

Stochastic resetting in backtrack recovery by RNA polymerasesÉdgar Roldán,^{1,2,3,*} Ana Lisica,^{4,5} Daniel Sánchez-Taltavull,⁶ and Stephan W. Grill^{4,5,1,*}¹Max Planck Institute for the Physics of Complex Systems, Nöthnitzer Strasse 38, 01187 Dresden, Germany²Center for Advancing Electronics Dresden, cfaed, Dresden, Germany³GISC - Grupo Interdisciplinar de Sistemas Complejos, Madrid, Spain⁴BIOTEC, Technische Universität Dresden, Tatzberg 47/49, 01307 Dresden, Germany⁵Max Planck Institute of Molecular Cell Biology and Genetics, Pfotenhauerstraße 108, 01307 Dresden, Germany⁶Regenerative Medicine Program, Ottawa Hospital Research Institute, Ottawa, Canada K1H 8L6

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Transcription is a key process in gene expression, in which RNA polymerases produce a complementary RNA copy from a DNA template. RNA polymerization is frequently interrupted by backtracking, a process in which polymerases perform a random walk along the DNA template. Recovery of polymerases from the transcriptionally inactive backtracked state is determined by a kinetic competition between one-dimensional diffusion and RNA cleavage. Here we describe backtrack recovery as a continuous-time random walk, where the time for a polymerase to recover from a backtrack of a given depth is described as a first-passage time of a random walker to reach an absorbing state. We represent RNA cleavage as a stochastic resetting process and derive exact expressions for the recovery time distributions and mean recovery times from a given initial backtrack depth for both continuous and discrete-lattice descriptions of the random walk. We show that recovery time statistics do not depend on the discreteness of the DNA lattice when the rate of one-dimensional diffusion is large compared to the rate of cleavage.

DOI: [10.1103/PhysRevE.93.062411](https://doi.org/10.1103/PhysRevE.93.062411)**I. INTRODUCTION**

Transcription of genetic information from DNA into RNA is the first step of gene expression and is fundamental for cellular regulation. The process is performed by macromolecular enzymes called RNA polymerases that move stepwise along a DNA template and produce a complementary RNA, as illustrated in Fig. 1. Transcription elongation is often interrupted by pausing and backtracking, a reverse movement of the RNA polymerase on the DNA template that displaces the RNA 3' end from the active site and leaves the enzyme transcriptionally inactive [1–5] (Fig. 1). Backtracking is a central mechanism of transcriptional proofreading and it facilitates important co-transcriptional processes, such as promoter-proximal pausing, co-transcriptional pre-mRNA splicing and arrest [6,7].

In a backtrack, a polymerase performs a random walk on the DNA template until it realigns the 3' end of the RNA with its active site [8]. Once the RNA 3' end is realigned, the polymerase is recovered from the backtracked state and is able to resume elongation. The recovery of the polymerase from a backtracked state, called *backtrack recovery*, results from the kinetic competition between two mechanisms [9]: polymerases can either recover by diffusing along the DNA until returning to the elongation-competent state [8,10–15] or by cleavage of the backtracked RNA which generates a new RNA 3' end in the active site [16–18] (see Fig. 1). The cleavage reaction can be performed by intrinsic cleavage mechanisms or it can be assisted by a transcription factor, TFIIS [19–21].

The stochastic motion of backtracked RNA polymerases was previously reported in single-molecule experiments (see Fig. 2 for an example) and described as continuous-time

Markov processes [8,10,12–15,22]. Specifically, backtracking has been modelled as a hopping process over a discrete lattice of nucleotides [11,13–15,23–25] but also as a diffusion process in continuous space [8]. However, it remains unclear which aspects of the backtracking process depend on the discreteness of the position lattice and which can be described with a diffusion process.

Here we present both discrete and continuous-space descriptions of backtrack recovery and investigate to which extent a diffusion process is a good approximation of the polymerase dynamics during a backtrack. We present a solvable stochastic model of RNA polymerase backtrack recovery that includes both diffusion and cleavage and study its main statistical features. The process shares similarities with recent development on diffusion processes with *stochastic resetting* introduced in Ref. [26]. In such problems a particle undergoes Brownian diffusion but can also stochastically reset its position [26–33]. The mean first-passage time to reach an absorber can be determined analytically, which depends on the statistics of resetting. A backtracked RNA polymerase undergoes a random walk to the elongation-competent state while also resetting its position via cleavage. Here we determine the first-passage time properties of this variant of a “diffusion with stochastic resetting” process.

In experiments, deep backtracks are readily identified, and it is possible to determine the time a polymerase takes to recover from a backtrack of a certain depth [9]. Hence we consider the recovery time τ_{rec} , defined as the first-passage time of a random walker to reach an absorbing barrier with the walker starting at a given “initial” backtrack depth. We derive exact expressions for relevant statistics, such as the mean time to recover from a backtrack, or mean recovery time, for both continuous and discrete stochastic models. For previously reported parameter values, where the hopping rate is much larger than the cleavage rate, we show that both

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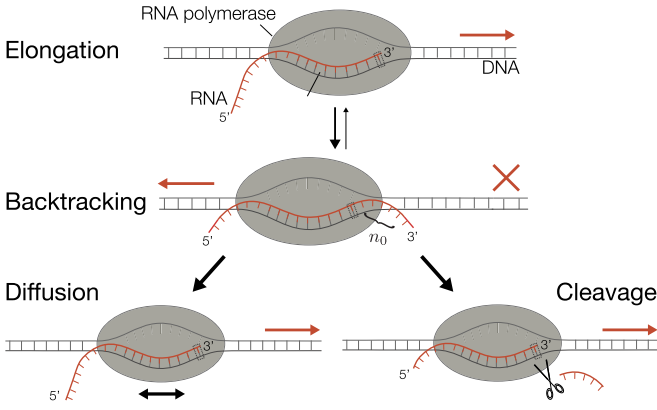


FIG. 1. Scheme of transcription elongation (top), backtracking (middle), and backtrack recovery (bottom) processes. The 3' end of the RNA is aligned with the active site of the polymerase (dashed square) during elongation but displaced in the backtracked state. This makes the polymerase transcriptionally inactive, as it cannot add new nucleotides to the 3' end of the RNA. Here, n_0 represents the number of backtracked nucleotides. Backtrack recovery can proceed through 1D diffusion of the polymerase along the DNA template, until the 3' end of the RNA realigns with the active site or through cleavage of the backtracked RNA and production of a new 3' end that is aligned with the active site.

discrete and continuous descriptions can be used concurrently to describe the statistics of backtrack recovery.

II. DISCRETE MODEL: HOPPING PROCESS WITH CLEAVAGE

We first describe the recovery of an RNA polymerase from a backtrack as a continuous-time one-dimensional (1D) hopping process on a semi-infinite discrete lattice. Each state of the lattice $n \in [1, 2, 3, \dots, \infty)$ represents the number of

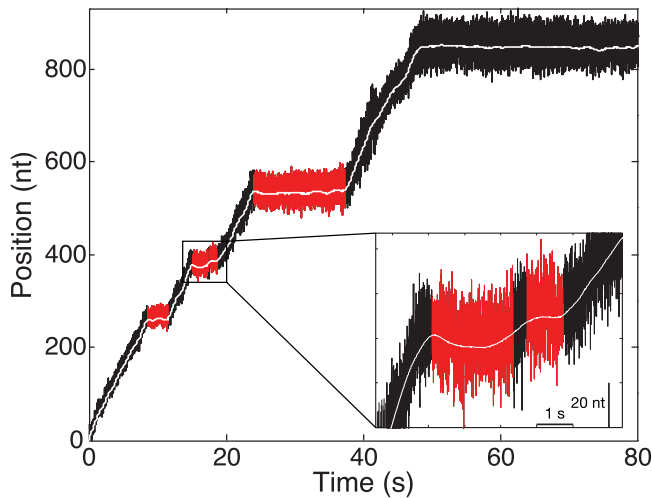


FIG. 2. Experimental trace of RNA polymerase I. Position of the polymerase on a DNA template (in nucleotides, nt) as a function of time obtained in a single-molecule experiment. The regions highlighted in red (light gray) correspond to pauses, and the inset shows a zoomed view of one of the pauses, which includes a backtrack. The data is obtained with the experimental setup described in [9,34], using a sampling rate of 1 kHz.

nucleotides backtracked by the polymerase (see Fig. 3 for a graphical illustration). For example, $n(t) = 3$ means that at time t the polymerase has backtracked three nucleotides. In our model, polymerases can jump between adjacent states with hopping rate k can cleave an RNA transcript of any length with a cleavage rate k_c . We consider that no external forces bias the hopping rates of the polymerase on the lattice. Cleavage is represented by an instantaneous jump or stochastic reset [26–30] to the elongation-competent state located in $n = 0$. The elongation-competent state is considered as an absorbing state because the probability to backtrack after cleavage is very low [14]. Our discrete model is a variant of the hopping models introduced by Depken *et al.* in Refs. [11] and [12].

The time evolution of the position of the polymerase can be described in a master equation formalism [35]. The probability of the polymerase to be at state n at time $t \geq 0$ is denoted by $p_n(t)$. We consider the initial condition $p_n(0) = \delta_{n,n_0}$, that is, polymerases are initially positioned at $n_0 \geq 1$. The dynamics of the probability of the polymerase to be at a given state at time t is described by the following master equation:

$$\frac{dp_1(t)}{dt} = k p_2(t) - (2k + k_c) p_1(t), \quad (1)$$

$$\frac{dp_n(t)}{dt} = k p_{n+1}(t) - (2k + k_c) p_n(t) + k p_{n-1}(t), \quad (2)$$

where $n \geq 2$. The elongation state $n = 0$ is an absorber. Recent experiments showed that the elongation rate from $n = 0$ is more than 10 times faster than the rate of backtracking by one nucleotide [14], so we neglect the possibility to make a jump from $n = 0$ to $n = 1$. Hence, the recovery time is the first-passage time of the polymerase to reach the absorber located in $n = 0$.

Equations (1) and (2) can be solved exactly. We now present the exact solution of the master equation and derive exact expressions for the recovery time distribution and the mean recovery time of a polymerase from a given initial backtracked state.

A. Solution of the master equation

We now derive the analytical solution for the master equation of the hopping model. Equations (1) and (2) can

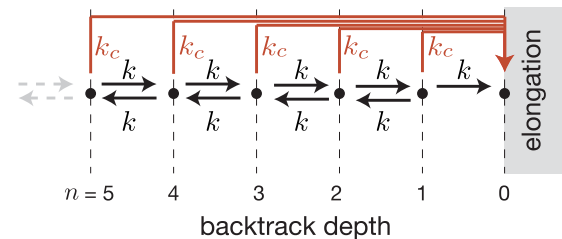


FIG. 3. Stochastic model of backtrack recovery: hopping process with cleavage. Each state n represents the number of backtracked nucleotides. The stochastic motion of the polymerases in a backtrack is described as a continuous-time hopping process between adjacent states with hopping rate k . Cleavage is represented as a stochastic reset to the elongation state with rate k_c . The recovery time from an initial backtrack depth n_0 is given by the first-passage time to the absorbing elongation state located at $n = 0$.

be rewritten as

$$\frac{d}{dt}\mathbf{P}(t) = \mathbf{A}\mathbf{P}(t), \quad (3)$$

where $\mathbf{P}(t) = [p_1(t) p_2(t) \dots]^\top$ is a column vector including the state probabilities at time t and \mathbf{A} is a tridiagonal symmetric Toeplitz matrix [36] of the form

$$\mathbf{A} = \begin{bmatrix} -(2k+k_c) & k & 0 & 0 & \dots \\ k & -(2k+k_c) & k & 0 & \dots \\ 0 & k & -(2k+k_c) & k & 0 \dots \\ \vdots & \vdots & \vdots & \ddots & \ddots \dots \end{bmatrix}.$$

The solution of Eq. (3) with initial condition $\mathbf{P}(0) = [0, 0, \dots, 0, 1, 0, \dots]^\top$, with $p_{n_0}(0) = 1$ and $p_n(0) = 0$ for $n \neq n_0$, is given by [37]

$$\mathbf{P}(t) = \mathbf{P}(0)e^{\mathbf{A}t}. \quad (4)$$

We now decompose \mathbf{A} in the following form:

$$\mathbf{A} = \mathbf{Q}\mathbf{D}\mathbf{Q}^{-1}, \quad (5)$$

where \mathbf{D} is a diagonal matrix containing the eigenvalues of \mathbf{A} and \mathbf{Q} is a matrix with the eigenvectors of \mathbf{A} in columns. Note that since \mathbf{A} is symmetric, $\mathbf{Q}^{-1} = \mathbf{Q}^\top$. To obtain the eigenvalues of \mathbf{A} we first assume that the matrix is of finite size $N \times N$ and then take the limit $N \rightarrow \infty$. For N finite, the matrix elements of the matrices \mathbf{D} and \mathbf{Q} are given by [36]

$$D_{ii} = -(2k + k_c) + 2k \cos\left(\frac{i\pi}{N+1}\right), \quad (6)$$

$$Q_{ij} = \sqrt{\frac{2}{N+1}} \sin\left(\frac{ij\pi}{N+1}\right). \quad (7)$$

The term $\sqrt{\frac{2}{N+1}}$ that appears in Eq. (7) is a normalization constant. As a result, Eq. (4) can be rewritten as

$$\mathbf{P}(t) = \mathbf{Q} e^{\mathbf{D}t} \mathbf{Q}^\top \mathbf{P}(0), \quad (8)$$

where $e^{\mathbf{D}t}$ is a diagonal matrix with elements $e^{D_{ii}t}$ ($i = 1, \dots, N$) in the diagonal. After some algebra, we obtain the following expression for the n th element of the vector $\mathbf{P}(t)$:

$$p_n(t) = \sum_{m=1}^N \sin\left(\frac{kn\pi}{N+1}\right) e^{[-(2k+k_c)+2k \cos(\frac{m\pi}{N+1})]t} \times \frac{2}{N+1} \sin\left(\frac{n_0k\pi}{N+1}\right). \quad (9)$$

We now take the asymptotic limit $N \rightarrow \infty$. In this limit, $k/N \rightarrow x$ where x is a continuous variable and the sum $\sum_{k=1}^N \frac{1}{N} \rightarrow \int_0^1 dx$. Using these approximations, and the property $\sin(ax) \sin(bx) = \frac{1}{2} [\cos[(a-b)x] - \cos[(a+b)x]]$ we obtain the following exact solution for the master equation:

$$\begin{aligned} p_n(t) &= \frac{2e^{-(2k+k_c)t}}{\pi} \int_0^\pi e^{2kt \cos x} \sin(n_0x) \sin(nx) dx \\ &= \frac{e^{-(2k+k_c)t}}{\pi} \left\{ \int_0^\pi e^{2kt \cos(x)} \cos[(n_0 - n)x] dx \right. \\ &\quad \left. - \int_0^\pi e^{2kt \cos(x)} \cos[(n_0 + n)x] dx \right\} \\ &= e^{-(2k+k_c)t} [I_{n_0-n}(2kt) - I_{n_0+n}(2kt)], \end{aligned} \quad (10)$$

where I_n is a modified Bessel function of the first kind, which is given by [38]

$$I_m(z) = \frac{1}{\pi} \int_0^\pi e^{z \cos x} \cos(mx) dx. \quad (11)$$

From Eq. (10) we can calculate the probability to be at state $n = 1$ at time t . Using the property $I_{m-1}(z) - I_{m+1}(z) = \frac{2m}{z} I_m(z)$ [38] in Eq. (10) we obtain

$$p_1(t) = e^{-(2k+k_c)t} \frac{n_0 I_{n_0}(2kt)}{kt}. \quad (12)$$

For $n_0 = 1$, the probability for a polymerase to return to the first backtracked state at time t equals the expression derived previously for a cleavage-deficient polymerase (see Eq. (2) in [11]) times an exponential factor $e^{-k_c t}$. The exponential factor $e^{-k_c t}$ equals the probability that cleavage does not occur in the time interval $[0, t]$.

B. Recovery time distribution

Next, using the analytical solution of the master equation we derive an analytical expression for the recovery time distribution from an initial backtrack depth, n_0 .

We first introduce a generating function

$$G(t, z) \equiv \sum_{n=1}^{\infty} p_n(t) z^{n-1}. \quad (13)$$

For $z = 0$, the generating function gives the probability to be in $n = 1$ at time t , $G(t, 0) = p_1(t)$. For $z = 1$, the generating function equals the survival probability $S(t; n_0)$ at time t starting from n_0 , $G(t, 1) = \sum_{n=1}^{\infty} p_n(t) = S(t; n_0)$.

Using the generating function, the full set of master equations [Eqs. (1) and (2)] can be rewritten as a single ordinary differential equation for the generating function,

$$\frac{\partial G(t, z)}{\partial t} = \left[kz - (2k + k_c) + \frac{k}{z} \right] G(t, z) - \frac{k}{z} G(t, 0). \quad (14)$$

The initial condition $p_n(0) = \delta_{n, n_0}$ can be expressed in terms of the generating function as $G(0, z) = \sum_{n=1}^{\infty} p_n(0) z^{n-1} = \sum_{n=1}^{\infty} \delta_{n, n_0} z^{n-1} = z^{n_0-1}$. The solution of Eq. (14) with this initial condition is

$$\begin{aligned} G(t, z; n_0) &= \exp\left[\left(kz - (2k + k_c) + \frac{k}{z}\right)t\right] \\ &\quad \times \left[z^{n_0-1} - \frac{k}{z} \int_0^t e^{-(kz - (2k + k_c) + k/z)s} G(s, 0) ds \right]. \end{aligned} \quad (15)$$

We next define $\Phi(\tau_{\text{rec}}; n_0) d\tau_{\text{rec}}$ as the probability of a polymerase to recover from an initial backtracked position n_0 in the time interval $[\tau_{\text{rec}}, \tau_{\text{rec}} + d\tau_{\text{rec}}]$. To calculate $\Phi(\tau_{\text{rec}}; n_0)$, we use the fact that a polymerase can exit a backtrack by hopping (from state $n = 1$ with rate k) or by cleavage (from any state with rate k_c). The probability density of the polymerase to reach the absorbing state at time τ_{rec} is then given by

$$\Phi(\tau_{\text{rec}}; n_0) = k G(\tau_{\text{rec}}, 0; n_0) + k_c G(\tau_{\text{rec}}, 1; n_0). \quad (16)$$

The probability to be at the state 1 in τ_{rec} , $G(\tau_{\text{rec}}, 0; n_0)$ is given by Eq. (12):

$$G(\tau_{\text{rec}}, 0; n_0) = e^{-(2k+k_c)\tau_{\text{rec}}} \frac{n_0 I_{n_0}(2k\tau_{\text{rec}})}{k\tau_{\text{rec}}}. \quad (17)$$

The survival probability in τ_{rec} , $S(\tau_{\text{rec}}; n_0) = G(\tau_{\text{rec}}, 1; n_0)$, equals

$$G(\tau_{\text{rec}}, 1; n_0) = e^{-k_c\tau_{\text{rec}}} \left[1 - k \int_0^{\tau_{\text{rec}}} e^{-2ks} \frac{n_0 I_{n_0}(2ks)}{ks} ds \right], \quad (18)$$

which yields

$$G(\tau_{\text{rec}}, 1; n_0) = e^{-k_c\tau_{\text{rec}}} \left[1 - \frac{(k\tau_{\text{rec}})^{n_0}}{n_0\Gamma(n_0)} H(\tau_{\text{rec}}; n_0) \right], \quad (19)$$

where Γ is the Gamma function and

$$H(\tau_{\text{rec}}; n_0) = {}_2F_2\left[\left\{n_0, n_0 + \frac{1}{2}\right\}; \left\{n_0 + 1, 2n_0 + 1\right\}; -4k\tau_{\text{rec}}\right]. \quad (20)$$

Here ${}_2F_2$ is a generalized hypergeometric function (see Ref. [38]). The recovery time distribution is obtained by substituting (17) and (19) in (16):

$$\Phi(\tau_{\text{rec}}; n_0) = e^{-(2k+k_c)\tau_{\text{rec}}} \frac{n_0 I_{n_0}(2k\tau_{\text{rec}})}{\tau_{\text{rec}}} + k_c e^{-k_c\tau_{\text{rec}}} \left[1 - \frac{(k\tau_{\text{rec}})^{n_0}}{n_0\Gamma(n_0)} H(\tau_{\text{rec}}; n_0) \right]. \quad (21)$$

For a cleavage-deficient polymerase $k_c = 0$ initially in the first backtracking state $n_0 = 1$, the recovery time distribution equals

$$\Psi(\tau_{\text{rec}}) = e^{-2k\tau_{\text{rec}}} \frac{I_1(2k\tau_{\text{rec}})}{\tau_{\text{rec}}}, \quad (22)$$

which coincides with the pause time distribution derived in previous works (Eq. (2) in Ref. [11]).

To verify our model, we perform numerical simulations of the hopping process with cleavage using the Gillespie algorithm [39] [Figs. 4(a) and 4(b)]. From our simulations, we calculate first-passage time distributions to the elongation state and compare them with the recovery time distribution derived in Eq. (21) [Figs. 4(c) and 4(d)]. In the presence of cleavage, recovery can happen from backtracks of any depth. Cleavage prevents backtracks of large duration, as shown by the sharp cutoff of the first-passage time distribution at large times [Fig. 4(c), inset]. In the absence of cleavage, deep backtracks are recovered at very large times, with a power-law tail $\Phi(\tau_{\text{rec}}; n_0) \sim \tau_{\text{rec}}^{-3/2}$ [Fig. 4(d), inset]. The first-passage time distributions obtained from numerical simulations in both the cleavage-assisted [Fig. 4(c)] and cleavage-deficient case [Fig. 4(d)] agree with the theoretical expression of the recovery time distribution derived here in Eq. (21).

C. Mean recovery time

The mean recovery time $\langle \tau_{\text{rec}} \rangle$ is a useful statistic that can be measured experimentally in single-molecule experiments. Moreover, the mean recovery time can provide a quantitative measure of kinetic rates of backtrack recovery, as shown in Ref. [9]. The mean recovery time can be obtained from

Eq. (21), and equals

$$\langle \tau_{\text{rec}} \rangle = \frac{1}{k_c} \left[1 - \left(\frac{\sqrt{\frac{4k}{k_c} + 1} - 1}{\sqrt{\frac{4k}{k_c} + 1} + 1} \right)^{n_0} \right]. \quad (23)$$

We introduce the following characteristic scales of time and backtrack position:

$$n_c = \sqrt{\frac{4k}{k_c}}, \quad (24)$$

$$\tau_c = \frac{1}{k_c}. \quad (25)$$

The mean recovery time then simplifies to

$$\langle \tau_{\text{rec}} \rangle = \tau_c \left[1 - \left(\frac{\sqrt{n_c^2 + 1} - 1}{\sqrt{n_c^2 + 1} + 1} \right)^{n_0} \right]. \quad (26)$$

For $n_0 = 0$, $\langle \tau_{\text{rec}} \rangle = 0$ since the polymerase is at time $t = 0$ already in the recovered state. For $n_0 = 1$ we obtain

$$\langle \tau_{\text{rec}} \rangle_{n_0=1} = \frac{2\tau_c}{\sqrt{n_c^2 + 1} + 1}. \quad (27)$$

Note that Eq. (27) is in agreement with previous results (see Eq. (5) in Ref. [24]).

For initial backtracked positions n_0 that are not large compared to n_c , i.e., when $n_0 \leq n_c$, the mean recovery time given by Eq. (26) depends linearly on the initial backtrack depth

$$\langle \tau_{\text{rec}} \rangle = \tau_c \ln \left(\frac{\sqrt{n_c^2 + 1} + 1}{\sqrt{n_c^2 + 1} - 1} \right) n_0 + O(n_0^2). \quad (28)$$

When the initial position is much larger than the characteristic backtrack position n_c , i.e., when $n_0 \gg n_c$, the mean recovery time saturates to τ_c .

If the hopping and cleavage rates are equal ($k = k_c$), the mean recovery time given by Eq. (26) can be rewritten in terms of the Golden ratio $\varphi = (\sqrt{5} + 1)/2$ and the Golden ratio conjugate $\Phi = (\sqrt{5} - 1)/2$:

$$\langle \tau_{\text{rec}} \rangle_{k=k_c} = \tau_c \left[1 - \left(\frac{\Phi}{\varphi} \right)^{n_0} \right]. \quad (29)$$

The duration of a transcriptional pause, or equivalently, the mean recovery time from $n_0 = 1$ is, for the case where $k = k_c$, equal to $\langle \tau_{\text{rec}} \rangle_{k=k_c, n_0=1} = \tau_c/\varphi$.

Figure 5 shows the analytical expression of the mean recovery time in the discrete model (23) compared to the average recovery time obtained from numerical simulations. The mean recovery time increases with increasing initial backtrack depth and saturates at $1/k_c$ for deep initial backtracks. The saturation of the mean recovery time at large n_0 was observed experimentally for Pol II recovery assisted with TFIIS [9].

In the absence of cleavage, the mean recovery time is not bounded, yielding $\langle \tau_{\text{rec}} \rangle = \infty$. Alternative statistics should therefore be considered to characterize the recovery in the absence of cleavage, such as the mode or the median recovery times.

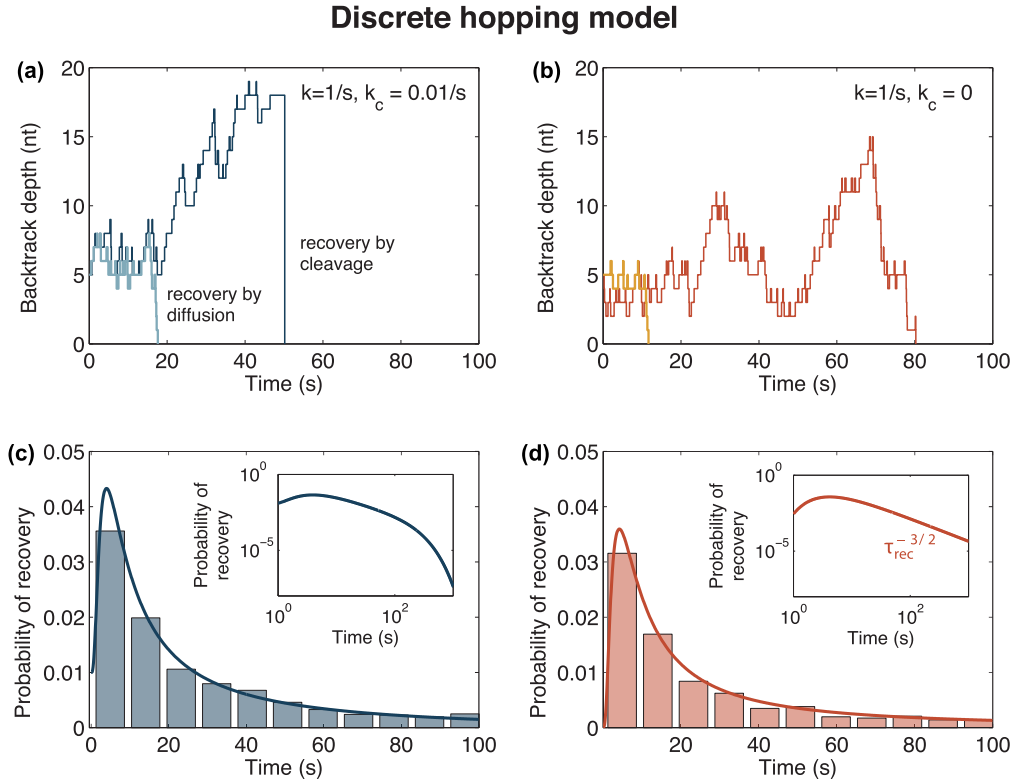


FIG. 4. Stochastic trajectories of the discrete hopping model and recovery time distributions. (a) Sample trajectories of the hopping model with diffusion and cleavage ($k = 1/s$, $k_c = 0.01/s$) simulated using the Gillespie algorithm. The light blue (light gray) trajectory represents a polymerase that recovers by diffusion, and the dark blue (dark gray) trajectory a polymerase that recovers by cleavage. (b) Sample trajectories for the discrete model with only diffusion, $k = 1/s$, $k_c = 0$, obtained using the Gillespie algorithm. (c) Recovery time probability density for the case where $k = 1/s$ and $k_c = 0.01/s$. The bars are obtained from histograms of 1000 numerical simulations, and the curve is the exact expression given by Eq. (21). The inset shows a log-log plot of the recovery time distribution for long recovery times. (d) Numerical and analytical probability density of the recovery time for the case where $k = 1/s$, $k_c = 0$. The inset shows the tail $\tau_{\text{rec}}^{-3/2}$ of the distribution at long times. In all cases the initial backtrack depth was set to $n_0 = 5$.

III. CONTINUOUS MODEL: DIFFUSION PROCESS WITH CLEAVAGE

To address which features of the backtrack recovery process depend on the details of the 1D lattice of the DNA template, we now consider a continuous-space model where the motion of the polymerase is described by a diffusion process with a stochastic resetting [26] to the elongation state due to RNA cleavage. Such a model can be envisioned as the continuous limit of the model in Fig. 3.

We consider that the position of the polymerase, x , is a continuous random variable. We define $\rho(x, t|x_0, 0)dx$ as the probability of a polymerase to be in the interval $[x, x + dx]$ at time t , given that it was at x_0 at time 0. In this continuous-space description the probability density $\rho(x, t|x_0, 0)$ evolves in time according to a Fokker-Planck equation with a diffusion term and a sink term,

$$\frac{\partial \rho(x, t|x_0, 0)}{\partial t} = D \frac{\partial^2 \rho(x, t|x_0, 0)}{\partial x^2} - k_c \rho(x, t|x_0, 0), \quad (30)$$

where we assume $x > 0$. Equation (30) results from taking the continuous limit in Eq. (2) and defining $x = an$, $x_0 = an_0$ and the diffusion coefficient $D = a^2 k$, with $a = 0.34$ nm the distance between two nucleotides. The solution of the Fokker-Planck equation (30) with initial condition

$\rho(x, 0|x_0, 0) = \delta(x - x_0)$ and the absorbing boundary condition $\rho(0, t|x_0, 0) = 0$ for $x > 0$ is given by [40]

$$\rho(x, t|x_0, 0) = \frac{e^{-k_c t}}{\sqrt{4\pi D t}} [e^{-(x-x_0)^2/4Dt} - e^{-(x+x_0)^2/4Dt}]. \quad (31)$$

The recovery time probability density is given by the probability density flux to $x = 0$ due to diffusion, plus the probability flux due to cleavage:

$$\Phi(\tau_{\text{rec}}; x_0) = \Phi_{\text{diff}}(\tau_{\text{rec}}; x_0) + \Phi_c(\tau_{\text{rec}}; x_0) \quad (32)$$

$$= D \left. \frac{\partial \rho(x, \tau_{\text{rec}}|x_0, 0)}{\partial x} \right|_{x=0} + k_c S(\tau_{\text{rec}}; x_0), \quad (33)$$

where $\Phi_{\text{diff}}(\tau_{\text{rec}}; x_0)d\tau_{\text{rec}}$ is the probability to recover by diffusion in the time interval $[\tau_{\text{rec}}, \tau_{\text{rec}} + d\tau_{\text{rec}}]$ and $\Phi_c(\tau_{\text{rec}}; x_0)d\tau_{\text{rec}}$ is the probability to recover by cleavage in the time interval $[\tau_{\text{rec}}, \tau_{\text{rec}} + d\tau_{\text{rec}}]$. The probability density flux across $x = 0$ due to diffusion equals

$$\Phi_{\text{diff}}(\tau_{\text{rec}}; x_0) = D \left. \frac{\partial \rho(x, \tau_{\text{rec}}|x_0, 0)}{\partial x} \right|_{x=0} \quad (34)$$

$$= e^{-k_c \tau_{\text{rec}}} \frac{x_0}{\sqrt{4\pi D \tau_{\text{rec}}^3}} e^{-x_0^2/4D\tau_{\text{rec}}}, \quad (35)$$

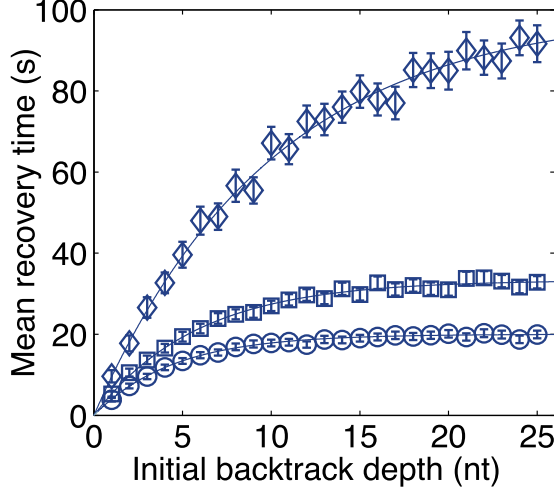


FIG. 5. Mean recovery time as a function of the backtrack depth for the discrete model shown in Fig. 3. Recovery time averaged over 1000 numerical simulations (symbols) of recovery from different initial backtrack depths. Diffusion rate was set to $k = 1/s$ in all cases and $k_c = 0.01/s$ (diamonds), $k_c = 0.03/s$ (squares) and $k_c = 0.05/s$ (circles). Error bars are standard errors of the mean with 90% statistical significance. The solid curves are obtained with the analytical expression given by Eq. (23) using $k = 1/s$ and $k_c = 0.01/s$ (top), $k_c = 0.03/s$ (center), and $k_c = 0.05/s$ (bottom).

where the spatial derivative in Eq. (34) is a derivative from the right. The survival probability at time τ_{rec} can be calculated by integrating the probability of the polymerase to be at time τ_{rec} in $x > 0$,

$$S(\tau_{\text{rec}}; x_0) = \int_0^{\infty} \rho(x, \tau_{\text{rec}} | x_0, 0) dx \quad (36)$$

$$= e^{-k_c \tau_{\text{rec}}} \operatorname{erf}\left(\frac{x_0}{\sqrt{4D\tau_{\text{rec}}}}\right), \quad (37)$$

where erf is the error function. The probability density $R(\tau_{\text{rec}}; x_0)$ of recovery from an initial backtrack depth x_0 in a time τ_{rec} (referred to as the recovery probability) is then given by

$$R(\tau_{\text{rec}}; x_0) = 1 - S(\tau_{\text{rec}}; x_0) = 1 - e^{-k_c \tau_{\text{rec}}} \operatorname{erf}\left(\frac{x_0}{\sqrt{4D\tau_{\text{rec}}}}\right). \quad (38)$$

For the case $k_c = 0$, the recovery probability simplifies to

$$R(\tau_{\text{rec}}; x_0) = \operatorname{erfc}\left(\frac{x_0}{\sqrt{4D\tau_{\text{rec}}}}\right), \quad (39)$$

where erfc is the complementary error function. From Eq. (37), we obtain the probability density flux through $x = 0$ via cleavage:

$$\Phi_c(\tau_{\text{rec}}; x_0) = k_c S(\tau_{\text{rec}}; x_0) = k_c e^{-k_c \tau_{\text{rec}}} \operatorname{erf}\left(\frac{x_0}{\sqrt{4D\tau_{\text{rec}}}}\right). \quad (40)$$

We obtain an exact expression for the recovery time distribution in the continuous-space model summing Eqs. (35)

and (40):

$$\Phi(\tau_{\text{rec}}; x_0) = e^{-k_c \tau_{\text{rec}}} \frac{x_0}{\sqrt{4\pi D \tau_{\text{rec}}^3}} e^{-x_0^2/4D\tau_{\text{rec}}} + k_c e^{-k_c \tau_{\text{rec}}} \operatorname{erf}\left(\frac{x_0}{\sqrt{4D\tau_{\text{rec}}}}\right). \quad (41)$$

We now write Eq. (41) scaling time with respect to $\tau_c = 1/k_c$ and the initial position with respect to $x_c = \sqrt{4D/k_c}$ similarly to Eqs. (24) and (25) in the hopping model. In units of a scaled time $\mathfrak{t}_{\text{rec}} = \tau_{\text{rec}}/\tau_c$ and a scaled initial position $\mathfrak{x}_0 = x_0/x_c$, we obtain a universal expression

$$\Phi(\mathfrak{t}_{\text{rec}}; \mathfrak{x}_0) = e^{-\mathfrak{t}_{\text{rec}}} \frac{\mathfrak{x}_0}{\sqrt{\pi \mathfrak{t}_{\text{rec}}^3}} e^{-\mathfrak{x}_0^2/\mathfrak{t}_{\text{rec}}} + e^{-\mathfrak{t}_{\text{rec}}} \operatorname{erf}\left(\frac{\mathfrak{x}_0}{\sqrt{\mathfrak{t}_{\text{rec}}}}\right). \quad (42)$$

To test the validity of the analytical expression for the recovery time distribution (42), we perform numerical simulations of the continuous model (see Fig. 6). The following Langevin equation, $dx(t)/dt = \xi(t)$, describes the evolution of the backtracked distance at time t in continuous space, denoted as $x(t)$. Here $\xi(t)$ models a stochastic force that drives the polymerase forward or backward. The stochastic force is described by a δ -correlated Gaussian white noise with zero mean $\langle \xi(t) \rangle = 0$ and an amplitude proportional to the diffusion coefficient, $\langle \xi(t)\xi(t') \rangle = 2D\delta(t-t')$. Cleavage events are modelled as a stochastic resetting process with a resetting probability independent of time and position [26]. In every simulation time step of duration Δt , the probability to cleave is set to $k_c \Delta t$. This ensures that in the limit of Δt small, the probability that cleavage does not occur in the time interval $[0, t]$ is equal to $e^{-k_c t}$. We perform numerical simulations of the Langevin equation using an Euler discrete-time numerical integration scheme with $\Delta t = 1$ ms, which is one order of magnitude smaller than any characteristic time of backtrack recovery given by the inverse of cleavage or diffusion rates [9].

The results shown in Fig. 6 validate the exact expression obtained for the recovery time distribution given by Eq. (41) both in the presence and in the absence of cleavage. The recovery time distributions obtained for the same initial backtrack distance $x_0 = 5$ have the same shape as those obtained in the discrete-space description [cf. Fig. 4].

A. Mean recovery time

In the continuous model, the mean recovery time can be obtained by calculating the mean value of the first-passage distribution [Eq. (41)]:

$$\langle \tau_{\text{rec}} \rangle = \frac{1}{k_c} [1 - e^{-x_0/\sqrt{D/k_c}}], \quad (43)$$

or equivalently,

$$\langle \tau_{\text{rec}} \rangle = \tau_c [1 - e^{-2x_0/x_c}]. \quad (44)$$

Note that the mean recovery time can be also calculated by a different route, using the backward Fokker-Planck equation together with the Laplace transform of the survival probability (see Appendix).

Equations (43) and (44) show that the mean recovery time for deep initial backtracks ($x_0 \gg x_c$) saturates to τ_c . Our results indicate that recovery happens mostly by diffusion for shallow backtracks, where $x_0 \ll x_c$, and mostly by cleavage

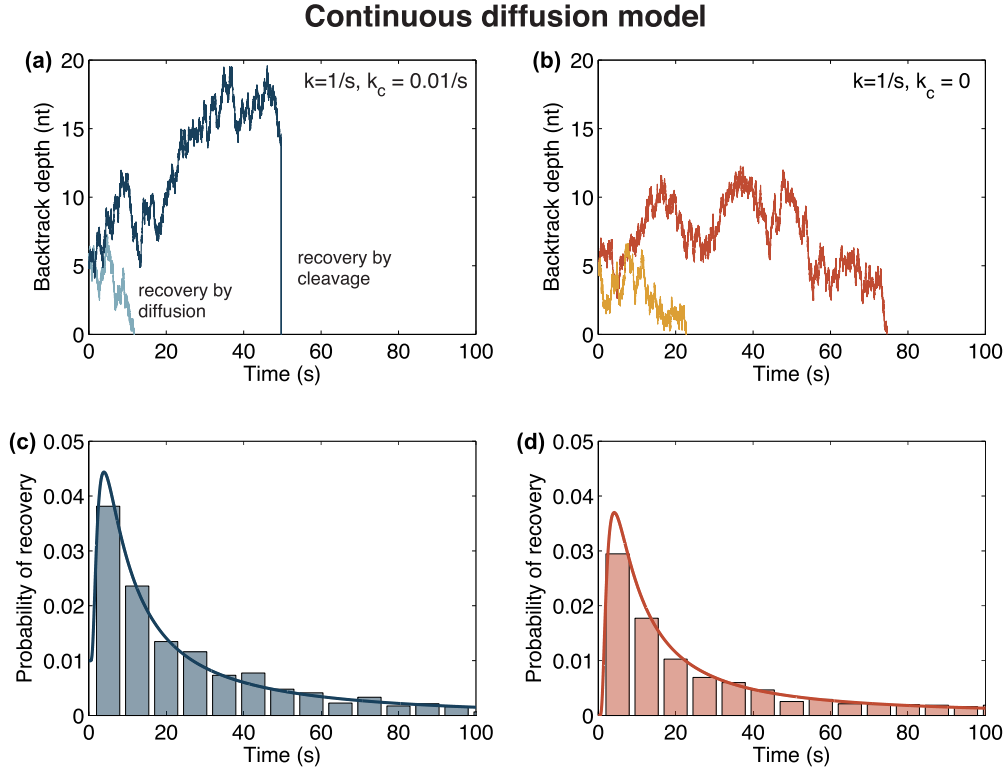


FIG. 6. Stochastic trajectories of the continuous diffusion model and recovery time distributions. (a) Sample trajectories of the continuous-space model with diffusion and cleavage ($k = 1/s, k_c = 0.01/s$) simulated using Euler numerical scheme for a discrete-time Langevin equation. The light blue (light gray) trajectory represents a polymerase that recovers by diffusion, and the dark blue (dark gray) trajectory a polymerase that recovers by cleavage. (b) Sample trajectories for the continuous model with only diffusion, $k = 1/s, k_c = 0$ obtained with the same numerical integration scheme. (c) Recovery time probability density for the case where $k = 1/s$ and $k_c = 0.01/s$. The bars are histograms obtained from 1000 numerical simulations and the curve is the exact expression given by Eq. (41). (d) Recovery time probability density for the case where $k = 1/s$ and $k_c = 0$. The bars are histograms obtained from 1000 numerical simulations, and the curve is the exact expression given by Eq. (41) with $k_c = 0$. In all simulations, the simulation time step was set to $\Delta t = 1$ ms and the initial distance to $x_0 = 5$ nt.

for deep backtracks, where $x_0 \gg x_c$. For shallow initial backtracks ($x_0 \leq x_c$), the mean recovery time scales linearly with x_0 ,

$$\frac{\langle \tau_{\text{rec}} \rangle}{\tau_c} = \frac{x_0}{x_c/2} + O(x_0^2), \quad (45)$$

similarly to the mean recovery time in the discrete hopping model [see Eq. (28)].

Taking the limit $n_c \gg 1$ in the expression for the mean recovery time in the discrete model [Eq. (26)], we obtain

$$\langle \tau_{\text{rec}} \rangle \simeq \tau_c [1 - e^{-2n_0/(\sqrt{n_c^2+1})}] \simeq \tau_c [1 - e^{-2x_0/x_c}], \quad (46)$$

where we have used $x_0 = an_0$ and $x_c = an_c$. Note that this expression is equal to the mean recovery time in the continuous model [Eq. (44)]. Hence, the mean recovery times in the discrete and continuous description coincide for large characteristic depth.

Figure 7 shows the scaled mean recovery time $\langle \tau_{\text{rec}} \rangle / \tau_c$ in the discrete and continuous models as a function of the scaled initial backtrack depth n_0/n_c (or x_0/x_c). The figure shows that the mean recovery time in the discrete model coincides with the mean recovery time in the continuous model for $n_c \geq 1$ and the agreement holds for any initial backtrack depth. When $n_c \geq 1$, the polymerase typically performs a large number of jumps prior to recovery. Hence, in this regime the details of

the DNA template do not impact on the mean recovery time, even for shallow initial backtracks.

Notably, the limit $n_c \geq 1$ is in agreement with the experimental data obtained from single-molecule experiments with RNA polymerase II, where $k \sim 1 \text{ s}^{-1}$ and $k_c \sim (0.01 - 0.1) \text{ s}^{-1}$ [9,13–15,41], yielding $n_c > 1$. Therefore, for reported values of diffusion and cleavage rates, the diffusion approximation can be used without loss of generality, with the advantage of providing a simpler mathematical framework with respect to the hopping process.

IV. DISCUSSION

Here we have described the diffusive backward motion of paused RNA polymerases as a diffusion process with stochastic resetting. For this purpose we have considered continuous-time stochastic models with the position of the backtracked polymerase described by a discrete or a continuous random variable.

We have provided exact results on the statistics of the time needed for an RNA polymerase to recover from an arbitrary initial backtrack depth in both discrete (hopping) and continuous-space (diffusion) stochastic descriptions. In our models, recovery times are equivalent to first-passage times to reach an absorber. We have presented a roadmap

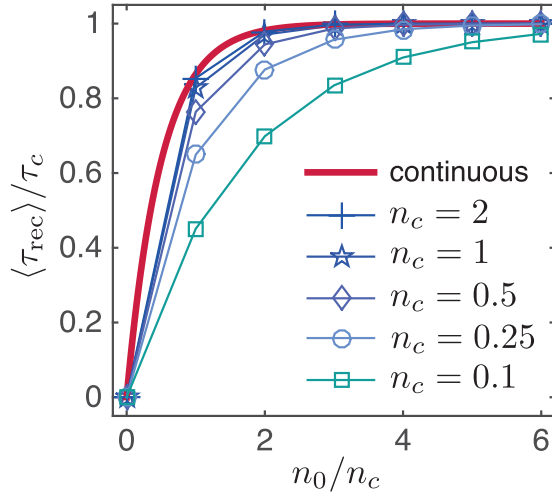


FIG. 7. Scaled mean recovery time as a function of the scaled initial backtrack depth for discrete and continuous models. Scaled mean recovery time $\langle \tau_{\text{rec}} \rangle / \tau_c$ as a function of the scaled initial backtrack depth n_0 / n_c for the discrete-space hopping model [Eq. (26), blue symbols] and as a function of x_0 / x_c for the continuous-space diffusion model [Eq. (44), magenta curve].

for the calculation of the first-passage time distribution for a continuous-time random walk with an absorbing state, which models RNA polymerase backtrack recovery with high fidelity. Both hopping and diffusion models provide similar recovery time distributions, with the majority of differences in the short recovery times and a complete overlap for long recovery times (see Table I for a summary of the main results).

We have shown that both a discrete and continuous description can be used concurrently for backtrack recovery analysis for short and long backtracks when the characteristic distance $n_c = 2\sqrt{k/k_c}$ is greater than one. This corresponds to cases where the hopping rate k is larger than the cleavage rate k_c and is in good agreement with estimated rates of RNA polymerase backtracking [9,14,15]. Future work in the framework of stochastic resetting will have to be done to consider the case where polymerases can cleave only until a critical backtrack

TABLE I. Summary of expressions for the probability distribution of the recovery time and the mean recovery time from a given initial backtrack depth in the hopping model with cleavage $\Phi(\tau_{\text{rec}}; n_0)$ and in the diffusion model with cleavage $\Phi(\tau_{\text{rec}}; x_0)$ with initial backtrack depths n_0 and x_0 , respectively. Here k is the diffusion rate, k_c is the cleavage rate, D is the diffusion coefficient, and $H(\tau_{\text{rec}}; n_0) = {}_2F_2(\{n_0, n_0 + 1/2\}; \{n_0 + 1, 2n_0 + 1\}; -4k\tau_{\text{rec}})$.

Discrete hopping model		
	Diffusion and cleavage ($k > 0$; $k_c > 0$)	Only diffusion ($k > 0$; $k_c = 0$)
$\Phi(\tau_{\text{rec}}; n_0)$	$e^{-(2k+k_c)\tau_{\text{rec}}} \frac{n_0}{\tau_{\text{rec}}} \int_0^{\tau_{\text{rec}}} \frac{I_0(2k\tau_{\text{rec}})}{\tau_{\text{rec}}} + k_c e^{-k_c\tau_{\text{rec}}} \left[1 - \frac{(k\tau_{\text{rec}})^{n_0}}{n_0!} \frac{H(\tau_{\text{rec}}; n_0)}{\Gamma(n_0)} \right]$	$e^{-(2k+k_c)\tau_{\text{rec}}} \frac{n_0}{\tau_{\text{rec}}} \int_0^{\tau_{\text{rec}}} \frac{I_0(2k\tau_{\text{rec}})}{\tau_{\text{rec}}}$
$\langle \tau_{\text{rec}} \rangle$	$\frac{1}{k_c} \left[1 - \left(\frac{\sqrt{(4k/k_c)+1}-1}{\sqrt{(4k/k_c)+1}+1} \right)^{n_0} \right]$	∞
Continuous diffusion model		
	Diffusion and cleavage ($D > 0$; $k_c > 0$)	Only diffusion ($D > 0$; $k_c = 0$)
$\Phi(\tau_{\text{rec}}; x_0)$	$e^{-k_c\tau_{\text{rec}}} \frac{x_0}{\sqrt{4\pi D\tau_{\text{rec}}^3}} e^{-x_0^2/4D\tau_{\text{rec}}} + k_c e^{-k_c\tau_{\text{rec}}} \text{erf}\left(\frac{x_0}{\sqrt{4D\tau_{\text{rec}}}}\right)$	$\frac{x_0}{\sqrt{4\pi D\tau_{\text{rec}}^3}} e^{-x_0^2/4D\tau_{\text{rec}}}$
$\langle \tau_{\text{rec}} \rangle$	$\frac{1}{k_c} \left[1 - e^{-x_0/\sqrt{D/k_c}} \right]$	∞

distance, as recently found in single-molecule experiments [9]. Single-molecule optical tweezers transcription experiments of RNA polymerase backtracking [8–10,13–15,25,42] would allow one to experimentally validate the stochastic models provided here and quantify the backtrack diffusion and cleavage rates of these enzymes.

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APPENDIX: CALCULATION OF THE MEAN RECOVERY TIME FROM THE BACKWARD FOKKER-PLANCK EQUATION

The backward Fokker-Planck equation corresponding to Eq. (30) in the continuous-space model reads

$$\frac{\partial \rho(x, t | x_0, 0)}{\partial t} = D \frac{\partial^2 \rho(x, t | x_0, 0)}{\partial x_0^2} - k_c \rho(x, t | x_0, 0). \quad (\text{A1})$$

Integrating Eq. (A2) with respect to x from $x = 0$ to $x = \infty$ we obtain the following equation for the survival probability:

$$\frac{\partial S(t; x_0)}{\partial t} = D \frac{\partial^2 S(t; x_0)}{\partial x_0^2} - k_c S(t; x_0). \quad (\text{A2})$$

Taking the Laplace transform, Eq. (A2) yields

$$qS(q; x_0) - 1 = D \frac{\partial^2 S(q; x_0)}{\partial x_0^2} - k_c S(q; x_0), \quad (\text{A3})$$

where $S(q; x_0) = \int_0^\infty dt e^{-qt} S(t; x_0)$ is the Laplace transform of the survival probability and we have used $S(0; x_0) = 1$. The solution of Eq. (A3) is given by

$$S(q; x_0) = \frac{1}{k_c + q} [1 - e^{-x_0 \sqrt{(k_c + q)/D}}]. \quad (\text{A4})$$

From Eq. (A4) one can find all the moments of the recovery time distribution. In particular, the mean recovery

time:

$$\langle \tau_{\text{rec}} \rangle = S_n(0) = \frac{1}{k_c} [1 - e^{-x_0 \sqrt{k_c/D}}], \quad (\text{A5})$$

which coincides with Eq. (43).

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