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Theory for the stability and regulation of epigenetic landscapes

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Abstract

Cells can often choose among several stably heritable phenotypes. Examples are the expressions of genes in eukaryotic cells where long chromosomal regions can adopt persistent and heritable silenced or active states that may be associated with positive feedback in dynamic modification of nucleosomes. We generalize this mechanism in terms of bistability associated with valleys in an epigenetic landscape. A transfer matrix method was used to rigorously follow the system through the disruptive process of cell division. This combined treatment of noisy dynamics both between and during cell division provides an efficient way to calculate the stability of alternative states in a broad range of epigenetic systems.

Introduction

Cells carry information handed down from their ancestors and are able to pass on information to their descendants. In many cases this ‘memory’ is epigenetic, that is, not stored in the DNA sequence, allowing cells with identical DNA to maintain distinct functional identities. Epigenetic cell memory implies alternative states of gene expression that are stable over time and are inherited through cell division.

A proposed mechanism for epigenetic cell memory invokes positive feedback loops in nucleosome modification [1–6]. Positive feedback is a mechanism seen in many other regulatory systems where for example the production of a regulatory protein activates its own production, or more robustly where two mutual repressors act strongly enough to prevent co-expression. A complementary view on cell memory is that of an epigenetic landscape [7, 8], where the state of a cell develops on some potential energy surface, and a state is maintained when the cell is caught at a particular valley for a long time.

In this paper we develop an epigenetic landscape formalism for cell memory by positive feedback in nucleosome modification. Instead of viewing cell differentiation as the ‘pushing’ of a cell over a fixed landscape [7, 8], our approach

suggests that cell fate could be controlled by changing the landscape.

Models

Inspired by the mating-type switch in *Saccharomyces pombe* [9], we introduced a model for bistability by positive feedback in nucleosome modification [4]. The model had one parameter, the positive feedback to noise ratio F , and modeled the dynamics of a system consisting of N nucleosomes where each could be in one of the three states modified, unmodified and anti-modified.

Here we introduce a simpler version of this modification system, in which there are only two chemical states of each nucleosome. We term these modified (M) and anti-modified (A) to indicate their mutual exclusivity, with the A nucleosome carrying either a different chemical modification or no modification (figure 1). Each nucleosome type recruits a modifying enzyme that converts the other type to its own type. Our results from [4] demonstrated that robust bistability requires an effective cooperativity in the recruitment process. Here cooperativity could be included directly by requiring that two local nucleosomes with the same modification, e.g. M, are needed to make an $A \rightarrow M$ conversion, as described in figure 1. Note that this model is not only just a simplified

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$$\begin{aligned}
& \frac{d}{dt} [R_+ - R_-] \frac{1}{2} \frac{d}{dt} [(R_+ + R_-) \alpha^2 \beta] = \frac{d}{dt} [\alpha m(1-m)(m-1) + (1-\alpha)(1-2m)] \frac{1}{2} \frac{d}{dt} [\alpha(1-m)m + (1-\alpha)\beta] \\
& = \frac{d}{dt} [\alpha m(1-m)(2m-1) + (1-\alpha)(1-2m)] \frac{1}{2} \frac{d}{dt} [\alpha(1-m)\alpha + (1-\alpha)\beta] \\
& \text{Phys. Biol. 7 (2010) 026010}
\end{aligned}$$

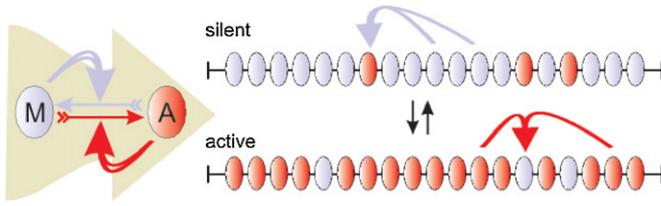


Figure 1. Model. Consider a system with N sites. Each site represents a nucleosome that can be modified (M) or anti-modified (A). Transitions between these two states are in part random, and in part auto-regulated by recruitment of histone-modifying enzymes by local nucleosomes. At each update, a nucleosome i is either, with probability $1 - \alpha$, set to an M- or an A-state randomly. Or with probability α , two other nucleosomes are chosen, and if these are in the same state, then the state of the nucleosome i is set to this state. The model is parametrized by the positive feedback to the noise ratio $F = \alpha/(1 - \alpha)$.

version of 3-state model but also has parallels with the mating-type silencing system in *S. cerevisiae*, where one typically considers acetylated and non-acetylated nucleosomes [10–12].

Suppose M nucleosomes are in the M-state at time t . We now express the development of the fraction $m = M/N$ sites in the M-state. Denoting $dm = 1/N$, we have

$$\frac{dm}{dt} = (R_+(m) - R_-(m)) \cdot dm + \text{noise} \quad (1)$$

with the rate that the system with fraction m of M-sites gets one more (or one less) M-sites being $R_+(m)$ (or $R_-(m)$) and with *noise* having zero mean and being associated with the randomness of processes in a finite system. The rates are given by

$$\begin{aligned}
R_+(m) &= \alpha(1 - m)m^2 + (1 - \alpha)(1 - m), \\
R_-(m) &= \alpha m(1 - m)^2 + (1 - \alpha)m.
\end{aligned} \quad (2)$$

Here, the first term is the nucleosome recruitment; in the case of $R_+(m)$, the recruitment occurs with probability α , and it must involve two M-sites (probability proportional to m^2) and must change the modification on an A-site (probability proportional to $(1 - m)$). The second term is the noise effect which is proportional to $(1 - \alpha)$, where a nucleosome can become M by random conversion from an A-state (probability proportional to $(1 - m)$), and vice versa. This noise represents all events from the cell that are not associated with the direct recruitment processes from other nucleosomes within our N nucleosome system. One should be aware that there is another level of noise in our stochastic description, represented by the *noise* in equation (1) which is the noise associated with the stochasticity of the molecular processes.

The ratio of recruitment (or the positive feedback) to the noise, $F = \alpha/(1 - \alpha)$, is the parameter of the model. The Langevin equation for m is then

$$\frac{dm}{dt} = \frac{\alpha}{N} (2m - 1)[m(1 - m) - 1/F] + \text{noise}, \quad (3)$$

implicitly implying that there is bistability when $F > 4$ provided that the *noise* term is small (system size large).

To analyze the time development of the distribution of m more carefully, we reformulate the model in terms of a master equation for the probability $P(m, t)$ as

$$\begin{aligned}
\frac{\partial}{\partial t} P(m, t) &= R_-(m + dm) P(m + dm, t) + R_+(m - dm) \\
&\times P(m - dm, t) - [R_+(m) + R_-(m)] P(m, t).
\end{aligned} \quad (4)$$

Results

Epigenetic landscape generated from a positive feedback system

We extract ‘the potential landscape’ in m -space by comparing equation (4) with the generic one-dimensional Fokker–Planck equation for diffusion of a particle in a potential $U(m)$:

$$\begin{aligned}
\frac{\partial}{\partial t} P &= -\frac{\partial J}{\partial m} = -\frac{\partial}{\partial m} \left[-\mu(m) \frac{dU(m)}{dm} P - \frac{\partial(D(m)P)}{\partial m} \right] \\
&= -\frac{\partial}{\partial m} \left[-\mu(m) \frac{dV(m)}{dm} P - D(m) \frac{\partial P}{\partial m} \right].
\end{aligned} \quad (5)$$

This equation defines the probability flux J . Here, $\mu(m)$ is the mobility and $D(m)$ quantifies the stochastic motion in terms of an m -dependent diffusion coefficient. In the last step, $V(m)$ represents an effective potential that includes both drift and noise events, defined as $\frac{dV}{dm} = \frac{dU}{dm} + \frac{D}{\mu} \frac{d \ln(D)}{dm}$.

Expanding equation (2) with equation (4) to second order in $dm = 1/N$ and comparing it with equation (5), we find the drift $\langle \frac{dm}{dt} \rangle = \mu(m) (dU/dm)$, the effective potential $V(m)$, diffusion $D(m)$ and mobility $\mu(m)$ as follows:

$$\left\langle \frac{dm}{dt} \right\rangle = \frac{\alpha}{N} (2m - 1)[m(1 - m) - 1/F] \quad (6)$$

$$V(m) = 2Nm(1 - m) + \left(1 - \frac{4N}{F}\right) \ln[Fm(1 - m) + 1] \quad (7)$$

$$D(m) = \mu(m) = \alpha \frac{m(1 - m) + 1/F}{2N^2}. \quad (8)$$

Here, the first equation could have been obtained directly from the Langevin equation (3). From these expressions we can again see that there is a critical recruitment to the noise ratio $F = \alpha/(1 - \alpha)$, with $m = 1/2$ being an unstable fixed point for $F > 4$.

Figure 2 shows $\langle dm/dt \rangle$, $V(m)$ and the steady-state distribution $P_0(m)$ for $F = 3$ and $F = 12$, thereby illustrating monostable and bistable systems. Also note that the analytic results fit the stochastic simulation, with a deviation that scales as $1/N$ with increased system size (not shown). Figure 3 shows how the epigenetic landscape changes gradually as F increases: from a single steep valley, through an almost equipotential ‘river plain’, to two valleys. Because F depends on protein concentrations and affinities, the shape of the epigenetic landscape is under biological control.

One can repeat these calculations for a model where recruitment is not requiring the cooperative action of two nucleosomes. (The second-order terms in equation (2) should then be replaced by first-order ones.) In that case one never obtains more than one stable fixed point, confirming that bistability indeed requires cooperativity [4, 13].

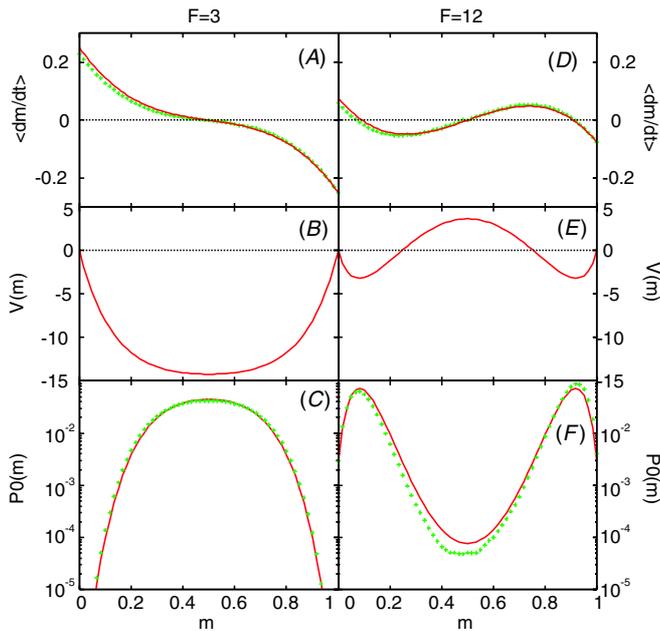


Figure 2. System properties. Analytical results (solid lines) for a system of size $N = 60$ showing (A, D) the drift $\langle dm/dt \rangle$, (B, E) the effective potential $V(m)$ and (C, F) the steady-state distribution $P_0(m)$ in the two regimes: (A, B, C)– $F = 3$ where there is no bistability and (D, E, F)– $F = 12$ where there is well-defined bistability, which can be seen in the effective potential (E) with two valleys separated by a hill. For $\langle dm/dt \rangle$ and $P_0(m)$ (A, C, D, F), the numerical results are also shown by symbols. Comparing the $V(m)$ (B, E) and $P_0(m)$ (C, F) note that $\ln(P_0(m)) \sim -V(m)$ as expected in the steady state from requiring that $J = 0$ in equation (9).

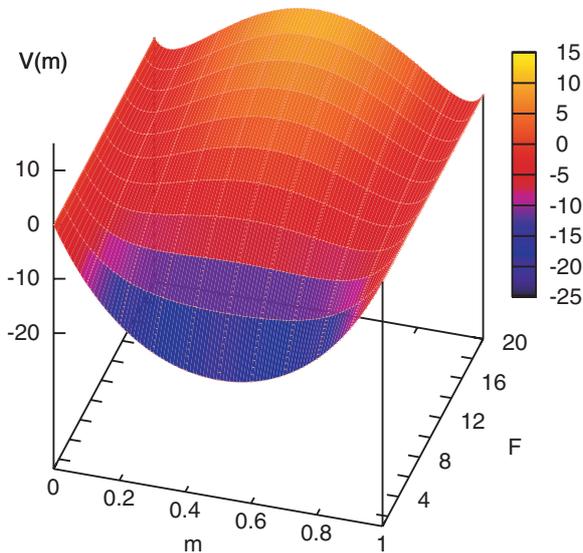


Figure 3. An epigenetic landscape generated from a positive feedback system. Here the effective potential $V(m)$ from equation (7) is plotted as a function of F with fixed $N = 60$. The landscape changes gradually as F increases, from a single steep valley, through an almost equipotential ‘river plain’, to two valleys. This change is associated with stronger recruitment processes at larger F values.

The potential $V(m)$ effectively describes the effective force on m from the combined effect of recruitment and noise events. Thus, a large positive gradient in $V(m)$

means that nucleosomes on average will tend to lose their m modification. A potential minimum, on the other hand, means that recruitment processes and noise events balance such that the number of modified states typically stays around this minimum. In this way, our potential $V(m)$ plays the role of an epigenetic landscape in the Waddington sense [7]. In particular, the valleys and hills of this landscape can be viewed as the metastable epigenetic states and the barriers between them. We will use this analogy to calculate first the probability for stochastic switching between such states, and subsequently we will discuss how one may alter the landscape by modifying the recruitment processes that define the landscapes, a modification that was also envisioned by strings in the Waddington landscape [7].

Stability of a macroscopic state

Now we quantify the stability of a macroscopic state by the average number of attempted updates per nucleosome before the full system switches for the first time to the alternate epigenetic state. Using $D = \mu$ from equation (8), we in analogy with Kramers [14] rewrite

$$J = -D \left[\frac{dV}{dm} P + \frac{\partial P}{\partial m} \right] = -D \exp(-V) \frac{\partial}{\partial m} [P \exp(V)] \quad (9)$$

and use the quasi-stationary approximation (i.e. the current J is constant) to write the flux for going from an A-state (the potential minimum at $m = m_A \sim 0$) to an M-state (the potential minimum at $m = m_M \sim 1$):

$$J = \frac{[P \exp(V)]_{m_A}^{m_M}}{\int_{m_A}^{m_M} (1/D(m)) \exp(V(m)) dm}. \quad (10)$$

Using a Gaussian approximation (i.e. $V(m)$ harmonic around both the initial state A and the transition state T with $m = m_T = 1/2$ and the initial distribution for $P(m, t)$ around the state A), we obtain the average lifetime of an epigenetic state τ as

$$\tau \equiv \frac{1}{|J|} \approx 4\pi N \sqrt{\frac{4}{F}} \exp[V_T - V_A] \quad (11)$$

for large N and F , where $V_T = V(m = 1/2)$ and $V_A = V(m_A)$ is the potential minimum for the A-state (the detailed calculation is given in the appendix). Figure 4 demonstrates that equation (11) reproduces stochastic simulations. However, when pushing toward very small N , there is a tendency that the continuous description deviates from the stochastic result. Thus, for N of order 10 or below, we recommend a stochastic simulation.

Equation (11) can also be used to obtain an interesting prediction from our model. Using the expression for the potential V from equation (7) for large N , we see that $V(m = \frac{1}{2}) \sim Nf(F)$ with a function $f(F)$ independent of N , and thus that stability scales exponentially with N , i.e. $\tau \propto N e^{Nf(F)}$.

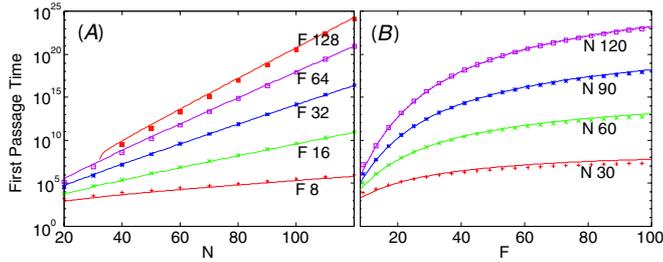


Figure 4. Stability of a macroscopic state. The first passage time, or the average lifetime of an epigenetic state τ , is shown as a function of N (A) and F (B). Symbols show numerical results and lines show analytical results from equation (11). Time is counted in units of attempted nucleosome updates per nucleosome.

Effect of cell divisions

Epigenetic states are capable of being inherited across cell divisions. This can give difficulties for stability of the states [4], particularly for 2-state systems [13]. At cell division the genome is duplicated, and following [4, 15] we assume that the resident nucleosomes are partitioned randomly between the daughter strands. The vacant positions are filled by new randomly selected nucleosomes where half are in the M-state and half in the A-state. We accordingly supplement our model above with cell divisions at certain fixed time intervals. This cell generation time is measured in units of the number of attempted nucleosome updates per nucleosome.

Whereas the potential landscape between cell divisions drives the system toward one of the epigenetic states, the randomization at cell divisions brings the system closer to the top of the potential barrier in the epigenetic landscape.

Consider that before cell division the system is in a state with $M_b = m_b \times N$ nucleosomes in the M-state and the remaining nucleosomes in the A-state. Cell division results in the distribution of number of M-state nucleosomes M_a :

$$D(M_a, M_b) = \sum_M \sum_A \frac{\binom{M_b}{M} \binom{N-M_b}{A} \binom{N-M-A}{M_a-M}}{2^{(2N-M-A)}} \quad (12)$$

where the sum runs over all the ways of getting from M_b to M_a by selecting $M \leq \min(M_a, M_b)$ nucleosomes in the M-state and $A \leq \min(N - M_a, N - M_b)$ nucleosomes in the A-state to be transferred directly at the cell division.

Between cell divisions, the system evolves by a stochastic sequence of single nucleosome exchanges that can be described by motion in the epigenetic landscape. The stochastic change $M \rightarrow M \pm 1$ can be followed by the master equation above, and the system evolves toward a steady-state distribution with two well-separated peaks, see figure 2.

To combine the gradual development in a well-defined epigenetic landscape between cell divisions, with the sudden reshuffling at cell divisions we express the gradual development in terms of matrix operations. The matrix G that corresponds to equation (2) is only non-zero at the diagonal and off-diagonal elements: $G(M, M+1) = R_+(m)$, $G(M, M-1) = R_-(m)$ and $G(M, M) = 1 - G(M, M-1) - G(M, M+1)$ where $m = M/N$ and $R_{\pm}(m)$ is from equation (2). The probability distribution evolves according

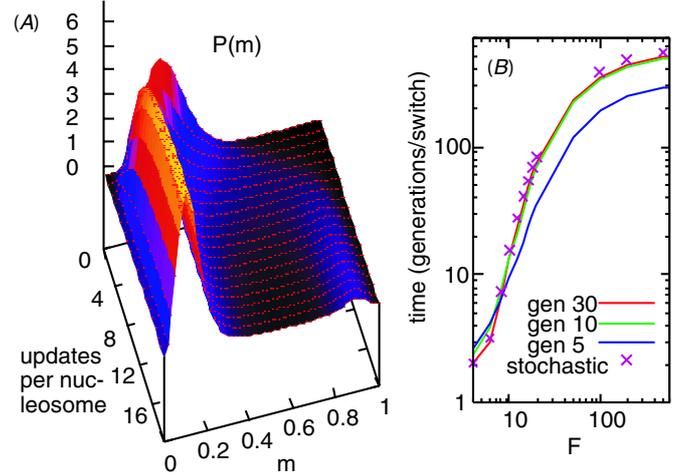


Figure 5. The switching of the macroscopic state via randomization at the cell division. (A) The averaged development of the M distribution over one cell generation, with ‘time’ measured in attempted updates per nucleosome. The simulation uses $F = 10$ and a generation length of 20 updates per nucleosome. The evolution starts just after a cell division, where a randomization (using equation 12) is followed by a drift imposed by the epigenetic landscape. After about ten updates, one sees that $P(M)$ reaches a nearly stationary distribution, where a fixed fraction has switched to the alternate state. Just before the next cell division, one resets $P(M) = 0$ for $M > N/2$, and renormalizes the distribution. Iterating this process, panel (B) shows the average number of generations needed before escape (see escape time discussion in the text). A direct Monte Carlo simulation result with a generation time of 30 is also shown by symbols.

to $P(M) \rightarrow P(M') = \sum_M G(M, M') P(M)$ for each update of a nucleosome in the system.

In figure 5 we show the time evolution of the probability distribution from one cell division to the next for a system with $N = 60$, $F = 10$ and $m \sim 0$. In panel (A), the simulation uses a generation length of 20 updates per nucleosome. The evolution starts just after a cell division, where a randomization (using equation (12)) is followed by a drift imposed by the epigenetic landscape. Just before the next cell division, one resets $P(M) = 0$ for $M > N/2$, and renormalizes the distribution. We see that at cell division a small fraction of cells reach large m values, and over the next ~ 10 updates per nucleosome can move to $m \sim 1$. After around 10 updates, the $P(m)$ distribution reaches a quasi-steady state, reflecting that from then on a very small flux goes over the barrier. Thus after 10 updates, the likelihood of further transitions between the two epigenetic states can be ignored (for $F > 10$).

The time evolution in figure 5 also illustrates that transitions are entirely dominated by the noise at cell divisions, at least for large enough F . In fact by stochastic simulation we have verified that switches only occur when the stochastic partitioning in a division brings the system close to the transition state, $m \sim 1/2$.

An entire cell generation with cell division is described by the matrix

$$C(M, M'') = \sum_{M'} G^{(g \cdot N)}(M, M') D(M', M'') \quad (13)$$

where g is the number of single nucleosome updates per cell generation. Iterating the updating process with renormalization of the distribution, we obtain the probability distribution $P(M')$ shortly before a cell division, and estimate the average number of generations needed before escape (escape time) as $n_e = (\sum_{M' > N/2} P(M'))^{-1}$ in panel (B). This escape time is the average time it takes for a system to switch from one state to another. From figure 5 we see that when $g > 10$, the escape time does not depend on the value of g for $F > 10$ because of the small escaping rate after 10 updates.

Epigenetic landscape with regulated tilt

Finally, we consider the case where the modification and anti-modification are not symmetric but one of the effects is stronger than the other. This asymmetry of modification could be under biological control in a real system by changing the concentration of modifying enzymes or by recruiting such enzymes by transcription factors [6].

One of the simplest ways to include such asymmetry is to modify the transition rate equation (2) into

$$\begin{aligned} R_+(m) &= 2(1 - \eta)\alpha(1 - m)m^2 + (1 - \alpha)(1 - m), \\ R_-(m) &= 2\eta\alpha m(1 - m)^2 + (1 - \alpha)m. \end{aligned} \quad (14)$$

Here, a new parameter η , defined in the range $0 < \eta < 1$, sets the relative strength of modification versus anti-modification and gives the symmetric case when $\eta = 1/2$.

Figure 6 shows how the potential landscape can be manipulated by changing the relative strengths of the two recruitment processes, η . This potential is directly defined as $V(m) = -\ln P_0(m)$, where $P_0(m)$ is defined as the steady-state probability distribution of m . For simplicity the cell division is not taken into account here. For small η , the valley at the M-state is much deeper than that of the A-state, and the landscape dramatically changes as η increases to give a landscape where the A-state has a deeper valley than the M-state.

Discussion

Positive feedback in nucleosome modification is a powerful mechanism to maintain a dynamic bistable system, even with destabilizing factors such as cell division. Here we demonstrated how positive feedback in itself can be reformulated into an epigenetic landscape with peaks and valleys that reflects the underlying balance between feedback and noise. As long as movements are small, dominated by single nucleosome modifications, the movement in the landscape can be fully modeled by a Langevin or Fokker–Planck equation with a first escape time calculated in analogy with Kramers. When stochastic events are large, as during cell divisions, a transfer matrix method allowed us to extend the Fokker–Planck formalism and thereby to set a minimum timescale for the dynamics of a robust positive feedback. Finally, we studied how the landscape could be ‘tilted’ by asymmetry in the nucleosome modification reactions.

We expect that the transfer matrix method can be extended relatively easily to include other nucleosome modification

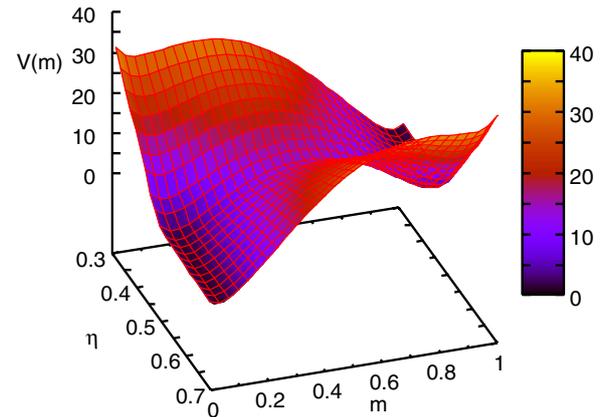


Figure 6. Epigenetic landscape with asymmetry. The figure shows $V(m) = -\ln(P_0(m))$ obtained from the model with asymmetric transition rate equation (14) using the transfer matrix method. For simplicity, the cell division is not taken into account here. The figure shows how the landscape gradually changes from monostable to bistable and then again to monostable as one changes the parameter η . The ‘asymmetry’ parameter η would in principle be under biological control through changes of concentrations of modifying enzymes associated with the recruitment processes. The total recruitment to noise ratio is fixed at $F = 20$. The figure illustrates a dramatic tilting of the epigenetic landscape by a moderate change in nucleosome modification rates.

schemes, for example the 3-state model of [4]. This approach is more powerful than the mean field approach [13] in the sense that it allows one to explore the probability distribution. The method can also deal with cases where the epigenetic system does not conform to a potential energy surface. For example total noise associated with cell divisions can be included in systems with double negative feedback between repressors, such as the CI-Cro feedback loop in the lysis-lysogeny switch of phage lambda [16].

Our results are consistent with recent observations in mammalian cells in which increased cell division rates accelerated stochastic transitions between epigenetic states [17].

Epigenetic landscapes present a particularly appealing way to discuss multi-stability of expression states in living systems. The presented coupling between positive feedback and the possibility for a drift in a landscape may be useful for understanding cases where bistable decisions are delayed, as often seems to be the case in development. Some epigenetic landscapes may define the activity of transcription factors that act as histone-modifying complexes, and thereby subsequently define the input parameters for other landscapes further down along a developmental pathway. Thereby understanding of epigenetic stability and regulated tilting of landscapes may speak to large classes of coupled switch systems.

Conclusion

This paper explored theoretical implications of epigenetics as a dynamic phenomenon, where alternate states of gene expression are selected and maintained over multiple generations by ongoing dynamic processes. Our approach

builds on the assumption that the epigenetic states are maintained through a positive feedback where nucleosomes of a certain kind recruit enzymes which in turn convert other nucleosomes to the same kind. By introducing a minimal model for such a dynamic system, we demonstrated that the on-going nucleosome updating rates only need to be $g \gtrsim 10$ updates per nucleosome per generation to provide robust maintenance. This result is closely linked to the convergence of the $P(M)$ distribution after cell division (figure 4), which we find to be rather insensitive to the value of F . Thus we expect that any model working with positive feedback as a key maintenance factor, in principle, would work with a moderate number of updates per generation.

It is important to note that the stability of the epigenetic state depends on the update rules at the cell division especially in the 2-state model. In our model, on average half of the nucleosomes come from parental DNA, and the rest of them are either in the modified or the unmodified state with equal probability; thus, effectively 75% nucleosomes are in the same epigenetic state as the parental DNA. Thus, most of the cells are still in the same valley in the epigenetic potential (figure 2(E)) and come back to the original epigenetic state. However, if half of the nucleosomes are replaced with unmodified nucleosomes at the cell division in the 2-state model, the system prefers unmodified states and one needs extra mechanisms to keep the modified state stable [13]. It is not clear which mechanism operates at DNA replication in different systems, but our formulation is applicable in both cases. More experimental information about the nucleosomes inserted after DNA replication will be critical in understanding the stability of epigenetic states.

Our analysis also showed formally that bistability requires cooperativity of recruitment, in the sense that equation (2) requires more than first-order terms in order to provide separation between two states. In the model in Dodd [4] the recruitment was implemented by requiring that two independent recruitment processes were of the same type, whereas we here simply assumed that the two simultaneously recruiting nucleosomes are of the same type. Our analogy between system size and effective randomness allowed us to show formally that stability of inherited states will grow exponentially with the number of nucleosomes in the considered region of the chromosome.

Our analysis opens for understanding development in epigenetic landscapes, in terms of positive feedback mechanisms that are linked to each other through expression of nucleosome-modifying enzymes.

Acknowledgments

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Appendix. Analytical calculation of the stability of a macroscopic state

Assuming $V(m)$ is harmonic around $m = m_A$ and hence the initial distribution $P(m)$ is a Gaussian around $m = m_A$ (and

$P(m_M) \approx 0$), we get

$$\begin{aligned} [P(m) \exp(V(m))]_{m_A}^{m_M} &\approx -P(m_A) \exp(V(m_A)) \\ &= -\frac{1}{\sqrt{2\pi\sigma_A^2}} \exp(V(m_A)), \end{aligned} \quad (\text{A.1})$$

with $1/\sigma_A^2 = (d^2V(m)/dm^2)_{m=m_A}$. From the condition $dV(m)/dm|_{m=m_A} = 0$ and equation (7), we have $m_A = 1/2 - \sqrt{1/4 - 1/F + 1/(2N)}$, and

$$\begin{aligned} \sigma_A^2 &= \left(\frac{d^2V(m)}{dm^2} \right)_{m=m_A}^{-1} = \frac{4N - F}{4N(FN + 2F - 4N)} \\ &\approx \frac{1}{N(F - 4)} \approx \frac{1}{NF}, \end{aligned} \quad (\text{A.2})$$

where we assume $N \gg 1$ and $F \gg 1$ (i.e. $\alpha \approx 1$).

Approximating $V(m)$ as harmonic around the transition state T with $m = m_T = 1/2$ and noting that $V(m)$ takes the maximum at $m = m_T$, we have

$$\begin{aligned} \int_{m_A}^{m_M} \frac{1}{D(m)} \exp(V(m)) dm \\ \approx \frac{1}{D(m_T)} \exp(V(m_T)) \int_{-\infty}^{\infty} \exp\left[-\frac{(m - m_T)^2}{2\sigma_T^2}\right] dm \\ = \frac{\sqrt{2\pi\sigma_T^2}}{D(m_T)} \exp(V(m_T)) \end{aligned} \quad (\text{A.3})$$

with

$$\begin{aligned} \sigma_T^2 &= -\left(\frac{d^2V(m)}{dm^2} \right)_{m=m_T}^{-1} = -\frac{1 + F/4}{(4 - F)N - 2F} \\ &\approx \frac{1 + F/4}{N(F - 4)} \approx \frac{1}{4N} \end{aligned} \quad (\text{A.4})$$

Noting

$$D(m_T) = \frac{\alpha(1/4 + 1/F)}{2N^2} \approx \frac{1}{8N^2}, \quad (\text{A.5})$$

we get

$$\tau = \frac{1}{|J|} \approx \frac{8N^2}{\alpha} \cdot \sqrt{2\pi}\sigma_T e^{V(m_T)} \cdot \sqrt{2\pi}\sigma_A e^{-V(m_A)} \quad (\text{A.6})$$

$$\approx 4\pi N \sqrt{\frac{4}{F}} \exp[V(m_T) - V(m_A)]. \quad (\text{A.7})$$

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