Infinite-dimensional epidemic models and optimal vaccination strategies

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November 26, 2021

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Principles of the SIS model

Susceptible ⟶ Infected ⟶ Susceptible

Infection: Law of mass action (Kermack-McKendrick 1927)

Susceptible individual gets infected at rate proportional to the concentration of infected people in the population.

Recovery

Infected individual recovers at constant rate.

Example: flu, common cold, gonorrhea...

Mathematical formulation of the 1-D SIS Model

The population is constant and is assigned to compartments $S + I = 1$ with:

- $S(t)$: proportion of susceptible individuals at time t.
- $I(t)$: proportion of infected individuals at time t.

Parameters

$\beta > 0$: transmission rate, $\gamma > 0$: recovery rate.

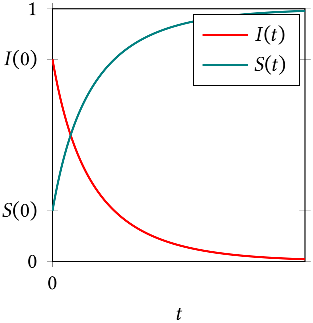
Evolution equation

$$\begin{cases} \dfrac{\mathrm{d}S}{\mathrm{d}t} = -S\beta I + \gamma I, \\ \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = S\beta I - \gamma I. \end{cases}$$

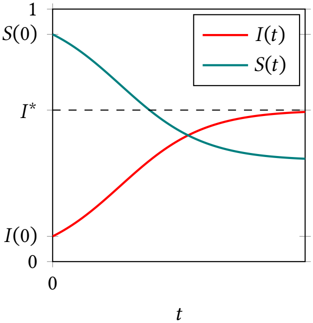
Long-time behavior of the solution

Suppose $I(0) > 0$. Then:

- if $R_0 \leq 1$: $\lim_{t\to\infty} I(t) = 0$,
- if $R_0 > 1$: $\lim_{t\to\infty} I(t) := I^* = 1 - 1/R_0 > 0$.



(a) $R_0 \leq 1$.



(b) $R_0 > 1$.

Figure: Convergence of the 1-D SIS model.

1-D SIS model with vaccination

At $t = 0$, a proportion V of the population is vaccinated.

We assume that vaccinated individuals are fully immunized to the disease.

The population is assigned to compartments $S + I + V = 1$ with:

- $S(t)$: proportion of susceptible individuals at time t.
- $I(t)$: proportion of infected individuals at time t.
- V: proportion of vaccinated/immunized individuals, constant over time.

Evolution equation

$$\frac{\mathrm{d}I}{\mathrm{d}t} = (1 - V - I)\beta I - \gamma I.$$

The Herd Immunity Threshold

Definition

The Herd Immunity Threshold is defined as the critical proportion of the population that is needed in order to eradicate the disease.

$$\mathrm{HIT} = 1 - 1/R_0.$$

Disease	Main Transmission mode	R_0	HIT
Measle (*Rougeole*)	Aerosol	12-18	92-95%
Varicella	Aerosol	10-12	90-92%
Mumps (*Oreillons*)	Respiratory droplets	10-12	90-92%
Polio	Fecal-oral route	5-7	80-86%
Covid-19	Aerosol	3-6	65-85%
Ebola	Body fluids	1.5-2.5	30-60%

Table: Values of R_0 and HIT of well-known diseases

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Heterogeneity of the population

Individuals do not mix homogeneously

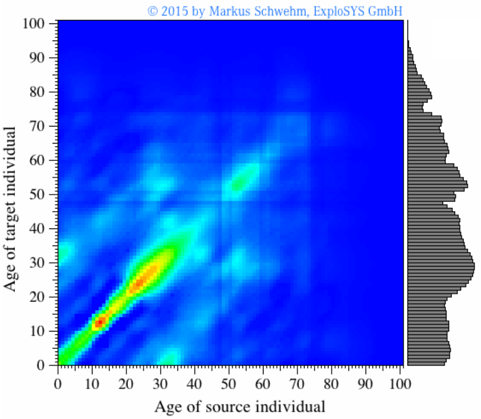

Figure: Contact matrix in an european population (Mossong et al. 2008)

The finite-dimensional SIS model

Lajmanovich and Yorke 1976

Metapopulation assumption

- The population is divided into N subpopulations labeled $\{1, 2, \ldots, N\}$.
- Individuals within a same subpopulation share the same characteristics.

Parameters

- $\mu_i \in (0, 1)$: proportion of individuals in subpopulation i.

$$\sum_{i=1}^{N} \mu_i = 1.$$

- $\beta_{ij} \geq 0$: transmission rate of the infection from an individual in subpopulation j to an individual in subpopulation i.
- $\gamma_i > 0$: is the recovery rate the individuals in subpopulation i.

Subpopulation i is assigned with compartments $S_i + I_i + V_i$ with:

- $S_i(t)$: proportion of susceptible individuals in subpop. i at time t.
- $I_i(t)$: proportion of infected individuals in subpop. i at time t.
- V_i: proportion of vaccinated individuals in subpop. i, constant over time.

Evolution equation

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = (1 - V_i - I_i) \sum_{j=1}^{N} \beta_{ij} I_j \mu_j - \gamma_i I_i.$$

Theorem (Lajmanovich and Yorke 1976)

Suppose $I(0) \neq (0, 0, \dots, 0)$.

- *If* $R_e(V) \leq 1$: $\lim_{t\to\infty} I(t) = (0, 0, \dots, 0)$.
- *If* β *is irreducible and* $R_e(V) > 1$: *there exists an unique* $I^* \in (0, 1]^N$ *such that* $\lim_{t\to\infty} I(t) = I^*$.

Graphon theory

Lovász 2012; Borgs et al. 2018

Question

How to represent the population when $N \to \infty$?

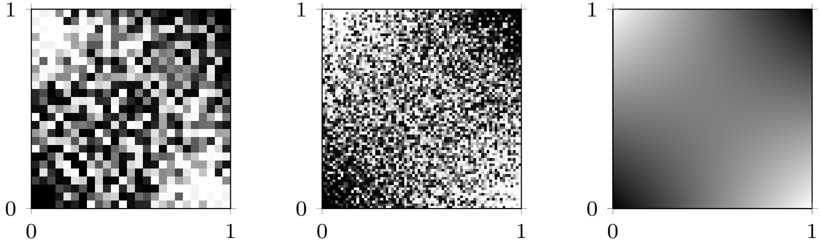

Figure: Convergence of a sequence of matrices to a kernel.

Infinite dimensional SIS model

Parameters

$(\Omega, \mathscr{F}, \mu)$: probability space representing the population.

$k : \Omega \times \Omega \to \mathbb{R}_+$: kernel representing the transmission rates between the individuals in the population.

$\gamma : \Omega \to \mathbb{R}_+$: positive function representing the recovery rate of the individuals

For $x \in \Omega$:

- $v(x)$: proportion of x-type individuals who are vaccinated,
- $u(t, x)$: proportion of x-type individuals who are infected at time t.

Evolution equation

$$\partial_t u(t,x) = (1 - v(x) - u(t,x)) \int_0^1 k(x,y) u(t,y)\, \mu(\mathrm{d}y) - \gamma(x) u(t,x).$$

Notation

$$\mathbf{k} \,:\, (x,y) \mapsto \frac{k(x,y)}{\gamma(y)}.$$

Definition (Next-generation operator with vaccination)

The integral operator associated to the kernel $(x,y) \mapsto \mathbf{k}(x,y)(1-v(y))$ is

$$T_{\mathbf{k}(1-v)}(g) \,:\, x \mapsto \int_\Omega \frac{k(x,y)}{\gamma(y)}(1-v(y))g(y)\,\mu(\mathrm{d}y).$$

Definition

The kernel $\mathbf{k}$ is said to be connected if for all $A \in \mathscr{F}$,

$$\int_{A\times A^c} \mathbf{k}(x,y)\mu(\mathrm{d}x)\mu(\mathrm{d}y) = 0 \implies \mu(A) \in \{0,1\}.$$

Theorem (Delmas, DD, Zitt)

Suppose an integrability condition on $\mathbf{k}$ *and* $\int_\Omega u_0(x)\,\mu(\mathrm{d}x) > 0$.

- *If* $R_e(v) \leq 1$, *then, for all* $x \in \Omega$:

$$\lim_{t\to+\infty} u(t,x) = 0.$$

- *If* $R_e(v) > 1$ *then, there exists a greatest equilibrium that is denoted* $u^* = u^*_v$ *and called the endemic state and satisfies:*

$$\int_\Omega u^*(x)\,\mu(\mathrm{d}x) > 0.$$

  If, besides, $\mathbf{k}$ *is connected, then* u^* *is positive almost surely and globally stable, i.e., for all* $x \in \Omega$:

$$\lim_{t\to+\infty} u(t,x) = u^*(x).$$

Comparison to other results and proof in the literature

Ruan and Xiao 2004; Feng, Huang, and Castillo-Chavez 2005; Thieme 2011; ...

Usual assumptions in the literature

- $\Omega \subset \mathbb{R}^d$ compact and μ is the Lebesgue measure
  $\rightarrow$ general probability space.
- k is continuous and bounded away from 0
  $\rightarrow$ connectedness and integrability condition on $\mathbf{k}$.
- γ is bounded away from 0
  $\rightarrow \gamma$ positive.

Strategy for the proof

- Adapt the theory of order preserving system (Hirsch and Smith 2006).
- $T_{\mathbf{k}(1-v)}$ is power compact.
- Find non-decreasing solution closed to the disease free equilibrium (thanks to the Krein-Rutman theorem).

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The threshold theorem in the infinite-dimensional setting

Overall proportion of vaccinated individuals:

$$C(v) = \int_\Omega v(x)\, \mu(\mathrm{d}x).$$

If the population is vaccinated uniformly at level c ($v(x) = c, \forall x$) then:

$$R_e(v) = \rho(T_{k(1-c)/\gamma}) = (1-c)\rho(T_{k/\gamma}) = (1-c)R_0.$$

Theorem (Threshold theorem)

Vaccinating a proportion $1 - 1/R_0$ of individuals uniformly is enough to reach herd immunity!

Question

Is it possible to reach herd immunity (*i.e.*, $R_e(v) = 1$) with a proportion $C(v)$ of vaccinated individuals smaller than $1 - 1/R_0$?

Vaccinating according to the endemic state

Proposition (Delmas, DD, Zitt)

Suppose $R_0 > 1$. Vaccinating according to the endemic state u_0^* (greatest equilibrium when nobody is vaccinated) is critical:

$$R_e(u_0^*) = 1.$$

Corollary

Herd immunity can be reached with a proportion of vaccinated individuals

$$C(u_0^*) = \int_\Omega u_0^*(x)\,\mu(\mathrm{d}x).$$

Questions

- Is it possible to reach herd immunity with less than $C(u_0^*)$?
- Compare $C(u_0^*)$ and $1 - 1/R_0$.

Optimal allocation of vaccine doses

If the society has only a limited quantity of vaccine, the decision-maker could try to solve:

$$\begin{cases}\textbf{Minimize:} & R_e(v)\\ \textbf{subject to:} & C(v) = c.\end{cases} \tag{1}$$

We will also be interested in:

$$\begin{cases}\textbf{Maximize:} & R_e(v)\\ \textbf{subject to:} & C(v) = c.\end{cases} \tag{2}$$

The set of vaccination strategies:

$$\Delta = \{v : \ \Omega \to [0,1] \quad \text{mesurable}\}.$$

Short topological digression

Weak topology on Δ:

$v_n \xrightarrow{\text{w}} v$ if, for all $g \in L^\infty(\Omega)$:

$$\lim_{n\to+\infty} \int_\Omega g(x)v_n(x)\,\mathrm{d}x = \int_\Omega g(x)v(x)\,\mathrm{d}x.$$

- Δ is compact (Banach-Alaoglu theorem).
- The function $C : \Delta \to [0,1]$ is continuous and increasing.

Lemma (Delmas, DD, Zitt)

The function $R_e : \Delta \to [0, R_0]$ is continuous, homogeneous, decreasing.

The proof is based on a result by Anselone 1971 which proves the convergence of the spectra of a **collectively compact** and **strongly convergent** sequence of operators.

Corollary

- *For all* $c \in [0,1]$*, there exist solution to Problem* (1) *and a solution to Problem* (2) *for a cost* $C(v) = c$*.*
- *If* $\mathbf{k} > 0$*, the solutions to Problem* (1) *are Pareto optimal.*
- *If* $\mathbf{k}$ *is connected, the solutions to Problem* (2) *are anti-Pareto optimal.*

$$R_e^\star(c) = \max\{R_e(v) \;:\; v \in \Delta,\, C(v) = c\}.$$
$$R_{e\star}(c) = \min\{R_e(v) \;:\; v \in \Delta,\, C(v) = c\},$$
$$\mathbf{F} = \{(C(v), R_e(v)) \;:\; v \in \Delta\}.$$

Corollary

The set of possible outcomes is simply connected:

$$\mathbf{F} = \{(c,r) \;:\; c \in [0,1],\, R_{e\star}(c) \le r \le R_e^\star(c)\}.$$

Another way to measure the efficacy of a strategy

The overall proportion of infected individuals in the endemic state is

$$I^*(v) = \int_\Omega u_v^*(x)\,\mu(\mathrm{d}x).$$

Lemma (Delmas, DD, Zitt)

The function $I^* : \Delta \to [0, R_0]$ *is continuous, subhomogeneous and decreasing.*

The proof is based on the continuity of R_e and the fact that u_0^* is the only equilibrium that satisfies $R_e(u_0^*) = 1$ when $R_0 > 1$.

Consequence

There exist solutions to Problems (1) and (2) where R_e is replaced by I^*.

Solving a conjecture by Hill and Longini

Hill and Longini 2003

Recall that:

- $\mathbf{k}(x, y) \geq 0$, for all $x, y \in \Omega$.
- if $\mathbf{k} \in L^2(\Omega \times \Omega)$, then $T_{\mathbf{k}}$ is Hilbert-Schmidt. In particular $T_{\mathbf{k}}$ is compact.

Hence, $R_0 = \rho(T_{\mathbf{k}})$ is an eigenvalue of $T_{\mathbf{k}}$ (Krein-Rutman theorem).

Theorem (Delmas, DD, Zitt)

Suppose $\mathbf{k}$ symmetric (i.e., $\mathbf{k}(x, y) = \mathbf{k}(y, x)$ almost-surely) and $\mathbf{k} \in L^2(\Omega \times \Omega)$.

- *If $\sigma(T_{\mathbf{k}}) \subset \mathbb{R}_+$, then R_e is convex.*
- *If $\mathbf{k}$ is connected and $\sigma(T_{\mathbf{k}}) \setminus \{R_0\} \subset \mathbb{R}^-$, then R_e is concave.*

Remarks:

- If R_e is convex, then $R_{e\star}$ is convex.
- If R_e is concave, then $R_e^\star$ is concave and $\mathbf{k}$ is connected.

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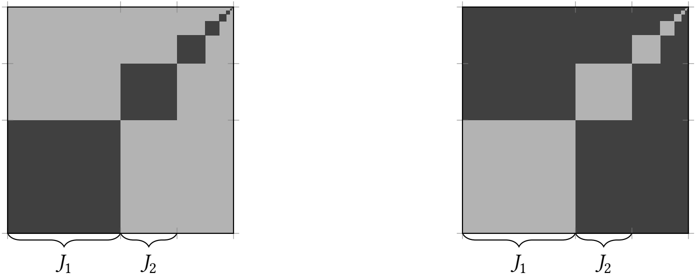
A toy model for studying the effect of assortativity

$\Omega = [0, 1]$ and μ is the Lebesgue measure. Consider the kernel:

$$\mathbf{k} = a \sum_{i} \mathbb{1}_{J_i \times J_i} + b \sum_{i \neq j} \mathbb{1}_{J_i \times J_j}.$$



(a) **Assortative** $a > b$.

(b) **Disassortative** $a < b$.

Figure: Grayplot of the kernels.

Proposition (Delmas, DD, Zitt)

- *If $a < b$ (disassortative), then $\mathbb{1}_{[1-c,1)}$ of cost c is Pareto optimal.*
- *If $a > b$ (assortative), then $\mathbb{1}_{[1-c,1)}$ of cost c is anti-Pareto optimal.*

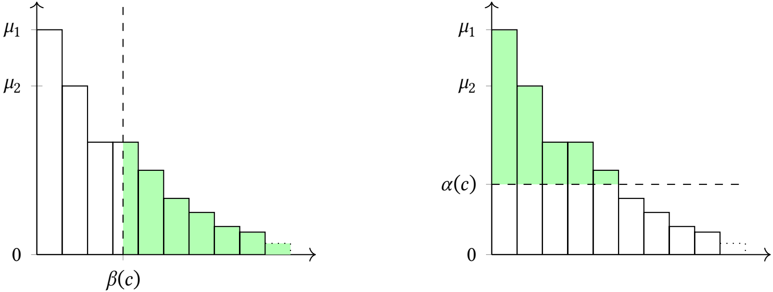
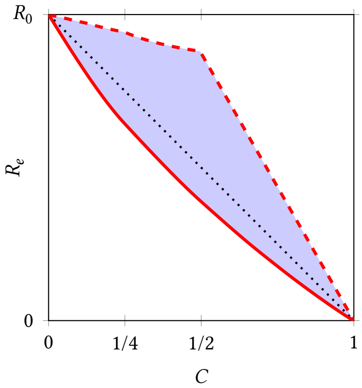
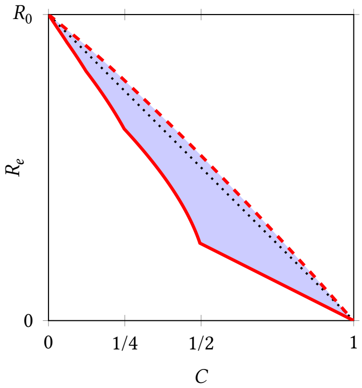


Figure: Representation of the optimal solutions.

Representation of set of outcomes when $\mu_n = 2^{-n}$ for $n \geq 1$



(a) The assortative case.



(b) The disassortative case.

Figure: Set of outcomes **F**.

Uniform strategies for constant degree kernels

Definition

$\mathbf{k}$ is a constant degree kernel if $x \mapsto \int \mathbf{k}(x,y)\mathrm{d}y$ and $x \mapsto \int \mathbf{k}(y,x)\mathrm{d}y$ are constant.

Proposition

Let $\mathbf{k}$ *be a constant degree kernel.*

- $\nabla R_e(v)$ *is constant when* $v \equiv c \in [0,1]$.
- *If* R_e *is convex, then the uniform vaccination strategies are Pareto optimal.*
- *If* R_e *is concave, then the uniform vaccination strategies are anti-Pareto optimal.*

The proof is based on Kloeckner 2019.

Symmetric regular kernel of rank 2

$\Omega = [0,1)$ equipped with μ the Lebesgue measure.
Consider the kernels:

$$\mathbf{k}^{+}(x,y) = R_0 + \theta(x)\theta(y),$$
$$\mathbf{k}^{-}(x,y) = R_0 - \theta(x)\theta(y).$$

where $\theta : [0,1] \to \mathbb{R}$ is increasing and satisfies the following conditions:

$$\theta(x) = -\theta(1-x) \quad \forall x \in [0,1], \qquad \theta(1)^2 \leq R_0.$$

We have:

$$\sigma(T_{\mathbf{k}^+}) = \{R_0, \|\theta\|_2^2, 0\}, \qquad \text{and} \quad \sigma(T_{\mathbf{k}^-}) = \{R_0, -\|\theta\|_2^2, 0\}.$$

Proposition (Solution for the kernel $k^+ = R_0 + \theta \otimes \theta$)

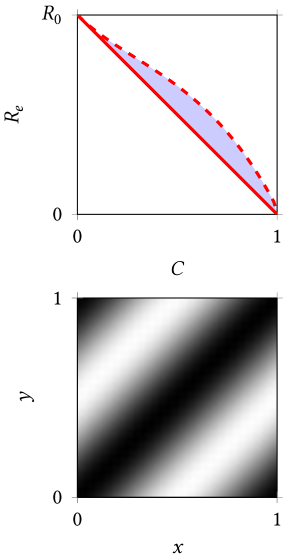
- *For all $c \in [0,1]$ the uniform vaccination strategies are Pareto optimal.*
- *For all $c \in [0,1]$, the strategies $\mathbb{1}_{[0,c)}$ and $\mathbb{1}_{[1-c,1)}$ of cost c are anti-Pareto optimal.*

Consequence

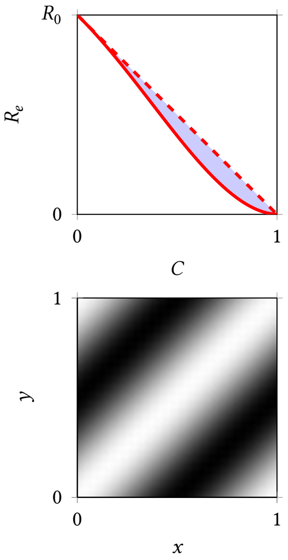
For the kernel $\mathbf{k}^+$, we need at least $\mathrm{HIT} = 1 - 1/R_0$ to reach herd immunity, even though the model is heterogeneous!

Proposition (Solution for the kernel $k^- = R_0 - \theta \otimes \theta$)

- *For all $c \in [0,1]$, the strategies $\mathbb{1}_{[0,c)}$ and $\mathbb{1}_{[1-c,1)}$ of cost c are Pareto optimal.*
- *For all $c \in [0,1]$ the uniform vaccination strategies are anti-Pareto optimal.*

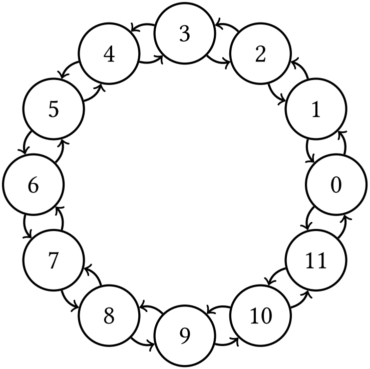


(a) $\mathbf{k}^{+}(x, y) = 1 + \cos(\pi x)\cos(\pi y)$

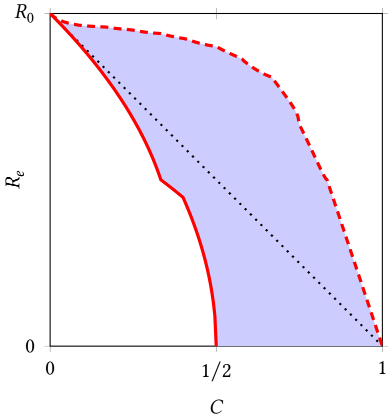


(b) $\mathbf{k}^{-}(x, y) = 1 - \cos(\pi x)\cos(\pi y)$

Uniform vaccination strategies are not always optimal.



(a) The graph.



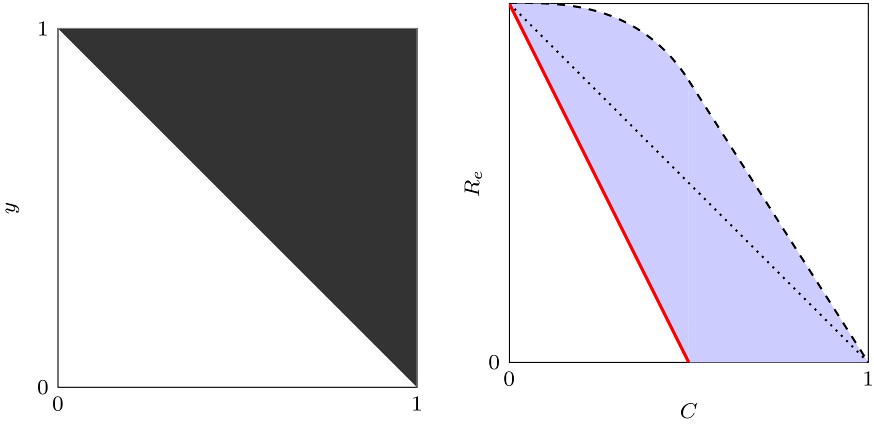
(b) Set of outcomes.

The Pareto optimal solution **cannot** be **parametrized greedily**.

Future research

- Monotonic kernels (*e.g.*, proportionate mixing/configuration model).
- Algorithm to compute the Pareto optimal solutions (greedy algorithm) and parametrization of the set of Pareto optimal strategies (gradient flow in L^1).
- Convergence of the SIS interacting particles system to the infinite-dimensional model?
- What happens when the graph of contacts is not dense?

A monotonic model



(a) The kernel

(b) Pareto and anti-Pareto front compared to the uniform strategies