Chemical Physics 435 (2014) 14–20

Contents lists available at ScienceDirect

Chemical Physics

journal homepage: www.elsevier.com/locate/chemphys

Kinetics of target searching by means of two diffusion-like motions

Konstantin L. Ivanov *, Nikita N. Lukzen

[a] International Tomography Center SB RAS, Institutskaya Str. 3a, Novosibirsk 630090, Russia
[b] Novosibirsk State University, Pirogova Str. 2, Novosibirsk 630090, Russia

ARTICLE INFO

Article history:
Received 9 December 2013
In final form 4 March 2014
Available online 12 March 2014

Keywords:
Diffusion-controlled processes
Diffusional search
DNA repair

ABSTRACT

A theoretical approach to stochastic searching of a small target is developed, which can be applied, for instance, to searching for a damaged site on the DNA molecule by a DNA repair enzyme. It is assumed that the searching molecule moves along a chain of sites by means of stochastic jumps to the adjacent positions (one-dimensional 'sliding'); the second motion models diffusion in three dimensions. A general expression is obtained for the flux to the damaged site. A special case is analyzed where the second motion is treated as effective 1D diffusion; the effective searching time is estimated. It is shown that the faster second motion shortens the searching time. A more realistic case where the second kind of motion leads to jumps not only to the adjacent site is also treated: it is shown that the diffusional search is facilitated even further.

1. Introduction

Biological processes are frequently dealing with protein–nucleic acid interactions, notably, with specific binding of various enzymes to nucleic acids. Among them is DNA repair (i.e., removal of molecular lesions caused by metabolic activities and environmental factors), which is an important process for keeping the integrity and stability of the genome. Understanding the mechanism of searching for the particular binding site on the large DNA molecule is an intriguing problem. It is known that the search is much more efficient as compared to the simple prediction coming from the Smoluchowski theory [1]: there is experimental evidence (both in *in vitro* [2] and *in vivo* [3] studies) that the rate constant, k_s, exceeds the Smoluchowski-like one, $k_{Sm} = 4\pi RD$, by a few orders of magnitude. (Here R is the sum of the linear sizes of the damaged site and the enzyme and D is the mutual diffusion coefficient of the enzyme and DNA). To rationalize this unexpected result several theoretical models have been proposed, with the most well-known being the Berg–Winter–von Hippel (BWH) model [4,5], which suggests that first the enzyme binds to an arbitrary site on the DNA (non-specific binding) and searches for the damaged site in the course of subsequent stages of 1D and 3D diffusion. 1D diffusion proceeds by means of 'sliding' [2,6,7] of the enzyme along the DNA strand, the sliding increases the effective size of the target [8]. After a sliding stage the enzyme dissociates from the DNA and diffuses in three dimensions in the solution, then it binds again to the DNA molecule and the sequence is repeated until the enzyme finds its target and binds to it (specific binding) so that the DNA repair process starts. It is often argued that the combination of 1D and 3D diffusion facilitates the process and makes the time required for searching for the damaged site considerably shorter. This is because 'sliding' of a large enzyme molecule along the DNA is relatively slow [3,9–12]; thus, purely 1D diffusional motion makes the search inefficient. On the other hand, 1D diffusion increases the effective target size: in this way the combination of two diffusional motions reduces the searching time.

Previously, several models have been considered to describe the complex process of searching by 1D and 3D diffusional walks. These are the co-localization mechanism [13,14] (assuming that that proteins are produced near their binding sites on the DNA thereby reducing the number of searching cycles) and the correlation mechanism [15–18] (taking account of the correlations between 1D sliding and 3D diffusion). Hu et al. [19] have developed a theoretical approach, which take into account the role of DNA conformation by using an electrostatic analogy. Description of these theoretical results can be found, for instance, in a recent review by Kolomeisky [20]. Analytical solutions of the problem are usually difficult to obtain even assuming simplified geometry of DNA and protein. Solutions for realistic cases are probably impossible because the enzyme is not a spherical molecule, moreover, it can bind to DNA only in specific orientations; DNA is also a highly complex molecule having different conformations. One should note that fast searching for DNA damages can be sometimes

* Corresponding author at: International Tomography Center SB RAS, Institutskaya Str. 3a, Novosibirsk 630090, Russia. Tel.: +7 (383) 330 8868; fax: +7 (383) 333 1399.
E-mail address: ivanov@tomo.nsc.ru (K.L. Ivanov).

http://dx.doi.org/10.1016/j.chemphys.2014.03.001
0301-0104/

accounted for by an alternative mechanism (charge transport through the DNA for carrying out redox chemistry at a distance) [21,22]; however, here we will not consider this mechanism and focus on subsequent diffusional motions of two different types.

The aim of this work is developing a physically reasonable model of searching, which enables analytical solution for the searching time after non-specific binding of the enzyme to DNA. Although a lot has already been done in this field we will propose a model, which allows one obtaining relatively simple analytical expressions for the searching time and for the kinetics of searching for the damaged site. On one hand, we will try to make the model simple; on the other hand, we will need to take account of two types of stochastic motions. To tackle the problem analytically we will exploit the formalism of generating functions. We will find out whether the combination of 1D and 3D diffusion facilitates the search or does not and also discuss peculiarities of diffusion, which make the kinetics different from frequently assumed monoexponential function. Last but not least, our general formulas will not be limited to the specific problem of the DNA repair kinetics but will also be applicable to other cases of searching for different targets by two types of stochastic motions.

2. Methods

2.1. Theoretical model

Describing subsequent stages of 1D and 3D diffusion of the repair enzyme is generally a complex problem, which can be solved analytically only assuming specific models for the enzyme motion. Here we propose a new model, which enables analytical treatment of the problem and obtaining both the effective DNA repair time, i.e., the time required to find the damaged nucleotide, and the repair kinetics.

The situation treated here is presented in Fig. 1. Here we assume that the enzyme can move along the DNA strand by stochastic jumps to the nearest nucleotides, the jump rate is equal to w_1. Taking 3D diffusion into account is generally problematic; to minimize this problem we assume that 3D diffusion is a process of jumping along a parallel chain with the jump rate equal to w_2. Of course, such assumption does not consider (i) the peculiarities of 3D diffusion (which is non-redundant in contrast to redundant 1D diffusion) and (ii) the conformation of the DNA. Nonetheless, as will be shown, it can account for the effect of facilitating the 1D search, which becomes inefficient when the enzyme spends too long time on the DNA fragment as the number of sites (nucleotides) visited by the repair enzyme grows with time only as $\sqrt{t}$. In this case dissociation from the DNA with subsequent diffusion in space (being faster than 'sliding') and association to a new site facilitates the search, since more sites on the DNA can be visited in the unit time. Here we will thus assume that $w_2 \gg w_1$ (free diffusion in space is much faster than the sliding process);

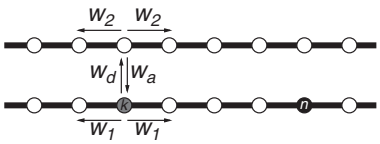

Fig. 1. Model of searching for a damaged site on the DNA molecule. The repair enzyme jumps along the DNA chain (1D sliding), which is an infinite chains of sites (nucleotides); the rate of jumps to the adjacent sites is equal to w_1. 3D diffusional motion is modeled by jumps along a parallel chain; the rate of such jumps to the adjacent sites is taken equal to w_2. Transitions between the two chains (dissociation and re-association) are occurring at rates w_d and w_a. The searching process starts at the k-th site of the first chain; the target site is the n-th site on the first chain: upon reaching this site irreversible specific binding immediately occurs.

dissociation and association will be modeled as transitions between the two chains with rates w_d and w_a, respectively. We will assume that both processes are slow even as compared to 1D 'sliding', in other words, the enzyme makes many stochastic jumps before it dissociates or re-associates. Thus, the following hierarchy of rates is assumed: $w_2 \gg w_1 \gg w_a, w_b$. This assumption is consistent with the current view on the DNA repair processes [3]. Motion along the two chains thus models 1D and 3D diffusion, dissociation and re-association events are taken into account by the transitions between the chains.

We also assume that each chain is infinite to ignore boundary effects. At $t = 0$ the enzyme is located on the k-th nucleotide, while the n-th nucleotide is damaged. When the enzyme reaches the damaged site, specific binding occurs immediately and irreversibly; thus the search is accomplished. In this model it is therefore sufficient to calculate the time of first arrival from the initially occupied site to the damaged site. Our model allows reasonable estimates for the searching time in the case where two different stochastic motions are present although the 3D motion is accounted for in a greatly simplified way. It is worth noting that replacing 3D diffusion by effectively 1D diffusion is also done in the correlation mechanism [16,20]. In principle, one can omit the second chain and introduce 3D diffusion by assuming that the enzyme can jump not only to the nearest site but to other sites as well (see Ref. [4] and Appendix therein). However, to do so it is required to calculate the specific distribution of rates of jumping to other sites. In our treatment the second stochastic process is incorporated in the model from the very beginning and is treated as effective 1D diffusion. As will be shown in the end of the paper, our method also allows one to consider jumps between arbitrary positions, i.e., to extend the treatment to a more realistic type of motion, which captures some properties of the 3D diffusion. We will obtain analytical results for one example of a specific probability distribution of the jump length.

It is worth noting that our model is bearing some similarity to the one proposed by Avetisov and coworkers [23] who treated conformational changes in frozen proteins with a hierarchy of the transition rates to describe dynamics of biomolecules on very different time scales. Cycles of 3D diffusion and 2D diffusion have also been treated in the problem of diffusional search for a small hole in a spherical cavity by Berezhkovskii and Barzykin (who developed a coarse-grained model for the search process) [24] and later by Rupprecht et al. (who obtained exact solution of the problem) [25,26].

2.2. General results for repair flux

To proceed further let us define the notations. Here we will introduce a set of values C_i, which are equal to the probability to find the enzyme on the i-th nucleotide at the first chain; C'_i is then the probability to find the enzyme on the i-th site at the second chain. It is more convenient to derive equations in the matrix-form, for this reason we will work with a set of vectors

$$\mathbf{C_i} = \begin{pmatrix} C_i \\ C'_i \end{pmatrix} \tag{1}$$

Kinetic behavior of the system is then described by the following set of equations for $\mathbf{C_i}$ written in the Laplace domain:

$$\begin{gathered}(s + 2\widehat{W} - \widehat{U})\tilde{\mathbf{C}}_i = \widehat{W}(\tilde{\mathbf{C}}_{i-1} + \tilde{\mathbf{C}}_{i+1}) - \delta_{in}\widehat{K}\tilde{\mathbf{C}}_n + \delta_{ik}\mathbf{f}_k, \\ \text{where } \widehat{W} = \begin{pmatrix} w_1 & 0 \\ 0 & w_2 \end{pmatrix}, \quad \widehat{U} = \begin{pmatrix} -w_d & w_a \\ w_d & -w_a \end{pmatrix}\end{gathered} \tag{2}$$

Hereafter s is the Laplace variable, tilde stands for the Laplace-transformed quantities; the matrices are defined by $\widehat{\cdot\cdot}$. In Eq. (2) the $\widehat{W}$-matrix stands for the stochastic jumps between the