Current Stem Cell Reports (2019) 5:66–72
https://doi.org/10.1007/s40778-019-00156-z

MATHEMATICAL MODELS OF STEM CELL BEHAVIOR (M KOHANDEL, SECTION EDITOR)

Mathematical Models of Stem Cell Differentiation and Dedifferentiation

Alexandra Jilkine[1]

Published online: 13 April 2019

Abstract

Purpose of Review To maintain and repair adult tissues, a balance must be maintained between stem cell proliferation and generation of differentiated offspring. This review explores recent mathematical and computational models that address stem cell fate decisions in adult tissues in the context of normal tissue regulation and cancer development.

Recent Findings Quantitative models suggest that upregulation of stem cell self-renewal has a crucial impact on the dynamics of differentiated cells and plays an important role in cancer progression. Assuming cancer stem cells are the primary cause of drug resistance, models have estimated how different treatments may influence the prognosis of the disease. Recent evidence of phenotype switching and plasticity in cancer cell populations complicates the cancer stem cell hypothesis of unidirectional differentiation.

Summary Mathematical models of stem cell dynamics can make counterintuitive predictions about cancer initiation, metastasis, and treatment response. By challenging current paradigms, they can shape future research in stem cell biology.

Keywords Stem cells · Cell fate determination · Tissue homeostasis · Cancer stem cells · Phenotypic plasticity · Mathematical modeling

Introduction

Stem cells are unspecialized cells that are characterized by two properties, the ability to self-renew, and the ability to differentiate into more specialized cell types. The ability to self-renew is what is thought to set stem cells apart from their more differentiated offspring, which are produced from less specialized cell types. Each daughter produced when a stem cell divides can either remain a stem cell or go on to become terminally differentiated. In many cases, the daughter that opts for terminal differentiation undergoes additional cell divisions before terminal differentiation.

To achieve homeostasis, stem cells in adult tissues must maintain a balance between self-renewal and differentiation. This, naturally, raises two important questions. (1) How do stem cells regulate the balance between self-renewal (stem cell proliferation) and differentiation? (2) How do cell fate decisions in stem and progenitor cells become subverted in the emergence diseased states such as cancer? This review focuses on the use of quantitative models to study these questions.

Distinguishing Between Stem and Non-stem Cells

The cells of tissues can be roughly grouped into three classes: stem cells, transit-amplifying progenitor cells, and fully differentiated cells [1]. Experimental discrimination of stem cells from more differentiated cells has traditionally been difficult, and efforts have focused on identifying stem cell–specific molecular markers in different tissues [2, 3]. Unfortunately, these markers are not always clearly linked to cellular function. Historically, label-retaining assays involved the incorporation of DNA analogs such as BrdU or transgenically induced GFP-tagged histone 2B in the epidermis [4], intestinal tissues [5], and the bone marrow [6]. Methods reliant on immunohistochemistry provide a one-time "snapshot" that provides limited information on stem cell dynamics. Recent experimental

This article is part of the Topical Collection on *Mathematical Models of Stem Cell Behavior*

✉ Alexandra Jilkine
ajilkine@nd.edu

[1] Department of Applied and Computational Mathematics and Statistics, University of Notre Dame, Notre Dame, IN, USA

techniques such as lineage tracing have allowed quantification of dynamics of stem cells and their progeny over time [7, 8]. Mathematical modeling of stem cells has often assumed them to be *quiescent*; i.e., stem cells have much slower division rate relative to more differentiated cells [9]. However, recent experimental studies based on inducible genetic labeling of rapidly cycling adult tissues, such as epidermis, gut, and male germline, have argued that stem cells can actually undergo divisions as frequently as other cell types [10–14]. Stem cells of those tissue types are now thought to be highly dynamic, with rapid turnover of cells over an organism's lifetime. However, other adult stem cells, such as hematopoietic and neuronal stem cells, are still considered to be mainly quiescent, slow-cycling populations during homeostatic conditions [6, 15, 16]. The environmental signals that enable these cells to leave the quiescent stage in order to repopulate the population are not well understood.

Over the last decade, many lineage studies have challenged the model that stem cells typically divide asymmetrically, producing one stem and one more differentiated cell [17–19]. These studies suggested that, in many tissue types, stem cell divisions are mainly symmetric, producing either two stem cells or two progenitor cells, depending on the surrounding cell types [12–14]. These studies support the idea that, in many adult tissues, division decisions and stem cell fate are usually strongly influenced by extrinsic factors associated with the cell's microenvironment, the so-called stem cell niche [20, 21].

Multi-Compartment Models of Hierarchical Tissues

The labeling of cells at different stages of differentiation as stem cells, progenitor cells, and fully differentiated cells naturally leads to multi-compartment ODE (ordinary differential equation) models, which track the numbers of cells transitioning between compartments during division [1, 22–25]. The number of compartments differs between the models, since the exact number of different stages of differentiation is ambiguous and may not exactly correspond to mitotic events, as cells may undergo more than one division in each compartment stage. Typically, these models have multiple steady states, and stability analysis has been performed for some simplified variants [26, 27]. Maturity-structured PDE (partial differential equation) models, where age of progenitor cells is a continuous variable, have also been considered [22, 28, 29, 30•]. The dynamics of multistage cell lineage models, such as the effect of feedbacks on oscillatory approaches toward steady state, continues to be an active topic of research [31, 32]. Coupling diffusive signals to this feedback architecture allows the emergence of self-organized patterns, such as tissue stratification and fingering [33, 34, 35••].

Many of these models have focused on the potential feedback mechanisms that enable robust homeostasis (keeping a constant number of cells) for a range of parameter values and provide efficient repopulation if the tissue needs to regenerate after injury [1, 24]. Feedback architecture in which both positive and negative signals act on stem and/or progenitor cells leads to the appearance of bistable or bi-modal growth behaviors [35••]. Modeling has also suggested that the loss of homeostasis and initiation of tumorigenesis occur when one of the feedback loops controlling self-renewal is affected and the rate of symmetric versus asymmetric division of the stem cells is altered [36, 37•]. An imbalance between self-renewal and differentiation will result in clonal immortalization and cancer development [38]. Cancer cells tend to divide more symmetrically than their healthy counterparts, and increased symmetric divisions are initiated when tumor suppressors are inactivated in a variety of cell types, including hematopoietic stem cells, neuronal stem cells, and mammary stem cells [39]. DNA damage in hematopoietic and mammary stem cells initiates symmetric self-renewing divisions, which allows the stem cell population to expand [40, 41]. Across several cancer types, asymmetric stem cell fate choice correlates with less advanced, more differentiated tumors, while symmetric stem cell divisions are correlated with more advanced cancers.

Stem Cells, Differentiation, and Cancer

The accumulation of mutations and the mutational extinction time are both influenced by tissues' hierarchical structure, where a small population of stem cells maintains a transient population of differentiating cells. The *waiting time to cancer* is defined as the time when a particular number of mutation events have occurred in at least one cell. The calculation of these times typically utilizes the theory of birth-death processes. Mathematical modeling suggests that having a hierarchical tissue structure may slow the accumulation of mutations and delay the emergence of cancer [42–45]. Cell division patterns are frequently deregulated in cancerous tissues [46], and several mathematical models have been developed to study accumulation of mutations treating the proportion of symmetric versus asymmetric stem cell divisions as a control variable [23, 30•, 47–49]. Stochastic modeling has shown that more symmetric divisions in the stem cell pool compared with the progenitor pool may slow down the accumulation of mutations, delaying carcinogenesis [50, 51]. The rationale is that symmetric divisions producing transient progenitor cells flushes out mutations from the stem cell lineage provided that the progenitor turnover is fast. Spatial modeling, focusing on dynamics in the colon crypt, suggests that location in the tissue where the cells are dividing rather

than mode of division is the limiting factor for how fast mutations can be flushed away [49, 52, 53].

There is a body of evidence that the driving forces behind tumor growth and invasion are "cancer stem cells," defined as cells within a tumor that can self-renew indefinitely and "differentiate" into different cell types present in the tumor. The cancer stem cell (CSC) hypothesis states that long-term self-renewal is confined to a discrete subpopulation of malignant cells, which alone has the ability to propagate tumors through metastasis [54]. The first evidence for the existence of CSCs came from acute myeloid leukemia (AML) in which a rare subset comprising only 0.01–1% of the total cancer cell population could induce leukemia when transplanted into immunodeficient mice [55]. A similar phenomenon is observed in mice when epithelial tumor cells are implanted into a new host (reviewed in [54]). The frequency of CSCs in solid tumors is highly variable. For example, CSC population in colorectal carcinomas ranges between 1.8–24.5% [56]. While cells in benign tumors mirror the clonal hierarchy organization of normal tissue, malignant tumors contain many more stem-like cells [57]. These studies suggest that cancers gradually lose their tissue-like hierarchical organization as they evolve from benign to malignant. Whether these cancer stem cells originate from stem cells that escape homeostasis or from dedifferentiated transit-amplifying cells that have acquired infinite proliferating potential and have dedifferentiated to a stem cell–like state remains an open question [46, 58]. For example, in the colonic crypt, a stem cell or a transit-amplifying cell may become a cancer stem cell, dependent on which cell type first circumvents inhibitory feedbacks [59]. By estimating whether the cancer cell of origin is more likely to be a stem cell or dedifferentiated progenitor cell, modeling can suggest whether differentiation cancer therapies (reviewed in [60]) can be effective.

Certain aspects of the cancer stem cell hypothesis have been addressed using mathematical models. Models have shown that cancer stem cells are not necessarily rare; the proportion of cancer stem cells in tumors can be arbitrarily large [61, 62•, 63]. Estimates of a fraction of cancer stem cells based on individual patient data was done in [64]. Quiescent or slow-cycling cancer stem cells are thought to be more resistant to chemotherapy, which targets rapidly dividing cells [65]. Stem cell–like gene expression signature is predictive of patient outcome in acute myeloid leukemia [66, 67]. High leukemic stem cell self-renewal rate is an indicator of poor prognosis [68••]. An early deterministic model by Michor et al. [69] found that for chronic myeloid leukemia (CML), imatinib can inhibit the production of differentiated leukemic cells, but does not deplete leukemic stem cells, leading to development of imatinib resistance. In general, to be successful, therapy must eradicate cancer stem cells [70]. Counterintuitively, increasing the rate of cell death due to cancer treatment reduces tumor size in the short term, but results ultimately in accelerated long-term growth (the so-called tumor growth paradox) [62•, 71]. Furthermore, the model predicts that the proportion of cancer stem cells in a tumor will increase over time. Assuming stem cell enrichment is the primary cause of drug resistance, negative feedback from differentiated cells to stem cells, which is required for homeostasis in normal tissue, leads to a worse outcome when it comes to treatment of hierarchically structured cancers [72]. All of these results arise from the fact that radiation or chemotherapy mainly targets the differentiated cells in the bulk of the tumor, thus freeing the cancer stem cells from having to compete with tumor progenitor cells. To be effective, therapy must target cancer stem cells [73]. Combining differentiation therapy that targets cancer stem cells together with radiation or chemotherapy can eradicate tumors, even if each therapy applied individually would not be successful [74, 75].

Modeling Plasticity Between Stem and Non-stem Cell Populations

Traditionally, the conversion dynamics between stem cells and non-stem cells have been assumed rigidly unidirectional, wherein a stem cell can differentiate into a non-stem cell, but the reverse transition cannot occur. It is now believed that non-stem cells are capable of dedifferentiating, thus complicating the cancer stem cell paradigm [76, 77]. The Nobel Prize winning work of Takahashi and Yamanaka [78] demonstrated that a non-stem cell becoming a stem cell was possible upon the introduction of four transcription factors. Later, spontaneous dedifferentiation to a stem cell–like state has been observed in cultures of non-stem mammary cancer cells [79, 80]. The idea that the microenvironment can induce cells to switch from non-CSC cancer cell into a more aggressive CSC phenotype was demonstrated by Medema and Vermeulen [81]. Dedifferentiation rates seem to be higher when cancer cells are under stress. For example, dedifferentiation of non-stem cells has been reported to occur in hypoxic regions of a tumor at higher frequencies compared with normoxic regions [82].

Experiments and modeling of this phenotypic switching in melanoma cells suggest that reducing the proportion of CSCs below a threshold causes the cells to switch. This suggests both that there is a regulatory network governing the switching response and that a therapeutic strategy based on CSC eradication alone is unlikely to succeed [83••]. Others have argued that imperfect cancer stem cell markers rather than phenotypic switching can explain the experimental results [84]. The biological factors regulating this conversion process are still not fully clear. There are

several recent phenomenological models of phenotype switching and plasticity in cancer cell populations [85, 86•, 87•, 88]. Rhodes and Hillen fit the experimental data to an ODE (ordinary differential equation) model of hierarchical tissue and suggest that dedifferentiation may be the cause of emerging resistance to radiation therapy [86•]. While generally, dedifferentiation results in greater likelihood of tumor initiation [30•], Wodarz argues that the presence of dedifferentiation can actually lower the rates of tumor initiation and progression [88]. A stochastic model, focusing on small cell populations, also showed that in some cases, the plasticity between stem and non-stem cell populations may reduce the survival probability of the cancer cell population [87•]. The effect of combination therapy on reducing CSC population in the presence of phenotypic transitions was computationally tested in [89••]

The dedifferentiation of non-CSCs into CSCs may be driven by the epithelial to mesenchymal transition (EMT), a cellular transdifferentiation program where epithelial cells adopt mesenchymal features that allows stationary epithelial cells to gain the ability to migrate and metastasize [90]. Recent quantitative studies have focused on modeling the feedback loops in the transcription factor network that regulates the epithelial-mesenchymal transition in the context of cancer development [91, 92, 93•].

Conclusion

Accurately identifying stem cells and cancer stem cells in tissues remains an open question due to imperfect stem cell markers. This makes model-based estimation of key parameters, such as rates of stem cell self-renewal, differentiation, dedifferentiation, and death, an important step in understanding stem cell dynamics in normal and diseased tissues. Such modeling should be performed in tandem with biological experiments.

Theoretical insights obtained from mathematical models of hierarchical stem cell dynamics have already influenced our understanding of cancer initiation, metastasis, and treatment response. The idea that cancer stem cells form a rare subpopulation has been challenged by modeling and confirmed by experiments. Modeling suggests that the proportion of cancer stem cells at time of treatment may influence prognosis of the disease. Furthermore, modeling argues treatment needs to selectively target cancer stem cells in order to be effective. Otherwise, it may actually speed and the probability of tumor survival. Recent insights from experimental studies of cell plasticity have challenged the hierarchical theory of tissue structure, but the exact molecular nature underlying dedifferentiation is still unclear. Existing mathematical models will need to be adapted to integrate new experimental data as it becomes available.

Compliance with Ethical Standards

Conflict of Interest Alexandra Jilkine declares that she has 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.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lander AD, Gokoffski KK, Wan FY, Nie Q, Calof AL. Cell lineages and the logic of proliferative control. PLoS Biol. 2009;7(1):e15.
2. Barker N, van Es JH, Kuipers J, Kujala P, van den Born M, Cozijnsen M, et al. Identification of stem cells in small intestine and colon by marker gene Lgr5. Nature. 2007;449(7165):1003–7.
3. Shinohara T, Avarbock MR, Brinster RL. β1-and α6-integrin are surface markers on mouse spermatogonial stem cells. Proc Natl Acad Sci. 1999;96(10):5504–9.
4. Tumbar T, Guasch G, Greco V, Blanpain C, Lowry WE, Rendl M, et al. Defining the epithelial stem cell niche in skin. Science. 2004;303(5656):359–63.
5. Potten CS, Kellett M, Roberts SA, Rew D, Wilson G. Measurement of in vivo proliferation in human colorectal mucosa using bromodeoxyuridine. Gut. 1992;33(1):71–8.
6. Wilson A, Laurenti E, Oser G, van der Wath RC, Blanco-Bose W, Jaworski M, et al. Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair. Cell. 2008;135(6):1118–29.
7. Kretzschmar K, Watt FM. Lineage tracing. Cell. 2012;148(1–2):33–45.
8. Simons BD, Clevers H. Strategies for homeostatic stem cell self-renewal in adult tissues. Cell. 2011;145(6):851–62.
9. Cheung TH, Rando TA. Molecular regulation of stem cell quiescence. Nature reviews. Mol Cell Biol. 2013;14(6):329.
10. Clayton E, Doupe DP, Klein AM, Winton DJ, Simons BD, Jones PH. A single type of progenitor cell maintains normal epidermis. Nature. 2007;446(7132):185–9.
11. Klein AM, Nakagawa T, Ichikawa R, Yoshida S, Simons BD. Mouse germ line stem cells undergo rapid and stochastic turnover. Cell Stem Cell. 2010;7(2):214–24.
12. Lopez-Garcia C, Klein AM, Simons BD, Winton DJ. Intestinal stem cell replacement follows a pattern of neutral drift. Science. 2010;330(6005):822–5.
13. Ritsma L, Ellenbroek SI, Zomer A, Snippert HJ, de Sauvage FJ, Simons BD, et al. Intestinal crypt homeostasis revealed at single-stem-cell level by in vivo live imaging. Nature. 2014;507(7492):362–5.
14. Snippert HJ, van der Flier LG, Sato T, van Es JH, van den Born M, Kroon-Veenboer C, et al. Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. Cell. 2010;143(1):134–44.
15. Weissman IL, Anderson DJ, Gage F. Stem and progenitor cells: origins, phenotypes, lineage commitments, and

transdifferentiations. Annu Rev Cell Dev Biol. 2001;17(1):387–403.
16. van der Wath RC, Wilson A, Laurenti E, Trumpp A, Lio P. Estimating dormant and active hematopoietic stem cell kinetics through extensive modeling of bromodeoxyuridine label-retaining cell dynamics. PLoS One. 2009;4(9):e6972.
17. Knoblich JA. Asymmetric cell division: recent developments and their implications for tumour biology. Nat Rev Mol Cell Biol. 2010;11(12):849–60.
18. Klein AM, Simons BD. Universal patterns of stem cell fate in cycling adult tissues. Development. 2011;138(15):3103–11.
19. Morrison SJ, Kimble J. Asymmetric and symmetric stem-cell divisions in development and cancer. Nature. 2006;441(7097):1068.
20. Lander AD, Kimble J, Clevers H, Fuchs E, Montarras D, Buckingham M, et al. What does the concept of the stem cell niche really mean today? BMC Biol. 2012;10(1):19.
21. Roberts KJ, Kershner AM, Beachy PA. The stromal niche for epithelial stem cells: a template for regeneration and a brake on malignancy. Cancer Cell. 2017;32(4):404–10.
22. Johnston MD, Edwards CM, Bodmer WF, Maini PK, Chapman SJ. Mathematical modeling of cell population dynamics in the colonic crypt and in colorectal cancer. Proc Natl Acad Sci U S A. 2007;104(10):4008–13.
23. Ashkenazi R, Gentry SN, Jackson TL. Pathways to tumorigenesis–modeling mutation acquisition in stem cells and their progeny. Neoplasia. 2008;10(11):1170–82.
24. Marciniak-Czochra A, Stiehl T, Ho AD, Jager W, Wagner W. Modeling of asymmetric cell division in hematopoietic stem cells-regulation of self-renewal is essential for efficient repopulation. Stem Cells Dev. 2009;18(3):377–85.
25. Weekes SL, Barker B, Bober S, Cisneros K, Cline J, Thompson A, et al. A multicompartment mathematical model of cancer stem cell-driven tumor growth dynamics. Bull Math Biol. 2014;76(7):1762–82.
26. Lo WC, Chou CS, Gokoffski KK, Wan FYM, Lander AD, Calof AL, et al. Feedback regulation in multistage cell lineages. Math Biosci Eng. 2009;6(1):59–82.
27. Nakata Y, Getto P, Marciniak-Czochra A, Alarcon T. Stability analysis of multi-compartment models for cell production systems. J Biol Dyn. 2012;6(sup1):2–18.
28. Gentry S, Ashkenazi R, Jackson T. A maturity-structured mathematical model of mutation acquisition in the absence of homeostatic regulation. Math Model Nat Phenom. 2009;4(3):156–82.
29. Doumic M, Marciniak-Czochra A, Perthame B, Zubelli JP. A structured population model of cell differentiation. SIAM J Appl Math. 2011;71(6):1918–40.
30.• Jilkine A, Gutenkunst R. Effect of dedifferentiation on time to mutation acquisition in stem cell-driven cancers. PLoS Comput Biol. 2014;10(3):e1003481. **This paper argues that dedifferentiation of progenitor cells to a stem cell–like state can significantly speed up the time to cancer emergence.**
31. Rodriguez-Brenes IA, Wodarz D, Komarova NL. Stem cell control, oscillations, and tissue regeneration in spatial and non-spatial models. Front Oncol. 2013;3:82.
32. Renardy M, Jilkine A, Shahriyari L, Chou CS. Control of cell fraction and population recovery during tissue regeneration in stem cell lineages. J Theor Biol. 2018;445:33–50.
33. Chou CS, Lo WC, Gokoffski KK, Zhang YT, Wan FY, Lander AD, et al. Spatial dynamics of multistage cell lineages in tissue stratification. Biophys J. 2010;99(10):3145–54.
34. Zhang L, Lander AD, Nie Q. A reaction–diffusion mechanism influences cell lineage progression as a basis for formation, regeneration, and stability of intestinal crypts. BMC Syst Biol. 2012;6(1):93.
35.•• Kunche S, Yan H, Calof AL, Lowengrub JS, Lander AD. Feedback, lineages and self-organizing morphogenesis. PLoS Comput Biol. 2016;12(3):e1004814. **This work considers the effect of both positive and negative feedbacks on the stem cell lineage in a spatial setting.**
36. Rodriguez-Brenes IA, Komarova NL, Wodarz D. Evolutionary dynamics of feedback escape and the development of stem-cell-driven cancers. Proc Natl Acad Sci U S A. 2011;108(47):18983–8.
37.• Walenda T, Stiehl T, Braun H, Fröbel J, Ho AD, Schroeder T, et al. Feedback signals in myelodysplastic syndromes: increased self-renewal of the malignant clone suppresses normal hematopoiesis. PLoS Comput Biol. 2014;10(4):e1003599. **Modeling suggests that initial mutations in myelodyspastic syndrome (MDS) favor high self-renewal rates. Accumulation of primitive MDS cells in the bone marrow then interferes with feedback signals for normal hematopoiesis, leading to the disease.**
38. Alcolea MP, Greulich P, Wabik A, Frede J, Simons BD, Jones PH. Differentiation imbalance in single oesophageal progenitor cells causes clonal immortalization and field change. Nat Cell Biol. 2014;16(6):612–9.
39. Bajaj J, Zimdahl B, Reya T. Fearful symmetry: subversion of asymmetric division in cancer development and progression. Cancer Res. 2015;75(5):792–7.
40. Insinga A, Cicalese A, Faretta M, Gallo B, Albano L, Ronzoni S, et al. DNA damage in stem cells activates p21, inhibits p53, and induces symmetric self-renewing divisions. Proc Natl Acad Sci U S A. 2013;110(10):3931–6.
41. Cicalese A, Bonizzi G, Pasi CE, Faretta M, Ronzoni S, Giulini B, et al. The tumor suppressor p53 regulates polarity of self-renewing divisions in mammary stem cells. Cell. 2009;138(6):1083–95.
42. Komarova NL. Cancer, aging and the optimal tissue design. Semin Cancer Biol. 2005;15(6):494–505.
43. Komarova NL, Cheng P. Epithelial tissue architecture protects against cancer. Math Biosci. 2006;200(1):90–117.
44. Werner B, Dingli D, Traulsen A. A deterministic model for the occurrence and dynamics of multiple mutations in hierarchically organized tissues. J R Soc Interface. 2013;10(85):20130349.
45. Derenyi I, Szöllősi GJ. Hierarchical tissue organization as a general mechanism to limit the accumulation of somatic mutations. Nat Commun. 2017;8:14545.
46. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001;414(6859):105–11.
47. Dingli D, Traulsen A, Michor F, Michor F. (A)symmetric stem cell replication and cancer. PLoS Comput Biol. 2007;3(3):e53.
48. Tomasetti C, Levy D. Role of symmetric and asymmetric division of stem cells in developing drug resistance. Proc Natl Acad Sci U S A. 2010;107(39):16766–71.
49. Shahriyari L, Komarova NL. The role of the bi-compartmental stem cell niche in delaying cancer. Phys Biol. 2015;12(5):055001.
50. Shahriyari L, Komarova NL. Symmetric vs. asymmetric stem cell divisions: an adaptation against cancer? PLoS One. 2013;8(10):e76195.
51. LA McHale PT. The protective role of symmetric stem cell division on the accumulation of heritable damage. PLoS Comput Biol. 2014;10(8):e1003802.
52. Zhao R, Michor F. Patterns of proliferative activity in the colonic crypt determine crypt stability and rates of somatic evolution. PLoS Comput Biol. 2013;9(6):e1003082.
53. Shahriyari L, Komarova NL, Jilkine A. The role of cell location and spatial gradients in the evolutionary dynamics of colon and intestinal crypts. Biol Direct. 2016;11(1):42.
54. Visvader JE, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. Nat Rev Cancer. 2008;8(10):755–68.
55. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature. 1994;367(6464):645–8.

56. OBrien CA, Pollett A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature. 2007;445(7123):106–10.
57. Driessens G, Beck B, Caauwe A, Simons BD, Blanpain C. Defining the mode of tumour growth by clonal analysis. Nature. 2012;488(7412):527–30.
58. Visvader JE. Cells of origin in cancer. Nature. 2011;469(7330): 314–22.
59. Schwitalla S, Fingerle AA, Cammareri P, Nebelsiek T, Goktuna SI, Ziegler PK, et al. Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties. Cell. 2013;152(1–2):25–38.
60. Sell S. Stem cell origin of cancer and differentiation therapy. Crit Rev Oncol Hematol. 2004;51(1):1–28.
61. Johnston MD, Maini PK, Chapman SJ, Edwards CM, Bodmer WF. On the proportion of cancer stem cells in a tumour. J Theor Biol. 2010;266(4):708–11.
62.• Hillen T, Enderling H, Hahnfeldt P. The tumor growth paradox and immune system-mediated selection for cancer stem cells. Bull Math Biol. 2013;75(1):161–84. **This paper provides a mathematical explanation for the tumor growth paradox observed in several computational models of cancer.**
63. Enderling H. Cancer stem cells: small subpopulation or evolving fraction? Integr Biol. 2015;7(1):14–23.
64. Werner B, Scott JG, Sottoriva A, Anderson AR, Traulsen A, Altrock PM. The cancer stem cell fraction in hierarchically organized tumors can be estimated using mathematical modeling and patient-specific treatment trajectories. Cancer Res. 2016;76(7): 1705–13.
65. Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu MF, et al. Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy. J Natl Cancer Inst. 2008;100(9):672–9.
66. Gentles AJ, Plevritis SK, Majeti R, Alizadeh AA. Association of a leukemic stem cell gene expression signature with clinical outcomes in acute myeloid leukemia. JAMA. 2010;304(24):2706–15.
67. Eppert K, Takenaka K, Lechman ER, Waldron L, Nilsson B, Van Galen P, et al. Stem cell gene expression programs influence clinical outcome in human leukemia. Nat Med. 2011;17(9):1086–93.
68.•• Stiehl T, Baran N, Ho AD, Marciniak-Czochra A. Cell division patterns in acute myeloid leukemia stem-like cells determine clinical course: a model to predict patient survival. Cancer Res. 2015;75(6):940–9. **This work provides evidence that the proliferation and self-renewal rates of the leukemic stem cell population have greater impact on the course of disease than proliferation and self-renewal rates of leukemia blast populations in acute myeloid leukemia.**
69. Michor F, Hughes TP, Iwasa Y, Branford S, Shah NP, Sawyers CL, et al. Dynamics of chronic myeloid leukaemia. Nature. 2005;435(7046):1267–70.
70. Dingli D, Michor F. Successful therapy must eradicate cancer stem cells. Stem Cells. 2006;24(12):2603–10.
71. Enderling H, Anderson AR, Chaplain MA, Beheshti A, Hlatky L, Hahnfeldt P. Paradoxical dependencies of tumor dormancy and progression on basic cell kinetics. Cancer Res. 2009;69(22):8814–21.
72. Rodriguez-Brenes IA, Kurtova AV, Lin C, Lee YC, Xiao J, Mims M, et al. Cellular hierarchy as a determinant of tumor sensitivity to chemotherapy. Cancer Res. 2017;77(9):2231–41.
73. Sehl ME, Sinsheimer JS, Zhou H, Lange KL. Differential destruction of stem cells: implications for targeted cancer stem cell therapy. Cancer Res. 2009;69(24):9481–9.
74. Youssefpour H, Li X, Lander A, Lowengrub J. Multispecies model of cell lineages and feedback control in solid tumors. J Theor Biol. 2012;304:39–59.
75. Bachman JW, Hillen T. Mathematical optimization of the combination of radiation and differentiation therapies for cancer. Front Oncol. 2013;3:52.
76. Visvader JE, Lindeman GJ. Cancer stem cells: current status and evolving complexities. Cell Stem Cell. 2012;10(6):717–28.
77. Medema JP. Cancer stem cells: the challenges ahead. Nat Cell Biol. 2013;15(4):338–44.
78. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663–76.
79. Chaffer CL, Brueckmann I, Scheel C, Kaestli AJ, Wiggins PA, Rodrigues LO, et al. Normal and neoplastic nonstem cells can spontaneously convert to a stem-like state. Proc Natl Acad Sci U S A. 2011;108(19):7950–5.
80. Gupta PB, Fillmore CM, Jiang G, Shapira SD, Tao K, Kuperwasser C, et al. Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells. Cell. 2011;146(4):633–44.
81. Medema JP, Vermeulen L. Microenvironmental regulation of stem cells in intestinal homeostasis and cancer. Nature. 2011;474(7351): 318–26.
82. Hill RP, Marie-Egyptienne DT, Hedley DW. Cancer stem cells, hypoxia and metastasis. In: Seminars in radiation oncology, vol. 19. Amsterdam: Elsevier; 2009. p. 106–11.
83.•• Sellerio AL, Ciusani E, Ben-Moshe NB, Coco S, Piccinini A, Myers CR, et al. Overshoot during phenotypic switching of cancer cell populations. Sci Rep. 2015;5:15464. **This work shows that the phenotypic switching in melanoma cells is not stochastic and is highly regulated.**
84. Zapperi S, La Porta CA. Do cancer cells undergo phenotypic switching? The case for imperfect cancer stem cell markers. Sci Rep. 2012;2:441.
85. Turner C, Kohandel M. Investigating the link between epithelial–mesenchymal transition and the cancer stem cell phenotype: a mathematical approach. J Theor Biol. 2010;265(3):329–35.
86.• Rhodes A, Hillen T. Mathematical modeling of the role of survivin on dedifferentiation and radioresistance in cancer. Bull Math Biol. 2016;78(6):1162–88. **This paper investigates the hypothesis that inhibiting the apoptosis protein survivin reduces resistance to radiation in non-small cell lung cancer. The model predicts that the optimal treatment strategy depends on the dose of radiation administered.**
87.• Tonekaboni SAM, Dhawan A, Kohandel M. Mathematical modelling of plasticity and phenotype switching in cancer cell populations. Math Biosci. 2017;283:30–7. **This paper analyses the effects of varying cellular plasticity on the survival of the cancer cell population.**
88. Wodarz D. Effect of cellular de-differentiation on the dynamics and evolution of tissue and tumor cells in mathematical models with feedback regulation. J Theor Biol. 2018;448:86–93.
89.•• Sehl ME, Shimada M, Landeros A, Lange K, Wicha MS. Modeling of cancer stem cell state transitions predicts therapeutic response. PLoS One. 2015;10(9):e0135797. **A stochastic population model of the breast cancer stem cell niche considers CSC eradication strategies. Combinatorial treatment in the model predicted that concurrent inhibition of HER2 and IL-6 is the most effective way to reduce the total number of CSCs, which is in agreement with earlier experimental findings.**
90. Scheel C, Weinberg RA. Cancer stem cells and epithelial–mesenchymal transition: concepts and molecular links. In: Seminars in cancer biology, vol. 22. Amsterdam: Elsevier; 2012. p. 396–403.
91. Tian XJ, Zhang H, Xing J. Coupled reversible and irreversible bistable switches underlying TGFβ- induced epithelial to mesenchymal transition. Biophys J. 2013;105(4):1079–89.
92. Jolly MK, Huang B, Lu M, Mani SA, Levine H, Ben-Jacob E. Towards elucidating the connection between epithelial–

mesenchymal transitions and stemness. J R Soc Interface. 2014;11(101):20140962.

93.• Dhawan A, Tonekaboni SAM, Taube JH, Hu S, Sphyris N, Mani SA, et al. Mathematical modelling of phenotypic plasticity and conversion to a stem-cell state under hypoxia. Sci Rep. 2016;6:18074**. A combination of mathematical modeling and experiment that demonstrates that hypoxia is a key contributor to the plasticity of transformed human mammary epithelial cells. This paper contributes to the evidence that the microenvironment plays a large role in cell dedifferentiation.**