Searching for targets on a model DNA:
Effects of inter-segment hopping, detachment and re-attachment

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For most of the important processes in DNA metabolism, a protein has to reach a specific binding
site on the DNA. The specific binding site may consist of just a few base pairs while the DNA is
usually several millions of base pairs long. How does the protein search for the target site? What
is the most efficient mechanism for a successful search? Motivated by these fundamental questions
on intracellular biological processes, we have developed a model for searching a specific site on a
model DNA by a single protein. We have made a comparative quantitative study of the efficiencies
of sliding, inter-segmental hoppings and detachment/re-attachments of the particle during its search
for the specific site on the DNA. We also introduce some new quantitative measures of efficiency
of a search process by defining a relevant quantity, which can be measured in in-vitro experiments.

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I. INTRODUCTION

Self-avoiding walk (SAW) on a lattice serves as a
paradigm for research in statistical properties of natu-
ral and artificial polymers [1]. A “bridge” is defined as a
bond on the lattice that connects two sites both of which
are located on the SAW and are nearest-neighbours on
the lattice but are not nearest neighbours along the con-
tour of the SAW. RWs on SAWs is an interesting problem
in its own right because of the interesting effects of the
hops of the random walker across the bridges. Many
years ago, motivated by the vibrational dynamics of pro-
teins, the root-mean-square displacement of the random
walker on a SAW was studied both in the absence and
presence of hops across bridges [2–8]. RW on SAW has
also been studied as one of the prototypes of RW in dis-
ordered and fractal media [9–11].

In this paper we report the effects of the hops of the
random walker across the bridges on the distributions
of their first passage times, (FPT) [12], i.e., the time
taken by the walker to reach a target site for the first
time. Moreover, we extend the model even further by al-
lowing the possibility of detachments and re-attachments
(to be described in detail in section IV); we also report
the effects of these processes of attachments/detachments
of the random walkers on the distributions of their first
passage times. This extension of the model and the com-
putation of the first passage times are motivated by a bi-
ological process which is discussed in the next section.
Therefore, this work may also be viewed as a biologically
motivated extension of the works reported earlier [2–8].

This paper is organised as follows: In section II we
discuss the biological motivation behind this problem.
In section III we review some of the earlier works and
compare our model to the previous models. In section
the DNA template,
(ii) it not only slides along the DNA chain but, occasionally, also hops from one segment of the DNA to a neighbouring segment; proteins with more than one DNA-binding sites can exploit this mechanism,
(iii) in addition to sliding and intersegmental hopping, it also carries out a three-dimensional search for the specific binding site by first detaching from the DNA strand and, then, after executing three-dimensional diffusion in the solution, re-attaching at a new site which is uncorrelated with the site from which it detached (see Fig. 1).
Various aspects of these mechanisms and their relative importance have been explored by many research groups in subsequent works (see next section for a brief review and comparison to our model). [15–37].

III. BRIEF REVIEW OF EARLIER MODELS

Bustamante et al. [16] showed experimental evidence of the intersegmental transfer and hopping movements of E. Coli RNA Polymerase (RNAP) on nonspecific DNA. They also showed the effect of Heparin, which disrupts the RNAP-DNA nonspecific complexes. (For a theoretical review of this phenomenon, see [17].)

Burdzy and Holyst [18] address an important question, namely the number of molecules needed to locate the target of a given size. However, the theoretical arguments are not supported by any simulations. Also, the arguments are not in terms of FPTs, which may be more relevant biologically in the given context.

The effect of sequential inhomogeneity of the DNA was taken into consideration by Slutsky et al. [21]. They however focused only on a combination of one and three dimensional search mechanisms, without focusing on the intersegmental transfers. Also, they modeled the DNA as a one-dimensional strand, which is not completely realistic in the biological context.

The DNA was modeled as a one-dimensional strip consisting of low and high affinity sites by Rezania et al. [36]. They also took a two dimensional strip which, in addition to the above mentioned sites, has zero affinity water. However, they did not investigate the role of the bridges explicitly in their simulations.

The model developed by Oshanin et al. [23] is similar to our model, in that the search is carried out in discrete time steps till a maximum of $N$ steps, until the immobile target is found. The survival probability is found in terms of the leakage probability and is optimized to minimize this probability. However, the calculations are done for a one-dimensional substrate, which may not be biologically realistic.

Recently, Sheinman et al. [37] studied the effect of intersegmental transfers on the search process. The DNA was however modeled by connecting an ideal gas of rods (of unit persistence length) randomly to form a small world network. The authors reported a decrease in the search time by using scaling arguments and numerical verification. They also found dependence on the length of the DNA, an aspect which we do not address in great detail here.

Therefore, in spite of the large attention that this problem has received recently, the role of all three mechanisms and, in particular, the role of intersegmental transfer together with the attachment/detachment have not been investigated thoroughly. In this paper, we study all the three mechanisms together, which complements some of the works which have been reported earlier for elucidating the relative importance of each.

FIG. 1: A pictorial depiction of the various mechanisms of searching for specific binding sites by a DNA-binding protein (e.g., searching of the promoter site by a transcription factor).

IV. THE MODEL

A DNA can be considered to be a freely jointed chain over length scales much longer than its persistence length. A freely jointed chain can be modeled using a SAW [1], where the length of each of the steps of the SAW is typically of the order of the persistence length. The persistence length of DNA is roughly 100 base-pairs (bps). Therefore, a SAW of total length $L = 100$ would correspond, approximately, to 10,000 base pairs which is comparable, for example, to the length of a bacteriophage DNA.
Motivated by the experimental and theoretical works summarized in sections III and IV, in this paper we explore the efficiency of searching the SAW by a random walker for a specific binding site on the SAW. We study the efficiency of various search mechanisms that the random walker may use in order to reach the target site. We have introduced a new quantitative measure of the efficiencies of the search mechanisms in terms of the time-scales that are relevant to this problem.

For the sake of simplicity, we consider SAWs in two-dimensions, rather than three-dimensions. The random walker is represented by a particle. The particle searches the binding site by a combination of sliding, intersegment hopping as well as detachments, two-dimensional diffusion followed by, possibly, re-attachments (see Fig.2). Sliding motion of the particle is captured by its one-dimensional RW where its position at the successive time steps are nearest-neighbours along the contour of the SAW. In contrast, an inter-segment hopping of the particle takes place across a “bridge” that connects two sites both of which are located on the SAW and are nearest-neighbours on the square lattice but are not nearest neighbours along the contour of the SAW. Finally, upon detachment from the SAW, a particle executes an unbiased RW on the square lattice and, during this process, may re-attach with the SAW if it hops onto a site occupied by the SAW.

In our model we generate SAW configurations, each of length $L = 101$, on a square lattice (Fig.2) using a combination of reptation and the kink jump algorithms [38]. Averaging over the configurations thus generated, we have verified that the mean-square end-to-end Euclidean distance of the SAWs satisfy the well known relation $<r_L^2> \propto L^{3/2}$. When the random walker was constrained to move only along the SAW, it performed, effectively, one-dimensional diffusion. We can determine the value of the effective diffusion constant $D$, where $D = \langle R_t^2 \rangle / (2t)$, $\langle R_t^2 \rangle$ being the mean square displacement along the contour of the SAW. We have also verified that the mean-square Euclidean displacement of the random walker, on the SAW, follows $\langle R_L^2(t) \rangle \propto t^{3/4}$, even when hopping across the bridges are allowed. This is in agreement with the results reported earlier 2, 3.

V. RESULTS AND DISCUSSION

We parametrize the positions along the contour of the SAW by the symbol $s$; $s = 1$ and $s = L$ correspond to the two end points on the SAW. We designate the two end points, i.e., $s = 1$ and $s = L$ as the specific binding sites for the particle. On each SAW of length $L$, we release a particle at the mid-point of the SAW (i.e., at $s = (L+1)/2$) and allow it to execute a RW for a total of $N$ discrete time steps. If the particle is unable to reach either of the target sites (i.e., $s = 1$ or $s = L$), then the search by that particle is aborted and the search by another particle starts again. $N$ is 5000 and $L$ is 101 in all our simulations. In three different sets of computer experiments we implemented three different types of RWs of the particle.

(i) Mechanism I (M I): The particle is allowed to perform random walk only along the contour of the SAW.

(ii) Mechanism II (M II): Hopping across the bridges is allowed, in addition to the process included in mechanism I [39].

(iii) Mechanism III (M III): Attachment and detachment of the particle are also allowed, in addition to the processes included in mechanism II [39].

For the random walkers, we impose absorbing boundary conditions at $s = 1$ and $s = L$, i.e. a successful search process is terminated once the walkers reach the target site for the first time. Under these boundary conditions, the time taken by a random walker to reach one of the two boundaries (i.e., $s = 1$ or $s = L$) is identified as the corresponding FPT.

A. Distributions of First Passage Times (FPTs)

The distribution $P(t)$ of the FPTs for the three mechanisms are plotted in Fig.3. Since all three mechanisms are based on diffusive search, the qualitative shape of the curve $P(t)$ is the same in all the three cases. But, comparing the most probable time for three mechanisms,
we conclude that the mechanism II is more efficient than mechanism I whereas mechanism III is the most efficient of all. This observation strongly suggests that the search for DNA-binding sites by proteins would be more efficient if, in addition to sliding, both inter-segment hopping and detachment/re-attachment are also allowed.

B. Relative importance of detachments/re-attachments

In order to compare the relative importance of detachment/re-attachment compared to sliding and inter-segment hopping, we have computed the fraction of the time steps the particle spends unattached with the SAW in each successful search process. Corresponding to every search time, \( t \), we compute the fraction of the search time that the particle spends unattached from the SAW. We plot this fraction as a function of the search time in Fig. 4. Note that the peak in Fig. 4 occurs at \( t = 191 \). Interestingly, this value is close to the most probable FPT in Fig. 3 corresponding to Mechanism III, namely \( t = 153 \). Thus, the target site is reached in the shortest possible time if the particle uses mechanism III, in which the searching particle spends a fraction of the search time outside the SAW.

We have also computed the probability of re-attachment of a particle after \( t \) time steps, following its detachment from the SAW; this probability distribution is shown in Fig. 5. The log-log plot in the inset indicates the possibility of an initial power law regime, which is most likely \( \sim t^{-1/2} \), crossing over to another power law regime at long times, which was found to be \( \sim t^{-3/2} \).

C. Mechanism I versus Mechanism II

In this subsection, we consider a modified version of Mechanism II (MM II) which reduces to the mechanism I in a special limit. In this modified version, we compute the effect of forced hopping across the bridges, with a given probability. We define a quantity \( R \) as follows,

\[
R = \frac{p_{\text{bridge}}}{p_{\text{contour}}} \quad (1)
\]

\[
p_{\text{bridge}} + p_{\text{contour}} = 1 \quad (2)
\]
FIG. 5: The re-attachment probability in Mechanism III. The inset shows the same data on a log scale

where $p_{\text{bridge}}$ is the probability of hopping across the bridge and $p_{\text{contour}}$ is the probability of diffusing along contour. In the limit $p_{\text{bridge}} = 0$ (i.e., $R = 0$), this modified version reduces to mechanism I.

In Fig. 5, we plot the distribution $P(t)$ of the FPTs for four different values of $R$.

A higher value of $R$ indicates a higher probability of hopping across a bridge. This gives rise to a higher probability of reaching the ends in roughly the same amount of time. Therefore, if the protein has some bio-chemical means of hopping across such bridges preferentially, then it can bind to the specific binding site in a more efficient manner.

However, as we see from Fig. 6 for an extremely high value of $R$, the walker tends to get trapped in the bridge and hence takes a longer time to reach the ends. For example, when $R = 100$, $p_{\text{bridge}} \approx 0.99$. For this value of $p_{\text{bridge}}$, the moment the walker encounters a bridge, it would tend to get trapped in a bridge between two sites (for example, the bridge connecting “A” and “D” in Fig. 2).

D. Quantitative estimates of efficiencies of search-times

We are now in a position to compare the values of the most probable time, $\tau_{\text{mp}}$, and the MFPT ($\tau_{\text{avg}}$) for the distribution of the FPTs of all the mechanisms that we have investigated till now. Let $\tau_{1D}$ be the most probable/MFPT for successful search using Mechanism I while $\tau$ be the corresponding most probable/MFPT for the specific mechanism under consideration.

FIG. 6: The distribution of the FPTs for the modified Mechanism II for (a) $R=0.1$, (b) $R=1$, (c) $R=10$, and (d) $R=100$. To each curve, we fit a Gamma Distribution and a Difference of Exponentials (see Appendix I).
We define
\[ \eta = |1 - \frac{\tau}{\tau_D}|, \]
which we use as a quantitative measure of the efficiency of the process, relative to purely one-dimensional diffusion. The data are summarised in the table below.

| Mechanism       | Most Probable Search Time (\(\tau_{mp}\)) | Mean Search Time (\(\tau_{avg}\)) |
|-----------------|--------------------------------------------|----------------------------------|
| Mechanism I     | 841                                        | 1931.6                           |
| Mechanism II    | 494                                        | 1419.8                           |
| Mechanism III   | 153                                        | 553.7                            |
| MM II (R=0.1)   | 115                                        | 1243.9                           |
| MM II (R=10)    | 112                                        | 598.3                            |
| MM II (R=100)   | 457                                        | 1243.9                           |

We conclude that among the possible mechanisms considered in this paper, the modified Mechanism II with \(R = 10\) turns out to be the most efficient search process, as far as \(\eta_{mp}\) is concerned. However, in terms of \(\eta_{avg}\), \(R = 1\) would be the most efficient search mechanism. Therefore, we conjecture that if both \(\eta_{mp}\) and \(\eta_{avg}\) play equally important roles in determining the efficiency of a given mechanism, then the most efficient search mechanism would correspond to the range \(1 \leq R \leq 10\).

We also observe another interesting feature in MM II. We note that \(P_{max} = P(\tau_{mp})\) is largest for \(R = 1\) and then for \(R = 10\). This implies that not only are they the most efficient of all the mechanisms considered, but that they also have the highest “success-rate” of reaching the taget sites. Therefore, we see that MM II with forced hopping across the bridges leads to the most efficient and successful search process. Whether all proteins with multiple DNA-binding sites actually make use of this mechanism to reach their target sites is something that needs to be tested experimentally under controlled conditions in the near future.

In Fig. 7 we plot the most probable search time and the mean first passage time as functions of \(R\). We do not show the point \(R = 0\) (in the limit \(R \rightarrow 0\), we recover \(\tau_{mp} = 841\) and \(\tau_{avg} = 1931.6\)) on the log-scale. The only quantitative difference between the two is that the turning point in the curve for the MFPT lies in the range \(0.1 \leq R \leq 1\), whereas, the turning point in the curve for the \(\tau_{mp}\) lies in the range \(0 \leq R \leq 0.1\).

### E. Multiple Walkers and Immovable Barriers

We have also investigated the search of the same binding sites simultaneously by \(N (> 1)\) interacting particles which are initially distributed randomly along the SAW. The positions of the particles are updated in parallel subject to the constraint that none of the lattice sites is occupied by more than one walker at a time. As is suggested by our intuition, the \(\langle R^2 \rangle\) decreases with an increasing number of random walkers. In case of pure
sliding, the interaction between the particles, effectively, constrains each one to a shorter region on the SAW. Consequently, \( \langle R_t^2 \rangle \) decreases with increasing \( N \). However, in the presence of Bridges, there arise some situations in which a particle can bypass the other particles on its way by hopping across the bridges and, thereby, increasing \( \langle R_t^2 \rangle \). Effects of mutual hindrance is further weakened by detachments/re-attachment processes.

We also considered the situation when there are immovable barriers placed randomly along the SAW. This could mimic the effect of various obstacles that are present \textit{in-vivo} in the crowded environment of the cell. The mechanism III is the most efficient search process in the presence of these barriers.

VI. SUMMARY AND CONCLUSION

In this paper, we have suggested a biologically motivated extension of random walk on self-avoiding walks. The results of this investigation provide insight into the relative importance of different mechanisms of search for specific binding on DNA by DNA-binding proteins. We studied the effect of preferential bias to hop across the bridges in the intersegmental transfer and found that for \( 1 \leq R \leq 10 \), the mechanism II turns out to be most efficient. Whether this is the mechanism that proteins actually use in order to find the target sites can be verified only by doing controlled experiments.

We also suggest experiments that can be performed to test the efficiency of the various search processes. The value of \( \tau_{1D} \) can be taken as an input from standard known results. The value of \( \tau_{\text{mp}} \) and \( \tau_{\text{avg}} \) can be measured using \textit{Fluorescence Spectroscopy}. The experimentally obtained \( \eta \) can then be compared with the above mentioned results obtained using simulations to throw light on the possible mechanism that the protein uses to search for its target site.

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Appendix A

In this appendix, we analyze the FPT distributions obtained for all the mechanisms, quantitatively. We know that the \textit{Gamma} distribution (GD) is one of the most appropriate forms for modelling waiting time distributions and other similar phenomena. We fit all our FPT distributions (apart from M I) using a two parameter GD: \( \mathcal{F}(t) = b^a e^{-b(t+k)} / \Gamma (a) \), where \( \Gamma (a) \) is the gamma-function of \( a \), while \( a \) and \( b \) are parameters to be fitted using least squares regression. For Mechanism I, we fit the FPT distribution to \( \mathcal{F}(t) = b^a (t-k)^{a-1} e^{-b(t-k)} / \Gamma (a) \), where \( k \) is also a parameter to be fitted using least squares regression.

We observe that the data for the FPT distribution fits equally well to the difference of two exponentials. We fit the distributions to a four parameter function as follows: \( \mathcal{F}(t) = ce^{-dt} - fe^{-ht} \), where \( c, d, f \) and \( h \) are the parameters to be fitted using least squares regression. Both the GD and the difference of exponential fits to the FPT distribution of Mechanism III were poor, and hence not shown in the figure.

We have listed the fit parameters in the tables in Section VI.D

In Fig.8 we plot the \( \tau_{\text{mp}} \) and \( \tau_{\text{avg}} \) as functions of \( R \). We find \( \tau_{\text{mp}} = ae^{bR} \), where \( a \approx 108.343 \) and \( b \approx 0.014 \). On the other hand, \( \tau_{\text{avg}} = ce^{dR} + fe^{hR} \), where \( c \approx 550.342, d \approx 0.008, f \approx 2180.460 \) and \( h \approx -11.462 \).

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[39] In Mechanism II, for example, the probability of jumping from site A to site D (see Fig. 2) is $\frac{1}{2}$, whereas the probability of jumping from D to A is $\frac{1}{4}$. For mechanism III, the probability of detachment varies from site to site. The probability of jumping from any site to the 4 neighboring sites is $\frac{1}{4}$ each. Therefore, for sites A, B, and C it is $\frac{1}{4}$, whereas for site F, it is $\frac{1}{2}$. Also, for site D, it is 0.