An introduction to evolutionary epidemiology of infectious diseases

Part 3

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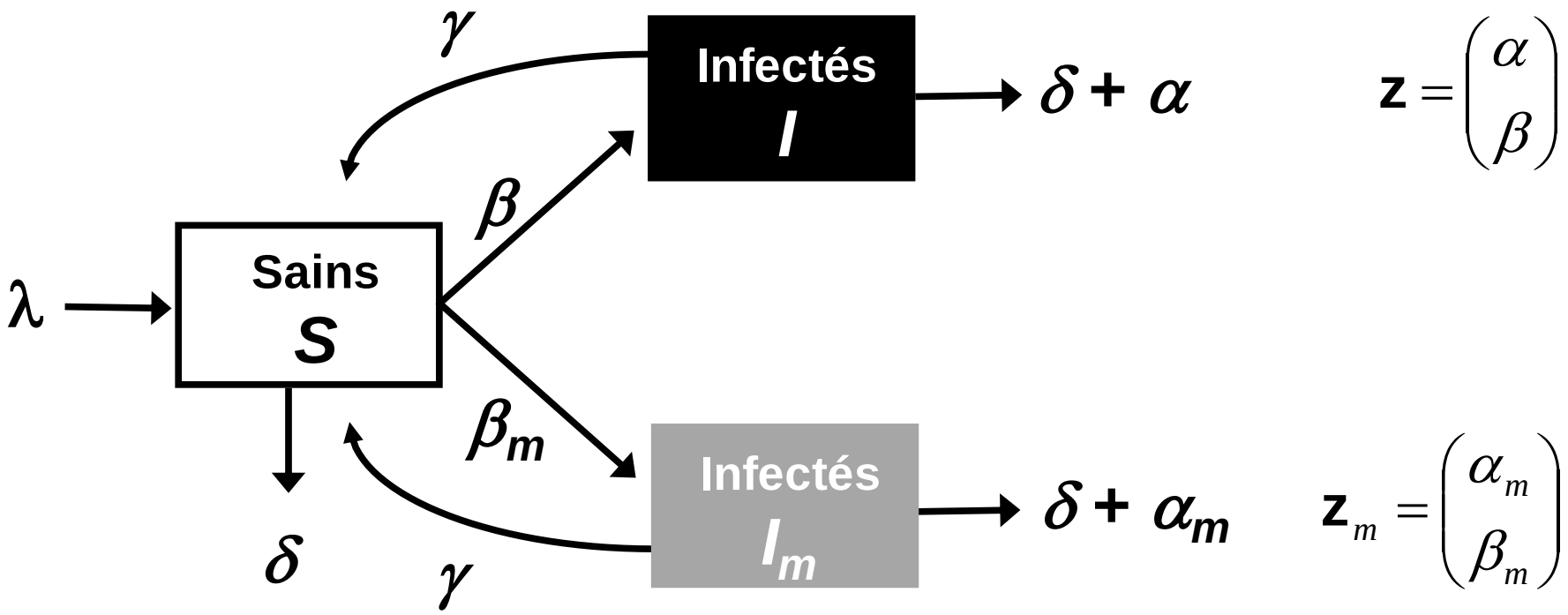
Dynamique adaptative

Est-ce que le mutant peut envahir?



$$\mathbf{z} = \begin{pmatrix} \alpha \\ \beta \end{pmatrix}$$

$$\mathbf{z}_m = \begin{pmatrix} \alpha_m \\ \beta_m \end{pmatrix}$$

Dynamique adaptative

Est-ce que le mutant peut envahir?

OUI si: $R_m = \frac{\beta_m}{\delta + \alpha_m + \gamma} > R = \frac{\beta}{\delta + \alpha + \gamma}$

$$R_m = \boxed{\beta_m} \boxed{\frac{1}{\delta + \alpha_m + \gamma}}$$

Fécondité

Durée de l'infection

Dynamique adaptative

Est-ce que le mutant peut envahir?

OUI si: $R_m = \frac{\beta_m}{\delta + \alpha_m + \gamma} > R = \frac{\beta}{\delta + \alpha + \gamma}$

L'évolution maximise R

L'évolution maximise $R_0 = RS_0$

Dynamique adaptative

Ce qu'on peut prédire:

- La stratégie évolutivement stable du parasite.
- L'effet, à long terme, d'une modification de l'environnement.

Ce qu'on ne peut pas prédire:

- La vitesse d'évolution du parasite.
- L'effet, à court terme, d'une modification de l'environnement.

Epidémiologie évolutive

Epidémiologie:

$$\begin{cases} \dfrac{dS}{dt} = \lambda - (\delta + \overline{\beta} I)S + \gamma S \\ \dfrac{dI}{dt} = \underbrace{\left(\overline{\beta} S - \left(\delta + \overline{\alpha} + \gamma\right)\right)}_{\bar{r}} I \end{cases}$$

Evolution des fréquences:

Day & Gandon 2006

$$\frac{dq_i}{dt} = q_i\left(r_i - \bar{r}\right) + \eta\left(\sum_k \left(m_{ki} q_k\right) - q_i\right)$$

Fréquence de la souche i

Fitness de la souche i

Fitness moyenne: $\bar{r} = \sum_i q_i r_i$

Mutation

Epidémiologie évolutive

Epidémiologie:

$$\begin{cases} \dfrac{dS}{dt} = \lambda - (\delta + \overline{\beta} I) S + \gamma S \\ \dfrac{dI}{dt} = \underbrace{\left(\overline{\beta} S - \left(\delta + \overline{\alpha} + \gamma\right)\right)}_{\bar{r}} I \end{cases}$$

Evolution des phénotypes, $\bar{\mathbf{z}} = \begin{pmatrix} \overline{\alpha} \\ \overline{\beta} \end{pmatrix}$:

$$\frac{\mathrm{d}\bar{\mathbf{z}}}{\mathrm{d}t} = \mathbf{G} \begin{pmatrix} -1 \\ S \end{pmatrix} + \eta \begin{pmatrix} \bar{v}_m - \bar{v} \\ \bar{\beta}_m - \bar{\beta} \end{pmatrix}$$

Matrice de variance-covariance

Gradient de sélection

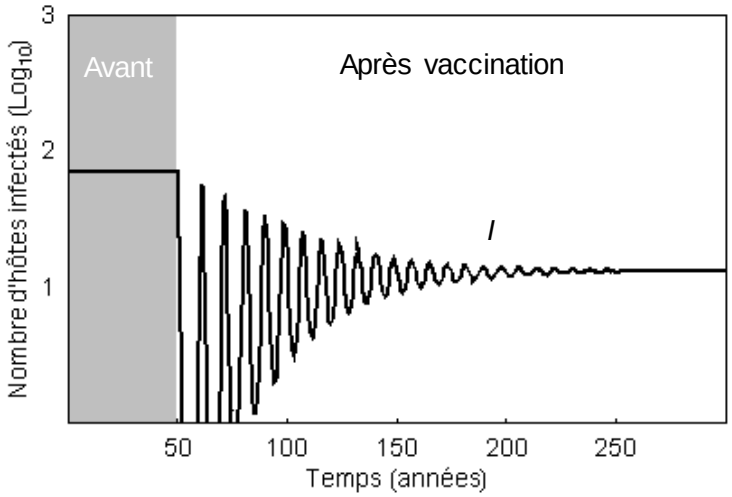
Mutation

Epidémiologie évolutive

Environnement variable **dans le temps**

Gandon & Day 2007

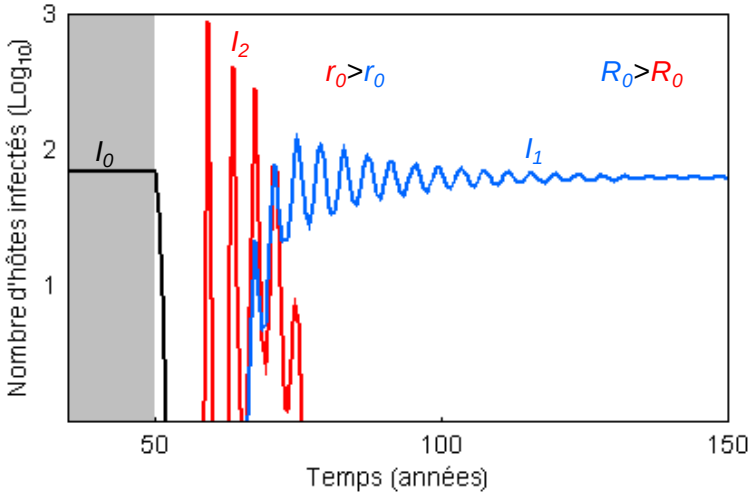
Epidémiologie:

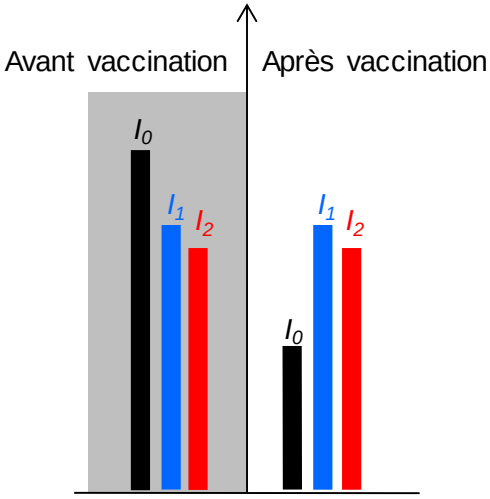


$$r_0 = \beta S_0 - \delta - \alpha - \gamma$$

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

Evolution:



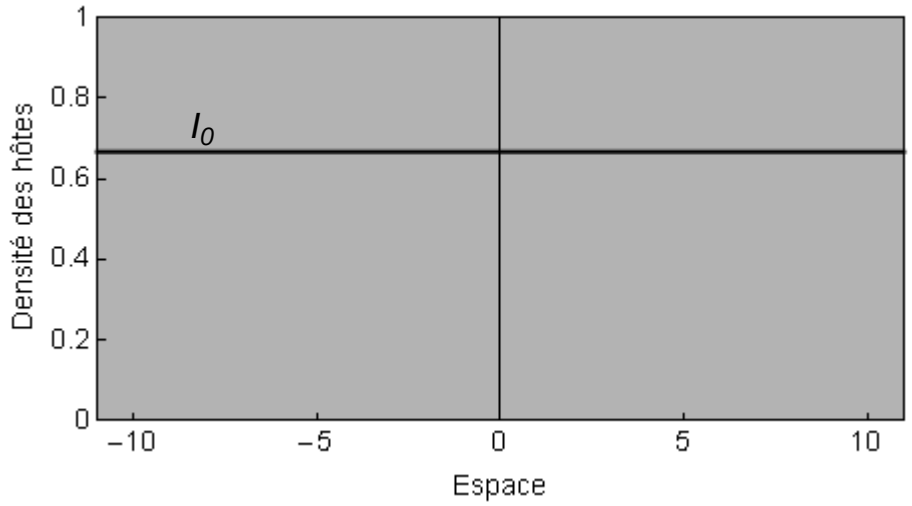


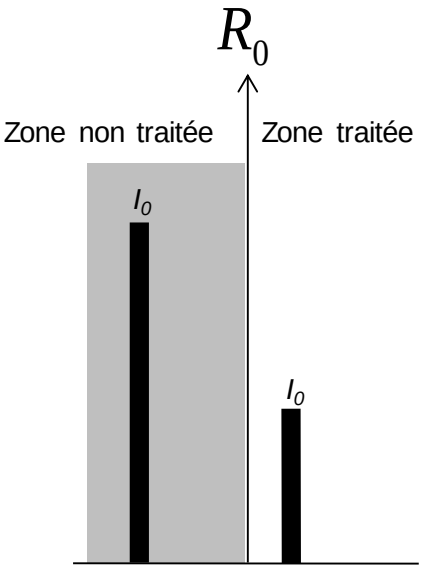
Epidémiologie évolutive

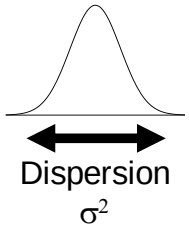
Environnement variable **dans l'espace**

Débarre et al 2009

Epidémiologie







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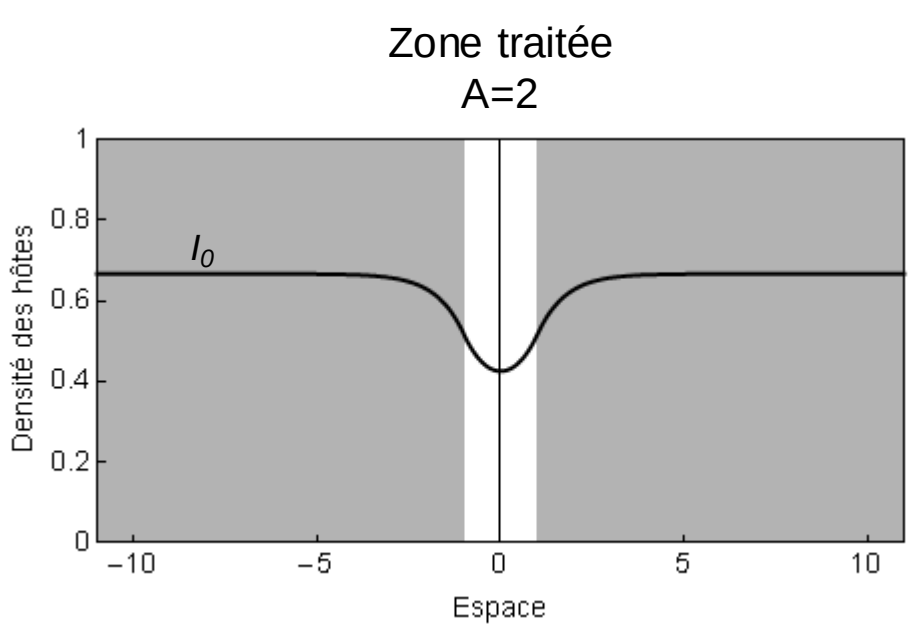

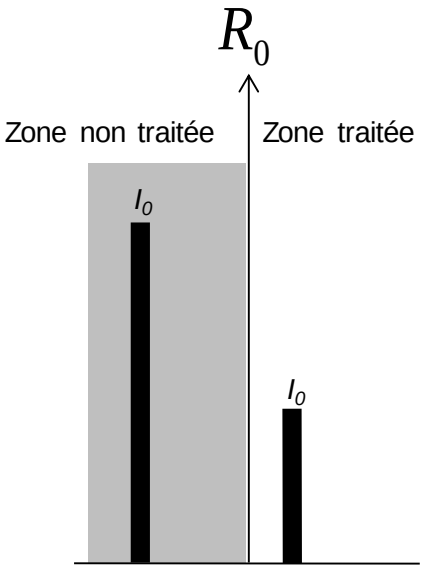

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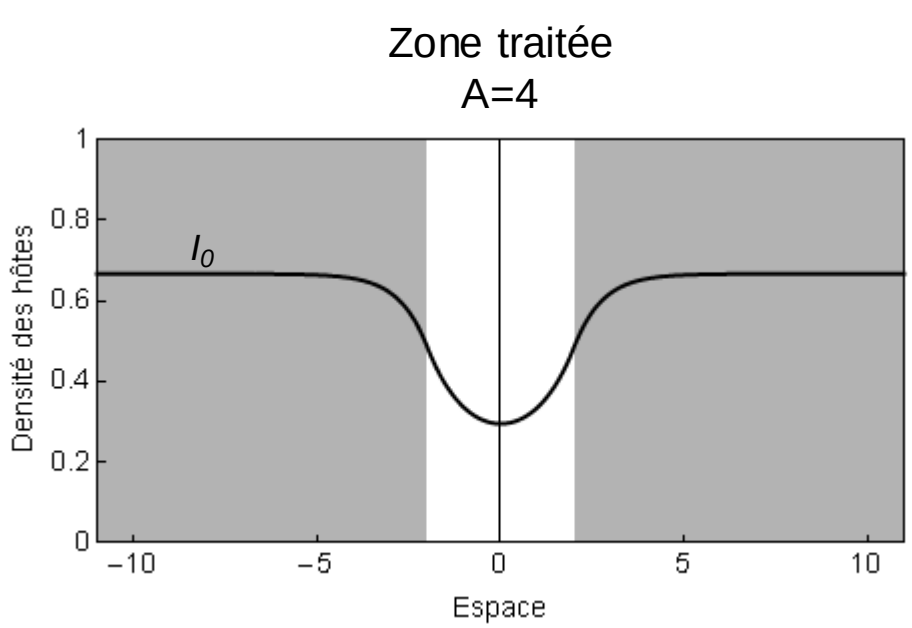
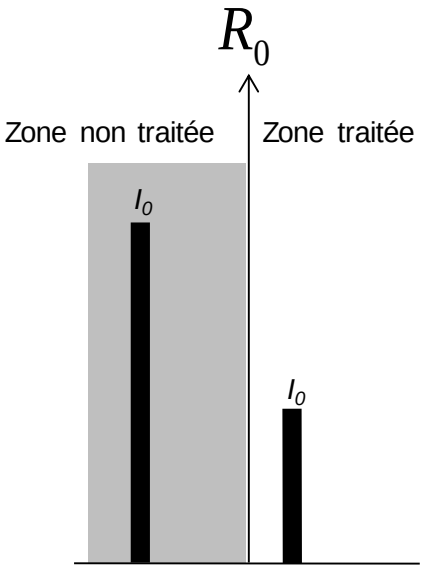
Epidémiologie





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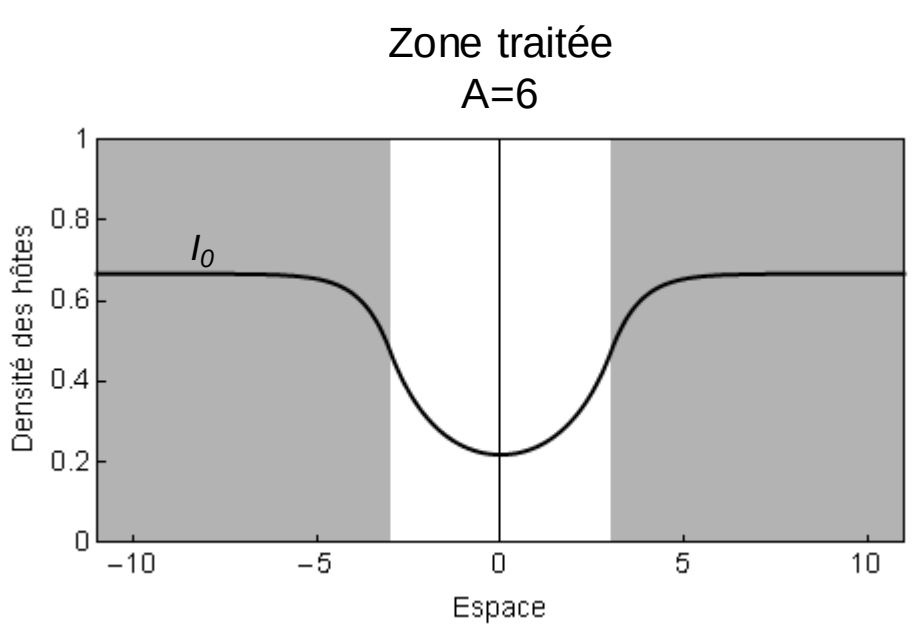

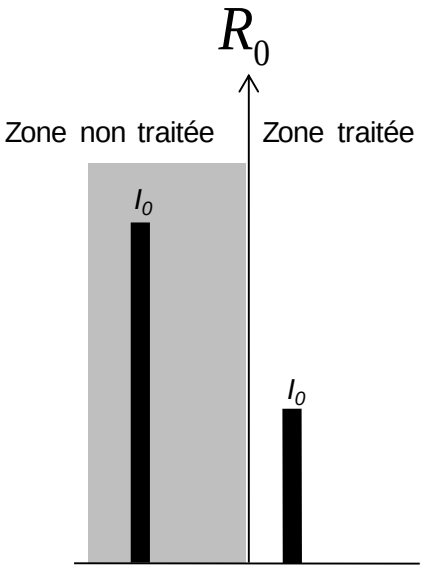

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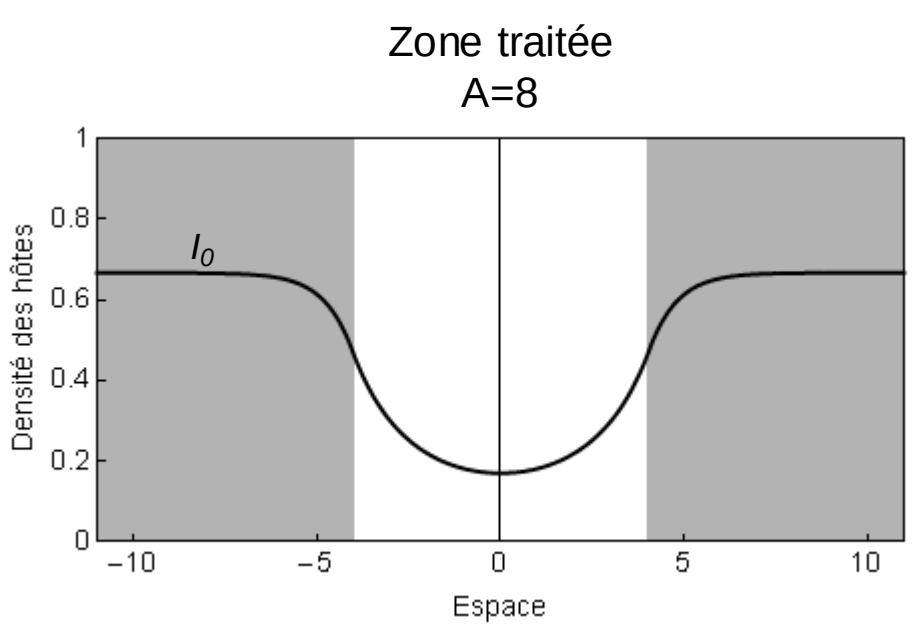

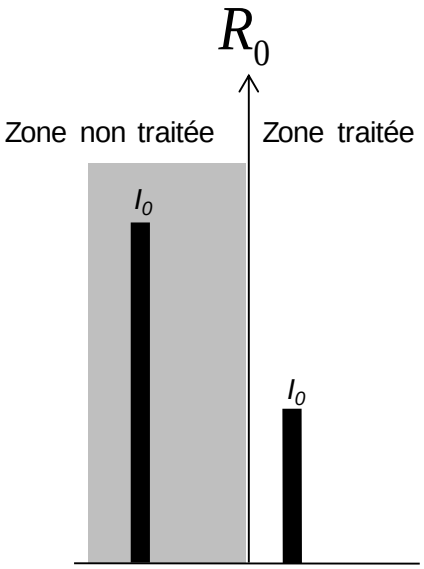

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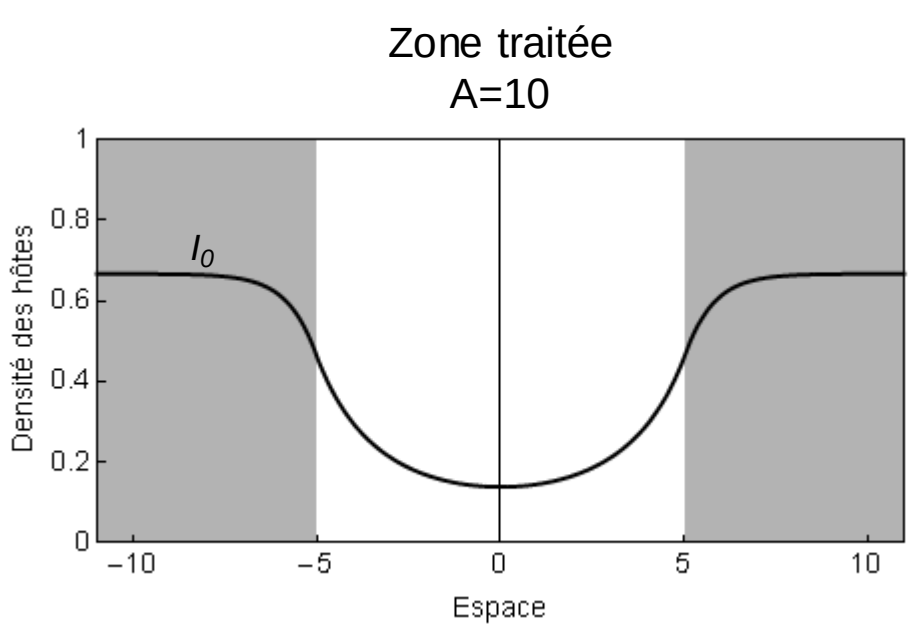

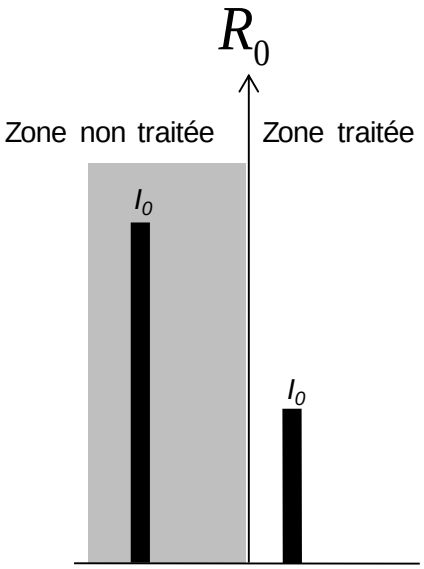

Epidémiologie évolutive

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Débarre et al 2009

Epidémiologie
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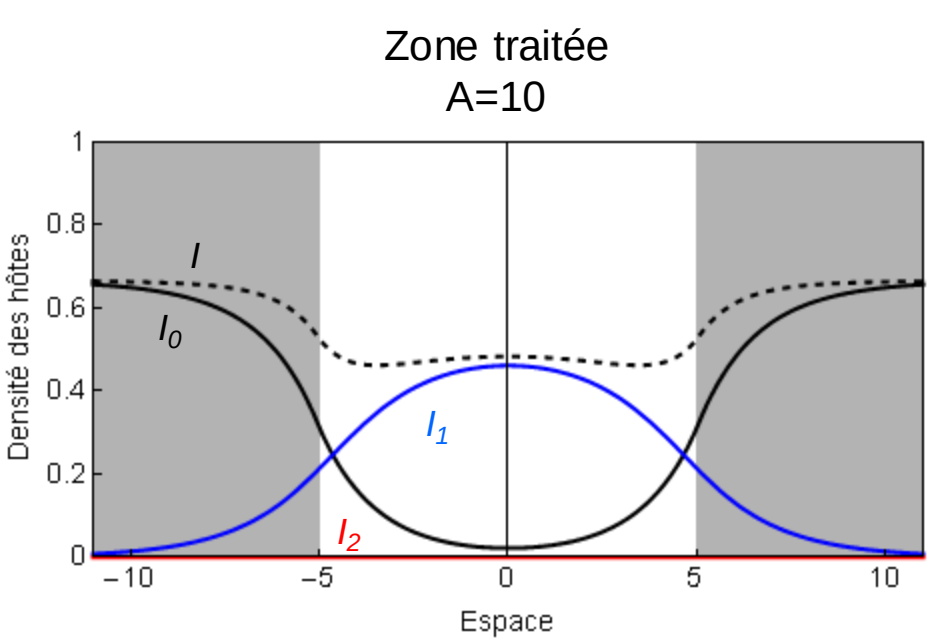
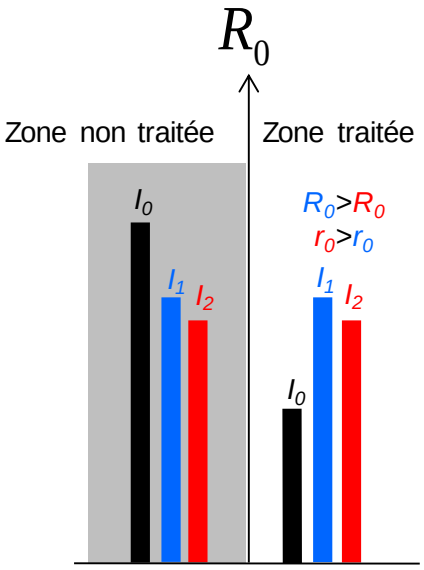
Evolution





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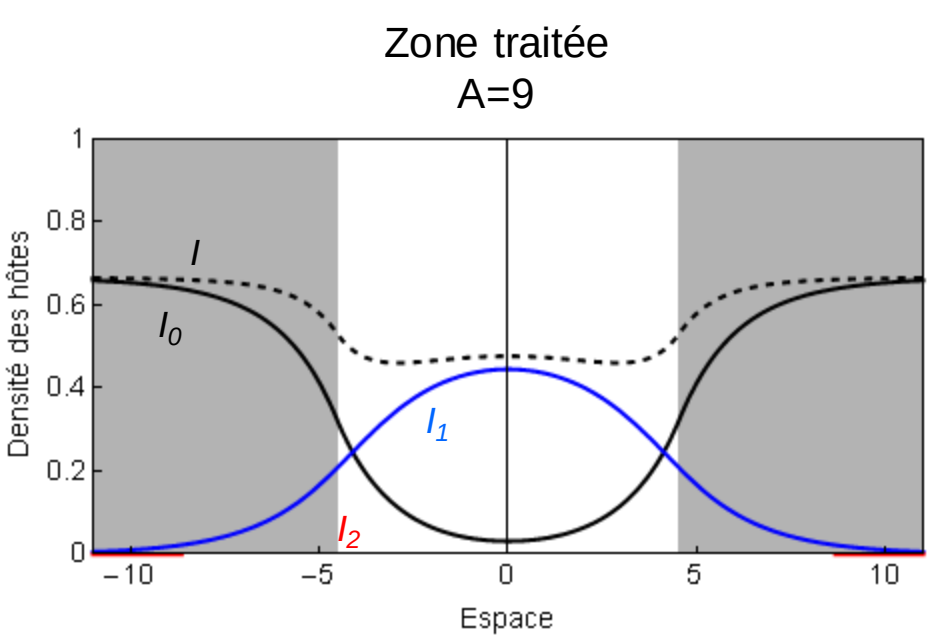

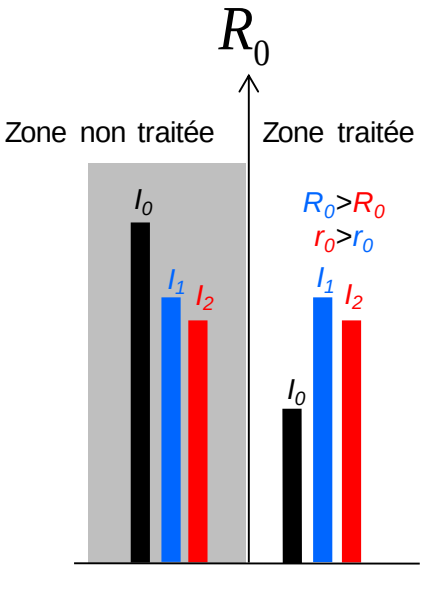

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Environnement variable **dans l'espace**

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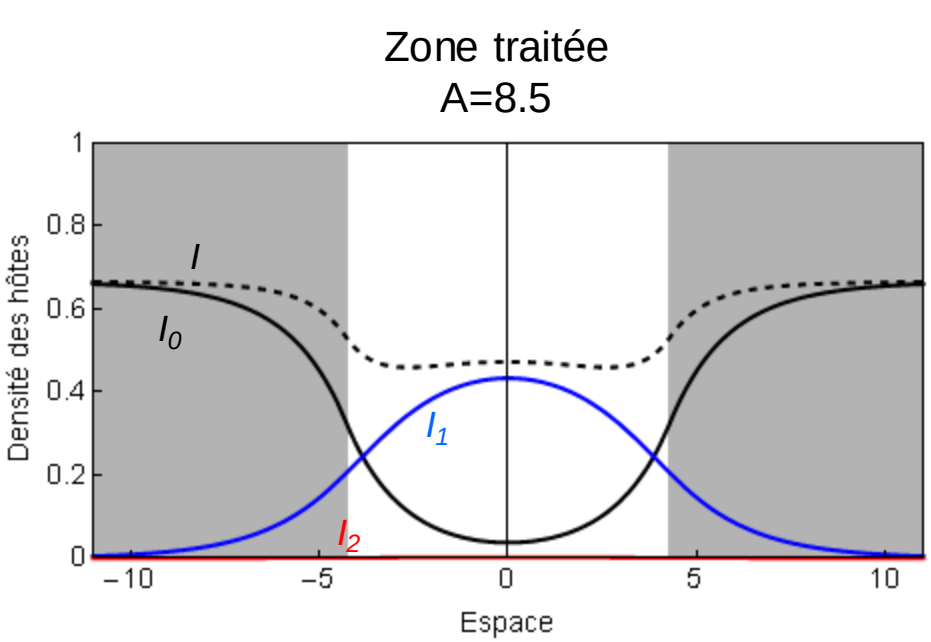

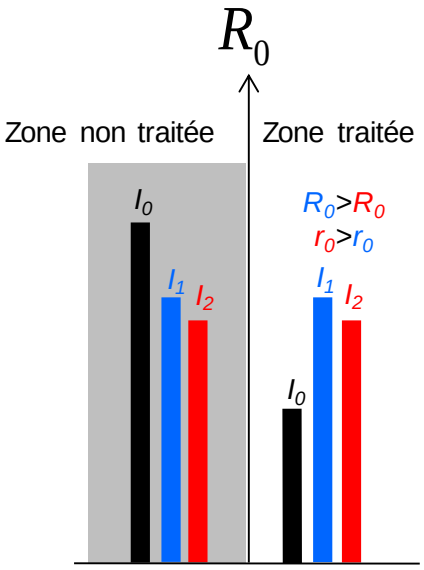

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Environnement variable **dans l'espace**

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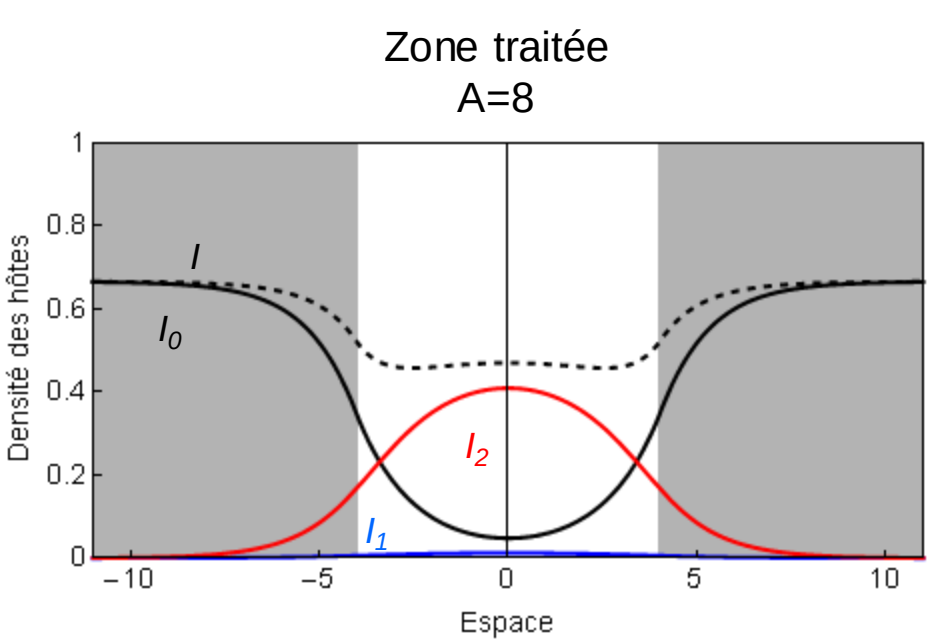

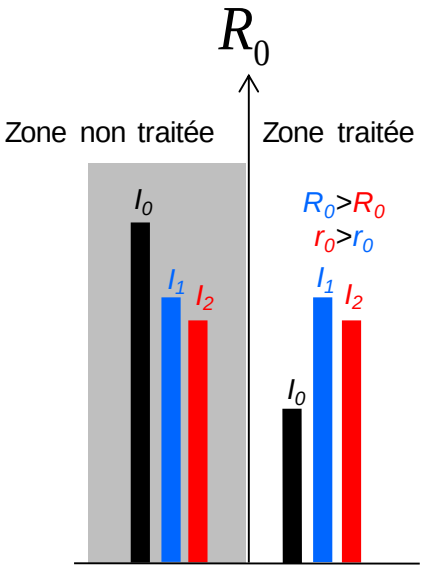

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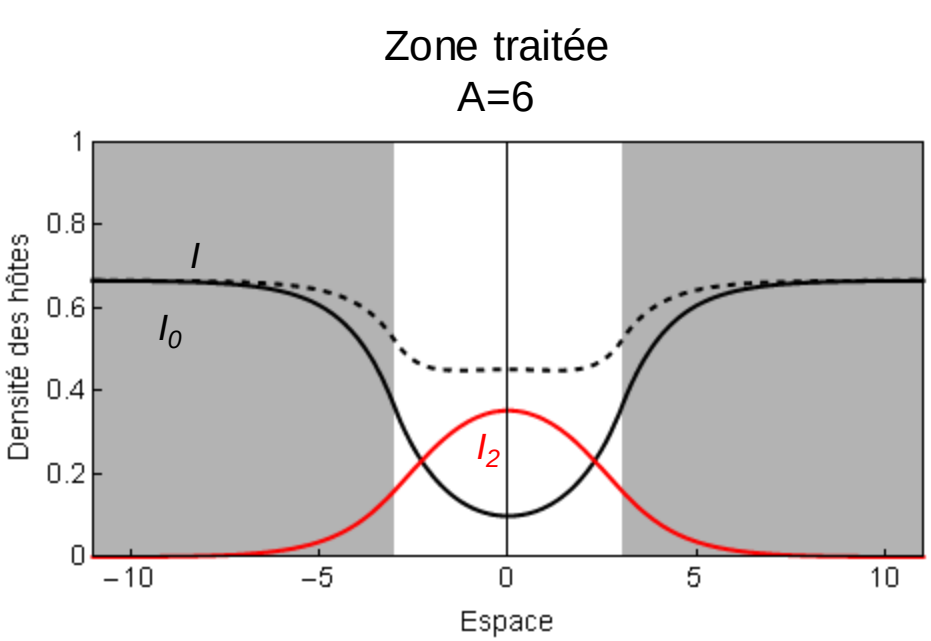

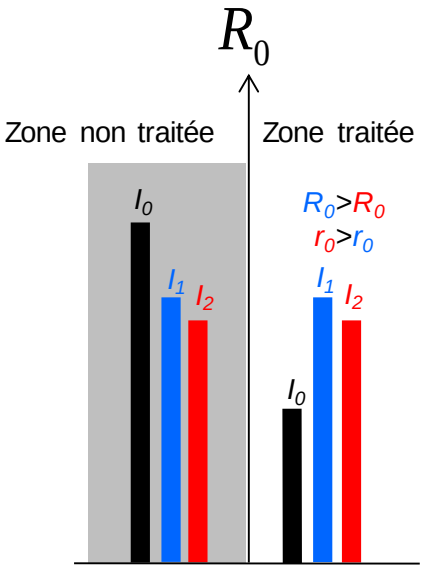

Epidémiologie évolutive

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Débarre et al 2009

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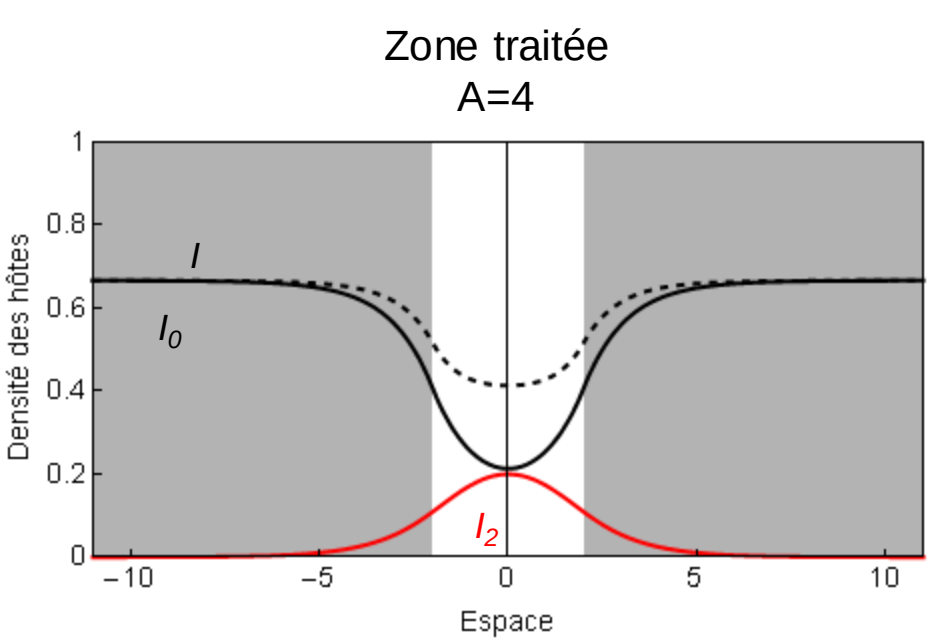

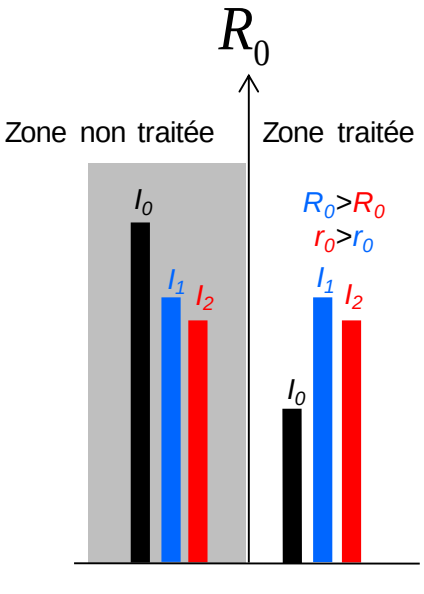

Epidémiologie évolutive

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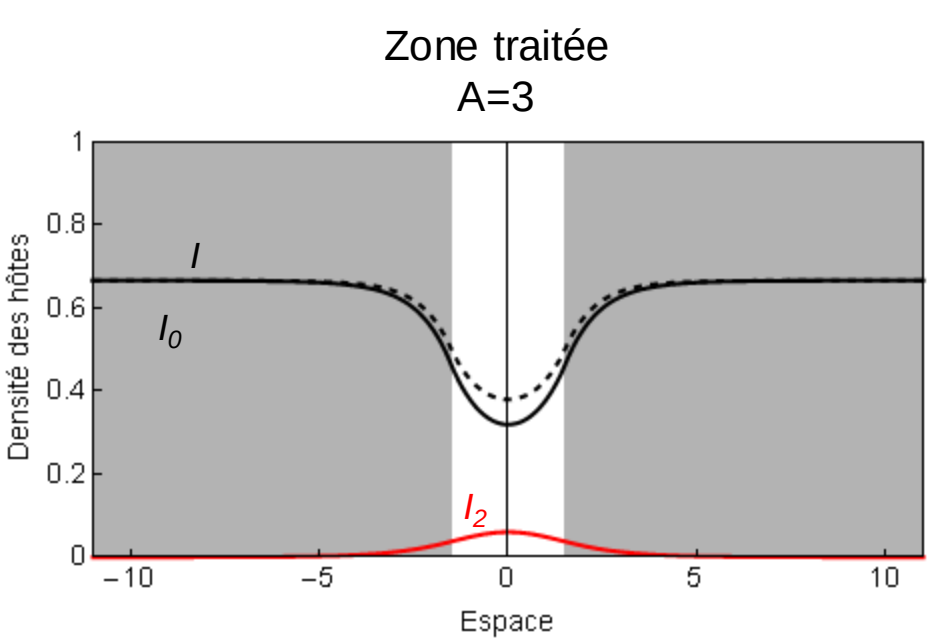

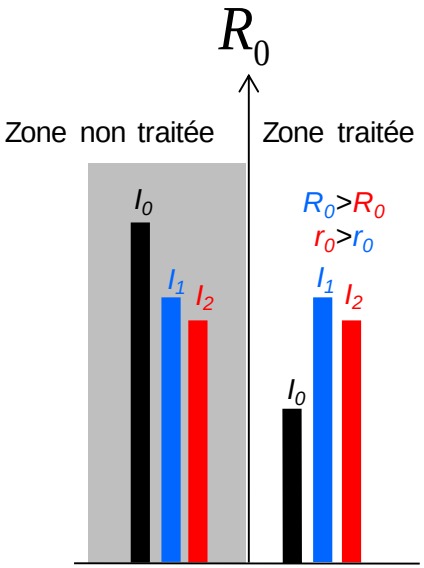

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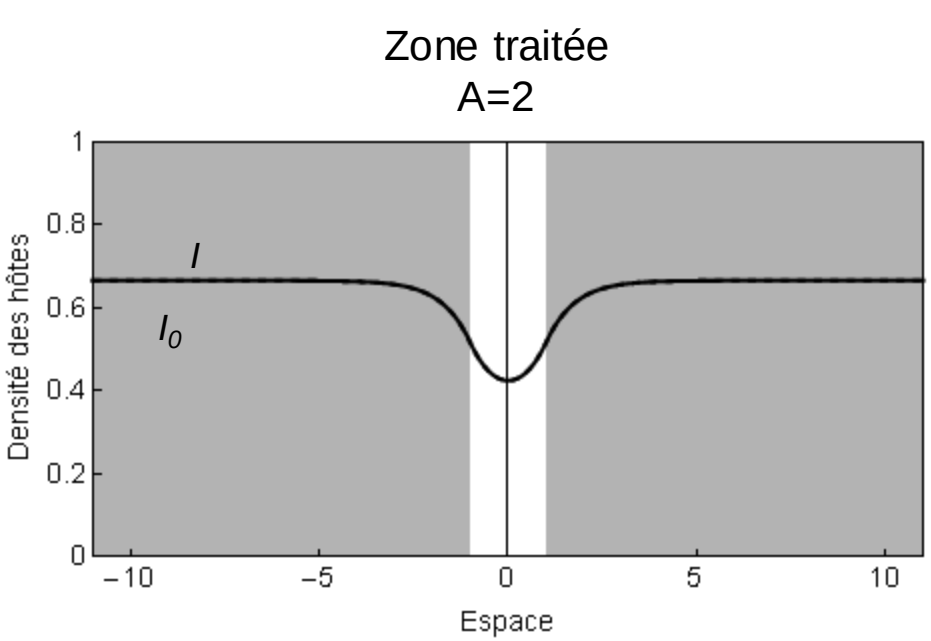
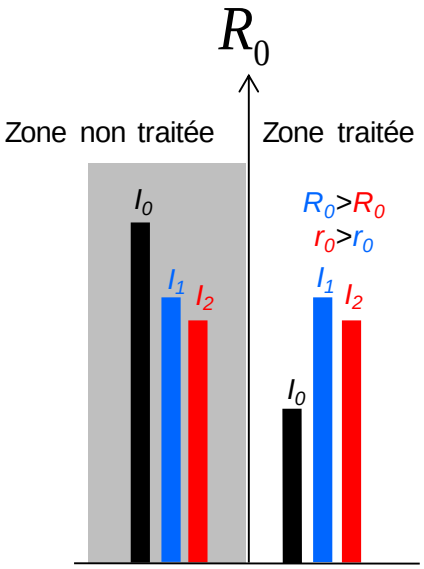




Taille critique de la zone traitée: $$A_c = \sqrt{\frac{2}{r_0^*}} \frac{\sigma}{\sqrt{\left(\frac{R_0^*/R_0^T - 1}{R_0^* - 1}\right)}} \arctan\left(\left(\frac{1-1/R_0^T}{1-1/R_0}\right)^2 \sqrt{-\frac{R_0^*/R_0 - 1}{R_0^*/R_0^T - 1}}\right)$$

Epidémiologie évolutive

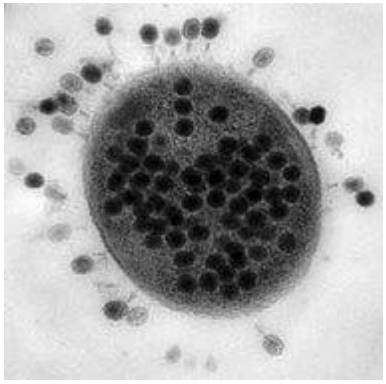
1. Evolution de populations polymorphes

2. Pas d'hypothèse d'équilibre endémique (R_0 pas toujours maximisé)

3. Permet de suivre la dynamique épidémiologique

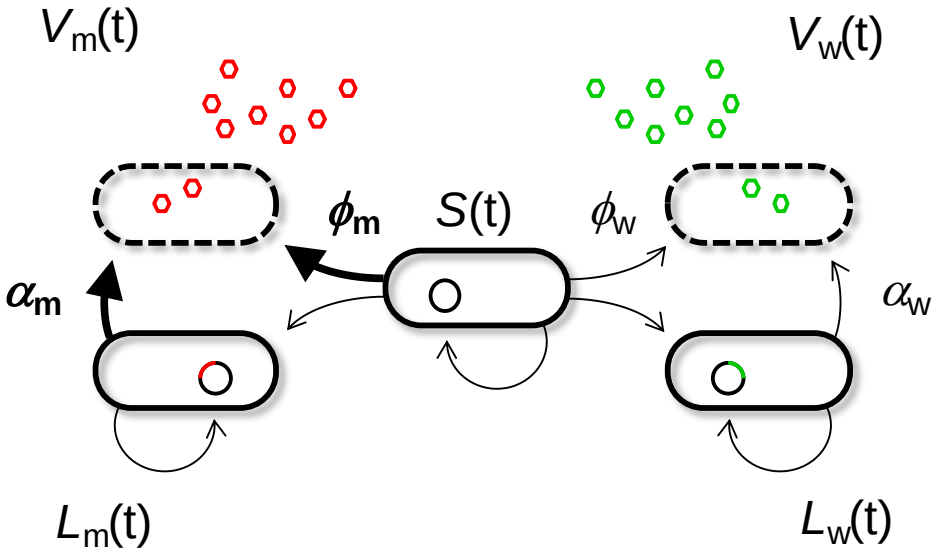
$$\begin{cases} \dfrac{dS}{dt} = \lambda - (\delta + \bar{\beta} I) S + \gamma S \\ \dfrac{dI}{dt} = \underbrace{\left(\bar{\beta} S - \left(\delta + \bar{\alpha} + \gamma\right)\right)}_{\bar{r}} I \end{cases}$$

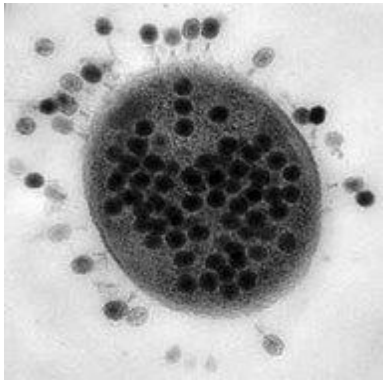
$$\frac{\mathrm{d}\bar{\mathbf{z}}}{\mathrm{d}t} = \mathbf{G} \begin{pmatrix} -1 \\ S \end{pmatrix} + \eta \begin{pmatrix} \bar{\nu}_m - \bar{\nu} \\ \bar{\beta}_m - \bar{\beta} \end{pmatrix}$$



Bacteriophage λ

Life cycle

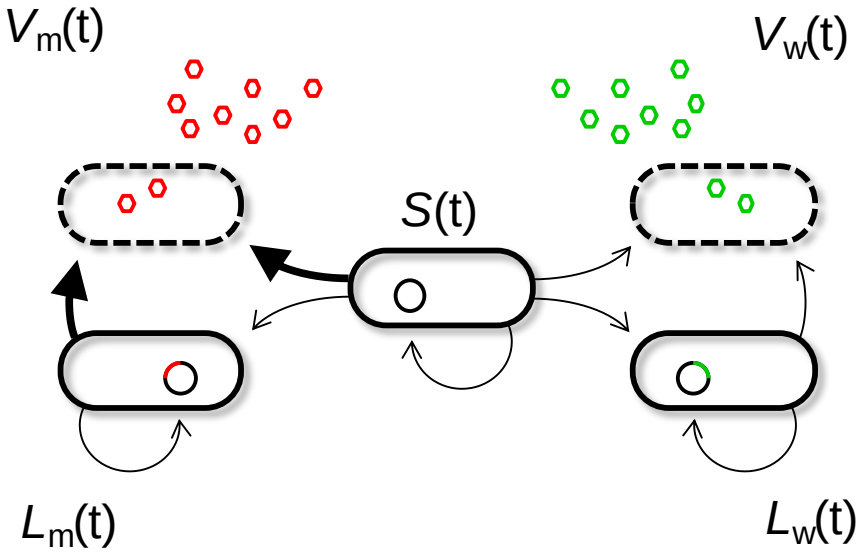




Bacteriophage λ

Life cycle

$q_m(t)=V_m(t)/V(t)$



$p_m(t)=L_m(t)/L(t)$

Evolutionary Epidemiology of λ

Theory

Epidemiology:

$$\dot{S} = rS(1-(S+L)/K) - abSV - mS$$
$$\dot{L} = \rho L(1-(S+L)/K) + ab\phi_{\circ}VS - (\alpha_{\bullet}+m)L$$
$$\dot{V} = ab(1-\phi_{\circ})VSB + \alpha_{\bullet}BL - mV - a(S+L)V$$

Evolution:

$$\dot{p}_m = p_m\left(-\overbrace{(\alpha_m-\alpha_{\bullet})}^{virulence} + \overbrace{abS\frac{V}{L}(\phi_m-\phi_{\circ})}^{genome\ integration}\right) + \underbrace{abV(q_m-p_m)\left(\frac{S}{L}\phi_m\right)}_{\text{gene flow}}$$

$$\dot{q}_m = \overbrace{abSBq_m(\phi_{\circ}-\phi_m)}^{failed\ genome\ integration} + B\frac{L}{V}\left(\overbrace{q_m(\alpha_m-\alpha_{\bullet})}^{virulence} + \underbrace{\alpha_m(p_m-q_m)}_{\text{gene flow}}\right)$$

Evolutionary Epidemiology of λ

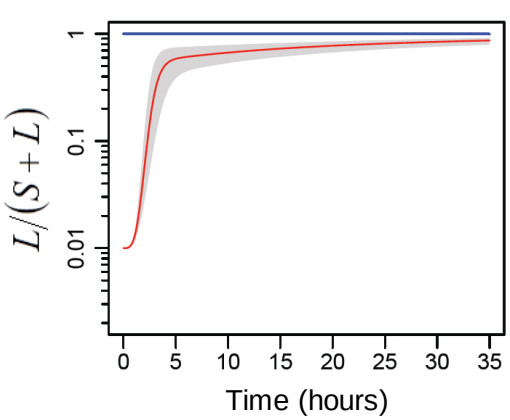
Berngruber et al. 2013, *PLoS Pathogens*

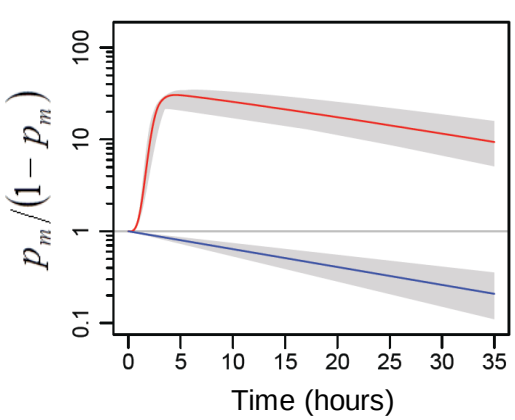
3 predictions:

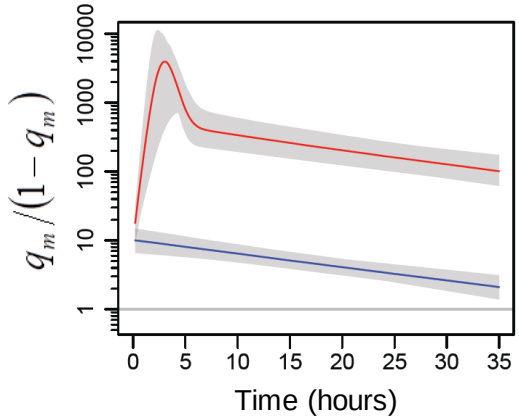
- selection on virulence varies with time
- the lower the initial dose, the higher the selection for virulence
- virulence is always higher in the free virus compartment

Prevalence | Lysogens | Free virus

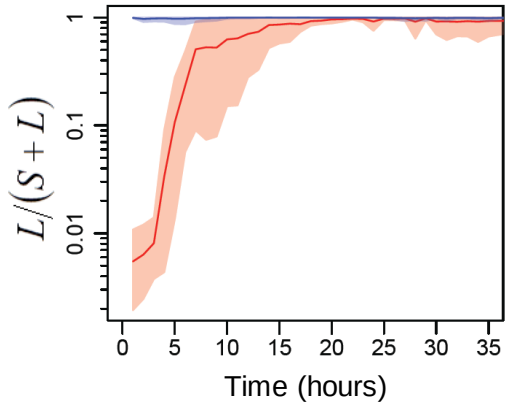
Theory

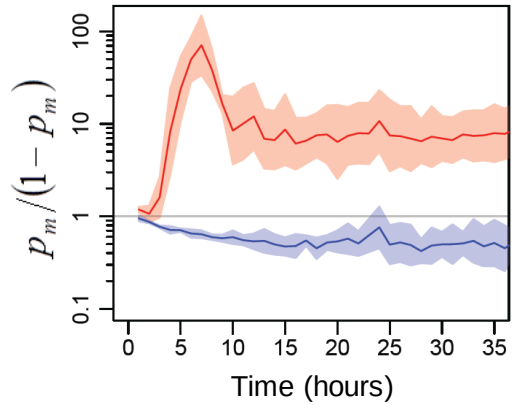


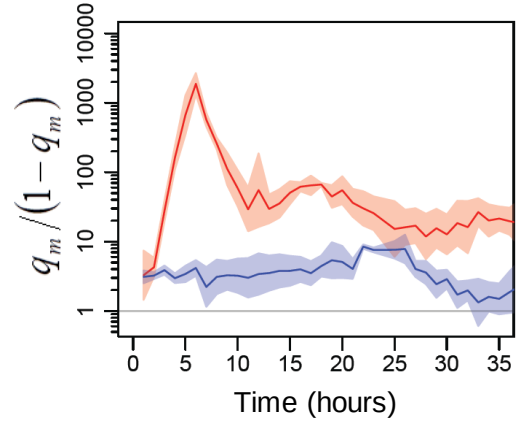




Experiment







Spatial structure

Theory

Epidemiology: slower epidemics

Evolution: selection for lower transmission/virulence

Experiment

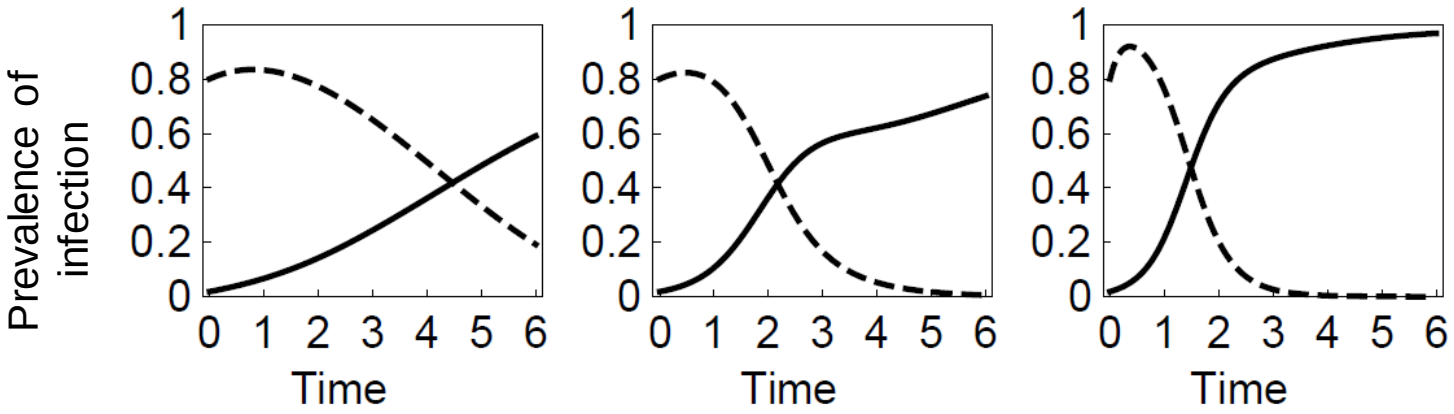
A few experimental tests
Only with horizontally transmitted pathogens

Spatial structure

Epidemiology

Theory

Berngruber et al. 2015, *PLoS Pathogens*



Structured

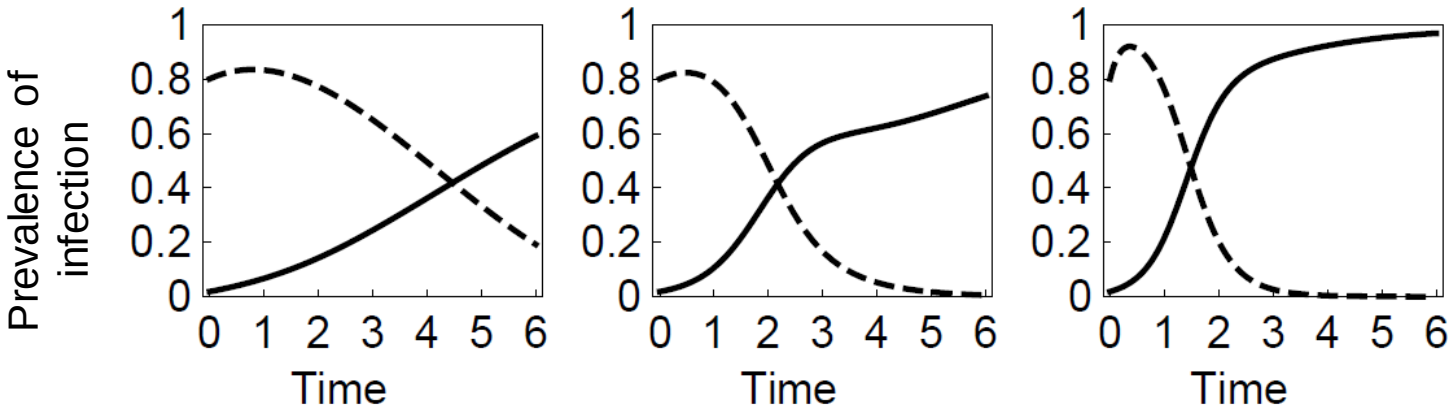
Well mixed

Spatial structure

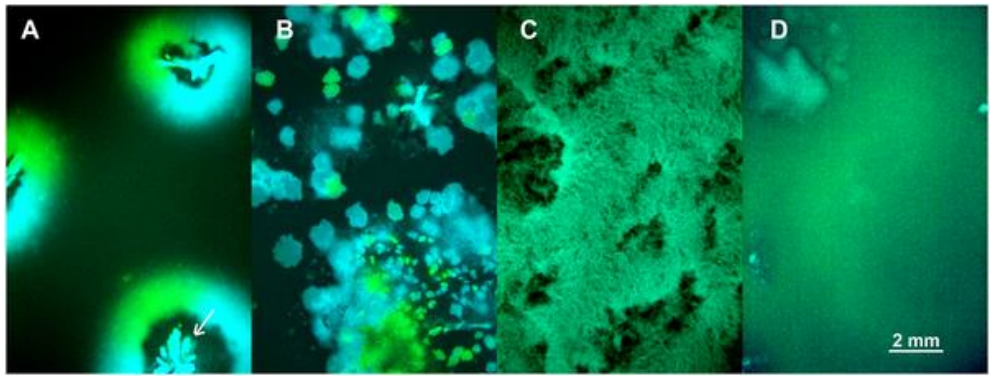
Epidemiology

Theory

Berngruber et al. 2015, *PLoS Pathogens*



Experiment



No beads 30s 24h 24h wet

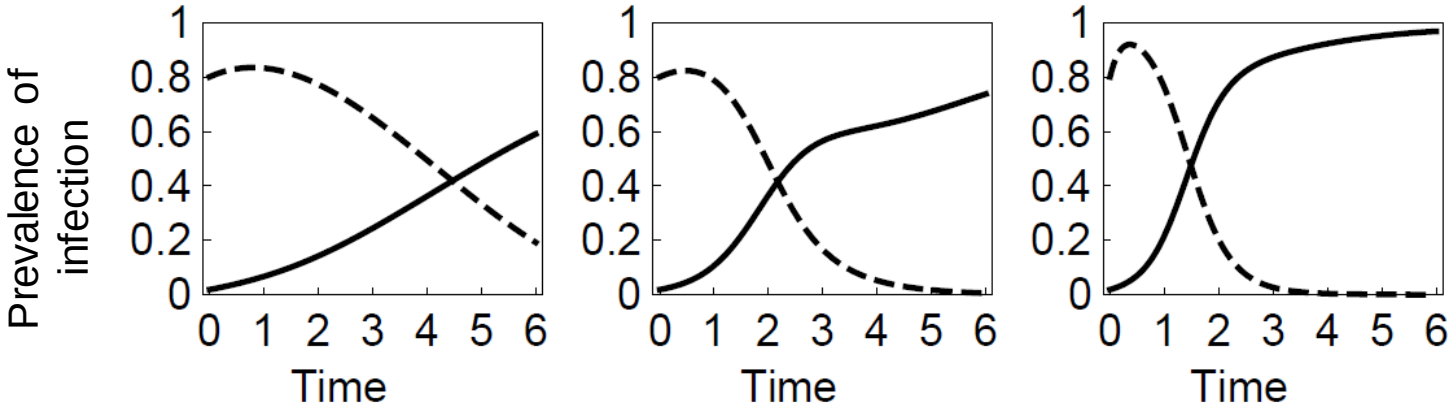
Mixing treatment

Spatial structure

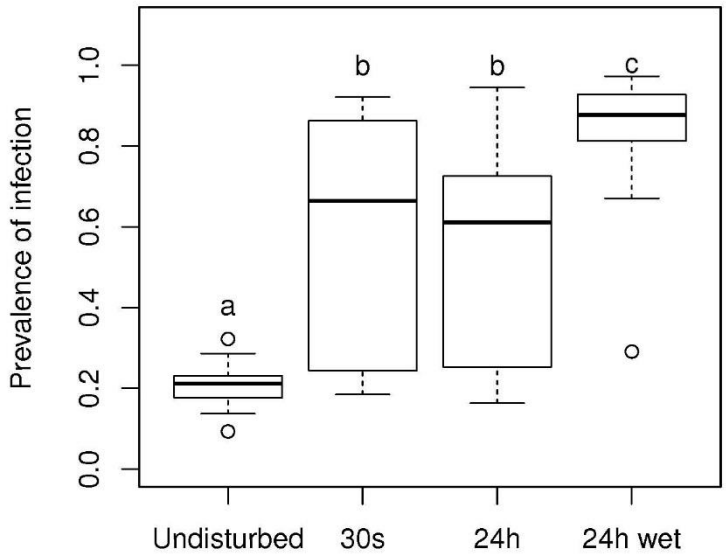
Epidemiology

Theory

Berngruber et al. 2015, *PLoS Pathogens*



Experiment



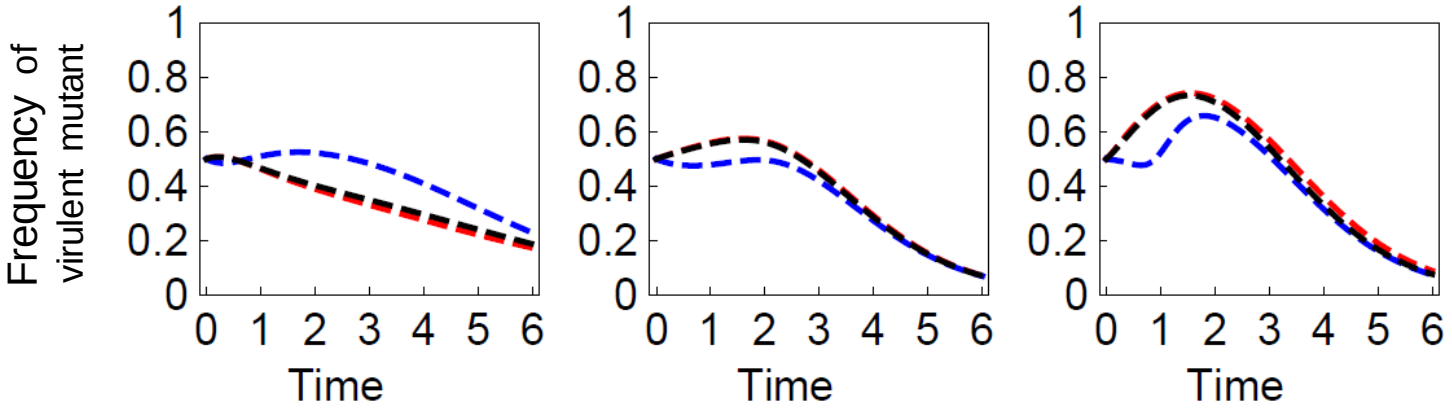
Mixing treatments

Spatial structure

Evolution

Theory

Berngruber et al. 2015, *PLoS Pathogens*



Structured

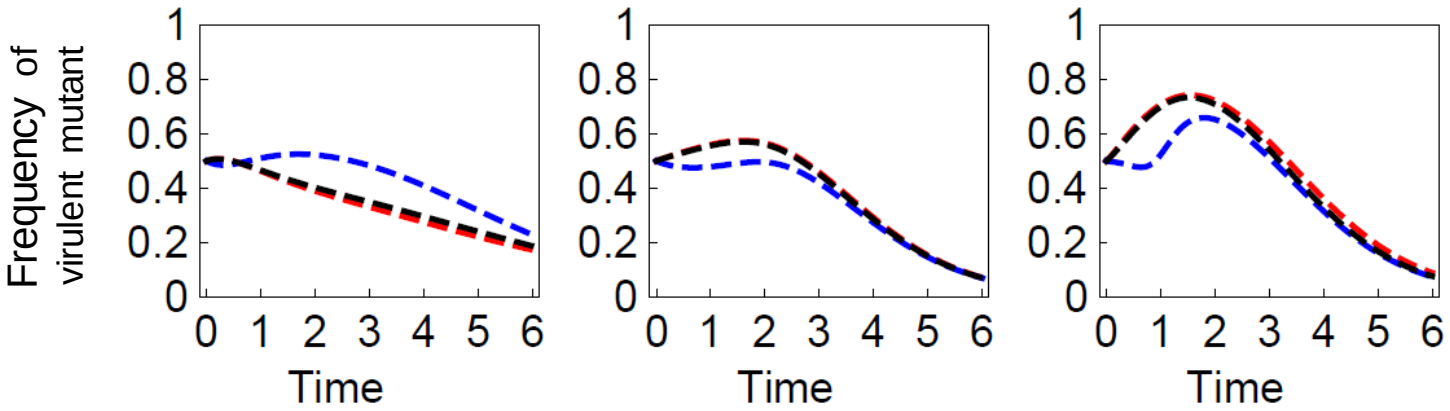
Well mixed

Spatial structure

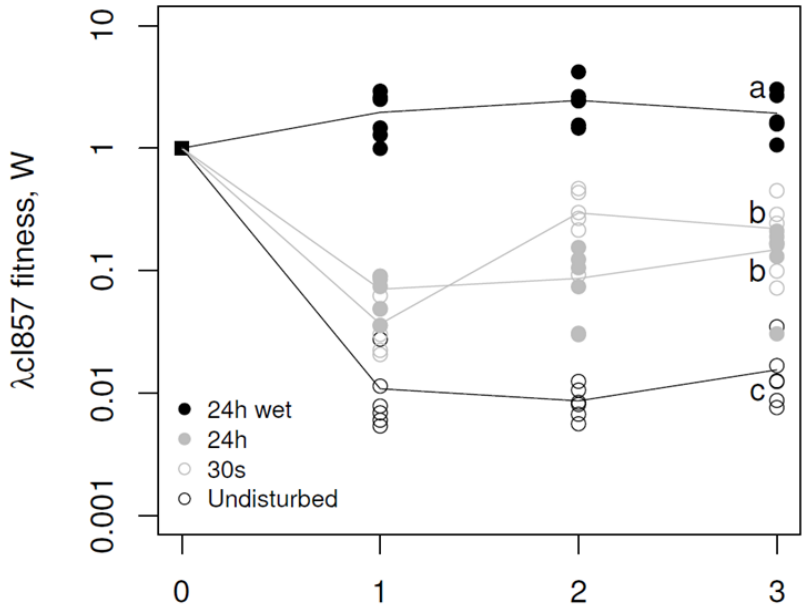
Evolution

Theory

Berngruber et al. 2015, *PLoS Pathogens*



Experiment

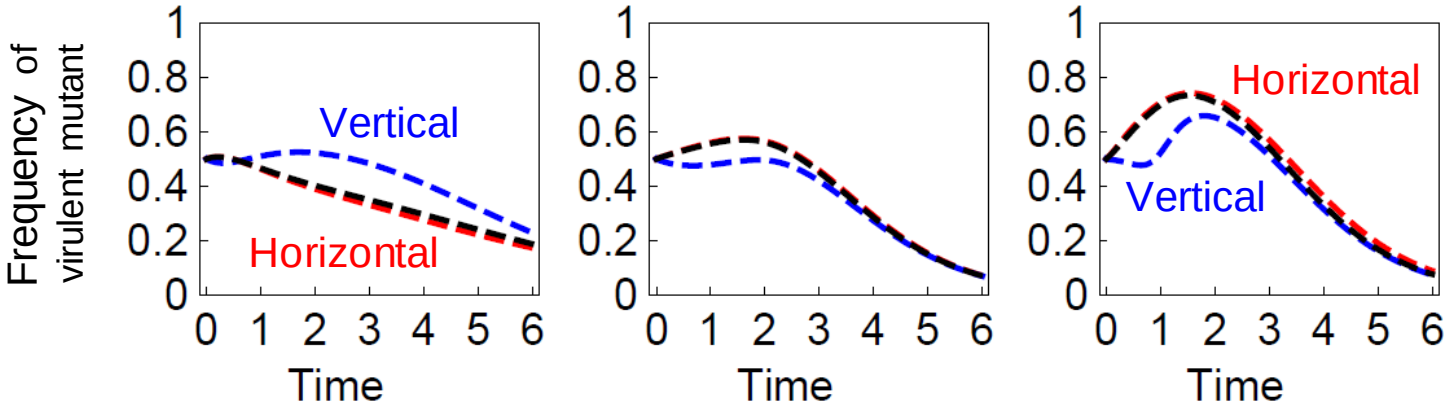


Spatial structure

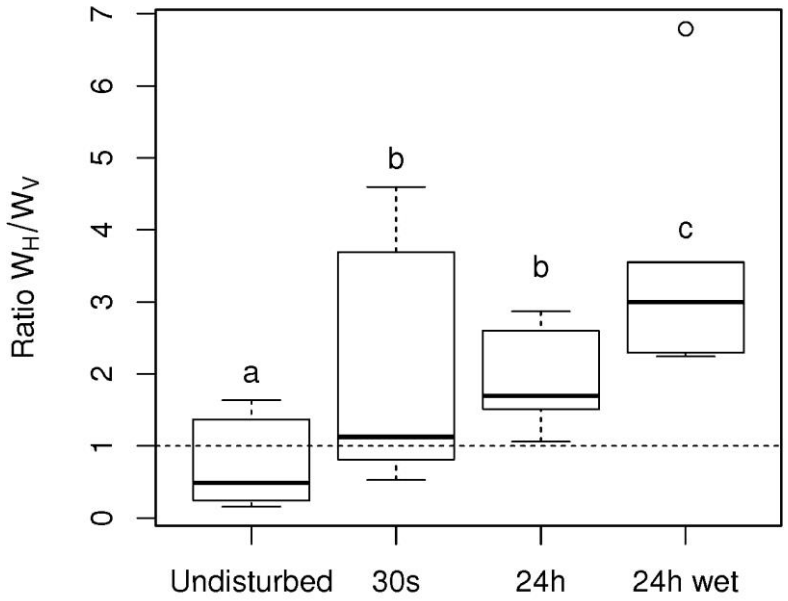
Evolution

Theory

Berngruber et al. 2015, *PLoS Pathogens*



Experiment



Mixing treatments

Spatial structure

Transient evolution

Griette et al., 2015

Neutral evolution

Virulence of mutant
=
Virulence of WT

Virulence evolution

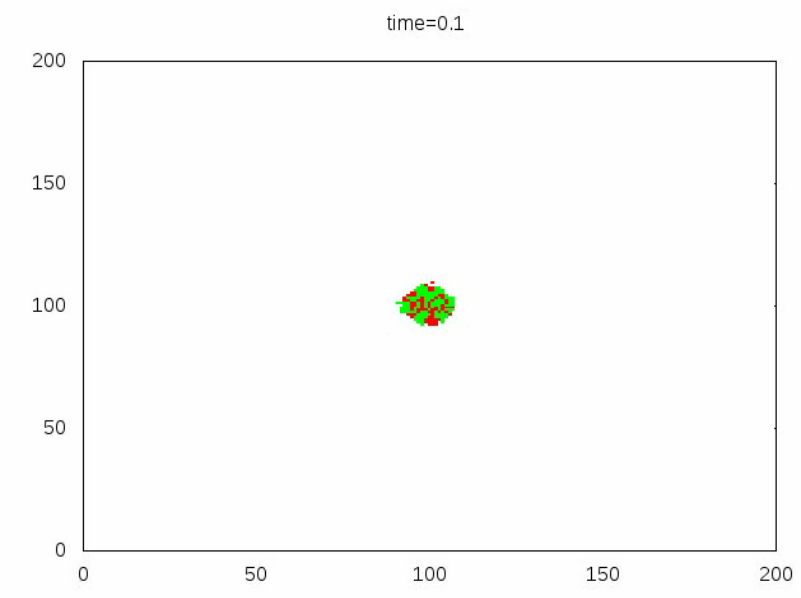
Virulence of mutant
>>
Virulence of WT

Spatial structure

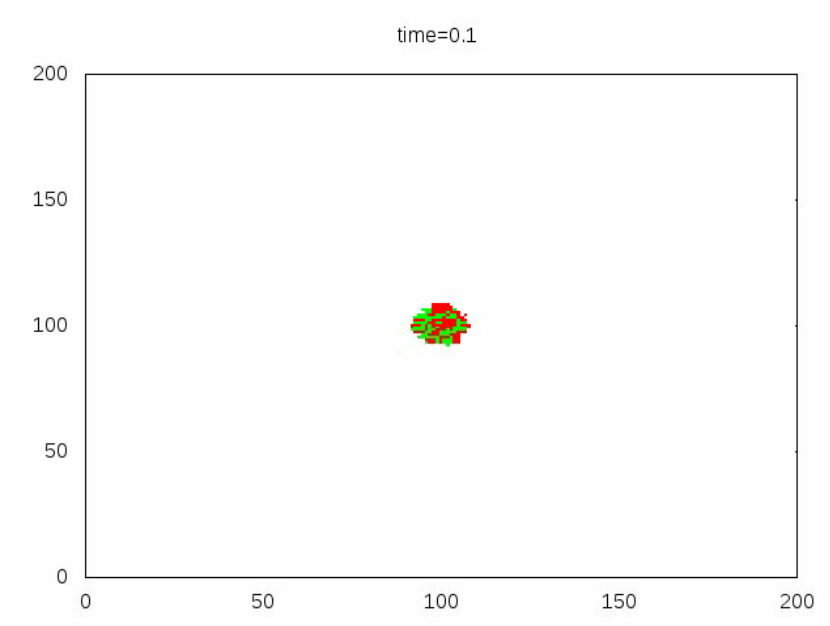
Transient evolution

Griette et al., 2015

Neutral evolution

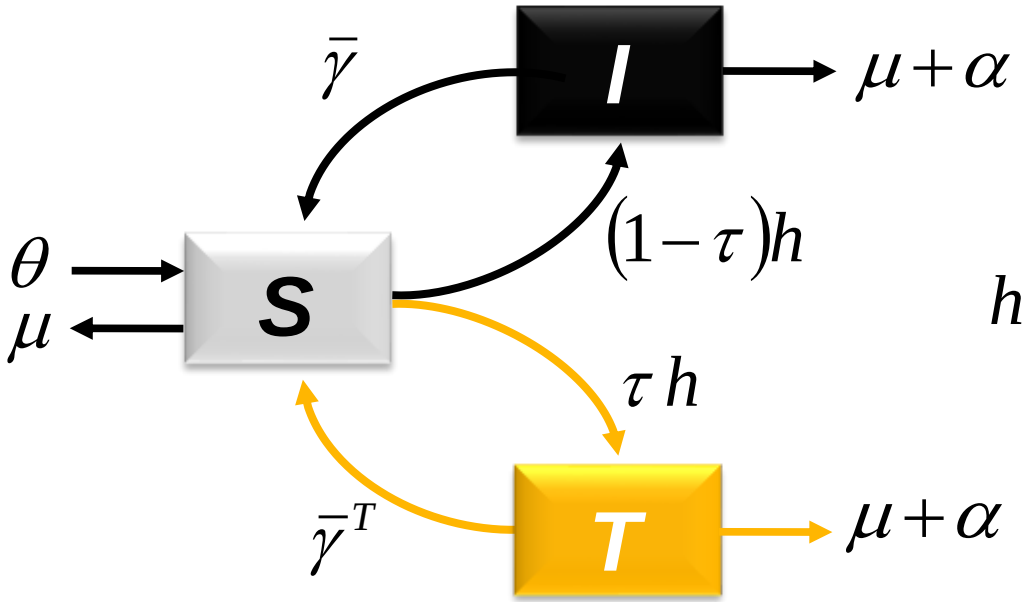


Virulence evolution



Multilocus resistance model

Epidemiology:



$$h = \bar{\beta} I + \bar{\beta}^T T$$

Multilocus resistance model

Epidemiology:

$$\frac{dS}{dt} = \theta - \mu S - \left(\bar{\beta} I + \bar{\beta}^T T\right) S + \left(\bar{\gamma} I + \bar{\gamma}^T T\right)$$

$$\frac{dI}{dt} = (1-\tau)\left(\bar{\beta} I + \bar{\beta}^T T\right) S - \left(\mu + \alpha + \bar{\gamma}\right) I$$

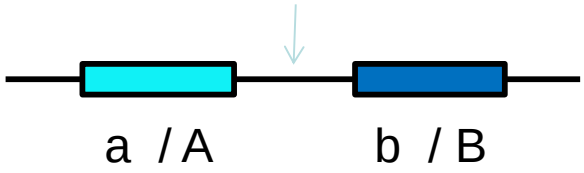
$$\frac{dT}{dt} = \tau\left(\bar{\beta} I + \bar{\beta}^T T\right) S - \left(\mu + \alpha + \bar{\gamma}^T\right) T$$

Multilocus resistance model

Evolution:

Superinfection: σ

Recombination: r



Four genotypes (parasites strains):

- ab — wild type
- Ab, aB — single mutants
- AB — double mutant

Resistance affects recovery γ or transmission β

Multilocus resistance model

Evolution:

Dynamics of allele frequencies:

$$\frac{dp_i^T}{dt} = \underbrace{p_i^T\left(1-p_i^T\right)\left(s_i^T+\delta_{j|i}^T s_E^T\right)}_{direct\ selection} + \underbrace{D^T s_j^T}_{indirect\ selection} + \underbrace{\frac{I}{T}\left(\tau S+\sigma T/2\right)\left(\overline{\beta}\left(p_i-p_i^T\right)+p_i\left(\beta_i-\overline{\beta}\right)\right)}_{gene\ flow}$$

$$s_A^T = \left(\tau S+\sigma T/2\right)\Delta\beta_A^T - \Delta\gamma_A^T$$
$$s_B^T = \left(\tau S+\sigma T/2\right)\Delta\beta_B^T - \Delta\gamma_B^T$$
$$s_E^T = \left(\tau S+\sigma T/2\right)\Delta\beta_E^T - \Delta\gamma_E^T$$
$$\delta_{j|i}^T = \frac{\left(p_i^T p_j^T + D^T\right)}{p_i^T}$$

Multilocus resistance model

Evolution:

Dynamics of allele frequencies:

$$\frac{dp_i^T}{dt} = \underbrace{p_i^T\left(1-p_i^T\right)\left(s_i^T+\delta_{j|i}^T s_E^T\right)}_{direct\ selection} + \underbrace{D^T s_j^T}_{indirect\ selection} + \underbrace{\frac{I}{T}\left(\tau S+\sigma T/2\right)\left(\overline{\beta}\left(p_i-p_i^T\right)+p_i\left(\beta_i-\overline{\beta}\right)\right)}_{gene\ flow}$$

Dynamics of linkage disequilibrium:

$$D^T = p_{ab}^T p_{AB}^T - p_{Ab}^T p_{aB}^T$$

Multilocus resistance model

Evolution:

Dynamics of allele frequencies:

$$\frac{dp_i^T}{dt} = \underbrace{p_i^T\left(1-p_i^T\right)\left(s_i^T+\delta_{j|i}^T s_E^T\right)}_{direct\ selection} + \underbrace{D^T s_j^T}_{indirect\ selection} + \underbrace{\frac{I}{T}\left(\tau S+\sigma T/2\right)\left(\overline{\beta}\left(p_i-p_i^T\right)+p_i\left(\beta_i-\overline{\beta}\right)\right)}_{gene\ flow}$$

Dynamics of linkage disequilibrium:

$$\frac{dD^T}{dt} = \underbrace{-\sigma r\left(\overline{\beta}I+\overline{\beta}^T T\right)D^T}_{recombination} + \underbrace{\left((1-2p_A^T)\hat{s}_A^T+(1-2p_B^T)\hat{s}_B^T\right)D^T}_{additive\ selection} + \underbrace{\left(D^T+p_A^T p_B^T\right)\left((1-p_A^T)(1-p_B^T)-D^T\right)\hat{s}_E^T}_{epistasis} + \underbrace{\overline{\beta}\frac{I}{T}\left(S\tau+\frac{\sigma I}{2}(1-r)\right)\left(\left(\overline{p}_A-p_A^T\right)\left(\overline{p}_B-p_B^T\right)+\overline{D}-D^T\right)}_{gene\ flow}$$

Conclusions

Conclusions

Pathogen virulence evolve **fast** during epidemics

Evolutionary epidemiology theory can « **predict »**:

- Epidemiological dynamics
- Evolution of virulence and transmission
- The effects of spatial structure

… for bacteriophage λ

What about other pathogens? Inférence!

What about the effects of stochasticity?