Modeling the Epidermis Homeostasis and the Psoriasis

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We present a computational model of the spatial-temporal dynamics of the epidermis homeostasis. The model consists of a population kinetics model of the central transition pathway of keratinocyte proliferation, differentiation and loss and an agent-based cell migration model that propagates cell movements and generates the stratified epidermis. The model recapitulates observed cell density distribution and the epidermal turnover time. We apply the model to study the onset, recurrence and phototherapy-induced remission of psoriasis. The model considers the psoriasis as a parallel homeostasis of normal and psoriatic keratinocytes originated from a shared stem-cell niche environment and predicts two steady-state modes of the psoriasis: a disease mode and a quiescent mode. The interconversion between the two modes is established by the interaction between psoriatic stem cells and the immune system and by the normal and psoriatic stem cells competing for niches. The prediction of a quiescent state potentially explains the efficacy of the multi-episode UVB irradiation therapy and recurrence of psoriasis plaques, which can further guide designs of therapeutics that target the immune system and/or the keratinocytes.

I. INTRODUCTION

The epidermis, the outermost layer of skin, provides the human body a physiological barrier to the environment and protects the body from water loss, pathogenic infection and physical injury. The epidermis organizes into a stratified structure of keratinocytes at several differentiated stages [1], which constitute 95% cell population in the epidermis [2]. Like other regenerative tissues, the epidermis constantly renews itself to replace desquamated and apoptotic keratinocytes, repair tissue damage and establish the homeostasis. The renewal is orchestrated by a cascade of cellular processes including proliferation, differentiation, migration, apoptosis and desquamation [2–4]. During its lifespan, a keratinocyte transits spatially from the stratum basale to the stratum corneum and experiences multi-stage biological and morphological changes. Many endogenous and exogenous factors (e.g., Ca$^{2+}$ concentration, cytokines, UV irradiation, etc.) affect the epidermal dynamics and the homeostasis of the epidermis by regulating one or more cellular processes.

Mathematical and computational models have long been useful tools to predict cellular behaviors of the epidermis renewal under normal or pathological conditions. Previous models for the epidermal dynamics usually adopted two approaches. One approach includes deterministic models that derived analytical solutions to stationary cell populations. For example, the model by Savill [2] described proliferation of stem cells and transit-amplifying cells and differentiation to post-mitotic cells, which predicted the influences of apoptosis, cell-cycle time and transit time on cell populations. Gandolﬁ et al. [7] proposed a spatiotemporal model to investigate the evolution of epidermis, which described cell motion by a constitutive equation. The other approach includes agent-based models that treat individual keratinocytes as computing entities operating under speciﬁc physical and biological rules. Such models can simulate the multi-layer epidermal structure organized by cell proliferation, differentiation, death and migration, in which nonspecific intracellular and extracellular biochemical factors affected cell proliferation and differentiation while physical adhesive and repulsive forces governed cell motion [8–12].

In this paper, we present a hybrid model to combine advantages of the above two approaches. The model uses a mean-field cell population kinetics together with an agent-based model for cell migration. The model computes population dynamics of the epidermal renewal without having to compute the cell movements simultaneously, allowing fast and analytical evaluations of modeling hypotheses and results. The population kinetics model describes cellular processes including cell division, differentiation, apoptosis and desquamation. Either deterministic or stochastic simulation can be used to generate the population dynamics of keratinocytes. The cell migration is described by a two-dimensional agent-based model that tracks the cell movement driven by cell-cell interactions. Simulation of the cell migration can be integrated with the stochastic population dynamics to visualize the tissue stratification and establishment of homeostasis. A properly parameterized model reproduces experimentally-observed epidermis growth, differentiation and desquamation dynamics, homeostatic density distribution over different types of keratinocytes and the epidermis turnover times of different cell compartments.

To investigate a pathological epidermis condition, we study the onset and recurrence of psoriasis plaques and their recovery under the phototherapy by UVB irradiation. The psoriasis is a complex epidermal disorder characterized by keratinocyte hyperproliferation and abnormal differentiation due to intricate interactions with the immune system. The
The model consists of (1) a kinetics model, which tracks the temporal evolution of cell population of keratinocytes at several differentiation stages, and (2) a migration model, the temporal evolution of cell population of keratinocytes in the tissue. Models to visualize the renewal kinetics and stratification of mean-field population dynamics or can integrate the two kinetic models as a standalone module to compute the stratified structure of the epidermis. One can choose the mechanism of stem cell-immune system interaction and disease affects 2.4% of the general population and currently has no cure [12]. Specifically, we hypothesize a novel mechanism of stem cell–immune system interaction and predict the chronic disorder as a bimodal switch between a disease phenotypic and a quiescent (seemingly-normal) state. The model hypothesizes a parallel epidermal homeostasis simultaneously maintained by the normal and the psoriatic keratinocytes. The psoriatic homeostasis is caused by permanent perturbations in cell division, apoptosis and differentiation, derived from defective stem cells and their interactions with a weakened immune system. For treatment, the model predicts that to achieve a controlled remission the effective treatment of UVB irradiation must reduce the chronicity and recurrences of the disorder and providing a guide to design feasible therapeutics.

II. THE MODEL

The model consists of (1) a kinetics model, which tracks the temporal evolution of cell population of keratinocytes at several differentiation stages, and (2) a migration model, which describes motion of individual cells to generate the stratified structure of the epidermis. One can choose the kinetic model as a standalone module to compute the mean-field population dynamics or can integrate the two models to visualize the renewal kinetics and stratification of the tissue.

A. Model of cell population kinetics

Figure 1 illustrates the central transition pathway of the epidermis renewal. The pathway considers the population dynamics of six categories of keratinocytes stratified from the stratum basale to the stratum corneum, including progenitors, stem cells (SC) and transit-amplifying (TA) cells in the proliferative compartment, and differentiated cells in the nonproliferative compartment with growth-arrested (GA) cells, spinous (SP) cells, granular cells (GC) and corneocytes (CC). The above classification is primarily based on known histological structure and physiological function of the human epidermis [14]. Growth-arrested cells are precursors for nonproliferating cells. Spinous cells and granular cells are fully differentiated keratinocytes, and the nonnucleated corneocytes represent the end-stage differentiation and eventually desquamate. The central transition pathway incorporates three main cellular processes: (1) proliferation of stem cells and transit-amplifying cells, (2) differentiation including several inter-category cell conversions, and (3) cell loss including apoptosis of nucleated cells and desquamation of the corneocytes.

How stem cells maintain the epidermal homeostasis remains unresolved [15]. However, recent long-term in vivo lineage tracing studies on mouse tail tissue by genetic labeling revealed remarkable details about clonal dynamics of epidermal progenitors, suggesting the existence of either single (stem cell alone) or two progenitors (stem cell and committed progenitor) [16–18]. As illustrated in Fig. 2 our model considers a slow cycling stem cell population together with a faster proliferating committed progenitors (or, transit-amplifying cells). A stem cell divides in one of three modes [19–21]: (i) self-proliferation, by which a...
stem cell divides into two daughter stem cells, (ii) symmetric division, by which a stem cell divides into two TA cells, or (iii) asymmetric division, by which a stem cell divides into a stem cell and a TA cell. Considering a finite availability of stem cell niches \cite{10,22}, we assume a logistic growth of stem cells to limit the stem cell density by a maximal growth capacity, which ensures the system to reach a well-defined steady state \cite{23} for a more general model that guarantees a steady state. Previous models \cite{16,23,26} required a precise balance between stem cell self-proliferation and symmetric division and were intolerable to arbitrary perturbations such as population random drift caused by intrinsic stochasticity in the three-mode stem cell division. Similarly, TA cells also divide in one of the three modes of self-proliferation, symmetric and asymmetric division into the GA cells \cite{16,23,26}. In addition, a TA cell may resume the stem cell state and a GA cell may resume a TA cell state by back conversions \cite{27}.

The rate of progenitor division is often characterized by the cell-cycle time and by the subpopulation of cells that are active to divide (also known as the “growth fraction”). Our mean-field model does not distinguish proliferative propensity in individual cells and therefore parameterizes cell divisions with empirical rate constants that integrate influences of the cell cycle and the growth fraction. Environmental changes regulate the proliferation rate of stem cells. For example, the need of repairing tissue damage promotes stem cell proliferation \cite{18,24,28}. Recent study of hair follicles showed that TA cells may signal to stem cells to regulate proliferation \cite{24}. To incorporate this feedback mechanism, we assume an empirical dependence of stem cell division rate constants, $\gamma_1$, $k_{1a}$ and $k_{1s}$, on the density of TA cells and define:

$$\frac{\gamma_1}{\gamma_{1,h}} = \frac{k_{1a}}{k_{1a,h}} = \frac{k_{1s}}{k_{1s,h}} = \frac{\omega}{1 + (\omega - 1)(p_{ta}/p_{ta,h})^n},$$

where the subscript $h$ indicates a homeostatic rate constant (see Table III for numerical values), and $\omega \equiv r_{x,max}/r_{x,h}$ is the ratio of the maximum division rate to the homeostatic rate and is assumed identical for all division processes. $\omega$ reflects the maximum increase in the growth fraction and/or decrease in the cell cycle time when stem cell proliferation accelerates. At homeostasis of the normal epidermis, the reported growth fraction varied from 20% to 70% \cite{30,31}. Study in mice epidermis found more than 10-fold decrease in the cell cycle time from 5-7 days to 11 hours following tissue abrasion \cite{32}, whereas no significant change in cell cycle time was found in psoriasis \cite{33,34}. The exponent $n$ models the sensitivity to the deviation of TA density from the homeostasis. In the limit of a much reduced TA cell density ($p_{ta} \ll p_{ta,h}$), stem cells divide at the maximum rate, $r_{x,max}$, whereas stem cells divide at a minimal rate when TA cells overpopulate ($p_{ta} \gg p_{ta,h}$). The total stem cell proliferating rate at homeostasis is set about $10^{-2}$ per day, aligned with 4-6 division events per year \cite{18}.

The nonproliferative compartment describes a cascade of differentiations from GA cells to corneocytes. The model also considers an apoptosis process for all nucleated keratinocytes. Early studies suggested that apoptosis was only significant for stem cells and transit-amplifying cells in the proliferative compartment \cite{35}. Recent experiment \cite{35} also showed that apoptosis was evident in the differentiated keratinocytes. The extent of apoptosis is commonly characterized by apoptotic index, which is typically quantified using the TUNEL (transferase-mediated uridine nick end labelling) assay \cite{35}.

For a cell type $i$, the apoptosis index equals the probability that a cell undergoes apoptosis, defined as the ratio of apoptosis rate $f_i^{apopt}$ to the total outflux $f_i^{tot}$ including rates

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Mechanics of cell migration. Keratinocytes are geometrically modeled as rotational ellipsoids with two principal axes staying horizontal or vertical. (a) A repulsive force is determined by an overlap between neighboring cells. The repulsion $F_{12}^r$ between cells 1 and 2 is proportional to the overlapping area $S_{12}$ approximated by the corresponding overlap rectangle. $F_{13}^r$ is determined similarly. The net repulsion on cell 1 is a vector sum $F_1^r = F_{12}^r + F_{13}^r$. (b) The adhesive force exists between two adjacent cells. The force $F_{12}^a$ is related to the distance between cell 1 and cell 2. The direction of $F_{12}^a$ or $F_{12}^r$ acting on cell 1 is parallel to the line (dashed) connecting centers of cell 1 and cell 2. The repulsive force and adhesive force between two overlapped cells are balanced by the force generated by viscosity due to cell motion. Cell motion is only translational without rotation. w and h denote the width and height of a cell. (c) Epidermis thickness, rete ridge height, and undulant basement membrane geometrically configure the epidermis in a 2D projection.}
\end{figure}
of apoptosis and transition to the downstream cell category:

\[ AI = \frac{f_{iout}^{\text{apo}}}{f_{iout}^{\text{nec}}} = \frac{\beta_i}{\beta_i + k_i}, \quad i = 1, \ldots, 5, \quad (2) \]

For stem cells and TA cells, \( k_1 = k_{1a} \) and \( k_2 = k_{2a} \) are symmetric division rate constants. Experiments often reported global apoptosis indices that did not differentiate apoptotic activities in proliferative and non-proliferative compartments. Apoptotic heterogeneities of cells within a compartment is even less known. Here each cell category assumes an identical apoptosis index that is used to calculate the apoptosis rate constants \( \beta_i \)’s. Governing system equations (ODEs) are listed in Table I and computation of the model is described in the Supplementary Material (Fig. S1).

**B. Model of cell migration**

The agent-based migration model describes movement of all keratinocytes in a two-dimensional (cross-sectional) epidermis volume. Keratinocytes once derived from stem cells move outward from the stratum basale to the outermost stratum corneum, to compose a stratified epidermis. The model describes cell mechanics that propels cell movement. An individual cell is subject to three forces: (i) a viscous force due to cell moving in the surrounding environment; (ii) a repulsive force due to cell-cell compression; and (iii) an adhesive force due to interactions among adhesive molecules on cell membranes. Considering the sluggish keratinocyte motion (in a scale of \( \mu \text{m/hr} \) in a fluidic environment with a low Reynolds number (i.e., viscosity dominates inertia) [37], the model neglects the acceleration due to inertia. The force balance for the \( i \)th cell is

\[ \mu \frac{dx_i}{dt} + F_{i}^r + F_{i}^a = 0, \quad (3) \]

where vector \( x_i \) is the cell-center coordinate, and \( \mu \) is the viscosity coefficient. The first term in Eq. (3) is the viscosity of the epidermis. \( F_{i}^r \) and \( F_{i}^a \) are repulsive and adhesive forces between neighboring cells, which are sums of forces derived from all individual pairwise contacts,

\[ F_{i}^r = \sum_{j \in \mathcal{O}(i)} F_{ij}^r, \quad F_{i}^a = \sum_{j \in \Omega(i)} F_{ij}^a, \quad (4) \]

where \( \mathcal{O}(i) \) and \( \Omega(i) \) denote sets of cells overlapping and neighboring with the \( i \)th cell and \( F_{ij}^r \) and \( F_{ij}^a \) are force vectors produced onto cell \( i \) by interaction (repulsion or adhesion) between cells \( i \) and \( j \). By symmetry, \( F_{ij}^r = -F_{ji}^r \) and \( F_{ij}^a = -F_{ji}^a \). The model treats individual cells as rigid-body agents and uses the extent of virtual cell overlap to determine the repulsive force [Fig. 3(a)]. Adhesion between two cells is a function of their spatial distance \[38, 39\] [Fig. 3(b)]. Computation of \( F_{ij}^r \) and \( F_{ij}^a \) is given in the Supplementary Material.

Previous agent-based models [4, 11, 40] treated keratinocytes as identically-sized circles or spheres. However, cells progressively adopt varied shapes and sizes at different stages of differentiation. Cells in an outer layer generally have more flattened cell body and larger surface area, compared to cells in layers underneath. Tissue location in the body can also influence the cell geometry. For example, compared to the mean basal cell diameter of 6-8 \( \mu \text{m} \) at the forearm and hand [11], at unexposed sites in the adult tissue [3], the average cell diameter in the proliferative compartment is about 10 \( \mu \text{m} \) whereas the average differentiated cell diameter is about 16 \( \mu \text{m} \). For simplicity, we use ellipsoids to model geometric heterogeneity in cell morphology and size. Cell types are distinguished by the mean major-to-minor axis ratio and the mean nominal size.

The basement membrane of the epidermis is undulant with rete ridges extending downward between the dermal papillae [Fig. 3(c)]. The average rete ridge height is about 40 \( \mu \text{m} \) in the adult tissue, and about six rete ridges along 1 mm cross-sectional tissue length were observed and about 14 cells reside inside each rete ridge valley [40]. The basement membrane is modeled by periodically-repeating Gaussian functions (see the Supplementary Material). Parameters of cell sizes and epidermis thickness are listed in Table II.

### III. RESULTS

The model recapitulates two important measures of the epidermis homeostasis: cell counts in different layers and the epidermal turnover times in different compartments.

#### A. Homeostatic cell density distribution

The mean homeostatic cell densities can be analytically calculated from the ordinary differential equations in Table II as follows (see Table III for definitions of parameters).

\[
p_{sc} = p_{sc}^{\text{max}} \left[ 1 - \frac{1}{\gamma_1} \left( \frac{k_{1a} + \beta_1}{k_{-1} + k_{1a} + 2k_{2a} + \beta_2 - \gamma_2} - \frac{k_{1a} + 2k_{2a}}{k_{-2} + k_{2a} + k_{3} + \beta_3} \right) \right], \quad (5)
\]

\[
p_{ta} = \frac{k_{1a} + 2k_{2a}}{k_{-1} + k_{2a} + \beta_2 - \gamma_2 - k_{-2}(k_{2a} + 2k_{2a})} p_{sc}^{\text{max}}, \quad (6)
\]

\[
p_{ga} = \frac{k_{2a} + 2k_{3} + k_{3}}{k_{-2} + k_{3} + \beta_3} p_{ta}, \quad (7)
\]

\[
p_{sp} = \frac{k_{3}}{k_{4} + \beta_4} p_{ga}, \quad (8)
\]

\[
p_{gc} = \frac{k_{5}}{k_{4} + \beta_5} p_{ga}, \quad (9)
\]

\[
p_{cc} = \frac{k_{5}}{\alpha} p_{gc}, \quad (10)
\]

and the total cell density is given as

\[
p_{ct} = p_{sc} + p_{ta} + p_{ga} + p_{sp} + p_{gc} + p_{cc}. \quad (11)
\]

The density of each cell category is proportional to the epidermis capacity of stem cells, \( p_{sc}^{\text{max}} \) and the ratio between densities of any pair of cell types is a constant. Therefore, observed cell density distribution can be used to identify kinetic parameters. The homeostatic TA-cell density is

\[
p_{ta,h} = \frac{k_{1a} + 2k_{1a} + 2k_{1a} + 2k_{2a} + k_{2a} + \beta_2 - \gamma_2 - k_{-2}(k_{2a} + 2k_{2a})}{k_{-2} + k_{2a} + k_{3} + \beta_3} p_{sc}^{\text{max}}, \quad (12)
\]
TABLE I. Kinetic equations for the epidermal renewal and homeostasis

| Cell type            | Rate equation                                                                 |
|----------------------|-------------------------------------------------------------------------------|
| Stem cell (SC)       | \( \frac{dp_{sc}}{dt} = [\gamma_1 (1 - \frac{p_{sc}}{p_{sc}^{\text{max}}}) - k_{1s} - \beta_1]p_{sc} + k_{-1}p_{ta} \) |
| Transit-amplifying (TA) cell | \( \frac{dp_{ta}}{dt} = (\gamma_2 - k_{2s} - \beta_2 - k_{-1})p_{ta} + (k_{1a} + 2k_{3s})p_{sc} + k_{-2}p_{ga} \) |
| Growth-arrested (GA) cell | \( \frac{dp_{ga}}{dt} = (k_{2a} + 2k_{2s})p_{ta} - (k_{-2} + k_{3} + \beta_2)p_{ga} \) |
| Spinosus cell (SP)   | \( \frac{dp_{sp}}{dt} = k_{3}p_{ga} - (k_{1} + \beta_1)p_{sp} \)              |
| Granular cell (GC)   | \( \frac{dp_{gc}}{dt} = k_{4}p_{sp} - (k_{5} + \beta_5)p_{gc} \)              |
| Corneocytes (CC)     | \( \frac{dp_{cc}}{dt} = k_{5}p_{gc} - \alpha p_{cc} \)                         |

\( p_{sc}, p_{ta}, p_{ga}, p_{sp}, p_{gc}, \) and \( p_{cc} \) are cell densities.

Kinetic parameters must satisfy two necessary conditions to establish a physiologically proper steady state:

\[
\gamma_{1,h} > \beta_1 + k_{1s,h} - \frac{k_{-1}(k_{1a,h} + 2k_{1s,h})}{k_{-1} + k_{2s} + \beta_2 - \gamma_2 - \frac{k_{2a} + 2k_{3s}}{k_{-2} + k_{3} + \beta_3}} \tag{13}
\]

\[
k_{-1} + k_{2s} + \beta_2 > \gamma_2 + \frac{k_{-2}(k_{2a} + 2k_{2s})}{k_{-2} + k_{3} + \beta_3}. \tag{14}
\]

Given small backconversion rate \((k_{-1})\) and \((k_{-2})\) assumed at \(10^{-6}\) per day, orders of magnitude smaller than the stem cell and TA proliferating rate constants, Table III, the above conditions simplify to

\[
\gamma_{1,h} > k_{1s,h} + \beta_1, \quad \text{and} \quad \gamma_2 < k_{2s} + \beta_2. \tag{15}
\]

The first condition ensures the establishment of a viable stem cell population, whereas the second condition prevents an unchecked growth of the epidermis because the proliferation of TA cells is not limited by a maximum capacity in the model. These conditions extend previous treatment that required a precise balance between self-proliferation and symmetric division in progenitor cells when apoptosis was neglected [16, 24]. Apoptosis is a rare event compared to progenitor self-proliferation and symmetric division (e.g., \(\beta_1 \ll \gamma_{1,h}\), and \(\ll k_{1s,h}\); see Table III) and plays a secondary role in regulating the epidermal homeostasis.

A recent study of progenitors in mice interfollicular epidermis by Mascré et al. [15] suggested that in homeostasis stem cells proliferate by 4-6 division events per year, 10-20 times slower than proliferation and differentiation (about 1.2 events per week) of committed progenitors (TA cells in our model). This information is reflected such that \(k_{1a,h} + 2k_{1s,h}\) is an order of magnitude smaller than \(\gamma_2 + 2k_{2s}\). However, considering that TA cells have a much larger population than stem cells \((p_{ta}/p_{sc} \approx 5 [51])\), rates of stem-cell asymmetric and symmetric divisions into TA cells \((k_{1a,h} + 2k_{1s,h})\) must be about 5-fold greater than the difference between TA-cell self-proliferation and symmetric division, i.e., \(k_{2a} + \beta_2 - \gamma_2\) based on Eq. (3), assuming backconversion rates \((k_{-1})\) and \((k_{-2})\) are negligible. Therefore, the model predicts that mild perturbations on TA-cell dynamics including proliferation and apoptosis may have substantial effects on the homeostatic keratinocyte population.

The model recapitulates the dynamics and the homeostatic cell density distribution and the epidermal turnover time, in both deterministic and stochastic simulations [Fig. 4(a)]. Starting from an initial stem-cell population, the cell density rapidly increases to reach about 80% of the homeostatic density in the transient phase of the first 100 days and significantly slows down when it approaches the homeostasis. The simulation reached the homeostasis in about 2000 days to a total density at 101984 cells/mm\(^2\). The total transient dynamics is more than an order of magnitude slower than that in the model by Grabe et al. [9, 47], where the authors reported a near 2000-hour transient dynamics. This discrepancy is caused by a slow stem cell dynamics of 4-6 cell events per year reported recently [18], which also agrees with early-reported cell cycle of 100-200 hrs in a 20% growth fraction in an animal model [48]. Therefore, the stem cell dynamics (Eq. 1) becomes a rate-limiting step to the dynamic establishment of a homeostasis.

Figure 4(b) shows a histogram of the simulated steady-state cell density distribution over different cell types. Stem cells, TA cells and GA cells in stratum basale consist of 22% total cell population, in which proliferating cells accounts for 13.2% total cell population, consistent with the experimental data [31, 49, 50]. Studies by Bergstresser et al. [51] also suggested that 30% of nucleated keratinocytes were in the basal layer where stem cells occupied 10% population [31]. Spinous and granular cells are the majority, consisting of 51.3% total keratinocytes with the population of spinous cells nearly two times that of granular cells, in agreement with a previous prediction by Grabe et al. [4, 47]. Corneocytes consist of 26.6% of the total cell population. Bauer et al. [17] measured a mean nucleated keratinocytes density of 75346 cells/mm\(^2\) whereas the non-nucleated corneocytes was estimated to be about 18000 cells/mm\(^2\), consisting of 19.3% total cell population [50].

Figure 4(c) shows temporal frames of two-dimensional stratified epidermis from an initial group of stem cells distributed along the basement membrane to the steady state. We compute the cell population dynamics and the cell migration within an area of 1 mm length by 10 µm thickness.

TABLE II. Parameters for cell size and the undulant rete ridge

| Cell type            | \(w (\mu m) \times h (\mu m)\) | Reference |
|----------------------|--------------------------------|-----------|
| Stem cell            | 10 \times 15                   | [3, 41]   |
| Transit-amplifying   | 10 \times 15                   | [3, 41]   |
| Growth-arrested      | 12 \times 10                   | [3, 41]   |
| Spinosus cell        | 12 \times 8                    | [3, 41]   |
| Granular cell        | 22.5 \times 4                  | [3, 41]   |
| Cornified cell       | 35 \times 15                   | [42, 45]  |

Rete ridge parameters (see Supplementary Materials): \(A = 63 \mu m, B = 23 \mu m, \sigma_x = 70 \mu m\) [46].
FIG. 4. Dynamic and homeostatic keratinocytes density distribution. (a) Temporal evolutions of cell population of different types of keratinocytes by a deterministic simulation (smooth curves) and a stochastic simulation (fluctuated curves). Deterministic simulations started with an initial stem cell density of 1000 mm$^{-2}$, which corresponds to 10 cells under a skin area of 0.01 mm$^{-2}$ for the stochastic simulation. (b) The histogram of the steady-state cell density distribution. (c) Snapshots at day 1, 35, 102, and 988 of the visualization of the two-dimensional epidermis with a thickness of 10 μm. Simulation started with stem cells randomly located along the basement membrane (day 1). Parameter values used in simulations are listed in Table III.

with an initial number of stem cells of 10 randomly located along the basement membrane. The choice of 10 μm is to visualize a two dimensional single layer of cells. The simulated tissue histology shows that the thickness of the nucleated epidermis is about 60 μm, aligning with observations ranging from 38 μm to 77 μm with a mean of 60 μm in the adult tissue, with little variation across age groups \cite{41, 46, 49}. A movie of the epidermis renewal process of the normal tissue is available at URL: http://www.picb.ac.cn/stab/epidermal.html.

B. The epidermal turnover time

Another common measure of epidermis homeostasis is the epidermal turnover time $\tau$. At the tissue level, $\tau$ is interpreted as a time required for replacing the entire epidermis with new keratinocytes. The epidermal turnover time varies significantly with age groups, tissue locations and cell densities. In earlier studies, $\tau$ has been reported approximately 6-7 weeks in the volar forearm with a nucleated cell density of 44000 mm$^{-2}$ \cite{52, 53}. Based on a more recent count of nucleated cell density of 75346 mm$^{-2}$ on
breast skin. Hoath and Leaky suggested that \( \tau \) should be calculated as 59.3 days. Renewal of a specific layer of keratinocytes takes a shorter turnover time. The turnover times of the stratum basale and the differentiated compartment were reported being about 22 and 12 days, whereas the stratum corneum has a turnover time that varies from 14 days to about 20 days in young adult. Following the convention, we calculate \( \tau \) as the ratio of total cell density to the rate of cell loss including desquamation and apoptosis, or alternatively, the ratio of total cell density to the rate of cell birth by stem cell and TA divisions because cell birth and death rates are balanced at homeostasis:

\[
\tau = \frac{r_{\text{tot}}}{r_{\text{growth}}} = \frac{p_{\text{tot}}}{r_{\text{loss}},}
\]

where the rates of cell growth and cell loss are

\[
r_{\text{growth}} = \left[ \gamma_1 \left(1 - \frac{p_{\text{sc}}}{p_{\text{sc}}^{\text{max}}} \right) + k_{1a} + k_{1k} \right] p_{\text{sc}} + \left[ \gamma_2 + k_{2a} + k_{2k} \right] p_{\text{a}}
\]

\[
r_{\text{loss}} = \beta_1 p_{\text{sc}} + \beta_2 p_{\text{a}} + \beta_3 p_{\text{p}} + \beta_4 p_{\text{sp}} + \beta_5 p_{\text{sq}} + \alpha p_{\text{sc}} .
\]

Analytical solution to \( \tau \) can be obtained by substituting Eqs. (9-10) into the above equation. Apoptosis events represent rare ramifications from the central transition pathway in the normal epidermis renewal. Rate constant of an apoptotic process \( \beta_i \) (10^{-4}-10^{-5}/day) is much smaller than the differentiation and desquamation rate constants \( k_1 \) and \( \alpha \) (about 10^{-4}/day, see Table III). We can approximate \( r_{\text{loss}} \) by the rate of desquamation. By also neglecting the backconversions, we have

\[
\tau = \tau_{\text{prolif}} + \tau_{\text{diff}} + \tau_{\text{corn}},
\]

where

\[
\tau_{\text{prolif}} = \left( \frac{k_{2a} - \gamma_2}{k_{1a} + 2k_{1k} + 1} \right) \frac{1}{k_{2a} + 2k_{2s}}
\]

\[
\tau_{\text{diff}} = \frac{1}{k_3} + \frac{1}{k_4} + \frac{1}{k_5}
\]

\[
\tau_{\text{corn}} = \frac{1}{\alpha}.
\]

\( \tau \) is the sum of contributions by sub-compartment turnover times as keratinocytes migrate from the proliferative compartment \( (\tau_{\text{prolif}}) \) through the differentiated compartment \( (\tau_{\text{diff}}) \) and then through the stratum corneum \( (\tau_{\text{corn}}) \). We note that \( \tau \) is independent of the stem cell self-proliferation \( \gamma_1 \) and the stem cell capacity \( p_{\text{sc}}^{\text{max}} \). These two parameters determine the steady-state stem cell density \( p_{\text{sc}} \). Both cell density and cell growth rate are proportional to \( p_{\text{sc}} \), which masks the effect of stem cell self-proliferation dynamics on the turnover times. The turnover time of a single cell category is the inverse of the rate constant for the transit to the next cell category. Therefore, \( \tau \) can be dominated by a rate-limiting step in the cell growth and differentiation cascade. From the calculation by Eq. (16) using parameters in Table III, \( \tau \) is about 52.5 days, partitioned into 7, 31.5 and 14 days in the proliferative compartment, differentiated compartment and the stratum corneum, respectively, within the wide range of reported adult-tissue measurements between 39 and 75 days.

To investigate an important epidermis disorder, we extend the above model to study the onset and recurrence of psoriasis and its management. Psoriasis, an immune system-mediated chronic skin condition, is characterized by an overproduction of keratinocytes accompanied by inflammation, resembling features found in many autoimmune diseases. Here, we focus on studying the most prominent type of the disorder, psoriasis vulgaris, a plaque-formed scaly silvery patch, affecting the majority of psoriasis patients.

Current studies are inconclusive about whether psoriasis is generated by (1) genetically hyperproliferative progenitor keratinocytes, or (2) alternatively induced by a faulty immune system, particularly T cells over-response to unresolved antigens, which in turn produces excessive cytokines (such as TNF \( \alpha \)) to promote keratinocyte proliferation, or (3) more likely an intricate interplay between keratinocytes and the immune system.

C. Pathogenesis of psoriasis

To examine the pathogenesis of psoriasis, we emphasize an interplay between keratinocytes overproduction and responses by the immune system. Our fundamental hypothesis is that a psoriatic epidermis assumes two groups of keratinocytes: normal and psoriatic, maintaining a parallel homeostasis. The psoriatic keratinocytes are derived from a hyperproliferative stem cell population co-residing with the normal stem cells at the basement membrane. This hypothesis can be justified by the existence of intrinsically hyper-proliferative stem cells or stem cells that are more responsive to growth stimulants originated from an activated immune system. We modify the above model with equations to describe competing dynamics between the normal and psoriatic stem cells. Dynamics of psoriatic TA and nonproliferative cells are governed by rate equations as in Table III for the normal keratinocytes, however, with different parameter values to generate known phenotypes in psoriatic plaques, with an exception of granular cells that are missing in psoriasis. The dynamics of psoriatic stem cells in our model is similar to the model of spruce budworm outbreak by Ludwig et al., which models a single-species...
TABLE III. Model parameters

| Description                                      | Parameter   | Value  | Source |
|--------------------------------------------------|-------------|--------|--------|
| SC growth capacity                               | $p_{sc}^{\text{max}}$ (mm$^{-2}$) | 4.50e3 | Assumed |
| Nominal SC self-proliferation rate constant       | $\gamma_{1,h}$ (d$^{-1}$) | 3.30e-3 | Estimated |
| Nominal symmetric SC division rate constant       | $k_{1s,h}$ (d$^{-1}$) | 1.64e-3 | [16, 18] |
| Nominal asymmetric SC division rate constant      | $k_{1a,h}$ (d$^{-1}$) | 1.31e-2 | [16, 18] |
| TA cell self-proliferation rate constant          | $\gamma_{2}$ (d$^{-1}$) | 1.40e-2 | [31, 49, 51] |
| TA cell symmetric division rate constant          | $k_{2s}$ (d$^{-1}$) | 1.73e-2 | [31, 49, 51] |
| TA cell asymmetric division rate constant         | $k_{2a}$ (d$^{-1}$) | 1.38e-1 | [31, 49, 51] |
| GA-to-SP cell differentiation rate constant       | $k_{3}$ (d$^{-1}$) | 2.16e-1 | 49, 50 |
| SP-to-GC cell transit rate constant†             | $k_{4}$ (d$^{-1}$) | 5.56e-2 | 49, 50 |
| GC-to-CC cell transit rate constant†             | $k_{5}$ (d$^{-1}$) | 1.11e-1 | 49, 50 |
| CC cell desquamation rate constant               | $\alpha$ (d$^{-1}$) | 7.14e-2 | [49, 50, 51] |
| Backconversion rate constant (TA to SC)          | $k_{-1}$ (d$^{-1}$) | 1.00e-6 | Assumed |
| Backconversion rate constant (GA to TA)          | $k_{-2}$ (d$^{-1}$) | 1.00e-6 | Assumed |
| Maximum fold increase of SC proliferation rate    | $\omega$ | 100    | [30–32] |
| Steepness SC proliferation rate regulation by TA population | $n$ | 3 | Assumed |
| Normal epidermal apoptosis index                 | $A_{ih}$ | 0.12%  | [35, 49, 50] |
| Psoriatic epidermal apoptosis index              | $A_{id}$ | 0.035% | [35, 49, 50] |
| Fold change of SC proliferation in psoriasis     | $\rho_{sc}$ | 4 | [56] |
| Fold change of TA proliferation in psoriasis     | $\rho_{ta}$ | 4 | [56] |
| Fold change of transit time in psoriasis†       | $\rho_{tr}$ | 5 | [57, 58] |
| Fold change of desquamation in psoriasis         | $\rho_{dc}$ | 4 | [54] |
| Fold change of SC growth capacity in psoriasis   | $\lambda$ | 3.5 | [59, 60] |
| Maximum fold increase of SC proliferation rate    | $K_{p}$ (mm$^{-2}$d$^{-1}$) | 6 | Assumed |
| Immune half-activation by psoriatic SC density   | $K_{a}$ (mm$^{-2}$) | 380 | Assumed |

**Cell migration model**

| Description                                      | Parameter   | Value  | Source |
|--------------------------------------------------|-------------|--------|--------|
| Viscosity constant                               | $\mu$ (nN·s·μm$^{-2}$) | 250    | [61]   |
| Elasticity constant                               | $k$ (nN·μm$^{-2}$) | 0.04   | Estimated |
| Strength of adhesion for proliferating cell      | $\sigma_{p}$ (nN) | 50     | [39, 61] |
| Strength of adhesion for GA and SP and GC        | $\sigma_{a}$ (nN) | 5      | [39, 61] |
| Strength of adhesion for CC                      | $\sigma_{c}$ (nN) | 0.5    | [39, 61] |
| Time constant of rete ridge remodeling           | $\tau$ (d) | 1000   | [62–64] |
| Maximum rete ridges height of psoriatic epidermis | $Y_{\text{max}}$ (μm) | 126    | Assumed |
| Minimal rete ridges height of normal epidermis   | $Y_{\text{min}}$ (μm) | 40     | [65]   |
| Maximum proportions of normal and psoriatic proliferating cells | $r_{\text{max}}$ | 1 | Estimated |
| Minimal proportions of normal and psoriatic proliferating cells | $r_{\text{min}}$ | 0.001  | Estimated |

$\frac{dp_{sc}}{dt} = \left[ \gamma_1 \left( 1 - \frac{p_{sc} + \tilde{p}_{sc} / \lambda}{p_{sc}^{\text{max}}} \right) - k_{1s} - \beta_1 \right] p_{sc} + k_{-1} \rho_{ta}$ \hspace{1cm} (23)

$\frac{d\tilde{p}_{sc}}{dt} = \left[ \rho_{sc} \gamma_1 \left( 1 - \frac{p_{sc} + \tilde{p}_{sc} / \lambda}{p_{sc}^{\text{max}}} \right) - \rho_{sc} k_{1s,h} - \tilde{\beta}_1 \right] \tilde{p}_{sc} - f(\tilde{p}_{sc}) + \tilde{k}_{-1} \rho_{ta}$ \hspace{1cm} (24)

The psoriatic tissue activates the immune system to combat disease cells. We assume that repertoires for normal $p_{sc}$ and psoriatic $\tilde{p}_{sc}$ stem cells are both limited by available niche environment and psoriatic stem cells can acquire a larger growth capacity. Parameter $\lambda$ ($>1$) accounts for the fold increase in the growth capacity accessible to stem cells. The density of normal stem cells remains limited by $p_{sc}^{\text{max}}$, which is invaded by a fraction ($1/\lambda$) of psoriatic stem cells (see...
In comparison, we assume that psoriatic stem cells are not parameterized the steepest change in the removal rate that the immune response substantially switches on when granular layer due to abnormal differentiation and contains a compartment \[59, 60\]. A disordered tissue usually loses the cell density \[56, 57, 69\] with a relatively higher growth in the total candidate for study by a predictive model. Depending on its severity a plaque exhibits 2-5 times increase in the total cell density \[54, 67\] with a relatively higher growth in the proliferative compartment compared to the nonproliferative compartment \[54, 67\]. A disordered tissue usually loses the granular layer due to abnormal differentiation and contains a subset of nucleated corneocytes. A psoriatic plaque also has a turnover time several fold faster \[53, 71\]. More specifically, studies found in the cell kinetics of psoriasis (i) significant increase of cell cycle marker Ki-67 in psoriatic tissue without much change in cell cycle time \[34, 71\], suggesting a substantial increase in growth fraction; (ii) transit time of keratinocytes through differentiated compartment is shortened to 48 hrs from 240-330 hrs, 5-7 times faster than in the normal tissue \[53\]; (iii) transit time through the cornium is also shortened from 14 days to 2 days \[53\]. These factors together result in a decrease in the epidermis turnover time \[Eq. (19)\]. In addition, the cell apoptotic index decreases nearly four fold from 0.12% to 0.035% \[33\], making a further contribution to keratinocytes overproduction. Table \[III\] lists parameter values based on the above observations, where coefficients \(p_{ta}, p_{tr}\) and \(p_{de}\) are fold changes over rate constants in normal kinetics of TA-cell proliferating \(\gamma_1, k_{ta}, k_{tr}\), transit in the nonproliferative compartment \(k_3\) and desquamation \(\alpha\), respectively. Like variations in normal tissues, severity and phenotype of psoriasis vary widely across individuals and disease subtypes and therefore for any specific condition or study the model should be parameterized accordingly.

As the main result, the model predicts two interconverting homeostatic modes of the psoriatic tissue (see the Appendix for mathematical details): (1) a disease state, which generates psoriasis phenotypes of keratinocytes overproduction and a shortened epidermal turnover time when psoriatic stem cells outcompete normal stem cells for available niches and overwhelm the immune system; and (2) a quiescent state, which predicts a coexistence of a small number of psoriatic cells with a dominant population of normal keratinocytes when the immune system keeps the psoriatic stem cell population low. The quiescent mode with remanent psoriatic stem cells is a symptomless state for a psoriasis susceptible population low. The quiescent mode with remanent psoriatic stem cells is a symptomless state for a psoriasis susceptible population low. The quiescent mode with remanent psoriatic stem cells is a symptomless state for a psoriasis susceptible population low. The quiescent mode with remanent psoriatic stem cells is a symptomless state for a psoriasis susceptible population low. The quiescent mode with remanent psoriatic stem cells is a symptomless state for a psoriasis susceptible population low. The quiescent mode with remanent psoriatic stem cells is a symptomless state for a psoriasis susceptible population low. The quiescent mode with remanent psoriatic stem cells is a symptomless state for a psoriasis susceptible population low.

The model is parameterized (Table \[III\]) to produce a specific psoriasis phenotype, in which the total cell density reaches 217000 mm\(^{-2}\) at homeostasis, more than two times the normal epidermis \((101600 \text{ mm}^2)\), with the pathological keratinocytes consisting of 99.5% of the total population. The relative growth of the proliferative compartment over the nonproliferative compartment is about 3 vs. 2 times the normal densities (Table \[IV\]). The epidermal turnover time is shortened more than 5 times from 52.5 days to 9.8 days.

The psoriatic epidermis may retreat to the “quiescent”

| TABLE IV. Cell density distribution (mm\(^{-2}\)) and turnover times (day) | Healthy tissue | Psoriasis† | Non-symptom† |
|---|---|---|---|
| SC | 2268 | 362+6459 | 2232+124 |
| TA | 11219 | 77+32008 | 10715+618 |
| GA | 8964 | 61+20536 | 8562+4395 |
| SP | 34799 | 238+79788 | 33236+1536 |
| GC | 17379 | 119+0 | 16598+0 |
| CC | 27055 | 185+77633 | 25840+1495 |
| Total | 101684 | 1042+21654 | 97183+4168 |
| \(\tau = \tau_{prolif} + \tau_{diff} + \tau_{corn}\) | 52.5=7.0+31.5+14.0 | 9.8=1.8+4.5+3.5 | 44.5=6.0+26.5+12.0 |

†Normal+Psoriatic \((p_a + p_s)\).

*Results are generated using parameters in Table III.

Fig. 4 for illustration). Eq. 25 models the immune activities triggered by psoriatic stem cells. An activated immune system induces apoptosis of psoriatic stem cells. The activity of the immune system (the killing rate, \(f(\tilde{p}_{sc})\)) is directly regulated by the psoriatic stem cell density, under the assumption that the immune system is activated in a faster time scale than the tissue growth. The immune response is significantly activated when \(\tilde{p}_{sc}\) exceeds a threshold parameterized by \(K_a\) and is saturated at the maximum rate \(K_p\) when the psoriatic stem-cell population overpowers that of cytotoxic T cells. This approach hypothesizes that the immune system combats disease stem cells, but does not exclude the commonly-believed role by the immune system of inducing keratinocyte overproduction, even though the model does not explicitly couple the immune system to stem-cell proliferation.

Proliferation rate constants \(\gamma_1, k_{ta}\) and \(k_{tr}\) for the normal stem cells are regulated by the total TA cells, \(p_{ta} + \tilde{p}_{ta}\), similarly to Eq. 1

\[
\frac{\gamma_{1}}{\gamma_{1,n}} = \frac{k_{ta}}{k_{ta,n}} = \frac{k_{tr}}{k_{tr,n}} = \frac{\omega}{1 + (\omega - 1)(p_{ta} + \tilde{p}_{ta})/p_{ta,n}}.
\]

(26)

In comparison, we assume that psoriatic stem cells are not subject to regulation by the TA population and proliferate with rates \(p_{de}\) fold higher than the homeostatic rate constants \((\gamma_{1,1}, k_{ta,1}, k_{tr,1})\) of normal stem cells. We assume that the immune response substantially switches on when the psoriatic stem cell population reaches 10% of stem cell population in the normal tissue. This assumption is used to parameterize the steepest change in the removal rate \(f(\tilde{p}_{sc})\) in response to \(\tilde{p}_{sc}\), which sets the half-activation density at \(K_a = \sqrt{3}p_{sc,n}/10\). The model does not consider immune responses against cells derived from psoriatic stem cells by observing that reduction in stem cell population results in a subsequent reduction in the derived keratinocyte population.

Despite its mechanistic uncertainties, psoriasis plaques have well-defined tissue-level phenotypes, making it a good candidate for study by a predictive model. Depending on its severity a plaque exhibits 2-5 times increase in the total cell density \[54, 57, 60\] with a relatively higher growth in the proliferative compartment compared to the nonproliferative compartment \[54, 67\]. A disordered tissue usually loses the granular layer due to abnormal differentiation and contains a subset of nucleated corneocytes. A psoriatic plaque also has a turnover time several fold faster \[54, 71\]. More specifically,
FIG. 6. Psoriasis and its management by phototherapy. (a) Three dynamical phases of cell densities from psoriasis, the UVB treatment and recovery. Trajectories are combined populations of psoriatic and normal cells. Both stochastic and deterministic trajectories are shown. The stochastic simulation was conducted in an area of 0.1 mm$^{-2}$. Inset: zoomed details of the UVB irradiation phase (from day 1 to day 17). Psoriatic (b) and normal (c) stem cell and TA cell densities before and after 6- or 7-episode treatment. The treatment started at time day 1. Each simulated UVB irradiation episode induces 6000-fold increases in apoptosis rate constants for stem cells and TA cells and lasts for 48 hours. The time interval between two consecutive episodes is 56 hours (48-hr irradiation + 8-hr resting). (d) and (e) Homeostatic cell density distributions and the epidermal turnover times for healthy, psoriatic and recovered tissues. Notice that the granular layer is missing in the psoriatic tissue.

State and achieve a remission provided that the psoriatic stem cell density can be managed below a threshold value (see the Appendix). Narrow-band 311 nm controlled UVB irradiation is known as an effective treatment for managing psoriasis [72]. For example, a recent study by Weatherhead et al. [57] applied sequential episodes of 0.75-3 MEDs (minimal erythemal dose) UVB irradiation to achieve psoriatic plaques remission by inducing strong apoptosis of proliferative cells. Figure 6(a) shows a model simulation of a psoriasis remission after a simulated sequence of 7-episode UVB irradiations. Each UVB
A treatment with inadequate UVB irradiation episodes may fail to recover a psoriatic plaque, which eventually returns to the disease state once the treatment stops due to an insufficient loss in psoriatic stem cells. Figure 6(b) and (c) show that after a 6-episode UVB irradiation treatment, the psoriatic stem cell and TA cell populations bounce back to the disease state after terminating the treatment. The total cell count drops to 18600 mm$^{-2}$, with normal and psoriatic stem cells respectively reduced to 260 and 960 mm$^{-2}$. Post-treatment stem-cell population continues to decline to the “quiescent” steady state due to a relatively stronger immune response [Fig. 6(b)], which later brings down the psoriatic cell density to a minimum (less than 0.5% of the total cell density, Table IV). The granular cells become visible during the recovery. The last phase indicates a recovery of keratinocytes derived from the normal stem cells that reclaim their niche reservoir with a slower kinetics [Fig. 6(c)]. The downstream differentiated cells follow similar dynamics of remission. Simulated dynamics is similar if the model considers UVB-induced apoptosis in all nucleated cells [results not shown].

A dynamic model of rete ridge remodeling, simulation snapshots of the homeostatic psoriatic epidermis, tissue under treatment and recovered tissue can be found in the Supplementary Material (Fig. S3-S4). Movies of simulations (normal and psoriatic tissues) are provided at URL: http://www.picb.ac.cn/stab/epidermal.html.

IV. DISCUSSION

We presented a hybrid model that simulates and visualizes spatiotemporal dynamics of the epidermal homeostasis. The model represents an efficient approach that separates the computation of cell kinetics from that of an agent-based cell migration. Compared to previous agent-based models [8, 9, 10, 11] , our population kinetics model describes cell proliferation, differentiation and cell death as empirical rate processes and can be simulated by integrating the governing ordinary differential equations (Table I) or the master equations by a kinetic Monte Carlo algorithm. The cell population kinetics model can be combined with a two-dimensional cell migration model to visualize dynamics of epidermis renewal and stratification. The model reproduces observed characteristics of the normal epidermis. Model analysis and simulations show that balancing cell production and cell loss in each subcompartment is critical to establishing and maintaining a proper epidermis homeostasis (Fig. 4).

The current model has some addressible limitations: (i) The cell population kinetics does not explicitly incorporate specific intracellular and extracellular factors that affect the dynamics and steady state of the epidermis homeostasis. However, physiological and physical factors including age and UV irradiation as well as many commonly investigated signaling molecules can be coarsely coupled to model parameters such as proliferation and differentiation rate constants and morphology of keratinocytes and the epidermis. (ii) We neglected the effects by backconversions from TA to stem cells and from differentiated cells to TA cells by assuming their minimal impact. These processes could be worth a close examination as suggested in a recent theoretical study [74] that showed rare backward transitions may cause catastrophic outcome such as a cancerous growth. (iii) Technically, as intensive modeling and computation is made possible by high-performance hardware [77], our two-dimensional cross-sectional model can be extended to simulate a more realistic three-dimensional epidermis even though we expect that the qualitative results obtained from the 2D model remain valid in a 3D model.

As an important application, a non-trivial extension to the above model allows us to investigate the pathogenesis of psoriasis, an immune-mediated skin disorder. Genetic origins of psoriasis have been recently explored by an increasing number of genome-wide association studies that identified a multitude of psoriasis susceptibility loci [26, 74]. Many psoriasis-associated loci are connected to genes in the immune system (e.g., MHC class I molecules) and proteins expressed in keratinocytes, suggesting a complex nature of the disease [80]. However, the mechanistic epidermis-immune system interactions implicated by these loci are yet to be resolved.

In this study, we propose an alternative hypothesis of interactions between the immune system and keratinocytes, in which the disordered epidermis maintains a parallel homeostasis of both normal and psoriatic keratinocytes, derived from respective stem cell populations. We examine this hypothesis in an extended model and demonstrate that treatment by UVB irradiation with consecutive episodes can potentially manage the disease and achieve a remission of the psoriatic phenotype.

Psoriasis has recently been studied by agent-based models [47, 57]. The model by Grabe and Neuber [47]
was able to generate the psoriasis phenotype of an increased cell density and a shortened epidermal turnover time, by adjusting the fractional time of TA cell proliferation. This parameter characterizes the amount time for proliferation during a constant life time of a TA cell, which in our model is embedded in the TA cell self-proliferation rate constants $\gamma_2$. Increasing $\gamma_2$ and keeping symmetric division rate constant $k_2$, unchanged (equivalent to keeping a constant TA cell life time) does increase TA population (Eq. 9). To obtain a relative growth of the proliferating compartment, rate constants for cell differentiation must have relatively higher increases than $\gamma_2$, which was achieved by modulating Ca$^{+2}$ gradient in the Grabe and Neuber model. The model however did not propose possible management that can target the hypothesized mechanism. For example, it is not obvious how apoptosis induced by episodes of UVB irradiation can attain a remission via recovering the normal TA cell proliferating time. Weatherhead et al. [54] developed a model to simulate UVB-induced apoptosis in stem cells and TA cells, which was able to demonstrate a psoriasis remission after a few episodes of UVB irradiation. The model assumed a constant pool of stem cells that derived TA cells by asymmetric division and the UVB-induced apoptotic hyperproliferative stem cells were replaced with normal stem cells by symmetric divisions. This model assumption consequently led to a permanent reduction in cell density after each UVB irradiation treatment and therefore did not explain relapses of psoriatic phenotypes once an ineffective treatment ends or recurrence of the disorder.

Interactions between the immune system and keratinocytes considered in our model can serve as a conceptual basis for interpreting the pathogenesis of psoriasis. Especially, we showed that the act of the immune system against psoriatic keratinocytes plays a pivotal role in the onset, remission and recurrence of the disease phenotype. The most common paradigm considers that faulty immune responses triggered by unknown self antigens or pathogens (introduced by injuries or trauma, known as Koebner phenomenon) produce cytokines and growth factors that promote keratinocyte hyperproliferation, immature differentiation and skin inflammation, establishing the psoriasis phenotype. Drugs that inhibit T cell activity and cytokine productions do improve psoriatic conditions [51]. In contrast, our model demonstrates that a psoriasis plaque develops when the immune system is genuinely weakened or locally overwhelmed by a large population of psoriatic keratinocytes, staging up a chronic condition. This prediction may explain high occurrence and increasing severity of psoriasis in HIV-infected, especially late-stage AIDS patients with substantially compromised immune systems when CD4+ and naive CD8+ T cell counts substantially decrease [52, 53]. Furthermore, the onset age of psoriasis has been known to have two separate populations, type I (early onset in patients younger than 40 with a peak at age 20) and type II (late onset after age 40 with a peak at about 60) [54]. Our model speculates that a vigorous immune system at a younger age can stimulate a strong hyperproliferation (a large $\rho_{sc}$) in a psoriatic epidermis and causes manifestation of plaque phenotypes. One the other hand, a weak immune system (a small $k_{h}$) at an older age can also have an equivalent effect.

The model prediction provides an alternative perspective of the pathogenesis of psoriasis, suggesting that the immune system as a double-edged sword plays two essential however opposing roles: (i) Cytotoxic (CD8+) T cells recruited to the epidermis induce apoptosis in psoriatic stem cells, which is implicated by studies that demonstrated CD8+ T cell (especially, CD45RO+ memory subtype) count substantially increases in the psoriatic epidermis [52]; and (ii) Immune activities in the meantime promote progenitor keratinocytes proliferation by producing a multitude of cytokines and growth factors (TNF, IFN-\(\alpha\), IFN-\(\gamma\), IL-17, IL-22, IL-23, etc.). Balance between the two acts determines the outcome of the disease.

Our model predicts that the psoriasis-susceptible tissue is a bimodal system and can switch between a non-symptom state and a phenotypical state, potentially explaining the recurring nature of the disorder and suggesting the feasibility of disease management by an effective treatment. We showed in UVB phototherapy simulation that psoriasis plaque clearance can be attained by inducing strong apoptosis in keratinocytes. The model only considered UVB-induced apoptosis in keratinocytes. UVB irradiation may promote proliferation and differentiation in skin cells [55, 56] or may alter immune responses. These effects could be incorporated and be examined in the model. For example, as suggested in Eq. (24), rebalance in self-proliferation $\gamma_{1,b}$ and symmetric division $k_{1,h}$ and change in immune activities $f(\rho_{sc})$ may affect the population of psoriatic stem cells and thus the therapeutic outcome.

Experiments did not demonstrate whether the UVB irradiation causes non-apoptotic cell death that was not reflected by an apoptosis marker [57]. Regardless the actual mechanism, induced cell deaths will result in a shift of the stem cell density from the disease state to the quiescent state across the phase boundary, an important parameter that determines the design of a phototherapy regimen, including irradiation dosage in each treatment episode, the number of episodes and the time interval between consecutive episodes.

The model also suggests the limitation of UVB irradiation or similar treatments that attempt to achieve plaque remission by killing keratinocytes below a critical threshold. First, psoriasis plaques may recur under a temporally-weakened immune system or a transient burst of cell proliferation caused by conditions such as wound healing. Second, the psoriatic condition may be worsen under a genuinely weak immune system (with a low $K_p$), in which the disease phenotype persists and cannot be adequately reverted by simple reduction in psoriatic stem cells because the system may not possess a quiescent state [see Fig. 7(a) and (b)].

Further insight from the model is that the bimodal psoriasis exhibits hysteresis, by which a mode of the epidermis, psoriatic or quiescent, once reached under a favorable condition, will tend to be relatively stable. For example, a symptomless epidermis as illustrated in Fig. 7(b) may switch to the disease state when $K_p$ is reduced beyond its lower threshold because of weakening in the immune system. However, restrengthening the immune system to revert the disease state back to the quiescent mode requires elevating $K_p$ in the model beyond the upper threshold, implying that the disease is resistant to mild natural or induced perturbations.

One definitive experimental test of our model hypothesis should aim at simultaneously tracing clones of psoriatic and normal stem cell lineages. Because of recent advancement in techniques, studies of epidermal stem cells become central to the understanding of the epidermal homeostasis. Especially, the emerging powerful in \textit{vivo} lineage tracing technology allows dynamic monitoring of stem cells and progenitors clone formation and differentiation and can achieve multicolor
simultaneous tracing of separate clones [20]. The technique has already been pioneered to study progenitor fates in normal skin tissue [16] and benign epidermal tumors [87] and can be potentially applicable to identify the coexistence of normal and psoriatic progenitors in psoriasis. One potential challenge is that in either quiescent or disease state one type of stem cells is in a small population (about a 1:20 ratio, according to Table IV), making it difficult for differential labeling. Alternatively, an experiment may tend to identify and isolate the two competing effects by the immune system on the epidermis: (1) apoptosis in epidermal progenitors by T-cell cytotoxic activities and (2) hyperproliferation due to elevated cytokines and growth factors.

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Appendix A: Mathematical details of the psoriasis model

Psoriasis as a bimodal switch — To illustrate the principle and simplify the analysis, we only present a two-dimensional model that describes dynamic interactions between normal and psoriatic stem cells. The complete model that produced the results (Fig. 6) is more complex and of a higher dimension because of the feedback regulation by TA cell population on the normal stem cell proliferation (Eq. 25), requiring analyzing the dynamics of normal and psoriatic TA cells together. Again, for convenience in analysis, we neglect the influences of backconversions and apoptosis. This simplification allows us to show insights of the model behaviors without much mathematical complication. We work with normalized quantities:

\[ x = \frac{p_{sc}}{K_a}, \quad y = \frac{p_{sc}}{K_a}, \quad y^{\max} = \frac{p_{sc}}{K_a}, \quad k_p = \frac{K_p}{K_a}. \]  

(A1)

Ratios between the normal stem-cell proliferation rate constants remain constant despite their dynamic modulations by the TA cell population (Eq. 1), i.e., \( k_{1s}/\gamma_1 = k_{1s,h}/\gamma_{1,h} \).

Ignoring the trivial steady states of zero density (\( x = 0, \) and/or \( y = 0 \)), based on Eqs. (23-25) we have the steady-state equations for stem cell densities as

\[ w \left( 1 - \frac{x}{u} \right) - \frac{x}{1 + x^2} = 0 , \]  

(A2)

\[ y = \frac{u - x}{\lambda} , \]  

(A3)

where

\[ w = \frac{p_{sc}(1 - 1/\lambda)(\gamma_{1,h} - k_{1s,h})}{k_p} , \]  

(A4)

\[ u = \lambda y^{\max}(1 - k_{1s,h}/\gamma_{1,h}) . \]  

(A5)

Eq. (A2) can solve for one or three steady-state psoriatic stem cell densities, depending on choices of two key parameters, \( w \) and \( u \), which is illustrated in Fig. 7(a).

To study plaque remission and relapse, we are interested in the region where the system has two stable steady states, “quiescent” and “disease”, and one unstable “transition” steady state. This scenario is illustrated in Fig. 7(a) with three intersections between the line \( w(1 - x/u) \) and the nonparametric curve \( x/(1 + x^2) \). Determination of the stability of these fixed points requires analysis similar to the spruce budworm model by Ludwig et al. [68]. Figure 7(a) shows that the “quiescent” state is more sensitive to \( w \),

\[ \text{FIG. 7. Steady states of the psoriasis model. (a) Intersections of the two functions give the steady states (Eq. A2) and can be modulated with } w \text{ by changing } K_p \text{ within the range of two bifurcation points (indicated by dashed lines). The “quiescent” and “disease” states (filled circles) are stable steady states. The “transition” state (empty circle) is unstable (i.e., arbitrarily small perturbations deviate the system away from it). (b) Bifurcation diagram under varying ratio } p_{sc}/k_p \text{ with three regions: (I) persistent disorder, (II) bimodal, and (III) symptomless. (c) Trajectories from basins of attraction: I and II, separated by the boundary (dashed line), converging to the quiescent and disease states, respectively. Blue and red curves are nullclines (Eqs. A2 and A3). Parameter values used for the simulation are listed in Table III.} \]
whereas the “disease” state is determined by both $u$ and $w$. This observation provides a guideline to parameterize the model to attain appropriate psoriatic phenotypes by identifying disease-related parameters $\rho_{sc}$, $\lambda$ and $k_p$. The ratio $\rho_{sc}/k_p$ is the key parameter that characterizes the interplay between proliferation of keratinocytes and strength of the immune system, playing a critical role in the interpretation of the pathogenesis of psoriasis.

Bifurcation diagrams in Fig. 7(b) of steady-state stem cell densities shows three classes of behaviors as $\rho_{sc}/k_p$ varies. Psoriatic stem cells only survive in the “quiescent” state ($\rho_{sc}/k_p < 159$ day) in a small population under a vigorous immune system (a large $k_p$) and/or a mild sensitivity in stem cell proliferation (a small $\rho_{sc}$). In contrast, a weak immune system (a small $k_p$) cannot adequately counterbalance the psoriatic proliferation (a large $\rho_{sc}$) and thus the epidermis assumes a persistent “disease” state ($\rho_{sc}/k_p > 440$ day). A bimodal system with an intermediate $\rho_{sc}/k_p$ has a potential to switch between the quiescent and disease modes when conditions change. Figure 7(c) shows a two-dimensional phase plane of normal and psoriatic stem cell densities. Starting from initial stem cell densities, located inside region I or II, a temporal trajectory will be attracted to either the quiescent or the disease state, respectively. Those starting on the boundary of the two regions will converge to the transition state, which is unsustainable because slight perturbations will dislocate a trajectory into either region I or II.

**Cell density and turnover time** — Below, we provide equations for homeostatic cell densities and the turnover time in the psoriatic model. As shorthands, we define

$$g = \frac{k_{1a} + 2k_{1s}}{k_{2a} - \gamma_2}, \quad \tilde{g}_n = \frac{k_{1a,n} + 2k_{1s,n}}{k_{2a} - \gamma_2},$$

(A6)

The ratio $\xi = g/g_n$ is a function of the steady-state TA cell population ($\rho_{ta} + \tilde{\rho}_{ta}$) by Eq. (26). The total steady-state cell density is given as

$$p_{tot} = \rho_{sc}(1 + \xi g_n W) + \tilde{\rho}_{sc} \left(1 + \frac{\rho_{sc}}{\rho_{ta}} g_n \tilde{W}\right),$$

(A7)

where

$$W = 1 + (k_{2a} + 2k_{2s}) \left(\frac{1}{k_3} + \frac{1}{k_4} + \frac{1}{k_5} + \frac{1}{\alpha}\right),$$

(A8)

$$\tilde{W} = 1 + (k_{2a} + 2k_{2s}) \left(\frac{1}{\rho_{ta} k_3} + \frac{1}{\rho_{ta} k_4} + \frac{1}{\rho_{de} \alpha}\right) \rho_{ta},$$

(A9)

Notice the lack of GC layer in the psoriatic cell population. The proliferative and differentiated cell populations are

$$p_{prolif} = \rho_{sc}(1 + \xi g_n) + \left(1 + \frac{\rho_{sc}}{\rho_{ta}} g_n\right) \tilde{\rho}_{sc},$$

(A10)

$$\rho_{diff} = g_n(k_{2a} + 2k_{2s}) \left(\frac{\rho_{sc} \xi + \rho_{sc}}{\rho_{cr} \tilde{\rho}_{cr}} \left(\frac{1}{k_3} + \frac{1}{k_4}\right)\right.\left.\frac{k_2a + 2k_{2s}}{k_5}\right),$$

(A11)

Corneocytes are not included in the differentiated compartment. By comparison, the cell densities in the healthy tissue are

$$p_{prolif, h} = \rho_{sc,h}(1 + g_n),$$

(A12)

$$\rho_{diff, h} = \rho_{cr}(k_{2a} + 2k_{2s}) \rho_{sc,h} \left(\frac{1}{k_3} + \frac{1}{k_4} + \frac{1}{k_5}\right).$$

(A13)

We can calculate the growth of the proliferative compartment relative to that of the nonproliferative compartment as

$$\frac{p_{prolif}}{p_{prolif, h}} = \frac{\rho_{sc}(1 + \xi g_n) + \left(1 + \frac{\rho_{sc}}{\rho_{ta}} g_n\right) \tilde{\rho}_{sc}}{(1 + g_n) \rho_{sc} \xi + \rho_{sc}} \frac{1}{\rho_{cr} \rho_{cr,h}},$$

(A14)

A relative increase in the proliferative population requires the above ratio to be greater than 1. In psoriasis, $\xi < 1$, reflecting a decreased proliferation rate in the cohabitating normal stem cell population due to a much elevated TA cell population. It is unclear whether stem cells and TA cells have differential increases in proliferation rates. For the lack of information, we assume $\rho_{sc}/\rho_{ta} \approx 1$. Therefore, $\rho_{cr} > \rho_{sc}$ becomes a sufficient (but not a necessary) condition to produce a relative increase in the proliferative compartment, requiring that the fold increase of transit rate in the differentiated compartment is higher than the fold increase of division rates in the proliferative compartment. This result agrees with an earlier prediction from Heenen et al. [59], showing that a relative growth in the proliferative compartment requires keratinocyte hyperproliferation and in the meantime an increased transit rate in the differentiated compartment. A proportional increase in both TA-cell proliferation rate and transit rate ($\rho_{sc} = \rho_{tp}$) does not cause relatively differential growth of the two compartments unless difference exists between increases of proliferating rates of stem cells and TA cells, $p_{sc} \neq p_{ta}$. Fast migration of differentiated keratinocytes also offsets overgrowth in the proliferative compartment.

An important insight from the model is that increasing keratinocyte population in psoriasis is not merely caused by elevated proliferation rates but also requires the increase in growth capacity in the progenitor repertoire. Observed morphological remodeling of the psoriatic epidermis suggests increased growth niches for stem cells [88].

Similarly to Eq. (19), the turnover time can be approximated as the ratio of the total cell density to the rate of desquamation:

$$\tilde{\tau}_{tot} \approx \frac{\rho_{tot}}{\alpha (\rho_{sc} + \rho_{de} \rho_{cc})} = \left(\frac{\rho_{sc} \xi + \rho_{sc}}{\rho_{sc} \xi + \rho_{sc} \tilde{\rho}_{sc}} \frac{1}{k_{2a} + 2k_{2s}} + \frac{\rho_{sc} \xi + \rho_{sc}}{\rho_{sc} \xi + \rho_{sc} \tilde{\rho}_{sc}} \frac{1}{k_{2a} + 2k_{2s}}\right) \rho_{sc} \xi + \rho_{sc} \tilde{\rho}_{sc} k_5\frac{1}{\rho_{sc} \xi + \rho_{sc} \tilde{\rho}_{sc} k_5},$$

(A15)

which can be analyzed for the two psoriasis modes (quiescent or disease). At the quiescent mode, $\xi \approx 1$ and $\rho_{sc} \gg \rho_{sc}$, the turnover time is approximated by

$$\tilde{\tau}_{tot} \approx \left(\frac{k_{2a} - \gamma_2}{k_{1a} + 2k_{1s}} + 1\right) \frac{1}{\rho_{sc} + 2k_{2s}} + \frac{1}{k_3} + \frac{1}{k_4} + \frac{1}{k_5} + \frac{1}{\alpha}.$$
converging back to $\tau_{\text{tot}}$. At the disease mode, $\xi < 1$ and $p_{sc} \ll \bar{p}_{sc}$. The turnover time is close to:

$$\tau_{\text{tot}} \approx \left( \frac{1}{\rho_{sc} g_b} + \frac{1}{\rho_{ta}} \right) \frac{1}{k_{2a} + 2k_{2s}} + \frac{1}{\rho_{tr}} \left( \frac{1}{k_3} + \frac{1}{k_4} \right) + \frac{1}{\rho_{de}} \alpha .$$

(A17)

Compared to the turnover time of the healthy tissue $\tau_{\text{tot}}$ (Eq. [19]), $\tau_{\text{tot}}$ of the psoriatic tissue is clearly shortened at each stage from the proliferative compartment (the first term) to differentiated compartment (the second term) and to the corneum (the third term). The turnover time of the granular layer is ignorable because of the minimal normal cell population.
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MODELING THE EPIDERMIS HOMEOSTASIS AND THE PSORIASIS SUPPLEMENTARY MATERIAL

Computation of population kinetics model

The central transition pathway of the epidermis renewal can be computed in two alternative ways (Fig. S1) to obtain the deterministic or stochastic dynamics of the system. The mathematical equations [the ordinary differential equations (ODEs) or the master equations] of the system for the normal tissue can be found in Table 1 of the paper.

Deterministic simulation — The deterministic model describes cell populations by a set of ODEs with the cell densities as the state variables according to the rate processes in the central transition pathway. Numerically integrating the ODEs obtains trajectories of the cell density distribution over all individual cell types.

Stochastic simulation — In this case, rate processes in the central transition pathway are sampled by the Gillespie’s algorithm [1] to generate probabilistic cellular events sequentially in time. An individual cell process is chosen by a probability proportional to the rate of the process, and the occurrence time interval is sampled as in a Poissonian process with a mean rate equal to the accumulated rate of all processes in the system. Time series of cell events generated by the stochastic simulation are fed to the agent-based cell migration model to simulate and visualize the spatiotemporal organization of keratinocytes in the epidermis.

Computation of agent-based cell migration model

Simulation of the cell migration model is coupled with the stochastic simulation of the cell population kinetics model described in the previous section. Because the cell population kinetics is treated independently from the cell migration in our model, the stochastic simulation of population dynamics can be completed before simulating the cell migration, and the generated cellular events of proliferation, differentiation, apoptosis and desquamation can be stored and later embedded into the time series of migration events.

Repulsive force — The amount of repulsive force $F_{ij}$ is assumed to be proportional to the overlapping area $S_{ij}$ and the direction of the force is along the line connecting the cell centers of cells $i$ and $j$. At time $t$, the two orthogonal components $F_{ij}^{x,t}(t) \equiv [F_{ij}^{x}\alpha(t), F_{ij}^{y}\beta(t)]$ is given as

$$F_{ij}^{x,t}(t) = kS_{ij}(t)\cos\theta_{ij}, \text{ and } F_{ij}^{y,t}(t) = kS_{ij}(t)\sin\theta_{ij},$$

where $\theta_{ij}$ is the angle of vector $F_{ij}^x$ and $k$ is a constant assumed identical for all cell types.

In theory, the overlapping area between two ellipsoids can be precisely calculated by a numerical integration. To increase computational efficiency, $S_{ij} = S_{ij}'$ is however approximated by the overlap between the two cells as if they are rectangles with widths and heights identical to the corresponding ellipsoids. An overlap happens between cells $i$ and $j$ if the following two conditions hold:

$$|x_i - x_j| < \frac{w_i + w_j}{2}, \text{ and } |y_i - y_j| < \frac{h_i + h_j}{2},$$

Repulsive force — The det $$w_{ij} = \min\{\frac{w_i + w_j}{2} - |x_i - x_j|, w_1, w_2\}$$

and the overlap area is approximated as $S_{ij} \approx w_{ij}h_{ij}$.

Adhesive force — The adhesion between two cells, $F_{ik}$, is assumed to be related to the distance of two adjacent cells and the direction of the force is along with the line connecting the cell centers. The adhesive force is a biphasic function of the distance between two adjacent cells (Fig. S2) and is given as

$$F_{ik}^a = -\sigma \left[\left(\frac{g_{ik}}{r} + c_1\right)e^{-\zeta(\frac{g_{ik}}{r} + c_1)^2} - c_2e^{-\zeta(\frac{g_{ik}}{r})^2}\right],$$

where $c_1 = 1/\sqrt{2}\zeta$, $c_2 = c_1e^{-1/2}$, $r$ is the average radius of cells, $g_{ik}$ is the distance between cell $i$ and cell $k$. $\sigma$ is a measure of the strength of the adhesion. The number of

FIG. S1. Schemes of model computation. Kinetics of the central transition pathway of the epidermis renewal can be computed by one of the two numerical methods: (i) integrating the system of ODEs, or (ii) stochastic simulation algorithm (SSA). As a third option (iii), the spatio-temporal dynamics of the epidermis renewal can be computed and visualized by incorporating cell events generated by the stochastic simulation into the cell migration model.

FIG. S2. Adhesive force. The normalized adhesive force ($F_{ik}^a/\sigma$) related the cell-cell distance under different $\zeta$ values. The adhesive force is zero at $\zeta = 7$ when the distance is bigger than the cell radius $r$. 

\[ \text{Cell Migration Model} \]

| Computation | Output |
|-------------|--------|
| Deterministic Simulation (ODE) | Deterministic Trajectories |
| Stochastic Simulation (KMC) | Stochastic Events |
| Agent-based Computing | Tissue Stratification |
desmosomes, a typical cell-junction, varies in different layers indicating a possible different adhesion strength in different layers. Here parameter $\sigma$ can be adjusted to reflect this variation. We assume that the adhesion strength in proliferating cells is the strongest and decreases from inner to outer layer in non-proliferating compartment due to the decreased desmosomes. Stem cells locate on niches and always attach on the basement membrane. Skerrow et al. showed that the ratio of desmosome densities of differentiated layers and corneocyte layer was about 6. Parameter $\zeta$ is usually assumed to be 7 with which the adhesive force is almost zero when the distance between two cells is larger than $r$. In other word, $\zeta \equiv 7$ implies $d_{ad} \equiv r$. The force increases as the distance decreases from zero and reaches a max force when the distance is about $0.3r$ (Fig. S2). As the distance increases further, the adhesion declines to zero. For computational efficiency, the distance between two adjacent cells is approximated by the shortest distance between cells represented as rectangles with width and height identical to the corresponding ellipsoids. The cell-cell distance is calculated by

$$g_{ik} = \sqrt{x_{ik}^2 + y_{ik}^2}. \quad (S6)$$

where

$$x_{ik} = \max\{|x_i - x_k| - \frac{w_i}{2}, \frac{w_k}{2}, 0\} \quad (S7)$$

$$y_{ik} = \max\{|y_i - y_k| - \frac{h_i}{2}, \frac{h_k}{2}, 0\} \quad (S8)$$

The equation of motion for cell migration

$$\mu \frac{dx_i}{dt} + F_i^r + F_i^v = 0, \quad (S9)$$

$$F_i^r = \sum_{j=O(i)} F_{ij}^r, \quad F_i^v = \sum_{j=O(i)} F_{ij}^v \quad (S10)$$

can be numerically solved for each individual cell by a finite difference method. With a small time step $\Delta t$, given the location of cell $i$ at time $t$, $x_i(t)$, one can estimate the cell location $x_i(t + \Delta t)$ as a first-order approximation,

$$x_i(t + \Delta t) \approx x_i(t) - \frac{F_i^r(t) + F_i^v(t)}{\mu} \Delta t. \quad (S11)$$

The basement membrane — Cell migration is bounded by the basement membrane, whose morphology and remodeling must be accounted for. The undulant basement membrane at location $x$, is generated by a shifted Gaussian function:

$$-H(x) = Ae^{-\frac{(x-x_0)^2}{2\sigma^2}} - B, \quad (S12)$$

where parameters $A$, $B$ and $\sigma$ model the depth and width of the rete ridge. The variable $x_0$ controls the location of a rete ridge along the basement membrane. Simulations introduce 10% fluctuations in cell size (width and height) about the means when a new (or newly differentiated) cell is produced. Periodical boundary condition was used to process cell motion across the left and right boundaries. In the normal tissue, proliferating cells including stem cells and TA cells only undergo lateral movement along the basement membrane.

The complete algorithm that simulates the stochastic spatiotemporal dynamics of the epidermis renewal is outlined as follows.

1. Simulate the cell population kinetics model with the Gillespie’s algorithm, and store the time series of cell events.
2. Specify cell coordinates of the initial population and calculate mechanical forces exerted on each individual cells using Eqs. (S10), and set the simulation time $t = 0$ and the time step $\Delta t$ (0.002 day was used).
3. Execute available cell events within $[t, t + \Delta t]$ according to the rules described in Table V.
4. Calculate mechanical forces for all affected cells and migrate cells to the new coordinates calculated by Eq. (S11), and advance the time $t \leftarrow t + \Delta t$.
5. Iterate Step 3 until stop.

The model simulation and visualization algorithms are implemented in the Matlab and Java Language and are available upon request.

**Simulation of psoriasis homeostasis and its treatment by UVB irradiation**

Simulated (deterministic and stochastic) dynamics of psoriasis plaque and its post-treatment recovery after UVB irradiations are shown in Fig. S3. Fig. S4 shows a few snapshots of 2D tissue stratification during a simulation. Simulation movies are available at URL: http://www.picb.ac.cn/stab/epidermal.html.
TABLE V. Operation rules for cell events in the cell migration model

| Event          | Operation rule                                                                 |
|----------------|-------------------------------------------------------------------------------|
| SC → SC + TA   | Randomly divide a SC and place daughter cells beside each other†               |
| SC → SC + SC   | Randomly divide a SC and place daughter cells beside each other†               |
| SC → TA + TA   | Randomly divide a SC and place daughter cells beside each other†               |
| TA → SC        | Randomly replace a TA cell at the boundary by a SC†                            |
| TA → TA + TA   | Randomly replace a TA cell and place daughter cells beside each other         |
| TA → GA + TA   | Randomly replace a TA cell at the boundary and place daughter cells beside each other |
| GA → TA        | Randomly replace a GA cell at the boundary by a TA                             |
| Differentiation| Randomly replace a cell at the boundary by a cell of the new type              |
| Apoptosis      | Randomly choose a cell of proper type and remove                               |
| Desquamation   | Randomly choose a CC at the outmost location to remove                         |

†SCs only move laterally along the basement membrane.

In the psoriatic tissue, because of high density of proliferating cells, TA cells are allowed to migrate within a larger (but restricted) area, within a band parallel to the basement membrane. The height of the band is modulated by the density of proliferating cells with a 15 μm increment (decrement) for every 18000 mm−2 increase (decrease) in proliferating cell density.

In comparison to a fixed rete ridge, the dynamics of rete ridge remodeling is considered in the psoriasis model. We assume that the rete ridge remodels between normal and psoriatic structures according to proportions of normal and psoriatic cells. The fraction of normal progenitor cells is defined as

\[ r = \frac{\text{normal SC + TA cells}}{\text{total SC + TA cells}} \]  

where \( r \) is the time constant for the dynamics. We further assume that the rete ridge follows a first-order dynamics

\[ \tau \frac{dy}{dt} = Y - y \]  

Let \( y \) be the rete ridge height in time and \( Y \) is the target steady-state height. We assume the dynamics of the rete ridge is achieved remission in about 3-4 months \([5–7]\), we set the time constant \( \tau = 100 \text{ day} \).

From estimation, \( Y_{\text{max}} = 126 \text{ μm}, Y_{\text{min}} = 40 \text{ μm}, r_{\text{max}} = 1 \), and \( r_{\text{min}} = 0.001, \Delta t = 20 \text{ day} \). Based on data from successful UVB treatments showing that psoriasis plaques achieved remission in about 3-4 months \([5–7]\), we set the time constant \( \tau = 100 \text{ day} \).

| Event          | Operation rule                                                                 |
|----------------|-------------------------------------------------------------------------------|
| SC → SC + TA   | Randomly divide a SC and place daughter cells beside each other†               |
| SC → SC + SC   | Randomly divide a SC and place daughter cells beside each other†               |
| SC → TA + TA   | Randomly divide a SC and place daughter cells beside each other†               |
| TA → SC        | Randomly replace a TA cell at the boundary by a SC†                            |
| TA → TA + TA   | Randomly replace a TA cell and place daughter cells beside each other         |
| TA → GA + TA   | Randomly replace a TA cell at the boundary and place daughter cells beside each other |
| GA → TA        | Randomly replace a GA cell at the boundary by a TA                             |
| Differentiation| Randomly replace a cell at the boundary by a cell of the new type              |
| Apoptosis      | Randomly choose a cell of proper type and remove                               |
| Desquamation   | Randomly choose a CC at the outmost location to remove                         |

†SCs only move laterally along the basement membrane.

where \( \tau \) is the time constant for the dynamics. We further assume \( Y \) is linearly regulated by \( r \):

\[ Y = Y_{\text{max}} - \frac{(Y_{\text{max}} - Y_{\text{min}})(r - r_{\text{min}})}{r_{\text{max}} - r_{\text{min}}} \]  

Eq. (S15) is numerically solved by the finite difference method as follows:

\[ y(t + \Delta t) = \frac{Y(t) - y(t)}{\tau} \Delta t + y(t) \]  

where \( Y(t) \) is calculated from Eq. (S15).

| Event          | Operation rule                                                                 |
|----------------|-------------------------------------------------------------------------------|
| SC → SC + TA   | Randomly divide a SC and place daughter cells beside each other†               |
| SC → SC + SC   | Randomly divide a SC and place daughter cells beside each other†               |
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where \( \tau \) is the time constant for the dynamics. We further assume \( Y \) is linearly regulated by \( r \):

\[ Y = Y_{\text{max}} - \frac{(Y_{\text{max}} - Y_{\text{min}})(r - r_{\text{min}})}{r_{\text{max}} - r_{\text{min}}} \]  

where \( Y_{\text{max}} (Y_{\text{min}}) \) is reached at \( r = r_{\text{min}} (r = r_{\text{max}}) \).

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| Event          | Operation rule                                                                 |
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FIG. S4. Snapshots of simulated psoriatic epidermis under UVB irradiation (visualization of simulation in Fig. S3(a)). Each snapshot shows two fifth of the simulated length of 5 mm. Same types of normal and psoriatic cells are identically colored but with different contrasts as annotated in the top panel. The simulation starts at day 1 with an initial number of stem cells randomly distributed on the basement membrane. The simulated tissue grows through a transient phase (Day 41, a mix of normal and psoriatic cells are visible. Note that in this phase the disparity in growth rates of normal and psoriatic keratinocytes generate morphological heterogeneity in the epidermis.) to achieve a parallel homeostasis between normal and psoriatic keratinocytes (Day 1040, most cells are psoriatic and the epidermis thickens with extended rete ridges). Episodes of UVB irradiation reduce the cell population (Day 3057, at the early recovery with normal cells). After recovery, the epidermis is composed primarily of normal keratinocytes (Day 3635). In simulation, the rete ridge in psoriasis is dynamically extended (see the text for the dynamic model of rete ridge) to reach a height of 126 µm at the homeostasis (about 3-4 times larger than that of the normal tissue). Psoriatic TA cells are not anchored but migrate within a confined region above the basement membrane with a height about 2-3 times the mean TA cell size.