The Role of the Human Immune System in the Aging Process: a Mathematical Model of Cell and Cytokine Activation

Kian Talaei, Steven A. Garan, Elliott K. Suen, Joshua W. Cho, Julia R. Jahansooz, Puneet Bhullar, Walter Piszker, Nuno Martins

BERKELEY LAB
LAWRENCE BERKELEY NATIONAL LABORATORY

CREA
Center for Research & Education in Aging

GSA 2021 ANNUAL SCIENTIFIC MEETING
Disruption to Transformation: Aging in the "New Normal"

INTRODUCTION

Simulations allow for the efficient mathematical modeling of complex biological systems and hold the potential to elucidate many of the intricate biological pathways within the human body. Immune system research, which involves elaborate relationships between various cytokines and cells, could benefit from a mathematical simulation of the immune response. As the computer models of the immune system continue to improve, the potential for enhanced drug testing could allow for expedited drug discovery. In addition, a more comprehensive simulation of the immune response can advance the field of aging research since the immune system plays an important role in the aging process.

Typically, as one ages, the immune system must work harder in order to keep the body alive and healthy. The production of pro-inflammatory cytokines, such as TNF-alpha, IL-6 and IL-10, generally also increases as one ages. In fact, frailty has been studied and shown to be associated with the increase levels of TNF-alpha and IL-6 in older humans. The inflammatory response ultimately changes as one gets older, therefore, aging research among these specific cytokines can help to simulate the various ways that the immune system responds to bacteria introduced into the human system.

METHOD

The current simulation consists of a series of PDE's[1] to simulate the spatial and temporal components of the immune system: *S. aureus* bacteria (A), Resting Macrophages (M_R), and Activated Macrophages (M_A). Additionally, the simulation incorporates ODE's of: Antibodies (F^L)[2] , Tumor Necrosis Function alpha (TNF-α), Interleukin-6 (IL-6), Interleukin-8 (IL-8), and Interleukin-10 (IL-10).

The ODE's outlining the cytokines TNF-α, IL-6, IL-8, and IL-10 were taken from Brady et al. This work incorporates *in vivo* clinical trials using LPS, found in Gram-negative bacteria, in order to model mathematical equations describing the relationships between these cytokines and active macrophages. Although *S. aureus*, a Gram-positive bacteria, does not contain LPS, the equations extracted from the Brady et al outline relationships between active macrophages and the cytokines stated (Figure B). The relationships between the cytokines and the pathogen are not directly linked but are rather connected through the concentration of active macrophages (Figure C). While activated macrophages concentration changes due to the concentration of the pathogen, the cytokines themselves are dependent only on active macrophage concentrations and, therefore, independent towards the change in concentration of the pathogen. Because active macrophages are already incorporated in the simulation created by Quintela et al (Figure A), the relationships between *S. aureus* and active macrophage concentration were taken from the simulation from Quintela et al and the relationships between the active macrophages and cytokines were taken from Brady et al.

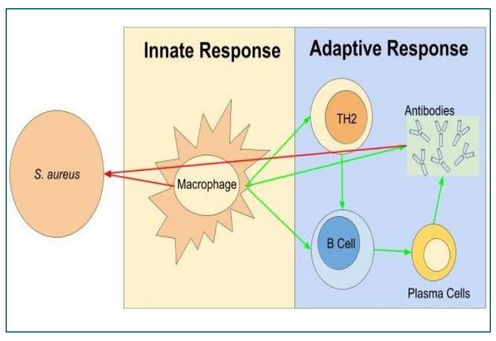


Figure A. The visual representation of the simulation created by Quintela et al.[1] All of the relationships between *S. aureus* and the different immune response cells were incorporated. The green arrows and red arrows indicate a positive (up-regulation) and negative (down-regulation) response, respectively.

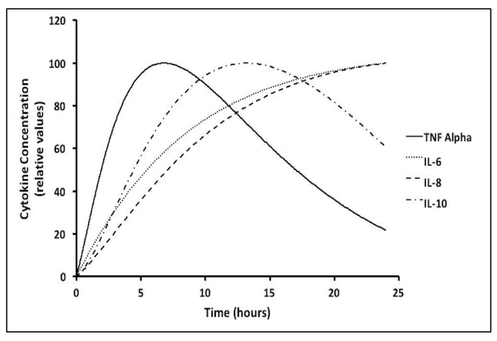


Figure B. Cytokine concentrations over a 24-hour period in the current simulation.

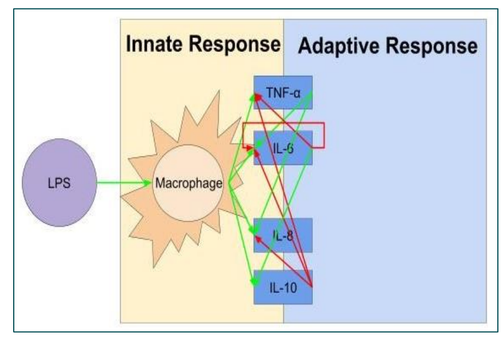


Figure C. A visual representation of the mathematical model as outlined by Brady et al[2]. These relationships were inputted into the simulation using the relationships the cytokines had to the active macrophages rather than the pathogen itself (See Figure C).

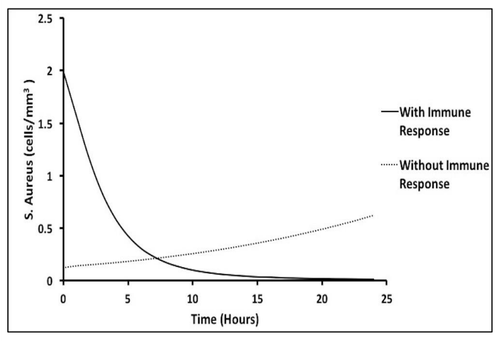


Figure D. *S. aureus* simulated average cell concentration in the tissue with and without immune response over a 24 hour period.

$$\frac{\partial A}{\partial t} = \beta_A A\left(1-\frac{A}{k_A}\right) - \mu_A A - \lambda_{MR} M_R A - \lambda_{MA} A M_A$$
$$-\lambda_{AF|MR} A_F M_R - \lambda_{AF|MA} A_F M_A + D_A \Delta A,$$
$$A(x_0, y_0, z_0, 0) = A0, \qquad \frac{\partial A}{\partial t}(\cdot, t)\Big|_{\partial\Omega} = 0.$$

Figure E. This equation describes the growth rate and elimination rate of the bacteria, *S. aureus* (A).

Figure G. The features of the current simulation. The various shapes indicate the parts of the simulation from Quintela et al while the dark blue boxes indicate the parts of the simulation from the mathematical equations from Brady et al.[2]

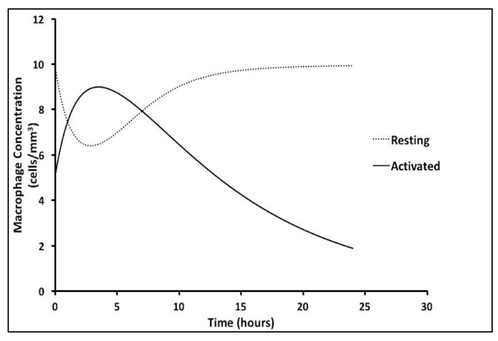
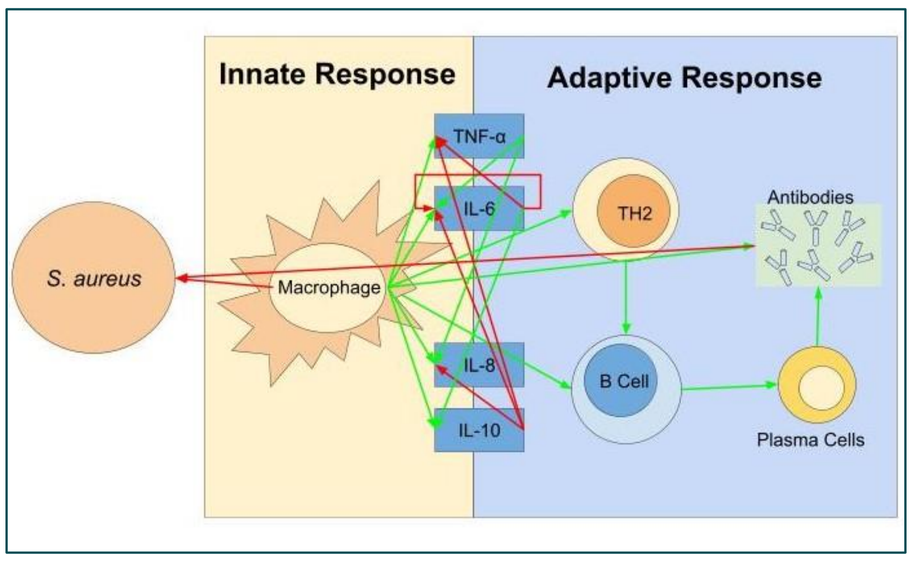


Figure F. Concentration of activated and resting macrophages over a 24 hour period in the simulation.

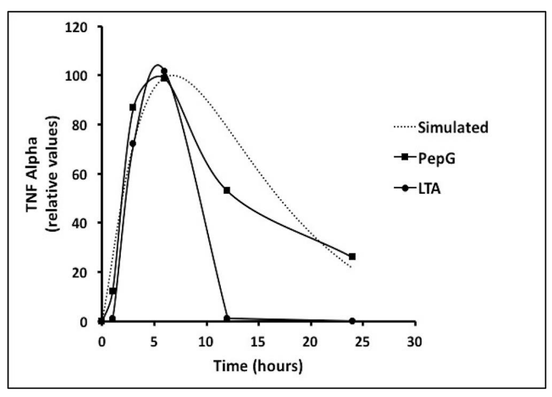


$$\frac{\partial M_A}{\partial t} = -\mu_{MA} M_A + \gamma_{MA} M_R A + D_{MA} \Delta M_A$$
$$-\alpha_M \theta_{\mathrm{LV}}(x,y,z)\left(M_A - M_A^L\right),$$
$$M_A(x,y,z,0) = MA_0, \qquad \frac{\partial M_A}{\partial t}(\cdot, t)\Big|_{\partial\Omega} = 0.$$

Figure H. This equation describes the response of activated macrophages (M_A) due to infection by the pathogen, *S. aureus* (A).

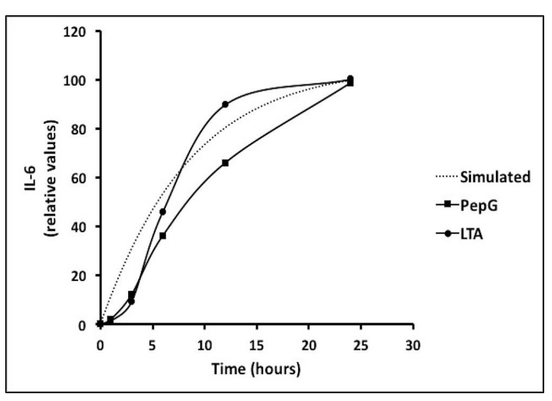
$$\frac{\partial M_R}{\partial t} = -\mu_{MR} M_R - \gamma_{MA} M_R A$$
$$+\alpha_{M_R} \theta_{\mathrm{BV}}(x,y,z)\left(M_R^* - M_R\right) + D_{M_R} \Delta M_R,$$
$$M_R(x,y,z,0) = M_{R0}, \qquad \frac{\partial M_R}{\partial t}(\cdot, t)\Big|_{\partial\Omega} = 0.$$

Figure I. This equation describes the activation of resting macrophages (MR) due to the pathogen, *S. aureus* (A).



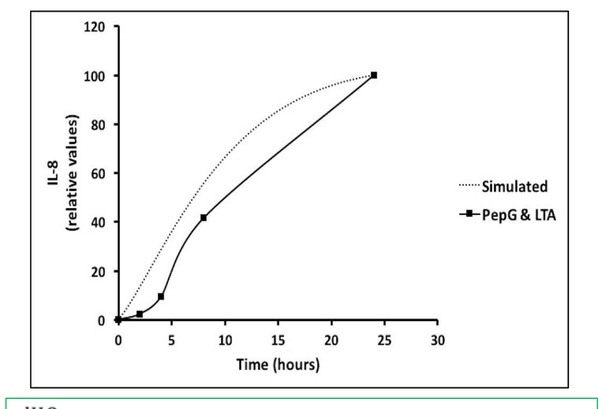
$$\frac{dTNF}{dt} = k_{TNFM} H^p_{TNF}(IL6) H^p_{TNF}(IL10) M_A - k_{TNF}(TNF - q_{TNF})$$

Figure J. This graph shows the comparison of the simulated TNF-α and clinical TNF-α activity over a 24 hour period. This equation describes the activation of TNF-α due to macrophage activation.



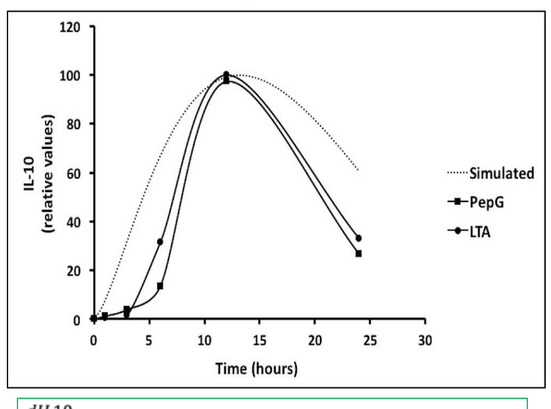
$$\frac{dIL6}{dt} = \left(k_{IL6M} + k_{IL6TNF} H^u_{IL6}(TNF)\right) H^p_{IL6}(IL6) H^p_{IL6}(IL10) M_A - k_{IL6}(IL6 - q_{IL6})$$

Figure K. This graph show the comparison of the simulated IL-6 and clinical IL-6 activity over a 24 hour period. This equation describes the activation of IL-6 due to TNF-α and down-regulation of IL-10 activation and IL-6 negative feedback loop.



$$\frac{dIL8}{dt} = \left(k_{IL8M} + k_{IL8TNF} H^u_{IL8}(TNF)\right) H^p_{IL8}(IL10) M_A - k_{IL8}(IL8 - q_{IL8})$$

Figure L. This graph shows the comparison of the simulated IL-8 and clinical IL-8 activity over a 24 hour period. This equation describes the activation of IL-8 due to TNF-α up-regulation and IL-10 down-regulation.



$$\frac{dIL10}{dt} = \left(k_{IL10M} + k_{IL10IL6} H^u_{IL10}(IL6)\right) M_A - k_{IL10}(IL10 - q_{IL10})$$

Figure M. This graph shows the comparison of the simulated IL-10 and clinical IL-10 activity over a 24 hour period. This equation describes the activation of IL-10 due to IL-6 macrophage activation

RESULTS

The cytokine concentrations are simulated over a 24-hour period upon the introduction of a bacteria, *S. aureus*. As depicted in figure B, our simulation shows two cytokines, TNF-α and IL-10 reach their peak concentration within the first 24 hours whereas IL-6 and IL-8 continue to increase beyond the 24-hour period. These results are affirmed based on the *in vitro* experimental data illustrated next to the simulated values in figures J-M. The septic endotoxins cause fluctuations in cytokine and immune cell response due to the tissue damage and are omitted from the simulation and experimental settings.

As shown in figure D, bacteria grows exponentially within the 24 hour period, in the absence of immune system functions. Through the various interactions between the macrophages and cytokines, the bacteria are eventually eliminated from the simulation. When introducing the bacteria into the immune system simulation, the simulated immune system eliminates the bacteria and we see a gradual increase in the activated macrophages until it reaches its maximum concentration at 5 hours. The inversely proportional resting macrophage count gradually decreases until it reaches its minimum concentration at 5 hours (figure F).

DISCUSSION

Cell-cytokine interaction. The coupled model in this study is the combination of the cell model set forth by Quintela et al. and the cytokine model presented by Brady et al. through their connection in regard to the similar roles of activated macrophages.

Parameter adjustment. The simulation validated against the experimental *in vitro* trials found in Wang et al. and Yao et al. Certain parameters in the ODEs affect the sensitivity of the simulated results, which are subsequently modified in order to offer a better comparison to the *in* vitro data. In addition, the initial concentrations of the bacteria and cytokines were too low for observable effects in the simulated results; the concentrations were therefore re-calibrated in order to generate meaningful data.

Drug effect. Pharmaceutical drugs play a significant role in controlling the effects and concentrations of the cells and cytokines in this model. For example, FOM breaks down Gram-positive bacteria while amplifying IL-6 and IL-10, whereas DEX reduces the production of IL-6 and IL-10. Extrapolating the effects to human trials can allow pharmaceutical drugs to be utilized in aiding the human immune response to infections and in explaining the long-term process of aging.

Model modifications in comparing observed and predicted results using relative values and future goals in the comprehensive simulation. In the process of coupling the models together, certain modifications to the original simulations were critical. The units used in the simulation were scaled to more closely model the conditions of the *in vitro* experimental data, which had different starting parameters. In addition, the current coupled cell-cytokine model does not take into account the effects of endotoxin activity. Future expansions to the model may include these effects.

Financial Disclosure

This study was funded by the Center for Research and Education in Aging, UC Berkeley.