Estimating variability in nonlinear & stochastic epidemiological models

An application to the transition from invasion to long-term persistence

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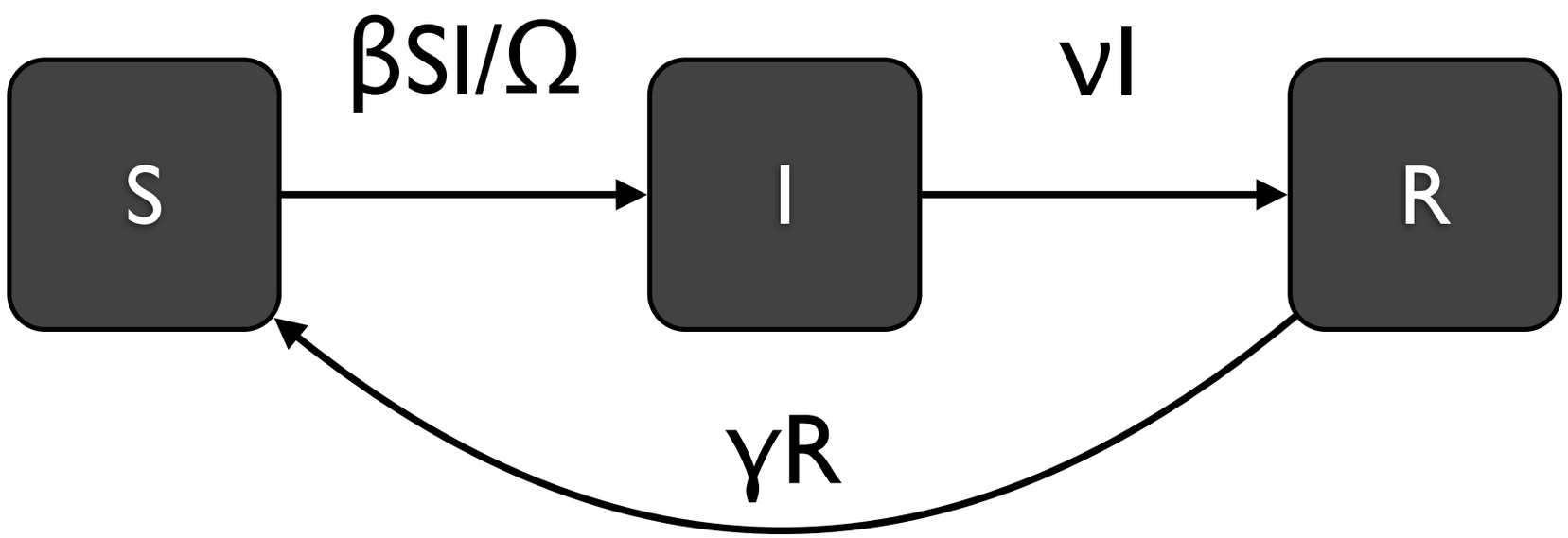
A paradigmatic model

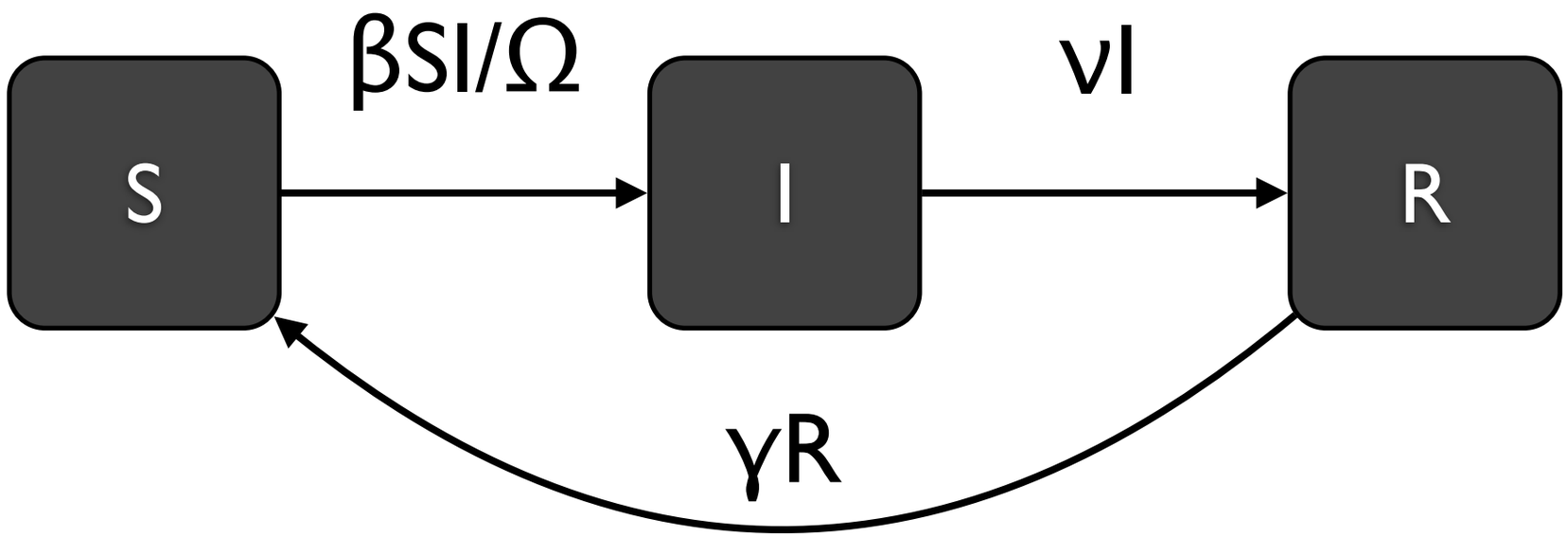


Key quantities:

$R_0 = \beta/\nu$ is the fitness of the pathogen

$1/\gamma$ is the mean duration of immunity

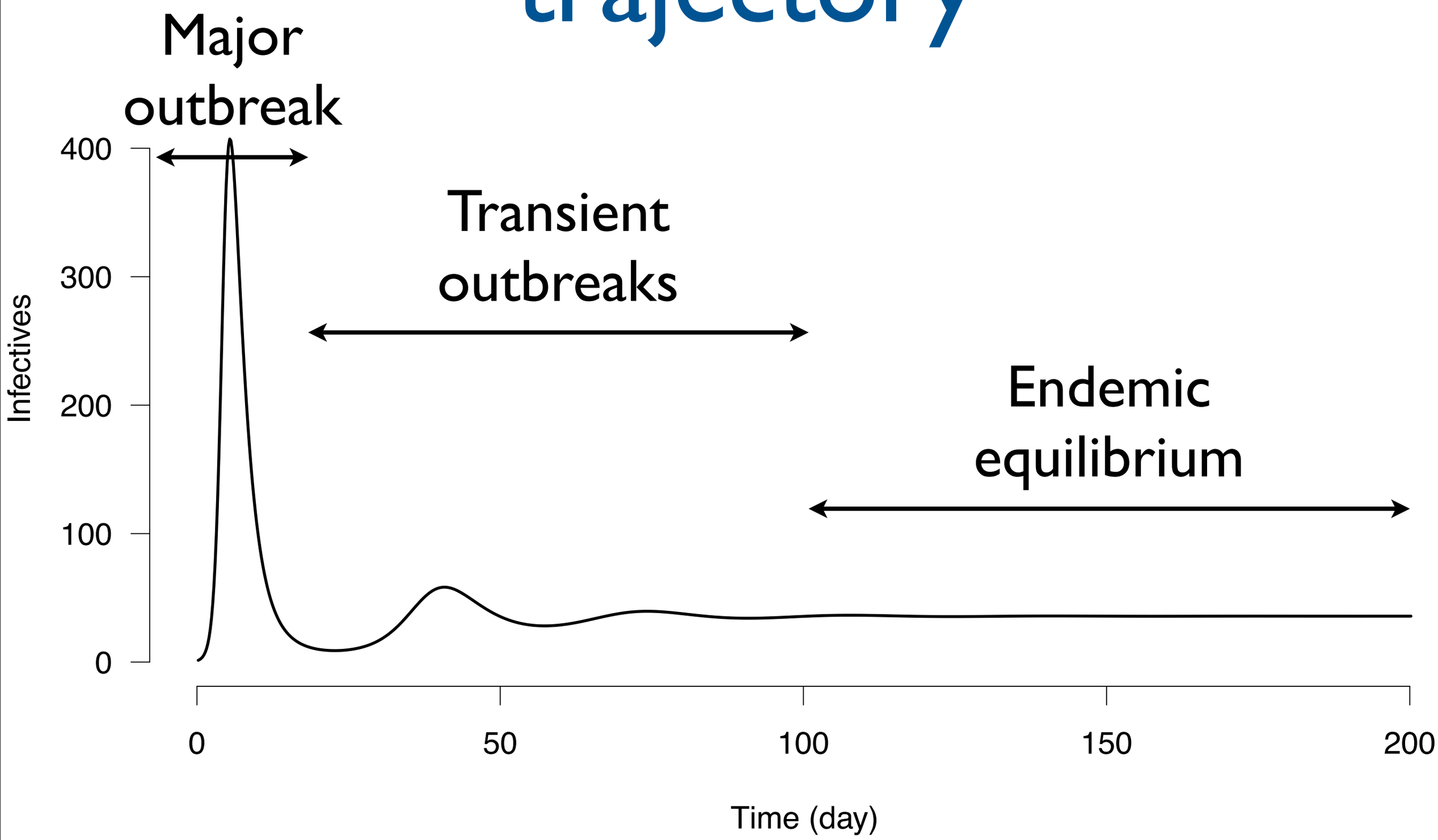
A paradigmatic model



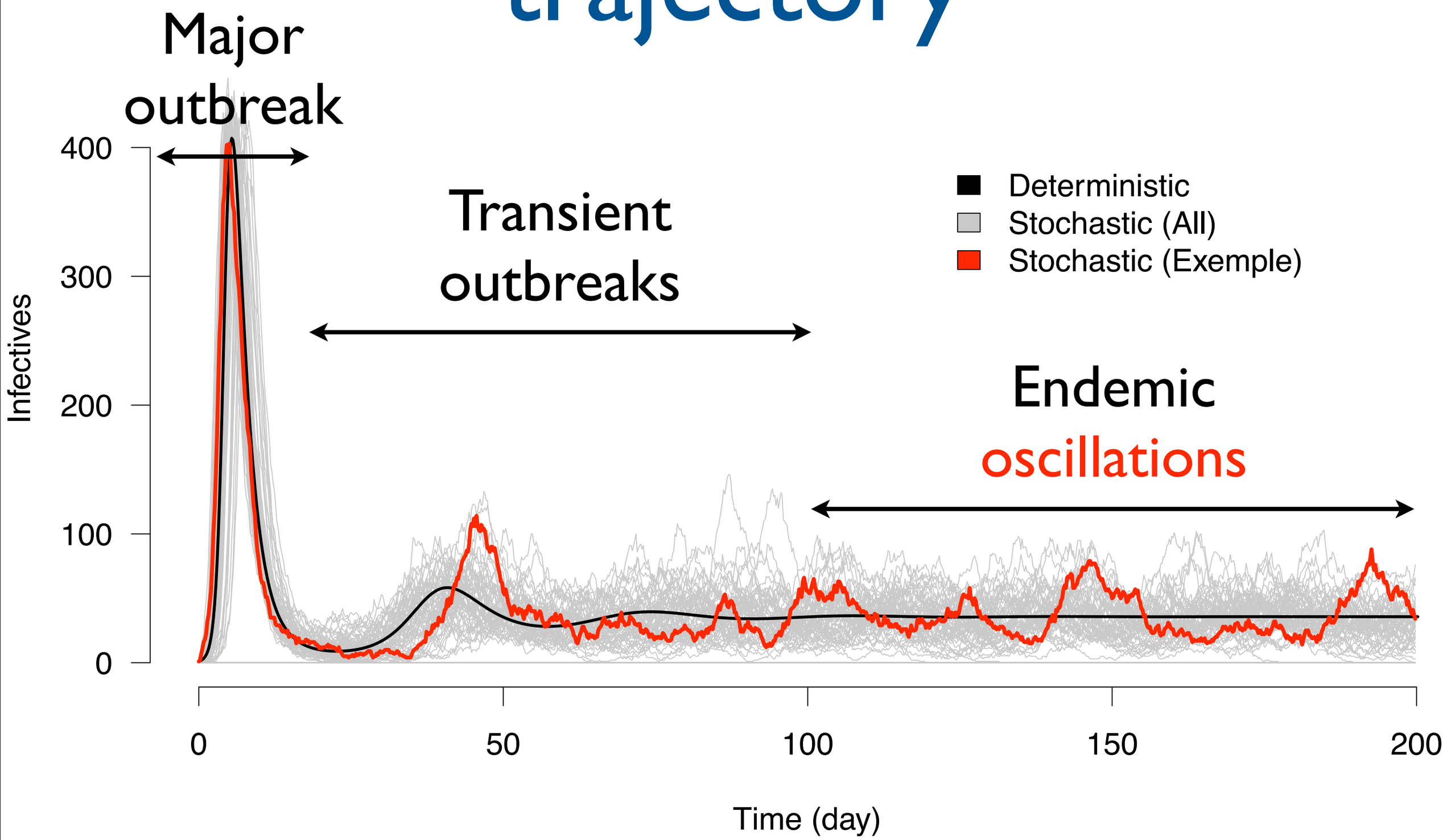
Basic assumptions:
Closed population
Homogeneous mixing
Exponential durations

Improve realism:
Latent period, seasonal forcing, gamma durations, heterogeneous mixing etc.

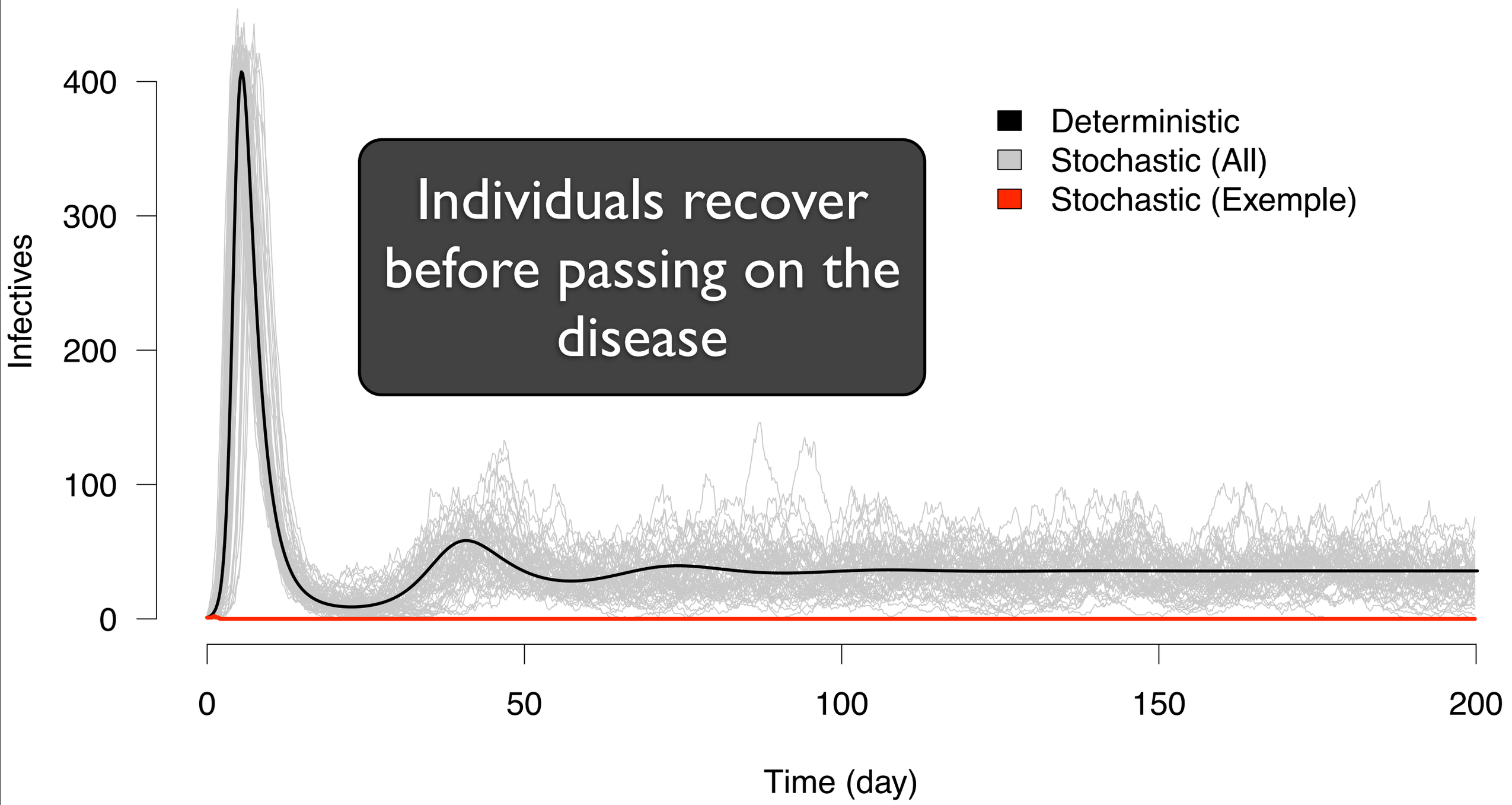
Deterministic trajectory



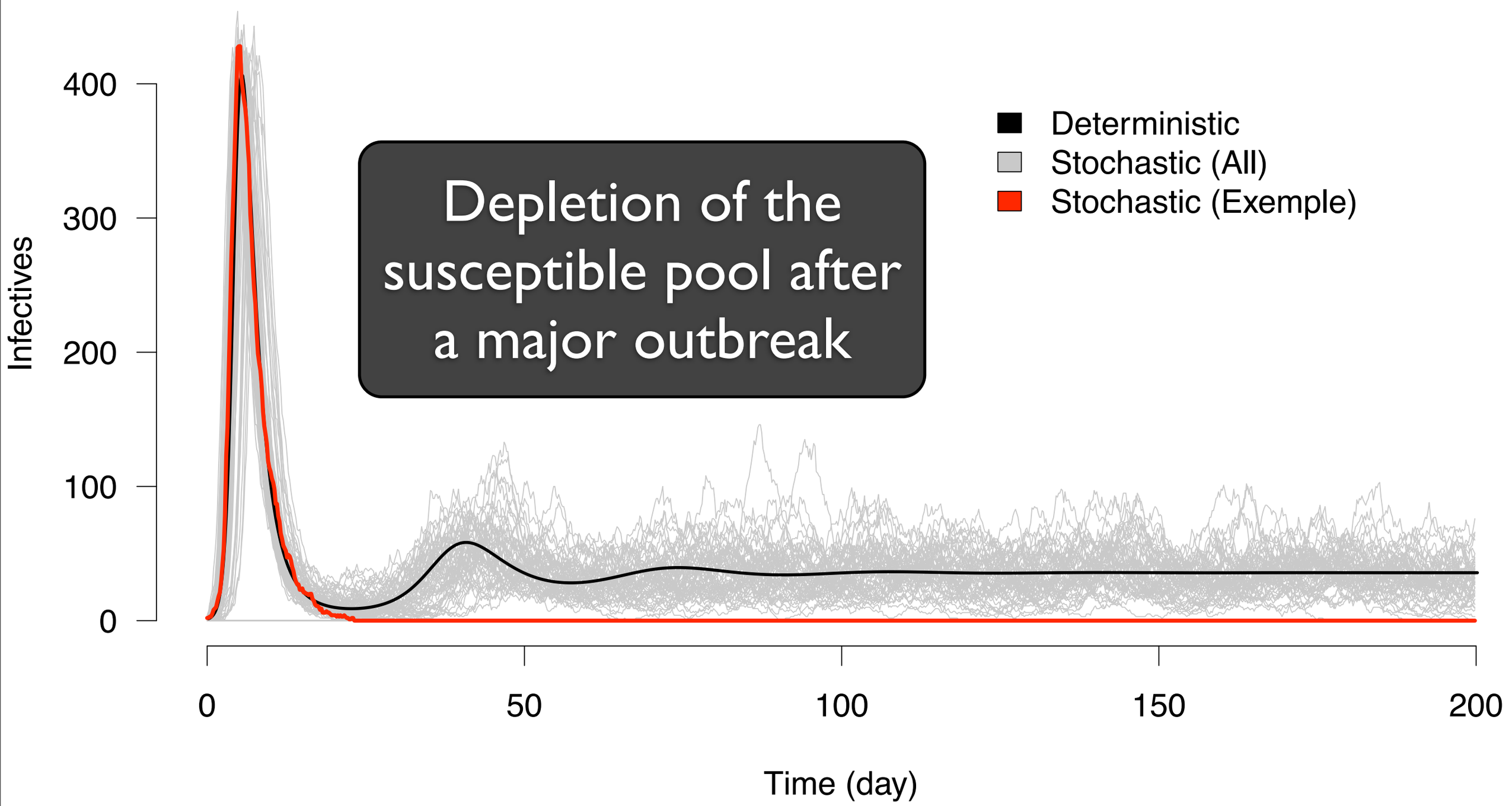
Typical stochastic trajectory



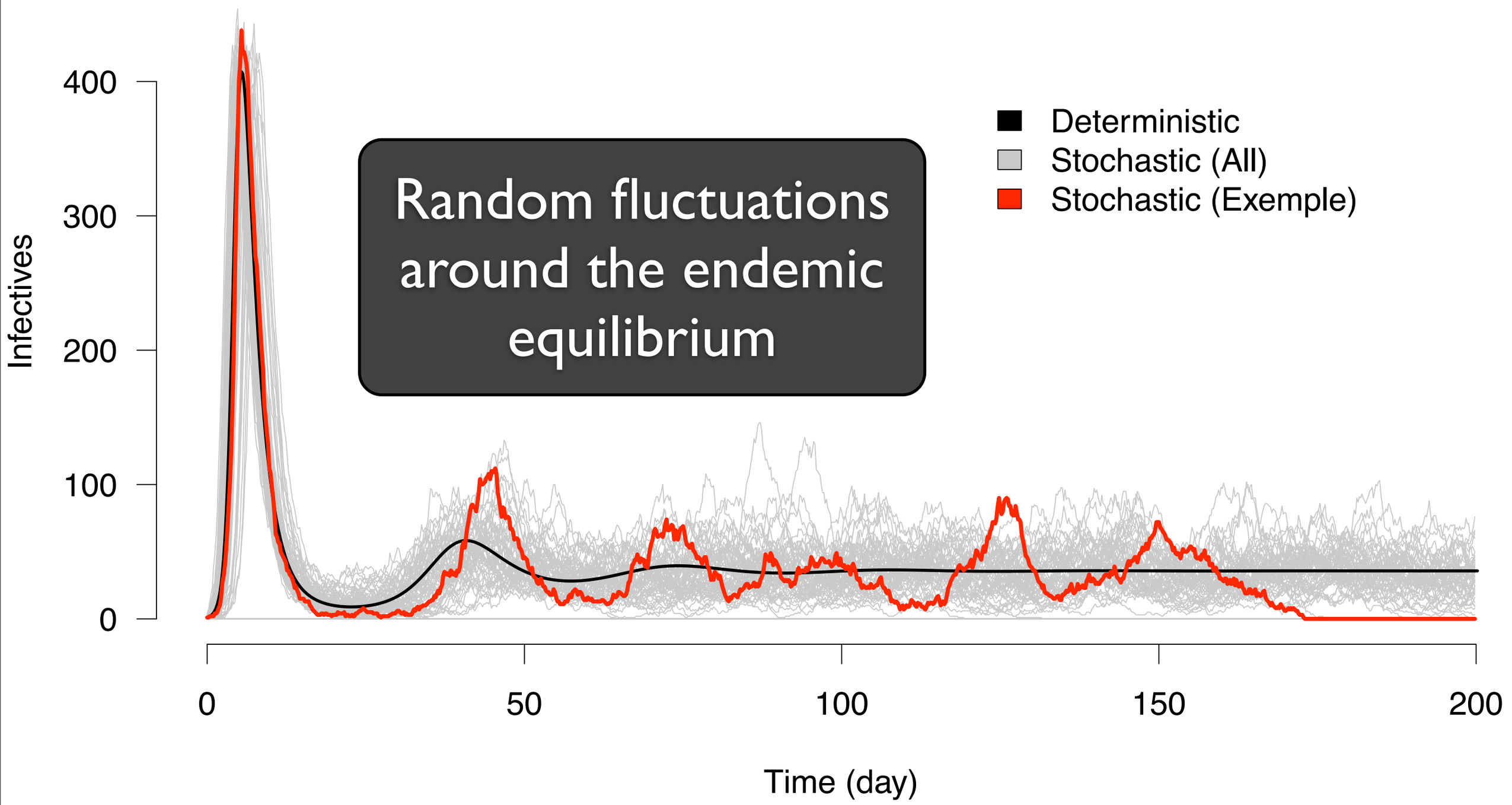
Stochastic extinctions (1/3)
Failed invasion



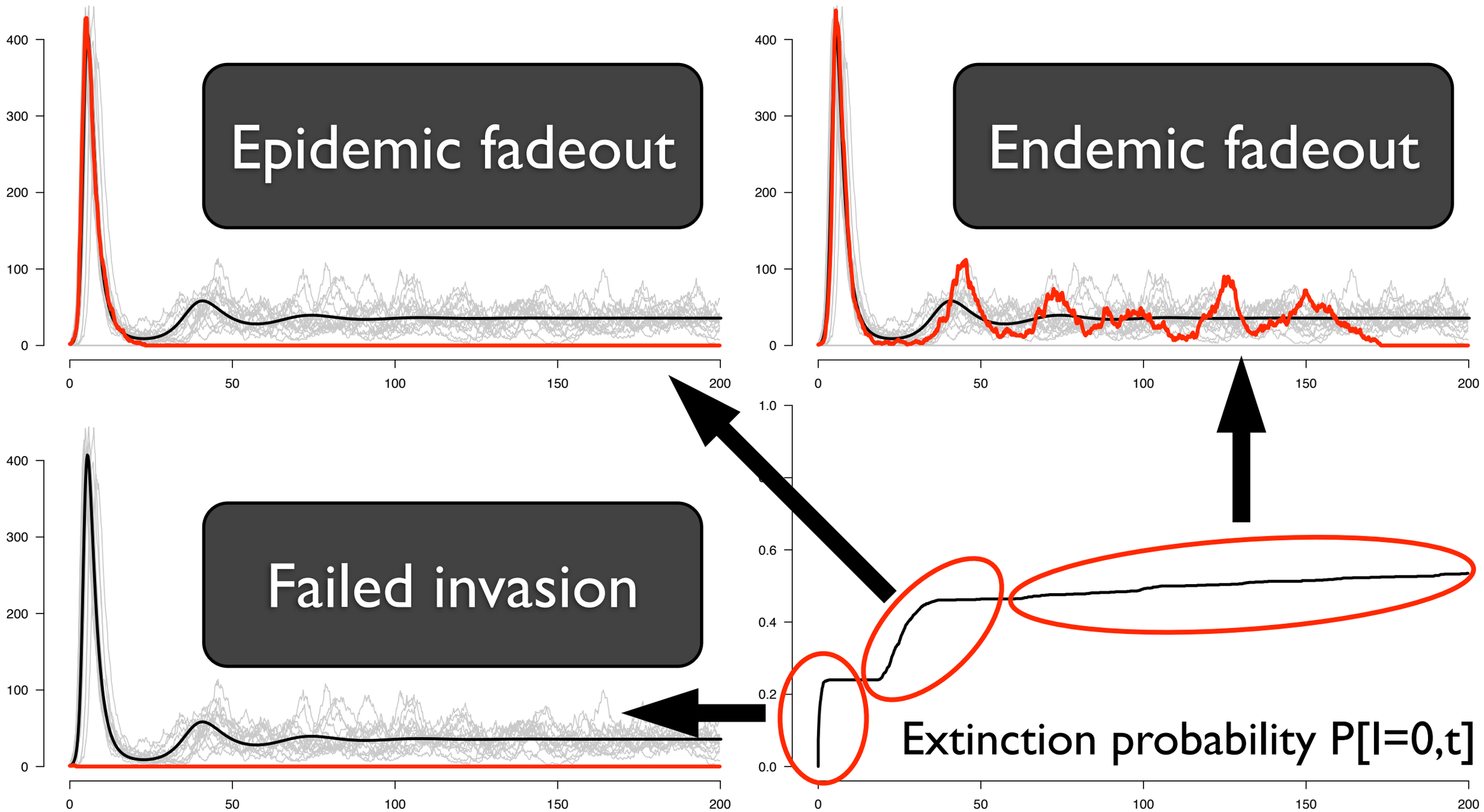
Stochastic extinction (2/3)
Epidemic fade-out



Stochastic extinction (3/3)
Endemic fade-out



Quantitative characterization of the dynamics (1/2): Monte-Carlo



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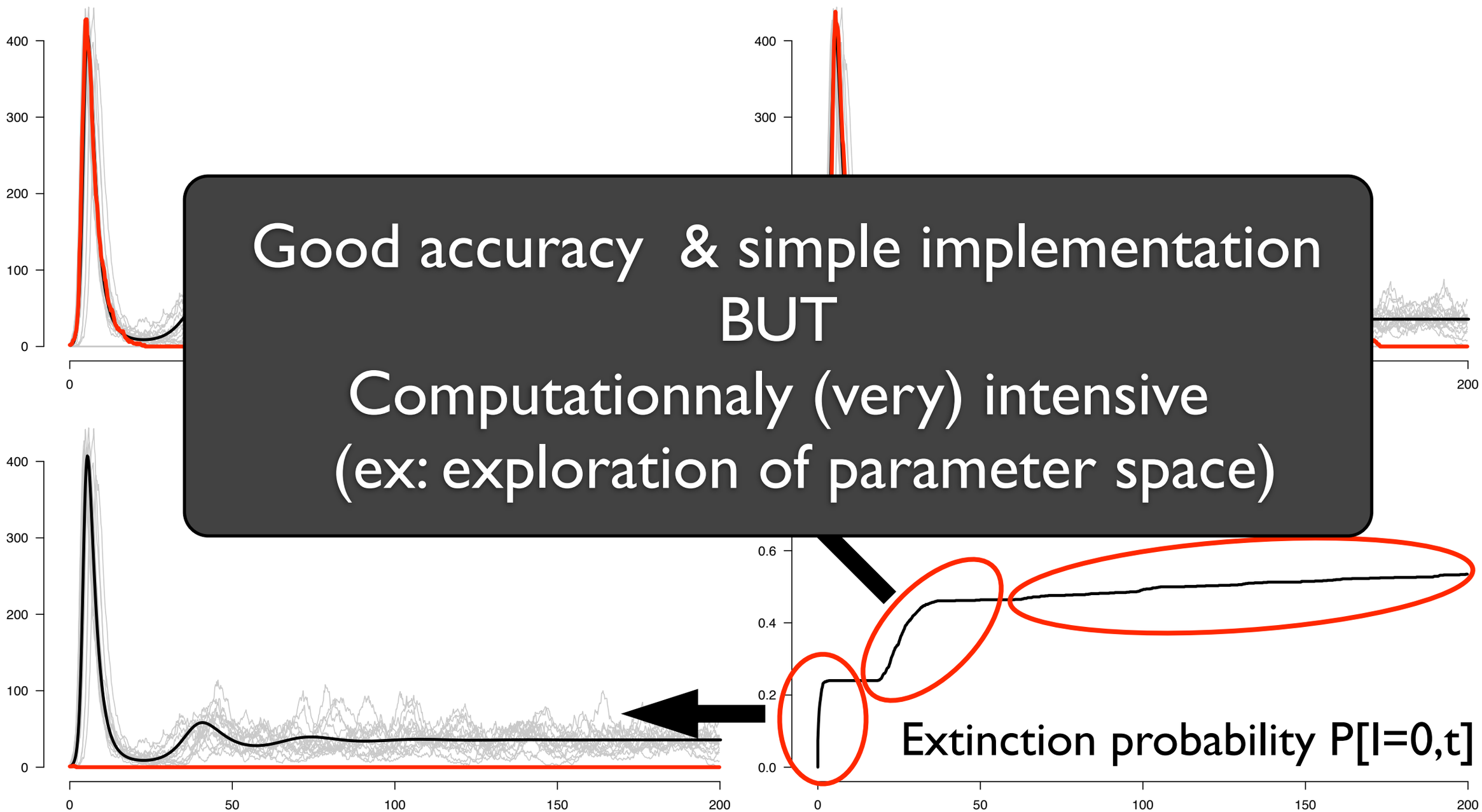
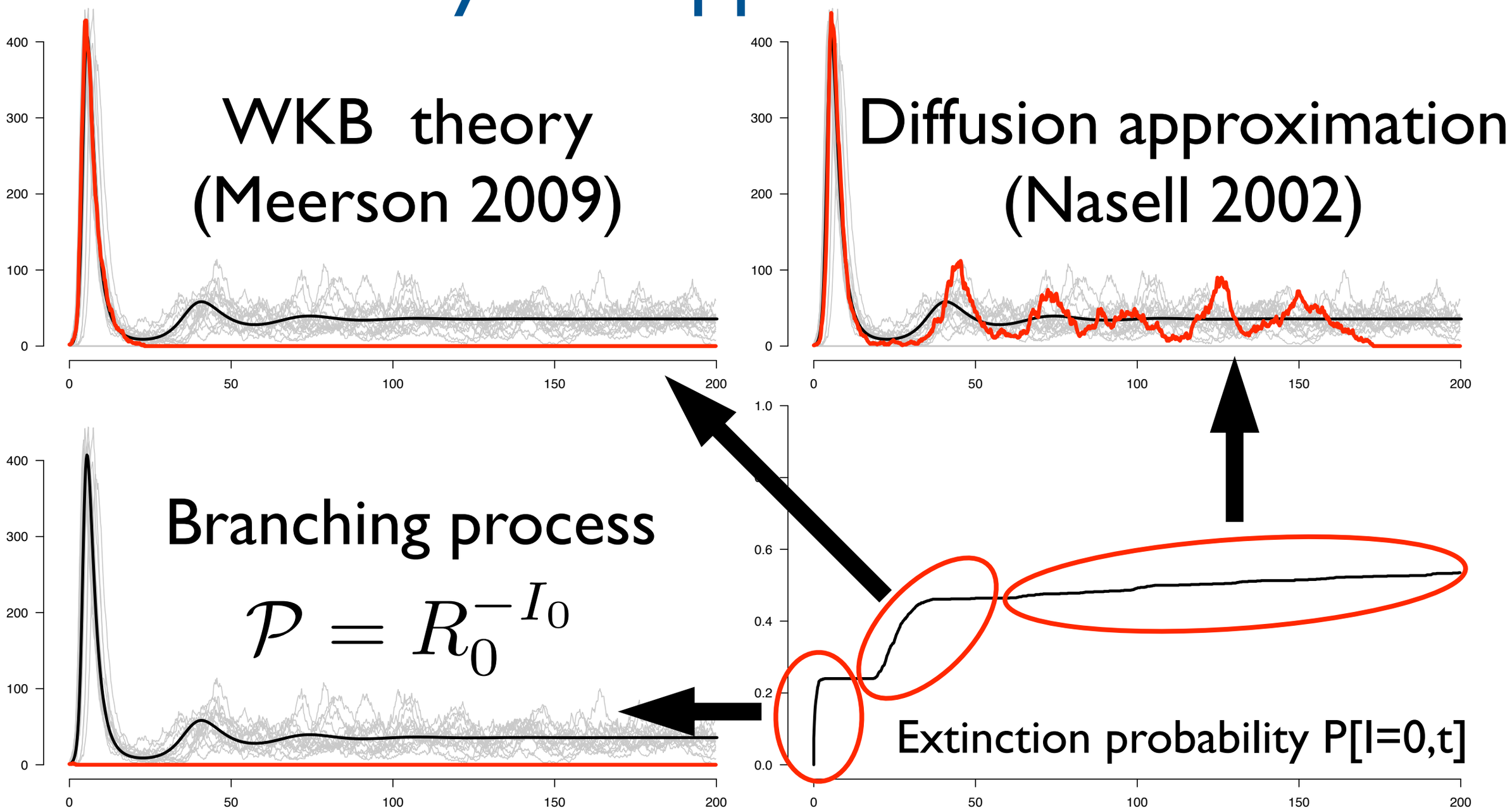
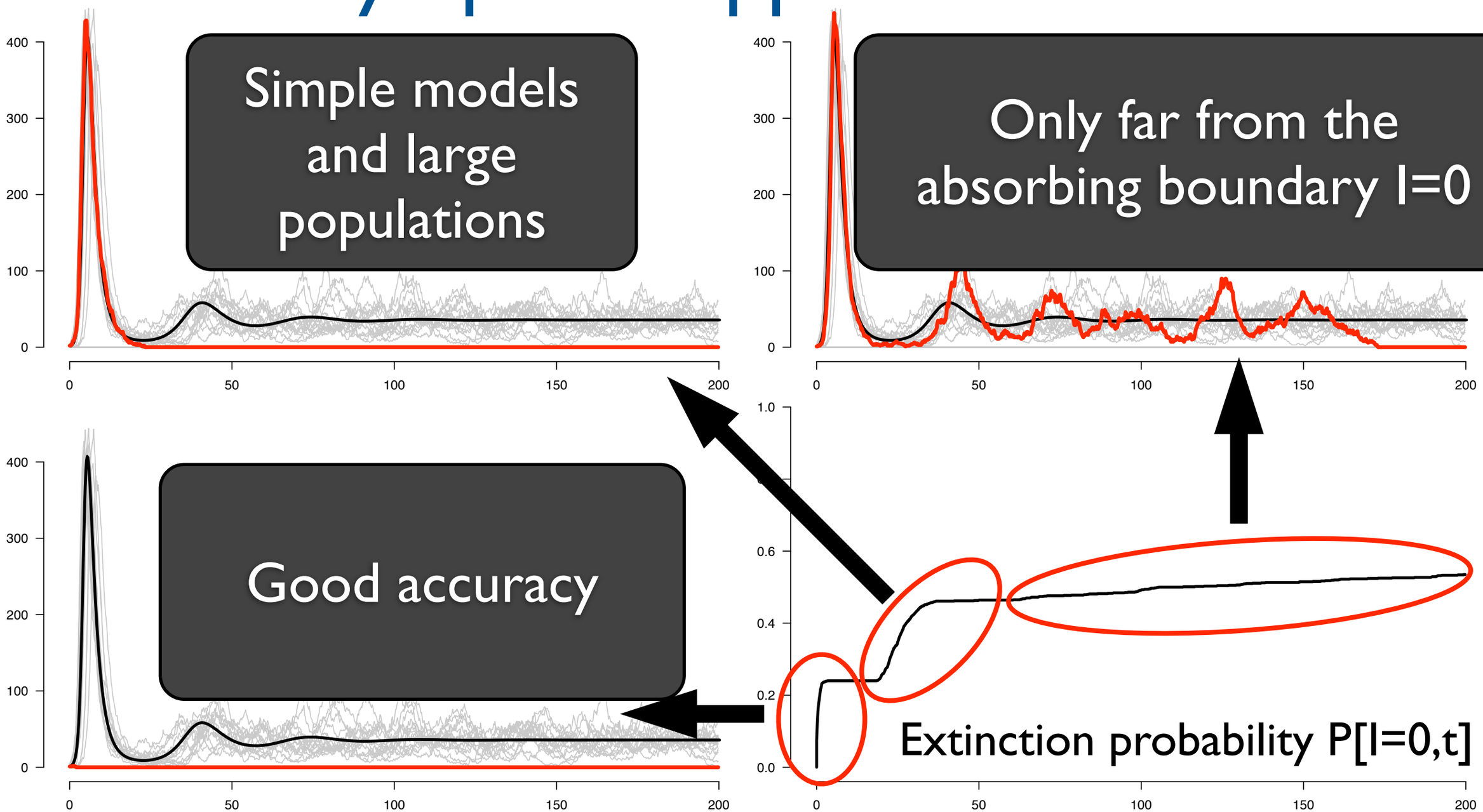


Good accuracy & simple implementation
BUT
Computationnaly (very) intensive
(ex: exploration of parameter space)

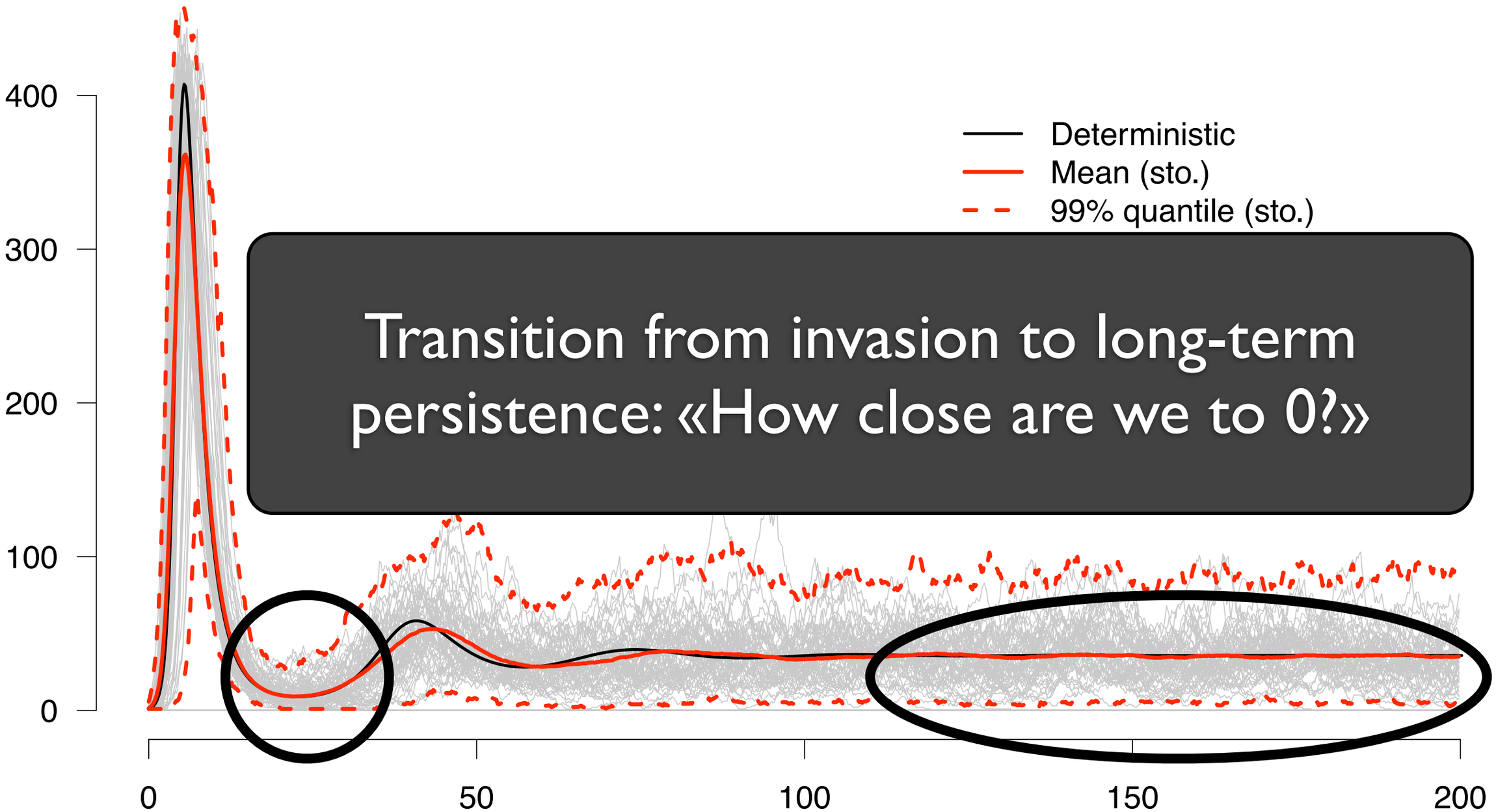
Quantitative characterization of the dynamics (2/2): Analytical approximations



Quantitative characterization of the dynamics (2/2): Asymptotic approximations

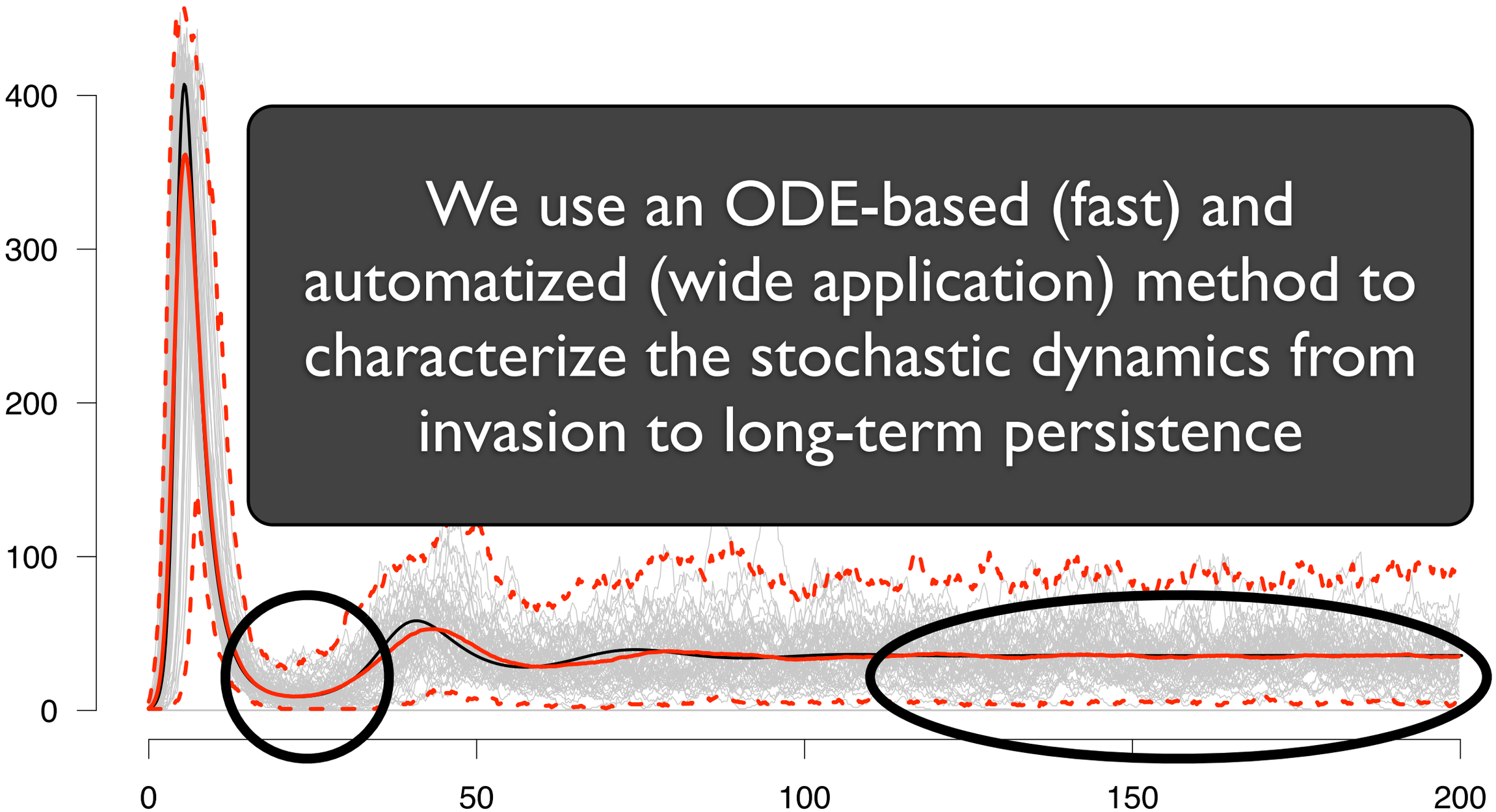


Qualitative characterization of the dynamics: basic idea



Transition from invasion to long-term persistence: «How close are we to 0?»

Qualitative characterization of the dynamics: basic idea



We use an ODE-based (fast) and automatized (wide application) method to characterize the stochastic dynamics from invasion to long-term persistence

Master equation

$$\boxed{S + I \xrightarrow{\beta \frac{SI}{\Omega}} 2I \qquad I \xrightarrow{\nu I} R \qquad R \xrightarrow{\gamma R} S}$$

$$\begin{aligned}
\frac{d}{dt}P(S,I,R,t) \quad = \quad & \beta(S+1)\frac{I-1}{\Omega}P(S+1,I-1,R,t) \\
& +\nu(I+1)P(S,I+1,R-1,t) \\
& +\gamma(R+1)P(S-1,I,R+1,t) \\
& -\left(\beta S\frac{I}{\Omega} + \nu I + \gamma R\right)P(S,I,R,t)
\end{aligned}$$

Cannot be solved analytically due to nonlinearity of the contact process

Notations

$$S + I \xrightarrow{\beta \frac{SI}{\Omega}} 2I \qquad I \xrightarrow{\nu I} R \qquad R \xrightarrow{\gamma R} S$$

Species vector (size: N)

$$\mathbf{X} := \begin{bmatrix} S \\ I \\ R \end{bmatrix} = \Omega \begin{bmatrix} S/\Omega \\ I/\Omega \\ R/\Omega \end{bmatrix} = \Omega \begin{bmatrix} s \\ i \\ r \end{bmatrix} = \Omega \mathbf{x}$$

Propensity function vector (size: M)

$$\begin{bmatrix} \beta \frac{SI}{\Omega} \\ \nu I \\ \gamma R \end{bmatrix} = \Omega \begin{bmatrix} \beta si \\ \nu i \\ \gamma r \end{bmatrix} = \Omega \mathbf{f}(\mathbf{x})$$

Stoichiometric matrix (size: NxM)

$$\mathbb{S} := \begin{bmatrix} -1 & 0 & +1 \\ +1 & -1 & 0 \\ 0 & +1 & -1 \end{bmatrix}$$

Linear Noise Approximation

We define:

$$\phi = \lim_{\Omega \to \infty} \mathbf{x}$$

and assume:

$$\mathbf{X} = \Omega\phi + \sqrt{\Omega}\xi$$

Following a Taylor expansion of the ME in powers of $1/\sqrt{\Omega}$, we find at the next to leading order:

$$\frac{d}{dt}\phi = \mathbb{S}\mathbf{f}(\phi) \qquad \xi \hookrightarrow \mathcal{N}(0, \Xi) \qquad \frac{d}{dt}\Xi = \mathbb{A}\Xi + \Xi\,\mathbb{A}^T + \mathbb{B}$$

with:

$$\Xi = \langle \xi\xi^T \rangle \quad \mathbb{A} = \frac{d}{d\phi}\mathbb{S}\mathbf{f}(\phi) \quad \mathbb{B} = \mathbb{S}\; diag(\mathbf{f}(\phi))\; \mathbb{S}^T$$

«How close are we to 0?»

Since $I_t = \Omega\phi_2(t) + \sqrt{\Omega}\xi_2$ we have:

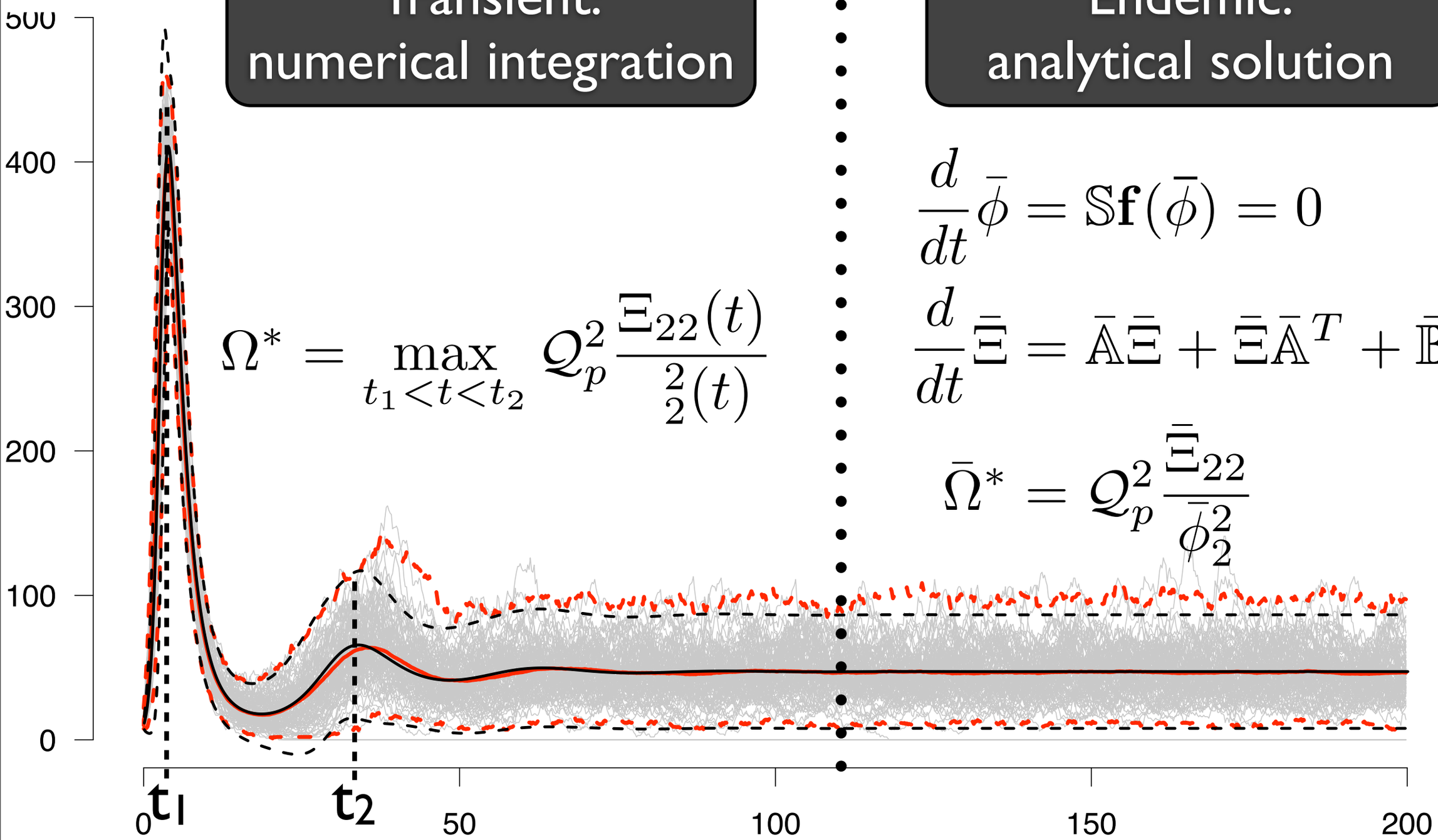
$$I_t \hookrightarrow \mathcal{N}\Big(\Omega\phi_2(t), \Omega\Xi_{22}(t)\Big)$$

We define: $I_t^* = \Omega\phi_2(t) - \mathcal{Q}_p\sqrt{\Omega\Xi_{22}(t)}$ as the lower bound of the p-quantile of the distribution. In practice we choose $p = 99\%$ and thus $\mathcal{Q}_{99\%} \approx 2.6$

We neglect the extinction probability whenever $I_t^* > 0$ and simply define the critical population size at time t, Ω_t^*, such that $I_t^* = 0$

$$\boxed{I_t^* = 0 \Leftrightarrow \Omega_t^* = \mathcal{Q}_p^2 \frac{\Xi_{22}(t)}{\phi_2^2(t)}}$$

«How close are we to 0?»



Transient:
numerical integration

$$\Omega^* = \max_{t_1<t<t_2} \mathcal{Q}_p^2 \frac{\Xi_{22}(t)}{\phi_2^2(t)}$$

Endemic:
analytical solution

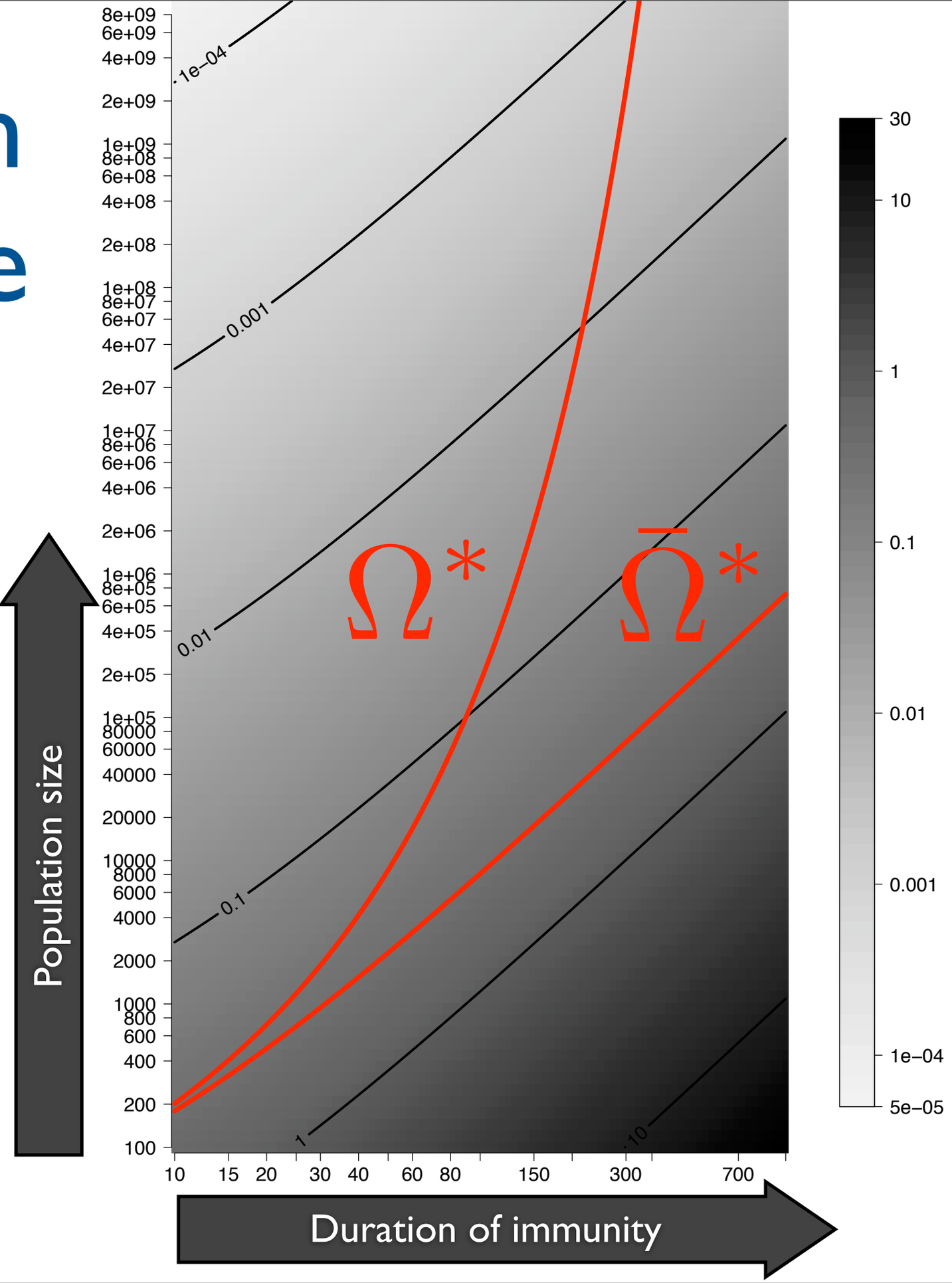
$$\frac{d}{dt}\bar{\phi} = \mathbb{S}\mathbf{f}(\bar{\phi}) = 0$$

$$\frac{d}{dt}\bar{\Xi} = \bar{\mathbb{A}}\bar{\Xi} + \bar{\Xi}\bar{\mathbb{A}}^T + \bar{\mathbb{B}} = 0$$

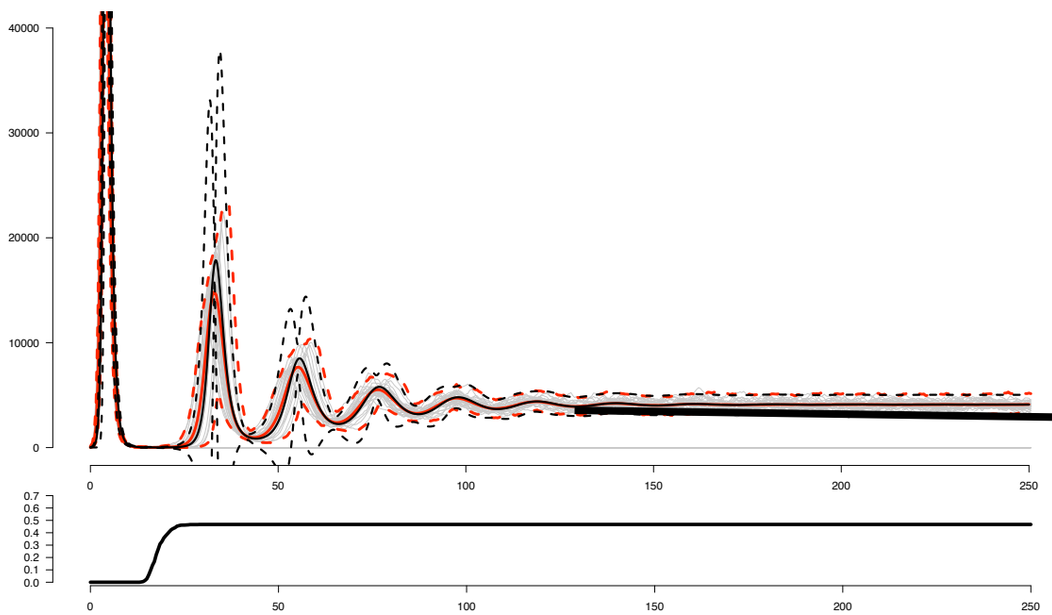
$$\bar{\Omega}^* = \mathcal{Q}_p^2 \frac{\bar{\Xi}_{22}}{\bar{\phi}_2^2}$$

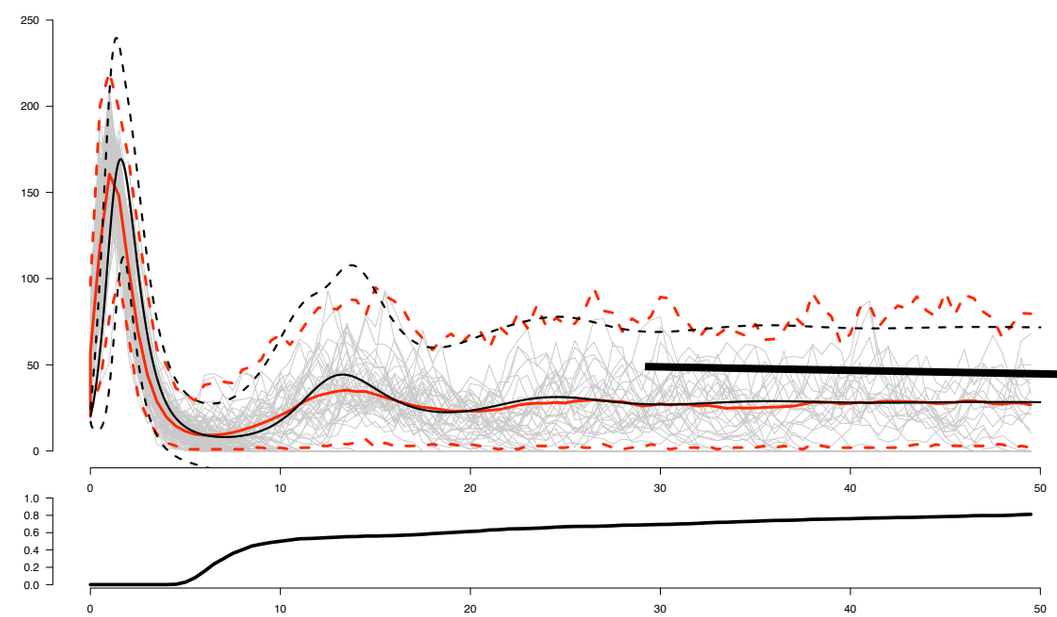
From invasion to persistence

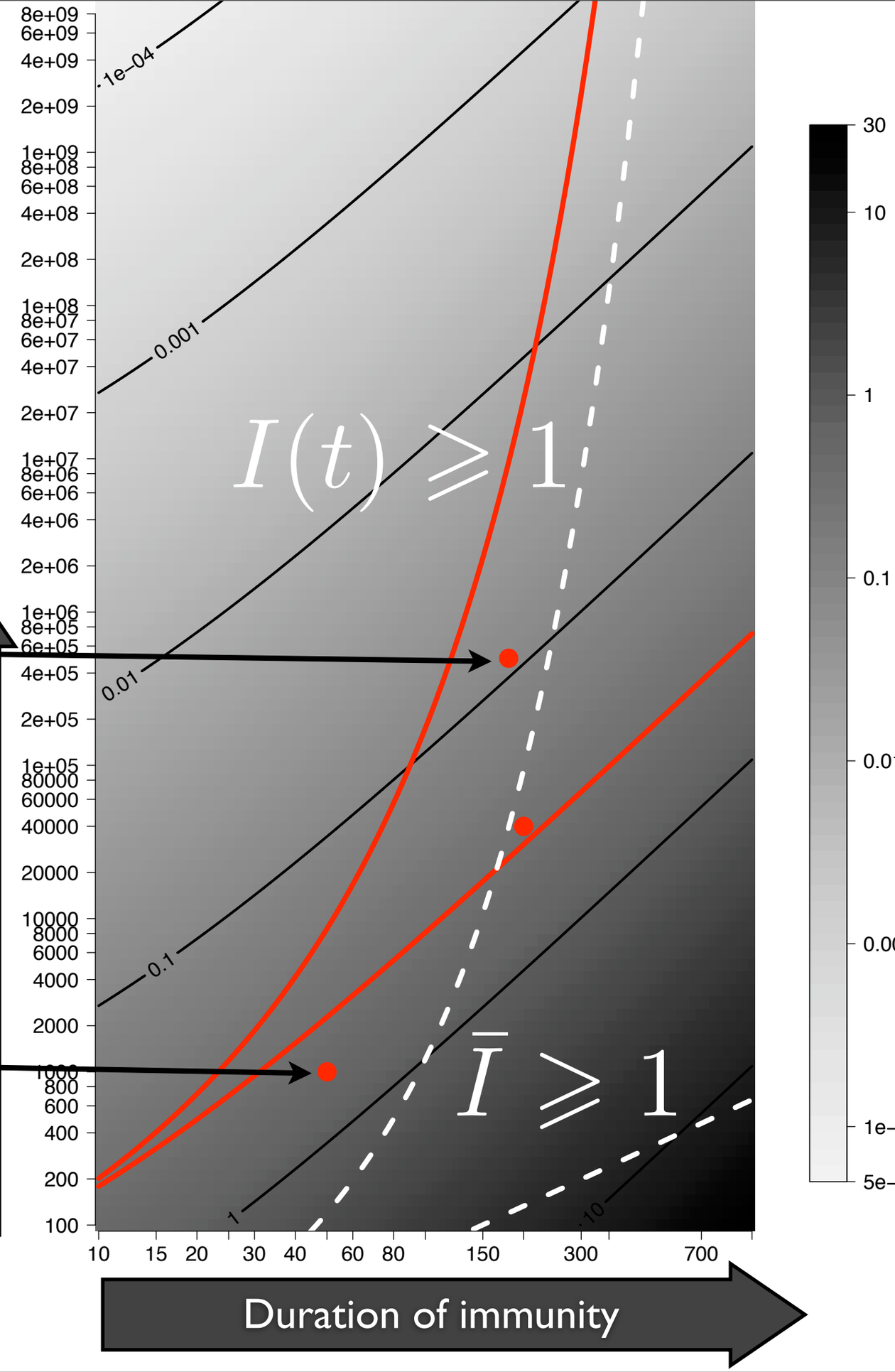
3 different qualitative outcomes

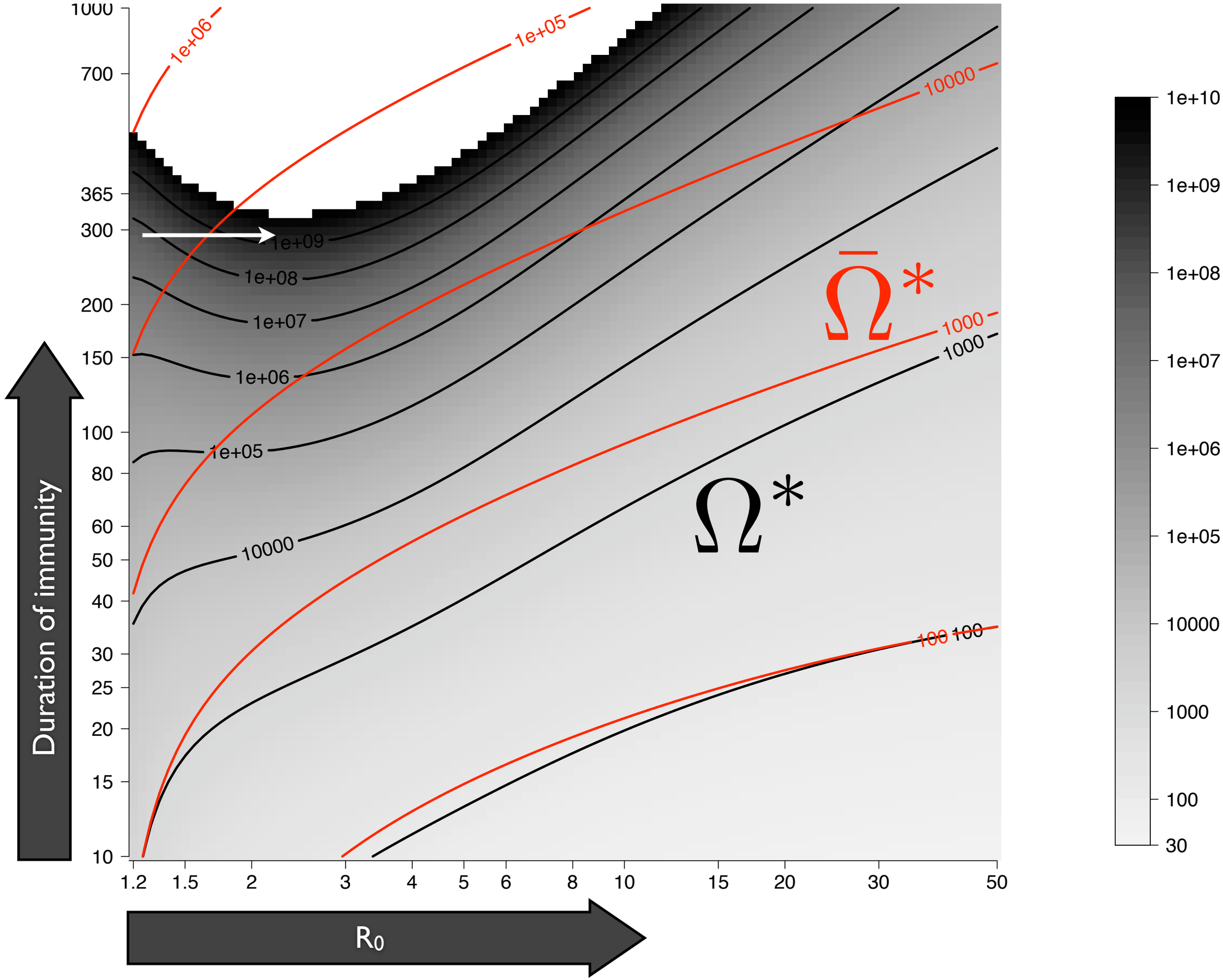


From invasion to persistence

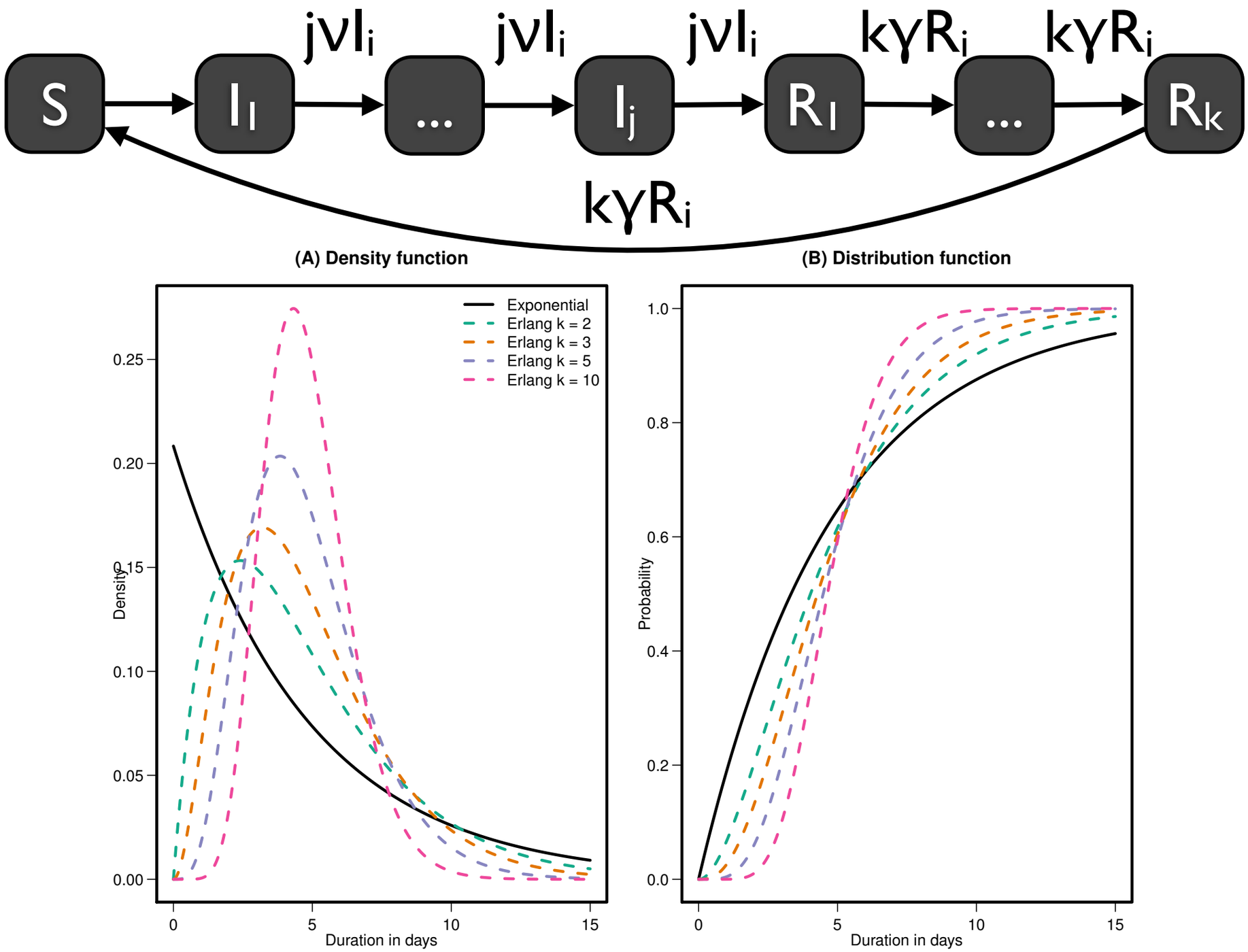


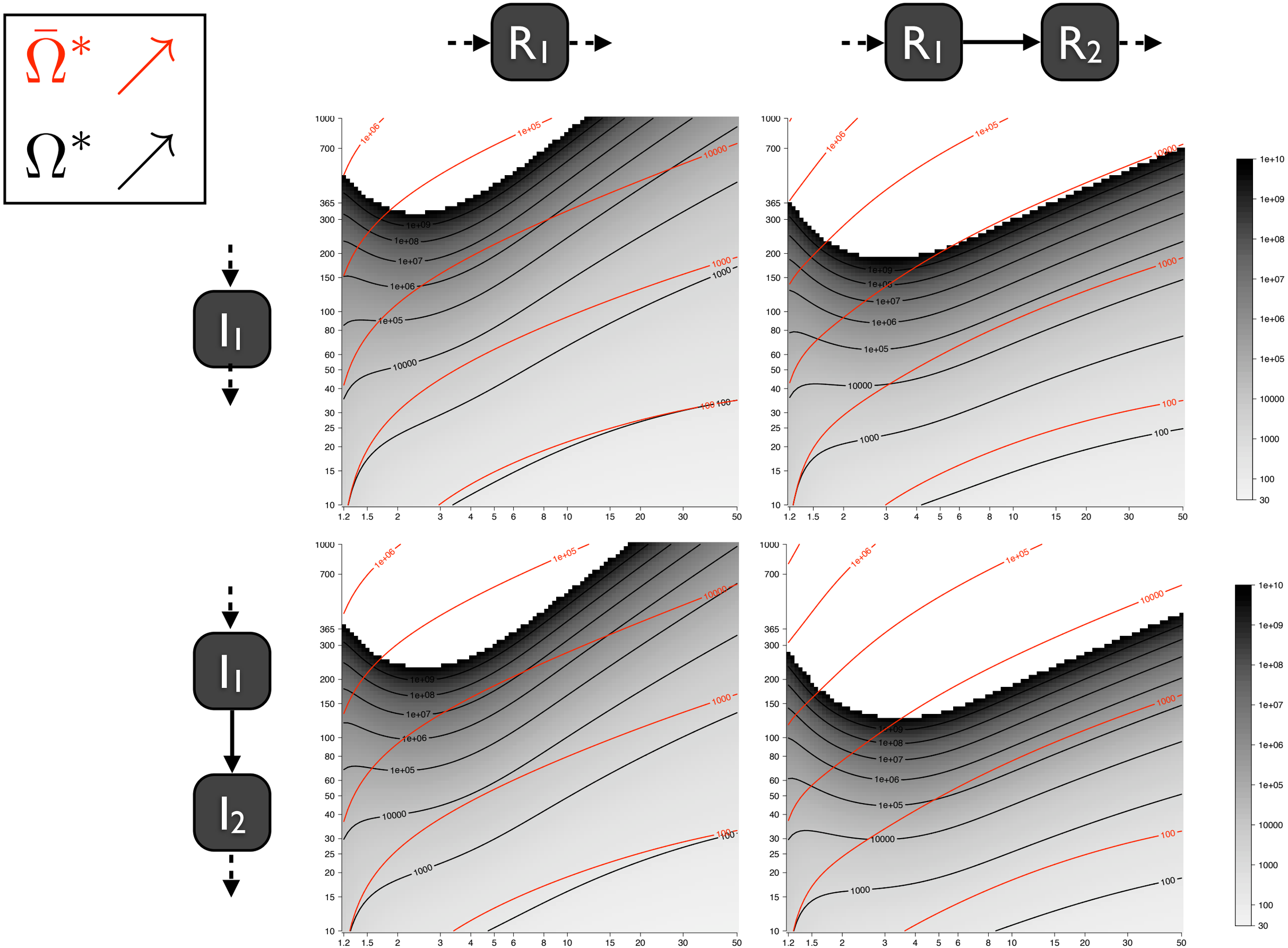





1000
700
365
300
200
150
100
80
60
50
40
30
25
20
15
10
Duration of immunity
1.2
1.5
2
3
4
5
6
8
10
15
20
30
50
R0
1e+06
1e+05
10000
1e+09
1e+08
1e+07
1e+06
1e+05
10000
1000
1000
100
100
$\bar{\Omega}^*$
Ω^*
1e+10
1e+09
1e+08
1e+07
1e+06
1e+05
10000
1000
100
30

Improve realism: gamma distributions




$\bar{\Omega}^*$
Ω^*
R_1
R_1
R_2
I_1
I_1
I_2
1000
700
365
300
200
150
100
80
60
50
40
30
25
20
15
10
1.2
1.5
2
3
4
5
6
8
10
15
20
30
50
1e+06
1e+05
10000
1000
100
1e+09
1e+08
1e+07
1e+10
30

Summary & Outlook

- Linear Noise Approximation: Fast & Automatized for complex models
- Evaluate stochastic fluctuations around the deterministic trajectory (stability analysis)
- Which regions of the parameter space (do not) require stochastic simulations?
- Qualitative & quantitative information on the stochastic dynamics

Summary & Outlook

- Improving realism: seasonal forcing (but no equilibrium), immigration (how to define extinction), more than 2 R classes (Hopf bifurcation of the endemic equilibrium)
- The linear noise approximation can also be used to derive the power spectral density of the endemic fluctuations