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Law of large numbers for epidemic models with countably many types

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[1]This presentation is based on joint work with Andrew Barbour

Introduction

- ▶ We consider a class of stochastic models of epidemics.
- ▶ These models describe the spread of a parasitic disease.
- ▶ They are generalisations of stochastic models studied by Barbour & Kafetzaki (1993) and Luchsinger (1999,2001).
- ▶ They also include a stochastic version (and with truncated infection rates) of the model studied by Kretzschmar (1993).
- ▶ In this context, it is natural to distinguish hosts according to the number of parasites that they carry.
- ▶ This leads to models with countably infinitely many types, one for each possible number of parasites.

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Laws of large numbers

- We want to show that the proportion of hosts with k parasites is close to a certain deterministic function, for each k, with explicit rates of convergence.

- Infinitely many types cause difficulty: many arguments standard in finite case are not so in infinite case.

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Laws of large numbers

For epidemics with finitely many types there are LLN approximations, in the limit of large populations (i.e. as population size goes to infinity). ⇒ FINITE DIMENSIONAL SYSTEMS OF DIFFERENTIAL EQUATIONS

INFINITE DIMENSIONAL SYSTEMS OF DIFFERENTIAL EQUATIONS: Barbour & Kafetzaki (1993), Luchsinger (2001), Arrigoni (2003).

But the arguments are involved, requiring special assumptions about detailed form of transition rates, and not quantitative.

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Laws of large numbers

- Things are considerably more delicate in infinite dimensions, for example, as it is often hard to find a good norm. An extra difficulty in our case is caused by the fact that the operator driving the limiting differential equation is non-Lipschitz.

- Our goal: TO ESTABLISH LLN IN SUBSTANTIAL GENERALITY, quantifying rate of convergence.

- Models constructed by superimposing state-dependent transitions upon a process with otherwise independent and well-behaved dynamics within the individuals.

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Laws of large numbers

- ▶ State-dependent components have Lipschitz and growth conditions.
- ▶ This ensures the perturbation of the underlying semi-group governing independent dynamics not too severe.
- ▶ Our methods may be applied in other contexts, e.g. models in genetics and cellular biology, random graph processes (e.g. web graphs), algorithms in random networks.

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Our model

- Sequence of processes $X_N = (X_N^i(t) : i \in \mathbb{Z}_+)_{t \geq 0}$

- State space $\mathcal{X} := \{X \in \mathbb{Z}_+^\infty : \sum_{i \geq 0} X^i < \infty\}$

- $X_N^i(t) \in \mathbb{Z}_+$ is the i-th component, interpreted as number of individuals who carry i parasites at time t.

- We assume that $\sum_{j \geq 0} X_N^j(0) = N$.

- X_N evolves are a pure jump MC, with transitions corresponding to individuals changing type, arrivals and departures.

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Transitions

$$\xi \quad \to \quad \xi + (e(j) - e(i)) \text{ at rate } \xi^i \{\bar{\alpha}_{ij} + \alpha_{ij}(N^{-1}\xi)\},$$
$$(i \geq 0, \ j \geq 0, \ j \neq i);$$

(Type changes.) This type of transition corresponds to an infection of one individual, or an individual's disease state evolving spontaneously or due to treatment.

$\bar{\alpha}_{ij}$ model independent infection dynamics within individuals.

$\alpha_{ij}(N^{-1}\xi)$ depends on the overall levels ξ of infection in community.

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$\alpha_{ij}(N^{-1}\xi)$ can thus model interactions involving both infection with new parasites and loss of infection through parasite death.

Principally there to allow hosts to acquire further parasites through infection but can also model state-dependent loss of infection e.g. through treatment offered when higher levels of infection observed.

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Transitions

$$\xi \;\to\; \xi + e(i) \text{ at rate } N\beta_i(N^{-1}\xi), \quad i \geq 0;$$

(Births/arrivals)

Thus type of transition models births and immigration of individuals of different types. We allow dependence on community levels of infection.

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Transitions

$$\xi \;\to\; \xi - e(i) \text{ at rate } \xi^i\{\bar{\delta}_i + \delta_i(N^{-1}\xi)\}, \quad i \geq 0.$$

(Deaths/departures)

This type of transition models deaths and emigration. Again, we
allow dependence on community levels of infection.

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Interpretation: $\bar{\delta}_i$ can model the increase in host death or departure rate with an increase in the number of parasites carried; e.g. $\bar{\delta}_i \sim i$ as $i \to \infty$.

$\delta_i(N^{-1}\xi)$ can model population dependent effects on that rate and is not allowed to behave wildly as $i \to \infty$.

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Transitions summary and comments

- ▶ Rates $\bar{\alpha}_{ij}, \alpha_{ij}, \beta_i, \bar{\delta}_i, \delta_i$ model different aspects of the underlying parasite life cycle.

- ▶ The rates $\bar{\alpha}_{ij}$ and $\bar{\delta}_i$ represent parasite communities developing independently within different hosts, according to a pure jump Markov process, with host death at rate $\bar{\delta}_i$ when parasite load is i.

- ▶ $\bar{\alpha}_0$ are all zero if only parasite mortality and reproduction are modelled by $\bar{\alpha}_{ij}$, but may include part of infection force, so not true in general.

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Technical device

Let Δ be an absorbing cemetery state, reached if a host dies. Set

$$\bar{\alpha}_{i\Delta} = \bar{\delta}_i, \quad \bar{\alpha}_{ii} = -\alpha^*(i) - \bar{\delta}_i, \qquad i \geq 0,$$

where $\alpha^*(i) = \sum_{j \neq i} \bar{\alpha}_{ij} < \infty$.

Then $\bar{\alpha}$ is the infinitesimal matrix of a time-homogeneous pure jump Markov chain W on $\mathbb{Z}^+ \cup \{\Delta\}$.

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Law of large numbers - candidate limit

Looking at the average drift of X_N, we find that the limit process must solve the infinite dimensional differential equation

$$\frac{dx^i(t)}{dt} = \sum_{l \geq 0} x^l(t)\bar{\alpha}_{li} + \sum_{l \neq i} x^l(t)\alpha_{li}(x(t)) - x^i(t)\sum_{l \neq i}\alpha_{il}(x(t))$$
$$+ \beta_i(x(t)) - x^i(t)\delta_i(x(t)), \quad i \geq 0,$$

with initial condition $x_N(0) = N^{-1}X_N(0)$;

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▶ This can be expressed as (suppressing N-dependence)

$$\frac{dx}{dt} = Ax + F(x), \qquad x(0) = N^{-1}X_N(0),$$

▶ where $(Ax)^i = \sum_{l \geq 0} x^l \bar{\alpha}_{li}, \quad i \geq 0$, is a linear operator;

▶ and operator F is given by

$$(Fx)^i = \sum_{l \neq i} x^l \alpha_{li}(x) - x^i \sum_{l \neq i} \alpha_{il}(x) + \beta_i(x) - x^i \delta_i(x), \quad i \geq 0.$$

Our space

We shall be working in two spaces:

- The space

$$\ell_{11} = \{x \in \mathbb{R}^\infty : \sum_{i \geq 0}(i+1)|x^i| < \infty\},$$

  with norm $\parallel x \parallel_{11} = \sum_{i \geq 0}(i+1)|x^i|$;
- And the usual ℓ_1 with norm $\parallel x \parallel_1 = \sum_{i \geq 0}|x^i|$.

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Main theorem

Theorem

Suppose that certain technical conditions are satisfied,and that $x_N(0) := N^{-1}X_N(0)$ satisfies $\|x_N(0) - x_0\|_{11} \to 0$ as $N \to \infty$, for some $x_0 \in \ell_{11}$. Let $[0, t_{max})$ denote the interval where the above equation with x_0 as initial condition has a solution x in ℓ_{11}. Then for any $T < t_{max}$, there exists a constant $K(T)$ such that, as $N \to \infty$,

$$\mathbf{P}[N^{-1}\sup_{0 \leq t \leq T} \| X_N(t) - Nx_N(t) \|_1 > K(T)N^{-1/2}\log^{3/2} N] = O(N^{-1/2}),$$

where x_N solves the differential equation with $x_N(0) = N^{-1}X_N(0)$.

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What are the conditions required?

Roughly speaking, we have conditions of the following types:

- ▶ Conditions ensuring the per capita infection, birth, immigration and death rates are finite, bounded by constant multiples of $\|x\|_1 + 1$.

- ▶ This excludes any model in which the per capita infection rate is a constant K times the parasite density $\|x\|_{11}$, e.g. Kretzschmar (1993).

- ▶ Conditions implying that cumulative differences between states x and y are limited by multiples of $\|x - y\|_1$, and these multiples are bounded if $\|x\|_{11} \wedge \|y\|_{11}$ is.

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Conditions continued

- ► Conditions constraining overall rate of flow of parasites into the system through immigration to be finite, and bounded if parasite density is bounded.
- ► Conditions limiting the way this influx may depend on infection state.
- ► Conditions restricting rates of influx of parasites into hosts through infection. (Limit imposed on the *multiplicative* rate of increase of parasites in host; useful if parasites can directly reproduce in their hosts, at rate influenced by immune response.)

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Technical conditions

- Let
$$p_{ij}(t) := \mathbf{P}[W(t) = j \mid W(0) = i],$$
for $i \geq 0$ and $j \in \mathbb{Z}^+ \cup \Delta$.

- Let
$$\mathbf{E}_i^0(f(W(t))) := \mathbf{E}\{f(W(t))I[W(t) \notin \Delta] \mid W(0) = i\}.$$

- We shall assume μ is such that
$$\mathbf{E}_i^0\{(W(t) + 1)\} = \sum_{j \geq 0}(j + 1)p_{ij}(t) \leq (i + 1)e^{wt}, \quad i \geq 0,$$
(3.1)
for some $w > 0$.

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Technical conditions continued

- Also assume that for some $1 \le m_1, m_2 < \infty$,

$$\alpha^*(i) + \bar{\delta}_i \; \le \; m_1(i+1)^{m_2} \quad \text{for all} \quad i \ge 0; \qquad (3.2)$$

- and also that, for each $j \ge 0$,

$$\limsup_{l \to \infty} \bar{\alpha}(l, j) \; < \; \infty. \qquad (3.3)$$

- Chain W is non-explosive.

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Remaining conditions

- Remaining elements depend on the state of the system through the argument $x := N^{-1}X$.

- In random model, $x \in N^{-1}\mathcal{X}$ has only finitely many non-zero elements, but when passing to a LLN this need not be appropriate.

- Work within larger space
  $\ell_{11} := \{x \in \mathbb{R}^\infty : \sum_{i \geq 0}(i+1)|x^i| < \infty\}$ endowed with the norm $\|x\|_{11} := \sum_{i \geq 0}(i+1)|x^i|$.

- Assume that $\alpha_{il}, \beta_i, \delta_i$ are locally bounded and locally Lipschitz.

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Additional assumptions

Uniformly in $i \geq 0$ and $x, y \in \ell_{11}$,

$$\sum_{l \geq 0} \alpha_{il}(0) \ \leq \ a_{00} \tag{3.4}$$

$$\sum_{l \geq 0} (l+1)\alpha_{il}(0) \ \leq \ (i+1)a_{10}, \tag{3.5}$$

$$\sum_{l \geq 0} |\alpha_{il}(x) - \alpha_{il}(y)| \ \leq \ a_{01}(x,y)\|x-y\|_1, \tag{3.6}$$

$$\sum_{l \geq 0} (l+1)|\alpha_{il}(x) - \alpha_{il}(y)| \ \leq \ (i+1)a_{11}(x,y)\|x-y\|_1 \tag{3.7}$$

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Conditions continued

- Above, a_{r0} are finite.
- Also,

$$a_{r1}(x, y) \leq \tilde{a}_{r1}(\|x\|_{11} \wedge \|y\|_{11}), \quad r = 0, 1, \qquad (3.8)$$

with $\tilde{a}_{r1}$ bounded on bounded intervals.

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Conditions - birth rates

For some b_{rs} finite, for all $x, y \in \ell_{11}$

$$\sum_{i \geq 0} \beta_i(0) \ \leq \ b_{00}, \tag{3.9}$$

$$\sum_{i \geq 0} |\beta_i(x) - \beta_i(y)| \ \leq \ b_{01}(x, y)\|x - y\|_1, \tag{3.10}$$

$$\sum_{i \geq 0} (i + 1)\beta_i(0) \ \leq \ b_{10}, \tag{3.11}$$

$$\sum_{i \geq 0} (i + 1)|\beta_i(x) - \beta_i(y)| \ \leq \ b_{11}(x, y)\|x - y\|_{11}, \tag{3.12}$$

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Conditions - birth rates

▶ And also

$$b_{r1}(x, y) \leq \tilde{b}_{r1}(\|x\|_{11} \wedge \|y\|_{11}), \quad r = 0, 1, \qquad (3.13)$$

with $\tilde{b}_{r1}$ bounded on bounded intervals.

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Conditions - death rates

$$\sup_{i \geq 0} \delta_i(0) \ \leq \ d_0, \tag{3.14}$$

$$\sup_{i \geq 0} |\delta_i(x) - \delta_i(y)| \ \leq \ d_1(x,y)\|x - y\|_1, \tag{3.15}$$

where d_0 is finite, and

$$d_1(x,y) \leq \tilde{d}_1(\|x\|_{11} \wedge \|y\|_{11}), \quad r = 0, 1, \tag{3.16}$$

and $\tilde{d}_1$ is bounded on bounded intervals.

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Biological interpretation of our norms

- Norms $\|\cdot\|_1$ and $\|\cdot\|_{11}$ have natural interpretations.
- $\|\xi - \eta\|_1$ is the 'natural' measure of difference as seen from the hosts' point of view, sum of differences $\|\xi^i - \eta^i\|_1$ between numbers of hosts in state i.
- $\|X - Y\|_{11}$ is the corresponding 'parasite norm', a measure of parasite density, weighting $\|\xi^i - \eta^i\|_1$ by number of parasites plus 1.

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Examples

▶ Our model includes the stochastic non-linear model from Barbour & Kafetzaki (1993) and stochastic linear model from Barbour (1994). Both generalised and studied in depth by Luchsinger (1999,2001).

▶ Also includes a stochastic version of Kretzschmar (1993) with truncated infection rates.

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Luchsinger's non-linear model

- ▶ Population size is always N;
- ▶ $\beta_i(x) = \delta_i(x) = \bar{\delta}_i = 0, \quad \forall i \geq 0, x \in \ell_{11}$;
- ▶ $\bar{\alpha}$ is a superposition of generator of pure death process rate $\mu > 0$ (parasites die independently) and catastrophe process jumping to 0 at rate $\kappa \geq 0$ (hosts die independently);
- ▶ if a host dies, it is replaced by a healthy individual; hence

$$\bar{\alpha}_{i,i-1} = i\mu, \ \bar{\alpha}_{i0} = \kappa, \quad i \geq 2; \qquad \bar{\alpha}_{10} = \mu + \kappa;$$

also $\bar{\alpha}_{0j} = 0$;

- ▶ contacts at rate $\lambda > 0$, only infections of healthy hosts;

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Luchsinger's non-linear model

- If host with i parasites contacts a healthy one, probability p_{il} of infection with l parasites, $\sum_{l \geq 0} p_{il} = 1, \quad \forall i, \quad p_{00} = 1$;
- $F_i = (p_{il}, l \geq 0)$ is i-fold convolution of F_1 (parasites independent in transmitting offspring), has finite mean;
- Thus $\alpha_{il}(x) = 0, \quad i \neq 0$, and

$$\alpha_{0l}(x) \; = \; \lambda \sum_{i \geq 1} x^i p_{il}, \quad l \geq 1, \; x \in \ell_{11};$$

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Luchsinger's linear model

- Tacitly assume infinite pool of potential infectives, so no 0-coordinate needed;

- Only infected hosts are of interest, their number may vary;

- $\bar{\alpha}$ is a generator of simple death process rate $\mu > 0$, but restricted to reduced state space, so $\bar{\alpha}_{i,i-1} = i\mu, \quad i \geq 2$;

- incorporate hosts losing infection by taking $\bar{\delta}_i = \kappa, \quad i \geq 2$ and $\bar{\delta}_1 = \kappa + \mu$;

- Only healthy individuals can be infected, and infections with i parasites occur at a rate $\lambda \sum_{l \geq 1} x^l p_{li}$, so that
$\beta_i(x) = \lambda \sum_{l \geq 1} x^l p_{li}, \quad i \geq 1,$ and all $\alpha_{il}(x) = \delta_i(x) = 0$;

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Proof

- What kind of obstacles are we likely to encounter?
- The first one is to establish that the candidate limit differential equation has a (unique) solution.
- This is not straightforward, as we are working in infinite dimensions.
- The representation

$$\frac{dx}{dt} = Ax + F(x),$$

with A a linear operator and F a 'nice' operator is crucial to establishing existence and uniqueness of solution x.

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- Recall: Δ denotes an absorbing 'cemetery' state (host's death).

-
$$\bar{\alpha}_{i,\Delta} := \bar{\delta}_i, \quad \bar{\alpha}_{ii} := -\alpha^*(i) - \bar{\delta}_i, \quad i \geq 0,$$

  where $\alpha^*(i) := \sum_{j \geq 0, j \neq i} \bar{\alpha}_{ij}$.

- We have seen that $\bar{\alpha}$ is the infinitesimal matrix of a time homogeneous pure jump Markov process W on $\mathbb{Z}_+ \cup \{\Delta\}$.

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Semigroups

- ▶ The adjoint A^T of A is the Q-matrix of the time-homogeneous pure jump Markov process W.
- ▶ By standard theory, the semigroup $T(t)$ it generates is strongly continuous on ℓ_1. (Can identify $T(t)x$ with $P(t)^T x$ for any $x \in \ell_1$.)
- ▶ However, we need it to be strongly continuous on ℓ_{11}, and we prove this is the case under our assumptions.
- ▶ We further show that F is locally ℓ_{11}-Lipschitz continuous, and then the existence and uniqueness of a continuous (weak) solution in ℓ_{11} follows.

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Mild solution

Every solution x also satisfies

$$x(t) = T(t)x(0) + \int_0^t T(t-s)F(x(s)) \, ds,$$

where $T(t)$ is the C_0 semigroup generated by A.

Conversely, a continuous solution x of the integral equation is called a mild solution of the initial value problem.

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Mild solution

The following result guarantees the existence and uniqueness of a mild solution if F is Lipschitz.

Theorem (Pazy 1983, Theorem 1.4, Chapter 6)

Let $F : S \to S$ be locally Lipschitz continuous. If A is the infinitesimal generator of a $\mathcal{C}_0$ semigroup e^{tA} on S then for every $x_0 \in S$ there is a $t_{\max} \leq \infty$ such that the initial value problem

$$\frac{dx}{dt} = Ax + F(x), \qquad x(0) \in S,$$

has a unique mild solution x on $[0, t_{\max})$. Moreover, if $t_{\max} < \infty$, then $\lim_{t \uparrow t_{\max}} \parallel x \parallel = \infty$.

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In other words, our infinite-dimensional differential equation has a unique weak solution, so we at least have a function x_N to give substance to our limit result.

In fact, we also show that, under our conditions, x_N is a classical solution to the differential equation system.

- It would naturally be good to have $t_{max} = \infty$.
- However, our assumptions may not be enough to guarantee that this is true.
- On the other hand, $t_{max} = \infty$ if, for some $C < \infty$,

$$\|F(x)\|_{11} \leq C\|x\|_{11}.$$

- This is the case, for example, in Luchsinger's models.

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Smooth dependence on initial conditions

▶ Our solution depends smoothly on initial conditions within the interval of existence.

▶ Useful for approximating sequence of processes, if initial condition not fixed for all N, but $N^{-1}X_N(0) \to x_0$; gives the same order of approximation if we replace x_N by x.

Lemma

Fix a solution x to the integral equation, and suppose that $T < t_{max}$. Then there is an $\varepsilon > 0$ such that, if y is a solution with initial condition $y(0)$ satisfying $\|y(0) - x(0)\|_{11} \le \varepsilon$, then

$$\sup_{0 \le t \le T} \|x(t) - y(t)\|_{11} \le \|x(0) - y(0)\|_{11} C_T,$$

for a constant $C_T < \infty$.

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Two-stage approximation

- We construct an approximating model $\tilde{X}_N(\cdot)$, starting with $\tilde{X}_N(0) = X_N(0)$, and consisting of independent individuals.

- The process $\tilde{X}_N$ differs from X_N in having the non-linear elements of the transition rates made linear, by replacing the Lipschitz state–dependent elements $\alpha_{ij}(x), \beta_i(x), \delta_i(x)$ at any time t by their 'typical' values, derived from the differential equation.

- Standard Chernoff-type bounds show that $\tilde{X}_N(\cdot)$ stays close to $x_N(t)$ throughout $[0, T]$.

- Then we couple $\tilde{X}_N(\cdot)$ and $X_N(\cdot)$ so that the distance between them is small throughout $[0, T]$.

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Independent process transition rates

Individual's parasite load evolves according to an inhomogeneous Markov process $\widetilde{W}$ on $\mathbb{Z}_+ \cup \Delta$ with infinitesimal matrix

$$
\begin{aligned}
q_{lj}(t) &= \bar{\alpha}_{lj} + \tilde{\alpha}_{lj}(t), && j \neq l, \Delta, \ l \geq 0, \\
q_{l,\Delta}(t) &= \bar{\delta}_l + \tilde{\delta}_l(t), && l \geq 0, \\
q_{ll}(t) &= -\sum_{j \neq l} q_{lj}(t) - \bar{\delta}_l - \tilde{\delta}_l(t), && l \geq 0, \quad (4.17)
\end{aligned}
$$

where

$$
\tilde{\alpha}_{il}(t) := \alpha_{il}(x_N(t)); \quad \tilde{\delta}_i(t) := \delta_i(x_N(t)). \quad (4.18)
$$

Individuals also immigrate with rates

$$
N\tilde{\beta}_i(t) := N\beta_i(x_N(t)). \quad (4.19)
$$

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Linearised process deviations

$N^{-1}\widetilde{X}_N(t)$ and $x(t)$ stay 'close' together.

Lemma

Suppose that our assumptions hold, and that $X_N(0) \in \ell_{11}$. Then, for any $t \in [0, T]$ with $T < t_{max}^N$,

$$\mathbf{E}\|\widetilde{X}_N(t) - Nx_N(t)\|_1 \leq 3(M_T^N + 1)\sqrt{N \log N},$$

where $M_T^N = \sup_{0 \leq t \leq T} \sum_{i \geq 1}(i + 1)|x_N^i(t)|$. Furthermore, for any $r > 0$, there exist constants $K_r^{(1)} > 1, K_r^{(2)}$ such that

$$\mathbf{P}[\|\widetilde{X}_N(t) - Nx_N(t)\|_1 > K_r^{(1)}(M_T^N + 1)N^{1/2}\log^{3/2} N] \leq K_r^{(2)}G_T^N(1)N^{-r},$$

where $G_T^N = \sup_{0 \leq t \leq T} \sum_{i \geq 0}|x_N^i(t)|$.

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Coupling strategy

▶ To estimate deviations of $\widetilde{X}_N$ from X_N we couple them so "distance" between them is small over any finite interval.

▶ We pair each individual in state $i \geq 1$ in $X_N(0)$ with individual in state i in $\widetilde{X}_N(0)$ so all their $\bar{\alpha}$- and $\bar{\delta}$-transitions are identical.

▶ Rates of remaining transitions not quite the same, and hence processes can gradually drift apart.

▶ Strategy: make transitions identical as far as we can; once a transition in one process is not matched in the other, the individuals are decoupled thereafter.

▶ We show that number of decoupled pairs is small.

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Coupling details

- Coupling between X_N and $\widetilde{X}_N$ realised via a process $Z(\cdot)$ with

$$Z(t) = ((Z_l^i(t), \, i \geq 0, \, 1 \leq l \leq 3), Z_4(t)) \in \mathcal{X}^3 \times \mathbb{Z}_+.$$

- Here, $X_N(\cdot) = Z_1(\cdot) + Z_2(\cdot)$ and $\widetilde{X}_N(\cdot) = Z_1(\cdot) + Z_3(\cdot)$.
- Also $Z_1(0) = X_N(0) = \widetilde{X}_N(0)$, $Z_2(0) = Z_3(0) = 0 \in \mathcal{X}$, $Z_4(0) = 0$.
- Z_4 used only to keep count of certain uncoupled individuals, either unmatched Z_2-immigrants, or Z_3 individuals that die; and of coupled individuals who become uncoupled when one but not the other dies.

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Coupling transition rates

For $\bar{\alpha}$- and α-transitions, for $i \neq l$ (writing $X = Z_1 + Z_2$ and e_l^i for coordinate vectors):

$$Z \rightarrow Z + (e_1^l - e_1^i) \quad \text{at rate} \quad Z_1^i\{\bar{\alpha}_{il} + (\alpha_{il}(N^{-1}X) \wedge \alpha_{il}(x_N(t)))\};$$
$$Z \rightarrow Z + (e_2^l + e_3^i - e_1^i) \quad \text{at rate} \quad Z_1^i\{\alpha_{il}(N^{-1}X) - \alpha_{il}(x_N(t))\}^+;$$
$$Z \rightarrow Z + (e_2^i + e_3^l - e_1^i) \quad \text{at rate} \quad Z_1^i\{\alpha_{il}(N^{-1}X) - \alpha_{il}(x_N(t))\}^-;$$
$$Z \rightarrow Z + (e_2^l - e_2^i) \quad \text{at rate} \quad Z_2^i\{\bar{\alpha}_{il} + \alpha_{il}(N^{-1}X)\};$$
$$Z \rightarrow Z + (e_3^l - e_3^i) \quad \text{at rate} \quad Z_3^i\{\bar{\alpha}_{il} + \alpha_{il}(x_N(t))\},$$

with possibilities for individuals in the two processes to become uncoupled, when $N^{-1}X \neq x(t)$.

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For birth/immigration transitions:

$$Z \; \rightarrow \; Z + e_1^i \quad \text{at rate} \quad N\{\beta_i(N^{-1}X) \wedge \beta_i(x_N(t))\}, \quad i \geq 0;$$
$$Z \; \rightarrow \; Z + e_2^i + e_4 \quad \text{at rate} \quad N\{\beta_i(N^{-1}X) - \beta_i(x_N(t))\}^+, \quad i \geq 0;$$
$$Z \; \rightarrow \; Z + e_3^i \quad \text{at rate} \quad N\{\beta_i(N^{-1}X) - \beta_i(x_N(t))\}^-, \quad i \geq 0,$$

with some immigrations not being precisely matched.
Second transition includes an e_4 so that each Z_2 individual has a
counterpart in either Z_3 or Z_4.

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For deaths/emigration:

$$Z \to Z - e_1^i \quad \text{at rate} \quad Z_1^i \{\bar{\delta}_i + (\delta_i(N^{-1}X) \wedge \delta_i(x_N(t)))\}, \quad i \geq 0;$$

$$Z \to Z - e_1^i + e_3^i \quad \text{at rate} \quad Z_1^i \{\delta_i(N^{-1}X) - \delta_i(x_N(t))\}^+, \quad i \geq 0;$$

$$Z \to Z - e_1^i + e_2^i + e_4 \quad \text{at rate} \quad Z_1^i \{\delta_i(N^{-1}X) - \delta_i(x_N(t))\}^-, \quad i$$

$$Z \to Z - e_2^i \quad \text{at rate} \quad Z_2^i \{\bar{\delta}_i + \delta_i(N^{-1}X)\}, \quad i \geq 0;$$

$$Z \to Z - e_3^i + e_4 \quad \text{at rate} \quad Z_3^i \{\bar{\delta}_i + \delta_i(x_N(t))\}, \quad i \geq 0.$$

Here $Z_4(\cdot)$ also counts deaths of uncoupled Z_3-individuals, and uncoupled deaths in $\tilde{X}_N$ of coupled Z_1 individuals.

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Coupling - key bounds

With this construction, we have

$$\sum_{i \geq 0} Z_2^i(t) \leq Z_4(t) + \sum_{i \geq 0} Z_3^i(t) \tag{4.20}$$

for all t.

Also

$$V_N(t) := Z_4(t) + \sum_{i \geq 0} Z_3^i(t) \tag{4.21}$$

is a counting process. We thus have the bound

$$\|X_N(t) - \widetilde{X}_N(t)\|_1 = \|(Z_1(t) + Z_2(t)) - (Z_1(t) + Z_3(t))\|_1$$
$$\leq \sum_{i \geq 0} \{Z_2^i(t) + Z_3^i(t)\} \leq 2V_N(t). \tag{4.22}$$

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Bounding $V_N(t)$

Now V_N has a compensator A_N with intensity a_N, satisfying

$$
\begin{aligned}
a_N(t) &= \sum_{i \geq 0} Z_1^i(t) \sum_{l \neq i} |\alpha_{il}(N^{-1}X_N(t)) - \alpha_{il}(x_N(t))| \\
&+ N \sum_{i \geq 0} |\beta_i(N^{-1}X_N(t)) - \beta_i(x_N(t))| \\
&+ \sum_{i \geq 0} Z_1^i(t) |\delta_i(N^{-1}X_N(t)) - \delta_i(x_N(t))|
\end{aligned}
$$

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Bounding compensator of $V_N(t)$

After some calculation we find the intensity $a_N(t)$ satisfies

$$N^{-1}a_N(t)$$
$$\leq \quad \Big(\sum_{i\geq 0} x_N^i(t)a_{01,T}^N + b_{01} + \sum_{i\geq 0} x_N^i(t)d_1\Big)\|N^{-1}X_N(t) - x_N(t)\|_1$$
$$+ \quad \|N^{-1}\widetilde{X}_N(t) - x_N(t)\|_1\Big(a_{01,T}^N + d_1\Big)\|N^{-1}X_N(t) - x_N(t)\|_1$$
$$\leq \quad \{H_T^{(1,N)} + H_T^{(2,N)}\|N^{-1}\widetilde{X}_N(t) - x_N(t)\|_1\}\|N^{-1}X_N(t) - x_N(t)\|_1,$$

where

$$H_T^{(1,N)} = G_T^N(1)a_{01,T}^N + b_{01} + G_T^N(1)d_1;$$
$$H_T^{(2,N)} = a_{01,T}^N + d_1.$$

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Bounding compensator of $V_N(t)$

In particular, letting

$$\tau_N := \inf\{t \geq 0 : \|N^{-1}\widetilde{X}_N(t) - x_N(t)\|_1 \geq 1\},$$

we have

$$N^{-1}a_N(t \wedge \tau_N) \leq \{H_T^{(1,N)} + H_T^{(2,N)}\}\|N^{-1}X_N(t \wedge \tau_N) - x_N(t \wedge \tau_N)\|_1.$$
$$(4.23)$$

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Bounding the expected difference between $\widetilde{X}_N(t)$ and $X_N(t)$

By the above estimates plus routine Gronwall argument:

Lemma

Under Conditions (3.1)–(3.15), *for any* $t \in [0, T]$ *and for all* N
sufficiently large,

$$N^{-1}\mathbf{E}\|X_N(t \wedge \tau_N) - \widetilde{X}_N(t \wedge \tau_N)\|_1$$
$$\leq 14M_T^N N^{-1/2}\sqrt{\log N}\, t(H_T^{(1,N)} + H_T^{(2,N)})$$
$$\times \exp\{2t(H_T^{(1,N)} + H_T^{(2,N)})\}.$$

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Bounding the martingale part of $V_N(t)$

Write $M_N(\cdot) = V_N(\cdot) - A_N(\cdot)$ for the martingale part of V_N.

Lemma

Under Conditions (3.1)–(3.15), for any $t \in [0, T]$ and $y > 0$, and for all N large enough

$$\mathbf{P}[\sup_{0 \leq s \leq t} |N^{-1}M_N(s \wedge \tau_N)| \geq y]$$
$$\leq \; g(t(H_T^{(1,N)} + H_T^{(2,N)}))M_T^N y^{-2} N^{-3/2} \sqrt{\log N},$$

where $g(x) := 7xe^{2x}$.

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Limitations of the approach

- ▶ The approach presented works for a class of population/epidemic processes with countably infinite dimensions and non-Lipschitz generator.
- ▶ But each interaction may only change the state of only one of the interacting individuals. Otherwise the coupling with a process of independent individuals does not work.
- ▶ Also restrictions on growth/infection rates that are violated by some known models (e.g. Kretzschmar's model).

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We are now working on another approach that we hope will overcome these.

Before we worked only with deterministic equation

$$x(t) = x(0) + \int_0^t Ax(s)ds + \int_0^t f(s, x(s))ds.$$

Now use the corresponding stochastic equation

$$X_N(t) = X_N(0) + \int_0^t AX_N(s)ds + \int_0^t f(s, X_N(s))ds.$$

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Under certain conditions, this is 'equivalent' to

$$X_N(t) = T(t)X_N(0) + \int_0^t T(t-s)f(s, X_N(s))ds.$$

When the semigroup T is well-behaved, this enables us to use a martingale argument to show that X_N must be close to x solving

$$x(t) = T(t)x(0) + \int_0^t T(t-s)f(s, x(s))ds.$$

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Concluding remarks

- One of our methods is the two-stage approximation used in this work. We are now also working on another method, using exponential martingales, which covers certain models we have not been able to handle here.

- Later: hope to establish a central limit theorem.

- ANOTHER IMPORTANT QUESTION: what happens to the stochastic process and its deterministic approximation long-term?

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Concluding remarks

▶ The issue of long-term behaviour is almost completely open; very little is known except in special cases.

▶ What about the convergence of the Markov chain to it stationary distribution? Under what conditions is it rapidly mixing, i.e. in time $O(\log N)$? (N is of the order of the population size.)

▶ Can we determine the stationary solutions of the limiting differential equation? In particular, when does it have a unique, globally attractive fixed point?

▶ Under what conditions does the stochastic process stay close to its deterministic limit long-term, perhaps even uniformly in time?