Эволюционная динамика смены доминирующих видов в математической модели биологических сообществ Кроу-Кимуры

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14 конференция по математическим моделям и численным методам в биологии и медицине

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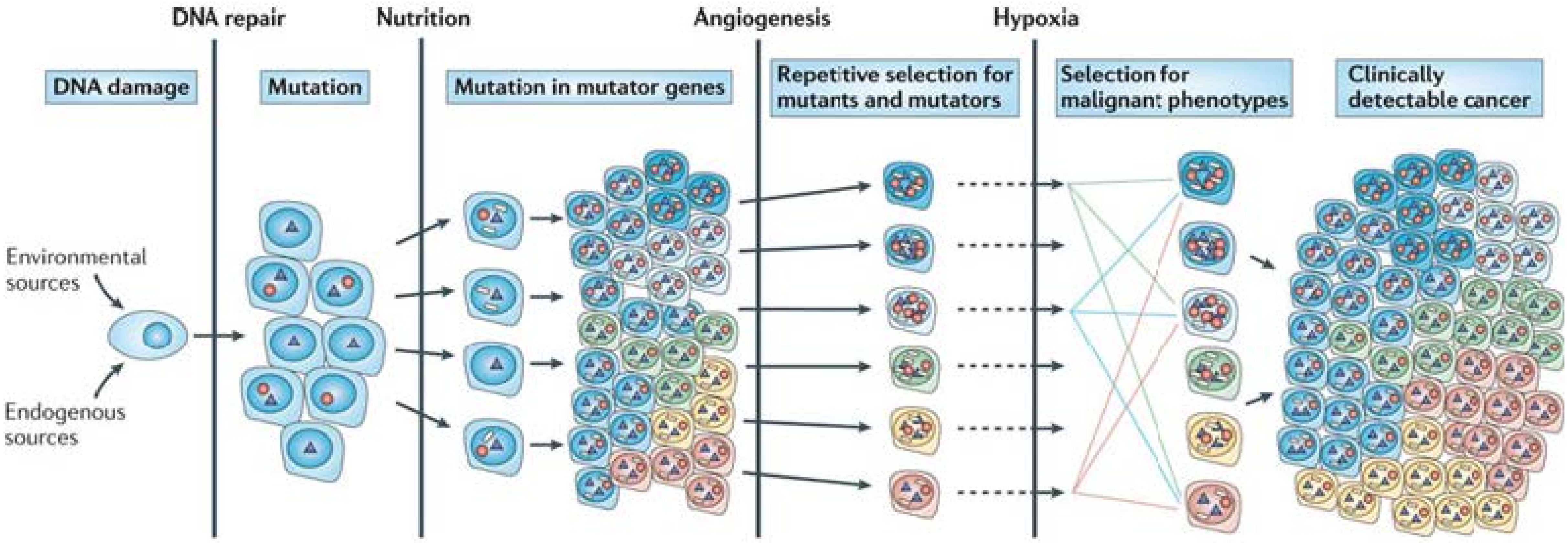
Cascade of Events in Cancer Development



Lawrence A. Loeb Human cancers express mutator phenotypes: origin, consequences and targeting// Nature Reviews Cancer 11, 450-457 (2011)

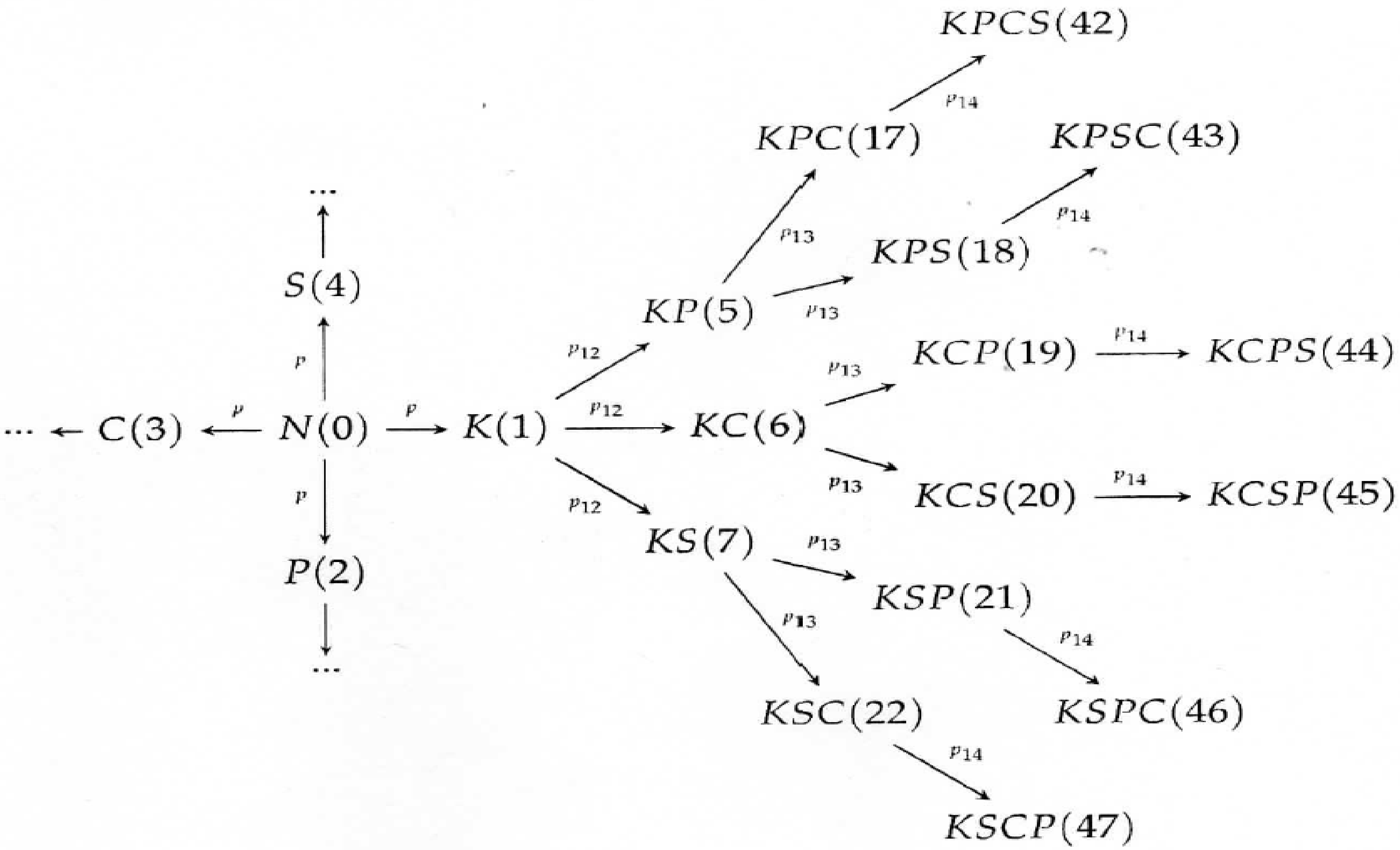
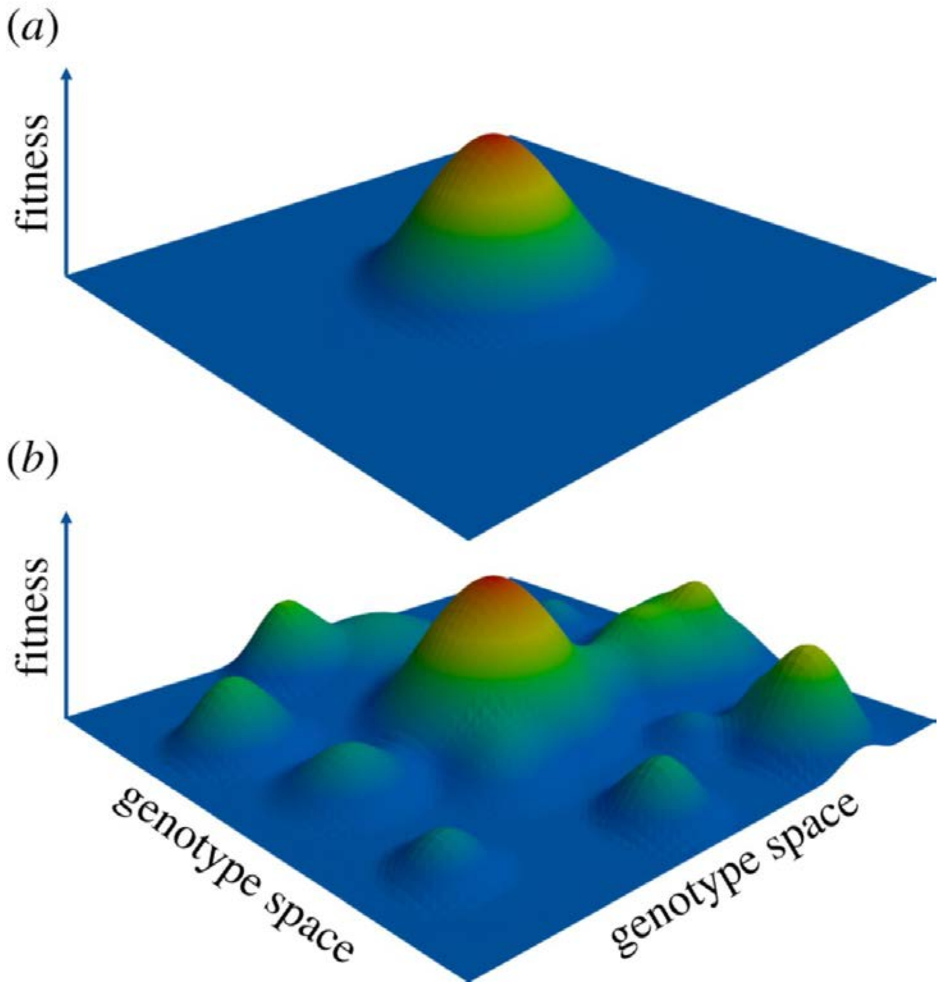
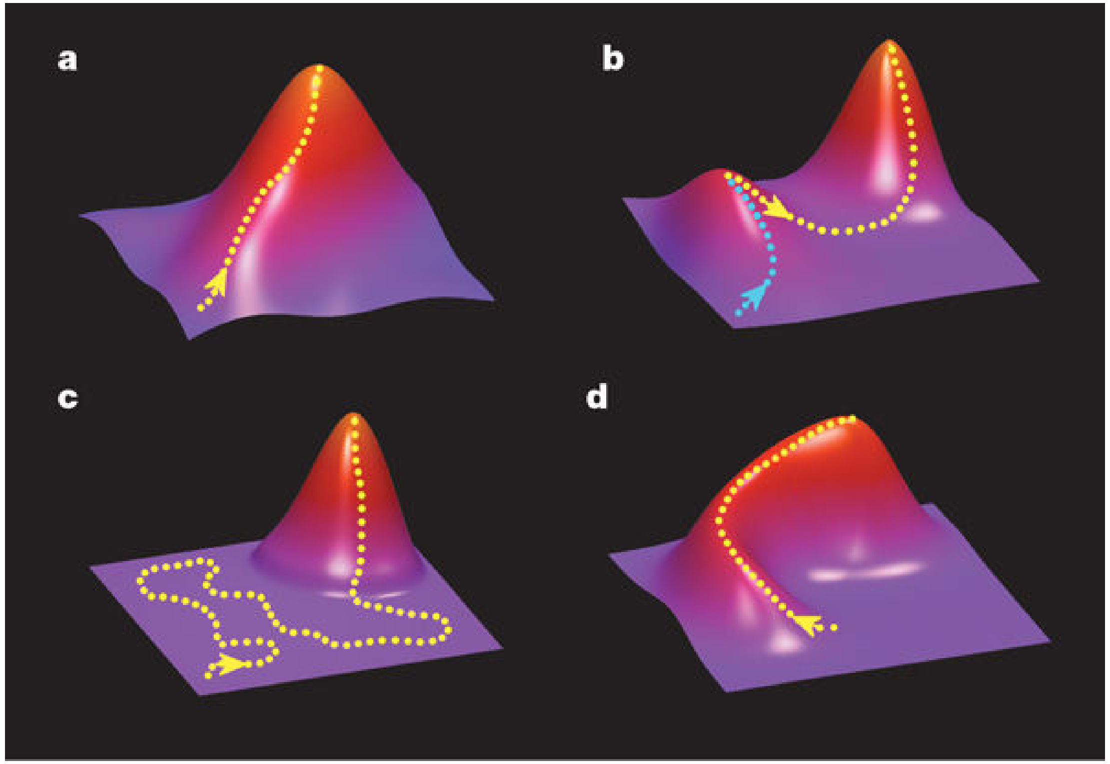


Figure 1. Scheme illustrating the evolution of possible mutations of healthy cell N. The branch following the initial mutation K is shown in detail.

Fitness Landscape Surface



Pesce, Diego, Niles Lehman, and J. Arjan GM de Visser. Phil. Trans. R. Soc. B 371.1706 (2016): 20150529.



Poelwijk, Frank J., et al. "Empirical fitness landscapes reveal accessible evolutionary paths." *Nature* 445.7126 (2007): 383.

The Eigen's Quasispecies Model

Selection is introduced by the set of **fitness landscape**:

$$\mathbf{M} = \mathbf{diag}(\boldsymbol{m_1}, \dots, \boldsymbol{m_l}),$$

Mutation is described by a **stochastic** matrix:

$$\mathbf{Q} = [\mathbf{q}_{\boldsymbol{ij}}]_{\boldsymbol{l \times l}},$$

$\boldsymbol{q_{ij}}$ ***is*** **probability of transition** $j \to i$:

$$\boldsymbol{q_{ij}} = \boldsymbol{q}^{\boldsymbol{N - d_{ij}}}(\mathbf{1} - \boldsymbol{q})^{\boldsymbol{d_{ij}}},$$

q – errorless replication rate per unit, $\boldsymbol{d_{ij}}$ $-$ **Hamming distance** for i and j.

$$\dot{\boldsymbol{p}}_{\boldsymbol{j}} = \sum_{\boldsymbol{i=1}}^{\boldsymbol{l}} \boldsymbol{q_{ji} m_i p_i} - \overline{\boldsymbol{m}}(\boldsymbol{t})\boldsymbol{p_j}, \qquad \boldsymbol{j} = \mathbf{1}, \dots, \mathbf{2}^{\boldsymbol{N}}.$$

$$\dot{\boldsymbol{p}} = \mathbf{Q}\boldsymbol{Mp} - \overline{\boldsymbol{m}}(\boldsymbol{t})\boldsymbol{p},$$

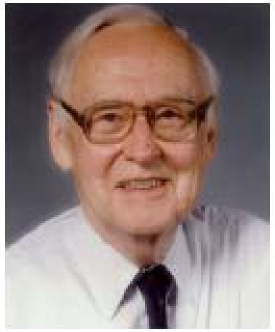
$$\overline{\boldsymbol{m}}(\boldsymbol{t}) = \sum_{\boldsymbol{j=1}}^{\boldsymbol{l}} \boldsymbol{m_j p_j}(\boldsymbol{t}) = \boldsymbol{m} \cdot \boldsymbol{p}(t).$$

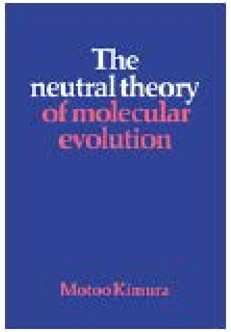
The Crow-Kimura model

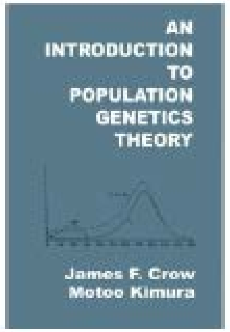
- l – Hamming distance to the reference sequence $S_0 = (0, \dots, 0)$
- $N + 1$ equations for Hamming classes
- $P_l(t)$ – probabilities for Hamming classes l

$$\frac{dP_l}{dt} = P_l N(m_l - \mu) + \mu(\mathrm{N} - \mathrm{l} + 1)\mathrm{P}_{l-1} + \mu(l+1)P_{l+1} - P_l \sum_l m_l P_l \,,$$

μ – mutation rate, m_l – fitness function for the symmetric fitness landscape and distance l.







J. F. Crow and M. Kimura, An Introduction to Population Genetics Theory (Harper Row, NY, 1970).

Matrix form for the Crow-Kimura

$$\mathcal{M} = (\mu_{ij}) = \mu Q = \mu \begin{bmatrix} -N & 1 & 0 & 0 & \dots & \dots & 0 \\ N & -N & 2 & 0 & \dots & \dots & 0 \\ 0 & N-1 & -N & 3 & \dots & \dots & 0 \\ 0 & 0 & N-2 & -N & \dots & \dots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & \dots & 2 & -N & N \\ 0 & 0 & \dots & \dots & 0 & 1 & -N \end{bmatrix},$$

$$\dot{\boldsymbol{p}}(t) = (\boldsymbol{M} + \mu\boldsymbol{Q})\boldsymbol{p}(t) - \overline{m}(t)\boldsymbol{p}(t),$$

$$\overline{m}(t) = \boldsymbol{m} \cdot \boldsymbol{p}(t) = \sum_{i=0}^{N} m_i p_i(t)\,.$$

Ref: Baake and Gabriel, Annual Reviews of Computational Physics VII, 1999: 203–264

Ref: Crow and Kimura, An introduction to population genetics theory, 1970

Open Quasispecies Model

Consider the mutation-selection process with explicit death rates under a different assumption:

$$\boldsymbol{Q = \{q_{ij}\}, \qquad M = diag(m_1, \dots, m_n)}$$

$$\boldsymbol{\frac{du(t)}{dt} = F(S(t))Q_m u(t) - Du(t), \qquad Q_m = QM, \qquad S(t) = \sum u_i(t)}$$

$$\boldsymbol{u(0) = u^0 > 0}$$

SF(S)* is restricted function and has only one maximum *(S>0)*. Examples: *F(S)=* $\boldsymbol{exp(-\gamma S)}$ or *F(S) =(K-S), K>0.

We introduce the new definition of fitness function for $\boldsymbol{\sum_{i=1}^{n} u_i > 0}$:

$$\boldsymbol{f(t) = \frac{\sum u_i(t) m_i}{\sum d_i u_i(t)}}$$

Ivan Yegorov, Artem Novozhilov, and Alexander Bratus. Open Quasispecies Models: Stability, Optimization, and Distributed Extension. 2021 Math. Analysis and Application.

Open Quasispecies Model: Properties

- **There are exist a unique smooth non-negative solution open quasispecies equations.**

  If $d_i > d > 0$, then function $S(t)$ is restricted.

  The steady-state is described by the following eigenvalue problem:

$$D^{-1}Q_m\bar{u} = \exp\big(\gamma S(\bar{u})\big)\bar{u}\,, \qquad \gamma > 0$$

Were D being diagonal death rates matrix.

- **For irreducible matrices Q_m, one can find the maximal of real eigenvalue λ^* and corresponding positive eigenvector: $u^* \geq 0$**
- $$S(\bar{u}) = \gamma^{-1} ln\lambda^*, \;\; \lambda^* = \frac{\sum_{i=1}^{n} m_i\bar{u}_i}{\sum_{i=1}^{n} d_i\bar{u}_i}$$

The last expression is mean steady state fitness value.

$$\bar{u}_i = \lim_{T\to\infty}\frac{1}{T}\int_0^T u(t)dt$$

Proposed Postulate:

- The specific time of the evolutionary adaptation (*evolutionary time*) for fitness landscape and mutations matrix elements *is much slower* than time describing the active dynamics system up to stabilization in a steady-state.
- Evolutionary changes happen during in *evolutionary time* on *restricted set of possible fitness landscape and mutation matrix elements.*
- Fisher's fundamental theorem of natural selection is valid in *evolutionary time* scale.

Mathematical Justification

$$\tau = \varepsilon t,$$

$$\varepsilon \frac{d\mathbf{u}\left(\frac{\tau}{\varepsilon},\tau\right)}{d\tau} = \exp\left(-\gamma S\left(\mathbf{u}\left(\frac{\tau}{\varepsilon},\tau\right)\right)\right)\mathbf{Q_m}(\tau)\,\mathbf{u}\left(\frac{\tau}{\varepsilon},\tau\right) - \mathbf{D}\mathbf{u}\left(\frac{\tau}{\varepsilon},\tau\right),$$

$$\exp\left(-\gamma S\left(\bar{\mathbf{u}}(\tau)\right)\right)\mathbf{Q_m}(\tau)\,\bar{\mathbf{u}}(\tau) - \mathbf{D}\bar{\mathbf{u}}(\tau) = 0,$$

$$\bar{\mathbf{u}}(\tau) = \lim_{t\to 0}\frac{1}{t}\int\limits_0^t \mathbf{u}(t,\tau)\,d\tau,$$

$$f\left(\bar{\mathbf{u}}(\tau)\right) = \exp\left(\gamma S\left(\bar{\mathbf{u}}(\tau)\right)\right) = \frac{\sum\limits_{i=1}^{l} m_i(\tau)\,\bar{u}_i(\tau)}{\sum\limits_{i=1}^{l} d_i\bar{u}_i(\tau)}.$$

Problem Statement: Fitness Landscape and Mutation matrix changing in the scale on evolutionary time

$$\boldsymbol{M(\tau) = diag\ (m_1(\tau), \dots m_n(\tau)),\ \ m_i(\tau) \geq 0}$$

The total available resource of fitness landscape elements is restricted by value **K.**

$$\boldsymbol{M_k(\tau) = \{\textstyle\sum_{i=1}^{n} m_i(\tau) \leq K, \forall \tau \geq 0\}, K > 0}$$

The total available resource of mutation matrix satisfied the following restrictions:

$$\boldsymbol{R(\tau) = \left\{ Q(\tau) = \left(q_{ij}\right)_{i,j=1}^{n} : q_{ij} \geq 0, i \neq j, q_{ii} \geq h > 0, \sum_{j=1}^{n} q_{ij} = 1 \right\}}$$

Reducing to Mathematical Programming Eigenvalue Problem.

Eigenvalue problem:

$$\boldsymbol{D^{-1}Q_m(\tau)\,\overline{u}(\tau) = \lambda\,\overline{u}(\tau)},$$

D is a death rate matrix

$$\boldsymbol{\lambda(\tau) = \exp\left(\gamma S\left(\overline{u}(\tau)\right)\right) = \frac{\sum m_i\,\overline{u_i}}{\sum d_i\overline{u_i}}} = (\text{mean steady state fitness on evolutionary time})$$

Mathematical programming problem:

$$\boldsymbol{\lambda(\tau) \to max}$$

$$\boldsymbol{M(\tau) \in M_k(\tau), \qquad Q(\tau) \in R(\tau), \forall \tau \geq 0}$$

Theorem

Let $\mathrm{D} = \mathrm{diag}(\mathrm{d}_1, \dots, \mathrm{d}_\mathrm{n}), \mathrm{d} > 0$ be a fixed death rate matrix.

$$M(\tau) \in M_k(\tau),\ \ Q(\tau) \in R(\tau), \forall\tau \geq 0$$

are convex set of restriction on elements of landscape and mutation matrix.

Then there exists a unique solution of mathematical programming extreme problem

$$U_\tau = \left\{ \bar{u}(\tau) \in \mathbb{R}_+^n, \qquad S\big(\bar{u}(\tau)\big) \leq \hat{S} = \gamma^{-1} \ln \frac{K}{d_{min}} \right\}$$

Numerical Maximization Method

Fitness variation in evolutionary time.

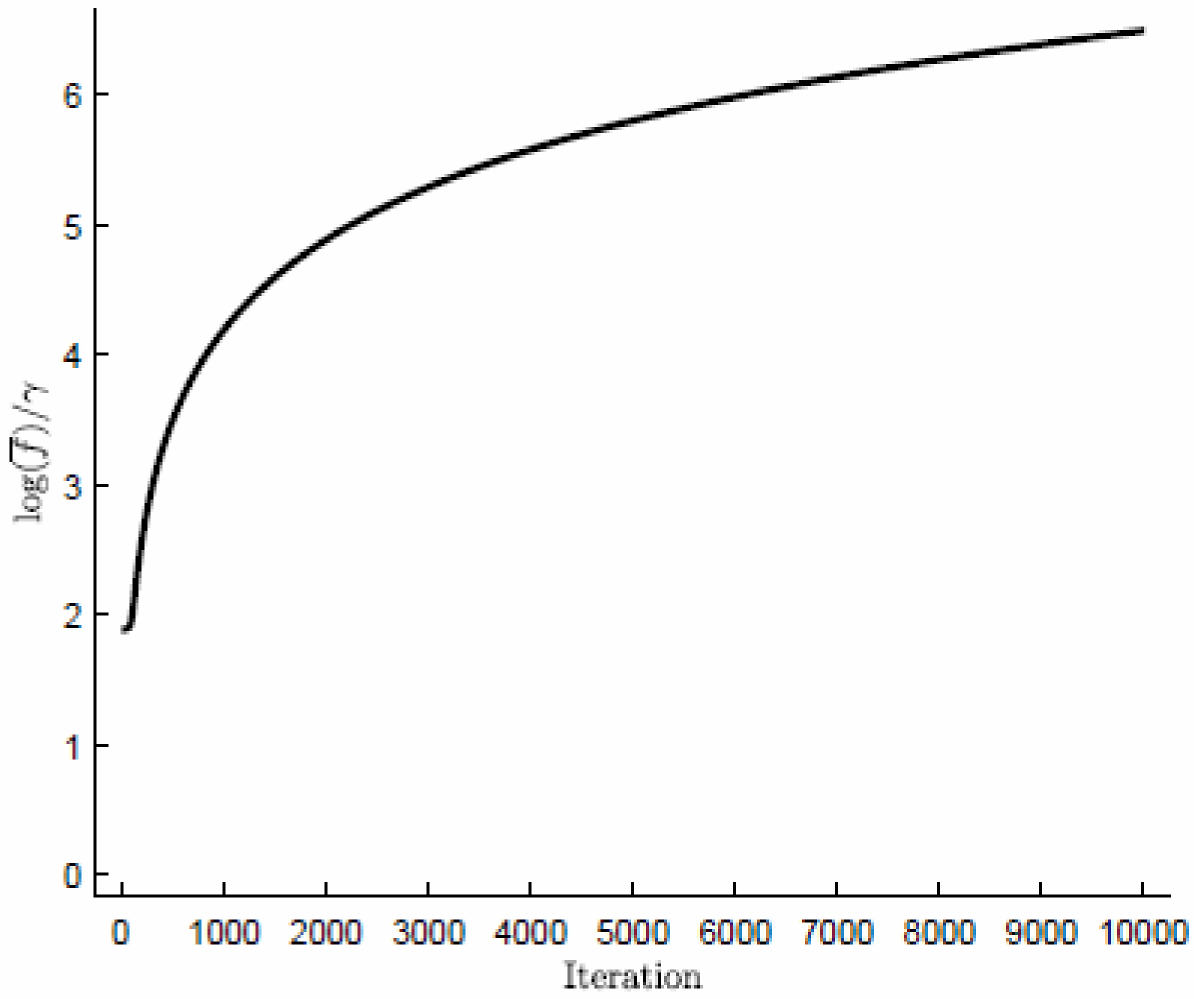
$$\boldsymbol{\delta\bar{f}} = \boldsymbol{\delta\lambda}^{*} = (\mathbf{D}^{-1}\left(\boldsymbol{\delta Q_m(\tau)}\right)\boldsymbol{\bar{u}(\tau)}, \mathbf{\bar{v}}\boldsymbol{(\tau)})$$

$$\boldsymbol{D^{-1}Qt_m\bar{v}} = \mathbf{exp}\left(\boldsymbol{\gamma S(v)}\right)\boldsymbol{\bar{v}}, \qquad \boldsymbol{\gamma} > \mathbf{0}$$

The maximization process takes the form of the multiple solutions of linear programming problem:

$$\boldsymbol{\delta\bar{f}(\tau)} \to \boldsymbol{max}$$

$$\sum_{\boldsymbol{i=1}}^{\boldsymbol{n}} \boldsymbol{\delta m_i(\tau)} = \mathbf{0}, \; \sum_{\boldsymbol{j=1}}^{\boldsymbol{n}} \boldsymbol{\delta q_{ij}(\tau)} = \mathbf{0}, \; \boldsymbol{\delta q_{ii}} \geq \mathbf{0}$$



Example 1.

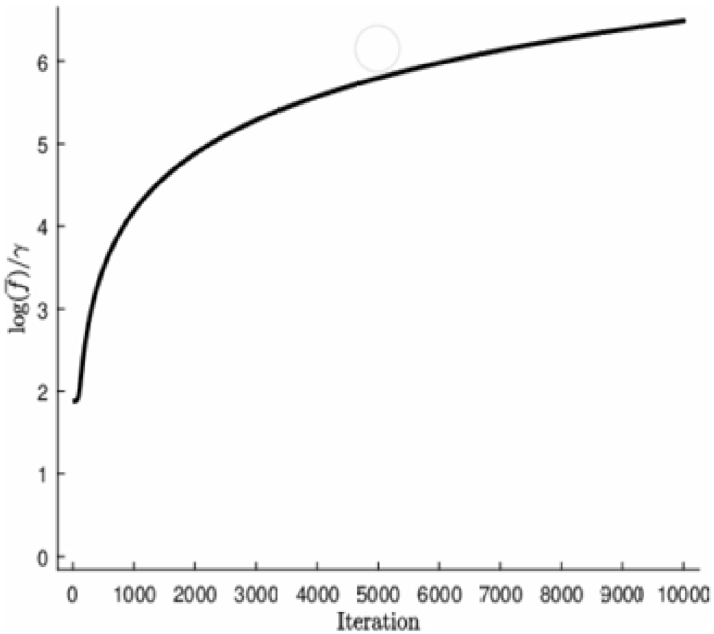
The result of the iteration algorithm of evolutionary process: numerical calculations in case, only **the fitness landscape variations**.

Genome length

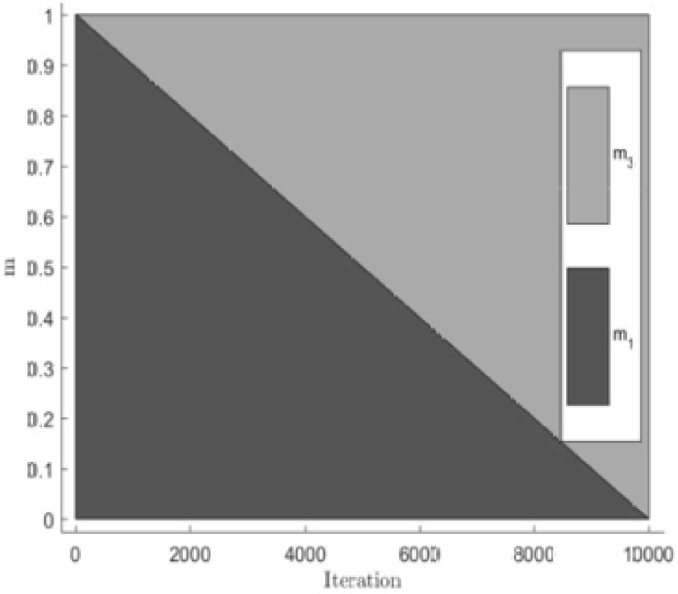
$$\boldsymbol{l = 16}, \quad \boldsymbol{q = 0.6}, \quad \boldsymbol{p = 0.9}$$

- M=(1,0,...,0)
- At the beginning, the first species m0 dominate, and its mortalities was a small. Increase mortality m0.
- $\boldsymbol{D} =$ diag(0.1, 0.001, 0.001, 0.00051, 0.001, 0.00051, 0.00051, 0.00034, 0.001, 0.00051, 0.00051,0.00034, 0.00051, 0.00034, 0.00034, 0.00026)
- After the evolution - third type dominates : m3=1
- The mean fitness increase in ~3.4 times
- The first species lost priority due to its high death rate

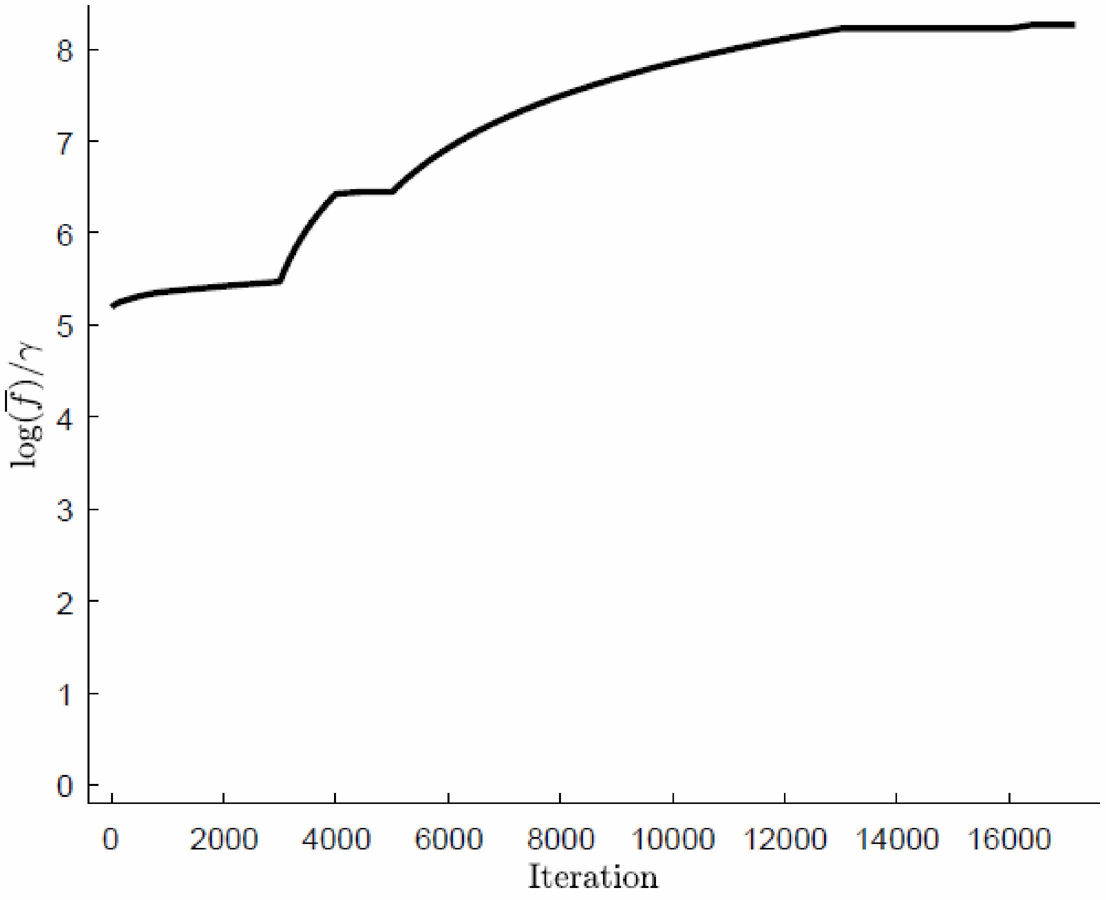
Example 1



Example 1 (changing **M** and **Q**): The mean fitness value changing over evolutionary time, which is represented by the number of iterations



Example 1 (changing **M** and **Q**): Dynamics of the fitness landscape parameters over evolutionary time: fitness matrix values m_i in steady-states with respect to the number iterations



Example 2.

The result of the iteration algorithm of evolutionary process: **fitness landscape and mutation matrix variations.**

$$l = 16, q = 0.6, p = 0.9$$

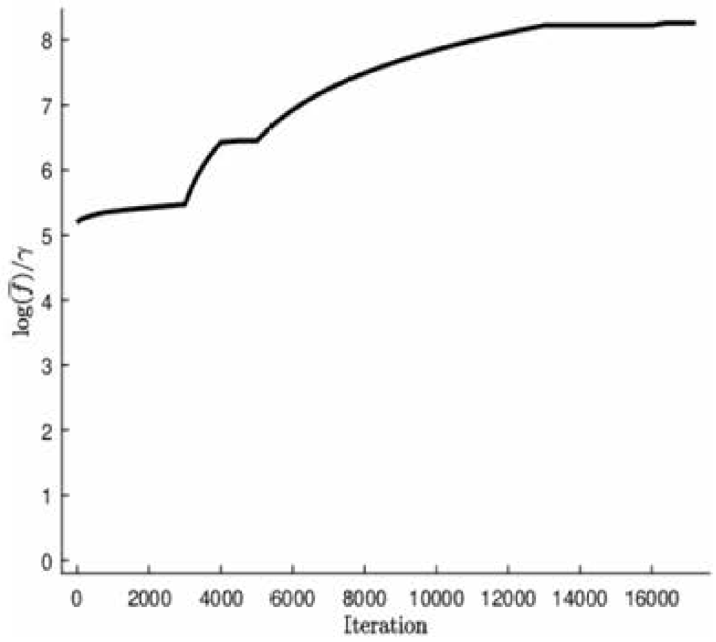
At the beginning of evolutionary adaptation first species dominates and its mortalities was a small.

M=diag(0.0625, 0.0625, ...,0.0625)

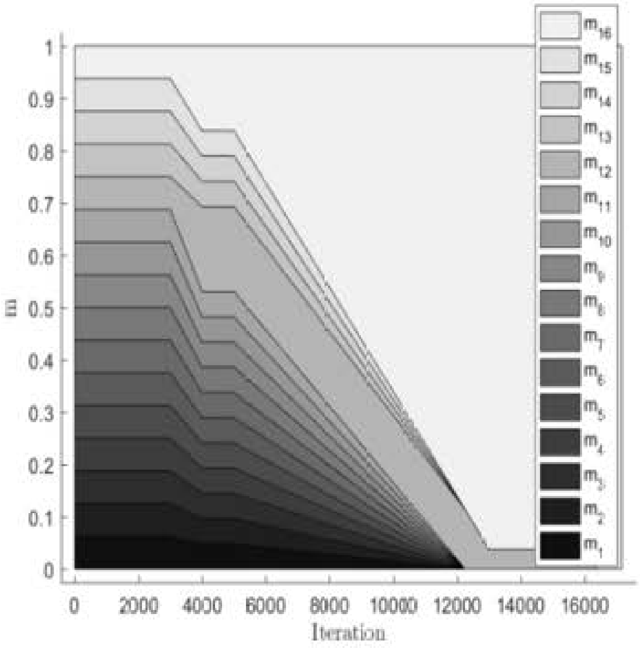
$$D = diag(0.1, 0.001, 0.001, 0.00051, 0.001, 0.00051, 0.00051, 0.00034, 0.001, 0.00051, 0.00051, 0.00034, 0.00051, 0.00034, 0.00034, 0.00030).$$

After evolution dominate the last one: m16=1. Fitness increased by almost 1.6 times.

Example 2

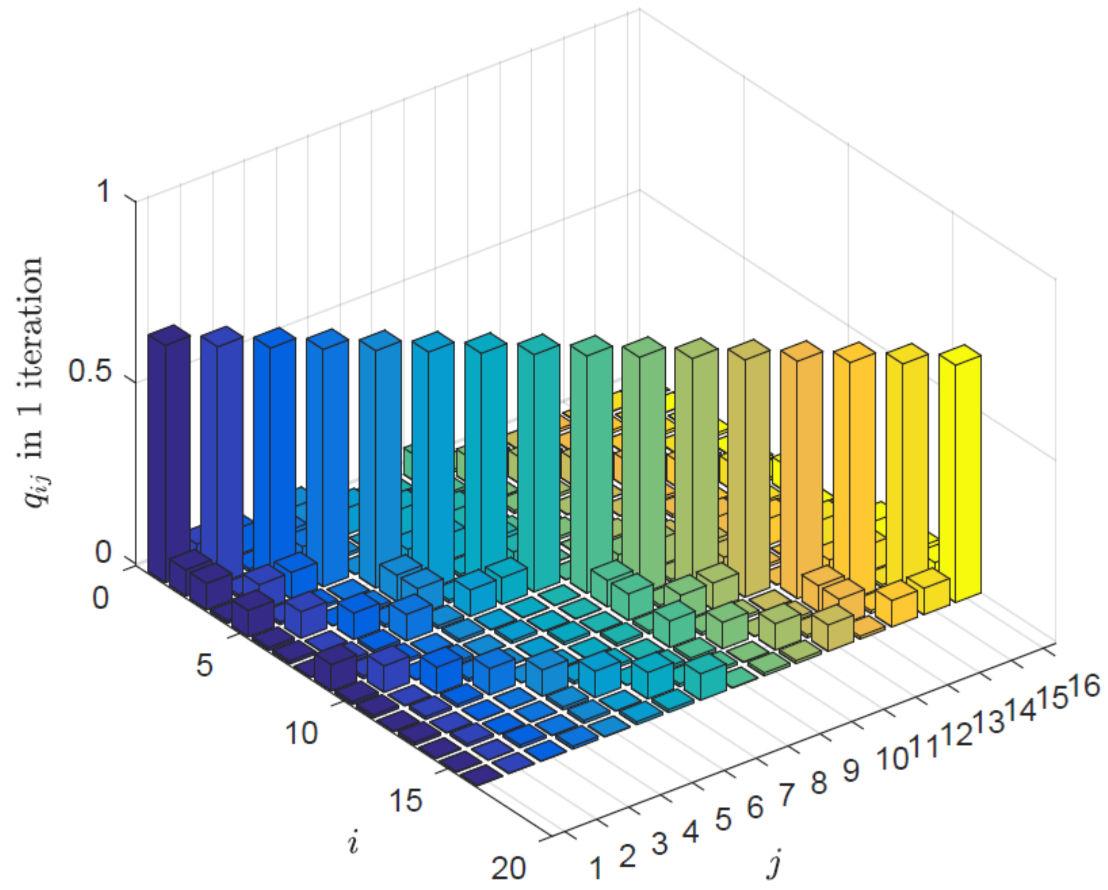


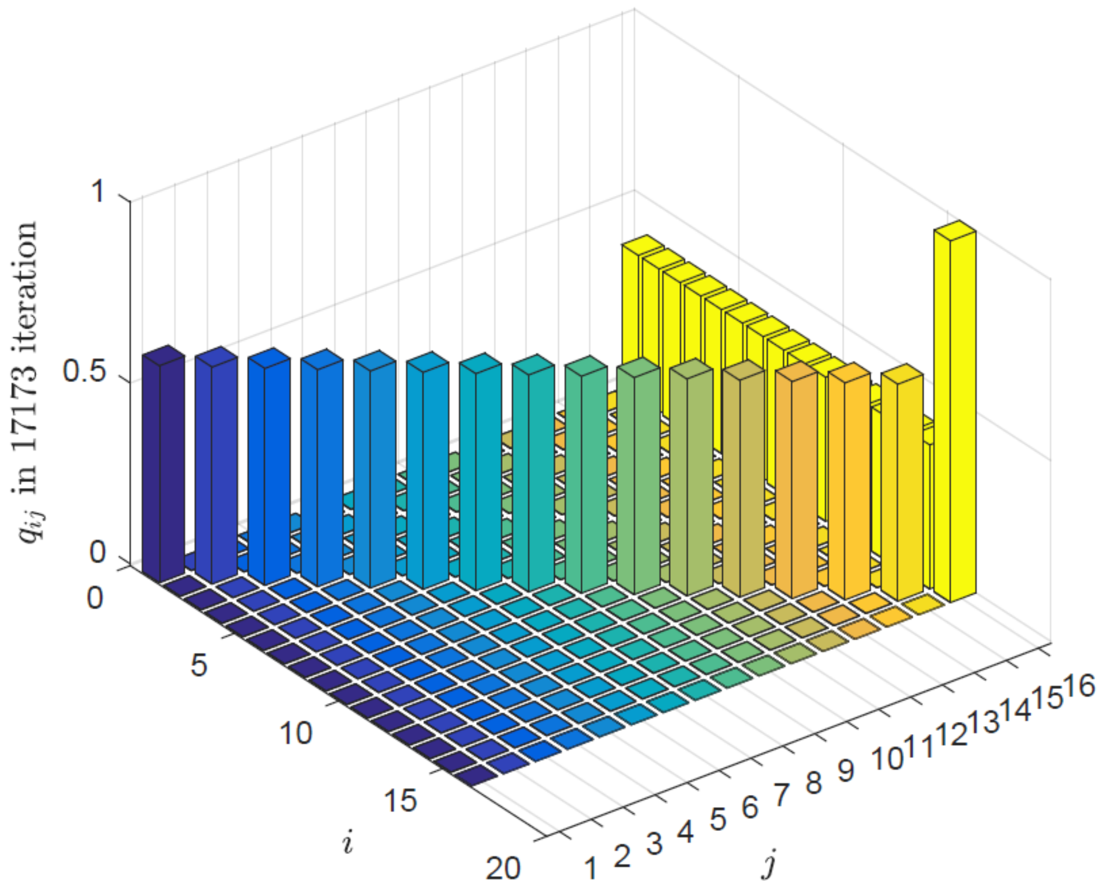
Example 3(subsequent $\mathbf{M}$ and $\mathbf{Q}$ changes): The mean fitness value changing over evolutionary time, which is represented by the number of iterations



Example 3(subsequent $\mathbf{M}$ and $\mathbf{Q}$ changes): Dynamics of the fitness landscape parameters over evolutionary time: fitness matrix values m_i in steady-states with respect to the number iterations

Example 2. The result of the iteration algorithm of evolutionary process: fitness matrix change





Open Crow-Kimura system with competition

$$\mathbf{Q}_N = \begin{pmatrix} -N & 1 & 0 & 0 & \dots & 0 & 0 & 0 & 0 \\ N & -N & 2 & 0 & \dots & 0 & 0 & 0 & 0 \\ 0 & N-1 & -N & 3 & \dots & 0 & 0 & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & 0 & 0 & \dots & 3 & -N & N-1 & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 & 2 & -N & N \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 & 1 & -N \end{pmatrix}$$

$$\mathbf{M} = diag(m_1, m_2, \dots, m_{N+1})$$

$$\mathbf{D} = diag(d_1, d_2, \dots, d_{N+1}) \text{ death rate matrix}$$

$$\mathbf{B} = (\beta_{ij})_{i,j=1}^{N+1},\ det|\mathbf{B}| \neq 0,\ \beta_{ij} \geq 0,\ i,j = \overline{1, N+1} \text{ competition matrix}$$

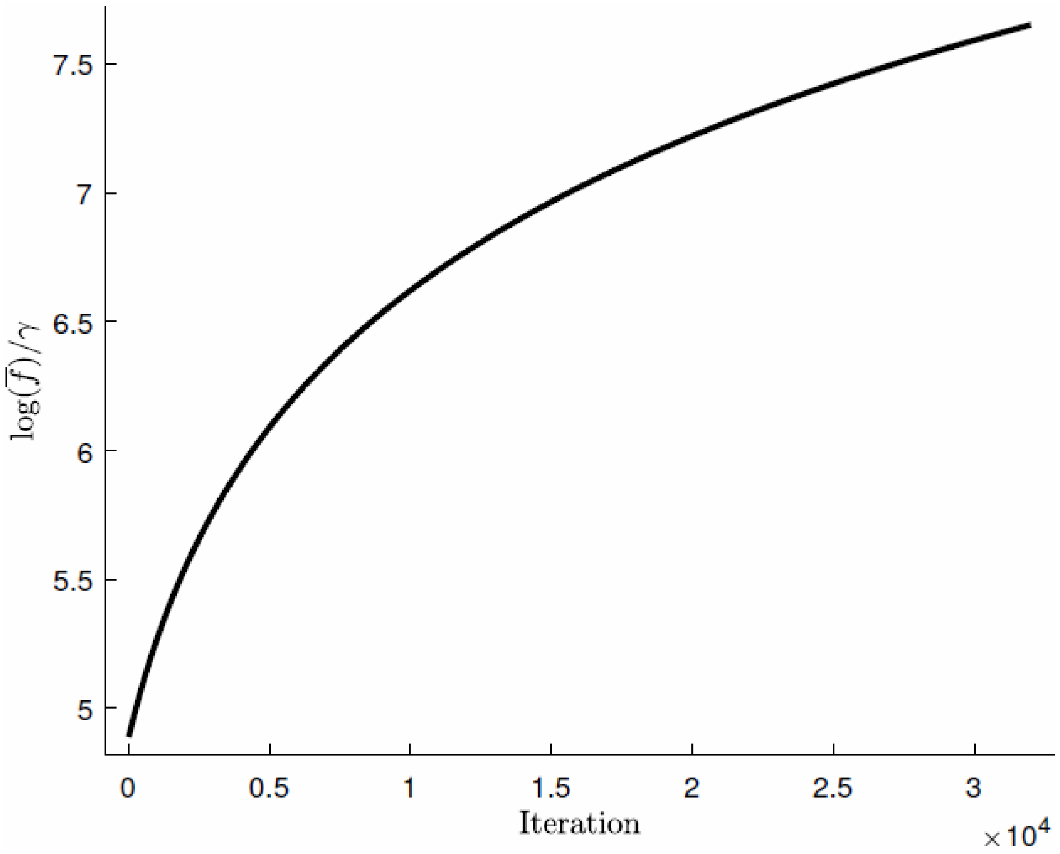
$$\frac{dv_i}{dt}(t) = \varphi(S(\mathbf{v}(t)))((\mathbf{M} + \mu\mathbf{Q}_N)\mathbf{v}(t))_i - d_i v_i(t) - (\mathbf{B}\mathbf{v}(t))_i v_i(t),$$

$$S(\mathbf{v}(t)) = \sum_{i=0}^{N+1} v_i(t).$$

The mean fitness of the system is defined by the expression

$$f(\mathbf{v}) = \begin{cases} 0, & S(\mathbf{v}) = 0, \\ \dfrac{(\mathbf{m}, \mathbf{v})}{(\mathbf{d}, \mathbf{v}) + (\mathbf{B}\mathbf{v}, \mathbf{v})}, & S(\mathbf{v}) > 0. \end{cases}$$

Example 3

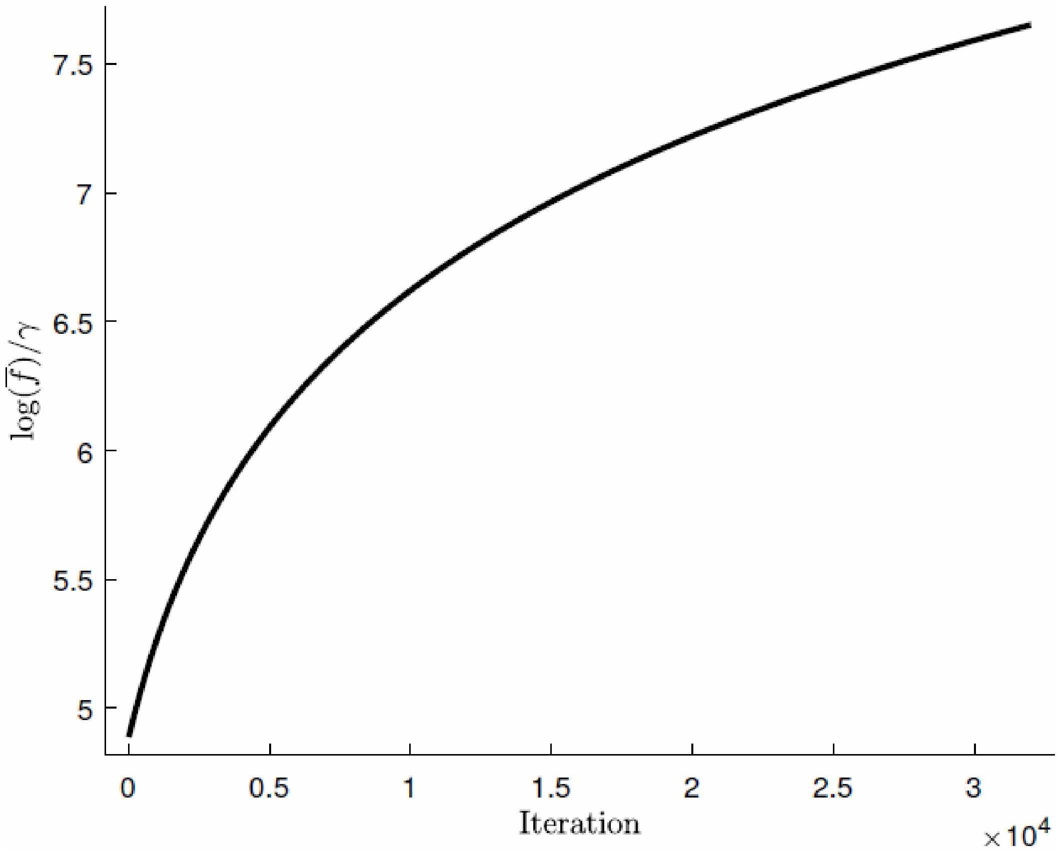


$\varphi(S(\mathbf{u})) = exp\left(-\gamma \sum_{i=1}^{16} u_i\right), \gamma = 1$. Competition matrix is given as $\mathbf{B} = \{b_{ij}\}_{i,j=1}^{16}$, $b_{ii} = 10^{-4}$, $b_{ij} = 10^{-5}$, $i \neq j$, $i, j = \overline{1,16}$. Death rates have the values $\overline{d}^0$ =(0.0025, 0.0035, 0.0035, 0.005, 0.0035, 0.005, 0.005, 0.0071, 0.0035, 0.005, 0.005, 0.0071, 0.005, 0.0071, 0.0071, 0.01). The set (11) is introduced by $\check{m} = 2$, $K = 64$. For the simulation process, we take the evolutionary time step as $\Delta\tau = 10^{-3}$.

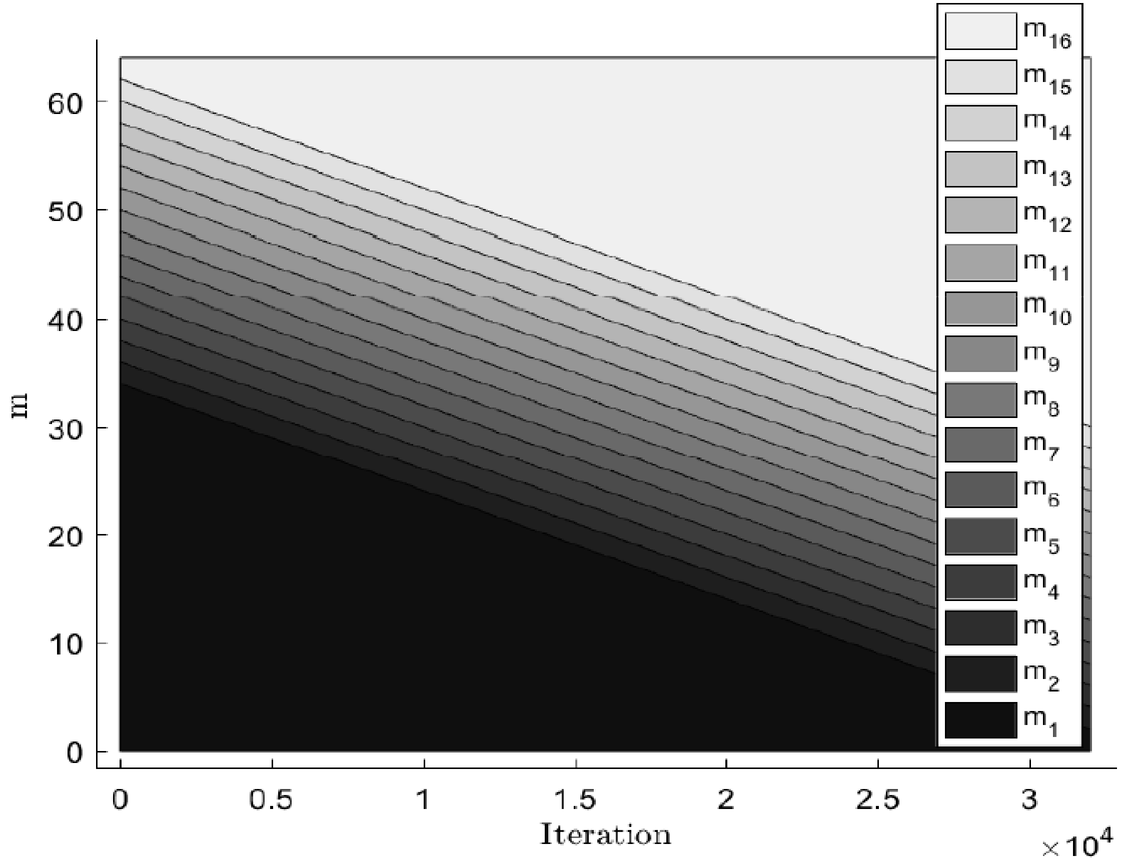
The fist type has both numerical and competitive advantage: $m_1^0 = \max_{i=\overline{1,16}} m_i^0 = 6$, $d_1^0 = \min_{i=\overline{1,16}} d_i^0 = 0.0025$.

According to our numerical analysis, the fitness landscape adaptation process during the mean fitness maximization with the parameter $\Delta\tau$ was completed after 28002 iterations of algorithm described in 3. At the initial time, the steady-state distribution of the population has the value $\overline{\mathbf{u}}_0$ =(3.2777, 0.7526, 0.7526, 0.1504, 0.7526, 0.1504, 0.1504, 0.0282, 0.7526, 0.1504, 0.1504, 0.0282, 0.1504, 0.0282, 0.0282, 0.0051). The mean fitness increased 6.1 times.

Example 3



7.5
7
6.5
6
5.5
5
$\log(\overline{f})/\gamma$
0
0.5
1
1.5
2
2.5
3
Iteration
$\times 10^4$



60
50
40
30
20
10
0
m
0
0.5
1
1.5
2
2.5
3
Iteration
$\times 10^4$
m_{16}
m_{15}
m_{14}
m_{13}
m_{12}
m_{11}
m_{10}
m_9
m_8
m_7
m_6
m_5
m_4
m_3
m_2
m_1

Conclusion

- Proposed evolutionary adaptation process of the fitness landscape and mutation matrix using the adopted hypothesis showed change in the population structure based on birth-death balance and competition interaction.
- During evolutionary adaptation, the mean fitness considerably increase.
- Replicator systems react on stress with population diversification, providing variation landscapes and mutations together with the fitness growth.

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Спасибо за внимание!

Questions?