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Accurate parameter optimization leads to
predictive dynamical models for systems biology
Angiotensin signaling model: Data Fitting, Convergence and
Identifiability issues

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Azé³, R. Yvinec¹, P. Crépieux¹, E. Reiter¹ & A. Poupon¹

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Signaling Biology

Modeling and data fitting framework

Optimization for parameter estimation

Results on the angiotensin signaling pathway

Outline

Signaling Biology

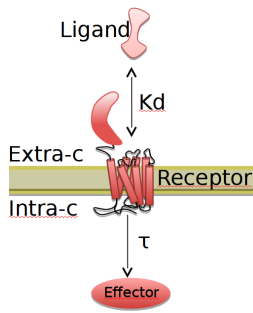
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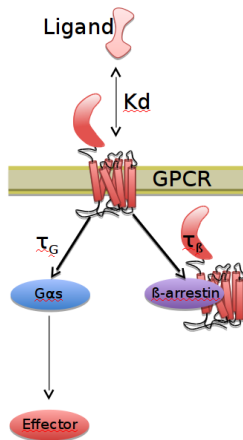
General issues

- ▶ 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.



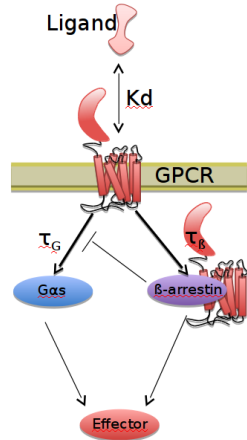
General issues

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

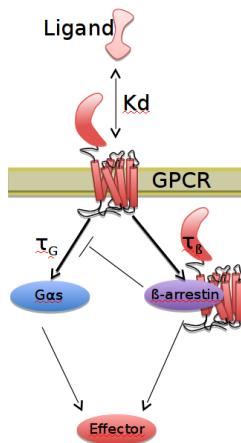


General issues

- ▶ A Ligand binds a receptor and signals.
- ▶ The bound receptor-ligand complex leads to a cascade of reactions.
- ▶ G Protein Coupled Receptor (GPCR)
- ▶ 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...)

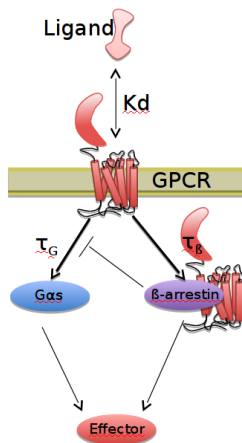


General issues

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- ▶ G Protein Coupled Receptor (GPCR)
- ▶ Complex interactions between G protein and β -arrestin pathways.

Computational Modeling

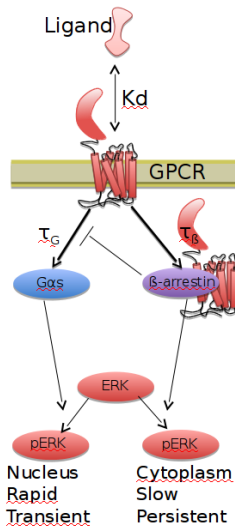
- ▶ Help **deciphering** the intricate effect of each pathway.
- ▶ **Quantify** the precise effect of a specific couple Ligand-Receptor.



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.

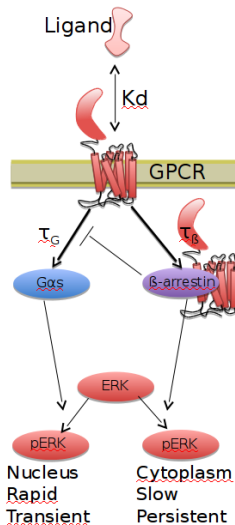


GPCR signaling through ERK phosphorylation

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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)*)

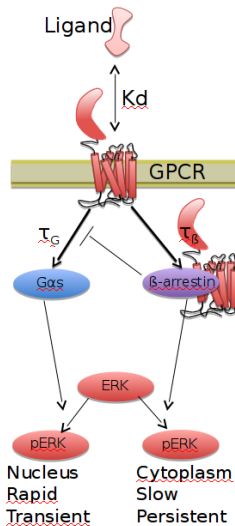


GPCR signaling through ERK phosphorylation

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

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.

Outline

Signaling Biology

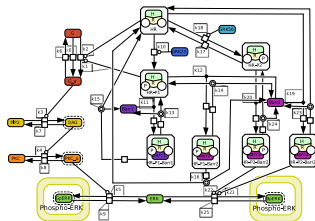
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Overview of the methodology

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

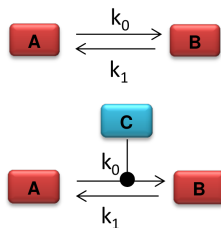


Overview of the methodology

- ▶ 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)

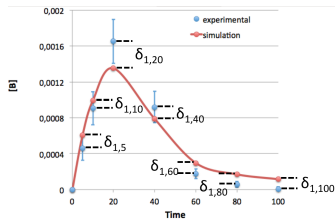
$$\frac{d[B]}{dt} = k_0[A] - k_1[B].$$

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



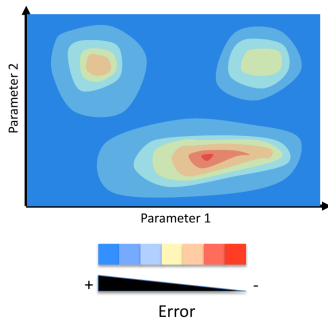
Overview of the methodology

- ▶ 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).



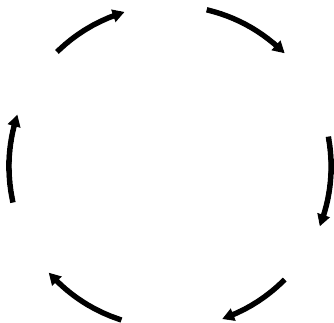
Overview of the methodology

- ▶ 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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A variety of methods can be employed : local/global methods and deterministic/stochastic methods, hybrid method.

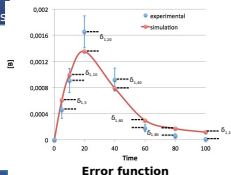
- ▶ **Gradient descent** methods with many random initial start (D2D, Raue A., et al. *Bioinformatics* (2015)).
- ▶ **Hybrid** local and global method, based on heuristics (HYPE, T. Bourquard & A. Poupon)

H.Y.P.E

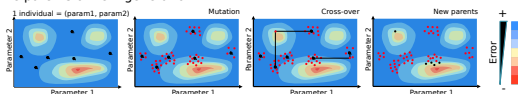
 Random set
of parameters

 Genetic
algorithm

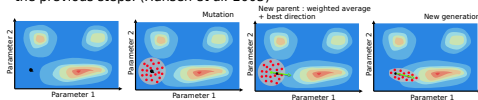
CMA-ES

 Final set
of parameters

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.

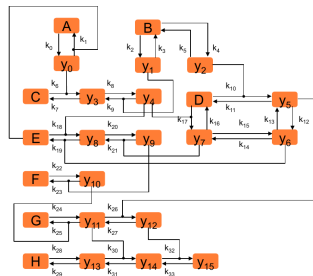
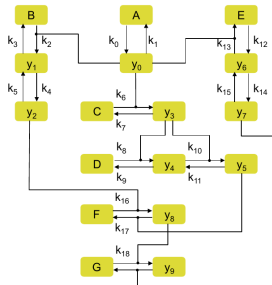
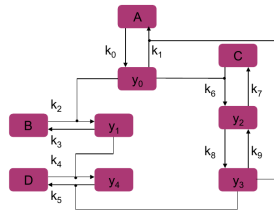
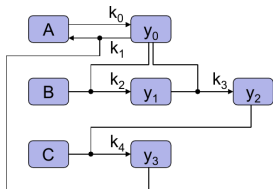
Critical assessment of methods

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

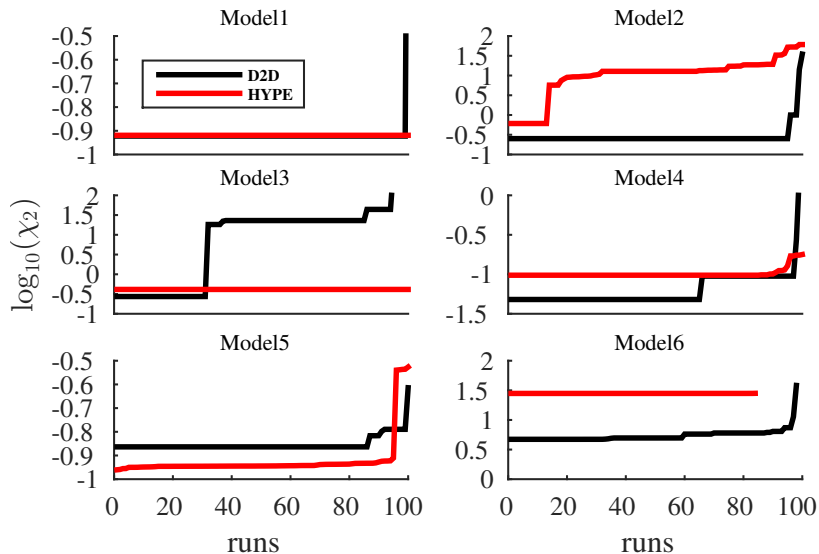
Why/How to deal with Non-Identifiability (NI) ?

- ▶ 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



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



Outline

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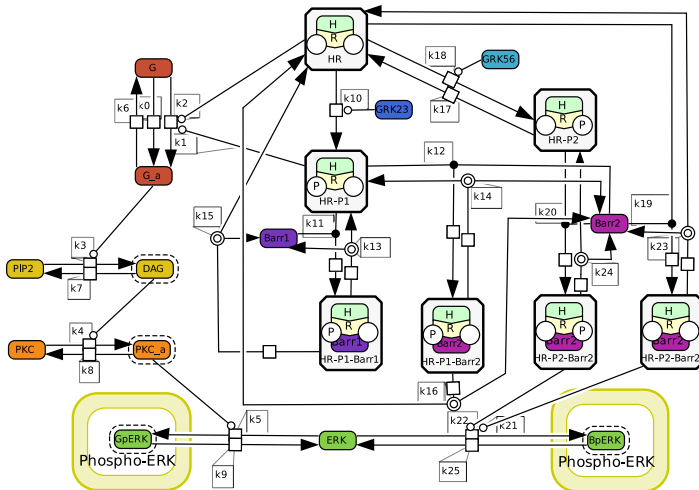
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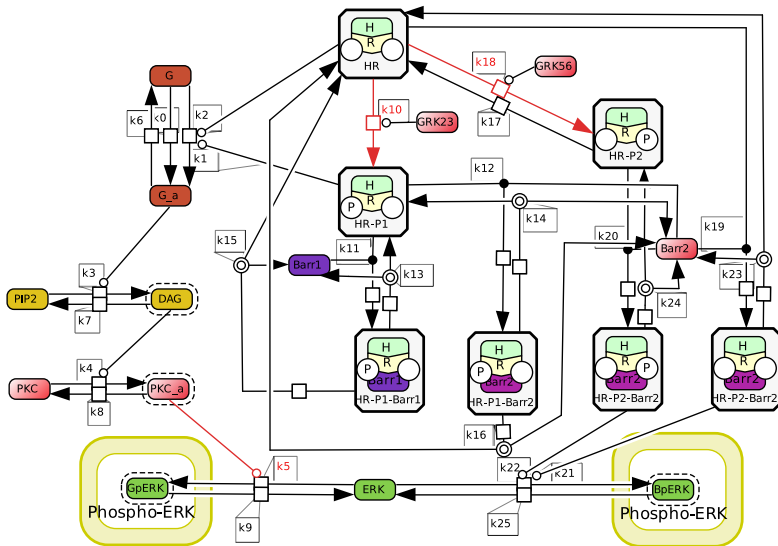
Results on the angiotensin signaling pathway

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

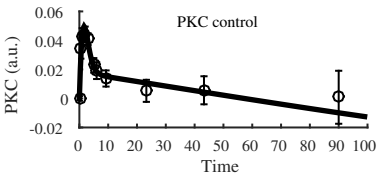
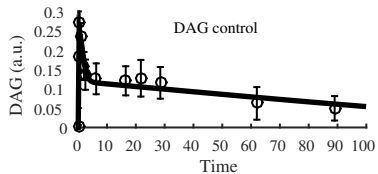
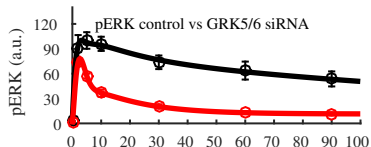
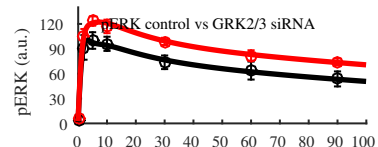
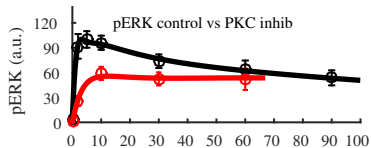
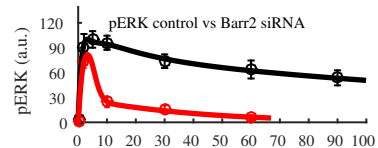
A model that fit the data : role of **G protein-coupled receptor kinases (GRK)** in the balance of signals.



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



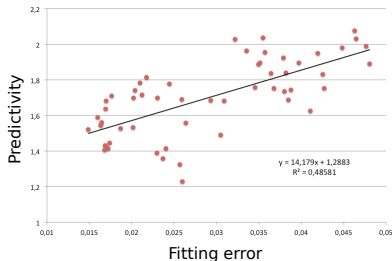
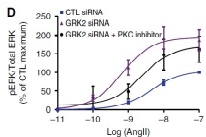
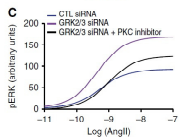
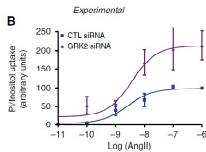
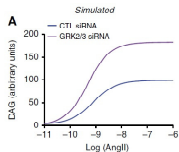
The model fits the data...



In black : control experiments.

In Red : perturbed experiments.

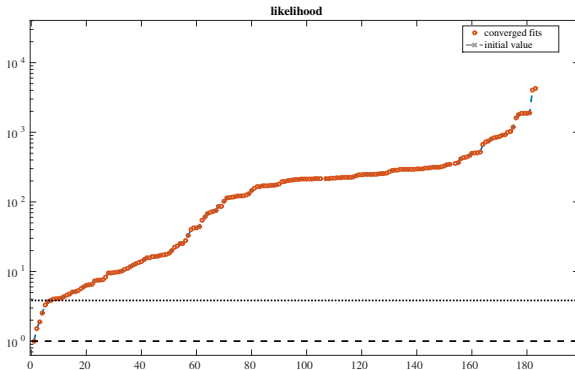
The model correctly predicts some validation data...



Remark

Good correlation between error and prediction.

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

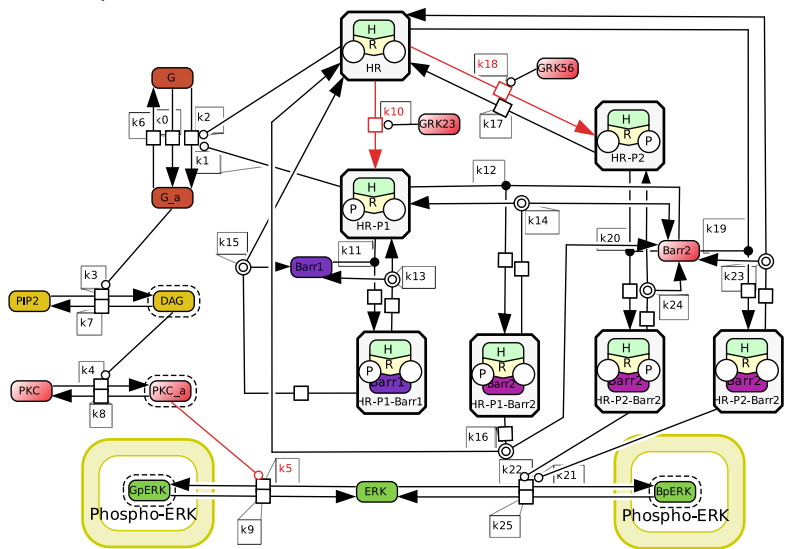


Critical assessments :

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

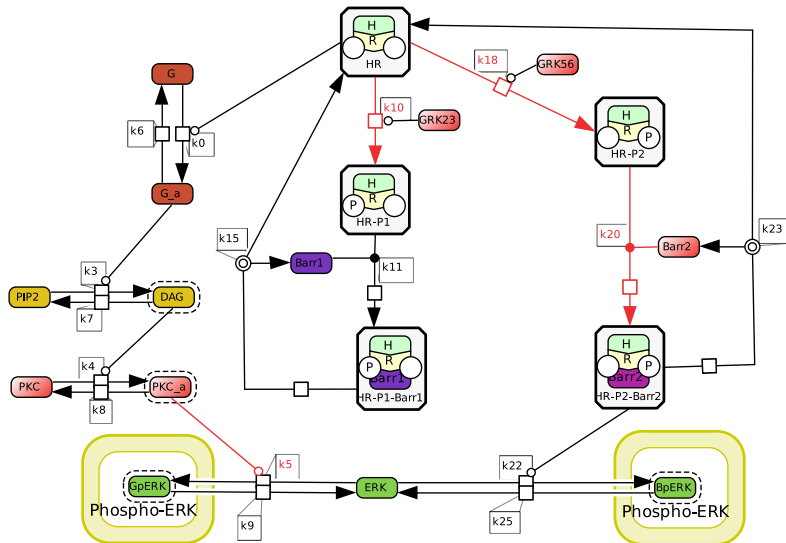
Model reduction

From **50** parameters...



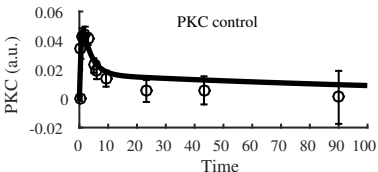
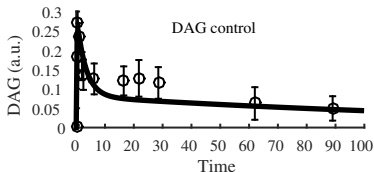
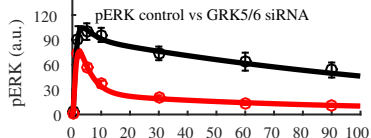
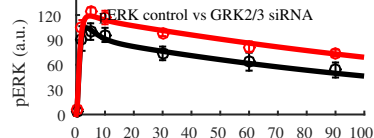
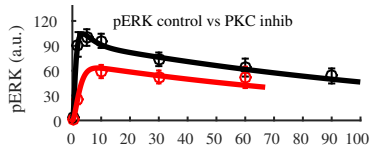
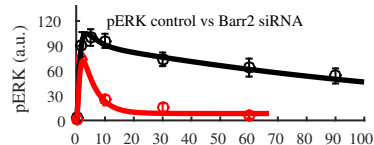
Model reduction

...to 22 parameters!



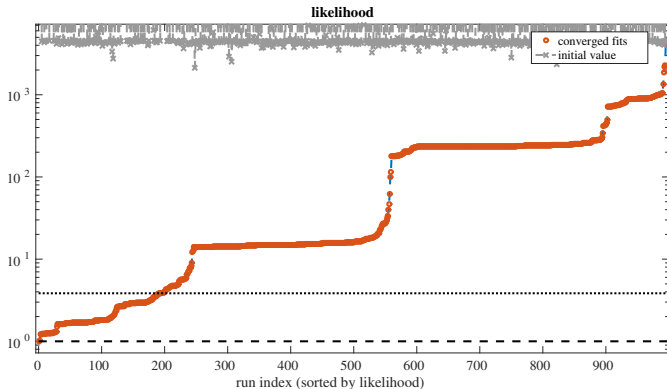
Model reduction

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



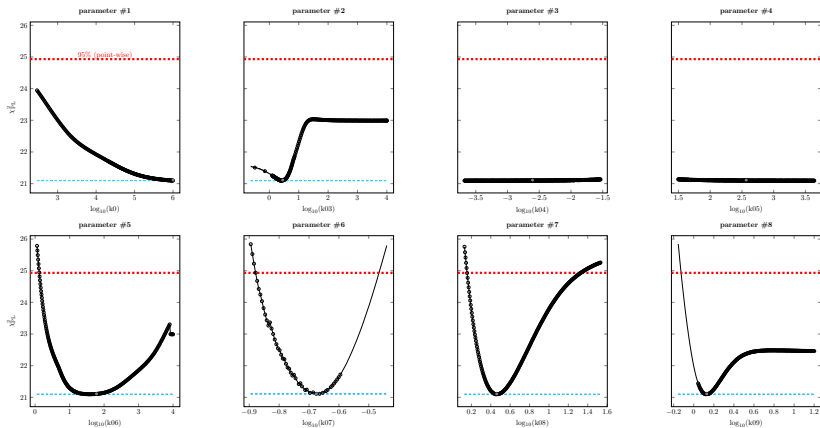
Model reduction

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



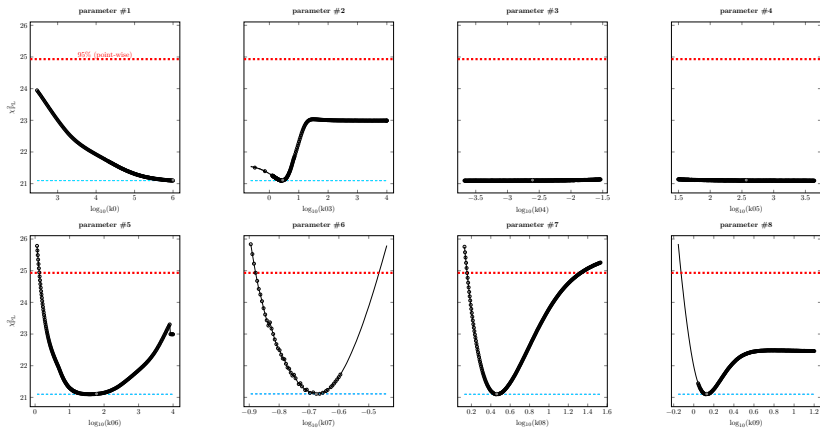
Model reduction

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

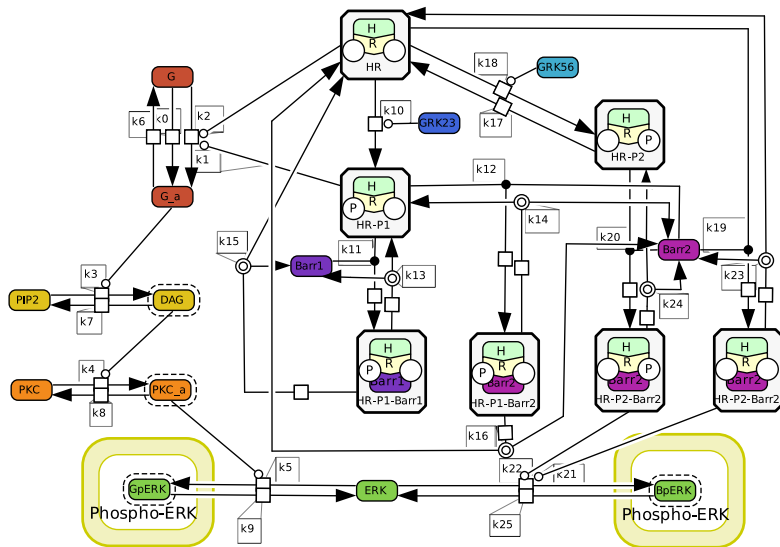


Model reduction

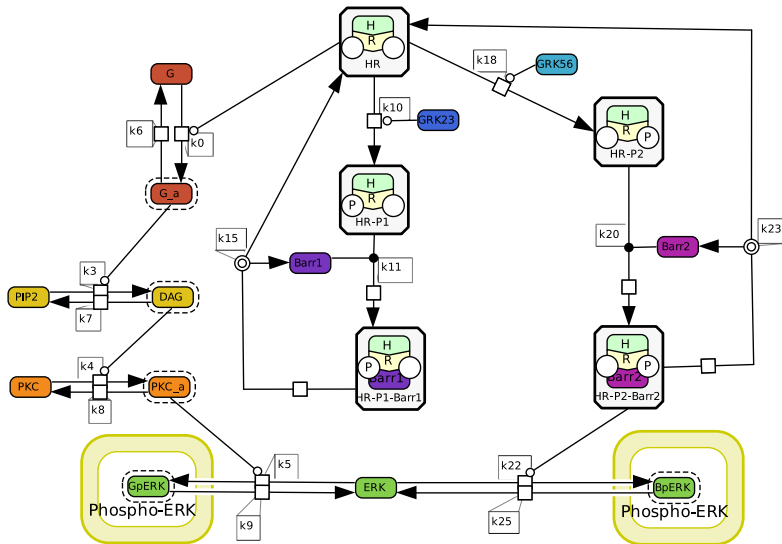
- ▶ The reduced model still fit well...
- ▶ and the convergence is better...
- ▶ but the identifiability is still poor! **Let's reduced further?**



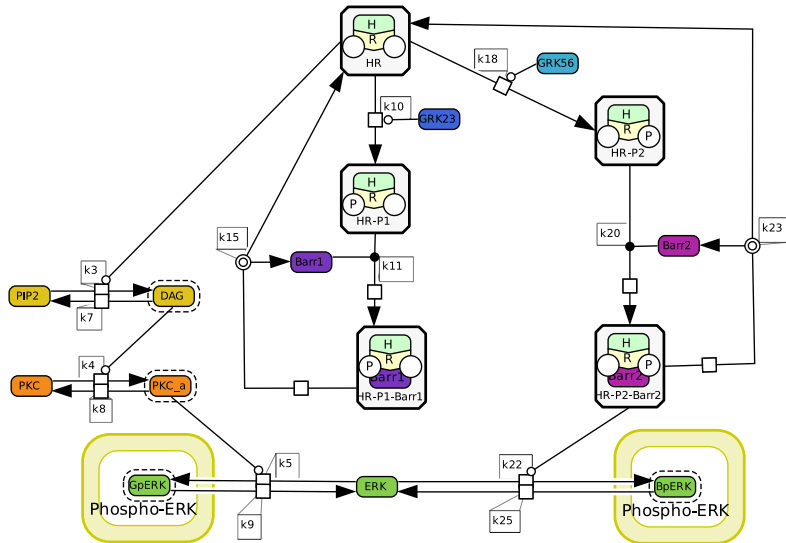
Systematic reduction



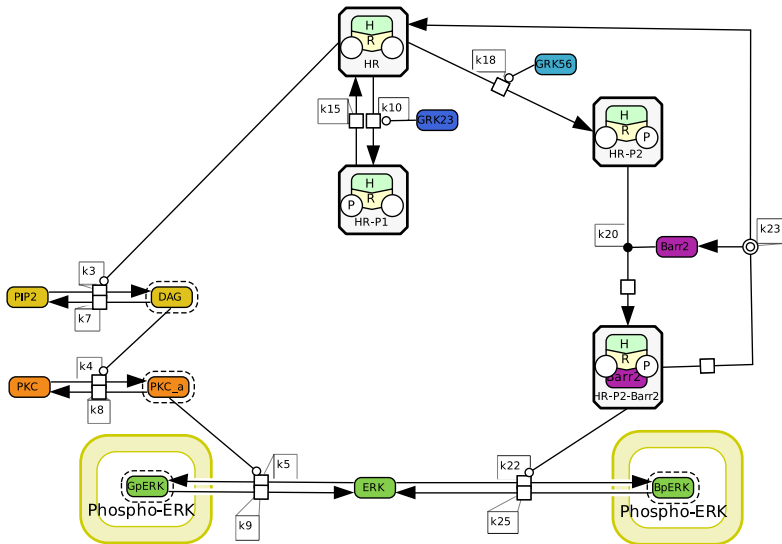
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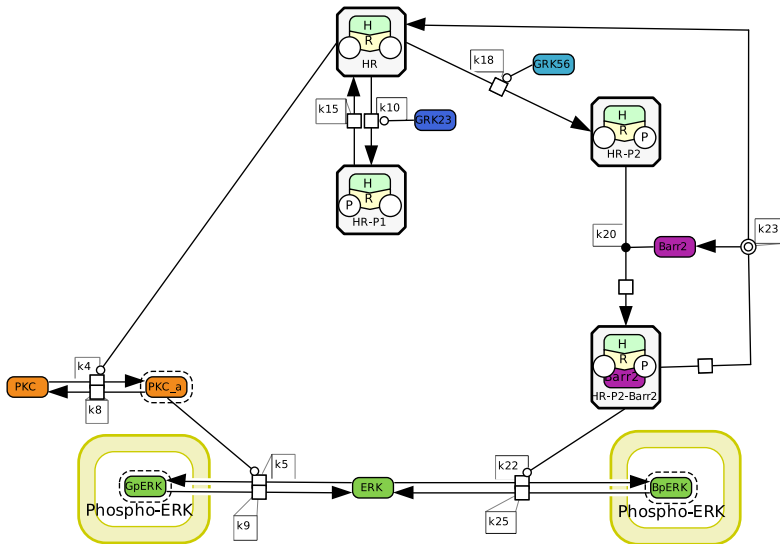
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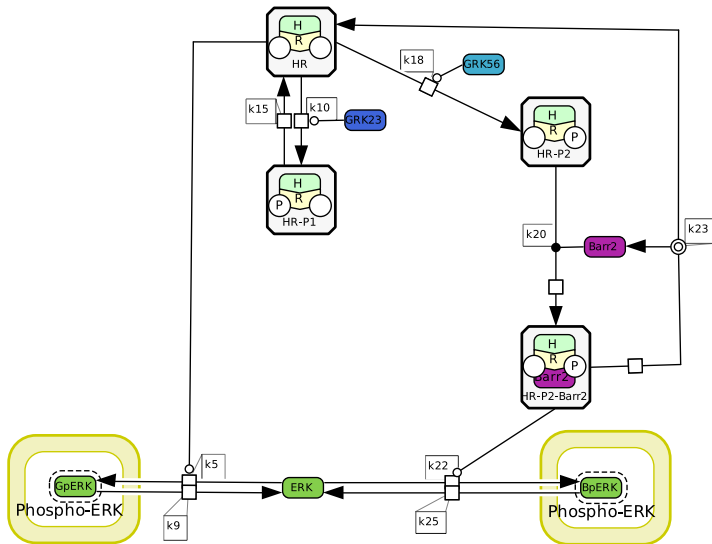
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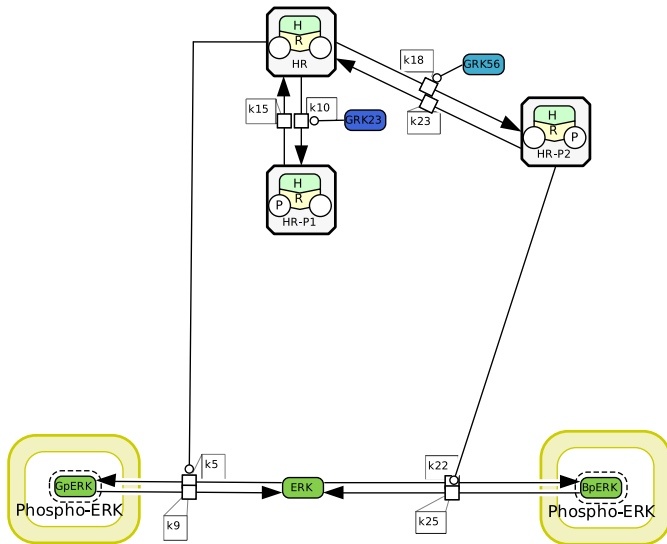
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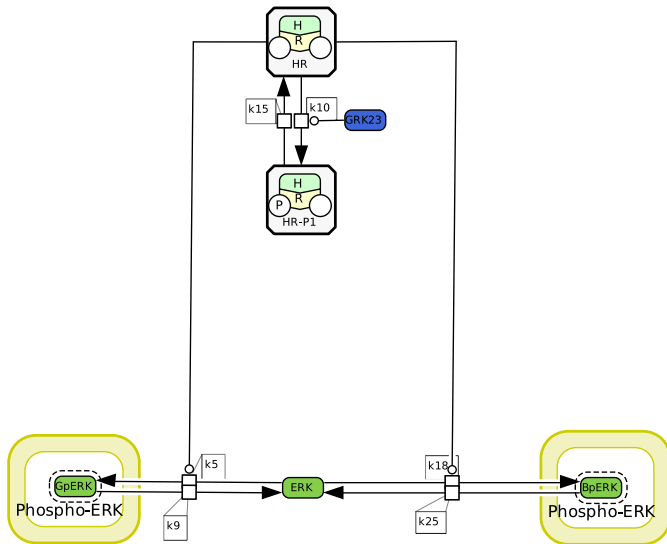
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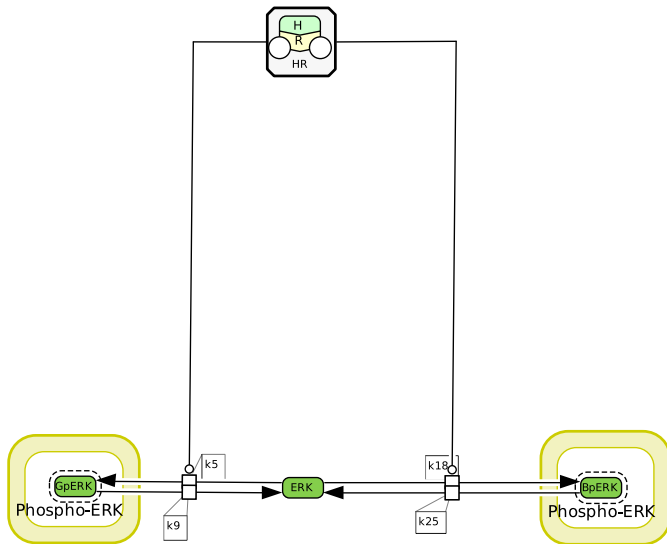
Systematic reduction



Systematic reduction



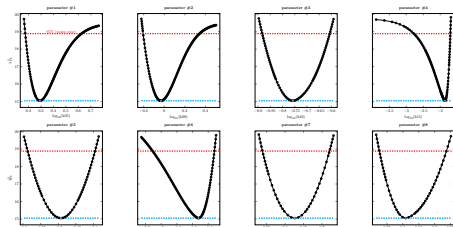
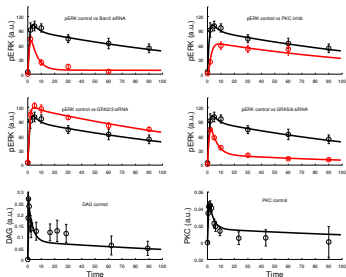
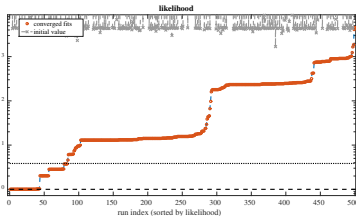
Systematic reduction



Results

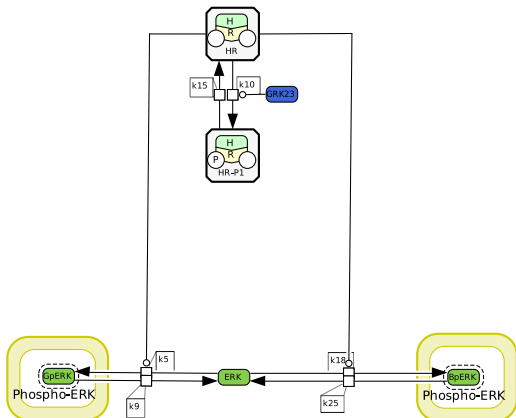
With model selection criteria :

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



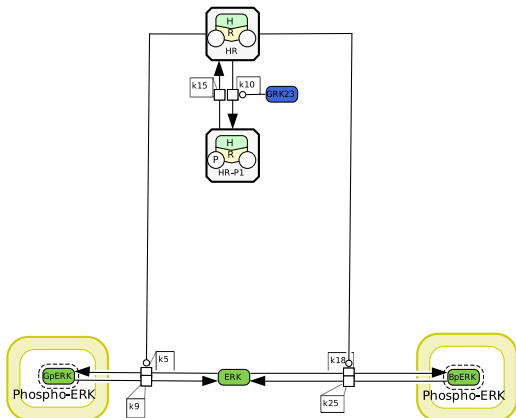
What do we learn (so far) ?

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



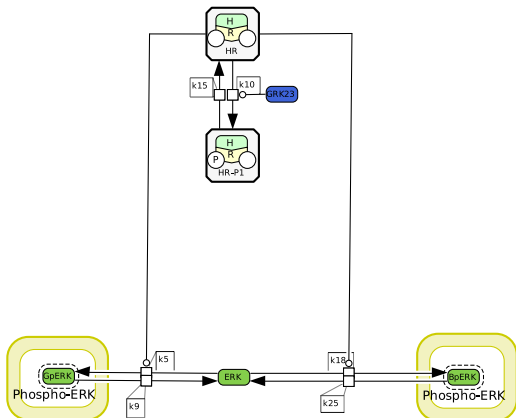
What do we learn (so far) ?

- ▶ Three pathways are necessary.
- ▶ An internalization pathway, **independent** of the β -arrestin signaling pathway, is mandatory.



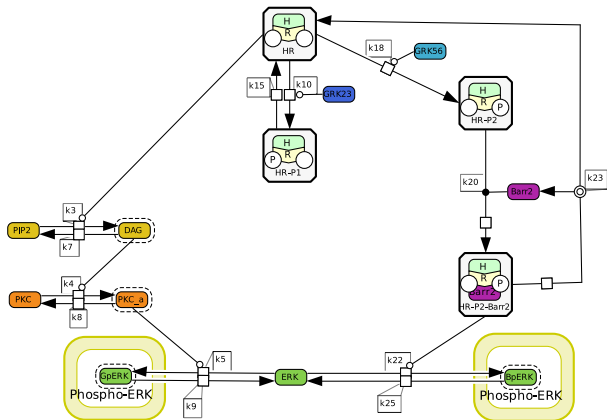
What do we learn (so far) ?

- ▶ Three pathways are necessary.
- ▶ An independent internalization pathway is mandatory.
- ▶ A **minimal** model with three reversible pathway with 10 parameter is able to fit the **phospho ERK data** and its parameter are **all identifiable**.



What do we learn (so far) ?

- ▶ Three pathways are necessary.
- ▶ An independent internalization pathway is mandatory.
- ▶ A minimal model can fit the **phospho ERK** data and is identifiable.
- ▶ The best model able to fit **all data** present non-identifiability
 ⇒ **Experimental design.**



Conclusion

- ▶ A full model able to fit the data (*Heitzler et 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.
- ▶ We have shed light on the importance of **three pathways** in GPCR signaling, and its regulations.

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Thanks for your attention !

validation data

