

# MATHEMATICAL MODELLING OF NEUROIMMUNOLOGICAL INTERACTIONS

Onur Pusuluk<sup>1,3</sup>, Burak Güçlü<sup>4</sup>, Eda Tahir Turanlı<sup>1,2</sup>

1 ITU, Molecular Biology and Genetics Department, Maslak, Istanbul, Turkey

2 ITU, Molecular Biology –Biotechnology and Genetics Research Center, Istanbul, Turkey

3 ITU, Physics Engineering Department, Maslak, Istanbul, Turkey

4 Boğaziçi University, Biomedical Engineering Institute, Bebek, Istanbul, Turkey



In general, the healthy state of the immune system is determined by the balance between two different cell types: Th1 (type one of helper CD4+ T cells) and Th2 (type two of helper CD4+ T cells). If the dominant cell and the related molecules turn into the Th1-type, then the organism goes into the diseased state. The aim of this study is to analyze and mathematically model the neuroimmunological interactions based on the findings from the biology of multiple sclerosis (a neuroimmunological disorder). Interactions between the cells and related molecules are modeled by using a set of nonlinear ordinary differential equations in MATLAB. First, the existence of two different steady states (i.e. health and disease) is shown. Then, the effects of the time course of a hypothetical treatment are studied. Effects of infection-induced neuroimmunological diseases and mutations related to cell apoptosis or aging can also be simulated by the mathematical model. The presented model is useful for predicting complex neuroimmunological interactions and for formulating experimental hypotheses.

## I. Introduction

Similarities between biochemical languages of nervous and immune systems and their functional dependence to each other have been demonstrated by neuroimmunological and psychoneuroimmunological studies since 1980s [1, 2]. Therefore, studies about bidirectional interactions of these two systems at molecular level, are very important in understanding each of them at system level. In general, nervous system contributes to immunoregulation through HPA (hypothalamic-pituitary-adrenal) axis, sympathetic neurons directly innervating to lymphoid organs, and Ach (acetylcholine) secreting parasympathetic neurons. Whereas immune system affects it primarily through cytokines (even sometimes like a sensory organ) [1].

Th1-type cytokines (such as IL-2, IL-12, IFN- $\gamma$ , TNF- $\alpha$ ) are involved in the immune response to intracellular infections and called as pro-inflammatory cytokines. On the other hand, Th2-type cytokines (such as IL-1, IL-4, IL-5, IL-6, IL-10, IL-13) are involved in the immune response to extracellular parasites and called as anti-inflammatory cytokines. In addition, Th1/Th2 balance is important in autoimmune diseases [3].

One way of analysing "healthy systems" may be studying the system when it turns into the unhealthy stage. It is thought that complex neuroimmunological interactions can be analysed using neuroimmunological diseases, such as Multiple Sclerosis (MS), as models. MS is a demyelinating, degenerative, and neuroinflammatory disease [4]. Myelin proteins are among the strong candidates of MS antigens. However, the only differences between proteins in health and disease are at the level of posttranslational modifications [5].

In all the phases of MS, both helper CD4+ T- and cytotoxic CD8+ T-cells (regulatory cells, Tc) are present although the number of CD4+ T-cells is generally more less than the other ones [6]. During the progression of MS, axonal injury is more important than demyelination and there is more direct correlation between axonal injury and number of Tc cells [7]. Besides this, CD4+ T-cells can protect neurons by secreting neurotrophin factors [6, 8]. Also, dominant CD4+ T-cells are Th2 cells in some MS situations [6].

## II. Model

The model includes Th1, Th2, T0 (nondifferentiated T-helper cell), Tc, and MPh (macrophages) cell types; cytokines of Th1, Th2, and MPh cells; and foreign antigens (Ag) from the immune system, and additionally, OLG (oligodendrocytes) cells with Ach and GC (glucocorticoids, especially cortisol) molecules from the nervous system. MPh cells are also used as APC. Furthermore, cytotoxic CD8+ cells are used as anti-idiotypic cells which are reactive to idiotypic cells. CD4+ T-helper cells. Concentration of these cells and molecules are written as ordinary differential equations that are set out with the aid of interactions.

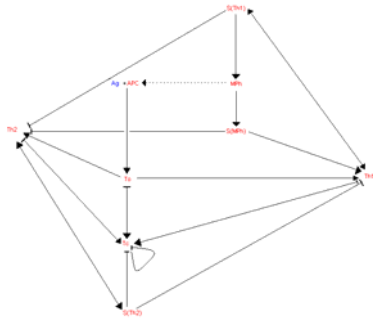


Figure-1: A schematic description of the interactions inside immune system [1-9]

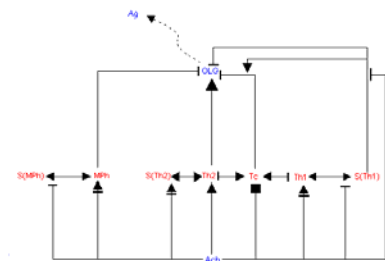


Figure-2: A schematic description of the interactions between immune system, OLG cells, and Ach molecules. [1-9]

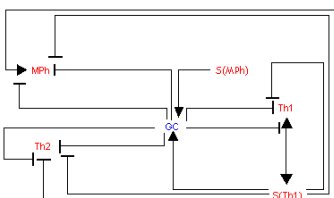


Figure-3: A schematic description of the interactions between immune system and GC molecules. [1-9]

In general, the equations of the model for the cells can be written as:

$$\frac{dy_i}{dt} = (\sum_j \omega_{ij} \times y_j \times y_i \times \prod_k \bar{y}_k) + \max(0, \sum_l \sigma_{il} \times \text{orig}_l \times y_i \times \prod_k \bar{y}_k) + (d_i \times y_i \times \prod_k \bar{y}_k) + k_i$$

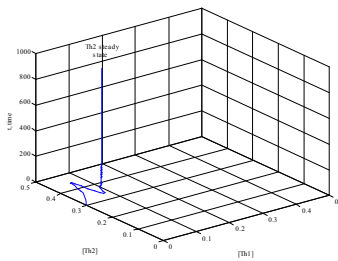
A similar equation for molecules can be written as:

$$\frac{dy_m}{dt} = (\sum_j \omega_{mj} \times y_j \times y_m \times \prod_k \bar{y}_k) + \max(0, \sum_l \sigma_{ml} \times \text{source}_l \times \prod_k \bar{y}_k) + (d_m \times y_m \times \prod_k \bar{y}_k) + k_m$$

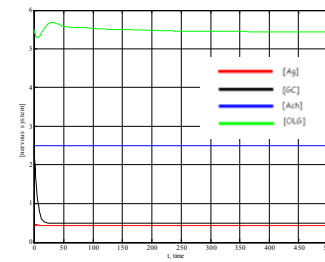
These equations are used with some modifications for some cell types and molecules.

## III. Results and Discussion

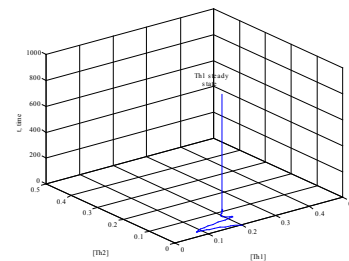
As a validation of the model existence of two different steady states of health from the immune system and bi-directional transitions between two steady states were shown. Then, the effects of the time course of a hypothetical treatment were studied and effects of cortisol was found to be time dependent. In addition, the effects of infection-induced neuroimmunological diseases was simulated by the model. These results correlate with general hypothesis in which only infectious factors mimicing [3] MS antigens at a certain level can trigger this autoimmune disease [9]. It was also simulated that if mutations were decreasing Ach-OLG interaction by three times, concentration of OLG cells were the same order with the ones in Th1 steady state. Moreover, effects of Fas mutations were tested since Tc mediated OLG apoptosis depends on the expression level of Fas gene. Same results were obtained when mutations were increasing the expression level of Fas gene by five times. In both of these two cases, the most interesting result was that autoimmune disease could be present also in Th2 dominant steady state [6] and most reactive immune cells were Tc cells in those situations.



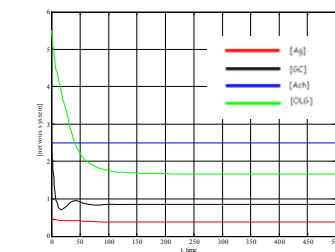
Graph-1: Th2 steady state



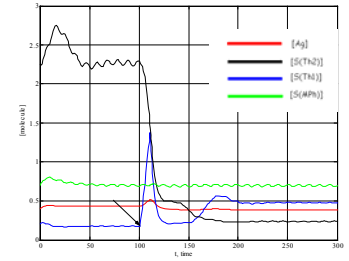
Graph-2: Th2 steady state



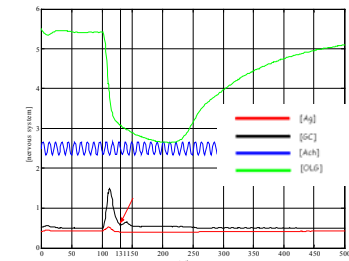
Graph-3: Th1 steady state



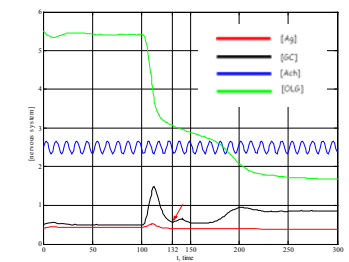
Graph-4: Th1 steady state



Graph-5: Th2 → Th1 transitions



Graph-6: Th1 → Th2 transitions



Graph-7: time course of a hypothetical treatment

Finally, the effects of aging in autoimmune disease were tested by the present model. It was assumed that all the coefficients for natural death rate of cells and molecules should increase by aging. Increase of natural death rates above a certain level (1/100 times per each 100 time units) decreased the OLG cell concentration to disease level, although the dominant T-helper cell type was still, Th2 cells. However, 5/100 times increase per each 100 time unit also shifted Th1/Th2 balance to Th1 dominance after a certain time. Higher increases only changed the shifting time.

The presented model is useful for predicting complex neuroimmunological interactions and for formulating experimental hypotheses. Major mechanisms such as release of free antigen due to cell destruction or effects of tissue cells on immune response were included in the model. However, it partially ignores the effects of localization and tissue barriers that are very important in neuroimmunological interactions. Moreover, T0 cells should be divided into two subpopulations as CD28+ve CTLA4+ T0 cells in order to make these results more reliable. Furthermore, nerve cells should be added into the present model in order to make the complexity of the model more real. Also, estrogen can be added to show the sexual selectivity of autoimmune diseases. After these additions, genetic effects and role of heredity on neuroimmunological interactions can be demonstrated by the model more easily and more efficiently. Finally, the uncertainty in the time unit should be removed by the correlations with clinical data.

## IV. References

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