Large Deviations in Epidemiology : Malaria modelling

Kouegou Kamen Boris
Supervised by : Etienne Pardoux

Ecole de printemps de la Chaire MMB - Aussois

May 13, 2018

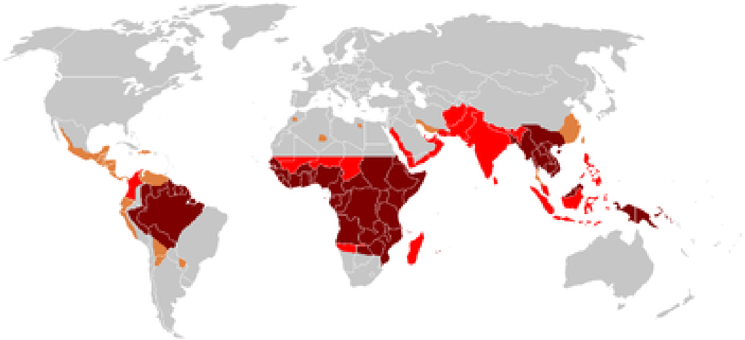


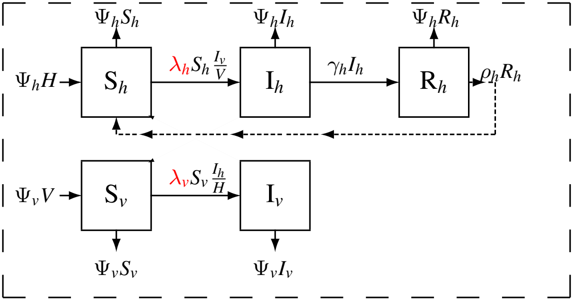
Figure: Internet...

- Mosquitoes are the deadliest animals for Humans ($\sim$ 745 000 pers./an)
- Guess who is second ?

Structure

1. Simplified Malaria model : SIRS-SI
   - SIRS-SI Malaria Model
2. Stochastic Modeling
3. Large deviations results
   - Large deviations for our process
   - Extinction time probability
   - Lower Bound
4. More general Problem in View

We consider an SIRS-SI Malaria model including both Human and mosquito populations:
$S_h \longrightarrow$ susceptibles Human $\dots$, $S_v \longrightarrow$ susceptibles vectors (mosquitoes) $\dots$,



$H = S_h + I_h + R_h$, $V = S_v + I_v$ are assumed to be constants.

Dynamic of the system :
In Human's comparments,

$$\begin{cases} \frac{dS_h}{dt} & = & \Psi_h H + \rho_h R_h - \lambda_h \frac{I_v}{V} S_h - \Psi_h S_h \\ \frac{dI_h}{dt} & = & \lambda_h \frac{I_v}{V} S_h - (\gamma_h + \Psi_h) I_h \\ \frac{dR_h}{dt} & = & \gamma_h I_h - (\rho_h + \Psi_h) R_h \end{cases}$$

where

$\lambda_h = \lambda_h \left(\frac{V}{H}\right) = \frac{\sigma_v \sigma_h V}{\sigma_v V + \sigma_h H} \beta_{hv}$ is seen as the *infectious force* of mosquitoes on humans

σ_v denotes the maximum number of time a mosquito can bite a human per unit time

σ_h denotes the maximum number of bites a human can have per unit time

β_{hv} denotes the transmission probability from an infected mosquito to a susceptible human assuming contact and in mosquito's one

$$\begin{cases} \dfrac{dS_v}{dt} & = & \Psi_v V - \lambda_v \dfrac{I_h}{H} S_v - \Psi_v S_v \\ \dfrac{dI_v}{dt} & = & \lambda_v \dfrac{I_h}{H} S_v - \Psi_v I_v \end{cases}$$

where

$\lambda_v = \lambda_v\left(\frac{V}{H}\right) = \dfrac{\sigma_v \sigma_h H}{\sigma_v V + \sigma_h H}\beta_{vh}$ is the *infectious force* of humans on mosquitoes

β_{vh} denotes the probability of transmition from an infected human ta a susceptible mosquito assuming contact

Proportions : Pose $s_h = S_h/H \ldots, \quad s_v = S_v/V \ldots, V/H = m >> 1$ and denote

.

$$a_v(m) = \lambda_v = \frac{\sigma_v \sigma_h}{\sigma_v m + \sigma_h}\beta_{vh} \quad , \quad a_h(m) = \lambda_h = \frac{\sigma_v \sigma_h m}{\sigma_v m + \sigma_h}\beta_{vh}$$

Renormalized deterministic system :

$$(1)\qquad \begin{cases} \dfrac{di_h}{dt} &= a_h(m)i_v(1-i_h-r_h)-\gamma_h i_h-\Psi_h i_h \\ \dfrac{dr_h}{dt} &= \gamma_h i_h-\rho_h r_h-\Psi_h r_h \\ \dfrac{di_v}{dt} &= a_v(m)i_h(1-i_v)-\Psi_v i_v \end{cases}$$

with $s_h = 1 - i_h - r_h$ and $s_v = 1 - i_v$
(1) is well posed for any given initial condition on his domain :

$$(2)\qquad \mathcal{D} := \left\{(i_h, r_h, i_v) \in \mathbb{R}_+^3 : i_h + r_h \leq 1,\ i_v \leq 1\right\}$$

- if $a_h(m)a_v(m) < \Psi_v(\gamma_h + \Psi_h)$: $\mathbf{z}^*_{\mathbf{fde}} = (0,0,0) \longrightarrow$ stable.
- • if $a_h(m)a_v(m) > \Psi_v(\gamma_h + \Psi_h)$: $\mathbf{z}^*_{\mathbf{fde}} = (0,0,0) \longrightarrow$ unstable

  and $\mathbf{z}^*_{\mathbf{end}} = (i_h^*, \dfrac{\gamma_h}{\rho_h + \Psi_h} i_h^*, \dfrac{1}{1 + \frac{\Psi_v}{a_v(m)i_h^*}}) \longrightarrow$ stable.

Basic reproductive number:
$R_0 = \sqrt{a_h(m)a_v(m)/\Psi_v(\gamma_h + \Psi_h)}$ average number of new cases induced by one cases.

Renormalized Transition rates : For $x = (x_1, x_2, x_3)$

$$\beta_1(x) = a_h(m)x_3(1 - x_1 - x_2), \quad \beta_2(x) = \gamma_h x_1, \quad \beta_3(x) = \Psi_h x_1$$
$$\beta_4(x) = \rho_h x_2 \quad \beta_5(x) = \Psi_h x_2 \quad \beta_6(x) = a_v(m)x_1(1 - x_3)$$
$$\beta_7(x) = \Psi_v x_3$$

We note $Z_t^{H,V} = (i_t^H, r_t^H, i_t^V)$. Thus Infected and recovered humans are described respectively by

$$i_t^H = i_0^H + \frac{1}{H}\int_0^t \int_0^{N\beta_1(Z_{s-}^{H,V})} Q_1(ds, du) - \frac{1}{H}\int_0^t \int_0^{\beta_2(Z_{s-}^{H,V})} Q_2(ds, du)$$
$$- \frac{1}{H}\int_0^t \int_0^{\beta_3(Z_{s-}^{H,V})} Q_3(ds, du)$$

and

$$r_t^H = r_0^H + \frac{1}{H}\int_0^t \int_0^{\beta_2(Z_{s-}^{H,V})} Q_2(ds, du) - \frac{1}{H}\int_0^t \int_0^{\beta_4(Z_{s-}^{H,V})} Q_2(ds, du)$$
$$- \frac{1}{H}\int_0^t \int_0^{\beta_5(Z_{s-}^{H,V})} Q_2(ds, du)$$

Samely define i_t^V

General form of the process :

$$Z_t^{H,V} = z_0 + \frac{1}{H}\sum_{j=1}^{k} h_j(m)\int_0^t \int_0^{H\beta_j(Z_{s-}^{H,V})} Q_j(ds,du), \qquad (k=7)$$

Proposition: (Large Number Law : m is fixed)

For any given initial condition z_0, the Renormalized stochastic process $Z_t^{H,V}(m)$ converges to the deterministic one $Z_t(m)$ a.s uniformly on $[0,T]$ and z_0.

That is

$$\lim_{H,V\to+\infty} \sup_{t\leq T} |Z_t^{H,V}(m) - Z_t(m)| = 0 \qquad a.s$$

Proposition: (Large Number Law : m goes to infinity)

For any given initial condition z_0, the Renormalized stochastic process $Z_t^{H,V}(m)$ converges to the deterministic one Z_t^* a.s uniformly on $[0,T]$ and z_0.

where Z^* is the same deterministic process as Z_t including the fact that

$$\lim_{m\to+\infty} a_h(m) = \lim_{m\to+\infty} \frac{\sigma_v\sigma_h m}{\sigma_v m+\sigma_h}\beta_{vh} = a_h^*, \qquad \lim_{m\to+\infty} a_v(m) = \lim_{m\to+\infty} \frac{\sigma_v\sigma_h}{\sigma_v m+\sigma_h} = 0$$

a sequence X_n define on a space $\mathcal{X}$ isatisfies a *LDP* with *good rate function* I,

* I is lower semicontinuous with level set $\{x \in \mathcal{X} | I(x) \leq a\}$ compact.

** For $O, F \subset \mathcal{X}$ respectively open and closed sets

$$\liminf_{n\to\infty} \frac{1}{n} \log \mathbb{P}\left[X_n \in O\right] \geq -\inf_{x\in O} I(x), \quad \limsup_{n\to\infty} \frac{1}{n} \log \mathbb{P}\left[X_n \in F\right] \leq -\inf_{x\in F} I(x)$$

Consider the general form of processes defined on $D([0,T], \mathbb{R}^d)$

$$Z_t^{N,z_0} = z_0 + \frac{1}{N} \sum_{j=1}^{k} h_j \int_0^t \int_0^{N\beta_j(s, Z_{s-}^{N,x})} Q_j(ds, du)$$

<u>Good rate Function</u> : Let note for all $\phi \in D([0,T], \mathbb{R}^d)$

$$L(t, \phi, \dot{\phi}) = \sup_{\theta \in \mathbb{R}^d} \left\{ \langle \theta, \dot{\phi}_t \rangle - \sum_{j=1}^{k} \beta_j(t, \phi)(e^{\langle \theta, h_j \rangle} - 1) \right\}$$

then the Cramer's Transform expression is

$$I_T(\phi) = \begin{cases} \int_0^T L(t, \phi, \dot{\phi}) dt & \text{if } \phi \text{ is absolutely continuous} \\ +\infty & \text{if not} \end{cases}$$

For a Poisson random variable of parameter $\lambda > 0$,

$$\text{Log-Laplace transform : } \quad \Lambda(\theta) = \lambda(e^{\theta} - 1)$$
$$\text{Legendre transform : } \quad f(y,\lambda) := \Lambda^*(y) = y \log \frac{y}{\lambda} - y + \lambda$$

Shwartz and Weiss rate function :

$$\hat{I}_T(\phi) = \int_0^T \inf_{c \in \mathcal{C}_t(\phi)} \sum_{j=1}^{k} f\left(c_j, \beta_j(t,\phi)\right)$$

where $\mathcal{C}_t(\phi) = \left\{ c \in \mathbb{R}_+^k \mid \dot{\phi}_t = \sum_{j=1}^k h_j c_j \quad \text{and} \quad c_j > 0 \text{ only if } \beta_j(t,\phi) > 0 \right\}$
Interchange integration and infimum :

$$\hat{I}_T(\phi) = \inf_{c \in \mathcal{C}_T(\phi)} \int_0^T L(c(t), \phi_t) dt$$

$\mathcal{C}_T(\phi) = \{ c \text{ Lebesgue integrable define on } [0,T] \; s.t \quad c(t) \in \mathcal{C}_t(\phi) \}$.

$$\text{Of course,} \qquad \hat{I}_T(\phi) = I_T(\phi).$$

Theorem (under Assumptions...)

Z^{N,z_0} satisfies a LDP with good rate function I_T on $D([0,T];\mathbb{R}_+^d)$, locally uniformly in the initial condition z_0

Proposition: (Malaria model : m fixed)

$Z^{H,V}$ satisfies a LDP with good rate function I_T on the space $D([0,T];\mathcal{D})$.

That is for any $O, F \subset D([0,T];\mathcal{D})$ open and closed sets respectively,

$$\liminf_{H,V\to+\infty} \frac{1}{H} \log \mathbb{P}\left[Z^{H,V} \in O\right] \geq -\inf_{\phi\in O} I_T(\phi)$$

,

$$\limsup_{H,V\to+\infty} \frac{1}{H} \log \mathbb{P}\left[Z^{H,V} \in F\right] \leq -\inf_{\phi\in F} I_T(\phi)$$

Freidlin-Wentzell Theory: (Exit time Problem)

For our SIRS-SI model, Remember if $R_0 > 1$, two equilibriums states :
$\mathbf{z}^*_{\mathbf{fde}}(unstable)$ and $\mathbf{z}^*_{\mathbf{end}}(stable)$.
$\mathcal{O}_{\mathbf{z}^*_{\mathbf{end}}} := \mathcal{D} - \{i_h = i_v = 0\}$ is the attractive domain of $\mathbf{z}^*_{\mathbf{end}}$.
If $z_0 \in \mathcal{O}_{\mathbf{z}^*_{\mathbf{end}}}$.

* The law of large number says that for H, V are large, $Z^{H,V} \sim \mathbf{z}^*_{\mathbf{end}}$.

** Large Deviations quantifies the rare event of going far from the limit $\mathbf{z}^*_{\mathbf{end}}$

How long could take the process to exit $\mathcal{O}_{\mathbf{z}^*_{\mathbf{end}}}$????

Let denote

$$\tau_z^{H,V} = \inf\{t > 0 |\ Z_t^{H,V} \notin \mathcal{O}_{\mathbf{z}^*_{\mathbf{end}}}\}$$

then $\quad \tau_z^{H,V} \sim e^{H\bar{E}}$ for large H

Proposition: (Under assumptions...)

$$\lim_{H,V\to+\infty} \mathbb{P}\left[e^{(\bar{E}-\delta)H} < \tau_z^{H,V} < e^{(\bar{E}+\delta)H}\right] = 1 \qquad \forall\delta > 0$$

and it follows that

$$\lim_{H,V\to+\infty} \frac{1}{H} \log \mathbb{E}\left[\tau_z^{H,V}\right] = \bar{E}$$

where

(3) $$\bar{E} = \inf\left\{E(\mathbf{z}^*_{\mathbf{end}}, z) : \quad z \in \partial\mathcal{O}_{\mathbf{z}^*_{\mathbf{end}}}\right\}$$

with

(4) $$E(\mathbf{z}^*_{\mathbf{end}}, z) = \inf\left\{E(\mathbf{z}^*_{\mathbf{end}}, z, T) : \quad T > 0\right\}$$

and

(5) $$E(\mathbf{z}^*_{\mathbf{end}}, z, T) = \inf\left\{I_T(\phi) : \quad \phi \in D([0,T]; \mathcal{D}),\ \phi(0) = \mathbf{z}^*_{\mathbf{end}}, \phi(T) = z\right\}$$

(3), (4) and (5) form a Bolza type minimisation Problem in optimal control theory.

$$\bar{E} = \min_{z,T,\phi.,c.} \int_0^T L(c_t, \phi_t)dt$$

subject to the dynamic $\dot{\phi}_t = \sum_{j=1}^{7} h_j c_t^j$.

Pontryagin minimum principle is helpfull to have some intiution on the optimal trajectory.

$\rightarrow$ The lower bound : $\displaystyle \lim_{N\to+\infty} \frac{1}{N} \log \mathbb{P}\left[Z^{N,z_0} \in O\right] \geq - \inf_{\phi\in O} I_T(\phi)$.

$$\text{Process :} \quad Z_t^{N,z_0} = z_0 + \frac{1}{N}\sum_{j=1}^{k} h_j \int_0^t \int_0^{N\beta_j(s,Z_{s-}^{N,z_0})} Q_j(ds,du),$$

$$\text{LLN limit :} \qquad Z_t = z_0 + \sum_{j=1}^{k} h_j \int_0^t \beta_j\left(s, Z_s\right) ds$$

if $\quad Q_j^N = \dfrac{1}{N}$ M.A.P with intensity $ds \times Ndu$, $\quad Q^N = (Q_1^N, \ldots, Q_k^N)$.

$$\text{then} \qquad Z_t^{N,z_0} = z_0 + \sum_{j=1}^{k} h_j \int_0^t \int_0^{\beta_j(s,Z_{s-}^{N,z_0})} Q_j^N(ds,du),$$

and if we consider the map defined on $\mathcal{M}^k$ by : $\eta = (\eta_1, \ldots, \eta_k)$

$$\Phi_t^{z_0}(\eta) := x + \sum_{j=1}^{k} h_j \int_0^t \int_0^{\beta_j\left(s,\Phi_{s-}^{z_0}\right)} \eta_j(ds,du) \tag{6}$$

we have $\Phi_t^{z_0}(Q^N) = Z^{N,z_0}$ and $Z_t = \Phi_t^x(\Lambda^2)$ where $\Lambda^2 = Leb \times Leb$

$\rightarrow$ Well known : Q^N satisfies a LDP on $\mathcal{M}^k$ with rate function say J_T
$\rightarrow$ If ϕ^{z_0} was a continuous map : CONTRACTION PRINCIPLE
$\rightarrow$ At least one ϕ in O is absolutely continuous.
$\rightarrow$ Note that if ϕ is absolutely continuous then $\phi_t = \Phi_t^{z_0}(\eta^\phi)$ where η^ϕ has density

$$h_j(s,u) = \frac{c_j(s)}{\beta_j(s,\phi)} \mathbf{1}_{(0,\beta_j(s,\phi)]}(u) + \mathbb{1}_{[\beta_j(s,\phi),\bar{\beta}]}(u), \qquad c \in \mathcal{C}_T(\phi).$$

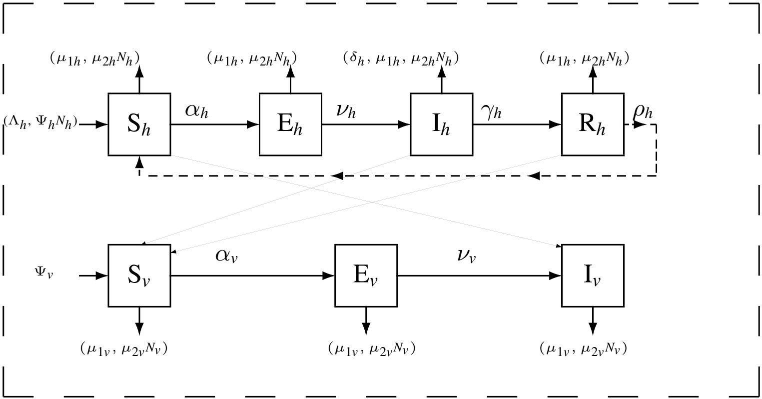
and $\bar{\beta} = \sup_t \beta(t,\phi)$
$\rightarrow$ QUASICONTINUITY : For every L, R we have N large enough and δ small enough

$$\mathbb{P}\left[||Z^{N,x^N} - \phi||_T > L \; ; \; d_{T,\bar{\beta}}\left(Q^N, \eta^\phi\right) \le \delta\right] \le e^{-NR}$$

where $$d_{T,\bar{\beta}}(\eta,\nu) := \sum_{j=1}^{k} \sup_{t,u} \left| \eta_j\left([0,t]\times[0,u]\right) - \nu_j\left([0,t]\times[0,u]\right) \right|.$$

$\rightarrow$ New rate function form : $\tilde{I}_T(\phi) = \inf\left\{ J_T(\eta) \; : \; \eta \in \left(\Phi^{z_0}\right)^{-1}(\phi) \right\}$

A More realistic model we had in mind:



- Populations sizes are not constant, the domain is no longer compact but at least convex.
- Need more for Wentzell freidlin theory to work .
- Coercivity of $z \mapsto E(z^*, z)$???