Introduction

MS affects about one million people worldwide and causes physical and cognitive disability. There are three types of MS: relapsing-remitting, secondary progressive, and primary progressive. These three types have different clinical courses and patterns of disease progression. There are as yet no known cures for MS. Patients with relapsing MS are currently treated with drugs that exert immunosuppressive effects to slow the progression of the disease. However, there are no effective treatment options for the progressive forms of MS [1].

The long-term goals of this research are to develop disease models that can be used to evaluate therapeutic strategies for this disease and, in this report, the specific focus is on evaluating a network model for MS lesion dynamics. Literature survey indicates that network approaches have not been studied extensively for disease modeling in MS.

Auto-Immunity

Conventional models for auto-immunity are premised on the occurrence of disease-specific pathogenic cell types from host tissue in the conventional models. The concomitant immune responses through the generation of appropriate "danger" signals [4, 5, 6, 7, 9, 8]. For example, in the case of MS, peripheral vegetation to contain forest fires. Inter-cellular signaling is a key characteristic of the immune system, orchestrate a complex cascade of events that cause blood brain barrier disruption and invasion of immunologically aggressive cells into the CNS. However, the exact causes of MS still remain unknown [2].

The present network model is inspired by the conceptual comprehension of autoimmunity, developed by Nevo et al. [7, 9] complements the alternate viewpoint, as also reported [8]. The present network model is inspired by the alternative viewpoint.

The key elements of the model consist of a pathologic process that causes cellular damage and programmed cell death initiated through an inter-cellular signaling component. The programmed cell death deprives the pathologic process of healthy tissue which is necessary for its propagation in space and time. In this, it resembles the action of firemen who burn peripheral vegetation to contain forest fires. Inter-cellular signaling is a key feature of the model that allows pathologically damaged cells to propagate abnormal signals and initiate programmed cell death.

Model

An undirected, fixed radius random graph $G(r, r_f)$ with $n$ nodes (vertices) and radius of connectivity, $r$, is constructed to represent the CNS in this 2D network model. Fixed radius implies that nodes are connected only if they are within a distance of $r$. Biologically, the nodes of the graph can be viewed as representing cell bodies or functional units and the edges (bonds) of the graph can be viewed as axons or the interconnections between functional units.

Three key parameters control the dynamics:

1. $r_f$ is the threshold at which the stressed/damaged cells send out alarm signals.
2. $h$ is the threshold at which the programmed cell death is initiated.
3. $C_{bf}$ controls the spatial extent of programmed cell death.

- Low value of $r_f$ i.e. quicker firing of alarm signals, lead to earlier activation of programmed cell death.
- $h$ indicates the sensitivity of the immune system. A low value indicates earlier activation of programmed cell death.
- Larger value of $C_{bf}$ indicates larger area near the alerted node is subjected to programmed cell death.

Results

Conclusion and extensions

A physically motivated 2D network model was developed for the CNS and employed to study the process of lesion formation and spread in MS. Inter-cellular signalling of distress by the damaged cells is a key feature of the model which leads to programmed cell death getting activated in an attempt to arrest the lesion progression. The model demonstrates that the spread of the pathologic process can be arrested by programmed cell death when the geometry of the damage inflicted by the latter leads to an envelope, of sufficient thickness, being created encompassing the area of pathologic process. Such an envelope of dead cells deprives the pathologic process of healthy cells which can sustain its growth. The model shows a smooth transition, as parameters are varied, from the situations of run-away pathologic process, through aggravated damage to the system caused by unsuccessful firing of programmed cell death, to the creation of successful envelope around the pathological process.

The model complements the alternate viewpoint on auto-immunity which posits that cells and tissues signal distress and activate the immune system. Such a viewpoint circumvents the need for the immune system to store information about likely pathogens and, also, makes it capable of acting in instances of cellular damage resulting from non-pathogenic causes. Further study of the model along with identification of the possible biological counterparts would enable comparisons with experiments and a more detailed exposition.

References