A simple stochastic model for the evolution of protein lengths

C. Destri\(^1\) and C. Miccio\(^1\)

1. Dipartimento di Fisica G.Occhialini, Università di Milano--Bicocca and INFN, Sezione di Milano, Piazza della Scienza 3 - I-20126 Milano, Italy.

(Dated: February 9, 2008)

We analyse a simple discrete-time stochastic process for the theoretical modeling of the evolution of protein lengths. At every step of the process a new protein is produced as a modification of one of the proteins already existing and its length is assumed to be random variable which depends only on the length of the originating protein. Thus a Random Recursive Trees (RRT) is produced over the natural integers. If (quasi) scale invariance is assumed, the length distribution in a single history tends to a lognormal form with a specific signature of the deviations from exact gaussianity. Comparison with the very large SIMAP protein database shows good agreement.

INTRODUCTION

Nowadays, it is well established that the great variety of proteins in biological systems has been produced during the course of evolution by means of gene mutations that take effect at the coding level \([4]\). The main mechanisms are: duplication of genome segments that contain sequences coding for one or more protein domains \([5, 6, 7, 8]\); divergence of the duplicated sequences by insertion, deletion and substitution of one or more base pairs \([9, 10, 11, 12]\); domain rearrangements, such as gene fusions and gene fission \([13, 14]\), domain recombination \([15, 16]\), gene shuffling (recombination between dissimilar genes) \([17]\) and domain insertions and deletions \([18, 19]\). By means of these microscopic mechanisms, iterated a huge number of times throughout the ages of evolution, an initial protein population, most likely very small and poorly assorted, has been enormously increased to the present very large number and complex variety.

A valuable framework for the effective modeling of the evolutions of genes and proteins could be provided by stochastic processes. In the most general formulation, one should take into account the complex organization of biological systems into independent organisms grouped in turn into species, genera and kingdoms, as well as the complicated effects of natural selection. However, since all evolution mechanisms generate new biological material by means of modifications of the biological material already existing, in the case of proteins we may imagine a simpler, more abstract discrete-time stochastic process over the space of all amino acid sequences such that at each time step \(t = 1, 2, 3, \ldots\) a new protein is generated with some prescribed random mechanism from the set of proteins already existing. Clearly the discrete time of the model has nothing to do with the time of the true biological evolution process, except that it is a (almost) monotonically increasing function of the latter, at least on time scales large enough (great mass extinctions correspond most likely to periods when this monotonicity is lost). Moreover, a single time step in the process would correspond to some averaging over a multitude of different effects, both at microscopic, or biochemical level, and at the macroscopic level of the selection–based evolution mechanisms.

This abstract stochastic process would be specified by \(\Pr\{p_{t+1}\mid\{p_t\}\}\), that is the conditional probability that the \(t + 1\) protein has the amino acid sequence \(p_{t+1}\), given that there is already a set \(\{p_i\} \equiv \{p_1, p_2, \ldots p_t\}\) of distinct proteins at time \(t\). In principle, \(\Pr\{p_{t+1}\mid\{p_t\}\}\) might embody the effects of many, if not all, of the complicated biochemical and evolutorial mechanisms alluded above and should depend explicitly on time. Moreover, the initial configuration of proteins could be assumed to coincide with the actual set of distinct amino acid sequences present in nature at some moment in the distant past, when their total number was much smaller than the present one. In any case, a huge amount of information is required for a complete specification of the model endowed with detailed predictive power. On the other hand, all what we may hope to reproduce in reasonably simple terms, to a large extent independent on the details of the model, are some broad characteristics of the distribution of protein currently observed. This is indeed our main working hypothesis, based on the fact that the very large number of proteins in the SIMAP database do show simple universal properties \([22, 23]\). Then we may rely on the basic universality property, typical of a wide class of stochastic processes, that is the capability to forget the details of the initial transient regime and to relax toward a statistical equilibrium or quasi-equilibrium state which depends only on very general features of the conditional probability \(\Pr\{p_{t+1}\mid\{p_t\}\}\) and is characterized by few, weakly time–dependent “macroscopic” parameters.

A STOCHASTIC PROCESS FOR PROTEIN LENGTHS

In the present work we concentrate our attention on the distribution of protein lengths, that is the observed frequency of proteins with a specific number of amino acids over the set of all known proteins. Thus we can consider only the protein length as the random vari-
able of the stochastic process. By definition this random length takes values in the natural numbers and we denote it with the symbol \( \ell \). We also observe that by construction all the proteins produced in the process can be ordered according to the time of production, starting from \( t = N_0 \), with \( N_0 \) the number of distinct proteins in the initial configuration, and arriving to \( t = N \), with \( N \) of the order of the number of distinct proteins that exist now in nature, which is of order \( 10^7 \) or more. The statistical dynamics of the process is fully determined by \( \Pr(\ell_{t+1}|\ell_t, \ell_{t-1}, \ldots, \ell_1) \), that is the conditional probability that the \( t+1 \) protein has length \( \ell_{t+1} \), given that the preceeding proteins have the indicated lengths. This conditional probability could depend explicitly on the formal time \( t \).

As already discussed above in a more general context, the detailed biological mechanisms that constrain \( \Pr(\ell_{t+1}|\ell_t, \ell_{t-1}, \ldots, \ell_1) \) are far too complex to be explicitly incorporated in the model. Therefore, we shall make simple and workable assumptions on the conditional probability, relying, in practice, on some sort of central limit theorem for the probability that a protein taken at random from the state of a very long random process has a certain length.

As a first simplifying assumption on the conditional probability \( \Pr(\ell_{t+1}|\ell_t, \ell_{t-1}, \ldots, \ell_1) \) we make that of locality. That is, we assume that a given protein length can be produced from a preceding length independently on all the other lengths already produced. Hence we can write

\[
\Pr(\ell_{t+1}|\ell_t, \ell_{t-1}, \ldots, \ell_1) = \sum_{s=1}^{t} q_s W_s(\ell_{t+1}|\ell_s) \tag{1}
\]

where the nonnegative weights \( q_s \) are properly normalized, \( \sum_{s=1}^{t} q_s = 1 \), and \( W_s(\ell|\ell') \) can be interpreted as Markovian transition probabilities. In the absence of any other information, one would assume equal a priori probabilities among the different proteins, that is \( q_s = 1/t \) and \( W_s(\ell|\ell') = W(\ell|\ell') \) with no explicit \( s \)-dependence. This might appear in conflict, however, with the global changes of ecosystems as well as with the complex organization of biological systems in kingdoms and species (which suggests that all proteins existing nowadays can be roughly divided into subsets of similar proteins having almost independent evolutionary histories, as least not too far in the past). We may take this into account by restricting the predictions of our stochastic process to suitable chosen subsets of the proteins of the SIMAP database, according, for instance, to given kingdoms. Moreover, we can neglect, on average, the global changes of ecosystems by placing the start of the process not too deep in the past. Altogether let us assume that

\[
\Pr(\ell_{t+1}|\ell_t, \ell_{t-1}, \ldots, \ell_1) = \frac{1}{t} \sum_{s=1}^{t} W(\ell_{t+1}|\ell_s) \tag{2}
\]

Our stochastic process now differs from a random walk on the natural integers only because at each step anyone of the already existing lengths, rather than only the last generated one, may serve as starting point for a jump to a new length. We are therefore dealing with the so-called Random Recursive Tree (RRT) \(^2,^3\) (more precisely, a random recursive forest) embedded by \( W(\ell|\ell') \) into the natural integers. It follows that the probability \( P(\ell, t) \) that the \( t \)-th protein has exactly length \( \ell \) satisfies the non–Markovian evolution equation

\[
P(\ell, t + 1) = \sum_{\ell' = 1}^{\infty} W(\ell|\ell') Q(\ell', t) \tag{3}
\]

where \( Q(\ell, t) \) is the average length distribution (that is the mean fraction of proteins of length \( \ell \) at time \( t \) and therefore evolves as

\[
(t + 1) Q(\ell, t + 1) = t Q(\ell, t) + P(\ell, t + 1) \tag{4}
\]

Together eqs. (3) and (4) define a stochastic process with memory and should be compared to the Markov chain recursion for a simple Random Walk (RW) on all possible lengths, which would read instead

\[
P^\text{RW}(\ell, t + 1) = \sum_{\ell' = 1}^{\infty} W(\ell|\ell') P^\text{RW}(\ell', t) \tag{5}
\]

without any memory of the past. We still do have to make some choice on the explicit form of \( W(\ell|\ell') \), in which case our stochastic process could be quite easily simulated on a computer. We expect, however, that the large time asymptotic regime of the process depends only on very general features of functional form of \( W(\ell|\ell') \), again thanks to the universality hypothesis which has its roots in the law of large numbers. In any case, to investigate the statistics of the produced lengths, we need beforehand some useful properties and formal manipulations valid for any \( W(\ell|\ell') \).

We recall first of all that by definition the nonnegative numbers \( W(\ell|\ell') \) satisfy the normalization condition:

\[
\sum_{\ell = 1}^{\infty} W(\ell|\ell') = 1
\]

These transition probabilities are the elements of a matrix \( W \), the so–called stochastic matrix in the case of Markov processes. Without loss of generality, we may take \( W \) to be ergodic, that is such that any finite length can be produced after a suitable number of steps starting from any other finite length.

Next we can exploit the linearity of eq. (3) to simplify the choice of initial conditions for \( P(\ell, t) \). As already stated above, the process is assumed to start with \( N_0 \) distinct proteins, which we may take to have \( n \) distinct
lengths \( \ell_j, j = 1, 2, \ldots, n \), each repeated \( n_j \) times so that \( \sum_j n_j = N_0 \). This defines the initial length distribution

\[
Q(\ell, N_0) = \frac{1}{N_0} \sum_{j=1}^{n} n_j \delta_{\ell \ell_j}
\]

when \( N_0 \) was the total number of distinct proteins. As the process may start from anyone of these initial proteins with equal probability \( 1/N_0 \), we may regard \( n_j/N_0 \) as probability that the process starts exactly from the length \( \ell_j \). Therefore the solution of eq. (5) can be written

\[
P(\ell, t) = \frac{1}{N_0} \sum_{j=1}^{n} n_j P(\ell, t-N_0+1|\ell_j) = \sum_{\ell'=1}^\infty P(\ell, t-N_0+1|\ell') Q(\ell', N_0)
\]

where \( P(\ell, t|\ell') \) is the special solution that is concentrated on the arbitrary value \( \ell' \) at \( t = 1 \), that is \( P(\ell, 1|\ell') = \delta_{\ell \ell'} \). Similarly we have

\[
Q(\ell, t) = \sum_{\ell'=1}^\infty Q(\ell, t-N_0+1|\ell') Q(\ell', N_0)
\]

where \( Q(\ell, t|\ell') \) is the solution of eq. (4) specialized to \( P(\ell, t|\ell') \), that is

\[
Q(\ell, t|\ell') = \frac{1}{t} \sum_{s=1}^{t} P(\ell, s|\ell')
\]

Clearly \( \ell' \) is the length of a specific protein which plays the role of root for the RRT, while the complete process is a forest of RRT’s each having root in one of the \( N_0 \) initial proteins and growing in parallel. That is, the unique protein labelled by \( t \) has a fixed probability \( n_j/N_0 \) of belonging to the tree rooted in a protein of length \( \ell_j \).

We may now introduce the matrix notation

\[
W(\ell|\ell') \equiv [W]_{\ell \ell'}
\]

\[
P(\ell, t|\ell') \equiv [P(t)]_{\ell \ell'}
\]

\[
Q(\ell, t|\ell') \equiv [Q(t)]_{\ell \ell'}
\]

which allows to write the evolution equation for \( P(t) \) more compactly as

\[
P(t+1) = WP(t) = \frac{1}{t} \sum_{s=1}^{t} WP(s)
\]

Or equivalently as

\[
t P(t+1) = \sum_{s=1}^{t-1} WP(s) + WP(t) = (t+W-1)P(t)
\]

which has the formal solution

\[
P(t) = \prod_{s=1}^{t-1} \left( 1 + \frac{W-1}{s} \right) = \frac{W^{t-1}}{(t-1)!}
\]

where \( z^n \) stands for the so-called raising factorial product \( z(z+1)\ldots(z+n-1) \). The raising factorial generates the (unsigned) Stirling numbers of the first kind as coefficients of its expansion in simple powers of \( z \):

\[
z^n = \sum_{k=1}^{n} \left[ \begin{array}{c} n \\ k \end{array} \right] z^k, \quad n > 0
\]

where we adopted the square bracket notation of ref. [20] for the Stirling numbers. Hence from eq. (11) we can write

\[
P(t) = \frac{1}{(t-1)!} \sum_{s=1}^{t-1} \left[ \begin{array}{c} t-1 \\ s \end{array} \right] P_{RW}^s(s)
\]

where \( P_{RW}^s(t) = W^t \) is the formal solution of the standard Random Walk. Notice that, by eq. (12), \( P(t) \) is indeed properly normalized, that is

\[
\sum_{\ell=1}^{\infty} P(\ell, t|\ell') = 1
\]

since \( W^t \) is also a stochastic matrix and Stirling numbers satisfy the normalization

\[
\sum_{k=1}^{n} \left[ \begin{array}{c} n \\ k \end{array} \right] = n!, \quad n > 0
\]

In fact, eq. (12) shows that the quantity

\[
p_s(t) = \frac{1}{(t-1)!} \left[ \begin{array}{c} t-1 \\ s \end{array} \right]
\]

has the interpretation, for the abstract RRT, of probability that the node added at time \( t \) is at a chemical distance \( s \) from the root of the tree, that is the original node present at \( t = 1 \). In terms of proteins, \( p_s(t-N_0+1) n_j/N_0 \) is therefore the probability that the \( t \)-th protein is obtained through \( s \) changes from one of the \( N_0 \) initial proteins of length \( \ell_j \).

Notice also that the evolution equation (2) allow to write an alternative expression for \( Q(t) \) which is local in time (but generally non local in “space”) w.r.t. \( P(t) \)

\[
Q(t) = W^{-1} P(t+1) = \frac{1}{t} \sum_{s=1}^{t} \left[ \begin{array}{c} t-1 \\ s \end{array} \right] W^{t-1}
\]

One can see that \( p_{s+1}(t+1) \), which by construction satisfies

\[
p_{s+1}(t+1) = \frac{1}{t} \sum_{k=1}^{t} p_s(k)
\]

represents the average fraction of nodes at a distance \( s \) from the root [2].
For very large \( n \) we can use the approximation

\[
\xi^n \approx \frac{\Gamma(n+1)}{\Gamma(n+1)} n^\xi \left[ 1 + O \left( \frac{1}{n} \right) \right]
\]

(14)

which follows from Euler’s infinite product representation of the \( \Gamma \) function \([21]\). From eqs. (11), (13) and (14) we then find

\[
Q(t) \approx \frac{\exp[(W - 1) \log t]}{\Gamma(W + 1)}
\]

(15)

where we neglected all inverse powers of \( t \) in the exponent, relying for uniformity on the boundedness of its spectrum of \( W \). The crucial point of eq. (15) is the very slow logarithmic dependence on time, which appear evident upon comparison with the formal solution

\[
W^t = \exp(t \log W)
\]

of the Markovian case.

In order to provide more explicit expressions for \( P(t) \) and \( Q(t) \) we need some special assumptions on the stochastic matrix \( W \). We do that in the next section.

**AVERAGE PROPERTIES OF SCALE–IN Variant MODELS**

We describe here a class of examples which can be treated in detail at the analytic level. These are characterized by the assumption that our stochastic process is (almost) scale invariant. Intuitively, one expects that longer proteins can be changed throughout evolutions more easily than shorter ones. Exact scale invariance would mean that changes are proportional to length.

To implement this picture, we first extend the lengths \( \ell \) from the positive integers to all real positive numbers. It will become apparent in the sequel that this extension has very little impact on our conclusions. Next we change variables, from \( \ell \) to its logarithm \( x = \log \ell \) and assume homogeneity in \( x \), namely that

\[
W(\ell | \ell') \, d\ell = \mathcal{W}(e^x | e^{x'}) \, d(e^x) = \mathcal{W}(x - x') \, dx
\]

is translation invariant, i.e., function only of \( x \)–space differences. The process is very simple: at each time step the random walker may pick anyone of the previously visited points as starting point for the next step, whose value \( x \) is extracted with the one–step pdf (probability distribution function) \( \mathcal{W}(x) \). In terms of protein lengths, at each step the length is rescaled by a factor \( e^x \). Since the true variables are discrete, we may take \( \mathcal{W}(x) \) to be very smooth for all \( x \). Likewise, since \( \ell \geq 1 \) we may take \( \mathcal{W}(x) \) to vanish very quickly (let us say “faster than any power”) for \( x \rightarrow -\infty \). For \( x \rightarrow +\infty \) we assume instead quite reasonably that \( \mathcal{W}(x) \) vanishes fast enough to have finite moments at least up to order four. We then introduce the following notation for the first two cumulants:

\[
\mu = \int dx \, x \, \mathcal{W}(x) , \quad \sigma^2 = \int dx \, (x - \mu)^2 \, \mathcal{W}(x)
\]

that is the mean value and the squared fluctuations.

We can now define the process probability in \( x \)–space as

\[
\mathcal{P}(x - x', t) = e^{\mu t} \mathcal{P}(e^x, t | e^{x'})
\]

and in the same way we can introduce the average distribution \( \mathcal{Q}(x, t) \) which by eq. (8) satisfy

\[
\mathcal{Q}(x, t) = \frac{1}{t} \sum_{s=1}^{t} \mathcal{P}(x, s)
\]

Since the stochastic matrix which correspond to \( \mathcal{W}(x - x') \) is diagonal in Fourier space, we can now write the formal expression eq. (11) as

\[
\mathcal{P}(x, t) = \int \frac{dk}{2\pi} e^{ikx} \tilde{\mathcal{P}}(k, t)
\]

(16)

where

\[
\tilde{\mathcal{P}}(k, t) = \prod_{s=1}^{t-1} \left[ 1 + \tilde{\mathcal{W}}(k) \frac{1}{s} \right]
\]

and \( \tilde{\mathcal{W}}(k) \) is the Fourier transform of \( \mathcal{W}(x) \). Clearly, by eq. (13), the Fourier transform of \( \mathcal{Q}(x, t) \) reads

\[
\tilde{\mathcal{Q}}(k, t) = \frac{\tilde{\mathcal{P}}(k, t + 1)}{\tilde{\mathcal{W}}(k)}
\]

The correct normalization of either \( \mathcal{P}(x, t) \) or \( \mathcal{Q}(x, t) \) follows from that of \( \mathcal{W}(x) \), which implies \( \tilde{\mathcal{W}}(0) = 1 \). Other consequences of the probabilistic nature of \( \mathcal{W}(x) \) is the symmetry \( \tilde{\mathcal{W}}(k) = \tilde{\mathcal{W}}(-k) \) and the bound \( |\tilde{\mathcal{W}}(k)| \leq 1 \). In addition, with the natural requirements made above on the one–step pdf \( \mathcal{W}(x) \), the function \( \tilde{\mathcal{W}}(k) \) has the expansion near \( k = 0 \)

\[
\tilde{\mathcal{W}}(k) \approx 1 - \frac{i}{\mu} k - \frac{1}{2} (\mu^2 + \sigma^2) k^2 + \ldots
\]

(17)

and vanishes for large \( |k| \).

In this context of a continuous logspace, the extension to a generic initial distribution is very simple: it amounts to multiply both Fourier transforms \( \tilde{\mathcal{P}}(k, t) \) and \( \tilde{\mathcal{Q}}(k, t) \) by the Fourier transform of the initial distribution.

Using eq. (15) we have for large \( t \)

\[
\mathcal{P}(x, t) = \int \frac{dk}{2\pi} e^{ikx} \frac{\exp[(\tilde{\mathcal{W}}(k) - 1) \log t]}{\Gamma(\tilde{\mathcal{W}}(k))}
\]

(18)

and

\[
\mathcal{Q}(x, t) = \int \frac{dk}{2\pi} e^{ikx} \frac{\exp[(\tilde{\mathcal{W}}(k) - 1) \log t]}{\Gamma(\tilde{\mathcal{W}}(k) + 1)}
\]

(19)

up to fully negligible inverse power corrections in \( t \). For any given \( \tilde{\mathcal{W}}(k) \) the Fourier integral in eqs. (18) and (19) can be computed numerically to high accuracy through
Fast Fourier Transform. Moreover, for large $t$ we can derive very similar asymptotic expansions in inverse powers of $\log t$ valid for any $\hat{\mathcal{W}}(k)$ in the class described above. Since our main interest is in the average distribution profile $\mathcal{Q}(x,t)$ we concentrate on this aspect.

The leading term for large $t$ is determined only by the first two terms of the $\hat{\mathcal{W}}(k)$ expansion (17) near $k = 0$, with the quadratic term providing the Gaussian dominance in eqs. (18) and (19), according to the central limit theorem. From the first and second derivatives in $k = 0$ of Fourier transform $\hat{\mathcal{Q}}(k,t)$, we first compute the mean value and standard deviation of the process for large $t$, as

$$
\mu_t \equiv \langle x \rangle_t = \mu + \log t + \gamma - 1
$$

$$
\sigma_t^2 \equiv \langle (x - \mu_t)^2 \rangle_t = (\mu^2 + \sigma^2)(\log t + \gamma - 1) - (\frac{\pi^2}{6} - 1)\mu^2
$$

where $\gamma = 0.5772156\ldots$ is Euler–Mascheroni constant. Then in terms of the standard centered scaled variable

$$
\xi = \xi(x,t) = \frac{x - \mu_t}{\sigma_t}
$$

we have to leading order

$$
\mathcal{Q}(x,t) \approx \frac{e^{-\xi^2/2}}{\sqrt{2\pi} \sigma_t}
$$

Going back the length variable $\ell$ through the definition $x = \log(\ell/\ell')$, we find the lognormal distribution

$$
\mathcal{Q}(\ell,t|\ell') \approx \frac{e^{-\log \ell - \log(\ell e^\mu_t)^2/(2\sigma_t^2)}}{\ell e^{\mu_t - \sigma_t^2}}
$$

peaked around the rescaled initial length $\ell' e^{\mu_t - \sigma_t^2}$.

Subleading contributions to the above results, of relative order $1/\log \log t$ and smaller, at fixed values of $\xi$, can be computed by the standard perturbation technique around Gaussian integrals: one includes also terms of order higher than $k^2$, say of order $n \geq 4$, in the power expansion of $\hat{\mathcal{W}}(k)$ around $k = 0$ and then expands to order $k^n$ also the exponentials of such terms; for completeness, also the expansion of the inverse $\Gamma$ function must be properly extended; finally one integrates explicitly each term of the complete expansion in terms of multiple derivatives of the leading Gaussian. One obtains in this way a $n$–degree polynomial in $\xi$ times the Gaussian $e^{-\xi^2/2}$. The $n + 1$ coefficients of the polynomial are fixed by the first $n + 1$ moments of the distribution, which in turn can be computed directly from the Taylor series in $k = 0$ of the Fourier transforms $\hat{\mathcal{Q}}(k,t)$ or $\hat{\mathcal{P}}(k,t)$ (by construction, we must impose $\langle \xi \rangle_t = 0$ and $\langle \xi^2 \rangle_t = 1$ for the first two moments). Taking into account the specific form of these Fourier transforms, it is more convenient to calculate the cumulants of $\mathcal{Q}(x,t)$ or $\mathcal{P}(x,t)$, since their $n$–order cumulant is given by $\log t$ times the $n$–order moment of the one–step pdf $\mathcal{W}(x)$, plus the $n$–order derivative w.r.t. $k \log[\Gamma(\mathcal{W}(k) + 1)]$ or $\log[\Gamma(\mathcal{W}(k))$ evaluated at $k = 0$. Moreover, the latter contributions are systematically subleading as compared to the moments of $\mathcal{W}(x)$, so that we have, for the third–order and the fourth–order cumulant of $\mathcal{Q}(x,t)$ (that is the average skewness $\bar{\xi}_t$ and kurtosis $\bar{\xi}_t$ of the process, up to normalization conventions):

$$
\bar{\xi}_t \equiv \langle \xi^3 \rangle_t = \frac{\mu_3}{\mu_2^{3/2}} \frac{1}{\sqrt{\log t}} \left[ 1 + \mathcal{O}\left( \frac{1}{\log t} \right) \right]
$$

$$
\bar{\xi}_t \equiv \langle \xi^4 \rangle_t - 3 = \frac{\mu_4}{\mu_2^2} \frac{1}{\sqrt{\log t}} \left[ 1 + \mathcal{O}\left( \frac{1}{\log t} \right) \right]
$$

where $\mu_3$ and $\mu_4$ are the third– and fourth–order moments of $\mathcal{W}(x)$, while $\mu_2 = \mu^2 + \sigma^2$ is the analogous notation for the second moment. In this expression one may regard the expectation values as evaluated with $\mathcal{P}(x,t)$ rather than with $\mathcal{Q}(x,t)$, since the differences are due solely to the change $\Gamma(\mathcal{W}(k)) \to \Gamma(\mathcal{W}(k) + 1)$ from eq. (18) to eq. (19) and are subleading. We can now recognize a distinctive mark of the RRT over the real line: for sufficiently large time, the kurtosis of the average distribution profile is certainly positive, since positive definite is the fourth moment of any $\mathcal{W}(x)$. Another important characteristic, which will be further discussed later on, is the positivity of the ratio between the skewness $\langle \xi^3 \rangle_t$ and the third moment $\mu_3$ of $\mathcal{W}(x)$.

The extension of the main results, eqs. (20)–(23), to the case of a generic initial distribution are straightforward. In particular, to the cumulants of $\mathcal{Q}(x,t)$ one would have to add the cumulants of the initial distribution, which are constant in time and therefore subleading. Thus eqs. (20) would get additive constants and eqs. (23) would hold unchanged. This is the standard way to see how the process forgets about the initial conditions (in a logarithmic slow way).

## Profile Fluctuations

Let us assume that, for a given stochastic matrix $\mathcal{W}$ and initial distribution $\mathcal{Q}(x,N)$, we can explicitly compute $\mathcal{P}(\ell,t)$ and $\mathcal{Q}(\ell,t)$ at least for large $t$, as in the preceding section. To compare the result to the length distribution in a single evolution history, or very few of them, which is indeed our case, we need to gather information also on the fluctuations of the profile of the length distribution from one history to the other.

Typically, one would like to rely on the law of large numbers. For ergodic Markov chains (with finitely many possible events) this law states that the probability that the frequency of a certain event in a given history differs from its equilibrium probability by any nonzero amount vanishes when the history becomes infinitely long. In
our case the elementary events are the observed protein lengths and the frequency in a given history is just the profile of the length distribution in a given evolution history. The quantity $Q(\ell, t)$ discussed above is just the expectation value of the profile, that is its average over all possible histories. In a Markovian setup with finitely many possible events there would be no difference between the profile of a specific history and its expectation value in the $t \to \infty$ limit, which means vanishing profile fluctuations in the limit and negligible ones for sufficiently large $t$. The stochastic process at hand, however, is not Markovian, having the (very specific, simple and itself random) RRT form of memory and has a number of possible events in principle arbitrarily large. In such a case we expect, thanks to stronger forms of law of large numbers like the central limit theorem (and have indeed verified in the example class of the preceding section), that the average length distribution $Q(\ell, t)$ assumes, for $t$ large enough, a universal nonconstant form which depends only on very general properties of $W$. What we need then is also that the fluctuations of the frequency for large $t$ do not spoil completely the profile of its expectation value $Q(\ell, t)$. Notice, for instance, that this is not true for random walks, not even when they are recurrent (as generally true in one dimension, which is our case). In other words, in the standard RW the frequency of times the walker visits any given small region keeps fluctuating strongly from one very long history to the other, never resembling the mean frequency profile. This is due to the characteristic dispersion of order $\sqrt{t}$ of the RW, which implies that each elementary event occurs an insufficient number of times of order $1/\sqrt{t}$ to guarantee a good convergence of the frequency along a single history (it would be even worse in $d > 1$ dimensions).

On the contrary, the random memory of the RRT dramatically helps the application of the law of large numbers, since the logarithmic time dependence leads to much slower drift and diffusion, strongly reducing the impact of fluctuations on the length distribution. One could say that the length distribution is an almost “self-averaging” array of random variables, which for sufficiently long time does not differ too much from its expected value. Indeed, at least in the case of the abstract RRT, there exist mathematically rigorous theorems about the convergence of the chemical distance profile of any RRT towards a normal form \cite{2}. In this section we provide some quantitative numerical evidence of the same property for lengths distribution profiles using a specific model for $W(\ell|\ell')$.

We first revert to the realistic situation of lengths as positive integers not smaller than some lower cutoff $\ell_{\text{min}} \geq 1$; next we consider the following RRT process (written as computer pseudocode)

\[
\ell = \text{integer part of } e^x \ell(n_t); \quad \text{if } \ell \geq \ell_{\text{min}} \text{ then } \ell(t+1) = \ell
\]  

(24)

where $n_t$ is an integer chosen at random from $1$ to $t$ and $x$ is extracted with the one-step pdf $W(x)$ over the continuous logspace; finally we pick for $W(x)$ the maximum entropy form compatible with our general setup, namely a Gaussian with mean $\mu$ and standard deviation $\sigma$. This minimum bias choice could even be regarded as natural in view of the many different “microscopic” and “macroscopic” mechanisms on which the stochastic process should depend, as discussed in the Introduction. However, we make it here mainly for numerical definiteness. In any case the analysis of the preceding section and the discussion below, at the end of this section, should make it clear that other choices of $W(x)$ in the same class would lead to relative changes that vanish as $1/\log t$, while preserving important characteristic properties like the positivity of the kurtosis.

It is quite easy on modern personal computers to accurately simulate the process (24) by running many very long random histories. In our simulations, we produced $10^6$ length distributions with the discrete time $t$ running from $N_0 \lesssim 50$ to $N = 5 \cdot 10^6$. For sake of definiteness we started from $25$ initial lengths chosen at random from $30$ to $50$ and set $\mu = 0.16$ and $\sigma = 0.19$. This setup was determined in such a way to fit the overall scales of the length distribution in the SIMAP database, as will be discussed in the next section. In particular, it turns out that the effects on the profiles of the lower cutoff $\ell_{\text{min}}$ are fully negligible, so that the scale–invariant framework adopted in the preceding section should apply. Indeed, one can also check that the discreteness of the lengths $\ell(t)$ does not play any significant role at all w.r.t. the continuous case.

For each distribution we computed the mean and standard deviation in the variable $x = \log \ell$:

\[
\mu_t = \frac{1}{t} \sum_{j=1}^{t} x(j), \quad \sigma_t^2 = \frac{1}{t} \sum_{j=1}^{t} [x(j) - \mu_t]^2
\]  

(25)

at prescribed intermediate values of $t$. Likewise, we computed the skewness and kurtosis

\[
s_t = \frac{1}{t} \sum_{j=1}^{t} \xi^3(j), \quad \kappa_t = -3 + \frac{1}{t} \sum_{j=1}^{t} \xi^4(j)
\]  

(26)

where as usual $\xi(j) = [x(j) - \mu_t]/\sigma_t$.

These four parameters are still random variables which fluctuate from one RRT to the other. Moreover, except for the mean $\mu_t$, their average values over all possible RRT realizations of $t$ steps do not coincide with the corresponding parameters of the average distribution $Q(x,t)$, since such average values receive contributions also from the profile fluctuations. Only the average $\langle \mu_t \rangle$ is given by the quantity $\bar{\mu}_t$ in the first eq. (20). The differences between $\langle \sigma_t \rangle$, $\langle s_t \rangle$, $\langle \kappa_t \rangle$ and $\bar{\sigma}_t$, $\bar{s}_t$, $\bar{\kappa}_t$ in the second eq. (20) and eqs. (23), respectively, cannot be even estimated with the help of $Q(x,t)$ alone. This is true a fortiori
for the fluctuations. Therefore it is important to provide some (numerical) evidence on their behaviour for large times. In particular, $s_t$ and $K_t$ provide a measure of the deviation from gaussianity of a given profile (we refer to above-mentioned mathematical literature for some rigorous bounds in the case of abstract RRT’s).

We also kept track of all the logspace profiles, after a suitable coarse graining: we fixed beforehand a uniform binning grid of $K$ intervals of width $h \ll 1$ over a portion of the real line large enough to contain almost all $\xi$ points produced (e.g. the interval $(-5,5)$ to comprise all points within 5 sigmas); then we computed the fraction $q_k$ of $\xi$ points in a given RRT that fall in the $k$-th interval of the grid. At this stage using continuous or discrete lengths does make a difference, since a binning grid too fine over the logarithms of integer lengths will induce spurious fluctuations. Hence in the discrete case, for each integer $j$ repeated $n_j$ times in a given length distribution we filled the real interval $(j - 1/2,j + 1/2$ with $n_j$ double precision lengths chosen at random; only after this smoothing we computed the distribution over the regularly space grid in logspace.

By construction, the average of the discretized density $q_k(t)/h$ over all possible histories will reproduce the integral of the average profile $Q(\xi,t)$ as a function of $\xi$ over the $k$-th interval of the grid. Then an estimate of the profile fluctuations is the standard deviation of $q_k(t)/h$ for each $k$.

With $q_k(t)$ we computed another important (and more robust) measure of deviation from gaussianity, that is the entropy:

$$S_t = \log h + \sum_{k=1}^{N} q_k(t) \log q_k(t)$$

In fact, in the $t \to \infty$ limit of an infinite RRT and then $h \to 0$ of vanishing grid width, a Gaussian profile for $\xi$ would have maximal entropy equal to $(\log 2\pi + 1)/2 = 1.41893853$ ...

In fig. 1 we show the evolution of the logarithmic length distribution along a single history and, for comparison, the evolution of the average profile $Q(\xi,t)$ obtained by numerically integrating through FFT eq. (19) and superposing the results as in eq. (7).

In fig. 2 we show the distributions of the statistical estimators defined above for few values of $t$ equally spaced in logspace. We see that the parameters that measure deviation from gaussianity, that is $s_t$, $K_t$ and $S_t$, have mean values that slowly tend to the Gaussian values with smaller and smaller fluctuations as $t \to \infty$. The convergence behaviour is roughly the ubiquitous one, $1/\log t$, with variances that vanish faster than the peaks movement. Also the variance of the standard deviation seems to slowly converge. On the other hand the fluctuations of the mean do not appear to converge at all; this is reflected in the reduction slower than $1/\log t$ of the standard deviation of the $\xi$ profile fluctuations. In table I we provide further numerical evidence through the standard deviations over the $10^5$ sample histories of $\mu_t$, $\sigma_t$, $s_t$, $K_t$ and $S_t$.

![FIG. 1: Evolution of the logspace length distribution in a specific history (left panel) and on average (right panel), starting from the same initial conditions.](image1)

![FIG. 2: Distributions over $10^5$ sample histories of the indicated statistical estimators of the logspace length profile for the same times as in fig. 1.](image2)

| $t$ | $\Delta \mu_t$ | $\Delta \sigma_t$ | $\Delta s_t$ | $\Delta K_t$ | $\Delta S_t$ |
|-----|----------------|-------------------|--------------|--------------|--------------|
| $5 \cdot 10^3$ | 0.0781 | 0.0401 | 0.1425 | 0.3840 | 0.0131 |
| $5 \cdot 10^4$ | 0.0784 | 0.0343 | 0.0927 | 0.2282 | 0.0072 |
| $5 \cdot 10^5$ | 0.0787 | 0.0304 | 0.0647 | 0.1440 | 0.0045 |
| $5 \cdot 10^6$ | 0.0785 | 0.0277 | 0.0482 | 0.0980 | 0.0031 |

**TABLE I: Standard deviations over $10^5$ samples of the statistical estimators of mean, standard deviation, skewness, kurtosis and entropy of the logspace length distribution.**
These results remain qualitatively unchanged under generalization from the Gaussian one–step pdf chosen above to a generic $W(x)$ of the class discussed in the previous section. For fixed $\mu$ and $\sigma$ only $t$–independent numerical variations appear due to the change in the higher moments of $W(x)$. In particular the skewness can be made to assume prevalently positive or negative values by choosing a $W(x)$ with positive or negative third moment (while keeping the first moment $\mu > 0$), while the kurtosis distribution remain always peaked around positive values, with a variance which appear to vanish faster than the mean. This is in agreement with the properties of the average length distribution as given by eq. (23).

In summary, very large RRT’s over the space of possible protein lengths are indeed almost auto-averaging objects and it is sensible to compare the average properties of the random process to a few, or even a single, realizations of it.

**COMPARISON WITH THE OBSERVED LENGTH DISTRIBUTIONS**

To test our simple model we compare here the predicted length distributions with the real length distributions of proteins observed in nature. In this last decade the number of known protein sequences has been rapidly growing and is still growing now at a steady pace. A huge number of protein sequences coming from very many different species are now stored in various databases.

In particular the SIMAP [22] (Similarity Matrix of Proteins, http://mips.gsf.de/genre/proj/simap) database collects about all amino acid sequences from public databases and completely sequenced genomes. On September 2006 it was storing more than 5.5 millions of not-redundant proteins coming from more than 100000 different species.

| kingdoms            | number of species | number of proteins |
|---------------------|-------------------|--------------------|
| bacteria            | 11130             | 2217301            |
| viruses             | 14631             | 319885             |
| plants              | 31232             | 1156929            |
| animalia invertebrates | 25951             | 383760             |
| animalia vertebrates | 19341             | 772605             |
| environmental samples | 1453              | 32591              |
| synthetic samples   | 822               | 14660              |

**TABLE II: Number of species and proteins for each kingdom in SIMAP on September 2006.**

We report in Table II a coarse subdivision of all SIMAP proteins and their corresponding species in five (non-standard) main kingdoms: bacteria, viruses, plants, invertebrates (animalia) and vertebrates (animalia). In fig. 3 we provide plots of the corresponding length distributions.

![Fig. 3: Length distributions of SIMAP proteins. Each box shows an enlargement of the (not normalized) length distributions of proteins coming from all kingdoms ($\bar{l} = 335, \text{max} = 38031$), bacteria ($\bar{l} = 316.9, \text{max} = 36805$), viruses ($\bar{l} = 273.9, \text{max} = 7312$), plants ($\bar{l} = 314.5, \text{max} = 20925$), invertebrates ($\bar{l} = 416.1, \text{max} = 23015$), vertebrates ($\bar{l} = 397.1, \text{max} = 38031$).](image)

One can see that all SIMAP distribution profiles have a global similar shape, with a well defined overall position and scale. There are however also large fluctuations on smaller scales. In particular the curves of viruses, invertebrates and vertebrates show very high and narrow peaks in correspondence to certain specific values of length. Of course, on general grounds, our model is too simple and generic to make predictions on other than global properties of the profiles, so we should restrict to the lowest moments or cumulants of the distribution and perform robust coarse graining on the data for more refined analysis. We believe, in any case, that these peaks are to a large extent spurious, being due to an over–representation in the SIMAP database of those particular protein lengths. SIMAP in fact contains a lot of proteins which not necessarily come from completely sequenced genomes: this fact makes the collection of proteins not homogeneous over the species present in the database and so it is possible that certain peculiar lengths are more represented since they correspond to proteins of many more different species than other lengths. If the collection were homogeneous over the species, we would expect length distributions without high narrow peaks and also less fluctuating in general. At any rate, we verified that the global analysis reported below is almost insensitive to the removal by hand of the high and narrow peaks.

The SIMAP database provides a very large sample of
real proteins which can be assumed to be statistically significant. We believe therefore that it is sensible as a testbed for our model and we make the basic assumption that the SIMAP length distributions for different kingdoms as (almost) independent realizations of our stochastic process. The motivation is that different kingdoms have been going through almost independent evolutionary histories since a long time and, even if one cannot forget that far enough in the past there was non distinction at all, the main characteristic of the stochastic process of forgetting the initial conditions suggests that at most a negligible trace remain of the common remote past in each kingdoms distribution.

In table III we list the measured values of the mean, standard deviation, skewness, kurtosis and entropy of the logarithmic length distributions for the five kingdoms separately and for the cumulative all kingdoms distribution. Except for the entropy, these parameters can be computed directly from the statistical estimators as in eqs. (25) and (26) without any coarse graining. To compute the entropy we performed a coarse graining in the logspace with the same procedure of the preceding section. One can see that the kurtosis is always positive, in accordance with the average property of the model [eq. (23)] and with the results of the previous section on the fluctuations. We also notice that the cumulative kurtosis is definitely higher than the individual ones, due to the fluctuations in the lower cumulants. Again, this is consistent with the interpretation of the kingdoms distributions as independent realizations of the process. Except for the viruses, the entropy is always close to the upper Gaussian limit, with the plant distribution the closest to a normal form.

| kingdom     | mean  | s.d.  | skewness | kurtosis | entropy |
|-------------|-------|-------|----------|----------|---------|
| bacteria    | 5.53  | 0.68  | −0.20    | 0.32     | 1.408   |
| viruses     | 5.26  | 0.79  | 0.30     | 0.53     | 1.397   |
| plants      | 5.44  | 0.78  | −0.01    | 0.04     | 1.414   |
| invertebrates| 5.65  | 0.87  | −0.03    | 0.31     | 1.409   |
| vertebrates | 5.60  | 0.89  | −0.18    | 0.25     | 1.394   |
| all kingdoms| 5.49  | 0.81  | −0.26    | 0.63     | 1.406   |

TABLE III: Global statistical indicators of the SIMAP length distributions in logspace.

In fig. 4 we show the Gaussian fits of the length distributions. As expected from the data in table III these fits appear rather good, apart from fluctuations, which are more important when the entropy is lower, that is for viruses and vertebrates. Explaining these fluctuations is beyond the scope of our model. Moreover, one must remember that the SIMAP database is incomplete and, as discussed above, probably biased toward particular species; these features contribute to local irregularities.

With fine–tuned choices of the two main parameters of $\mathcal{W}(x)$, $\mu$ and $\sigma$, a specific large value of $\ell$ and values of the initial lengths in the range $30 - 50$, one can produce simulations with eq. (24), like those reported in fig. 2 whose distributions profiles fit well the peak positions and the sizes of the SIMAP length distributions.

Our choice for the initial distribution is based on the quite natural assumption that today’s proteins are evolved from shorter peptide ancestors [4, 23]. In any case, according to the model, $\tau$–independent changes in the initial distribution might affects the final distribution only by terms of relative order $1/\log \tau$.

We remark also that in our purely probabilistic framework no fine quantitative check can be performed, for some good reasons.

Firstly, even assuming that for each kingdom the proteins in the database constitute a statistically significant fraction of the total existing in nature, we do not know what the total number might actually be. So we cannot fix the precise value of the total discrete time of the stochastic process. This does not lead to large uncertainties, though, since the evolution is only logarithmic in this discrete time.

Secondly, the one–step pdf $\mathcal{W}(x)$ governing the model can hardly have any precise quantitative relation with the multitude of microscopic and macroscopic effects that drive the evolution. So one could not ascribe any particular value to a specific functional form of $\mathcal{W}(x)$ whose most relevant free parameters were determined from data fitting. Rather we must restrict to very general properties valid for a wide class of one–step pdf’s. This
argument applies also to the lowest moments of $W(x)$, that might very well differ in distinct independent
processes.

Let us examine therefore in more detail to what extent the model agrees with the observed distributions.

First of all, according to the model, the length distribution of a large set of protein belonging to a single
long evolutional history must be almost a Gaussian in logspace, that is a lognormal over the lengths. As we
have just seen, this agrees quite well with the SIMAP distributions. The approximate lognormality of protein
sizes was observed several years ago on much smaller data sets [24].

Next there are the two scales of the fluctuations of the two parameters of a Gaussian, namely the mean and the
standard deviation, which were denoted as $\mu$ and $\sigma$ in the previous section. Once a process simulation is fine-
tuned to produce the correct average values of $\mu$ and $\sigma$, their fluctuations have a scale which depends mildly on
the higher moments of $W(x)$, does not depend on $t$ in the case of $\mu$ and depend at most as $1/\log t$ in the case of $\sigma$.
These scales agree fairly well with those observed over the SIMAP kingdom distributions [see tables I and III],
the higher moments of $W(x)$, at least when $W(x)$ has skewness and kurtosis not too large. Notice that also the lower cutoff $\ell_{\text{min}}$ on the possible lengths acts as constraint on the higher cumulants of $W(x)$. For instance, an excessively negative skewness in $W(x)$ would typically lead to large left tails also in the length distributions which are then abruptly cutoff at $\ell_{\text{min}}$; such abrupt cuts are absent in the observed data, as evident from fig. 4.

Then there are the systematic deviations from gaussianity. The model predicts a positive kurtosis for any
$W(x)$ and the SIMAP data agree very well with this. Also the entropy is very close to the expected values,
extcept for the viruses, whose protein distribution is the least abundant, has the smallest mean length and the
largest relative fluctuations. However, the data in table III show also always negative skewness, again except
for the viruses. This characteristic cannot be accounted for too easily in the model.

Indeed, as we have already noted, it is natural to assume that the average protein length has been growing in
time. This requires that the first moment $\mu$ of the one–step pdf $W(x)$ is positive, that is that a positive shifts in
$x$–space prevails over negative ones. Now, from the average relation (23) and the numerical analysis reported
in the preceding section, a prevalently negative skewness requires that the third moment $\mu_3$ of $W(x)$ is negative.
The simplest Gaussian one–step pdf used to produce the results in fig. 2 has by definition $\mu$ and $\mu_3$ with the same
sign, but other pdf’s with positive $\mu$ and negative $\mu_3$ are certainly possible. However, this would mean even more
negative skewness in $W(x)$, causing problems with the lower cutoff $\ell_{\text{min}}$, unless very large unrealistic values of
the initial lengths are assumed, which in turns would typically spoil the overall scale fitting. Thus, after all, there
is tension on the model in spite of its many free parameters.

Our simple model for the protein length distributions is based on RRT embedded in the natural numbers, with the
assumption of almost scale invariance for the transition probability $W(\ell'|\ell)$. By this we mean that the
stochastic process is uniform in continuous logspace, with translation invariance broken only by length discreteness and the lower cutoff $\ell_{\text{min}}$, in both cases with negligible effects. This is an idealization suggested by simplicity (it translates the intuitive idea that longer pro-
teins can change more than shorter ones throughout evolu-
tions) and ease of analytic investigation of average properties. It has some difficulties in accounting for neg-
ative skewness (viruses apart), but it is in overall good agreement with observations, especially for the positive-
ness of the kurtosis. This suggests to keep to a minimum the modifications in more realistic models for $W(\ell'|\ell)$. We
describe one minimal change in the next section.

**INTRINSIC SMOOTH CUTOFF ON LARGE LENGTHS**

In the stochastic framework we have considered up to now, the vanishing of the length distribution for large $\ell$
is determined by the slowly drifting and diffusing charac-
ter of the process with the assumption of relatively small
initial lengths.

On the other hand there are physical reasons to ex-
pect that very long proteins are intrinsically less proba-
ble than shorter ones, in the sense that the “microscopic”
mechanisms that determine, upon countless repetitions,
the production of longer and longer proteins are eventually
limited by simple stability criteria: very long pro-
teins, to be stable against thermal fluctuations in the
natural environment, must fold in the biologically ac-
tive form more “tightly” than shorter ones, as could be
measured by their growing spectral dimension [26]; but
this requires more and more complex stereoscopic order-
ings while the building blocks (amino acids at the lowest
level and larger structures at the second and third level)
are limited in number and typology. We could there-
define some form of smooth cutoff on long lengths, parametrized by a stability scale $\ell_s$.

The minimal change on the model, as anticipated
above, could therefore be the following:

$$
W(\ell'|\ell) = \ell^{-1} g(\ell / \ell_s) W(\log(\ell / \ell'))
$$

(27)

where $W(x)$ is the usual one–step pdf in logspace and
$g(u)$ a smooth function which is almost constant for $u \ll 1$ and monotonically decreases to zero for large $u$.

The random recursion corresponding to eq. (28) is a
simple modification of eq. (24)

\[
\ell = \text{integer part of } e^\alpha \ell(n_t); \\
\text{if } \ell \geq \ell_{\text{min}} \text{ and } \tau < g(\ell/\ell_s) \text{ then } \ell(t + 1) = \ell
\]

(28)

where, as before, \(n_t\) is a random integer from 1 to \(t\) and \(x\) is extracted from \(\mathcal{W}(x)\), while the new random number \(\tau\) is extracted uniformly in the interval \((0, \ell_{\text{max}})\), with \(\ell_{\text{max}} = g(\ell_{\text{min}}/\ell_s)\) the assumed largest value of the function \(g\).

Another possibility could be to introduce an explicit \(\ell\)–dependence in \(\mathcal{W}(x)\), in such a way that length reductions \((x < 0)\) become more probable than length growths \((x > 0)\) for large enough lengths. In this case the random recursion would be the same of eq. (24); the only change is that \(x\) is extracted in a weakly non scale–invariant way from a one–step pdf \(\mathcal{W}(x; \ell)\).

Once some specific form for \(\mathcal{W}(x)\) and \(g(u)\), or for \(\mathcal{W}(x; \ell)\), is chosen, simulations with weakly broken scale invariance can be performed as easily as before. Since there are now more tunable parameters, it is almost obvious that data fitting can be improved. From a purely quantitative point of view this better fits have little significance. Instead we want to stress the main new qualitative aspects: the smooth cutoff typically induces shorter right tails in the simulated distribution, thus slightly reducing both skewness and kurtosis. If the one–step pdf has the right characteristics, it is possible to obtain almost always length distributions with still positive kurtosis but negative skewness after a few million steps. The cutoff prevents the formation of proteins too long, thus allowing to reproduce the observed mean length and length variance typically \(\ell_s\), which by construction provides the scale of the rightmost tail, need to be chosen between 5000 and 10000, depending on other details of the model.

It is also interesting to observe that the positive skewness of length distribution of the viruses does not constitute a problem to the above scenario, since the overall size of this distribution is smaller than the others and might very well be too small to feel the effects of the smooth cutoff on higher lengths.

**CONCLUSIONS AND OUTLOOK**

In this work we have described a simple stochastic framework for the theoretical modeling of the evolution of protein lengths. It is based on the idea of Recursive Random Trees over the set of natural numbers. RRT’s represent the simplest formal implementation of the main feature of the evolution process: new biological material is produced through modifications of the biological material already existing. In the case of proteins the full space over which the RRT grows is that of all amino acid sequences, but it can be reduced to more tractable spaces when only specific observables are considered, as is the case of the protein lengths.

Of course, the details of the stochastic process, as encoded in the conditional probabilities, are practically out of reach, due to the multitudes of natural causes ranging from biochemical interactions to selection mechanisms in varying environments. The relevance of the stochastic framework is based therefore on the concept of universality; namely that, under the law of large numbers, statistical coarse grained observations tend to take universal forms which depend only on few fundamental features of the stochastic process. In the case at hand, the main features are the auto-averaging property of RRT’s and the approximate scale invariance of the one–step transition probability; they imply the universal properties that protein length distributions are almost lognormal, with positive kurtosis and a specific scale for the overall deviations from exact gaussianity.

There are several routes for improvements. First of all, the choice of RRT’s (which have a uniform probability over all nodes of the tree for the attachment of the new node) is by itself an ideal simplification. In a more realistic setup one should consider differently weighted nodes in order to mimic certain aspects of the evolution process such as selection and differentiation. Then there are many more observables other than the distribution length in protein databases such as SIMAP. The global statistical analysis of the SIMAP protein homology network carried through in ref. [23] shows several interesting features which deserve to be studied within some generalization of the stochastic process described here.

**ACKNOWLEDGMENTS**

We are thankful to Thomas Rattei for his kind permission to access the SIMAP database.

[1] M. Drmota and H.-K. Hwang, *Bimodality and phase transitions in the profile variance of random binary search trees*. SIAM Journal on Discrete Mathematics 19, 1945 (2005)

[2] M. Drmota and H.-K. Hwang, *Profiles of random trees: correlation and width of random recursive trees and binary search trees*. Advances in Applied Probability 37, 321–341 (2005)

[3] A. Meir and J. W. Moon, *On the altitude of nodes in random trees*. Canadian Journal of Mathematics 30, 997 – 1015 (1978)

[4] P. Bialas, Z. Burda, J. Jurkiewicz, A. Krzywicki. *Tree Networks with Causal Structure*, Phys. Rev. E 67, 066106 (2003)

[5] J. Soding, A.N. Lupas, *More than sum of their part: on the evolution of proteins from peptides*. BioEssays 25, 837 – 846 (2003)
[5] T. Ohta, Role of gene duplication in evolution. Genome 31, 304 – 310 (1989)
[6] K.H. Wolfe, D.C. Shields, Molecular evidence for an ancient duplication of the entire yeast genome. Nature 387, 708 – 713 (1997)
[7] T.J. Vision, D.G. Brown, S.D. Tanksley, The origins of genome duplications in Arabidopsis. Science 290, 2114 – 2117 (2000)
[8] A. McLysaght, K. Hokamp, K.H. Wolfe, Extensive genomic duplication during early chordate evolution. Nature Genet 31, 300 – 304 (2002)
[9] M. Lynch, J.S. Conery, The evolutionary fate and consequences of duplicate genes. Science 290, 1151 – 1155 (2000)
[10] G.C. Conant e A. Wagner, Asymmetric Sequence Divergence of Duplicate Genes. Genome Res. 13, 2052 – 2058 (2003)
[11] S. Pascarella, P. Argos, Analysis of insertions/deletions in protein structures. J. Mol. Biol. 224, 461–471 (1992)
[12] S.A. Benner, M.A. Cohen, G.H. Gonnet, Empirical and structural models for insertions and deletions in the divergent evolution of proteins. J. Mol. Biol. 229, 1065 – 1082 (1993)
[13] B. Snel, P. Bork, M. Huynen Genome evolution: gene fusion versus gene fission. Trends Genet. 16, 9–11 (2000)
[14] B. Snel, P. Bork, M. Huynen The identification of functional modules from genomic association of genes. Proc. Natl. Acad. Sci USA 99, 5890 – 5895 (2002)
[15] W.F. Doolittle Genes in pieces: Were they ever together? Nature 272, 581 – 582 (1978)
[16] C.A. Voigt, C. Martinez, Z-G. Wang, S.L. Mayo, F.H. Arnold Protein building blocks preserved by recombination. Nat. Struct. Biol. 9, 553 – 558 (2002)
[17] G.C. Conant, A. Wagner The rarity of gene shuffling in conserved genes. Genome Biol. 6, R50 (2005)
[18] R. Aroul-Selvam, T. Hubbard, R. Sasidharan Domain insertions in protein structures. J. Mol. Biol. 338, 633 – 641 (2004)
[19] J. Weiner, F. Beausart, E. Bornberg-Bauer Domain deletions and substitutions in the modular protein. FEBS J. 273, 2037 – 2047 (2006)
[20] R.L. Graham, D. E. Knuth, O. Patashnik Concrete mathematics : a foundation for computer science Addison-Wesley, Reading, Mass. (1989).
[21] M. Abramowitz, I. A. Stegun, Handbook of mathematical functions: with formulas graphs and mathematical tables, Dover, New York (1972)
[22] R. Arnold, T. Rattei, P. Tischler, M. Truong, V. Stümpflen, W. Mewes, SIMAP - The similarity matrix of proteins. Bioinformatics 21, ii42 – ii46 (2005)
[23] C. Miccio, T. Rattei . Global statistical analysis of the protein homology network. q-bio.QM/0703053
[24] S.S. Sommer, J.E. Cohen, The size distributions of proteins, mRNA, and nuclear RNA. J. Mol. Evol. 15, 37 – 57 (1980)
[25] A.N. Lupas, C.P. Ponting, R.B. Russell On the evolution of protein folds: are similar motifs in different protein folds the result of convergence, insertion or relics of an ancient peptide world?. J. Struct. Biol. 134, 191 – 203 (2001)
[26] R. Burioni, D. Cassi, F. Cecconi, A. Vulpiani, Topological thermal instability and length of proteins. Proteins 55, 529 – 535 (2004)