**Comparison Tables**

In table 1, I have provided a quick comparison between the process of parameter estimation for Kholodenko’s model of EGFR pathway. In one of these model, the parameter estimation has been done under the constrained conditions such that the model obeys the detailed balance analysis, while the original Kholodenko model, does not obey 3 of 5 constrained rules.

The second and third columns of the table 1 show the results for the detailed-balance enforced model and Non-detailed-balance enforced model, respectively.

Table 1: Comparison of detailed balance and non-detailed balance parameter estimation for EGFR model

|  |  |  |
| --- | --- | --- |
| **Specification** | **Detailed-Balance enforced Model** | **Non-Detailed-Balance enforced Model** |
| Number of starts | 200 | 100 |
| min f-value | -116.15 | -126.26 |
| fvalue trace |  |  |
| EGFR-P |  |  |
| Shc-P |  |  |
| Grb2-EGFR  Grb2-Shc |  |  |
| PLCgP |  |  |
| Comparison  of estimated  parameters | C:\Users\mansour\Desktop\Parameters_withoutIC.png | |

It seems that:

It needs more number of start points for the detailed balance model to get the min f-values.

The min f-values are almost nearly the same (unconstrained f-val < constrained f-val)

The number of local minimums are lower in the detailed balance version of the model.

In the unconstrained model, EGFR-P, Shc-P, and PLCg-P better fit the data, while Grb2 is a bit better in the constrained model.

I also repeated the parameter estimation for these two models while the initial concentrations of EGFR, Shc, Grb2, and PLCg are unknown and the optimization approach try to find the best values for them. You can find a brief comparison between the optimization results of the detailed-balance and non-detailed-balance models in table 2. Furthermore, comparisons between the detailed-balance models is shown in table 3 (one model considers initial concentrations as unknown parameters and they are estimated, while in the other model, the initial concentrations are known.)

Table 2: Comparison of detailed balance and non-detailed balance parameter estimation for EGFR model which both contain the initial concentrations as unknown parameters

|  |  |  |
| --- | --- | --- |
| **Specification** | **Detailed-Balance enforced Model** | **Non-Detailed-Balance enforced Model** |
| Number of starts | 200 | 100 |
| min f-value | -122.16 | -126.26 |
| fvalue trace | C:\Users\mansour\Desktop\Waterfall_DB.png |  |
| EGFR-P | C:\Users\mansour\Desktop\Optimization_DB_1.png |  |
| Shc-P | C:\Users\mansour\Desktop\Optimization_DB_2.png |  |
| Grb2-EGFR  Grb2-Shc | C:\Users\mansour\Desktop\Optimization_DB_3.png |  |
| PLCgP | C:\Users\mansour\Desktop\Optimization_DB_4.png |  |
| Comparison  of estimated  parameters |  | |

Table 3: Comparison of detailed balance parameter estimation for EGFR models such that one contains the initial concentrations as unknown parameters while in the other initial concentrations are known

|  |  |  |
| --- | --- | --- |
| **Specification** | **Initial Concentration are estimated** | **Initial Concentration are known** |
| Number of starts | 200 | 200 |
| min f-value | -122.16 | -116.15 |
| fvalue trace | C:\Users\mansour\Desktop\Waterfall_DB.png |  |
| EGFR-P | C:\Users\mansour\Desktop\Optimization_DB_1.png |  |
| Shc-P | C:\Users\mansour\Desktop\Optimization_DB_2.png |  |
| Grb2-EGFR  Grb2-Shc | C:\Users\mansour\Desktop\Optimization_DB_3.png |  |
| PLCgP | C:\Users\mansour\Desktop\Optimization_DB_4.png |  |
| Comparison  of estimated  parameters | C:\Users\mansour\Desktop\Parameters_InitialCon.png | |

It seems that allowing the initial concentrations

makes the fit a bit better.

Decreasing the min f-value in the optimization

Increasing the number of global and local minimums