Stochastic population models: the dynamics of invasion and extinction

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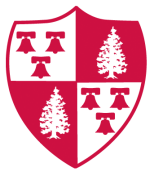
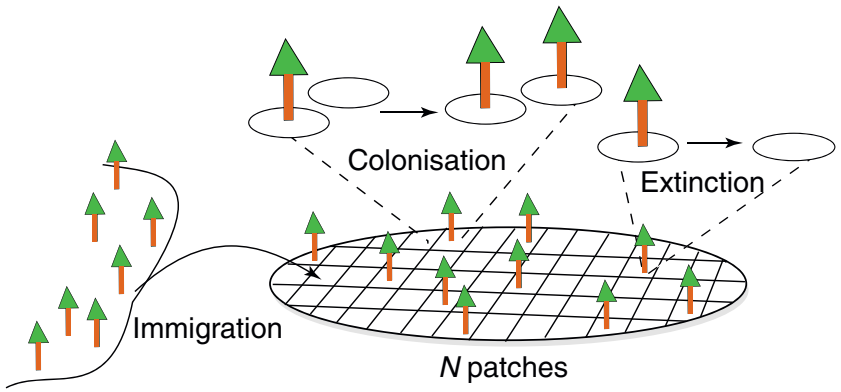


Stochastic population models?

Stochastic processes have been rigorously studied in many fields: probability theory, math finance, physics ...

These models have tremendous potential in math biology to capture the inherent complexity and uncertainty in the systems.

Black and McKane, "Stochastic formulation of ecological models and their applications," *Trends in Ecology & Evolution* (2012).



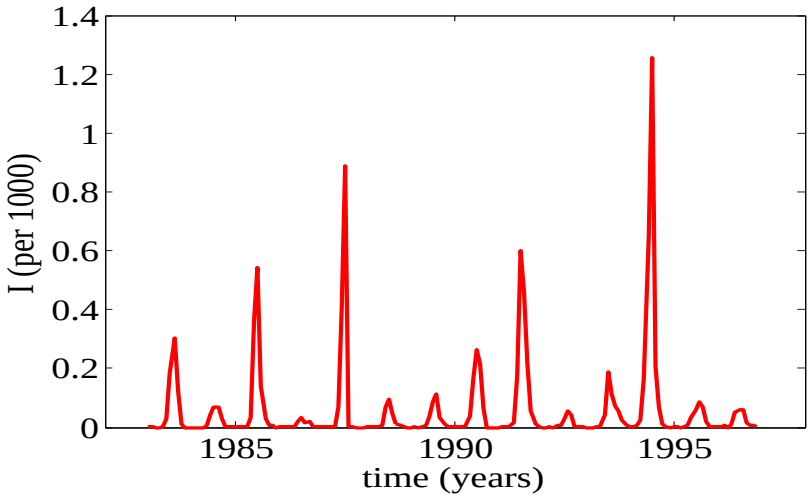
Uncertainty and randomness - modeled as noise (stochasticity)

- External: environmental factors including climatic effects, natural enemies, or inter-specific competition
- Internal: random interactions of individuals in a population or demography

Applications in Epidemiology

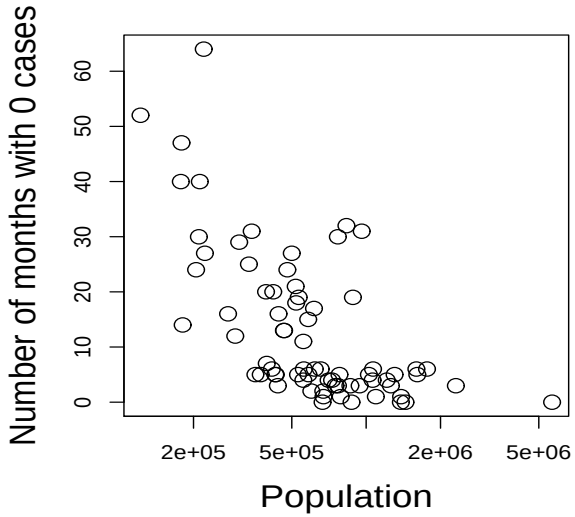
- Control and eradication of infectious diseases would have important societal benefits.
- Where do we observe extinction in disease data?
  - Local extinction of a disease, but reintroduced later in time (fadeout)
  - Extinction more common in smaller populations

Dengue Incidence for
Chiang Mai province, Thailand.



**Data provided by Derek Cummings (JHU).

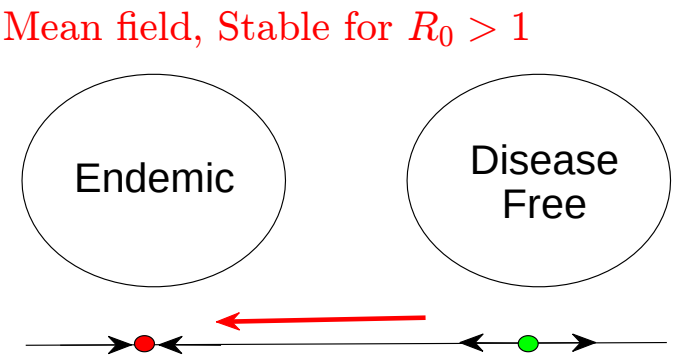
Measles Incidence by
Thailand province (1980-2001).

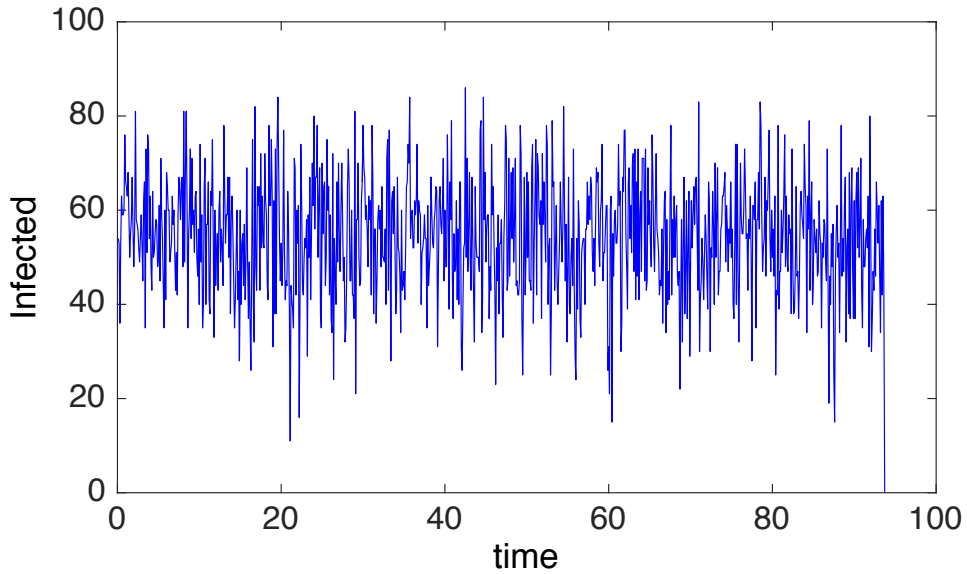


The Classical Problem - Extinction

There has been a significant amount of work to understand extinction in simple epidemiological systems.

Simulation of an extinction event in an endemic model.





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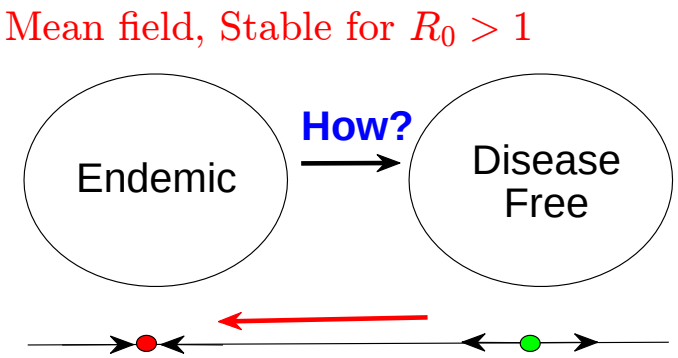
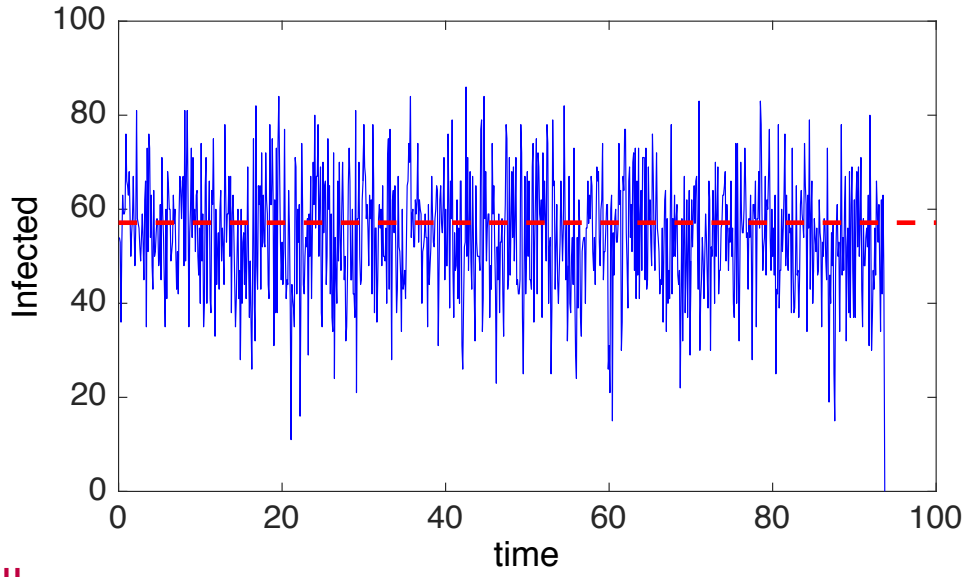




Extinction = escape from a potential well

Doering, et al., Multiscale Model. Simul. (2005); Dykman, et al., PRL 101 (2008); Schwartz, et al., J Stat Mech, P01005 (2009), ... many, many others

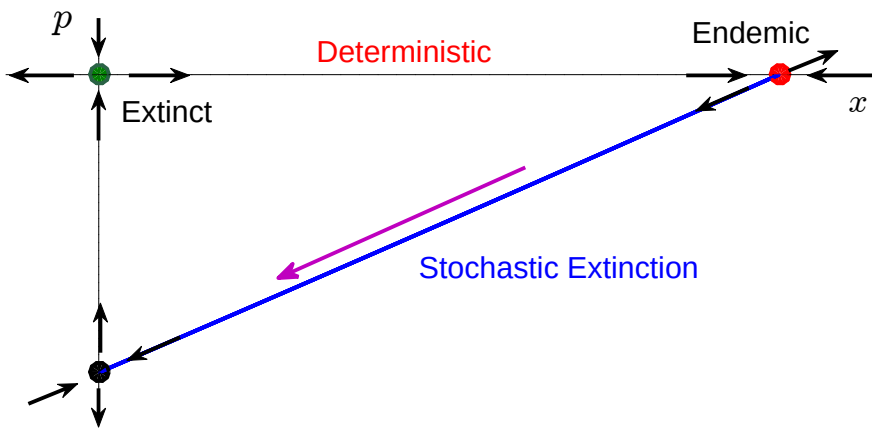
We want to extend this understanding of extinction to more complex topologies and develop optimal control methods.

The Dynamical Systems Fun

We can analyze the deterministic system –even if it is more complicated!

The Dynamical Systems Fun

By incorporating the effect of the noise,
we double the dimension and allow escape.



New dynamics to be explored!

Areas of study:

- higher dimensions
- networks of steady states
- time-dependent parameters
- numerical simulations

Heteroclinic trajectories connect
the saddle steady states.

Outline

- Background: Stochastic master equation, large deviation theory
- SIR example (the basic set-up)
- Seasonality: extinction in models with time varying parameters
- Ebola: invasion and extinction in a high dimensional model
- Conclusions

Master Equation Approach (Review)

Consider a well-mixed finite population of size N

- Discrete state vector $\mathbf{X} = (x_1, x_2, \ldots, x_n)$.
- Random state transition rates: $W(\mathbf{X}, \mathbf{r})$.
- Probability $\rho(\mathbf{X}, t)$ of finding the system in state $\mathbf{X}$ at time t:

The master equation definition

$$\frac{\partial \rho(\mathbf{X}, t)}{\partial t} = \sum_{\mathbf{r}} [\underbrace{W(\mathbf{X} - \mathbf{r}; \mathbf{r}) \rho(\mathbf{X} - \mathbf{r}, t)}_{\substack{\text{the gain to state } \mathbf{X} \\ \text{from state } \mathbf{X}\text{-}\mathbf{r}}} - \underbrace{W(\mathbf{X}; \mathbf{r}) \rho(\mathbf{X}, t)}_{\substack{\text{the loss of state } \mathbf{X} \\ \text{to other states}}}].$$

It is the gain-loss equation for the probabilities of the separate states $\mathbf{X}$.

Van Kampen, N.G., Stochastic processes in physics and chemistry, Elsevier (1992).

Approximating switching/extinction events

The master equation

$$\frac{\partial \rho(\mathbf{X}, t)}{\partial t} = \sum_{\mathbf{r}} [W(\mathbf{X} - \mathbf{r}; \mathbf{r})\rho(\mathbf{X} - \mathbf{r}, t) - W(\mathbf{X}; \mathbf{r})\rho(\mathbf{X}, t)].$$

Assume the Eikonal approximation:

$$\rho(\mathbf{X}, t) = \exp(-N\mathcal{S}(\mathbf{q})), \text{ for } \mathbf{q} = \mathbf{X}/N.$$

Since $\mathcal{S}$ satisfies the PDE of Hamilton-Jacobi form:

$$\frac{\partial \mathcal{S}}{\partial t} + H\left(\mathbf{q}, \frac{\partial \mathcal{S}}{\partial \mathbf{q}}\right) = 0,$$

$\mathcal{S}$ is known as the action, and the Hamiltonian is given by

$$H(\mathbf{q}; \mathbf{p}) = \sum_{\mathbf{r}} w(\mathbf{q}; \mathbf{r})[\exp(\mathbf{p} \cdot \mathbf{r}) - 1]$$

Define the conjugate momenta $\mathbf{p} = \partial \mathcal{S}/\partial \mathbf{q}$.

We assume the distribution is **quasi-stationary**, $\frac{\partial \mathcal{S}}{\partial t} = 0$. (Rare event)

Kubo, et al., J. Stat. Phys. 9 (1973); Gang, PRA, 36 (1987); Dykman, et al., J. Chem Phys, 100 (1994); Elgart, et al., PRE, 70 (2004); and many others.

The most likely observed paths to extinction

The shape of the distribution is described by Hamilton's eqns:

$$\begin{aligned} \dot{\mathbf{q}} &= \partial_{\mathbf{p}} H(\mathbf{q}, \mathbf{p}; t), \\ \dot{\mathbf{p}} &= -\partial_{\mathbf{q}} H(\mathbf{q}, \mathbf{p}; t), \end{aligned}$$

We study this **deterministic** system to describe the dynamics of the **stochastic** system.

Cost: it doubles the dimension of the system

Benefit: Heteroclinic trajectories connect the saddle steady states

Call the manifold connected to the desired state the optimal path: $p_{opt}(q)$, where the action is minimized so that the probability (ρ) is maximized.

Find the action along the path

$$\mathcal{S}_{opt} = \int_{q_2}^{q_1} p_{opt}(q) dq$$

to approximate the mean time to extinction (MTE): $MTE = B\, e^{N\mathcal{S}_{opt}}$

Since $\rho(\mathbf{X}, t) = e^{-N\mathcal{S}(\mathbf{q})}$

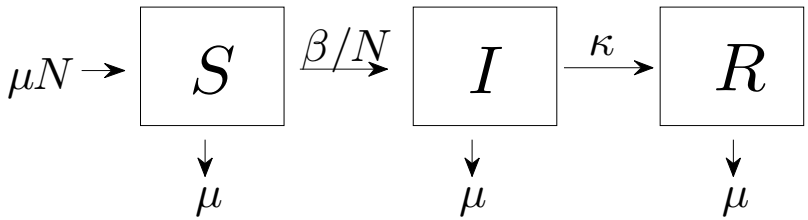
SIR model (Deterministic)

Captures dynamics of most common childhood diseases that confer long-lasting immunity: chickenpox, measles, mumps, rubella, etc.

Population of individuals: susceptible (S), infected (I) or recovered (R). Mass action assumption. Total population: $N = S + I + R$.

Mean field equations:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \frac{\beta}{N} SI - \mu S \\
\frac{dI}{dt} &= \frac{\beta}{N} SI - \kappa I - \mu I \\
\frac{dR}{dt} &= \kappa I - \mu R
\end{aligned}$$

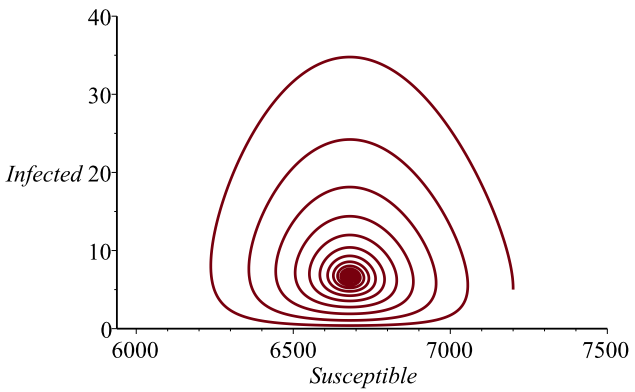


Basic reproduction #: $R_0 = \frac{\beta}{\mu+\kappa}$

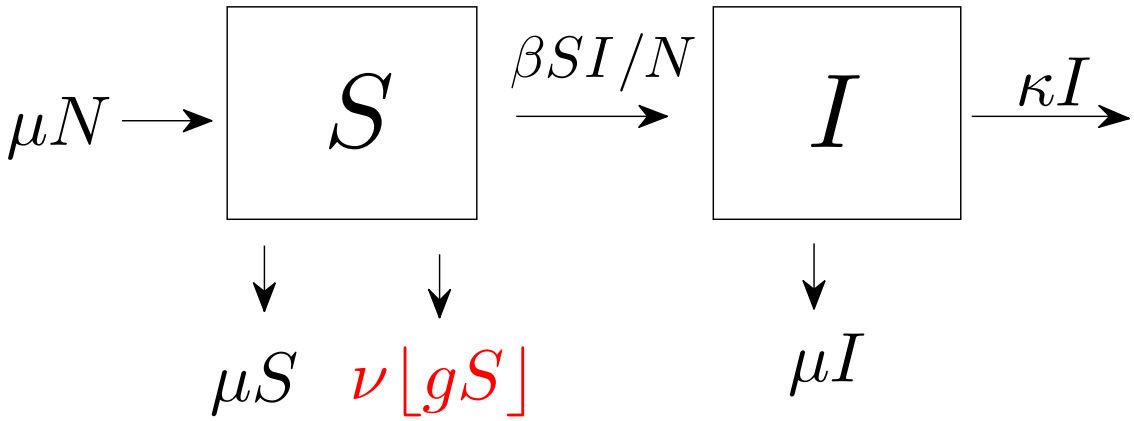
$R_0 > 1 \rightarrow$ endemic stable

Steady states:

- disease free, $(S, I) = (N, 0)$
- endemic, $(S, I) = (\frac{N}{R_0}, \frac{\mu N}{\beta}(R_0 - 1))$



The stochastic SIR model



Master equation approach: susceptible ($S = X_1$) or infected ($I = X_2$).

$$
\begin{aligned}
W\big((X_1, X_2); (1, 0)\big) &= \mu N, && \text{birth} \\
W\big((X_1, X_2); (-1, 1)\big) &= \beta X_1 X_2 / N, && \text{infection of susceptible} \\
W\big((X_1, X_2); (-1, 0)\big) &= \mu X_1, && \text{death for susceptible} \\
W\big((X_1, X_2); (0, -1)\big) &= \mu X_2, && \text{death for infected} \\
W\big((X_1, X_2); (0, -1)\big) &= \kappa X_2, && \text{recovery for infected} \\
W\big((X_1, X_2); (-\lfloor gX_1 \rfloor, 0)\big) &= \nu, && \text{vaccination}.
\end{aligned}
$$

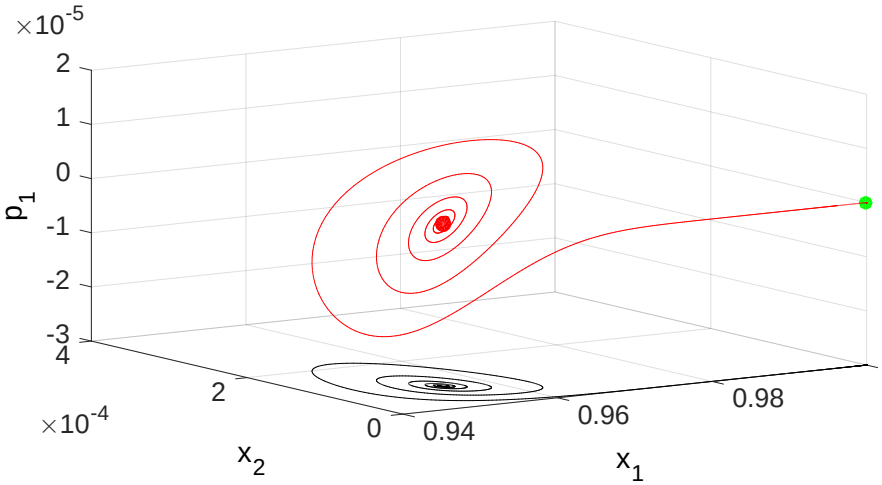
Stochastic SIR model - optimal path

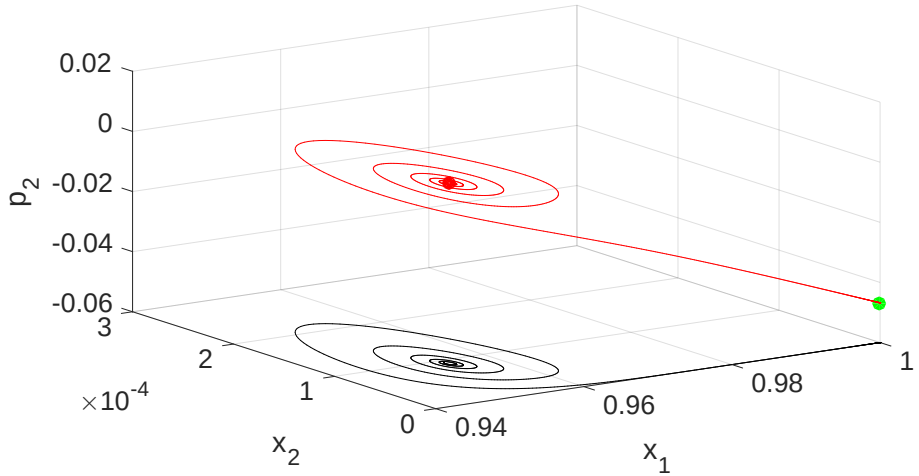
The Hamiltonian equation ($\mathbf{q} = (x_1, x_2)$)

$$H(\mathbf{q}, \mathbf{p}) = \mu(e^{p_1} - 1) + \beta(t)x_1x_2(e^{-p_1+p_2} - 1) + \kappa x_2(e^{-p_2} - 1) + \mu x_1(e^{-p_1} - 1) + \mu x_2(e^{-p_2} - 1).$$

Hamilton's eqns:

$$\dot{x}_1 = \partial_{p_1} H(x_1, x_2, p_1, p_2; t), \qquad \dot{x}_2 = \partial_{p_2} H(x_1, x_2, p_1, p_2; t),$$
$$\dot{p}_1 = -\partial_{x_1} H(x_1, x_2, p_1, p_2; t), \qquad \dot{p}_2 = -\partial_{x_2} H(x_1, x_2, p_1, p_2; t),$$

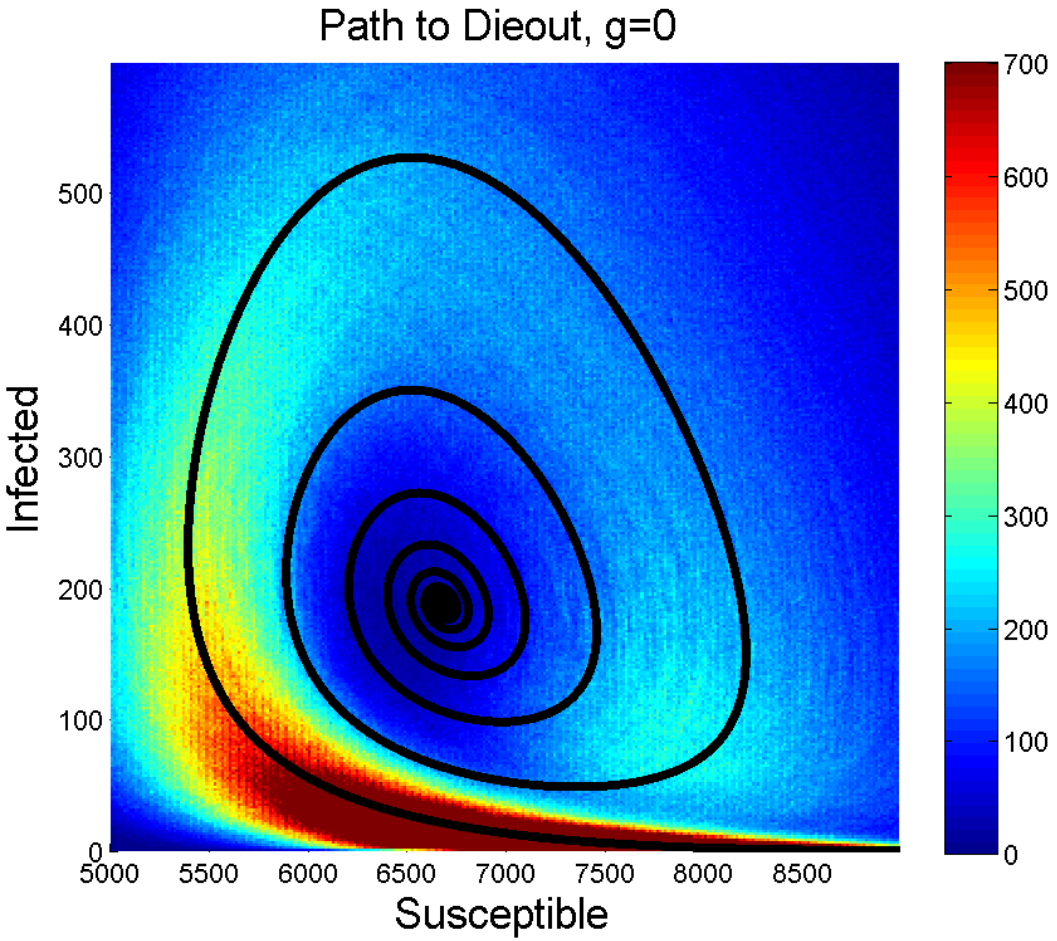




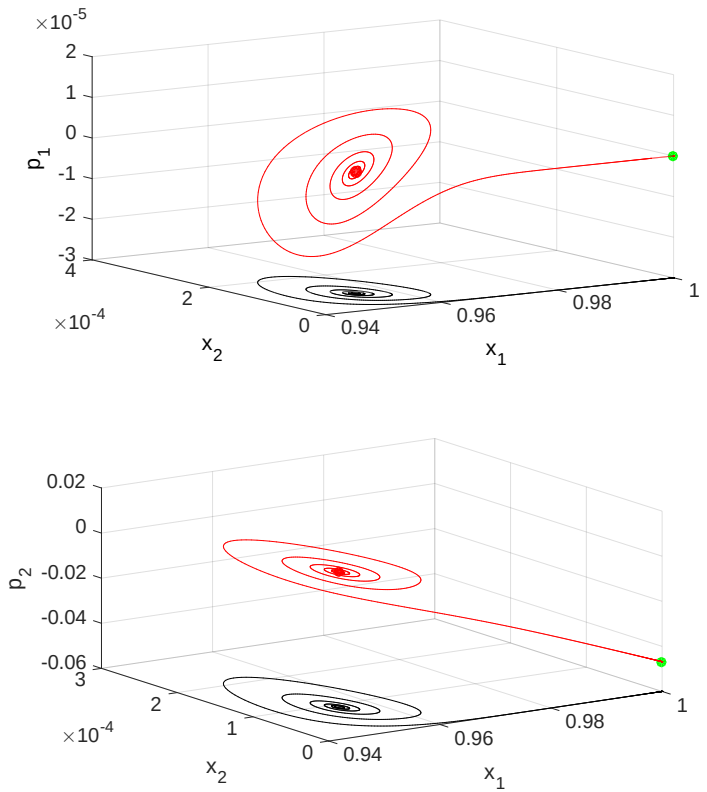
Lindley & Schwartz, Physica D (2013) [Iterative action minimizing method]

The stochastic SIR model - validation

Compare the optimal path to the simulations



Probability density of extinction prehistory.



Optimal path approximation.

Schwartz, et al., J R Soc Interface, 2011

Stochastic SIR - Time varying parameters

Mathematical models with periodic forcing developed to capture seasonal variation.

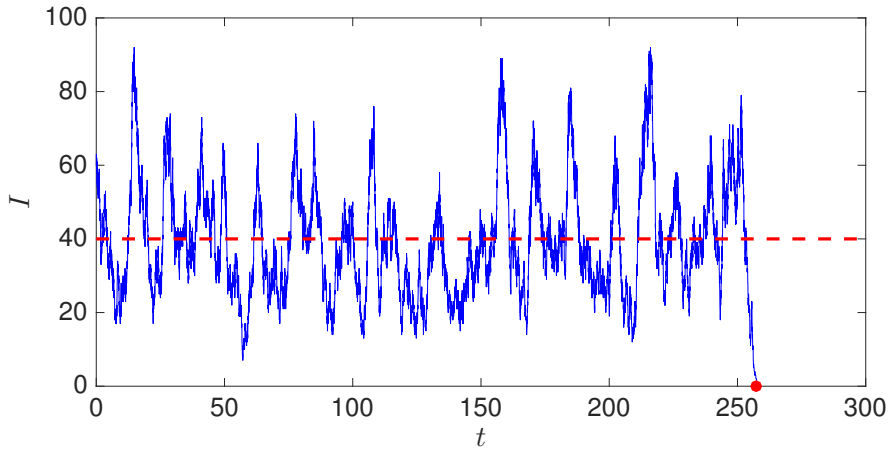
– Vary the contact rate $\beta(t)$ periodically

Mean field equations:

$$\begin{aligned}\frac{dS}{dt} &= \mu N - \frac{\beta(t)}{N} SI - \mu S \\ \frac{dI}{dt} &= \frac{\beta(t)}{N} SI - \kappa I - \mu I\end{aligned}$$

$$\beta(t) = \beta_0(1 + \delta\cos(2\pi t))$$

Stochastic simulations



Deterministic steady states:

- disease free, $(S, I) = (N, 0)$
- endemic, $(S, I) = \left(\frac{(\gamma+\mu)N}{\beta(t)}, \frac{\mu N}{\beta(t)}\left(\frac{\beta(t)}{\gamma+\mu} - 1\right)\right)$ **periodic orbit, careful with stability

Stochastic SIR model - Finding the optimal path

The Hamiltonian equation ($\mathbf{q} = (x_1, x_2)$)

$$\mathcal{H}(\mathbf{q}, \mathbf{p}; t) = \mu(e^{p_1} - 1) + \beta(t)x_1x_2(e^{-p_1+p_2} - 1) + \kappa x_2(e^{-p_2} - 1)$$
$$+\mu x_1(e^{-p_1} - 1) + \mu x_2(e^{-p_2} - 1).$$

Problem: The existence of the perturbed hyperbolic fixed points is a necessary but not sufficient condition for the existence of a heteroclinic trajectory (optimal path).

Linear expansion of Hamiltonian: $0 < \delta \ll 1$ for $\beta(t) = \beta_0(1 + \delta\cos(2\pi t))$,

$$\mathcal{H}(\mathbf{q}, \mathbf{p}; t) = H_0(\mathbf{q}, \mathbf{p}; t) + \delta H_1(\mathbf{q}, \mathbf{p}; t).$$

Assume the existence of a perturbed optimal path: $\mathbf{q}(t, t_0)$, $\mathbf{p}(t, t_0)$
and the action along this path:

$$\mathcal{S} = \int_{-\infty}^{\infty} \left(\mathbf{p}(t, t_0) \cdot \frac{d\mathbf{q}(t, t_0)}{dt} - H_0(\mathbf{q}(t, t_0), \mathbf{p}(t, t_0); t) - \delta H_1(\mathbf{q}(t, t_0), \mathbf{p}(t, t_0), t) \right) dt$$

Stochastic SIR model - Finding the optimal path

The change in the action: $\mathcal{S} = \mathcal{S}_0 + \Delta\mathcal{S}$, approximation to first order, **

$$\Delta\mathcal{S}(t_0) = -\delta \int_{-\infty}^{\infty} H_1\left(\mathbf{q}(t - t_0, t_0), \mathbf{p}(t - t_0, t_0), t\right) dt.$$

To find the optimal correction to the action, minimize $\mathcal{S}(t_0)$ with respect to t_0. Consider the zeros of its derivative,

$$\frac{d\mathcal{S}(t_0)}{dt_0} = -\delta \int_{-\infty}^{\infty} \{H_0, H_1\}_0 \, dt = 0,$$

$\{H_0, H_1\}_0$ is the Poisson bracket evaluated on the unperturbed optimal path.

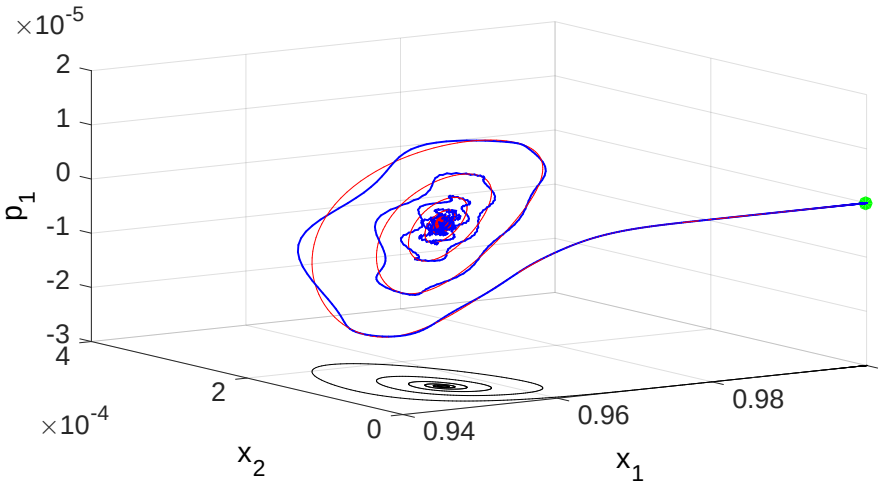
$\int_{-\infty}^{\infty} \{H_0, H_1\}_0 \, dt$ is the Melnikov function of the perturbed problem. It is proportional to the distance between the unstable and stable manifolds of perturbed fixed points.

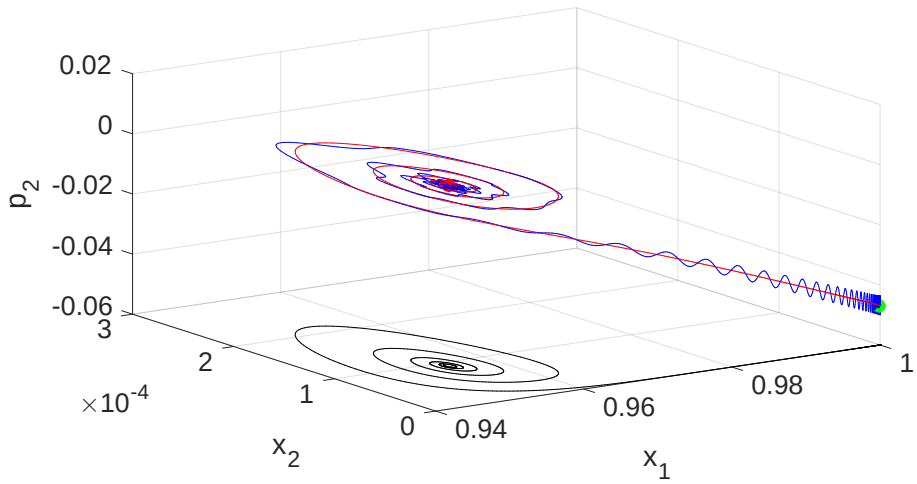
A sufficient condition for the existence of the perturbed optimal path is for the Melnikov function to have simple zeros. These zeros are the critical points of the action, which yields the minimal action along the optimal path of the perturbed problem.

**Assaf, et al.,"Population extinction in a time-modulated environment" PRE 78(4), (2008)

Stochastic SIR model - Finding the optimal path

After finding the zeros and the approximating the phase shift for the minimizing t_0, we find the optimal path to extinction



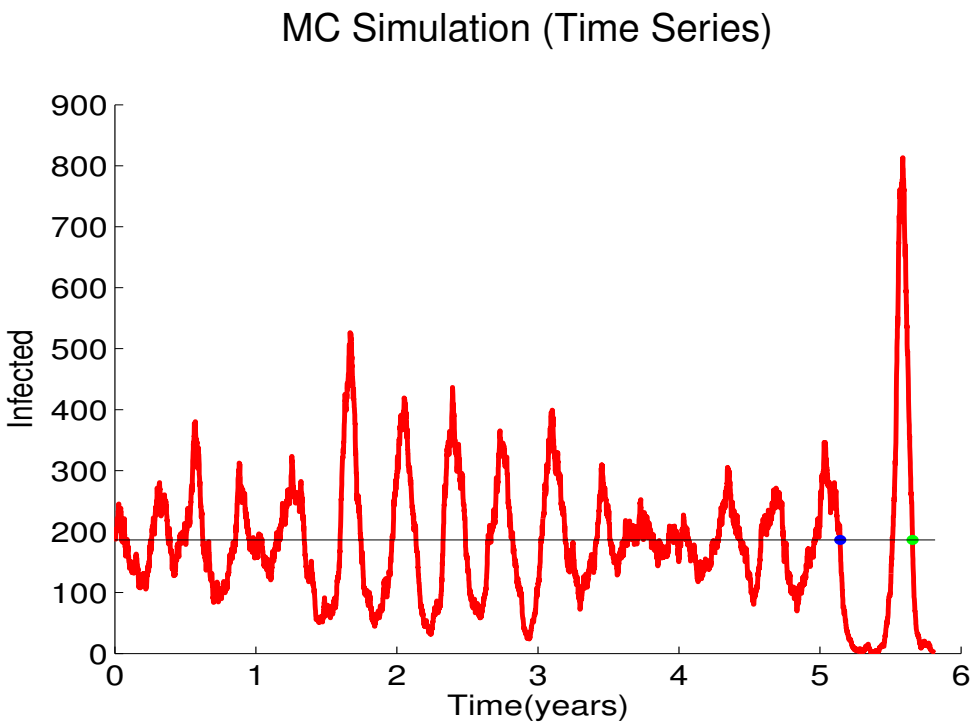


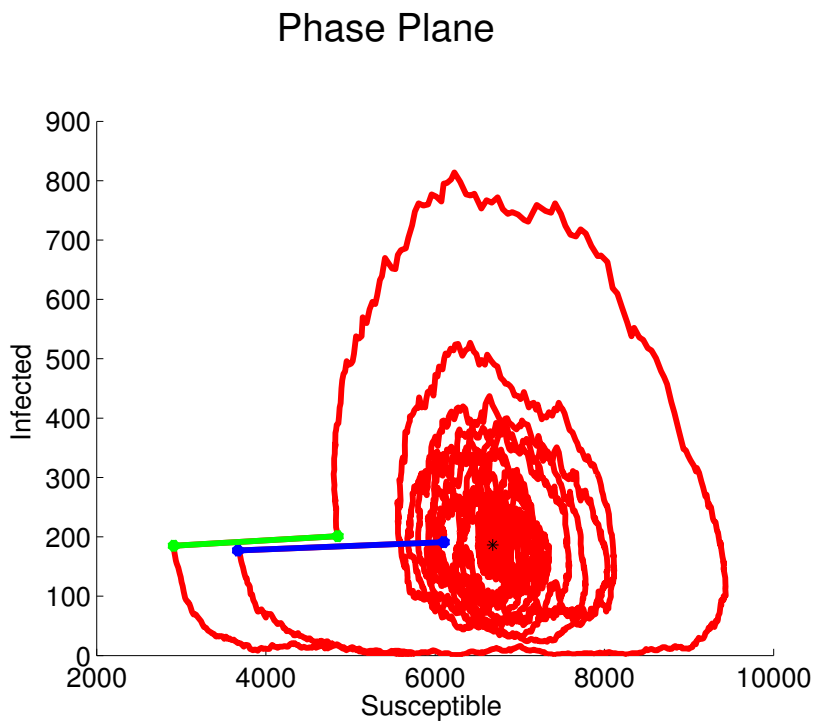
[LB and Forgoston, Ricerche di Matematica, to appear 2017]

Optimal Control

Khasin, Dykman, and Meerson, “Speeding up disease extinction with a limited amount of vaccine," PRE, 81 (2010) 051925.

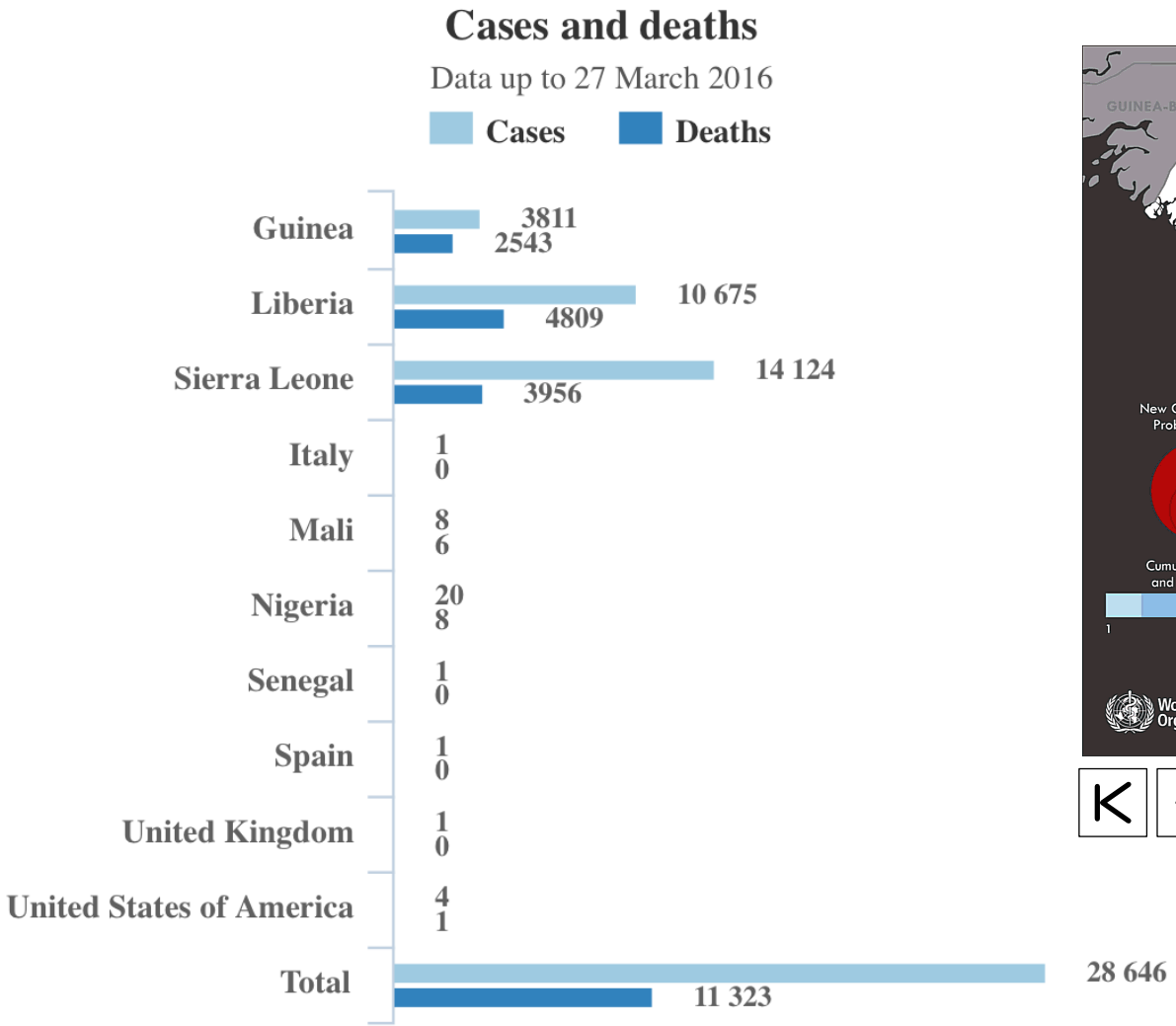
“The optimal vaccination strategy for periodic vaccination is to apply the vaccine in the form of δ-like pulses. Tuning these pulses in resonance with the system dynamics leads to a further exponential enhancement of the effect of the vaccination.”

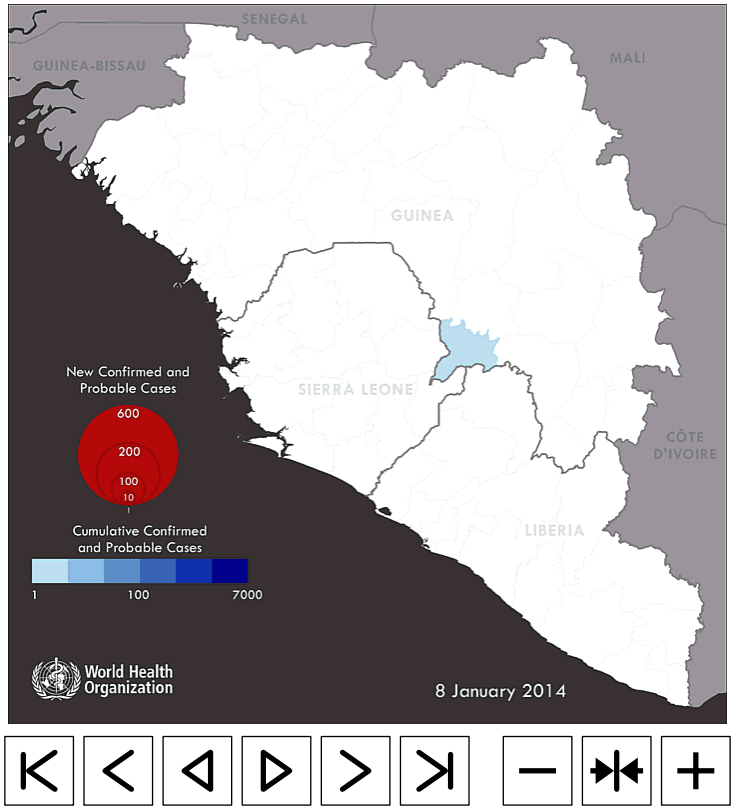




Invasion

Ebola Virus... no vaccine yet, some data



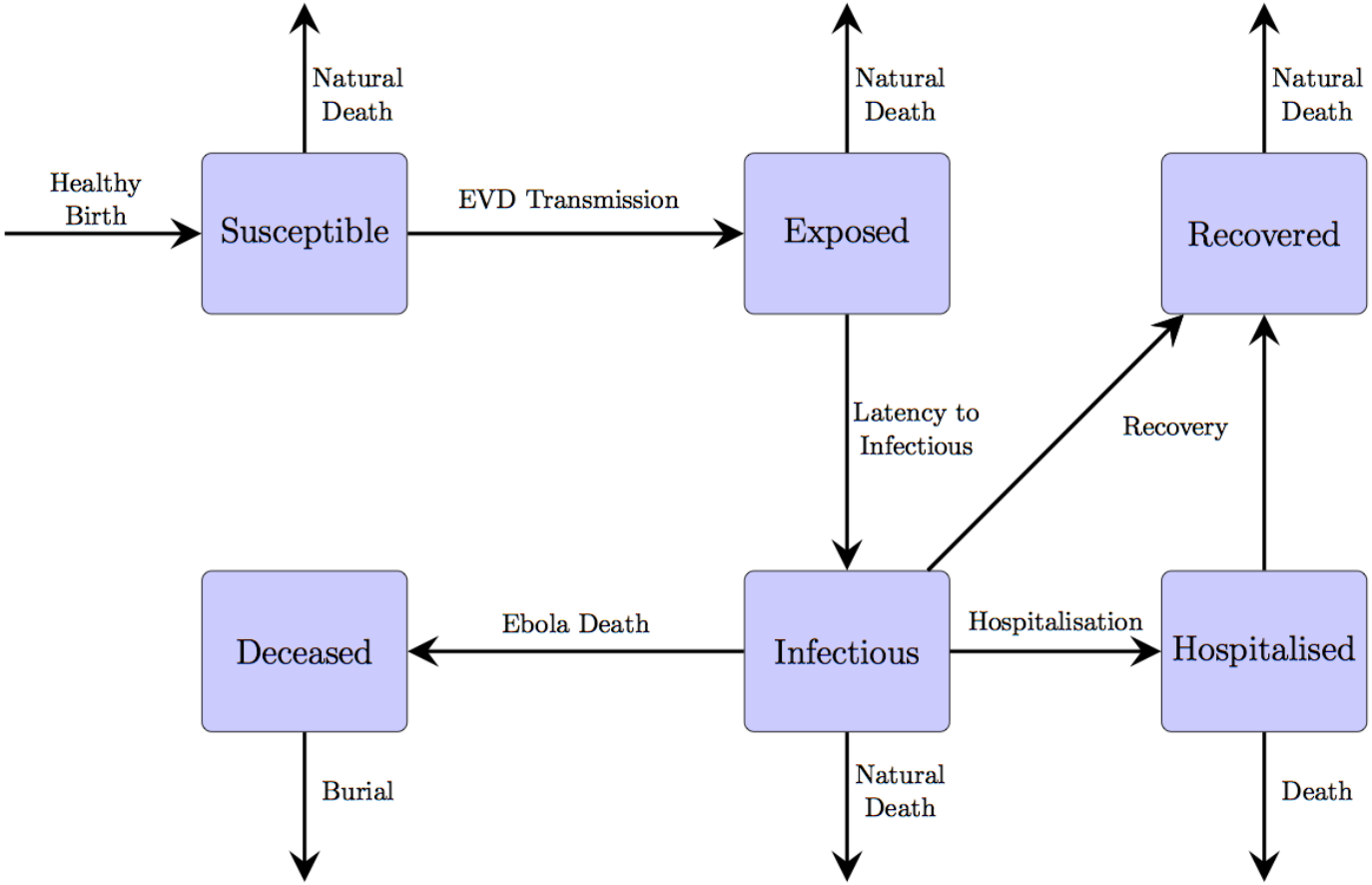


June 2016 – WHO declares the end of Ebola virus transmission in the Republic of Guinea and in Liberia.

The basic reproductive number is estimated to be $R_0 \leq 2$

Ebola Virus Disease

- an infectious zoonosis found in several mammals including humans, bats, and apes.



Note that EVD transmission can occur though both infectious human contact and an animal reservoir (random).

Ebola Virus Disease

The transition events and transition rates for the stochastic EVD model

Event	Transition	Rate
Healthy Birth	$\varnothing \rightarrow$ S	μ N
EVD Transmission (human)	S $\rightarrow$ E	$(\beta_i$ I+β_d D+β_h H$)\frac{S}{N}$
EVD Transmission (animal)	S $\rightarrow$ E	κ S
Latency to Infectious	E $\rightarrow$ I	σ E
Recovery	I $\rightarrow$ R	γ_{ir} I
EVD Death	I $\rightarrow$ D	μ_e I
Hospitalisation	I $\rightarrow$ H	τ I
Burial	D $\rightarrow \varnothing$	δ D
Death from Hospital	H $\rightarrow \varnothing$	μ_e H
Recovery from Hospital	H $\rightarrow$ R	γ_{hr} H
Natural Death	{S,E,I,D,H,R} $\rightarrow \varnothing$	μ {S,E,I,D,H,R}

Ebola Virus Disease

The deterministic mean-field equations:

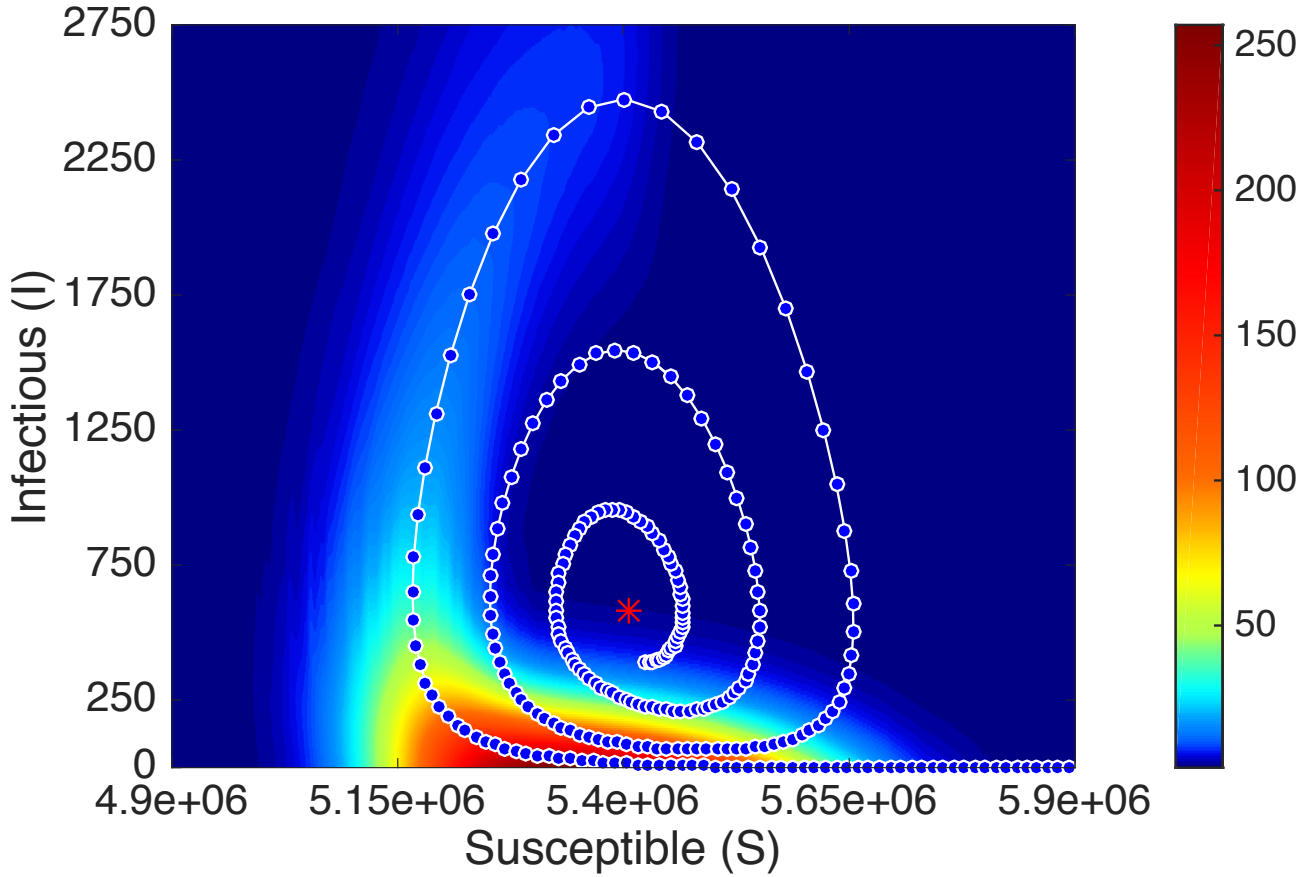
$$
\begin{aligned}
\frac{dx_S}{dt} &= \mu - \beta_i x_I x_S - \beta_d x_D x_S - \beta_h x_H x_S - \mu x_S - \kappa x_S \\
\frac{dx_E}{dt} &= \beta_i x_I x_S + \beta_d x_D x_S + \beta_h x_H x_S - (\mu + \sigma) x_E + \kappa x_S \\
\frac{dx_I}{dt} &= \sigma x_E - (\gamma_{ir} + \mu_e + \tau + \mu) x_I \\
\frac{dx_D}{dt} &= \mu_e x_I - (\delta + \mu)\, x_D \\
\frac{dx_H}{dt} &= \tau x_I - (\gamma_{hr} + \mu_e + \mu)\, x_H \\
\frac{dx_R}{dt} &= \gamma_{ir} x_I + \gamma_{hr} x_H - \mu x_R.
\end{aligned}
$$

Steady states for $\kappa = 0$,

Disease free equilibrium: $(x_S{}^{(i)}, x_E{}^{(i)}, x_I{}^{(i)}, x_D{}^{(i)}, x_H{}^{(i)}, x_R{}^{(i)}) = (1, 0, 0, 0, 0, 0)$.

Endemic equilibrium: $(x_S{}^{(e)}, x_E{}^{(e)}, x_I{}^{(e)}, x_D{}^{(e)}, x_H{}^{(e)}, x_R{}^{(e)})$

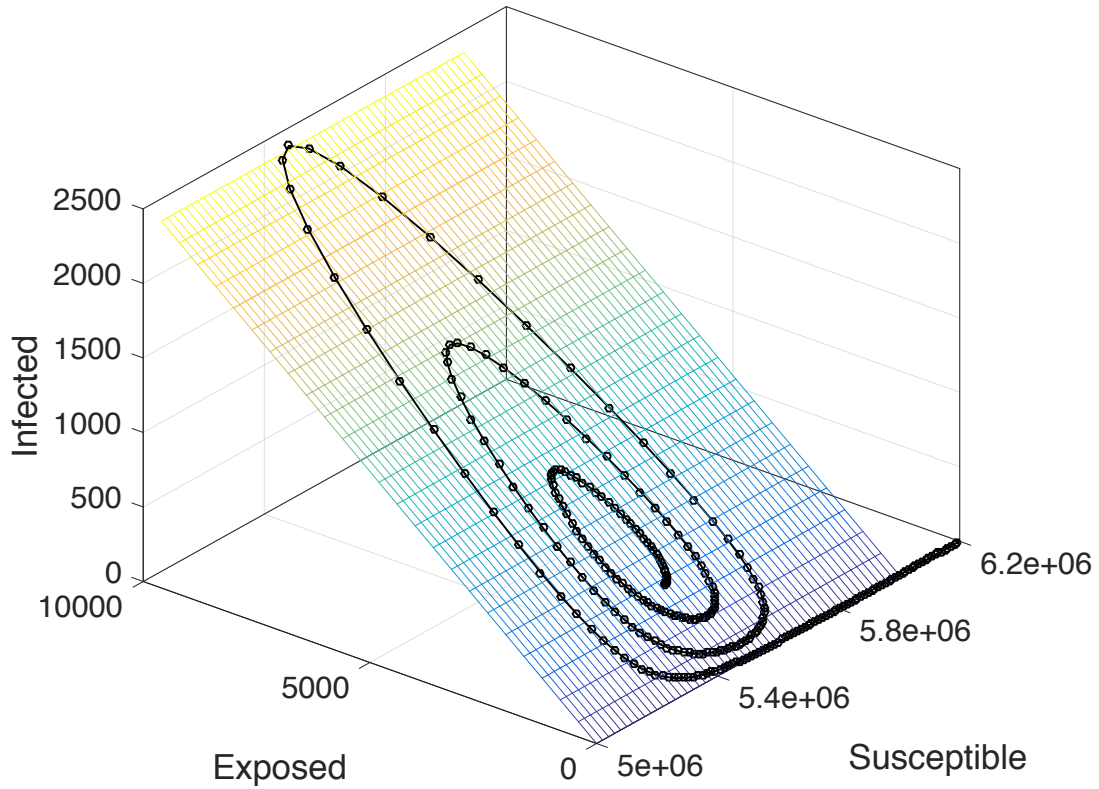
Ebola Virus Disease - Optimal Path (Extinction)



A 12 dimensional optimal extinction path for a stochastic EVD system with $\kappa = 0$ found by the IAMM method (2400 blue points).

The path is overlaid on the probability density of extinction prehistories for $10,000$ stochastic realizations for a population $N = 10,000,000$.

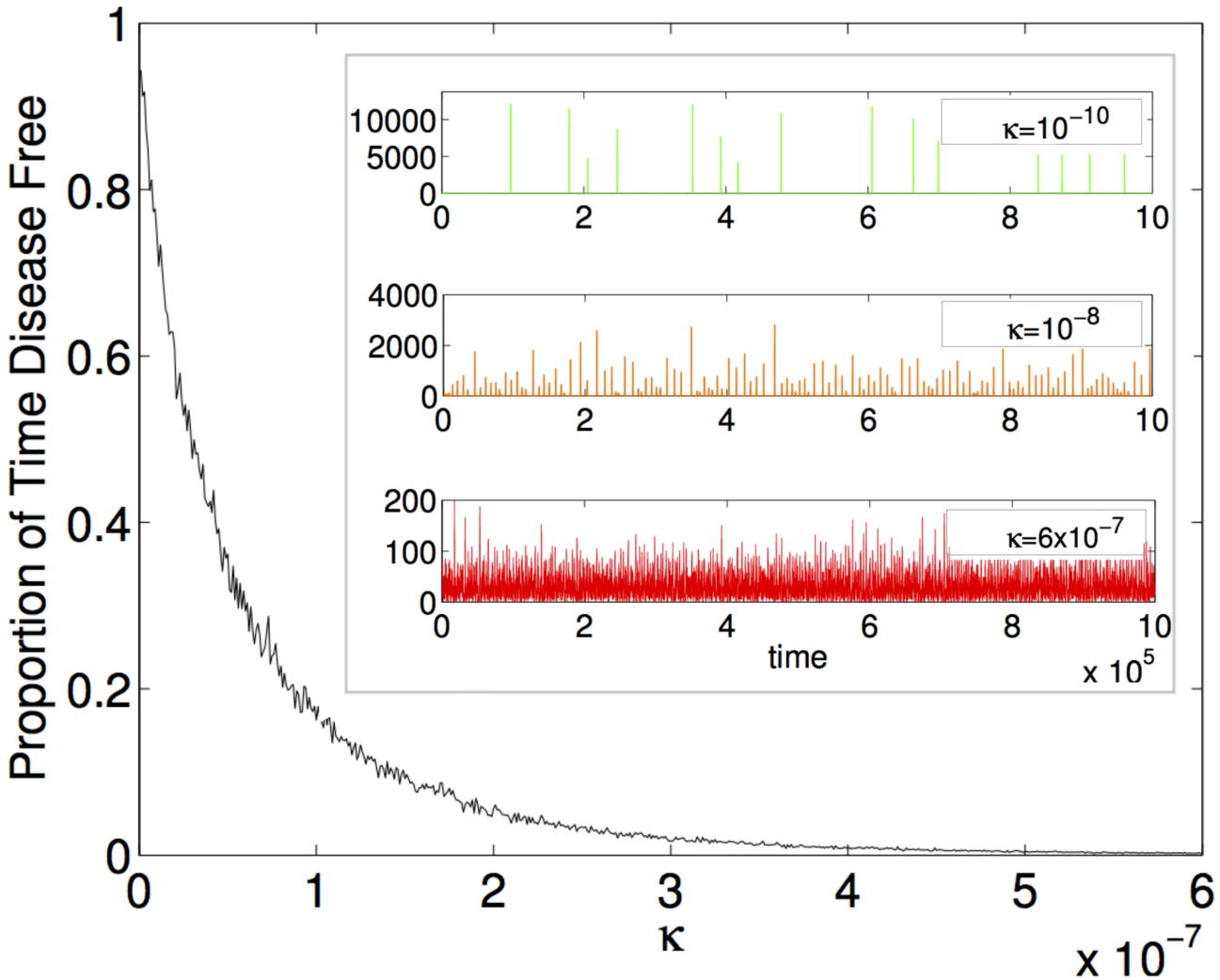
Ebola Virus Disease - Center Manifold



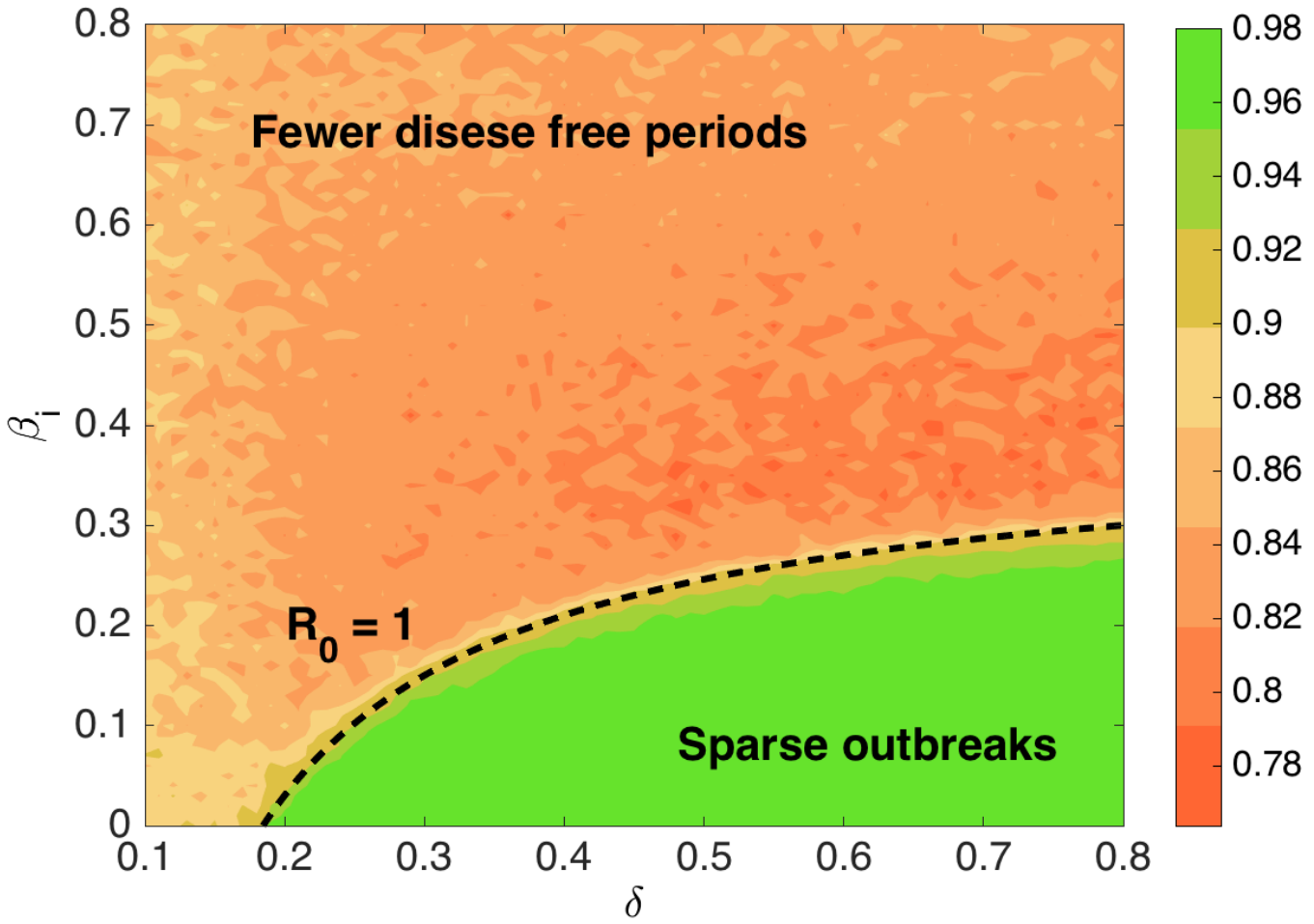
Additional verification of our numerically computed optimal path is achieved by projecting it onto the lower-dimensional stochastic center manifold.

$$x_I = \frac{\sigma(x_E - x_E^{(e)})}{(\gamma_{ir} + \tau + \mu_e + \mu)} + x_I^{(e)}.$$

The other side - Invasion



Ebola Virus Disease - Intervention



A measure of intervention effectiveness – the impact of limiting the contact rate with the infectious EVD group (β_i) and increasing the burial rate for deceased EVD group (δ)

Remarks

- Stochastic modeling allows one to make quantitative, statistical predictions, while simultaneously providing qualitative descriptions of system dynamics.
- We present the foundation for the analysis of stochastic epidemiological models with seasonal forcing.
- We also described invasion dynamics and the qualitative use of the traditional basic reproduction number.
- Stochastic models can help quantify the impact of intervention methods, such as behavioral changes.
- A lot more work to be done:
  - approximation for the mean time to extinction in these systems
  - devise and optimize improved control methods
  - understand/quantify invasion dynamics
  - experimental verification ... (ecological systems)

Collaborators

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- Lora Billings and Eric Forgoston, "Seasonal Forcing in Stochastic Epidemiology Models." Richerche di Matematica, accepted 2017.
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Ebola Virus Disease

Table 1. Summary of model parameters obtained from literature and model calibration

Model input / Parameter	Value	Range	Sources (ref.)	Unit
R_0, basic reproductive number	1.32	1.30-2.30	[5, 8, 9]	dimension-less
β_i, infectious transmission rate	0.29*	0.16-0.45	[8, 10]	day^{-1}
β_d, postmortem transmission rate	0.65*	0.16-0.69	[8, 10]	day^{-1}
β_h^*, infectious transmission rate from admitted in hospital	0.00016	N.A.	[6, 10]	day^{-1}
σ, incubation rate	0.10	0.08-0.19	[2, 5, 8, 9]	day^{-1}
γ_1, infectious recovery rate human in general community	0.07	0.05-0.18	[2, 5, 8, 9]	day^{-1}
γ_2, infectious recovery rate of human from hospital	0.10	0.05-0.18	[2, 5, 8, 9]	day^{-1}
μ, disease death rate	0.12	0.08-0.13	[2, 9]	day^{-1}
δ , corpse burial rate	0.33	0.22-0.50	[2, 9]	day^{-1}
τ hospital admission rate	0.20	0.20-0.31	[9]	day^{-1}

N.A.: not available

* calibrated value from the WHO public available data

Hu, K., Bianco, S., Edlund, S. & Kaufman, J. 2015 Social computing, behavioral-cultural modeling, and prediction, chap. The Impact of Human Behavioral Changes in 2014 West Africa Ebola Outbreak, pp. 75-84.