The Renewal of the Epidermis: A Topological Mechanism

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ABSTRACT Using a topological approach, we study the dynamics of the basement membrane of the mammalian epidermis when basal cells detach or divide. A theoretical characterization of the steady state of the tissue, in very good agreement with experimental data, includes for the first time the division and the disappearance of cells in a two-dimensional random cellular structure. We predict a strong correlation between the size of the attachment of basal cells to the basement membrane and their biological behavior (division or detachment). This suggests that the main factor determining the fate of basal cells, and thus controlling the renewal of the epidermis, is the cells' surface tension and adhesion.

INTRODUCTION

Many natural or engineered materials are disordered space-filling cellular structures. Common examples are bone tissues, plant stem, cork, food (bread, meringue, etc.), or polyurethane foams. Their simple topology and mechanical properties (obtainable from dimensional analysis; Gibson and Ashby, 1988) make them useful models in scientific fields as various as biology (epidermal tissues; Lewis, 1928; Rivier et al., 1995), metallurgy (polycrystals; Aboav, 1970), fluid interfaces (soap froth; Weaire and Phelan, 1994; Glazier and Weaire, 1992), and geography (administrative divisions; Pignol et al., 1993). The structural similarities between these different systems (despite the different forces involved) suggest that their topology may play a central role in their evolution.

During the last 10 years, many experimental, numerical, and theoretical studies have been made of the structural properties of cellular systems. Because of the complexity of three-dimensional structures, most of the work concerns two-dimensional (2D) systems (Rivier, 1994; Telley, 1989; Lemaitre et al., 1993).

The fact that tissue geometry and evolution can be described by simple physical or mathematical (filling space at random) models was recognized early on by Hales (1727), Errera (1886), Matzke (1950), Lewis (1928), and others (Dormer, 1980; Smoljaninov, 1980). So far, despite some interesting results (Rivier et al., 1995), the limitation to two dimensions did not allow a realistic description of the dynamics of biological tissues.

Our purpose in this paper is to take advantage of the layered structure of the epidermis of mammals to characterize its steady state and to model its renewal solely by topological means. The theory—which includes the detachment and mitosis of basal cells—predicts a strong correlation between the size of the attachment of basal cells to the basement membrane (an extracellular matrix rich in laminin and collagen isoforms) and their biological fate (division or detachment). The very small number of hypotheses and the topological description of the system imply that the results obtained are necessary conditions for the tissue to remain in steady state.

TOPOLOGICAL REPRESENTATION OF BIOLOGICAL TISSUES

To a first geometrical approximation, the epidermis of mammals can be regarded as a fluid of cells, filling at random the space between the dermis and the outer surface. Cells transit through the Malphigi layer from the one-cell-deep basal layer, where they are born (through mitosis), to the corneum layer, where they die (Montagna and Parakkal, 1974) (Fig. 1). The constant supply of cells needed for the renewal of the tissue is provided by the basal layer through the division and the detachment of its cells (the basal cells). They are the only cells of the epidermis that can divide. Modeling the dynamics of the renewal of the epidermis is thus tantamount to modeling the evolution and the dynamics of the basal layer.

The basal layer completely covers the dermis. Structurally, it consists of three-dimensional cells joined together without gaps. The space occupied by a leaving cell is automatically filled by its neighbors (T2 process of Fig. 4). Flat when the rate of division is low (epidermis of the chest or the ear), the basal layer becomes more corrugated as the rate of division increases (e.g., the skin of the palm of the hand). Because it is difficult to model the behavior of 3D cells (even when they all lie on a plane), we focus on the two-dimensional membrane that separates the dermis and the basal layer: the basement membrane.

Each basal cell is attached to the basement membrane through a polygonal facet (pentagon, hexagon, heptagon, etc.). If one assumes that the basement membrane is flat, the arrangement of the cells on the basement membrane looks like a jigsaw puzzle with polygonal pieces. Because no free space is left, this puzzle of simple geometrical elements fills

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Received for publication 30 December 1996 and in final form 17 April 1997.

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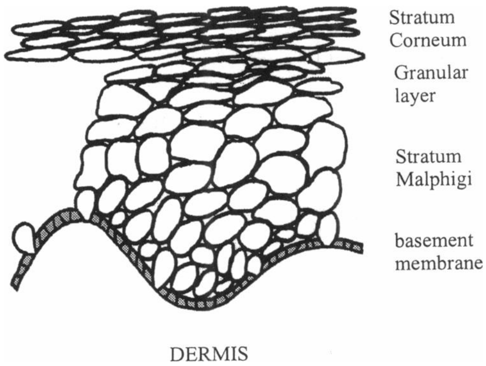

FIGURE 1 Vertical schematic cut of human epidermis (after Montagna and Parakkal, 1974).

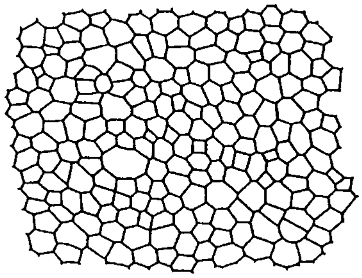

FIGURE 3 Schematic view of a cut of the epithelium of the cucumber (after Lewis, 1928). It is a typical example of a two-dimensional topological foam.

the two-dimensional basal layer completely and, at first sight, randomly (Fig. 2).

The link with physics is now more apparent: each cell's attachment can be compared to a topological cell, and the imprint of basal cells on the basement membrane to a two-dimensional topological foam (Fig. 3). Only the number of sides s of a polygon is relevant, not its specific shape or size.

Because both mitosis and detachment affect the attachment of basal cells, it is possible to reproduce the dynamics of the basal layer with the topological foam introduced above. When a basal cell leaves the basal layer, its attachment to the basement membrane disappears (the topological polygon representing this attachment disappears). The topological foam loses one cell and six interfaces. When a basal cell divides, its attachment also divides into two daughter cells (only vertical division is relevant; Dover and Wright, 1991). The two-dimensional cell representing this attachment also divides. It thus appears that the steady state of the basal layer (and hence the renewal of the epidermis) can be studied through the evolution of a two-dimensional topological foam that symbolizes a schematic but realistic view of the imprint of the attachment of basal cells on the basal layer (Figs. 2 and 3).

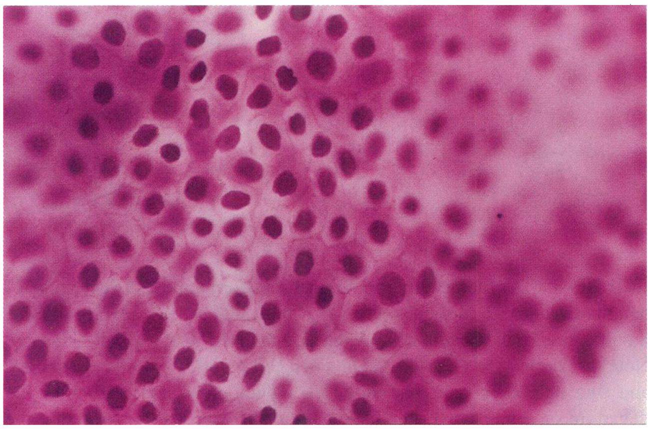

FIGURE 2 Horizontal cut of the basal layer of a stained sample of human epidermis, viewed with an optical microscope. The polygonal shape of the attachment of basal cells appears clearly in the focal plane. By changing the focal plane slightly and moving the sample around, we were able to obtain the frequency of the numbers of sides of the bottom of basal cells. The statistics are from 500 cells. The mean number of sides per cell is 5.99, in agreement with Euler's relation. The frequencies of s-sided cells are: 0.012 (s = 4); 0.208 (s = 5); 0.566 (s = 6); 0.194 (s = 7); 0.020 (s = 8).

STATISTICS OF 2D TOPOLOGICAL FOAMS

A topological foam (an example of which is shown Fig. 3) may be characterized statistically at different levels of sophistication. The simplest characterization—and the one most often used—is the frequency (or probability distribution) p_s of the number of sides s of the cells. Such a topological approach focuses on elementary, relevant features of the system. It gives geometrical information on the various ways the plane may be broken into jointed polygons (with the only rule that three polygons meet at every vertex). In our case, it also gives some information on the dynamic processes that drive the system during its evolution (here mitosis and detachment).

The set of all possible arrangements of the topological polygons is explored through local topological transformations of the cellular structure: disappearance and fragmentation of topological cells. These elementary topological transformations play the role of the collisions between the gas molecules. They shuffle the local, random variable s, and are responsible for the randomness and the steady state of the foam.

CHARACTERIZATION OF THE STEADY STATE OF THE BASEMENT MEMBRANE

The stage is now set for the calculation of the stationary distribution p_s. This can be done by using rate equations, which allow a local approach of the variation of cells' population. Used with success to model the equilibrium state of the cucumber's epithelium (Rivier et al., 1995), it gives (as we will see) a realistic description of the dynamics of the epidermis.

Four hypotheses are necessary:

1. The basal layer is flat (and so is the basement membrane).
2. No neighbors of a detaching (or dividing) cell divide or detach until detachment (or division) is over. This hypothesis enables us to study locally the influence of the dynamics of a cell on its neighbors.
3. The tissue is in statistical equilibrium ($dp_s/dt = 0$).
4. The horizontal pressure on the basal layer is isotropic (we need this to be able to calculate the way the neighborhood of a detaching cell is affected).

The prints of basal cells constitute a foam with N_s s-sided cells. The probability of finding a cell with an s-sided attachment is $p_s = N_s/N$, where $N = \Sigma_s N_s$ is the total number of foam cells. The system is assumed to be in statistical equilibrium; thus,

$$0 = \frac{dp_s}{dt} = \frac{1}{N}\left[\frac{dN_s}{dt} - p_s\frac{dN}{dt}\right] \tag{1}$$

Rate equation due to mitosis

When a cell divides, the population of s-sided cells is affected if 1) an s-sided cell divides, 2) a dividing k-cell has an s-sided daughter, 3) a neighboring s-sided cell is affected by the division, or 4) the affected neighbor had ($s - 1$) sides before division.

The distribution of the number of sides of the topological cells is a function of $P_m(k)$ (conditional probability that an existing k-sided cell divides), the break-up kernel $\Gamma(k \rightarrow s)$ (conditional probability that a k-sided dividing cell has an s-sided daughter), and the rate of cell division $D_m(k)$ (number of mitosis of k-sided cells per unit of time). Altogether, Eq. 1 reads:

$$\begin{aligned} 0 = {} & \sum_k p_k P_m(k) D_m(k) \\ & \left[\overbrace{-\delta ks}^{i} + \overbrace{\Gamma(k \rightarrow s)}^{ii} + (2/k)(\overbrace{M_{s-1}(k)}^{iii} - \overbrace{M_s(k)}^{iv}) - p_s\right] \end{aligned} \tag{2}$$

where the first four terms in the brackets correspond, respectively, to the topological mechanisms 1) through 4) described above. $M_s(k)$ is the mean number of k-sided cells neighboring an s-sided cell. The last term expresses the production of one extra cell during mitosis.

Rate equation due to the departure of basal cells

Apart from cell division, there is another topological process that allows the tissue to reach statistical equilibrium or to respond to local demand in cells: the departure from the basal layer (Fig. 4). When an s-sided cell leaves the basal layer, its attachment disappears and the attachment of its neighbors on the basement membrane may be topologically affected by losing or gaining sides. When a three-sided cell disappears, each neighbor loses one side; when a four-sided cell leaves, two of its neighbors lose one side, two are left unchanged; etc. (Fig. 4). On the whole, the departing cell takes exactly six sides with it, ensuring the global flatness of the tissue. The number of sides redistributed to its neigh-

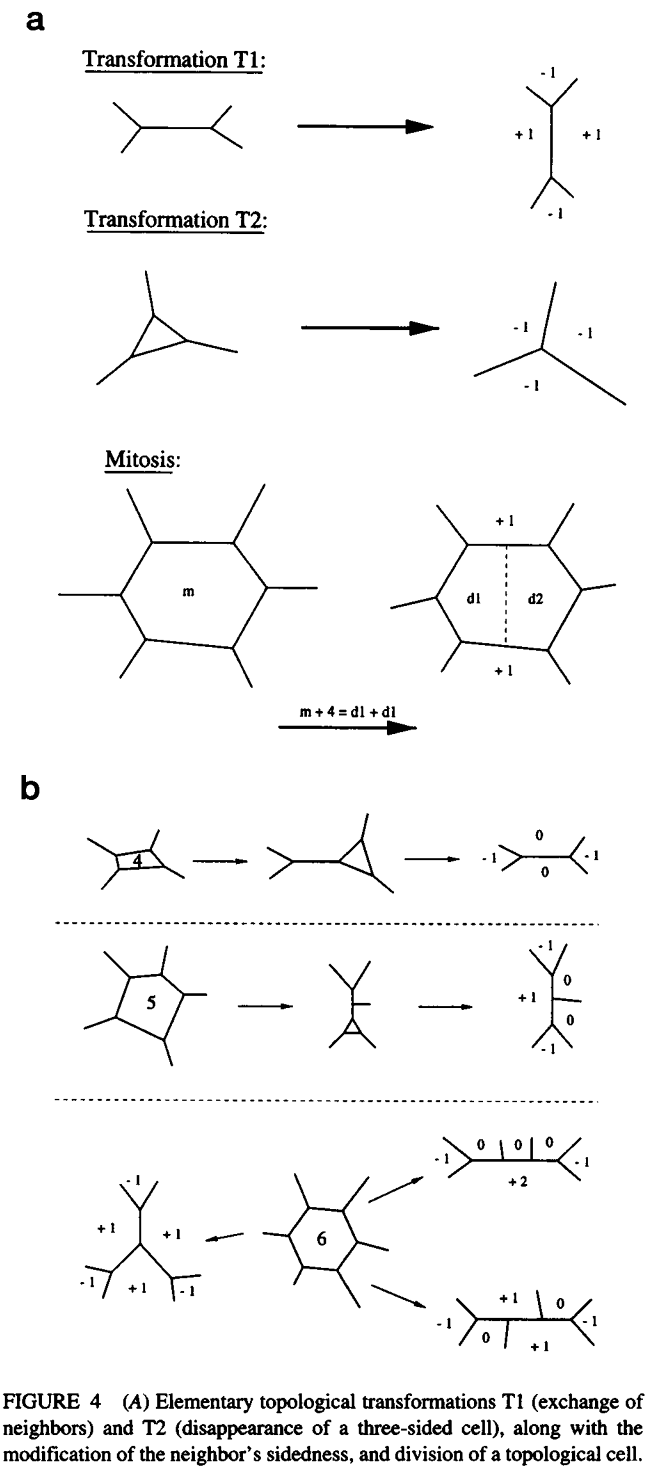

FIGURE 4 (*A*) Elementary topological transformations T1 (exchange of neighbors) and T2 (disappearance of a three-sided cell), along with the modification of the neighbor's sidedness, and division of a topological cell. Note that during the process, one m-sided cell is lost, two cells are gained, and two neighbors gain one side. (*B*) Topological scars left after the departure of a four-, five-, and six-sided cell, respectively. Note that the sum of the number of sides given (or taken) to the neighbors of an n-sided leaving cell is equal to $6 - n$. Disappearance of a cell is tantamount to the local disappearance of six sides; the global topological flatness of the tissue is conserved.

borhood is $n - 6$, a term proportional to the topological curvature of the leaving cell. One can understand this phenomenon as a local conservation of the topological curvature of the foam.

The detachment can be modeled on the topological foam through a cascade of two elementary topological process (see Fig. 4): the exchange of neighbors (T1 process) and the disappearance of a three-sided cell (T2 process). Actually, these two elementary transformations can be obtained from Alexander moves (Alexander, 1930) and may easily be generalized to higher dimensions. To model this cascade of topological processes, we choose a mean-field approach. We suppose that the pressure surrounding a departing cell is isotropic. Thus, during detachment, the sides of the polygon will move parallel to themselves and the smallest one will disappear first. This hypothesis enables us to compute analytically the conditional probability $a_i(k)$ that a k-sided detaching cell gives i sides $(-1 \leq i \leq k - 3)$ to one of its neighbors:

$$a_{-1}(k) = [(k - 3)a_{-1}(k - 1) + 1]/k, \qquad \text{for } k > 4$$

$$a_i(k) = [(k - 3)a_i(k - 1) + 2a_{i-1}(k - 1)]/k, \qquad \text{for } k > i + 5 \quad (3)$$

The initial condition is $a_{-1}(3) = 1$. Three-sided cells always take one side from each of their neighbors when going through a T2 process.

Incidentally, the problem of redistributing the sides of a disappearing topological cell was first analytically tackled by Le Caër (1991a,b). We preferred the mean field approximation because it is biologically realistic.

When a topological cell disappears, it leaves a "topological scar" (Fig. 4), which is actually a rearrangement of the neighborhood. Following the same reasoning as in the preceding paragraph, during the process of detachment, the population of s-sided cells is affected if 1) an s-sided cell detaches, 2) an s-sided neighbor of a detaching cell gains or looses sides, 3) a disappearing k-cell gives i sides to an $(s - i)$-sided neighbor, 4) a disappearing k-cell takes one side from an $(s + 1)$-sided neighbor.

For detachment, Eq. 1 reads:

$$0 = \sum_{k} p_k P_d(k) D_d(k)[\underbrace{-\delta_{ks}}_{i} - \underbrace{M_s(k)(1 - a_0(k))}_{ii} \\ + \underbrace{\sum_{i=1}^{s-3} M_{s-i}(k)a_i(k)}_{iii} + \underbrace{M_{s+1}(k)a_{-1}(k)}_{iv} + \mathrm{p_s}] \qquad (4)$$

The distribution of the number of sides of the topological cells is also a function of $P_d(k)$ (conditional probability that an existing k-sided cell leaves) and the rate of cell departure $D_d(k)$ (number of disappearing k-sided cells per unit of time).

Rate equation of the prints of basal cells

By adding Eqs. 2 and 4, one obtains the system of rate equations whose solution represents the steady state of the prints of basal cells upon renewal of the tissue:

$$0 = \sum_{k} p_k P_m(k) D_m(k)[-\delta_{ks} + \Gamma(k \rightarrow s) + (2/k)(M_{s-1}(k) \\ - M_s(k)) - p_s] + \\ \sum_{k} p_k P_d(k) D_d(k) \cdot [-\delta_{ks} - M_s(k)(1 - a_0(k)) \\ + \sum_{i=1}^{s-3} M_{s-i}(k)a_i(k) + M_{s+1}(k)a_{-1}(k) + p_s] \qquad (5)$$

Let us recall the parameters of the system:

1. $P_m(k)D_m(k)$ and $P_d(k)D_d(k)$: the conditional probabilities that a k-sided cell divides or detaches.
2. $\Gamma(k \rightarrow s)$, which depicts the way cells divide.
3. $M_s(k)$, the mean number of k-sided cells neighboring an s-sided cell. In the next section, we will give an analytical expression for $M_s(k)$, based on the principle of maximum entropy. This expression depends on a single structural parameter σ.

SOLUTION IN THE CASE OF A FLAT TISSUE

Calculation of $M_s(k)$

We have assumed that the tissue is in statistical equilibrium. Indeed, the human epidermis is invariant over a lifetime, whereas each cell divides or detaches every week. For an experimental verification of statistical equilibrium, see Lewis (1928).

Statistical equilibrium is a state of maximum entropy. It is the overall spatial arrangement that can be realized by the largest number of local configurations of cells and their neighbors. It is the state of maximum disorder allowed within a given set of constraints. For topological foams, there are three constraints:

$$\sum_{s} p_s = 1 \qquad (6)$$

$$\sum_{s} s p_s = 6 \qquad (7)$$

$$\sum_{s} M_s(k) = \sum_{s} N_{ks} p_s = k \qquad (8)$$

The first constraint normalizes the distribution p_s. The second states that the mean number of sides of the cells is exactly six. This comes from the fact that three edges meet at one vertex and from the Euler relation: for a cellular system, the number of cells minus the number of edges plus the number of vertices is a topological invariant. Equation 8 states that k-sided cells have k neighbors. It features the correlator $N_{ks} = N_{sk}$, which is six times the probability that, given a k-sided cell and an s-sided cell, they are neighbors.

N_{ks} is inferred by maximum entropy arguments to vary linearly as a function of s for structures in statistical equilibrium (Rivier and Lissowski, 1982; Peshkin et al., 1991): If the last constraint (Eq. 8) is a linear combination of the first two, it duplicates them, reduces the number of independent constraints, and thus increases the entropy.

The duplication yields the equation of state for N_{ks},

$$N_{ks} = (k - 6)\sigma(s - 6) + s + k - 6 \qquad (9)$$

σ is a structural parameter (Lagrange multiplier) resulting from the duplication condition. σ is in general negative and found to be approximatively $-1/\mu_2$ in natural structures (Rivier, 1993). $\mu_2 = \Sigma_n p_n(n - \langle n\rangle)^2$ is the second moment of the distribution p_n.

$M_s(k)$ can then be written:

$$M_s(k) = p_s N_{ks} = p_s[(k - 6)\sigma(s - 6) + s + k - 6].$$

Solution

The constrained system (Eq. 5) is a system of algebraic nonlinear equations. Up to now, to our knowledge, no efficient methods have been available for solving such systems. We choose to use the module HYBRD from the package MINPACK (retrieved from NETLIB). This code finds a zero of a system of n nonlinear functions in n variables by a modification of the Powell hybrid method.

It turns out that the range of parameters giving a mathematical solution ($1 \geq p_s \geq 0$) for the system of equations in Eq. 5 is very restricted. The best physical solution given by the solver is obtained for $D_m(k)P_m(k) = (|5.11 - k|)^8$, $D_d(k)P_d(k) = (|k - 7.01|)^8$, $\sigma = -1.3$, and a kernel of division $\Gamma(k \rightarrow s)$ that is fully symmetrical. This solution reproduces very well the experimental data shown in Fig. 5.

Methods and discussion

Because of the high number of parameters, we decided to investigate the possible solutions using a functional form for the families of parameters $P_d(k)D_d(k)$ and $P_m(k)D_m(k)$ (hereafter referred to as $F1(k)$ and $F2(k)$). The other parameters (σ and the kernel of division) are, in a first step, set to the experimentally known values: $\sigma = -1.3$ and a fully symmetrical division kernel. This method, which may appear arbitrary and restrictive, was applied with great success to solving the rate equation for mitosis alone (Eq. 2). In particular, we were able to check very precisely the analytical results found by Delannay and Le Caër (1994).

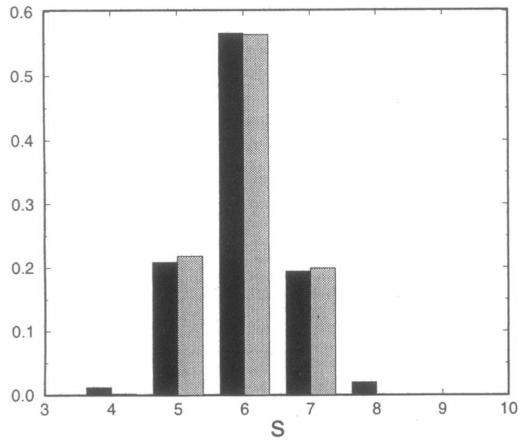

FIGURE 5 Experimental (*shaded*) and theoretical (*black*) distributions.

We tried several classical functions (exponential, logarithmic, polynomial) for $F1(k)$ and $F2(k)$. The only ones for which the numerical solver gives acceptable solutions are of the type $Fi(k) = (|a_i - k|)^{n_i}$, where a_i and n_i ($i \in 1, 2$) are four real parameters characterizing $Fi(k)$.

Within this class of acceptable solutions, we then search for the ones that verify the topological constraints (Eqs. 6 and 7) and the steady-state condition (number of leaving cells equals the number of dividing cells).

The steady-state condition yields $\mu_m = \Sigma_k p_k P_d(k)D_d(k) = \Sigma_k p_k P_m(k)D_m(k) = \mu_d$. This is equivalent to setting $dN/dt = 0$ in Eq. 1.

The steady-state condition is drastic. To satisfy it, σ must be negative ($\sigma \approx -1/\mu_2$), a_1 must be close to 5.1, a_2 must be close to 7.0, and n_1 must be equal to n_2. An increase or decrease in either a_i by less than 2% drives the system completely out of steady state (setting a_1 to 5.0 instead of 5.1 gives a ratio μ_m/μ_d equal to 2). The evolution of the system is therefore very sensitive to the parameter a_i. To fix n_i, we referred to the experimental distribution. $n_1 = n_2 = 8$ gives the best value for p_6, the maximum of the distribution. Decreasing n_i gives flatter distributions; increasing it drives the system out of steady state. However, this parameter is very much less crucial than a_i, as shown in Fig. 6 *A*.

Finally, Fig. 6 *B* depicts the influence on the steady-state distribution by the way cells divide. Only a few changes in the kernel of division are allowed if one wants to satisfy the steady-state condition. $\Gamma(k \rightarrow s)$ therefore appears to be another highly sensitive parameter of the system.

THE FATE OF BASAL CELLS

From the theoretical solution, we calculate the model predictions for the sidedness of the attachment of basal cells just when they are about to leave or divide. Biologically speaking, we are looking for a correlation between the fate of basal cells and the sidedness (i.e., topological size) of their attachment. $P_1(s) = p_s P_d D_d(s)/\mu_d$ (or $P_2(s) = p_s P_m D_m(s)/\mu_m$) is the probability that a cell about to leave (or divide) has an s-sided attachment to the basement membrane. These two distributions are plotted in Fig. 7. The relevant information of the plot is threefold: cells that will leave have a four- or five-sided attachment (smaller than average) before they start detaching; cells about to divide have a seven, eight, or nine-sided attachment (bigger than average) before they start dividing; six-sided cells neither divide nor detach. It is interesting to note that these prop-

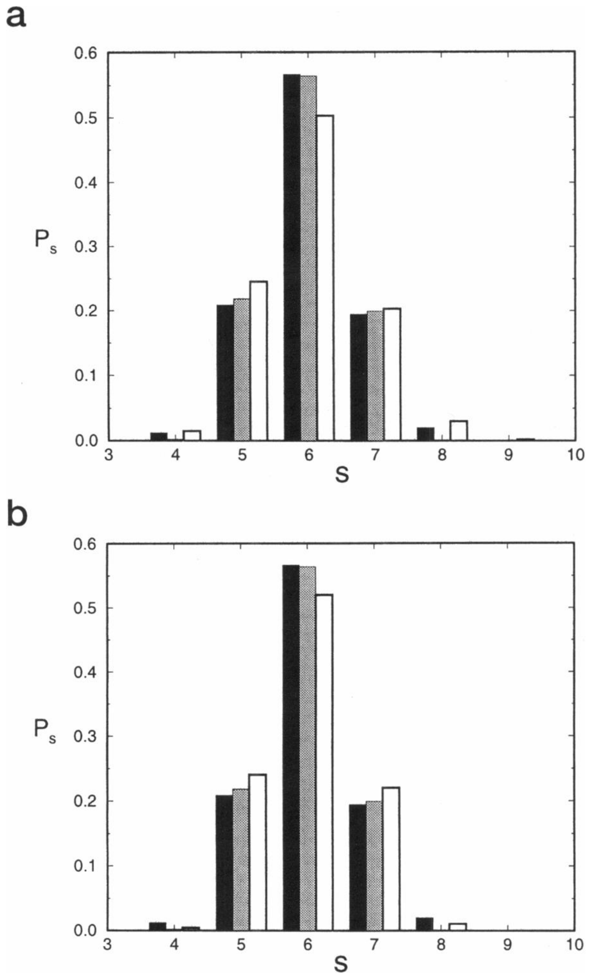

FIGURE 6 Influence of the variation of the different parameters. The theoretical (*gray columns*) and experimental (*black columns*) distributions of Fig. 5 are shown for comparison on both figures. (*A*) *White columns*, Distribution obtained for $F1(k) = (|5.11 - k|)^4$, $D_d(k)P_d(k) = (|k - 7.01|)^4$, $\sigma = -1.3$, and kernel of division $\Gamma(k \rightarrow s)$ fully symmetrical. (*B*) *White columns*, Distribution obtained for $F1(k) = (|5.11 - k|)^8$, $D_d(k)P_d(k) = (|k - 7.01|)^8$, $\sigma = -1.3$, and kernel of division $\Gamma(k \rightarrow s)$ not fully symmetrical.

erties stay valid for all of the parameters we tried. Even solutions out of steady state give this result.

Although the model is purely topological, its solutions are the ones expected in 2D foams whose dynamics are driven by the surface tension of the cells; the results of Fig. 7 are in perfect agreement with von Neumann's law (von Neumann, 1952). As pointed out by Rivier (1993), it is energetically favorable for a topological cell (with surface tension) of more than six sides to increase its surface, whereas it is the opposite if it has less than six sides.

The surface tension of basal cells may therefore be an intrinsic signal sufficient to drive the cells toward division, detachment, or the resting state. Although this may not be the only mechanism involved in the process of the tissue renewal, it is—in the point of view of physicists—sufficient to explain the steady state of the basal layer.

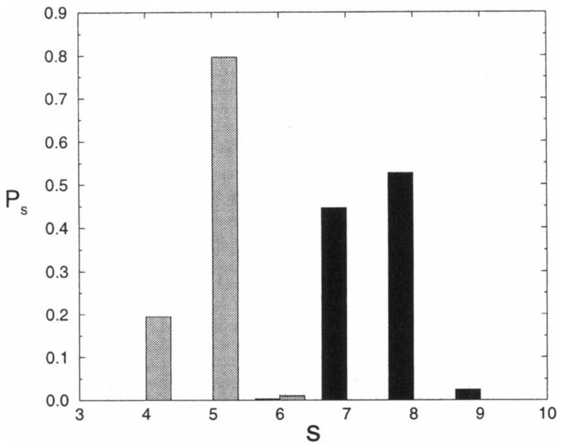

FIGURE 7 *Gray columns*, Distribution of the number of sides of the cells about to detach. *Black columns*, Distribution of the number of sides of the cells about to divide.

CONCLUSIONS

Although the renewal of the epidermis is a complex process that is not yet fully understood, this work shows that, by means of elementary topology, and by using the layered structure of the epidermis, one is able to characterize (at the crudest level) the steady state of the system.

We model the renewal of the basal layer using the 2D prints of the cells on the basement membrane. We made the following hypotheses: 1) the basement membrane is flat and is in statistical equilibrium, 2) the horizontal pressure on the basal layer is isotropic, 3) no neighbors of a detaching (or dividing) cell divide or detach until detachment (or division) is over. Although the problem features many parameters, only a few are relevant, and their range is drastically reduced by the steady-state constraint.

All solutions imply that the larger the attachment of a basal cell to the basement membrane, the more likely it is to divide. Cells with a smaller attachment than average are likely to detach and ascend in the epidermis. This suggests that a cell's surface tension and adhesion (Graner and Sawada, 1993; Jones et al., 1995) play a paramount role in the renewal of the epidermis.

The authors thank Dr. G. Schliecker for her contributions to this work and its presentation and D. Chatenay for helpful discussions. BD thanks Dr. Lorna Gibson (M.I.T.) for greeting him in her group, and the research team INSERM U312 for biological data and very useful discussions. The tissue was stained and pictures were made with help from Dr. Bronson (Tufts University).

This work was partially supported by the EU Mobility Program; the FOAMPHYS Network, contract ERBCHRXCT940542; and by La Société Christian Dior (BD).

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