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The Follicular Automaton Model: Effect of Stochasticity and of Synchronization of Hair Cycles

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Human scalp hair consists of a set of about 10^5 follicles which progress independently through developmental cycles. Each hair follicle successively goes through the anagen (A), catagen (C), telogen (T) and latency (L) phases that correspond, respectively, to growth, arrest and hair shedding before a new anagen phase is initiated. Long-term experimental observations in a group of ten male, alopecic and non-alopecic volunteers allowed determination of the characteristics of hair follicle cycles. On the basis of these observations, we previously proposed a follicular automaton model to simulate the dynamics of human hair cycles and the development of different patterns of alopecia [Halloy *et al.* (2000) *Proc. Natl Acad. Sci. U.S.A.* **97**, 8328–8333]. The automaton model is defined by a set of rules that govern the stochastic transitions of each follicle between the successive states A, T, L and the subsequent return to A. These transitions occur independently for each follicle, after time intervals given stochastically by a distribution characterized by a mean and a standard deviation. The follicular automaton model was shown to account both for the dynamical transitions observed in a single follicle, and for the behaviour of an ensemble of independently cycling follicles. Here, we extend these results and investigate additional properties of the model. We present a deterministic version of the follicular automaton.We show that numerical simulations of the stochastic version of the automaton yield steady-state level of follicles in the different phases which approach the levels predicted by the deterministic equations as the number of follicles progressively increases. Only the stochastic version can successfully reproduce the fluctuations of the fractions of follicles in each of the three phases, observed in small follicle populations. When the standard deviation is reduced or when the follicles become otherwise synchronized, e.g. by a periodic external signal inducing the transition of anagen follicles into telogen phase, large-amplitude oscillations occur in the fractions of follicles in the three phases. These oscillations are not observed in humans but are reminiscent of the phenomenon of moulting observed in a number of mammalian species.

1. Introduction

Hair coverage of human scalp is the result of a dynamical process involving some 10^5 hair follicles which continually evolve in the course of time. At any moment, a follicle is either growing (anagen phase), ceasing to grow and involuting (catagen phase) but still on the scalp (telogen phase) before shedding, or in latency before entering a new cycle (latency phase). These successive

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phases constitute a follicular cycle (Hardy, 1992; Stenn *et al.*, 1998). The duration of such a cycle is variable, but typically ranges from a few months to several years (Courtois *et al.*, 1994, 1995). Each follicle can undergo repeated cycles until it eventually dies or miniaturizes (Whiting, 1998). Local loss of follicles may lead to various patterns of alopecia (Hamilton, 1951). A different type of dynamic behaviour is seen in some mammalian species in which periodic moulting is observed (Milne *et al.*, 1990; Dicks *et al.*, 1994; Thornton *et al.*, 1996).

A study carried out over a period of 14 years in a group of ten normal and alopecic male volunteers has provided a comprehensive set of data on the dynamics of the human hair cycle (Courtois *et al.*, 1994, 1995, 1996). These data yield for a group of subjects the detailed timing of transitions between the successive follicular phases over more than a decade. Thus, about 9000 hair cycles were recorded and characterized for a total of about 930 hair follicles followed monthly.

In a previous publication (Halloy *et al.*, 2000), we have used this large body of data on follicular cycles for normal and alopecic subjects to develop an automaton model for the dynamics of human hair cycles. This model simulates stochastic transitions between the successive phases of the follicular cycle, and was therefore referred to as the "follicular automaton". The model was used to investigate the short- and long-term dynamics of human hair. We first simulated by means of the follicular automaton the time evolution of the distribution of hair follicles in the anagen, telogen and latency phases in a few non-alopecic and alopecic subjects considered in the experimental study. In a second stage, by including the death or miniaturization of a follicle after a critical number of hair cycles, we applied the follicular automaton model to the spatio-temporal evolution of an ensemble of cycling follicles (Halloy *et al.*, 2000) to account for patterns of androgenetic alopecia seen in men (Hamilton, 1951) or diffuse alopecia seen in women (Ludwig, 1977).

Here, we further investigate the follicular automaton to refine our previous analysis and to bring to light additional properties of the model. In Section 2, we recall the rules governing the time evolution of the automaton model. In Section 3, we introduce a deterministic version of the follicular automaton that predicts the mean levels of follicles in anagen, telogen and latency phases when the number of follicles considered becomes large. In Section 4, we account for the time evolution of a population of follicles in non-alopecic and alopecic subjects and investigate how the fluctuations of populations of follicles in the different phases depend on the number of follicles. We compare the predictions of the stochastic and deterministic versions of the model. In Section 5, we show how the synchronization of follicular cycles in the model leads to moulting, as observed in various animal species.

2. The Follicular Automaton

We begin by summarizing the rules governing the time evolution of the follicular automaton (Halloy *et al.*, 2000). The hair cycle is represented as the succession of the anagen (A), telogen (T) and latency (L) phases. The catagen phase is relatively brief (< 1 month) and cannot be distinguished from telogen phase by the phototrichogram method; therefore, it is lumped into the longer telogen phase. The follicular automaton (schematized in Fig. 1) remains in a given phase during a variable interval of time, after which it moves to the next phase. The automaton completes a cycle when entering a new A phase. Follicular death or miniaturization (M) can be included in the model by adding a transition from state T, that removes the follicle from its developmental cycle. Data from the experimental study on which the present model is based indicate that the latter transition remains negligible, so that it will not be considered in the following.

Most models of the "cellular automaton" type (Ermentrout & Edelstein-Keshet, 1993) incorporate interactions between neighbouring automata. This will not be the case for the follicular automaton, because follicles to a large extent appear to behave independently (Hardy, 1992; Stenn *et al.*, 1998).

The follicular automaton model will primarily be treated in a stochastic manner. However, we will also consider in Section 3 the limiting case in which the model is deterministic in nature. In the stochastic version of the model, each follicle in

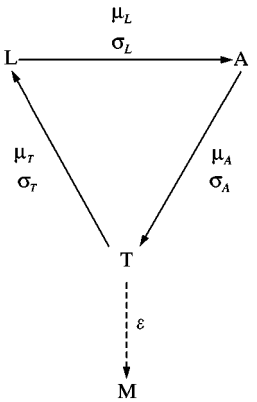

FIG. 1. The follicular automaton (Halloy *et al*., 2000). The figure represents the transition of a model follicle from anagen (A) to telogen (T) and to latency (L) phase, successively. After phase T, the follicle may either die or miniaturize (transition to M; this may happen after some critical number of cycles), or complete a cycle by entering a new A phase. In the deterministic version of the model, the transitions occur with "kinetic" constants that are inversely proportional to the mean durations μ_A, μ_T, μ_L of A, T and L phases. The transition to M is characterized by a rate constant ε. In the stochastic version of the model, the values of the duration of each phase are given by distributions characterized by mean values and by standard deviations σ_A, σ_T, σ_L. The time evolution generated by the follicular automaton is obtained numerically following the procedure described in the text (see Section 2).

a field of hair follicles is characterized by (a) its spatial position, (b) its state (phase A, T, L, or M), (c) the time to the next transition, and (d) the number of cycles performed since entering the first anagen phase.

Given that the measurements were performed for a limited number of hair cycles on any given volunteer, typically ten successive cycles on average for 100 follicles, the duration of the different phases fluctuates significantly from cycle to cycle. In our previous study, we compared the theoretical predictions with experimental observations bearing on three typical subjects, designated 1, 2, and 3, who correspond, respectively, to subjects A, F, and G of the experimental study (Courtois *et al*., 1994, 1995, 1996). Subject 1 is non-alopecic, whereas subjects 2 and 3 are alopecic. Here, we will illustrate the model predictions by means of additional comparisons with subjects 4 and 5 who correspond, respectively, to subjects B (non-alopecic) and H (alopecic) of the experimental study (Courtois *et al*., 1994, 1995, 1996).

Figures 2(a)–(c) show the duration of phases A, T and L measured over 144 successive months on subject 4. These data indicate that the phase duration (in months) fluctuates around mean values of 19.8, 2.1 and 4.9 for phases A, T, and L, respectively. For phase A the standard deviation is of the order of the mean, for phase L the standard deviation is larger, while it is relatively low with respect to the mean for the telogen phase. As will be shown below, the stochastic nature of the transitions has important consequences for the collective behaviour of a field of cycling hair follicles.

We have chosen to represent the distribution of the durations of each follicular phase by a lognormal function (Halloy *et al*., 2000):

$$f(x;\,\mu,\,\sigma) = \frac{1}{x\sqrt{2\pi\sigma}} \exp\left[-\frac{1}{2\sigma^2}(\log x - \mu)^2 \right], \tag{1}$$

where x is the duration, and μ and σ are, respectively, the mean and standard deviation of the distribution of durations for a given phase. The three phases generally differ by the values of μ and σ. For simulations with the follicular automaton, we take for μ and σ the values calculated from experimental data for each phase and subject. The choice of a lognormal distribution stems from the fact that, in agreement with experimental observations, this positively defined function is skewed toward small durations but still presents a long tail corresponding to durations that are long with respect to the mean. Other distributions, such as the exponential one, would likely lead to similar results.

Figures 2(d)–(f) show histograms generated by the model for the parameters of subject 4, when considering a reduced number of follicles (about 100), as in the experimental study. Because (i) the simulations are carried out with a limited number of follicles, (ii) during a finite time, (iii) by drawing random numbers distributed according to the lognormal equation (1) (Press *et al*., 1986), the theoretical distributions give mean values and standard deviations close (but not identical) to the experimental ones, even though the experimental values of μ and σ were used in eqn (1).

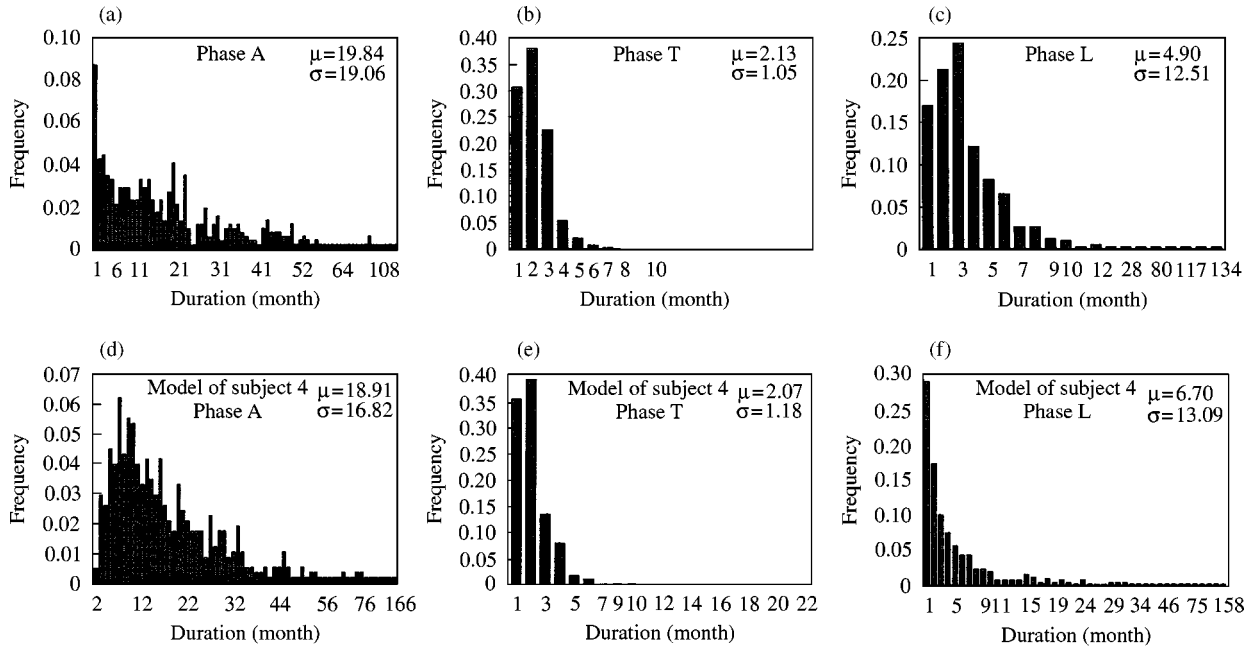

FIG. 2. Histograms of the durations of anagen, telogen and latency phases. Panels (a)–(c): experimental data obtained for subject B (referred to here as subject 4) in the experimental study of Courtois *et al.* (1994, 1995). Panels (d)–(f): histograms obtained theoretically by means of lognormal distribution [eqn (1)], when using for each phase the mean value and the standard deviation as determined and indicated in the corresponding panel (a), (b) or (c). The mean value and standard deviation predicted by the model are indicated in panels (d)–(f). The scale of abscissas is not continuous as durations corresponding to nil frequencies have been omitted from the histograms.

To generate the evolution of cycling follicles, we iterate the following steps (Halloy *et al.*, 2000), assuming that all follicles evolve independently from one another. (1) We begin by fixing the initial conditions, i.e. the state (A, T or L) of each follicle. The initial number of cycles is set equal to zero. The time interval to the next transition in the cycle $A \rightarrow T \rightarrow L \rightarrow A$ is determined randomly for each follicle according to the distribution of durations given for each phase by eqn (1). (2) At each time step (equal to 1 month), the time to the next transition is reduced by 1 month. Each follicle is tested to determine if the time has come to undergo a transition to the next phase in the cycle. For the follicles that undergo such a transition, a time interval to the next transition in the cycle is again determined randomly according to the distribution of durations given for the new phases by eqn (1). As soon as the follicle enters a new anagen phase, the count of cycles increases by one. (3) At each time step, we determine the number of follicles in phase A, T or L as well as other characteristics such as the mean number of cycles performed by follicles in the area considered. The algorithm returns to step 2 until the specified end of the simulation is reached.

Before turning to the collective dynamics of a field of cycling follicles, it is useful to compare the time evolution of a given follicle in the experimental study and in the automaton model. In our previous publication (Halloy *et al.*, 2000), we performed such a comparison for alopecic subject 3 of the experimental study. Here, we illustrate the dynamics of a single follicle for another subject of the experimental study. The transitions observed over the whole course of the experimental study for non-alopecic subject 4 are shown in Fig. 3(a). Figure 3(b) shows the transitions generated by the follicular automaton model when inserting into eqn (1) the values of μ and σ calculated for each phase from the experimental data for this subject. The comparison of the two panels of Fig. 3 indicates that the model generates a time course that captures the essential features of the transitions between anagen, telogen and latency phases.

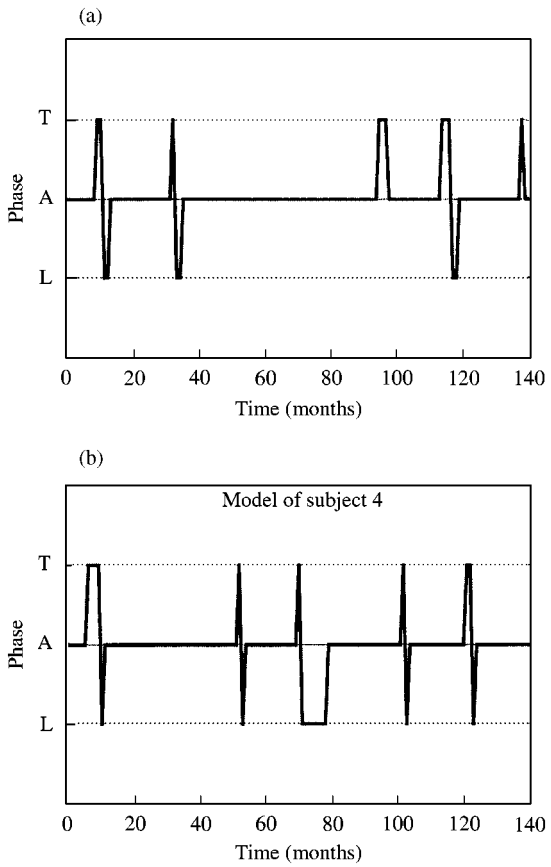

FIG. 3. Typical sequence of transitions between anagen (A), telogen (T) and latency (L) phases for a single follicle, as observed for subject 4 of the experimental study [panel (a)] and generated by the follicular automaton model using eqn (1) [panel (b)]. For the three duration distributions, the values considered for the mean and standard deviation, determined from the experimental data, are (in months) $\mu_A = 18.91$, $\sigma_A = 16.82$, $\mu_T = 2.07$, $\sigma_T = 1.18$, $\mu_L = 6.70$, $\sigma_L = 13.09$; see Figs. 2(d)–(f)

3. Deterministic Version of the Follicular Automaton

In the deterministic version of the follicular automaton model, we ignore the variability of durations of the different phases that is observed for any given follicle and consider only the mean duration of each of the three follicular phases. Thus, much as in chemical reaction systems, the transition from one phase to the next is governed by a kinetic constant that is inversely proportional to the duration of the phase from which the transition occurs (Nicolis & Prigogine, 1977). Denoting by A, T and L the fractions of follicles in the corresponding phases, we obtain the following differential equations which yield their time evolution:

$$\mathrm{d}A/\mathrm{d}t = (1/\mu_L)L - (1/\mu_A)A,$$

$$\mathrm{d}T/\mathrm{d}t = (1/\mu_A)A - (1/\mu_T)T,$$

$$\mathrm{d}L/\mathrm{d}t = (1/\mu_T)T - (1/\mu_L)L - \varepsilon M. \qquad (2)$$

These equations admit a unique, stable steady-state solution that yields the proportions of follicles in the three phases after transients have died out. For $\varepsilon = 0$, i.e. when disregarding follicular death or miniaturization (see above), this steady state, denoted by subscript 0, is given by

$$A_0 = \mu_A/(\mu_A + \mu_T + \mu_L),$$

$$T_0 = \mu_T/(\mu_A + \mu_T + \mu_L),$$

$$L_0 = \mu_L/(\mu_A + \mu_T + \mu_L). \qquad (3)$$

4. Dynamics of a Population of Hair Follicles

Experimentally it is possible to characterize the general state of hair for any given individual by determining the relative proportions of hair follicles in anagen, telogen and latency phases. Panels (a) and (b) of Fig. 4 show the time evolution of the fractions of follicles in the three phases recorded for non-alopecic subject 4 and alopecic subject 5, respectively. Panels (c) and (d) of Fig.4 present the corresponding simulations of the follicular automaton model in which the values of μ_A, μ_T and μ_L considered in eqn (1) are equal to the mean values of the durations of A, T and L phases as determined from experimental observations on the two subjects. In the simulations, all the 100 follicles considered are taken initially as being in anagen phase. Very quickly the fractions evolve toward a level around which they fluctuate, similarly to what is experimentally observed. To a large degree, the follicular automaton model reproduces the qualitative and quantitative characteristics which differentiate the two individuals compared in Figs. 4(a) and (b). Because of the stochastic nature of the model, another simulation would give a similar, though

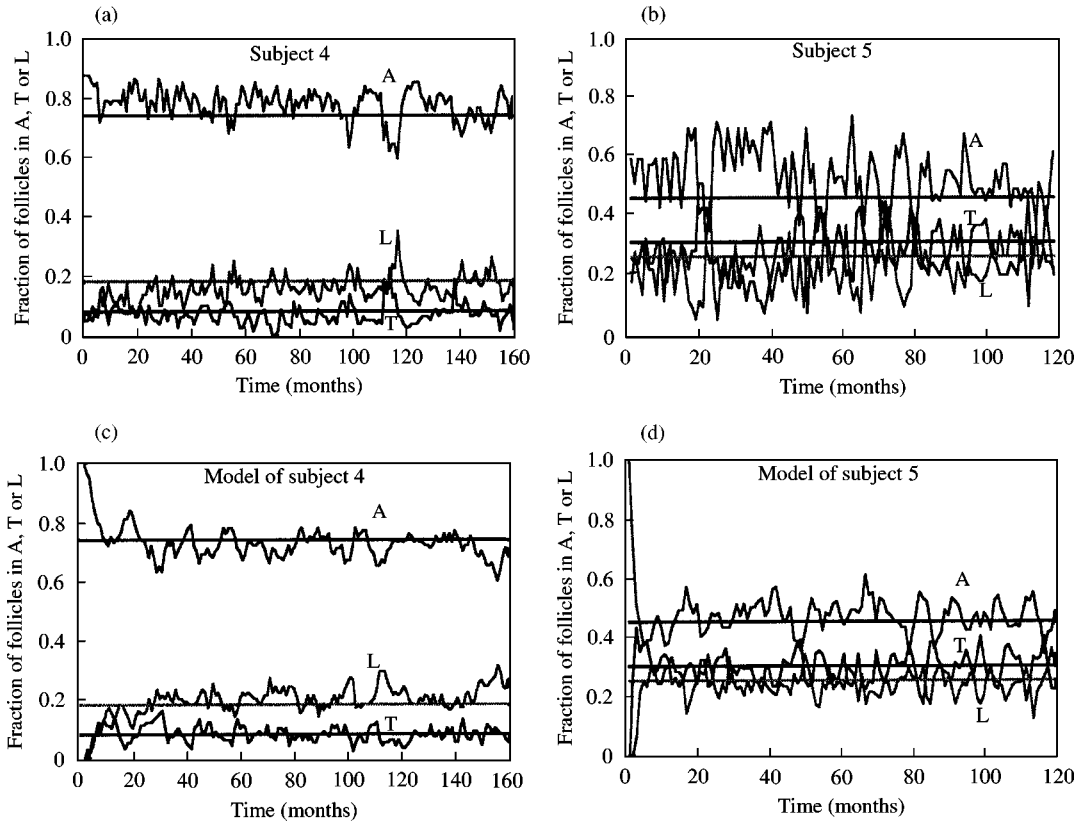

FIG. 4. Proportions of follicles in anagen, telogen and latency phases. The experimental data have been obtained for nonalopecic subject 4 [panel (a)] and for alopecic subject 5 [panel (b)]. The corresponding theoretical curves, shown in panels (c) and (d), are generated by the follicular automaton, taking for the mean and standard deviation in eqn (1) the values determined from the corresponding experimental data in panels (a) and (b). These values, for subject 4, are those given in the legend to Fig. 3, while for subject 5, the values are (in months) $\mu_A = 3.6$, $\sigma_A = 2.8$, $\mu_T = 2.4$, $\sigma_T = 1.1$, $\mu_L = 2.0$, $\sigma_L = 1.0$. The horizontal lines in panels (a)–(d) indicate the steady-state values obtained using eqns (3) for subjects 4 and 5 in the deterministic version of the follicular automaton model governed by eqns (2). The initial conditions in panels (c) and (d) correspond to a situation in which 100 (independent) follicles start in anagen phase.

not identical, evolution of the three fractions for each individual.

The data of Fig. 4 indicate that the fraction of anagen follicles is significantly larger for nonalopecic subject 4 compared with alopecic subject 5. This results from the fact that the mean duration of anagen phase is longer for the nonalopecic subject. Moreover, the fraction of telogen follicles is higher for subjects 5 vs. subject 4. Similar differences between alopecic and nonalopecic subjects were noted when comparing the experimental and theoretical distributions of hair follicles in the three phases for subjects 1 and 2 of the experimental study (Halloy *et al.*, 2000).

In (a) and (b), the fractions, determined experimentally for some 100 cycling follicles, fluctuate around a roughly constant level. This evolution is well reproduced by the stochastic version of the follicular automaton, as shown in panels (c) and (d) of Fig. 4, which correspond to the experimental results shown in panels (a) and (b), respectively. When inserting into eqns (3) for μ_A, μ_T and μ_L the mean values of the duration of the A, T and L phases determined from experimental observations (see Fig. 2 and legend to Fig. 4), we obtain for subjects 4 and 5 the steady-state fractions of follicles in the three phases. These fractions are indicated in panels (a) and (b) of Fig. 4 by solid lines. The results indicate that the deterministic version of the model roughly predicts for the different subjects the values generated by stochastic simulations for the mean proportions of follicles in the different phases.

The fluctuations seen in Fig. 4 are due to the small number of follicles—of the order of 100—followed in the course of time. As shown in Fig. 5, established for the parameter values corresponding to subject 5, the amplitude of the fluctuations reduces as the number of follicles considered increases. Thus, when the number of follicles passes successively from 100 [as in Fig. 4(d) established for different initial values of the fractions of follicles in A, T or L phase] to 10^3, 10^4 and 10^5, the effect of stochasticity subsides as the fractions tend with less and less fluctuations to the steady-state values predicted by the deterministic equations (3).

For subject 5, the values given by eqns (3) for the steady-state fractions of follicles in A, T and L phases are 0.450, 0.300, and 0.250 [see Fig. 4(d)]. These values compare with the results of numerical simulations of the stochastic version of the follicular automaton performed with large numbers of follicles (see Fig. 5), which yield the corresponding values of 0.476, 0.285, and 0.239. The difference between the values obtained from the deterministic analytical expressions and the numerical simulations is of the order of 5%. This difference is not so large, given that (i) the stochastic and deterministic descriptions only share the same values of the mean durations of the three follicular phases, and (ii) the stochastic treatment relies on a particular, lognormal distribution of phase durations around these mean values.

What is clearly gained with respect to the deterministic result given by eqns (3) is that the stochastic version of the follicular automaton is capable of accounting for the observation that for measurements performed on low numbers of follicles (a constraint that holds in the

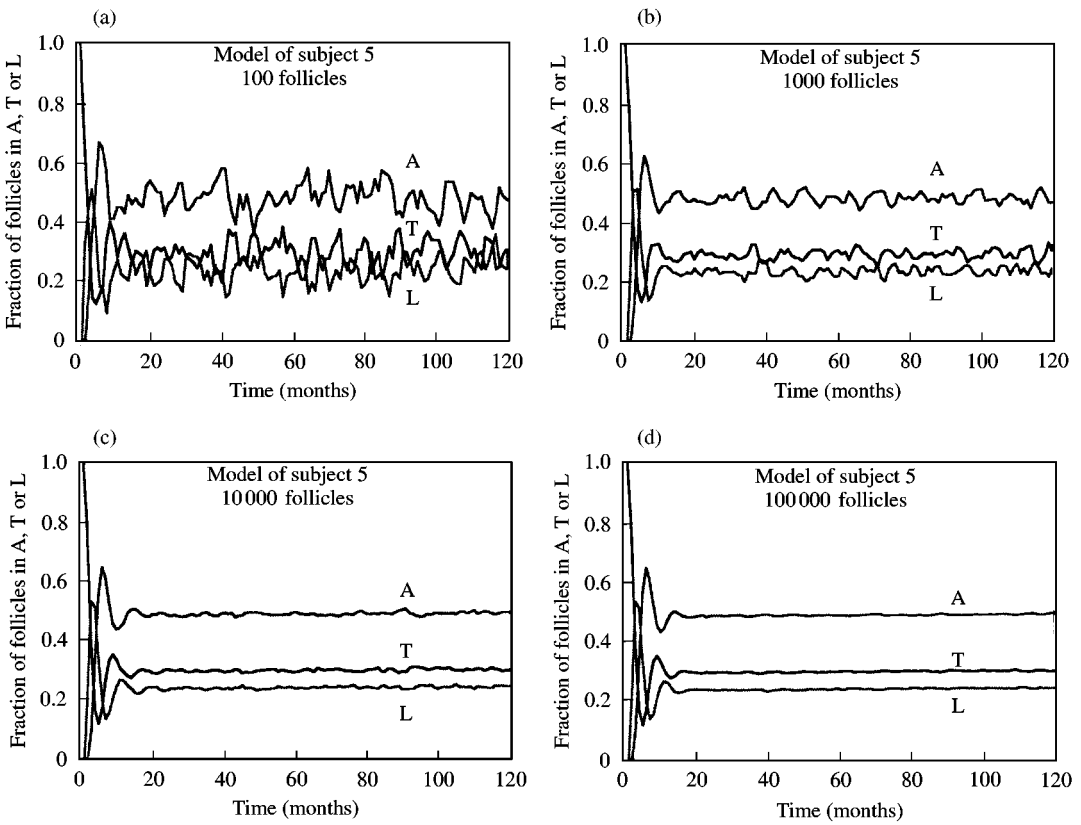

FIG. 5. Effect of number of follicles on the dynamics of a population of independently cycling follicles. The theoretical curves yielding the proportions of follicles in A, T and L phases are obtained for the parameter values corresponding to subject 5 at various numbers of follicles equal to (a) 100 [as in Fig. 4(d), obtained for other initial conditions], (b) 10^3, (c) 10^4, and (d) 10^5. As can be expected, the amplitude of fluctuations progressively diminishes as the number of follicles increases. Parameter values are those considered in Fig. 4(d).

experimental study involving human volunteers, on which the present model is based), the fraction of follicles in each of the three phases fluctuates around the level predicted by the deterministic model.

5. Effect of Synchronization of Hair Follicular Cycles: Oscillatory Dynamics

The standard deviation σ of the distribution of duration of each of the three follicular phases measures the variability of these durations around the mean value μ. The question arises as to what happens when this standard deviation is progressively reduced. In the limit $\sigma \to 0$, all follicles become synchronized since the durations for the three phases tend to be the same for each follicle. The result of a simulation in these conditions is illustrated in Fig. 6. Starting from initial conditions corresponding to fractions of follicles in A, T and L phases between 0.3 and 0.4, we generate by means of the procedure outlined in Section 2 the time evolution of the three fractions for mean durations of 20, 2 and 4 months for the A, T and L phases, respectively. Now, however, the standard deviation for each of the three distributions is set equal to 1 month. This value is much reduced as compared to the mean and to the experimental values (see Figs 2, 4 and 5).

In contrast to the results shown in Fig. 4 for larger σ values, the behaviour of the cycling follicles becomes highly regular. The data of Fig. 6 indeed indicate the existence of large-amplitude oscillations over time. The follicles rapidly synchronize due to the low standard deviation that characterizes the duration of each phase, they undergo nearly concomitantly the successive transitions in the follicular cycle. After a few cycles, the fraction of anagen follicles oscillates between about 0.6 and 1.0 in the case considered. However, because the standard deviation is not nil, the oscillations progressively diminish in amplitude and finally transform into fluctuations around the steady-state levels. As expected, the trough in anagen follicles during oscillations corresponds to peaks in the fractions of follicles in telogen and latency. The period of these oscillations is roughly equal to the sum of the durations of the three phases, i.e. 26 months in the case considered in Fig. 6.

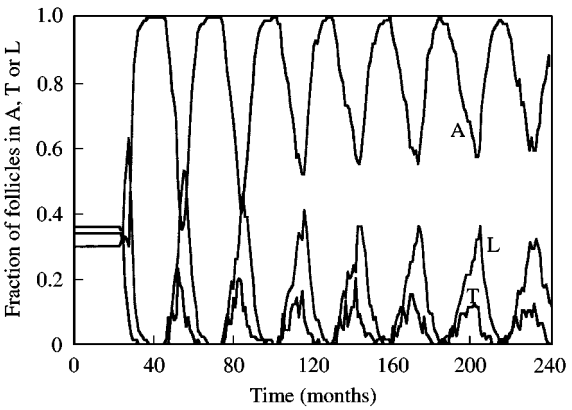

FIG. 6. Effect of synchronization of cycling follicles. When the standard deviation σ of the distributions of durations of anagen, telogen and latency phases is small, large-amplitude oscillations occur in the fractions of follicles in A, T and L phases. Because the standard deviation of each duration distribution is not nil, however, the oscillations progressively decrease in amplitude and finally transform into fluctuations around mean levels, as in panels (c) or (d) in Fig. 4. The curves are generated by the stochastic version of the follicular automaton model using eqn (1), taking the values (in months) $\mu_A = 20$, $\mu_T = 4$, $\mu_L = 2$ for the mean of the duration distribution of the A, T and L phases, respectively. The standard deviation σ of each of the three distributions is set equal to 1 month, which is a much smaller value than in panels (c) and (d) of Fig. 4. Initial conditions correspond to fractions of follicles in A, T and L phases equal to 0.34, 0.36, and 0.3, respectively. Similar results are obtained for different initial conditions, even when the latter are close to the deterministic steady state predicted by eqn (3).

The rapid synchronization illustrated in Fig. 6 occurs despite the nearly equal initial proportions of follicles in the three phases. We verified that the synchronization is independent of initial conditions and occurs even if the system is started from conditions close to steady state. Synchronization is enhanced by the choice of mean durations for the T and L phases that are much smaller than the mean duration of the A phase. If the duration of the latter phase is decreased to, e.g. 10 months, the oscillations lose their coherence more rapidly (results not shown).

Although seasonal changes and periodicity in the growth and shedding of hair have been reported (Randall & Ebling, 1991; Courtois *et al.*, 1996), large-amplitude oscillations resulting from follicular synchronization are not observed for the human scalp, because each follicle in this case behaves independently of its neighbours. However, the oscillatory behaviour shown in Fig. 6 is

reminiscent of the periodic moulting that characterizes a number of mammalian species (Milne *et al*., 1990; Randall *et al*., 1993; Dicks *et al*., 1994; Thornton *et al*., 1996). Synchronization of follicular cycles can sometimes occur in man but only in particular physiological conditions. Thus, synchronized hair loss can be observed after pregnancy, a phenomenon known as *post-partum telogen effluvium* (Headington, 1993); this transient synchronization, however, does not given rise to successive cycles of the kind shown in Fig. 6 and seen in moulting.

There is, however, another mechanism that may give rise to synchronization of follicles and to their oscillatory dynamics. Rather than relying on a sustained decrease of the standard deviation, a more physiologically plausible scenario involves the action of an external signal that would trigger the passage of all anagen follicles into telogen phase. Such an effect is thought to underlie the action of melatonin which displays a yearly rise in some animals and triggers periodic shedding of their hair (Milne *et al*., 1990). The effect of such a periodic external signal can readily be simulated by the model, as illustrated for a set of 100 follicles in Fig. 7(a), where after 70 months of unperturbed evolution, the follicles are subjected to a signal that induces the transition of each anagen follicle into telogen phase. As shown in the enlargement [Fig. 7(b)], when the signal is given, the fraction of follicles in A drops to zero and the fraction of follicles in T instantaneously rises. Because of the relatively brief duration of the telogen phase, the follicles in T soon enter latency phase. The increase in anagen follicles follows after several months, as the follicles emerge from latency.

In the case illustrated in Fig. 7, the external signal triggering the $A \rightarrow T$ transition is given every 12 months, to simulate the effect of an annual rise in the level of some hormone controlling hair shedding. The periodicity of the resulting oscillations in follicular dynamics is then equal to the periodicity of the external signal. As shown in Fig. 7(a), the oscillations stop when the external synchronizing signal is suppressed after 170 months. The follicles then return to the unsynchronized behaviour observed prior to periodic forcing by the external signal.

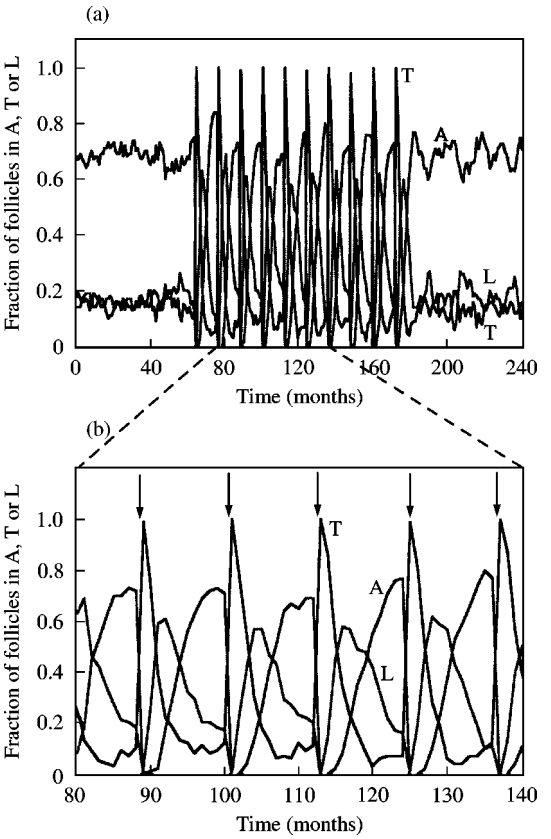

FIG. 7. Oscillations resulting from synchronization by a periodic signal inducing transition from the anagen to the telogen phase. (a) After some 70 months of autonomous evolution, an external signal given in 12-month intervals synchronizes the follicular population and triggers periodic changes in the proportions of follicles in the A, T and L phases. The pattern existing prior to stimulation is rapidly restored when the external signal is suppressed. (b) Enlargement of a portion of the region of panel (a) in which the external signal (vertical arrows) induces transition of anagen follicles into the telogen phase. The curves show the initial concomitant increase in T follicles and decrease in A follicles, followed sequentially by a rise in the proportions of follicles in L and then in A. A new signal, given after 12 months, repeats this sequence of follicular transitions. Such a mechanism may underlie the phenomenon of moulting, which appears to be induced in some mammalian species by a periodic increase in a hormonal signal such as melatonin. The curves are obtained by means of the stochastic version of the follicular automaton model according to eqn (1); parameter values are (in months) $\mu_A = 13.0$, $\sigma_A = 13.0$, $\mu_T = 3.0$, $\sigma_T = 1.0$, $\mu_L = 3.0$, $\sigma_L = 3.0$.

The follicular automaton model can thus account for the two modes of dynamic behaviour of cycling hair follicles, synchronized or unsynchronized. Moreover, two types of synchronization may occur. The first depends on reducing the value of the standard deviation characterizing the distributions of durations of the three phases of

the follicular cycle. The second requires the action of an external synchronizing signal.

6. Discussion

On the basis of data collected over a period of 14 years on the characteristics of hair cycles in a group of ten human male volunteers, we have proposed a follicular automaton model for the dynamics of human hair cycles (Halloy *et al.*, 2000). The model is based on the assumption that each follicle, independent of its neighbours, undergoes cyclical transitions through anagen, telogen, and latency phases, successively, before entering a new anagen phase or dying. The transitions possess a stochastic nature and occur according to a distribution of durations characteristic of each phase (Fig. 2). The time evolution of the follicular automaton is governed by a set of algorithmic rules. Application of these rules by successive iterations generates the time evolution of any number of hair follicles on a specified area of the scalp.

The follicular automaton reproduces the typical dynamics of a single hair follicle as well as the evolution of a field of independently cycling follicles. Thus, the model generates the evolution toward a regime in which the fractions of follicles in A, T, or L phases fluctuate around steady state or slowly drifting values. The steady-state values depend on the mean duration of each of the three follicular phases. We have extended our previous results by showing that a deterministic version of the follicular automaton model is already capable of accounting for the evolution to this steady state (see Fig. 4). However, the deterministic version of the automaton cannot reproduce the fluctuations seen in experimental observations which were carried out on a limited number of about 100 follicles. In contrast, the fluctuations can successfully be accounted for by the stochastic version of the automaton model, both in the case where the duration of the anagen phase remains constant [Figs. 4(c) and (d)] or varies (Halloy *et al.*, 2000) in the course of time.

To account for the occurrence of fluctuations, the continuous approach in terms of differential equations presented in Section 3 could, as an alternative, be extended to include random variations in the parameters in eqns (2). Such an approach based on stochastic differential equations should yield results analogous to those obtained with the follicular automaton.

By running the automaton model for various numbers of follicles, we showed that the effect of stochasticity progressively diminishes as the number of follicles considered rises. Then, the proportions of follicles in the different phases approach the steady-state values predicted by the deterministic version of the model with smaller and smaller fluctuations. The data of Fig. 5 were obtained in the case of an absence of change in parameter values in the course of time. Similar agreement between the stochastic simulations and the deterministic equations is obtained when changes in parameters give rise to a drift in the mean levels of follicles in the three phases (Halloy *et al.*, 2000).

As the number of human hair follicles considered in experimental studies remains necessarily small, of the order of 100, fluctuations are inevitable. As shown in Fig. 5, these fluctuations progressively vanish as the number of follicles increases up to 10^4 or 10^5. We should recall that such numbers correspond to larger areas of the scalp. Gradients in the spatial distribution of parameters such as the mean duration of anagen phase might then be encountered. This aspect, which does not alter the above conclusions as to the effect of increasing numbers of follicles on the occurrence of fluctuations, bears on the development of various patterns of alopecia as shown by Halloy *et al.* (2000).

A striking result is obtained when the standard deviation of the distribution of mean duration of each of the three follicular phases is significantly reduced. Then, large-amplitude oscillations in the proportions of follicles in the three phases occur, roughly in the opposite phase for the A versus T and L follicles (Fig. 6). The highly coordinated behaviour is obtained only with the stochastic version of the model and not with the linear deterministic equations (2). This is because in the stochastic model, regardless of initial conditions, follicles are forced to undergo their transitions in a quasi-concomitant manner when the standard deviation is considered to be small. Since the standard deviation is not nil, however, progressive desynchronization leads to a break-up of the oscillations (Fig. 6).

Oscillations in follicle populations are generally not observed in humans, where follicles are desynchronized, but are reminiscent of the phenomenon of moulting observed in many mammalian species. However, the latter phenomenon is likely triggered by some hormonal signal. We have verified that synchronization by an external periodic signal inducing at regular intervals the transition of all anagen follicles into telogen phase can result in synchronization and oscillations in the fractions of follicles in anagen, telogen and latency phase (Fig. 7).

The present results further corroborate our previous conclusion (Halloy *et al*., 2000) that the degree of synchronization within a field of growing follicles represents a major determinant of the collective dynamics of hair cycles. While moulting-like behaviour occurs when the follicles are synchronized, variability in the duration of the anagen phase plays a primary role in ensuring that hair coverage of the human scalp remains continuous rather than being periodic.

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