A Reduced Ordinary Differential Equation Model of Acute Inflammatory Response to Endotoxin Challenge

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Introduction

- The body responds to bacterial infection or tissue trauma by the activation of acute inflammatory response to combat the threat posed by gram-negative bacteria (endotoxin).
- Meanwhile, an uncontrolled inflammatory response can cause tissue damage, and ultimately death.
- Roy et al [2] developed an 8-state (8D) ODE model of the acute inflammatory response system to endotoxin challenge.
- In this work, we proposed a reduced 7-state (7D) ODE model. Model comparison and validation were done against experimental data.

Why Reduced Model?
To reduced the complexity of the 8D model, but not at the expense of calibrating the model to the experimental data.

8D Model State Variables
The variables used in the model are:
- Endotoxin concentration: \( P(t) \)
- Total number of activated phagocytic cells: \( N(t) \)
- A non-accessible tissue damage marker: \( D(t) \)
- Interleukin-6 \( (IL6(t)) \)
- Tumor necrosis factor \( (TNF(t)) \)
- Interleukin-10 \( (IL10(t)) \)
- A tissue damage driven IL-10 promoter \( (Y_{IL10}) \)
- Transforming Growth Factor-\( \beta1 \) & Cortisol \( (C_A(t)) \)

Experimental Data
Experiment on three cohorts of Sprague-Dawley rats were performed to study the acute inflammatory response to endotoxin insults at dose levels 3, 6, or 12mg/kg intraperitoneally. Concentrations of IL6, IL10, and TNF were measured.

8D Mathematical Model

![Diagram of 8D Mathematical Model]

7D Model Sensitivity Ranking

- IL6 Relative ranking plot
- IL10 Relative ranking plot
The relative sensitivity ranking plots at 12mg/kg.

Derivation of Reduced 7D Model
From the 8D model description and ideas gotten from literature, state variables can be categorized as:
- Endotoxin concentration: \( P(t) \)
- Inflammation: \( N(t) \)
- Pro-inflammatory mediators: \( IL6(t) \) & \( TNF(t) \)
- Anti-inflammatory mediators: \( IL10(t) \) & \( C_A(t) \)
- Tissue damage: \( D(t) \) & \( Y_{IL10} \)
- In view of this, \( C_A(t) \) was dropped as it is relatively less significant; \( IL10(t) \) becomes the only anti-inflammatory mediator.

Parameter Estimation

To determine the parameters for estimation, we did:
- Sensitivity Analysis: This identifies an approximate number of sensitive parameters.
- Subset Selection: Using “SVD followed by QR factorization with column pivoting” method, we obtained the most identifiable parameters.
- Parameter Estimation: We used Nonlinear Least Squares with a normalized residual.

Experimental Data

Exponentially least squares with a normalized residual.

AIC [1] compares models quantitatively. The model with lower AIC value is preferred.

Model Prediction

Predictability of 7D (red dashed line) and 8D (blue solid line) against experimental data (black circle)(mean ± SD) using 6mg/kg endotoxin dose level.

What Next?
AIC values and curve fitting revealed 7D is better. WHAT NEXT?
- Propose treatment strategy.

References