Crossing a fitness valley in a stochastic population model

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- Fixation probability and fixation time of new mutations widely studied from the work of the 'Great Trinity' (Fisher 1922, 1931, Wright 1931, Haldane 1927)
- Fundamental questions to understand how and how fast a population can adapt to a changing environment, the dynamics of genetic diversity, the long term behaviour of ecological systems...

Three basic mechanisms

- Heredity: offsprings acquire the genetic information of their parents
- Mutation: permanent alteration of DNA
- Natural selection: differential survival and reproduction of individuals due to differences in phenotype

Eco-Evolutionary framework: take into account the underlying environment

- Varying size populations
- Interactions with other individuals (competition for resource)
- Quantity of available resources
- In the context of stochastic individual based models: Fournier and Méléard 2004, Champagnat 2006, Tran 2008,...

Fate of an initially monomorphic population:

- On a fast (ecological) time scale, population size reaches ecological equilibrium
- If mutations to types of positive invasion fitness are possible, population is replaced by a fitter type, if fixation
- If coexistence with this mutant is possible, a branching occurs

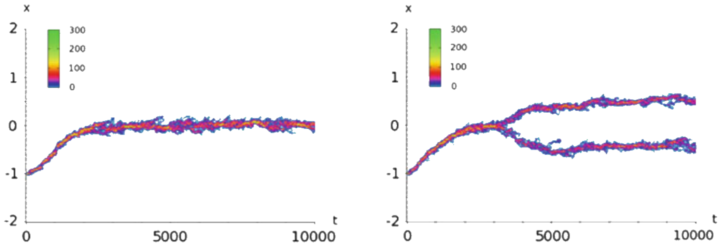


Figure : Champagnat and Méléard 2011

What happens if several counterselected mutations are necessary to produce a fit mutant?

- Evolution to self-incompatibility in hermaphroditic plants: "Recognition of pollen by pistils expressing cognate specificities at two linked genes leads to rejection of self pollen and pollen from close relatives, i.e., to avoidance of self-fertilization and inbred matings." (Gervais et al. 2011)
- Mutations from normal to cancer cells: oncogene (promotes differentiation and proliferation), antioncogene (produces tumor suppressor proteins), caretaker (prevents the accumulation of DNA damage)
- More generally, positive epistasis between counterselected mutations

Model and fate of a fit mutant

Fitness valley

Results

Haploid asexual population

Ecological parameters

- β_i and δ_i birth rate and intrinsic death rate
- $C_{i,j}$ competitive pressure $j \to i$.
- $K \in \mathbb{N}$ rescales the competition $\approx$ carrying capacity.

Birth and death rate

$$b_i(X) = \beta_i X_i \quad \text{and} \quad d_i(X) = \Big[\delta_i + \sum_{j \in I} \frac{C_{i,j}}{K} X_j\Big] X_i$$

Monomorphic population

When population size of order K, rescaled population process $n_i = N_i/K$ evolves as a competitive Lotka-Volterra equation (Ethier and Kurtz 1986):

$$\dot{n}_i = (\beta_i - \delta_i - C_{i,i} n_i) n_i$$

Positive equilibrium for a monomorphic population if $\beta_i > \delta_i$

$$\beta_i - \delta_i - C_{i,i} n_i = 0 \Longleftrightarrow n_i = \bar{n}_i = \frac{\beta_i - \delta_i}{C_{i,i}}$$

Invasion of a positively selected mutant

Invasion fitness

$$S_{ji} = \beta_j - \delta_j - \frac{C_{j,i}}{K} K \bar{n}_i = \beta_j - \delta_j - C_{j,i} \bar{n}_i$$

$=$ *per capita* growth rate of a mutant j appearing in an i-population at its equilibrium size $\bar{n}_i K$

j is said:

- positively selected in a j-population if $S_{ji} > 0$
- counterselected in a j-population if $S_{ji} < 0$

$$n_i = N_i/K, \quad n_j = N_j/K$$

Two-dimensional Lotka-Volterra system

$$\begin{cases} \dot{n}_i = (\beta_i - \delta_i - C_{i,i}n_i - C_{i,}n_j)n_i \\ \dot{n}_j = (\beta_j - \delta_j - C_{j,i}n_i - C_{j,j}n_j)n_j \end{cases}$$

If $\quad \bar{n}_i > 0, \quad \bar{n}_j > 0, \quad$ and $\quad S_{ji} > 0$ and $S_{ij} < 0.$

$\Rightarrow$ Unique attracting stable equilibrium $(0, \bar{n}_j)$

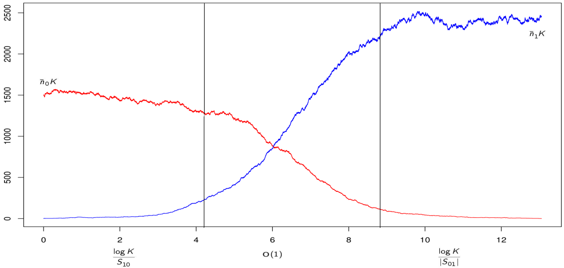
If $\quad \bar{n}_i > 0, \quad \bar{n}_j > 0, \quad S_{ji} > 0 \quad$ and $\quad S_{ij} > 0.$

$\Rightarrow$ Unique attracting stable equilibrium $(\bar{n}_i^{(ij)}, \bar{n}_j^{(ij)})$

If $\bar{n}_0, \bar{n}_1 > 0, \quad S_{10} > 0$ and $S_{01} < 0, \quad X_0(0) = \lfloor \bar{n}_0 K \rfloor, \; X_1(0) = 1$

(Champagnat 2006) $\lim_{K\to\infty} \mathbb{P}(\text{fixation of type 1}) \sim S_{10}/\beta_1 > 0,$

$$\text{total time} \sim \frac{\log K}{S_{10}} + \frac{\log K}{|S_{01}|}.$$



Model and fate of a fit mutant

Fitness valley

Results

We are interested in the case where several successive counterselected mutants are necessary to produce a positively selected mutant

Assumptions

- Trait $i := i$ mutations
- All traits unfit with respect to 0 except L:

$$S_{i0} < 0,\ 1 \leq i \leq L-1 \text{ and } S_{L0} > 0.$$

- All traits unfit with respect to L:

$$S_{iL} < 0,\ 0 \leq i \leq L-1.$$

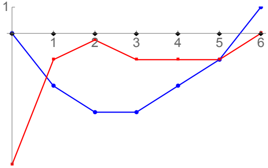


Figure : In blue (resp. red), invasive fitness of the mutant in the 0-population (resp. L-population)

- L mutations necessary to produce a positively selected mutant
- $\mu_K :=$ mutation probability per reproductive event
- Mutation kernels:

$$m_{ij}^{(1)} = \mu_K \delta_{i+1,j} \quad \text{or} \quad m_{ij}^{(2)} = \frac{\mu_K}{2}(\delta_{i+1,j} + \delta_{i-1,j}),$$

  where $\delta_{i,j}$ is the Kronecker delta (1 if $i = j$, 0 otherwise).
- When the population is large (large K), does the mutant L get fixed, how the fixation time of the mutant L depends on L, the scaling of μ_K with respect to K, and the parameters?

Model and fate of a fit mutant

Fitness valley

Results

- Deterministic limit $(K, \mu_K) \to (\infty, \mu)$, then $\mu \to 0$
- Stochastic limit $(K, \mu_K) \to (\infty, 0)$
- On the extinction of the population

Notation: rescaled population

$$X^K(t) = \left(\frac{X_0(t)}{K}, \frac{X_1(t)}{K}, ..., \frac{X_L(t)}{K} \right)$$

We will first consider the case of frequent mutations, when μ_K does not go to 0 when K goes to infinity.

Proposition (Ethier and Kurtz, 1986)

Suppose that $\lim_{K\to\infty} X^K(0) = x(0)$ *in probability. Then, for each* $T \in \mathbb{R}_+$, $(X^K(t), 0 \leq t \leq T)$ *converges in probability, as* $K \to \infty$, *to the deterministic process* $x^\mu = (x_0^\mu, \dots, x_L^\mu)$ *unique solution to:*

$$\frac{dx_i^\mu}{dt} = \Big((1-\mu)\beta_i - \delta_i - \sum_{i=0}^{L} C_{i,j} x_j^\mu\Big) x_i^\mu + \mu \sum_j m_{ji} \beta_j x_j^\mu.$$

Theorem

Take as initial condition $x^\mu(0) = (\bar{x}_0, 0, \dots, 0)$. Then for $i \in \mathcal{X}$, as $\mu \to 0$, uniformly on bounded time intervals,

$$\frac{\log\left[x_i^\mu\left(t \cdot \log\left(1/\mu\right)\right)\right]}{\log(1/\mu)} \to x_i(t), \quad \left(x_i^\mu(t \log \frac{1}{\mu}) \asymp \left(\frac{1}{\mu}\right)^{x_i(t)}\right)$$

where $x_i(t)$ is piece-wise linear.

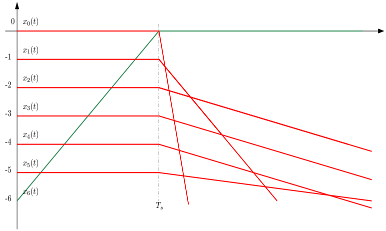


Figure : 1-sided mutation kernel

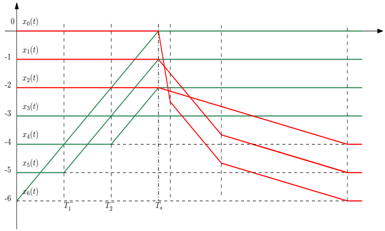
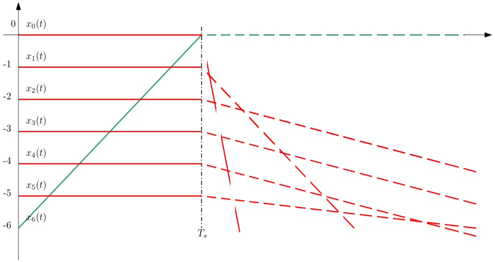


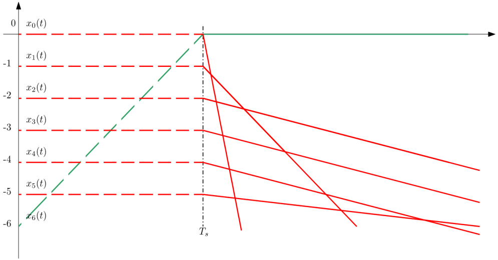
Figure : 2-sided mutation kernel

Deterministic limit $(K, \mu_K) \to (\infty, \mu)$, then $\mu \to 0$



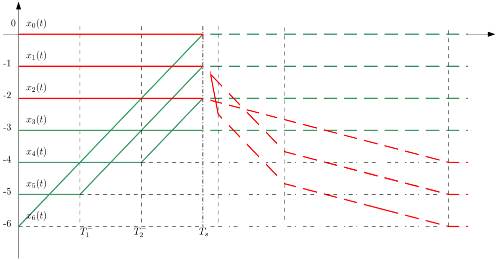
$$x_i^{\mu}(t \log \tfrac{1}{\mu}) \asymp \left(\frac{1}{\mu}\right)^{x_i(t)}$$

- i-population stabilizes around $O(\mu_K^i)$ in a time of order one
- L-population grows exponentially with a rate S_{L0}
- Swap between populations 0 and L (Lotka-Volterra system)



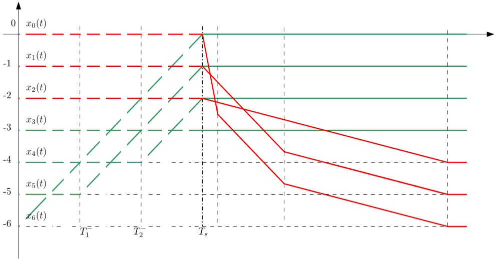
$$x_i^{\mu}(t \log \tfrac{1}{\mu}) \asymp \left(\frac{1}{\mu}\right)^{x_i(t)}$$

- i-population ($i \neq L$) decays exponentially with a rate given by the lowest fitness of its left neighbours $\min_{0 \leq j \leq i} |S_{jL}|$
- When a i-population decreasing more slowly than the $i+1$-population reaches a size higher than $1/\mu_K *$ the $(i+1)$-population size, the $(i+1)$-population starts decreasing exponentially with the same rate as the i-population



$$x_i^\mu(t \log \tfrac{1}{\mu}) \asymp \left(\frac{1}{\mu}\right)^{x_i(t)}$$

- First phase: when the $(i+1)$-population reaches a size higher than $1/\mu_K *$ the i-population size, the i-population starts growing exponentially with a rate S_{L0}



$$x_i^{\mu}(t \log \tfrac{1}{\mu}) \asymp \left(\frac{1}{\mu}\right)^{x_i(t)}$$

- Second phase: when the $i+1$-population reaches a size higher than $1/\mu_K *$ the i-population size, the i-population starts decreasing with a slower rate (the same as the one of the $(i+1)$-population)

- Dynamics and time scale of the invasion process depend on the scaling of μ_K with respect to K.
- For simplicity, no more back mutations
- We consider a mutation probability of the form:

$$\mu_K = c_\mu K^{-1/\alpha}, \quad c_\mu, \alpha > 0.$$

- (Durrett and Mayberry 2011): constant population size or Yule process models, with directional mutations and increasing fitness, and (Champagnat, Méléard and Tran 2019+): horizontal transfer; case with a trade-off between larger birth rates for small trait values and transfer to higher traits.
- In a time of order one, there will be of order $K\mu^i = c_\mu^i K^{1-i/\alpha}$ mutants of type i
  - If $L < \alpha$, large mutation regime, type L mutants appear rapidly.
  - If $L > \alpha$, slow mutation regime, first type L mutants appear after a long and stochastic time.

Remark

Reminiscent of the deterministic limit.

- When $\alpha > L$, small fluctuations around deterministic evolution.
- One "just needs" to replace μ by $K^{-1/\alpha}$

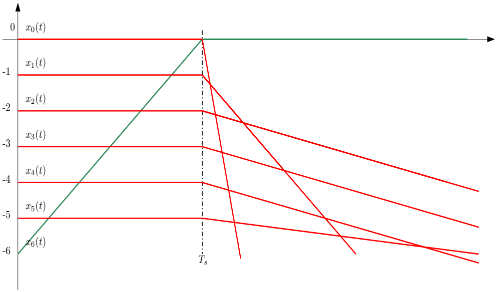
Notation

$$t(L,\alpha) := \frac{L}{\alpha S_{L0}} + \sup\left\{\left(1 - \frac{i}{\alpha}\right)\frac{1}{|S_{iL}|}, 0 \leq i \leq L-1\right\}$$

Theorem

Assume that $L < \alpha < \infty$.

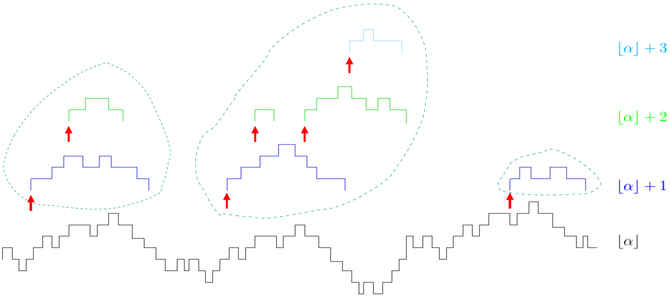
- *It takes a time of order $t(L,\alpha)\log K$ for the L-population to outcompete the other populations and enter in a neighbourhood of its monomorphic equilibrium size $\bar{n}_L K$.*



- *Then stays close to this equilibrium for at least a time e^{KV}, where V is a positive constant.*

Case $0 < \alpha < L$

$$K\mu_K^{\lfloor\alpha\rfloor} = c_\mu K^{1-\frac{\lfloor\alpha\rfloor}{\alpha}} \gg 1, \qquad K\mu_K^{\lfloor\alpha\rfloor+1} = c_\mu K^{1-\frac{\lfloor\alpha\rfloor+1}{\alpha}} \ll 1$$



Notation

$$\lambda(\rho) := \sum_{k=0}^{\infty} \frac{(2k)!}{(k!)^2} \rho^k (1-\rho)^{k+1},$$

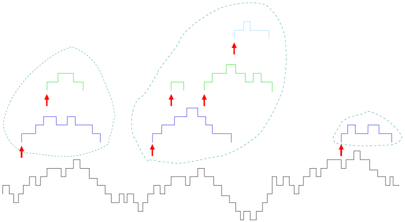
$=$ Expected number of individuals in an excursion of a subcritical branching process of birth and death rates b and d such that $b/(b+d) = \rho$ (Van Der Hofstad 2016, Britton and Pardoux 2018+)

For $\lfloor \alpha \rfloor + 1 \le i \le L-1$, set

$$\rho_i := \beta_i / (\beta_i + \delta_i + C_{i,0}\bar{x}_0).$$

Typical trajectories:

- i-populations ($1 \leq i \leq \lfloor \alpha \rfloor$) reach a size of order $K\mu^i \gg 1$ in a time of order one
- Last 'large' population: $\lfloor \alpha \rfloor$-population, which reaches a size of order $K\mu^{\lfloor \alpha \rfloor} \cong K^{1-\lfloor \alpha \rfloor/\alpha}$ after a time of order one
- i-populations ($\lfloor \alpha \rfloor + 1 \leq i \leq L$), describe a.s. finite excursions, whose a proportion of order μ_K produces a mutant of type $i+1$
- The term $\lambda(\rho_i)$ is the expected number of individuals in an excursion of an i-population ($\to \mu_K \lambda(\rho_i)$).
- Every L-mutant has a probability S_{L0}/β_L to produce a population which outcompetes all the other populations



Theorem

Assume that $0 < \alpha < L$.

- $$\text{Fixation time} \sim \mathcal{E}xp\left(\frac{\bar{n}_0\beta_0\ldots\beta_{\lfloor\alpha\rfloor-1}}{|S_{10}|\ldots|S_{\lfloor\alpha\rfloor0}|}K\mu_K^{\lfloor\alpha\rfloor}\left(\prod_{i=\lfloor\alpha\rfloor+1}^{L-1}\lambda(\rho_i)\mu_K\right)\frac{S_{L0}}{\beta_L}\right)$$
- *Then stays close to this equilibrium for at least a time e^{KV}, where V is a positive constant.*

- Key advantage of stochastic logistic birth and death processes on constant size processes: we can compare time scales of mutation processes and population lifetime.
- Quantification of the lifetime of populations with interacting individuals is a tricky question (Chazottes, Collet, Méléard 2016, 2017).
- Not able to determine necessary and sufficient conditions for the L-mutants to succeed in invading before the population extinction. However we managed to provide some bounds.

Notation

$$\rho_0(K) := \sqrt{K} \exp\left(-K\left(\beta_0 - \delta_0 + \delta_0 \ln\left(\frac{\delta_0}{\beta_0}\right)\right)\right)$$

Chazottes, Collet, Méléard 2016

If $x > 0$, $t \gg 1/\rho_0(K)$ and X_0 monomorphic population

$$d_{TV}\left(\mathbb{P}_{xK}(X_0(t) \in .), \delta_0(.)\right) = o(1).$$

$$T_0 := \inf\{t \geq 0, \sum_{i=0}^{L} X_i(t) = 0\} \quad B_L := \inf\{t \geq 0, X_L(t) > 0\}.$$

Theorem

If $K\mu \ll \rho_0(K)$, then $\mathbb{P}\left(T_0 < B_L\right) \underset{K\to\infty}{\to} 1$.

Proof

1. Coupling of the 0-population size with a larger population
2. First type 1 mutant has no time to appear

Assumption

$$\beta_i < \delta_i, \quad 1 \leq i \leq L-1.$$

Theorem

If $K\mu^L \ll \rho_0(K)$, then

$$\mathbb{P}\left(T_0 < B_L\right) \underset{K\to\infty}{\to} 1.$$

Proof

- Coupling of the 0-population size with a larger population
- Bounding of the probability that a type 1 individual has a L-mutant in its line of descent

Possible generalizations

- If coexistence possible between 0 and L ($S_{L0}, S_{0L} > 0$), same invasion phase, but X_0^K and X_L^K stabilise around $(n_0^{(0L)}, n_L^{(0L)})$, positive fixed point of the 2-species Lotka-Volterra system. Moreover, unfit mutant populations stay microscopic if $S_{i,\{0,L\}} := \beta_i - \delta_i - C_{i,0}n_0^{(0L)} - C_{i,L}n_L^{(0L)} < 0 \ \forall\ 1 \leq i \leq L-1$. In the 1-sided case, those stay of order $K\mu^i$, while in the 2-sided case, they stay of order $K\mu^{\min\{i,L-i\}}$.
- Mutation probability could depend on the trait.
- If order of mutations not important, each individual bearing k mutations can be labeled by the trait k. $\Rightarrow L!$ ways of reaching an individual of trait L with a sequence of L mutations. $\Rightarrow$ invasion time of the population L divided by $L!$.

THANK YOU FOR YOUR ATTENTION!