

Numerical qualitative analysis of a large-scale model for measles spread

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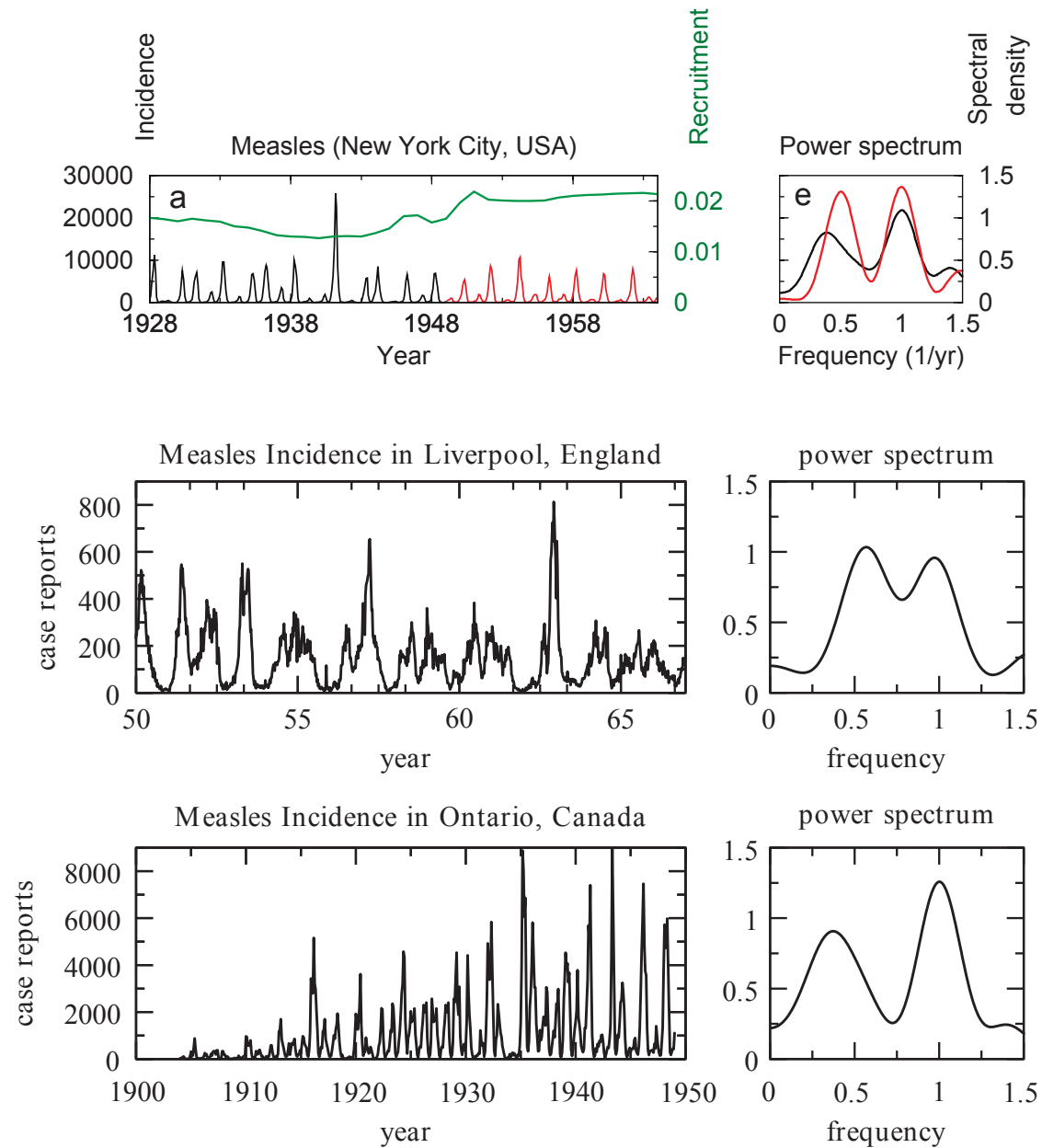
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(joint work with Jane Heffernan)

- Periodic Measles
- From In-Host Model to Between-Host Model
- Numerical Bifurcation Analysis of Large-Scale Systems
- Numerics for Measles
- Ongoing and Future Work

Periodic Measles



(source: *Mathematical Epidemiology*; Brauer et al., 2008)

In-Host Model

The within-host model consists of uninfected peripheral blood mononuclear cells (PBMCs, the main target of measles infection) (x), infected PBMCs (y) and virus (v), as well as naive (w), activated (z) and memory (m) CD8 T-cells:

$$\frac{dx}{dt} = \lambda_x - d_x x - \beta \phi x v$$

$$\frac{dy}{dt} = \beta \phi x v - d_y y - \xi y z$$

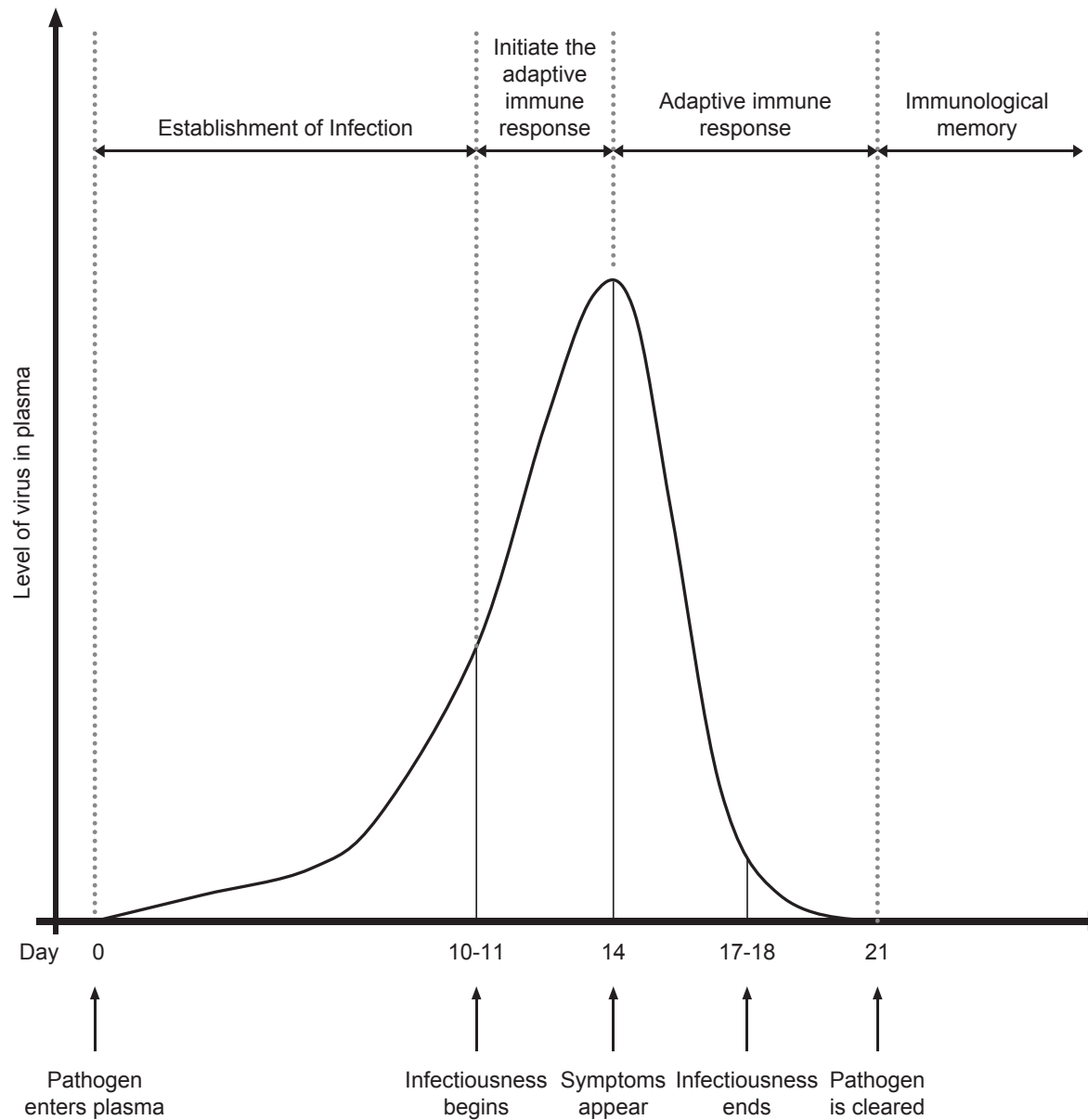
$$\frac{dv}{dt} = k y - u v - \beta \phi v x$$

$$\frac{dw}{dt} = \lambda_z - \frac{c \phi w v}{C_1 \phi v + K_1} - d_w w$$

$$\frac{dz}{dt} = \frac{c \phi v w}{C_1 \phi v + K_1} + \frac{p \phi v z}{C_2 \phi v + K_2} - \frac{(\rho + d_z) z}{C_3 \phi v + K_3} + \frac{f c_m \phi v m}{C_4 \phi v + K_4}$$

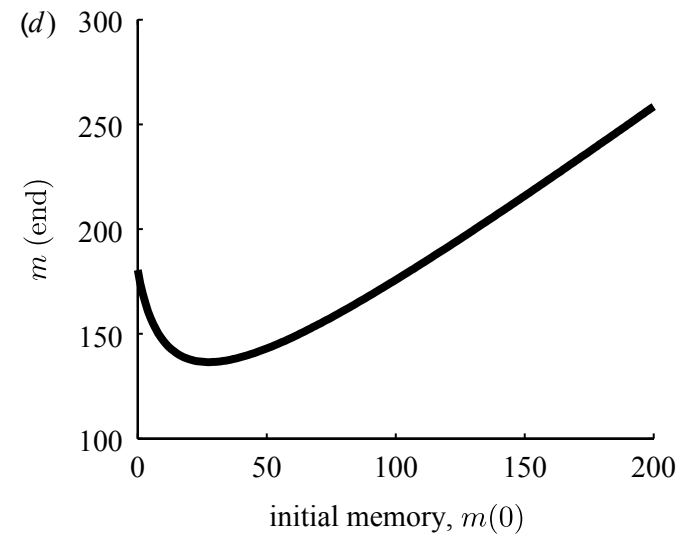
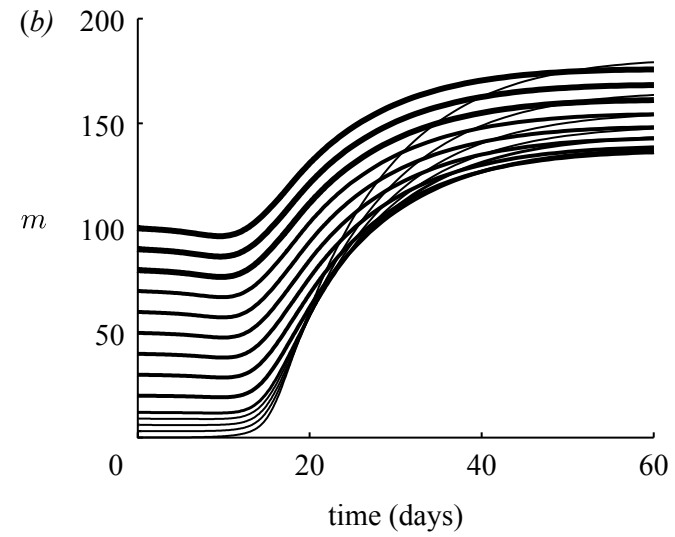
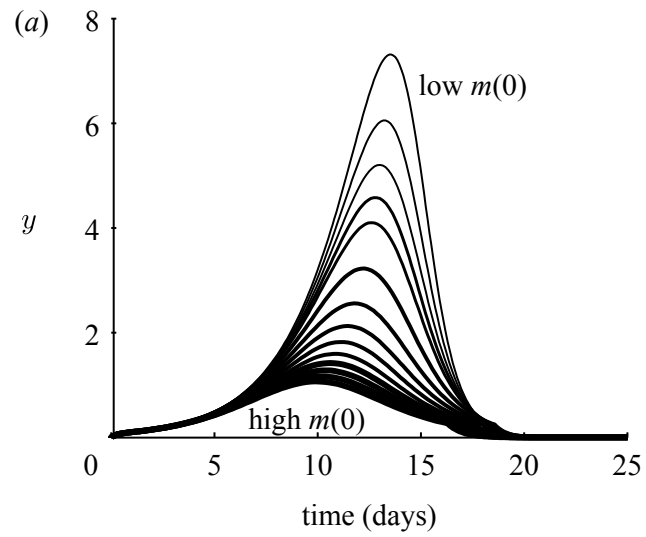
$$\frac{dm}{dt} = \frac{\rho z}{C_3 \phi v + K_3} - d_m m - \frac{c_m \phi v m}{C_4 \phi v + K_4}$$

In-Host Model



(source: Heffernan and Keeling, 2008)

In-Host Model



(source: Heffernan and Keeling, 2010)

Between-Host Model

No vaccine

$$\frac{dS_0}{dt} = B + qR_0 + w_1S_1 - \lambda S_0 - dS_0$$

$$\frac{dS_i}{dt} = qR_i + w_{i+1}S_{i+1} - \lambda S_i - dS_i - w_iS_i$$

$$\frac{dE_i}{dt} = \lambda S_i - a_iE_i - dE_i$$

$$\frac{dI_i}{dt} = a_iE_i - g_iI_i - dI_i$$

$$\frac{dR_i}{dt} = w_{i+1}R_{i+1} + \sum_j b_{i,j}g_jI_j - w_iR_i - qR_i - dR_i$$

$$\lambda = \sum_i \beta_i I_i$$

Class R refers to individuals protected by short-term immune memory (or humoral responses), who clear the virus before T-cell activation preventing boosting. Class S refers to those individuals who have lost this short-term protection

Between-Host Model

With vaccine

$$\frac{dS_0}{dt} = B(1-p) + qR_0 + w_1S_1 - \lambda S_0 - dS_0$$

$$\frac{dS_v}{dt} = Bp + qR_v + w_{v+1}S_{v+1} - \lambda S_v - dS_v - w_vS_v$$

$$\frac{dS_i}{dt} = qR_i + w_{i+1}S_{i+1} - \lambda S_i - dS_i - w_iS_i \quad \forall i \neq 0, v$$

$$\frac{dE_i}{dt} = \lambda S_i - a_i E_i - dE_i$$

$$\frac{dI_i}{dt} = a_i E_i - g_i I_i - dI_i$$

$$\frac{dR_i}{dt} = w_{i+1}R_{i+1} + \sum_j b_{i,j} g_j I_j - w_i R_i - qR_i - dR_i$$

$$\lambda = \sum_i \beta_i I_i$$

The value $v = 90$ is determined by the within-host model.

Dimension = (#S) + (#E) + (#I) + (#R) = 200(300) + 15 + 15 + 200(300) = 430(630)

Numerical Bifurcation Analysis of Large-Scale Systems

■ Commonly Used Bifurcation Software

- ◆ AUTO (Doedel & Oldeman), XPPAUT (B. Ermentrout) [C, Fortran, Python]
- ◆ BIFPACK (R. Seydel)[Fortran]
- ◆ MATCONT(Dhooge & Govaerts & Kuznetsov)[Matlab]
- ◆ CONTENT(Kuznetsov & Levitin & Skovoroda) [C++]

■ Methods Adapted for Large-Scale Problems (discretizations of partial differential equations)

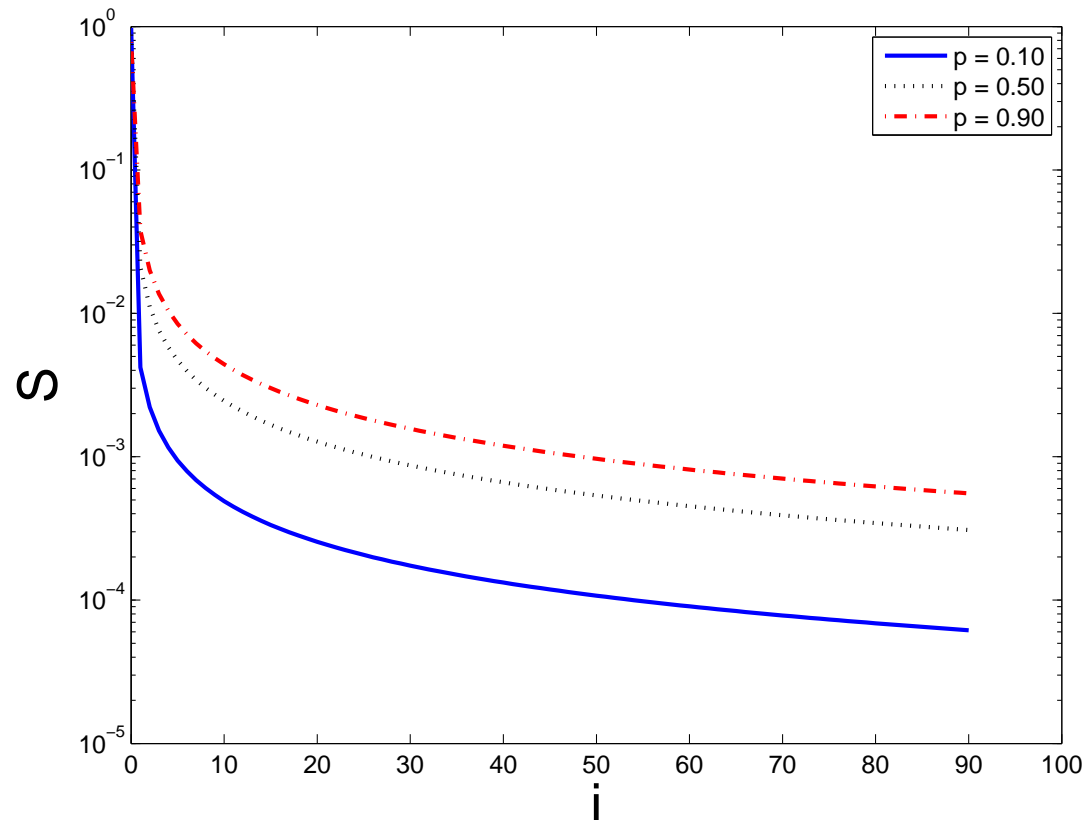
- ◆ CL MATCONTL (Bindel & Friedmany & Govaerts & Hughes & Kuznetsov):
Steady-State (Find-Continue), Hopf (Find-Continue), Fold (Find-Continue) [Matlab]
- ◆ PDECONT (K. Lust): Steady-State (Find-Continue), Periodic Solutions
(Find-Continue) [C]
- ◆ LOCA (A. G. Salinger, et al.): Steady-State (Find-Continue), Hopf (Find-Continue),
Fold (Find-Continue) , Phase Transition (Find-Continue) [C]

These methods are based on (some kind of) *subspace continuation*.

Numerics for Measles → Steady States

Disease Free Equilibrium, $(E_i \Big|_{t=0} = 0, \quad I_j \Big|_{t=0} = 0)$

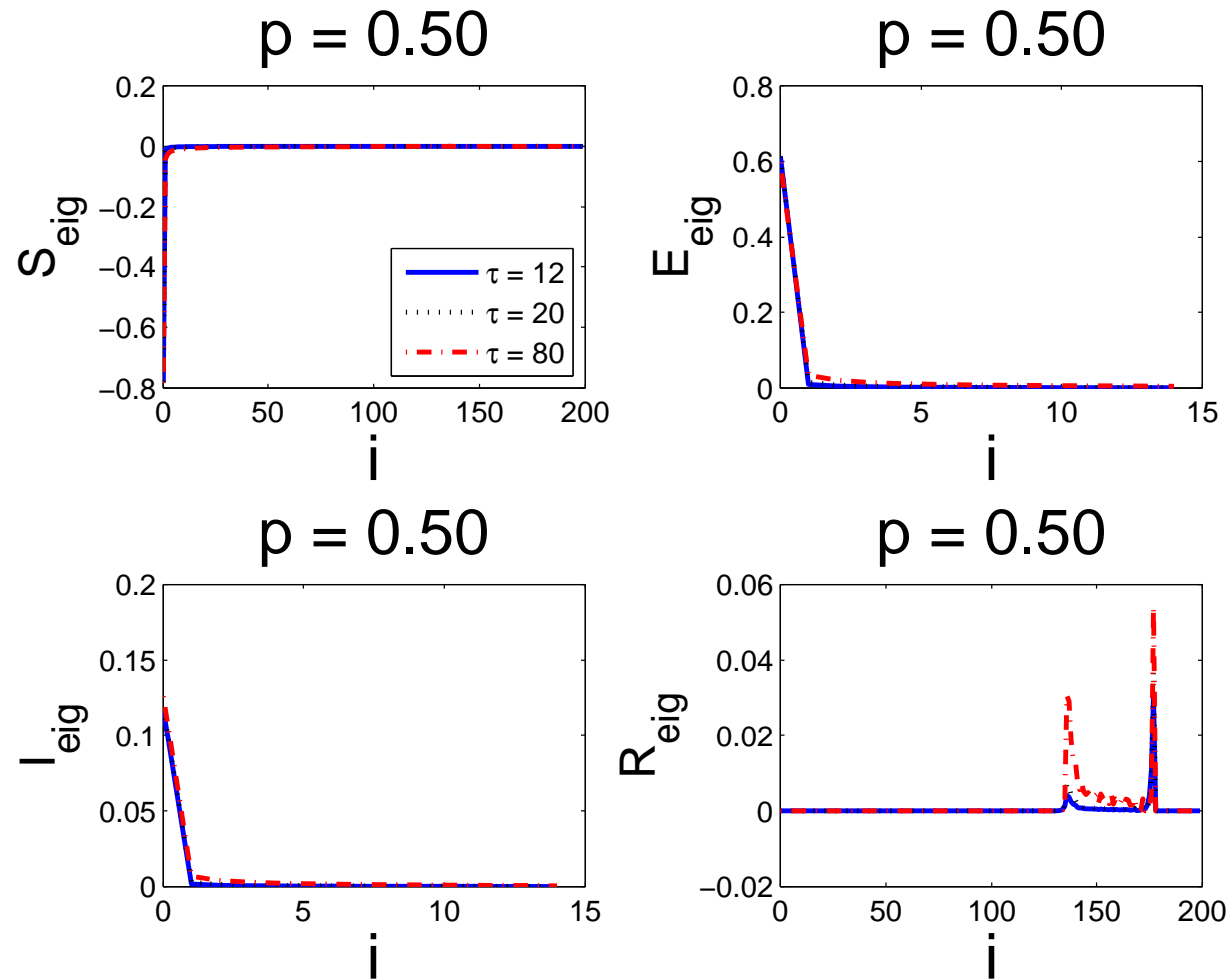
$\tau = 20$



Extensive numerical simulations show that the Jacobian at the disease free equilibrium always has one and only one positive eigenvalue. Hence, this equilibrium is always unstable and there is no local bifurcation for our desired parameter range ($0 \leq P \leq 1, 10 \leq \tau \leq 100$).

Numerics for Measles \rightarrow Steady States

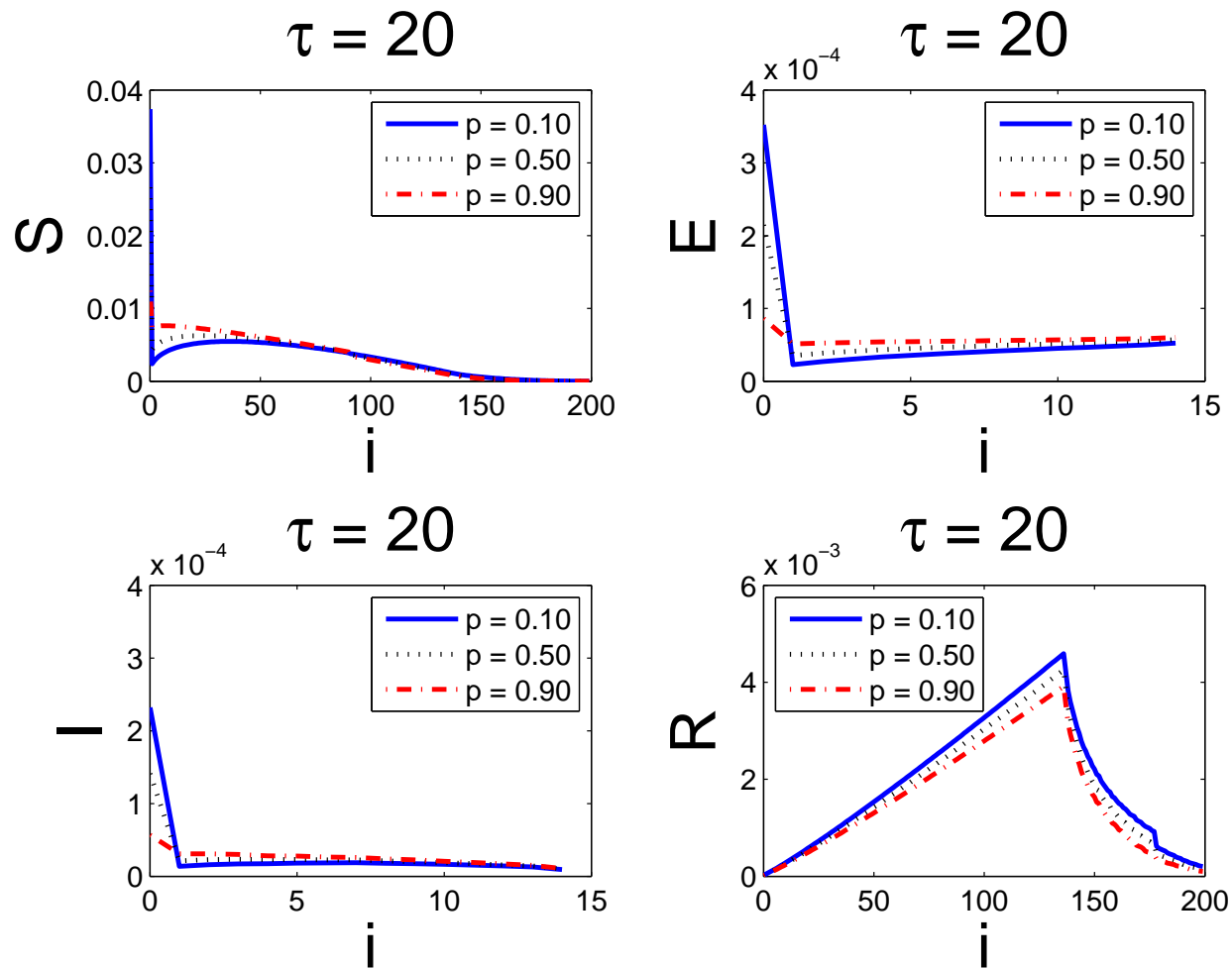
Disease Free Equilibrium, $(E_i \Big|_{t=0} = 0, \quad I_j \Big|_{t=0} = 0)$



unstable direction

Numerics for Measles \rightarrow Steady States

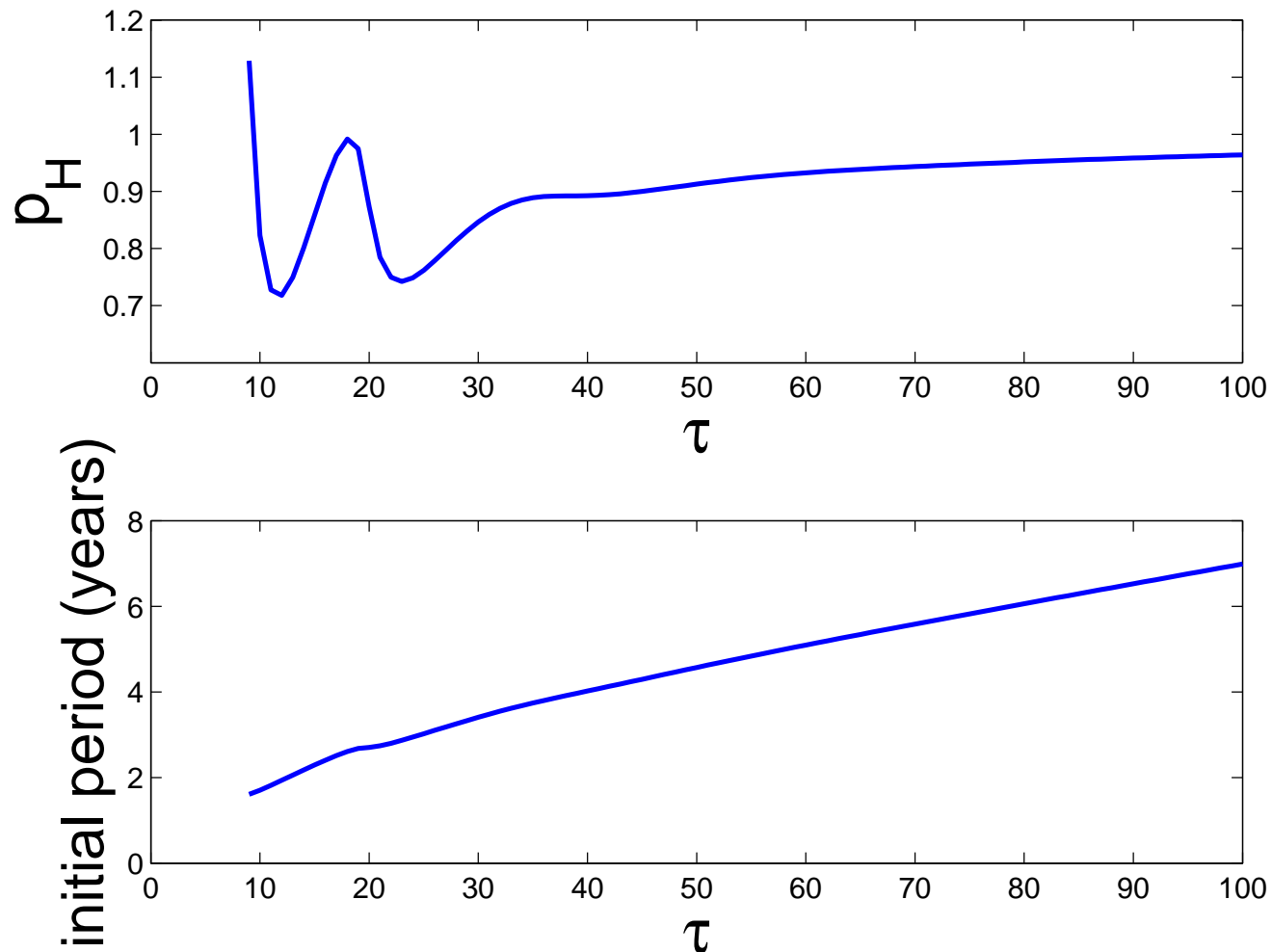
Endemic Equilibrium



This stable equilibrium goes under a Hopf bifurcation and loses its stability at $p = p_H$. The Hopf bifurcation is supercritical.

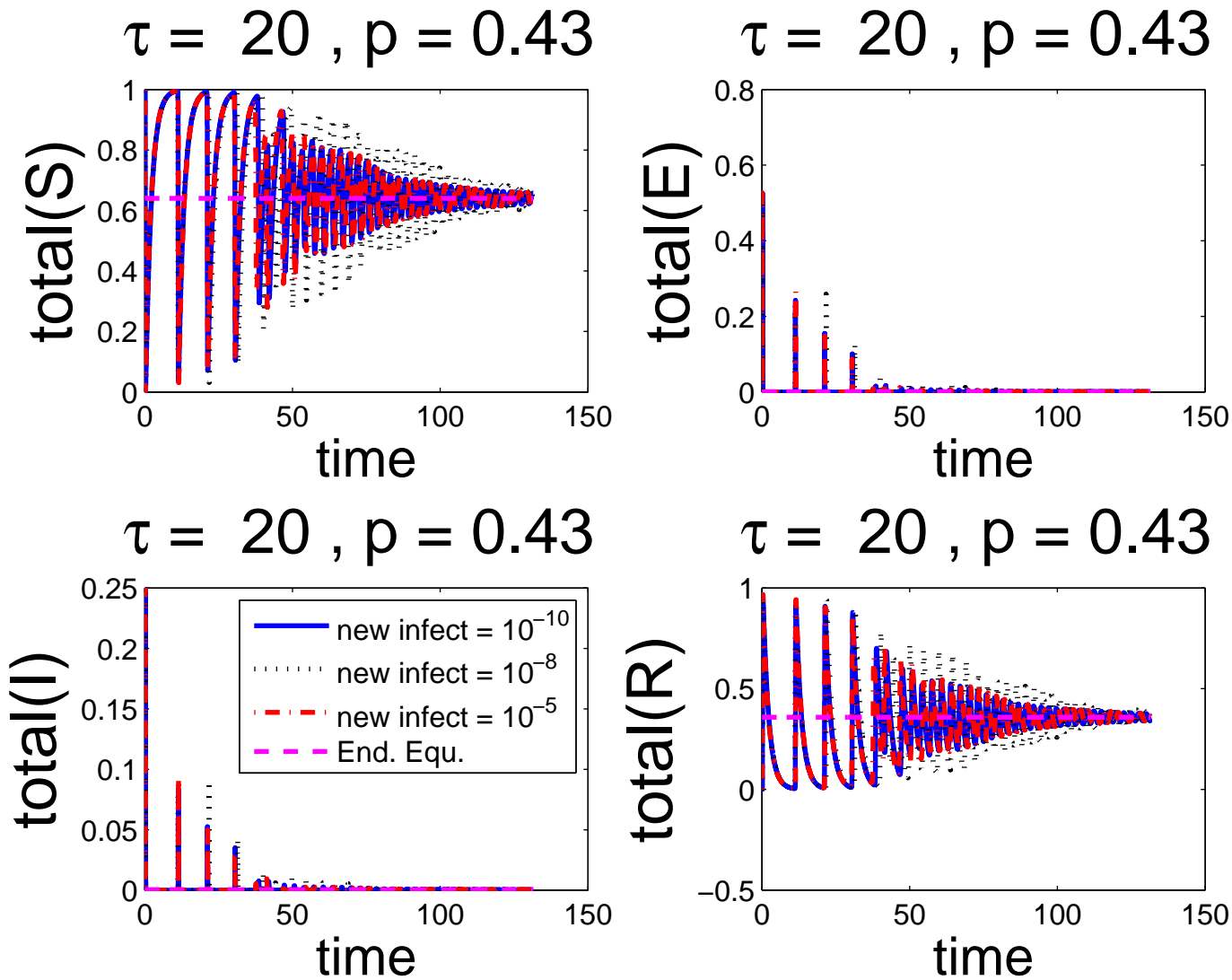
Numerics for Measles → Bifurcations

Continuation of Hopf bifurcation



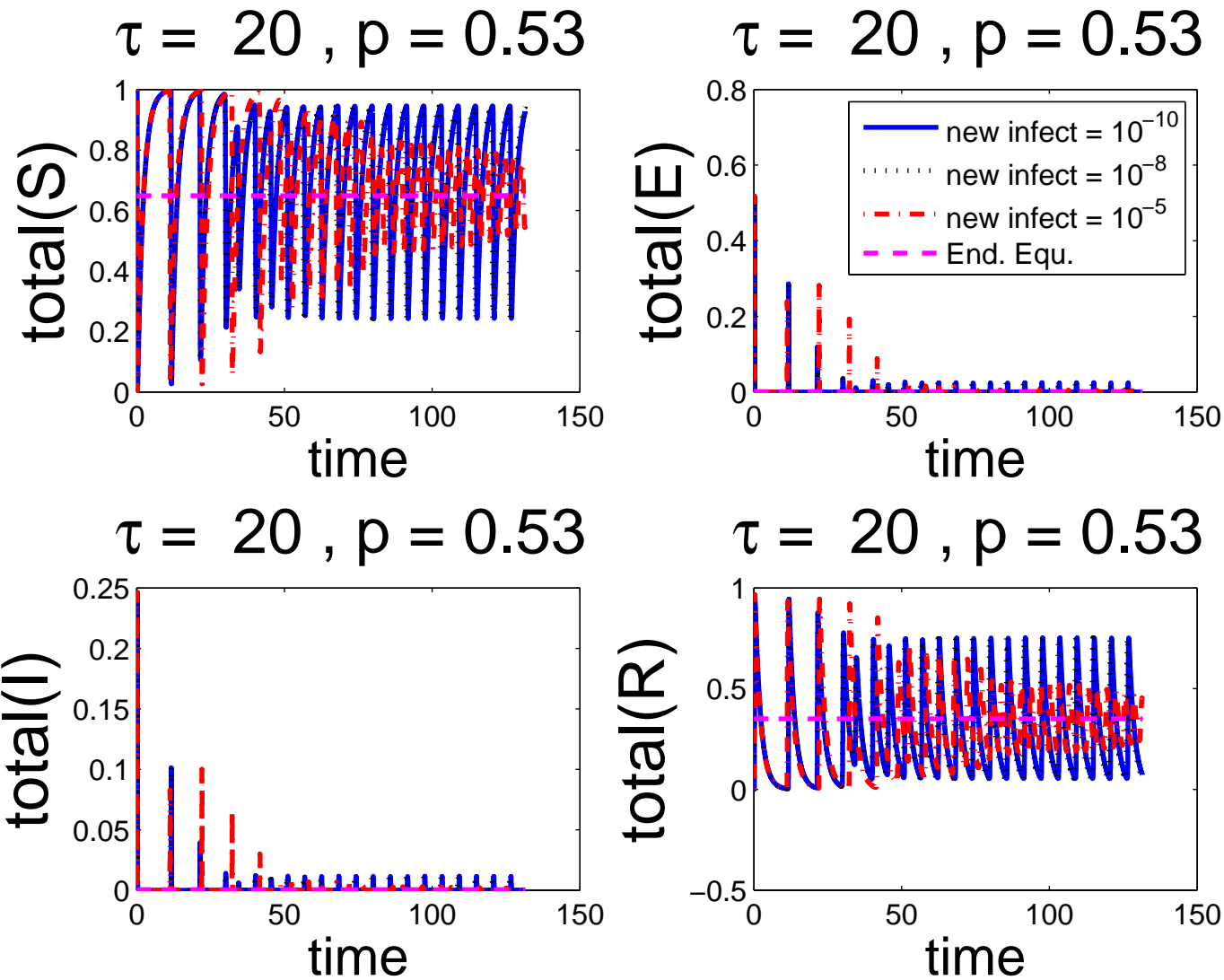
This was our first guess for oscillation mechanism. BUT, soon we observed that the amplitudes of oscillations were very small (not surprising for Hopf bifurcation).

Numerics for Measles \rightarrow Bifurcations



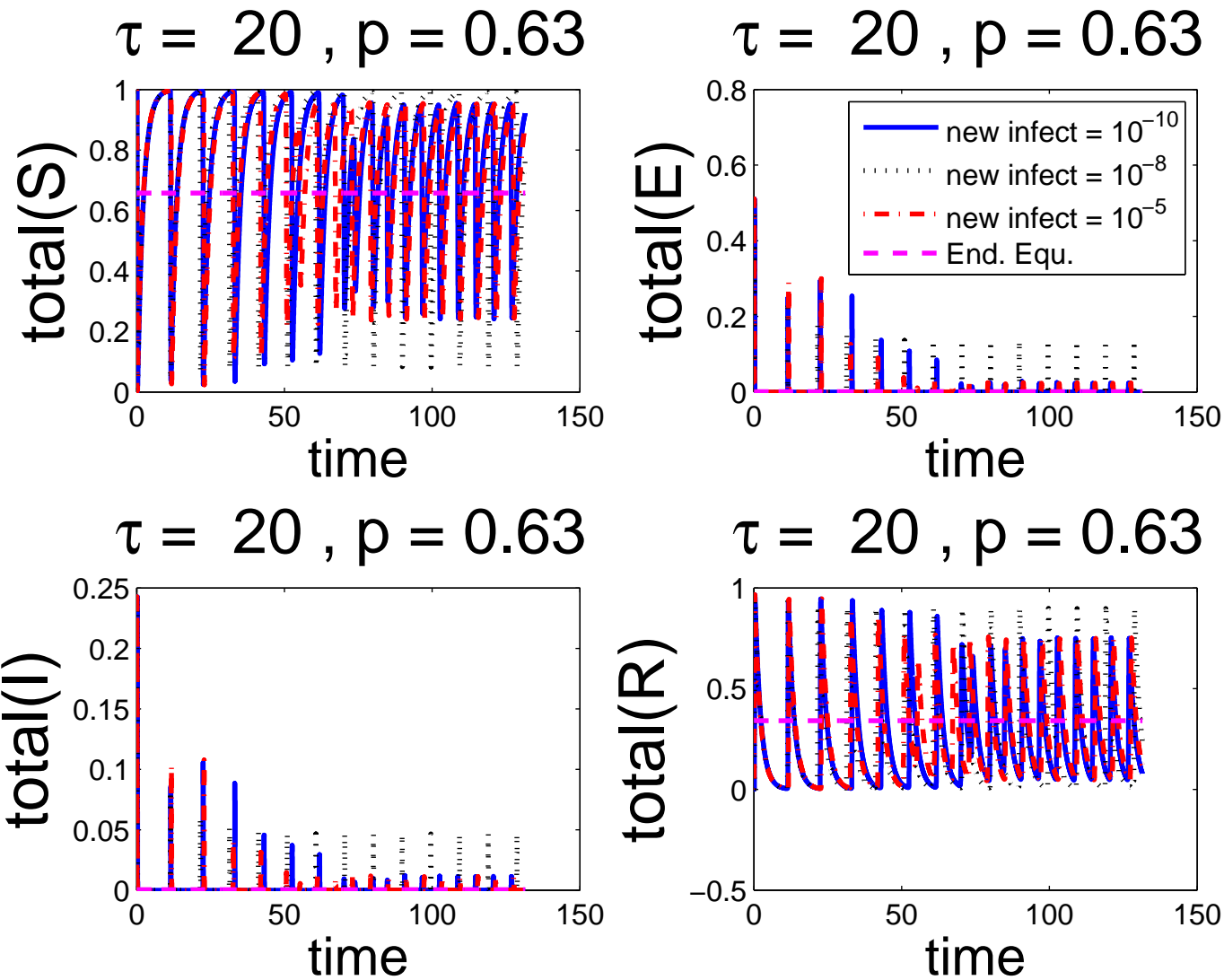
introducing infection into Disease Free Equilibrium

Numerics for Measles \rightarrow Bifurcations



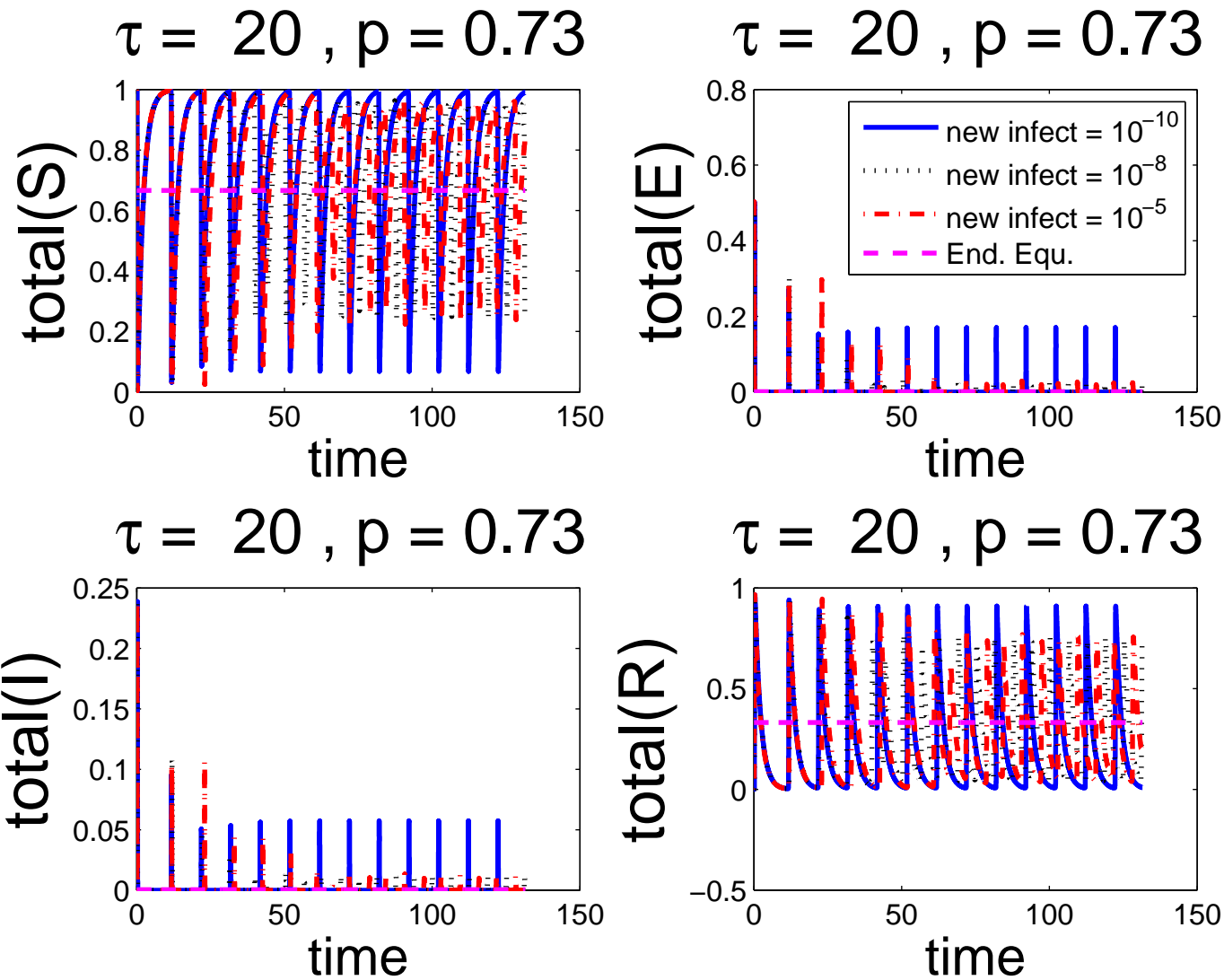
introducing infection into Disease Free Equilibrium

Numerics for Measles → Bifurcations



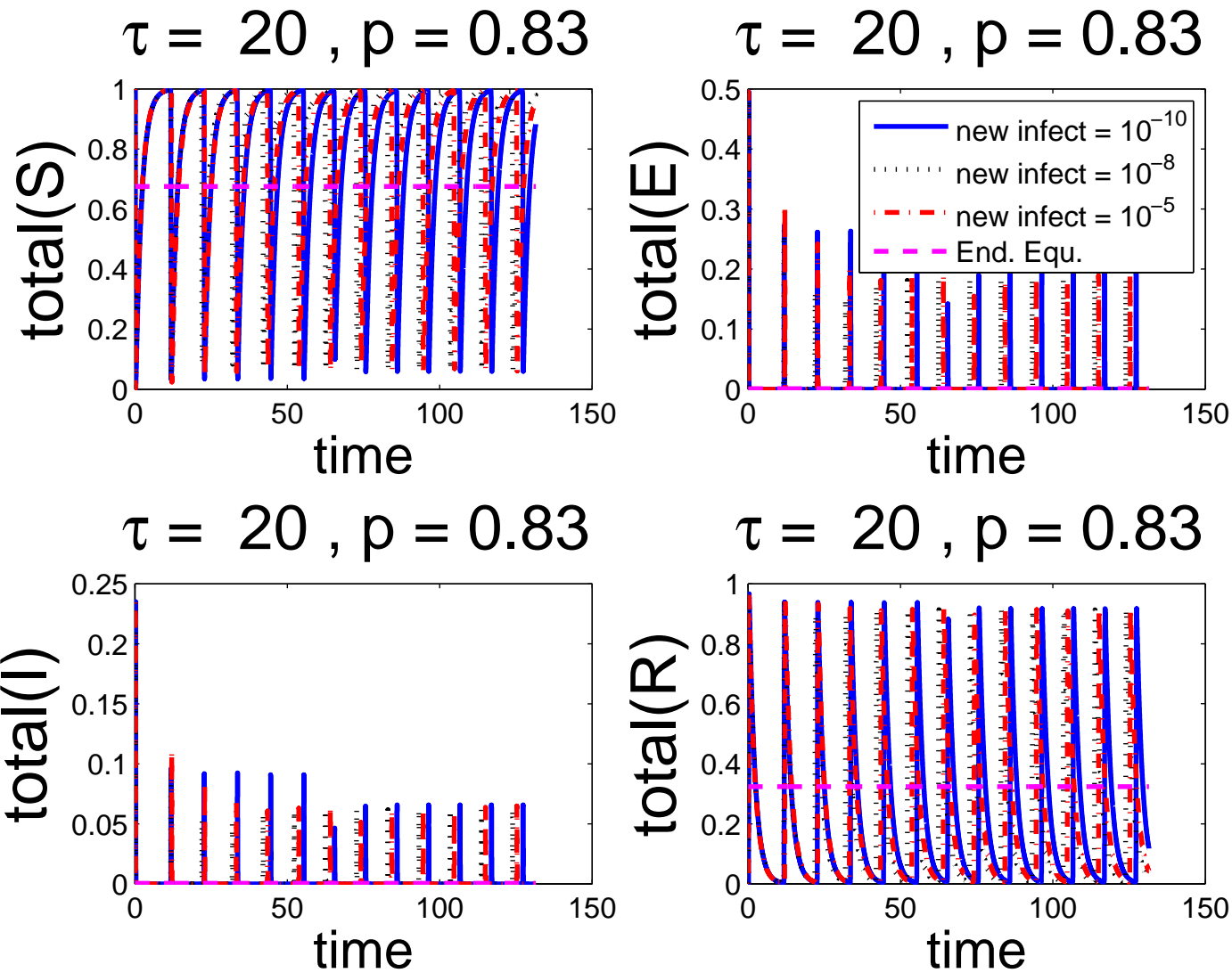
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Numerics for Measles → Bifurcations



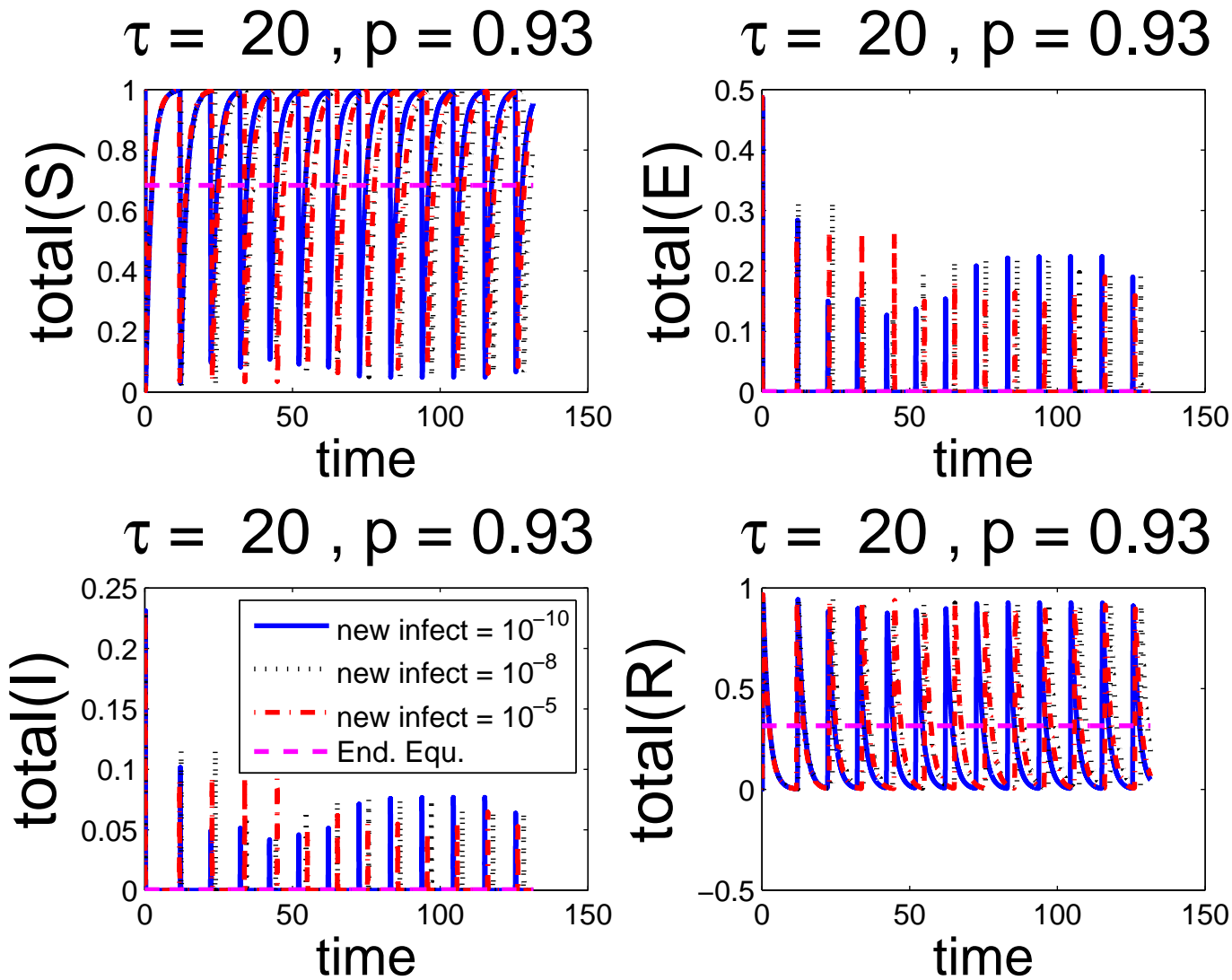
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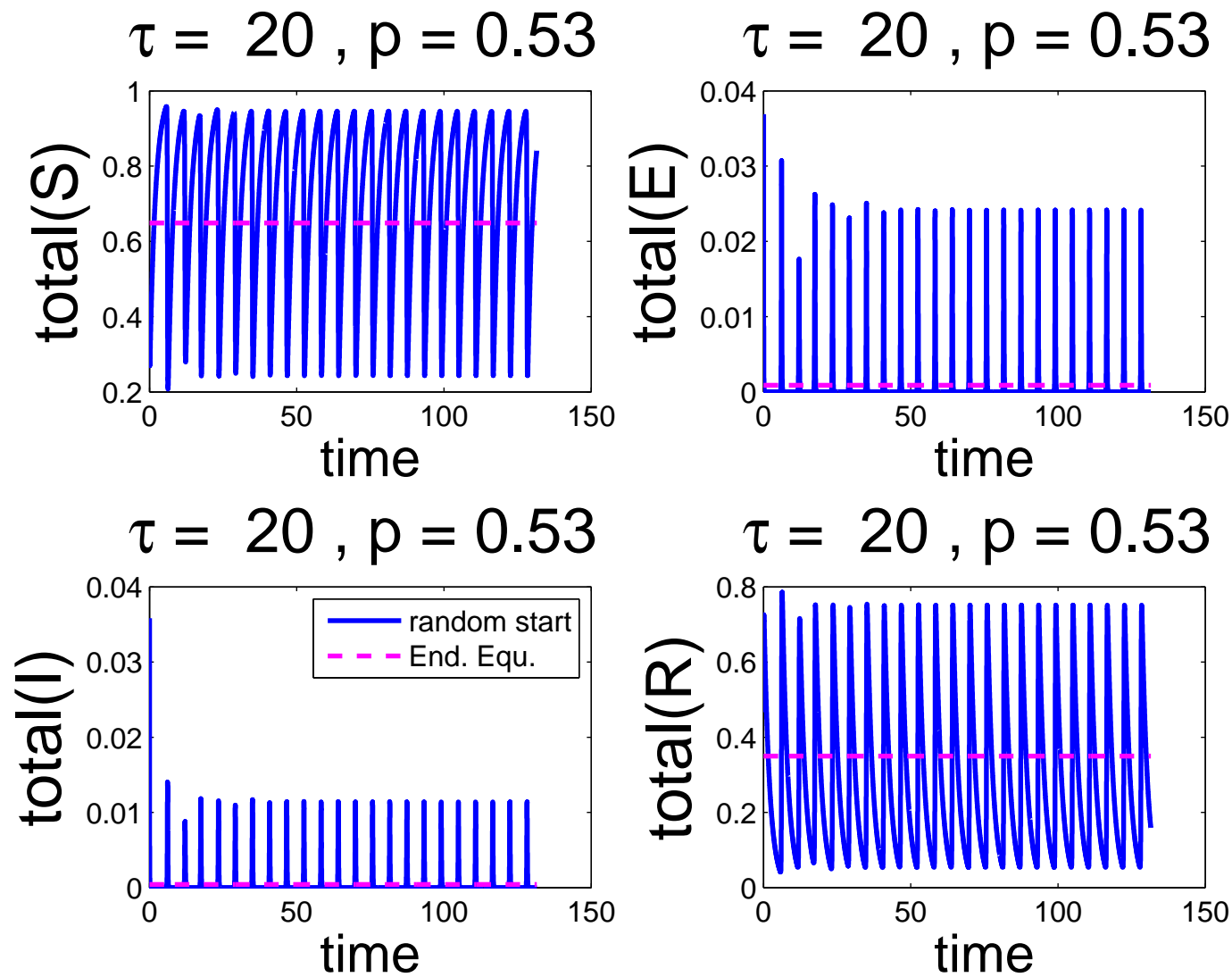
introducing infection into Disease Free Equilibrium

Numerics for Measles \rightarrow Bifurcations



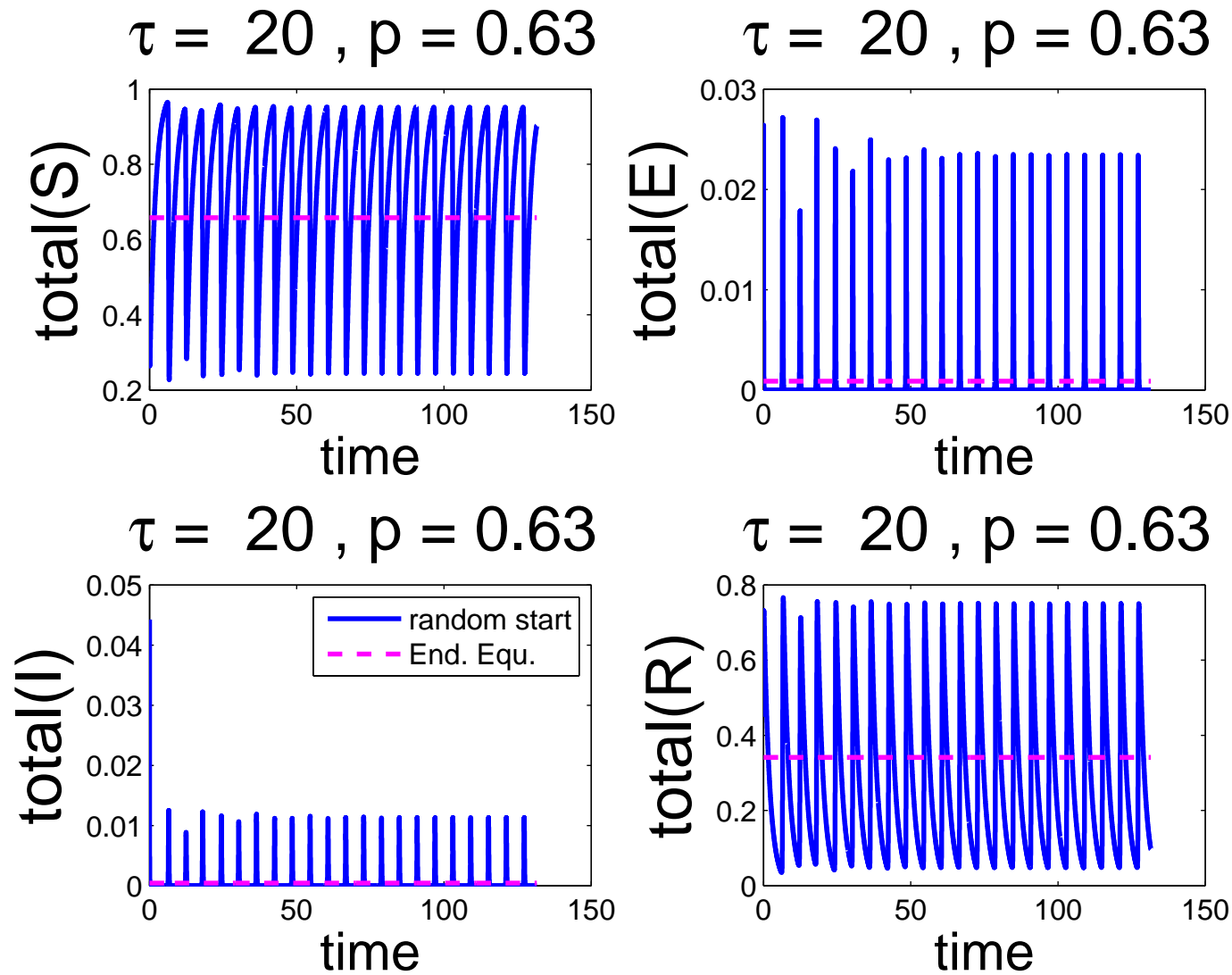
introducing infection into Disease Free Equilibrium

Numerics for Measles \rightarrow Bifurcations



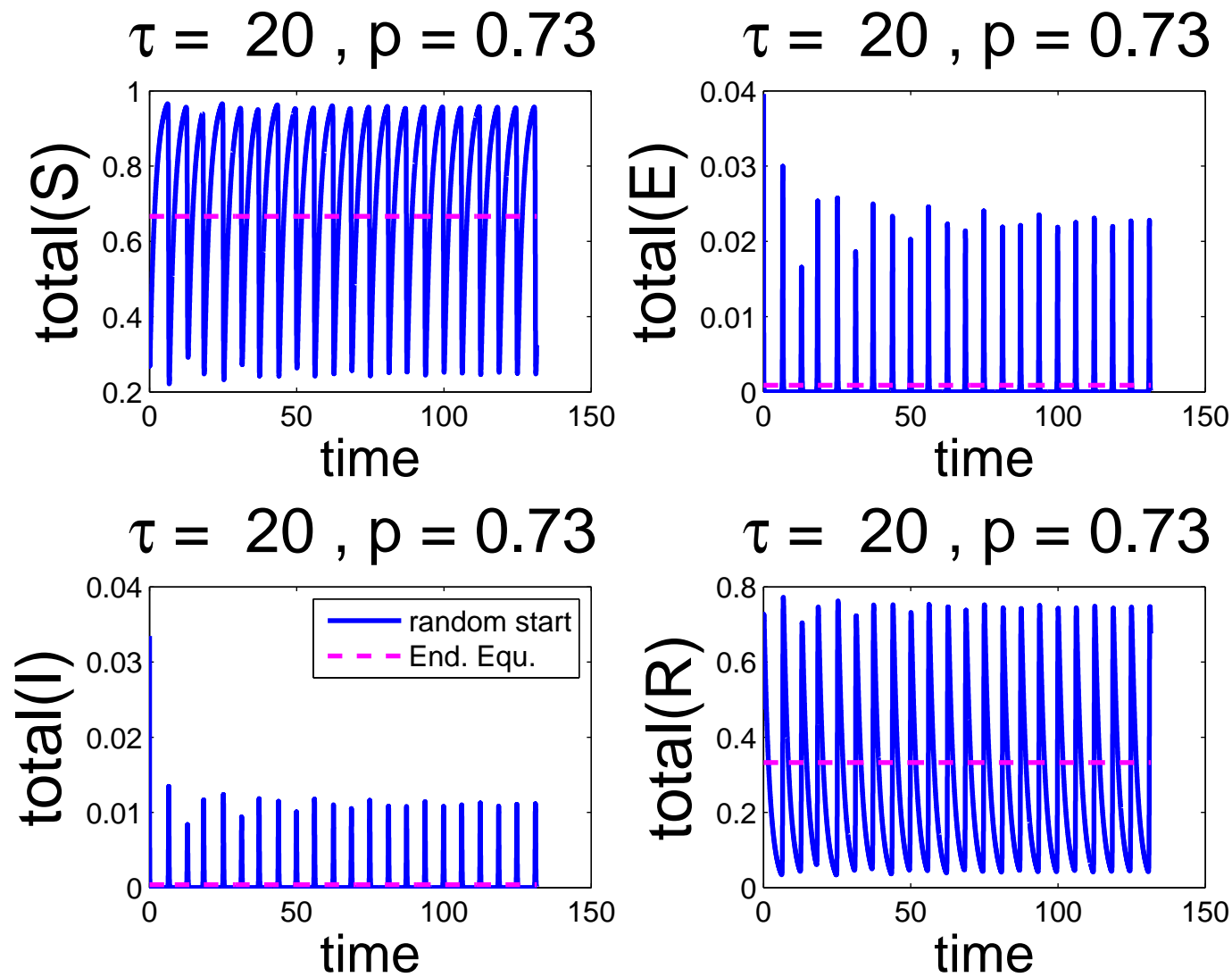
SIMULATING from a RANDOM state

Numerics for Measles \rightarrow Bifurcations



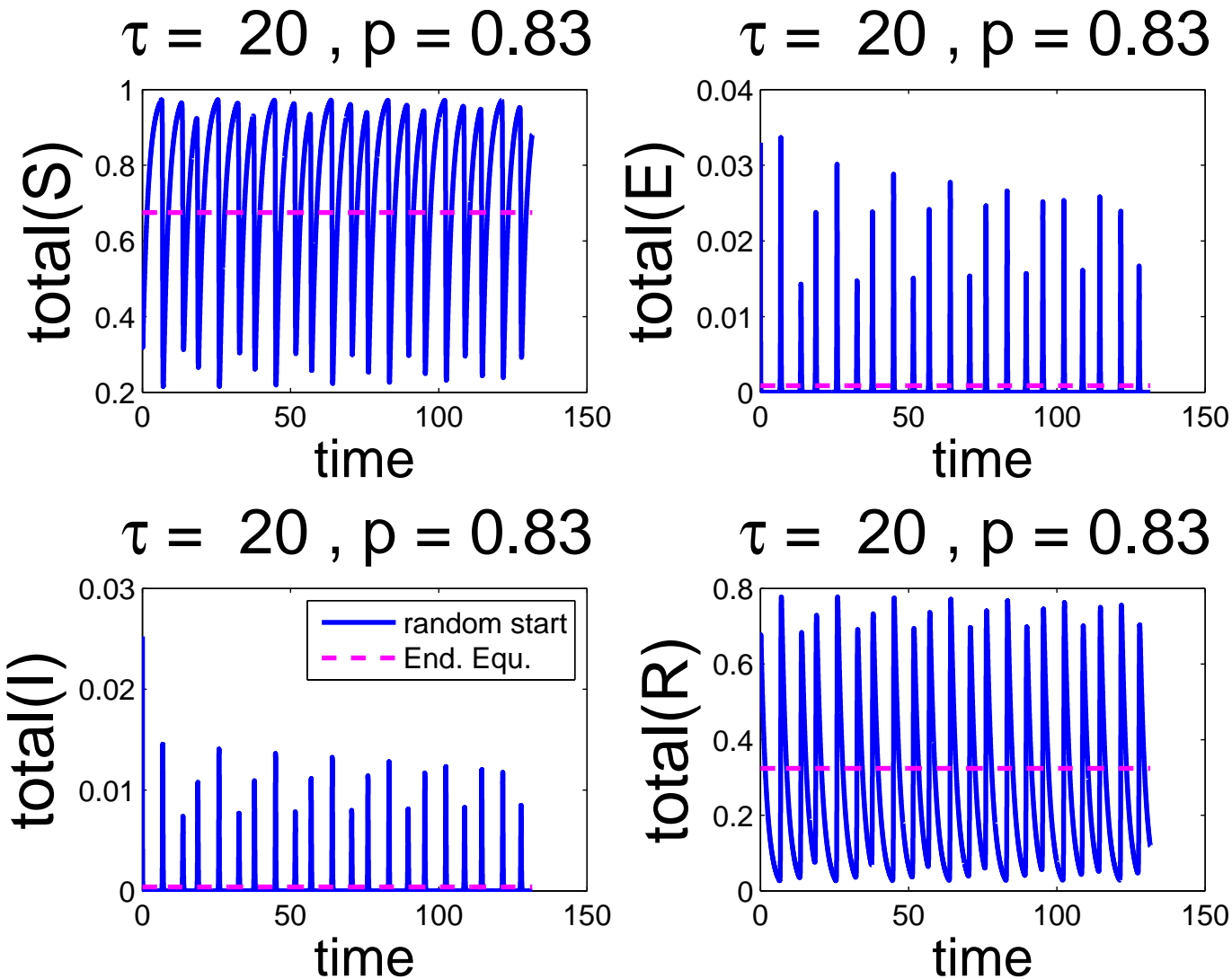
introducing infection into Disease Free Equilibrium

Numerics for Measles \rightarrow Bifurcations



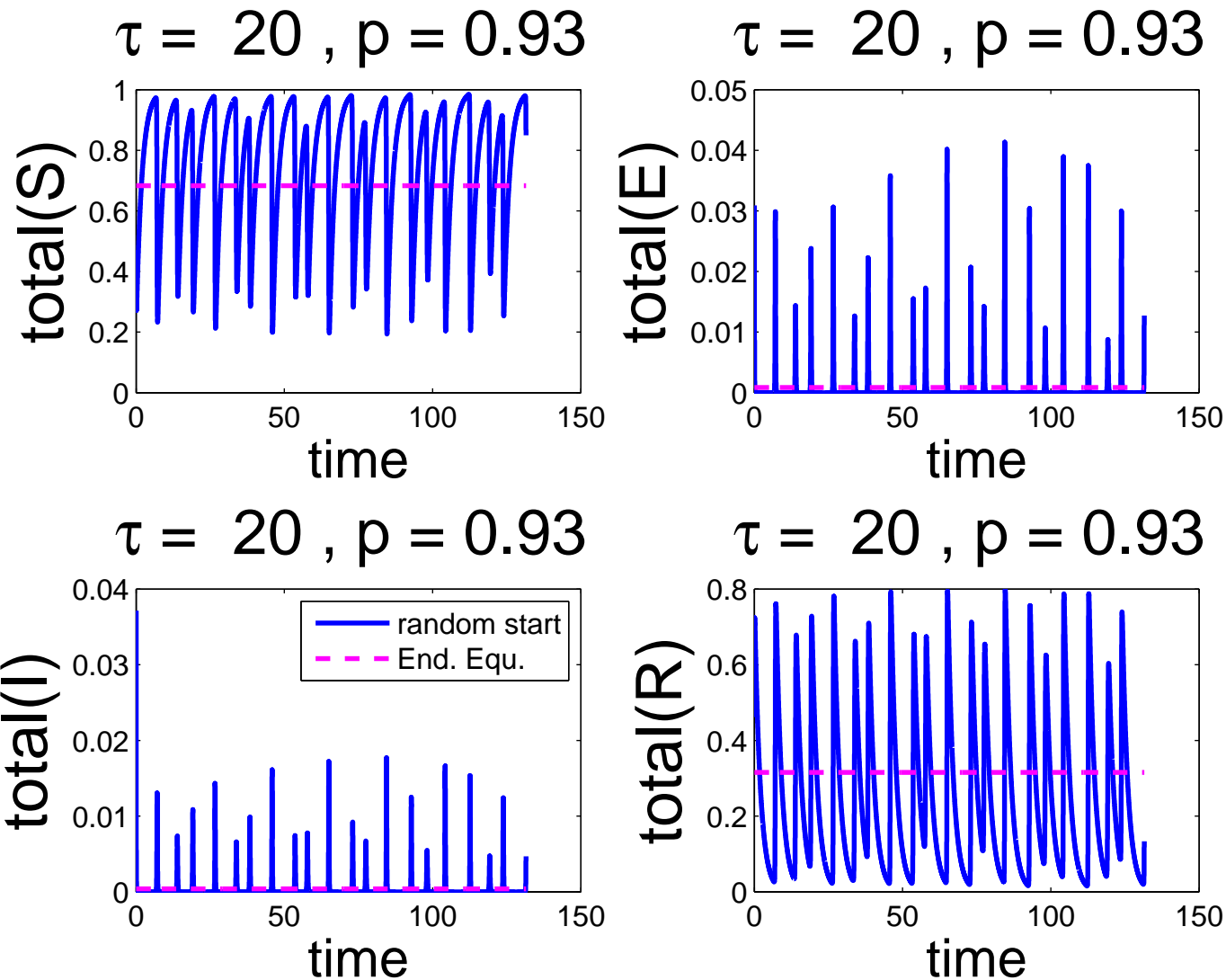
introducing infection into Disease Free Equilibrium

Numerics for Measles \rightarrow Bifurcations



introducing infection into Disease Free Equilibrium

Numerics for Measles \rightarrow Bifurcations



introducing infection into Disease Free Equilibrium

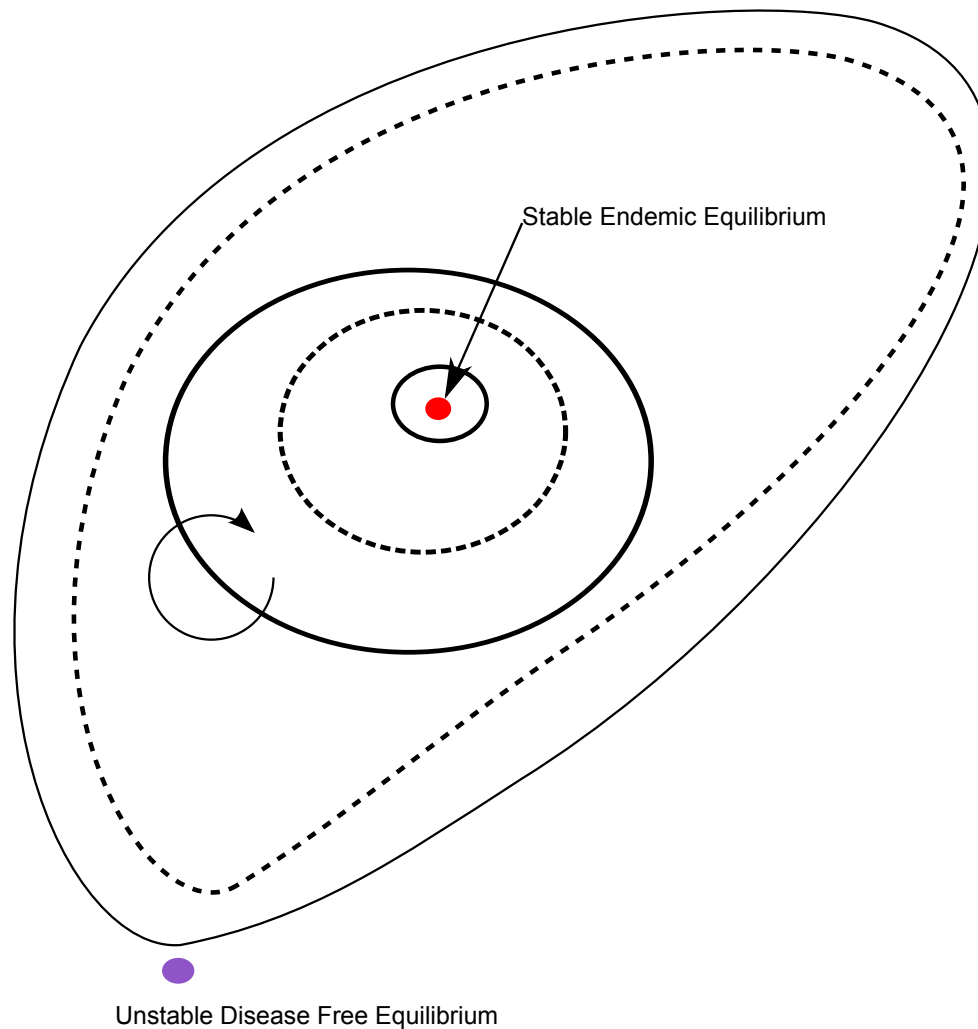
Numerics for Measles → Bifurcations

Question: WHAT HAPPENES to the medium-sized cycle?

SHORT Answer:

- Neimark-Sacker bifurcation happens in the Poincare map of the cycle
- The resulting invariant two-dimensional torus is still stable; however, it loses its strong absorbance in some directions.
- Therefore (almost) inaccessible from Disease Free Equilibrium by introducing new infected individuals.

Numerics for Measles \rightarrow Bifurcations



This is based on strong evidence from numerical simulations and eigenvalue investigation. The middle cycles should be continued, and stable/unstable pair is verified if fold bifurcation of cycles found. Currently there is no numerical method/software that can investigate homoclinic-like cycles for large-scale systems. A combination of analytic and numerical techniques should be developed and used.

Ongoing and Future Work

- Confirm and find exact values for parameters at bifurcations using continuation methods.
- Develop a framework for extraction of underlying low-dimensional dynamics.