Accurate parameter optimization leads to predictive dynamical models for systems biology

Angiotensin signaling model: Data Fitting, Convergence and Identifiability issues

T. Bourquard[1], M. A. Ayoub[1], D. Heitzler[1], N. Hansen[2], J. Azé[3], R. Yvinec[1], P. Crépieux[1], E. Reiter[1] & A. Poupon[1]

[1] BIOS group, UMR7247, INRA Tours
[2] LRI, UMR8623, CNRS, Orsay
[3]LIRMM, UMR5506, CNRS, Montpellier

Signaling Biology

Modeling and data fitting framework

Optimization for parameter estimation

Results on the angiontensin signaling pathway

Outline

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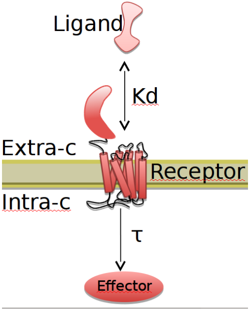
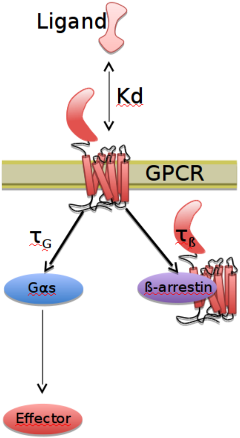
General issues

- A **Ligand** binds a **receptor** in the cell surface and leads to a signal.
- The bound receptor-ligand complex leads to a **cascade of reactions** (enzymatic catalysis, phosphorylation,...) up to some effector molecule that leads to a cellular response.



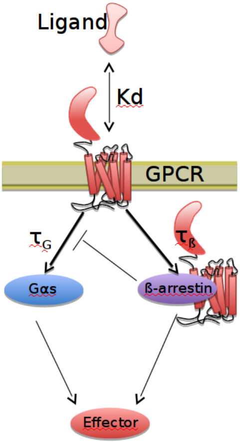
General issues

- A Ligand binds a receptor and signals.
- The bound receptor-ligand complex leads to a cascade of reactions.
- **G Protein Coupled Receptor** (GPRC) : Family of receptor, widely targeted by drugs.
- Two main pathways : **G protein** pathway and β-**arrestin** (signal vs internalization)



General issues

- A Ligand binds a receptor and signals.
- The bound receptor-ligand complex leads to a cascade of reactions.
- G Protein Coupled Receptor (GPRC)
- Two pathways : G protein and β-arrestin.
- More complex issues : β-arrestin induced pathway leads to a **different signal on the same effector**.



General issues

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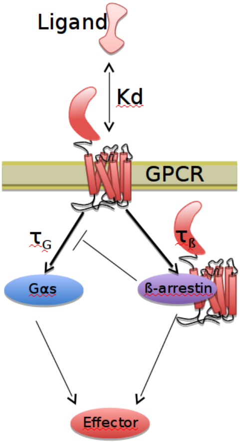
- Complex interactions between G protein and β-arrestin pathways.



Drug discovery

- Signaling through one pathway and not another one : **Bias** (synthetic hormone, mutant receptor, small molecules...)

General issues

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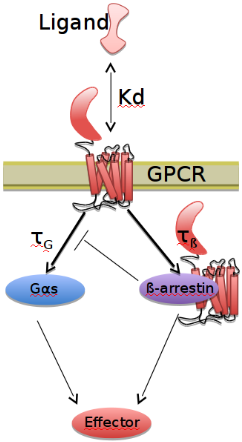


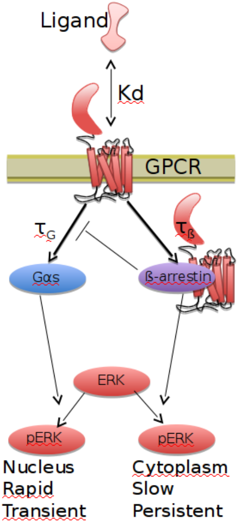
Computational Modeling

- Help **deciphering** the intricate effect of each pathway.
- **Quantify** the precise effect of a specific couple Ligand-Receptor.

GPCR signaling through ERK phosphorylation

The extracellular signal-regulated kinase ERK is activated both by the G protein and the β-arrestin pathway but (*Ahn et al. J Biol Chem (2004)*) :

- The **spatial distribution** are distinct.
- The **kinetics** are distinct.



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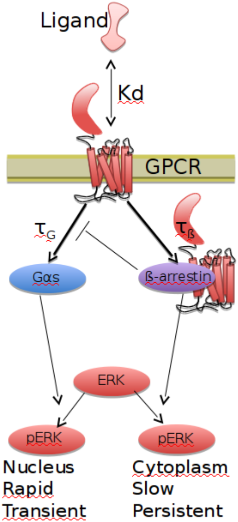
- The kinetics are distinct.

Transient and sustained ERK activation have been shown to regulate cell fates such as **growth** and **differentiation**.(*Sasagawa et al. Nat Cell Biol (2005)*)



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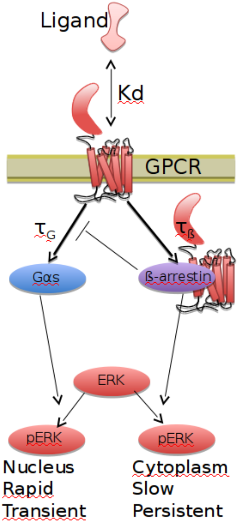
β-arrestin 2 dependent ERK pathway can be activated **independently** of G proteins with a mutant receptor (*Wei et al. PNAS (2004)*).



Case study : Angiotensin receptor

- **Angiotensin** II type 1A receptor (AT1AR) transfected in cultured human embryonic kidney (HEK 293 cells).
- **ERK phosphorylation** data : Phosphorylated ERK in immunoblots, quantified by densitometry (*Kim et al. PNAS 2005*)
- **DAG** accumulation and **PKC** activity data, measured in real time by FRET sensors.
- **Four perturbed** conditions in addition to control :
  - β-arrestin 2 siRNA
  - G protein-coupled receptor kinases (GRK2/3 and GRK5/6) siRNA
  - PKC inhibitor.

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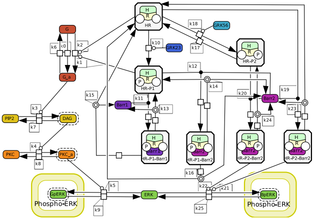
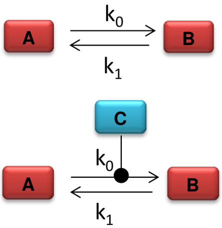
Overview of the methodology

- Starting point : **graph** of interaction of molecules (based on biological knowledge, literature)



Overview of the methodology

- Graph of interaction of molecules
- Law of mass-action : Ordinary Differential Equations (ODE) produce time-dependent trajectories, that depend on **parameters** (kinetic rate, initial condition)

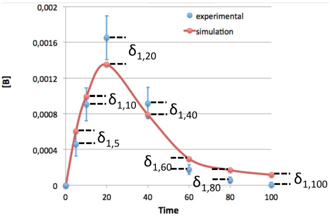


$$\frac{d[B]}{dt} = k_0[A] - k_1[B]\,.$$

$$\frac{d[B]}{dt} = k_0[A][C] - k_1[B]\,.$$

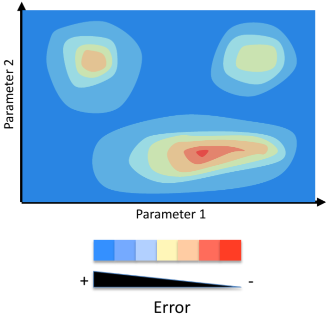
Overview of the methodology

- Graph of interaction of molecules.
- Law of mass-action : ODE.
- Quality of the model based on the introduction of a **cost function** (based on statistical error model, or heuristic arguments).



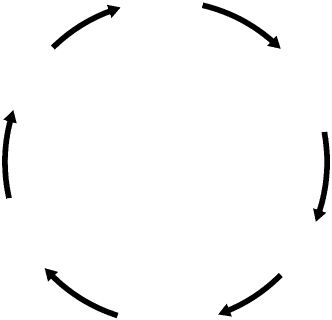
Overview of the methodology

- Graph of interaction of molecules.
- Law of mass-action : ODE.
- Cost function.
- **Optimization** of the cost function (Frequentist / Bayesian approach). Numerical search.



Overview of the methodology

- Graph of interaction of molecules.
- Law of mass-action : ODE.
- Cost function.
- Optimization.
- Validation data, prediction and experimental design...



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The major difficulties are due to

- **Large dimension** of parameter space $(10 - 100)$ and state space (> 10).
- **Few** molecule concentrations measured, and not in absolute numbers.
- Large ODE's may be numerically costly to simulate if they are **stiff**.
- Parameters can be **non-identifiable** (non-convexity, presence of many local minima)

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- **Large dimension** of parameter space $(10 - 100)$ and state space (> 10).
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A variety of methods can be employed : local/global methods and deterministic/stochastic methods, hybrid method.

- **Gradient descent** methods with many random initial start (D2D, *Raue A., et al. Bioinformatics (2015)*).
- **Hybrid** local and global method, based on heuristics (HYPE, T. Bourquard & A. Poupon)

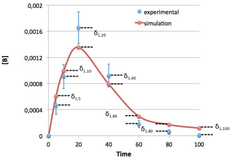
H.Y.P.E

Random set of parameters

Genetic algorithm

CMA-ES

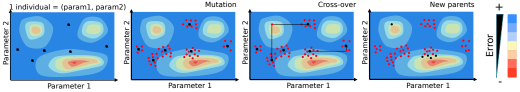
Final set of parameters



Error function

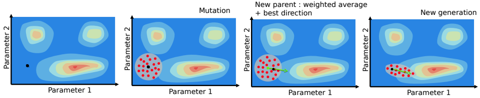
GENETIC ALGORITHM:

- A random set of *n* *parameter sets* is chosen, called **parents.**
- **Mutation** and **cross-over** produce new sets of parameters, as **offsprings**.
- The *n* *best* parameter sets giving the lowest errors are **selected**, and become the parents of next generation.



CMA-ES:

- Start with one set of parameter, called **parent**.
- Local **mutations** (gaussian) produce **offsprings.**
- The next parent is the **average** of the children weighted by their errors.
- Successive steps have **memory**, mutation are made along the direction of the previous steps. (Hansen *et al.* 2003)



A random set of parameters is optimized using Genetic algorithm. The resulting parameter set is optimized using CMA-ES. This operation is repeated until a sufficient number of parameter sets giving small errors is obtained.

Critical assessment of methods

How to judge different method ? How to asses the quality of a fit ?

- **Toy models** with *in silico* simulated data / Benchmark models.
- Absolute value of the **error function**.
- **Speed** of the algorithm.
- **Convergence curve** (number of best error function value over number of runs/function evaluation.
- Robustness of the minima.

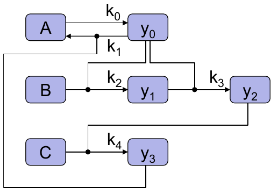
Critical assessment of methods

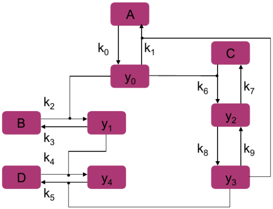
How to judge different method ? How to asses the quality of a fit ?

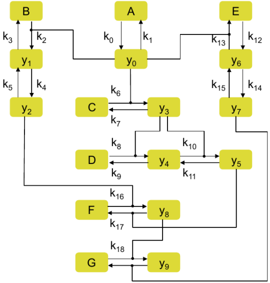
Why/How to deal with Non-Identifiability (NI) ?

- It slows down the numerical search and leads to **unreliable results**.
- **Theoretical** NI : reduction / algebraic relations.
- **Numerical** NI : distinguish between **structural** and **practical** NI. Calculate sensitivity and one-dimensional profile likelihood.

Toy models


A
k_0
y_0
k_1
B
k_2
y_1
k_3
y_2
C
k_4
y_3


A
k_0
k_1
C
y_0
k_6
k_7
k_2
B
y_1
y_2
k_3
k_4
k_8
k_9
D
y_4
y_3
k_5


B
A
E
k_3
k_2
k_0
k_1
k_{13}
k_{12}
y_1
y_0
y_6
k_5
k_4
k_6
k_{15}
k_{14}
y_2
C
y_3
y_7
k_7
k_8
k_{10}
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k_{11}
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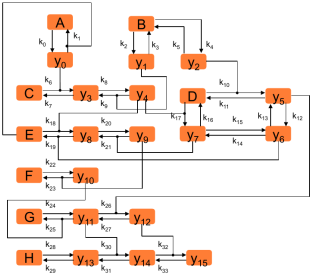
F
y_8
k_{17}
k_{18}
G
y_9


A
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C
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D
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k_{11}
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k_{13}
k_{12}
E
y_8
y_9
y_7
y_6
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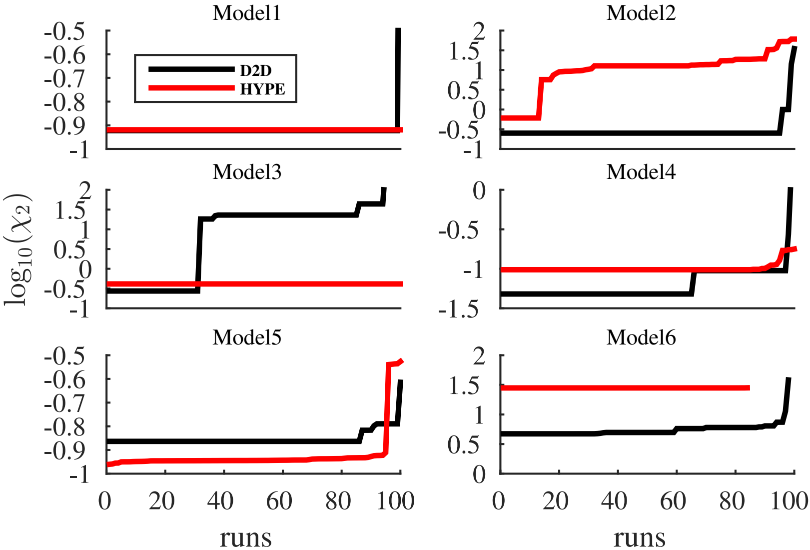
k_{21}
k_{14}
k_{22}
F
y_{10}
k_{23}
k_{24}
k_{26}
G
y_{11}
y_{12}
k_{25}
k_{27}
k_{28}
k_{30}
k_{32}
H
y_{13}
y_{14}
y_{15}
k_{29}
k_{31}
k_{33}

Toy models : HYPE gives comparable results to high quality optimization methods



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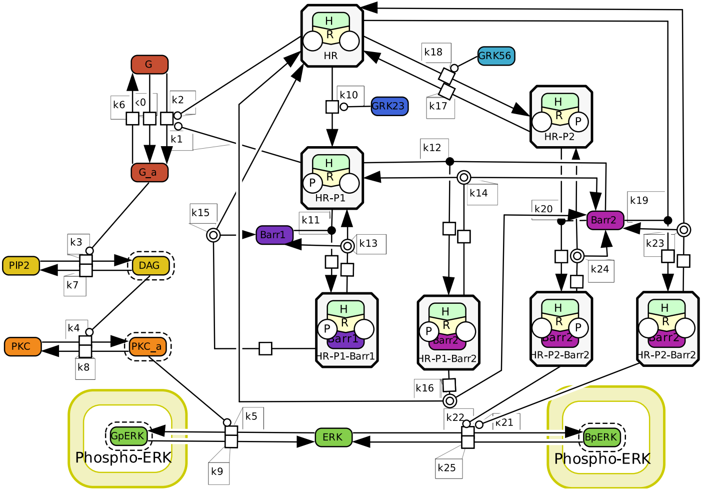
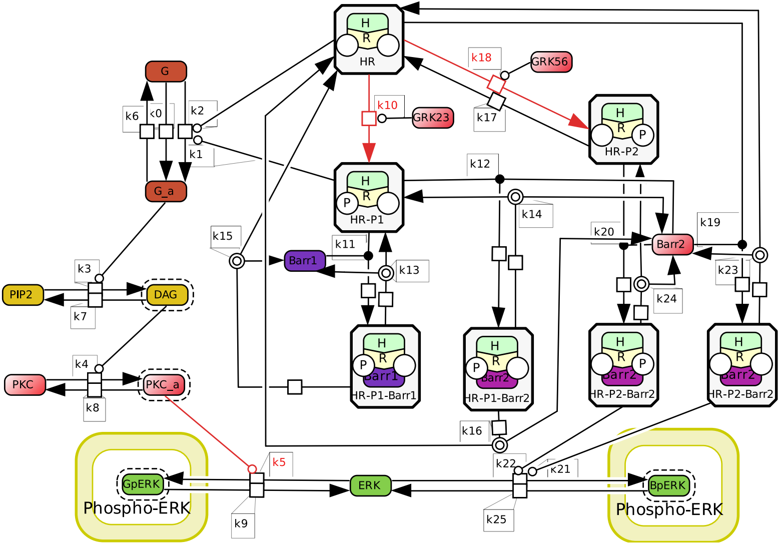
Full model (Heitzler el al. MSB 2012) : 3 pathways

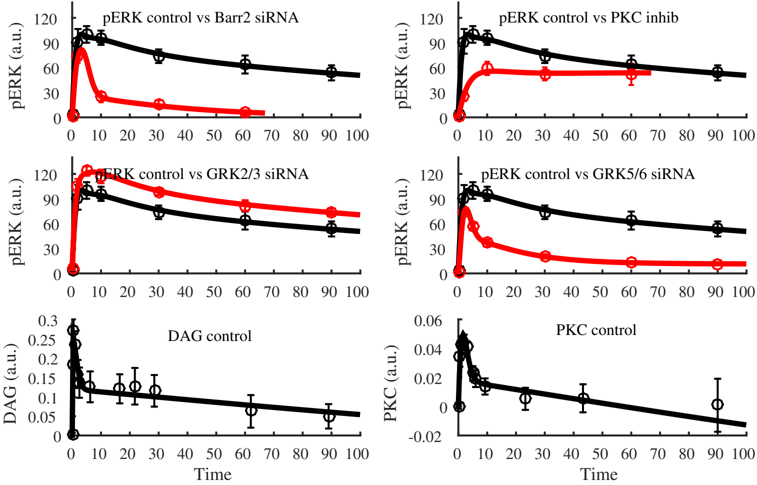
A model that fit the data : role of **G protein-coupled receptor kinases** (GRK) in the balance of signals.



Full model (Heitzler el al. MSB 2012) : Control + 4 pert.



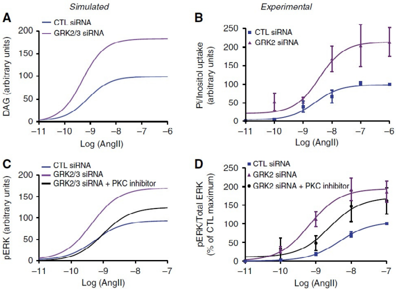
The model fits the data...

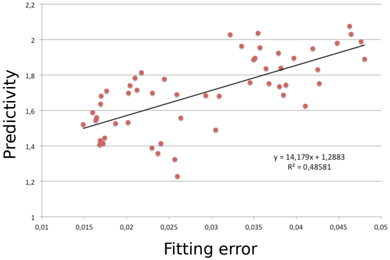


In black : control experiments.

In Red : perturbated experiments.

The model correctly predicts some validation data...

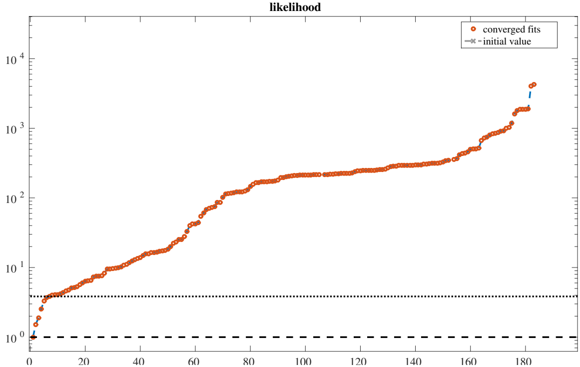




Remark

Good correlation between error and prediction.

…but the convergence is poor, and the identifiability a serious issue !

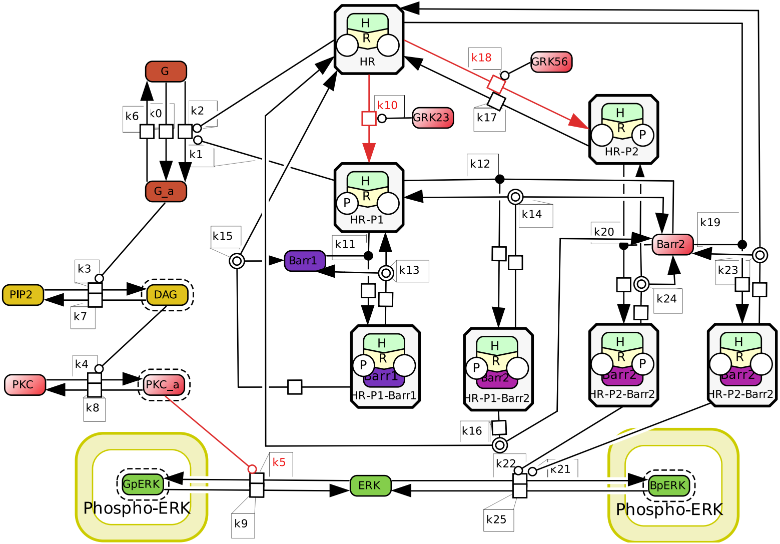


Critical assessments :

- Convergence curve. Identifiability of parameters.
- Parsimonious use of parameters. Model selection.

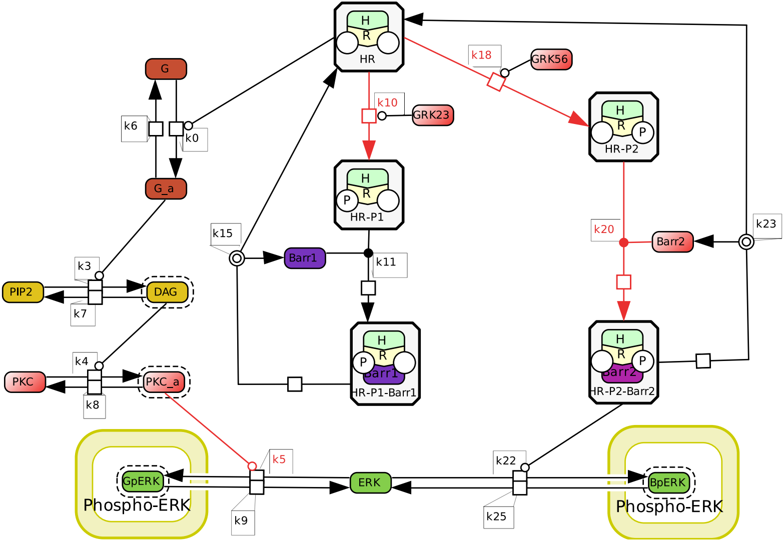
Model reduction

From **50** parameters...



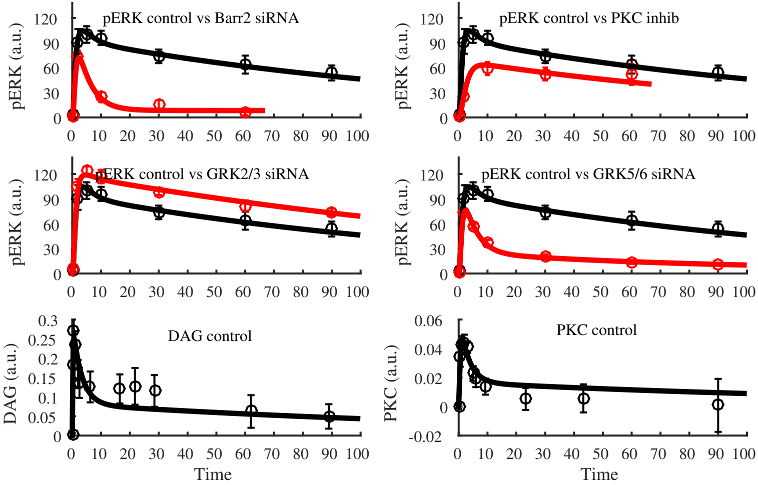
Model reduction

...to **22** parameters !



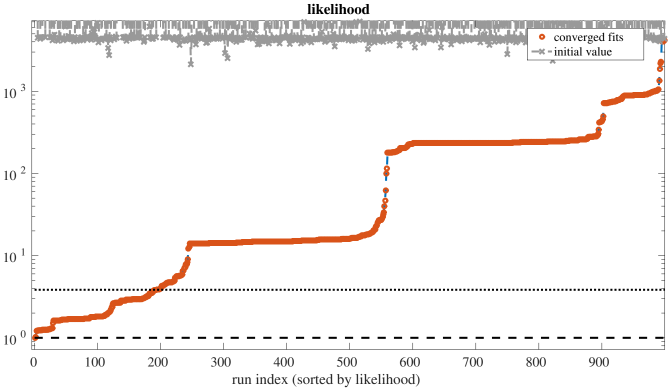
Model reduction

- The reduced model still **fit** (reasonably) well...



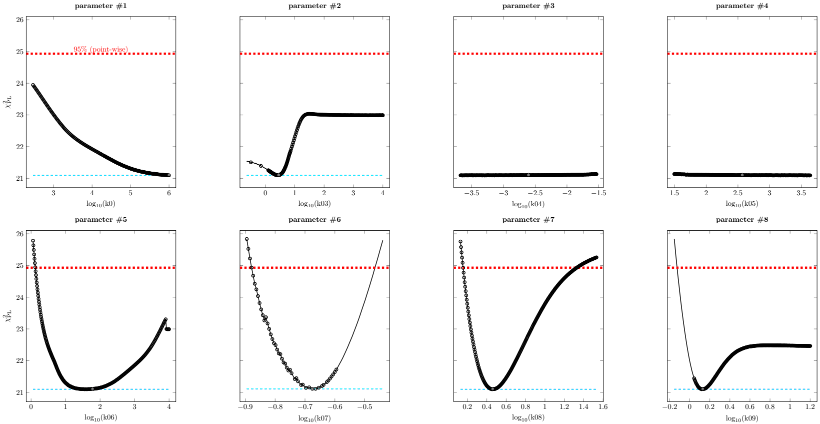
Model reduction

- The reduced model still fit well...
- and the **convergence** is **better**...



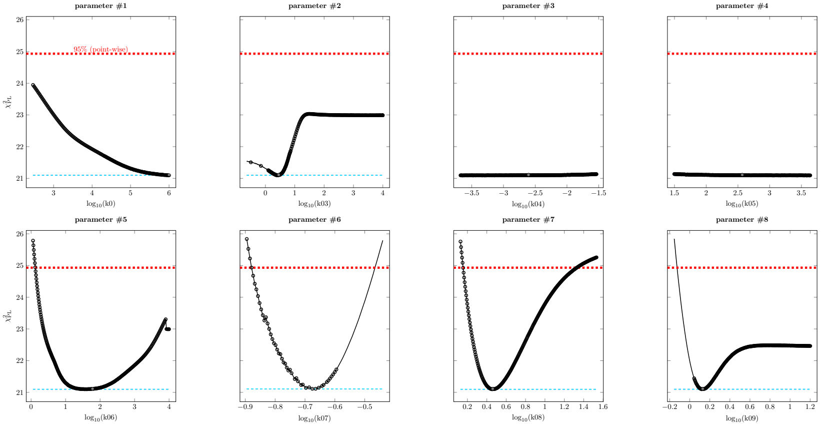
Model reduction

- The reduced model still fit well...
- and the convergence is better...
- but the **identifiability** is still **poor** !

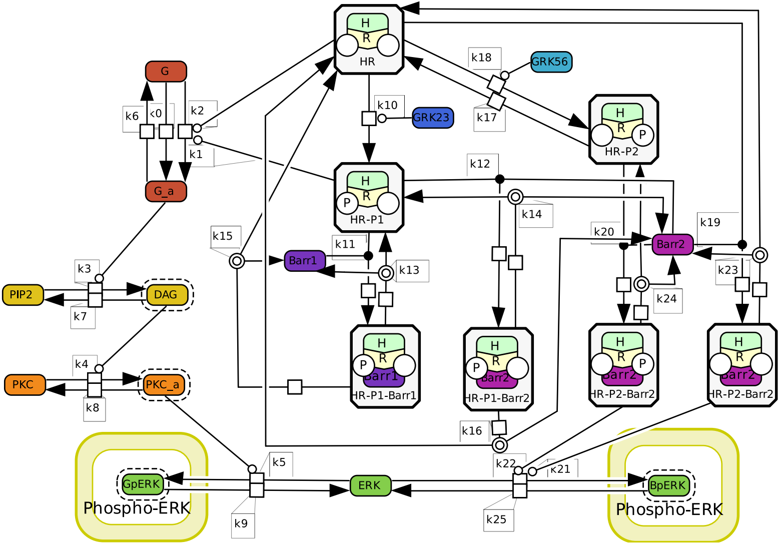


Model reduction

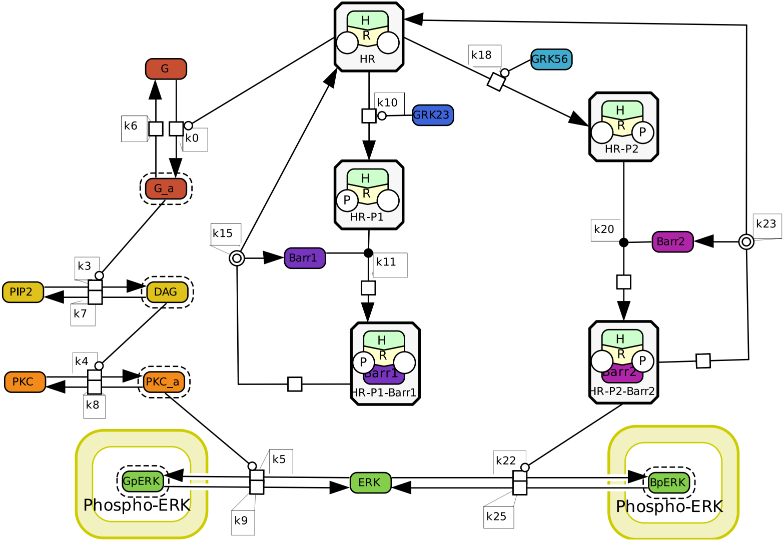
- The reduced model still fit well...
- and the convergence is better...
- but the identifiability is still poor ! Let's **reduced further** ?



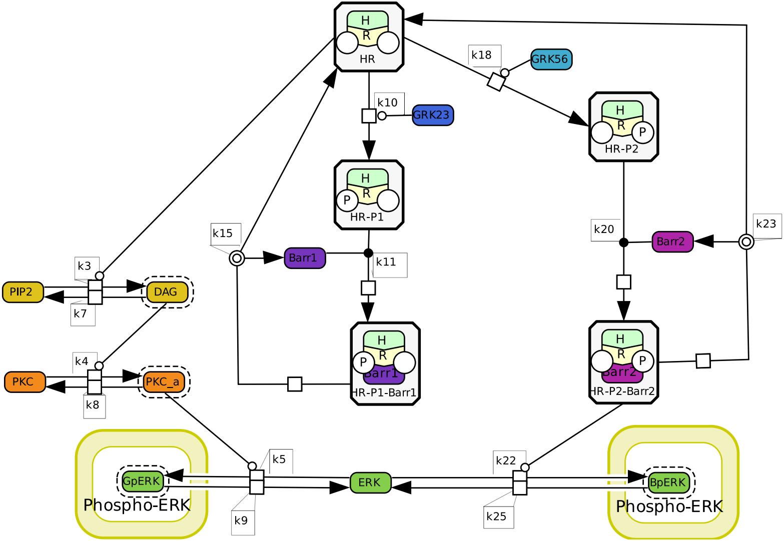
Systematic reduction



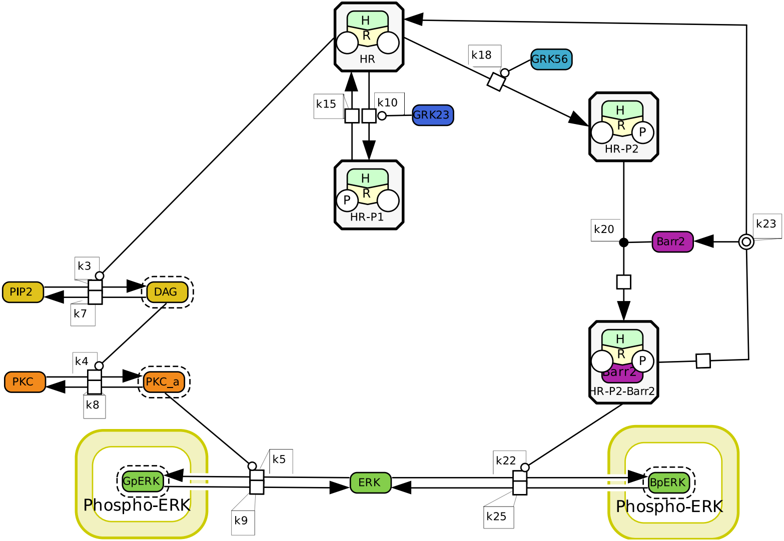
Systematic reduction



Systematic reduction



Systematic reduction



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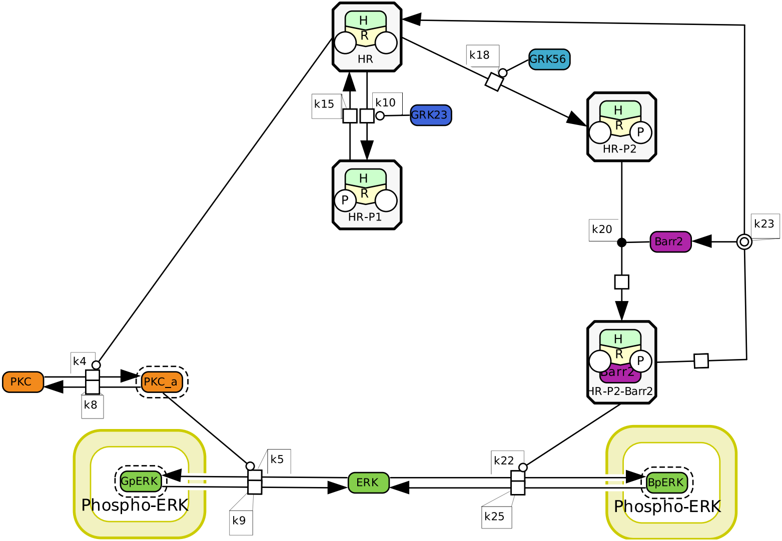
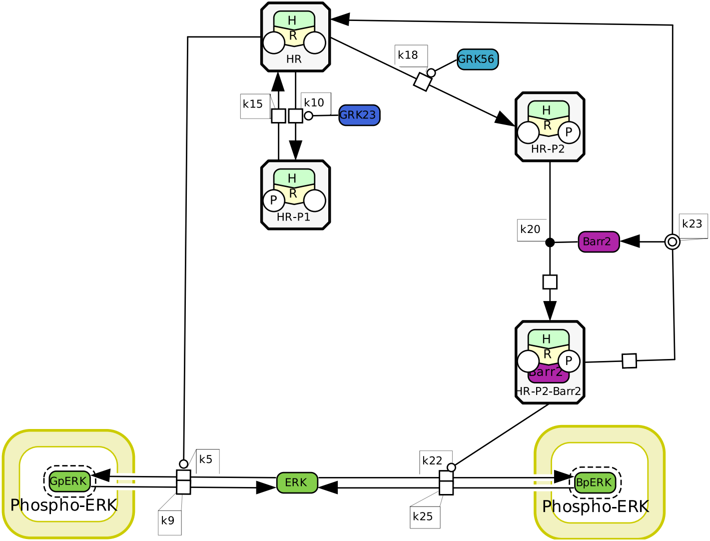
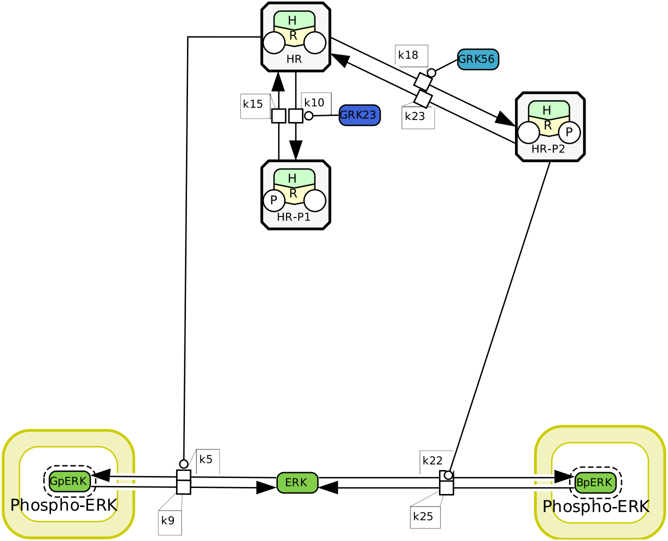


Systematic reduction



Systematic reduction



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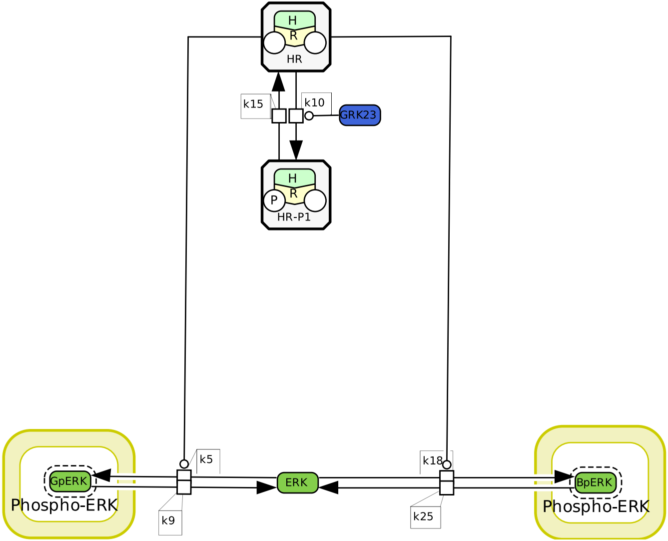
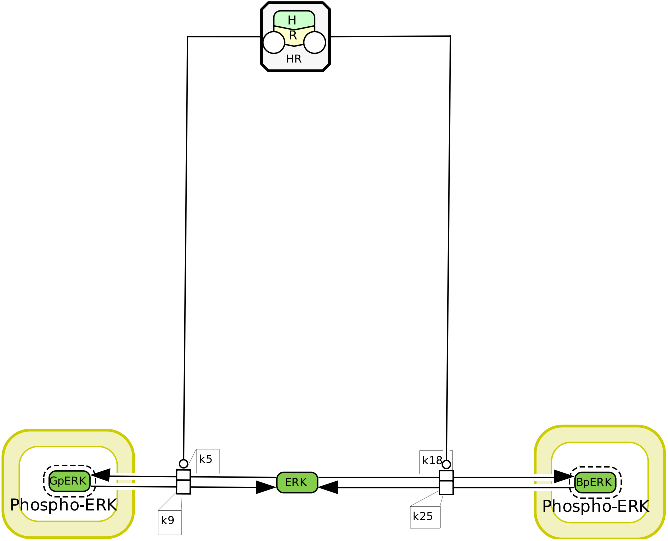


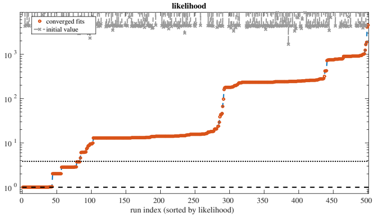
Systematic reduction

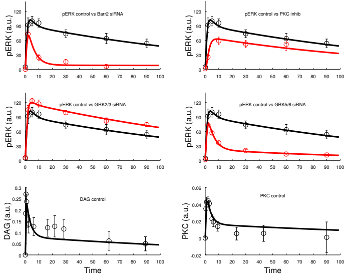


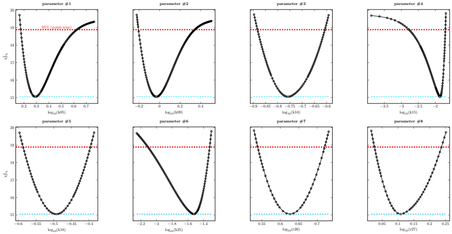
Results

With model selection criteria :

- a model with **19** parameters
- **good convergence** properties (10% of runs reached the optima)
- most parameters are **identifiable**

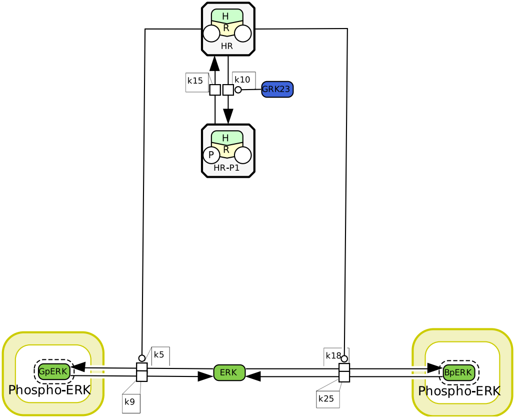






What do we learn (so far) ?

- The **three pathways** are a **necessary** condition to reproduce the data.



What do we learn (so far) ?

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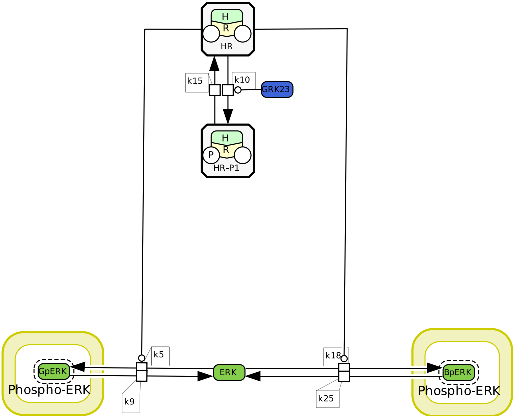
- An internalization pathway, **independent** of the β-arrestin signaling pathway, is mandatory.



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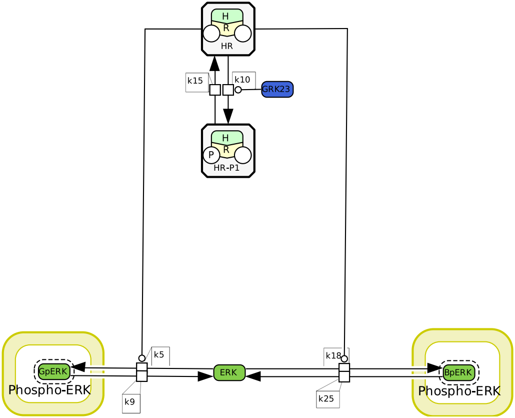
- A **minimal** model with three reversible pathway with 10 parameter is able to fit the **phospho ERK data** and its parameter are **all identifiable**.



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- Three pathways are necessary.
- An independent internalization pathway is mandatory.
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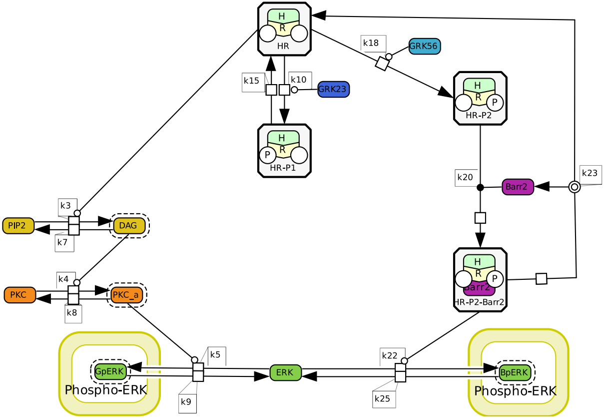
- The best model able to fit **all data** present non-identifiability ⇒ **Experimental design**.



Conclusion

- A full model able to fit the data (*Heitzler el al. MSB 2012*).
- Accurate parameter estimation leads to **accurate prediction**.
- Further improvements with **model reduction/selection**.
- Parameter **identifiability** with a good fit can be achieved.
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Thanks for your attention !

validation data