npj | systems biology and applications

Article

Published in partnership with the Systems Biology Institute

https://doi.org/10.1038/s41540-025-00524-y

An in silico approach deciphering the commensal dynamics in the cutaneous milieu

Sumathi Kalankariyan[1], Anjana Thottapillil[1], Abha Saxena[1], Manoj Srivatsn S[1], Vinitha Kadamkode[2], Renu Kapoor[2], Rupak Mitra[2], Janhavi Raut[2] & KV Venkatesh[1,3] ✉

The skin microbiota, particularly coagulase-negative staphylococci (CoNS) such as *S. epidermidis*, plays a crucial role in maintaining skin health and immunity. *S. epidermidis*, a predominant commensal species, interacts intimately with keratinocytes to regulate immune responses and antimicrobial defence mechanisms. Metabolic byproducts like short-chain fatty acids (SCFAs) influence keratinocyte activation, while cell wall components engage Toll-like receptors (TLRs) to modulate inflammation. These interactions are fundamental for preserving skin homeostasis and combating pathogenic invaders. Our comprehensive mathematical model, integrating commensal dynamics, immune responses, and skin microenvironment variables, provides insights into these intricate interactions. The model delves into the complexities of skin scenarios and perturbations, aiming to understand the colonization dynamics of *S. epidermidis* and its influence on skin barrier functions. It examines how disruptions in key factors such as AMP, growth factor-mediated repair pathways, and filaggrin mutations influence the behaviour of the system. The study depicts the skin microenvironment as a highly dynamic one, highlighting the critical role of *S. epidermidis* and capturing its role in barrier dysfunction caused by internal and external factors. By offering insights into skin barrier function and immune responses, the model illuminates key interactions of commensals within the skin microenvironment which can ultimately benefit skin health.

Skin serves as the outermost barrier against pathogenic invasion and plays an important role in adapting the systemic responses to changing environments. Epidermal barrier consists of several specialized cellular constructs (desmosomes, tight junctions and structural proteins) which interconnect and maintain tightly regulated and balanced interface. Epidermal barrier integrity relies on the concerted actions of these components along with the resident immune cells and microbiota and contributes to its defense mechanisms[1,2].

The innate immune response recruit's neutrophils, phagocytic cells, to combat skin pathogens through multiple mechanisms such as induction of proinflammatory cytokines[3–5]. Antimicrobial peptides (AMPs) actively secreted by the keratinocytes such as hBDs and S100A7, fortify the skin against pathogens, and their expression is modulated by cues from the skin microbiota[6]. A constant interaction between host cells and skin microbes plays a vital role in fostering immune tolerance and shaping the development of host immune cells from early life. Commensal skin microbiota establishes a mutualistic relationship with the skin's immune system, enhancing the immune barrier through controlled inflammation[7]. Among the diverse population of the resident commensals, *S. epidermidis* is one of the abundant skin commensals extensively studied for its beneficial effects on skin barrier maintenance such as its role in inflammation and wound healing[8]. *S. epidermidis* enhances antimicrobial defense by the upregulation of specific AMP as well as contributes to skin hydration by enhancing lipid mediators and tight junctions in keratinocytes[8–11].

In contrast, studies also indicate *S. epidermidis* behaving as opportunistic pathogen thereby has been called as "Pathobiont", often existing along a spectrum between mutualism and pathogenicity[12]. The cause and consequences on the factors driving its transition from commensal to pathogenic state postulates the question on the precise role of *S. epidermidis* on skin and the key facilitators of its commensal behaviour.

S. epidermidis is identified as the second most common microbe isolated from lesions affected by Atopic dermatitis (AD)[8], a prevalent skin condition characterized by a dysfunctional skin barrier, with filaggrin mutations serving as key contributing factors. Filaggrin contributes to the

[1]MetFlux Research Private Limited, Bengaluru, India. [2]Unilever R & D, Bangalore, India. [3]Department of Chemical Engineering, Indian Institute of Technology Bombay, Mumbai, Maharashtra, India. ✉e-mail: venks@metflux.in; venks@iitb.ac.in

structural integrity of the skin by forming aggregates with the keratin[13]. In the upper-most layer of the skin, stratum corneum, Filaggrin is broken down into free amino acids, pyrrolidone carboxylic acid, and urocanic acid (UCA), which are key components of the skin's natural moisturizing factors (NMF)[14]. These molecules help regulate skin hydration, pH and have important immunomodulatory effects. Maintaining skin pH is essential for metabolism and organization of the lipids of the extracellular matrix and anti-microbial activities[13]. In addition, component of NMF also play a role in photoprotection[15]. The deficit of Filaggrin in skin causes altered organization of the skin barrier resulting in an elevated pH and protease activity, making skin susceptible to infections. Loss of function variants in Filaggrin and other critical barrier proteins disrupts the normal epidermal functions and leads to increased water loss (TEWL)[15–17] making host susceptible to many skin diseases, including Atopic dermatitis[18]. The mechanism underpinning the AD pathogenesis, particularly in relation to skin barrier dysfunction and filaggrin mutations, is well established[18], but the interplay between *S. epidermidis* and these factors is poorly understood. Gaining a clearer understanding into the filaggrin mutation and its influence on commensal could be valuable for designing novel therapeutic strategies for AD.

Mathematical models have emerged as a significant advancement in understanding the skin milieu in recent years, offering a valuable tool to overcome the limitations of traditional in vitro methods[19,20]. A dearth of computational models is reported in the study by Elea et al. who has developed an ODE based model addressing the interaction between two microbial populations and has well stated the limitation in the number of models even on addressing the bacterial population and skin interaction[21]. This sets our model unique and stand -alone on having a deeper look on the commensal *S epidermidis* dynamics aiming to understand the aspects that preserve healthy levels of commensals on the skin and their interactions with skin cells to sustain cutaneous immune homeostasis under both normal and compromised conditions. The model also attempts to provide a basis for "pathobiont" state of *S. epidermidis*, focusing on how the system calibrates a critical threshold of commensal growth beyond which pathogenicity ensues. This study investigates the commensal behaviour of *S. epidermidis* and its relationship with epidermal barrier responses in conditions such as compromised skin immunity or filaggrin mutations, both of which are associated with the development of skin atopy. More importantly, the role of *S. epidermidis* in dysfunctional skin barrier conditions, as addressed through our in silico approach, underscores its relevance in exacerbating inflammatory dermatoses and contributing to various pathological skin conditions. This highlights the potential applications and translational value of the model in advancing skin health research. By employing approaches such as phase plane plots, parameter perturbation, and sensitivity analysis, we have elucidated key aspects in the mechanisms driving host-microbe interactions.

The in silico skin model on commensal-host interactions

Our mathematical model represents the interactions and pathways in the skin consisting of microbial signaling, immune response, hydration, and barrier repair. Mechanistic interactions in the skin microenvironment captured in our meticulously developed network include 21 nodes and 44 edges (Fig. 1). Directed edges emphasize the functional importance of each interaction, with 12 edges dedicated to commensal bacterial product signaling, 11 to immune signaling, and 8 to hydration-related components, while 10 are linked to epidermal damage and repair signaling pathways. Our model has captured the essential features of signaling pathways such as nonlinear interactions and feedback loops.

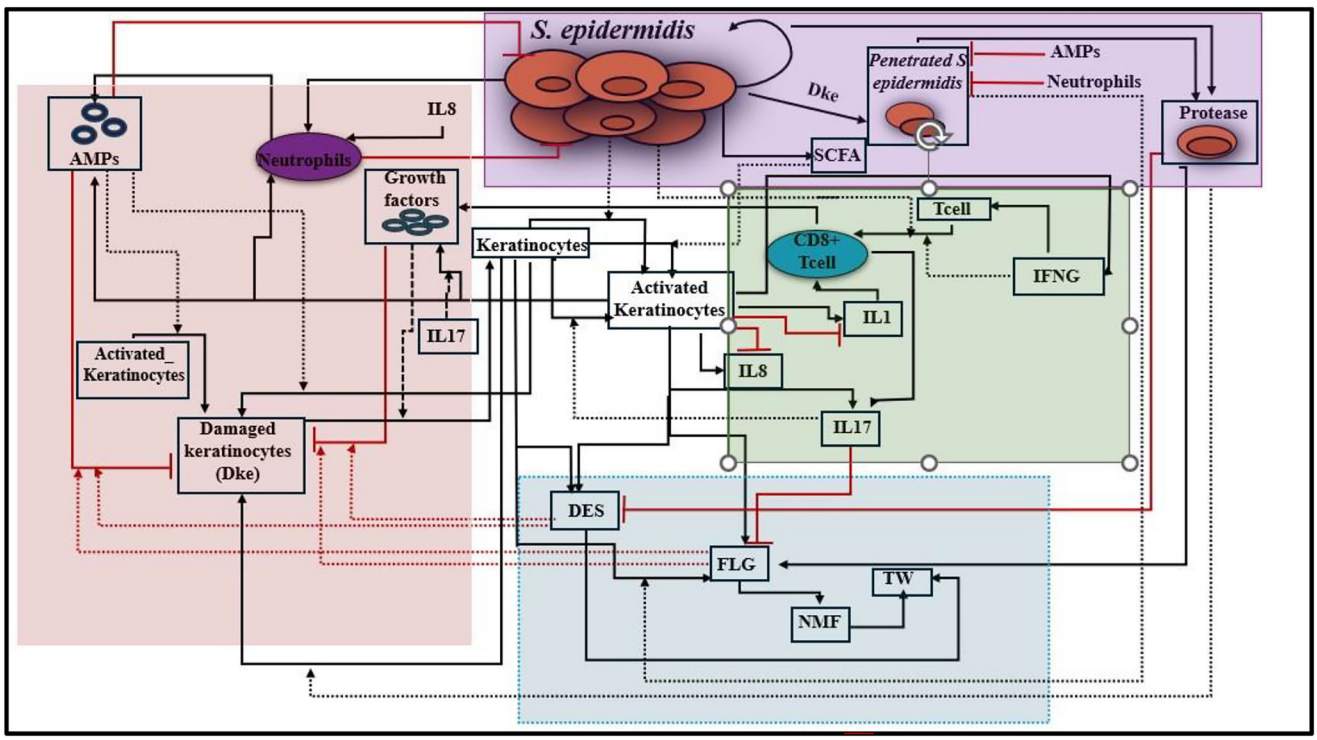

Fig. 1 | A holistic in silico model of skin: the model illustrates the skin microenvironment as a complex network of interactions. In the model, commensal bacteria trigger an immune response via T cells, which activate keratinocytes. These cells sustain both commensal and damaged keratinocytes by synthesizing growth factors, neutrophils, and antimicrobial peptides (AMPs). AMPs, while promoting skin health, also result in damage when the pathogenic community increases. Growth factors, along with filaggrin and desmoglein, an important desmosomal protein, help repair this damage. Filaggrin synthesis is influenced by the microbial population, which in turn regulates Natural Moisturizing Factor. The model visually represents these interactions and pathways like microbial signaling (Purple), immune response (Green), hydration (Blue), and barrier repair (Red). Short Chain Fatty Acids – SCFA, Anti-Microbial Peptides-AMP, Desmoglein- DES, Filaggrin – FLG, Natural Moisturizing Factor – NMF, Total Water Content – TW, Damaged Keratinocytes – Dke.

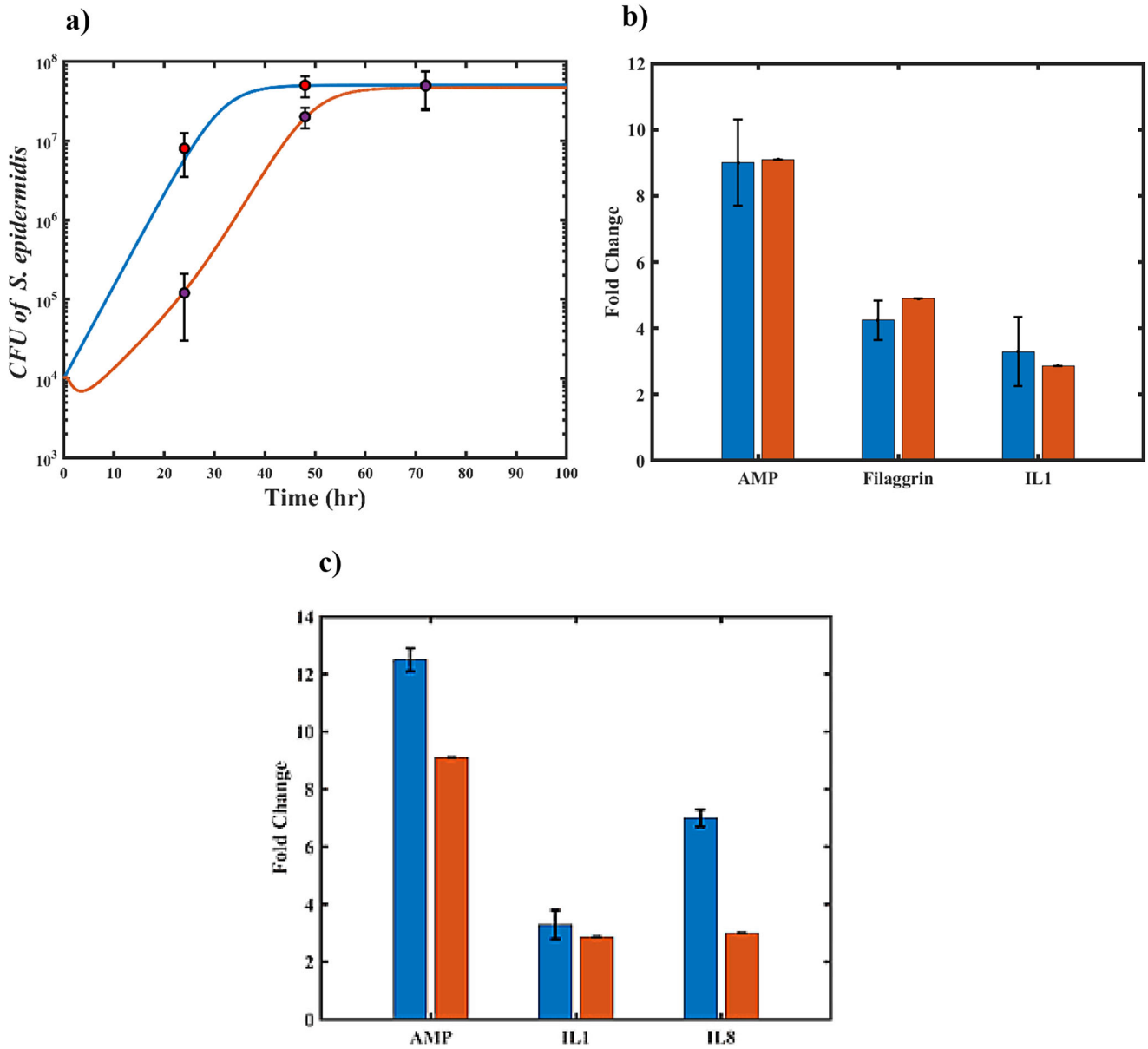

Fig. 2 | Model benchmarking and validation of *S. epidermidis* growth dynamics and AMP, IL1, IL8 responses. a *S. epidermidis* (B1) growth rate in the presence (red) and absence of keratinocytes (blue) with respect to the experimental data (red and purple dot) given at 24th hour and 48th hour **b** Comparison between the predicted (Red) fold change and the observed (Blue) fold change in AMP, IL1, and Filaggrin **c** Model Validation for the variables: Comparison between the predicted (Red) fold change and the observed (Blue) fold change in AMP, IL1 and IL8. Plot Representation: (**a**)Blue- Absence of *S. epidermidis*, Red -Presence of *S. epidermidis*. Blue-Observed, Red -Predicted.

Results

Model Benchmarking and Model Validation

The model development and validation leveraged all relevant published datasets, along with in-house growth curve experiments with commensal on keratinocytes (Supplementary Table 1). The model was benchmarked in stages, wherein the first stage drew upon in vitro experimental data capturing commensal growth in presence and absence of keratinocytes starting with an initial concentration of 1×10^5. Note that in such a scenario, only the variable pertaining to short chain fatty acids (SCFA) and antimicrobial peptides (AMP) were accounted for. The other variables relating to immune response, filaggrin, NMF, damaged keratinocytes and growth factors etc. in the system were not considered. The parameters pertaining to commensal's growth curve, AMP levels, neutrophils and SCFA were benchmarked using dynamic data sets until the saturation of commensal growth. As shown in Fig. 2a, the blue curve represents the stabilized growth rate of *S. epidermidis* without keratinocyte interactions, indicating isolated growth. In contrast, the red curve demonstrates keratinocyte-mediated interactions, showing a lag due to the negative feedback from AMP. The model equations were then simulated to match the immune interactions in keratinocytes, from available literature data focusing on AMP[22]. In the second stage, parameters pertaining to skin microenvironment, such as immune and growth factors and filaggrin, (equations 6–21, Mathematical model; ODEs, Supplementary information) were fitted using literature data, while the parameters pertaining to equation 1–5 were fixed as estimated in stage one). Data from the literature showed that the presence of *S. epidermidis* elicits an immune response in the skin microenvironment. The model recapitulation of the increase in interleukin-1 (IL-1)[11], interleukin-8 (IL-8)[23] and filaggrin levels[24] (Fig. 2b) was achieved by fine-tuning the model parameters. These variables had two time points while certain variables for e.g., interleukin-17 (IL-17), growth factors, desmoglein[25] and neutrophils where only the fold changes were available under two physiological conditions, in such cases, parametric values were set to match the overall physiological trends.

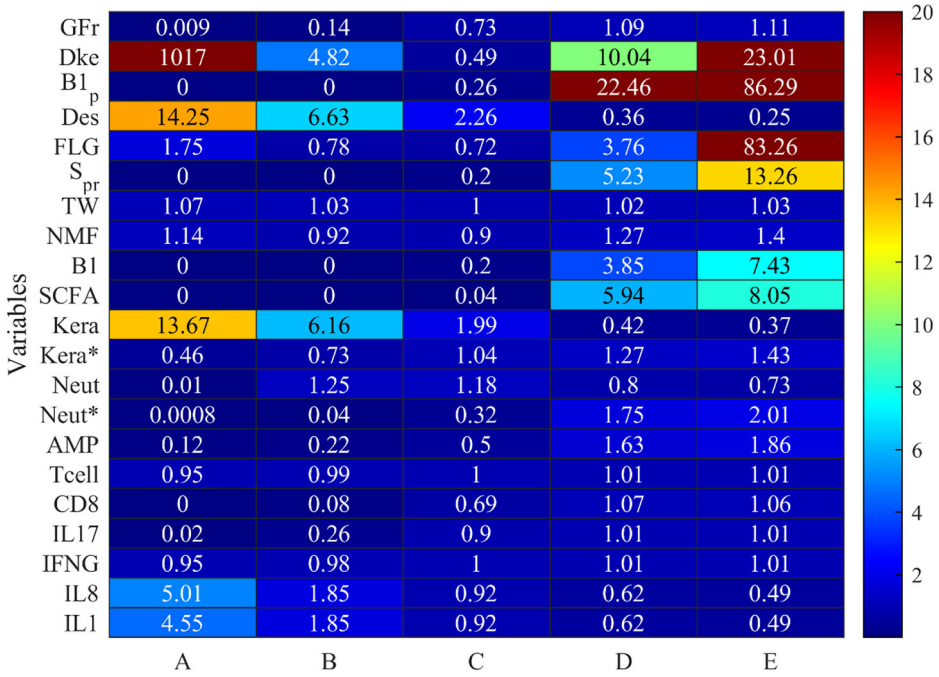

Fig. 3 | Heat map showing steady-state responses of key variables to variations in *S. epidermidis* growth rate. A Heat map representing the steady-state values of variables when only keratinocyte-induced conditions are present. Varying *S. epidermidis* growth rate parameter ($k1_{B1}$) to a fold change of (**B**) 0.19 (**C**) 0.56 (**D**) 1.48 (**E**) 1.67. The growth rate parameter ($k1_{B1}$) value for healthy condition was 0.27 h^{-1}. Plot Representation: (Fold change relative to healthy state, Kera* - Activated Keratinocytes, Neut* - Activated Neutrophil, GFr – Growth Factor, DKe – Damaged Keratinocytes, B1 – *S. epidermidis*, B1p – Penetrated *S. epidermidis*, Spr – *S. epidermidis* Protease).

Following this iterative process of benchmarking to converge on the relevant parametric space accommodating all the above constraints, the model was refined further by quantitative validation against literature datasets of key epidermal markers, including IL-1[23] (3-fold), AMP[26] (10-fold), and IL-8[23] as seen in Fig. 2c. The model could also capture the trends like elevated IL-17[11,22], neutrophil levels[11] and growth factors[26] along with a slight decrease in desmoglein[24]. In addition to quantitative validations, the model successfully predicted qualitative phenotypic observations. Total water content (TW) and natural moisturizing factor (NMF) were maintained at optimal levels due to the predicted increase in filaggrin, while desmoglein remained stable. The initial condition and the parametric value in the model represent the normal (healthy) state of the commensal interaction with the keratinocyte. Supplementary Fig. 1 and 2 showcase the model's ability to stabilize over time and reach a healthy state, demonstrating the model's robustness.

Parameter sensitivity analysis

The certainty of model predictions regarding underlying mechanisms was quantified using parameter sensitivity analysis, which estimates the relative change in system outputs based on input parameters. The method section details the complete metric used for this estimation. Parameters with sensitivity coefficient (S) of 0 indicate that a 100% change in input resulted in no change in output, suggesting no effect on the system. Conversely, $S = 1$ signifies that the output changed proportionally to the input, indicating a substantial impact. Parameters with a $S > 0.5$, regardless of the sign, were considered sensitive, indicating that a 100% change in the parameter value resulted in a 50% or greater change in the output. It was observed that for $S > 0.5$ the physiologically relevant impact on the output variables were observed, such as in the AMP synthesis, therefore, a threshold value of $S = 0.5$ was chosen as the sensitivity cut off. The observed results shown in Supplementary Fig. 3 indicate that the growth of *S. epidermidis* was seen to be highly sensitive ($S = -1.02$) when parameters such as Rate of AMP synthesis by activated keratinocytes ($k6_{AMP}$), Rate of IL8 synthesis by activated keratinocytes ($k14_{IL8}$), and Rate of Neutrophil activation by B1 ($k7_{Neut}$) were increased which highlighted the antimicrobial activity of AMP and neutrophils against *S. epidermidis*. This has further led to a decline in Growth factors ($S = -1.01$, $S = -1.01$, $S = -0.88$), filaggrin ($S = -0.85$, $S = -0.74$,) and thereby an increase in damaged keratinocytes ($S = 1.01$, $S = 1.01$, $S = 0.91$) indicating that these skin immune components associated parameters are notably sensitive for various outputs through the antimicrobial and immune activity. However, certain parameters such as Rate of Desmoglein synthesis by keratinocytes ($k20_{Des}$), Rate of IFNγ synthesis by activated keratinocytes ($k13_{IFN\gamma}$) and Rate of CD8 activation by B1and IFNγ ($k9_{CD8}$) did not change the growth of *S. epidermidis* when increased, but their decrease significantly reduced the commensal growth ($S = 1.02$; $S = 0.94$; $S = 0.83$) indicating the non-linearity of the system. The nonlinear relationship of the parameters $k20_{Des}$, $k13_{IFN\gamma}$, $k9_{CD8}$ was also observed in neutrophil ($S = 0.93$; $S = 0.83$; $S = 0.69$), AMP ($S = 0.65$; $S = 0.53$) levels which decreased, while damaged keratinocytes ($S = -1.02$; $S = -1.01$; $S = -1.01$) and filaggrin ($S = -0.60$; $S = -1.02$; $S = -0.96$) showed an increase. Conversely, the parameters demonstrated linearity with the growth factor levels ($S = 0.98$; $S = 1.02$). This revealed a crucial effect of $k20_{Des}$, $k13_{IFN\gamma}$, $k9_{CD8}$ which influences *S. epidermidis* growth, growth factor production via CD8-IFNγ cross-talk and filaggrin production through IL17 via CD8-IL17 cross talk. Other sensitive parameters include Rate of FLG synthesis by keratinocytes ($k22_{FLG}$). It significantly impacts NMF ($S = 0.94$) by affecting filaggrin synthesis and therefore hydration of skin. Thus, the sensitivity analysis revealed that parameters could elicit differential effects in outputs, demonstrating the robustness of our model in simulating a living system, wherein several biological functions are maintained in rigidness and some processes adapt as per the changes. This could be observed in our skin model where some parameters are very sensitive while others do not change significantly, which represents a homeostatic state in a healthy skin barrier.

Simulation of Skin microenvironment in response to the commensal *S. epidermidis*

The healthy state of the model was perturbed by removing the commensal interactions to examine the commensal role in healthy skin. The observed changes were given in terms of fold change in comparison to a healthy state (Fig. 3). In the absence of *S. epidermidis*, the decrease in the activation of keratinocytes to 0.46-fold results in a massive increase in damaged keratinocytes. Due to the lack of microbial interactions, there is a decline in CD8 + T cells and IL17 levels, nearly reaching zero, as depicted in Supplementary Fig. 4a. The synthesis of growth factors, mediated by IL17 and CD8 + T cells, was reduced by 99% relative to the presence of commensal (Supplementary Fig. 4b). The reduction significantly hampered the repair of

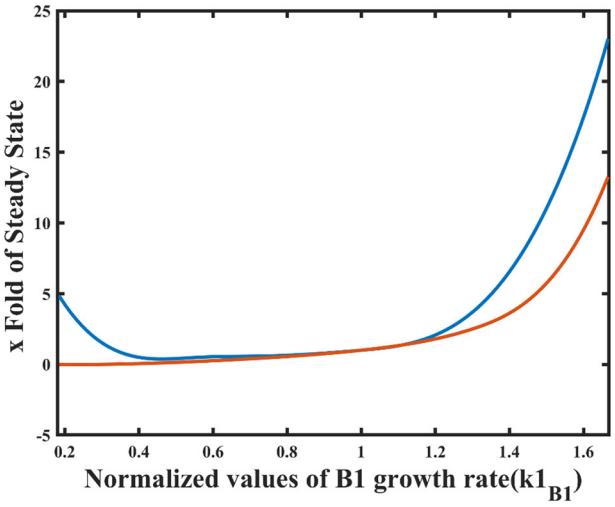

Fig. 4 | The steady-state values of damaged keratinocytes and S protease in relation to the corresponding commensal growth rate (*k*1B1) values. Plot Representation: (Fold change relative to healthy state, (a) Blue- Damaged keratinocytes, Red – S Protease).

damaged keratinocytes, resulting in a continuous accumulation of damaged keratinocytes by 1017-fold over time (Fig. 3 column A, Supplementary Fig. 4e). With the loss of microbial interaction, activated neutrophils decreased and consequently reduced AMP levels to 0.12-fold. In response to the loss of S protease interaction, desmoglein synthesis increased by 13% and a slight increase in filaggrin and subsequent water content, which can be an attempt to revive the repair process. This disruption underscored the impaired epidermal homeostasis in the absence of commensal microorganism, highlighting the crucial role of commensal-keratinocyte interactions, mediated through the immune response. This demonstrated that *S. epidermidis* exerts a beneficial effect on the skin through upregulation of pro inflammatory signals and antimicrobial peptides respectively. These physiological response in the skin niche has been captured both quantitatively and qualitatively in our model, showing the alignment with real world data[22,27].

The impact of *S. epidermidis* growth rate on skin microenvironment

As observed in the previous results section, the presence of commensal microorganisms plays a vital role in maintaining the delicate homeostasis of the skin environment. This elicits the question on the bacterial load necessary to sustain this equilibrium and how deviations from these levels can disrupt homeostasis. To understand this impact, we perturbed the growth rate parameter (*k1*B1) within the range of 0.05 – 0.45 h^{-1} (0.19–1.67-fold), as depicted in the respective columns of Fig. 3. Fig. 3 column B shows a lowered growth rate (*k1*B1) of 0.19-fold, reduced the activated keratinocytes (0.73-fold) thereby decreasing the growth factors (0.14-fold) and increasing the damaged keratinocytes (4.82-fold). We observed in Fig. 3 column C that increasing growth rate parameter by 0.56-fold does not significantly differ from the healthy state, indicating commensal behaviour. But an increased *S. epidermidis* proliferation to around 3.85 and 7.43 folds (Fig. 3 column D & E) heightened the protease activity (5.23 and 13.26 folds) followed by an increase of 22 and 85 folds in the penetrated population (Fig. 3 column D & E). This surge in protease activity exacerbated the tissue damage (23-fold). This indicated that only at a certain range of growth rate, *S. epidermidis* exhibits commensal properties. To predict the critical bounds of the range, the growth rate values against the corresponding steady-state values of Damaged keratinocytes and S protease were checked as depicted in Fig. 4. The data shows that when the growth rate falls below 0.1 h^{-1} (0.4-fold), damage increases even with minimal AMP. This is due to the loss of activation of keratinocytes via microbial interaction, which is essential for synthesizing repair components like growth factors. A growth rate above 0.33 h^{-1} (1.2-fold) facilitates higher penetration through excessive protease, potentially transitioning the *S. epidermidis* to a pathogen. These overall observations highlight a key finding of our study: *S. epidermidis* maintains its role as a commensal when its growth is kept within a critical window.

The model provides a basis for the dual role as explored in the reviews by Brown & Horswill, 2020 and Nguyen et al., 2017[8,12].

The impact of AMP and immune killing of *S. epidermidis* on Skin Microenvironment

Conditions such as immunocompromised states can significantly weaken the immune response to commensal microorganisms, altering the dynamics and mechanisms that sustain commensal populations. To investigate the effects of such conditions on commensal growth, an immunocompromised condition was simulated in the model by reducing antimicrobial peptide (AMP) production and immune-mediated killing by 10-fold. Due to the reduced immune activity, the healthy commensal population is now perturbed, surging up to 10^5-fold. (Supplementary Fig. 5a). The microbial protease from the commensal targets desmoglein, decreasing its levels and resulting in deeper skin infiltration. The increase in IL-8 and IL-1 levels (Supplementary Fig. 5f, Supplementary Fig. 5c) further intensifies the skin inflammation and the epidermal damage (Supplementary Fig. 5e). However, the system doesn't settle at these states, indicating absence of monotonic progression from the initial to a steady state instead, exhibits oscillatory behaviour. Generally, the characteristics and amplitude of oscillations depend on negative feedback and time delays. The tuning mechanism for these sustained oscillations involved the neutrophil negative feedback, yet the key mechanism was unclear. To understand feedback mechanisms, the phase plane stimulation-response curve (Fig. 5a) was studied, which represents the steady-state response of neutrophils to the activated keratinocytes. As shown in Fig. 5a, the system starts at a value of 1 and eventually progresses towards cyclic behavior, indicating that an increase in activated keratinocytes leads to an increase in neutrophils. The delay in this feedback from the neutrophil loop prevents the system from settling into a steady state, causing a cyclic pattern hence maintaining a continuum of oscillations. As a physiological response this validates the point that neutrophils play a particularly important role in the immune response during *S. epidermidis* associated infection[8]. Notably, the activation of keratinocytes is initiated by the commensal, which triggers additional reinforcement mechanisms, such as growth factor production that gradually reduces damage. Consequently, the response of the commensal to damaged keratinocytes, as depicted in Fig. 5b, also exhibits limit cycle characteristics. This visualization captures the interplay between the skin's immune system and the maintenance of commensal populations at optimal levels, mediated by neutrophils and the innate immune response, alongside the ongoing damage. Additionally, conditions like immunocompromise, which can lead to sepsis, further exacerbate this damage. Overall, the delayed negative feedback is the primary driver of the system's spikes and sustained oscillations indicating the delay in immune response is critical to balancing the transition between sepsis and homeostasis. This approach allowed the investigation of how the skin's immune response influences the maintenance of commensal populations under impaired immune function.

The oscillatory behaviour exhibited by the immunocompromised system when checked for the range of growth rate showed a maximum amplitude of 10^7-fold for protease (Fig. 5c) and the resultant damage to 10^2 -10^3-fold (Fig. 5d) respectively. The lower amplitude of the same is indicated by dotted lines. Comparing with the healthy condition (Fig. 4), it is evident that under an immunocompromised condition, even a minimal growth rate of commensal is sufficient to shift its behaviour to a pathogenic characteristic causing damage to the skin microenvironment. Conversely, increased immune sensitivity, such as in autoimmune conditions, results in the killing of commensal leading to a no- commensal state (Supplementary Fig. 6). Enhanced immune sensitivity does not bring any oscillations within the system, as the commensal population drops too low to restore balance, highlighting the need for homeostasis within the environment. The initial damage that occurs with the excessive immune condition persists at the 7-fold

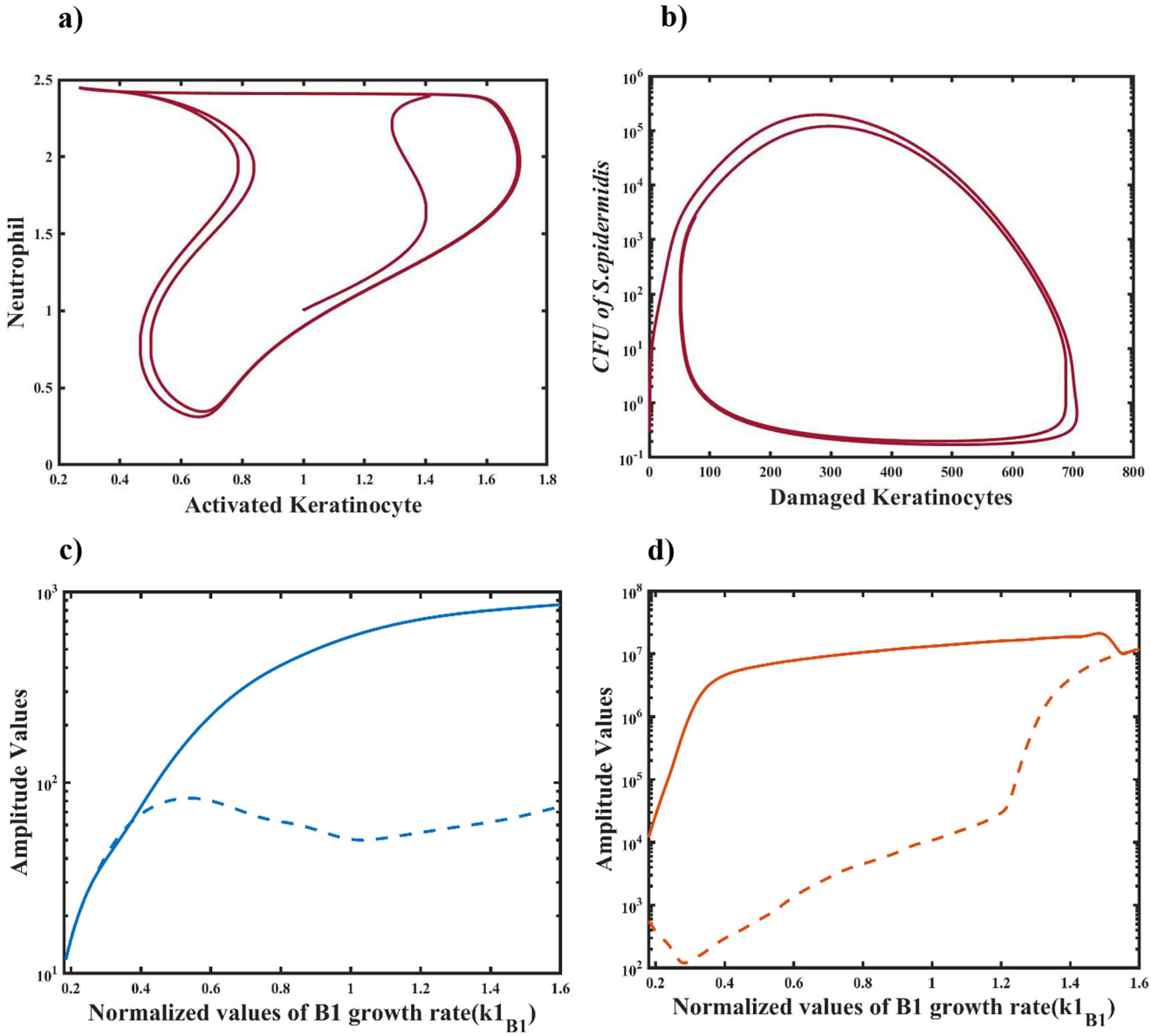

Fig. 5 | Phase plane analysis of the state variables and their amplitude responses under varying immune sensitivity. Phase plane plot of (**a**) neutrophil levels and activated keratinocytes (**b**) *S. epidermidis and* damaged keratinocytes. The maximum and minimum amplitude values of damaged keratinocytes and S Protease corresponding to commensal growth rate ($k1_{B1}$) values (**c**) S protease response for reduced immune sensitivity against commensal, (**d**) damaged keratinocyte response for reduced immune sensitivity against commensal. Plot Representation: ((**d**)Blue-Damaged keratinocytes, (**c**) Red – S Protease; Solid line- Maximum amplitude, Dotted lines – Minimum amplitude).

higher state (Supplementary Fig. 6) as with loss in repair mechanism. These predictions point out that conditions such as reduced immunity (higher growth rate) or excessive immune reaction (lesser growth rate) can transition *S. epidermidis* to either an infectious pathogen and cause loss of balance in epithelial flora. Thus, through the in silico skin model, we could get insights into the fine regulation of the commensal and the immune response to maintain the symbiotic relationship in the skin microenvironment.

A comparative evaluation of epidermal barrier integrity with and without *S. epidermidis*

A dysregulated skin barrier marks the onset for the sequelae of pathological skin conditions. Perturbations to the barrier can range from minor cues to extensive cutaneous damage. The complex dynamic system of the skin actively works to restore its integrity. To visualize the cellular interaction involving the commensal participation in the restoration process, a disrupted barrier scenario was set up in the model by increasing the damaged keratinocytes of the model (Dke) to a concentration of 10^4 (Supplementary Fig. 7a). The increased damage has been done to simulate a physiological scenario where barrier integrity is compromised as in a mechanical abrasion which disturbs the barrier integrity triggering a response process, as evidenced by multiple studies in vitro[28]. The damaged barrier disruption resulted in a temporary rise in the penetrated population (penetrated population B1) as depicted in Supplementary Fig. 7f, and a subsequent decline in commensal growth. In the presence of commensal, several changes occur such as an increase in activated keratinocytes (Kera*) as shown in Fig. 6, along with filaggrin[29] (10.47-folds), and AMP[30] (2.29-folds) as a response to mitigate the damage levels and eventually bringing it down to 8.86-fold within 2 h (Fig. 6 column A) ensuring a healthy steady state (Fig. 6 column C, Supplementary Fig. 7a). Supplementary Figs. 7c and g, demonstrate the dynamics of filaggrin and AMP, both of which rise in response to the barrier damage and finally attain a steady state along with other variables. The commensal population eventually stabilizes within 40

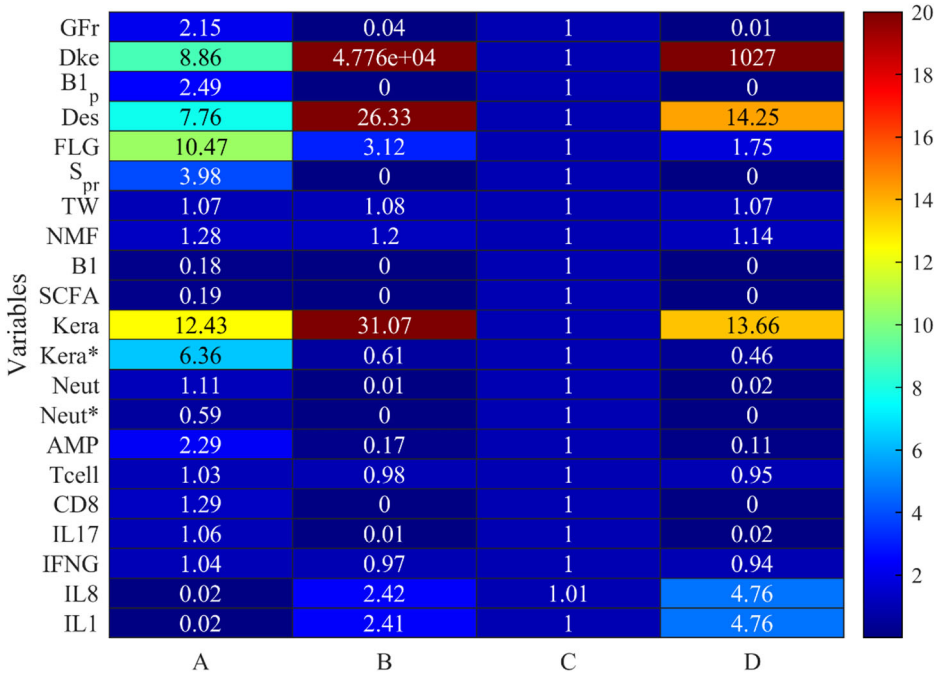

Fig. 6 | Heat map showing steady state values of variables for barrier disruption condition in presence and absence of S. epidermidis. A Value at 2nd hour in presence of *S. epidermidis* (**B**) Value at 2nd hour in absence of *S. epidermidis* (**C**) Steady State Value in presence of *S. epidermidis* (**D**) Steady State Value in absence of *S. epidermidis*. Plot Representation: (Fold change relative to healthy state, Kera* - Activated Keratinocytes, Neut* - Activated Neutrophil, GFr – Growth Factor, DKe – Damaged Keratinocytes, B1 – *S. epidermidis*, B1p – Penetrated *S. epidermidis*, Spr – *S. epidermidis* Protease).

to 60 h (Supplementary Fig. 7b). In contrast, the absence of commensal causes the AMP and growth factors to decrease by 0.11 and 0.01-folds (Fig. 6 column D), attributed to the loss of CD8-mediated interaction and neutrophil activation (Fig. 6 column D). Consequently, restoration of barrier integrity is significantly delayed (Fig. 6 column B) thereby leaving the damaged cells 1017-fold higher (Fig. 6 column D, Supplementary Fig. 7a) than a healthy state. The high epidermal damage is also accompanied by severe inflammation as seen by an increase in cytokines such as IL1, IL8 (4.76-fold), and the protease target, desmoglein (14.25-fold) in an over-expressed state (Fig. 6 column D), aggravating the barrier damage. Figs. S8b and d validate the observed delay in response to varying degrees of barrier disruption. They demonstrate a 1000-fold difference in the time required for damaged keratinocytes to reach a steady state, whereas, in the presence of commensal, the maximum time observed was 9 h (Supplementary Fig. 8a, c). The growth factor-mediated mechanism of tissue restoration was seen to be crucial and dominant in this process. Supplementary Fig. 9 provides data for this observation. Thus, the model has captured the beneficial influence of *S. epidermidis* in maintaining barrier integrity, when the barrier breach occurs further affirming its strong role in maintaining skin functionality as evidenced by multiple studies[22,27] and indicated the alignment of the model to real world trends.

The effect of filaggrin mutation on epidermal barrier repair

Filaggrin is a well-studied protein that contributes to epidermal barrier integrity and skin hydration, and its mutation is known to elevate the risk of epidermal damage[16,17]. To capture the mechanism by which the filaggrin mutation influences the commensal dynamics in the skin, a perturbation of the filaggrin knockout is replicated by making FLG zero in the model. Filaggrin-deficient skin becomes susceptible to commensal penetration, increasing it by 43.07- -fold (Fig. 7 column A) and the resultant protease (3.54-fold), resulting in a 128-fold increase in damaged keratinocytes (Fig. 7 column A, Supplementary Fig. 10e). Furthermore, the commensal population in the skin was eliminated by AMP action (Fig. 7 column A, Supplementary Fig. 10c) subsequently reducing the neutrophil levels to 0.28-fold. (Fig. 7 column A). Loss of microbial interaction with CD8 cells causes the growth factor decline (Supplementary Fig. 10f), leading to the continuous accumulation of damaged cells (Supplementary Fig. 10e, Fig. 7 column A). With filaggrin reduction, a significant decline in total water content to 0.47-fold (Fig. 7 column A, Supplementary Fig. 10a) consistent with loss of hydration due to the complete deterioration of Natural Moisturizing Factor (Supplementary Fig. 10b, Fig. 7 column A) within 3–4 h aligning with the findings from De & Handa, 2012; Jakasa et al., 2011; Kezic et al., 2011[16,18,29,31]. Overall, it is evident that with filaggrin knockdown, barrier functionality and skin immune response are severely compromised. Through model perturbation, we were able to simulate the physiological effect of filaggrin loss of skin.

The effect of filaggrin mutation on damaged skin (Dke=10^4) was evaluated as well. The damaged keratinocytes remained elevated with filaggrin mutation (Supplementary Fig. 11a, Fig. 7 column B). This is because of the decline in commensal (Supplementary Fig. 11b, Fig. 7 column B), leading to a reduction in AMP (0.7-fold) and growth factor (0.09-fold), through the loss of CD8 (0.01-fold) and IL17 (0.03-fold) (Fig. 7 column B). This left the damage unresolved and in a heightened state. Additionally, Supplementary Figs. 11e, f, and Fig. 7 column B indicate reduced natural moisturizing factors and water content, signifying skin dryness. This underscores the crucial role of filaggrin in maintaining a healthy, moisturized state of the skin and its impact on commensal dynamics.

Discussion

Epidermal skin barrier is constantly exposed to environmental stress. The skin microbiome exerts a symbiotic relationship by relaying multiple signals to maintain barrier integrity. Among a myriad of microbial species inhabiting the skin, *S. epidermidis* is one of the extensively studied commensals for its beneficial effects on the skin microenvironment[32–34]. To understand the unique role of commensals in the skin, the present study investigated the effect of commensal growth dynamics on epidermal barrier integrity and response in immunocompromised and weakened skin barrier with the filaggrin mutation.

Through the in silico model, *S. epidermidis*-keratinocytes interactions and the consequences of commensal growth were simulated. For this, the model was validated using *S. epidermidis* population data from growth curve experiments (Supplementary Table 1) followed by an accurate depiction of skin immune responses, highlighting *S. epidermidis's* pivotal role in priming the system (Fig. 2a). From the literature data, an increased hBD (human beta-defensin) expression in keratinocytes in the presence of *S. epidermidis* was observed which matched with our in silico model prediction of

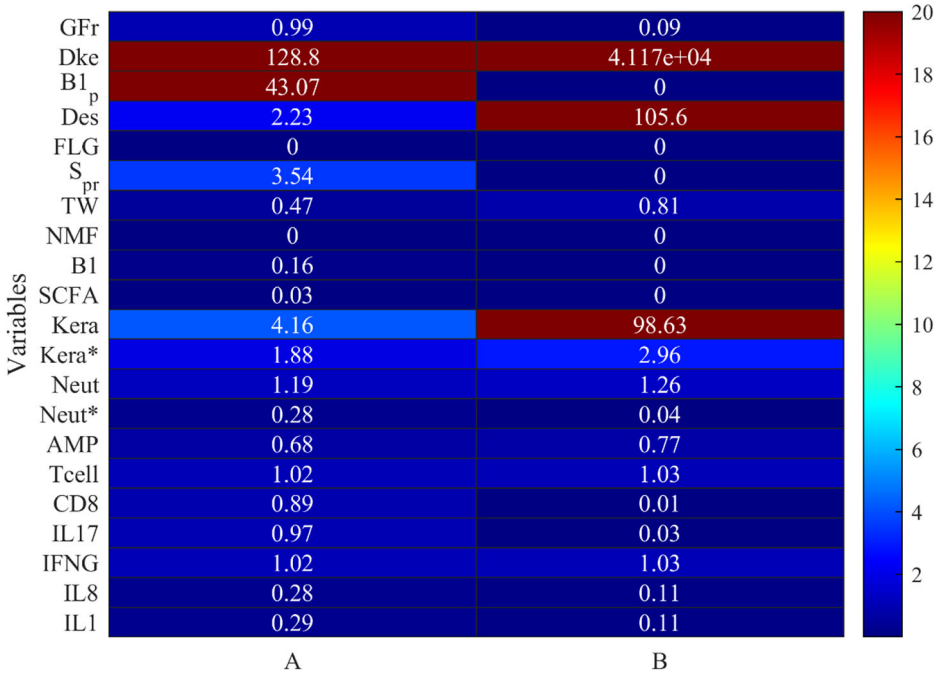

Fig. 7 | Heat map showing steady-state variable profiles at 72 hours under filaggrin mutation conditions. A Steady-state values of variables at 72 hours under normal skin conditions with filaggrin mutation (**B**) Steady-state values of biological at 72 hours under damaged skin conditions with filaggrin mutation. Plot Representation: (Fold change relative to healthy state, Kera* - Activated Keratinocytes, Neut* - Activated Neutrophil, GFr – Growth Factor, DKe – Damaged Keratinocytes, B1 – S. epidermidis, B1p – Penetrated S. epidermidis, Spr – S. epidermidis Protease).

increased antimicrobial peptides (AMPs) as seen in Fig. 2b in the Results section 'Advancing Model Accuracy: Model Benchmarking and Model Validation'. The qualitative observations in the model such as enhanced inflammatory signals and growth factors, indicate immune activation, while also upregulating hydration markers like filaggrin, thereby supporting epidermal homeostasis in the presence of commensals. These align with observation in recent studies such as Ommori et al., 2024; Williams et al., 2024 highlighting role of commensal in the skin's defense against external insults or injury. These findings further support the model's ability to capture the dynamic interplay between the skin, immune responses, and growth factors in maintaining a healthy epidermal barrier, characterized by basal levels of growth factors, cytokines, and antimicrobial peptides (AMPs) in the presence of *S. epidermidis*.

In a healthy condition, commensals co-exist with the resident immune cells of the maintaining overall skin health by maintaining the barrier integrity. These model observations are demonstrated in Results section 'Simulation of Skin microenvironment in response to the commensal *S. epidermidis*' Figs. 3 and 4. The tolerance towards the commensal colonization is complexly regulated by regulatory T cells (Treg) within a threshold, which allows the maintenance of the relative abundance of *S. epidermidis* in an optimal level[32–34]. But certain conditions such as barrier disruption or genetic mutations such as filaggrin can lower the threshold for commensal population to overgrow resulting in impaired barrier function[16,35]. A recent study by Khadka et al.[36], confirms that the commensal exacerbates inflammation in a barrier disruption model thus emphasizing the host barrier context and the permissive window of commensal growth. Our model reflects the transitional state beyond which commensal becomes a pathogen as observed in Fig. 4. Such increased abundance of *S. epidermidis* correlates with diseases like Atopic dermatitis, where it can elicit inflammatory responses[24,37]. A greater understanding of this threshold can help in identifying skin types which are infection prone and can help in designing tailored skin regimen for sensitive skin conditions.

Further, our skin model investigated the effect of commensal growth dynamics in an immunocompromised condition, the results of which can be seen in Results section 'The impact of AMP and immune killing of *S. epidermidis* on Skin Microenvironment', Fig. S5a–e. As per the findings of (Natsis & Cohen, 2018), an immunocompromised condition makes skin vulnerable leading to infections by the commensal S. *epidermidis* itself[38]. The model was able to capture the detrimental effects of *S. epidermidis*. Disruption to the intact skin is a conducive environment for the transition of commensal to pathogen through higher colonization causing damage to the keratinocytes. In a study by Oh et al., 2013, an increased permissiveness and microbial alterations is observed in patient immunocompromised skin leading to greater microbial colonization[39]. The system tries to counter this overgrowth by the feedback interactions from the immune cells in the skin which leads to oscillatory behaviour starting with a transient sudden increase of immune cells infiltration followed by dampening of the response (Fig. 5a–d). Immune response is characterized by oscillatory behaviour starting with a transient sudden increase of immune cells infiltration followed by dampening of the response when the pathogen load clears[40]. The autoimmune disorders model by Valeyev et al.[41] demonstrates oscillatory immune cell behavior, supporting our findings that a compromised skin barrier triggers pathogenic disruptions and inflammatory responses, offering valuable insights into the mechanisms driving cutaneous flares. The increase in neutrophils and the delayed negative feedback towards the rising commensal level leads to cyclic trends. Studying the aberrant oscillatory dynamics in immune cells and other skin components can provide greater diagnostic significance for chronic skin diseases like Atopic dermatitis and psoriasis where skin immune is derailed.

The model also demonstrated a scenario of heightened immune response by neutrophils and AMPs on commensal. This parallels with autoimmune skin diseases such as psoriasis[42], characterized by a higher expression of AMPs which triggers multiple cutaneous inflammatory pathways resulting in skin barrier damage further exacerbated by the loss of *S. epidermidis* interactions that help maintain immune balance. Hence, the study effectively captures the key cross-talk among the skin components and the commensal highlighting the dual behavior of *S. epidermidis* depending on the skin microenvironmental changes.

In a healthy condition, commensals co-exist with the resident cells of the immune system maintaining overall skin health by maintaining the barrier integrity. The mechanisms ensuring the immune tolerance are exceedingly complex, involving the interplay of diverse regulatory mechanisms. The threshold represents the level of immunogenic stimulation required to elicit an immune response[43] which is observed in Fig. 4, where beyond a critical point, commensal transitions into pathogenic behavior. An immunocompromised condition makes the skin vulnerable, reducing the threshold of immunogenic response. For e.g., presence of a filaggrin mutation disrupts the stratum corneum integrity lowering skin

inflammatory thresholds leading to higher antigen penetration[24]. A better understanding of immune regulatory thresholds may hold greater value in designing better therapies for skin barrier conditions.

Filaggrin mutations have long been linked to compromised barrier function and increased susceptibility to various diseases such as Atopic dermatitis[13,44,45]. Our investigation into the impact of filaggrin mutations on both healthy and barrier-disrupted skin showed that the antimicrobial activity decreased with filaggrin mutation as reported by Nath et al.[17]. We simulated the effect of filaggrin mutation by a virtual knockdown of FLG. This led to a loss of moisturizing effect as observed in decreased NMF in the Results section 'The effect of Filaggrin Mutation on epidermal barrier repair', Fig. 7. This led to more penetration due to protease action present in the skin barrier leading to a barrier breach triggering AMPs for antimicrobial action against the commensal population. Our model predicts that a filaggrin deficit skin characterized by a dry skin and higher protease action becomes hostile for normal commensal colonization, triggering a higher epidermal damage as seen in Fig. 7 A. The greater penetration and abnormal commensal -immune response is also seen in an in vivo murine study where filaggrin null mice exhibit an abnormal early life skin response in barrier disruption scenario[46,47].

The present work demonstrated the unique features of commensal-host interrelations and how coordinated regulation of commensal *S. epidermidis*, and the skin cells such as neutrophils, cytokines and growth factors cross talks are required for a balanced and functional skin environment. The model not only effectively captured essential biological responses to commensal colonization, such as AMP production and inflammation, but also provided key predictive hypotheses which can be studied further experimentally. The impact of filaggrin mutation on commensal behaviour has not been previously studied, though several studies on the impact of filaggrin loss on *S. aureus* colonization exist. Our findings reveal a dysregulated immune response driven by increased barrier permeability due to filaggrin loss, underscoring the need for experimental validation. Similarly, though oscillations in inflammation have been modelled in other diseases like rheumatoid Arthritis[48] and psoriasis[49], our model predicts that aberrant oscillations are generated in an immunocompromised skin which can again be experimentally validated for better understanding of cutaneous inflammatory responses. Future experiments focusing on quantifying threshold dynamics and commensal behavior based on our model predictions can enhance our understanding the commensal behaviour and interplay along with other pathogens like *Staphylococcus aureus* and *Cutibacterium acnes* in inflammatory skin conditions like Atopic dermatitis and acne respectively.

While many studies have examined the impact of microbes on skin health, a systems biology approach such as this may help in deciphering the complex dynamics within the skin environment. We believe that this model can be utilized to explore skin dysbiosis which is the basis of many cutaneous diseases and also in the rational designing of therapeutic strategies for skin.

Methods

Mathematical modelling and simulation

The quantitative description of the model was set by ordinary differential equations (ODEs) which were formulated using mass balance and Hill's equation representing the multiple interactions and the feedback within the system (detailed in the Supplementary information). It was subsequently visualized using Ode45 solver in MATLAB. Following parameter optimization, the model's suitability was evaluated by achieving a controlled, non-zero steady state that reflects the healthy condition.

Advancing model accuracy: parameter sensitivity analysis

In our study, we worked with approximately 129 model parameters, some of which were fitted based on experimental data, while others were assumed based on known physiological outcomes. Each parameter within the system was analyzed to understand its distinct role in the overall operation. The comprehensive list of all parameters and their corresponding values can be found in the (Supplementary Tables 3 and 4). A defined quantitative metric to evaluate the change in the system variables, namely, *S. epidermidis*, Growth Factor, AMP, Neutrophil, Damaged Keratinocytes, Filaggrin (termed as outputs, O) with a change in the parameter values (termed as Input, I) ranging from 10% to 100%, considering both increase and decrease facilitated the understanding on the sensitive parameters along with the relationship between input and output. The sensitivity coefficient '*S*' was quantified by comparing the relative change in the output (O) to its mean value with the relative change in the input (I) parameter to its mean value. This metric measures the system's responsiveness to variations in the input parameter. Mathematically '*S*' is expressed as:

$$\frac{O}{O} = \frac{\Delta O}{\frac{O_f+O_i}{2}} = \frac{o_f - o_i}{\frac{O_f+O_i}{2}}, \frac{I}{I} = \frac{\Delta I}{\frac{I_f+I_i}{2}} = \frac{I_f - I_i}{\frac{I_f+I_i}{2}}$$

$$S = \frac{\partial O}{\partial I} \cdot \frac{\bar{I}}{\bar{O}}$$

therefore,

$$S = \frac{o_f - o_i}{o_f + o_i} \cdot \frac{I_f + I_i}{I_f - I_i}$$

The subscript i indicates the initial value, and f represents the final value obtained after the parameter change.

Cell culture experiments

Culturing of HaCaT. HaCaT cells (Cat No. T0020001, Addexbio) were grown and maintained in high glucose DMEM (Cat. No. AL219A, Himedia) supplemented with 0.03 mM Calcium chloride (C5670, Sigma), 1 mM sodium pyruvate, and 10% FBS (Fetal Bovine Serum) at 37 °C with 5%CO2. 80% confluent cells were trypsinized and plated in 24 well plates at a density of 80,000 cells/well. Post confluency, the cells were differentiated for 72 h by adding a differentiation medium containing 1.4 mM Calcium chloride.

Culturing of *S. epidermidis*. *S. epidermidis* (ATCC 12228) was subcultured from glycerol stock on a TSA plate and incubated at room temperature at 37 °C for 20 h, the OD was adjusted accordingly and used for growth experiments.

Growth of *S. epidermidis* on HaCaT. After differentiation of HaCaT, OD of *S. epidermidis* was adjusted to 0.2 and the cells were further diluted and 10^4 CFU was added on to HaCat wells and in wells with no HaCaT cells, the plates were incubated at 37 °C with 5% CO2 for 24 and 48 h, the growth of *S. epidermidis* was enumerated by plating them on TSA (BD Cat log- 236950) plates. The colonies after 24 h were counted, and number of CFU/ml of *S. epidermidis* was plotted against the time of incubation.

Data availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Received: 29 August 2024; Accepted: 14 April 2025;
Published online: 07 May 2025

References

1. Abdallah, F., Mijouin, L. & Pichon, C. Skin immune landscape: inside and outside the organism. *Mediators Inflamm.* **2017**, 5095293 (2017).
2. Park, Y. J., Kim, C. W. & Lee, H. K. Interactions between host immunity and skin-colonizing staphylococci: no two siblings are alike. *Int. J. Mol. Sci.* **20**, 718 (2019).
3. Ann, Q. Neutrophil Extracellular Traps: As Antimicrobial Peptides. *Oral. Rehabilitation Dent.* (2019).
4. Ohnemus, U. et al. Regulation of epidermal tight-junctions (TJ) during infection with exfoliative toxin-negative Staphylococcus strains. *J. Investig. Dermatol.* **128**, (2008).

5. Piipponen, M., Li, D. & Landén, N. X. The immune functions of keratinocytes in skin wound healing. *Int. J. Mol. Sci.* **21**, 8790 (2020).
6. Harder, J., Gläser, R. & Schröder, J. M. Human antimicrobial proteins – effectors of innate immunity. *J. Endotoxin Res.* **13**, 317–338 (2007).
7. Nakamizo, S. et al. Commensal bacteria and cutaneous immunity. *Semin. Immunopathol.* **37**, 73–80 (2015).
8. Nguyen, T. H., Park, M. D. & Otto, M. Host response to Staphylococcus epidermidis colonization and infections. *Front. Cell. Infect. Microbiol.* **7**, 90 (2017).
9. Zheng, Y. et al. Commensal Staphylococcus epidermidis contributes to skin barrier homeostasis by generating protective ceramides. *Cell Host Microbe* **30**, 301–313 (2022).
10. Nakatsuji, T. et al. Staphylococcus aureus Exploits Epidermal Barrier Defects in Atopic Dermatitis to Trigger Cytokine Expression. *J. Investig. Dermatol.* **136**, 2192–2200 (2016).
11. Williams, M. R. et al. Staphylococcus epidermidis activates keratinocyte cytokine expression and promotes skin inflammation through the production of phenol-soluble modulins. *Cell Rep.* **42**, 113024 (2023).
12. Brown, M. M. & Horswill, A. R. Staphylococcus epidermidis-Skin friend or foe? *PLoS Pathog.* **16**, e1009026 (2020).
13. Stefanovic, N. & Irvine, A. D. Filaggrin and beyond: new insights into the skin barrier in atopic dermatitis and allergic diseases, from genetics to therapeutic perspectives. *Ann. Allergy Asthma Immunol.* **132**, 187–195 (2024).
14. Riethmuller, C. et al. Filaggrin breakdown products determine corneocyte conformation in patients with atopic dermatitis. *J. Allergy Clin. Immunol.* **136**, 1573–1580 (2015).
15. Armengot-Carbo, M., Hernández-Martín, A. & Torrelo, A. The role of filaggrin in the skin barrier and disease development. *Actas Dermosifiliogr.* **106**, 86–95 (2015).
16. De, D. & Handa, S. Filaggrin mutations and the skin. *Indian J. Dermatol. Venereol. Leprol.* **78**, 545–551 (2012).
17. Nath, S. et al. Dysbiotic Lesional Microbiome With Filaggrin Missense Variants Associate With Atopic Dermatitis in India. *Front. Cell Infect. Microbiol.* **10**, 570423 (2020).
18. Jakasa, I. et al. Skin barrier function in healthy subjects and patients with atopic dermatitis in relation to filaggrin loss-of-function mutations. *J. Invest. Dermatol.* **131**, 540–542 (2011).
19. Tanaka, R. J. & Ono, M. Skin disease modeling from a mathematical perspective. *J. Investig. Dermatol.* **133**, 1472–1478 (2013).
20. Yue, R. & Dutta, A. Computational systems biology in disease modeling and control: review and perspectives. *npj Syst. Biol. Appl.* **8**, 37 (2022).
21. Thibault Greugny, E., Fages, F., Radulescu, O., Szmolyan, P. & Stamatas, G. N. A skin microbiome model with AMP interactions and analysis of quasi-stability vs stability in population dynamics. *Theor. Comput. Sci.* **983**, 114294 (2024).
22. Naik, S. et al. Commensal-dendritic-cell interaction specifies a unique protective skin immune signature. *Nature* **520**, 104–108 (2015).
23. Duckney, P. et al. The role of the skin barrier in modulating the effects of common skin microbial species on the inflammation, differentiation and proliferation status of epidermal keratinocytes. *BMC Res Notes* **6**, 474 (2013).
24. Cau, L. et al. Staphylococcus epidermidis protease EcpA can be a deleterious component of the skin microbiome in atopic dermatitis. *J. Allergy Clin. Immunol.* **147**, 955–966 (2021).
25. Landemaine, L. et al. Staphylococcus epidermidis isolates from atopic or healthy skin have opposite effect on skin cells: potential implication of the AHR pathway modulation. *Front. Immunol.* **14**, 1098160 (2023).
26. Ommori, R., Shinkuma, Satoru & Asada, Hideo Staphylococcus epidermidis augments human β-defensin-3 synthesis through the transforming growth factor alpha-epidermal growth factor receptor cascade. *J. Dermatol. Sci.* **116**, 34–40 (2024).
27. Lai, Y. et al. Activation of TLR2 by a small molecule produced by staphylococcus epidermidis increases antimicrobial defense against bacterial skin infections. *J. Investig. Dermatol.* **130**, 2211–2221 (2010).
28. Hughes, A. J., Tawfik, S. S., Baruah, K. P., O'Toole, E. A. & O'Shaughnessy, R. F. L. Tape strips in dermatology research. *Br. J. Dermatol.* **185**, 26–35 (2021).
29. Archer, N. K. et al. Injury, dysbiosis, and filaggrin deficiency drive skin inflammation through keratinocyte IL-1α release. *J. Allergy Clin. Immunol.* **143**, 1426–1443 (2019).
30. Pfalzgraff, A. et al. Antimicrobial endotoxin-neutralizing peptides promote keratinocyte migration via P2X7 receptor activation and accelerate wound healing in vivo. *Br. J. Pharmacol.* **175**, 3581–3593 (2018).
31. Kezic, S. et al. Levels of filaggrin degradation products are influenced by both filaggrin genotype and atopic dermatitis severity. *Allergy.: Eur. J. Allergy. Clin. Immunol.* **66**, 934–940 (2011).
32. Scharschmidt, T. C. et al. A Wave of Regulatory T Cells into Neonatal Skin Mediates Tolerance to Commensal Microbes. *Immunity* **43**, 1011–1021 (2015).
33. Scharschmidt, T. C. Establishing tolerance to commensal skin bacteria: timing is everything. *Dermatol. Clin.* **35**, 1–9 (2017).
34. Abt, M. C. et al. Commensal Bacteria Calibrate the Activation Threshold of Innate Antiviral. *Immun. Immun.* **37**, 158–170 (2012).
35. Parlet, C. P., Brown, M. M. & Horswill, A. R. Commensal staphylococci influence Staphylococcus aureus skin colonization and disease. *Trends Microbiol.* **27**, 497–507 (2019).
36. Khadka, V. D., Markey, L., Boucher, M. & Lieberman, T. D. Commensal Skin Bacteria Exacerbate Inflammation and Delay Skin Barrier Repair. *J. Investig. Dermatol.* **144**, 2541–2552 (2024).
37. Byrd, A. L. et al. Staphylococcus aureus and Staphylococcus epidermidis strain diversity underlying pediatric atopic dermatitis. *Sci. Transl. Med*. **9**, eaal4651 (2017).
38. Natsis, N. E. & Cohen, P. R. Coagulase-negative Staphylococcus skin and soft tissue infections. *Am. J. Clin. Dermatol.* **19**, 671–677 (2018).
39. Oh, J. et al. The altered landscape of the human skin microbiome in patients with primary immunodeficiencies. *Genome Res* **23**, 2103–2114 (2013).
40. Della Marca, R., Machado Ramos, M., da, P., Ribeiro, C. & Soares, A. J. Mathematical modelling of oscillating patterns for chronic autoimmune diseases. *Math. Methods Appl. Sci.* **45**, 7144–7161 (2022).
41. Valeyev, N. V. et al. A systems model for immune cell interactions unravels the mechanism of inflammation in human skin. *PLoS Comput. Biol.* **6**, e1001024 (2010).
42. Chang, H. W. et al. Alteration of the cutaneous microbiome in psoriasis and potential role in Th17 polarization. *Microbiome* **6**, 154 (2018).
43. Guram, K. et al. A threshold model for T-cell activation in the era of checkpoint blockade immunotherapy. *Front. Immunol.* **10**, 491 (2019).
44. Scharschmidt, T. C. et al. Filaggrin deficiency confers a paracellular barrier abnormality that reduces inflammatory thresholds to irritants and haptens. *J. Allergy Clin. Immunol.* **124**, 496–506 (2009).
45. Clausen, M. L. et al. Association of disease severity with skin microbiome and filaggrin gene mutations in adult atopic dermatitis. *JAMA Dermatol* **154**, 293–300 (2018).
46. Gonzalez, J. R. & Scharschmidt, T. C. Elucidating the Role of the Skin Barrier Protein Filaggrin in the Adaptive Immune Response to Commensals. *FASEB J.* **34**, (2020).
47. Gonzalez, J. R. et al. FLG Deficiency in Mice Alters the Early-Life CD4+ T-Cell Response to Skin Commensal Bacteria. *J. Investig. Dermatol.* **143**, 790–800 (2023).
48. Moise, N. & Friedman, A. Rheumatoid arthritis — a mathematical model. *J. Theor. Biol.* **461**, 17–33 (2019).
49. Özköse, F. Modeling of psoriasis by considering drug influence: a mathematical approach with memory trace. *Comput. Biol. Med.* **168**, 107791 (2024).

Acknowledgements
The research findings presented in this manuscript were funded by Unilever Research Ltd., Bangalore to MetFlux Research Private Limited, India. We acknowledge the contributions of Vijayalakshmi AB and Umesh Vazirani in data mining.

Author contributions
M.S.S. developed the model and codes for it. S.K. performed model validation, simulation and analysis, manuscript writing and editing. A.T. manuscript writing, review and editing. A.S. supervised and managed the project. V.K., R.K., R.M., J.R. conceptualization, experimental results and manuscript review. K.V.V. conceptualization, supervised the model validation and analysis, manuscript review.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41540-025-00524-y.

Correspondence and requests for materials should be addressed to KV Venkatesh.