Epidemics in populations with demography and importation of infectives

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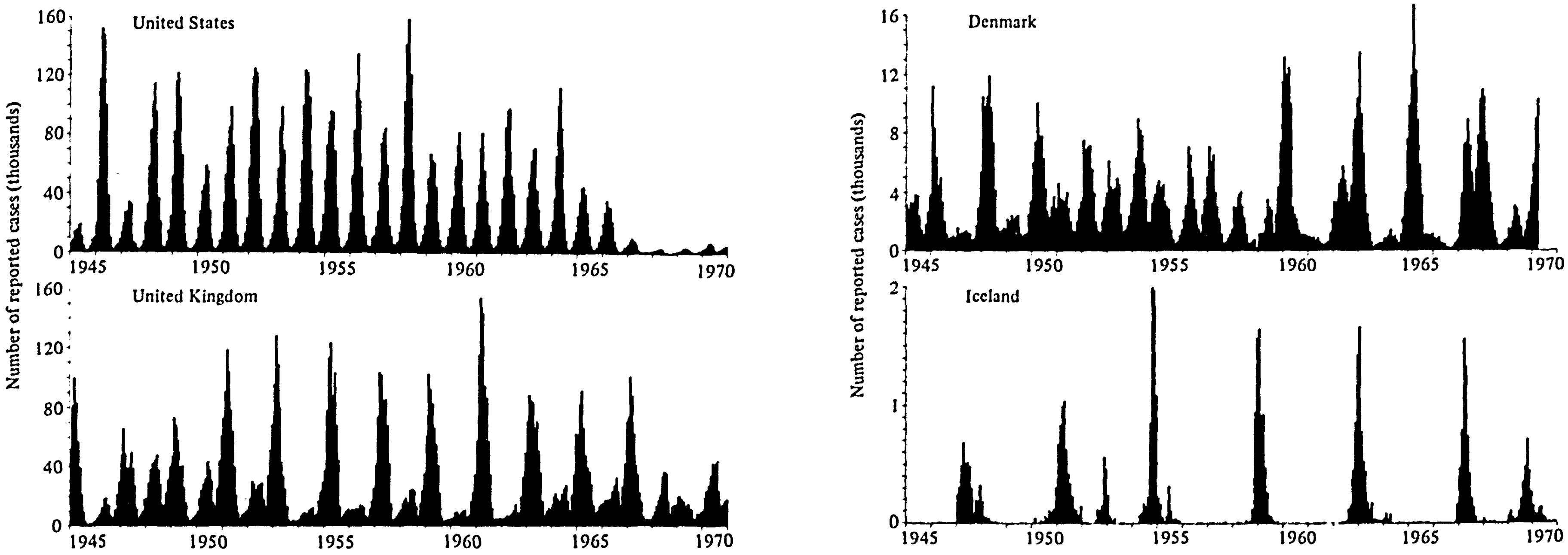
Measles



Reported case of measles, 1945–70. Source: W.H.O. bulletins. Taken from Cliff and Haggett (1980).

Population model

- Process indexed by a target population size n.
- Let $N^{(n)}(t)$ be the population size at time t. Then $\{N^{(n)}(t) : t \geq 0\}$ is modelled as a Markov immigration-death process with constant immigration rate $n\mu$ and individual death rate μ.
- In the absence of infection, if $n^{-1}N^{(n)}(0) \to s_0$ as $n \to \infty$ then $\{\bar{N}^{(n)}(t) : t \geq 0\} = \{n^{-1}N^{(n)}(t) : t \geq 0\}$ converges almost surely to the deterministic model

$$\frac{ds}{dt} = \mu - \mu s, \qquad s(0) = s_0,$$

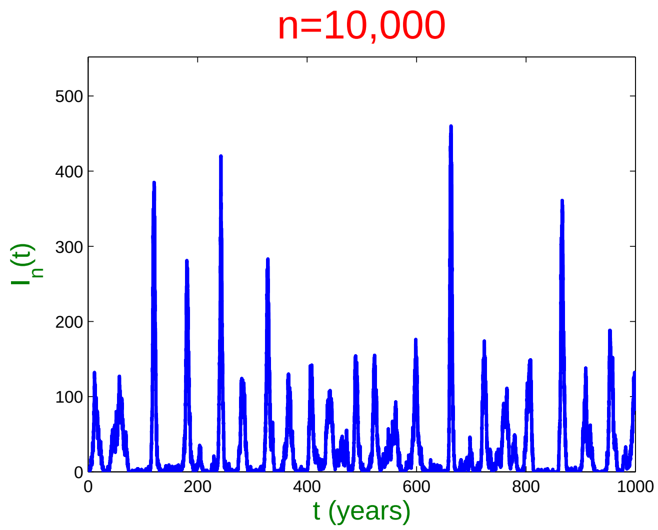
having solution

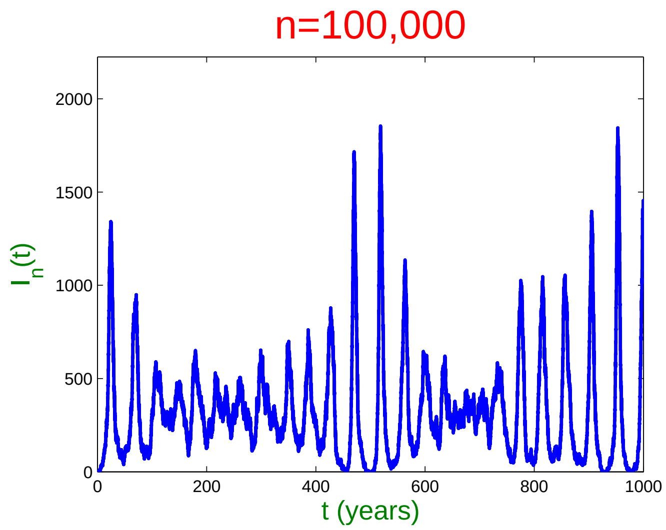
$$s(t) = 1 - (1 - s_0)\mathrm{e}^{-\mu t} \qquad (t \geq 0).$$

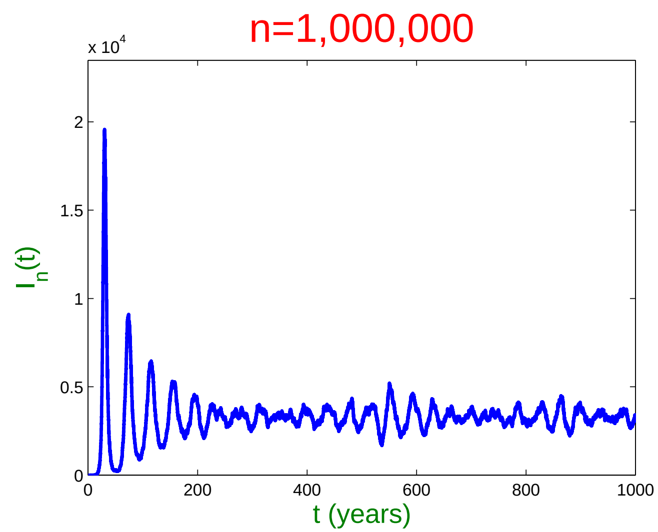
Epidemic model

- Homogeneously mixing population.
- SIR (susceptible $\to$ infective $\to$ recovered)
- Fraction κ_n of all births (i.e. immigrants) are infectives, with the remaining births being susceptibles.
- While infectious, each infective infects any given susceptible at rate $n^{-1}\lambda_n$, independently between each distinct pair of individuals.
- Each infective recovers and becomes permanently immune at rate γ_n.
- Let $S^{(n)}(t)$, $I^{(n)}(t)$ and $R^{(n)}(t)$ denote respectively the number of susceptibles, infectives and recovered at time t. Assume that $I^{(n)}(0) = 0$ and $\bar{S}^{(n)}(0) \to s_0$ as $n \to \infty$. (The initial number of recovered $R^{(n)}(0)$ has no effect on the ensuing epidemic.)

Effect of populations size n



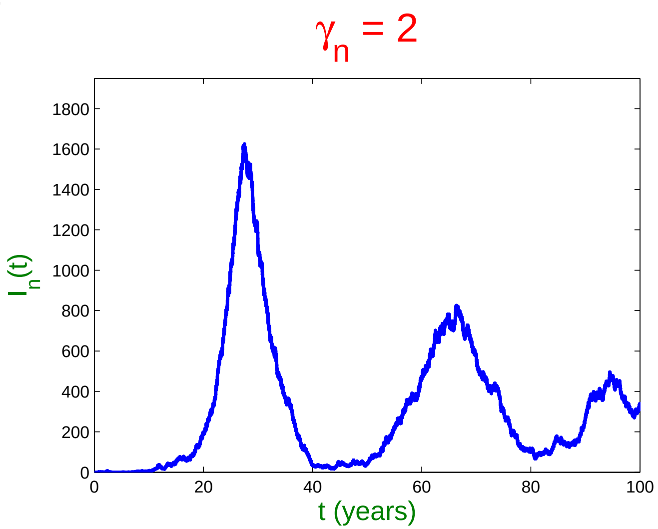


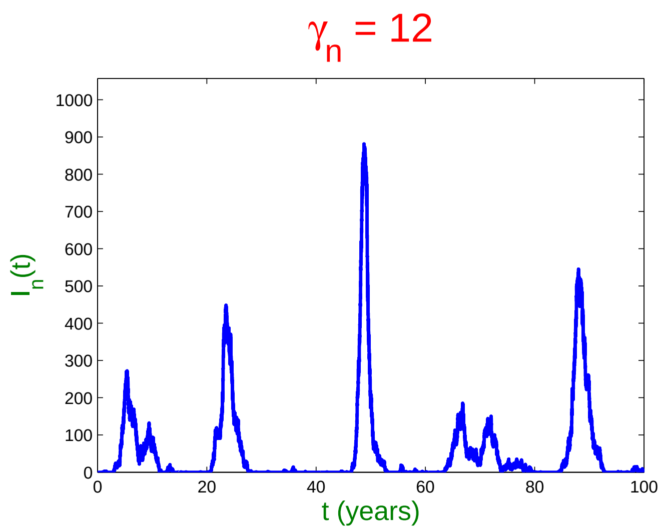


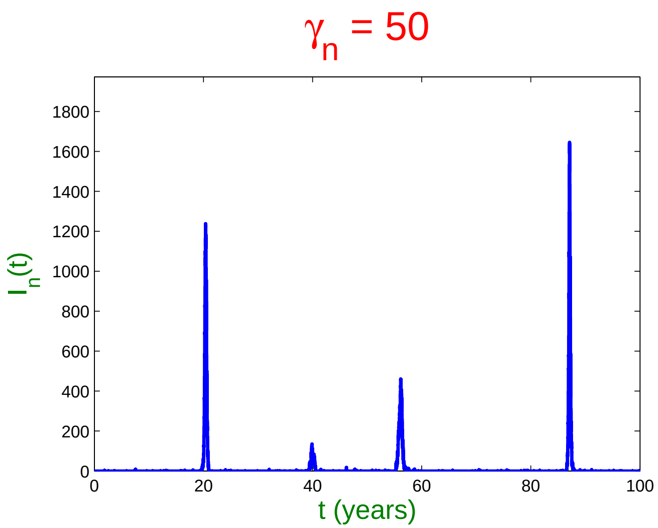
$\mu = \frac{1}{75}$, $\gamma_n = 2$, $\lambda_n = 4$

Importation rate of infectives is one per two years

Effect of rate of disease dynamics



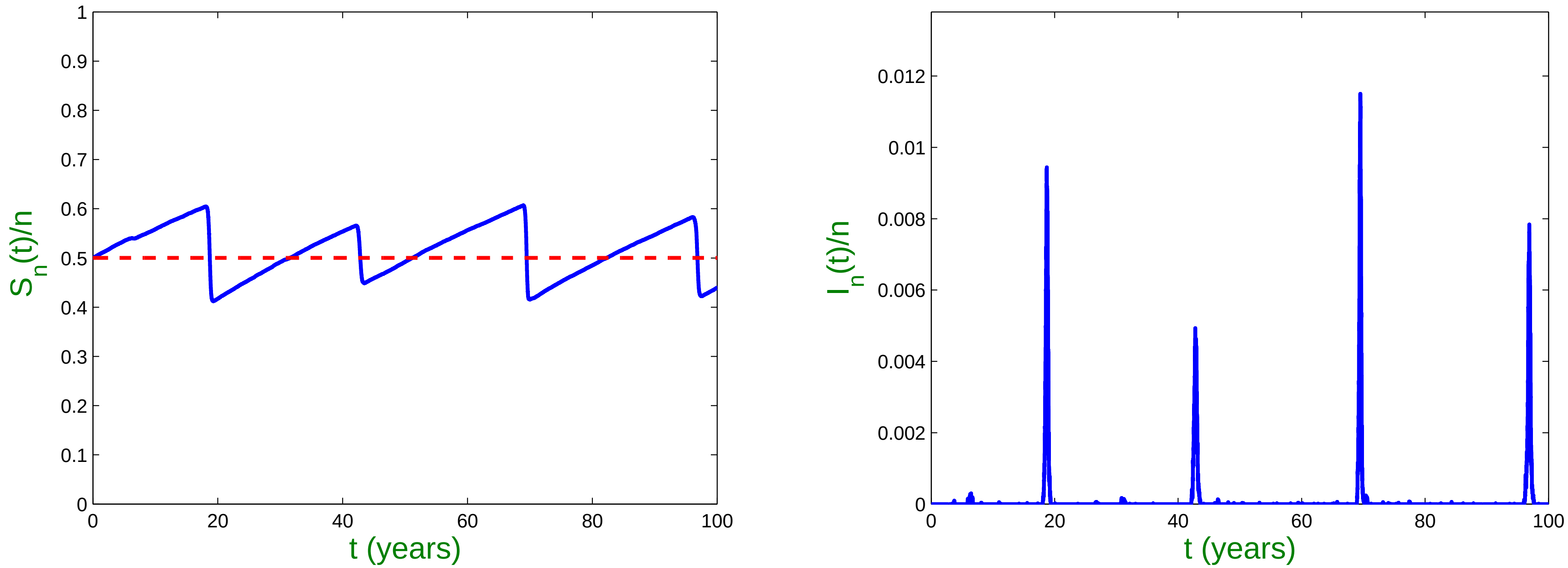




$\mu = \frac{1}{75}$, $n = 100,000$, $\lambda_n = 2\gamma_n$

Importation rate of infectives is one per year

Simulation of epidemic model



Simulation of epidemic model with population size $n = 100,000$, $\mu = \frac{1}{75}$, $\gamma_n = 50$ (so the mean infectious period is about 1 week), $\lambda_n = 2\gamma_n$. Importation rate of infectives is one per year

Asymptotic regimes

We assume that the target population size $n \to \infty$ such that

(a) $\kappa_n n \to \kappa$, so the total importation rate of infectives $\mu n \kappa_n \to \mu\kappa > 0$;

(b) $\lambda_n = c_n$ and $\gamma_n = c_n \gamma$, where $\gamma \in (0,1)$.

Asymptotic regimes As $n \to \infty$:

(i) $c_n / \log n \to \infty$,

(ii) $c_n / \log n \to c \in (0, \infty)$,

(iii) $c_n \to \infty$ slower than $\log n$,

(iv) $c_n \to c' \in (0, \infty)$.

SIR epidemic without demography

Suppose that $\mu = 0$. Then $\{(S^{(n)}(t), I^{(n)}(t)) : t \geq 0\}$ has transition rates:

Transition	Type	Rate
$(s,i) \rightarrow (s-1, i+1)$	infection of susceptible	$n^{-1}\lambda_n si$
$(s,i) \rightarrow (s, i-1)$	recovery of infective	$\gamma_n i$

- Suppose that $I^{(n)}(0) = 1$ and $n \rightarrow \infty$ such that $\lambda_n \rightarrow 1$, $\gamma_n \rightarrow \gamma \in (0,1)$ and $\bar{S}^{(n)}(0) \rightarrow s_0 \in (0,1)$.
- Then $\{I^{(n)}(t) : t \geq 0\}$ converges almost surely to a time-homogeneous linear birth-and-death process, Z say, with birth rate s_0, death rate γ and one initial individual.
- Z is supercritical $\iff$ $s_0 > \gamma$.

SIR epidemic without demography

Let $D^{(n)} = \inf\{t : I^{(n)}(t) = 0\}$ be the duration of the epidemic, so the final number of susceptibles is $S^{(n)}(D^{(n)})$, and let $\hat{D}^{(n)} = \inf\{t : I^{(n)}(t) \geq \log n\}$. Then

$$\lim_{n\to\infty} \mathrm{P}\left(\hat{D}^{(n)} < \infty\right) = \begin{cases} 0 & \text{if } s_0 \leq \gamma, \\ 1 - \frac{\gamma}{s_0} & \text{if } s_0 > \gamma. \end{cases}$$

If $\hat{D}^{(n)} < \infty$ then, as $n \to \infty$,

- $\{(\bar{S}^{(n)}(t), \bar{I}^{(n)}(t)) : t \geq 0\}$ converges to a random time translate of the deterministic model

$$\frac{ds}{dt} = -si, \qquad \frac{di}{dt} = si - \gamma i;$$

- $\bar{S}^{(n)}(D^{(n)}) \xrightarrow{\mathrm{D}} s_0(1 - \tau_\gamma(s_0))$, where for $s > \gamma$, $\tau_\gamma(s)$ is the unique strictly positive solution of the equation

$$1 - \tau = \mathrm{e}^{-\frac{1}{\gamma}s\tau};$$

- there exists $d \in (0, \infty)$ such that $D^{(n)} / \log n \xrightarrow{\mathrm{P}} d$.

(Barbour (1975), von Bahr and Martin-Löf (1980), Barbour and Reinert (2013))

Asymptotic regime (i): $c_n / \log n \to \infty$

- Let $S = \{S(t) : t \geq 0\}$ be a Markovian regenerative process, with renewals occurring whenever $S(t) = \gamma$. Between each renewal, $S(t)$ increases deterministically according to

$$S'(t) = \mu(1 - S(t)),$$

except for one down jump (from above γ to below γ), corresponding to a major outbreak.

- Under asymptotic regime (i), $\bar{S}^{(n)} \Rightarrow S$ as $n \to \infty$, where $\Rightarrow$ denotes convergence in the Skorohod M_1 (or M_2) topology.

- Note that $\bar{S}^{(n)}$ does NOT converge to S in the usual Skorohod J_1 topology as the sample paths of S are almost surely discontinuous but the sample paths of $\bar{S}^{(n)}$ contain only jumps of size n^{-1}, so are "close" to being continuous for large n.

Asymptotic regime (i) – limiting process S

- If a renewal occurs at time 0 and T is the time of the down jump then

$$S(t) = 1 - (1-\gamma)\mathrm{e}^{-\mu t} \quad (0 \leq t < T).$$

- An infective immigrating at time t since the last renewal has probability $1 - \frac{\gamma}{S(t)}$ of triggering a major outbreak, so, for $t \geq 0$,

$$\mathrm{P}(T \leq t) = 1 - \exp\left[-\mu\kappa \int_0^t \left(1 - \frac{\gamma}{S(u)}\right) \mathrm{d}u\right] = 1 - \mathrm{e}^{-\mu\kappa t}\left(\frac{\mathrm{e}^{\mu t} - 1 + \gamma}{\gamma}\right)^{\kappa\gamma}.$$

- After the down jump, $S(T) = S(T-)(1 - \tau_\gamma(S(T-)))$.

- Properties of S such as the inter-arrival time distribution, the distribution of the down-jump size and the stationary distribution of $S(t)$ are available.

Asymptotic regime (ii) – invasion

- Recall $\lambda_n = c_n$, $\gamma_n = c_n\gamma$, where $\gamma \in (0,1)$, and $\lim_{n\to\infty} c_n/\log n = c$.
- Suppose that $I^{(n)}(0) = 1$, $\lim_{n\to\infty} \bar{S}^{(n)}(0) = \hat{s}_0 \in (0,1]$ and there is no immigration of infectives.
- While $I^{(n)}(t) \leq n/(\log n)^2$, $\{I^{(n)}(t) : t \geq 0\}$ can be approximated by a time-inhomogeneous linear birth-and-death process $\{Z^{(n)} : t \geq 0\}$, with birth rate $\lambda^{(n)}(t) = c_n\left[1-(1-\hat{s}_0)\mathrm{e}^{-\mu t}\right]$ and death rate $\mu^{(n)}(t) = \gamma c_n + \mu$.
- Let $t_1^{(n)} = \inf\{t \geq 0 : Z^{(n)}(t) \geq n/(\log n)^2\}$. Then, as $n \to \infty$,

$$\mathrm{P}(t_1^{(n)} < \infty) \to \max\left(1 - \frac{\gamma}{\hat{s}_0}, 0\right) \qquad \text{and} \qquad t_1^{(n)} | t_1^{(n)} < \infty \xrightarrow{\mathrm{p}} t_G,$$

where $t_G = t_G(c, \gamma, \mu, \hat{s}_0)$ is the unique solution in $(0,\infty)$ of

$$c\left[(1-\gamma)t - \frac{(1-\hat{s}_0)}{\mu}\left(1-\mathrm{e}^{-\mu t}\right)\right] = 1.$$

Asymptotic regime (ii) – body of epidemics

- Suppose that $I^{(n)}(0) = \lceil n/(\log n)^2 \rceil$ and $\bar{S}^{(n)}(0) \xrightarrow{\text{p}} \tilde{s}_1 = 1 - (1 - \hat{s}_0)\mathrm{e}^{-\mu t_G}$ as $n \to \infty$.

- Let $u_1^{(n)} = \inf\left\{t \geq 0 : I^{(n)}(t) \leq \frac{n}{(\log n)^2} \text{ and } \bar{S}^{(n)}(t) < \gamma\right\}$.

- Then, since $c_n \to \infty$ as $n \to \infty$, the main body of an epidemic is instantaneous in the limit as $n \to \infty$, so

  (i) $u_1^{(n)} \xrightarrow{\text{p}} 0$ as $n \to \infty$; and

  (ii) $\bar{S}^{(n)}(u_1^{(n)}) \xrightarrow{\text{p}} s_1 = \tilde{s}_1(1 - \tau_\gamma(\tilde{s}_1))$ as $n \to \infty$.

Asymptotic regime (ii) – fade out

- Suppose that $I^{(n)}(0) = \lfloor n/(\log n)^2 \rfloor$ and $\bar{S}^{(n)}(0) \xrightarrow{\mathrm{p}} s_1 < \gamma$ as $n \to \infty$.
- Then $\{I^{(n)}(t) : t \geq 0\}$ can be approximated by the birth-and-death process $\{Z^{(n)}(t) : t \geq 0\}$ with birth rate $\lambda^{(n)}(t) = c_n \left[1 - (1 - s_1)\mathrm{e}^{-\mu t}\right]$ and death rate $\mu^{(n)}(t) = \gamma c_n + \mu$.
- As $n \to \infty$, $\{Z^{(n)}(t) : t \geq 0\}$ is critical at time $t = \check{t} = \frac{1}{\mu}\left(\frac{1-s_1}{1-\gamma}\right)$.
- Using Kendall (1948),

$$\begin{aligned} \mathrm{E}\left[Z^{(n)}(\check{t})\right] &= \lfloor n/(\log n)^2 \rfloor \exp\left\{c_n \left[(1-\gamma)\check{t} - \frac{(1-s_1)}{\mu}\left(1 - \mathrm{e}^{-\mu\check{t}}\right)\right] - \mu\check{t}\right\} \\ &= \lfloor n/(\log n)^2 \rfloor \, n^{\frac{c_n}{\log n}\left[(1-\gamma)\check{t} - \frac{(1-s_1)}{\mu}\left(1-\mathrm{e}^{-\mu\check{t}}\right)\right]} \mathrm{e}^{-\mu\check{t}}. \end{aligned}$$

- $\lim_{n\to\infty} \mathrm{E}\left[Z^{(n)}(\check{t})\right] = 0 \iff c\left[(1-\gamma)\check{t} - \frac{(1-s_1)}{\mu}\left(1 - \mathrm{e}^{-\mu\check{t}}\right)\right] < -1$.

Asymptotic regime (ii) – fade out

- Let $s_{\rm crit} = s_{\rm crit}(\gamma, \mu, c) = \gamma - (1-\gamma)h^{-1}\left(\frac{\mu}{c(1-\gamma)}\right)$, where $h(x) = x - \log(1+x)$ $(x \geq 0)$. Then,

$$\lim_{n\to\infty} \mathrm{P}(\text{fade out}) = \begin{cases} 1 & \text{if } s_1 < s_{\rm crit}, \\ 0 & \text{if } s_1 > s_{\rm crit}. \end{cases}$$

- For fixed (γ, μ),
  - $s_{\rm crit}$ is monotonically increasing in c;
  - $s_{\rm crit} \uparrow \gamma$ as $c \to \infty$ and $s_{\rm crit} \downarrow -\infty$ as $c \downarrow 0$.
- There exists $c_{\rm crit} = c_{\rm crit}(\gamma, \mu)$ such that if $c < c_{\rm crit}$ then

$$\lim_{n\to\infty} \mathrm{P}(\text{fade out}) = 0 \quad \text{for all } \hat{s}_0 \in (0, 1].$$

Asymptotic regime (ii) – endemicity

- Suppose $s_1 > s_{\text{crit}}$ and $\bar{t}_2^{(n)} > 0$ solves $\mathrm{E}\left[Z^{(n)}(\bar{t}_2^{(n)})\right] = \lceil n/(\log n)^2 \rceil$. Then

$$\lfloor n/(\log n)^2 \rfloor \exp\left\{c_n \left[(1-\gamma)\bar{t}_2^{(n)} - \frac{(1-s_1)}{\mu}\left(1-\mathrm{e}^{-\mu\bar{t}_2^{(n)}}\right)\right] - \mu\bar{t}_2^{(n)}\right\} = \lceil n/(\log n)^2 \rceil,$$

  so, $\bar{t}_2^{(n)} \to \hat{t}_2$ as $n \to \infty$, where $\hat{t}_2$ is the unique solution in $(0,\infty)$ of

$$(1-\gamma)t - \frac{(1-s_1)}{\mu}\left(1-\mathrm{e}^{-\mu t}\right) = 0.$$

- Let $\hat{t}_2^{(n)} = \inf\left\{t > 0 : I^{(n)}(t) \geq \frac{n}{(\log n)^2} \text{ and } \bar{S}^{(n)}(t) > \gamma\right\}$. Then, as $n \to \infty$,

$$\hat{t}_2^{(n)} \xrightarrow{\mathrm{p}} \hat{t}_2 \qquad \text{and} \qquad \bar{S}^{(n)}(\hat{t}_2^{(n)}) \xrightarrow{\mathrm{p}} \tilde{s}_2 = 1-(1-s_1)\mathrm{e}^{-\mu\hat{t}_2}.$$

- Note that $\hat{t}_2$ and $\tilde{s}_2$ are independent of c.

Asymptotic regime (ii) – endemicity

- For $\tilde{s}_1 \in (\gamma, 1]$, let $f_E(\tilde{s}_1) = \tilde{s}_1(1 - \tau_\gamma(\tilde{s}_1))$ and for $s_1 \in (s_{\text{crit}}, \gamma)$, let $f_R(s_1) = 1 - (1 - s_1)\mathrm{e}^{-\mu \hat{t}_2}$.
- Suppose that $\tilde{s}_1 \in (\gamma, 1]$ satisfies $s_1 = f_E(\tilde{s}_1) > s_{\text{crit}}$. Then, as $n \to \infty$ the epidemic process is encapsulated by the iterative map given by

$$\tilde{s_k} = f_R(s_{k-1}) \qquad \text{and} \qquad s_k = f_E(\tilde{s}_k) \qquad (k = 2, 3, \dots).$$

- For $k = 2, 3, \dots$ let $\hat{t}_k$ be the unique solution in $(0, \infty)$ of

$$(1 - \gamma)t - \frac{(1 - s_{k-1})}{\mu}\left(1 - \mathrm{e}^{-\mu t}\right) = 0.$$

$\hat{t}_k$ is the time elapsing between the $(k-1)$th and kth down jump in the limiting process S.

Asymptotic regime (ii) – endemicity

Lemma

(a) For $\tilde{s} \in (\gamma, 1]$, we have $f_E(\tilde{s}) < \gamma$ and $\gamma - f_E(\tilde{s}) < \tilde{s} - \gamma$.

(b) For $s \in (s_{\mathrm{crit}}, \gamma)$, we have $f_R(s) > \gamma$ and $f_R(s) - \gamma < \gamma - s$.

Theorem Suppose that $\tilde{s}_1 \in (\gamma, 1]$ satisfies $s_1 = f_E(\tilde{s}_1) > s_{\mathrm{crit}}$. Then

(a) for $k = 1, 2 \ldots$, $\tilde{s}_k > \tilde{s}_{k+1} > \gamma$ and $s_k < s_{k+1} < \gamma$;

(b) $\lim_{k\to\infty} \tilde{s}_k = \lim_{k\to\infty} s_k = \gamma$;

(c) $\hat{t}_2 > \hat{t}_3 > \cdots > 0$ and $\sum_{k=2}^{\infty} \hat{t}_k = \infty$.

Remark The lemma implies that there exists $\hat{s}_0 \in (\gamma, 1]$ such that that $s_1 = f_E(\tilde{s}_1) > s_{\mathrm{crit}}$, where $\tilde{s}_1 = 1 - (1 - \hat{s}_0)\mathrm{e}^{-\mu t_G(\hat{s}_0)}$.

Asymptotic regime (ii) – limiting process S

- $\bar{S}^{(n)} \Rightarrow S$ as $n \to \infty$, where S increases deterministically according to

$$S'(t) = \mu(1 - S(t))$$

  between down jumps.

- If $c \leq c_{\text{crit}}$ and $s_0 \in [0, 1)$ then after the first down jump S becomes endemic and “follows" the iterative map, so the only randomness in S is determined by the time of the first down jump.

- If $c > c_{\text{crit}}$ then S has J fade outs before it becomes endemic and “follows" the iterative map, where J has a (possibly modified) geometric distribution, with support $0, 1, \ldots$ if $s_0 < \hat{s}_{\text{crit}}$ and support $1, 2, \ldots$ if $s_0 \geq \hat{s}_{\text{crit}}$, where $\hat{s}_{\text{crit}} > \gamma$. (If $s_0 = \hat{s}_{\text{crit}}$ and a successful invasion occurs at time $t = 0$ then $S(t) = s_{\text{crit}}$ after the first down jump.)

Asymptotic regime (ii) – limiting process I^*

- $\left\{\frac{1}{\log n}\left(\log I^{(n)}(t)\right)_+ : t \geq 0\right\} \Rightarrow I^* = \{I^*(t) : t \geq 0\}$ as $n \to \infty$, where I^* can be constructed from S.
- For example, in the endemic phase, suppose that a down jump occurs at time t_G, $S(t_G) = s_1 \in (s_{\text{crit}}, \gamma)$ and the next down jump occurs at time $t_G + \hat{t}$, then

$$I^*(t_G + t) = 1 + c\left[(1-\gamma)t - \frac{(1-s_1)}{\mu}\left(1 - \mathrm{e}^{-\mu t}\right)\right] \qquad (0 \leq t \leq \hat{t}).$$

Asymptotic regime (iii)

- Assume that $c_n/g(n) \to c'' \in (0, \infty)$ as $n \to \infty$, for some function $g(n)$ satisfying $g(n) \to \infty$ and $g(n)/\log n \to 0$ as $n \to \infty$.
- Let $t_1^{(n)} = \inf\{t \geq 0 : I^{(n)}(t) \geq n/g(n)^2\}$. Then

$$t_1^{(n)} \xrightarrow{\mathrm{p}} \infty \qquad \text{and} \qquad \bar{S}^{(n)}(t_1^{(n)}) \xrightarrow{\mathrm{p}} 1 \qquad \text{as } n \to \infty.$$

- $\lim_{n\to\infty} \mathrm{P}($fade out after first large outbreak$) = 0$, so

$$\left\{\bar{S}^{(n)}(t_1^{(n)} + t) : t \geq 0\right\} \Rightarrow S \qquad \text{as } n \to \infty,$$

where S is determined by the iterative map with $\tilde{s}_1 = 1$.

- S is purely deterministic.