Modeling Relapse and Remission in Multiple Sclerosis Through T-Cell Dynamics

Mahita Chava, Vedant Desikamani*

Abstract

Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by unpredictable transitions between relapse, remission, and progressive neurological decline. A key driver of this variability lies in the complex interplay between autoreactive T cells that mediate tissue damage and regulatory T cells that suppress autoimmune responses. In this study, we present a minimal yet powerful dynamical systems model that captures the spectrum of immune behaviors observed in MS, including stable remission, periodic flare-ups, and persistent inflammation. Our model couples nonlinear growth, logistic saturation, mutual inhibition, and stochastic perturbations to simulate autoreactive-regulatory T cell dynamics. Phase-plane and bifurcation analyses reveal four distinct immune states: (i) immune tolerance (remission), (ii) oscillatory dynamics (cyclical relapses), (iii) excitable regimes (sporadic flares), and (iv) chronic inflammatory states (progressive MS). Time-series simulations replicate clinical trajectories, while parameter sweeps identify thresholds for immune stability. Notably, the model predicts how modest increases in regulatory T-cell efficacy or reductions in pro-inflammatory sensitivity can shift the system from relapse-prone to stable remission. These findings suggest that MS progression may be governed by low-dimensional immune feedback loops, and that precision interventions can be designed by tuning key regulatory parameters. This framework offers a tractable, mechanistic approach for understanding MS heterogeneity and guiding personalized therapeutic strategies.

Introduction

Autoimmune conditions affect 230 million people annually - approximately 4% of the global population - and this percentage is expected to rise in the coming years[7]. Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that affects over 2.8 million people worldwide. It is marked by the immune system mistakenly attacking the myelin sheath—a protective covering around nerve fibers—leading to inflammation, demyelination, and neurodegeneration. Clinically, MS is known for its diverse and often unpredictable disease courses, including relapsing-remitting episodes, secondary progression, and chronic continuous activity. While the clinical manifestations vary, a central hallmark of MS is the imbalance between autoreactive immune cells that drive inflammation and regulatory mechanisms that attempt to suppress this response.

These conditions are characterized by the immune system attacking the body's own cells. The thymus is the organ at which T cells are created. Here, T cells need to develop a functioning receptor, be able to communicate with other cells, and recognize other cells in the body as self. If one of these three requirements are not met, the T cells will be killed in a process known as apoptosis. T cells that cannot recognize other cells in the body can either undergo apoptosis or become regulatory T cells. Sometimes T cells that need to undergo apoptosis evade the immune system. These T cells are known as autoreactive T cells, which cause autoimmune conditions [1]. Autoimmune conditions are analogous to positive feedback loops. During an autoimmune response, autoreactive T cells attack the body's cells and release molecules known as autoantigens. The

*Grade 11, California High School, San Ramon, California

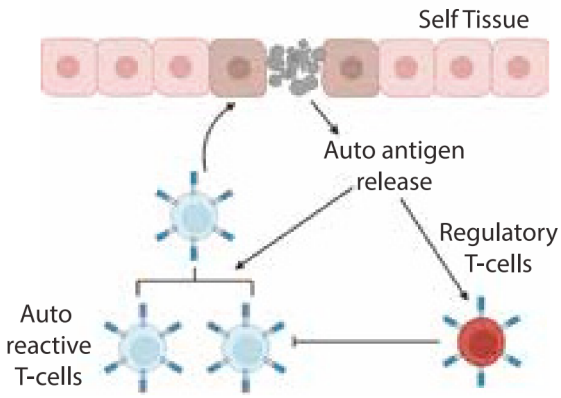

Figure 1: Damage to self tissue releases auto-antigen that activates autoreactive T-cells (blue). These autoreactive T-cells clonally expand and can further amplify antigen release, forming a positive feedback loop. Regulatory T-cells (red) are recruited by the same antigen but suppress autoreactive T-cell proliferation through contact-dependent inhibition (flat bar). The dynamic balance between antigen-driven activation (black arrows) and regulatory suppression (blunt arrow) underlies the four disease states explored in this paper. Adapted from [5]

.

presence of autoantigens triggers the release of regulatory T cells which inhibit the autoreactive T cells from attacking the body. In a healthy person, this would normally suppress the response. However, it is when this system fails that an autoimmune condition arises.

Autoimmune conditions can be characterized by their dynamics such as persistent healthy state, flare ups, oscillations, and persistent sick state. These dynamics are characterized by the relative concentrations of regulatory and autoreactive T cells. Persistent healthy states have consistently high regulatory T cell concentrations and low autoreactive T cell concentrations. Persistent sick states have consistently low regulatory T cell concentrations and high autoreactive T cells concentrations. Flare ups occur when the concentration of autoreactive T cells increase at unequal intervals. Oscillations occur when the concentration of autoreactive T cells increase at consistent intervals.

Previous theoretical models of autoimmune conditions don't consider the flare up dynamics. Previously, a model proposing idiotype-antiidiotype reactions was developed [3, 6]. This refers to the ability of antibodies to not only recognize external antigens but also other antibodies which served as the basic understanding of autoimmunity. In 1997, mathematical modeling would be used for the first time to model autoimmune behavior [8, 11]. These models used ordinary differential equations to demonstrate the evolution of immune cell populations like T cells and B cells which helped describe immune cell proliferation and antigen-antibody interactions. Recent research suggests that these unpredictable flares may be driven by excitable dynamics within the immune system, triggered by stochastic events such as stress, infections, or other environmental factors. In this context, excitable dynamics refer to a system's heightened sensitivity, where minor perturbations can lead to significant responses.

To explore these dynamics, we present a mathematical model that captures the nonlinear interactions between autoreactive and regulatory T cells using coupled differential equations. Building upon prior theoretical work in autoimmune dynamics, our model incorporates biologically relevant processes such as thymic production, antigen-driven activation, saturation effects, and stochastic perturbations that mimic random environmental triggers. Importantly, we apply this framework to interpret MS-specific disease trajectories, including stable remission, excitable flare-ups, periodic relapses, and chronic progression.

By analyzing the system's phase portraits and bifurcations, we reveal how small changes in regulatory strength, antigen sensitivity, or noise amplitude can drive the immune system between

qualitatively distinct regimes. This not only helps explain the variability observed across MS patients but also suggests targeted strategies for therapeutic modulation. Our goal is to provide a tractable, mechanistic framework that connects cellular-level interactions to patient-level disease outcomes, with implications for understanding MS pathophysiology and designing personalized interventions.

Methods

Model

The autoimmune disease progression is modeled using a system of two differential equations representing the dynamics of autoreactive T cells and regulatory T cells respectively [5]. Equation 1 represents the rate of growth of auto-reactive T cells in the body.

$$\frac{dA}{dt} = l_A + \gamma A^2(1 - \frac{A}{C}) - hAR - r_A A + \sqrt{2D}\eta(t) \tag{1}$$

Auto-reactive T cells are constantly produced by the thymus, but also grow at an accelerating rate of A with limitations due to carrying capacity (C). The concentration of auto-reactive T cells is reduced as a result of interactions between A and R, as well as the natural degradation of the auto-reactive T cells. It is a stochastic differential equation as it consists of multiple deterministic terms and a stochastic term. Such terms include the rate of production of auto-reactive T cells from the thymus, the rate of production of regulatory T cells, and the rate at which auto-reactive T cells decline due to interactions with regulatory T cells. Stochastic terms are the unpredictable parts of the system, which is seen through the noise term.

Equation 2 represents the rate of production of regulatory T cells.

$$\frac{dR}{dt} = l_R + \beta AR - r_R R \tag{2}$$

This differential equation is also known as a deterministic differential equation consisting of multiple deterministic terms. Such terms include the rate of production of regulatory T cells from the thymus and the rate at which the concentration of regulatory T cells grow due to interactions with auto-reactive T cells. Through this equation, we see regulatory T cells that are constantly being produced by the thymus and grow faster when they interact with auto-reactive T cells. Due to the natural removal rate, the concentration of regulatory T cells decreases in proportion to its current population.

- l_A: Rate of production of auto-reactive cells [cell/time].
- l_R: Rate of production of regulatory cells [cell/time].
- m_A: Natural turnover rate of auto-reactive cells [1/time].
- m_R: Natural turnover rate of regulatory cells [1/time].
- γ: Reactivity of auto-reactive cells to antigen [cell^{-1} time^{-1}].
- C: Carrying capacity of auto-reactive cells [cell].
- h: Rate of inhibition of auto-reactive cells by regulatory cells [cell^{-1} time^{-1}].
- β: Reactivity of regulatory cells to antigen [cell^{-1} time^{-1}].
- D: Noise amplitude [cell^2/time].

Non-dimensionalizing equations

For ease of simulation and analysis we non-dimensionalize the equations [10]. To define non-dimensional variables, we introduce characteristic scales for A and R. A natural choice is based on their baseline levels.

Baseline levels A_0 and R_0 are taken to be:

$$A_0 = \frac{I_A}{hR_0} = \frac{I_A r_R}{hI_R}, \quad R_0 = \frac{I_R}{r_R}$$

where $\tilde{A}$ and $\tilde{R}$ are dimensionless versions of A and R, and $\tilde{t}$ is a rescaled time variable. Using these substitutions:

$$A = A_0\tilde{A}, \quad R = R_0\tilde{R}$$

Computing derivatives:

$$\frac{dA}{dt} = A_0\frac{d\tilde{A}}{d\tilde{t}} \cdot \frac{d\tilde{t}}{dt} = A_0 r_A \frac{d\tilde{A}}{d\tilde{t}}$$
$$\frac{dR}{dt} = R_0\frac{d\tilde{R}}{d\tilde{t}} \cdot \frac{d\tilde{t}}{dt} = R_0 r_A \frac{d\tilde{R}}{d\tilde{t}}$$

Substituting into the first equation:

$$A_0 m_A \frac{d\tilde{A}}{d\tilde{t}} = I_A - r_A A_0\tilde{A} + \gamma A_0^2\tilde{A}^2\left(1 - \frac{A_0\tilde{A}}{C}\right) - hA_0\tilde{A}R_0\tilde{R} + \sqrt{2D}\eta(t)$$

Dividing by $A_0 r_A$:

$$\frac{d\tilde{A}}{d\tilde{t}} = \frac{I_A}{A_0 r_A} - \tilde{A} + \frac{\gamma A_0}{r_A}\tilde{A}^2\left(1 - \frac{A_0}{C}\tilde{A}\right) - \frac{hR_0}{r_A}\tilde{A}\tilde{R} + \frac{\sqrt{2D}}{A_0 r_A}\xi(t)$$

Using $A_0 = I_A r_R / hI_R$ and substituting $I_A/A_0 r_A = 1$, we get:

$$\frac{d\tilde{A}}{d\tilde{t}} = 1 + G\tilde{A}^2\left(1 - \frac{\tilde{A}}{C}\right) - \tilde{A}\tilde{R} + \sqrt{2\Sigma}\eta(\tilde{t})$$

For the second equation:

$$R_0 r_A \frac{d\tilde{R}}{d\tilde{t}} = I_R - r_R R_0\tilde{R} + \beta A_0\tilde{A}R_0\tilde{R}$$

Dividing by $R_0 r_A$:

$$\frac{d\tilde{R}}{d\tilde{t}} = D(1 - \tilde{R}) + B\tilde{A}\tilde{R}$$

Thus, the final dimensionless equations are:

$$\frac{d\tilde{A}}{d\tilde{t}} = 1 + G\tilde{A}^2\left(1 - \frac{\tilde{A}}{C}\right) - \tilde{A}\tilde{R} + \sqrt{2\Sigma}\eta(\tilde{t}) \tag{3}$$

$$\frac{d\tilde{R}}{d\tilde{t}} = D(1 - \tilde{R}) + B\tilde{A}\tilde{R} \tag{4}$$

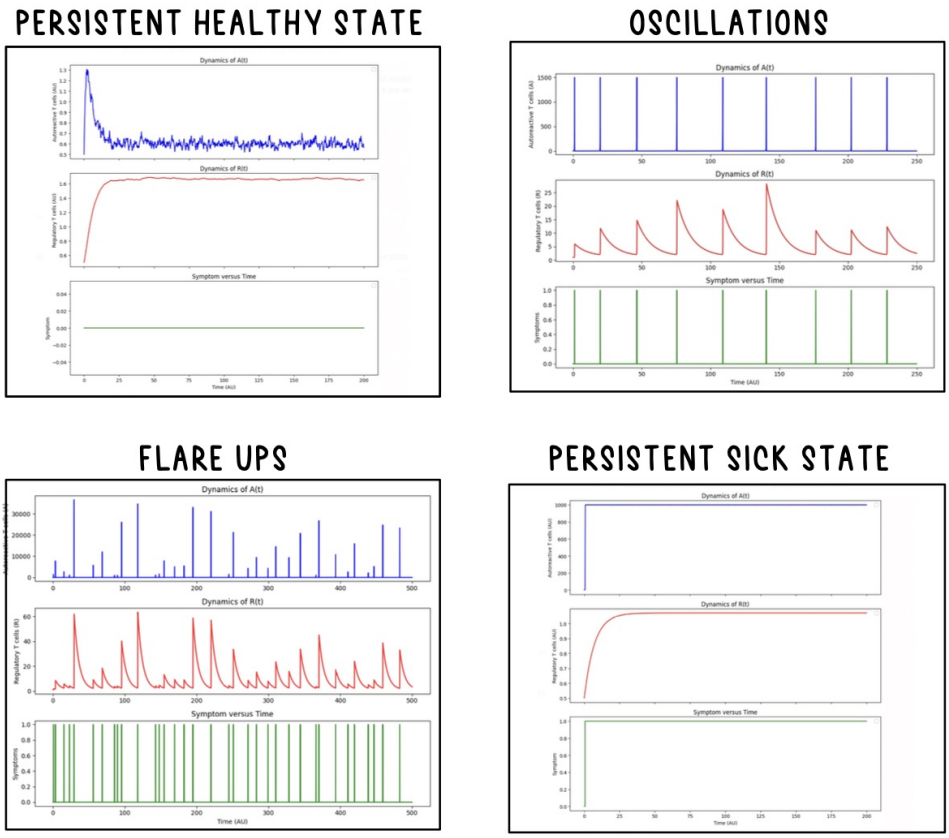

Figure 2: **Time-series of the four dynamical regimes generated by the autoreactive and regulatory T cells**. Each panel displays simulated trajectories of autoreactive T-cells (A, blue), regulatory T-cells (R, red), and a binary symptom proxy (green) under parameter sets that reproduce (a) Persistent healthy state – rapid decay of A to low levels maintained by robust R, with no symptoms; (b) Oscillatory state – self-sustained, regular cycles in which surges of A are followed by delayed rises in R, producing periodic symptom bouts; (c) Flare-up state – an excitable regime where stochastic perturbations trigger rare, high-amplitude spikes in A against a quiescent baseline, yielding sporadic symptoms; and (d) Persistent sick state – collapse of regulation leads to steady, high A and continuous symptoms despite a saturated R response. Together these profiles illustrate how variations in feedback strength, carrying capacity and noise translate into the diverse clinical courses observed in autoimmune disease.

Results

One of the charts seen above models the persistent healthy state, a constantly low level of autoreactive T cells and a constantly high level of regulatory T cells. The persistent healthy state can be associated with someone who doesn't suffer from an autoimmune condition such as multiple sclerosis. Moreover, we see that there is a sharp increase in the concentration of the autoreactive T cells before suddenly declining, but this is masked by the higher concentration of regulatory T cells. Such a pattern allows the immune system to stay strong and resilient to fight other pathogens. Contrary to the persistent healthy graph is the persistent sick state, a constantly high

Physiological Condition	**G**	**D**	**C**[9]	**B**	Σ
Persistent Healthy State	1.25	0.15	1000	0.1	0.15
Oscillations	1000	0.1	1000	0.02	0.15
Flare Ups	0.5	0.15	1000	0.005	0.15
Persistent Sick State	0.5	0.15	1000	0.00001	0.15

Table 1: Model parameters and their values

level of autoreactive T cells and a constantly low level of regulatory T cells. The persistent healthy state can be associated with someone constantly suffers from an autoimmune condition. Although the concentration of regulatory T cells seems to be increasing, which would allow for a healthy immune system, this concentration is masked by the large number of autoreactive T cells. This weakens the immune system because there's a positive feedback loop between the concentration of autoreactive T cells and regulatory T cells. As more autoreactive T cells are summoned, more regulatory T cells are sent in by the immune system, causing it to go into overdrive. Persistent sick autoimmune conditions include Type I Diabetes, some cases of Multiple Sclerosis, and Lupus.

Another chart shows us a single flare-up, a sharp and clear decline in the amount of autoreactive T cells present, and then a return to the baseline level. Several factors can trigger a flare, including infections, stress and exposure to certain drugs or other environmental factors [12, 4]. An external stimulant causes the flare, and in this simulation, it is caused by modeled noise, which causes the system to push past its limit. Once it occurs, A(t) is quickly amplified, and then it is also suppressed soon by a regulatory response from R(t) (Regulatory T cells). The regulatory T cells also spike in their amount and then gradually decrease, which causes the immune system to remain healthy. This kind of flare-up that can occur randomly is present in many autoimmune diseases, like MS, during a relapse. Symptoms could increase rapidly due to stressors and then resolve for long and extended periods of time.

Our last chart is showing us oscillations that happen regularly, and they happen in autoreactive T cells. They are caused by a weak regulatory response and a strong self-amplification from a high level of G. Each spike in A triggers a delayed rise in regulatory T cells, suppressing the flare, causing A to drop sharply. After R slowly declines, the cycle repeats. This pattern reflects an immune system that is caught in a loop of attack and recovery. This is a great example of a seasonal autoimmune condition. It promotes the idea that the immune system's dynamics can produce rhythmic flare-ups even without external triggers when regulation is slow to respond.

Implications for Multiple Sclerosis

The dynamical regimes uncovered by our model offer insights into therapeutic strategies for managing multiple sclerosis (MS)[2], particularly in the relapsing-remitting and secondary progressive phases. Our analysis reveals that the immune system may operate near a critical threshold separating quiescence, flare-ups, and sustained oscillations. This suggests that effective treatment may not require complete immune suppression but rather subtle modulation of key parameters—such as regulatory cell strength or effector cell inhibition—to steer the system away from bifurcation points that predispose it to instability.

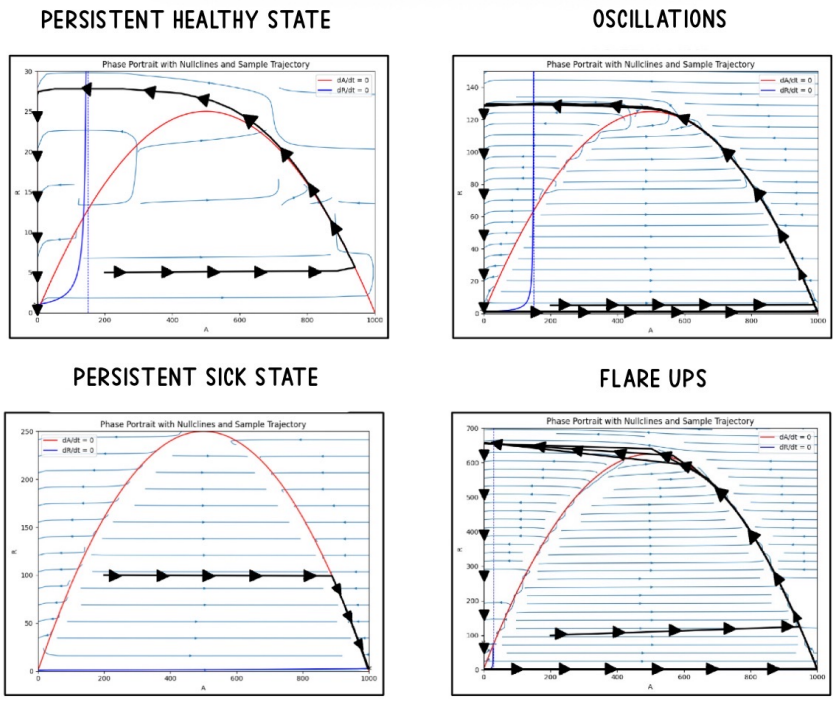

Figure 3: Phase Portraits of Autoimmune Disease Dynamics under Different Regimes. **Top Left: Persistent Healthy State** – The system evolves toward a stable equilibrium with low immune activity and strong regulation, indicating disease remission or immune tolerance. **Top Right: Oscillations** – The trajectories spiral around an unstable fixed point, depicting recurrent immune activation and remission, characteristic of cyclical autoimmune diseases. **Bottom Left: Persistent Sick State** – The system stabilizes at a high immune activity level with weak regulation, indicating chronic inflammation or autoimmunity. **Bottom Right: Flare-Ups** – The system shows abrupt transitions and transient peaks in immune activity, representing episodic exacerbations despite partial regulation.

For instance, increasing the baseline activation of regulatory T cells (modeled via the parameter l_R) or enhancing their suppressive efficacy (h) can transition the system from an excitable or oscillatory regime into a monostable state associated with long-term remission. This supports therapeutic strategies aimed at expanding the regulatory T cell pool (e.g., through low-dose IL-2 or Treg adoptive transfer). Conversely, transient increases in pro-inflammatory drive (G)—as might occur during infection or stress—can push the system into a relapse-prone state, emphasizing the importance of lifestyle and comorbidity management.

Moreover, the model highlights the potential utility of pulsed or targeted interventions that shift the immune trajectory during vulnerable phases, rather than relying solely on continuous immunosuppression. This is particularly relevant in light of the adverse effects associated with long-term use of disease-modifying therapies (DMTs). Therapies that dampen noise-induced transitions—such as antioxidants or neuroprotective agents—may also reduce the frequency of stochastic flare-ups.

Finally, the model provides a computational platform to explore patient-specific responses by tuning parameters to reflect immune profiles, potentially enabling personalized treatment planning. As such, our findings underscore the value of dynamical systems approaches in informing both mechanistic understanding and clinical decision-making in MS.

Conclusion

In this study, we developed and analyzed a minimal dynamical systems model that captures the diverse immune trajectories observed in multiple sclerosis (MS). By focusing on the nonlinear interplay between autoreactive and regulatory T cells, we identified four distinct immune regimes—remission, oscillatory relapses, stochastic flare-ups, and chronic inflammation—that map directly onto clinically observed MS phenotypes, including relapsing-remitting and progressive forms.

Through bifurcation analysis, phase portraits, and time-series simulations, we demonstrated how small perturbations in immune parameters—such as increased pro-inflammatory drive or weakened regulatory response—can lead to qualitative shifts in disease course. These findings highlight that MS may not require broad immune suppression to achieve stability; rather, subtle modulation of key immune pathways can steer the system toward long-term remission. Therapeutic strategies aimed at enhancing regulatory T cell activity or reducing antigen sensitivity may be particularly effective in maintaining immune equilibrium and preventing relapses.

Moreover, our framework provides a tractable platform for simulating patient-specific immune dynamics and testing intervention strategies under varying conditions of noise and regulation. By translating immunological mechanisms into predictive models of disease evolution, this work contributes to the growing effort to personalize MS treatment and understand its complex behavior from a systems-level perspective.

Future extensions of this model could incorporate additional immune cell types, spatial heterogeneity, and long-term neurodegenerative processes to capture the full complexity of MS. Nonetheless, the current model lays a strong foundation for bridging theoretical immunology with clinical application in MS care.

Code link: `https://github.com/vedantd124/Research-Project`

References

[1] Cleveland Clinic. *Autoimmune diseases*. `https://my.clevelandclinic.org/health/diseases/21624-autoimmune-diseases`. Retrieved May 18, 2025. n.d.

[2] Massimo Filippi et al. "Multiple Sclerosis". In: *Nature Reviews Disease Primers* 4 (2018). DOI: 10.1038/s41572-018-0041-4.

[3] Niels K Jerne. "Towards a network theory of the immune system". In: *Ann. Immunol.(Inst. Pasteur), C* 125 (1974), pp. 373–389.

[4] Fatma O. Kamel. "Factors Involved in Relapse of Multiple Sclerosis". In: *Journal of Microscopy and Ultrastructure* 7 (2019), pp. 103–108. DOI: 10.4103/JMAU.JMAU_59_18.

[5] Yael Lebel et al. "Excitable dynamics of flares and relapses in autoimmune diseases". In: *iScience* 26.11 (2023), p. 108084. DOI: 10.1016/j.isci.2023.108084.

[6] Ivan Lefkovits. *Portrait of the Immune System: Scientific Publications of Niels Kaj Jerne*. Vol. 2. World Scientific, 1996.

[7] Frederick W. Miller. "The Increasing Prevalence of Autoimmunity and Autoimmune Diseases: An Urgent Call to Action for Improved Understanding, Diagnosis, Treatment and Prevention". In: *Current Opinion in Immunology* 80 (2023), p. 102266. DOI: 10.1016/j.coi.2022.102266. URL: https://pmc.ncbi.nlm.nih.gov/articles/PMC9918670/.

[8] Alan S. Perelson and Gérard Weisbuch. "Immunology for physicists". In: *Rev. Mod. Phys.* 69 (4 Oct. 1997), pp. 1219–1268. DOI: 10.1103/RevModPhys.69.1219. URL: https://link.aps.org/doi/10.1103/RevModPhys.69.1219.

[9] Mireia Sospedra and Roland Martin. "Immunology of Multiple Sclerosis". In: *Seminars in Neurology* 36 (2016), pp. 115–127. DOI: 10.1055/s-0036-1579739.

[10] Steven H. Strogatz. *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering*. 2nd ed. Boca Raton, FL: CRC Press, 2018. ISBN: 9780429961113. URL: https://www.taylorfrancis.com/books/mono/10.1201/9780429492563/nonlinear-dynamics-chaos-steven-strogatz.

[11] Bernhard Sulzer and Alan S Perelson. "Immunons revisited: binding of multivalent antigens to B cells". In: *Molecular immunology* 34.1 (1997), pp. 63–74.

[12] Emmanuelle Waubant et al. "Environmental and Genetic Risk Factors for MS: An Integrated Review". In: *Annals of Clinical and Translational Neurology* 6 (2019), pp. 1905–1922. DOI: 10.1002/acn3.50862.