



Using dynamical reaction network to infer drugs selectivity in pharmacology

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USING DYNAMICAL REACTION NETWORK TO INFER DRUGS SELECTIVITY IN PHARMACOLOGY

Romain Yvinec

BIOS, INRA Centre Val-de-Loire

What is Drugs Selectivity ?

Some examples

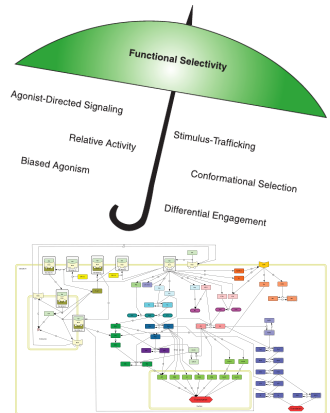
Bias quantification - standard method : operational model

Biased quantification using dynamical model

Functional selectivity, biased signaling

What is Drugs Selectivity ?

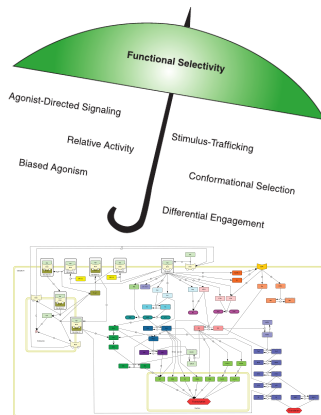
- Several reaction pathways are generally associated to a given receptor, and lead to various cell response.



Functional selectivity, biased signaling

What is Drugs Selectivity ?

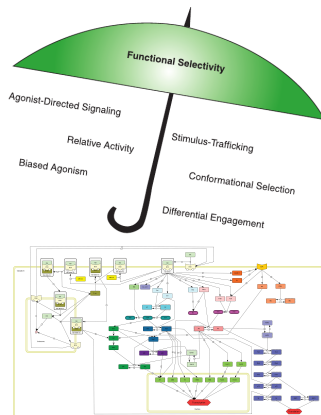
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- Differential activation of those reaction pathways, that differs between (natural or synthetic) ligand



Functional selectivity, biased signaling

What is Drugs Selectivity ?

- Several reaction pathways are generally associated to a given receptor, and lead to various cell response.
- Differential activation of those reaction pathways, that differs between (natural or synthetic) ligand
- **Drugs Selectivity** = Ligand-dependent selectivity for certain signal transduction pathways at one given receptor



Key concept in pharmacology

- ◇ Drugs Selectivity (or Biased Signaling) is a key concept to be distinguish from
 - Partial or full agonist.
 - Antagonist, inverse agonist.
 - Affinity (K_d), potency (EC_{50}), efficacy (E_{max}).

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 - Partial or full agonist.
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- ◇ A bias might be **context-dependent** (cell type, physiological state, etc.)

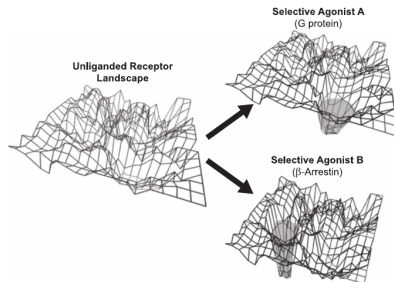
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 - Partial or full agonist.
 - Antagonist, inverse agonist.
 - Affinity (K_d), potency (EC_{50}), efficacy (E_{max}).
 - ◇ A bias might be **context-dependent** (cell type, physiological state, etc.)
 - ◇ Biased agonism is becoming a major tool in drug discovery.
- ⇒ Candidate screening requires to accurately quantify bias.

Theoretical foundation

A receptor may adopt several spatial conformations, each of which has different activation pathway profiles.

Conformational selectivity =
Ligand-specific modification
of the energetic landscape,
changing affinities and
efficacies of signaling
pathways.



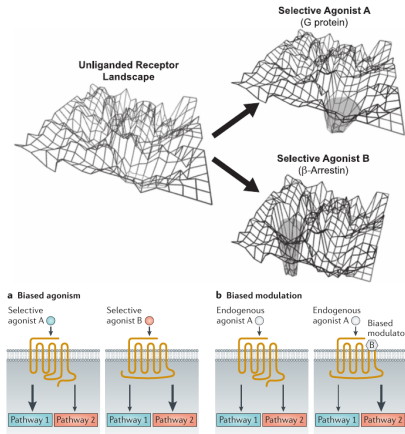
Kenakin, *J Pharmacol Exp Ther* (2011)

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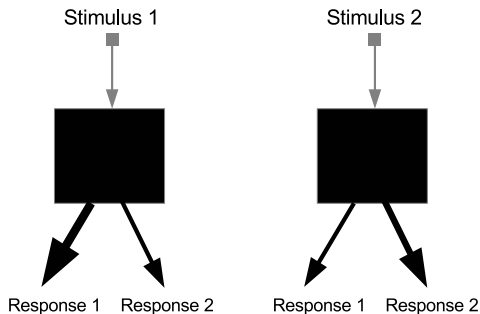
Conformational selectivity =
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Similar concept : modulating
bias



Minimal setting

To speak about signaling bias, one necessarily needs **two** ligands and **two** responses, in a **same** cellular context.



⇒ We always compare *a ligand with respect to a reference one*.

What is Drugs Selectivity?

Some examples

Bias quantification - standard method : operational model

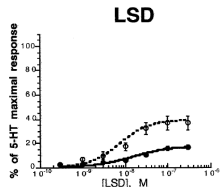
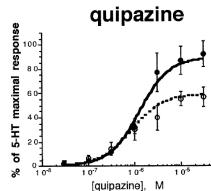
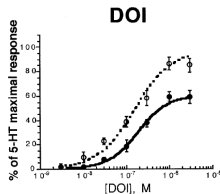
Biased quantification using dynamical model

Serotonin receptor 5 – HT_{2C}

- Quipazine is biased towards PI accumulation with respect to AA production, compared to the reference agonist DOI.
- LSD is not biased.



Berg et al., *Mol. Pharmacol.* (1998)



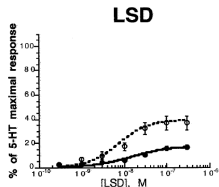
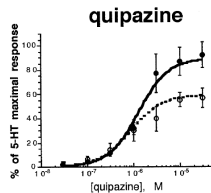
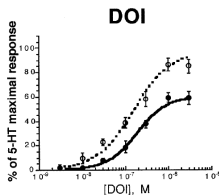
--○-- AA release
—●— IP accumulation

Serotonin receptor 5 – HT_{2C}

- Quipazine is biased towards *PI* accumulation with respect to AA production, *compared to the reference agonist DOI*.

- *LSD* is not biased.

⇒ Bias due to an E_{max} difference.

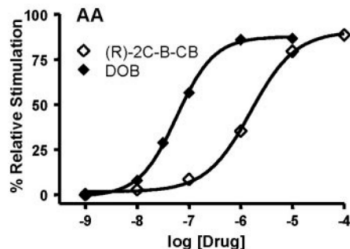
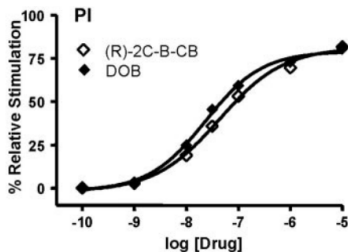


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Berg et al., *Mol. Pharmacol.* (1998)

Serotonin receptor 5 – HT_{2A}

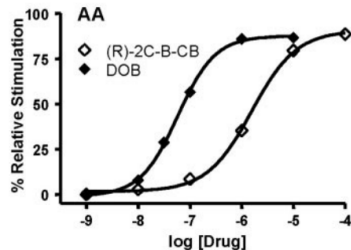
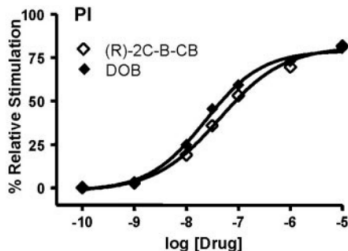


- (R) – 2C – B – CB is biased towards *PI* accumulation with respect to *AA* production, compared to the reference agonist *DOB*.



Urban et al., *J Pharmacol Exp Ther* (2007)

Serotonin receptor 5 – HT_{2A}



- (*R*) – 2C – B – CB is biased towards *PI* accumulation with respect to *AA* production, *compared to the reference agonist DOB*.

⇒ Bias due to an EC_{50} difference.



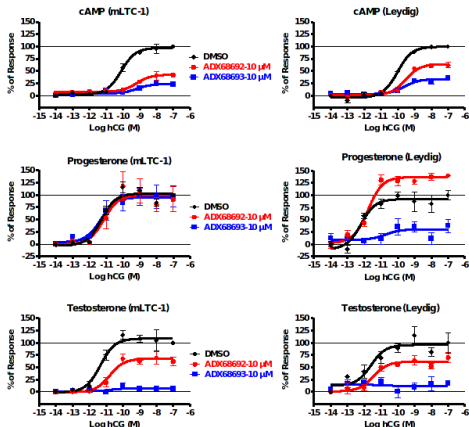
Urban et al., *J Pharmacol Exp Ther* (2007)

Steroidogenesis modulated by NAM

Some negative allosteric modulators (NAM) can biased Progesterone production with respect to Testosterone production, under stimulation of LH/CG receptor by hCG.



Ayoub et al., *Mol. Cell. Endocrinol* (2016)



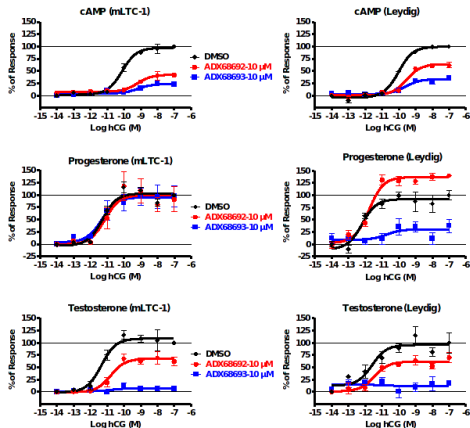
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⇒ Selective (biased) allosteric modulation



Ayoub et al., *Mol. Cell. Endocrinol* (2016)

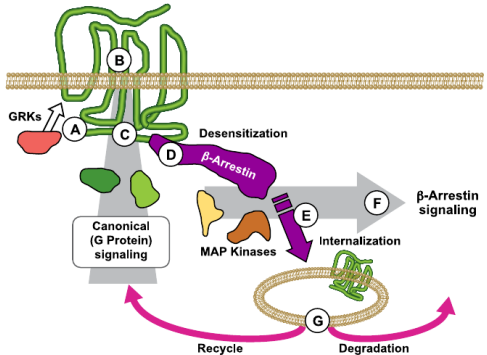


Many more examples on GPCR (principle drug target)

Many GPCR's are known to have biased ligands (G / β -arrestin)



Kenakin, *Chem Rev* (2017)



What is Drugs Selectivity?

Some examples

Bias quantification - standard method : operational model

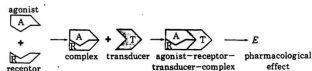
Biased quantification using dynamical model

Dose-response data are fitted with the function

$$y = E_{tot} \frac{\tau^n [L]^n}{([L] + Ka)^n + \tau^n [L]^n}.$$

- Response at equilibrium of a Michaelis-Menten type model.
- Ka = **Dissociation constant** of the couple Ligand/Receptor
- τ = **Efficacy coefficient** of the transduction pathway

J. W. Black and P. Leff



Black and Leff, *Proc. R. Soc. Lond. B* (1983)

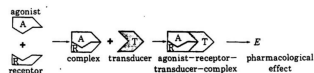
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For $n = 1$,

- $EC_{50} = \frac{Ka}{\tau + 1}$
- Efficacy $y_{\infty}/E_{tot} = \frac{\tau}{\tau + 1}$

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Operational model

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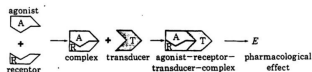
- $EC_{50} = \frac{Ka}{\tau + 1}$
- Efficacy $y_{\infty}/E_{tot} = \frac{\tau}{\tau + 1}$

Then, we define

⇒ **Transduction coefficient** :

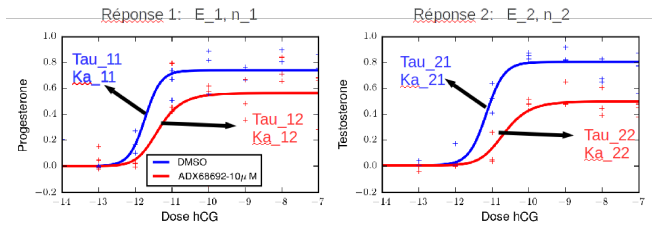
$$R := \log \left(\frac{\tau}{Ka} \right)$$

J. W. Black and P. Leff



Black and Leff, *Proc. R. Soc. Lond. B* (1983)

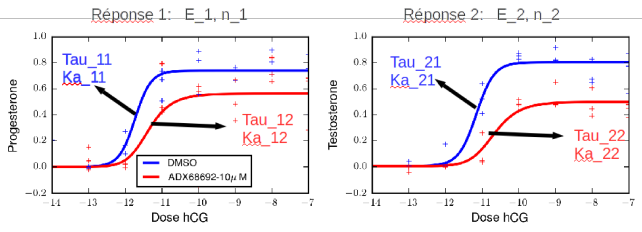
Bias quantification : with the operational model



Two ligands ($j = 1, 2$) and **two** measured responses ($i = 1, 2$) :
Each dose-response data is fitted with the operational model :

$$y_{ij} = E_i \frac{\tau_{ij}^{n_i} [L]^{n_i}}{([L] + Ka_{ij})^{n_i} + \tau_{ij}^{n_i} [L]^{n_i}} .$$

Bias quantification : with the operational model

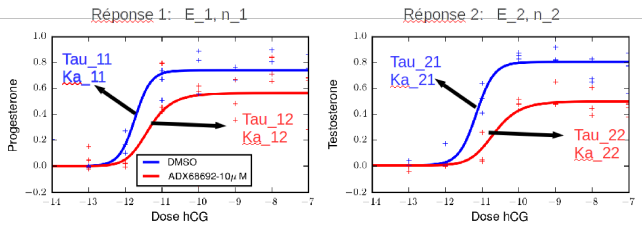


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For a given response i , we calculate
 $\Delta_i \log(\tau/Ka) = \log(\tau_{i2}/Ka_{i2}) - \log(\tau_{i1}/Ka_{i1})$.

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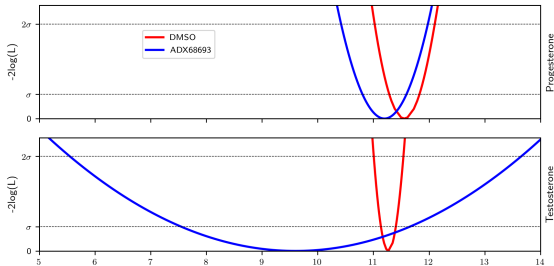
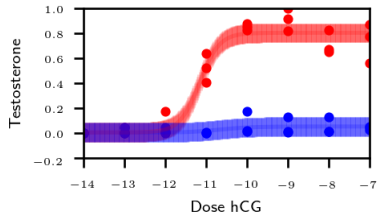
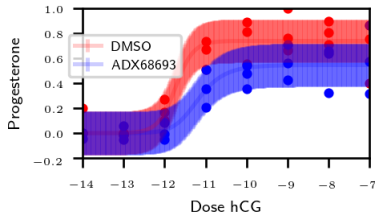
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The **Bias** is then defined by

$$\Delta\Delta \log(\tau/Ka) = \Delta_2 \log(\tau/Ka) - \Delta_1 \log(\tau/Ka)$$

Statistical consideration : parameter confidence interval and (un-)identifiability



What is Drugs Selectivity?

Some examples

Bias quantification - standard method : operational model

Biased quantification using dynamical model

Time-dependent bias?

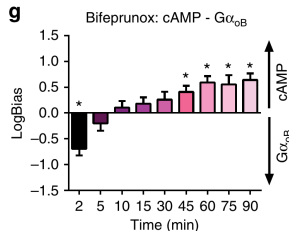
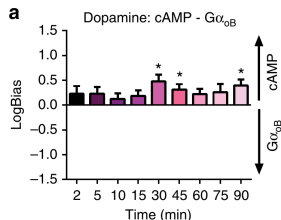
The role of kinetic context in apparent biased agonism at GPCRs

Carmen Klein Herenbrink¹, David A. Sykes², Prashant Donthamsetti^{3,4}, Meritxell Canals¹, Thomas Coudrat¹, Jeremy Shonberg⁵, Peter J. Scammells⁵, Ben Capuano⁵, Patrick M. Sexton¹, Steven J. Charlton², Jonathan A. Javitch^{3,4,6}, Arthur Christopoulos¹ & J Robert Lane¹

- Bias value may change according to the response time after stimulation.
- Kinetic explanation : Ligands with a slow binding kinetics may have changing bias value according to time.



Klein Herenbrink et al., *Nat. Commun* (2016)

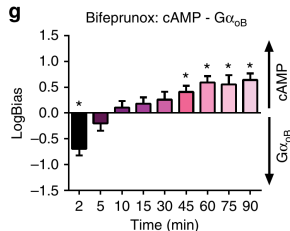
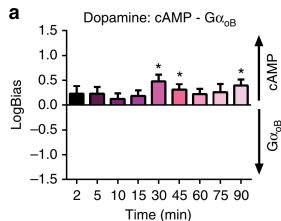


Time-dependent bias?

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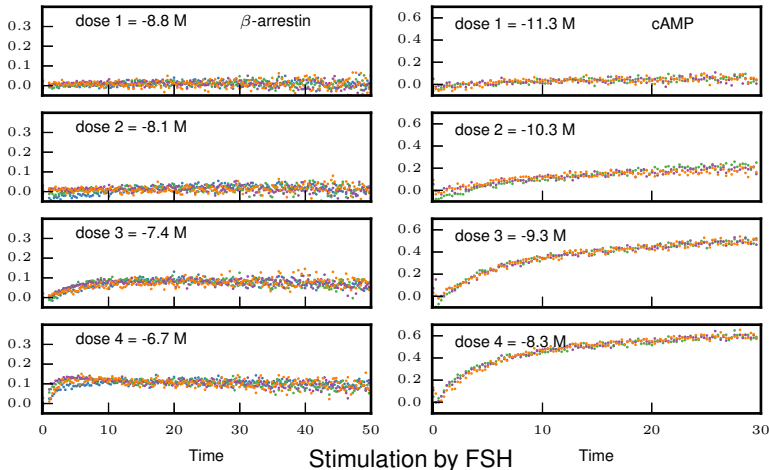
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- Bias value may change according to the response time after stimulation.
 - Kinetic explanation : Ligands with a slow binding kinetics may have changing bias value according to time.
- ⇒ **We need to take into account dynamic patterns in bias quantification**



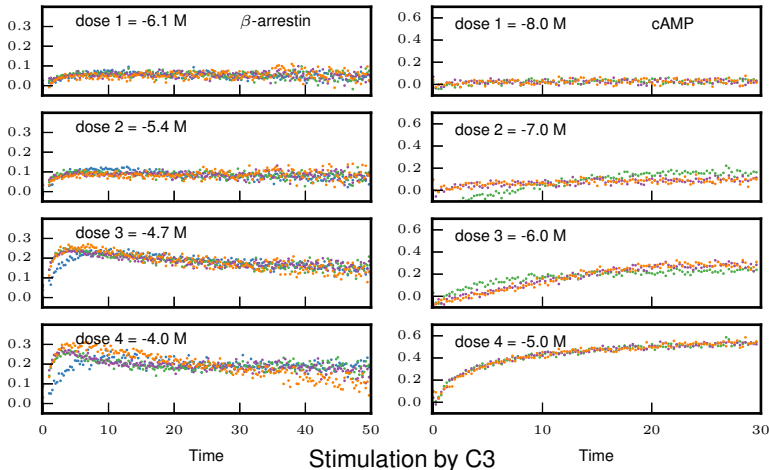
Dynamic data (on FHSR in HEK cells)

Instead of focusing on dose-response curves, we deal with **kinetic data** performed at several doses (here : induced BRET data)



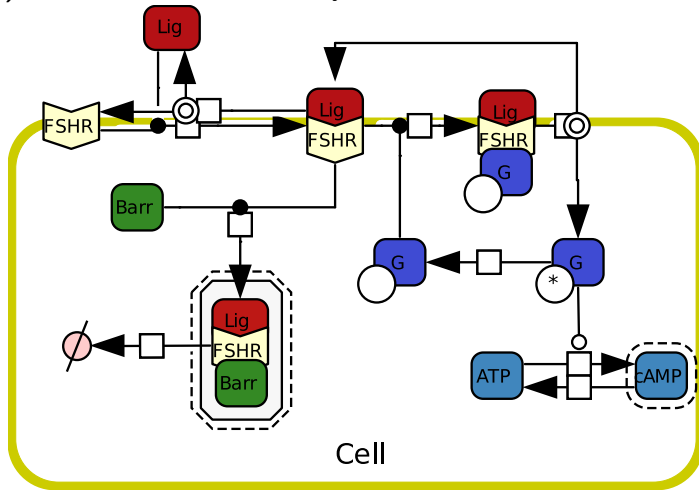
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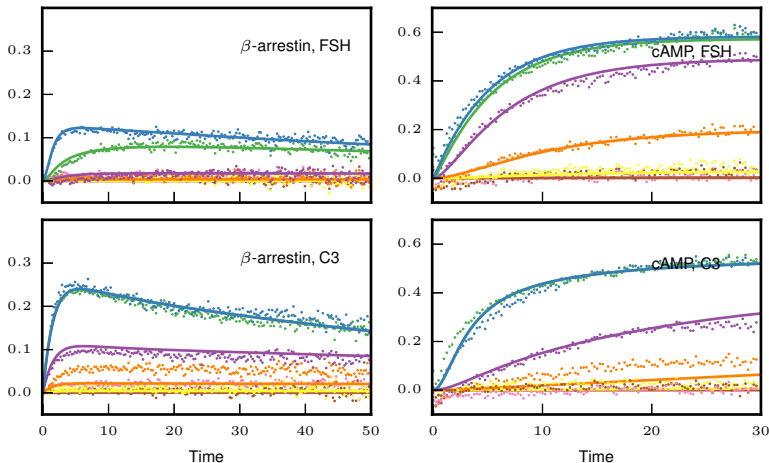
Principle of the methodology

I) We start with a sufficiently detailed chemical reaction network



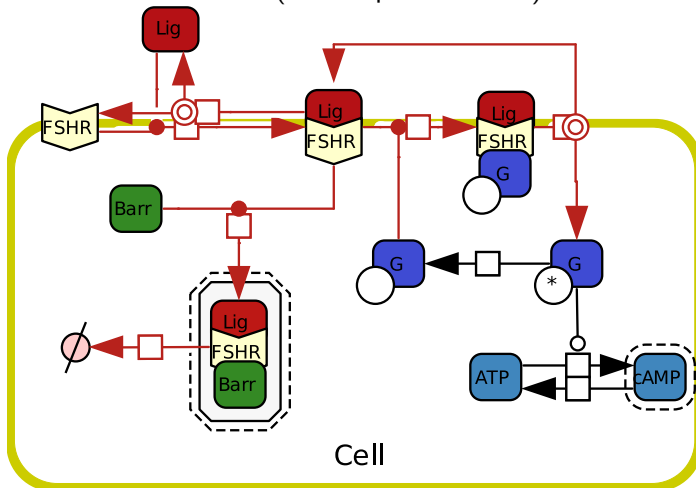
Principle of the methodology

I) We start with a sufficiently detailed chemical reaction network to accurately fit the data (one **separate** model for each Ligand)



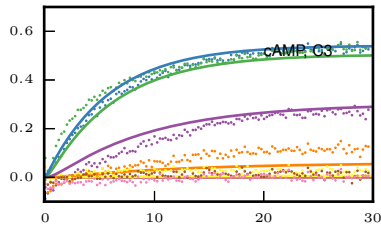
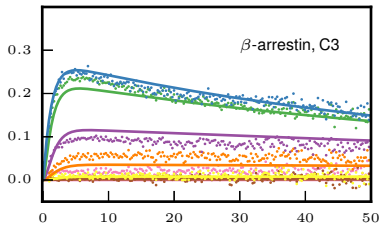
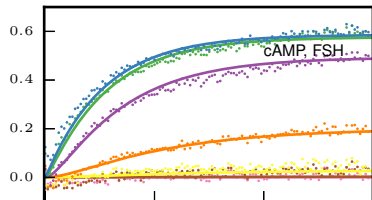
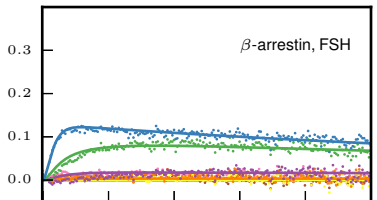
Principle of the methodology

II) We fit **all data at once**, using some **common** parameters (initial concentration of molecules, measurement parameters...) and some **different** ones (kinetic parameters...)



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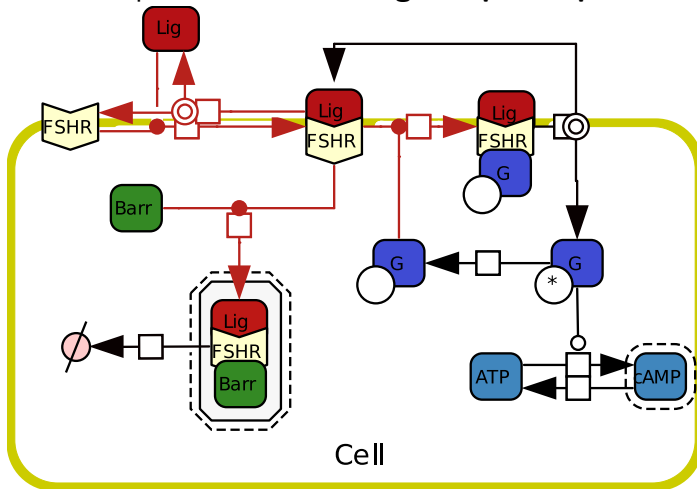


Time

Time

Principle of the methodology

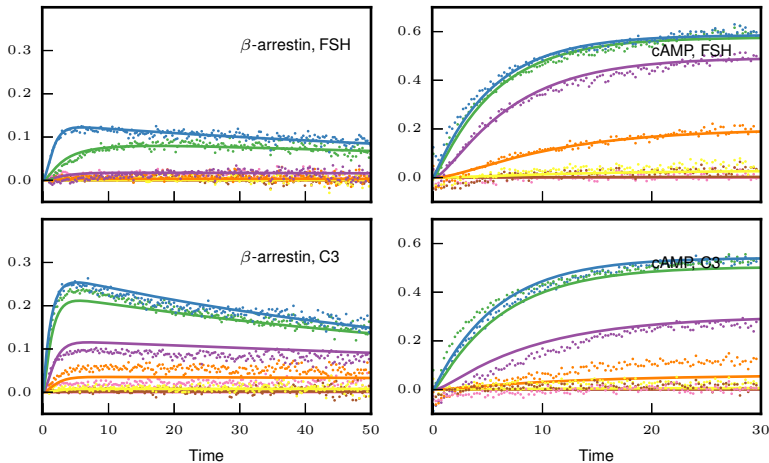
III) We use L^1 -penalization to find **ligand specific parameters**



Data2Dynamics : Steiert, Timmer and Kreutz, *Bioinformatics* (2016)

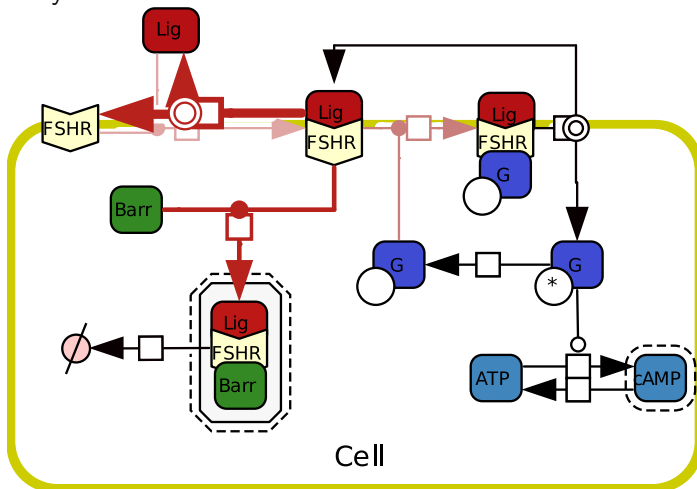
Principle of the methodology

III) We use L^1 -penalization to find **ligand specific parameters**, keeping the fit 'as good as before'



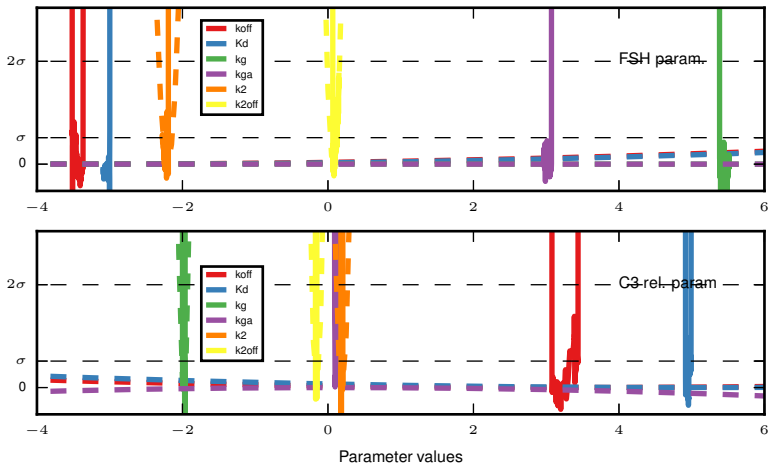
Principle of the methodology

IV) After re-optimization, the set of distinct (ligand-specific) kinetic parameters gives us an accurate description of ligand specificity.



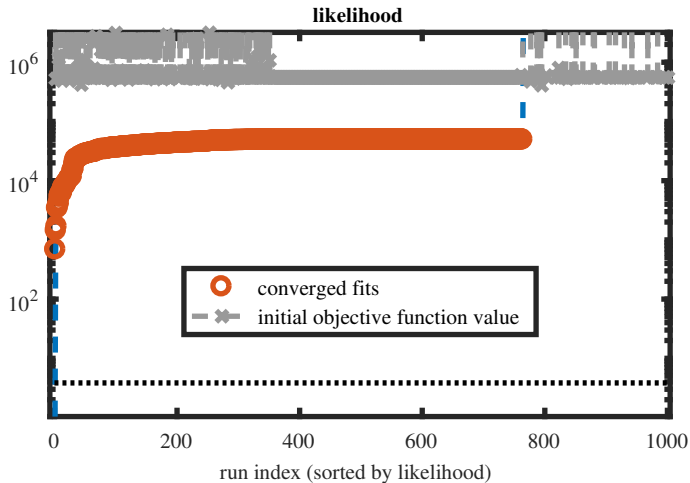
Principle of the methodology

V) Significant differences between parameters is assessed by PLE

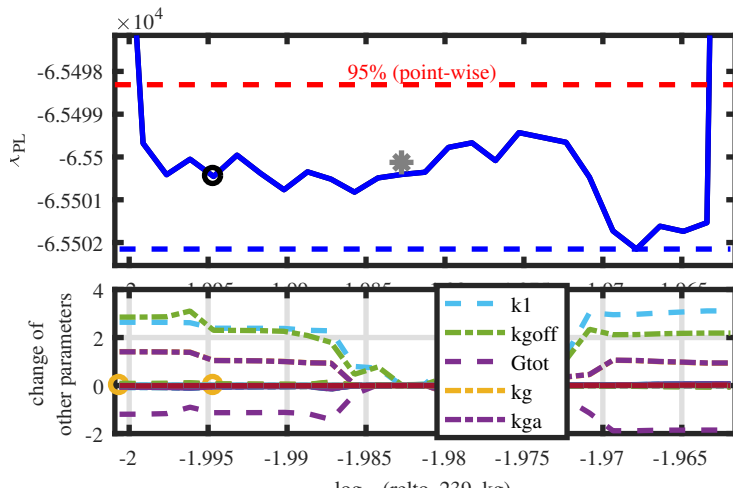


→ **here** : C3 is biased towards β -arr, compared to cAMP, in comparison to FSH.

Practical problems...

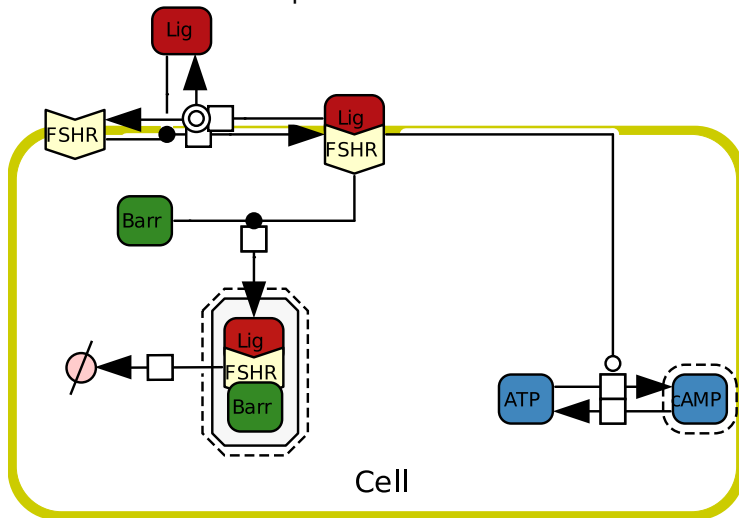


Practical problems...



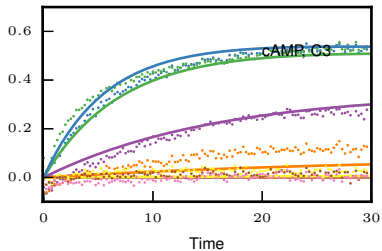
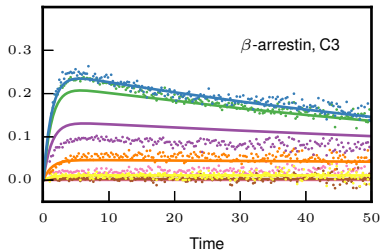
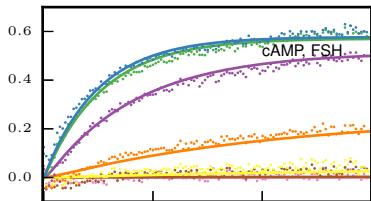
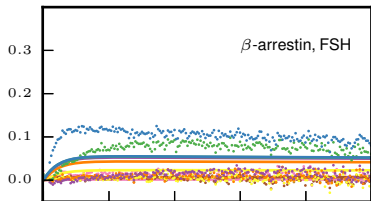
With a "simpler" model

Kinetic model without G-protein



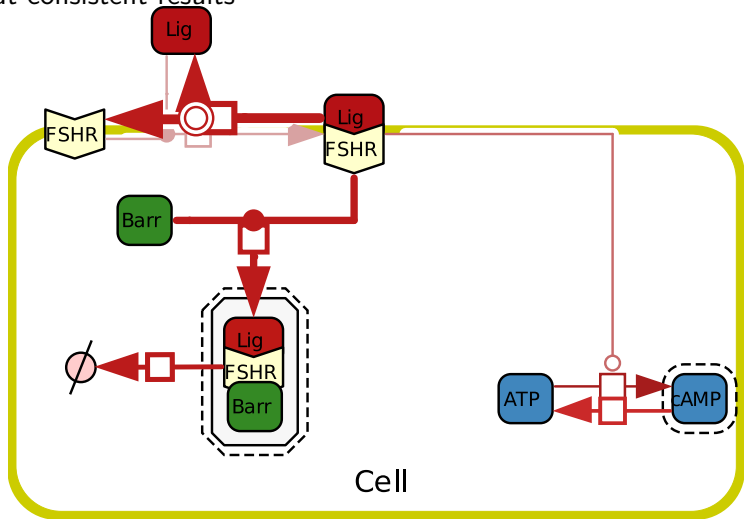
With a "simpler" model

We obtain a slightly worse fit



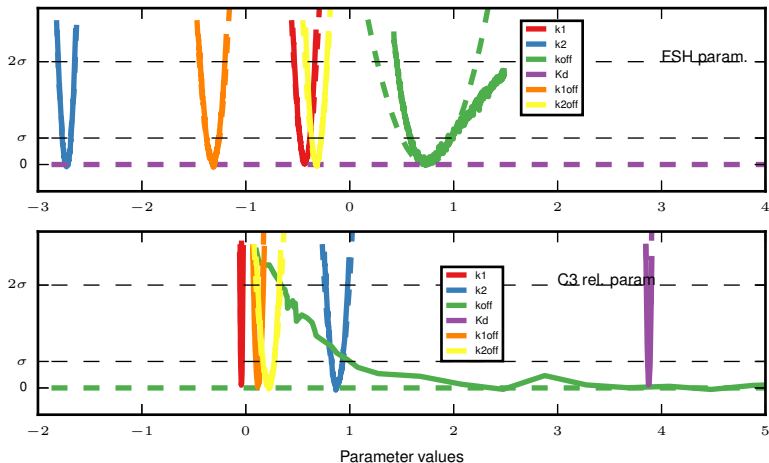
With a "simpler" model

But consistent results



With a "simpler" model

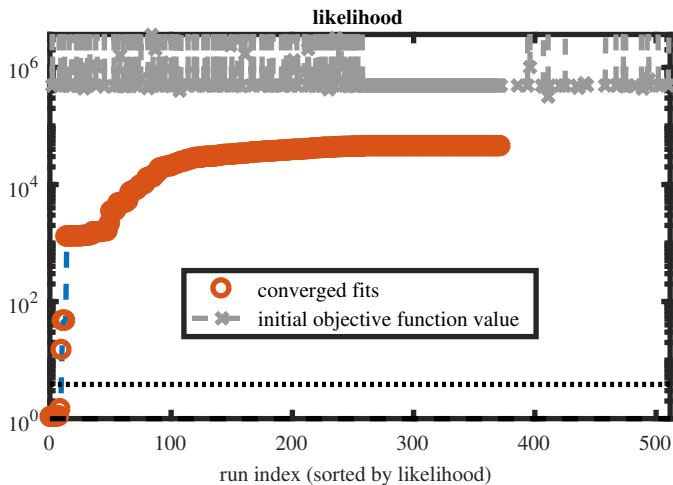
And "better" parameter identifiability



C3 is biased towards β -arr, compared to cAMP, in comparison to FSH.

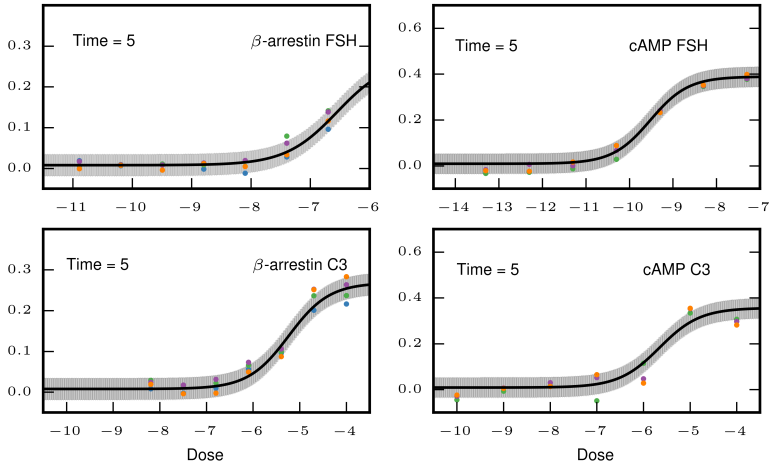
With a "simpler" model

And "better" convergence curves



Comparison with dose-response (on FHSR in HEK cells)

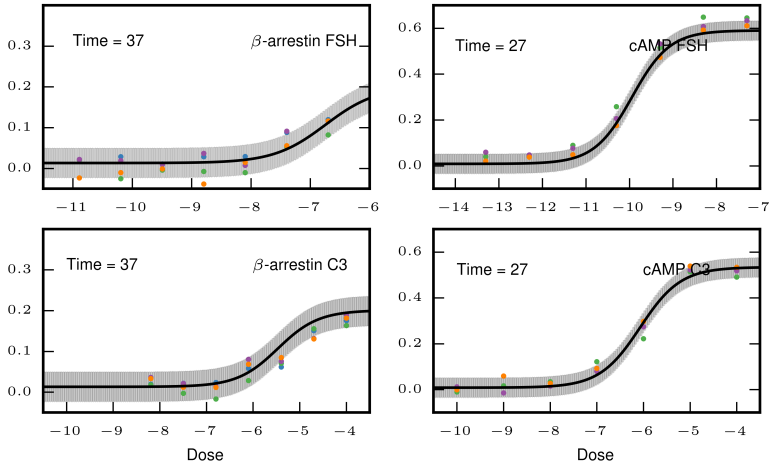
We systematically calculate bias value using standard method
(operational model on dose-response curves :)



Bias=2.3 : C1 is biased towards β -arr, compared to cAMP, in comparison to FSH.

Comparison with dose-response (on FHSR in HEK cells)

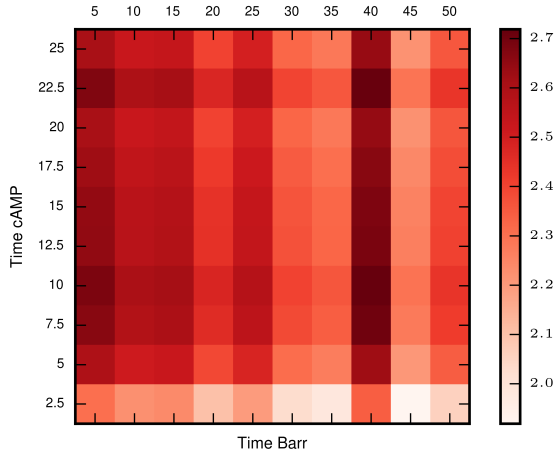
We systematically calculate bias value using standard method
(operational model on dose-response curves :)



Bias=2.64 : C1 is biased towards β -arr, compared to cAMP, in comparison to FSH.

Comparison with dose-response (on FHSR in HEK cells)

We systematically calculate bias value using standard method
Different times gives (slightly) different bias values

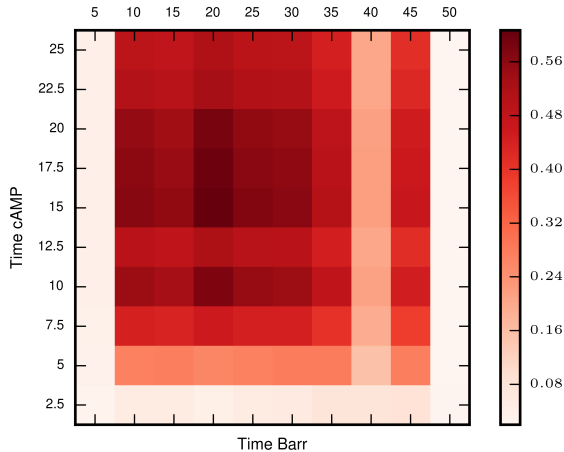


C1 is biased towards β -arr, compared to cAMP, in comparison to FSH.

Comparison with dose-response (on FHSR in HEK cells)

We systematically calculate bias value using standard method

Uncertainty can be large according to the time of measurement



Summary

- Notion of signaling bias to quantify differential activation of several pathways by a Ligand at a given receptor.
- Standard quantification has several drawbacks (no time, limited to sigmoid scenario, et).
- We gave a kinetic interpretation of Ligand biased, which rely on dynamic (ODE) modeling and parameter estimation with L^1 penalization.

Summary

- Notion of signaling bias to quantify differential activation of several pathways by a Ligand at a given receptor.
 - Standard quantification has several drawbacks (no time, limited to sigmoid scenario, et).
 - We gave a kinetic interpretation of Ligand biased, which rely on dynamic (ODE) modeling and parameter estimation with L^1 penalization.
- ⇒ How to deal with "fuzzy/noisy" PLE / Densely sampled time data ?
- ⇒ How to deal with non uniqueness of the penalized solution ?
- ⇒ How to perform a model reduction that would lead to both a satisfactory fit and identifiable parameters ?

Thanks for your attention !

Bios Team, PRC, INRA (Tours, Fr)



- ★ Eric Reiter
- ★ Pascale Crépieux
- ★ Anne Poupon
- ★ Francesco De Pascali

United Arab Emirates University

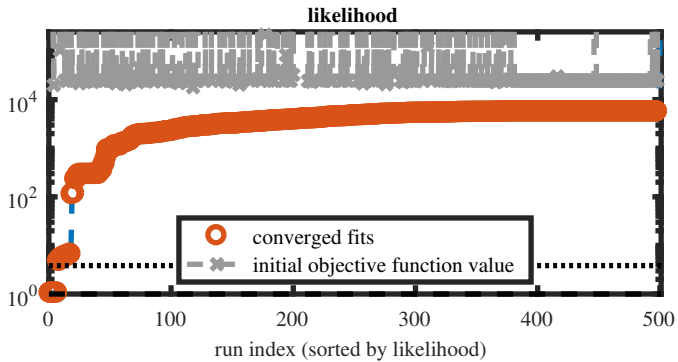
- ★ Mohammed Ayoub

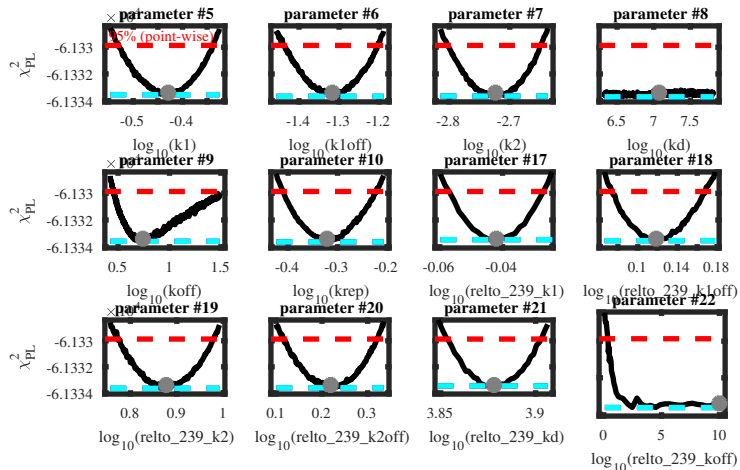


M. Ayoub et al., Molecular and Cellular Endocrinology 436 (2016)

L. Riccetti et al., Scientific Reports 7 :940 (2017)

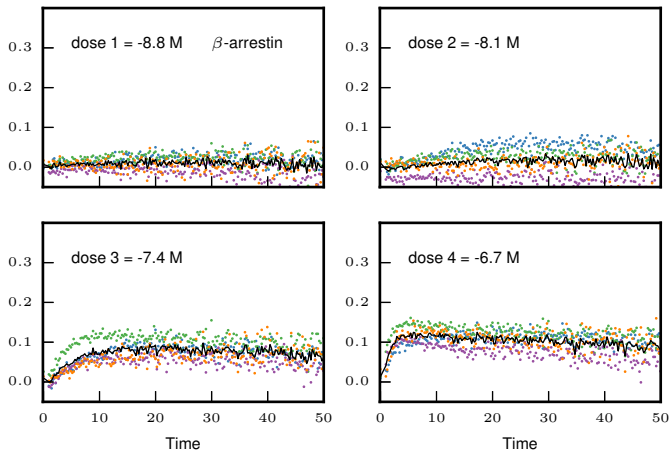
R.Y. et al., Methods in Molecular Biology, in press (2018)





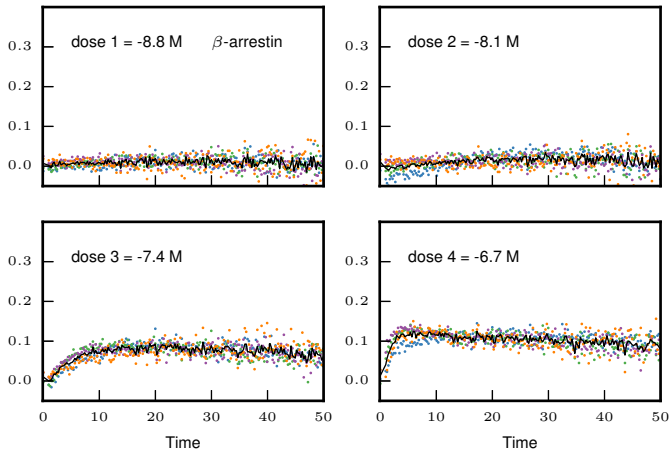
("trick" to minimize variance...)

Original "raw" data



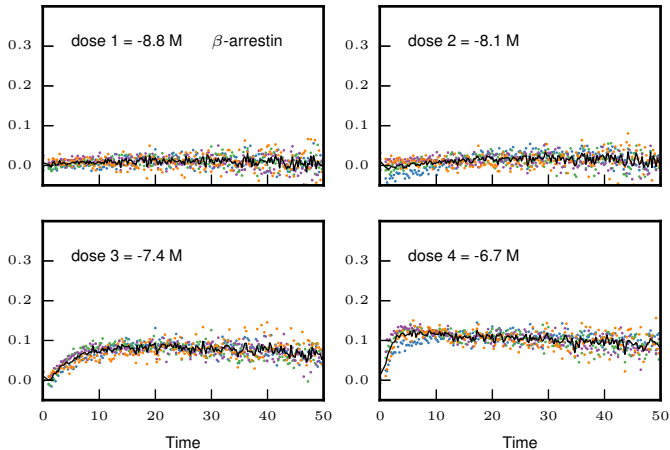
("trick" to minimize variance...)

"Adjusted" data



("trick" to minimize variance...)

"Adjusted" data



+ adjusting the number of data points ...

Other extensions

Dose-dependent bias



Barak and Peterson et al.,
Biochem. (2012)

Extension of the operational
model

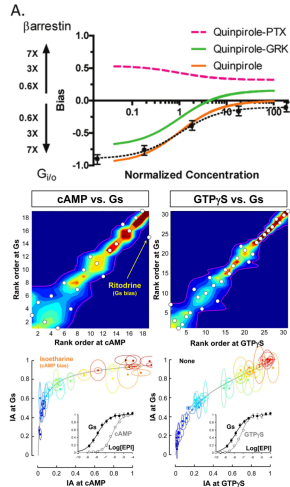


Kenakin, *Chem. Rev.* (2017)

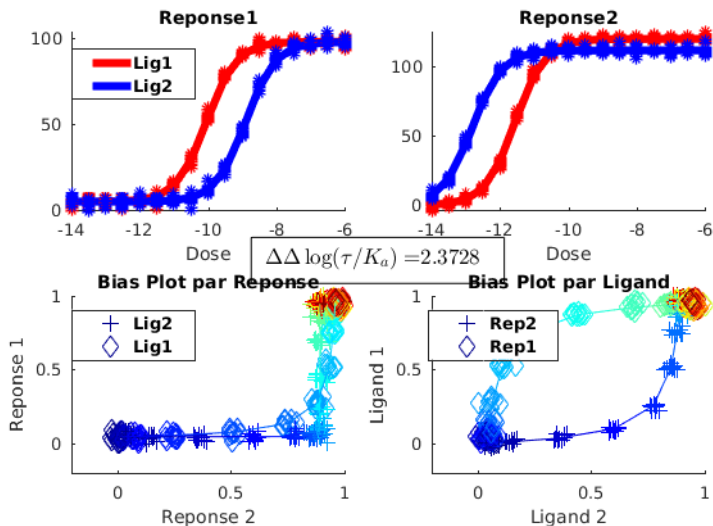
Method based on Intrinsic
activities and rank ordering



Onaran et al., *Sci. Rep.*
(2017)

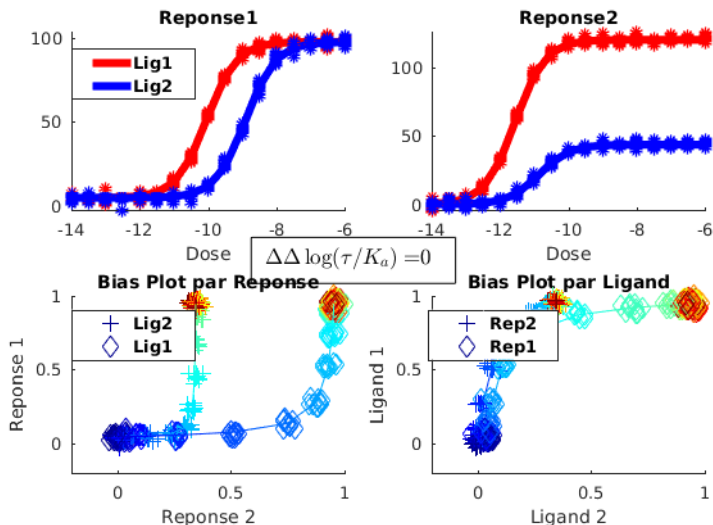


Is bias calculation intuitive? (simulated data)



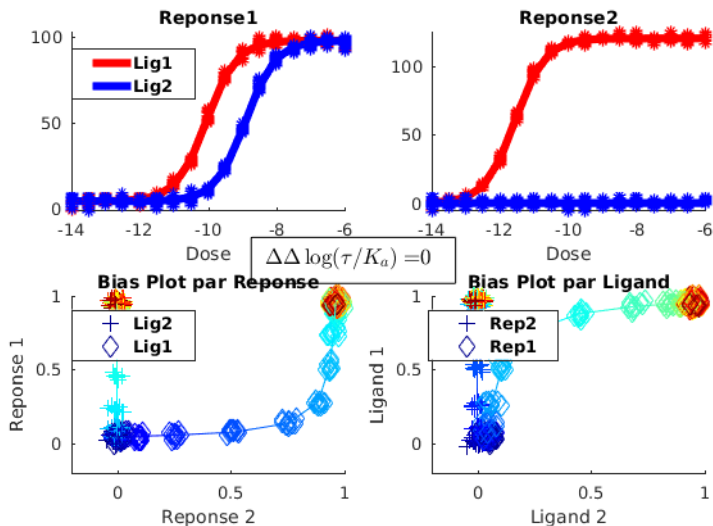
A strong bias is usually 'apparent' on dose-response curves or bias plot

Is bias calculation intuitive? (simulated data)



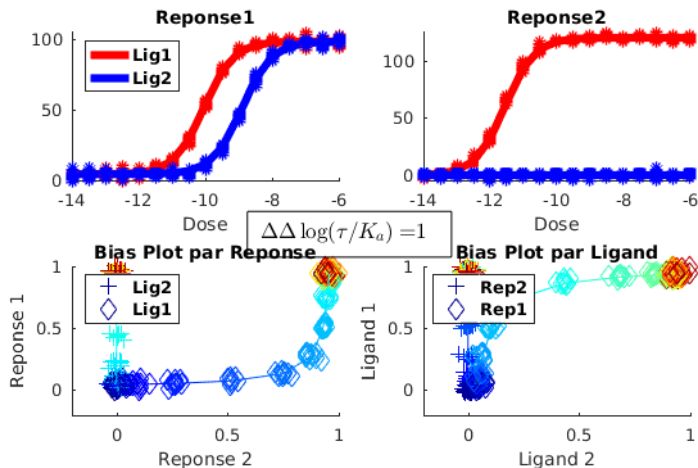
But there may be counter-intuitive situation...

Is bias calculation intuitive? (simulated data)



But there may be counter-intuitive situation...

Is bias calculation intuitive? (simulated data)



But there may be counter-intuitive situation...

... and those situations occur in real life!

