Dynamic Modeling of Human Complement System using Reduced Ordered Models

Adithya Sagar, Wei Dai, Mason Minor, and Jeffrey D. Varner*

School of Chemical and Biomolecular Engineering

Cornell University, Ithaca NY 14853

Running Title: Dynamic Modeling of Human Complement System using Reduced Ordered Models

To be submitted: *???????*

*Corresponding author:

Jeffrey D. Varner,

Professor, School of Chemical and Biomolecular Engineering,

244 Olin Hall, Cornell University, Ithaca NY, 14853

Email: jdv27@cornell.edu

Phone: (607) 255 - 4258

Fax: (607) 255 - 9166

Abstract

Fill me in.

Keywords: Biochemical engineering, systems biology, reduced order models, complement system

Introduction

The introduction has three paragraphs (introduction no longer than 3 pages):

1. **First paragraph**: Introduce human complement system, history, role in adaptive/innate immunity.

2. **Second paragraph**: Introduce mathematical models of complement system, current place in the field, our work was not possible without xyz who pioneered abc. Address shortcomings in the field .

3. **Third paragraph**: In this study, [Repeat the abstract with some additional detail]. Taken together, [killer statement].

Results

The results are presented in **past tense**. Each paragraph starts with a statement of the result in that paragraph in active voice. Each results paragraph ends with a Taken together type statement followed by a link statement e.g., Next we considered etc. When referring to figures, state what the figures shows (Fig. ZZ).

Discussion

The discussion has three (sometimes four) paragraphs:

1. **First paragraph**: Present a modified version of the last paragraph of the introduction. In this study, [...]. Taken together, [killer statement]

2. **Second paragraph**: Contrast the key findings of the study with other computational/experimental studies

3. **Third paragraph**: Present future directions. If you had more time, what would like to do? Highlight the key shortcomings of the approach and how will we address them in the future. In this case, we will have a scaling issue if we extend to genome scale. We should extend to dynamic cases, and we need to experimentally validate the findings.

Materials and Methods

1. **Model formulation**: Present the reduced order modeling approach of the human complement network, . Outline parameter estimation, and state all parameter assumptions, sensitivity analysis

Acknowledgements

This study was supported by an award from [FILL ME IN].

References

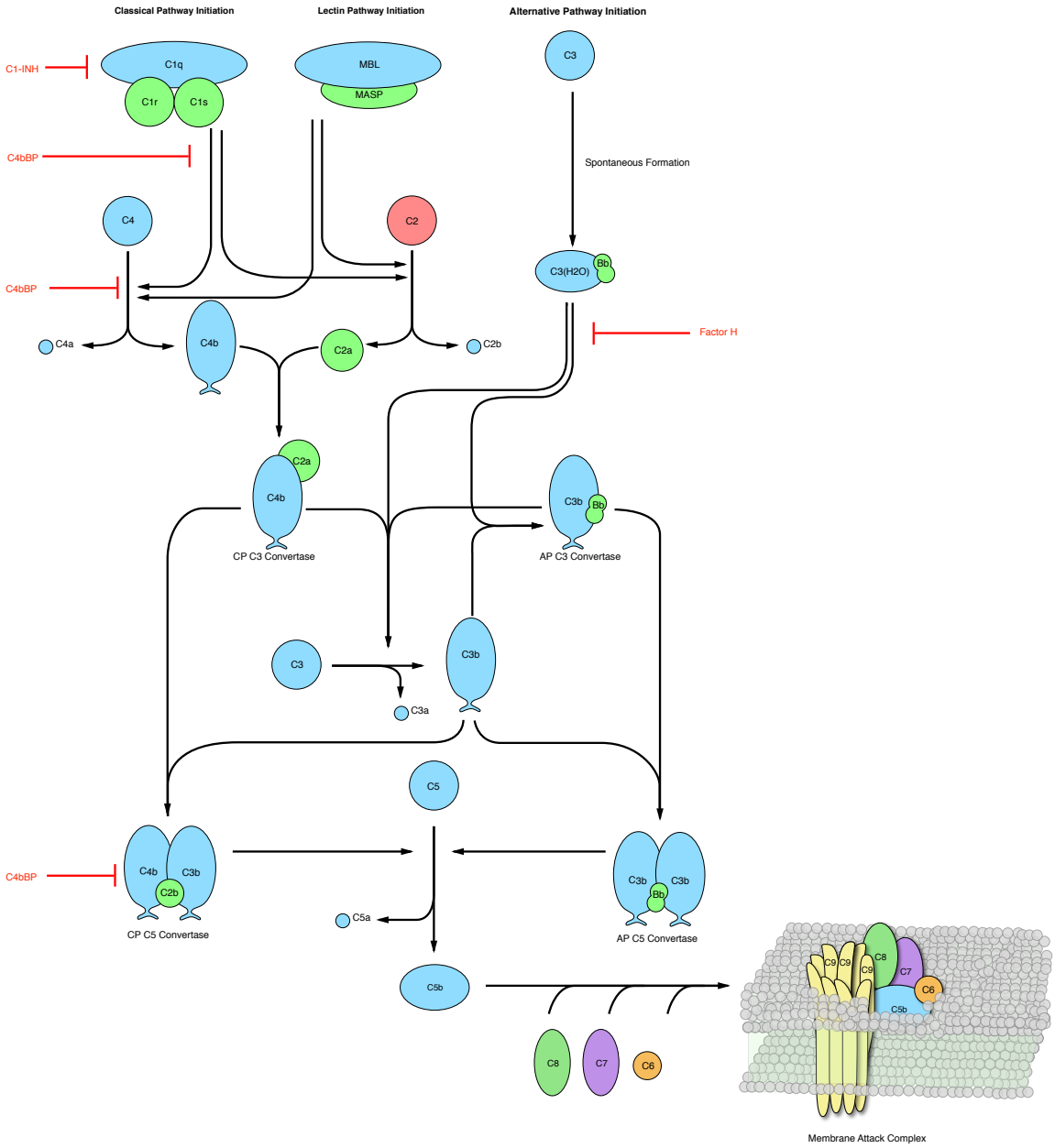

Fig. 1: Simplified schematic representation of the human complement system. The complement cascade is activated through any one, or more, of the three pathways: classical, lectin, and alternate pathway. The classical pathway is activated by the complex formation of $C1q$, $C1r$, and $C1s$ by the recogniztion of antibody:antigen complexes. Similarly, the lecin pathway is initiation by binding mannan-binding lectin to mannose on pathogen surfaces. Lastly, the alternative pathway is activated when a complement component is spontaneously bound to the surface of the pathogen of virus. The activation from the three pathways creates a cascades of reactions that forms the proteases, $C3$ Convertase that cleaves $C3$ into $C3a$, and $C3b$, the main effector molecule of the complement system. $C3b$ can find to a $C3$ convertase and form a $C5$ convertase that cleaves $C5$ into $C5a$, and $C5b$ that undergoes a series of reactions to form the membrane attach complex (MAC).

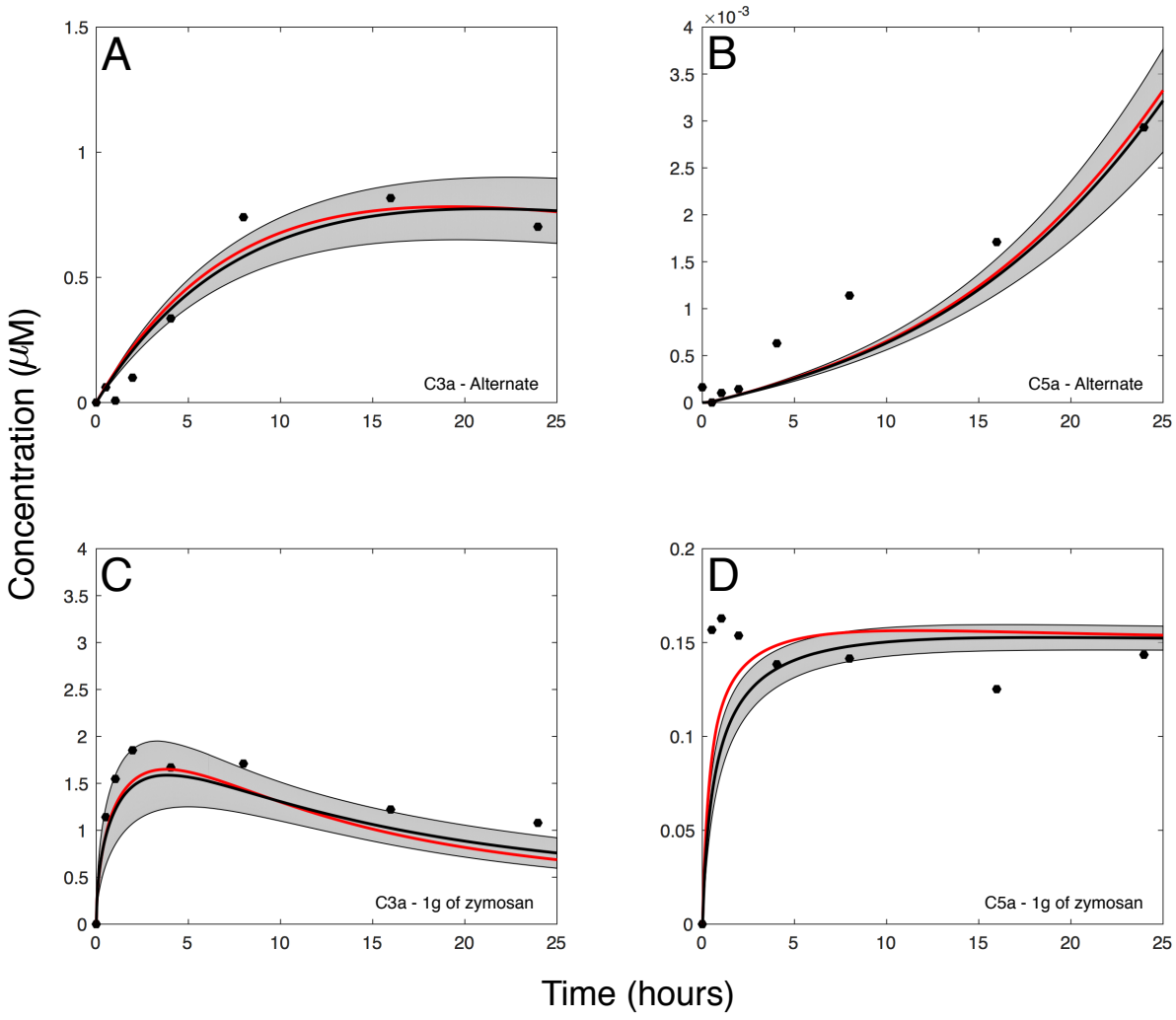

Fig. 2: Reduced order complement model training simulation for lectin and alternative pathway in presence of zymosan. Reduced order complement model parameters were estimated using dynamically dimensioned search (DDS) [Tolson and Shoemaker,2007,WRR] using the availability of zymosan as a function of lectin pathway initiation. Only parameters that govern the behavior of alternative pathway were allowed to vary when zymosan was not present. Our model training was conducted in a hierarchal fashion where the alternate parameters were trained and then used and fixed in estimating the lectin parameters. The red line shows the best-fit parameter, the black lines denotes the simulated mean value of $C3a$ or $C5a$ for a 50 parameter set ensemble. The shaded region denotes the distribution of $C3a$ and $C5a$ of the ensemble.

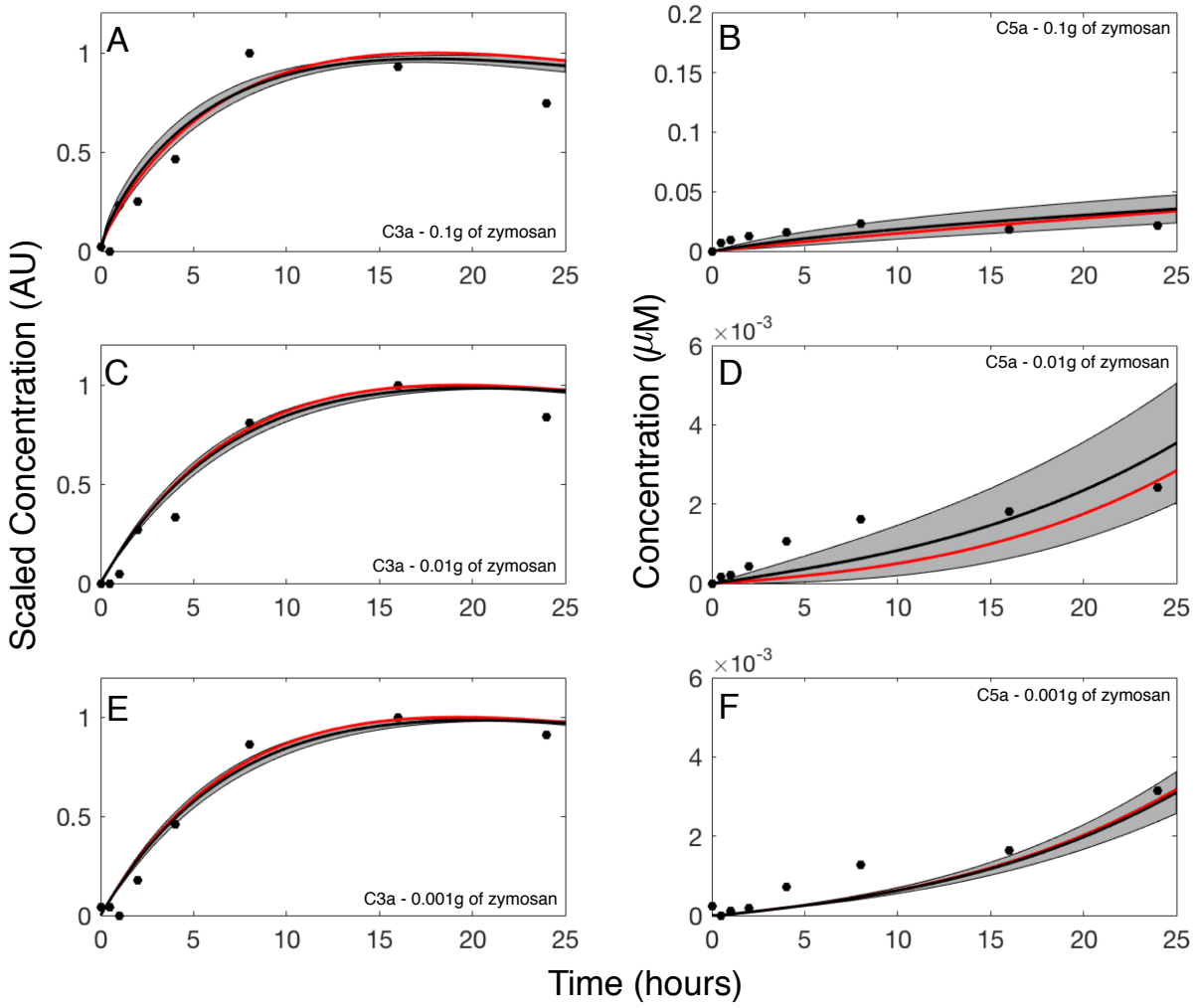

Fig. 3: Reduced order complement model predictions of lectin and alternative pathway in presence of zymosan. (A-F) Simulation of complement dynamics in the presence of zymosan were conducted for a range of trigger values (0.1, 0.01, and 0.001 grams of zymosan). The time-course profiles of $C3a$ and $C5a$ under three different zymosan concentrations were simulated using 50 ensembles of trained parameter sets against experimental data of Shaw et al [REF]. The red curve represents the best fit parameter, grey shaded region denotes the prediction results from 50 ensembles of parameter sets, and the black curve is the mean of the ensemble. All complement protein and factor initial concentrations coincided with human serum levels unless otherwise noted.

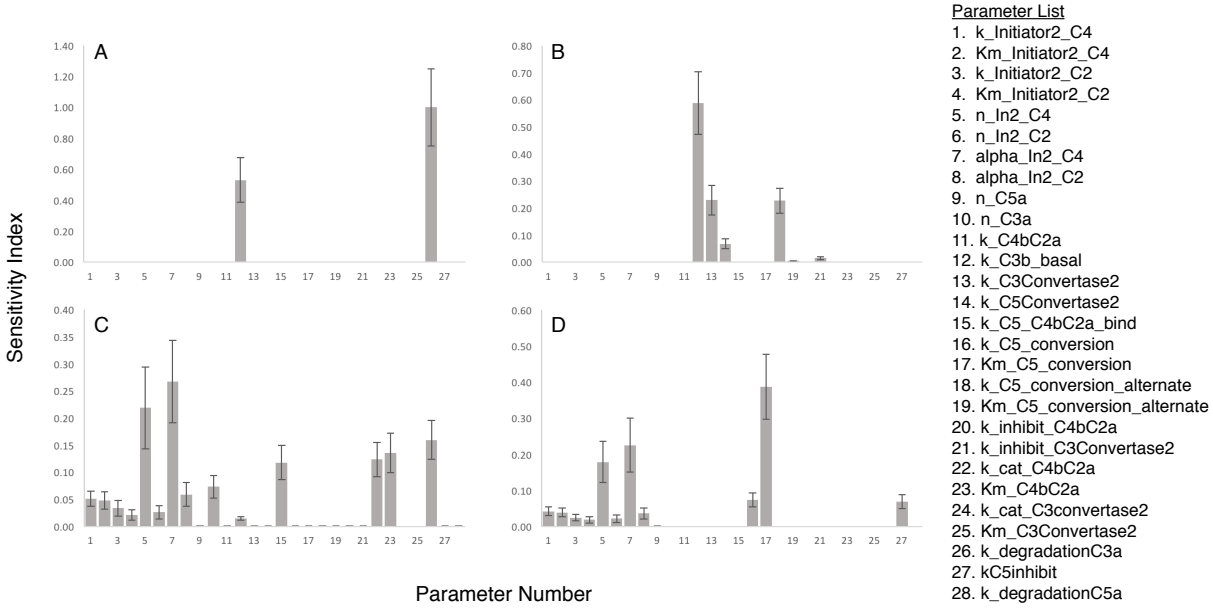

Fig. 4: Sensitivity Analysis