Cancer as a system dysfunction

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Extended abstract

In this paper, we describe a system dynamics model that views cancer as a dysfunction of the cellular system analogous to those of human societies. Our experiments with the model replicate the propagation of the ailment and the impacts of the treatments. It also represents work in progress and should be viewed as a proposition that can be further developed to understand cancer and used to create appropriate combinations of interventions for specific situations. Our model represents the interaction between the various types of cells in an organ or a subsystem of the body. It depicts the common structure in the simplest possible terms. It defines a generic system that can be applied to solid as well as blood and bone-related diseases, although we mainly address it to proliferation of sold cancers and their response to treatments in this paper.

Whether viewed in the context of an afflicted organ or a body subsystem, the interacting cell populations can be placed in four broad categories: normal cells, pre-cancer cells, cancer cells and immune system cells. Thus, our model contains four stocks connected by flows shown in Figure 1. Normal cells and Immune system cells have disciplined growth regimes in that they tend to grow to their indicated levels – the former goal is determined by the internal intelligence of the cell, while the later by the surveillance need created by the very existence of the unwanted cells in the body. The cancer cell stock is initially populated by a transformation of precancerous cells meant to reflect the accumulation of tumor-promoting mutations that increase with age. Once transformed, the cancerous cells exhibit unregulated proliferation and thus cancer grows exponentially. The immune response increases to combat the rising cancer cell population, and it is ultimately the imbalance of tumor growth vs immune response that yields a proliferation of cancerous cells.

Model behavior

The model is supplied with an internally consistent set of parameters and initial conditions so under normal conditions, all cell populations except cancer are maintained in a dynamic equilibrium or homeostasis. Cancer population is initialized at zero value. The simulation time is set at 1000 months (83.3 years) that approximates the average life expectancy of a healthy individual. It should be noted that despite the equilibrium, all cell populations constantly turn over rather than remaining constant. The in- and out- flows tied to each stock continue while the stocks remain in a dynamic balance.

When initially populated by the transformation of pre-cancer cells, the cancer cells begin to grow exponentially. Low and intermediate rates of growth of cancer are contained however by a concomitant increase in the immune activity that constantly kills the cancer cells and keeps their population under control. The absolute number of cancer cells is influenced by cancer cell proliferation, as well as the rate at which normal cells acquire pre-cancerous characteristics and

then are ultimately transformed into cancer cells. To model rates of proliferation that may differ between aggressively growing and slow growing tumors, the model allows for modulation of cancer cell proliferation rates.

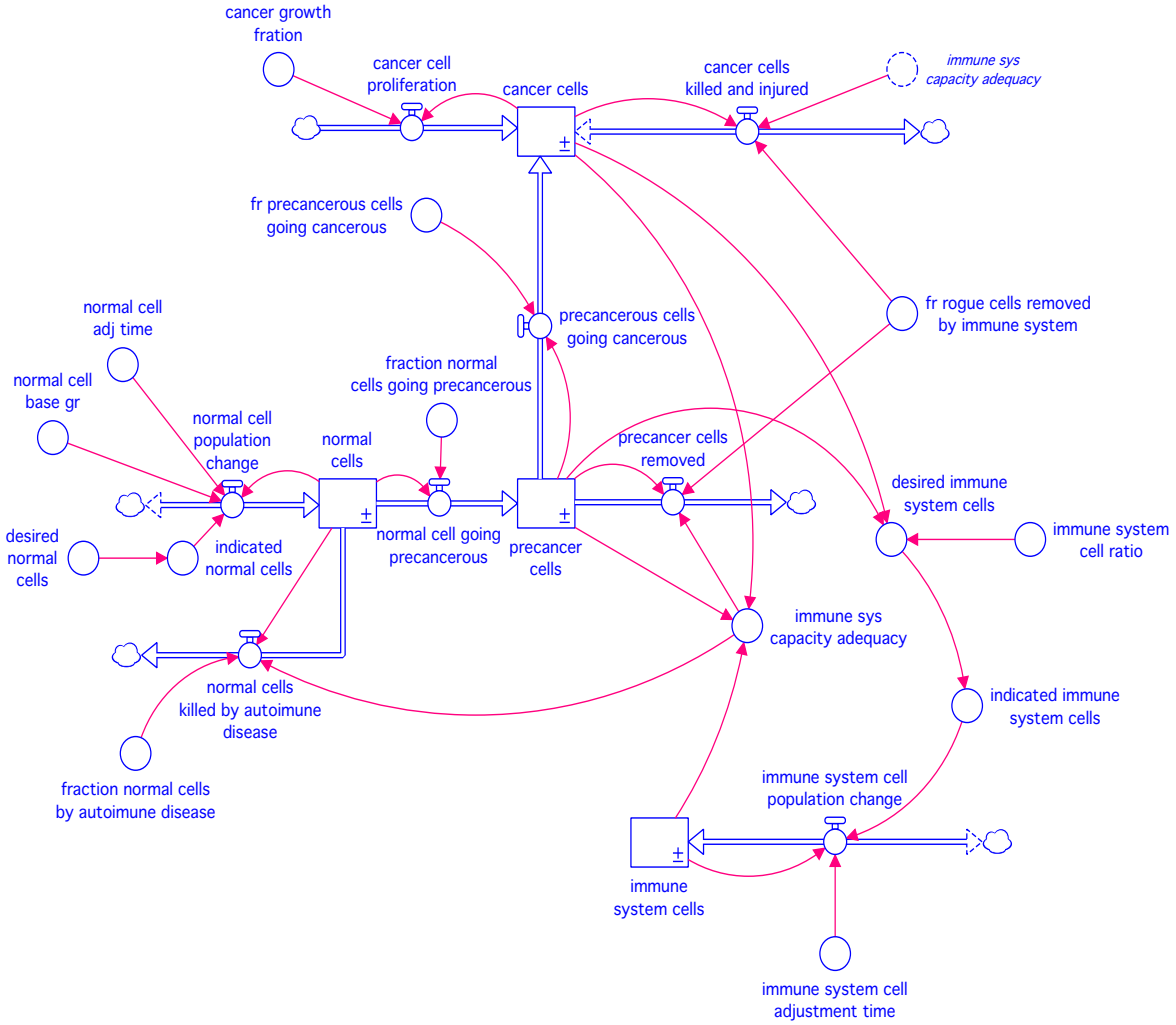

Figure 1 Key cell population stocks, their connecting flows and rules of conduct in the cellular society.

Conclusion

We have made a preliminary attempt in this paper to model the development of cancer as an interaction between normal, immune system, pre-cancer and cancer cell populations. The model is used to test hypotheses about lifetime risk of cancer and the performance of Cancer treatments, and shows credible results. It is also simulated for experimental treatment options, which reveals interesting contingencies. We recognize the importance of the inclusive nourishment commons of the body embodied in its blood supply and propose extending the model to include this for future work.

References

Arta M. Monjazeb AM, Hui-Hua Hsiao HH, Gail D. Sckisel GD, WJ. 2012. The role of antigen-specific and non-specific immunotherapy in the treatment of cancer. *Journal of Immunotoxicology*, 9(3): 248-258, DOI: 10.3109/1547691X.2012.685527

Bakhoum SF, Ngo B, Laughney AM, Cavallo JA, Murphy CJ, Ly P, Shah P, Sriram RK, Watkins TBK, Taunk NK, Duran M, Pauli C, Shaw C, Chadalavada K, Rajasekhar VK, Genovese G, Venkatesan S, Birkbak NJ, McGranahan N, Lundquist M, LaPlant Q, Healey JH, Elemento O, Chung CH, Lee NY, Imielenski M, Nanjangud G, Pe'er D, Cleveland DW, Powell SN, Lammerding J, Swanton C, Cantley LC. 2018. Chromosomal instability drives metastasis through a cytosolic DNA response. *Nature*. 553: 467–472

Bast RC. (09/1976). Critical Review of Previously Reported Animal Studies of Tumor Immunotherapy with Non-Specific Immunostimulants. *Annals of the New York Academy of Sciences (0077-8923)*, 277 (1): 60.

Bertalanffy LV (1968) General Systems Theory, New York: George Braziller.

Crookes DJ, De Wit MP. 2014. Is system dynamics modeling of relevance to neoclassical economists? South African Journal of Economics 82(2): 181–192.

Forrester JW. 1961. Industrial Dynamics. Cambridge, MA: MIT Press.

Forrester JW. 1968. Principles of Systems. Cambridge, MA: Wright-Allen

Forrester JW. 1994. System dynamics, systems thinking, and soft OR. System Dynamics Review.10(2-3): 245-256

Gleason, DF. 1977. The Veteran's Administration Cooperative Urologic Research Group: histologic grading and clinical staging of prostatic carcinoma. In Tannenbaum M. *Urologic Pathology: The Prostate*. Philadelphia: Lea and Febiger. pp. 171–198

Hanahan D, Weinberg RA. 2000. The hallmarks of cancer. Cell. 100(1): 57-70.

Hirsch G, Saeed K, McCleary K, Myer K. 2012. Deceased Donor Potential for Organ Transplantation: A System Dynamics Framework. *30th annual conference of the International System Dynamics Society*. St. Gallen Switzerland: System Dynamics Society.

Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, Sarkar S. 2014. Drug Resistance in Cancer: An Overview . *Cancers*. *6*(3), 1769-1792

Liberti MV, Locasale JW. 2016. The Warburg Effect: How Does it Benefit Cancer Cells? Trends Biochem Sci. 41(3): 211–218.

Marin-Acevedo JA, Bhagirathbhai D, Soyano ES, Knutson KL, Chumsri S, Lou Y. 2018. Next generation of immune checkpoint therapy in cancer: new developments and challenges. *Journal of Hematology & Oncology*. 39(11):1-20

Meadows DH, Meadows DL, Randers J, Berhens III BW. 1972. Limits to Growth. Washington DC: Potomac.

Montecino-Rodriguez, E., Berent-Maoz, B., & Dorshkind, K. (2013). Causes, consequences, and reversal of immune system aging. *The Journal of Clinical Investigation*, *123*(3), 958–965. http://doi.org/10.1172/JCI64096

Richmond BM. 1977. Towards a Structural Theory of Cancer. MIT: System Dynamics Group Memo D-2718

Saeed K, Pavlov O, Skorinko J, Smith A. 2014. Farmers, Bandits and Soldiers: A generic system for addressing peace agendas. System Dynamics Review. 29(4): 237–252

Saeed, K. 1986. The Dynamics of Economic Growth and Political Instability in the Developing Countries. System Dynamics Review. 2(1).

Saeed, K. 1990. Government Support of Economic Agendas in Developing Countries: A Behavioral Model. World Development. 18(6).
Saeed, K. 1998. Maintaining Professional Competence in Innovation Organizations. Human Systems Management. 17(1): 69-87.
Saeed, K. 2017. Circumscribing System Dynamics Modeling and Building Confidence in Models: A Personal Perspective. Working paper. Available at SSRN: https://ssrn.com/abstract=3093080
Saeed, K. and O. Pavlov. 2008. Dynastic cycle: A generic structure describing resource allocation in political economies, markets and firms. Journal of Operations Research Society. 59(10): 1289-1298.
Sterman JD. 2000. Business Dynamics, Systems Thinking and Modeling for a Complex World. Boston: Irwin McGraw-Hill
Thompson KM, Tebbens RJD. (2008). Using system dynamics to develop policies that matter: global management of poliomyelitis and beyond. System Dynamics Review 24(4): 433–449.
Weidner N. 1995. Current pathologic methods for measuring intratumoral microvessel density within breast carcinoma and other solid tumors. Breast Cancer Research and Treatment. 36(2): 169–180.
White MC, Holman DM, Boehm JE, Peipins LA, Grossman M Henley J. 2014. Age and Cancer Risk: A Potentially Modifiable Relationship. *Am J Prev Med*. 46(301):S7–15.