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Derivation and experimental comparison of cell-division probability densities

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HIGHLIGHTS

- We present a simple stochastic model of the cell cycle.
- We derive an analytical expression for the distribution of intermitotic times.
- We test the model's ability to describe heterogeneous intermitotic distributions.
- We use the model to explain heterogeneity in response to drug-treatment.

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ABSTRACT

Experiments have shown that, even in a homogeneous population of cells, the distribution of division times is highly variable. In addition, a homogeneous population of cells will exhibit a heterogeneous response to drug therapy. We present a simple stochastic model of the cell cycle as a multistep stochastic process. The model, which is based on our conception of the cell cycle checkpoint, is used to derive an analytical expression for the distribution of cell cycle times. We demonstrate that this distribution provides an accurate representation of cell cycle time variability and show how the model relates drug-induced changes in basic biological parameters to variability in response to drug treatment.

1. Introduction

Cancer is a result of uncontrolled cellular proliferation. Our understanding of the molecular underpinnings of cancer initiation and progression has burgeoned with the dawn of molecular biology, yet our understanding of how the complex system of molecular interactions and processes acts in concert to regulate the cell cycle remains incomplete. However, recent technological advances which enable biologists to track and record individual mitotic events within a large population of cells have begun to fill this gap (Tyson et al., 2012). In particular, we now know that, even among cells of the same lineage, there is marked variability, not only in the time it takes an individual cell to divide, but also in the response to drug treatment (Kar et al., 2009; Tyson et al., 2012). What can this variability teach us about the proliferative process?

In the present paper, we address this question by constructing and analyzing a simple stochastic model of the cell cycle. The model is mechanistic, in the sense that it is motivated by our current understanding of cell cycle control, yet simple enough that it can be used to derive an analytical expression for the distribution of intermitotic times. We use this distribution to validate the model's ability to provide a more accurate description of cell cycle variability and show how the model can be used to relate variability in response to drug treatment to changes in fundamental (albeit abstract) biological parameters.

The cell cycle is divided into two main phases: S phase, when DNA replication (synthesis) occurs, and the M phase, when mitosis occurs; M and S phases are separated by gap phases (G1 occurs before S phase and G2 occurs before M phase) during which the cell senses sufficiency of mitogenic stimuli, oxygen, nutrients, and physical space. Progression from one part of the cell cycle to the next requires the temporal control of specialized molecules including cyclins, and cyclin dependent kinases (CDKs). In general, distinct cyclins and CDKs are activated in sequence to control the transversal of distinct checkpoints (Vermeulen et al., 2003; Kastan and Bartek, 2004), with the activation of one CDK promoting that

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of another. In transitioning from one phase to the next, a cell undergoes a discrete and irreversible phenotypic change.

Our model assumes that the cell cycle is controlled by multiple checkpoints which are transversed in sequence. Each checkpoint is associated with an abstract internal state that determines if the cell will proceed toward division (for example, the internal state might represent the cellular protein content and/or the concentration of a specific CDK or transcription factor). The value of each internal state is given by a random variable. The cell passes a checkpoint when the associated random variable reaches a critical threshold value. The problem of determining the time it takes the cell to pass a checkpoint can be interpreted as a first exit time problem where exit occurs at checkpoint passage. The distribution of times spent in one part of the cell cycle corresponds to the probability density of the first exit time.

2. Models of cell cycle progression

A discrete model of cell cycle progression: Underlying each of the stochastic models below is a discrete model. In the discrete model the value of an abstract internal state is given by a variable, $\hat{y}_t$, which is subject to positive and negative regulations. It is assumed that $\hat{y}_0 = 0$, and when $\hat{y}_t = M$ the cell passes a checkpoint that is determined by the state. In addition we assume that over a short period of time Δt, $\hat{y}$ may increase by one unit with probability $b\Delta t$, decrease by one unit with probability $d\Delta t$ or remain the same. If we define $y_t = \hat{y}_t/M$ then $y_0 = 0$, exit occurs at $y_t = 1$, and over a short period of time Δt, Δy is governed by the probabilities given in Table 1 $y_t = \hat{y}_t/M$. This model is equivalent to the first in that the two models share the same probability density of exit times. This discrete stochastic model leads to a certain stochastic differential equation (Allen, 2007) which has approximately the same probability distribution as the discrete stochastic model. This Itô stochastic differential equation (SDE) has the form

$$dy(t) = \mu\, dt + \sigma\, dW(t), \tag{1}$$

where $t > 0$, $\mu = (1/M)(b-d)$ and $\sigma^2 = (1/M^2)(b+d)$, and $W(t)$ is a standard Wiener process.

Different interpretations or variations of stochastic model (1) lead to three simple but biologically reasonable probability distributions for cell intermitotic time. In the simplest interpretation, it is hypothesized that the dynamics of the cell cycle can be approximated by a single phase. In the second two models, it is hypothesized that the dynamics of the cell cycle can be approximated by two phases with different characteristics.

Model 1: The first model assumes that after exiting from mitosis the cell monitors an internal state, the value of which is given by a random variable $y(t)$. As explained above, we assume that $y(t)$ evolves according to the following SDE:

$$dy(t) = \mu\, dt + \sigma\, dW(t), \tag{2}$$

where $t > 0$, $\mu = (1/M)(b-d)$ and $\sigma^2 = (1/M^2)(b+d)$, and $W(t)$ is a standard Wiener process. For this model, division (exit) occurs when $y(t) = 1$. For this simple SDE model, an analytical expression for the probability density of cell exit times has the form

Table 1
Discrete probabilities: equivalent model.

Δy	Probability
$\frac{1}{M}$	$b\Delta t$
$\frac{-1}{M}$	$d\Delta t$
0	$1-b\Delta t-d\Delta t$

(De-La-Peña et al., 2009; Scheike, 1992; Tuckwell and Wan, 1984):

$$p(t,a,c) = \frac{a}{\sqrt{2\pi t^3}}\exp\left(\frac{-(ct+a)^2}{2t}\right) \tag{3}$$

where $c = -\mu/\sigma$ and $a = 1/\sigma$. This probability density is simple and it follows from reasonable biological assumptions.

Model 2: In the second model, it is assumed that the cell cycle is separated into two phases. After exiting mitosis, the cell monitors an internal state, the value of which is given by a random variable $y(t)$. After $y(t)$ reaches a threshold value, the cell passes a checkpoint and commits to divide. The duration of the remaining part of the cell cycle is determined by a parameter, τ, i.e. it is deterministic.

In particular, we assume that $y(t)$ satisfies the same SDE as for model 1, i.e., $y(t)$ satisfies a stochastic differential equation of the form:

$$dy(t) = \mu\, dt + \sigma\, dW(t),$$

where $t > 0$, $y(0) = 0$, $\mu = (1/M)(b-d)$ and $\sigma^2 = (1/M^2)(b+d)$ and $W(t)$ is a standard Wiener process. For this model checkpoint passage (exit) occurs when $y(t) = 1$. Under these assumptions, an analytical expression for the probability density of cell exit times has the form

$$p(t,a,c,\tau) = \frac{a}{\sqrt{2\pi(t-\tau)^3}}\exp\left(\frac{-(c(t-\tau)+a)^2}{2(t-\tau)}\right)$$

for $t > \tau$ where $c = -\mu/\sigma$ and $a = 1/\sigma$. This probability density is simple, it has only three parameters, and it follows from reasonable biological assumptions.

Model 3: The third model also separates the cell cycle into two parts. However, unlike the previous model, the duration of both parts of the cell cycle are associated with a random variable. In particular, the model assumes that two distinct random variables must reach threshold values in sequence before division can occur.

After exiting mitosis, the cell enters the first part of the cell cycle, the duration of which is determined by a random variable $z(t)$ that satisfies an SDE of the form

$$dz(t) = \mu_z\, dt + \sigma_z\, dW(t),$$

where $0 < t < \tau$, $z(0) = 0$, $\mu_z = (1/M_z)(b_z - d_z)$, $\sigma_z^2 = (1/M_z^2)(b_z + d_z)$ and $W(t)$ is a standard Wiener process. Checkpoint passage (exit) occurs at τ such that $z(\tau) = 1$.

An analytical expression for the probability density of cell exit times from the first part of the cell cycle has the form

$$p_1(t,a_z,c_z) = \frac{a_z}{\sqrt{2\pi t^3}}\exp\left(\frac{-(c_z t + a_z)^2}{2t}\right)$$

where $c_z = -\mu_z/\sigma_z$ and $a_z = 1/\sigma_z$. We let τ be the exit time from the first part of the cell cycle, where τ is a random variable satisfying probability density p_1.

After exiting from the first part of the cell cycle the cell enters the second part of the cell cycle, the duration of which is determined by another random variable $y(t)$ that satisfies an SDE model of the form

$$dy(t) = \mu_y\, dt + \sigma_y\, dW(t),$$

where $t > \tau$, $y(\tau) = 0$, $\mu_y = (1/M_y)(b_y - d_y)$, $\sigma_y^2 = (1/M_y^2)(b_y + d_y)$ and $W(t)$ is a standard Wiener process. Division (exit) occurs when $y(t) = 1$.

For a particular value of the exit time, τ, from the first part of the cell cycle, an analytical expression for the probability density

of cell exit times from the second part of the cell cycle is given by

$$p_2(t, a_y, c_y, \tau) = \frac{a_y}{\sqrt{2\pi(t-\tau)^3}} \exp\left(\frac{-(c_y(t-\tau)+a_y)^2}{2(t-\tau)}\right)$$

for $t \geq \tau$ where $c_y = -\mu_y/\sigma_y$ and $a_y = 1/\sigma_y$. Therefore, the probability density of intermitotic times from the entire cell cycle has the form

$$p(t, a_y, c_y, a_z, c_z) = \int_0^t p_1(\tau, a_z, c_z) p_2(t, a_y, c_y, \tau)\, d\tau.$$

This model has four parameters a_y, c_y, a_z, and c_z.

EMG model: Previously, distributions of intermitotic times have been fit with exponentially modified Gaussian probability distributions (Golubev, 2010, 2012). In this model, intermitotic time is divided into two parts. It is assumed that the duration of the first part is normally distributed while the duration of the second part is exponentially distributed, so that the distribution of intermitotic times is the convolution of a Gaussian and an exponential distribution (Golubev, 2010). Mechanistically, it is assumed that the duration of the first part is determined by numerous tasks that occur in sequence, while that of the second part is generated by a dominant rate-limiting event that corresponds to the passage of a checkpoint (Golubev, 2012). Previously the Gaussian part of the cell cycle has been identified with G2, S, M, and the majority of G1, while the exponential part of the cell cycle has been identified with the G1/S checkpoint (Golubev, 2010). Like the stochastic model 2, the EMG model has three parameters. The first parameter of the EMG distribution, λ, is the rate at which cells exit from the second part of the cell cycle. The second two parameters, σ and μ, are the standard deviation and the mean of the normal distribution of exit times from the first part of the cell cycle respectively.

3. Analysis

In this section, we examine data on intermitotic time (IMT) distributions in order to evaluate each model. In particular, maximum likelihood estimation (MATLAB, mle) is used to fit the model parameters to IMT distributions for cancer cells treated with DMSO (343 observations), Erlotinib (267 observations), and CHX (164 observations). Best fit parameters are used to evaluate each model's ability to represent the data and to explain drug-induced changes in the distribution of IMTs. For each distribution and model we present the maximum likelihood estimates of the parameters in Tables 2–5. All the models provide close approximations of the data. As the number of parameters varies between models, we use the Akaike information criterion with correction for finite size (AICc) to compare them (Burnham and Anderson, 2002):

$$AICc = 2k - 2\ln(ML) - \frac{2k(k+1)}{n-k-1}, \quad (4)$$

where k is the number of parameters in the model and ML is the maximum likelihood of the model. Models with lower AICc values are considered as superior representations of the data, and the quantity, $\exp((AICc_{min} - AICc)/2)$, represents the relative probability such that a given model provides a better representation of the data than the model with the lowest AICc value. Results are presented in Tables 6–8.

We note that stochastic model 3 has the lowest AICc value for each data set. In particular, model 3 is much superior to any of the other models at describing the DMSO and Erlotinib data. Hence this analysis supports our hypotheses that cell cycle is a multistep stochastic process.

The best fits of model 3 and the EMG model are shown in Figs. 1–3. In Tables 9–11, the expected durations of each part of the cell cycle are presented for stochastic models 2 and 3 and for the EMG model.

Table 2
Log maximum likelihood parameter estimates (Model 1).

Drug	μ	σ	Log-likelihood
DMSO	.0725	.0425	−746.83
erlot	.0516	.0868	−881.90
CHX	.0445	.0408	−468.90

Table 3
Maximum likelihood parameter estimates (Model 2).

Drug	μ	σ	τ	Log-likelihood
DMSO	.2013	.1926	8.829	−699.61
erlot	.1071	.3116	10.03	−822.61
CHX	.1130	.1765	13.64	−453.91

Table 4
Maximum likelihood parameter estimates (Model 3).

Drug	μ_z	σ_z	μ_y	σ_y	Log-likelihood
DMSO	.0789	.0237	.8898	2.2098	−665.78
erlot	.0821	.0276	.1396	.5999	−816.85
CHX	.0551	.0248	.2298	.5041	−451.94

Table 5
Maximum likelihood parameter estimates (EMG).

Drug	λ	σ	μ	Log-likelihood
DMSO	.5163	.7670	11.86	−683.04
erlot	.1335	.6526	11.87	−825.36
CHX	.2335	1.6051	18.21	−453.60

Table 6
AICc (DMSO).

Model	Log-likelihood	AICc	$\exp((AICc_{min} - AICc)/2)$
Model 1	−746.83	1497.7	0
Model 2	−699.61	1405.3	0
Model 3	−665.78	1339.7	1
EMG	−683.04	1372.2	0

Table 7
AICc (erlot).

Model	Log-likelihood	AICc	$\exp((AICc_{min} - AICc)/2)$
Model 1	−881.90	1767.8	0
Model 2	−822.61	1651.3	.0088
Model 3	−816.85	1641.9	1
EMG	−825.36	1656.7	.0006

Table 8
AICc (CHX).

Model	Log-likelihood	AICc	$\exp((AICc_{min} - AICc)/2)$
Model 1	−468.90	941.8745	0
Model 2	−453.91	913.9700	.3988
Model 3	−451.94	912.1316	1
EMG	−453.60	913.3500	.5438

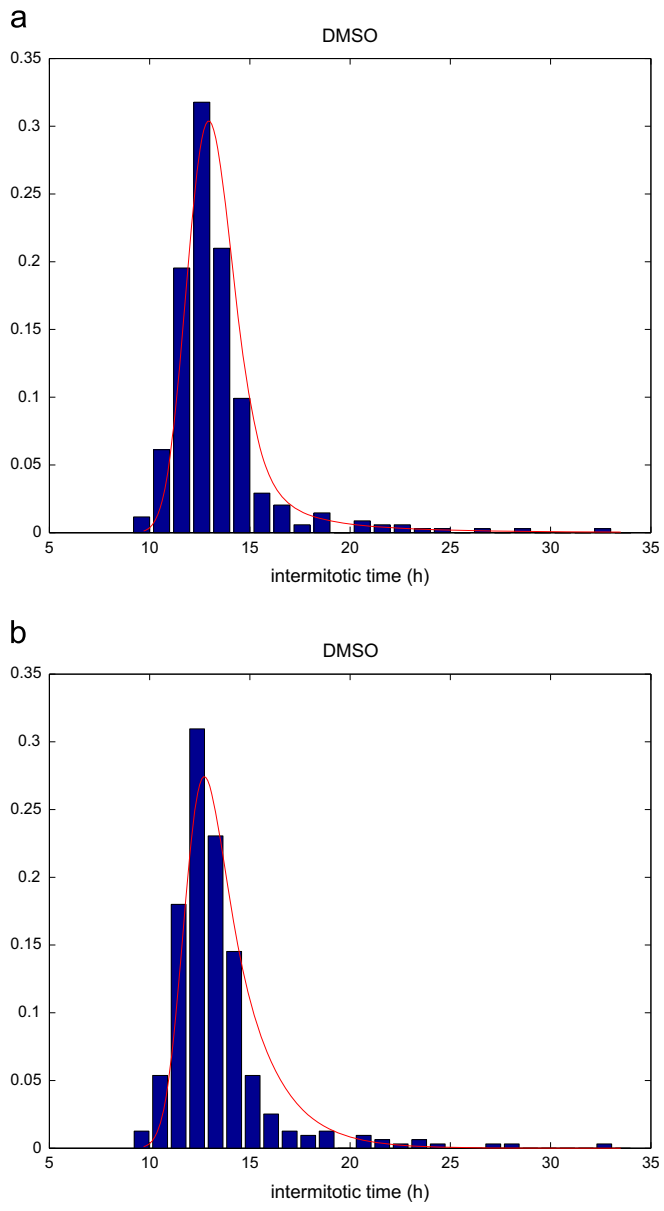

Fig. 1. The maximum likelihood pdfs derived from the stochastic model 3 and the EMG were fit to IMT distributions for cells treated with DMSO. (a) Stochastic model and (b) EMG.

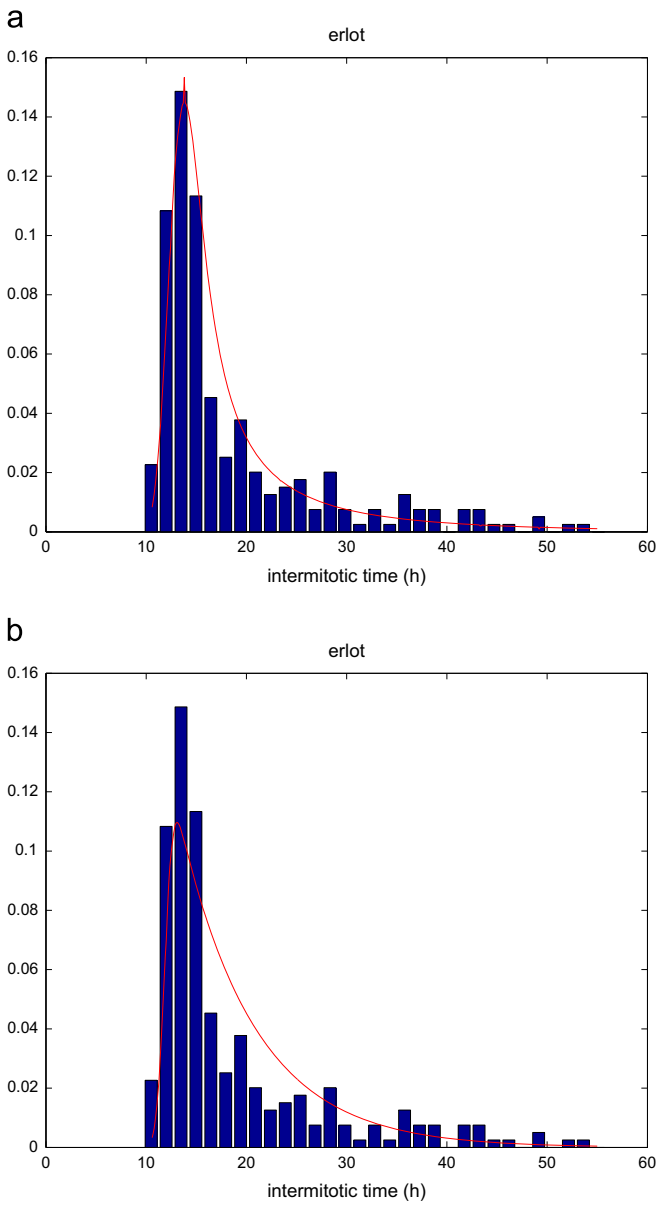

Fig. 2. The maximum likelihood pdfs derived from the stochastic model 3 and the EMG were fit to IMT distributions for cells treated with erlot. (a) Stochastic model and (b) EMG.

Next we consider how model parameters change with drug treatment in order to see if drug-induced changes in the models' mechanistic parameters can be reconciled with a drug's mechanisms of action and our knowledge of cell cycle control. In performing this analysis it is important to note that stochastic models 1–3 assume that the duration of the cell cycle is determined by one or two abstract internal states, the biological identity of which may vary with the experimental conditions. Furthermore, although stochastic model 3 and the EMG model divide the cell cycle into two parts that occur in sequence, the associated IMT distributions are invariant with respect to the order in which the two parts occur. Hence, although we have designated the phases of the cell cycle as Part 1 and Part 2, the order in which the two phases occur is, in fact, undetermined.

In gathering the experimental data, dimethyl sulfoxide (DMSO) was used to dilute the drugs. Hence the DMSO data is treated as a control. In addition, cells were treated with Erlotinib, which interferes with mitotic signaling through the EGFR, and CHX which inhibits protein biosynthesis. Since protein synthesis is necessary for CDK activation, cell growth, and DNA replication; multiple processes can limit the proliferation of CHX treated cells.

Models 1, 2, and 3 indicate that Erlotinib lowers μ while increasing σ^2. Since $b=(M\mu+M^2\sigma^2)/2$ and $d=(M^2\sigma^2-M\mu)/2$, we conclude that Erlotinib increases d, the probability that the value of the cell's internal state decreases. In other words Erlotinib promotes processes that inhibit proliferation. This increase in d could be explained through an Erlotinib-mediated increase in the activity of the cyclin dependent kinase p-21 (Gartel and Radhakrishnan, 2005). In addition, model 2 indicates that Erlotinib lengthens the mean duration of both parts of the cell cycle. Although EGFR signaling is typically associated with G1 arrest, and failure to transverse the restriction point in particular, inhibition of EGFR signaling could also foster G2 arrest (Besson and WeeYong, 2001; Cariveau et al., 2005; Maeda et al., 2002), or prevent DNA synthesis (Gartel and Radhakrishnan, 2005) through p21. Model 3 indicates that Erlotinib increases the duration of Part 2 of the cell cycle. In summary, the Erlotinib-induced changes in

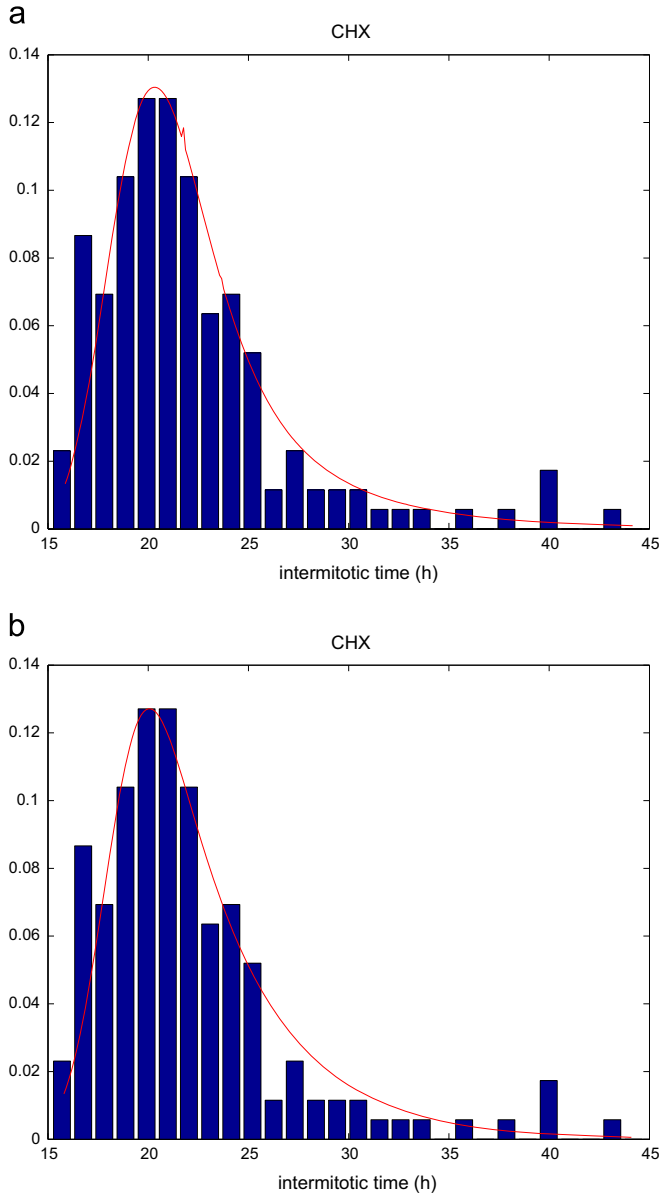

Fig. 3. The maximum likelihood pdfs derived from the stochastic model 3 and the EMG were fit to IMT distributions for cells treated with CHX. (a) Stochastic model and (b) EMG.

Table 9
Expected duration of cell cycle parts (Model 2).

Drug	Part 1	Part 2
DMSO	8.83	4.97
Erlot	10.03	9.34
CHX	13.64	8.85

Table 10
Expected duration of cell cycle parts (Model 3).

Drug	Part 1	Part 2
DMSO	12.67	1.12
Erlot	12.18	7.16
CHX	18.15	4.35

Table 11
Expected duration of cell cycle parts (EMG).

Drug	Part 1	Part 2
DMSO	11.86	1.94
Erlot	11.87	7.49
CHX	18.21	4.28

each of the models' parameters are consistent with our knowledge of cell cycle regulation and Erlotinib's mechanism of action.

Consider how CHX changes the parameters that control cell cycle progression. Models 1, 2, and 3 indicate that CHX decreases μ and σ. Hence, we can conclude that CHX decreases b, the probability that value of the cell's internal state increases. Since protein synthesis is necessary for the completion of multiple division related tasks, including cyclin dependent CDK activation (Vermeulen et al., 2003; Kastan and Bartek, 2004), we see that the model-driven interpretation of this data is consistent with our knowledge of cell cycle control and CHX.

4. Conclusions

Several detailed stochastic models of the cell cycle are already available (Kar et al., 2009; Steuer, 2004; Mur and Csikász-Nagy, 2008; Zhang et al., 2006; Ge et al., 2008; Braunewell and Bornholdt, 2007; Okabe and Sasai, 2007; Li et al., 2004). These models, which involve complex networks of cell cycle related genes and proteins, have been used to study the robustness of the cell cycle to noise (Zhang et al., 2006; Ge et al., 2008; Braunewell and Bornholdt, 2007; Okabe and Sasai, 2007; Li et al., 2004), to better capture experimental dynamics (Steuer, 2004) and to study cell cycle variability (Kar et al., 2009; Mur and Csikász-Nagy, 2008). In particular, model cell cycle statistics were compared to experimental statistics in Kar et al. (2009) and Mur and Csikász-Nagy (2008). In the present paper we take a top-down approach to modeling stochasticity in the cell cycle. Our simple stochastic model serves as an explanation for heterogeneity in the distribution of IMTs and in the response to drug treatment. In particular, the model is useful in generating a closed form expression for the distribution of intermitotic times. In addition, because the model relates changes in the shape of IMT distributions to changes in basic biological parameters, it can be used as a platform to study how drug treatment affects the proliferative process. Future work will be aimed at extending the model to capture the evolution of IMT distributions through time and at comparing the importance of genetic heterogeneity and stochasticity in characterizing these distributions.

Acknowledgments

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Appendix A

In this work we consider models of cell cycle progression in which an internal state, $y(t)$, satisfies an SDE of the form:

$$dy(t) = \mu\, dt + \sigma\, dW(t), \tag{5}$$

where $t > \tau$, $y(\tau) = y_0 \le y_{max}$, $W(t)$ is a standard Wiener process. Exit occurs when $y(t) = y_{max}$. For this simple SDE model, an analytical expression for the probability density of cell exit times has the form (De-La-Peña et al., 2009, Scheike, 1992, Tuckwell and

Table 12
The moments of the data.

Drug	n	$E(T)$	$E(T-E(T))^2$	$E(T-E(T))^3$
DMSO	343	13.7977	6.8077	59.3523
erlot	267	19.3618	77.9692	1275.8859
CHX	164	22.4872	23.7640	222.1999

Table 13
The moments of the maximum likelihood fit for Model 1.

Drug	$E(T)$	$E(T-E(T))^2$	$E(T-E(T))^3$
DMSO	13.7931	4.7398	4.8864
erlot	19.4175	55.1592	470.0716
CHX	22.4719	18.8904	47.6389

Table 14
The moments of the maximum likelihood fit for Model 2.

Drug	$E(T)$	$E(T-E(T))^2$	$E(T-E(T))^3$
DMSO	13.7967	4.5476	12.4888
erlot	19.3671	79.0219	2004.9179
CHX	22.4896	21.5901	158.0185

Table 15
The moments of the maximum likelihood fit for Model 3.

Drug	$E(T)$	$E(T-E(T))^2$	$E(T-E(T))^3$
DMSO	13.6235	5.2594	58.7178
erlot	19.9030	162.0269	9234.8487
CHX	22.5099	24.1252	285.8645

Table 16
The moments of the maximum likelihood fit for the EMG model.

Drug	$E(T)$	$E(T-E(T))^2$	$E(T-E(T))^3$
DMSO	13.7969	4.3397	14.5319
erlot	19.3606	56.5355	840.5937
CHX	22.4927	20.9175	157.0975

Wan, 1984):

$$p(t)=\frac{a}{\sqrt{2\pi(t-\tau)^3}}\exp\left(\frac{-(c(t-\tau)+a)^2}{2(t-\tau)}\right) \tag{6}$$

for $t\geq\tau$ where $c=-\mu/\sigma<0$ and $a=(y_{max}-y_0)/\sigma>0$. The probability density, $p(t)$, is an inverse Gaussian probability density with many well-known properties (Tweedie, 1957).

It is also useful to know the moments of the probability density. These moments provide a simple means of parameter estimation and can be used to initialize the maximum likelihood routine. Although the moments of the probability density (6) are known (Tuckwell and Wan, 1984; Tweedie, 1957), it is interesting to see how the moments can be obtained indirectly through the theory developed for stochastic differential equations. In the present investigation, it is useful to have analytic expressions for the first, second and third moments of first-exit times for the probability density. For convenience, these moments are found when τ is set equal to zero. The mean first-exit time is then increased by τ for a nonzero value of τ.

A backward Kolmogorov equation is associated with SDE (5) whose solution is the reliability function $R(y,t)$ (Langtangen, 1994; Roberts, 1986). Specifically, $R(y,t)$ satisfies

$$\frac{\partial R(y,t)}{\partial t}=\mu\frac{\partial R(y,t)}{\partial y}+\frac{\sigma^2}{2}\frac{\partial^2 R(y,t)}{\partial y^2} \tag{7}$$

with $R(y_{max},t)=0$. The probability density of first-exit times satisfies $p(t)=p_{y_0}(t)=-\partial R(y_0,t)/\partial t$ where y_0 is the initial value of the internal state. In addition, moments of the exit time satisfy

$$E(t^r)=\tau_y^r=-\int_0^\infty t^r\frac{\partial R(y,t)}{\partial t}dt \tag{8}$$

for $r=0,1,2,3,\ldots$ with $\tau_{y_{max}}^r=0$. Integrating over (7) and applying (8), the moments satisfy the second-order ordinary differential equation (Allen and Allen, 2003; Langtangen, 1994)

$$-r\tau_y^{r-1}=\mu\frac{d\tau_y^r}{dy}+\frac{\sigma^2}{2}\frac{d^2\tau_y^r}{dy^2} \tag{9}$$

with $\tau_{y_{max}}^r=0$. Eq. (9) can be solved recursively for the moments for $r=1,2,\ldots$. Solving Eq. (9) for the first three moments about the mean results in

$$\begin{aligned}E(t)&=\frac{y_{max}-y_0}{\mu},\\ Var(t)&=E((t-\tau_{y_0}^1)^2)=\frac{\sigma^2(y_{max}-y_0)}{\mu^3},\\ E((t-\tau_{y_0}^1)^3)&=\frac{3\sigma^4(y_{max}-y_0)}{\mu^5},\end{aligned} \tag{10}$$

with $E(t)=\tau_{y_0}^1$.

Finally, in terms of probability density (6), since $c=-\mu/\sigma$, $a=(y_{max}-y_0)/\sigma$, and $\tau>0$, the moments about the mean directly implied by (10) are given by

$$\begin{aligned}E(t)&=\frac{-a}{c}+\tau,\\ Var(t)&=E((t-\tau_{y_0}^1)^2)=\frac{-a}{c^3},\\ E((t-\tau_{y_0}^1)^3)&=\frac{-3a}{c^5}.\end{aligned} \tag{11}$$

The moments of the data and the maximum likelihood fits of models are shown in Tables 12–16. Here n denotes the size of the data set.

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