LETTER

Time-shift experiments and patterns of adaptation across time and space

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Abstract

Time-shift experiments provide measures of the mean fitness of a population in environments of different points in time. Here, we show how to use this type of data to decompose mean fitness into (1) the effect of the environment in which the population is transplanted, (2) the effect of the genetic composition of the population and (3) 'temporal adaptation', which measures how the population fits the environment at that time. We derive analytical results for the pattern of 'temporal adaptation' and show that it is in general maximal in the recent past. The link between 'temporal adaptation' and 'local adaptation' is discussed, and we show when patterns of adaptation in time and space are expected to be similar. Finally, we illustrate the potential use of this approach using a data set measuring the adaptation of HIV to the immune response of several recently infected patients.

Keywords

AIDS, experimental evolution, fluctuating environment, HIV, host-parasite coevolution, local adaptation, neutralising antibodies, red queen, spatial heterogeneity, transplant experiments.

INTRODUCTION

Understanding adaptation to a changing world is a major challenge of theoretical evolutionary biology. Changing selection pressures are thought to promote the maintenance of genetic polymorphism (Gillespie 1974), the evolution of mutation rates (Ishii *et al.* 1989; M'Gonigle & Otto 2009), sexual reproduction (Barton 1995; Gandon & Otto 2007) or migration (Blanquart & Gandon 2011). Understanding the evolution of populations in changing environment raises the following problem: a change in the mean trait of a population may be due to adaptive evolution of the trait and/or to a change in the environment, which affects the trait (Cooke *et al.* 1990; Garant *et al.* 2004). Hence, the distinction between evolutionary and environmental changes in the mean trait of a population is key to our understanding of adaptation in a changing environment (Price 1972; Frank & Slatkin 1992; Gandon & Day 2009). For example, people studying evolution in the wild separate these components by using the 'animal model' (Kruuk 2004), based on the calculation of the breeding value of the trait (i.e., the total of additive genetic effects on this trait). In practice, however, this approach can be difficult to carry out because it requires knowledge of the pedigree of the populations.

An alternative approach is provided by *time-shift experiments*, a tool that has been increasingly used in the last few years to understand the dynamics of adaptation to changing environments (see Gaba & Ebert 2009 for a review). A time-shift experiment consists in comparing the mean fitness (or a trait used as a proxy for the fitness) of a population in its contemporary, past or future environments. This type of data is becoming available in a wide diversity of biological systems. The emerging research field of 'resurrection ecology' uses revived dormant stages to demonstrate rapid genetic change in response to eutrophication of a lake (Hairston *et al.* 1999) or to drought (Franks *et al.* 2007). The possibility to revive 30 Kyr old seeds (Yashina *et al.* 2012) and 1 Myr bacteria (Johnson *et al.* 2007) offer exciting perspectives for such assays. Time-shift experiments are used in longitudinal studies, where individuals are sampled and assayed at regular time intervals, and are particularly promising to study genetic response of populations to global climate change (Bradshaw & Holzapfel 2001; Pulido & Berthold 2010). Time-shift experiments are also easily conducted with microorganisms in experimental evolution (Bennett *et al.* 1992; Reboud & Bell 1997; Kassen & Bell 1998; Collins *et al.* 2006; Cooper & Lenski 2010). Furthermore, time-shift experiments are routinely used in the study of parasite-immune system coevolution in infectious diseases (Shimizu *et al.* 1994; Richman *et al.* 2003; Smith *et al.* 2004; Moore *et al.* 2009). More recently, several time-shift experiments have been performed to reveal the coevolutionary interactions driving host parasite interactions (Buckling & Rainey 2002; Decaestecker *et al.* 2007; Koskella & Lively 2007; Gandon *et al.* 2008; Gaba & Ebert 2009; Bérénos *et al.* 2011; Gómez & Buckling 2011; Hall *et al.* 2011; Rode *et al.* 2011; Thrall *et al.* 2012). In these systems indeed, reciprocal coevolution is expected to generate very dynamic changes in both partners of the interaction (e.g., Burdon & Thrall 1999; Sasaki 2000).

In practice, however, inferring the details of the evolutionary dynamics is difficult because, as pointed out above, multiple effects affect the mean fitness of the population. In particular, very different scenarios of environmental change can lead to very similar patterns of mean fitness variation across time (Gandon *et al.* 2008; Gaba & Ebert 2009). In this study, we view time-shift experiments as a general tool to study adaptation to changing environments. This broader perspective leads us to develop a theoretical framework to help develop predictions and interpret the result of time-shift experiments. As explained above, the performance of a population transferred to the environment of another time depends on the impact of the environment and the properties of the population on mean fitness. But actually, this simple description misses the fact that mean fitness may also depend on the *interaction* between the environment and the genetic composition of the population. More formally, the mean fitness of a population sampled at time t transferred into the environment at time $t + \tau$ can be written as $\overline{W}_{t \to t+\tau} = e_{t+\tau} + g_t + \delta_{t,t+\tau}$, where the three terms represent the effect of the environment, E, on mean fitness, the effect of the intrinsic quality of population, G, that *does not* depend on the envi-

ronment and, finally, the interaction $G \times E$ between the population and the environment for fitness respectively.

The pattern of mean fitness through time shifts is the sum of these three components. Yet these three components are not disentangled in existing studies, which is why the full pattern may be hard to interpret. In particular, the $G \times E$ interaction term captures the fact that the population is developing specific adaptations matching the peculiarities of the environment at that time. In this study, we focus on the $G \times E$ interaction. First, we present a conceptual method to extract this component of the mean fitness under different ecological scenarios. Second, we illustrate the potential use of this approach using a data set examining the adaptation of HIV to the immune response launched in several recently infected patients (Richman *et al.* 2003). This analysis unveils several new aspects of the within-host evolution of HIV and demonstrates the power of this decomposition of mean fitness in the three above mentioned components.

TEMPORAL AND LOCAL ADAPTATION IN A MODEL WITH NON-EVOLVING VARIANCE

General model of temporal adaptation

First we develop a simple quantitative genetics model to describe the evolution of a population in a temporally variable environment and predict the pattern of temporal adaptation through time shifts. We formalise in a general way the relationship between the fitness of an individual, its traits and the environment. We assume that the individuals are characterised by a set of ecologically relevant traits which may change through time, and the environment is defined by a set of environmental variables which also change through time. The fitness of the individual k sampled at time t and transplanted into time $t + \tau$ is given by:

$$W_{k,t \rightarrow t+\tau} = f(\mathbf{Z}_{k,t}, \mathbf{X}_{t+\tau}) \tag{1}$$

where f is the fitness function, $\mathbf{Z}_{k,t}$ is a vector with the values of the m traits, $z_{j,k,t}$ with $j \in \{1, \cdots, m\}$, of the individual, and $\mathbf{X}_{t+\tau}$ is a vector with the values of the n environmental variables, $x_{j,t}$ with $j \in \{1, \ldots, n\}$. Equation 1 means that fitness may depend on the traits of the individual, on the properties of the environment, but also on the interaction between the traits and the environment. Approximating the fitness function as a second order taylor series around the average environment $\tilde{\mathbf{X}}$ and the average trait $\tilde{\mathbf{Z}}$, we find the part of mean fitness that depends on the $G \times E$ interaction has the form

$$\delta_{t \rightarrow t+\tau} = \sum_{j=1}^{n} \sum_{i=1}^{m} \bar{z}_{t,i} x_{t+\tau,j} \left. \frac{\partial^2 f}{\partial z_i \partial x_j} \right|_{\tilde{Z}, \tilde{X}}$$

where $\bar{z}_{t,i}$ is the mean trait i in the population at time t. In this framework, we define a component of the $G \times E$ interaction, which we call 'temporal adaptation', and which reads:

$$C_{TA}^{(\tau)} = \sum_{j=1}^{n} \sum_{i=1}^{m} \mathrm{Cov}[\bar{Z}_{i,t}, X_{j,t+\tau}] \left. \frac{\partial^2 f}{\partial z_i \partial x_j} \right|_{\tilde{z}, \tilde{x}} \tag{2}$$

where the capital letters $\bar{Z}_{i,t}$ and $X_{j,t+\tau}$ represents the variables that define the mean traits and environmental variables through time. Temporal adaptation depends on the covariances between the mean traits and the environments in which the populations are transplanted.

Besides, these covariances are weighted by the derivatives $\left. \frac{\partial^2 f}{\partial z_i \partial x_j} \right|_{\tilde{z}, \tilde{x}}$ which measure how a change in each environmental variable impacts the selection gradient for each trait (i.e., the specificity between the environment and the traits). In other words, temporal adaptation quantifies how well the populations fit the environments in which they are transplanted. In principle, the traits may themselves depend on the environment (see discussion on phenotypic plasticity). In this study, however, we assume the phenotype is directly determined by additive genetic effects. This is why we refer to temporal adaptation as representing the '$G \times E$' component of the interaction rather than the interaction between the *phenotypic* composition of the population and the environment.

Two methods to calculate temporal adaptation

Temporal adaptation may be calculated in two ways. First, we developed an original method, inspired by a local adaptation experiment, to calculate temporal adaptation (Appendix A). This method has the advantage of giving the *absolute* value of the covariance; but it relies on having a full-factorial time-shift experiment. Second, the linear model $\overline{W}_{t \rightarrow t+\tau} = e_{t+\tau} + g_t + \delta_\tau$ may be fitted to the data, following Rode *et al.* (2011). Such linear model may seem problematic, because the three effects are in theory not independent, and the structure of the error may be far from normal (Appendix A). In spite of these shortcomings, δ_τ estimates temporal adaptation in a number of scenarios, and fails to do so only when there is a sustained directional change in the environment (see below). Furthermore, this approach has the advantages of relying on standard statistical techniques, and it also provides estimates of the effects of the environment and genotypes through time.

To summarise, we showed that the result of a time-shift experiment depends on three components that vary through time shifts, and we introduced two methods to estimate 'temporal adaptation', a component of the $G \times E$ interaction for fitness that represents how the population matches the environment of a time. Although the context of the experiment may provide predictions for the direct effect of the environment, E (e.g., pollution or decreased resource level deteriorates the environment), and for the genotypic composition of the population, G (e.g., it should increase under the action of natural selection), it is difficult to develop intuitions on how 'temporal adaptation' may change through time under different scenarios of environmental change. We derive such predictions in the next part.

A model of adaptation to a moving optimum

What are the effects of different forms of temporal changes of the environment on temporal adaptation? We try to answer this question in the next section where we allow the phenotypic traits of the population to vary under the action of temporally variable selection. We assume a large population under selection for a single trait towards a moving optimum. Generations are discrete and non-overlapping. The environment is characterised by the optimum $\theta_{t+\tau}$ and each individual by its trait $z_{k,t}$ ($n = 1$ and $m = 1$ in eqn 2). The fitness of the individual k at time t transplanted into the environment of time $t + \tau$ is given by $f(z_{k,t}, \theta_{t+\tau}) = 1 - \gamma(z_{k,t} - \theta_{t+\tau})^2$ where γ is the strength of selection (Lande & Shannon 1996). Selection may act at any stage of the life cycle. In principle, this function can return negative fitness values, but in practice this does not happen when individuals' traits are not too far from the optimum and/or selection is weak. Under this scenario temporal

adaptation is given by $C_{TA}^{(\tau)} = 2\gamma \text{Cov}[\bar{Z}_t, \Theta_{t+\tau}]$. We assume that the phenotype of an individual only depends on the additive genetic effects on the phenotype. For simplicity, we further assume that the additive genetic variance V_G is constant, which is a valid hypothesis when selection on each locus (which erodes polymorphism) is weak relative to processes restoring polymorphism such as mutation or migration (Burger & Lande 1994). We also assume that the distribution of the trait in the population is characterised by its mean and variance (the skew and other higher order moments are assumed to be negligible). It can be readily shown in this case (Lande 1976; Lande & Shannon 1996) that the mean trait in the population evolves as:

$$\bar{z}_{t+1} = \bar{z}_t + 2\gamma V_G (\theta_t - \bar{z}_t) \tag{3}$$

Temporal adaptation quickly stabilises to (Appendix B):

$$C_{TA}^{(\tau)} = 4 V_G \gamma^2 \sum_{j=1}^{\infty} (1 - 2 V_G \gamma)^{j-1} \text{Cov}[\Theta_{t-j}, \Theta_{t+\tau}] \tag{4}$$

The covariances $\text{Cov}[\Theta_{t-j}, \Theta_{t+\tau}]$ are between the set of environments in which the populations are transplanted $\Theta_{t+\tau}$, and the successive sets of environments in which these populations evolved Θ_{t-j}. The sum integrates all past selection pressures, but more recent selection pressures have more impact on temporal adaptation. This is because the older the selective pressures, the weaker their effect on the current phenotypic state of the population.

Temporal adaptation for specific environmental changes

We made eqn 4 explicit under several scenarios of environmental change (Fig. 1; Appendix B). In general, we found that temporal adaptation is maximal not far in the past. The lag between the populations and the environments depends on the strength of selection and the genetic variance (Appendix B). When the environment change is characterised by an exponentially decaying autocovariance function, the covariances in eqn 4 are all positive, so temporal adaptation is positive and tends to zero as populations are transplanted further in the future or the past (Fig. 1, second row = white noise, third row = autocorrelated random change). In contrast, a periodical change of the optimum generates a periodical pattern of temporal adaptation where half of the time temporal adaptation is negative (Fig. 1, first row).

We also investigated a scenario where the optimum changes linearly through time (Fig. 1, last row). In this scenario, temporal adaptation is constant when the same number of populations is sampled for each time shifts. In many experimental designs, however, the number of transplants is smaller as time shifts are further away from the present. Because the covariance in (4) increases with the number of transplants (Appendix B), such designs make the pattern of temporal adaptation maximal in the present and decreasing symmetrically in the past and future (Fig. 1, last row). Besides, note that in this scenario, the assumptions of the statistical model $\overline{W}_{t \to t+\tau} = e_{t+\tau} + g_t + \delta_\tau$ we use to estimate temporal adaptation are strongly violated because the trait and the environment both increase linearly through time (Appendix A). This may explain the relatively poor match between δ_τ and temporal adaptation in Fig. 1, last row.

Comparing temporal and local adaptation

Time-shift experiments are very similar to transplant experiments in space between different populations (local adaptation experiments). As such it is tempting to push this analogy further to explore when and why these two patterns could be similar, or different. Local adaptation is a quantity commonly measured in studies of adaptation in spatially heterogeneous environments. Local adaptation is obtained by measuring the difference between mean fitness of populations in sympatry and their performance in allopatry (when transplanted to other site; see Kawecki & Ebert 2004). We consider a set of populations that evolve following the assumptions of the above quantitative genetics model, where the trait of each of these populations is selected towards a different optimum. Using a framework similar to the one used in the first part, it can be shown that the expected level of local adaptation over the different populations is equal to (Blanquart *et al.* 2012):

$$C_{LA} = 2\gamma \text{Cov}^S[\bar{Z}, \Theta] \tag{5}$$

where $\text{Cov}^S[\bar{Z}, \Theta]$ is the covariance between the mean traits $\bar{Z}$ and the local optima *in the metapopulation* at time t. Local adaptation quantifies how well populations fit their local environment. Note that this expression is very similar to the one describing temporal adaptation at $\tau = 0$, $C_{TA}^{(0)} = 2\gamma \text{Cov}[\bar{Z}_t, \Theta_t]$, the only difference being that the latter involves a *temporal* covariance between the mean traits and the environment. In other words, temporal adaptation at $\tau = 0$ can be thought of as an analogous in time of local adaptation.

In the following, we pursue our comparison between patterns of adaptation in space and in time under a general model of temporal variation of the optimum. To track the dynamics of local adaptation we need to characterise the change in the covariance of the local trait and the local environment in eqn 5. If migration between demes is neglected, we find that local adaptation is given by (Appendix C):

$$C_{LA} = 4 V_G \gamma^2 \sum_{j=1}^{\infty} (1 - 2 V_G \gamma)^{j-1} \text{Cov}^S[\Theta_t, \Theta_{t-j}] \tag{6}$$

where $\text{Cov}^S[\Theta_t, \Theta_{t-j}]$ is the covariance between the sets of environments in the metapopulation at time $t - j$ and t. This expression bears some similarity with temporal adaptation at $\tau = 0$ (eqn 4 with $\tau = 0$) because it quantifies the match between the set of environments in which the populations are transplanted, and the successive sets of environments in which these populations evolved. Again, the sum integrates all past selection pressures, with more recent selection pressures having more impact on temporal adaptation.

To compare local and temporal adaptation in more general scenarios, we calculate the average of C_{LA} over the time interval of the experiment and similarly, we calculate the average of $C_{TA}^{(0)}$ over all demes, and find (Appendix C):

$$E^T[C_{LA}] = \Gamma^{S,T} - \Gamma^T \tag{7a}$$

$$E^S\left[C_{TA}^{(0)}\right] = \Gamma^{S,T} - \Gamma^S \tag{7b}$$

Both local and temporal adaptation have in common the term $\Gamma^{S,T}$. The difference between local and temporal adaptation only emerges from the difference between the last terms Γ^T and Γ^S in eqns 7a and b. The component Γ^T quantifies the temporal autocovariance of the average environment in the whole metapopulation. Γ^S quantifies the temporal autocovariance of the environments within local populations, between successive time intervals. Large, correlated fluctuations at the level of the metapopulation will generate more
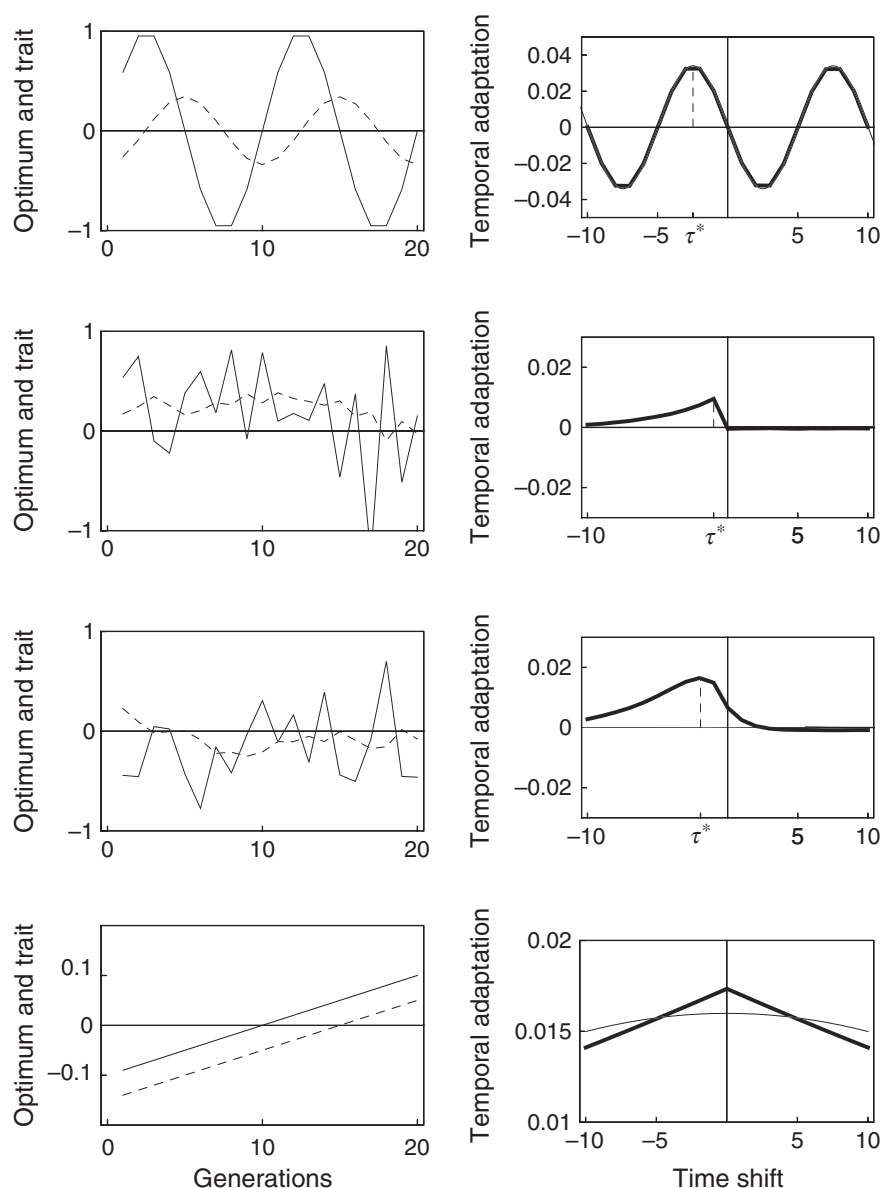
Figure 1 'Temporal adaptation' pattern $\mathrm{Cov}^{(\tau)}_{TA}$ resulting from a time-shift experiment with 100 populations and 100 environments sampled (the fitness for 10 000 transfers is measured). Left panel: change in the optimum (plain line) and in the trait (dashed line) through time for a sine wave, white noise, autocorrelated random and linearly changing optimum (from bottom to top). Right panel: temporal adaptation pattern through time shifts (thick line; analytical prediction given by eqn 4 is identical) with the theoretical lags τ^* (Appendix B). The interaction term δ_τ estimated with a statistical model is identical to temporal adaptation in all cases, except in the 'linearly changing' scenario (thin line).

temporal than local adaptation (Fig. S1, second column). Diverging selection pressures across demes will generate more local than temporal adaptation (Fig. S1, third column).

In fact, a major insight of eqns (5–7) is that under the assumption that sampling the mean trait over time or over space is equivalent (Frank 1991), local and temporal adaptation at $\tau = 0$ will be equal because the spatial and the temporal covariances will be equal. It will be the case, specifically, when the optimum follows a stationary or periodic change in each deme, and the environment at the scale of the metapopulation is constant (Fig. S1, first column). This prediction leads us to suggest that a key comparison between patterns of adaptation in space and in time is the

comparison between local adaptation and temporal adaptation at $\tau = 0$.

In this section, we showed that (1) 'temporal adaptation' quantifies how populations fit the local environmental conditions to which they are transplanted, (2) the dynamic of adaptation generates temporal adaptation patterns that are often maximal in the recent past and (3) that temporal adaptation at $\tau = 0$ is identical to local adaptation under the assumption that sampling environments over space and time is the same. In the next section, we use a remarkable data set on HIV (Richman *et al.* 2003) to illustrate how our theoretical framework can be used to study patterns of adaptation in space (between hosts) and in time (within hosts).

WITHIN-HOST ADAPTATION IN HIV

Immunological assays on patients infected by HIV

Upon infection by HIV, patients produce neutralising antibodies that bind and inhibit the growth of circulating viral particles. The viral population evolves to avoid being recognised by antibodies; but at the same time, antibodies with a higher affinity to viral particles are produced, resulting in a very dynamic process of coevolution (Burton *et al.* 2005).

We used data from Richman's *et al.* (2003) study to analyse the adaptation of the virus to their antibody environment. Samples of antibodies and viruses were collected from 14 patients recently diagnosed for HIV infection (samples across space), at regular time intervals over the course of the infection (samples across time). The extent to which viral growth is inhibited by antibodies was quantified *in vitro* by measuring the neutralisation titre, defined as the reciprocal of the dilution of plasma (containing antibodies) that produces 50% inhibition of virus replication. We used this data set to obtain an estimation of the mean fitness of each viral sample (Appendix D). Interestingly, this experiment tested the virus against the antibodies from the same patient, but at many different points in time (autologous response), as well as from different patients at three points in time (heterologous response).

### Method

Time-shift experiment and temporal adaptation
We decomposed the mean fitness of a population transplanted to another environment using the linear model $\overline{W}_{t\rightarrow t+\tau} = e_{t+\tau} + g_t + \delta_\tau$. We assessed significance of the term that estimates temporal adaptation (δ_τ) using a F-test. We conducted this analysis for three patients only, because time-shift experiments' data on the other 11 patients were not directly available in Richman *et al.*'s paper.

Local adaptation
We estimated local adaptation of the viral population across 14 patients at three time points: 0, 6 and 12 months after primary infection. We assessed statistical significance of local adaptation using a linear model with the viral population, the antibody population and the sympatric vs. allopatric contrast as fixed effects.

RESULTS

We found, as noted in Richman *et al.* (2003), that two of the three patients (patients 1 and 3) develop the neutralising response. Within these two patients viral populations evolve in very similar ways (not shown) and, in the following, we focus on patient 1. The mean fitness of the virus is higher when tested with past serum (negative τ) than with future serum (positive τ) (Fig. 2, top row). This pattern is difficult to interpret. Is it only due to the build up of a more effective immunity against the virus? Does the virus population also change through time? Is it possible to characterise further this evolution and, in particular, to demonstrate the existence of some specificity in the interaction between the antibodies and the virus? Our method is an attempt to answer these questions through a decomposition of mean fitness into the effects of the change of immunity, the evolution of the virus and temporal adaptation (i.e. the interaction between the immunity and the virus).
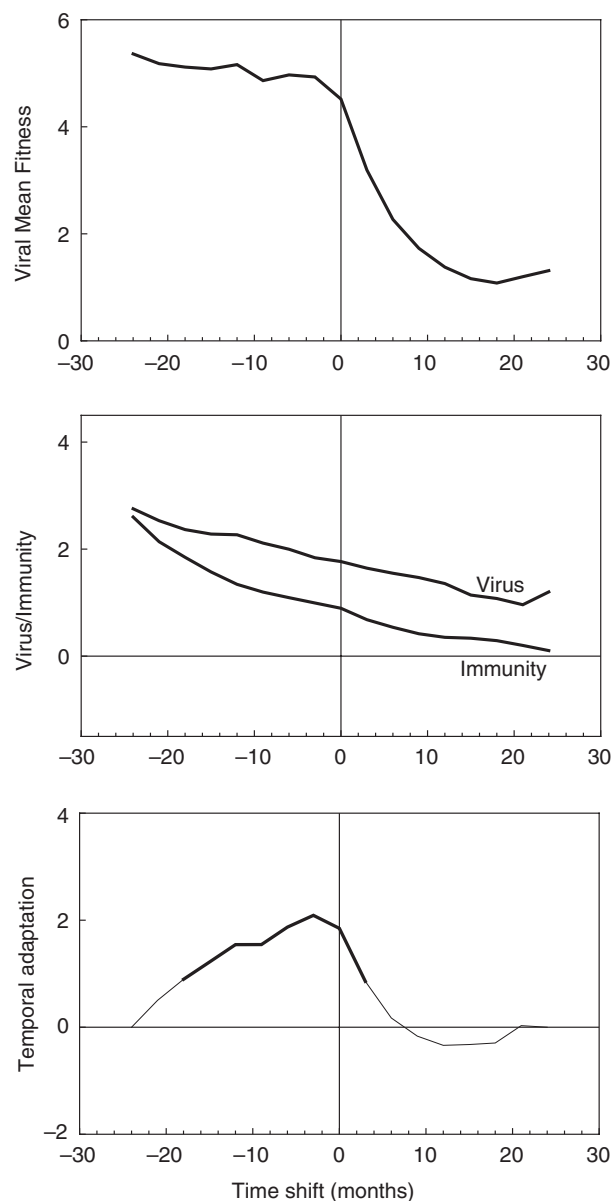
Figure 2 Patterns of adaptation through time shifts in the HIV – neutralising antibody coevolutionary dynamic. Top row: Mean fitness through time shifts as classically represented in time-shift experiments. Middle and bottom row: decomposition of the pattern of mean fitness into the components corresponding to the change in the virus and the environment through time-shifts, and the component corresponding to the $G \times E$ interaction ('temporal adaptation'; significant estimates of δ_τ are highlighted with a thicker line).

First, we show (Fig. S2) that the environment of the virus (here the immune system) degrades through time (a linear regression was fitted, with slope $= -0.09$, $P = 1.5 \ 10^{-7}$). This is due to the general increase in the efficacy of the neutralising antibodies against HIV. Second, we show (Fig. S2) that the component of mean fitness only due to the change in the virus increases with time (slope $= 0.08$, $P = 7.10^{-6}$). This measures the general (i.e. non-specific) ability of the virus to adapt to the immune response. This pattern of variation through time translates into the pattern of mean fitness through time shifts observed in Fig. 2, middle row. Both the G (virus) and E (immunity) components of the decomposition of

mean fitness decrease with time shift because positive values of time shifts combine low quality virus from the past and efficient immune response from the future. Last, our framework unveils the strong effect of temporal adaptation on the pattern of mean fitness ($P < 2.10^{-16}$), demonstrating the specificity of the interaction between the viral population and its environment. Furthermore, as predicted under several simple scenarios of environmental change (see Fig. 1) temporal adaptation is maximal in the recent past (Fig. 2, last row). In the overall pattern of mean fitness, this contribution of temporal adaptation is masked by the strong effects of viral and environmental change. This probably explains why such effects had been overlooked in previous studies (Richman *et al.* 2003; Frost *et al.* 2005).

How do these effects influence the pattern of mean fitness of the virus through time? Interestingly, mean fitness of the virus does not change much through time, because of the concurrent effects of viral adaptation and environmental deterioration (Fig. S2; Hadfield *et al.* 2011). However, the virus is relatively well adapted to the environment of its time, as evidenced by the strong temporal adaptation in the present as compared with the transfers further in the past or in the future.

The analysis of the heterologous immune response revealed the build up of a pattern of local maladaptation over the course of the infection of viruses to their local antibodies (Fig. 3). This contrasts with the evidence of positive temporal adaptation revealed by the autologous immune response. In the light of the previous theoretical analysis, this difference indicates that this system is far from being in a stationary state where the temporal and spatial variations of the environment (the immune response) are similar. The fact that the virus is not well recognised by heterologous antibodies may result from the high dimension of the fitness landscape in which HIV is evolving. It would be particularly interesting to extend our predictions which focus on a simple scenario with a single phenotypic trait to more realistic situations where populations evolve in a multi-dimensional space.

DISCUSSION

We showed that the mean fitness of a population when it is measured in a new environment can be decomposed into (1) the effect of the environment E on mean fitness, (2) the intrinsic (i.e. genetic) quality G of the population and (3) the $G \times E$ interaction.
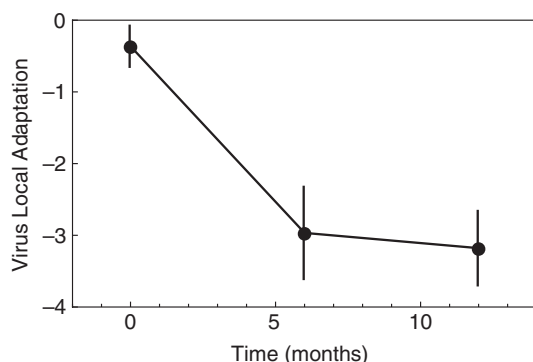
Figure 3 Patterns of local adaptation in the HIV – neutralising antibody coevolutionary dynamic. Local adaptation of the viral populations in 14 patients is shown as a function of time. Confidence intervals are indicated.

Although these three effects are well recognised in local adaptation experiments (Kawecki & Ebert 2004), they are often overlooked in the context of time-shift experiments. Specific experimental designs controlling for the effects of populations or environments have been suggested (Gaba & Ebert 2009), but to our knowledge no method has been proposed to estimate the component of mean fitness that depends on the $G \times E$ interaction.

Here, we propose two methods to estimate 'temporal adaptation', a component of the $G \times E$ interaction that depends on the time shift. Temporal adaptation quantifies how the changes in the genetic composition of the population fit the specificity of the environment for several time shifts. Comparing temporal adaptation in the present to temporal adaptation at other time points shows the extent to which the population follows closely (or not) the fluctuations in the environment. In particular, we showed temporal adaptation is in general positive in the present, but often maximum in the past, as the population lags behind the moving optimum. Given a specific type of temporal variability, the time point at which temporal adaptation is maximised informs us about the capacity of the population to respond to changes in the environment, which depends on the speed of these changes, the strength of selection and the amount of genetic variability (Appendix B). Last, temporal adaptation in the present is a quantity that is exactly analogous to local adaptation. Both quantities are linked and may be equal if the environment variation is such that its average properties are the same over time and over space.

As an illustration of our framework, we analysed data on the neutralising antibody response to HIV in newly infected patients. In this system, it is important to understand whether the rapid change of the virus through time is driven by the neutralising response or not (Frost *et al.* 2005). Also, quantifying the specificity of the antibodies (the extent to which their ability to recognise HIV depends on the specific virus strain considered) is also key, first because it strongly determines the immune system – virus coevolutionary dynamic (Haraguchi & Sasaki 1997), and second because the existence of 'broadly neutralising antibodies' may have implications for vaccine developments (Burton *et al.* 2005). Using our framework, we revealed several features of the evolutionary dynamic of HIV that had been overlooked in previous studies (Richman *et al.* 2003; Frost *et al.* 2005). We showed that the changes in the environment through time are closely matched by corresponding changes in the viral populations, demonstrating that diversification of HIV is driven, at least partly, by the specific interactions between antibodies and HIV (Frost *et al.* 2005; Moore *et al.* 2009). We were also able to quantify the parts of mean fitness of the virus that are due to general adaptation of the virus to all antibodies, to general adaptation of antibodies to all viruses, and to the specificity of the immune response. Last, HIV populations are locally maladapted, meaning that even though HIV escapes well the antibodies of their host, they would escape even better the antibodies of naïve hosts. A full understanding of the difference between these patterns of adaptation in space and in time deserves further investigation.

Experimental perspectives

As mentioned in the introduction, time-shift experiments are mostly used in the context of antagonistic interactions. More precisely, these experiments have been used as a tool to try disentangle 'arms race' dynamic, where coevolution leads to ever-increasing traits in the host and the parasite, from 'fluctuating selection' dynamic,

where negative 'frequency-dependence' leads to cycling dynamics of allele frequencies in both partners of the interaction. Yet both kinds of dynamic may yield similar patterns of mean fitness across time shifts, which have made such interpretations difficult (Gandon *et al.* 2008). The decomposition we propose in this study is actually linked to the conceptual distinction between 'arms race' and 'fluctuating selection'. Simulations show that an arms race dynamic generates a pattern of population improvement and environmental deterioration through time shift, while a fluctuating selection dynamic, if the time scale of the experiment is greater than the period of the fluctuations, only generates a pattern of temporal adaptation (Fig. S3).

The statistical decomposition requires having data on enough transfers to be able to fit the population, environment and time-shift effects. Specifically, if a full factorial design is used, at least four populations and environments must be sampled (that is, 16 transfers). An alternative approach is to study the pattern of variation at the level of genotypes. For example the pattern of $G \times E$ interaction may be obtained by measuring fitness of several genotypes of the focal population through time shifts, as in Hall *et al.* (2011).

Theoretical perspectives

Temporal and local adaptation patterns are shaped by selection changing in time and space, but also by several other processes that have potentially important effects on the dynamic of adaptation and that we neglected in our analysis. A precise interpretation of data certainly requires developing theoretical predictions for the pattern of temporal adaptation under more complex scenarios. In the HIV example, our model could be extended to account for several features of the system, namely multiple dimensions of the trait space, frequency-dependent or changing population sizes. In general, phenotypic plasticity may also play an important role in adaptation to changing environments (Charmantier *et al.* 2008). Indeed, plasticity will have two impacts on a temporal adaptation experiment. It will affect the evolutionary dynamics of the trait by attenuating the genetic changes in the population in response to environmental change. It will also modify the outcome of the transplant experiments by reducing differences in performance of genetically distinct populations. Phenotypic plasticity is therefore likely to reduce temporal adaptation. It would also be interesting to investigate the effects of gene flow in space (dispersal) and in time (dormancy) on temporal adaptation. In particular, migrant genes come from any close location, while dormant genes come only from the past, so both processes probably shape adaptation in different ways.

AUTHORSHIP

FB and SG conceived the model; FB designed and analysed the model; FB and SG wrote the article.

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