LARGE-SCALE INference of Correlation AMong Mixed-Type Biological TrAITS with Phylogenetic Multivariate Probit Models

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Inferring concerted changes among biological traits along an evolutionary history remains an important yet challenging problem. Besides adjusting for spurious correlation induced from the shared history, the task also requires sufficient flexibility and computational efficiency to incorporate multiple continuous and discrete traits as data size increases. To accomplish this, we jointly model mixed-type traits by assuming latent parameters for binary outcome dimensions at the tips of an unknown tree informed by molecular sequences. This gives rise to a phylogenetic multivariate probit model. With large sample sizes, posterior computation under this model is problematic, as it requires repeated sampling from a high-dimensional truncated normal distribution. Current best practices employ multiple-try rejection sampling that suffers from slow-mixing and a computational cost that scales quadratically in sample size. We develop a new inference approach that exploits 1) the bouncy particle sampler based on piecewise deterministic Markov processes and 2) novel dynamic programming that reduces the cost of likelihood and gradient evaluations to linear in sample size. In an application with 535 HIV viruses and 24 traits that necessitates sampling from a 12,840-dimensional truncated normal, our method makes it possible to estimate the across-trait correlation and detect factors that affect the pathogen’s capacity to cause disease. This inference framework is also applicable to a broader class of covariance structures beyond comparative biology.

1. Introduction. Phylogenetics stands as a key tool in assessing rapidly evolving pathogen diversity and its impact on human disease. Important taxonic examples include RNA viruses, such as influenza and human immunodeficiency virus (HIV). Pathogens sampled from infected individuals are implicitly correlated with each other through their shared evolutionary history, often described through a phylogenetic tree that one reconstructs

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by sequencing the pathogen genomes. Models for inference about concerted changes within multiple pathogen and host traits along this history are highly structured. They must simultaneously adjust for the across-taxon correlation and the between-trait correlation that characterizes the trait evolutionary process, leading to heavy computational burden. This burden becomes more severe as the sample size increases and when traits are of mixed-type, including both continuous quantities and discrete outcomes. Even the state-of-the-art approach (Cybis et al., 2015) fails to provide reliable estimates for emerging biological problems due to high computational complexity.

To jointly model continuous and binary trait evolution along an unknown tree, we adopt and extend the popular phylogenetic threshold model for binary traits (Felsenstein, 2005, 2011) with a long tradition in statistical genetics (Wright, 1934). This model assumes unobserved continuous latent parameters for each tip taxon in the tree determine the observed binary traits according to a threshold. The latent parameters themselves arise from a Brownian diffusion along the tree (Felsenstein, 1985). The correlation matrix of the diffusion process informs correlation between latent parameters that map to concerted changes between binary traits. Here one interprets the latent parameters as the combined effect of all relevant genetic factors that influence the binary traits after adjusting for the shared evolutionary history.

We extend the threshold model to include continuous traits by treating them as directly observed dimensions of latent parameters and place specific constraints on the diffusion covariance for parameter identifiability. We arrive at a mixed-type generalization of the multivariate probit model (Chib and Greenberg, 1998) that allows us to jointly model continuous and binary traits. We call this the phylogenetic multivariate probit model.

Alternative approaches for mixed-type traits on unknown trees are limited. Phylogenetic regression models (Grafen, 1989) assume a known fixed tree and their logistic extensions (Ives and Garland, 2009) take a single binary trait as the regression outcome. On the other hand, for continuous traits, comparative methods (Felsenstein, 1985) scale well on random trees (Pybus et al., 2012; Tung Ho and Ané, 2014). Likewise, continuous-time Markov chain based methods (Pagel, 1994; Lewis, 2001) are popular for multiple binary traits, but restrictively assume independence between traits given the tree.

Bayesian inference for the phylogenetic multivariate probit model involves, however, repeatedly sampling latent parameters from an $NP$-dimensional truncated normal distribution, with $N$ being the number of taxa and $P$ the number of traits. To attempt this, Cybis et al. (2015) uses Markov chain
Monte Carlo (MCMC) based on a multiple-try rejection sampler. The sampler has a computational complexity of $O(NP^2)$ to update $P$ dimensions of the latent parameters for just one taxon within a Gibbs cycle. Hence, to touch all dimensions, the resulting cost is $O(N^2P^2)$. Further, since only a small portion of the latent parameter dimensions are updated per rejection-sample, the resulting MCMC chain is highly auto-correlated, hurting efficiency.

To overcome this limitation, we develop a scalable approach to sampling from the multivariate truncated normal by combining the recently developed bouncy particle sampler (BPS) (Bouchard-Côté, Vollmer and Doucet, 2018) and an extension of the dynamic programming strategy by Pybus et al. (2012). BPS samples from a target distribution by simulating a Markov process with a piecewise linear trajectory. The simulation generally requires solving a one-dimensional optimization problem within each line segment. When sampling from a truncated normal, however, this optimization problem can be solved via a single log-density gradient evaluation. In the phylogenetic multivariate probit model, a direct evaluation of this gradient requires $O(N^2P + NP^2)$ computation. By extending the dynamic programming strategy of Pybus et al. (2012) for diffusion processes on trees, we reduce this computational cost to $O(NP^2)$ — a major practical gain as $N \gg P$ in most applications. Compared to the current practice, our BPS sampler achieves superior mixing rate at comparable computational complexity, allowing us to attack previously unworkable problems.

We apply this Bayesian inference framework to assess correlation between HIV-1 gag gene immune-escape mutations and viral virulence, the pathogen’s capacity to cause disease. By adjusting for the unknown evolutionary history that confounds our epidemiologically collected data, we identify significant correlations that closely match with the biological experimental literature and increase our understanding of the underlying molecular mechanisms of HIV.

2. Modeling.

2.1. Phylogenetic multivariate probit model for mixed-type traits. Consider $N$ biological taxa, each with $P$ trait measurements. These measurements partition as $\mathbf{Y} = \{y_{ij}\} = [\mathbf{Y}^b, \mathbf{Y}^c]$ with $\mathbf{Y}^b$ being an $N \times P_b$ matrix of $P_b$ binary traits and $\mathbf{Y}^c$ an $N \times P_c$ matrix of $P_c$ continuous traits, where $P = P_b + P_c$. We extend the phylogenetic threshold model (Felsenstein, 2005) to jointly model $\mathbf{Y}$. In this manner, we assume that $\mathbf{Y}$ arises from a partially observed multivariate Brownian diffusion process along a phylogenetic tree $\mathcal{F}$. The tree $\mathcal{F} = (\mathcal{V}, \mathcal{t})$ is a directed, bifurcating acyclic graph with a set
of nodes $V$ and branch lengths $t$. The node set $V$ contains $N$ degree-1 tip nodes, $N - 2$ internal nodes of degree 3, and one root node of degree 2. The branch lengths $t = (t_1, \ldots, t_{2N - 2})$ denote the distance in real time from each node to its parent (Figure 1, left). The tree $F$ is either known or informed by molecular sequence alignment $S$ (Suchard et al., 2018). Sequences $S$ only affect the parameters of primary interest through $F$ since $S$ is assumed conditionally independent of other parameters given $F$. We refer interested readers to Suchard et al. (2018) for the construction of $p(S|F)$ and choices for tree priors $p(F)$.

We associate each node $i$ in $F$ with a latent parameter $X_i \in \mathbb{R}^P$ for $i = 1, \ldots, 2N - 1$. A Brownian diffusion process characterizes the evolutionary relationship between latent parameters, such that $X_i$ is multivariate normal (MVN) distributed,

\begin{equation}
X_i \sim \text{MVN}(X_{\text{pa}(i)}, t_i \Omega),
\end{equation}

centered at its parent node value $X_{\text{pa}(i)}$ with across-trait, per-unit-time, $P \times P$ variance matrix $\Omega$ that is shared by all branches along $F$.

At the tips of $F$, we collect the $N \times P$ matrix $X = \{x_{ij}\} = [X_1, \ldots, X_N]^T$ and map it to the observed traits through the function

\begin{equation}
y_{ij} = g(x_{ij}) = \begin{cases} 
\text{sign}(x_{ij}), & j = 1, \ldots, P_b, \\
x_{ij}, & j = P_b + 1, \ldots, P,
\end{cases}
\end{equation}

where $\text{sign}(x_{ij})$ takes the value 1 on positive values and -1 on negative values. As a result, latent parameters at the tips and a threshold (without loss of generality, $= 0$) determine the corresponding binary traits, and continuous traits can be seen as directly observed.

Turning our attention to the joint distribution of tip latent parameters $X$, we can integrate out $X_{N+1}, \ldots, X_{2N-1}$ by assuming a conjugate prior on the tree root, $X_{2N-1} \sim \text{MVN}(\mu_0, \tau_0^{-1} \Omega)$ with prior mean $\mu_0$ and prior sample size $\tau_0$. Then $X$ follows a matrix normal distribution

\begin{equation}
X \sim \text{MTN}(M; \Psi, \Omega),
\end{equation}

where $M = (\mu_0, \ldots, \mu_0)^T$ is an $N \times P$ matrix and the across-taxa tree covariance matrix $\Psi = V(F) + \tau_0^{-1} J$ (Pybus et al., 2012). The tree diffusion matrix $V(F)$ is a deterministic function of $F$ and $J$ is an $N \times N$ matrix of all ones, such that the term $\tau_0^{-1} J$ comes from the integrated-out tree root prior. Figure 1 illustrates how the tree structure determines $V(F)$: the diagonals are equal to the sum of branch lengths from tip to root, and the
off-diagonals are equal to the branch length from root to the most recent common ancestor of two tips.

Combining equations (2.2) and (2.3) enables us to write down the augmented likelihood of $X$ and $Y$ through factorization

\[ p(Y, X \mid \Upsilon, \Omega, \mu_0, \tau_0, g) = p(Y \mid X)p(X \mid \Upsilon, \Omega, \mu_0, \tau_0), \]

where $p(Y \mid X) = \mathbb{I}(Y \mid X, g)$, the indicator function that takes the value 1 if $X$ are consistent with the observations $Y$ and 0 otherwise.

### 2.2. Decomposition of trait-covariance to account for varying data scales.

The previous work of Cybis et al. (2015) uses a conjugate Wishart prior on $\Omega^{-1}$ for computational convenience. This approach is inappropriate when dealing with mixed-type data. A Wishart prior can be restrictive (Gelman et al., 2004) as it prescribes the same degree of freedom for every diagonal element of $\Omega^{-1}$. This is unrealistic with mixed-type data because for continuous traits we observe numeric values with potentially differing rates of change along $\mathcal{F}$, while for the latent dimensions only their signs are known and their absolute values are arbitrary. As a result, the Wishart prior leaves the model not parameter-identifiable. Also, the joint distribution of the correlation under a Wishart prior is considerably different from uniform (Tokuda et al., 2011). We solve these two problems by decomposing $\Omega$ into a across-trait correlation matrix and standard deviations, with a jointly uniform prior on the correlation matrix.

Specifically, we decompose $\Omega = DRD$, where $R$ is the $P \times P$ correlation matrix and $D$ is a diagonal matrix with elements $D_{ii} = 1$, for $i = 1, \ldots, P_b$ and $D_{ii} = \sigma_i > 0$ for $i = P_b + 1, \ldots, P$. We use the prior of Lewandowski, Kurowicka, and Joe (LKJ) on positive-definite correlation
matrix \( R \) (Lewandowski, Kurowicka and Joe, 2009), such that

\[
\text{LKJ}(R|\eta) \sim c(\eta)\det(R)^{\eta-1},
\]

where \( \eta > 0 \) is a shape parameter and \( c(\eta) \) is the normalizing constant. When \( \eta = 1 \), the LKJ prior implies a uniform distribution over all correlation matrices of dimension \( P \). For the diagonal standard deviation matrix \( D \), we assume independent log normal priors on \( \sigma_i \) for \( i = P_b + 1, \ldots, P \) with mean 0 and variance 1 on the log scale. We describe how to carry out the posterior inference under this prior in Section 3.2.

3. Inference. Primary scientific interest lies in the across-trait correlation matrix \( R \). We integrate out the nuisance parameters by sampling from the joint posterior

\[
p(R, D, X, \mathcal{F} | Y, S) \propto p(Y | X) \times p(X | R, D, \mathcal{F}) \times p(R, D | \mathcal{F}) \times p(S | \mathcal{F}) \times p(\mathcal{F})
\]

via a random-scan Gibbs scheme (Liu, Wong and Kong, 1995), and drop the posterior’s dependence on the hyper-parameters \((\Upsilon, \mu_0, \tau_0, g)\) to ease notation.

The Gibbs sampler alternately update \( \mathcal{F}, X, \) and \((R, D)\) from their full conditionals, taking advantage of the conditional independence structure. We update \( \mathcal{F} \) from \( p(\mathcal{F} | S, X, Y, \Omega) \) using standard algorithms as described in Suchard et al. (2018). This section focuses on overcoming the scalability bottleneck of updating \( X \) from an \( NP \)-dimensional truncated normal distribution by combining BPS with dynamic programming strategy. We also describe how we deploy Hamiltonian Monte Carlo (HMC) to update \((R, D)\) to accommodate the non-conjugate prior on \( \Omega = DRD \).

3.1. BPS for updating high-dimensional latent parameters. BPS is a non-reversible “rejection-free” sampler originally introduced in the computational physics literature by Peters and de With (2012) for simulating particle systems. Bouchard-Côté, Vollmer and Doucet (2018) later adapt the algorithm with modifications to better suit statistical applications. BPS explores a target distribution \( p(x) \) by simulating a piecewise deterministic Markov process. The simulated particle follows a piecewise linear trajectory, with its evolution governed by the landscape of the energy function \( U(x) := -\log p(x) \). To respect the target distribution, classical Monte Carlo algorithms “reject” a move toward areas of low probability or, equivalently, of high energy. On the other hand, BPS modifies its particle trajectory via
a Newtonian elastic collision against the energy gradient, thereby avoiding wasteful rejected moves.

BPS is an efficient sampler for log-concave target distributions in general, with the additional ability to account for parameter constraints by treating them as “hard-walls” against which the particle bounces. Of particular interest to us is the fact that, when the target distribution is a truncated MVN, the critical computation for BPS implementation is multiplying the precision matrix of the unconstrained MVN by an arbitrary vector. So when the precision matrix has special structure that allows fast matrix-vector operations, BPS becomes an especially efficient approach. Luckily, in our application, such a special structure arises from the tree diffusion process.

BPS also allows us to condition on a subset of dimensions that correspond to the continuous traits without extra computation. We begin with an overview of BPS following Bouchard-Côté, Vollmer and Doucet (2018) and describe how to incorporate parameter constraints (Bierkens et al., 2018); the subsequent sections describe how to optimize the implementation when sampling from a truncated MVN.

3.1.1. BPS overview. To sample from the target distribution \( p(x) \), BPS simulates a particle with position \( x(t) \) and velocity \( v(t) \) for time \( t \geq 0 \), initialized from \( v_0 \sim \mathcal{N}(0, I) \) and a given \( x_0 \) at time \( t = 0 \). The particle follows a piecewise linear path with velocity \( v(t) = v_k \) and position \( x(t) = x_k + (t - t_k)v_k \) over time intervals \( t \in [t_k, t_{k+1}] \). An inhomogeneous Poisson process governs the inter-event times \( s_{k+1} = t_{k+1} - t_k \) with rate

\[
\lambda(x(t), v_k) = \max \{0, \langle v_k, \nabla U(x(t)) \rangle \},
\]

where \( \langle \cdot, \cdot \rangle \) denotes an inner product. When \( U(x) \) is convex, one can conveniently simulate this Markov process for a pre-specified amount of time \( t_{\text{total}} > 0 \) as follows:

1. Solve a one-dimensional optimization problem to find

\[
s_{\min} = \arg\min_{s \geq 0} U(x_{k-1} + sv_{k-1}) \quad \text{and} \quad U_{\min} = U(x_{k-1} + s_{\min}v_{k-1}).
\]

2. Draw \( T \sim \text{Exp}(1) \), an exponential random variable with rate 1, and solve for the next inter-event time

\[
s_k = \inf_{s > s_{\min}} \{U(x_{k-1} + s v_{k-1}) - U_{\min} = T\}.
\]

3. Update \((x, v)\) as

\[
x_k \leftarrow x_{k-1} + s_k v_{k-1}, \quad v_k \leftarrow v_{k-1} - 2\frac{\langle v_{k-1}, \nabla U(x_k) \rangle}{\|\nabla U(x_k)\|^2} \nabla U(x_k).
\]
4. Stop if \( \sum_{j=1}^{k} s_j \geq t_{\text{total}} \) and return \( x(t_{\text{total}}) = x_{k-1} + (t_{\text{total}} - t_{k-1})v_{k-1} \) where \( t_{k-1} = \sum_{j=1}^{k-1} s_j \), otherwise repeat Step 1 - 3.

The mapping \( x_0 \rightarrow x(t_{\text{total}}) \) described above defines a Markov transition kernel with \( p(x) \) as the stationary density. The “bounce” at Step 3 replaces the usual accept/reject step, thereby yielding a rejection-free algorithm.

When the target distribution is constrained to some region \( x \in D \), the bounce events are caused not only by the gradient \( \nabla U(x) \) but also by the domain boundary \( \partial D \). We call these bounces “gradient events” and “boundary events” respectively. Whichever occurs first is the actual bounce. More precisely, define the boundary event time \( s_{\text{bd},k} \) as

\[
 s_{\text{bd},k} = \inf_{s > 0} \{ x_{k-1} + sv_{k-1} \notin D \}.
\]

Then the bounce time is given by \( s_k = \min\{s_{\text{bd},k}, s_{\text{gr},k}\} \), where \( s_{\text{gr},k} \) denotes the gradient event time of (3.4). If \( s_{\text{bd},k} < s_{\text{gr},k} \), we have a boundary bounce and the position is updated as in (3.5) while the velocity is updated as

\[
 v_k \leftarrow v_{k-1} - 2 \frac{\langle v_{k-1}, \nu \rangle}{\langle v_{k-1}, v_{k-1} \rangle} \nu,
\]

where \( \nu = \nu(x_k) \) is a unit vector orthogonal to the boundary at \( x_k \in \partial D \).

3.1.2. BPS for truncated MVNs. We now describe how the BPS simulation simplifies when the target density is a \( d \)-dimensional truncated MVN of the form

\[
 x \sim \text{MVN}(m, \Sigma) \quad \text{subject to} \quad x \in D = \{ \text{sign}(x) = y \} \quad \text{for} \quad y \in \{ \pm 1 \}^d.
\]

Importantly, we can implement BPS so that, aside from basic and computationally inexpensive operations, it relies solely on matrix-vector multiplications by the precision matrix \( \Phi = \Sigma^{-1} \). Moreover, under the orthonormal constraint \( \{ \text{sign}(x) = y \} \), we can handle a bounce against the boundary in a particularly efficient manner, only requiring an access to a column of \( \Phi \).

We start with gradient events and then describe how to find boundary event times. Now \( U(x) = -\log p(x) = \frac{1}{2}(x - m)^T \Phi (x - m) \) and therefore

\[
 U(x + sv) = \frac{1}{2} \langle v, \varphi_v \rangle s^2 + \langle v, \varphi_x \rangle s + \frac{1}{2} \langle x, \varphi_x \rangle
\]

where \( \varphi_v = \Phi v \) and \( \varphi_x = \Phi (x - m) = \nabla U(x) \).

The solution to the optimization problem (3.3) is given by

\[
 s_{\text{min}} = \max \left\{ 0, -\frac{\langle v, \varphi_x \rangle}{\langle v, \varphi_v \rangle} \right\},
\]

\[
 U_{\text{min}} = \frac{1}{2} \langle v, \varphi_v \rangle s_{\text{min}}^2 + \langle v, \varphi_x \rangle s_{\text{min}} + \frac{1}{2} \langle x, \varphi_x \rangle.
\]
It follows from (3.9) that the gradient event time in (3.4) coincides with the larger root of the quadratic equation $as^2 + bs + c = 0$ with

$$a = \frac{1}{2} \langle v, \varphi_v \rangle, \quad b = \langle v, \varphi_x \rangle,$$

and

$$c = -\frac{1}{2} \langle v, \varphi_v \rangle s_{\min}^2 - \langle v, \varphi_x \rangle s_{\min} - T,$$

so

$$s_{gr} = -\frac{b + \sqrt{b^2 - 4ac}}{2a}.$$

When a gradient event takes place, the position and velocity are updated according to (3.5) with

$$(3.11) \quad \nabla U(x + sv) = \varphi_{x+s\nu} = \Phi(x - m) + s\Phi v = \varphi_x + s\varphi_v.$$

Note that $\varphi_{x+s\nu}$ can be computed by an element-wise addition of $\varphi_x$ and $s\varphi_v$, rather than the expensive matrix-vector operation $x + sv \rightarrow \Phi(x + sv)$.

The orthant boundary is given by $\cup_i \{x_i = 0\}$. When $\text{sign}(x_i) = \text{sign}(v_i)$, where $x_i$ and $v_i$ denotes the $i$-th coordinate of particle position and velocity, the particle is moving away from the $i$-th coordinate boundary $\{x_i = 0\}$ and thus never reaches it. Otherwise, the coordinate boundary is reached at time $s = |x_i/v_i|$. Hence $s_{bd}$ can be expressed as

$$s_{bd} = |x_{i_{bd}}/v_{i_{bd}}|, \quad i_{bd} = \arg\min_{i \in I} |x_i/v_i| \quad \text{for} \quad I = \{i : x_i v_i < 0\}.$$

When a boundary event takes place, the particle bounces against the plane orthogonal to the standard basis vector $\nu = e_{i_{bd}}$. As the updated velocity takes the form $v^* \leftarrow v - 2v_{i_{bd}} e_{i_{bd}}$, we can save computational cost of simulating the next line segment by realizing that

$$(3.12) \quad \varphi_{v^*} = \Phi v^* = \varphi_v + 2v_{i_{bd}}^* \Phi e_{i_{bd}} \quad \text{where} \quad v_{i_{bd}}^* = -v_{i_{bd}}.$$

In other words, we can compute $\varphi_{v^*}$ by simply extracting the $i_{bd}$-th column of $\Phi$ and updating $\varphi_v$ with an element-wise addition. This avoids the expensive matrix-vector operation $v^* \rightarrow \Phi v^*$.

Algorithm 1 describes BPS implementation for truncated MVNs based on the discussion above, with the most critical calculations optimized. Within each line segment, $\varphi_x$ and $\varphi_v$ once efficiently computed (Section 3.1.3) can be re-used throughout. To condition on the fixed dimensions that correspond to observed, continuous traits, we slightly modify the algorithm to sample from conditional truncated MVNs (details in Appendix A.1). We choose the tuning parameter $t_{\text{total}}$ based on a heuristic that works well in practice (Section A.2).
Algorithm 1 Bouncy particle sampler for multivariate truncated normal distributions

Require: $t_{\text{total}}$, initial value for $x$

1: $v \sim N(0, I)$
2: $\varphi_x \leftarrow \Phi(x - m)$ \hspace{1cm} \triangleright \varphi_x = \nabla U(x)$ is the gradient of energy
3: \textbf{while } $t_{\text{total}} > 0$ \textbf{do}
4: \hspace{0.5cm} \triangleright \text{compute reused quantities once}
5: \hspace{1cm} \textbf{if} previous bounce is a boundary event at coordinate $i$ \textbf{then}
6: \hspace{2cm} $\varphi_v \leftarrow \varphi_v + 2v_i \Phi e_i$
7: \hspace{1cm} \textbf{else}
8: \hspace{2cm} $\varphi_v \leftarrow \Phi v$ \hspace{1cm} \triangleright \text{the expensive step}
9: \hspace{2cm} $\varphi_{v,x}, \varphi_{v,v} \leftarrow v^T \varphi_v$
10: \hspace{1cm} \triangleright \text{find gradient event time}
11: \hspace{2cm} $s_{\text{min}} \leftarrow \max \{0, -\varphi_{v,x}/\varphi_{v,v}\}$
12: \hspace{2cm} $T \sim \text{Exp}(1)$
13: \hspace{2cm} $a \leftarrow \frac{1}{2} \varphi_{v,v}, b \leftarrow \varphi_{v,x}, c \leftarrow -\frac{1}{2} s_{\text{min}} \varphi_{v,v} - s_{\text{min}} \varphi_{v,x} - T$
14: \hspace{2cm} $s_{\text{gr}} \leftarrow (-b + \sqrt{b^2 - 4ac})/(2a)$ \hspace{1cm} \triangleright \text{find truncation event time at coordinate } i$
15: \hspace{2cm} $s_{\text{bd}} \leftarrow \text{argmin } i \frac{x_i}{v_i}, \text{ for } i \text{ with } x_i v_i < 0$
16: \hspace{1cm} \triangleright \text{bounce happens}
17: \hspace{2cm} $s \leftarrow \min \{s_{\text{gr}}, s_{\text{bd}}, t_{\text{total}}\}$
18: \hspace{2cm} $x \leftarrow x + sv, \varphi_x \leftarrow \varphi_x + s\varphi_v$
19: \hspace{2cm} \textbf{if } $s = s_{\text{bd}}$ \textbf{then}
20: \hspace{3cm} $v_i \leftarrow -v_i$
21: \hspace{2cm} \textbf{else if } $s = s_{\text{gr}}$ \textbf{then}
22: \hspace{3cm} $v \leftarrow v - \langle v, \varphi_x \rangle/\|\varphi_x\|^2 \varphi_x$
23: \hspace{2cm} \textbf{end if}
24: \hspace{2cm} $t_{\text{total}} \leftarrow t_{\text{total}} - s$
25: \hspace{1cm} \textbf{end while}

3.1.3. Dynamic programming strategy to overcome computational bottleneck. A straight implementation of BPS remains computationally challenging, as computing $\varphi_x$ and $\varphi_v$ in Algorithm 1 involves a high-dimensional matrix inverse when the model is parameterized in terms of $\Sigma$. From (2.3) and the equivalence between matrix normal and multivariate normal distributions, to sample latent parameters $X$ from their conditional posterior, the target distribution (3.8) specifies as $x = \text{vec}(X), m = \text{vec}(M), \Sigma = \Omega \otimes \Upsilon$, and $y = \text{vec}(Y)$, where $\text{vec}(\cdot)$ is the vectorization that converts an $N \times P$ matrix into an $NP \times 1$ vector and $\otimes$ denotes the Kronecker product. A naive matrix inverse operation $\Sigma^{-1} = \Omega^{-1} \otimes \Upsilon^{-1}$ has a intimidating complexity of $O(N^3 + P^3)$. If we have a fixed tree, such that $\Upsilon^{-1}$ is known, the typical
computation proceeds via

\[
\Sigma^{-1} (x - m) = (\Omega^{-1} \otimes \Upsilon^{-1}) (x - m) = \text{vec} (\Upsilon^{-1} (X - M) \Omega^{-1}),
\]

with a cost \( O(N^2P + NP^2) \). When the tree is random, the \( O(N^3) \) cost to get \( \Upsilon^{-1} \) seems unavoidable. However, we show that even with a random tree, evaluating \( \phi_x \) and \( \phi_v \) can be \( O(NP^2) \). We use conditional densities to evaluate these products (Lemma 1) and obtain all conditional densities simultaneously via a dynamic programming strategy that avoids explicitly inverting \( \Upsilon \).

**Lemma 1.** Given joint variance matrix \( \Sigma \) and vectorized latent data \( x \), the energy gradient \( \nabla U(x) \) is

\[
\phi_x = \Sigma^{-1} (x - m) = \begin{pmatrix}
Q_1 (X_1 - \mu_1) \\
\vdots \\
Q_N (X_N - \mu_N)
\end{pmatrix},
\]

where \( \mu_i \) and \( Q_i \) are the mean and the precision matrix of the distributions \( p(X_i | X_{(i)}) \) for \( i = 1, \ldots, N \), and \( p(X_i | X_{(i)}) \) is the conditional distribution of latent parameters at one tree tip given those of all the other tips.

**Proof.** \( x \sim \text{MVN}(m, \Sigma) \), so \( p(X_i | X_{(i)}) \) are also multivariate normally distributed. Note that

\[
\frac{\partial}{\partial x} [\log p(x)] = \frac{\partial}{\partial x} [p(x)] / p(x) = -\frac{1}{2} \Sigma^{-1} (x - m).
\]

Likewise,

\[
\frac{\partial}{\partial x} [\log p(x)] = \left( \frac{\partial}{\partial X_1} [\log p(x)], \ldots, \frac{\partial}{\partial X_N} [\log p(x)] \right)^T
\]

with

\[
\frac{\partial}{\partial X_i} [\log p(x)] = \frac{\partial}{\partial X_i} \left[ \log p(X_i | X_{(i)}) + \log p(X_{(i)}) \right] = -\frac{1}{2} Q_i (X_i - \mu_i).
\]

Equating (3.15) and (3.16) completes the proof. In Lemma 1, the partition is by taxon, but we can generalize to any arbitrary partitioning of the
dimensions. By replacing $\mathbf{x} - \mathbf{m}$ with $\mathbf{v}$ (or $\mathbf{e}_i$), we achieve a similar result for $\varphi_v$ (or $\Phi \mathbf{e}_i$). Given $\mathbf{\mu}_i$ and $Q_i$, the $O(NP^2)$ matrix-vector operation $\mathbf{v}^* \rightarrow \Phi \mathbf{v}^*$ based on Lemma 1 is generally required for updating $\varphi_{v^*}$, but for boundary bounces, we can exploit (3.12) and update $\varphi_{v^*}$ in $O(NP)$. For the conditional posterior distribution in our HIV application (Section 4), boundary bounces occur far more frequently than gradient ones and thus the efficient update via (3.12) leads to further significant speed-up.

Fortunately, we are able to efficiently compute $\mathbf{\mu}_i$ and $Q_i$ through a dynamic programming strategy that recursively traverses the tree (Pybus et al., 2012) and enjoys a complexity of $O(NP)$. Here we give the results and omit the derivatives found in Pybus et al. (2012) and Cybis et al. (2015).

The recursive traversals visit every node first in post-order (child $\rightarrow$ parent) and then again in pre-order (parent $\rightarrow$ child) to calculate partial data likelihoods that lead to $\mathbf{\mu}_i$ and $Q_i$. The post-order traversal begins at a tip and ends at the root, while pre-order starts at the root and reaches every tip. The following results are in terms of the node triplets $(i, j, k)$ where $\text{pa}(i) = \text{pa}(j) = k$ as in Figure 2. We define $[i]$ as the tree tips that are decedents to or include (“below”) node $i$ and $[\bar{i}]$ as the tree tips that are not decedents to (“above”) node $i$.

![Fig 2: A sample tree to illustrate post- and pre- traversals for efficiently computing $p(\mathbf{X}_i | \mathbf{X}_{(i)})$. In the triplet $(i, j, k)$, parent node $k$ has two children $i$ and $j$. We group the tip nodes into two disjoint and exhaustive classes: $[i]$ = tree tips that are decedents to or include node $i$ and $[\bar{i}]$ = tree tips that are not decedents to $i$.]

During the post-order traversal, we determine partial likelihoods of the
data $X_{[i]}$ given latent $X_i$,

$$p(X_{[i]} | X_i) \propto \text{MVN}(X_i; m_i, v_i \Omega),$$

in terms of a post-order mean $m_i$ and variance $v_i \Omega$. We re-employ these quantities shortly in the pre-order traversal. At the tree tips, $m_i = X_i$ and the variance scalar $v_i = 0$. For internal nodes,

$$m_k = v_k \left[ (v_i + t_i)^{-1} m_i + (v_j + t_j)^{-1} m_j \right],$$

$$v_k = \left[ (v_i + t_i)^{-1} + (v_j + t_j)^{-1} \right]^{-1}.$$

Similarly, for the pre-order traversal, we calculate the conditional density of $X_i$ at node $i$ given the data above it,

$$p(X_i | X_{[i]}) \propto \text{MVN}(X_i; \mu_i, w_i \Omega),$$

in terms of a pre-order mean $\mu_i$ and variance $w_i \Omega$. Starting from the root where $w_{2N-1} = \tau_0^{-1}$ and $\mu_{2N-1} = \mu_0$, the traversal proceeds via

$$\mu_i = w_i \left[ (v_j + t_j)^{-1} m_j + w_k^{-1} \mu_k \right],$$

$$w_i = \left[ (v_j + t_j)^{-1} + w_k^{-1} \right]^{-1} + t_i.$$

When reaching the tips where $[i] = (i)$, we obtain both the desired conditional mean $\mu_i$ and precision $Q_i = (w_i \Omega)^{-1}$.

For both pre- and post-order traversals, at each node we require $O(P)$ elementary operations to obtain the mean vector and variance scalar; so, visiting all the nodes costs $O(NP)$. With $\mu_i$ and $Q_i$ for $i = 1, \ldots, N$ ready in hand, the computation in (3.14) remains $O(NP^2)$.

3.2. Hamiltonian Monte Carlo for updating trait covariance components. The across-trait covariance components $R$ and $D$ have complex and high-dimensional full conditional distributions, with no obvious structure to admit sampling via specialized algorithms. We therefore rely on HMC (Neal, 2011), a state-of-the-art general purpose sampler. HMC only requires evaluations of the log-density and its gradient, yet is capable of sampling efficiently from complex high-dimensional distributions (Gelman et al., 2013).

To introduce the main ideas behind HMC, we denote the distribution of interest by $p(\theta) = p(R, D | X, F)$. In order to sample from $\theta = (R, D)$, HMC introduces an auxiliary momentum variable $\phi \sim \mathcal{N}(0, I)$ and samples from the product density $p(\theta, \phi) = p(\theta)p(\phi)$. HMC explores the joint space
by approximating Hamiltonian dynamics that evolve according to the differential equation:

\[
\frac{d\theta}{dt} = \phi, \quad \frac{d\phi}{dt} = \nabla \log p(\theta).
\]

More precisely, each HMC iteration proceeds as follows. We first draw a new value of \( \phi \) from its marginal distribution. We then approximate the evolution in (3.21) from time \( t = 0 \) to \( t = \tau \) by applying \( L = \lceil \tau/\epsilon \rceil \) steps of the leapfrog update with stepsize \( \epsilon \):

\[
\phi \leftarrow \phi + \frac{\epsilon}{2} \nabla_\theta \log p(\theta), \quad \theta \leftarrow \theta + \epsilon \phi, \quad \phi \leftarrow \phi + \frac{\epsilon}{2} \nabla_\theta \log p(\theta).
\]

The end point of the approximated dynamics constitutes a valid Metropolis proposal (Metropolis et al., 1953) that is accepted or rejected according to the standard acceptance probability formula.

By virtue of the properties of Hamiltonian dynamics, the HMC proposals generated above can be far away from the current state yet be accepted with high probability. Good performance of HMC depends critically on well-calibrated choices of \( L \) and \( \epsilon \). We automate these choices via the stochastic optimization approach of Andrieu and Thoms (2008) and the No-U-Turn algorithm of Hoffman and Gelman (2014) that have been shown to achieve performance competitive with manually optimized HMC. Because HMC applies most conveniently to a distribution without parameter constraints, we map \( \mathbb{R} \) and \( \mathbb{D} \) to an unconstrained space using standard transformations (Stan Development Team, 2016).

4. Application.

4.1. HIV immune escape. As a rapidly evolving RNA virus, HIV-1 has established extensive genetic diversity that researchers classify into different major groups and, for HIV-1 group M, into different subtypes (Hemelaar, 2012). Such diversity implies that phenotypic traits can vary remarkably among strains circulating in different patients. Differences in viral virulence and their determinants, together with host factors, may explain the large variability in disease progression rates among patients. On the host side, human leukocyte antigen (HLA) class I alleles are important determinants of immune control that are known to be associated with differential HIV disease outcome, with particular HLA alleles offering considerable protective effect (Goulder and Walker, 2012). An interesting phenomenon is that HIV-1 can evolve to escape the HLA-mediated immune response, but the responsible escape mutations may compromise fitness and hence reduce viral...
virulence (Nomura et al., 2013; Payne et al., 2014). Identifying these mutations and their effect on virulence while controlling for the evolutionary relationships among the viruses that spread in populations with heterogeneous HLA backgrounds represents a particular challenge. Here, we address this by estimating the posterior distribution of across-trait correlation while controlling for the unknown viral evolutionary history.

We analyze a set of HIV-1 sequences and associated traits that Payne et al. (2014) collected from patients in Botswana and South Africa between 2003 and 2010. Both Botswana and South Africa are severely affected by the subtype C variant of HIV-1 group M. The data set encompasses 535 \textit{gag} gene sequences for HIV-1 subtype C with known sampling dates and three continuous traits including replicative capacity (RC), viral load (VL), and cluster of differentiation 4 (CD4) cell count. An increasing VL and a decreasing CD4 count in the asymptomatic stage characterize a typical HIV infection; RC is a viral fitness measure obtained by an assay that, in this case, assesses the growth rate of recombinant viruses containing the patient-specific \textit{gag-protease} gene relative to a control virus (Payne et al., 2014).

We consider the presence/absence of candidate HLA-associated escape mutations at 20 different amino acid positions in the \textit{gag} protein, plus another binary trait for the country of sampling (Botswana or South Africa). In cases where ambiguous nucleotide states in a codon prevent the determination of presence/absence of escape mutations, we encode binary trait states as unobserved (ranging from 0.2% to 21% across taxa) and set them as unbounded dimensions in the truncated normal distribution sampled by BPS.

We revisit the original study questions in Payne et al. (2014) concerning the extent to which HLA-driven HIV adaptation impacts virulence in both populations. Differences in HIV adaptation and virulence may arise from the fact the HIV epidemic in Botswana precedes that in South Africa, leaving more time for the virus to adapt to protective HLA alleles. Our approach employing a Bayesian inference framework based on the phylogenetic multivariate probit model, is substantially different from Payne et al. (2014) as they did not control for the shared evolutionary history between samples.

4.1.1. Correlation among traits. The heat map in Figure 3 depicts significant across-trait correlation determined by a 90% highest posterior density (HPD) interval that does not contain zero. We mainly focus on the last 4 rows that relate to questions addressed by Payne et al. (2014), e.g. difference in HLA escape mutations between the two countries and correlation between escape mutations and infection traits (VL and CD4 count) as well as replicative capacity. We identify one escape mutation I147X being signif-
Fig 3: Significant across-trait correlation with < 10% posterior tail probability and their posterior mean estimates (in color). HIV \textit{gag} mutations are named by the wild type amino acid state, the amino acid site number according to the standard reference genome (HXB2), and the amino acid ‘escape’ state that is any other amino acid or a deletion (‘X’) in almost all cases. Country = sample region: 1 = South Africa, -1 = Botswana; RC = replicative capacity; VL = viral load; CD4 = CD4 cell count.

icantly more prevalent in Botswana as indicated by its negative correlation with South Africa. Located at the amino-terminal position of an HLA-B57-restricted epitope (‘ISW9’), variation at \textit{gag} residue 147 is known to be associated with expression of B57 (Draenert \textit{et al.}, 2004). We also find a significantly more prevalent escape mutation in South Africa (T190X), but its elevated frequency (4.2% relative to 3.4% for Botswana) is on a much smaller scale as compared to the frequency differences for I147X (41.4% for Botswana vs. 25.2% for South Africa). Both escape mutations are not significantly correlated with RC. It is worth noting that three of the four escape mutations that correlate negatively with RC (I61X, Q182X and T242X)
have a higher frequency in Botswana and may therefore have contributed to the lower RC found in Botswana by Payne et al. (2014). Interestingly, the negative effect on RC we estimate for two mutations finds clear confirmation in experimental testing: in vitro experiments provide evidence for a reduction in RC by T242X (Martinez-Picado et al., 2006; Song et al., 2012) and T186X is also found to greatly impair RC (Huang et al., 2011).

Our analysis recovers the expected inverse correlation between CD4 count and RC or VL, as well as the positive correlation between RC and VL (Prince et al., 2012), confirming that more virulent viruses result in faster disease progression.

Also, South Africa is associated with higher VL and lower CD4, suggesting that the South African cohort may comprise individuals with more advanced disease, even though the two cohorts are closely matched in age (Payne et al., 2014). This is somewhat at odds with the original study that also finds a higher VL for South Africa, but at the same time a higher CD4 count for patients from this country. Such differences are likely to arise from controlling or not for the phylogeny.

The remaining significant correlation between escape mutations (row 1 to 19 in Figure 3) can be considered as epistatic interactions, some of which are strongly positive. For example, we find a strong positive correlation between T186X and T190X. The former represents an escape mutation for HLA-B*81-mediated immune responses and has been reported to be strongly correlated with reduced virus replication (Huang et al., 2011; Wright et al., 2010), as also reflected in the negative correlation between this mutation and RC. In fact, Wright et al. (2012) show T186X requires T190I (or Q182X, also positively correlated with T186X, Figure 3) to partly compensate for this impaired replication capacity. The other strong positive correlation between A163X and S165X has also been found to be a case of a compensatory mutation, with S165N partially compensating for the reduced viral replicative capacity of A163G (Crawford et al., 2007). The same holds true for the positive correlation between A146X and I147X, with I147L partially compensating the fitness cost associated with the escape mutation A146P (Troyer et al., 2009).

4.1.2. Tree inference. Figure 4 reports the maximum clade credibility tree from the posterior sample. The tree maximizes the sum of posterior clade probabilities. The posterior mean tree height is roughly 30 years; so with the most recent samples from 2010, we date the common ancestor of all viruses back to around 1980, consistent with the beginning of this epidemic.
Fig 4: The maximum clade credibility tree with branches colored by the posterior mean of the latent parameter corresponding to mutation T186X. Outer circle shows log(RC) in gray scale.

4.2. Efficiency comparison. To compare efficiency of BPS with the multiple-try rejection sampling in Cybis et al. (2015), we run both samplers on the whole data set and a subset of it with the number of traits $P = 8$ including the three continuous traits. We fix the tree and across-trait covariance at the same values from preliminary runs. Because the rejection sampling leaves some dimensions very poorly explored, effective sample size (ESS) estimates are inaccurate. So we choose expected squared jumping distance (ESJD, Pasarica and Gelman (2010)) per unit-time as the efficiency criterion,

$$
(4.1) \quad \text{ESJD}_{ij} = \frac{1}{K-B} \sum_{k=B}^{K} (x_{ij}^{(k)} - x_{ij}^{(k-1)})^2, \quad i = 1, \ldots, N, j = 1, \ldots P,
$$

where $B$ is a sufficiently long burnin given MCMC chain length $K$ and $x_{ij}^{(k)}$ is the sample value of $x_{ij}$ at iteration $k$. BPS outperforms rejection sampling to a greater extent as $P$ increases. For $P = 24$, BPS yields a $387 \times$ increase in terms of the minimum ESJD and a $21 \times$ increase for the median ESJD (Table 1). This order-of-magnitude improvement is more clear in Figure 5. Because rejection sampling only updates one taxon per iteration, some latent parameters rarely change their values and remain far from convergence (Figure 6).
As a result, the minimum ESJD of multiple-try rejection sampling is much lower than BPS which jointly updates all latent dimensions.

### Table 1

Efficiency comparison between the bouncy particle sampler (BPS) and multiple-try rejection sampling in terms of minimum and median of expected squared jumping distance (ESJD) per hour run-time. ESJD values and speed-up folds report medians across 10 independent chain simulations.

| ESJD/hr | P = 8 | P = 24 |
|---------|-------|--------|
| BPS     | 4593  | 50372  |
| Rejection | 449  | 6657  |
| Speed-up | 10×   | 7.6×   |

Fig 5: A representative histogram of all univariate ESJD measurements across latent parameters, sampled by BPS or rejection sampling in one hour run-time. Arrows and dashed lines denote the minimum and median ESJD ($N = 535, P = 24$).

5. **Discussion.** We present an efficient Bayesian inference framework to learn the correlation among mixed-type traits across a large number of taxa, while jointly inferring the phylogenetic tree through sequence data. Our approach significantly improves upon Cybis et al. (2015) in both modeling and inference. Better modeling comes from the decomposition of across-trait covariance matrix $\Omega = DRD$ that keeps the generalized probit model identifiable and allows a jointly uniform LKJ prior on $R$. Compared to the
Fig 6: Trace plot of the latent parameter with the least univariate ESJD by rejection sampling (bottom) and trace plot of the same latent parameter sampled by BPS (top) for a 15 minute run-time. BPS and rejection sampling run $4.3 \times 10^3$ and $7.8 \times 10^4$ iterations, respectively. The y-axis is in log scale ($N = 535, P = 24$).

C) Convenient but restrictive Wishart prior that causes mixing problems for sampling $\Omega^{-1}$ and $\mathbf{X}$, this decomposition facilitates correlation inference among continuous traits and latent parameters (Appendix Figure A.2). Our main contribution lies in an efficient inference framework, specifically, an optimized BPS to sample latent parameters from a high-dimensional truncated normal distribution. In contrast to the “one-taxon-at-a-time” design in Cybis et al. (2015), BPS updates all dimensions jointly therefore reducing auto-correlation among MCMC samples. As the most expensive steps involved are matrix-vector multiplications by the precision matrix $\Phi = \Sigma^{-1}$, BPS becomes a good choice when $\Phi$ possesses special structures that facilitate this multiplication. One obvious example arises with sparse precision matrices in spatial statistics (Datta et al., 2016). However, in our case, the tree precision matrix is not sparse and getting it by matrix inversion is notoriously $O(N^3)$. Thanks to the insight in Lemma 1, we circumvent this obstacle by utilizing a dynamic programming strategy and obtain the desired matrix-vector products in $O(NP^2)$. BPS also enjoys an advantage especially important for mixed-type traits. That is, we can simply “mask out” the fixed continuous traits when sampling latent parameters for binary traits. Whereas the rejection sampling in Cybis et al. (2015) has to calculate the conditional distribution of latent dimensions given continuous traits at each tip. This cost-free “masking” technique to condition on a subset of dimensions exploits properties of normal distributions and can be shared with other dynamics-based sampler, like HMC. Taking all of these points
together, the optimized BPS provides a huge gain in efficiency.

Our application provides important information on the complex association between HLA-driven HIV \textit{gag} mutations and virulence that was previously assessed by experimental and epidemiological studies. To our best knowledge, this is the first study to examine essential HIV virus-host interactions while explicitly modeling the phylogenetic tree. Our setup is also different from the original study (Payne et al., 2014) in that we attempt to identify correlation between individual epitope escape mutations, virulence, and country of sampling, instead of considering all mutations together or grouping them with particular HLA types (e.g. HLA-B*57/58:01). While the latter may increase power to detect population-level differences in escape mutation frequencies, our approach allows us to pinpoint particular mutations contributing to virulence. Good consistency between the mutations that we associate with reduced RC and literature reports on virological assays suggests that our approach may complement or help in prioritizing experimental testing, and therefore further assist in the battle against HIV-1. Our method contributes to a general framework to assess correlation among mixed-type traits in virology, but also more broadly in evolutionary biology.

One limitation lies in the arbitrary threshold we have picked to determine significance. Specifically, we view correlations with 90% HPD intervals not covering zero as significant. Obviously, the higher the threshold, the fewer significant correlations we would detect. We can adjust the decision threshold via concerns about resource availability for follow-up experimental studies. One may, however, favor a systematic solution, especially with large \( P \) and when only a small portion of the observed traits are truly involved in the mechanism, in which case it is vital to control for false positive signals. We can assume a shrinkage-based prior on \( \mathbf{R} \) that shrinks individual elements towards zero. Ideas like the graphical lasso prior (Wang et al., 2012) and factor models with shrinkage prior on the loading elements (Bhattacharya and Dunson, 2011) are potential directions to explore.

Lastly, as understanding the relationship among mixed-type variables is a common question in different fields, our method suits a large class of problems beyond evolutionary biology. The optimized BPS sampler through dynamic programming serves as an efficient inference tool for any multilevel (hierarchical) model (Gelman, 2006) with an additive covariance structure on a directed acyclic graph (Figure 1). The tree variance matrix \( \mathbf{\Upsilon} \) that we use to describe the covariation of shared evolutionary descent also arises from other kinds of relationships. For example, additive covariance captures pedigree-based or genomic relationship matrices in animal breeding (Vitezica, Varona and Legarra, 2013; Mrode, 2014) and distance matrices decided
by geographical locations in infectious disease research (Barbu et al., 2013). Intriguingly, piecing together the products \( \Upsilon^{-1} e_i \) for \( i = 1, \ldots, N \) returns \( \Upsilon^{-1} \) directly in just \( \mathcal{O}(N^2) \) through our dynamic programming. While this seems likely a well-known result, we have failed to find precedence in the literature. Finally, the phylogenetic probit model can be generalized to categorical and ordinal data, which will only add to its broad applicability.

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APPENDIX A: BPS DETAILS

A.1. BPS modification for conditional truncated MVNs. Here we consider modifying the BPS to incorporate fixed dimensions that are the observed, continuous traits in our mixed-type model. We partition \( \mathbf{x} = (\mathbf{x}_b, \mathbf{x}_c) \) by latent and observed dimensions, with the aim to generate samples from the conditional distribution \( p(\mathbf{x}_b | \mathbf{x}_c) \). To make progress, we parameterize \( p(\mathbf{x}_b | \mathbf{x}_c) \) in terms of \( p(\mathbf{x}) \) with partitioned mean \( \mathbf{m} = (\mathbf{m}_b, \mathbf{m}_c) \) and precision matrix

\[
\Sigma^{-1} = \begin{bmatrix}
\Phi_{bb} & \Phi_{bc} \\
\Phi_{cb} & \Phi_{cc}
\end{bmatrix}.
\]

With a similarly partitioned velocity \( \mathbf{v} = (\mathbf{v}_b, \mathbf{v}_c) \), the distribution \( p(\mathbf{x}_b | \mathbf{x}_c) \) carries potential energy

\[
U_{b|c}(\mathbf{x}_b + t\mathbf{v}_b) = \frac{t^2}{2} \mathbf{v}_b^\top \Phi_{bb} \mathbf{v}_b + t \mathbf{v}_b^\top \Phi_{bb} (\mathbf{x}_b - \mathbf{m}_b|c) + C,
\]

where constant \( C \) does not depend on \( t \). The conditional mean \( \mathbf{m}_{b|c} = \mathbf{m}_b - \Phi_{bb}^{-1} \Phi_{bc} (\mathbf{x}_c - \mathbf{m}_c) \), so

\[
U_{b|c}(\mathbf{x}_b + t\mathbf{v}_b) = \frac{t^2}{2} \mathbf{v}_b^\top \Phi_{bb} \mathbf{v}_b + t \mathbf{v}_b^\top \left[ \Phi_{bb} (\mathbf{x}_b - \mathbf{m}_b) + \Phi_{bc} (\mathbf{x}_c - \mathbf{m}_c) \right] + C.
\]
This expression is equivalent to masking out the dimensions of \( \mathbf{v} \) in (3.9) that corresponds to \( \mathbf{x}_c \) via the vector \( \tilde{\mathbf{v}} = (\mathbf{v}_b, 0) \). To be explicit, we rewrite (A.3) as

\[
U_{b|c}(\mathbf{x}_b + t\mathbf{v}_b) = \frac{t^2}{2} \tilde{\mathbf{v}}^T \Phi \tilde{\mathbf{v}} + t\tilde{\mathbf{v}}^T \Phi (\mathbf{x} - \mathbf{m}) + C.
\]

Therefore, adding this masking operation for \( \mathbf{v}, \varphi_{\mathbf{x}}, \varphi_{\mathbf{v}} \) in Lines 1, 2, 5, 7 in Algorithm 1 allows sampling from the conditional truncated MVN \( p(\mathbf{x}_b | \mathbf{x}_c) \) without any additional cost.

**A.2. Tuning** \( t_{\text{total}} \) **for BPS.** The total simulation time \( t_{\text{total}} \) for the Markov process is a tuning parameter in Algorithm 1. If \( t_{\text{total}} \) is too small, the particle does not travel far enough from the initial position, leading to high auto-correlation among MCMC samples. One would choose a \( t_{\text{total}} \) large enough that \( \mathbf{x}(t_{\text{total}}) \) is effectively independent of \( \mathbf{x}(0) \) but no larger as further simulation is wasteful. We calibrate \( t_{\text{total}} \) based on the following observations. For all \( t > 0 \), the BPS trajectory has velocity \( \mathbf{v}(t) \sim \mathcal{N}(0, \mathbf{I}) \) (Bouchard-Côté, Vollmer and Doucet, 2018) and hence \( \langle \mathbf{v}(t), \mathbf{u} \rangle \sim \mathcal{N}(0, 1) \) for any unit vector \( \mathbf{u} \). This means, on average, the particle moves one unit of distance during one unit of time, regardless of its direction. On the other hand, the diameter of a MVN’s high density region is proportional to \( \sqrt{\lambda_{\text{max}}} \), where \( \lambda_{\text{max}} \) denotes the largest eigenvalue of the covariance matrix \( \Sigma \). Therefore, aside from the truncation, we expect the BPS trajectory to require \( t_{\text{total}} \propto \sqrt{\lambda_{\text{max}}} \) to fully explore a MVN distribution. We find that BPS performance is not overly sensitive to a specific choice of \( t_{\text{total}} \). After preliminary runs (Table A.1), we choose \( t_{\text{total}} = 0.01\sqrt{\lambda_{\text{max}}} \) for our \( N = 535, P = 24 \) application, as it yields the maximum median effective sample size (ESS) per hour run-time.

| \( t_{\text{total}} \) | \( 5 \times 10^{-3} \sqrt{\lambda_{\text{max}}} \) | \( 10^{-2} \sqrt{\lambda_{\text{max}}} \) | \( 10^{-1} \sqrt{\lambda_{\text{max}}} \) |
|----------------------|-----------------------------|-----------------------------|-----------------------------|
| min                  | 72                          | 68                          | 27                          |
| 5%                   | 227                         | 428                         | 357                         |
| 50%                  | 515                         | 1050                        | 885                         |
APPENDIX B: IDENTIFIABILITY ISSUE WITH A WISHART PRIOR

We examine differences between assuming an LKJ + log normal priors on \( \text{DRD} \) and a Wishart prior on \( \Omega^{-1} \). For the Wishart case, we set the degree of freedom equal to \( P + 1 \), so each correlation marginally follows a uniform distribution on \([-1, 1]\) (Gelman et al., 2013), and the Normal-Wishart conjugacy yields easy Gibbs sampling for \( \Omega^{-1} \). Without constraining the marginal variance of any latent dimension, the Wishart prior leaves the model not parameter-identifiable and causes mixing problems, even with a small \( P = 8 \) (Figure A.2).

![Trace plot of a representative \( \Omega^{-1} \) element (top) in log scale and the latent parameter with the least ESS when assuming a Wishart prior on \( \Omega^{-1} \) (bottom).](image)

Fig A.2: Trace plot of a representative \( \Omega^{-1} \) element (top) in log scale and the latent parameter with the least ESS when assuming a Wishart prior on \( \Omega^{-1} \) (bottom).
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