Optimization Aspects of Carcinogenesis

B. Brutovsky\textsuperscript{a} and D. Horvath\textsuperscript{b,c}

\textsuperscript{a}Department of Biophysics, P. J. Safarík University, Jesená 5, 04154 Kosice, Slovakia
\textsuperscript{b}Centre de Biophysique Moléculaire, CNRS; Rue Charles Sadron, 45071 Orléans, France and
\textsuperscript{c}Department of Physics, Faculty of Electrical Engineering and Informatics, Technical University, Letná 9, 042 00 Kosice

Any process in which competing solutions replicate with errors and numbers of their copies depend on their respective fitnesses is the evolutionary optimization process. As during carcinogenesis mutated genomes replicate according to their respective qualities, carcinogenesis obviously qualifies as the evolutionary optimization process and conforms to common mathematical basis. The optimization view accents statistical nature of carcinogenesis proposing that during it the crucial role is actually played by the allocation of trials. Optimal allocation of trials requires reliable schemas’ fitness estimations which necessitate appropriate, fitness landscape dependent, statistics of population. In the spirit of the applied conceptual framework, features which are known to decrease efficiency of any evolutionary optimization procedure (or inhibit it completely) are anticipated as “therapies” and reviewed. Strict adherence to the evolutionary optimization framework leads us to some counterintuitive implications which are, however, in agreement with recent experimental findings, such as sometimes observed more aggressive and malignant growth of therapy surviving cancer cells.

INTRODUCTION

The term cancer refers to hundreds types of neoplasms which share specific prototypical traits, summarized by Hanahan and Weinberg \cite{1}, collectively leading to malignant growth. During the past few decades molecular biologists have produced much cancer-related data which has shown cancer as an extremely stochastic, heterogeneous and complex disease \cite{2}. To analyze them, cancer research applies many concepts originally developed in different branches of science, such as applied mathematics, nonlinear dynamical systems, and statistical physics. At present, evolutionary nature of carcinogenesis is accepted and implications for cancer robustness (exemplified by resistance to therapy) are often emphasized \cite{3,4}. Darwinian view to carcinogenesis implicitly puts genetic (and epigenetic) changes into microenvironmental context \cite{5}. Consequently, tumor microenvironment is viewed as an eventual target for chemoprevention and cancer reversion \cite{6,7}. On the other hand, anticancer research and therapy concentrate mainly on molecular data and tend to overlook its evolutionary nature.

Optimality model applied in experimental evolution \cite{8} describes the evolution as simple generalized trade-offs, presuming that genomes adapt successfully and freely enough and, consequently, genetic details become irrelevant. Mathematical approaches to carcinogenesis often apply concepts of feedback and optimal control theory \cite{9} instead of molecular or genetic data. Komarova et al. \cite{10} have solved the optimization problem for cancerous growth and proposed optimal strategies. However, as they state, the ideal (optimal) strategy may be not realistic due to many constraints in nature which escape modeling, but can make a strategy impossible.

In the paper we concentrate on the abstract mechanisms of attaining an optimal strategy instead of the strategy itself. We view any process in which solutions replicate with errors and numbers of their copies depend on their respective qualities as an evolutionary optimization process. As carcinogenesis conforms the above definition, we identify it with an evolutionary optimization process and apply concepts and results of the long lasting research in the evolutionary optimization \cite{11}. Keeping in mind an eventual therapeutic application, we focus on those aspects of evolutionary optimization which decrease or inhibit efficiency of the optimization process. Strict adherence to the optimization framework has led us to counterintuitive implications.

EVOLUTIONARY OPTIMIZATION

In the optimization theory, the quality of a solution is usually defined explicitly in the form of a fitness function (also fitness landscape or fitness), quantifying how well a candidate solution meets required criteria. The ultimate aim of the optimization procedure is to find a solution for which the fitness function receives optimum value. Large group of optimization algorithms, called evolutionary algorithms (EA), performs the task by mimicking biological evolution implementing the genetic-like mechanisms, such as mutation, selection and reproduction. Applying EA in various engineering optimization applications has enabled to recognize those aspects of fitness landscapes which support efficient evolutionary optimization and, at the same time, those which prevent it. Theoretical analysis of the most popular
Let’s have 4 binary strings at the respective position:

\[
\begin{align*}
\text{alphabet schema can be easily constructed over the ternary schema Y.} \\
X \text{ and the strings B and D are the instances of the schema Y. It is usually said that strings B and C are instances of the schema X. The schema Y in the strings B and D. It is usually said that strings B and C are instances of the schema X. And the strings B and D are the instances of the schema Y.}
\end{align*}
\]

Theoretical analysis of the process enabled to identify the driving force behind the biological-like manipulations with binary strings representing parameters of the model. It was recognized that the population-based optimization algorithm is driven by the fitnesses of the correlations of bits in the binary strings (called "schemas"). The schema can be viewed as a bit pattern over the bit positions in the string. If the bit alphabet \(\{0,1\}\) is assumed, the schema can be easily constructed over the ternary alphabet \(\{0,1,*\}\), where \(*\) matches both, 0 and 1, at the respective position:

Let’s have 4 binary strings

\[
\begin{align*}
A & \quad 10100101 \\
B & \quad 01011011 \\
C & \quad 11100010 \\
D & \quad 00010001
\end{align*}
\]

and two schemas, X and Y

\[
\begin{align*}
X & \quad *1***01* \\
Y & \quad 0*01***1
\end{align*}
\]

The schema X is contained in the strings B and C, the schema Y in the strings B and D. It is usually said that strings B and C are instances of the schema X and the strings B and D are the instances of the schema Y.
sporadically populated, or even empty. The role of the observed increase of population heterogeneity in changed environment is well interpretable using the terms of evolutionary optimization, namely evolution algorithms in dynamic environments. Therefore, mechanisms of heterogeneity maintenance have been developed in optimization theory and deeply studied \[12\]. Efficient transition from the old optimum to optimum(a) in a new fitness landscape requires i) detection of the fitness landscape change, and ii) response to that change \[12\]. For that, candidate solutions must be appropriately distributed in the search space so that evolutionary algorithms could perform representative statistical sampling to determine reliable schemas’ fitnesses estimates which are necessary for optimal allocation of trials during optimization. If there are no (or too few) evaluations in the changed part of the fitness landscape, the change goes undetected.

### iii) Deceptiveness of fitness landscape.

To answer the question which fitness landscapes are GA-hard, Bethke \[13\] expressed a fitness function as a linear combination of Walsh monomials and showed the relationship between the schema’s fitness and Walsh coefficients. Consequently, he applied the Walsh transform to characterize functions as easy or hard for GA optimization. It has been understood that the principal problem for GA optimization is the class of deceptive fitness functions, in which lower order (lower number of defined bits) schemas lead the search towards bad higher order schemas. Goldberg showed the possibility of constructing high-order deceptive functions using low-order Walsh coefficients in special cases \[14\].

### CARCINOGENESIS AS EVOLUTIONARY OPTIMIZATION PROCESS

Exact convergence analysis of EA requires much better mathematical definition of the relevant fitness landscape and more obvious parametrization of a solution than one typically disposes with biological systems. Regarding the above introduced schema formalism a few differences between CGA and carcinogenesis should be mentioned. At first, carcinogenesis is an asexual process, therefore constant $P_e$ in (1) equals zero. The second difference is that no spatial relation between offsprings and their parents is assumed in (1). The third difference regards unknown parametrization - obviously higher structures than nucleotides (or genes) are relevant. Nevertheless, neither of the differences puts in doubt importance of reliable estimates of the schemas’ fitnesses for optimal allocation of trials during carcinogenesis. In addition, as often used in evolutionary optimization practice, we use the term optimum solution in a sense of a winning solution, i. e. the best solution obtained after reasonable (or affordable) long optimization, instead of exact, mathematically proved, solution.

### Fitness landscape

The term represents central concept in biological evolution as well as in optimization theory \[15\]. In biology, the fitness is usually understood in a sense of “reproduction” fitness, meaning that the more copies solution has the more fit it is (and vice versa), and obtains factual meaning in specific environment and time scales. During the genome’s evolution selection acts at two different hierarchical levels respective to the two units of replication: cells and organisms (multicellular bodies). As a result, the genome is the trade-off between two processes: i) maximization of the multicellular (organismic) reproduction fitness (acting during millenia), and ii) maximization of cellular reproduction fitness (acting during individual lifespan), respectively. The former process presumes social cooperation of cells (such as limited replicative potential, production of growth signals, sensitivity to antigrowth signals, cellular senescence, apoptosis, etc.) and severe prohibition of the cells' selfishness, the latter favors selfishness instead of cooperation \[16\]. The trade-off is mediated by the initial genomic stability, evolved to postpone short scale evolution in the respective environment beyond reproduction period of the respective organism.

### Heterogeneity

Extensive genomic studies by Sjöblom et al. \[2\] have clearly demonstrated extreme heterogeneity in colorectal cancer tumors. They have revealed that mutational patterns in samples of colorectal cancers are unexpectedly individualistic, with none of the three most often mutated genes (APC, p53, K-ras) mutated in all the samples \[17\]. It has been shown that sets of mutated genes in two samples of colorectal cancers overlap to only a small extent and it is anticipated to be general feature of most solid tumors \[18\]. Similarly, resuming studies in breast and renal cancer, Gatenby and Frieden \[19\] concluded that probably no prototypical cancer genotype exists and every tumor seems to possess a unique set of mutations indicating that multiple genetic pathways may lead to invasive cancer as would be expected in a stochastic non-linear dynamical system. Clonal diversity in a subset of patients with early stage haematopoietic malignancy has been demonstrated and it has been shown that such clones may arise independently \[20\]. It has been also observed \[21\], that time to disease progression and overall survival after treatment were significantly shorter in those patients with EGFR heterogeneity. Maley et
al. have demonstrated that clonal diversity predicts progression to cancer and that accumulation of viable clonal genetic variants is a greater risk for progressing to cancer than homogenizing clonal expansion. Mathematical model by Komarova et al. shows that tumors thrive when cancerous cells mutate to speed up malignant transformation, and then stay that way by turning off the mutation rate. Interpretation of heterogeneity is crucial for understanding of carcinogenesis. It can be, in extreme cases, interpreted either as noise hiding a common pattern, or redundancy (all the cases are causative as a whole, no common pattern exists). If interpreted as a noise, the effort to filter it out by analyzing as many cancer cases as possible to see the common mechanism is justified. If, however, each sample is interpreted as a unique, nevertheless causative set of genes, alternative approaches are needed. The above mentioned studies at genetic level indicate that heterogeneity should be interpreted in the latter way. They report that every tumor harbors a complex combinations of low-frequency mutations thought to drive the cancer phenotypes. Consequently, a strategy to study mechanisms of cancer by reducing heterogeneity may be assumed to be a flawed approach.

**Optimization behind**

Putting fitness landscape and heterogeneity into optimization context, the wild-type genome represents optimum solution in the respective past fitness landscape; its further optimization in unchanged fitness landscape is, by definition, inhibited. After the fitness landscape has changed, optimization of the genome becomes possible. Regarding the structure of the fitness landscape, during the optimization two fitness landscapes are sampled, each for the respective unit of replication - organism or cell. As there are many cellular fitness evaluations during the organism’s lifetime, only cellular fitness landscape may be sampled representatively enough to provide reliable schemas’ fitnesses which result in optimal allocation of trials driving the short time evolution of the genome into an optimum in the changed cellular fitness landscape. The organismic fitness landscape, selecting for intercellular cooperation, does not apply during the lifetime of the body and the optimization process is driven purely by cellular fitness landscape for which the intercellular cooperation is not selectable trait. From this point of view, any short-scale change of the fitness landscape is not only mutagenic but also carcinogenic, as it selects for destroying intercellular cooperation. Applying the quasispecies model, Forster and Wilke have demonstrated that competitive dynamics of finite populations of as few as two strains, adapted to the long-term and short-term environment changes, respectively, is quite complex.

Heterogeneity represents crucial aspect of carcinogenesis. At the same time, in engineering applications, evolutionary optimization starts with heterogeneous, typically randomly generated, initial population of candidate solutions. In the case of stationary fitness landscapes, heterogeneity decreases towards some minimum level as the optimization procedure converges to the best solution (the analogy with a homogenizing clonal expansion inflicts itself), despite keeping constant mutation rate. On the other hand, evolutionary optimization in changing fitness landscapes shows importance of avoiding total homogenization. In computer experiments where mutation rate is not exempted from optimization, its increase (followed by the increase of heterogeneity) is observed after the fitness landscape has changed. It has been reliably demonstrated that rapid or extreme environmental change leads to the selection for greater evolvability. Similarly, selection of mechanisms for increased mutation rate in biological systems, like RNA viruses, in unstable environments was reported. Donaldson-Matasci et al. have shown that optimal amount of diversity depends on environmental uncertainty which can lead to the evolution of either generalist or specialist strategy.

Cancer-susceptibility genes are classified as caretakers, gatekeepers and landscapers. Mutations in caretakers leads to genomic instability, mutated gatekeepers are responsible for increased cellular proliferation and landscapers defects generate an abnormal stromal environment. In general, the cancer-susceptible genes govern statistics of the cell population, either directly (caretakers and gatekeepers), or indirectly by maintaining fitness landscape (landscapers). Within the frame of evolutionary theory it is understood that heterogeneity confers cancer cells population with the ability to cope with environment uncertainties. Optimization theory derives efficiency of an optimization method from its ability to allocate appropriately future trials. The schema theorem guarantees giving at least exponentially increasing number of trials to the observed best building blocks. Implicitly, optimal allocation of trials between alternative solutions requires as reliable schemas’ fitnesses estimates as possible. In addition, as evolving clones implicitly undergo competition, the schemas’ fitnesses must be determined as fast as possible. For that, representative (regarding the respective fitness landscape) statistics of the population must be at hand. The ability of the clone to evolve (or not) towards representative statistics comes from specific defects in cancer susceptibility genes.

Causality in evolutionary processes is actually provided by the feedback from environment. The evolutionary process is a fitting procedure, which is the method of solving (typically ill-posed) inverse problems. Enormous genetic heterogeneity of
cancers indicates that most cancer occurrences are the unique solution of the fitting problem. It implies that the fitting problem solved by cancer is highly underdetermined, which results in the arbitrariness of a fit (i.e., model) and it is consistent with the metaphoric conclusion by Witz and Levy-Nissenbaum [8], who stated "...the extreme complexity of the signaling cascades operating in the microenvironment and the interactive cross-talk between these cascades, generates the feeling that 'anything that can happen - it will'.

**IMPLICATIONS FOR THERAPY**

Traditional therapies are based on comparisons of cancerous and non-cancerous cells, which, by definition, presumes existence of reliable enough (in an ideal case dichotomic) splitting into two respective groups. Consequently, therapeutic actions are taken to attack the tumor cells group (cancer cell-kill paradigm). It is implicitly believed that therapeutic efficiency depends on how close to dichotomic the splitting is. For instance, the two main therapeutic treatments, chemotherapy and radiation, exploit the enhanced sensitivity of cancer cells to DNA damage. Novel targeted and gene therapies go even further - they are aimed to interfere directly with the specific molecules or genes participating in carcinogenesis (the 'magic bullet' concept). The effort to find the criterion(a) enabling to approach to dichotomic splitting as close as possible is omnipresent in cancer therapy. Varshavsky [33] proposed the therapy which distinguishes cancer and normal cells according to harboring (or not) homozygous DNA deletions. Skordalakes [34] points out that inappropriate activation of a single enzyme, telomerase, is associated with the uncontrollable proliferation of cells observed in as many as 90% of all of human cancers and proposes that the high-resolution structure of the enzyme will be the key to efficient anti-cancer therapies.

However, putative existence of dichotomic splitting is in contradiction with the evolutionary nature of carcinogenesis which, as any other evolutionary process, crucially depends on the variability of traits observed at many levels [2, 14, 35, 36]. Extreme tumor cells heterogeneity gives cancer robustness, exemplified by the resistance to therapy [3, 4], and it is the most tormenting problem in cancer research to which therapies and experimental models must face [37, 38]. Heng et al. [25] emphasize the key role of heterogeneity by stating that without heterogeneity, there would be no cancer.

Below we present specific insights and implications for anti-cancer therapy stemming from the above presented optimization view to carcinogenesis. Some of them are intuitive and consistent with established anti-cancer therapies, some others are quite counterintuitive and, hopefully, novel and put in question some current trends in the development of anti-cancer therapies. Within the frame of the above outlined identification of carcinogenesis as the evolutionary optimization process, therapy is a purposeful effort to decrease the efficiency of that optimization process or, hopefully, inhibit it completely. For that purposes, we have listed above the three most frequent obstacles to the efficient evolutionary optimization, stemming from validity of the schema theorem [11]. These are: too large sampling errors, dynamic (or changing) fitness landscapes and deceptiveness of fitness landscape. In all the cases the estimation of the schemas’ fitnesses is not reliable (or systematically wrong) which prevents the optimization process to allocate its trials optimally.

**i) Too large sampling errors.** It is understood that heterogeneity plays a central role in evolution and provides species (or clones) with the capacity to cope with environmental uncertainty. On the other hand, if it exceeds a certain threshold, deleterious effects outweigh the above selection advantage. The existence of the critical mutation rate in evolution beyond which Darwinian selection does not operate has been predicted by Eigen’s theory of quasispecies [26]. Sole and Deisboeck [39] applied the simple mathematical model of quasispecies dynamics to quantify the upper limit of affordable genetic instability (error threshold) in cancer cells population, beyond which genetic information is lost. Consistently with the fact that tumor cells have defective stability pathways, Cahill et al. proposed that tumor cells could be target for direct attack by instability drugs [40]. However, from the point of view of the evolutionary optimization theory, competitiveness of the clone depends on its capability to allocate its further trials among emerging alternatives [11] which requires representative statistics of the cells population, not merely specific genetic (in)stability. Therefore we speculate that forced increase of sampling errors by instability drugs, abruptly shifting population statistics away from the optimal in the respective fitness landscape, would be compensated by selecting for change(s) in other evolutionary attribute(s), such as reproduction rate, cellular mortality rate, internal stability (the mechanism does not matter at this point), etc.

**ii) Dynamic fitness landscape.** Changing the fitness landscape can be a double edged sword. On the one hand, cancer cells reveal increased adaptivity enabling them to respond to environmental changes to keep high (reproductive) fitness. On the other hand, higher adaptivity of cancer cells can be therapeutically exploited, as outlined by Maley et al. [41].
They proposed to select for the cells sensitive to cytotoxins before applying cytotoxic therapy.

**iii) Deceptiveness of fitness landscape.** Deceptive landscapes can be interpreted as the landscapes in which correlations of traits systematically lead away the search from the global optima. To our knowledge, there is no therapeutic approach explicitly exploiting deceptiveness of the fitness landscape. We anticipate that combining biological intuition, the results of mathematical analysis of deceptive fitness landscapes [14] and digitized evolution [42] can bring novel insights into the evolution of cancer phenotype.

**Is therapy a penalty function?**

From the evolutionary optimization point of view therapy is a purposeful change of the fitness landscape, namely decrease of reproduction fitness in the relevant area of the search (sequence) space at reasonable time scales. All the well established traditional therapies (surgery, radiotherapy and chemotherapy) make an effort to remove all the cancer cells, or, at least, as many of them as possible. Evolutionary optimization theory implies that ultimate therapeutic success depends not only on how many cancer cells survived the therapy, but also on the distribution of the cells in the search space, i.e. statistics of the remaining population. If the population statistics is sufficient for the efficient optimization, the regrowth appears. Below we present eventual counterintuitive consequence of therapy resulting from the optimization facet of carcinogenesis.

It has been reported that therapy-surviving tumor cells are frequently more malignant and aggressive than the initial tumor population [43]. Inhibition of angiogenesis has been envisioned as promising anticancer therapeutic strategy for a long time [44]. Since then, modes of resistance to antiangiogenic therapy, such as evasive and intrinsic resistance, has been reported [45]. It has been found by Paez-Ribes et al. [46] that targeting the vascular endothelial growth factor (VEGF) induces (apart from anti-tumor effects to primary tumor) higher invasiveness and, in some cases, increased lymphatic and distant metastasis. Ebos et al. [47] have found that the VEGFR/PDGFR kinase inhibitor can accelerate metastatic tumor growth and decrease overall survival in mice receiving short-term therapy. Similarly, it has been reported that the resistance to some synergistic drug combinations evolves faster than the resistance to individual drugs [48]. In their review Kim and Tannock [49] report that repopulation of cancer cells after radiotherapy as well as chemotherapy is often accelerated in comparison to untreated cases. The mechanism of this acceleration has not yet been understood.

In the spirit of our work we attribute the above increase of invasiveness and acceleration of the evolution of resistance during repopulation to the optimization facet of carcinogenesis. In engineering applications of evolutionary optimization one often applies *ad hoc* penalty function to disadvantage some part(s) of fitness landscape to accelerate convergence of the process into the optimum in desirable parts (Figure 1). The simplification of fitness landscape enables to perform more representative schema sampling of more promising parts at the same price obtaining more reliable schemas’ fitnesses evaluations resulting, accordingly to (1), in closer-to-optimum allocation of the trials among alternative solutions. If cancer, metaphorically said, solves the optimization problem, the same mechanism applies. We hypothesize, that if therapy does not remove decisive portion of cancer cells (hopefully all), it may, eventually, result in unwanted simplification of fitness landscape for therapy-resistant clone(s). We emphasize, that this hypothesis is aimed purely to interpret sometimes reported cases when accelerated progression of therapy-resistant tumors was observed and it does not propose any alternative to well established therapies.

**DISCUSSION**

Recent experimental evidence shows that heterogeneity, stochasticity and dynamics play in carcinogenesis much more important role than envisioned a few decades ago. This new picture requires corresponding conceptual framework. Here presented evolutionary optimization view to carcinogenesis implicitly includes connection between statistics of cells population and statistics of fitness landscape [27, 51, 51, 52, 53, 54] and applies results of long-standing research in the stochastic evolutionary optimization algorithms, especially in dynamic fitness
Here we have put some of the observed cancer features, such as increased heterogeneity, clonal expansion, consequences of changing the fitness landscape and accelerated evolution of resistance to chemotherapy into optimization scenario. Carcinogenesis is, unquestionably, a physical process. At the same time, it can be formally viewed, as all the evolutionary processes, as the optimization procedure. Straightforward approaches study carcinogenesis and develop anticancer strategies analyzing biochemical or genetic details. In the paper we have speculated that it may be not relevant per se. Instead, we have proposed that cancer relates primarily to the cells population statistics and all the therapies lead (more or less intentionally or explicitly) to its modification. Traditional therapies rely on comparison between cancerous and non-cancerous cells which may be motivated by the long lasting effort to reduce cancer cells population by some straightforward action. Evolutionary view suggests that carcinogenesis could be inhibited by a purposeful modification of evolutionary attributes, such as mutation rate, effective population size or generation time of the self-renewing cells. Nevertheless, except for trivial cases, evolutionary theory does not give instructive enough answer how should be the evolutionary attributes changed. Here presented optimization view to carcinogenesis proposes that the crucial mechanism of cancer progression is, as in any other evolutionary optimization process, optimal (or, more realistically, better than by other clones) allocation of trials, based on more representative population statistics enabling more reliable estimations of schemas’ fitnesses. Efficiency of the schema sampling depends on the number of sampled points and their distribution in the fitness landscape, as well as the cell’s fitness estimation time. These attributes adapt to statistical features of the fitness landscape by selecting respective mutations in genes (a posteriori denoted as cancer-susceptible genes). As, at the same time, efficiency of the sampling determines the cancer’s perspective, we conclude that the therapeutic outcome could be influenced by manipulation with statistical properties of the fitness landscape, such as roughness or dynamics, in a purposeful cancer-inhibiting way. The above statistical view may be relevant especially for advanced malignancies, where high heterogeneity of the cancer cells population enables them to adapt successfully to therapeutically-changed environment. Classifying carcinogenesis as the evolutionary optimization process does not contradict to often presented view of cancer as the result of accumulating specific mutations in the only transformed cell. It emphasizes, however, importance to combine molecular data with statistical view which may play crucial role before and during carcinogenesis. The principal question remains if the novel conceptual framework can be exploited to trigger novel, explicitly anti-optimization based, therapeutic approach.

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