Math Modeling for the Erythropoietin Receptor

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The Monte Carlo Markov Chain method, MCMC Hammer, is used to estimate the value of parameters in mathematical models. The Sobol Method is used to measure the sensitivity of parameters in mathematical models. V. Becker, *et al.*, (*1*) created a mathematical Erythrpoietin Receptor (EpoR) model based on the characteristics of similar receptors. We used the MCMC Hammer and Sobol methods for their model. The MCMC Hammer method allowed the model to provide on average 56.11% coverage of the experimental data. The Sobol method found that the amount of degraded Epo released to extracellular space has the most effect on the EpoR model.

Introduction

Methods for the creation and analysis of mathematical models can vary greatly. When a particular problem is identified with a method, the fix for that problem can cause a different problem. Testing the solutions to a model with different methods can provide alternative approaches to the real life application of the model.

Systems biology can use mathematical models to better understand diseases and the effects

of drugs (*1*) (*2*). V. Becker, *et al.*, (*1*) created a mathematical model to understand the factors that allow erythropoietin receptors (EpoR) to handle dynamic ranges of ligand concentrations.

The model was built and analyzed (*1*) using a MATLAB toolbox known as PottersWheel (*3*). We used an alternative approach to find the parameters and sensitivity analysis.

Background

Erythroproietin (Epo) is a glycoprotein hormone that stimulates blood cell growth (*4*). The erythropoietin (EpoR) receptor is a cell surface receptor that helps cells respond to their environment (*2*). Epo resides in the medium around the cell (*2*). EpoR on the cell surface binds with Epo in the medium (*2*). When Epo and EpoR bind (Epo-EpoR), the Epo-EpoR can degrade and move into the cell or move outside the cell (*2*). There are many factors that control this process which make the model. Experiments can be run to measure the concentrations of Epo in the medium, on the surface, and in the cell (*2*).

Streptavidin (SAv) is a protein that also binds with the EpoR (*4*). It has the same interactions with EpoR that Epo has. Experiments can be run to measure the concentrations of SAv in the medium, on the surface, and in the cell (*2*).

Monte Carlo methods use the Law of Large Numbers and random sampling to solve large problems. Markov Chains define the probability of any node in a sequence to be dependent only on it's immediate predecessor. Monte Carlo Markov Chains use Markov Chains to pick the next random sample. The Monte Carlo Markov Chain method, MCMC Hammer, is "an MIT licensed pure-Python implementation of Goodman & Weares Affine Invariant Markov chain Monte Carlo (MCMC) Ensemble sampler (*5*)" (*6*).

Methods

V. Becker, *et al.*, (*1*) used 2 systems of ordinary differential equations (the ”core model” and ”auxiliary model”) with 12 elements (6 per system) and 12 parameters (8 shared between the 2 systems). 2 of the initial values were also solved for (Epo concentration and SAv concentration).

Experimental data was collected from the graphs of Epo and SAv in medium, on the surface, and in the cell from V. Becker, *et al.*, (*1*). All data was collected using WebPlotDigitizer. Initially, 30 points were gathered from the Epo graphs and 5 points from the SAv graphs. The Epo graphs were plotted for 300 minutes while the SAv graphs were ploted for 60 minutes. The 5 points from the SAv graphs were from 0, 15, 30, 45, and 60 minutes. To duplicate the model, points from the same time steps were used from the original 30 points gathered from Epo graphs.

All programming was completed in an Anaconda Jupyter notebook using a python kernel.

In order to implement the MCMC Hammer method (*6*), the Ipython parallel package was used with 4 parallel processes. Log likelihood, log prior, log posterior, and maximize posterior functions were manually coded.

Log prior used ranges for all parameters defined in by V. Becker, *et al.*, (*1*). The Epo and SAv ranges were defined as +- 10% of experimental values. Since only one set of experimental data was plotted, the experimental values were set to be the found values after V. Becker, *et al.*, (*1*) solved for them.

The maximize posterior requires an initial guess. While the model was being built, the initial guess was set to the found values found by V. Becker, *et al.*, (*1*). When the parameters were actually being solved for, the initial guess was set to be 10% greater than the minimum value in the range.

The MCMC Hammer method (*6*) was run using the following parameter values:

chains	36
steps	3000
burn	500

The Sobol Method was run using 333 steps.

All calculations were performed on a computer with the following specifications:

Processor	Intel(R) Core(TM) i5-2450M CPU @ 2.50GHz
RAM	6.00 GB
System Type	64-bit
Cores	2
Logical Processors	4

The version of every programming language involved is listed below:

WebPlotDigitizer	3.8
Python	2.7.12
Anaconda	4.2.0 (32 bit)
Jupyter-client	4.4.0

Results

In implementing the MCMC Hammer method, the following results were produced: estimations from maximize posterior, acceptance percent, sample plots, uncertainty plots, residual plots, estimated values from MCMC Hammer, coverage percentages, and correlation plots. I have only presented the estimated values from MCMC Hammer and coverage percentages.

The estimated values from MCMC Hammer (*6*) are:

Estimated m	standard deviation percentage	0.900000
Estimated kt	ligand independent endocytosis	197.801936
Estimated kdi	Degraded Epo is retained in intracellular compartments	598.511304
Estimated kde	Degraded Epo is released to the extracellular space in an inactive state	340.547344
Estimated kon_SAv	SAv association rate	25.609470
Estimated kex_SAv	EpoR and SAv recycle back to the plasma membrane	171.051743
Estimated kon	Epo association rate	54.804303
Estimated ke	Epo-EpoR endocytosis	230.709304
Estimated kex	EpoR and Epo recycle back to the plasma membrane	125.883640
Estimated Epo	Epo Initial Concentration	2026.092511
Estimated SAv	SAv Initial Concetration	1013.350835

The coverage percentages are:

Coverage EpoInCells	83.33
Coverage EpoInMedium	93.33
Coverage EpoOnSurface	10.00
Coverage SAvInCells	63.33
Coverage SAvInMedium	76.67
Coverage SAvOnSurface	10.00
Coverage Average	56.11

The sensitivity ranks from the Sobol method are as follows:

01	kde
02	Epo
03	SAv
04	kdi
05	kt
06	kon
07	ke
08	kex_Sav
09	kex
10	kon_SAv

Conclusions

There are two conclusions that should be considered: the most sensitive parameters and the observed versus simulated concentration levels. The most sensitive parameter is ligand independent endocytosis. The concentration of Epo/SAv in the cells was simulated to be higher than the concentration of observed Epo/SAv in cells. Therefore, the act of pulling matter into the cell could have been the cause of over prediction of the concentrations in the cells.

The Epo and SAv concentrations were not tested with different concentration levels. This lack of testing may have lead to these initial conditions being one of the most sensitive. It does follow that the concentration of Epo/SAv to start would have a strong effect on the amount of Epo/SAv over time.

Finally, the second most sensitive parameter is the degraded Epo retained in intracellular compartments. This also lends to the idea that the amount of Epo in the cells remains high. The amount of SAv in the cells was less, but SAv did not have a parameter that represented the amount of SAv retained in intracellular departments.

References

1. V. Becker, *et al.*, *Science* **328**, 1404 (2010).

2. J. Bachmann, *et al.*, *Journal of Internal Medicine* **271**, 155 (2012).

3. T. Maiwald, J. Timmer, *Bioinformatics* **24**, 2037 (2008).

4. What Is Erythropoietin (EPO)? Test, Definition, Side Effects.

5. J. Goodman, J. Weare, *Communications in Applied Mathematics and Computational Science* **5**, 65 (2010).

6. emcee emcee 2.2.1 documentation.