Fitness valleys and multi-scale analysis ~~in changing environment~~ on general trait graphs

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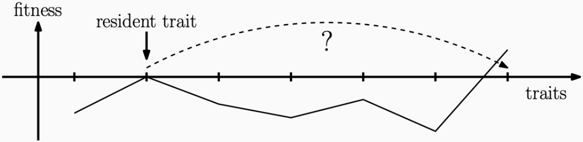
Motivation and goals

Motivation



Cancer initiation:
Need to be accumulated multiple driver mutations to induce an outgrowing population.

Flagella in bacteria:
Partially functional intermediate stages of flagella yield an evolutionary disadvantage but fully functional apparatuses lead to increased fitness.

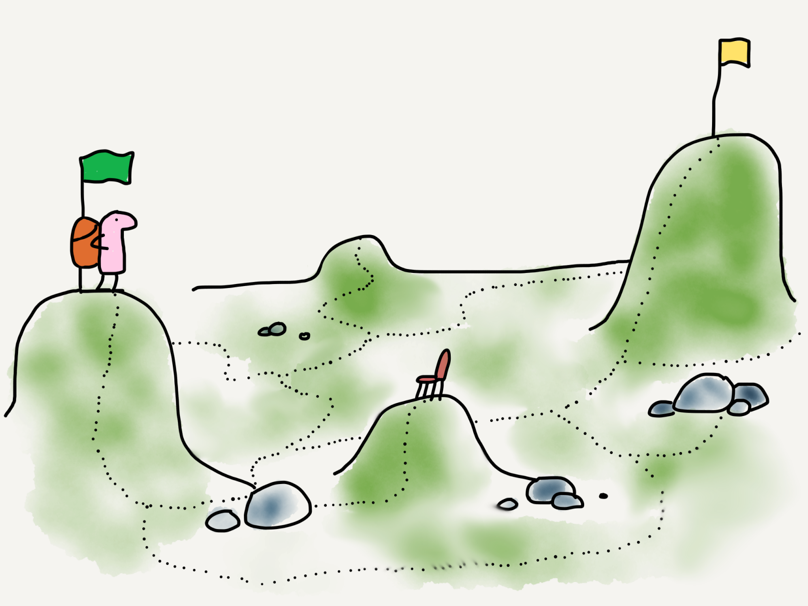
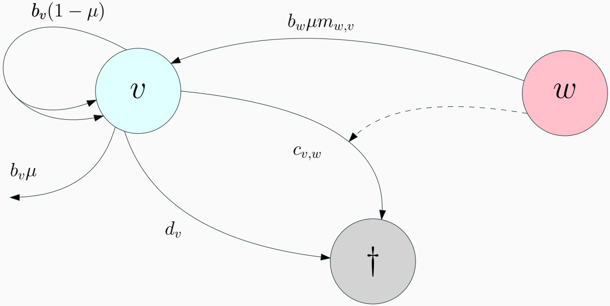


Figure 1: Population at an evolutionary stable state (©Konstanze Ebel)

The individual-based model of adaptive dynamics

Individuals are determined by a trait taken from a finite **trait space** V.
Count individuals by Markov Process $t \mapsto N(t) = (N_v(t), v \in V) \in \mathbb{N}_0^V$ driven by



Birth: $N_v b_v(1-\mu) + \sum_{w \in V} N_w b_w \mu m_{w,v}$
Death: $N_v \left(d_v + \sum_{w \in V} N_w c_{v,w}\right)$

Scaling

Scale the competition kernel $c^K(v,w) = c(v,w)/K$, by **carrying capacity** $K \to \infty$.
This leads to a total population size of $|N| = \mathcal{O}(K)$.

Small mutation rate: $\mu_K \searrow 0$.

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An LLN for Markov processes gives us convergence for finite times.

Theorem (Ethier, Kurtz '86)

On finite time intervals $[0,T]$

$$\left(\frac{N^K(t)}{K}\right)_{t\in[0,T]} \xrightarrow{K\nearrow\infty} (n(t))_{t\in[0,T]},$$

where n *solves to the competitive Lotka-Volterra equations*

$$\dot{n}_v(t) = n_v(t)\left[b_v - d_v - \sum_{w\in \text{v}} c_{v,w} n_w(t)\right] \qquad \forall v \in V.$$

Equilibria and invasion fitness

Lotka-Volterra equation

$$\dot{n}_v(t) = n_v(t)\left[b(v) - d(v) - \sum_{w\in\mathbf{v}} c(v,w)n_w(t)\right] \qquad \forall v \in V.$$

Lotka-Volterra equilibrium

Stable fixed point $\bar{n}(\mathbf{v}) \in \mathbb{R}^{\mathbf{v}}_{>0}$ and solving

$$0 = b(v) - d(v) - \sum_{w\in\mathbf{v}} c(v,w)\bar{n}_w(\mathbf{v}) \qquad \forall v \in \mathbf{v}.$$

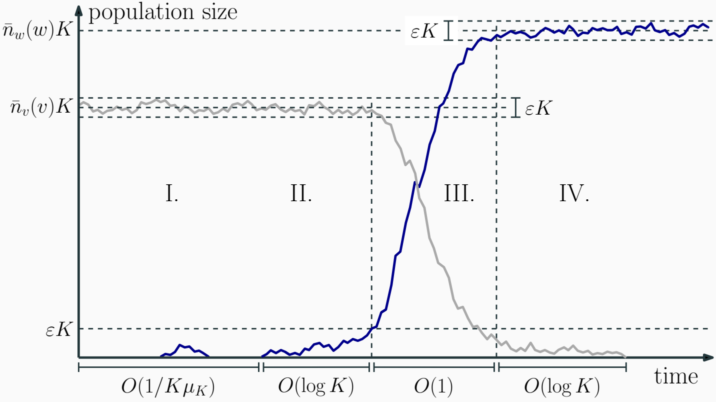
concering a set of resident traits $\mathbf{v} \subset V$

Invasion fitness

Initial growth rate of a new mutant $w \in V\backslash\mathbf{v}$

$$f(w,\mathbf{v}) = b(w) - d(w) - \sum_{v\in\mathbf{v}} c(w,v)\bar{n}_v(\mathbf{v}).$$

Phases of Invasion



0. equilibrium state (LDP, stability analysis)
I. mutation phase $\sim \mathrm{Pois}(K\mu_K)$
II. growth phase $\sim$ supercritical BD-process (exponential growth)
III. invasion phase $\sim$ deterministic Lotka-Volterra (LLN)
IV. extinction phase $\sim$ subcritical BD-process

Very rare mutations, TSS/PES

Champagnat Scaling $1/K\mu_K \gg \log K$

- Dominant time scale: Occurrence of mutants $1/K\mu_K$
- Mutations are separated

Theorem (Champagnat '06, Méléard-Champagnat'11)

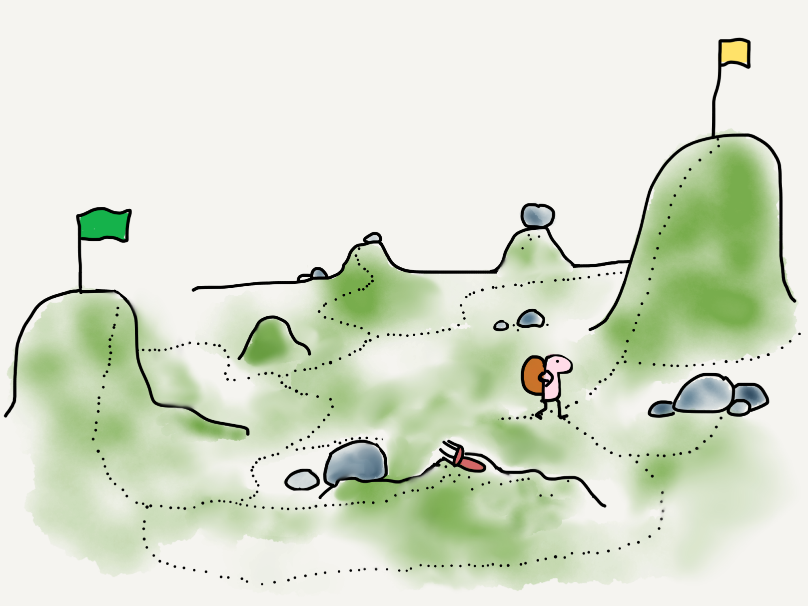
As $K \nearrow \infty$, $\left(\frac{N^K(t/K\mu_K)}{K}\right)_{t\geq 0}$ *converges to a Markov jump process with transition rates*

$$r(v \mapsto w) = \underbrace{\bar{n}(v)b(v)m(v,w)}_{\text{rate to produce mutant}} \cdot \underbrace{\frac{[f(w,v)]_+}{b(w)}}_{\text{fixation probability}} .$$

Evolution:

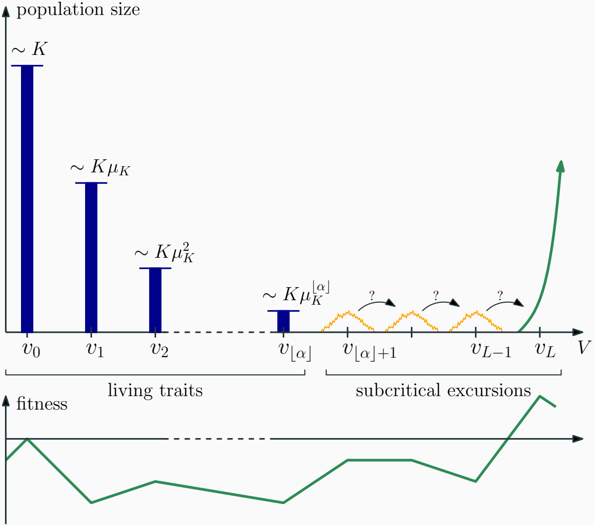
- only to next-neighbours
- stops in local fitness maxima

Fitness valleys

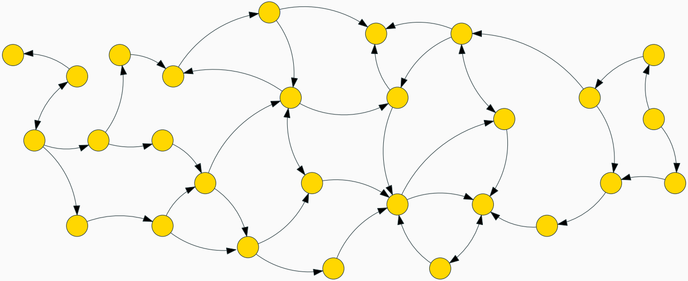


Evolutionary stable conditions (ESC)

Moderately small mutation rate: $\mu_K = K^{-1/\alpha}, 0 < \alpha < L$

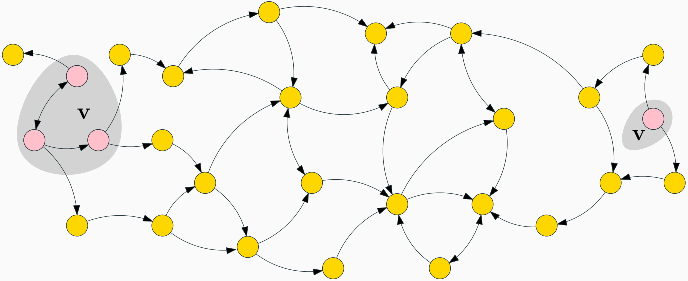


General graphs



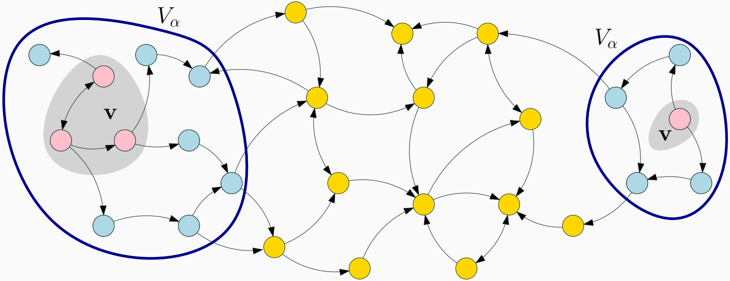
- General trait graph with possible mutations

General graphs



- General trait graph with possible mutations
- Set of coexisting resident traits at equilibrium $\bar{n}(\mathbf{v})$

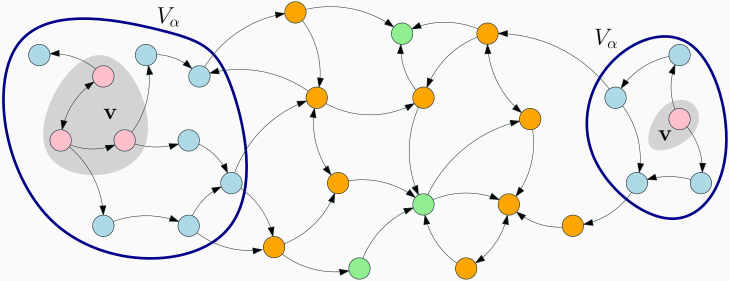
General graphs



$\alpha \in (2,3)$,

- General trait graph with possible mutations
- Set of coexisting resident traits at equilibrium $\bar{n}(\mathbf{v})$
- Mutation spreading neighbourhood $V_\alpha(\mathbf{v})$

General graphs



$$\alpha \in (2,3), \qquad f(\bullet, \mathbf{v}) < 0, \qquad f(\bullet, \mathbf{v}) < 0, \qquad f(\bullet, \mathbf{v}) > 0$$

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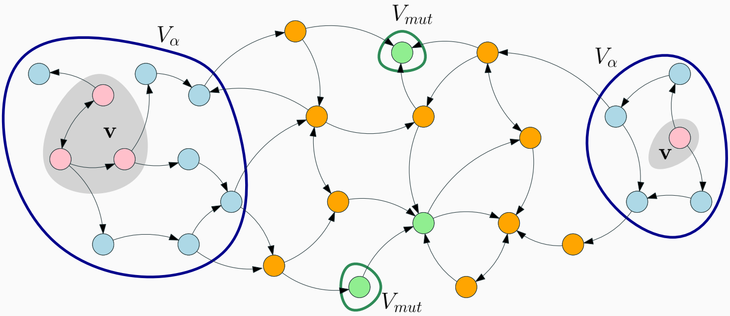

$$\alpha \in (2,3), \qquad f(\bullet, \mathbf{v}) < 0, \qquad f(\bullet, \mathbf{v}) < 0, \qquad f(\bullet, \mathbf{v}) > 0$$

- General trait graph with possible mutations
- Set of coexisting resident traits at equilibrium $\bar{n}(\mathbf{v})$
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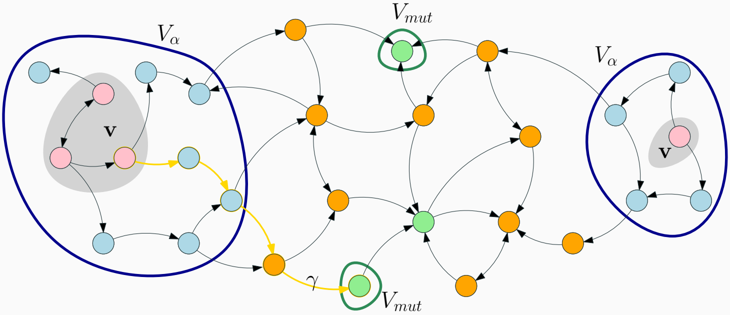
- Only the nearest traits are reachable $V_{mut}(\mathbf{v})$

General graphs



$$\alpha \in (2,3), \qquad f({\color{cyan}\bullet}, \mathbf{v}) < 0, \qquad f({\color{orange}\bullet}, \mathbf{v}) < 0, \qquad f({\color{green}\bullet}, \mathbf{v}) > 0$$

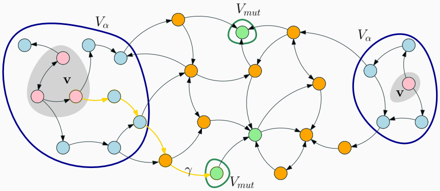
- General trait graph with possible mutations
- Set of coexisting resident traits at equilibrium $\bar{n}(\mathbf{v})$
- Mutation spreading neighbourhood $V_\alpha(\mathbf{v})$
- Some traits outside $V_\alpha(\mathbf{v})$ are fit
- Only the nearest traits are reachable $V_{mut}(\mathbf{v})$
- Rates are computed along paths $\gamma : \mathbf{v} \to w$

Pathwise approach

Independence of Paths

$$R(\mathbf{v}, w) = \sum_{\gamma:\mathbf{v}\to w} R(\mathbf{v}, \gamma), \qquad R(\mathbf{v}) = \sum_{w\in V_{mut}(\mathbf{v})} R(\mathbf{v}, w)$$

$$p(\mathbf{v}, w) = \frac{R(\mathbf{v}, w)}{R(\mathbf{v})}.$$



$\alpha \in (2,3)$, $f(●, \mathbf{v}) < 0$, $f(●, \mathbf{v}) < 0$, $f(●, \mathbf{v}) > 0$

Fixation of a mutant leads to next ESC $v_{ESC}(\mathbf{v}, w)$.

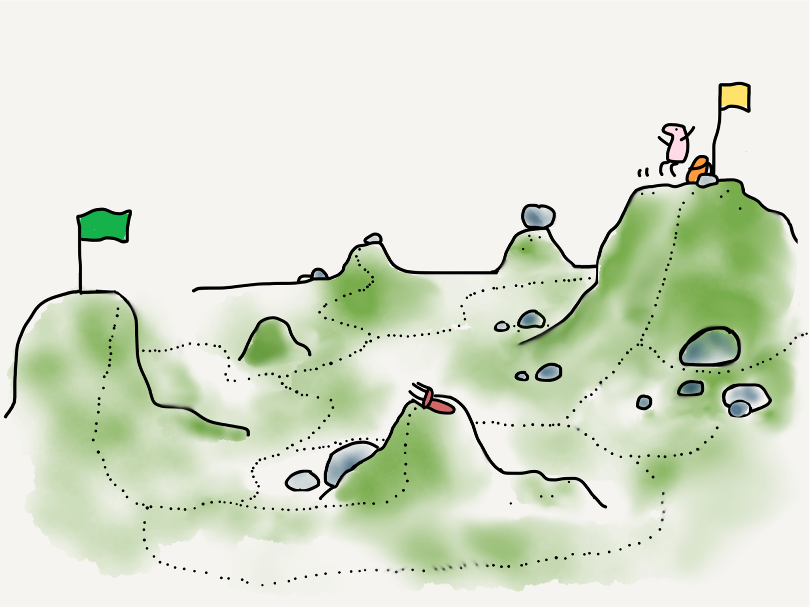
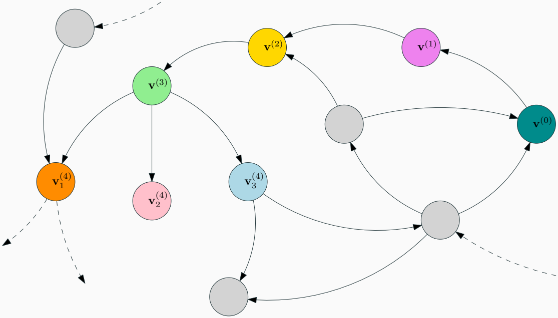


Figure 2: Population has reached a new ESC and thus changes the fitness-landscape.

Metastability graph (E.,Kraut '21)

We can witness consecutive jumps on *different state dependend time scales*. These can be represented as chains in a metastability graph $\mathcal{G}_{ESC}$.



Limiting process

Focusing on a particular timescale $1/K\mu_K^L$

- larger valleys ($d(\mathbf{v}, w) > L$) cannot be crossed,
- smaller valleys ($d(\mathbf{v}, w) < L$) are crossed immediately.

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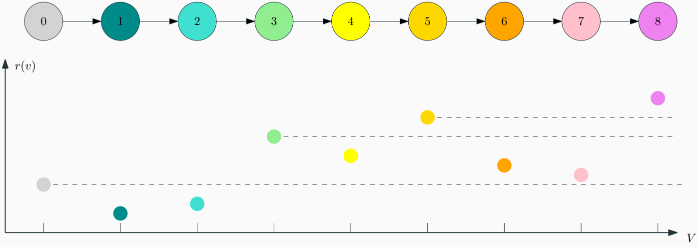
The metastability graph collabses to a *L*-scale graph $\mathcal{G}^L$. And we can deduce convergence to a Markov jump process.

Theorem (E., Kraut '21)

$$\frac{N_v^K(t/K\mu_K^L)}{K} \overset{K\nearrow\infty}{\longrightarrow} \mathcal{N}_v^L(t) = 1_{v\in \mathrm{v}^L(t)}\bar{n}_v(\mathrm{v}^L(t)), \qquad \forall v \in V,\ in\ \mathbb{D}([0,T])$$

First example

$\alpha \in (1,2)$



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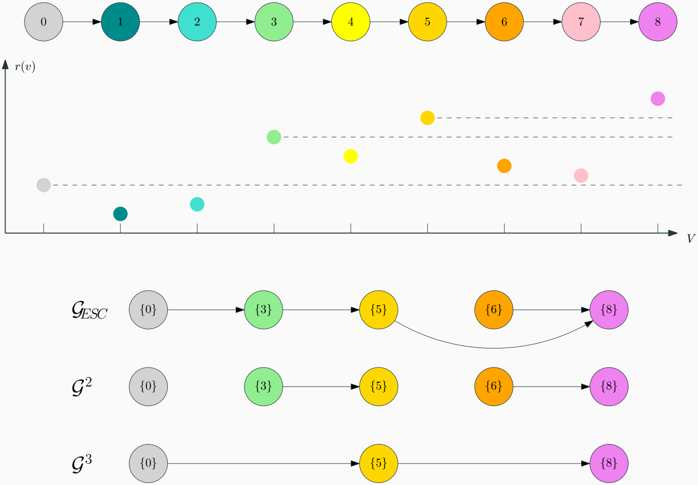
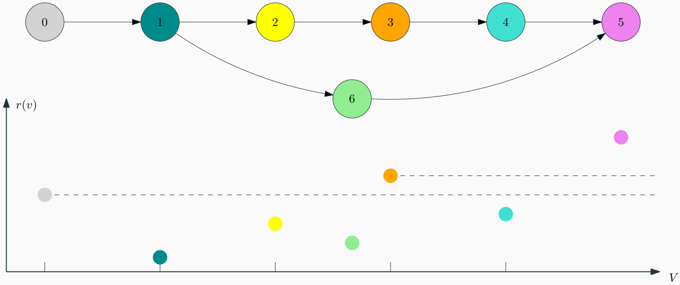


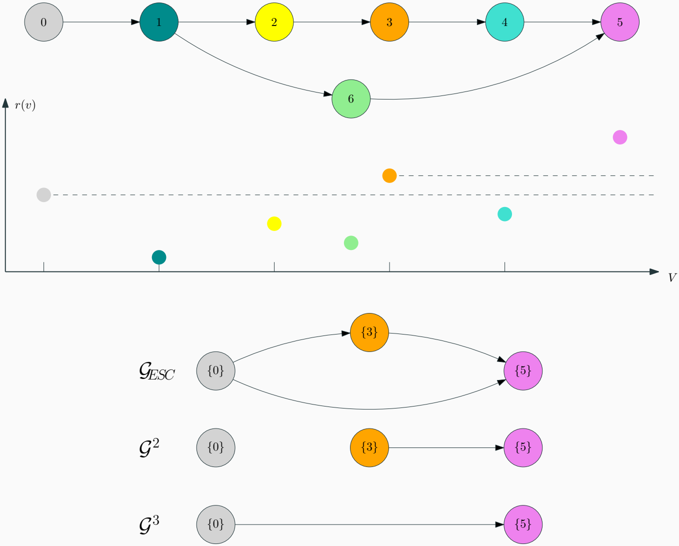
Second example

$\alpha \in (1, 2)$



Second example

$\alpha \in (1, 2)$



Conclusion

What we have:

- Full description of limiting adaptive jump process on general trait graphs.
- Different phenomena are visible on different time scales.
- Dynamic fiteness landscape determines transition rates/probabilities and time scales

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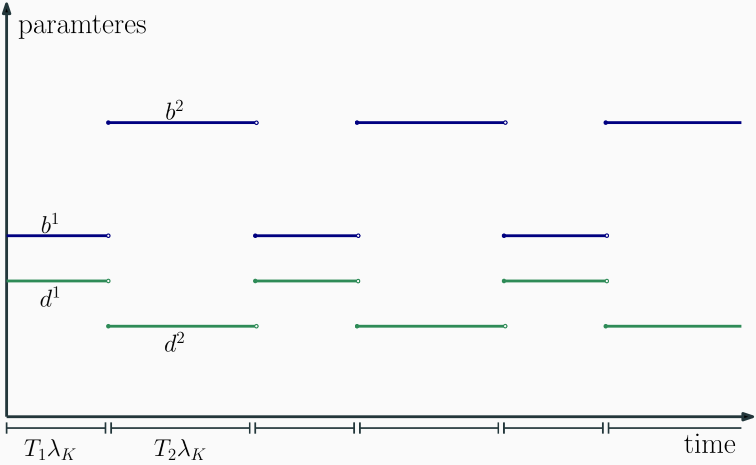
Work in progress:

- Relax assumptions on the stability on lower time scales.
- Analyse processes of cyclic bahaviour.
- Investigate periodic changes in the environment.

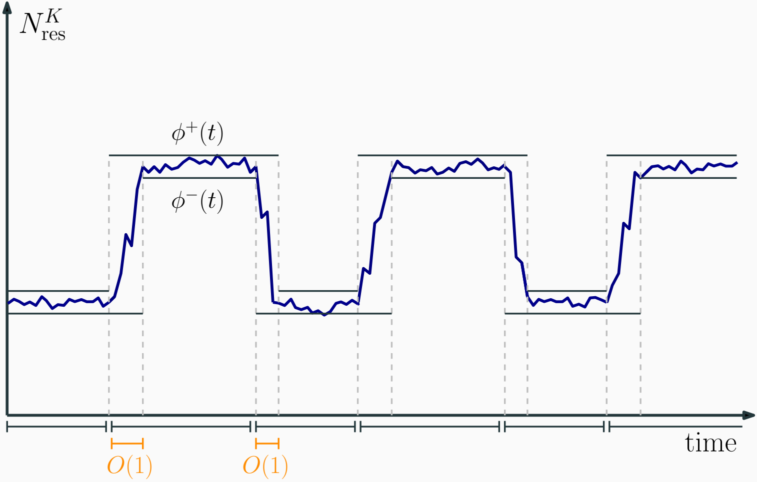
Changing environment

Varry system parameters periodically on an intermediate timescale $1 \ll \lambda_K \ll \ln K$.



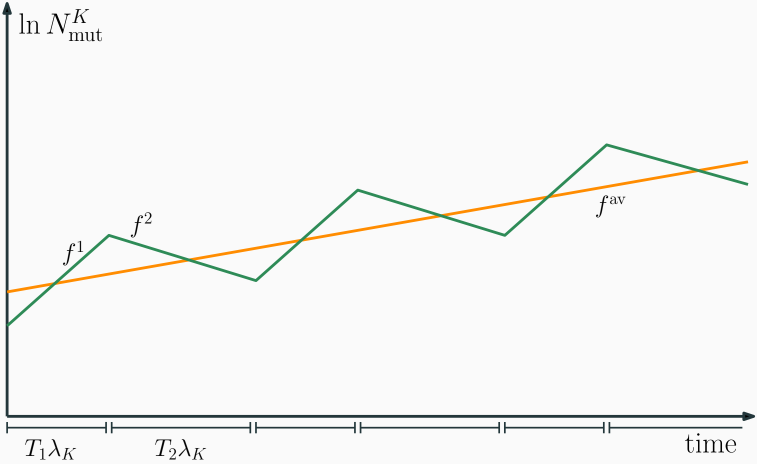
Changing environment

Quick adaptation of the residents in time of order $\mathcal{O}(1)$



Changing environment

Averaging of exponential growth of a mutant population on the time scale ln K



Thank you for your attention!

Questions?

Stability degree

The length of the valley is referred to as stability degree.

$$L(\mathbf{v}) := \min_{w \in V : f(w,\mathbf{v}) > 0} d(\mathbf{v}, w).$$

The time scale for the first arrival of fit individual is

$$1/K\mu_K^{L(\mathbf{v})}$$

We consider the nearest fit traits as mutant candidates

$$V_{\mathrm{mut}}(\mathbf{v}) := \{w \in V : f(w, \mathbf{v}) > 0 \ \wedge \ d(\mathbf{v}, w) = L(\mathbf{v})\}.$$

Rates

The rates of the exponentials can be computed pathwise

$$
\begin{aligned}
R(\mathbf{v},\gamma) :=& \bar{n}_{\gamma_0}(\mathbf{v}) \left(\prod_{i=1}^{\lfloor \alpha \rfloor} \frac{b(\gamma_{i-1}) m(\gamma_{i-1},\gamma_i)}{|f(\gamma_i,\mathbf{v})|} \right) b(\gamma_{\lfloor \alpha \rfloor}) m(\gamma_{\lfloor \alpha \rfloor},\gamma_{\lfloor \alpha \rfloor +1}) \\
&\times \left(\prod_{j=\lfloor \alpha \rfloor +1}^{L(\mathbf{v})-1} \lambda(\rho(\gamma_j,\mathbf{v})) m(\gamma_j,\gamma_{j+1}) \right) \cdot \frac{f(\gamma_{L(\mathbf{v})},\mathbf{v})}{b(\gamma_{L(\mathbf{v})})},
\end{aligned}
$$

$$
R(\mathbf{v},w) := \sum_{\substack{\gamma:\mathbf{v}\to w,\\ |\gamma|=L(\mathbf{v})}} R(\mathbf{v},\gamma), \qquad R(\mathbf{v}) := \sum_{w\in V_{\mathrm{mut}}(\mathbf{v})} R(\mathbf{v},w).
$$

Small valleys ($L < \alpha$)

Theorem (Bovier-Coquille-Smadi 2019, Thm. 3.2)

$$\liminf_{K\to\infty} \mathbb{P}\left((1-c\epsilon)\frac{1}{\alpha}\frac{L}{f_{L,0}} < \frac{T_{\epsilon}^{(K,L)}}{\log K} < \frac{T_{\bar{z}_L-\epsilon}^{(K,L)}}{\log K} < (1+c\epsilon)\frac{1}{\alpha}\frac{L}{f_{L,0}} \right) \geq 1 - c\epsilon.$$

Large valleys ($L > \alpha$)

Theorem (Bovier-Coquille-Smadi 2019, Thm. 3.3)

There exist two exponential rv. $E_\pm \sim \mathfrak{Exp}(a_\pm)$ *such that*

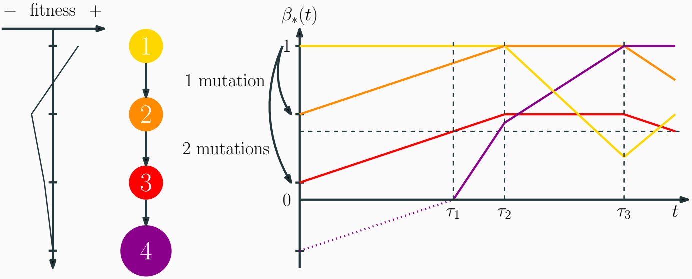
$$\liminf_{K\to\infty} \mathbb{P}\left(E_- \leq \left(T^{(K,L)}_{\bar{z}_L-\epsilon} \vee T^{(K,\Sigma_L)}_0\right) K\mu^L \leq E_+\right) \geq 1 - c\epsilon.$$

The frequencies are given by

$$a_\pm = (1 \pm c\epsilon)\bar{z}_0 \frac{b_0 \;\cdot\; b_1 \;\;\cdots\;\; b_{\lfloor\alpha\rfloor-1}}{|f_{1,0}|\,|f_{2,0}|\cdots|f_{\lfloor\alpha\rfloor,0}|} b_{\lfloor\alpha\rfloor} \left(\prod_{i=\lfloor\alpha\rfloor+1}^{L-1} \lambda(\rho_i)\right) \frac{f_{L,0}}{b_L},$$

$$\rho_i = \frac{b_i}{b_i + d_i + c_{i,0}\bar{z}_0}, \quad \lambda(\rho) = \sum_{k=1}^{\infty} \frac{(2k)!}{(k+1)!(k-1)!} \rho^k (1-\rho)^{k+1}.$$

log K-**limit**



- Trait 2 grows exponentially and produces an increasing number of type 3-mutants
- An $O(1)$-amount of type 4-mutants is produced and has a higher fitness
- Trait 2 invades and thus the fitness landscape gets changed
- Trait 4 invades and trait 1 becomes fit again

Theorem (Coquille, Kraut, Smadi ’21)

Algorithmic characterisation of limiting deterministic *growth process in term of the fitness landscape for power law mutation rates* $\mu_K = K^{-1/\alpha}$ *on general finite graphs.*

$$\beta^K(t) \xrightarrow{K \nearrow \infty} \beta(t), \qquad \textit{in } \mathbb{D}([0,T], \mathbb{R}^V),$$

where the functions $t \mapsto \beta_v(t)$ *are continuous and piecewise affine.*