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Reduction of dimensionality in a diffusion search process and kinetics of gene expression

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Abstract

In order to activate a gene in a DNA molecule a specific protein (transcription factor) has to bind to the promoter of the gene. We formulate and partially answer the following question: how much time does a transcription factor, which activates a given gene, need in order to find this gene inside the nucleus of a cell? The estimate based on the simplest model of diffusion gives a very long time of days. We discuss various mechanisms by which the time can be reduced to seconds, in particular, the reduction of dimensionality, in which diffusion takes place, from three-dimensional space to two-dimensional space. The potential needed to keep the diffusing particle in 2D (i.e, at the surface of size L^2 in a volume of size L^3) should scale as $U \sim k_B T \ln L$. For $aL = 1$ μm and a target size $a = 10$ Å we find $U = 8k_B T$, i.e., it is a potential strength of the order of the strength of ionic interactions in water.

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1. Introduction

The conversion of the genetic instruction in DNA into RNA and RNA into proteins is termed the gene expression [1]. DNA–RNA transcription occurs inside the nucleus of the cell, while RNA-protein translation occurs in the cytoplasm outside the nucleus. After the removal of introns (not coding pieces of the given gene) from RNA the

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mRNA (messenger RNA) is produced in the nucleus. It carries the information about the production of proteins from the nucleus into the cytoplasm. The production of proteins occurs in ribosomes, large ribonucleoprotein assemblies located in the cytoplasm. These molecular machines translate the nucleotide sequence of mRNA into the protein structure. The whole process DNA–RNA-protein is regulated by a specific protein (transcription factor). It must bind to the gene (in fact, it binds to the part of the promoter of the gene) in order to activate DNA–RNA transcription. Without the specific protein the DNA–RNA transcription process cannot take place and the genes are not expressed. In other words, the transcription factors regulate the gene expression. The protein must physically move from the cytoplasm into the nucleus of the cell and find its binding site in order to activate a given gene. It may be present inside the cytoplasm in the inactive form and the external signal may activate it. For example, the transcription factor may be released from the tight complex with other protein that otherwise holds it in the cytoplasm preventing it from entering the nucleus. The place where the specific transcription factor must attach is very small (of the order of 20 Å) while the size of the nucleus is as large as 10 μm. Based on this observation it is legitimate to ask the following question: *How much time does a transcription factor need in order to find the specific binding site inside the nucleus of the cell*?

Before we proceed we must specify the typical time scale with which we are going to compare our result. Since the biological systems act as a well synchronized assembly plant we think that the time needed to carry the information from the cytoplasm into the nucleus should be of the same order of magnitude as the time needed to produce a small protein in the ribosomes. The time needed to produce a small protein consisiting of 400 amino acids is about 30 s [2] and we assume that this is our time scale.

The second information needed to solve the problem is the size of the specific site and the size of the transcription factor. In fact, the whole transcription process requires many proteins assemblied on DNA, but usually only one is specific for a particular gene. As a model of the transcription factors we can take the TATA binding protein (TBP) consisting of 180 amino acids forming a compact structure [3] of size $32 \times 45 \times 60$ Å. This particular protein is the general transcription factor common to many living organisms [4,5] and taking part in every gene expression. We think that for the general estimate of the time for the specific protein we can use the data for this most conservative transcription factor. The TBP binds to the TATA box, a small part of the promoter of the gene, of size 20 Å. The TATA box is also common to many genes so we can use its size as the size of the model binding site.

In the paper we will concentrate on the diffusion processes since they are very common and effective in biological systems [6,7]. Therefore, we need to know what is the viscosity inside the nucleus or the diffusion constant for the transcription factor in the nucleus. In general, it would be helpful to know the entire organization of DNA and proteins inside the nucleus. Unfortunately, neither the spacial organization of the DNA and proteins in the nucleus nor the diffusion constants are known. Here we can only estimate the diffusion constant, D, inside the nucleus on the basis of measured diffusion constants inside the cytoplasm and/or the cellular membranes. In the cytoplasm

and membranes the diffusion constant is between 10^{-6} cm^2/s (for a small protein in the cytoplasm) and 10^{-7}–10^{-11} cm^2/s (for proteins and lipids in the membrane) depending on the size of proteins and structure of environment [8–11]. The two methods used for the determination of the diffusion constant are: the photobleaching recovery of green fluorescent protein (GFP) for the study of the diffusion in the cytoplasm and the tracking of nanometer-size gold colloidal particles attached to the lipids in the membrane with the video-enhanced microscopy. The latter technique is justified since the gold particles in solution diffuse 1000-fold faster than the fastest movement in the membrane. Since the nucleus is much denser than the cytoplasm we guess that the value of the diffusion constant inside the nucleus is much closer to the value of the diffusion constant inside the membrane, than to the one inside the cytoplasm. Here for the purpose of the estimate we take $D = 10^{-8}$ cm^2/s. The final remark concerns the steps of the process. First of all, the protein must find the nucleus inside the cell and next, the specific site inside the nucleus. Because the nucleus has a comparable size to the cell itself and the diffusion constant in the cytoplasm is (in our estimate) two orders of magnitude larger than that inside the nucleus the former process should be many orders of magnitude faster than the latter. Therefore, we can concentrate on the latter.

2. Simple diffusion

Assuming that the protein moves like a Brownian particle, the average time, t, needed to find the specific binding site of linear size, a, inside a nucleus of volume, V, is: $t \sim V/(aD)$, where D is the diffusion constant. Assuming that the nucleus is a sphere of radius $R \approx$ μm, $a \approx 20$ Å (e.g. TATA-box) and the diffusion constant for a small transcription factor (e.g. TBP [3]) is $D \approx 10^{-8}$ cm^2/s we find that $t \approx 240\,000$ s, i.e., almost three days for a single specific protein and a single specific site. The distribution of the times is exponential $P(\tau) \sim \exp(-\tau/t)$. The average time is definitely too long in comparison to our time scale of 30 s. We also have to remember that all biological molecules have a finite "lifetime", i.e., after a very well-defined period of time they are disintegrated by the enzymes. For example, the mRNA in bacteria is cut by the enzyme after 180 s of its existence [1]. The RNA polymerase (machine for DNA–RNA transcription) in the liver of rat has a "lifetime" of only 1 h [12].

There is a simple mechanism which can reduce the search time, namely N specific proteins of the same type can enter the nucleus and search for the site. The time taken to find the site should scale as $1/N$ assuming that the proteins search the space in the nucleus independently. The number of $N = 10\,000$ proteins is reasonable since the nuclear envelope can handle the traffic of up to million small proteins per 3 min [13,14]. Moreover, the nuclear pore complexes which regulate the transport of molecules across the membrane are large enough (90 Å in diameter) [13,14] to allow the free diffusion of the transcription factor across the membrane. As we see it, the process of blind search of the space by 10 000 searchers is reasonable, since the search time reduces in

this case to 24 s. Additionally, if we had n copies of the same gene on DNA the time would be further reduced by a factor of n.

We have performed the random walk simulations on the cubic lattice to get the rough estimate of the numerical prefactors in our formula. The walkers enter the cube
of size $L \times L \times L$ ($L = 10$ up to 100) via the side of a cube and the specific single lattice site ($n = 1$), searched by the walkers, is located in the middle of the cube (its precise location is not important). We find that the time needed to find the specific site is $t \approx 1.5 t_0 L^3$ ($t_0 = a^2/(6D)$ and $V = (aL)^3$). We have also performed numerical simulations for n specific sites ($n = 2$ up to 10) located far away from each other and verified that the law $t \approx 1.5 t_0 L^3/n$ holds, for all n and $L = 100$. Therefore, the final formula for the time needed to find a specific site on DNA is

$$t \approx \frac{V}{4aD}\frac{1}{N}\frac{1}{n} . \tag{1}$$

The prefactor actually depends on the size and shape of the volume where the search process takes place [7], i.e., for a spherical volume V and a spherical region of radius a one has [6] $t = V/(4\pi Da)$. This formula was known for a long time and was first derived by Smoluchowski in 1917 [15,16] in connection with diffusion-controlled (self-stirred) chemical reactions. In fact, Eq (1) is nothing else but the relation between the chemical reaction rate constant, K and diffusion constant, D for the diffusion-controlled reaction (i.e., $K \sim D$) derived by Smoluchowski.

We are aware that the transcription needs, in general, several transcription factors, nonetheless, the formula can be useful as a starting point for further generalizations. One can use this formula to estimate the number of specific proteins on the basis of time needed to activate or stop a gene expression, providing that this simple mechanism is valid. One of the simple examples is found in *E. coli* where the production of tryptophan can be stopped if it is present in the growth medium. The tryptophan binds to the specific repressor and activates it. The latter binds to the specific site on DNA and stops the production of tryptophan [17]. The tryptophan molecules are small so we can safely assume that the process of activation of repressor by tryptophan and the process of searching the space by the activated repressor are separated in time. Now measuring the time needed to stop the production of tryptophan (using e.g. a marker gene) we can estimate the number of repressor proteins in *E. coli* using Eq (1).

3. Two stage processes: reduction of dimensionality

3.1. 3D–1D reduction

The simple mechanism presented above is by no means the only one possible. Let us now consider the two-stage process. In the first step of the searching process a protein finds the DNA chain in time t_1 and in the next step it moves along the chain by diffusion and finds the specific binding site of size a in time t_2. The total time t should

be the larger one. The fact that we can split the searching time into two steps is due to the fact that between DNA and specific proteins exist the specific long-range attractive interactions acting on the distances of a few hundred Angstroms. Such long-range interactions have been measured between mica surfaces covered with DNA bases [18]. The DNA molecule is very long. Its total length, in the 5 μm nucleus, can easily exceed centimeters. The process of finding a strand of 1 cm size in the nucleus of size 5 μm should be very fast, at least 6 orders of magnitude faster than finding a TATA box of size 20 Å. Of course, it depends on the geometry of the chain, but here we based our rough estimate on the asymptotic formula for finding a line of length aL in the volume of size V. The time is given by $t_1 \sim V \ln L/(DLa)$. Now, the time needed to find the specific site on DNA for the molecule diffusing along the chain is $t_2 \sim (La)^2/D_0$, where D_0 is the new diffusion constant for the diffusion along the chain and a is the size of the target. Even assuming that D_0 is very large, i.e., $D_0 = 10^{-6}$ cm^2/s (like in the cytoplasm) we find that $t_2 \sim 10^6$ s, which is far too large. In fact we know that $D_0 = 10^{-9}$ cm^2/s, therefore the diffusion coefficient for 1D diffusion along the chain is orders of magnitude slower than the same coefficient for the 3D diffusion. Nonetheless, the linear diffusion along the DNA has been observed in vitro and has been shown to facilitate the formation of the protein–gene complex [19–22]. But it has also been shown that such linear diffusion is only restricted to rather short DNA fragments, i.e., the protein attaches to the DNA strand, moves along it and after covering a distance of approximately 400 bp (bp=base pairs=3.4 Å) detaches. Thus, it scans only a short fragment of DNA before the dissociation from the chain. What the protein gains in such a process is the correct orientation with respect to DNA which can enhance the reaction rate many folds. In a 3D diffusion finding the target does not mean that the reaction will take place since both substrates must have the correct orientation with respect to each other. Concluding: this two-stage searching process of first finding a DNA chain and next moving along this chain is reasonable, providing that the motion along the chain is directed and only partially diffusive or the protein diffusing along the chain scans only short DNA fragments before dissociation from the chain.

3.2. 3D–3D and 3D–2D reduction

Another two-stage mechanism is similar to the previous one, but more probable. We know that DNA in the nucleus appears in compact structures called the chromosomes. The two-stage process can look as follows: first, the protein finds the given chromosome in time t_1 and next, it finds the specific site inside a smaller volume (that of the chromosome) in time t_2. The first time is $t_1 \sim V/RD$ where R is the linear size of the chromosome and the second time is $t_2 \sim V_0/aD$ where a is the size of the binding site and V_0 is the volume of the chromosome. Even in this case we would need more than one specific protein if we wanted to have the time $t = \max(t_1, t_2)$ of the order of 30 s.

Another possibility discussed long time ago by Adam and Delbrück [6] is the 3D–2D reduction in a search process. First, the protein finds the surface (say, of the chromosome) on which the active gene is located and then by the diffusion along

the surface it finds its target. Let us estimate the gain factor. On the surface of linear dimension La the average time needed to find a gene of size a is

$$t \sim \frac{(La)^2}{D} \ln (L) \ , \tag{2}$$

and the time of finding the surface in a volume of size aL is $(aL)^2/D$. Therefore, the time needed to find a specific site is $L/\ln(L)$ times faster by this mechanism than by the mechanism of simple 3D diffusion. In this way, we can speed up the process by 3–4 orders of magnitude. *However, we still do not know how strong the potential between the protein and the surface should be in order to capture it and during the search process keep it in* 2*D*. Here, we will give an estimate of its strength. Such a problem, to our knowledge, has not been studied so far.

Let us consider a volume of linear size aL and the surface inside the volume also of linear size aL. Now, let us denote the probability of attaching a particle to the surface by p_{in} and the probability of detaching it from the surface by p_{out}.

From the Boltzmann distribution we have

$$\frac{p_{\text{out}}}{p_{\text{in}}} = \exp\left(-\frac{U}{k_B T}\right), \tag{3}$$

where U is the potential binding the particle to the surface. Now, we can ask as to how small the p_{out} should be in order to make the 3D–2D reduction. The number of times the particle leaves the surface during time t is $N_{\text{out}} = t * p_{\text{out}}$. Since the particle stays at the surface for a period of time of the order of $t \sim L^2$ it is clear that if $p_{\text{out}} < 1/L^2$ the particle will practically not leave the surface during the search time. Therefore, $p_{\text{out}} = 1/L^2$ sets the lower limit for the probability for which 3D–2D reduction is possible. Now, we will try to find the upper limit for p_{out}. Once the particle leaves the surface it has a probability of $1/L$ to move at a distance L from the surface. Since from the distance L it will take L^2 time steps to move back to the surface the average time which the particle spends in the volume before getting back to the surface is $L^2 * 1/L = L$. Let us state the criterion for the 3D–2D reduction of dimensionality, namely, if the time spent outside the surface t_{out} has the same scaling form (with L) as the time spent on the surface t_{in} during the search process, then in the limit $L \to \infty$ we can say that we have achieved the 3D–2D reduction of dimensionality. We observe the following:

$$t_{\text{out}} = N_{\text{out}} L \tag{4}$$

and

$$t_{\text{in}} = L^2 \ln(L) \, , \tag{5}$$

where both quantities are given in dimensionless units. For t_{in} we have just chosen the time needed to find a target as if the diffusion was in 2D. By comparing Eqs. (4) and (5) and observing that $N_{\text{out}} = t_{\text{in}} * p_{\text{out}}$ we find that

$$p_{\text{out}} = \frac{1}{L} \, . \tag{6}$$

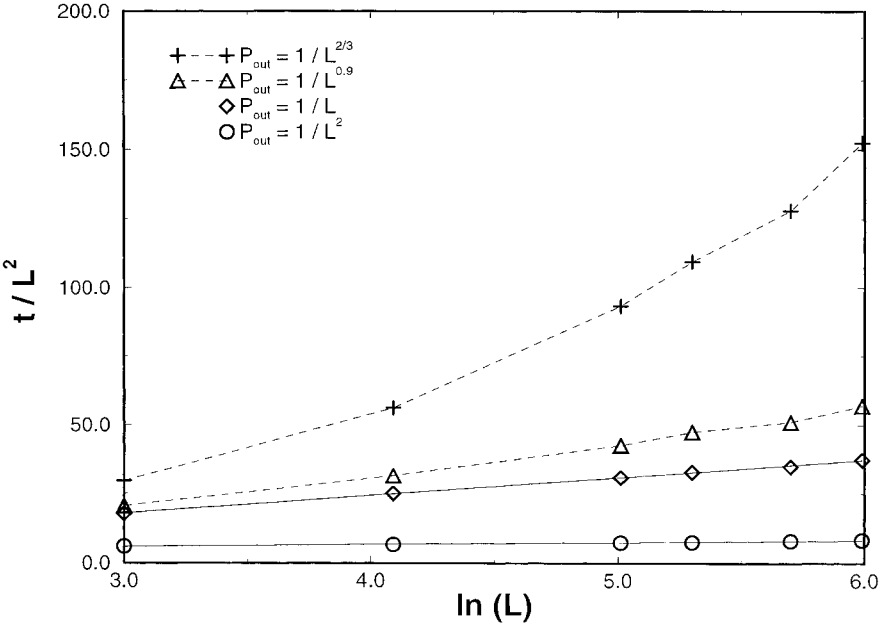

Fig. 1. The average time (in units of a^2/D), for a diffusing particle with diffusion constant D, needed to find a target of size a located on the surface of size $(aL)^2$ in a volume of size $(aL)^3$ (computer simulations on a cubic latttice). The probability of leaving the surface is $p_{\text{out}} = 1/L^k$, $k = 2$ (circles), $k = 1$ (triangles), $k = 0.9$ (diamond) and $k = \frac{2}{3}$ (crosses). For $k = 2, 1$ we verify that the scaling $t \sim L^2 \ln L$ holds as for the diffusion in 2D while for $k = \frac{2}{3}, 0.9$ we observe deviations from this scaling. Solid lines are linear fits to the data points, while dashed lines have been added as guide-lines.

This is the upper value of the probability, p_{out} for which 3D–2D reduction of dimensionality is possible. Now the potential U follows from Eq. (3):

$$U \sim k_B T \ln(L)\,. \tag{7}$$

We still need a prefactor in the equation which cannot be found without the detailed numerical simulations. In order to do so we have performed a numerical simulation of a random walk on a cubic lattice with the reflecting boundary conditions at the sides of the cube of linear size L with L ranging from 10 up to 1000. The surface of size L^2 is located in the middle of the cube. The probability p_{in} is $\frac{1}{6}$ as in the volume and the probability $p_{\text{out}} = 1/L^k$ where $k = \frac{2}{3}, 0.9, 1, \frac{3}{2}, 2$. The averages were taken over 10 000 up to 30 000 independent runs. First of all, we have verified the scaling for the search time. In Fig. 1 we show the average search time divided by L^2 as a function of $\ln L$, for $k = 2, 1, \frac{2}{3}, 0.9$. We see straight lines for $k = 2$ and 1 and deviations from the straight line for $k = \frac{2}{3}$ and 0.9. It is the first verification that the upper limit for $p_{\text{out}} = 1/L^k$ is given by $k = 1$. For any $k < 1$ the 3D–2D reduction is not achieved in the limit of $L \to \infty$. In Fig. 2 we plot the number of times the molecule leaves the surface during the search process confirming the scaling $N_{\text{out}} = t_{\text{in}} * p_{\text{out}}$. In Fig. 3 we show the plot of t_{out}/L^2 as a function of $\ln L$ confirming that for $k = 1$, $t_{\text{in}} \sim t_{\text{out}}$ as

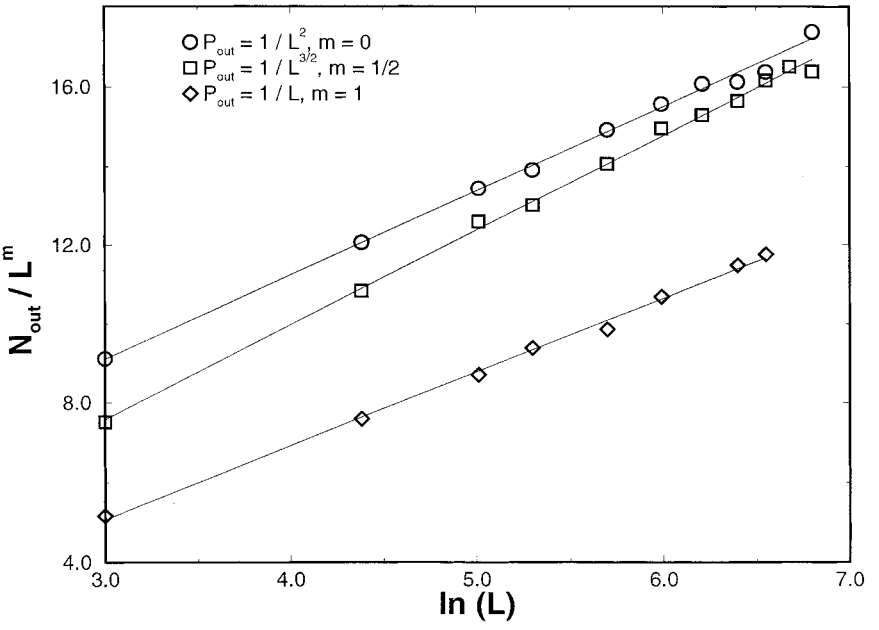

Fig. 2. The average number of times a particle leaves the surface during the search process (see also the legend of Fig. 1). In this way, we have verified the relation $N_{\text{out}} = t_{\text{in}} * p_{\text{out}}$, where t_{in} is the time spent on the surface and $p_{\text{out}} = 1/L^k$ is the probability of leaving the surface. Here $k = 2$ (circles), $k = 3/2$ (squares) and $k = 1$ (triangles). Solid lines are linear fits to the data.

far as the scaling is concerned. For $k > 1$, $t_{\text{in}}/t_{\text{out}} \to \infty$ and for $k < 1$, $t_{\text{in}}/t_{\text{out}} \to 0$ in the limit of $L \to \infty$. In Fig. 4 we show the plot of $t_{\text{in}}/t_{\text{out}}$ for $k = 0.9$ and 1. It is clear that for $k = 0.9$ the aforementioned ratio decreases rapidly. Please note that for $p_{\text{out}} = 1/L$ the particle stays off the surface almost an order of magnitude longer than the time which it spends on the surface. For comparison, we show on Fig. 5 the same ratio $(t_{\text{in}}/t_{\text{out}})$ for $k = 2$ and $\frac{3}{2}$. For practical reasons, $k = \frac{3}{2}$ should be chosen in order to have the time spent at the surface comparable to the time spent out of the surface. Concluding: in order to achieve the 3D–2D reduction of dimensionality in large systems of linear size L we need a sufficiently strong potential which scales with L as $\ln L$. Practically, the potential needed to make the 3D–2D reduction effective is

$$U = k_B T \ln\left(\frac{L^{3/2}}{6}\right) , \tag{8}$$

where the coefficient $\frac{1}{6}$ comes from p_{in} in Eq. (3). For $aL = 1\,\mu\text{m}$ and $a = 10$ Å we have

$$U \approx 8 k_B T . \tag{9}$$

The strength of the potential is comparable to the strength of the ionic interactions in water.

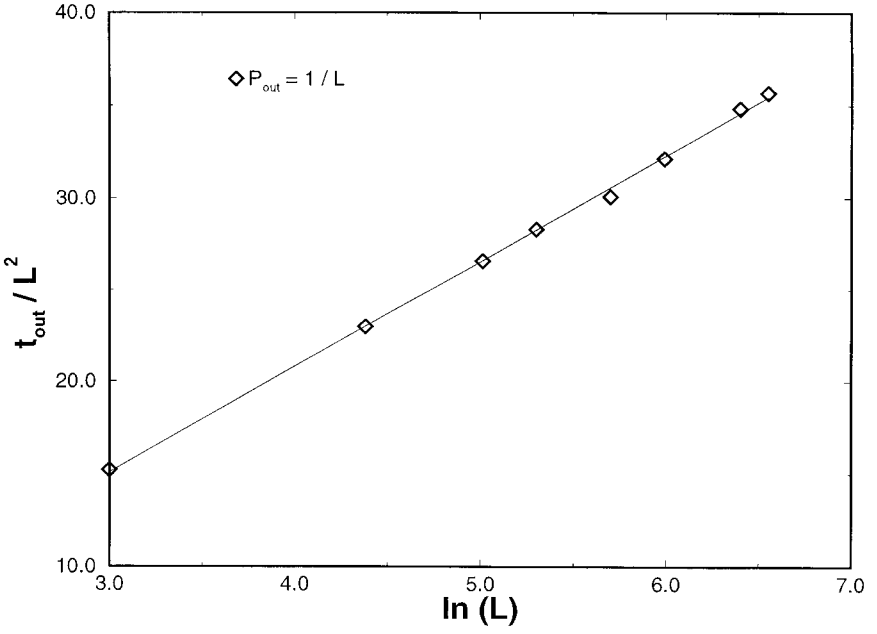

Fig. 3. The average time spent outside the surface for $p_{\text{out}} = 1/L$. We find that $t_{\text{out}} \sim L^2 \ln L$ (see also the legend of Fig. 1).

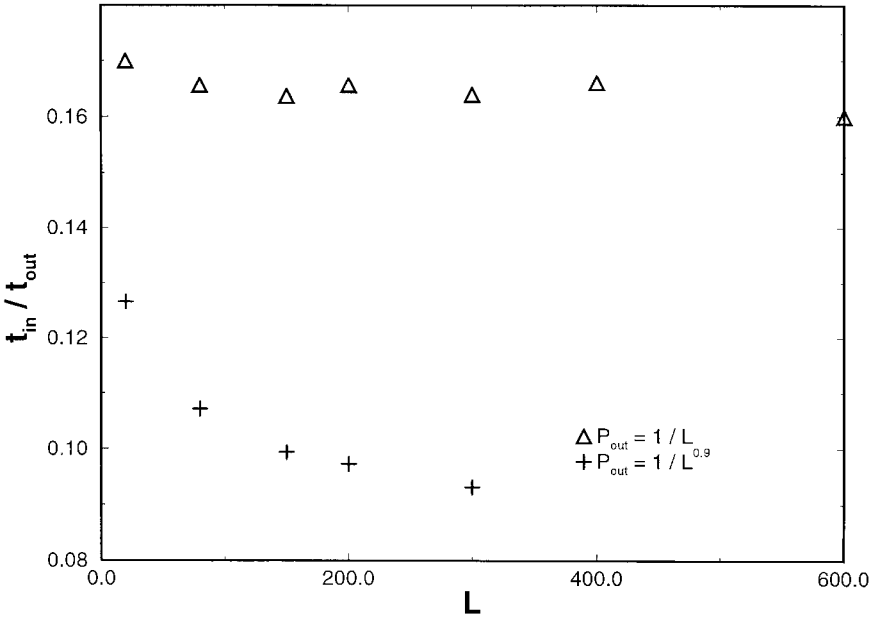

Fig. 4. The ratio of the time spent on the surface t_{in} to the time spent outside the surface t_{out} for $p_{\text{out}} = 1/L^k$ for $k = 1$ (triangles) and $k = 0.9$ (crosses).

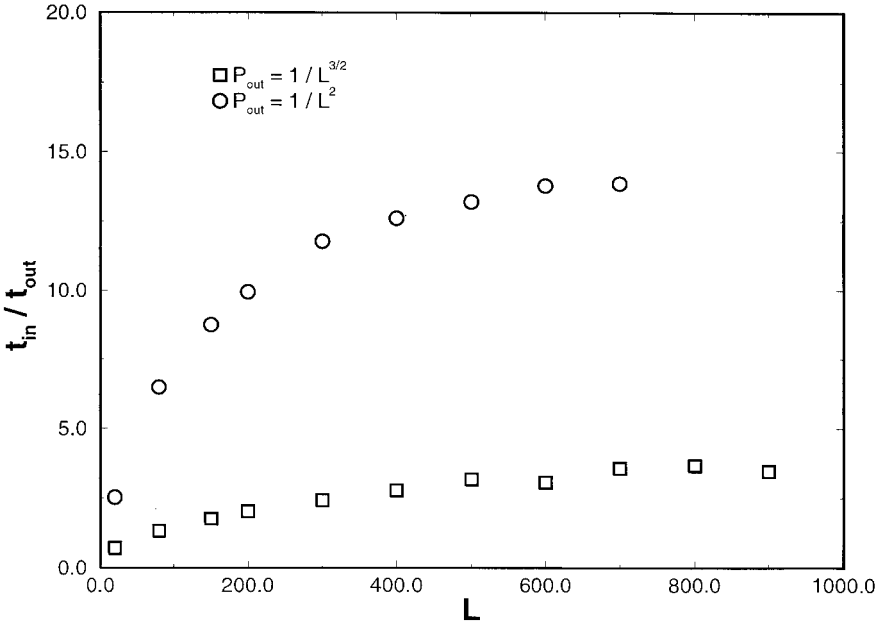

Fig. 5. The same legend as in Fig. 4. $k = 2$ (circles) and $k = 3/2$ (squares).

4. Front propagation

Finally, let us consider the cascade diffusion process which although least probable from the biological point of view is quite interesting from the point of view of physics. Let us consider N inactive proteins inside the volume V and assume that the proteins can bind to a specific site of size a only when they are activated. The active protein can activate another protein if it hits it. Now, one active protein enters the volume and moves in space by the Brownian motion with the diffusion coefficient D. As it moves it hits other molecules and activates them, which in turn activate other molecules. All the active molecules search the space in order to find the binding site of size a. The number of activated proteins grows as $R^3 \sim t^3$ (in 3D) and the boundary of the region occupied by the active proteins should move as a front with constant velocity, ω of the order of $D\rho^{1/3}$, where $\rho = N/V$ is the average density of the proteins. One can see the analogy of this problem with the population growth problem represented as the solution of the diffusion equation with the growth term $m(\rho - m)$ where $m(t)$ is the density number of activated molecules [23,24]. The size of the volume, where the density of activated proteins approaches the constant density ρ grows with the constant speed, ω defined above. The time needed to activate all the specific proteins in the nucleus is given by the size of the nucleus, $V^{1/3}$, divided by this velocity, ω. Thus, for the cascade diffusion process we find the activation time in the following form:

$$t \sim \frac{V^{2/3}}{DN^{1/3}} \,. \tag{10}$$

If we take $N = 10\,000$ and the volume $4/3\pi R^3$ with $R = 5$ μm we obtain $t \sim 5$ seconds, which is comparable to the search time given by Eq. (1). Now, the time for finding the site is the maximum of the activation time given by Eq. (9) and the search time given by Eq. (1).

5. Discussion

We hope that the fast development of monitoring techniques (e.g. for green fluorescent protein [25–27]) will soon provide us with quantitative time relations for gene regulation in the cell. We think that nature combines various mechanisms in order to reduce the search time: the number of proteins N is large, the 3D–2D reduction is used and in the final stage of the formation of a protein–gene complex the 2D–1D reduction appears.

The architecture of the cell has an influence on the search time. Unfortunately, although some recent measurements revealed that DNA in the dense medium can form many ordered structures its full structure inside the nucleus is not known [28,29]. This is not surprising, since even the structure of the cytoplasm is still not very well known and new experiments show that the matter inside the cell is far better organized than usually expected [30–32]. For example, the inner membrane structures in the cytoplasm [30], e.g. the endoplasmatic reticulum has the topology and geometry of periodic surfaces [33–35]. The nucleus of the cell and the membrane of the cell are "hard-wired" by protein fibers [31,32]. A hard pull on the cell membrane results in an elastic response in the nucleus of the cell [32]. The diffusion certainly depends on the architecture of the nucleus as it depends on the cytoskeletal geometry in the cytoplasm [36] and the structure of the cytoplasm [37,38]. We believe that the combination of the study of the structure of the cell and the time relations inside the cell will lead to new discoveries in biology and physics of living matter.

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