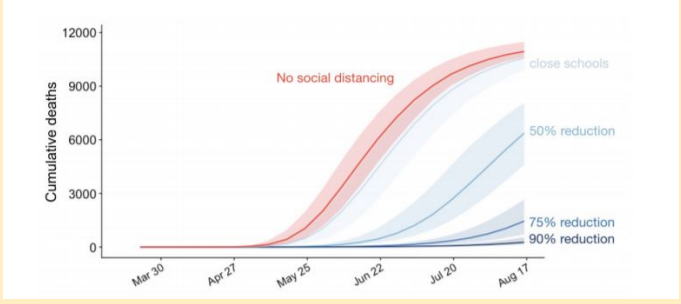
Reactions networks applications range from

- Chemistry
- molecular biology
- epidemiology
- and beyond !

Binding experiments



Covid-19 models



Outline

Reaction Network, vocabulary

Definition

A reaction network is given by three sets $(\mathcal{S}, \mathcal{C}, \mathcal{R})$:

- Species, $\mathcal{S} := \{S_1, \cdots, S_d\}$: molecules that undergo a serie of chemical reactions.
- Reactant / Product, $\mathcal{C} := \{y^1, \cdots y^n\}$: Linear combination of species, that represent either 'what is consumed', or 'what is produced', in any reaction.
- Reaction, $\mathcal{R} := \{y^k \to y^{k'}, y^k, y^{k'} \in \mathcal{C}\}$: ensemble of reactions between species or combination of species (directed graph between Reactant / Product).

Reaction Network, vocabulary

Definition

A reaction network is given by three sets $(\mathcal{S}, \mathcal{C}, \mathcal{R})$:

- Species, $\mathcal{S} := \{S_1, \cdots, S_d\}$: molecules that undergo a serie of chemical reactions.
- Reactant / Product, $\mathcal{C} := \{y^1, \cdots y^n\}$: Linear combination of species, that represent either 'what is consumed', or 'what is produced', in any reaction.
- Reaction, $\mathcal{R} := \{y^k \to y^{k'}, y^k, y^{k'} \in \mathcal{C}\}$: ensemble of reactions between species or combination of species (directed graph between Reactant / Product).
- Mass-action law, κ : a list of positive parameter (kinetic rate) for each reaction in $\mathcal{R}$

Chemical Reaction Network, vocabulary

Example

$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} B$$

Species $\mathcal{E} := \{A, B\}$

R / P $\mathcal{C} := \{A, B\}$

Reaction $\mathcal{R} := \{A \to B, B \to A\}$

Rate $\{k^+, k^-\}$

Reaction Network, vocabulary

Example (small cAMP production model)

$$
\begin{aligned}
L + R &\underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} LR \\
ATP + LR &\xrightarrow{k^+} cAMP + LR \\
cAMP &\xrightarrow{k^-} AMP
\end{aligned}
$$

Species $\mathcal{E} := \{L, R, LR, ATP, cAMP, AMP\}$

R / P $\mathcal{C} := \{L + R, LR, ATP + LR, cAMP + LR, cAMP, AMP\}$

Reaction $\mathcal{R} := \{L + R \to LR, LR \to L + R, ATP + LR \to cAMP + LR, cAMP \to AMP\}$

Rate $\{k_{on}, k_{off}, k^+, k^-\}$

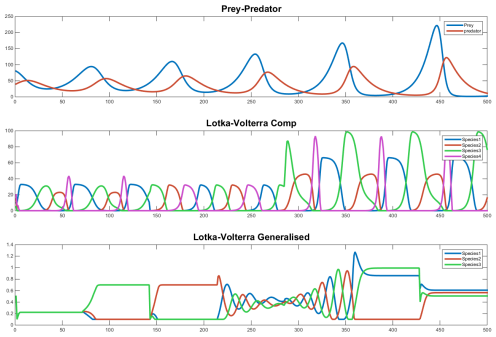
Examples of Reaction Networks at different scales

Small networks in Population dynamics

(Interactions between populations, Epidemiology)

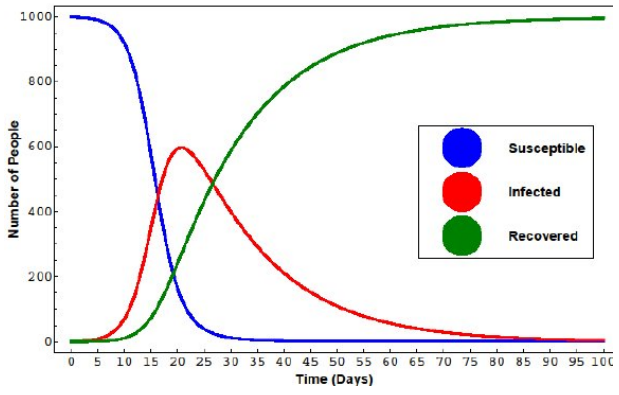
Lotka-Volterra model

$$\begin{aligned} \varnothing &\xrightarrow{k_1} A \\ A + B &\xrightarrow{k_2} 2B \\ B &\xrightarrow{k_3} \varnothing \end{aligned}$$



S.I.R model

$$\begin{aligned} S + I &\xrightarrow{k_1} I + I \\ I &\xrightarrow{k_2} R \end{aligned}$$



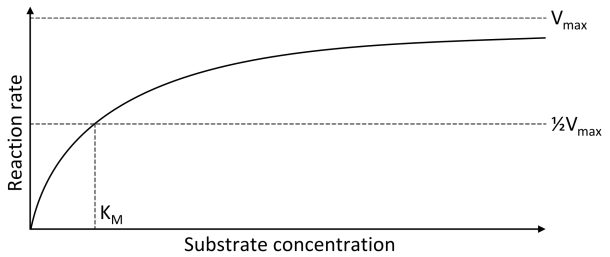
Examples of Reaction Networks at different scales

Small networks in molecular biology

('Toy' molecular models with isolated components)

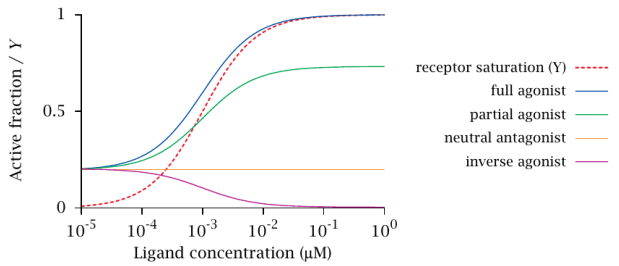
Enzymatic kinetics

$$E + S \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} ES \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} E + P$$



Pharmacology model

$$\begin{aligned} R_i &\rightleftarrows R_a \\ A + R_i &\rightleftarrows AR_i \\ A + R_a &\rightleftarrows AR_a \\ AR_a &\rightleftarrows AR_i \end{aligned}$$

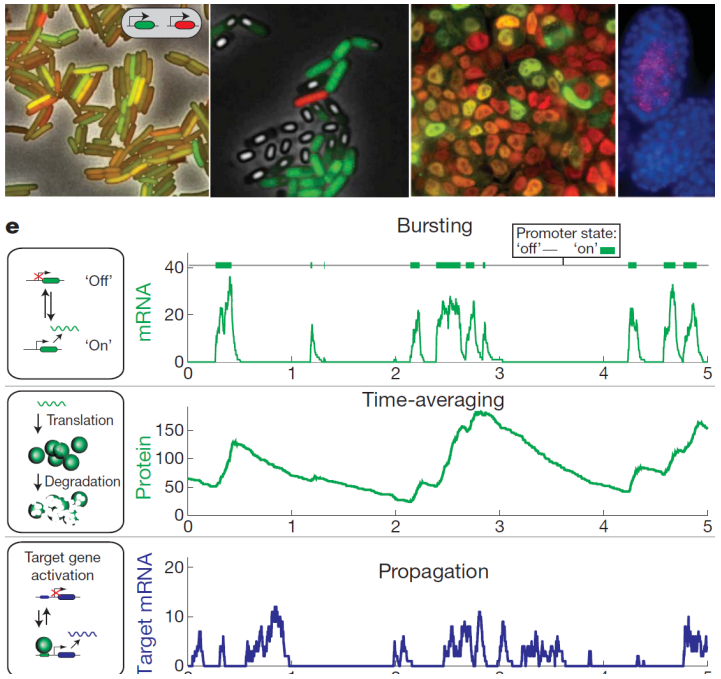


Examples of Reaction Networks at different scales

(Single) Gene Expression

$$
\begin{aligned}
G &\xrightarrow{\lambda_1} G + M \\
M &\xrightarrow{\lambda_2} M + P \\
M &\xrightarrow{\gamma_1} \varnothing \\
P &\xrightarrow{\gamma_2} \varnothing \\
G &\underset{k_{on}}{\overset{k_{off}}{\rightleftharpoons}} G_{off}
\end{aligned}
$$

Eldar and Elowitz (Nature 2010)



Outline

- List of species and reactions are not very fancy...
- We may of course use software for visualizing reaction network

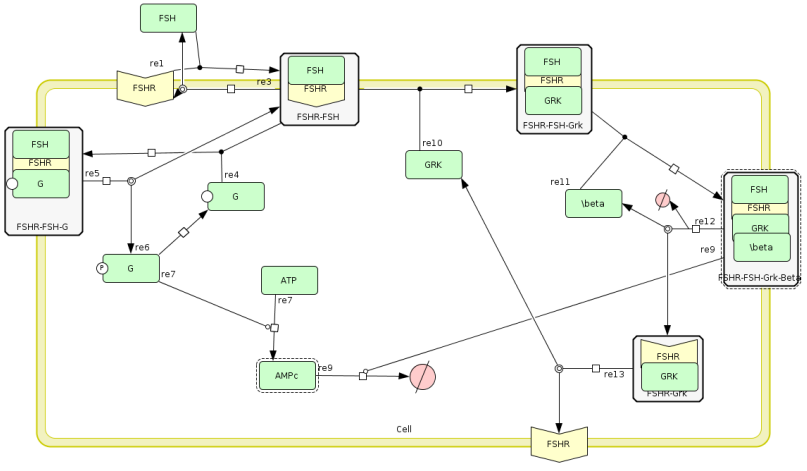
Reaction Network Visualization

$$L + R \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} LR$$

$$LR + GRK \xrightarrow{} LRGRK$$

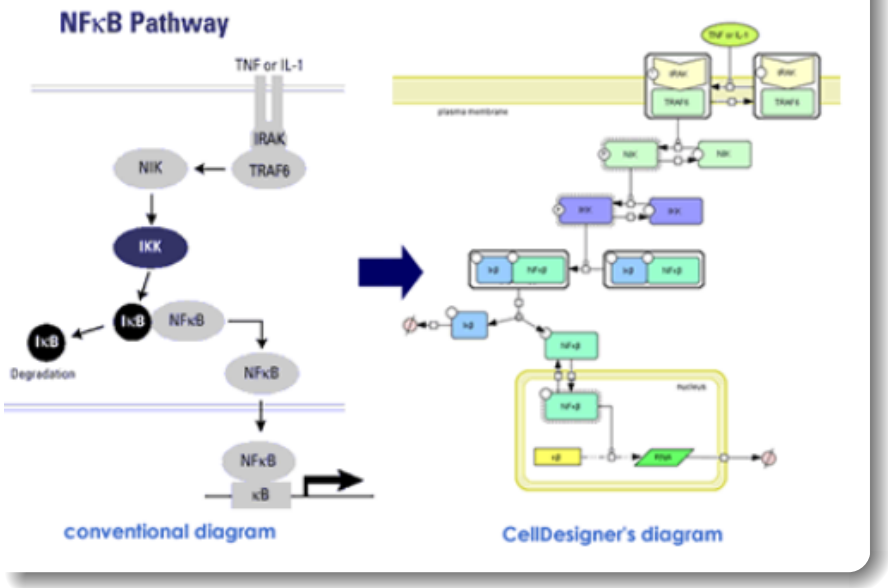
$$ATP + LR \xrightarrow{k^+} cAMP + LR$$

$$cAMP \xrightarrow{k^-} AMP$$

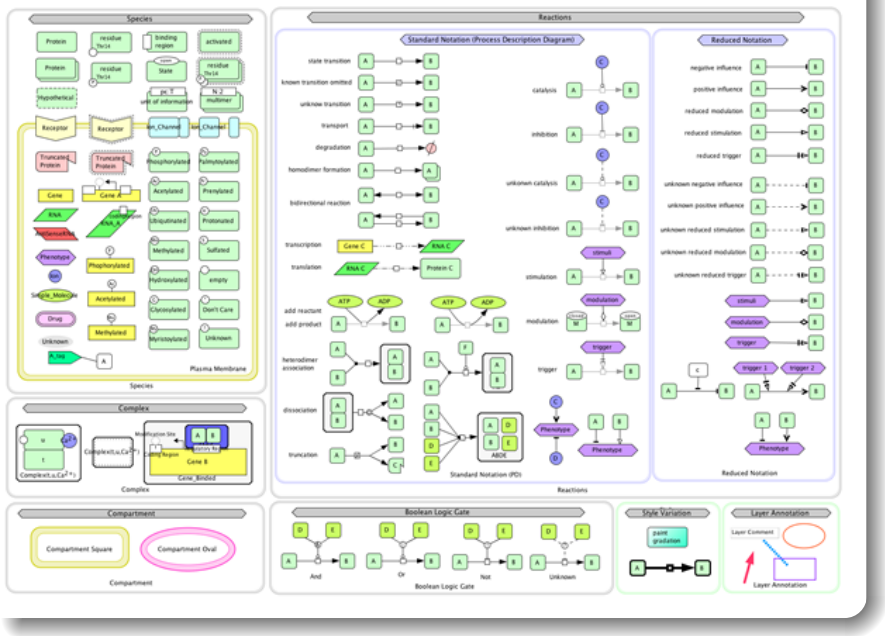


Cell Designer

About diagrams and layout...



...with well-defined conventions



Funahashi, A., Tanimura, N., Morohashi, M., and Kitano, H., CellDesigner : a process diagram editor for gene-regulatory and biochemical networks, BIOSILICO, 1 :159-162, 2003

Summary so far

We have seen

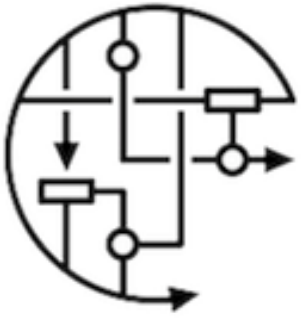
- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build* a reaction network within Cell Designer

Summary so far

We have seen

- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build* a reaction network within Cell Designer

NB : there exists public databases of (reaction) network models.



BioModels

Pathguide» the pathway resource list

KEGG NETWORK Database

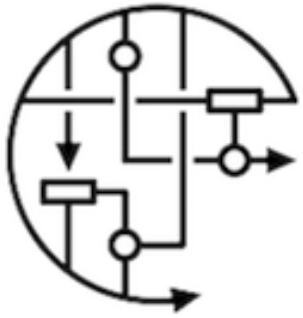
From gene variation to network variation

Summary so far

We have seen

- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build* a reaction network within Cell Designer

NB : there exists public databases of (reaction) network models.



BioModels

Pathguide» the pathway resource list

KEGG NETWORK Database

From gene variation to network variation

But ! Extracting reaction network from database require some care

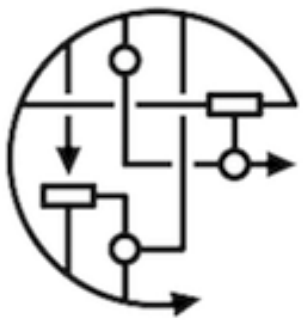
(See  Fearnley et al. Brief Bioinform. 2014)

Summary so far

We have seen

- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build* a reaction network within Cell Designer

NB : there exists public databases of (reaction) network models.



BioModels

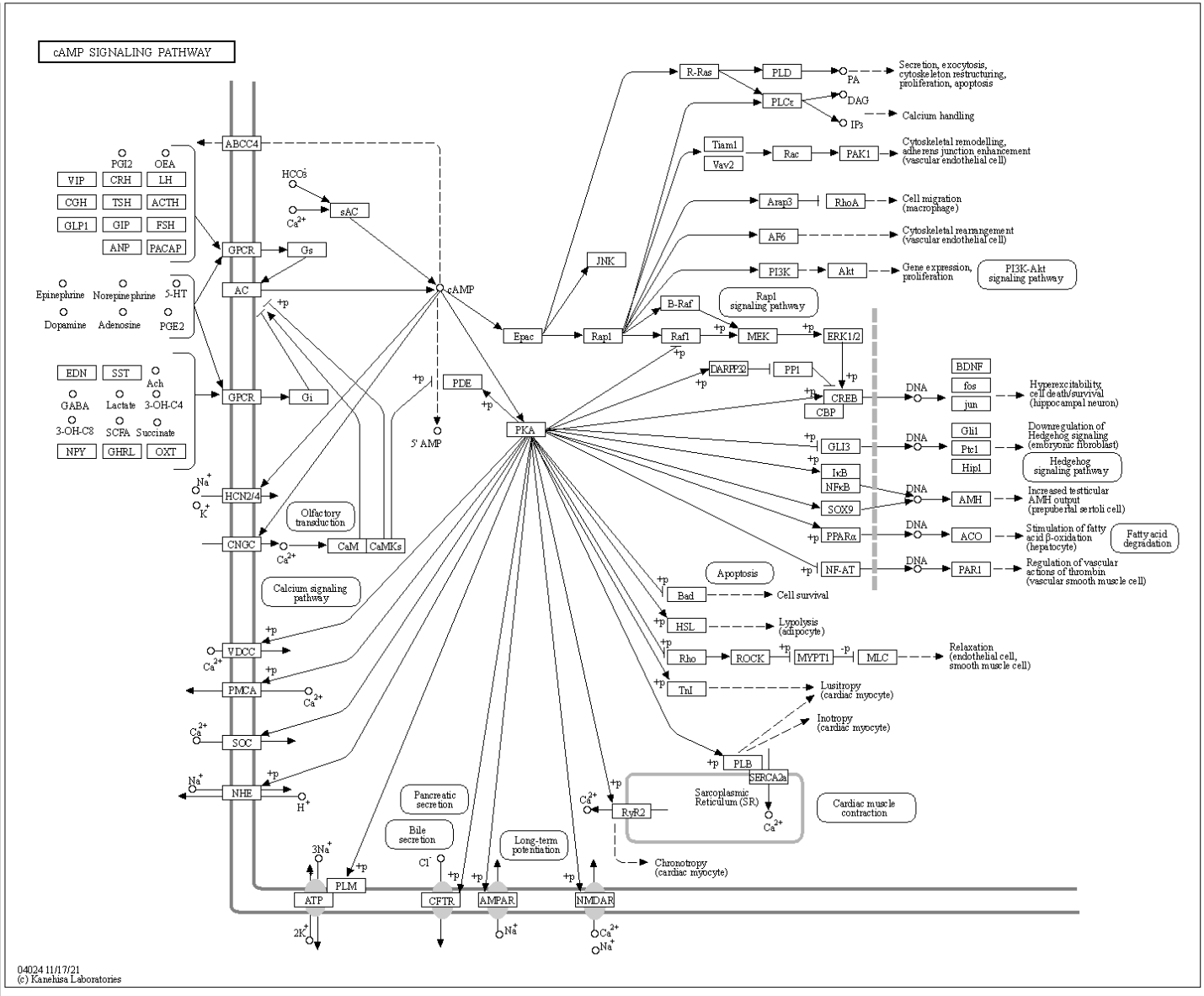
Pathguide the pathway resource list

KEGG NETWORK Database

From gene variation to network variation

NB (bis) : A reaction network is a network... but a network is **NOT** a reaction network !

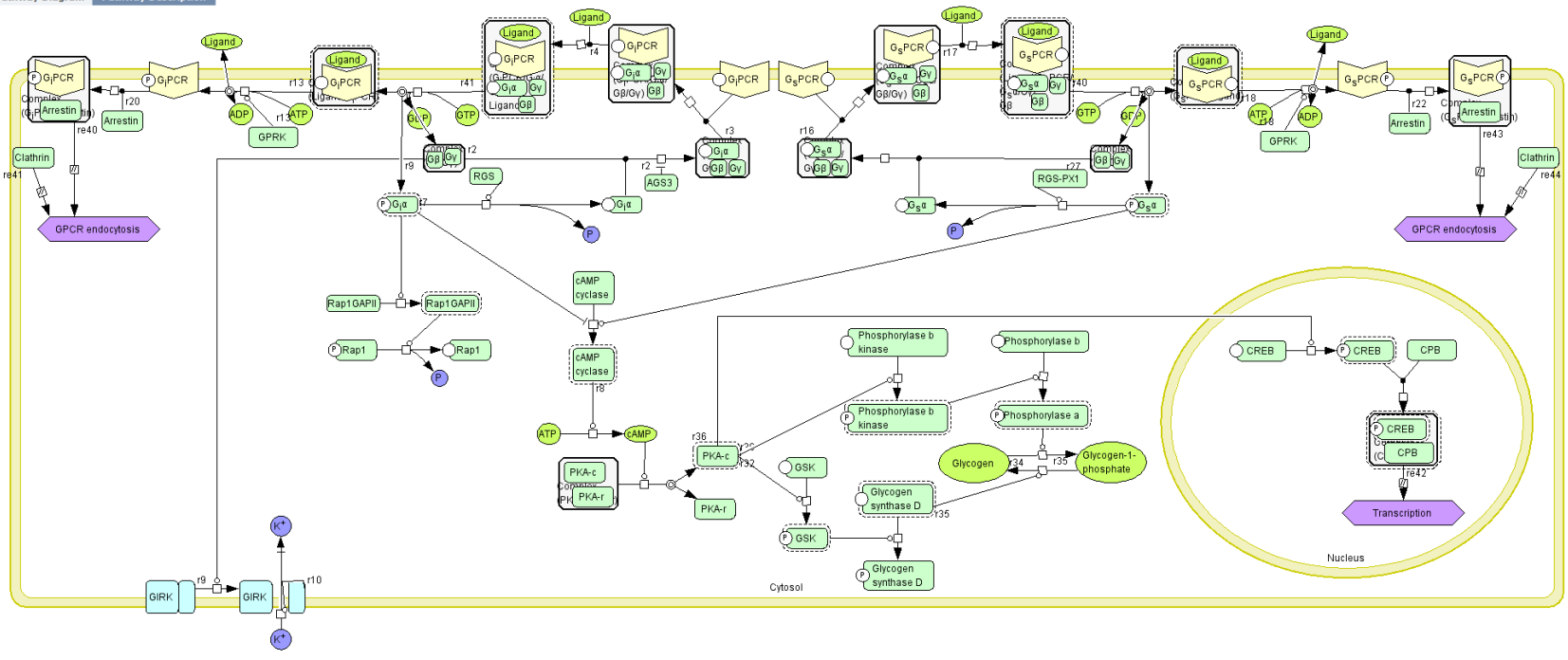
cAMP signaling pathway - Reference pathway

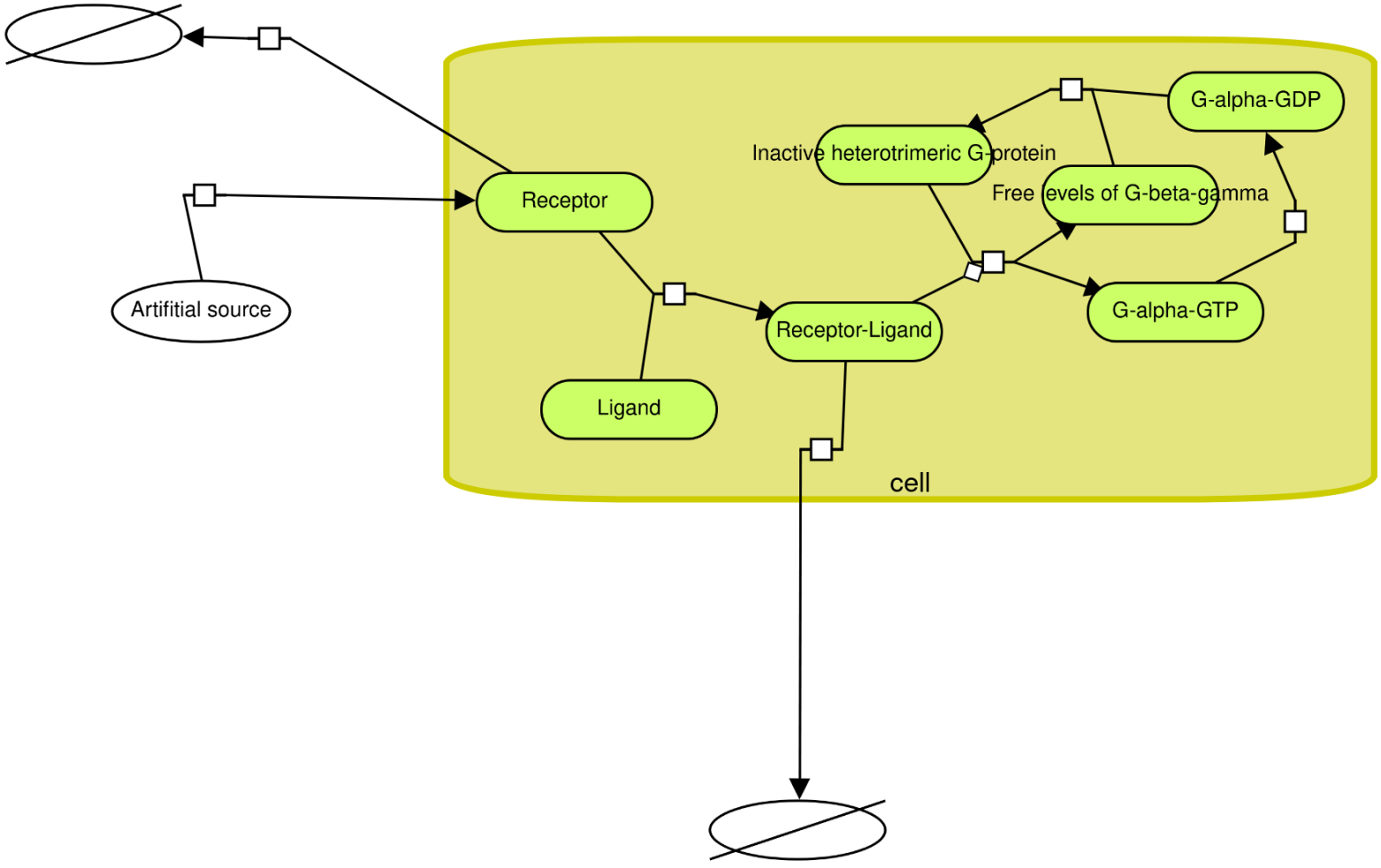


HETEROTRIMERIC G-PROTEIN SIGNALING PATHWAY-GI ALPHA AND GS ALPHA MEDIATED PATHWAY

Export: Select one

Pathway Diagram | Pathway Description




G-alpha-GDP
Inactive heterotrimeric G-protein
Free levels of G-beta-gamma
Receptor
Artifitial source
G-alpha-GTP
Receptor-Ligand
Ligand
cell

Summary so far

We have seen

- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build* a reaction network within Cell Designer
- **What about dynamics ?**

Outline

Possible applications of Dynamics modeling

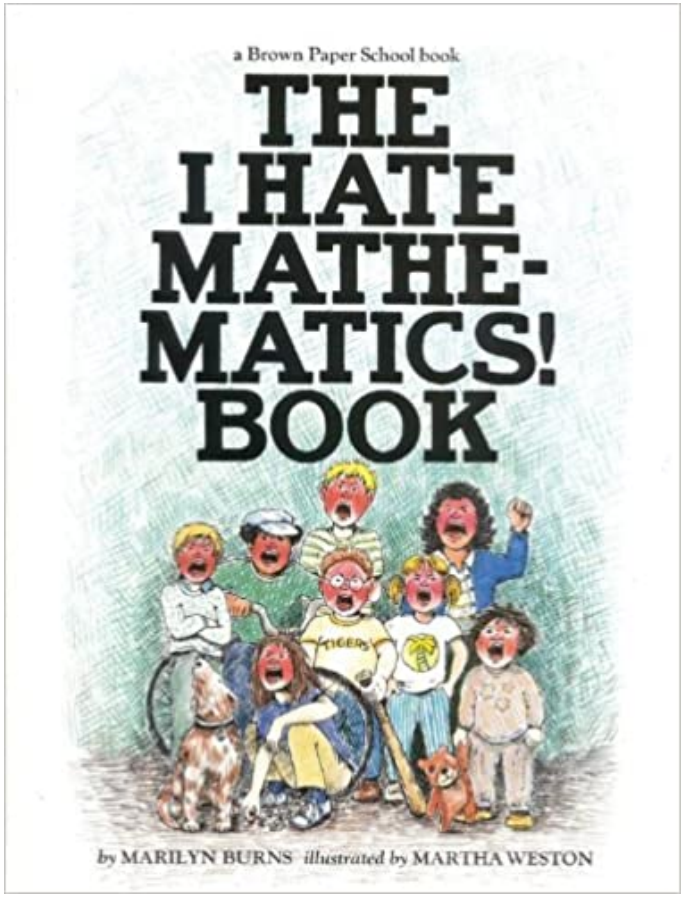
- Understand non-trivial behavior of a biological system (by reproducing this behavior with an understandable model, starting from 'first principles')
- Help to identify key regulatory process in signaling cascades
- Quantify some non-observables quantities, in particular : molecules concentrations, reaction rates.

Possible applications of Dynamics modeling

Now : Understand the mathematical formalism of dynamical reactions network

- Build and simulate a dynamical model from a reaction network [Cell Designer]
- Parameter calibration with kinetic data [GraphPad Prism / Copasi]

Warning !



#Ihatemathematics

The following couples of slides contain some abstract notions...let's try to catch the meaning !

Chemical Reaction Network and Dynamical models

We build a model that

- Keep track of concentration of species along time.
- Satisfy Law of Mass action : The velocity of a reaction is proportional to the concentrations of its reactants.
- Is a system of Ordinary Differential Equations, in which reactions are "added" on top of each other, e.g. they happens continuously and simultaneously *(Rate equations)*.

Chemical Reaction Network and Dynamical models

Example

$$A \underset{0.1}{\overset{2}{\rightleftharpoons}} B$$

$$\begin{aligned} \frac{dx_A}{dt}(t) &= -0.1x_A(t) + 2x_B(t)\,, \quad x_A(t=0) = A_{tot} \\ \frac{dx_B}{dt} &= +0.1x_A(t) - 2x_B(t)\,, \quad x_B(t=0) = 0 \end{aligned}$$

$x_A(t) =$ time dependent concentration of species A

Chemical Reaction Network and Dynamical models

Example

$$L + R \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} LR$$

$$\begin{aligned}
\frac{dx_L}{dt}(t) &= -k_{on}x_L(t)x_R(t) + k_{off}x_{LR}(t)\,, \quad x_L(0) = Dose \\
\frac{dx_R}{dt}(t) &= -k_{on}x_L(t)x_R(t) + k_{off}x_{LR}(t)\,, \quad x_R(0) = R_{tot} \\
\frac{dx_{LR}}{dt}(t) &= k_{on}x_L(t)x_R(t) - k_{off}x_{LR}(t)\,, \quad x_{LR}(0) = 0.
\end{aligned}$$

Chemical Reaction Network and Dynamical models

Example (minimal cAMP production model)

$$
\begin{aligned}
L + R &\underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} LR \\
ATP + LR &\xrightarrow{k^+} cAMP + LR \\
cAMP &\xrightarrow{k^-} AMP
\end{aligned}
$$

$$
\begin{aligned}
\frac{dx_L}{dt} &= -k_{on}x_L x_R + k_{off}x_{LR}\,, \quad x_L(0) = Dose \\
\frac{dx_R}{dt} &= -k_{on}x_L x_R + k_{off}x_{LR}\,, \quad x_R(0) = R_{tot} \\
\frac{dx_{LR}}{dt} &= k_{on}x_L x_R - k_{off}x_{LR}\,, \quad x_{LR}(0) = 0 \\
\frac{dx_{cAMP}}{dt} &= k^+ x_{ATP}x_{LR} - k^- x_{cAMP}\,, \quad x_{cAMP}(0) = 0 \\
\frac{dx_{ATP}}{dt} &= -k^+ x_{ATP}x_{LR} \quad x_{ATP}(0) = ATP_{tot}\,.
\end{aligned}
$$

But what is an "Ordinary Differential Equation"? A math theory in one slide !

The equation

$$\frac{dx}{dt} = v(x)\,,$$

is numerically solved by successive time-step iteration, of small length $\Delta t \ll 1$:

1) Start at *a given initial condition* x_0 at time $t_0 = 0$

But what is an "Ordinary Differential Equation"? A math theory in one slide !

The equation

$$\frac{dx}{dt} = v(x)\,,$$

is numerically solved by successive time-step iteration, of small length $\Delta t \ll 1$:

1) Start at *a given initial condition* x_0 at time $t_0 = 0$
2) To calculate the value of x at the first time step, remember that *(assuming constant speed)*

$$\text{Final Position} = \text{Initial Position} + \text{velocity} * \text{Time}\,,$$

which becomes, in mathematical notations,

$$x(\Delta t) = x_0 + v(x_0) * \Delta t\,,$$

But what is an "Ordinary Differential Equation"? A math theory in one slide !

The equation

$$\frac{dx}{dt} = v(x)\,,$$

is numerically solved by successive time-step iteration, of small length $\Delta t \ll 1$:

1) Start at *a given initial condition* x_0 at time $t_0 = 0$
2) To calculate the value of x at the first time step, remember that *(assuming constant speed)*

$$\text{Final Position} = \text{Initial Position} + \text{velocity} * \text{Time}\,,$$

which becomes, in mathematical notations,

$$x(\Delta t) = x_0 + v(x_0) * \Delta t\,,$$

Iterate : To calculate the value of x at the next time step, use

$$x((i+1) * \Delta t) = x(i * \Delta t) + v\left(x(i * \Delta t)\right) * \Delta t\,,$$

But what is an "Ordinary Differential Equation"? A math theory in one slide...and a figure!

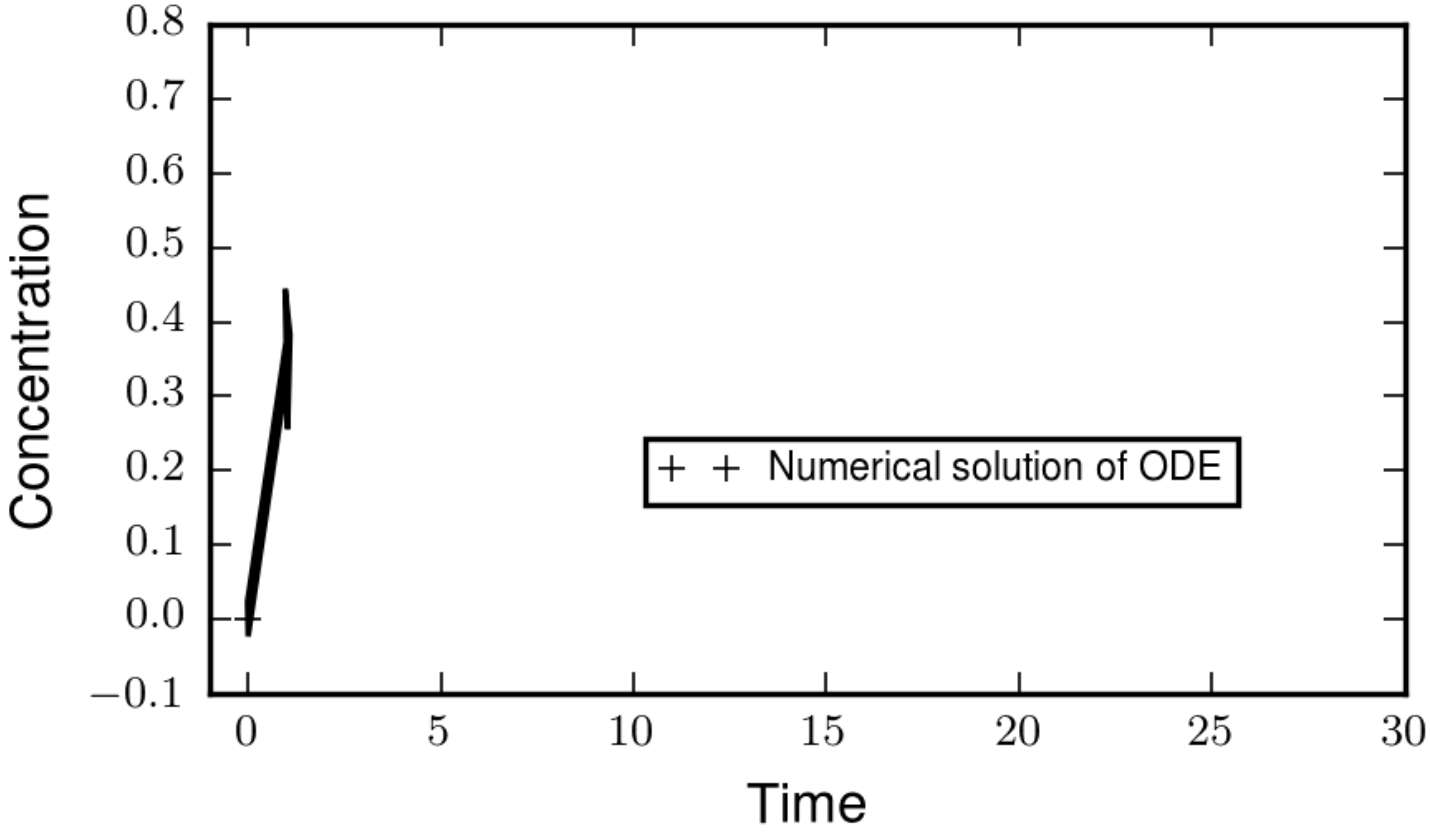


Figure – Solving an ODE

But what is an "Ordinary Differential Equation"? A math theory in one slide...and a figure!

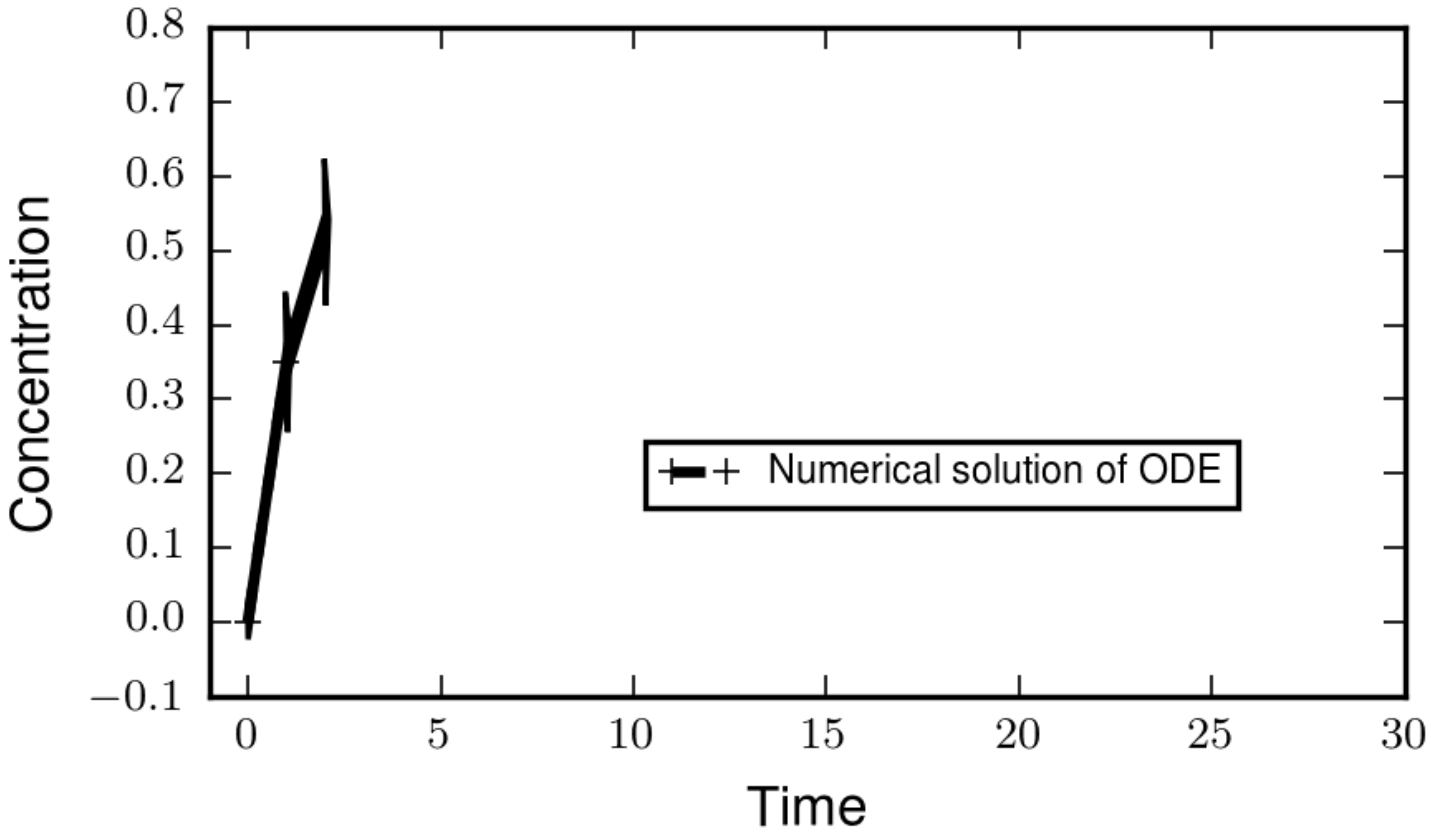


Figure – Solving an ODE

But what is an "Ordinary Differential Equation"? A math theory in one slide...and a figure!

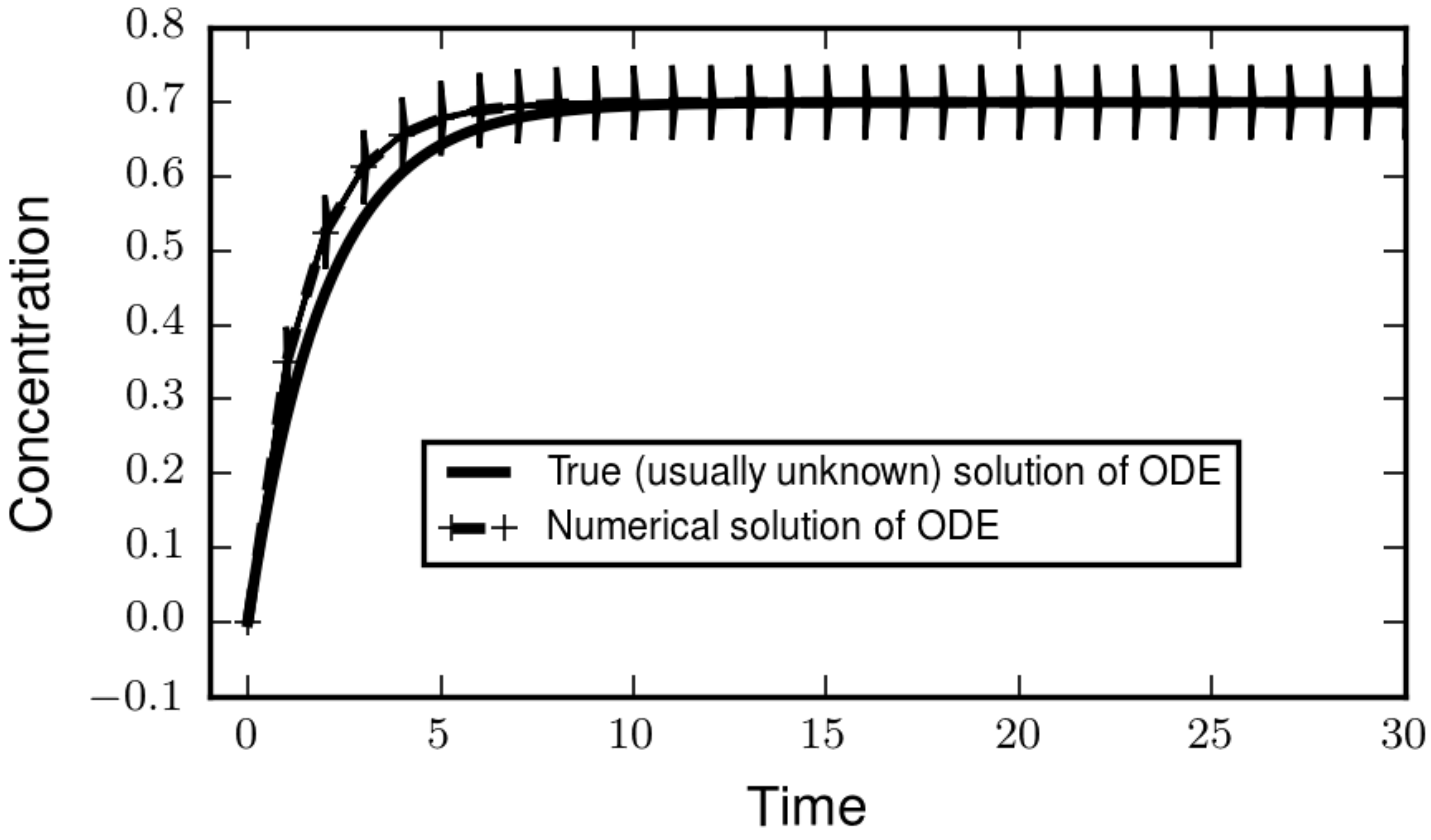
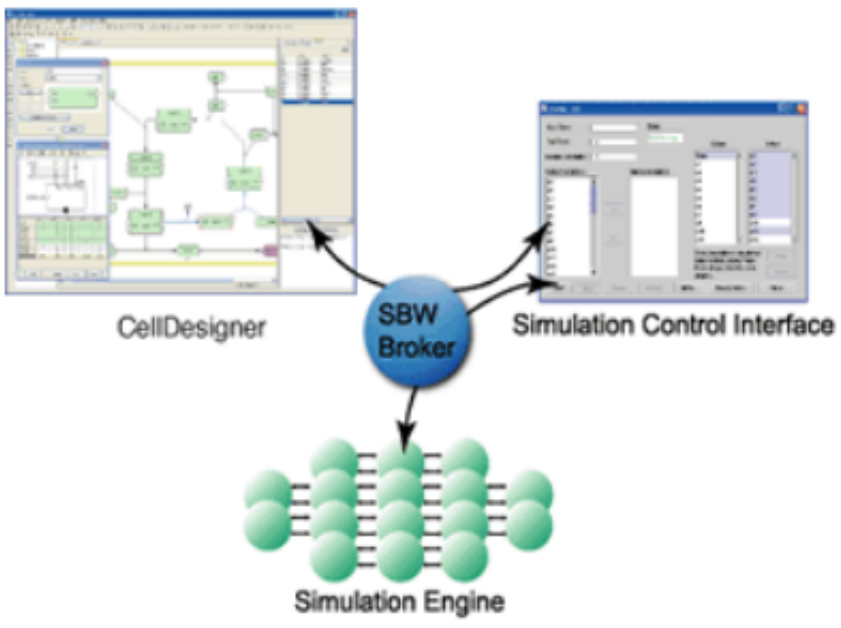
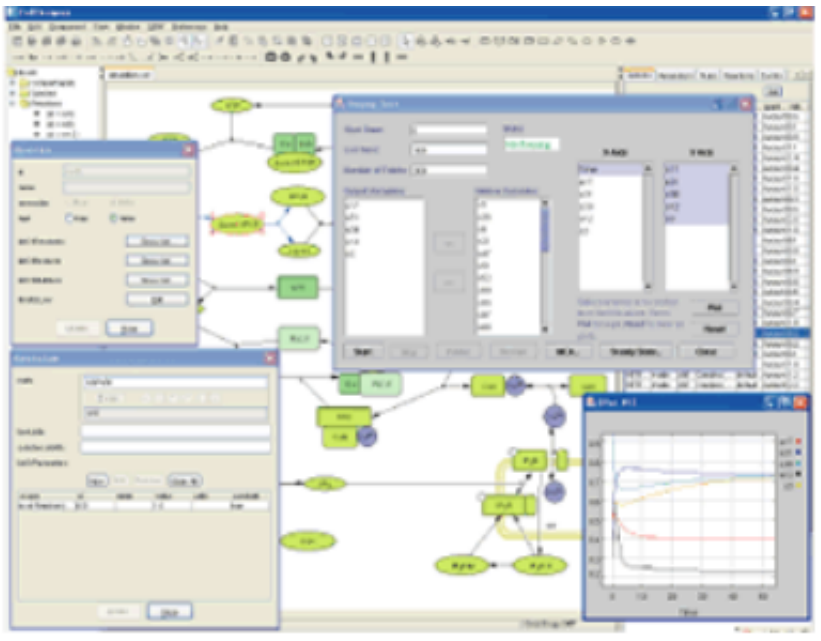


Figure – Solving an ODE

Solving an ODE in practice : no need to code !

ODE solver within Cell Designer





Funahashi, A., Tanimura, N., Morohashi, M., and Kitano, H., CellDesigner : a process diagram editor for gene-regulatory and biochemical networks, BIOSILICO, 1 :159-162, 2003

Summary so far

We have seen

- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build and simulate* a reaction network within Cell Designer

Summary so far

We have seen

- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build and simulate* a reaction network within Cell Designer

NB : You don't need to code, but you need to specify kinetic rate and initial condition values to simulate a reaction network.

Summary so far

We have seen

- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build and simulate* a reaction network within Cell Designer

NB : You don't need to code, but you need to specify kinetic rate and initial condition values to simulate a reaction network.

NB (bis) : You can play with this tools to "explore" the behavior of a model. But that can be time consuming and inefficient...

Summary so far

We have seen

- Examples of network and reaction network models
- The formalism of *reaction network* models
- How to *build and simulate* a reaction network within Cell Designer

What about inferring those values from data ?

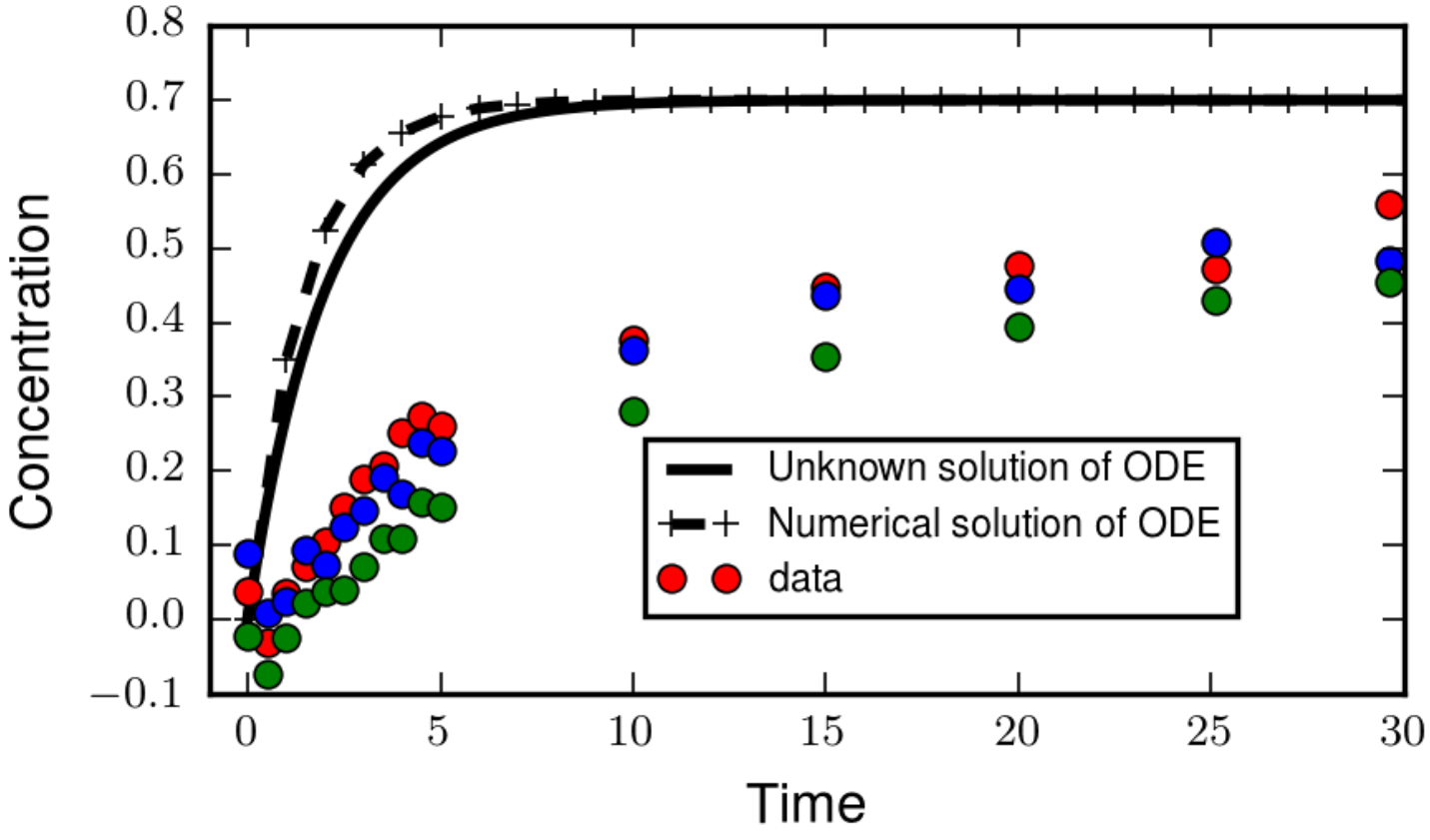
Outline

Parameter and network inference in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.

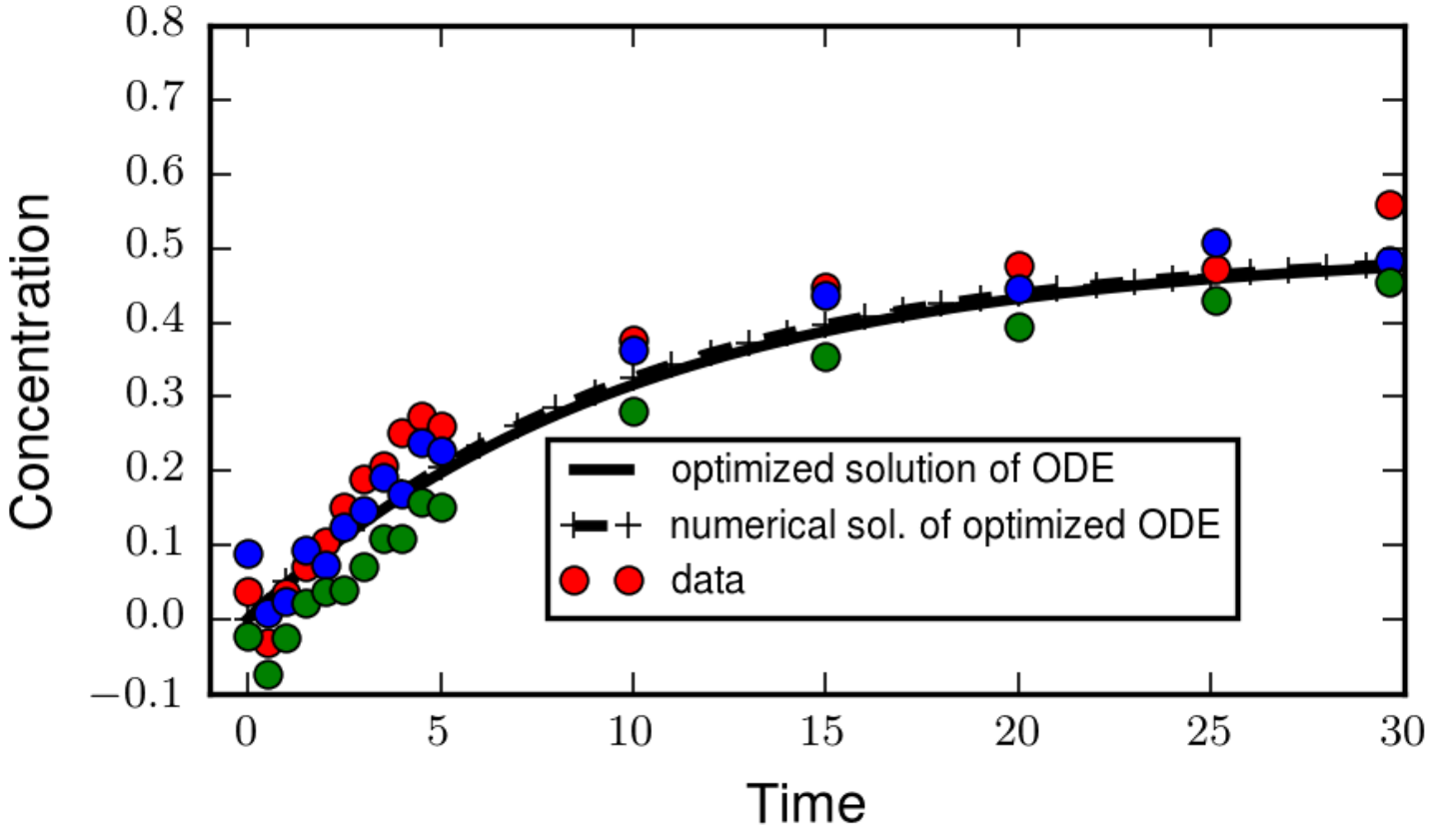
Parameter and network inference in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.



Parameter and network inference in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.



Regression analysis and Parameter estimation with time series : What is difficult ?

- In linear models, there exists a *unique optimal* solution
- Yet in practice, (generalized) linear models do not perform well on biochemical data due to Heteroscedasticity and highly dependent time point data.

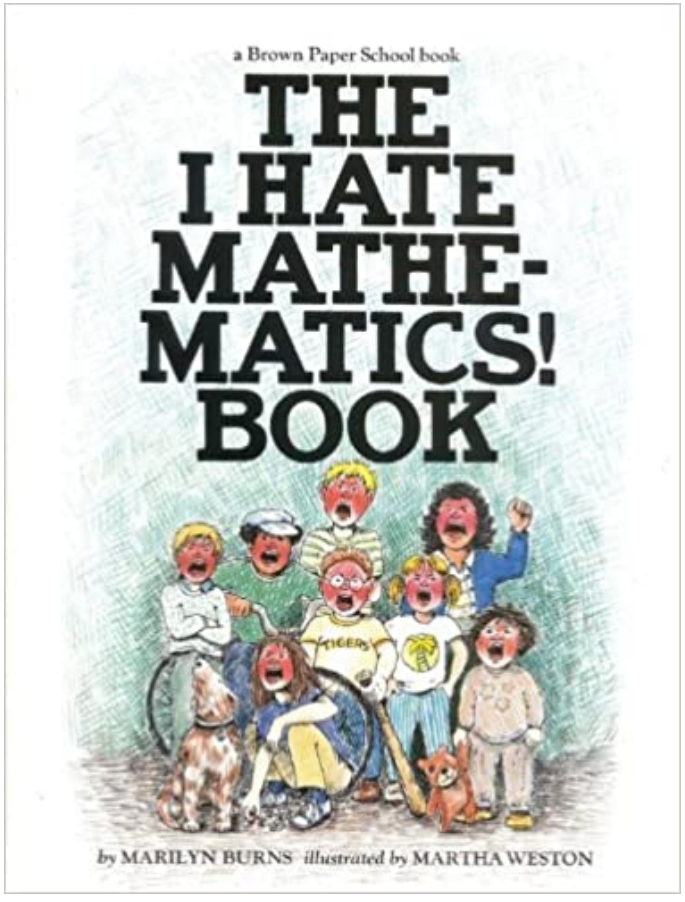
Regression analysis and Parameter estimation with time series : What is difficult ?

- For most of (nonlinear) reaction network, there is no guarantee to find a unique optimal solution.
- Reaction network models allows to perform multifactorial analysis ("Anova-like")

Regression analysis and Parameter estimation with time series : What is difficult ?

- For most of (nonlinear) reaction network, there is no guarantee to find a unique optimal solution.
- Reaction network models allows to perform multifactorial analysis ("Anova-like")
- Many other tools exists from the statistical field of *time series analysis*.

Warning !



#Ihatemathematics

The following couples of slides contain some abstract notions...*but that the last ones !*

Parameter and network optimization in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.

Strategy 1) From a given network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, with given parameter values, solve the ODEs,

$$\frac{dx}{dt} = v(x, k)\,, \quad x(0) = x_0\,,$$

and compute a **distance** between the solution and the data.

Parameter and network optimization in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.

Strategy 1) From a given network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, with given parameter values, solve the ODEs,

$$\frac{dx}{dt} = v(x, k)\,, \quad x(0) = x_0\,,$$

and compute a **distance** between the solution and the data.

Strategy 2) Using **optimization** algorithms, find the best parameter values k, x_0, to minimize the distance

Parameter and network optimization in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.

Strategy 1) From a given network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, with given parameter values, solve the ODEs,

$$\frac{dx}{dt} = v(x, k)\,, \quad x(0) = x_0\,,$$

and compute a **distance** between the solution and the data.

Strategy 2) Using **optimization** algorithms, find the best parameter values k, x_0, to minimize the distance

Strategy 3) If needed, change the reaction network (add or delete species/reactions)

Parameter and network optimization in Chemical Reaction Network

Goal : Given some time series data, find the minimal (biologically plausible) reaction network with its parameter (=reaction rates and initial conditions) that fits consistently the data.

Statistics There exists a well developed statistical theory to assess the **quality of a fit** and to give **confidence interval** on parameter values (-> See Likelihood maximization or Bayesian statistics).

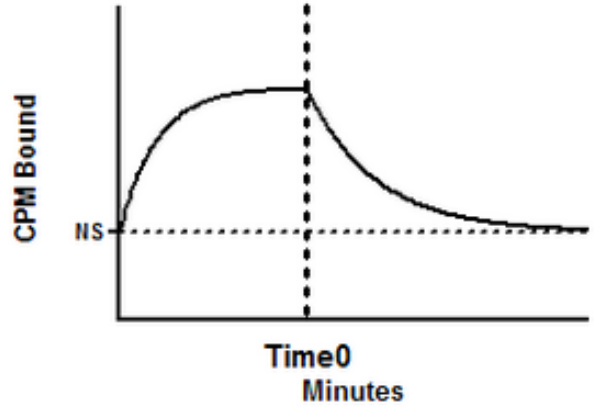
Parameter estimation in

GraphPad

Predefined or user-defined time-dependent equations

Model

```
Radioligand=HotNM*1e-9
Kob=[Radioligand]*Kon+Koff
Kd=Koff/Kon
Eq=Bmax*radioligand/(radioligand + Kd)
Association=Eq*(1-exp(-1*Kob*X))
YatTime0 = Eq*(1-exp(-1*Kob*Time0))
Dissociation= YatTime0*exp(-1*Koff*(X-Time0))
Y=IF(X<Time0, Association, Dissociation) + NS
```



Parameter estimation in

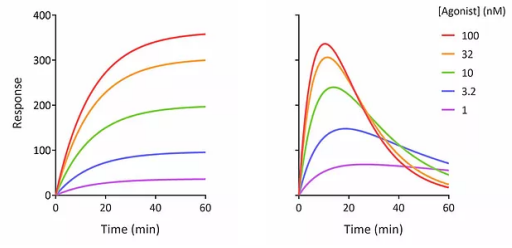
GraphPad

- Limited to *solvable* models
- Adapted to analyze one single output at a time, assuming excess of Ligand.

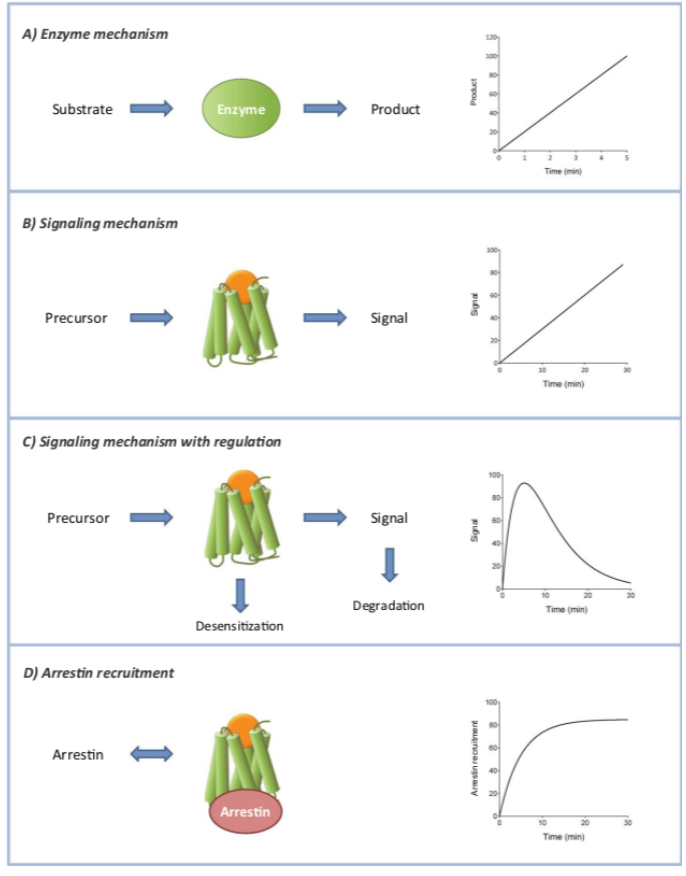
Pharmechanics

Pharmacology Data Analysis and Consulting

HOME DATA ANALYSIS CURVE FITTING CONSULTING ABOUT CONTACT

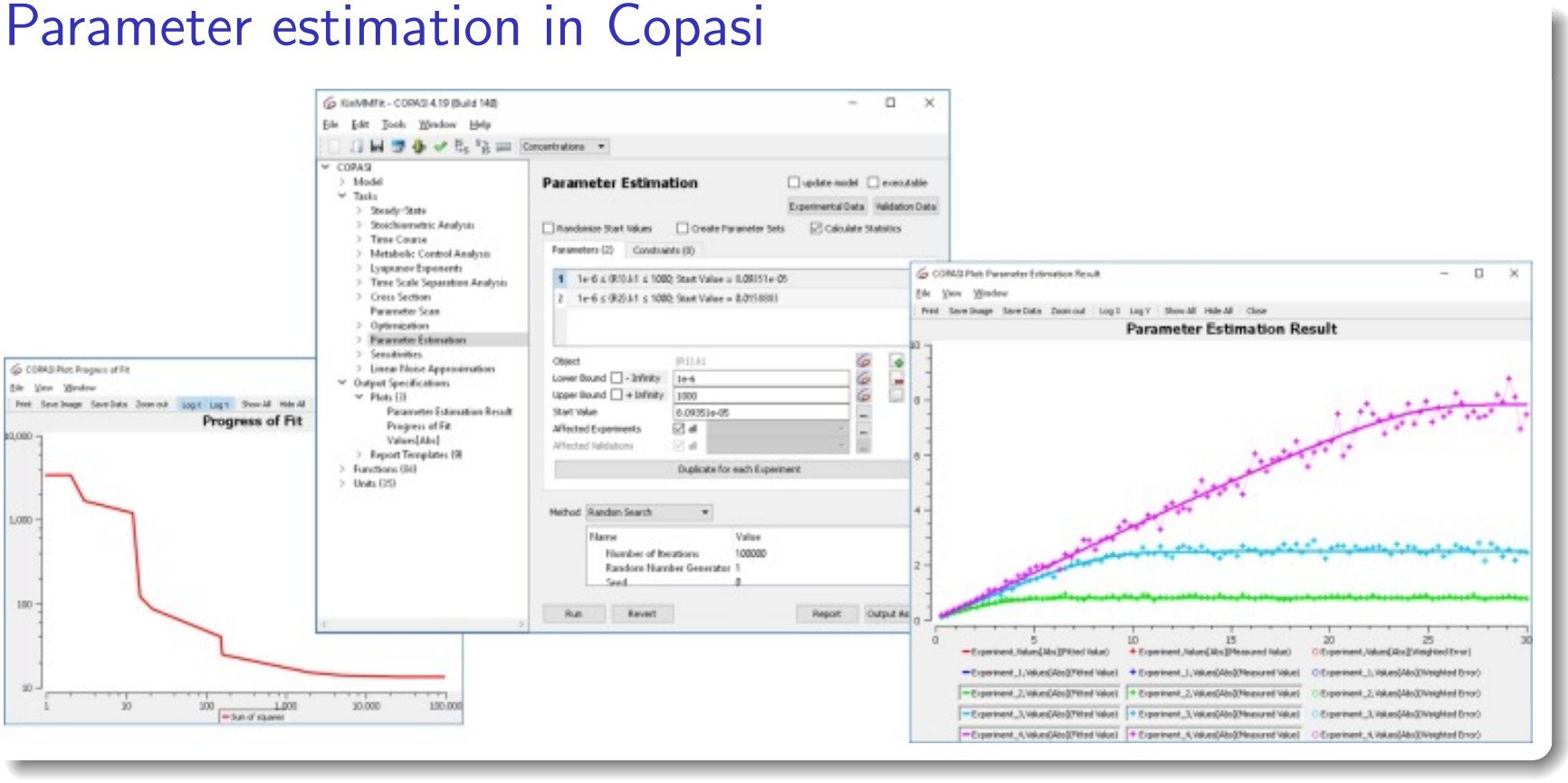


Predefined or user-defined time-dependent equations



Hoare et al., Analyzing kinetic signaling data for G-protein-coupled receptors, Scientific Reports 10(1) :12263 2020

Parameter estimation in Copasi

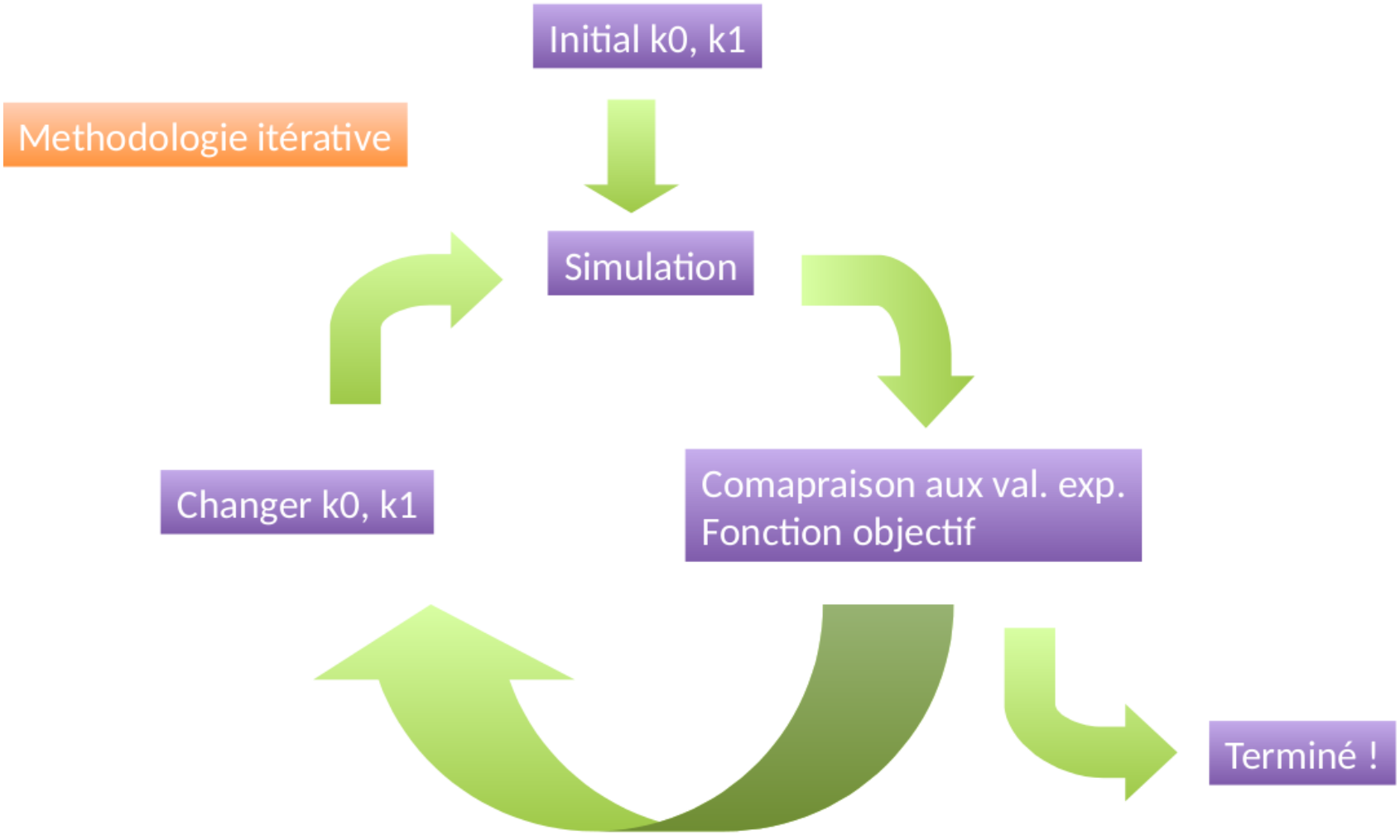


- Models can be imported from Cell Designer.
- Supports both graphical interface and command line.

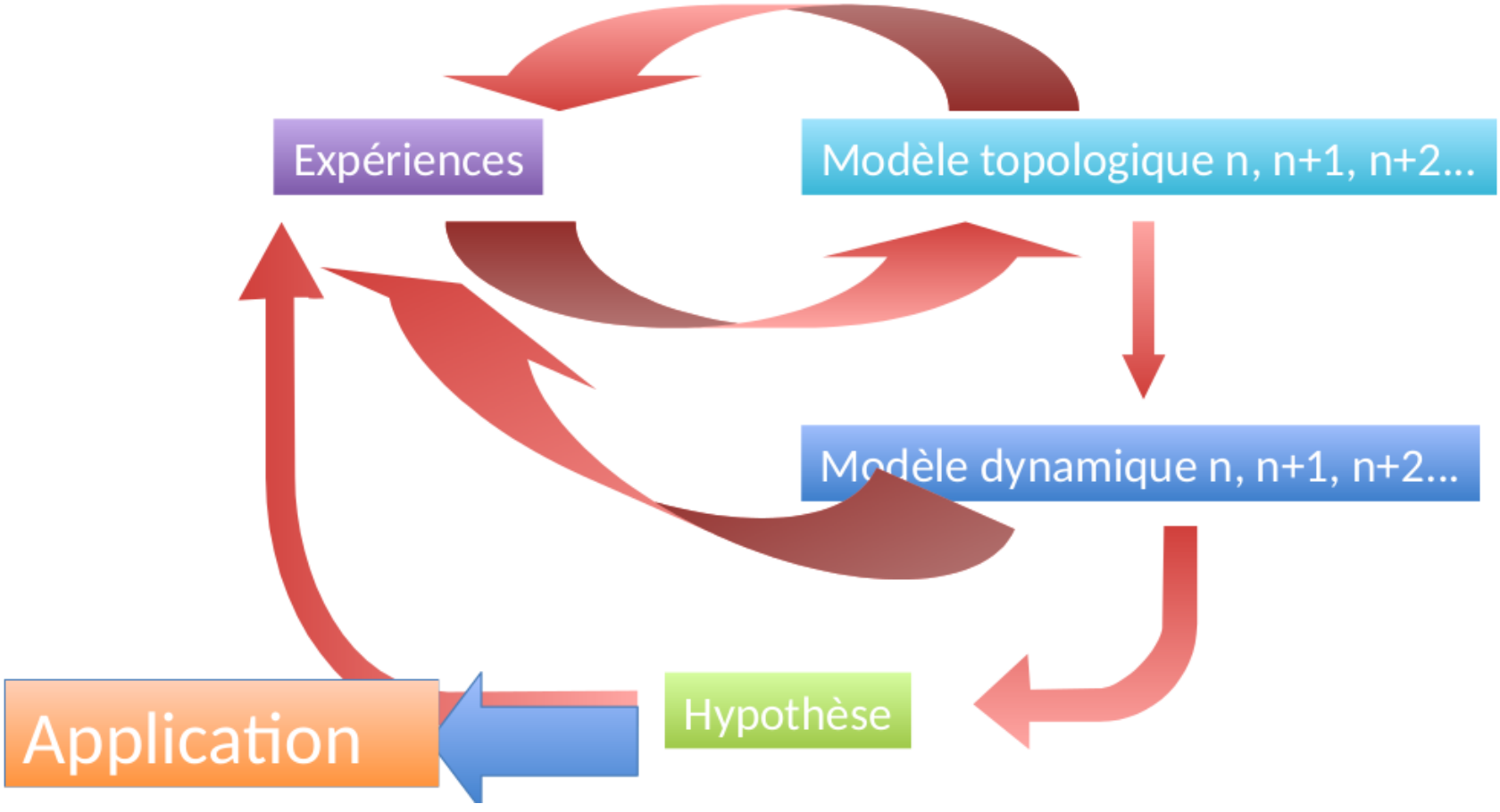
Bergman et al. COPASI and its applications in biotechnology, Journal of Biotechnology 261 :215-220, 2017.

Hoops et al. COPASI : a COmplex PAthway SImulator. Bioinformatics 22 :3067-74, 2006.

Remember ! it's an iterative and interdisciplinary workflow !

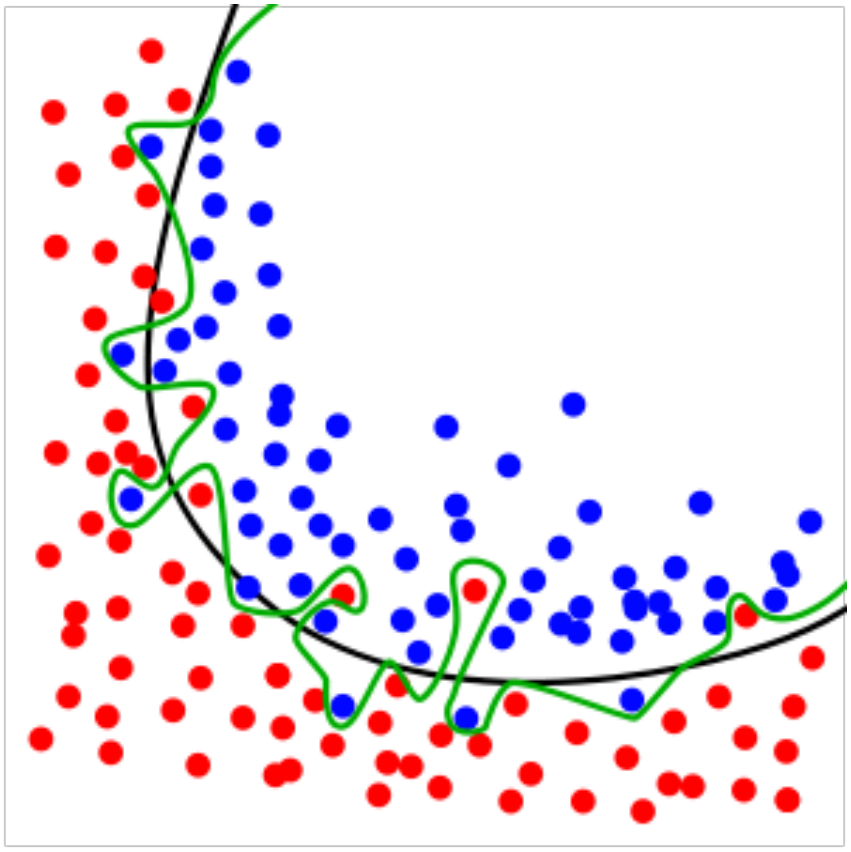


Remember ! it's an iterative and interdisciplinary workflow !



Is the monkey who typed Hamlet actually a good writer ?

Overfitting



- There is a trade-off between toy minimal models and detailed biochemistry pathways.
- Overfitting leads to unreliable prediction and meaningless model / parameter value.
- (Advanced) statistical tools exist to sort this out : model selection (especially for hierarchical models) and parameter identifiability.

Summary so far

We have seen

- Many examples of dynamical system biology models
- The formalism of dynamical reaction network models
- How to build and simulate a reaction network model within Cell Designer.
- How to calibrate parameters of a dynamical reaction network model with GraphPad Prism and/or Copasi.

Summary so far

We have seen

- Many examples of dynamical system biology models
- The formalism of dynamical reaction network models
- How to build and simulate a reaction network model within Cell Designer.
- How to calibrate parameters of a dynamical reaction network model with GraphPad Prism and/or Copasi.

NB : The full workflow can be long and require collaboration with statistician / applied mathematician.

Summary so far

We have seen

- Many examples of dynamical system biology models
- The formalism of dynamical reaction network models
- How to build and simulate a reaction network model within Cell Designer.
- How to calibrate parameters of a dynamical reaction network model with GraphPad Prism and/or Copasi.

NB bis : **What about applications ?**

Outline

Motivations and Case study

Use reaction network modeling *(kinetic pathway)* to

- Fully exploit kinetic data
- Give more mechanistic insight of signaling bias
- Develop a parsimonious and statistically significant framework to characterize pharmacological ligand properties

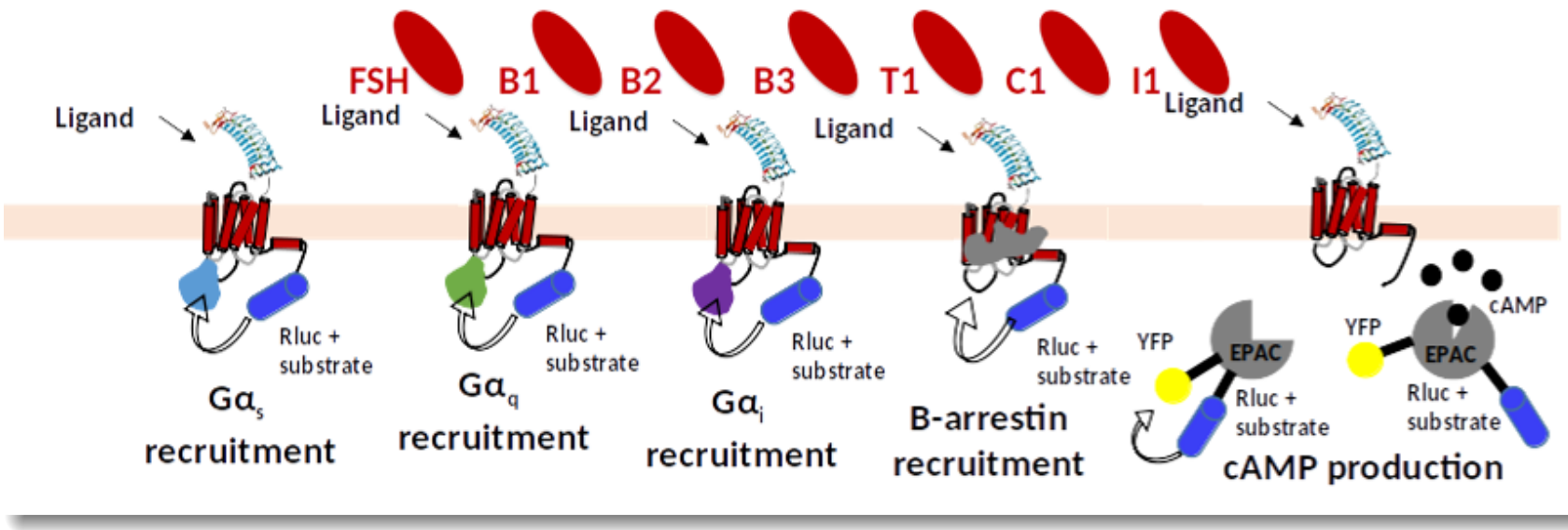
Motivations and Case study

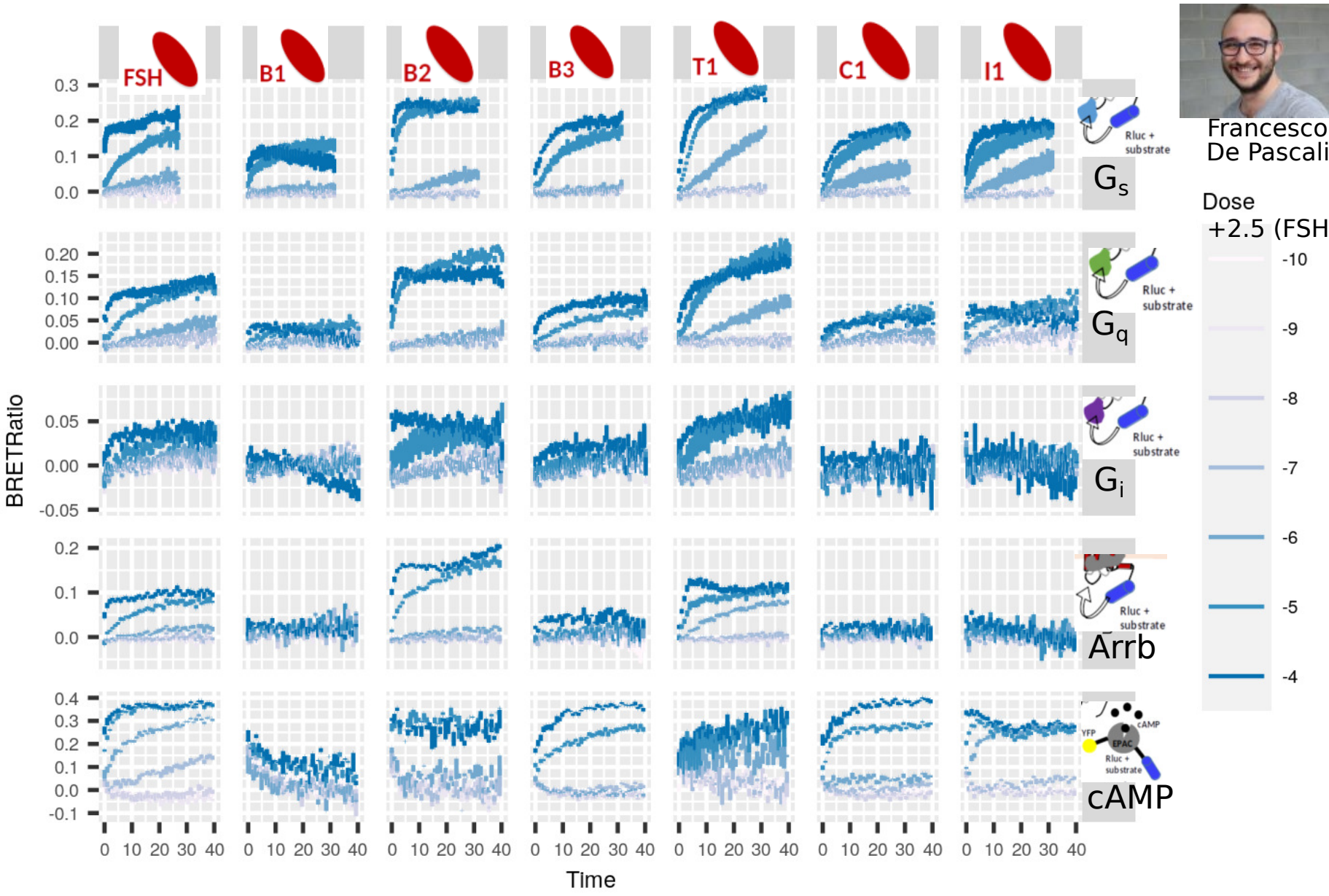
Use reaction network modeling *(kinetic pathway)* to

- Fully exploit kinetic data
- Give more mechanistic insight of signaling bias
- Develop a parsimonious and statistically significant framework to characterize pharmacological ligand properties

Case study on FSHR

- ⋆ 5 BRET sensors : NES-Venus mG, yPET- β-arrestin 2, Camyel
- ⋆ FSH + 6 LMW compounds (Benzamides, Thiazolidinone, Chromenopyrazole, Imidazole) (TocopheRx, Burlington, VT, USA).

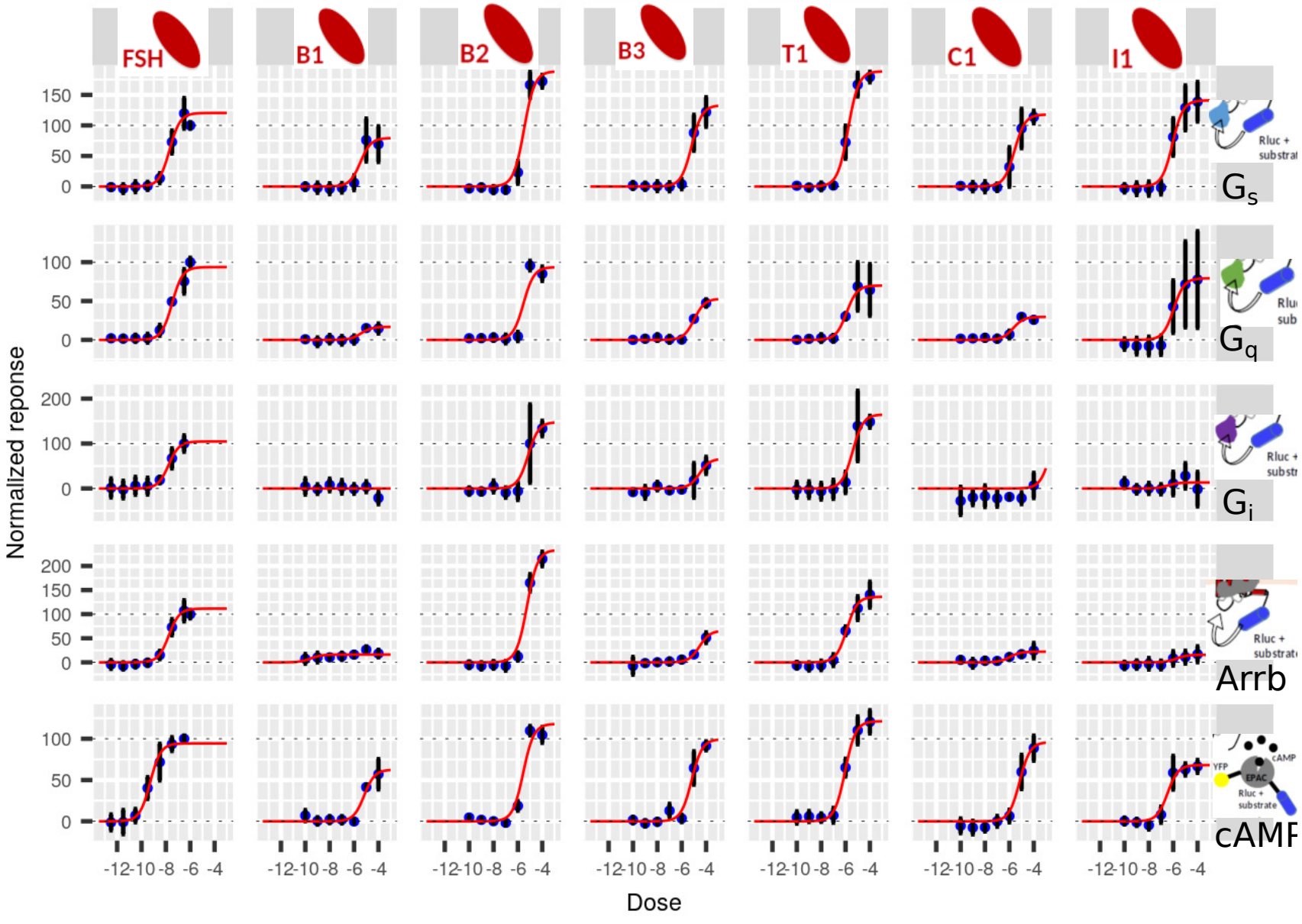




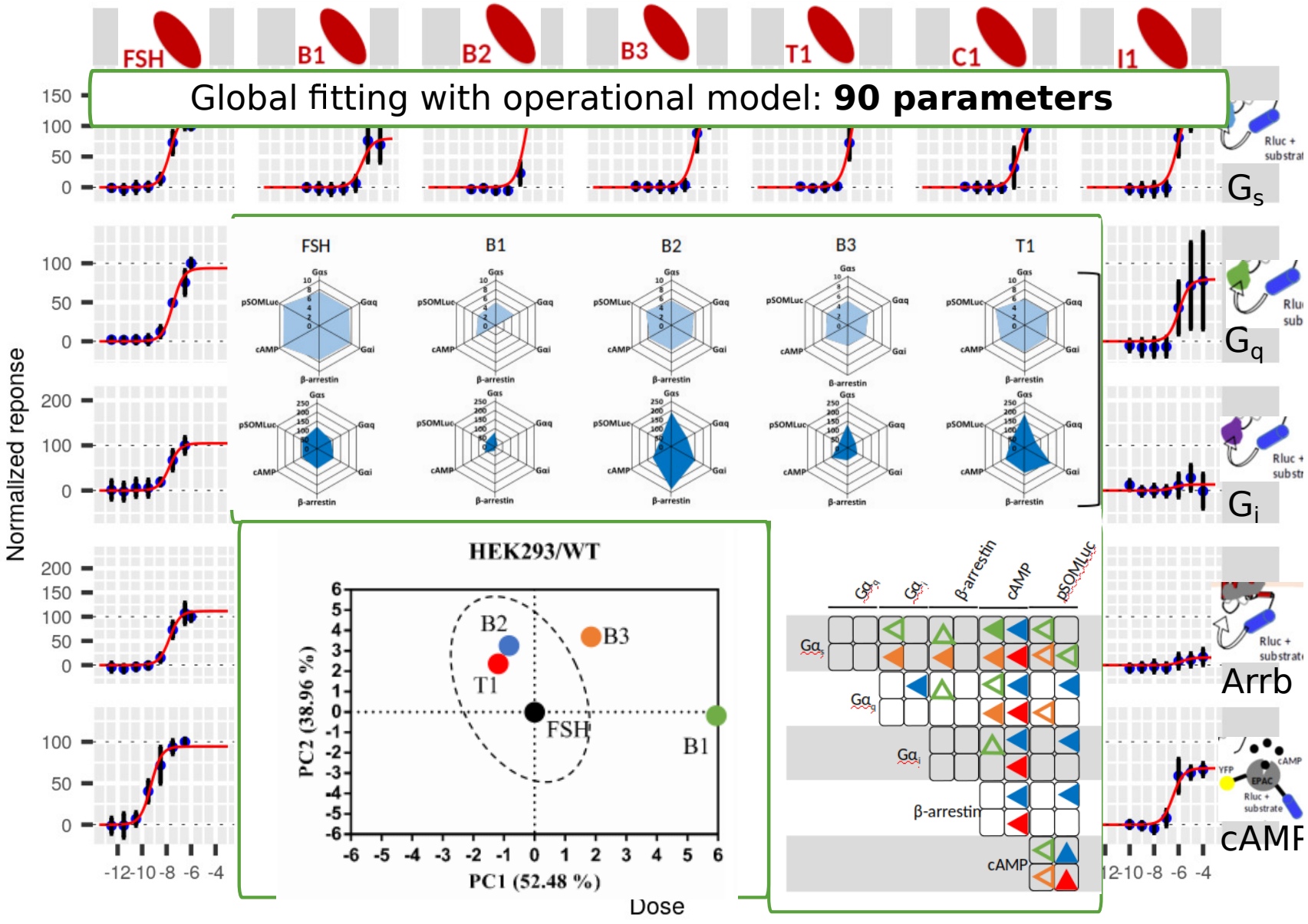
Francesco De Pascali

De Pascali et al. Pharmacological Characterization of Low Molecular Weight Biased Agonists at the Follicle Stimulating Hormone Receptor, IJMS, 2021.

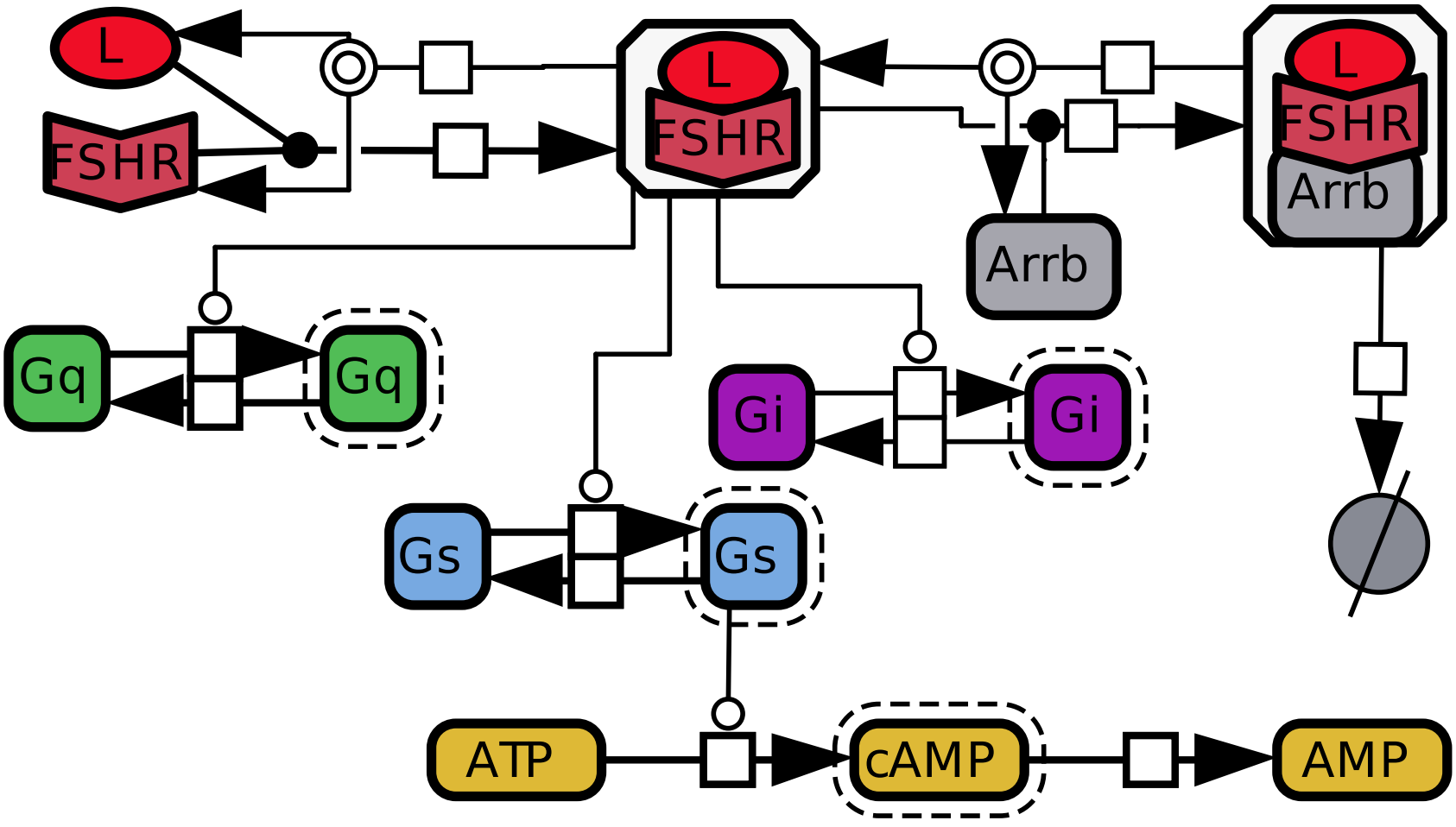
Operational model with A.U.C



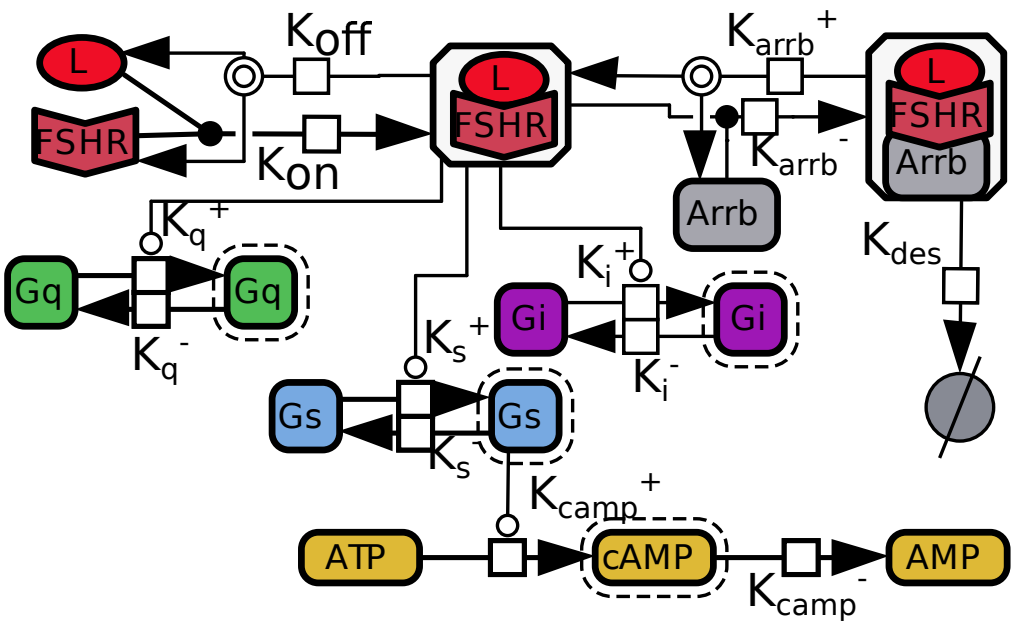
Operational model with A.U.C



Reaction network : multiple Pathways modeling

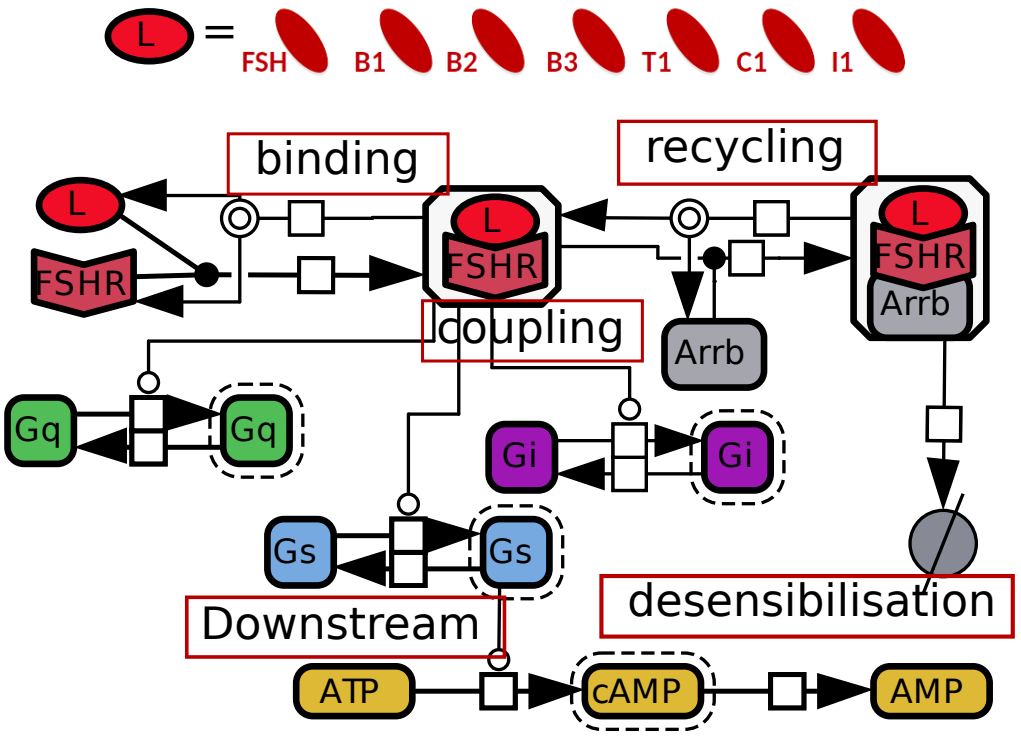


Generate all pathways at once



- Dynamic reaction networks (ODE) keep track of concentration of each molecule along time.
- Parameters : initial quantity of molecules and kinetic rates (13).

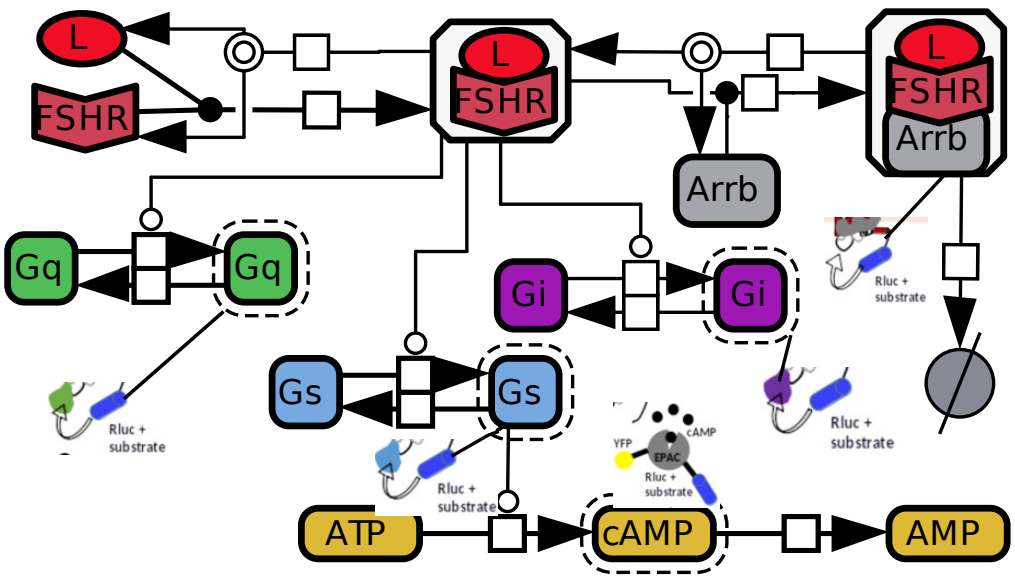
Mechanistic link with data



We hypothesize that

- Kinetic rate values reflects pharmacological ligand properties.
- Measurements are performed in a same cellular context.
- Measurements are proportional to concentration of molecules.

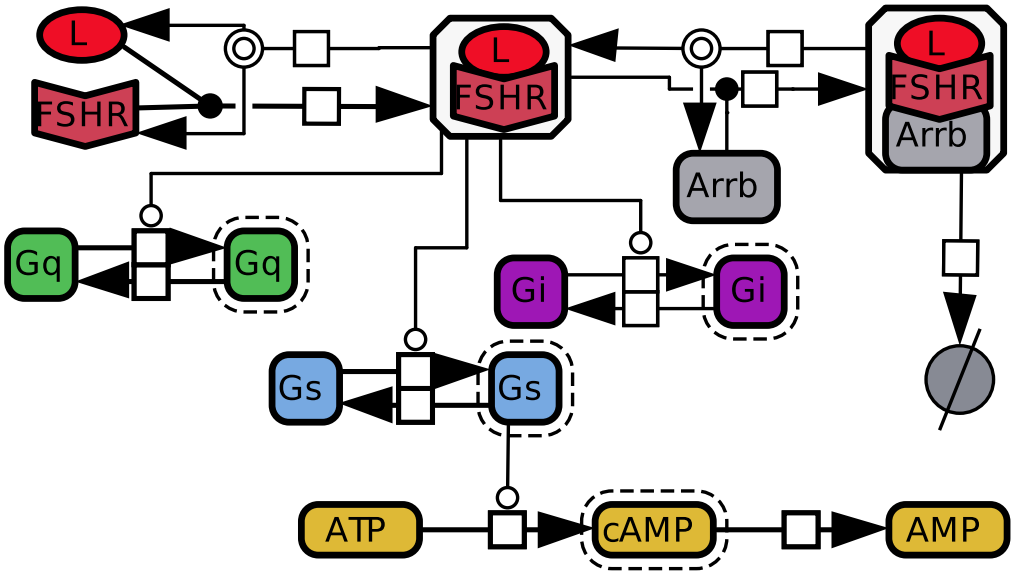
Mechanistic link with data

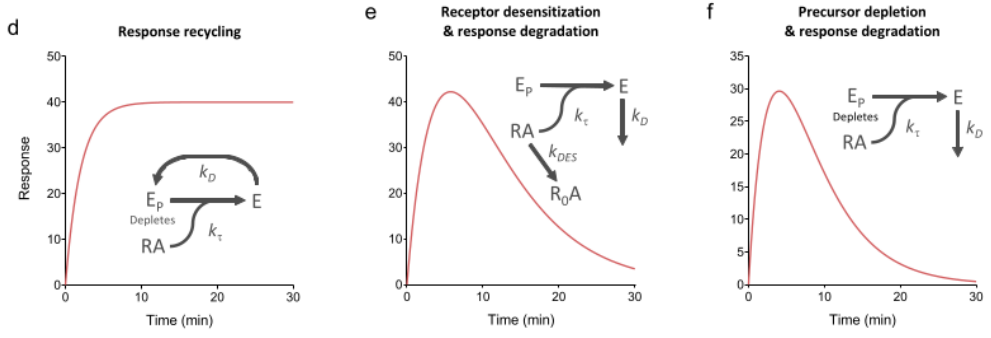


We hypothesize that

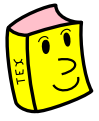
- Kinetic rate values reflects pharmacological ligand properties.
- Measurements are performed in a same cellular context.
- Measurements are proportional to concentration of molecules.

Signaling profile diversity



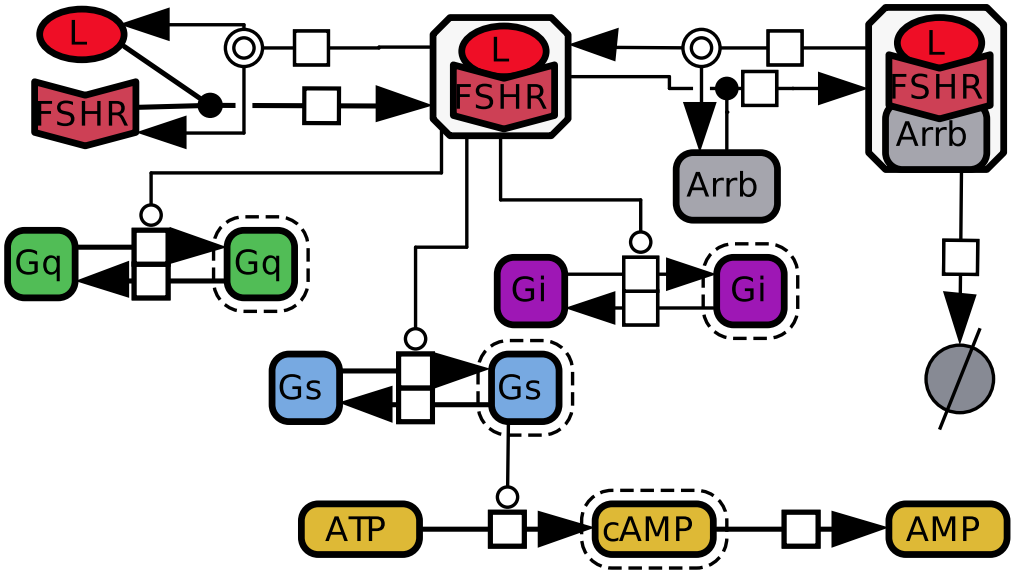


- The model is "minimal" *(model selection criteria)*
- We generalize recent attempts to define a "kinetic operational model" (Watch Nicola Dijon's flash presentation)



Hoare et al., Analyzing kinetic signaling data for G-protein-coupled receptors, Scientific Reports 2020

Global fitting enforcing sparsity

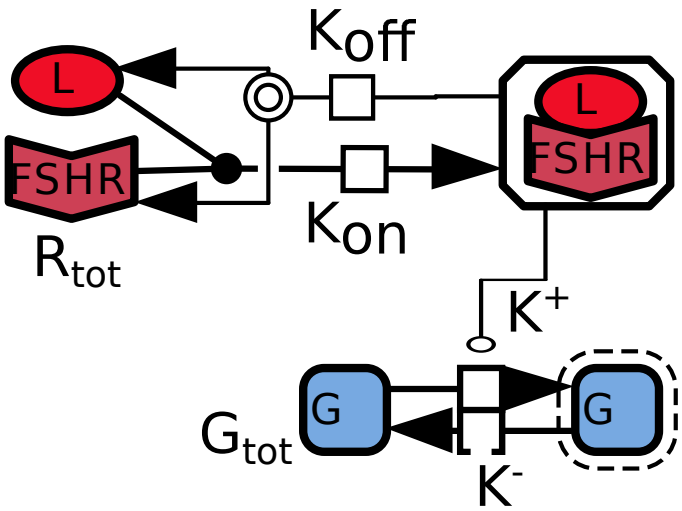


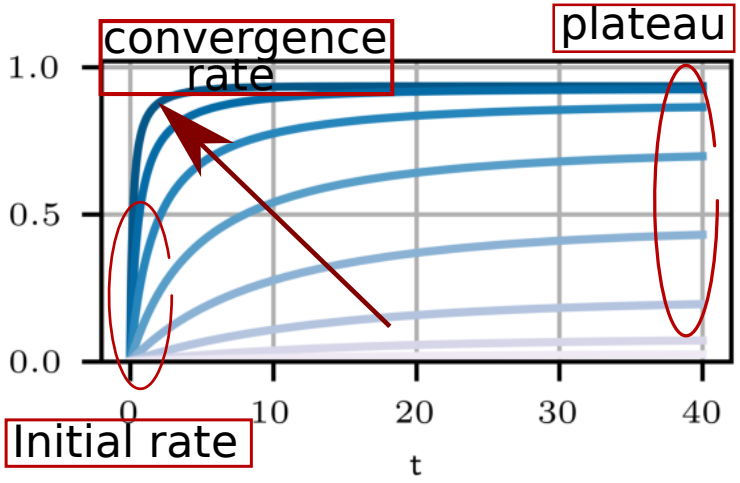
- Our method is a global fitting approach (all pathways, all ligand).
- We enforce Ligand specific parameters through penalization.

Raue et al., Data2Dynamics : a modeling environment tailored to parameter estimation in dynamical systems, Bioinformatics 2015

Steiert et al., L1 regularization facilitates detection of cell type-specific parameters in dynamical systems, Bioinformatics 2016

Can we really infer parameter from kinetic data ?





- Initial rate

$$\frac{1}{2} R_{tot} G_{tot} k_{on} k^{+} [L] t^2$$

- Equilibrium

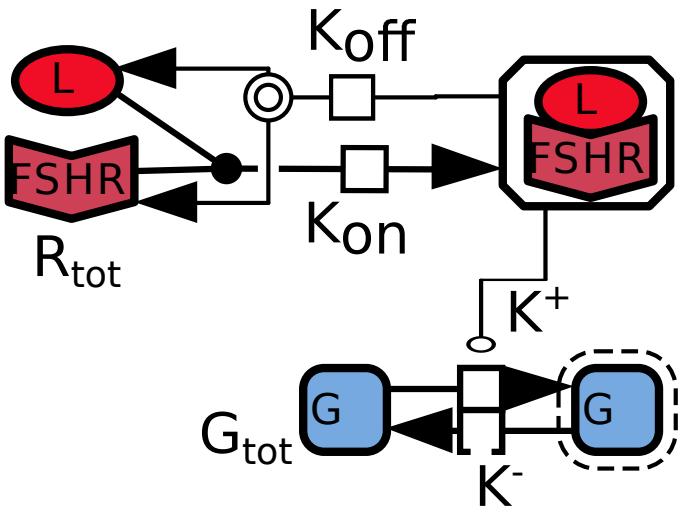
$$\frac{R_{tot} G_{tot} [L]}{K_A + (R_{tot} + K_E)[L]}$$

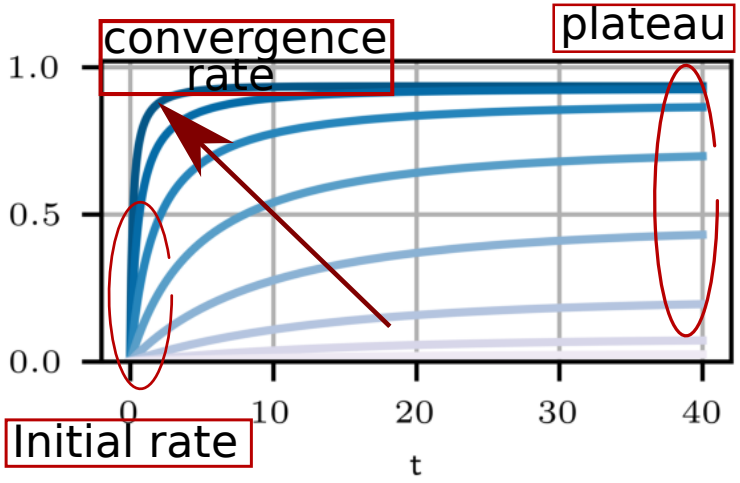
- Convergence rate

$$k^{+} \frac{R_{tot}[L]}{K_A + [L]} + k^{-}$$

$$K_A = \frac{K_{off}}{K_{on}} , K_E = \frac{K^{-}}{K^{+}}$$

Can we really infer parameter from kinetic data ?

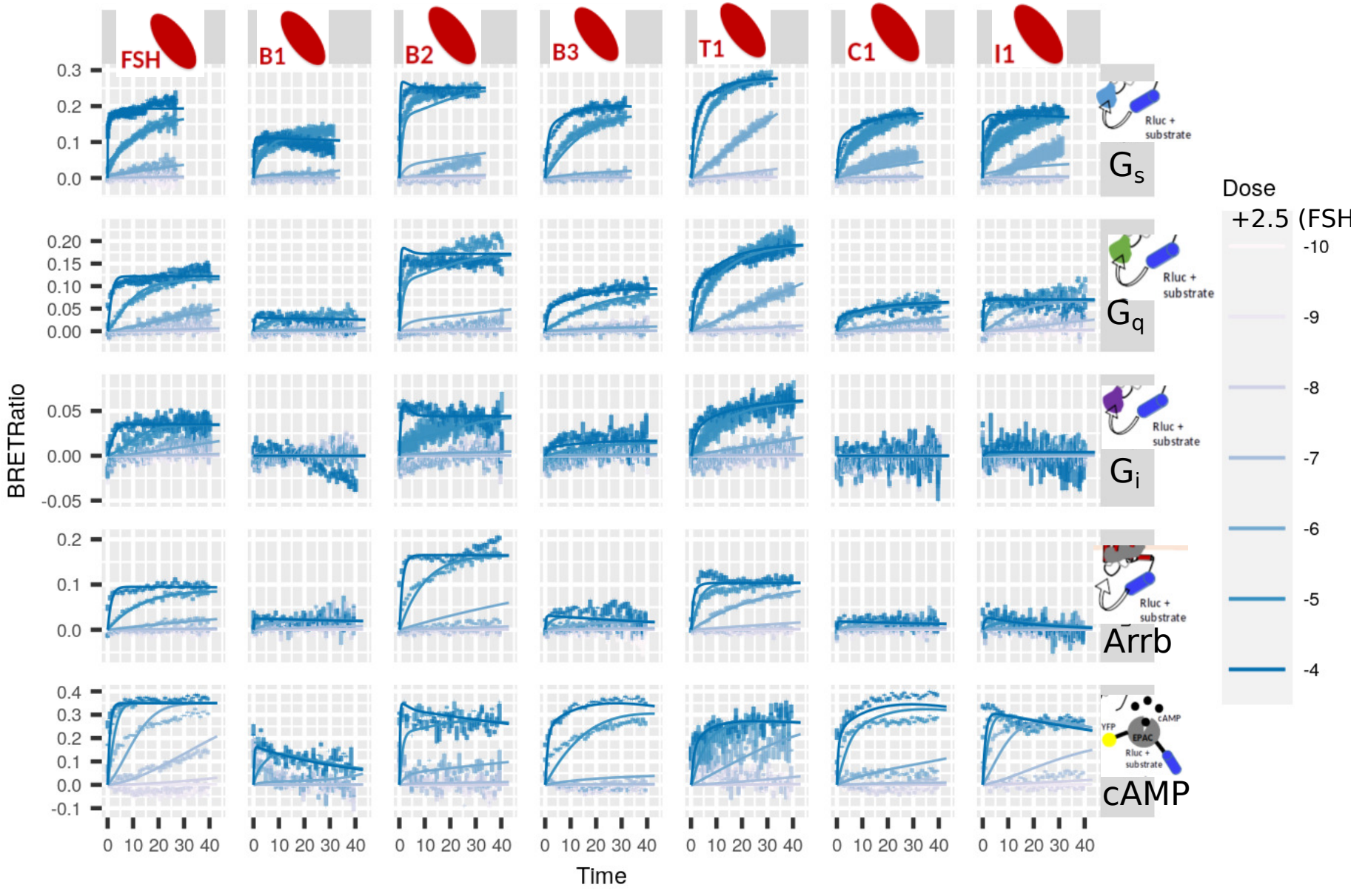


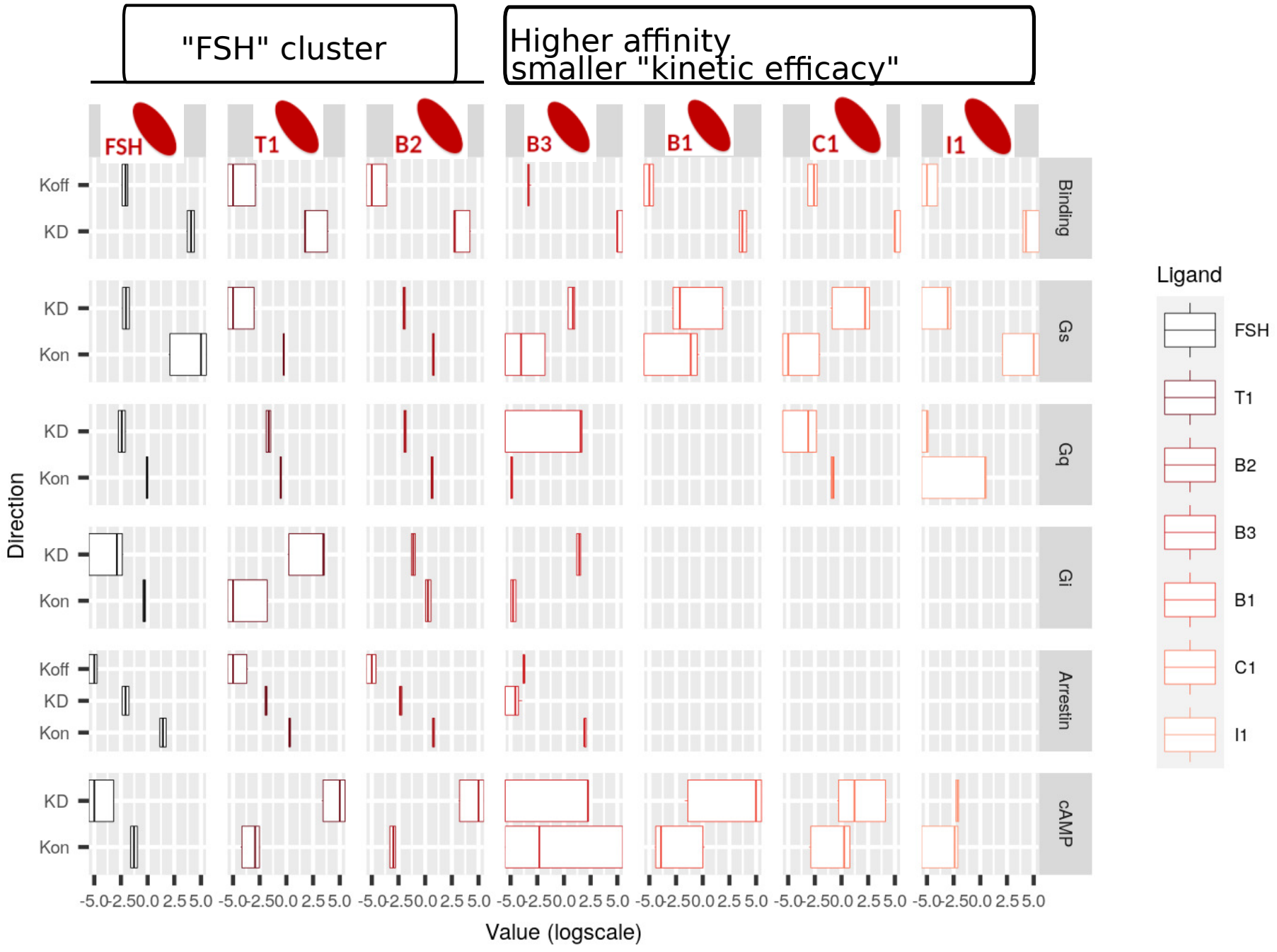


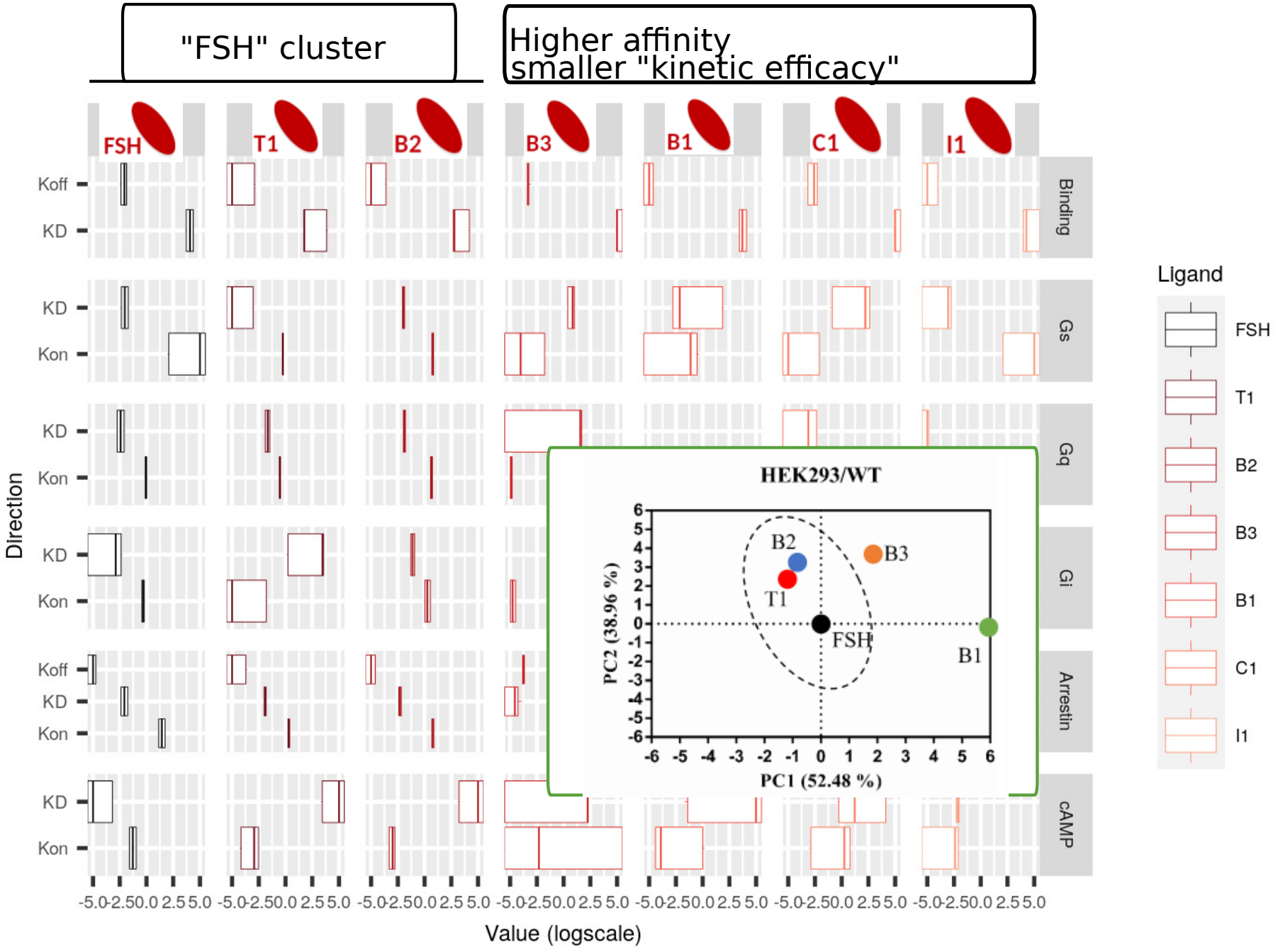
- Initial rate $\frac{1}{2} R_{tot}\, G_{tot}\, k_{on} k^{+} [L] t^2$
- Equilibrium $\frac{R_{tot}\, G_{tot} [L]}{K_A + (R_{tot} + K_E)[L]}$
- Convergence rate $k^{+} \frac{R_{tot}[L]}{K_A + [L]} + k^{-}$

→ In practice the global fitting improves parameter identifiability.

→ Low doses and long time signal are important.


FSH
B1
B2
B3
T1
C1
I1
Rluc + substrate
G_s
G_q
G_i
Arrb
YFP
cAMP
EPAC
cAMP
BRETRatio
Time
Dose
+2.5 (FSH
-10
-9
-8
-7
-6
-5
-4

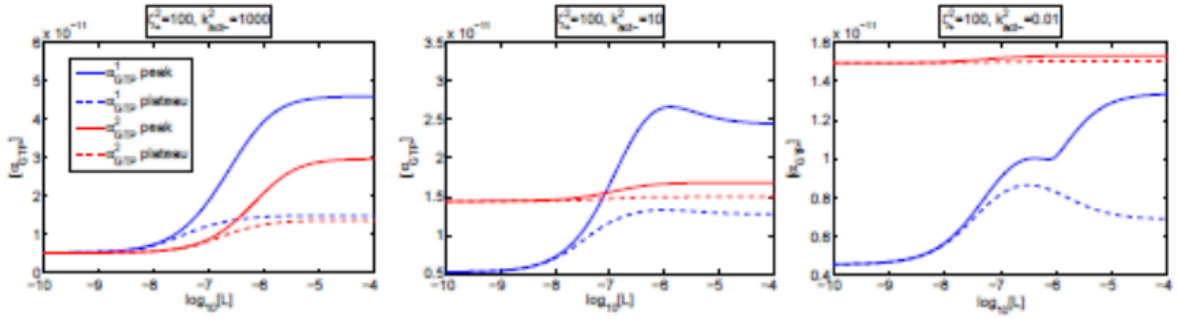

"FSH" cluster
Higher affinity
smaller "kinetic efficacy"
FSH
T1
B2
B3
B1
C1
I1
Binding
Gs
Gq
Gi
Arrestin
cAMP
Koff
KD
Kon
Direction
-5.0 -2.5 0.0 2.5 5.0
Value (logscale)
Ligand
FSH
T1
B2
B3
B1
C1
I1


"FSH" cluster
Higher affinity
smaller "kinetic efficacy"
FSH
T1
B2
B3
B1
C1
I1
Koff
KD
Kon
Binding
Gs
Gq
Gi
Arrestin
cAMP
Direction
Value (logscale)
-5.0 -2.5 0.0 2.5 5.0
HEK293/WT
PC1 (52.48 %)
PC2 (38.96 %)
Ligand
FSH
T1
B2
B3
B1
C1
I1

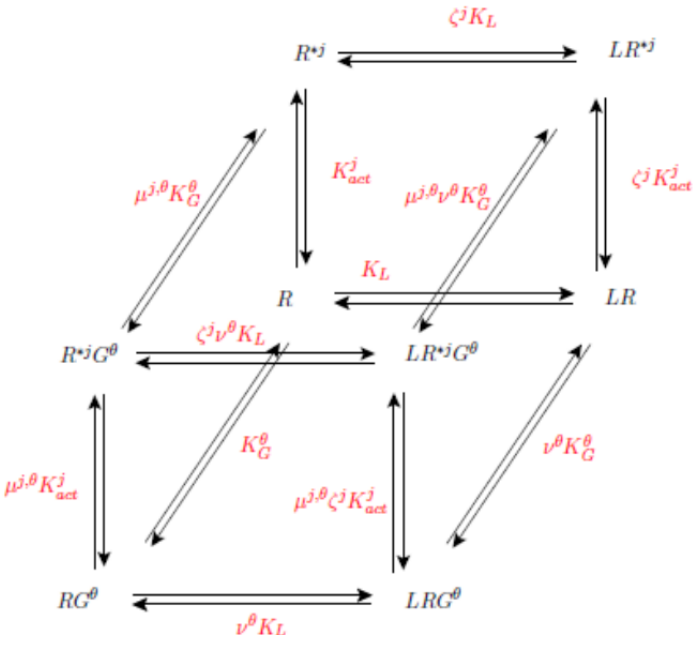
Conclusions

- Dynamical reaction network framework has many different applications.
- Its a powerful framework to reveal comprehensive spatio-temporal patterns behind signaling pathways complexities.
- Its a powerful framework to analyze quantitatively time series data in signaling pathways.
- Adequate tools foster necessary interdisciplinary collaborations by providing a common language.

Some applications : Understanding G protein activation cycle

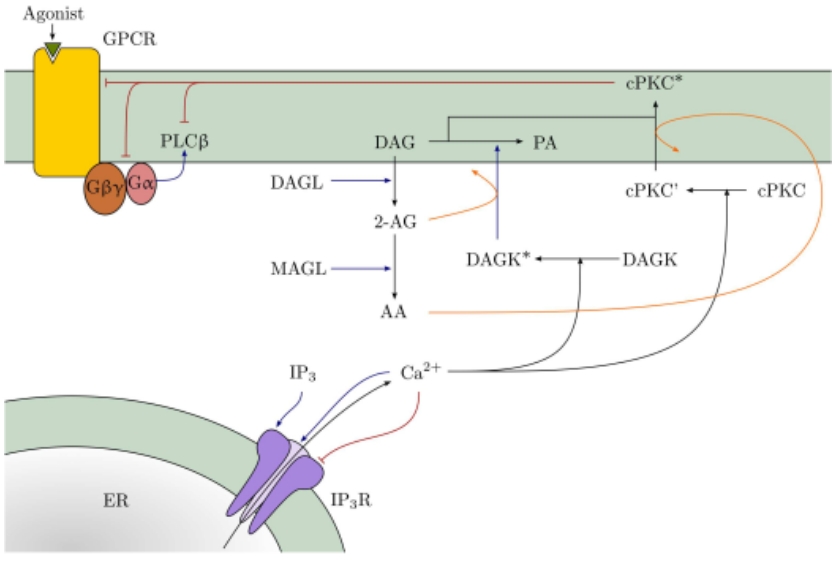


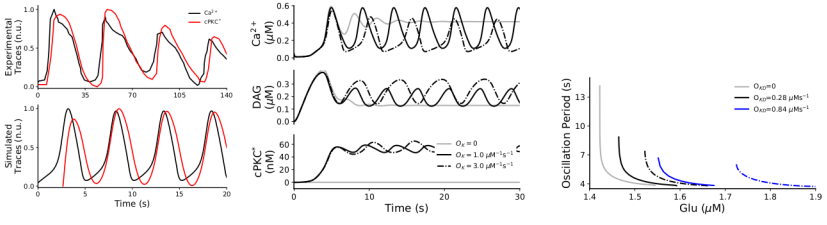
$$\alpha^{\theta}_{GTP} \underset{k_{hyd-}}{\overset{k_{hyd+}}{\rightleftharpoons}} \alpha^{\theta}_{GDP}, \qquad \alpha^{\theta}_{GDP} + \beta\gamma^{\theta} \underset{k_{RA-}}{\overset{k_{RA+}}{\rightleftharpoons}} G^{\theta}.$$



Bridge, Meads, Frattini, Winfield, Ladds, Modelling and simulation of biased agonism dynamics at a G protein-coupled receptor, J. Theoret. Biol. 442 :44–65, 2018

Some applications : Shedding light on GPCR-induced Calcium oscillations in Astrocytes





De Pittà, Ben-Jacob, Berry, G protein-coupled receptor-mediated calcium signaling in astrocytes, in Computational Glioscience, Springer 2019.