A model of MRSA transmission incorporating epidemiological and genetic data

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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 quantities we want to infer.

Data and parameters

Data

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

- s_i: the genetic sequence obtained for patient i
- t_i: the collection time for s_i
- $d_{i,j}$: the number of transitions between s_i and s_j
- $g_{i,j}$: the number of transversion between s_i and s_j
- $l_{i,j}$: the number of loci typed in both s_i and s_j
- $w(\Delta_t)$: likelihood that a secondary infection occurs Δ_t unit times after the primary infection; we assume $w(\Delta_t) = 0$ for $\Delta_t \leq 0$.

Augmented data

Augmented data are noted using capital latin letters:

- T_i^{inf}: time at which patient i has been infected
- A_i: the infector of i; $A_i = j$ indicates that j has infected i

Parameters

Parameters are indicated using greek letters:

- μ_1, μ_2: rates of transitions and transversions.
- μ_2: rate of transversions, assumed proportional to μ_1 so that $\mu_2 = \kappa\mu_1$.

Model

The posterior distribution for patient i is proportional to the joint distribution:

$$p(s_i, t_i, T_i^{inf}, A_i, w, \mu_1, \mu_2) \tag{1}$$

which can be decomposed in:

$$\begin{aligned} & p(s_i|t_i, T_i^{inf}, A_i, w, \mu_1, \mu_2)p(t_i, T_i^{inf}, A_i, w, \mu_1, \mu_2) && (2)\\ = \; & p(s_i|t_i, T_i^{inf}, A_i, w, \mu_1, \mu_2)p(T_i^{inf}|t_i, A_i, w, \mu_1, \mu_2)p(t_i, A_i, w, \mu_1, \mu_2) && (3)\\ = \; & \underbrace{p(s_i|t_i, T_i^{inf}, A_i, \mu_1, \mu_2)}_{\Omega_1}\underbrace{p(T_i^{inf}|A_i, w)}_{\Omega_2}\underbrace{p(t_i, A_i, w, \mu_1, \mu_2)}_{\Omega_3} && (4)\end{aligned}$$

Where Ω_1 is the genetic likelihood, Ω_2 if the epidemiological likelihood (from W&T), and Ω_3 is mixture of constants and priors.

Ω_1 is computed as:

$$\underbrace{\mathcal{P}\left(d_{i,A_i}|(t_i - t_{A_i})l_{i,A_i}\mu_1\right)}_{\text{transitions}} \times \underbrace{\mathcal{P}\left(g_{i,A_i}|(t_i - t_{A_i})l_{i,A_i}\mu_2\right)}_{\text{transversions}}$$

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

$$\underbrace{\mathcal{P}\left(d_{i,A_i}|(t_{A_i} - T_i^{inf} + t_i - T_i^{inf})l_{i,A_i}\mu_1\right)}_{\text{transitions}} \times \underbrace{\mathcal{P}\left(g_{i,A_i}|(t_{A_i} - T_i^{inf} + t_i - T_i^{inf})l_{i,A_i}\mu_2\right)}_{\text{transversions}}$$

otherwise, with $\mathcal{P}(.|\lambda)$ being the density of a Poisson distribution of parameter λ.

Ω_2 is defined by the (known) distribution of the generation time:

$$\Omega_2 = \frac{w(t_i - t_{A_i})}{\sum_{k=1}^{n} w(t_i - t_{A_k})}$$

The term Ω_3 can be rewritten:

$$\begin{aligned} \Omega_3 &= p(t_i, A_i, w, \mu_1, \mu_2) && (5)\\ &= p(t_i, w)p(A_i, \mu_1, \mu_2) && (6)\\ &= p(t_i, w)p(A_i)p(\mu_1)p(\kappa) && (7)\end{aligned}$$

as the different components are independent. $p(t_i, w)$ is a constant and does not need to be known to sample from (1). $p(A_i)$ is the prior on ancestries, set to $1/(n-1)$. $p(\mu_1)$ and $p(\kappa)$ are the priors for the mutations rates.