Evolutionary Epidemiology of Drug-Resistance in Space

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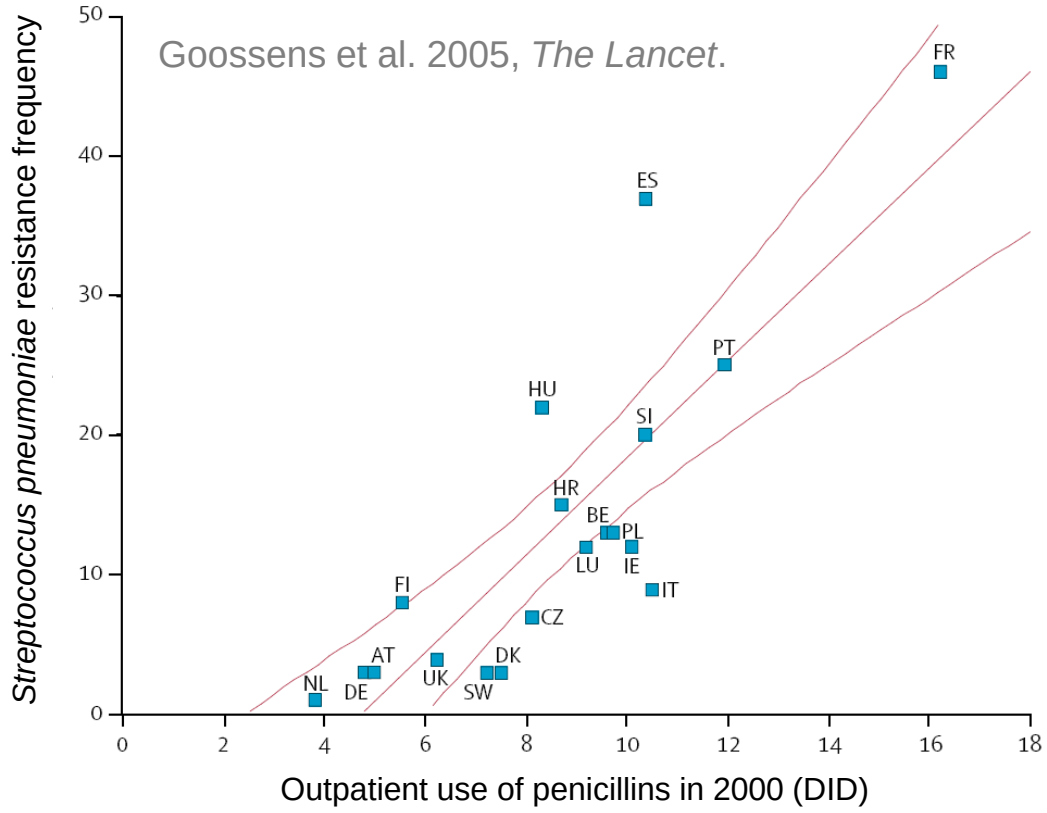
CEFE – Montpellier, France

Florence Débarre

Thomas Lenormand

Antibiotic use and antibiotic resistance



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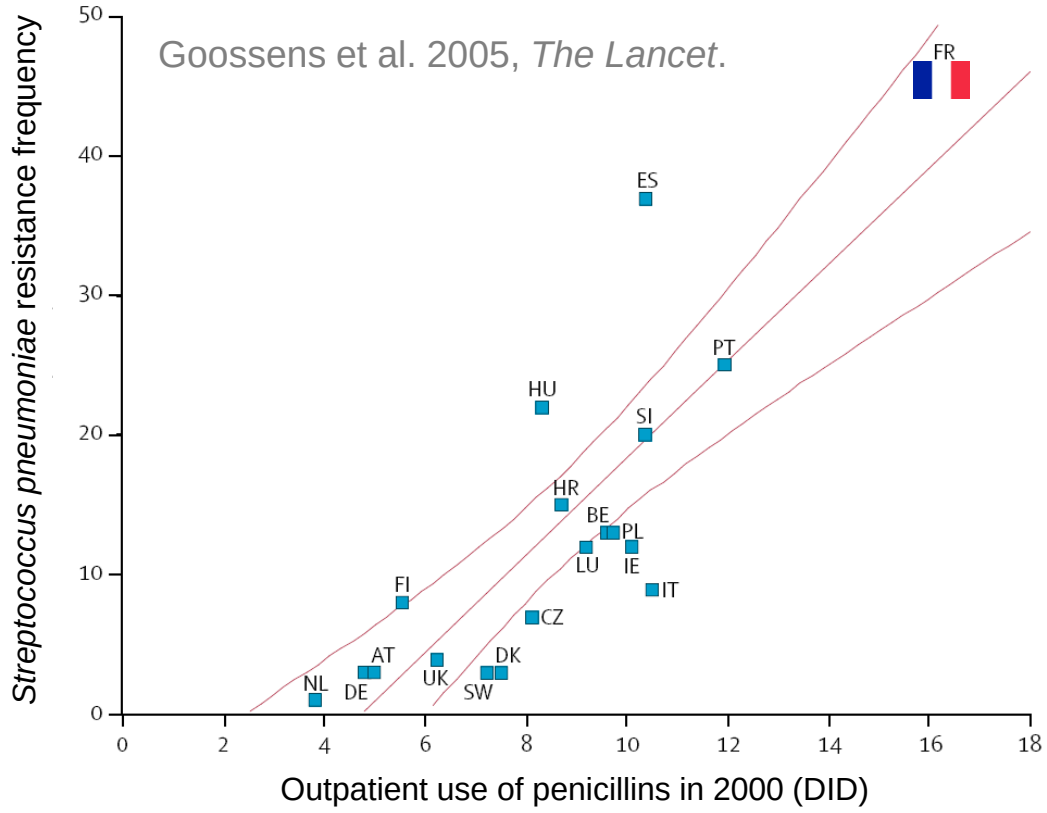

Resistance management:
How to limit the rise of drug resistance?

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1. Reduce drug use

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1. Reduce drug use
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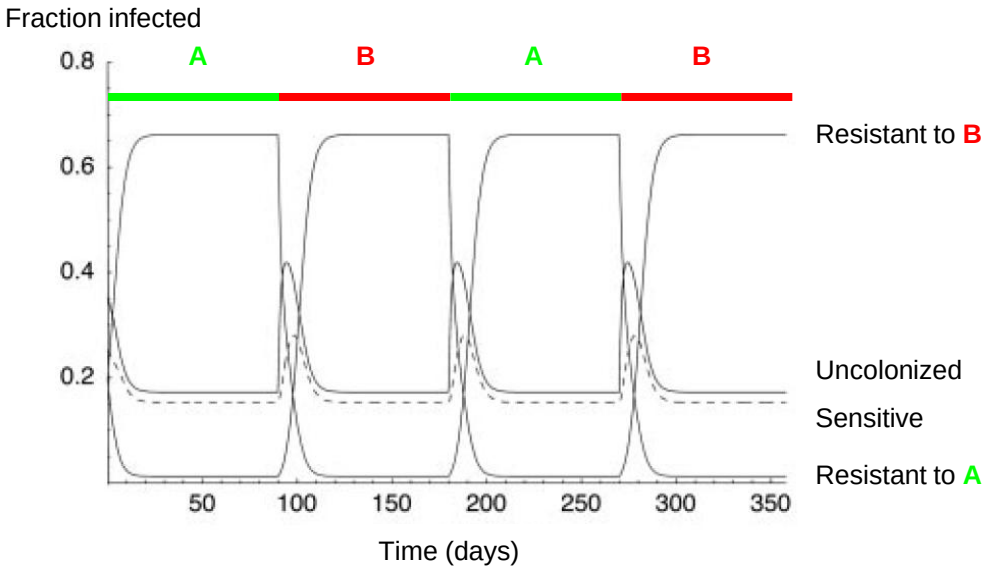
Bergstrom et al. 2004, *PNAS*.



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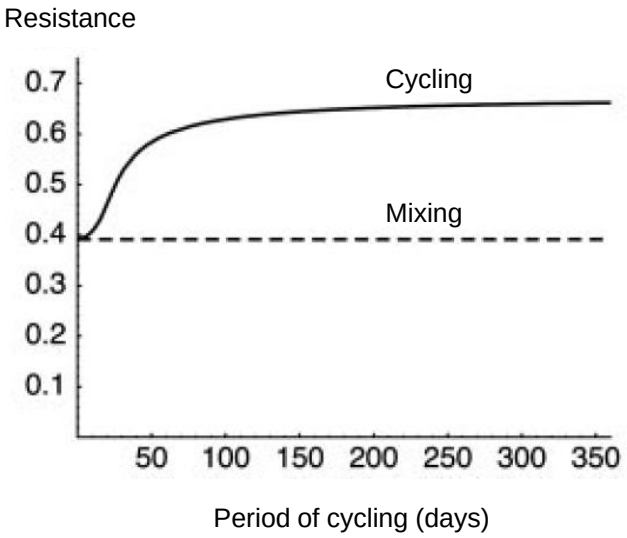

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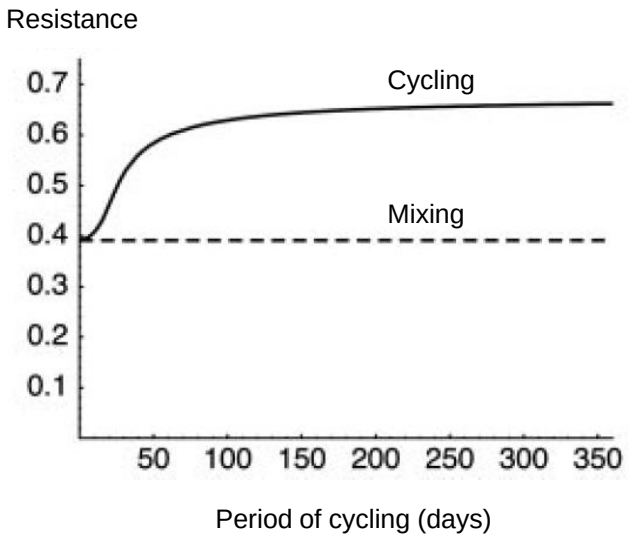

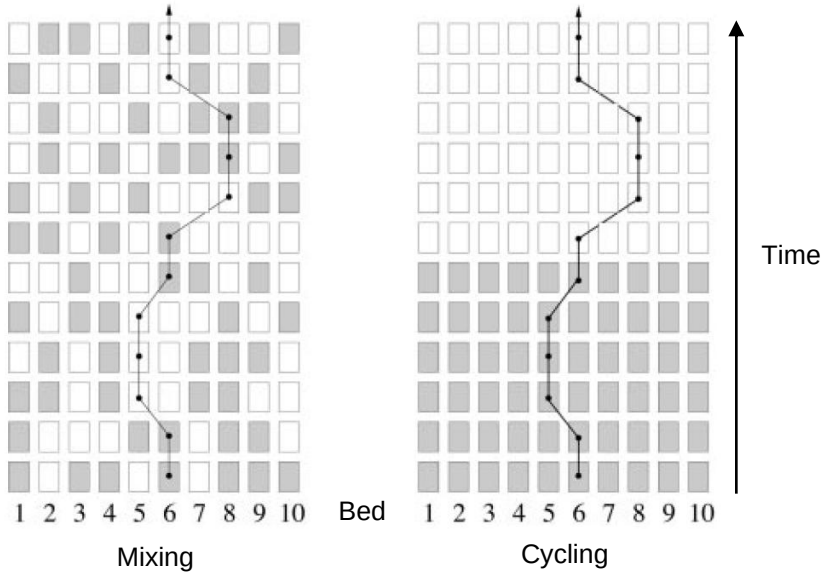

Resistance management:
How to limit the rise of drug resistance?

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Smith et al. 2004, *PNAS*.

Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: Resistance is a regional problem

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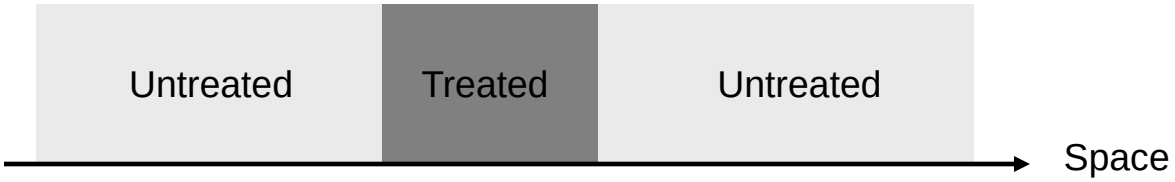

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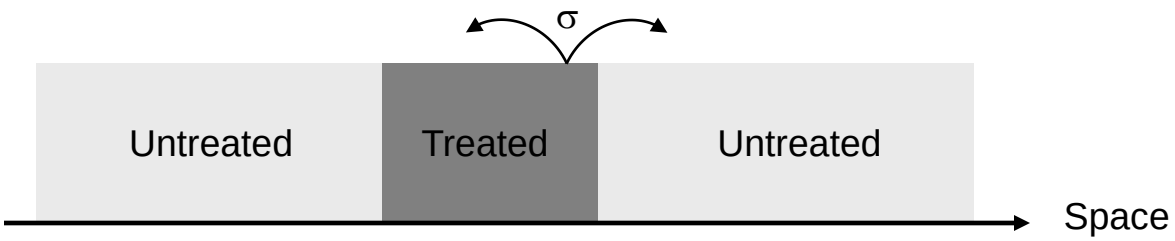

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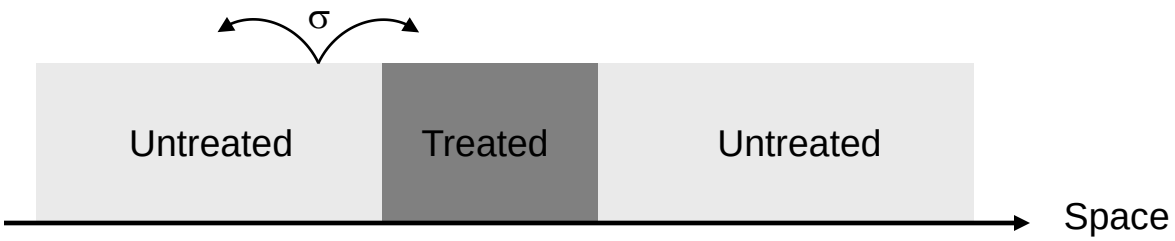

Resistance management:
How to limit the rise of drug resistance?

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   - Epidemiology

Resistance management:
How to limit the rise of drug resistance?

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   - Conclusions & perspectives

Resistance management:
How to limit the rise of drug resistance?

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   - Epidemiology
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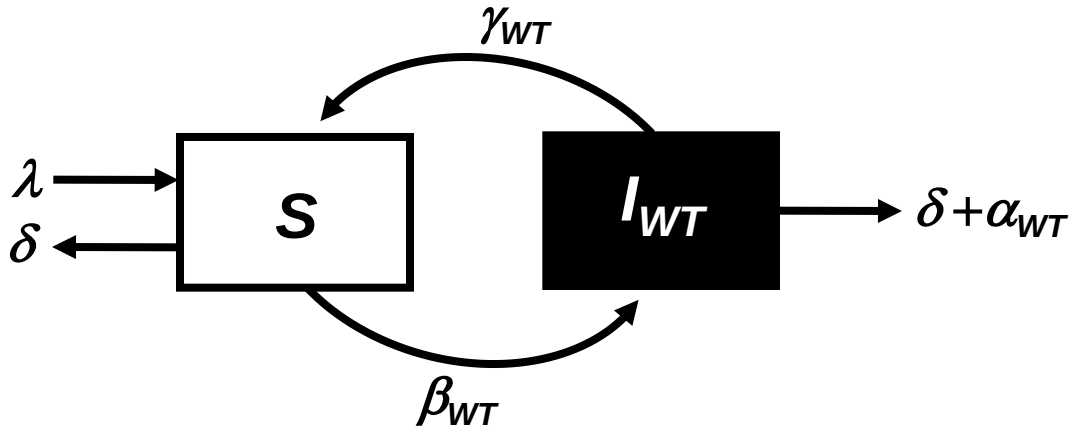
   - Conclusions & perspectives

Epidemiology in space

Epidemiology:



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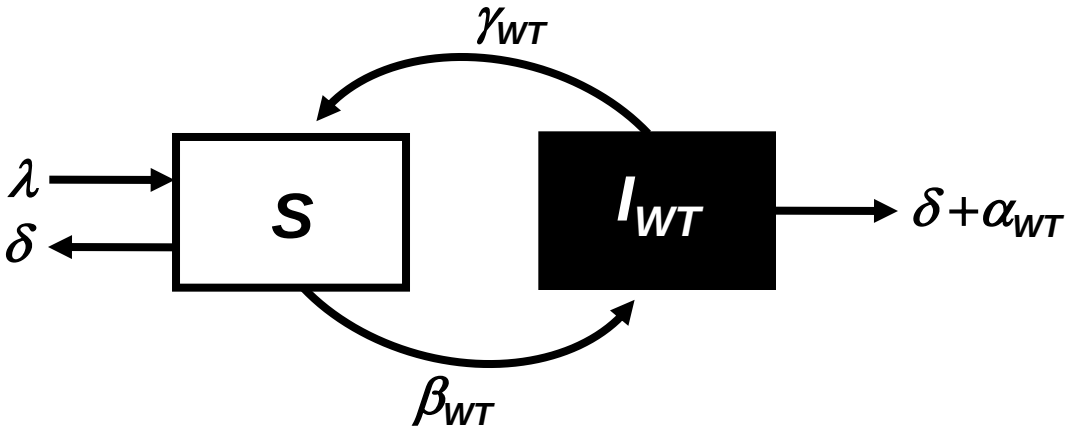

$$R_0^{WT} = \frac{\beta_{WT}}{\delta + \alpha_{WT} + \gamma_{WT}} N$$

Epidemiology in space

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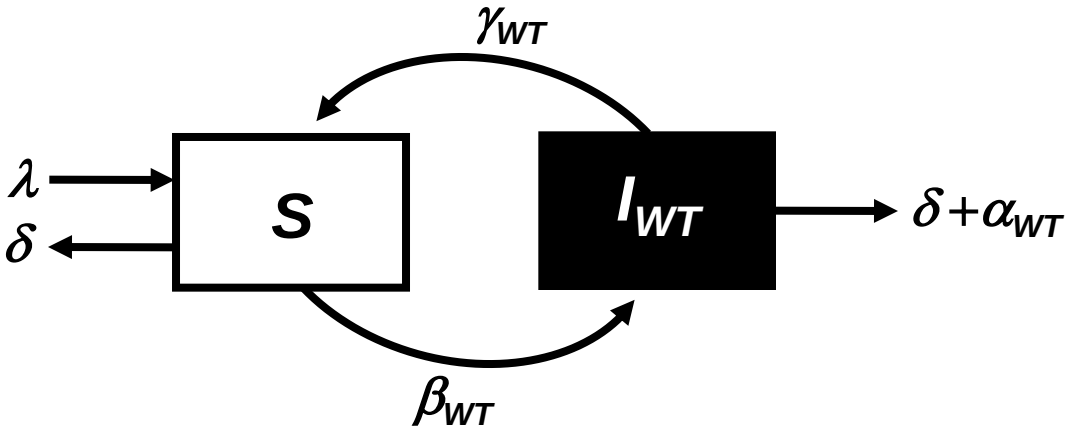

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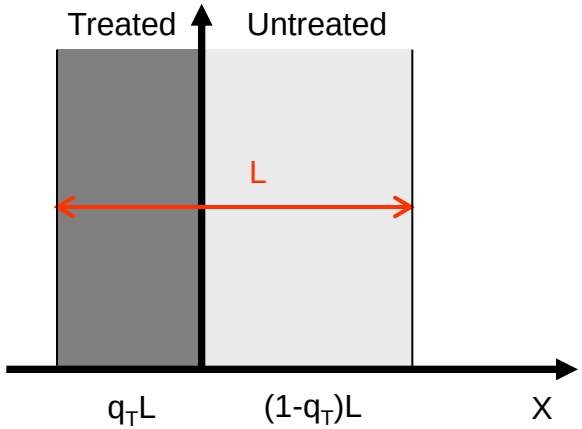

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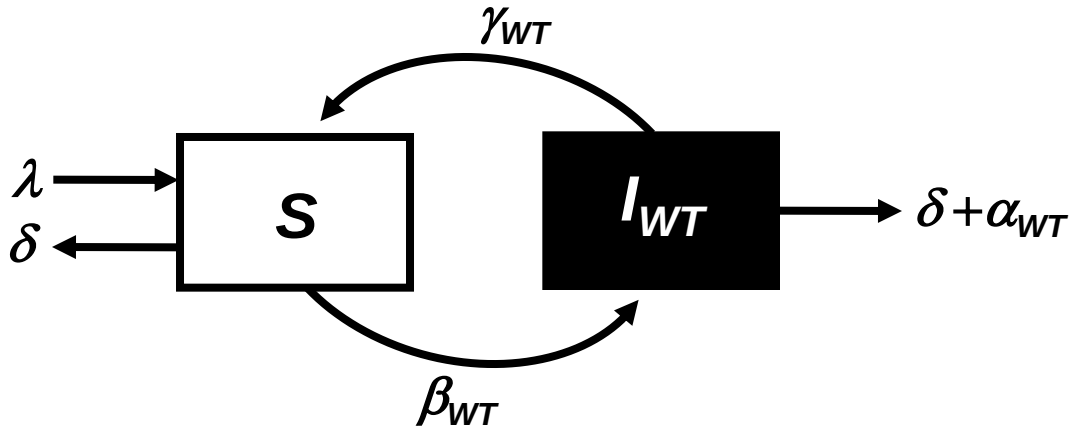

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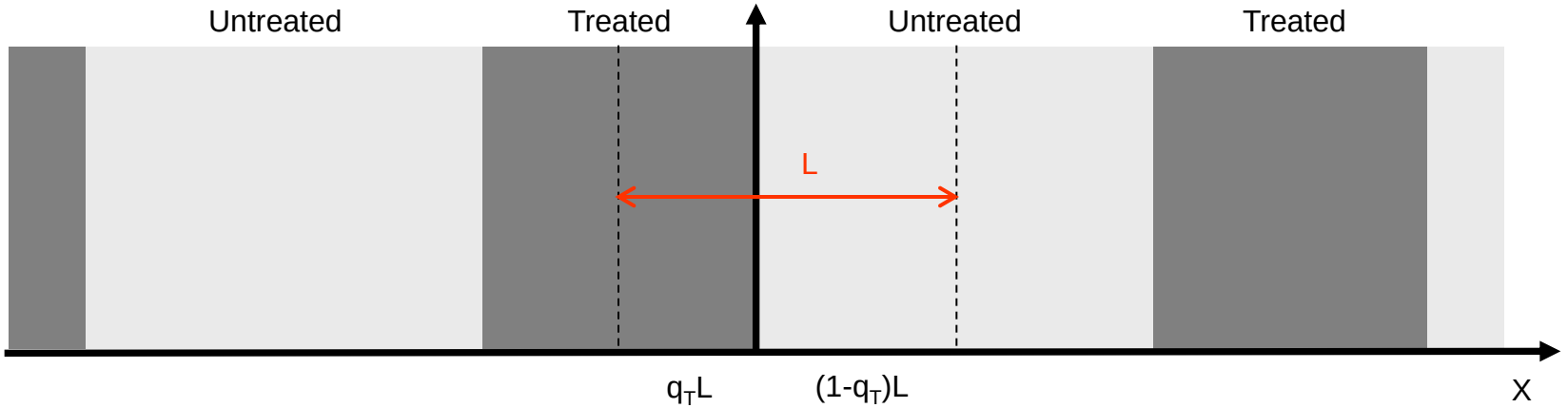


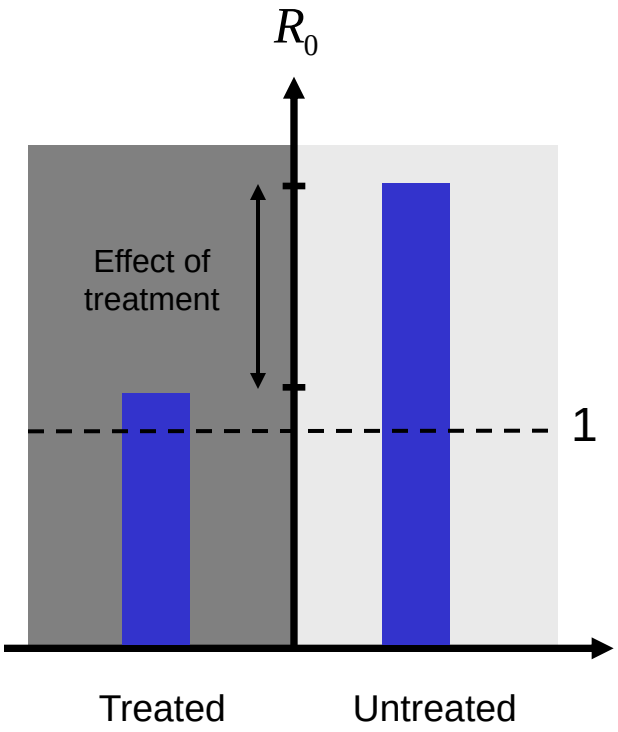
Epidemiology in space

How much drug to eradicate the disease?

Epidemiology in space

How much drug to eradicate the disease?

$$R_0^{WT,T} = \frac{\beta_{WT}^T}{\delta + \alpha_{WT}^T + \gamma_{WT}^T} N > 1$$



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Epidemiology in space

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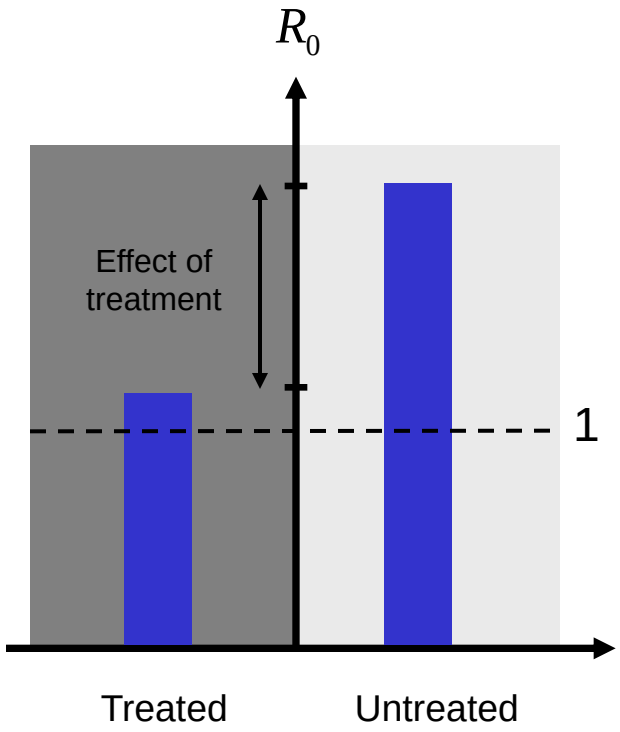

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Never eradication

Epidemiology in space

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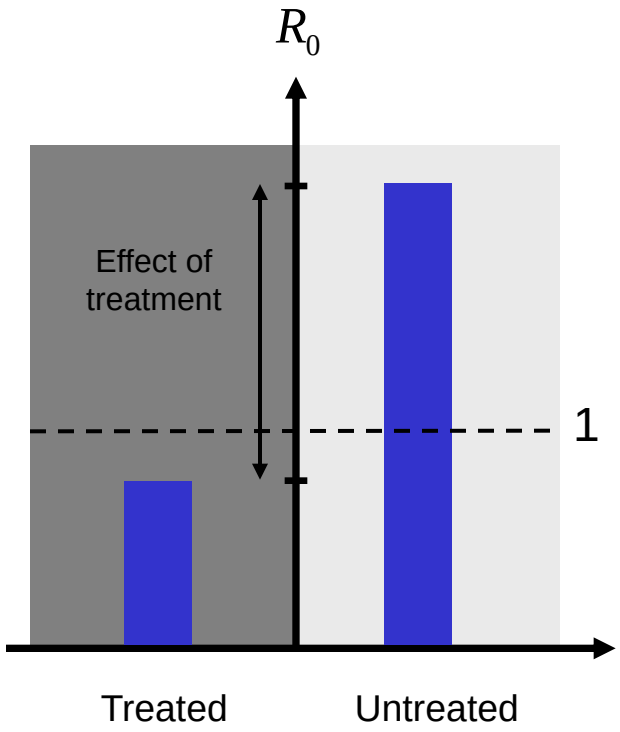

$$R_0^{WT,U} = \frac{\beta_{WT}^{U}}{\delta + \alpha_{WT}^{U} + \gamma_{WT}^{U}} N$$

Eradication?

Epidemiology in space

How much drug to eradicate the disease?

$$\frac{\partial I_{WT}}{\partial t} = \beta_{WT}^{x}\left(N - I_{WT}\right)I_{WT} - \gamma_{WT}^{x} I_{WT} + \frac{\sigma}{2}\frac{\partial^2 I_{WT}}{\partial x^2}$$

Epidemiology in space

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Reaction

Epidemiology in space

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Reaction

Diffusion

Epidemiology in space

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Reaction

Diffusion

Eradication if:

$$q_T > 1 - \frac{\sigma}{L}\frac{1}{\sqrt{2\gamma^{U}_{WT}\left(R_0^{WT,U} - 1\right)}}\arctan\left[\sqrt{\frac{\gamma^{T}_{WT}\left(1 - R_0^{WT,T}\right)}{\gamma^{U}_{WT}\left(R_0^{WT,U} - 1\right)}}\tanh\left(\frac{q_T L\sqrt{2}}{\sigma}\sqrt{\gamma^{T}_{WT}\left(1 - R_0^{WT,T}\right)}\right)\right]$$

Epidemiology in space

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Reaction

Diffusion

Eradication if:

More diffusion ⟶ eradication is easier

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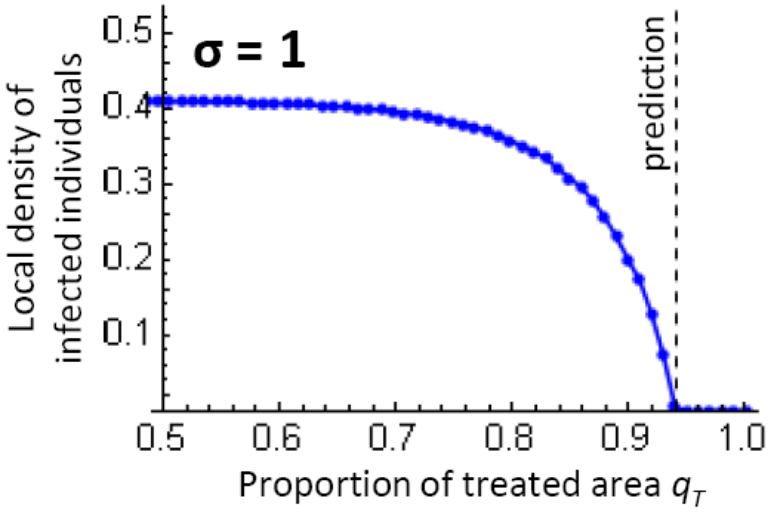

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$$q_T > 1 - \frac{\sigma}{L} \frac{1}{\sqrt{2\gamma_{WT}^{U}\left(R_0^{WT,U}-1\right)}} \arctan\left[\sqrt{\frac{\gamma_{WT}^{T}\left(1-R_0^{WT,T}\right)}{\gamma_{WT}^{U}\left(R_0^{WT,U}-1\right)}} \tanh\left(\frac{q_T L\sqrt{2}}{\sigma}\sqrt{\gamma_{WT}^{T}\left(1-R_0^{WT,T}\right)}\right)\right]$$

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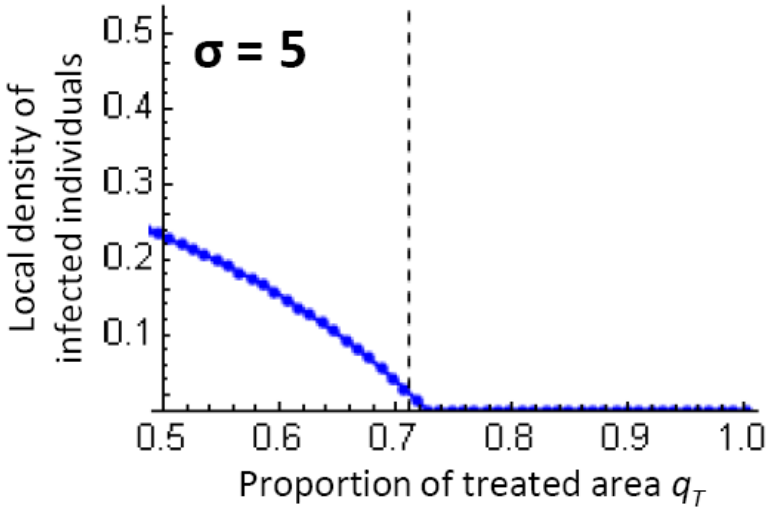

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Epidemiology in space

How much drug to eradicate the disease?

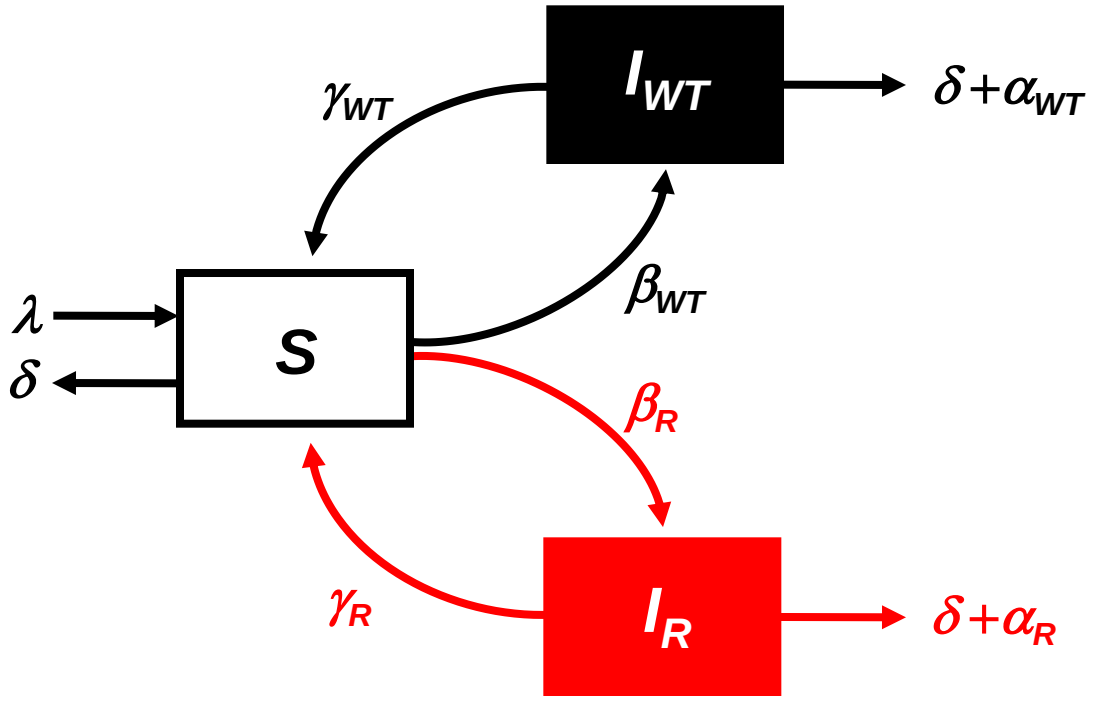
Migration → Maladaptation (source-sink dynamics) → Eradication

Eradication if:

More diffusion → eradication is easier

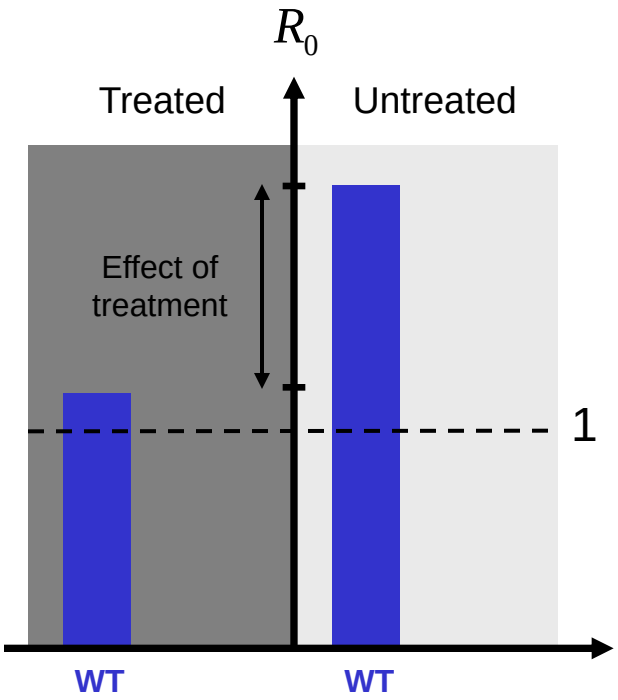
$$q_T > 1 - \frac{\sigma}{L} \frac{1}{\sqrt{2\gamma_{WT}^{U}\left(R_0^{WT,U}-1\right)}} \arctan\left[\sqrt{\frac{\gamma_{WT}^{T}\left(1-R_0^{WT,T}\right)}{\gamma_{WT}^{U}\left(R_0^{WT,U}-1\right)}} \tanh\left(\frac{q_T L\sqrt{2}}{\sigma}\sqrt{\gamma_{WT}^{T}\left(1-R_0^{WT,T}\right)}\right)\right]$$

Evolutionary epidemiology in space



Evolutionary epidemiology in space

$$R_0^{WT,T} = \frac{\beta_{WT}^T}{\delta + \alpha_{WT}^T + \gamma_{WT}^T} N$$



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Evolutionary epidemiology in space

$$R_0^{R,T} = \frac{\beta_R^T}{\delta + \alpha_R^T + \gamma_R^T} N$$

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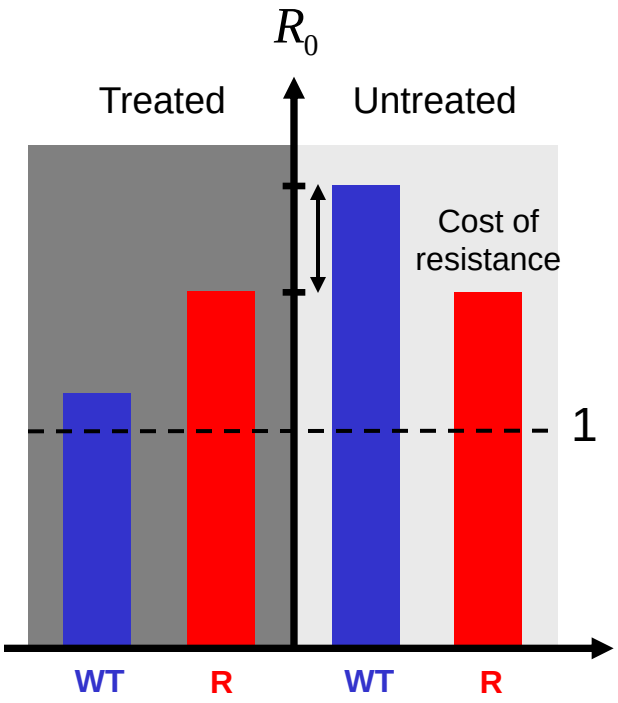

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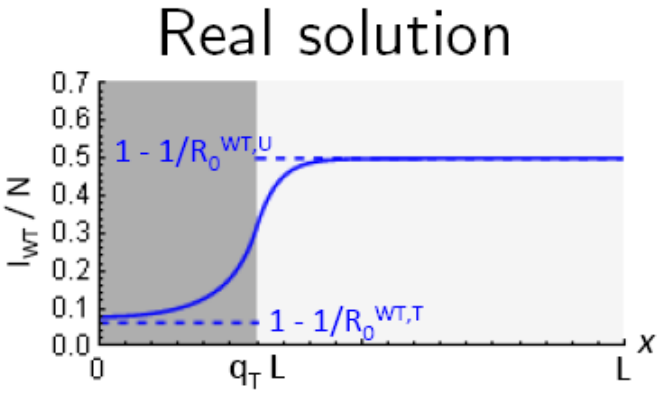
Evolutionary epidemiology in space

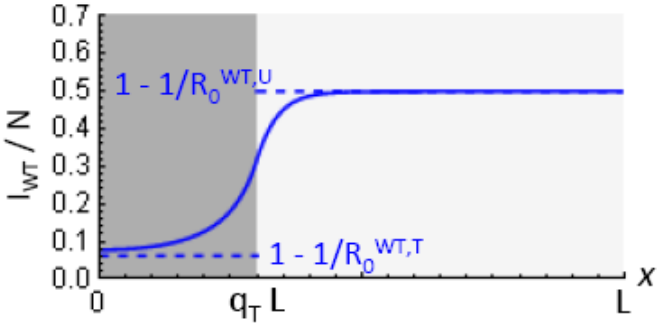
Can the resistant strain invade?



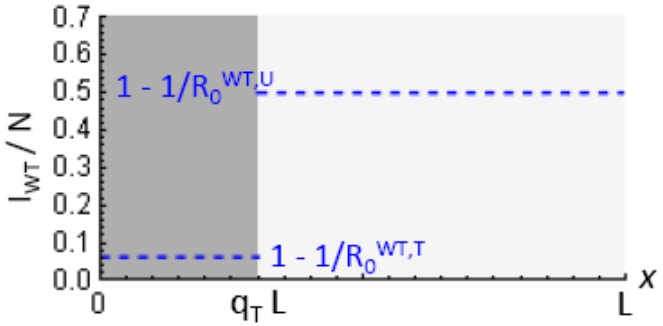
Evolutionary epidemiology in space

Can the resistant strain invade?

Real solution



Low migration approximation



Evolutionary epidemiology in space

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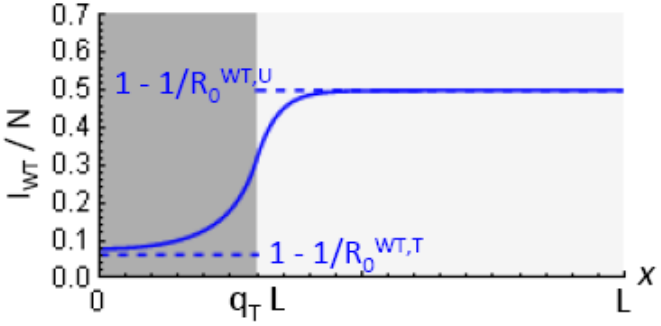

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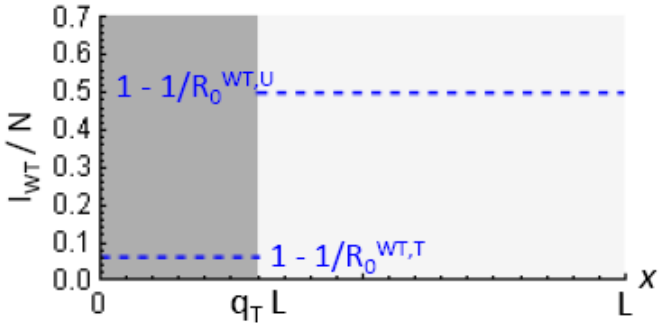

$$\tau = \frac{1 - 1/R_0^{\mathrm{WT,U}}}{1 - 1/R_0^{\mathrm{WT,T}}}$$

Evolutionary epidemiology in space

Can the resistant strain invade?

Evolutionary epidemiology in space

Can the resistant strain invade?

$$q_T > \sigma \frac{1}{L\sqrt{\gamma_R}} \frac{1}{\sqrt{2\left(\frac{R_0^R}{R_0^{WT,T}} - 1\right)}} \arctan\left[\tau^2 \sqrt{\frac{1 - \frac{R_0^R}{R_0^{WT,U}}}{\frac{R_0^{WT,U}}{R_0^{WT,T}} - 1}} \tanh\left(\frac{(1-q_T)L\sqrt{2\gamma_R}}{\sigma} \sqrt{1 - \frac{R_0^R}{R_0^{WT,U}}}\right)\right]$$

Evolutionary epidemiology in space

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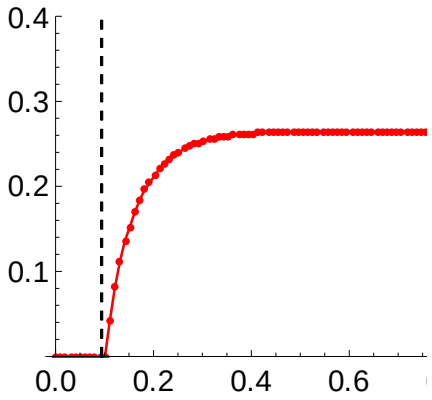
Local frequency of resistant strain



Proportion of treated area q_T

$\sigma = 0.5$

Evolutionary epidemiology in space

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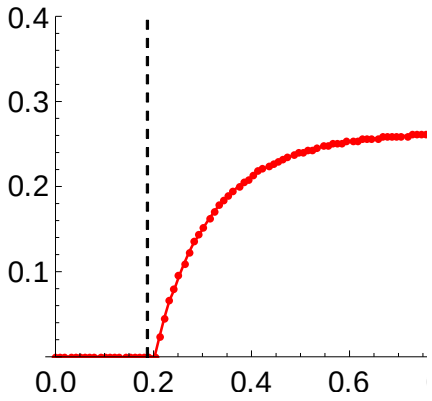

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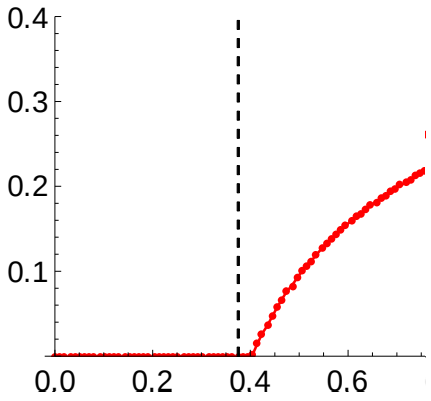

Evolutionary epidemiology in space

Can the resistant strain invade?

$$q_T > \sigma \frac{1}{L\sqrt{\gamma_R}} \frac{1}{\sqrt{2\left(\frac{R_0^R}{R_0^{WT,T}} - 1\right)}} \arctan\left[\tau^2 \sqrt{\frac{1 - \frac{R_0^R}{R_0^{WT,U}}}{\frac{R_0^{WT,U}}{R_0^{WT,T}} - 1}} \tanh\left(\frac{(1-q_T)L\sqrt{2\gamma_R}}{\sigma} \sqrt{1 - \frac{R_0^R}{R_0^{WT,U}}}\right)\right]$$

Migration counteracts selection → Maladaptation

Evolutionary epidemiology in space

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Evolutionary epidemiology in space

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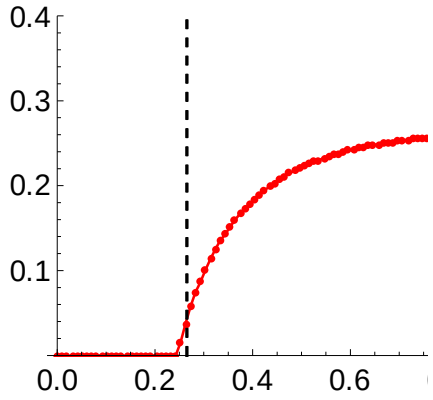
Local frequency of resistant strain



$\gamma_R = 0.6$

Proportion of treated area q_T

Evolutionary epidemiology in space

Can the resistant strain invade?

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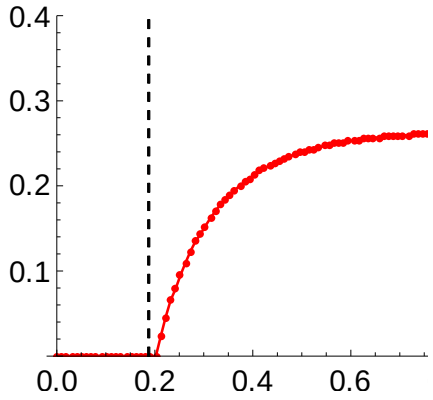
Local frequency of resistant strain



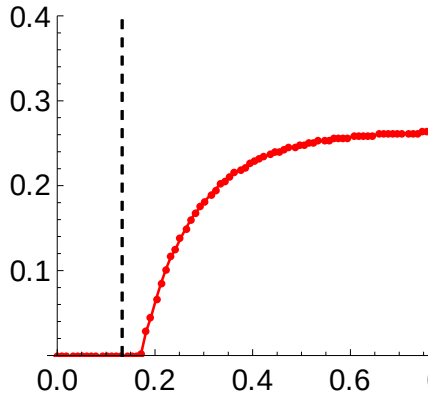
$\gamma_R = 1.2$

Evolutionary epidemiology in space

Can the resistant strain invade?

$$q_T > \sigma \frac{1}{L\sqrt{\gamma_R}} \frac{1}{\sqrt{2\left(\frac{R_0^R}{R_0^{WT,T}} - 1\right)}} \arctan\left[\tau^2 \sqrt{\frac{1 - \frac{R_0^R}{R_0^{WT,U}}}{\frac{R_0^{WT,U}}{R_0^{WT,T}} - 1}} \tanh\left(\frac{(1-q_T)L\sqrt{2\gamma_R}}{\sigma} \sqrt{1 - \frac{R_0^R}{R_0^{WT,U}}}\right)\right]$$

Local frequency of resistant strain



$\gamma_R = 2.5$

Proportion of treated area q_T

Evolutionary epidemiology in space

Can the resistant strain invade?

$$q_T > \sigma \frac{1}{L\sqrt{\gamma_R}} \frac{1}{\sqrt{2\left(\frac{R_0^R}{R_0^{WT,T}} - 1\right)}} \arctan\left[\tau^2 \sqrt{\frac{1 - \frac{R_0^R}{R_0^{WT,U}}}{\frac{R_0^{WT,U}}{R_0^{WT,T}} - 1}} \tanh\left(\frac{(1-q_T)L\sqrt{2\gamma_R}}{\sigma} \sqrt{1 - \frac{R_0^R}{R_0^{WT,U}}}\right)\right]$$

Faster clearance → Shorter generation time & higher *r*

Evolutionary epidemiology in space

Can the resistant strain invade?

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Faster clearance → Shorter generation time & higher *r*

$$R_0 = \frac{\beta}{\gamma} N \quad \neq \quad r_0 = \beta N - \gamma$$

Evolutionary epidemiology in space

Can the resistant strain invade?

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Faster clearance → Shorter generation time & higher *r* → Stronger selection

$$R_0 = \frac{\beta}{\gamma} N \quad \neq \quad r_0 = \beta N - \gamma$$

Evolutionary epidemiology in space

Can the resistant strain invade?

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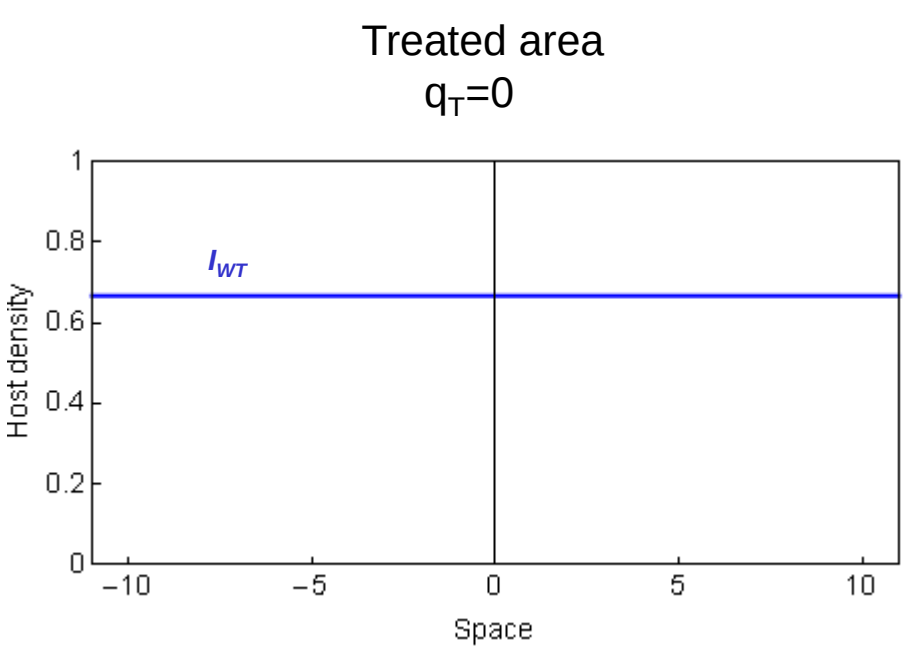
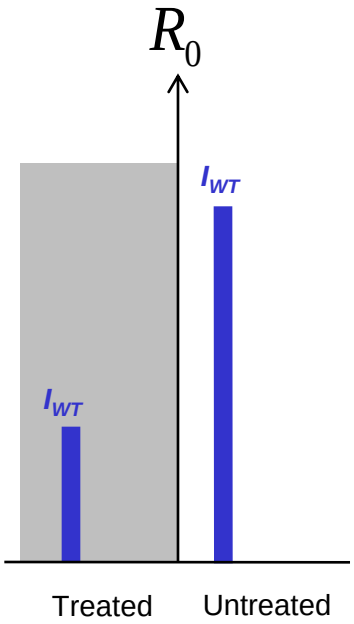
Faster clearance → Shorter generation time & higher *r* → Stronger selection → Easier to evolve resistance

$$R_0 = \frac{\beta}{\gamma} N \quad \neq \quad r_0 = \beta N - \gamma$$

Evolutionary epidemiology in space

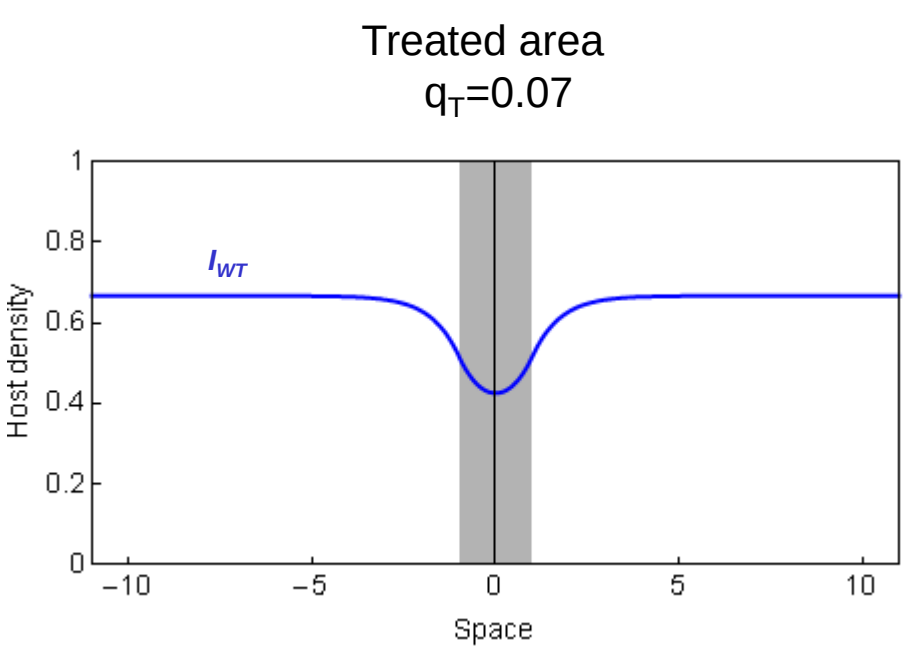
Epidemiology

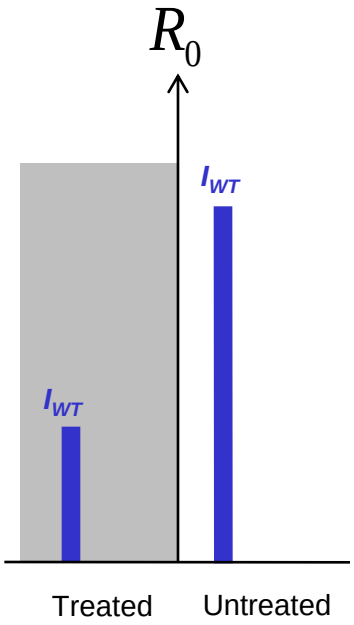




Evolutionary epidemiology in space

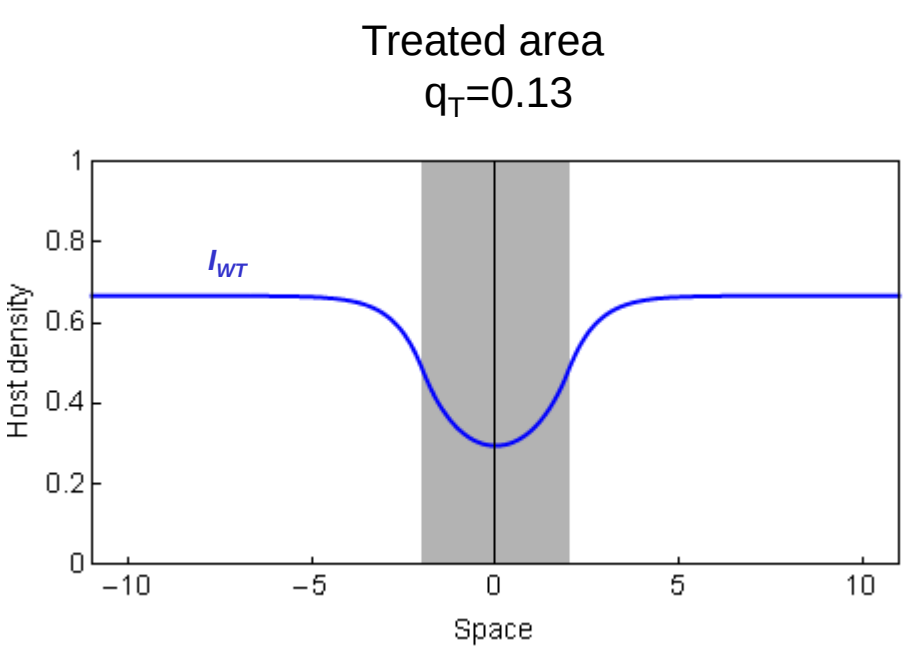
Epidemiology

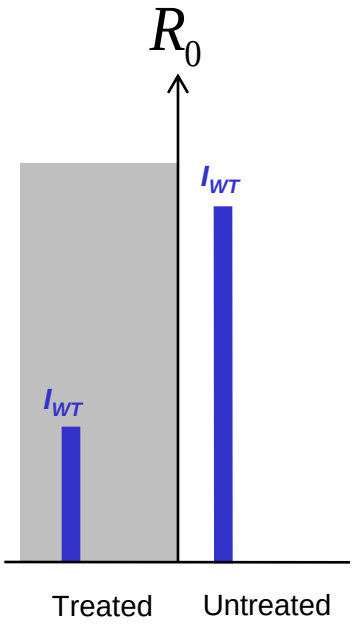




Evolutionary epidemiology in space

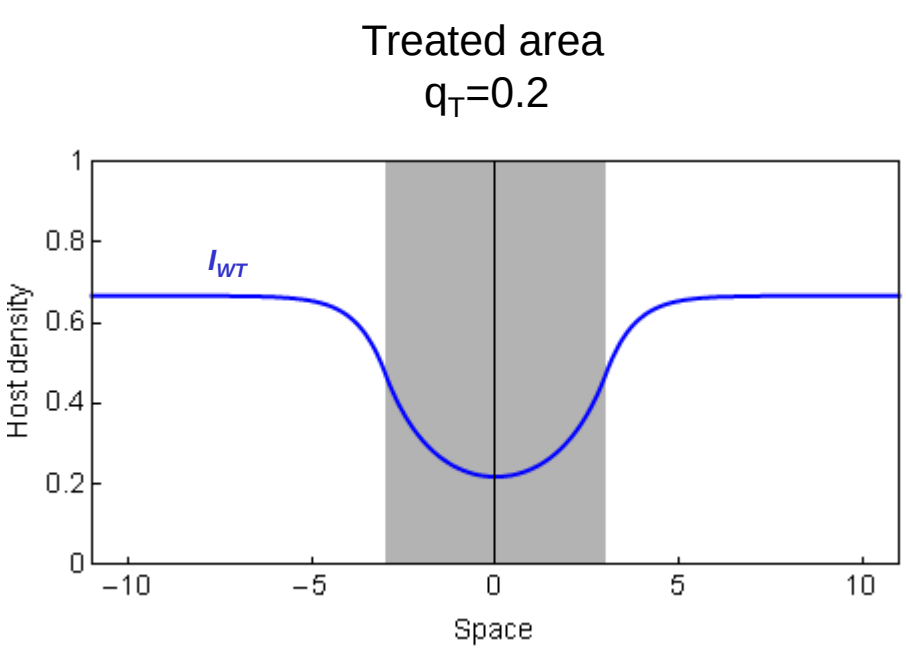
Epidemiology

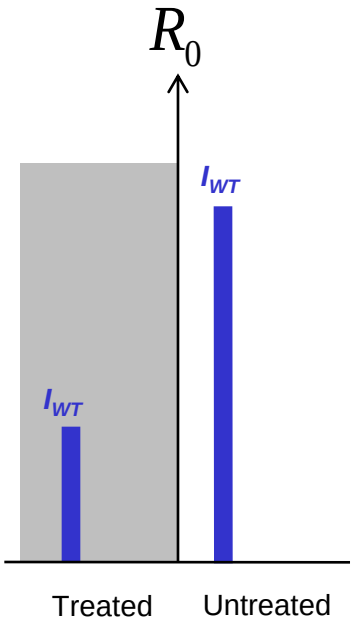




Evolutionary epidemiology in space

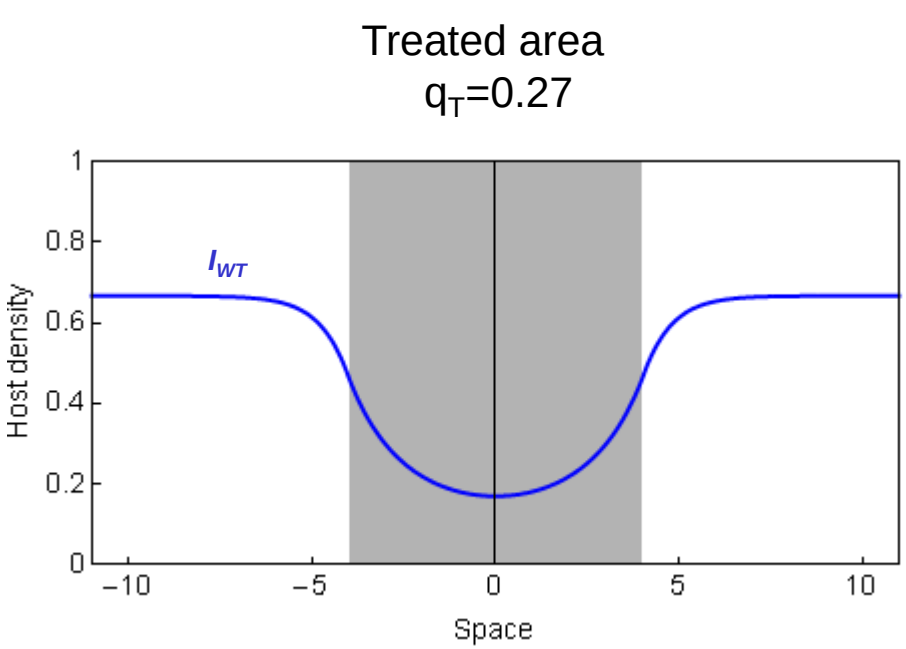
Epidemiology

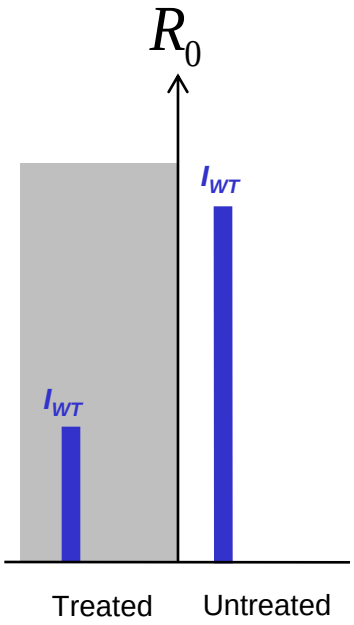




Evolutionary epidemiology in space

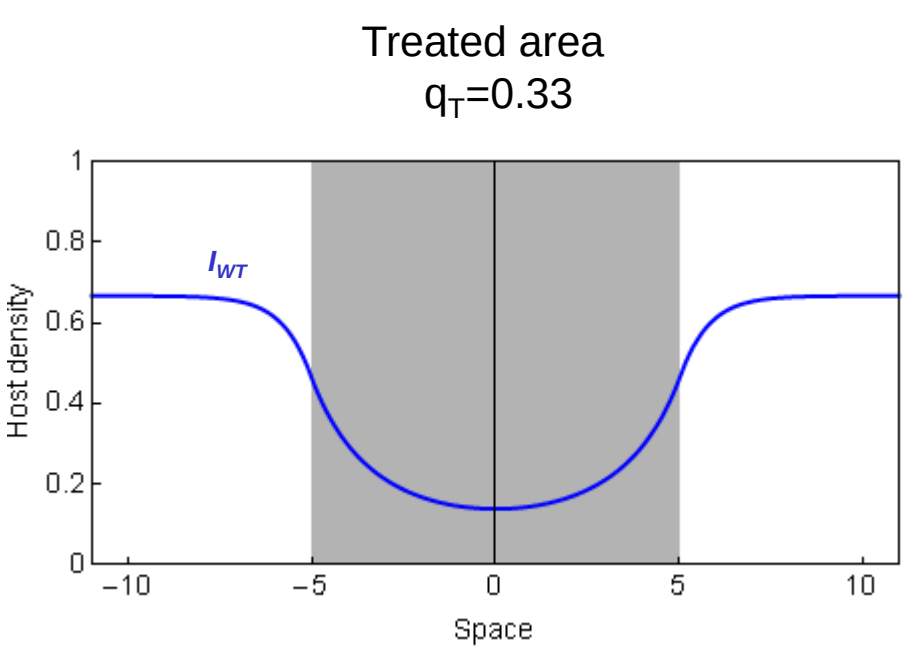
Epidemiology

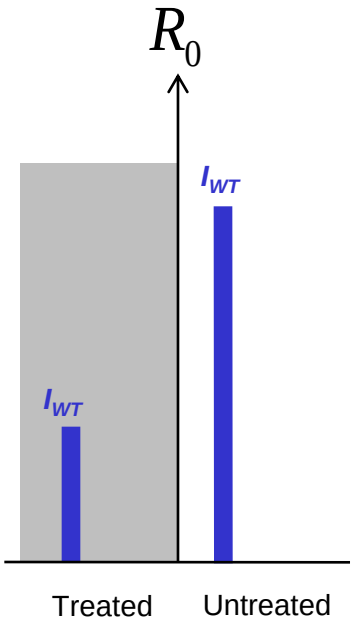




Evolutionary epidemiology in space

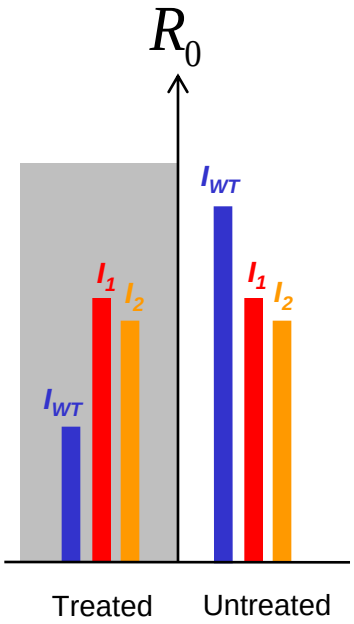
Epidemiology





Evolutionary epidemiology in space

Epidemiology
+
Evolution



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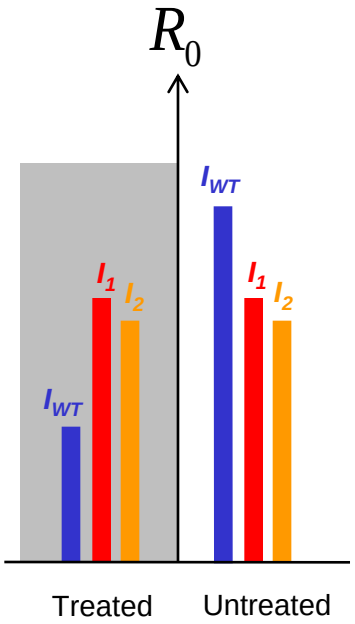

$\gamma_{R,2} > \gamma_{R,1}$

$r_2 > r_1$

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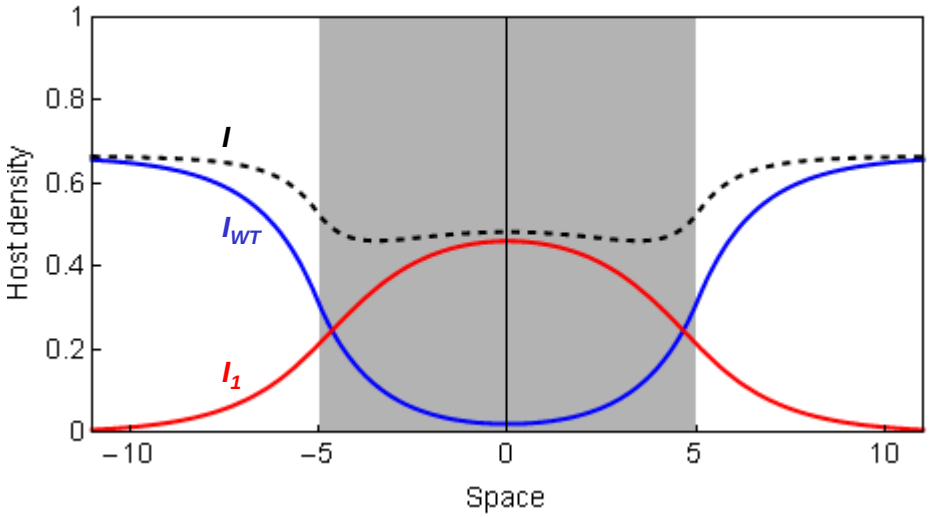
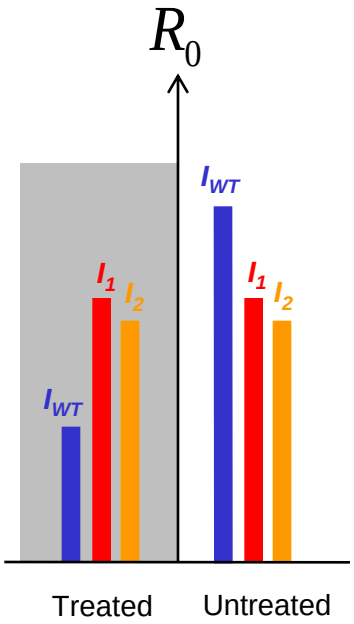
Treated area
q_T=0.33





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Evolutionary epidemiology in space

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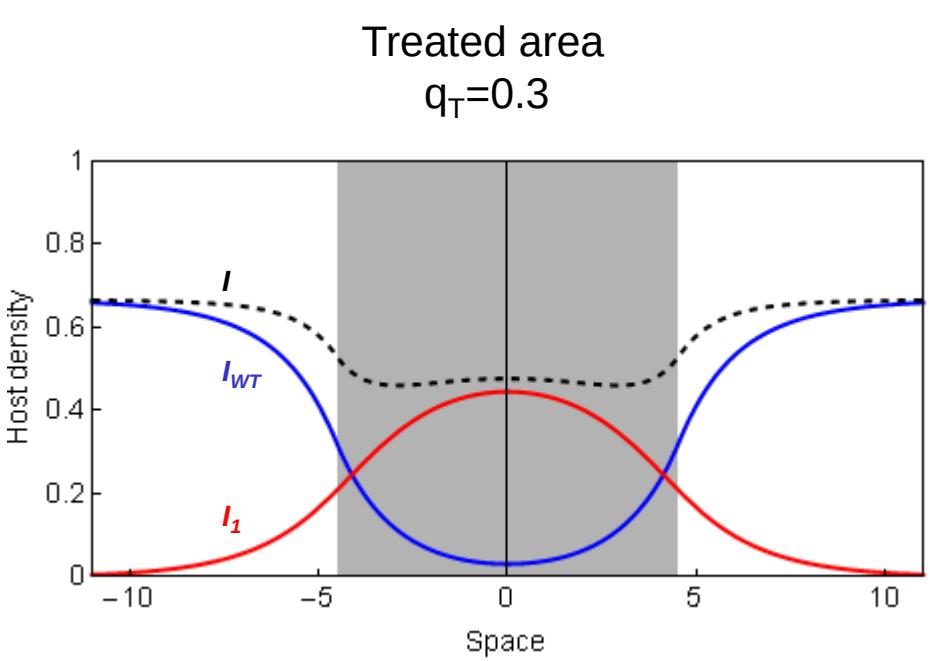
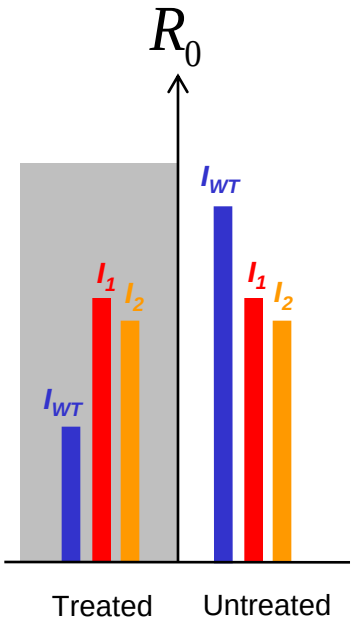
Evolution





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Evolutionary epidemiology in space

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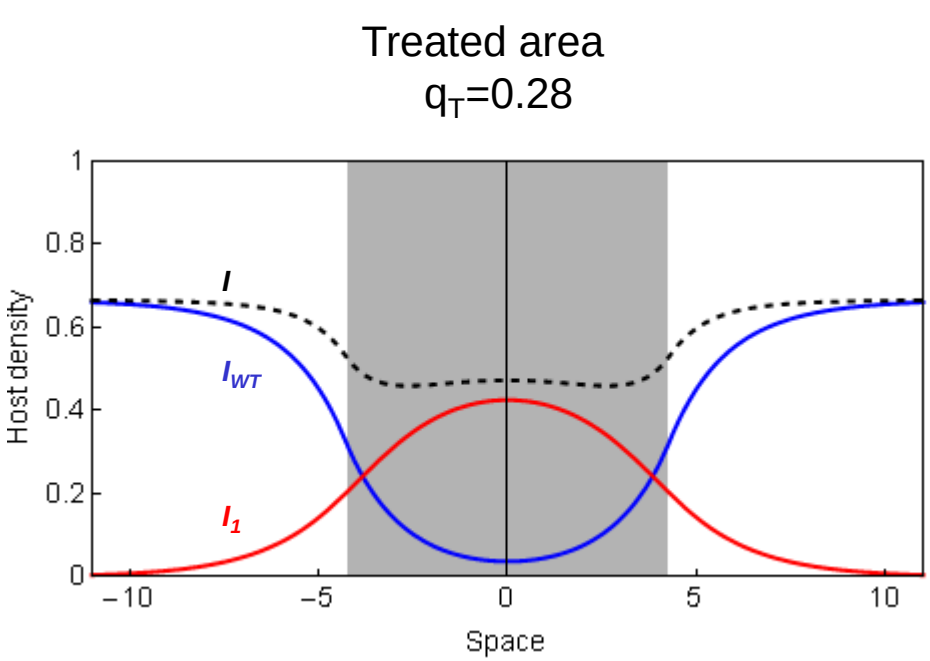

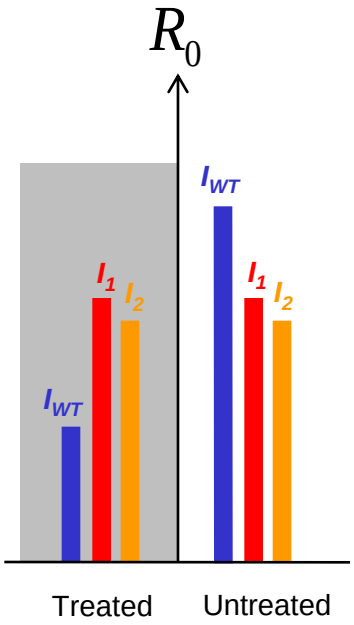

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Evolutionary epidemiology in space

Epidemiology
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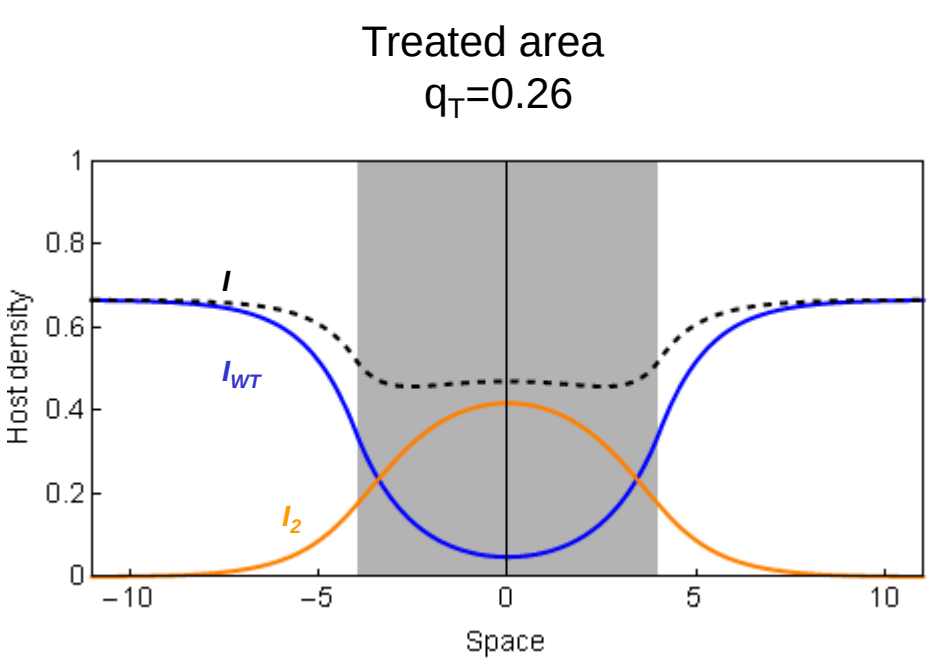
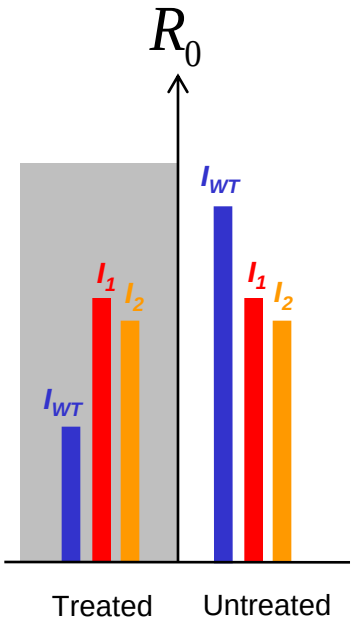
Evolution





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Evolutionary epidemiology in space

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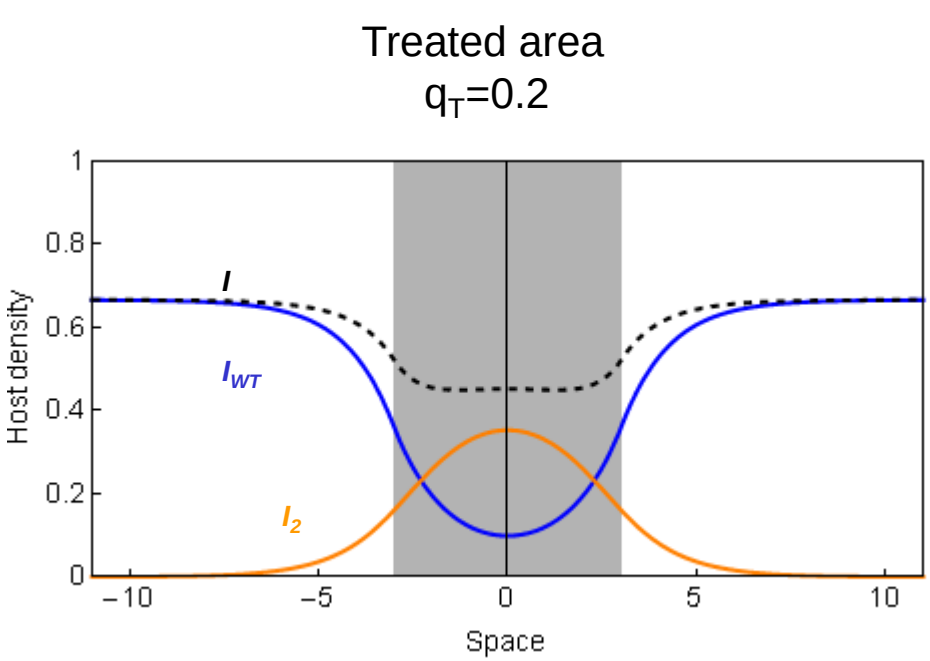

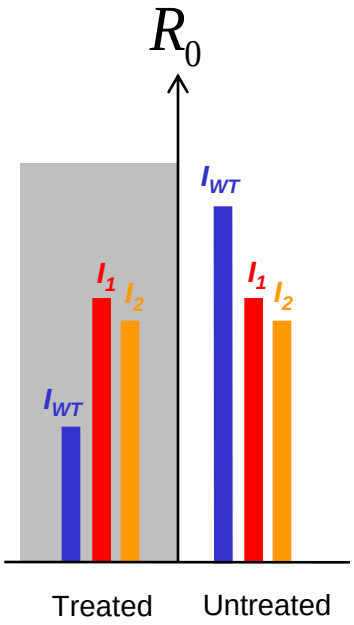

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Evolutionary epidemiology in space

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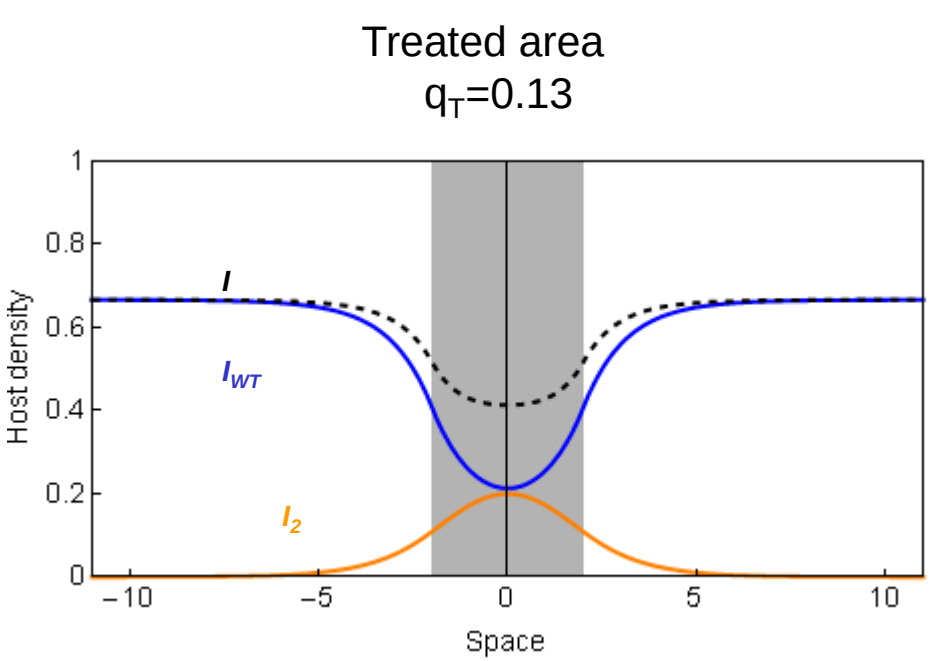

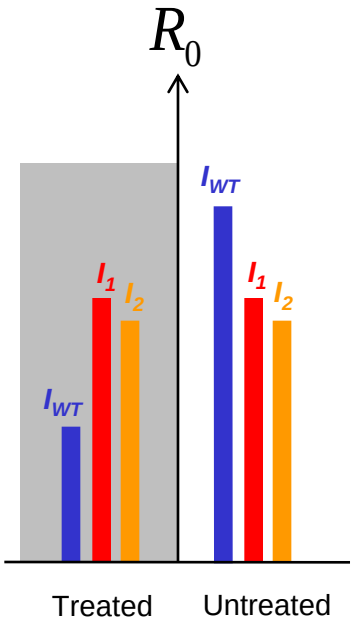

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Evolutionary epidemiology in space

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+
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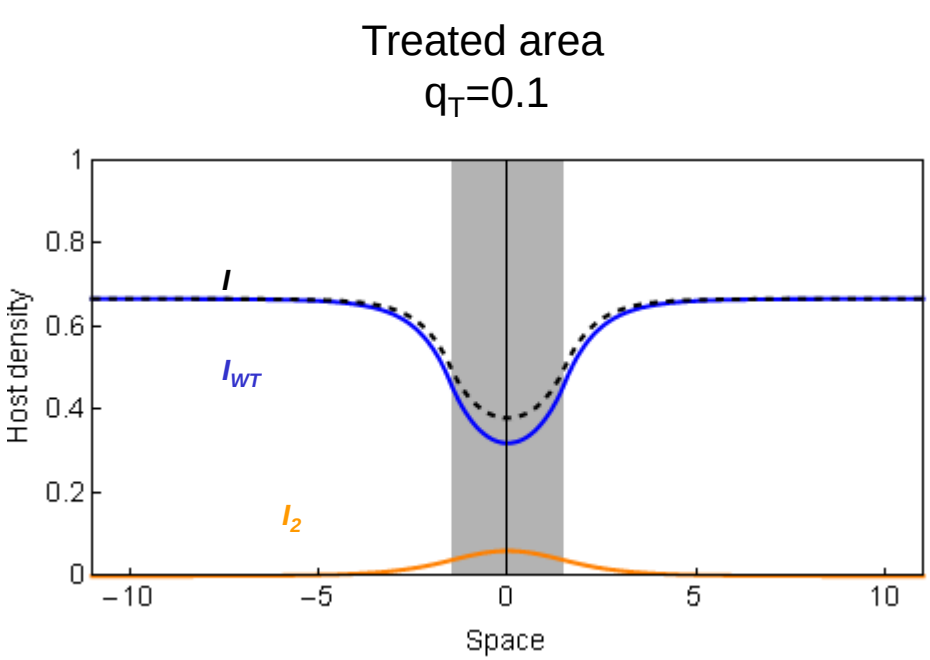

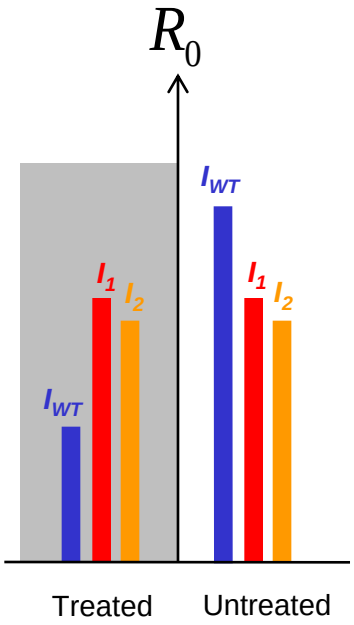

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Evolutionary epidemiology in space

Epidemiology
+
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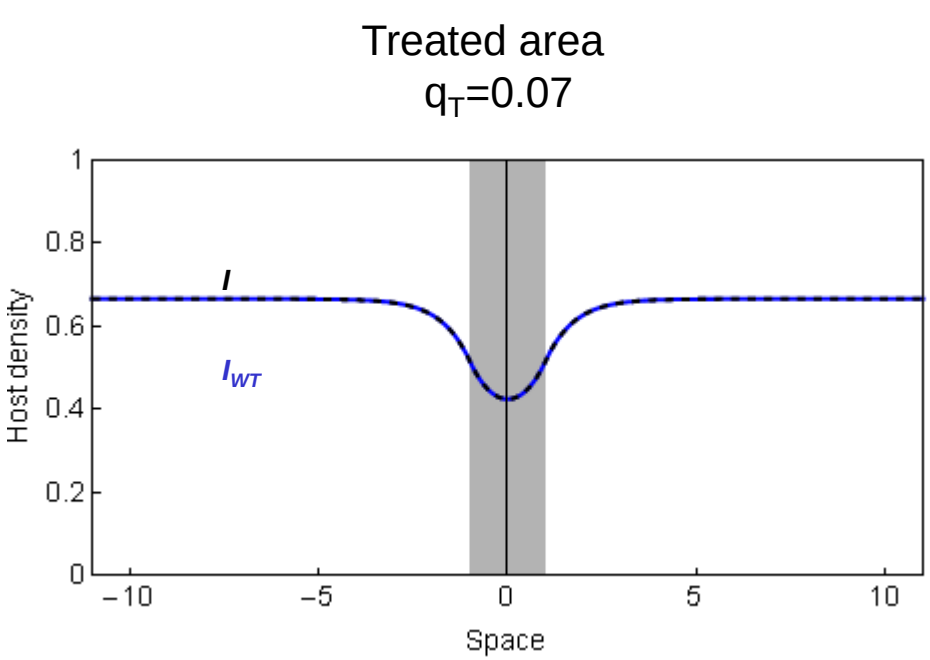
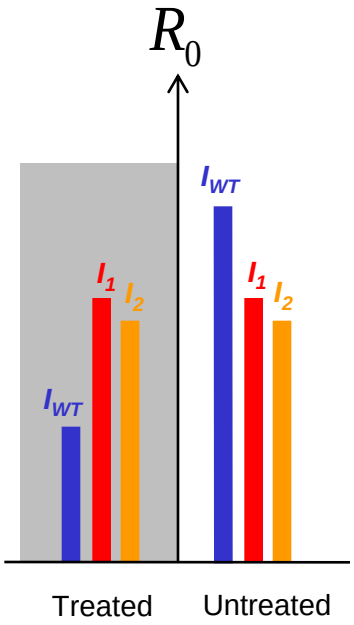


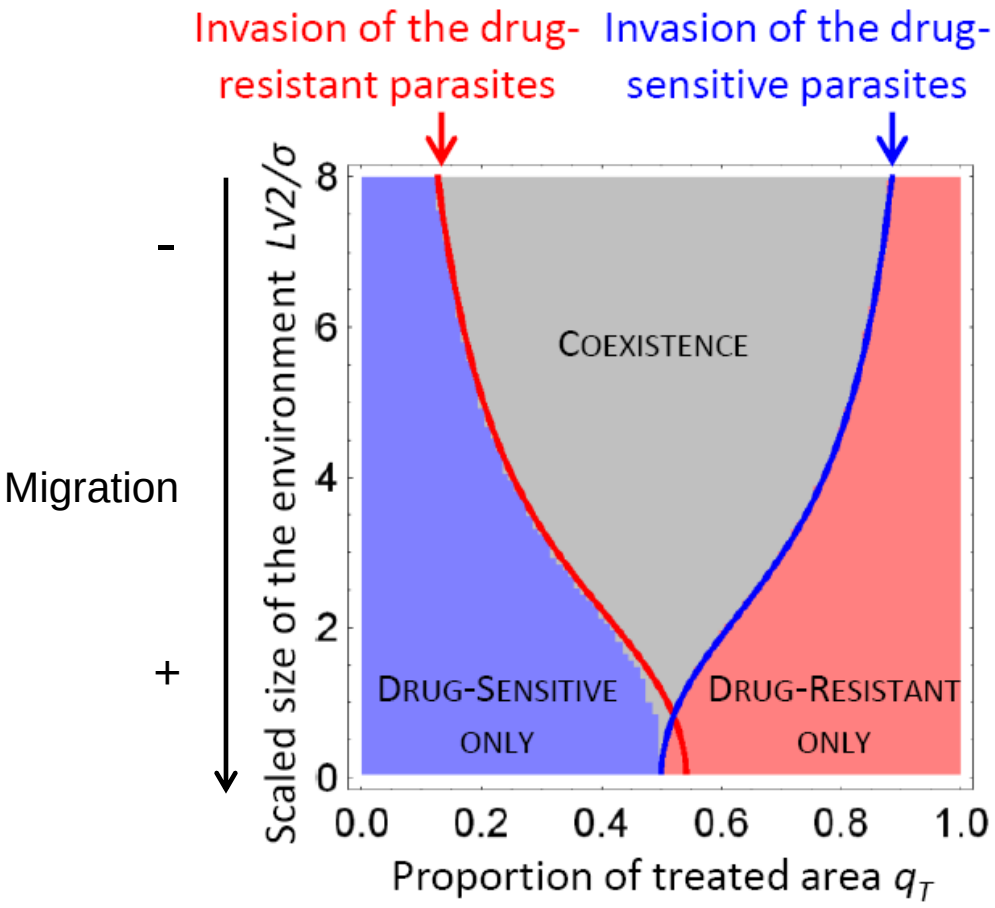


$\gamma_{R,2} > \gamma_{R,1}$

$r_2 > r_1$

Evolutionary epidemiology in space

Coexistence and migration



Evolutionary epidemiology in space

Generalization to two-host systems

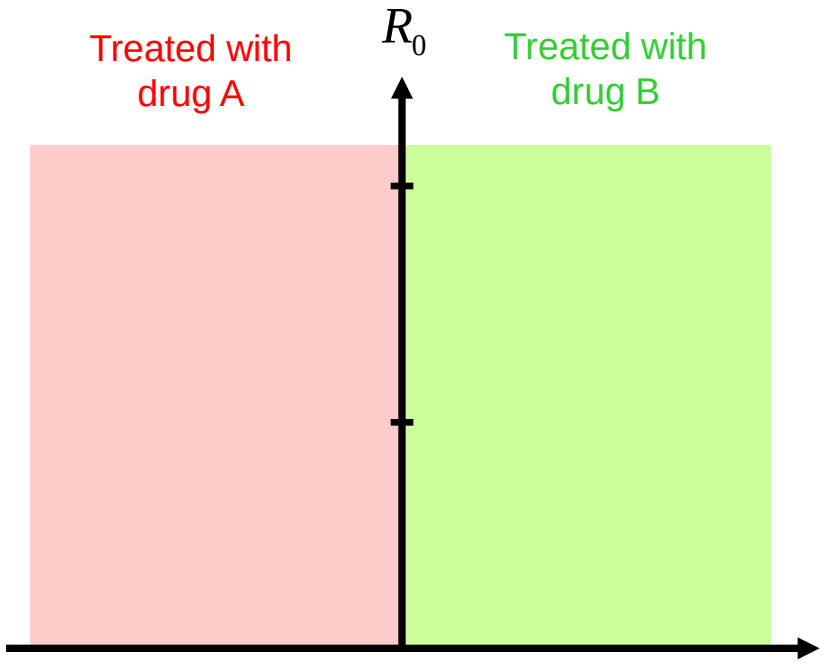
$$q_T > \sigma_e \frac{1}{L\sqrt{\Gamma_R}} \frac{1}{\sqrt{2\left(\frac{R_0^R}{R_0^{WT,T}} - 1\right)}} \arctan\left[\tau^2 \sqrt{\frac{1 - \frac{R_0^R}{R_0^{WT,U}}}{\frac{R_0^{WT,U}}{R_0^{WT,T}} - 1}} \tanh\left(\frac{(1-q_T)L\sqrt{2\Gamma_R}}{\sigma} \sqrt{1 - \frac{R_0^R}{R_0^{WT,U}}}\right)\right]$$

$$\sigma_e = \frac{\sigma_H^2 / \gamma_R + \sigma_V^2 / \nu_R}{1/\gamma_R + 1/\nu_R}$$

$$\Gamma_R = \frac{1}{1/\gamma_R + 1/\nu_R}$$

Evolutionary epidemiology in space

Spatial mosaic with two drugs



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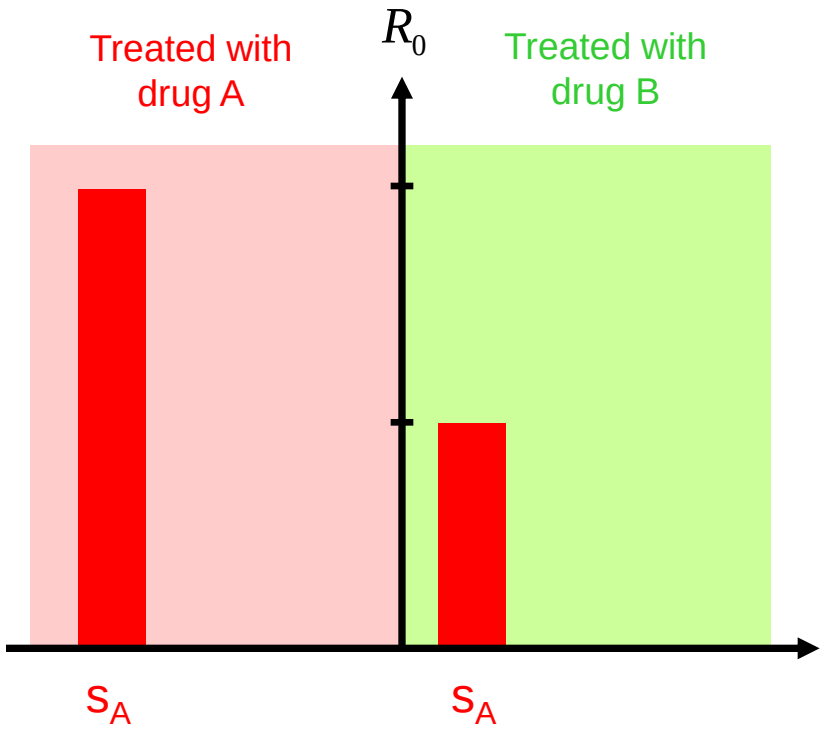
Spatial mosaic with two drugs



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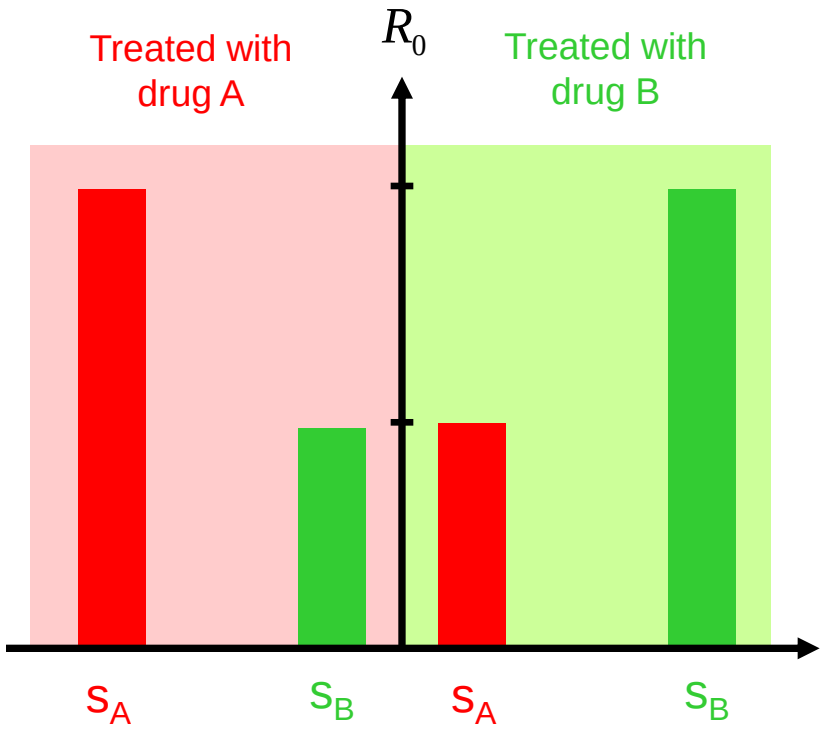
Spatial mosaic with two drugs



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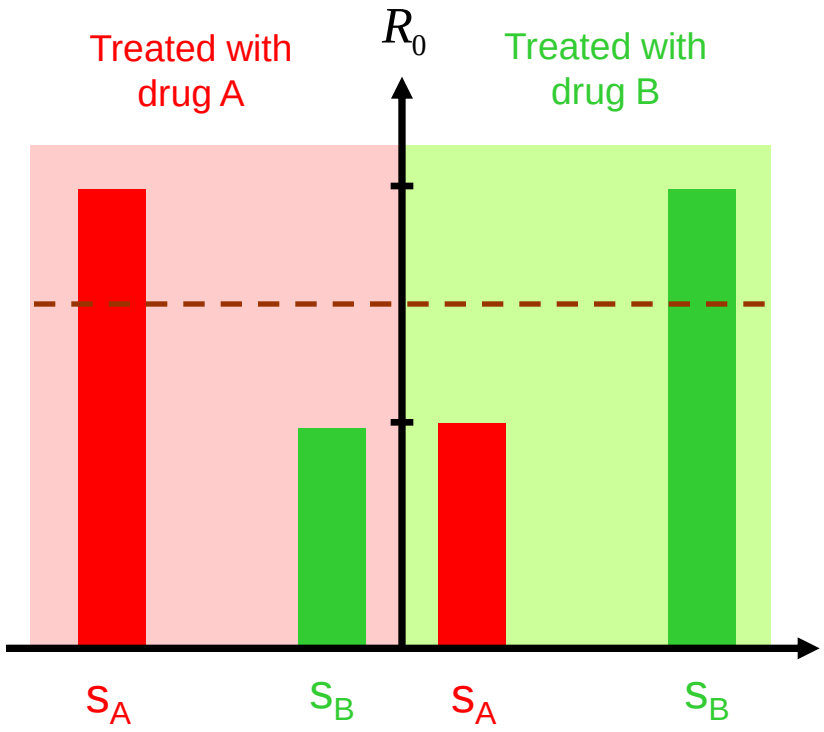
Spatial mosaic with two drugs



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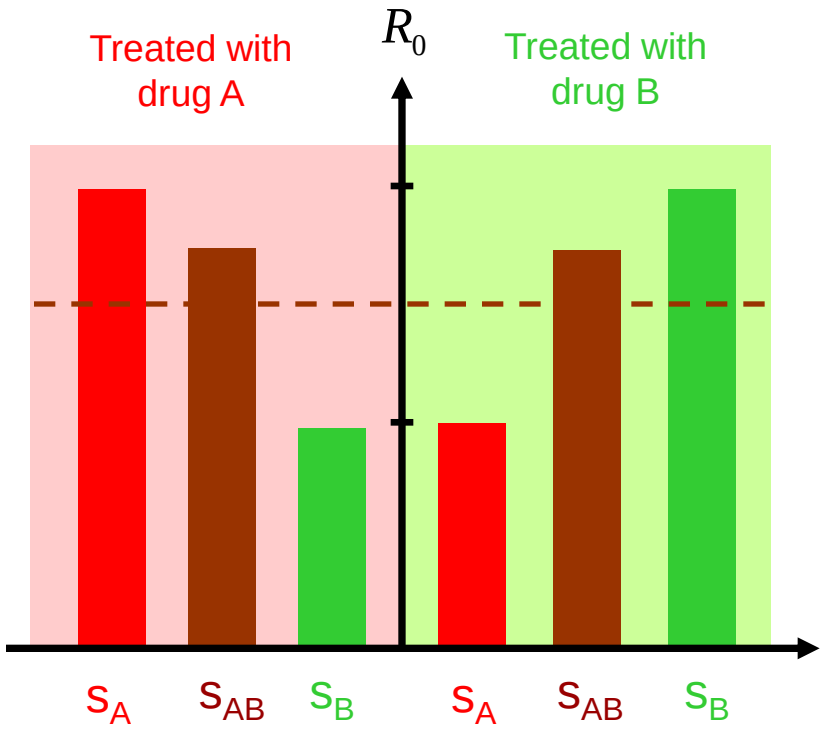
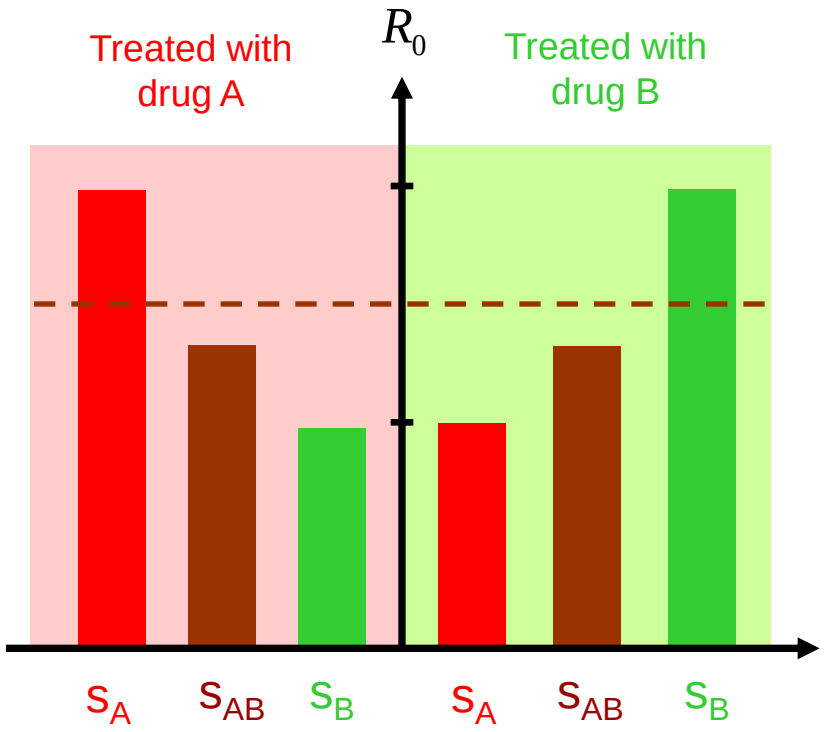


Evolutionary epidemiology in space

Spatial mosaic with two drugs



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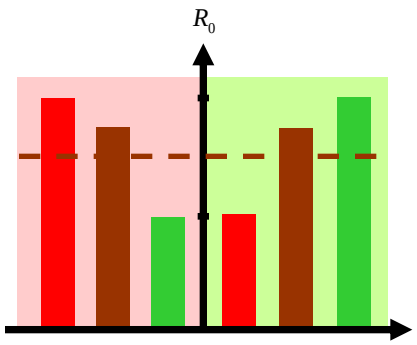

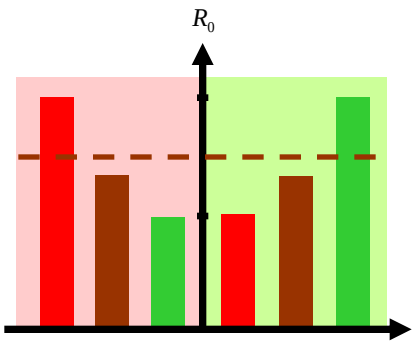

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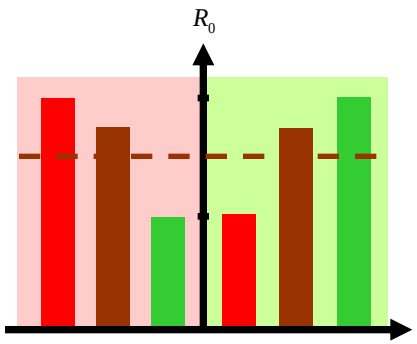

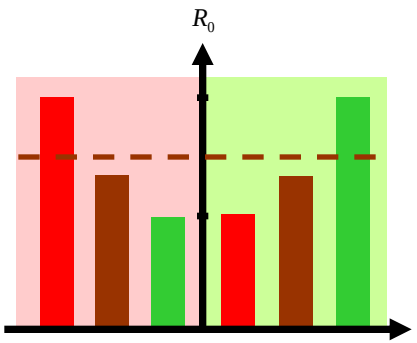

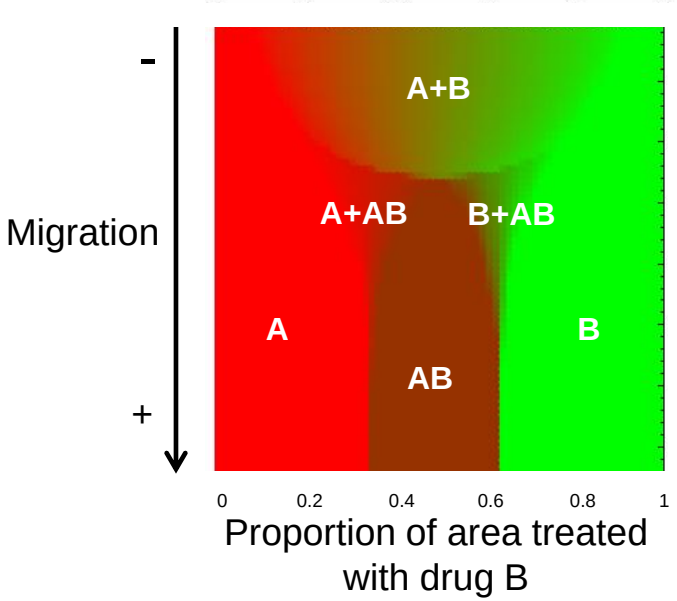

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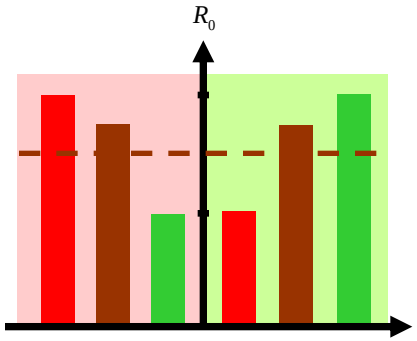

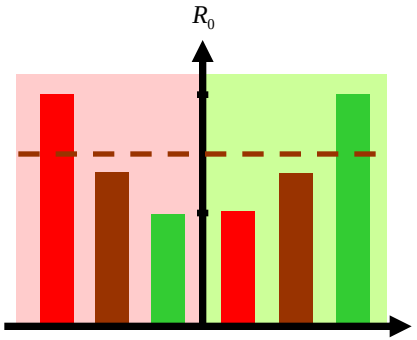

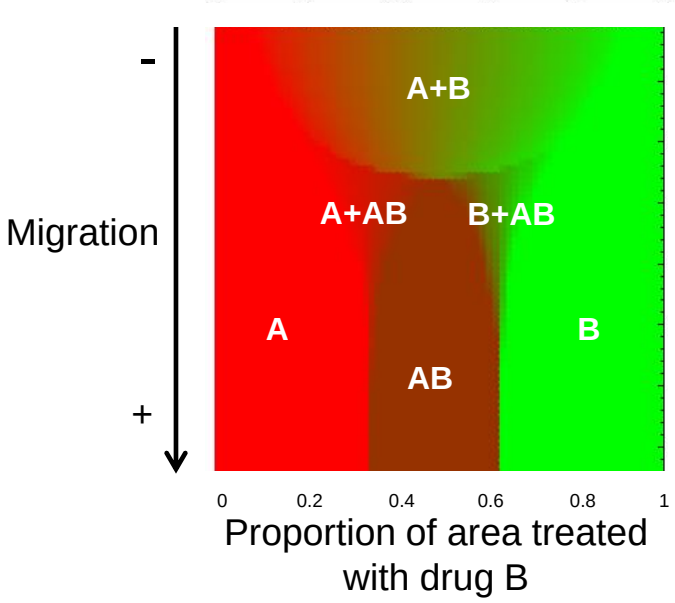

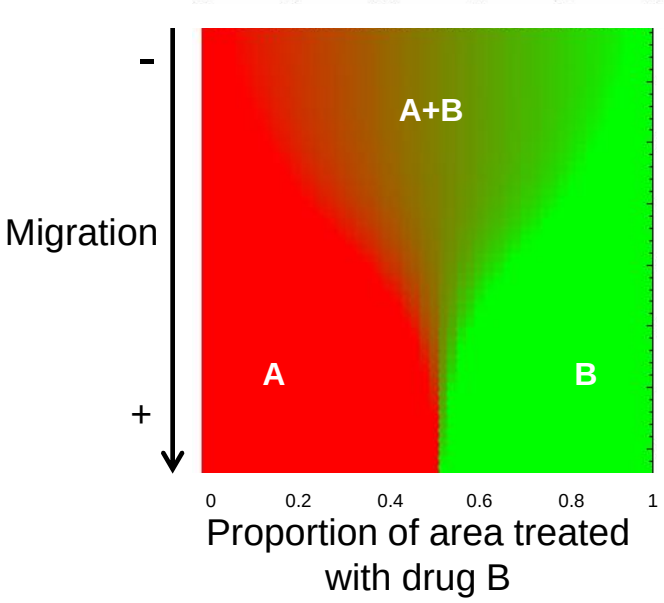

Conclusions:
take home messages

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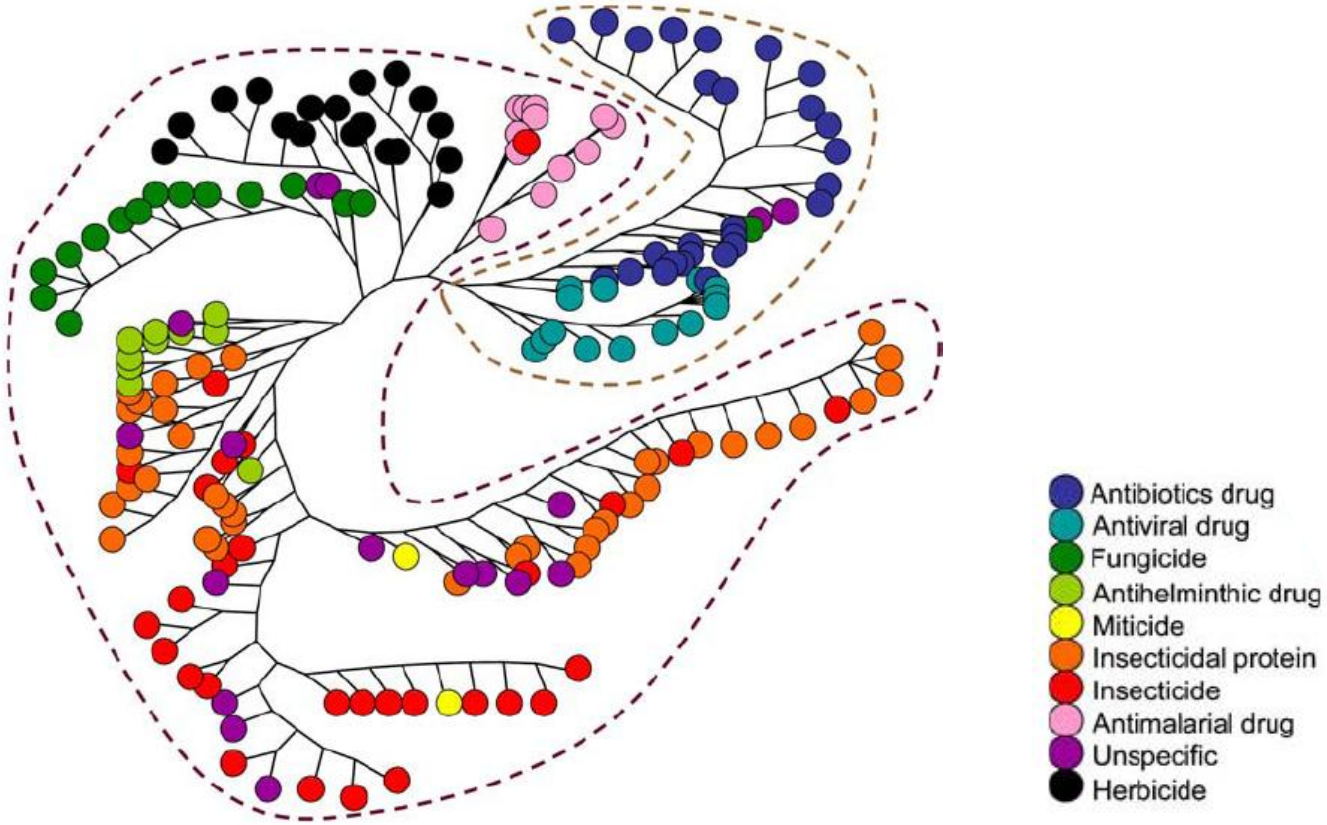
- **Spatial evolutionary epidemiology**
  An attempt to bridge the gap between population genetics & epidemiology

OPEN ACCESS Freely available online

PLoS one

Structure of the Scientific Community Modelling the Evolution of Resistance

REsistance against Xenobiotics consortium (REX) 2007, *PLoS One*.



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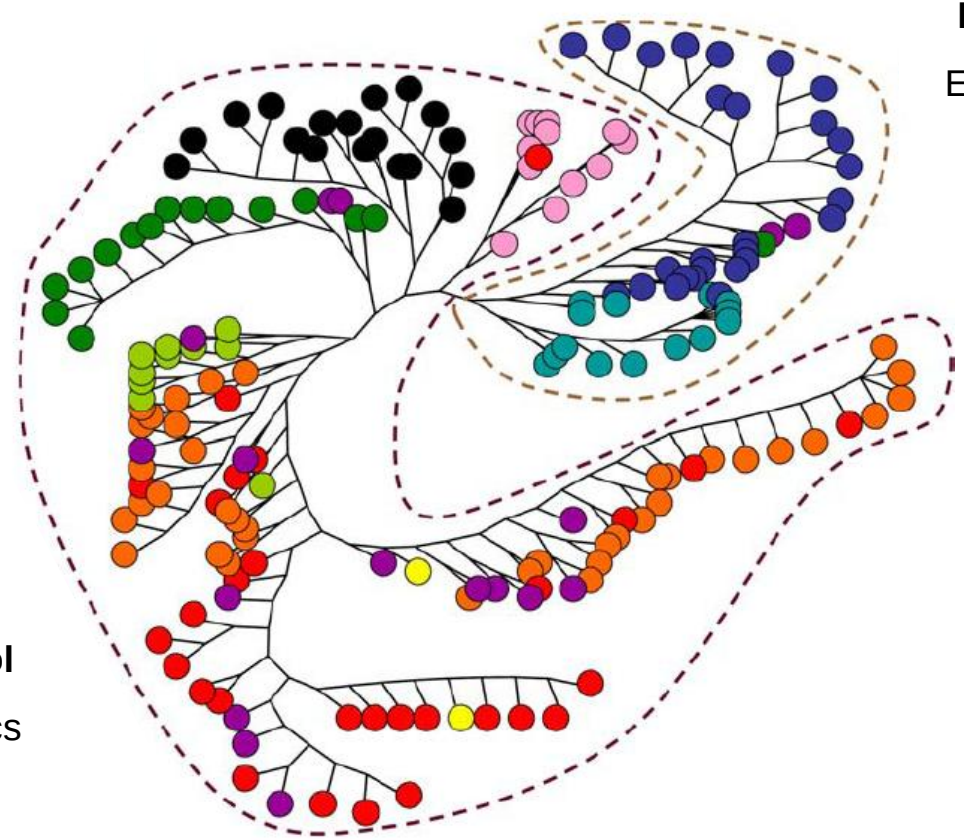
Biomedical

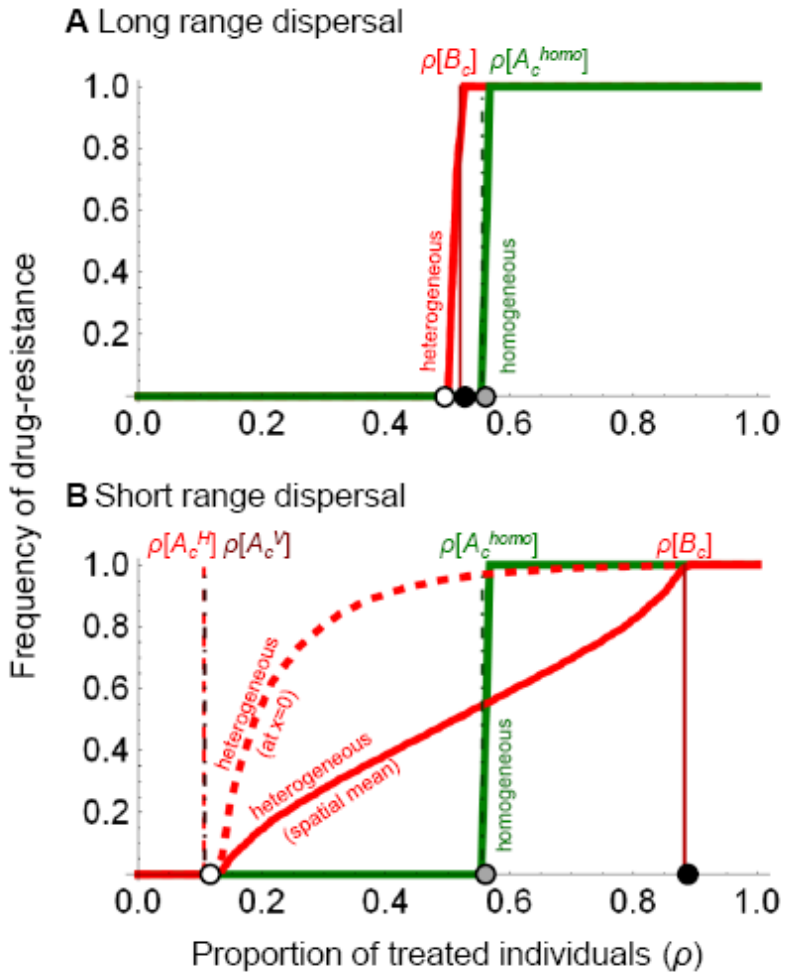
Epidemiology

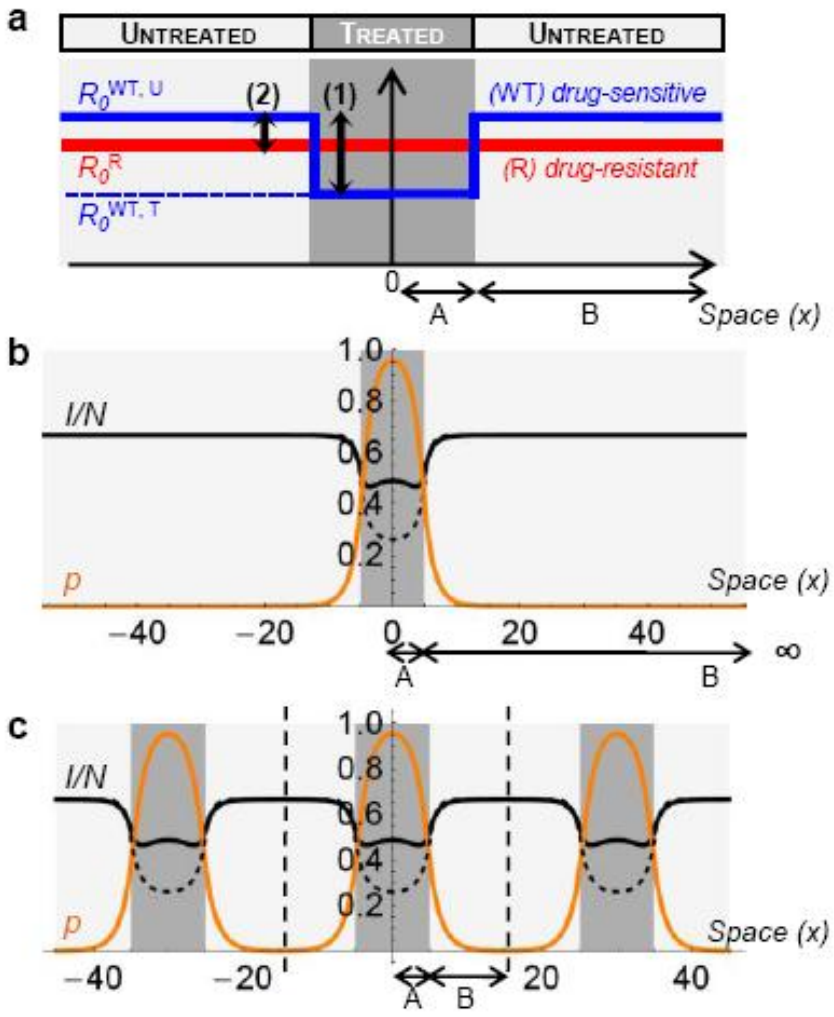


Agronomy and biological control

Population genetics

Homogeneous *versus* heterogeneous treatment



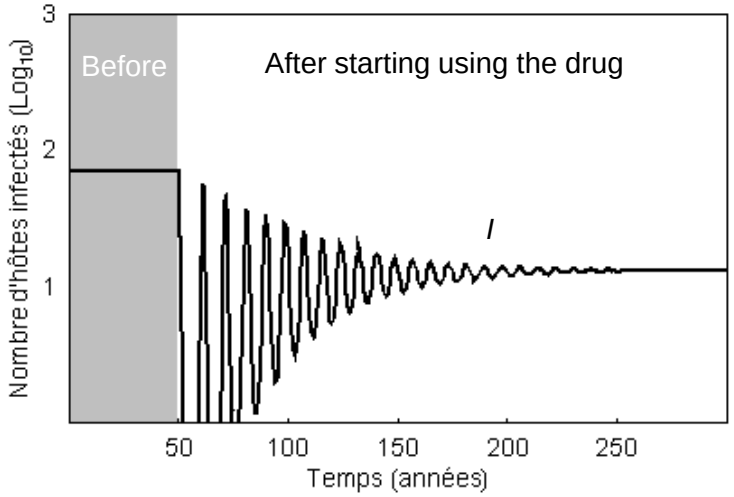

a
UNTREATED
TREATED
UNTREATED
$R_0^{WT,U}$
(2)
(1)
(WT) drug-sensitive
R_0^{R}
(R) drug-resistant
$R_0^{WT,T}$
0
A
B
Space (x)
b
I/N
p
1.0
0.8
0.6
0.4
0.2
Space (x)
−40
−20
0
20
40
∞
A
B
c
I/N
p
1.0
0.8
0.6
0.4
0.2
Space (x)
−40
−20
A
B
20
40

Evolutionary epidemiology

Transient dynamics

Gandon & Day 2007

Epidemiology:



$$r_0 = \beta S_0 - \delta - \alpha - \gamma$$

$$R_0 = \frac{\beta S_0}{\delta + \alpha + \gamma}$$

Evolution: