



KINETIC BIASED SIGNALING : A SYSTEM BIOLOGY DEFINITION OF DRUGS SELECTIVITY

F. Depascali, M. Akiliayoub, S. Nataraja, H. Yu, S. Palmer, Romain Yvinec,
Eric Reiter

► To cite this version:

F. Depascali, M. Akiliayoub, S. Nataraja, H. Yu, S. Palmer, et al.. KINETIC BIASED SIGNALING : A SYSTEM BIOLOGY DEFINITION OF DRUGS SELECTIVITY. 8ème conférence internationale GDR3545-GPCR, Oct 2019, Montpellier, France. hal-03115082

HAL Id: hal-03115082

<https://hal.science/hal-03115082>

Submitted on 19 Jan 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

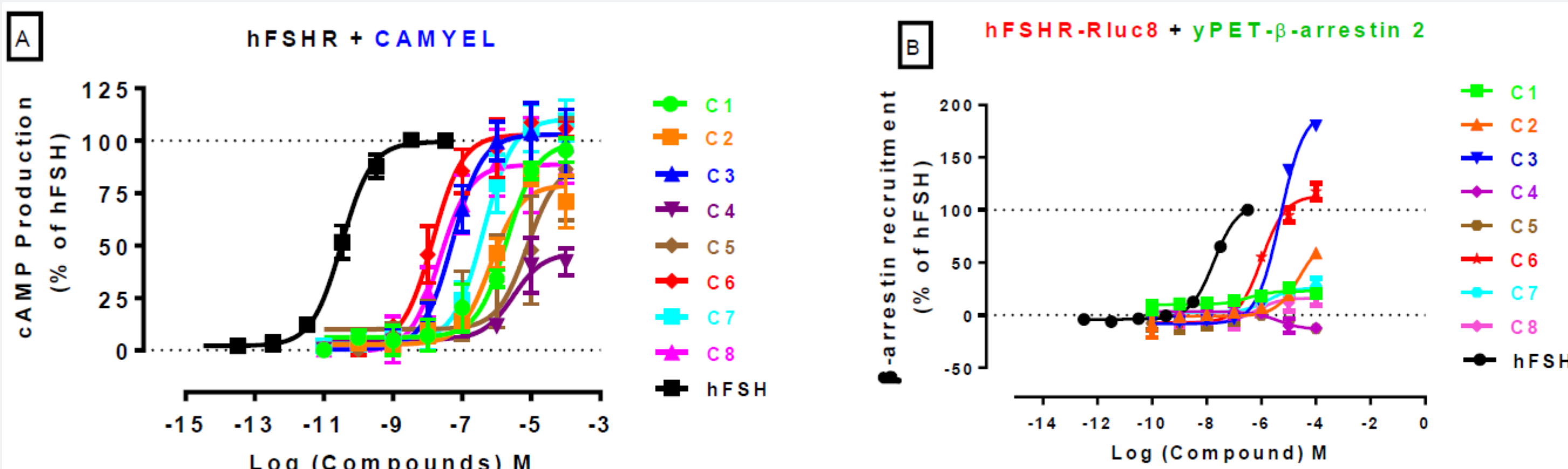
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

BIASED SIGNALING : SELECTIVE ACTIVATION OF TRANSDUCTION PATHWAYS

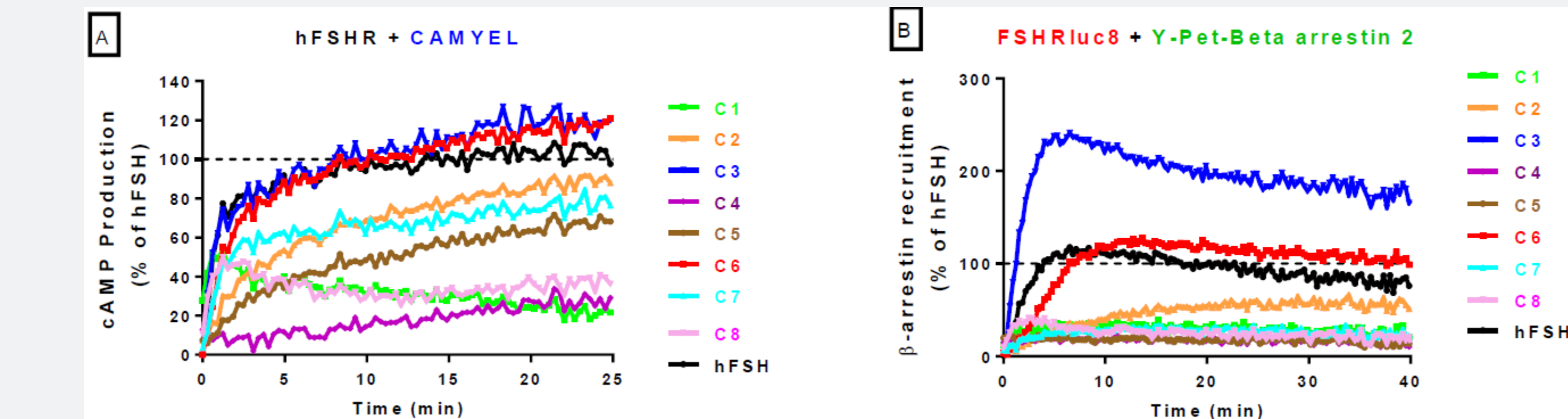
- Receptor conformations **selectively stabilized** by a ligand → activation of downstream signaling pathways with **different efficacies**.
 - Quantitative pharmacology aims to **quantify ligand bias** in order to **classify** ligands according to their selectivity.
 - Gold-standard method [3] use the **operational model** with dose-response curves to infer transduction coefficient and bias factor.
 - Several groups have pointed out **limitations** of this method [2, 4]. Yet, most improvements keep with **fitting dose-response curves**.
- ⇒ Following recent works [2, 1], we suggest to take into account kinetic data by using a **dynamical model** to provide a complete “bias map” of a ligand, taking into account the **full complexity of signaling networks** and their **kinetic signatures**.

DOSE-RESPONSE VS KINETIC DATA

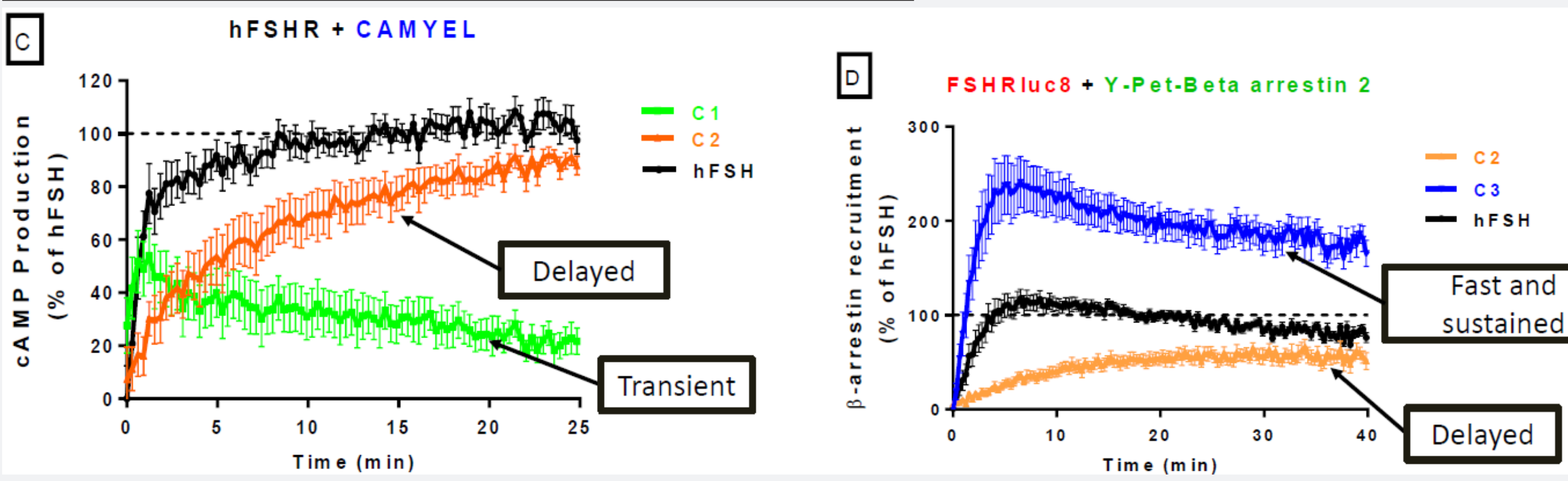
Dose-response data: end-point or AUC



Kinetic data



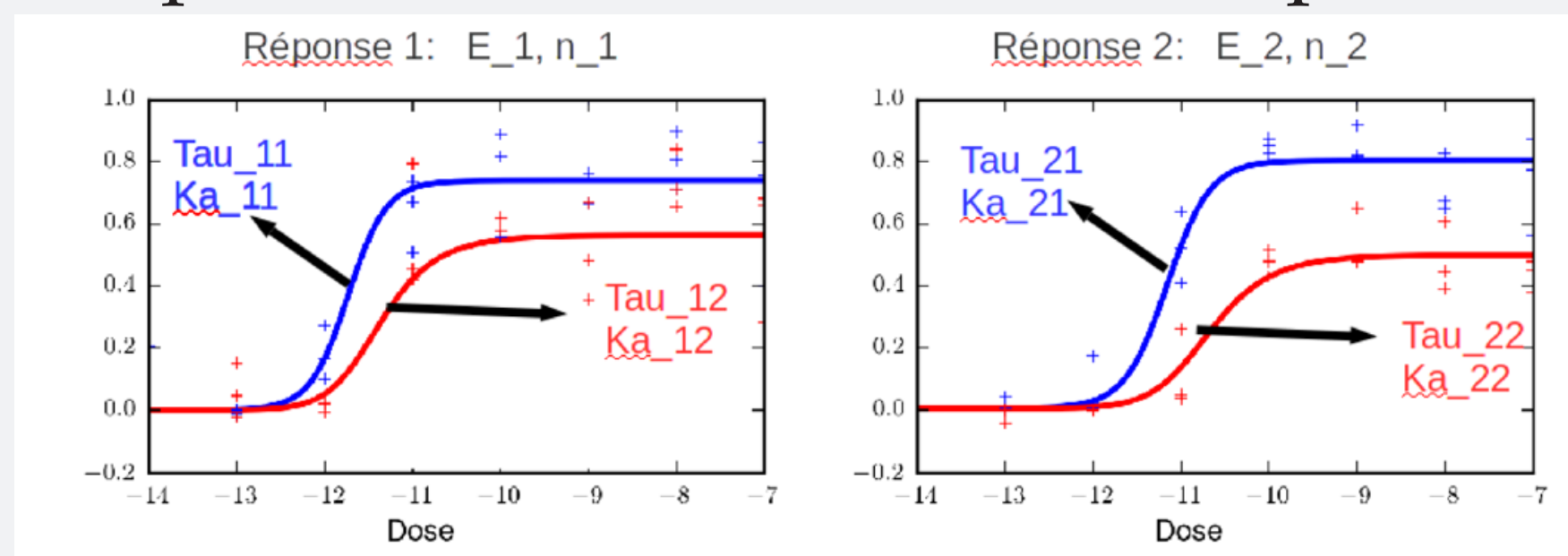
Why taking into account kinetic data ?



DOSE-RESPONSE BASED BIAS QUANTIFICATION

Fitting a parametrized sigmoid curve

Each dose-response data is fitted with the operational model:



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

The transduction coefficient is $R = \tau/Ka$. For a given response i , we calculate $\Delta_i \log(R) = \log(R_{i2}) - \log(R_{i1})$. The **Bias** is then defined by

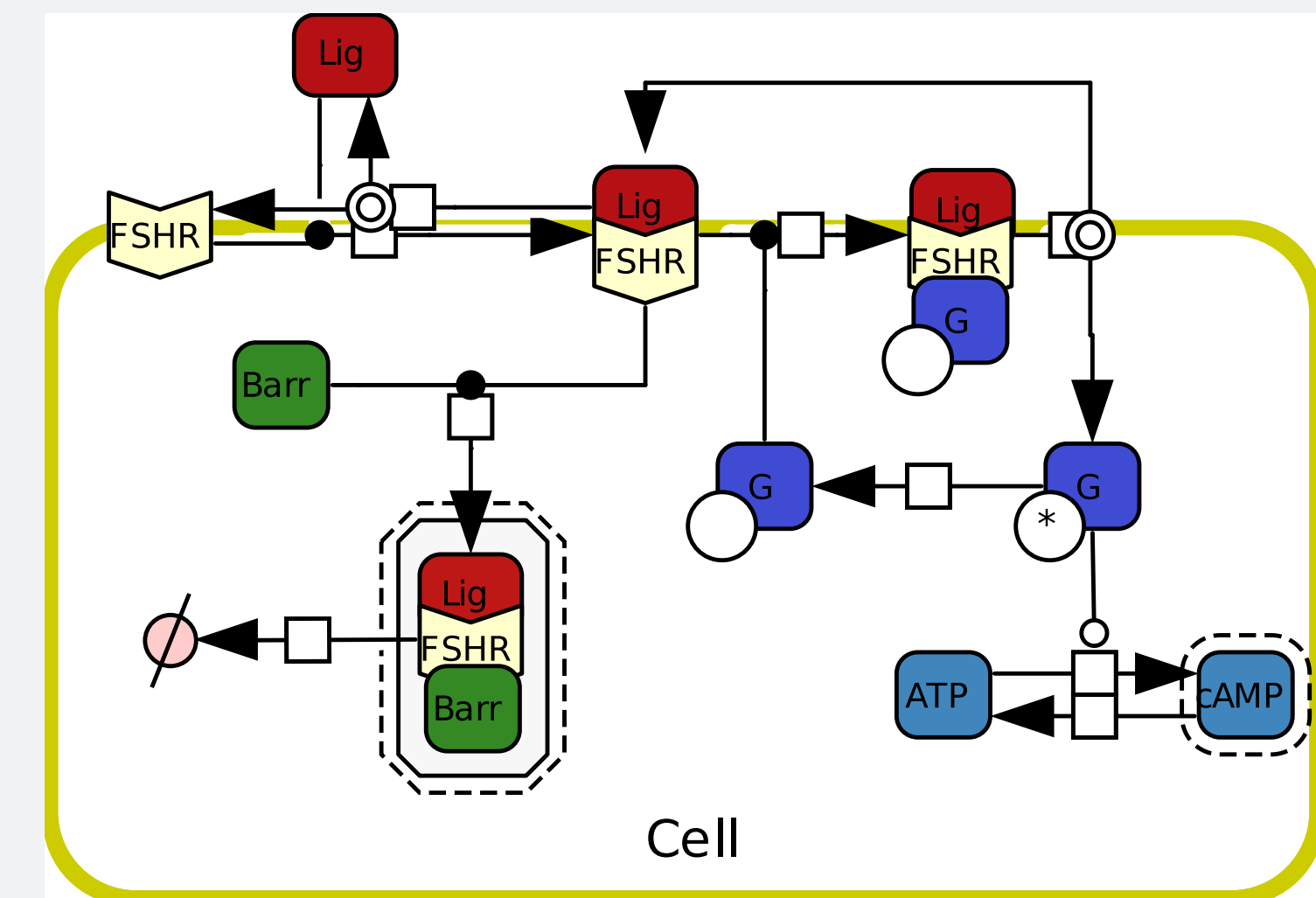
$$\Delta \Delta \log(R) = \Delta_2 \log(R) - \Delta_1 \log(R)$$

PROS AND CONS OF THE STANDARD METHOD

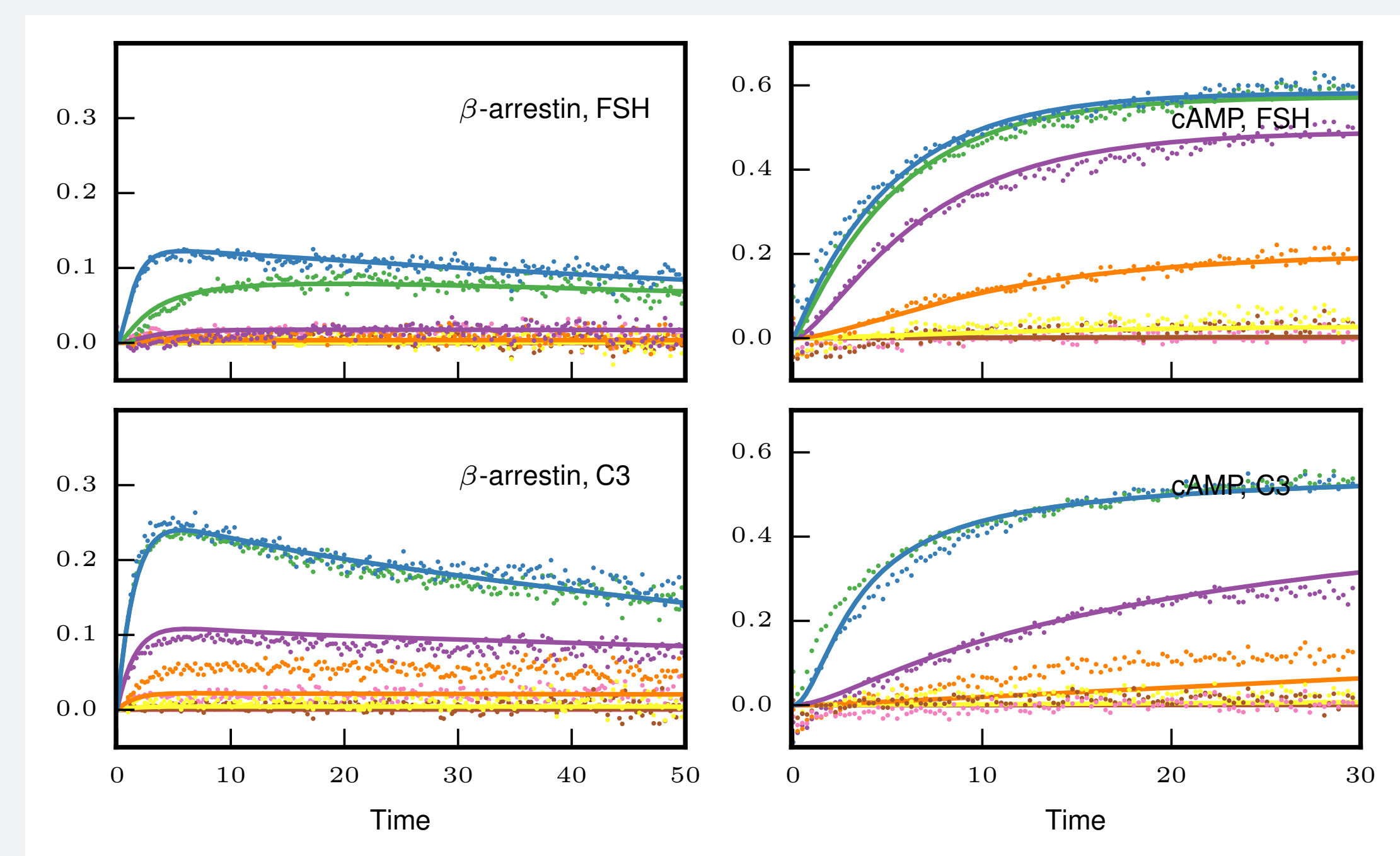
- Identifiability issues despite of a parsimonious model.
- Limited to increasing sigmoid scenario (yet more general model are possible)
- Lack of kinetic information, but genericity of the method

DYNAMIC BIAS SIGNALING

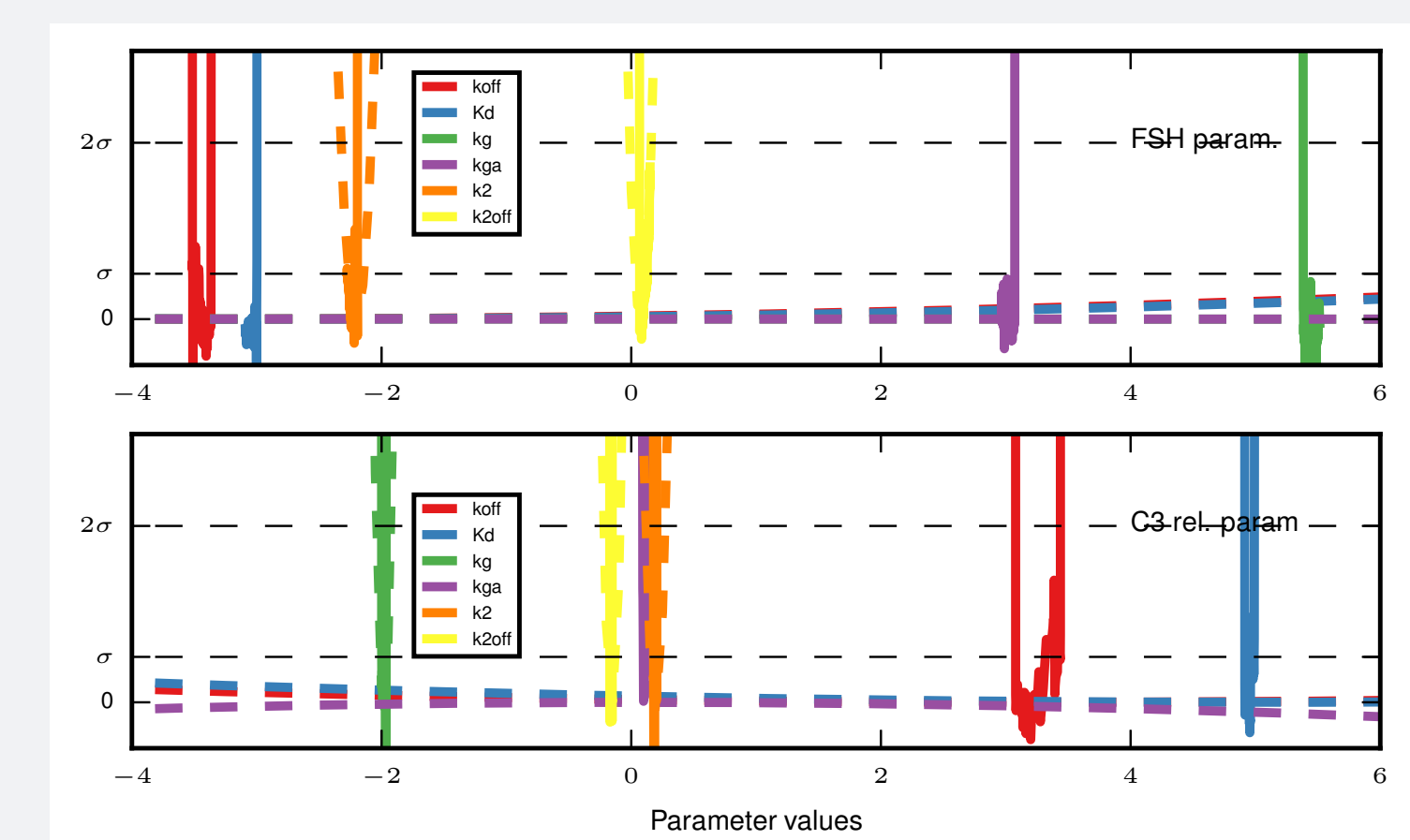
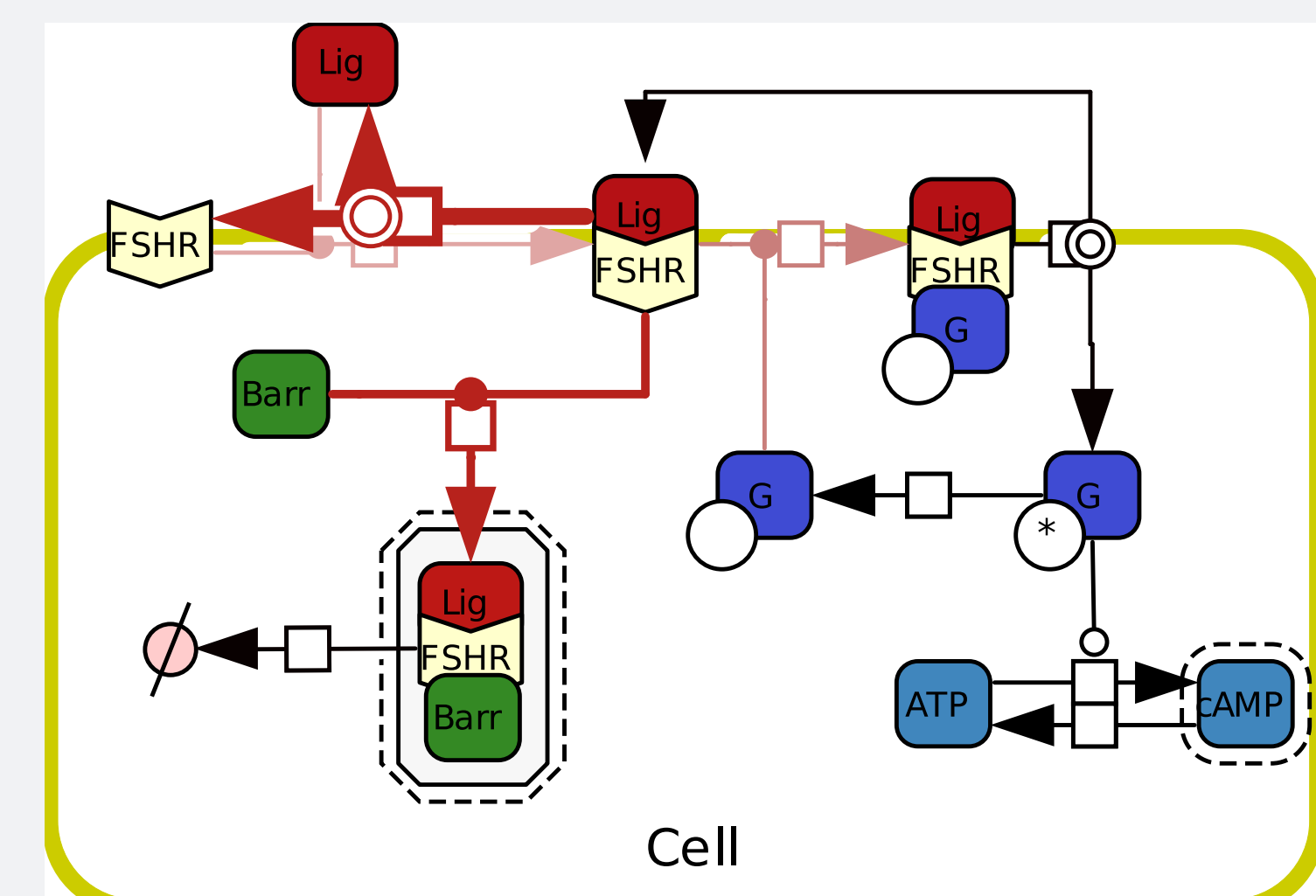
1) Chemical reaction network:



2) Model simulation and fitting (Parameter estimation)



3) Ligand-specific kinetic parameter and identifiability



PROS AND CONS OF THE NEW METHOD

- Kinetic data are fully taken into account, but the bias is not a single value.
- Identifiability is an issue, but can be resolved by model reduction.
- The framework is generic [5], but needs to be adapted to each situation.

REFERENCES

- S. R. J. Hoare, N. Pierre, A. G. Moya, and B. Larson. Kinetic Operational Models of Agonism for G-Protein-Coupled Receptors. *Journal of Theoretical Biology*, 446:168–204, 2018.
- H. Klein and et al. The role of kinetic context in apparent biased agonism at GPCRs. *Nature Communications*, 7(10842), Feb. 2016.
- Y. Namkung, O. Radresa, S. Armando, D. Devost, A. Beutrait, C. Le Gouill, and S. A. Laporte. Quantifying biased signaling in GPCRs using BRET-based biosensors. *Methods*, 92:5–10, 2016.
- H. O. Onaran and et al. Systematic errors in detecting biased agonism: Analysis of current methods and development of a new model-free approach. *Scientific Reports*, 7:44247, Mar. 2017.
- R. Yvinec, M. A. Ayoub, F. De Pascali, P. Crépieux, E. Reiter, and A. Poupon. Workflow description to dynamically model β-arrestin signaling networks. *In press*.