Reducing NF-kappa B signaling pathways models using quasi-steady state approximation and sensitivity analysis

Atiyeh Ahmadi*, Alireza Doustmohammadi
Department of Biology, University of Waterloo; Department of Biophysics, Tarbiat Modares University
**Corresponding Author Email Address:a94ahmad@uwaterloo.ca*

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Abstract

NF-κB has a vital role in regulating immune system response to the infectious; and misregulation of NF-κB is related to cancers, autoimmune diseases, and viral infections [1].
Our goal is reducing the latest model of NF-κB in order to make it easier and more understandable for pharmaceutical research to target important elements of the pathway. To address this goal, minimizing NF-kappa B signaling pathways ODEs using the quasi-steady-state method and sensitivity analysis is implemented.
As a result, the number of differential equations and parameters of the canonical pathway was reduced from 14 to 10 and 25 to 23, and the non-canonical pathway reduced from 14 to 10 and 27 to 23.
Using sensitivity analysis, the parameters that had little effect on changes of the concentration of species eliminated.

Keywords: NF-κB signalling pathway, model reduction, mathematical modeling, sensitivity analysis, systems biology

Introduction

NF-κB (Nuclear factor-kappa B) stands for a group of factors by which DNA transcription is controlled. They are generally responsible for responding to stresses, cytokines, radiation, oxidized LDL, bacterial and viral antigens [2]. And it has vital role in regulating immune system response to the infectious. One important concern in this area is that NF-κB signalling pathway and its effects on inflammatory diseases (like rheumatoid arthritis) have not been recognized completely and it is required more and more studies. Along with Bing Ji and his colleagues studies in 2020 and Lipniacki, mathematically analyzing NF-κB signalling pathway is set more complete than earlier studies [3] [4].

Materials and Methods

The Quasi-Steady-State approximation, conservation statements ,and sensitivity analysis were used to reduce the model. Of note, the behavior of changing the species concentrations against each other is investigated, so that if there is a relationship between changes in the species concentrations with each other, this relation can be used to reduce the model as follows.
Moreover, After activating the TNF signal, the total concentrations of $IKKn, IKKa, IKKi$ are approximately constant. And changing the concentrations of complexes $IKKa|I\kappa B\alpha$ and complexes $IKKa|I\kappa B\alpha|NF\kappa B$ is almost zero. Its concentration is constant and reach equilibrium rapidly.
Also, the relationship between some species concentration changes are linear. Therefore, this relation can be modeled with a liner equation. By having one of the two species concentration at any time, the concentration of the other species can be obtained.

Results

- The number of differential equations of the canonical pathway was reduced from 14 to 10 and the non-canonical pathway reduced from 14 to 10 and the number of canonical pathway model parameters was reduced from 25 to 23 and the non-canonical pathway model parameters was reduced from 27 to 23.
- This methodology shows the importance of A20 specis. Because the concentration of 4 species of NF-κB signalling pathway can be obtained by using a concentration of A20.
- The reduced model can well simulate the behavior of the original model.

Discussion, Conclusion and Suggestions

- Minimizing the NF-κB model helps us studying the pathway easier and faster for pharmaceutical research to target important elements of the pathway. To address this goal, using the quasi-steady-state method and sensitivity analysis can be useful and the reduced model can well simulate the behavior of the original model.

References

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