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REVIEW

A Review of Stochastic and Deterministic Modeling of Stem Cell Dynamics

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Abstract

Purpose of Review This paper briefly describes recent mathematical models that use stochastic and deterministic approaches to understand stem cell dynamics and how these models are utilized to study the roles of stem cells' dynamics in cancer and aging.

Recent Findings Stochastic compartmental models have been developed to investigate the generalized double-hit mutant production under the influence of different types of stem cell divisions. More specialized examination of the generation, spread, and optimizing structure of 2-hit mutants in the colon crypts has also been conducted. The recent introduction of a hybrid stochastic-deterministic model creates innovative approaches to studying carcinogenesis, while other stochastic models interested in the stem cell renewal process have explored the phenomenon of aging.

Summary The results of these studies indicate that asymmetric stem cell divisions increase the probability of mutants production and their fixation probability. Moreover, the hybrid stochastic-deterministic model demonstrates how a low rate of dedifferentiation can significantly accelerate carcinogenesis. Finally, a stochastic model for the stem cell renewal process behind aging shows that the fixation probability of an altered stem cell with a longer cell cycle than the rest is higher than other stem cells.

Keywords Stem cell dynamics · Mathematical models · Stochastic processes · Deterministic models · Cancer · Aging

Introduction

The study of stem cell population dynamics has attracted the attention of many scholars in recent years, as an increasing amount of research has revealed the significance of stem cells in maintaining normal body functions and causing diseases such as cancer [1–10]. For example, the so-called cancer stem-cell hypothesis suggests that some cancers, including leukemia, breast cancer, and brain cancer, originate from stem cells [4, 11–15], while some are developed as a result of chronic inflammation, such as some colon cancers [16]. The great potential of stem cell applications has also prompted scholars to seek innovative stem cell therapies for intractable illnesses [17–21]. Therefore, it is crucial to understand the complexity of stem cell movement and analyze its impact on maintaining or deteriorating body functions, as related studies provide opportunities to propose promising therapeutic options.

As new insights from interdisciplinary research become increasingly popular in academia, researchers investigating the field of stem cell dynamics have become acquainted with mathematical models and numerical simulations [22–31]. The hierarchical structure of stem cells in many tissues, such as the intestine and mammary gland, also makes stem cells suitable for modeling [23–27, 32•, 33•, 34, 35]. Through mathematical modeling, researchers are able to obtain data and predict the movement patterns of stem cells to compensate for experimental or clinical observations. This paper examines recent simple stochastic and deterministic models, focusing on the accumulation of mutations in different stem cell division patterns and the stem cell renewal processes.

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Stochastic Models for the Generation and Spread of Double-Hit Mutants in Stem Cell Division

According to Knudson's findings, most tumor suppressor genes require two mutations to be inactivated and lead to cancer initiation [36, 37]. Therefore, the generation and accumulation of double-hit mutants become a determinant of cancer development and treatment. In 2013, Shahriyari and Komarova investigated the tumor suppressor gene inactivation process under the influence of symmetric and asymmetric stem cell divisions [22]. In their work, a stochastic model that follows the generalized Moran process indicates that symmetrically dividing stem cells generate double-hit mutants, which inactivate tumor suppressor genes and lead to future carcinogenesis, at a significantly lower rate than asymmetrically dividing stem cells.

The model distinguishes four types of cells — wild-type stem cells (i_*), one-hit mutant stem cells (j_*), wild-type Transit Amplifying cells (TAs) (i), and one-hit mutant TA cells (j) — which add up to N, a constant total population size. TA cells are a group of undifferentiated cells that are intermediate between stem cells and differentiated cells. During each simulation update, a TA cell is randomly replaced with a child of another cell to maintain a stable population size. All cells have a division probability based on their fitness. The fitness of mutated cells is given by r, while the fitness of wild-type cells is 1. Thus, the probability of a wild-type stem cell dividing is given by $\frac{i_*}{N}$, and the probability of a one-hit mutant stem cell dividing is given by $\frac{r(j_*)}{N}$. The probability for a wild-type TA cell to divide is given by $\frac{i}{N}$, and the probability for a one-hit mutant TA cell to divide is given by $\frac{rj}{N}$. When a wild-type TA cell divides, the probability of its child being another wild-type TA cell is $1-\mu_1$, while the probability of the child being a one-hit mutant TA cell is μ_1. Similarly, when a mutant TA cell divides, it has a probability of $1-\mu_2$ to create another one-hit mutant TA cell and a probability of μ_2 to create a double-hit mutant TA cell. The updates stop when a double-hit mutant is generated. There are two types of divisions for stem cells: symmetric (with probability σ) and asymmetric (with probability $1-\sigma$). In the case of asymmetric stem cell division, a TA cell is produced. When a wild-type stem cell divides asymmetrically, there is a probability of $1-\mu_1$ where no mutation occurs and a probability of μ_1 where a one-hit mutant is created. In this case, the probability of the created TA cell getting a mutation is $\frac{1}{2}$, while the probability of the stem cell getting a mutation is $\frac{1}{2}$. Symmetric stem cell division can lead to differentiation, where the stem cell is replaced by two TA cells, or proliferation, where a new stem cell is generated. The probability of proliferation is given by $1-p$, where $p=\frac{(i_*+j_*)^{10}}{S^{10}+(i_*+j_*)^{10}}$, and S is a constant parameter that measures the expected number of stem cells in the system. If a wild-type stem cell divides, the probability that both daughter cells are wild-type is $1-\mu_1$, and the probability that both daughters are mutant stem cells is μ_1. If a one-hit mutant cell divides symmetrically, there is a probability of μ_2 that a double-hit mutant is created, and the process stops.

After performing 1000 times simulation updates until either a double-hit mutant is produced or the maximum number of time steps, which is 1000, is reached, the results show that for stem cells, symmetric division leads to slower production of double-hit mutants compared to asymmetric division, implying that symmetric division of stem cells possesses a cancer-delaying effect. It also concludes that TA cells contribute equally or more to the production of double mutants than stem cells.

Based on these findings, Shahriyari and Komarova investigated the dynamics of the heterogeneous stem cell niche in relation to double-hit mutants production by utilizing a class of bi-compartmental stochastic models comprised of the border stem cells (BSCs) and the central stem cells (CeSCs) [24]. According to their results, the bi-compartmental stem cell system possesses a significantly smaller double mutant production rate than a homogeneous single-compartmental stem cell niche structure.

CeSCs and BSCs are two groups of stem cells in the intestinal crypts, each constituting a compartment in the model. BSCs mostly control the number of non-stem cells through differentiation, as BSCs locate closely to TAs, while CeSCs mostly control the total number of stem cells through proliferation. Thus, in the following models, asymmetric division and differentiation occur only in the BSC compartment, while the proliferation of stem cells may occur in both compartments.

In the study, the population consisted of four types of cells: stem cells in the BSC compartment (wild-type, i, one-hit mutants, j) and stem cells in the CeSC compartment (wild-type, i_*, one-hit mutants, j_*), where $i+j+i_*+j_*=N$ and N is a constant [24]. Each update of the simulations starts with the death of two random TA cells, which are replenished by two divisions of stem cells randomly selected from the two compartments (Fig. 1). All stem cells have a probability of dividing based on their fitness: the fitness of a single-mutant is given by r, and the fitness of a wild-type stem cell is 1. Therefore, when a stem cell divides asymmetrically or differentiates, the probability of a wild-type stem cell in BSCs being chosen is $\frac{i}{i+rj}$, while the probability of a mutated stem cell in BSCs being chosen is $\frac{rj}{i+rj}$. When a stem cell proliferates, i.e., divides symmetrically and produces two stem cells, the probability of a wild-type stem cell in CeSCs being selected is $\frac{\gamma i_*}{i_*+rj_*}$, while the probability of a mutated stem cell in CeSCs being chosen is $\frac{\gamma rj_*}{i_*+rj_*}$; the probability of a wild-type stem cell in BSC compartment dividing is $\frac{(1-\gamma)i}{i+rj}$, while the probability of a one-hit stem cell in BSCs to divide is $\frac{(1-\gamma)rj}{i+rj}$.

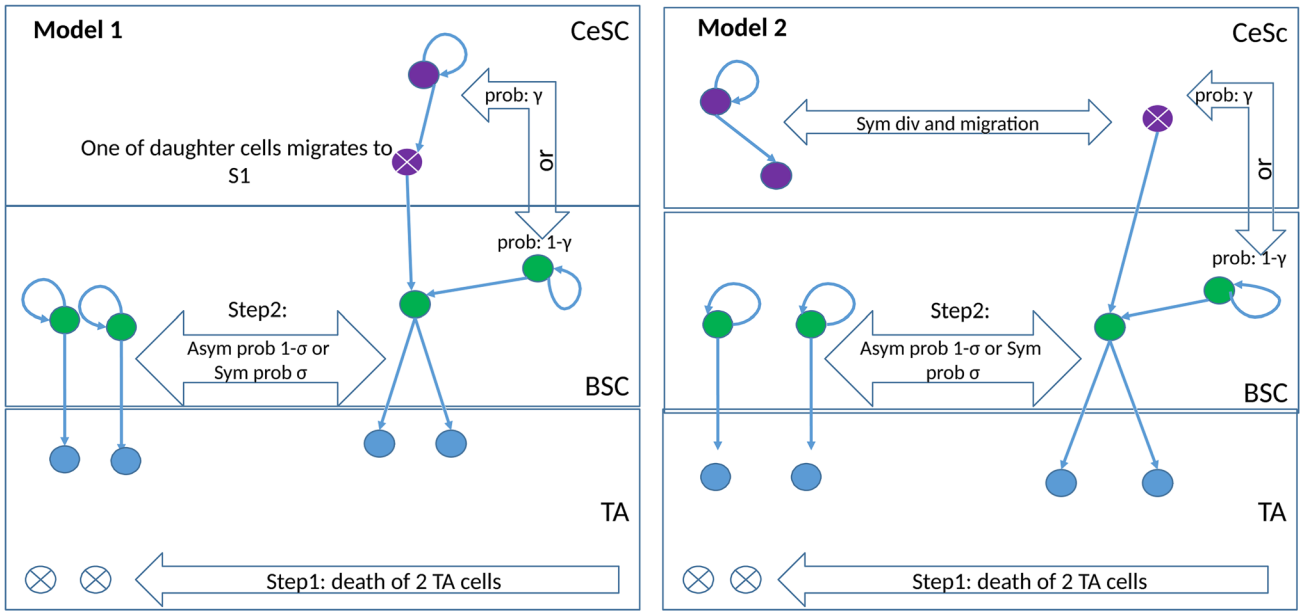

Fig. 1 A schematic representation of the models presented in [24]. The BSC compartment controls the TA cells and the BSCs, while the CeSC compartment controls the total number of stem cells. At each updating time step, two TA cells die and are followed by two stem cell divisions

The simulation progresses with two types of models based on the type of division. In the first model, there is a probability $1-\alpha$ that two asymmetric divisions in the BSCs replenish two lost TA cells and a probability α that a symmetric differentiation in the BSCs replenishes lost TAs. In the latter case, there is a probability of $1-\gamma$ that another stem cell in the BSC compartment proliferates and also a probability γ that a stem cell in the CeSC compartment divides and one of the progeny moves to the BSC compartment. Model 2 follows a similar setup, but the only difference is that when the lost two TA cells are replenished by symmetric differentiation in the BSCs with probability α, there is a probability of γ that a random stem cell in the CeSCs migrates to the BSCs, following a proliferation in the CeSCs to maintain the equilibrium state. The notation γ represents the intensity of symmetric division in the CeSCs, and the probability for stem cells to divide symmetrically is σ. When a wild-type stem cell divides following any patterns of divisions, it has a probability of μ_1 to create a one-hit mutant daughter and a probability of $1-\mu_1$ to create another wild-type stem cell. When a mutated stem cell divide, it has a probability of $1-\mu_2$ to produce another one-hit mutant and a probability of μ_2 to produce a double-hit mutant. If an asymmetric division occurs, the probability of the daughter stem cells acquiring a mutation is ν. The simulation proceeds until a double-hit mutant is produced or 1000 updates are reached, and the researchers approximate the probability of double-hit mutant production at a given time. The researchers calculated the mean and standard deviation of the results after running the above procedures only ten times as the reported standard deviations were small.

Calculating and comparing the probability of double-hit mutant generation in the above-mentioned models suggest that the proposed cooperative pattern of stem cells in the bi-compartmental niche results in a significantly lower rate of double-hit mutant production than in a single-compartmental architecture. Furthermore, the optimal structure for minimizing the rate of double-hit mutant generation requires that most of the proliferation occurs in BSCs, accompanied by a small, non-zero proliferation rate of stem cells in CeSCs. The proposed models also confirm the role of symmetric division in delaying double-hit mutant production.

As researchers observed a small amount of backward migration from the BSC compartment to CeCs, Bollas and Shahriyari improved the former models to further study the probability of double-hit mutants generation in the stem cell niche factoring in the backward cell migration from BSCs to CeSCs [23]. The updated model suggests that the probability of double-hit mutant production increases as the frequency of backward cell migration increases, providing a new perspective for understanding the dynamics of stem cells. The proposed Moran model follows a similar setting to the former models, as two TA cells die and are replaced by two stem cell divisions to keep the total number of cells constant at each updating time step. The model chooses the death of two TA cells to accommodate the stem cell symmetric division pattern. At each update, two stem cells divide symmetrically (a differentiation is coupled with a proliferation) with a probability of σ or asymmetrically with a probability of $1-\sigma$. In the asymmetric division, there is a probability ν that the stem child cell will get mutated. Stem cells are

selected to divide according to their fitness, as described above. While the model limits asymmetric division and differentiation to occur only in the BSC compartment, the proliferation of stem cells may occur in both compartments, with a probability of γ in the CeSC compartment and $1-\gamma$ in the BSC compartment. When a proliferation occurs in the CeSC compartment, a random cell migrates to the BSC compartment to keep the number of cells in each compartment constant. When a proliferation occurs in the BSC compartment, a random cell migrates from the BSC compartment to the CeSC compartment with probability α, followed by another random cell that migrates from the CeSCs to the BSCs to keep the number of cells in each compartment constant. Each time a wild-type stem cell proliferates, the probability of one of the children acquiring a mutation is μ_1, and the probability of another wild-type stem cell being generated is $1-\mu_1$. When a one-hit mutant stem cell proliferates, there is a probability $1-\mu_2$ of producing another one-hit mutant and a probability μ_2 of creating a double-hit mutant. The simulation was repeated 100 times until either a double-hit mutant was generated or the total number of updates reached 100. The researchers repeated the procedure ten times and calculated the mean and standard deviation of the probability of double-hit mutant production.

According to the results, when $0 < \gamma < 1$, the probability of generating a double-hit mutant is an increasing function of α, which is the probability that a random cell migrates backward from the BSC compartment to CeSCs. In other words, an increased probability of backward migration leads to an increased probability of generating two-hit mutants. However, the probability of double-hit mutant production is not very sensitive to α unless $\alpha = 0$ and is significantly influenced by the probability of symmetric division, as symmetric division delays the production of double-hit mutants when $\gamma < 1$ and $\alpha > 0$. Moreover, the results reveal that a small non-zero percentage of backward cell migration leads to a higher range of optimal values for the frequency of symmetric division σ and the proliferation probability of CeSC γ in terms of delaying two-hit mutant production.

While this model explores the probability of double-hit mutant production in a bi-compartmental system, Shahriyari and Mahdipour-Shirayeh employed the same model structure to study the spread of mutants in the stem cell niche [25]. Their paper shows that the progeny of mutant CeSCs has a high probability of taking over the CeSC compartment and the entire stem cell niche, while the progeny of mutant BSCs has a very small probability of taking over the BSC compartment as well as the entire stem cell niche. Moreover, when $\sigma > 0$, the fixation probability of mutants in the stem cell niche is independent of the probability of symmetric division (α). The paper also indicates that a higher backward migration rate from BSCs to CeSCs delays tumorigenesis by delaying the fixation of mutants in the niche.

In 2018, a study advanced the research of mutant dynamics in colonic and intestinal crypts by adding two compartments — the TA cells compartment and the fully differentiated cells (FDs) compartment — to the existing bi-compartmental models and provided an extended explanation for the fixation of double-hit mutants in the crypts [26]. Similar to the previous model setup, two FD cells die at each updating time step, after which two random cells divide according to their fitness, which is calculated in the same way as in the previous model (Fig. 2). There is a probability λ_f that two FD cells divide to replenish the two dead FD cells. When a TA cell differentiates into two FD cells with probability $1-\lambda_f$, there is a probability of $1-\lambda_s$ that a TA cell proliferates to replace the differentiated TA cell and a probability of λ_s that one stem cell divides. The assumptions and patterns of stem cell division are consistent with the proposed bi-compartmental model by Bollas and Shahriyari [23]. The proposed four-compartmental model simulates the crypt's actual structure and confirms that the progeny of CeSCs have a high probability (close to 1) of taking over the entire crypt, while the probability of the progeny of BSCs taking over the crypt is close to zero. Based on the parameters obtained, the model also predicts that the progeny of wild-type CeSCs will take over the mouse intestinal crypt at around 60 days, in accordance with experimental results. Furthermore, advantageous mutants will be washed out more quickly than disadvantageous mutants by wild-type CeSCs.

A Stochastic Optimization Model of Homeostatic Cell Renewal in Hierarchical Tissues

To explore the mechanism of the self-renewal process in hierarchical tissues and its relation to carcinogenesis, a 2018 study presents a stochastic model of tissue self-renewal and investigates the accumulation of mutations under this stochastic mechanism [27]. By computing the model under different scenarios with stochastic simulations and deterministic approximations, the researchers obtained results for one-hit and two-hit mutation generation and discovered optimized architecture that could delay carcinogenesis in hierarchical tissues like colon crypts.

The model consists of $n+1$ layers of compartments, $C_0 \ldots C_n$, with a constant total number of cells $N_0 \ldots N_n$. The C_0 is the least mature stem cell compartment, while C_n is the most mature compartment with differentiated cells that will be eliminated and replaced during the simulation. At each update, 2^n cells from C_n are removed and replaced by 2^n divisions in successive upstream compartments. The probability for a cell in compartment C_i to be replaced through self-renewal is $0 \le v_i \le 1$, and v_n is set to zero so that terminally

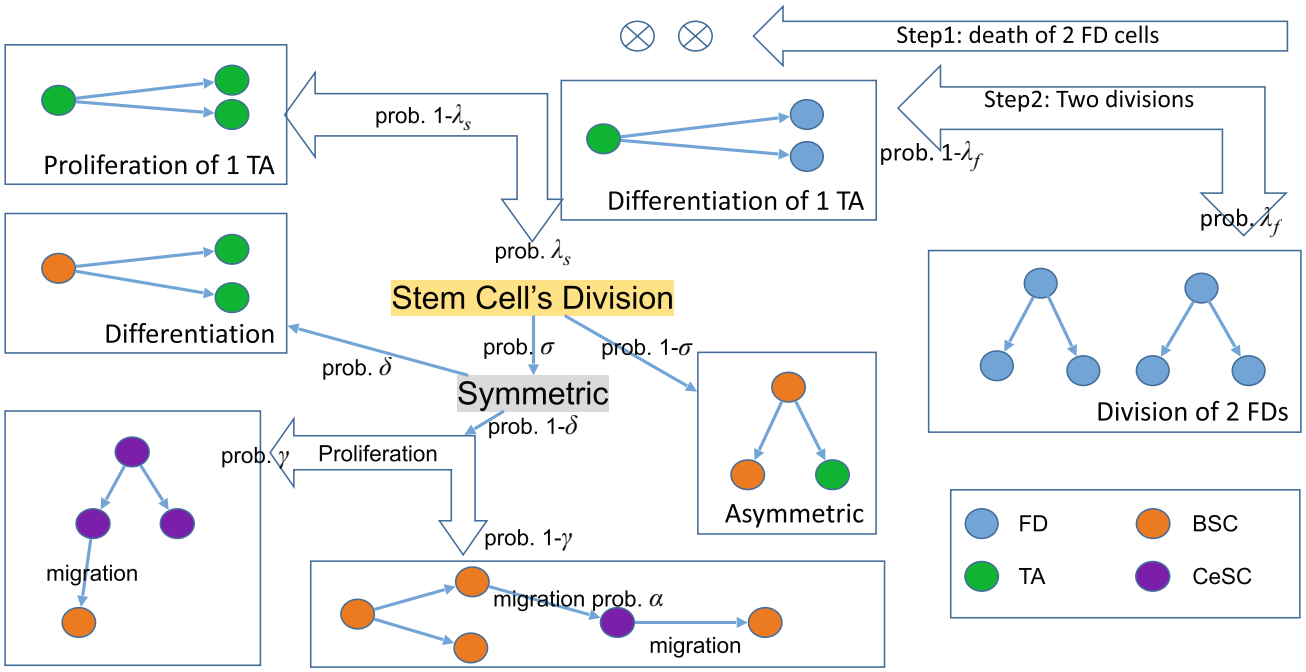

Fig. 2 A schematic representation of the model from [26]. The figure represents the algorithm: at each updating time step, two FD cells die and are replenished by two cell divisions

differentiated cells do not self-renew. For the least mature compartment C_0 of stem cells, $v_0 = 1$ since there is no layer below that can divide and replenish the missing stem cells. The number of mutants in each compartment is denoted as m_i, and the number of wild-type cells is thus $N_i - m_i$. The probability of each selected dividing cell obtaining a mutation is μ.

When the simulation starts with 2^n cells being removed from C_n, 2^{n-1} cells in C_{n-1} will differentiate and replenish the removed cells in the downstream compartment. There is a probability of $\frac{m_n}{N_n}$ that a mutant is eliminated from C_n, and for divisions in C_{n-1}, there is a probability of $\frac{m_{n-1}}{N_{n-1}}$ that a mutant is chosen to proliferate. When a wild-type cell is selected, the probability of its progeny getting a mutation is μ. After the 2^{n-1} differentiations, there are 2^{n-1} cells that need to be replaced in C_{n-1} either by self-renewal with probability v_{n-1} or by differentiation from C_{n-2} with probability $1 - v_{n-1}$. When an odd number of differentiations occurs, the researchers add an extra self-renewal in C_{n-1} to obtain an even number of openings. Similar to the previous process, the probability of a mutant being selected and self-renewing is $\frac{m_{n-1}}{N_{n-1}}$, while a wild-type cell has a probability of μ to mutate if being chosen. Cells missing in C_{n-2} will be replaced according to the same procedure described above, and these differentiations and replacements repeat until C_0 is reached. For each cell division selection from compartment C_i, the probability for a mutant to be chosen is $\frac{m_i}{N_i}$.

After obtaining results from the ODE approximation derived from the stochastic system and comparing the results to the average number of mutants from 100 stochastic simulations, researchers conclude that a lower probability of self-renewal, v, correspondingly accompanied by a longer division tree for differentiation, delays the double-hit mutant production since mutants are more likely to be flushed out during the long differentiation process. The study also suggests that an increasing compartmental size in the downstream direction minimizes the population of mutants in stem cells, which is consistent with the ODE function.

A Hybrid Stochastic-Deterministic Model Assessing the Effect of Dedifferentiation on Carcinogenesis

In 2014, Jilkine and Gutenkunst proposed a hybrid stochastic-deterministic model of mutation accumulation in stem and progenitor cells to study the effect of dedifferentiation, which results in progenitor cells acquiring a stem cell-like state, on carcinogenesis [29]. Due to the abundance of progenitor cells, the dynamics of progenitors are described by a deterministic model, while a stochastic structure models the dynamics of stem cells as in previously mentioned studies [22–26]. As the differentiated progeny of stem cells migrate to the progenitor cells compartment, there is also a rate of "dedifferentiation" migrating from

the deterministic progenitor population to the stochastic compartment of stem cells. To assess the effect of dedifferentiation on carcinogenesis, researchers compare models with fixed and variable numbers of stem cells and factors dedifferentiation in both categories of models.

In the coupled system, the researchers first developed a Moran model that guarantees the homeostasis of stem cells caused by strictly asymmetric divisions. The number of stem cells is denoted as N_{sc}, the fraction of replicating stem cells from dedifferentiated progenitors is ϵ, and the stem cell mutation rate at each renewal time step is μ. The model restricts only double-mutant progenitors to be able to undergo dedifferentiation. The model assumes that when a stem cell dies and is replaced by another stem cell at each update, there is a probability of ϵ times the proportion of double-hit mutants in the progenitor compartment that the new entrant comes from the double-hit mutant progenitor population. In this case, the number of dedifferentiation of progenitors depends on the number of niche openings. From simulation results, which are in close agreement with the analytical approximations, the distribution of times to fixation is relatively constant if $\epsilon \lesssim \frac{1}{N_{sc}}$, and when μ is small, an increase in ϵ, which passed the threshold, slightly shortens the total time to fixation. The researchers also considered an alternative model in which all progenitors can dedifferentiate. The model yields similar results, namely that dedifferentiation has little effect for $\epsilon \lesssim \frac{1}{N_{sc}}$ and a more substantial effect after passing that threshold. Thus, with strict homeostasis of the stem cell population and regular stem cell mutation rate μ, dedifferentiation plays a relatively minor role in accelerating the time to cancer onset and instead serves as a selective advantage for mutant stem cells.

This paper also considers the case where a strict stem cell equilibrium state is not guaranteed as in real life by including symmetric stem cell divisions. All double-mutant progenitor cells have a probability δ of dedifferentiation, and the dedifferentiated cells are directly added to the stem cell compartment. Thus, unlike previous models, the generation of dedifferentiated cells is controlled by the number of 2-mutant progenitors rather than niche openings. The results imply that in this stochastic stem cell homeostasis, a low rate of dedifferentiation can significantly accelerate carcinogenesis, even with a low μ, because double mutants can arise from the dedifferentiation of large populations of progenitors, and the number of stem cells will increase exponentially.

A Stochastic Model Examining the Process of Stem Cell Renewal in Relation to Aging

The relationship between the dynamics of stem cell populations and homeostatic cell renewal processes is explored in the study by Fendrik et al. in 2019 [28]. In this paper, researchers first sample the realization of the stochastic process of altered cells and calculate the exact fixed probability vector of the associated stochastic matrix to check the system's stability to fluctuations. After reaching the stability requirements and obtaining analytical expressions for the probability of altered cell fixation, the researchers turn to a simplified Moran model and investigate the impact of the accumulation of altered cell fixation. The paper concludes that the cell renewal process favors the fixation of cells with longer cell cycles.

After confirming that the fixation of the altered stem cells does not change the equilibrium stem cell population nor the fluctuations around it, the researchers fixed the stem cell population to reach the Moran process. The population of wild-type stem cells is denoted as s, and the population of altered stem cells is denoted as s'. $s + s' = n_e$, which is the constant total population. At each update time step, the loss of a stem cell is accompanied by the birth of a new stem cell, leading to only three possible events:

- The death of a wild-type stem cell is accompanied by the birth of an altered stem cell.
- The death of an altered stem cell is accompanied by the birth of a wild-type stem cell.
- The numbers of wild-type and altered stem cells remain constant.

Starting from the initial state $(n_e - s', s')$, two potential absorbent states can be reached. When $\alpha > 0$, the probability of ending at $(0, n_e)$ is

$$P_{(0,n_e)}^{(n_e-s',s')} = \left[\frac{2(n_e - s')}{\alpha - 1} + (s' - 1)\right]\frac{s'}{n_e(n_e - 1)}, \tag{1}$$

while the probability of ending at $(n_e, 0)$ is

$$P_{(n_e,0)}^{(n_e-s',s')} = 1 - P_{(0,n_e)}^{(n_e-s',s')}, \tag{2}$$

where any initially existing $(n_e - 1)$ wild-type stem cell is fixed. Under the latter circumstance, the probability of fixing each of the initial wild-type stem cells is

$$\tilde{P}_{(n_e,0)}^{(n_e-s',s')} = \frac{P_{(0,n_e)}^{(n_e-s',s')}}{n_e - 1}. \tag{3}$$

When an altered stem cell exists in the population, the above functions can be written as:

$$P_{(0,n_e)}^{(n_e-1,1)} = \frac{2}{(\alpha + 1)n_e}, \tag{4}$$

$$\tilde{P}_{(n_e,0)}^{(n_e-1,1)} = \frac{(\alpha + 1)n_e - 2}{(\alpha + 1)n_e(n_e - 1)}. \tag{5}$$

The researchers conclude that the results of the Moran model Eqs. (4) and (5) are consistent with previous analytical calculations that the fixation of stem cells with longer cell cycle lengths is favored during cell renewal from symmetric division. This effect is a feature of cell renewal dynamics and significantly contributes to aging. The researchers also obtained algebraic expressions based on Eqs. (4) and (5) to explore the situation where successive alterations in stem cells occur. However, no experimental results so far exist to compare with the analytical calculations.

Discussion and Conclusion

In mathematical models applied to the study of stem cell dynamics, the complex patterns of stem cell movement are broken down into critical mechanisms that enable scholars to model and analyze the progression of stem cells. Many recent studies have employed various mathematical methods to unravel the complexity of stem cell dynamics and its interaction with the human body [30, 31, 38–41]. This paper discusses a small selection of representative stochastic and deterministic models that can substantially impact stem cell research [22–29]. The first section of models following the multi-compartmental Moran process describes stem cell division and its effect on the generation and propagation of double-hit mutants under the assumption of stem cell homeostasis. These models suggest that increasing the probability of symmetric stem cell division can significantly delay cancer generation and reduce mutants' fixation rate, which provides insight into potential cancer prevention and treatment at the cellular level [22–26]. These results hold true in hierarchical tissues such as intestinal crypts, while the researchers also identify that the optimal structure for delaying double-hit mutants is when the majority of stem cell proliferation occurs in border stem cells in the niche and the probability of self-renewal is low [23–27]. Through a stochastic-deterministic model exploring the effect of dedifferentiation on cancer initiation, researchers suggest a lower probability of dedifferentiation accelerates the creation of 2-hit mutants and thus expedites carcinogenesis [29]. In addition to cancer, the final model delivered in this paper discusses the homeostasis renewal process of stem cells and cellular aging [28].

Mathematical models of stem cell dynamics are advantageous in predicting the onset of disease or cellular dysfunction and can help advance disease prevention and treatment. Through the presentation of various models, this paper aims to illustrate the significance and efficiency of mathematical models in proposing new theories in stem cell dynamics and validating existing hypotheses.

Author Contribution SG carried out the study and drafted the manuscript; LS designed and supervised the study. All authors gave final approval for publication.

Compliance with Ethical Standards

Conflict of Interest Authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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