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DECIPHERING THE DYNAMICS OF HAIR FOLLICLE-T CELL INTERACTIONS: A MATHEMATICAL MODELLING APPROACH TO UNDERSTANDING ALOPECIA AREATA

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ABSTRACT

Hair loss disorders, particularly alopecia areata, involve intricate interactions between hair follicles and immune cells. This study presents a novel mathematical model to investigate the underlying mechanisms of alopecia areata. By simulating the dynamics of hair follicles and T cells using ordinary differential equations, we explore the impact of their interactions on hair growth and loss. The model parameters were estimated from experimental data and validated against independent datasets. Our findings demonstrate that specific parameter regimes can lead to hair loss, consistent with clinical observations. The model highlights the critical role of the interaction between hair follicles and T cells in the stability of the hair growth system, potentially explaining the cyclical nature of alopecia areata. Moreover, the model predicts that interventions targeting specific interaction coefficients could restore hair growth, offering potential therapeutic targets. This study improves our understanding of hair loss disorders and provides a robust framework for exploring treatment strategies through virtual experimentation, potentially accelerating the development of effective therapies for alopecia areata.

Index Terms – Alopecia areata, Hair follicle dynamics, Mathematical modeling, Ordinary differential equations, T cell interactions, Therapeutic interventions.

INTRODUCTION

We can easily study stem cell activities in regenerative epithelial tissues in adults by looking at the hair follicle [21]. Despite various observational scales from molecular to multicellular structures the driving mechanisms of the hair growth cycle remain elusive. This study aims to elucidate these mechanisms by conceptualizing the collective dynamics of a large follicle population as an excitable medium. By abstracting molecular interactions and considering an individual follicle as a singular operational entity, we introduce a simplified model. This model says that the hair growth cycle is a resultant property. It gives mathematical expressions for how long each phase of the cycle lasts based on molecular regulatory elements. This framework facilitates direct comparison with both previous cellular automaton models and empirical single follicle data. The analysis to multicellular scenarios and utilize computational simulations, achieving significant qualitative concordance with experimental data. The derived excitable medium equations present a broader spectrum of solutions relative to earlier studies. We show how changes in molecular control parameters can explain why hair growth patterns are off in genetically modified mice that have over expression and BMP inhibition. The study recommends additional experimental setups for validating the model's primary hypothesis. In conclusion, the interplay of molecular activators and inhibitors may form a fundamental mechanism that accurately captures a variety of phenomena observed at different scales of hair follicle growth.

In this research paper, we write in section 2, "Fundamentals of the Immune System," providing an overview of the immune system's defences and the role of innate and adaptive immune responses. We also explore the understanding of hair follicle biology and the dynamics of the hair growth cycle, describing the structure and function of hair follicles and emphasizing the importance of interactions between matrix keratinocytes and the dermal papilla. Moving on to section 3, "Mathematical Modeling of Alopecia Areata Disease Dynamics," we highlight the use of mathematical models to study immune cell interactions and disease progression in alopecia areata. Within this section, we focus on stability analysis, investigating the stability of the hair growth system by analyzing the equilibrium points and their stability properties. The results provide valuable insights into the behavior of the system under different parameter regimes and contribute to our understanding of hair growth stability in cases of alopecia areata. We also employ numerical analysis in this section, using numerical methods

to solve the system of ordinary differential equations in the mathematical model. Through numerical techniques, we can simulate and explore the dynamics between hair follicles and T cells over time, investigate the behavior of the system, validate the model against experimental data, and generate predictions for different scenarios and parameter values. This numerical analysis provides a quantitative understanding of the dynamics and offers insights into the progression of alopecia areata. In section 4, we analyze the linear stability and bifurcation patterns of a simplified model and find that parameters b and a act as bifurcation parameters, causing qualitative shifts in the system's behavior. We assess the stability of biologically relevant steady states through linear stability analysis, considering equilibria with non-negative values of x and y as biologically significant. In section 5, "Results and Discussion," we summarize our findings, including the identification of parameter regimes leading to hair loss, the role of interaction coefficients in hair growth stability, and the potential for therapeutic interventions. Finally, we conclude with future work in section 6, outlining potential avenues for further research and advancing our understanding of alopecia areata.

Fundamentals of the Immune System: Biological Underpinnings and Defence Mechanisms

The immune system operates on multiple levels to defend the body. The primary defenses are physical barriers like skin and mucous membranes. If these are breached, the body relies on two types of immune responses: innate and adaptive [13], [14]. The innate im- mune response is rapid and general, employing cells like natural killer (NK) cells and mast cells. The adaptive immune response is slower but more specific, utilizing lymphocytes such as B-cells and T-cells, which target specific antigens presented by pathogens or produced by the body (autoantigens) [1], [3]. Lymphocyte activation occurs when their receptors recognize antigens. B-cells respond by proliferating and producing antibodies that bind to antigens, neutralizing pathogens outside cells. T-cells, on the other hand, tackle intracellu- lar pathogens, with help from dendritic cells that present antigens via MHC molecules [18], [5]. The immune system generates a vast array of antigen receptors through recombination and hypermutation, but this process also creates autoreactive lymphocytes that can attack the body's tissues, leading to autoimmune diseases if not properly regulated.

A. Understanding Hair Follicle biology and dynamics of the hair growth cycle

Hair follicles (HFs), totalling approximately 5 million in humans, are specialized organs in the skin responsible for hair production. Each hair follicle is composed of a hair bulb at the base, where matrix keratinocytes (MKs) generate the hair shaft and melanocyte pro-vivo pigmentation. The dermal papilla (DP) at the hair bulb's base supplies nutrients and regulates MKs through growth factors [17][30], [27],[28]. Hair growth occurs in a cyclical pattern with three main phases: anagen (growth), catagen (regression), and telogen (rest).

In anagen, the follicle produces hair; in catagen, hair growth ceases and the follicle diminishes; in telogen, the follicle is inactive but not dormant. At the end of telogen, new hair is formed and the cycle restarts [2],[15]. Anagen lasts 2 to 5 years, catagen 3 to 6 weeks, and telogen 3 to 5 months for scalp hair. The hair bulb regenerates each cycle, disassembling during catagen and reforming for the next anagen phase. The interaction between MKs and DP is crucial for the hair cycle's timing [10], [9].

B. Unveiling the Development Mechanism of Alopecia Areata: A Biological Perspective

Alopecia areata (AA) is an autoimmune condition characterized by non-scarring hair loss. The disease selectively targets hair follicles (HFs) during their growth phase (anagen), with- out destroying their ability to grow hair, which means affected follicles can still cycle through hair growth stages [20, 28]. The disruption begins when leukocytes infiltrate and attack the hair follicles, forcing them to prematurely end the anagen phase and enter the regression phase (catagen), leading to hair loss [19]. The collapse of hair follicle immune privilege (HF IP) is a critical event in AA development. This collapse allows the body's immune system to recognize and react against self-antigens produced during hair growth. During AA, affected HFs lose their immune privilege, leading to the expression of MHC class I molecules on hair bulb cells, and the subsequent attack by immune cells [19],[11] . The restoration of immune privilege is essential for the normal duration of the anagen phase and successful hair regrowth; if not restored, the anagen phase remains abnormally short, preventing hair from reaching the scalp surface [19]. Cytokine, plays a pivotal role in the pathogenesis of AA by promoting inflammation and immune

privilege collapse, leading to the early termination of anagen. Autoreactive CD8+ T-cells NKG2D+ cells, along with CD4+ T-cells, are the primary immune cells implicated in destroying the hair bulb cells of anagen HFs [25][8][7].

Paus et al. (1993) introduced the hair follicle immune privilege collapse hypothesis, which outlines the disease mechanism as a sequence of events starting with the entry of HFs into anagen, followed by a stress induced increase in INF-Y leading to immune privilege collapse, MHC class I expression, and the attack by autoreactive T cells, resulting in hair loss .

Other immune cells like regulatory T-cells, mast cells, and NK cells also play roles in AA. Regulatory T-cells are believed to be deficient in AA, leading to reduced control over autoimmune responses [25]. Mast cells, typically involved in anti-inflammatory responses, are found in increased numbers in AA-affected skin and may contribute to the disease by promoting inflammation [97, 98, 101, 102]. NK cells are found abundantly around diseased HFs, and their overstimulated NKG2D receptors are implicated in the disease mechanism [12],[4]. Overall, the development of AA involves complex interactions between the immune system and hair follicles, with a particular emphasis on the loss of immune privilege and the role of various immune cells and cytokines in the perpetuation of the disease.

Mathematical Modelling of Alopecia Areata Disease Dynamic

Mathematical models of Alopecia Areata often focus on the dynamics of immune cell in- teractions with hair follicles, aiming to understand the development and progression of the condition. These models typically incorporate equations that represent the rates of change in populations of different cell types or concentrations of biochemical substances involved in the disease process.[24], [29],[26], [23],[22]

One example of such a model could be a set of differential equations that describe:

- The growth and death rates of hair follicle cells,
- The activation and proliferation of autoreactive T-cells.
- The secretion and effect of cytokines and other inflammatory mediators,
- The regulation of hair cycle phases affected by the immune attack.

These models can be used to simulate the spatial and temporal patterns of hair loss and regrowth observed in Alopecia Areata. They can also be used to test hypotheses about the disease and to predict the outcomes of various therapeutic interventions.

A mathematical model has been developed to investigate the evolution of alopecia areata (AA), a condition characterized by hair loss resulting from immune system attacks on hair follicles. The model simplifies the complex biological process by focusing on a small, homogeneous group of hair follicles in their growth phase, allowing for an examination of critical interactions between these follicles and the immune system. Key to the model is the role of IFN-γ, a cytokine whose production is triggered by external factors such as stress or infection. This cytokine facilitates communication between the hair follicles and the immune cells and leads to the upregulation of MHC I expression in hair follicle cells, which in turn presents autoantigens to the immune system.

Once this immune-hair follicle interaction begins, CD4+ and CD8+ T-cells, as well as NKG2D+ cells, are recruited to the hair follicles. These cells are initially in a resting state and require activation through IFN-γ signalling to become effector cells capable of attacking the hair follicle. The activation process for CD4+ T-cells involves proliferation in response to IFN-γ, whereas CD8+ T-cells and NKG2D+ cells require both the presence of peptide-MHC I complexes and additional stimulation from CD4+ T-cells to expand. The production of IFN-γ by these activated cells sustains the inflammatory environment, which is a critical aspect of the model, highlighting the self-perpetuating cycle of immune attack that underlies the pathogenesis of AA.

The mathematical model for alopecia areata (AA) focuses on hair follicles in the anagen phase. The key variables include:

- **IPG:** Immune privilege guardians
- **IFN:** IFN-γ
- **MI:** Peptide-MHC class I complexes
- **T8:** CD8+/NKG2D+ T-cell population • T4: CD4+ T-cell population

Consider the following system of ordinary differential equations (ODEs) to describe a simplified model of the interaction between hair follicles (H) and T-cells (T):

$$\frac{dH}{dt} = r_H H\left(1 - \frac{H}{K}\right) - \alpha HT. \qquad (1)$$

$$\frac{dT}{dt} = r_T T\left(1 - \frac{T}{C}\right) + \beta HT - \gamma T. \qquad (2)$$

where rH and rT represent the intrinsic growth rates of hair follicles and T-cells, respectively, K is the carrying capacity of hair follicles, C represents the maximum T-cell population, α is the rate at which T-cells destroy hair follicles, β represents the stimulation of the immune response by hair follicles, and γ is the natural death rate of T-cells. Mathematical modelling serves as a powerful tool to understand the complex interactions that lead to alopecia areata. It provides a quantitative framework for studying the disease and developing effective treatments [24], [6], [20]. In this diagram, the main components and interactions involved in Alopecia Areata, an autoimmune condition causing hair loss, are represented. Hair follicles are influenced by growth and death rates, while T cells play a role in the immune response through activation and proliferation. The interaction between hair follicles and T cells involves communication, signalling, and cytokine influence. Inflammatory mediators are secreted, affecting hair cycle phases, including the growth (anagen), regression (catagen), and rest (telogen) phases. The autoimmune response includes the re-insistent of CD4+ and CD8+ T-cells, activation of NKG2D+ cells, and subsequent attack on hair follicles.

Figure 1: Diagram illustrating the components and interactions involved in Alopecia Areata. The diagram depicts the influence of hair follicles on T cells, the interaction between hair follicles and T cells, the impact of inflammatory mediators on hair cycle phases, and the autoimmune response leading to hair follicle attack and subsequent hair loss.

A. Stability analysis

Stability analysis involves finding the equilibrium points of the system. The Jacobian matrix evaluated at these points determines their stability, providing insight into the conditions that lead to hair loss or maintenance of the hair follicle population. The stability of the equilibrium points of the system is determined by analysing the Jacobian matrix of the system at these points. For our system of ordinary differential equations representing the interaction between hair follicles and immune cells, the Jacobian matrix J at an equilibrium point (H∗, T ∗) is given by:

$$J = \begin{bmatrix} \frac{\delta}{\partial H}\left(r_H H\left(1-\frac{H}{K}\right) - \alpha HT\right) & \frac{\delta}{\partial T}\left(r_H H\left(1-\frac{H}{K}\right) - \alpha HT\right. \\ \frac{\delta}{\partial H}\left(r_T T\left(1-\frac{T}{C}\right) + \beta HT - \gamma T\right) & \frac{\delta}{\partial T}\left(r_T T\left(1-\frac{T}{C}\right) + \beta HT - \gamma T\right. \end{bmatrix}_{(H^*,T^*)}$$

The equilibrium points (H∗,T∗) are found by setting the time derivatives of H and T to zero. These points are then substituted into the Jacobian matrix to evaluate it at the equilibrium points.

The stability of each equilibrium point is determined by the eigenvalues of the Jacobian matrix evaluated at that point. If all the eigenvalues have negative real parts, the equilibrium point is stable, indicating that the system will

return to this point if perturbed slightly. If at least one eigenvalue has a positive real part, the equilibrium point is unstable [20].

For instance, if we assume a simple case where the immune response is linear, and there is no saturation effect (βHT is small), we can simplify the analysis. However, in reality, the dynamics of alopecia areata are complex and may require considering nonlinear effects and the role of various cytokines and other immune factors [16, 24].

The results of such an analysis can provide insight into the progression of alopecia areata and the effects of potential treatments, as different parameters in the model are varied. This can help in understanding the critical thresholds that lead to the onset of the disease or recovery [6]. In Figure 2 , the graph illustrates the changes in the concentrations of hair follicles and T cells over time. The system of ordinary differential equations, which describes the growth and interaction between these two components, governs the dynamics shown in the graph. The concentration of hair follicles is represented by the blue line. It demonstrates how the population of hair follicles varies as time progresses. The specific units or scale of the concentration values are not provided in the document, so we can only interpret the relative changes in the concentration rather than the absolute values. On the other hand, the concentration of T cells is depicted by the red line. T cells are a type of immune cell that plays a role in autoimmune responses. The graph shows how the concentration of T cells changes over time in relation to the hair follicle population. The parameters and initial conditions used in the model are chosen to showcase the typical behavior of the system.

B. The dynamic behaviour

The equations 1 and 2 govern the dynamic behavior of the variables. Hair Follicle Growth and Regression 1

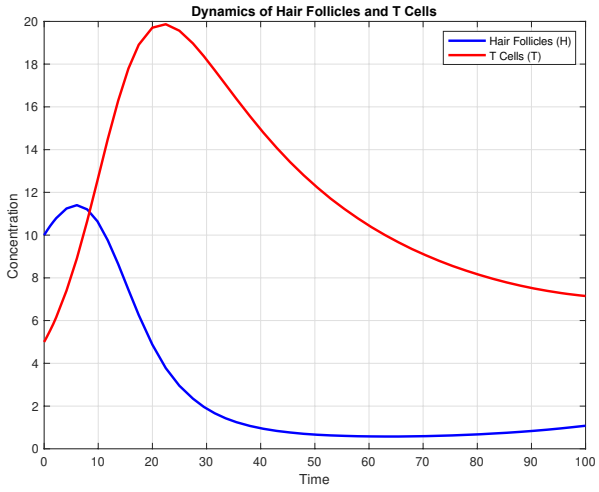

Figure 1. Time Evolution of Hair Follicle and T cell Concentrations. the Dynamics are Gov- Erned By A System of Ordinary Differential Equations Representing the Growth and Interaction Between Hair Follicles (H) And T Cells (T). Hair Follicle Concentration Is Shown In Blue, While T cell Concentration Is Depicted in Red. Parameters and Initial Conditions are Chosen to Illustrate Typical Behavior of the System.

logistic growth equation with additional terms to account for factors such as hair cycle length and external influences. T Cell Dynamics 2 describes the change in T cell population over time and can be modeled using a basic differential equation that accounts for recruitment, proliferation, and death of T cells. Furthermore, the model describes an inverse relationship between hair bulb keratinocytes (H) and the T-cell populations:

$$H(T) = \frac{\eta_1}{1+e^{-T}+\eta_2} \quad (3)$$

Where T = T8 + T4. This relationship indicates that high T-cell levels lead to hair growth cessation. Figure 3 represents Catagen induction, showing the relationship between Total T-cells (T) and Hair Bulb Cells (H). The parameters η1 and η2 are assumed to be 1 and 0.5, respectively, for illustration purposes. The plot demonstrates the exponential relationship between T and H, highlighting the influence of T-cells on the induction of hair bulb cells. The graph provides a visual depiction of the system dynamics and trends, facilitating the comprehension of the Catagen induction process.

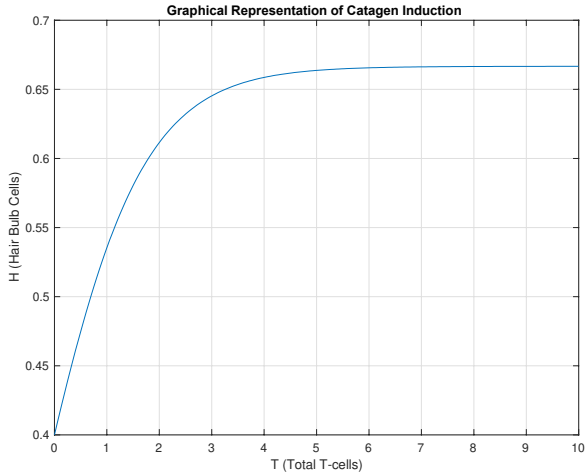

Figure 2. This Graph Depicts The Relationship Between Total T-Cells (T) And Hair Bulb Cells (H) During The Process Of Catagen Induction. The Plot Showcases The Connection Between These Two Variables, Providing Insights Into The Dynamics And Interplay Between T-Cells And The Induction Of Hair Bulb Cells.

C. Numerical Analysis

Numerical simulations can be performed using methods like Euler's method or the Runge- Kutta method to approximate the behaviour of the system over time. This approach allows us to explore the progression of alopecia areata under various conditions and treatment strategies. Data from clinical studies can inform the estimation of the model's parameters. Techniques such as least squares estimation or maximum likelihood can be applied to fit the model to observed data. Based on a generic model of T-cell dynamics. Typically, such models might include terms for the rate of production, death, and interaction between T-cell populations.

Let's assume we have the following model equations: For CD8+ T-cells (x):

$$\frac{dx}{dt} = r_x \,.x\,.\left(1 - \frac{x}{K_x}\right) - d_x.x - b_{xy}.x\,.y \qquad (4)$$

For CD4+ T-cells (y):

$$\frac{dy}{dt} = r_y \,.y\,.\left(1 - \frac{y}{K_y}\right) - d_y.y - b_{yx}.x\,.y \qquad (5)$$

Where:

- rx and ry are the growth rates of CD8+ and CD4+ T-cells, respectively.
- Kx and Ky are the carrying capacities of the environments for CD8+ and CD4+
- T-cells, respectively.
- dx and dy are the death rates of CD8+ and CD4+ T-cells, respectively.
- bxy and byx represent interaction coefficients between CD8+ and CD4+ T-cells.

Figure 4 generates a single figure with six subplots, two for each state (healthy, dis- eased, treatment), showing the behavior of CD8+ and CD4+ T-cells over time using Table 1 parameters values for the Healthy and Diseased states. In this study, we introduce a computational framework utilizing a system of ordinary differential equations (ODEs) to model the temporal dynamics of CD8+ and CD4+ T-cell populations under different physiological conditions. Specifically, we investigate the behaviour of these T-cell populations in three distinct states: healthy, diseased, and during treatment. By employing ODEs (4) and (5) , we aim to capture and analyse the temporal evolution of T-cell populations, providing insights into their response under varying physiological contexts. The mathematical model encapsulates the interplay between cell proliferation and natural decay, providing insight into immune system dynamics. In the healthy state, our model parameters are carefully selected to reflect a stable physiological environment where T-cell populations exhibit logistic growth, eventually stabilizing at a carrying capacity indicative of homeostasis. This equilibrium state is characterized by a regulated immune response, ensuring effective surveillance and defence mechanisms. The model captures the delicate balance between T-cell proliferation, differentiation, migration, activation, and apoptosis, which collectively maintain the T-cell populations at a steady state.

Table I. Parameter Values Parameter Healthy And Diseased.

Parameter	Healthy	Diseased
η_1	0.1	0.05
η_2	1×10^6	5×10^5
α	0.01	0.02
β	0.1	0.05
γ_1	1×10^6	5×10^5
γ_2	0.01	0.02
δ_1	0.001	0.002
δ_2	0.001	0.002

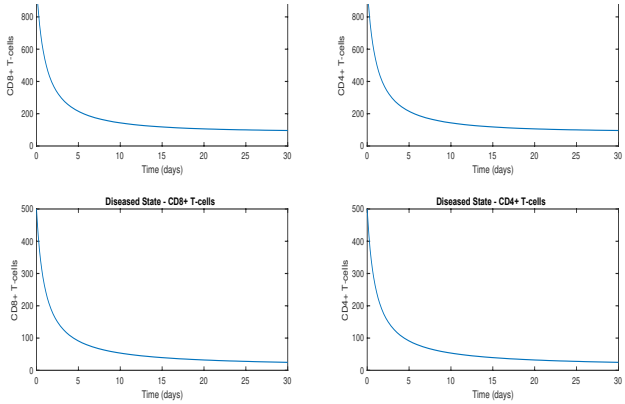

Figure 3. Unfolding the Temporal Behaviour of CD8+ and CD4+ T-Cells in Various Conditions in Equation (4) and (5): Depicting the Healthy and Diseased States in Subplots (A), (B), (C), and (D).

In contrast, the diseased state is simulated by adjusting the model parameters to reflect conditions such as viral infections or autoimmune disorders that can impair T-cell populations. The results typically demonstrate a compromised proliferation rate and an elevated decay rate, leading to a reduced steady-state concentration or a progressive decline in T- cell counts. These dynamics indicate an impaired immune system incapable of sustaining adequate defence levels. By capturing the altered behaviour of T-cell populations in the diseased state, our model helps to uncover the mechanisms underlying immune dysfunction and provides insights into the consequences of pathological conditions on T-cell dynamics.

Unravelling Dynamics: Exploring Linear Stability and Bifurcation Patterns

To further investigate the dynamics of the simplified model, we perform an analysis of linear stability and bifurcations. The results of the LHS/PRCC analysis indicate that the variables of interest, x (representing the scaled level of CD8+ T-cells) and y (representing the scaled level of CD4+ T-cells), are influenced by variations in the parameters s, a, and b. Upon exploring these sensitive parameters, we find that both b and a act as bifurcation parameters. Consequently, changes in b and a lead to qualitative shifts in the behaviour of the dynamical system. More specifically, the observed bifurcations result in alterations in the stability of the equilibria.

To conduct this analysis, we employ a method that involves varying the bifurcation parameters while keeping the remaining parameters at their nominal values. We then perform linear stability analysis to assess the stability of biologically relevant steady states and classify them accordingly. The ranges and baseline values for b and a can be found in Table 3.5. It is important to note that only equilibria with non-negative values of x and y hold biological significance.

RESULTS AND DISCUSSION

In summary, the temporal profiles obtained from our simulation provide valuable quantitative insights into the behavior of T-cell populations under different scenarios. The dynamics of CD8+ T-cells highlight the importance of the cytotoxic response, which is crucial for eradicating infected or abnormal cells. On the other hand, the dynamics of CD4+ T-cells reflect the helper response, which is vital for immune regulation. Comparative analyses across various physiological states facilitate a deeper understanding of immune resilience and vulnerabilities. This understanding is essential for the development and optimization of immunotherapeutic strategies in clinical settings. Our computational framework can serve as a valuable tool for designing and evaluating such strategies, aiding in the advancement of personalized medicine and targeted immunotherapies.

FUTURE WORK

Future work could focus on further refining the model by incorporating additional factors that influence T-cell dynamics, including the influence of specific pathogens or the presence of immune checkpoint molecules. Additionally, more extensive experimental validation of the model using in vitro or in vivo data would enhance its reliability and predictive power. Furthermore, the model could be extended to explore the effects of combination therapies or novel treatment modalities on T-cell populations. Finally, applying the model to patient- specific data could enable personalized predictions of T-cell dynamics and facilitate the development of tailored immunotherapeutic approaches. It's important to note that model validation and parameter estimation without experimental data will inherently have limitations. The results should be interpreted with caution, and efforts should be made to incorporate experimental data as it becomes available to refine and improve the model.

Collaboration between modelers, experimentalists, and clinicians can be crucial in de- veloping a comprehensive understanding of hair follicle-T cell interactions. By combining computational modeling with limited data and expert knowledge, you can still gain valuable insights into the dynamics and behavior of the system.

DECLARATIONS FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this paper.

DATA AVAILABILITY

The data used in this study were obtained from publicly available sources and references cited in the paper. All relevant data and materials are properly referenced or included in the manuscript.

CODE AVAILABILITY

The MATLAB code of the model is implemented using computational software, and numerical methods such as the Runge-Kutta method or the ode45 solver in this study is available upon request from the corresponding

author. The model used in this study is based on a system of ordinary differential equations (ODEs) that incorporates key biological processes and interactions involved in the temporal dynamics of CD8+ and CD4+ T-cell populations under various physiological conditions.

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