Dear Editors -

On behalf of my coauthors and myself, I'm delighted to submit the manuscript entitled "Reduced order modeling and analysis of the human complement system" for publication in PLoS ONE.

Abstract:
Complement is an important pathway in innate immunity, inflammation, and many dis- ease processes. However, despite its importance, there are few validated mathematical models of complement activation. In this study, we developed an ensemble of experimentally validated reduced order complement models. We combined ordinary differential equations with logical rules to produce a compact yet predictive model of complement activation. The model, which described the lectin and alternative pathways, was an order of magnitude smaller than comparable models in the literature. We estimated an ensemble of model parameters from in vitro dynamic measurements of the C3a and C5a complement proteins. Subsequently, we validated the model on unseen C3a and C5a measurements not used for model training. Despite its small size, the model was surprisingly predictive. Global sensitivity and robustness analysis suggested complement was robust to any single therapeutic intervention. Only the simultaneous knockdown of both C3 and C5 consistently reduced C3a and C5a formation from all pathways. Taken together, we developed a validated mathematical model of complement activation that was computationally inexpensive, and could easily be incorporated into pre-existing or new pharmacokinetic models of immune system function. The model described experimental data, and predicted the need for multiple points of therapeutic intervention to fully disrupt complement activation.

Funding:
This material is based upon work supported by, or in part by, the U. S. Army Research Laboratory and the U. S. Army Research Office under contract/grant number W911NF1020114.
The authors declare that they have no competing interests.

Best regards,

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