Optimization strategies of chromosome search-and-capture by microtubules: exact analytical results for a single fixed target

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The mitotic spindle is an important intermediate structure in eucaryotic cell division, in which each of a pair of duplicated chromosomes is attached through microtubules to centrosomal bodies located close to the two poles of the dividing cell. It is widely believed that the spindle starts forming by the ‘capture’ of chromosome pairs, held together by kinetochores, by randomly searching microtubules. We present a complete analytical formulation of this problem, in the case of a single fixed target and for arbitrary cell size. We derive a set of Green’s functions for the microtubule dynamics and an associated set of first passage quantities. An implicit analytical expression for the probability distribution of the search time is then obtained, with appropriate boundary conditions at the outer cell membrane. We extract the conditions of optimized search from our formalism. Our results are in qualitative and semi-quantitative agreement with known experimental results for different cell types.

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I. INTRODUCTION

Microtubules are one class of polymeric filaments in the eucaryotic cell, whose sub-unit is a hetero-dimer of alpha- and beta-tubulin. Microtubules therefore possess structural polarity, and the ends are differentiated as plus and minus ends. A hallmark of microtubules is their unique mechanism of assembly and disassembly: a polymerizing microtubule can abruptly start shrinking by losing sub-units and vice-versa, a process referred to as dynamic instability (reviewed in [1]). The stochastic switching process between growth and shrinkage is referred to as catastrophe and the reverse process is called rescue. Between a rescue and a catastrophe, a microtubule grows in length by polymerizing and between a catastrophe and rescue, it shrinks. In vivo, a third state called pause is also observed where the length remains static. Microtubules usually nucleate from organizing centers called centrosomes, but may also be found free in the cytoplasm.

Microtubules play a central role in eucaryotic cell division. An important milestone in the cell division cycle is the formation of the metaphase spindle, where all the duplicated chromosome pairs, held together by kinetochores are aligned along the cell ‘equator’ (the “metaphase plate”) in such a way that each chromosome of a pair is facing one of the poles of the cell, and attached to one or more microtubules emanating from a centrosome located near that pole. How is the spindle assembled? It is generally believed that microtubules nucleating from each centrosome randomly searches the surrounding space for chromosomes by alternately growing and shrinking (the random search-and-capture model, and are stabilized upon contact with a kinetochore [2], which has also been supported by experimental observations [3]. However, investigations over the last decade or so have revealed that the chromosomes do not remain passive in this process; rather, the kinetochores nucleate and stabilize microtubules in their vicinity, a process facilitated by RanGTP, which then connect to the astral microtubules emanating from the chromosomes, assisted by motor proteins such as dyenin (see [4] for a recent review).

Theoretical investigation of the random search-and-capture model was done first by Holy and Leibler [5] and more recently by Wollman et al [6]. The latter paper investigated the possible effects of a microtubule-stabilizing RanGTP gradient around chromosomes, and concluded that when many chromosomes are involved, the search cannot be completed within the observed time-scales without this additional biochemical regulation. However, both the papers did not discuss the effects of the cell boundary and its constraining effect on the search. Also, the analytical results were restricted to the case where rescue is completely absent.

The present paper complements these earlier investigations into this important problem and extends them in several ways. We restrict ourselves to the base search-and-capture model (i.e., without considering the additional biochemical mechanisms for search), and present a complete theoretical solution to the problem of finding the search time for a fixed target by dynamic microtubules. Our approach permits the calculation of a compact mathematical expression in Laplace space for the probability distribution function (PDF) of the capture time of a single fixed chromosome by successive microtubules nucleating from a single nucleating site (one at a time), for arbitrary cell size and kinetic parameters. In particular, we are able to find the search time distribution also for non-zero rescue frequency, unlike the earlier approaches. We investigate the conditions which opti-

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mize the search process using this PDF, and conclude that the cell size is an important factor in the optimization process. For small cell sizes, the search time is minimized when both catastrophe and rescue frequencies are small, while for large cells, the rescue frequency need to be close to zero, while the catastrophe frequency need to be around a certain optimal value. These conclusions are found to be in agreement with available experimental results for various cell types and existing theoretical results where applicable.

In the following sections, we discuss the problem and the model, develop the formalism to address the problem, and present our results. The results are then analyzed in the context of available experimental observations.

II. THEORETICAL FORMALISM

A. The Model

We approximate the cell as a sphere of radius $R$, at the center of which we place a microtubule nucleating center. A single target (chromosome) of cross-sectional area $A$ is placed at a distance $d$ from the center. This simplified geometry of a mitotic cell permits a complete analytical solution of the problem. Microtubules nucleate from the center at a rate $\nu$. Catastrophe and rescue frequencies are denoted by $\nu_c$ and $\nu_r$ respectively, and are assumed to be the same everywhere inside the cell, as are the growth and shrinkage velocities, denoted $v_g$ and $v_s$. From the nucleating center, a single microtubule initially nucleates in a random direction and grows by polymerization as long as it is in the growth phase, while the same microtubule shrinks in length by depolymerization in the shrinking phase. In the process, the microtubule scans the surrounding space for chromosomes, and is stabilized when the growing end encounters a kinetochore.

A microtubule from a certain nucleation site on the centrosome can nucleate in many possible directions; however, given the finite size of the centrosome, the orientation is likely to be constrained by the geometry of the centrosome. In an extreme case, one may imagine that a microtubule will always grow only along the local normal to the surface, but this case is pathological when the target is fixed in space, since no microtubule might ever grow in the right direction to find it. It is therefore, more realistic to imagine that microtubules from each nucleation site in the centrosome will grow within a certain solid angle $\Delta \Omega$, which defines a search cone for the corresponding nucleation site. In this case, if the fixed target falls inside the cone, and has a cross-sectional area $a$, a microtubule originating at that particular site has a probability

$$p = \frac{a}{d^2 \Delta \Omega}$$

for nucleating in the right direction, within the search cone.

We now need to determine $\Delta \Omega$. We assume that if there are $M$ nucleating sites on the surface of the inner hemisphere of the centrosome, all the microtubules emanating these sites together will be searching a solid angle $4\pi$, without interfering with each other. In this case, we require that $M \Delta \Omega \geq 4\pi$, and the inequality allow for some overlap of the search-cones in general. To be specific, we concentrate on the lower limit of $M$, and assume that $M \approx 100 - 300$, which fixes the search-cone angle as above. In assuming that the search is distributive, our model differs from the previous theoretical treatments, where each microtubule in the searching population was assumed to search the entire solid angle of $4\pi$ in the surrounding space, which, we feel is an unrealistic assumption. It must also be added that some amount of overlap between search-cones may be allowed in our model also, but for the time being, we disregard this possibility for the sake of simplicity.

![FIG. 1: A schematic illustration of the problem under consideration. Microtubules nucleate from nucleating sites on the centrosome, and search within a certain solid angle about the normal to the surface at the site. The single target is assumed fixed in space. The search cones are assumed to cover the entire solid angle, and are assumed non-overlapping.](image)
again from the center in a randomly chosen direction, at rate \( \nu \). We denote by \( C(T) \) the probability density of the capture time, from which the mean capture time follows:

\[
\langle T \rangle = \frac{\int_0^\infty dTC(T)T}{\int_0^\infty dTC(T)} \tag{2}
\]

In the above equation, \( \int_0^\infty dTC(T) \) gives the probability that the search will be eventually successful.

**B. Capture time distribution**

Since the basic process under consideration here is the capture of a certain target by one (or a set) of dynamically unstable filaments, it is natural to base our theory on consideration of first passage probability densities [11].

We define three conditional first passage probability densities (CFPD), which completely describe the search process. These CFPDs are defined below, with their corresponding conditions in italics.

1. \( p\Phi(d, T) \) is the CFPD for a freshly nucleated microtubule to nucleate in the right direction and reach a distance \( d \) for the first time after a time interval \( T \), without ever shrinking back to the origin in between.

2. \( (1-p)Q_X(T) \) is the CFPD for shrinking to the origin after a life-time \( T \), after nucleating in a wrong direction, without ever reaching a length \( X \) in between.

3. \((1-p)\Psi(T)\) is the CFPD for return to the origin after a time interval \( T \), following nucleation in a wrong direction, after encounter with the boundary (and consequent catastrophe) at least once (and possibly several times) in between.

We now denote by \((1-p)^n \Omega_n(T)\) the probability of \( n \) unsuccessful nucleation-search-disappearance events within a time interval \( T \), prior to a successful event, so that

\[
C(T) = \sum_{n=0}^\infty \int_0^T \Omega_n(T - T')p\Phi(d, T')\nu dT' \tag{3}
\]

Let us now assume that among the \( n \) unsuccessful nucleation events, there are \( n_1 \) events where the microtubule nucleated in the right direction, but did not reach the chromosome, \( n_2 \) events where it nucleated in a wrong direction, but shrank back to origin before encountering the boundary, and \( n_3 = n - n_1 - n_2 \) events where the microtubule nucleated in a wrong direction, encountered the boundary, underwent catastrophe and then shrank to the origin.

In terms of the FPDs described above, we find that

\[
\Omega_n(T) = \int_0^T \nu dT'_1 e^{-\nu T'_1} \int_0^{T-T'_1} dT_1 K_1(T_1) \ldots \int_0^{T-T'_1-\ldots-T'_{n-1}} \nu dT'_n K_n(T_n) e^{-\nu[T - \sum_{k=1}^n (T_k + T'_k)]} \tag{4}
\]

where \( K(T) \) could be \( Q_d(T) \), \( Q_R(t) \) or \( \Psi(T) \). The preceding equation has the form of a \( 2n \)-fold convolution, a generalized form of the standard convolution theorem may be applied here. The result is

\[
\hat{\Omega}_n(s) = \frac{1}{(s+\nu)} \left( \frac{\nu}{s+\nu} \right)^n \prod_{j=1}^n \hat{K}_j(s) = \sum_{n_1=0}^n \sum_{n_2=0}^{n-n_1} \frac{1}{(s+\nu)} \left( \frac{\nu \hat{Q}_d(s)}{s+\nu} \right)^{n_1} \left( \frac{\nu \hat{Q}_R(s)}{s+\nu} \right)^{n_2} \left( \frac{\nu \hat{\Psi}(s)}{s+\nu} \right)^{n-n_1-n_2} \tag{5}
\]

From Eq \( \ref{5} \) we find \( \hat{C}(s) = \nu \hat{p}\Phi(d, s) \sum_{n=0}^\infty (1 - p)^n \hat{\Omega}_n(s) \). After using Eq \( \ref{4} \) and performing the geometric summation above, we arrive at the following expression:

\[
\hat{C}(s) = \frac{\nu \hat{p}\Phi(d, s)}{s + \nu \left( 1 - p \hat{Q}_d(s) - (1-p)[\hat{Q}_R(s) + \hat{\Psi}(s)] \right)} \tag{6}
\]
In particular, if we assume that MT nucleation is sufficiently fast and not therefore, rate-limiting, we arrive at the limiting form

$$
\tilde{C}(s) = \frac{p \tilde{\Phi}(d, s)}{1 - \left[ p \tilde{Q}_d(s) + (1 - p) \left( \tilde{Q}_R(s) + \tilde{\Psi}(s) \right) \right]} \quad (7)
$$

Eq\[6\] is the central result of this paper. Using this expression, the mean search time for a single target, and its variance may be expressed as

$$
\langle T \rangle = -\frac{\partial_s \tilde{C}(s)|_{s=0}}{C(0)} \quad ; \quad \langle T^2 \rangle = \frac{1}{C(0)} \frac{\partial^2 \tilde{C}(s)|_{s=0}}{s^2} \quad (8)
$$

where \( \tilde{C}(0) \) is the probability that the search is eventually successful, which we find to be unity in all cases studied here.

The FPDs introduced above are now calculated from the Green’s functions for MT kinetics, derived explicitly in the next section.

**C. Green’s functions**

The stochastic state of a MT at a given point in time \( t \) is characterized by two variables, its length \( l \) and its state of polymerization versus depolymerization, which we denote by an index \( i \), which takes one of the two values, \( 1 \) or \( 0 \) respectively for growing and shrinking states. In this case, therefore, we need to compute four Green’s functions, or propagators, \( G_{ij}(x, t; x_0, 0) \), for \( i, j = 0, 1 \); by definition, \( G_{ij}(x, t; x_0, 0)dx \) gives the probability that a given MT will have length \( l \) between \( x \) and \( x + dx \), and will be in state \( i \) at time \( t \), provided that it had a length \( x_0 \) and was at state \( j \) at an earlier time \( t = 0 \).

Calculating the above Green’s functions for a physically realistic situation would also require specification of appropriate boundary conditions at the origin (nucleating site) and this has been done earlier\[12\]. However, we deem this unnecessary for our purpose, since we are only interested in using these Green’s functions to compute the CFPDs introduced above. Therefore, for the rest of this paper, we will allow the ‘length’ \( x \) to be a continuously varying variable between positive and negative values, with no boundary condition imposed on the dynamics at \( x = 0 \). The boundary conditions are used in the definition of the CFPDs later.

The Dogterom-Leibler\[11\] rate equations for MT kinetics takes the form

$$
\partial_t G_{1j} = -v_g \partial_x G_{1j} + \nu_c G_{0j} - \nu_c G_{1j} \quad \partial_t G_{0j} = v_r \partial_x G_{0j} + \nu_c G_{1j} - \nu_c G_{0j} \quad (9)
$$

The equations may be solved together using combined Laplace-Fourier transforms, defined as \( \tilde{G}_{ij}(k, s; x_0) = \int_{-\infty}^{\infty} e^{-ikx} dx \int_{0}^{\infty} dt e^{-st} G_{ij}(x, t; x_0, 0) \). The solution is

$$
\tilde{G}_{ij}(k, s) = \frac{e^{-ikx_0[\nu_r - \delta_{ij}(ikv_s - s)]}}{v_sv_g[k^2 - ikA(s) + B(s)]} \quad (10)
$$

where \( A(s) = [\nu_c \nu_r - v_g \nu_r + s(v_s - v_g)]/v_s v_g \) and \( B(s) = [s(s + \nu_r + \nu_c)]/v_s v_g \).

For connection with the FPDs introduced earlier, it is convenient to define the Green’s function in such a way as that they have dimensions of inverse time, and not inverse length. This is done by defining

$$
\tilde{F}_{ij} = v_g G_{ij} \quad ; \quad \tilde{F}_{0j} = v_g G_{0j} \quad (11)
$$

It will be convenient for later calculations to carry out the inversion \( k \rightarrow x \) explicitly:

\[
\tilde{F}_{ij}(x, s; x_0) = \frac{\nu_r + s \delta_{ij}}{v_s [\alpha_s + \beta_s]} \left[ e^{-\alpha_s(x-x_0)} \Theta(x-x_0) + e^{\beta_s(x-x_0)} \Theta(x_0-x) \right] + \\
\frac{\delta_{ij}}{[\alpha_s + \beta_s]} \left[ \alpha_s e^{-\alpha_s(x-x_0)} \Theta(x-x_0) - \beta_s e^{\beta_s(x-x_0)} \Theta(x_0-x) \right]
\]

and

\[
\tilde{F}_{0j}(x, s; x_0) = \frac{\nu_r + s \delta_{ij}}{v_g [\alpha_s + \beta_s]} \left[ e^{-\alpha_s(x-x_0)} \Theta(x-x_0) + e^{\beta_s(x-x_0)} \Theta(x_0-x) \right] - \\
\frac{\delta_{ij}}{[\alpha_s + \beta_s]} \left[ \alpha_s e^{-\alpha_s(x-x_0)} \Theta(x-x_0) - \beta_s e^{\beta_s(x-x_0)} \Theta(x_0-x) \right]
\]

where

\[
\alpha_s = \frac{A(s)}{2} + \sqrt{B(s) + A^2(s)/4} \\
\beta_s = -\frac{A(s)}{2} + \sqrt{B(s) + A^2(s)/4} \quad (13)
\]
and $\Theta(x)$ is the usual step-function: $\Theta(x) = 1$ for $x \geq 0$ and 0 otherwise.

**D. General relations between FPD and Green’s functions**

The Green’s functions calculated in the last section may now be used to compute the CPFDs which we used before. For this purpose, it is convenient to define first a set of *unconditional* first passage densities (denoted FPD) as follows: let $C_{ij}(x, t; x_0, 0)$ denote the probability, per unit time, for a MT in state $j$ and with length $x_0$ at time $t = 0$, to reach a length $x$ for the first time at time $t$, and in state $i$.

For $l > 0$, $C_{11}(l, t; 0, 0)$ is given by the implicit equation

$$F_{11}(l, t; 0, 0) = C_{11}(l, t; 0, 0) + \lim_{\epsilon \to 0^+} \int_0^t dt' C_{11}(l, t'; 0, 0) F_{11}(l - \epsilon, t; t', t')$$

In the above equation (and the following equations), the $\epsilon$-factors take into account the following restriction on its dynamics: starting from a growing state at $t = 0$, with a length $l$, it can return to the same length $l$ at a later time, in a growing state, only from below (which decides which of the $\Theta$-functions appearing in $F_{11}$ is non-zero). Similar restrictions apply to the equations below.

Similarly, $C_{01}(0, T; d, 0)$ and $C_{10}(d, T; 0, 0)$ are given by the equations

$$F_{01}(0, T; d, 0) = C_{01}(0, T; d, 0) + \lim_{\epsilon \to 0^+} \int_0^T dt' C_{01}(0, T'; d, 0) F_{01}(\epsilon, T; 0, T')$$

$$F_{10}(d, T; 0, 0) = C_{10}(d, T; 0, 0) + \lim_{\epsilon \to 0^+} \int_0^T dt' C_{10}(d, T'; 0, 0) F_{11}(d - \epsilon, T; d, T')$$

Using these two FPDs, we are now in a position to write down the following relations between the CPFDs introduced earlier:

$$C_{11}(d, t; 0, 0) = \Phi(d, t) + \int_0^t dt' Q_d(0, t') C_{10}(d, t; 0, t')$$

$$C_{01}(0, T; d, 0) = Q_d(T) + \int_0^T dt' \Phi(d, t') C_{01}(0, T; d, t')$$

Eq.11,13 may now be solved using Laplace transforms. From Eq.13, we find that

$$\tilde{C}_{11}(d, s; 0) = \lim_{\epsilon \to 0^+} \frac{\tilde{F}_{11}(d, s; 0)}{1 + \tilde{F}_{11}(d - \epsilon, s; d)} = e^{-\alpha_d s}$$

Similarly,

$$\tilde{C}_{10}(d, s; 0) = \frac{\nu_p e^{-\alpha_d s}}{\nu_r + s + \alpha_s v_s}; \quad \tilde{C}_{01}(0, s; d) = \frac{\nu_r e^{-\beta_d s}}{\nu_c + s + \beta_s v_g}$$

(20)

After solving Eq.11, Eq.13 together, we find the explicit expressions

$$\tilde{\Phi}(d, s) = \frac{D(s) e^{-\alpha_d s}}{\nu_r \nu_c [1 - e^{-(\alpha_d + \beta_d) s}] + D(s)}$$

$$\tilde{Q}_d(s) = \frac{\nu_r}{\nu_c + s + \beta_s v_g} [1 - e^{-\beta_d s} \tilde{\Phi}(d, s)]$$

(21)

where $D(s)$ is given by

$$D(s) = (s + \alpha_s v_s)(s + \beta_s v_g) + \nu_r (s + \beta_s v_g) + \nu_c (s + \alpha_s v_s).$$

(22)

**E. Catastrophes at the cell boundary**

We assume that when a MT hits the cell boundary by growing, it undergoes catastrophe there at a rate $\nu'$. We now compute $\Psi(T)$, which is the CPFD of return to origin (i.e., complete depolymerization) of a MT after a lifetime $T$, and an encounter with the boundary at least once.

Clearly, along the line of our previous arguments, $\Psi(T)$ may be given by the expression

$$\Psi(T) = \int_0^T dT_1 \Phi(R, T_1) \times \int_0^{T-T_1} \nu' dT_2 e^{-\nu' T_2} \chi(R, T - T_1 - T_2),$$

(23)

where $\chi(R, T)$ gives the FPD of complete depolymerization of a MT, starting at the boundary, at length $R$ in shrinking state, with possibly multiple visits back to the boundary in between. This quantity may now be expressed implicitly through the equation

$$\chi(R, T) = \Phi^*(R, T) + \int_0^T dT_1 Q'_R(T_1) \times \int_0^{T-T_1} \nu'_d dT_2 e^{-\nu' T_2} \chi(R, T - T_1 - T_2)$$

(24)

where $Q'_R(T)$ is a ‘mirror’ image of $Q_R(T)$ introduced earlier, and represents the CPFD of a return to boundary over a time interval $T$, without ever reaching the origin (i.e., shrinking to zero) in between. Similarly, $\Phi^*(R, T)$ is the ‘inverse’ of $\Phi(R, T)$, and gives the CPFD of complete depolymerization of a MT starting at the boundary, without ever returning to the boundary in between.
Eq.23 and Eq.24 may now be solved together using Laplace transforms, and we find

\[ \tilde{\Psi}(s) = \frac{\nu'\tilde{\Phi}(R,s)\tilde{\Phi}^*(R,s)}{s + \nu'_e(1 - \tilde{Q}'_R(s))} \]  \hspace{1cm} (25)

\[ \tilde{\Phi}^*(R,s) = \frac{\nu_r}{\nu_r + s + \alpha_s v_s} \left[ 1 - e^{-\alpha_s R} \tilde{\Phi}^*(R,s) \right] \]  \hspace{1cm} (26)

\[ \tilde{Q}'_R(s) = \frac{\nu_r}{\nu_r + s + \alpha_s v_s} \left[ 1 - e^{-\alpha_s R} \tilde{\Phi}^*(R,s) \right] \]  \hspace{1cm} (27)

III. RESULTS

The mean time of capture of the target is now evaluated using Eq.10 and Eq.8 directly in Laplace space, since explicit inversion of Eq.11 turned out to be too difficult, and an explicit expression for the mean time in the most general case turned out to be too lengthy for reproduction here. We, therefore, used MATHEMATICA (Wolfram Research Inc., version 7) to compute the mean time from Eq.10 after substituting Eq.21, 22 and Eq.25, 27. In all the following analysis, we use the limits \( \nu \to \infty \) and \( \nu'_e \to \infty \), i.e., microtubule nucleation is assumed very fast and boundary-induced catastrophes are assumed to be instantaneous. These assumptions are not strictly necessary, but reduces the number of active parameters. Since a finite nucleation rate and a non-zero delay before catastrophe at the boundary would increase the total time, our estimates for the mean search time obtained henceforth may be regarded as theoretical lower limits.

Experimental measurements of the microtubule kinetic parameters show some distinct changes as the cell progresses from interphase to mitosis. However, the nature of the changes are different for different types of cells, and the general qualitative features appear to bear a strong correlation to the cell size. Yeast cells show a reduction in both catastrophe and rescue frequencies, but the changes are relatively small. In mammalian cells, which are typically larger, there is a marked fall in rescue frequency between interphase and mitosis, and a two-fold increase in catastrophe frequency. In Xenopus oocytes (frog egg cells, which are large and almost a mm in radius), the effects are somewhat different; while the rescue frequency, while small, is almost doubled, there is a sharp, seven-fold rise in the catastrophe frequency.

In order to understand the optimization criteria used by cells, we investigated the mean search time for three sets of parameter values, corresponding to Yeast (I), mammalian (II) and Xenopus (III) cells, whose experimentally observed values are summarized in Table I. Of these, we use only the growth and shortening velocities precisely, while \( \nu_r \) and \( \nu_c \) are varied in the range 0-5 min\(^{-1}\). The cell sizes given are only approximate estimates. For case III, we used a somewhat smaller cell radius to avoid over-flow in computation. In addition, we also study a theoretical case where \( R \to \infty \) separately, for which an exact expression for the mean search time is obtained in Appendix I, when \( \nu_r = 0 \).

A. Contour plots of mean search time

Fig.2 displays a contour plot of the mean search time for case I, and Fig.3 gives the same for case II, with \( M = 100 \) searching microtubules in both cases. We verified that when the number of microtubules is doubled, the search time is almost halved in all these cases. It may also be noted that our contour plots are similar with those obtained numerically in [27].

B. Optimization of \( \nu_c \) at fixed \( \nu_r \)

We now check how the search time varies as a function of \( \nu_c \), for various fixed values of \( \nu_r \), i.e., horizontal cross-sections of the contour plots presented earlier.

1. Small cells: \( R = 5\mu m, d = 3\mu m \)

Fig.4 shows the variation of the mean search time versus catastrophe frequency for three different \( \nu_r \), corresponding to Fig.2 earlier. The smallest search times are obtained for \( \nu_r = 0 \) and \( \nu_c = 0 \), implying that for small cells, the search is optimized by ensuring that the microtubules simply grow all the way to the cell boundary and undergo catastrophe, but with no rescue or catastrophe.
FIG. 2: Contour plot of the mean time of capture (in minutes) of a single chromosome by $M = 100$ microtubules for a cell of radius $R = 5 \mu m$. The chromosome is fixed at a radial distance of $d = 3 \mu m$ from the centrosome.

FIG. 3: Contour plot of the mean time of capture (in minutes) of a single chromosome by $M = 100$ microtubules for a cell of radius $R = 10 \mu m$. The chromosome is fixed at a radial distance of $d = 5 \mu m$ from the centrosome.

in the cytoplasm itself. These observations are in agreement with the experimental observations in Yeast cells (Table I), where both these events are seen to become rarer in mitosis as compared to interphase.

2. Large cells: $R = 10 – 20 \mu m$, $d = 5 – 10 \mu m$

We next consider somewhat larger cells of radius $10 – 20 \mu m$. Fig. 5 shows a cross-section of Fig. 4 at three rescue frequencies. In this case, again, the absolute minimum in the mean search time is observed to occur at the extremal values $\nu_r = 0, \nu_c = 0$, while for $\nu_r > 0$, the minimum occurs at a non-zero value of $\nu_c$, which increases with $\nu_r$. Fig. 6 shows similar curves for a larger cell: $R = 20 \mu m$ and $d = 10 \mu m$, and with more searching microtubules; $M = 400$ in this case. The number of microtubules were chosen such that the minimum of the mean search time remains less than 30 minutes.

When comparing these predictions with the experimental data in Table I, we observe that, while $\nu_c$ doubles between interphase and mitosis, $\nu_r$ is reduced by almost a factor of 4. This may be interpreted as follows: since $\nu_r$ is high in the interphase, it is more important to reduce it to levels low enough that the search does not become prohibitively costly, time-wise, and the relatively smaller change in $\nu_c$ is likely to be a fine-tuning exercise.

FIG. 4: The mean time of capture of a single chromosome by $M = 100$ microtubules for a cell of radius $R = 5 \mu m$. The chromosome is fixed at a radial distance of $d = 3 \mu m$ from the centrosome.

FIG. 5: The mean time of capture of a single chromosome by $M = 100$ microtubules for a cell of radius $R = 10 \mu m$. The chromosome is fixed at a radial distance of $d = 5 \mu m$ from the centrosome.
FIG. 6: The mean time of capture of a single chromosome by
*M = 400* microtubules for a cell of radius \( R = 20 \mu m \). The
chromosome is fixed at a radial distance of \( d = 10 \mu m \) from
the centrosome.

3. **Very large cells:** \( R = 100 \mu m, d = 20 \mu m \)

As the last case, we consider very large cells, with ra-
dius \( R = 100 \mu m \). This case is motivated by *Xenopus* egg
cells, which are known to have radii of the order of 1mm.
We fixed the chromosome separation \( d = 50 \mu m \) here,
and increased the number of searching microtubules to
\( M = 1000 \). Fig.7 shows the results. In this case, except
for \( \nu_r = 0 \), we see a pronounced minimum of the mean
search time as a function of \( \nu_c \). This trend agrees with
the observations in *Xenopus* extracts (Table I), which
show a modest increase in rescue frequency, but an al-
most seven-fold increase in \( \nu_c \). We interpret the latter
as arising from the requirement to tune \( \nu_c \) in order to
minimize the search time. Note also from the figure that
the curve is very strongly asymmetric on either side of
the minimum: a larger \( \nu_c \) would increase the search time,
but to a much lesser extent compared to a lower \( \nu_c \).

We also studied the fluctuations in the time of capture,
by looking at the RMS deviation \( \Delta T = \sqrt{\langle T^2 \rangle - \langle T \rangle^2} \).
Fig.8A shows the relative fluctuation, i.e., \( \Delta T/\langle T \rangle \) for
the three different cases of small, large and very large
cells studied here, when \( \nu_r = 0 \). The relative fluctua-
tion stays close to 1 for the entire range of \( \nu_c \) studied,
but when the rescue is increased to \( \nu_r = 1.0 \text{min}^{-1} \),
the relative fluctuation increases by 10 to 20\% (Fig.8B). The
trends in the relative fluctuation indices that, at least
for small \( \nu_r \), the probability distribution of the search
time might be exponentially decaying (a distribution of
the form \( C(T) = \lambda e^{-\lambda T} \) has a mean of \( \lambda^{-1} \) and relative
fluctuation 1); however, more investigations are needed
here.

FIG. 7: (A). The mean time of capture of a single chromosome
by \( M = 10^3 \) microtubules for a cell of radius \( R = 100 \mu m \). The
chromosome is fixed at a radial distance of \( d = 20 \mu m \) from
the centrosome.(B)The mean time for \( \nu_r = 1.0 \), for a smaller
range of \( \nu_c \).

**IV. CONCLUSIONS**

In this paper, we introduced a rigorous first-passage-
time-based stochastic formalism to study the problem of
calculating the time of capture of a fixed target by a set of
dynamic microtubules, nucleating from a center (the cen-
trosome). In contrast with earlier theoretical approaches,
we have been able to obtain estimates of the mean search
time for arbitrary rescue frequency and cell size.

Our results show that the cell size is an important fac-
tor in determining the optimization of microtubule kinetics
in the mitotic phase so as to minimize the search time.
For very small cells, with size \( R \leq 5 \mu m \), it is advan-
tageous to minimize both the cytoplasmic catastrophe
and rescue events, with only the boundary terminating
the search. In larger cells, the primary condition is to mi-
imize cytoplasmic rescue, and a certain amount of tuning
of \( \nu_c \) is advantageous, though it is not catastrophic if the
actual \( \nu_c \) is somewhat smaller or larger, as the minimum
is quite shallow. In much larger cells, the search time
becomes a rather sensitive function of \( \nu_c \), and tuning \( \nu_c \)
becomes the priority; while \( \nu_r \) is required to be as low
as possible, changes in \( \nu_r \) does not affect the search time
as much as changes in \( \nu_c \). In particular, the search time
rises rather steeply below the optimum value. The trends
in microtubule kinetics as predicted by this analysis are
in good qualitative agreement with the existing experi-
mental results.

We are presently working on extracting information
about the probability distribution \( C(T) \) from our formal-
A. \[ \frac{\Delta T}{<T>} \]

B. \[ \frac{\Delta T}{<T>} \]

FIG. 8: (A). The relative fluctuation in the time of capture of the target for three cases, I, II and III (Table I), when \( \nu_r = 0.0 \text{min}^{-1} \) (A) and \( \nu_r = 1.0 \text{min}^{-1} \) (B).

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APPENDIX A: CALCULATION OF MEAN SEARCH TIME WHEN \( \nu_r = 0 \) AND \( R = \infty \)

When \( \nu_r = 0 \), we find that

\[ \alpha = \frac{(s + \nu_c)}{v_g}; \quad \beta = \frac{s}{v_s}, \quad (A1) \]

from Eq[13]. Upon substitution into Eq[22] this gives

\[ D(s) = s^2 + \theta' s + \theta, \quad (A2) \]

where

\[ \theta = \frac{\nu_c^2 v_s}{v_g}; \quad \theta' = 2 \nu_c (1 + v_s/v_g). \quad (A3) \]

Let us now consider Eq[17]. When \( R \to \infty \), \( \tilde{\Psi}(s) = 0 \), and \( \tilde{Q}_R(s) \to \tilde{Q}_\infty(s) \), where

\[ \tilde{Q}_\infty(s) = \frac{\nu_c}{\nu_c + s(1 + v_g/v_s)} \quad (A4) \]

from Eq[21] and using Eq[12] and Eq[13] above. Therefore, we have the following limiting form for \( \tilde{C}(s) \):

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\[ \tilde{C}_\infty(s) = p \frac{\tilde{\Phi}(d, s)}{1 - [p \tilde{Q}_d(s) + (1 - p) \tilde{Q}_\infty(s)]} \quad (A5) \]

If we now expand \( \tilde{C}_\infty(s) = C_0 - sC_1 + \ldots \), it is clear that \( \langle T \rangle = C_1 / C_0 \) from Eq.8. We can therefore substitute Eqs.1-4 in Eq.21, substitute into Eq.A5 and expand the resulting expression up to the linear term in \( s \). The result is \( C_0 = 1 \) and \( C_1 = -\langle T \rangle \infty \), where

\[ \langle T \rangle \infty = \frac{1}{\nu_c} \left( 1 + \frac{v_g}{v_s} \right) \left[ \frac{e^{\nu_c d}}{p} - 1 \right] - \frac{d}{v_s} \quad (A6) \]

is the mean search time in an infinitely large cell, with no rescue. Note that, in the limit \( p \to 0 \), the above expression reduces to \( (1 + v_g/v_s)e^{\nu_c d/v_s}/p\nu_c \), as derived in \( \text{Eq.6} \), using a somewhat less rigorous method. In this limit, the search is optimized at \( \nu_c = d/v_g \).

The expression in Eq.A6 above may be approximately reproduced by physical arguments as follows. The probability that a microtubule will nucleate in the right direction, and will not undergo catastrophe until it reaches the target is given by \( p_s = pe^{-\nu_c d/v_g} \), and it will take at least \( N \sim \nu_c^{-1} \) unsuccessful attempts before this is accomplished. Each of these unsuccessful search events lasts a time \( \tau \sim \nu_c^{-1} \), and therefore, the total search time is

\[ T_s \sim N\nu_c^{-1} = \frac{e^{\nu_c d/v_g}}{p\nu_c}. \quad (A7) \]

Note that Eq.A6 reduces to Eq.A7 in the limit \( p \to 0 \) and \( v_g \ll v_s \).