Maternal effects in molecular evolution

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We introduce a model of molecular evolution in which the fitness of an individual depends both on its own and on the parent’s genotype. The model can be solved by means of a nonlinear mapping onto the standard quasispecies model. The dependency on the parental genotypes cancels from the mean fitness, but not from the individual sequence concentrations. For finite populations, the position of the error threshold is very sensitive to the influence from parent genotypes. In addition to biological applications, our model is important for understanding the dynamics of self-replicating computer programs.

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Simple models of asexual evolution, such as the quasispecies model, typically assume that the fitness of an organism is a function of only its genotype and the environment. This allows for the analysis of evolution in static or variable environments, many to one mappings from genotype to phenotype (neutral-}

ity) [11–13], and phenotypic plasticity [14]. These models disregard the potential influence of the mother (or parent, in general) on the organism’s phenotype. This influence comes about because in addition to the genetic material, a wealth of proteins and other substances is transferred from mother to child. In the context of sexual reproduction, the influence of the mother on a child’s phenotype is usually called a maternal effect. A classic example is that of the snail Partula suturalis [15], for which the directionality in the coiling of the shells is determined by the genotype of the mother of an organism, rather than the organism’s own genotype. Maternal effects are not exclusive to sexually reproducing organisms, however, they can be observed in simple asexual organisms as well. In bacteria, for example, the fitness of a strain in a given environment may depend on the environment that was experienced by the strain’s immediate ancestors [16, 17].

Here, our objective is to define and study a model of the evolution of asexual organisms that takes such maternal effects into account. We assume that the fitness of an organism is given by the product of two quantities \(a\) and \(b\), where \(a\) depends solely on the genotype of the mother of the organism, and \(b\) depends solely on the organism’s own genotype. Since we need to keep track of the abundances of all possible mother/child combinations, we need \(n^2\) concentration variables if we distinguish \(n\) different genotypes in our model. In the following, we denote by \(x_{ij}\), the concentration of organisms of genotype \(j\) descended from genotype \(i\), and by \(q_{ij}\) the probability that a genotype \(i\) mutates into genotype \(j\). The time evolution of the \(x_{ij}\) is then, in analogy to the quasispecies model,

\[
\dot{x}_{ij}(t) = \sum_k a_{kj} q_{ji} x_{ki}(t) - f(t) x_{ij}(t),
\]

with \(f(t) = \sum_{ij} a_{ij} b_j x_{ij}(t)\). The function \(f(t)\) gives the average fitness of the population at time \(t\). In principle, this model can be solved by diagonalizing a \(n^2 \times n^2\) matrix. However, since even for relatively short genetic sequences the number of possible genotypes \(n\) is enormous, this direct method is very cumbersome. Fortunately, a simple transformation exists that reduces the above problem to one in which the diagonalization of a \(n \times n\) matrix is sufficient. Namely, if we introduce variables \(x_i\) such that

\[
x_{ij} = b_i q_{ji} x_i \left( \sum_k b_k x_k \right),
\]

then, after inserting Eq. (2) into Eq. (1), we obtain in the steady state (\(\dot{x}_{ij} = 0\))

\[
\tilde{f} x_i = \sum_j a_{ij} b_j q_{ij} x_j
\]

with \(\tilde{f} = \sum_j a_{ij} b_j x_j\). The inverse transformation, which converts Eq. (3) back into the right-hand-side of Eq. (1), can be achieved with

\[
x_i = \left( \sum_j a_{ij} x_{ji} \right) \left( \sum_{j,k} a_{jk} x_{jk} \right).
\]

Therefore, Eq. (3) is fully equivalent to the steady state of Eq. (1). This leads to an interesting conclusion. Note that Eq. (3) is simply the steady state equation of the quasispecies model if we assume that genotypes \(j\) replicate with replication rate \(c_j = a_j b_j\) and mutate into genotypes \(i\) with \(q_{ij}\), while \(x_i\) gives the relative concentration of genotype \(i\). Consequently, the model with maternal effects is mathematically equivalent to the standard quasispecies model. Moreover, with the aid of Eq. (3) and Eq. (4), it can be shown that \(f(t \to \infty) = \tilde{f}\). Therefore,
the average fitness in both models is the same; the maternal effects drop out of the expression for the average fitness.

While the average fitness depends only on the values of $c_i$, the individual sequence concentrations actually depend on the details of the maternal effects. In particular, the total amount of sequences of a given genotype $i$ is not identical to the corresponding value $x_i$ in the standard quasispecies model ($\sum_j x_{ji} \neq x_i$ in general). From Eq. (3), we see that for every given mutation matrix $q_{ij}$, we can suppress any sequence concentration to as small a level as we please, by reducing the corresponding $b_i$ and holding the other $b_j$ constant ($\lim_{b_i \to 0} x_{ij} = 0$). Enhancement of sequence concentrations is also possible, although there exists an upper bound that cannot be exceeded. The upper bound is given by the matrix element $q_{ii}$ ($\lim_{b_i \to \infty} x_{ij} = q_{ii}$). Its existence is easy to understand: by changing $b_i$, we can only jointly manipulate the concentrations of all sequences descended from genotype $i$. The ratio between different genotypes $j$ descended from $i$ is always fixed, and it is determined by the matrix elements $q_{ij}$. At most, the sum over all descendants from all genotypes $i$ in the population can be one, $\sum_j x_{ij} = 1$, which implies $x_{ij} = q_{ij}$.

We will now classify the different types of maternal effects. If all $a_i = 1$, such that $b_i = c_i$, no maternal effects are present, and we obtain the normal sequence concentrations from the quasispecies model. We will refer to this situation as the neutral case. In order to classify all non-neutral situations, we compare concentrations of those sequences that are true copies of their parents (this is the only reasonable way, given that all genotypes descended from the same ancestor $i$ scale identically with $b_j$). If the concentration $x_{ii}$ of a sequence with large $c_i$ is reduced, while the concentration $x_{ij}$ of some other sequence with smaller $c_j$ is enhanced, we will speak of positive maternal effects. Likewise, if the sequence concentration of a faster replicating sequence is enhanced, at the expense of some slower replicating sequence, we will speak of negative maternal effects. In short, positive maternal effects promote slower replicators, and negative maternal effects promote faster replicators. We refer to the above classification as the direction of the maternal effects. Likewise, the strength of the maternal effects indicates the degree to which a system deviates from the neutral case (weak maternal effects show only a small deviation, strong maternal effects show a large deviation from the neutral case).

With Eq. (3) we can solve the model, as long as there exists an analytical solution for the corresponding quasispecies landscape. This means that solutions for multiplicative landscapes [18,19], the single peak landscape [20], and certain spin-glass landscapes [21,22] are readily available. In the following, we discuss the well-known example of the sharp single-peak landscape [2]. We assume that the genetic sequences are binary of length $\ell$. Moreover, we assume a uniform copy fidelity $q$ per digit. The sequence 000...0 may replicate (in the absence of mutations) with rate $c_0 = a_0b_0$. We will refer to this sequence as the master sequence. Let all other sequences replicate with $c_1 = a_1b_1 \ll c_0$. If $\ell$ is large, we may neglect back-mutations onto the master sequence, in which case it is sufficient to keep track of the total concentration of all sequences off the peak in a single variable, $x_1$. The mutation matrix $q_{ij}$ is then a $2 \times 2$ matrix with the elements $q_{00} = q^4$, $q_{10} = 1 - q^4$, $q_{01} = q_{10}/(2^\ell - 1)$, and $q_{11} = 1 - q_{01}$ (the elements $q_{00}$ and $q_{01}$ are approximated). In the standard quasispecies model, the equilibrium concentration of the master sequence $x_0$ is given by

$$x_0 = (c_0q_{00} - c_1)/(c_0 - c_1),$$

and $x_1$ likewise as $x_1 = 1 - x_0$. The average fitness follows as

$$f = \begin{cases}
    c_0q_{00} & \text{for } x_0 \geq 0, \\
    c_1 & \text{else}.
\end{cases}$$

Now, for the sequence concentrations with maternal effects, we obtain from Eq. (3) in conjunction with Eq. (2)

$$x_{0i} = b_iq_{00}(c_0q_{00} - c_1)/\Lambda,$n

$$x_{1i} = b_iq_{11}(c_0 - c_0q_{00})/\Lambda,$$

with $\Lambda = (b_0 - b_1)c_0q_{00} + b_1c_0 - b_0c_1$ and $i = 0, 1$.

Figure 1 displays the four sequence concentrations $x_{00}$, $x_{01}$, $x_{10}$, $x_{11}$ of the above defined landscape, for positive, negative, and neutral maternal effects. We see that indeed the maternal effects result in a significant shift in the sequence concentrations. The concentration $x_{11}$ (shown in the lower right of Fig. 1), e.g., encompasses almost the complete population for positive maternal effects at an error rate of about 0.04, while it constitutes less than 20% in the case of the negative maternal effects for the same error rate.

The potential shift in the individual sequence concentrations has important implications for finite populations. When the concentration of a sequence (as predicted for an infinite population) approaches the inverse of the population size, that sequence will most certainly be lost through sampling fluctuations. In the case of the master sequence, this effect is responsible for the shift of the error catastrophe towards smaller error rates for finite populations in the ordinary quasispecies model [23,28]. Now, since the concentration of the master sequence can be made arbitrarily small with suitable maternal effects, it follows that the error threshold can be shifted. This effect is illustrated in Fig. 2 for a population size of $N = 1000$, for which the error transition in the normal quasispecies model (as represented by the 'neutral' case) is already significantly shifted. Positive maternal effects increase this shift by a fair amount, while negative maternal effects can almost completely counteract
the finite population effect, and move the error transition very close to the infinite population limit. Besides the shift in the error transition, Fig. 2 shows that the average fitness is indeed unaffected by strength and/or direction of the maternal effects, as all three curves lie exactly on the infinite population result for error rates below the respective error transitions.

We have seen above that the mean fitness in the population is not influenced by the existence of maternal effects. Since selection acts only on the average fitness [24,31], it follows that the maternal effects cannot be under selective pressure. In order to verify this, we have performed simulations in which strength and direction of the maternal effects were allowed to evolve. To each sequence in the population, we added an inheritable variable $z$. On reproduction, the offspring received a value $z' = z + d z$, where $d z$ was a normally distributed random variable. For the master sequence, $z$ was then mapped into $a_0$ and $b_0$ via $a_0 = (\alpha + z)/\alpha$ for $z > 0$, $a_0 = \alpha/(\alpha + z)$ for $z \leq 0$, and $b_0 = 1/a_0$, with $\alpha$ defining the scale between $z$ and $a_0$, $b_0$. For $a_1$ and $b_1$, the value of $z$ was ignored. Figure 3 shows a typical simulation run in such a system. We chose $N = 1000$ and $1 - q = 0.06$, so that the population was below the error threshold in the absence of maternal effects, and we initialized all sequences in the population to $z = 0$. Over the course of a simulation, the $z$ values drift randomly, which can be seen in increasing and diminishing fluctuations about the average fitness. When the average $z$ drifts below zero, the fluctuations decrease, because $z < 0$ corresponds to negative maternal effects, which shift the population away from the error threshold. When the average $z$ drifts above zero, on the other hand, the fluctuations increase. If there is no upper limit to $z$, the fluctuations will eventually grow so large that the population is pushed over the error threshold. In Fig. 3 this happened around generation 5400.

The model we have introduced in this paper oversimplifies the situation for bacteria, where substances can remain in the cytoplasm for several generations, such that not only the parent, but also the grand- and the grand-grand-parent etc. have an influence on the phenotype of an individual. However, it is an exact description of the dynamics of the digital organisms (self-replicating and evolving computer programs) of the Avida system, which has been used extensively in experimental evolution research [24,31]. The replication rate of these digital organisms is the ratio between the number of instructions per unit time that they can execute [the speed of their central processing unit (CPU)] and the number of instructions they have to execute in order to produce a new offspring (length of the gestation cycle). The CPU speed depends on the number and type of logical operations that these organisms perform in addition to their replicatory activity (the more logical operations an organism performs, the faster its CPU will operate). Since the logical operations an organism can perform are only known a posteriori, these organisms obtain their initial CPU speed from their parent organism. The CPU speed corresponds thus to the parameter $a$ of the present work, and the length of the gestation cycle to the inverse of the parameter $b$. Therefore, we have shown in that a quasispecies description of the digital organisms is indeed justified, as was proposed in [30]. Also, our model might lead to a detailed quantitative description of the dynamics of digital organisms in future work.

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FIG. 1. Relative sequence concentrations vs. error rate $1 - q$. From left to right, and from top to bottom, we display $x_{00}$, $x_{10}$, $x_{01}$, $x_{11}$. Solid lines are the analytical predictions Eqs. (7), (8), dashed lines stem from simulations with $N = 10000$ sequences of length $l = 20$. The parameters of the fitness landscapes were $c_0 = 10$ and $c_1 = 1$, with $b_0 = 0.1, b_1 = 1$ (positive); $b_0 = 1$, $b_1 = 1$ (neutral); $b_0 = 1, b_1 = 0.1$ (negative).

FIG. 2. Average fitness vs. error rate $1 - q$. The solid line represents Eq. (6), and the dashed lines stem from simulations with $N = 1000$ sequences of length $l = 20$. The fitness landscapes were identical to Fig. 1.
FIG. 3. Average fitness vs. time in a population with evolving maternal effects. The dashed line indicates the infinite population result [Eq. (13)]. The population consisted of $N = 1000$ sequences of $l = 20$, the error rate was $1 - q = 0.06$, and the landscape was defined by $c_0 = 10$, $c_1 = 1$. The scale parameter $\alpha$ was set to $\alpha = 10$. 