

Reconstructing transmission trees from genetic data: a Bayesian approach

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June 7, 2012

Purpose of the model

We seek a probabilistic model allowing to reconstruct the transmission tree of a disease outbreak based on RNA/DNA sequences sampled at given time points. We consider a single pathogen and genetic sequence per infection. The generation time is assumed to follow a known distribution. The transmission tree and the mutation rates are the elements we want to infer.

Data and parameters

Data

For each patient $i = 1, \dots, n$ we note the data:

- s_i : the genetic sequence obtained for patient i .
- t_i : the collection time for s_i (time is considered as a discrete variable).

Augmented data

Augmented data are noted using capital latin letters:

- T_i^{inf} : time at which patient i has been infected.
- A_i : the closest observed ancestor of i in the infection tree; $A_i = j$ indicates that j has infected i , either directly, or with one or several intermediate generations, which were unobserved.
- K_i : an integer ≥ 1 indicating how many generations separate A_i and i : $K_i = 1$ indicates that A_i infected i ; $K_i = 2$ indicates that j has infected an unobserved individual, who has in turn infected i .
- T_i^{ini} : time at which A_i caused the initial infection of the lineage of i . For $K_i = 1$, $T_i^{inf} = T_i^{ini}$.

As a first simple approach, K_i could be set to 1 for all i , hence assuming that the whole outbreak was observed.

Functions

We use the following functions of the data/augmented data:

- $d(i, j)$: the number of transitions between s_i and s_j .
- $g(i, j)$: the number of transversions between s_i and s_j .
- $l(i, j)$: the number of nucleotide positions typed in both s_i and s_j .
- $w(\Delta_t)$: generation time distribution (likelihood function for a secondary infection occurring Δ_t unit times after the primary infection); we assume $w(\Delta_t) = 0$ for $\Delta_t \leq 0$; while not a requirement in theory, in practice this function will be truncated at a value Δ_{max} so that $w(\Delta_t) = 0$ if $\Delta_t \geq \Delta_{max}$.

Parameters

Parameters are indicated using greek letters:

- μ_1 : rates of transitions, given per site and unit time (likely day).
- μ_2 : rate of transversions, parametrised as $\mu_2 = \kappa\mu_1$ to account for the correlation between the two rates.

Model

This model assumes that cases are ordered by increasing infection dates ($T_i^{inf} \leq T_{i+1}^{inf}$). The posterior distribution is proportional to the joint distribution:

$$p(\{s_i, t_i, T_i^{inf}, T_i^{ini}, A_i, K_i\}_{(i=1, \dots, n)}, w, \mu_1, \kappa) \quad (1)$$

$$= p(\{s_i, t_i, T_i^{inf}, T_i^{ini}, A_i, K_i\}_{(i=1, \dots, n)} | w, \mu_1, \kappa) \times p(w, \mu_1, \kappa) \quad (2)$$

where the first term is the likelihood of observed and augmented data, and the second, the prior. The likelihood can be decomposed as:

$$p(\{s_i, t_i, T_i^{inf}, T_i^{ini}, A_i, K_i\}_{(i=1, \dots, n)} | w, \mu_1, \kappa) \quad (3)$$

$$= \prod_{i=2}^n p(s_i, t_i, T_i^{inf}, T_i^{ini}, A_i, K_i | \{s_k, t_k, T_k^{inf}, T_k^{ini}, A_k, K_k | w, \mu_1, \kappa\}_{(k=1, \dots, i-1)}) \quad (4)$$

$$= \prod_{i=2}^n p(s_i, t_i, T_i^{inf}, T_i^{ini}, A_i, K_i | s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa) \quad (5)$$

The term $p(s_1, t_1, T_1^{inf}, T_1^{ini}, A_1, K_1 | w, \mu_1, \kappa)$ is the probability of the first infection, treated as a constant. This may be modified if we explicitly model infections from outside the system. The term for case i ($i = 2, \dots, n$) is:

$$p(s_i, t_i, T_i^{inf}, T_i^{ini}, A_i, K_i | s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa) \quad (6)$$

which can be decomposed into:

$$\begin{aligned}
& p(s_i|t_i, T_i^{inf}, T_i^{ini}, A_i, K_i, s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa) \\
& \times p(t_i|T_i^{inf}, T_i^{ini}, A_i, K_i, s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa) \\
& \times p(T_i^{inf}|T_i^{ini}, A_i, K_i, s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa) \\
& \times p(T_i^{ini}|A_i, K_i, s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa) \\
& \times p(A_i, K_i|s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa)
\end{aligned} \tag{7}$$

$$\begin{aligned}
& = \underbrace{p(s_i|t_i, T_i^{ini}, A_i, s_{A_i}, t_{A_i}, \mu_1, \kappa)}_{\Omega_i^1} \\
& \times \underbrace{p(t_i|T_i^{inf}, w)p(T_i^{inf}|K_i, T_i^{ini}, w)p(T_i^{ini}|T_{A_i}^{inf}, w)}_{\Omega_i^2} \\
& \times \underbrace{p(A_i, K_i|s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa)}_{\Omega_i^3}
\end{aligned} \tag{8}$$

where Ω_i^1 is the genetic likelihood, Ω_i^2 if the epidemiological likelihood (derived from W&T), and Ω_i^3 are priors for the augmented data A_i and K_i .

Assuming that there is no within-host diversity, Ω_i^1 is computed as:

$$\underbrace{\mathcal{B}(d(i, A_i)|(t_i - t_{A_i})l(i, A_i), \mu_1)}_{\text{transitions}} \times \underbrace{\mathcal{B}(g(i, A_i)|(t_i - t_{A_i})l(i, A_i), \kappa\mu_1)}_{\text{transversions}} \tag{9}$$

if $t_{A_i} \leq T_i^{ini}$, and as:

$$\underbrace{\mathcal{B}(d(i, A_i)|(t_{A_i} - T_i^{ini} + t_i - T_i^{ini})l(i, A_i), \mu_1)}_{\text{transitions}} \times \underbrace{\mathcal{B}(g(i, A_i)|(t_{A_i} - T_i^{ini} + t_i - T_i^{ini})l(i, A_i), \kappa\mu_1)}_{\text{transversions}} \tag{10}$$

otherwise; $\mathcal{B}(\cdot|n, p)$ is the probability mass function of a Binomial distribution with n draws and a probability p .

Ω_i^2 is determined by the (known) distribution of the generation time, and the collection and infection dates:

$$\begin{aligned}
\Omega_i^2 & = p(t_i|T_i^{inf}, w) \times p(T_i^{inf}|K_i, T_i^{ini}, w) \times p(T_i^{ini}|T_{A_i}^{inf}, w) \\
& = w(t_i - T_i^{inf}) \times w^{(K_i-1)}(T_i^{inf} - T_i^{ini}) \times w(T_i^{ini} - T_{A_i}^{inf})
\end{aligned} \tag{11}$$

with $\mathbf{1}$ the indicator function and $w^{(k)} = \underbrace{w * w * \dots * w}_{k \text{ times}}$, where $*$ denotes the convolution operator,

defined, for two discrete distributions a and b , by $(a * b)(t) = \sum_{u=-\infty}^{+\infty} a(t-u)b(u)$. By convention, $w^{(0)}(t) = 1$. The first term assumes that the probability of sequencing an isolate at time t_i is proportional to the infectiousness of the host at this time. The second term is an extension of Wallinga & Teunis's model for $K_i - 1$ unobserved intermediate infections. The third term is a strict application of Wallinga & Teunis's model for the initial infection.

The term Ω_i^3 can be rewritten as:

$$\begin{aligned}\Omega_i^3 &= p(A_i, K_i | s_{A_i}, t_{A_i}, T_{A_i}^{inf}, T_{A_i}^{ini}, w, \mu_1, \kappa) \\ &= p(A_i)p(K_i)\end{aligned}\tag{12}$$

as the different components are independent. $p(A_i)$ is the prior on ancestries, set to $1/(n-1)$. $p(K_i)$ is the prior on the number of unobserved transmission steps. This is given by a binomial distribution of parameter π , which is the proportion of observed (sampled) cases in the outbreak. If we assume that the entire outbreak has been sampled, this would be set to $p(K_i) = \mathbf{1}_{\{K_i=1\}}$.