The dynamics of epidemics: An overview of (our) modeling and analysis methods

Ira B. Schwartz and Leah B. Shaw

US Naval Research Laboratory

Code 6792,PPD

Washington, DC 20375

Schwartz@nlschaos.nrl.navy.mil

Lshaw@nls6.nrl.navy.mil

Lora Billings

Montclair State University Dept. of Mathematics

Don Burke and Derek Cummings

JHU School of Public Health

IPAM

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Goals of Epidemic Modeling

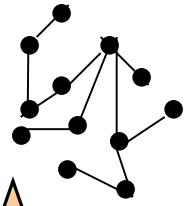
To predict disease spread or outbreaks in large population structures.

<u>Predict</u> the occurrence of natural or unnatural disease outbreaks in the presence of uncertainties in population structure and biological parameters.

Develop computational and analysis tools to predict (probabilistically) disease spread, with the goal of helping to aid decision making for disease control.

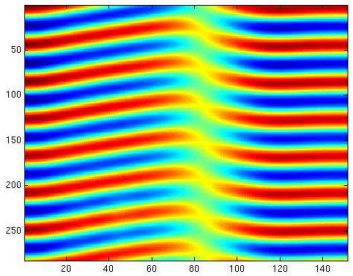
Types of Epidemic Models
Simple to Complex

Network of individuals

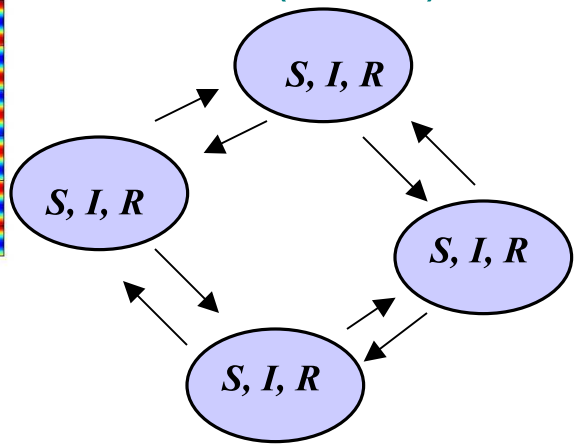


Detail

Spatial continuum

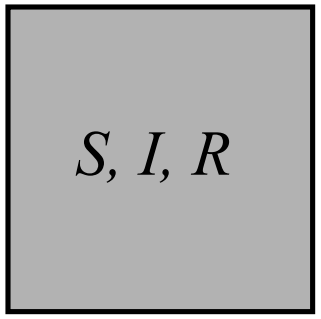


Coupled population (Patch) model



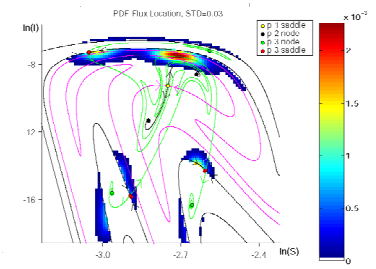
Computational ease - analyzable

Single, well-mixed compartment

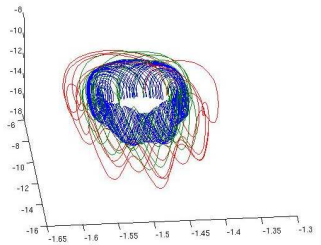


Outline

Basic epidemic modeling
- **single population**
- **single strain**

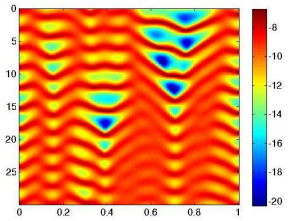


Multistrain modeling
- **strain organization**
- **uncovering asymptotmatics**

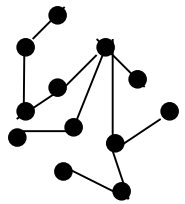


Spatial

- **continuum (multistrain)**



- **adaptive network**



Single strain model

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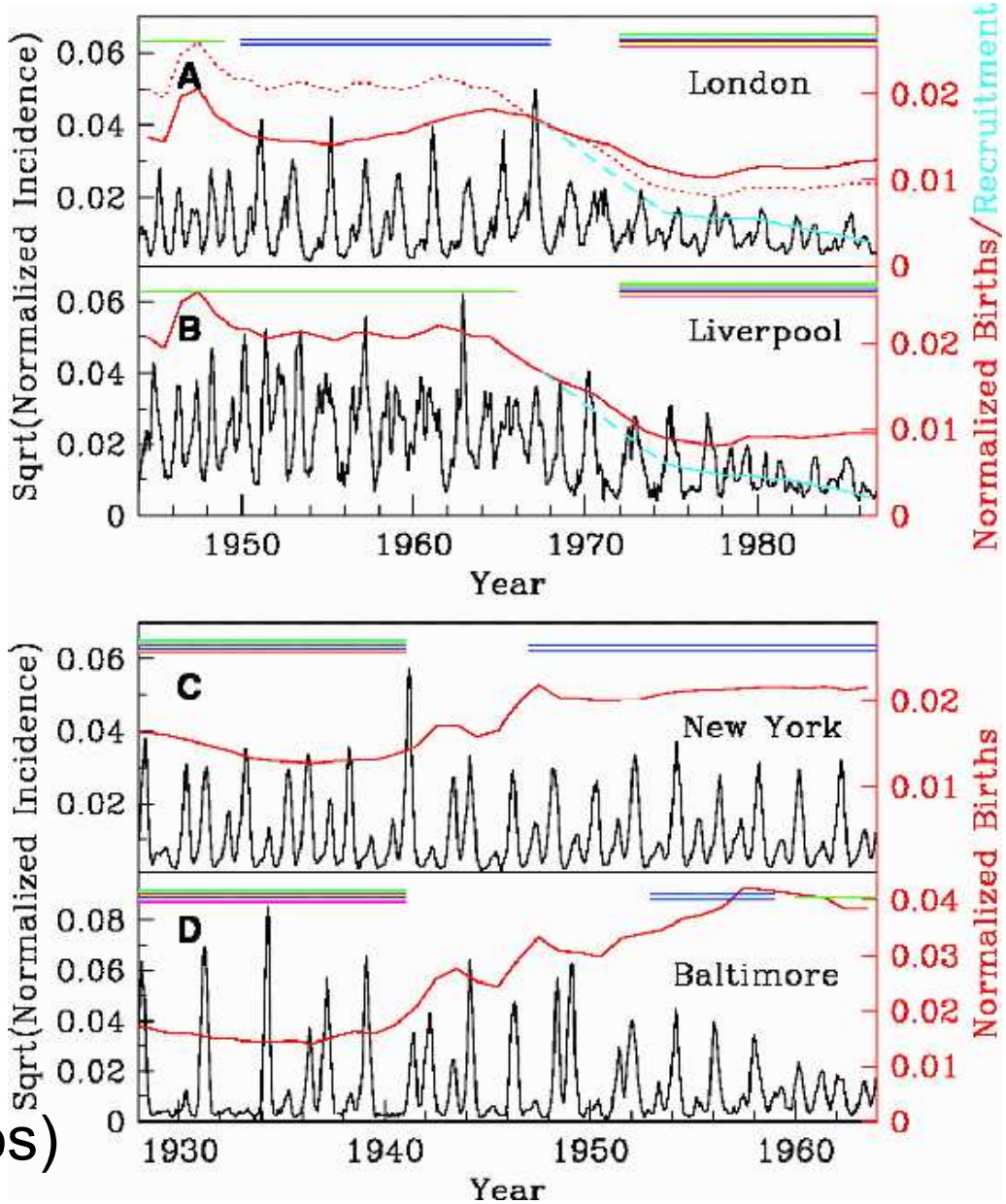
D. Earn, et al. Science, 2000

Single strain data set
Measles in UK and US

Question:
What causes the pre-vaccine time series to be complex?

Answer:
Undetermined
(Not enough data
To say if it is
deterministic or
noise induced chaos)



Modeling Simple Epidemics: Assumptions

The population:

- Assume the population is large and well mixed.
- Variables and parameters:

S:	Susceptibles
E:	Exposed
I:	Infectives
R:	Recovered

α^{-1}:	mean latent exposed period
σ^{-1}:	mean infectious period
μ:	birth and death rate
β:	contact rate (for S & I)

- Normalize the population: **S + E + I + R** = 1

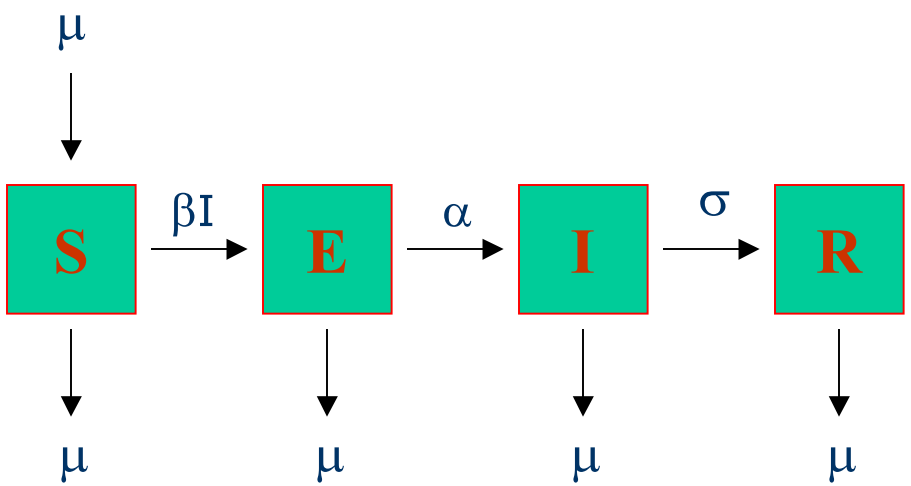
The standard SEIR model

$$\frac{dS}{dt} = \mu - \beta(t) IS - \mu S + \eta_1(t) S$$

$$\frac{dE}{dt} = \beta(t) IS - \alpha E - \mu E + \eta_2(t) E$$

$$\frac{dI}{dt} = \alpha E - \sigma I - \mu I + \eta_2(t) I$$

$$\frac{dR}{dt} = \sigma I - \mu R + \eta_4(t) R$$



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

$$I(t) \approx \left(\frac{\alpha}{\mu + \sigma} \right) E(t)$$

$\eta_i(t)$ Noise terms

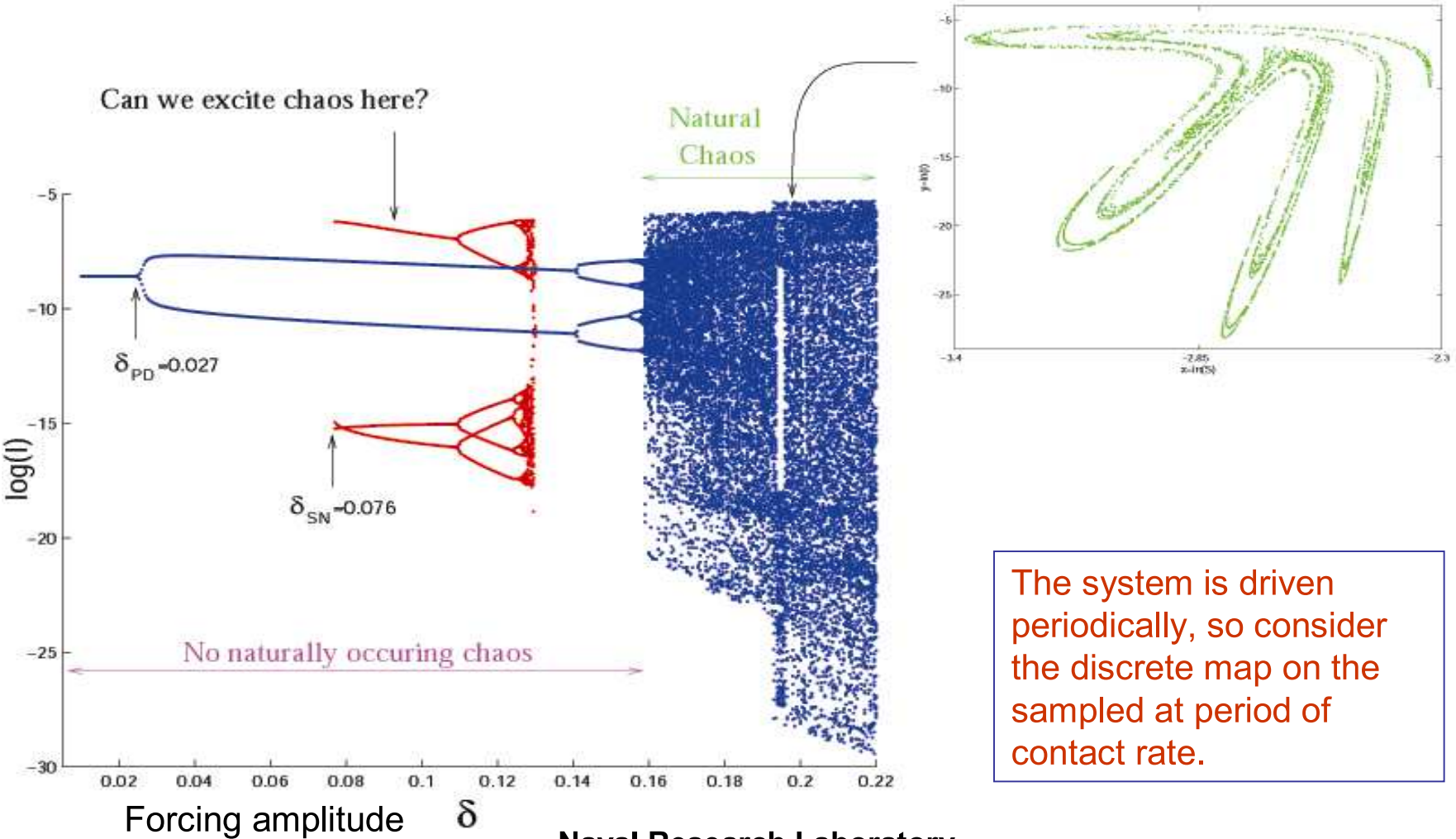
Steady State Solution for Constant Contact Between People

- Reproductive rate of infection

$$R_0 = \frac{\beta}{\sigma + \mu} \approx \frac{\beta}{\sigma}$$ (Contact rate*infectious period)

- Number of additional infections one infective will generate
- R_0<1 : stable disease-free steady state (I=0)
- R_0>1 : stable endemic steady state
- No complex behavior

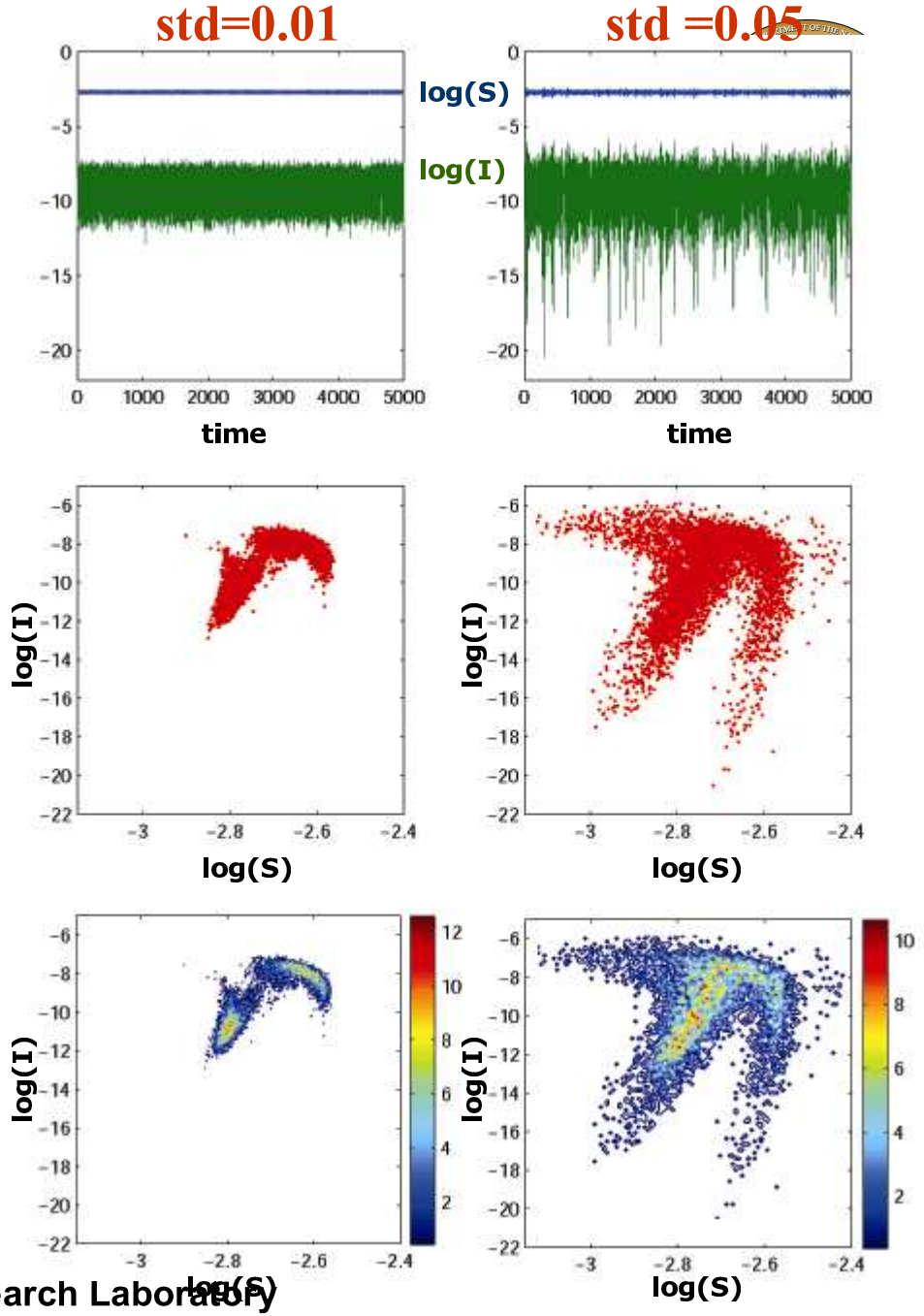
Bifurcation diagram-periodic contact rate



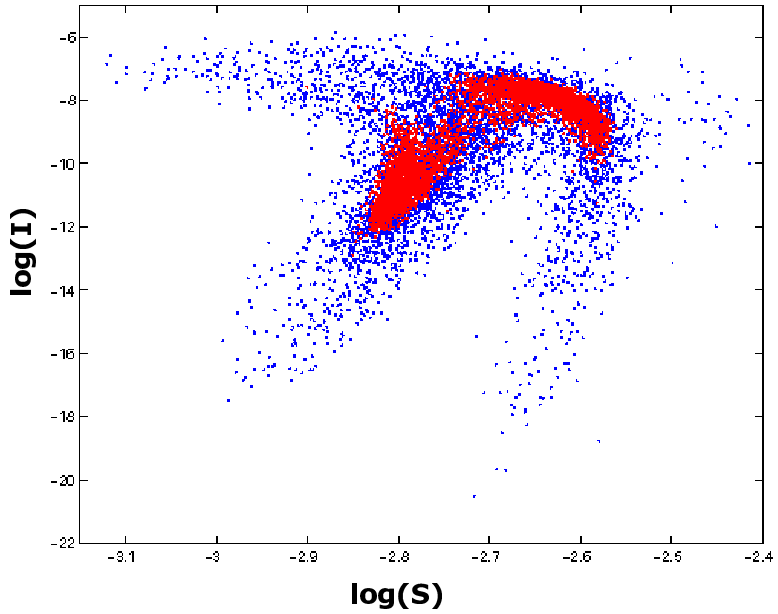
The system is driven periodically, so consider the discrete map on the sampled at period of contact rate.

Adding Noise Generates Complex Dynamics

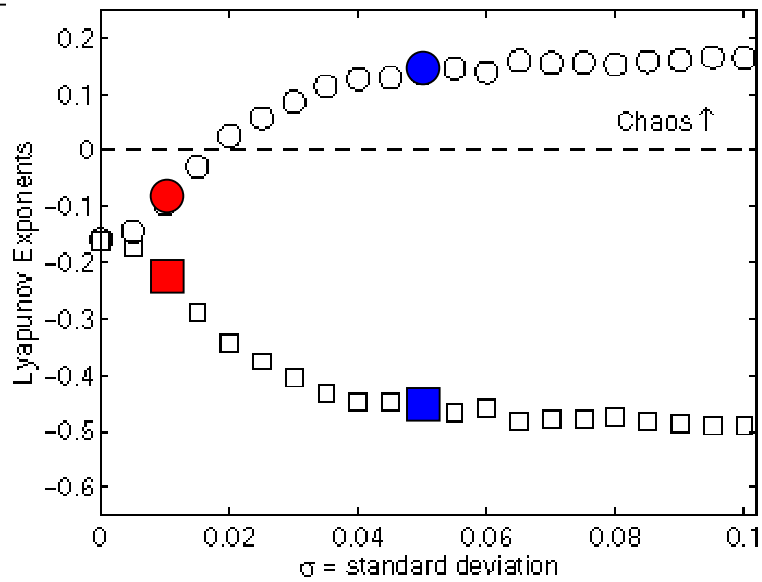
- Time series
- Phase space diagram
- Probability density function



Lyapunov exponents
Test for Chaotic Dynamics



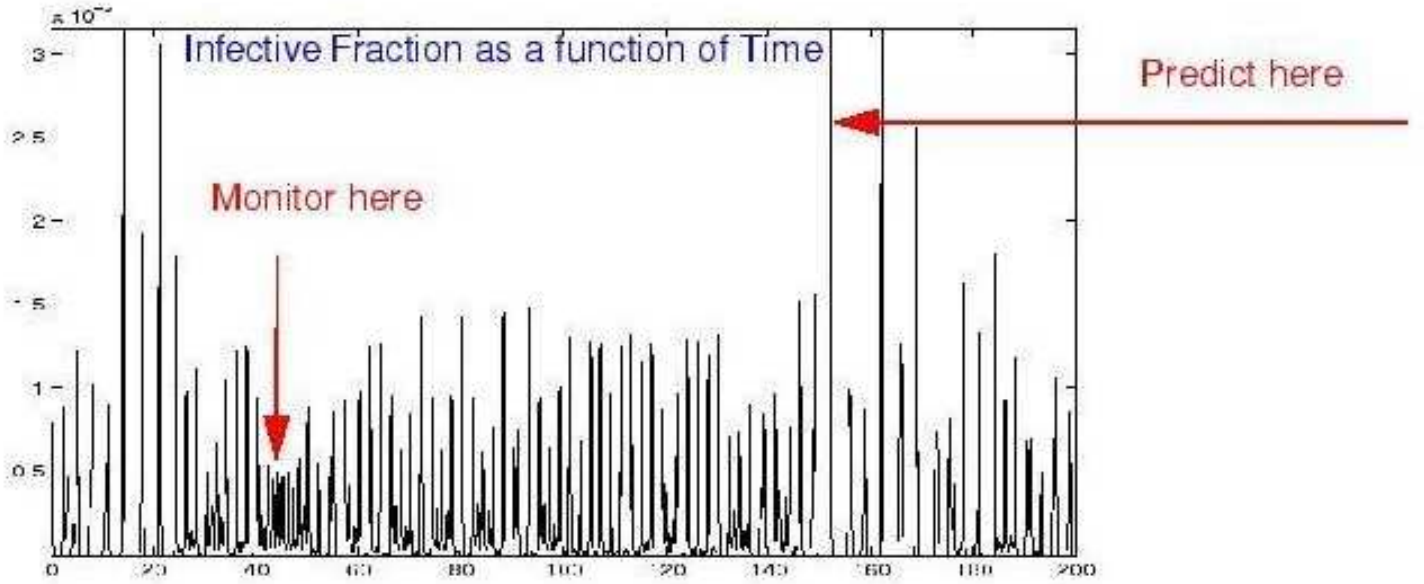
- Red: std = 0.01 (noisy)
- Blue: std = 0.05 (chaotic)



But Lyapunov exponents can yield false results

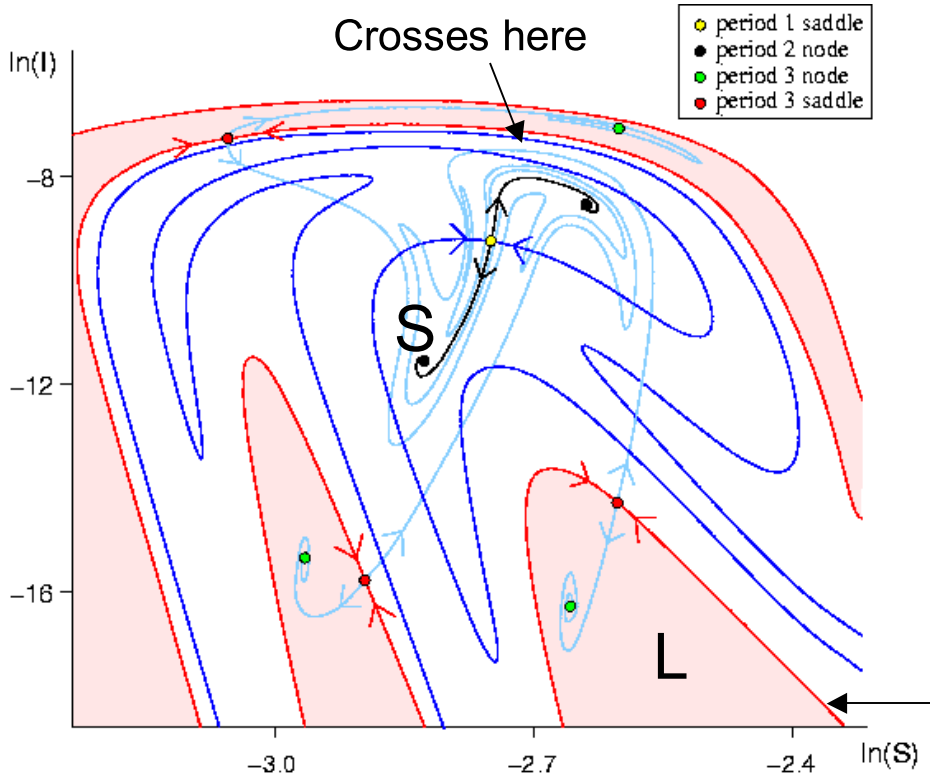
Conditional Prediction of Large Outbreaks in Stochastic Outbreaks

std = 0.03



Mix of large and small outbreaks – noise induced

Chaotic Saddle in Bi-stable Epidemic



Two attractors: S and L

S is small 2 year outbreak
L is large 3 year outbreak

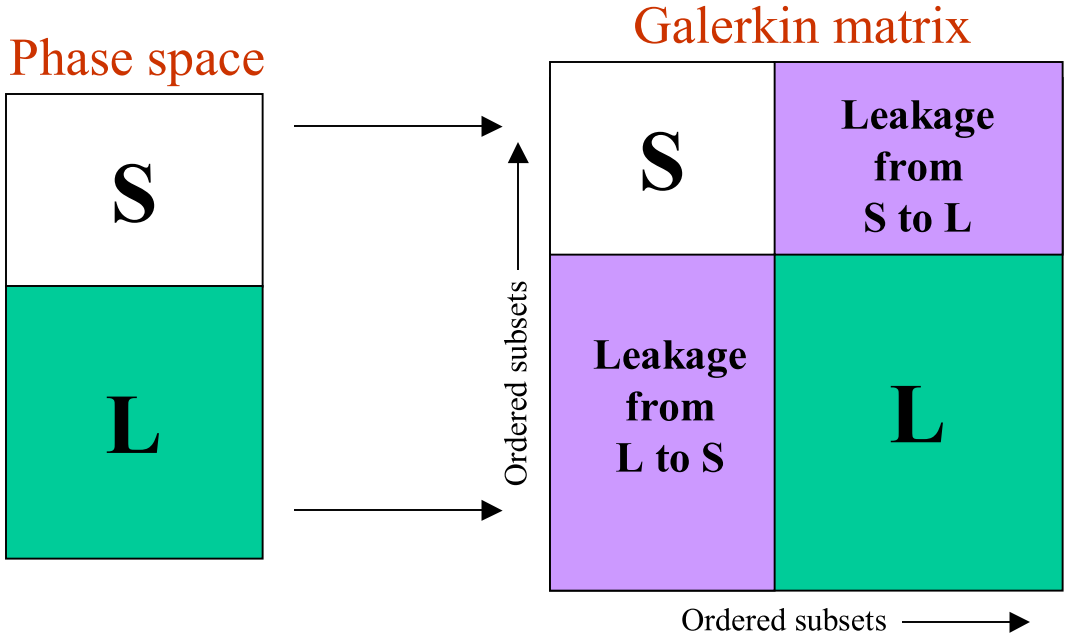
White is basin of S
Red is basin of L

Basin Boundary

- Noise uses the topological structure to induce “chaos”
- Noise induces single attractor by mixing two deterministic outbreaks
- Now we want to provide numerical evidence that this is the case.

Tool to detect transport across basins

Use a Galerkin approximation of the Stochastic Frobenius-Perron Operator to detect the flux across basin boundaries and predict the most probable regions of transport created by noise.



Transport Operator

- Add noise using a random variable h (mean=0 and standard deviation σ)

$$F : M \to M,\ x \to F(x) + \eta$$

- Frobenius-Perron operator – acting on a probability density function r:

$$\int_{F^{-1}(M)} \rho(x)\, dx = \int_{M} P_F[\rho(x)]\, dx$$

- Stochastic Frobenius-Perron operator acting on a probability density function r (after differentiation):

$$P_F[\rho(x)] = \int_{M} v(x - F(y))\, \rho(y)\, dy$$

Stochastic kernal describing the noise

Transport Matrix

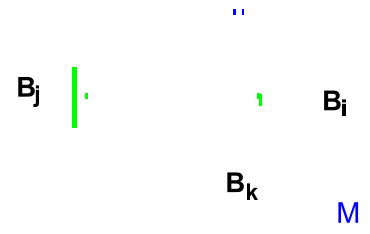
- Stochastic Frobenius-Perron operator

$$P_F[\rho(x)] = \frac{1}{\sqrt{2\,\pi s^2}} \int_M e^{-\frac{\|x-F(y)\|^2}{2(\mathrm{std})^2}} \rho(y)\,dy$$

Can use any noise distribution!

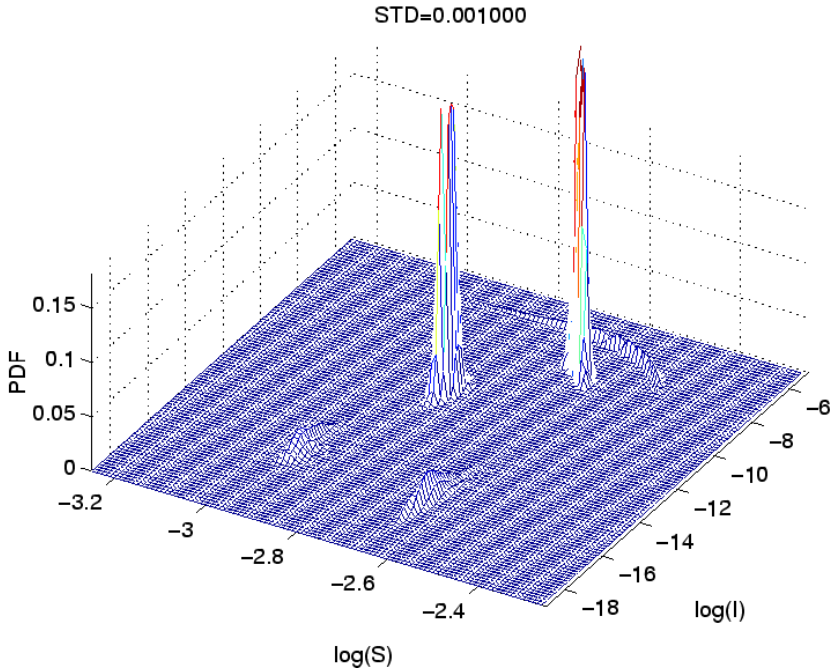
- Galerkin approximation

$$A_{i,j} = (P_F[\varphi_i], \varphi_j) = \int_M P_F[\varphi_i(x)]\,\varphi_j(x)\,dx$$

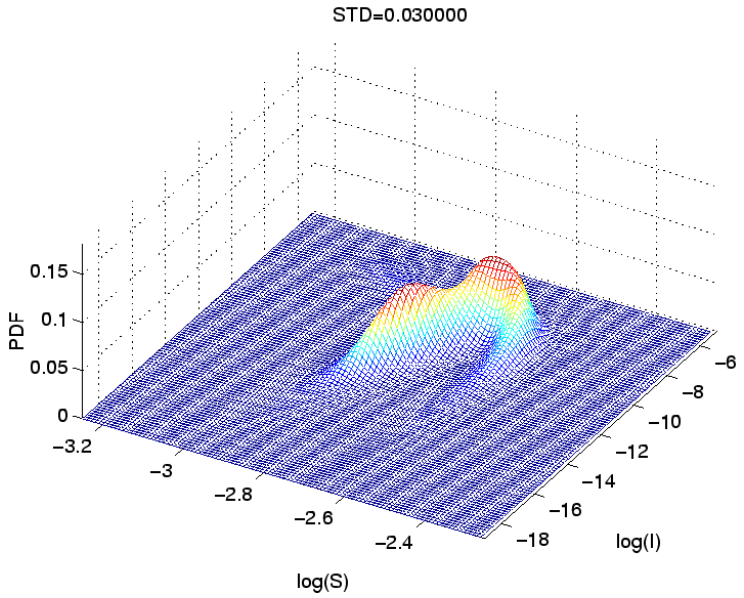


Probability Distribution of Outbreaks

Small Noise in Population



Large Noise in Population



Lora Billings, Erik M. Bollt, and Ira B. Schwartz, Phase space transport of stochastic chaos in population dynamics of virus spread,**PHYS REV LETT 88 (23): art. no. 234101** .

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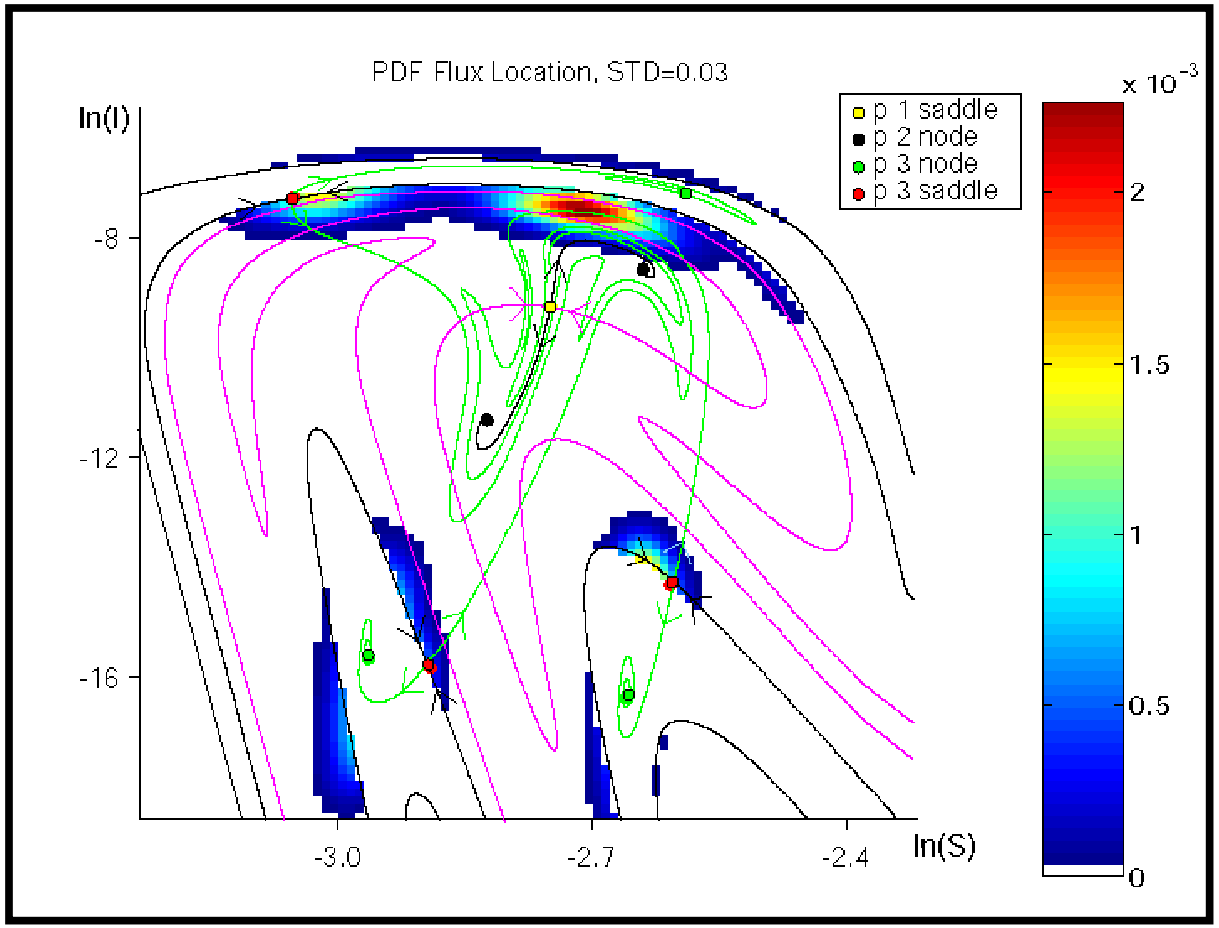
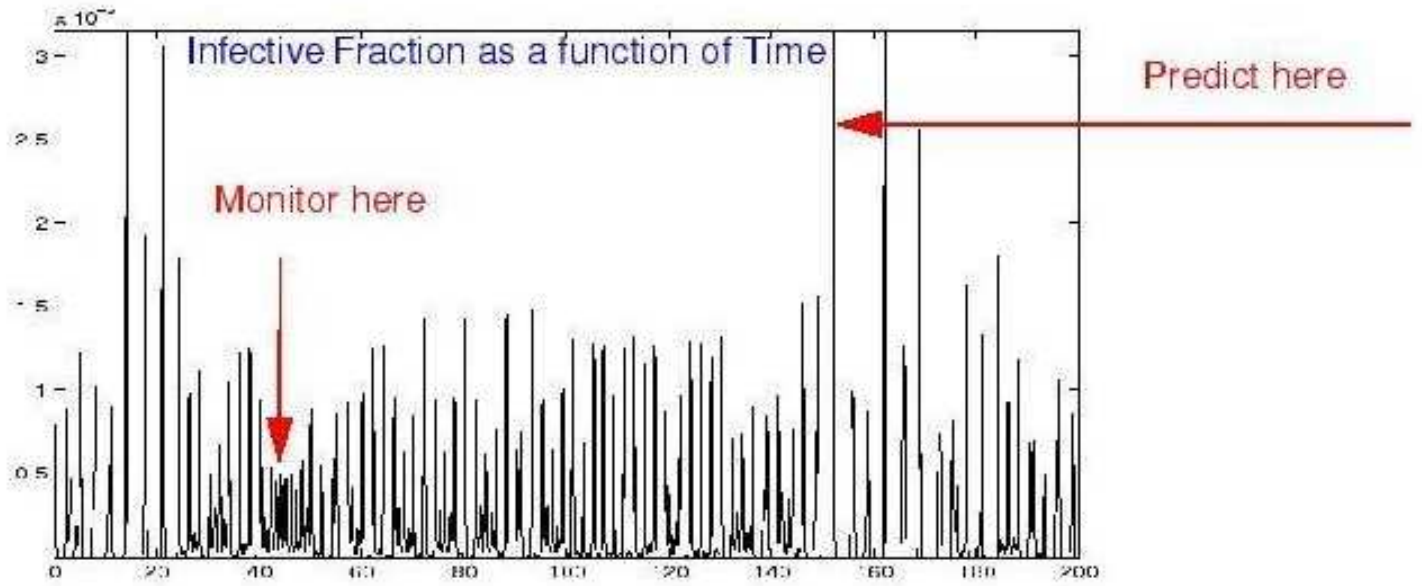
PDF Flux for epidemic model



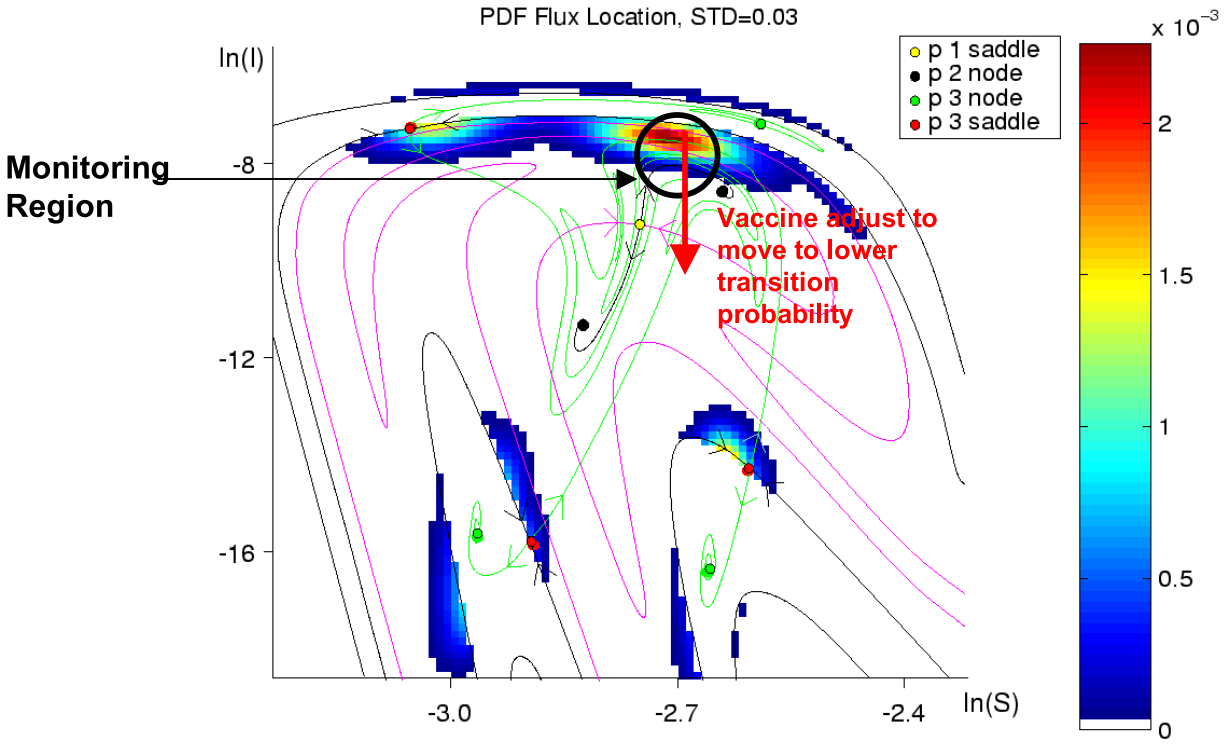
std=0.03

Probability a large outbreak occurs after observing a small outbreak

Stochastic Prediction and Control



Stochastic Prediction and Control of Large Outbreaks



Color Bar: Probability a large outbreak occurs next given small amplitude infectives observed

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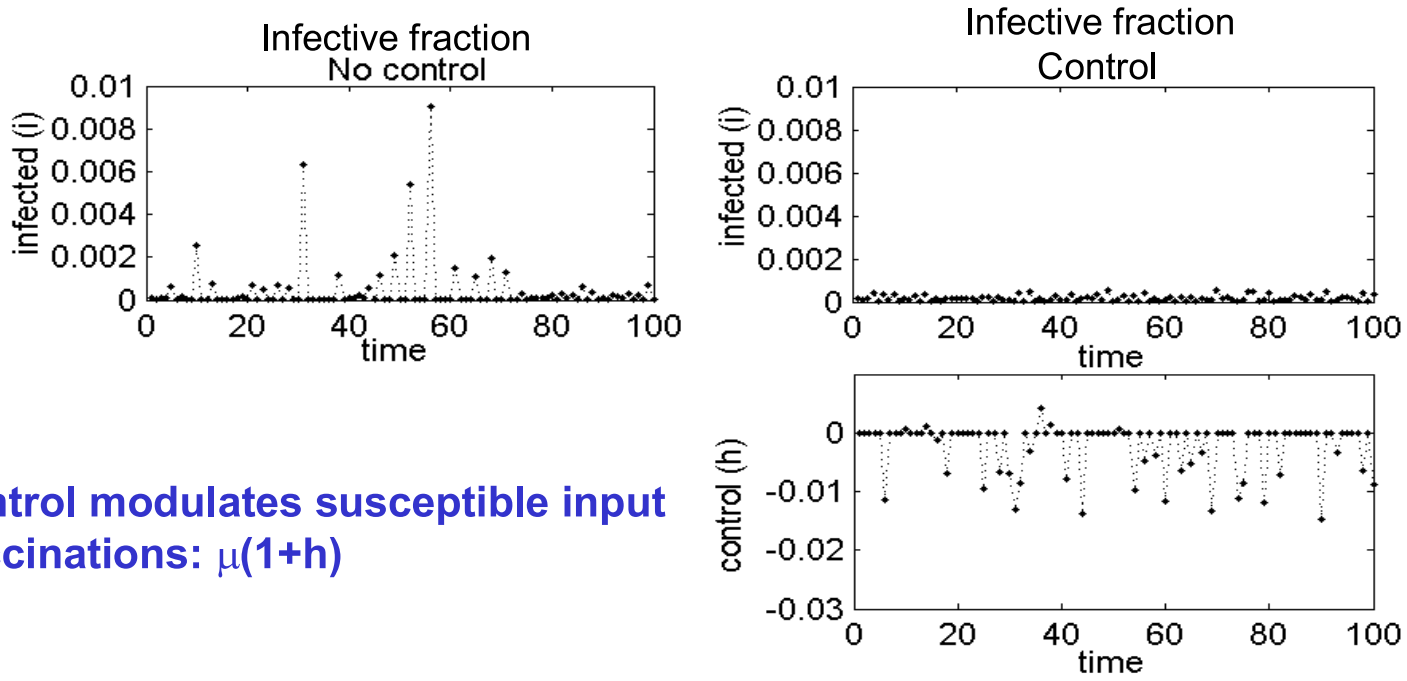
Controlling size of epidemics



Control modulates susceptible input
Vaccinations: $\mu(1+h)$

I. B. Schwartz, L. Billings, and E.M. Bollt, Epidemic outbreak suppression using stochastic prediction and control, Phys. Rev. E., 2005

Multistrain Modeling

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Multistrain Disease

- Multistrain diseases are those with more than one co-circulating strain or serotype
  - Includes influenza, malaria, dengue
- When multiple infections with different strains occur, can have antibody dependent enhancement (ADE)
- ADE hypothesis:
  - Virus forms complexes with pre-existing antibodies and infects more cells
  - Viral load is higher
- ADE has been observed in vitro for HIV, Ebola, coronaviruses, and certain bacteria

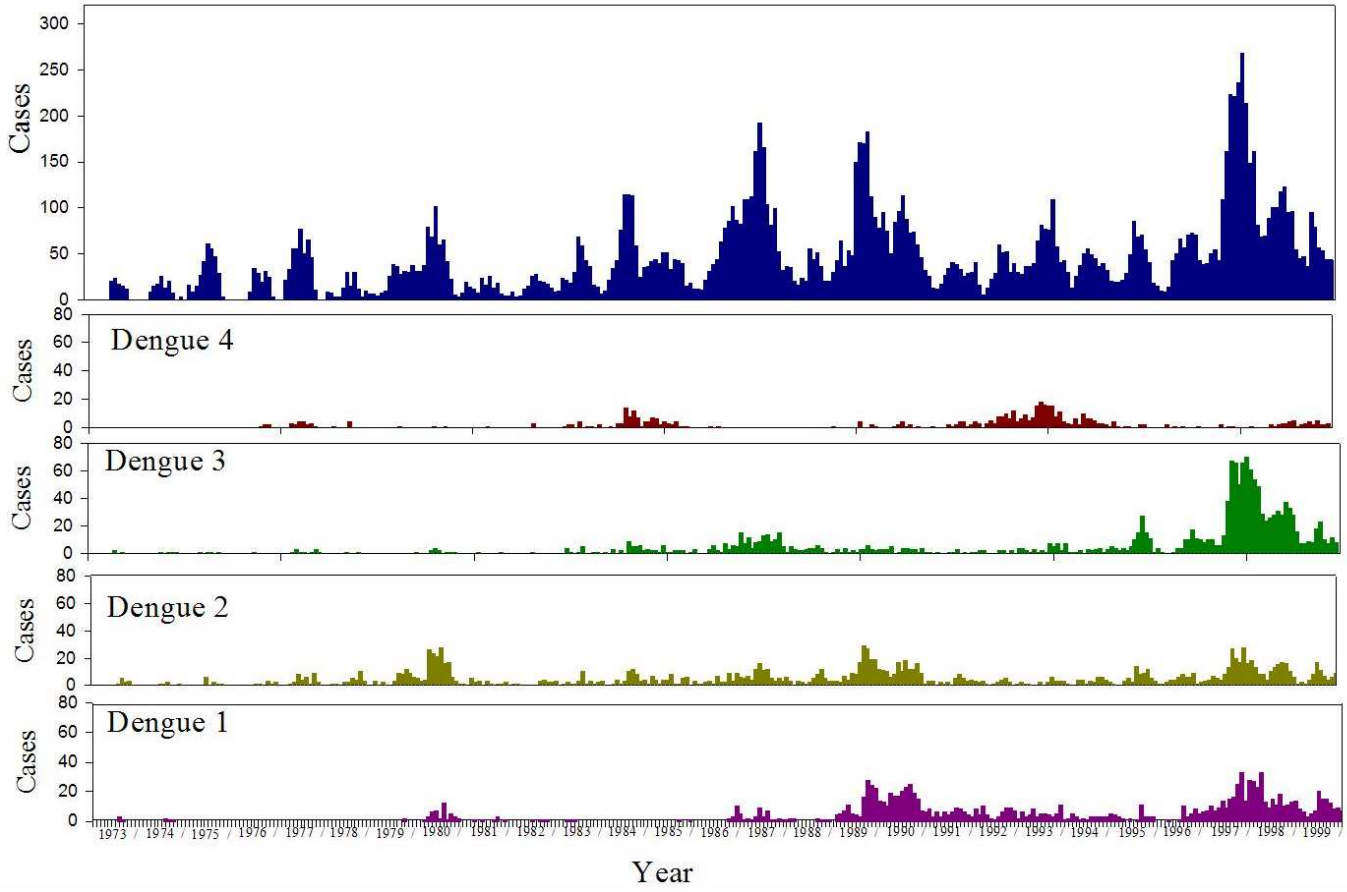
Antibody-dependent enhancement

- Primary infection is often asymptomatic
- Patients with secondary infections (recovered from one strain, later catch a second strain) are at increased risk for DHF and hospitalization
- ADE hypothesis:
  - Virus forms complexes with pre-existing antibodies and infects more cells
  - Viral load is higher
  - Secondary infectives are more contagious
- Goal: Predict asymptomatic individuals

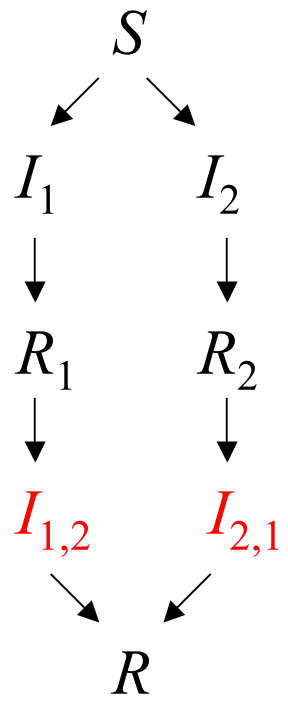
Epidemiological Data (Thailand)

Outbreaks of the 4 serotypes can occur asynchronously

(Nisalak, et.al (2003) Am. J. Trop. Med. Hyg.)



Multistrain model with ADE
2 Serotypes



susceptible to all serotypes

primary infectious

primary recovered

antibody dependent enhancement (ADE)

secondary infectious

recovered

(Schwartz *et al.,* Phys Rev E 72: 066201, 2005)

Multistrain model, n serotypes

$$\frac{dS}{dt} = \mu - \beta(t) S \sum_k \left(I_k + \varphi \sum_{j \neq k} I_{j,k} \right) - \mu S$$

susceptible to all n serotypes

$$\frac{dI_k}{dt} = \beta(t) S \left(I_k + \varphi \sum_{j \neq k} I_{j,k} \right) - \sigma I_k - \mu I_k$$

primary infectious, serotype k

$$\frac{dR_k}{dt} = \sigma I_k - \beta(t) R_k \sum_{j \neq k} \left(I_j + \varphi \sum_{l \neq j} I_{l,j} \right) - \mu R_k$$

primary recovered, serotype k

$$\frac{dI_{j,k}}{dt} = \beta(t) R_j \left(I_k + \varphi \sum_{j \neq k} I_{j,k} \right) - \sigma I_{j,k} - \mu I_{j,k}$$

secondary infectious, infected with serotype j then k ($j \neq k$)

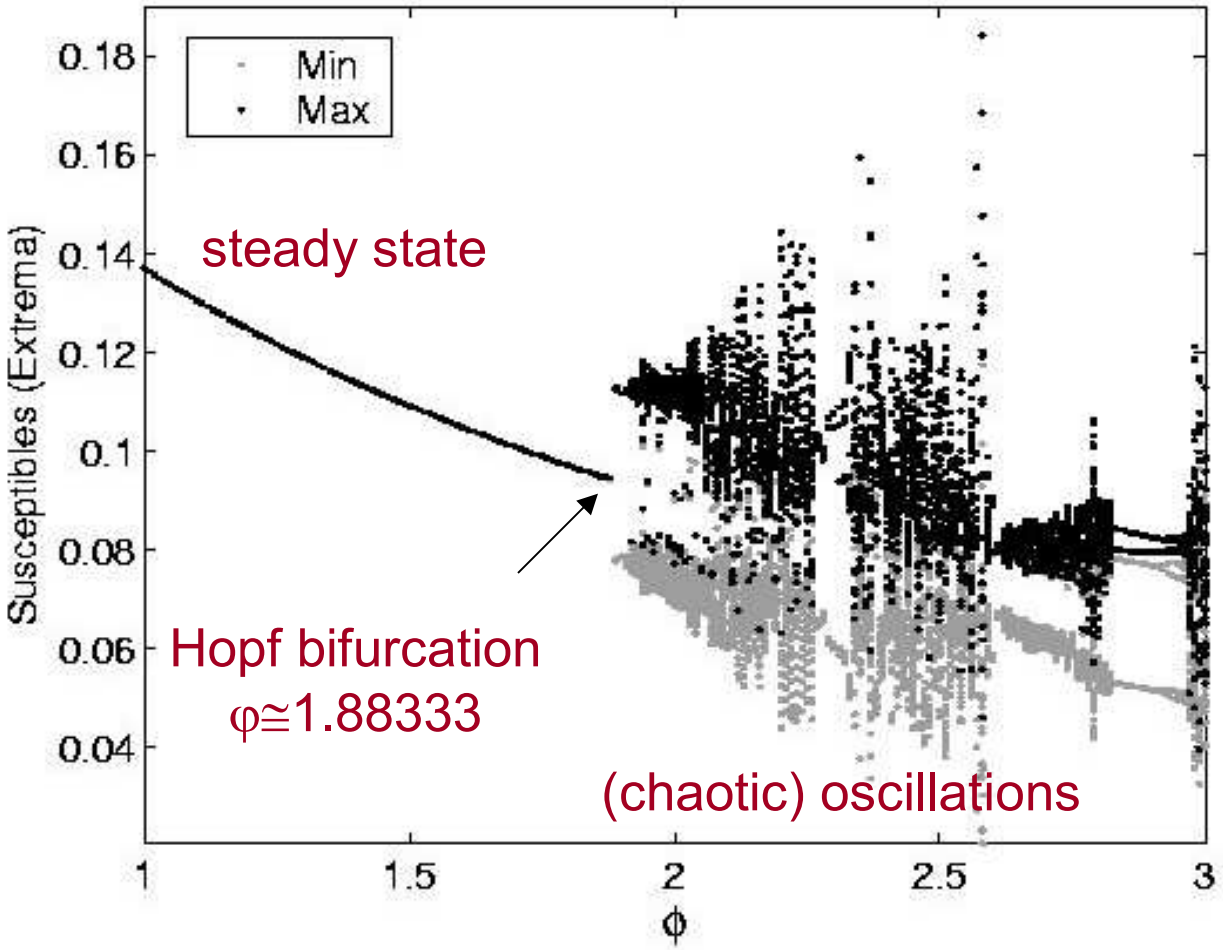
$$\begin{cases} \beta(t) = \beta_0 \\ \beta(t) = \beta_0 (1 + \lambda \cos 2\pi t) \end{cases}$$

constant contact rate

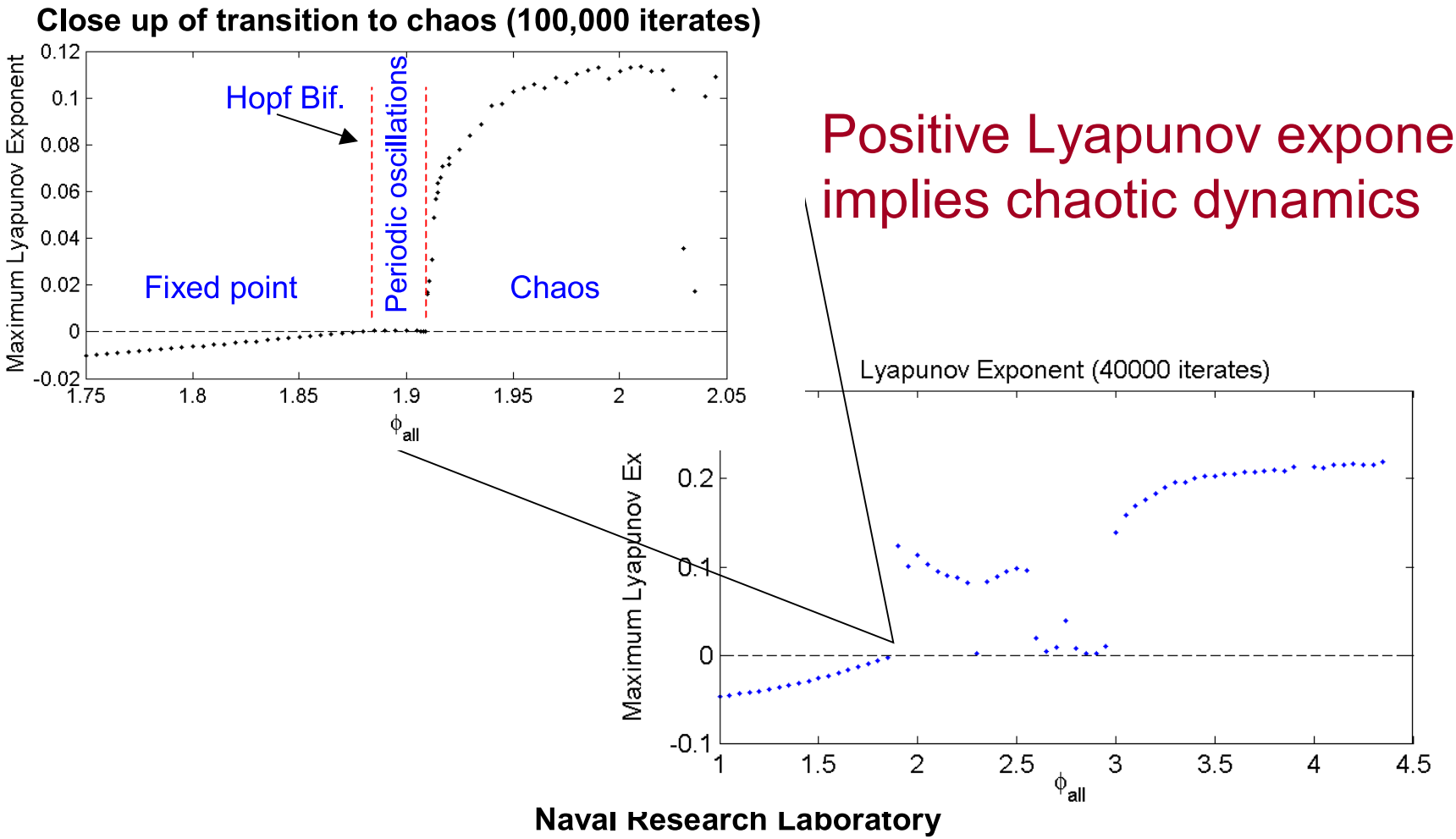
seasonal forcing

ADE factor: $\varphi \geq 1$
Birth rate: μ=0.02 years^{-1}
Recovery rate: σ=100 years^{-1}
Contact rate: β_0=400 years^{-1}
Forcing amplitude: λ=0.05

No seasonal forcing:
Bifurcation diagram-n=4

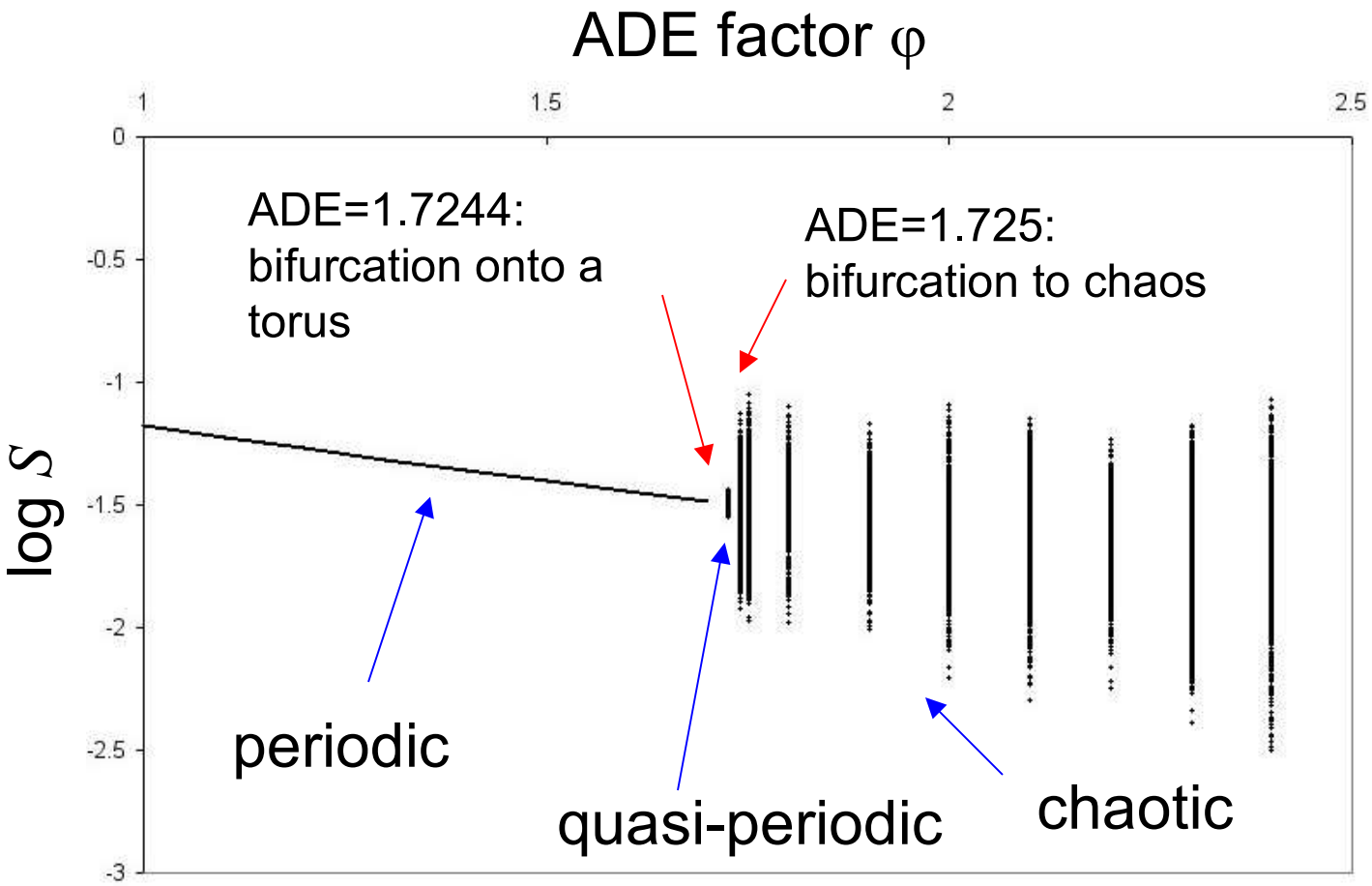


Lyapunov exponents



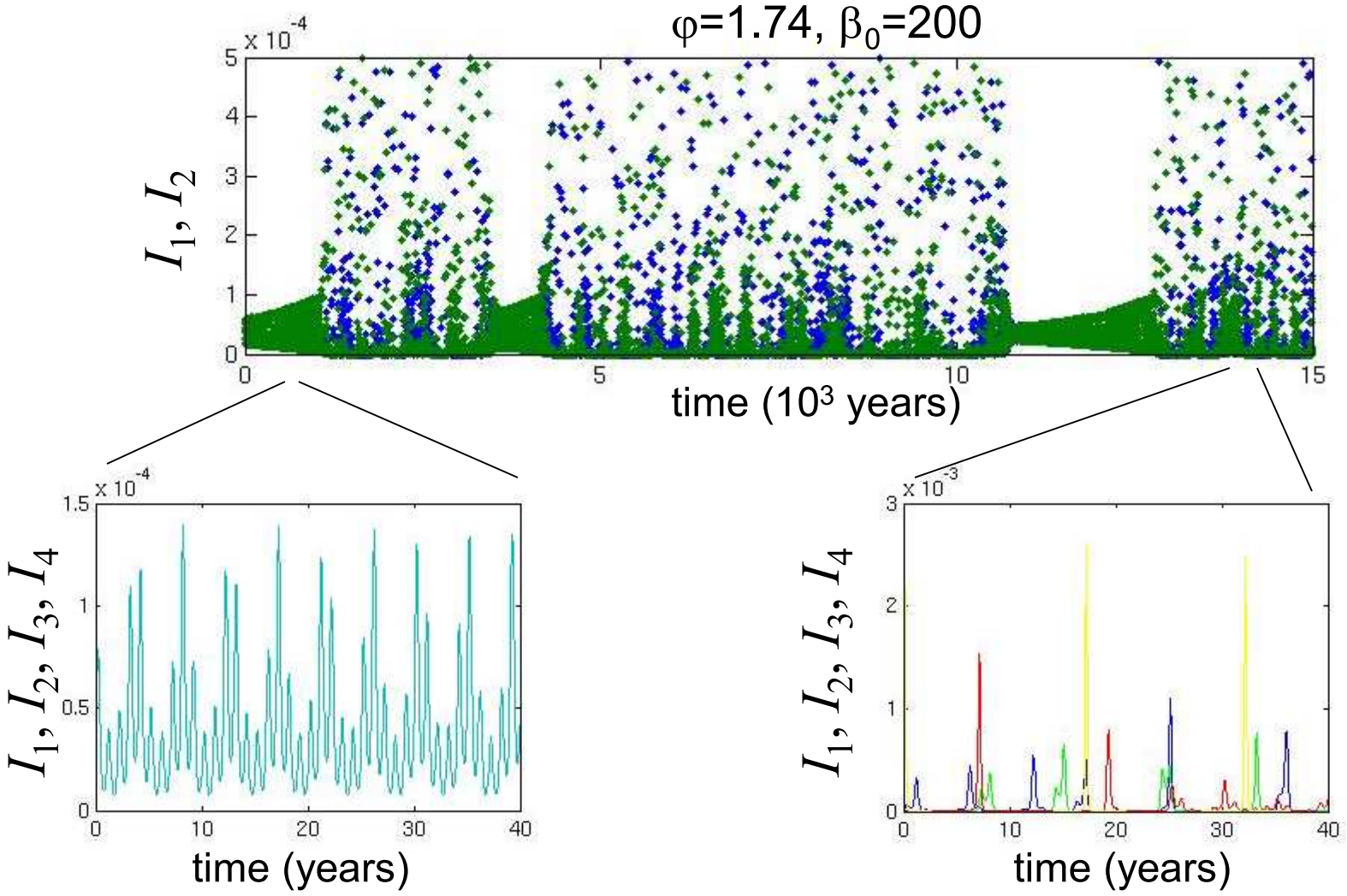
Positive Lyapunov exponent implies chaotic dynamics

Bifurcation Diagram with Seasonality in Contact



sampled once every period of the drive

Larger ADE: Desynchronization



Measuring phase desynchronization

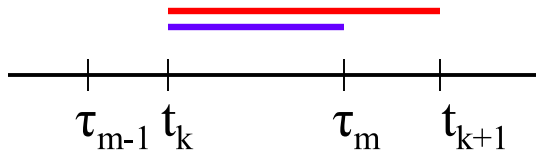
Goal: measure phase differences with respect to a reference infective

Let $Y(t)$ be the reference infective and $Z(t)$ another infective.

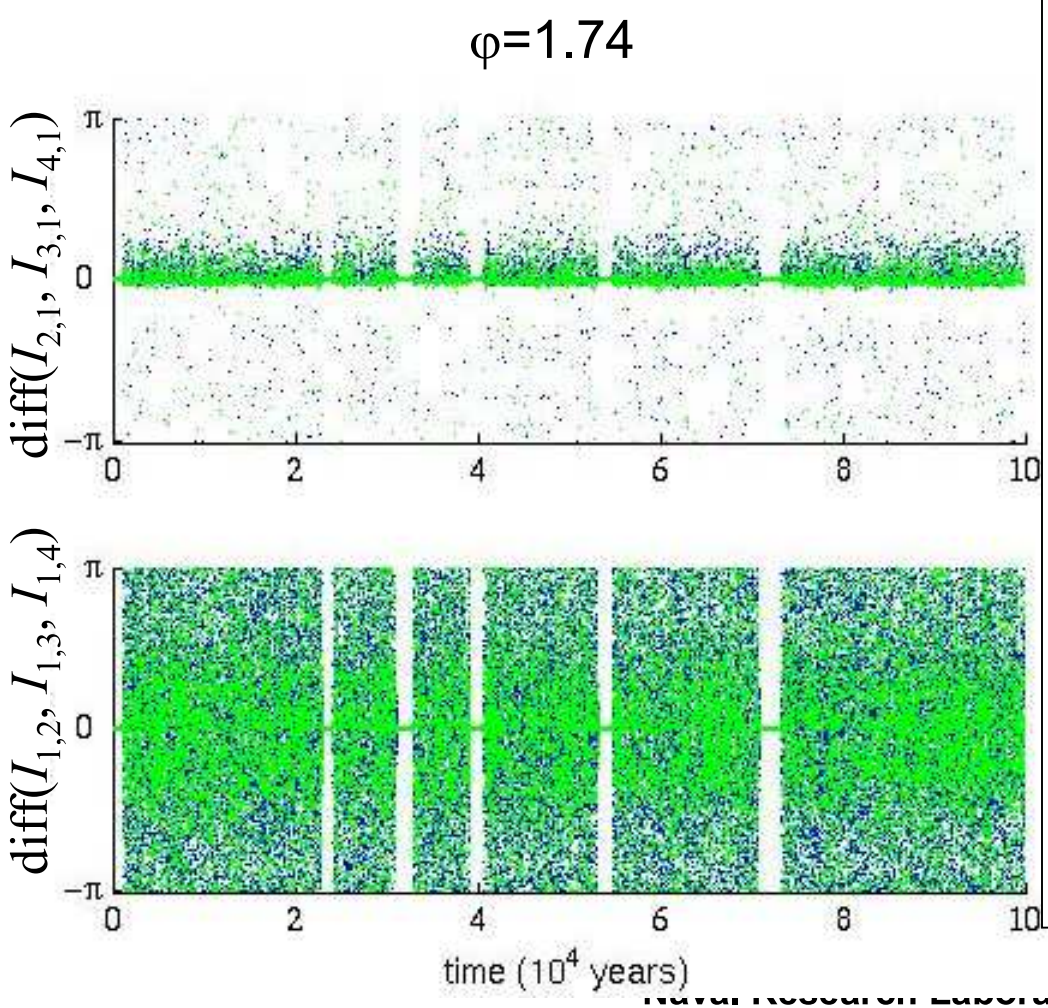
$\{t_k\}$ = the sequence of times for local maxima of $Y(t)$,
$\{\tau_k\}$ = the sequence of times for local maxima of $Z(t)$.

For $\tau_m \in \{t_k, t_{k+1}\}$, the phase of Z relative to Y in the interval is

$$\Psi_{ZY}(\tau_m) = 2\pi \frac{\tau_m - t_k}{t_{k+1} - t_k}$$

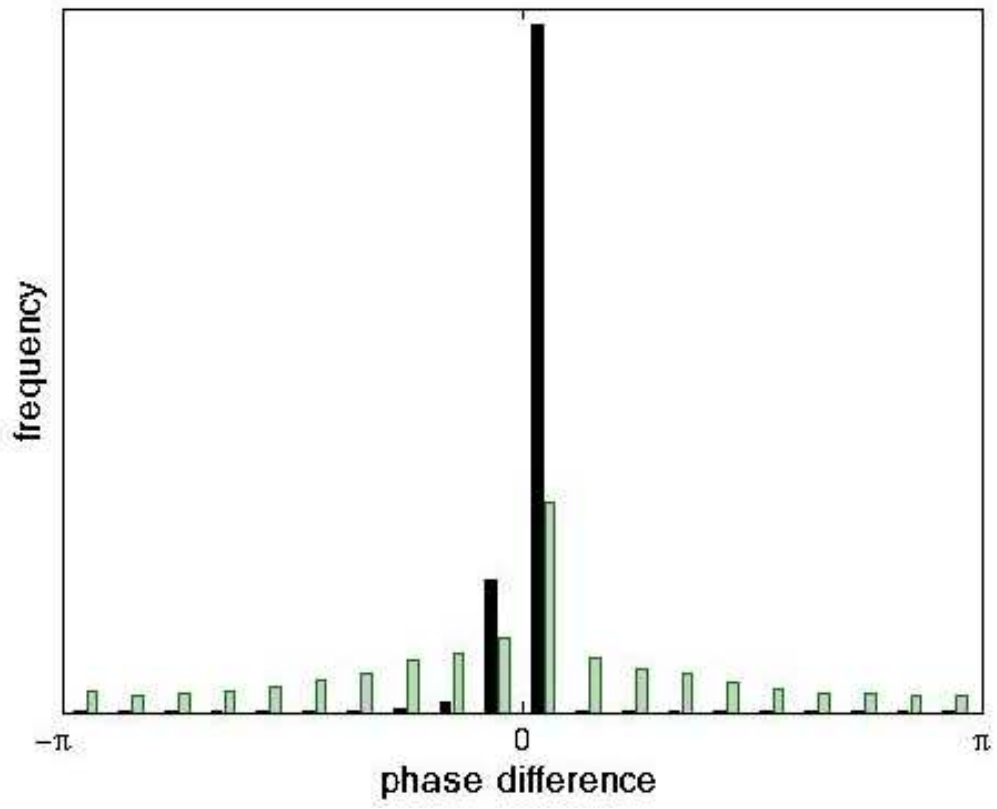


Phase differences



- Measure phase differences with respect to I_1
- Secondary infectives currently infected with strain 1 are in phase
- Other secondary infectives are out of phase

Phase differences (cont.)



primary and secondary infectives with same strain

primary and secondary infectives with different strains

Detecting Asymptomatics using Dimension Reduction
Center manifold analysis

- Consider the system

$$\frac{dx}{dt} = \mathbf{A}x + \varepsilon f(x, y, \varepsilon)$$

$$\frac{dy}{dt} = \mathbf{B}y + \varepsilon g(x, y, \varepsilon)$$

$$\frac{d\varepsilon}{dt} = 0$$

  where
  - the eigenvalues of **A** have zero real parts
  - the eigenvalues of **B** have negative real parts
- Then for ε sufficiently small, there exists an invariant manifold

$$y = h(x, \varepsilon)$$

Center manifold equations

- Shift to new set of variables $\overline{X}$ with unforced steady state at origin
- Combine secondary infectives currently infected with strain *k*

$$Z_k = \sum_{i \neq k} \bar{I}_{i,k}$$

- System rapidly collapses onto lower dimensional surface

$$\sigma[\bar{I}_k - Z_k] = \beta\left[\bar{S} - \sum_{i \neq k} \bar{R}_i\right](\bar{I}_k + \varphi Z_k)$$

$$\sigma[(n-1)\bar{I}_{j,k} - Z_k] = \beta\left[(n-1)\bar{R}_j - \sum_{i \neq k} \bar{R}_k\right](\bar{I}_k + \varphi Z_k)$$

•(Shaw *et al.*, J. Math Bio. In press, nlin.CD/0607022)

Dynamics on center manifold

- From center manifold equations, we can show that

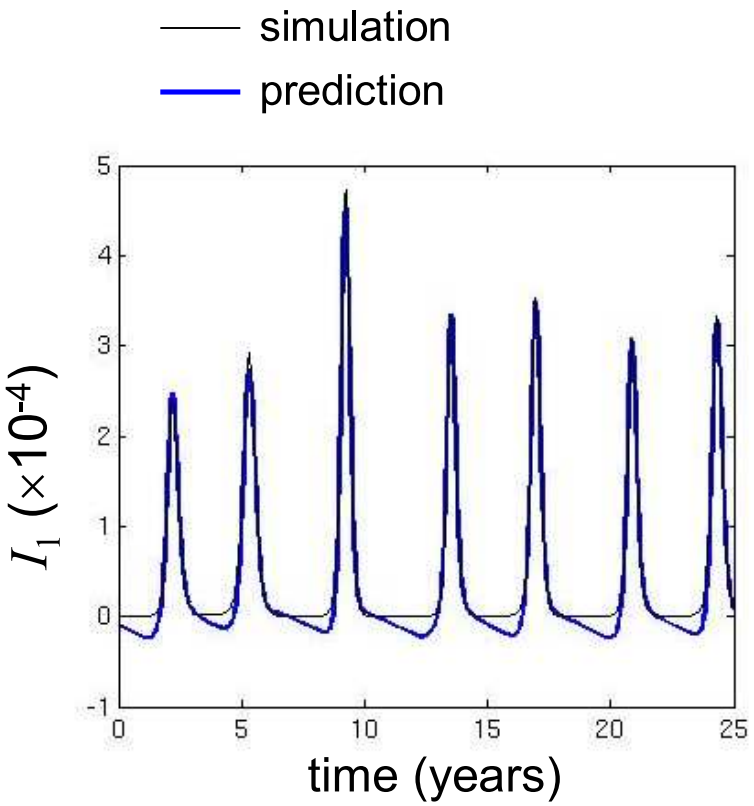
$$I_k(t) \approx (n-1) I_{j,k}(t)$$

(approximately… under certain conditions…)

- Explains why primary and secondary infectives currently infected with strain k are synchronized

Prediction asymptomatics using center manifold equations

- Patients hospitalized for dengue generally have a secondary infection
- Z_k, the sum of secondary infectives that currently have strain k, might be estimated from serology measurements of patients
- If susceptibles, recovereds, and disease parameters are known, primary infectives may be estimated from CM equations



φ=2.0, no seasonal forcing, β=400

Coupled Population Models

Built model to include

Mass coupling - instantaneous mixing between infectives and susceptibles
Migration of infectives and susceptibles

Example of Migration in Population

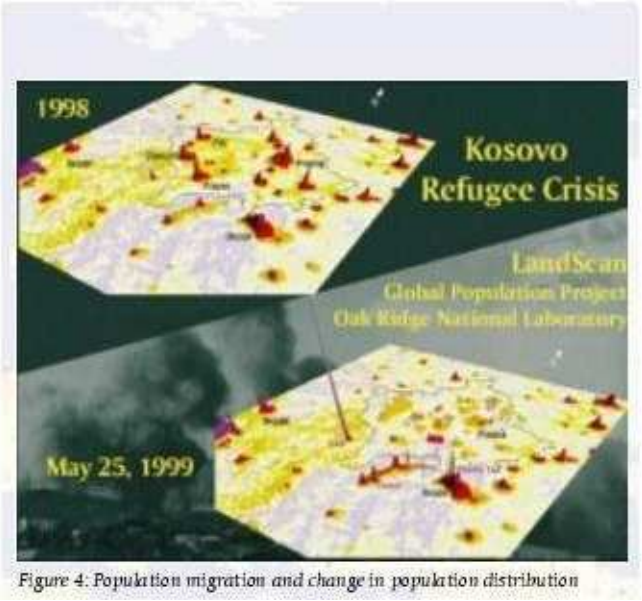
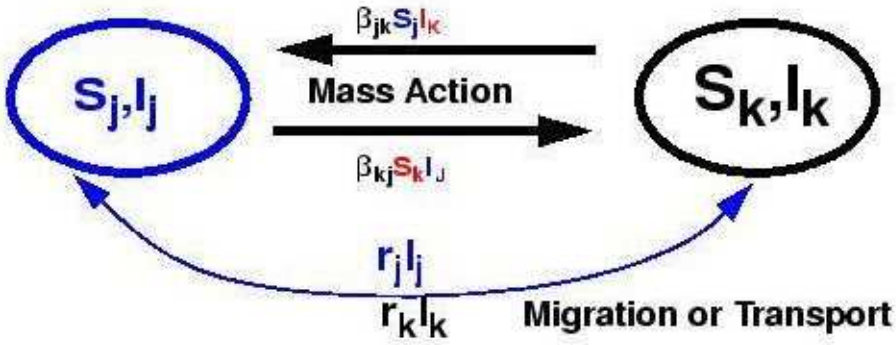


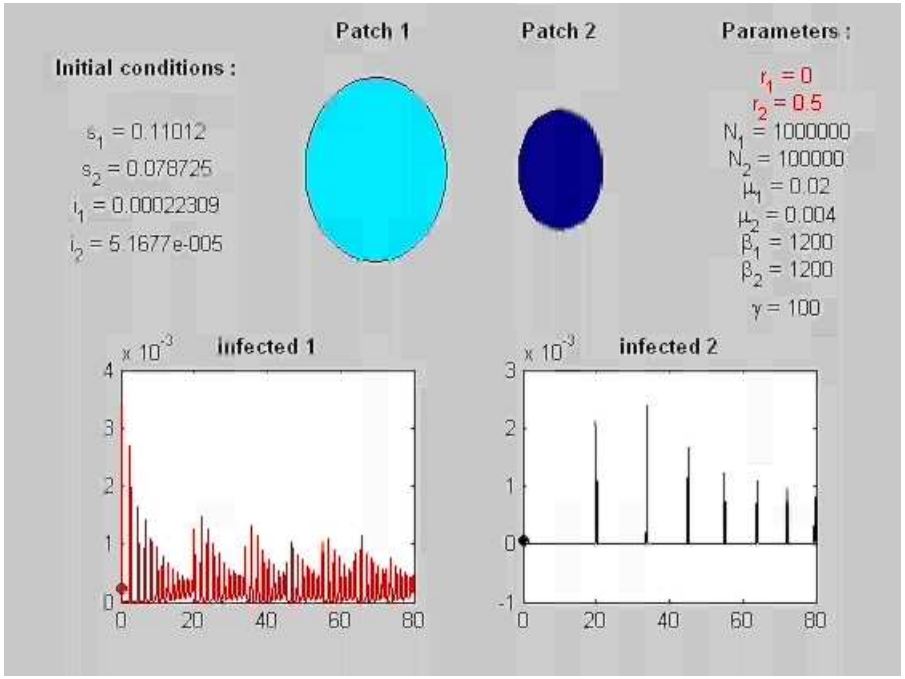
Figure 4: Population migration and change in population distribution

Epidemic Model of Coupled Patches



Coupled Population Models

Indigenous population disease driven by a smaller inserted force of infection

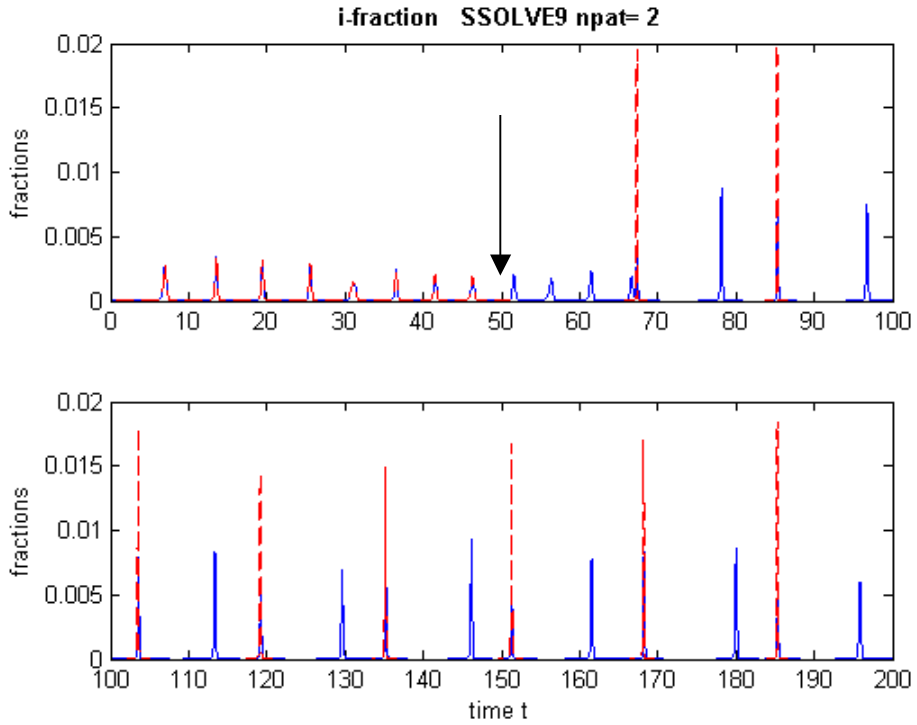


L. Liebovitch and I. B. Schwartz, Migration induced epidemics:Dynamics of flux-based multi-patch models, Phys. Letts. A, 332, 256-267 (2004)

Low Infectivity, Moderate Transmission

R=1, periodic, $r_1 = 0$, $r_2 = 0.3$, initial off: 0.1

off-steady-state-initial-conditions



Red dash: small patch, Blue patch: large patch

Additional epidemics

Preliminary Conclusion

- In low infectivity periodic case epidemics occur when infectives are injected from the small patch
- Due to the large patch being sufficiently disturbed from its steady state values.

- Potential policy implication

  In low infectivity parameter regime, a recurring epidemic is produced by a covert injection from one population into another.

  The presence of a later epidemic may represent a rebound of the system, rather than a second covert event.

Conclusions Noise Driven Basic Model

- Stochastic perturbations can induce new, emergent dynamics in models
- Chaotic-like behavior can be induced in models by additive noise
- The topology reveals the mechanism that facilitates these dynamics
- We can use the topology to our advantage and control the system

Conclusions on Multi-strain Modeling

- A new model a multistrain disease with antibody-dependent enhancement
- At realistic ADE values, outbreaks of the strains occur asynchronously (consistent with data)
- Certain primary and secondary infectives remained synchronized even in the chaotic regime
- Prediction of asymptomatic primary infectives may lead to more effective monitoring of outbreaks

Recent References

http://pages.csam.montclair.edu/~billings/

http://pages.physics.cornell.edu/~lshaw/

- Schwartz *et al.*, Phys Rev E 72: 066201, 2005. "Chaotic desynchronization of multi-strain diseases"
- Cummings *et al.*, PNAS 102: 15259, 2005. "Dynamic effects of antibody dependent enhancement on the fitness of viruses"
- Shaw *et al*., J. Math. Bio, in press. "Using dimension reduction to improve outbreak predictability of multistrain diseases" nlin.CD/0607022
- Billings *et al*., J. Theor. Bio., in press "Instabilities in multi-serotype disease models with antibody-dependent enhancement"