Supporting material

Bifurcation in epigenetics: implications in development, proliferation and disease

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As a reminder, we recall the biochemical reactions corresponding to the epigenetic system of interest, with their respective propensities:

$$U \to A \qquad r_{u,a} \equiv (k_0 + \epsilon_A \rho_A)(n - n_A - n_I), \tag{1}$$
$$U \to I \qquad r_{u,i} \equiv (k_0 + \epsilon_I \rho_I)(n - n_A - n_I), \tag{2}$$
$$A \to U \qquad r_{a,u} \equiv (k_0 + \epsilon_I \rho_I) n_A, \tag{3}$$
$$I \to U \qquad r_{i,u} \equiv (k_0 + \epsilon_A \rho_A) n_I. \tag{4}$$

1 Dynamical system

In this section, we detail the study of the mass-action model corresponding to reactions 1-4:

$$\frac{d\rho_A}{dt} = (k_0 + \epsilon_A \rho_A)(1 - \rho_A - \rho_I) - (k_0 + \epsilon_I \rho_I)\rho_A, \tag{5}$$
$$\frac{d\rho_I}{dt} = (k_0 + \epsilon_I \rho_I)(1 - \rho_A - \rho_I) - (k_0 + \epsilon_A \rho_A)\rho_I. \tag{6}$$

In order to introduce the effective magnetization $m = \rho_A - \rho_I$, we change the variables from (ρ_A, ρ_I) to $(m, s \equiv \rho_A + \rho_I)$. This leads to the following dynamical system

$$\begin{aligned} \frac{dm}{dt} &= (r_{u,a} + r_{i,u} - r_{u,i} - r_{a,u})/n \\ &= \left[k_0 + \epsilon_A \left(\frac{s+m}{2}\right)\right]\left[1 - \left(\frac{s+m}{2}\right)\right] - \left[k_0 + \epsilon_I \left(\frac{s-m}{2}\right)\right]\left[1 - \left(\frac{s-m}{2}\right)\right] \end{aligned} \tag{7}$$

$$\begin{aligned} \frac{ds}{dt} &= (r_{u,a} + r_{u,i} - r_{a,u} - r_{i,u})/n \\ &= \left[2k_0 + \epsilon_A \left(\frac{s+m}{2}\right) + \epsilon_I \left(\frac{s-m}{2}\right)\right](1-s) - k_0 s - \left(\frac{\epsilon_A + \epsilon_I}{4}\right)(s^2 - m^2) \end{aligned} \tag{8}$$

This system has at most three positive fixed points. Their general analytical expressions are quite cumbersome and not informative so we do not give their exact forms here. For the symmetric regime where $\epsilon_A = \epsilon_I \equiv \epsilon$, we find

$$m_0 = 0 \qquad s_0 = 2/3, \tag{9}$$
$$m_+ = (k_0/\epsilon)\sqrt{(\epsilon/k_0 + 1)(\epsilon/k_0 - 3)} \qquad s_+ = (\epsilon - 1)/\epsilon, \tag{10}$$
$$m_- = -(k_0/\epsilon)\sqrt{(\epsilon/k_0 + 1)(\epsilon/k_0 - 3)} \qquad s_- = (\epsilon - 1)/\epsilon, \tag{11}$$

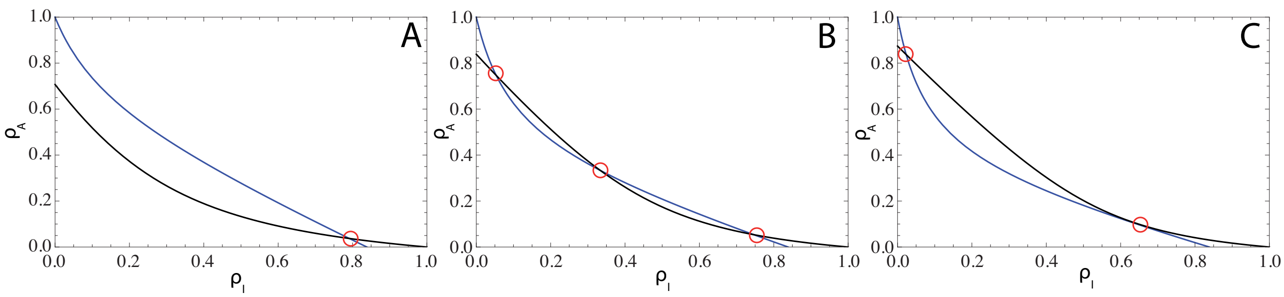

Fig. S 1: Nullclines $\rho_{A,1}$ (black, Eq.12) and $\rho_{A,2}$ (blue, Eq.13) of the dynamical system for $\epsilon_I = 5k_0$ and $\epsilon_A = 2k_0$ (A), $5k_0$ (B) and $6.8k_0$ (C).

where $(m_\pm, s_\pm)$ exist only for $\epsilon \geq \epsilon_c \equiv 3k_0$.

Back to the general situation, numerical analysis of the fixed points and of their stability (by linear stability analysis) demonstrates that the stability diagram is made of two regions: one region with one stable fixed point and another with two stable and one unstable fixed points (Fig. 2 of the main text). In order to determine the boundaries between these two regions, we use canonical analysis techniques of non-linear dynamical systems [1].

For simplicity, we perform the computation for the system of original variables (ρ_A, ρ_I). By definition, the fixed points are the intersections of the nullclines of Eq.(5-6), defined as the two lines in the (ρ_A, ρ_I)-plan given by $d\rho_A/dt = 0$ and $d\rho_I/dt = 0$. In the monostability region, the two curves intersect at only one point (Fig.S1A), while in the bistability region, we find three points of intersection (Fig.S1B). At the boundaries, they are two points of intersection and at one of them the nullclines are tangent (Fig.S1C). We use these properties to determine parametric expressions for the boundaries. We first derive the expression of the two nullclines. Setting $d\rho_A/dt = 0$ and $d\rho_I/dt = 0$ gives

$$\rho_{A,1} = \frac{-2k_0 + \epsilon_A - (\epsilon_A + \epsilon_I)\rho_I + \sqrt{4\epsilon_A k_0(1-\rho_I) + (2k_0 - \epsilon_A + (\epsilon_A + \epsilon_I)\rho_I)^2}}{2\epsilon_A} \tag{12}$$

$$\rho_{A,2} = \frac{k_0 - 2k_0\rho_I + \epsilon_I\rho_I(1-\rho_I)}{k_0 + (\epsilon_A + \epsilon_I)\rho_I} \tag{13}$$

Then, from the condition $\rho_{A,1} = \rho_{A,2}$ (fixed point), we derive an expression for ϵ_I as a function of ϵ_A and ρ_I. Finally, injecting this relation in the equation related to the tangency condition $(\partial\rho_{A,1}/\partial\rho_I = \partial\rho_{A,2}/\partial\rho_I)$, we find parametric expressions for the boundaries (for $0 \leq \rho_I \leq 1$)

$$\begin{aligned}
\epsilon_I/k_0 = \; & \frac{1}{8\left(\rho_i-1\right)^4\rho_i^2}\Big(\sqrt{2}\Big[\left(\rho_i-1\right)^4\rho_i^2\left(3\rho_i-4\right)\Big(\rho_i\Big(\rho_i\Big(\rho_i\left(9\rho_i^2-30\rho_i+55\right)-60\Big)+30\Big) \\
& -10\sqrt{\left(4-3\rho_i\right)\rho_i^3}+21\sqrt{\left(4-3\rho_i\right)\rho_i^5}-24\sqrt{\left(4-3\rho_i\right)\rho_i^7}+9\sqrt{\left(4-3\rho_i\right)\rho_i^9}-8\Big)\Big]^{1/2} \\
& -\rho_i\Big(2\rho_i\left(3\rho_i-1\right)\left(\rho_i-1\right)^3+\sqrt{2}\Big[-\left(\rho_i-1\right)^4\rho_i\Big(\rho_i\Big(\rho_i\Big(\rho_i\left(9\rho_i^2-30\rho_i+55\right)-60\Big) \\
& +30)-10\sqrt{\left(4-3\rho_i\right)\rho_i^3}+21\sqrt{\left(4-3\rho_i\right)\rho_i^5}-24\sqrt{\left(4-3\rho_i\right)\rho_i^7}+9\sqrt{\left(4-3\rho_i\right)\rho_i^9}-8\Big)\Big]^{1/2}\Big) \\
& -2\sqrt{\left(4-3\rho_i\right)\rho_i^3}+12\sqrt{\left(4-3\rho_i\right)\rho_i^5}-24\sqrt{\left(4-3\rho_i\right)\rho_i^7}+20\sqrt{\left(4-3\rho_i\right)\rho_i^9} \\
& -6\sqrt{\left(4-3\rho_i\right)\rho_i^{11}}\Big)
\end{aligned} \tag{14}$$

$$\epsilon_A/k_0 = \frac{1}{4(\rho_i-1)^4\rho_i}\Big(-\rho_i(3\rho_i-4)(\rho_i-1)^3+\sqrt{2}\Big[-(\rho_i-1)^4\rho_i\Big(\rho_i\Big(\rho_i\Big(\rho_i\Big(9\rho_i^2-30\rho_i+55\Big) -60)+30)-10\sqrt{(4-3\rho_i)\rho_i^3}+21\sqrt{(4-3\rho_i)\rho_i^5}-24\sqrt{(4-3\rho_i)\rho_i^7}+9\sqrt{(4-3\rho_i)\rho_i^9}-8\Big)\Big]^{1/2} +2\sqrt{(4-3\rho_i)\rho_i}-9\sqrt{(4-3\rho_i)\rho_i^3}+15\sqrt{(4-3\rho_i)\rho_i^5}-11\sqrt{(4-3\rho_i)\rho_i^7}+3\sqrt{(4-3\rho_i)\rho_i^9}\Big) \quad (15)$$

2 Master-equation and approximations

In this section, we detail the methods and approximations used to derive the probability distribution function (pdf) of m at steady-state and to compute the mean first passage time $\langle\tau\rangle$.

2.1 Derivation of the master-equation for m

From the propensities of the different reactions 1-4, we write the master-equation for the pdf of (m, s)

$$\begin{aligned}\frac{dP(m,s)}{dt} &= r_{u,a}(m-1/n,s-1/n)P(m-1/n,s-1/n)+r_{u,i}(m+1/n,s-1/n)P(m+1/n,s-1/n)\\ &+r_{a,u}(m+1/n,s+1/n)P(m+1/n,s+1/n)+r_{i,u}(m-1/n,s+1/n)P(m-1/n,s+1/n)\\ &-(r_{u,a}+r_{u,i}+r_{a,u}+r_{i,u})P(m,s) \qquad (16)\end{aligned}$$

with

$$r_{u,a}(m,s) = n\left(k_0+\epsilon_A\frac{s+m}{2}\right)(1-s) \quad (17)$$

$$r_{u,i}(m,s) = n\left(k_0+\epsilon_I\frac{s-m}{2}\right)(1-s) \quad (18)$$

$$r_{a,u}(m,s) = n\left(k_0+\epsilon_I\frac{s-m}{2}\right)\left(\frac{s+m}{2}\right) \quad (19)$$

$$r_{i,u}(m,s) = n\left(k_0+\epsilon_A\frac{s+m}{2}\right)\left(\frac{s-m}{2}\right) \quad (20)$$

We make the assumption that s is always closed to 1 and its dynamics is fast compared to the dynamics of m. This means that we neglect the fluctuations of s and that at every time the value of s is given by the solution $s(m)$ of Eq.8$=0$ for a fixed value of m. For example, in the symmetric regime, we find

$$s(m) = (k_0/\epsilon)\left(\frac{\epsilon/k_0-3+\left[(\epsilon/k_0+3)^2+3(m\epsilon/k_0)^2\right]^{1/2}}{3}\right) \quad (21)$$

Within this limit, the pdf of m is given by $P(m,t)=\sum_s P(m,s,t)\approx P(m,s(m),t)$ and follows the master-equation

$$\frac{dP(m)}{dt} = n\left[w_+(m-1/n)P(m-1/n)+w_-(m+1/n)P(m+1/n)-(w_+(m)+w_-(m))P(m)\right] \quad (22)$$

with

$$w_+(m) \equiv (r_{u,a}+r_{i,u})/n = \left[k_0+\epsilon_A\left(\frac{s(m)+m}{2}\right)\right]\left[1-\left(\frac{s(m)+m}{2}\right)\right] \quad (23)$$

$$w_-(m) \equiv (r_{a,u}+r_{u,i})/n = \left[k_0+\epsilon_I\left(\frac{s(m)-m}{2}\right)\right]\left[1-\left(\frac{s(m)-m}{2}\right)\right] \quad (24)$$

the propensities to respectively increase (using reactions 1 and 4) or decrease (2 and 3) m by 1. In the limit of a high number of nucleosomes ($n \gg 1$), we derive the Fokker-Planck approximation of Eq.22 by expanding it to second order in $1/n$:

$$\begin{aligned}\frac{\partial P(m)}{\partial t} &\approx n\left[w_+P - \frac{1}{n}\frac{\partial}{\partial m}(w_+P) + \frac{1}{2n^2}\frac{\partial^2}{\partial m^2}(w_+P) + w_-P + \frac{1}{n}\frac{\partial}{\partial m}(w_-P) + \frac{1}{2n^2}\frac{\partial^2}{\partial m^2}(w_-P)\right. \\ &\quad -(w_+ + w_-)P] \\ &= -\frac{\partial}{\partial m}\left\{(w_+ - w_-)P - \frac{1}{2n}\frac{\partial}{\partial m}\left([w_+ + w_-]P\right)\right\} \equiv -\frac{\partial J}{\partial m} \qquad (25)\end{aligned}$$

with J defined as the flux of probability.

2.2 Steady-state solution

There is no source of probability, therefore, at steady-state ($\partial P(m)/\partial t = 0$), $J = 0$. This leads to

$$\frac{\partial_m P_\infty}{P_\infty} = 2n\frac{w_+ - w_-}{w_+ + w_-} - \frac{\partial_m(w_+ + w_-)}{w_+ + w_-} \qquad (26)$$

$$P_\infty(m) = \frac{1}{Z}\frac{\exp\left[2n\int_{-\infty}^{m} dm'\left(\frac{w_+ - w_-}{w_+ + w_-}\right)\right]}{w_+(m) + w_-(m)} \qquad (27)$$

The local optima of P_∞ are given by solving Eq.26=0. In the limit of large n, this is approximatively equivalent to solve $w_+ - w_- = 0$ which is exactly the steady-state equation of the mass-action model of the first section (Eq.7).

In the symmetric regime, we find analytical expression for the optima

$$m_0^* = m_0 = 0 \qquad (28)$$

$$m_\pm^* = \pm(k_0/\epsilon)\sqrt{(\epsilon/k_0 + 1)(\epsilon/k_0 - 3) + \frac{(\epsilon/k_0)^2}{3n^2}\left[2 + 3n - 2n^2 + 2(1+n)\sqrt{1 + n + n^2}\right]} \qquad (29)$$

$$\approx m_\pm\left(1 + \left(\frac{1}{n}\right)\left(\frac{(\epsilon/k_0)^2}{(\epsilon/k_0 + 1)(\epsilon/k_0 - 3)}\right) + o\left(\frac{1}{n^2}\right)\right) \qquad (30)$$

Where $m_\pm^*$ exist only for

$$\epsilon \geq \epsilon_c^* = \frac{3k_0 n}{\sqrt{2n^2 + 3n + 2 + 2(1+n)\sqrt{1 + n + n^2}}} \qquad (31)$$

$$\approx \epsilon_c\left(1 - \frac{3}{2n} + o\left(\frac{1}{n^2}\right)\right) \qquad (32)$$

We remark that the local optima of P_∞ are approximatively given by the fixed point of the dynamical system up to $1/n$- correction.

In the bistable regime, the widths of the peaks around $m_\pm^*$ are determined by modeling locally the probability by a gaussian distribution $P_\infty(m) \approx \exp[-(m - m_\pm^*)^2/(2\sigma^2)]/z$ centered around $m_\pm^*$ with

$$\sigma = \left[\frac{\partial^2 V}{\partial m^2}\right]_{m_\pm^*}^{-1/2} \qquad (33)$$

$$\approx \sqrt{\frac{2k_0}{n(\epsilon - \epsilon_c)}} + o\left(\frac{1}{n^{3/2}}\right) \qquad (34)$$

where $V = -\log P_\infty$ is the effective landscape.

2.3 Mean first-passage time

By definition, the mean first-passage time to switch from m_-^* to m_+^* is given by $\langle\tau\rangle = \int_0^\infty dT p(T)\times T$ with $p(T) = -\frac{d}{dt}\left[\int_{-\infty}^{m_+^*} P(m,t)dm\right]$ the probability distribution function of first-passage time and $P(m,t)$ the solution of the Fokker-Planck equation (Eq.25) for the initial condition $P(m,0) = \delta(m-m_-^*)$. By inverting integration over m and over T and by making integration by parts, it is easy to show that [2]

$$\langle\tau\rangle = \int_{-\infty}^{m_+^*} f(m) \tag{35}$$

with $f(m)$ solution of the ordinary differential equation

$$-\frac{d}{dm}\left\{(w_+ - w_-)f - \frac{1}{2n}\frac{d}{dm}\left([w_+ + w_-]f\right)\right\} = -\delta(m-m_-^*) \tag{36}$$

$$f(m_+^*) = f(-\infty) = 0 \tag{37}$$

Note that the left-hand side of Eq.36 is the same Fokker-Planck operator than in Eq.25. Since P_∞ is the homogeneous solution of Eq.36, we can express $f(m)$ as

$$f(m) = 2nP_\infty(m)\left[\int_{m_-^*}^{m_+^*} \frac{dm'}{[w_+(m') + w_-(m')]P_\infty(m')} - \Theta(m-m_-^*)\int_{m_-^*}^{m} \frac{dm'}{[w_+(m') + w_-(m')]P_\infty(m')}\right] \tag{38}$$

with $\Theta(x)$ the Heaviside function. Injecting this expression in Eq.35 and inverting integration over m and over m', leads to

$$\langle\tau\rangle = 2n\int_{m_-^*}^{m_+^*} \frac{dm'}{[w_+(m') + w_-(m')]}\int_{-\infty}^{m'} dm\frac{P_\infty(m)}{P_\infty(m')} \tag{39}$$

Remarking that $P_\infty(m)$ is maximal around $m = m_-^*$ and that $1/([w_+(m') + w_-(m')]P_\infty(m'))$ is maximal around $m' = 0$, we approximate these functions by gaussians around their respective maximum. This leads to

$$\langle\tau\rangle = \frac{4\pi n\sigma_0\sigma_-}{[w_+(0) + w_-(0)]}\exp[V(0) - V(m_-^*)] \tag{40}$$

$$\approx \frac{18\pi}{\sqrt{\epsilon/k_0 + 3}(\epsilon-\epsilon_c)\sqrt{3}}\exp[V(0) - V(m_-^*)] \tag{41}$$

with $\sigma_0 = \left[-\frac{\partial^2 V}{\partial m^2}\right]_{m_0}^{-1/2}$, $\sigma_- = \left[\frac{\partial^2 V}{\partial m^2}\right]_{m_-^*}^{-1/2}$ and

$$\begin{aligned} V(0) - V(m_-^*) \approx\ & \frac{n}{(\epsilon/k_0)(2+\epsilon/k_0)}\Big(-6 + \log[8] + \epsilon/k_0(-1 + \epsilon/k_0 + \log[9]) - 2\epsilon/k_0\log[\epsilon/k_0] \\ & +3\log\left[\frac{3+\epsilon/k_0}{\epsilon/k_0(\epsilon/k_0+1)}\right] + \epsilon/k_0(4+\epsilon/k_0)\log\left[\frac{(2(3+\epsilon/k_0))}{3(1+\epsilon/k_0)}\right]\Big) \\ & -\log\left[\frac{9(1+\epsilon/k_0)}{2\epsilon/k_0(3+\epsilon/k_0)}\right] + o\left(\frac{1}{n}\right) \end{aligned} \tag{42}$$

References

[1] S.H. Strogatz (1994) Nonlinear dynamics and chaos. *Westview Press.*

[2] H. Risken (1989) The Fokker-Planck equation. *Springer-Verlag.*