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KINETIC BIASED SIGNALING : A SYSTEM BIOLOGY DEFINITION OF DRUGS SELECTIVITY

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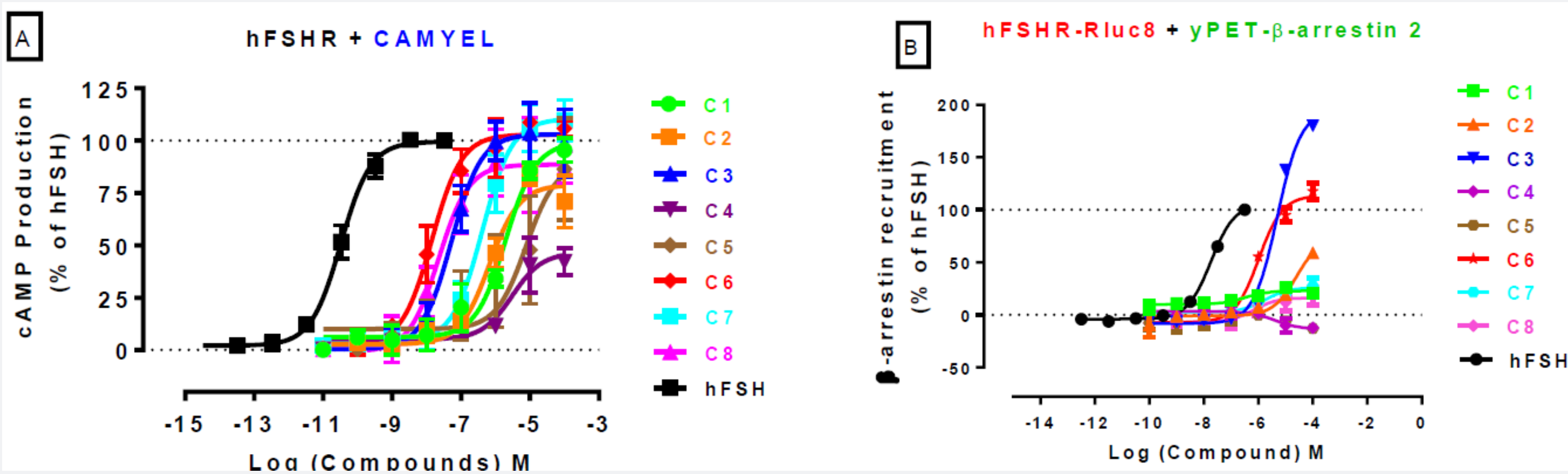
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BIASED SIGNALING : SELECTIVE ACTIVATION OF TRANSDUCTION PATHWAYS

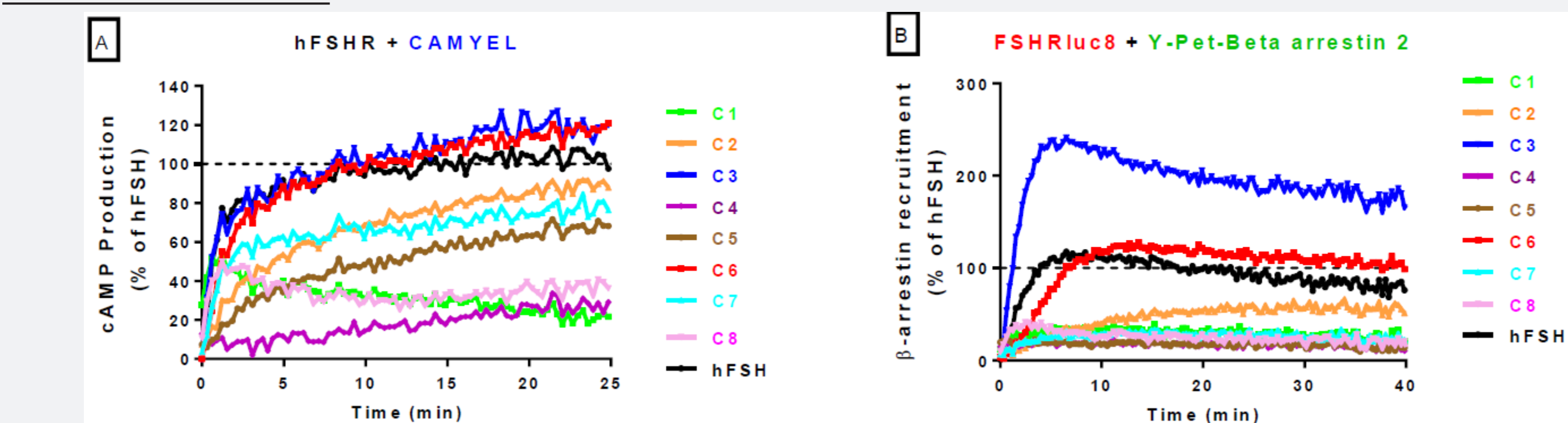
- Receptor conformations **selectively stabilized** by a ligand → activation of downstream signaling pathways with **different efficacies**.
- Quantitative pharmacology aims to **quantify ligand bias** in order to **classify** ligands according to their selectivity.
- Gold-standard method [3] use the **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

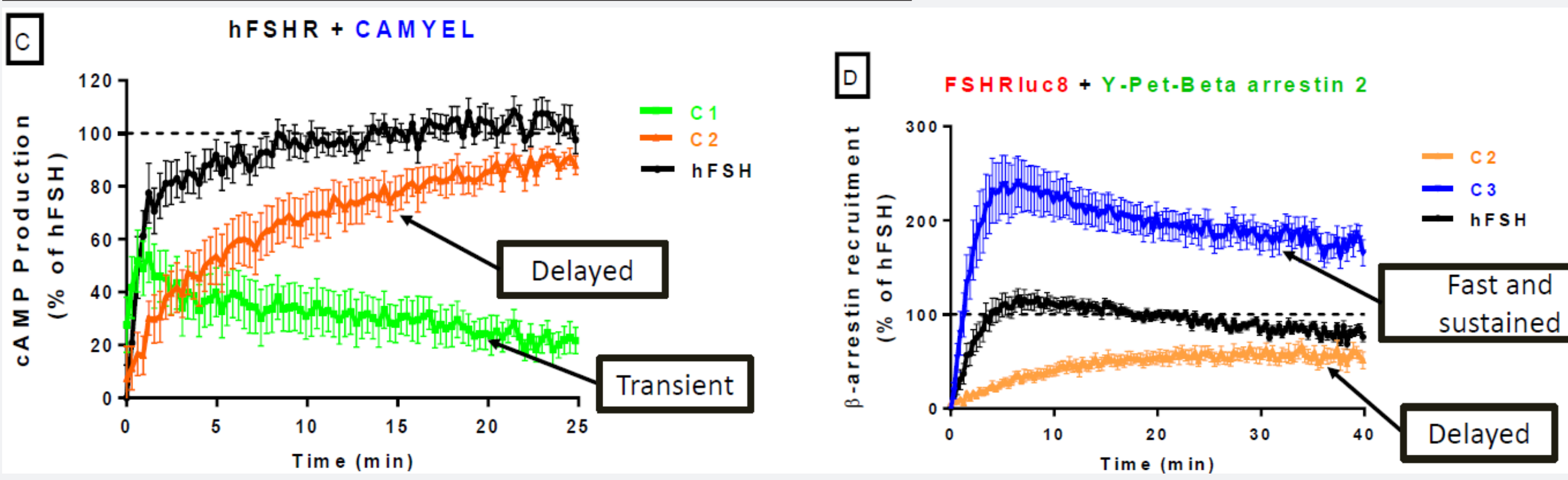
Dose-response data: end-point or AUC



Kinetic data



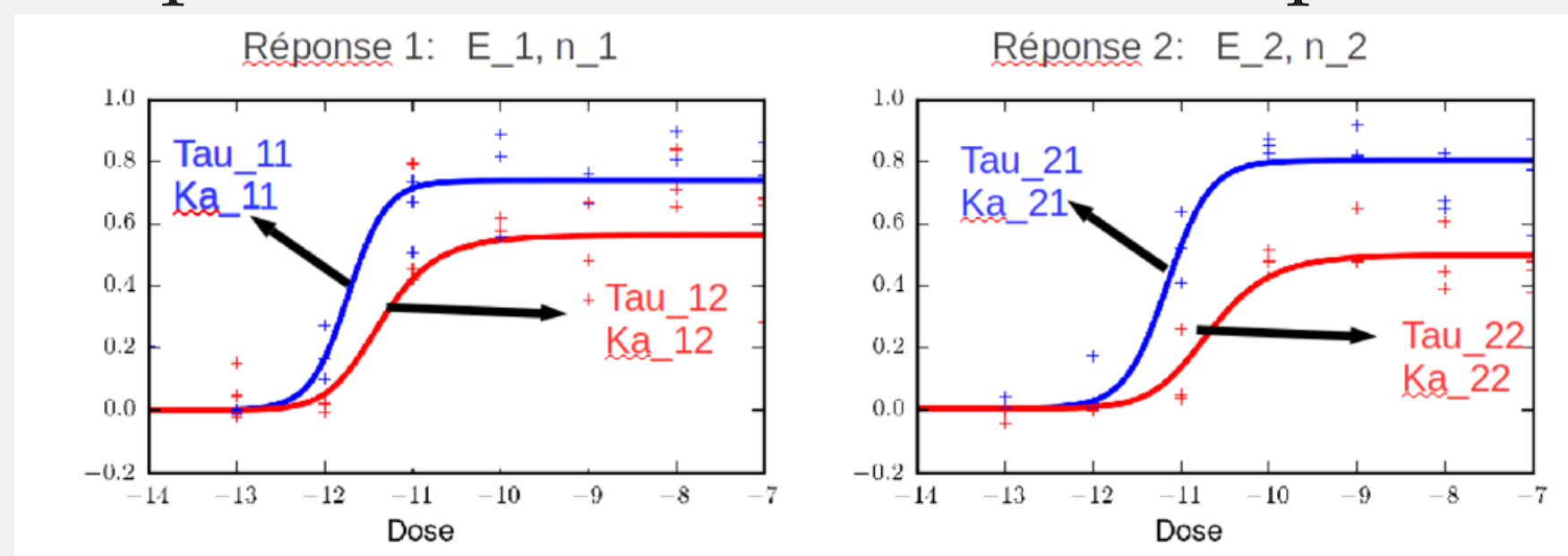
Why taking into account kinetic data?



DOSE-RESPONSE BASED BIAS QUANTIFICATION

Fitting a parametrized sigmoid curve

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



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

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

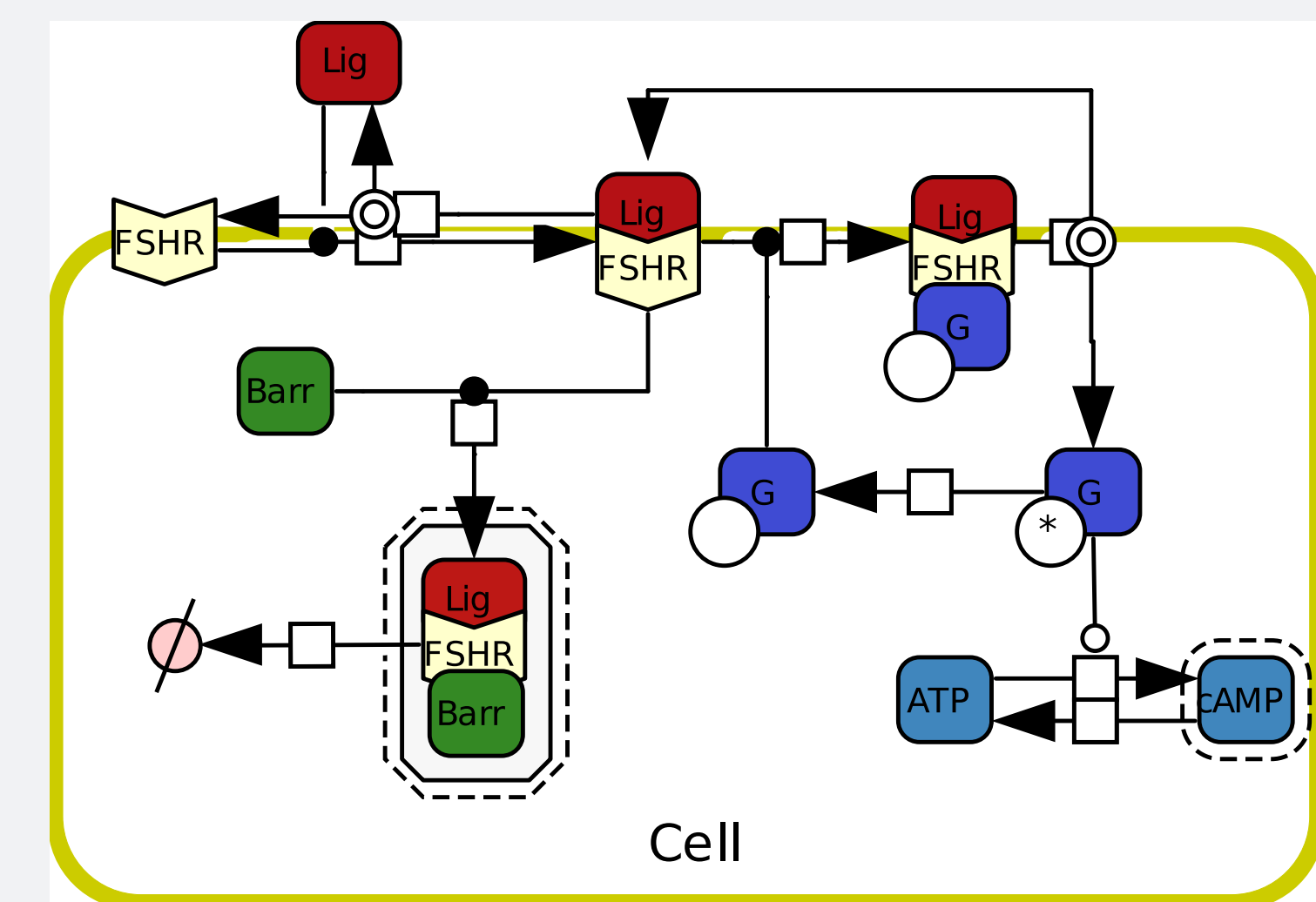
$$\Delta \Delta \log(R) = \Delta_2 \log(R) - \Delta_1 \log(R)$$

PROS AND CONS OF THE STANDARD METHOD

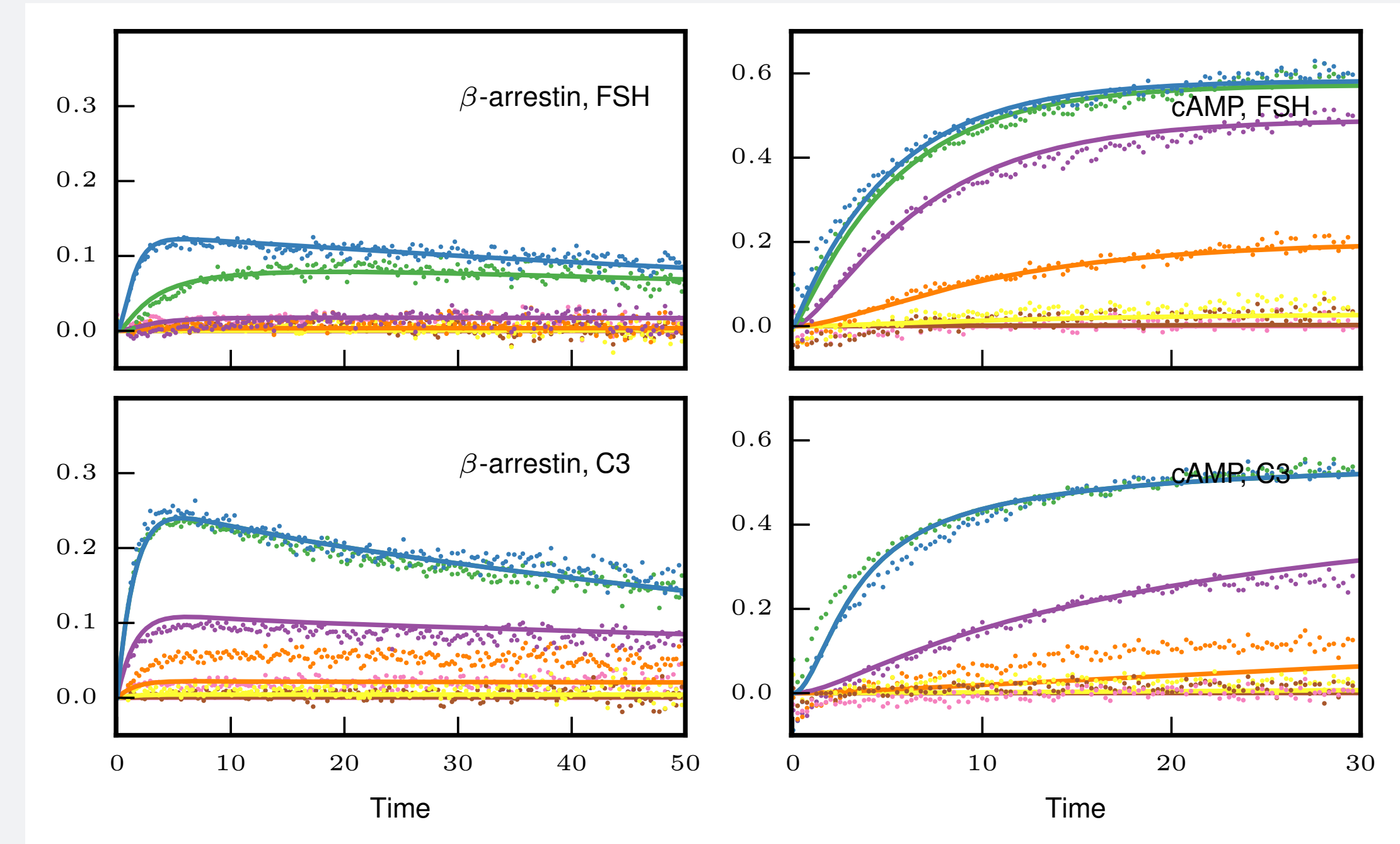
- Identifiability issues despite of a parsimonious model.
- Limited to increasing sigmoid scenario (yet more general model are possible)
- Lack of kinetic information, but genericity of the method

DYNAMIC BIAS SIGNALING

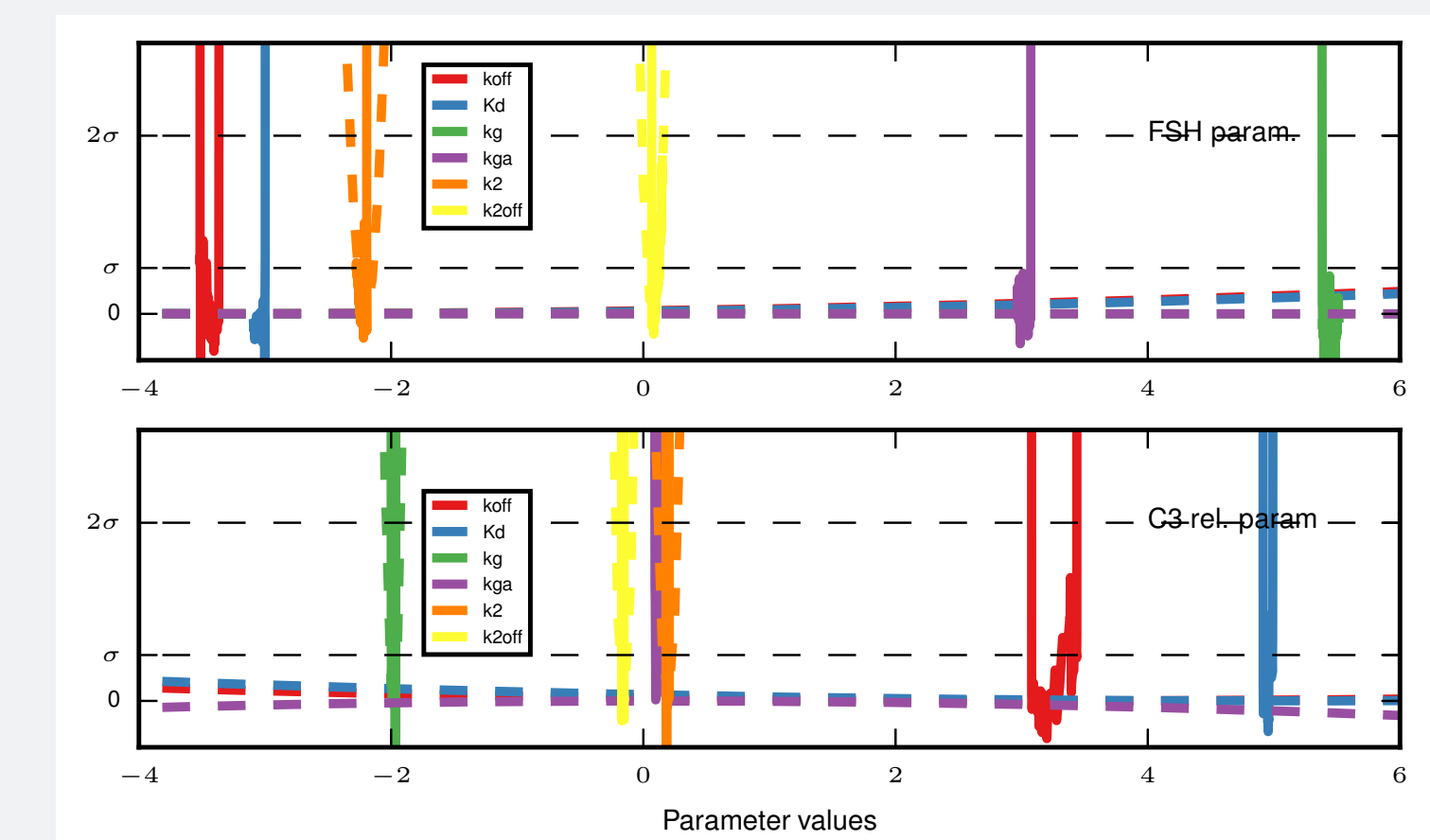
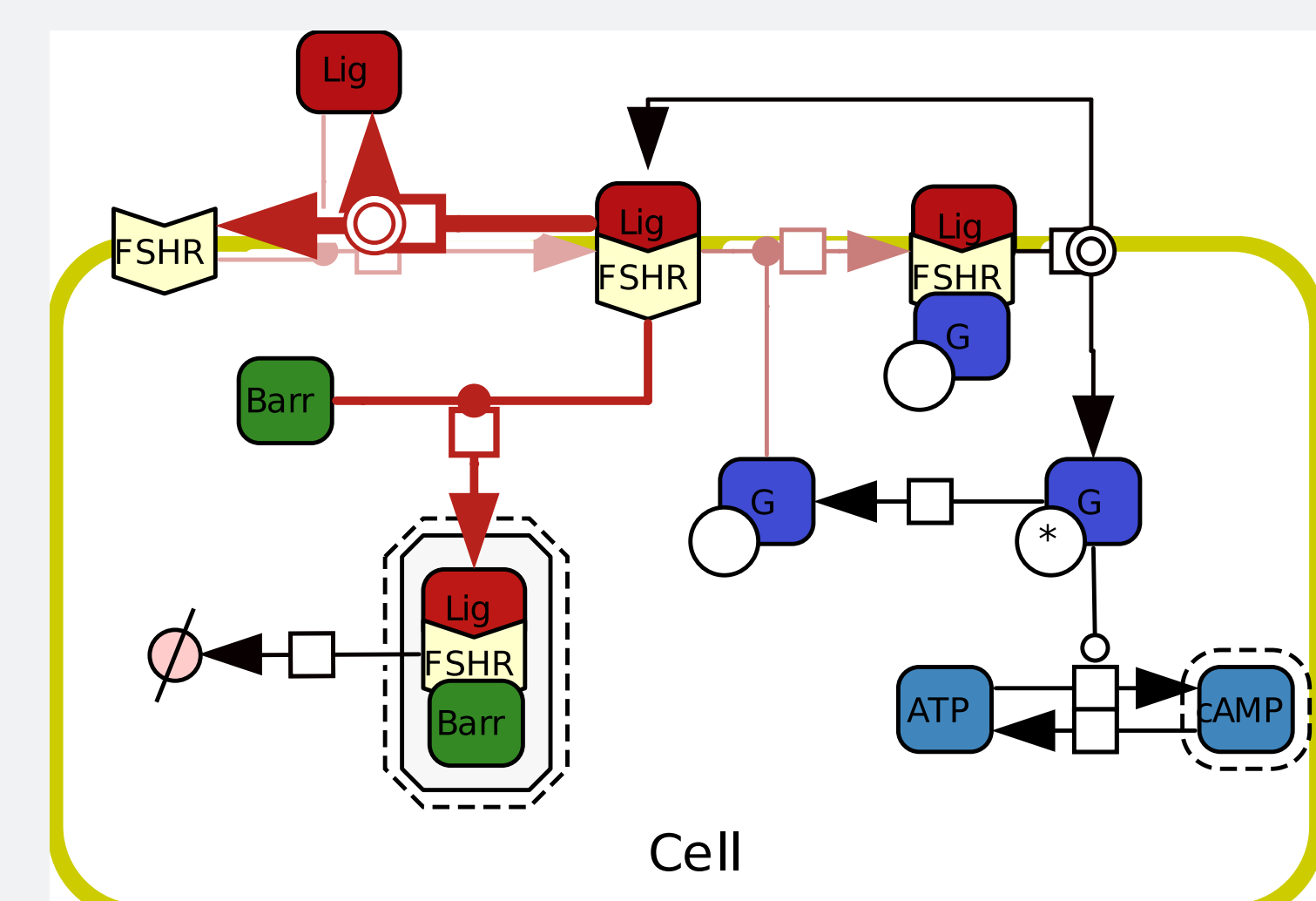
1) Chemical reaction network:



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.

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