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Concise Review: Stem Cell Population Biology: Insights from Hematopoiesis

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ABSTRACT

Stem cells are fundamental to human life and offer great therapeutic potential, yet their biology remains incompletely—or in cases even poorly—understood. The field of stem cell biology has grown substantially in recent years due to a combination of experimental and theoretical contributions: the experimental branch of this work provides data in an ever-increasing number of dimensions, while the theoretical branch seeks to determine suitable models of the fundamental stem cell processes that these data describe. The application of population dynamics to biology is amongst the oldest applications of mathematics to biology, and the population dynamics perspective continues to offer much today. Here we describe the impact that such a perspective has made in the field of stem cell biology. Using hematopoietic stem cells as our model system, we discuss the approaches that have been used to study their key properties, such as capacity for self-renewal, differentiation, and cell fate lineage choice. We will also discuss the relevance of population dynamics in models of stem cells and cancer, where competition naturally emerges as an influential factor on the temporal evolution of cell populations. STEM CELLS *2016; 00:000–000*

SIGNIFICANCE STATEMENT

Adult stem cells engage in complex interactions with their environment and progeny; these are believed to maintain their stemness. Here we put these observations into a population biology framework which allows us to take ideas from ecology and shed light on the dynamics within the stem cell niche. Using the particular example of hematopoietic stem cells, we show that this perspective helps to understand stem cell dynamics both in cases of health and disease.

INTRODUCTION

Mathematical modeling already has a rich history of application to biology, despite the perceived dichotomy between mathematical and biological science [1]. However, it is only in the last decade or so, with leaps in our ability to quantify cellular and molecular biology, that systems biology of cells and tissues has arisen, and greatly enhanced our knowledge of human biology in health and disease.

Stem cell biology concerns cells (in development and adulthood) that exhibit *stemness*; an elusive characteristic as we will discuss, it is loosely defined by the ability of a cell to self-renew and to produce progeny indefinitely. Hematopoiesis describes the formation of blood cells, driven by a population of hematopoietic stem cells (HSCs) in the bone marrow [2]. This is a highly dynamic system, producing two million new red blood cells every second [3], and it is perhaps the best characterized mammalian stem cell system. It is thus well-suited to addressing general questions about stem cell behavior, in addition to addressing questions about the regulation of hematopoiesis.

Population biology studies the behavior and interactions of groups of species—traditionally whole organisms, but these can also be cellular species including stem cells. We argue that—in the tradition of Dobzhansky and Lynch [4, 5]—nothing in stem cell biology makes sense except in the light of population biology. In order to answer questions regarding (for example) stem cell differentiation, lineage fate, and competition, one must consider more than individual cells or even lineages, but the complex set of interactions within and between cell lineages and the extent of environmental influences. Indeed, as the body of literature on stem cell mathematical models grows (see Population Dynamics section below), efforts increasingly include a population perspective, and the results are rewarding. For example, we now have better theories

of how stem cell (a)symmetric division is controlled, and of the role that competition plays in determining outcome, following incidence of cancer.

In the next section, we give an overview of population biology in a historical context and introduce the key concepts of competition and stability. We go on to discuss current understanding of stem cell function, behavior, and the role of the niche with focus on the HSC system. Subsequently, we explain how the population perspective has brought insights into stem cell models, first for the healthy hematopoietic system and second in cases of disease. We end by drawing some conclusions and tentatively mapping out the road ahead for both biologists and theoreticians.

Theoretical Population Biology—An Introduction for Cell Biologists

One of the best-known models describing a dynamical system, which arguably marked the beginnings of mathematical biology, is given by the 100-year-old Lotka-Volterra equations [6, 7]. The system describes two populations, X and Y, which interact in the following way:

$$\frac{dx}{dt} = x(\alpha - \gamma y) \quad (1)$$

$$\frac{dy}{dt} = y(\gamma x - \beta) \quad (2)$$

where x and y denote the abundances of species X and Y respectively. In the absence of Y, X will grow exponentially at rate α; in the absence of X, Y dies (decays) at rate β. When both species are present, Y consumes or depletes X at rate γxy: proportional to parameter γ and the interaction between X and Y. This system is interesting dynamically because it permits, depending on the values of the parameters α, β, and γ, stable oscillations between X and Y. In Figure 1, we plot the solutions to equations (1) and (2), denoting X as "hares" and Y as "lynxes" (a classic pair of predator-prey species). It can be seen that both species exhibit stable oscillations; the stationary state at these parameter values is known as a limit cycle.

There are three important concepts to highlight from the Lotka-Volterra example. The first is that by specifying our biological assumptions precisely using mathematics, we are able to test them quantitatively in a way that was not possible before. Rather than suggesting that "hare population growth is limited by the rate at which hares are eaten by lynxes," we can quantify this statement by creating a mathematical model and then test it by simulating the model and evaluating its ability to describe biological data. For example, after 2 years (48 months) in the simulation of Figure 1, there are approximately equal populations of hares and lynxes. The model predicts that 6 months later there will be many more hares than lynxes. We can ask what would happen if, at 48 months, lynxes began to predate on hares twice as much. Under these conditions, the lynx population would not have dropped and still be around 5-6 months later, and the hare population would have risen more slowly than before.

The second concept to highlight is that this very simple model with only three parameters already describes quite well the interactions between two species. Additional terms

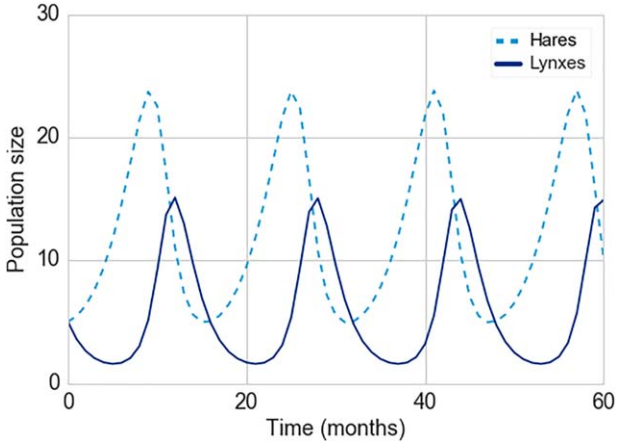

Figure 1. Population dynamics of competition. Simulation of the Lotka-Volterra equations as given by equations (1)–(2) with parameters $\alpha = 0.3$, $\beta = 0.6$, $\gamma = 0.05$.

are needed to provide a good fit to most real predator-prey datasets, but this basic model is a good first step. That (vastly) complicated biological systems can be described successfully by (very) simple models is perhaps the most important lesson here. Finally, by establishing the validity of this model, we are able to use it to make predictions and thus prompt new biological hypotheses.

In the 1960s, MacArthur and Wilson [8] made a pivotal contribution to population biology with the introduction of the concept of *Island Biogeography*, which they used to predict how ecological dynamics would determine species' richness in island habitats. These can be islands of land surrounded by water, or less traditional "islands" such as mountain peaks, trees or areas of a lake divided according to their temperatures [9]. Alternatively, islands (referred to as *niches*) could be areas defined spatially or functionally within multicellular organisms that determine the function or dynamics of particular cell types. In 1972, May [10] proved a theorem stating that as systems (of randomly interacting species) grow, their stability in general will decrease and tend toward zeros for large enough (or very highly connected) systems. This went against scientific opinion at the time, which had assumed that stability ought to increase with complexity [11, 12]. May [13] went on to develop the concept of niche overlap, demonstrating how variability between species can impact their ability to occupy the same niche. Competition naturally arises in cases where niches overlap; this becomes particularly relevant when we consider healthy and malignant stem cells, as we will see below.

Evolutionary game theory, pioneered by Maynard Smith and others [14], was developed alongside theoretical ecology and provided new tools for studying dynamics within populations of species. Given a set of players and for each player a set of strategies, it can be found whether there are evolutionary stable strategies: these are ones for which, if adopted by the whole (large $\rightarrow$ infinite) population, no mutant can enter and displace the existing species. Despite their different origins, both May's stability criteria [10] and the evolutionary stable strategies of Maynard Smith [14] define conditions under which a system, if perturbed, will return to its initial

state. Such frameworks enable us to interrogate the capacity for systems to perform robustly in dynamic environments. The multicellular organism provides a prime example of such an environment.

Alongside these developments, significant contributions to the study of population dynamics were also made through use of models in cell biology. Mackey [15] developed mathematical models to describe cyclical dynamics in hematopoiesis, enabling assessment of the impact to the system of certain parameters, such as proliferation or differentiation rates [15–17]. This represents one of the earliest mathematical models considering directly testable hypotheses (following, e.g., Till et al. [18]), and enabling rigorous investigation of stability within the hematopoietic system. Other early example of fruitful modeling work regarding hematopoiesis stem from immunology, in particular on regulatory immune cell dynamics in response to viral infections; for example [19], and reviewed in [20].

More recent work has shed new light onto the topics of complexity and stability in biological systems. Allesina and Tang [21] advanced the results of [10] by deriving stability properties of randomly interacting communities that exhibited structure, however these structured systems still do not behave according to a known set of interactions (such as e.g., for equations. (1) and (2)). This is addressed in [22] by a statistical analysis of stability. Here it is shown that stability properties depend crucially on the type of model that is considered, and that great care must be taken in drawing conclusions regarding the stability of systems without reference to a particular model. It has also been shown for models of stem cell differentiation [23] that the niche confers stability onto stem cell systems with remarkably high probability [24], in contrast to previous results. Thus, despite the time that has passed since the work of Lotka and Volterra, questions regarding the stability of ecosystems remain very topical today, and the debate rumbles on [25, 26].

Stem Cell Niche Dynamics

Stem cells are governed by intrinsic and extrinsic processes that remain incompletely characterized. We are going to focus on hematopoiesis as a model system because it is well-suited to addressing questions of stem cell biology, and population biology. Thus, the results of studies of the hematopoietic system can inform stem cell behavior more generally; in particular regarding questions of niche population dynamics and competition. Here the ideas from ecology developed above can prove useful.

Hematopoietic Stem Cells

Hematopoiesis occurs in all vertebrates and accounts for the production and renewal of all types of blood cell throughout the lifetime of an animal. Driven by HSCs, this process begins in the yolk sac, aorta-gonad-mesonephros region, and placenta during early development [2]. HSCs subsequently move through the fetal liver and finally migrate to the bone marrow [27], which remains the dominant site of hematopoiesis throughout life, although HSCs can be (reversibly) mobilized into the blood [28]. In the case of severe perturbations, hematopoiesis can occur in the spleen, albeit with sub

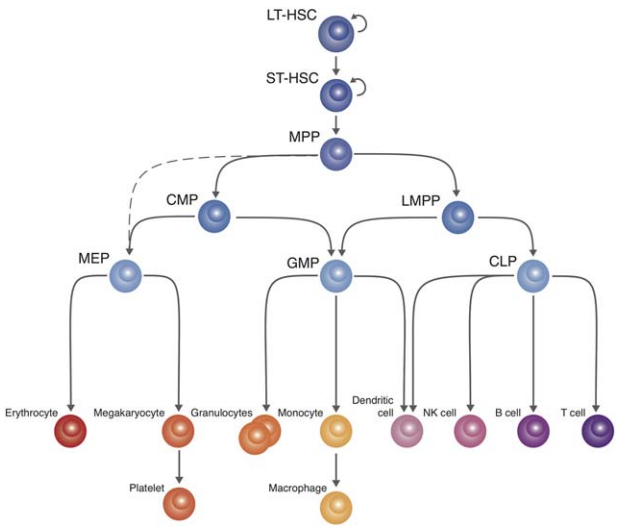

Figure 2. A proposed hierarchical description of hematopoiesis. Dashed arrow denotes a putative transition. Abbreviations: CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte-macrophage progenitor; HSCs, hematopoietic stem cells; LMPP, lymphoid-primed multipotent progenitor; LT, long term; MEP, megakaryocyte-erythroid progenitor; NK, natural killer, ST, short term.

optimal output [29]. Hematopoiesis is hierarchical, and can be pictured as a series of branchings in which HSCs give rise to successively more lineage-restricted progenitor, and eventually terminally differentiated cell populations. A schematic of this hierarchy is shown in Figure 2. Recent work has challenged the status of the hematopoietic hierarchy [30, 31], and suggests a move toward fewer branch points and greater heterogeneity within the system than was previously thought. This should, if substantiated, also shape the stability of the dynamics of the hematopoietic system [22, 24].

Qualifying the *stemness* of a cell is not straightforward [32, 33]. The long-term follow-up required to prove that the cell can regenerate tissue successfully, coupled with the heterogeneity of most (if not all) cell populations means that we cannot ever say with certainty that a particular cell is an HSC. The best we can do is to define as HSCs the population we obtain by sorting cells using the best available cell surface markers with the knowledge that probably only a subpopulation of these are "true" HSCs. It is thus worth keeping in mind that, due to the elusive nature of stem cells, analyses can be difficult and may at times rely on inaccurate assumptions.

Competition in a Stem Cell Niche

The niche of an organism is defined as the space it occupies within its habitat and the resources that it requires to function. This definition is applicable to cellular species in the same way as it is to complete organisms. There exists a mammalian niche—found within the bone marrow—that is necessarily occupied by HSCs. This dependence of a (cell) species on its niche bears clear resemblance to many examples in ecology, such as the koala bear, who relies almost entirely on eucalyptus leaves for sustenance: a eucalyptus-supporting environment describes the koala bear's niche. First introduced by Schofield [34], our understanding of the HSC niche has

grown dramatically in recent years: a combination of effects from vasculature, endosteum, endothelial and mesenchymal stromal cells contributes to the niche, although their relative importance is still subject to further analysis [35].

In 2003, it was first shown that osteoblasts regulate HSCs in the niche [36, 37]. Osteoblasts reside in the endosteum—the surface between bone and bone marrow, thus suggesting that the endosteum could be an HSC niche location. Using cell surface markers [38], and then using two-photon and confocal microscopy [39], it was demonstrated that HSCs are indeed found near to vessels and/or osteoblasts and the endosteal surface. The question of whether HSCs are located at or near the endosteum remains under debate, with evidence from Kiel et al. [40] suggesting that HSCs reside near but not at the endosteum. An important role in defining HSC niches is also played by perivascular cells (residing at the periphery of blood vessels) [38, 41]. Other works [42–46] suggest that HSCs occupy a perivascular niche with support from mesenchymal stem cells, endothelial cells, and CXCL12-abudant reticular cells but without support from osteoblasts, based on conditional depletion studies involving the stem cell factor ligand and CXCL12 from different cell types.

In addition to these factors, the progeny of HSCs can directly exert an influence on the niche [47]; and macrophages play a role in niche maintenance [48]. The picture we have is thus complicated and far from complete. The complexity increases further when we consider functional aspects of the niche: how is HSC dormancy controlled [49]? Is the niche solely a place of quiescence or does it also allow for HSC self-renewal [50]? If the niche allows for both quiescence and renewal, does this happen through temporary changes to niche-supporting factors or do HSCs traffic between distinct (sub-)niches when changing fate? Is the niche purely local, or does a level of quorum sensing (of soluble factors) exist?, the contributions of which could appear during steady state hematopoiesis or following some perturbation.

Within the framework of population biology, the definition of the niche may be broader: shifting toward a definition that is functional rather than strictly anatomical [51]. When constructing a model, choice of the niche must depend on the goal of the model and be justified accordingly. In the case of hematopoiesis, it could be defined as the area in which an HSC is in direct contact with a niche-supporting cell, or the extent of influence of all extrinsic niche signals on HSCs, or (more broadly) as the volume of the whole inner bone marrow cavity.

Following malignant transformation in the hematopoietic hierarchy, leukemia can arise, interact with, and disrupt normal hematopoiesis. It has been shown in vivo that leukemia progression disrupts different hematopoietic cell species in different ways [52, 53]. Leukemia might compete with healthy hematopoietic species by directly changing the microenvironment to create abnormal niches [54]. Leukemia stem cells (LSCs) can also drastically alter the niche by affecting mesenchymal stem cell and, in turn, osteoblast function through a number of signaling pathways [55]. As such, bone marrow niches may need to be redefined (both in terms of size and composition) once leukemia is established. What remains unknown is the extent to which HSCs and LSCs respond in similar or different manners to signals from the niche. In some cases, leukemia might interact directly with hematopoietic progenitor cells affecting the parent HSC population only indirectly [56, 57]. There is, in general, a growing role for hematopoietic progenitor populations, challenging the influence that HSCs exert over hematopoiesis [58].

Given this picture of HSCs and LSCs occupying the same or similar niches, competition naturally emerges as an important component of leukemia progression. Describing the nature of competition, how it influences disease, and how it may be overcome becomes a central goal of modeling such systems. Here, by borrowing ideas from ecology, we are set to make much progress and gain greater insight than by considering populations in isolation. Recently, competition has been shown unequivocally to play a role in hematopoietic processes in the thymus [59].

Cancer stem cells, first identified in the leukemia system [60, 61] have also been found in solid tumors including those developing in the brain [62], colon [63, 64], and epidermis [65]. Even given a clonal (nonhierarchical) description of cancer, competition will exist between malignant species and the healthy cells that immediately surround them. Some of the recent work that attempts to elucidate HSC competition can inform our understanding of competition and cancer more generally. Such work may help to answer questions in cancer research from a stem cell perspective, such as the poorly understood mechanisms of metastasis, and the relationship between cell competition within the body and cancer growth/dormancy [66].

Population Dynamics of Hematopoiesis

Here we describe recent attempts to model healthy and malignant hematopoiesis from the perspective of population biology. We also describe a few results from studies of solid tumors, and highlight how such work has yielded insight into the function and dynamics of stem cells.

Models of Healthy Hematopoiesis

Despite considerable success in characterizing hematopoiesis, crucial remaining questions include how stem and multipotent progenitor cells control the balance of symmetric and asymmetric differentiation, and how the system responds to perturbations, such as anemia, infection, or inflammation. Another crucial question regards the nature of stemness itself; as we have discussed, defining a cell as a stem cell is difficult. This was addressed mathematically by Wolkenhauer et al. [67], who propose a definition of stemness based on lineages rather than cells. They go on to prove a theorem showing that tissue fates emerge in a consistent manner from this lineage-based definition of stemness. We are also of the opinion that this approach—moving away from cells and toward lineages—ought to be adopted more often in practice. It frames stem cell biology within a population perspective and in doing so it helps to elucidate tissue-level phenomena.

To study the dynamics of hematopoiesis, Manesso et al. [68] present an ordinary differential equation (ODE) model containing details for many species in the hematopoietic hierarchy. This model is appealing for its coverage of species within the hierarchy (including many stem and progenitor species explicitly). By the inclusion of feedback signaling, the model is able to recapitulate observed steady state levels of species

within the hierarchy following perturbations such as hemorrhage or irradiation. Manesso et al. [68] predict that lymphoid cell maturation is time demanding, especially for the transition from common lymphoid progenitors to naive T cell progenitors, which could take 2,000 days (greater that the average lifespan of a mouse). This result, for which there also exists experimental evidence [69, 70], thus provides evidence against the hematopoiesis paradigm which states that lymphocyte production occurs via a common lymphoid progenitor cell population.

The branching point that divides erythroid and myeloid lineages is particularly well-studied within the hematopoietic hierarchy, and has been shown to be controlled by two master genes: GATA1 and PU.1 [71–73]. These models are able to describe the process of choosing between the two cell fates and propose that (a) cells are "primed" before differentiation and that (b) the primed state can arise following a loss of cooperativity between the two genes. Buzi et al. [74] also address questions of HSC differentiation and identify—via control theory feedback modeling—that the introduction of lineage branching greatly improves the robustness of the system.

Cell-fate decision processes are not instantaneous but depend on the "history" of the cell/lineage; that is an outcome reflects signals that the cell received sometime in the (typically recent) past and acts upon. This can be modeled using delay differential equations [75] and difference equations [76], which have been used to study hematopoiesis, and in particular to investigate fluctuating population sizes. Mackey [75] recapitulate the behavior of periodic fluctuations in different blood cell populations and show that, while stable oscillations exist, the system is chaotic in other regions of parameter space. Xu et al. [76] build on this work to address HSC differentiation via difference equations. They derive conditions that define HSC behavior: either by permitting oscillatory behavior or by guaranteeing a single-valued equilibrium for HSCs (via global asymptotic stability).

In addition to these deterministic models used to study the hematopoietic system, stochastic methods have also been employed [77–80]. These are appropriate when small species numbers make the effects of noise important. Since HSCs are indeed a rare population of cells (they make up approximately 0.01% of cells in the hematopoietic system [81]), stochastic effects are at times important; however the additional computational cost of most stochastic models means that their use should be justified; despite their assumptions, deterministic models often suffice.

A mixture of stochastic kinetics and ODEs (as the mean approximation of the stochastic case) are used by Mangel and Bonsall [77] to model HSC processes of self-renewal and differentiation. The authors use results from life history theory [82] to describe conditions for which HSCs can survive for longest in the niche, and find interesting similarities between the distribution of cell cycle times and the results of Till et al. [18] in their seminal stem cell paper. This suggests that the variation that is seen is the progeny of stem cells in colony-forming assays can be connected to variability in the HSC cell cycle.

The GATA1–PU.1 gene circuit that was considered above from a deterministic perspective has also been analyzed stochastically, via construction of a Boolean network in order to elucidate different attractors of the system [79]. Using this method, the authors claim to describe successfully the four different cell fates (erythrocytes, megakaryocytes, monocytes, and granulocytes) according to their gene expression profiles. In a similar approach, Villani et al. [80] present an interesting model that describes cell differentiation as an emergent property [83] of the underlying gene transcriptional network, using random Boolean networks and linking network attractors to different cell fates. They use this model to stress the role that noise may have in driving differentiation. There is enormous scope for developing further variations of such multiscale models, where molecular processes inside the cell drive and are in turn influenced by, population-level processes.

Inference of general pathways for differentiation is a more difficult problem, yet progress here—in deciphering the qualitative characteristics of hematopoiesis—begins to be made [84, 85]. Buchholz et al. [84] describe immune cell dynamics with a probabilistic model, from which a framework with which to describe T cell specification emerges, stressing the importance of stochastic processes in the determination of phenotype. Perié et al. [85] study pathway specification in the hematopoietic stem and progenitor cell compartments, using cellular barcoding as a means to reconstruct specific lineages. Both of these examples enable analysis of the qualitative pathways that define cell fate during hematopoiesis; as data resolution improves (in particular single-cell data), a need for significant further efforts along similar lines to these will emerge.

Concepts from statistical mechanics are also beginning to gain traction in stem cell biology. Statistical mechanics describes how systems-level (macroscopic) properties emerge from the (microscopic) interactions of a very large number of interacting particles. There has been interest in its application to topics ranging from protein folding to gene regulatory networks [86, 87]. More recently, concepts from statistical mechanics have been applied to stem cell potency and fate determination [88, 89] These works pose the question: how do cell fates (e.g., pluripotent, lineage-specifc) emerge from large networks of interacting transcription factors? Thus progress toward constructing a theory for the statistical mechanics of stem cell states has been made, although these ideas remain generalized and the topic clearly deserves closer attention at all scales ranging from the molecular processes inside cells to the population-level processes inside the niche or the whole organism. Here, too, we can draw on useful analogies to ecology, where concepts from statistical mechanics have yielded qualitative insights into the spatio-temporal dynamics of ecosystems (especially the persistence of species).

Inferring the Parameters of Hematopoiesis

Models allow us to estimate key parameters of hematopoiesis, such as the number of HSCs, their proliferation, and their differentiation rates. Evidence that the total number of HSCs is conserved in mammals—on the order of 10,000 cells per animal [90, 91]—was contested by later models that suggested instead an allometric scaling relationship between the number of active HSCs and the total body mass [92].

Several modeling studies, coupled with experimental observations, have attempted to derive the fundamental rate parameters governing HSCs. To estimate the proliferation rate

of HSCs, different cell labeling assays including bromodeoxyuridine (BrdU), Histone H2B green fluorescent protein (H2B-GFP), and Carboxyfluorescein succinimidyl ester (CFSE) have been used [93–95]. An active/dormant model of HSCs proposes that a subset (15%–45%) of the HSC population are active, with the rest comprising a dormant HSC subset [93, 96]. Estimates for the rate of proliferation of the active fraction of HSCs based on H2B-GFP and BrdU label-retaining assays suggest that stem cells divide approximately once every 28-36 days; and that so-called dormant HSCs divide once every 149-193 days [96]. These numbers are roughly consist with [97], who estimate that, on average, (long-term) HSCs divide once every 110 days and short-term HSCs divide once every 24 days. Foudi et al. [94] derive an even more conservative estimate for the dormants HSCs, dividing at a rate of only 0.8%–1.8% per day. Similar studies have been performed based on CFSE labeling, giving an estimate of active stem cell divisions of seven times in five weeks [95], however the population studied here (Lineage$^-$c-Kit$^+$Sca-1$^+$) is heterogeneous for HSCs. Heterogeneity overall is likely to substantially affect efforts to identify these parameters, so much so that caution must be taken in their application. Furthermore, all of these estimates relate to steady state hematopoiesis, and how these may change following perturbations is largely open to speculation.

In addition to stem cell proliferation rates, the rates of transition (differentiation) between early hematopoietic stem and progenitor cell compartments have been estimated using a Cre-derived reporter mouse whose HSCs selectively express yellow fluorescent protein in response to tamoxifen [97]. This model enables detailed analysis of the rates by which specific (e.g., myeloid) branches of hematopoietic cells are produced, and, coupled with a mathematical model, was used to estimate the proliferation and differentiation rates, via fluxes through the compartments.

As has already been mentioned, the estimates derived in this section do not apply to the system under perturbations, such as irradiation or infection. For such inferences, we require data for control and perturbation scenarios in sufficiently high resolution, and inference ought to be performed within a Bayesian framework. Preliminary efforts toward such goals have been made, however the current disparity between data and model complexity forgoes comprehensive studies [78, 98, 99].

Finally, it is important to keep in mind that our models of hematopoiesis are hopelessly oversimplified representations of a much more complicated real process. This, in turn, needs explicit accounting for [98, 100].

Models of Leukemia and Competition

We now turn our attention to mechanistic models that describe how hematopoiesis is perturbed following cancer incidence. Many models have been developed to study this and related questions, highlighting the need for an explicit description of competition from the outset and providing direction for therapeutic strategies that are most beneficial for disease eradication.

Roeder et al. [101] develop an agent-based model to describe the stem cell dynamics of self-renewal and differentiation and from this work and its extensions [102–104]; the model demonstrates the ability to reproduce expected stem cell behaviors both in health and disease. In the latter case, competition naturally emerges from the model between agents that define healthy and LSCs; the implications of which can thus be studied. The model is used to predict how the hematopoietic system will respond to chronic myeloid leukemia (CML). Here the authors suggest that the efficacy of drug therapy can be increased by stimulating proliferation during therapy [103]. They also provide a predictor for the chance that an individual patient will relapse, thus offering the potential for patients who are predicted not to relapse to be taken off treatment after some time [104].

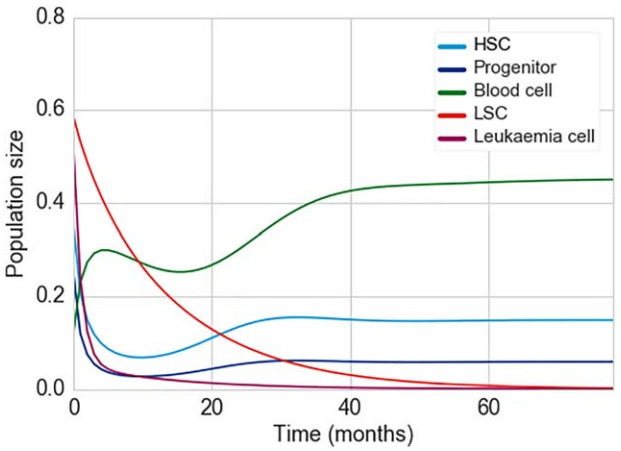

Figure 3. The competition taking place between healthy and LSCs within the HSC niche. Under the in vivo conditions simulated here, leukemia is eradicated from the bone marrow after approximately 60 weeks. [98]. Abbreviations: HSCs, hematopoietic stem cells; LSCs, leukemia stem cells

In 2005, Michor et al. [105] presented an alternative, deterministic model for CML using ODEs. This model was used to suggest that leukemia progresses by a biphasic decline (during treatment), with the first phase representing death of differentiated leukemia cells and the second representing death of leukemia progenitor cells. This model was one of the first descriptions of CML dynamics and provides interesting results, but it does not take into account interactions between healthy and CML lineages. Failure to account for this leads to unrealistic vast overestimation of the abundances of LSCs [98].

Extensions to this model added interactions between HSCs and LSCs, and these new versions were used to model CML dynamics and attempt to provide better treatment practice. The authors predict that adding a stem cell stimulating factor does not enhance treatment of CML [106] and suggest that it might not be safe to discontinue treatment even when disease reaches very low levels [107].

In work that followed, we contended these results, and suggested that in fact maintenance of HSCs is an effective strategy against leukemia [51]. When accounting for population-level feedback mechanisms, it appears that maintenance of a viable HSC pool was more important than a focus on eradication of leukemia cells for disease recovery. In Figure 3, the trajectories of healthy and leukemia cell species are shown as they interact within the bone marrow niche; here we start with a diseased niche but over time find that healthy hematopoiesis is restored and the leukemia species

are driven to extinction. Testing these predictions is currently at the limits of our experimental capabilities, although this is changing [108, 109].

A model comparison study of CML revealed that models without explicit competition between healthy and cancer stem cell lineages could not provide realistic predictions, and demonstrated that those models which do consider competition do so in different, testable ways [98]. In particular, it proposed an important role for progenitor expansion in maintaining remission. This has not yet to our knowledge been tested, but is in line with current thinking in HSC biology which supports a more important role for progenitor cells than had previously been assumed [58].

While these models deal with the dynamics of disease, Traulsen et al. [110] look at how disease in the hematopoietic system can arise from a neutral mutation (rather than one that confers a selective advantage to its progeny) using a Moran process (a type of branching process used to describe genetic drift). They also go on to suggest that leukemias that arise due to a neutral rather than selective process may be harder to treat; this again reflects processes that are already reasonably well understood in population genetics [5].

Conclusion

Stem cell regulation occurs across many tissues with remarkable sensitivity and robustness: enabling tissues to respond to a host of external perturbations and restore homeostasis. Yet stem cells themselves are rare, elusive, and driven by noisy stochastic processes [111, 112]. To reconcile these phenomena, a systems perspective seems sensible, if not necessary. Moreover, here we have suggested that stem cell systems are fundamentally systems of populations, not individuals. As such, a century of theoretical results from population biology are applicable, and we believe that much will be gained from their application.

Cancer has been frequently and correctly be described as an "evolutionary disease," and evolution always occurs in (and shapes) a given ecological setting. Thus understanding the drivers of population dynamics, and identifying ways of influencing the "fate" of a population will have obvious implications for control and therapy of cancer. But also in healthy tissue homeostasis—including a healthy hematopoietic system—we will find fruitful applications for concepts from population biology. The "ecology of blood," or any other tissue, also provides a framework in which we consider the processes underlying development and growth. As new technologies emerge [113, 114], these population-based models will become more useful, and—in places—essential to make sense of ever-increasing complexity in biological data.

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Author Contributions

A.L.M., C.L.C, and M.P.H.S.: Conception and design, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflict of Interest

The authors have no potential conflicts of interest.

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