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Inflammation dynamics of atopic dermatitis: Phase transition and scaling law of remission time

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ABSTRACT

Atopic dermatitis (AD) is a prevalent skin disorder affecting individuals globally, with many patients experiencing a range of symptoms. A pronounced clinical phenomenon associated with AD is the cyclic alternation of two distinct phases in time: inflammation and remission, depending on patients' immune response and skin permeability. Frequent and relatively long inflammatory times lead to symptoms that can severely deteriorate the quality of life for the patient. Through mathematical modeling, we find that patients with similar AD symptoms can be categorized into two phases depending on the skin permeability and immune response that constitute the most clinically relevant parameter plane; the inflammatory time is shorter or longer than the remission time, respectively and the transition between the two phases is of the second-order type. In the parameter plane, a critical threshold curve emerges, which separates the two phases. Computing the frequency and duration of the inflammatory response, we uncover a logarithmic scaling law governing the inflammatory and remission times and discuss its clinical implications. In particular, when the skin condition is managed to be near the phase transition point, the benefits of treatment are more pronounced. However, at this stage, the effectiveness of skincare in reducing flare-ups tends to be less noticeable, making it difficult to evaluate the success of the treatment, largely due to the nature of logarithmic decay in the remission time. Our study provides insights into the mechanisms of AD that can enhance diagnostic accuracy and treatment by understanding the alternation between inflammation and remission periods.

1. Introduction

Utilizing the principles and methodologies of nonlinear dynamics for understanding diseases has a long history [1,2]. The pioneering work by Glass and Mackey proposed that certain physiological disorders may be understood as dynamical diseases [1,3], where the diseases are viewed as the manifestation of often sudden qualitative changes in the dynamics of the underlying physiological control mechanism [4,5]. Another extensively studied dynamical disease is epilepsy [6,7], where the occurrence of an epileptic seizure is believed to be related to the onset of some kind of synchrony or hypersynchrony among the neurons in certain brain regions [8]. There is extensive literature on applying nonlinear dynamics to analyzing and understanding the mechanism of epilepsy, including those based on the Lyapunov exponents [9,10], the correlation dimension [11], and phase synchronization [12]. In this paper, we apply nonlinear dynamics to a major class of human skin diseases: atopic dermatitis (AD). It is a prevalent skin condition influenced by the complex interplay among genetic, immunological, and environmental factors [13]. The disease manifests differently across various age groups, ethnicity, and genders, making it difficult to develop universally effective methods of treatment [14–20]. Another complicating issue is the absence of reliable animal models, making it difficult for turning research findings into clinical therapeutic methods. Recently, *in-vivo*, *in-vitro*, and *in-silico* approaches have been developed for understanding the pathophysiological mechanisms underlying AD [21–26]. These methods also aim to identify key therapeutic targets and biomarkers. AD evolves continuously in time and there are different clinical stages of AD, which can thus be viewed as the result of the evolution of a nonlinear, nonautonomous dynamical system with time-varying parameters. As such, mathematical and

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computational models can play a role in understanding the underlying disease mechanism [24–26].

Investigating the AD progression in time is critical to understanding the underlying mechanisms of the disease and developing treatments. A key clinical manifestation of AD is inflammation, also known as the inflammatory response. It is a biological reaction of the immune system triggered by various factors such as pathogens, damaged cells, and toxic substances [20,27,28], which plays a crucial role in the body's immune defenses. Common symptoms of inflammation include swelling, heat, and pain. Patients with AD frequently experience recurring inflammatory responses and their daily lives consist of alternating periods of inflammatory responses and periods without such responses. The time during which an inflammatory response occurs is the inflammatory time, denoted as τ_I , while the period without an inflammatory response is the remission time τ_R . From the standpoint of dynamics, the daily lives of patients with AD involve oscillations between the inflammatory and remission periods, as pictorially illustrated in Fig. 1(a). The duration and intensity of these inflammatory episodes can vary among patients with the same AD phenotype, influenced by individual factors such as the immune response levels and skin permeability [24,25]. This raises a basic question: what roles do the inflammatory oscillation patterns play in the symptoms, phenotype, and progression of AD?

A necessary step towards addressing this question is to obtain information about the inflammatory response time. Measuring the duration of the inflammatory response in AD using the traditional in-vivo and in-vitro methods is challenging. Realistically, it is infeasible to track the inflammatory response in AD patients with various symptoms over an extended period of time. To overcome this difficulty, we shall adopt an in-silico approach by which the inflammatory response time is simulated using the recently developed mathematical model for AD [24-26] based on a reasonable description of the characteristics of the disease. A pioneering model was proposed based on the mechanisms underlying the pathogenesis of AD, including genetic defects in skin barrier function and immune cell activity related to barrier dysfunction [24]. In this regard, In silico computational experiments utilizing various nominal values corresponding to the human body functions associated with AD have provided valuable insights into the progression of the disease over time. Especially, through a dynamical analysis of AD model, four stages of AD with distinct symptoms were identified: recovery, chronic damage, mild oscillations, and severe oscillations [24-26].

Our present study focuses on the characteristics of inflammatory and remission times under different physiological/biological conditions. Two key parameters can be used to characterize these conditions: the skin permeability κ_p and the immune response α_I . We set out to investigate how τ_I and τ_R vary on the parameter plane (κ_n, α_I) , with a special eye towards the mild and severe oscillations of the AD symptoms. The main findings of this work are as follows. Patients with similar AD symptoms can be categorized into two phases in the parameter plane: the inflammatory time is shorter or longer than the remission time: $\tau_I < \tau_R$ or $\tau_I > \tau_R$, respectively. A critical threshold curve arises in the parameter plane, with the behaviors $\tau_I < \tau_R$ or $\tau_I >$ τ_R occurring on the two sides of the curve. As the parameters change, the system's movement across the critical curve is effectively a secondorder phase transition, as both τ_I and τ_R vary continuously through some critical point. A pertinent issue is the frequency and duration of the inflammatory response and the impact on the "quality of life" of the patients. Our computations reveal that the values for AD onset conditions change significantly before and after the phase transition, indicating that even in patients with similar AD symptoms, different variants can occur, depending on the skin permeability and immune response. In clinical terms, a prolonged activation of a particular switch underlying AD (the R switch - to be introduced in model description below) is indicative of an extended period during which the patient experiences symptoms such as itching and scratching, leading to an unhealthy period. Understanding the duration in which the R switch remains active or inactive within a day can be useful for determining



Fig. 1. AD modeled as a nonsmooth nonlinear dynamical system. (a) A cycle of processes with or without an inflammatory response. (b) A schematic representation of the processes involved in AD. (c) Oscillatory behavior of the skin barrier *B* over time for two *in-silico* symptoms O_m and O_s , illustrating the periods of activation (inflammatory time, τ_l) and inactivation (remission time, τ_R) of the *R*-switch, as well as the activation of the *G*-switch.

the appropriate treatment strategy. Clinically, when the skin condition is managed such that the system is close to the phase transition point, the benefits of treatment are more pronounced. A logarithmic scaling law governing the inflammatory and remission times with parameter changes has been computationally uncovered and mathematically explained. The key clinical implication of the logarithmic scaling is that it provides a significant window of opportunity for treating the disease. Overall, our computations and analysis have generated insights into the dynamical mechanisms of AD for improving the diagnosis and treatment, giving another demonstration of the power of nonlinear dynamics in probing into human diseases to garner a mechanistic understanding.

2. Nonlinear dynamics of atopic dermatitis

2.1. AD modeled as a nonsmooth dynamical system

We conduct an in-silico study on inflammation and remission times by using the recently developed mathematical model of AD [24-26]. Fig. 1(b) shows the progression of AD pathogenesis [24], highlighting the dynamical interplay between skin barrier, immune regulation, and environmental stress. Under normal conditions, small amounts of pathogens that enter through compromised skin barriers are typically contained and do not pose a significant threat. However, when the amount of pathogens exceeds a certain threshold, it activates physiological mechanisms such as toll-like receptors (TLRs) and proteaseactivated receptor 2 (PAR2), leading to an AD flare. The immune response involves the release of antimicrobial peptides that fight against the invading pathogens and signal various immune processes that mobilize dendritic cells to the lymph nodes. If the pathogen load decreases below a deactivation threshold, these physiological mechanisms shut off, halting the flare. Conversely, if the dendritic cell count in the lymph nodes exceeds a critical threshold, it can lead to a significant and irreversible change in the immune state, which may exacerbate the skin condition considerably.

Quantitatively, the AD mechanism can be described by the following set of nonlinear differential equations [24]:

$$\begin{aligned} \frac{dP}{dt} &= \frac{P_{\text{env}}\kappa_P}{1 + \gamma_B B(t)} - \alpha_I R(t) P(t) - \delta_P P(t), \\ \frac{dB}{dt} &= \frac{\kappa_B [1 - B(t)]}{[1 + \gamma_R R(t)] [1 + \gamma_G G(t)]} - \delta_B K(t) B(t), \end{aligned} \tag{1}$$

$$\begin{aligned} \frac{dD}{dt} &= \kappa_D R(t) - \delta_D D(t), \end{aligned}$$

where the dynamical variables P(t), B(t) and D(t) represent the infiltrated pathogen load (in milligrams per milliliter), the strength of barrier integrity (relative to the maximum strength), and the concentration of dendritic cells (DCs) in the lymph node (cells per milliliter), respectively. We have $P(t) \ge 0$, $0 \le B(t) \le 1$ and $D(t) \ge 0$. The parameter values and their description are listed in Table A.2 in Appendix A.

A key aspect of the AD model is the use of three switches with an on-off function to describe the inflammatory responses, which play a crucial role in the progression of AD. The three switches R(t), G(t)and K(t) control the levels of activated immune receptors, *Gata3* transcription (relative to the maximum transcription level), and active kallikreins, respectively, and are described as

$$R(t) = \begin{cases} R_{\text{off}}, \text{ if } P(t) < P^{-} \text{ or} \\ \{P^{-} \le P(t) \le P^{+}, R(t^{-}) = R_{\text{off}}\}, \\ R_{\text{on}}, \text{ if } P(t) > P^{+} \text{ or} \\ \{P^{-} \le P(t) \le P^{+}, R(t^{-}) = R_{\text{on}}\}, \end{cases}$$
(2)
$$K(t) = \begin{cases} K_{\text{off}}, \text{ if } P(t) < P^{-} \text{ or} \\ \{P^{-} \le P(t) \le P^{+}, R(t^{-}) = R_{\text{off}}\}, \\ m_{\text{on}} P(t) - \beta_{\text{on}}, \text{ if } P(t) > P^{+} \text{ or} \\ \{P^{-} \le P(t) \le P^{+}, R(t^{-}) = R_{\text{on}}\}, \end{cases}$$
(3)
$$G(t) = \begin{cases} G_{\text{off}}, \text{ if } D(t) < D^{+} \text{ and } G(t^{-}) = G_{\text{off}}, \\ G_{\text{on}}, \text{ if } D(t) \ge D^{+} \text{ or } G(t^{-}) = G_{\text{on}}, \end{cases}$$
(4)

where R_{on} , R_{off} , G_{on} , G_{off} and K_{off} indicate the activating or inactivating constant-level of each switch, but only K_{on} depends on P(t): $K_{on} = m_{on}P(t) - \beta_{on}$. Note that the switches R and K are hysteretic, which activate and cease AD flares. In contrast, switch G is irreversible: once activated, it remains on permanently. Because of the on-off switches, the AD model Eq. (1) constitutes a nonsmooth dynamical system with subsystems. That is, the main system can evolve into a subsystem S_i as the AD system evolves. All subsystems of the AD system Eq. (1) are described in Appendix B.

For a clinical classification of the AD phenotypes, we use the SCO-RAD (SCORing Atopic Dermatitis) index to evaluate the extent and severity of eczema, which is associated with cytokine levels [20]. There are four classifications in SCORAD: none, mild, moderate and severe. In the *in-silico* study of AD, four attractors of AD were found [24–26]: Recovery (*R*), Mild Oscillation (O_m), Serious Oscillation (O_s) and Chronic damage (*C*).

2.2. Oscillation states associated with AD

The two attractors, namely R and C, do not exhibit any oscillatory behaviors: their skin integrity correspond to B = 1 (healthy skin state) and B = 0 (severe damage in skin), respectively. However, the attractors O_m and O_s present oscillating behavior in skin integrity, providing insights into the dynamical evolution of AD and treatment. In particular, depending on responses of inflammation or activation of the immune receptors, either O_m or O_s can arise. Fig. 2(a) shows the onset conditions [25] of O_m (blue) and O_s (red) with respect to the parameters κ_p and α_l . In the overlapping region of two onset conditions, the outcomes can be either O_m or O_s , depending on the initial condition. To study the oscillating behavior of AD in a concrete way, we focus on the parameter region highlighted by the two colors in Fig. 2(a). For a fixed parameter pair (κ_p , α_I) in this region, the steadystate attractors R and C might also arise due to the multistability [25]. Fig. 1(c) shows, for $\kappa_p = 0.85$ and $\alpha_I = 0.13$, the oscillating behaviors from the attractors O_m and O_s . The corresponding switch activation is illustrated in Fig. 1(c). The skin integrity of mild oscillatory attractor O_m , shown on the left in Fig. 1(b), is close to a healthy state (B = 1), while the attractor O_s with serious oscillations, shown on the right in Fig. 1(b), approaches chromatic damage (B = 0). A difference between the two oscillatory attractors is activation of the G switch, as shown in Fig. 1(c), where the state of G switch of O_m (O_s) is always off (on), respectively.

How do the oscillatory states O_m and O_s emerge? The subsystems involved in the creation of O_m are S_1 and S_3 . In particular, when S_1 is activated, AD progresses to a healthy state. However, the S_3 subsystem leads to a progression of AD when its inflammatory response is triggered (R and K switches turned on). The oscillating behavior of O_m thus results from the repeated involvement of the subsystems: $S_1 \rightleftharpoons S_3$, from periodic inflammation and remission of AD. Similarly, O_s is generated by utilizing different subsystems: $S_2 \leftrightarrows S_4$ when the Gswitch is turned on (Table 1). That is, periodic inflammatory responses in AD, combined with an activated immune response, contribute to the emergence of O_s . As a general rule, the oscillatory behavior consists of a repetition between a *inflammatory time* τ_I (R and K switches-on) and a *remission time* τ_R (R and K switches-off) of AD. Understanding these oscillatory states is crucial for more accurate prediction of the clinical outcome and for improving the quality of life in patients with AD.

3. Emergence of phase transition and scaling laws governing inflammatory and remission times

3.1. Comparison of inflammatory and remission times and clinical significance

When the inflammatory response of AD as triggered by the R and K-switches is activated, commonly the patients will experience pain or



Fig. 2. Two distinct AD oscillation states. (a) Onset conditions for O_m (blue) and O_s (red) in the (κ_p, α_I) space. (b, c) Cycles of inflammatory and remission times, along with the corresponding skin barrier *B* for O_m and O_s , respectively. (d, e) Distributions of inflammatory and remission times observed under the corresponding onset conditions for O_m and O_s , respectively.

Table 1

Properties	of	O_m	and	O_s	from	а	dynamical	point	of	view.
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Property	<i>O</i> _{<i>m</i>}	O_s	Time
Value of B	high	low	
R, K-switches	off \leftrightarrows on	off \leq on	$\tau_R \leftrightarrows \tau_I$
G-switch	off	on	
Subsystems of AD	$S_1 \leftrightarrows S_3$	$S_2 \leftrightarrows S_4$	



Fig. 3. Comparison of inflammatory and remission times. (a) Inflammatory and remission times $\tau_{1,R}^{m,s}$ versus κ_p for $\alpha_I = 0.13$, where two dashed lines denote the critical onset points: κ_p^m and κ_p^s . The red and blue colors represent the inflammatory and remission times for O_s and O_m , respectively. (b) Scaling of the remission time on logarithmic and linear scales for $\alpha_I = 0.13$. The critical onset point κ_p^* corresponds to κ_p^m for O_s and κ_p^s for O_m . (c, d) Similar to (a, b), respectively, but for $\alpha_I = 0.1$.

discomfort due to symptoms such as itching and scratching. During the time periods without inflammation, the skin begins to heal towards a return to the healthy state. The characteristics of the inflammatory and remission times are mainly determined by the parameters κ_p and α_I . Understanding the relationship between two different times and their scaling behaviors is critical for both clinical assessment and therapeutic decision-making.

Based on the fact that AD patients with different nominal values (κ_p, α_I) can show the same symptoms, we investigate the inflammatory and remission times in terms of the onset conditions of the two oscillating states O_m and O_s , represented by the blue and red colored parameter regions in Fig. 2(a), respectively. Figs. 2(b) and 2(c) present the cycles of inflammatory and remission times, along with the corresponding skin barrier *B* for O_m and O_s , respectively. Fig. 2(d) presents the probabilistic distributions of τ_I^m and τ_R^m associated with the O_m symptoms. For τ_I^m , the mean and variance are approximately 0.29 and 0.01, respectively, while those for τ_R^m are 1.00 and 0.18. The relatively small variance of τ_I^m suggests that AD patients exhibiting the O_m symptom tend to have a nearly consistent inflammatory response time. The remission time τ_R^m demonstrates a broader distribution characterized by an exponential tail, indicating that AD patients with the O_m symptom generally experience a similar duration of pain before entering the recovery phase.

For O_s , we also examine the inflammatory and remission times associated with its onset condition, and their probabilistic distributions are shown in Fig. 2(e). Compared to the those for O_m , the two distributions exhibit a significant overlap. The mean and variance of τ_I^s are approximately 0.36 and 0.02, respectively, while those for τ_R^s are 0.64 and 0.10. Overall, the mean value of τ_R^s is approximately twice of that of τ_I^s . For O_m , the mean value of τ_R^m is approximately four times larger than that of τ_I^m . We also have that the mean value of τ_I^m is slightly larger than that of τ_I^s . These observations can be summarized as

 $\langle \tau_R^s \rangle \approx 1.77 \langle \tau_I^s \rangle, \ \langle \tau_R^m \rangle \approx 3.51 \langle \tau_I^m \rangle, \text{ and } \langle \tau_I^m \rangle \approx 1.26 \langle \tau_I^s \rangle,$

indicating that AD patients with O_s endure a longer duration of pain compared to those with O_m .

3.2. Phase transition and logarithmic scaling of inflammatory and remission times

We examine how the inflammatory time τ_I and the remission time τ_R depend on the skin permeability κ_P under the distinct onset conditions of O_m and O_s , for a fixed rate α_I of pathogen eradication by innate immune responses. In this case, the critical onset points: κ_p^m for O_m and κ_p^s for O_s , are different, as exemplified in Fig. 2(a). For example, for $\alpha_I = 0.13$, we have $\kappa_p^m \approx 0.82$ and $\kappa_p^s \approx 0.77$. Fig. 3(a) illustrates $\tau_{I,R}^m$ and $\tau_{I,R}^s$ as a function of κ_p for the two states O_m and O_s , represented in blue and red, respectively. It can be seen that the remission time τ_R for both types of oscillation decreases sharply as κ_p increases beyond the onset. In contrast, the inflammatory time τ_I increases as κ_p increases from the critical point, indicating that, as the skin integrity deteriorates, the patients begin to experience longer periods of inflammation and shorter periods of remission.

Under the onset condition of O_m with $\alpha_I = 0.13$, we observe that the remission time is consistently longer than the inflammatory time: $\tau_I^m < \tau_R^m$, suggesting that the patients with O_m spend the majority of their time in the remission phase, experiencing only occasional pain due to inflammatory responses. Clinically, the AD patients with the O_m symptoms spend a considerable amount of time during which their skin conditions improve. In contrast, for patients exhibiting the O_s symptoms, there exists a critical value κ_p^c beyond which the relationship between the remission and inflammatory times exchanges, as shown in Fig. 3(a). Specifically, for $\kappa_p < \kappa_p^c$, the inequality $\tau_I^s < \tau_R^s$ holds. However, for $\kappa_p > \kappa_p^c$, this relationship reverses. We have

$$\tau_I^s < \tau_R^s$$
, if $\kappa_p < \kappa_p^c$, and

$$\tau_I^s > \tau_R^s, \quad \text{if} \quad \kappa_p > \kappa_p^c, \tag{5}$$

signifying a second-order phase transition at κ_p^c . Clinically, when the skin permeability of the patients exhibiting the O_s symptom exceeds a critical threshold, they are likely to remain in an inflammatory state most of the time. As a result, patients may experience constant pain all times, compromising their quality of life.

To quantify the change in the remission time τ_R after the onset of AD symptoms, we plot τ_R on a logarithmic-linear scale: $\tau_R^{m,s}$ versus $\kappa_p - \kappa_p^*$, where κ_p^* corresponds to κ_p^m for O_m or κ_p^s for O_s . The results are shown in Fig. 3(b), suggesting the following scaling laws:

$$\tau_R^m \sim m_R \log(\kappa_p - \kappa_p^m) \text{ for } O_m, \text{ and}$$
(6)

$$\tau_R^s \sim s_R \log(\kappa_p - \kappa_p^s) \text{ for } O_s, \tag{7}$$

with the respective slopes $m_R \approx -0.45$ and $s_R \approx -0.1$. As κ_p approaches the critical value κ_p^* , the remission time exhibits a logarithmic decay law.

What are the clinical implications of the logarithmic scaling law? To address this question, we note that the variation of the remission time for the AD patient depends on the specific AD symptoms and decrease as κ_n undergoes a slight change from the onset point κ_n^* . Because of the constraint $m_R < s_R$, the remission time for O_s decreases more quickly than that for O_m . For κ_p is far above κ_p^* , a reduction in the remission time occurs at a much slower rate due to the nature of the logarithmic decay, suggesting that taking care of the skin immediately after the onset of AD can significantly prolong the remission period. In contrast, when AD progresses to a stage where κ_p is greater than κ_n^* , the impact on the remission time becomes minimal. Specifically, when the skin condition is managed so that κ_p is close to κ_p^* ($\kappa_p^* \lesssim$ κ_p), the benefits of treatment are more pronounced. However, at this stage, the effectiveness of skincare in reducing flare-ups tends to be less noticeable, making it difficult to evaluate the success of the treatment, largely due to the nature of logarithmic decay in the remission time.

We now investigate the dependence of the inflammatory and remission times on κ_p as the immune response is reduced. For this purpose, we set $\alpha_I = 0.1$. The results are shown in Fig. 3(c), where there is a phase transition for both the O_m and O_s states:

$$\begin{aligned} \tau_I^m < \tau_R^m, & \text{if } \kappa_p < \kappa_p^{c1}, \qquad \tau_I^s < \tau_R^s, & \text{if } \kappa_p < \kappa_p^{c2}, \\ \tau_I^m > \tau_R^m, & \text{if } \kappa_p > \kappa_p^{c1}, \qquad \tau_I^s > \tau_R^s, & \text{if } \kappa_p > \kappa_p^{c2}. \end{aligned} \tag{8}$$

The scaling of the remission time remains to be logarithmic [(6)], as shown in Fig. 3(d). Considering that, at a higher level of immune response ($\alpha_I = 0.13$), only the O_s state exhibits a phase transition, as shown in Fig. 3(a), we see that a reduced level of immune response can lead to a phase transition in both the O_m and O_s states.

To further explore the phase transition phenomenon between τ_R and τ_I , we examine these times under the onset conditions of the two oscillating states. Figs. 4(a) and 4(b) illustrate the critical points of the phase transition for O_m and O_s (marked in black). Remarkably, the numerically determined critical points form a straight line, as shown by the black lines in Figs. 4(a) and 4(b):

$$\alpha_I \approx 0.253\kappa_p - 0.119$$
, for O_m , and (9)

$$\alpha_I \approx 0.283\kappa_p - 0.121 \text{ for } O_s. \tag{10}$$

These are the critical phase-transition line, denoted as P_{line} . For the onset condition of O_m , the critical line P_{line} is positioned close to the boundary of this condition. The proximity indicates a relatively small area below the line P_{line} in the onset condition of O_m . As a result, the AD patients with O_m are less likely to experience the phase transition. In contrast, for the onset condition of O_s , the area below the line P_{line} is significantly larger, indicating that the AD patients with O_s are more likely to experience the phase transition, which could complicate the progression of the AD symptoms. Overall, for both O_m and O_s , the inequality $\tau_I^m < \tau_R^m$ holds in the area above the straight line, while



Fig. 4. Phase transition associated with the O_m and O_s states. (a, b) Critical phasetransition line P_{line} marked by black line with respect to the onset conditions of O_m and O_s , respectively. In the (κ_p, α_I) plane, the critical points of phase transitions are indicated by the black lines on the onset conditions of O_m and O_s , corresponding to the blue and red regions, respectively.

opposite holds below the line. Consequently, depending on the immune responses α_I and skin permeability κ_P , the order in the length of the inflammatory and remission time can be changed:

$$\tau_I^m < \tau_R^m \to \tau_R^m < \tau_I^m \quad \text{and} \quad \tau_I^s < \tau_R^s \to \tau_R^s < \tau_I^s, \tag{11}$$

implying a significant disparity in the quality of life for patients with AD, even when they exhibit similar symptoms, as characterized by the scaling relation (9).

3.3. Behaviors of inflammatory response

Associated with the inflammatory response, the key dynamical variable underlying the AD, namely the strength of barrier integrity B(t), exhibits periodic oscillations, as exemplified in Figs. 2(a) and 2(b). Each period contains a cycle of inflammation and remission. As stronger inflammatory responses lead to more severe AD symptoms, a question is how frequent these cycles are. To address this question, we define the frequencies of the inflammatory response for the O_m and O_s states as

$$F_m = \frac{1}{\tau_I^m + \tau_R^m} \quad \text{and} \quad F_s = \frac{1}{\tau_I^s + \tau_R^s}.$$
 (12)

Figs. 4(c) and 4(d) show the values of F_m and F_s under their respective onset conditions in the parameter plane (κ_p, α_I) . As κ_p increases, the maximum frequencies occur just above the critical line P_{line} , indicating a correlation between the frequency and phase transition. Especially, when the immune response and skin permeability are near the critical line, the frequency of the inflammatory response is significantly elevated. Within each oscillatory state, the frequency distribution is wide: the ranges of F_m and F_s are (0.3, 1.2) and (0.4, 1.5), respectively.

Within a cycle, the fraction of the inflammatory time can also vary widely, depending on the parameter values. The fractions associated with the O_m and O_s states are given by

$$P_m = \frac{\tau_I^m}{\tau_I^m + \tau_R^m} \quad \text{and} \quad P_s = \frac{\tau_I^s}{\tau_I^s + \tau_R^s}.$$
 (13)

As $P_{m,s}$ approaches the value 1, patients will incur persistent inflammation most of the time. Figs. 4(e) and 4(f) illustrate the values of P_m and P_s , respectively, in the parameter plane (κ_p, α_I) . Below the critical line P_{line} , the fraction of time that the system is in an inflammatory state is large, due to the occurrence of a phase transition. In general, the fractions can vary significantly, depending on the severity of the AD symptoms: the ranges of P_m and P_s are (0.04, 0.6) and (0.04, 0.8), respectively.

Clinically, maintaining a healthy quality of life is an important goal for any AD patient, as prolonged flare-ups will significantly impact both the physical and emotional well-being. These symptomatic periods disrupt daily activities and sleep, further compounding the effects on the patient's Quality of Life (QoL). Conversely, inactivation of the R-switch represents periods of remission or reduced disease activity, during which the patients experience relief from symptoms. In general, when the condition of the skin worsens, patients experience symptoms such as itching, swelling, heat, and pain due to inflammation [28–30]. The health-related QoL for AD patients is determined by the dynamical behaviors of the oscillatory states O_m and O_s . Quantitatively, the QoL can be assessed by examining how the degree of inflammatory response varies with the skin integrity. To this end, we define a measure reflecting the QoL:

$$Q_L = (1 - \langle B \rangle) P_{m,s},\tag{14}$$

where $\langle B \rangle$ is the average skin integrity throughout a cycle that includes both inflammatory and remission periods. A near zero value of Q_L indicates that the skin condition of the patients is good or that the inflammation levels are low. In contrast, as Q_L approaches one, a high level of inflammatory response can be expected, signifying poor skin conditions.

Figs. 4(g) and 4(h) show the variations of Q_L in the parameter plane (κ_p, α_I) the O_m and O_s states, respectively. While the AD symptoms may vary, an AD patient's quality of life can diminish when their skin condition falls below a critical threshold of phase transition. When the oscillations are mild (O_m) , the values of Q_L range from 0.01 to 0.4. In contrast, for the severe oscillation state O_s , Q_L ranges from 0.01 to 0.7, indicating a more significant decline of the quality of life as compared with the case of mild oscillations.

For a fixed value of $\kappa_p = 0.85$, we examine how changes in the immune response parameter α_I affect the inflammatory and remission times, the frequency of the inflammatory response, the fraction of time spent in inflammation, and the overall quality of life, as shown in Fig. 5. In Fig. 5, each column corresponds to one type of symptom and the dashed lines indicate the values of α_I on the critical phase-transition line P_{line} in Fig. 4, corresponding to $\kappa_p = 0.85$. As α_I increases beyond the dashed critical line, the inflammatory time τ_I , the fraction of time $P_{m,s}$ spent in inflammation, and the measure Q_L of the quality of life all decrease, while the remission time τ_R increases. This suggests that a stronger immune response is associated with better health outcomes. Notably, the local maximum of the inflammatory response frequency $F_{m,s}$ occurs right after the critical dashed line and subsequently begins to decrease. As a result, after the phase transition, a delay arises before the frequency of the inflammatory response begins to change.

4. Discussion

A unique feature common to the AD disease is the emergence of oscillations. For example, as the skin conditions deteriorate, before severe damage occurs, the symptoms as determined by the strength of barrier integrity can undergo periodic cycles, with each cycle consisting



Fig. 5. Effect of varying the immune response parameter α_1 on the dynamics of AD. For a fixed $\kappa_p = 0.85$, the effects of varying α_1 on inflammatory and remission times (a, b), the frequency of the inflammatory response (c, d) the fraction of inflammatory time (e, f), and quality of life (g, h). The left and right columns correspond to mild and severe oscillations, respectively.

of two characteristically distinct types of behaviors: inflammation and remission. During the inflammatory time, severe discomfort can arise, making low the quality of life for the patients, whereas not much discomfort occurs during the remission time. Qualitatively, two distinct types of oscillations in the skin integrity exist among the AD patients: depending on the inflammatory and immune responses of the patient, the oscillations can be mild or severe. Regardless of the type of oscillations, to effectively reduce the inflammatory time or, equivalently, to prolong the remission time in a cycle of oscillation is a goal for treatment strategies. To achieve this goal, it is necessary to uncover the quantitative dependence of the inflammatory and remission times on the skin condition. Due to the long time span of the AD, clinical tests to determine this dependence are infeasible, and mathematical modeling provides a viable approach to gaining insights into how the inflammatory and remission times change as some parameter characterizing the skin condition changes.

The two findings of our work are: (1) the emergence of a phase transition in the inflammatory and remission times and (2) a logarithmic scaling law governing the remission time. In particular, as a key bifurcation parameter, the skin permeability, continuously increases from a small, healthy value so that the skin's barrier becomes less and less effective to protect the body from harmful substances, either mild or severe oscillations in the strength of the barrier integrity can arise, depending on the skin conditions of the individuals. At the onset of the oscillations, the remission time is much larger than the inflammatory time. As the skin permeability increases further, the remission time decreases, accompanied by a corresponding increase in the inflammatory time. At the critical value of the skin permeability, the two types are equal, after which the inflammatory time surpasses the remission time, signifying a phase transition. Since both times change continuously through the critical point, the phase transition is of the second-order type. Prior to the critical point, the discomfort is less serious. A balance between comfort and discomfort is reached at the critical point, after which the time period of discomfort exceeds that of comfort, leading to a decrease in patient's quality of life. Measuring the skin permeability parameter from the onset of the oscillations, the remission time decreases logarithmically with the parameter increment from the onset. From a clinical point of view, the logarithmic dependence is beneficial as it provides a time window for treatment or intervention.

It is worth stressing that, while the findings in this work are from mathematical modeling and a dynamical analysis of the AD, to verify the findings clinically is infeasible at the present time. For understanding the AD, mathematical model will continue to be effective to provide insights into the underpinnings of the skin disease for better treatment strategies.

In summary, previous studies on the inflammatory response in AD have primarily focused on the immune system's biological reactions to various factors, including pathogens and toxic substances [20,27,28]. These studies typically employed *in-vivo* and *in-vitro* methods. However, these approaches can complicate the assessment of inflammation duration in AD. By utilizing well-established AD models [24] that accurately reflect its pathophysiology, for instance, it can evaluate the effects of treatments [31,32] and identify new phenotypes [25]. In the absence of real-world data, our *in-silico* study has produced two significant findings: (1) a phase transition between periods of inflammation and remission, and (2) a logarithmic scaling law that governs the duration of remission. These findings highlight the crucial role of *in-silico* research in improving our understanding of AD.

CRediT authorship contribution statement

Yoseb Kang: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jaewoo Hwang:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yong Hyun Jang:** Writing – review & editing, Writing – original draft, Supervision, Project administration. **Ying-Cheng Lai:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Formal analysis, Conceptualization. **Younghae Do:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table A.2

Description and	l values of	the	parameters	of	the	AD	system	Eq.	(1)).
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Parameter	Description	Value
Peny	Environmental stress load	95 (mg/mL)
γ _B	Barrier-mediated inhibition	1
	of pathogen infiltration	
κ _p	Nominal skin permeability	(1/day)
α_I	Rate of pathogen eradication	(1/day)
	by innate immune responses	
δ_P	Basal pathogen death rate	1 (1/day)
κ _B	Barrier production rate	0.5 (1/day)
γ_R	Innate immunity-mediated inhibition	10
	of barrier production	
δ_B	Rate of kallikrein-dependent	0.1
	barrier degradation	
γ_G	Adaptive immunity-mediated inhibition	1
	of barrier production	
κ _D	Rate of DC activation by receptors	4 cells/(mL 3 day)
δ_D	Rate of DC degradation	0.5 (1/day)
P^-	Receptor inactivation threshold	26.6 (mg/mL)
P^+	Receptor activation threshold	40 (mg/mL)
D^+	Gata3 activation threshold	85 (cells/mL)
R _{off}	Receptor off level	0
R _{on}	Receptor on level	16.7
$G_{\rm off}$	Gata3 off level	0
Gon	Gata3 on level	1
K _{off}	Kallikrein off level	0
mon	Slope of the linear relation	0.45
	between $P(t)$ and K_{on}	
$\beta_{\rm on}$	Y-intercept of the linear relation	6.71
	between $P(t)$ and K_{on}	

Appendix A. Parameters of AD model

Parameters of the AD system Eq. (1) and their description are listed in Table A.2.

Appendix B. Subsystem of AD model

Depending on status of three switches or inflammation responses, the AD model Eq. (1) can have a different form or representation, leading to the following subsystems.

 S_1 -subsystem. All switches in the AD system Eq. (1) are off: $(R, K, G) = (R_{\text{off}}, K_{\text{off}}, G_{\text{off}}) = (0, 0, 0)$, leading to

$$\frac{dP}{dt} = \frac{P_{env} \cdot \kappa_p}{1 + \gamma_B B(t)} - \delta_p P(t),$$

$$\frac{dB}{dt} = \kappa_B [1 - B(t)],$$

$$\frac{dD}{dt} = -\delta_D D(t),$$
(B.1)

 S_2 -subsystem. Only the *G* switch is on, indicating a deficiency in the immune response: $(R, K, G) = (R_{\text{off}}, K_{\text{off}}, G_{\text{on}} = 1)$. The system becomes

$$\frac{dP}{dt} = \frac{P_{env} \cdot \kappa_p}{1 + \gamma_B B(t)} - \delta_p P(t),$$

$$\frac{dB}{dt} = \frac{\kappa_B [1 - B(t)]}{[1 + \gamma_G G_{on}]},$$
(B.2)
$$\frac{dD}{dt} = -\delta_D D(t),$$

 S_3 -subsystem. Only the *R* and *K* switches are on: $(R, K, G) = (R_{on}, K_{on}, G_{off} = 0)$. In this case, the environment is such that a critical level of the infiltrated pathogen load is exceeded. The system becomes

$$\frac{dP}{dt} = \frac{P_{env} \cdot \kappa_p}{1 + \gamma_B B(t)} - \alpha_I R_{on} P(t) - \delta_p P(t),$$

$$\frac{dB}{dt} = \frac{\kappa_B [1 - B(t)]}{[1 + \gamma_R R_{on}]} - \delta_B K(t) B(t),$$
(B.3)

$$\frac{dD}{dt} = \kappa_D R_{\rm on} - \delta_D D(t),$$

 S_4 -subsystem. All switches in the AD system are on, $(R, K, G) = (R_{on}, K_{on}, G_{on})$ signifying the situation where the AD immune response is deficient and the environmental infiltrated pathogen load exceeds a critical level. The system equations are

$$\frac{dP}{dt} = \frac{P_{env} \cdot \kappa_p}{1 + \gamma_B B(t)} - \alpha_I R_{on} P(t) - \delta_p P(t),$$

$$\frac{dB}{dt} = \frac{\kappa_B [1 - B(t)]}{[1 + \gamma_R R_{on}][1 + \gamma_G G_{on}]} - \delta_B K(t) B(t),$$

$$\frac{dD}{dt} = \kappa_D R_{on} - \delta_D D(t),$$
(B.4)

Appendix C. Logarithmic scaling governing the remission time

When the *R* and *K* switches are turned off, the remission time τ_R represents the travel time from the point (P^-, B_1) to (P^+, B_2) , as illustrated in Fig. C.6(a). Therefore, we can determine the remission time from the *S*₁-system, Eq. (B.1), by satisfying the following conditions:

$$\begin{split} P(0) &= P^{-}, B(0) &= B_{1} \quad \text{at } t = 0, \\ P(\tau_{R}) &= P^{+}, B(\tau_{R}) = B_{2} \quad \text{at } t = \tau_{R}. \end{split}$$

From Eq. (B.1), we can easily find B(t):

$$B(t) = 1 + (B_1 - 1)e^{-\kappa_B t}.$$
(C.1)

By substituting this into the equation for P, we get

$$\frac{dP}{dt} = \frac{P_{env} \cdot \kappa_p}{1 + \gamma_B \left[1 + (B_1 - 1)e^{-\kappa_B t}\right]} - \delta_p P(t).$$
(C.2)

Using the parameter values provided in Table A.2, *i.e.*, $\delta_P = 1$, $\gamma_B = 1$ and $\kappa_B = 0.5$, and then multiplying both sides by e^t , we obtain

$$\frac{d}{dt}(e^t P(t)) = e^t P'(t) + e^t P(t) = \frac{e^t}{c_1 + c_2 e^{-t/2}},$$
(C.3)

where
$$c_1 = \frac{2}{P_{env}\kappa_P}$$
 and $c_2 = \frac{(B_1 - 1)}{P_{env}\kappa_P}$. Thus, we get

$$P(t) = e^{-t} \left(\int \frac{e^x}{c_1 + c_2 e^{-x/2}} dt \right) \equiv e^{-t} I(t).$$
(C.4)

Let $u(t) = c_1 e^{t/2} + c_2$, then I(t) can be calculated by the following way:

$$I(t) = \int \frac{e^x}{c_1 + c_2 e^{-x/2}} dt = \int \frac{e^{3x/2}}{c_1 e^{x/2} + c_2} dt$$

=
$$\int \left(\frac{u - c_2}{c_1}\right)^3 \frac{1}{u} \frac{2}{c_1} \frac{c_1}{u - c_2} du$$

=
$$\frac{2}{c_1^3} \left((c_1 e^{t/2} + c_2)^2 / 2 - 2c_2 (c_1 e^{t/2} + c_2) + c_2^2 \log |c_1 e^{t/2} + c_2| \right) + C,$$

where *C* is a constant of integration. Using the initial condition $P(0) = P^{-}$, we can determine the constant, *C*:

$$C = P^{-} - \frac{2}{c_1^3} \left\{ \frac{(c_1 + c_2)^2}{2} - 2c_2(c_1 + c_2) + c_2^2 \log |c_1 + c_2| \right\}.$$

Therefore, we finally obtain P(t) as the following form from Eq. (C.4):

$$P(t) = e^{-t}I(t) = d_1e^{-t} + d_2e^{-t/2} + d_3,$$
(C.5)

where

$$d_1 = \frac{2}{c_1^3} \left\{ -\frac{3c_2^2}{2} + \frac{c_1^3}{2}C + c_2^2 \log(c_1 e^{t/2} + c_2) \right\},$$
 (C.6)

$$d_2 = -\frac{2c_2}{c_1^2} = \frac{1}{2}(1 - B_1)P_{env}\kappa_p,$$
(C.7)



Fig. C.6. (a) Illustration of oscillation between two points (P^-, B_1) and (P^+, B_2) , for the remission and inflammatory times. For the fixed value of $\alpha_I = 0.13$, (b–d) display the numerically calculated coefficients B_1 , d_1 , and d_2 associated with κ_p . Each dashed line (or curve) in (b–d) represents the fitted regression results.

$$d_3 = \frac{1}{c_1} = \frac{P_{env}\kappa_p}{2}.$$
 (C.8)

Since the remission time τ_R is a solution that satisfies $P(\tau_R) = P^+$, we need to solve the following algebraic equation:

$$P^+ = d_1 T^2 + d_2 T + d_3, (C.9)$$

where $T = e^{-t/2}$. Eq. (C.9) is implicit because the coefficient d_1 depends on the variable *t* and B_1 is determined by its relationship with κ_p , making it infeasible to obtain an analytic solution. We thus resort to numerically solving the coefficients B_1 , d_1 , and d_2 using the data τ_R in Fig. 3 with the fixed $\alpha_I = 0.13$. The results are illustrated in Figs. C.6(b– d). In particular, Figs. C.6(c) and C.6(d) demonstrate that d_1 has a linear relationship with κ_p and d_2 exhibits a quadratic relationship, with the correlation coefficients of $R^2 = 0.9998$ and $R^2 = 1$, respectively. These relations enable us to express the coefficients in the following forms:

$$d_1 = m_1 \kappa_p + n_1,$$

$$d_2 = m_2 \kappa_p^2 + n_2 \kappa_p,$$
(C.10)

where $m_1 \approx -163.1$, $m_2 \approx 120$, $n_1 \approx 114.2$ and $n_2 \approx -87.97$. For different values of α_I , we have verified that the coefficients d_1 and d_2 retain the same form as in Eq. (C.10).

Solving Eq. (C.9) for T, we obtain:

$$T = \frac{-d_2 + \sqrt{d_2^2 - 4d_1d_4}}{2d_1},\tag{C.11}$$

where $d_4 = d_3 - P^+$ and can be expressed as $m_4\kappa_p + n_4$. Since the numerator of *T* is a quadratic function of κ_p and the denominator is a linear function, the dependence of *T* on κ_p is linear:

$$T \sim a\kappa_p - b, \tag{C.12}$$

where *a* and *b* are constants. Since $T = e^{-\tau_R/2}$, we obtain the logarithmic scaling law between τ_R and κ_p :

$$\tau_R \sim -2\log(\kappa_p - c),\tag{C.13}$$

where c is a constant.

Data availability

The data supporting the findings of this study are available in the article.

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