Centro de Física da Matéria Condensada
Universidade de Lisboa

Faculdade de Ciências
Universidade de Lisboa

MANCHESTER
1824
The University of Manchester
School of Physics and Astronomy
Theoretical Physics Group

Stochastic models of infection dynamics

Ganna Rozhnova, Ana Nunes & Alan McKane

Kavli Institute for Theoretical Physics
Microbial and Viral Evolution
March 22, 2011

Childhood infectious diseases

- *Examples: measles, whooping cough (pertussis), rubella, chicken pox, etc.*
- *Pathogen: virus (measles, rubella, chicken pox) or bacteria (pertussis)*
- *The diseases are spread easily among children through coughing, sneezing or spitting*
- *The diseases are highly contagious (high* R_0 *)*
- *Latent and infectious periods: 1 week-2 months*
- *Confer permanent (measles) or long lasting immunity (pertussis)*

Outline

Motivation

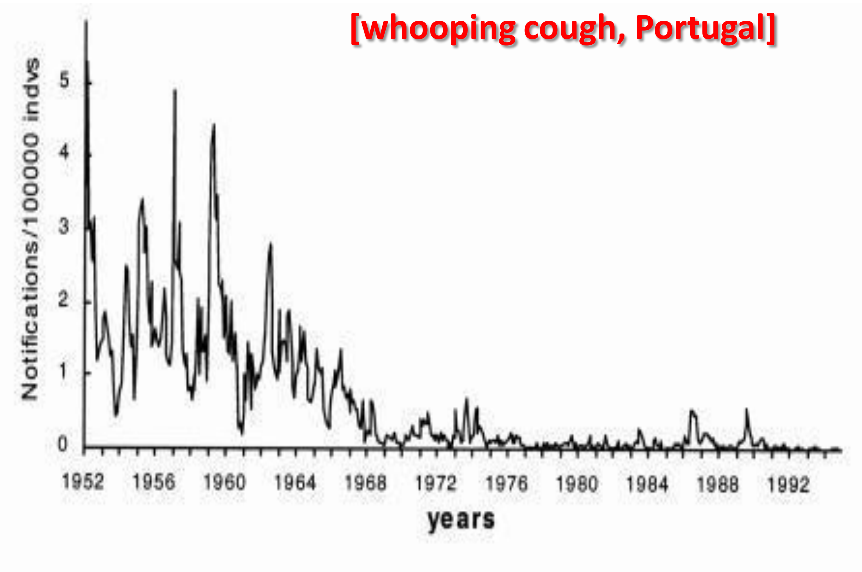
- *What is the origin of recurrent epidemics of childhood infections?*

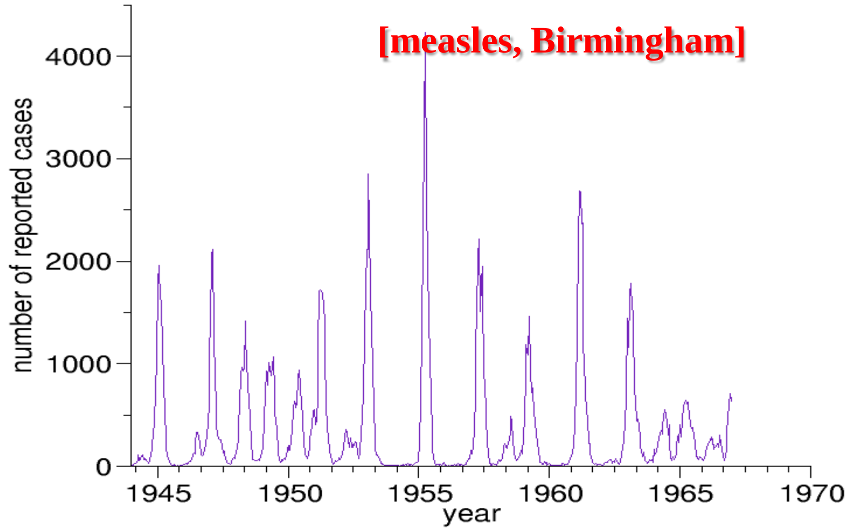
Our results/Contribution

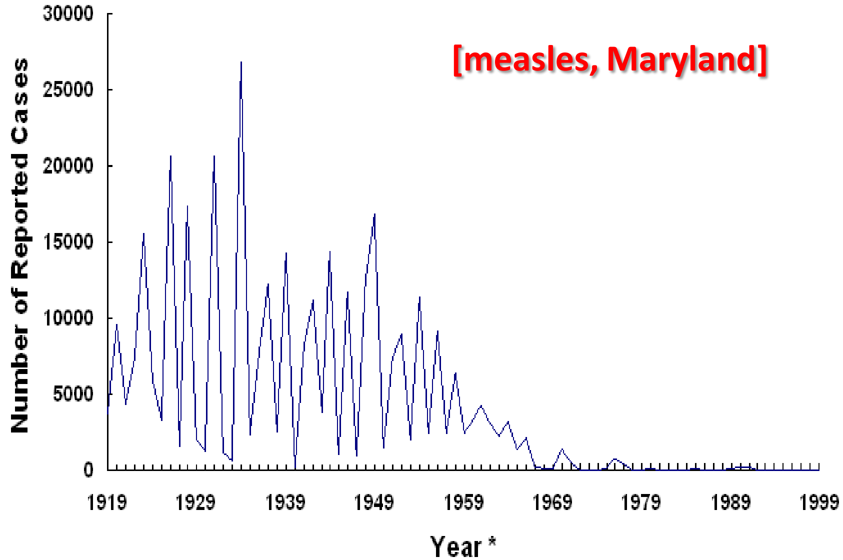
- *Development of the methods capable to explain the diversity of temporal patterns*
- *Description of stochastic and spatial correlation effects for well mixed and network structured populations*
- *Study of the interplay of seasonality, the system's nonlinearities and intrinsic stochasticity*
- *Application to the pertussis and measles dynamics in the prevaccine era*

Conclusions

Historical data



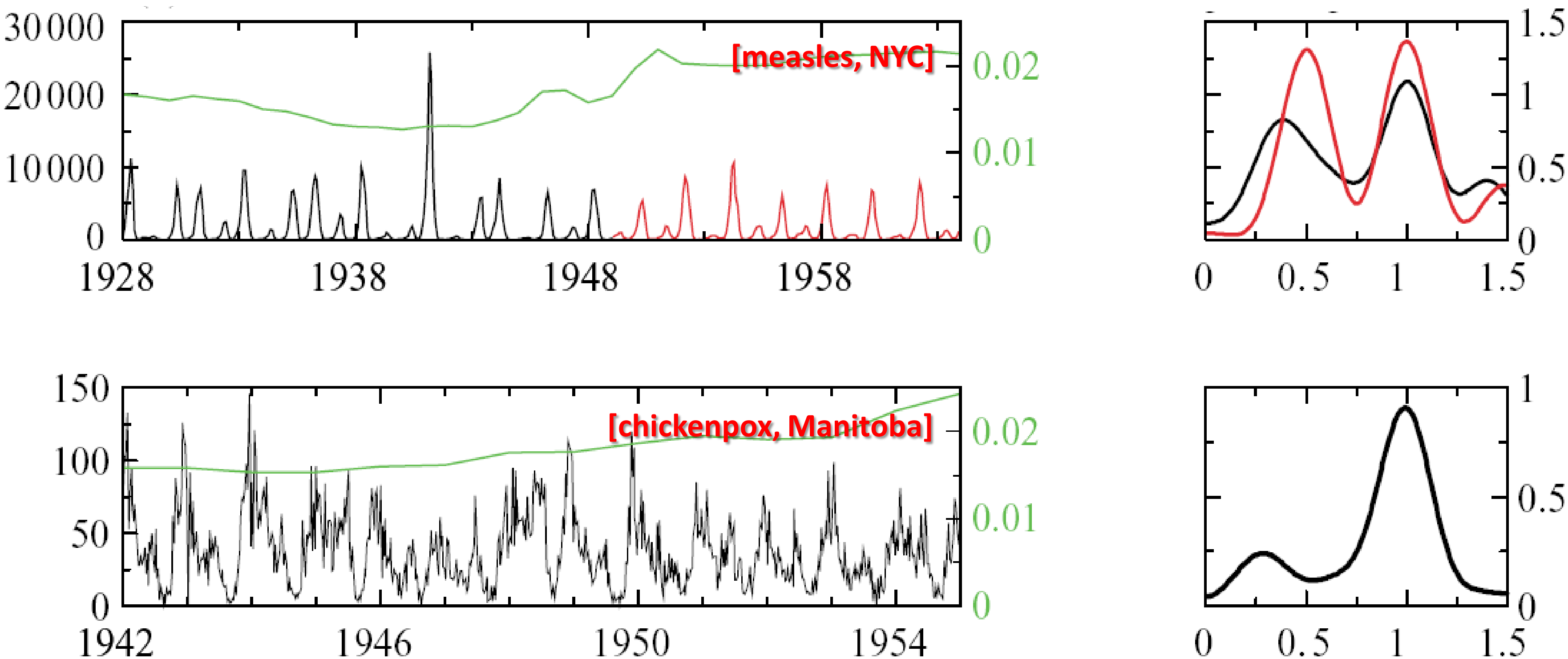




- ❑ *recurrent epidemics/noisy oscillations*
- ❑ *disease dependent patterns*
- ❑ *location dependent patterns*
- ❑ *extinctions of disease*
- ❑ *power spectra with one or two peaks (seasonal + ?)*

Time series analysis

Time series *Power spectra*

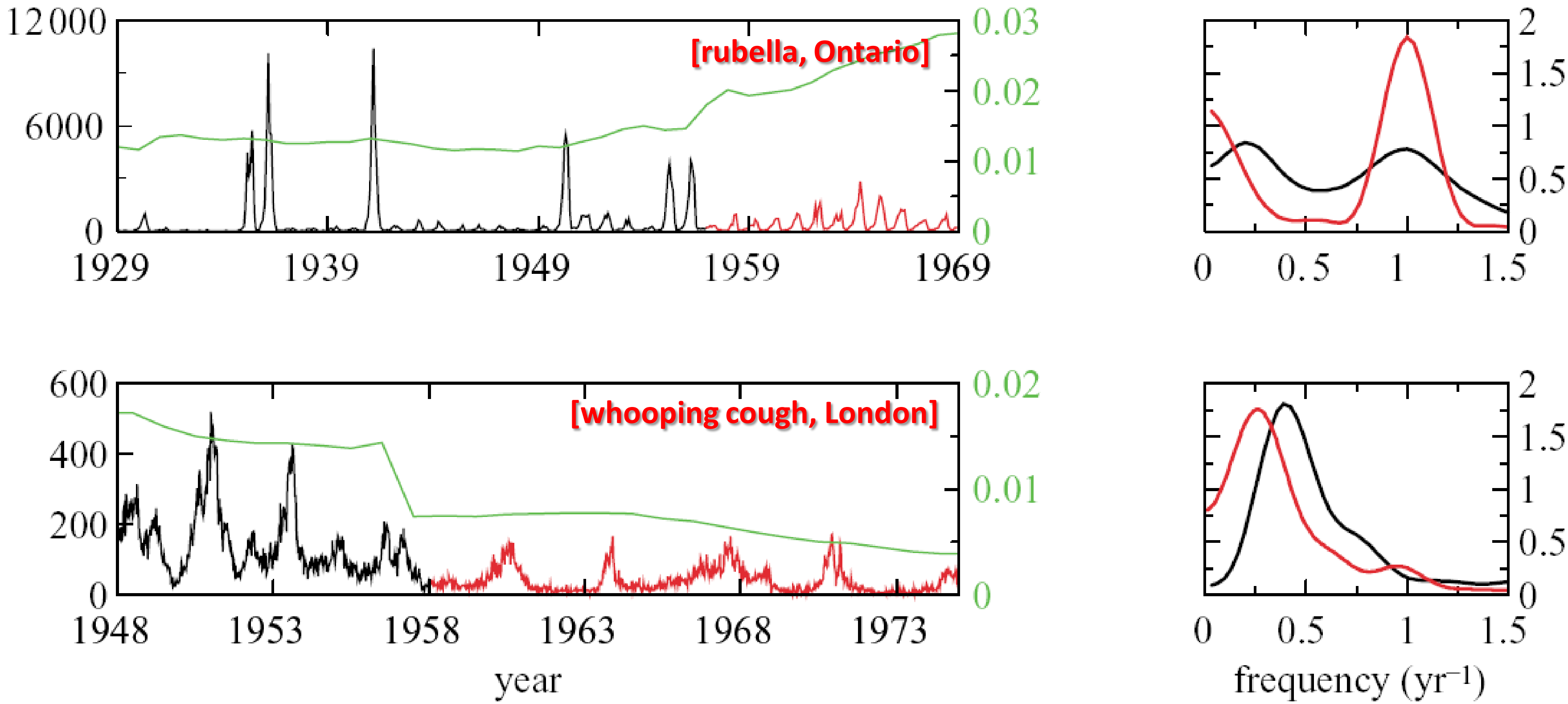


- ❑ *power spectra with one or two peaks (seasonal + ?)*
- ❑ *different power spectra for diseases with similar parameters*

C. T. Bauch & D. J. D. Earn, Proc. R. Soc. Lond. B 270, 1573-1578 (2003)

Time series analysis

Time series *Power spectra*



- *power spectra with one or two peaks (seasonal + ?)*
- *different power spectra for diseases with similar parameters*

C. T. Bauch & D. J. D. Earn, Proc. R. Soc. Lond. B 270, 1573-1578 (2003)

Basic deterministic SIRS model

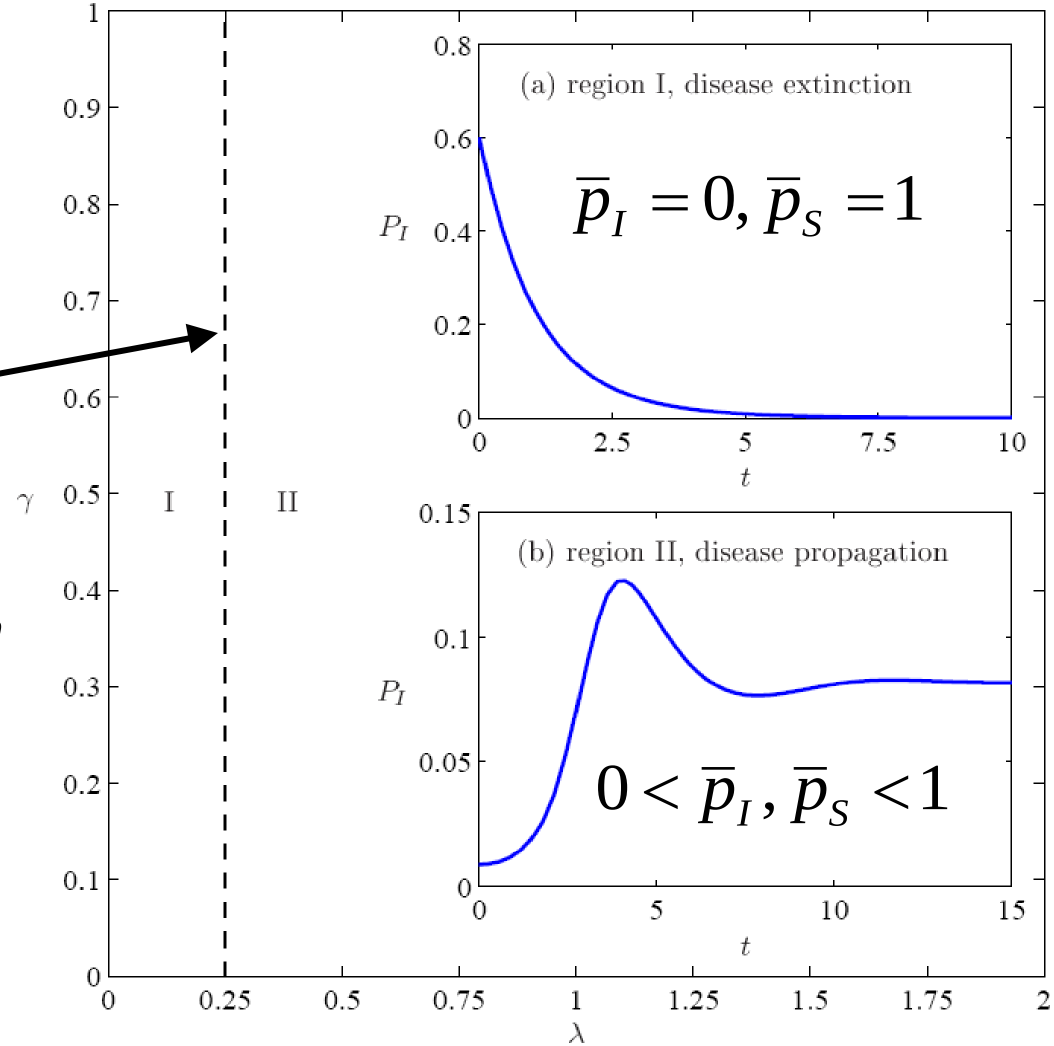
- *Population of constant size N, compartments – susceptible (S), infectious (I) and recovered (R)*
- *Parameters:* λ *(infection rate),* δ *(recovery rate) and* γ *(immunity waning rate)*
- *Differential equations for the susceptible and infected densities:*

$$\frac{dp_S}{dt} = \gamma(1 - p_S - p_I) - \lambda p_S p_I,$$

$$\frac{dp_I}{dt} = \lambda p_S p_I - \delta p_I.$$

- *Two possible steady states: disease-free and endemic*
- *Overdamped or underdamped oscillations in the endemic phase*

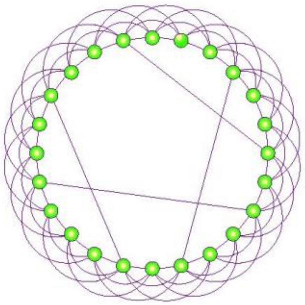
Phase diagram of the deterministic SIRS model



epidemic/endemic threshold

Damped oscillations in the endemic phase for small values of immunity waning rate

Basic deterministic models missing ingredients



- *contact network structure*
- *partial immunity and reinfection*
- *incubation period*
- *environmental and seasonal forcing*

More advanced popular models – seasonally forced systems

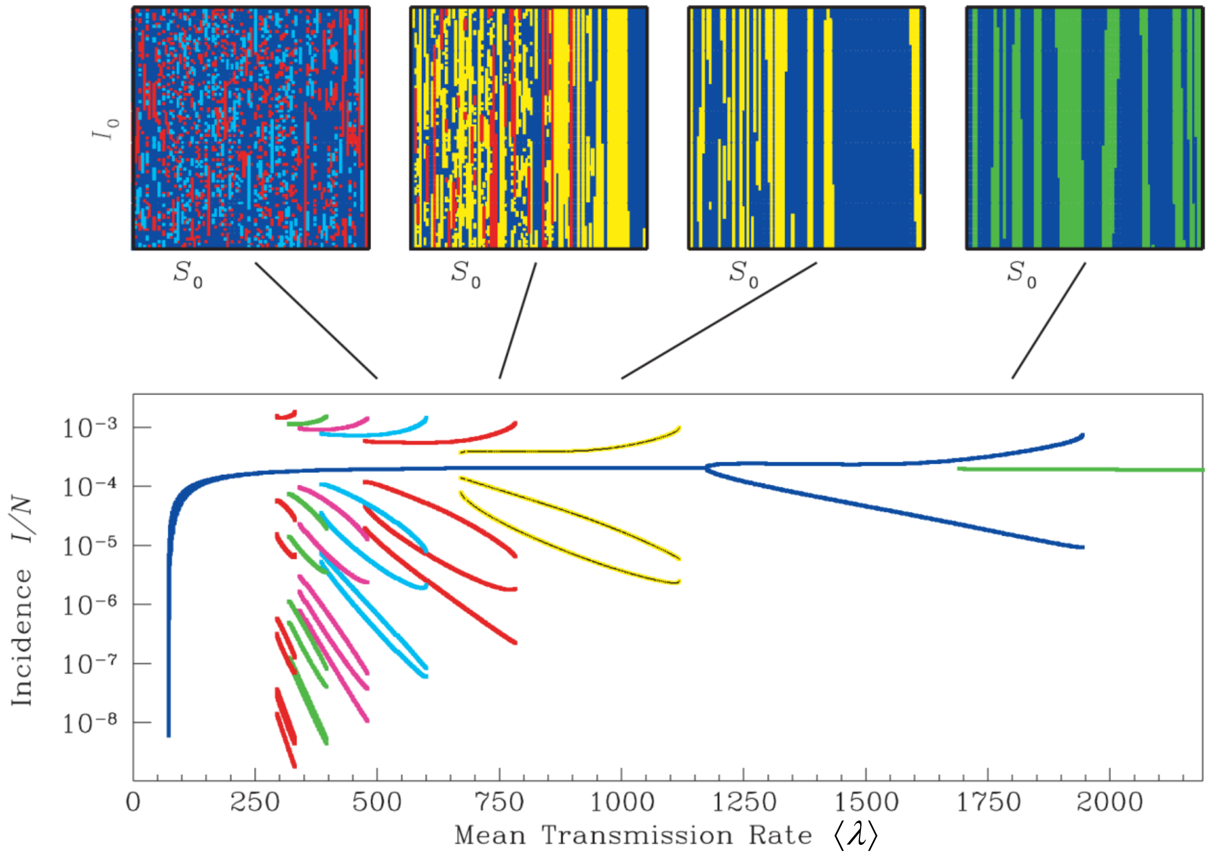
- *Seasonally forced deterministic SIRS model*

$$\frac{dp_S}{dt} = \gamma(1 - p_S - p_I) - \lambda(t)\, p_S\, p_I,$$

$$\frac{dp_I}{dt} = \lambda(t)\, p_S\, p_I - \delta\, p_I.$$

$$\lambda(t) = \langle \lambda \rangle (1 + \varepsilon \cos 2\pi t)$$

Seasonally forced deterministic SEIR model



- ❑ *stable attractors are stable limit cycles*
- ❑ *rich bifurcation diagrams*
- ❑ *highly intertwined basins of attraction*

D. J. D. Earn, P. Rohani, B. M. Bolker & B. T. Grenfell, Science 287, 667-670 (2000)

Seasonality versus stochasticity debate

- *Seasonally forced nonlinear models explain the data for some diseases (for example, measles)*

- *Stochasticity has a secondary role (extinctions, switching between different attractors and sustaining small amplitude fluctuations around a deterministic system's equilibrium)*

- *Many data records cannot be understood in a deterministic framework, fluctuations can be dominant (in particular, for whooping cough)*

Resonant amplification of stochastic fluctuations (non-spatial stochastic predator-prey model)

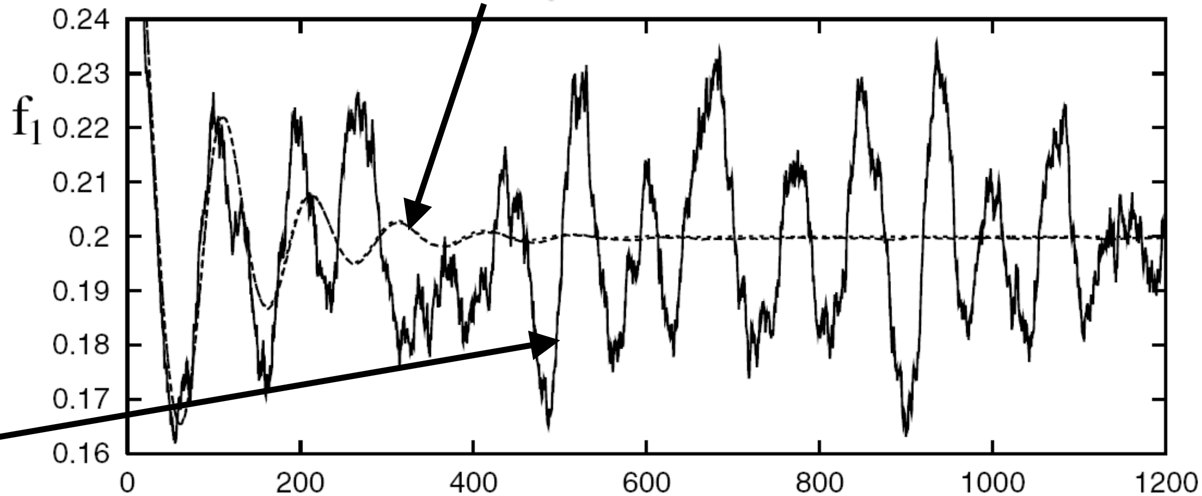
- *Ecological and epidemiological data show **noisy oscillations***
- *Individual realizations of stochastic simulations show **large persistent cycles***
- *Mean field equations and average densities exhibit **damped oscillations***

Damped oscillations

analytical (dashed line)

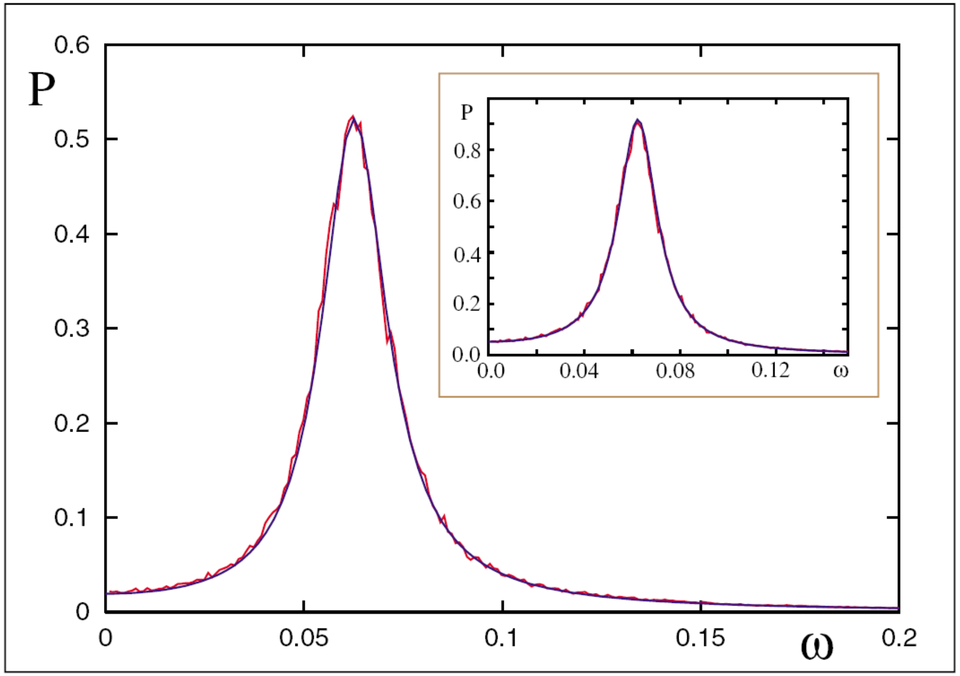
simulations (solid line)

Fluctuations



A. J. McKane & T. J. Newman, Phys. Rev. Lett. 94, 218102 (2005)

Resonant amplification of stochastic fluctuations (non-spatial stochastic predator-prey model)



analytical (solid lines)

simulations (noisy lines)

$$P(\omega) = \frac{\alpha + \beta\omega^2}{(\omega^2 - \Omega_0^2)^2 + \Gamma^2\omega^2}$$

- *Sustained oscillatory patterns arise through resonant amplification of internal noise*
- *Power spectrum can be computed from the van Kampen expansion of the master equation around a coexistence equilibrium of the deterministic equations*

N. G. van Kampen, Stochastic Processes in Physics and Chemistry (Elsevier, Amsterdam, 1981)

Resonant amplification of stochastic fluctuations (the general theory)

$$\frac{dP(\boldsymbol{\sigma};t)}{dt} = \sum_{\boldsymbol{\sigma}'\neq\boldsymbol{\sigma}} T(\boldsymbol{\sigma}\,|\,\boldsymbol{\sigma}')P(\boldsymbol{\sigma}';t) - \sum_{\boldsymbol{\sigma}'\neq\boldsymbol{\sigma}} T(\boldsymbol{\sigma}'\,|\,\boldsymbol{\sigma})P(\boldsymbol{\sigma};t)$$ *master equation*

- ❑ *1st order in N → deterministic equations*
- ❑ *2nd order in N → fluctuation equations*

$$\frac{\partial \Pi}{\partial t} = -\sum_{i,j} A_{ij} \frac{\partial (x_j \Pi)}{\partial x_i} + \frac{1}{2}\sum_{i,j} B_{ij} \frac{\partial^2 \Pi}{\partial x_i \partial x_j}$$ *multivariate linear Fokker-Planck/Langevin*

⇓

$$\frac{dx_i}{dt} = \sum_j A_{ij} x_j + \eta_i$$

$$\langle \eta_i(t)\eta_j(t') \rangle = B_{ij}\,\delta(t-t')$$

$$\Rightarrow \quad P_I(\omega) = \langle |\,\tilde{x}_2\,|^2 \rangle$$

Stochastic mean field approximation SIRS system modeled as a network of fixed coordination number k

- *Infection* $S \xrightarrow{k\lambda S I/N} I$
- *Recovery* $I \xrightarrow{\delta I} R$
- *Immunity waning* $R \xrightarrow{\gamma R} S$

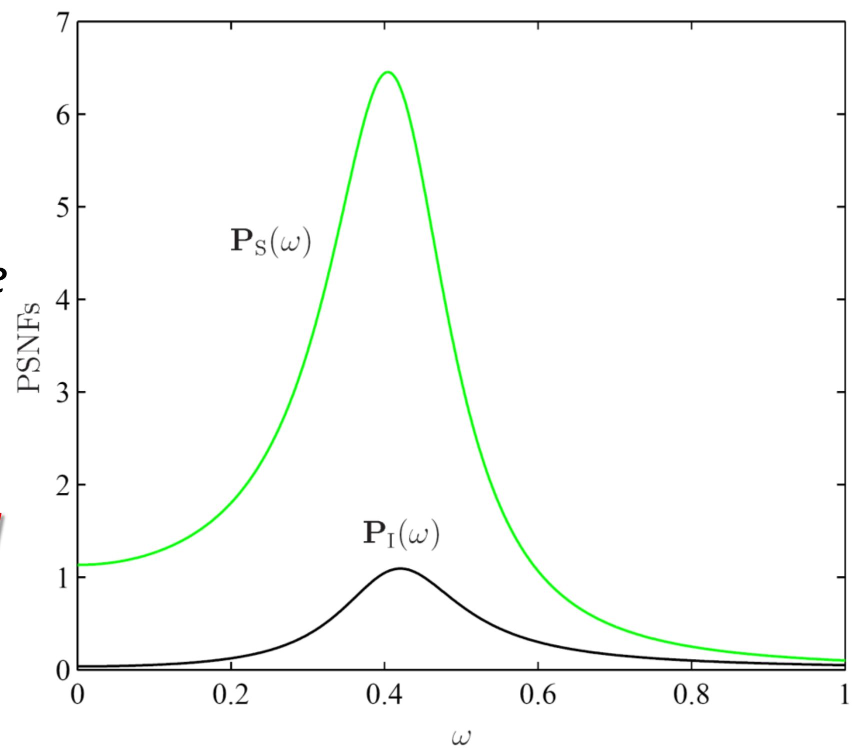
Two independent variables:

$$S, I$$

$$S + I + R = N$$

$$P(\omega) = \frac{\alpha + \beta\omega^2}{(\omega^2 - \Omega_0^2)^2 + \Gamma^2\omega^2}$$

The fluctuations power spectrum around the deterministic equilibrium is 'resonant like'



We now want to study the behavior of resonant fluctuations in network structured populations (stochasticity + spatial correlations)

Stochastic pair approximation SIRS system modeled as a network of fixed coordination number k

- *Infection* $SI \xrightarrow{\lambda SI} II$
- *Recovery* $I \xrightarrow{\delta I} R$
- *Immunity waning* $R \xrightarrow{\gamma R} S$

Five independent variables: S, I, SI, SR, RI

$S + I + R = N$ *individuals*

$SI + SR + RI + SS + II + RR = \frac{Nk}{2}$ *contacts*

$$P_i(\omega) \equiv \left\langle \left| \widetilde{x}_i(\omega) \right|^2 \right\rangle = \sum_{j,k} M_{ik}^{-1}(\omega) B_{kj} M_{ji}^{-1}(-\omega),$$

$$M_{ik}(\omega) = i\omega\delta_{ik} - A_{ik}, \quad \left\langle \widetilde{L}_i(\omega) \widetilde{L}_j(\omega') \right\rangle = B_{ij}\delta(\omega + \omega')$$

G. Rozhnova & A. Nunes, Phys. Rev. E 79, 041922 (2009)

Phase diagram of the PA and MFA deterministic models (d=2)

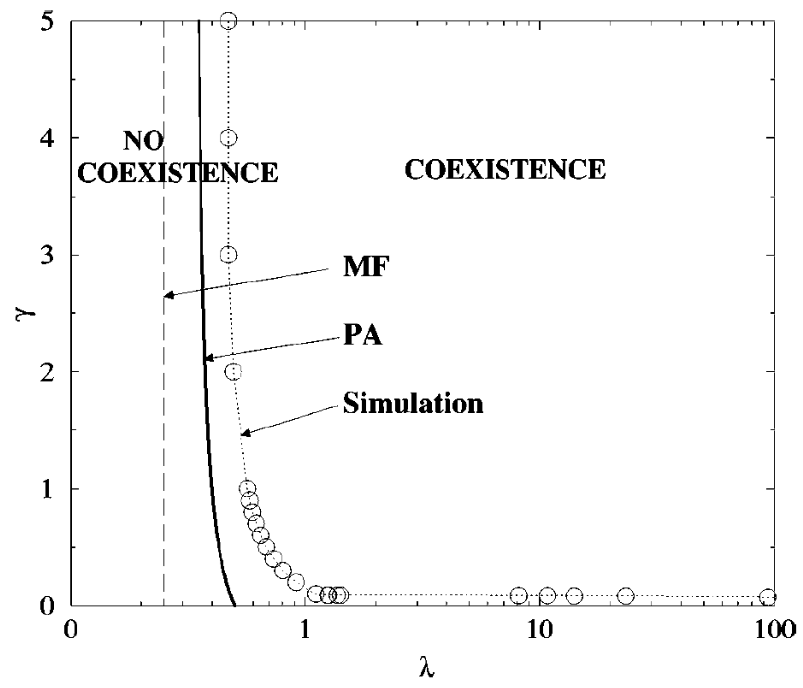
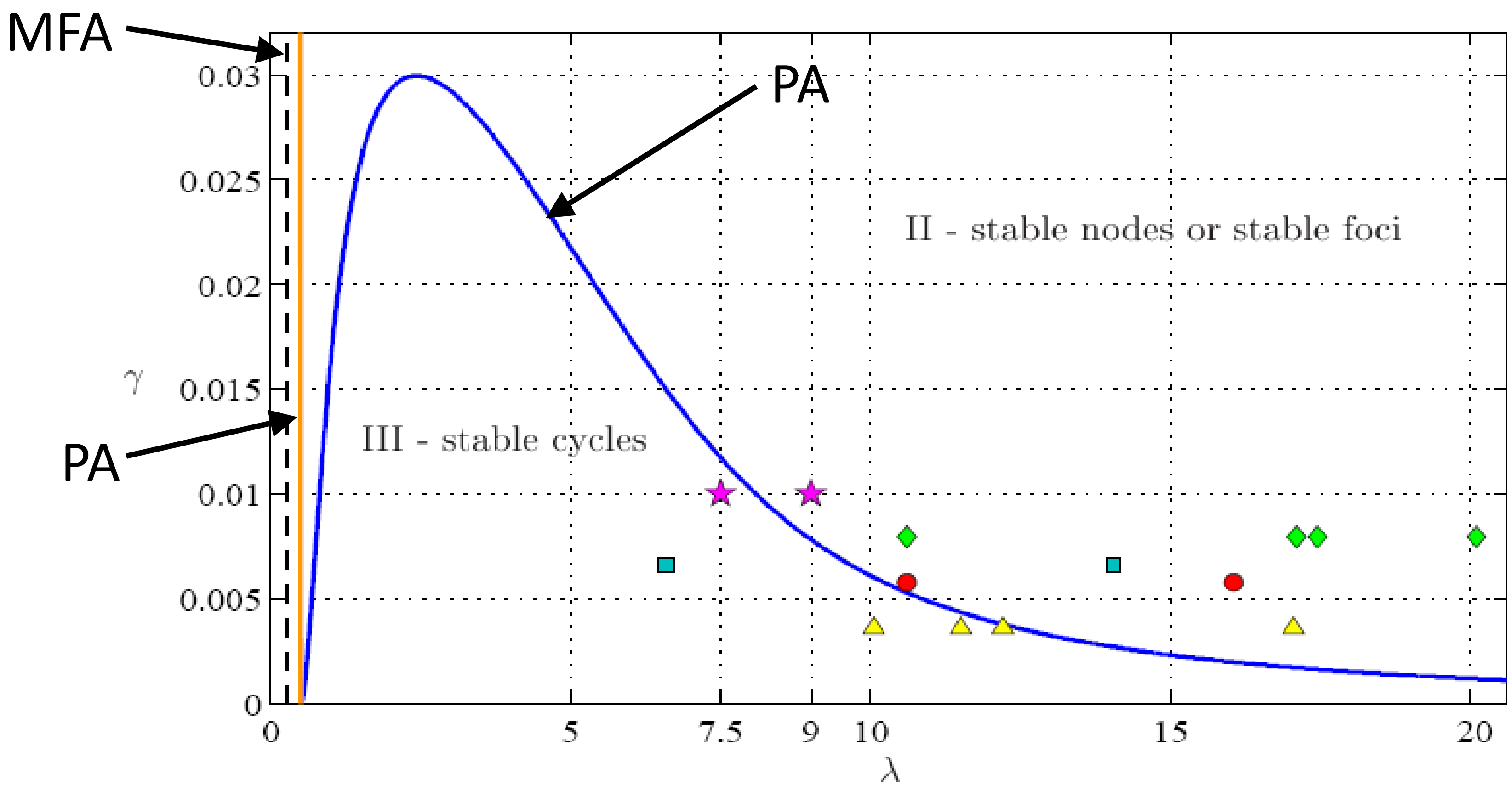


FIG. 1. Phase diagram of the SIRS process in two dimensions. The coexistence phase of *S*-*I*-*R* and the no-coexistence phase are separated by the critical curve from the simulation (open circles with dotted line to guide the eye), the PA (thick solid line), and the MFA (long dashed line). The critical curve is obtained on a periodic square lattice of different sizes N from simulations extrapolated to an infinite system: $N = 50^2, 70^2, 100^2, 150^2, 200^2$.

J. Joo & J. L. Lebowitz, Phys. Rev. E 70, 036114 (2004)

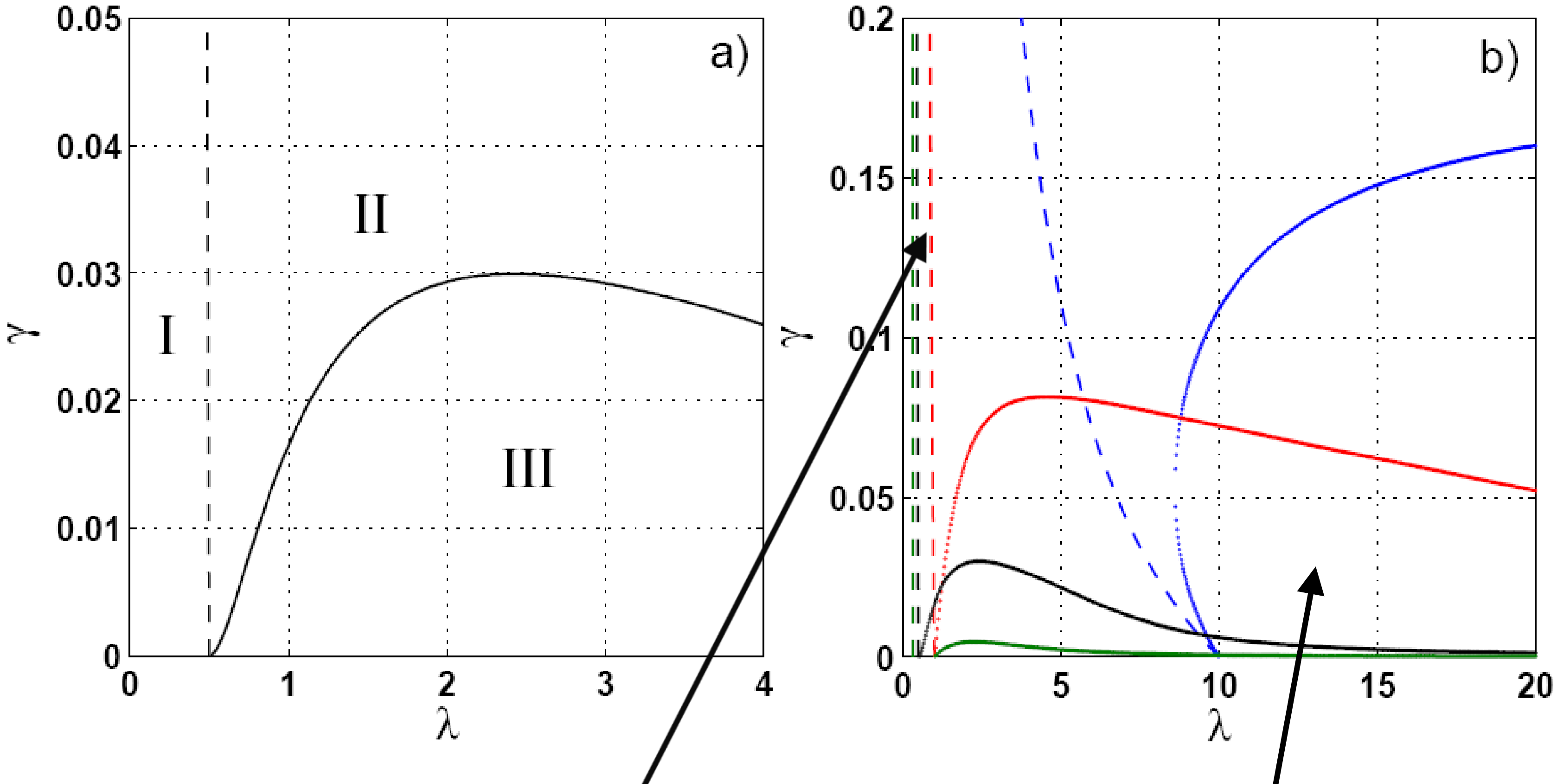
Phase diagram of the PA and MFA deterministic models (k=4)



- *This region corresponds to childhood infectious diseases for which the immunity period is much larger than the infectious period*

G. Rozhnova & A. Nunes, Phys. Rev. E 79, 041922 (2009)

Phase diagram of the PA deterministic model
k = 2.1 (blue), k = 3 (red), k = 4 (black), k = 5 (green)

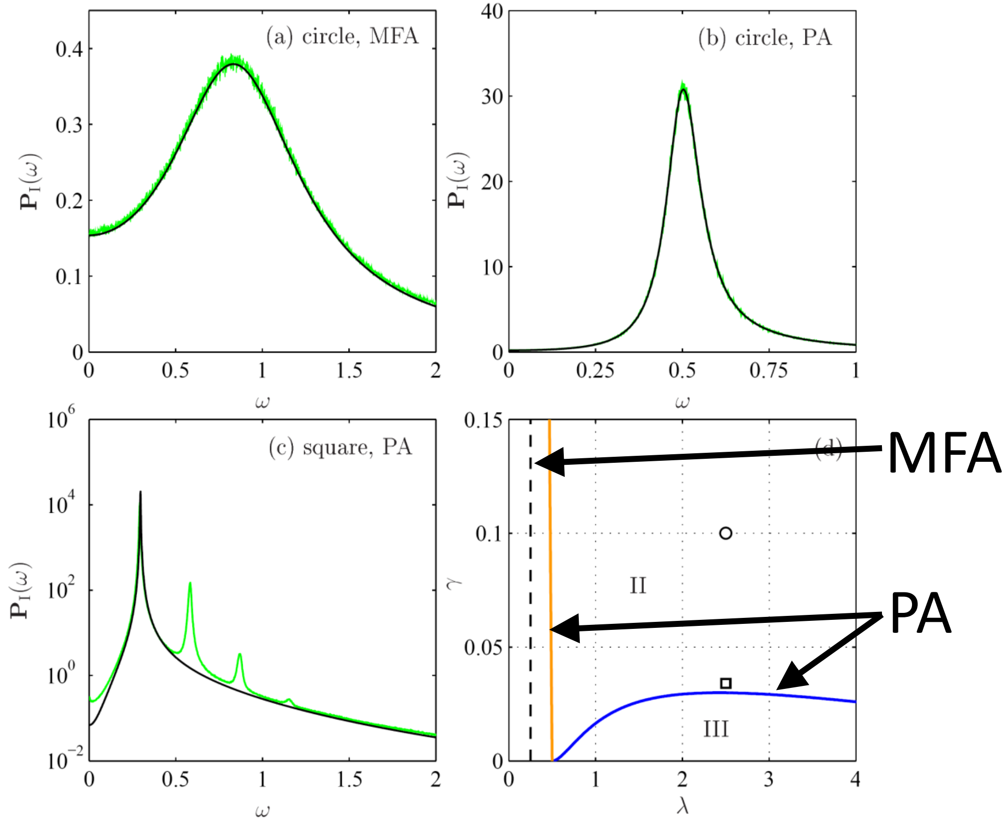


$$\lambda_c(\gamma) = \frac{\gamma + 1}{(k-1)\gamma + k - 2}$$

$$2 < k \lesssim 6$$

Analysis of the spectra of stochastic fluctuations in the PA stochastic model

analytical (black lines)
simulations (green lines)



- *Resonant stochastic fluctuations are larger and more coherent*
- *The main frequency is shifted*
- *The peak increases sharply and harmonic peaks appear close to the region III*

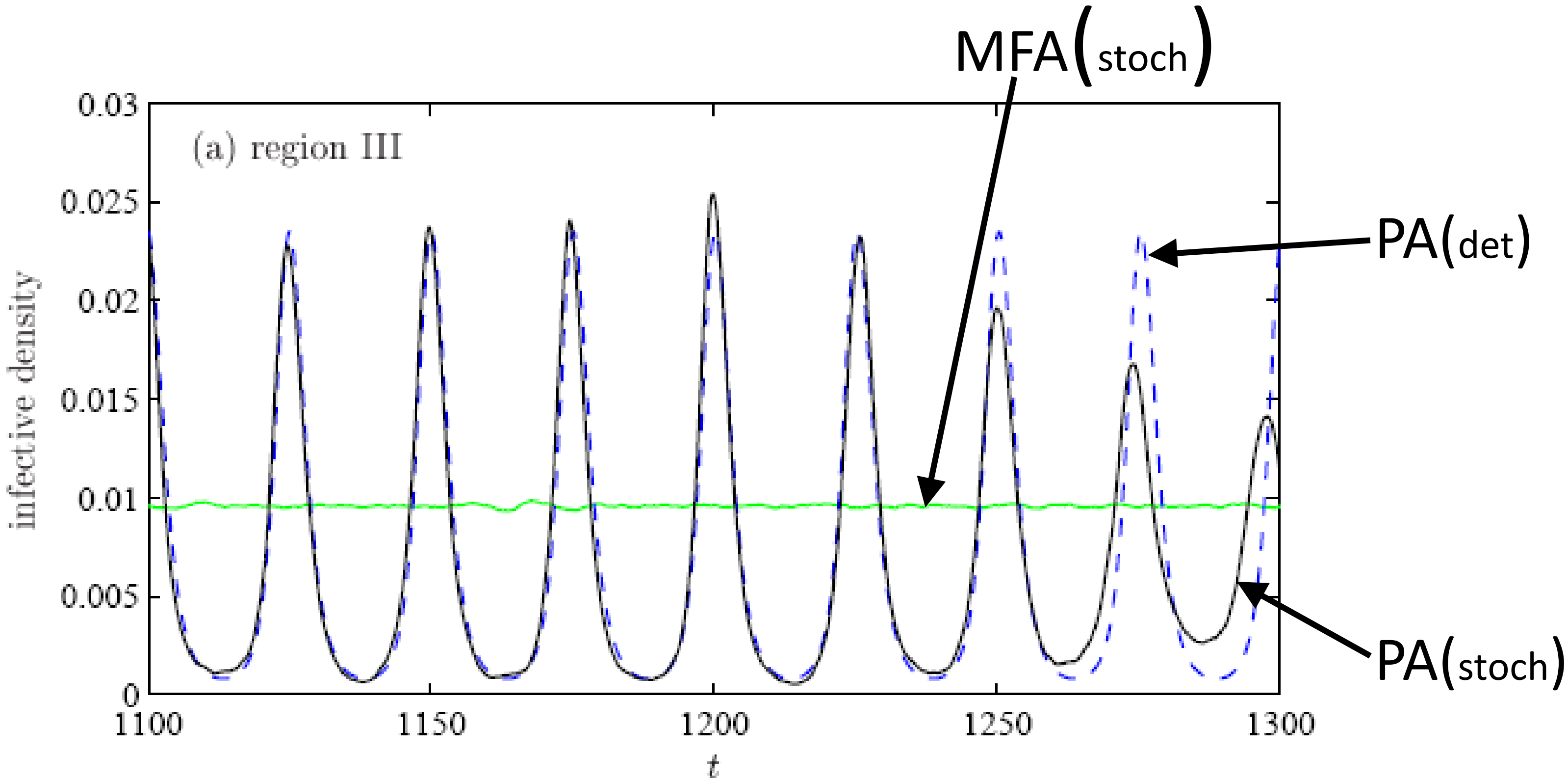
Power spectra of the stochastic fluctuations for the SIRS system

- *In the slow driving regime, the power spectrum of the stochastic fluctuations of long time series is 'resonant like'*

- *Sustained oscillatory patterns arise in the time series of discrete systems through resonant amplification of internal noise*

- *The noise is amplified by the spatial correlations*

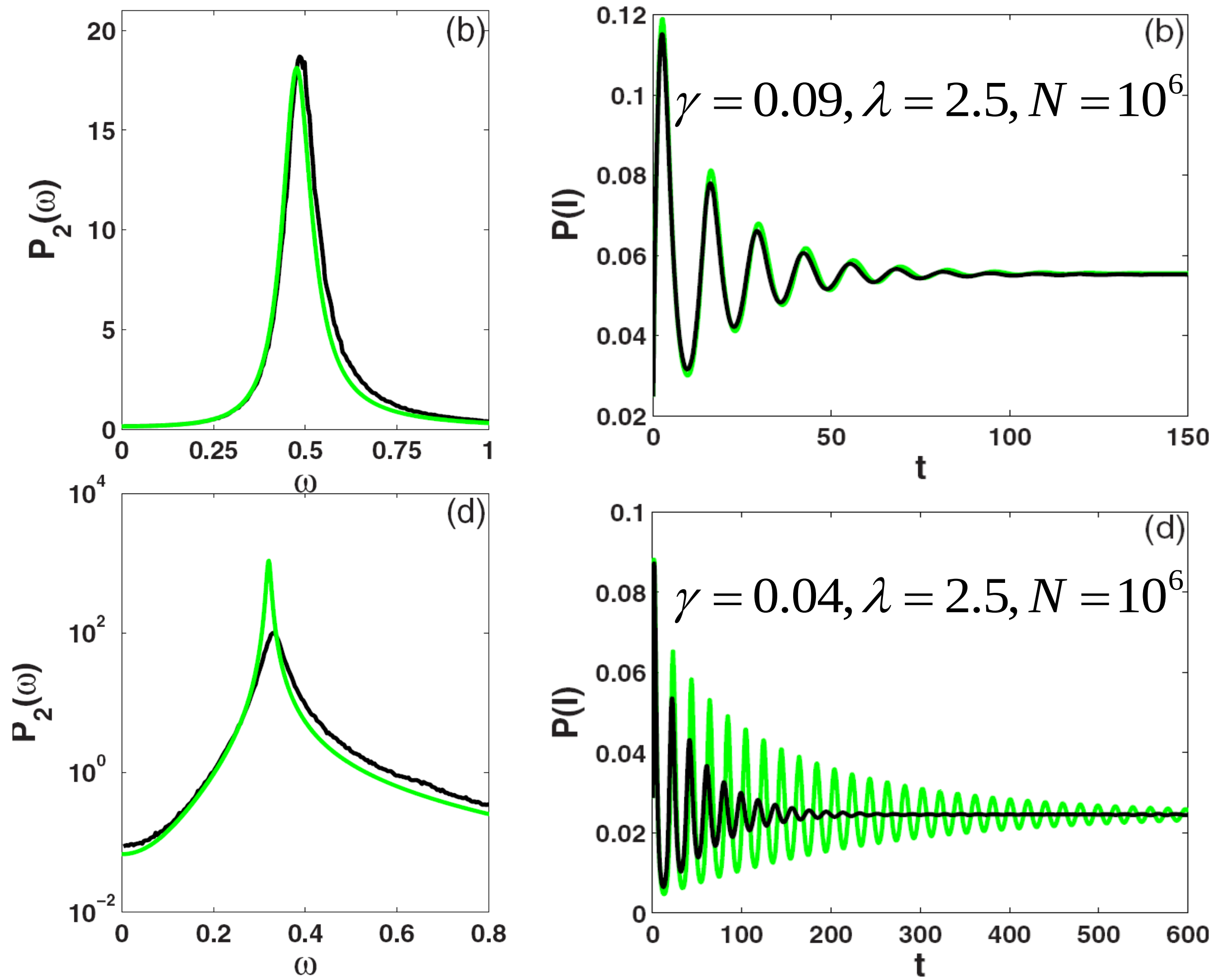
Density of infectives in the steady state as predicted by the PA and MFA deterministic and stochastic models (region III)



- PA deterministic model predicts periodic solutions in region III
- Global oscillations are predicted by the PA stochastic model
- Low amplitude fluctuations in the MFA stochastic model

Spectra of the stochastic fluctuations on a RRG-4

analytical (green lines)
simulations (black lines)

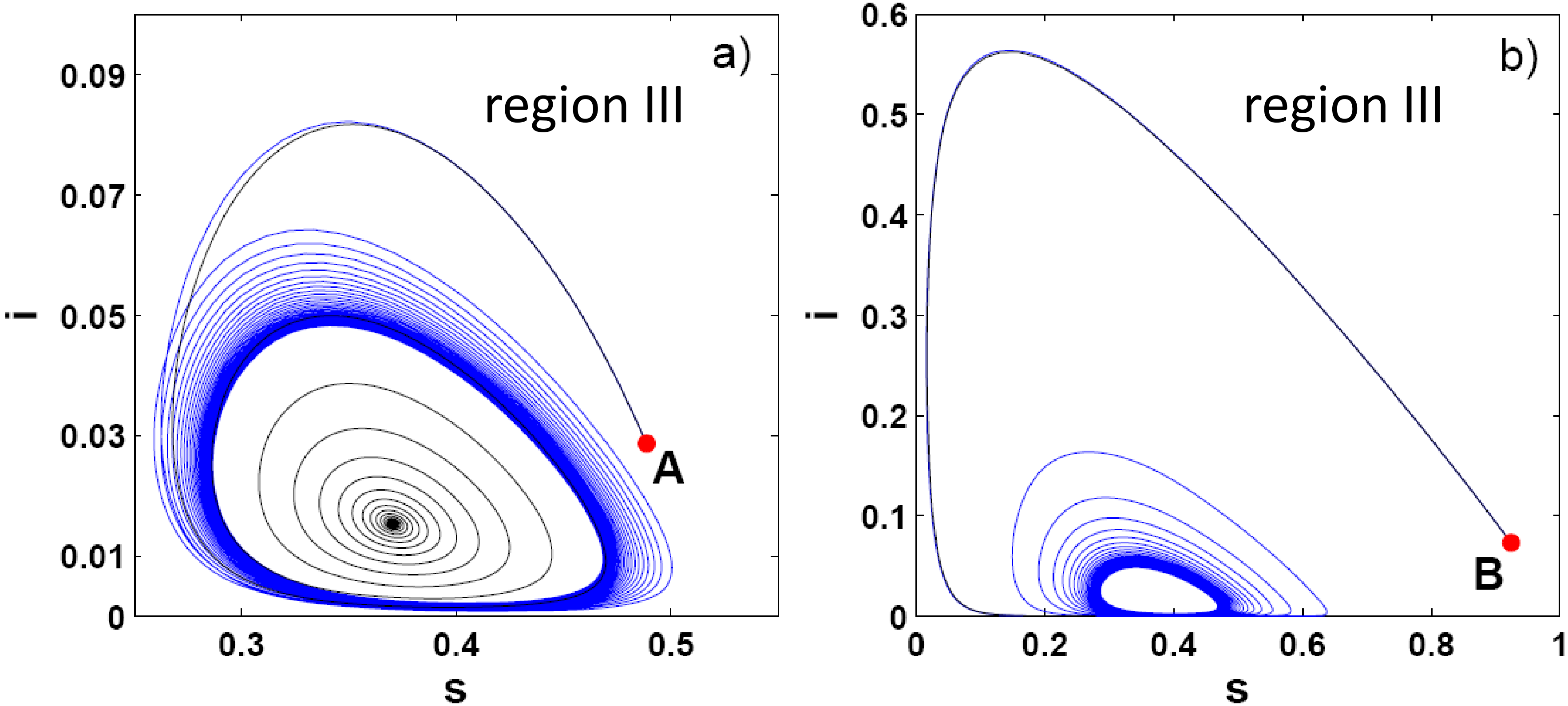


RRG-4 is a random regular graph of degree 4

- ❑ *The detailed PA stochastic model is necessary to describe the power spectra*
- ❑ *The full description requires resorting to higher order cluster approximations*

G. Rozhnova & A. Nunes, Phys. Rev. E 80, 051915 (2009)

PA deterministic model (blue lines) vs stochastic simulations (black lines) on a RRG-4 in region III



Stochastic seasonally forced SEIR model

- *Infection* $S \xrightarrow{\lambda(t)SI/N} E$
- *Disease onset* $E \xrightarrow{\chi E} I$
- *Recovery* $I \xrightarrow{\gamma I} R$
- *Death* $S, E, I \xrightarrow{\mu S, \mu E, \mu I} R$
- *Birth* $R \xrightarrow{\mu N} S$

$$\lambda(t) = \langle \lambda \rangle (1 + \varepsilon \cos 2\pi t)$$

$$S + I + R = N$$

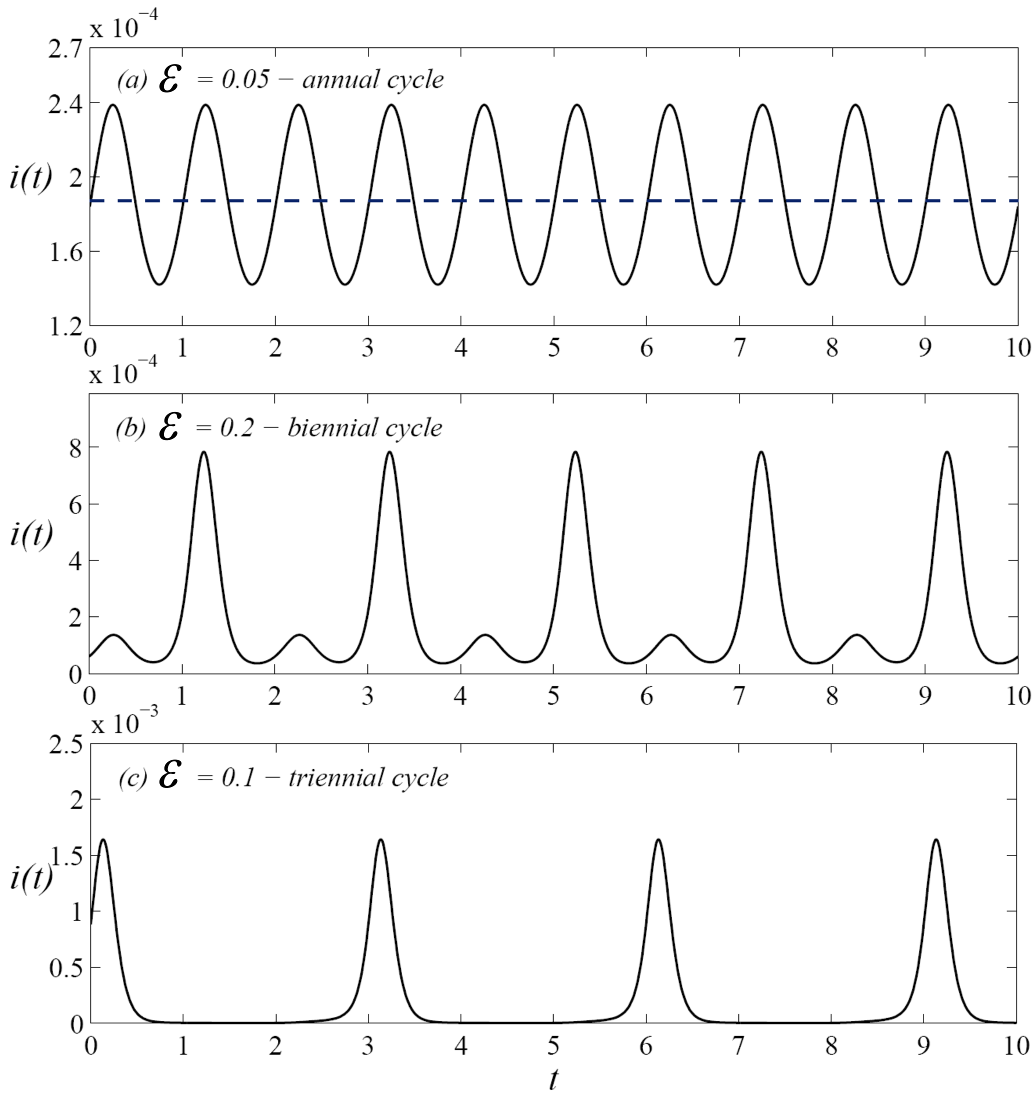
- *Seasonally forced deterministic SEIR model*

$$\frac{dp_S}{dt} = \mu(1 - p_S) - \lambda(t) p_S p_I,$$

$$\frac{dp_E}{dt} = \lambda(t) p_S p_I - (\chi + \mu) p_E(t),$$

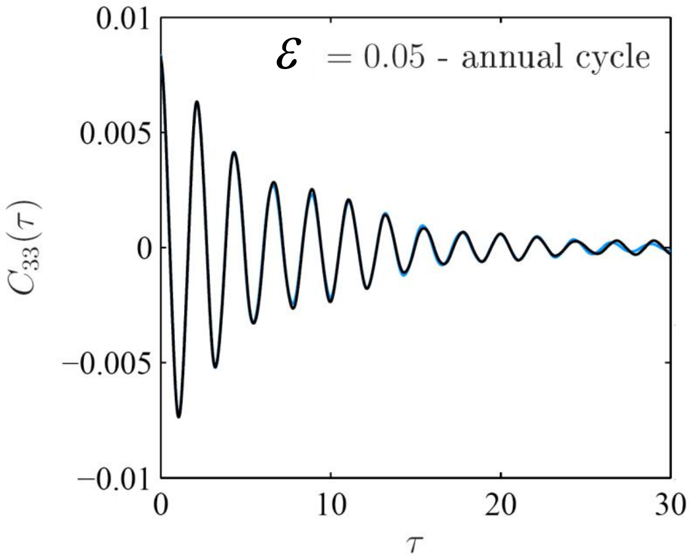
$$\frac{dp_I}{dt} = \chi p_E - (\gamma + \mu) p_I.$$

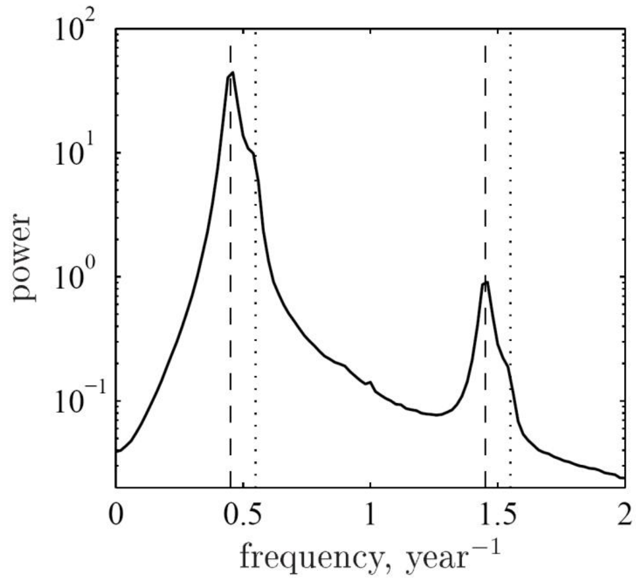
Behavior of the deterministic SEIR model

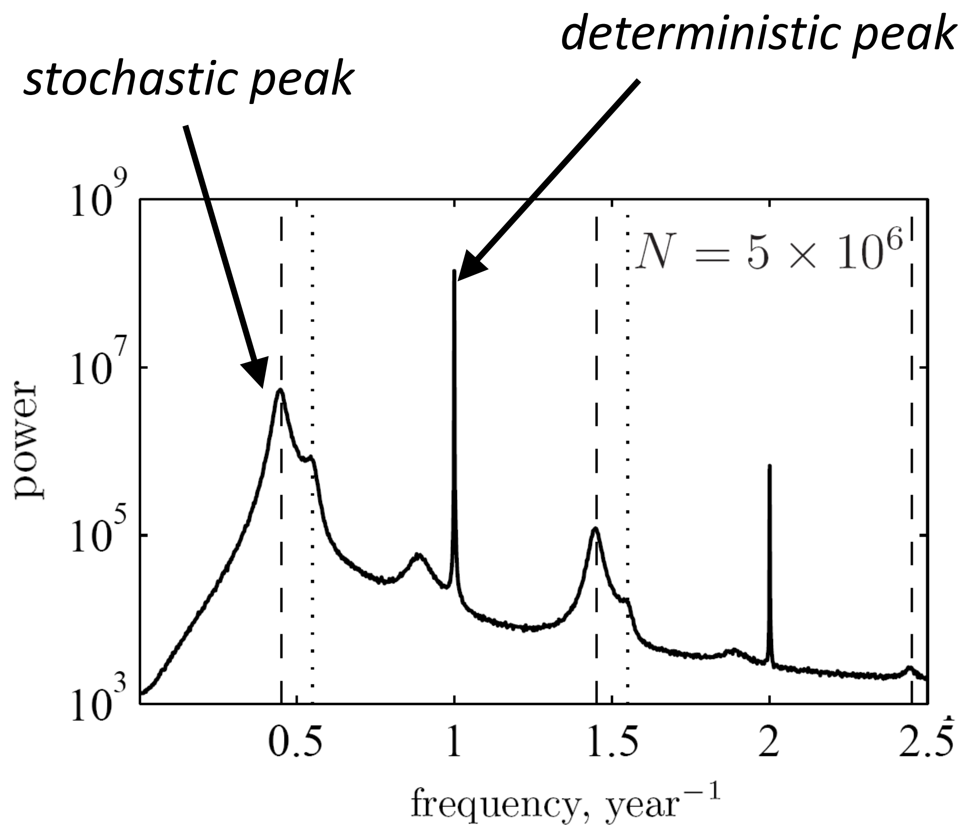


- *The main attractors are stable limit cycles of periods 1, 2 and 3*

Analysis of the spectra of stochastic fluctuations (annual cycle)



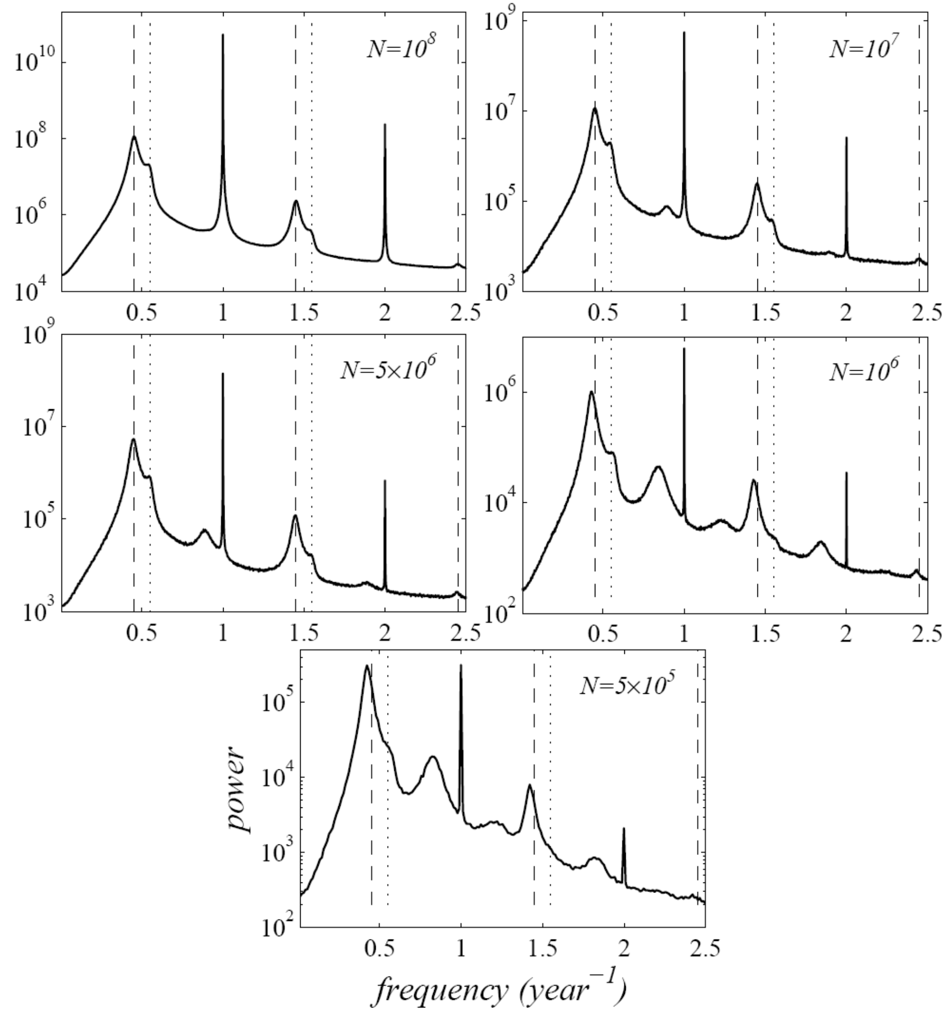




$$\nu_n = \frac{n}{T} \pm \frac{|\mathrm{Im}\,\rho_{1,2}|}{2\pi}, \quad n = 0, \pm 1, \pm 2, \ldots$$

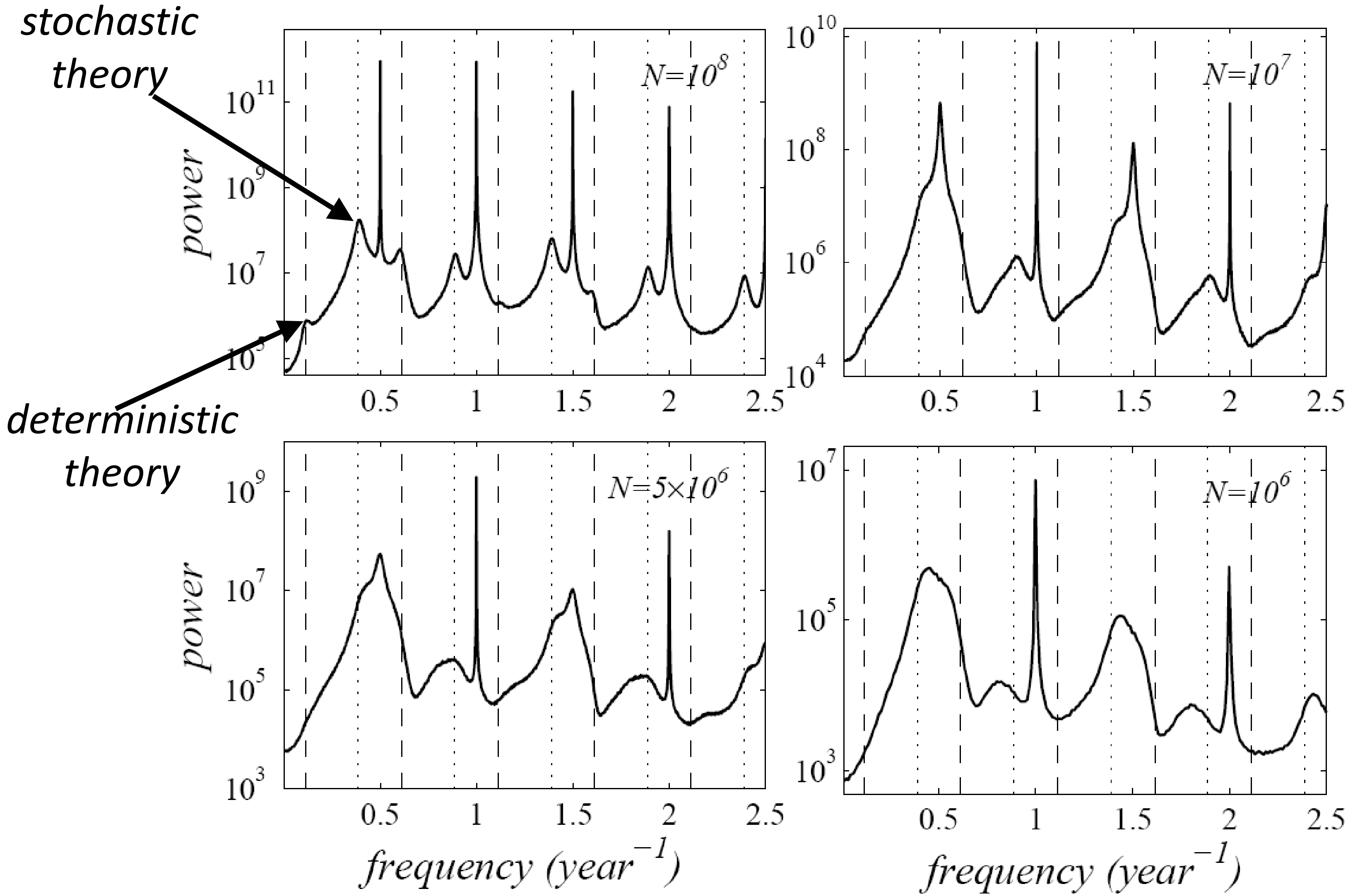
G. Rozhnova, A. Nunes, Phys. Rev. E 82, 041906 (2010)

Analysis of the spectra of stochastic fluctuations (annual cycle)



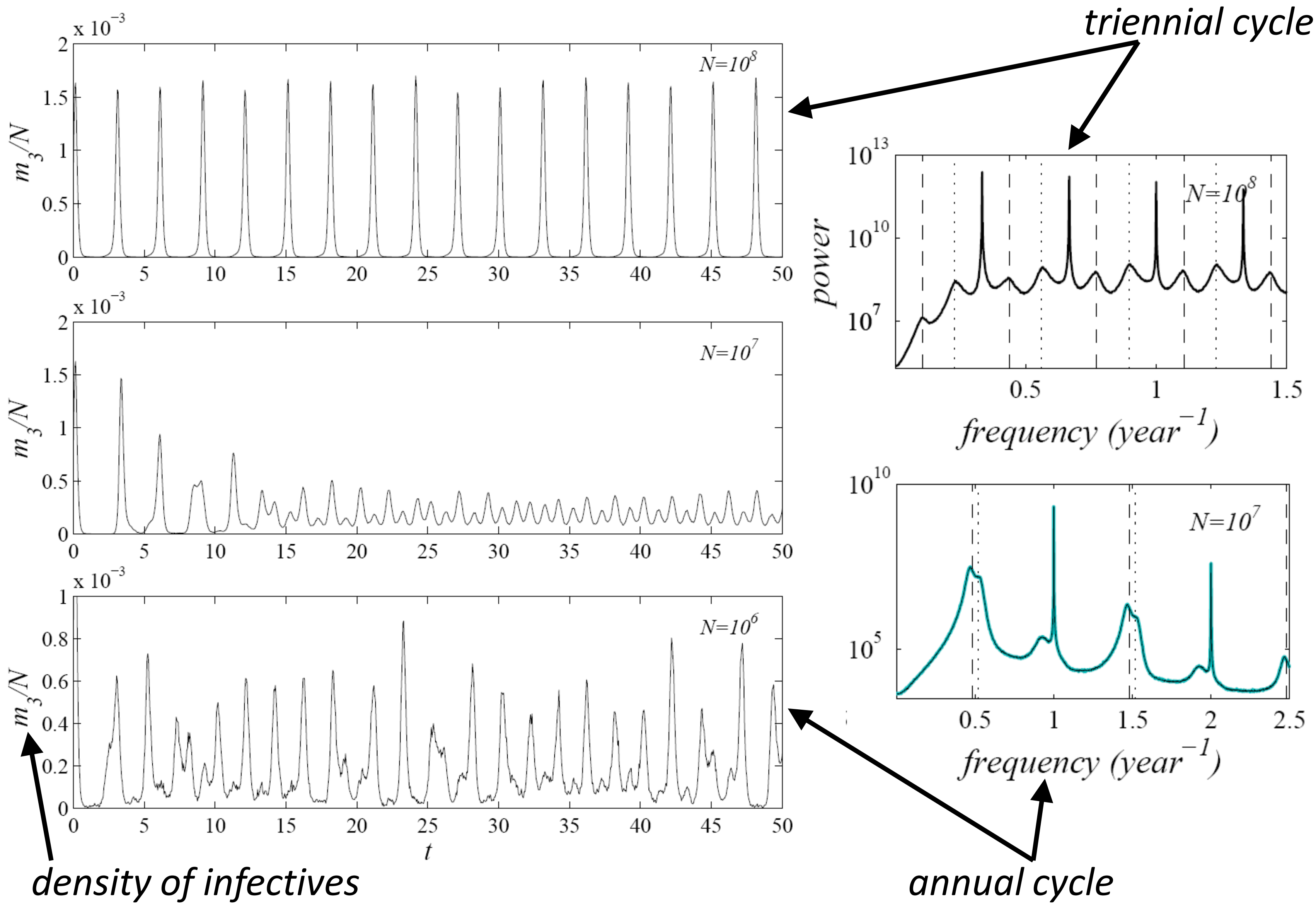
- *The shape of the power spectrum is sensitive to all the basic epidemiological parameters and the system size and so, despite its simplicity, the model is capable of reproducing the diversity of the temporal patterns of real diseases*

Analysis of the spectra of stochastic fluctuations (biennial cycle)

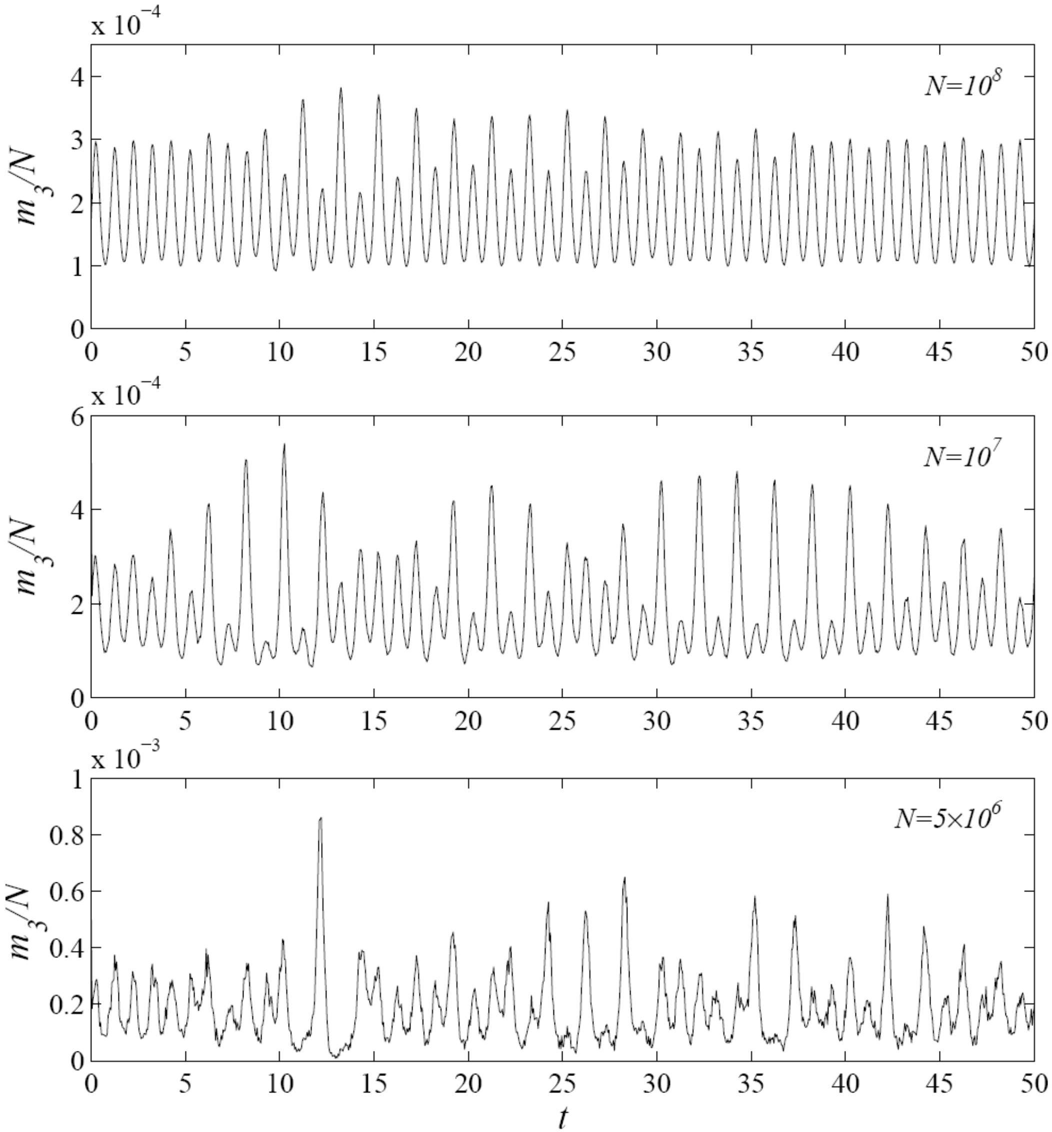


- *The main frequency of the stochastic peak does not necessarily equal the frequency of the damped oscillations of deterministic perturbations around the cycle*

Switching between the deterministic attractors?
No, between the limit cycles of periods 1 and 3 (or 2 and 3).

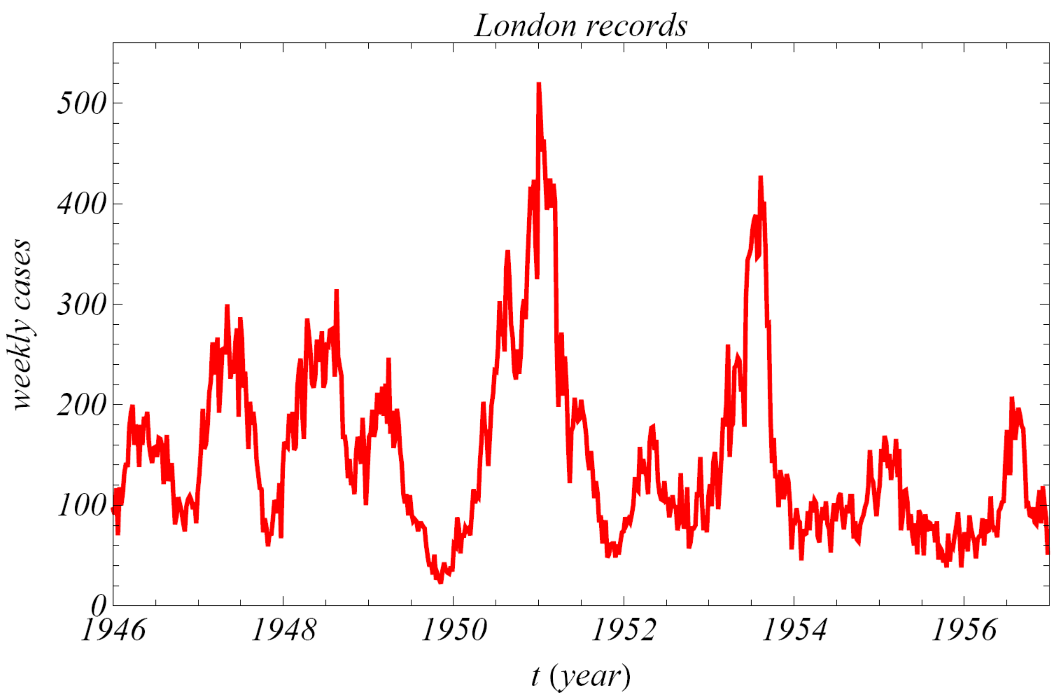


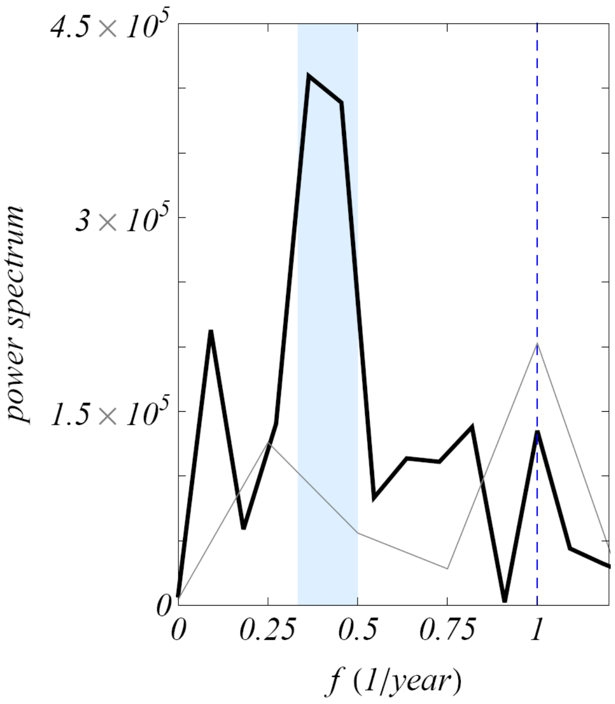
Switching between the deterministic attractors? Yes, between the limit cycles of periods 1 and 2.



- *Switching depends strongly on* ***the shape*** *of the deterministic limit cycle*
- *The bifurcation diagram of the SIR model is* ***not robust*** *with respect to the modifications of the model*
- *The* ***resonant amplification*** *rather than noise induced switching between competing attractors of the deterministic system is the* ***key ingredient*** *to understand the observed incidence patterns of childhood infectious diseases*

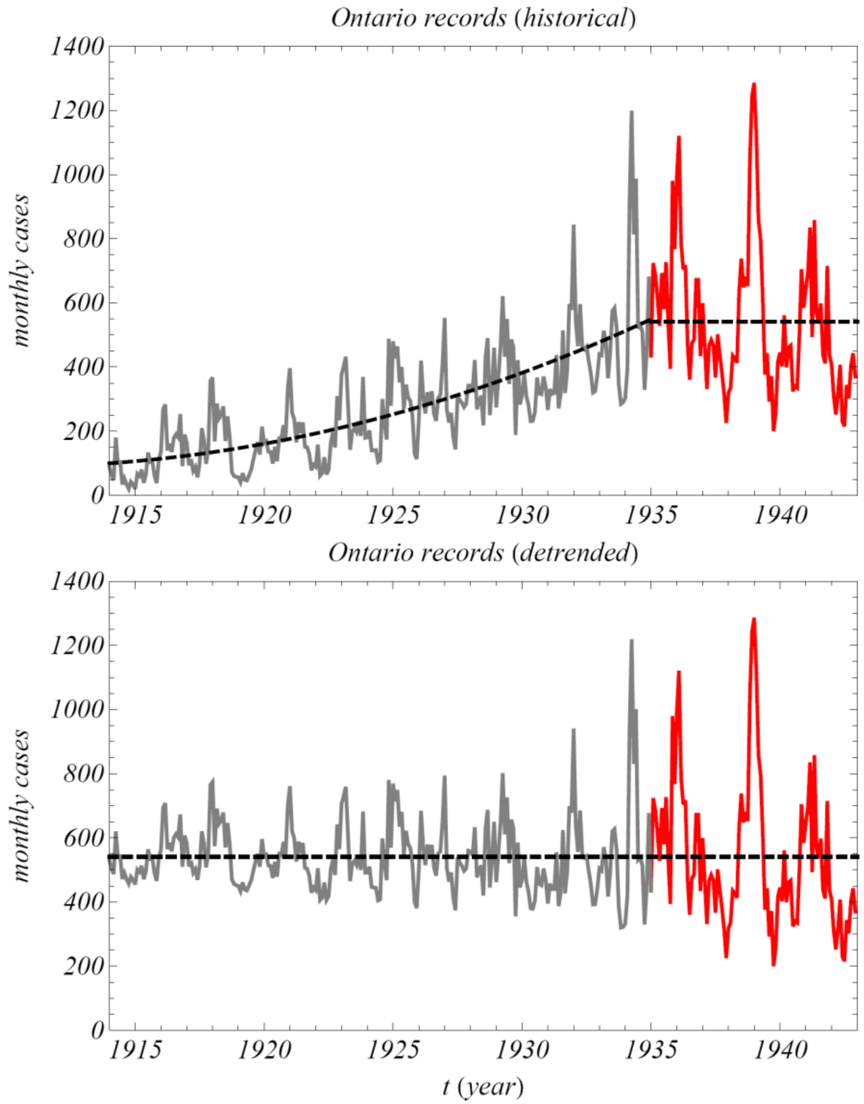
Dynamics of pertussis in the prevaccine era
Analysis of the historical data records

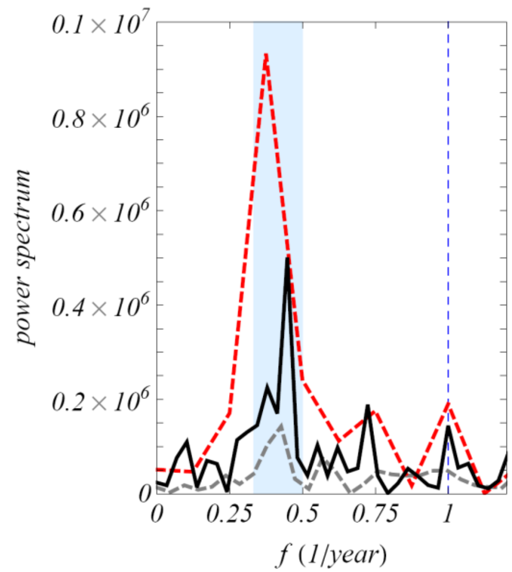




G. Rozhnova & A. Nunes, in preparation (2011)

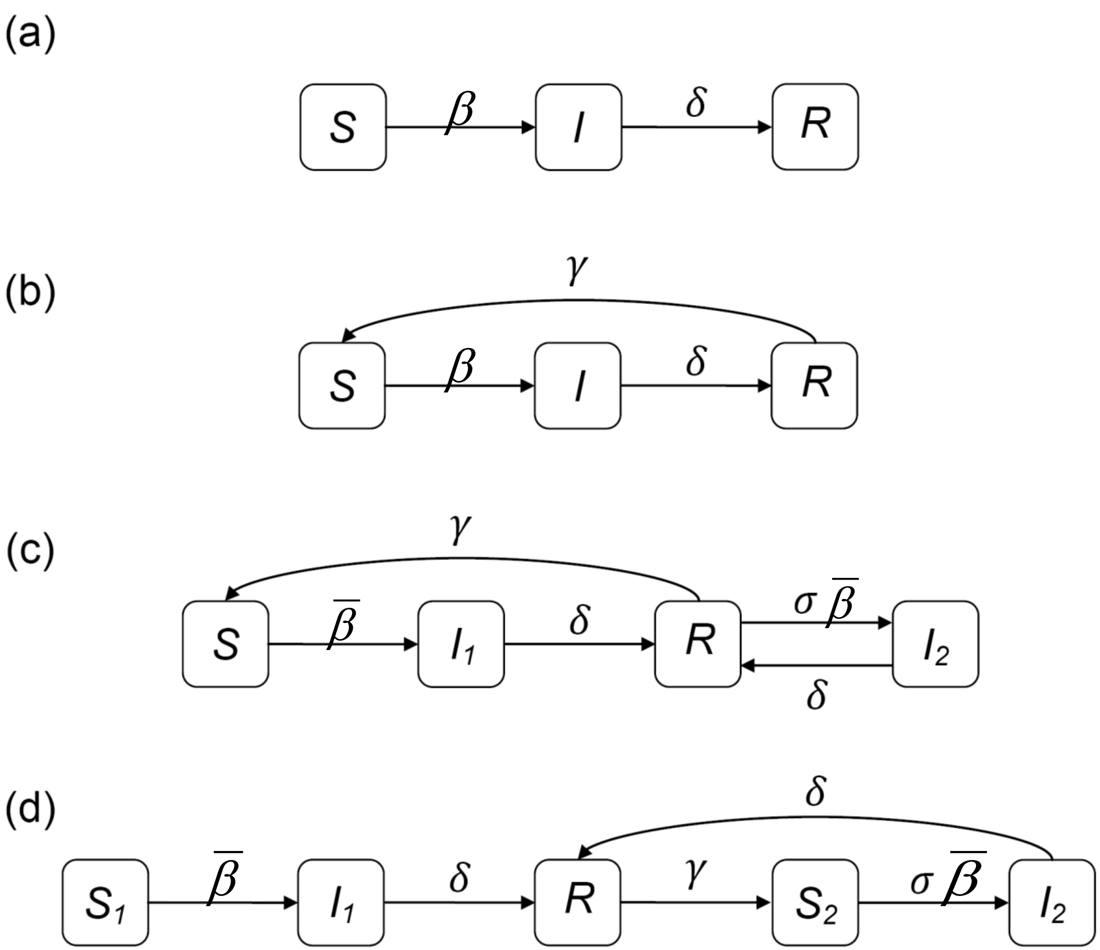
Dynamics of pertussis in the prevaccine era
Analysis of the historical data records





G. Rozhnova & A. Nunes, in preparation (2011)

Dynamics of pertussis in the prevaccine era
Analytical models



$$\lambda(t) = \langle \lambda \rangle (1 + \varepsilon \cos 2\pi t)$$

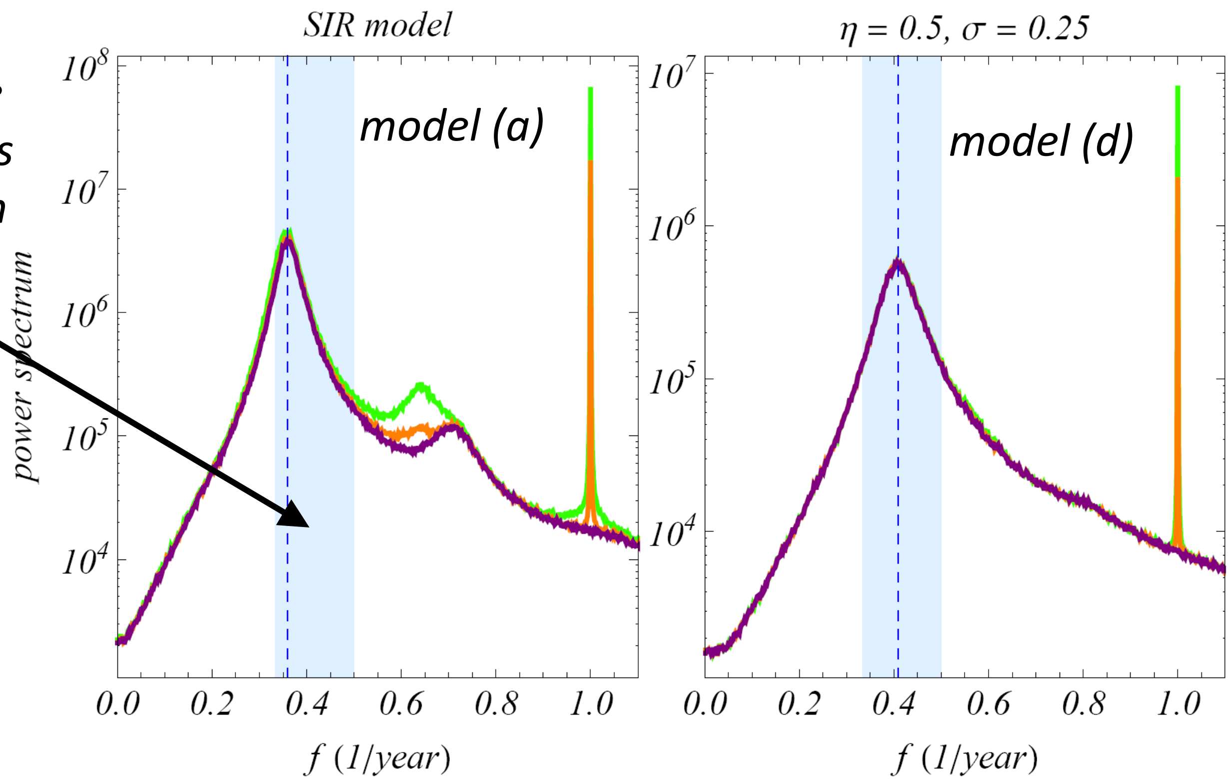
$$\beta = \lambda(t) I / N$$

$$\bar{\beta} = (\lambda(t) I_1 + \eta \langle \lambda \rangle I_2) / N$$

model (a) → the SIR model
model (b) → the SIRS model
model (c) → R. Aguas, G. Goncalves & M. G. Gomes, Lancet Infect. Dis. 6, 112–117 (2006)
model (d) → H. J. Wearing & P. Rohani, PLoS Pathog. 5(10), e1000647 (2009)

Dynamics of pertussis in the prevaccine era
Comparison of the models

shaded region shows the frequencies of the stochastic peaks calculated from the data



- ❑ *Power spectrum for the model with temporary immunity and subsequent reinfection [model (d)] is compatible with the power spectra obtained from the data*
- ❑ *This model [(d)] is also robust with respect to variation of the parameter values and predicts a lower value for the ratio A(det. peak)/A(stoch. peak)*
- ❑ *The stochastic peaks in the spectra for models (b) and (c) lie outside of the shaded region (results not shown), the SIR model is the model (a) whose spectrum is shown on the left*

Conclusions

- *In stochastic epidemic models, the fluctuations power spectrum is resonant-like indicating that stochastic effects can give rise to the patterns of recurrent epidemics*
- *Resonant amplification of demographic stochasticity occurs in the parameter region relevant for childhood infectious diseases modeling*
- *The spatial correlations have a relevant influence on the behavior of fluctuations by enhancing their amplitude and coherence and by changing the characteristic frequency*
- *The interplay between seasonality and the mechanism of resonant amplification of demographic fluctuations provides the description of power spectra with seasonal and non-seasonal peaks*
- *The developed methods are capable to explain the diversity of temporal patterns of infectious diseases*

References

- C. T. Bauch & D. J. D. Earn, *Proc. R. Soc. Lond. B* 270, 1573-1578 (2003)
- D. J. D. Earn, P. Rohani, B. M. Bolker & B. T. Grenfell, *Science* 287, 667-670 (2000)
- A. J. McKane & T. J. Newman, *Phys. Rev. Lett*. 94, 218102 (2005)
- J. Joo & J. L. Lebowitz, *Phys. Rev. E* 70, 036114 (2004)
- G. Rozhnova & A. Nunes, *Phys. Rev. E* 79, 041922 (2009) & Virt. J. Biol. Phys. Research 17 (2009)
- G. Rozhnova & A. Nunes, *Phys. Rev. E* 80, 051915 (2009) & Virt. J. Biol. Phys. Research 18 (2009)
- G. Rozhnova & A. Nunes, *Phys. Rev. E* 82, 041906 (2010) & Virt. J. Biol. Phys. Research 20 (2010)
- G. Rozhnova & A. Nunes, *in preparation* (2011)
- R. Aguas, G. Goncalves & M. G. Gomes, *Lancet Infect. Dis.* 6, 112–117 (2006)
- H. J. Wearing & P. Rohani, *PLoS Pathog.* 5(10), e1000647 (2009)

Thank you!

FCT
Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

FUNDAÇÃO
CALOUSTE
GULBENKIAN