Building GPCR signalisation networks. Example of the FSH receptor

Romain Yvinec

Mathematics of system biology

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Systems Biology

Motivation

(Bio)chemical reaction network formalism

Practice !

Outline

Systems Biology

- Describe the behaviors and functions of a system (*cell, individual, ecosystem*) by studying interactions between its constituents (*molecules, tissue, individuals*) : holistic approach, complex system.
- "Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term" (Denis Noble).

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- Computer science and Mathematical modeling of complex system biology.
- Theory of dynamical systems applied to molecular biology.

Population dynamics
(Birth and death processes)

$$\varnothing \rightleftarrows A$$

Goal : Understand when a population goes to extinct, survive, invades...

Small networks

(Interaction between population, 'toy' molecular models)

Logistique model

$$\begin{aligned} \emptyset &\rightarrow A \\ A + A &\rightarrow \emptyset \end{aligned}$$

Lotka-Volterra model

$$\begin{aligned} \emptyset &\rightarrow A \\ A + B &\rightarrow 2B \\ B &\rightarrow \emptyset \end{aligned}$$

Goal : gives simple description/explanation of yet complex behaviors (oscillation, multi-stability...)

Small networks

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Enzymatic kinetics

$$E + S \rightleftarrows ES \rightleftarrows E + P$$

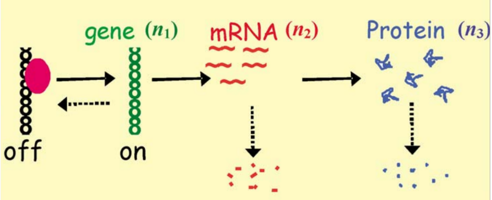
Pharmacology model

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

Goal : gives simple description/explanation of yet complex behaviors (oscillation, multi-stability...)

(Single) Gene Expression

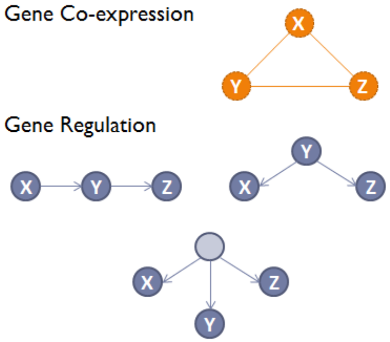
$$
\begin{aligned}
G &\rightarrow G + M \\
M &\rightarrow M + P \\
M &\rightarrow \emptyset \\
P &\rightarrow \emptyset \\
G + P &\rightarrow G_{off}
\end{aligned}
$$



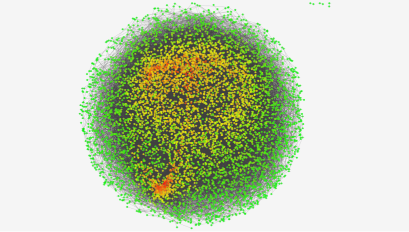
Goal : Understand the variability of level of expression between cells

Co-expression genes network

Small motifs

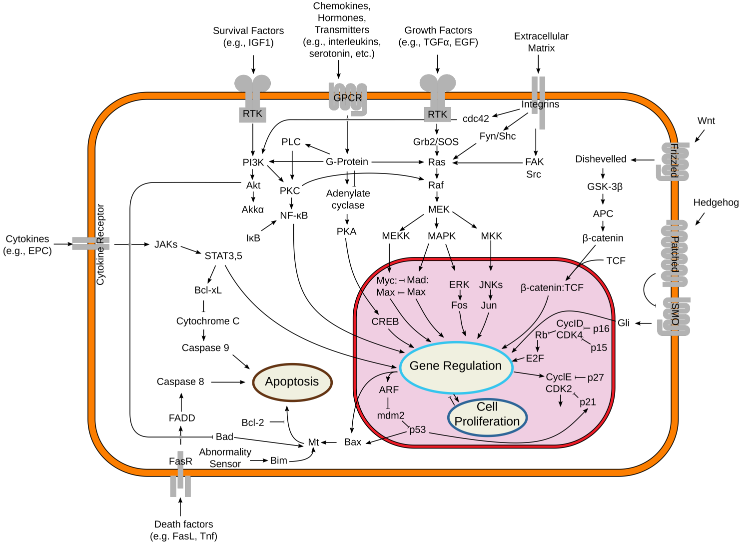


Large networks



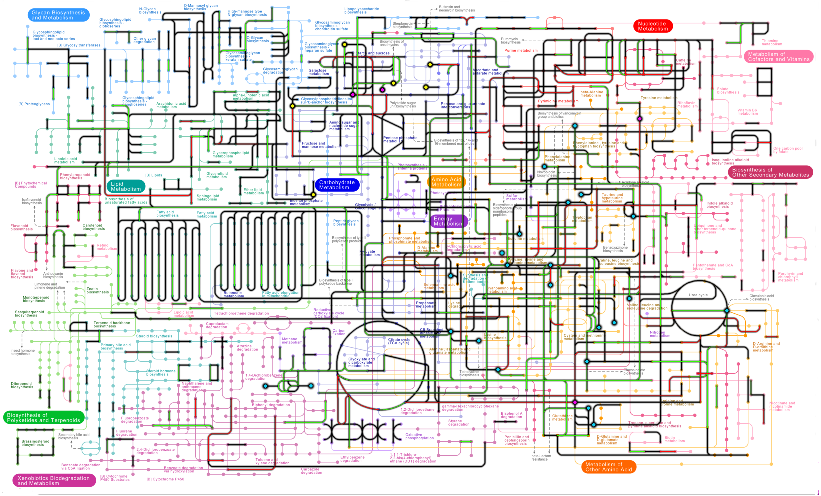
Goal : characterize network topology (and dynamics) associated to certain conditions, diseases, etc.)

Signaling system



Goal : Understand cell response to external stimuli (to control it)

Metabolomic Network



Goal : Understand regulations of key metabolites, explain toxicity or determine phenotype...

Outline

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Possible applications of mathematical modelling

- Understand non-trivial behavior of a biological system (by reproducing this behavior with an understandable model)
- Help to identify intermediate molecules and/or give some evidence for direct interactions between molecules
- Quantify some non-observables quantities, in particular : molecules concentrations, reaction rates.

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Today : Compare quantitatively the effect of two Ligands on two signalling pathways : biais signalling

Outline

Chemical Reaction Network, vocabulary

Definition

A chemical reaction network is given by thee 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).

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- Mass-action law, a function $\kappa : \mathcal{R} \to \mathbb{R}_+^*$ that gives to any reaction a positive parameter (kinetic rate)

Chemical Reaction Network, vocabulary

Exemple

$$\varnothing \rightleftarrows A$$

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

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

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

Chemical Reaction Network, vocabulary

Exemple

$$
\begin{array}{ccc}
A & \rightleftarrows & 2B \\
A + C & \rightleftarrows & D \\
\nwarrow & & \swarrow \\
& B + E &
\end{array}
$$

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

R / P $\mathcal{C} := \{A, 2B, A + C, D, B + E\}$

Reaction $\mathcal{R} := \{A \to 2B, 2B \to A, A + C \to D, D \to A + C, D \to B + E, B + E \to A + C\}$

Chemical Reaction Network, vocabulary

Exemple (the one we will consider later on)

$$
\begin{aligned}
FSH + FSHR &\rightleftarrows FSH/FSHR \\
ATP + FSH/FSHR &\rightarrow cAMP + FSH/FSHR \\
cAMP &\rightarrow AMP \\
\cdots &\rightarrow \cdots
\end{aligned}
$$

Species $\mathcal{E} := \{FSH, FSHR, FSH - FSHR, ATP, cAMP, AMP\}$

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Chemical Reaction Network, "real" example

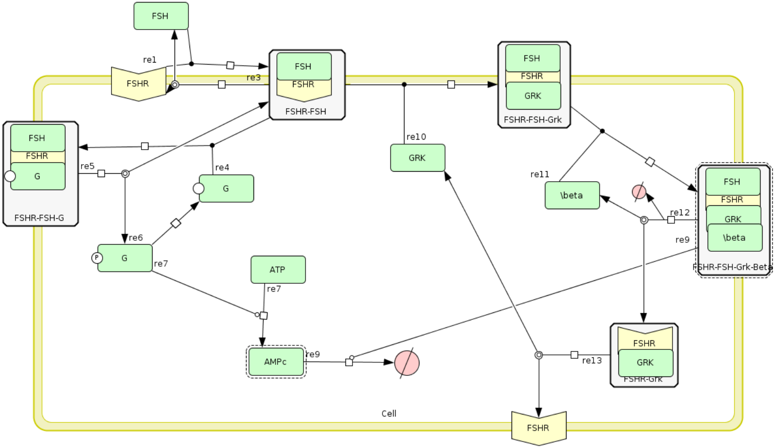

Figure – Classical GPCR models

Chemical Reaction Network, "real" example

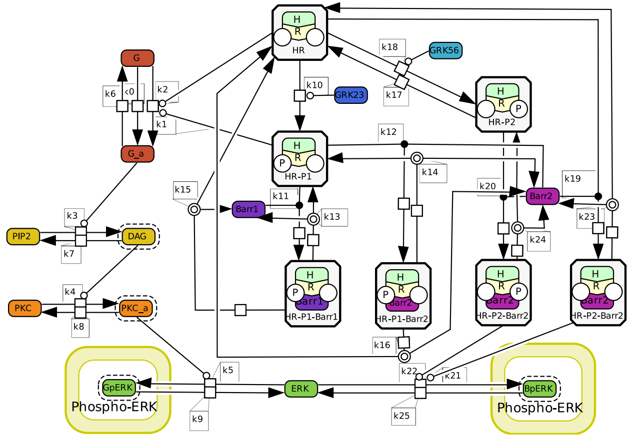

Figure – ERK Phosphorylation pathways, Heitzler et al. MSB 2012

Chemical Reaction Network and Dynamical models

A (deterministic) dynamical model of a Chemical Reaction Network keep track of

- concentration of species : $x_i \in \mathbb{R}_+$, $i = 1..d$.
- Reactions happens continuously and simultaneously
- [Law of Mass action] The velocity of a reaction is proportional to the concentrations of its reactants.
- Systems of Ordinary Differential Equations.

Chemical Reaction Network and Dynamical models

Exemple

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

$$\frac{dx_A}{dt} = 2 - 0.1x_A\,.$$

Chemical Reaction Network and Dynamical models

Exemple

$$
\begin{aligned}
A &\underset{100}{\overset{0.8}{\rightleftharpoons}} 2B \\
A + C &\xrightarrow{0.33} D \\
D &\xrightarrow{1.0} B + E
\end{aligned}
$$

$$
\begin{aligned}
\frac{dx_A}{dt} &= -0.8x_A + 100x_B^2 - 0.33x_Ax_C \,, \\
\frac{dx_B}{dt} &= +0.8x_A - 2 \times 100x_B^2 + x_D \,, \\
\frac{dx_C}{dt} &= -0.33x_Ax_C \,, \\
\frac{dx_D}{dt} &= 0.33x_Ax_C - x_D \,, \\
\frac{dx_E}{dt} &= x_D \,.
\end{aligned}
$$

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 $t_0 = 0$

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

which becomes, in mathematical notations,

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

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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 !

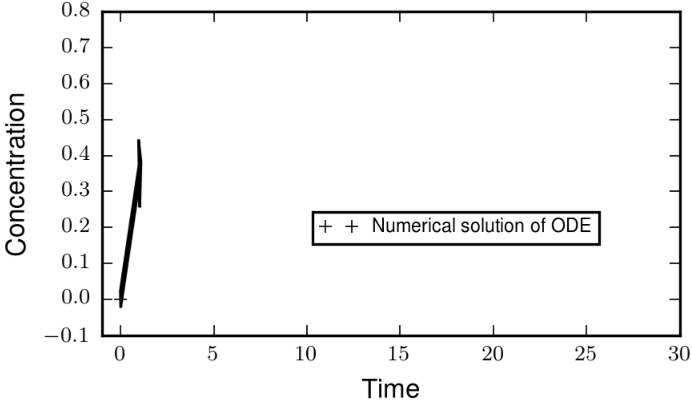

Figure – Solving an ODE

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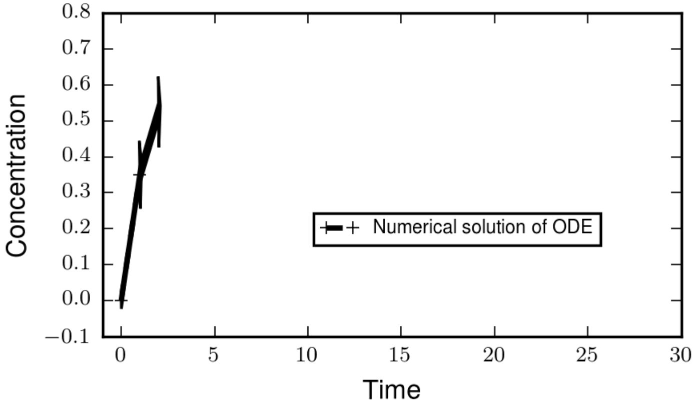

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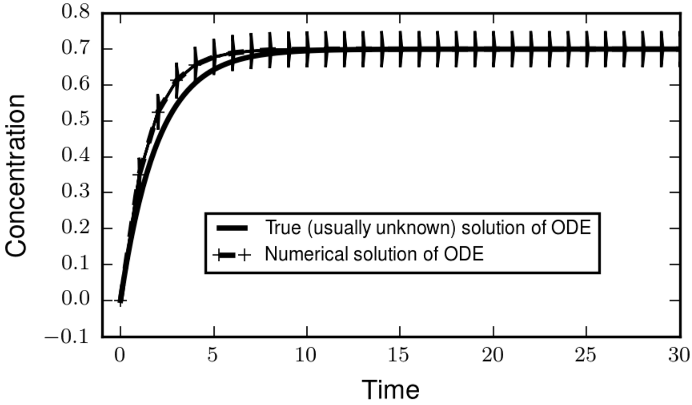

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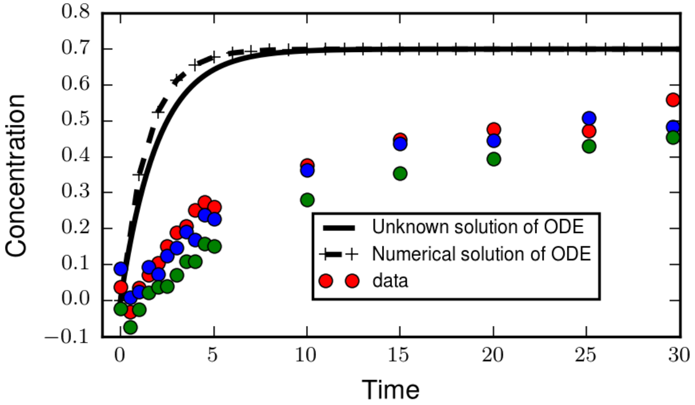

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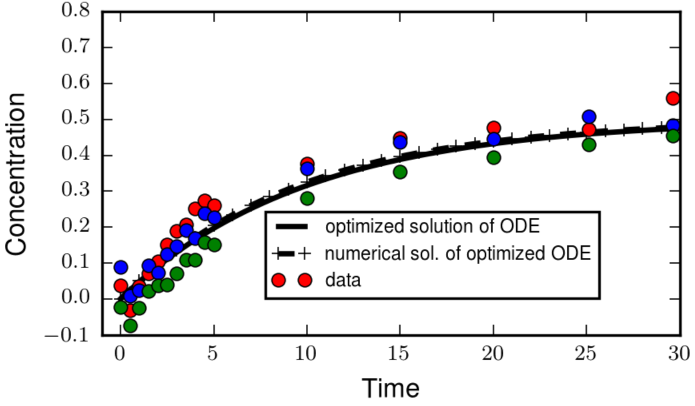

Figure – Solving an ODE

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.

Parameter and network optimization in Chemical Reaction Network

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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.

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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 resolve parameter **non-identifiability** (-> See Likelihood maximization or Bayesian statistics).

Outline

Let's go to practice !

Dose-response curves and operational model

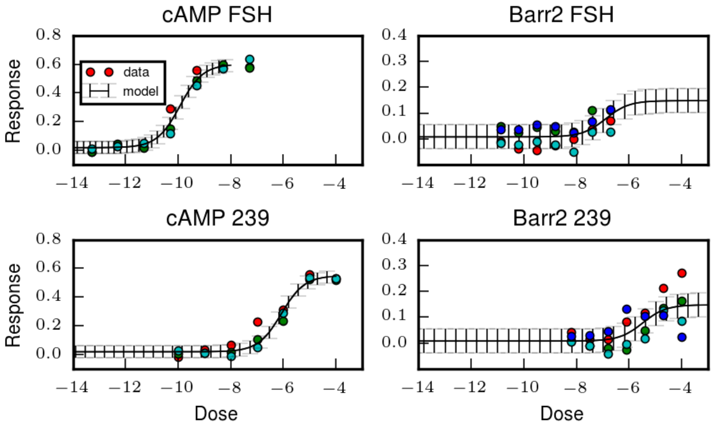

Figure – End-point Dose-response curves

Dose-response curves and operational model

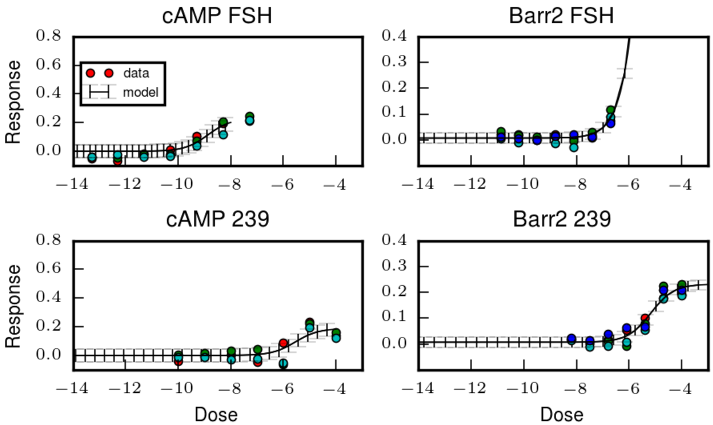

Figure – 2 minutes Dose-response curves

Dose-response curves and operational model

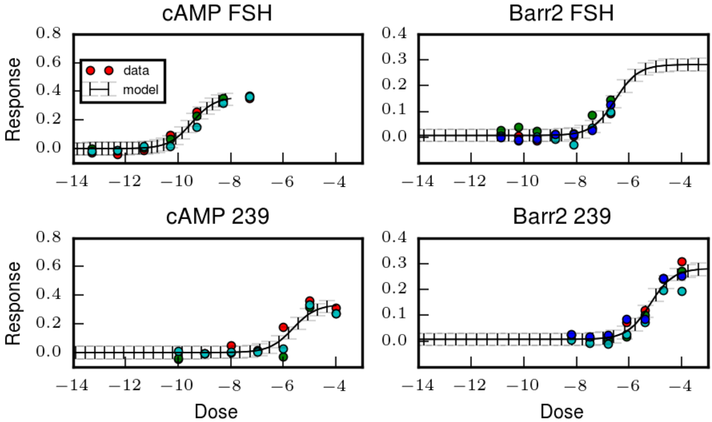

Figure – 5 minutes Dose-response curves

Dose-response curves and operational model

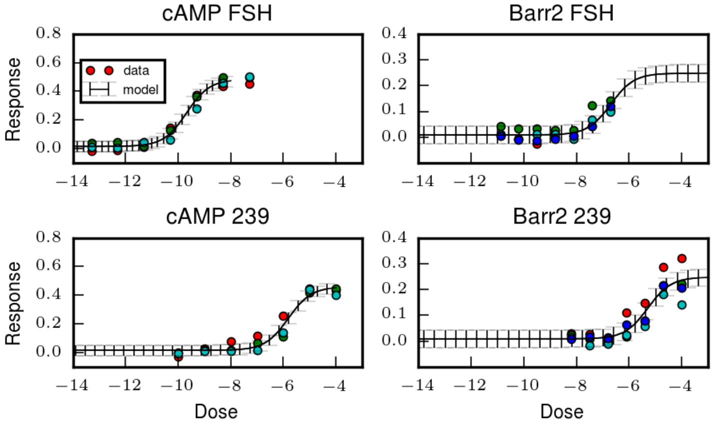

Figure – 10 minutes Dose-response curves

Dose-response curves and operational model

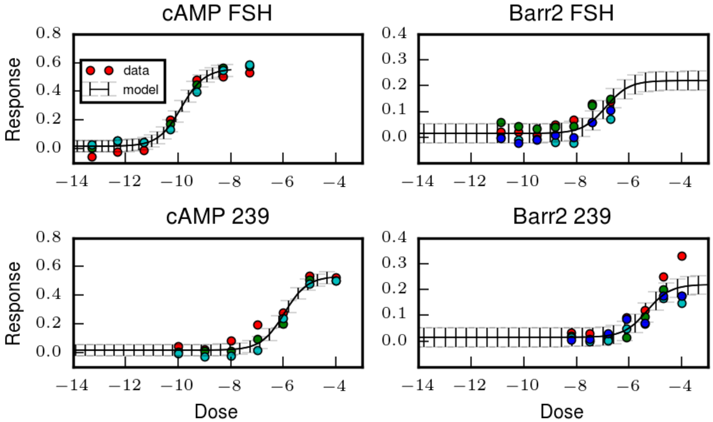

Figure – 20 minutes Dose-response curves

Dose-response curves and operational model

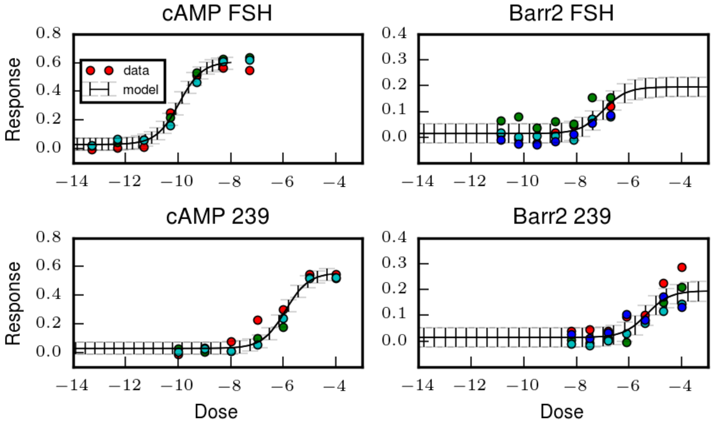

Figure – 30 minutes Dose-response curves

Dose-response curve and kinetic data

- All the analyses of dose-response curves at particular time points might not be consistent with respect to each other !
- See for instance "The role of kinetic context in apparent biased agonism at GPCRs", Klein Herenbrink et al. Nature Communications, 7, 2016.

Dose-response curve and kinetic data

- All the analyses of dose-response curves at particular time points might not be consistent with respect to each other !
- See for instance "The role of kinetic context in apparent biased agonism at GPCRs", Klein Herenbrink et al. Nature Communications, 7, 2016.
- Go for a dynamical model !

Reaction network model

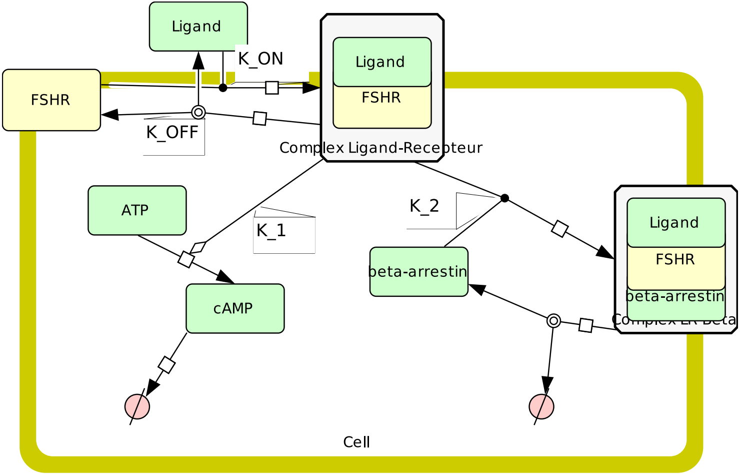

Figure – One possible model

Time-dependent data

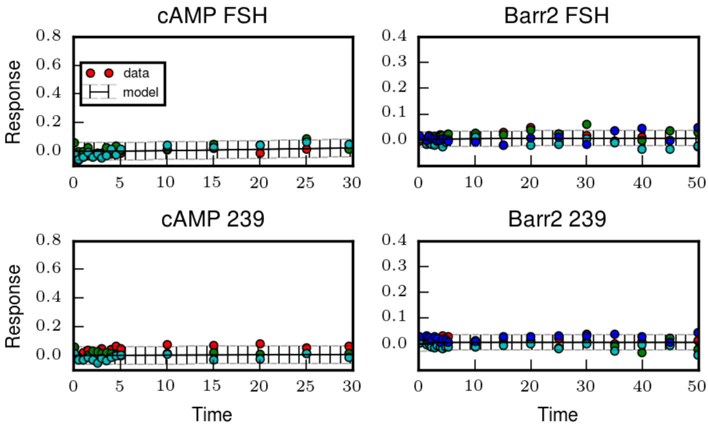

Figure – Dose 1

Time-dependent data

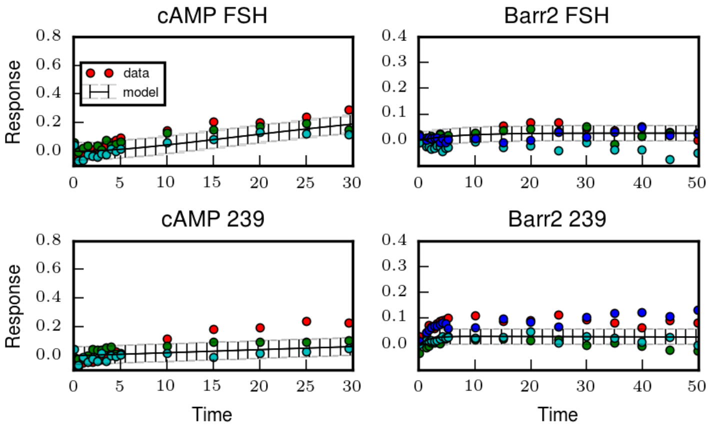

Figure – Dose 2

Time-dependent data

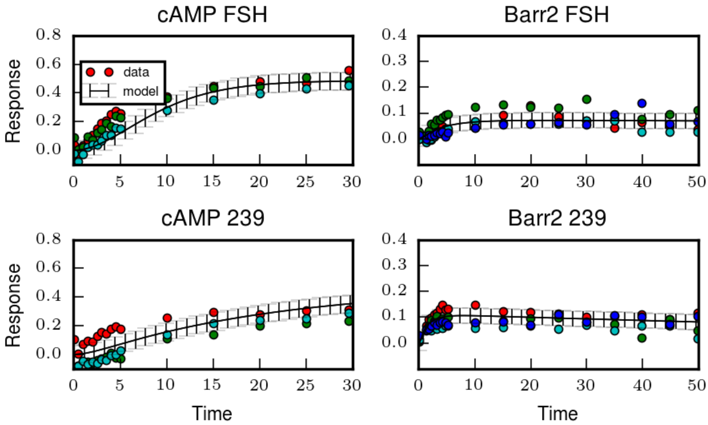

Figure – Dose 3

Time-dependent data

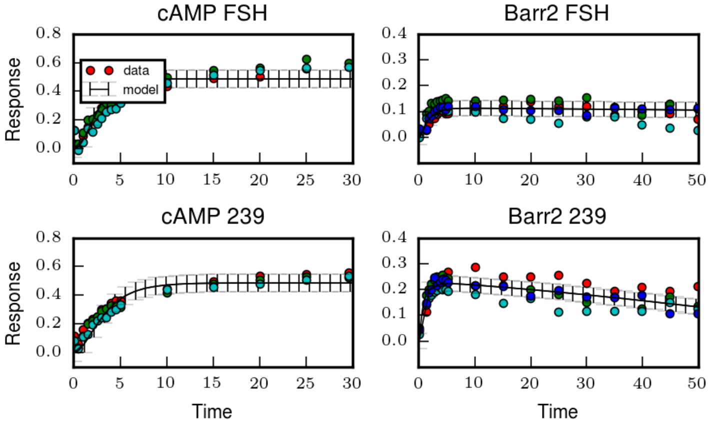

Figure – Dose 4

Time-dependent data

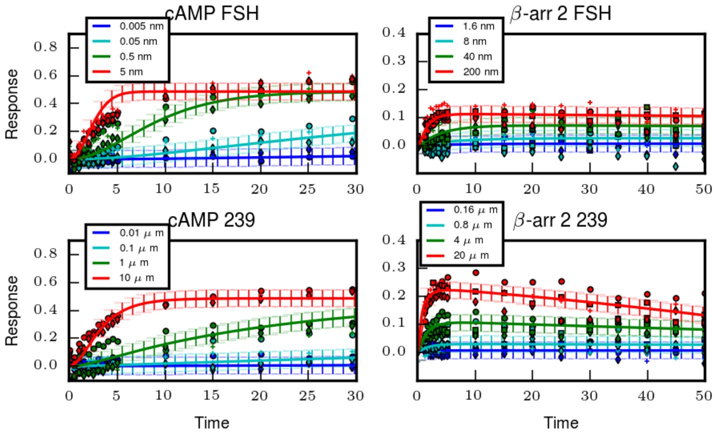

Figure – All doses in one fitted model

Parameter identifiability

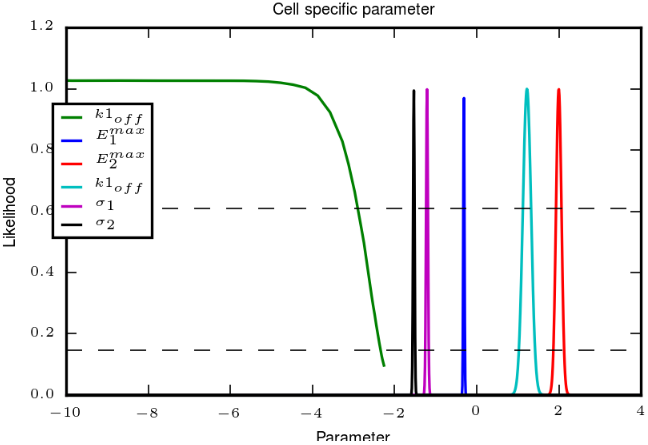

Figure – Cell parameters

Parameter identifiability

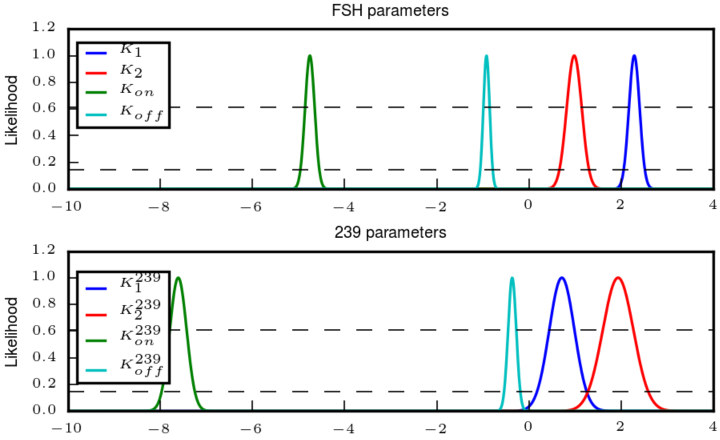

Figure – Ligand specific parameters

Reaction network model : bias between FSH and 239

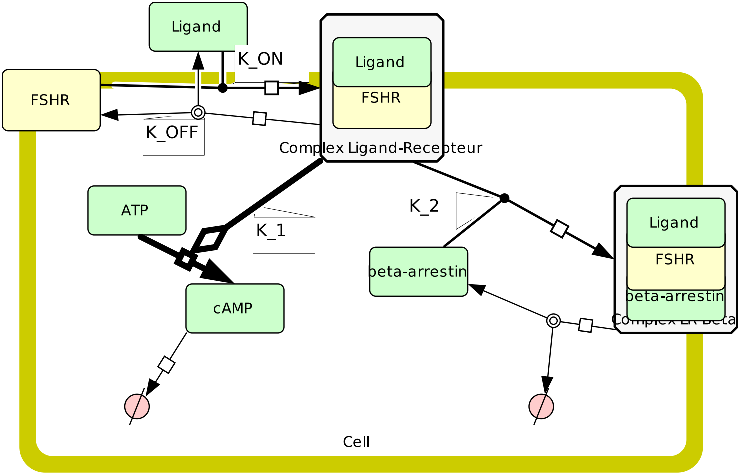

Figure – One possible model for FSH

Reaction network model : bias between FSH and 239

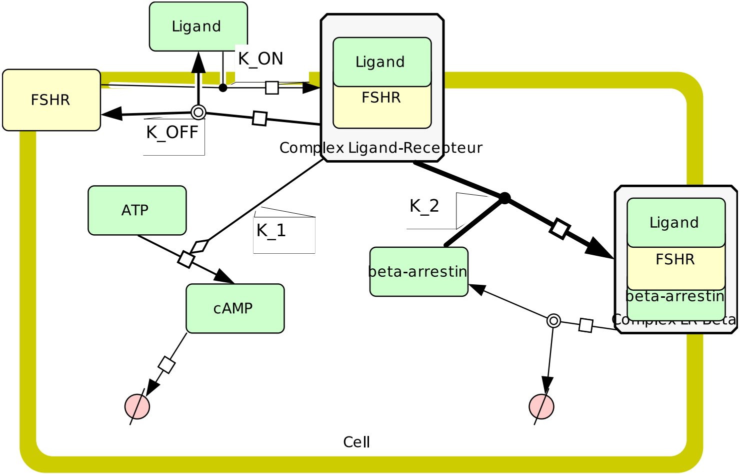

Figure – One possible model for 239