Genetic Variability in the Mendelian Diploid Model

Loren Coquille
(Institut Fourier, Grenoble)

joint work in progress with A. Bovier and R. Neukirch
(University of Bonn)

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Outline

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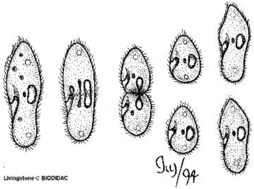
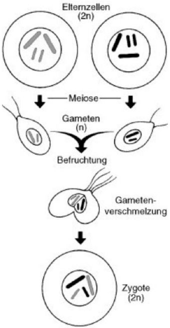
Clonal Reproduction versus Sexual Reproduction

Clonal Reproduction vs. **Sexual Reproduction**



- individual reproduces out of itself
- offspring = copy of the parent
- offspring genom:
  - 100% of genes of the parent



- individual needs a partner for reproduction
- offspring genom:
  - 50% genes of mother
  - 50% genes of father

Clonal Reproduction versus Sexual Reproduction

Clonal Reproduction

+ fast growing populations
+ no time loss for partner selection
- genes stay constant over generations
- hard adaptation to changing environment

Sexual Reproduction

- slowly growing population
- time cost for partner selection
+ genetic variability
+ possible adaptation to changing environment
+ correction of genetic defects
+ elimination of disadvantageous mutations

Outline

Clonal reproduction model

Bolker, Pacala, Dieckmann, Law, Champagnat, Méléard,...

$\Theta \simeq \mathbb{N}$: Trait space
$n_i(t)$: Number of individuals of trait $i \in \Theta$

Dynamics of the process

$$n(t) = (n_0(t), n_1(t), \dots) \in \mathbb{N}^{\mathbb{N}} \quad :$$

Each individual of trait i

- reproduces clonally with rate $b_i(1 - \mu)$
- reproduces with mutation with rate $b_i\mu$ according to some mutation kernel $M(i, j)$
- dies due to age or competition with rate $d_i + \sum_j c_{ij} n_j$

Clonal reproduction model

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Dynamics of the process

$$n(t) = (n_0(t), n_1(t), \dots) \in \mathbb{N}^{\mathbb{N}} \quad :$$

The population n_i

- increases by 1 with rate $b_i(1-\mu)n_i$
- makes n_j increase by 1 with rate $b_i\mu \cdot M(i,j) \cdot n_i$
- deceases by 1 with rate $(d_i + \sum_j c_{ij}n_j)n_i$

Clonal reproduction model

Bolker, Pacala, Dieckmann, Law, Champagnat, Méléard,...

$\Theta \simeq \mathbb{N}$: Trait space
$n_i(t)$: Number of individuals of trait $i \in \Theta$

Dynamics of the rescaled process (with competition c_{ij}/K)

$$n^K(t) = \frac{1}{K}(n_0(t), n_1(t), \ldots) \in (\mathbb{N}/K)^{\mathbb{N}} \quad :$$

The population n_i^K

- increases by $1/K$ with rate $b_i(1-\mu) \cdot K n_i^K$
- makes n_j^K increase by $1/K$ with rate $b_i \mu M(i,j) \cdot K n_i^K$
- deceases by $1/K$ with rate $(d_i + \sum_j c_{ij} n_j^K) \cdot K n_i^K$

Large populations limit
$\mu = 0$ and $K \to \infty$

Fournier, Méléard, 2004

Proposition

Let $\Theta = \{1, 2\}$, assume that the initial condition $(n_1^K(0), n_2^K(0))$ converges to a deterministic vector (x_0, y_0) for $K \to \infty$. Then the process $(n_1^K(t), n_2^K(t))$ converges in law, on bounded time intervals, to the solution of

$$\frac{d}{dt}\begin{pmatrix} x(t) \\ y(t) \end{pmatrix} = X(x(t), y(t)) = \begin{pmatrix} (b_1 - d_1 - c_{11}x - c_{12}y)x \\ (b_2 - d_2 - c_{21}x - c_{22}y)y \end{pmatrix}.$$

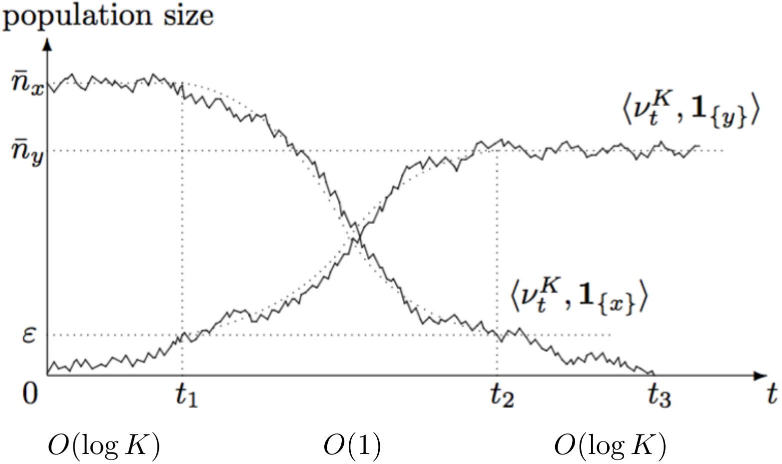
with initial condition $(x(0), y(0)) = (x_0, y_0)$.

Monomorphic equilibria : $\bar{n}_i = \frac{b_i - d_i}{c_{ii}}$
Invasion fitness : $f_{ij} = b_i - d_i - c_{ij}\bar{n}_j$.

Large populations and rare mutations limit $\mu = \mu(K) \ll (K \log K)^{-1}$

Champagnat, 2006

Start with $n_i^K(0) = \bar{n}_x 1_{i=x} + \frac{1}{K} 1_{i=y}$ (time of the first mutation).
If y is fitter than x, i.e. $f_{yx} > 0$ and $f_{xy} < 0$, then with proba $\to 1$:



Supercritical BP | LLN | Subcritical BP

Proposition

Assume

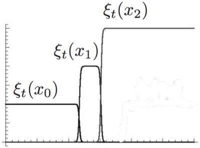
- $\log K \ll \frac{1}{K\mu} \ll \exp(cK)$
- $\forall (i,j) \in \Theta^2$, either $f_{ji} < 0$ or $f_{ji} > 0$ and $f_{ij} < 0$.

Then the rescaled process

$$(n^K_{t/K\mu})_{t\geq 0} \Rightarrow (\bar{n}_{X_t} 1_{X_t})_{t\geq 0}$$

where X_t is a Markov chain on Θ with transition kernel

$$P(i,j) = b_i \frac{[f_{ji}]_+}{b_j} M(i,j).$$



Outline

Mendelian Diploid Model

Collet, Méléard, Metz, 2013

Let $\mathcal{U}$ be the allelic trait space, a countable set.
For example $\mathcal{U} = \{a, A\}$.

- An individual i is determined by two alleles out of $\mathcal{U}$:
  - genotype: $(u_1^i, u_2^i) \in \mathcal{U}^2$
  - phenotype: $\phi((u_1^i, u_2^i))$, with $\phi : \mathcal{U}^2 \to \mathbb{R}_+$
- Rescaled population:
  let N_t be the total number of individuals at time t,

$$n^K_{u_1,u_2}(t) = \frac{1}{K} \sum_{i=1}^{N_t} 1_{(u_1^i, u_2^i)}(t)$$

Reproduction

Reproduction rate of (u_1^i, u_2^i) with (u_1^j, u_2^j):

$$\frac{f_{u_1^i u_2^i} f_{u_1^j u_2^j}}{\text{Number of potential partners of } (u_1^i, u_2^i) \times \text{ their mean fertility}}$$

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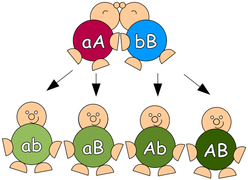
Reproduction without mutation: Probability $1 - \mu_K$
$\Rightarrow$ Mendelian rules: newborn getting genotype with coordinates that are sampled at random from each parent.



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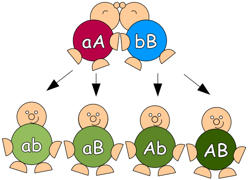
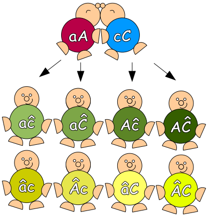


Reproduction with mutation: Probability μ_K
$\Rightarrow$ changing one of the two allelic traits of the newborn from a to b according to the kernel $M(a, b)$.

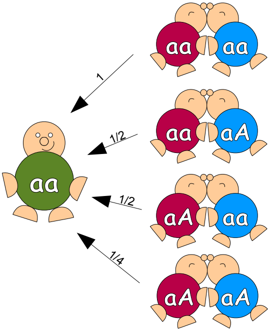


Birth and Death Rate

Let $\mathcal{U} = \{a, A\}$, and $\mu_K = 0$.

- The populations increase by 1 with rate

$$
\begin{aligned}
b_{aa} &= \frac{(f_{aa}n_{aa}+\frac{1}{2}f_{aA}n_{aA})^2}{f_{aa}n_{aa}+f_{aA}n_{aA}+f_{AA}n_{AA}} \\
b_{aA} &= 2\ \frac{(f_{aa}n_{aa}+\frac{1}{2}f_{aA}n_{aA})(f_{AA}n_{AA}+\frac{1}{2}f_{aA}n_{aA})}{f_{aa}n_{aa}+f_{aA}n_{aA}+f_{AA}n_{AA}} \\
b_{AA} &= \frac{(f_{AA}n_{AA}+\frac{1}{2}f_{aA}n_{aA})^2}{f_{aa}n_{aa}+f_{aA}n_{aA}+f_{AA}n_{AA}}
\end{aligned}
$$



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$$b_{aA} = 2\,\frac{(f_{aa}n_{aa}+\frac{1}{2}f_{aA}n_{aA})(f_{AA}n_{AA}+\frac{1}{2}f_{aA}n_{aA})}{f_{aa}n_{aa}+f_{aA}n_{aA}+f_{AA}n_{AA}}$$

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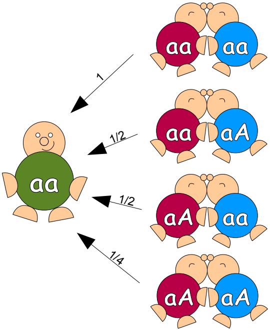


- The populations decrease by 1 with rate

$$d_{aa} = (D_{aa} + C_{aa,aa}n_{aa} + C_{aa,aA}n_{aA} + C_{aa,AA}n_{AA})n_{aa}$$

$$d_{aA} = (D_{aA} + C_{aA,aa}n_{aa} + C_{aA,aA}n_{aA} + C_{aA,AA}n_{AA})n_{aA}$$

$$d_{AA} = (D_{AA} + C_{AA,AA}n_{AA} + C_{AA,aA}n_{aA} + C_{AA,aa}n_{aa})n_{AA}$$

Proposition

Assume that the initial condition $(n^K_{aa}(0), n^K_{aA}(0), n^K_{AA}(0))$ converges to a deterministic vector (x_0, y_0, z_0) for $K \to \infty$. Then the process $(n^K_{aa}(t), n^K_{aA}(t), n^K_{AA}(t))$ converges in law to the solution of

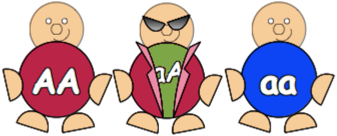
$$\frac{d}{dt}\begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix} = X(x(t), y(t), z(t)) = \begin{pmatrix} b_{aa}(x,y,z) - d_{aa}(x,y,z) \\ b_{aA}(x,y,z) - d_{aA}(x,y,z) \\ b_{AA}(x,y,z) - d_{AA}(x,y,z) \end{pmatrix}.$$

- $b_{AA}(x,y,z) = \frac{(f_{AA}z + \frac{1}{2}f_{aA}y)^2}{f_{aa}x + f_{aA}y + f_{AA}z}$
- $d_{AA}(x,y,z) = (D_{AA} + C_{AA,aa}x + C_{AA,aA}y + C_{AA,AA}z)z$
- and similar expressions for the other terms

The 3-System (aa, aA, AA)

Phenotypic viewpoint

- allele A dominant
- allele a recessive



The dominant allele A defines the phenotype $\Rightarrow \phi(aA) = \phi(AA)$

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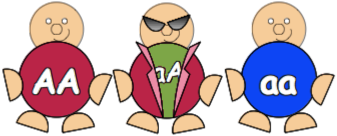

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- $c_{u_1u_2,v_1v_2} \equiv c, \quad \forall u_1u_2, v_1v_2 \in \{aa, aA, AA\}$
- $f_{AA} = f_{aA} = f_{aa} \equiv f$
- $D_{AA} = D_{aA} \equiv D$ but $D_{aa} = D + \Delta$

The 3-System (aa, aA, AA)

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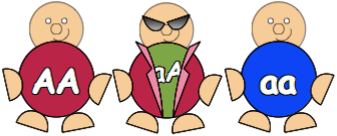

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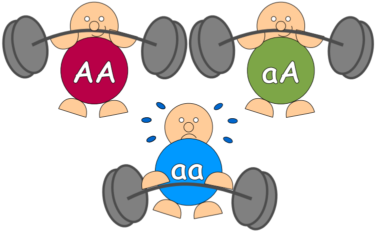
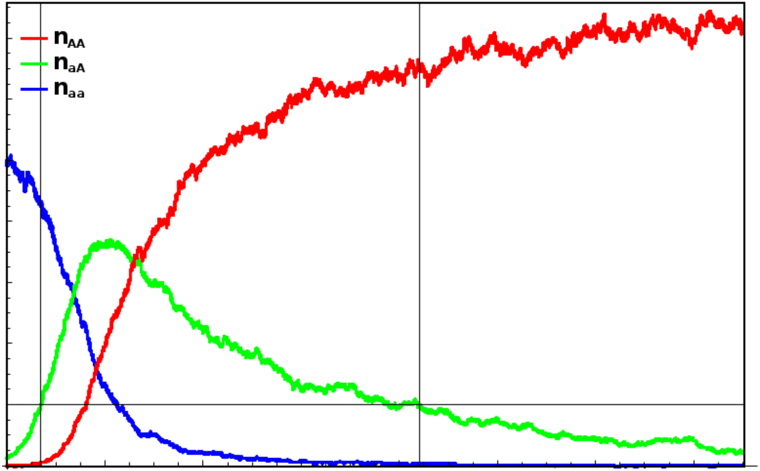
- $f_{AA} = f_{aA} = f_{aa} \equiv f$
- $D_{AA} = D_{aA} \equiv D$ but $D_{aa} = D + \Delta$

$\Rightarrow$ **type aA is as fit as AA and both are fitter than type aa**



Work of Bovier, Neukirch (2015)

Start with $n_i^K(t) = \bar{n}_{aa} 1_{i=aa} + \frac{1}{K} 1_{i=aA}$ then :



$O(\log K)$ $O(1)$ $\geq O(K^{1/4+\epsilon})$

The system converges to $(0, 0, \bar{n}_{AA})$ as $t \to \infty$ but slowly !

Genetic Variability ? Polymorphism?

Suppose a new dominant mutant allele B appears before aA dies out.

Suppose that phenotypes a and B cannot reproduce.

Can the aa-population recover and coexist with the mutant population ?

We will study the deterministic sytem and start with initial condition

$$n_i(0) = \bar{n}_{AA} 1_{i=AA} + \epsilon 1_{i=aA} + \epsilon^2 1_{i=aa} + \epsilon^3 1_{i=AB}$$

Model with a second mutant

Mutation to allele $B \to \mathcal{U} = \{a, A, B\}$

Model with a second mutant

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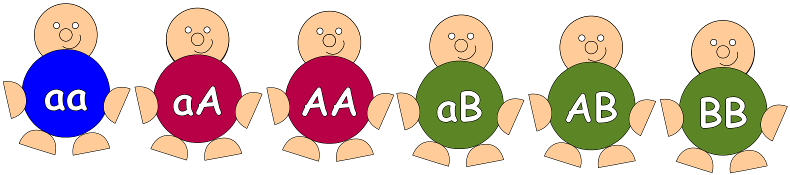
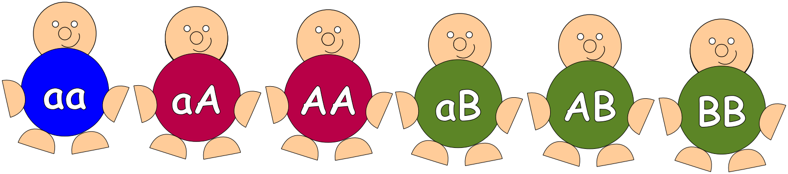


$\Rightarrow$ 6 possible genotypes: aa, aA, AA, aB, AB, BB

$\Rightarrow$ Dominance of alleles $a < A < B$

Model with a second mutant

Mutation to allele $B \to \mathcal{U} = \{a, A, B\}$



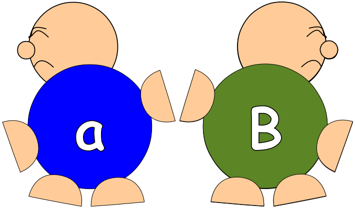
$\Rightarrow$ 6 possible genotypes: aa, aA, AA, aB, AB, BB

$\Rightarrow$ Dominance of alleles $a < A < B$

Differences in Fitness:

- fertility: $f_a = f_A = f_B = f$
- natural death: $D_a = D + \Delta > D_A = D > D_B = D - \Delta$

No **recombination** between a and B

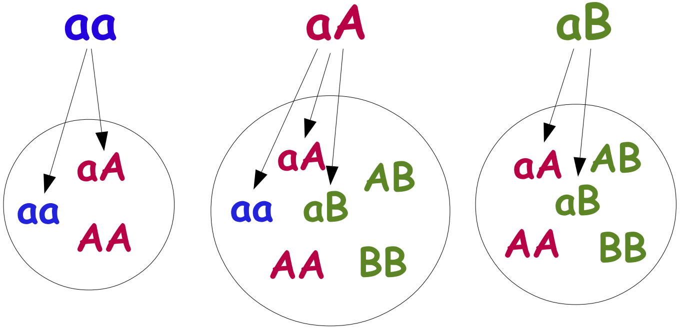


Birth Rates

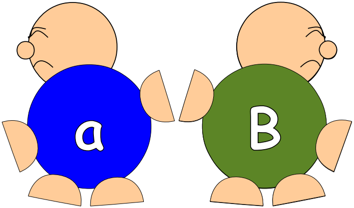
birth-rate of aa-individual:

$$b_{aa} = \frac{n_{aa}\left(n_{aa} + \frac{1}{2}n_{aA}\right)}{\mathsf{Pool}(aa)} + \frac{\frac{1}{2}n_{aB}\left(\frac{1}{2}n_{aA} + \frac{1}{2}n_{aB}\right)}{\mathsf{Pool}(aB)} + \frac{\frac{1}{2}n_{aA}\left(n_{aa} + \frac{1}{2}n_{aA} + \frac{1}{2}n_{aB}\right)}{\mathsf{Pool}(aA)}$$

Pools of potential partners:



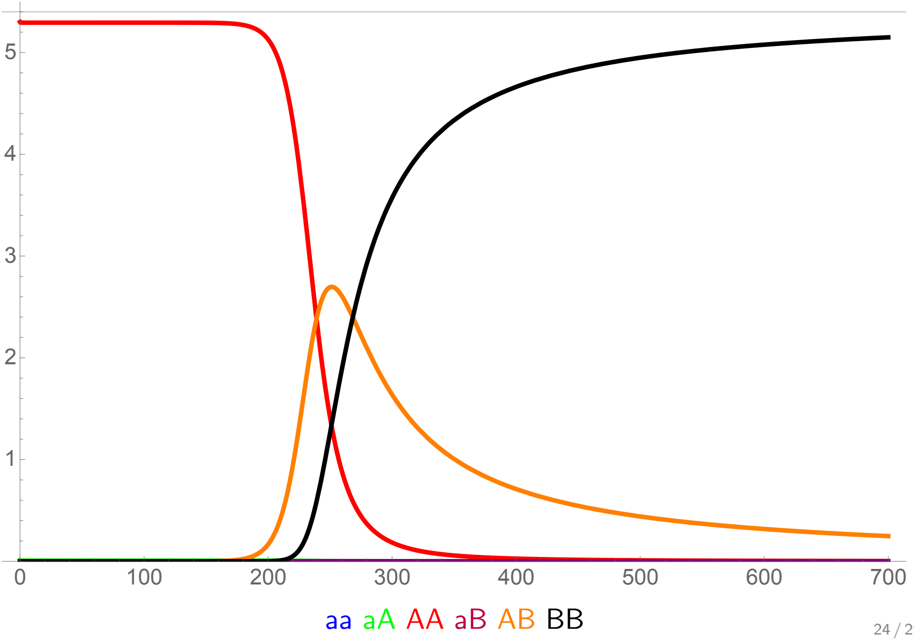
No **competition** between a and B



Competition - first try

	aa	aA	AA	aB	AB	BB
aa	c	c	c	0	0	0
aA	c	c	c	c	c	c
AA	c	c	c	c	c	c
aB	0	c	c	c	c	c
AB	0	c	c	c	c	c
BB	0	c	c	c	c	c

Competition - first try



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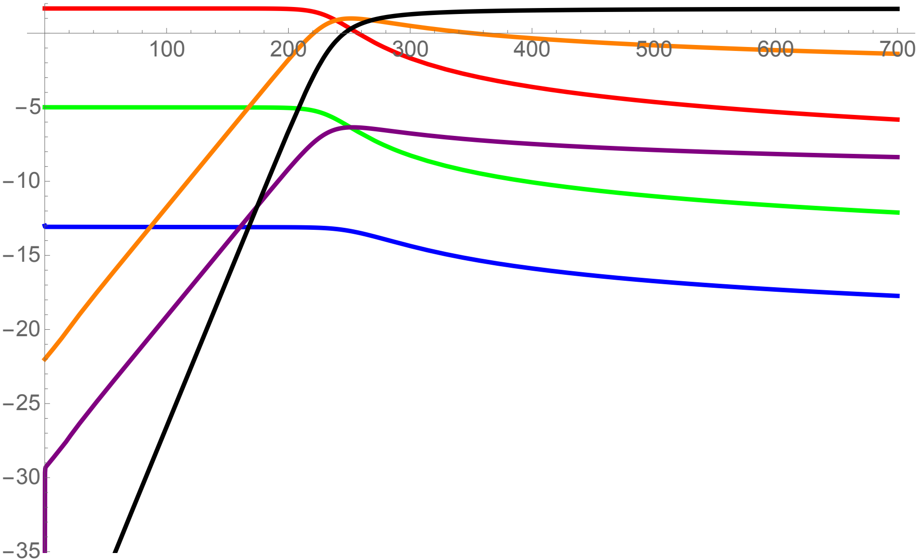
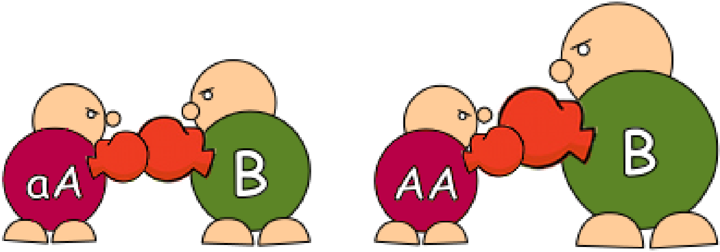


aa aA AA aB AB BB

Competition - second try

competition felt by n_{aA} from B-individuals $<$ competition felt by n_{AA} from B-individuals

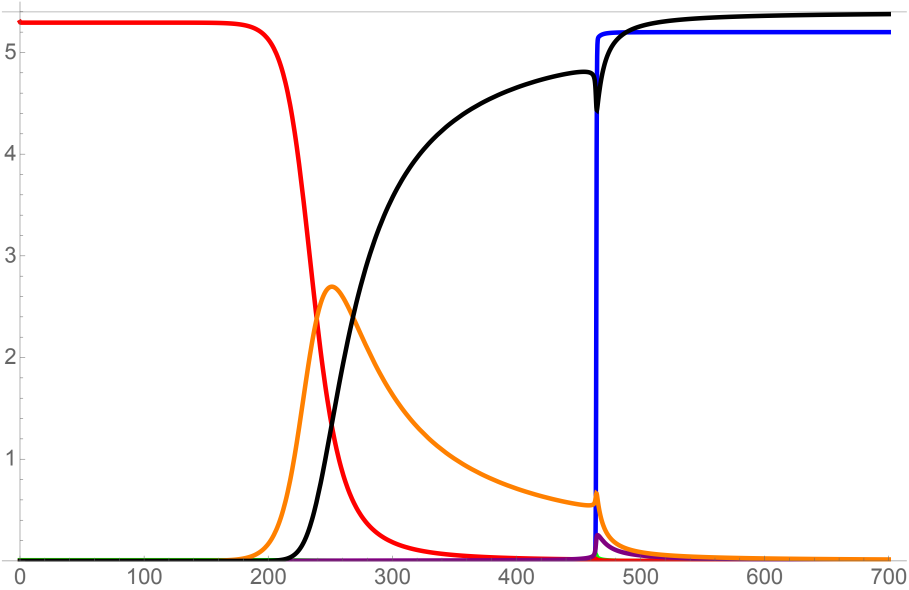


- the decay of aA-population slows down
- aa-population can recover

Competition - second try

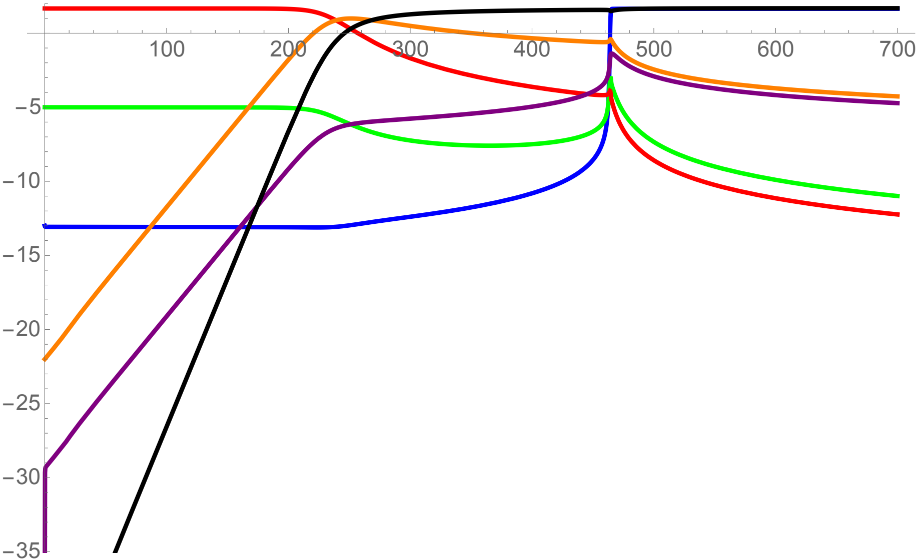
	aa	aA	AA	aB	AB	BB
aa	c	c	c	0	0	0
aA	c	c	c	c	c	$c-\eta$
AA	c	c	c	c	c	c
aB	0	c	c	c	c	c
AB	0	c	c	c	c	c
BB	0	$c-\eta$	c	c	c	c

Competition - second try



aa aA AA aB AB BB

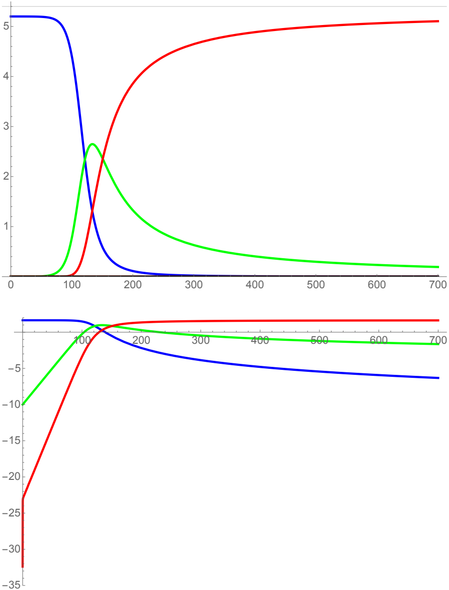
Competition - second try



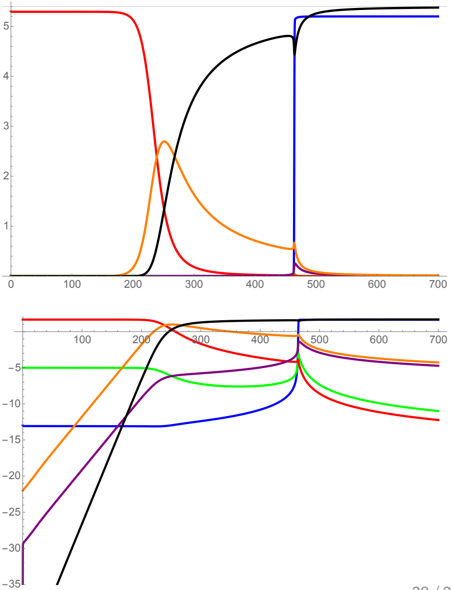
aa aA AA aB AB BB

Recap - Dimorphism in two mutations

Mutation 1

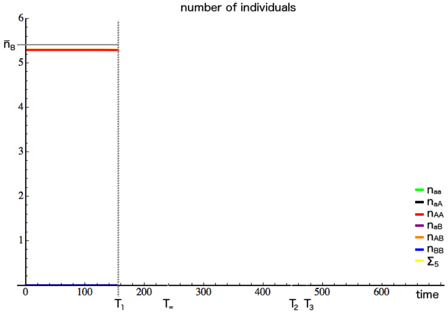


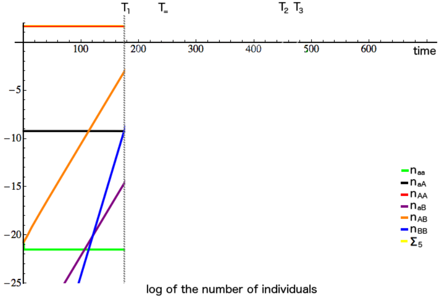
Mutation 2



Proof

1.Phase: Fixation of the mutant



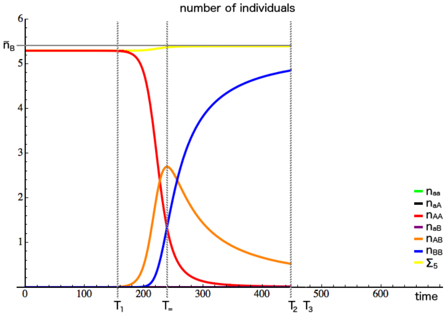


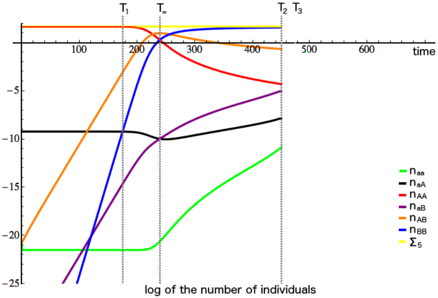
- AB grows to level ε_0
- $aB, BB \leq \varepsilon_0$

$\Rightarrow$ perturbation of the 3-system (aa, aA, AA) of at most $\mathcal{O}(\varepsilon_0)$

Proof

2.Phase: Invasion of the mutant





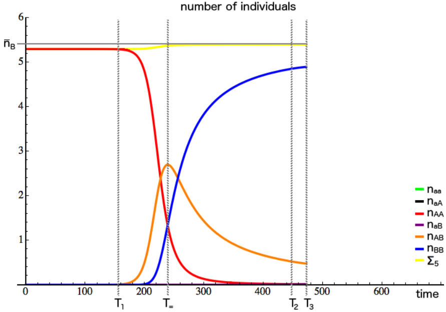
- $aa, aA, aB \leq \varepsilon_0$

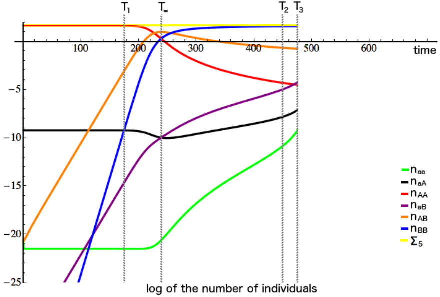
$\Rightarrow$ perturbation of the new 3-system (AA, AB, BB) of at most $\mathcal{O}(\varepsilon_0)$
$\Rightarrow$ use results of Bovier, Neukirch (2015)

- $n_{aA} + n_{aB}$ increases if $\eta > 0$

Proof

3. Phase: Recovery of aa



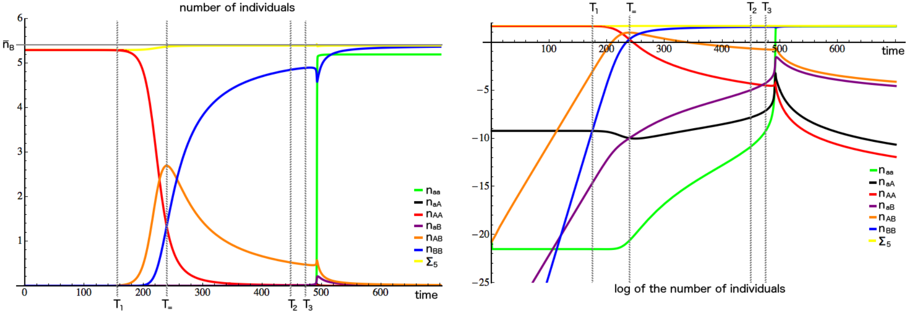


- AA small enough
- aA big enough

$\Rightarrow$ aa starts to reproduce out of itself as much as with the other partners.

Proof

4. Phase: Coexistence



Delicate phase : aa grows out of itself and feels no competition with BB
$\Rightarrow$ convergence to coexistence-fixed-point $\bar{n}_{aa,BB}$
BUT meanwhile :
due to Mendelian recombination, aA, aB, AB have a "bump" upwards, and due to competition with them BB has a "bump" downwards.


THANK
YOU