Explained Equation

Certainly! To enhance your thesis with a detailed explanation of differential equations and their biological relevance, incorporating Hill's Equation will provide a more nuanced model. Hill's Equation is particularly useful for representing dose-response relationships in cellular biology, such as the activation or inhibition of pathways by cytokines.

Here is an expanded version of the previous models using Hill's Equation where applicable:

Differential Equations with Hill's Equation

1. Macrophage-Like Synoviocytes (MLS)

$$\frac{d[MLS]}{dt} = k_{birth,MLS} - k_{death,MLS} \cdot [MLS] + \frac{k_{TNF-\alpha,act} \cdot [TNF-\alpha]^n}{K_{TNF-\alpha}^n + [TNF-\alpha]^n} + \frac{k_{IL-6,act} \cdot [IL-6]^m}{K_{IL-6}^m + [IL-6]^m}$$

Explanation: This equation models the birth and death rates of MLS. The activation terms for TNF-α and IL-6 use Hill's Equation, where (n) and (m) are Hill coefficients (sensitivity), and (K*{TNF-α}) *and (K*{IL-6}) are half-maximal activation concentrations.

2. Recruited Macrophages

$$\frac{d[Macrophage]}{dt} = k_{birth,Macro} - k_{death,Macro} \cdot [Macrophage] + \frac{k_{TNF-\alpha,act} \cdot [TNF-\alpha]^n}{K_{TNF-\alpha}^n + [TNF-\alpha]^n} + \frac{k_{IL-6,act} \cdot [IL-6]^m}{K_{IL-6}^m + [IL-6]^m}$$

Explanation: Similar to MLS, this equation models the birth and death rates of recruited macrophages. The activation terms for TNF-α and IL-6 use Hill's Equation.

3. T Regulatory Cells (Treg)

$$\frac{d[Treg]}{dt} = k_{birth,Treg} - k_{death,Treg} \cdot [Treg] + \frac{k_{TGF-\beta,act} \cdot [TGF-\beta]^p}{K_{TGF-\beta}^p + [TGF-\beta]^p}$$

Explanation: This equation models the birth and death rates of Treg cells. The activation term for TGF-β uses Hill's Equation.

4. Osteoclasts

$$\frac{d[Osteoclast]}{dt} = k_{birth,Osteo} - k_{death,Osteo} \cdot [Osteoclast] + \frac{k_{RANKL,act} \cdot [RANKL]^q}{K_{RANKL}^q + [RANKL]^q} + \frac{k_{TNF-\alpha,act} \cdot [TNF-\alpha]^r}{K_{TNF-\alpha}^r + [TNF-\alpha]^r}$$

Explanation: This equation models the birth and death rates of osteoclasts. The activation terms for RANKL and TNF-α use Hill's Equation.

5. Fibroblast-like Synoviocytes (FLS)

$$\frac{d[FLS]}{dt} = k_{birth,FLS} - k_{death,FLS} \cdot [FLS] + \frac{k_{TNF-\alpha,act} \cdot [TNF-\alpha]^n}{K_{TNF-\alpha}^n + [TNF-\alpha]^n}$$

Explanation: This equation models the birth and death rates of FLS. The activation term for TNF-α uses Hill's Equation.

6. Th17 Cells

$$\frac{d[Th17]}{dt} = k_{birth,Th17} - k_{death,Th17} \cdot [Th17] + \frac{k_{TGF-\beta,act} \cdot [TGF-\beta]^p}{K_{TGF-\beta}^p + [TGF-\beta]^p}$$

Explanation: This equation models the birth and death rates of Th17 cells. The activation term for TGF-β uses Hill's Equation.

Cytokine Dynamics

$$\frac{d[TNF-\alpha]}{dt} = k_{TNF-\alpha,prod} - k_{TNF-\alpha,decay} \cdot [TNF-\alpha] + \frac{k_{MLS,prod} \cdot [MLS]^s}{K_{MLS}^s + [MLS]^s} + \frac{k_{Macro,prod} \cdot [Macrophage]^t}{K_{Macro}^t + [Macrophage]^t}$$

$$\frac{d[IL-1\beta]}{dt} = k_{IL-1\beta,prod} - k_{IL-1\beta,decay} \cdot [IL-1\beta] + \frac{k_{MLS,prod} \cdot [MLS]^s}{K_{MLS}^s + [MLS]^s} + \frac{k_{Macro,prod} \cdot [Macrophage]^t}{K_{Macro}^t + [Macrophage]^t}$$

$$\frac{d[IL-6]}{dt} = k_{IL-6,prod} - k_{IL-6,decay} \cdot [IL-6] + \frac{k_{MLS,prod} \cdot [MLS]^s}{K_{MLS}^s + [MLS]^s} + \frac{k_{Macro,prod} \cdot [Macrophage]^t}{K_{Macro}^t + [Macrophage]^t}$$

$$\frac{d[TGF-\beta]}{dt} = k_{TGF-\beta,prod} - k_{TGF-\beta,decay} \cdot [TGF-\beta] + \frac{k_{MLS,prod} \cdot [MLS]^s}{K_{MLS}^s + [MLS]^s} + \frac{k_{Treg,prod} \cdot [Treg]^u}{K_{Treg}^u + [Treg]^u}$$

$$\frac{d[IL-8]}{dt} = k_{IL-8,prod} - k_{IL-8,decay} \cdot [IL-8] + \frac{k_{FLS,prod} \cdot [FLS]^v}{K_{FLS}^v + [FLS]^v}$$

Explanation: These equations model the production and decay of cytokines. The production terms use Hill's Equation to represent the dependence on their respective sources.

Combined Effects

To capture the combined effects of cytokines and cells, you can add interaction terms:

$$\frac{d[MLS]}{dt} = k_{birth,MLS} - k_{death,MLS} \cdot [MLS] + \frac{k_{TNF-\alpha,act} \cdot [TNF-\alpha]^n}{K_{TNF-\alpha}^n + [TNF-\alpha]^n} + \frac{k_{IL-6,act} \cdot [IL-6]^m}{K_{IL-6}^m + [IL-6]^m}$$

$$\frac{d[Macrophage]}{dt} = k_{birth,Macro} - k_{death,Macro} \cdot [Macrophage] + \frac{k_{TNF-\alpha,act} \cdot [TNF-\alpha]^n}{K_{TNF-\alpha}^n + [TNF-\alpha]^n} + \frac{k_{IL-6,act} \cdot [IL-6]^m}{K_{IL-6}^m + [IL-6]^m}$$

Parameters

The parameters in the equations (e.g., (k*{birth}), (k*{death}), (k_{act})) need to be determined experimentally or estimated from data. These parameters represent rates of birth, death, activation, production, and decay.

Summary

These differential equations with Hill's Equation provide a more detailed framework for modeling the interactions between cytokines and immune cells in RA. They capture the non-linear dose-response relationships that are common in biological systems. Hill's Equation allows you to model the sensitivity and threshold effects of cytokine activation on cell behavior, which is essential for accurate representation.

To simulate these models, you would typically use numerical methods to solve the differential equations. Tools like MATLAB, Python (with libraries like SciPy or PySB), or specialized software for systems biology modeling might be used for this purpose.

This approach should provide a comprehensive and biologically relevant model that can be effectively described and discussed in your thesis.