Multistrain models

Model types are fuzzy

Statistical

Mechanistic (mathematical v. agent-based)

Advantages and disadvantages of each?

History-based models

Track individuals' histories of infection, $S_{(0)}, S_{(1)}, S_{(1,2)}, \ldots$

Cross-immunity reduces probability of infection or infectiousness

Numerically unwieldy: 2^n histories for n strains

Dimensional reduction

Requires cross-immunity through reduced transmission (only)

Cross-immunity must be in context of antigenic "neighborhoods"

(with n strains in m neighborhoods, system is n x $(m+1)$)

Impossible to calculate immunity to new strains

Kucharski et al. 2015

Status-based models

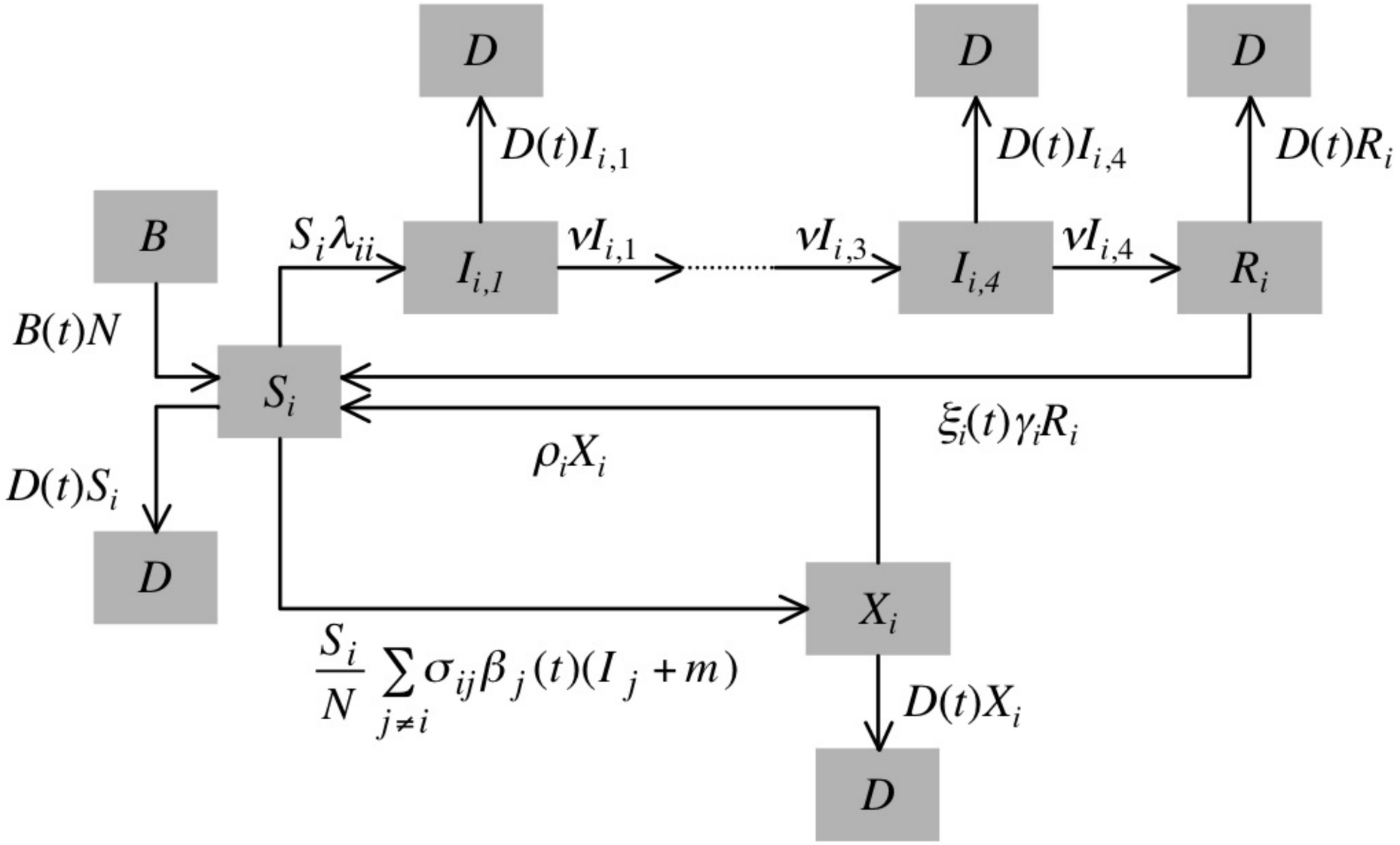
Track individuals S, I, or R to each strain

$O(n)$ equations possible

"Polarized" immunity: If i and j cross-react, infection with j leads to perfect immunity to i in some fraction of hosts

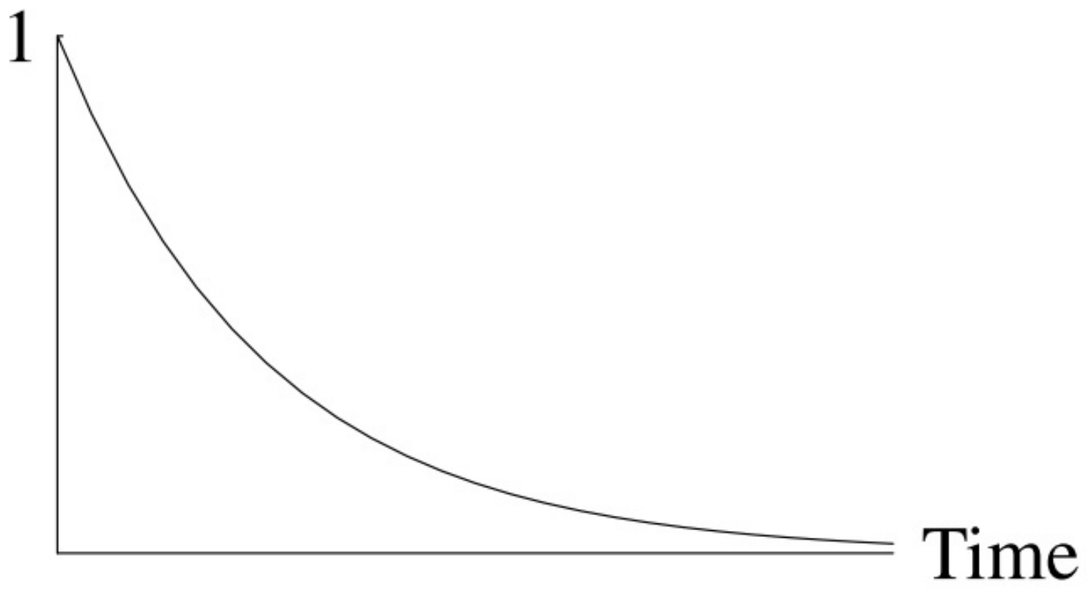
Gog and Swinton, 2002

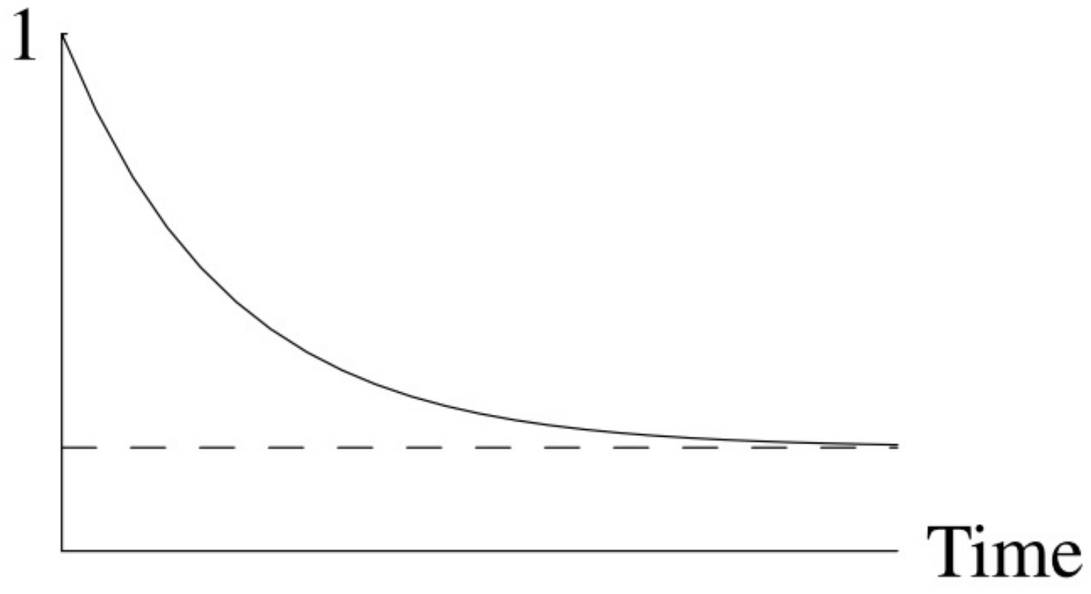
A "simple" status-based model



Implicit assumption

Proportion of population not infected by second strain





Gog and Swinton, 2002

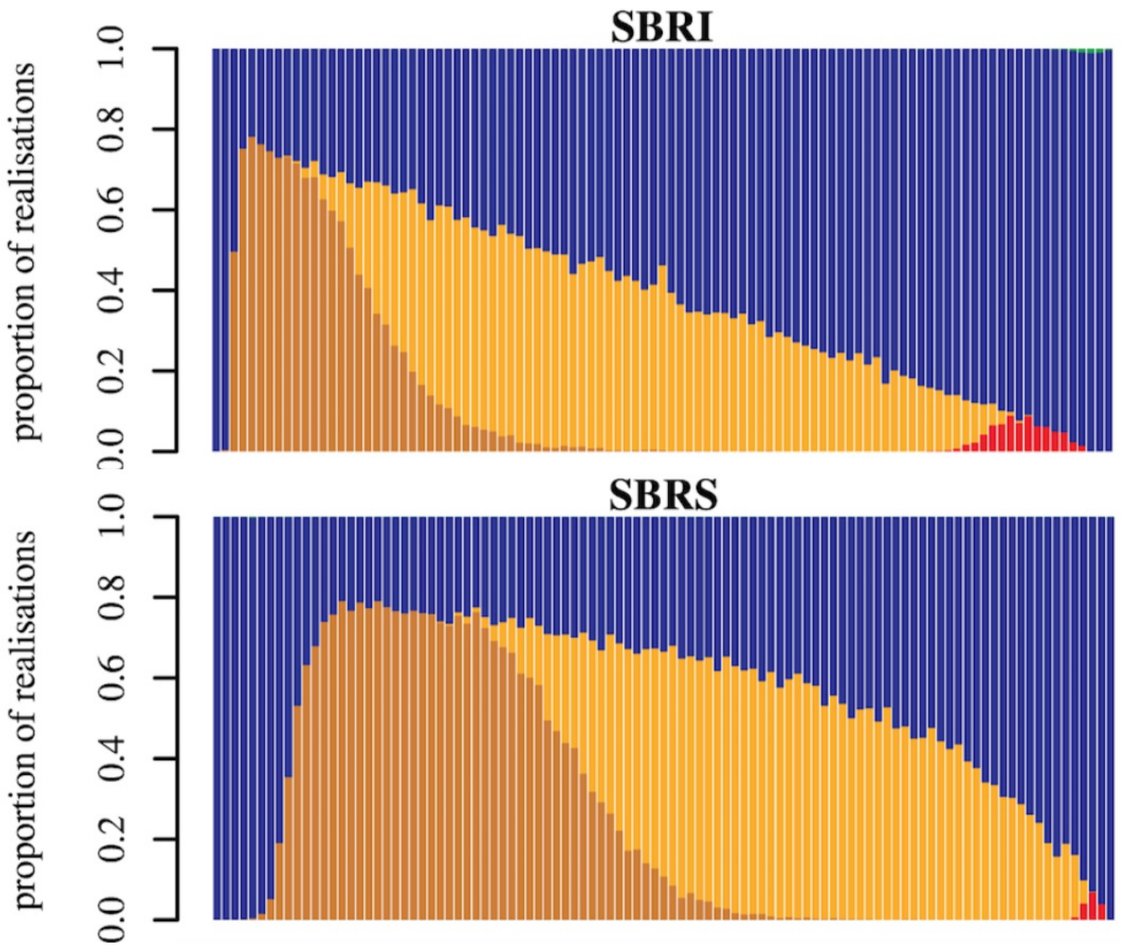
Some options for multistrain models

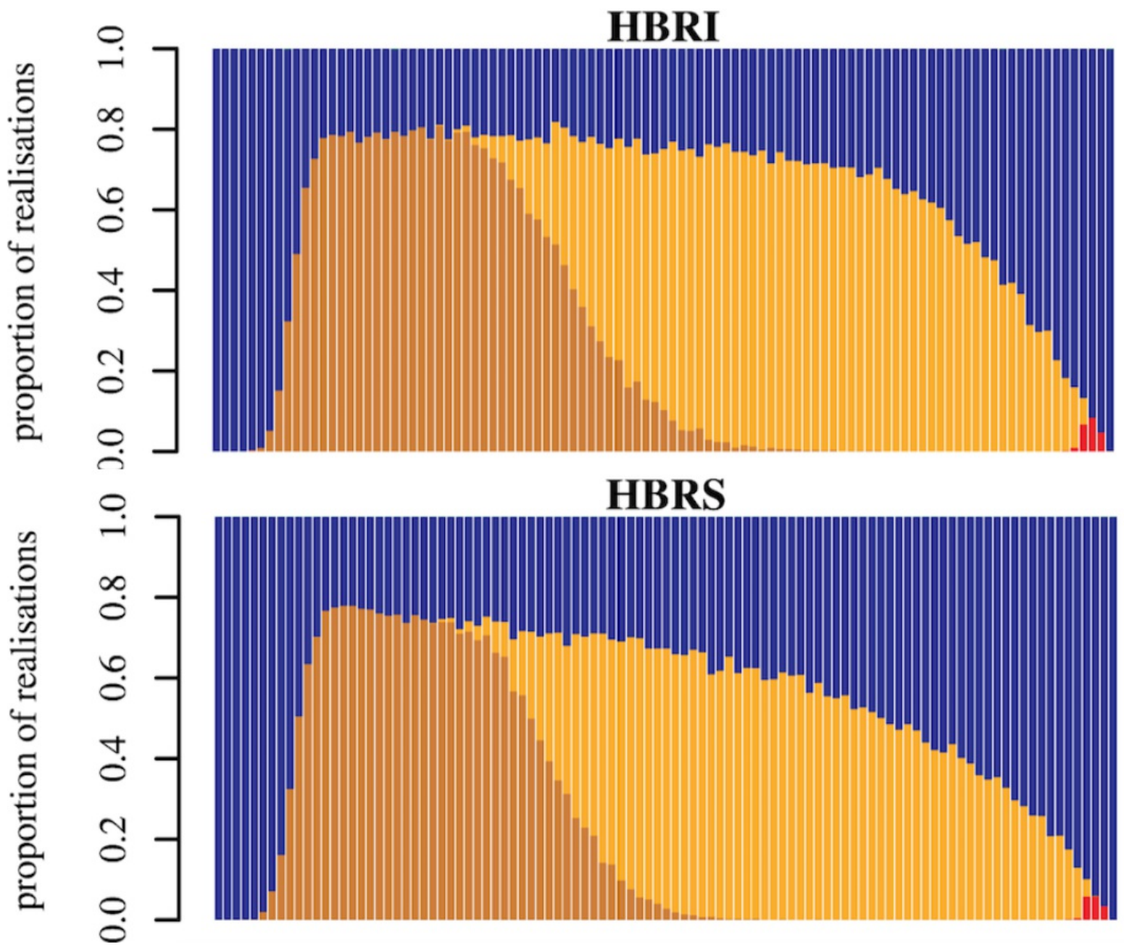
Model	Type	Variables	New strains	Immunity reduces
Individual-based model	–	Many	Yes	Susceptibility/transmission
Andreasen et al. (1997)	HB	$\mathcal{O}(2^n)$	Yes	Susceptibility/transmission
Gupta et al. (1998)*	HB	$\mathcal{O}(n)$	No	Transmission
Kucharski and Gog (2012a)	HB	$\mathcal{O}(n)$	Yes	Transmission
Gog and Swinton (2002)	SB	$\mathcal{O}(2^n)$	No	Susceptibility
Gog and Grenfell (2002)	SB	$\mathcal{O}(n)$	No	Transmission
Kryazhimskiy et al. (2007)	SB	$\mathcal{O}(n^2)$	No	Susceptibility/transmission

Only two models store enough information to permit the introduction of new strains
HB history-based, *SB* status-based
* Generalised by Ferguson and Andreasen (2002)

Kucharski et al. 2015

Subtle differences change dynamics



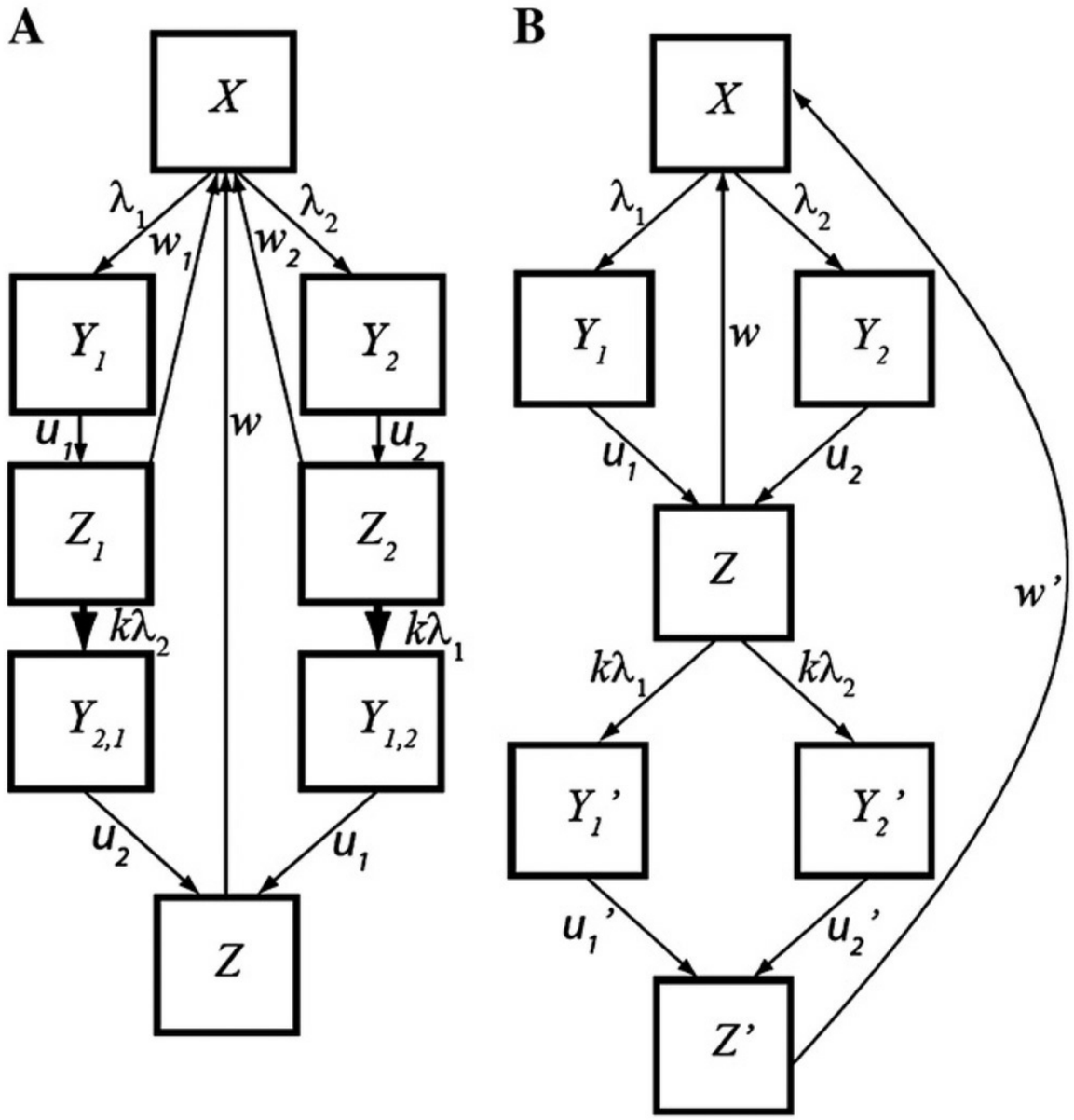


Cross-immunity

Ballesteros et al., 2009

Know your assumptions

Which model promotes coexistence?



Lipsitch et al. 2009

Model A

$$\frac{dX}{dt} = -(\lambda_1 + \lambda_2)X + w_1 Z_1 + w_2 Z_2 + wZ$$
$$\frac{dY_1}{dt} = \lambda_1 X - u_1 Y_1$$
$$\frac{dY_2}{dt} = \lambda_2 X - u_2 Y_2$$
$$\frac{dZ_1}{dt} = u_1 Y_1 - k\lambda_2 Z_1 - w_1 Z_1$$
$$\frac{dZ_2}{dt} = u_2 Y_2 - k\lambda_1 Z_2 - w_2 Z_2$$
$$\frac{dY_{1,2}}{dt} = k\lambda_1 Z_2 - u_1 Y_{1,2}$$
$$\frac{dY_{2,1}}{dt} = k\lambda_2 Z_1 - u_2 Y_{2,1}$$
$$\frac{dZ}{dt} = u_1 Y_{1,2} + u_2 Y_{2,1} - wZ$$
$$\lambda_i = \beta_i (Y_i + qY_{i,\sim i}), i = 1, 2$$

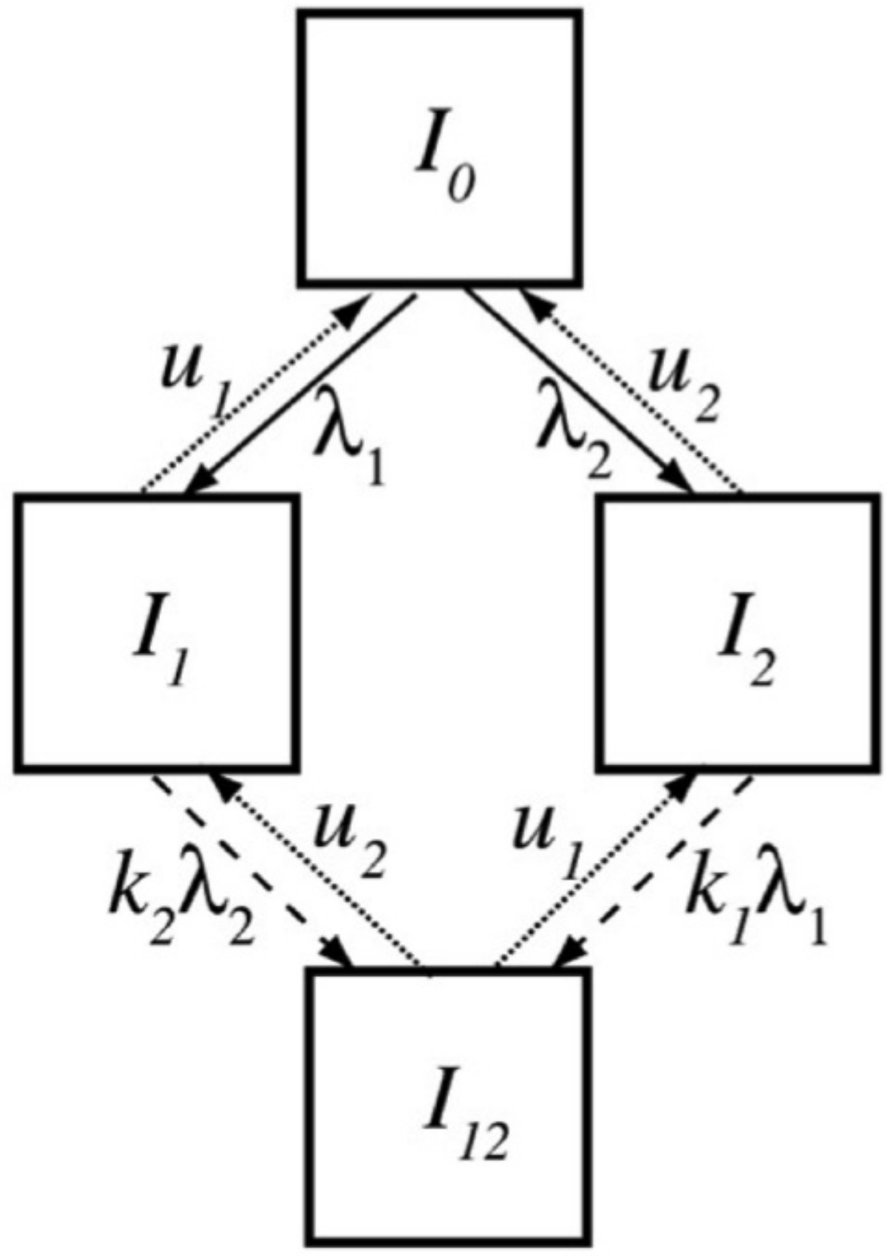
Lipsitch et al. 2009

Model B

$$\frac{dX}{dt} = -(\lambda_1 + \lambda_2)X + w'Z' + wZ$$
$$\frac{dY_1}{dt} = \lambda_1 X - u_1 Y_1$$
$$\frac{dY_2}{dt} = \lambda_2 X - u_2 Y_2$$
$$\frac{dZ}{dt} = u_1 Y_1 + u_2 Y_2 - k(\lambda_1 + \lambda_2)Z - wZ$$
$$\frac{dY'_1}{dt} = k\lambda_1 Z - u'_1 Y'_1$$
$$\frac{dY'_2}{dt} = k\lambda_2 Z - u'_2 Y'_2$$
$$\frac{dZ'}{dt} = u'_1 Y'_1 + u'_2 Y'_2 - w'Z'$$
$$\lambda_i = \beta_i(Y_i + qY'_i), i = 1, 2$$

Lipsitch et al. 2009

Does this model bias for coexistence?



Lipsitch et al. 2009

Equations

$$\frac{dI_0}{dt} \equiv -(\lambda_1 + \lambda_2)I_0 + u_1 I_1 + u_2 I_2$$

$$\frac{dI_1}{dt} \equiv \lambda_1 I_0 - u_1 I_1 - k_2 \lambda_2 I_1 + u_2 I_{12}$$

$$\frac{dI_2}{dt} \equiv \lambda_2 I_0 - u_2 I_2 - k_1 \lambda_1 I_2 + u_1 I_{12}$$

$$\frac{dI_{12}}{dt} \equiv k_2 \lambda_2 I_1 + k_1 \lambda_1 I_2 - (u_1 + u_2) I_{12}$$

$$\lambda_1 \equiv \beta_1 (I_1 + q I_{12})$$

$$\lambda_2 \equiv \beta_2 (I_2 + q I_{12})$$

Lipsitch et al. 2009

Equations

Ecological dynamics depend on strain composition

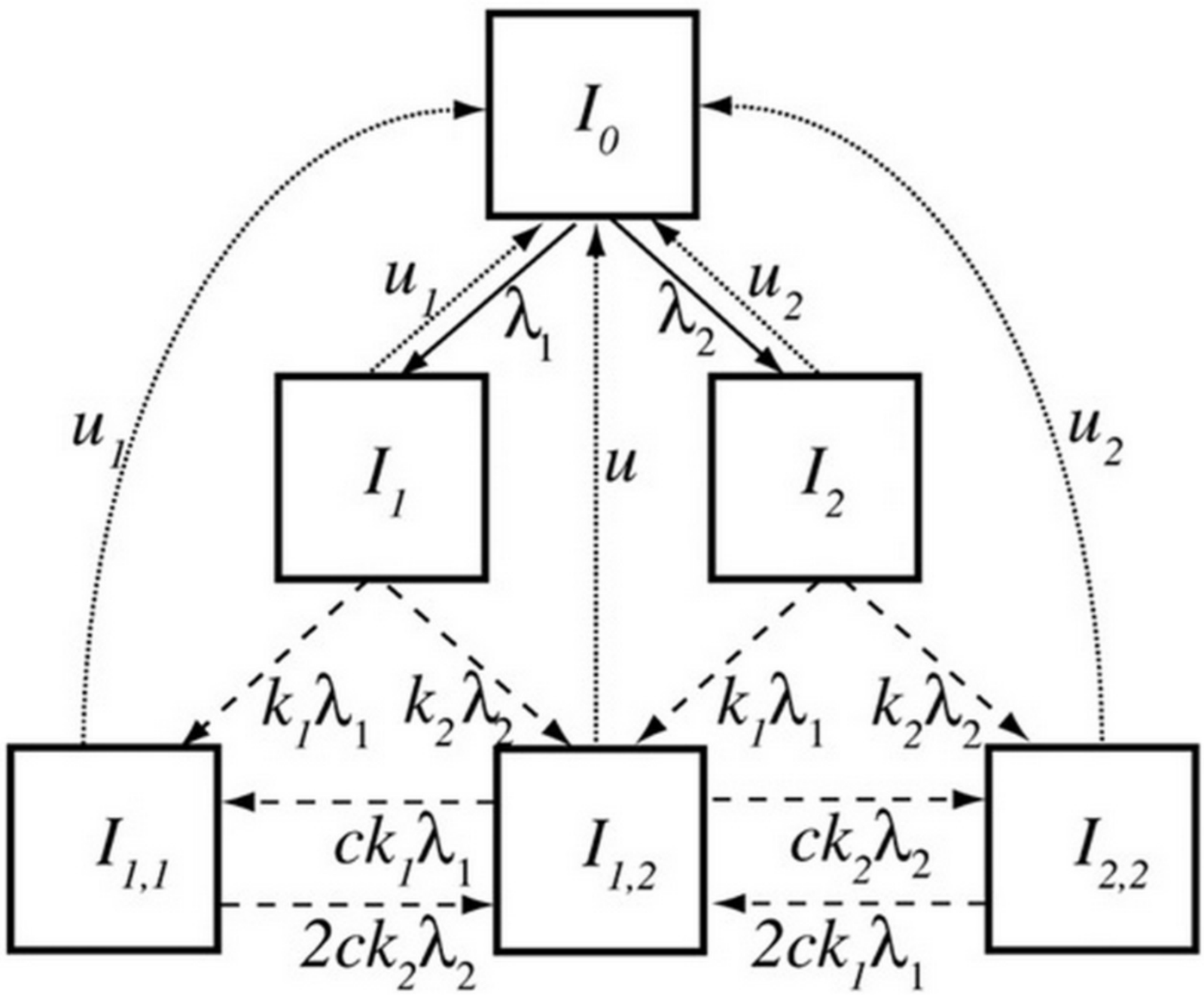
$$\frac{dN_0}{dt} = -\beta(N_1 + qN_2)N_0 + uN_1$$

$$\frac{dN_1}{dt} = \beta(N_1 + qN_2)N_0 - uN_1 - 2k\beta[I_1 I_2 + qN_2 N_1]$$

$$\frac{dN_2}{dt} = -2uN_2 + 2k\beta[I_1 I_2 + qN_2 N_1]$$

Lipsitch et al. 2009

Multiplicity of infection



Lipsitch et al. 2009

ODEs

$$\frac{dI_0}{dt} = -(\lambda_1 + \lambda_2)I_0 + u_1 I_1 + u_2 I_2 + uI_{11} + uI_{12} + uI_{22}$$
$$\frac{dI_1}{dt} = \lambda_1 I_0 - k_1\lambda_1 I_1 - k_2\lambda_2 I_1 - u_1 I_1$$
$$\frac{dI_2}{dt} = \lambda_2 I_0 - k_1\lambda_1 I_2 - k_2\lambda_2 I_2 - u_2 I_2$$
$$\frac{dI_{11}}{dt} = k_1\lambda_1 I_1 - uI_{11} - 2ck_2\lambda_2 I_{11} + ck_1\lambda_1 I_{12}$$
$$\frac{dI_{12}}{dt} = k_1\lambda_1 I_2 + k_2\lambda_2 I_1 - uI_{12} + 2ck_2\lambda_2 I_{11} + 2ck_1\lambda_1 I_{22} - ck_1\lambda_1 I_{12} - ck_2\lambda_2 I_{12}$$
$$\frac{dI_{22}}{dt} = k_2\lambda_2 I_2 - uI_{22} - 2ck_1\lambda_1 I_{22} + ck_2\lambda_2 I_{12}$$
$$\lambda_1 = \beta_1(I_1 + qI_{12} + 2qI_{11})$$
$$\lambda_2 = \beta_2(I_2 + qI_{12} + 2qI_{22})$$

Lipsitch et al. 2009

Ecological dynamics

$$\frac{dN_0}{dt} = -\beta(N_1 + 2qN_2)N_0 + u(N_1 + N_2)$$

$$\frac{dN_1}{dt} = \beta(N_1 + 2qN_2)N_0 - k\beta(N_1 + 2qN_2)N_1 - uN_1$$

$$\frac{dN_2}{dt} = k\beta(N_1 + 2qN_2)N_1 - uN_2$$

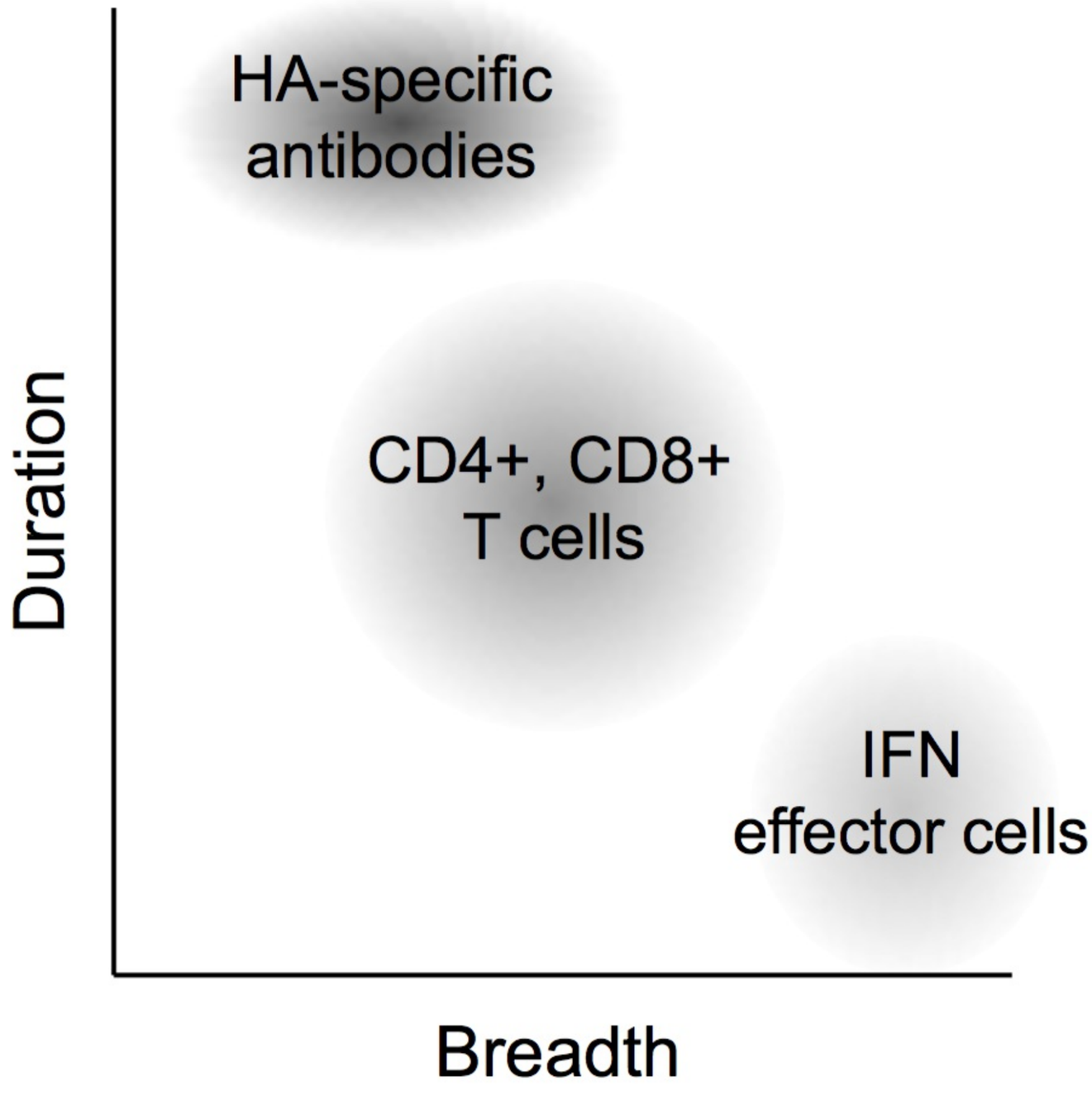
Lipsitch et al. 2009

Ancestor tracing

$$\dot{M}_{11} = \beta(M_{11} + qM_{21})N_0 - uM_{11} - k\lambda_{\text{total}}M_{11}$$
$$\dot{M}_{12} = \beta(M_{12} + qM_{22})N_0 - uM_{12} - k\lambda_{\text{total}}M_{12}$$
$$\dot{M}_{21} = \beta k(M_{11} + qM_{21})N_1 + k\lambda_{\text{total}}M_{11} - uM_{12} - c\beta k(M_{12} + qM_{22})M_{21} + c\beta k(M_{11} + qM_{21})M_{22}$$
$$\dot{M}_{22} = \beta k(M_{12} + qM_{22})N_1 + k\lambda_{\text{total}}M_{12} - uM_{22} + c\beta k(M_{12} + qM_{22})M_{21} - c\beta k(M_{11} + qM_{21})M_{22}$$
$$\lambda_{\text{total}} = \beta(M_{11} + M_{12} + qM_{21} + qM_{22}) = \beta(N_1 + 2qN_2)$$

Lipsitch et al. 2009

Immune response to flu



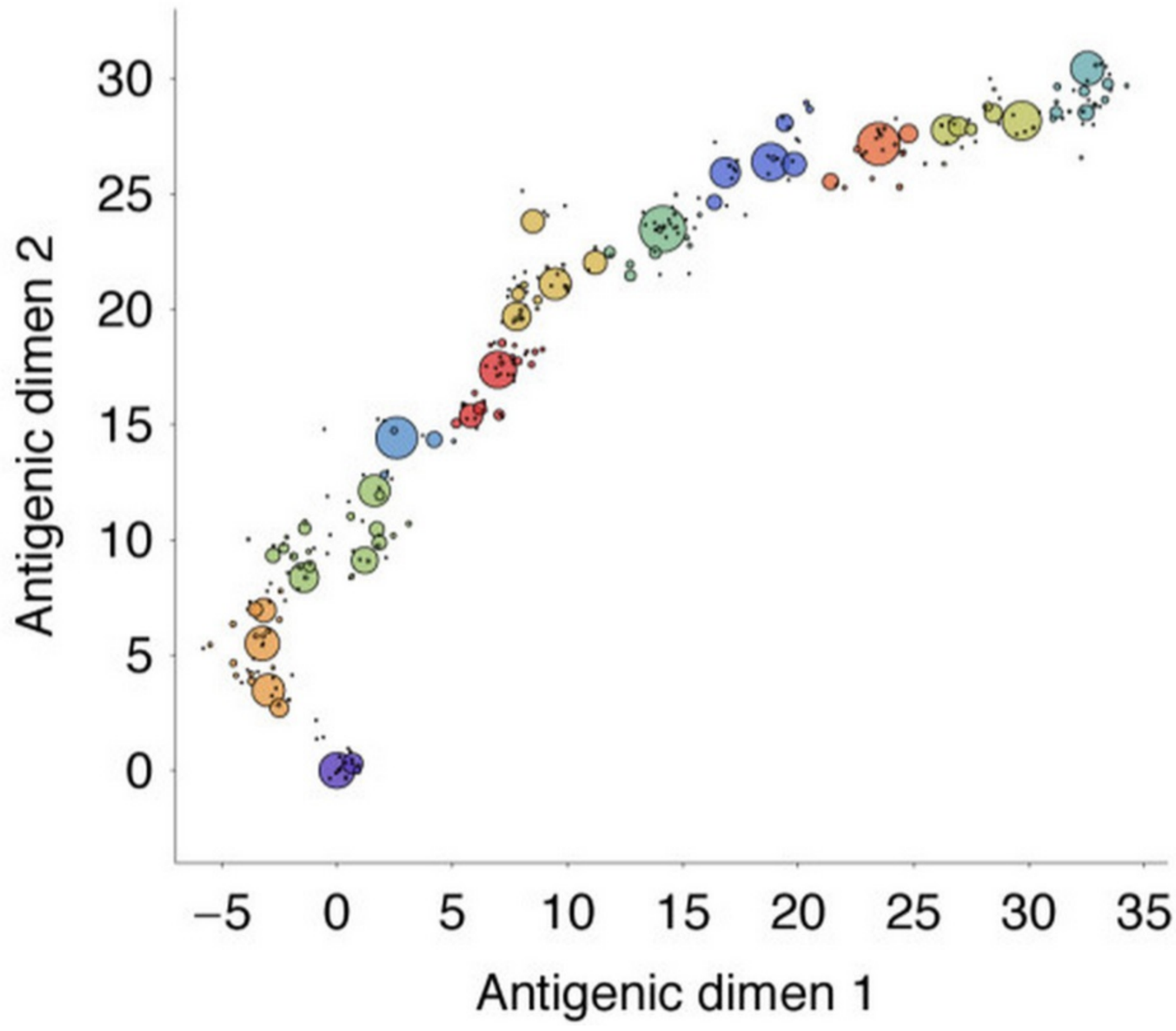
Cobey 2014

The question of strain space

Continuous or discrete?

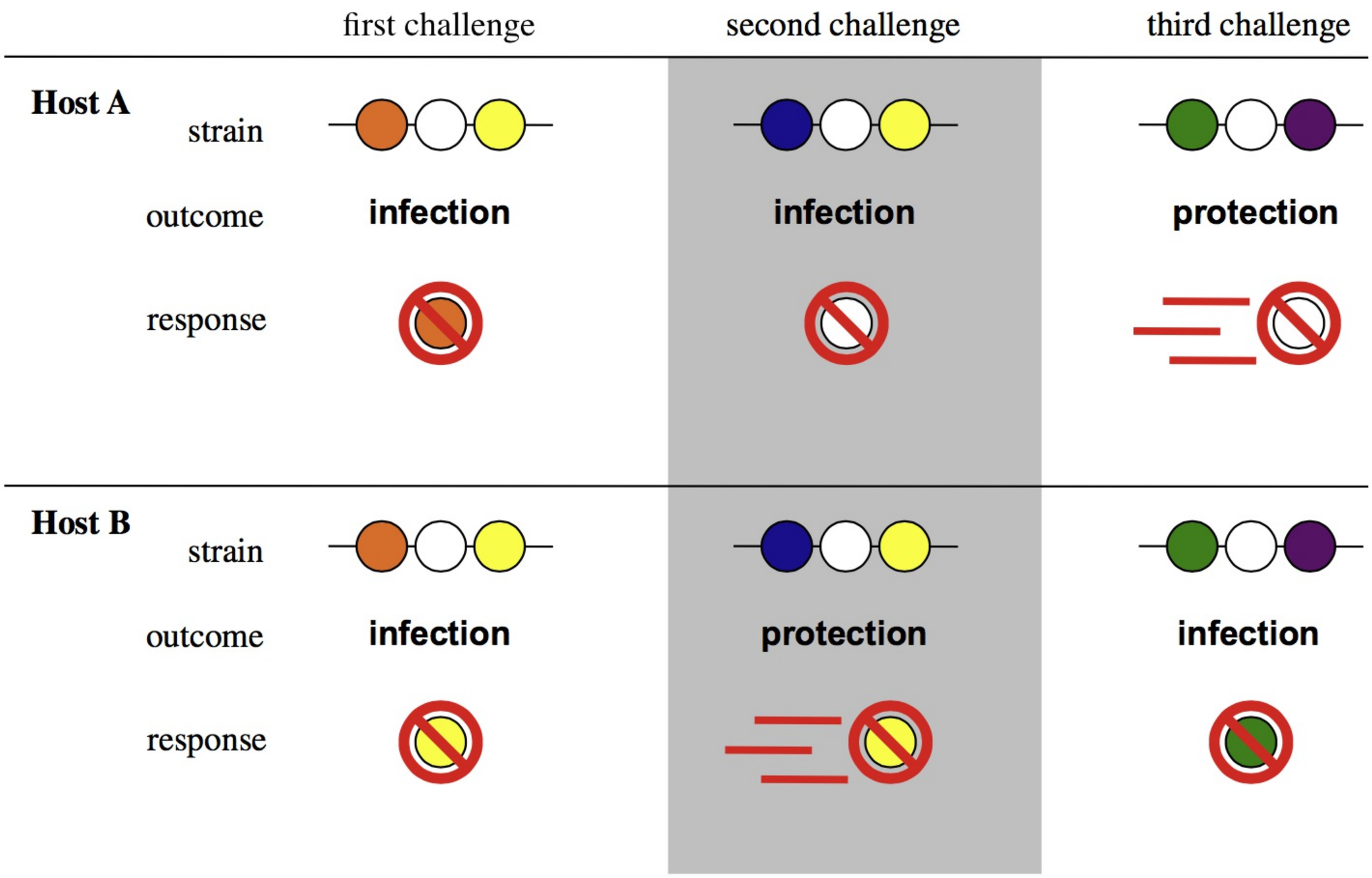
How many dimensions?

Continuous space



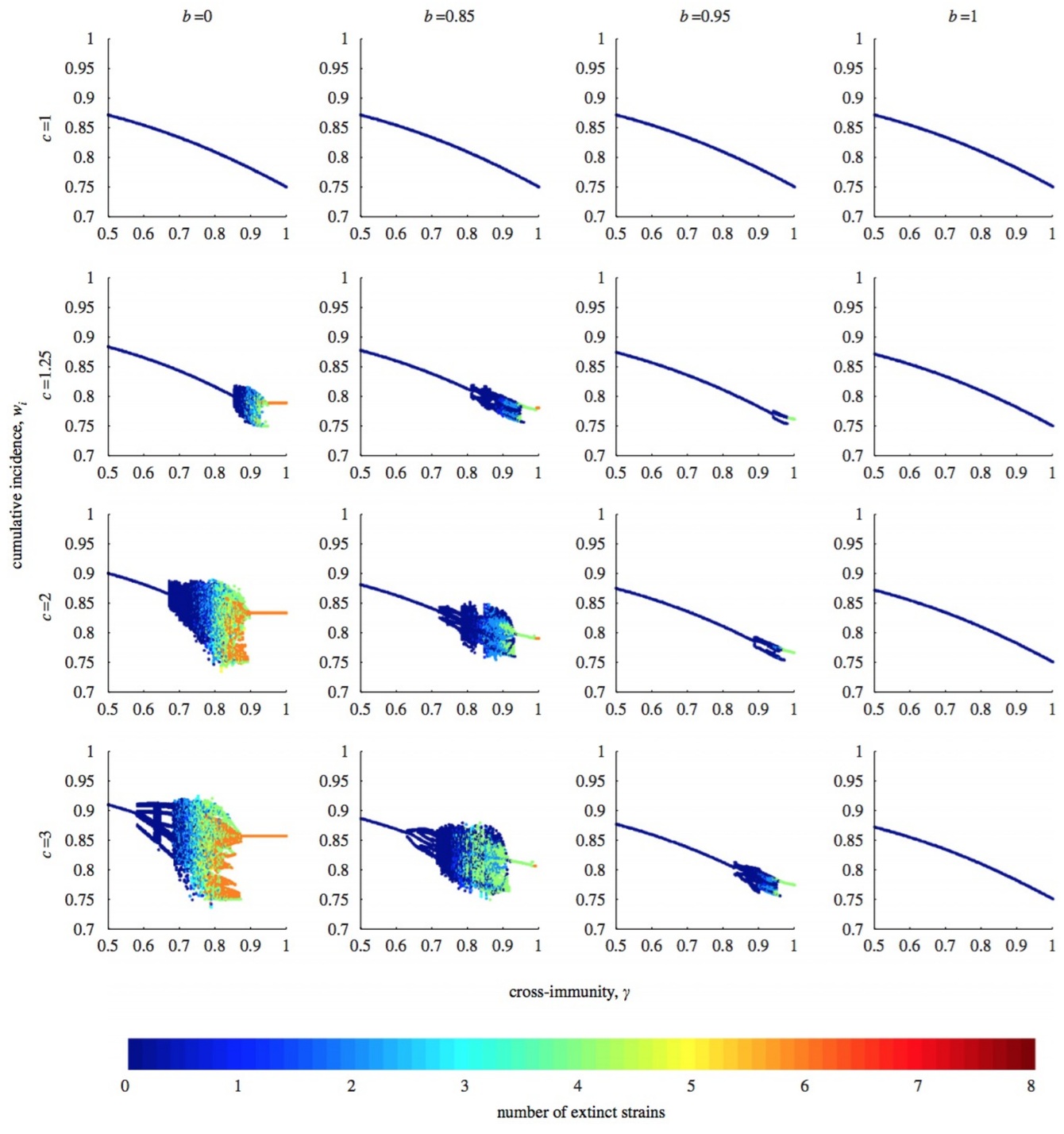
Bedford et al. 2012

Discrete space



Cobey and Pascual 2010

Immunodominance and breadth affect diversity



Cobey and Pascual 2010

Agent-based models

Potentially most efficient with many strains

Support complex interactions

Naturally incorporate demographic stochasticity

Analytic approaches

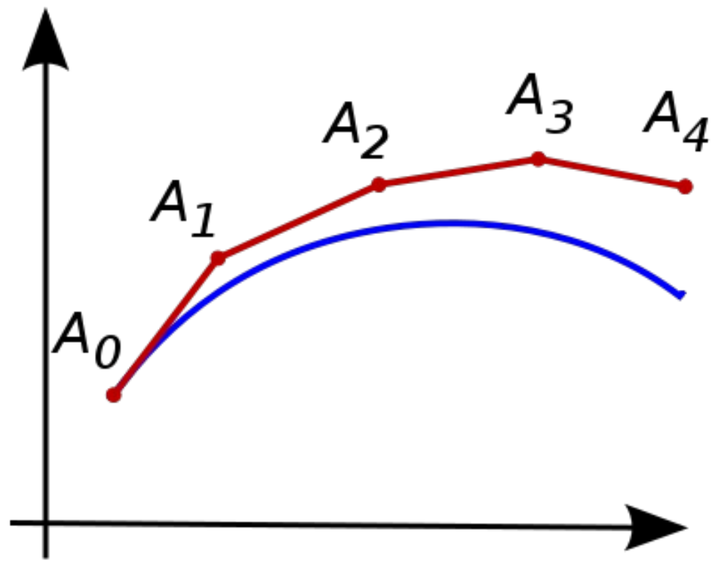
Equilibria: Solve for $\boldsymbol{S_i' = I_i' = \ldots = 0}$

Stability analysis: Linearize at equilibria

Invasion analysis: Is $\boldsymbol{I_2' > 0}$ at $\boldsymbol{I_1^*}$?

Integration: Calculate $\boldsymbol{I_1(t), I_2(t), \ldots}$

Numerical integration



Approximate solution to $\boldsymbol{N' = f(N)}$:

$$\boldsymbol{N(t_0 + \Delta t) \approx N_0 + f(N_0)\Delta t = N_1}$$

Re-iterating, we get

$$\boldsymbol{N_{z+1} \approx N_z + f(N_z)\Delta t}$$

Wikipedia

$$N_{z+1} \approx N_z + f(N_z)\Delta t$$

We could assume $f(x)$ is constant for Δt (Euler's method)

Even better, average over multiple points!

A second-order method

$$\boldsymbol{N}_{z+1} \approx \boldsymbol{N}_z + \boldsymbol{f}(\boldsymbol{N}_z)\boldsymbol{\Delta t}$$

$$\boldsymbol{M}_{z+1} = \boldsymbol{N}_z + \boldsymbol{f}(\boldsymbol{N}_z)\boldsymbol{\Delta t}$$

$$N_{z+1} = N_z + \frac{1}{2}\left[f(N_z) + f(M_{z+1})\right]\Delta t$$

4th-order Runge-Kutta

$$k_1 = f(N_z)\Delta t$$

$$k_2 = f\left(N_z + \frac{1}{2}k_1\right)\Delta t$$

$$k_3 = f\left(N_z + \frac{1}{2}k_2\right)\Delta t$$

$$k_4 = f\left(N_z + k_3\right)\Delta t$$

$$N_{z+1} = N_z + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

Why not just pick an extremely small Δt?

Considerations for multistrain models

Form of immunity (duration, strength, polarity)

Effect of immunity (susceptibility, infectiousness, clearance)

Coinfections and timing of interactions

Accuracy for individuals v. populations

Dimensionality and discretization of strain space

Analytic and numeric approaches, including stochasticity