A Flexible Bayesian Framework to Study Viral Trait Evolution

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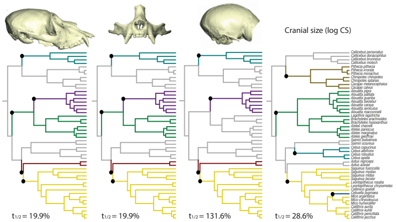
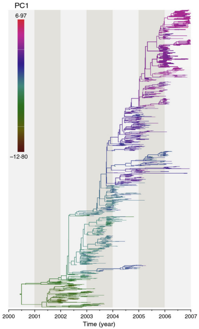
21 January 2019

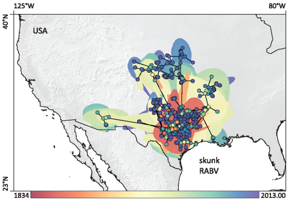
Phylogenetic Comparative Methods



Aristide et al. (2018)



Vrancken et al. (2015)



Dellicour et al. (2017)

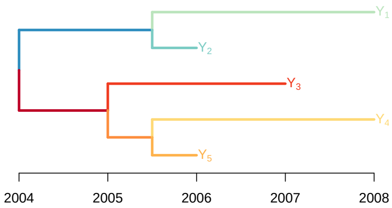
- Various time scales: Myr – decade.
- Various traits: morpho, geo, viral.

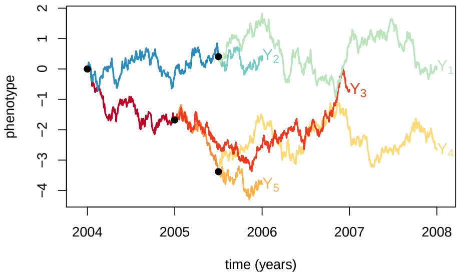
Question: Trait dynamics for an evolving organism ?

Outline

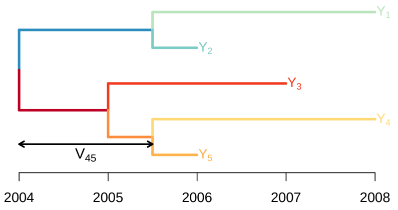
1. Models of Trait Evolution
2. Efficient Bayesian Inference
3. HIV Virulence Heritability Study

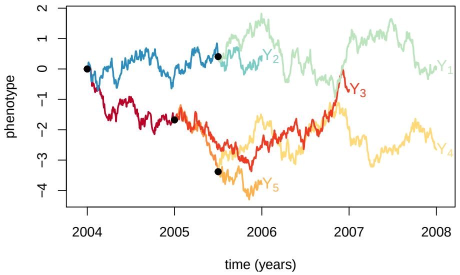
BM on a Tree


Y1
Y2
Y3
Y4
Y5
2004
2005
2006
2007
2008


phenotype
time (years)
Y1
Y2
Y3
Y4
Y5

BM on a Tree



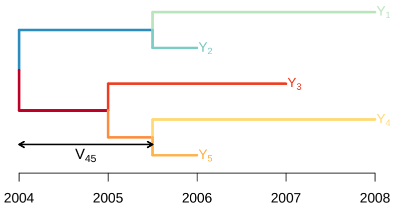


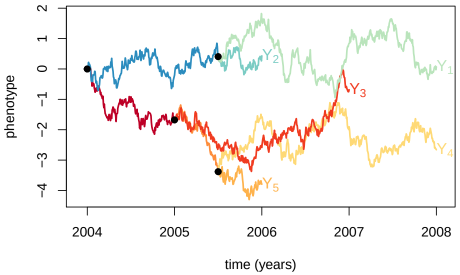
EDS: $\mathrm{d}\, X_t = \sigma \,\mathrm{d}\, B_t$

Variance: $\mathbb{C}\mathrm{ov}\,[Y_4; Y_5] = \sigma^2 \times V_{45}$ shared evolution time

Expectation: $\mathbb{E}\,[Y_i] = \mu$ ancestral root value

BM on a Tree

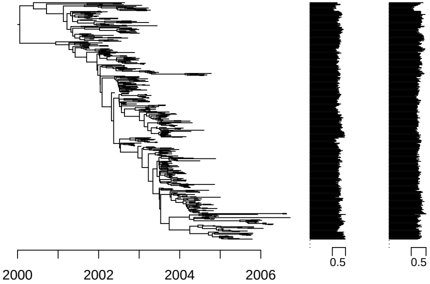




Distribution: Normal

$$\mathbf{Y} \sim \mathcal{N}(\mu \mathbf{1}_n, \sigma^2 \mathbf{V})$$

Multivariate BM

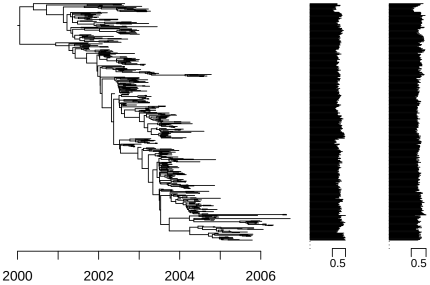


Data: Vectors of p traits

$$\mathbf{Y}_i^T = (Y_{i1}, \dots, Y_{ip})$$

Tree: Influenza H3N2 (Lemey et al., 2014)

Multivariate BM



Data: Vectors of p traits

$$\mathbf{Y}_i^T = (Y_{i1}, \dots, Y_{ip})$$

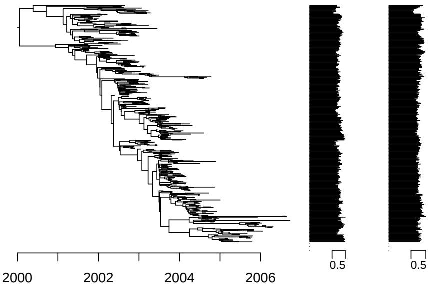
EDS: $\mathrm{d}\,\mathbf{X}_t = \mathbf{\Sigma}\,\mathrm{d}\,\mathbf{B}_t$ $\quad\mathbf{R} = \mathbf{\Sigma}^T\mathbf{\Sigma}$

Variance: $\mathbb{C}\mathrm{ov}\left[Y_{ik}; Y_{jl}\right] = R_{kl} \times V_{ij}$ shared evolution time

Expectation: $\mathbb{E}\left[\mathbf{Y}_{\cdot k}\right] = \mu_k$ ancestral root value

Tree: Influenza H3N2 (Lemey et al., 2014)

Multivariate BM



Data: Vectors of p traits

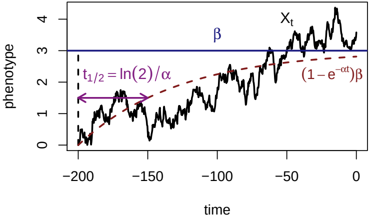
$$\mathbf{Y}_i^T = (Y_{i1}, \dots, Y_{ip})$$

Distribution: Matrix Normal

$$\mathbf{Y} \sim \mathcal{MN}(\mathbf{1}_n \boldsymbol{\mu}^T, \mathbf{V}, \mathbf{R}) \qquad \mathbb{V}\text{ar}\left[\text{vec}(\mathbf{Y})\right] = \mathbf{R} \otimes \mathbf{V}$$

Tree: Influenza H3N2 (Lemey et al., 2014)

Ornstein-Uhlenbeck Modeling (Hansen, 1997)



$$\mathrm{d}\,X_t = \alpha[\beta - X_t]\,\mathrm{d}\,t + \sigma\,\mathrm{d}\,B_t$$

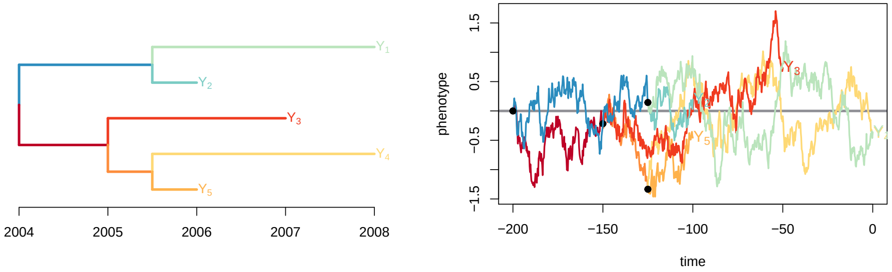
Deterministic part:

- β: primary optimum (mechanistically defined).
- $\ln(2)/\alpha$: phylogenetic half live.

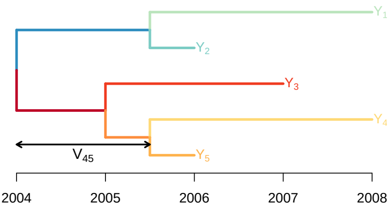
Stochastic part:

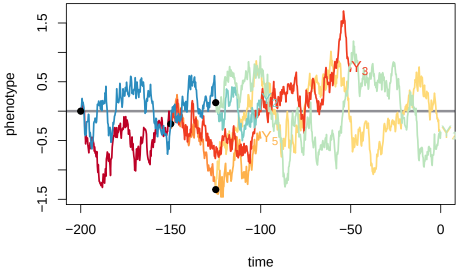
- X_t: trait value (actual optimum).
- $\sigma dB(t)$: Brownian fluctuations.

OU on a Tree


Y1
Y2
Y3
Y4
Y5
2004
2005
2006
2007
2008
phenotype
1.5
0.5
−0.5
−1.5
−200
−150
−100
−50
0
time

OU on a Tree





EDS: $\mathrm{d}\, X_t = \alpha[\beta - X_t]\,\mathrm{d}\, t + \sigma\,\mathrm{d}\, B_t$

Variance: $\mathbb{C}\mathrm{ov}\left[Y_4; Y_5\right] = \frac{\sigma^2}{2\alpha} e^{-\alpha(V_4+V_5)}(e^{2\alpha V_{45}} - 1)$

Expectation: $\mathbb{E}\left[Y_i\right] = \mu e^{-\alpha V_i} + \beta(1 - e^{-\alpha V_i})$

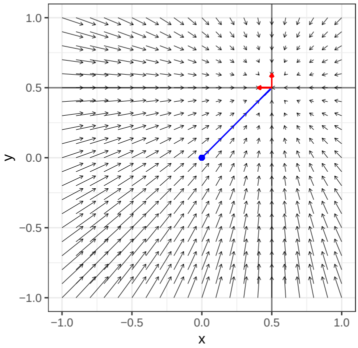
Multivariate OU Modeling

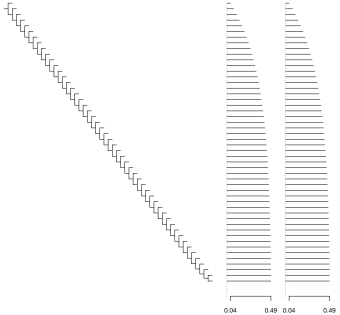
$$\mathrm{d}\,\mathbf{X}_t = \mathbf{A}[\beta - \mathbf{X}_t]\,\mathrm{d}\,t + \mathbf{\Sigma}\,\mathrm{d}\,\mathbf{B}_t$$

Multivariate OU Modeling

$$d\,\mathbf{X}_t = \mathbf{A}[\beta - \mathbf{X}_t]\,d\,t + \mathbf{\Sigma}\,d\,\mathbf{B}_t$$

Scalar: $\mathbf{A} = \begin{pmatrix} 0.1 & 0 \\ 0 & 0.1 \end{pmatrix}$ $\beta = \begin{pmatrix} 0.5 \\ 0.5 \end{pmatrix}$

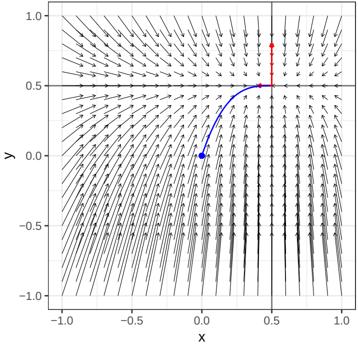


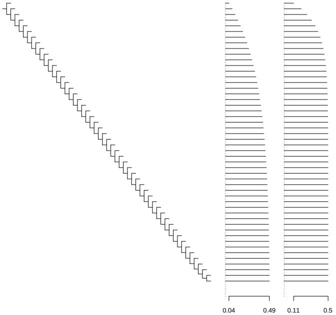


Multivariate OU Modeling

$$\mathrm{d}\,\mathbf{X}_t = \mathbf{A}[\beta - \mathbf{X}_t]\,\mathrm{d}\,t + \mathbf{\Sigma}\,\mathrm{d}\,\mathbf{B}_t$$

Diagonal: $\mathbf{A} = \begin{pmatrix} 0.1 & 0 \\ 0 & 0.3 \end{pmatrix}$ $\beta = \begin{pmatrix} 0.5 \\ 0.5 \end{pmatrix}$

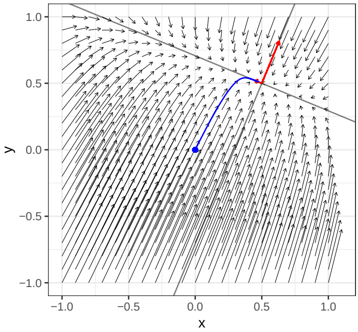


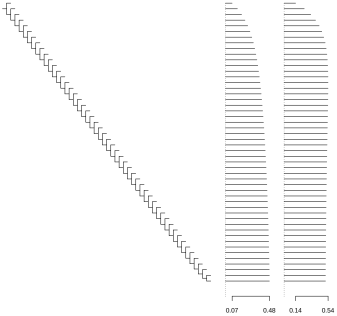


Multivariate OU Modeling

$$\mathrm{d}\,\mathbf{X}_t = \mathbf{A}[\beta - \mathbf{X}_t]\,\mathrm{d}\,t + \mathbf{\Sigma}\,\mathrm{d}\,\mathbf{B}_t$$

Symmetric: $\mathbf{A} = \begin{pmatrix} 0.1 & 0.1 \\ 0.1 & 0.3 \end{pmatrix}$ $\beta = \begin{pmatrix} 0.5 \\ 0.5 \end{pmatrix}$

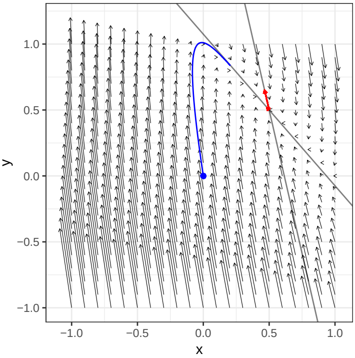


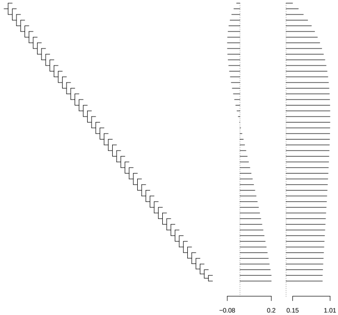


Multivariate OU Modeling

$$\mathrm{d}\,\mathbf{X}_t = \mathbf{A}[\beta - \mathbf{X}_t]\,\mathrm{d}\,t + \mathbf{\Sigma}\,\mathrm{d}\,\mathbf{B}_t$$

Diagonalizable in $\mathbb{R}$: $\mathbf{A} = \begin{pmatrix} -0.02 & -0.04 \\ 0.2 & 0.2 \end{pmatrix}$ $\beta = \begin{pmatrix} 0.5 \\ 0.5 \end{pmatrix}$





Multivariate OU

$$\mathrm{d}\,\mathbf{X}_t = \mathbf{A}[\beta - \mathbf{X}_t]\,\mathrm{d}\,t + \mathbf{\Sigma}\,\mathrm{d}\,\mathbf{B}_t$$

Diagonalizable: $\mathbf{A} = \mathbf{P\Lambda P}^{-1} \quad \lambda_k > 0$

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Expectation: $\mathbb{E}[\mathbf{Y}_i] = \boldsymbol{\mu} e^{-\mathbf{A}V_i} + \beta(1 - e^{-\mathbf{A}V_i})$

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Variance: $\mathbb{C}\mathrm{ov}\left[\mathbf{Y}_i; \mathbf{Y}_j\right] = \mathbf{P}\left[\mathbf{W}_{ij} \odot \mathbf{P}^{-1}\mathbf{R}\mathbf{P}^{-T}\right]\mathbf{P}^T$

$$\mathbf{W}_{ij} = \left[\frac{1}{\lambda_q + \lambda_r} e^{-\lambda_q V_i} e^{-\lambda_r V_j}\left(e^{(\lambda_q+\lambda_r)V_{ij}} - 1\right)\right]_{1\leq q,r\leq p}$$

Multivariate OU

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Distribution: Still Gaussian.

No nice Kronecker product.

Bayesian Phylogenetics

Goal:

$$p\left(\boldsymbol{\theta}, \mathcal{T}, \psi \mid \mathbf{Y}, \mathbf{S}\right)$$

Bayesian Phylogenetics

Goal:

$$p\left(\boldsymbol{\theta}, \mathcal{T}, \psi \mid \mathbf{Y}, \mathbf{S}\right) \propto p\left(\mathbf{Y}, \mathbf{S} \mid \boldsymbol{\theta}, \mathcal{T}, \boldsymbol{\psi}\right) p\left(\boldsymbol{\theta}, \mathcal{T}, \boldsymbol{\psi}\right)$$

Bayesian Phylogenetics

Goal:

$$\begin{aligned} p(\boldsymbol{\theta}, \mathcal{T}, \boldsymbol{\psi} \mid \mathbf{Y}, \mathbf{S}) &\propto p(\mathbf{Y}, \mathbf{S} \mid \boldsymbol{\theta}, \mathcal{T}, \boldsymbol{\psi})\, p(\boldsymbol{\theta}, \mathcal{T}, \boldsymbol{\psi}) \\ &\propto p(\mathbf{Y} \mid \boldsymbol{\theta}, \mathcal{T})\, p(\mathbf{S} \mid \mathcal{T}, \boldsymbol{\psi})\, p(\boldsymbol{\theta}, \mathcal{T}, \boldsymbol{\psi}) \end{aligned}$$

Assumption: $\mathbf{Y}$ and $\mathbf{S}$ independent conditionally on $\mathcal{T}$.

Bayesian Phylogenetics

Goal:

$$
\begin{aligned}
p(\boldsymbol{\theta}, \mathcal{T}, \psi \mid \mathbf{Y}, \mathbf{S}) &\propto p(\mathbf{Y}, \mathbf{S} \mid \boldsymbol{\theta}, \mathcal{T}, \psi)\, p(\boldsymbol{\theta}, \mathcal{T}, \psi) \\
&\propto p(\mathbf{Y} \mid \boldsymbol{\theta}, \mathcal{T})\, p(\mathbf{S} \mid \mathcal{T}, \psi)\, p(\boldsymbol{\theta}, \mathcal{T}, \psi) \\
&\propto p(\mathbf{Y} \mid \boldsymbol{\theta}, \mathcal{T})\, p(\boldsymbol{\theta})\, p(\mathbf{S} \mid \mathcal{T}, \psi)\, p(\mathcal{T}, \psi)
\end{aligned}
$$

Assumption: **Y** and **S** independent conditionally on $\mathcal{T}$.

This talk: $\mathcal{T}$ fixed.

MCMC

Goal: Sample from $p(\boldsymbol{\theta} \mid \mathbf{Y}) \propto p(\mathbf{Y} \mid \boldsymbol{\theta})\, p(\boldsymbol{\theta})$

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Metropolis - Hasting: Iterate:

- Draw $\boldsymbol{\theta}^*$ in $q\left(\boldsymbol{\theta} \,\middle|\, \boldsymbol{\theta}^t\right)$.
- Set $\boldsymbol{\theta}^{(t+1)} = \boldsymbol{\theta}^*$ with probability:

$$r_t = \min\left\{1, \frac{p\left(\mathbf{Y} \mid \boldsymbol{\theta}^*\right)}{p\left(\mathbf{Y} \,\middle|\, \boldsymbol{\theta}^t\right)} \frac{p\left(\boldsymbol{\theta}^*\right)}{p\left(\boldsymbol{\theta}^t\right)} \frac{q(\boldsymbol{\theta}^{(t)}|\boldsymbol{\theta}^*)}{q(\boldsymbol{\theta}^*|\boldsymbol{\theta}^{(t)})}\right\}.$$

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Gibbs:

- Split $\boldsymbol{\theta} = (\boldsymbol{\theta}_{[1]}, \dots, \boldsymbol{\theta}_{[K]})$.
- Draw $\boldsymbol{\theta}^*$ in $p(\boldsymbol{\theta}_{[k]}|\boldsymbol{\theta}^{(t)}_{[-k]}, \mathbf{Y})$ so that $r_t = 1$.

BM: Gibbs with Conjugate Priors

Likelihood:

$$\mathbf{Y}|\mathbf{R}, \boldsymbol{\mu} \sim \mathcal{MN}(\mathbf{1}_n \boldsymbol{\mu}^T, \mathbf{V}, \mathbf{R})$$

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Conjugate Priors:

$$\mathbf{R} \sim \mathcal{IW}(\mathbf{R}_0, \nu)$$
$$\boldsymbol{\mu}|\mathbf{R} \sim \mathcal{N}(\boldsymbol{\mu}_0, \kappa_0^{-1}\mathbf{R})$$

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Gibbs:

$$\mathbf{R}|\mathbf{Y}, \boldsymbol{\mu} \sim \mathcal{IW}(\mathbf{R}_n, \nu_n) \quad \text{with} \quad \mathbf{R}_n = f(\mathbf{Y}, \boldsymbol{\mu}, \mathbf{V})$$

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$\hookrightarrow$ Automatic sampling in the space of variance matrices.

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$\hookrightarrow$ Automatic sampling in the space of variance matrices. :-)

OU: No Gibbs

Likelihood:

$$\mathbf{Y}|\mathbf{A}, \mathbf{R}, \boldsymbol{\mu} \not\sim \mathcal{MN}$$

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Conjugate Priors: ???

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Gibbs: Not possible.

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Conjugate Priors: ???

Gibbs: Not possible.

Metropolis - Hasting:

Need to sample in constrained spaces (**A**, **R**).

MH in constrained space

Transformation:

$$f : \begin{cases} \mathcal{C}_q \to \mathbb{R}^q \\ \boldsymbol{\theta} \mapsto \boldsymbol{\nu} = f(\boldsymbol{\theta}) \end{cases}$$

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$$\pi_{\boldsymbol{\theta}}(\boldsymbol{\theta}) = \pi_{\boldsymbol{\nu}}(f(\boldsymbol{\theta})) \times |J_f(\boldsymbol{\theta})|$$

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$$r_t = \min\left\{1, \frac{p\left(\mathbf{Y} \mid \boldsymbol{\theta}^*\right)}{p\left(\mathbf{Y} \mid \boldsymbol{\theta}^t\right)} \frac{p\left(\boldsymbol{\theta}^*\right)}{p\left(\boldsymbol{\theta}^t\right)} \frac{q(\boldsymbol{\nu}^{(t)}|\boldsymbol{\nu}^*)}{q(\boldsymbol{\nu}^*|\boldsymbol{\nu}^{(t)})} \frac{|J_f(\boldsymbol{\theta}^{(t)})|}{|J_f(\boldsymbol{\theta}^*)|}\right\}.$$

Variance matrix: LKJ transformation (Lewandowski et al., 2009)

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Decomposition: Use correlation matrix $\mathbf{C}$

$$\mathbf{R} = \begin{pmatrix} \sigma_1 & & 0 \\ & \ddots & \\ 0 & & \sigma_p \end{pmatrix} \begin{pmatrix} 1 & & C_{kl} \\ & \ddots & \\ C_{kl} & & 1 \end{pmatrix} \begin{pmatrix} \sigma_1 & & 0 \\ & \ddots & \\ 0 & & \sigma_p \end{pmatrix}$$

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$\boldsymbol{\sigma}$: Real positive :-)

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$\boldsymbol{\sigma}$: Real positive :-)

C: Correlation matrix :-(

Variance matrix: LKJ transformation (Lewandowski et al., 2009)

Decomposition: Use correlation matrix $\mathbf{C}$

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$\boldsymbol{\sigma}$: Real positive :-)

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$\hookrightarrow$ Easier and more efficient: Cholesky representation.

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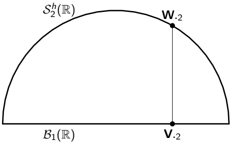
$\hookrightarrow$ Diffeomorphism to the euclidian (open) ball $\mathcal{B}_{k-1}(\mathbb{R})$:

$$\mathbf{F} : \begin{cases} \mathcal{B}_{k-1}(\mathbb{R}) & \to \mathcal{S}_k^{\mathrm{h}}(\mathbb{R}) \\ \mathbf{V}_{\cdot k} & \mapsto \mathbf{W}_{\cdot k} = \left(\mathbf{V}_{\cdot k},\ \sqrt{1 - \|\mathbf{V}_{\cdot k}\|^2}\right) \end{cases}$$



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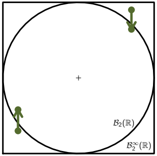
$\hookrightarrow$ Transformation $\mathcal{B}^{\infty}_{k-1}(\mathbb{R}) \rightarrow \mathcal{B}_{k-1}(\mathbb{R})$?

$$\mathbf{LKJ}_i(\mathbf{z}) = \begin{cases} z_i & \text{if } i = 1 \\ z_i \prod_{k=1}^{i-1}(1 - z_k^2)^{1/2} & \text{if } 1 < i \leq k-1. \end{cases}$$



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$$\mathrm{LKJ}(\mathbf{C} \mid \eta) = c_p(\eta) \left|\mathbf{C}\right|^{\eta-1}$$

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$\hookrightarrow$ Same as taking a "spherical beta" on each of the $\mathbf{V}_{\cdot k}$:

$$\mathrm{SBeta}(\mathbf{V}_{\cdot k}|\beta) \propto (1 - \|\mathbf{V}_{\cdot k}\|^2)^{\beta_k} \quad \text{with} \quad \beta_k = \eta + (p-k)/2$$

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Question: Can we use the tree ?

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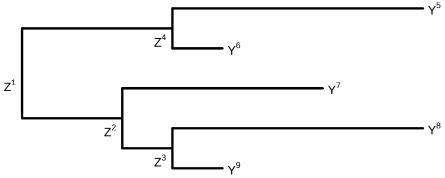

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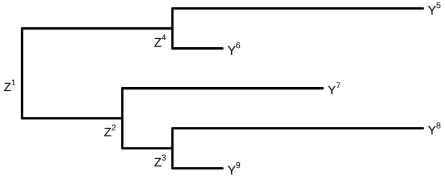

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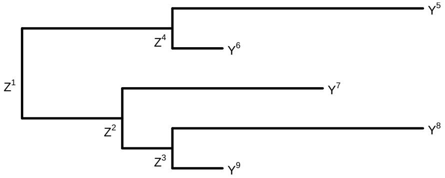

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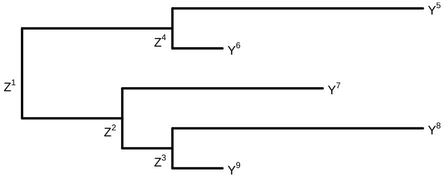

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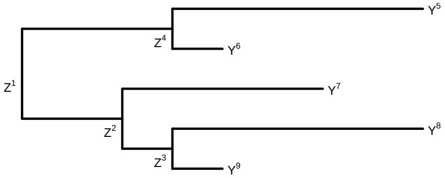
Drift, shifts, Integrated OU...

Efficient Computations



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Likelihood: $p(\mathbf{X}^1 | \mathbf{Y})$ in one post-order traversal of the tree.

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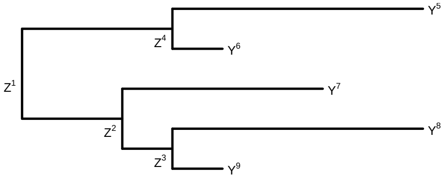

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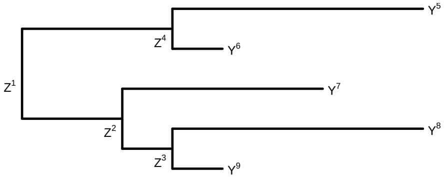

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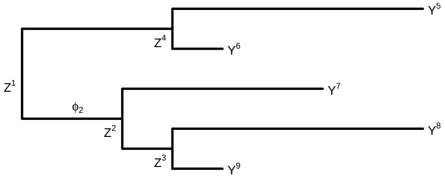
Difficulty: Numerical robustness.

Efficient Computations: Gradient



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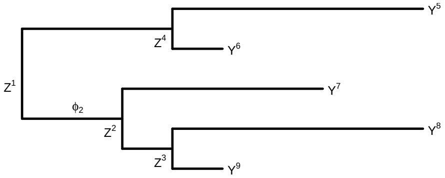
Branch-specific Gradient: $\frac{\partial}{\partial \phi_j} [\log p(\mathbf{Y})] = \mathbb{E}\left[\mathbf{F}(\mathbf{X}^j; \phi_j) \,\middle|\, \mathbf{Y}\right]$

Efficient Computations: Gradient



$$\mathbf{X} = \begin{cases} \mathbf{Z} & : \text{latent nodes} \\ \mathbf{Y} & : \text{tips} \end{cases}$$

$$\mathbf{X}^1 \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Gamma}) \qquad \text{root}$$

$$\mathbf{X}^j \mid \mathbf{X}^{\mathrm{pa}(j)} \sim \mathcal{N}\left(\mathbf{q}_i \mathbf{X}^{\mathrm{pa}(i)} + \mathbf{r}_i,\ \boldsymbol{\Sigma}_i\right) \qquad \text{tips and nodes}$$

Branch-specific Gradient: $\frac{\partial}{\partial \phi_j}[\log p(\mathbf{Y})] = \mathbb{E}\left[\mathbf{F}(\mathbf{X}^j; \phi_j) \mid \mathbf{Y}\right]$

$\hookrightarrow$ One pre-order traversal.

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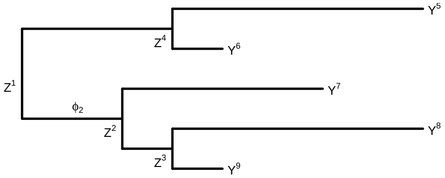

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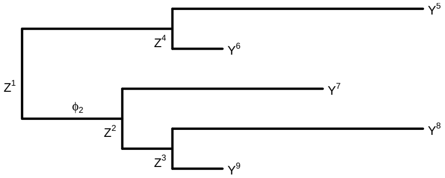

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$\hookrightarrow$ One pre-order traversal.

Chain rule: Get the gradient w.r.t. any parameter. $\rightarrow$ HMC

Implementation

(Suchard et al., 2018)

BEAST

Bayesian Evolutionary Analysis Sampling Trees

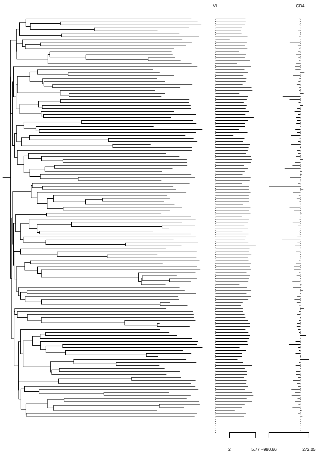
- MCMC for tree estimation
- Comprehensive set of tools:
  - Factor model
  - Marginal Likelihood
  - ...
- Developed in `Java` since 2002.
- This is `BEAST` 1.10.

Don't ask about `BEAST 2`.

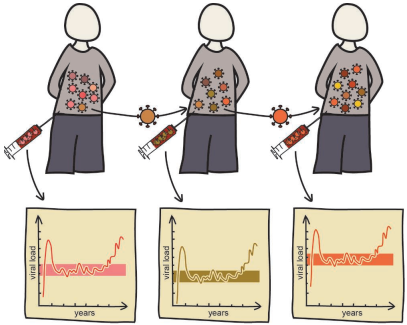
What's new:

- Flexible OU models
- Efficient sampling of variance
- Efficient HMC (in progress)

HIV virulence heritability (Alizon et al., 2010; Vrancken et al., 2015)



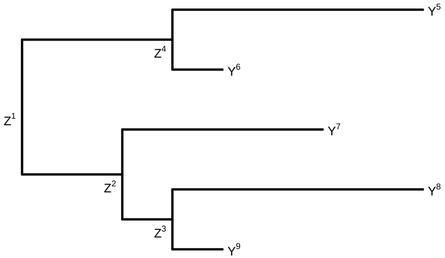
CD4: CD4+ T cells decline rate
VL: Set point viral load



Fraser et al. (2014)

Questions: Is virulence "heritable"? What model of trait evolution?

Heritability



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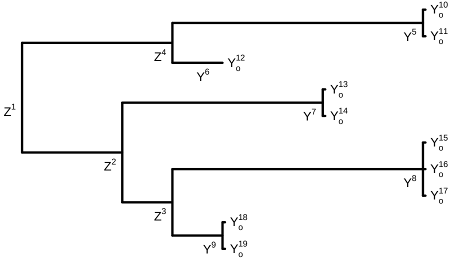

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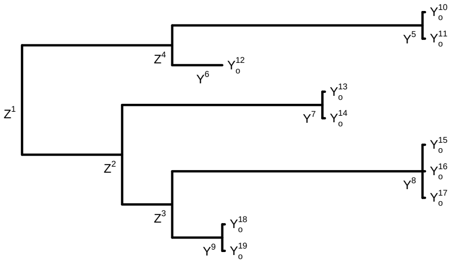
$$\mathbf{Y}_o^i \mid \mathbf{Y}^{\mathrm{pa}(i)} \sim \mathcal{N}\left(\mathbf{Y}^{\mathrm{pa}(i)}, \mathbf{S}\right) \qquad \text{observations}$$

Heritability



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"Heritability": $$h_k^2 = \frac{V(\mathbf{Y}_{\cdot k})}{V(\mathbf{Y}_{o\cdot k})} \approx \frac{\sigma_k^2 \tilde{t}}{\sigma_k^2 \tilde{t} + s_k}$$

Models

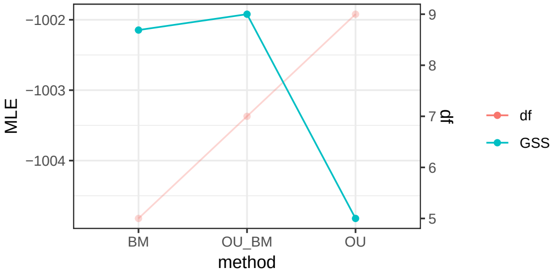
(Alizon et al., 2010)

We use three different models:

- **BM** no selection on the traits.
- **OU-BM** selection on VL, not on CD4.
- **OU** selection on both traits.

- Each model is fitted using a MCMC.
- Estimated Marginal likelihood is used to compare them.

Results



Heritability (using OU-BM):

VL $h^2 = 17\%$ $[0.007, 82.5]\%$ (95% CI)

CD4 $h^2 = 0.02\%$ $[0.0024, 0.16]\%$

"Consistent" with previous estimates.

Conclusion and Perspectives

A general framework for trait evolution with dated tips.

Main Features:

- Flexible models
- Flexible implementation
- Efficient algorithms
- Applicable to virology

Perspectives:

- Develop HMC
- Apply to larger datasets
- Other questions: geographical spread, comparative studies, ...

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Photo Credits:

Thank you for listening

Kasteel van Arenberg

Appendices

Hamiltonian Monte Carlo (Betancourt, 2017)

Idea: Introduce the "momentum" $\mathbf{p}$ of the parameters $\mathbf{q}$.

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$$\begin{aligned}\text{Hamiltonian } H(\mathbf{q}, \mathbf{p}) &= \text{Potential energy} + \text{Kinetic energy}\\ &= U(\mathbf{q}) + K(\mathbf{p})\\ &= -\log \underbrace{p(\mathbf{Y}|\mathbf{q})p(\mathbf{q})}_{\text{posterior}} - \log \underbrace{\phi(\mathbf{p})}_{\text{Gaussian}}\end{aligned}$$

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H **total energy** invariant by Hamiltonian dynamic: $\begin{cases} \dfrac{d\mathbf{p}}{dt} = \nabla_{\mathbf{q}} U(\mathbf{q}) \\ \dfrac{d\mathbf{q}}{dt} = -\nabla_{\mathbf{p}} K(\mathbf{p}) \end{cases}$

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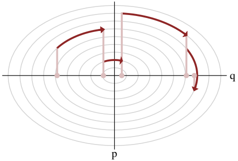

1. Draw random moments $\mathbf{p}$.
2. Propose a new $\mathbf{q}$ from the dynamic.

back