A Systems Theory of Small-Cell Lung Cancer

Ajish George, PhD Student
Computational & Systems Biology
Tenenbaum Lab for Ribonomics/Dept. of Biomedical Sciences
Wadsworth Center/SUNY School of Public Health
One Discovery Dr. Rensselaer, NY 12144
ajishg@gmail.com

Ryan Taylor, PhD Student
Decision and Policy Sciences
Dept of Public Admin. & Policy
Rockefeller College of Public Affairs & Policy
135 Western Ave, Albany NY 12222
ryantaylor79@gmail.com

A Systems Theory of Small-Cell Lung Cancer

Background

Cancer is a problem that has long been wrought over by philosopher and biologist alike. It provides a tremendous insight into the diversity of complex phenomena, into the ontogeny of order, into the deepest deterministic principles of life itself. Here we try to sketch dynamically the emergence of such a metastatic and invasive process, tying together chemical, molecular, and physiological insights to more clearly define the problem. We follow the progression of small-cell lung cancer in a population of brachial lung cells – tracing the molecular, cellular, and systems etiology of this complex disease.

Defining the Cancer Biological System

Cancer is a multifaceted disease that manifests on different levels. On one hand, it is a molecular disease -- radical oxide particles undermining the nucleotide regulatory codes of individual cells. On the other hand, it is a social disease of a cell population – one group of cells has become unruly, growing and dividing rapidly in a distinctly hostile fashion. Yet another hand presents the compromise of an organ system, the disease state undermining an essential physiological function. A final hand completes the symmetry, revealing cancer to be a recapitulation of an earlier developmental phase, a paradoxical retracing of ontogeny.

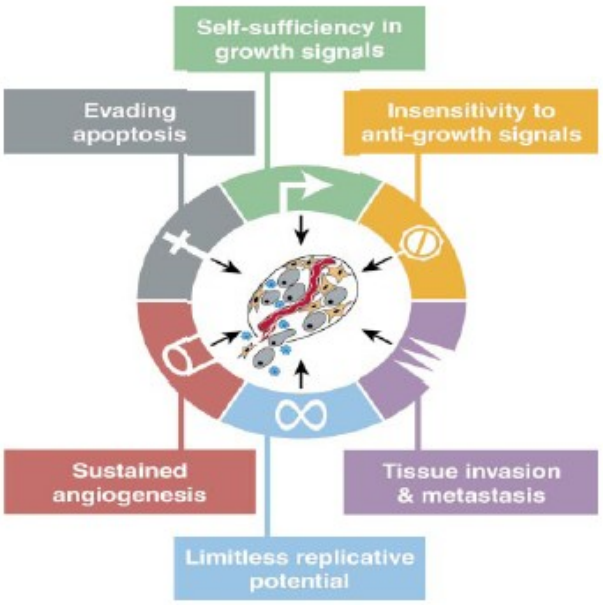


Figure 1: Commonly acquired and often necessary characteristics of cancer cells. (Hanahan et al.)

Cancer is a molecular disease caused by a variety of chemical agents. These carcinogens are usually mutagens that induce changes in DNA or RNA, changes which then alter the regulatory and functional characteristics of the code to induce drastic behavioral changes at the cellular level. Chemical mutations tend to distribute randomly across exposed (actively transcribed/regulatory) regions of the genome and while most mutations are harmless, the few that affect cell-cycle checkpoints can prove fatal to the local cell cooperative. Cell-cycle mutants can become proliferative, breaking free of the cellular matrix and compromising systems level goals. (Hanahan et al.) Cancer, then, becomes a social disease of a cell population.

Cancer is a disease of an organ system. A human composed of eyes, noses, mouths, hearts, and lungs is necessarily an ordered systems of different types of cells and tissues. This order arises from the ontogeny of development. All tissue and systems arise from pluripotent stem cells, who based on extracellular cues, commit to ever more limited and specialized fates. The cell maintains a population of stem cells in any given tissue that replicate and differentiate when the organ is damaged. Progenitors give rise to committed cells which in turn give rise to terminally differentiated cells that can no longer divide and who are locked into functional roles through epigenetic means. In cancer, this developmental progression is upset and progenitor and committed cells break free of their fate programming to pursue

their own replicative agendas. (Werner et al., Warburton et al.)

The first attempts at a systems model of cancer was undertaken by Barry Richmond in 1977. He developed a model and a structural theory that intergrated much of the available information then. It is well past time for an update, though, as the past 25 years have brought unparallel discoveries in this field on the molecular, cellular, and physiological levels. We strive, as he did to develop a thorough understanding of the cancer problem and try to find a modeling approach that captures the complex behaviours associated with cancer while remaining simple enough to be useful as a tool for understanding the disease process.

The Story of Small-Cell Lung Cancer

There are many different types of cancer, usually named by and taking on characteristics of the tissue in which it arises. Lymphomas affect the lymph nodes, melanomas affect melanocytes in the skin, and carcinomas afflict the epithelial cells that line tissue surfaces. In addition, tumors are heterogenous, polyclonal (having different genetic strains) tissues composed of cells with many different mutations and functional changes. (Hanahan et al.) When it comes to modelling cancer, it would be better to focus on a specific type, thus avoiding reckoning with the many unrelated parallel and even opposing pathways that produce the phenotype. Instead, we draw our attention to a particular cause and effect relationship in a well-studied but incompletely understood system of cancer.

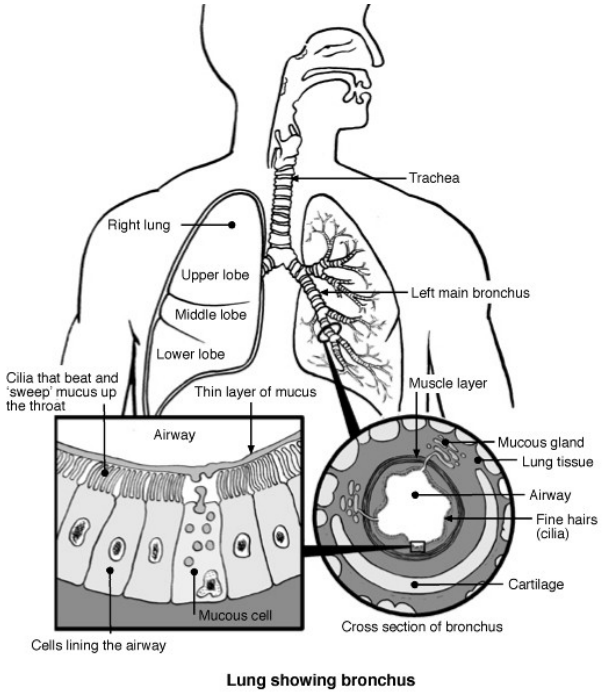


Figure 2: Schematic view of the bronchi, revealing epithelial cells where lung carcinomas arise. http://www.patient.co.uk/showdoc/21692519/

Small-cell lung cancer is a carcinoma of the epithelial cells lining the bronchi (see figure). Though it accounts for less than 20% of all lung cancers, small-cell (or oat-cell) carcinoma is the one most strongly associated with smoking. The small-cell moniker arises from the fact that these fast proliferating tumor cells are small and oval with a high chromatin concentration. Small-cell lung cancers are also among the fastest to metastasize to distal locations and are even known to produce ectopic neuroendocrine effects. (Jackman et al., Kotton et al.)

Unlike most cancers where the causes of malignancy are mostly uncorrelated with behaviour or exposure, small-cell lung cancer has been tied firmly to smoking. Besides the usual slew of carcinogens known to transform cells into cancers, bronchial epithelial progenitors also have a close relationship with nicotine. During the growth of the embryonic lung, epithelial progenitors express neuromedin and gastrin-releasing peptide (GRP) receptors. Activation of these receptors by their targets stimulates lung stem cell proliferation. It turns out that elevated nicotine concentration induces expression of GRP and neuromedin receptors producing a sort of developmental regression. When other cell-cycle checks are similarly broken and tissue repair mechanisms induce stem cell proliferation to replace epithelial cells damaged by smoking, this autocrine growth loop can produce and explosive expansion of the cancer cell population. (Seigfried et al., Werner et al., Wistuba et al.)

Developing A Structural Model

In this phase of our project, we strive to develop a structural understanding of cancer dynamics. We trace the genesis of cancer in a microcosm of lung tissue following the different cell types, their developmental progression, replication, mutation and death. We try to determine the simplest structures that can accurately simulate cell metabolic processes and the impact of blood supply requirements on growth and death. We examine the impact of smoking – it's toxic effects on tissue, it's induction of endocrine factors and it's effect on mutagenesis. Finally, we trace the developmental process of tissue repair following progenitor cells as they divide and differentiate highlighting the impetus they provide for proliferative processes like the ones operating in cancer.

Tissue Cell Populations

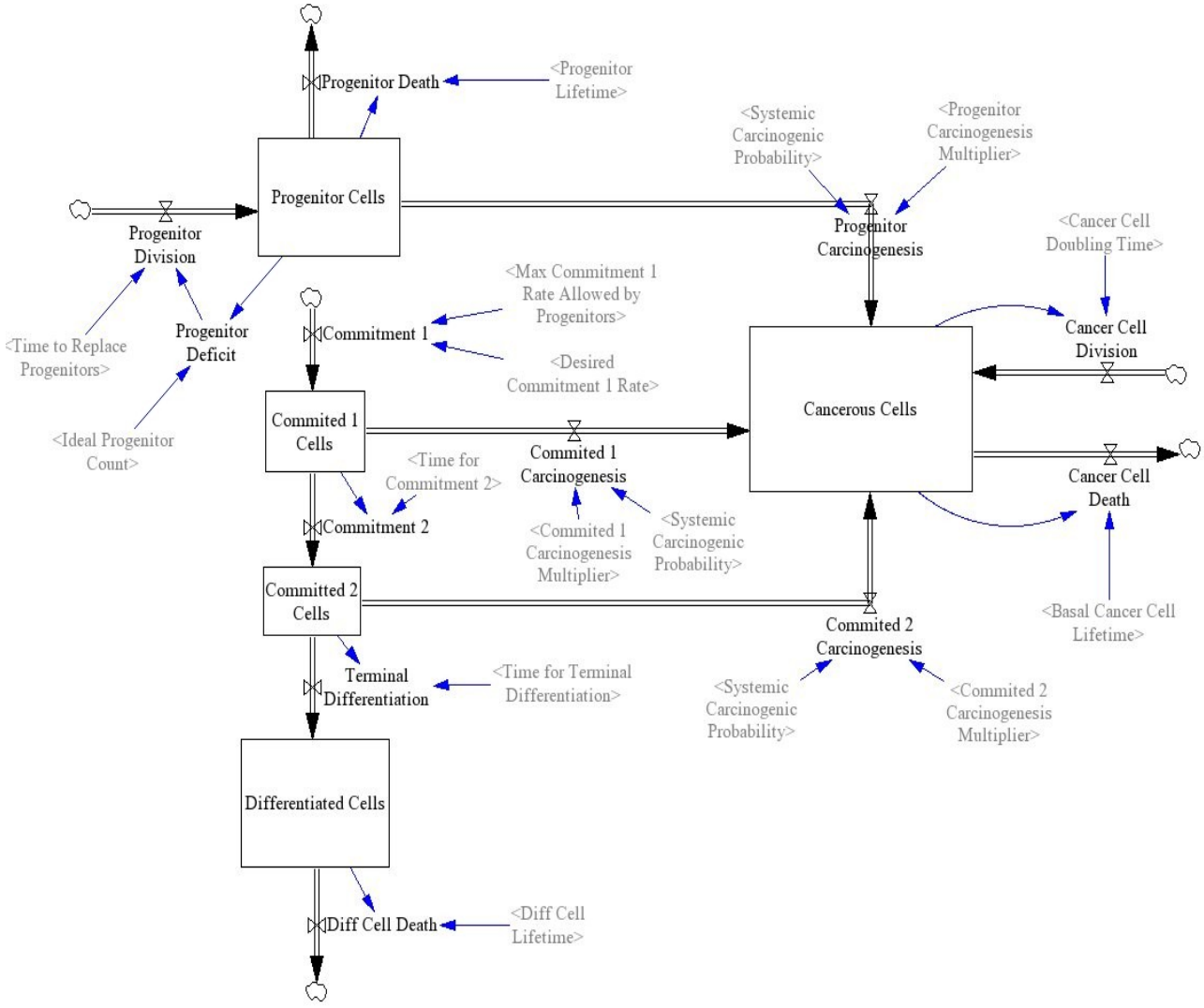


Figure 3: Tissue cell populations represented as stocks with flows into their normal and cancerous developmental fates.

We model the lung cell populations as a developmental progression. There is a pool of pluripotent progenitor stem cells at the top of the developmental potential hill. As fully differentiated cells at the bottom of the potential are depleted by death or tissue damage, these progenitors progress into successively more committed cell types. Each of these developmental progressions has it's own

rate that is dependent on the total number of differentiated cells that need to be replaced and on other factors such as nutrient availability and cellular toxicity. Progenitor and differentiated cells are born as a continuous adjustment to an ideal target population of each cell type (Ideal Progenitor Cell Count and Ideal Differentiated Cell Count) and die according to their respective lifespans. Divisions rates for progenitor and cancer cells are additionally affected by the levels of extracellular mitotic signals. They produce exponential increases in cell division rates on an order corresponding to the population's responsiveness to such mitotic stimuli.

A cell in any of the undifferentiated stages has a probability of becoming cancerous with stem cells being the most likely to transform, committed progenitors being less likely, fully committed cells even less likely, and differentiated cells being unable to transition. The probability of transitioning normal cells into cancerous cells is also influenced by the mutagenesis rates, which in this model corresponds to inhaled smoke exposure.

Metabolism

A key component of any realistic biological model is a representation of metabolism – the energetics of cellular life in terms of nutrition waste. We use some of the insights and techniques developed by Richmond to formulate a very simple representation of cellular metabolism. In this representation, Nutrients and Metabolic Wastes are stocks. The nutritional inflow and waste outflow are dependent on the size of the local blood supply while nutrition consumption and waste generation are based on the cell's given metabolic rate.

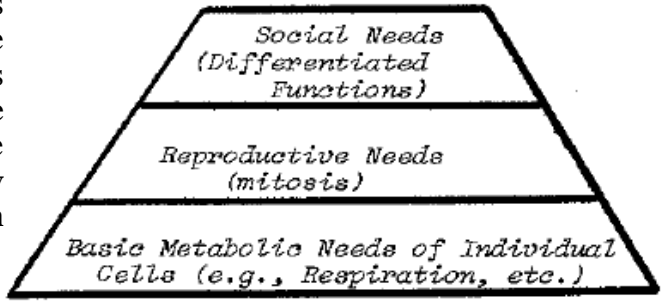


Figure 4: Richmond's hierarchy of cellular needs.

The structure of this metabolic formulation reflects Richmond's hierarchy of cellular needs and bears out the simple assumption that food and waste clearance are the most basic and most essential processes of cellular life. We design the model such that nutritional shortages and toxic metabolic waste accumulation (relative to normally tolerated amounts) act to slow the growth and division of any cellular population, produce cause angiogenic factor production in the cell neighborhood, and in the case of progenitor cells even works to slow their differentiation rates.

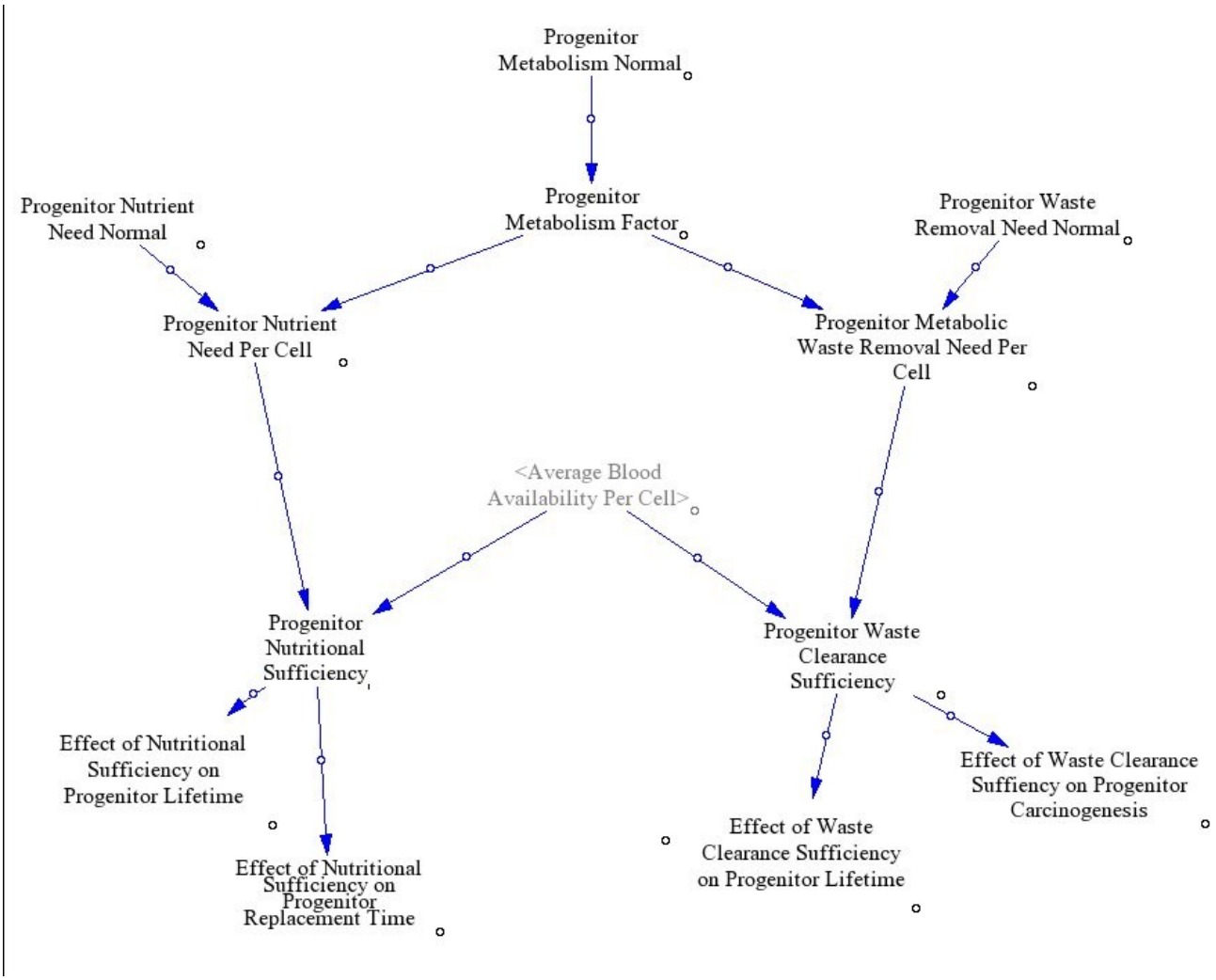


Figure 5: Structure of progenitor cell metabolism and waste elimination.

Separately formulating a parallel structure for each of our three major cell populations (progenitor, differentiated, and cancer), we manage to independently and symmetrically assess the metabolic status of each.

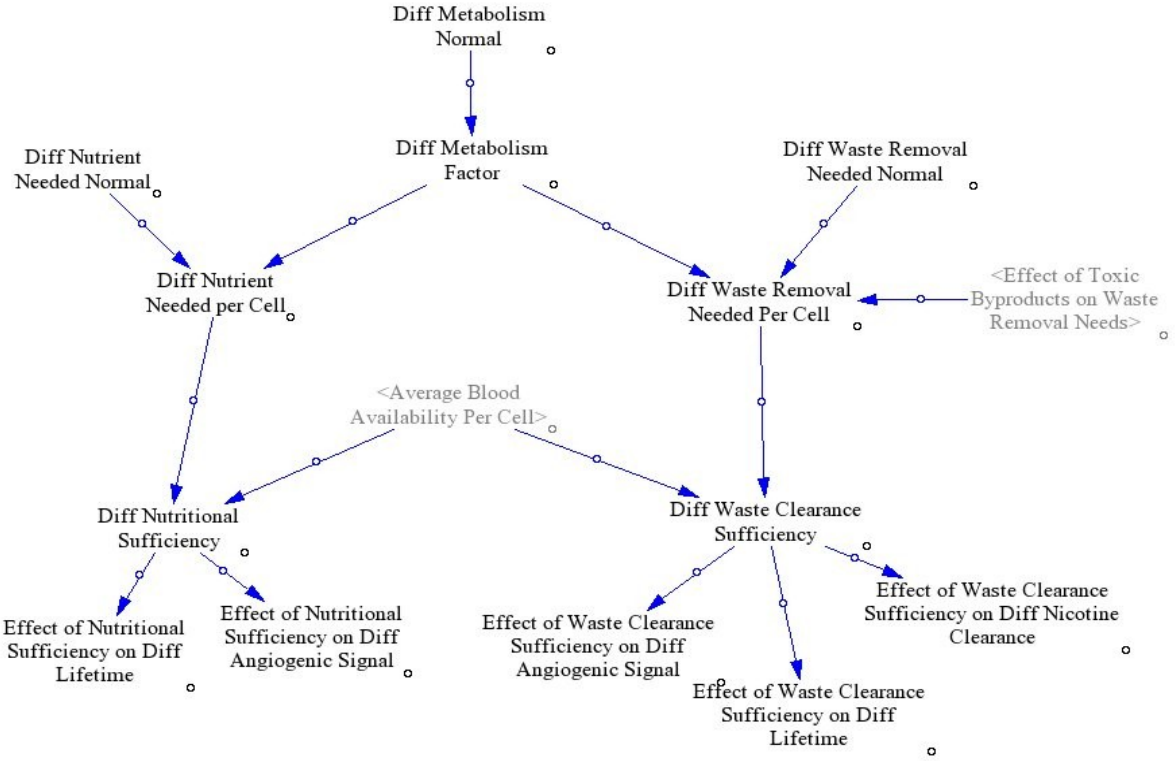


Figure 6: Metabolism of the Differentiated Cells

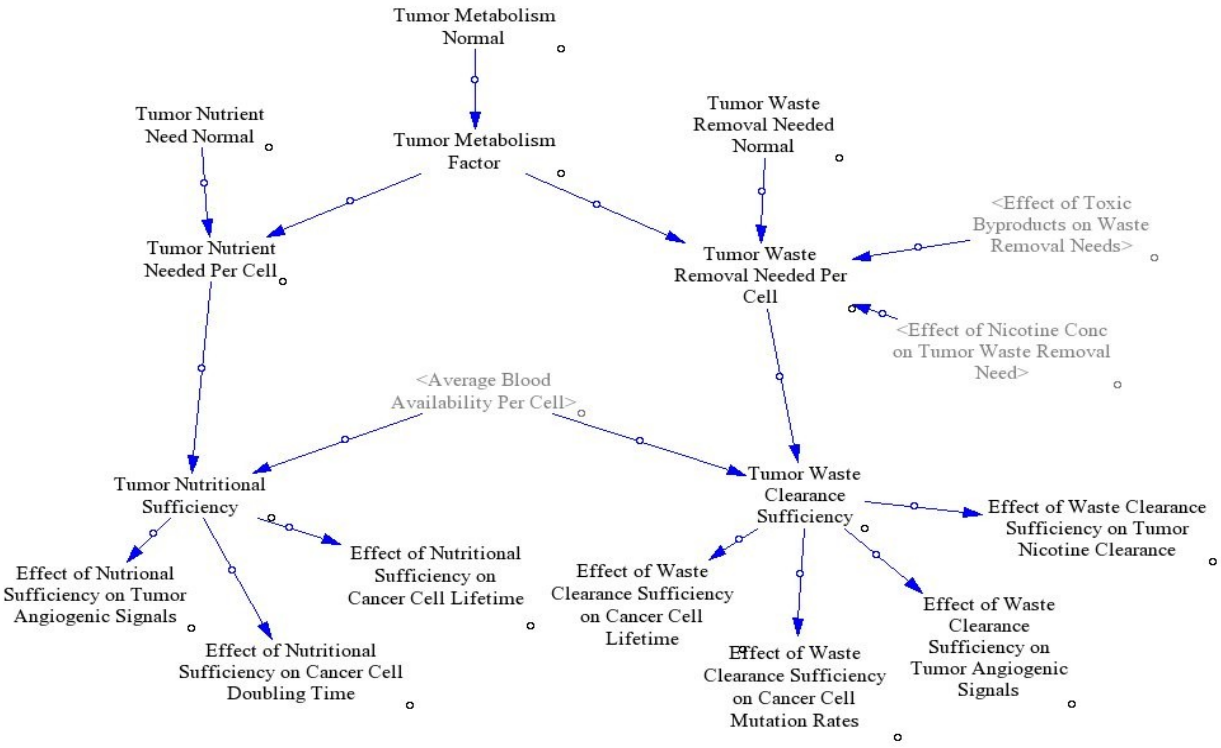


Figure 7: Metabolism of the Tumor Cells

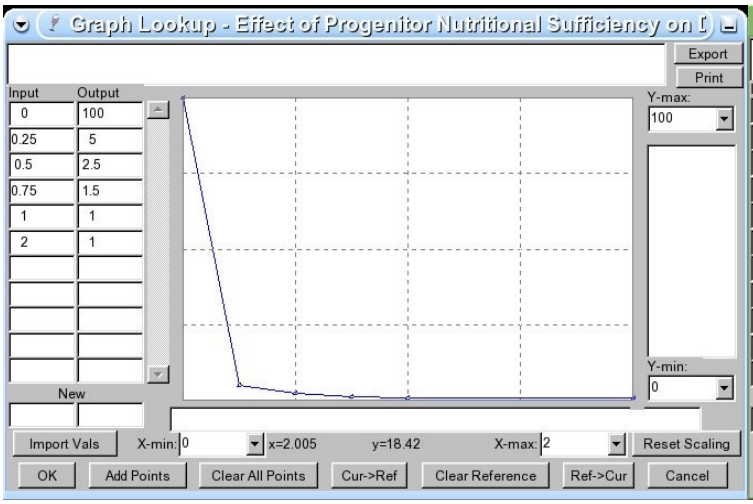


Figure 8: Effect of Nutritional Sufficiency on Differentiation times is formulated as a exponentially decaying function

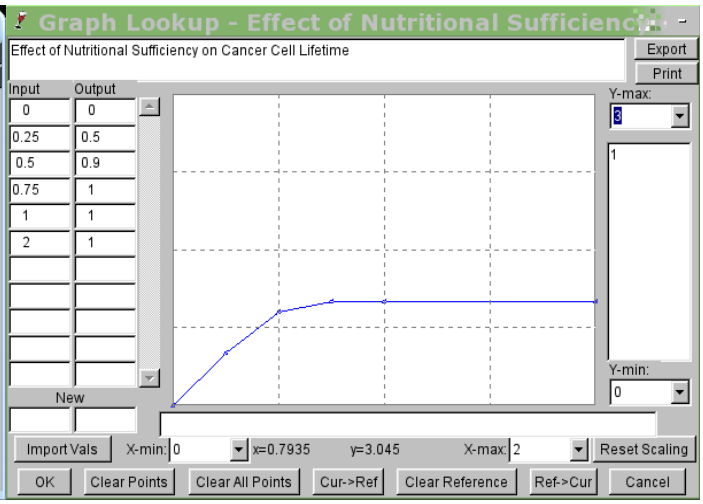


Figure 9: Effect of Nutritional Sufficiency on Cancer Cell Lifetimes is formulated as a logarithmically increasing function

The effects of metabolic deficiencies on population parameters are formulated as lookup tables. There are basically two types of lookup tables we formulate in this sufficiency model. The first is a exponential decay effect on carcinogenesis rates and angiogenic factor production for each cell type, or time to replace progenitor cells and its value drops from an arbitrarily large value at 0 sufficiency to a normal value of 1 for sufficiency equal or greater than 1 (Figure 8). The second is a logarithmic growth effect on cell lifetimes or fractional nicotine clearance rates and its value increases from a minimum of 0 at 0 sufficiency to a maximum of 1 at sufficiency greater than or equal 1 (Figure 9).

Blood Supply

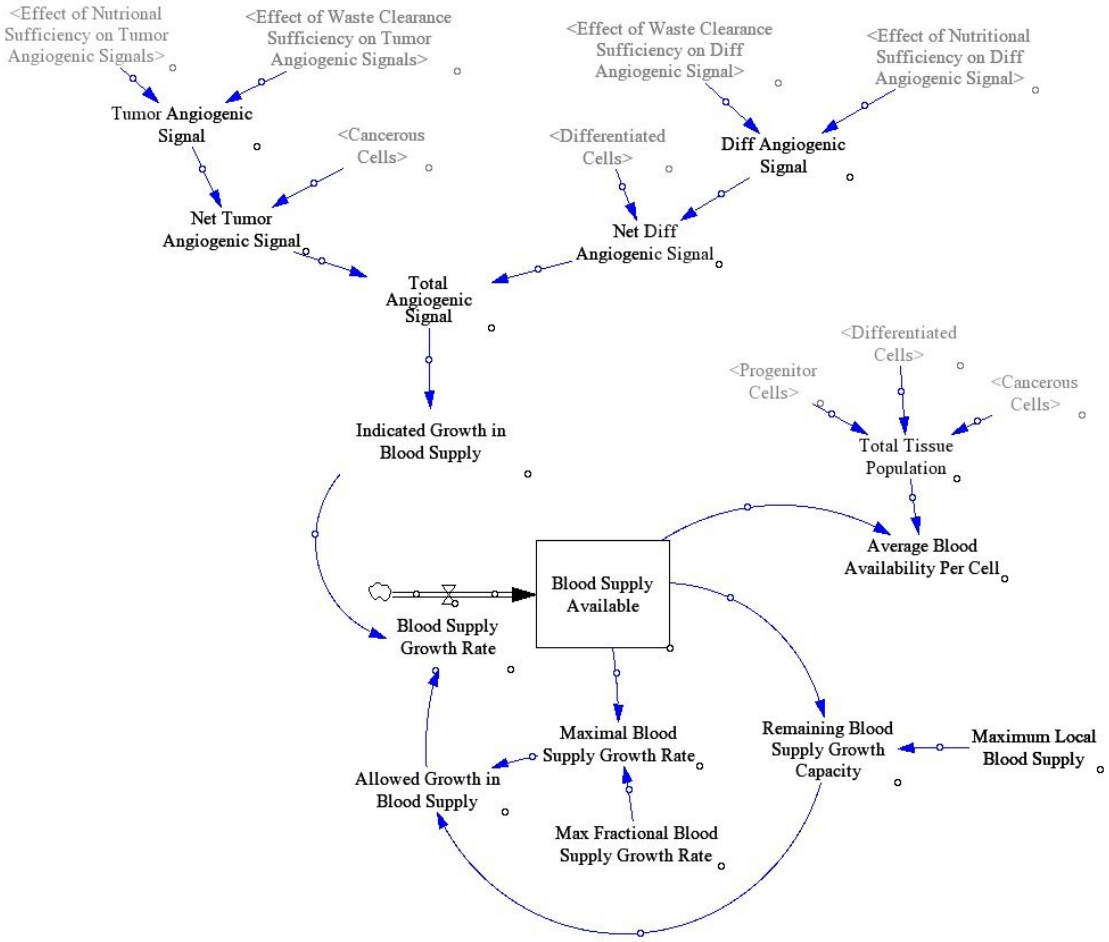


Figure 8: Blood Supply Sector

Blood supply is modelled as a stock that can grow to a maximum capacity for the given tissue microcosm. The growth rate is determined by the growth level indicated by the total angiogenic signals from the cancer and differentiated cells, and limited by a maximum fractional and maximum total blood supply growth rate. The average blood available per cell is simple division of blood units by number of cells.

Angiogenic signals are produced by tumor and differentiated cells in response to nutritional insufficiency or waste clearance insufficiency. The dominant signal from either nutritional insuffiency or waste clearance insufficiency is then multiplied by the number of cells in each population to simulate the diffusive effect of the angiogenic signal – the more cells putting out the signal, the stronger the indicated growth in blood supply will be.

Differentiation, Division and Death

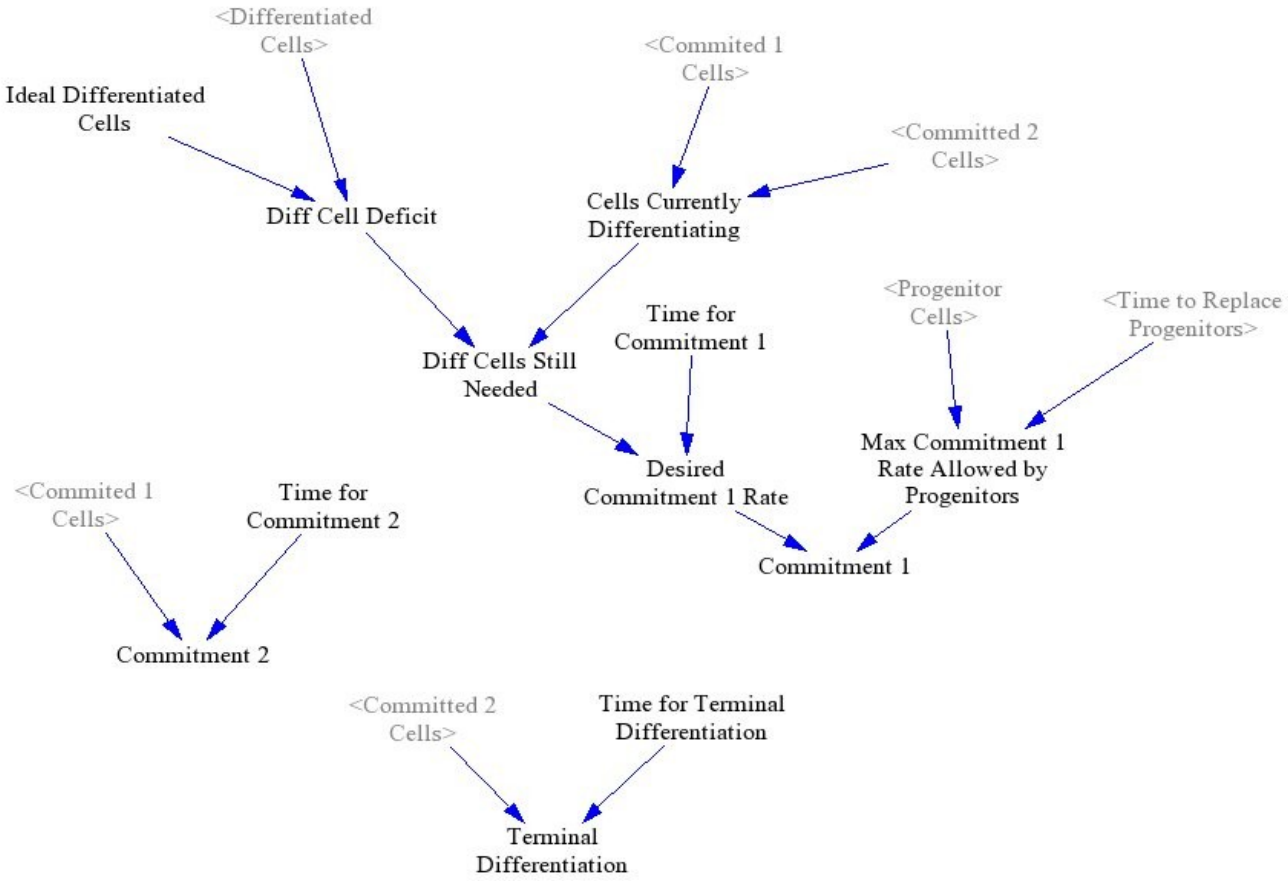


Figure 11: Differentiation Rates

Differentiation rates (Figure 11) are computed in terms of making up a deficit of differentiated cells. We take the difference between the ideal number of differentiated cells and existing or currently differentiating cells and have progenitors transition into the first differentiation step at this desired commitment rate as long as it's less than the maximum commitment rate allowed. Commitment 2 and Terminal Differentiation simply take the cells from the previous step into the next state in the given time.

Division is tabulated in terms of making up a deficit of progenitor cells and calculating a doubling time for cancerous cells. Both rates are affected by systemic adjustments for the mitotic signal level, by their own responsiveness to these signals, and by metabolic adjustments to their division rates. In the case of cancer cells, the nicotine concentration can have an effect on their responsiveness to mitotic signals.

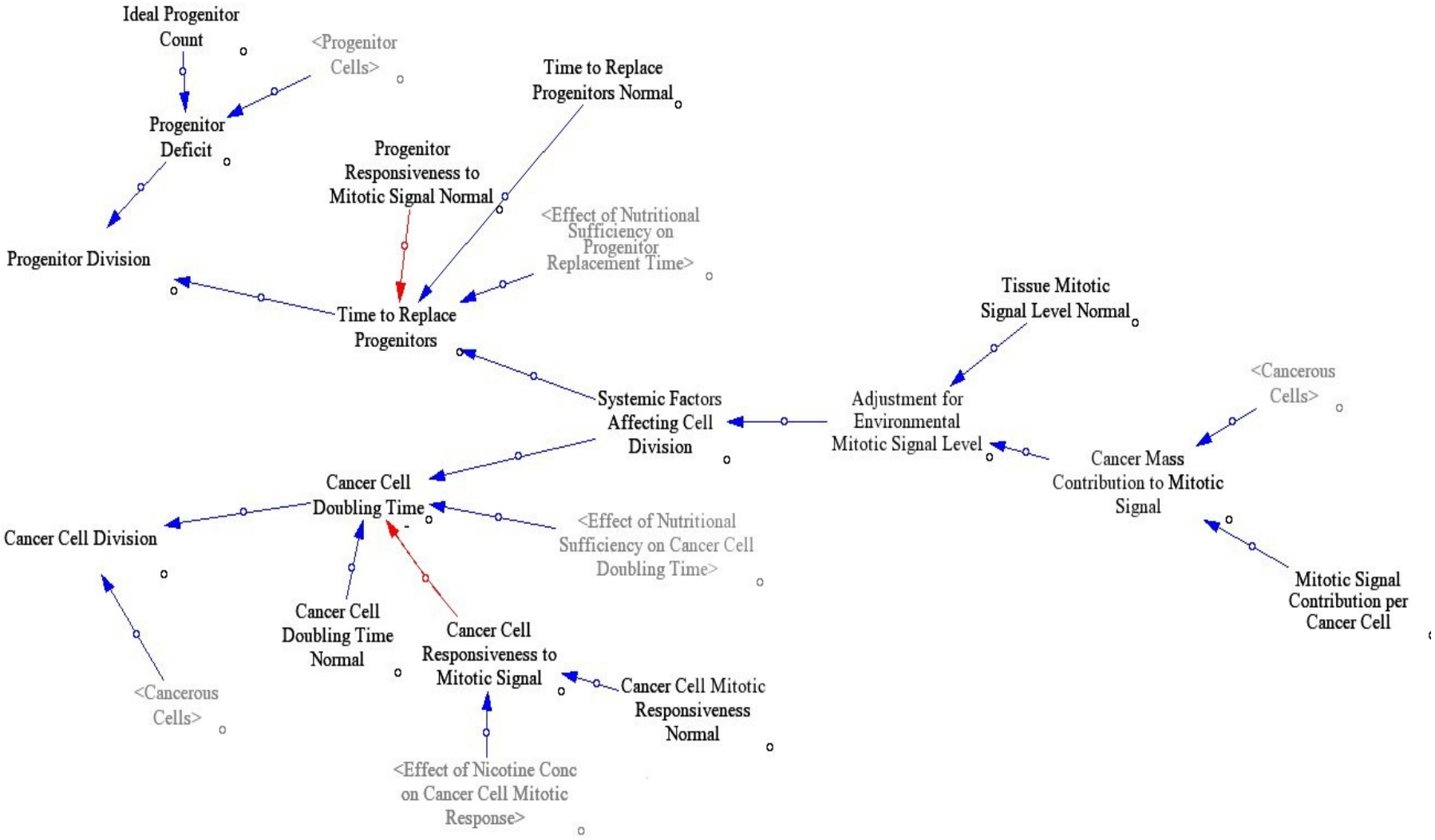


Figure 12: Division Rates

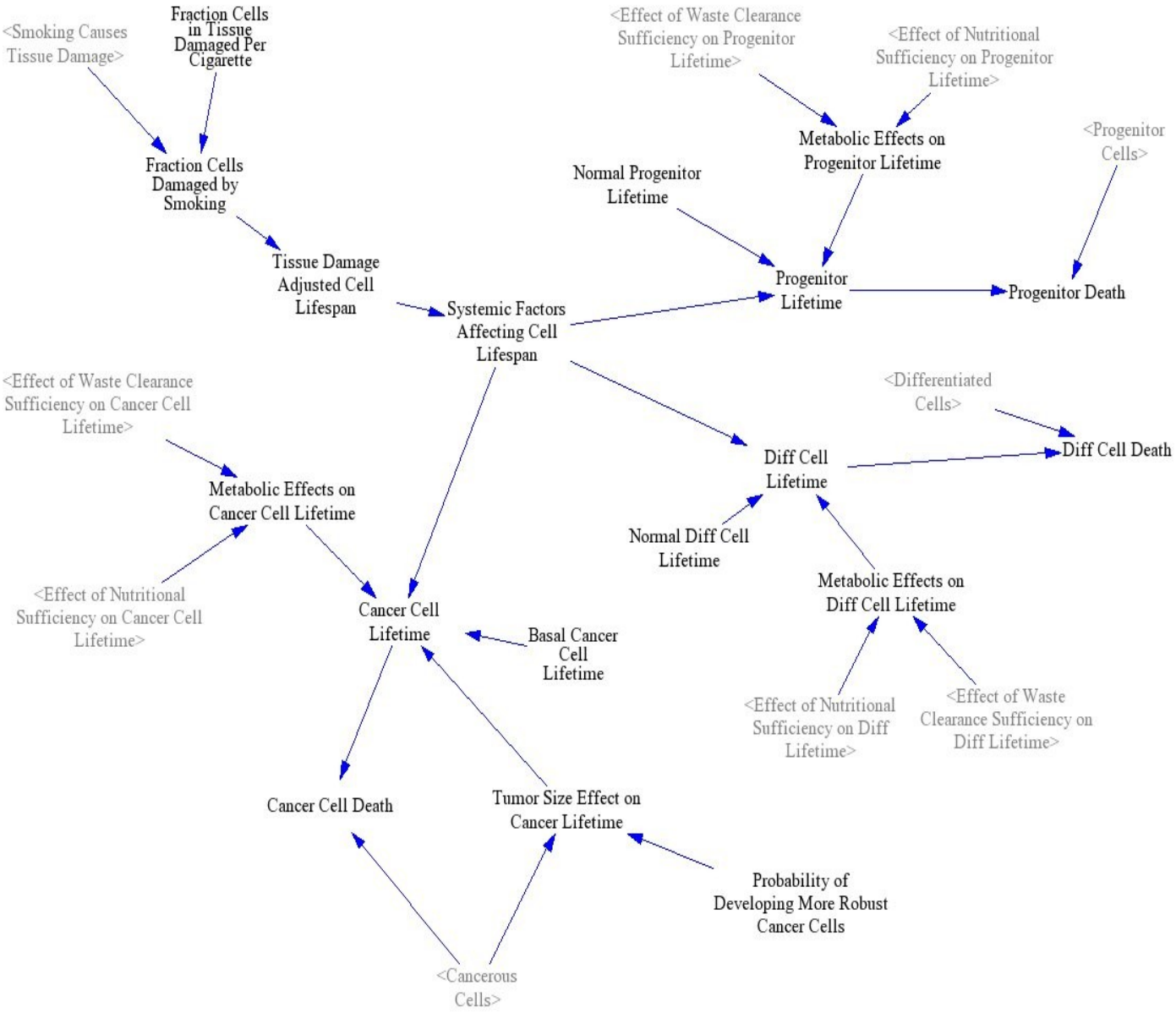


Figure 13: Damage and Death

Tissue damage is calculated simply as a global adjustment of cell lifespans based on a fractional damage rate based on the cigarette consumption rate. Metabolic sufficiency is accounted for each of the cell types and the lifetimes are correspondingly adjusted from their normal values. For cancer cells, we have a peculiar feedback process where the number of cancer cells increases the probability of long-lived mutants in the population which would drive up the average cancer cell lifetime.

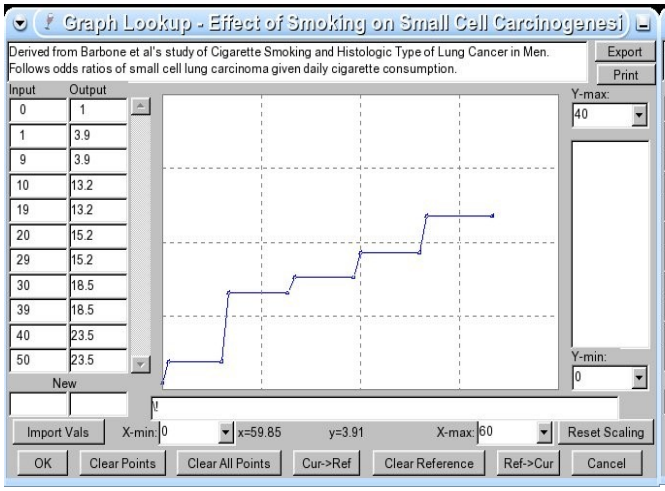


Figure 14: Effect of Smoking on Small Cell Carcinogenesis

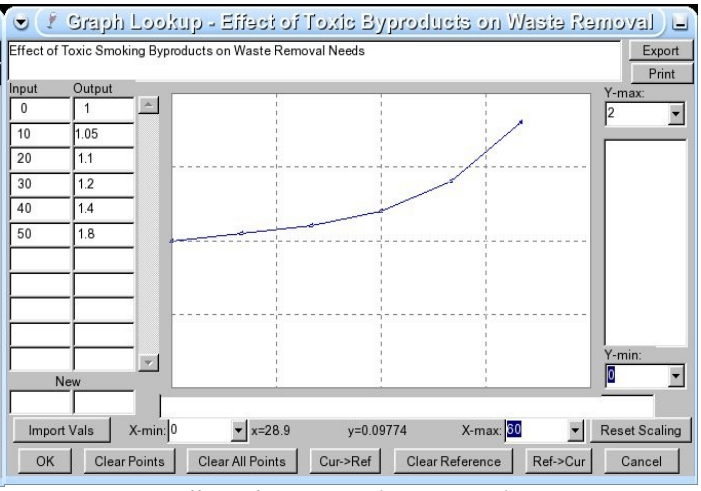


Figure 15: Effect of Toxic Smoking Byproducts on Waste Removal Needs

Mitotic Signals

Tissue repair pathways as well as several cancer pathways induce extracellular mitotic signals. These diffusive signals permeate the local cell neighborhood and trigger mitosis in all responsive cells. We model these extracellular mitotic signals as a stock that accumulates with repair signals or cancer processes and decays exponentially with a given signal lifetime.

Smoking

We model smoking as a constant accumulation process of nicotine and a constant exposure to other toxic substances whose magnitude depends on the effect of one cigarette and the number cigarretes consumed per day. The model here posits four parallel processes with which smoking interferes. Firstly, smoking and the free radical particles inhaled with cigarettes increases the mutagenesis rate in the local tissues. Next, both this free radical load and the drying effect of hot smoke in lung tissue contribute to the metabolic load of the lung's epithelial cells. Third, these same factors also direct kill a small portion of epithelial cells. Finally, smoking slowly increases nicotine concentration, especially in the lungs and peripheral vasculature.

The second half of our smoking sector captures the effect of this nicotine dependent autocrine growth loop in small-cell lung cancer. In this view, nicotine accumulation in the local tissue results from intensive smoking and from reduced elimination rates (associated with rapidly expanding cancers that can never maintain a sufficient blood supply). Elevated nicotine concentration induces expression of growth factor receptors which make the cancerous cells more responsive to mitogenic signals and accelerate the disease progression. This process is captured in the Effect of Nicotine Conc on Cancer Cell Mitotic Response.

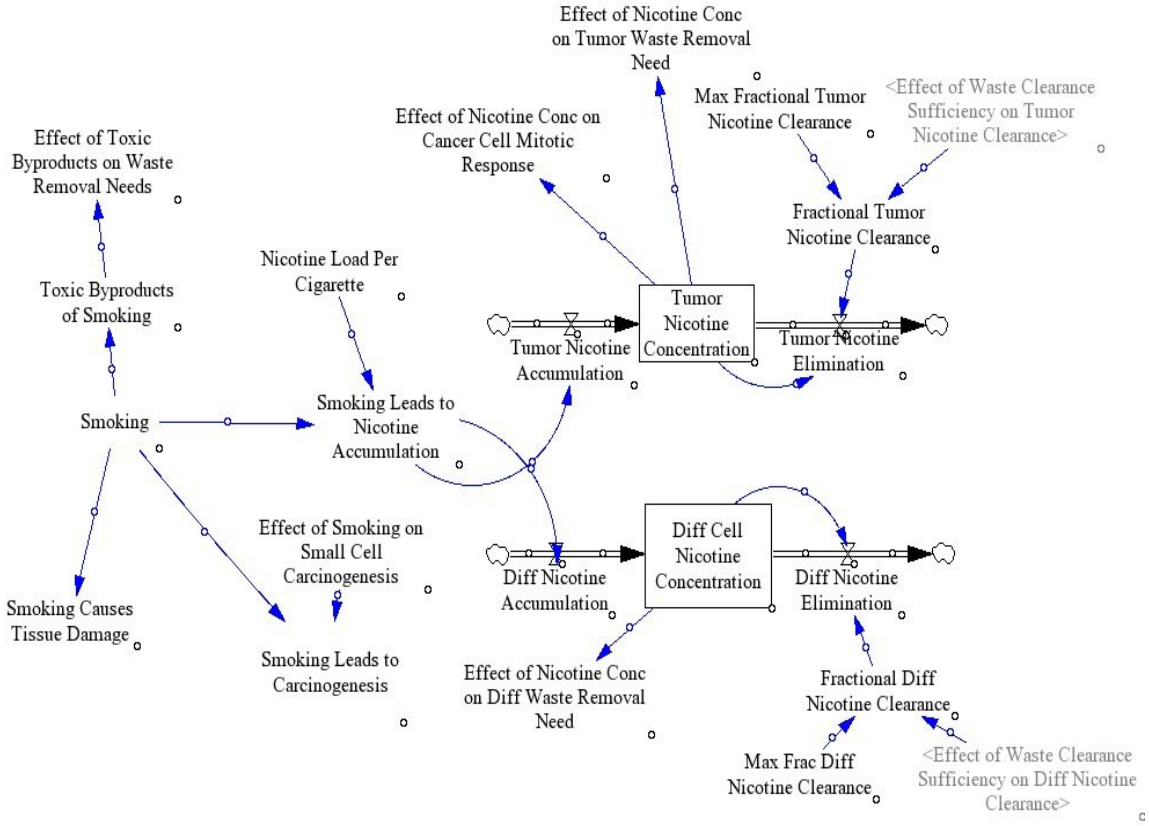


Figure 16: Smoking Effects

The way in which smoking affects carcinogenesis rates has not been explicitly studied but we can use a study that associated levels of cigarette consumption with risk of developing small cell lung cancer to derive an empirical estimate of these effects. Barbone et al have studied this and published comparative odds ratios of small cell lung cancer development given cigarette consumption. We incorporate this into our model as the Effect of Smoking on Small Cell Carcinogenesis.

Mutagenesis, Rebellion and Death

While random mutations, the rate of which climbs drastically with carcinogen exposure from tobacco, are the cause of cancer initiation, once a cancer population exists, it becomes an organism in it's own right pursuing and independent proliferative course of action. Cancer cells tend to divide without waiting for the normal error-proofing steps undertaken by normal cells. This rapid proliferative phase is characterized by a high mutation rate. It is in the mutants that arise here that cancers find their modes of terminating the host. Mutations that invoke senesence and resistance to environmental stresses are added to the tumor's repertoire of cells, along with ones that allow bloodstream or immune invasion. Collectively, these phenomena serve to increase the tumor's robustness increasing the average cancer cell lifespan and making therapeutic intervention ever more difficult.

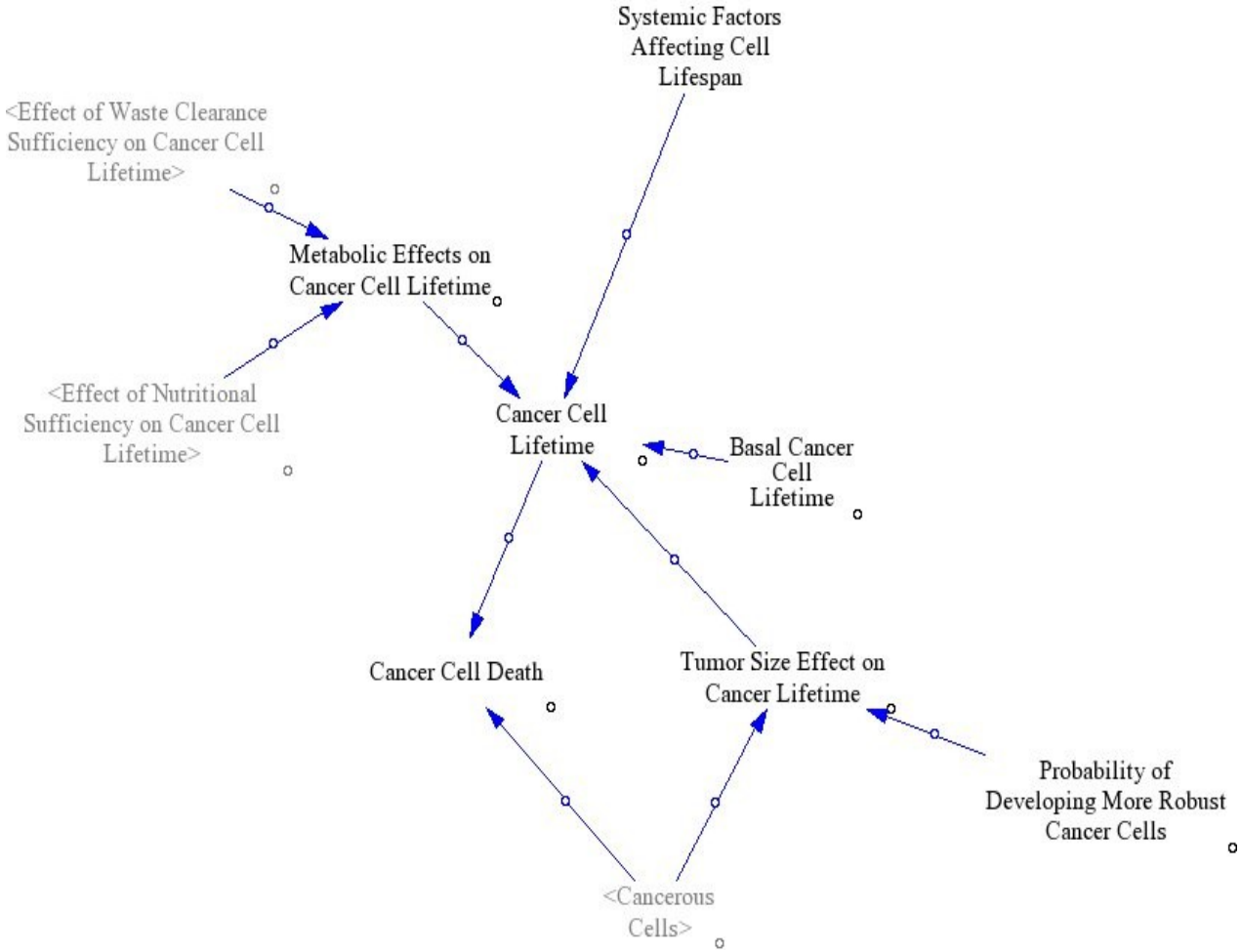


Figure 17: Cancer Cell Lifetimes - Relation to Tumor Size and Robustness

Simulation Runs

In this draft of the structural cancer model we try to recreate the well-established quantitative correspondence between smoking and small-cell lung cancer. By varying cigarette consumption, we find that we can affect the probability of cancer onset in the twenty years of the the simulation run. As expected, we find exponential increases in cancer populations once the founding cells encounter the necessary proliferative stimulus. In some exceptionally intense smokers, we find that the cancer has multiplied to the point where the normal cell and progenitor cell populations have crashed after stretching the blood supply to the limit. We wind up, in these most successful cases, with a bona-fide tumor – a clump of cells in exponential growth phase actively recruiting it's own blood supply and causing havoc in the surrounding tissue.

We run the model with daily cigarette consumptions of 0, 20, 40, 60, and 80 per day and then examine the system and state variables. We find that the 20 per day smokers are slowly increasing their cumulative risk of developing a metastasis over the course of the 10 years and that the other smokers show differing onsets and initial progressions for an invasive tumor that changes the local tissue composition.

We vary the number of cigarettes consumed per day from 0 to 100, measuring the sensitivity of the tumor development process to this parameter. Graphs and tables of key variables from the sensitivity and regular runs follow the short summary below.

Summary of Model Behavior

At some critical threshold value of cigarette comsumption between 20 and 40 per day, we can see a transition from a simple probability of tumor development to a non-zero tumor cell population. In the 20 cigarettes per day run, we are left with a greater risk of developing cancer –it transitions from the 3.95e-29 that comes with normal aging given our model to 2.50e-26, a value indicating a cancer risk more than 1000 times higher in the given tissue.

In the consumption value range that develops a growing tumor, we find that the cancer population grows exponentially at first expanding into any available free blood supply capacity and by replacing peripheral cells (specifically differentiated cells) that have a shorter lifespan and therefore lower population expansion rate. Once the replacement processes and the equilibration of populations based on birth and death rates is done, the tumor population grows linearly as the blood supply finishes expanding at the maximum allowed rate. All of this behaviour is in line with what little is known about the initial growth phases of a primary tumor – that it will expand based on it's indicated population growth rate (difference between division and death rates) until it reaches the resource limit for the tissue, and that it will then grow based on it's angiogenic ability and the local tissue angiogenic rate maxima until it reaches the maximum blood supply capacity for the locality. Further growth is dependent on ability to grow and invade into the surrounding periphery.

The tumor population is growing even as it's starving and though initially cells are drifting towards compensating for the nicotine and toxic waste clearance load by increasing blood supply, the development of even one tumor cell soon leads to explosive tumor growth irrelevant of the metabolic checks on its growth. This process of growing in toxic surroundings also gives the tumor cells a competitive edge in replacing the differentiated cells surrounding them.

Dependence of Model on Tumor Size Parameter

The trickiest parameter to estimate here is the probability that a growing tumor colony will develop the long-lived phenotype that lets them outlive and thereby replace the differentiated cells in the local tissue. Given that we don't explicitly model invasive metastatic features or active immune response in tumor cells, tumor replaces healthy tissue in a replacement process where a resource (blood supply) slot opened by a dying differentiated cell is filled by a much longer lived tumor cell. The lifetime of the tumor cell in this case is decided mainly by the probability of developing cell-death evasion mutations in a subpopulation of tumor cells which eventually leads to replacement of the entire tumor population by cells that on average live longer and expand into differentiated cell resource supply. The difference between division and death is the key determining factor here and a longer lived population has no trouble maintaining a growth rate that far exceeds the death rate.

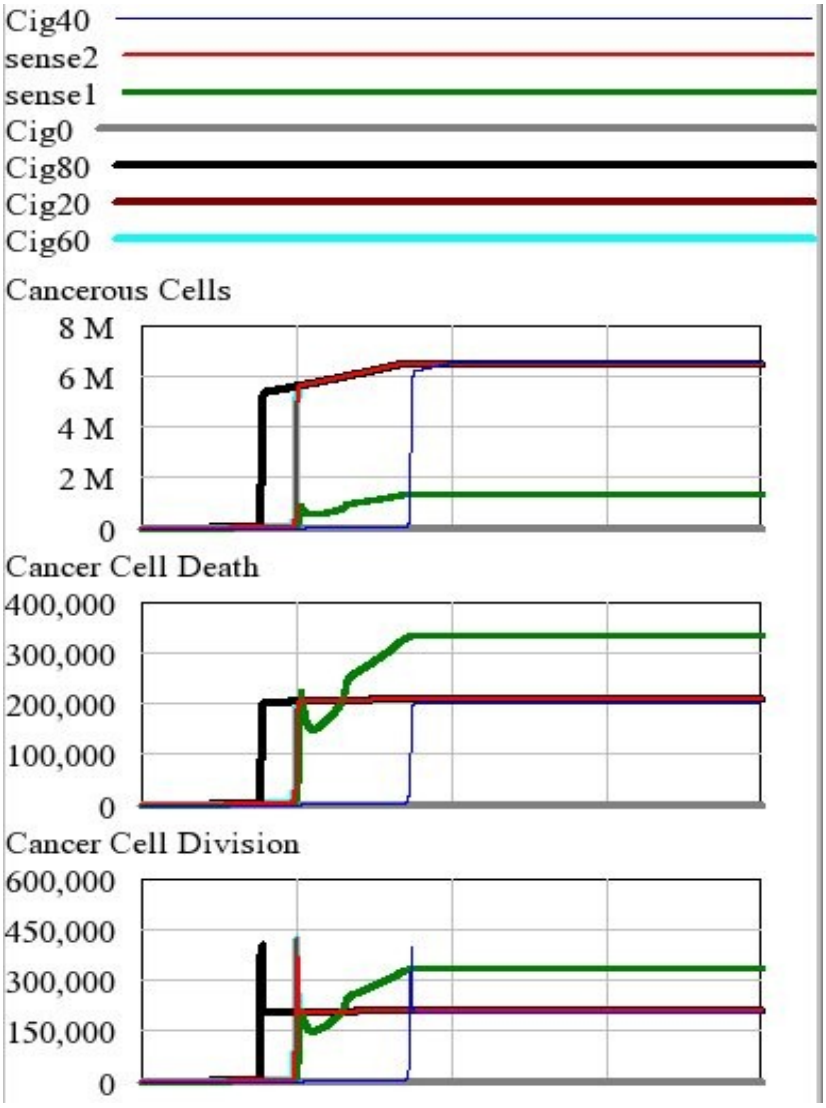


Figure 18: Dependence of Division to Death Ratio on Cancer Cell Lifetime and in turn on Probability of More Robust Cancer Cells Arising

The green run in the figure above uses a Probability of Robust Cells Arising that's 10 times lower than the original value. It shows a tumor population that has trouble expanding into differentiated cells showing a profile more indicative of a benign and growth-limited tumor type.

The Effect of Smoking on Carcinogenesis

Cigarette Consumption (number/day)	*Cancerous Cells (cells after 20 years)*	*Differentiated Cells (cells after 20 years)*	*Years To Develop Cancer*
0	3.95e-29	9.09e+05	>20
20 (1 pack/day)	2.50e-26	9.09e+05	>20
40 (2 packs/day)	6.49e+06	3.42e+04	~10
60 (3 packs/day)	6.46e+06	3.17e+04	~5
80 (4 packs/day)	6.47e+06	3.16e+04	~3

Table 1: Cigarette Consumption as it affects normal tissue and tumour populations.

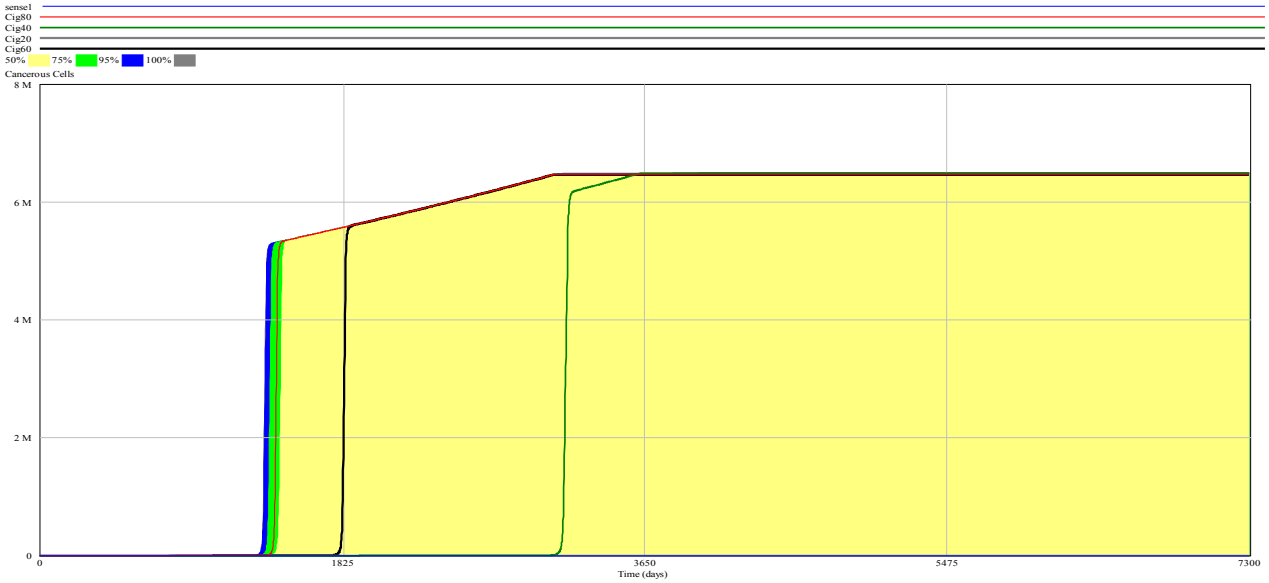


Figure 19: Cancerous Cells as Smoking varied 0-100.

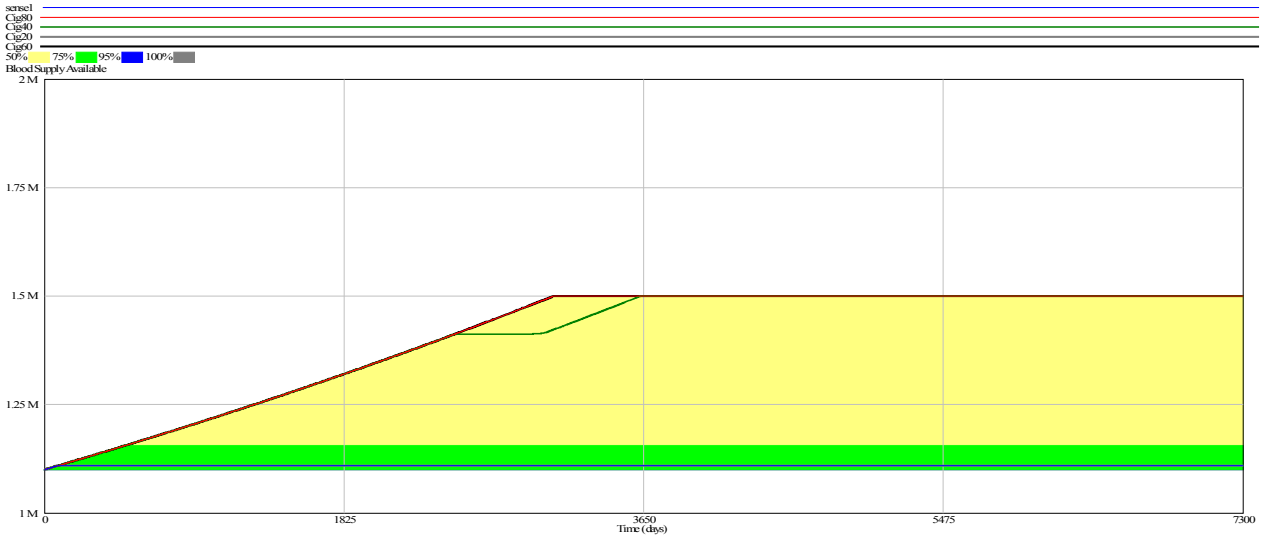


Figure 20: Blood Supply as Smoking varied 0-100.

Looking at the above graphs, the primary insight we gain is that tumor development progresses initially as an exponential process where tumor cells are first growing to the excess blood supply capacity of the local tissue, then competing with the differentiated cell population as the blood supply and number of cells is grown up linearly (based on the limits to blood supply growth), and finally replacing differentiated cells as long lived variants increase tumor robustness. The differentiated cells are unable to survive as well given the comparative fitness of tumor cells in the resource scarce scenario and have a crash in their lifetimes that leads to a population collapse (graphs below).

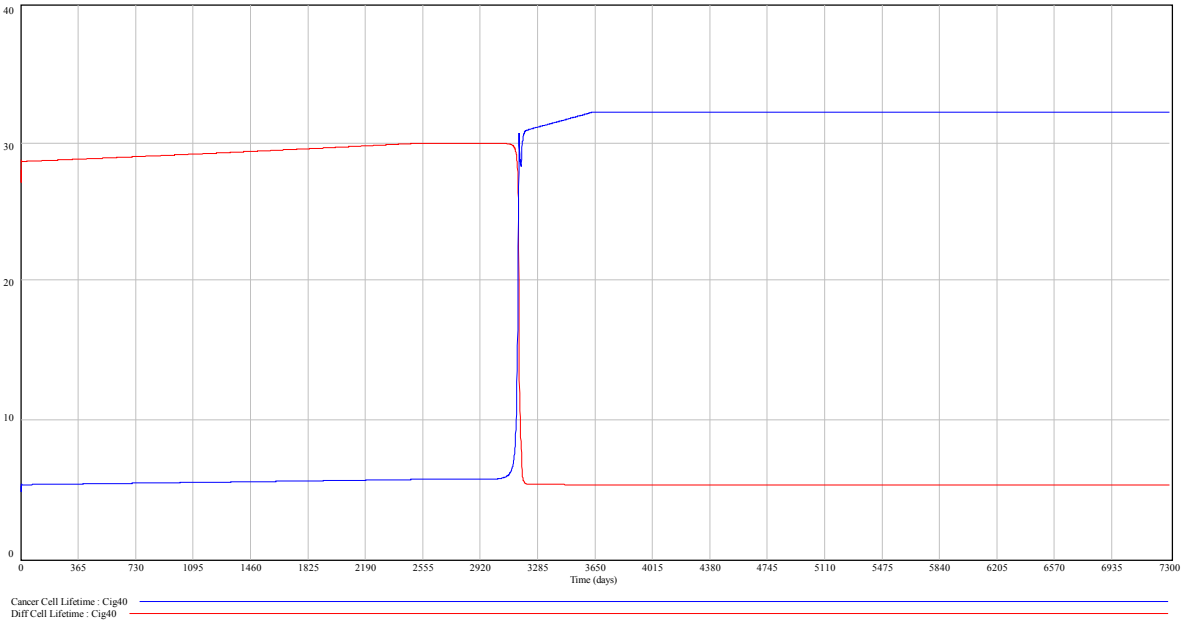
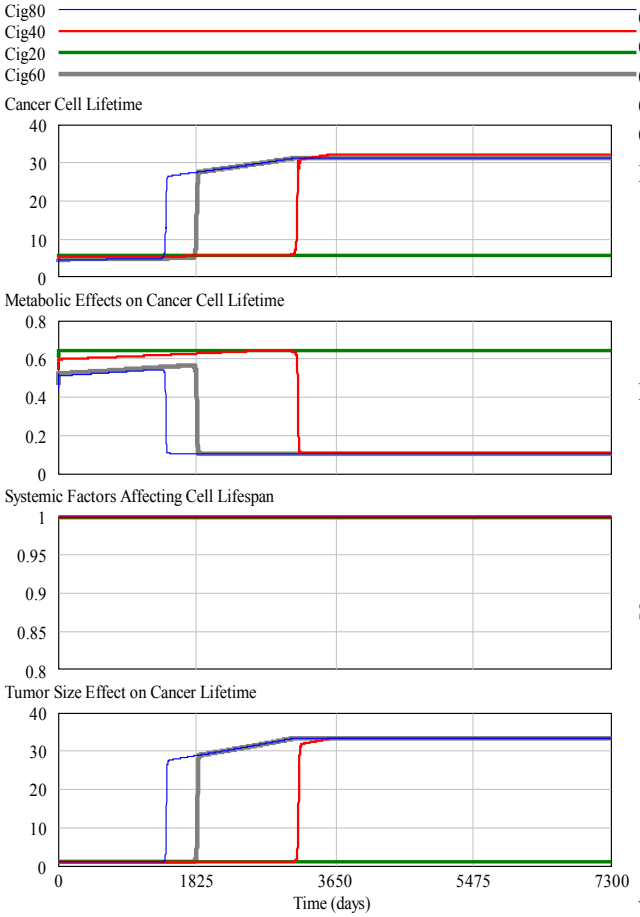


Figure 21: Comparison of Cancer and Diff Cell Lifetimes at Cig40

We have recapitulated these basic relationships found in small-cell lung cancer and validated the correspondence between smoking and carcinogenesis in our model. We've developed the structural relationships between population parameters, metabolic, and angiogenic processes. We've rebuilt Barry Richmond's first model of cancer progression to reflect the new understanding of tumorigenesis as a probabilistic process and the new insights we have into tumor biology in terms comparative lifecycles and growth parameters. In the end, we've constructed the base framework for thinking about small cell lung cancer as a system process, which with some evidence gathering and pathological work on the population growth structure of these tumors, should be an effective tool for studying the the disease.

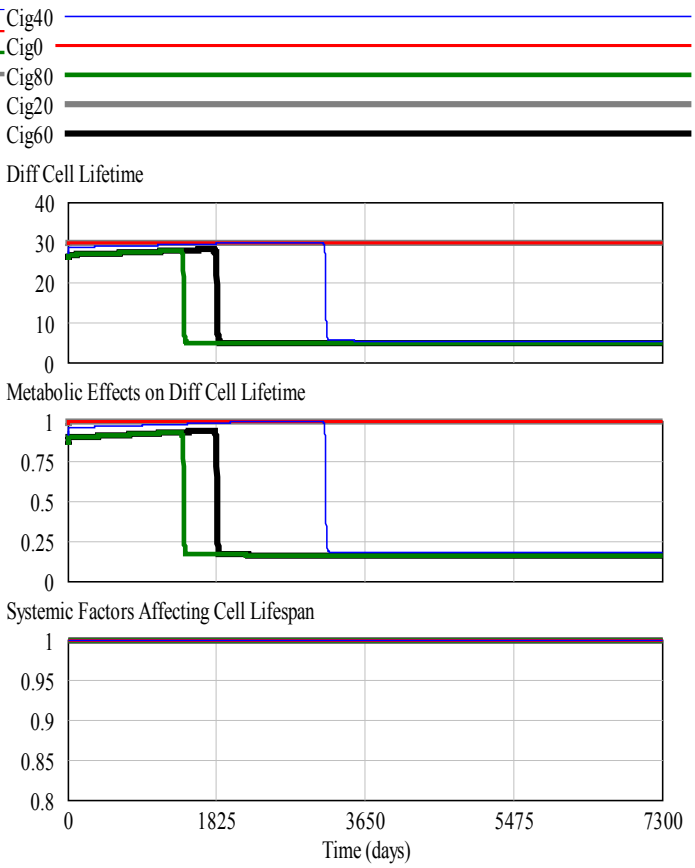
Supplementary Graphs



Basal Cancer Cell Lifetime

Cig80: 9	Cig40: 9
Cig20: 9	Cig60: 9

Figure 22: Cause Trace of Cancer Cell Lifetime



Normal Diff Cell Lifetime

Cig40: 30	Cig0: 30
Cig80: 30	Cig20: 30
Cig60: 30	

Figure 23: Cause Trace of Diff Cell Lifetimes

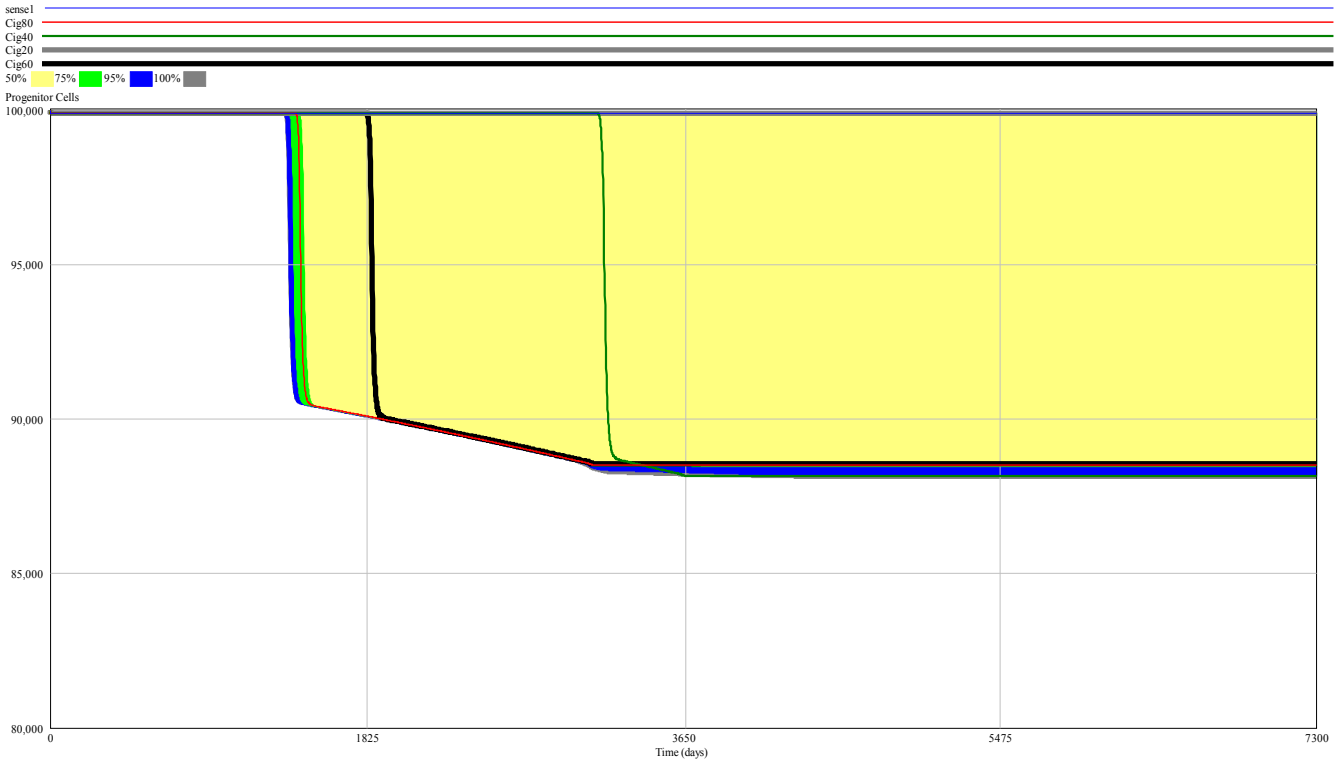


Figure 24: Progenitor Cells as Smoking varied 0-100.

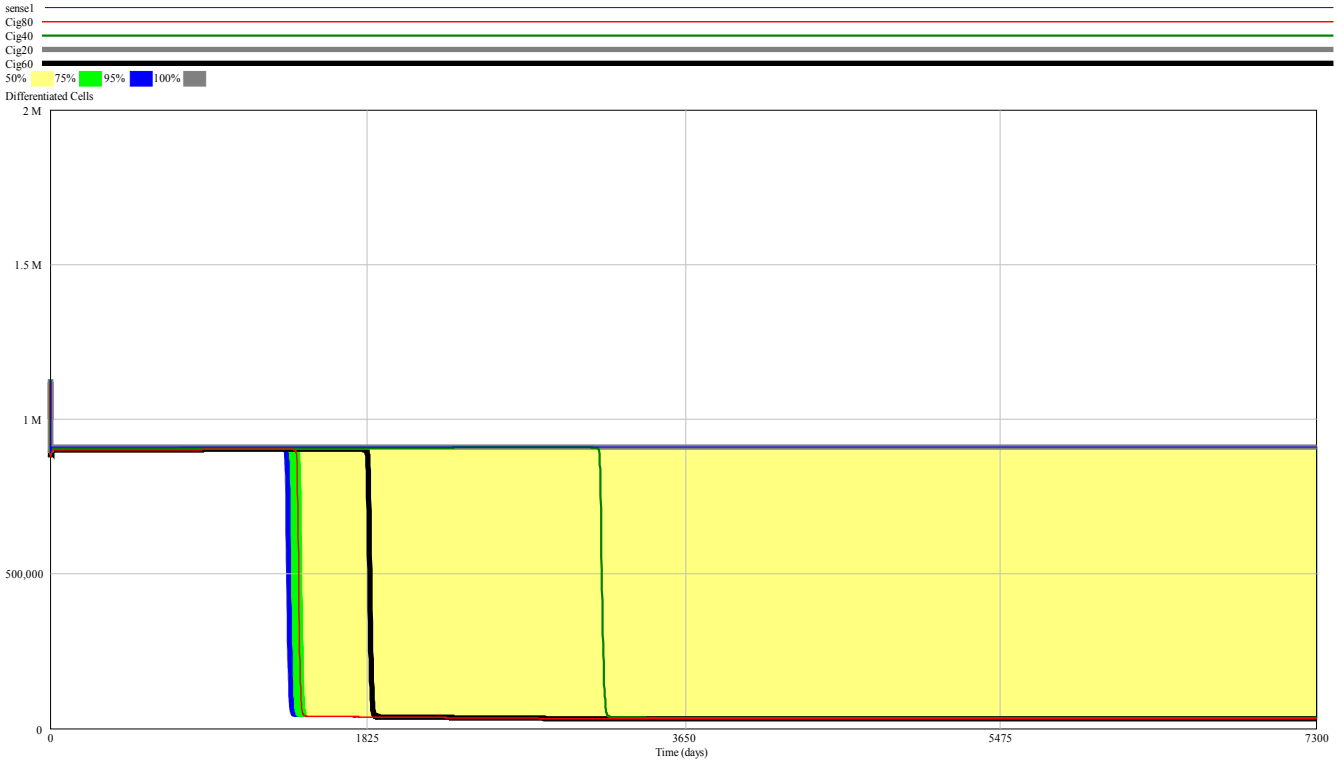


Figure 25: Differentiated Cells as Smoking varied 0-100.

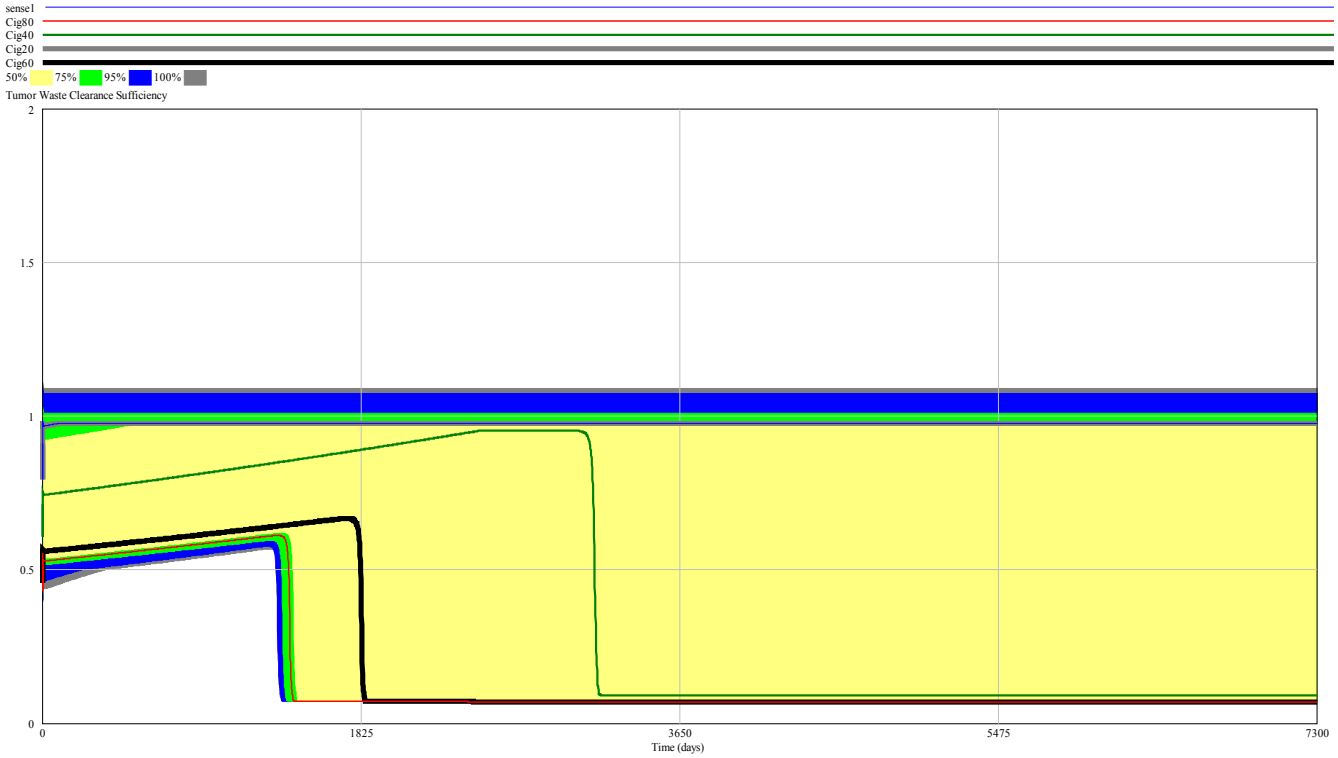


Figure 26: Tumor Waste Clearance Sufficiency as Smoking varied 0-100.

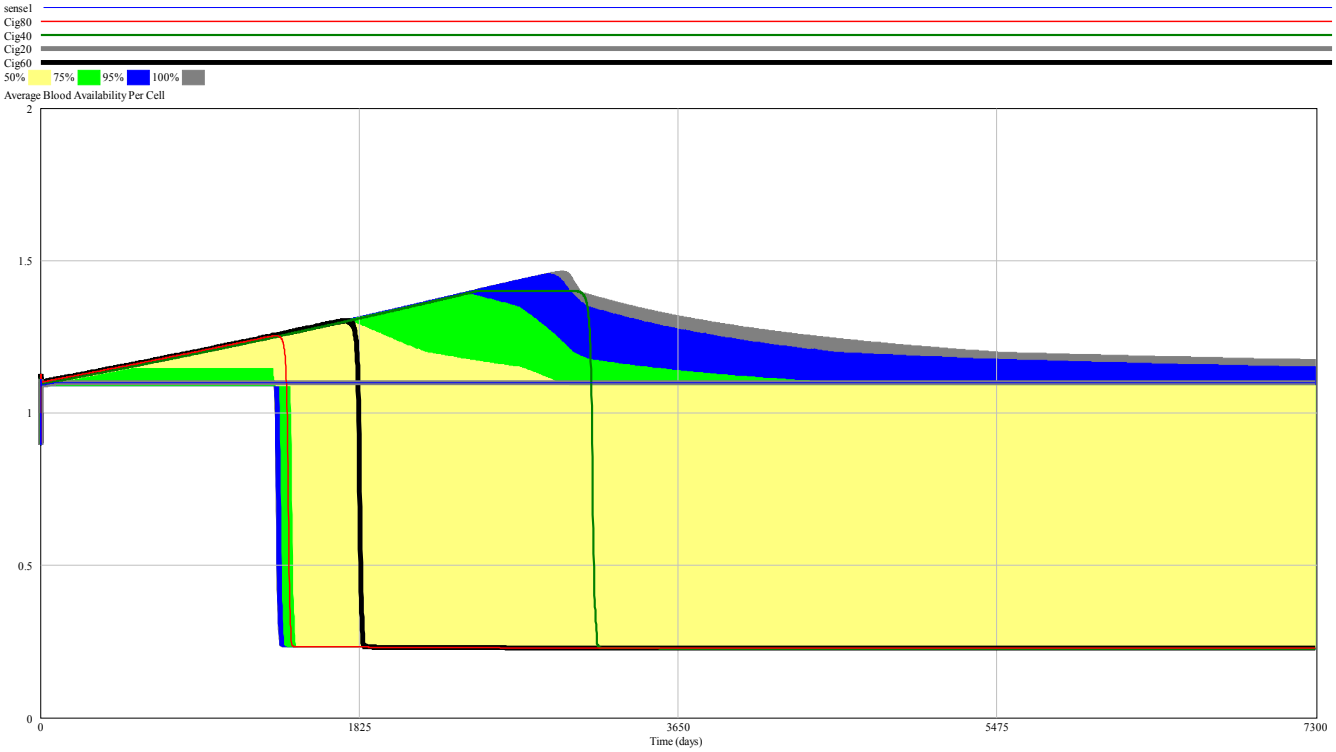


Figure 27: Average Blood Available Per Cell as Smoking varied 0-100.

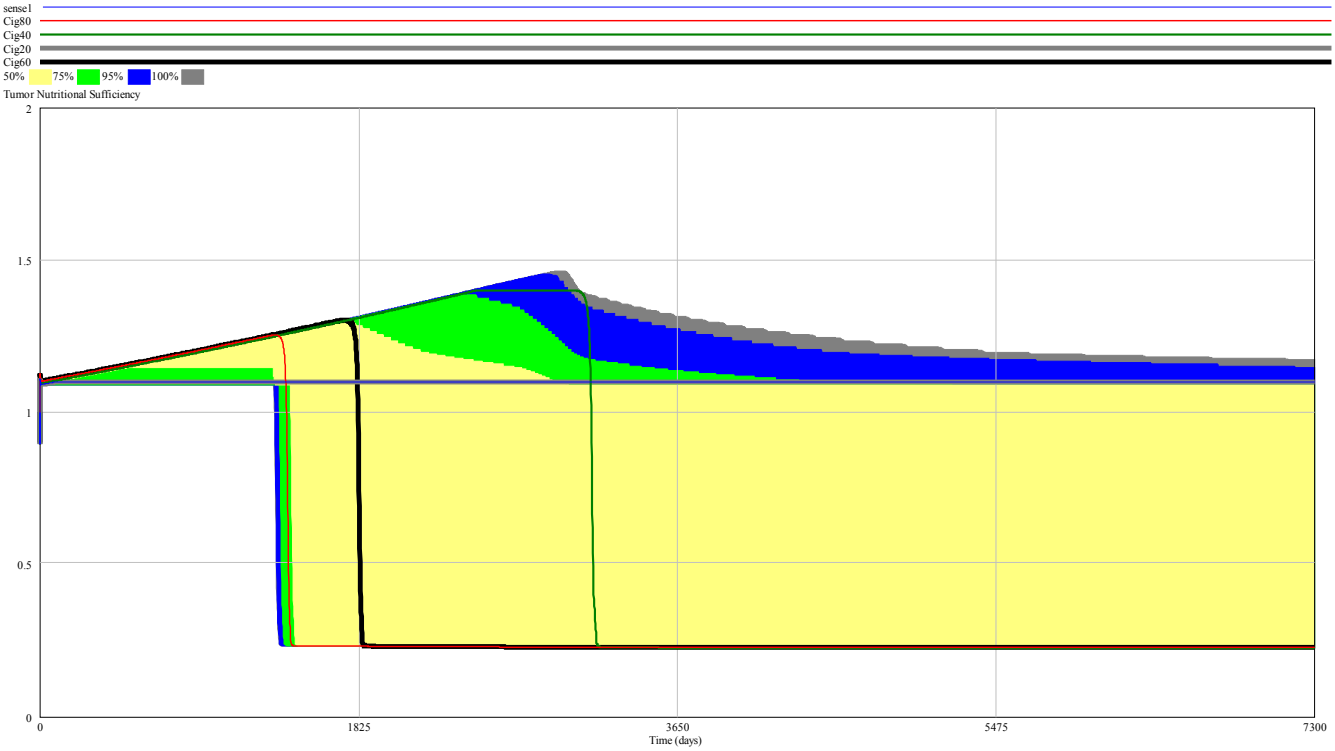


Figure 28: Tumor Nutritional Sufficiency as Smoking varied 0-100.

References

Abbott R. “CancerSim: A Computer-Based Simulation of Hanahan and Weinberg's Hallmarks of Cancer. April 2002. Master Thesis in Computer Science. University of New Mexico.

Abbott R, Forrest S, Pienta K. Simulating the Hallmarks of Cancer. Artificial Life. (In Press Feb 2006).

Dunsmore SE, Rannels DE. Extracellular matrix biology in the lung. Am J Physiol. 1996 Jan;270(1 Pt 1):L3-27.

Elias AD. Small cell lung cancer: state-of-the-art therapy in 1996. Chest. 1997 Oct;112(4 Suppl):251S-258S.

Fehrenbach H. Alveolar epithelial type II cell: defender of the alveolus revisited. Respir Res. 2001;2(1):33-46. Epub 2001 Jan 15.

Fong KM, Sekido Y, Gazdar AF, Minna JD. Lung cancer. 9: Molecular biology of lung cancer: clinical implications. Thorax. 2003 Oct;58(10):892-900.

Granville CA, Dennis PA. An overview of lung cancer genomics and proteomics. Am J Respir Cell Mol Biol. 2005 Mar;32(3):169-76.

Griffiths MJ, Bonnet D, Janes SM. Stem cells of the alveolar epithelium. Lancet. 2005 Jul 16-22;366(9481):249-60.

Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 Jan 7;100(1):57-70.

Jackman DM, Johnson BE. Small-cell lung cancer. Lancet. 2005 Oct 15-21;366(9494):1385-96.

Kotton DN, Summer R, Fine A. Lung stem cells: new paradigms. Exp Hematol. 2004 Apr;32(4):340-3.

McGowan SE. Extracellular matrix and the regulation of lung development and repair. FASEB J. 1992 Aug;6(11):2895-904.

Neuringer IP, Randell SH. Stem cells and repair of lung injuries. Respir Res. 2004 Jul 20;5(1):6.

Richmond B. Toward a Structural Theory of Cancer. System Dynamics and Analysis of Change. Paulre, B.E.(ed), North-Holland Pub. Co, 1981.

Shriver SP, Bourdeau HA, Gubish CT, Tirpak DL, Davis AL, Luketich JD, Siegfried JM. Sex-specific expression of gastrin-releasing peptide receptor: relationship to smoking history and risk of lung cancer. J Natl Cancer Inst. 2000 Jan 5;92(1):24-33.

Siegfried JM, DeMichele MA, Hunt JD, Davis AG, Vohra KP, Pilewski JM. Expression of mRNA for gastrin-releasing peptide receptor by human bronchial epithelial cells. Association with prolonged tobacco exposure and responsiveness to bombesin-like peptides. Am J Respir Crit Care Med. 1997 Aug;156(2 Pt 1):358-66.

Trosko JE, Chang CC, Upham BL, Tai MH. Ignored hallmarks of carcinogenesis: stem cells and cell-cell communication. Ann N Y Acad Sci. 2004 Dec;1028:192-201. Review.

Wang D, Yeger H, Cutz E. Expression of gastrin-releasing peptide receptor gene in developing lung. Am J Respir Cell Mol Biol. 1996 May;14(5):409-16.

Warburton D, Olver BE. Coordination of genetic, epigenetic, and environmental factors in lung development, injury, and repair. Chest. 1997 Jun;111(6 Suppl):119S-122S.

Werner S, Grose R. Regulation of Wound Healing by Growth Factors and Cytokines. Physiol Rev. 2003 83: 835-870.

Wistuba II, Gazdar AF, Minna JD. Molecular genetics of small cell lung carcinoma. Semin Oncol. 2001 Apr;28(2 Suppl 4):3-13.

Zochbauer-Muller S, Gazdar AF, Minna JD. Molecular pathogenesis of lung cancer. Annu Rev Physiol. 2002;64:681-708.

Garner, A.L., Y. Y. Lau, D. W. Jordan, M. D. Uhler, R. M. Gilgenbach. Implications of a simple mathematical model to cancer cell population dynamics. Cell Proliferation 2006 39:1-15.

Kimball, John W. “Apoptosis”. Kimball's Biology Pages. October 14, 2005. http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/A/Apoptosis.html#cancer.

“How Cancer Grows”. Nova Online: Cancer Warrior. http://www.pbs.org/wgbh/nova/cancer/ February 21, 2001.