Hamiltonian zigzag accelerates large-scale inference for conditional dependencies between complex biological traits

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Abstract

Inferring dependencies between complex biological traits while accounting for evolutionary relationships between specimens is of great scientific interest yet remains infeasible when trait and specimen counts grow large. The phylogenetic multivariate probit model uses a latent variable framework to accommodate binary and continuous traits, but integrating many latent variables requires many computationally expensive draws from a high-dimensional truncated normal. The state-of-the-art approach, which combines the bouncy particle sampler (BPS) with dynamically programmed gradient evaluations, breaks down as the number of specimens grows and fails to reliably characterize conditional dependencies between traits. We develop an inference scheme that combines the recent Zigzag Hamiltonian Monte Carlo (Zigzag-HMC) with linear-time gradient evaluations and joint updates for highly correlated latent variables and correlation matrix elements. In an application exploring HIV-1 evolution from 535 viruses, the inference requires joint sampling from an 11,235-dimensional truncated normal and a 24-dimensional covariance matrix. Our method yields a 5-fold speedup compared to BPS and makes it possible to learn partial correlations between candidate viral mutations and virulence. Computational speedups now allow us to tackle larger problems: we study the evolution of influenza H1N1 glycosylations on around 900 viruses. For broader applicability, we extend the phylogenetic probit model to incorporate categorical traits, and demonstrate its use to study Aquilegia flower and pollinator co-evolution.

Keywords: Bayesian phylogenetics, Probit models, Truncated normal, Zigzag Hamiltonian Monte Carlo, Viral evolution
1 Introduction

An essential goal in evolutionary biology is to understand the associations between traits observed within biological samples, or taxa, ranging from plants and animals to microorganisms and pathogens such as human immunodeficiency virus (HIV) and influenza. This task is difficult because taxa are implicitly correlated through their shared evolutionary history often described with a reconstructed phylogenetic tree. Here, tree tips correspond to the taxa themselves, and internal nodes are their unobserved ancestors. Inferring across-trait covariation requires a highly structured model that can explicitly describe the tree structure and adjust for across-taxon covariation. Phylogenetic models do exactly this but are computationally challenging because one must integrate out unobserved ancestor traits while accounting for uncertainties arising from tree estimation. The computational burden increases when taxon and trait counts grow large and becomes worse when traits include continuous and discrete quantities. Zhang et al. (2021) show that their phylogenetic multivariate probit model provides a promising tool to learn correlations among complex traits at scale when combined with an efficient inference scheme that achieves order-of-magnitudes efficiency gains over the previous best approach (Cybis et al., 2015). Zhang et al. (2021) demonstrate their method on a data set with $N = 535$ HIV viruses and $P = 24$ traits that requires sampling from a truncated normal distribution with more than 11,000 dimensions. In this work, we overcome several shortcomings of Zhang et al. (2021) to significantly advance performance and solve more challenging problems including the (a) inference of across-trait partial correlations that present clues for potential causal pathways and (b) integration of complex
traits with categorical outcomes.

To jointly model complex traits, the phylogenetic probit model assumes discrete traits arise from continuously valued latent variables that follow a Brownian diffusion along the tree (Felsenstein, 1985; Cybis et al., 2015; Zhang et al., 2021). Assuming latent processes is a common strategy for modeling complex data and it finds uses across various fields (Fedorov et al., 2012; Schliep and Hoeting, 2013; Irvine et al., 2016; Pourmohamad et al., 2016; Clark et al., 2017). For \( N \) taxa and \( P \) continuous or binary traits, Bayesian inference for the phylogenetic probit model involves repeatedly sampling latent variables from their conditional posterior, an \((N \times P)\)-dimensional truncated normal distribution. For this task, Zhang et al. (2021) develop a bouncy particle sampler (BPS) (Bouchard-Côté et al., 2018) augmented with an efficient dynamic programming approach that speeds up the most expensive step in the BPS implementation. Two remaining limitations of BPS motivate this present work. First, BPS can have a near-reducible behavior without frequent velocity refreshment, but such refreshment significantly reduces efficiency and leads to “random-walk” behavior (Bouchard-Côté et al., 2018; Fearnhead et al., 2018; Neal, 2011; Andrieu and Livingstone, 2019). Second, in the phylogenetic probit model, the latent variables \( \mathbf{X} \) and the trait correlation \( \mathbf{C} \) are themselves highly correlated by model assumption, so a joint update would be more efficient. Because BPS does not allow such joint sampling, Zhang et al. (2021) use a separate Hamiltonian Monte Carlo sampler (HMC) (Neal, 2011) to infer \( \mathbf{C} \) and update the two sets of parameters alternately within a random-scan Gibbs scheme (Liu et al., 1995).

Our solution to these issues leverages a state-of-the-art Markov chain
Monte Carlo (MCMC) method called Zigzag-HMC (Nishimura et al., 2020) that overcomes the two limitations of BPS. First, Zigzag-HMC better explores the parameter spaces of high-dimensional truncated normals than BPS does (Section 3.1). Second, Zigzag-HMC enables a joint update of \( \mathbf{X} \) and \( \mathbf{C} \) through differential operator splitting (Strang, 1968; Nishimura et al., 2020), generalizing the previously proposed split HMC framework based on Hamiltonian splitting (Neal, 2011; Shahbaba et al., 2014). Zigzag-HMC can take advantage of the same \( \mathcal{O}(N) \) gradient evaluation strategy advanced by Zhang et al. (2021) and greatly improves the mixing of elements in \( \mathbf{C} \). The new inference scheme thus provides reliable estimates of across-trait partial correlations that describe the conditional dependence between any two traits, free of confounding from other traits in the model. As seen in our applications, these conditional dependencies provide insights into potential causal pathways driven by real biological processes.

We apply our methodology to three real-world examples. First, we re-evaluate the HIV evolution application in Zhang et al. (2021) and identify HIV-1 \( gag \) immune-escape mutations linked with virulence through strong conditional dependence relationships. Our findings closely match with the experimental literature and indicate a general pattern in the immune escape mechanism of HIV. Second, we examine the influenza H1N1 glycosylation pattern across different hosts and detect strong conditional dependencies between glycosylation sites closely related to host switching. Finally, we investigate how floral traits of \textit{Aquilegia} flower attract different pollinators, for which we generalize the phylogenetic probit model to accommodate a categorical pollinator trait.
2 Methods

2.1 Complex trait evolution

We describe biological trait evolution with the phylogenetic multivariate probit model following Zhang et al. (2021) and extend it to categorical traits as in Cybis et al. (2015). Consider \( N \) taxa on a phylogenetic tree \( \mathcal{F} = (\mathcal{V}, \mathbf{t}) \) that is a directed, bifurcating acyclic graph. We either know the tree \textit{a priori} or infer it from a molecular sequence alignment \( \mathbf{S} \) (Suchard et al., 2018). The node set \( \mathcal{V} \) of size \( 2N - 1 \) contains \( N \) tip nodes, \( N - 2 \) internal nodes and one root node. The branch lengths \( \mathbf{t} = (t_1, \ldots, t_{2N-2}) \) denote the child-parent distance in real time. We observe \( P \) traits of complex for each taxon. The trait data \( \mathbf{Y} = \{y_{ij}\} = (\mathbf{Y}^{\text{cont}}, \mathbf{Y}^{\text{disc}}) \) partition as \( \mathbf{Y}^{\text{cont}} \), an \( N \times P_{\text{cont}} \) matrix of continuous traits and \( \mathbf{Y}^{\text{disc}} \), an \( N \times P_{\text{disc}} \) matrix of discrete ones. For each node \( i \) in \( \mathcal{F} \), we assume a \( d \)-dimensional latent variable \( \mathbf{X}_i \in \mathbb{R}^d \), \( i = 1, \ldots, 2N - 1 \), where \( d = P_{\text{cont}} + \sum_{j=1}^{P_{\text{disc}}} (m_j - 1) \) and \( m_j \) is the number of classes for the \( j \)th discrete trait. To relate latent variables to observed discrete traits, we assume a threshold model for binary traits and a choice model for traits with more than two classes. For a categorical trait \( y_{ij} \), the possible classes are \( \{c_1, \ldots, c_{m_j}\} \) with the reference class being \( c_1 \). Multiple latent variables \( x_{i,j'}, \ldots, x_{i,j'+m_j-2} \) decide the value of \( y_{ij} \). We summarize the
mapping from $\mathbf{X}$ to $\mathbf{Y}$ as

$$
\begin{align*}
y_{ij} = \\
\begin{cases}
x_{ij}, & \text{if } y_{ij} \text{ is continuous,} \\
\text{sign}(x_{ij}), & \text{if } y_{ij} \text{ is binary,} \\
c_1, & \text{if } y_{ij} \text{ is categorical and } M = 0, \\
c_m, & \text{if } y_{ij} \text{ is categorical, } m > 1, \text{ and } M = x_{i,j'+m-2} > 0,
\end{cases}
\end{align*}
$$

(1)

where $M = \max(x_{i,j'}, \ldots, x_{i,j'+m-2})$ and $\text{sign}(x_{ij})$ returns the value 1 on positive values and -1 on negative values. This data augmentation strategy is a common choice to model categorical data (Albert and Chib, 1993).

The latent variables follow a multivariate Brownian diffusion process along $\mathcal{F}$ such that $\mathbf{X}_i$ distributes as a multivariate normal (MVN)

$$
\mathbf{X}_i \sim \mathcal{N}\left(\mathbf{X}_{\text{pa}(i)}, t_i \Omega\right), i = 1, \ldots, 2N - 2,
$$

(2)

where $\mathbf{X}_{\text{pa}(i)}$ is the parent node value and the $d \times d$ covariance matrix $\Omega$ describes the across-trait association. Assuming a conjugate root prior $\mathbf{X}_{2N-1} \sim \mathcal{N}\left(\mathbf{\mu}_0, \omega^{-1} \Omega\right)$ with prior mean $\mathbf{\mu}_0$ and prior sample size $\omega$, we can analytically integrate out latent variables on all internal nodes. Marginally, then, the $N \times d$ tip latent variables $\mathbf{X}$ have the matrix normal (MTN) distribution

$$
\mathbf{X} \sim \text{MTN}_{Nd}(\mathbf{M}, \mathbf{Y}, \Omega),
$$

(3)

where $\mathbf{M} = (\mathbf{\mu}_0, \ldots, \mathbf{\mu}_0)^T$ is an $N \times d$ mean matrix and the across-taxa covariance matrix $\mathbf{Y}$ equals $\mathbf{V}(\mathcal{F}) + \omega^{-1} \mathbf{J}$ (Pybus et al., 2012). The tree $\mathcal{F}$ determines the diffusion matrix $\mathbf{V}(\mathcal{F})$ and $\omega^{-1} \mathbf{J}$ comes from the integrated-
out tree root prior, where $J$ is an all-one $N \times N$ matrix. The augmented likelihood of $X$ and $Y$ factorizes as

$$p(Y, X | \Upsilon, \Omega, \mu_0, \omega) = p(Y | X)p(X | \Upsilon, \Omega, \mu_0, \omega), \quad (4)$$

where $p(Y | X) = 1$ if $X$ are consistent with $Y$ according to Equation (1) and 0 otherwise. To ensure that the model is parameter-identifiable and also allow a non-informative prior on trait correlations, we decompose $\Omega$ as $\text{DCD}$ such that $C$ is the $d \times d$ correlation matrix and $D$ is a diagonal matrix with marginal standard deviations (Zhang et al., 2021).

### 2.2 A novel inference scheme

We sample from the joint posterior to learn the across-trait correlation $C$

$$p(C, D, X, \mathcal{F} | Y, S) \propto p(Y | X) \times p(X | C, D, \mathcal{F}) \times p(C, D) \times p(S | \mathcal{F}) \times p(\mathcal{F}), \quad (5)$$

where we drop the dependence on hyper-parameters $(\Upsilon, \mu_0, \omega)$ to ease notation. Zhang et al. (2021) use a random-scan Gibbs (Liu et al., 1995) scheme to alternately update $X$, $\{C, D\}$ and $\mathcal{F}$ from their full conditionals (Suchard et al., 2018). They sample $X$ from an $Nd$-dimensional truncated normal distribution with BPS and deploy the standard HMC based on Gaussian momentum (Hoffman and Gelman, 2014) to update $\{C, D\}$. Instead, we simulate the joint Hamiltonian dynamics on $\{X, C, D\}$ by combining novel Hamiltonian zigzag dynamics on $X$ (Nishimura et al., 2021) and traditional Hamiltonian dynamics on $\{C, D\}$. This strategy enables an efficient joint
update of the two highly-correlated sets of parameters. We first describe how Zigzag-HMC samples $X$ from a truncated normal and then detail the joint update of $\{X, C, D\}$.

### 2.2.1 Zigzag-HMC for truncated multivariate normals

We outline the main ideas behind HMC (Neal, 2011) before describing Zigzag-HMC as a version of HMC based on Hamiltonian zigzag dynamics (Nishimura et al., 2020, 2021). In order to sample a $d$-dimensional parameter $x = (x_1, \ldots, x_d)$ from the target distribution $\pi(x)$, HMC introduces an auxiliary momentum variable $p = (p_1, \ldots, p_d) \in \mathbb{R}^d$ and samples from the product density $\pi(x, p) = \pi(x)\pi(p)$ by numerically discretizing the Hamiltonian dynamics

$$\frac{dx}{dt} = \nabla K(p), \quad \frac{dp}{dt} = -\nabla U(x),$$

where $U(x) = -\log \pi(x)$ and $K(p) = -\log \pi(p)$ are the potential and kinetic energy. In each HMC iteration, we first draw $p$ from its marginal distribution $\pi(p) \sim \mathcal{N}(0, I)$, a standard Gaussian and then approximate (6) from time $t = 0$ to $t = \tau$ by $L = \lfloor \tau/\epsilon \rfloor$ steps of the leapfrog update with stepsize $\epsilon$ (Leimkuhler and Reich, 2004):

$$p \leftarrow p + \frac{\epsilon}{2} \nabla_x \log \pi(x), \quad x \leftarrow x + \epsilon p, \quad p \leftarrow p + \frac{\epsilon}{2} \nabla_x \log \pi(x).$$

The end state is a valid Metropolis proposal that one accepts or rejects according to the standard acceptance probability formula (Metropolis et al., 1953; Hastings, 1970).

Zigzag-HMC differs from standard HMC insofar as it posits a Laplace mo-
mentum $\pi(p) \propto \prod_i \exp(-|p_i|), i = 1, \ldots, d$. The Hamiltonian differential equations now become

$$\frac{dx}{dt} = \text{sign}(p), \quad \frac{dp}{dt} = -\nabla U(x),$$

and the velocity $v := \frac{dx}{dt} \in \{\pm 1\}^d$ depends only on the sign of $p$ and thus remains constant until one of $p_i$'s undergoes a sign change (an "event"). To understand how the Hamiltonian zigzag dynamics (8) evolve over time, one must investigate when such events happen. Before moving to the truncated MVN, we first review the event time calculation for a general $\pi(x)$ following Nishimura et al. (2021). Let $\tau^{(k)}$ be the $k$th event time and $(x(\tau^{(0)}), v(\tau^{(0)}), p(\tau^{(0)}))$ is the initial state at time $\tau^{(0)}$. Between $\tau^{(k)}$ and $\tau^{(k+1)}$, $x$ follows a piecewise linear path and the dynamics evolve as

$$x(\tau^{(k)} + t) = x(\tau^{(k)}) + tv(\tau^{(k)}), \quad v(\tau^{(k)} + t) = v(\tau^{(k)}), \quad t \in \left[0, \tau^{(k+1)} - \tau^{(k)}\right],$$

and

$$p_i(\tau^{(k)} + t) = p_i(\tau^{(k)}) - \int_0^t \partial_i U \left[x(\tau^{(k)}) + sv(\tau^{(k)})\right] ds \quad \text{for } i = 1, \ldots, d.$$

Therefore we can derive the $(k+1)$th event time

$$\tau^{(k+1)} = \tau^{(k)} + \min_i t_i, \quad t_i = \min_{t>0} \left\{p_i(\tau^{(k)}) = \int_0^t \partial_i U \left[x(\tau^{(k)}) + sv(\tau^{(k)})\right] ds \right\},$$

and the dimension causing this event is $i^* = \arg\min_i t_i$. At the moment of
\( \tau^{(k+1)} \), the \( i^* \)th velocity component flips its sign

\[
v_{i^*}(\tau^{(k+1)}) = -v_{i^*}(\tau^{(k)}), \quad v_j(\tau^{(k+1)}) = v_j(\tau^{(k)}) \text{ for } j \neq i^*.
\]  

Then the dynamics continue for the next interval \( [\tau^{(k+1)}, \tau^{(k+2)}] \).

We now consider simulating the Hamiltonian zigzag dynamics for a \( d \)-dimensional truncated MVN defined as

\[
x \sim \mathcal{N}(\mu, \Sigma) \text{ subject to } x \in \{\text{map}(x) = y\},
\]

where \( y \in \mathbb{R}^P \) is the complex data, \( \text{map}(\cdot) \) is the mapping from latent variables \( x \) to \( y \) as in Equation (1), \( x \in \mathbb{R}^d \) and \( d \geq P \). In this setting, we have \( \nabla U(x) = \Sigma^{-1}x \) whenever \( x \in \{\text{map}(x) = y\} \). Importantly, this structure allows us to simulate the Hamiltonian zigzag dynamics exactly and efficiently (Nishimura et al., 2021). We handle the constraint \( \text{map}(x) = y \) with a technique from Neal (2011) where the constraint boundaries embody “hard walls” that the Hamiltonian zigzag dynamics “bounce” against upon impact. To distinguish different types of events, we define gradient events arising from solutions of Equation (11), binary events arising from hitting binary data boundaries and categorical events arising from hitting categorical data boundaries.

We first consider how to find the gradient event time. Starting from a state \( (x, v, p) \), by plugging in \( \nabla U(x) = \Sigma^{-1}x \) to Equation (11), we can calculate the gradient event time \( t_g \) by first solving \( d \) quadratic equations

\[
p = t\Sigma^{-1}(x - \mu) + \frac{t^2}{2}\Sigma^{-1}v,
\]  

\[ \tag{14} \]
and then taking the minimum among all positive roots of Equation (14). When $\pi(x)$ is a truncated MVN arising from the phylogenetic probit model, we exploit the efficient gradient evaluation strategy in Zhang et al. (2021) to obtain $\Sigma^{-1}(x - \mu)$ and $\Sigma^{-1}v$ without the notorious $O(d^3)$ cost to invert $\Sigma$.

Next, we focus on the binary and categorical events. We partition $x$ into three sets: $S_{\text{cont}} = \{ x_i : x_i \text{ is for continuous data} \}$, $S_{\text{bin}} = \{ x_i : x_i \text{ is for binary data} \}$, and $S_{\text{cat}} = \{ x_i : x_i \text{ is for categorical data} \}$. Since latent variables in $S_{\text{cont}}$ are fixed, we “mask” them out following Zhang et al. (2021). Starting from a state $(x, v, p)$, a binary event happens at time $t_b$ when the trajectory first reaches a binary boundary at dimension $i_b$

$$t_b = \left| \frac{x_{i_b}}{v_{i_b}} \right|, \quad i_b = \arg\min_{i \in I_{\text{bin}}} \left| \frac{x_i}{v_i} \right| \quad \text{for} \quad I_{\text{bin}} = \{ i : x_i v_i < 0 \text{ and } x_i \in S_{\text{bin}} \}.$$  

(15)

Here, we only need to check the dimensions satisfying $x_i v_i < 0$, i.e., those for which the trajectory is heading towards the boundary. At time $t_b$, the trajectory bounces against the binary boundary, and so the $i_b$th velocity and momentum element both undergo an instantaneous flip $v_{i_b} \leftarrow -v_{i_b}$, $p_{i_b} \leftarrow -p_{i_b}$, while other dimensions stay unchanged.

Finally, we turn to categorical events. Suppose that a categorical trait $y_j = c_m$ belongs to one of $n$ possible classes, and $x_1, x_2, \ldots, x_{n-1}$ the underlying latent variables. Equation (1) specifies the boundary constraints. If $m = 1$, the $n - 1$ latent variables must be all negative, which poses the same constraint as if they were for $n - 1$ binary traits, therefore we can solve the event time using Equation (15). If $m > 1$, we must check when and which two dimensions first violate the order constraint $x_{m-1} = \max(x_1, \ldots, x_{n-1}) > 0$. 

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With the dynamics starting from \((x, v, p)\), the categorical event time \(t^j_c\) is given by

\[
t^j_c = |(x_{m-1} - x_{ic})/(v_{m-1} - v_{ic})|, \quad i_c = \arg\min_{i \in I_{\text{cat}}} |(x_{m-1} - x_i)/(v_{m-1} - v_i)|, \\
\text{for } I_{\text{cat}} = \{i : v_{m-1} < v_i \text{ and } x_i \in S_{\text{cat}}\},
\]

(16)

when \(x_{ic}\) reaches \(x_{m-1}\) and violates the constraint. To identify \(i_c\) we only need to check dimensions with \(v_{m-1} < v_i\) where the distance \(x_{m-1} - x_i\) is decreasing. At \(t^j_c\), the two dimensions involved \((m-1 \text{ and } i_c)\) bounce against each other such that \(v_{m-1} \leftarrow -v_{m-1}, v_{ic} \leftarrow -v_{ic}, p_{m-1} \leftarrow -p_{m-1}, p_{ic} \leftarrow -p_{ic}\).

Note \(t^j_c\) is for a single \(y_j\) and we need to consider all categorical data to find the actual categorical event time \(t_c = \min_j t^j_c\).

We now present the dynamics simulation with all three event types included, starting from a state \((x, v, p)\) with \(x \in \{\text{map}(x) = y\}\):

1. Solve \(t_g, t_b, t_c\) using Equations (14), (15) and (16) respectively.

2. Determine the actual (first) event time \(t = \min\{t_g, t_b, t_c\}\) and update \(x\) and \(p\) as in Equations (9) and (10) for a duration of \(t\).

3. Make instantaneous velocity and momentum sign flips according to the rules of the actual event type, then go back to Step 1.

Based on the above discussion, Algorithm 1 describes one iteration of Zigzag-HMC on truncated MVNs where we simulate the Hamiltonian zigzag dynamic for a pre-specified duration \(t_{\text{total}}\). For a truncated MVN arising from the phylogenetic probit model, we adopt the dynamic programming strategy of Zhang et al. (2021) to speed up the most expensive gradient evaluation.
step in line 3 and reduce its cost from $O(N^2d + Nd^2)$ to $O(Nd^2)$. In brief, this strategy avoids explicitly inverting $\Upsilon$ by recursively traversing the tree (Pybus et al., 2012) to obtain $N$ conditional densities that directly translate to the desired gradient.

2.2.2 Jointly updating latent variables and across-trait covariance

The $N \times d$ latent variables and $d \times d$ across-trait covariance are highly correlated with each other, so individual Gibbs updates can be inefficient. The posterior conditional of $X$ is truncated normal and thus allows for the efficient Hamiltonian zigzag simulation as described in Section 2.2.1. The conditional distribution for covariance components $C$ and $D$ has no such special structure, so we map them to an unconstrained space and deploy standard Hamiltonian dynamics based on Gaussian momentum. We then construct the joint update of latent variables and covariance via differential operator splitting (Strang, 1968; Nishimura et al., 2020) to approximate the joint dynamics of Laplace-Gauss mixed momenta.

We denote the two concatenated sets of parameters $X$ and $\{C, D\}$ as $x = (x_G, x_L)$ with momenta $p = (p_G, p_L)$, where indices G and L refer to Gaussian or Laplace momenta. The joint sampler updates $(x_G, p_G)$ first, then $(x_L, p_L)$, followed by another update of $(x_G, p_G)$. This symmetric splitting ensures that the simulated dynamics is reversible and hence constitute a valid Metropolis proposal mechanism (Nishimura et al., 2020). Algorithm 2 describes the process of simulating the joint dynamics for time duration $2\epsilon$ via the analytical Hamiltonian zigzag dynamics for $(x_L, p_L)$ and the approximate leapfrog dynamics (7) for $(x_G, p_G)$. Because $x_G$ and $x_L$ can have
Zigzag-HMC for multivariate truncated normal distributions

1: function HzzTMVN(x, p, t_total)
2:   v ← sign(p)
3:   ϕ_x ← Φ(x − μ)
4:   t_remain ← t_total
5:   while t_remain > 0 do
6:     ▶ find gradient event time \( t_g \)
7:       a ← ϕ_v/2, b ← ϕ_x, c ← −p
8:       \( t_g ← \min_i \{ \min \) PositiveRoot\( (a_i, b_i, c_i) \} \) ▶ “minPositiveRoot” defined below
9:     ▶ find binary boundary event time
10:        \( t_b ← \min_i x_i/v_i \) for \( i \) with \( x_i v_i < 0 \) and \( x_i \in S_{\text{bin}} \)
11:     ▶ find categorical boundary event time, \( n_c = \text{number of categorical traits} \)
12:        for \( j = 1, \ldots, n_c \) do
13:          \( t^j_c ← \min_i |(x_{k-1} - x_k)/(v_{k-1} - v_i)| \) for \( i \) with \( v_{k-1} < v_i \) and \( x_i \in S_{\text{cat}} \)
14:       end for
15:       \( t_c ← \min_j t^j_c \) ▶ the actual event happens at time \( t \)
16:     t ← \min \{ \( t_g \), \( t_b \), \( t_c \), \( t \) \}
17:     \( x ← x + t v, p ← p - t \varphi_x - t^2 \varphi_v/2, \varphi_x ← \varphi_x + t \varphi_v \)
18:       if a gradient event happens at \( i_g \) then
19:         \( v_{i_g} ← -v_{i_g} \)
20:       else if a binary boundary event happens at \( i_b \) then
21:         \( v_{i_b} ← -v_{i_b}, p_{i_b} ← -p_{i_b} \)
22:       else if a categorical boundary event happens at \( i_{c1}, i_{c2} \) then
23:         \( v_{i_{c1}} ← -v_{i_{c1}}, v_{i_{c2}} ← -v_{i_{c2}}, p_{i_{c1}} ← -p_{i_{c1}}, p_{i_{c2}} ← -p_{i_{c2}} \)
24:       end if
25:     \( \varphi_v ← \varphi_v + 2 v \Phi \epsilon \)
26:     \( t \) remain ← t \) remain − t
27:   end while
28: return \( x, p \)
29: end function

* \( \min \) PositiveRoot\( (a_i, b_i, c_i) \) returns the minimal positive root of the equation \( a_i x^2 + b_i x + c = 0 \), or else returns +\( \infty \) if no positive root exists.
very different scales, we incorporate a tuning parameter, the step size ratio \( r \), to allow different step sizes for the two dynamics. To approximate a trajectory of the joint dynamics from \( t = 0 \) to \( t = \tau \), we apply the function \( \text{LG-STEP} \, m = \lfloor \tau / 2\epsilon \rfloor \) times, and accept or reject the end point following the standard acceptance probability formula (Metropolis et al., 1953; Hastings, 1970). We call this version of HMC based on Laplace-Gauss mixed momenta as \( \text{LG-HMC} \).

We use LG-HMC to update \( \{X, C, D\} \) as a Metropolis-within-Gibbs step of our random-scan Gibbs scheme. The overall sampling efficiency strongly depends on \( m \), the step size \( \epsilon \) and the step size ratio \( r \), so it is preferable to auto-tune all of them. Appendix A provides an empirical method to automatically tune \( r \). We utilize the no-U-turn algorithm to automatically decide the trajectory length \( m \) (Hoffman and Gelman, 2014) and call the resulting algorithm \( \text{LG No-U-Turn Sampler} \) (LG-NUTS). We adapt the step size \( \epsilon \) with primal-dual averaging to achieve an optimal acceptance rate (Hoffman and Gelman, 2014).

3 Results

3.1 Zigzag-HMC explores the energy space more efficiently than BPS

In our experience, BPS tends to generate samples with high auto-correlation between their respective energy function evaluations \(-\log \pi(x)\). In other words, it slowly traverses the target distribution’s energy contours even when
the marginal dimensions all appear to demonstrate good mixing. A similar behavior has also been reported by Bouchard-Côté et al. (2018), who introduce a velocity refreshment to address the issue. As we demonstrate below, however, even velocity refreshments cannot fully remedy BPS’s slow-mixing on the energy space. We apply BPS and Zigzag-HMC to a 256-dimensional standard normal target and Zigzag-HMC returns a clear win in the mixing of joint density (Figure 1). The sampling inefficiency for $-\log \pi(\mathbf{x})$ is less of a problem if one only needs to sample from a truncated normal with a fixed covariance matrix, but we are keenly interested in sampling the covariance matrix as a target of scientific interest. In this context, inefficient traversal across energy contours harms the sampling efficiency for all model parameters (Section 3.2).
Figure 1: Trace plot of the log density of a 256-dimensional standard normal sampled by BPS and Zigzag-HMC for 1000 MCMC iterations.

While a formal theoretical analysis is beyond the scope of this work, we empirically investigate a cause of BPS’s slow movement in energy space. Assume the $d$-dimensional parameter at the $t$th MCMC iteration is $\mathbf{x}(t) = (x_1(t), \ldots, x_d(t)) \in \mathbb{R}^d$, $t = 1, \ldots, T$, with $T$ being the total number of iterations. For a standard normal, its log density $\log \pi(\mathbf{x}) \propto \sum_i x_i^2$, and a high auto-correlation suggests $\log \pi(\mathbf{x})$ changes little between successive iterations, that is, the squared jumping distances

$$J_D = \left[ \sum_i x_i^2(t+1) - \sum_i x_i^2(t) \right]^2, \quad t = 0, \ldots, T - 1$$

are small. We then decompose $J_D$ into two components

$$J_D = J_1 + J_2,$$

$$J_1 = \sum_i \left[ x_i^2(t+1) - x_i^2(t) \right]^2,$$

$$J_2 = \sum_{j \neq k} \left[ x_j^2(t+1) - x_j^2(t) \right] \left[ x_k^2(t+1) - x_k^2(t) \right], \quad t = 0, \ldots, T - 1,$$ (17)
where $J_1$ measures the sum of the marginal travel distances and $J_2$ the covariance among them. We compare $J_D$, $J_1$ and $J_2$ between BPS and Zigzag-HMC on a 256-dimensional standard normal distribution. Since BPS requires a Poisson velocity refreshment to avoid reducible behavior (Bouchard-Côté et al., 2018), we include such a velocity refreshment with the Poisson rate set to an optimal value 1.4 (Bierkens et al., 2018). At every unit time interval, we collect samples for both samplers, and also refresh Zigzag-HMC’s momentum by redrawing it from the marginal Laplace distribution. Clearly seen in Table 1, BPS yields a much lower $J_D$ than Zigzag-HMC because its $J_2$ is largely negative, suggesting strong negative correlation among the coordinates.

Table 1: Squared jumping distance ($J_D$) of $\log \pi(x)$ sampled by the bouncy particle sampler (BPS) and Zigzag Hamiltonian Monte Carlo (Zigzag-HMC). We report the empirical mean of $J_1$ and $J_2$ in their means and standard deviations (SD) across ten independent simulations with $T = 2000$ samples. Both samplers have a per-iteration travel time 1.

| Quantity | BPS mean SD | Zigzag-HMC mean SD |
|----------|-------------|---------------------|
| $J_D$    | 9 0.4       | 560 13.9            |
| $J_1$    | 558 18.4    | 564 2.2             |
| $J_2$    | -549 18.3   | -4 13.8             |

3.2 Efficiency gain from the new inference scheme

We demonstrate that Zigzag-HMC and the joint update of latent variables $X$ and the covariance matrix $\Omega$ significantly improve inference efficiency. Table 2 compares the performance of four sampling schemes on
the HIV immune escape example (described in Section 3.3 below) with 
\( N = 535, P_{\text{disc}} = 21, P_{\text{cont}} = 3 \). We choose our efficiency criterion to be 
the per run-time, effective sample size (ESS) for the across-trait correlation 
\( C = \{\sigma_{ij}\} \) and partial correlation \( R = \{r_{ij}\} \) that are of chief scientific interest. We obtain \( R \) by transforming the sampled \( \Omega \) through

\[
\Omega^{-1} = P = \{p_{ij}\}, \quad r_{ij} = -\frac{p_{ij}}{\sqrt{p_{ii}p_{jj}}}. \tag{18}
\]

BPS and Zigzag-HMC only update \( X \) and we use the standard NUTS transition kernel (i.e. standard HMC combined with no-U-turn algorithm) for the \( \Omega \) elements. LG-HMC employs the joint update of \( X \) and \( \Omega \) described in 
Section 2.2.2. LG-NUTS additionally employs the No-U-Turn algorithm to 
decide the number of steps and a primal-dual averaging algorithm to cali-
brate the step size. We set the same \( t_{\text{total}} \) for BPS and Zigzag-HMC for a 
fair comparison. To tune LG-HMC, we first supply it with an optimal step 
size \( \epsilon \) learned by LG-NUTS, then decide the number of steps \( m = 100 \) as it 
gives the best performance among the choices (10, 100, 1000). As reported 
in Table 2, it is indeed harder to infer partial correlations than correlations 
and jointly updating \( X \) and \( \Omega \) largely eliminates this problem. BPS loses to 
the three other samplers and LG-HMC performs the best in terms of ESS for 
\( r_{ij} \), yielding a 5\times speed-up. LG-NUTS has a slightly lower efficiency than 
the manually optimized LG-HMC likely because the No-U-Turn algorithm 
requires simulating trajectory both forward and backward to maintain re-
versibility and this process incurs additional steps (Hoffman and Gelman, 
2014). In practice, we recommend using the tuning-free LG-NUTS.
Table 2: Efficiency comparison among different sampling schemes. Efficiency is in terms of minimal effective sample size (ESS) per running hour (hr) for correlation and partial correlation matrix elements $\sigma_{ij}$ and $r_{ij}$. We report median values across 3 independent simulations and all numbers are relative to the minimal per-hr ESS of $r_{ij}$ using BPS ($= 1^*$).

| Sampler        | $\sigma_{ij}$ | $r_{ij}$ |
|----------------|---------------|----------|
| BPS            | 4.0           | 1*       |
| Zigzag-HMC     | 9.4           | 1.6      |
| LG-HMC         | 5.1           | 5.0      |
| LG-NUTS        | 5.3           | 4.2      |

3.3 HIV immune escape

We revisit the HIV evolution application of Zhang et al. (2021) where a main scientific focus lies on the association between HIV-1 immune escape mutations and virulence, the pathogen’s ability to cause disease. The human leukocyte antigen (HLA) system is predictive of the disease course as it plays an important role in the immune response against HIV-1. Through its rapid evolution, HIV-1 can acquire mutations that aid in escaping HLA-mediated immune response, but the escape mutations may reduce its fitness and virulence (Nomura et al., 2013; Payne et al., 2014). Zhang et al. (2021) identify HLA escape mutations associated with virulence while controlling for the unknown evolutionary history of the viruses. However, Zhang et al. (2021) interpret their results based on the across-trait correlation $C$ which only informs marginal associations that can be confounded. Armed with a more efficient inference method, we are now able to estimate the across-trait partial correlation with adequate ESS and to reveal the conditional dependence...
The data contain $N = 535$ aligned HIV-1 $gag$ gene sequences collected from 535 patients between 2003 and 2010 in Botswana and South Africa (Payne et al., 2014). Each sequence is associated with 3 continuous and 21 binary traits. The continuous virulence measurements are replicative capacity (RC), viral load (VL) and cluster of differentiation 4 (CD4) cell count. The binary traits include the existence of HLA-associated escape mutations at 20 different amino acid positions in the $gag$ protein and another trait for the sampling country (Botswana or South Africa). Figure 2 depicts across-trait correlations and partial correlations with posterior medians $> 0.2$ (or $< −0.2$). Compared to correlations (Figure 2a), we observe more partial correlations with greater magnitude (Figure 2b). They indicate conditional dependencies among traits after removing effects from other variables in the model, helping to explore the causal pathway. For example, we only detect a negative conditional dependence between RC and CD4. In other words, holding one of CD4 and RC as constant, the other does not affect VL, suggesting that RC increases VL via reducing CD4. The fact that RC is not found to share a strong conditional dependence with VL may be explained by the strong modulatory role of immune system on VL. Only when viruses with higher RC also lead to more immune damage, as reflected in the CD4 count, higher VL may be observed as a consequence of less suppression of viral replication. As such, our findings are in line with the demonstration that viral RC impacts HIV-1 immunopathogenesis independent of VL (Claiborne et al., 2015).

The partial correlation also helps to decipher epistatic interactions and
Figure 2: (a) Across-trait correlation and (b) partial correlation with a posterior median $> 0.2$ or $< -0.2$ (in color). HIV gag mutation names start with the wild type amino acid state, followed by the amino acid site number according to the HXB2 reference genome and end with the amino acid as a result of the mutation ('X' means a deletion). Country = sample region: 1 = South Africa, -1 = Botswana; RC = replicative capacity; VL = viral load; CD4 = CD4 cell count. (c) Conditional dependencies between HIV-1 immune escape mutations that affect RC or VL. Node and edge color indicates whether the dependence is positive (orange) or negative (blue).
how the escape mutations and potential compensatory mutations affect HIV-1 virulence. For example, we find a strong positive partial correlation between T186X and T190X. Studies have shown that T186X is highly associated with reduced VL (Huang et al., 2011; Wright et al., 2010) and it requires T190I to partly compensate for this impaired fitness so the virus stays replication competent (Wright et al., 2012). The negative conditional dependence between T186X and RC and the positive conditional dependence between T190I and RC are consistent with this experimental observation. In contrast, with the strong positive association between T186X and T190, the marginal association fails to identify their opposite effects on RC. Another pair of mutations that potentially shows a similar interaction is H28X and M30X, which have a positive and negative partial correlation with VL, respectively. These mutations have indeed been observed to co-occur in gag epitopes from longitudinally followed-up patients (Olusola et al., 2020). Figure 2b keeps all the other compensatory mutation pairs in Figure 2a such as A146X-I147X and A163X-S165X that find confirmation in experimental studies (Crawford et al., 2007; Troyer et al., 2009).

More generally, when considering the viral trait RC and the infection trait VL, for which their variation are to a considerable extent attributable to viral genetic variation (Blanquart et al., 2017), we reveal an intriguing pattern. As in Figure 2c, when two escape mutations impair virulence, and there is a conditional dependence between them, it is always negative. When two mutations have opposing effects on these virulence traits, the conditional dependence between them (if present) is almost always positive, with one exception of the negative effect between V168I and S357X. For example,
T186X and I61X both have a negative impact on RC and the negative effect between them suggests that their additive, or even potentially synergistic, impact on RC is inhibited. Moreover, they appear to benefit from a compensatory mutation, T190X, which has been corroborated for the T186X-T190X pair at least as reported above. Also for VL, the conditional dependence between mutations that both have a negative impact on this virulence trait is consistently negative. Several of these individual mutations may benefit from H28X as a compensatory mutation, as indicated by the positive effect between pairs that include this mutation, and as suggested above for H28X - M30X. This illustrates the extent to which escape mutations may have a negative impact on virulence and the need to evolve compensatory mutations to restore it. We note that our analysis is not designed to recover compensatory mutations at great length as we restrict it to a limited set of known escape mutations, while mutations on many other sites may be compensatory. In fact, our analysis suggests that some of the considered mutations may be implicated in immune escape due to their compensatory effect rather than a direct escape benefit.

3.4 Glycosylation of Influenza A virus H1N1

Influenza A viruses of the H1N1 subtype currently circulate in birds, humans, and swine (Webster et al., 1992; Song et al., 2008; Trovão and Nelson, 2020), where they are responsible for substantial morbidity and mortality (Boni et al., 2013; Ma, 2020). The two surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) interact with a cell surface receptor and so their characteristics largely affect virus fitness and transmissibility. Mutations in
the HA and NA, particularly in their immunodominant head domain, sometimes produce glycosylations that shield the antigenic sites against detection by host antibodies and so help the virus evade antibody detection (Skehel et al., 1984; Hebert et al., 1997; Daniels et al., 2003; Östbye et al., 2020). On the other hand, glycosylation may interfere with the receptor binding and also be targeted by the innate host immunity to neutralize viruses. Therefore there must be an equilibrium between competing pressures to evade immune detection and maintain virus fitness (Tate et al., 2014; Lin et al., 2020). The number of glycosylations that leads to this balance is expected to vary in host species experiencing different strengths of immune selection. Despite decades of tracking IAVs evolution in humans for vaccine strain selection and recent expansions of zoonotic surveillance, the evolvability and selective pressures on the HA and NA have not been rigorously compared across multiple host species. Here, we examine the conditional dependence between host type and multiple glycosylation sites by estimating the posterior distribution of across-trait partial correlation while jointly inferring the IAVs evolutionary history.

We use hemagglutinin (H1) and neuraminidase (N1) sequence data sets for influenza A H1N1 produced by Trovão et al. as described in Trovão et al. (2022). We scan all H1 and N1 sequences to identify potential N-linked glycosylation sites, based on the motif Asn-X-Ser/Thr-X, where X is any amino acid other than proline (Pro) (Mellquist et al., 1998). We then set a binary trait for each sequence encoding for the presence or absence of glycosylations at a particular amino acid site. We keep sites with a glycosylation frequency between 20% and 80% for our analysis. This gives six sites in H1 and four
sites in N1. We include another binary trait for the host type being mammalian (human or swine) or avian, so the sample sizes are \(N = 964, P = 7\) (H1) and \(N = 896, P = 5\) (N1).

The six H1 glycosylation sites consist of three pairs that are physically close (63/94, 129/163, and 278/289, see Figure 3). Sites 63 and 94 are particularly close to each other, though distances will vary slightly with sequence. A negative conditional dependence suggests glycosylation at two close sites may be harmful for the virus (63/94 and 278/289) while a positive effect between two sites suggests a potential benefit (63/129 and 94/278). We detect a negative conditional dependence between mammalian host and glycosylation site 94 and 289. Avian viruses have a stronger tendency to have site 289 glycosylated (Figure 3). In N1, glycosylations are more strongly correlated than H1 (Figure 4). Two pairs of glycosylation sites have a positive conditional dependency in between (50/68 and 50/389) and two pairs (44/68 and 68/389) have a negative one. We omit a structural interpretation since all sites but 389 are located in the NA stalk, for which no protein structure is available. There is a positive conditional dependence between mammalian host and glycosylations at sites 44 and 68. None of the avian lineages has glycosylation site 44 while most swine and some human lineages have it. Similarly, glycosylation at site 68 is present in most swine and human lineages but only in avian lineages circulating in wild birds, not those in poultry.

3.5  *Aquilegia* flower and pollinator co-evolution

Reproductive isolation allows two groups of organisms to evolve separately, eventually forming new species. For plants, pollinators play an important
Figure 3: (a) Across-trait partial correlation among H1 glycosylation sites and host type with a posterior median $> 0.2$ or $< -0.2$ (in color and number). (b) HA structure of a 2009 H1N1 influenza virus (PDB entry 3LZG) with six glycosylation sites highlighted. Site 278 and 289 are in the stalk domain and all others are in the head domain. (c) The maximum clade credibility (MCC) tree with branches colored by the posterior median of the latent variable underlying H1 glycosylation site 289. The heatmap on the right indicates the host type of each taxon.
Figure 4: (a) Across-trait partial correlation among N1 glycosylation sites and host type with a posterior median $> 0.2$ or $< -0.2$ (in color and number). (b)(c) The maximum clade credibility (MCC) tree with branches colored by the posterior median of the latent variable underlying N1 glycosylation site 44 and 68.
role in reproductive isolation (Lowry et al., 2008). We examine the relationship between floral phenotypes and the three main pollinators for the columbine genus *Aquilegia*: bumblebees, hummingbirds, and hawk moths (Whittall and Hodges, 2007). Here, the pollinator species represents a categorical trait with three classes and we choose bumblebee with the shortest tongue as the reference class. Figure 5 provides the across-trait correlation and partial correlation. Compared to a similar analysis on the same data set that only looks at correlation or marginal association (Cybis et al., 2015), partial correlation controls confounding and indicates the conditional dependencies between pollinators and floral phenotypes that can bring new insights.

For example, we observe a positive marginal association between hawk moth pollinator and spur length but no conditional dependence between them. The marginal association matches with the observation that flowers with long spur length have pollinators with long tongues (Whittall and Hodges, 2007; Rosas-Guerrero et al., 2014). The absence of a conditional dependence makes intuitive sense because hawk moth’s long tongue is not likely to stop them from visiting a flower with short spurs when the other floral traits are held constant. In fact, researchers observe that shortening the nectar spurs does not affect hawk moth visitation (Fulton and Hodges, 1999). Similarly, the positive partial correlation between orientation and hawk moth also finds experimental support. The orientation trait is the angle of flower axis relative to gravity, in the range of (0, 180). A small orientation value implies a pendent flower whereas a large value represents a more upright flower (Hodges et al., 2002). Due to their different mor-
phologies, hawk moths prefer upright flowers while hummingbirds tend to visit pendent ones. Making the naturally pendent *Aquilegia formosa* flowers upright increases hawk moth visitation (Hodges et al., 2002). These results suggest that partial correlation may have predictive power for results from carefully designed experiments with controlled variables.

![Correlation](image1)

![Partial correlation](image2)

Figure 5: Across-trait correlations and partial correlations with posterior medians > 0.2 or < −0.2 (in color). BB = bumblebee.

### 3.6 MCMC convergence assessment

We run all simulations on a node equipped with AMD EPYC 7642 server processors. For every MCMC run, the minimal ESS across all dimensions of $X$ and $R$ after burn-in is above 100. As another diagnostic, for our two large-scale applications (Section 3.3 and 3.4) we run three independent chains and confirm the potential scale reduction statistic $\hat{R}$ for all partial correlation elements falls between [1, 1.03], below the common criterion of 1.1 (Gelman 2004).
et al., 1992). To reach a minimal ESS = 100 across all \( R \) elements, the post
burn-in run-time and number of MCMC transition kernels applied for the
joint inference are 21 hours and \( 1.3 \times 10^6 \) (HIV-1), 113 hours and \( 7.9 \times 10^7 \)
(H1), 76 hours and \( 1.4 \times 10^8 \) (N1).

4 Discussion

Learning how different biological traits interact with each other from many
evolutionarily related taxa is a long-standing problem of scientific interest
that sheds light on various aspects of evolution. Towards this goal, we de-
velop a scalable solution that significantly improves inferential efficiency com-
pared to established state-of-the-art approaches (Cybis et al., 2015; Zhang
et al., 2021). Our novel strategy enables learning across-trait conditional
dependencies that are more informative than the previous marginal associa-
tion based analyses. This approach provides reliable estimates of across-trait
partial correlations for large problems, on which the established BPS-based
method struggles. In two large-scale analyses featuring HIV-1 and H1N1
influenza, the improved efficiency allows us to infer conditional dependen-
cies among traits of scientific interest and therefore investigate some of the
most important molecular mechanisms underlying the disease. In addition,
our approach incorporates automatic tuning, so that the most influential
tuning parameters automatically adapt to the specific challenge the target
distribution presents. Finally, we extend the phylogenetic probit model to
include categorical traits and illustrate its use in examining the co-evolution
of *Aquilegia* flower and pollinators.
The novelty of our approach lies in two aspects. First, we leverage the cutting-edge Zigzag-HMC (Nishimura et al., 2020) to tackle the exceedingly difficult computational task of sampling from a high-dimensional truncated normal distribution. In the context of the phylogenetic probit model, Zigzag-HMC proves to be more efficient than the previously optimal approach that uses the BPS (Section 3.2). It is worth mentioning that another closely related sampler, the Markovian zigzag sampler (Bierkens et al., 2019), or MZZ, may also be appropriate for this task but provides lower efficiency than Zigzag-HMC (Nishimura et al., 2021). While Zigzag-HMC is a recent and less explored version of HMC, BPS and MZZ are two central methods within the piecewise deterministic Markov process literature that have attracted growing interest in recent years (Fearnhead et al., 2018; Dunson and Johndrow, 2020). Intriguingly, the most expensive step of all three samplers is to obtain the log-density gradient, and the same linear-order gradient evaluation method (Zhang et al., 2021) largely speeds it up. As a second source of novelty, we utilize differential operator splitting to jointly update two sets of parameters $X$ and $\Omega$ that are highly correlated. This strategy further improves efficiency and therefore allows us to obtain reliable estimates of the conditional dependencies among traits. In our applications, we find that these conditional dependencies better describe trait interactions than do the marginal associations.

We now consider limitations of this work and the future directions to which they point. First, the phylogenetic probit model does not currently accommodate a directional effect among traits since it only describes pairwise and symmetric correlations. However, the real biological processes are
often not symmetric but directional, where it is common that one reaction may trigger another but not the opposite way. A model allowing directed paths is preferable since it better describes the complicated causal network among multiple traits. Graphical models with directed edges (Lauritzen, 1996) are commonly used to learn molecular pathways (Neapolitan et al., 2014; Benedetti et al., 2017), but challenges remain to integrate these methods with a large and randomly distributed phylogenetic tree. Toward this goal, one may construct a continuous-time Markov chain to describe how discrete traits evolve (Pagel, 1994; O’Meara, 2012), but with $P$ binary traits the transition rate matrix grows to the astronomical size $2^P$. Second, though our method achieves the current best inference efficiency under the phylogenetic probit model, there is still room for improvement. In the influenza glycosylation example, we use a binary trait indicating the host being either avian or mammal (human or swine), instead of setting a categorical trait for host type. In fact, we choose not to use a three-class host type trait because it causes poor mixing for the partial correlation elements. We suspect two potential reasons for this. First, according to our model assumptions for categorical traits (Equation 1), the latent variables underneath the same trait are very negatively correlated, leading to a more correlated and challenging posterior. Second, in our specific data sets, the glycosylation sites tend to be similar in human and swine viruses, further increasing the correlation among posterior dimensions. One potential solution is to de-correlate some latent variables by grouping them into independent factors using phylogenetic factor analysis (Tolkoff et al., 2018; Hassler et al., 2021). Finally, one may consider a logistic or softmax function to map latent variables to the probability of a discrete
trait. This avoids the hard truncations in the probit model but also adds another layer of noise. It requires substantial effort to develop an approach that overcomes the above limitations while supporting efficient inference at the scale of applications in this work.

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SUPPLEMENTARY MATERIAL

We implement our algorithms within BEAST (Suchard et al., 2018)
A Auto-tuning of $r$

We describe a simple heuristic to auto-tune the step size ratio $r$ on the fly. Let $\Sigma_G$ and $\Sigma_L$ be the covariance matrices for $x_G$ and $x_L$ respectively, then their minimal eigenvalues $\lambda_{\text{min},G}$ and $\lambda_{\text{min},L}$ describe the variance magnitude in the most constrained direction. Intuitively, for both HMC and Zigzag-HMC, the step size should be proportional to the diameter of this most constrained density region, which is $\sqrt{\lambda_{\text{min},G}}$ or $\frac{\sqrt{\lambda_{\text{min},L}}}{\sqrt{\lambda_{\text{min},G}}}$. Therefore we propose a choice of $r = \frac{\sqrt{\lambda_{\text{min},L}}}{\sqrt{\lambda_{\text{min},G}}}$, assuming the two types of momenta lead to similar travel distance during one unit time. It is straightforward to check this assumption.

At stationarity, HMC has a velocity $v_G \sim \mathcal{N}(0, I)$, so its velocity along any unit vector $u$ would be distributed as $\langle v_G, u \rangle \sim \mathcal{N}(0, 1)$, and the travel distance $E|\langle v_G, u \rangle| = \sqrt{2/\pi}$. For Zigzag-HMC, as $\langle v_L, u \rangle$ does not follow a simple distribution, we estimate $E|\langle v_L, u \rangle|$ by Monte Carlo simulation and it turns out to be $\approx 0.8$, close to $\sqrt{2/\pi}$.

We test this intuitive choice of $r$ on a subset of the HIV data in Zhang et al. (2021) with 535 taxa, 5 binary and 3 continuous traits. We calculate the optimal $r = \frac{\sqrt{\lambda_{\text{min},L}}}{\sqrt{\lambda_{\text{min},G}}} \approx 2.5$ with $\Sigma_G$ and $\Sigma_L$ estimated from the MCMC samples. Clearly, $r$ has a significant impact on the efficiency as a very small or large $r$ leads to lower ESS (Table 3). Also, an $r$ in the order of our optimal value generates the best result, so we recommend this on-the-fly automatic tuning $r = \frac{\sqrt{\lambda_{\text{min},L}}}{\sqrt{\lambda_{\text{min},G}}}$ (Table 3).
Table 3: Minimal effective sample size (ESS) per running hour (hr) for partial correlation matrix elements $r_{ij}$ with different $r$ ($N = 535, P_{disc} = 5, P_{cont} = 3$). ESS values report medians across 3 independent simulations.

| $r$ | ESS/hr min | ESS/hr median |
|-----|------------|---------------|
| 0.1 | 32         | 266           |
| 1   | 106        | 771           |
| 10  | 118        | 855           |
| 100 | 25         | 110           |

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