

Flare-Ups and Remission in Crohn's Disease Using T-Cell Model Dynamics

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Abstract

Crohn's disease is a type of inflammatory bowel disease (IBD) which causes irritation and swelling, called inflammation, most often in the digestive tract. Patients often experience periods of remission followed by unpredictable flare-ups. These changes are influenced by interactions between immune cells, especially autoreactive T cells that promote inflammation and regulatory T cells that suppress excessive immune activity. This paper develops a mathematical model to investigate how interactions between these two T-cell populations can produce different patterns of Crohn's disease activity. The model uses coupled differential equations to describe the production, growth, suppression, and decay of autoreactive and regulatory T cells. Random fluctuations are also included to represent possible triggers such as infection, diet changes, or stress. Simulations produce four distinct behaviors: a persistent healthy state, regular oscillations between low and high inflammation, a persistent inflammatory state, and irregular flare-ups separated by periods of low activity. In the flare-up regime, random disturbances cause temporary increases in autoreactive T cells, followed by a regulatory response that returns the system toward baseline. These results show how relatively simple immune-cell interactions may generate disease patterns resembling remission, chronic inflammation, and recurrent flare-ups in Crohn's disease.

Introduction

Crohn's disease has an extremely large financial burden on the economy, as well as tremendous effects on the physical, mental, and social lives of patients experiencing this condition [5], [11]. A major review surrounding Crohn's disease-related healthcare showed that the average yearly cost for a patient was approximately \$ 17495 due to the expensive biologic treatment and medication needed to keep people in remission. Despite having these high class medications, surgery and hospitalization costs have not substantially decreased. Crohn's disease also has an immense impact on patients, as it can cause a wide range of symptoms, including chronic diarrhea, drastic weight loss, constant stomach pain and fatigue, as well as unexpected flare-ups [2]. Another major review of 83 total studies showed that people with Crohn's disease felt they had a much poorer life during active flare-ups than they did during remission [3].

Crohn's disease is a chronic inflammatory bowel disease, or IBD for short, and it can affect the body's digestive tract anywhere from the mouth to the anus [1]. The symptoms listed above can vary by person and the severity of their disease. These symptoms can come and go at any time, known as flare-ups and remission. Crohn's doesn't have one definitive single cause, as scientists think it is caused by a combination of factors, such as genetics, environmental exposure, immune system activity, and damage to or bacteria in the intestines [8], [9]. Although Crohn's disease can be seen anywhere in the digestive tract, it mostly commonly appears in the terminal ileum, which is the end of the small intestine, and the beginning of the colon (see Figure 1a and 1b) [10].

Autoreactive T cells and regulatory T cells are two types of cells found in the immune system, and they are crucial in order to understand Crohn's disease [6]. Autoreactive T cells mistakenly

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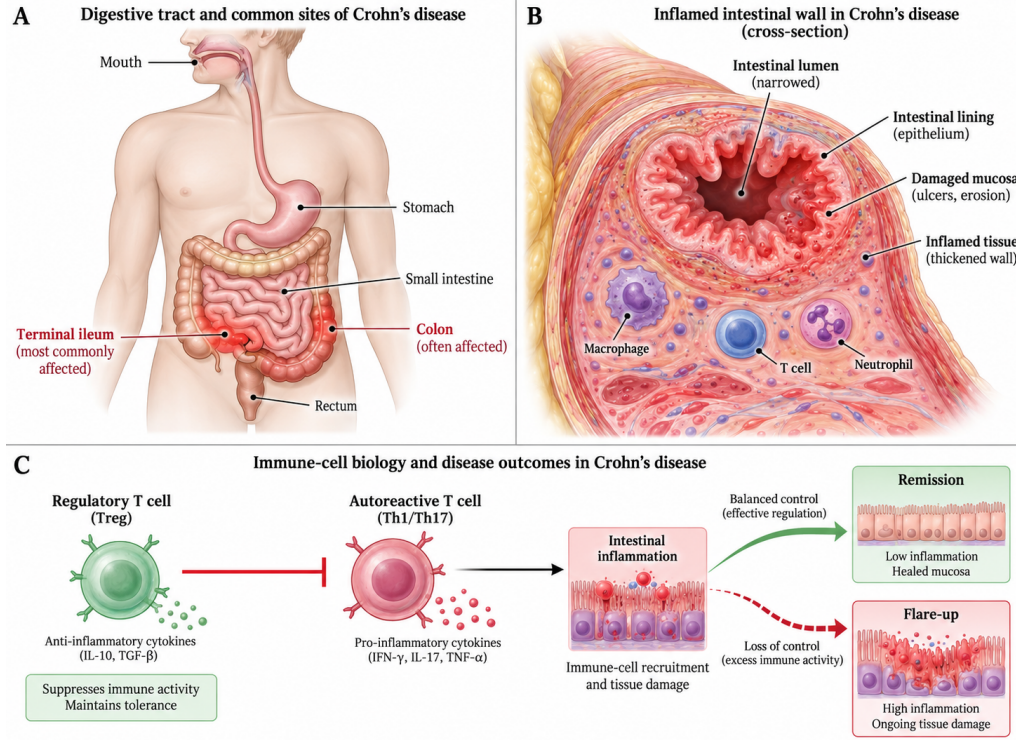


Figure 1: The Anatomy and Immunology of Crohn's Disease

classify the body's own tissue as harmful, leading to the immune system attacking itself, while regulatory T cells keep these autoreactive cells in check to prevent any unnecessary reactions (see Figure 1c) [7]. In some people, these regulatory T cells may not control some or all of the autoreactive T cells. This allows the autoreactive T cells to be overactive and keep attacking the intestinal lining, causing inflammation. As this goes on, the continuous inflammation results in the autoimmune disorder known as Crohn's disease.

In this paper, I propose a model of immune dynamics in Crohn's disease which captures the different manifestations of the disease. During a healthy state of this disease, regulatory cells are able to make sure autoreactive T cells are in control and not overactively causing inflammation. During an oscillatory state, the immune system moves back and forth between low inflammation and high inflammation, which causes both flare-ups and remission at regular intervals[4]. When a flare-up occurs, it is being caused by a temporary period of harmful immune activity where the regulatory cells are unable to maintain control, leading to a sudden appearance of symptoms. After the flare-up, regulatory cells gain back control over the autoreactive cells, sending the disease into remission. When a person has reached a permanent sick state, the regulatory system is constantly unable to maintain control, which leads to continuous inflammation without any remission.

Methods

Crohn's disease is modeled as a dynamical system with two interacting components: autoreactive T cells and regulatory T cells. The goal is to capture how inflammation develops, how it is suppressed, and how random triggers can lead to flare-ups.

The variable $A(t)$ represents the concentration of autoreactive T cells, which drive inflammation. The variable $R(t)$ represents the concentration of regulatory T cells, which suppress immune activity. Both variables are treated as continuous quantities that change over time.

Model Equations

The system is described by two coupled differential equations:

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

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

These equations describe how autoreactive and regulatory T cell populations evolve due to production, interaction, and decay. The first equation describes the dynamics of autoreactive T cells. There is a baseline production term l_A . The nonlinear term $\gamma A^2(1 - A/C)$ models self-amplification with a limit, meaning that autoreactive T cells can expand rapidly but cannot exceed a carrying capacity. This term also captures the effect of antigen stimulation in an implicit way.

The interaction term $-hAR$ represents suppression by regulatory T cells. The term $-r_A A$ represents natural decay. A stochastic term is included to account for random fluctuations in the immune system.

The second equation describes the dynamics of regulatory T cells. These cells are produced at a baseline rate l_R . Their population increases in response to autoreactive T cells, modeled by the term βAR . The term $-r_R R$ represents natural turnover.

Noise Term

The term $\eta(t)$ represents random fluctuations and is modeled as Gaussian white noise with zero mean and unit variance. The parameter D controls the strength of this noise. This term captures unpredictable triggers such as infections, diet changes, or stress, which are known to induce flare-ups in Crohn's disease.

Non-Dimensionalization

To simplify the system, variables are rescaled to remove units. Define $a = A/A_0$, $r = R/R_0$, and $\tau = r_A t$. After rescaling and grouping parameters, the system can be written in dimensionless form as:

$$\frac{da}{d\tau} = 1 + Ga^2 \left(1 - \frac{a}{C}\right) - ar + \sqrt{2\Sigma} \eta(\tau) \quad (3)$$

$$\frac{dr}{d\tau} = D(1 - r) + Bar \quad (4)$$

Here, the new parameters are dimensionless combinations of the original constants. The model captures the balance between autoreactive T cells that drive inflammation and regulatory T cells that suppress it. Small changes in parameters or random fluctuations can shift the system between different disease states.

Results

The model produces four distinct dynamical behaviors that correspond to different immune states. These behaviors arise from changes in a small set of parameters controlling immune amplification, regulation, and stochastic fluctuations.

In the persistent healthy state (Figure 2a), autoreactive T cells remain at very low levels throughout the simulation. Regulatory T cells maintain a stable baseline. Small fluctuations are present due to noise, but they do not amplify. The system quickly suppresses any increase in inflammatory activity. As a result, the symptom remains inactive. This behavior reflects a stable and well-regulated immune system.

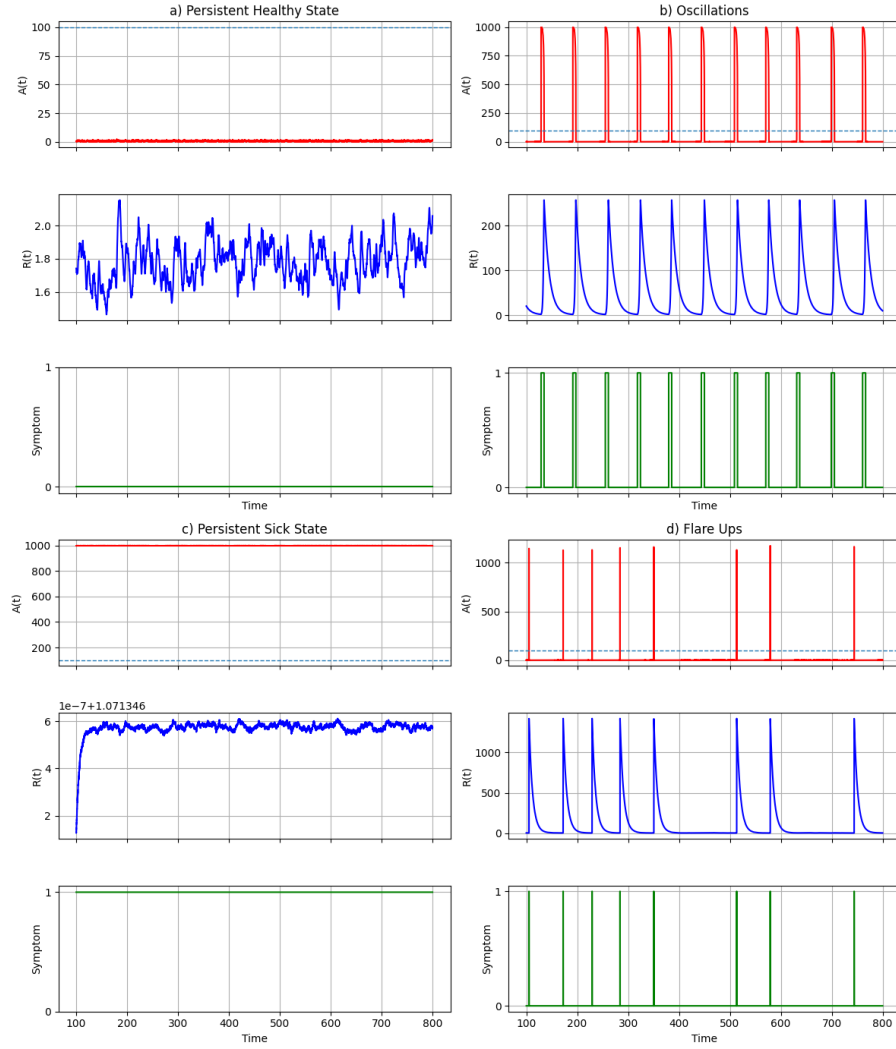


Figure 2: Time-series of autoreactive T cells (A), regulatory T cells (R), and a binary symptom proxy under four parameter regimes: (a) persistent healthy state, (b) oscillations, (c) persistent sick state, and (d) flare-ups.

Regime	G	D	C	B	Σ
Persistent Healthy	0.25	0.15	1000	0.1	0.2
Oscillations	1	0.1	1000	0.001	0.2
Persistent Sick	1	0.15	1000	0.00001	0.2
Flare-Ups	3	0.15	1000	0.3	0.2

Table 1: Model parameters used to generate the four dynamical regimes.

In the oscillatory regime (Figure 2b), the system shows regular cycles of activation and suppression. Autoreactive T cells exhibit sharp, periodic spikes. These spikes are followed by delayed increases in regulatory T cells. This delay allows inflammation to rise before it is controlled. Once regulatory activity increases, it suppresses the autoreactive population, and both variables decrease. The cycle then repeats. The symptom switches on during each spike, indicating recurring flare-like events.

In the persistent sick state (Figure 2c), autoreactive T cells remain at a high level over time. Regulatory T cells are present but are not strong enough to suppress the inflammatory response. The system settles into a steady state with sustained immune activation. The symptom remains continuously active. This behavior corresponds to chronic inflammation.

In the flare-up regime (Figure 2d), the system stays near a low-activity baseline for most of the simulation. However, intermittent spikes in autoreactive T cells occur at irregular times. These spikes are driven by stochastic fluctuations. Each spike triggers a temporary increase in regulatory T cells, which brings the system back to baseline. The symptom occurs only during these events. This regime captures unpredictable flare behavior.

Conclusion

Using a mathematical model, I was able to investigate how regulatory and autoreactive T cells can interact to cause changes in Crohn’s disease activity. The simulations used in the paper showed 4 different states of the disease. These consist of a persistent healthy state, regular oscillations, persistent inflammation, and irregular flare-ups. When flare-ups are occurring, unknown changes or disturbances led to a higher count of autoreactive T cells. This was then followed up by a regulatory response that sends the system back down to normal. This incidence showed that immune system activation and suppression could be closely tied in with remission and periodic flare-ups.

A potential drug target would be one that could reduce the value G , which represents how rapidly autoreactive T cells communicate with each other. One biological target that could significantly help with this is IL-23, which has been proven to help proliferate inflammatory T cells in models used to simulate intestinal inflammation. By blocking the pathway, the level at which G is present can possibly be weakened. However, this would need to be further tested in future simulations and models, where the level of G is varied, while other parameters are kept constant.

The model used in this article isn’t perfect, as it comes with some limitations. It only used two immune-cell populations, which means it may not be completely representative of others. It also doesn’t consider other factors of Crohn’s disease, such as microbes and bacteria in the intestines, other immune cells, and tissue damage. Future research conducted should include the other factors of the disease, and compare simulation data to real clinical data. It should also use possible treatment options and drugs to see how parameters would be affected. With more in-depth research, the ideas presented in this paper may go a long way in helping researches under the unpredictable patterns of Crohn’s disease.

References

- [1] Daniel C Baumgart and William J Sandborn. “Crohn’s disease”. In: *The Lancet* 380.9853 (2012), pp. 1590–1605.
- [2] Michael Dolinger, Joana Torres, and Séverine Vermeire. “Crohn’s disease”. In: *The Lancet* 403.10432 (2024), pp. 1177–1191.
- [3] Simon R Knowles et al. “Quality of life in inflammatory bowel disease: A systematic review and meta-analyses—Part II”. In: *Inflammatory Bowel Diseases* 24.5 (2018), pp. 966–976.
- [4] Yael Lebel et al. “Excitable dynamics of flares and relapses in autoimmune diseases”. In: *iScience* 26.11 (2023), p. 108084.
- [5] Reinier Cornelis Anthonius van Linschoten et al. “Systematic review: Societal cost of illness of inflammatory bowel disease is increasing due to biologics and varies between continents”. In: *Alimentary Pharmacology & Therapeutics* 54.3 (2021), pp. 234–248.
- [6] Wing-Cheong Lo, Razvan I Arsenescu, and Avner Friedman. “Mathematical model of the roles of T cells in inflammatory bowel disease”. In: *Bulletin of Mathematical Biology* 75.9 (2013), pp. 1417–1433.
- [7] Christopher G Mayne and Calvin B Williams. “Induced and natural regulatory T cells in the development of inflammatory bowel disease”. In: *Inflammatory Bowel Diseases* 19.8 (2013), pp. 1772–1788.
- [8] Guilherme Piovezani Ramos and Konstantinos A Papadakis. “Mechanisms of disease: Inflammatory bowel diseases”. In: *Mayo Clinic Proceedings* 94.1 (2019), pp. 155–165.
- [9] Giulia Roda et al. “Crohn’s disease”. In: *Nature Reviews Disease Primers* 6.1 (2020), p. 22.
- [10] Joana Torres et al. “Crohn’s disease”. In: *The Lancet* 389.10080 (2017), pp. 1741–1755.
- [11] Michael Youssef et al. “Work productivity impairment in persons with inflammatory bowel diseases: A systematic review and meta-analysis”. In: *Journal of Crohn’s and Colitis* 18.9 (2024), pp. 1486–1504.