Evolution de la resistance de pathogènes lors d'une propagation spatiale

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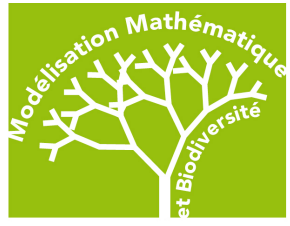

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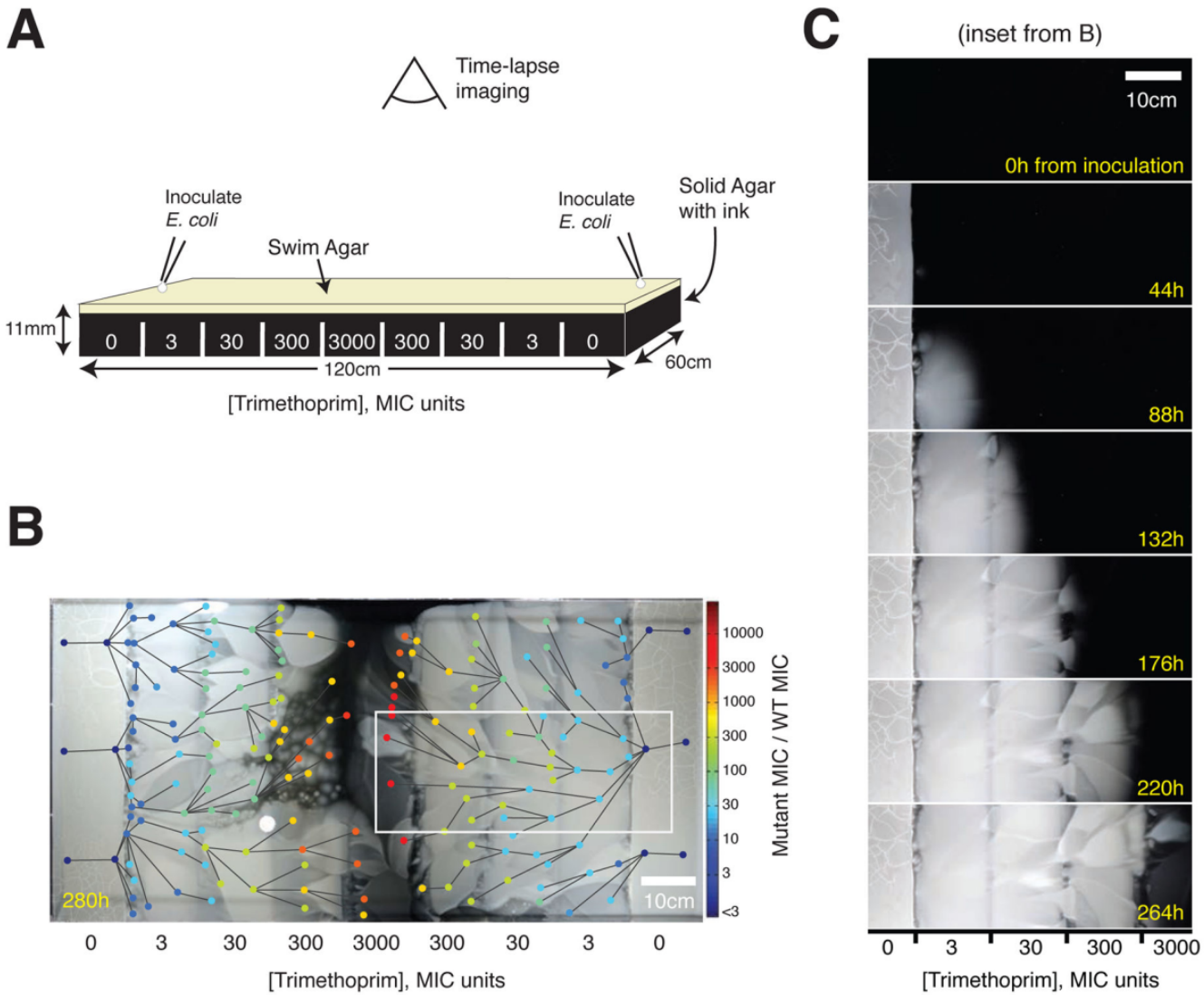
- Matthieu Alfaro, LMRS, Université Rouen Normandie,
- Sylvain Gandon, CEFE Montpellier,
- Quentin Griette, LMAH, Université le Havre Normandie.

Q. Griette, G. Raoul, Existence and qualitative properties of travelling waves for an epidemiological model with mutations. *J. Diff. eq.* **260**, 7115-7151 (2016).

Q. Griette, G. R., S. Gandon, Virulence evolution at the front line of spreading epidemics. *Evolution* **11**(69), 2810-2819 (2015).

Griette Q, Alfaro M, Raoul G, Gandon S. Evolution and spread of multiadapted pathogens in a spatially heterogeneous environment. *Evolution Letters* (2024).

A wonderful experiment: space + evolution[1]

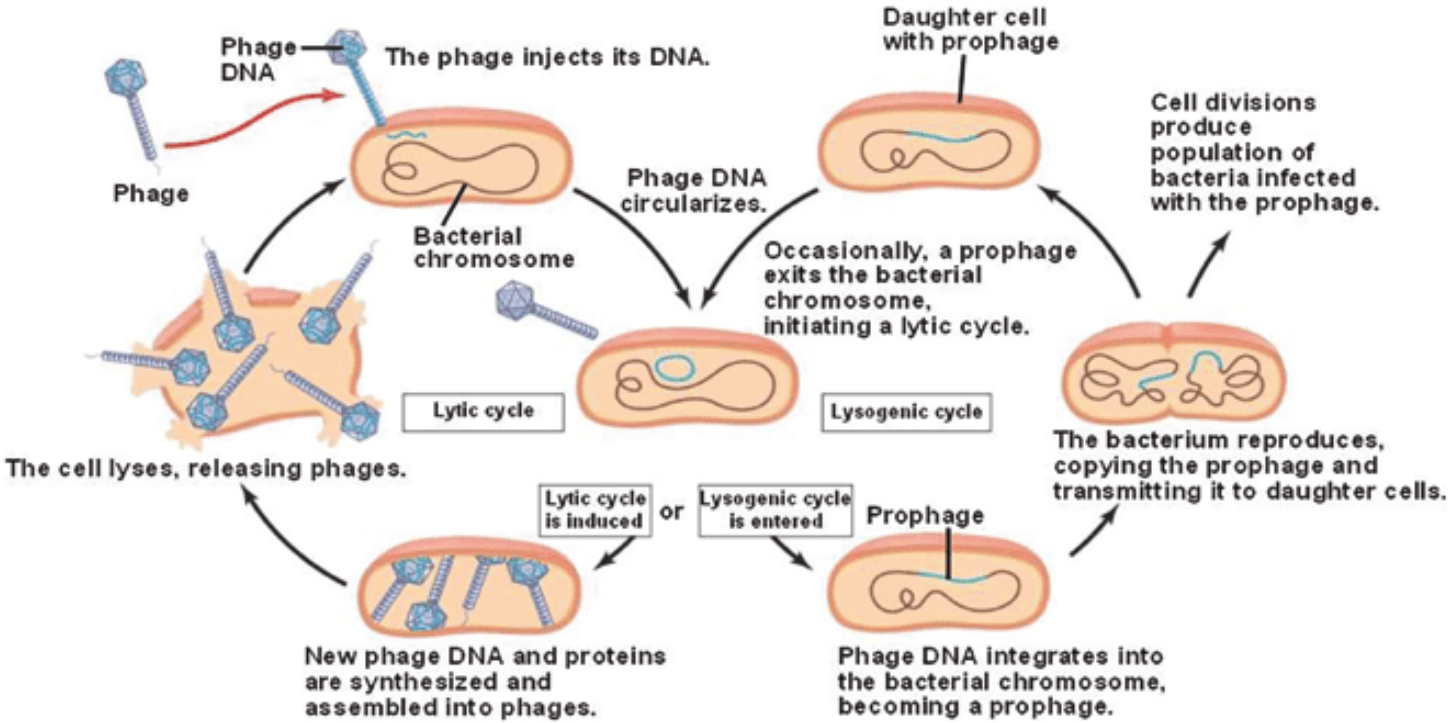


[1] M. Baym et al, *Science*, 2017.

I. Spreading epidemics with a wild type and a mutant

II. Spreading epidemics with drug resistant types

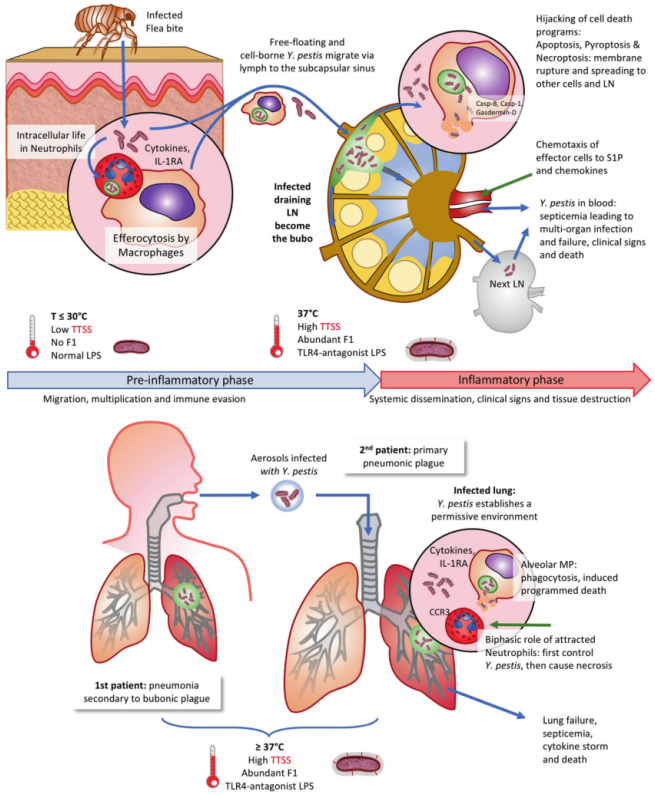
Example[2,3]: wild type and mutant (λcI857) phage λ



- Wild type: $\sim 60\%$ Lysogenic cycle,
- λcI857: $\sim 96\%$ Lysogenic cycle.

[2] Vander E.N., and E. Meyer, *Vlaams Diergeneeskd Tijdschr* 2018.
[3] Berngruber, T.W., S. Lion, and S. Gandon, *PLoS pathogens* 2015.

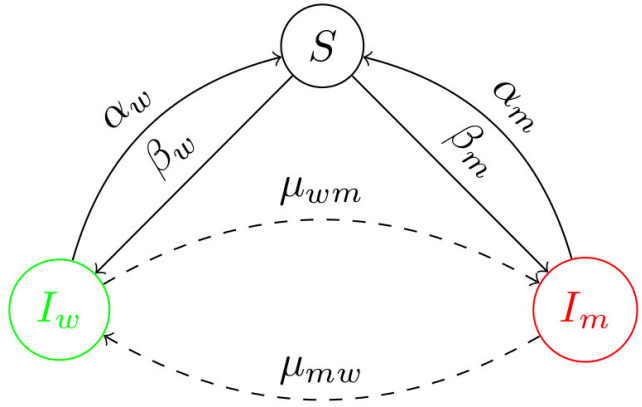
Example[4]: Yersinia pestis and plague



- Bubonic plague: death $\sim$ 7 days, death rate 30 $\sim$ 60%
- Pneumonic Plague: death $\sim$ 2 days, death rate $\sim$ 100%

[4] C. E. Demeure et al, *Genes & Immunity* 2019

Epidemic model

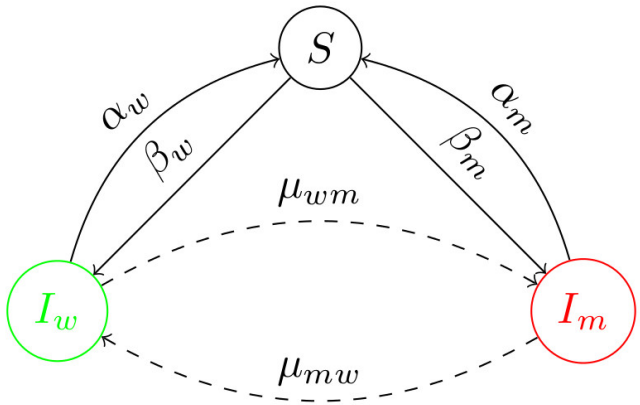


Let $r_i = \beta_i - \alpha_i$ and $K_i = N\left(1 - \frac{\alpha_i}{\beta_i}\right)$. We are interested in situations where

$$r_w < r_m \qquad \text{and} \qquad K_w > K_m.$$

We assume that $S + I_w + I_m \equiv N$ is constant (constant number of hosts)
$\Rightarrow$ We only need to describe $I_w(t)$ and $I_m(t)$.

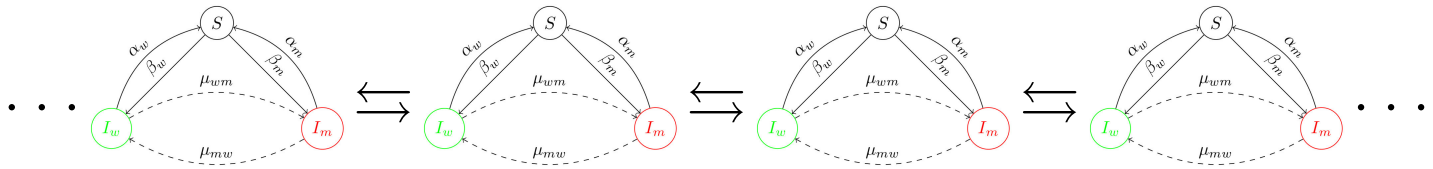
Epidemic model

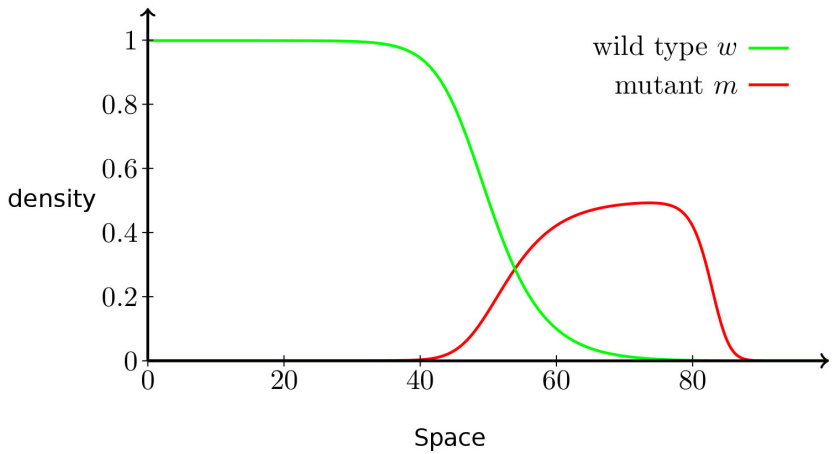


We only need to describe $I_w(t)$ and $I_m(t)$

$$\begin{cases} \frac{\partial I_w}{\partial t} = r_w I_w \left(1 - \frac{I_w + I_m}{K_w}\right) + \mu_m I_m - \mu_w I_w, \\ \\ \frac{\partial I_m}{\partial t} = r_m I_m \left(1 - \frac{I_w + I_m}{K_m}\right) + \mu_w I_w - \mu_m I_m, \end{cases}$$

Our model: Epidemic model + spatial structure

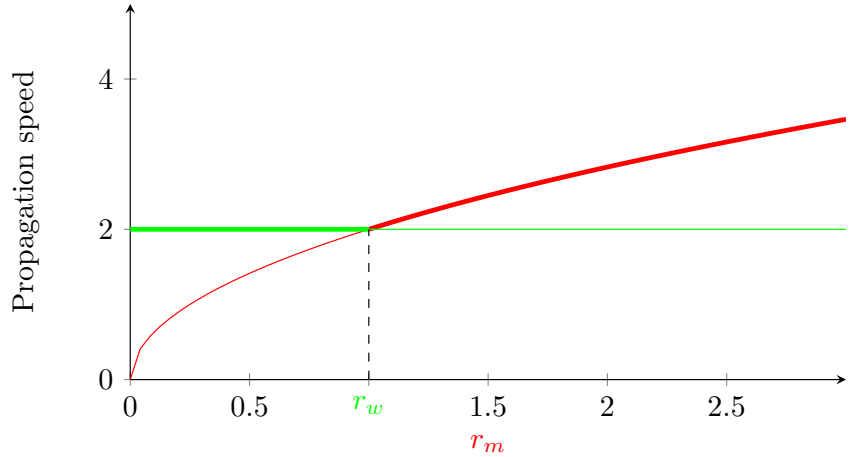


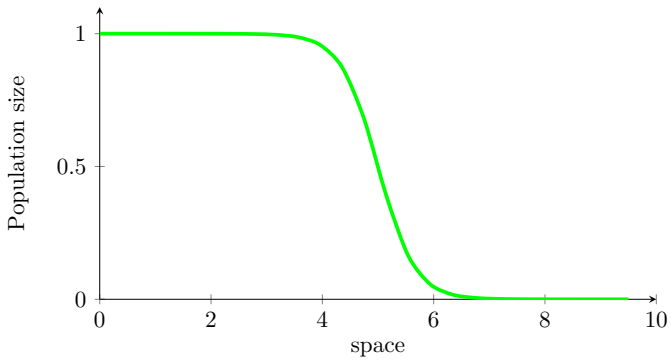


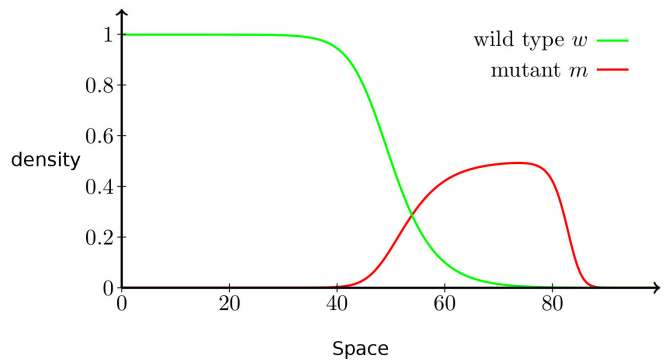
We now describe $I_w(t,x)$ and $I_m(t,x)$.

$$\begin{cases} \dfrac{\partial I_w}{\partial t} = \sigma \dfrac{\partial^2 I_w}{\partial x^2} + r_w I_w \left(1 - \dfrac{I_w + I_m}{K_w}\right) + \mu_m I_m - \mu_w I_w, \\ \\ \dfrac{\partial I_m}{\partial t} = \sigma \dfrac{\partial^2 I_m}{\partial x^2} + r_m I_m \left(1 - \dfrac{I_w + I_m}{K_m}\right) + \mu_w I_w - \mu_m I_m, \end{cases}$$

Simulations: effect of the growth rate r_m of the mutant



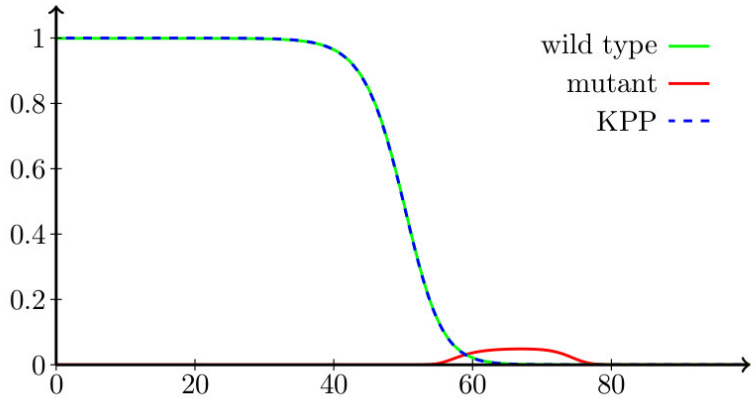


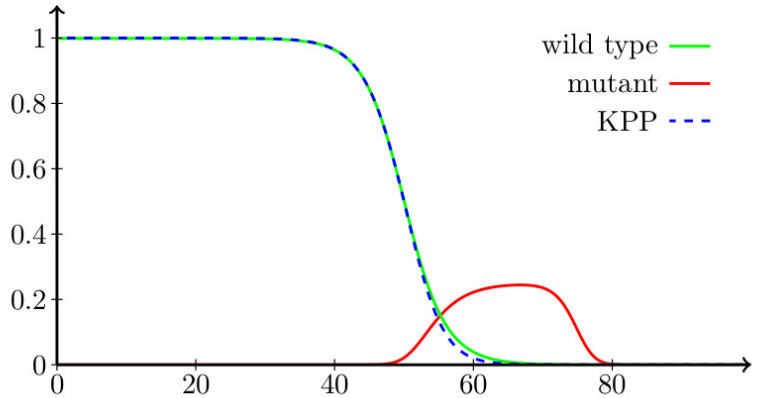


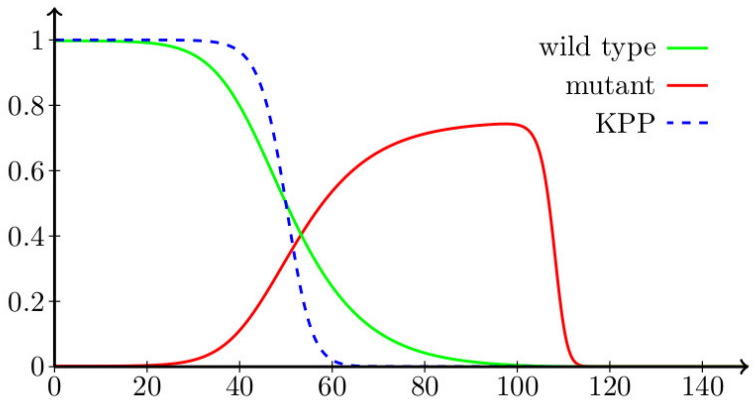
- Behind the front: always the wild type,
- At the edge of the epidemics: the pathogen type that can propagate the fastest.

(propagation speed)$\Rightarrow$ (Pathogen type at the edge)

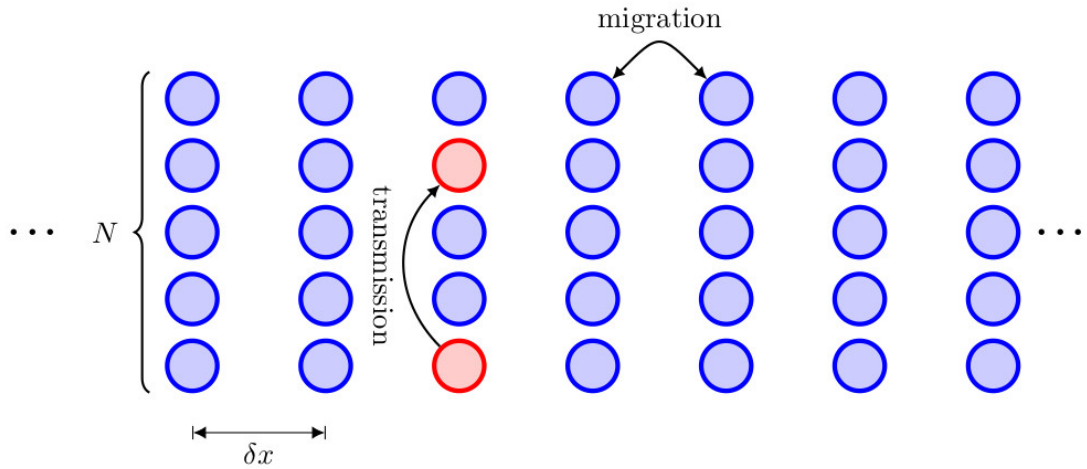
Propagation speed and the effect of the carrying capacity K_m of the mutant







The stochastic model

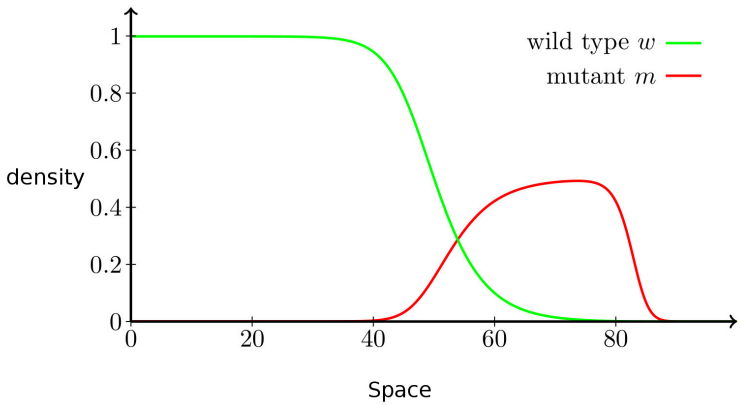


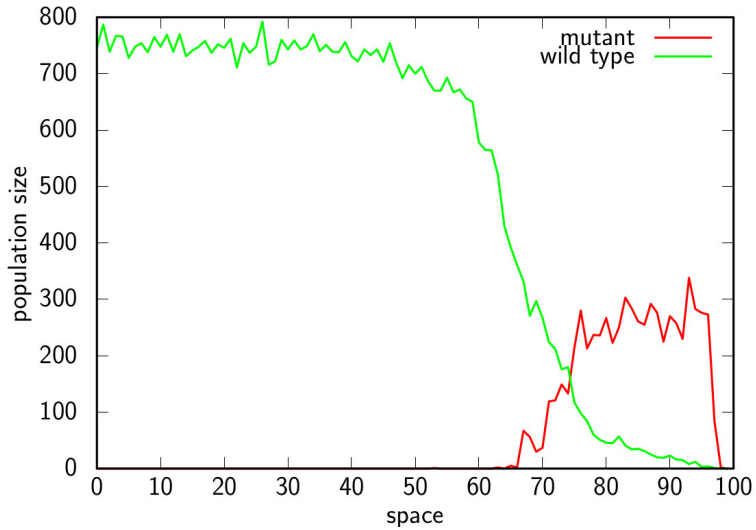
Additional parameters:

- $N \in \mathbb{N}$, number of hosts per site,
- $\delta x > 0$, spatial discretisation.

When $N \to \infty$ (and then $\delta x \to 0$), we recover our deterministic model.

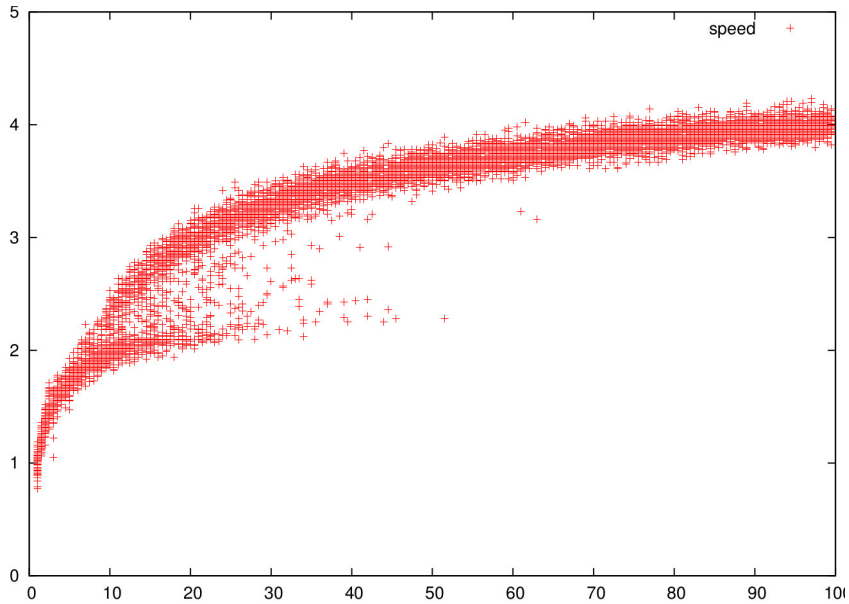
Simulations: deterministic vs stochastic





Similar dynamics when the number of hosts per site N is large.

Propagation speed of the epidemics as a function of the number of hosts per site N



- N large: we recover the deterministic speed
- N smaller: slower propagation

The Brunet-Derrida approximation[5]

Model for a single species of pathogen:

$$\partial_t n(t,x) - \sigma \Delta_x n(t,x) = r\left(1 - \frac{n(t,x)}{K}\right) n(t,x),$$

- Propagation speed: $2\sqrt{r\sigma}$.

In the stochastic model, if $n(t,x) \ll \frac{1}{N}$, there are no individuals!
$\Rightarrow$ Slower propagation:

- Propagation speed: $\nu \sim 2\sqrt{r\sigma} - \sqrt{r\sigma}\frac{\pi^2}{\log(KN)^2}$.

[5] E. Brunet, B. Derrida, *Physical Review E*, 1997.

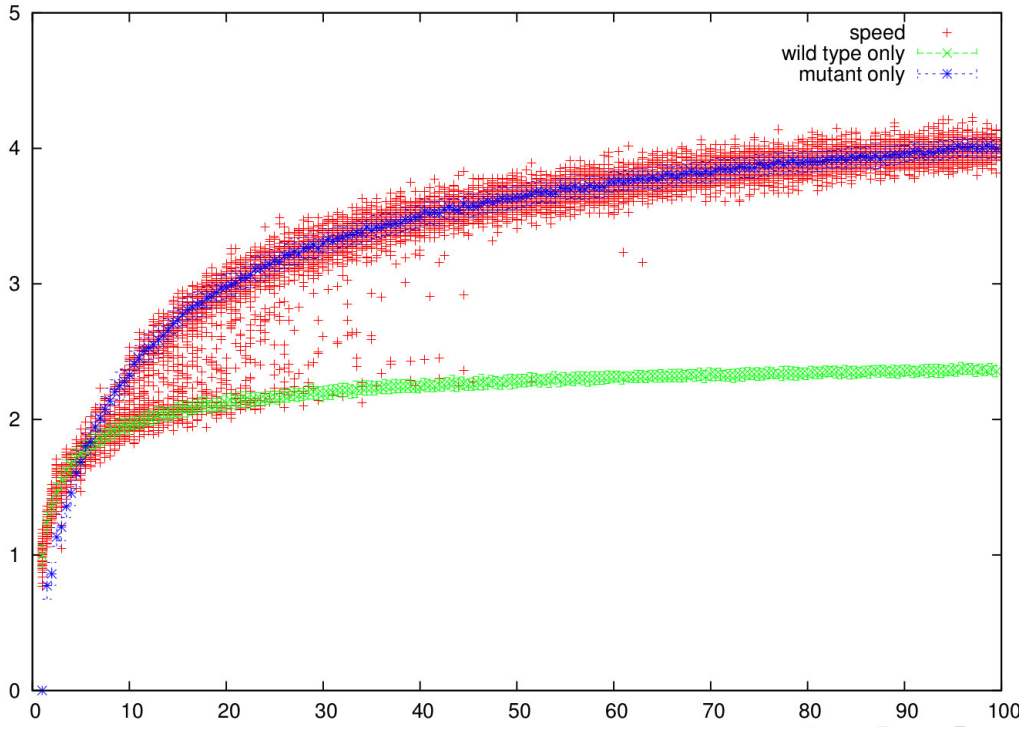
The Brunet-Derrida approximation

This Brunet-Derrida approximation applied to the two pathogen types provides:

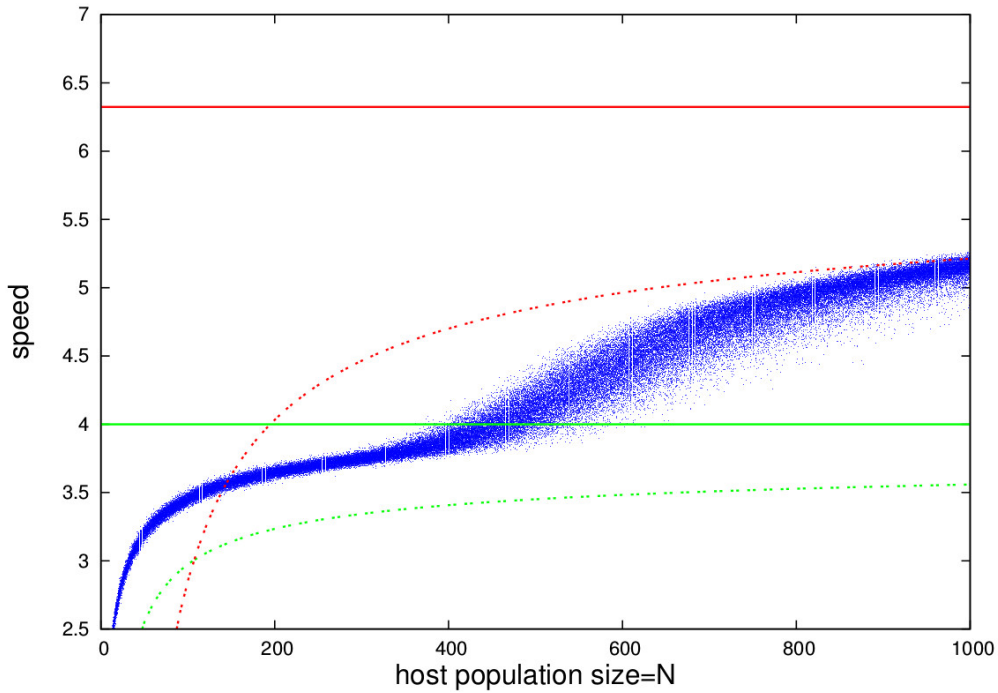
$$\nu_m \sim 2\sqrt{r_m \sigma} - \sqrt{r_m \sigma} \frac{\pi^2}{\log^2 (K_m N)}.$$

$$\nu_w \sim 2\sqrt{r_w \sigma} - \sqrt{r_w \sigma} \frac{\pi^2}{\log^2 (K_w N)}.$$

Propagation for the stochastic full model and for monomorphic pathogen populations

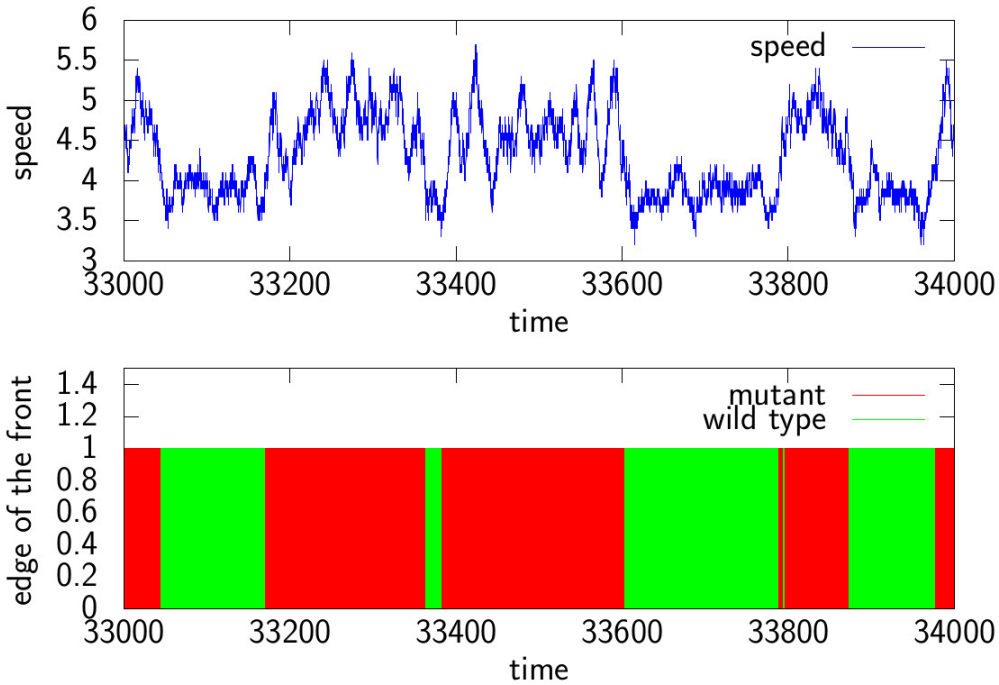


Propagation for the stochastic model: simulations and approximations

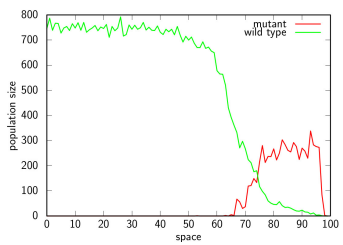


- Small N: The wild types lead the propagation,
- Intermediate N: ???
- Large N: The mutant types lead the propagation,

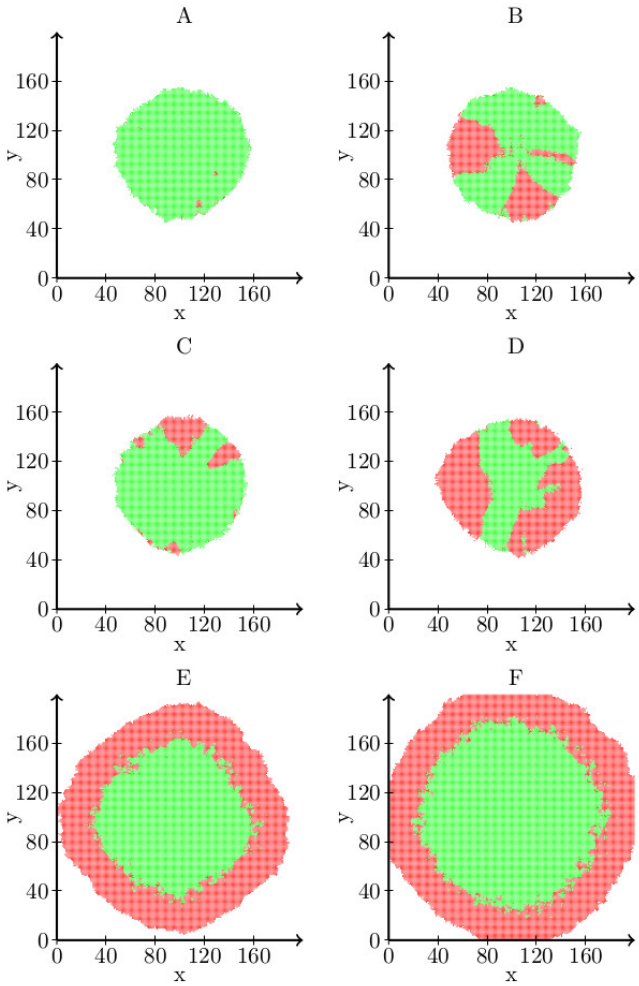
Instantaneous speed and pathogen type at the edge of the epidemics

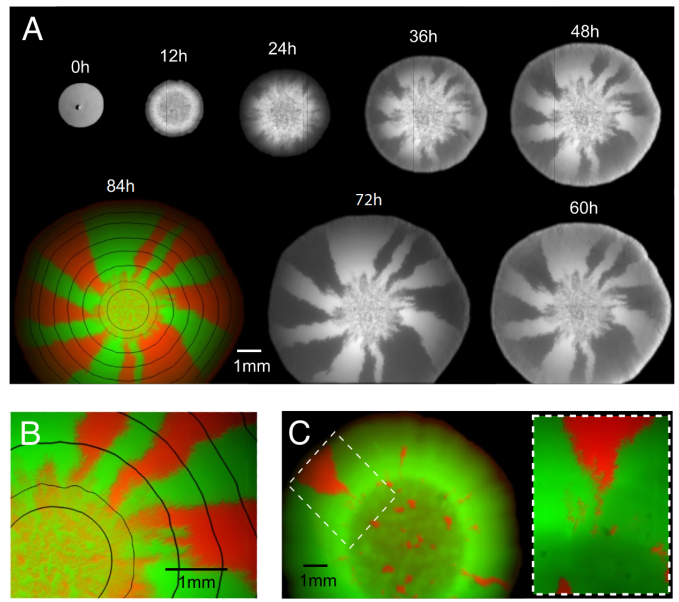


- Intermediate N: Sporadic emergence of the mutant type.



2*D* simulations[6]





[6] Hallatschek et al, PNAS, 2007.

I. Spreading epidemics with a wild type and a mutant

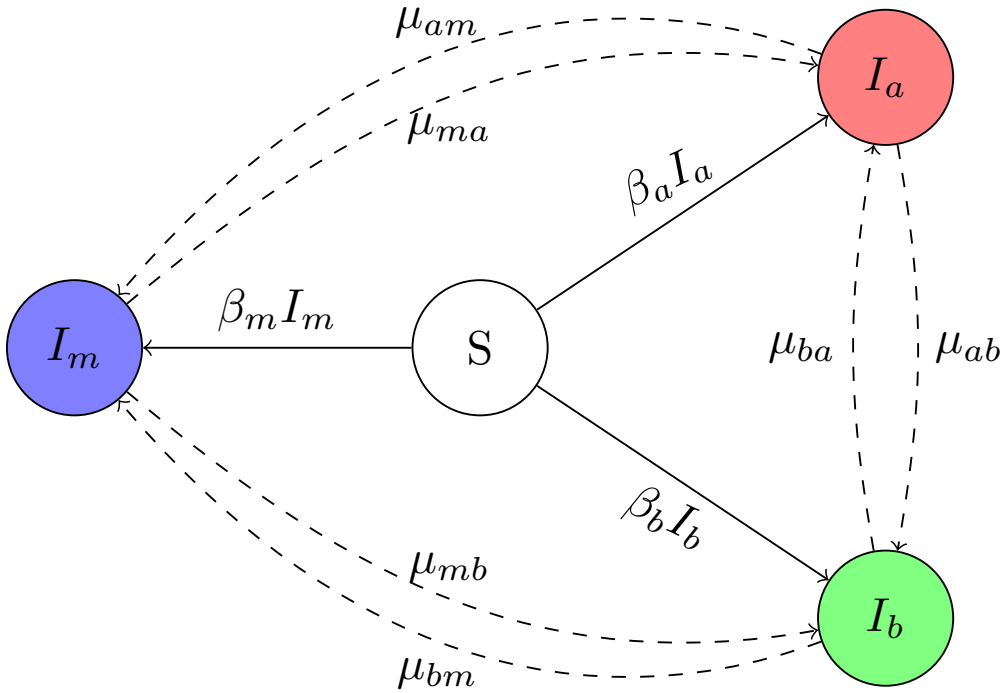
II. Spreading epidemics with drug resistant types

Three types of antibiotic resistant bacteria

We consider two antibiotics, A and B, and three bacteria types:

- I_a: type resistant to A
- I_b: type resistant to B
- I_m: multi-resistant type, resistant to both A and B

Epidemic model



- S Uninfected host
- I_a: host infected by the type resistant to A
- I_b: host infected by the type resistant to B
- I_m: host infected by the type, resistant to both A and B

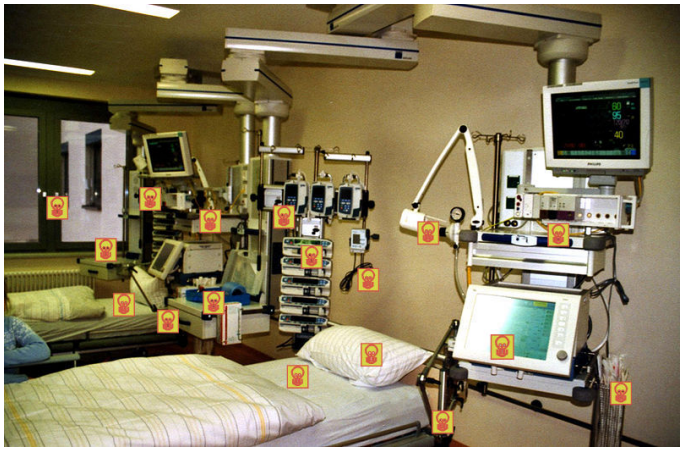
Epidemic model

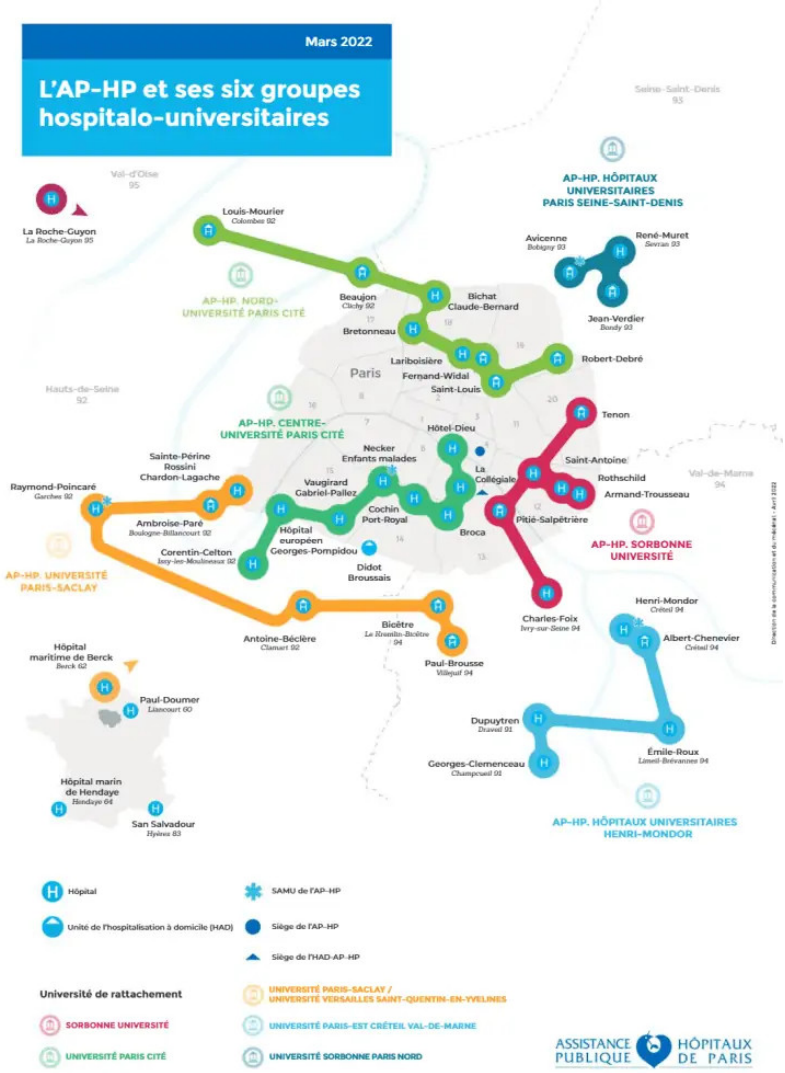
$$\begin{cases} \frac{\partial I_a}{\partial t} = I_a\left[r_a - \beta_a\left(I_a + I_b + I_m\right)\right] + \mu I_m + \mu I_b - 2\mu I_a \\ \frac{\partial I_b}{\partial t} = I_b\left[r_b - \beta_b\left(I_a + I_b + I_m\right)\right] + \mu I_m + \mu I_a - 2\mu I_b \\ \frac{\partial I_m}{\partial t} = I_m\left[r_m - \beta_m(I_a + I_b + I_m)\right] + \mu I_a + \mu I_b - 2\mu I_m \end{cases}$$

with

$$r_a = \beta_a - \alpha, \quad r_b = \beta_b - \alpha, \quad r_m = \beta_m - \alpha.$$

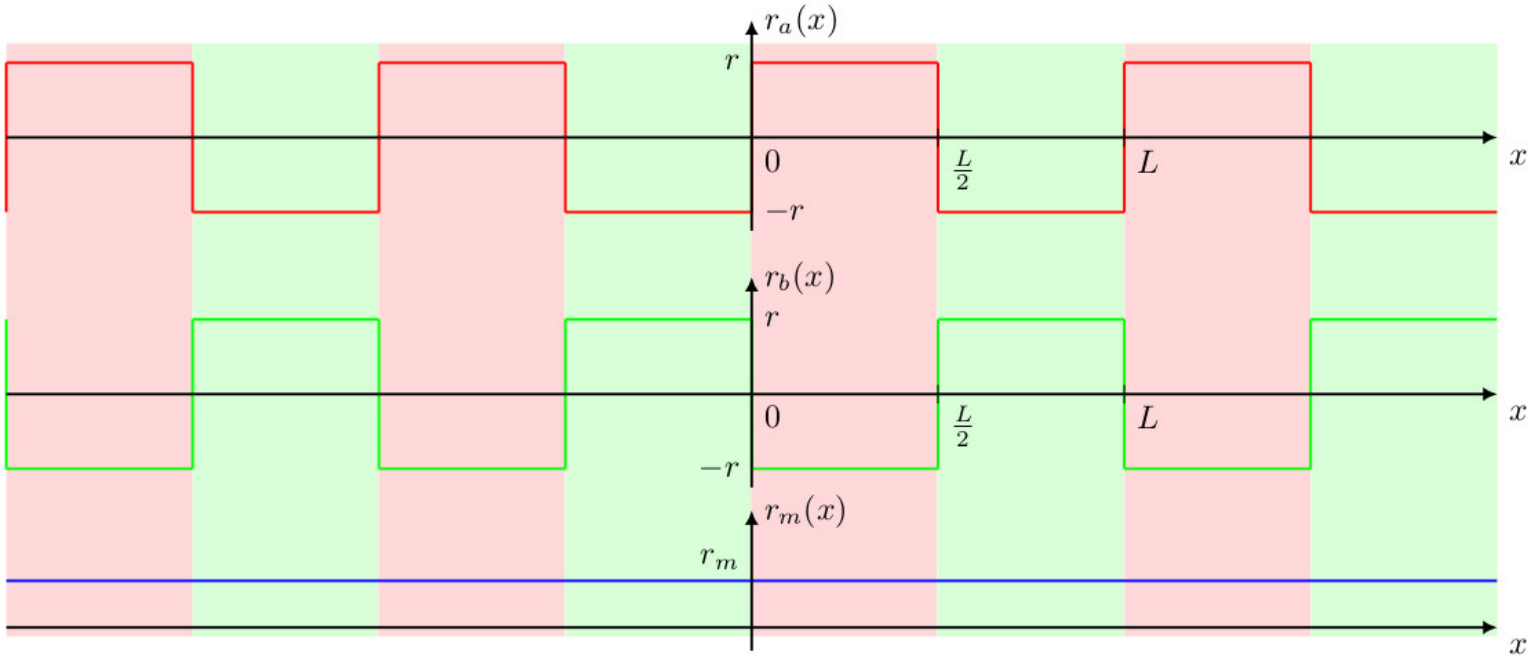
Spatial heterogeneity[7]





[7] L. Rimbaud et al, *PLoS computational biology*, 2018.

Spatial heterogeneity



Drug A , Drug B.

Parameters: $\mu > 0$ small, and

- L spatial period of the drug treatments
- r_m growth rate of the multi-resistant type

The model

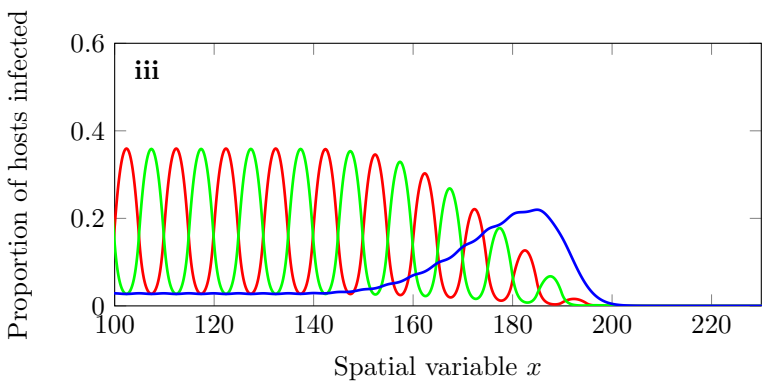
We obtain the model

$$\begin{cases} \frac{\partial I_a}{\partial t} = \sigma \frac{\partial^2 I_a}{\partial x^2} + I_a\left[r_a(x) - \beta_a(x)\left(I_a + I_b + I_m\right)\right] + \mu I_m + \mu I_b - 2\mu I_a \\ \frac{\partial I_b}{\partial t} = \sigma \frac{\partial^2 I_b}{\partial x^2} + I_b\left[r_b(x) - \beta_b(x)\left(I_a + I_b + I_m\right)\right] + \mu I_m + \mu I_a - 2\mu I_b \\ \frac{\partial I_m}{\partial t} = \sigma \frac{\partial^2 I_m}{\partial x^2} + I_m\left[r_m - \beta_m(I_a + I_b + I_m)\right] + \mu I_a + \mu I_b - 2\mu I_m \end{cases}$$

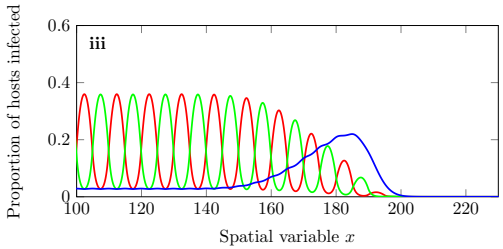
with

$$r_a(x) = \beta_a(x) - \alpha, \quad r_b(x) = \beta_b(x) - \alpha, \quad r_m = \beta_m - \alpha.$$

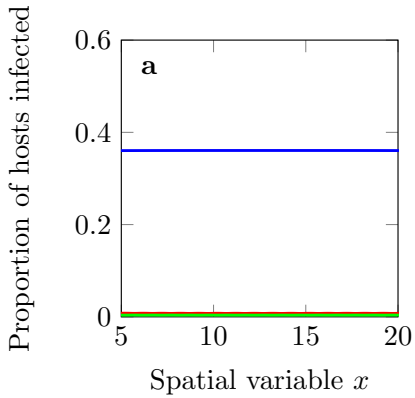
MOVIE



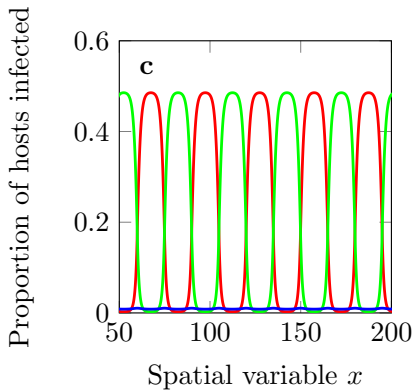
Steady states of the model



- $r_m \sim 1$: when the cost of multi-resistance is small, the multi-resistant type is dominant

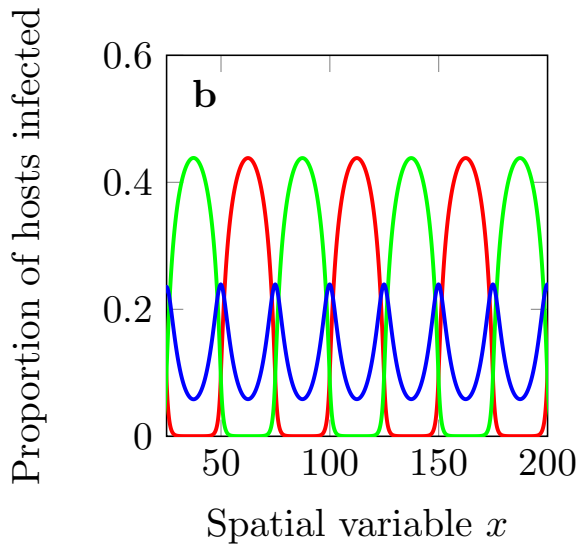


- $r_m \sim 0$: when the cost of multi-resistance is high, the specialists types are dominant

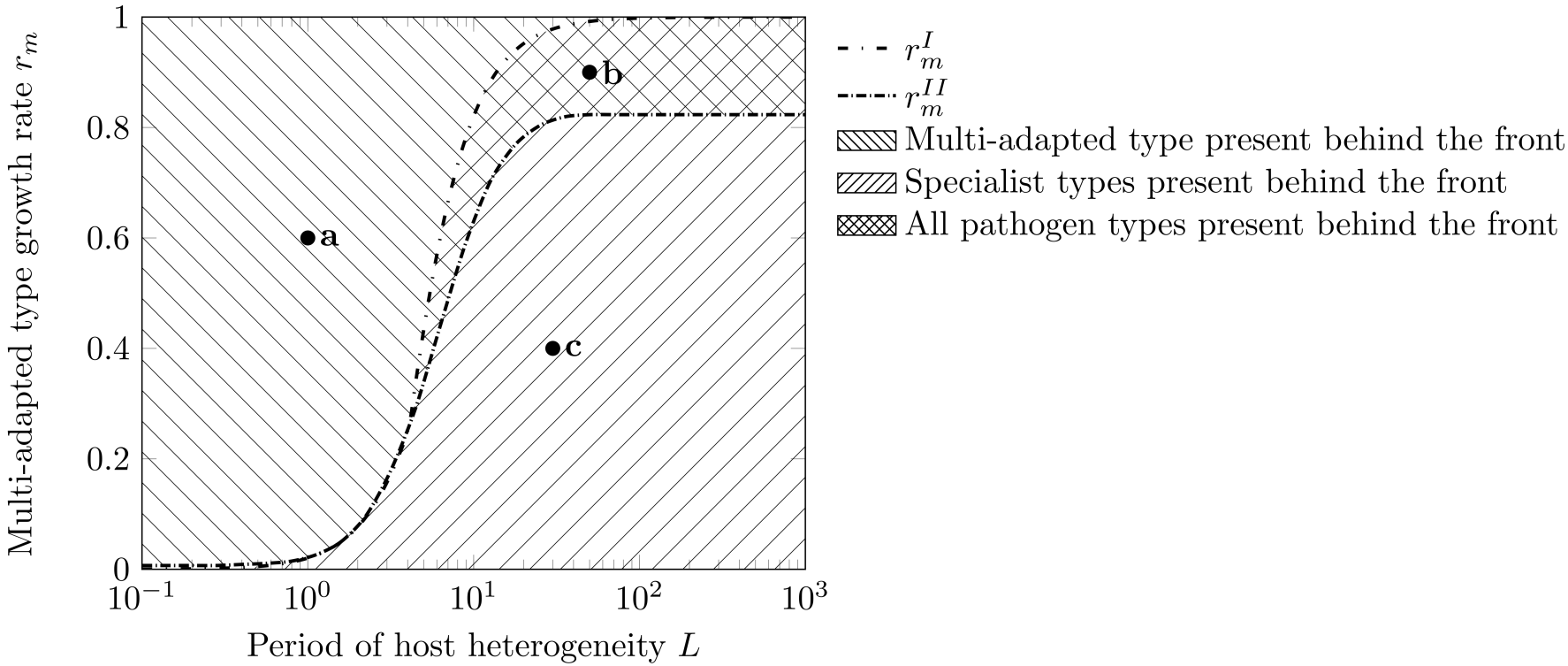


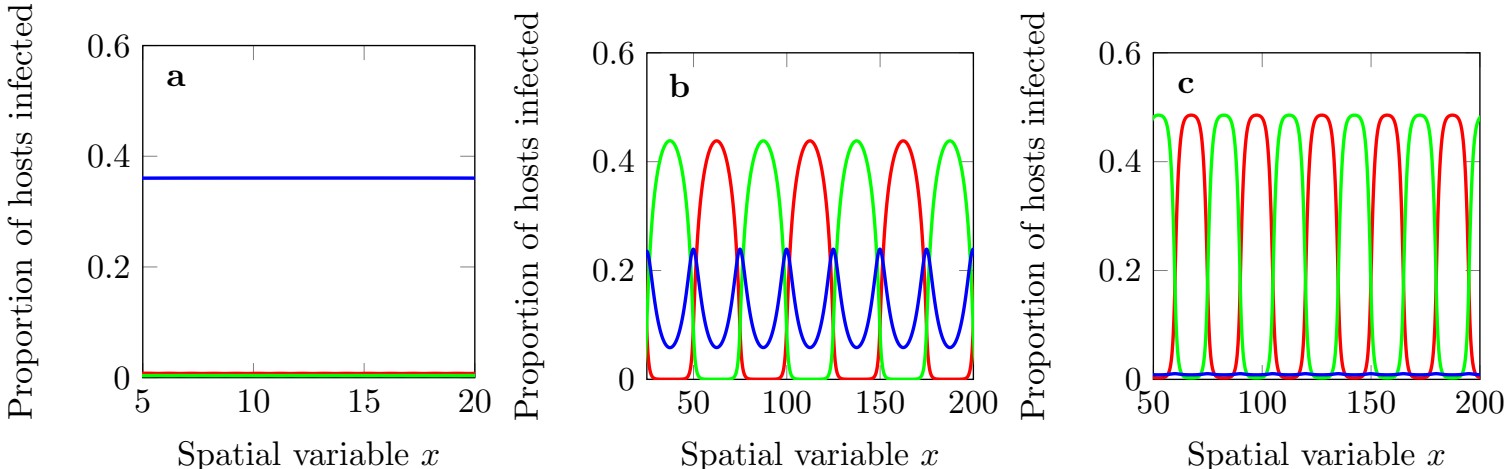
Steady states of the model

- Intermediate values of r: for intermediate multi-resistance costs, all types can co-exist

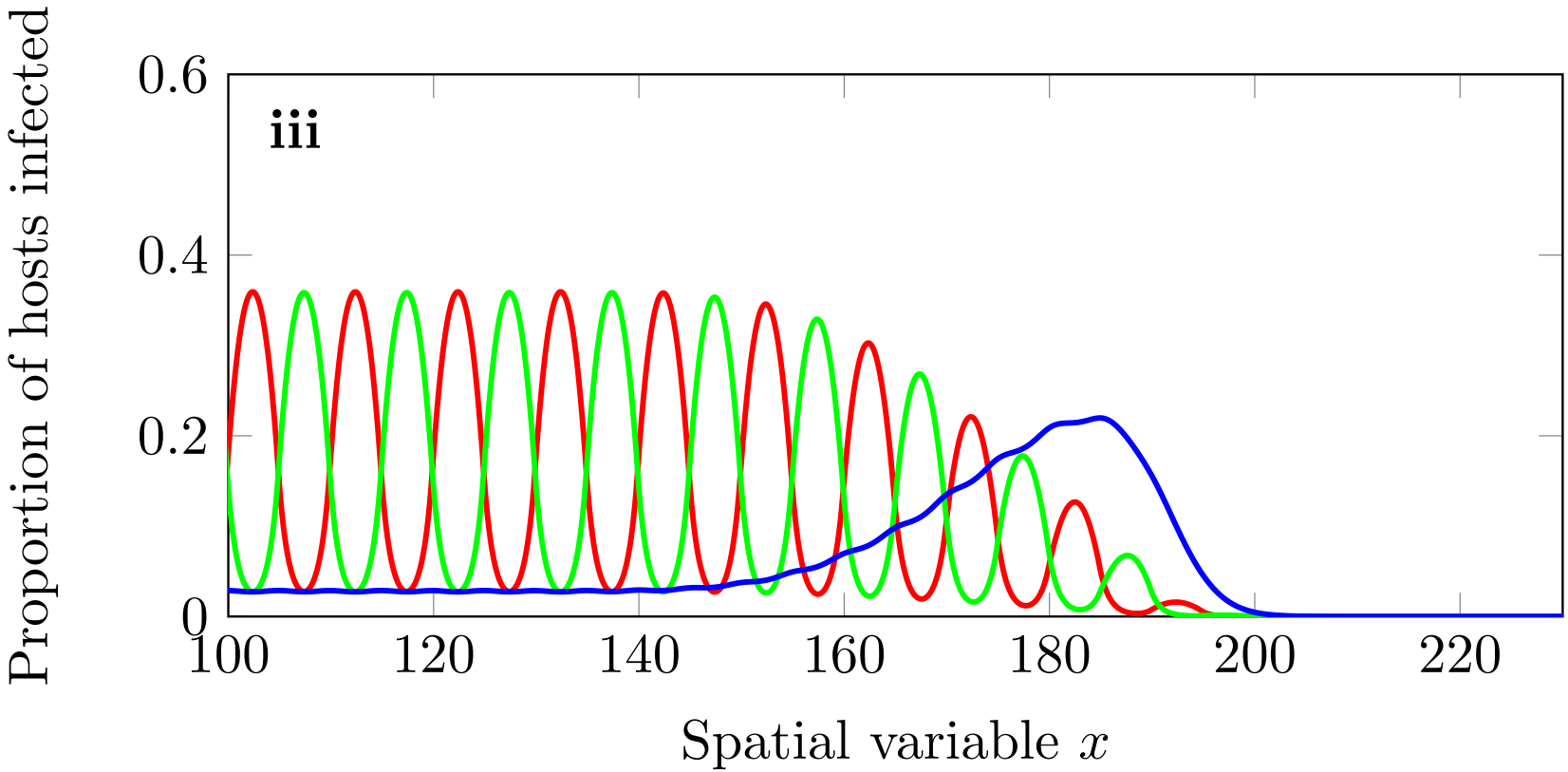


Steady states of the model





Propagating epidemics



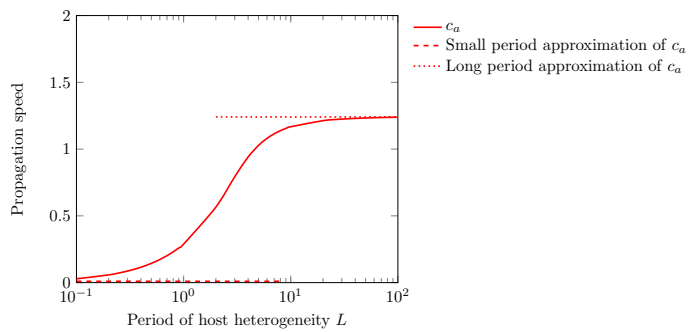
Propagation of a single pathogen type

$$\begin{cases} \frac{\partial I_a}{\partial t} = \sigma \frac{\partial^2 I_a}{\partial x^2} + I_a \left[r_a(x) - \beta_a(x) \left(I_a + I_b + I_m \right) \right] + \mu I_m + \mu I_b - 2\mu I_a \\ \frac{\partial I_b}{\partial t} = \sigma \frac{\partial^2 I_b}{\partial x^2} + I_b \left[r_b(x) - \beta_b(x) \left(I_a + I_b + I_m \right) \right] + \mu I_m + \mu I_a - 2\mu I_b \\ \frac{\partial I_m}{\partial t} = \sigma \frac{\partial^2 I_m}{\partial x^2} + I_m \left[r_m - \beta_m (I_a + I_b + I_m) \right] + \mu I_a + \mu I_b - 2\mu I_m \end{cases}$$

- Multiresistant type alone: F-KPP model, $c_m = 2\sqrt{\sigma(\beta_m - \alpha)}$

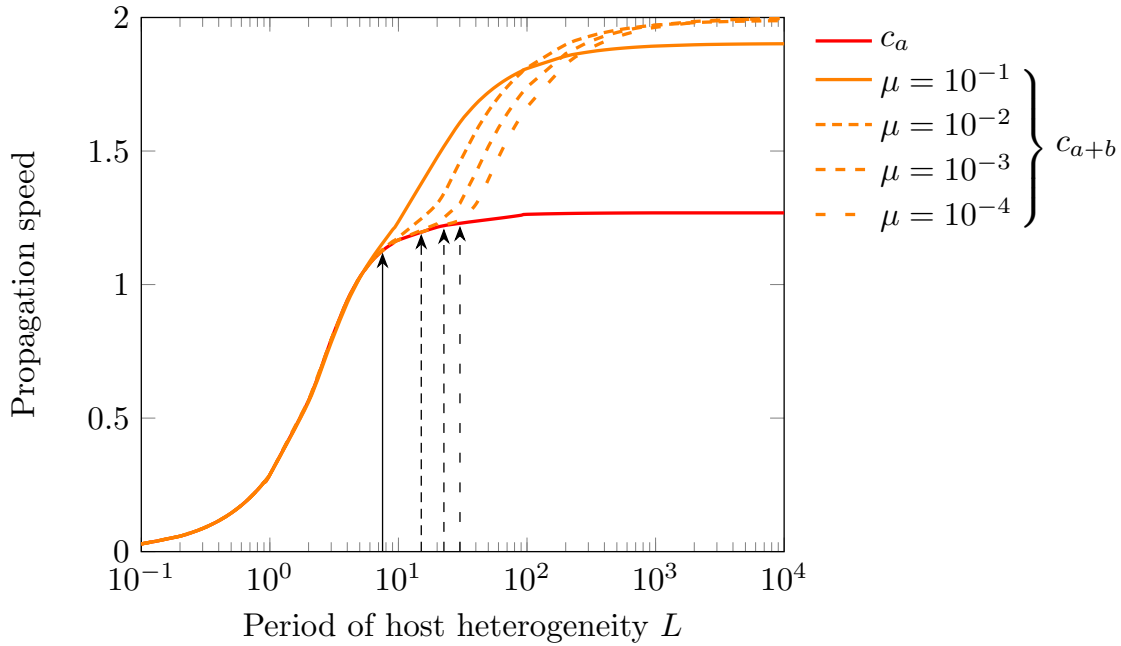
$$\frac{\partial I_m}{\partial t} = \sigma \frac{\partial^2 I_m}{\partial x^2} + I_m \left[\beta_m - \alpha - \beta_m I_m \right]$$

- A specialist type alone: Pulsating fronts c_a



Propagation of the coalition of specialists, c_{a+b}

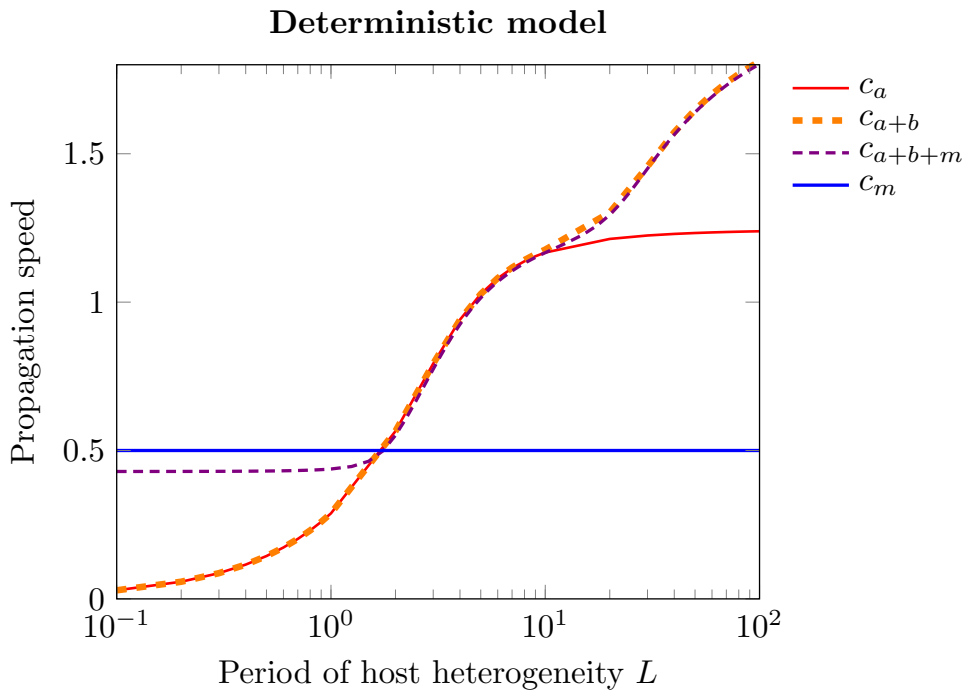
$$\begin{cases} \frac{\partial I_a}{\partial t} = \sigma \frac{\partial^2 I_a}{\partial x^2} + I_a \left[r_a(x) - \beta_a(x) \left(I_a + I_b + I_m \right) \right] + \mu I_m + \mu I_b - 2\mu I_a \\ \frac{\partial I_b}{\partial t} = \sigma \frac{\partial^2 I_b}{\partial x^2} + I_b \left[r_b(x) - \beta_b(x) \left(I_a + I_b + I_m \right) \right] + \mu I_m + \mu I_a - 2\mu I_b \\ \frac{\partial I_m}{\partial t} = \sigma \frac{\partial^2 I_m}{\partial x^2} + I_m \left[r_m - \beta_m (I_a + I_b + I_m) \right] + \mu I_a + \mu I_b - 2\mu I_m. \end{cases}$$



$$L_c \sim \frac{8\sigma r \ln\left(\frac{r}{\mu}\sqrt{\frac{r}{\sigma}}\right)}{2r^{3/2}\sqrt{\sigma}}.$$

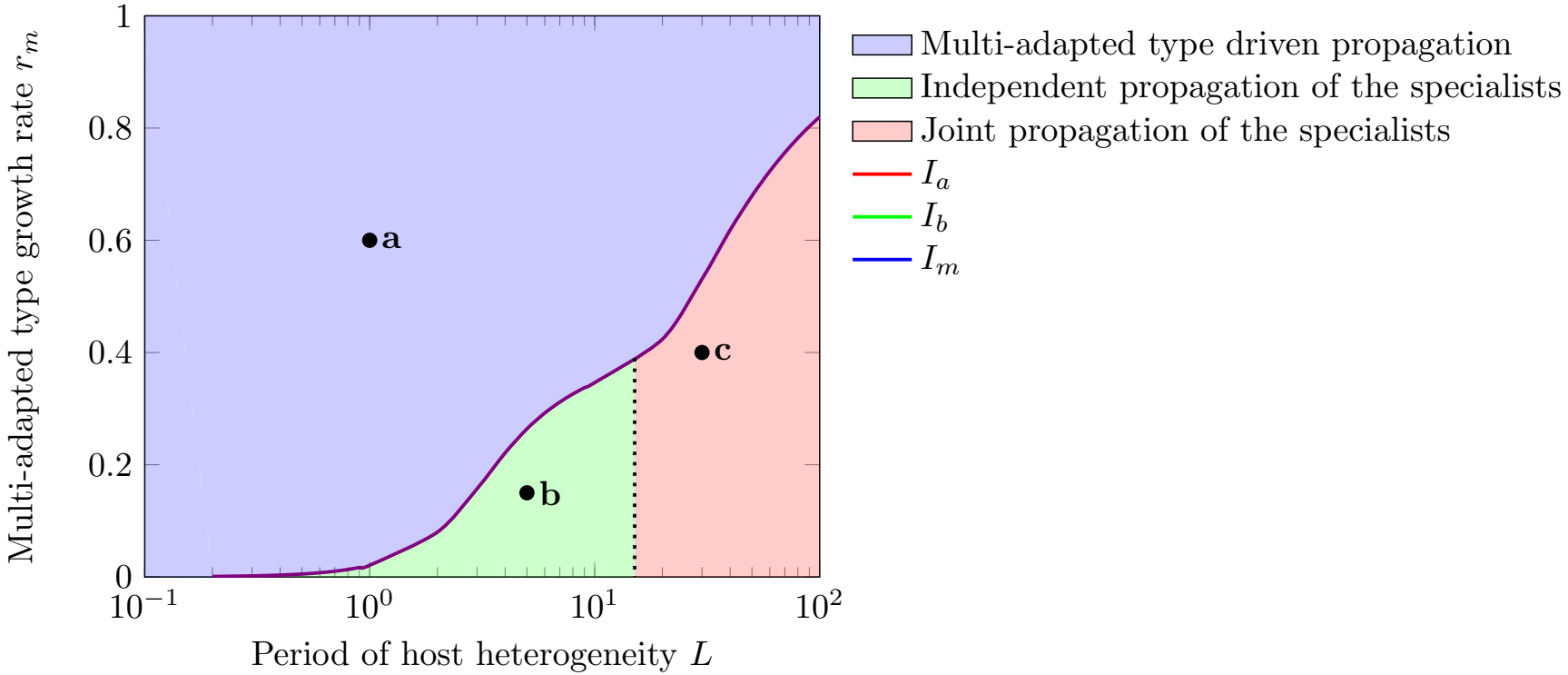
Propagation for the full model, c_{a+b+m}

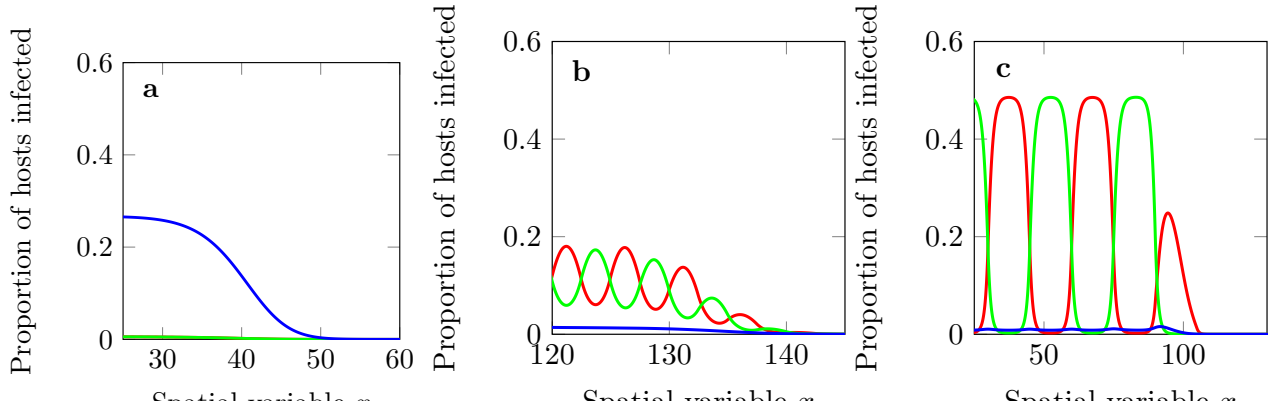
$$\begin{cases} \frac{\partial I_a}{\partial t} = \sigma \frac{\partial^2 I_a}{\partial x^2} + I_a \left[r_a(x) - \beta_a(x) \left(I_a + I_b + I_m \right) \right] + \mu I_m + \mu I_b - 2\mu I_a \\ \frac{\partial I_b}{\partial t} = \sigma \frac{\partial^2 I_b}{\partial x^2} + I_b \left[r_b(x) - \beta_b(x) \left(I_a + I_b + I_m \right) \right] + \mu I_m + \mu I_a - 2\mu I_b \\ \frac{\partial I_m}{\partial t} = \sigma \frac{\partial^2 I_m}{\partial x^2} + I_m \left[r_m - \beta_m (I_a + I_b + I_m) \right] + \mu I_a + \mu I_b - 2\mu I_m \end{cases}$$



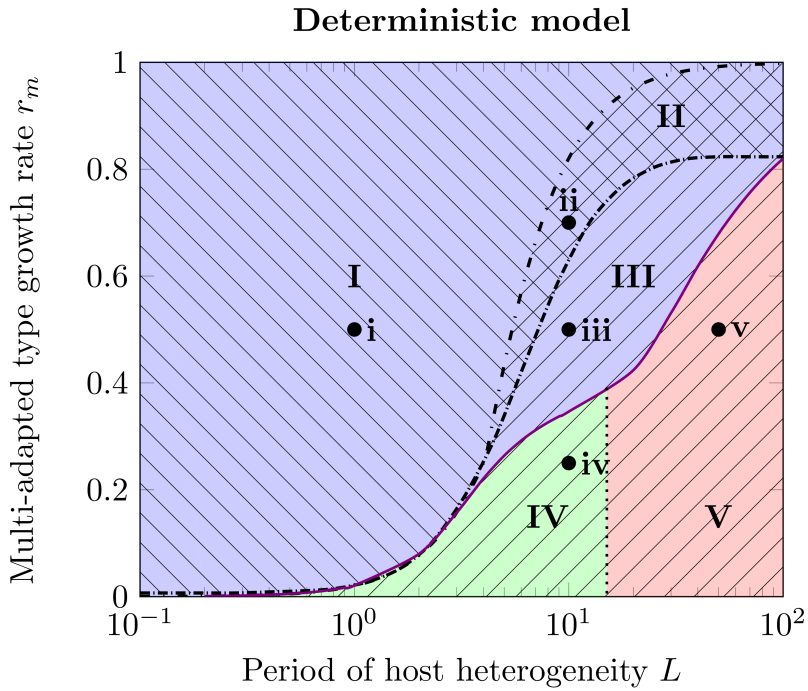
- Note the three modes of propagation.

Composition of the pathogen population at the front of the epidemics





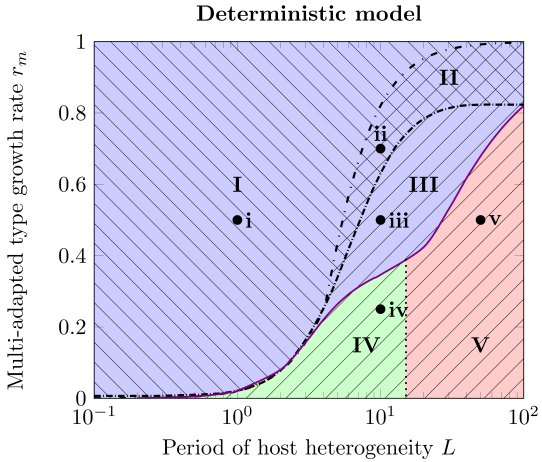
Qualitative description of the propagating population

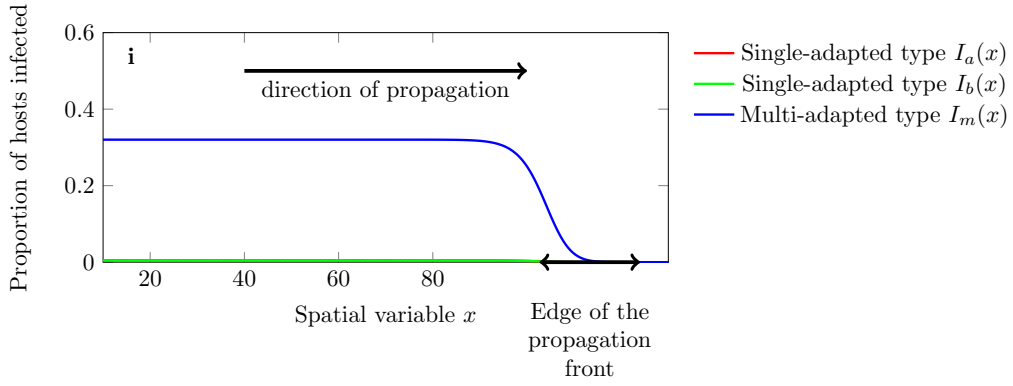


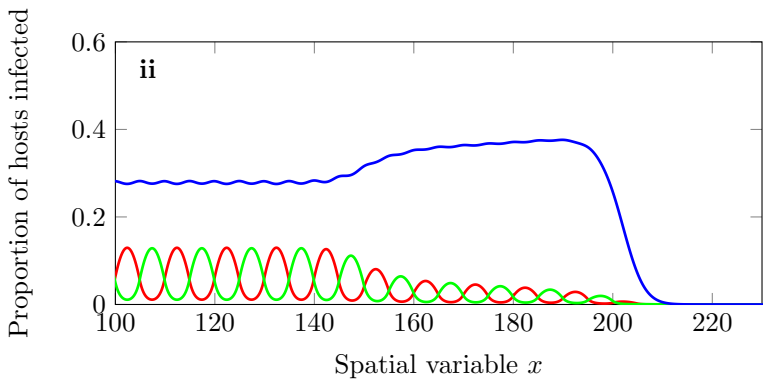
- Steady population: multi-resistant in (north-west lines hatches)
- Propagating populations: multi-resistant in (blue area)

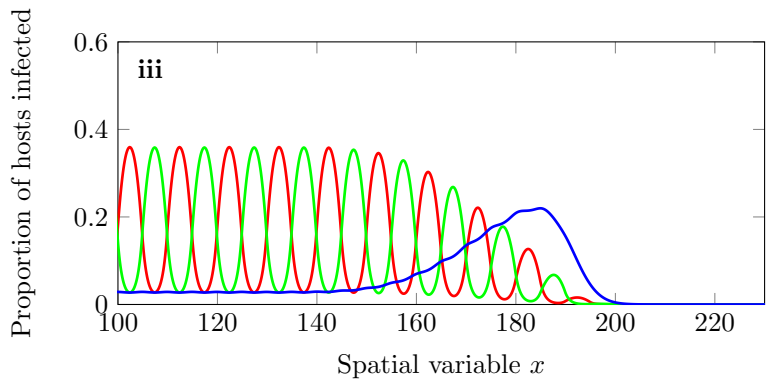
It is easier for the multi-resistant to appear at the edge of the epidemics

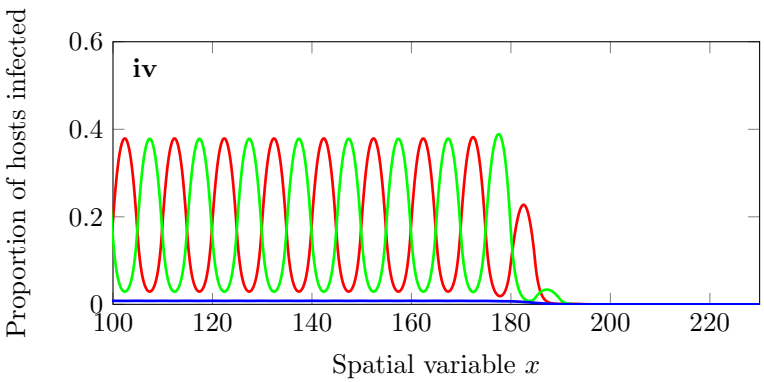
Qualitative description of the propagating population

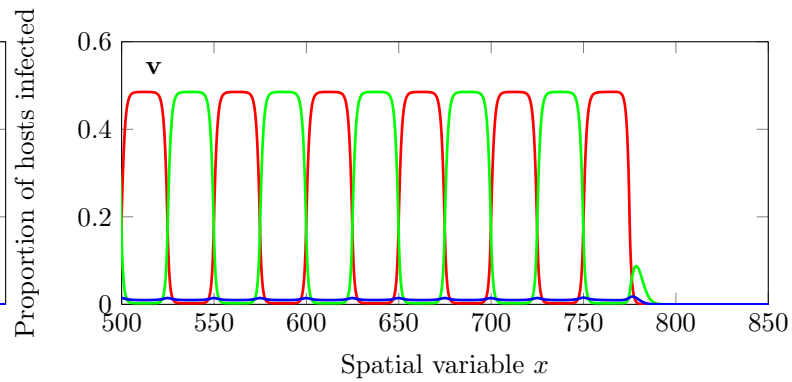




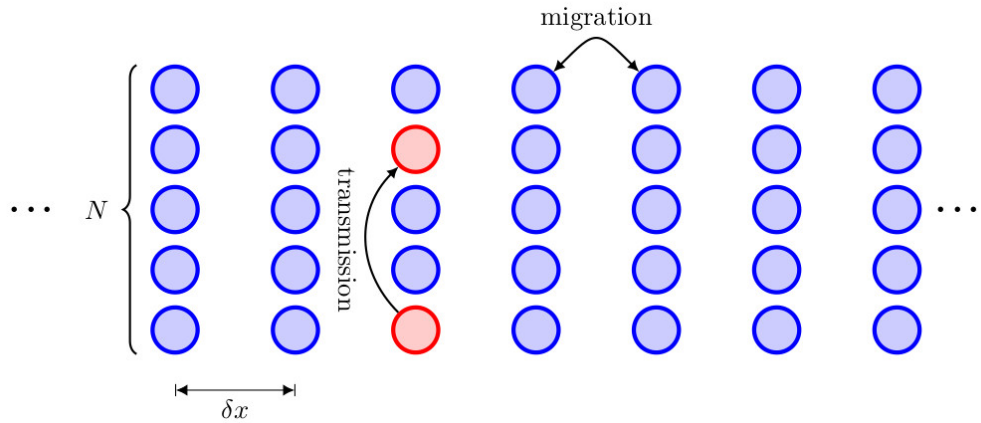








The stochastic model



Additional parameters:

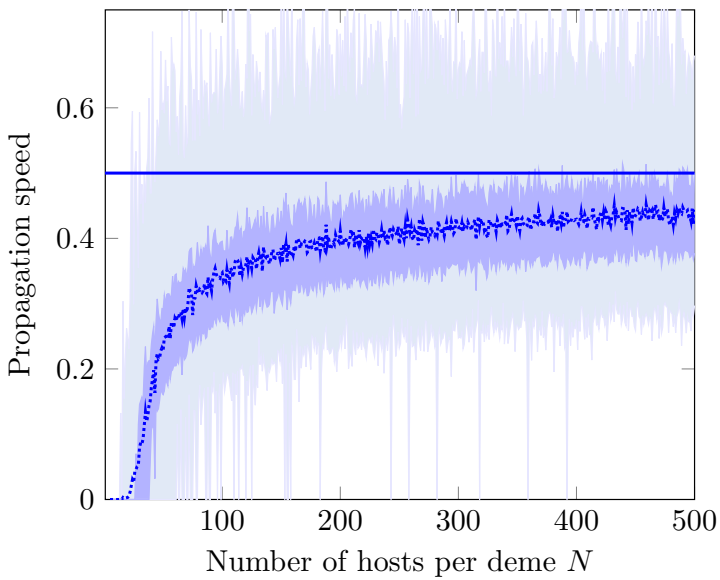
- $\delta x > 0$, spatial discretisation,
- $N \in \mathbb{N}$, number of hosts per site.

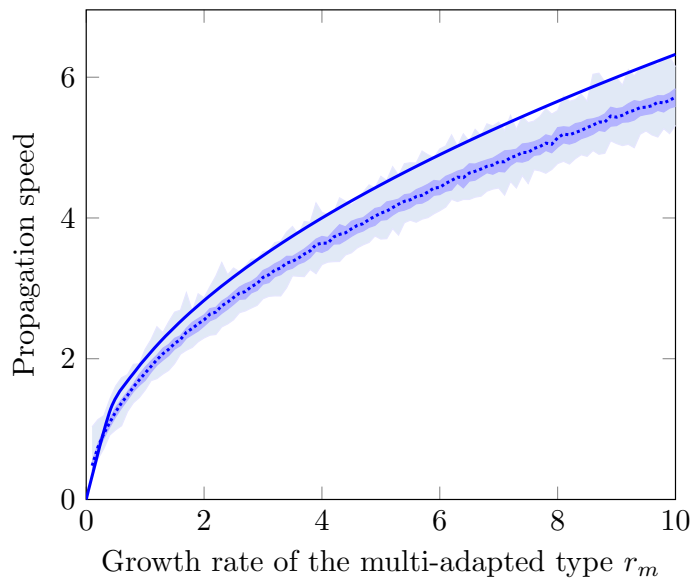
When $N \to \infty$ and then $\delta x \to 0$, we *should* recover our deterministic model.

Propagation of the multi-resistant type alone

Multiresistant type alone: Brunet-Derrida approximation[8],

$$\nu_m \sim 2\sqrt{\sigma r_m} - \frac{\kappa}{(\ln(KN))^2}$$





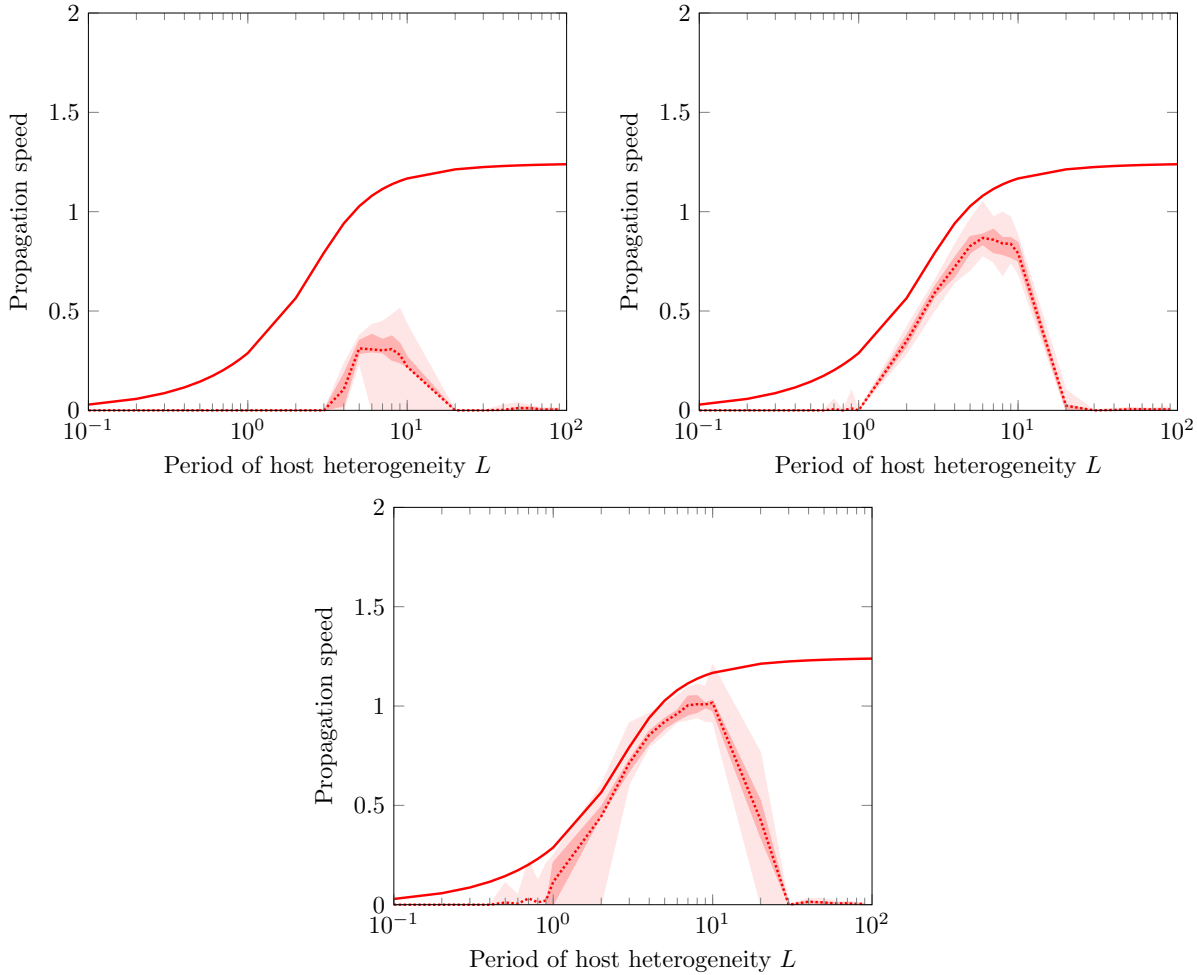
Right: $N = 100$, $\delta = 0.1$.

- Dynamics similar to the deterministic model if N is large.

[8] E. Brunet, B. Derrida, *Physical Review E*, 1997.

Propagation of a specialist type alone $N = 10, 100, 1000$

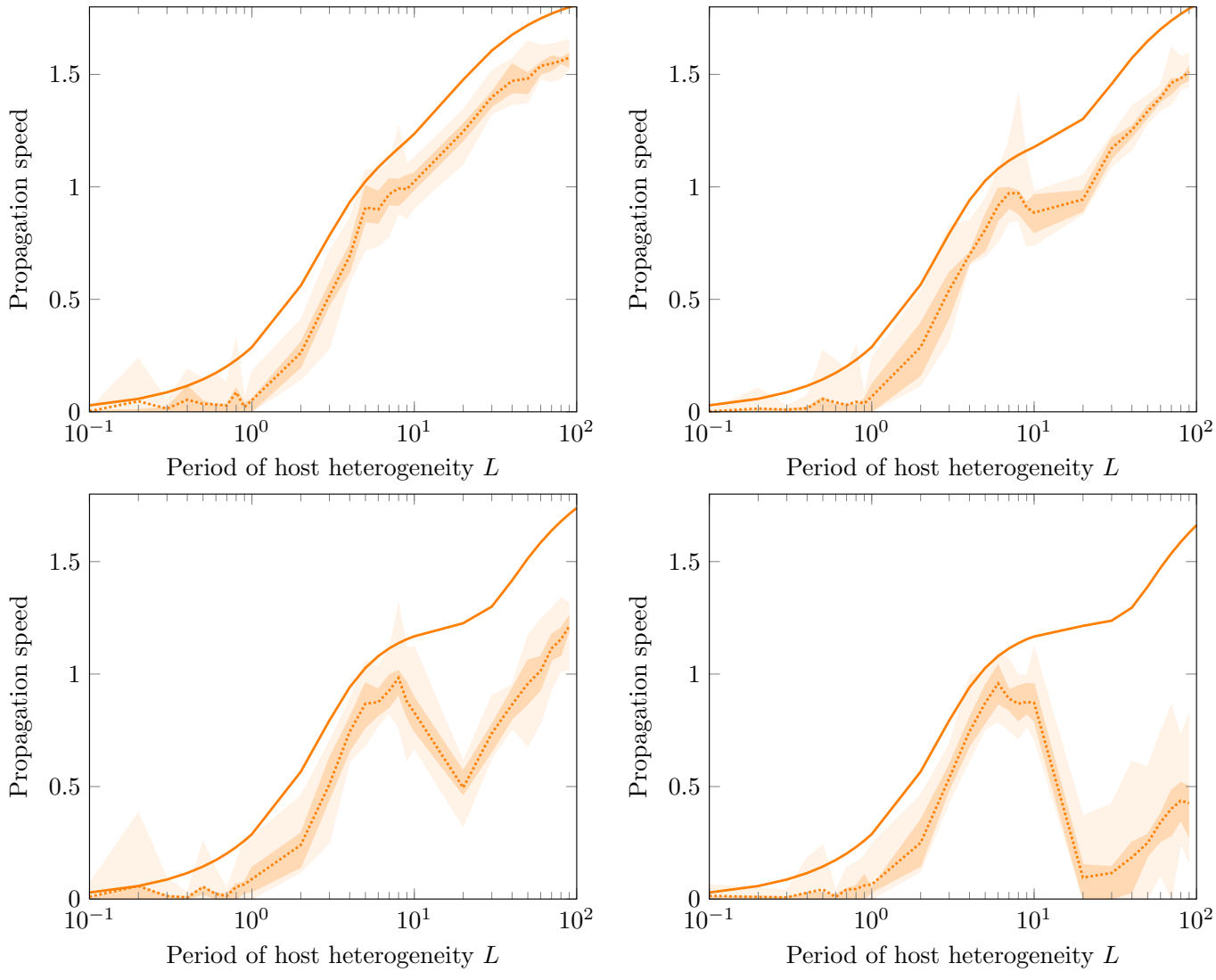
A specialist type alone (Speed$\sim e^{-\frac{3L}{4}\sqrt{\frac{r}{\sigma}}+\log N/\delta x}$ for L large),



- For a specialist alone, no propagation if L is too large!

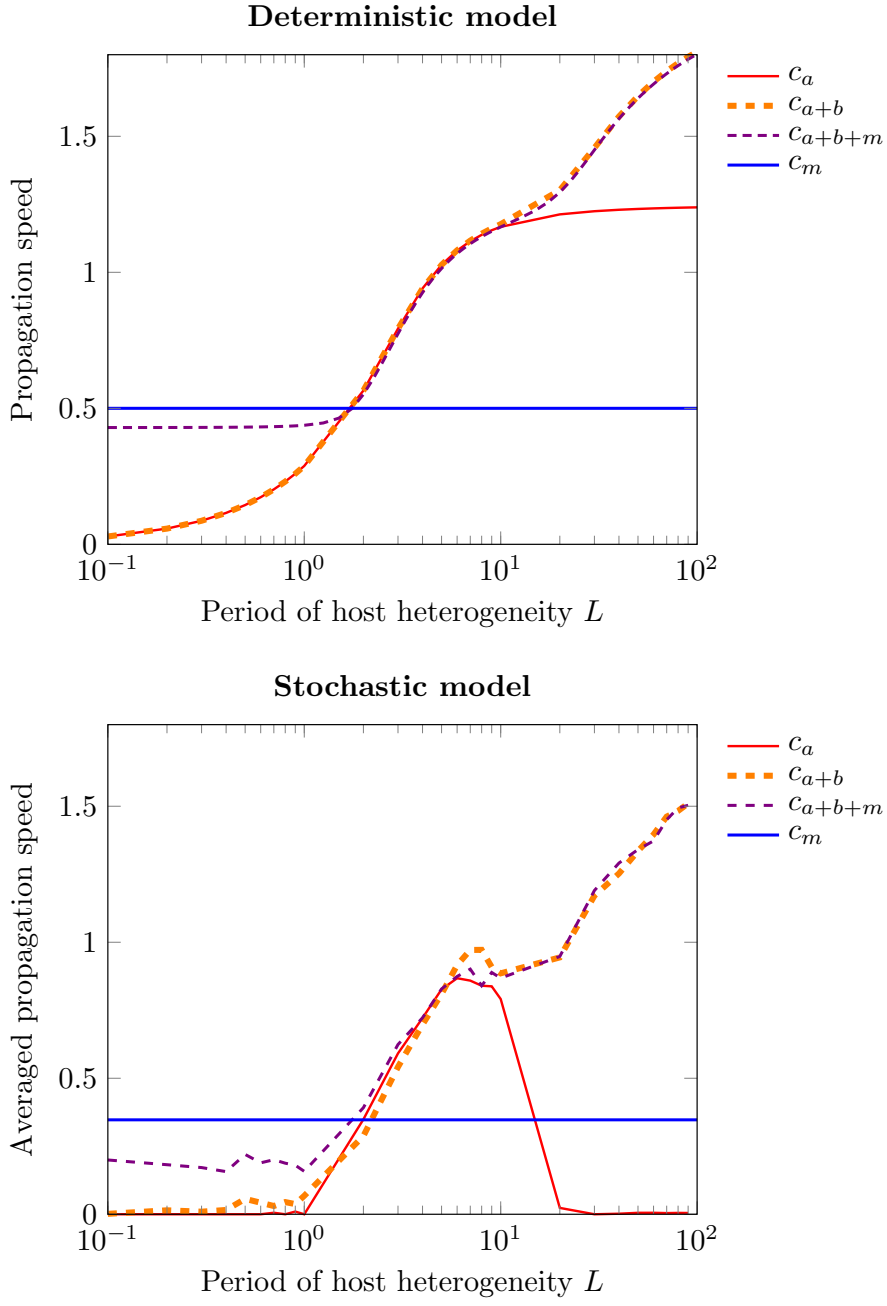
MOVIE

Propagation for both specialist types together(stochastic case) $\mu = 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}$

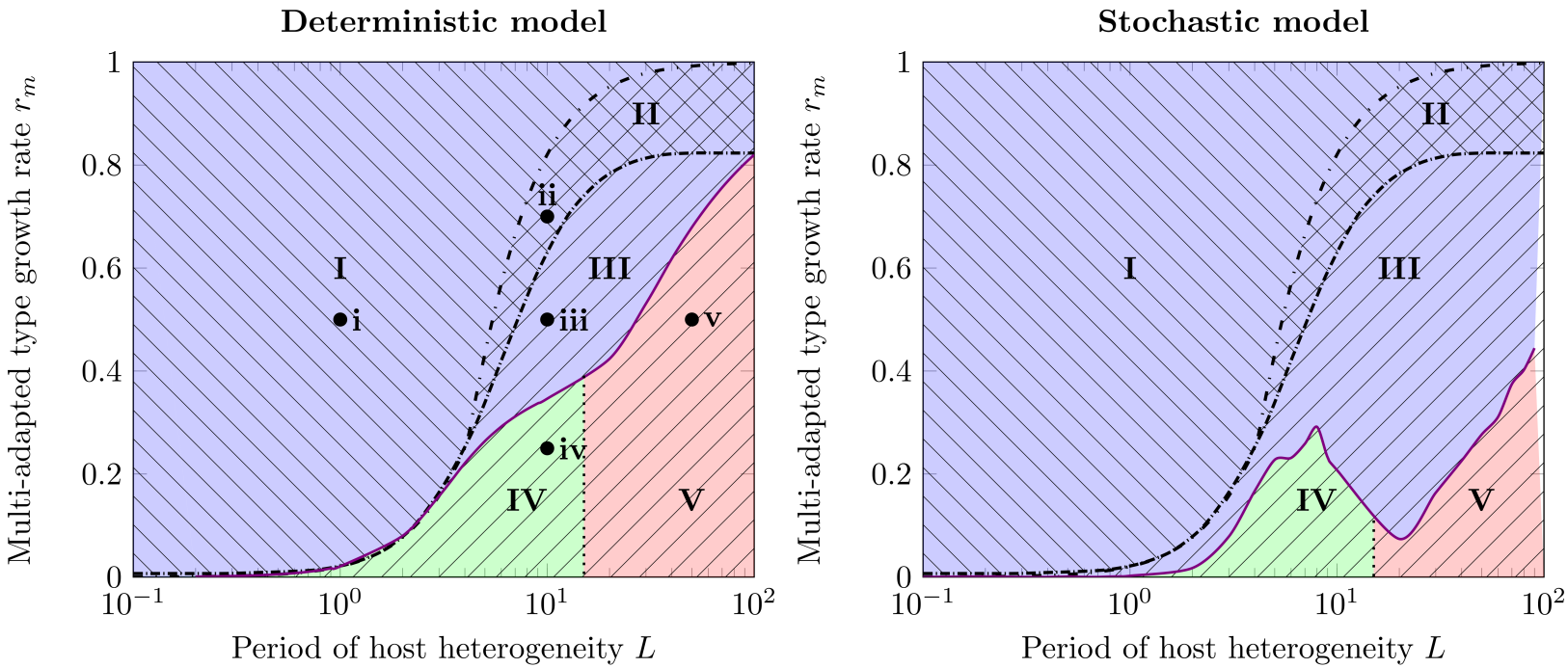


MOVIE

Propagation for the full model



Composition of the pathogen population



- Steady population: multi-resistant in (north-west lines hatches)
- Propagating populations: multi-resistant in (blue area)

In the stochastic model, the emergence of the multi-resistant type at the edge of the epidemics is more common.

Perspectives

- Mutants with a lower growth rate appear: gene surfing[9], etc.
- Genealogies generated? [10][11]
- Experimental/field data collection and treatments?
- Dynamics and diversity of *commensal bacteria*?

[9] J. Paulose, O. Hallatschek, *PNAS* 2020
[10] Berestycki-Berestycki-Schweinsberg *Annals of Probability* 2013
[11] J. Tourniaire, Accepted in *Annals of Probability* 2021.

Merci pour votre attention !

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