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Kinetic biased signaling: towards a system biology definition of drugs selectivity.

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Kinetic biased signaling: towards a system
biology definition of drugs selectivity.
Illustration on the Follicle Stimulating Hormone
Receptor

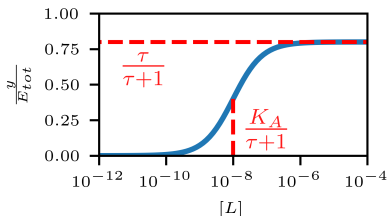
Romain Yvinec

BIOS, INRAE Tours

Intro : Bias quantification

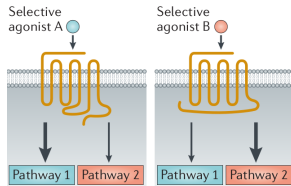
Operational model

$$y = E_{tot} \frac{\tau [L]}{K_A + (\tau + 1)[L]}$$



⇒ **Transduction coefficient :**

$$\log(R) := \log\left(\frac{\tau}{K_A}\right) = \frac{\text{Observed Efficacy}}{\text{Observed Potency}}$$



Kenakin and Christopoulos, *Nat. Rev. Drug Discov.* (2013)

J. W. Black and P. Leff



Equilibrium operational model

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

Intro : Time-dependent bias ?

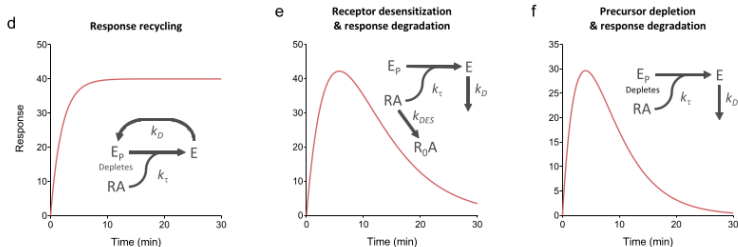
The role of kinetic context in apparent biased agonism at GPCRs

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



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

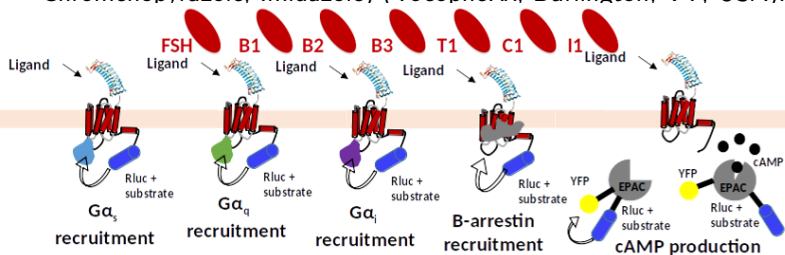
⇒ **We need to take into account dynamic patterns in bias quantification**



Hoare et al., *JTB* (2018)

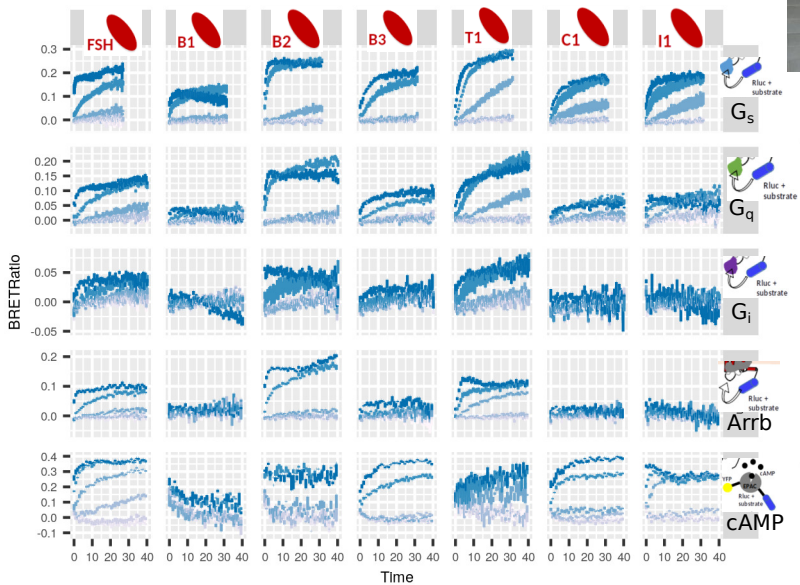
Case study on FSHR : De Pascali et al IJMS 2021

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

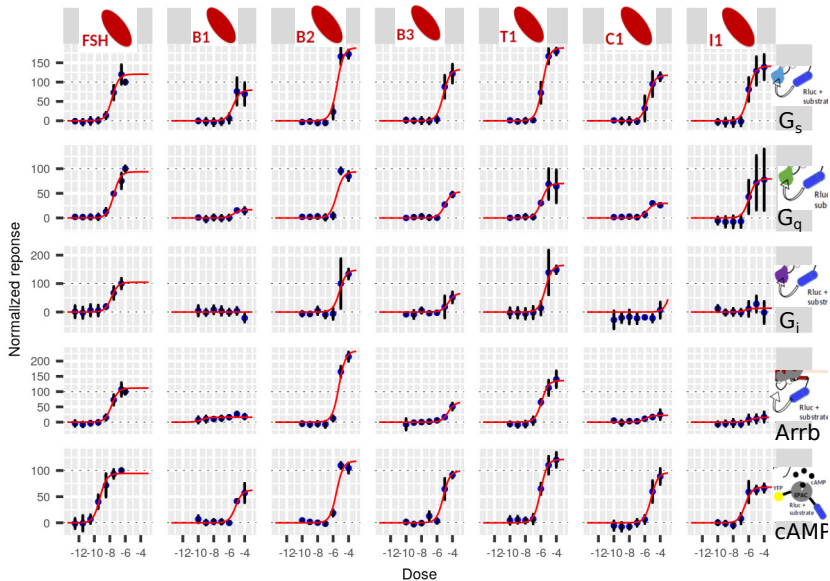




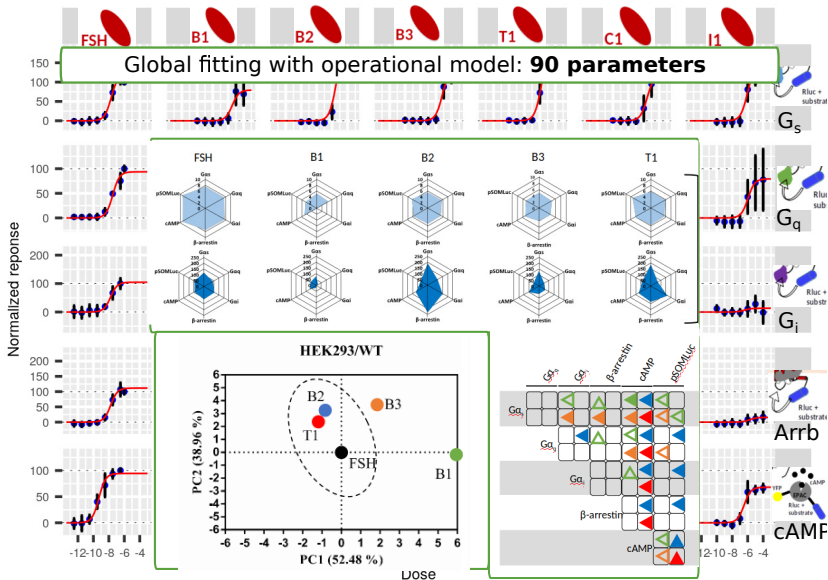
Francesco De Pascali



Operational model with A.U.C (De Pascali et al 21)

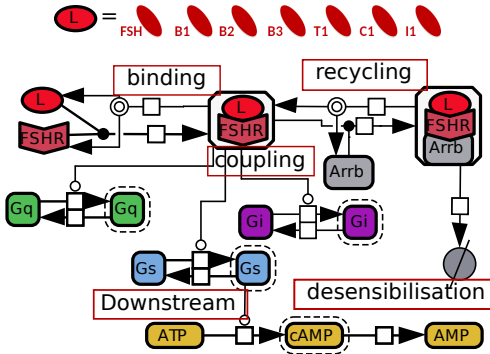


Operational model with A.U.C (De Pascali et al 21)



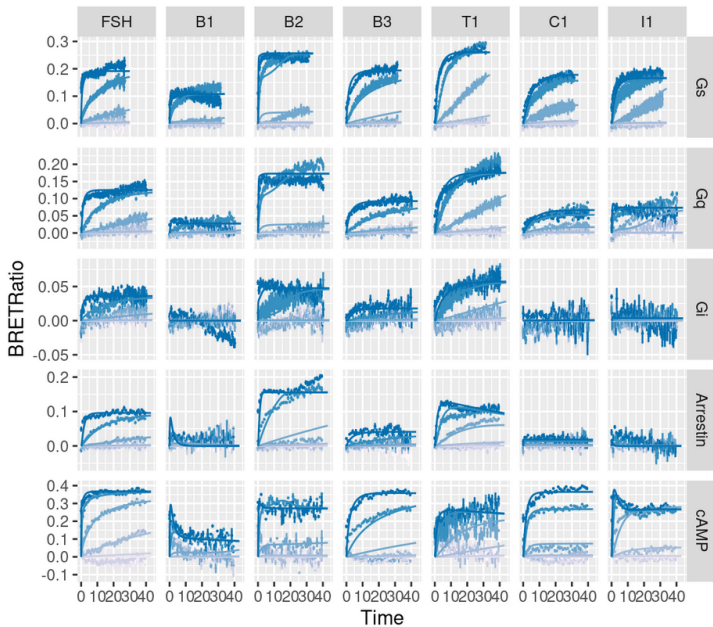
Reaction network : multiple Pathways modeling

Mechanistic link with data

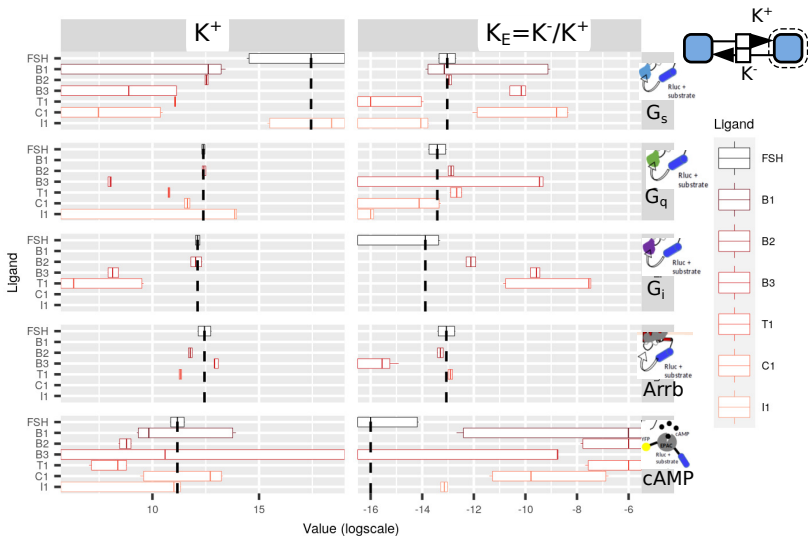


- Parameters : **initial quantity** of molecules (6) and **kinetic rates** (13)
- Kinetic rates values are **ligand dependent** (13*7) and reflect " **pharmacological ligand properties**."

Result 1 : it fits (global fit)



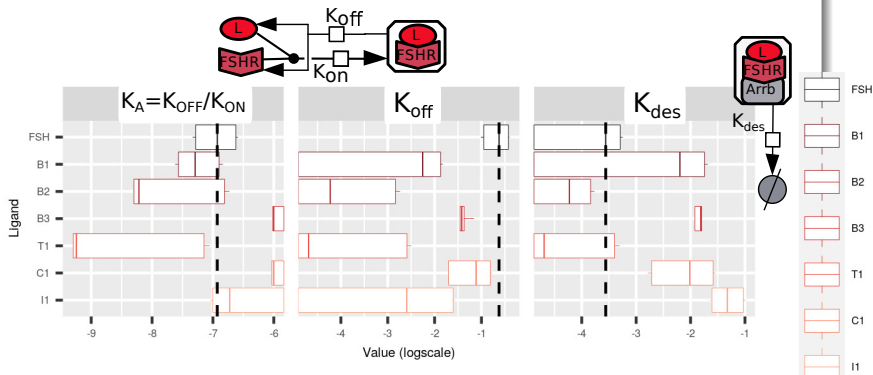
Result 2 : parameter values for each output



⇒ Large confidence intervals result from no signals and/or "incomplete/noisy" time series.

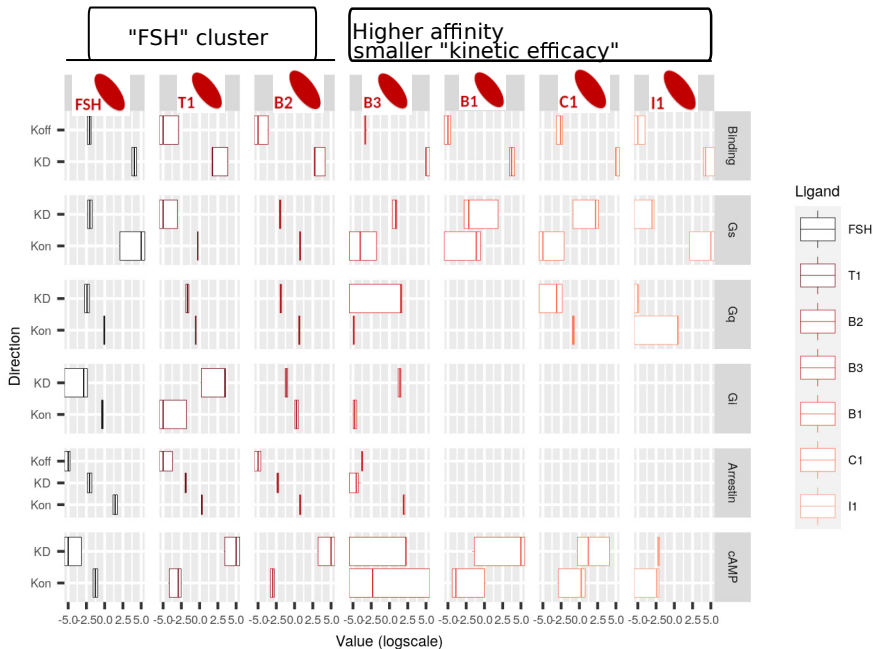
Result 2bis : parameter values for binding rates

Inferring Binding and Desensibilisation constants

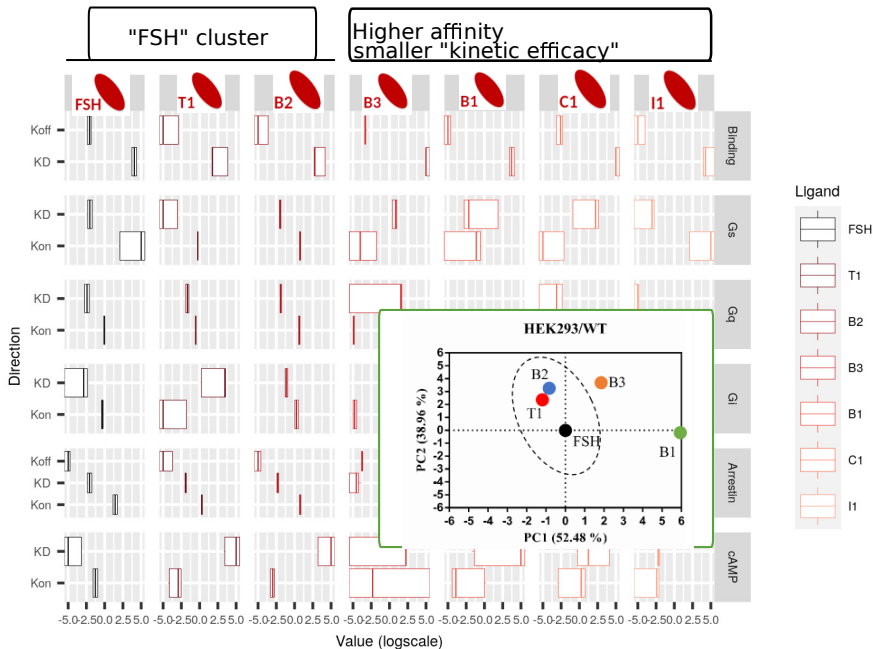


⇒ We can infer K_A (with potentially asymmetric confidence intervals).

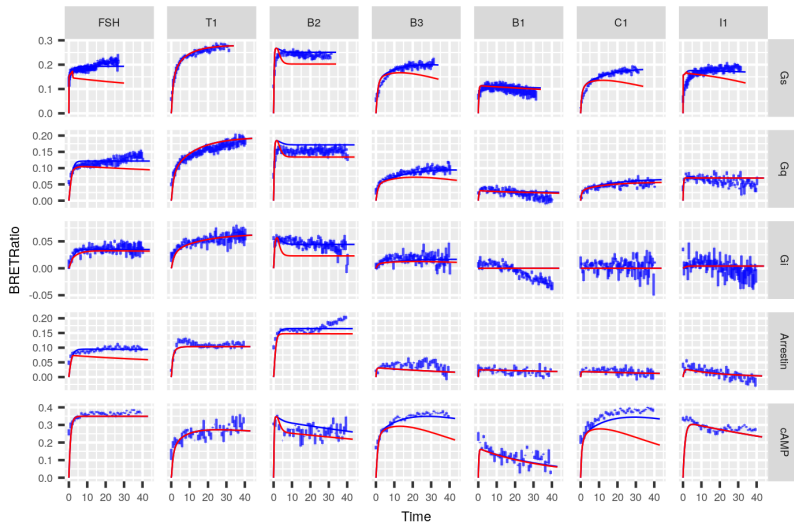
Result 3 : consistency with the Operational model



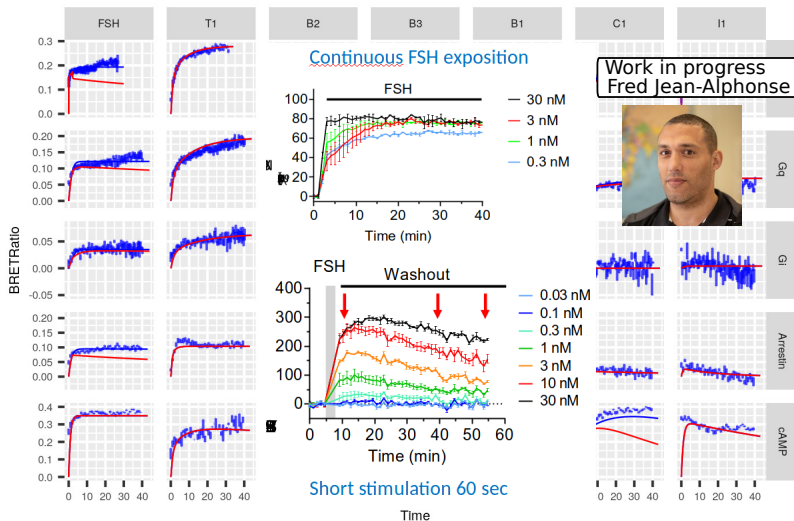
Result 3 : consistency with the Operational model



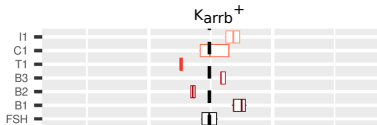
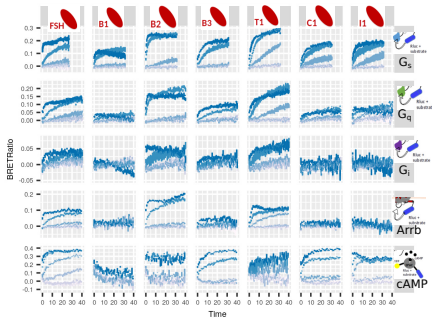
Additional feature : prediction



Additional feature : prediction



Take home message : use Maths!



Kinetic pathway modeling to

- # Fully exploit kinetic data
- # Give mechanistic insight of Bias signaling and infer ligand dependent kinetic

$$\frac{d}{dt}[LR] = k_{ON}[L][R] - k_{OFF}[LR]$$

