Multiple mutant clones in blood rarely coexist

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Leukemias arise due to mutations in the genome of hematopoietic (blood) cells. Hematopoiesis has a multicompartment architecture, with cells exhibiting different rates of replication and differentiation. At the root of this process, one finds a small number of stem cells, and hence the description of the mutation-selection dynamics of blood cells calls for a stochastic approach. We use stochastic dynamics to investigate to which extent acquired hematopoietic disorders are associated with mutations of single or multiple genes within developing blood cells. Our analysis considers the appearance of mutations both in the stem cell compartment as well as in more committed compartments. We conclude that in the absence of genomic instability, acquired hematopoietic disorders due to mutations in multiple genes are most likely very rare events, as multiple mutations typically require much longer development times compared to those associated with a single mutation.

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I. INTRODUCTION

The emergence of large multicellular organisms required the development of systems for the mass transport of oxygen and nutrients to cells far from exchange surfaces. The problem was solved by the evolution of the circulatory system and hematopoiesis. Hematopoiesis is the process for the generation of all the cellular blood elements. A continuous supply of cells is necessary to compensate for the loss of cells due to apoptotic senescence or migration out of the circulating compartment. Blood cell formation has at its root hematopoietic stem cells (HSC) that have the dual property of self-renewal and the ability to differentiate into all types of blood cells [1–3]. This hierarchical architecture protects the organism against accumulation of mutations in the system [4,5].

Unlike other forms of cancer, which have benefited from the application of techniques developed in theoretical physics, in particular, those aspects related with the growth and vascularization of solid tumors [6–11], blood cancers have not been under such an intensive focus by physicists, despite recent applications more related with cell replication and proliferation [12,13]. This is likely related to the fact that, despite the tremendous advances and improved techniques achieved in the meantime, only recently a quantitative estimate of the number of stem cells actively contributing to hematopoiesis at any time in adult mammals has been provided [14]. In adult humans the number is very small ($\approx$400) (being even smaller in young infants [15]), and each cell replicates, on average, once per year. Both features lead to an efficient mechanism which protects mammals against hematopoietic stem cell disorders [16]. Such small numbers and long time scales are to be contrasted with the fact that, per day, $\approx 3.5 \times 10^{11}$ blood cells are routinely replaced in an adult human. Only recently, a bridge between stem cells and circulating blood cells has been established [17]. In this new picture, hematopoiesis is described as a multicompartment model in which cells flow from upstream to downstream compartments at increasing rates. Normal hematopoiesis corresponds to a stationary state of this multicompartment system characterized by a conserved (on average) number of cells in each compartment.

From a physics perspective, the hematopoietic system constitutes a fascinating system, spanning 11 orders of magnitude in size and over 4 orders of magnitude in time at the cell level. In particular, the small number and slow replication rate of stem cells calls for a stochastic description of their mutation-selection dynamics, justifying the well-known hypothesis of the intrinsically stochastic nature of hematopoiesis [18,19].

Current understanding of acquired hematopoietic disorders places their origin to mutations in the cellular genome, which typically occur during cell division. Mutations can lead to neoplastic (e.g., chronic myeloid leukemia, CML) or non-neoplastic cell proliferation (e.g., paroxysmal nocturnal hemoglobinuria, PNH). In the latter disorder, patients often have more than one distinct group of mutated cells (clones), each having an independent mutation in the same PIG-A gene (which is specific for this disorder [20]). Usually, patients have a dominant clone and a smaller clone and it is pertinent to ask what the cell of origin is for these two distinct mutations. Moreover, given the known mutation rate in these cells [21], how likely is it that a given cell will acquire a mutation in two distinct genes that could interact in this disorder?

Here we investigate these issues by explicitly taking into consideration the stochastic nature of hematopoiesis. Because not all hematopoietic disorders originate necessarily in the stem cell compartment [22], we make use of the compartmental model of hematopoiesis recently developed to address the aforementioned question for mutations occurring in an arbitrary compartment, and to elucidate the probable cellular origin of such multiple mutants. To this end we use stochastic selection-mutation dynamics and provide a detailed analysis of the processes and also of the nature of the

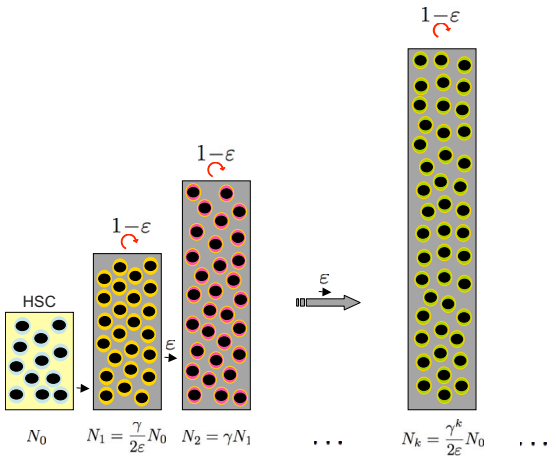

FIG. 1. (Color online) Hierarchical organization of the hematopoeitic system. On the stem cell level, we have N_0 stem cells, which can differentiate into all types of blood cells. After one differentiation step, we have N_1 cells, which can either differentiate further or divide symmetrically to increase the compartment size. We assume that this process is the same in all downstream compartments.

approximations used in order to derive analytical results. Furthermore, our analytical predictions are compared to full stochastic simulations of our model system. A preliminary account of some of these results has been published elsewhere [23].

Our paper is organized as follows: In Sec. II we summarize the multicompartment model of hematopoiesis on which we build the present study; Sec. III investigates the origin of multiple mutations, both for those originating in the stem cell compartment, as well as for those originating in downstream compartments. In Sec. III B we investigate the survival time of mutations, whereas in Sec. IV we discuss the results and offer conclusions.

II. MODEL OF THE HEMATOPOIETIC SYSTEM

We consider the following hierarchical model of blood cell formation [17]: A compartment 0 with N_0 active stem cells drives hematopoiesis (see Fig. 1). Within this stem cell compartment, a Moran (stochastic birth-death) process with constant population size is assumed [24]. Each active stem cell replicates at the rate η_0. Replication may lead to two differentiated cells $\bullet \rightarrow \circ + \circ$, that move to compartment 1, or to two identical cells (self-renewal) $\bullet \rightarrow \bullet + \bullet$, which remain in compartment 0. To ensure that the stem cell population remains constant, differentiation and self-renewal occur with the same probability. The same quantitative outcome could be produced by stem cells that divide asymmetrically and produce (i) one cell that remains in the stem cell compartment, and (ii) a differentiated cell that moves into compartment 1. However, in that case there would be no dynamics at the stem cell level.

We assume that the dynamics follows a similar mechanism in all downstream compartments. With probability ε, any cell in compartment k produces two differentiated cells, $\bullet \rightarrow \circ + \circ$, that move to the next (downstream) compartment $k+1$. With probability $1-\varepsilon$, the cell contributes to increase the number of cells in compartment k by dividing without differentiation, $\bullet \rightarrow \bullet + \bullet$. Thus, the number of cells in compartment k increases by influx from the upstream compartment $k-1$ and self-renewal within the compartment. It decreases by differentiation into the next compartment $k+1$. In compartment 1, cells divide at a rate $\eta_1 > \eta_0$. The influx from the stem cell compartment 0 is $N_0\eta_0$. The outflow to compartment 2 is $N_1\varepsilon\eta_1$. Self-renewal changes the number of cells at a rate $N_1(1-\varepsilon)\eta_1$. Therefore, under stationary conditions in the first compartment, we have $\eta_0 N_0 + N_1(1-\varepsilon)\eta_1 = N_1\varepsilon\eta_1$. In compartments $k>2$, under stationary conditions we have

$$2N_{k-1}\varepsilon\eta_{k-1} + N_k(1-\varepsilon)\eta_k = N_k\varepsilon\eta_k. \tag{1}$$

We assume that η_k/η_{k-1} is constant, which leads to an exponential increase of the replication rate. Similarly, the number of cells in the compartments is assumed to increase exponentially with k. In [17], we estimated

$$N_k = \frac{1}{2\varepsilon}N_0\gamma^k \quad \text{and} \quad \eta_k = \eta_0\eta^k, \tag{2}$$

where $N_0=400$, $\eta_0=1/\text{year}$, $\varepsilon=0.85$, $\eta=1.26$, and $\gamma=\frac{1}{\eta}\frac{2\varepsilon}{2\varepsilon-1} \approx 1.93$. The parameters have been fixed using (i) data from the expansion during polymorphonuclear leukocyte production [25,26]; (ii) the number of active hematopoeitc stem cells and average daily output of the blood system [14,27]; and (iii) the cell division rates of stem cells and granulocyte precursors [27–29].

This process maintains the average number of cells in each compartment. Consequently, in the following we will profit from this conservation of cell number and concentrate on those processes in which the number of mutant cells increases or decreases. The dynamics of hematopoiesis in this model and the compatibility of the model predictions with the limited experimental data available is discussed in [17].

III. ORIGIN OF MULTIPLE MUTATIONS

Let us now consider the role of mutations in this system. A mutation that appears at the level of the stem cells can either be ultimately lost (if the mutant cells differentiate and no mutant stem cell remains) or then end up taking over the stem cell pool. Throughout this paper, we concentrate on mutations that do not have a significant influence on the reproduction properties of cells, i.e., we consider neutral mutations only. Thus, in each compartment k, both wild-type and mutated cells all replicate at the same rate η_k. Because we assume that cells never move upstream, i.e., from compartment k to $k-1$, new mutations originating in a downstream compartment $k>0$ are ultimately lost. The upstream compartment $k-1$ consists of wild-type cells that do not carry this new mutation and thus leads to a constant influx of nonmutated cells into compartment k. This architecture leads to an effective disadvantage of mutants arising in non-stem cell compartments and constitutes a very efficient mechanism of organism protection against tumor invasion [16].

A. Multiple mutations at the stem cell level

First, we address the question of how likely it is that a second independent mutation in the same gene appears at the stem cell level before the number of cells with an initial mutation reaches a certain threshold number M. Such a threshold reflects the fact that a minimum number of mutated cells must be present before diagnosis is possible [30–34]. The current definitions for diagnosis require a threshold of 20% of "blasts" in the bone marrow in the case of leukemia or PIG-A mutated mononuclear cells in PNH. These thresholds are expected to decrease as diagnostic technologies improve. Nonetheless, current experimental and clinical diagnosis relies on such thresholds and we incorporate them to be in compliance with current medical practice.

We consider a stem cell pool of N_0 cells. If the number of mutant cells is j, then the probability that an additional neutral mutant is produced in each time step is $T_j^+ = \frac{N_0-j}{N_0}\frac{j}{N_0}$. The first term is the probability that a normal cell differentiates and the second term is the probability for self-renewal of a mutant cell. Similarly, we have $T_j^- = \frac{j}{N_0}\frac{N_0-j}{N_0}$. Since $T_j^+ = T_j^-$, the probability to reach M mutant cells starting from j is simply $\phi_j^M = j/M$. The general equation for the conditional average time to reach the threshold M starting from 1, given as Eq. (A4) in the Appendix, simplifies to

$$t_1^M = M(R_0^M - R_1^M) - R_0^M, \tag{3}$$

with

$$R_i^M = \frac{N_0}{M}\sum_{l=i+1}^{M-1}\sum_{k=l}^{M-1}\frac{1}{N-k}. \tag{4}$$

We have $R_0^M - R_1^M = \frac{1}{M}\sum_{k=1}^{M-1}\frac{N_0}{N_0-k}$. Now, we can reorganize the equation for t_1^M by counting the terms in $N_0/(N_0-i)$. From the first term in Eq. (3) we have one such term. In the second term R_0^M with the double sum we have a factor $(M-i)/M$ in front of the term $N_0/(N_0-i)$. We can rearrange all the terms from $i=1$ to $i=M-1$ in this way and obtain

$$t_1^M = \frac{N_0}{M}\sum_{i=1}^{M-1}\frac{M-i}{N_0-i}. \tag{5}$$

This is the average number of cell divisions per stem cell until the initial mutant has produced M mutated cells within the stem cell compartment. The maximum number of cell divisions occurring in the mutant population is bounded by $t_1^M N_0$. If the mutation rate per gene per cell division is μ, then the upper limit for the expected number of new second mutants during the time until the first mutant reaches the threshold M is given by

$$F < \mu\frac{N_0^2}{M}\sum_{i=1}^{M-1}\frac{M-i}{N_0-i}. \tag{6}$$

For $N_0=400$, $M=0.2N$, and $\mu=10^{-7}$, we obtain $F<0.0085$. Here, we have used the estimate of the number of HSC N_0 from [17] and the mutation rate from [35]. Since $F \ll 1$, it is unlikely that a second mutant appears at the stem cell level. Recent experiments support this [36]. When the mutants have a higher fitness than wild-type cells, the time until the threshold is reached is smaller. Thus, in this case it is even less likely that a second stem cell mutation appears during this process.

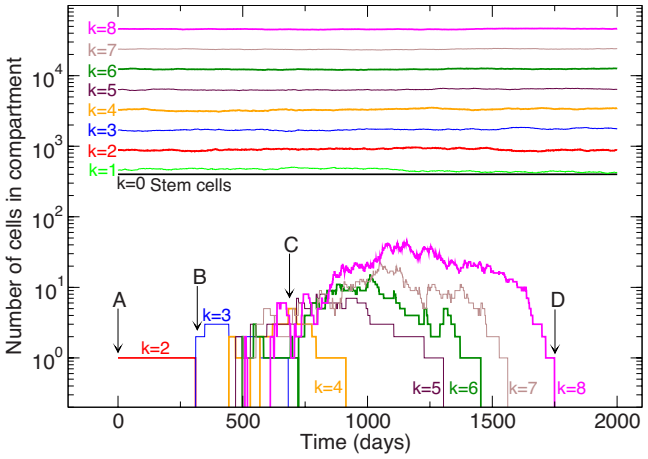

FIG. 2. (Color online) Growth and extinction of a mutant clone arising in compartment $k=2$. The upper part of the figure shows the sizes of the first nine compartments. The average size of these compartments increases exponentially, starting from the stem cell compartment $k=0$ with $N_0=400$ cells. The lower part shows the number of mutant cells, coded with the same colors. The typical development of a mutant clone can be illustrated as follows: (A), a mutation in one of the cells in compartment $k=2$ occurs during cell division. (B), the mutant cell divides and produces two mutant cells in compartment $k=3$. Thus, no mutants are left in compartment $k=2$. (C), the mutant cells in compartment $k=3$ vanish, after producing several mutated cells in the downstream compartments. (D), the last mutated cells in compartment $k=8$ differentiates into compartment $k=9$ (not shown).

So far, we have neglected the possibility of asymmetric cell division in which a stem cell divides and produces one stem cell and one differentiated cell. If we assume that 50% of the cell divisions are asymmetric, then every second cell division leaves the stem cell pool unchanged. Thus, the time until the threshold M is reached doubles. In this case, one also has to be careful if the mutation rate is the same for asymmetric and symmetric cell divisions. Nonetheless, even a factor 2 in F does not change the conclusion that a second independent mutant is unlikely to occur at the level of the stem cell compartment. The impact of asymmetric cell divisions on stem cell behavior is discussed in more detail in [37].

B. Survival time of downstream mutations

Now, let us calculate the average time a mutated cell, originating in a downstream compartment, survives in that compartment. This process is illustrated in Fig. 2. In each time step, the number of mutants j in compartment k can either increase by one, remain the same, or decrease by one.

Their number will increase if a mutant cell undergoes self-renewal and produces a second mutant in compartment k. This process occurs at rate η_k, which is specific for each compartment and increases exponentially with k [see Eq.

(2)]. The probability to increase the number of mutant cells in compartment k during a time interval $1/\eta_k$ is

$$T_j^+ = (1-\varepsilon)\frac{j}{N_k}. \tag{7}$$

Similarly, the number of mutant cells is decreased in a time interval $1/\eta_k$ if they differentiate and leave the compartment. This process occurs with probability $T_j^- = \varepsilon\frac{j}{N_k}$ [42]. Self-renewal is less likely than differentiation [25,26,28], otherwise the number of cells does not increase with increasing compartment number. In our case, this means $\varepsilon > 0.5$. Thus, in each downstream compartment mutant cells are effectively at a disadvantage. To see this, we can compute the effective relative fitness of mutated cells (wild-type cells, by definition, have a relative fitness of 1) as

$$r = \frac{T_j^+}{T_j^-} \approx \frac{1-\varepsilon}{\varepsilon} < 1. \tag{8}$$

For normal hematopoiesis, we obtain $r \approx 0.19$, which shows that mutant cells are very disadvantageous. Consequently, it is extremely unlikely that mutant cells reach a significant fraction of the population in compartment k, i.e., $j \ll N_k$.

The fixation probability for j mutants with fitness r in a population of size N_k is

$$\phi_j^{N_k} = \frac{1-r^{-j}}{1-r^{-N_k}} \ll \frac{j}{N_k}. \tag{9}$$

Given the very low probability of fixation, we concentrate on the opposite fate, namely, extinction of the mutated cell lineage. Since extinction is very likely, we calculate the average time until it occurs.

The general equation for the extinction time can be found in the Appendix. Using our approximations, the conditional extinction time of a single mutant with relative fitness r is given by

$$\tau = t_1^0 = \frac{1+r}{r}\frac{\phi_1^{N_k}}{1-\phi_1^{N_k}}\sum_{l=1}^{N_k-1}\sum_{p=1}^{l}\frac{1-\phi_p^{N_k}}{p}r^{p-l}. \tag{10}$$

For the sake of simplicity, we measure the time scale in generations (1 generation=N_k cell divisions in the population). Thus, we have to divide by the rate η_k to recover the time in, e.g., days. Our aim is to find a simpler formulation given that the mutant is disadvantageous, $r<1$. First, we note that $\phi_1^{N_k} \approx \phi_p^{N_k}$ if p is not too large. Both probabilities are very small for disadvantageous mutants in large populations. From this, we obtain

$$\tau \approx \frac{1+r}{r}\phi_1^{N_k}\sum_{l=1}^{N_k-1}\sum_{p=1}^{l}\frac{1}{p}r^{p-l}. \tag{11}$$

Next, we use the definition of $\phi_1^{N_k}$ and observe that for disadvantageous mutants with $r<1$, we have $r^{-N_k} \gg 1$. Thus, we have $\phi_1^{N_k} \approx (r^{-1}-1)r^{N_k}$. With this, we arrive at

$$\tau \approx \frac{1-r^2}{r^2}\sum_{l=1}^{N_k-1}\sum_{p=1}^{l}\frac{1}{p}r^{N_k+p-l}. \tag{12}$$

Because r^p decreases rapidly with p, we can assume that the second sum goes from 1 to N_k-1 rather than only to l. Then, we can exchange the sums and solve one of them,

$$\tau \approx \frac{1-r^2}{r^2}\sum_{p=1}^{N_k-1}\frac{1}{p}r^{N_k+p}\sum_{l=1}^{N_k-1}r^{-l} = \frac{1-r^2}{r^2}\sum_{p=1}^{N_k-1}\frac{1}{p}r^{N_k+p}\frac{r^{1-N_k}-1}{1-r}. \tag{13}$$

With $r^p \gg r^{N_k+p-1}$, this can be well approximated by

$$\tau \approx \frac{1+r}{r}\sum_{p=1}^{N_k-1}\frac{1}{p}r^p. \tag{14}$$

Next, we use the identity $\frac{1}{p}r^p = \int_0^r x^{p-1}dx$ and change the order of the sum and the integral. Since $r<1$, we also have $x<1$. This yields

$$\tau \approx \frac{1+r}{r}\int_0^r\sum_{p=1}^{N_k-1}x^{p-1}dx = \frac{1+r}{r}\int_0^r\frac{1-x^{N_k-1}}{1-x}dx. \tag{15}$$

Neglecting the x^{N_k-1} (since N_k is large and $x<1$), we can solve the integral and finally arrive at

$$\tau \approx \frac{1+r}{r}\ln\left(\frac{1}{1-r}\right) = \frac{1}{1-\varepsilon}\ln\left(\frac{1}{2\varepsilon-1}\right). \tag{16}$$

In order to recover the time in, e.g., days, we have to divide this by the cell division rate η_k, which gives the natural time scale of cell division in each compartment. Thus, the average time $\mathcal{T}_k$ a mutant in compartment k survives in days is given by

$$\mathcal{T}_k \approx \frac{\eta^{-k}}{\eta_0}\frac{2\varepsilon}{1-\varepsilon}\ln\left(\frac{1}{2\varepsilon-1}\right). \tag{17}$$

Consequently, the average survival time decreases exponentially with the compartment number, i.e., the more differentiated the cell of the original mutation, the shorter the survival time (Fig. 3). Since mutations in more differentiated cells also lead to smaller clones, we predict that smaller clones will survive for shorter times [23]. Very recently, this has been supported by experiments [38].

This approximation works well if r is not too close to 1 and if the population is large. For a biologically plausible $\varepsilon=0.85$, it is a good approximation even for small compartment sizes [43].

IV. DISCUSSION

Our results provide important insights on the evolutionary dynamics of mutations within hematopoiesis. With respect to PNH, we can conclude that in the vast majority of patients, only one of the clones originates within the SC pool. The mutant SC population would be responsible for the larger of the clones detectable in these patients. The other (smaller) clone most likely originates in a cell downstream of the SC pool. This clone will be expected to survive for a shorter

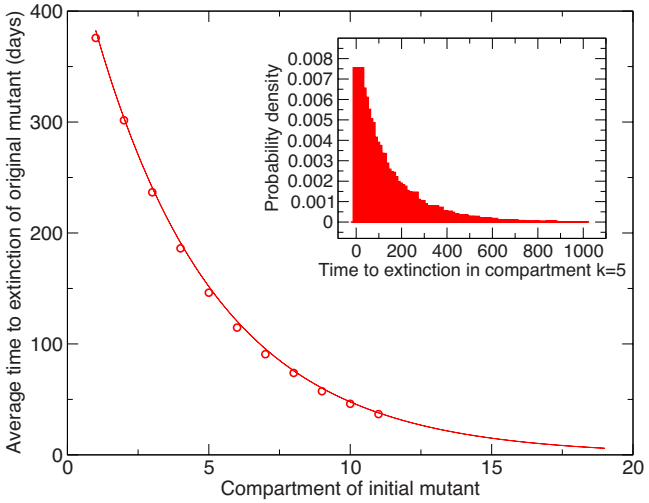

FIG. 3. (Color online) Average time to extinction of the original clone. The symbols show full stochastic simulations of a system with a hierarchy of $K=12$ compartments. Our analytical approximation Eq. (17) (full line) agrees very well with these numerical results. For the simulation, we consider K competing rate processes. For each compartment, we choose an exponentially distributed random number with parameter $N_k\eta_k$, which corresponds to the waiting time for the next cell division in each compartment. In the compartment with the shortest waiting time, either self-renewal or differentiation occurs. The inset shows the exponential probability distribution of the extinction times of a mutant originating in compartment $k=5$ (averages over 10^4 extinction events).

time interval compared to the larger clone, although this can be long due to stochastic effects, more so if the size of the compartment is small as occurs in hypoplastic or aplastic anemia [23].

There is experimental evidence that some forms of acute leukemia can arise within the progenitor cell pool [22]. According to the present hierarchical model of hematopoiesis, one expects these cells to contribute to hematopoiesis for several months, being subsequently replaced. Consequently, in order to account for the known persistence of acute leukemic disorders, we conclude that such a mutant cell must acquire the capability for long-term self-renewal early on, in this way bypassing their own constraints related to the hierarchical model. Indeed, if this does not happen, the mutant population will be washed out in time, as it will appear as a clone with reduced fitness. Moreover, our results suggest that, if a hematopoietic neoplasm requires a combination of multiple mutations, then it will most likely develop in the presence of genomic instability. Indeed, genomic instability may provide the pathway for the development of abnormal mutation rates, which are necessary to explain the kinetics of the disease within such a small pool of cells. In the specific case of PNH, available data clearly rule out genomic instability [21], and consequently our results are expected to apply more accurately. In this context, our results also suggest that it is unlikely that a SC with a mutation in the PIG-A gene will acquire a mutation in a second gene with high frequency. Hence, clonal expansion of the mutant population is unlikely to be correlated with the presence of a second mutated gene (e.g., HMGA2 [39]) that would confer a fitness advantage to the cells. In other words, clonal expansion in most patients with PNH requires an alternative explanation.

Overall, our results show the power of a stochastic dynamics approach to biological systems encompassing simultaneously several orders of magnitude in what concerns size and characteristic time scales. Our approach was motivated by the physiology of the hematopoietic system and associated disorders, and benefits from a recent hierarchical model in which the nature of stochastic effects assumes a prominent role. The framework adopted, however, is very general and, consequently, we expect it to be applicable to other biological processes as well.

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APPENDIX: GENERAL FORMULATION FOR CONDITIONAL AVERAGE FIXATION TIMES

We consider a birth-death process with transition probabilities $T_j^{\pm}$ from state j to state $j\pm1$. With probability $1-T_j^+-T_j^-$, the system remains in state j. From the transition probabilities, the conditional average time until a certain other state is reached for the first time can be calculated. The derivation of these average times shown here can be found e.g., in [40,41].

1. Time until a threshold is reached

The conditional average time to reach threshold $M>i$ (associated with medical diagnosis of the disorder) starting from i is given by

$$t_i^M=\left(\frac{1}{\phi_i^M}-1\right)R_0^M-\frac{1}{\phi_i^M}R_i^M. \tag{A1}$$

Here, the probability to reach M is given by

$$\phi_i^M=\frac{1+\sum_{j=1}^{i-1}\prod_{k=1}^{j}\frac{T_j^-}{T_j^+}}{1+\sum_{j=1}^{M-1}\prod_{k=1}^{j}\frac{T_j^-}{T_j^+}}. \tag{A2}$$

Further, the quantity R_i^M is defined as

$$R_i^M=\frac{1}{N}\sum_{l=i+1}^{M-1}\left(\prod_{j=1}^{l-1}\frac{T_j^-}{T_j^+}\right)\sum_{k=l}^{M-1}\frac{\phi_k^M}{T_k^+\left(\prod_{j=1}^{k}\frac{T_j^-}{T_j^+}\right)}. \tag{A3}$$

We note that we only consider average times here. It is known that these times can have a very large variability, in

particular, in the case considered here, where mutants are neutral [30].

2. Extinction time

The conditional average time until i mutants are removed from the system in a birth-death process is

$$t_i^0 = \left(\frac{1}{\phi_i^0} - 1\right) Q_N - \frac{1}{\phi_i^0} Q_i. \tag{A4}$$

Here, one time unit is identical to one birth-death event. The probability $\phi_i^0 = 1 - \phi_i^N$ for extinction of the mutants is given by

$$\phi_i^0 = 1 - \frac{\sum_{j=0}^{i-1} \prod_{k=1}^{j} \frac{T_j^-}{T_j^+}}{\sum_{j=0}^{N-1} \prod_{k=1}^{j} \frac{T_j^-}{T_j^+}}. \tag{A5}$$

The function Q_i is defined as

$$Q_i = \frac{1}{N} \sum_{l=1}^{i-1} \left(\prod_{j=1}^{l} \frac{T_j^-}{T_j^+} \right) \sum_{p=1}^{l} \frac{\phi_p^0}{T_p^+ \left(\prod_{j=1}^{p} \frac{T_j^-}{T_j^+} \right)}. \tag{A6}$$

In our case, this general equation can be simplified significantly, as shown in the main text.

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[42] The conservation of the average number of cells N_k in each compartment k, reflected in the values of ε and η_k used, allow us to use a Moran birth-death process to study cell dynamics in downstream compartments.
[43] If the mutated cells proliferate faster, the ratio T_j^+/T_j^- is not affected. Thus, the probabilities of fixation do not change, only the time scale. On average, faster cell proliferation will lead to a faster differentiation (and extinction) of the mutant cells in the compartment in which the mutants arise.