Modélisation de l'adaptation des pathogènes aux résistances partielles

Romain Bourget, Natalia Sapoukhina, Loïc Chaumont

Aout 2012

What is a resistance ?

Genetic resistances

Chemical treatments

Vaccines - Antibiotics

$\longrightarrow$ Limit or prevent pathogens development on treated hosts

What is a resistance ?

Genetic resistances

Chemical treatments

Vaccines - Antibiotics

$\longrightarrow$ Limit or prevent pathogens development on treated hosts

Biological point of view

What biologist already know about partial resistance erosion ?

- Mecanismes of partial resistance erosion are poorly know
- A pathogen can live on a environment with partial resistance with a reduced fitness
- Erosion pass by a succession of mutations which increase the fitness

$\rightarrow$ How make a durable resistance ?

Biological point of view

What biologist already know about partial resistance erosion ?

- Mecanismes of partial resistance erosion are poorly know
- A pathogen can live on a environment with partial resistance with a reduced fitness
- Erosion pass by a succession of mutations which increase the fitness

$\rightarrow$ How make a durable resistance ?

Biological point of view

What biologist already know about partial resistance erosion ?

- Mecanismes of partial resistance erosion are poorly know
- A pathogen can live on a environment with partial resistance with a reduced fitness
- Erosion pass by a succession of mutations which increase the fitness

$\rightarrow$ How make a durable resistance ?

Biological point of view

What biologist already know about partial resistance erosion ?

- Mecanismes of partial resistance erosion are poorly know
- A pathogen can live on a environment with partial resistance with a reduced fitness
- Erosion pass by a succession of mutations which increase the fitness

$\longrightarrow$ How make a durable resistance ?

Biological point of view

What biologist already know about partial resistance erosion ?

- Mecanismes of partial resistance erosion are poorly know
- A pathogen can live on a environment with partial resistance with a reduced fitness
- Erosion pass by a succession of mutations which increase the fitness

$\rightarrow$ How make a durable resistance ?

How to model partial resistance ?

A pathogen can live on a environment with partial resistance with a reduced fitness

→ Pathogen populations with different fitness

→ Competition between pathogens

Erosion pass by a succession of mutations which increase the fitness

→ Mutation as a stochastic event

→ Small population dynamics when new mutant appears

How to model partial resistance ?

A pathogen can live on a environment with partial resistance with a reduced fitness

$\rightarrow$ Pathogen populations with different fitness

$\rightarrow$ Competition between pathogens

Erosion pass by a succession of mutations which increase the fitness

$\rightarrow$ Mutation as a stochastic event

$\rightarrow$ Small population dynamics when new mutant appears

Birth and death process :

$$0 \underset{\lambda_0}{\overset{\mu_1}{\leftrightarrows}} 1 \underset{\lambda_1}{\overset{\mu_2}{\leftrightarrows}} \dots \underset{\lambda_{n-2}}{\overset{\mu_{n-1}}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}}{\overset{\mu_n}{\leftrightarrows}} n \underset{\lambda_n}{\overset{\mu_{n+1}}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}}{\overset{\mu_{n+2}}{\leftrightarrows}} \dots$$

Multi dimensional Birth and death process :

$$\begin{cases} 0 \underset{\lambda_0^1}{\overset{\mu_1^1}{\leftrightarrows}} 1 \underset{\lambda_1^1}{\overset{\mu_2^1}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^1}{\overset{\mu_{n-1}^1}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^1}{\overset{\mu_n^1}{\leftrightarrows}} n \underset{\lambda_n^1}{\overset{\mu_{n+1}^1}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^1}{\overset{\mu_{n+2}^1}{\leftrightarrows}} \dots \\ 0 \underset{\lambda_0^2}{\overset{\mu_1^2}{\leftrightarrows}} 1 \underset{\lambda_1^2}{\overset{\mu_2^2}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^2}{\overset{\mu_{n-1}^2}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^2}{\overset{\mu_n^2}{\leftrightarrows}} n \underset{\lambda_n^2}{\overset{\mu_{n+1}^2}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^2}{\overset{\mu_{n+2}^2}{\leftrightarrows}} \dots \\ \vdots \\ 0 \underset{\lambda_0^k}{\overset{\mu_1^k}{\leftrightarrows}} 1 \underset{\lambda_1^k}{\overset{\mu_2^k}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^k}{\overset{\mu_{n-1}^k}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^k}{\overset{\mu_n^k}{\leftrightarrows}} n \underset{\lambda_n^k}{\overset{\mu_{n+1}^k}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^k}{\overset{\mu_{n+2}^k}{\leftrightarrows}} \dots \end{cases}$$

Birth and death process :

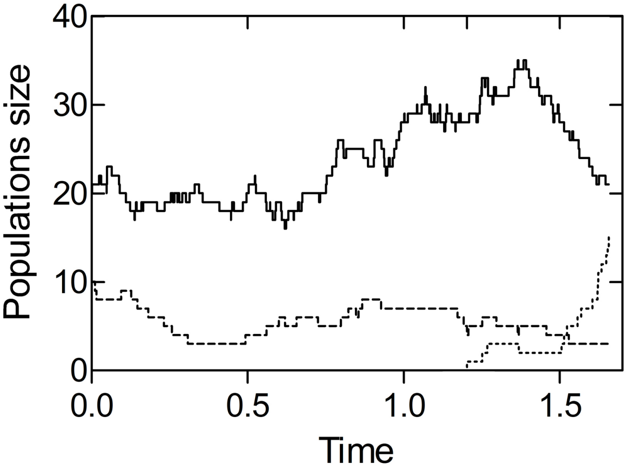
$$0 \underset{\lambda_0}{\overset{\mu_1}{\leftrightarrows}} 1 \underset{\lambda_1}{\overset{\mu_2}{\leftrightarrows}} \dots \underset{\lambda_{n-2}}{\overset{\mu_{n-1}}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}}{\overset{\mu_n}{\leftrightarrows}} n \underset{\lambda_n}{\overset{\mu_{n+1}}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}}{\overset{\mu_{n+2}}{\leftrightarrows}} \dots$$

Multi dimensional Birth and death process :

$$\begin{cases} 0 \underset{\lambda_0^1}{\overset{\mu_1^1}{\leftrightarrows}} 1 \underset{\lambda_1^1}{\overset{\mu_2^1}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^1}{\overset{\mu_{n-1}^1}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^1}{\overset{\mu_n^1}{\leftrightarrows}} n \underset{\lambda_n^1}{\overset{\mu_{n+1}^1}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^1}{\overset{\mu_{n+2}^1}{\leftrightarrows}} \dots \\ 0 \underset{\lambda_0^2}{\overset{\mu_1^2}{\leftrightarrows}} 1 \underset{\lambda_1^2}{\overset{\mu_2^2}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^2}{\overset{\mu_{n-1}^2}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^2}{\overset{\mu_n^2}{\leftrightarrows}} n \underset{\lambda_n^2}{\overset{\mu_{n+1}^2}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^2}{\overset{\mu_{n+2}^2}{\leftrightarrows}} \dots \\ \vdots \\ 0 \underset{\lambda_0^k}{\overset{\mu_1^k}{\leftrightarrows}} 1 \underset{\lambda_1^k}{\overset{\mu_2^k}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^k}{\overset{\mu_{n-1}^k}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^k}{\overset{\mu_n^k}{\leftrightarrows}} n \underset{\lambda_n^k}{\overset{\mu_{n+1}^k}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^k}{\overset{\mu_{n+2}^k}{\leftrightarrows}} \dots \end{cases}$$

Multi dimensional birth-death processes

Natural extensions of birth-death processes



Birth-death processes and partial resistances

Infinite states multi dimensional birth-death processes

$$
\left\{
\begin{array}{l}
\beta(X_1) : 0 \underset{\lambda_0^1}{\overset{\mu_1^1}{\leftrightarrows}} 1 \underset{\lambda_1^1}{\overset{\mu_2^1}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^1}{\overset{\mu_{n-1}^1}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^1}{\overset{\mu_n^1}{\leftrightarrows}} n \underset{\lambda_n^1}{\overset{\mu_{n+1}^1}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^1}{\overset{\mu_{n+2}^1}{\leftrightarrows}} \dots \\
\beta(X_2) : 0 \underset{\lambda_0^2}{\overset{\mu_1^2}{\leftrightarrows}} 1 \underset{\lambda_1^2}{\overset{\mu_2^2}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^2}{\overset{\mu_{n-1}^2}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^2}{\overset{\mu_n^2}{\leftrightarrows}} n \underset{\lambda_n^2}{\overset{\mu_{n+1}^2}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^2}{\overset{\mu_{n+2}^2}{\leftrightarrows}} \dots \\
\qquad\qquad\qquad\qquad\vdots \\
\beta(X_k) : 0 \underset{\lambda_0^k}{\overset{\mu_1^k}{\leftrightarrows}} 1 \underset{\lambda_1^k}{\overset{\mu_2^k}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^k}{\overset{\mu_{n-1}^k}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^k}{\overset{\mu_n^k}{\leftrightarrows}} n \underset{\lambda_n^k}{\overset{\mu_{n+1}^k}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^k}{\overset{\mu_{n+2}^k}{\leftrightarrows}} \dots \\
\qquad\qquad\qquad\qquad\vdots
\end{array}
\right.
$$

$$
\left\{
\begin{array}{lll}
X_i \longrightarrow X_i + 1 & \lambda(X_i) & = \beta(X_i) r X_i (1-\nu) \\
X_i \longrightarrow X_i - 1 & \mu(X_1, \dots, X_n) & = \left(\frac{\beta(X_i) r X_i}{\beta(X_i) K}\left(\frac{\sum_{j=1}^{n} X_j \beta(X_j)}{\beta(X_i)} - 1\right)\right) \\
X_i \longrightarrow X_{n+1} + 1 & \gamma_i(X_i) & = \beta(X_i) r X_i \nu
\end{array}
\right.
$$

Birth-death processes and partial resistances

Infinite states multi dimensional birth-death processes

$$
\begin{cases}
\beta(X_1) : 0 \underset{\lambda_0^1}{\overset{\mu_1^1}{\leftrightarrows}} 1 \underset{\lambda_1^1}{\overset{\mu_2^1}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^1}{\overset{\mu_{n-1}^1}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^1}{\overset{\mu_n^1}{\leftrightarrows}} n \underset{\lambda_n^1}{\overset{\mu_{n+1}^1}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^1}{\overset{\mu_{n+2}^1}{\leftrightarrows}} \dots \\
\beta(X_2) : 0 \underset{\lambda_0^2}{\overset{\mu_1^2}{\leftrightarrows}} 1 \underset{\lambda_1^2}{\overset{\mu_2^2}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^2}{\overset{\mu_{n-1}^2}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^2}{\overset{\mu_n^2}{\leftrightarrows}} n \underset{\lambda_n^2}{\overset{\mu_{n+1}^2}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^2}{\overset{\mu_{n+2}^2}{\leftrightarrows}} \dots \\
\vdots \\
\beta(X_k) : 0 \underset{\lambda_0^k}{\overset{\mu_1^k}{\leftrightarrows}} 1 \underset{\lambda_1^k}{\overset{\mu_2^k}{\leftrightarrows}} \dots \underset{\lambda_{n-2}^k}{\overset{\mu_{n-1}^k}{\leftrightarrows}} n-1 \underset{\lambda_{n-1}^k}{\overset{\mu_n^k}{\leftrightarrows}} n \underset{\lambda_n^k}{\overset{\mu_{n+1}^k}{\leftrightarrows}} n+1 \underset{\lambda_{n+1}^k}{\overset{\mu_{n+2}^k}{\leftrightarrows}} \dots \\
\vdots
\end{cases}
$$

$$
\begin{cases}
X_i \longrightarrow X_i + 1 & \lambda(X_i) & = & \beta(X_i) r X_i (1-\nu) \\
X_i \longrightarrow X_i - 1 & \mu(X_1, \dots, X_n) & = & \left(\frac{\beta(X_i) r X_i}{\beta(X_i) K}\left(\frac{\sum_{j=1}^{n} X_j \beta(X_j)}{\beta(X_i)} - 1\right)\right) \\
X_i \longrightarrow X_{n+1} + 1 & \gamma_i(X_i) & = & \beta(X_i) r X_i \nu
\end{cases}
$$

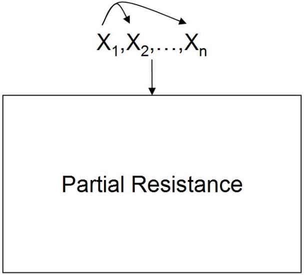
Birth-death processes and partial resistances

Infinite states multi dimensional birth-death processes

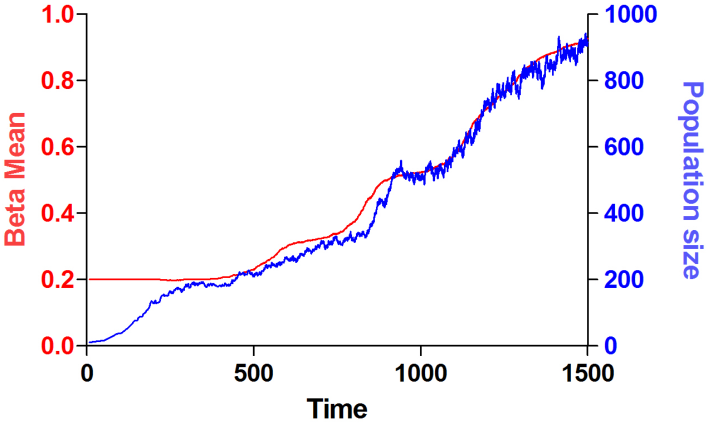
$$\left\{\begin{array}{llll} X_i \longrightarrow X_i+1 & \lambda(X_i) & = & \beta(X_i)rX_i(1-\nu) \\ X_i \longrightarrow X_i-1 & \mu(X_1,\ldots,X_n) & = & \left(\frac{\beta(X_i)rX_i}{\beta(X_i)K}\left(\frac{\sum\limits_{j=1}^{n} X_j\beta(X_j)}{\beta(X_i)}-1\right)\right) \\ X_i \longrightarrow X_{n+1}+1 & \gamma_i(X_i) & = & \beta(X_i)rX_i\nu \end{array}\right.$$

$$\beta(X_{n+1}) = \beta(X_i) + U$$

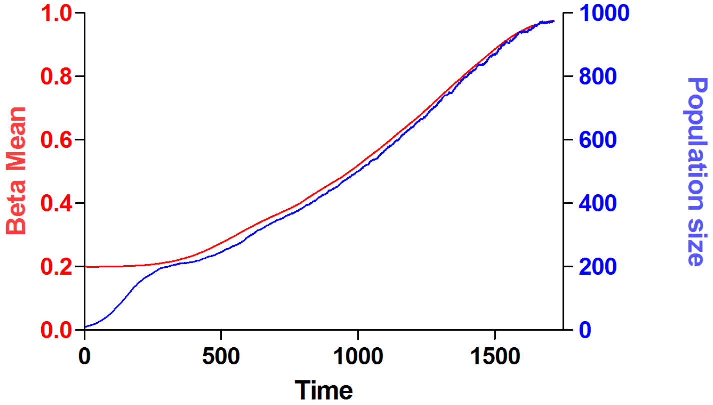
where $U \hookrightarrow U[-0.1;0.1]$

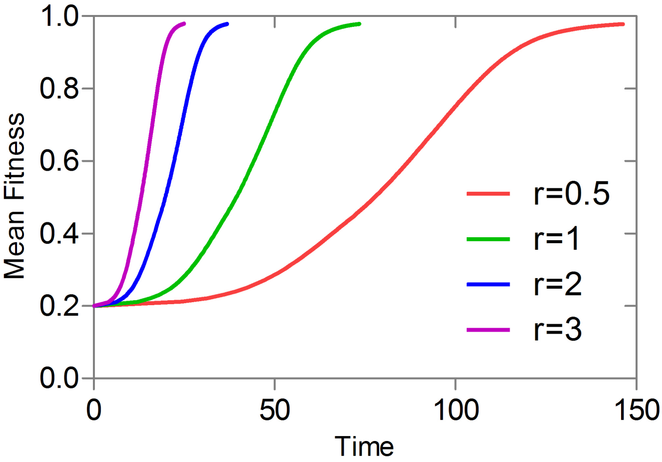


Simulations results



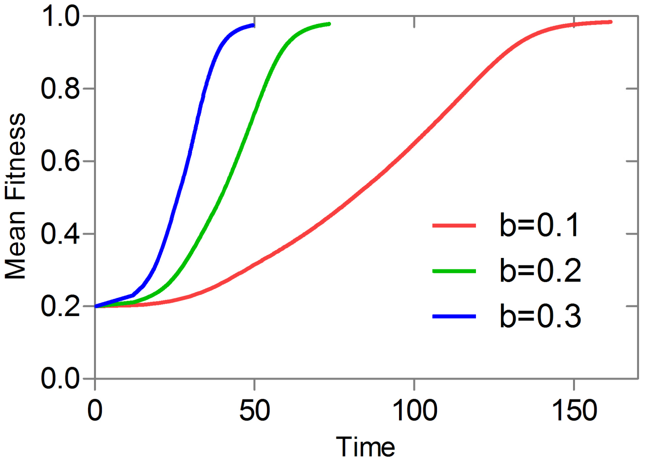
Simulations results




1.0
0.8
0.6
0.4
0.2
0.0
Mean Fitness
0
50
100
150
Time
r=0.5
r=1
r=2
r=3

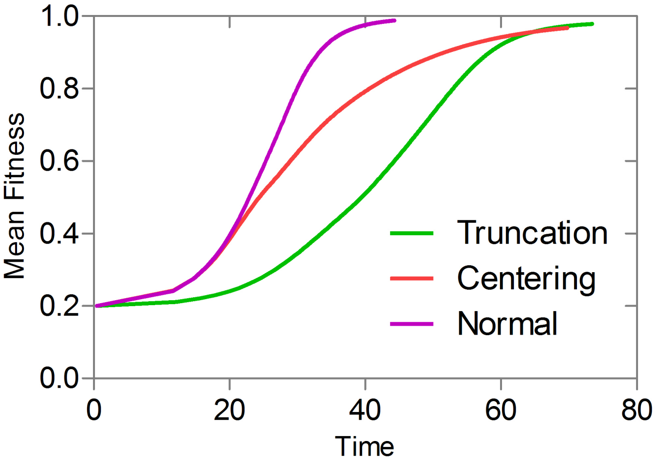
Speed of Erosion

Mutation strength effect

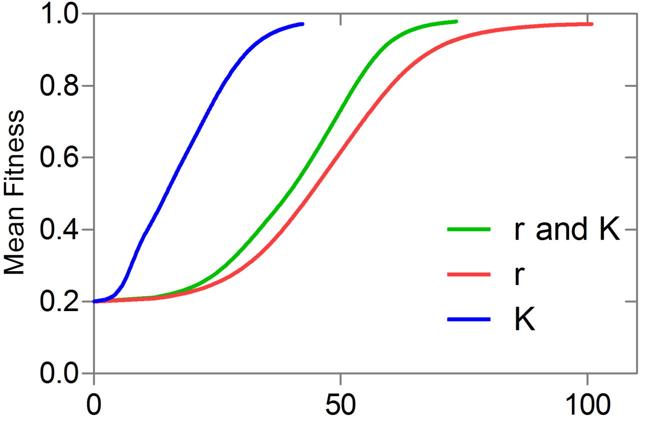


Shape of erosion

Mutation law effect

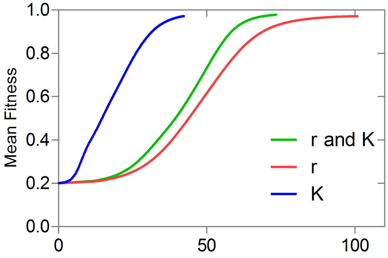


Shape of erosion
Partial resistance effect



Shape of erosion

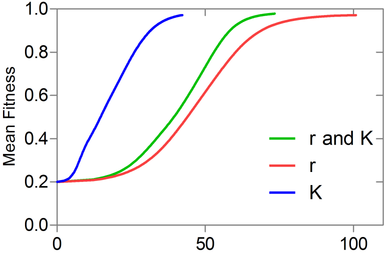
Partial resistance effect



$$\begin{cases} X_i \longrightarrow X_i + 1 & \lambda(X_i) = \beta(X_i) r X_i (1-\nu) \\ X_i \longrightarrow X_i - 1 & \mu(X_1, \ldots, X_n) = \left(\frac{\beta(X_i) r X_i}{\beta(X_i) K}\left(\frac{\sum_{j=1}^{n} X_j \beta(X_j)}{\beta(X_i)} - 1\right)\right) \\ X_i \longrightarrow X_{n+1} + 1 & \gamma_i(X_i) = \beta(X_i) r X_i \nu \end{cases}$$

Shape of erosion

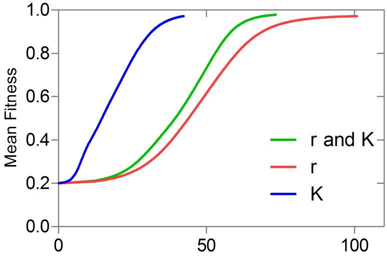
Partial resistance effect



$$\begin{cases} X_i \longrightarrow X_i + 1 & \lambda(X_i) & = & \beta(X_i) r X_i (1-\nu) \\ X_i \longrightarrow X_i - 1 & \mu(X_1, \dots, X_n) & = & \left(\frac{\beta(X_i) r X_i}{K}\left(\frac{\sum_{j=1}^{n} X_j \beta(X_j)}{\beta(X_i)} - 1\right)\right) \\ X_i \longrightarrow X_{n+1} + 1 & \gamma_i(X_i) & = & \beta(X_i) r X_i \nu \end{cases}$$

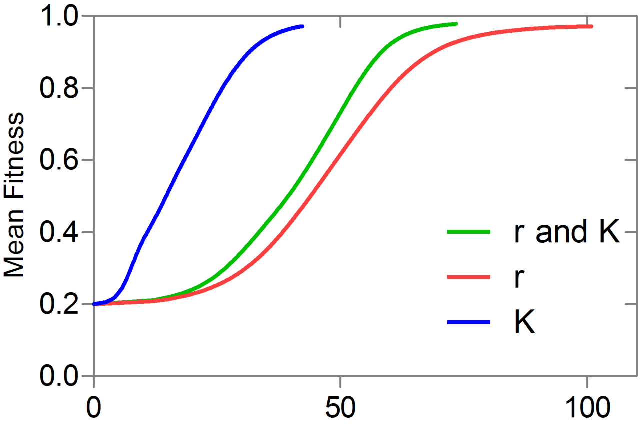
Shape of erosion

Partial resistance effect

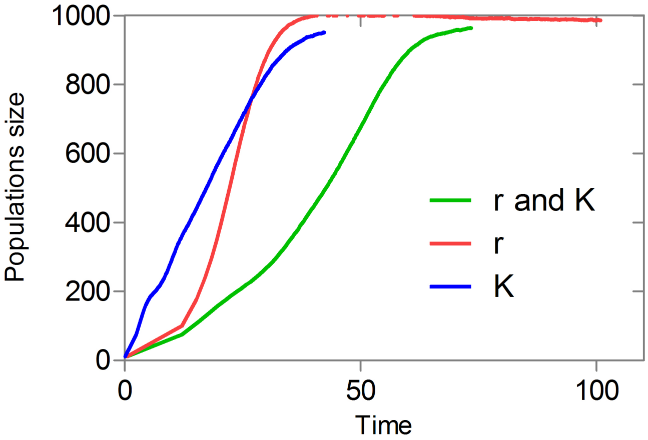


$$\begin{cases} X_i \longrightarrow X_i + 1 & \lambda(X_i) & = & rX_i(1-\nu) \\ X_i \longrightarrow X_i - 1 & \mu(X_1,\ldots,X_n) & = & \left(\frac{rX_i}{\beta(X_i)K}\left(\frac{\sum_{j=1}^{n} X_j\beta(X_j)}{\beta(X_i)} - 1\right)\right) \\ X_i \longrightarrow X_{n+1} + 1 & \gamma_i(X_i) & = & rX_i\nu \end{cases}$$

Shape of erosion
Partial resistance effect



Shape of erosion
Partial resistance effect



Conclusions and Perspectives

Conclusions :

- We built a model to study the erosion of partial resistance
  $\longrightarrow$ Adjustable to different biological situations
- Both speed of adaptation and shape of adaptation should be used to breed partial resistance
- Partial resistance which decrease the pathogen population size increase the speed of adaptation

Perspectives :

- Biological data
- Combination partial and total resistance : gene pyramiding

Conclusions and Perspectives

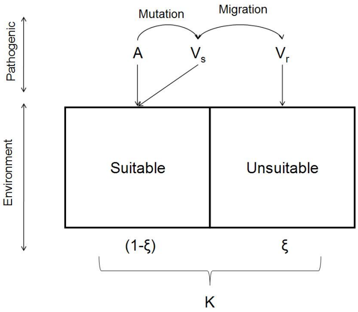
Conclusions :

- We built a model to study the erosion of partial resistance
  $\longrightarrow$ Adjustable to different biological situations
- Both speed of adaptation and shape of adaptation should be used to breed partial resistance
- Partial resistance which decrease the pathogen population size increase the speed of adaptation

Perspectives :

- Biological data
- Combination partial and total resistance : gene pyramiding

Multi dimensional processes to model total resistance



Bourget Romain, Chaumont Loïc and Sapoukhina Natalia, Exponentiality of first passage times of continuous time Markov Chains, under submission

Bourget Romain, Chaumont Loïc and Sapoukhina Natalia,Timing of pathogen adaptation to a multicomponent treatment, under submission

Conclusions and Perspectives

Conclusions :

- We built a model to study the erosion of partial resistance
  $\longrightarrow$ Adjustable to different biological situations
- Both speed of adaptation and shape of adaptation should be used to breed partial resistance
- Partial resistance which decrease the pathogen population size increase the speed of adaptation

Perspectives :

- Biological data
- Combination partial and total resistance : gene pyramiding
- Optimization algorithm

Conclusions and Perspectives

Conclusions :

- We built a model to study the erosion of partial resistance
  $\longrightarrow$ Adjustable to different biological situations
- Both speed of adaptation and shape of adaptation should be used to breed partial resistance
- Partial resistance which decrease the pathogen population size increase the speed of adaptation

Perspectives :

- Biological data
- Combination partial and total resistance : gene pyramiding
- Optimization algorithm

Thanks for your attention

References :

Nicolas Champagnat, Régis Ferriére, Sylvie Méléard, Unifying evolutionary dynamics : From individual stochastic processes to macroscopic models, Theoretical Population Biology, Volume 69, Issue 3, May 2006

Nicolas Champagnat and Amaury Lambert, Evolution of Discrete Populations and the Canonical Diffusion of Adaptive Dynamics, The Annals of Applied Probability, Vol. 17, No. 1, Feb. 2007