Inferring Transmission Structure from HIV Sequence Data via Latent Spatial Poisson Processes

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on behalf of the Rakai Community Cohort Study and PANGEA-HIV

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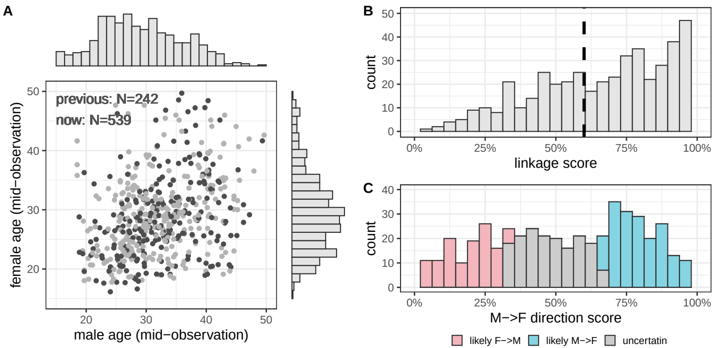
Major objectives

- Infer age structure in HIV transmissions based on phylogenetic analysis outcomes
- Without any pre-classification on phylogenetic summary statistics while making use of more data
- Exploit a continuous spatial process (with marks) and thus avoid manual discretization

The data

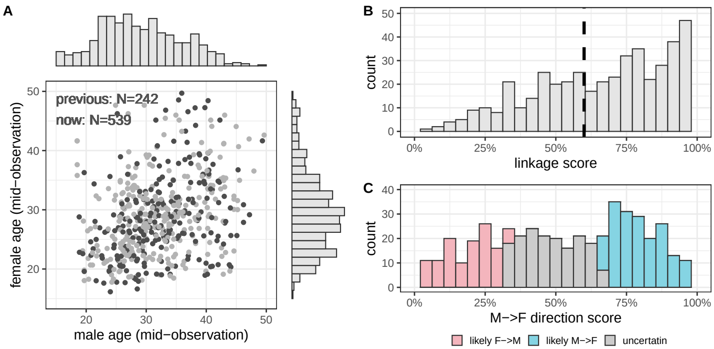


A male and female ages (mid-observation) for each potential transmission pair (s_{i1}, s_{i2})

B "posterior" linkage score ℓ_i ($\in [0, 1]$)

C "posterior" direction score d_i ($\in [0, 1]$)

The data



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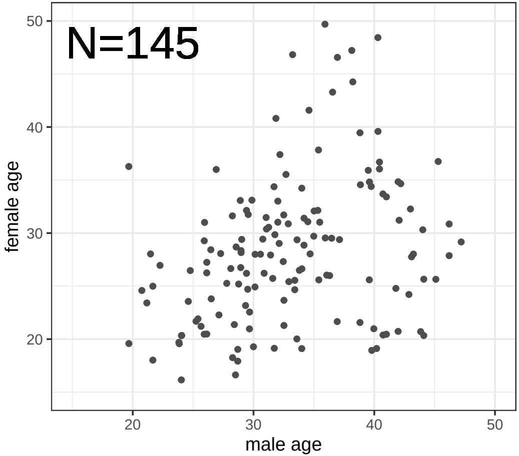
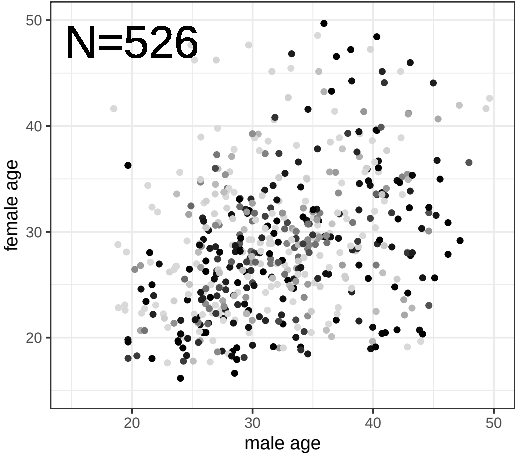
Goal: leverage the phylogenetic scores (ℓ_i and d_i) to infer transmission links and directions

The model

Existing approach: pre-classify points on ℓ_i and d_i; discretize on age bands (below: pre-classified MF transmissions)

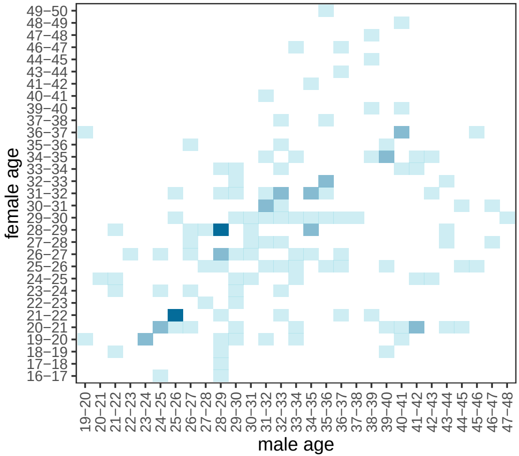


Our approach: no need for any pre-classification or discretization, directly accounting for uncertainty



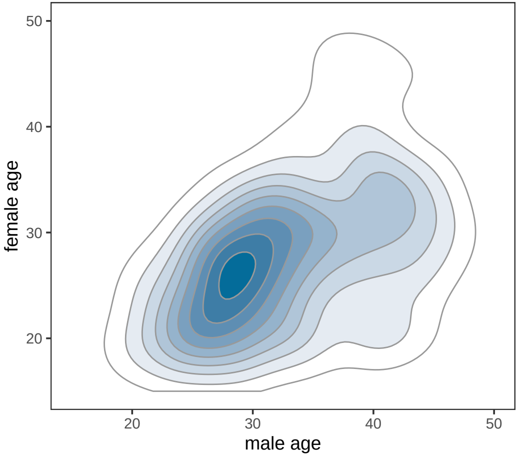
The model

Existing approach:



End result: transmission rate π_{ab} between (discrete) age groups a and b

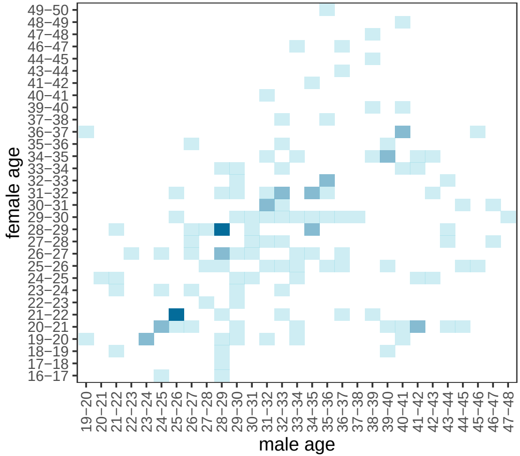
Our approach:



End result: a continuous spatial intensity function $\boldsymbol{\lambda}(\cdot,\cdot)$

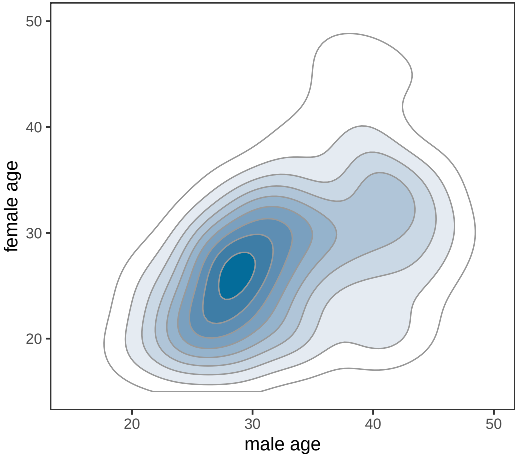
The model

Existing approach:



π_{ab} specific to age discretization;
hard to convert to different resolutions

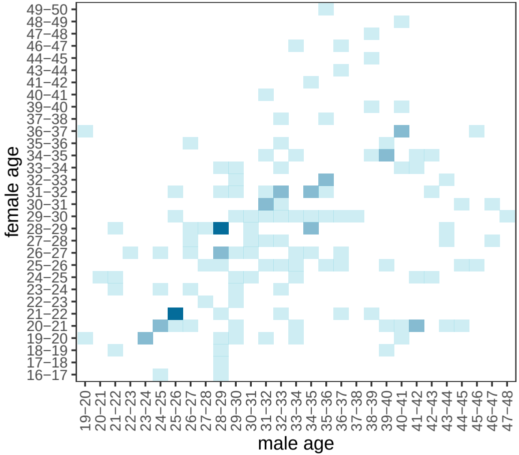
Our approach:



Easy to discretize to any age group resolution by integrating $\boldsymbol{\lambda}(\cdot,\cdot)$

The model

Existing approach:



π_{ab} specific to age discretization; hard to convert to different resolutions

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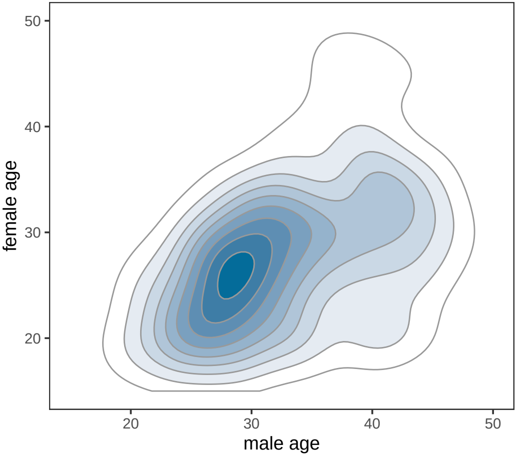

E.g., Source age (marginal) for recipient age $b = \int_{a \in \mathcal{A}} \boldsymbol{\lambda}(a, b) da$

The model

- Assume age pairs $\mathbb{E} = \{(s_{i1}, s_{i2})\}_{i=1}^{N}$ are point patterns from a 2D spatial Poisson process with intensity function $\boldsymbol{\lambda}$.
- Introduce (latent) variable c_i as (unknown) type label for point i:
  - $c_i = 0$: no transmission event
  - $c_i = 1$: M→F transmission
  - $c_i = 2$: F→M transmission

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- Two parts of model:
  1. Spatial process (mixture model on spatial density function)
  2. “Marks” distribution: logit-normal model on the linkage and direction scores

More on the spatial process

Decompose the intensity function $\boldsymbol{\lambda}$) into scale and density functions, and then model the density function as a mixture.

$$\begin{aligned}
\boldsymbol{\lambda}(\cdot) &= \gamma\pi(\cdot) \\
\pi(\cdot) &= \sum_{k\in\{0,1,2\}} p_k \pi_k(\cdot) \\
\pi_k(\cdot) &= \sum_{h=1}^{H_k} w_{kh} \mathrm{BVN}(\cdot; \theta_{kh}, \Sigma_{kh}).
\end{aligned}$$

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Spatial density function π_k:

- "continuous" version of discrete rate π_{ab}'s
- integrates to 1 over the 2D age space
- bivariate normal mixture model with Dirichlet process prior (flexible number of components)

Likelihood function

Construct complete data likelihood given type labels c_i's for paramters $\Theta = \{\gamma, \mathbf{p}, \boldsymbol{\mu}, \sigma_\ell^2, \sigma_d^2, \{(\theta_{kh}, \Sigma_{kh})\}, \{\alpha_k\}\}$.

$$\begin{aligned} L(\Theta; \{\mathbf{x}_i\}, \{c_i\}, \{\mathbf{s}_i\}) &= \gamma^N \frac{e^{-\gamma}}{N!} \prod_{k \in \{0,1,2\}} \prod_{i : c_i = k} p_k f_k(\mathbf{s}_i) \phi_k(\mathbf{x}_i) \\ &= \prod_{i=1:N} \phi(x_{i1} \mid \tilde{\mu}_{\ell,i}, \sigma_\ell^2) \phi(x_{i2} \mid \tilde{\mu}_{d,i}, \sigma_d^2) \\ &\quad \times \gamma^N \frac{e^{-\gamma}}{N!} \prod_{k \in \{0,1,2\}} \prod_{i : c_i = k} \left(p_k \sum_{h=1}^{H_k} w_{kh} \mathrm{BVN}((s_{i1}, s_{i2}); \theta_h, \Sigma_h) \right). \end{aligned}$$

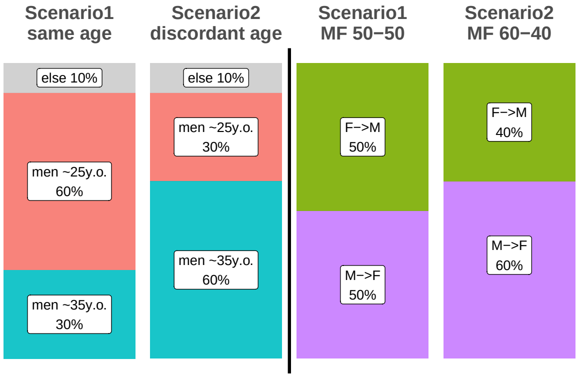
Inference

- Data augmentation approach in a Bayesian inference framework to make it tractable
- Treat unknown type label c_i as latent variables; in each iteration:
    1. sample c_i conditional on everything else
    2. sample parameters Θ conditional on configurations of c_i

Simulation study - setup

Two key problems:

- male source age for young women (∼ 15-24 y.o.)
- proportions of each transmission direction (more MF or more FM?)



Simulation study - setup

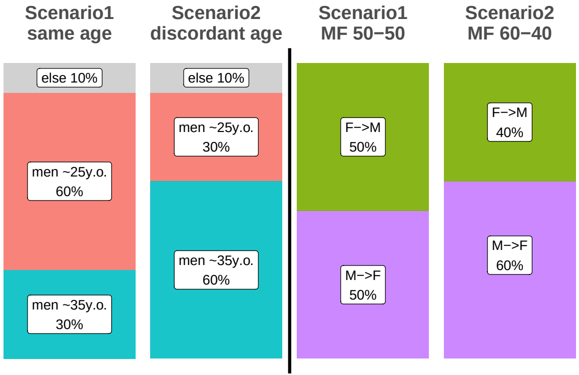
Two key problems:

- male source age for young women ($\sim$ 15-24 y.o.)
- proportions of each transmission direction (more MF or more FM?)

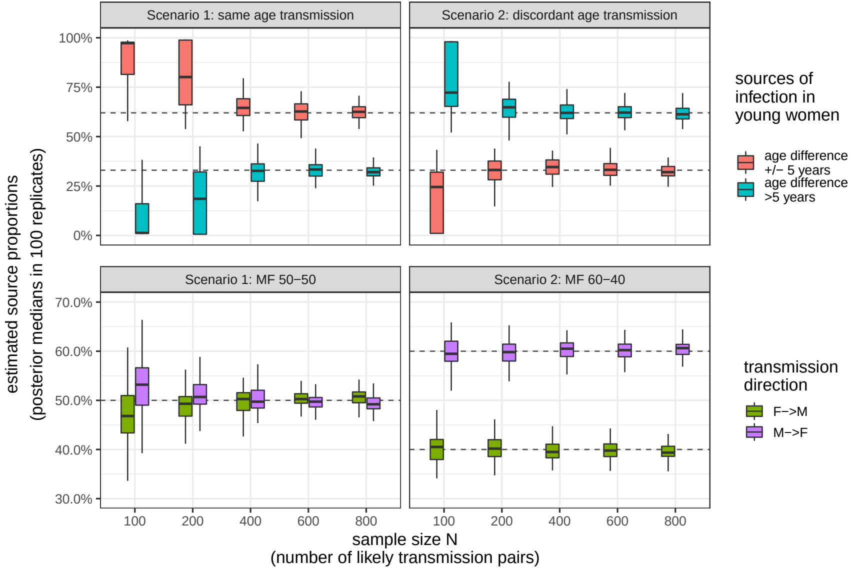
Sample size

$N = 100, 200, 400, 600, 800$;

100 runs for each setup.



Simulation study - results



Simulation study - results commentary

- As sample size N increases, better accuracy at estimating the quantities of interest
- Satisfactory performance with $N = 400$ or 600 already; this is the sample size range of the real data
- For the age source problem, difference between younger/older men proportions is over-estimated when N is small – to be expected with the parsimony nature of the Dirichlet process prior

Real data analysis

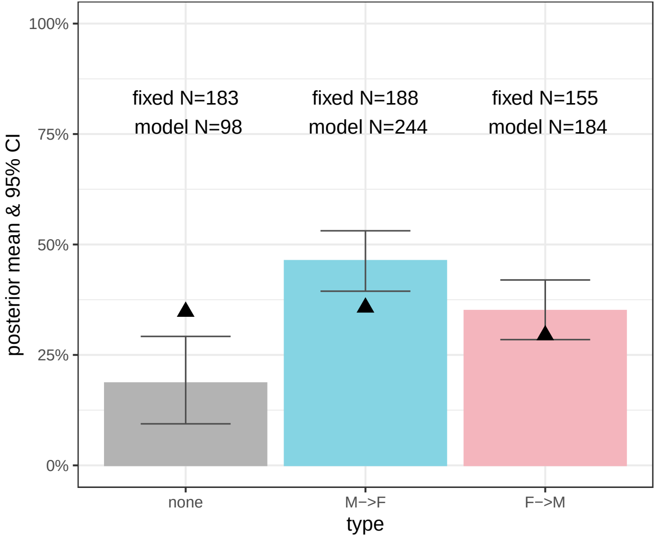
Data overview

- $\sim$ 540 potential transmission pairs, with male and female ages, and linkage and direction scores obtained from phylogenetic analysis
- pre-processing: keep pairs with $\ell_i > 0.2 \rightarrow$ 526 pairs in total

Comparison of our approach with existing approach

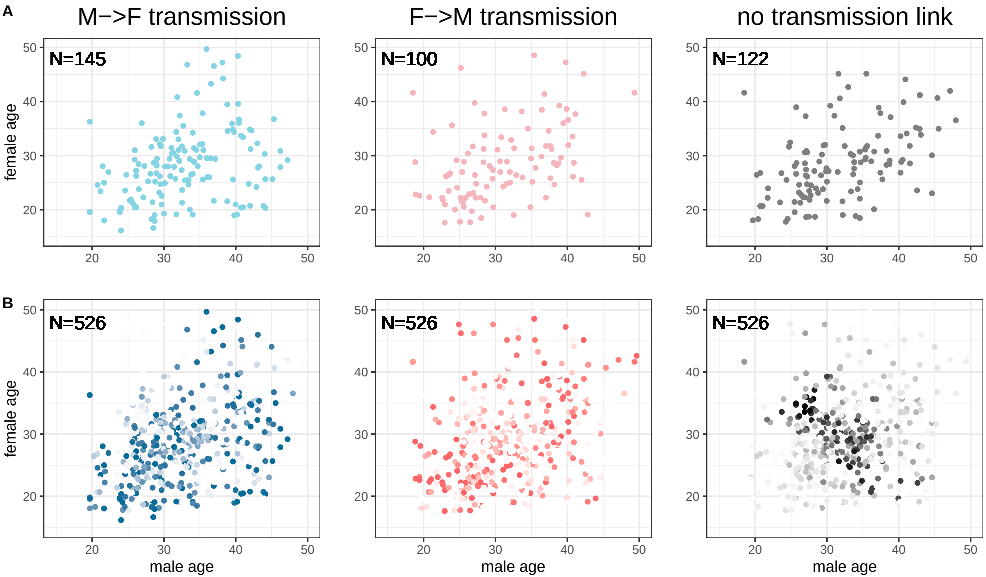
- **“fixed”**: pre-classify with fixed type labels. $\ell_i > 0.6 \rightarrow$ real events; $d_i > 0.5 \rightarrow$ MF transmission, otherwise FM transmissions.
- **“model”**: full model with flexible type labels learned as latent variables.

Real data analysis - transmission type proportions



- ▲ = proportions using fixed thresholds ($\ell_i > 0.6$, $d_i > 0.5 \rightarrow$ M→F, $d_i < 0.5 \rightarrow$ F→M)
- our model includes more data points as transmission events
- yet, ratio between MF and FM directions stays similar

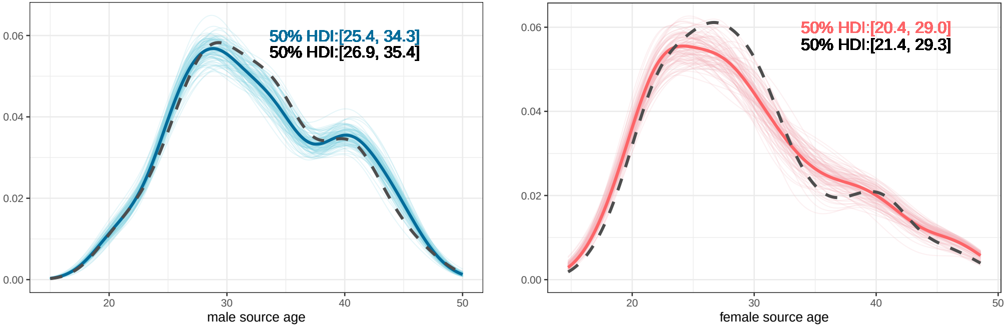
Real data analysis - transmission age structure with uncertainty



Real data analysis - transmission age structure with uncertainty

- Row A: “**fixed**” analysis with pre-classification; Row B: “**model**”-learned flexible type labels, with point color shades representing the posterior probabilities of each data point belonging to each type.
- Similar point patterns are identified by proposed model compared to a fixed-label ad-hoc approach.
- However, our model is able to differentiate the strengths of evidence among different data points and thus leverage and respect data uncertainty.

Real data analysis - source age distribution (overall)

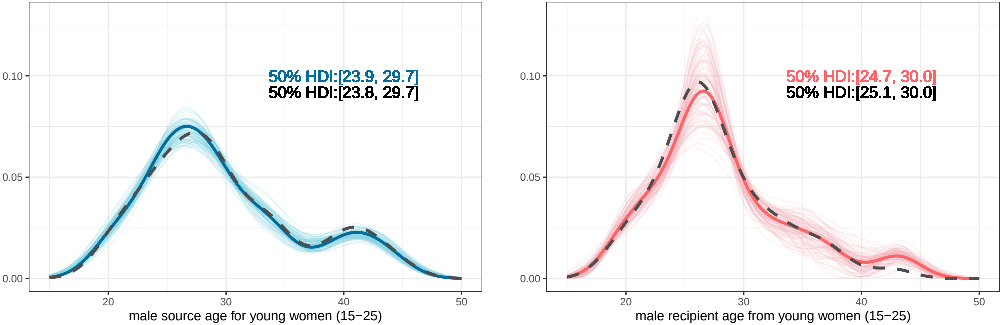


Dark dashed lines: “**fixed**” analysis; solid colored lines: “**model**” with 100 posterior samples, overlaid with posterior mean.

There are more older male sources than older female sources.

Real data analysis - the story of young women (15-25 y.o.)

Whom do they get infected by, and whom do they transmit to?



Notable peak at male source around 40y.o., but younger women transmit much heavily to younger men.

There are “sugar-daddy” transmissions that result in HIV infections in young women (a deviation from typical age assortative behavior).

Real data analysis - the story of young men (15-25 y.o.)

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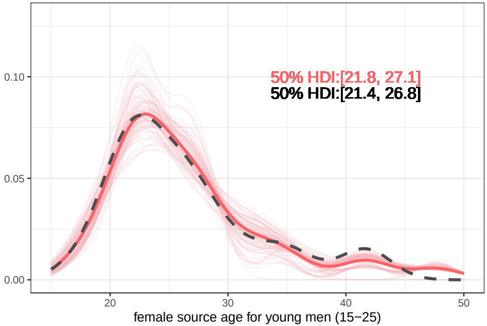

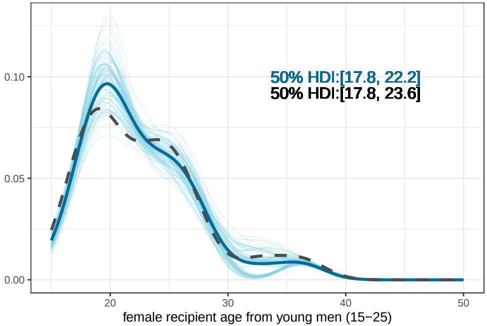

Very different story for young men: mainly get infected by young women, and mainly transmit back to young women. Age assortative behavior.

Summary

- Proposed a novel model for inferring HIV transmission flow between age groups
- Included more data points in the model while considering uncertainty in identifying transmission links/directions
- Utilized spatial process with marks to leverage both phylogenetic information and age structure
- Avoided manual discretization with a continuous construction

Thank you!

Supplement slides

More on the "marks" distributions

Specify a logit-normal model for the phylogenetic scores.

$$
\begin{aligned}
\operatorname{logit}(\ell_i) \mid c_i &\sim N(\tilde{\mu}_{\ell,i}, \sigma_\ell^2), \\
\operatorname{logit}(d_i) \mid c_i &\sim N(\tilde{\mu}_{d,i}, \sigma_d^2),
\end{aligned}
$$

where

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\tilde{\mu}_{\ell,i} &= \mu_\ell \mathbb{1}\left[c_i \neq 0\right], \\
\tilde{\mu}_{d,i} &= \mu_d \mathbb{1}\left[c_i = 1\right] + \mu_{-d} \mathbb{1}\left[c_i = -1\right].
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$\ell_i > 0.5$ → more likely to be real transmission
$d_i > 0.5$ → more likely to be M→F transmission
$d_i < 0.5$ → more likely to be F→M transmission