Law of large numbers for epidemic models with countably many types

Malwina J Luczak [1]

Department of Mathematics
London School of Economics
London WC2A 2AE
UK
e-mail: m.j.luczak@lse.ac.uk

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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 certain 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.
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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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- State-dependent components have Lipschitz and growth conditions.
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Long-term behaviour

- This problem is almost completely wide-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?
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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 $\sum_{j \geq 0} X_N^j(0) = N$.
- Transitions correspond to individuals changing type, new arrivals/births and departures/deaths.

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Transitions

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

(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.

$\alpha_{ij}(x)$ depends on the overall levels x of infection in community. 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 summary and comments

- In the above the 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.
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Law of large numbers - candidate limit

Natural candidate approximation is by the solution to the 'average drift' infinite dimensional differential equation

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

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- This can be expressed as

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

- 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

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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 $\| x \|_{11} = \sum_{i \geq 0} (i+1)|x^i|$;
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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* $N \to \infty$*,*

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

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

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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* $N \to \infty$,

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Then, for any $1/2 < \gamma \leq 1$*, and for any* $T < t_{max}$*, there exists a constant* $K_\gamma(T)$ *such that, as* $N \to \infty$*,*

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What are the conditions required?

Without getting into technical details, 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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Biological interpretation of our norms

- Norms $\|\cdot\|_1$ and $\|\cdot\|_{11}$ have natural interpretations.
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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).
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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

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

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- Tacitly assume infinite pool of potential infectives, so no 0-coordinate needed;
- Only infected hosts are of interest, their number may vary;
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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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- Let Δ denote an absorbing ‘cemetery’ state (host’s death).
- Let

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

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

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Semigroups

- Then in our representation, the adjoint A^T of A is the Q-matrix of a time-homogeneous pure jump Markov process.
- By standard theory, the semigroup $T(t)$ it generates is strongly continuous on ℓ_1.
- However, we need it to be strongly continuous on ℓ_{11}, and we prove this is the case under our assumptions.
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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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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 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 $\lim_{t \uparrow t_{\max}} \| x \| = \infty$.

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

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

Mild solution

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

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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.
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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 $\|y - x\|_{11} \leq \varepsilon$, then

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

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Two-stage approximation

The rest of our proof goes in two stages:

- First we construct an approximating model $\tilde{X}_N(\cdot)$, starting with $\widetilde{X}_N(0) = X_N(0)$, and consisting of independent individuals.
- The process $\widetilde{X}_N$ 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 a time inhomogeneous Markov process $\widetilde{W}$ on $\mathbb{Z}_+ \cup \Delta$ with infinitesimal matrix

$$\begin{aligned} q_{lj}(t) &= \bar{\alpha}_{lj} + \tilde{\alpha}_{lj}(t), \qquad j \neq l, \Delta, \; l \geq 0, \\ q_{l,\Delta}(t) &= \bar{\delta}_l + \tilde{\delta}_l(t), \qquad l \geq 0, \\ q_{ll}(t) &= -\sum_{j \neq l} q_{lj}(t) - \bar{\delta}_l - \tilde{\delta}_l(t), \qquad l \geq 0, \end{aligned} \tag{4.1}$$

where

$$\tilde{\alpha}_{il}(t) := \alpha_{il}(x_N(t)); \quad \tilde{\delta}_i(t) := \delta_i(x_N(t)). \tag{4.2}$$

Individuals also immigrate with rates

$$N\tilde{\beta}_i(t) := N\beta_i(x_N(t)). \tag{4.3}$$

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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 $T < t^N_{max}$,

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

where $M^N_T = \sup_{0 \le t \le T} \sum_{i \ge 1}(i+1)|x^i_N(t)|$. Furthermore, for any $r > 0$, there exist constants $K^{(1)}_r > 1, K^{(2)}_r$ such that

$$\mathbf{P}[\|\widetilde{X}_N(t) - Nx_N(t)\|_1 > K^{(1)}_r(M^N_T + 1)N^{1/2}\log^{3/2} N] \;\le\; K^{(2)}_r G^N_T(1)N^{-r},$$

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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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- 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.

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):

$$
\begin{aligned}
Z &\to 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 &\to 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 &\to 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 &\to Z + (e_2^l - e_2^i) \quad \text{at rate} \quad Z_2^i\{\bar{\alpha}_{il} + \alpha_{il}(N^{-1}X)\};\\
Z &\to Z + (e_3^l - e_3^i) \quad \text{at rate} \quad Z_3^i\{\bar{\alpha}_{il} + \alpha_{il}(x_N(t))\},
\end{aligned}
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with possibilities for individuals in the two processes to become uncoupled, when $N^{-1}X \neq x(t)$.

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Z &\to Z + (e^l_1 - e^i_1) \quad \text{at rate} \quad Z^i_1\{\bar{\alpha}_{il} + (\alpha_{il}(N^{-1}X) \wedge \alpha_{il}(x_N(t)))\};\\
Z &\to Z + (e^l_2 + e^i_3 - e^i_1) \quad \text{at rate} \quad Z^i_1\{\alpha_{il}(N^{-1}X) - \alpha_{il}(x_N(t))\}^+;\\
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with possibilities for individuals in the two processes to become uncoupled, when $N^{-1}X \neq x(t)$.

Coupling transition rates

For birth/immigration transitions:

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

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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Coupling transition rates

For deaths/emigration:

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

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

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

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

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

Coupling - key bounds

With this construction, we have

$$\sum_{i\geq 0} Z_2^i(t) \leq Z_4(t) + \sum_{i\geq 0} Z_3^i(t) \tag{4.4}$$

for all t.

Also

$$V_N(t) \ := \ Z_4(t) + \sum_{i\geq 0} Z_3^i(t) \tag{4.5}$$

is a counting process. We thus have the bound

$$\begin{aligned} \|X_N(t) - \widetilde{X}_N(t)\|_1 \ &= \ \|(Z_1(t) + Z_2(t)) - (Z_1(t) + Z_3(t))\|_1 \\ &\leq \ \sum_{i\geq 0}\{Z_2^i(t) + Z_3^i(t)\} \ \leq \ 2V_N(t). \end{aligned} \tag{4.6}$$

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$$\begin{aligned} \|X_N(t) - \widetilde{X}_N(t)\|_1 \;&=\; \|(Z_1(t)+Z_2(t)) - (Z_1(t)+Z_3(t))\|_1 \\ &\leq\; \sum_{i\geq 0}\{Z_2^i(t) + Z_3^i(t)\} \;\leq\; 2V_N(t). \end{aligned} \tag{4.6}$$