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Extreme values in epidemic models with two strains of a disease

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Talk

Based on

[1] Amador J, Armesto D, Gómez-Corral A (2018) *Extreme values in SIR epidemic models with two strains and cross-immunity.* Under review

But also related to

[2] Almaraz E, Gómez-Corral A (2018) *Number of infections suffered by a focal individual in a two-strain SIS-model.* In elaboration

[3] Gómez-Corral A, López-García M (2018) *Perturbation analysis in finite LD-QBD processes and applications to epidemic models.* Numerical Linear Algebra with Applications. DOI: https://doi.org/10.1002/nla.2160

Organization

- Motivating bacterial transmission model
- The two-strain SIR-model with total cross-immunity
- Global outbreaks (and type-k outbreaks)

    a. Final size of the epidemic
    b. Maximum number X_{max} of individuals simultaneously infected by the disease
    c. Time T_{max} to reach the number X_{max} for the first time

- Getting back to the bacterial transmission model
- Conclusions and references

Antibiotic-sensitive bacterial strain *versus* antibiotic-resistant bacterial strain

We link **multi-type epidemic models** to the deterministic model in Lipsitch et al. (2000) for the **spread of two bacterial strains** in a hospital ward.

Two bacterial strains spreading among patients are considered:

Strain 1: **antibiotic-sensitive** (AS) bacterial strain;

Strain 2: **antibiotic-resistant** (AR) bacterial strain.

The infection by one bacterial strain provides immunity against the other.

Patients are provided antibiotics 1 and 2:

Antibiotic 1 is only effective against the **AS bacterial strain**;

Antibiotic 2 is effective against **both strains** of bacteria.

N patients are accommodated in the hospital ward.

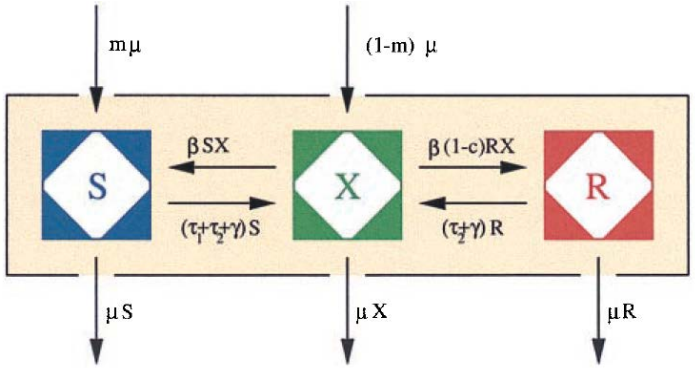
M Lipsitch, CT Bergstrom & BR Levin (2000) “The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions”, *PNAS* **97:**1938-1943

For an infection rate $\beta = 1.0\ days^{-1}$, the acquisition of resistance by bacteria can lead to some *fitness cost* $c \in (0,1)$, which is translated into rates $\beta_1 = \beta$ and $\beta_2 = (1-c)\beta$

Patients are admitted by and discharged from the hospital ward at a common rate μ

Contributions of antibiotics 1 & 2 to the recovery of a patient at rates τ_1 and τ_2

Spontaneous clearance of AS and AR bacteria occurs at rate γ



$$\dot{S} = m\mu + \beta SX - (\tau_1 + \tau_2 + \gamma + \mu)S$$

$$\dot{R} = \beta(1-c)RX - (\mu + \tau_2 + \gamma)R$$

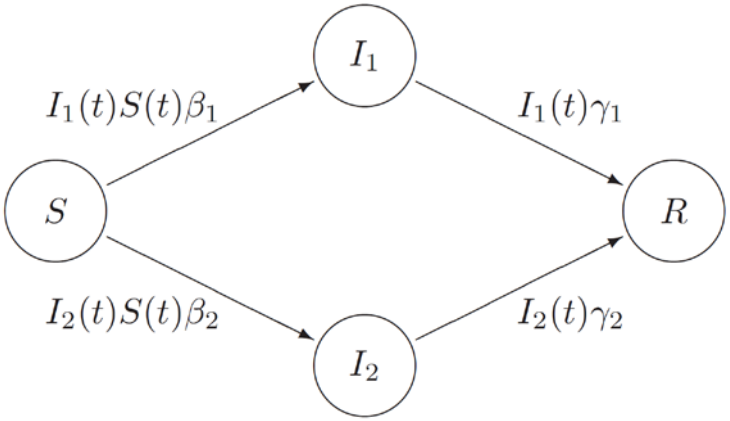
$$\dot{X} = (1-m)\mu + (\tau_1 + \tau_2 + \gamma)S + (\tau_2 + \gamma)R - \beta SX - \beta(1-c)RX - \mu X,$$

The model is designed to describe the transmission dynamics of any one of several species of bacteria that commonly reside in or on the skin, respiratory passages, or digestive tracts of humans: e.g., *Staphylococcus* spp., *Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter*.

A multi-type epidemic model as a LD-QBD process

In the terminology of epidemics, we deal with the $\boldsymbol{SI_1, I_2R}$ **epidemic model** with

- **type-1 infection** (strain 1): **antibiotic-sensitive** (AS) bacterial strain;
- **type-2 infection** (strain 2): **antibiotic-resistant** (AR) bacterial strain.



$S(t)$: number of susceptible individuals
$I_1(t)$: number of type-1 infected individuals
$I_2(t)$: number of type-2 infected individuals
$R(t)$: number of recovered individuals

For a population of N individuals, we have

$$S(t) + I_1(t) + I_2(t) + R(t) = N$$

Defined from the rates:

$\beta_1 = N^{-1}\beta$, type-1 infectious rate,

$\beta_2 = N^{-1}(1-c)\beta$, type-2 infectious rate,

$\gamma_1 = \gamma + \tau_1 + \tau_2 + \mu$, with $\boldsymbol{\mu = 0}$, type-1 recovery rate,

$\gamma_2 = \gamma + \tau_2 + \mu$, with $\boldsymbol{\mu = 0}$, type-2 recovery rate.

Under exponential distributional assumptions, the 3-dimensional process

$$\mathcal{X} = \{X(t) = (I(t), J(t), R(t)) : t \geq 0\},$$

with $I(t) = I_1(t) + I_2(t)$ and $J(t) = I_2(t)$, can be seen as an absorbing level-dependent quasi-birth-and-death (LD-QBD) process on the set of states

$$\mathcal{S} = \cup_{i=0}^{N} l(i)$$

provided that $I_1(0) = I_2(0) = 1$ and $S(0) = N - 2$, where the *i*th level is given by

$$l(i) = \bigcup_{j=\delta_{i,N}}^{\min\{i,N-1\}} l(i,j),$$

As a result, the infinitesimal generator has the structured form

$$\mathbf{Q} = \begin{pmatrix} \mathbf{0}_{L(0)\times L(0)} & \mathbf{0}_{L(0)\times L'} \\ \mathbf{T}_0 & \mathbf{T} \end{pmatrix},$$

From the non-null infinitesimal rates

$$q_{(i,j,r),(i',j',r')} = \begin{cases} (i-j)(N-i-r)\beta_1, & \text{if } i'=i+1, j'=j, r'=r, \\ j(N-i-r)\beta_2, & \text{if } i'=i+1, j'=j+1, r'=r, \\ (i-j)\gamma_1, & \text{if } i'=i-1, j'=j, r'=r+1, \\ j\gamma_2, & \text{if } i'=i-1, j'=j-1, r'=r+1, \end{cases}$$

and $-q_{(i,j,r)} = -((i-j)((N-i-r)\beta_1+\gamma_1)+j((N-i-r)\beta_2+\gamma_2))$, sub-matrices $\boldsymbol{T}_0$ and $\boldsymbol{T}$ are given by

$$\mathbf{T}_0 = \begin{pmatrix} \mathbf{Q}_{1,0} \\ \mathbf{0}_{(L'-L(1))\times L(0)} \end{pmatrix},$$

$$\mathbf{T} = \begin{pmatrix} \mathbf{Q}_{1,1} & \mathbf{Q}_{1,2} & & & & \\ \mathbf{Q}_{2,1} & \mathbf{Q}_{2,2} & \mathbf{Q}_{2,3} & & & \\ & \ddots & \ddots & \ddots & & \\ & & \mathbf{Q}_{N-1,N-2} & \mathbf{Q}_{N-1,N-1} & \mathbf{Q}_{N-1,N} \\ & & & \mathbf{Q}_{N,N-1} & \mathbf{Q}_{N,N} \end{pmatrix},$$

where $\mathbf{Q}_{i,i} = diag(\mathbf{Q}_{(i,0)}^{(i,0)}, \mathbf{Q}_{(i,1)}^{(i,1)}, ..., \mathbf{Q}_{(i,i)}^{(i,i)})$ with

$$\mathbf{Q}_{(i,j)}^{(i,j)} = \begin{cases} diag(-q_{(i,j,1)}, ..., -q_{(i,j,N-i)}), & \text{if } j \in \{0, i\}, \\ diag(-q_{(i,j,0)}, ..., -q_{(i,j,N-i)}), & \text{if } j \in \{1, ..., i-1\}. \end{cases}$$

The sub-matrices $\boldsymbol{Q}_{i,i+1}$ have the structured form

$$\begin{pmatrix} \mathbf{Q}_{(i,0)}^{(i+1,0)} & \mathbf{0}_{(N-i)\times(N-i)} & & & & \\ & \mathbf{Q}_{(i,1)}^{(i+1,1)} & \mathbf{Q}_{(i,1)}^{(i+1,2)} & & & \\ & & \ddots & \ddots & & \\ & & & \mathbf{Q}_{(i,i-1)}^{(i+1,i-1)} & \mathbf{Q}_{(i,i-1)}^{(i+1,i)} & \\ & & & & \mathbf{0}_{(N-i)\times(N-i)} & \mathbf{Q}_{(i,i)}^{(i+1,i+1)} \end{pmatrix},$$

with

$$\mathbf{Q}_{(i,j)}^{(i+1,j)} = \begin{cases} i\beta_1 \mathbf{V}_{N-i-1}, & \text{if } i \in \{1,...,N-2\},\ j=0, \\ (i-j)\beta_1 \mathbf{V}_{N-i}, & \text{if } i \in \{2,...,N-1\},\ j \in \{1,...,i-1\}, \end{cases}$$

$$\mathbf{Q}_{(i,j)}^{(i+1,j+1)} = \begin{cases} j\beta_2 \mathbf{V}_{N-i}, & \text{if } i \in \{2,...,N-1\},\ j \in \{1,...,i-1\}, \\ i\beta_2 \mathbf{V}_{N-i-1}, & \text{if } i \in \{1,...,N-2\},\ j=i, \end{cases}$$

where

$$\mathbf{V}_k = \begin{pmatrix} k & 0 & \cdots & 0 \\ 0 & k-1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 \\ 0 & 0 & \cdots & 0 \end{pmatrix}.$$

The sub-matrices $\boldsymbol{Q}_{i,i-1}$ have the structured form

$$\begin{pmatrix} \mathbf{Q}_{(i,0)}^{(i-1,0)} & & & & \\ \mathbf{Q}_{(i,1)}^{(i-1,0)} & \mathbf{Q}_{(i,1)}^{(i-1,1)} & & & \\ & \ddots & \ddots & & \\ & & \mathbf{Q}_{(i,i-1)}^{(i-1,i-2)} & \mathbf{Q}_{(i,i-1)}^{(i-1,i-1)} & \\ & & & \mathbf{Q}_{(i,i)}^{(i-1,i-1)} & \end{pmatrix},$$

with

$$\mathbf{Q}_{(i,j)}^{(i-1,j)} = \begin{cases} \gamma_1 \mathbf{I}_{N-1}, & \text{if } i = 1,\ j = 0, \\ i\gamma_1 \mathbf{U}_{N-i}, & \text{if } i \in \{2, ..., N-1\},\ j = 0, \\ (i-j)\gamma_1 \mathbf{U}_{N-i+1}, & \text{if } i \in \{2, ..., N\},\ j \in \{1, ..., i-2\}, \\ \gamma_1 \mathbf{I}_{N-i+1}, & \text{if } i \in \{2, ..., N\},\ j = i-1, \end{cases}$$

$$\mathbf{Q}_{(i,j)}^{(i-1,j-1)} = \begin{cases} \gamma_2 \mathbf{I}_{N-1}, & \text{if } i = 1,\ j = 1, \\ \gamma_2 \mathbf{I}_{N-i+1}, & \text{if } i \in \{2, ..., N\},\ j = 1, \\ j\gamma_2 \mathbf{U}_{N-i+1}, & \text{if } i \in \{2, ..., N\},\ j \in \{2, ..., i-1\}, \\ i\gamma_2 \mathbf{U}_{N-i}, & \text{if } i \in \{2, ..., N-1\},\ j = i, \end{cases}$$

where $\mathbf{U}_k = (\mathbf{0}_k, \mathbf{I}_k)$

Global outbreaks

A ***global outbreak*** begins when the population initially consists of one type-1 infective, one type-2 infective and *N-2* susceptible individuals (i.e. $I_1(0) = I_2(0) = 1,\ S(0) = N - 2$ and $R(0) = 0$), the disease spreads from infectives to susceptible individuals, in such a way that new infectives try to infect other susceptibles and then recover…

The global outbreak is said to end when no infectives remain.

In terms of $\mathcal{X}$, the process will reach states of level *I(0),* starting from the initial state *X(0)=(2,1,0),* and the epidemic will always die out. As a result, the ***random length of a global outbreak***

$$T = \inf\{t \geq 0 : I(t) = 0\}$$

follows a continuous **phase-type (PH) random variable** of order *L'* and representation $(\alpha, \mathbf{T})$ where $\alpha = \mathbf{e}_{L'}(3(N-1))$

The mass function

$$\{P(r) = P(R(\infty) = r)|X(0) = (2,1,0)) : r \in \{2, ..., N\}$$

of the ***final epidemic size*** is specified from

$$P(r) \quad = \quad \alpha\left(-\mathbf{T}^{-1}\right)\mathbf{T}_0\mathbf{e}_{N-1}^T(r-1), \quad r \in \{2, ..., N\}.$$

The interest is in the joint distribution of $(X_{\max}, T_{\max})$, where

$X_{\max}$ the ***maximum number of individuals simultaneously infected*** by the disease (regardless of the strain) during a global outbreak

$$X_{\max} = \max\{I(t) : t \in [0, T)\}$$

$T_{\max}$ the ***time to reach*** the maximum number $X_{\max}$ for the first time

$$T_{\max} = \inf\{t \geq 0 : I(t) = X_{\max}\}$$

We proceed in two steps:

First, we derive the marginal distribution of $X_{\max}$

Second, we determine the distribution of $T_{\max}$ on $\{X_{\max} = x\}$

Marginal distribution of $X_{\max}$

For the initial state $X(0) = (2,1,0)$, we determine the mass function

$$\{P_{(2,1,0)}(x) = P(X_{\max} = x | X(0) = (2,1,0)) : x \in \{2,...,N\}\}$$

In terms of

$$P_{(2,1,0)}(x) = F_{\max}(x;(2,1,0)) - (1-\delta_{2,x})F_{\max}(x-1;(2,1,0)),$$

where

$$F_{\max}(x;(2,1,0)) = P(X_{\max} \leq x | X(0) = (2,1,0))$$

For each fixed integer $x \in \{2,\ldots,N\}$, this probability is related to an absorbing LD-QBD process defined on the set of states

$$\overline{\mathcal{S}}(x) = \{0\} \cup \bigcup_{i=1}^{x} l(i) \cup \{x+1\},$$

and with infinitesimal generator

$$\overline{\mathbf{Q}}(x) = \begin{pmatrix} 0 & \mathbf{0}^T_{\overline{L}(x)} & 0 \\ \mathbf{t}_0(x) & \mathbf{T}(x) & \mathbf{t}_{x+1}(x) \\ 0 & \mathbf{0}^T_{\overline{L}(x)} & 0 \end{pmatrix},$$

where

$$\mathbf{t}_0(x) = \begin{pmatrix} \gamma_1 \mathbf{1}_{N-1} \\ \gamma_2 \mathbf{1}_{N-1} \\ \mathbf{0}_{\overline{L}(x)-L(1)} \end{pmatrix},$$

$$\mathbf{t}_{x+1}(x) = \begin{pmatrix} \mathbf{0}_{\overline{L}(x-1)} \\ \mathbf{Q}_{x,x+1}\mathbf{1}_{L(x+1)} \end{pmatrix},$$

$$\mathbf{T}(x) = \begin{pmatrix} \mathbf{Q}_{1,1} & \mathbf{Q}_{1,2} & & & & \\ \mathbf{Q}_{2,1} & \mathbf{Q}_{2,2} & \mathbf{Q}_{2,3} & & & \\ & \ddots & \ddots & \ddots & & \\ & & \mathbf{Q}_{x-1,x-2} & \mathbf{Q}_{x-1,x-1} & \mathbf{Q}_{x-1,x} & \\ & & & \mathbf{Q}_{x,x-1} & \mathbf{Q}_{x,x} & \end{pmatrix}.$$

Theorem 3.2. *Under the assumption of initial numbers* $I_1(0) = I_2(0) = 1$ *of infectives and* $S(0) = N - 2$ *of susceptibles, the probability distribution function of* $X_{\max}$ *is given by* $F_{\max}(x;(2,1,0)) = \mathbf{e}_{\overline{L}(x)}(3(N-1))(-\mathbf{T}^{-1}(x))\mathbf{t}_0(x)$ *if* $x \in \{2,...,N\}$, *and* 0 *if* $x \in \{0,1\}$.

Algorithm 3.3. *Computation of the mass function* $\{P_{(2,1,0)}(x) : x \in \{2, ..., N\}\}$.

Step 0: $x := 2$;

$\mathbf{p}(x) := -\mathbf{T}^{-1}(x)\mathbf{t}_0(x)$;

$F_{\max}(x;(2,1,0)) := \mathbf{e}^T_{\overline{L}(x)}(3(N-1))\mathbf{p}(x)$;

$P_{(2,1,0)}(x) := F_{\max}(x;(2,1,0))$.

Step 1: *While* $x < N$,

$x := x + 1$;

$$\mathbf{A}_{1,2}(x) := \begin{pmatrix} \mathbf{0}_{\overline{L}(x-2)\times L(x)} \\ \mathbf{Q}_{x-1,x} \end{pmatrix};$$

$$\mathbf{A}_{2,1}(x) := \left(\mathbf{0}_{L(x)\times\overline{L}(x-2)}, \mathbf{Q}_{x,x-1}\right);$$

$$\mathbf{B}_{2,2}(x) := \left(-\mathbf{Q}_{x,x} - \mathbf{A}_{2,1}(x)(-\mathbf{T}^{-1}(x-1))\mathbf{A}_{1,2}(x)\right)^{-1};$$

$$\mathbf{B}_{2,1}(x) := \mathbf{B}_{2,2}(x)\mathbf{A}_{2,1}(x)(-\mathbf{T}^{-1}(x-1));$$

$$\mathbf{B}_{1,2}(x) := -\mathbf{T}^{-1}(x-1)\mathbf{A}_{1,2}(x)\mathbf{B}_{2,2}(x);$$

$$\mathbf{B}_{1,1}(x) := -\mathbf{T}^{-1}(x-1)(\mathbf{I}_{\overline{L}(x-1)} + \mathbf{A}_{1,2}(x)\mathbf{B}_{2,1}(x));$$

$$-\mathbf{T}^{-1}(x) := \begin{pmatrix} \mathbf{B}_{1,1}(x) & \mathbf{B}_{1,2}(x) \\ \mathbf{B}_{2,1}(x) & \mathbf{B}_{2,2}(x) \end{pmatrix};$$

$\mathbf{p}(x) := -\mathbf{T}^{-1}(x)\mathbf{t}_0(x)$;

$F_{\max}(x;(2,1,0)) := \mathbf{e}^T_{\overline{L}(x)}(3(N-1))\mathbf{p}(x)$;

$P_{(2,1,0)}(x) := F_{\max}(x;(2,1,0)) - F_{\max}(x-1;(2,1,0))$.

$T = T(N)$

Step 2: $E[T|X(0) = (2,1,0)] := \mathbf{e}^T_{\overline{L}(x)}(3(N-1))(-\mathbf{T}^{-1}(x))\mathbf{1}_{\overline{L}(x)}$;

$r := 1$;

while $r < N$,

$r := r + 1$;

$P(r) := \mathbf{e}^T_{\overline{L}(x)}(3(N-1))(-\mathbf{T}^{-1}(x))\mathbf{T}_0\mathbf{e}^T_{N-1}(r-1)$.

The marginal distribution of $T_{\max}$ has a discrete contribution on $\{T_{\max} = 0\}$:

$$P(X_{\max} = 2, T_{\max} = 0 | X(0) = (2,1,0)) = P_{(2,1,0)}(x) \quad \text{for } x=2.$$

and a continuous contribution on $\{T_{\max} > 0\}$:

$$P(X_{\max} = x, T_{\max} > 0 | X(0) = (2,1,0)) \text{ if } x \in \{3, ..., N\}$$

For $x \in \{3, \dots, N\}$, we define restricted Laplace-Stieltjes transforms

$$\varphi_{(2,1,0)}(\theta; x) = E\left[e^{-\theta T_{\max}} 1\{X_{\max} = x\} | X(0) = (2,1,0)\right]$$

and we express

$$\varphi_{(2,1,0)}(\theta; x) = \sum_{(x,j,r) \in l(x)} \phi_{(2,1,0)}(\theta; (x,j,r)) P_{(x,j,r)}(x),$$

where $\phi_{(2,1,0)}(\theta; (x,j,r))$ is the restricted Laplace-Stieltjes transform of the first-passage time *U(x)* to states of level *l(x)* on the set $\{X(U(x)) = (x,j,r)\}$ of sample paths, provided that $X(0) = (2,1,0)$.

The Laplace-Stieltjes transform $\varphi_{(2,1,0)}(\theta;x)$ is obtained by solving the matrix equation

$$\begin{aligned}\left(\theta\mathbf{I}_{L(i')}-\mathbf{Q}_{i',i'}\right)\varphi_{i'}(\theta;x) &= (1-\delta_{1,i'})\mathbf{Q}_{i',i'-1}\varphi_{i'-1}(\theta;x)\\ &\quad +(1-\delta_{i',x-1})\mathbf{Q}_{i',i'+1}\varphi_{i'+1}(\theta;x)+\delta_{i',x-1}\mathbf{b}(x),\end{aligned}$$

where **b**(x) consists of sub-vectors

$$\mathbf{b}_{j'}(x) = \begin{pmatrix} (x-1-j')(N-x+1)\beta_1 P_{(x,j',0)}(x)+j'(N-x+1)\beta_2 P_{(x,j'+1,0)}(x)\\ (x-1-j')(N-x)\beta_1 P_{(x,j',1)}(x)+j'(N-x)\beta_2 P_{(x,j'+1,1)}(x)\\ \vdots\\ (x-1-j')\beta_1 P_{(x,j',N-x)}(x)+j'\beta_2 P_{(x,j'+1,N-x)}(x)\\ 0\end{pmatrix}$$

The sub-vector $\mathbf{m}_i^{(n)}(x) = (-1)^n \left.\frac{d^n\varphi_i(\theta;x)}{d\theta^n}\right|_{\theta=0}$ of moments

$$E[T_{\max}^n 1\{X_{\max}=x\}|X(0)=(i,j,r)]$$

satisfies

$$-n\mathbf{m}_i^{(n-1)}(x)-\mathbf{Q}_{i,i}\mathbf{m}_i^{(n)}(x) = (1-\delta_{1,i})\mathbf{Q}_{i,i-1}\mathbf{m}_{i-1}^{(n)}(x)+(1-\delta_{i,x-1})\mathbf{Q}_{i,i+1}\mathbf{m}_{i+1}^{(n)}(x)$$

Algorithm 3.4. *Computation of the column vectors* $\varphi_i(\theta;x)$ *with* $i \in \{1,...,x-1\}$, *for a fixed integer* $x \in \{3,...,N\}$ *and* $Re(\theta) \geq 0$.

Step 0: From $i = 1$ *to* $x-2$,

$$\mathbf{H}_i(\theta) := (\theta \mathbf{I}_{L(i)} - \mathbf{Q}_{i,i} - (1-\delta_{1,i})\mathbf{Q}_{i,i-1}\mathbf{H}_{i-1}(\theta))^{-1}\mathbf{Q}_{i,i+1};$$

$$\mathbf{H}_{x-1}(\theta) := (\theta \mathbf{I}_{L(x-1)} - \mathbf{Q}_{x-1,x-1} - \mathbf{Q}_{x-1,x-2}\mathbf{H}_{x-2}(\theta))^{-1}\mathbf{b}(x).$$

Step 1: $\varphi_{x-1}(\theta;x) := \mathbf{H}_{x-1}(\theta)$;

from $i = x-2$ *to* 1,

$$\varphi_i(\theta;x) := \mathbf{H}_i(\theta)\varphi_{i+1}(\theta;x).$$

Algorithm 3.5. *Computation of the column vectors* $\mathbf{m}_i^{(n)}(x)$, *with* $i \in \{1,...,x-1\}$, *for fixed integers* $x \in \{3,...,N\}$ *and* $n \geq 1$.

Step 0: From $i = 1$ *to* $x-2$,

$$\overline{\mathbf{H}}_i := (-\mathbf{Q}_{i,i} - (1-\delta_{1,i})\mathbf{Q}_{i,i-1}\overline{\mathbf{H}}_{i-1})^{-1}\mathbf{Q}_{i,i+1};$$

$$\overline{\mathbf{h}}_i^{(n)} := (-\mathbf{Q}_{i,i} - (1-\delta_{1,i})\mathbf{Q}_{i,i-1}\overline{\mathbf{H}}_{i-1})^{-1}((1-\delta_{1,i})\mathbf{Q}_{i,i-1}\overline{\mathbf{h}}_{i-1}^{(n)} + n\mathbf{m}_i^{(n-1)}(x));$$

$$\overline{\mathbf{h}}_{x-1}^{(n)} := (-\mathbf{Q}_{x-1,x-1} - \mathbf{Q}_{x-1,x-2}\overline{\mathbf{H}}_{x-2})^{-1}(\mathbf{Q}_{x-1,x-2}\overline{\mathbf{h}}_{x-2}^{(n)} + n\mathbf{m}_{x-1}^{(n-1)}(x)).$$

Step 1: $\mathbf{m}_{x-1}^{(n)}(x) := \overline{\mathbf{h}}_{x-1}^{(n)}$;

from $i = x-2$ *to* 1,

$$\mathbf{m}_i^{(n)}(x) := \overline{\mathbf{H}}_i\mathbf{m}_{i+1}^{(n)}(x) + \overline{\mathbf{h}}_i^{(n)}.$$

Under the assumption that *X(0)=(*2,1,0), the *n*-th moment of $T_{\max}$ is given by

$$E\left[T_{\max}^{n}\,|X(0)=(2,1,0)\right] \;=\; \sum_{x=3}^{N}\left(\mathbf{m}_{2}^{(n)}(x)\right)_{N-1}, \quad n\geq 1$$

since $\mathbf{m}_{i}^{(n)}(x)$ contains the restricted moments $E[T_{\max}^{n}1\{X_{\max}=x\}|X(0)=(i,j,r)]$

Type-k outbreaks

A ***type-k outbreak*** begins when the population initially consists of one type-1 infective, one type-2 infective and *N-2* susceptible individuals (i.e. $I_1(0) = I_2(0) = 1,\ S(0) = N - 2$ and $R(0) = 0$), the disease spreads from infectives to susceptible individuals, in such a way that new infectives try to infect other susceptibles and then recover…

The type-k outbreak ***ends when no type-k infectives remain***.

Random variables under consideration:

- The random length of a type-k outbreak

$$T(k) = \inf\{t \geq 0 : I_k(t) = 0\}$$

- The maximum number of individuals simultaneously infected by the type-k strain during a type-k outbreak

$$X_{\max}(k) = \max\{I_k(t) : t \in [0, T(k))\}$$

- The random time to reach the maximum number $X_{\max}(k)$ of type-k infectives

$$T_{\max}(k) = \inf\{t \geq 0 : I_k(t) = X_{\max}(k)\}$$

For the case *k=2*, we may use the LD-QBD process $\mathcal{Y} = \{Y(t) : t \geq 0\}$ with

$$Y(t) = (J(t), I(t), R(t))$$

instead of $X(t) = (I(t), J(t), R(t))$.

It is seen that the joint distribution of $(X_{\max}(2), T_{\max}(2))$ can be characterized by

(i) The conditional probabilities

$$P^*_{(1,2,0)}(x) \quad = \quad P(X_{\max}(2) = x | Y(0) = (1,2,0))$$

(ii) The restricted Laplace-Stieltjes transforms

$$\varphi^*_{(1,2,0)}(\theta; x) \quad = \quad E\left[e^{-\theta T_{\max}(2)} 1\{X_{\max}(2) = x\} \, | Y(0) = (1,2,0)\right]$$

for integers $x \in \{1, \ldots, N-1\}$.

Getting back to the bacterial transmission model

A hospital ward with $N = 20$ patients, and initial numbers $(I_1, I_2) = (1,1)$ of infectives.

Fitness cost $c \in \{0.25, 0.5, 0.75\}$.

Three scenarios: $\tau_2^{-1} = 10\ days$
$\tau_2^{-1} = 15\ days$
$\tau_2^{-1} = 20\ days$

For the common infection rate $\beta = 1.0\ days^{-1}$, we assume the values

$$\beta_1 = N^{-1}\beta \qquad \gamma_1 = \gamma + \tau_1 + \tau_2 + \mu$$
$$\beta_2 = N^{-1}(1-c)\beta \qquad \gamma_2 = \gamma + \tau_2 + \mu$$

with $\mu = 0\ days$, $\tau_1^{-1} = 5\ days$ and $\gamma^{-1} = 45\ days$.

Global outbreak: T, X_{max}, T_{max} and $R(\infty)$.

Type-k outbreaks:

- For the AR bacterial strain: $T(AR)$, $X_{max}(AR)$, $T_{max}(AR)$ and $R(T(AR))$.
- For the AS bacterial strain: $T(AS)$, $X_{max}(AS)$, $T_{max}(AS)$ and $R(T(AS))$.

c		Scenario 1	Scenario 2	Scenario 3
0.25	$E[T]$	26.27371	34.76114	41.88924
	$E[T(AR)]$	24.01639	32.79190	40.13705
	$E[T(AS)]$	8.50971	9.58226	10.19692
0.5	$E[T]$	24.61975	32.56713	39.02344
	$E[T(AR)]$	21.51826	29.75937	36.47506
	$E[T(AS)]$	9.26060	10.51253	11.22971
0.75	$E[T]$	20.34260	27.87451	33.90622
	$E[T(AR)]$	16.06746	23.78456	30.07184
	$E[T(AS)]$	9.90273	11.32948	12.15068

TABLE 1. Expected values $E[T]$, $E[T(AR)]$ and $E[T(AS)]$ versus c, for scenarios 1-3.

c		Scenario 1	Scenario 2	Scenario 3
0.25	$E[R(\infty)]$	18.22813	18.91643	19.19926
	$E[R(T(AR))]$	15.91515	17.03942	17.59343
	$E[R(T(AS))]$	10.46318	10.76494	10.81756
0.5	$E[R(\infty)]$	17.11785	18.22629	18.69461
	$E[R(T(AR))]$	13.97200	15.60096	16.41606
	$E[R(T(AS))]$	11.00747	11.54376	11.74507
0.75	$E[R(\infty)]$	14.62776	16.29528	17.17700
	$E[R(T(AR))]$	10.27924	12.49899	13.79785
	$E[R(T(AS))]$	11.49554	12.24802	12.59538

TABLE 2. Expected values $E[R(\infty)]$, $E[R(T(AR))]$ and $E[R(T(AS))]$ versus c, for scenarios 1-3.

c		Scenario 1	Scenario 2	Scenario 3
0.25	$E[T_{\max}]$	5.13457	5.48122	5.65083
	$E[T_{\max}(AR)]$	4.86172	5.39012	5.69173
	$E[T_{\max}(AS)]$	2.36220	2.52703	2.60989
0.5	$E[T_{\max}]$	5.71485	6.33872	6.62726
	$E[T_{\max}(AR)]$	5.10333	5.91361	6.35878
	$E[T_{\max}(AS)]$	2.70987	2.93823	3.05512
0.75	$E[T_{\max}]$	5.45941	6.88858	7.72598
	$E[T_{\max}(AR)]$	4.20225	5.69292	6.62775
	$E[T_{\max}(AS)]$	2.99747	3.28760	3.43865

TABLE 3. Expected values $E[T_{\max}]$, $E[T_{\max}(AR)]$ and $E[T_{\max}(AS)]$ versus c, for scenarios 1-3.

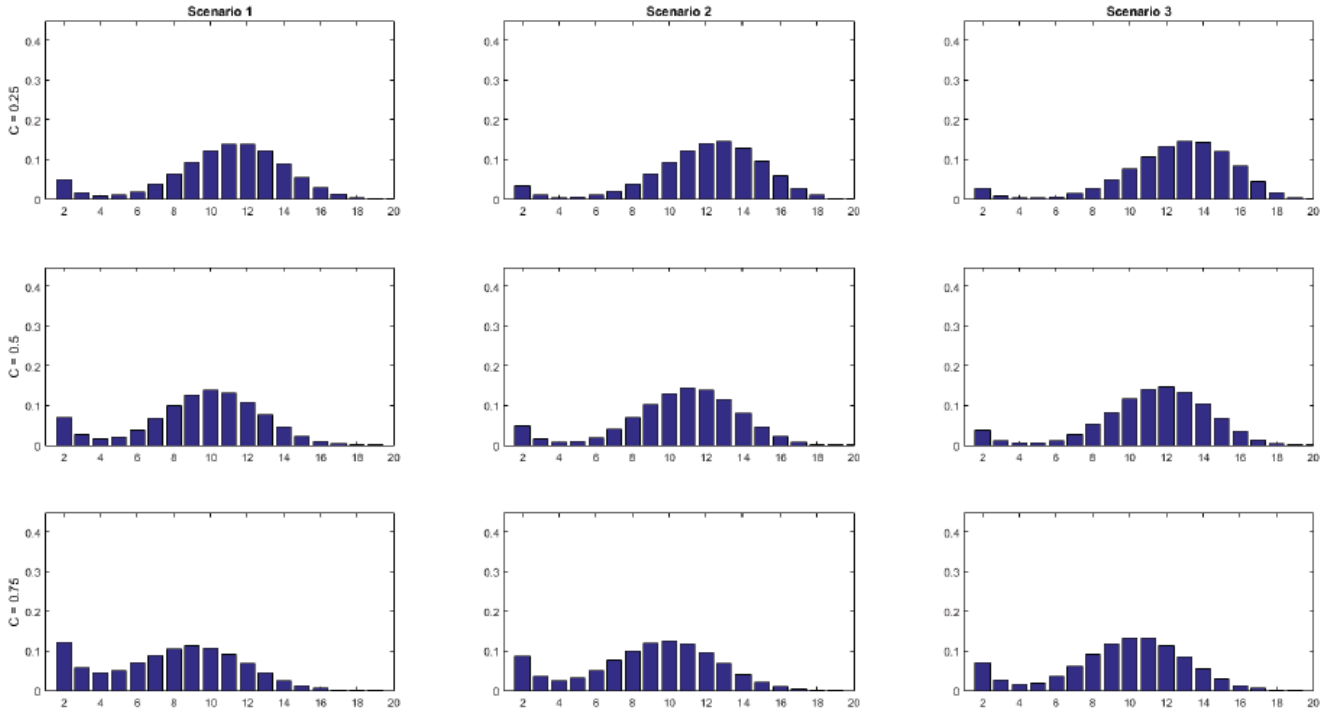


FIGURE 5. Mass function $\{P_{(2,1,0)}(x) : x \in \{2, ..., N\}\}$ of the maximum number of patients simultaneously colonized by the bacteria during a global outbreak versus c, for scenarios 1-3.

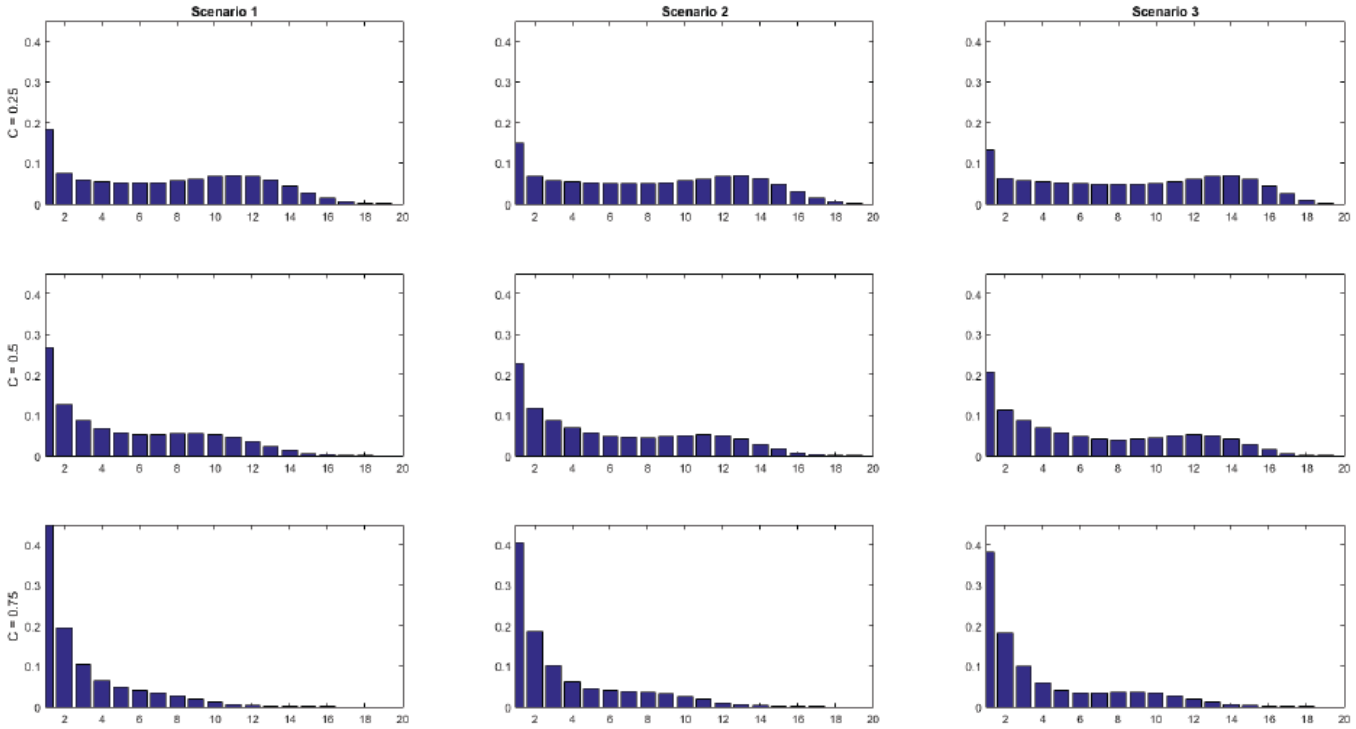


FIGURE 6. Mass function $\{P(X_{\max}(AR) = x) : x \in \{1, ..., N-1\}\}$ of the maximum number of patients simultaneously colonized by the AR bacterial strain during an AR bacteria outbreak versus c, for scenarios 1-3.

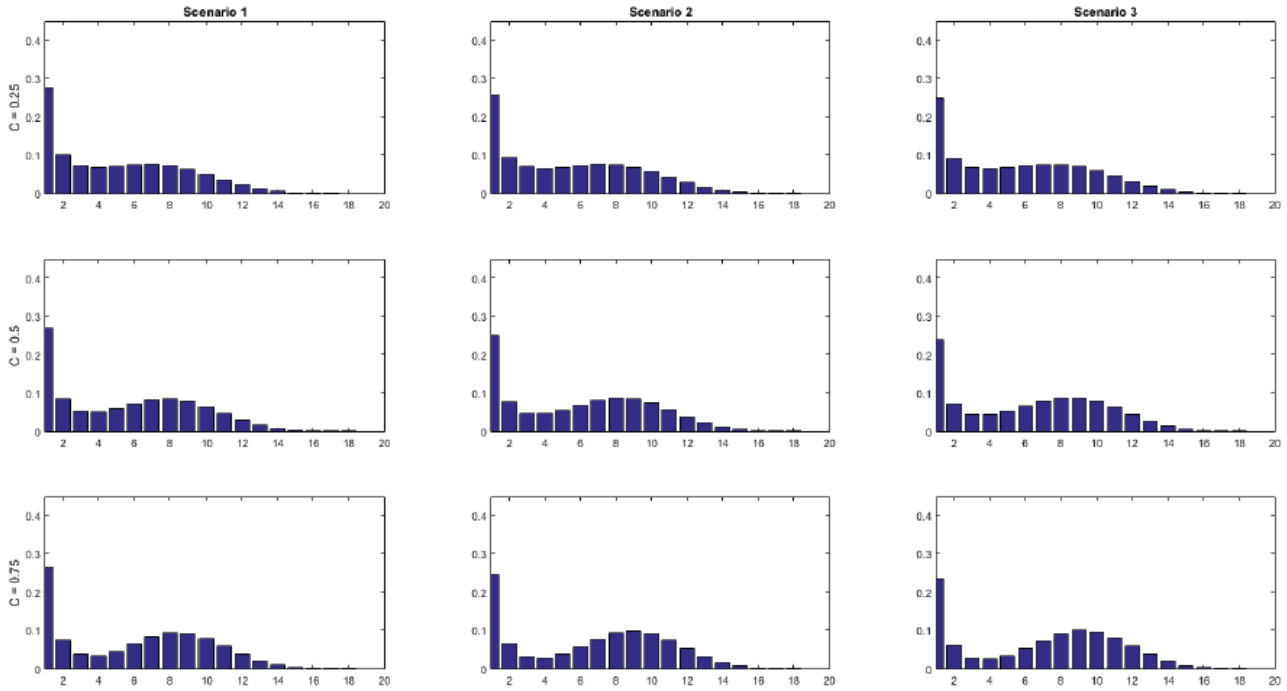


FIGURE 7. Mass function $\{P(X_{\max}(AS) = x) : x \in \{1, ..., N-1\}\}$ of the maximum number of patients simultaneously colonized by the AS bacterial strain during an AS bacteria outbreak versus c, for scenarios 1-3.

Conclusions and references

The talk focuses on two issues concerning the SIR-model with two strains analyzed in

> WS Kendall and IW Saunders, Epidemics in competition II: The general epidemic. J*R Statist Soc B*, **45** (1983), 238-244

1. The derivation of the joint distribution of the random vector (X_{max}, T_{max}), as well two specialized versions $(X_{max}(k), T_{max}(k))$ for type-*k* outbreaks.
2. The use of absorbing LD-QBD processes allowing us to formulate the maximum numbers X_{max} and $X_{max}(k)$ as maximum levels visited by the process before its absorption in level *I(0),* and the random times T_{max} and $T_{max}(k)$ as suitably defined first-passage times.

The approach is motivated by the deterministic models in

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Thank you for your attention!

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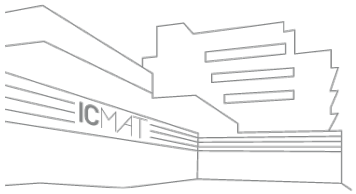

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