Mathematical Biosciences xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

A minimal unified model of disease trajectories captures hallmarks of multiple sclerosis

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ARTICLE INFO

Article history:
Received 10 October 2016
Revised 4 March 2017
Accepted 16 March 2017
Available online xxx

ABSTRACT

Multiple Sclerosis (MS) is an autoimmune disease targeting the central nervous system (CNS) causing demyelination and neurodegeneration leading to accumulation of neurological disability. Here we present a minimal, computational model involving the immune system and CNS that generates the principal subtypes of the disease observed in patients. The model captures several key features of MS, especially those that distinguish the chronic progressive phase from that of the relapse-remitting. In addition, a rare subtype of the disease, progressive relapsing MS naturally emerges from the model. The model posits the existence of two key thresholds, one in the immune system and the other in the CNS, that separate dynamically distinct behavior of the model. Exploring the two-dimensional space of these thresholds, we obtain multiple phases of disease evolution and these shows greater variation than the clinical classification of MS, thus capturing the heterogeneity that is manifested in patients.

1. Introduction

Multiple Sclerosis (MS) is an inflammatory, autoimmune disease targeting the central nervous system (CNS) inducing demyelination, axonal loss and neurodegeneration[1]. Most patients initially display a relapsing-remitting disease course (RRMS), with bouts of attacks followed by a variable degree of recovery of neurological functions. During this phase, inflammatory lesions occur intermittently as demonstrated by magnetic resonance imaging. With time, most RRMS patients convert to a (secondary) progressive disease state (SPMS), characterized by irreversible deterioration of neurological health and abilities. It has been hypothesized that the transition from RRMS to SPMS occurs when the extent or nature of injury reaches a certain threshold [2,3]. In addition, a smaller fraction of patients (10–15%) display a progressive disease course from onset - primary progressive MS (PPMS) [4].

Despite plenty of research, there is as yet no convincing explanation for the origins and mechanisms for MS [5]. The common classification into the three subtypes (RRMS, SPMS, PPMS) ignores the immense heterogeneity that exists among patients at the clinical, immunological and histopathological level [6,7]. For example, while both demyleination and axonal neurodegeneration are commonly observed in MS patients, the relationship between the two processes and their combined effect on disability or disease progression is not well-understood [3,8]. Given these large variations in MS characteristics, stitching together different observations and results to produce a consistent framework describing the disease has been and remains an elusive goal.

Here we present a minimal, computational model that reproduces the principal types of MS and accounts for several features of the disease progression. The model is shaped by specific assumptions that are supported by various fragments of evidence from histopathological and neurological sources. We locate the origin of the disease in the immune system, in line with the current understanding [9]. The spatial and temporal scales describing the processes are macroscopic, representing a coarse-grained behavior of the system. The perturbations and fluctuations in the model are represented as stochastic noise.

The model also posits the existence of two independent thresholds or capacities, one that regulates the immune system

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http://dx.doi.org/10.1016/j.mbs.2017.03.006

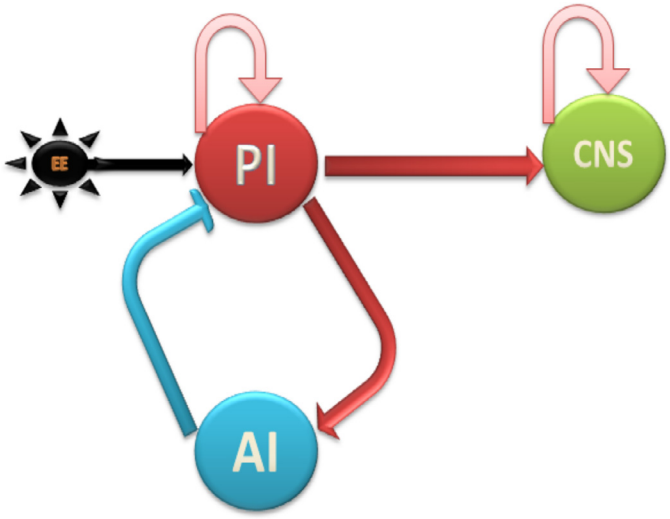

Fig. 1. Interaction diagram representing the immune system and CNS. The pro (PI) and anti-inflammatory (AI) components form a negative feedback loop (AI suppresses PI while increase of PI enhances AI). The two modules are linked by the infiltration of the CNS by PI and causing demyelination and lesions. The self-loops on PI and CNS represent the effect of breaching their thresholds, which leads to unregulated increase of the inflammatory component and neurodegeneration respectively. The notion that pro-inflammatory processes or degenerative processes, can increase beyond control of is indicated with a positive feedback loop (self-arrow) at PI and CNS respectively. The random perturbation on the pro-inflammatory component is represented by an incoming arrow from the node EE (environmental fluctuations).

dynamics, and the other representing the protective capacity against neurodegeneration. These induce irreversible transitions in the progress of the disease. With all other parameters of the model held fixed, studying the classes of disease trajectories obtained across the two dimensional space of the thresholds reveals a varied set of 'phases'. Thus our minimal model is sufficient to capture the observed heterogeneity of the disease, above and beyond the standard clinical classification.

2. Model construction

Fig. 1shows the interaction graph of the model. The immune system components are one of two possible types: pro-inflammatory (PI) and anti-inflammatory (AI) [10]. Following earlier work [11,12] we assume that there exists a cross-regulatory interaction between the two components setting up oscillations in their respective numbers. The anti-inflammatory factors suppresses inflammation while increase of the inflammatory component in turn strengthens the anti-inflammatory response. The initial damage to the CNS is the demyelination of white matter caused by inflammatory attacks [13]; the greater the inflammatory component in the immune system, the more their infiltration into the CNS, and hence, more widespread the demyelination. There is simultaneously an internal process within the CNS that repairs the damage and remyelinates the axons [14]. In addition, neurodegeneration and neuronal death [8] occurs in the CNS and we model the combined effect of demyelination and neurodegeneration as the overall disease pathology.

Apart from the above well-established processes, there are a couple of additional dynamics that we propose as model hypotheses. First, the immune system is subjected to random noise that represents (a) the fluctuations of the coarse-grained model and (b) the perturbations from the interactions with other elements that do not comprise the core processes of the disease [15]. It is important to note that, while the actual interactions that produce the noise are external to the central disease mechanisms, their combined effect as noise has a very important role in determining the disease evolution as we will see later on. The second is a pair of critical events that irreversibly change the interaction dynamics. The first of these is the collapse of the negative feedback loop in the immune system when the inflammatory component reaches a certain threshold following which the inflammatory component increases unremittingly [16,17]. The primary motivation for introducing this threshold is the observation that the interactions of Fig. 1 implies that the presence (or absence) of oscillations in the demyelination of the CNS necessarily requires presence (or absence) of similar oscillations in the immune system, and specifically the PI. This is a very general result and is proved in Supplement Section A.

The second critical event represents the triggering of neurodegeneration in the CNS when axonal demyelination reaches a certain threshold (see Methods for details). This happens when the protective capacity of the CNS against neuronal damage from inflammatory demyelination is overwhelmed. Once triggered, the process of neuronal death spreads across the CNS unabated. The reasoning leading to the hypothesis of a CNS threshold arises from the fact that while demyelination and CNS lesions are the associated forms of pathology during the relapsing remitting phase, axonal loss and brain atrophy are the key contributors to the disability in the progressive form of MS [18–20].

The full set of ordinary differential equations that underpin the model is given in Eqs. (1)–(5).

$$\frac{dI}{dt} = -c_1 I \frac{A - A_S}{b_1 + A} \mathbb{1}[I_C - I] + \xi_0 e^{-\frac{t-t_C}{\tau}} \mathbb{1}[I - I_C] + F_\lambda(t) \tag{1}$$

$$\frac{dA}{dt} = c_2 A \frac{I - I_S}{b_2 + I} \mathbb{1}[I_C - I] \tag{2}$$

$$\frac{dZ_{Demy}}{dt} = c_3 \frac{I - I_S}{b_3 + I} \left(\frac{Z_{Tot} - Z_{Demy} - Z_{Dead}}{Z_{Tot}} \right) \mathbb{1}[I - I_S] - \kappa Z_{Demy}(t) \tag{3}$$

$$\frac{dZ_{Dead}}{dt} = c_4 \left(\frac{Z_{Tot} - Z_{Dead}}{Z_{Tot}} \right) \mathbb{1}[Z_{Demy} - Z_C] \tag{4}$$

$$Z_{Path} = Z_{Demy} + Z_{Dead} \tag{5}$$

Eqs. (1) and (2) represent the immune system processes. I and A are the inflammatory and anti-inflammatory components, I_S, A_S being their stationary values respectively, c_1, c_2 kinetic constants. F is the stochastic noise

$$F_\lambda(t) = \sum_i \delta(t - t_i) v_i$$

characterized by instantaneous stimulus v_i that occurs at times that are Poisson distributed with average rate λ. v_i's are drawn independently from a uniform distribution $U[-0.1, 0.1]$.

$\mathbb{1}[x]$ is a step function taking 1 when $x \geq 0$ and 0 otherwise. This is used to represent the threshold in the immune system, such that when $I < I_C$ the trajectory around the stable fixed point (I_S, A_S) is oscillatory. The stochastic term introduces random, uncorrelated perturbations to the oscillations. If, as a result of such deflections, $I > I_C$ at some point t_C, the negative feedback loop is severed and the increase of I is governed by a factor that exponentially decays over time and with time-scale τ. We emphasize that the qualitative features of the model would be equally valid with any non-decreasing function determining the rate of change of I, and this particular factor was meant to capture the finiteness of inflammatory factors and also the time-span over which the proliferation of I occurs. The interaction term between the two components that