A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation

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Based on a paper by: G. Bard Ermentrout, Angela Reynolds, Jonathan Rubin, Gilles Clermont, Judy Day, and Yoram Yodocotz
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Purpose

- Create a model that accurately depicts the anti-inflammatory response in relation to macrophage activity and pathogen levels.
- Study the effects of a time-dependent anti-inflammatory response in an immune system while simultaneously monitoring pathogen levels and macrophage counts.
Review of Terms

- **Pathogen:** an agent that causes disease.
- **Phagocytes:** A cell, such as a white blood cell, that engulfs and absorbs waste material, harmful microorganisms, or other foreign bodies in the bloodstream and tissues.
- **Septic Death:** death caused by the presence of pathogenic organisms in the blood or tissue.
- **Aseptic Death:** death caused by excessive tissue damage, due to increased phagocyte levels.

Definitions obtained from dictionary.com
Important Variables

- **M**: non-specific local response
- **P**: initiating event (pathogen levels)
- **N\(^*\)**: inflammation (# of phagocytes)
- **N\(_R\)**: # of resting phagocytes
- **D**: collateral damage to tissue
- **C\(_A\)**: anti-inflammation
Interactions

- Initiating Event occurs and alerts the immune system (non-specific local response)
- Phagocytes lower pathogen levels but also cause inflammation
- Inflammation runs in a positive feedback loop
- Inflammation causes damage in tissue
- Inflammation and damage in tissue both cause anti-inflammation levels to rise
Model

- M/P Subsystem
- N*/P Subsystem
- N*/D Subsystem
- Three-Variable Subsystem
- Four-Variable Subsystem
The M/P subsystem models the human immune system defending its body against foreign attack.

\[
\frac{dM}{dt} = s_m - \mu_m M - k_{mp} MP \\
\frac{dP}{dt} = -k_{mp} MP \\
\frac{dP}{dt} = k_{pg} P\left(1 - \frac{P}{P_\infty}\right) - \frac{k_{pm} s_m P}{\mu_m + k_{mp} MP}
\]
N*/P Subsystem

- As pathogen levels increase, phagocytes are induced, and inflammation occurs as a result.
- Resting phagocytes are activated by active phagocytes.

\[
\frac{dP}{dt} = k_{pg} P\left(1 - \frac{P}{P_\infty}\right) - \frac{k_{pm} s_m P}{\mu_m + k_{mp} P} - kN^* P
\]

\[
\frac{dN_R}{dt} = s_{nr} - \mu_{nr} N_R - (k_{nn} N^* + k_{np} P) N_R
\]

\[
\frac{dN^*}{dt} = (k_{nn} N^* + k_{np} P) N_R - \mu_n N^*
\]
N*/D Subsystem

- Activated phagocytes induce collateral tissue damage.
- Damaged tissue releases pro-inflammatory cytokines, which causes further phagocyte activation.

\[
\frac{dN^*}{dt} = \frac{s_{nr} (k_{nn} N^* + k_{nd} D)}{\mu_{nr} + (k_{nn} N^* + k_{nd} D)} - \mu_n N^*
\]

\[
\frac{dD}{dt} = k_{dn} \left( \frac{N^{*6}}{x_{dn}^6 + N^{*6}} \right) - \mu_d D
\]
Three-Variable Subsystem

\[
\begin{align*}
\frac{dP}{dt} &= k_{pg} P \left(1 - \frac{P}{P_\infty}\right) - \frac{k_{pm} s_m P}{\mu_m + k_{mp} P} - k_{pn} N^* P \\
\frac{dN^*}{dt} &= \frac{s_{nr} \left(k_{nn} N^* + k_{np} P + k_{nd} D\right)}{\mu_{nr} + \left(k_{nn} N^* + k_{np} P + k_{nd} D\right)} - \mu_n N^* \\
\frac{dD}{dt} &= k_{dn} \left(\frac{N^*}{x_{dn}^6 + N^*^6}\right) - \mu_d D
\end{align*}
\]
Three Variable Subsystem Cont'd

(a) Graph showing:
- Activated Phagocytosis ($N^*$) vs. Growth Rate of Pathogen ($k_{pg}$)
- Hopf equilibrium ($k_{pg} = 1.707$)
- Saddle-node equilibrium ($k_{pg} = 1.702$)
- Transcritical equilibrium ($k_{pg} = 2.769$)

(b) Graph showing:
- Anti-inflammatory Mediator ($C_A$) vs. Growth Rate of Pathogen ($k_{pg}$)
- Health
- Septic Death
- Health & Septic Death
- Health, Aseptic & Septic Death
- Aseptic Death
- Aseptic & Septic Death
Four Variable Subsystem

\[
\frac{dP}{dt} = k_{pg} P \left(1 - \frac{P}{P_{\infty}} \right) - \frac{k_{pm} s \, m \, P}{\mu_m + k_{mp} P} - k_{pn} f(N^*) P
\]

\[
\frac{dN^*}{dt} = \frac{s_{nr} f(k_{nn} N^* + k_{np} P + k_{nd} D)}{\mu_{nr} + f(k_{nn} N^* + k_{np} P + k_{nd} D)} - \mu_n N^*
\]

\[
\frac{dD}{dt} = k_{dn} \left(\frac{f(N^*)^6}{x_{dn}^6 + f(N^*)^6} \right) - \mu_d D
\]

\[
\frac{dC_A}{dt} = s_c + \frac{k_{cn} f(N^* + k_{cnd} D)}{1 + f(N^* + k_{cnd} D)} - \mu_c C_A
\]

\[
f(V) = \frac{V}{1 + \left(\frac{C_A}{c_\infty}\right)^2}
\]


P=1, N*=0, D=0, Ca=0.125, Kpq=0.3

P=1.5, N*=0, D=0, Ca=0.125, Kpq=0.3

P=1, N*=0, D=0, Ca=0.125, Kpq=0.6
Conclusion

- It is advantageous to have dynamic anti-inflammatory levels.
- There is a specific range of $N^*$ and $C_A$ for optimal health.
Limitations

Because of our oversimplified model, the biological aspects are not as accurate as we had hoped them to be.

It is difficult to provide quantitative measurements for functions like “pro-inflammation”, “anti-inflammation”, and “damage”.
Future Research

- How the various features of the inflammatory response interact to govern the outcome following multiple insults.
- Models that are more detailed in anti-inflammatory substances and analyze anti-inflammatory mediators as “therapeutic agents”.