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Chromosome progression and mitotic times behavior are mimicked by an stochastic unstable dynamics

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ABSTRACT

Mitosis is one of the most important processes of living matter. In this paper we analyze the consequences of assuming mitosis as being dictated by an unstable dynamics grounded in an antagonist genetic circuit. Based on this approach main characteristics of chromosome movement behavior in different mitotic stages can be mimicked. We describe the statistical variability of mitotic progression times – an aspect unvisited in previous studies – and find a remarkable relationship between mitosis times, both in healthy and malignant eukaryotic cells. We propose a tentative methodological approach to reconstruct the mitotic dynamical attractor.

Mitosis is the shortest phase in the cell cycle and proceeds with remarkable precision. Throughout its course sister chromatids with duplicated copies of the genome are translated towards two opposite spacial locations before cell division materializes. Chromosomes movement exhibit directional instability [1], i.e., oscillations conducing to abrupt changes in direction. This is observed in the prometaphase of animal cells where mono-oriented chromosomes switch between episodes of poleward and away from the pole movement. Indeed, oscillation persists in chromosome congression, metaphase and early anaphase stages [1–4]. Such a behavior is a signature of the underlying governing process. An analytical approach to this important phenomenon would help our understandings on the control mechanisms involved in mitotic duplication. Several works have addressed this challenge, e.g., analyzing the role played by the collective dynamics of chromokines in a tug-of-war context [5], through the formulation of a mechanobiochemical feedback mechanism [6], modeling drosophila embryos' chromosome motility with a force-balance model [7] or building a mechanomolecular model driven by a minimal kinetochore bicyclic cascade [8]. Here we adopted a novel perspective to explain results of broad relevance. In particular, we hypothesize that mitosis is dictated by unstable dynamics, determined by an underlying antagonist genetic circuit. It is known that a balance in the observed antagonism between the activities of the anaphase-promoting complex/cyclosome (APC/C) and the spindle assembly checkpoint (SAC) delivers an efficient mitosis with faithfully segregated chromosomes [9]. Antagonist dynamics often produces unstable dynamics [10]. Our approach reproduces qualitatively well several characteristics of chromosome behavior and, as a byproduct, allows unprecedented insights into the statistical variability of progression times and establishes a remarkable relationship between mitosis times, both in healthy and malignant eukaryotic cells, which in turn opens the door to a methodological proposition for mitosis attractor reconstruction, an aspect never intended before.

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1. The stochastic unstable mitosis

Random fluctuations affects biological dynamics in many ways. A notorious one is the transitory stabilization of unstable states, i.e., the appearance of new dynamical behavior observed exclusively in the presence of noise [11]. It is known to occur in a simple genetic circuit composed of interacting positive and negative feedback loops [12] where intrinsic noise stabilizes a functionally relevant unstable state. Similar genetic circuits are known to control transient processes as differentiation in bacteria [13–15] or neurons' membrane polarization [16] and yeast [17]; or to be related to the cell cycle [18] or to circadian clocks [19]. We consider such a simple genetic circuit as a fundamental dynamical rule for a transient description of chromosome movements in the course of mitotic progression. The circuit is composed by a promoter, P_a, expressing the transcription factor, A, able to activate both, its own promoter, P_a, and repressor promoter, P_r. R, the repressor protein, acts on the activity of A inhibiting it by targeting it for degradation. The circuit comprises a positive feedback loop given by selfregulation of A and a negative feedback loop defined by the activation of R and the consecutive inhibition of A. Thus, the expression of the transcription factors of A and R is synchronized. For simplicity's sake we consider solely the equations governing the temporal evolution of A and R, given by [12]:

$$\begin{aligned}\frac{dA}{dt_g} &= \alpha_a + \frac{\beta_a A^n}{k_a^n + A^n} - \delta AR - \lambda_a A \\ \frac{dR}{dt_g} &= \alpha_r + \frac{\beta_r A^p}{k_r^p + A^p} - \lambda_r R\end{aligned} \tag{1}$$

Here, α_x, λ_x, β_x, k_x, are basal rates, degradation rates, Hill functions strengths and Michaelis constant of the species x, while δ, is the repression intensity of A by R. For adequate parameter values Eq. (1) exhibits an unstable fixed point stabilized by noise [12] producing transient oscillations of proteins A and R. It must be noted that the temporal scale associated with Eq. (1) is not that observed in mitosis. Thus, time needs to be rescaled: the original time scale associated with the genetic regulation, denoted by t_g in Eq. (1), is modified such that $t_g \to \phi\, t$, $\phi > 1$, where t is a new temporal variable properly rescaled on the mitosis meaningful time range. While the resulting evolution equations have the same form as Eq. (1), they are now expressed in terms of new parameters rescaled by the factor ϕ, i.e.,

$$\begin{aligned}\hat{\alpha}_x &= \phi\, \alpha_x \\ \hat{\lambda}_x &= \phi\, \lambda_x \\ \hat{\beta}_x &= \phi\, \beta_x \\ \hat{k}_x &= \phi\, k_x \\ \hat{\delta} &= \phi\, \delta\end{aligned} \tag{2}$$

Chromosome position, i.e., the kinetochore position with respect to a convenient coordinate system, is arbitrarily defined in terms of the variables A and R, such that

$$X(t) \equiv \begin{cases} aA(t) + b_1 & t_0 \le t < t^* \\ rR(t + t^*) + b_2 & t^* < t \le T \\ 0 & t > T \end{cases} \tag{3}$$

Here, t^*, is the prometaphase stage duration, T, is identified with the ending time of anaphase A and a and r are arbitrary constant strength parameters, while b_1 and b_2 are arbitrary biases. Note that the interval $T - t^*$, is the time spent in the metaphase and anaphase A. The initial time t_0 is defined such that a trajectory will be significant if and only if $T - t^* > \tau$. We set $\tau > 7$ min to ensure that we are dealing with trajectories around the transitorily stabilized unstable fixed point [12]. Definition (3) establishes that proteins A and R rule chromosome motion. However, it should be remarked that mitosis consist of still unknown molecular mechanisms behind many concurrent processes. Consequently, it is assumed that these mechanisms determine synchrony breaking between the effects of A and R on the downstream movements of chromosomes. Furthermore, at this stage our intention is not to establish a strict relationship between A and R, and specific complexes like APC/C and SAC, but to keep our attention focused of the consequences of assuming Eq. (3) as a simplistic dynamical backbone mimicking important and unexplained signatures of chromosome behavior.

2. Mimicking chromosome movements

Now, let us consider directional instability during prometaphase. This behavior is reproduced by Eq. (3) for $t < t^*$, as depicted in Fig. 1 (bottom). Chromosome movement shows a directional instability qualitatively similar to that reported in experiments with mitotic newt cells mono-oriented chromosomes during *in vivo* prometaphase [20]. To be specific, the oscillation's period and amplitude, and the stochastic fluctuations present in the chromosome's displacement, are comparable to experimental results (Fig. 1(top)) - this last feature is not reproduced by alternative approaches [5] -. Additional stages can also be well mimicked: in Fig. 2 we show temporal series for the chromosome position during prometaphase, congression, metaphase and anaphase A (PCMAA) as obtained with Eq. (3) for $t < T$. The chromosome position during these stages shows features as those already mentioned above regarding oscillation's period, amplitude