On a chain of fragmentation equations for duplication-mutation dynamics in DNA sequences

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Recent studies have revealed that for the majority of species the length distributions of duplicated sequences in natural DNA follow a power-law tail. We study duplication-mutation models for processes in natural DNA sequences and the length distributions of exact matches computed from both synthetic and natural sequences. Here we present a hierarchy of equations for various number of exact matches for these models. The reduction of these equations to one equation for pairs of exact repeats is found. Quantitative correspondence of solutions of the equation to simulations is demonstrated.

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In recent years a series of duplication-mutation models related to processes occurring in natural DNA sequences have been reported [1-3]. The motivation for introducing these models was earlier empirical observations on length distributions [4] of identical repeats in natural DNA sequences [7, 8]. In part it was observed that when computing the length distributions within single chromosomes or whole genome sequences these distributions tended to exhibit power-law tails with the exponent close to \(-3\) [9]. These observations naturally drew attention to potential mechanisms accounting for them.

The first step in this direction was done in [1] where empirical computational models based on duplications were suggested. The duplications in the models for a synthetic chromosome as well as in the models that it was followed by were thought of as random events of copying and pasting a part of the chromosome. Each such event resulted in the appearance of a pair of identical sequences which then underwent further destruction by new duplication events and eventually disappeared but as the source of duplications generated new pairs at each time unit some balance in the number of duplicates might be expected. It was demonstrated that the model of random duplications generates length distributions of exact matches or maxmers [10] with power-law tails; it was also demonstrated that the slope of these tails with the exponent \(-3\) can be obtained in the model by varying a parameter of the source of duplications. When referring to the source of duplications, we imply a random mechanism of copying and pasting regions of a chromosome; it is characterized by several parameters, e.g., by the length of the region for copying-pasting which is chosen in accordance with some probability distribution.

The models independent of the source but incorporating additional mechanisms for generating exact repeats in the sequences were represented in [2, 3]. Two basic mechanisms utilized in the models, duplication as in [1] and point mutation, represent those in natural chromosomes. It was demonstrated that the length distributions [4] of repetitive sequences simulated by the models correspond to those observed in natural chromosomes and that the form of those distributions also was close to algebraic with exponents of typically around \(-3\). Thus the models in question were able to reproduce these exponents and even the amplitudes of the distributions were fitted [3] but unlike [1], the structure of the duplication source did not influence the exponents of length distributions reproduced by those models.

The distinctive feature observed for the length distributions in [2] was the algebraic behavior for a broad range of parameters, while [3] demonstrated that when mutations occurred as often as duplications (simplistically speaking), the algebraic behavior disappeared; this point is discussed in more detail in [3]. In this paper we suggest dynamic equations reproducing both the exponent and the amplitude of the length distribution for pairs of exact matches and demonstrate their relation and difference to the previous models. Our calculations also demonstrate that the stationary equation that we derived, reproducing the amplitude and the exponent for length distributions of pairs of exact repeats can be represented as a (infinite) sum of equations for different types of exact repeats which we discuss below.

A detailed explanation of the duplication-mutation models which we are interested in can be found, e.g., in [1, 3] but we summarize them here for convenience and thus, the paper can be read independently of [3].

We consider a synthetic chromosome represented as a string of \(L\) bases chosen from a finite alphabet; in natural genomes the alphabet typically consists of four bases A, G, C, and T. The distance between bases is a length scale denoted by \(a\); for natural genomes it is close to 1. The fundamental sequence feature that we study is the set of repeated sequences within the chromosome, counted in an algorithm-independent way. The work [3] focused on ‘supermaximal repeats’ (or ‘super maxmers’): sequence duplications, neither copy of which is contained within any longer sequence duplication in the chromo-
some \cite{[1][11]}. However for the purposes of this work we do not use the computation of supermaximal repeats; instead, we use \textit{mummer}\cite{[12]} to search for exact repeats in long sequences. Mummer searches for maximal repeats or \textit{maxmers}\cite{[10]} which are akin to supermaxmers\cite{[13]} in the sense that are based on some maximality condition, but observations show that the output of these computations is noticeably different if we compare the length distributions obtained in the models \cite{[2]} and \cite{[3]}. Our aim here is the model capable to reproduce the simulated length distributions obtained in the models \cite{[2]} and \cite{[3]}. Our aim here is the model capable to reproduce the simulated length distributions obtained with \textit{mummer}. In the discussion below it is always implied that \textit{mummer} is used with the option -maxmatch which according to the \textit{mummer} manual produces computations of exact matches ‘regardless of their uniqueness’\cite{[14]}.

Within our models a subsequence of length \(m\) is chosen randomly within the chromosome according to a predetermined source distribution \(P(m)\) and is substituted for a sequence of length \(m\) at another randomly chosen position in the chromosome. As in \cite{[1]}, duplicates are realized not as fragments but as substrings within a single chromosomal polymer \cite{[3]}.

Let the number of pairs of duplicates of the length \(m\) at time moment \(t\) is \(g_2(t,m)\). We assume that new duplication events occur with the rate \(\lambda\) per base, per time unit; at the same time the chromosome undergoes point mutation events occurring with the rate \(\mu\) per base, per time unit. Then the evolutionary (balance) equation for the average number of pairs of duplicates \(g_2\) can be written as \cite{[3]}

\[
\frac{\Delta g_2}{\Delta t} = -2 \left[(m + D - a) \frac{a\lambda}{D} + \mu m\right] g_2(t,m) + \sum_{k=m+1}^{D} g_{2}(t,k) + L \frac{a\lambda}{D} \delta_{c}(D - m)
\]

The main difference between this equation and the equation of \cite{[3]} notation (we use \(g_2\) here instead of \(f\)). In addition, there is no prefactor 2 in the last term of the equation because in \cite{[3]} we studied the number of duplicated sequences while here we look at the number of pairs of duplicates; thus, the source produces 1 pair of duplicates at each time step. We also confine ourselves to the equation for the mono-scale source using Kronecker delta function \(\delta_{c}(D - m)\); different source terms are also possible and will be presented elsewhere.

We will then focus on the stationary version of the equation implying that when \(t \to \infty\) \(g_2(t, m) \to g_2(m)\) (this can be demonstrated by analytic calculation)

\[
0 = -2 \left[(m + D - a) \frac{a\lambda}{D} + \mu m\right] g_2(m) + \sum_{k=m+1}^{D} g_{2}(k) + L \frac{a\lambda}{D} \delta_{c}(D - m).
\]

Now in the same way as we looked at pairs of identical duplicates we can look at triplets, quadruplets, etc. of identical sequences and write down the corresponding equations for them. For \(i\)-plets we will have the following stationary equation

\[
0 = -i \left[(m + D - a) \frac{a\lambda}{D} + \mu m\right] g_i(m) + 2i \left( \frac{a^2\lambda}{D} + a\mu \right) \sum_{k=m+1}^{D} g_i(k) + \]

\[
+ (i - 1) \left( \frac{a\lambda}{D}(D - m - a) \right) g_{i-1}(m) + 2(i - 1) \frac{a^2\lambda}{D} \sum_{k=m+1}^{D} g_{i-1}(k), i > 2
\]

We see that unlike the equation for duplicates containing the source term with the delta function in it, other equations also have sources of new \(i\)-plets; these sources are \(i - 1\)-plets. Moreover, these sources have two terms: one produces \(i\)-plets of \(i - 1\)-plets of the same length \(m\) (the first term in the second line of \cite{[3]}); the other generates \(i\)-plets of longer \(i - 1\)-plets by copying and pasting their parts of the length \(m\) (the second term in the second line of \cite{[3]}), i.e., new duplicates, \(g_2(m)\) generated by the source, in turn produce triplicates \(g_3(m)\), triplicates produce quadruplicates \(g_4\) etc. The first term in the first line of \cite{[3]} is responsible for the destruction of sequences by new duplications and point mutations; coefficients represent the corresponding rates. The second term in the first line of \cite{[3]} shows that longer sequences are turned into shorter ones, again, by duplications and point mutations. The general mechanism has much in common with models studied in fragmentation theory\cite{[15]}. Thus for each \(m = 1, \ldots D\) we have a set of equations for various sets of identical repeats (maxmers).
We can sum up all the equations and find a new equation for the function $G(m) = \sum ig_i(m)$; the equation has the form

$$-(\zeta + 2)mG(m) + 2aG(m) + 2(\zeta + 2)a \sum_{m>n} G(n) + L\deltac(D-m) = 0,$$

where $\zeta = D\mu/a\lambda$ is a dimensionless parameter.

Now we can compare the results of the simulations with the solutions of (4); the comparison is represented in fig. 1. Additional comparisons for different sets of parameters are given in supplemental figures (see Supplemental materials). Let us now compare solutions of the equation presented in [2] with the simulations of the same duplication-mutation dynamics. For that we used equation presented in [2] with the simulations of the same materials. Let us now compare solutions of the equation (4); the comparison is represented in fig. 1. The solutions of (4) as seen in fig. 1 and supplemental figures 1 and 2[17]. The results of simulations were averaged over $10^2$ realizations.

One then can easily understand the qualitative correspondence of length distributions observed in [2] and [3]: the growth of mutation rate $\mu$ evidently affects $g_i(m)$ for larger $i$ as the growth of $i$ means more sequences in the set. Thus the main contribution to $G(m)$ comes from $g_2(m)$, i.e., $G(m) \sim g_2(m)$ as $\zeta \to \infty$ and the dynamics is described by [2] in the main order. Also it is instructive to note that the situation $\mu \gg \lambda$ generally implies $\zeta \gg 1$ and one can neglect in (4) all terms compared to those containing $\zeta$ and the source term with delta function to keep the algebraic tail, hence $L$ has to grow as $\sim \zeta$. However this is not applicable even for $\zeta \sim 1$. On the other hand, if $\mu \ll \lambda$ then $\zeta \to 0$ and we can write down the equation corresponding to the limit of absent mutations

$$-2mG(m) + 2aG(m) + 4a \sum_{m>n} G(n) + L\deltac(D-m) = 0.$$

If $D$ is fixed as in figs. 1, 2 then the limit amplitude of the algebraic tail is controlled by the only parameter $L$ and all distributions have the same saturation line; this line establishes an upper boundary for fitting the model to the natural sequence. This also can be seen from the exact solution of [2] that has the form

$$G(m) = \begin{cases} \frac{aDL}{(m-a)m(m+a)}, & m < D \\ \frac{L}{2(D-a)}, & m = D \end{cases}$$

with obvious main order term $\sim 1/m^3$ as $a \ll m$. The solution is applicable if $a \ll D \ll L$; otherwise finite size effects turn out to be strong.

For the comparison of our results with natural data we take C. elegans chromosome 2, for which we show the length distribution of exact matches on fig. 3. As all synthetic sequences when processed with mummer do not contain “self-hits”, i.e., identical sequences located
FIG. 3: The length distribution for repeat-masked *C. elegans* chromosome 2 was computed using *mummer* with the options `-maxmatch -n -b -l 20`; self-hits were removed from the distribution. The length of the chromosome is \( \sim 10^9 \). The sequence of the same length was chosen for simulation with parameters \( D = 10^2 \), \( \mu = 10^{-1} \), \( \lambda = 10^{-1} \). The green line represents the solution of (4) for the same parameters.

Exactly in the same positions for both copies of the chromosome, the self-hits were removed from the *mummer* output for the natural sequence. To estimate the parameters of our model for this chromosome we use the estimate for the duplication rate 0.0208 per gene, per 1 my (million years) or \( \approx 400 \) duplications occur in genes per 1 my [18], as the number of genes in the *C. elegans* genome is estimated to be around \( 2 \times 10^4 \); taking into account that genes (including exons and introns) cover around 50\% of the *C. elegans* genome we find the duplication rate \( \approx 800 \) per 1 my for chromosome 2 of length \( \sim 10^7 \) bases; for the rate per base \( \lambda_0 \) we have \( \beta_0/L_0 \), where \( L_0 \) are bases in the *C. elegans* chromosome 2 belonging to genes. We assume that the duplication rate for non-coding parts of the chromosome \( \lambda = \lambda_0 = 16 \times 10^{-6} \) per base, per 1 my. Then we find that \( \lambda L = 160 \) duplications occur in coding and non-coding parts of *C. elegans* chromosome 2 per 1 my.

For the mutation rate in eukaryotes we accept \( \sim 10^{-2} \) per base, per 1 my, that for the chromosome of length \( 10^7 \) yields \( 10^5 \) per 1 my. In the model we have \( \lambda L/D \) duplications per time unit that yields with \( D = 10^3 \) and \( \lambda = 10^{-1} 10^4 \) duplications per time unit. Comparing this estimate with that obtained for the natural chromosome we obtain the estimate 1 time unit \( \approx 6 \times 10^6 \) y and comparison for mutations gives the estimate \( \sim 10^7 \). Thus, our choice of \( \lambda \) and \( \mu \) corresponds to the natural rates if we accept the time unit of the model as above. The choice of \( D \) remains uncertain, but we have to assume \( D \ll L \). To observe the power-law slopes we have to assume \( m < D \); fig. 2 indicates that the tail disappears on the double log scale for \( m \gtrsim 600 \). Thus the choice \( D = 10^3 \) is justified by the length distribution for *C. elegans* and the model.

A natural sequence does not provide information on the choice of \( D \), though for the monoscale source the algebraic regime is observed for \( m < D \); thus we can have an upper bound.

The equations (4) have several features worth stressing. First of all, the equations we derived for \( G(m) \) allow the length distributions of exact matches computed by *mummer* in a broad range of parameters to be reproduced correctly. That means, in part, that histograms computed by counting pairs of exact repeats with *mummer* can be understood as \( \sum g_i(m) \) i.e., they consists of sums of all sequences of duplicates, triplicates, etc. It is worth noting that the *mummer* output does not compute functions \( g_i(m) \) directly and thus the question of interpretation of \( g_i \) in terms of biologically meaningful sequences remains open: we observe only some cumulative effect of distributions for \( g_i(m) \). On the other hand, the correspondence of functions \( g_2(m) \) to the length distribution of *supermaxmers* indicates a potential way to resolve this issue: if functions \( g_2(m) \) were interpreted as *supermaxmers* then the candidates for \( g_2(m) \) etc. could be so called ‘local maxmers’ [19, 20]. At the same time the observed correspondence of *mummer* output and the function \( G(m) \) suggest we have an analytic interpretation for the length distributions computed by *mummer* for natural sequences: the length distributions for natural sequences exhibiting algebraic behaviour with the exponent \(-3 \) can be understood in terms of equations (3) and (4) and their solutions.

We proposed a hierarchy of equations for \( g_i \); the first of this equations, i.e., for \( g_2 \), was derived in [3] and we see that the equations of [2] and [3] as well as those presented here treat different subjects focusing on various restrictions imposed on exact matches; in part, the work in [3] deals with the collection of ‘supermaxmers’, specific pairs of exact repeats computed with additional conditions of maximality which are discussed in [19]; they are important as the equations for them not only account for the observed algebraic behaviour in length distributions of natural DNA sequences but demonstrate, in part, non-algebraic length distributions also observed both in simulations and natural DNA and also because their definition provides them with a natural biological interpretation [19]. They are accounted for by equation (2) and demonstrate obvious discrepancy from the length distribution of exact matches (suppl. fig. 3). Our equation (4) treats all pairs of exact matches neglecting their uniqueness and reproduces their length distributions. Then \( G(m) \) in our interpretation may be represented as a sum of ‘supermaxmers’ for which the biological interpretation was already discussed and other sets of sequences obtained by natural extension of the concept of supermaxmers; in this sense, we expect that such an interpretation of \( g_i(m) \), \( m > 2 \) will appear soon.

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FIG. S1: Comparisons of simulations with solutions of equation (4) of the main text. The parameters are: $L = 10^6$, $D = 10^3$, $\lambda = 10^{-1}$. Empirical length distributions were computed with the same switches of mummer as indicated in the caption for figure 1 of the main text. The distributions were averaged over 100 realizations.
FIG. S2: Parameters of the model are: $L = 10^6$, $D = 10^4$, $\lambda = 10^{-1}$. All other parameters and options are the same as in figure 1 of the main text and supplemental figure 1.
FIG. S3: Length distributions obtained with duplication-mutation dynamics using *mummer* with the parameters `-n -b -l 20`. Parameters of the model are: $L = 10^6$, $D = 10^3$, $\lambda = 10^{-4}$ and correspond to those indicated in the fig. 1 of the main text. Magenta curves represent the solutions of the equation (3) of the main text.