Co-Evolution of quasispecies: B-cell mutation rates maximize viral error catastrophes

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Co-evolution of two coupled quasispecies is studied, motivated by the competition between viral evolution and adapting immune response. In this co-adaptive model, besides the classical error catastrophe for high virus mutation rates, a second “adaptation-” catastrophe occurs, when virus mutation rates are too small to escape immune attack. Maximizing both regimes of viral error catastrophes is a possible strategy for an optimal immune response, reducing the range of allowed viral mutation rates to a minimum. From this requirement, one obtains constraints on B-cell mutation rates and receptor lengths, yielding an estimate of somatic hypermutation rates in the germinal center in accordance with observation.

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During the past 30 years, the concept of quasispecies has developed into a valuable tool for modeling key features of molecular and viral evolution. It draws a simple picture of sequence evolution in the presence of a peaked fitness function, resulting in the formation of a central master sequence surrounded by a cloud of mutant sequences, summarized as the quasispecies. A prominent feature of such systems is the occurrence of an error catastrophe, a sudden breakdown of stability when mutation rates get large. Recent developments of quasispecies models include their formulation within a statistical mechanics framework and a characterization of the error catastrophe as a phase transition.

While traditionally defined on static fitness landscapes, the concept of quasispecies recently has been extended to non-stationary fitness environments. This has important applications, as viruses usually face quickly changing environments in the tight and temporal niches of their hosts. This new approach allows for studies of the adaptive response of a quasispecies to changing external conditions. This has been studied for different choices of time dependent fitness functions.

Here, we further extend this approach and study a virus in the environment of an adaptive immune system. To include the adaptive response of an immune system into the model, a further step has to be taken beyond a simple time dependent viral fitness function. An interesting observation is that motifs of immune receptors often form something very similar to quasispecies: A “master” sequence of the immune receptor, corresponding to the complementary epitope motif of the virus, is surrounded by a cloud of closely related receptor sequences that emerge from somatic hypermutation in the germinal centers. As the presence of the viral motif induces the proliferation of the corresponding receptor sequence, one can argue that this process can be represented in the framework of quasispecies, interpreting the conditions that lead to proliferation of specific immune receptors as the fitness of the particular receptors. Let us, therefore, formally consider the B-cell population induced by a specific viral epitope as a quasispecies itself.

In this paper, we, therefore, study the co-evolution of two asymmetrically coupled quasispecies under competition. While the immune quasispecies is strongly attracted by the virus, the viral quasispecies is driven away from its current master sequence by the immune system. This results in a migration through sequence space as observed in many infectious diseases as in HIV. In the following, let us first define the model in detail. Then, dynamical regimes and stability bounds are discussed which occur as a result of the selective forces acting on both sides of the system. Finally, from the perspective of an optimal immune response, a relationship between receptor size and mutability is derived. By maximizing the ranges of error catastrophes for the virus, bounds on observable mutation rates in the immune system are derived.

Consider a model with two quasispecies of genetic sequences, one of them coding for a virus and the second one coding for the variable part of an immune receptor. Sequence lengths are \( n_v \) and \( n_{is} \), respectively, with bases taken from an alphabet of length \( \lambda = 4 \). Mutation rates are quantified by the copy fidelities per base \( q_v \), \( q_{is} < 1 \). The time evolution of the two distributions, the concentration \( z_k(t) \) of viral sequence \( k \), as well as the concentration of immune cells \( y_k(t) \), representing receptor coding sequence \( k \), is described by two sets of coupled differential equations of the type introduced by Eigen:

\[
\dot{y}_k = \sum_{l} W_{kl}^{is} A(z_l) y_l - f y_k \quad (1)
\]

\[
\dot{z}_k = \sum_{l} (W_{kl}^v B_l - \delta_{kl} C(y_l)) z_l \quad (2)
\]

\[
W_{kl}^{is} = \frac{q_{is}^{n-d(k,l)}(1-q_{is})^{d(k,l)}}{(\lambda - 1)^{d(k,l)}} \quad (3)
\]

\( i \in \{is,v \}; \quad k,l \in \{1,...,\lambda^n \} \).

Locally in sequence space, we assume a simple one-to-one map between viral sequence and the sequence coding for the immune receptor that maximally fits the viral...
epitope (within the local neighborhood of mutated receptors). For simplicity, both sequences share the same subscript $l$ in the above formulation. Therefore, $A(z_l)$ denotes the growth rate of the B-cell clone corresponding to receptor sequence $l$ and depends on the concentration of its complementary viral sequence $z_l$. The viral replication rate is $B_l$, and its decay rate $C(y_l)$, which depends on the associated immune cell concentration. For viral, as well as immune receptor evolution, a transition probability $W_{kl}$ from a sequence $l$ to sequence $k$ by mutation is assumed, depending on the respective mutation rate $q_l$, sequence length $n_l$ and the Hamming distance of the two sequences $d(k, l)$. For simplicity let us assume $n_{is} = n_v = n$ with the comparable complexity of viral epitopes and corresponding immune receptors in mind. Equation (1) models the relative concentrations of immune receptor coding sequences, with constant overall population size normalized by $f = \sum_l A(z_l) y_l$. The viral population (2), on the other hand, does not reach a constant population size, as the immune system usually works efficiently enough for the virus not to enter the regime of saturation. Therefore, absolute concentration is considered here and is the adequate quantity to quantify viral feed-back to immune cell proliferation.

As viral existence in sequence space often is restricted to narrow niches with high fitness, let us assume a fitness landscape with a single peak with $B_l = \sigma_v \gg B_{m\neq l} = \eta_v$ that moves as a result of immune system pressure. Vice versa, as the immune response represents a very specific answer to a pathogen, let us also model the immune fitness landscape to have a single peak, corresponding to the receptor matching the current antigenic master sequence. This simplifies the co-evolution model to a few discrete alternatives: $A(z_l) = \sigma_{is}$ if and only if $z_l$ represents the concentration of the viral master sequence, otherwise $A(z_l) = \eta_{is} \ll \sigma_{is}$. Analogously, $C(y_l) = \delta$ if and only if $y_l$ represents the dominant immune receptor’s concentration, otherwise $C(y_l) = 0$. This makes the complicated couplings in the above equations tractable and allows us to neglect mutational backflow to the respective master sequences. Let us first write down simplified equations that apply to both quasispecies (1) and (2).

For this purpose we use non-normalized concentrations \(^{[14,15]}\) for quasispecies (1) also, and neglect the decay term in (2) for the moment. Then, each of the two quasispecies can be written in terms of the concentrations of a master sequence $x_0$ and of an arbitrary sequence of the first error class $\Gamma_1 x_1$.

$$\dot{x}_0(t) = q^n \sigma x_0(t)$$

$$\dot{x}_1(t) = \frac{1 - q}{1 - q} q^{n-1} \sigma x_0(t) + q^n \eta x_1(t)$$

The interaction between the two systems has to be specified by extra rules on the basis of the above definition of growth and decay rates. To keep the model as simple as possible, the decay rate $\delta$ only affects the viral sequence matching the dominant immune receptor. If this happens to coincide with the viral master sequence, the viral fitness peak will effectively move. Depending on its strength, the former fitness peak eventually will drop below the environmental growth rate. To be specific, the dynamical rules of this process are defined as follows:

1. Once the immune system imposes a decay rate $\delta > 0$ on the viral master sequence (so far stabilized at the viral fitness peak), the narrow niche of the virus is assumed to move to an arbitrary sequence of the first error class.

2. The viral quasispecies adapts to the new fitness peak on a time scale $\tau_v$ given by the dynamical equations above.

3. The fitness peak of the immune quasispecies is adjusted to the new maximum of the viral distribution.

4. The immune system adapts to the new fitness peak on a second time scale $\tau_{is}$ determined as above.

These steps are then iterated. While this is a strongly simplified picture of the co-evolutionary dynamics of two coupled quasispecies, the localization of the interaction to their respective master sequences, as well as the restriction to only two growth rates for each quasispecies, allow a simple estimate of the dynamical regimes of the two coupled sets of equations of type \(^{[14,15]}\). Each of the fitness peaks is adjusted once during each cycle of duration $\tau = \tau_v + \tau_{is}$ (in steps 1 resp. 3). This allows us to follow the arguments of Nilsson and Snoad \(^{[8]}\) to determine the relative growth of the respective future master sequences over a full cycle $\tau$ as a criterion for the quasispecies’ survival \(^{[8]}\).

$$\kappa = \frac{1}{e^{\sigma \tau}} \frac{x_1(\tau)}{x_0(0)} = \frac{e^{(q^n \sigma - \eta) \tau} - e^{(q^n \eta - \eta) \tau} (1 - q) \sigma}{(\lambda - 1)(\sigma - \eta) q}.$$ (6)

This expression is applied to each one of the two quasispecies (with the respective variables), defined over the full interval $\tau = \tau_v + \tau_{is}$ between two adjustments of its fitness peak. For a relative growth coefficient $\kappa > 1$ a species will survive and for $\kappa \leq 1$ it will get extinct.

Now consider a coupled system of viral and immune quasispecies where the immune part exerts a selective kill or decay rate $\delta$. To estimate the migration time scale of the virus $\tau_v$, let us iterate the model for a full cycle $\tau$ starting at the moment of the move of the fitness peak at $t = 0$. The relative size of the old and new master sequence peaks is then subsequently determined for another time interval $\tau_v$. Let us assume $x_1(0) = 0$ since the new error class one sequence members are mainly recruited from the former, weakly populated error class two. The time
scale \( \tau_v \) is given by the waiting time until the new master sequence population exceeds the old one:

\[
e^{(q_v^0 v_0 - \delta) \tau_v} x_{0v}(\tau) = e^{q_v^0 \sigma_v \tau_v} x_1(\tau) \quad \Rightarrow \quad e^{(q_v^0 v_0 - \delta) \tau_v} e^{q_v^0 \sigma_v \tau_v} = e^{q_v^0 \sigma_v \tau_v} (1 - q_v) \sigma_v \frac{(\lambda - 1)(\sigma_v - \eta_v)q_v}{(\lambda - 1)(\sigma_v - \eta_v)q_v}.
\]

Mutational flows between the involved sequences can be neglected due to the small growth of the former master sequence and the small size of the initial new master sequence population. Assuming \( \sigma_v \gg \eta_v \) and \( q_v \approx 1 \) the viral adaptation timescale can be estimated to

\[
\tau_v \approx - \frac{\ln \left( \frac{1 - q_0}{\lambda - 1} \right)}{q_0^v (\sigma_v - \eta_v) + \delta}.
\]

Similarly, for the migration time for the immune quasispecies \( \tau_{is} \) we obtain

\[
\tau_{is} \approx - \frac{\ln \left( \frac{1 - q_v}{\lambda - 1} \right)}{q_0^{is} (\sigma_{is} - \eta_{is})}.
\]

Both, \( \tau_v \) as well as \( \tau_{is} \), exhibit a local minimum at specific values of their copy fidelities \( q_v \) and \( q_{is} \), mainly determined by the balance between the requirement of a sufficiently large initial population for the formation of a future master sequence and sufficiently low mutational losses of the new master sequence. Inserting \( \tau \) into the expressions for viral stability \( \kappa_v \) and immune stability \( \kappa_{is} \) according to (6), one obtains estimates for the regimes of viral and immune (co-)existence.

Fig. 1 shows these regimes in terms of the respective mutation rates \( \mu_v = 1 - q_0 \). The classical error catastrophe occurs at lower mutation rates in comparison to the static error threshold \( \mu_{err}^{stat} = 1 - (\frac{2}{\sigma})^\frac{1}{\lambda} = 0.045 \) (cf. [1]). This effect is due to additional mutational losses by migration and becomes large for small \( \tau \). In addition, Fig. 1 shows different limiting behaviors for \( \kappa_v \) and \( \kappa_{is} \) for \( \mu_v \rightarrow 0 \) and \( \mu_{is} \rightarrow 0 \), respectively, which can be summarized as

\[
\kappa_v \quad \mu_v \rightarrow 0 \quad \Rightarrow \quad 0
\]

\[
\kappa_{is} \quad \mu_{is} \rightarrow 0 \quad \Rightarrow \quad e^{(\sigma_v - \eta_v)\tau_v}.
\]

For the viral quasispecies one observes a second error (“adaptability”) catastrophe at small viral mutation rates, because a minimum viral mutation rate is needed to escape the decay rate \( \delta \) induced by the immune response at the viral master sequence.

FIG. 1. Regimes of viral and immune quasispecies (co-)existence, with \( +/− \) denoting stable/unstable regions of the respective quasispecies in dependence on mutation rates \( \mu_v \) and \( \mu_{is} \). Parameters are \( \sigma_v = \sigma_{is} = 10 \), \( \eta_v = \eta_{is} = 1 \), \( \delta = 200 \), \( n_v = n_{is} = 50 \), and \( \lambda = 4 \). A large value of \( \delta \) is chosen to get a good qualitative view of the system’s behavior.

The \( \kappa_v \)-surface in the \( \mu_v - \mu_{is} \)-plane, whose \( \kappa = 0 \) contour lines are shown in Fig. 1, is dominated by a saddle point: \( \kappa_v(\mu_v) \) exhibits a local maximum while \( \kappa_v(\mu_{is}) \) shows a local minimum. An optimal strategy for viral suppression is, therefore, to adjust the mutation rate \( \mu_{is} \) of the immune quasispecies such that \( \kappa_v \) operates in its valley, with maximum regions of error catastrophes on both sides. One obtains the condition

\[
\frac{\partial \kappa_v}{\partial \mu_{is}} \biggl|_{1} = 0,
\]

which can be written as

\[
\mu_{is} - 1 + n_{is} \mu_{is} \ln \left( \frac{\mu_{is}}{\lambda - 1} \right) = 0.
\]

This mutation rate minimizes the regime of possible existence of the viral quasispecies in Fig. 1. Depending on the involved viral and immune growth rates, this range of allowed viral mutation rates \( \mu_v \) may vary (and even vanish for some values).

How does this compare with experimental results? Let us focus on B-cells and their antibodies. Each antibody has at least two antigen receptors located in the variable regions of the antibody’s heavy and light chains, each of which contains about 110 amino acids. Each receptor is coded by approximately 660 nucleotides. Antigen detection takes place in 6 subregions, the complementarity
determining regions (CDRs) that represent 20 – 30% of the antibody’s variable (V-) regions [15,17]. In the course of the primary immune response one observes somatic hypermutation in the recombined V-region genes, with mutational hot spots at the CDRs, resulting in an enhanced affinity towards the invading antigen [19,18,18]. Observed mutation rates are in the range of $10^{-4}$ to $10^{-3}$ mutations per base pair per generation [20,22]. Mutation rates in the CDRs are approximately twice to tenfold higher than those found in the entire V-region [23,21]. These observations are quite universal to adaptive immune systems that are common to jawed vertebrates. Differences are mainly found in the effectivity of selection due to varying stages of germinal centers’ expression [24,25].

As Fig. 2 shows, the model prediction agrees well with the observed somatic hypermutation rates and CDR receptor lengths.

To summarize, the dynamics of the co-evolution of two coupled quasispecies has been studied. In particular this model was formulated to provide a simple toy model for the co-adaptive system of viral evolution and immune adaptation. The model characterizes the different regimes of (co-)existence of viral and immune quasispecies and predicts the correct range of somatic mutation rates in accordance with observation. Possible extensions of this work are numerous, as this is only a first account of basic principles of co-evolving quasispecies. Analytical approaches beyond the simple approximation presented here, as well as numerical extensions may provide a more accurate picture of the dynamics and further possibilities to relate to biological data. Further applications include modeling HIV dynamics, e.g. by adding an overall decay rate representing the HIV-induced loss of CD4+ T-cells.

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![FIG. 2. Predicted mutation rates vs. receptor coding lengths for an optimal immune response, in comparison to observed rates of somatic hypermutation and observed CDR coding lengths.](image)

| No. of nucleotides coding the CDRs | $\mu_{is}$ | observed mutation rates |
|-----------------------------------|-----------|-------------------------|
| $10^{-8}$                          | $10^{-5}$ |                         |
| $10^{-7}$                          | $10^{-4}$ |                         |
| $10^{-6}$                          | $10^{-3}$ |                         |
| $10^{-5}$                          | $10^{-2}$ |                         |
| $10^{-4}$                          | $10^{-1}$ |                         |

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