Mathematical Model of Cancer Therapy with Multiplicity of Phenotypes and Mutation

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Model Assumptions

Motivation:
What is an appropriate therapeutic strategy in cancer treatment, if we use the drug which targets only the wild-type and genetically closest cells?
Key assumptions:

- Mathematical model is based on the M. Eigen's quasispecies theory
- Population size is growing
- The mutation-selection process is governed by the fitness landscape adaptation: the **maximization of the mean fitness value**
- The fitness landscape changes slower than systems dynamics, which allows considering **a steady state**
- The therapeutic drug eliminates the wild-type and its neighboring phenotypes from the population with a decrease in the mean fitness so that the change of the landscape can be understood as **a reaction of the system** balancing fitness value
- There is **a competition** between different types in the population, and the wild-type dominates in it
- Each type is associated with its **death rate**, where the wild-type has the lowest one in the absence of therapy.

Open Quasispecies System: Problem Statement

The system of equations:

$$\begin{aligned} &\frac{du}{dt} = \exp(-\gamma S) Q_m u - Du, \quad Q_m = QM, \quad u = (u_1, u_2, \ldots, u_n), \\ &u(0) = u^0 > 0, \quad S = \sum_{i=1}^{n} u_i(t), \quad \gamma > 0 \end{aligned} \tag{1}$$

- The growing population consists of n different genotypes, each one corresponds to a binary genetic sequence with a fixed length
- $u_i(t)$ denotes the number of i-th subpopulation (type)
- Total population size: $S(t) = \sum_{i=1}^{n} u_i(t)$
- Mutation in the system: $Q = ||q_{ij}||_{i,j=\overline{1,n}}$, where q_{ij} is the probability of replication $i \to j$.
  If we introduce the probability of errorless replication p and Hamming distance d_{ij}, then
  $$q_{ij} = p^{l-d_{ij}}(1-p)^{d_{ij}}, \quad 0 < p < 1,$$
- Selection in the system: $M = diag(m_1, m_2, \ldots, m_n)$, where $0 \le \check{m} \le m_i \le \hat{m}$, — replication rates
- Death rates: $D = diag(d_1, d_2, \ldots, d_n)$, $0 \le \check{d} \le d_i \le \hat{d}$

Analysis of Open System

Definition

Let us denote by $f(t)$ the mean fitness of the system (1) at the time t:

$$f(t) = \frac{\sum_{i=1}^{n} u_i(t) m_i}{\sum_{i=1}^{n} d_i u_i(t)} = \frac{(m, u(t))}{(Du(t), I)}, \quad I = (1, 1, \ldots, 1) \in \mathbb{R}^n$$

Theorem

The solution of the system (1) is a smooth nonnegative function. If $\check{d} < \hat{m}$, then functions $S(t)$ and $f(t)$ are bounded for $t \geq 0$.

Statement

If the matrices $Q_m - D$ and $M - D$ are nonnegative and $m_i \geq d_i, \quad i = \overline{1, n}$, then functions $u_i(t)$ and $S(t)$, $i = \overline{1, n}$ monotonically increase for $t \geq 0$.

Steady-state Mean Fitness Variation

- Let $\overline{u}$ denote a steady-state distribution of the system (1):

$$D^{-1}Q_m\overline{u} = \lambda\overline{u}, \lambda = \exp(\gamma\overline{S}), \quad \overline{S} = \sum_{i=1}^{n} \overline{u}_i$$

- We use $\mathbb{M} = \{(m_1, m_2, \dots, m_n) : \sum_{i=1}^{n} m_i = M_0\}$ for the set of different fitness landscapes with a finite sum $M_0 > 0$.

The problem statement:
To maximize the mean fitness function $\bar{f}$ in a steady-state over the set $\mathbb{M}$.

Steady-state Mean Fitness Variation

For the fitness value variation in a steady-state $\delta \overline{f}$, we obtain:

$$\delta \overline{f} = (\delta Q_m \overline{u}, \overline{v}), \tag{2}$$

where $\delta Q_m = \{q_{ij} \delta m_j\}$ and $\bar{v}$ is an adjoint vector of the corresponding eigenvalue problem.

It has a linear form:

$$\delta \overline{f} = (\delta m, c), \quad c = diag(\overline{u}) Q^T \overline{v}, \tag{3}$$

where

$$\sum_{j=1}^{n} \delta m_j = 0, \quad \max(-\varepsilon I, -m) \leq \delta m \leq \varepsilon I \tag{4}$$

Example: Numerical Simulations

Parameters:
$n = 16$, $\gamma = 1$, $m_1^0 = 10, m_i^0 = 0$, $p = 0.9$, $\varepsilon = 0.000625$, After 16009 iteration there fitness landscape changes: $m_5 = 10, m_i = 0$.

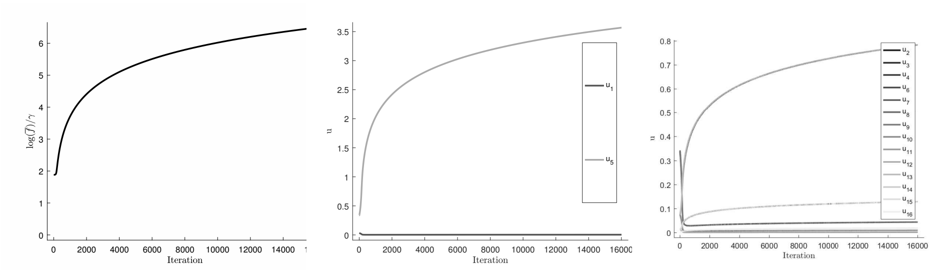

Figure: 1) Fitness value $\overline{f}$ in a steady-state changing over the iteration number 2) The number of the wild-type sub-population 3) The number of the other sub-populations

System with Therapy

$$\begin{aligned}
\frac{du_1}{dt} &= \exp(-\gamma S)(Q_m u)_1 - d_1(h)u_1 \\
\frac{du_i}{dt} &= \exp(-\gamma S)(Q_m u)_i - d_i(h)u_i - \beta_i u_1 u_i, \quad i = \overline{2, n} \\
\frac{dh}{dt} &= U(t) - \alpha h \\
u_i(0) &= u_i^0, \quad i = \overline{1, n}, \quad h(0) = 0, \quad S = \sum_{i=1}^{n} u_i(t)
\end{aligned} \tag{5}$$

Where

$$(Q_m u)_i = \sum_{j=1}^{n} q_{ij} \alpha_j u_j, \quad i = \overline{1, n}$$

$h(t)$ — the drug concentration function
$U(t)$ — the control therapy function: $0 \leq U(t) \leq R$
α — the dissipation coefficient
$d_i(h) = d_i^0 + k_i(h) = d_j(h) = d_j^0 + \dfrac{d_0 h}{1 + \mu d_{1j}}$ — the death rates β_i — the competition coefficient

Therapeutic strategy

Applying the result obtained for the system, we derive the following strategy:

1. the first intensive therapy stage: $U(t) = R$ for $0 \leq t \leq T$, where we observe the fitness landscape change
2. the relaxation stage: $U(t) = 0, \quad T \leq t \leq T_1$
3. the second intensive therapy stage: $U(t) = r, \quad 0 \leq r \leq R$ while maximizing the steady-state mean fitness

Example 2: Numerical Simulations for Therapy

Parameters: $n = 16$, $p = 0.9$, $\sum_{i=1}^{n} m_i = 10$, $\beta_i = 0.0001$, $\varepsilon = 0.000625$, $T = 3000$, $T_1 = 6000$.

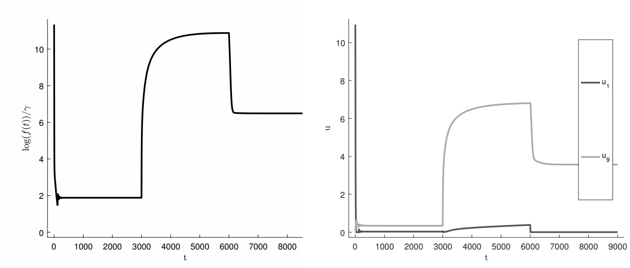

Figure: 1) Fitness value $\overline{f}$ in a steady-state changing over tine 2) The number of sub-populations 1 and 9

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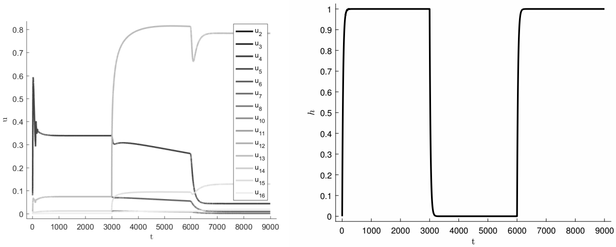

Figure: 1) The number of sub-populations 2) The amount of drug

Example 3: Numerical Simulations for Therapy

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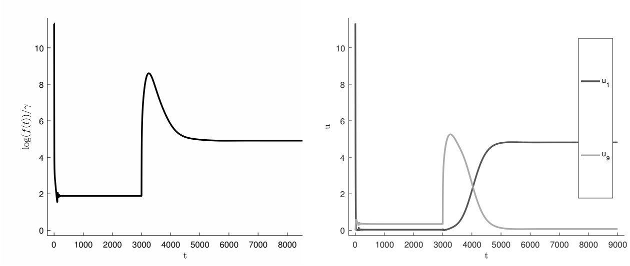

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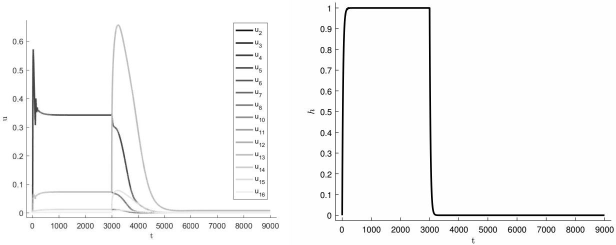

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Do you have any questions?