A model of MRSA transmission incorporating epidemiological and genetic data

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April 30, 2012

Observed data (Y)

For each patient $i = 1, \ldots, N$ admitted to one of the wards in the study period, we denote

- w_i the ward where the patient is admitted (1 for adult ICU, 2 for paediatric ICU)
- k_i the number of times the patient is admitted (1 if no readmission)
- A_i and D_i vectors containing the times of admission and discharge from the ward
- P_i and N_i vectors containing the times of positive and negative swabs (positive defined as any of the samples taken is positive ; negative defined as all samples taken are negative).
- p_i and n_i the size of those vectors, ie the number of positive and negative swabs.
- $S_i = \{s_i^1, \ldots, s_i^{m_i}\}$ a set of m_i genetic sequences of MRSA isolated in patient i at times $T_i = \{t_i^1, \ldots, t_i^{m_i}\}$; collection dates T_i are ordered so that $t_i^k \leq t_i^{k+1}$.
- $d_{s_i^k, s_j^q}$ the number of transitions between sequence k of patient i and sequence q of patient j.
- $g_{s_i^k, s_j^q}$ the number of transversions between sequence k of patient i and sequence q of patient j.
- $l_{s_i^k, s_j^q}$ the number of typed nucleotides common to sequences s_i^k and s_j^q.

Augmented (unobserved) data (Z)

For each patient i admitted to one of the wards in the study period, we denote

- C_i the colonisation time (we assume no supercolonisations)
- E_i the time of end of colonisation.

We denote $I_w(t) = \sum_{i=1}^{N} \mathbf{1}_{\{w_i = w\}} \mathbf{1}_{\{C_i \leq t < E_i\}} \sum_{l=1}^{k_i} \mathbf{1}_{\{A_i[l] \leq t < D_i[l]\}}$ the number of patients in ward w who are colonized at time t.

Parameters (θ)

Parameters of the model are:

- β a 2 by 2 matrix containing $\beta_{i \leftarrow j}$, the person to person transmission rate from ward j to ward i
- $\beta_{\text{ward} \leftarrow \text{out}}$ the force of infection from outside the 2 wards applied to patients in the wards
- $\beta_{\text{out} \leftarrow \text{out}}$ the force of infection from outside the 2 wards applied to patients when they are not in the wards (eg inbetween two admissions)
- Sp the specificity of the testing, ie the probability of getting a negative test given uncolonized (assumed 100%)
- Se the sensitivity of the testing, ie the probability of getting a positive test given colonized
- π the probability of being already colonized at first admission
- μ and σ the mean and standard deviation of the duration of colonization.
- ν_1 and ν_2 the rate of transitions ($A \leftrightarrow G$ and $C \leftrightarrow T$) and transversions (other changes) of the DNA sequences. In practice, we will use $\nu_2 = \kappa \nu_1$ with $\kappa \in \mathbb{R}_+$.
- α_i is the within host 'pathogenic diversity', defined as the number of pathogenic lineages infecting patient i; all lineages are supposed to be as likely to be have been sequenced.

Statistical Model

In the following, $\mathbf{1}_{\{.\}}$ denotes the indicator function, defined by $\mathbf{1}_{\{X\}} = 1$ if X is true, and 0 otherwise.

The joint density of the observed data, the augmented data, and the model parameters is:

$$P(\boldsymbol{Y}, \boldsymbol{Z}, \boldsymbol{\theta}) = P(\boldsymbol{Y}|\boldsymbol{Z})\, P(\boldsymbol{Z}|\boldsymbol{\theta})\, P(\boldsymbol{\theta})$$

where $P(\boldsymbol{Y}|\boldsymbol{Z})$, $P(\boldsymbol{Z}|\boldsymbol{\theta})$ and $P(\boldsymbol{\theta})$ refer to the observation level, the transmission level and the prior level respectively.

Observation level

The observation level ensures that the observed data are consistent with the augmented data:

$$\begin{aligned} P(\boldsymbol{Y}|\boldsymbol{Z}) = \prod_{i=1}^{N} & \mathbf{1}_{\{C_i < E_i\}} \\ & \prod_{j=1}^{p_i} \left(\left(\mathbf{1}_{\{P_i[j] < C_i\}} + \mathbf{1}_{\{P_i[j] \geq E_i\}} \right) \times (1 - Sp) + \mathbf{1}_{\{C_i \leq P_i[j] < E_i\}} \times Se \right) \\ & \prod_{k=1}^{n_i} \left(\left(\mathbf{1}_{\{N_i[k] < C_i\}} + \mathbf{1}_{\{N_i[k] \geq E_i\}} \right) \times Sp + \mathbf{1}_{\{C_i \leq N_i[k] < E_i\}} \times (1 - Se) \right) \end{aligned}$$

The first line describes the positive tests, which can be either false positives (first term) or true positives (second term). The second line describes the negative tests, which can be either true negatives (first term) or false negatives (second term).

Transmission level (discrete time version ; time step = half day or day ?)

In the discrete version $A_i[k]$ is the first time step where individual i is in hospital (for his/her k_{th} stay), and $D_i[k]$ is the first time step where he/she is out of hospital (after his/her k_{th} stay). Individual i can transmit staph aureus from time step C_i to time step $E_i - 1$.

$$P\left(\boldsymbol{Z}|\boldsymbol{\theta}\right) = \prod_{i=1}^{N} \left(\Omega_i^{(1)} + \Omega_i^{(2)}\right) \times \left(\Phi_{\mu,\sigma}\left(E_i - C_i + 0.5\right) - \Phi_{\mu,\sigma}\left(E_i - C_i - 0.5\right)\right)$$

where $\Phi_{\mu,\sigma}$ is the cumulative density function of a Gamma distribution with mean μ and standard deviation σ (we assume that the duration of colonisation is Gamma distributed), and:

$$\begin{aligned}
\Omega_i^{(1)} &= \pi \times \mathbf{1}_{\{C_i < A_i[1]\}} \\
\Omega_i^{(2)} &= (1-\pi) \times \mathbf{1}_{\{C_i \geq A_i[1]\}} \times e^{-\sum_{t=A_i[1]}^{C_i - 1} \lambda_i(t)} \left(1 - e^{-\lambda_i(C_i)}\right) \eta_i\left(C_i\right)
\end{aligned}$$

$\Omega_i^{(1)}$ is the probability that individual i is colonized before his/her first admission in the wards ; $\Omega_i^{(2)}$ is the probability that individual i is colonized after his/her first admission in the wards. $\lambda_i\left(t\right)$ is the force of transmission applied to individual i at time t. It is equal to:

$$\begin{aligned}
\lambda_i^{(t)} &= \sum_{w=1}^{2} \beta_{w_i \leftarrow w} I_w\left(t\right) + \beta_{\text{ward}\leftarrow\text{out}} \text{ if individual } i \text{ is in a ward at time } t \\
&= \beta_{\text{out}\leftarrow\text{out}} \text{ otherwise}
\end{aligned}$$

$\eta_i\left(C_i\right)$ is the probability of observing sequences S_i given the possible contamination sources at time C_i.

It is equal to:

$$\begin{aligned}
\eta_i\left(C_i\right) &= \frac{\sum_{j \text{ colonized and in a ward at time } C_i} \beta_{w_i \leftarrow w_j} f_{i \leftarrow j} + \beta_{\text{ward}\leftarrow\text{out}} f_{\text{i,ward}\leftarrow\text{out}}}{\sum_{j \text{ colonized and in a ward at time } C_i} \beta_{w_i \leftarrow w_j} + \beta_{\text{ward}\leftarrow\text{out}}} \text{ if individual } i \text{ is in a ward at time } C_i \\
&= f_{\text{i,out}\leftarrow\text{out}} \text{ otherwise}
\end{aligned}$$

$f_{i,j}$ is the probability of observing sequences s_i and s_j at respective time steps t_i and t_j given that individual j infected individual i (see next section on the genetic likelihood). Similarly, $f_{\text{i,ward}\leftarrow\text{out}}$ and $f_{\text{i,out}\leftarrow\text{out}}$ are the probability of observing sequence s_i at time t_i given that individual i was infected from outside the wards while he was in or outsite hospital respectively.

Genetic likelihood

Ancestors and lineages

We say that B is an *ancestor* of A if and only if there is a path leading from B to A in the directed acyclic graph (DAG) representing the genealogy of A. Put simply, B is an ancestor of A if A derives

from B. We will say that B is the *most recent ancestor* (MRA) of A if there is no older ancestor of A in the considered set. A *lineage* is defined as a set of (temporally ordered) individuals $\{x_1, ..., x_n\}$ so that x_i is the MRA of x_{i+1} for $i = 1, \ldots, n-1$. For instance, in the lineage $(D \to C \to B \to A)$, B, C, D are all ancestors of A and B is the MRA of A. The genetic likelihood of A will be defined as the probability of the observed mutations between B and A, and is not conditional on previous ancestries.

Genetic likelihood of an infection

The genetic likelihood of the infection of i by j (noted $i \leftarrow j$) relies on how likely it is to observe the genetic differences between sequences in S_i and their most recent ancestors (MRA) in S_j. We first focus on the probability of observing a given sequence S_i^k in i given that j infected i. We will note $\phi(s_i^k, s_j^q)$ the probability that s_j^q is an ancestor of s_i^k, defined as:

$$\phi(s_i^k, s_j^q) = \mathbf{1}_{\{t_i^k \geq t_j^q\}} \times \underbrace{\mathcal{P}\left(d_{s_i^k, s_j^q} | \nu_1 (t_i^k - t_j^q) l_{s_i^k, s_j^q}\right)}_{\text{transitions}} \times \underbrace{\mathcal{P}\left(g_{s_i^k, s_j^q} | \nu_2 (t_i^k - t_j^q) l_{s_i^k, s_j^q}\right)}_{\text{transversions}}$$

with:

- $\mathbf{1}_{\{\text{statement}\}}$: indicator function, 1 if 'statement' is true, 0 otherwise
- $\mathcal{P}(.|\lambda)$: the probability mass function of a Poisson distribution with parameter λ

. The three terms respectively correspond to the indicator function ensuring that s_j^q is older than s_i^k, the probability of the observed transitions ($d_{s_i^k, s_j^q}$), and the probability of the observed transversions ($g_{s_i^k, s_j^q}$).

We are now interested in $\xi(s_i^k, s_j^q)$,the probability that the sequence s_j^q is the MRA of s_i^k. This requires two elements: i) that s_j^q is an ancestor of s_i^k, and ii) that no ancestor of s_i^k has been collected after s_j^q. This is given by:

$$\xi(s_i^k, s_j^q) = \underbrace{\phi(s_i^k, s_j^q)}_{s_j^q \text{ ances. of } s_i^k} \times \prod_{r=q+1}^{m_j} \underbrace{(1 - \phi(s_i^k, s_j^r))}_{s_j^r \text{ not ances. of } s_i^k}$$

The genetic likelihood also needs to account for the possibility that no ancestor of s_i^k has been isolated and sequenced in S_j. Assuming that all lineages are as likely to have been sequenced, the probability $\gamma(s_i^k, S_j)$ that the sampled S_j contains at least one ancestor of s_i^k is:

$$\gamma(s_i^k, S_j) = 1 - \mathcal{B}\left(0 | \sum_{j=1}^{m_j} \mathbf{1}_{\{t_i^k \geq t_j^q\}}, 1/\alpha_i\right)$$

with:

- $\mathcal{B}(.|n, p)$: probability mass function of the Binomial distribution with n draws and probability p
- $\sum_{j=1}^{m_j} \mathbf{1}_{\{t_i^k \geq t_j^q\}}$: number of isolates sequenced in patient j and collected before the sequence s_i^k
- α_i: number of lineages in patient j

The probability $p(s_i^k|S_j, i \leftarrow j)$ of observing the sequence s_i^k given that patient j infected patient i can now be computed as:

$$p(s_i^k|S_j, i \leftarrow j) = (\underbrace{\gamma(s_i^k, S_j)}_{\text{ances. in } S_j} \times \underbrace{\sum_{q=1}^{m_j} \xi(s_i^k, s_j^q)}_{\text{prob. MRA for each } S_j}) + \underbrace{1 - \gamma(s_i^k, S_j)}_{\text{ances. not sampled}}$$

The probability of observing the set of sequences S_i given that j infected i is simply computed as the product over all sequences in S_i:

$$p(S_i|S_j, i \leftarrow j) = \prod_{k=1}^{m_i} p(s_i^k|S_j, i \leftarrow j)$$

For the sake of simplicity, we shall refer to this quantity as $f_{i,j}$.

Assumptions of the model

The genetic model makes a few key assumptions:

- different types of mutations happen independently
- all lineages within a host are as likely to have been sampled and sequenced; when lineages have different within-host population sizes, this may still be ensured by extensive sequencing where only new haplotypes are retained; this assumption could be relaxed by parametrizing α_i as distributions.
- all lineages present in a host are transmitted during a new infection; models excplicitly incorporating possible losses of diversity during the sampling process will be much more complex, and it will likely be difficult to disentangle this from sampling biases.

Prior level

For all model parameters, independent prior distributions were chosen:

- uniform on $[0, 1]$ for Sp, Se, and π,
- flat exponential (mean 1000) for all other parameters.

Parameter Estimation

A Markov chain Monte Carlo (MCMC) method was used to sample the joint posterior distribution $P(\boldsymbol{Y}, \boldsymbol{Z}, \boldsymbol{\theta})$. Sp, Se and π were updated using the Gibbs sampler, and all other parameters using a Metropolis algorithm.

Appendix: Full formulation of the transmission level

In the discrete version $A_i[k]$ is the first time step where individual i is in hospital (for his/her k_{th} stay), and $D_i[k]$ is the first time step where he/she is out of hospital (after his/her k_{th} stay). Individual i can transmit staph aureus from time step C_i to time step $E_i - 1$.

$$P\left(\boldsymbol{Z}|\boldsymbol{\theta}\right)=\prod_{i=1}^{N}\left(\Omega_i^{(1)}+\Omega_i^{(2)}+\Omega_i^{(3)}\right)\times\left(\Phi_{\mu,\sigma}\left(E_i-C_i+0.5\right)-\Phi_{\mu,\sigma}\left(E_i-C_i-0.5\right)\right)$$

where $\Phi_{\mu,\sigma}$ is the cumulative density function of a Gamma distribution with mean μ and standard deviation σ (we assume that the duration of colonisation is Gamma distributed), and:

$$\begin{aligned}
\Omega_i^{(1)} &= \pi\times\mathbf{1}_{\{C_i<A_i[1]\}}\\
\Omega_i^{(2)} &= (1-\pi)\sum_{l=1}^{k_i}\mathbf{1}_{\{A_i[l]\leq C_i<D_i[l]\}}\\
&\quad\times\exp\left(-\mathbf{1}_{\{l\geq 2\}}\sum_{s=1}^{l-1}\left[\sum_{t=A_i[s]}^{D_i[s]-1}\left(\sum_{w=1}^{2}\beta_{w_i\leftarrow w}I_w\left(t\right)\right)+\beta_{\text{ward}\leftarrow\text{out}}\left(D_i[s]-A_i[s]\right)\right]\right)\\
&\quad\times\exp\left(-\mathbf{1}_{\{l\geq 2\}}\sum_{s=1}^{l-1}\left[\beta_{\text{out}\leftarrow\text{out}}\left(A_i[s+1]-D_i[s]\right)\right]\right)\\
&\quad\times\exp\left(-\sum_{t=A_i[l]}^{C_i-1}\left(\sum_{w=1}^{2}\beta_{w_i\leftarrow w}I_w\left(t\right)\right)-\beta_{\text{ward}\leftarrow\text{out}}\left(C_i-A_i[l]\right)\right)\\
&\quad\times\left(1-\exp\left(-\sum_{w=1}^{2}\beta_{w_i\leftarrow w}I_w\left(C_i\right)-\beta_{\text{ward}\leftarrow\text{out}}\right)\right)\\
&\quad\times\frac{\sum_{j=1}^{N}\mathbf{1}_{\{C_j\leq C_i<E_j\}}\sum_{r=1}^{k_j}\mathbf{1}_{\{A_j[r]\leq C_i<D_j[r]\}}\beta_{w_i\leftarrow w_j}f_{i\leftarrow j}+\beta_{\text{ward}\leftarrow\text{out}}f_{\text{i,ward}\leftarrow\text{out}}}{\sum_{j=1}^{N}\mathbf{1}_{\{C_j\leq C_i<E_j\}}\sum_{r=1}^{k_j}\mathbf{1}_{\{A_j[r]\leq C_i<D_j[r]\}}\beta_{w_i\leftarrow w_j}+\beta_{\text{ward}\leftarrow\text{out}}}\\
\Omega_i^{(3)} &= \mathbf{1}_{\{k_i>1\}}\left(1-\pi\right)\sum_{l=1}^{k_i-1}\mathbf{1}_{\{D_i[l]\leq C_i<A_i[l+1]\}}\\
&\quad\times\exp\left(-\sum_{s=1}^{l}\left[\sum_{t=A_i[s]}^{D_i[s]-1}\left(\sum_{w=1}^{2}\beta_{w_i\leftarrow w}I_w\left(t\right)\right)+\beta_{\text{ward}\leftarrow\text{out}}\left(D_i[s]-A_i[s]\right)\right]\right)\\
&\quad\times\exp\left(-\mathbf{1}_{\{l\geq 2\}}\sum_{s=1}^{l-1}\left[\beta_{\text{out}\leftarrow\text{out}}\left(A_i[s+1]-D_i[s]\right)\right]\right)\\
&\quad\times\exp\left(-\beta_{\text{out}\leftarrow\text{out}}\left(C_i-D_i[l]\right)\right)\\
&\quad\times\left(1-\exp\left(-\beta_{\text{out}\leftarrow\text{out}}\right)\right)\\
&\quad\times f_{\text{i,out}\leftarrow\text{out}}
\end{aligned}$$

$\Omega_i^{(1)}$ is the probability that individual i is colonized before his/her first admission in the wards ; $\Omega_i^{(2)}$ is the probability that individual i is colonized during one of his/her stays in the wards ; $\Omega_i^{(3)}$ is the probability, that individual i, if admitted several times, is colonized between successive stays in the wards.

$f_{i,j}$ is the probability of observing sequences s_i and s_j at respective time steps t_i and t_j given that individual j infected individual i (see next section on the genetic likelihood). Similarly, $f_{\text{i,ward}\leftarrow\text{out}}$ and $f_{\text{i,out}\leftarrow\text{out}}$ are the probability of observing sequence s_i at time t_i given that individual i was infected from outside the wards while he was in or outsite hospital respectively.