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

Romain Yvinec

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

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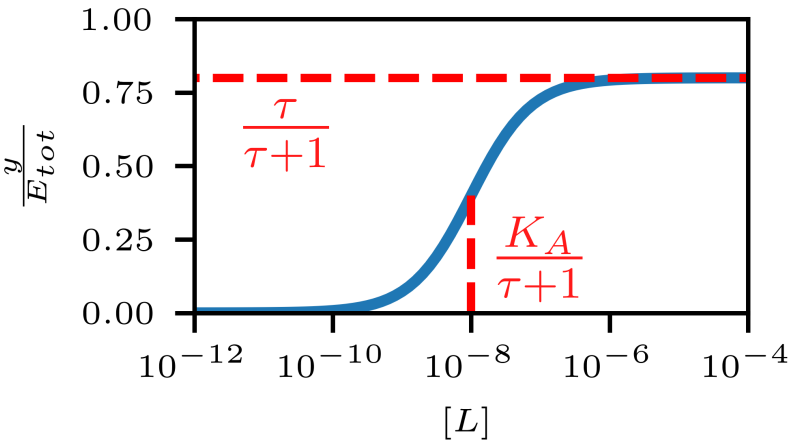
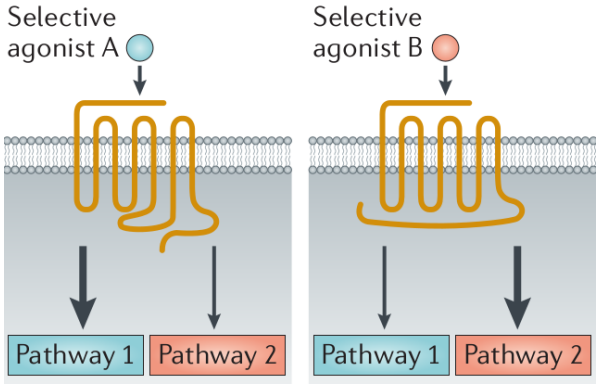
Intro : Bias quantification

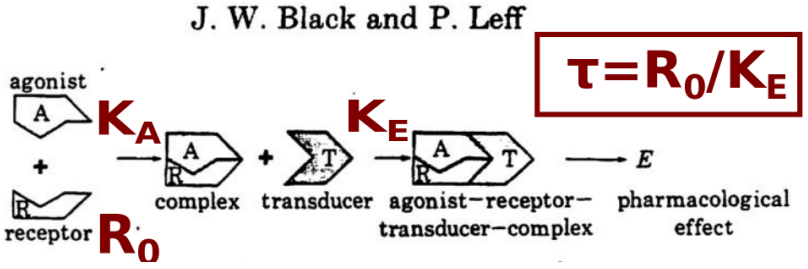
Operational model

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





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



Equilibrium operational model

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

$\Rightarrow$ **Transduction coefficient** :

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

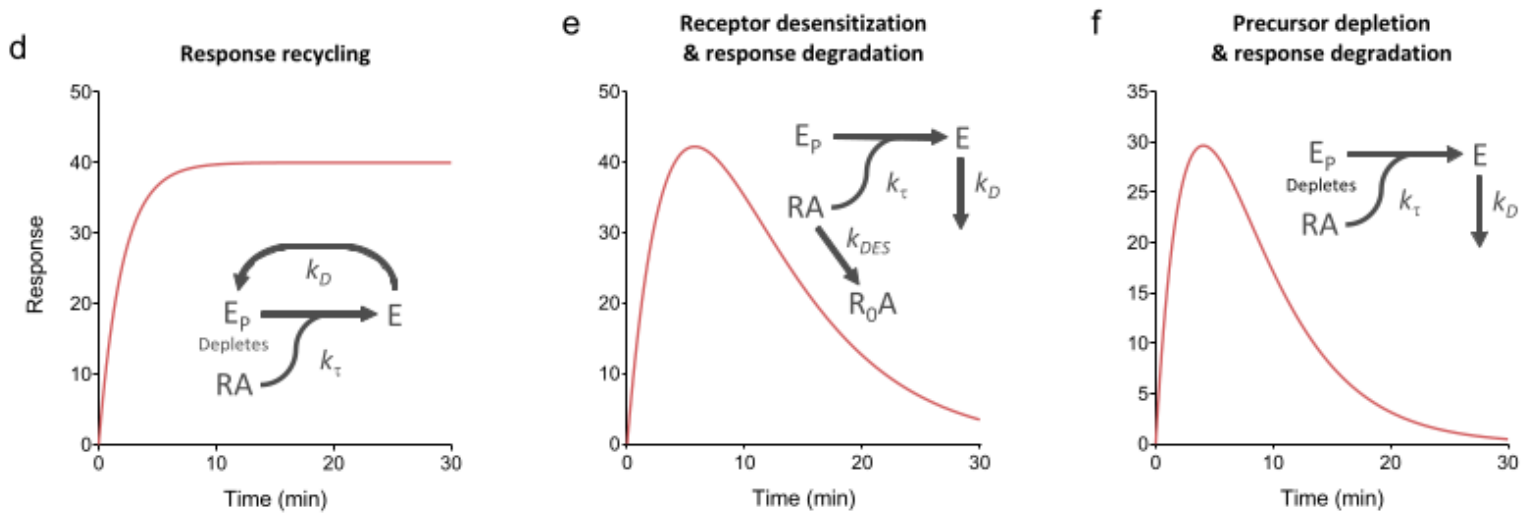
Intro : Time-dependent bias ?

The role of kinetic context in apparent biased agonism at GPCRs

Carmen Klein Herenbrink[1], David A. Sykes[2], Prashant Donthamsetti[3,4], Meritxell Canals[1], Thomas Coudrat[1], Jeremy Shonberg[5], Peter J. Scammells[5], Ben Capuano[5], Patrick M. Sexton[1], Steven J. Charlton[2], Jonathan A. Javitch[3,4,6], Arthur Christopoulos[1] & J Robert Lane[1]

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

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

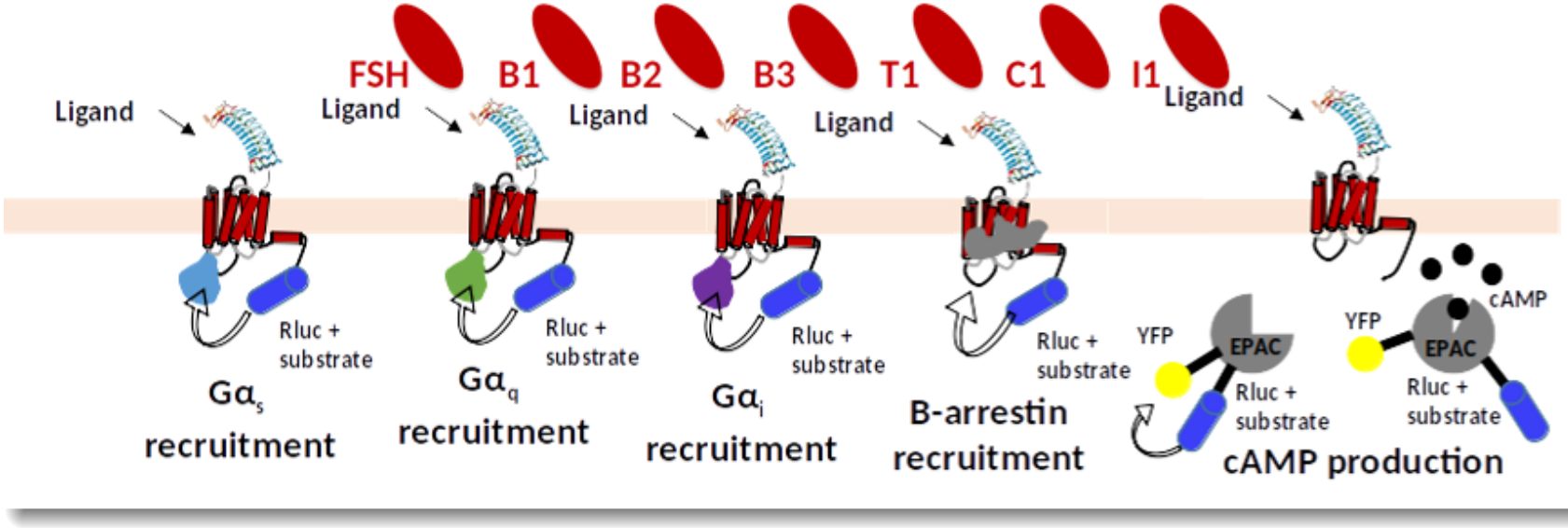


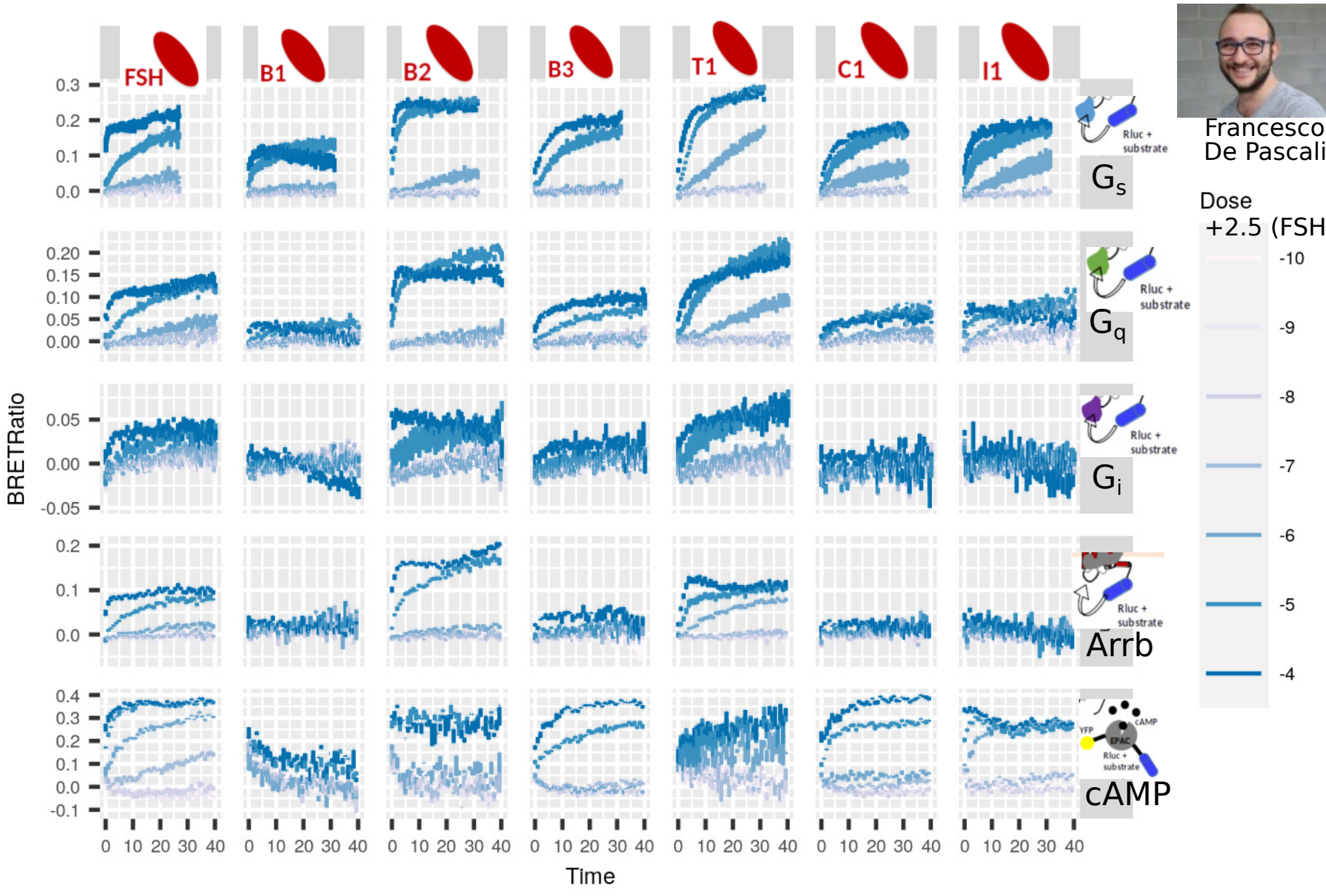
Hoare et al., *JTB* (2018)

Case study

Case study on FSHR : De Pascali et al IJMS 2021

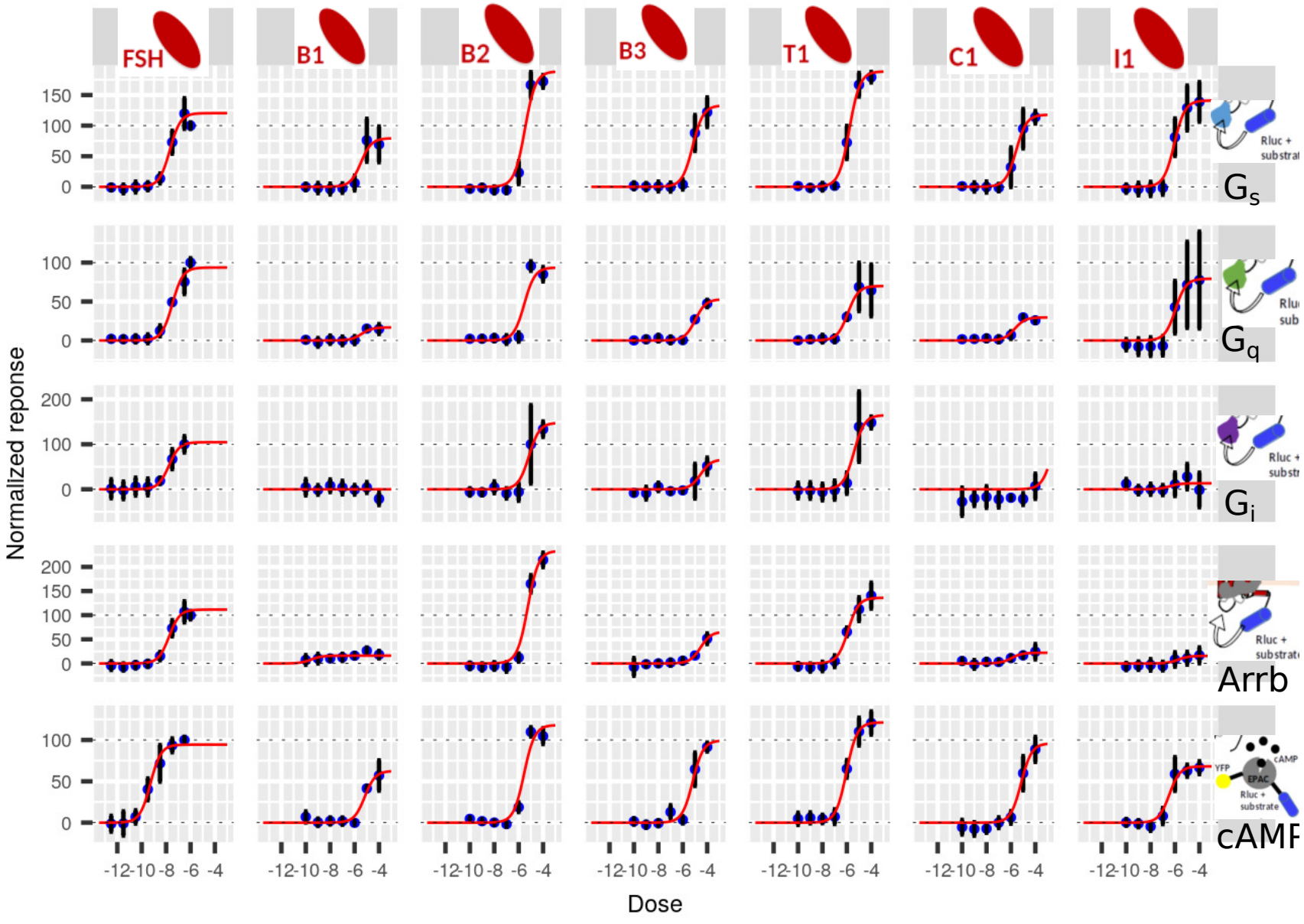
- ⋆ 5 BRET sensors : NES-Venus mG, yPET- β-arrestin 2, Camyel
- ⋆ FSH + 6 LMW compounds (Benzamides, Thiazolidinone, Chromenopyrazole, Imidazole) (TocopheRx, Burlington, VT, USA).



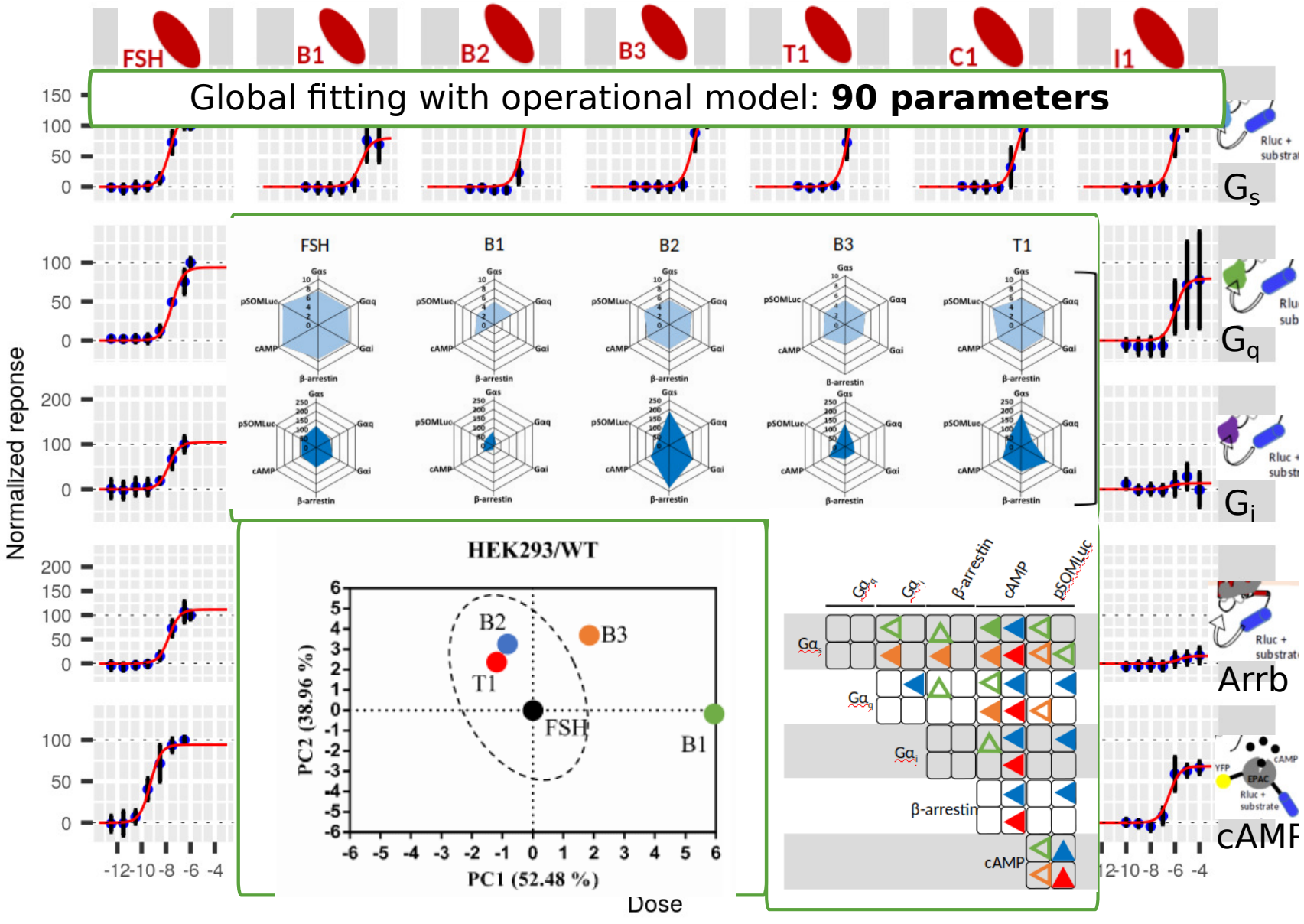


Francesco De Pascali

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

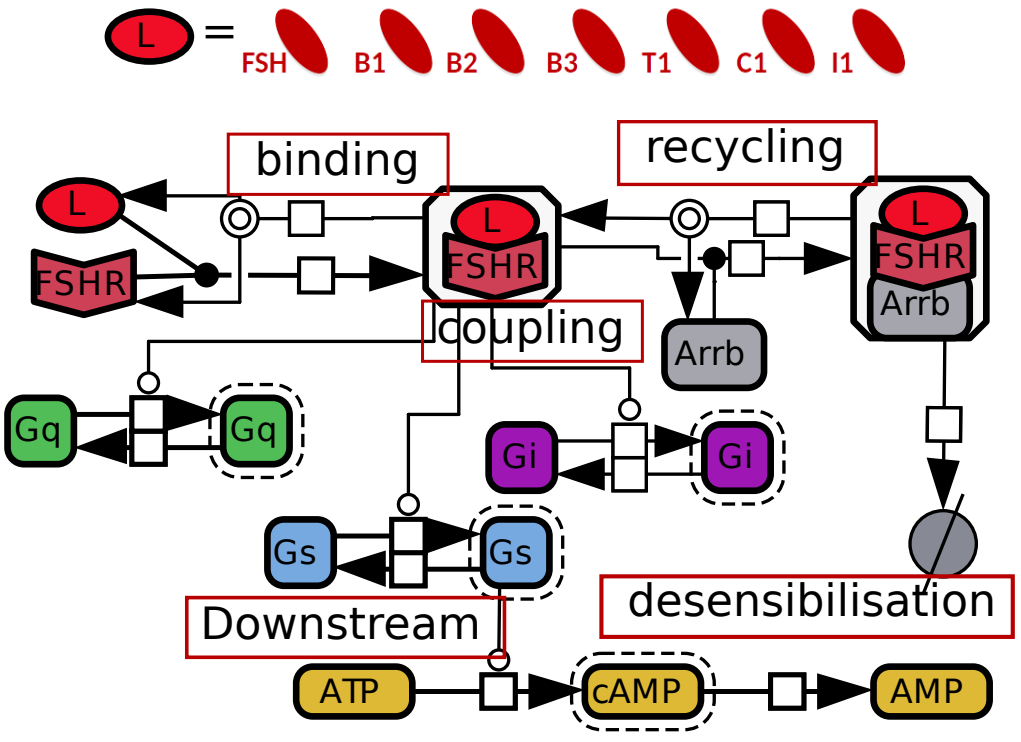


Operational model with A.U.C (De Pascali et al 21)



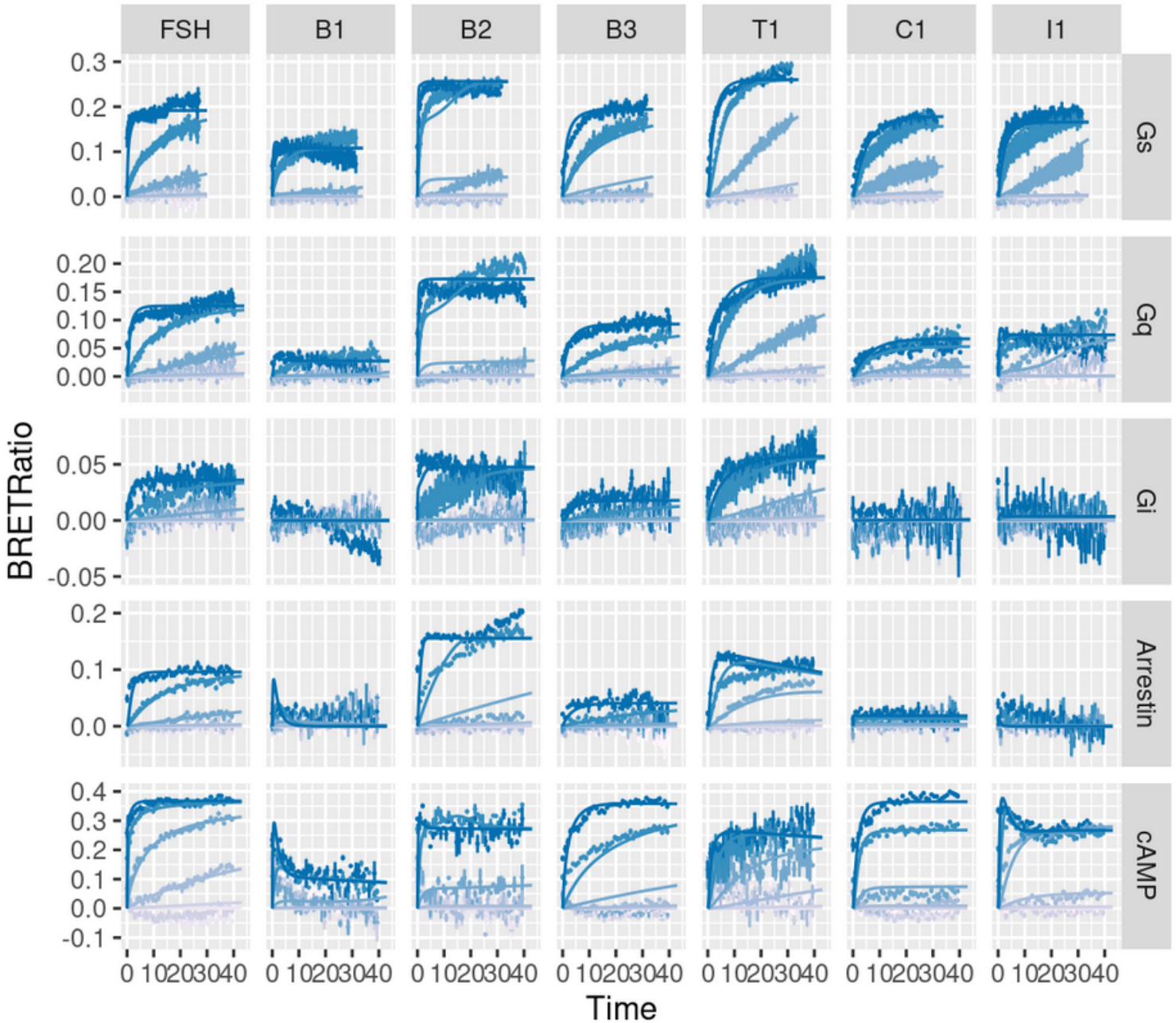
Reaction network : multiple Pathways modeling

Mechanistic link with data

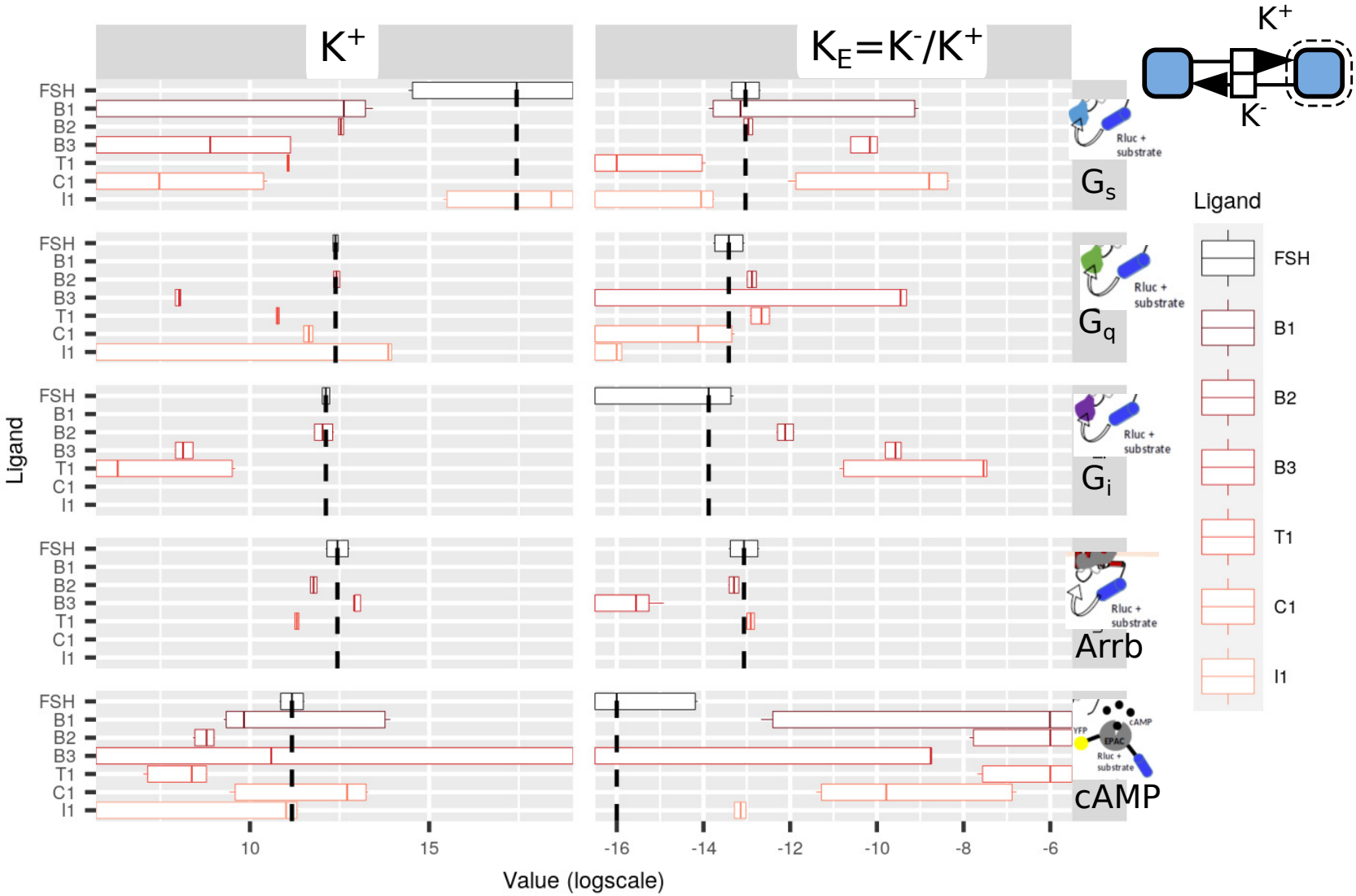


- Paramaters : initial quantity of molecules (6) and kinetic rates (13)
- Kinetic rates values are ligand dependent (13*7) and reflect¨ pharmacological ligand properties.

Result 1 : it fits (global fit)



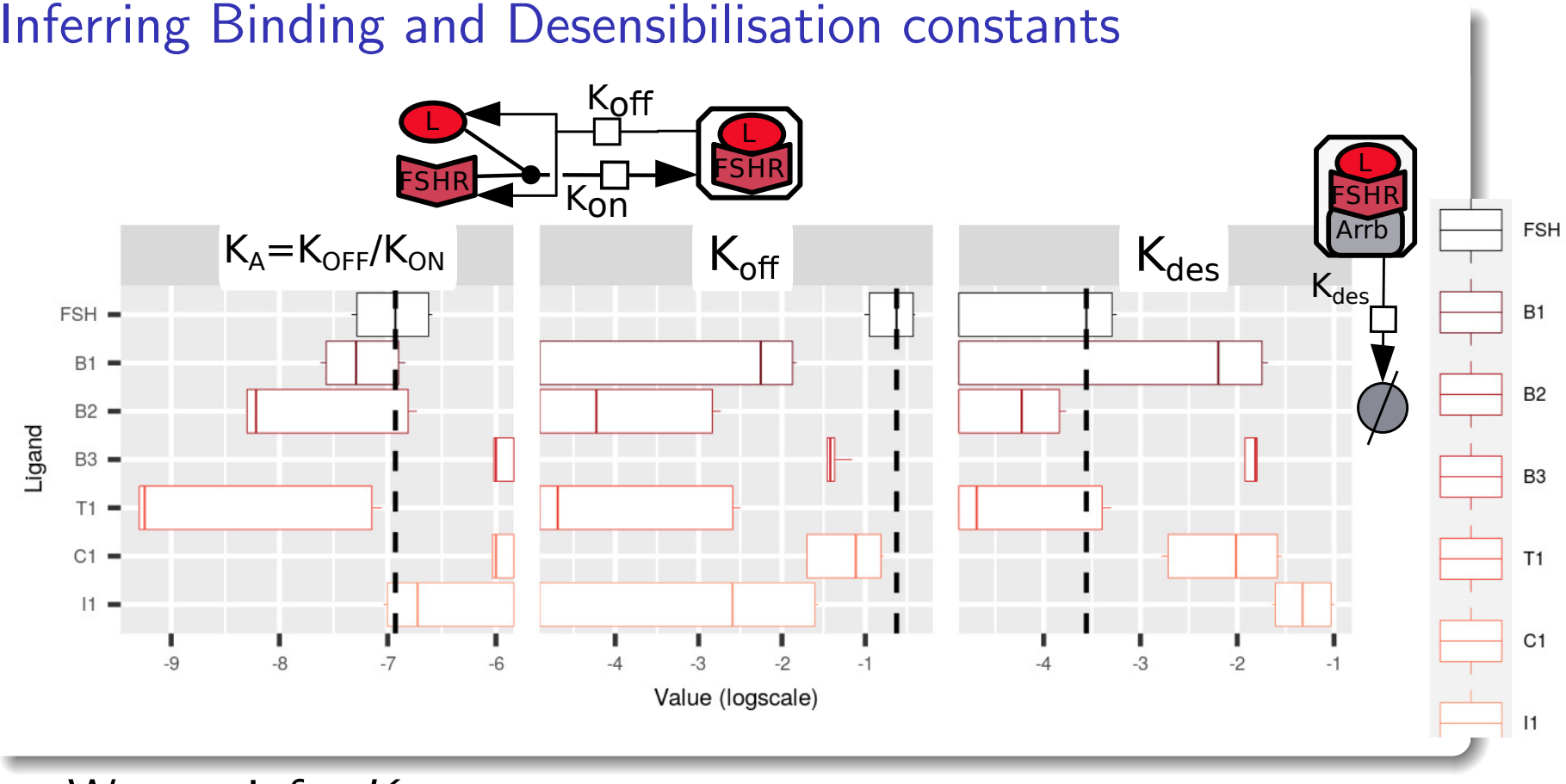
Result 2 : parameter values for each output



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

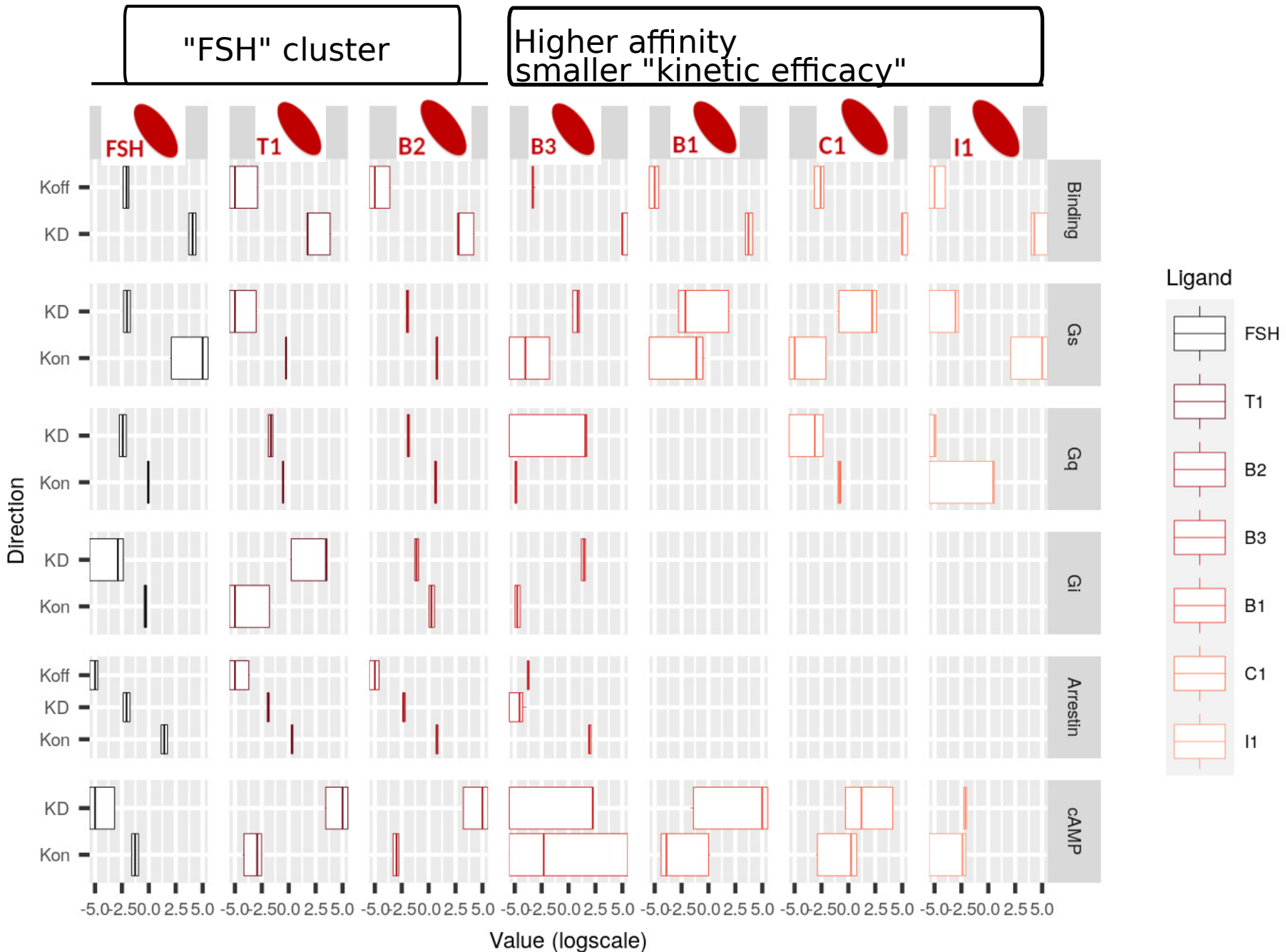
Result 2bis : parameter values for binding rates

Inferring Binding and Desensibilisation constants



$\Rightarrow$ We can infer K_A (with potentially asymmetric confidence intervals).

Result 3 : consistency with the Operational model



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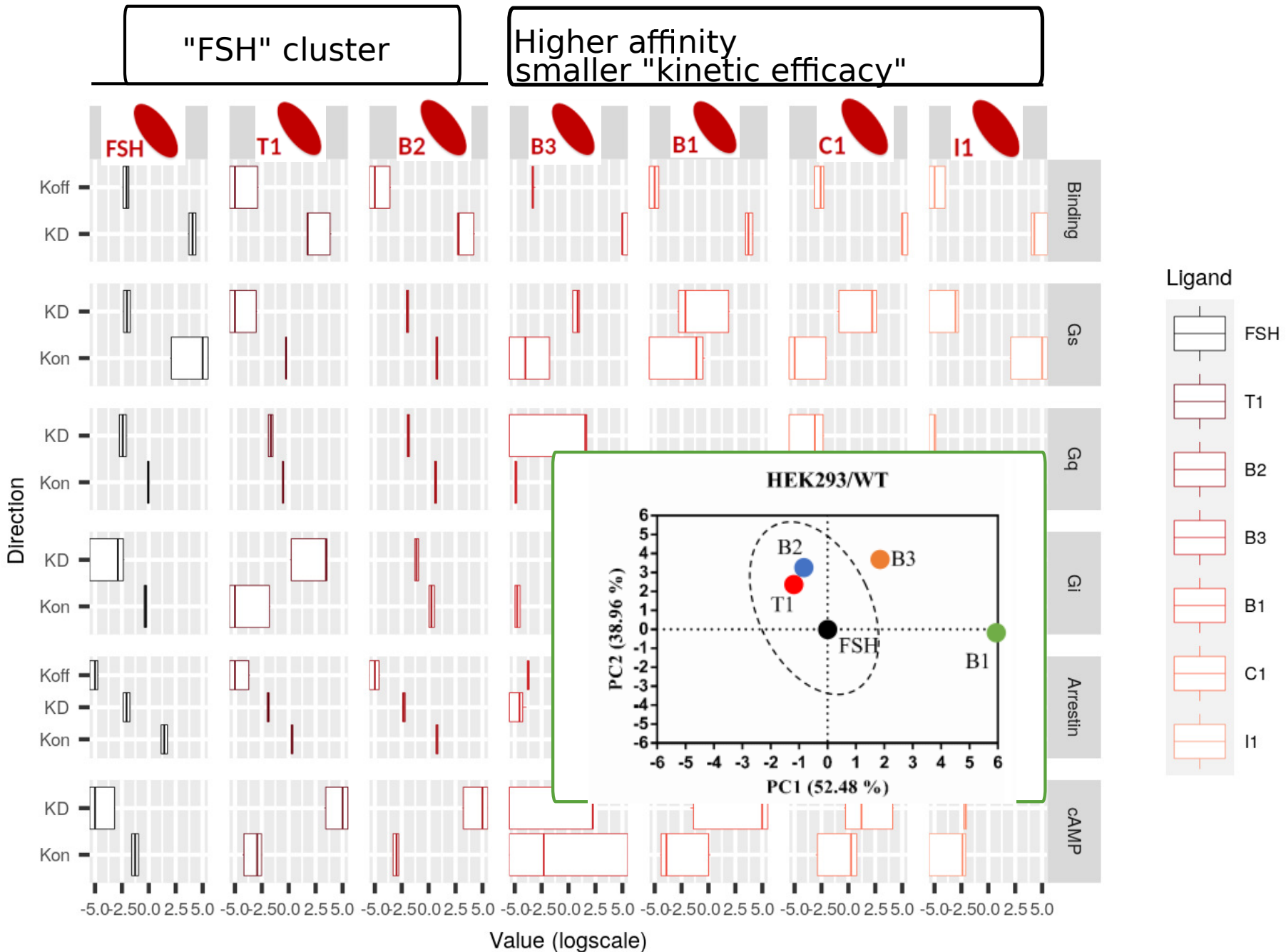
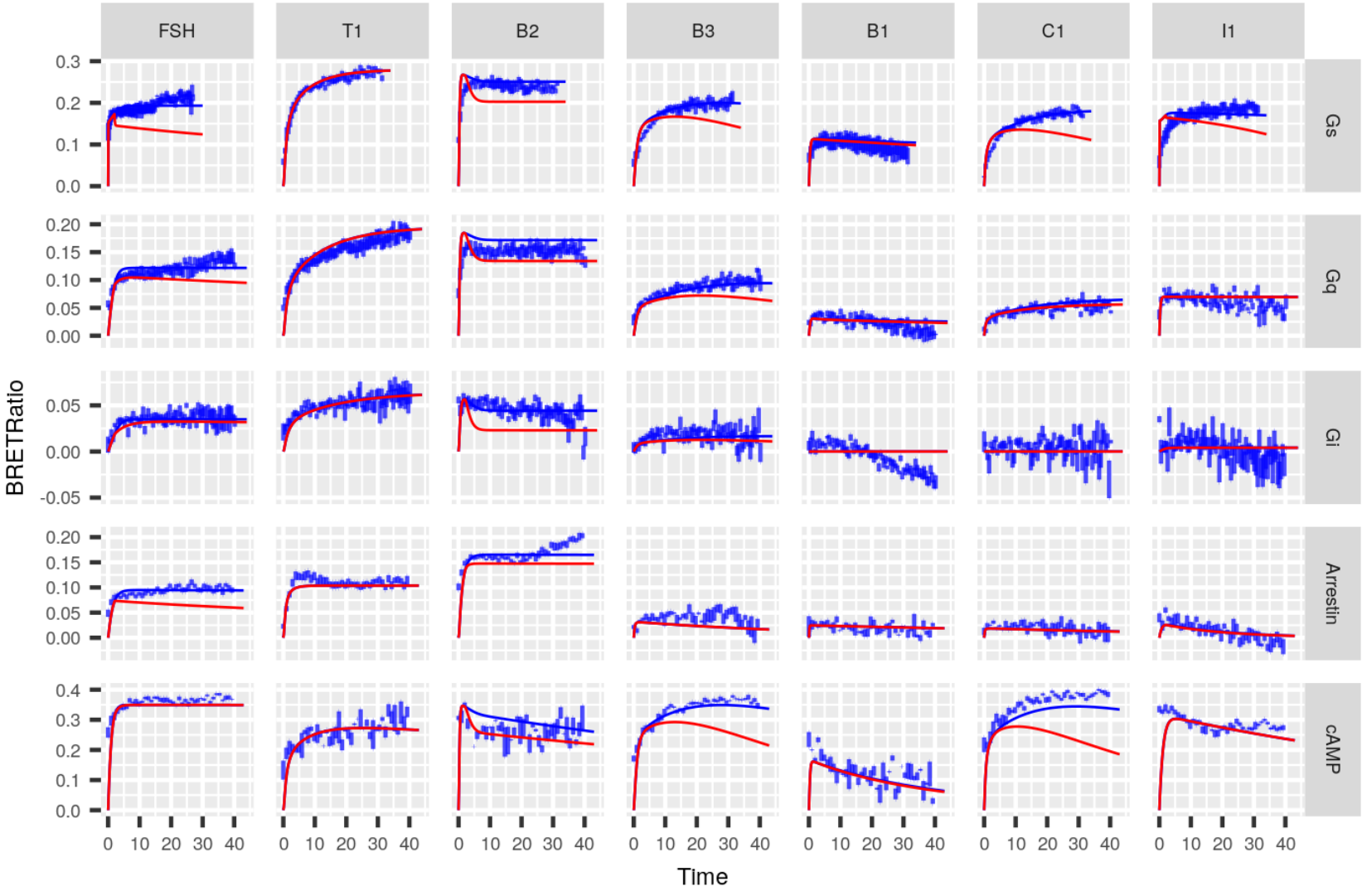
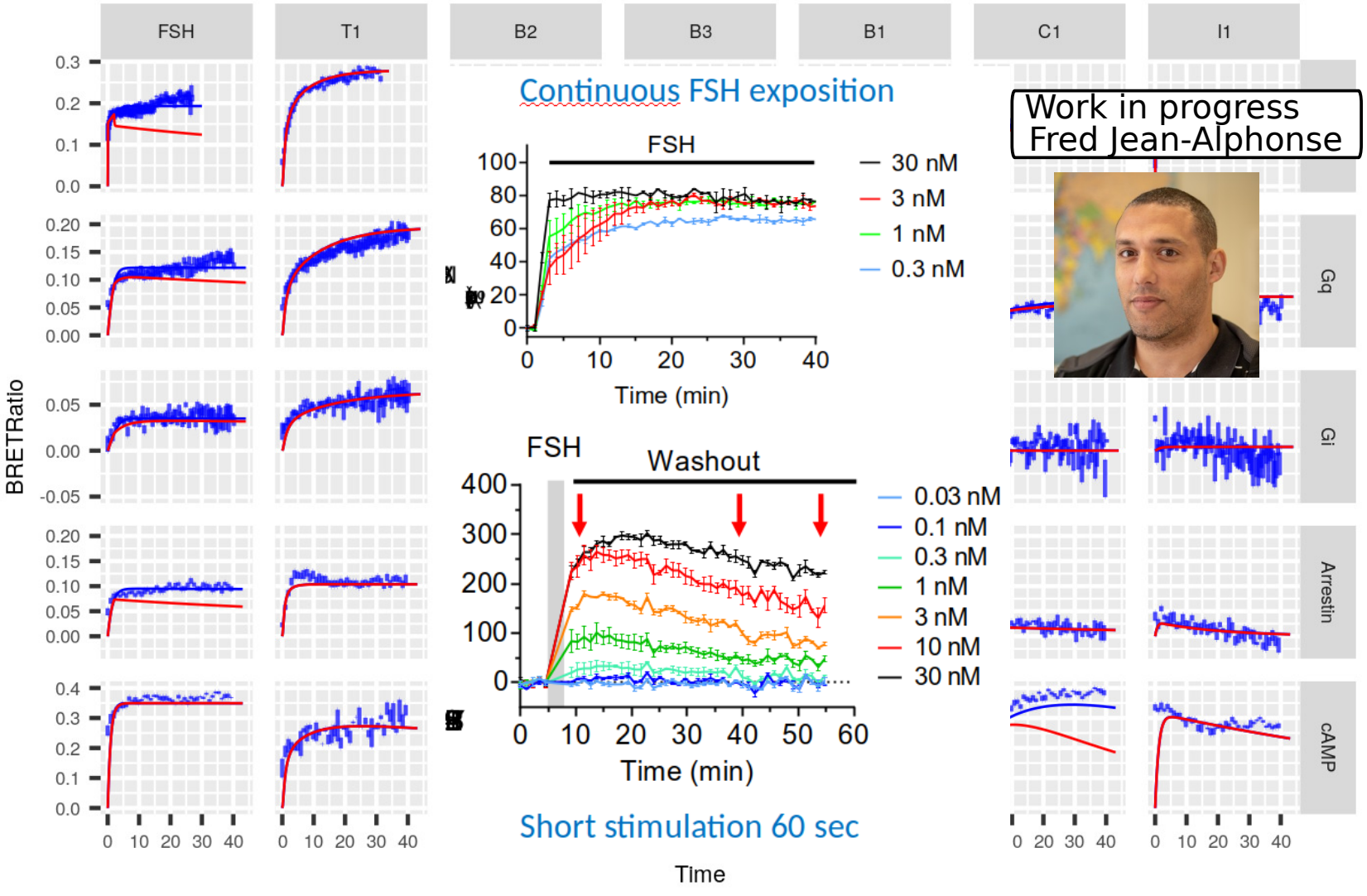


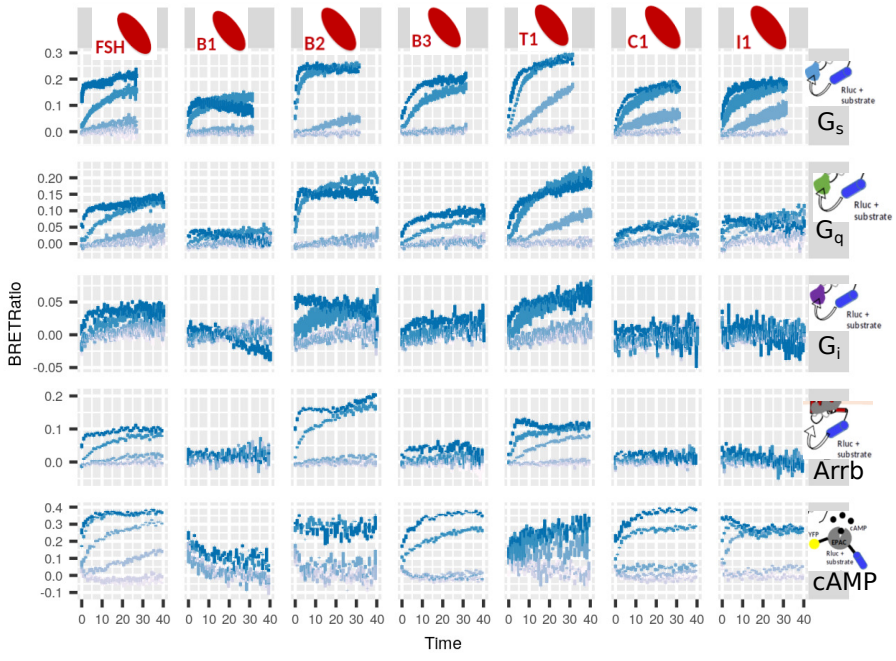
Additional feature : prediction

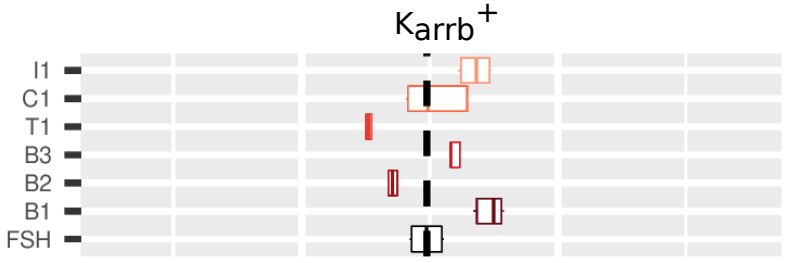


Additional feature : prediction



Take home message : use Maths !





Kinetic pathway modeling to

Fully exploit kinetic data

Give mechanistic insight of Bias signaling and infer ligand dependent kinetic

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