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

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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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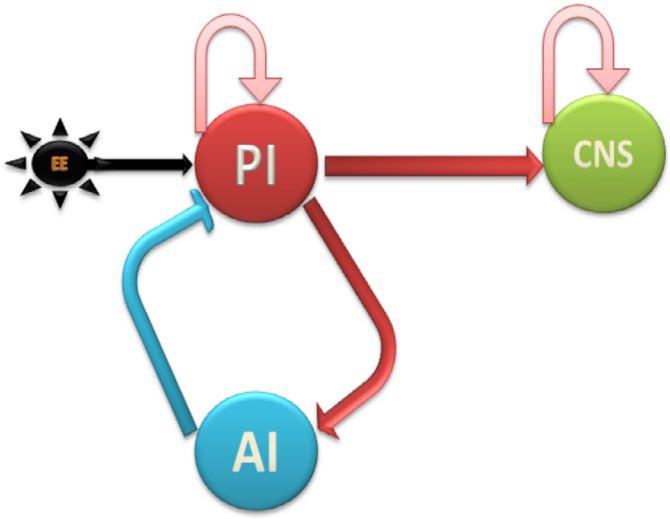

Fig. 1. Interaction diagram representing the immune system and CNS. The pro (PI) and anti-inflammatory (AI) components form a negative feedback loop (AI suppresses PI while increase of PI enhances AI). The two modules are linked by the infiltration of the CNS by PI and causing demyelination and lesions. 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

Table 1
Parameters used in the model and their values.

Parameter	Description	Value
c_1, b_1	Controls rate of change of inflammatory component.	$c_1 = 20, b_1 = 30$
I_S, A_S	Stationary state values of pro and anti inflammatory components.	$I_S = 7, A_S = 7$
ξ_0	Initial rate of increase of inflammatory component upon immune threshold breach.	0.5
τ	Time scale determining the proliferation of inflammatory component following immune breach.	20
λ	Poisson rate at which the random perturbations occur.	20
I_C	Immune threshold.	Varies
c_2, b_2	Controls rate of change of anti-inflammatory component.	$c_2 = 50, b_1 = 30$
c_3, b_3	Controls rate of change of demyelination.	$c_3 = 20, b_3 = 40$
Z_{tot}	Total volume of the region susceptible to damage.	2
κ	Rate of remyelination.	1
c_4	Controls the growth of dead cells	$c_4 = 0.5$
Z_C	CNS threshold	Varies

Table 2
List of abbreviations.

Abbreviation	Expansion
CNS	Central Nervous System
RRMS	Relapse Remitting MS
SPMS	Secondary Progressive MS
PPMS	Primary Progressive MS
PI	Pro-Inflammatory
AI	Anti-Inflammatory

determines their rate of change is modeled as a hyperbolic factor [21].

Eq. (3) represents the demyelination in the CNS Z_{Demy} caused by the inflammatory attacks on the undamaged fraction of the total volume Z_{tot}; the last term in that equation represents remyelination at rate κ. The other threshold, in Eq. (4), triggers the neurodegeneration in the CNS when $Z_{Demy} > Z_C$ causing neuronal death Z_{Dead}. The overall pathology in the CNS is the sum of the demyelination and death in CNS, Eq. (5).

3. Results

We demonstrate the generation of the basic clinical subtypes of the disease using the model described above. Although the model generically produces the different subtypes, in order to study the qualitative variations introduced by differences in thresholds, all the parameters of the model (except the thresholds I_C, Z_C) are maintained constant to generate the different subtypes that are discussed below. These parameter values are given in Table 1 in the Methods section.

Fig. 2a shows the progression of RRMS in the CNS, where the disease pathology - here, equivalent to demyelination - follows a quasi-periodic behavior of expansion and retraction (due to remyelination). Fig. 2b shows the corresponding oscillations in the immune system between the pro and anti inflammatory components. The waxing and waning of the inflammatory component directly leads to the relapses and remissions in the disease pathology.

The random noise term in the immune system creates the irregularities in the periodic behavior of the inflammatory components in Fig. 2b. For a given trajectory, the stochastic term is critical in determining if and when the immune threshold is breached. During relapse-remitting, if the inflammatory component breaches the threshold, the disease course turns towards progressive phase (SPMS) and this is shown in Fig. 3a. The threshold eliminates the negative feedback loop in the immune system and induces a switch from oscillatory behavior to monotonic increase of the inflammatory component Fig. 3b. This is relayed to the CNS leading to steady increase in disease pathology (Fig. 3a).

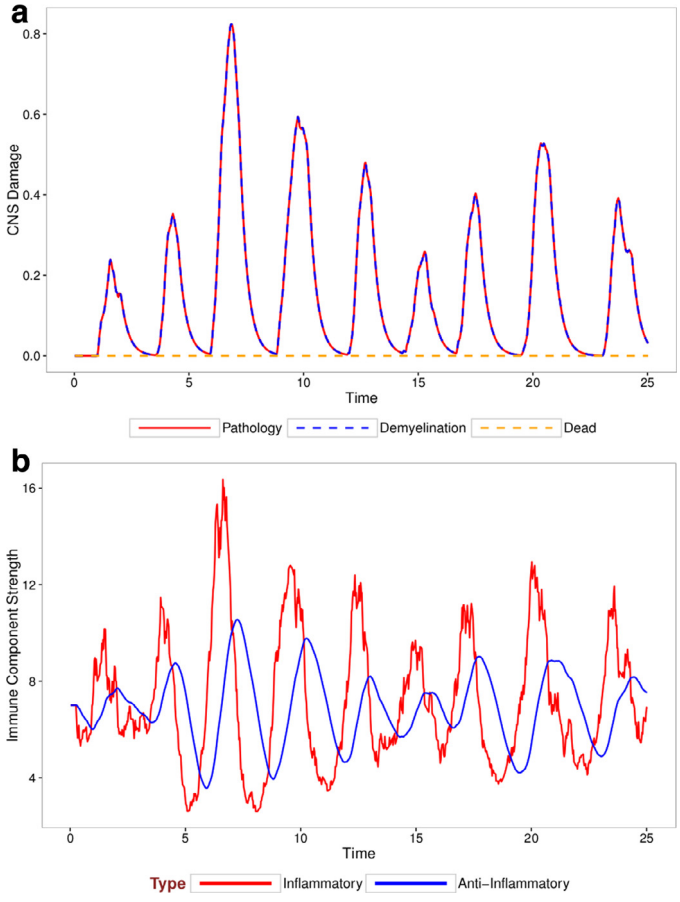

Fig. 2. (a) Disease trajectory for RRMS and (b) the corresponding dynamics in the immune system. Immune and CNS thresholds are 25 and 4 respectively.

Finally, the PPMS subtype, characterized by unremitting worsening of the condition from the start, is shown in Fig. 4a. This is the outcome of the lower immune threshold that is breached by the inflammatory component very early in the evolution (see Fig. 4b). Fig. 4a also shows another phenomena - dead cells start accumulating from around time $t = 18$, that is triggered by the breach of CNS threshold. Yet another subtype that emerges from our model is the progressive relapsing (PRMS) [22] where the disease deteriorates steadily except there are intervals of partial remissions, leading to quasi-periodic ripples over a growing pathology (Fig. 5a). This arises when the CNS threshold against neurodegeneration is overcome first, leading to accumulation of neuronal death, while the oscillations in the immune system are relayed

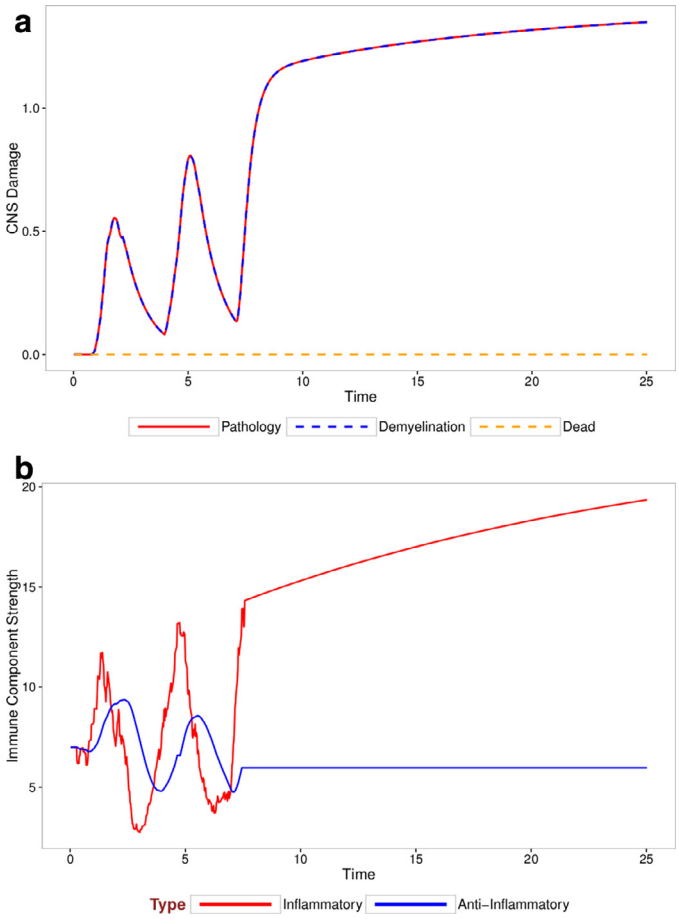

Fig. 3. (a) Disease trajectory for SPMS and (b) the corresponding dynamics in the immune system. Immune and CNS thresholds are 13 and 4 respectively.

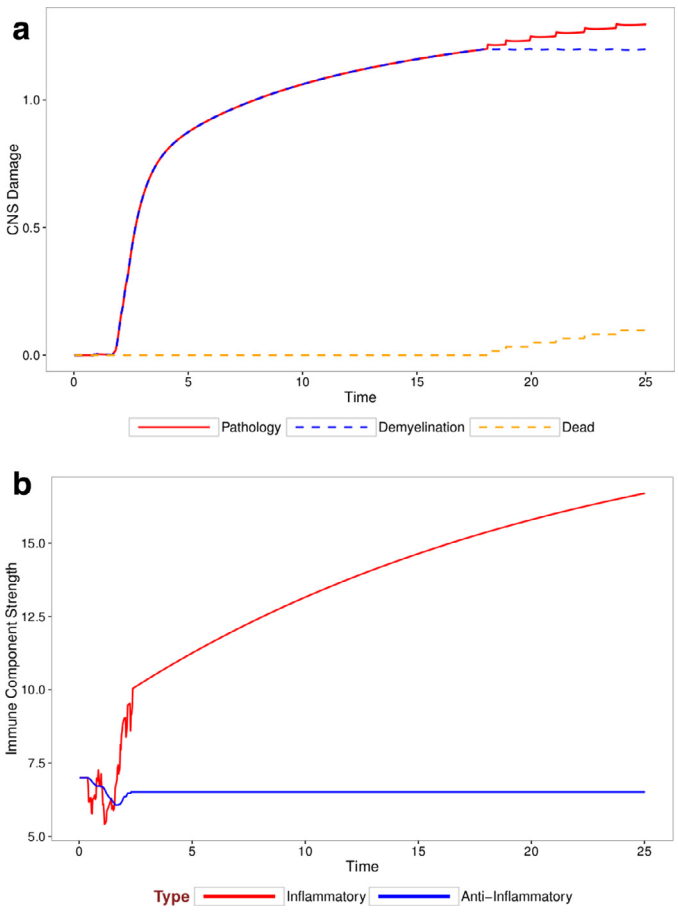

Fig. 4. (a) Disease trajectory for PPMS and (b) the corresponding dynamics in the immune system. Immune and CNS thresholds are 9 and 1.2 respectively.

to the CNS in the form of waxing-waning demyelinating pattern (Fig. 5b). The overall pathology is the combined effect of neuronal death and demyelination.

4. Model reproduces disease characteristics

Disease evolution thus depends on the two thresholds and the magnitude of the fluctuation term in the immune system. Together, we show that they generate model features that are consistent with the existing knowledge of MS. If the initial appearance of MS is relapse-remitting, then the different thresholds correspond to transitions to progressive phase at different levels of disability [23]. An immediate but important consequence of the model is the increase in probability of overcoming the thresholds and switching to chronic progressive type increases with age [24]. For any given threshold, shorter time to progressive transition in our model implies faster deterioration of the disease condition [24]. The thresholds being independent of the negative feedback dynamics implies that the time between onset of the disease and transition to progressive phase is independent of the frequency of relapse [25] (Fig. 6a).

The relapse-remitting and the progressive courses are decoupled in our model by design. The natural consequences of this are that (a) the characteristics of the progressive course is independent to that of the relapse-remitting phase and (b) the progressive phase in SPMS or PPMS is similar to each other. There is significant evidence that this is indeed true with MS patients. First, while the median age for initial symptoms in both RRMS and SPMS is 29, the median age for the onset of the progressive phase in SPMS is 39, which is exactly the median age for onset of the PPMS variant of the disease [23]. More strikingly, even the distribution of age of onset among patients is nearly identical for the RRMS/SPMS, as is the similarity in the corresponding curves for the age of onset of the progressive phase in SPMS and PPMS [23]. This shows that the development of disease pathology on an average is similar during the chronic progressive phase in both PPMS and SPMS.

Second, the immuno-suppressive treatments found to be effective during the relapse-remitting phase [2] of the disease have little to no benefits in patients who have already reached the progressive stage of the disease [26,27]. This is certainly the case in our model once the CNS threshold is breached, as progression of neurodegeneration is independent of the immune system dynamics. Likewise, if the progressive course were to be initiated by overcoming the immune threshold, then the suppressive mechanism would no longer be effective against the inflammatory growth.

5. Different regimes of MS

To characterize the full spectrum of disease types arising from different combinations of the two thresholds, we consider the two-dimensional parameter space and examine the disease courses in each. However, we begin by considering the immune threshold only. Fig. 6b shows the variation of the fraction of RRMS with the immune threshold based on 200 realizations (keeping other parameters fixed). The stochastic nature of the immune dynamics implies that for a threshold in an intermediate range demarcated by vertical blue lines, a certain fraction of the realizations will breach

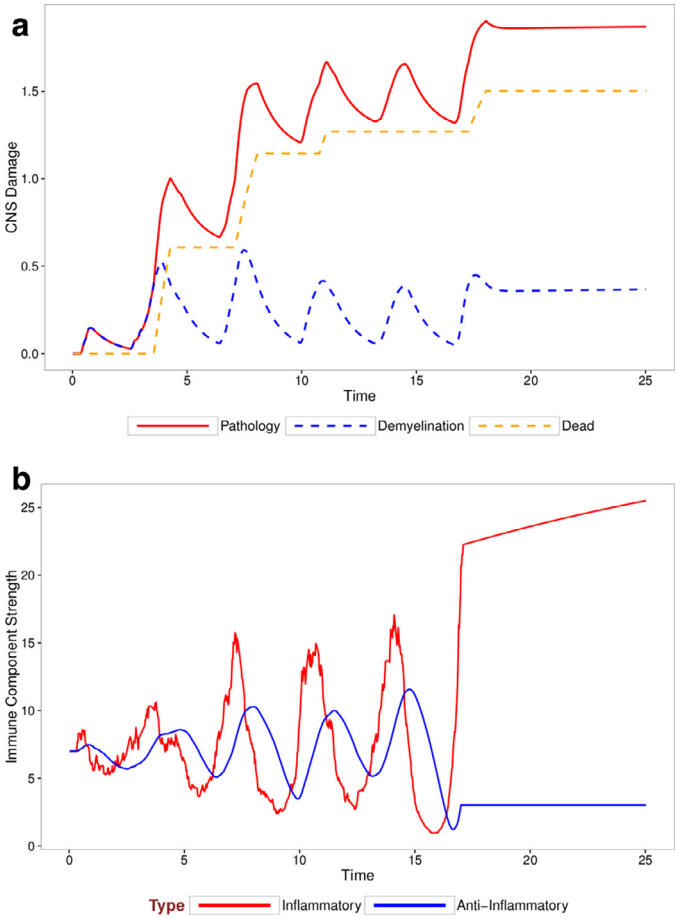

Fig. 5. (a) Disease trajectory for PRMS and (b) the corresponding dynamics in the immune system. Immune and CNS thresholds are 20 and 0.4 respectively.

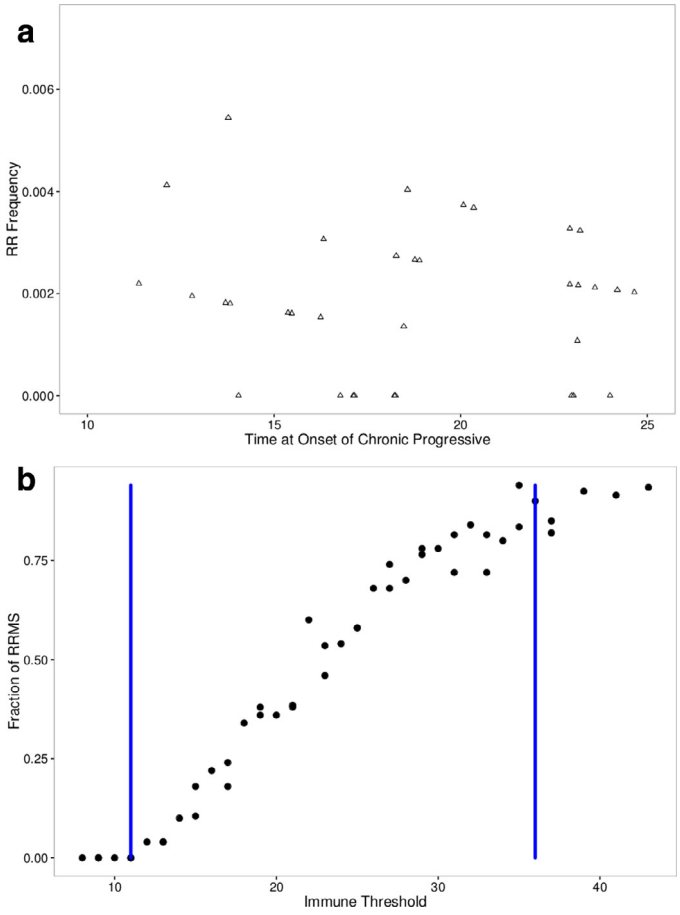

Fig. 6. (a) Plot of the frequency of relapses with the time at onset of progressive phase. The immune and CNS thresholds are fixed at 25 and 4 respectively. c_1 was set equal to c_2 in Eqs. (1) and (2), and was sampled from a uniform distribution in the interval $U[16, 28]$. All other parameters were kept fixed. (b) Fraction of RRMS cases as the immune threshold is varied (CNS threshold is 4). For each threshold value, a set of 200 realizations was performed to determine the fractions.

it. The thresholds to the left of this region are invariably breached (SPMS/PPMS) and those to the right exhibit only RRMS.

The two-dimensional phase diagram should agree with the above results as a limiting case of CNS threshold $Z_C \to \infty$. Likewise, we can argue that there is function $\sigma(I_C)$ of the immune threshold, corresponding to a phase transition curve, such that, for every $Z_C < \sigma(T_C)$, there would invariably be a breach of the CNS threshold before that of the immune system. We also note that, if the immune system threshold is breached, the probability of an eventual CNS breach markedly increases. Thus, even before we perform detailed simulations over the entire parameter space, we can see that this scenario quite correctly captures the fact that neurodegeneration frequently accompanies the progressive phase of the disease, regardless of the history of the disease [2].

The complete classification of the two-dimensional parameter space is shown in Fig. 7. Following the previous discussion, the two vertical light green lines have the same x-intercepts as the blue lines in Fig. 6b and, as expected, we recover the three regions seen in that figure at the band above the blue curve of this plot. These two vertical lines together with the three curves represent the phase boundaries between qualitatively different regimes of model behavior. The red curve is the one whose existence we argued for above, below which CNS breach invariably occurs prior to that of the immune system. Thus the entire region below that curve in the parameter space would map to PPMS or SPMS. The dark green curve separates the phase just above the red curve, where both RRMS and SPMS co-exist and the phase where the progressive phase (when it occurs) is always initiated first by the immune breach (may or may not be followed by the CNS threshold breach). Finally, the blue curve represents the boundary beyond which no CNS threshold (including secondary breaches) ever occurs. Note that a given pair of dashed and solid curves of the same color correspond to the original demarcation from simulation results and the smoothed out spline fit of the same respectively.

Fig. 7admits a rich spectrum of disease courses, more so than the standard clinical classification of the disease types. Specifically, SPMS can occur in different regions of the phase space, and while the manifestations of disability are likely to be similar, these have mechanistically different origins. In fact, even if we consider the subset of SPMS characterized by neurodegeneration, the phase space of our model indicates that it can be either from a breach of CNS threshold (below the red curve) or an immune breach followed by a CNS breach (above the green curve). In the band between the red and green curves (and between the vertical lines), the progressive course could have been triggered by overcoming either the CNS or the immune threshold.

6. Methods

The above equations were integrated numerically by fourth order Runge–Kutta method. The step function was approximated by terms of the form $\frac{1}{1+e^{\gamma(I\pm I_C)}}$ for ($\gamma \gg 1$, a constant). Indeed the key features of the model do not depend on the sharpness of the threshold. A full listing of all the parameters and their values is given in Table 1. In all the realizations of disease evolution, the

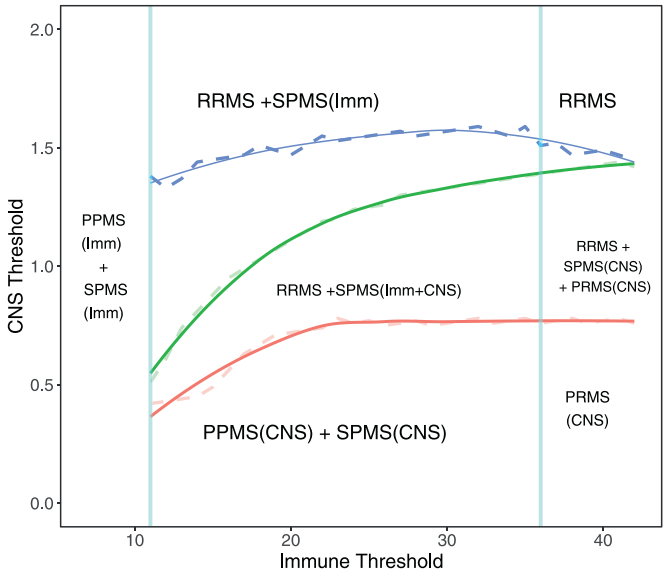

Fig. 7. Immune and CNS threshold phase space split into different regimes, each marked by the types of disease evolution that is possible. This is a logical extension of Fig. 6 to include the CNS threshold (the vertical cyan lines match the immune threshold boundaries indicated in Fig. 6). The 'phases' indicated in the figure are determined from the distribution of outcomes of model simulations. The three curves running from left to right represent the phase boundaries, where the model exhibits a qualitative change in terms of the classes of disease trajectories that are generated (see Methods section for details on how these boundaries were calculated from the simulations; Table 2 provides a list of abbreviations to interpret the text for the various phases.).

overall duration (simulation time/number of steps) was also maintained constant, except where we study the dependence of the relative prevalence of the different forms of MS on it.

To obtain the phase diagram Fig. 7, the two dimensional parameter space was covered by a rectangular grid with the dimension of each cell being 1×0.03 along the x and y axis respectively. At every grid intersection, a set 100 realizations of the disease trajectories were carried out with all other parameters and initial conditions fixed. Each realization was categorized as a specific disease type depending on how, if at all, the transition to progressive phase occurred. We classify the solution as RRMS if no threshold was breached, and SPMS/PPMS if either of the thresholds is crossed. The latter case is divided into three cases - in the first scenario, the breach happens only at the immune system, the second where the breach occurs in the CNS initially, and the third which is similar to the first case except that the CNS threshold is eventually overcome too. In the case the CNS is originally breached, we obtain progressive relapsing MS, that subtype of the disease where relapses are superimposed on progressive degeneration.

The phase boundaries in the two dimensional parameter space separating the different phases were determined by setting thresholds on the appropriate fractions from the numerical simulations. The boundary separating purely neurodegenerative progressive cases from the others (red) comes from determining, for each parameter value of the immune threshold, the CNS threshold at which the fraction of CNS breaches drops below 95%. A spline fit on these points gives the smooth red curve. Likewise, the curve separating regions of parameter space where CNS (primary) breach occurs with finite probability (below) and never (above) is set when the same fraction is diminished to 5% (green). Finally, the blue curve splits the region where CNS (secondary) breach is observed with a finite probability (below) and where it vanishes (above) and is identified by the CNS threshold value for which the fraction of CNS (secondary) breaches falls under 5%. Secondary breach is defined as disease trajectories where the transition to progressive phase occurs in the immune system, but the elevated damage to the myelin sheaths triggers the neurodegeneration as well.

7. Discussion

A set of prescriptive guidelines were used to devise our model, some of which are general to computational modeling while others are specific to the MS case. First, given the complexity of the interaction dynamics in biological systems (different time-scales, nonlinearity, external perturbations, physical and biochemical constraints), we focus on reproducing the qualitative aspects of the system correctly [28]. This is especially true for MS where mechanistic understanding of the disease is very limited and at the same time, the vast heterogeneity in its clinical course [6,7] renders quantitative fitting of the model to training data sets futile. Second, the key characteristics of the model should emerge *generically* from the equations. Equivalently, parameter fine-tuning is not necessary to generate a specific type of behavior.

Indeed our full set of equations (1)–(5) have several parameters but the nature and properties of the different disease trajectories emerging from the model across different thresholds do not depend sensitively upon those parameters (aside from the thresholds, of course). For example, the coefficients $\{c_i, b_i\}$ are the kinetic rate parameters and a perturbation in their values would not change the phase space features of Fig. 7. It is precisely because of this fact that we do not specify the scale (i.e., units) for the time, the immune system components or the CNS damage. Similarly, our results do not require sensitivity analysis because we are neither fitting the model to some specific disease course (patients or otherwise) nor are we arriving at specific magnitudes for quantities that can be measured. We however stress that our model aims to elucidate the mechanisms of the disease process and not precise fitting to specific cases. In much the same spirit, the key claims and results of our model are based on the interaction structure of the model (e.g., the existence of cross-regulation setting up oscillations) and not on the specific mathematical form of the interaction dynamics, allowing us to draw more general and robust conclusions about the disease processes.

As a further step in the direction of generality, we have described the immune system in terms of inflammatory and anti-inflammatory components without specifying whether these are T cells, B cells, macrophages, cytokines, antibodies, chemokines etc. The reasons are two fold: first, it must be noted that any component-pair with the regulatory dynamics we have considered here is sufficient to generate the patterns observed; second, what constitutes a regulatory or an inflammatory component may vary across time, and the same cell might switch from being one to the other, or a new entity may contribute to these roles.

It could be argued that the lack of clear causal explanation for the disease, and especially the transition to the progressive form, and the heterogeneity of its pathogenesis permits several competing hypothesis to be equally valid descriptions of MS development and progress. This may be true as a general principle but to the best of our knowledge there have been very few models of MS, computational or otherwise, dealing with the mechanism of the onset and progress of the disease. Even these focus on narrower aspects such as reproducing the relapse-remitting behavior [29] or modeling the development of lesions[30]. More important, there are definite assumptions that go into our model, and examining the validity of these assumptions provides a falsifiability test.

First, we argue that periodic or quasi-periodic dynamics in the immune system is the key to explaining the relapse-remit behavior of patients (see Supplement Section A). Although oscillations in the immune system are manifested in several ways [31] the negative

feedback loop between the inflammatory and suppressive factors has only recently been explored [11]. The cross regulation of the inflammatory *T* effector cells and the *T* regulatory cells has been presented as model of the immune system dynamics generating solutions corresponding to natural protective immunity or to autoimmunity [12,29]. Second, we posit that immune-mediated transition from relapse-remitting to progressive phase occurs following the breakdown of the suppressive mechanism and hence the negative feedback loop. The resistance of inflammatory cells to regulation by regulatory cells has been observed in several cases of autoimmune diseases [32,33]. While we model the transition using a threshold for the inflammatory component, we should point out that any mechanism that weakens or destroys the regulatory effect would lead to the same behavior as well.

Third, the disease pathology originates from two sources - the immune-mediated inflammatory attacks causing demyelination and neurodegeneration in the CNS. Neurodegeneration itself is triggered when demyelination exceeds a certain threshold. The distinction between the two subtypes is also observed in the analysis of the cerebrospinal fluid [34]. However, it should be noted that axonal injury has often been observed during the early stages of MS [35] but nonetheless a similar concept of threshold or protective capacity has been used to describe its effects on neurological functioning [36,37] adding further evidence in support of our model.

Author Contributions

The study was designed and conducted by V.K and J.T. N.K participated in design and conceptual discussions. V.K, F.P and J.T designed the model, and V.K performed the mathematical modeling and analysis. J.T and V.K drafted the manuscript. All authors participated in interpretation of data, manuscript preparation and have read and approved the final manuscript.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at 10.1016/j.mbs.2017.03.006

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