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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

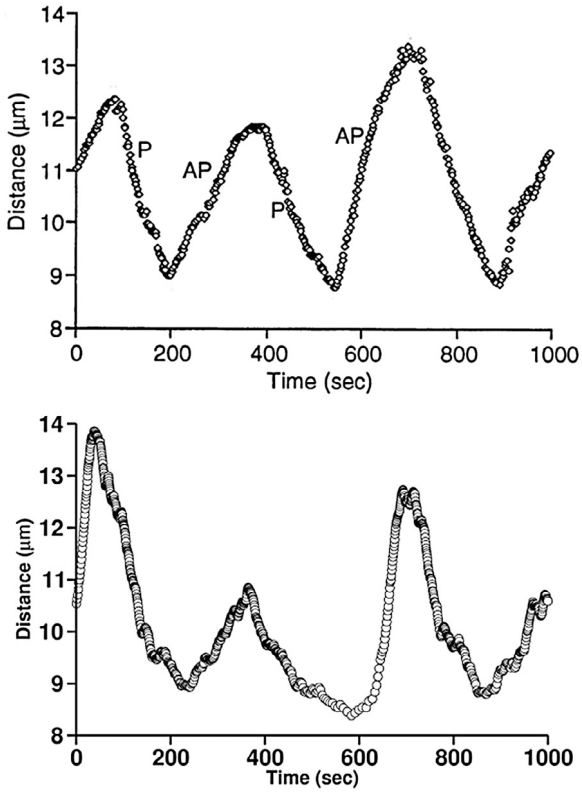

Fig. 1. Top: Kinetochore directional instability for a mono-oriented chromosome showing (P) poleward and (AP) away from the poles movements (taken from [20]). Bottom: Particular event showing the transitory stabilization of the unstable equilibria obtained simulating chromosome movements with Gillespie method [21] using (3) with parameters values $k_r = 0.145$, $k_a = 0.2$, $\phi = 98$, $a = 0.0004$ # de mol./ μm and $b_1 = 8$ μm.

and stochastic variability. This qualitative behavior can be reproduced plausibly well based on the dynamics around the instability [12].

Contrary to what one would think Eq. (3) dynamics also account for cases where no apparent oscillatory behavior has been reported. For example, reported analysis of Drosophila S2 chromosome movement shows evident Anaphase A fluctuations [22] fully compatible with the dynamics around an unstable noise assisted small amplitude limit cycle.

3. Statistical variability of mitotic duration times

An main aspect concerns the diversity of duration times shown by a same type set of cells during mitotic progression exposed to same conditions. To the best of our knowledge the fundamental processes dictating such a diversity are unknown. Only in rare exceptional cases experimentally determined times are fully reported and statistically explored as in [23]. Most studies mostly report average values. Now, if we assume mitosis is dictated by an unstable dynamics one would expect to obtain an acceptable approach to the observed statistical variability of mitotic times. To analyze this aspect, we defined mitotic time as the time spent from nuclear envelope breakdown to anaphase A. This definition is rooted in the fact that we are considering mitosis as being determined by an escape process from an unstable state transitorily stabilized by noise. Now, equipped with Eq. (3) a set of duration times comprising the PCMAA sequence are obtained for particular values of the parameters k_a, k_r and ϕ. We compare times obtained from a sequence of events with a set of 143 duration times from HeLa cells experiments. Such a comparison is achieved calculating the survival function, $S(t)$, defined as the probability for mitosis to last $t_m > t$, (see Fig. 3). The cumulative distribution, $C(t) = 1 - S(t)$, was also calculated as this quantity has been reported in works dealing with duration times [23]. While mitotic times obtained with Eq. (3) fitted remarkably well the experimental data describing the abrupt decaying in the survival function, it departs from the long experimental data tail. Even so, Eq. (3) seems to captures main features of the survival (and cumulative) distribution of experimental mitotic times.

4. ϕ-ordering of mitotic times

We recall that the aforementioned figures are related to different cell types: Figs. 1 and 2 belong to newt lung cells while Fig. 3 belong to HeLa cells. Consequently, these curves were obtained for different ϕ and k_r values. In principle we could

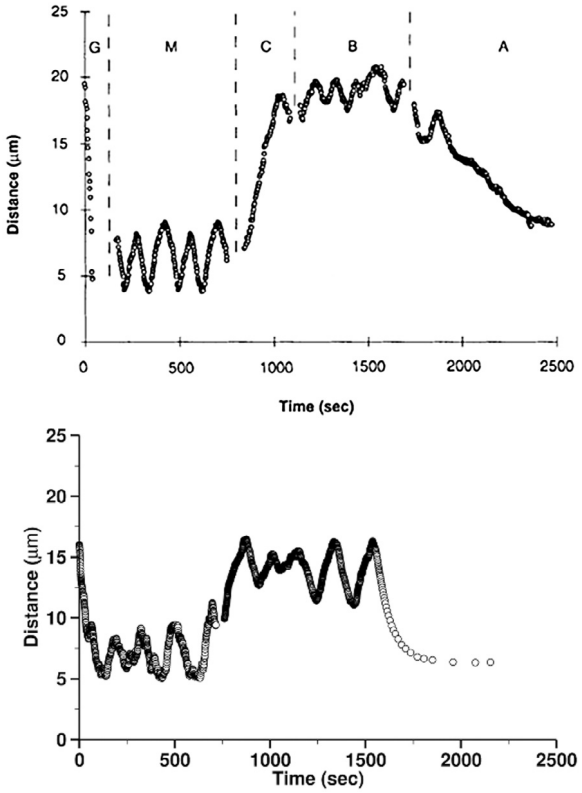

Fig. 2. Top: Distance vs time plot of the kinetochore movement during mitosis in newt lung cells. (G) gliding, (M) mono-oriented, (C) congression of a bi-oriented chromosome towards the equator, (B) bi-oriented near the equator; and (A), anaphase A poleward movement (figure taken from [1]). Bottom: Particular event showing different mitotic stages obtained simulating chromosome movements with Gillespie method [21] using (3) with parameters values $k_r = 0.15$, $k_a = 0.2$, $\phi = 140$, $a = 0.001$ # de mol./ μm, $r = 0.002$ # de mol./ μm and $b_1 = 0$ μm and $b_2 = 2.5$ μm, $t^* = 750$ s. The reported event was selected from an sequence of continuously simulated events and shifted to the origin.

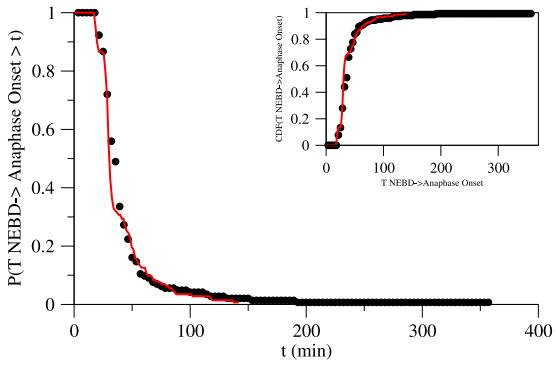

Fig. 3. Survival function for (a) $N = 143$ mitotic times from HeLa cells (dots) and simulations of 143 events obtained with Eq. (3) with $k_r = 0.143$, $k_a = 0.2$ and $\phi = 46$ (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mimic mitotic progression for different cells types modifying these values accordingly. Given the limited open availability of chromosome position data for distinct cell types, a test of our hypothesis using many cell types seems hard to accomplish. So, to further testing we pay attention to the average time spent through the metaphase and anaphase A (MAA) sequence[1]. While average mitosis times are abundant in the literature, it is not to be the case for single stage times. After reviewing the literature currently available to us, we were able to gather a set of 80 average mitotic duration times strictly through the

[1] By selecting only these two stages we increase the number of experimental available data. This decision does not affect the subjacent idea as far as both *A* and *R* are governed by the same escaping dynamics. Considering full PCMAA times produces similar results.

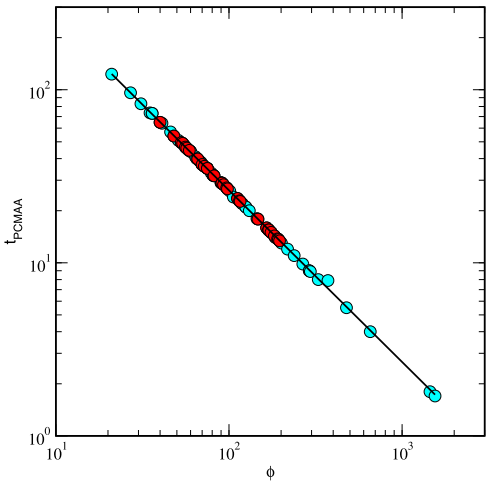

Fig. 4. Average mitotic duration times through the metaphase and anaphase A (MAA) sequence for different healthy (cyan) and neoplastic (red) cell types plotted as a function of the scaling factor ϕ. Please check supplementary data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

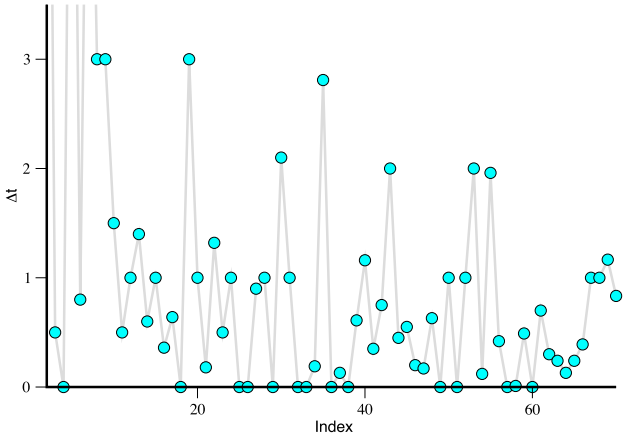

Fig. 5. Temporal distance between two successive times Δt_i from Fig. 4.

MAA sequence for different healthy and neoplastic cell types (see Supplementary material for details). We are unaware of the existence of another set of times similar to our small survey. With this information we can simulate Eq. (3) in order to obtain the specific value of ϕ needed to reproduce a given experimentally determined time through the MAA sequence. The MAA duration times for different cells types log–log plotted versus the scaling factor ϕ that is needed to reproduce such a time are shown in Fig. 4. MAA duration times follow a power law with a characteristic exponent close to $\gamma = -0.974$, i.e.,

$$t_{MAA} \sim \phi^{\gamma}. \tag{4}$$

Early studies founded a relationship between mitosis duration and DNA content [24]. In contrast, Eq. (4) establishes a relationship with the scaling parameter ϕ. This suggest that ϕ could be indirectly related with DNA content, however such a fact is just a weak conjecture at this moment.

5. Searching for the mitotic attractor

In what follows we will propose a methodological framework to dive into the dynamical origins of mitosis. The finding of Eq. (4) seems remarkable considering that the times used to plot it were determined in very different experimental situations – involving different physical conditions and/or experimental techniques – on a time spam covering a century. One may think that the scaling factor contributes to "disentangle" the effects of such a diversity of situations, in such a way that Fig. 4 could be carrying information on the underlying dynamics. Potential errors generated because of considering this set of times can be minimized by calculating the temporal distance between two successive times $\Delta t_i \equiv t_{i+1} - t_i$. Obviously, the

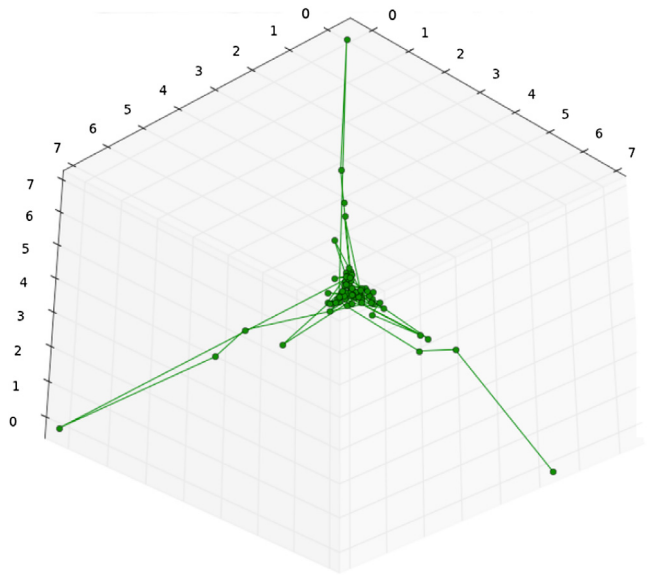

Fig. 6. Tentative phase space attractor reconstruction for components $[\Delta t_0, \Delta t_7, \Delta t_{18}]$.

arrangement of this set is artificially dictated by data availability and not by any real ordering. Even so, we assume that at this level of description the following approach could be useful and expect it to be refined and validated by others using larger datasets. With this in mind we build the time series $\{\Delta t_1, \ldots, \Delta t_{N-1}\}$ which is independent of the scaling factor. This temporal series can be seem in Fig. 5. A convenient way to unveil the dynamics of a complex system corresponds to phase space reconstruction [25]. Currently, a most accepted method is Pecora et al.'s unified approach for attractor reconstruction [26]. We are aware of the very small set of points but we proceed with the ambitious challenge of reconstructing the phase space just as a methodological proposition. We calculated the continuity statistics using time delays or advances of 50 time steps and imposing periodic conditions. Under this very restrictive situation the resulting reconstruction for the best set of components is obtained with $[\Delta t_0, \Delta t_7, \Delta t_{18}]$ as depicted in Fig. 6. Notwithstanding the very short temporal series, the unified approach is able to yield an apparently clean, quite coherent topological object. The unified approach in known to be robust under noise [26]. An underlining assumption of this approach is that the diversity of sources, methods and conditions implicit in our dataset are managed as noise affecting the data. We expect that an increasing availability of mitotic stage times will allow further advances to unveil the mitotic attractor following our or other non-related methodologies.

6. Final remarks

Increasing evidence points to the fact that unstable dynamics is responsible for functionally relevant behavior in complex systems. Notorious examples are: (i) human stick balancing where the combination of instability and noise allows for overcoming the limitation imposed by time latencies for maintaining control in the presence of rapid, random perturbations [27]; (ii) winnerless competition rooted on heteroclinic trajectories between unstable states, constituting a theoretical foundation to interpret information flow in neuronal systems [28,29]; (iii) financial crisis caused by market instabilities whose unstable potential can be reconstructed from time series [30] and (iv) the appearance, prediction and control of dragon kings in experimental set ups [31], opening the door to extreme events management. We have shown how a simple unstable circulation in phase space can account plausibly well for the main signatures observed during mitotic progression including – for the first time in the literature – the statistical variability of mitotic times. Duration times can be ordered, allowing to formulate a methodological approach for the identification of the mitotic attractor. At the current stage the question of whether the dynamics of neoplastic cells mitosis could be separately characterized is still open. However, our findings point out to a common dynamical origin for both healthy and malignant cells. It should be noted that in many situations pathological conditions share the same dynamical rules as healthy ones [32]. The establishment of solid grounds about this important aspect would be a tremendous influence in our understanding on the dynamical origins of aneuploidy and metastasis [33]. Our approach does provide a fully innovative conceptual framework that must help experimentalist studying the problem of mitosis to build new insights with potential predictive value. The simple dynamical rule given by Eq. (3) not only provides oscillatory fluctuations but a floor to analyze mitotic times that may signify a shortcut to reconstruct the mitotic attractor. Knowledge of this dynamics fundamentals will probably shed light on the process of mitosis. We think this research will contribute to a change of perspective regarding eukaryotic cell division and chromosome dynamics.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.physa.2018.08.139.

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