Bézier interpolation improves the inference of dynamical models from data

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Many dynamical systems, from quantum many-body systems to evolving populations to financial markets, are described by stochastic processes. Parameters characterizing such processes can often be inferred using information integrated over stochastic paths. However, estimating time-integrated quantities from real data with limited time resolution is challenging. Here, we propose a framework for accurately estimating time-integrated quantities using Bézier interpolation. We applied our approach to two dynamical inference problems: determining fitness parameters for evolving populations and inferring forces driving Ornstein-Uhlenbeck processes. We found that Bézier interpolation reduces the estimation bias for both dynamical inference problems. This improvement was especially noticeable for data sets with limited time resolution. Our method could be broadly applied to improve accuracy for other dynamical inference problems using finitely sampled data.

Introduction

Stochastic processes are ubiquitous in nature. In biology, the evolution of genetic sequences can be formulated as a stochastic process. The Wright-Fisher (WF) model\(^1\), a discrete-time stochastic process, has been used to study the evolution of organisms from viruses\(^2–4\) to humans\(^5\). Models such as the Ornstein-Uhlenbeck (OU) process\(^6,7\) have been applied to describe a wide range of phenomena, from the fluctuation of currency exchange rates\(^8\) and cell migration\(^9\) to driven quantum many-body systems\(^10\).

Appropriate model parameters are needed to accurately describe the behavior or real systems. To infer such parameters from data, it is often necessary to compute statistics over a path, i.e., a complete realization of the stochastic processes. For example, the restoring force of the OU process can be estimated by taking the ratio of the deviation from the equilibrium position and the magnitude of the intrinsic fluctuations, both integrated over a stochastic path\(^11,12\).

However, real data often consists of incomplete, occasional measurements of a system, which may also be limited by experimental constraints. This makes it more difficult to accurately estimate model parameters since statistics over the path must be estimated from incomplete information. A workaround used in a previous study\(^4\) for this problem is to use linear interpolation to estimate the state of the system between the observed data points. However, this approximation may fail when gaps in time are large enough such that the behavior of the system is highly nonlinear\(^13\).

Here, we propose a tractable nonlinear interpolation framework using Bézier curves. In addition to incorporating nonlinearity, this approach has the added advantage of conserving sums of categorical variables, which is not guaranteed under arbitrary nonlinear transformations of data. This property can be especially useful for conserved quantities such as probabilities. Historically, the Bézier method has been used in computer graphics to draw smooth curves\(^14–17\).

We applied Bézier interpolation to two example problems: inferring natural selection in evolving populations through the WF model and inferring restoring forces for OU processes. Here, our method reduces estimation bias and improves the precision of model inferences. Furthermore, we show that the autocorrelation function of statistics over a path identifies time scales over which nonlinear interpolation is particularly effective, which is consistent with our observations in simulations. We show that Bézier interpolation can generically improve solutions of dynamical inference problems by accurately estimating statistics over stochastic paths. We expect that this nonlinear interpolation method can improve a wide range of dynamical inference problems beyond the specific examples we consider, such as parameter estimation for stochastic differential equations. Our approach is particularly well-suited for situations in which difficult to obtain samples with good time resolution.

Bézier interpolation

Consider a function \(x(t)\) sampled at discrete times \(t_k\), for \(k \in \{0, 1, \ldots, K\}\). Then the interpolated value of the function \(x_B^{(k)}(t)\) between two successive discrete time points \(t_k\) and \(t_{k+1}\) is given by

\[
x_B^{(k)}(t) = \sum_{n=0}^{P} \beta_n \left( \frac{t-t_k}{t_{k+1}-t_k} \right) \phi_n^{(k)} ((x(t_k'))_{k'=0}^K).
\]

Here, \(\beta_n\) is the \(n\)th Bernstein basis polynomial of degree \(P\), with \(\beta_n(\tau) = \binom{P}{n} \tau^n (1-\tau)^{P-n} \geq 0\). The control points \(\phi_n^{(k)} ((x(t_k'))_{k'=0}^K)\) depend on the ensemble of data points \((x(t_k'))_{k'=0}^K\) and determine the outline of the interpolation curves.

For simplicity we consider cubic (\(P=3\)) interpolation, but our approach can be extended to polynomials of different degrees \(P\). We impose the following conditions to ensure that the segment at each interval \([t_k, t_{k+1}]\) for \(k\) is seamlessly connected,

\[
\phi_0^{(k)} ((x(t_k'))_{k'=0}^K) = x(t_k), \quad \phi_3^{(k)} ((x(t_k'))_{k'=0}^K) = x(t_{k+1}).
\]
In (2), \( f_a \) denotes the fitness of genotype \( a \). Individuals with higher fitness values reproduce more readily than those with lower fitness values. Here \( \mu_{ab} \) is the probability to mutate from genotype \( a \) to genotype \( b \).

In principle, fitness values can be estimated from genetic sequence data by identifying the \( f_a \) that are most likely to generate the observed evolutionary history of a population. Given the enormous size of the genotype space, however, simplifying assumptions are often needed. A common choice is to assume that fitness values are additive, \( f_a = 1 + \sum_{i=1}^{L} \sigma_{ai} s_i \), where \( \sigma_{ai} = 1 \) if the nucleotide at site \( i \) in genotype \( a \) is a mutant and 0 otherwise. The \( s_i \) are referred to as selection coefficients, which are positive if the mutation at site \( i \) is beneficial for reproduction and negative if mutation at site \( i \) is deleterious. Similarly, the mutation rate \( \mu_{ab} \) can be simplified to a constant \( \mu \) if genotypes \( a \) and \( b \) differ from one another by only a single mutation and zero otherwise.

Sohail et al. solved this problem analytically in the limit that the population size \( N \to \infty \) while the selection coefficients \( s_i \) and mutation rate \( \mu \) scale as \( 1/N \) (ref. \(^4\)). In this case, the maximum a posteriori vector of selection coefficients \( \hat{s} = (\hat{s}_i)_{i=1}^{L} \) that best explain the data are given by

\[
\hat{s} = \left( \int_{t_0}^{t_K} dt \frac{C(t) + \gamma I}{d\hat{x}(t)} \right)^{-1} \times \left[ \hat{x}(t_K) - \hat{x}(t_0) - \mu \int_{t_0}^{t_K} dt \left( 1 - 2\hat{x}(t) \right) \right],
\]

where the time of observation runs from \( t_0 \) to \( t_K \). In Eq. (3), \( \hat{x}(t) = (x_i(t))_{i=1}^{L} \) is a vector of mutant frequencies (i.e., the number of individuals in the population with a mutation at site \( i \) at time \( t \)), and \( C(t) \) is the covariance matrix of mutant frequencies at time \( t \). Here \( \gamma \) is the precision of a Gaussian prior distribution for the selection coefficients with mean zero, and \( I \) is the identity matrix.

Extensive past work has also considered numerical solutions to this problem \(^{3,5,18–22}\), though the analytical formula in Eq. (3) typically outperforms numerical approaches\(^4\). Sohail et al. referred to Eq. (3) as the marginal path likelihood (MPL) estimate for the selection coefficients, obtained by maximizing the posterior probability of an evolutionary history (i.e., a stochastic path) with respect to the selection coefficients. The MPL approach has also been extended to consider more complex evolutionary models\(^23\) and epidemiological dynamics\(^24\).

**Bézier interpolation for WF model inference**

In practice, Eq. (3) is not straightforward to evaluate because data is not available in continuous time. Instead, sequence data comes at discrete times \( (t_k)_{k=0}^{K} \), which may also be spaced heterogeneously in time. To solve this problem, we apply Bézier interpolation to finitely sampled mutant frequency trajectories. This allows us to analytically integrate both mutant frequency trajectories \( \hat{x}(t) \) and covariances \( C(t) \), obtained by interpolating frequencies and computing \( C_{ij}(t) = \hat{x}_{ij}(t) - \hat{x}_i(t)\hat{x}_j(t) \). Here \( \hat{x}_{ij}(t) \) is the pairwise frequency of individuals in the population at time \( t \) that have mutations at both sites \( i \) and \( j \).
terpolation (beneficial, neutral, and deleterious mutations using Bézier in-
between the distribution of inferred selection coefficients for

Fig. 3a—beneficial, neutral, and deleterious selection coefficients from this data using MPL with linear and Bézier
interpolation, applied to data sampled at discrete intervals
$\Delta t = 75$ generations apart. While MPL with linear interpo-
lation readily distinguishes between beneficial, neutral, and
deleterious parameters, the inferred selection coefficients are
shrunken toward zero. However, parameters inferred using
Bézier interpolation are distributed around their true values.

(b) Bézier interpolation reduces estimation bias due
to long intervals between observations intervals by produc-
ing better estimates of underlying covariances (which we will
quantify below). Here we used a regularization strength of
$\gamma = 0.1$, but similar results are obtained with different choices
for the regularization (Methods).

Next we studied how Bézier interpolation affects our abil-
ity to classify mutations as beneficial or deleterious, which we
evaluated by ranking mutations according to their inferred
selection coefficients. This metric is distinct from the issue
of biased estimation of selection coefficients. We quantified
classification accuracy using positive predictive value (PPV),
$PPV = TP / (TP + FP)$, where TP and FP are the num-
bers of true positive and false positive predictions. The PPV
curves for beneficial/deleterious mutations estimated by MPL
with Bézier interpolation are higher than those with linear inter-
polation, indicating more accurate classification (Fig. 3a—
b). This can be understood by observing reduced overlap
between the distribution of inferred selection coefficients for
beneficial, neutral, and deleterious mutations using Bézier in-
terpolation (Fig. 3c).

Performance of Bézier interpolation on real data

To apply Bézier interpolation to biological sequence data, we
extended the approach described above from binary variables
to multivariates. This is necessary because DNA or RNA se-
quences have five possible states at each site, including four
nucleotides and a “gap” symbol, which represents the ab-

ence of a nucleotide at a site that is present in other related
sequences.

We applied multivariate Bézier interpolation to study hu-
man immunodeficiency virus (HIV-1) evolution in a set of
13 individuals (see Methods for details). The distribution
of selection coefficients inferred using Bézier interpolation
is highly correlated with previous analysis using linear in-
terpolation, indicating broad consistency with past results
(Fig. 4). However, as we observed in simulations, inference
using Bézier interpolation tends to result in slightly larger
selection coefficients.

Consistent with past analyses, we found that the largest
inferred selection coefficients are overwhelmingly associated
with potentially functional mutations. Among the largest 1% of
selection coefficients inferred across these 13 individuals,
around 40% correspond to mutations that help the virus to
escape from the host immune system. This represents a more
than 20-fold enrichment in immune escape mutations among
the most highly selected mutations, compared to chance ex-
pectations.

In summary, Bézier interpolation applied to real data leads
to the inference of selection coefficients that are stronger
than, but broadly consistent with, those that are found using
linear interpolation. Large inferred selection coefficients
also have clear biological interpretations. For HIV-1, many
highly beneficial mutations correspond to ones that the virus
uses to escape from the immune system.
Recovery of rapidly decaying correlations underlies improved accuracy

To understand why MPL with Bézier interpolation yields more accurate inferences, we studied errors between true and estimated parameters as a function of the time interval $\Delta t$ between samples. For arbitrary matrices $M$ we define an error function $\mathcal{E}(\Delta t) = \|M(\Delta t) - M(1)\|/\|M(1)\|$, normalizing by the matrix norm $\|M(1)\|$, which corresponds to perfect sampling for the WF model. In the discussion below we apply the $L_2$ norm, $\|M\| = \sqrt{\sum_{i,j} M_{ij}^2}$, but other conventions could also be considered.

Using the metric defined above, we found that Bézier interpolation yields better estimates for both the diagonal and off-diagonal terms of the mutant frequency covariance matrix. However, the error for the off-diagonal covariances is larger and increases much more rapidly with increasing $\Delta t$ than the error for the diagonal variances (Fig. 5a-b). The reduction in error for Bézier interpolation is more substantial for off-diagonal terms compared to diagonal ones. Consistent with this observation, Bézier interpolation yields smaller improvements in performance for a simple version of MPL in which the off-diagonal terms of the integrated covariance matrix are ignored (Methods; referred to as the single locus (SL) method in ref. 4).

To study the time scale $\tau$ on which nonlinear effects become important and Bézier interpolation is advantageous, we modeled the covariance elements using a simple Langevin equation, $\dot{z}(t) = -\lambda z(t) + \xi(t)$. Here $z(t)$ represents an element of the covariance matrix, $\lambda > 0$ is a damping coefficient, and $\xi(t)$ is a standard white noise with $\langle \xi(t) \rangle = 0$ and $\langle \xi(t) \xi(t + \tau) \rangle = 2\delta(\tau)$. Following this approach, a linear approximation should describe the evolution of $z(t)$ accurately if $\lambda \Delta t \ll 1$. The nonlinear nature of the $z(t)$ should become significant for $\lambda \Delta t \sim 1$, and at this point the linear approximation cannot capture the actual evolution of $z(t)$. Therefore, $\lambda \Delta t$ acts as a parameter that indicates whether linear interpolation is sufficient or inadequate.

The damping coefficient $\lambda$ can be estimated by computing the autocorrelation function (ACF) of the covariance matrix elements, which can be matched to expectations from the Langevin equation, $\langle x(t)x(t + \tau) \rangle \propto \exp(-\lambda \tau)$. In our simulations, the exponents of the ACF for diagonal and off-diagonal terms are around $\lambda_o \sim 1/325$ and $\lambda_o \sim 1/50$, respectively. At this point, $\lambda_o \Delta t$ is $O(1)$, indicating the onset of nonlinearity for off-diagonal terms. Consistent with this observation, for this value of $\Delta t$, Bézier interpolation has notably lower error for off-diagonal covariances than linear interpolation, while errors for the diagonal terms are comparable.

While we focused specifically on the WF model in this example, the principle of autocorrelations and transitioning between linear and nonlinear behavior is general. This can allow us to anticipate the benefit of nonlinear interpolation for a wide range of problems.

Inference of forces in Ornstein-Uhlenbeck processes

We further applied Bézier interpolation to accurately infer the collective forces in Ornstein-Uhlenbeck (OU) processes. Due to the mathematical simplicity and versatility of the OU process, it has played important roles in various fields such as physics, biology, and mathematical finance. Data
has been used to infer the parameters of OU processes describing phenomena including cell migration\textsuperscript{30}, coevolution of species\textsuperscript{31}, and currency exchange rates\textsuperscript{32}, to name a few examples.

We consider the following OU process, a stochastic relaxation process of multivariate variables,

\[ d\mathbf{X}_t = J\mathbf{X}_t + \Sigma^{1/2}d\mathbf{W}_t. \]

\[ (4) \]

Here \( t \) is the time variable, \( L \) is the number of OU stochastic variables, \( \mathbf{X}_t \in \mathbb{R}^L \), \( J \in \mathbb{R}^{L \times L} \) is a negative semidefinite matrix, \( \Sigma \) is a time-independent noise covariance, and \( \mathbf{W}_t \) is a Wiener process. We assume that the noise covariance matrix is constant over the evolution and given. Therefore, the unknown variable in the SDE in Eq. (4) is only the drift term, the interaction matrix \( J \).

One of the most commonly used approaches for inferring stochastic force in OU processes is maximizing the likelihood ratio or Radon-Nikodym derivative, which is the ratio of two probability measures\textsuperscript{12,33}. Because of its ease of calculation and its mathematical rigor, this method is commonly employed in broad fields, such as mathematical finance\textsuperscript{14}. In our problem, the likelihood ratio is defined as the probability density obeying the dynamics of Eq. (4) with interactions divided by the probability density of a “null” model with no interactions. Here, we inferred OU interactions by directly maximizing the path likelihood, as described for the WF model. Interestingly, this leads to exactly the same solution as the one for the standard likelihood/Radon-Nikodym derivative methods (Methods).

The interaction matrix \( J \) that best describes the data is given by

\[ \hat{J} = \left( \sum_{k=0}^{K-1} \Delta \mathbf{x}(t_k)\mathbf{x}(t_k)^\top \right) \times \left( \sum_{k=0}^{K-1} \Delta t_k \mathbf{x}(t_k)\mathbf{x}(t_k)^\top \right)^{-1} \]

\[ (5) \]

Here \( \mathbf{x}(t_k) \) is the amount of change during the \( k \)th observation interval.

To generate test data, we simulated the OU process using negative definite interaction matrices parameterized as \( J = -\frac{\alpha}{\sqrt{P}} \sum_{\nu=1}^{P} \xi_{\nu}\xi_{\nu}^\top \). This follows the construction of a Hopf-field network, where \( \xi_{\nu} \) is a pattern generated from the multivariate normal distribution, \( \xi_{\nu} \sim \mathcal{N}(0,1)^L \), \( \alpha = O(1/L) \) is a small parameter, and \( P \) is the number of embedded patterns. Hopf-field networks were first constructed to study associative memory\textsuperscript{34}, and have since been applied to problems such as the prediction of protein structure\textsuperscript{35–38}. This construction ensures that the OU process does not diverge. We used the Euler-Maruyama (EM) scheme\textsuperscript{3} to simulate Eq. (4) (Fig. 6a). We simulated 1000 trajectories each for 10 randomly generated interaction matrices, as described above. We chose \( L = 50 \), and \( \alpha = 1/L = 0.02 \) in our simulations. For inference, we sampled data from the simulations every \( \Delta t = 1.0 \) units of time.

Interaction parameters estimated using Bézier interpolation matched better with the true, underlying parameters than those inferred using linear interpolation or a piecewise-constant assumption for the \( \mathbf{x}(t) \) (Fig. 7a). In particular, large parameters inferred with linear interpolation or the piecewise-constant assumption tended to be underestimated. In addition, we found that the slope relating the true and inferred parameters decreases as the sampling interval \( \Delta t \) increases. However, the slope between the inferred and true parameters decreases more slowly for Bézier interpolation compared to linear interpolation (Fig. 7b-c). Overall, OU interaction parameters inferred using Bézier interpolation more...
closely match the true, underlying parameters, than those inferred with simpler interpolation approaches or assumptions, with gains in performance that increase as data becomes more limited.

Discussion

Here we developed a nonlinear interpolation method based using Bézier curves that improves the inference of dynamical models from finite data. We applied our approach to two problems: the inference of natural selection in evolving populations and interactions in multivariate Ornstein-Uhlenbeck processes. Bézier interpolation makes inference more precise and reduces bias, especially for data sets that are more sparsely sampled.

Bézier interpolation also has the advantage that it conserves sums of categorical variables, which is not typically guaranteed for standard stochastic regression methods such as Gaussian process regression/Kriging or nonlinear approaches such as kernel regression or least squares. This property is especially useful for interpolating quantities that can be interpreted as probabilities (e.g., frequency vectors, as we considered above) or other conserved parameters. A few studies have applied regression methods to probabilities using logarithmic transformations. However, in such cases, regions around the 0 and 1 boundaries in the probability space tend to dominate regression results due to the coordinate transformation.

Because of its generality, Bézier interpolation could be broadly applied to give more reliable results for dynamic inference problems. For example, our approach could be combined with methods to learn forces from non-equilibrium dynamics or ones used to learn parameters of stochastic differential equations from finitely-sampled data.

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AUTHOR CONTRIBUTIONS

All authors contributed to methods development, data analysis, interpretation of results, and writing the paper. K.S. performed simulations and computational analyses. J.P.B. supervised the project.

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Methods

Data and code
Raw data and code used in our analysis is available in the GitHub repository located at https://github.com/bartonlab/paper-Bézier-interpolation. This repository also contains Jupyter notebooks that can be run to reproduce the results presented here.

Optimization of control points for Bézier curves
For simplicity, we will discuss a one-dimensional case, but the following discussion can easily be extended to arbitrary dimensions. The control points of Bézier curves are obtained by solving an optimization problem that is derived from properties we want the Bézier curve to satisfy. In this study, we impose the \( C^2 \) smoothness condition, which is that up to the second derivative of the curve exist. Formally, we can represent these conditions as follows,

\[
\partial_{\tau} x_B^{(k-1)}(\tau = 1) = \partial_{\tau} x_B^{(k)}(\tau = 0),
\]

and,

\[
\partial_{\tau}^2 x_B^{(k-1)}(\tau = 1) = \partial_{\tau}^2 x_B^{(k)}(\tau = 0),
\]

Where, \( x_B^{(k)}(\tau) \) is the interpolated function between successive discrete time points \( t_k \) and \( t_{k+1} \) and defined in Eq. (1).

Since these constraints are defined at each junction of adjacent segments, the number of conditions is \( 2(K-1) \). On the other hand, the number of control points is \( 2K \), so we will introduce two more constraints to make the problem solvable:

\[
\partial_{\tau}^2 x_B^{(0)}(\tau = 0) = 0
\]

\[
\partial_{\tau} x_B^{(K-1)}(\tau = 0) = 0
\]

By rearranging Eq. (6) and Eq. (7), we can reduce them to the following difference equations.

\[
\phi_1^{(k)} - 2x^{(k)} = \phi_2^{(k-1)},
\]

and

\[-2\phi_1^{(k)} + \phi_2^{(k)} = \phi_1^{(k-1)} - 2\phi_2^{(k-1)}.
\]

Also, the additional boundary constraints lead to

\[x^{(0)} - 2\phi_1^{(0)} + \phi_2^{(0)} = 0,
\]

\[
\phi_1^{(k-1)} - 2\phi_2^{(k-1)} + x^{(k)} = 0.
\]

These difference equations are summarized as the following single linear equation by assuming that \( \{\phi_2^{(k)}\}_{k=0}^{K-1} \) is a function of \( \{\phi_1^{(k)}, x^{(k)}\}_{k=0}^{K-1} \) and then marginalizing \( \{\phi_2^{(k)}\}_{k=0}^{K-1} \) from the difference equations,

\[
M_B^{\text{Bez}, K} \phi_1 = \psi((x^{(k)})_{k=0}^{K+1}),
\]

where \( \phi_1 = (\phi_1^{(0)}, \ldots, \phi_1^{(K)})^T \), and let

\[
\psi((x^{(k)})_{k=0}^{K+1}) = \begin{pmatrix}
x^{(0)} + 2x^{(1)} \\
2(2x^{(1)} + x^{(2)}) \\
\vdots \\
2(2x^{(K-1)} + x^{(K)}) \\
x^{(K)} + x^{(K+1)}
\end{pmatrix},
\]

and the matrix \( M_B^{(K)} \) is defined as

\[
M_B^{(K)} = \begin{pmatrix}
2 & 1 & 0 & \ldots & \ldots & \ldots & 0 \\
1 & 4 & 1 & 0 & \ldots & \ldots & \vdots \\
0 & 1 & 4 & 1 & 0 & \ldots & \vdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \ddots & 0 \\
0 & \ldots & \ldots & 0 & 1 & 4 & 1 \\
0 & \ldots & \ldots & 0 & 2 & 7
\end{pmatrix}.
\]

By solving Eq. (9), we get a set of control points, hence we get a Bézier curve. Interestingly, instead of the \( C^2 \) smoothness constraint, assuming a \( C^1 \) smoothness condition and imposing a constraint that minimizes the Euclidean distance of the total trajectory leads to almost the same linear equation in Eq. (9) depending on Eq. (11) and Eq. (10).

For multivariate frequencies, the Bézier curve can be obtained by solving each linear equation individually. Practically, the control points are obtained by operating the inverse of \( M_B^{(K)} \) to \( \psi((x^{(k)})_{k=0}^{K+1}) \) vectors on each site \( i \in \{1, \ldots, L\} \). Thus, we can efficiently perform the operation and its computational time is fast. Also, the above arguments are held for the arbitrary \( q > 1 \) dimension case, which is relevant, for example, when considering the frequency of individuals with multiple possible nucleotides or amino acids at each site in a genetic sequence. Replacing scalar variables with vector variables leads to exactly the same linear equation in Eq. (9).

Integrated frequency and covariance using Bézier interpolation
In this section, we will show explicit representations of the integrated mutant frequencies and covariances from the WF model using Bézier interpolation.

To derive it, we apply the following useful properties of \( P \)-th order Bernstein basis \( (P = 3 \) for quadratic Bézier interpolation), for \( \forall n \in \{0, 1, \ldots, P\} \),

\[
m_n := \int_0^1 \beta_n(\tau)d\tau = \frac{1}{P+1},
\]

and, for \( \forall n, m \in \{0, 1, \ldots, P\} \),

\[
Q_{nm}^{(P)} := \int_0^1 \beta_n(\tau)\beta_m(\tau)d\tau = \frac{(P)_n (P)_m}{(2P+1)_{n+m}}.
\]

More general properties of the Bernstein basis can be found in refs. \(^46^{49}\).

First, we will get the integrated single mutant frequency at
site \( i \), which is shown below,

\[
\Delta x_{B,i}^{(k)} := \Delta t_k \int_0^1 x_{B,i}^{(k)}(\tau) d\tau \\
= \Delta t_k \sum_{n=0}^P \left( \int_0^1 \beta_n(\tau) \phi_{i,n}^{(k)} \right) \\
= \Delta t_k \sum_{n=0}^P m_n^P(\tau) \phi_{i,n}^{(k)} \\
= \frac{1}{(P+1)} \sum_{n=0}^P \phi_{i,n}^{(k)},
\]

we used the property of Bernstein in Eq. (12).

Next, we will get the integrated covariance for different sites at \( i \) and \( j \),

\[
\Delta C_{ij}^{(k)} := \Delta t_k \int_0^1 \left( x_{B,i}^{(k)}(\tau) - x_{B,i}^{(k)}(\tau) x_{B,j}^{(k)}(\tau) \right) d\tau,
\]

the first term in Eq. (15) is the same as in Eq. (14) but we replaced a single interpolated mutant frequency by a matrix that contains the entire interpolated pairwise mutant frequencies as its elements.

The second term of the covariance in Eq. (15) is also straightforward,

\[
\int_0^1 x_{B,i}^{(k)}(\tau) x_{B,j}^{(k)}(\tau) d\tau \\
= \int_0^1 \left( \sum_{n=0}^P \beta_n(\tau) \phi_{i,n}^{(k)} \right) \left( \sum_{m=0}^P \beta_m(\tau) \phi_{j,m}^{(k)} \right) d\tau \\
= \sum_{n=0}^P \sum_{m=0}^P \left( \int_0^1 \beta_n(\tau) \beta_m(\tau) d\tau \right) \phi_{i,n}^{(k)} \phi_{j,m}^{(k)} \\
= \sum_{n=0}^P \sum_{m=0}^P Q_{nm}^P \phi_{i,n}^{(k)} \phi_{j,m}^{(k)}.
\]

Here we used the property of Bernstein Eq. (13) in the last equality.

In the case of the \( P = 3 \), which is the cubic Bézier, \( Q^{(3)}(\alpha \beta \gamma \delta) \) matrix will be

\[
Q^{(3)} = \begin{pmatrix}
\alpha & \beta & \gamma & \delta \\
\beta & \gamma & \delta & \gamma \\
\gamma & \delta & \gamma & \beta \\
\delta & \gamma & \beta & \alpha
\end{pmatrix},
\]

where \( \alpha = 1/7, \beta = 1/14, \gamma = 1/35, \delta = 1/140 \).

**Normalization of probabilities**

We will show that the interpolation of probability trajectories using the Bézier interpolation is always normalized. We refer to this property as normalizability, hereafter.

First, we will discuss the normalizability of the interpolated probability distribution for a categorical distribution depending on an arbitrary number of states \( q > 1 \). Next, we denote a probability distribution depending on the data points \( k \) and index \( i \) as \( x_i^{(k)} = (x_{i,1}^{(k)}, \ldots, x_{i,q}^{(k)})^T \), and a sum of the all states is normalized, that is \( \sum_{a=1}^q x_{i,a}^{(k)} = 1 \) for all \( k, i \).

Then, we can prove that when probability distributions are interpolated using Bézier’s method, any interpolated function \( x_{B,i}^{(k)} = (x_{B,i,1}^{(k)}, \ldots, x_{B,i,q}^{(k)})^T \) is also normalized in arbitrary point \( \tau \in [0, 1] \):

\[
\sum_{a=1}^q x_{B,i,a}^{(k)} = 1.
\]

For the sake of simplicity, we will omit the site index hereafter. To see the proof, we will start by showing the normalizability of the control points \( \sum_{a=1}^q \phi_{i,a}^{(k)} = 1, \forall k \) because this condition immediately leads to \( \sum_{a=1}^q \phi_{2,a}^{(k)} = 1 \) by plugging it into the Eq. (8), and the following part is straightforward as shown below,

\[
\phi_{2,a}^{(k-1)} = 2x_{a}^{(k)} - \phi_{1,a}^{(k)} \\
= 2(1 - \sum_{b=1\neq a}^q x_{b}^{(k)}) - (1 - \sum_{b=1\neq a}^q \phi_{1,b}^{(k)}) \\
= 1 - 2 \sum_{b=1\neq a}^q \phi_{2,a}^{(k)},
\]

so \( \sum_{a=1}^q \phi_{2,a}^{(k)} = 1 \) and it is normalized when \( \phi_{1,a}^{(k)} \) is normalized for \( k \in \{1, \ldots, K - 1\} \). In the case of boundaries, time points at \( k = 0, K \), exactly the same argument holds, which is almost trivial, so we omit to repeat the same kind of proof.

Therefore, we will show the normalizability of \( \phi_{1,a}^{(k)} \) as follows. First, we consider a sum of all the states on the left hand side in Eq. (10),

\[
I.h.s. = M_B^{K} \begin{pmatrix}
\sum_{a=1}^q \phi_{1,a}^{(0)} \\
\vdots \\
\sum_{a=1}^q \phi_{1,a}^{(K)}
\end{pmatrix}.
\]

Next, we also perform a sum of all the states on the right hand side in Eq. (10),

\[
r.h.s. = \sum_{a=1}^q \begin{pmatrix}
x_{a}^{(0)} + 2x_{a}^{(1)} \\
2(2x_{a}^{(1)} + x_{a}^{(2)}) \\
\vdots \\
8x_{a}^{(K-1)} + x_{a}^{(K)}
\end{pmatrix} = \begin{pmatrix}
3 \\
6 \\
\vdots \\
9
\end{pmatrix}.
\]

Then, we immediately notice that

\[
M_B^{K} 1 = (3, 6, \ldots, 6, 9)^T.
\]

Therefore, we find the normalization of the control points \( \sum_{a=1}^q \phi_{1,a}^{(k)} = 1, \forall k \in \{0, 1, \ldots, K\} \).
which is characterized by the drift and diffusion terms, \( \Delta \)

Based on the stochastic differential equation (STD) defined in

the frequency changes sharply within one time interval (more

x middle time points (1 sequence data), then we insert mean frequency points at

a threshold value (set to 50 days for the analysis of HIV-
sampling points are heterogeneously and sparsely distributed.

occur when frequency trajectories are close to the boundaries,

is conserved, guaranteeing the conservation of probability

negative eigenvalues in real data

bases is one.

Treatment for negative interpolated frequencies and

negative eigenvalues in real data

The sum of \( q \) categorical variables using Bézier interpolation

is conserved, guaranteeing the conservation of probability
density. However, interpolated probabilities can occasionally

exceed the boundaries at 0 and 1, and eigenvalues of the inte-
_guide covariance matrix can become negative. This issue can

occur when frequency trajectories are close to the boundaries,

variables take one of the multiple possible states (\( q > 0 \)), and

sampling points are heterogeneously and sparsely distributed.

To alleviate this problem, we employed the following treat-

ment: if the time interval \( \Delta t_k = t_{k+1} - t_k \) is greater than

a threshold value (set to 50 days for the analysis of HIV-

sequence data), then we insert mean frequency points at

the middle time points \((t_{k+1} + t_k)/2 \) such that \( x(t_k) +

x(t_{k+1})/2 \). In addition, for each frequency individually,

we insert mean frequency points at middle time points when

the frequency changes sharply within one time interval (more

than 70% change in the case of HIV-1 data).

Maximum path-likelihood estimation for the Ornstein-

Uhlenbeck process

Based on the stochastic differential equation (STD) defined in

Eq. (4), We can get the following Fokker-Planck equation \(^{48}\),

which is characterized by the drift and diffusion terms,

\[
\frac{\partial}{\partial t} p(x(t), t) = \mathcal{L} p(x(t), t)
\]

\[
\mathcal{L} = - \sum_{i=1}^{L} \sum_{j=1}^{L} J_{ij} x_j \frac{\partial}{\partial x_i} + \sum_{i,j=1}^{L} \Sigma_{ij} \frac{\partial^2}{\partial x_i \partial x_j} .
\]

(16)

The first term corresponds to the drift due to the pairwise

interaction, and the second term corresponds to the diffusion
due to the white noise.

The FP equation in Eq. (16) is effectively a diffusion equa-
tion for probability measures, and the general solution of the

diffusion equation characterized by the drift and diffusion
terms is known and defined as a transition probability be-
tween time points \( t_k \) and \( t_{k+1} = t_k + \Delta t_k \),

\[
p(x(t_{k+1}), t_{k+1} \mid x(t_k), t_k)
\]

\[
= \frac{1}{\sqrt{2\pi \Sigma_{\Delta t_k}}} \exp \left( - \frac{1}{2 \Delta t_k} \left( \Delta x(t_k) - \Delta t_k J x(t_k) \right)^\top \Sigma_{\Delta t_k}^{-1} \left( \Delta x(t_k) - \Delta t_k J x(t_k) \right) \right),
\]

where \( \Delta x(t_k) = x(t_{k+1}) - x(t_k) \). The solution of the FP

equation tells that as the time interval approaches zero, the

transition probability goes to the

\( t \equiv 0 \) distribution having a finite probability density around the previous

time step. As the time interval increase, the variance increase

as the square root of time, which is the nature of Brownian
diffusion.

The likelihood path function for the OU model can be de-

fined as a product of the transition probability because of

the independence of the increments of the Wiener processes.

Hence the log-path-likelihood can be written as

\[
S(J | \Gamma((x(t_k))_{k=0}^{K-1}))
\]

\[
= \sum_{k=0}^{K-1} \left( \frac{1}{2 \Delta t_k} (\Delta x(t_k) - J x(t_k)) \top \Sigma_{\Delta t_k}^{-1} (\Delta x(t_k) - J x(t_k)) \right)
\]

\[
+ \text{const.}
\]

(17)

The log-likelihood corresponds to the action in statistical

physics, where \( \Gamma((x(t_k))_{k=0}^{K-1}) = (x(t_0), \ldots, x(t_{K-1})) \) is a

single trajectory of the stochastic variable.

Since the action in Eq. (17) is a convex function of the

coupling matrix, the most probable coupling matrix (i.e., the

one that maximizes the likelihood of the observed path) can

be obtained by computing the derivative of the action with

respect to the coupling matrix, setting it to zero, and solving

for the coupling matrix.

The derivative of the log-path-likelihood function with re-
spect to the coupling matrix can be factorized by the noise
covariance because of its time-independence, giving the fol-

lowing closed-form solution

\[
\hat{J} = \left( \sum_{k=0}^{K-1} \Delta x(t_k) x(t_k) \top \right)^{-1} \times \left( \sum_{k=0}^{K-1} \Delta t_k x(t_k) x(t_k) \top \right),
\]

(18)

The single trajectory maximum path likelihood estimate
(MPLE) in Eq. (18) can be easily generalized to the case of

multiple trajectories or paths by replacing the action in

Eq. (17) to an ensemble-averaged action \( \langle S(J | \Gamma) \rangle_{\Gamma \in \text{ensemble}} \)

(or, equivalently, by observing that the likelihood of a set of

independent paths is equal to the product of the likelihoods

for each individual path). The corresponding MPLE solution

after ensemble averaging is

\[
\hat{J} = \left( \sum_{m=1}^{M} \sum_{k=0}^{K-1} \Delta x^m(t_k) x^m(t_k) \top \right)^{-1} \times \left( \sum_{m=1}^{M} \sum_{k=0}^{K-1} \Delta t_k x^m(t_k) x^m(t_k) \top \right),
\]

where \( m = 1, \ldots, M \) is the ensemble index.
In fact, by assuming the discretization of Eq. (4), we can estimate sample size dependence on the MPLE, and it is an unbiased estimator, as shown below,

\[
\hat{J} = \left( \sum_{m=1}^{M} \sum_{k=0}^{K^m-1} \Delta t_k \left( \hat{J}^* x^m(t_k) + W(t_k) \right) x^m(t_k)^\top \right) \times \left( \sum_{m=1}^{M} \sum_{k=0}^{K^m-1} \Delta t_k x^m(t_k)x^m(t_k)^\top \right)^{-1}
\sim \hat{J}^* + \hat{W}/\sqrt{M} \xrightarrow{M \to \infty} \hat{J}^*.
\]

To derive the scaling of the estimation bias, we used the assumption of the independence of the white noise.

**Cameron-Martin-Girsanov theorem and application for Ornstein-Uhlenbeck process inference**

In this section, we will show that the inference problem of the OU model can be solved by maximizing the Radon-Nikodym (RN) derivative or likelihood ratio, which is facilitated by the Cameron-Martin-Girsanov (CMG) theorem\(^{48-51}\). Since the aim of this section is only to rationalize the inference approach based on the CMG theorem, we will discuss minimal ingredients of the CMG theory. A more general and comprehensive description can be found in refs.\(^{48,51}\).

First, let us define the RN derivative. If two probability measures \(\mathbb{P}\) and \(\mathbb{Q}\) satisfy the following conditions, then the \(\mathbb{P}\) and \(\mathbb{Q}\) are said to be mutually absolutely continuous,

\[
E_\mathbb{Q}[Y] = E_\mathbb{P}[YZ] \\
E_\mathbb{P}[Y] = E_\mathbb{Q}[Y/Z],
\]

where \(\forall Y > 0\), \(Z\) is some random variable, and if it satisfies the condition, \(E_\mathbb{P}[Z] = 1\), then \(Z\) is called Radon-Nikodym derivative (or likelihood ratio). In fact, it is nothing more than the changing of the probability measures

\[
E_\mathbb{Q}[Y] = \int Y d\mathbb{Q} = \int Y \frac{d\mathbb{Q}}{d\mathbb{P}} d\mathbb{P} = E_\mathbb{P} \left[ Y \frac{d\mathbb{Q}}{d\mathbb{P}} \right].
\]

Therefore, such a random variable \(Z\) is denoted as \(\frac{d\mathbb{Q}}{d\mathbb{P}} := Z\) in general. Since the RN derivative gives transformation of a probability measure to another probability measure without obtaining (or even knowing explicit form of) the probability measure \(\mathbb{Q}\), it enables us to estimate some statistics under the probability measure \(\mathbb{Q}\) that are unobtainable directly. For example, importance sampling falls in this class of problems and is widely used in computational studies.

Informally speaking, the CMG theorem states that under some transformation of the drift term in a Wiener process, a probability measure after the transformation exists and can represent its explicit RN derivative. So, the CMG theorem provides a way to estimate the statistics under a probability density after a general transformation of the drift of the Wiener process.

More formally, the statement of the Cameron-Martin-Girsanov theorem is that for a Brownian motion \(\{W_t\}_{t \geq 0}\) that follows a probability measure \(\mathbb{P}\) and observable process \(\gamma_t\) that satisfies the following Nikodym condition

\[
E_\mathbb{P} \left[ \exp \left( \frac{1}{2} \int_0^t \gamma_s^2 ds \right) \right] < \infty, \ \forall t \geq 0,
\]

the probability measure \(\mathbb{Q}\) that corresponds to the stochastic process \(dX_t = -\gamma_t dt + dW_t\) \(^1\) exists and the \(\mathbb{Q}\)-process is equivalent to \(\mathbb{P}\)-Brownian motion by modifying the Wiener process such that

\[
\hat{W}_t = W_t + \int_0^t \gamma_s ds.
\]

These probability measures \(\mathbb{P}\) and \(\mathbb{Q}\) are related by the Radon-Nikodym derivative, which is defined as follows,

\[
\frac{d\mathbb{Q}}{d\mathbb{P}} = \exp \left( -\int_0^t \gamma_s dW_s - \frac{1}{2} \int_0^t \gamma_s^2 ds \right).
\]

Using the CMG theorem, we can estimate statistical quantities under a more general probability measure \(\mathbb{Q}\). Since the CMG theorem provides explicit transformation of probability measures, the maximization of the likelihood ratio can be a substitution of the maximum likelihood,

\[
\max_{\theta} Q_\theta(A) = \max_{\theta} \int_A \frac{dQ_\theta}{d\mathbb{P}}(x) d\mathbb{P}(x) \\
\leq \int_A \max_{\theta} \left\{ \frac{dQ_\theta}{d\mathbb{P}}(x) \right\} d\mathbb{P}(x).
\]

Thus, we can estimate the most probable parameters by maximizing the likelihood ratio.

Now, we can apply the CMG theorem to the inference problem of the OU model. The CMG theorem lets the SDE Eq. (4) transform into the following

\[
d\hat{X}_t = -\gamma_t dt + dW_t,
\]

where \(\hat{X}_t = \Sigma^{-1/2} X_t\) and \(\gamma_t = -\Sigma^{-1/2} J X_t\). More general transformation can be done by the Lamperti transformation that provides a systematic variable transformation rule so that a given SDE with multiplicative noise transforms to another SDE with an additive noise\(^{32}\).

\(^1\)We can transform most stochastic processes to this type of stochastic process. For example, a stochastic process given by

\[
dX_t = \sigma_t dW_t + \sigma_t dW_t,
\]

Here, \(\sigma_t(X_t)\) is a covariance that can depend not only on time but also on random variables, so it becomes a multiplicative noise\(^{51}\). Then we transform the stochastic process and drift such that \(X_t = \sigma_t(X_t)^{-1} X_t\) and \(\gamma_t(X_t) = \sigma_t(X_t)^{-1} \gamma_t\), then we can get the following stochastic process

\[
d\hat{X}_t = \gamma_t dt + dW_t.
\]
Therefore, the likelihood ratio of the OU model becomes as follows,
\[
\frac{dQ}{d\mathcal{P}} = \exp \left( -\int_0^t \tilde{\gamma}_s^\top dX_s - \frac{1}{2} \int_0^t \tilde{\gamma}_s^\top \tilde{\gamma}_s ds \right)
\]
\[
= \exp \left( \int_0^t (JX_s)\Sigma^{-1}dX_s - \frac{1}{2} \int_0^t (JX_s)\Sigma^{-1}(JX_s) ds \right),
\]
where we used the symmetry of the covariance matrix and definition of the square matrix, \(\Sigma^{1/2}\Sigma^{1/2} = \Sigma\).

Since the likelihood ratio Eq. (19) is a convex function of the coupling matrix, its derivative with respect to the coupling matrix gives the equation to solve the maximum likelihood estimator. So the derivative of the likelihood ratio is
\[
\frac{\partial}{\partial J} \log \frac{dQ}{d\mathcal{P}} = -\int_0^t \Sigma^{-1}dX_sX_s^\top - \int_0^t \Sigma^{-1}(JX_s)X_s^\top ds
\]
\[
\xrightarrow{J\to J^*} 0.
\]
This immediately leads the maximum likelihood ratio estimator
\[
\hat{J} = \left( \int_0^t dX_sX_s^\top \right) \left( \int_0^t X_sX_s^\top ds \right)^{-1}.
\]
To derive this solution, we used the fact that the inverse of the covariance is independent from the time and stochastic process.

The important consequence is that the maximum likelihood ratio based on the CMG theorem gives exactly the same solution as in the case of the path-likelihood maximization shown in Eq. (5).

**Another derivation of optimal Wright-Fisher selection coefficients via Cameron-Martin-Girsanov theorem**

In this section, we will rederive the maximum path likelihood solution of the selection in the WF model using the CMG theorem.

We can write the Langevin equation for the Wright-Fisher diffusion as
\[
dX_t = (C(X_t)s + \mu(X_t)) + \sqrt{C(X_t)}dW_t.
\]
Applying the formulation of the Radon-Nikodym derivative to this Langevin equation, we obtain
\[
\frac{dQ}{d\mathcal{P}} = \exp \left( \int_0^t (C(x_s)s + \mu(x_s))^\top C(x_s)^{-1}C(x_s) - \frac{1}{2} \int_0^t (C(x_s)s + \mu(x_s))^\top C(x_s)^{-1}(C(x_s)s + \mu(x_s)) ds \right).
\]

**Effect of regularization strength \(\gamma\)**

We report the influence of the regularization on the precision of the selection coefficients based on positive predictive value (PPV) curves. In this test, we chose the following different regularization values \(\gamma \in \{10^{-3}, 0.1, 1, 5, 10\}\). Through the all tests, we fixed the sampling interval as \(\Delta t = 75\). For the other parameters, we use the same parameters that are used in the main section.

**Supplementary Fig. 1** shows how inference accuracy depends on the regularization strength for MPL using different interpolation methods: piece-wise constant, linear, and Bézier interpolation.

In the case of the small to medium regularization values \((\gamma = 10^{-3}, 0.1, 1)\), PPV curves using the Bézier interpolation are significantly higher than the PPV curves using other interpolation methods. As the regularization value increases, the difference between the PPV curves for linear and Bézier interpolations becomes smaller.

**Supplementary Fig. 2** shows that MPL with Bézier interpolation outperforms MPL with linear interpolation for any regularization strength \(\gamma\). The best PPV curves of MPL with linear interpolation are still lower than the majority of PPV curves for MPL using Bézier interpolation. Moreover, although a large regularization improves the PPV curves of
MPL with linear interpolation, due to the strong regularization effect, the estimated selection coefficients are strongly biased and are underestimated as shown in Supplementary Fig. 3.

**Effect of sampling interval $\Delta t$**

Here, we discuss the effects of the sampling interval $\Delta t$ on the different interpolation methods in detail. In this study, the model parameters for the population size and mutation rate are the same as in the main text, and the regularization coefficient is fixed as $\gamma = 0.1$.

Supplementary Fig. 4 shows PPV curves for estimated selection coefficients using MPL with piece-wise constant, linear, and Bézier interpolation depending on various sampling intervals $\Delta t \in \{1, 10, 30, 75, 100\}$.

For $\Delta t = 1, 10$, there is no difference among these methods. However, when $\Delta t = 30$, the PPV curves for the piece-wise constant case deteriorate compared with the other methods and the ones for the linear and Bézier interpolations are indistinguishable. This is consistent with the argument in the main section: the characteristic time scale, $\gamma \Delta t$, is not so large that nonlinear effects are noticeable, hence PPV curves for the linear and Bézier interpolation are indistinguishable.

In the $\Delta t = 75$ case, the PPV curves of the MPL with Bézier interpolation are systematically higher than the cases of MPL with linear interpolation, hence MPL with Bézier interpolation outperforms other approaches.

In general, as the time interval increases, Bézier interpolation has a greater advantage in capturing the underlying dynamics of trajectories (Supplementary Fig. 4). However, for large enough time gaps, all interpolation methods suffer because data is sampled too sparsely to reveal any information about the underlying dynamics. For large enough $\Delta t$, there is no connection between the covariances at consecutively sampled points, and “trajectory information” is no longer contained in the data. This is also consistent with the negligible size of the autocorrelation for off-diagonal covariances at very large time gaps.
Supplementary Fig. 1. Across a wide range of regularization values, Bézier interpolation achieves more accurate inference than linear interpolation. (a.1) PPV curves for beneficial selection coefficients using $\gamma = 10^{-3}$. Other conditions are the same as in the main text. (a.2) PPV curves for deleterious coefficients using $\gamma = 10^{-3}$. (b), (c), (d) the same type of figures but using $\gamma = 1.0$, $\gamma = 5.0$ and $\gamma = 10.0$. MPL with linear interpolation is sensitive to the regularization strength, and larger regularization is necessary to make more precise inferences. However, the most accurate PPV using MPL with linear interpolation ($\gamma = 30.0$) has almost the same performance as the least accurate inferences using MPL with Bézier interpolation (see Supplementary Fig. 2). Moreover, the larger regularization induces a strong estimation bias, as shown in Supplementary Fig. 3.

Positive semidefiniteness of the interpolated covariance

The eigenvalues of the covariance matrix are strictly nonnegative. This positive semi-definiteness is an essential property of the covariance matrix and is practically important. We numerically confirmed the positive semidefiniteness of interpolated covariance matrices using the Bézier interpolation.

To evaluate the positive semidefiniteness, we generated a test data set by running the WF model 100 times. The dependent parameters of the WF model are the same as the main text. Then, we estimated integrated covariance matrices and their covariance matrix eigenvalues for different interpolation methods and different sampling intervals.

In either interpolation method, the eigenvalue distribution of the integrated covariance matrix showed little change, and only positive eigenvalues were observed in each case (Supplementary Fig. 5).

Selection coefficient inference without off-diagonals of integrated covariance elements

As shown in the main text, Bézier interpolation is better than linear interpolation in the sense of the more accurate reconstruction of the covariance matrix depending on perfectly observed trajectories (when the sampling interval $\Delta t = 1$) from the covariance matrix depending on “sparsely” observed trajectories, especially for the “off-diagonal” elements (corresponding to pairwise covariances $C_{ij} = x_{ij} - x_i x_j$, with $i \neq j$) of the integrated covariance matrix. On the other hand, the difference between linear and Bézier interpolation for the “diagonal” elements (variance $C_{ii} = x_i (1 - x_i)$) was relatively minor. To understand how exactly this observation is associated with the accuracy of the selection coefficients, we examine the effect of the off-diagonal entries of the integrated covariance matrix on the selection coefficients in this section.

Supplementary Fig. 6 shows the inference accuracy for both deleterious and beneficial mutations using MPL and the single locus (SL) method, a simplified inference method that ignores the off-diagonal of the integrated covariance matrix.
Supplementary Fig. 2. In a wide range of regularization, MPL with Bézier interpolation achieves higher PPVs than MPL with linear interpolation. Here we show PPV curves between rank 60 and 900, where changes due to the different regularization values $\gamma = 10^{-3}, 0.1, 1.0, 5.0, 10.0$ and $30.0$ are most noticeable. PPV curves of MPL with Bézier interpolation maintain high values stably. In contrast, PPV curves of MPL with linear interpolation are sensitive to the choice of the regularization strength and tend to be lower than those for MPL with Bézier interpolation. In the linear interpolation case, larger regularization yields higher the PPV curves, but also larger estimation bias.

Supplementary Fig. 3. MPL with Bézier interpolation reduces estimation bias in a wide range of regularization, and small regularization is needed to avoid strong estimation bias. (a) Distribution of inferred selection coefficients using a strong regularization $\gamma = 10$. Other conditions are the same as in the main text. (b) Estimated selection coefficients using a weak regularization $\gamma = 10^{-3}$. Smaller regularization $\gamma = 10^{-3}$ reduces estimation bias, especially for MPL with linear interpolation.

The PPV of MPL with Bézier interpolation achieves systematically higher values than the PPV of MPL with linear interpolation. However, the difference between linear and Bézier interpolation becomes unclear for inferences using SL. Thus, the main reason MPL with Bézier interpolation can infer better than MPL with linear interpolation is the accurate estimation of off-diagonal covariances (including pairwise frequencies).

Ornstein-Uhlenbeck process inference comparison

In this section, we report a more detailed analysis of the estimated coupling parameters of OU processes. The input data sets for the inference are the same as in the main section. To compare the inference accuracy between various inference methods, besides the path-likelihood-based methods, we included mean-field theory-based inference. In this approach, the effective solution is given by the inverse of the integrated covariance matrix, which effectively predicts interaction matrices for input data following an equilibrium distribution. Supplementary Fig. 7 shows comparisons of a true interaction matrix and estimated interactions. The accuracy of the
Supplementary Fig. 4. As the sampling interval increases, the advantage of the Bézier interpolation becomes more notable. (a.1) PPV curves for beneficial selection coefficient inference using the sampling interval $\Delta t = 1$, using MPL with Bézier, linear, and piece-wise constant interpolations. Other conditions are the same as in the main text ($\gamma = 0.1, N = 10^3$, and $\mu = 10^{-3}$). (a.2) PPV curves for deleterious selection coefficient inference using $\Delta t = 1$. Subplots, (b), (c) and (d) are the same type of figures but for $\Delta t = 30, 75$, and $100$, respectively. As the sampling interval increases, the inference accuracy decreases in the PPV sense. However, inferences using Bézier interpolation degrade more slowly than other methods. For the longest sampling interval ($\Delta t = 100$), consecutive time points are poorly correlated. As a result, none of the interpolation methods can completely accurately infer selection coefficients, and hence the PPV curves roughly converge.

Supplementary Fig. 5. Covariance matrix with Bézier interpolation maintains positive semidefiniteness. Comparison of the minimum eigenvalue distributions of the integrated covariance matrices: As the $\Delta t$ increases, the minimum eigenvalues are smaller, but they remain nonnegative values. Thus, all the integrated covariances are positive definite.
Supplementary Fig. 6. Improvement of the selection inference accuracy is due to the accurate restoration of pairwise frequencies. PPV curves for (a) deleterious and (b) beneficial selection coefficients using MPL methods. The sampling interval is fixed as $\Delta t = 75$. PPV curves for (c) deleterious and (d) beneficial selection coefficients, but using the single locus (SL) method, a simplified version of MPL which sets off-diagonal elements of the covariance matrix to zero. Bézier interpolation improves the precision of MPL, but the choice between linear and Bézier interpolation does not significantly affect the accuracy of SL. This implies that the accurate estimation of pairwise frequencies (corresponding to off-diagonal covariances) improves selection inference accuracy.

Path-likelihood-based methods is significantly better than the path-likelihood-based methods is significantly better than the inverse of the covariance matrix in terms of Pearson’s correlation and linear regression’s slope. This is an anticipated result since the input data sets were generated from the relaxation processes, and the probability distributions that characterize these dynamics are in non-steady states. Therefore, MPL methods outperform inference methods assuming equilibrium states.

The path-likelihood-based inference method with Bézier interpolation achieves the best inference accuracy for both diagonal and off-diagonal interaction matrix elements in terms of Pearson’s correlation coefficients and regression slope values.

Supplementary Fig. 8 shows sampling interval dependence for Pearson’s correlation coefficients between true interaction matrices and inferred interaction matrices. The input data sets and conditions of the inferences are the same as the main text. As the sampling interval regime increases, the difference between Pearson’s $r$ of linear and Bézier interpolations becomes more pronounced, and the inferences using Bézier interpolation achieve higher Pearson’s $r$ values among all sampling intervals.

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Supplementary Fig. 7. Path-likelihood-based inference method with Bézier interpolation achieves the best inference accuracy. Comparison of true and inferred OU process interaction matrices. Mean-field based methods were used for (a.1) diagonal and (a.2) off-diagonal elements of the interaction matrix. Panels (b), (c), and (d) are the same type of plots, but using the path-likelihood-based inference with piecewise constant, linear, and Bézier interpolation, respectively. Among all the methods, inference with Bézier interpolation achieves the highest accuracy in terms of Pearson's correlation coefficient and regression slope value.
Supplementary Fig. 8. As the sampling interval increases, the advantage of Bézier interpolation becomes more pronounced. Dependence of Pearson's correlation coefficients for (a) diagonal and (b) off-diagonal interaction matrices on the sampling interval. Pearson's correlation coefficients for Bézier interpolation are significantly higher than the ones for linear interpolation, especially when the sampling interval is large.