Applications of large deviations in epidemiology

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Overview

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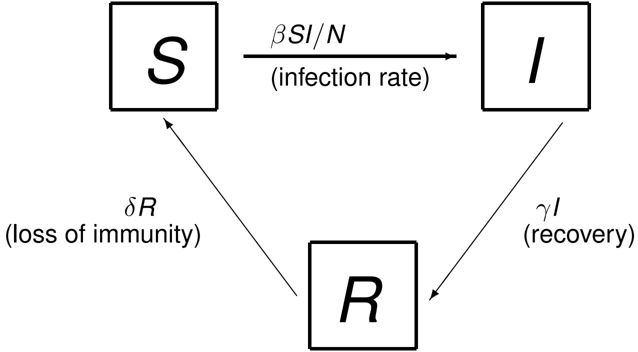
Example: SIRS-model

- SIRS (susceptible, infective, removed, susceptible)-model without demography
- S =# of susceptible individuals, I = # of infective ind., R = # of removed/immune ind., $N = S + I + R$ population size



ODE representation

- $$\begin{aligned} S' &= -\beta \frac{SI}{N} + \delta R \\ I' &= \beta \frac{SI}{N} - \gamma I \\ R' &= \gamma I - \delta R \end{aligned} \tag{1}$$
- Equation (1) has a unique solution satisfying $0 \le S, I, R \le S + I + R = N$

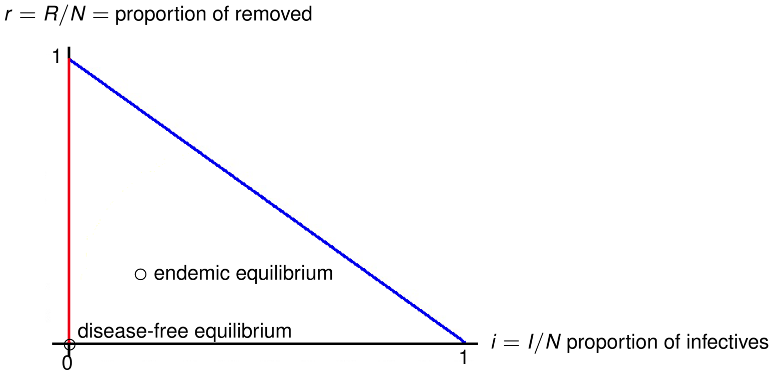
ODE and equilibria

- We are interested in the long-term behavior of the model
  - Does the disease become extinct or endemic?
- Find equilibria of the ODE (1)
  - A disease-free equilibrium ($I = 0$) of (1) exists ($R = 0$, $S = N$)
  - $R_0 = \frac{\beta}{\gamma}$ = *basic reproduction number*
    = "# of cases one case generates in its infectious period"
    $R_0 < 1 \Rightarrow$ the equilibrium is asymptotically stable
  - $R_0 > 1 \Rightarrow$ the disease-free equilibrium is unstable
    A stable endemic equilibrium exists

$$\frac{I}{N} = \frac{\delta}{\delta+\gamma}\frac{\beta-\gamma}{\beta}, \quad \frac{R}{N} = \frac{\gamma}{\delta+\gamma}\frac{\beta-\gamma}{\beta}, \quad \frac{S}{N} = \frac{\gamma}{\beta}$$

Equilibria of the ODE

- Reduction of dimension
  $s = S/N = 1 - i - r =$ proportion of susceptible individuals
  $\beta = 1.5$, $\gamma = 1$, $\delta = 1$, $R_0 = 1.5$



Overview

Stochastic models

- Stochastic model corresponding to the deterministic model
- Replace the deterministic rates by (independent) non-homogenous Poisson processes
  - An individual of type S becomes of type I at the jump time of the respective processes
  - Jump rates are constant in-between jumps
  - e.g. SIRS: infection rate (at time t): $\beta\frac{S(t)I(t)}{N} = N\beta s(t)i(t)$
- Questions
  - What is the difference between the two processes for large N?
  - Endemic situation ($R_0 > 1$): can the disease die out? (and vice versa)
  - When does this happen?
  - For which population size N is it possible/probable?

Overview

Poisson models

$$Z^N(t) := x + \frac{1}{N}\sum_{j=1}^{k} h_j P_j\Big(\int_0^t N\beta_j(Z^N(s))ds\Big) \tag{2}$$

$$= x + \int_0^t b(Z^N(s))ds + \frac{1}{N}\sum_j h_j M_j\Big(\int_0^t N\beta_j(Z^N(s))ds\Big)$$

- d = number of compartments (susceptible individuals, ...)
  N = "natural size" of the population
  $Z_i^N(t)$ = proportion of individuals in compartment i at time t
  A = domain of process (compact)
- P_j ($j = 1, \ldots, k$): independent standard Poisson processes
- $M_j(t) = P_j(t) - t$: compensated Poisson processes
- $h_j \in \mathbb{Z}^d$: jump directions
  $\beta_j : A \to \mathbb{R}_+$: jump intensities
  $b(x) = \sum_j h_j \beta_j(x)$

Law of large numbers

- Deterministic model

$$\phi(t) := x + \int_0^t b(\phi(s))ds = x + \int_0^t \sum_{j=1}^{k} h_j \beta_j(\phi(s))ds \qquad (3)$$

Theorem (Kurtz)

$x \in A$, $T > 0$, $\beta_j : A \to \mathbb{R}_+$ Lipschitz. Then,

$$Z^N \longrightarrow \phi$$

almost surely uniformly on $[0, T]$.

- A rate of convergence can be computed

Overview

Rare events

- Despite the LLN, a (large) deviation of Z^N from the ODE solution ϕ is possible (even for large N, cf. Campillo and Lobry (2012))
- $T > 0$ fixed, $D([0,T];A) := \{\phi : [0,T] \to A | \phi \text{ càdlàg}\}$
- Quantify
$$\mathbb{P}[Z^N \in G], \quad \mathbb{P}[Z^N \in F]$$
for $G \subset D$ open, $F \subset D$ closed (N large)

Diminishing rates

- Standard literature is not applicable (e.g., Shwartz and Weiss (1995), Dupuis and Ellis (1997), Feng and Kurtz (2006))
- Problem: some rates diminish as the process approaches the boundary
  - e.g. SIRS model: $\beta x_1(1 - x_1 - x_2) \to 0$ as $x_1 \to 0$
- Large deviations principle (LDP) with diminishing rates by Shwartz and Weiss (2005)
  - Modifications are required

Overview

Legendre-Fenchel transform

- Legendre-Fenchel transform
  $x \in A$ position, $y \in \mathbb{R}^d$ direction of movement

$$L(x,y) := \sup_{\theta \in \mathbb{R}^d} \ell(\theta, x, y)$$

$$\text{for} \quad \ell(\theta, x, y) = \langle \theta, y \rangle - \sum_j \beta_j(x)(e^{\langle \theta, h_j \rangle} - 1)$$

- $L(x,y) \geq L\big(x, \sum_j \beta_j(x) h_j\big) = 0$
- $L(x,y) < \infty$ iff
  $\exists \mu \in \mathbb{R}_+^k$ s.t. $y = \sum_j \mu_j h_j$ and $\mu_j > 0 \Rightarrow \beta_j(x) > 0$
  e.g. SIRS: $x_1 = 0$, $y_1 \neq 0 \Rightarrow L(x,y) = \infty$
- "Local measure" for the "energy" required for a movement from x in direction y

Rate function

- Rate function ($x \in A$)

$$I_{x,T}(\tilde{\phi}) := \begin{cases} \int_0^T L(\tilde{\phi}(t), \tilde{\phi}'(t))dt & \text{for } \tilde{\phi}(0) = x \text{ and } \tilde{\phi} \text{ is abs. cont.} \\ \infty & \text{else} \end{cases}$$

- $I_{x,T}(\phi) = 0$ iff ϕ solves (3) on $[0, T]$
- Interpretation of $I_{x,T}(\tilde{\phi})$: the “energy” required for a deviation from ϕ

Overview

Large deviations principle

- $\tilde{A} =$ "set where the process Z^N gets stuck" $\subset \partial A$
  - e.g. SIRS: $\tilde{A} = \{x \in A | x_1 = 0\}$
  - $I_{x,T}(\tilde{\phi}) = \infty$ if $\phi(s) \in \tilde{A}$, $\phi(t) \notin \tilde{A}$ for $s < t$
- For appropriate assumptions (which are, e.g., satisfied for the SIRS-model)

Theorem

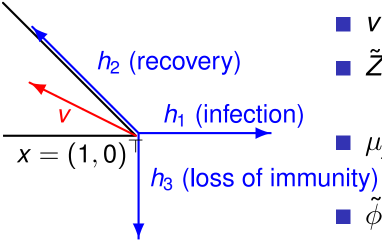
$x \in A$, $G \subset D([0,T];A)$ open, $F \subset D([0,T];A)$ closed with $\mathrm{dist}(\phi, \tilde{A}) > \eta$ ($\phi \in G \cup F$) for some $\eta > 0$.

$$\liminf_{N \to \infty} \frac{1}{N} \log \mathbb{P}[Z^N \in G] \geq - \inf_{\tilde{\phi} \in G} I_{x,T}(\tilde{\phi}),$$

$$\limsup_{N \to \infty} \frac{1}{N} \log \mathbb{P}[Z^N \in F] \leq - \inf_{\tilde{\phi} \in F} I_{x,T}(\tilde{\phi}).$$

Required modifications

- We can only consider sets G, F with positive distance to $\tilde{A}$
- Approximate functions by shifting them inside via a finite number of vectors v_i (cf. Shwartz and Weiss (2005))



- $v = \mu_2 h_2 + \mu_3 h_3$, $\mu_1 = 0$, $\mu_2, \mu_3 > 0$
- $\tilde{Z}^N(t) = x + \sum_j \frac{h_j}{N} P_j\left(N \int_0^t \tilde{\mu}_j(\tilde{Z}^N(s))ds\right)$
- $\mu_j(z) = \begin{cases} 0 & \text{if } h_j \text{ “points outside” at } z \in \partial A \\ \mu_j & \text{else} \end{cases}$
- $\tilde{\phi}(t) = x + tv$

- Show LLN: $\tilde{Z}^N \to \tilde{\phi}$ a.s. uniformly (with appropriate rate of convergence)

Overview

Exit from domain

- $O =$ domain of attraction of stable equilibrium x^*; $x \in O$
  - relatively open with respect to A
  - e.g. SIRS: endemic equilibrium, $O = \{z \in A | z_1 > 0\}$
- When does Z^N exit from O?
  - $\tau^N := \inf\{t > 0 | Z^N(t) \in A \setminus O\}$
  - e.g. SIRS: when does the disease become extinct?
- $T > 0$, $y, z \in A$.

$$V(y, z, T) := \inf_{\phi:\, \phi(0)=y, \phi(T)=z} I_{y,T}(\phi)$$

$$V(y, z) := \inf_{T>0} V(y, z, T)$$

$$\bar{V} := \inf_{z \in \widetilde{\partial O}} V(x^*, z)$$

- The minimal energy required to go from y to z in $[0, T]$, respectively from y to z, respectively form x^* to the boundary

Time of exit

- For appropriate assumptions (e.g. satisfied for the SIRS model):

Theorem

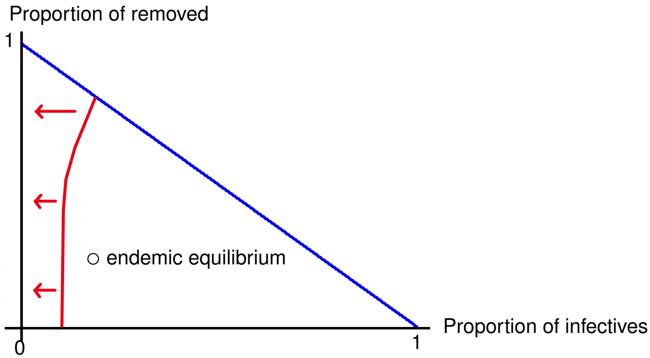
$x \in O$, $\delta > 0$.

$$\lim_{N\to\infty} \mathbb{P}[\tau^N < e^{N(\bar{V}+\delta)}] = 1, \quad \lim_{N\to\infty} \mathbb{P}[\tau^N > e^{N(\bar{V}-\delta)}] = 1.$$

- For N large $\tau^N \approx e^{N\bar{V}}$

Approximation by smaller domains

- The LDP does not hold for all open/closed sets G/F
- Approximate by exit times $\tau^{N,x,\eta}$ of domains O^η, $O^\eta \uparrow O$, for $z \in O^\eta$, $\text{dist}(z, \widetilde{\partial O}) > \eta$



Overview

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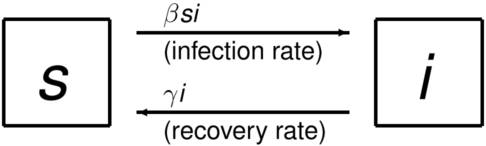
SIS-model

- $N =$ population size, $S =$# of susceptibles, $I =$ # of infectives, $s = S/N =$ proportion of susceptibles, $i = I/N =$ proportion of infectives

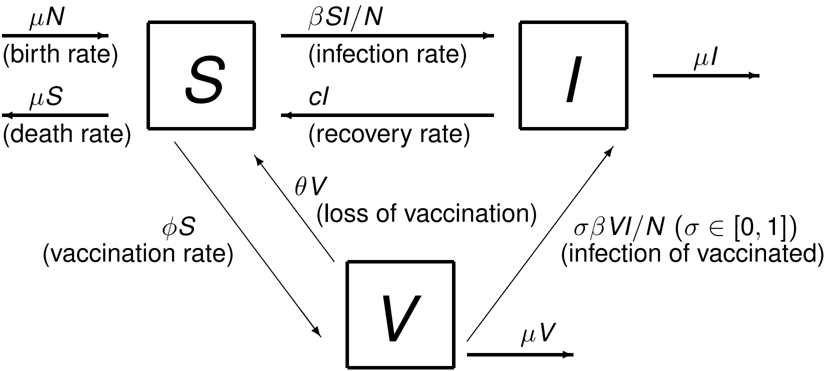


- $A = [0, 1], \quad i' = \beta si - \gamma i = \beta(1-i)i - \gamma i, \quad s = 1 - i$
- $R_0 = \frac{\beta}{\gamma}$; $R_0 > 1$: the endemic equilibrium $i = \frac{\beta - \gamma}{\beta}$ is stable
- $0 = (0, 1]$, $\tilde{A} = \{0\}$, no “problematic points”
  When does the disease become extinct?

Overview

A model with vaccination

- SIV model by Kribs-Zaleta and Velasco-Hernández (2000)
- S =# of susceptibles, I = # of infectives, V = # of vaccinated, $N = S + I + V$ population size

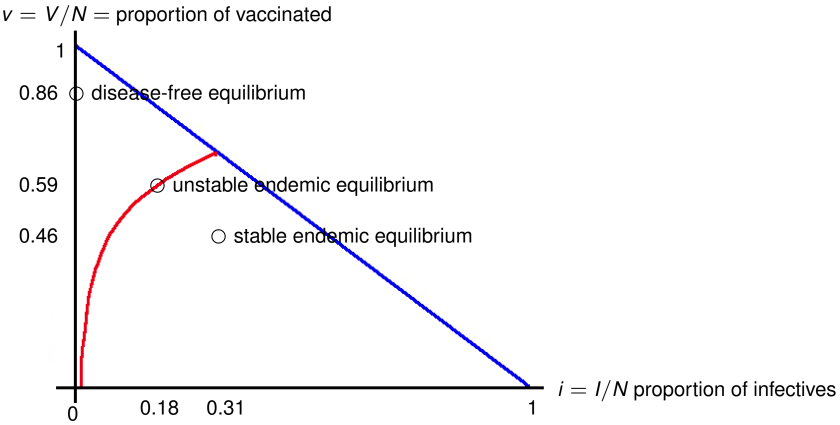


Equilibria

- Find equilibria of the ODE
- A disease-free equilibrium ($I = 0$) of (1) exists
  $R_0 < 1 \Rightarrow$ the equilibrium is asymptotically stable
- $\tilde{R}_0 =$ basic reproduction number without vaccination
  $\tilde{R}_0 > 1 \Rightarrow$ the disease-free equilibrium is unstable
- $R_0 < 1 < \tilde{R}_0$ (and appropriate parameter choice)
  $\Rightarrow$ two endemic equilibria ($I > 0$) exist
  one is asymptotically stable, one is unstable

Equilibria

- $s = S/N = 1 - i - v =$ proportion of susceptibles



Exit from domain

- Despite the demography, we assume constant population size (by synchronizing birth and death)
- O= domain of attraction of the stable endemic equilibrium
  When does the process leave O?
  $\tilde{A} = \{x \in A | x_1 = 0\}$; despite $\mathrm{dist}(O, \tilde{A}) > \eta > 0$ we have to approximate by O^η as $\widetilde{\partial O}$ is the "characteristic boundary" (i.e. for $x \in \widetilde{\partial O}$, $\lim_{t\to\infty} \phi(t) \neq x^*$)
- $x \in A \setminus \bar{O}$: When does the disease become endemic?
  A modification of the model is required in order to achieve $\tilde{A} = \emptyset$
  - Introduce (small) immigration of infective individuals
  - The "disease-free" equilibrium then satisfies $i \approx 0$ but $i > 0$.

Overview

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Place of exit

- Conjecture:
  $C \subset \widetilde{\partial O}$, $\inf_{z \in C} V(x^*, z) > \bar{V}$

$$\lim_{N \to \infty} \mathbb{P}[Z^N(\tau^N) \in C] = 0$$

If $\exists z^* \in \widetilde{\partial O}$ with $V(x^*, z^*) < V(x^*, z) \; \forall z \neq z^*$, then for $\delta > 0$,

$$\lim_{N \to \infty} \mathbb{P}[|Z^N(\tau^N) - z^*| < \delta] = 1$$

- Problem: $\widetilde{\partial O}$ is the characteristic boundary and/or $\tilde{A} = \widetilde{\partial O}$

Overview

Unbounded processes

- Models with demography: constant (or bounded) population size is artificial (e.g. through synchronized birth/death, immigration/emigration)
  - e.g. model with vaccination: $A = \{x \in \mathbb{R}^2 | x_1, x_2 \geq 0\}$
  - For the deterministic model, population size (can) remain constant
- The LDP of Shwartz and Weiss (2005) can be transferred to unbounded A if the rates grow at most linearly
  - This result can be transferred directly to our setting
  - Usually in epidemiology: rates grow quadratically (e.g. $\beta s(t) i(t)$)
- The place of exit should be in a bounded set
- Once the place of exit result is proven, unbounded domains can be treated

Literature

F. Campillo and C. Lobry. Effect of population size in a predator-prey model. *Ecological Modelling*, 246:1–10, 2012.

P. Dupuis and R. S. Ellis. *A week convergence approach to the theory of large deviations*. Wiley series in probability and statistics. Wiley, New York, 1997.

J. Feng and T. G. Kurtz. *Large deviations for stochastic processes*, volume 131 of *Mathematical Surveys and Monographs*. American Mathematical Society, Providence, 2006.

C. M. Kribs-Zaleta and Velasco-Hernández. A simple vaccination model with multiple endemic states. *Math. Biosci.*, 164(2):183–201, 2000.

A. Shwartz and A. Weiss. *Large Deviations for Performance Analysis*. Chapman Hall, London, 1995.

A. Shwartz and A. Weiss. Large deviations with diminishing rates. *Mathematics of Operations Research*, 30(2):281–310, 2005.