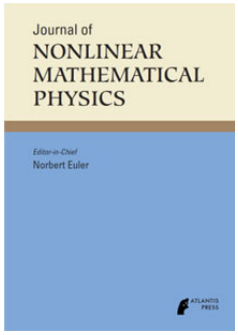

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A MEAN-FIELD VERSION OF THE SSB MODEL FOR X-CHROMOSOME INACTIVATION

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Nicodemi and Prisco recently proposed a model for X-chromosome inactivation in mammals, explaining this phenomenon in terms of a spontaneous symmetry-breaking mechanism [*Phys. Rev. Lett.* **99** (2007) 108104]. Here we provide a mean-field version of their model.

Keywords: Spontaneous symmetry breaking; X-chromosome inactivation; mean-field theory.

1. Introduction

The nucleus of female mammals embryo cells contain two X chromosomes; one of these has to be inactivated in order to equalize the dosage of X genes product with respect to males, and this inactivation is crucial to survival [1–3]. Moreover, the X chromosome is conjectured to play a key role in the arising of certain types of cancer [4, 5].

The mechanism by which one of the two X chromosomes is inactivated is poorly understood, despite extensive work on this problem [1–3]; it is known that co-localization of chromosomes at the time X-chromosome inactivation (XCI) is established plays a key role [6–8].

Very recently, Nicodemi and Prisco [9] proposed a model to explain XCI on the basis of a spontaneous symmetry-breaking mechanism, related to the classical Ising model of Statistical Mechanics, in a dynamical stochastic model of the single-agent type.

Their idea is that blocking factor (BF) molecules diffuse in the cell and can bind randomly to one or the other of the X-chromosomes; however, by a collective effect, the affinity to a chromosome increases when this already binds to other BF molecules. The net effect is that once one of the two chromosomes, by the effect of a fluctuation, binds to a larger number of BF molecules, it will bind to more and more of these — at a rate higher than the other chromosome (note that the BF molecules could have a greater probability to escape when more of them bind to the chromosome; this effect should be dominated by the growth in affinity in order for the collective effect devised by Nicodemi and Prisco to set in). In the whole, as a result of diffusive behavior, fluctuation and the affinity-enhancing collective effect, a net current will be established leading to BF concentration on one of the two X-chromosomes.

The model can also account for the relevance of co-localization at the establishment of XCI; in facts, if the two X-chromosomes are too far away, the diffusive behavior will prevail, and the BF

molecules escaping from the less populated X-chromosome will have a very low probability to reach the other one.

The purpose of this short note is to provide a deterministic (simplified) version of the Nicodemi–Prisco symmetry-breaking XCI model, considering average exchanges of blocking factors between each of the two X-chromosomes and the cell fluid environment. Thus our model will amount to a mean-field version of the Nicodemi–Prisco model; we will formulate it first in terms of transition probabilities between states for a single BF molecule, and then pass to a formulation in terms of a first order system of ODEs, i.e. a Dynamical System [10–12], following a procedure which is standard in Physics or in Quantitative Biology [13, 14].

Here we will consider the fluid environment as a homogeneous reservoir, i.e. overlook the effects connected with the spatial localization of the X-chromosomes; thus the model will be able to predict the symmetry breaking leading to inactivation of one of the X-chromosomes, but (in its simplest form, presented here) not its dependence on co-localization of the chromosomes. An extension of the model aiming at including co-localization effects will be developed in forthcoming work.

Similarly, here we will only deal with average quantities and flows; fluctuations can be included within this kind of modeling by promoting the ODEs we obtain to *stochastic differential equations* [15–17], as briefly discussed below.

2. The Model

We will consider a fixed total amount (n units) of BF molecules; these can be in three mutually exclusive states: they can bind to one (state 1) or the other (state 2) of the two X-chromosomes, or be diffusing in the cell environment (state 3). We denote the number of units binding to the first X-chromosome at time t as $\widehat{X}(t)$, that of units binding to the second X-chromosome at time t as $\widehat{Y}(t)$, and that of units diffusing in the cell fluid at time t as $\widehat{Z}(t)$. We will refer to $x(t)$ and $y(t)$ as the *occupation numbers* for the two X-chromosomes (or more precisely, for the Xic of the chromosomes). Obviously,

$$\widehat{X}(t) + \widehat{Y}(t) + \widehat{Z}(t) = N. \tag{2.1}$$

2.1. *Transition probabilities for a single BF molecule*

Let us consider the probabilities $P(i \to j, \delta t)$ for transitions between these states — in particular, transition from state i to state j — for each BF molecule (referred to as a "particle" in the following) in a time interval of length δt. In the following, we will use a simplified notation, and write

$$p_{ij} := P(i \to j, \delta t). \tag{2.2}$$

We assume that for δt sufficiently small, the probability a particle initially in state 3 will end up being in state 1 or 2 (i.e. bound to one of the two X-chromosomes) is

$$p_{31} \simeq \alpha(\widehat{X})\delta t + o(\delta t); \quad p_{32} \simeq \alpha(\widehat{Y})\delta t + o(\delta t). \tag{2.3}$$

That is, it will be proportional to the length of the time interval (but independent of time t itself) via a function $\alpha(x)$ or $\alpha(y)$ representing the affinity with the concerned X-chromosome and depending on the number of particles already binding to it.

Similarly, the probability that a particle initially binding to one of the X-chromosomes will escape from it in a time interval δt will be given by

$$p_{13} \simeq \beta(\widehat{X}, \widehat{Z})\delta t + o(\delta t); \quad p_{23} \simeq \beta(\widehat{Y}, \widehat{Z})\delta t + o(\delta t). \tag{2.4}$$

That is, the escape probability will be proportional to the length of the time interval via a function of the number of particles binding to the concerned X-chromosome and of the number of particles

fluctuating in the fluid environment (it is natural to assume these should enter only through their density $z = Z/N$).

As for direct transitions from one to the other of the two X-chromosomes, these will be impossible on account of their nonzero space separation (the particle will have to diffuse through the fluid to do that), so we will set

$$p_{12} = o(\delta t); \quad p_{21} = o(\delta t). \tag{2.5}$$

Needless to say, the probabilities of permanence in a given state are obtained simply requiring the conservation of particles, i.e. that the sum of probabilities for all transitions from a given state to all possible state is one (Markov property); thus

$$\begin{aligned} p_{11} &= 1 - p_{12} - p_{13} = 1 - \beta(\widehat{X}, \widehat{Z})\delta t + o(\delta t), \\ p_{22} &= 1 - p_{21} - p_{23} = 1 - \beta(\widehat{Y}, \widehat{Z})\delta t + o(\delta t), \\ p_{33} &= 1 - p_{31} - p_{32} = 1 - [\alpha(\widehat{X}) + \alpha(\widehat{Y})]\delta t + o(\delta t). \end{aligned} \tag{2.6}$$

2.2. *Evolution equations for occupation numbers*

Let now $\{X(t), Y(t), Z(t)\}$ be the average occupation numbers for states $\{1, 2, 3\}$ at time t; we look at the average occupation numbers at time $t + \delta t$. Note $Z(t)$ can be expressed using (2.1), hence we need only two equations. These will be given by

$$\begin{aligned} X(t + \delta t) &= X(t) - p_{13}X(t) + p_{31}Z(t), \\ Y(t + \delta t) &= Y(t) - p_{23}Y(t) + p_{32}Z(t). \end{aligned} \tag{2.7}$$

Using the expressions given above for p_{ij} — and omitting $o(\delta t)$ terms — the (2.7) yield

$$\begin{aligned} X(t + \delta t) &= X(t) + [\alpha(X(t))Z(t) - \beta(X(t), Z(t))X(t)]\delta t \\ Y(t + \delta t) &= Y(t) + [\alpha(Y(t))Z(t) - \beta(Y(t), Z(t))Y(t)]\delta t. \end{aligned} \tag{2.8}$$

Dividing by δt and letting $\delta t \to 0$, Eq. (2.8) yields a system of ODEs describing the evolution of the average occupation numbers for the three states (in which we make explicit the expression of $Z(t)$ implied by the conservation law (2.1)):

$$\begin{aligned} dX/dt &= \alpha(X)(N - X - Y) - \beta(X, N - X - Y)X, \\ dY/dt &= \alpha(Y)(N - X - Y) - \beta(Y, N - X - Y)Y. \end{aligned} \tag{2.9}$$

Passing to consider the densities $x = X/N$ and $y = Y/N$, and introducing the functions a and b defined through

$$a(w) := \alpha(Nw), \quad b(w_1, w_2) := \beta(Nw_1, Nw_2), \tag{2.10}$$

we get in the end the equations (symmetric under the exchange of x and y)

$$\begin{aligned} dx/dt &= a(x)(1 - x - y) - b(x, 1 - x - y)x, \\ dy/dt &= a(y)(1 - x - y) - b(y, 1 - x - y)y. \end{aligned} \tag{2.11}$$

2.3. *Minimal model*

So far we have worked in completely general terms within the three-states description of the system. In order to have a specific model, we should choose concrete forms for the functions $\alpha(W)$ and $\beta(W)$ — and hence of the $a(w)$ and $b(w)$ — describing the probability of capture by and escape

from chromosomes in function of the associated occupation numbers X, Y or densities x, y; this will yield a specific expression for the evolution equations (2.9) and (2.11).

In their work, Nicodemi and Prisco [9] argued that the essential feature of their model for XCI is the collective phenomenon enhancing affinity and hence the probability of capture by X-chromosomes with a substantial number of binding particles.

Thus the function $\alpha(W)$ should go to a finite limit α_0 for $W \to 0$ (the BF have a nonzero affinity with the chromosomes even when no BF molecules are binding to chromosomes, and more generally when the collective behavior has not set in), and grow with W, i.e. $\alpha'(W) > 0$.

As for $\beta(W, Z)$, we should similarly have a function with a finite limit β_0 for $W \to 0$; as for its dependence on W and Z, we assume it is only through the ratio X/Z of BF molecules binding to the chromosome and BF molecules in the fluid environment.

In the following, we choose to deal with a "minimal" model, i.e. consider a linear dependence on w for both these quantities; we set

$$\alpha(W) = a_0 + a_1 W, \quad \beta(W) = b_0 + b_1(W/Z); \tag{2.12}$$

this implies of course

$$a(w) = a_0 + a_1 N w, \quad b(w) = b_0 + b_1(w/z). \tag{2.13}$$

The parameters (a_0, a_1, b_0, b_1) are all positive (we could always set one of these parameters equal to one by rescaling the time unit). We also stress that in view of the discussion by Nicodemi and Prisco [9], we should expect the cooperative effects enhancing affinity should be predominant over those depressing the escape rate; this means we should expect $a_1 \gg |b_1|$.

With these choices, the evolution equations for densities (2.11) read

$$\begin{aligned} dx/dt &= (a_0 + a_1 N x)(1 - x - y) - [b_0 + (b_1/(1 - N(x + y)))Nx]x, \\ dy/dt &= (a_0 + a_1 N y)(1 - x - y) - [b_0 + (b_1/(1 - N(x + y)))Ny]y. \end{aligned} \tag{2.14}$$

We are specially interested in the large N regime. In order to study this, it is convenient to rescale time (note that Eqs. (2.14) become singular for $N \to \infty$) and pass to consider as independent variable

$$\tau := Nt. \tag{2.15}$$

We also set

$$\varepsilon := 1/N \tag{2.16}$$

(hence $t = \varepsilon\tau$); the Eqs. (2.11) read then

$$\begin{aligned} dx/d\tau &= a_1(1 - x - y)x + \varepsilon[a_0(1 - x - y) - b_0 x] + \varepsilon b_1 x^2 (x + y - \varepsilon)^{-1}, \\ dy/d\tau &= a_1(1 - x - y)y + \varepsilon[a_0(1 - x - y) - b_0 y] + \varepsilon b_1 y^2 (x + y - \varepsilon)^{-1}; \end{aligned} \tag{2.17}$$

at first order in ε, we have

$$\begin{aligned} dx/d\tau &= a_1(1 - x - y)x + \varepsilon[a_0(1 - x - y) - (b_0 - b_1 x/(x + y))x], \\ dy/d\tau &= a_1(1 - x - y)y + \varepsilon[a_0(1 - x - y) - (b_0 - b_1 y/(x + y))y]. \end{aligned} \tag{2.18}$$

2.4. *Equilibria and their properties*

We are interested in equilibrium distributions for the BF molecules, i.e. in stationary solutions (equilibria) of the above Eqs. (2.14). They correspond, at first order in ε, to equilibria of (2.18).

They are given (discarding an equilibrium with negative populations $x = y = -(a_0/a_1)\varepsilon$) by:

$$\begin{aligned} E_1 &= \left(\frac{a_0(b_0 - b_1)}{a_1 b_1}\varepsilon,\ 1 - \frac{(a_0 + b_1)(b_0 - b_1)}{a_1 b_1}\varepsilon \right), \\ E_2 &= \left(1 - \frac{(a_0 + b_1)(b_0 - b_1)}{a_1 b_1}\varepsilon,\ \frac{a_0(b_0 - b_1)}{a_1 b_1}\varepsilon \right), \\ E_3 &= \left(\frac{1}{2} - \frac{2b_0 - b_1}{4a_1}\varepsilon,\ \frac{1}{2} - \frac{2b_0 - b_1}{4a_1}\varepsilon \right). \end{aligned} \tag{2.19}$$

The asymmetric equilibria $E_{1,2}$ are only acceptable for $b_0 > b_1$, while E_3 only requires $b_0 > b_1/2$ (in the opposite case, it would correspond to $X + Y > N$).

In order to study stability of equilibria for (2.18), we note that their linearization at a point (x_0, y_0) is defined at order ε by the matrix

$$M(x_0, y_0) = M_0(x_0, y_0) + \varepsilon M_1(x_0, y_0), \tag{2.20}$$

where

$$\begin{gathered} M_0(x, y) = a_1 \begin{pmatrix} 1 - 2x - y & -x \\ -y & 1 - x - 2y \end{pmatrix}, \quad M_1(x, y) = -\begin{pmatrix} \mu_1(x, y) & \mu_2(x, y) \\ \mu_2(y, x) & \mu_1(y, x) \end{pmatrix}; \\ \mu_1(x, y) := a_0 + b_0 - b_1 x(x + 2y)/(x + y)^2, \\ \mu_2(x, y) := a_0 + b_1 x^2/(x + y)^2. \end{gathered} \tag{2.21}$$

The stability of E_i is controlled by the eigenvalues λ_1, λ_2 of $M_i = M(x_i, y_i)$. With standard computations, one obtains that the situation is the following:

	λ_1	λ_2
E_1	$-a_1 - (2a_0 - b_0 + b_1)\varepsilon$	$-b_1\varepsilon$
E_2	$-a_1 - (2a_0 - b_0 + b_1)\varepsilon$	$-b_1\varepsilon$
E_3	$-a_1 - (2a_0 - b_0 + b_1/2)\varepsilon$	$(b_1/2)\varepsilon$

(2.22)

Note it follows from (2.22) that the symmetry-breaking equilibria E_1 and E_2, when they exist (i.e. for $b_1 < b_0$), are stable; the symmetric equilibrium E_3 is unstable.

Thus, for large N and $b_1 < b_0$, the dynamics will lead to a *spontaneous symmetry breaking*: a symmetric equilibrium exists but is unstable, while there are symmetry-related non-symmetric equilibria, which are stable. The system will evolve towards either one of the non-symmetric equilibria, depending on initial conditions.

The approach to (stable) equilibria is controlled by the smaller eigenvalue, i.e. $\lambda_2 = -b_1\varepsilon$. Thus, once the system is near equilibrium, the distance ρ from equilibrium will evolve in time as $\rho(\tau) \approx \rho_0 \exp[-b_1\varepsilon\tau]$; we can as well express this in terms of the physical time t as $\rho(t) \approx \rho_0 \exp[-b_1\varepsilon^2 t]$.

3. Different Time-Scales for the Dynamics

We want now to discuss some point concerning the qualitative behavior of the dynamical system defined by (2.14); we should consider it in the region (invariant under the dynamics) of $\mathbf{R}^2$ delimited by the coordinate axes and by the line $x + y = 1$.

As noted above, the symmetric fixed point E_3 is a saddle point for the dynamics. It is easy to see that its (invariant) stable manifold [10–12] is just the line $y = x$.

Let us consider the situation where at first very few BF molecules are binding to either one of the X-chromosomes, i.e. $x(0) \approx 0 \approx y(0)$; note that as $x(0) \approx y(0)$, the initial data are close to the stable manifold for the saddle point E_3.

In a first stage, both $x(t)$ and $x(t)$ will grow exponentially in τ, with exponent a_1; this is easily seen from (2.14) (assuming $x \ll 1$, $y \ll 1$). More precisely, near the origin one has $dx/d\tau \approx a_1 x$, $dy/d\tau \approx a_1 y$; it follows that in this first phase, $x(t) \approx y(t)$, i.e. the dynamics remains in a neighborhood of the symmetric line $x = y$.

This fast growth will go on until the system gets near to E_3 (note this also means $1 - (x + y) = O(\varepsilon)$); at this point, a slower evolution gets in. Once it reaches the vicinity of E_3, the dynamics is dominated by the expansion rate near E_3, i.e. by the positive eigenvalue $\lambda_2(E_3) \approx (b_1/2)\varepsilon$, and evolution takes place at a speed of order ε.

However, at some point (after a time of order $1/\varepsilon$) the system gets far enough from E_3 to have again a dynamics non fully described by the linearized system identified by M_3, and a somewhat faster — albeit not as fast as in the first phase — evolution can take place.

This will lead the system near one of the non-symmetric equilibria (depending on the initial data), where again the dynamics is dominated by the eigenvalue which is smaller in modulus; this is $\lambda_2(E_{1,2}) = \varepsilon b_1$, i.e. the system gets again a speed of order ε, and thus approaches the final equilibrium, as already discussed, with a rate of order ε.

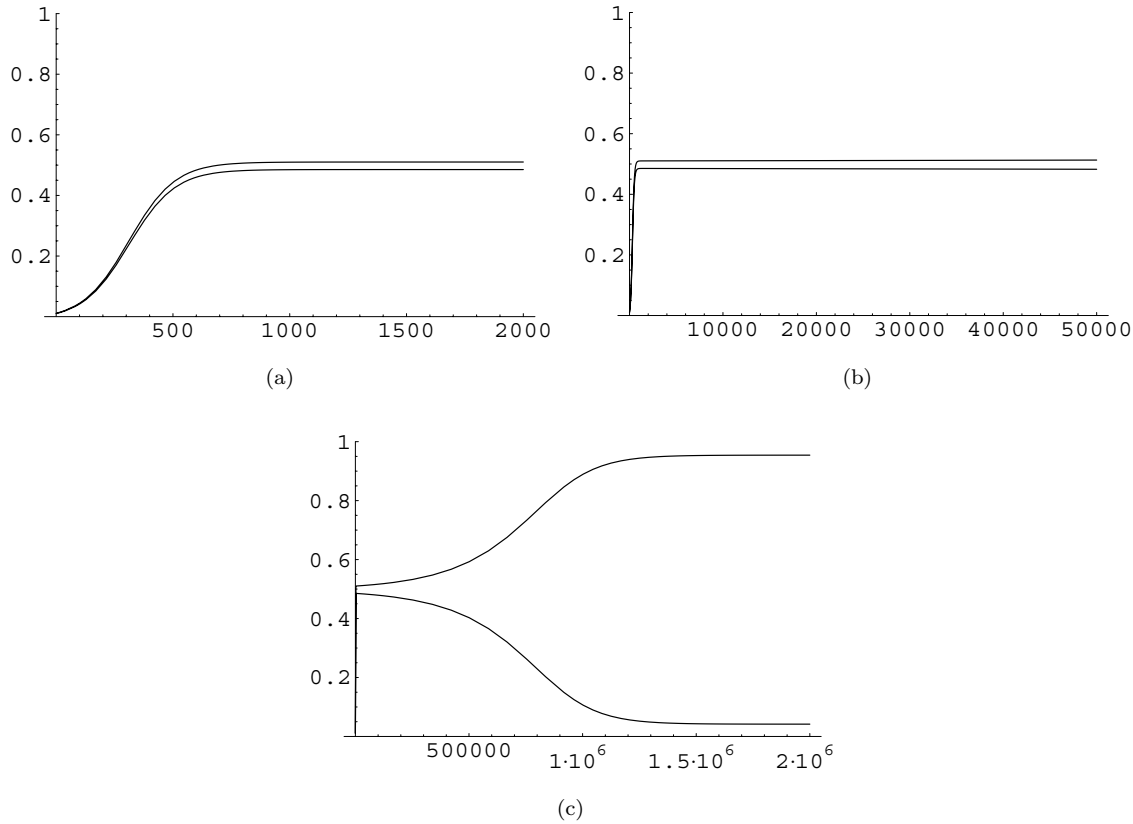

Fig. 1. Evolution of $x(t)$ (upper curves) and $y(t)$ (lower curves) as a function of the rescaled time τ, obtained numerically integrating the Eqs. (2.17). The parameters defining the model have been set as follows: $a_0 = 1$, $a_1 = 0.01$, $b_0 = 0.5$, $b_1 = 0.1$; while for N we have used $N = 10{,}000$, giving $\varepsilon = 0.0001$. Initial conditions are $x(0) = 0.011$, $y(0) = 0.01$. (a) The initial expansion (this plot shows the evolution for $0 \leq \tau \leq 10^3$); note the two densities grow together. (b) On a longer timescale one observes how the slow phase sets in and the densities remain nearly constant over a long time (this plot shows the evolution for $\tau \leq 5 \cdot 10^4$). (c) On a still longer timescale, the transition from the saddle point E_3 to the stable equilibrium — in this case, E_2 — is clearly visible and happens at an intermediate speed (this plot shows the evolution for $\tau \leq 2 \cdot 10^6$).

Summarizing, the evolution of our system will have (assuming initial conditions are near to zero) four distinct phases:

(1) A phase of rapid growth, exponential with expansion rate of order a_1;
(2) A slow phase (speed of order ε) spent in the vicinity of the saddle point E_3;
(3) An intermediate (moderate) speed phase, in which the system travels from a neighborhood of E_3 to a neighborhood of either ones of the asymmetric stable equilibria $E_{1,2}$ with a speed substantially higher than ε;
(4) A new slow phase, in which the system approaches exponentially the stable equilibrium at a rate of order ε.

This behavior is clearly shown in Fig. 1, where we plot the numerical solution to the full equations for $x(\tau)$ and $y(\tau)$ (that is, without truncation to first order in ε) on different time scales.

In Fig. 2, we look at the evolution of the quantities $\xi(t) := x(t) + y(t)$ and $\eta(t) := x(t) - y(t)$, representing the total fraction of BF molecules binding to either one of the X-chromosomes and the symmetry breaking measure respectively. This again shows clearly that the overall evolution of the system goes through the different phases enumerated above.

Confirmation is also obtained by Fig. 3, where we plot $d\xi/d\tau$ and $d\eta/d\tau$ on different timescales.

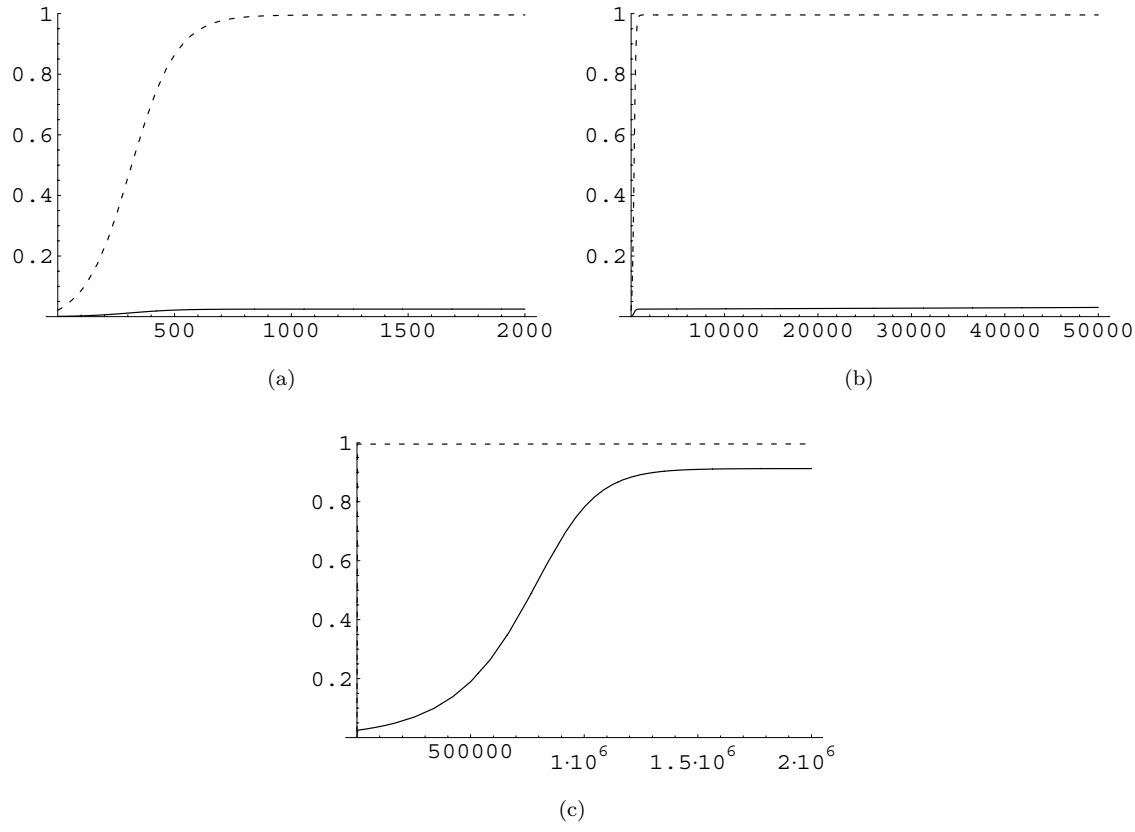

Fig. 2. Evolution of $\xi(t) = x(t) + y(t)$ (dotted curves) and $\eta(t) = x(t) - y(t)$ (solid curves) as a function of the rescaled time τ, obtained numerically integrating the Eqs. (2.17). Parameters and initial conditions as in Fig. 1. (a) In the initial expansion ξ grow abruptly, while η remains near to zero (this plot shows the evolution for $0 \leq \tau \leq 10^3$). (b) In the slow phase both ξ and η remain nearly constant over a long time (this plot shows the evolution for $\tau \leq 5 \cdot 10^4$). (c) In the intermediate speed phase, ξ remains nearly constant, while η undergoes a relatively fast growth (this plot shows the evolution for $\tau \leq 2 \cdot 10^6$).

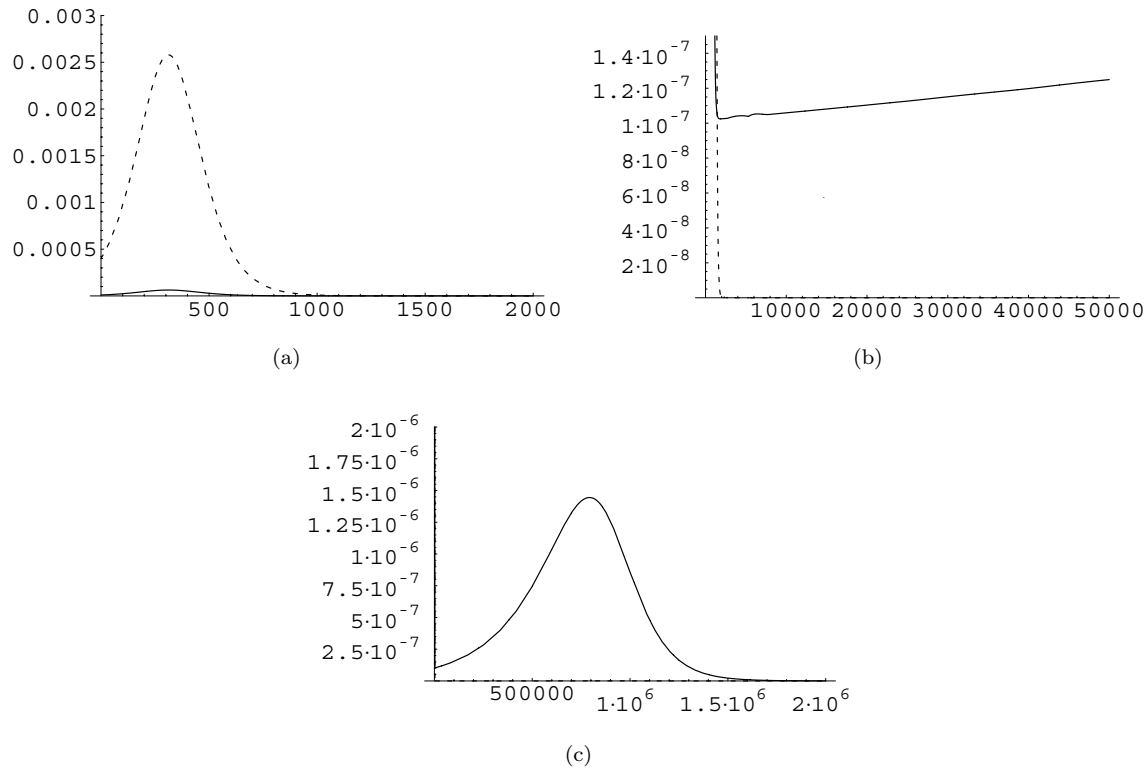

Fig. 3. Evolution of $\xi'(\tau)$ (dotted curves) and $\eta'(\tau)$ (solid curves) resulting from the numerical integration of the Eqs. (2.17). Parameters and initial conditions as in Fig. 1. (a) In the initial expansion $\xi'(\tau)$ reaches values of order $2.5 \cdot 10^{-3}$, while $\eta'(\tau)$ remains smaller than $7 \cdot 10^{-5}$. (b) In the slow phase both speeds are very small, but $\xi' < 10^{-8}$ while $\eta' \simeq 10^{-7}$. (c) In the intermediate speed phase, ξ' remains extremely small (in this case we actually have $\xi' \simeq 10^{-9}$), while η' slightly grows again; in this case $\eta' \simeq 10^{-6}$.

4. Fluctuations

The model equations (2.17) or the limit ones (2.18) only deal with evolution of average quantities, i.e. do not take into account in any way fluctuations. Our present task is to go beyond this level of description, and take into account *fluctuations* around the average dynamics.

As a first approximation, these can be taken into account by transforming the equations (2.17) or (2.18) into stochastic differential equations [15–17] by adding a noise term (see the Appendix for details). In other words, if the deterministic equations are $dx/d\tau = f(x,y)$, $dy/d\tau = g(x,y)$, we will write

$$\begin{aligned} dx &= f(x,y)d\tau + \gamma d\omega(\tau), \\ dy &= g(x,y)d\tau + \gamma d\omega(\tau), \end{aligned} \tag{4.1}$$

with $\omega(\tau)$ a standard Wiener process and γ a parameter describing the size of fluctuations. Note that (as these are fluctuations for an average) γ will depend on N and hence on ε; more precisely, $\gamma \simeq \gamma_0\sqrt{\varepsilon}$. This dependence — and the estimate $\gamma_0 \leq \gamma_0 = \sqrt{a_1}/2$ — can be obtained by a standard procedure.

At first order in ε, we have

$$\begin{aligned} dx &= [a_1(1-x-y)x + \varepsilon[a_0(1-x-y) - (b_0 - b_1 x/(x+y))x]]d\tau + \sqrt{\varepsilon}\gamma_0 d\omega(\tau), \\ dy &= [a_1(1-x-y)y + \varepsilon[a_0(1-x-y) - (b_0 - b_1 y/(x+y))y]]d\tau + \sqrt{\varepsilon}\gamma_0 d\omega(\tau). \end{aligned} \tag{4.2}$$

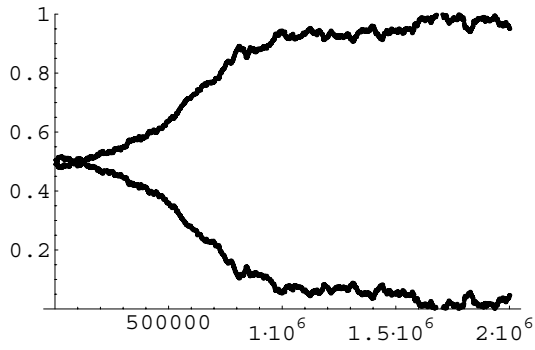

Fig. 4. Simulation of the stochastic process defined by (4.2); the parameters of the model have been chosen as in the previous figures (see caption to Fig. 1 for their values), and we have set $\gamma = 10^{-4}$. In this case the fluctuation do not seriously modify the dynamics, and the discussion based on the deterministic model confirms its validity.

When $1 - x - y = O(\varepsilon)$, the noise term could — depending on the relation between ε, a_1 and γ_0 — dominate the dynamics. That is, in the slow phase near the saddle point (see the discussion in Sec. 3) random motion due to fluctuations could be dominant: if γ is large enough, the time spent in a neighborhood $\mathcal{B}$ of E_3 will be determined by the escape time needed to exit $\mathcal{B}$ due to fluctuations. This will produce an acceleration of the dynamics with respect to the purely deterministic one — and possibly could cause the system to cross the line $x = y$ and end up near the other stable equilibrium (this happens in the numerical simulation plotted in Fig. 4). On the other hand, if γ is small enough then the fluctuations will cause just a twiggling of trajectories around deterministic ones.

Obviously dominance of fluctuation in the dynamics will take place once the system gets near — or very near if γ is small — to the stable equilibrium point E_1 or E_2. There will be a metastable equilibrium distribution around $E_{1,2}$ and — over extremely long times — large fluctuations could drive the system near to the other stable equilibrium; the equilibrium distribution and the time needed for large fluctuations to appear can be estimated via standard stochastic processes techniques [17].

In Fig. 4 we show a numerical simulation of (the stochastic process defined by) the stochastic differential equations (4.2).

5. Conclusions

We have provided a mean-field formulation of the model recently proposed by Nicodemi and Prisco [9] for the X-chromosome inactivation in mammals [1–3, 6–8].

Like their model, the version proposed here explains X-chromosome inactivation as the result of a *spontaneous symmetry breaking* in the dynamics of blocking factors molecules binding to the X-chromosome inactivation centers (Xic). While their approach was based on a single-agent model, in our version the considered equations deal directly with average quantities.

After discussing a general formulation of the model, we considered a minimal version, in which the affinity grows linearly with the number of BF molecules already binding to the Xic and the rate of escape of BF molecules increases linearly on the ratio between density of BF molecules binding to the X-chromosomes and of BF molecules floating in the fluid environment with the same number. Our model contains four positive parameters, related to affinity and escape probability for the BF molecules.

We showed that when $b_1 < b_0$, non-symmetric equilibria exist; under the same condition they are stable (while symmetric equilibria are unstable). Thus in such case we have a *spontaneous symmetry breaking*, i.e. non-symmetric equilibria describe the asymptotic state of the system. We were also

able to estimate the rate of approach to equilibrium as a function of the parameters describing the system and the total BF population.

A qualitative discussion showed that when the initial situation corresponds to most of the BF molecules floating in the fluid, one should expect the dynamics to undergo different phases. We ran some numerical simulations (one of these is shown in the figures) confirming the conclusions reached by the qualitative discussion mentioned above. We also briefly discussed how fluctuations can be taken into account within our scheme.

Finally, we would like to stress that our model differs from that of Nicodemi and Prisco only in the mathematical description it considers, while the physical basis is the same. Thus, we are just providing an alternative description — in terms of dynamical systems and ODEs rather than of stochastic processes — for the Physics described by Nicodemi and Prisco in their paper [9].

This mathematically simpler description allows to make more detailed predictions, in particular about different timescales in the dynamics; these were fully confirmed by numerical simulations.

Our model, like the one of Nicodemi and Prisco [9], did not take into account co-localization; work is in progress to take this into account within the present description of X-inactivation.

Appendix. Stochastic Modelling

In this appendix we will briefly discuss the passage from the physical model of Sec. 2 to the stochastic differential equations (4.1) and (4.2).

In order to take into account full detail of fluctuations in our model, we should consider the flows Φ_{ij} of particles from state i to state j. Denoting by $\nu_{ij}(\delta t)$ the number of particles passing from state i to state j in a time interval of length δt, we have of course

$$\Phi_{ij} = \nu_{ij} - \nu_{ji}.$$

The transition probabilities p_{ij} for a single particle are given in Subsec. 2.1; the ν_{ij} will thus be Poisson distributed with parameter $\lambda_{ij} = p_{ij} n_i$, where n_i is the population of state i at the beginning of the time interval.

Needless to say, if we look just at expectation values we obtain again (2.8); however, our present task is to go beyond this level of description, and take into account first and higher order momenta of the Poisson distribution — that is, in physical terms, *fluctuations* around the average dynamics.

Let us fix our attention, for the sake of concreteness, on the population X (or density $x = X/N$) of the state 1 and its variation δX (or δx) in a time interval of length δt; we also write Z and z rather than expressing these quantities in terms of (X, Y) and (x, y), for ease of notation.

We obviously have $\delta X = \nu_{31} - \nu_{13}$. Recall that ν_{31} is Poisson distributed with parameter $\lambda = \alpha(X) Z \delta t$ (i.e. $\mathcal{P}(\nu_{31} = k) = \lambda^k e^{-\lambda}/k!$), and ν_{13} is also Poisson distributed but with parameter $\mu = \beta(X, Z) X$. Thus Φ_{31} is Poisson with mean $\lambda - \mu$ and variance $\sigma_{31}^2 = (\lambda + \mu)$. Thus for X we have the stochastic differential equation $dX = (\lambda - \mu) dt + \sigma d\omega(t)$; in the case of our minimal model this reads

$$dX = [(a_0 + a_1 X) Z - (b_0 + b_1 X/Z) X] dt + \sqrt{(a_0 + a_1 X) Z - (b_0 + b_1 X/Z) X}\, d\omega(t).$$

Passing to density variables this reads $dx = N^{-1}[(a_0 + a_1 N x) N z - (b_0 + b_1 x/z) N x] dt + N^{-1}[(a_0 + a_1 N x) - (b_0 + b_1 x/z) N x]^{1/2} d\omega(t)$; we should also pass to the rescaled time variable $\tau = Nt$, so that $dt = (1/N)(d\tau)$ and $dw(t) = (1/\sqrt{N}) d\omega(\tau)$.

In this way we get, using again $N^{-1} = \varepsilon$,

$$dx = [a_1 x z + \varepsilon(a_0 z - (b_0 + b_1 x/z) x] d\tau + \sqrt{a_1 x z + \varepsilon(a_0 z - (b_0 + b_1 x/z) x}\, \sqrt{\varepsilon}\, d\omega(\tau).$$

We thus have a noise of intensity $\gamma = \widehat{\gamma}_0 \sqrt{\varepsilon}$; note that at order zero in ε, $\widehat{\gamma}_0 = \sqrt{a_1 x z}$; as the sum of x and z cannot be higher than one, this can be estimated by $\widehat{\gamma}_0 \leq \gamma_0 = \sqrt{a_1}/2$.

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