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Electronic Supplementary Information (ESI)

to

Theoretical insights into the full description of DNA target search by subdiffusing proteins

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A. Solving the FFPE to obtain Survival probability, $\tilde{S}(r,\theta;s)$ and determining the surface-averaged FPTD, $\tilde{F}(r;s)$

We solve for an approximate solution of the survival probability for a DBP, $\tilde{S}(r,\theta;s)$, from the FFPE in Eq. (4) under the self-consistent approximation (SCA) used previously[1-2] for a similar system. We replace the mixed boundary condition in Eq. (5) with the in-homogeneous condition $D_\alpha\left(\partial_r\tilde{S}(r,\theta;s)\right)_{r=\rho} = Q\ \Theta(\varepsilon-\theta)$ where $\Theta(w)$ is the Heaviside step function and Q is the effective flux which needs to be determined by assuring the condition

$$D_\alpha \int_0^\varepsilon \left(\frac{\partial\tilde{S}(r,\theta;s)}{\partial r}\right)_{r=\rho} d\theta = \kappa \int_0^\varepsilon \tilde{S}(r=\rho,\theta;s)d\theta \qquad \text{(S.1)}$$

We will begin by finding the general solution of Eq. (4) written as

$$\tilde{S}(r,\theta;s) = \tilde{a}(r;s) + \sum_{n=0}^{\infty} c_n \tilde{b}_n(r;s)\cos(n\theta) \qquad \text{(S.2)}$$

where the first term is the solution of the non-homogeneous problem, the constants c_n need to be determined and $\tilde{b}_n(r;s)$ is the solution of the differential equation

$$r^2\tilde{b}_n''(r;s) + r\tilde{b}_n'(r;s) - r^2\left(\frac{n^2\pi^2}{L^2} + \frac{s^\alpha}{D_\alpha}\right)\tilde{b}_n(r;s) = 0 \qquad \text{(S.3)}$$

By applying the appropriate boundary conditions, we get the solution of Eq. (S.3) as a linear combination of modified Bessel functions of the first, $I_\nu(x)$, and the second kind, $K_\nu(x)$, as shown in Eq. (7) of the main text. The solution of the non-homogeneous problem is obtained through Dirichlet boundary condition at $r = \rho$ such that we get

$$\tilde{a}(r;s) = \frac{1}{s}\left[1 - \frac{b_0(r;s)}{b_0(\rho;s)}\right]. \qquad \text{(S.4)}$$

Following the method previously explained in detail for normally diffusing DBPs,[2] we find the effective flux Q and the constants c_n in terms of c_0, respectively. This independent constant c_0 is determined by using the condition described in Eq. (S.1) and eventually the expression for the survival probability, $\tilde{S}(r,\theta;s)$, is obtained. We choose to skip the details of our derivation as they can be readily followed from Ref. 2 as well and we write the final expressions of our quantities which are

$$Q = \frac{\pi D_\alpha}{\varepsilon\kappa}\left[\tilde{a}'(\rho;s) + c_0\, b_0'(\rho;s)\right] \qquad \text{(S.5)}$$

$$c_n = \frac{2Q\kappa}{\pi D_\alpha\, b_n'(\rho;s)} \frac{\sin(n\varepsilon)}{n} \qquad \text{(S.6)}$$

$$c_0 = \frac{1 - \tilde{\eta}(\rho;s)}{s\, b_0(\rho;s)}. \qquad \text{(S.7)}$$

The parameter $\tilde{\eta}(\rho;s)$ is defined in Eq. (8) of the main text. Finally, we arrive at the survival probability in the Laplace domain as

$$\tilde{S}(r,\theta;s) = \frac{1}{s}\left[1 - \frac{\tilde{\eta}(\rho;s)}{b_0(\rho;s)}\left\{b_0(r;s) + 2b_0'(\rho;s)\sum_{n=1}^{\infty}\frac{b_n(r;s)}{b_n'(\rho;s)}\frac{\sin(n\varepsilon)}{n\varepsilon}\cos(n\theta)\right\}\right]. \qquad \text{(S.8)}$$

From this expression of Survival probability, one can determine the FPTD, $\tilde{F}(r,\theta;s)$, which is described in Eq. (6) of the main text.

The surface-averaged FPTD, $\tilde{F}(r;s)$, represents the distribution for recognizing the target region for the first time provided the search of the DBP started from some fixed radial distance from the entire DNA molecule. This distribution is determined by integrating out the θ coordinate from Eq. (6),

$$\tilde{F}(r;s) = \frac{1}{\theta}\int_0^{\theta} \tilde{F}(r,\theta;s)\, d\theta$$

$$= \tilde{\eta}(\rho;s)\frac{\tilde{b}_0(r;s)}{\tilde{b}_0(\rho;s)} \quad \text{(S.9)}$$

Using Eq. (9), we may also write $\tilde{F}(r;s) = \tilde{F}(r;s)_{\varepsilon} + \tilde{\xi}(r;s)\frac{\tilde{b}_0'(\rho;s)}{\tilde{b}_0(\rho;s)}$. The most-probable time and the conditional MFPT in this case may be determined by using similar calculations as discussed in the main text.

If $r = \rho$, then $\tilde{F}(r = \rho;s) = \tilde{\eta}(\rho;s)$, i.e., the search of the subdiffusing DBP will begin from the surface of the DNA. Further, the surface-averaged FPTD can be useful in probing the 1D diffusion of the DBP while it searches for the target site along the DNA. This may be achieved by using the condition $R = r = \rho$ in the expression of $\tilde{F}(r;s)$. However, our results may not be suitable to study the movement of microtubule-associated protein complexes because the motion of motor-proteins is driven by certain directionality which is not the case for DBPs searching for their targets.

B. Numerical simulations to determine the FPTD

To ensure the accuracy of our analytical result of $\tilde{F}(r;s)_{\varepsilon}$ in Eq. (9) of the main text which is obtained under SCA (as detailed in the previous section), we have performed numerical simulations to solve to original FFPE for the FPTD $\tilde{F}(r,z;s)$. Here, we are not using the dimensionless notation for the z-coordinate. By using the substitution present in Eq. (6a) within Eq. (4), we arrive at

$$\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}\right)\tilde{F}(r,z;s) + \frac{\partial}{\partial z}\left(r\frac{\partial}{\partial z}\right)\tilde{F}(r,z;s) = r\frac{s^{\alpha}}{D_{\alpha}}\tilde{F}(r,z;s) \quad \text{(S.10)}$$

With the help of PDEtool in MATLAB, we were able to solve for $\tilde{F}(r,z;s)$ for appropriate boundary conditions using Finite Elements Method at various values of the Laplace variable

s.[2] We constructed a rectangular domain of dimensions $(\rho,R)\times(0,L)$ with reflective boundaries (Neumann boundary condition) applied everywhere except $(\rho)\times(0,\varepsilon)$ where lies the partially absorbing boundary condition which is

$$\tilde{F}(\rho,z;s) - \frac{D_\alpha}{\kappa}\left(\frac{\partial \tilde{F}(r,z;s)}{\partial r}\right)_{r=\rho} = 1; \qquad (0 < z < \varepsilon) \qquad \text{(S.11)}$$

To determine the radially dependent FPTDs, $\tilde{F}(r;s)_\varepsilon$, we first linearly interpolated the solution at a fixed radial distance and then performed numerical integration according to Eq. (9). Our results obtained through numerical calculations are in excellent agreement with the analytically determined FPTD, Eq. (9), within SCA (Fig. S1). An agreement within the Laplace space assures an agreement within the time space as well because both the quantities are uniquely associated through Laplace transforms. Thus, to avoid time-consuming simulation analysis in the time domain, we resort to solving the FFPE in the Laplace space along with other reasons discussed elsewhere.[2]

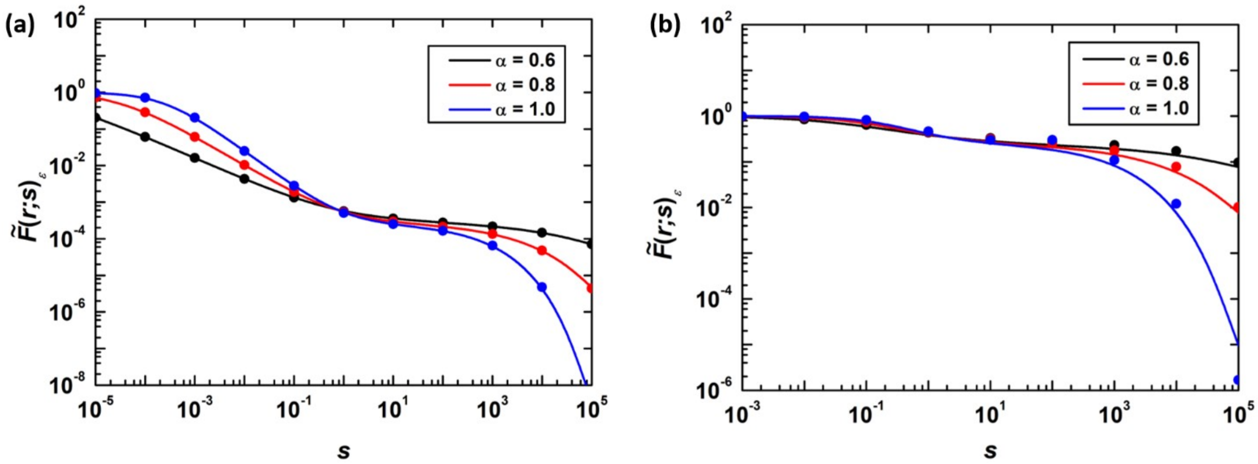

Fig. S1: The function $\tilde{F}(r;s)_\varepsilon$ (solid lines) defined in Eq. (9) of the main text is compared with the numerical solutions (filled circles), with respect to the Laplace variable s at different values of α depicting the degree of sub-diffusion of the DBP. Parameters chosen are: $R = 1\ \mu$m, $L = \pi\ \mu$m, $D_1 = 10\ \mu$m^2/s, $\rho = 2$ nm, $r = 0.1\ \mu$m and $\varepsilon = 0.2\ \mu$m $\equiv 0.2$. For (a), $\kappa = 1\ \mu$m/s and for (b), we assumed perfect reactions $\kappa = \infty$.

C. Short time asymptotic expression of FPTDs - Most probable time

The short-time asymptotic of $F(r;t)_\varepsilon$ may be obtained by applying the limit $s \to \infty$ in the Laplace space. By following the procedure detailed previously for normally diffusing DBP, we have arrived at general expressions that are valid for any type of subdiffusing particle.[2]

To find the short-time asymptote of $F(r;t)_\varepsilon$ using Eq. (9), we first need to determine $\tilde{\xi}(r;s\to\infty)$ to eventually obtain $\tilde{\eta}(\rho;s\to\infty)$. We begin by using the large-argument asymptotic expansion of $K_\nu(x\to\infty)$[3] and we find

$$\frac{\mathfrak{b}_n(r;s)}{\mathfrak{b}_n'(r;s)} \cong -\frac{K_0(rk_n)}{k_n K_1(\rho k_n)} \cong -\frac{e^{-k_n(r-\rho)}}{k_n}\left[\sqrt{\frac{\rho}{r}} - \frac{3r+\rho}{8rk_n\sqrt{r\rho}} + \ldots\right] \tag{S.12a}$$

$$\frac{\mathfrak{b}_0'(\rho;s)}{\mathfrak{b}_0(\rho;s)} \cong -k_0\left[1 + \frac{1}{2\rho k_0} - \frac{1}{8(\rho k_0)^2} + \ldots\right] \tag{S.12b}$$

Now, from the definition of $\tilde{\xi}(r;s)$ in Eq. (8b) and writing $1/k_n$ from Eq. (7b) as

$$\frac{1}{k_n} = \frac{1}{k_0}\left[1 - \frac{n^2\pi^2}{L^2 k_n(k_n+k_0)}\right] \tag{S.13}$$

we have,

$$\tilde{\xi}(r;s\to\infty) \cong 2\sum_{n=1}^{\infty}\left(\frac{\sin(n\varepsilon)}{n\varepsilon}\right)^2 \times \frac{e^{-k_0(r-\rho)}}{k_0}\left[\sqrt{\frac{\rho}{r}} - \frac{1}{k_n}\left(\frac{n^2\pi^2\sqrt{\rho/r}}{L^2(k_n+k_0)} + \frac{3r+\rho}{8r\sqrt{r\rho}}\right) + \ldots\right]. \tag{S.14}$$

To proceed, we will consider each term in Eq. (S.14) separately. Using the identity $\sum_{n=1}^{\infty} sin^2(n\varepsilon)/(n\varepsilon)^2 = (\pi-\varepsilon)/2\varepsilon$, the first term of Eq. (S.14) becomes

$$\tilde{\xi}(r;s\to\infty)^{(1)} \cong e^{-k_0(r-\rho)}\sqrt{\frac{\rho}{r}}\frac{(\pi-\varepsilon)}{k_0\varepsilon}. \tag{S.15}$$

The second term is simplified to

$$\tilde{\xi}(r;s\to\infty)^{(2)} \cong -\frac{2\pi^2}{k_0\varepsilon^2}e^{-k_0(r-\rho)}\sum_{n=1}^{\infty}\frac{sin^2(n\varepsilon)}{n^2\pi^2+2k_0^2L^2}. \tag{S.16}$$

Considering $z=\sqrt{2}k_0L$ and $x=\varepsilon/\pi$, we use the identity

$$\sum_{n=1}^{\infty}\frac{sin^2(nx)}{n^2\pi^2+z^2}=\frac{1-e^{-2xz}}{4z} \tag{S.17}$$

to eventually determine the second term of Eq. (S.14) which is

$$\tilde{\xi}(r;s\to\infty)^{(2)} \cong -\frac{\pi^2}{2\sqrt{2}\,k_0^2\varepsilon^2L}\sqrt{\frac{\rho}{r}}e^{-k_0(r-\rho)}\left(1-e^{-2\sqrt{2}\,k_0L}\right)$$

$$\simeq -\frac{\pi^2\sqrt{\rho/r}}{2\sqrt{2}\,k_0^2\varepsilon^2L}e^{-k_0(r-\rho)} \tag{S.18}$$

For the third term and other subsequent terms, we substitute $k_n \approx k_0$ as they are in higher orders of powers and they may even be neglected after the third term. Thus, after combining all the terms we finally obtain the function $\tilde{\xi}(r;s\to\infty)$ as

$$\tilde{\xi}(r;s\to\infty) \cong e^{-k_0(r-\rho)}\left[\sqrt{\frac{\rho}{r}}\frac{(\pi-\varepsilon)}{k_0\varepsilon}-\frac{1}{k_0^2}\left\{\frac{\pi^2\sqrt{\rho/r}}{2\sqrt{2}\,k_0^2\varepsilon^2L}+\frac{(3r+\rho)(\pi-\varepsilon)}{8r\varepsilon\sqrt{r\rho}}\right\}+\dots\right]. \tag{S.19}$$

Since we have $\tilde{\xi}(r;s\to\infty)$ now, we may obtain the function $\tilde{\eta}(\rho;s\to\infty)$ corresponding to perfect and imperfect reactions in the target search process after the subdiffusing DBP arrives at the target on the DNA. For the case of perfect reactions, i.e., $\kappa=\infty$, we have

$$\tilde{\eta}(\rho;s\to\infty) \cong \frac{\varepsilon}{\pi}+\frac{1}{2\sqrt{2}\,k_0L}+\frac{(\sqrt{2}\,L\varepsilon+\rho\pi)}{8L^2\varepsilon\rho k_0^2}+O\left(k_0^{-3}\right) \tag{S.20}$$

whereas, for the case of imperfect reactions, i.e., $\kappa<\infty$, we will have

$$\tilde{\eta}(\rho;s\to\infty) \cong \frac{\varepsilon\kappa}{D_\alpha\pi k_0}-\frac{\varepsilon\kappa}{D_\alpha\pi k_0}\left(\frac{\kappa}{D_\alpha}+\frac{1}{2\rho}\right)+O\left(k_0^{-3}\right). \tag{S.21}$$

Now, we are left with $\tilde{b}_0(r;s\to\infty)$ to determine the function $\tilde{F}(r;s\to\infty)$. From the asymptotic expansions of $K_\nu(x)$ and $I_\nu(x)$, we find

$$\tilde{b}_0(r;s\to\infty)\cong\frac{\cosh\left(k_0(R-r)\right)}{\sqrt{k_0^2 rR}}\left[1-\frac{(3r+R)}{8k_0 rR}\tanh\left(k_0(R-r)\right)\right]\cong\frac{\cosh\left(k_0(R-r)\right)}{\sqrt{k_0^2 rR}}. \quad \text{(S.22)}$$

Thus, we eventually obtain

$$\left(\frac{\tilde{b}_0(r;s)}{\tilde{b}_0(\rho;s)}\right)_{s\to\infty}\cong\sqrt{\frac{\rho}{r}}e^{-k_0(r-\rho)}. \quad \text{(S.23)}$$

Finally, after combining Eqs. (S.12), (S.20), (S.21) and (S.23), we were able to determine the short time FPTDs in the Laplace space for the target search process. In the case of perfect reactions, i.e., $\kappa = \infty$, we have

$$\tilde{F}(r;s\to\infty)_\varepsilon \simeq \sqrt{\frac{\rho}{r}}e^{-(r-\rho)\sqrt{s^\alpha/D_\alpha}}\left[1+\frac{(\pi-\varepsilon)(r-\rho)}{8\pi r\rho\sqrt{s^\alpha/D_\alpha}}+O\left(s^{-\alpha}\right)\right] \quad \text{(S.24)}$$

and in the case of imperfect reactions, i.e., $\kappa < \infty$, we will have

$$\tilde{F}(r;s\to\infty)_\varepsilon \simeq \kappa\sqrt{\frac{\rho}{rD_\alpha s^\alpha}}e^{-(r-\rho)\sqrt{s^\alpha/D_\alpha}}. \quad \text{(S.25)}$$

The inverse Laplace transform of the above equations (S.24)-(S.25) is obtained in terms of Wright functions[4] described by $W_{\lambda,\mu}(x)=\sum_{n=0}^{\infty}x^n/[n!\Gamma(\mu+\lambda n)]$ and are provided in Eq. (11) of the main text. To determine the most probable time, t_{mp}, we use the method of derivatives. The time derivative of Eq. (11b) after simplifications results in

$$W_{-\frac{\alpha}{2},\frac{\alpha}{2}-1}\left(-\frac{r-\rho}{\sqrt{D_\alpha t^\alpha}}\right)=0. \quad \text{(S.26)}$$

From the relation $W_{\lambda,\mu-1}(x)+(1-\mu)W_{\lambda,\mu-1}(x)=\lambda x W_{\lambda,\lambda+\mu}(x)$ known[5] and using the asymptotic expansion of the Wright functions,[6] one can obtain t_{mp} provided in Eq. (12) of the main text. The most-probable time increases with respect to the parameter α (Fig. S2(a)) and the initial distance of the DBP (Fig. S2(b)).

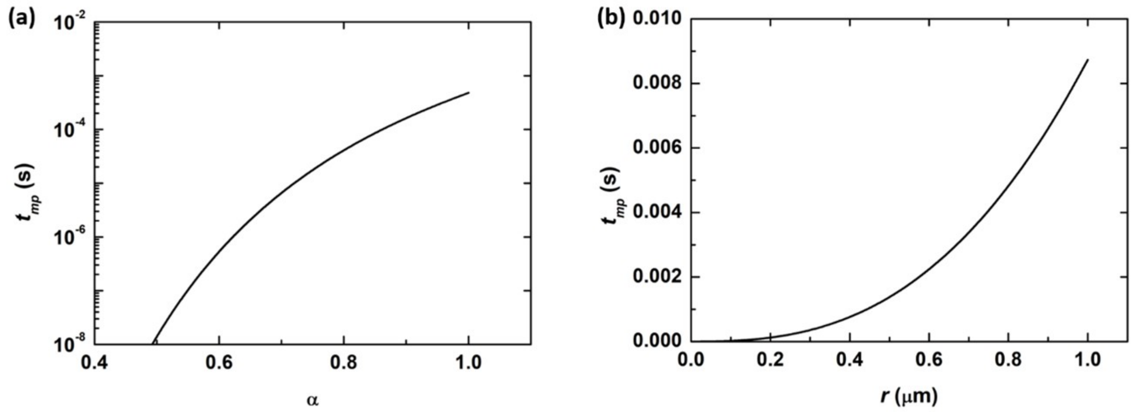

Fig. S2: The time t_{mp} in Eq. (12) with respect to (a) α and (b) the initial distance, r. Parameters used are: $D_1 = 10\ \mu$m²/s and $\rho = 0.2$ nm. For (a), $r = 0.1\ \mu$m and (b), $\alpha = 0.75$.

D. Large time asymptotic expression of FPTDs - Conditional mean time

Since the MFPT may be analytically determined using the expression

$$\tilde{S}(r;s=0)_\varepsilon = \left(\frac{1 - \tilde{F}(r;s)_\varepsilon}{s}\right)_{s=0}, \tag{S.27}$$

we obtain the large-time asymptotic of $\tilde{F}(r;s)_\varepsilon$ by applying the limit $s \to 0$. To begin with, from the definition of k_n in Eq. (7b), we may write the function $\tilde{\xi}(r;s\to 0) \cong \tilde{\xi}(r;s=0)$. Next, we use to small-argument asymptotic expansion of the modified Bessel functions[3] to obtain

$$\left(\frac{\tilde{b}_0(r;s)}{\tilde{b}_0(\rho;s)}\right)_{s\to 0} \simeq 1 - \frac{R^2 \ln(r/\rho)}{2D_\alpha} s^\alpha + O(s^{2\alpha}) \tag{S.28a}$$

$$\left(\frac{\tilde{b}_0'(\rho;s)}{\tilde{b}_0(\rho;s)}\right)_{s\to 0} \simeq -\frac{(R^2 - \rho^2)}{2\rho D_\alpha} s^\alpha + O(s^{2\alpha}). \tag{S.28b}$$

Using these approximations in Eq. (8), we find the long-time approximation for

$$\tilde{\eta}(\rho;s\to 0) \simeq \left[1 + \left\{\frac{D_\alpha \pi}{\kappa\varepsilon} + \tilde{\xi}(\rho;s=0)\right\}\frac{(R^2 - \rho^2)}{2\rho D_\alpha} s^\alpha\right]^{-1} \tag{S.29}$$

Finally, we may write the long-time expression of the FPTD $\tilde{F}(r;s)_\varepsilon$ in the Laplace space as

$$\tilde{F}(r;s\to 0)_\varepsilon \simeq \frac{1+(C-B)s^\alpha}{1+A\,s^\alpha} \qquad \text{(S.30)}$$

where, the constants A, B and C are defined in Eq. (15) of the main text.

Now, to obtain the MFPT for the case when the subdiffusing DBP ($\alpha < 1$) starts its search from a fixed *radial* distance away from the target, we use Eq. (S.27) to determine

$$MFPT = \tilde{S}(r;s=0)_\varepsilon \simeq \left(\frac{(A+B-C)s^{\alpha-1}}{1+As^\alpha}\right)_{s=0} = \infty.$$

It should also be noted that if $\alpha = 1$ for a normally diffusing DBP, the MFPT would have been a finite quantity MFPT($\alpha = 1$) = $\tilde{S}(r;s=0)_\varepsilon = A+B-C$. The divergence of the MFPT for a single subdiffusing DBP is the reason we resort to obtain the conditional MFPT, T_c, instead. The inverse Laplace transform of $\tilde{F}(r;s\to 0)_\varepsilon$ (which is provided in Eq. (14) of the main text) is performed using properties of Mittag-Leffler functions,[7-8] defined by $E_{p,q}(y) = \sum_{n=0}^{\infty} y^n/\Gamma(q+pn)$. The behaviour of T_c (Eq. (16) of the main text) with respect to different parameters is presented in Fig. (S3) and the corresponding discussions are in the main text.

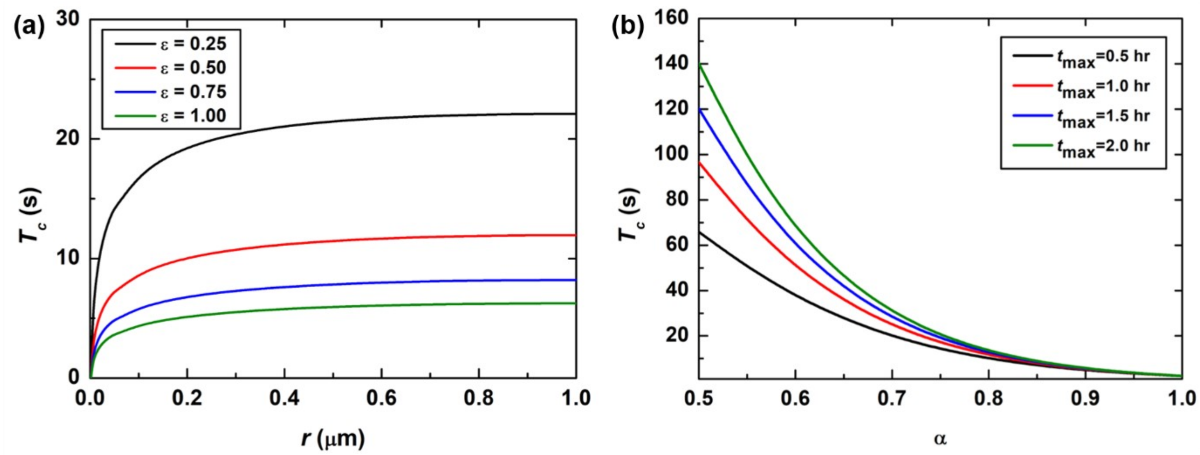

Fig. S3: The time T_c obtained via Eq. (16) represented as a function of (a) initial distance between the DBP and the target, r and (b) the anomaly exponent α. Other parameters chosen are: $R = 1\ \mu$m, $L = \pi\ \mu$m, $D_1 = 10\ \mu$m^2/s, $\kappa = \infty$ and $\rho = 2$ nm. For (a), $t_{max} = 3600$ s (1 hour) and $\alpha = 0.75$ while for (b), $\varepsilon = 0.25\ \mu$m $\equiv 0.25$ and $r = 0.1\ \mu$m.

E. Application of our theory to real systems

The typical dimensions of the nucleus of U2OS cells are 10 μm × 10 μm × 6 μm.[9] Suppose that a single P-TEFb protein is initially situated 0.25 μm away from the target site which is roughly about 1 μm in size. The apparent radius of the DNA is considered to be 2 nm.[10] Thus, according to our theoretical model, we will have R = 5 μm, L = 6 μm, r = 0.25 μm, ε = 1 μm and ρ = 2 nm. Additionally, we consider the target to be perfectly absorbing, i.e., $\kappa = \infty$ for convenience. Since, it is more appropriate to consider the target site in the middle of the DNA, we may as well halve the values of L and ε. Moreover, we need to consider the dimensionless form of the target size to use our results and thus, we will have $\varepsilon \equiv \pi\varepsilon/L = 0.52$. From Eq. (17), the anomaly exponent $\alpha = 0.61$ and $D_1 = 1.46\ \mu$m^2/s as discussed in the main text. We use all these parameters in Eq. (9) to determine the distance dependent FPTD, $\tilde{F}(r;s)_\varepsilon$, in the Laplace space. Numerical inversion of $\tilde{F}(r;s)_\varepsilon$ is performed using Gaver-Stehfest menthod[11] and the results are shown in Fig. 4 of the main text.

Using Eq. (12), we find that the most-probable times are $t_{mp}(\alpha = 0.61) = 3.54 \times 10^{-4}$ s and $t_{mp}(\alpha = 1) = 0.021$ s. The single particle tracking experiments were performed for about 45 minutes which means that the observation time becomes $t_{max} = 2700$ s and thus, by using Eq. (16) we find that the conditional MFPTs for these two situations are $T_c(\alpha = 0.61) = 897.14$ s $\simeq 15$ minutes and $T_c(\alpha = 1) = 231.42$ s $\simeq 4$ minutes. It should also be noted that the numerical value of the mean times are quite high because we have considered the target search of a single DBP in our system and for multiple particles searching for the same target, the time would be less.[12-13]

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