Stochastic modelling of chromosomal segregation: Errors can introduce correction

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Abstract

Cell division is a complex process requiring the cell to have many internal checks so that division may proceed and be completed correctly. Failure to divide correctly can have serious consequences, including progression to cancer. During mitosis, chromosomal segregation is one such process that is crucial for successful progression. Accurate segregation of chromosomes during mitosis requires regulation of the interactions between chromosomes and spindle microtubules. If left uncorrected, chromosome attachment errors can cause chromosome segregation defects which have serious effects on cell fates. In early prometaphase, where kinetochores are exposed to multiple microtubules originating from the two poles, there are frequent errors in kinetochore-microtubule attachment. Erroneous attachments are classified into two categories, syntelic and merotelic. In this paper we consider a stochastic model for a possible function of syntelic and merotelic kinetochores and we provide theoretical evidence that merotely can contribute to lessening the stochastic noise in the time for completion of the mitotic process in eukaryotic cells.

1 Introduction

Accurate segregation of chromosomes during mitosis requires regulation of the interactions between chromosomes and spindle microtubules. Equal partitioning of the genetic material is achieved by ensuring that mitotic spindle forces align all sister chromatids at the cell equator. At the centromere of each sister chromatid, kinetochore complexes provide a scaffold for chromosome/microtubule interactions (Cheeseman and Desai, 2002). Precise genome partitioning requires stable attachment of each sister kinetochore to opposite spindle poles. This bipolar attachment generates mechanical tension between the two sister cohesin linked chromatids caused by the pulling force of the mitotic spindle.

In early prometaphase, where kinetochores are exposed to multiple microtubules originating from the two poles, there are frequent errors in kinetochore-microtubule attachment (Ault and Rieder, 1992). Erroneous attachments are classified into two categories, syntelic and merotelic. A chromosome is said to be syntelically attached if both sister kinetochores are attached to chromosomes nucleated from the same spindle pole, whereas when a kinetochore is attached to each spindle pole at the same time a chromosome is considered to be merotelically attached. In contrast to the above described two cases, an amphitelic attachment is established when a chromosome has each sister kinetochore attached to one spindle pole.

If left uncorrected, chromosome attachment errors can cause chromosome segregation defects which have serious effects on cell fates. To this end, the cell has developed error-correcting mechanisms which ensure that all chromosomes become amphitelically attached before the anaphase separation signal is released. Aurora B, a member of serine/threonine protein kinsases, has been identified as the principal component of error correcting mechanisms (Carmena and Earnshaw, 2003; Biggins et al., 1999; Cheeseman

et al., 2002; Francisco et al., 1994; Tanaka et al., 2002). Aurora B is part of the chromosomal passenger complex (CPC), which also includes the inner centromere protein (INCEP), Survivin and Borealin (Bolton et al., 2002; Ruchaud et al., 2007). The CPC is thought to contribute to the localization of the kinase at the inner centromeric regions close to kinetochores, in close proximity to attached microtubules. The inhibition of Aurora B in vertebrate cells leads to the stabilization of incorrect attachments (Lampson et al., 2004). Conversely, when Aurora B is activated by removal of its inhibitors it is observed that erroneous attachments are selectively destabilized (Hauf et al., 2003; Kallio et al., 2002; Ditchfield et al., 2003). There are several models for how Aurora B might regulate erroneous attachments (for a review see Maresca and Salmon, 2010; Lampson and Cheeseman, 2011), however the common theme is that Aurora B phosphorylates kinetochore substrates in the absence of mechanical tension between sister kinetochores, which destabilizes incorrect attachments until amphitelic attachments are achieved.

Eukaryotic cells employ a highly sensitive surveillance mechanism, called the spindle-assembly checkpoint (SAC), which enforces that anaphase onset is delayed until the very last chromosome has achieved amphitelic attachments (Musacchio and Salmon, 2007; Maresca and Salmon, 2010). The signaling molecules that comprise the SAC are localized and regulated at kinetochores and Aurora B has been suggested to play a role in the SAC. Anaphase initiation requires the activation of the anaphase-promoting complex /cyclosome(APC/C), which targets the mitotic substrates cyclin B and securin for degradation. The SAC pathway generates a signal that blocks the activation of the APC. More specifically, the SAC negatively regulates the ability of an APC/C cofactor, called CDC20, to activate the polyubiquination of cyclin B and securin. By controlling Cdc20 activity the SAC can prolong metaphase until all chromosomes are correctly attached. At a molecular level, APC/C inhibition is achieved with the help of four protein complex, known as the mitotic checkpoint complex (MCC), which is composed of checkpoint proteins Mad2, BubR1, Bub3 and Cdc20 (Musacchio and Salmon, 2007). Aurora B affects MCC formation by destabilizing the localization of BubR1, Mad2 and Cenp-E at centrosomes (Ditchfield et al., 2003; Morrow et al., 2005). The process of SAC signal formation is not well understood and models which propose a role for Aurora B have been proposed in an effort to clarify the role of various kinetochore signaling proteins in anaphase onset control (see, e.g., Mistry et al. (2008) and references therein).

In this paper, we investigate how chromosome attachment errors and error-correcting mechanisms control the noise in the time for completion of the mitotic process. In particular, we provide theoretical evidence that a tightly controlled *strictly positive* rate of erroneous attachments facilitates a more accurate timing of the mitotic process than in the complete absence of attachment errors. The plan of the paper is the following. In section 2, we briefly introduce the model of Mistry et al. (2008) on the dynamics of merotelic and syntelic kinetochore attachments. In section 3, we present a complete analytical derivation of the dependence of the (stochastic) time T at which all kinetochores become amphitelically attached on the system parameters and present numerical computations that corroborate these results. Finally, we conclude with a discussion of our results in section 4.

2 The mathematical model

Following Mistry et al. (2008), we consider a continuous time Markov jump process that is associated with the graphical representation of the possible kinetochore attachment transitions shown in Figure 1. The vertices of this graph correspond to the possible attachment states of the kinetochore pairs with directed edges connecting two vertices if kinetochore pair attachments can transition between the corresponding states.

As seen in Figure 1, the possible kinetochore attachment transitions are:

$$U \xrightarrow{k_1} M,\ U \xrightarrow{k_2} S,\ U \xrightarrow{k_3} C,\ S \xrightarrow{k_4} C, \text{ and } M \xrightarrow{k_5} C,$$

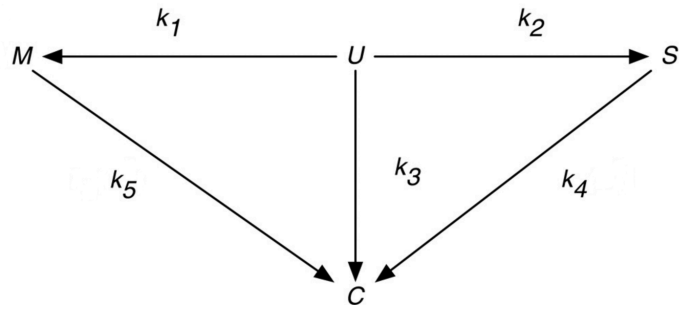

Figure 1: Network diagram showing the possible states each kinetochore unit could be in at any given time and how they can move from state to state. In particular, each kinetochore pair can be in one of the following states: unattached (U), syntelic (S), merotelic (M), or amphitelic (C).

where the parameters $k_1, k_2, \ldots, k_5$ correspond to the rate constants at which a kinetochore pair transitions between the corresponding attachment states. We denote the state vector at time $t > 0$ as

$$X(t) = (X_U(t), X_S(t), X_M(t), X_C(t)), \tag{1}$$

where X_U, X_S, X_M, and X_C are integer-valued stochastic processes representing the number of the 46 possible kinetochore pairs in the unattached (U), syntelic (S), merotelic (M), and amphitelic (C) attachment states, respectively. Throughout the paper, the initial value of the state vector is given by $X(0) = (46, 0, 0, 0)$.

We define $P(x,t)$ to be the joint probability that $X(t) = x$ at time t. Hence, $P(x,t)$ denotes the probability that the state of the system at time t is given by $x = (x_1, x_2, x_3, x_4)$, where for each $i \leq 4$, x_i is a non-negative integer and $\sum_{i=1}^{4} x_i = 46$. In this context, the master equation (Gardiner, 1985) that governs the evolution of $P(x,t)$ is

$$\frac{d}{dt}P(x,t) = \sum_{i=1}^{5} a_i(x - \nu_i) \cdot P(x - \nu_i, t) - \sum_{j=1}^{5} a_j(x) \cdot P(x,t), \tag{2}$$

where $a_i(x - \nu_i)$ can be understood as the probability per unit time of a transition from state $x - \nu_i$ to state x. In the chemical literature the rate functions a_i are usually referred to as the propensities of the corresponding transitions (see, e.g., Gillespie, 2007). In general, the relation between the propensities a_i and the deterministic kinetic rate constants k_i depends on the order of the corresponding reaction schemes (Highham, 2008). In the case of the first order transitions shown in Figure 1, we have that $a_i(x - \nu_i) = k_i N_i(x - \nu_i)$, where $N_i(x - \nu_i)$ is the number of kinetochores acting as the substrate of the i-th reaction scheme. The *"stoichiometric vector"* ν_i represents the change in population that occurs when the i-th reaction fires (Gillespie, 2007). Specifically, in what follows we consider the five transitions shown in Figure 1 given by:

$$\nu_1 = (-1, 0, 1, 0),\ \nu_2 = (-1, 1, 0, 0),\ \nu_3 = (-1, 0, 0, 1),\ \nu_4 = (0, -1, 0, 1),\ \text{and}\ \nu_5 = (0, 0, -1, 1). \tag{3}$$

The master equation (2) along with the specified "connectivity" of the system provided by (3) uniquely determine a continuous time Markov jump process, the analysis of which is the main focus of this paper. More precisely, in what follows we analyze the dependence of the distribution of the time T at which all kinetochores reach the amphitelic state (C) on the kinetic parameters of the model. We subsequently use these results to understand how stochastic fluctuations of T are controlled by the system.

3 Results

We focus on the question of how fluctuations in the random time T at which all kinetochores become amphitelically attached are controlled by the system parameters. We address this question in two different ways. First we derive analytically the probability distribution of T in Section 3.1, and then in Section 3.2 we employ a stochastic simulation algorithm that allows us to perform statistics on numerically generated ensembles of independent realizations of the process under consideration.

3.1 The distribution of the absorption time T.

In this section, we derive analytically the probability distribution of the time it takes the process to get absorbed at the state $(0, 0, 0, 46)$. The latter corresponds to the configuration of the system where all 46 kinetochores are amphitelically attached. As specified in Section 2, we assume that the system is initially at state $(46, 0, 0, 0)$ with probability one. In addition to the state vector given by (1), we define the auxiliary random vector

$$\gamma(t) = (\gamma_1(t), \gamma_2(t), \ldots, \gamma_m(t)),$$

where $m = 46$ is the number of kinetochores and each random variable $\gamma_i(t) \in \{U, M, S, C\}$ gives the attachment state of the corresponding kinetochore pair at time $t \geq 0$.

The amount of time it takes for all 46 kinetochore pairs to reach the amphitelic attachment state is formally defined as

$$T = \inf \{t > 0 : X(t) = (0, 0, 0, 46)\},$$

where we use the standard convention that the infimum over an empty set is infinity. The hitting time T can also be represented as

$$T = \sup_{i \leq m} T_i,$$

where

$$T_i(\text{state}) = \inf \{t > 0 : \gamma_i(t) = \text{state}\}$$

with state $\in \{U, M, S, C\}$. Correspondingly, for the distribution function of T we have

$$P(T \leq t) = P(T_i \leq t, \forall\ i = 1, 2, \ldots, m).$$

Using the fact that the kinetochore pairs are assumed to be identical and act independently, this yields

$$P(T \leq t) \ = \ \big[P(T_1 \leq t)\big]^m \ = \ \big[1 - P(T_1 > t)\big]^m$$

Hence,

$$P(T > t) = 1 - \big[1 - P(T_1 > t)\big]^m, \tag{4}$$

which gives the probability that all kinetochore pairs have not reached the amphitelic attachment state by time t. Therefore, we only need to calculate $P(T_1 > t)$, the probability that the first kinetochore pair has not reached the amphitelic attachment state by time $t > 0$, in order to determine the tail of the probability distribution of the hitting time T.

In order to compute the distribution of T_1 we introduce the events that the first kinetochore pair reaches the amphitelic attachment state through the merotelic attachment state as

$$\mathcal{A} = \{T_1(M) < \infty,\, T_1(S) = \infty\},$$

through the syntelic attachment state as

$$\mathcal{B} = \{T_1(M) = \infty,\, T_1(S) < \infty\},$$

and by going directly to the amphitelic attachment state as

$$\mathcal{C} = \{T_1(M) = \infty,\, T_1(S) = \infty\}.$$

Hence, the tail end of the probability distribution of the hitting time T_1 is given by

$$\begin{aligned} P(T_1 > t) \;&=\; P\big(T_1(M) + T_1 - T_1(M) > t \mid \mathcal{A}\big) \cdot P(\mathcal{A}) \\ &\quad +\; P\big(T_1(S) + T_1 - T_1(S) > t \mid \mathcal{B}\big) \cdot P(\mathcal{B}) + P\big(T_1 > t \mid \mathcal{C}\big) \cdot P(\mathcal{C}) \\ &=\; P\big(T_1(M) + T_1 - T_1(M) > t \mid \mathcal{A}\big) \cdot \frac{k_1}{k_0} \\ &\quad +\; P\big(T_1(S) + T_1 - T_1(S) > t \mid \mathcal{B}\big) \cdot \frac{k_2}{k_0} + P\big(T_1 > t \mid \mathcal{C}\big) \cdot \frac{k_3}{k_0}, \end{aligned} \tag{5}$$

where

$$k_0 = k_1 + k_2 + k_3.$$

Notice that $T_1(M)$ and $T_1 - T_1(M)$ are independent under the conditional measure $P(\cdot \,|\, \mathcal{A})$. Similarly, $T_1(S)$ and $T_1 - T_1(S)$ are independent under the conditional measure $P(\cdot \,|\, \mathcal{B})$. We now consider the conditional probability,

$$P\big(T_1(M) > t \mid \mathcal{A}\big) = \frac{P\big(T_1(M) > t, \mathcal{A}\big)}{P(\mathcal{A})},$$

which determines the probability that the first kinetochore pair transitions to the merotelic attachment state at some moment in time after time t given event $\mathcal{A}$ occurs. Since, $P(\mathcal{A}) = k_1/k_0$ and the event $\mathcal{A}$ occurs when the reaction scheme $U \to M$ fires before $U \to S$ and $U \to C$, we obtain:

$$P\big(T_1(M) > t \mid \mathcal{A}\big) = \frac{k_0}{k_1} \int_t^\infty k_1 e^{-k_1 a} da \int_a^\infty k_2 e^{-k_2 b} db \int_a^\infty k_3 e^{-k_3 c} dc = \frac{k_0}{k_1} \int_t^\infty k_1 e^{-k_0 y} dy = e^{-k_0 t}.$$

Following a similar derivation as above,

$$P\big(T_1(M) > t \mid \mathcal{A}\big) = P\big(T_1(S) > t \mid \mathcal{B}\big) = P\big(T_1 > t \mid \mathcal{C}\big) = e^{-k_0 t}. \tag{6}$$

We note that (6) is a manifestation of a general property of a collection of independent exponential random variables. Therefore,

$$P(T_1 > t \mid \mathcal{A}) = P\big(T_1(M) + T_1 - T_1(M) > t \mid \mathcal{A}\big) = \int_t^\infty f_a(\tau) d\tau, \tag{7}$$

where the continuous probability density $f_a(t)$ is determined by the convolution integral:

$$f_a(t) = \int_0^t k_0 e^{-k_0 \tau} k_5 e^{-k_5 (t-\tau)} d\tau = k_0 k_5 e^{-k_4 t} \int_0^t e^{-(k_0 - k_5)\tau} d\tau = \frac{k_0 k_5}{k_0 - k_5} \big(e^{-k_5 t} - e^{-k_0 t}\big). \tag{8}$$

It follows from equations (7) and (8) that

$$P(T_1 > t \mid \mathcal{A}) = \frac{k_0}{k_0 - k_5} e^{-k_5 t} - \frac{k_5}{k_0 - k_5} e^{-k_0 t}.$$

Similarly,

$$P(T_1 > t \mid \mathcal{B}) = \frac{k_0}{k_0 - k_4} e^{-k_4 t} - \frac{k_4}{k_0 - k_4} e^{-k_0 t},$$

and

$$P(T_1 > t \mid \mathcal{C}) = e^{-k_0 t}$$

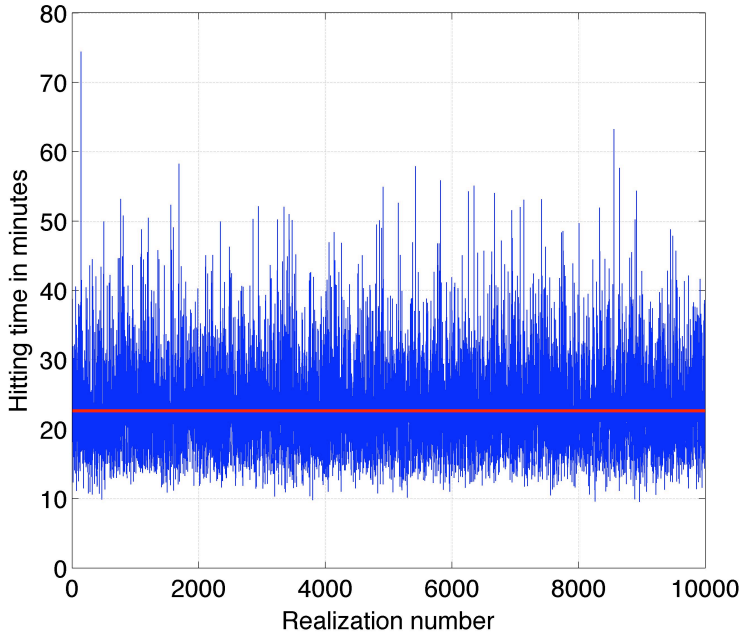

Figure 2: Plot showing 10,000 realizations of the time it takes for all sister kinetochores to form amphitelic attachments. The red line represents the empirical mean of these realizations and can serve as an estimation of the mean hitting time T (see text for details).

from equation (6).

Thus, in lieu of (5) we obtain the probality distribution

$$P(T_1 > t) = \frac{k_1}{k_0 - k_5} e^{-k_5 t} + \frac{k_2}{k_0 - k_4} e^{-k_4 t} - \Big(\frac{k_1 k_5}{k_0(k_0 - k_5)} + \frac{k_2 k_4}{k_0(k_0 - k_4)} - \frac{k_3}{k_0} \Big) e^{-k_0 t}.$$

Plugging this expression into (4) yields an explicit expression for the distribution function of T. The biological implications of the latter are delineated in the following sections. We note that extensions of the analysis presented in this section for more complex models that include explicitly the effect of Aurora B, such as the models discussed by Mistry et al. (2008), are highly non-trivial, and hence numerical approaches like the one presented in the following section become crucial.

3.2 Simulations and numerical results

In this section, we employ the Gillespie simulation algorithm (Gillespie, 2007; Gillespie, 1976) to compute an ensemble of independent realizations of the master equation (2). This allows us, among other things, to numerically approximate the distribution of the hitting time of the amphitelic state, i.e., of the state where all kinetochores are amphitelically attached. As we will see, the results of the numerical computations corroborate the analytical derivation of Section 3.1.

As explained in Section 2, because of the small numbers of chemically interacting species in the system, we treat the evolution of the latter as a Markovian stochastic process, rather than as a deterministic process (Highham, 2008), and use the standard master equation formalism (Gardiner, 1985; van Kampen, 2007). In this context, Monte Carlo methods are commonly used to generate realizations of the underlying stochastic process. For chemical reaction networks this is frequently done using one of the two stochastic simulation

algorithms, called the direct method and first reaction method, respectively, developed by Gillespie (1976). Modern variations of these algorithms, aimed at improving the computational performance, include the methods developed by Gibson and Bruck (2000), Cao et al. (2004) and E et al. (2005), among others. In the following, all simulations have been performed with an in-house implementation of Gillespie's direct method. The latter is computationally efficient for generating numerical realizations of (2).

Our main focus in the numerical computations that follow is the dependence of the first two moments of the all-amphitelic hitting time on the kinetic parameters associated with kinetochore transitions. While it would be of interest to explore the relationships between all five of the parameters k_1, k_2, k_3, k_4, and k_5, we note that we narrowed our focus to the relationship between the parameters k_1 and k_3 for the purpose of this paper. We allowed the parameter that governs transitions from the unattached to merotelic attachment states, k_1, to take on values in the range 0.01 min^{-1} to 0.25 min^{-1}, and the parameter that governs transitions from the unattached to amphitelic attachment states, k_3, to take on values in the range 0.01 min^{-1} to 0.5 min^{-1}. The rest of the kinetic parameters were set to the values adopted by Mistry et al. (2008). A simulation was then conducted by choosing a value in the range above for the parameters k_1 and k_3 and performing 10,000 realizations using Gillespie's direct method on these parameter values.

Following the assumptions outlined in Mistry et al. (2008), each realization started with all 46 kinetochore pairs in the unattached state and then proceeded by updating the populations of the kinetochore attachment types in the previous time step according to Gillespie's direct method, with possible transitions following the network diagram in Figure 1. A realization was then deemed to have finished when all 46 kinetochore pairs reached the amphitelic state. The amount of time required to reach this state, i.e. the hitting time for the specific realization, was then recorded. This process was repeated for each of the 10,000 realizations. The results for all realizations for a specific choice of parameter values are shown in Figure 2.

The data in Figure 2 (and similar data sets for other combinations of parameter values) were used to compute the empirical mean μ and empirical standard deviation σ of the all-amphitelic hitting time distribution. Moreover, for each choice of values for k_1 and k_3, μ and σ were used to quantify the stochastic fluctuations in the time at which the system reaches the all-amphitelic state. Two measures commonly employed in the stochastic chemical kinetics literature for quantifying noise/fluctuations include the coefficient of variation (see, e.g., Laurenzi, 2000; Kepler and Elston, 2001; Elowitz et al., 2002; Swain et al., 2002) and the Fano factor (Thattai and van Oudenaarden, 2001; Ozbudak et al., 2002; Blake et al., 2003). The former is defined as the standard deviation divided by the mean, whereas the latter is defined as the variance σ^2 divided by the mean.

Ensembles of 10,000 realizations were generated for all possible combinations of values in the range of the parameters k_1 and k_3 described above, and the respective coefficients of variation were calculated for all possible pairs of parameter values. The results of these simulations are plotted in Figure 3(a). Moreover, Figure 3(b) shows the values of the coefficient of variation over the same range of values for the parameters k_1 and k_3 as computed by using the analytically derived probability distribution for the hitting time, discussed in Section 3.1.

The comparison of Figures 3(a) and 3(b) clearly shows that both the stochastic simulation approach based on Gillespie's direct method and the analytical derivation of Section 3.1 return similar results. Recall that the parameters k_1 and k_3 correspond to transitions from the unattached to the merotelic and amphitelic attachment states respectively. The results show that noise in the all-amphitelic hitting time for this system is minimized when $k_1 \approx 0.15$ min^{-1} and $k_3 \approx 0.07$ min^{-1}. The model also predicts that the noise in the hitting time is much more dependent on the values of the parameter k_3. This can be seen in the much steeper increase in values of the coefficient of variation along the k_3 axis versus the k_1 axis.

Figures 4(a) and 4(b) show the dependence of the coefficient of variation and Fano factor, respectively, on parameter k_3 when $k_1 = 0.1$ min^{-1}. As can be seen, both measures predict a nonlinear dependence of noise on the rate of transition from the unattached to the amphitelic state, albeit they provide a different value of k_3 for which the noise is minimized and the timing of the process is most accurate. This is expected,

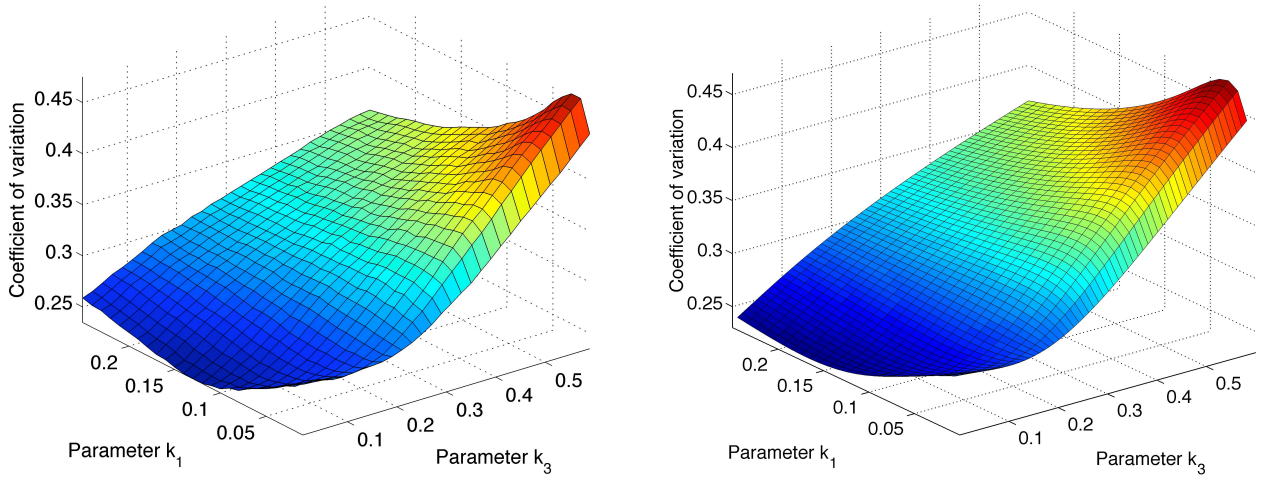

Figure 3: Plots showing the dependence of the coefficient of variation for the hitting time T on k_1 and k_3, as computed (a) numerically by the Gillespie method and (b) analytically by the approach taken in section 3.1.

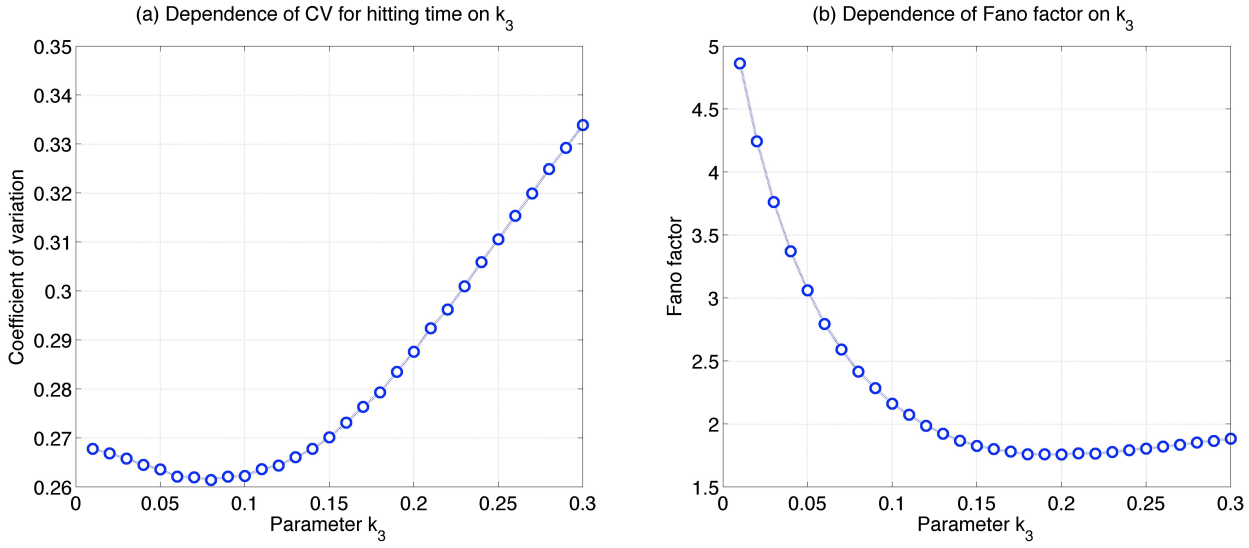

Figure 4: Plots showing the dependence on parameter k_3 of (a) the coefficient of variation and (b) the Fano factor for the hitting time T.

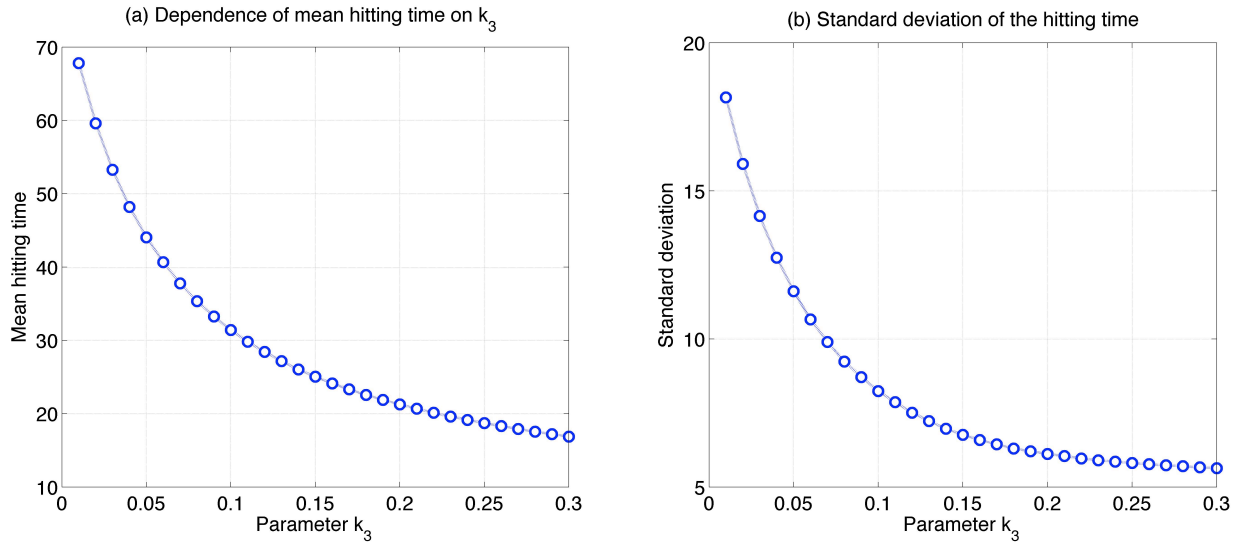

Figure 5: Plots showing the dependence of (a) the mean hitting time and (b) the standard deviation of the hitting time on parameter k_3.

as it has been pointed out by various authors that the coefficient of variation and the Fano factor can lead to different conclusions with respect to noise (see, e.g., Swain et al., 2002; Gadgil et al., 2005). Nonetheless, both measures predict that merotely can contribute to lessening the noise in the time for completion of the mitotic process.

In addition to computing the dependence of the coefficient of variation and Fano factor on k_3, we investigated whether the variation of these quantities depends on variations of the mean hitting time only, i.e., whether or not there is an essential dependence of the standard deviation on k_3. Figure 5 clearly shows that both mean and standard deviation of the hitting time distribution decrease as the parameter k_3 increases, and hence neither the mean nor the standard deviation alone is the dominant factor for variations in the level of noise when varying parameter values.

4 Discussion

Cell division is a complex process requiring the cell to have many internal checks so that division may proceed and be completed correctly. Failure to divide correctly can have serious consequences, including progression to cancer. During mitosis, chromosomal segregation is one such process that is crucial for successful progression. Accurate segregation of chromosomes during mitosis requires regulation of the interactions between chromosomes and spindle microtubules. These chromosome/microtubule interactions are controlled by kinetochore complexes which provide a scaffold at the centromere of each sister chromatid, and progression through mitosis depends upon the stable attachment of each sister kinetochore to opposite spindle poles. This process of kinetochore-microtubule attachment is prone to errors and erroneous attachments are classified into two categories - syntelic and merotelic. In the former category, a chromosome is said to be syntelically attached if both sister kinetochores are attached to chromosomes nucleated from the same spindle pole. In the latter category, a chromosome is said to be merotelically attached if a kinetochore is attached to each spindle pole at the same time (in contrast to the above described two cases, an amphitelic attachment is established when a chromosome has each sister kinetochore attached to one spindle pole).

In this paper, we have developed a stochastic model of kinetochore attachment transitions. Following Mistry et al. (2008), we considered a continuous time Markov jump process that is associated with all possible kinetochore attachment transitions and derived a system of stochastic differential equations governing the evolution in time of the probability of being in one of the possible attachment states of kinetochore pairs i.e. unattached (U), syntelic (S), merotelic (M), and amphitelic (C).

Having developed the model, we first derived specific expressions for the dependence of the distribution of the time T, at which all kinetochores reach the amphitelic state, on the kinetic parameters of the model. Next, we used the Gillespie simulation algorithm to compute an ensemble of independent realizations of the master equation (2). This enabled us to numerically approximate the distribution of the hitting time of the amphitelic state where all kinetochores are amphitelically attached. Our computational results appeared to verify the analytical results we had obtained.

One of the key results from our model is that the process of merotely (i.e. *erroneous attachment*) can contribute to a lessening of the noise in the time for completion of the mitotic process. Specifically, both our computational and analytical results show that, paradoxically and counter-intuitively, a tightly controlled strictly positive rate of erroneous attachments facilitates a more accurate timing of the mitotic process than in the complete absence of attachment errors.

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