PERSPECTIVE

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Perspective

Can we understand the mechanisms of tumor formation by analyzing dynamics of cancer initiation?

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Abstract – Cancer is a collection of related genetic diseases exhibiting uncontrolled cell growth that interferes with normal functioning of human organisms. It results from accumulation of unfavorable mutations in tissues. While the biochemical picture of how cancer appears is known, the molecular mechanisms of tumor formation remain not fully understood despite tremendous efforts of researchers in multiple fields. New approaches for investigating cancer are constantly sought. In this paper, we discuss a powerful method of clarifying better a more microscopic picture of cancer by analyzing the dynamics of tumor formation. Using physics- and chemistry-inspired discrete-state stochastic description of cancer initiation, it is shown how the mechanisms of tumor formation can be uncovered. This approach is suggested as a powerful new physical-chemical tool for a better understanding of complex processes associated with cancer.

As the second leading cause of mortality, cancer remains one of the most serious health issues in our society [1–4]. Significant resources that included large funding, concentrated research efforts and multiple public campaigns have been devoted to fighting cancer in the last 100 years. These activities already led to huge advances, both in understanding the origins of tumor formation as well as in lowering of the dangers of cancer for human population [1–5]. It has been reported that in the last 30 years the cancer death rate in the USA has decreased by more than 30% [5], which is credited to the developments of multiple new medical treatments and drugs as well as to drastic changes in human lifestyles. However, despite these tremendous achievements, many aspects of cancer, especially the microscopic origins of tumor formation and progression, still remain not well understood.

Cancer is a collection of highly complex genetic deceases that exhibit abnormal cell growth in various human tissues and organs [4]. It is initiated when some cells start to divide much faster than other normal cells, hijacking precious cellular resources, invading healthy tissues, and eventually disrupting totally the normal functioning of the organism. It is also widely accepted that this is a result of accumulation of unfavorable mutations that randomly appear during cell replications and that are not captured by error-correcting cellular machinery [6–9].

It is clear that the formation of a tumor is a result of a large number of coupled chemical, biological and physical processes [4]. Such complexity suggests that a wide spectrum of experimental and theoretical tools must be simultaneously applied to explain cancer and its origins. In this paper, we discuss a powerful theoretical approach of stochastic mapping that aims to draw a more microscopic picture of the tumor formation by analyzing the dynamics of cancer initiation and progression [3,10–14]. It is inspired by multiple studies of complex stochastic processes in chemistry, physics and biology. The idea of this approach is that the dynamics reflects the underlying effective free-energy landscape of the system, allowing for better understanding of processes.

Knudson hypothesis. – To illustrate the importance of dynamics in uncovering the microscopic origins of cancer, let us consider a concept known as "Knudson hypothesis" or "two-hit hypothesis" [15–17]. It was developed by Dr. Alfred Knudson in 1971 when he statistically analyzed 48 cases of retinoblastoma, an eye-tissue cancer in children [17]. In this investigation, he recorded

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the age at which cancer was diagnosed and the family history of cancer. The analysis revealed that the inherited retinoblastoma occurs at a younger age than the non-hereditary disease. The most interesting observation was that hereditary and non-hereditary patients followed different quantitative trends. The key conclusion from the analysis was that the logarithm of fraction of cases not yet diagnosed S was linearly decreasing as a function of time ($\log S \sim t$) for hereditary cases, while a parabolic dependence ($\log S \sim t^2$) was observed for non-hereditary patients.

Based on these observations, Knudson argued that two events ("two hits") must happen for the cancer to start in non-hereditary cases, while only one event is required for tumors to appear in hereditary cases. To rationalize, he proposed the hypothesis that there are tumor-suppressing genes that must be fully inactivated in order for cancer to initiate. Since there are two copies of chromosomes in cells, the mutations on both chromosomes must occur in non-hereditary patients ("two hits"), while in the hereditary patients one chromosome is already damaged by the corresponding mutation and only one event is needed for cancer to start ("one hit"). This means that for non-hereditary patients the appearance of cancer is a two-step process, while it is only a one-step process for hereditary patients, leading to corresponding linear and quadratic dependencies on time for dynamics of the tumor formation. It was quite a revolutionary proposal in 1971 that eventually led to an important discovery of tumor-suppressing genes. In 1986, an Rb gene responsible for retinoblastoma was cloned. It was the first tumor suppressor gene to be identified in cancer history [16].

The importance of Knudson hypothesis is that it was one of the first successful examples of exploring the dynamics to obtain a more microscopic picture of cancer processes. By noticing a different quantitative behavior of tumor formation processes, a model consistent with these observations has been proposed and later experimentally proven.

Method of stochastic mapping. – There are multiple mathematical models for the analysis of cancer initiation and progression that have been proposed in recent years [3,11,14,18–24]. However, in this paper we would like to concentrate on recently developed method of stochastic mapping that provides a more specific quantitative description of cancer dynamics [12,13]. In this approach, an originally healthy tissue with N wild-type stem cells, as schematically shown in fig. 1 (top), is considered. The mutation might happen in one of these cells [6,7,25]. A time zero ($t = 0$) is defined in the system when such mutation appears for the first time. Both normal and mutated cells in the tissue can replicate, but with different rates. The wild-type stem cells divide with a rate b, while the mutated cells divide with a rate rb. The parameter r, known as a *fitness parameter*, plays an important role in cancer initiation dynamics since it specifies how the division rate

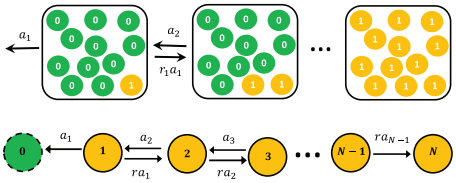

Fig. 1: Top: a schematic view of a tissue with the fixed number N cells and with the different numbers of mutated cells. The normal stem cells are shown in green, while the mutated cells are in yellow. Bottom: a discrete-state stochastic model of cancer initiation. The state label corresponds to the number of mutated cells in the tissue.

of the mutated cells differ from the normal cells. The situation when $r > 1$ describes the advantageous mutations (mutated cells divide faster than the normal cells), $r = 1$ corresponds to neutral mutations (the same division rates for mutated and normal cells), and for $r < 1$ the mutations are disadvantageous (mutated cells divide slower than the normal cells).

Before the tumor forms, the organism operates normally. One of the most important characteristics of healthy tissues is a so-called "homeostatic equilibrium" [26]. It is important to emphasize that this is not a thermodynamic equilibrium, but rather a stationary dynamic state because all biological systems are always out of equilibrium. For healthy tissues in grown-up organisms, the homeostasis is exhibited by keeping the total number of cells more or less constant. For the cancer initiation process this means that the total number of cells in the tissue N must be fixed, suggesting that any cell division that increases the total number of cells in the tissue must be accompanied by immediate removal of the cell. The microscopic details of how this happens in cells are still not well understood. To mimic such process, the method of stochastic mapping utilizes a procedure known as a *Moran process* [18,27,28]. In this process, one of the N cells is randomly chosen for division, which increases the total number of cells in the tissue temporarily by one. But then immediately another randomly chosen cell from current $N + 1$ cells is removed, returning the number of cells to the original count: see fig. 1. In addition, this theoretical approach assumes that in the system only a single mutation might happen with a very low probability $\mu \sim 10^{-8}$–10^{-10} [18,29]. The only way to change the number of mutated cells in the tissue is via cell divisions of already mutated cells.

Because of the random nature of cell divisions and deaths, there are two types of cells in the tissue at any moment, normal and mutated, but the overall composition changes with time. In addition, every state of the tissue can be characterized by a single variable, the number of mutated cells n ($1 \leq n \leq N$) [12]. This is because the total number of cells in the tissue is fixed due to homeostasis. So, if there are n mutated cells then we must have simultaneously $N - n$ normal cells. Now all changes in the

system can be viewed as stochastic transitions between discrete states as visualized in fig. 1 (bottom). In the sequence of states with different numbers of mutated cells, there are only two possible outcomes. Due to the random transitions, the mutation can be completely removed from the system, and this corresponds to the $1 \to 0$ transition. But the other outcome is that the mutated cells might fully occupy the tissue, *i.e.*, the system will reach the state $n = N$ (fig. 1). This is known as a mutation *fixation*, and the method of stochastic mapping assumes that this event marks the beginning of cancer [3,12,18].

The main idea of this theoretical approach is to map the complex dynamics of cellular processes before the cancer initiation into a set of stochastic transformations between discrete states specified by different compositions of the normal and mutated cells. The cancer starting point is associated then with reaching the state with all cells being mutated, while the mutations might also leave the system, indicating that the appearance of the mutation in the tissues does not guarantee that the tumor will form at all. Using the Moran process rules [18], the transition rates between the individual states of the system can be explicitly evaluated [12],

$$a_n = b\frac{n(N-n)}{N+1}. \tag{1}$$

More specifically, the transition from the state n to $n+1$, which increases the number of the mutated cells by one, is taking place with the rate ra_n. At the same time, the transition $n \to n-1$, which decreases the number of the mutated cells, is taking place with the rate a_n.

The stochastic mapping method postulates that the tumor appears as soon as the system reaches the state $n = N$ for the first time, starting at $t = 0$ in the state $n = 1$ (when the first mutation appears). This suggests that to quantify the cancer initiation dynamics it is convenient to utilize a first-passage approach, a powerful tool that has been successfully applied for the analysis of various complex processes in chemistry, physics and biology [30–32]. For this purpose, one can introduce a first-passage probability density function $F_n(t)$ that is defined as the probability of reaching the state N (fixation) for the first time at time t if at $t = 0$ the system started in the state n. The temporal evolution of these functions is governed by a set of backward master equations, [30,32]

$$\frac{\mathrm{d}F_n(t)}{\mathrm{d}t} = ra_nF_{n+1}(t) + a_nF_{n-1}(t) - a_n(1+r)F_n(t). \tag{2}$$

In addition, the initial condition $F_N(t) = \delta(t)$ must be satisfied. The physical meaning of this condition is that the fixation process is immediately accomplished if the system starts from the state N.

Master equations (2) can be explicitly solved, allowing to obtain a full dynamic description of the cancer initiation process [12]. More specifically, one might concentrate on two important characteristics. One of them is a fixation probability, $\pi_n \equiv \int_0^\infty F_n(t)\mathrm{d}t$, and another one is a fixation time, $T_n/\pi_n \equiv \int_0^\infty tF_n(t)\mathrm{d}t$. The first parameter gives the overall probability to initiate cancer starting from the state with n mutations already in the system, while the second parameter measures the average time before this happens. Analytical calculations provide explicit expressions for both of these quantities [33]. For the fixation probability, it has been shown that [12,18]

$$\pi_n = \frac{1-1/r^n}{1-1/r^N}. \tag{3}$$

Considering a process that starts in the state $n = 1$, when the first mutation appears, it can be shown that increasing the fitness parameter r enhances the probability of tumor formation [12]. This is clearly due to the fact that for $r > 1$ the mutated cells divide faster than the normal cells without mutations. Another observation is that for realistically large values of number of cells in the tissue N (typically, $N \sim 10^5$–10^9) the fixation probability is independent of the size of the tissue [12].

More interesting observations are found by analyzing the fixation times that are viewed as the mean times between the appearance of the first mutation and the state when all cells in the tissue are mutated. Analytical calculations yield [12]

$$T_1 = \frac{N+1}{b}\sum_{n=1}^{N-1}\frac{1}{n(N-n)}\left(\frac{r^n-1}{r-1}\right)\left(\frac{r^{N-n}-1}{r^N-1}\right). \tag{4}$$

Explicit calculations of the fixation times show some surprising results. While increasing the fitness parameter r should accelerate the formation of the tumors because the mutated cells replicate faster, the slowest cancer initiation dynamics is found for neutral mutations ($r = 1$). One could explain this by arguing that for $r = 1$ the discrete-state stochastic model in fig. 1 is effectively reduced into the unbiased random walk, which is known to exhibit a slow dynamics. The unexpected result, however, is that even for $r < 1$ the tumor formation might be fast, which contradicts to naive expectations. Since the normal cells divide faster than the mutated cells, one would expect much slower fixation dynamics for $r < 1$, which is not realized. The reason for this surprising result is that the fixation time is a conditional quantity. It is the mean time to achieve the state $n = N$ given that the system can reach it. For disadvantageous mutations ($r < 1$), the fixation probability is low since the system dynamics is biased in the direction of eliminating the mutations. But those rare successful fixation events must happen fast because at every intermediate step the system can reverse the direction due to the bias against the fixation.

Now let us show how the method of stochastic mapping can be used to clarify some specific aspects of cancer processes. It has already been applied to analyze the data from most common 28 types of cancer [12]. For the first time, this approach provided explicit estimates of the average times before the formation of different types of tumors [12]. But most importantly, it was able to probe

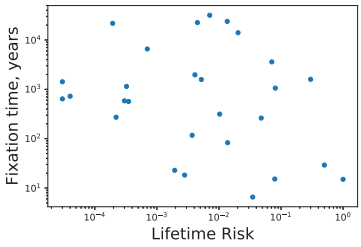

Fig. 2: Calculated fixation times and measured lifetime risks for different types of cancer. The figure is reproduced with permission from ref. [12].

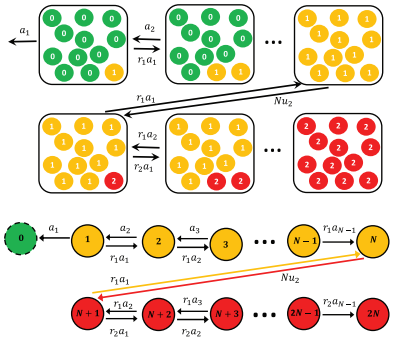

Fig. 3: Top: a schematic view of a cancer initiation process with two mutations in the tissue with N cells. Normal stem cells are green, while cells with single and double mutations are shown in yellow and red, respectively. Bottom: a discrete-state stochastic model for two sequential mutations in the tissue. The state n corresponds to n cells with one mutations for $1 \leq n \leq N$, and $n - N$ cells with two mutations for $N < n \leq 2N$.

the correlations between the cancer lifetime risks and the mean cancer initiation times. The cancer lifetime risk, which is defined as the probability to get cancer or to die from cancer during the human lifetime, is a widely used concept in forecasting the chances of getting cancers. It was generally assumed before that the more probable cancers (higher lifetime risks) will happen faster. However, the systematic investigation of such correlations has been done only recently [12]. Surprisingly, theoretical calculations found that there is no correlation between the cancer lifetime risks and mean times to get the tumor. Statistical analysis of the data presented in fig. 2 gives a Spearman's correlation coefficient 0.2 between the cancer lifetime risks and the fixation times, the magnitude of which is significantly smaller than the value -1 expected for the perfect correlation. Another statistical test, the p-value analysis, also pointed out the lack of correlations between two dynamic properties of cancer initiation [12].

While the lack of correlations between the cancer lifetime risks and cancer initiation times is clearly unexpected, one should notice that similar situations have been already encountered in other complex natural systems. For example, this is frequently observed in chemical reactions. While the probability for a reaction to happen is determined by the free energy difference between the products and the reagents, the actual time for reaction to occur is given by the height of the activation energy barrier [34]. These two energy scales are not always correlating, leading to multiple observations when the reaction that thermodynamically allowed is not happening due to kinetic reasons. The fact that similar events are taking place in the cancer initiation dynamics opens a new perspective on underlying microscopic processes during the tumor formation that clearly needed to be investigated further. It suggests possibly a similar mechanism with an effective barrier in the mutation fixation process for some cancers. It also means that if the mutated cells divide faster (larger fitness r) it does not necessary lead to faster tumor formation because of these barriers that might be the rate-limiting steps in the overall cancer initiation.

Temporal order of mutations influences cancer initiation dynamics. – Another example of successful use of dynamics in clarifying the microscopic picture of cancer has been recently presented [13]. It extended the original method of stochastic mapping to investigating the role of temporal order of mutations in the tumor formation. It is known that typically between 5 to 10 mutations lead to tumor formation. Until recently, it was generally believed that the overall set of properties associated with cancer is a result of additive contributions from each mutation, *i.e.*, the effect of each mutation is independent of each other [1]. Recent experimental discoveries, however, pointed out to a very different picture [35–37]. It was found that alternating the order of mutation acquisitions might surprisingly produce very different outcomes in the cancer development. In some systems, it delayed the formation of tumors, or produced benign (non-cancerous) tumors, or even led to different types of cancers [35–37].

To explain the effect of the temporal order of mutations, the theoretical analysis concentrated on the situation with just 2 mutations as illustrated in fig. 3 [13]. It was postulated that cancer starts when all cells in the tissue will have both mutations. Since the appearance of mutation that might lead to cancer is a rare event, it was assumed that the tissue will first get only one mutation, and a second mutation will appear only after all normal cells become mutated with one mutation: see fig. 3. Eventually the fixation of the second mutation is finally associated with cancer initiation [13]. Because each cell might have up to two mutations, there are three types of cells that can be found in the tissue at different times. The normal cells (labeled as 0, green circles) divide with a rate b, while the cells with one mutation (labeled as 1, yellow circles) divide with a rate $r_1 b$ and the cells with two mutations (labeled as 2, red circles) divide with a rate $r_2 b$. The parameters r_1 and r_2 are fitness parameters that specify how faster the mutated cells divide in comparison with the wild-type cells. One can see now that all dynamic transformations in the system can be viewed as a set of random transitions between $2N$ discrete states of the tissue with different compositions of cells (fig. 3, bottom).

There are two branches of states in the stochastic model of cancer initiation with two mutations. A state n ($1 \leq n \leq N$) in the first branch has n cells with one mutation and $N-n$ normal cells without mutations. In the second branch, the state n ($N < n \leq 2N$) describes the situation with $n-N$ cells with two mutations and $2N-n$ cells with one mutations. The state $n = N$ corresponds to a transitional fixation of the first mutation (all cells with one mutation), and the state $n = 2N$ describes the final fixation of both mutations, which is associated with the beginning of cancer in this model. It has been shown that the forward and backward transition rates out of the state n in the first branch (yellow states in fig. 3, bottom) are equal to $r_1 a_n$ and a_n, respectively, where the rates a_n are already given by eq. (1). Similarly, the forward and backward transition rates out of the state n in the second branch (red states in fig. 3, bottom) are given by $r_2 a_{N-n}$ and $r_1 a_n$, respectively [13].

The dynamics of cancer initiation in this model can again be obtained using the method of first-passage probabilities [13]. It was found that the overall fixation probability starting from the state n is given by

$$\Pi_n = \frac{1 - 1/r_1^n}{1 - 1/r_1^N}, \tag{5}$$

for $1 \leq n < N$, while $\Pi_n = 1$ for $N \leq n < 2N$. This surprising observation suggests that the probability of cancer initiation by two mutations is determined only by the properties of the first mutation (via the parameter r_1). In other words, the overall fixation probability is given by the transitional fixation probability of only the first mutation. One can understand this by analyzing the corresponding discrete-state stochastic scheme in fig. 3, bottom. This is because the transition from the state $N-1$ to N is irreversible since after that transition there are no more normal wild-type cells in the tissue, and the overall fixation is guaranteed. This unexpected result gave the first indication that the order of mutation is important for determining the nature of the cancer.

Theoretical calculations also allowed to explicitly estimate the mean cancer initiation times. It was found that if the system starts in the state $n = 1$ the corresponding time is given by

$$\begin{aligned} T_1 = {} & \frac{N+1}{b} \sum_{n=1}^{N-1} \frac{1}{n(N-n)} \left(\frac{r_1^n - 1}{r_1 - 1} \right) \left(\frac{r_1^{N-n} - 1}{r_1^N - 1} \right) \\ & + \frac{1}{N u_2} \left[\frac{1 - (r_1/r_2)^N}{1 - r_1/r_2} \right] \\ & + \frac{N+1}{b r_2} \sum_{n=1}^{N-1} \frac{1}{n(N-n)} \left(\frac{1 - (r_1/r_2)^{N-n}}{1 - r_1/r_2} \right). \end{aligned} \tag{6}$$

To understand the physical meaning of this result, one can notice that the average fixation time has three contributions, $T_1 = T_{11} + T_{trans} + T_{12}$, that can be explained in the following way. The first term T_{11} describes the time for the system to reach the state N. This is the residence time for the system to be found on the first branch. The second term, T_{trans}, describes the effective rate of acquiring the second mutation in cells that are fully fixed by the first mutation. It can be shown that

$$T_{trans} = \frac{1}{N u_2} \frac{1}{\Pi_{12}}, \qquad \Pi_{12} = \frac{1 - r_1/r_2}{1 - (r_1/r_2)^N}, \tag{7}$$

where Π_{12} is a fixation probability for the second mutation starting from the state $N+1$. This means that this contribution, which corresponds to the transition between the first and the second branches of discrete states, also reflects the possibility of multiple reverse transitions from the state $N+1$ back to the state N. The third term, T_{12}, describes the time to reach the final fixation starting from the state $N+1$. It corresponds to the time to be found only on the second branch.

The discrete-state stochastic model for cancer initiation with two mutations allows to explicitly evaluate the effect of mutations order [13]. For this purpose, one might consider two specific mutations A and B with the fitness parameters given by r_A and r_B, respectively. There are two different scenarios for acquiring mutations. In the sequence AB, the mutation A is the first and the mutation B is the second one. One can assign then $r_1 = r_A$ and $r_2 = r_A r_B$. This is because the tissue might have cells without any mutations, with mutation A or with both mutations A and B. Similarly, in the sequence BA the mutation B comes first followed by the mutation A. In this case, the fitness parameters are given by $r_1 = r_B$ and $r_2 = r_A r_B$. For two different mutational scenarios, AB and BA, the corresponding fixation probabilities are defined as Π_{AB} and Π_{BA}, respectively. It is convenient to quantify the difference between these two alternating sequences by considering a parameter

$$\Delta_p = \frac{\Pi_{AB}}{\Pi_{BA}} = \left(\frac{1 - 1/r_A}{1 - 1/r_B} \right) \left(\frac{1 - 1/r_B^N}{1 - 1/r_A^N} \right). \tag{8}$$

Theoretical calculations for this ratio are presented in fig. 4(a). One can see that for any $r_A \neq r_B$ both mutational scenarios are not equally probable. If the first mutation is more advantageous ($r_A > r_B$) then it is more probable for sequence AB to lead to cancer, and it is less probable for the sequence BA. This is a consequence of the theoretical result that the overall fixation depends only on the nature of the first mutation in the sequence [13].

In a similar way, one can evaluate the cancer initiation dynamics for two different mutation scenarios [13]. Using the explicit expressions for fixation times T_{AB} and T_{BA} for mutational sequences AB and BA, respectively, one can define a parameter

$$\Delta_T = \frac{T_{AB}}{T_{BA}}, \tag{9}$$

which is explicitly calculated in fig. 4(b). It shows that the cancer initiation dynamics is different for alternating mutational sequences. However, comparing the results in

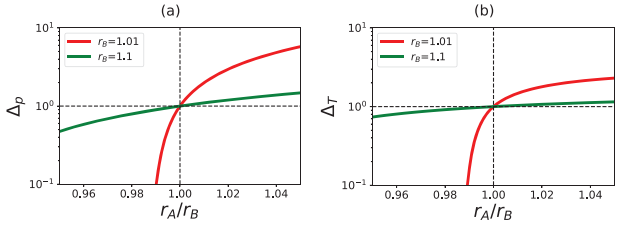

Fig. 4: (a) The ratio of fixation probabilities Π_{AB}/Π_{BA} for two alternative sequences of mutations. (b) The ratio of fixation times T_{AB}/T_{BA} for two alternative sequences of mutations. Adapted with permission from ref. [13].

fig. 4(a) and fig. 4(b), there is a surprising observation. Those mutational sequences that are more probable (for example, AB for $r_A > r_B$) exhibit longer cancer initiation times, in contrast to naive expectations.

The advantage of the method of stochastic mapping is that it allows to provide more microscopic explanations on the surprising observations of anti-correlations between the probabilities and times before cancer [13]. The idea is that the observed cancer initiation dynamics reflects the underlying effective "free-energy" landscape [13,38] On its path to cancer initiation, the system moves via peaks and valleys of this effective free-energy landscape. Longer transition times correspond to higher effective barriers, while shorter transition times describe smaller effective barriers. This leads to a simplest schematic representation of the cancer initiation process as a motion along the one-dimensional "reaction" coordinate as shown in fig. 5 for the case $r_A > r_B$ for two different scenarios. The first barrier describes the process of moving along the first branch of the discrete states (fig. 3, bottom), while the second barrier similarly describes the motion along the second branch of discrete states (fig. 3, bottom). The deep valley between two barriers reflects the irreversible transition from the state $N-1$ to N, meaning that it is impossible to return back to the first branch after hitting the state N.

Now the effective free-energy landscape picture can be utilized to explain the dynamics of cancer initiation and the role of mutations order. The probability of the overall fixation depends only on the height of the first barrier. For $r_A > r_B$, the barrier for the AB sequence (left part of fig. 5) is lower than the barrier for the sequence BA (right part of fig. 5). This obviously justifies the higher cancer lifetime risk for the sequence AB. To explain the cancer initiation dynamics, we notice that both barriers are now important, but the highest barrier might be viewed as a rate-limiting step that determines the overall rate of the process. One can see that the highest barrier is the second one in the sequence AB (left part of fig. 5) for $r_A > r_B$, while both barriers for the sequence BA (right part of fig. 5) are smaller. These simple qualitative arguments explain the origin of the anti-correlations between the fixation probabilities and the mean fixation times.

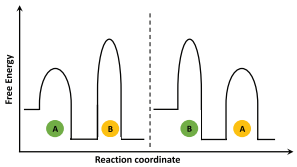

Fig. 5: The effective "free-energy" landscapes for cancer initiation with two alternative sequences of mutations: the left panel describes AB mutations ($r_A > r_B$), while the right panel describes BA mutations ($r_B < r_A$). Adapted with permission from ref. [13].

Future directions. – In this paper, we discussed several examples of how the information on the dynamics of cancer processes can be utilized for clarifying the mechanisms of tumor formation. Stimulated by studies in chemistry and physics, it was shown that the cancer initiation processes can be effectively considered as a set of stochastic transitions. Such approach allows for quantitative mapping of underlying free-energy landscape, significantly advancing our knowledge on the microscopic origin of tumor formation.

While the method of getting more microscopic information on cancer origin from dynamics seems to be quite powerful, there is still a long road before it might be also useful for the development of specific anti-cancer treatments. It is important to extend this approach to more realistic situations. One might suggest the following directions for future investigations. In real cancers, several mutations usually start and proceed in parallel. This might be viewed as a branched model of cancer initiation that contrasts with the sequential model assumed above for the case of two mutations. In the language of discrete states with stochastic transitions this will correspond to the motion in the multi-dimensional space. In addition, it will be important to investigate the spatial effects because the tissues might have different spatial structures. Furthermore, it will be interesting to couple this approach with more mechanical views on cancer dynamics [39]. There are multiple exciting directions that hopefully will be fully explored in the near future.

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Data availability statement: All data that support the findings of this study are included within the article (and any supplementary files).

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