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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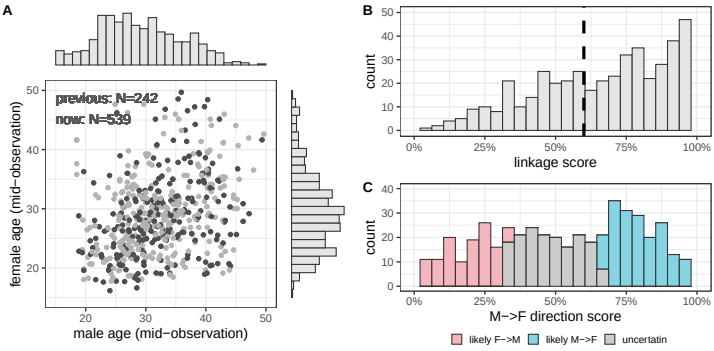
Major objectives

- 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

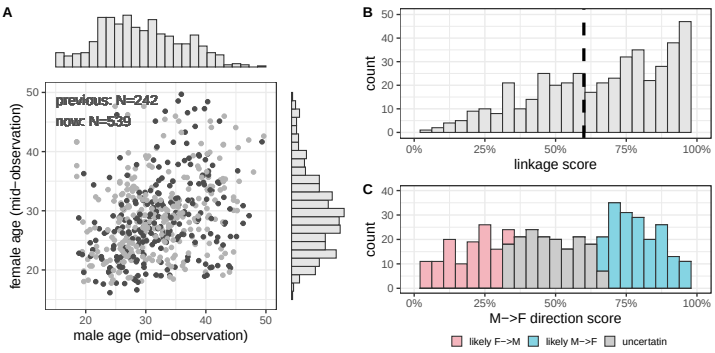


A male and female ages (mid-observation) for each potential transmission pair (s_{i1}, s_{i2})

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

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

The data

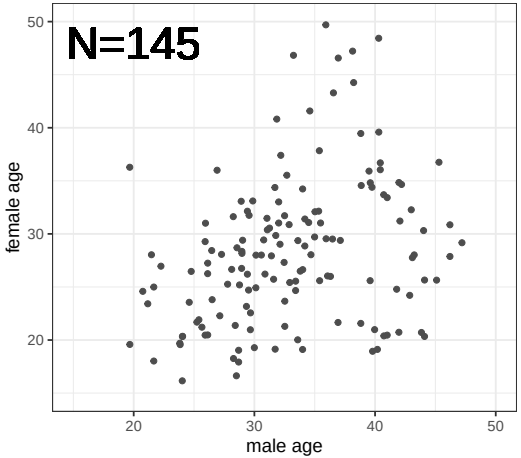


- A male and female ages (mid-observation) for each potential transmission pair (s_{i1}, s_{i2})
- B "posterior" linkage score ℓ_i $(\in [0,1])$
- C "posterior" direction score d_i $(\in [0,1])$

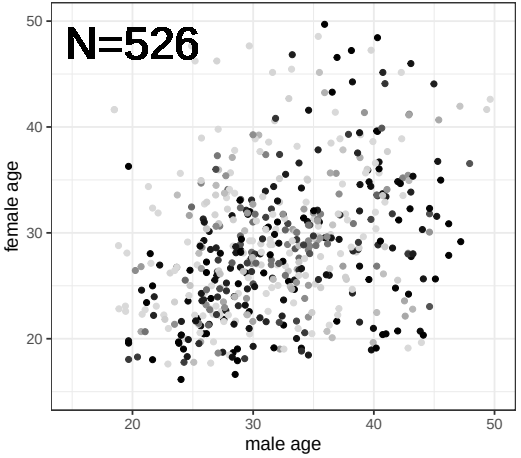
Goal: leverage the phylogenetic scores (ℓ_i and d_i) to infer transmission links and directions

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

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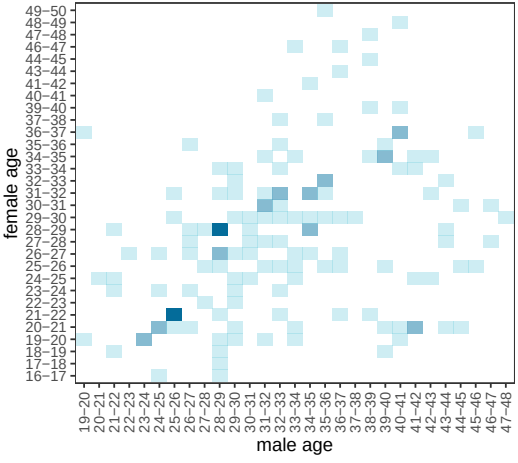
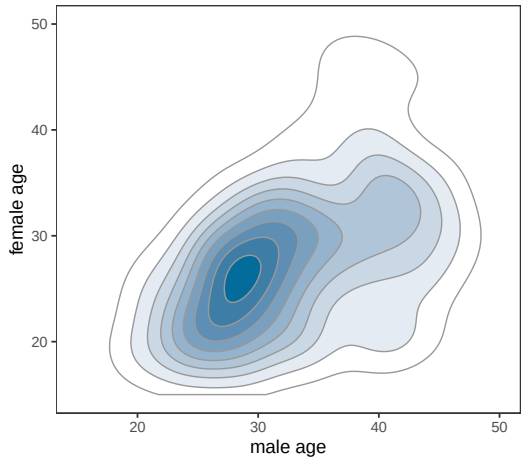


End result: transmission rate π_{ab} between (discrete) age groups a and b

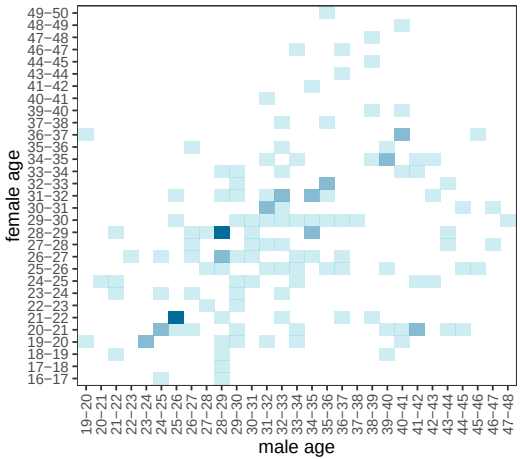
Our approach:



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

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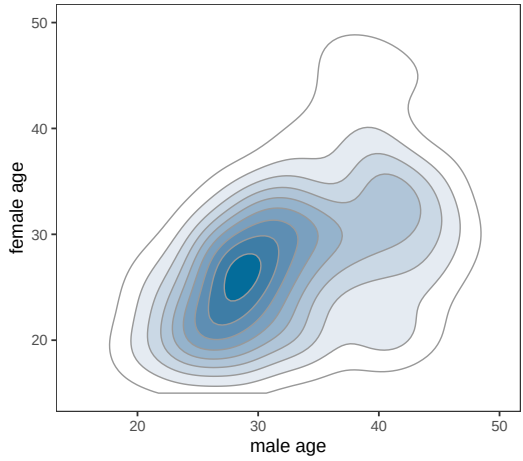

Easy to discretize to any age group resolution by integrating $\boldsymbol{\lambda}(\cdot, \cdot)$

The model

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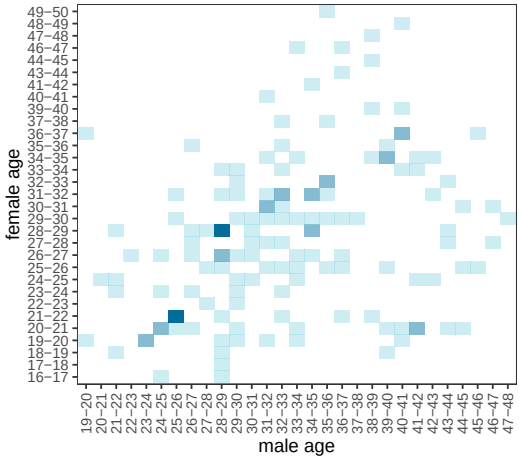

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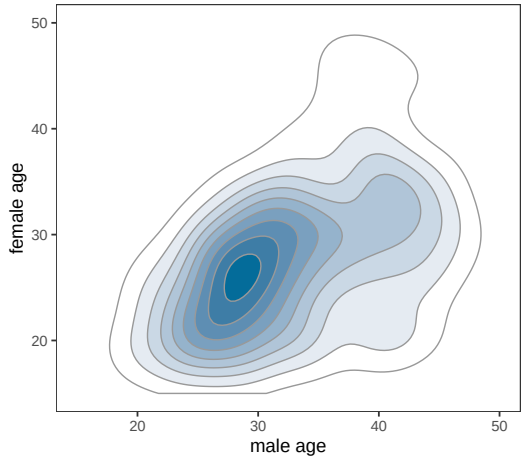

E.g., Source age (marginal) for recipient age $b = \int_{a \in \mathcal{A}} \boldsymbol{\lambda}(a, b) da$

The model

- Assume age pairs $\mathbb{E} = \{(a_{i1}, a_{i2})\}_{i=1}^{N}$ 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$\rightarrow$F transmission
  - $c_i = 2$: F$\rightarrow$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 $\boldsymbol{\lambda}(\cdot)$ 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}).
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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 $\Theta = \{\gamma, \mathbf{p}, \boldsymbol{\mu}, \sigma_\ell^2, \sigma_d^2, \{(\theta_{kh}, \Sigma_{kh})\}, \{\alpha_k\}\}$.

$$L(\Theta; \{\mathbf{x}_i\}, \{c_i\}, \{\mathbf{s}_i\}) = \gamma^N \frac{e^{-\gamma}}{N!} \prod_{k\in\{0,1,2\}} \prod_{i:c_i=k} p_k f_k(\mathbf{s}_i)\phi_k(\mathbf{x}_i)$$

$$= \prod_{i=1:N} \phi(x_{i1} \mid \tilde{\mu}_{\ell,i}, \sigma_\ell^2)\phi(x_{i2} \mid \tilde{\mu}_{d,i}, \sigma_d^2)$$

$$\times \gamma^N \frac{e^{-\gamma}}{N!} \prod_{k\in\{0,1,2\}} \prod_{i:c_i=k} \left(p_k \sum_{h=1}^{H_k} w_{kh} \mathrm{BVN}((s_{i1}, s_{i2}); \theta_h, \Sigma_h) \right).$$

blue terms: spatial process for 2D paired ages
red terms: "marks" distribution for phylogenetic scores

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

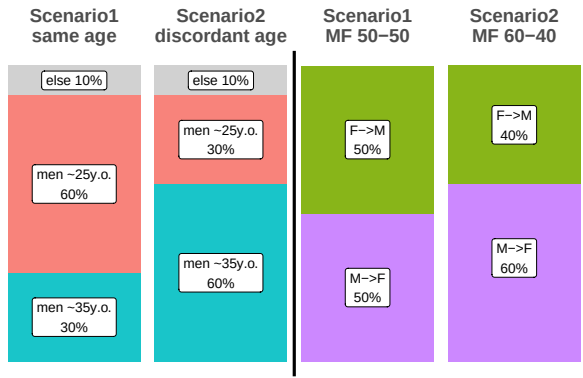
Inference

- 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
- Rationale: can utilize the factorized nice form of "complete data" likelihood, once c_i's are "augmented"

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?)

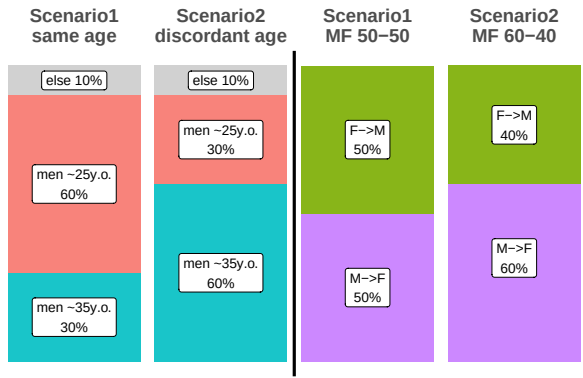


Simulation study - setup

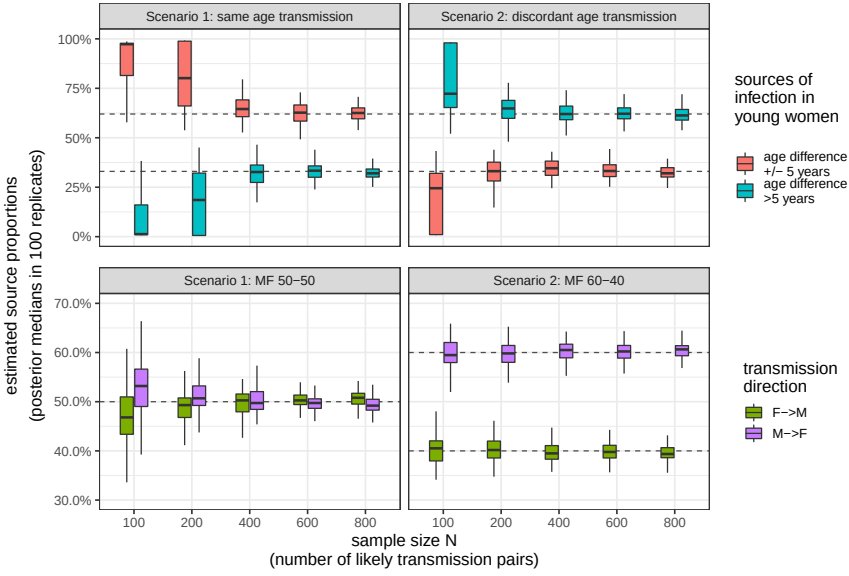
Two key problems:

- 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

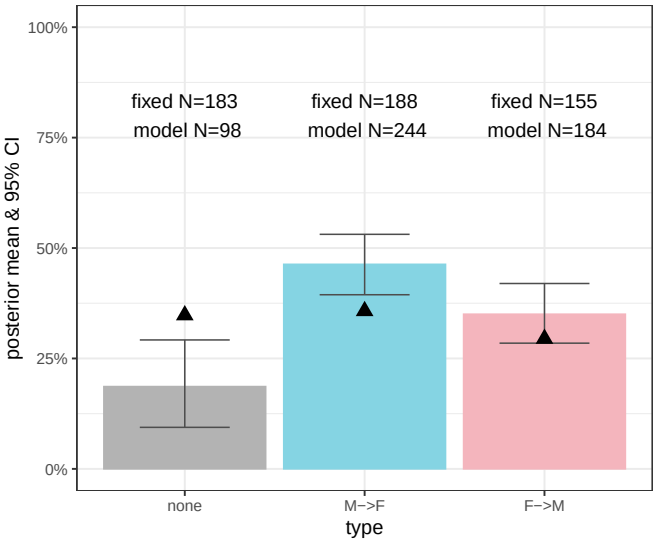
Data overview

- $\sim$ 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

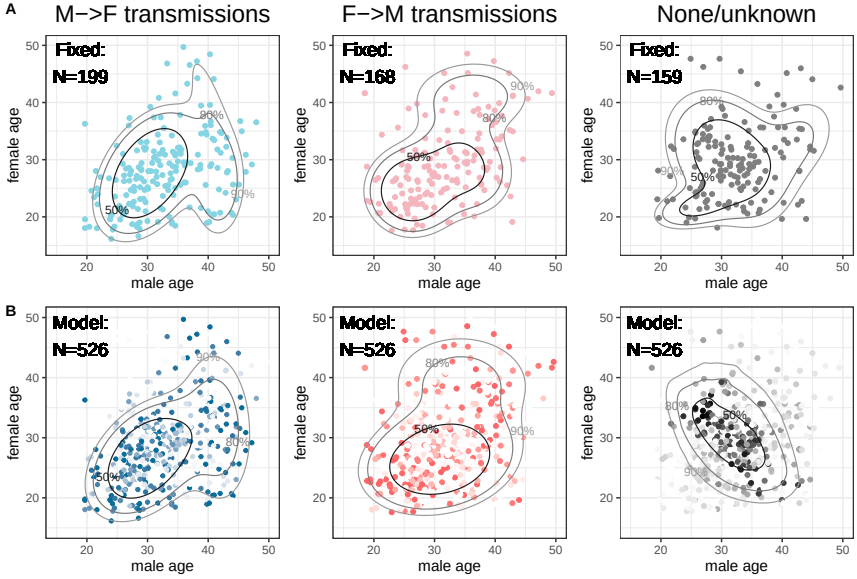
- **"fixed"**: pre-classify with fixed type labels. $\ell_i > 0.6 \rightarrow$ real events; $d_i > 0.5 \rightarrow$ MF transmission, otherwise FM transmissions.
- **"model"**: full model with flexible type labels learned as latent variables.

Real data analysis - transmission type proportions



- ▲ = proportions using fixed thresholds ($\ell_i > 0.6$, $d_i > 0.5 \rightarrow$ M$\rightarrow$F, $d_i < 0.5 \rightarrow$ F$\rightarrow$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.
- Contour lines: 50%, 80% and 90% highest-density regions for point patterns (MAP estimates of spatial process).
- Similar point patterns are identified by proposed model compared to a fixed-label ad-hoc approach.

Real data analysis - transmission age structure with uncertainty

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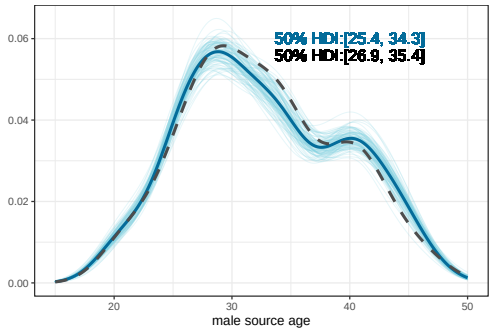
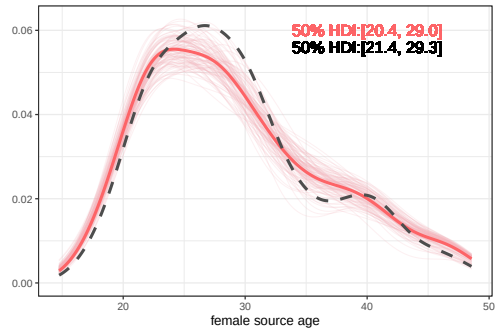
- Contour lines: 50%, 80% and 90% highest-density regions for point patterns (MAP estimates of spatial process).
- Similar point patterns are identified by proposed model compared to a fixed-label ad-hoc approach.
  - Overall age assortative transmissions, but...
  - Older men transmit to a wide range of female age groups (both young and old) and get infected by slightly older women (still wide range).
  - Much more old-men-to-young-women transmissions than old-women-to-young-men.
  - No clear patterns for the "none/unknown" type – can be considered as background noise.

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.
- Contour lines: 50%, 80% and 90% highest-density regions for point patterns (MAP estimates of spatial process).
- 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)



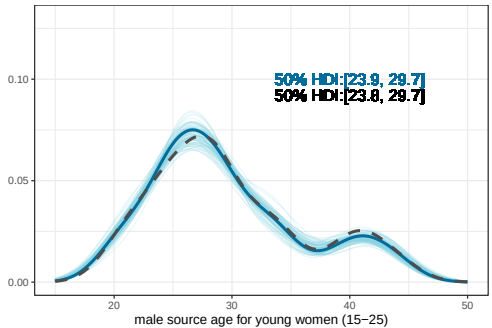


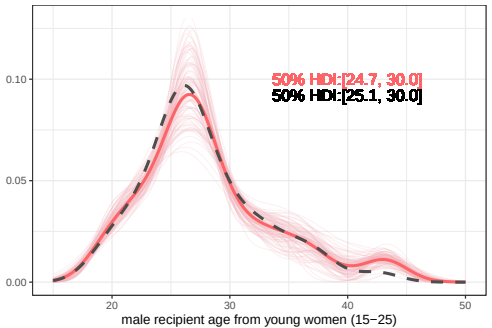
Dark dashed lines: "**fixed**" analysis; solid colored lines: "**model**" with 100 posterior samples, overlaid with posterior mean.

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?



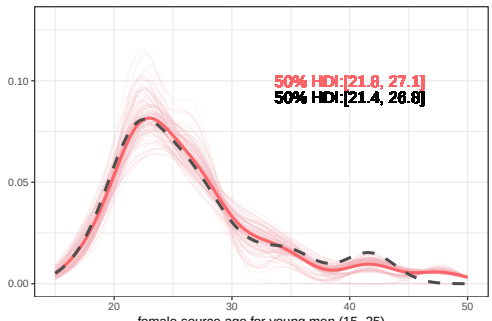


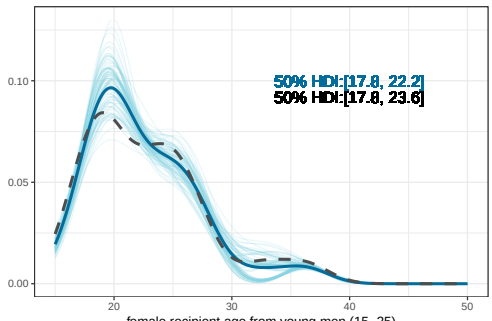
Notable peak at male source around 40y.o., but younger women transmit more to younger men.

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.)

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





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.

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

where

$$\begin{aligned}\tilde{\mu}_{\ell,i} &= \mu_\ell \mathbb{1}\left[c_i \neq 0\right],\\ \tilde{\mu}_{d,i} &= \mu_d \mathbb{1}\left[c_i = 1\right] + \mu_{-d} \mathbb{1}\left[c_i = -1\right].\end{aligned}$$

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$\ell_i > 0.5 \rightarrow$ more likely to be real transmission
$d_i > 0.5 \rightarrow$ more likely to be M$\rightarrow$F transmission
$d_i < 0.5 \rightarrow$ more likely to be F$\rightarrow$M transmission