Spatial structure undermines parasite suppression by gene drive cargo

Steve Krone (with Dick Gomulkiewicz, Jim Bull, and Chris Remien)

Vector-borne diseases (Malaria, Dengue, Zika, ...)

Two types of gene drive:

- Lethal drive: kill the mosquito
- Gene drive cargo: kill the pathogen

Gene drive and CRISPR

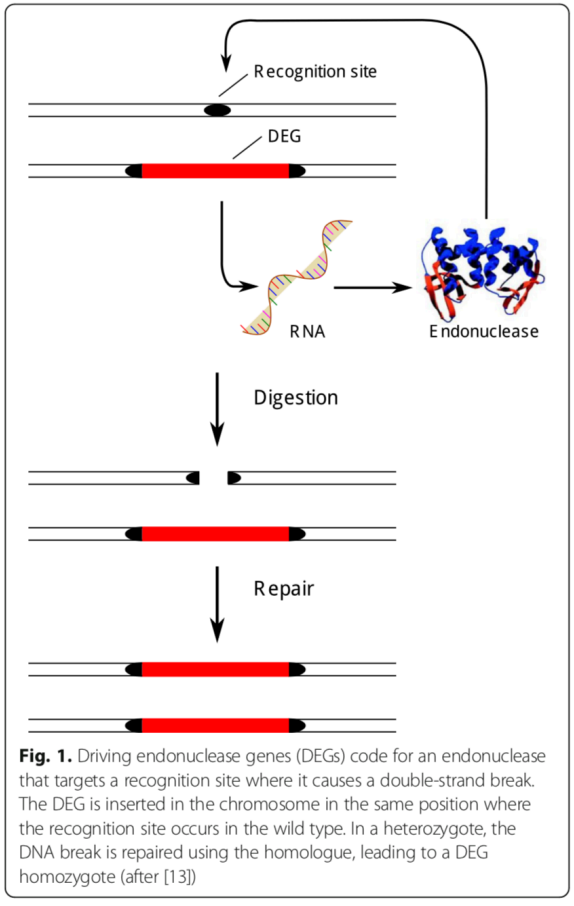


Fig. 1. Driving endonuclease genes (DEGs) code for an endonuclease that targets a recognition site where it causes a double-strand break. The DEG is inserted in the chromosome in the same position where the recognition site occurs in the wild type. In a heterozygote, the DNA break is repaired using the homologue, leading to a DEG homozygote (after [13])

Image from Godfray, North, and Burt (2017).

The promise of gene drive

- CRISPR provided the genetic tool to implement theoretical predictions
- Lab studies: gene drive spreads very quickly, even when lethal (15 generations to spread to all flies in a well-mixed cage population)
- Potential for eradicating or controlling devastating diseases like Malaria (1 Million deaths per year; 400 Million infected)
- New Zealand proposing to eliminate all invasive predators through gene drive applications

What could go wrong?

- Unintended consequences such as the drive jumping to another species (No releases in wild populations; lab populations tightly controlled)
- Failure of the drive to spread due to population structure (spatial, inbreeding, etc.) or environment
- Evolution of resistance — strong selective pressure
  - in mosquitoes (lethal drive)
  - in pathogen (cargo)

  Could adversely affect future gene drive applications

Connection to Evolutionary Rescue Ideas

- It's a race! Gene drive (ideally) works VERY quickly; pathogen is DOOMED, unless ...
- Spread of drive is incomplete (spatial structure) or variation in gene expression
- Lower selective pressure (slowing down the path to oblivion) provides more time for rescue mutants to arise — how it's done in the lab
- Standing genetic variation (resistance mutations from previous gene drive applications)

Can spatial structure undermine cargo-based pathogen suppression?

Model 1. very simple discrete-time model with implicit spatial structure, no human dynamics.

-Mosquitoes: fraction x_0 no cargo; fraction x_1 with cargo
-Pathogen strains: 0=WT, 1=mutant. Fecundities in
cargo-free mosquitoes: $b_{00} > b_{10}$
cargo-bearing mosquitoes: $b_{01} < b_{11}$

Growth of pathogen strain j in mosquito type k:
$n'_{jk} = \alpha n_{jk} b_{jk} + (1-\alpha) N_j x_k$,
where N_j is strain j production in all mosquitoes.
$\alpha =$ fidelity of progeny to mosquito type

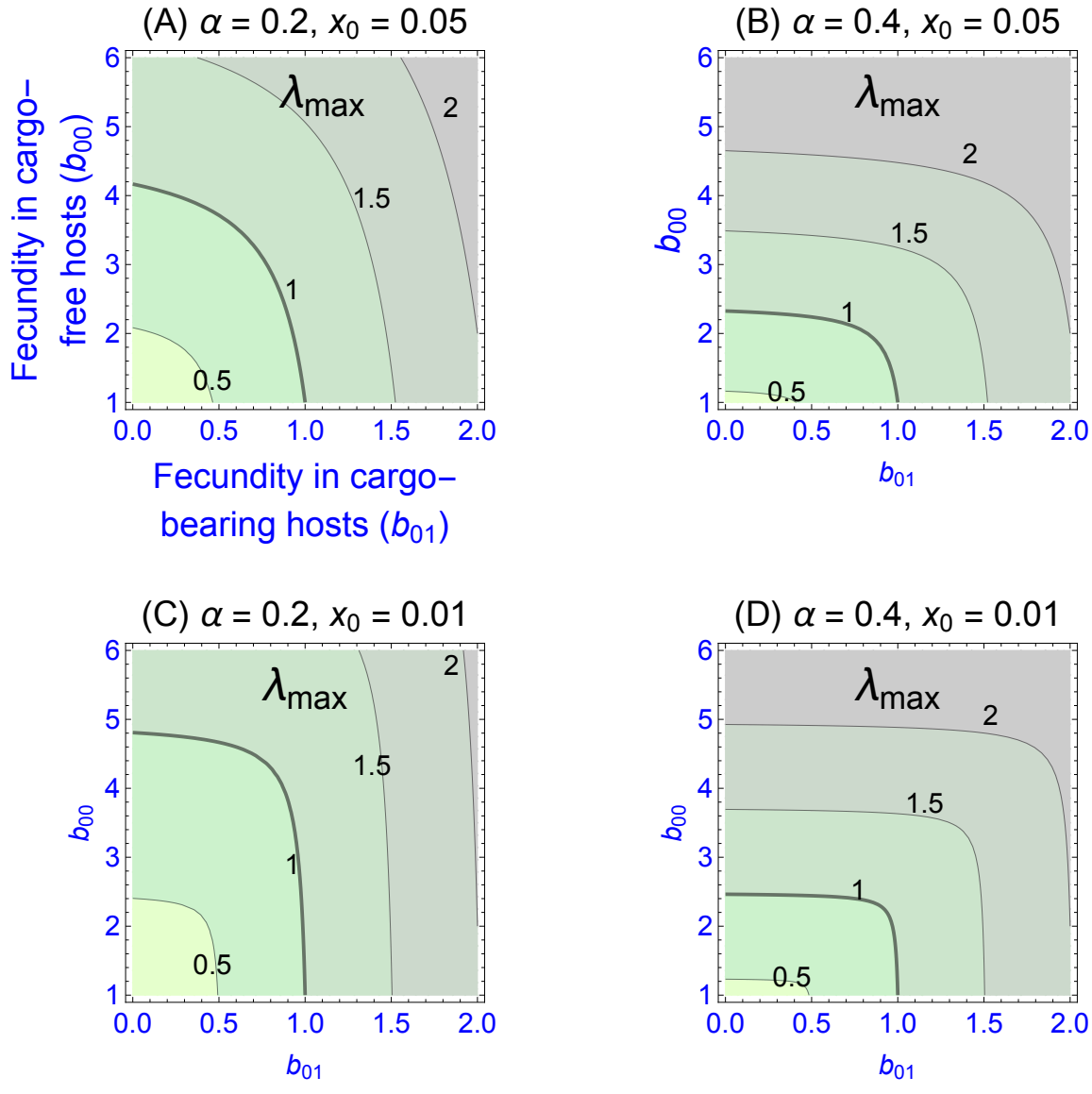
Adding density regulation complicates things, but idea is similar:
Pathogen strain 1 in cargo-bearing mosquitoes:

$$\alpha p_{11}\Pi_1 + (1-\alpha)[p_{10}\Pi_0 + p_{11}\Pi_1]x_1$$

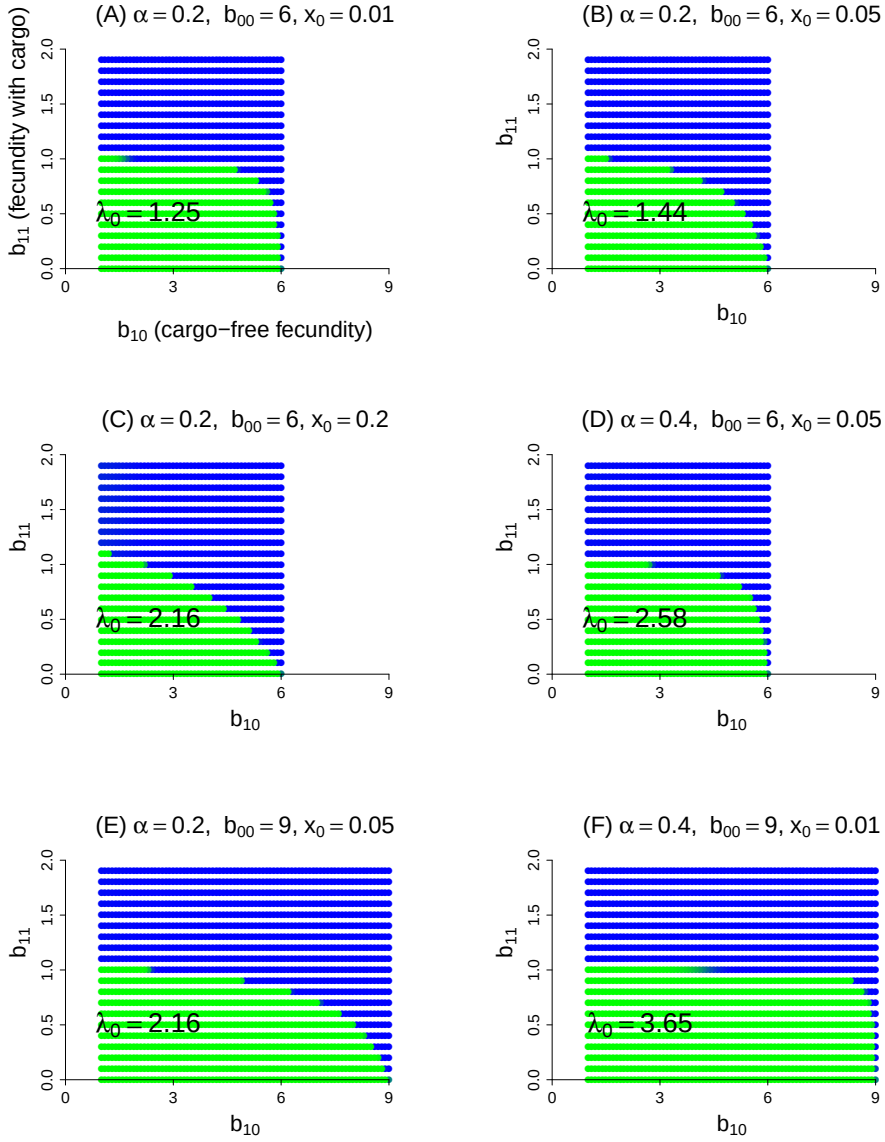
Pathogen strain 0 in cargo-bearing mosquitoes:

$$\alpha p_{01}\Pi_1 + (1-\alpha)[p_{00}\Pi_0 + p_{01}\Pi_1]x_1$$

$\alpha > 0$: spatial segregation of cargo-free and cargo-bearing mosquitoes
$\alpha = 0$: well mixed



Dominant eigenvalue contours for WT growth. Spatial structure (α) enhances pathogen persistence.



Mutant vs WT pathogen. Blue: mutant wins. λ_0: how well WT grows by itself.

Model 2. More complex cargo patch model with human and mosquito dynamics

- 2 physical patches: #1 cargo suppression weak or absent; #2 cargo suppression strong
- Susceptible $M_s^{(1)}$ and infected $M_i^{(1)}$ mosquitoes in patch 1; $M_s^{(1)} + M_i^{(1)} = M^{(1)}$, ...
- Susceptible $H_s^{(1)}$ and infected $H_i^{(1)}$ humans in patch 1; $H_s^{(1)} + H_i^{(1)} = H^{(1)}$, ...
- Mosquitoes do not move. Humans spend fraction of time "visiting" other patch: c_{12} = fraction of time humans who reside in patch 1 spend visiting patch 2.

Q. Does spatial heterogeneity in cargo suppression + human movement lead to pathogen persistence (cargo failure)?

Two models of vector-mediated pathogen transmission ($M \to H$, $H \to M$):

- density-dependent transmission
- frequency-dependent transmission (Ross-MacDonald)

Single pathogen strain (ignore mutants for now)

Density-dependent vector transmission model

Patch 1 residents:

$$\dot{H}_s^{(1)} = -bH_s^{(1)}\left[c_{11}a_{MH}^{(1)}M_i^{(1)} + c_{12}a_{MH}^{(2)}M_i^{(2)}\right] + \gamma H_i^{(1)}$$

$$\dot{H}_i^{(1)} = bH_s^{(1)}\left[c_{11}a_{MH}^{(1)}M_i^{(1)} + c_{12}a_{MH}^{(2)}M_i^{(2)}\right] - \gamma H_i^{(1)}$$

$$\dot{M}_s^{(1)} = \alpha_1 - ba_{HM}M_s^{(1)}\left[c_{11}H_i^{(1)} + c_{21}H_i^{(2)}\right] - \delta M_s^{(1)}$$

$$\dot{M}_i^{(1)} = ba_{HM}M_s^{(1)}\left[c_{11}H_i^{(1)} + c_{21}H_i^{(2)}\right] - \delta M_i^{(1)}$$

Patch 2 residents:

$$\dot{H}_s^{(2)} = -\, bH_s^{(2)} \left[c_{21} a_{MH}^{(1)} M_i^{(1)} + c_{22} a_{MH}^{(2)} M_i^{(2)} \right] + \gamma H_i^{(2)}$$

$$\dot{H}_i^{(2)} = bH_s^{(2)} \left[c_{21} a_{MH}^{(1)} M_i^{(1)} + c_{22} a_{MH}^{(2)} M_i^{(2)} \right] - \gamma H_i^{(2)}$$

$$\dot{M}_s^{(2)} = \alpha_2 \; - b\, a_{HM} M_s^{(2)} \left[c_{22} H_i^{(2)} + c_{12} H_i^{(1)} \right] - \delta M_s^{(2)}$$

$$\dot{M}_i^{(2)} = b\, a_{HM} M_s^{(2)} \left[c_{22} H_i^{(2)} + c_{12} H_i^{(1)} \right] - \delta M_i^{(2)}$$

$\mathcal{R}_0$ calculation

Compute the numbers of secondary infections of mosquitoes; requires two steps: Mosquito $\rightarrow$ Human followed by Human $\rightarrow$ Mosquito transmission.

1. # humans directly infected from primary mosquitoes before they die is:

   - in patch 1:

$$H^{(1)}_{i,\text{new}} = \frac{bH^{(1)}}{\delta}\left[c_{11}a^{(1)}_{MH}M^{(1)}_i(0) + c_{12}a^{(2)}_{MH}M^{(2)}_i(0)\right]$$

   - in patch 2:

$$H^{(2)}_{i,\text{new}} = \frac{bH^{(2)}}{\delta}\left[c_{21}a^{(1)}_{MH}M^{(1)}_i(0) + c_{22}a^{(2)}_{MH}M^{(2)}_i(0)\right]$$

2. # mosquitoes infected by these newly infected humans before they recover is:

   - in patch 1:

$$M_{i,\text{new}}^{(1)} = \frac{ba_{HM}M^{(1)}}{\gamma} \cdot \left[c_{11}H_{i,\text{new}}^{(1)} + c_{21}H_{i,\text{new}}^{(2)}\right]$$

   - in patch 2:

$$M_{i,\text{new}}^{(2)} = \frac{ba_{HM}M^{(2)}}{\gamma} \cdot \left[c_{12}H_{i,\text{new}}^{(1)} + c_{22}H_{i,\text{new}}^{(2)}\right]$$

Putting these together allows us to specify patterns of secondary infection (*per primary infected mosquito in each patch*) in the matrix

$$R = \begin{pmatrix} R(1,1) & R(1,2) \\ \\ R(2,1) & R(2,2) \end{pmatrix},$$

where $R(j,k)$ denotes the number of secondary mosquito infections in patch j that arose from primary infected mosquitoes in patch k, for $j,k \in \{1,2\}$.

Global $\mathcal{R}_0$ is leading eigenvalue of R

Tracking the patterns of infection in steps 1 and 2 above, we arrive at

$$R(1,1) = \frac{b^2 a^{(1)}_{MH} a_{HM} M^{(1)}}{\delta\gamma}\left[c_{11}^2 H^{(1)} + c_{21}^2 H^{(2)}\right]$$

$$R(1,2) = \frac{b^2 a^{(2)}_{MH} a_{HM} M^{(1)}}{\delta\gamma}\left[c_{12}c_{11} H^{(1)} + c_{22}c_{21} H^{(2)}\right]$$

$$R(2,1) = \frac{b^2 a^{(1)}_{MH} a_{HM} M^{(2)}}{\delta\gamma}\left[c_{11}c_{12} H^{(1)} + c_{21}c_{22} H^{(2)}\right]$$

$$R(2,2) = \frac{b^2 a^{(2)}_{MH} a_{HM} M^{(2)}}{\delta\gamma}\left[c_{12}^2 H^{(1)} + c_{22}^2 H^{(2)}\right].$$

Special case $a^{(2)}_{MH} = 0$ (no Mosquito $\rightarrow$ Human transmission in patch 2) $\Longrightarrow$ $R(1,2) = 0 = R(2,2)$ and hence

$$\mathcal{R}_0 = R(1,1) = \frac{b^2 a^{(1)}_{MH} a_{HM} M^{(1)}}{\delta\gamma}\left[c_{11}^2 H^{(1)} + c_{21}^2 H^{(2)}\right].$$

(Notice the MH form in this density-dependent model, as opposed to the M/H form in the Ross-MacDonald frequency dependent model—next.)

Frequency-dependent vector transmission model

In this Ross-MacDonald-type model, per-human bite rates for a mosquito are of the form $\tilde{b}/H$ instead of b.

$$\dot{H}_i^{(1)} = \tilde{b} H_s^{(1)} \left[\frac{c_{11} a_{MH}^{(1)} M_i^{(1)}}{\left[c_{11} H^{(1)} + c_{21} H^{(2)} \right]} + \frac{c_{12} a_{MH}^{(2)} M_i^{(2)}}{\left[c_{22} H^{(2)} + c_{12} H^{(1)} \right]} \right] - \gamma H_i^{(1)}$$

$$\dot{M}_i^{(1)} = \frac{\tilde{b} a_{HM} M_s^{(1)}}{\left[c_{11} H^{(1)} + c_{21} H^{(2)} \right]} \left[c_{11} H_i^{(1)} + c_{21} H_i^{(2)} \right] - \delta M_i^{(1)}$$

$$R = \begin{pmatrix} R(1,1) & R(1,2) \\ \\ R(2,1) & R(2,2) \end{pmatrix},$$

where

$$R(1,1) = \frac{\tilde{b}^2 a^{(1)}_{MH} a_{HM} M^{(1)}}{\delta\gamma} \frac{[c_{11}^2 H^{(1)} + c_{21}^2 H^{(2)}]}{\left[c_{11} H^{(1)} + c_{21} H^{(2)}\right]^2},$$

etc. Special case $a^{(2)}_{MH} = 0 \implies$

$$\mathcal{R}_0 = R(1,1) = \frac{\tilde{b}^2 a^{(1)}_{MH} a_{HM} M^{(1)}}{\delta\gamma} \frac{[c_{11}^2 H^{(1)} + c_{21}^2 H^{(2)}]}{\left[c_{11} H^{(1)} + c_{21} H^{(2)}\right]^2}.$$

Spatial cline model of cargo suppression

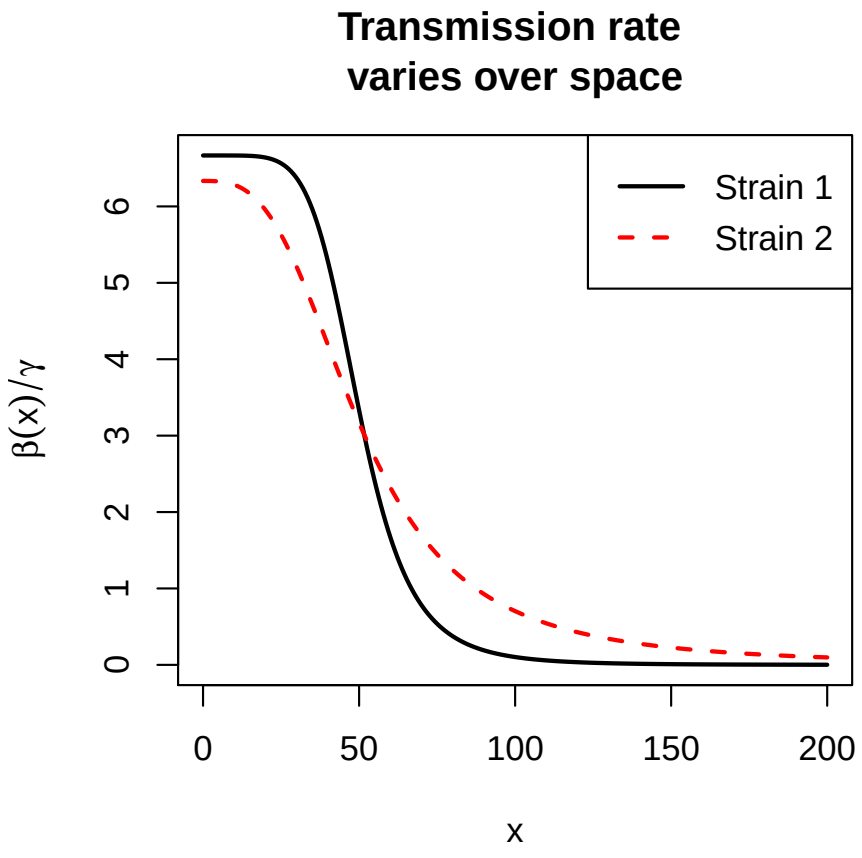
Multi-strain SIS model for infection of mosquitoes (ignoring human dynamics)

$$\frac{\partial I_j(x,t)}{\partial t} = \beta_j(x) I_j(x,t) \left(1 - \sum_{i=1}^{M} I_i(x,t)\right) - \gamma I_j(x,t) + D\Delta I_j(x,t)$$

-pathogen strains $j = 1, \ldots, M$
-transmission rates $\beta_j(x)$ vary spatially as function of cargo-based suppression

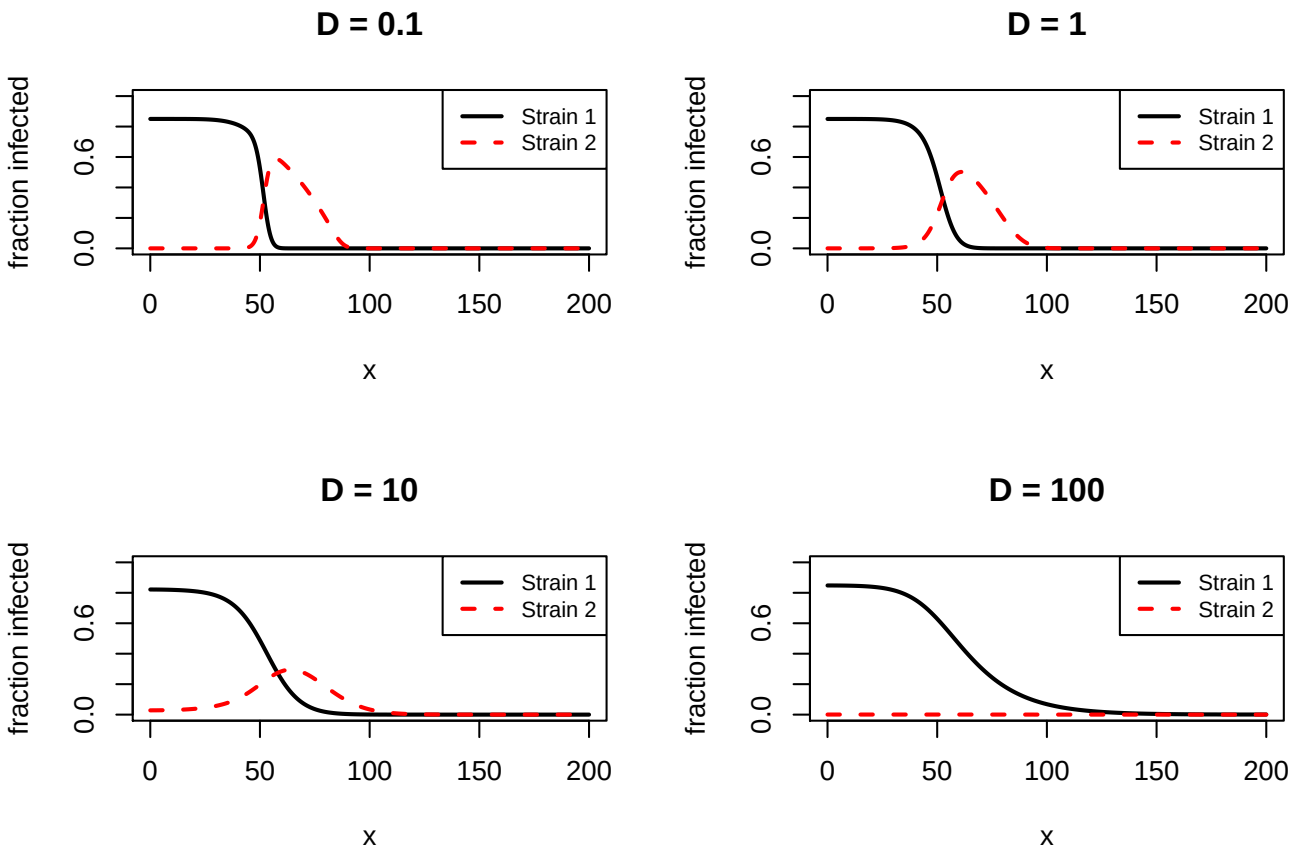
cf. Tuncer and Martcheva (2012)

Transmission rates for competing pathogen strains



Cargo-based suppression stronger to the right

Coexistence vs. Exclusion as function of diffusion



Spatial coexistence of mutant pathogen strains facilitates recombination (enhance rescue; expand range)

Thank you