Dec 22, 2022

**Outline**

**Introduction:**

- EGFR pathway

- Previous models and short term signaling experimental data:

1- Kholodenko

2- Blinov –

Describing the strengths and weaknesses of these models.

Kholodenko developed a detailed kinetic model of early signaling events that considered a fairly large number of components and interaction parameters. Thermodynamic constraints had to be manually incorporated. On the experimental side, they showed it was possible to measure dynamics at fairly high temporal resolution using standard biochemical methods with fairly high precision, especially in comparison to most data that is reported in the literature. One drawback is that all data represents population average of a large number of cells and so does not take into account cell-to-cell variability. Are there datasets that have this time resolution and precision at single-cell resolution? Live-cell would be limited to at most 2-3 readouts. Fixed cell could have many more readouts and similar time resolution, but would not be longitudinal.

Blinov addressed combinatorial complexity but not the regulatory complexity – same number of rules as reactions in this case and the same issue of enforcing detailed balance constraint on the parameters, which can lead to errors as we know all too well!

- Rule-based modeling

- Energy Modeling

- Scope of this paper: Presenting an eBNG model for EGFR pathway that, in

contrast to the previous models, is fitted to the data and address the problem of regulatory

complexity brought on by the cooperative interactions between different sites in the EGFR

signaling pathway.

**Methods:**

We might want to try to demonstrate some of the key features of the energy model with a simpler example. What I'm thinking about is maybe a model with just a receptor, R, and two adaptors, A and B. The receptor could have two sites, one that binds A and one that binds B. Upon binding to R, A could become phosphorylated and B could bind to it. We could try to find parameters that would make the simpler model exhibit transient kinetics for A or B binding similar to what Kholodenko et al. observed in their experiments

- Building the rule-based model

- Building the energy-based model in 5 steps

- Model fitting

1- Parameter estimation using PEtab format and pyPESTO

2- MCMC sampling using pyPESTO

- Sensitivity Analysis

- ...

**Results:**

- Blinov model violates detailed balance (Detailed balance proof) ??

- Fitting the rule-based version of the Kholodenko’s model to the data

1- pyPESTO results for parameter estimation and comparison to the original

Kholodenko’s model fit

2 - MCMC sampling and convergence diagnostics of the fitted Kholodenko’s model

3- Showing that the presented model by Kholodenko is able to describe the EGFR

transient behavior (identifiability of all the parameters in the model) but in the

original paper, they have not using a systematic approach which has been addressed

in this paper

- Energy-based model of EGFR pathway

1- Step by step energy modeling of EGFR signaling pathway

2- EGFR eBNG model in step 4 recovers the Kholodenko’s original output

3- Expanding the energy-based model using multiple binding partners on EGFR in step 5

- Fitting the energy-based version of the EGFR model to the data

1- Parameter estimation results

2- MCMC sampling results

3 - ...

- Sensitivity analysis results

**Discussion:**

**References:**

**Tables:**

**Figures:**