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On the scattering of DNA replication completion times

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Stochasticity of Eukaryotes' DNA replication should not lead to large fluctuations of replication times which could result in mitotic catastrophes. Fundamental problem that cells face is how to be ensured that entire genome is replicated on time. We develop analytic approach of calculating DNA replication times, that being simplified and approximate, leads, nevertheless, to results practically coincident with those which have been obtained by some sophisticated methods. In the framework of that model we consider replication times' scattering and discuss the influence of repair stopping on kinetics of DNA replication. Our main explicit formulae for DNA replication time $t_r \propto \sqrt{\ln N}$ (N is the total number of DNA base pairs) is of general character and explains basic features of DNA replication kinetics.

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The dream of every cell is to become two cells [1]. This dream is realized by the process of cell division, in which a cell duplicates its contents in order to provide sufficient materials for both daughter cells. Before every cell division, DNA replication must be carried out. In Eukaryotes, the replication starts in multiple origins being activated in diverse time and space points during S phase, when DNA replication proceeds [2]. DNA synthesis occurs in two opposite directions on replication forks and terminates when two converging forks meet. Complete genome replication in Eukaryotic cells should come to end in a definite time [3, 4]. Loss of the only origin or stopping a single fork may result in that DNA does not succeed to replicate before mitosis, making inviable daughter cells.

In the course of lengthy genome replication, numerous potential origins arise stochastically [5]. Nevertheless, that stochasticity does not lead to large fluctuations of replication times which could, otherwise, result in frequent mitotic catastrophes. This means that, despite the random character of arising and activating origins, duration of S phase has solid timetable. That is the essence of the so-called random-completion paradox: stochasticity leads to the exponential distribution of interorigin gaps, whereby the probability of large gaps (and, thus, unduly long replication times) is too high [6, 7].

To solve the random completion problem two distinct models have been proposed [4]:

1) the model of regular spacings [8] with origins being positioned at regular (not random) intervals. The lack of this model is that accidental failure of just one or two out of consecutive origins could be lethal;

2) the origin redundancy model [3, 9] with randomly spaced origins being much more abundant than actual activated replication centers whose number increases as S phase progresses to allow rapid completion of unreplicated gaps.

Though experiments [10] favor the second model, much needs to be done for developing quantitative description of the replication process. For this purpose the formal *analogy between DNA replication and one-dimensional crystal growth* could be employed [11]. In this model, the replication process is defined by two base parameters – the replication fork velocity u (assumed to be constant through S phase), and the time-dependent rate $I(t)$ of origin activation assumed to be spatially homogeneous.

In the framework of that model, a temporal profile $I(t)$ extracted from the data occurred to be growing through S phase [12]. A formal study based on the above-mentioned analogy demonstrates that initiating all origins at the beginning of S phase leads to a broad completion time distribution, whereas a growing dependency $I(t)$ narrows this distribution [12]. Therefore, both experimental and theoretical work support the origin redundancy model with a non-constant $I(t)$ (though the molecular mechanism that underlies the observed changes in $I(t)$ remained unknown).

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A fundamental control problem that cells face is how to be ensured that every last part of the genome is replicated on time [3]. To answer this question, ideas of condensed-matter physics have been used in [13], where stochastic Kolmogorov model [14] has been employed to describe the kinetics of replication. In that solidification model, the kinetics results from three simultaneous processes: (i) nucleation of solid domains, (ii) growth of domains, and (iii) domain coalescence, which occurs when two expanding domains merge. In the simplest form of the model, solid domains nucleate anywhere in the liquid, with equal probability for all locations.

These features of Kolmogorov model can be adapted to DNA replication: (i) DNA replication starts at multiple activated origins, where replication forks are created, (ii) DNA synthesis propagates bidirectionally from each activated origin, and (iii) DNA synthesis stops when two replication forks meet. For cells to achieve an acceptable distribution of replication completion times, the initiation rate $I(t)$ should increase during replication [13], in agreement with extracted values of $I(t)$ from experimental data.

Though being new and perspective, the analytical study [13] of replication kinetics is rather complicated. Here we present some simple approach which seems to be more transparent and intuitive, and delivers some simple expressions for scattering replication times.

In [15] another problem has been considered – how do defects of replication slow the duplication process and, thereby, result in increasing replication times. However, they could not obtain analytic expressions for the replication kinetics and completion times, and the analysis has been based on the *numerical* solution of kinetic equations. We will show that Kolmogorov model (appropriately generalized) allows to obtain some simple analytic relations in that case, as well.

In the present paper, we analyze replication kinetics of DNA basing on the Kolmogorov approach [14]. Replication begins around randomly arising special centers (origins) after their activation (firing). The process is analogous to the melt crystallization under decreasing temperature, when solid state nuclei arise randomly in the bulk, grow gradually, and eventually forms a complete solid state due to coalescence.

Kolmogorov model includes two physical parameters: the time-varying rate $I(t)$ of generating new phase nuclei (in our case, the rate of arising activated centers of replication – origins) and constant velocity u of those nuclei growth (in our case, the movement velocity of the boundary between the replicated and non-replicated DNA parts). Below, for brevity we call non-replicated DNA part as phase 0, while the replicated one – as the phase 1.

The Kolmogorov result for the disappearing phase 0 is

$$q_0(t) = \exp\left[-2u\int\limits_0^t I(\xi)\xi d\xi\right], \qquad (1)$$

wherefrom it follows that the fraction $q_1(t) = 1 - q_0(t)$ of the new phase varies by the law

$$q_1(t) = 1 - \exp\left[-2u\int\limits_0^t I(\xi)\xi d\xi\right]. \qquad (2)$$

If the rate of generating active replication centers is constant ($I(t) = \alpha_0$, we will call such a source as α-source), then

$$q_1(t) = 1 - \exp[-t^2/\tau_0^2], \qquad (3)$$

where $\tau_0 = (u\alpha_0)^{-1/2}$.

One of the relevant experimental results is shown in the inset of Fig. 1 where the dynamics of genome repli-

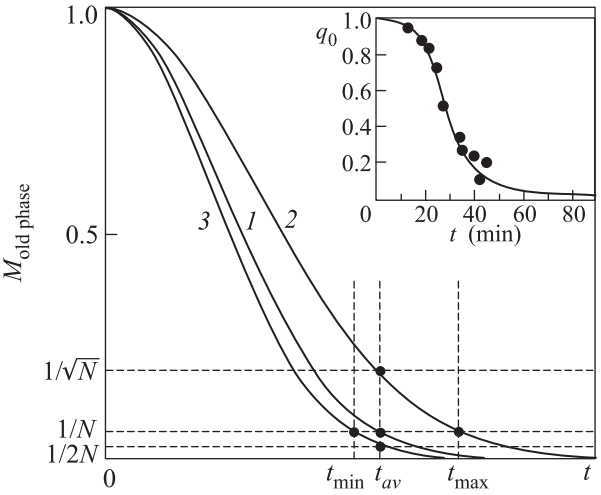

Fig. 1. Average (*1*), slow (*2*), and fast (*3*) replication kinetics for non-replicated DNA fraction $q_0(t)$. In the inset – experimental dependence $q_0(t)$ (points) and the theoretical curve calculated with Eq. (3)

cation in the baker's yeast *Saccharomyces cerevisiae* is presented [16]. Points are experimental data, the solid curve is calculated one, corresponding to $\tau_0 \approx 30$ min.

Formally, the phase transition finishes at the moment when the fraction $q_1(t)$ of new phase turns to be unit. From this viewpoint, the phase transition in the infinite medium is never ending process because the fraction $q_0 = 1 - q_1$ of the old phase never becomes equal to unit exactly (see Fig. 1). In the finite system consisting of a large but finite number $N \gg 1$ of molecules (in

our case, base pairs) the transition (replication) is completed at the moment when the fraction of old phase turns out to be less than $1/N$, that corresponds to one non-replicated DNA base pair only (curve *1* in Fig. 1). That condition defines the replication time

$$t^* = \tau_0\sqrt{\ln N}. \tag{4}$$

However, due to stochasticity of the process that time fluctuates from one cell to another, so Eq. (4) could be considered as definition of some average ("standard") value of time required for the total replication. One could estimate typical scattering of replication completion times from following reasons. Due to fluctuations, relaxation dependencies of the type (3) are not identical for different cells, and near entering $q_1(t)$ to the plateau (where $1 - q_1 \ll 1$) they disperse by the value on the order of mean-square deviation $1/\sqrt{N}$. As the formal reason of that scattering one could consider variations of the effective values of the parameter τ_0.

As it has been mentioned, the typical replication time is defined by the relation $q_1(t^*) = 1/N$, or (cf. (3))

$$\exp(-t^{*2}/\tau_0^2) = 1/N. \tag{5}$$

Another replication curve, displaced due to the fluctuation shift $\tau_0 \to \tau$, goes beneath (curve *2* in Fig. 1), and for it

$$\exp(-t^{*2}/\tau^2) = 1/\sqrt{N}. \tag{6}$$

That curve corresponds to later completion of replication at the time moment $t_{\max} > t^*$, defined by the condition

$$\exp(-{t_{\max}}^2/\tau^2) = 1/N. \tag{7}$$

From (5)–(7), it follows

$$t_{\max} = \sqrt{2}t^*, \tag{8}$$

i.e., upward scattering of replication times reaches $\Delta t \approx \approx t_{\max} - t^* = (\sqrt{2} - 1)t^* \approx 0.4t^*$. That is provided by twofold fluctuation decrease of the parameter τ_0 ($\tau_0 \to \tau = \tau_0/2$), associated with the process stochasticity and possible random variations of the generation rate α_0 and replication velocity u. For different organisms, replication times t^* vary over a wide range from a few minutes to several days. E.g., for Xenopus cell embryos experiments give $u \approx 10^{-6}\,\mathrm{cm/s}$ and $\alpha_0 \approx 1\,\mathrm{cm^{-1}{\cdot}s^{-1}}$, that corresponds to $t^* \approx 20$ min in agreement with experimentally known value of $t^* \approx 40$ min.

All those conclusions are based on the ansatz: mean-square fluctuation of base number, replicated upto to the moment t^*, is on the order of $1/\sqrt{N}$ (see Eq. (6)). To substantiate that estimate, let us replace (6) by the more general relation

$$\exp(-t^{*2}/\tau^2) = 1/N + \delta N/\sqrt{N} \tag{9}$$

with, for the moment, non-defined fluctuation δN. From Eqs. (5), (7), and (9) we could find the relationship between the fluctuation δN and the corresponding replication time $T \equiv t_{\max}/\tau_0$:

$$\delta N = N\exp(-\ln^2 N/T^2 - 1). \tag{10}$$

Now we could calculate the distribution function $f(T)$ of replication times providing the distribution function $\Phi(\delta N)$ of fluctuations is known. Let us take as a trial the Gaussian $\Phi(\delta N) = (\sqrt{2\pi}\sigma)^{-1}\exp[-(\delta N)^2/2\sigma^2]$ with the unknown dispersion σ. Then

$$f(T) = \Phi(\delta N)(\partial\,\delta N/\partial T) = \frac{2N\ln^2 N}{\sqrt{2\pi}\sigma T^3} \times \\ \times \exp\left[-\frac{\ln^2 N}{T^2} - \frac{(Ne^{-\ln^2 N/T^2} - 1)^2}{2\sigma^2}\right]. \tag{11}$$

We need to define now what is the dispersion σ which provides the distribution function $f(T)$ being similar to that obtained by *computer* modelling (see, for example, [13]). Direct comparing shows that the distribution (11) is similar to the modelled one at $\sigma = (0.5{-}0.25)\sqrt{N}$ (for $N = 10^6$). Analogous results have been obtained with some other trial distribution functions $\Phi(\delta N)$. That confirms our foregone suggestion of the N-fluctuation value.

Thus, in the case considered one should expect 40-percent upword scattering of replication times (in relation to the average time t^*). That is unacceptably wide scattering preventing the normal passage of the cell division process. Evidently, live cell use somewhat different scenario which provides lesser scattering of replication times. To realize such a scenario, it could use an unsteady rate law $I(t)$ of origin generation.

Suppose that some portion of active origins arises instantaneously at the replication start time, and other are added gradually in the course of that process by a power temporal law:

$$I(t) = \beta_0\delta(t) + I_k t^k. \tag{12}$$

Here β_0 [1/cm] and I_k [$1/(\mathrm{cm{\cdot}s}^k)$] are, correspondingly, potencies of the delta-like origin source (it will be called β-source), and gradual source (which we will name I_k-source). Above-considered situation $I(t) = \alpha_0$ corresponds to the set of parameters $k = 0$, $\beta_0 = 0$, $I_k = \alpha_0$. Substituting (12) in (2), one finds

$$q_1(t) = 1 - \exp\left[-2u\left(\beta_0 t + I_k\frac{t^{k+2}}{k+2}\right)\right]. \tag{13}$$

(In [4], there is evidence of decreasing part of $I_k(t)$ at the end of S phase. That influences the replication

time slightly and is not important in the context of our model.)

Numbers of origins generated during the replication time t_{av} by each of the mentioned sources equal, accordingly, β_0 and $I_k t_{av}^{k+1}/(k+1)$. Our goal is not only to estimate the relative scattering of replication times for various scenarios of generating origins but also to compare absolute values of those times. This comparison makes sense in that case only if both sources (delta-like and gradual) produce in common during the replication time t_{av} the same total number ($\alpha_0 t^*$) of origins as the single α-source above-considered, that is if

$$\beta_0 + I_k \frac{t_{av}^{k+1}}{k+1} = \alpha_0 t^*. \tag{14}$$

Then, calculating the average replication time t_{av} following the same receipt as has been used above (i.e., by taking $q_1(t_{av}) = 1 - 1/N$), one finds

$$t_{av} = \frac{1}{2}\, t^* \left(\frac{k+2}{k+1}\right) \frac{t^*}{t^* + (\beta_0/\alpha_0)/(k+1)}. \tag{15}$$

At $\beta_0 = 0$, $k = 0$ Eq. (14) leads, as could be expected, to the previous result: $t_{av} = t^*$. In all other cases $t_{av} < t^*$. For instance, $t_{av} = t^*/2$ at $I_k = 0$, when according to (14), $\beta_0 = \alpha_0 t^*$.

Thus, the replication scenario with constant rate of origin generation turns out to be the most slow (under the condition of equality of origin numbers generated during the replication process).

As for the scattering of replication times, in the case of a single β-source of origins Eq. (13) gives

$$q_1(t) = 1 - \exp\left(-2t^* t/\tau_0^2\right), \tag{16}$$

and that scattering (determined to the same recept, see (5)–(7)) turns out to be even greater than for the only α-source: $\Delta t = t_{av}$. Hence, one could expect smaller scattering of replication times in the case of gradually growing I_k-source only. So, we consider the case when such a source is the only one and from (13) it follows

$$q_1(t) = 1 - \exp\left[-2uI_k \frac{t^{k+2}}{k+2}\right]. \tag{17}$$

Once again, using the above-considered receipt of estimating the upward scattering of replication times, one finds $t_{\max}/t_{av} = 2^{1/(k+2)}$, or

$$\Delta t \equiv t_{\max} - t_{av} = [2^{1/(k+2)} - 1] t_{av}. \tag{18}$$

At $k = 0$ we return to the previous result (8). However, with increasing k scattering diminishes and amounts, for instance, $\sim 26\,\%$ for $k = 1$ and $\sim 19\,\%$ for $k = 2$ (against 40-percent scattering at $k = 0$).

Up to now the question was to estimate upward scattering of replication time with respect to the average time t^* (for α-source) or t_{av} (for β- and I_k-sources). As for the possibility of shortening replication time (relatively to the average one), it is rather limited. In fact, with accelerated replication values $q_0(t^*) \equiv 1 - q_1(t^*)$ (for α-source) or $q_0(t_{av})$ (for β- and I_k-sources) could range in the interval from 0 to $1/N$ only, whose boundaries correspond either to replication completion or to a single non-replicated base-pair. Conditionally, the border between those two states is in the middle of the indicated interval, when $q_0 = 1/2N$. Thus, to estimate the possible shortened replication time $t_{\min}$, for example, in the case of I_k-source (see Eq. (17)), we have the following set of equations

$$\exp\left(-2At_{av}^{k+2}\right) = 1/N \tag{19}$$

(here $A = 2uI_k$),

$$\exp\left(-2A'' t_{av}^{k+2}\right) = 1/2N, \tag{20}$$

$$\exp\left(-2A'' t_{\min}^{k+2}\right) = 1/N, \tag{21}$$

the first of which corresponds to the average replication process (17), the second one – to the relaxation curve displaced due to fluctuation change $A \to A''$, and the third one corresponds to the curve for earlier completion of the replication phase transition at the moment $t_{\min}$ (curve *3* in Fig. 1). From (19)–(21), it follows

$$t_{\min} \approx t_{av} \left(1 - \frac{1}{k+2} \frac{\ln 2}{\ln N}\right), \tag{22}$$

i.e., the replication time shrinkage amounts $\Delta t \approx t_{av} - t_{\min} = t_{av} \ln 2/[(k+2)\ln N]$. It provides by small fluctuation increase of the parameter A ($A \to A'' = A(1 + \ln 2/\ln N)$), associated with the process stochasticity and random variations of parameters u and I_k. (Notice, that the formulae (22) is valid for β-source and α-source if one set $k = -1$ or 0, correspondingly.)

With increasing k, the scatter $(t_{av} - t_{\min})/t_{av} \approx \ln 2/[(k+2)\ln N]$ goes down and amounts, for instance, $\sim 2.5\,\%$ for $k = 0$, $\sim 1.7\,\%$ for $k = 1$, and $\sim 1.25\,\%$ for $k = 2$. In any case, the amount of possible random replication shortage is much less (on the order value) than its possible random elongation. This also means that voluntary choice of the boundary value $q_0 = 1/(2N)$ does not influences $t_{\min} \approx t_{av}$ significantly. For example, with $q_0 = 1/(10N)$ the difference $t_{av} - t_{\min}$ would be by three times higher only, and reach $\sim 3\,\%$ (at $k = 2$) instead of $\sim 1\,\%$.

In the course of DNA replication, some base pairing faults happen. In bacteria, that occurs once in every

10.000 nucleotides, to which the mean concentration of mismatch centers of about $n \sim 10^3\,\mathrm{cm}^{-1}$ corresponds. A considerable part of those faults is corrected by DNA-polymerase that, naturally, results in a stoppage of the replication process [17, 18]. If improperly inserted nucleotide is not able to form the hydrogen bond with a complementary base, polymerase suspends the replication process for some time $\Delta\tau$, which is necessary for the wanted nucleotide to click into place.

Such a process (with breaks in random sites) could be also considered in the framework of Kolmogorov model and leads to the following result for the temporal dependency of the old phase fraction, for the case of origin α-source [19]:

$$q_0(t) = e^{-2t/\Delta\tau}\left(1 + \frac{Bt}{\Delta\tau}\right)^{2/B-2}, \qquad (23)$$

where $B = \alpha_0\Delta\tau/n$. That relation is valid at high density of stoppage centers ($n \gg (\alpha_0/u)^{1/2}$) and long stoppage time ($\Delta\tau \gg 1/nu$). In that case, the replication process slows down essentially and resulting from Eq. (23) relation $q_0(t^*) = 1/N$, which defines the average replication time t_{av}, could be written in the form

$$\frac{t_{av}}{\Delta\tau} \approx \sqrt{\frac{\ln N}{B}}. \qquad (24)$$

At the same moment $t = t_{av}$, in another replication process which is delayed due to fluctuation decreasing $B \to B'$, the non-replicated DNA fraction is yet high enough and amounts $q_0(t_{av}) = 1/\sqrt{N}$. By analogy with (24), that condition could be written in the form

$$\frac{t_{av}}{\Delta\tau} \approx \sqrt{\frac{\ln N}{2B'}}. \qquad (25)$$

This replication process finishes later, at the moment $t_{\max} > t_{av}$ being defined by the condition $q_0(t_{\max}) = 1/N$, or

$$\frac{t_{\max}}{\Delta\tau} \approx \sqrt{\frac{\ln N}{B'}}. \qquad (26)$$

Eqs. (24)–(26) are identical to previous relations (5)–(7). Therefrom, it follows $B' = B/2$ and

$$t_{av} = \left(\frac{n\ln N}{\alpha_0}\Delta\tau\right)^{1/2}, \quad t_{\max} \approx \sqrt{2}t_{av}. \qquad (27)$$

Thus, repair delay of the replication does not change the relative increasing $(t_{\max} - t_{av})/t_{av}$ of replication time (cf. (8)).

Similarly, employing the idea of estimating the possible shortage of replication time leading to Eqs. (19)–(21), in the considered case we obtain $B''/B = 1 + \ln 2/\ln N$ and

$$t_{\min} \approx t_{av}\left(1 - \frac{\ln 2}{2\ln N}\right), \qquad (28)$$

that is analogous to the result (22) at $k = 0$ (α-source). So, the repair slowing of the replication process, though lengthens the replication time, but remains possible relative scattering $(t_{av} - t_{\min})/t_{av}$ of replication times as before.

The method used in [19] could be easily extended for the case of delta-like origin β-source. In that case,

$$q_0(t) \approx \exp\left(-\frac{t}{\Delta\tau + 1/2\beta_0\bar{u}}\right), \quad \bar{u} = \frac{u}{1 + nu\Delta\tau}. \qquad (29)$$

At $\Delta\tau = 0$, Eq. (29) goes into canonical formulae (13) (for $I_k = 0$). At finite, but small, stoppage time ($\Delta\tau \ll \ll 1/nu$) it differs from (13) by renormalization ($u \to \bar{u}$) of the mean replication front velocity only, which originates due to the fact that the mean distance between defects $1/n$ is covered in a total time composed of the free movement time $1/nu$ between them and the stoppage time $\Delta\tau$. But if the stoppage time is long, then the mean replication velocity $\bar{u} = 1/n\Delta\tau$ is defined, basically, by delays at defects.

However, it is easy to verify that in any case the kinetic dependency (29) leads to the previous relative scattering of replication times which could vary in the diapason from $t_{av}(1 - \ln 2/\ln N)$ up to $2t_{av}$. So, the conclusion remains valid, that the least scattering of replication times takes place for gradually growing origin source (I_k-source with $k \geqslant 2$).

To conclude we first present the set of results in compact graphical and tabular forms. Table show average, maximum and minimum replication times for different rates of origins' firing, including the case of the repair stoppage.

Estimated relative scattering $(t_{\max} - t_{\min})/t_{av}$ of replication times for different scenarios of origin activation is shown (○) in Fig. 2 (the value $k = -1$ corresponds formally to the origin β-source). In the same figure, are presented data (■) which has been found on the basis of the distribution function of replication times for *Xenopus embryos*, obtained in [13] (at the level 0.25 % to the right and the left from the average value). Our results agree with results of that paper. It is seen that the least scattering is realized for scenarios with growing origin source ($I(t) \propto t^k$, $k = 1, 2$). That scattering is by 2–5 times less than for scenarios with constant and delta-like $I(t)$ functions, correspondingly. This conclusion agrees with results of numerical calculations [20], as well. In

DNA replication – completion times

Rate of origin firing, $I(t)$	Average, maximum and minimum completion times, t_{av}, $t_{\max}$, $t_{\min}$ $(\tau_0 = (u\alpha_0)^{-1/2})$	Time scatter, $\frac{t_{\max}-t_{\min}}{t_{av}}$
$I(t) = \alpha_0$	$t_{av} = \tau_0\sqrt{\ln N}$, $t_{\max} = \sqrt{2}t_{av}$, $t_{\min} = t_{av}(1 - \ln 2/2\ln N)$	$\sqrt{2}-1$
$I(t) = \beta\delta(t)$	$t_{av} = \frac{1}{2}\tau_0\sqrt{\ln N}$, $t_{\max} = 2t_{av}$, $t_{\min} = t_{av}(1 - \ln 2/\ln N)$	2
$I(t) = I_k t^k$	$t_{av} = \frac{k+2}{2(k+1)}\tau_0\sqrt{\ln N}$, $t_{\max} = 2^{\frac{1}{k+2}}t_{av}$, $t_{\min} = t_{av}\left[1 - \frac{\ln 2}{(k+2)\ln N}\right]$	$2^{1/(k+2)}-1$
$I(t) = \alpha_0$ + stopping	$t_{av} = \left(\frac{n\ln N}{\alpha_0}\Delta\tau\right)^{1/2}$, $t_{\max} = \sqrt{2}t_{av}$, $t_{\min} = t_{av}(1 - \ln 2/2\ln N)$	$\sqrt{2}-1$

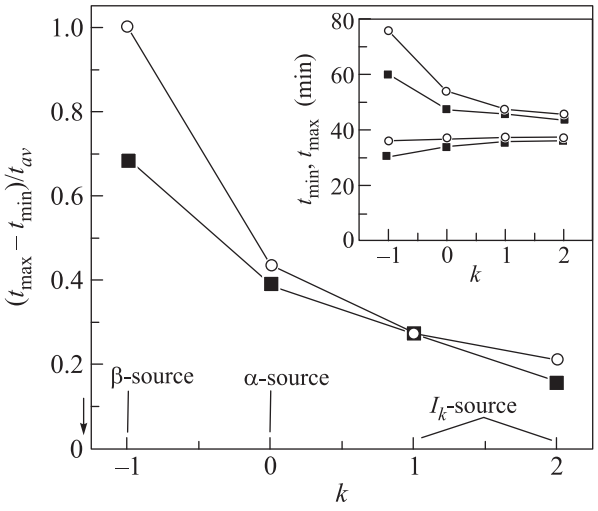

Fig. 2. Relative scattering $(t_{\max} - t_{\min})/t_{av}$ of replication times for different scenarios of origin activation; in the insert – replication times $t_{\min}$ and $t_{\max}$ (○ – the present work, ■ – according to results [13])

the insert of Fig. 2, replication times $t_{\min}$ and $t_{\max}$, determined with receipt of this paper with $t_{av} = 38$ min and calculated in [13], are also shown and compared separately. Again, they are close to each other.

Notice, that Kolmogorov model is valid for multiple origin firing when the effective number n_{orig} of origins per unit length (the density of origins) is large: $n_{\text{orig}} \gtrsim (\alpha_0/u)^{1/2}$. With $\alpha_0 \sim 1\,\text{cm}^{-1}\cdot\text{s}^{-1}$, $u \sim 10^{-6}\,\text{cm/s}$, that leads to $n_{\text{orig}} \gtrsim 10^3$ cm^{-1} (for, say, human genom of the length on the order of 100 cm, the total number of origins should be higher than 10^5). At the rate α_0 given, generating that density of active origins takes time $\tau_{\text{orig}} = n_{\text{orig}}/\alpha_0 \sim 10$ min, that is much shorter than the whole replication time of about 5 h. That means that Kolmogorov model answers the purpose to describe the replication process.

From results obtained it follows that completion times are always depends not on the number N of DNA base pairs, but on $\sqrt{\ln N}$:

$$t_{av} \approx \tau_0\sqrt{\ln N}. \qquad (30)$$

This is very weak dependency. That explains the moderate scatter of completion times for DNAs with strongly different N numbers from ∼0.5 h for, say, *Xenopus* (with $N = N_1 \sim 10^6$) up to ∼ 5–10 hours for human DNA (with $N = N_2 \sim 10^9$). Here, $N_2/N_1 \sim 1000$, and if t_{av} would be proportional to N one should expect 1000-fold increasing of replication time. However, $\ln N_2/\ln N_1 \approx 1.2$ and such a small scatter of replication times is really associated with increasing rate α_0 and/or velocity u. In fact, velocities u and rates α_0 for two mentioned DNAs differ, correspondingly, by ∼5 and ∼10 times for the example given, and that could really provide the ∼10-fold difference of replication times (because $\tau_0 = (\alpha_0 u)^{-1/2} \approx 7$).

Thus, our approach, though being simplified and approximate, leads to the results practically coincident with those which have been obtained by some sophisticated methods in [13, 20]. In addition, we have discussed the influence of the repair stopping on the kinetics of DNA replication and scattering of replication times. Our main explicit formulae $t_r \propto \sqrt{\ln N}$ for the replication time t_r is of general character and explains basic features of DNA kinetics.

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