A Systems Theory of Small-Cell Lung Cancer: Phase 1

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.

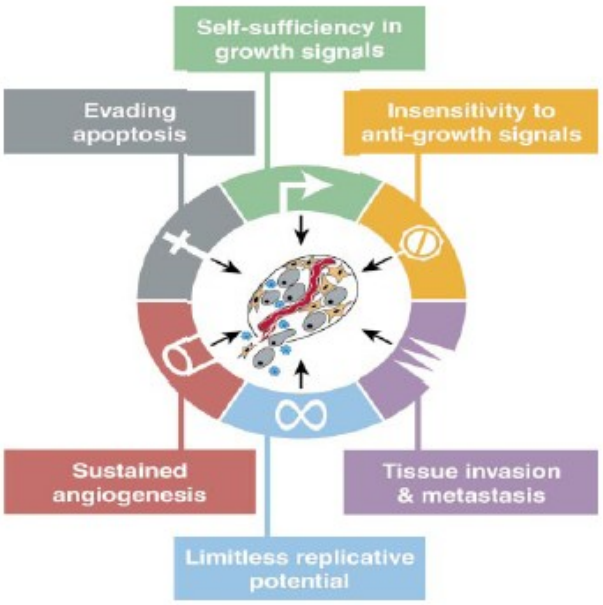


Figure 1: Commonly acquired and often necessary characteristics of cancer cells. (Hanahan et al.)

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 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.

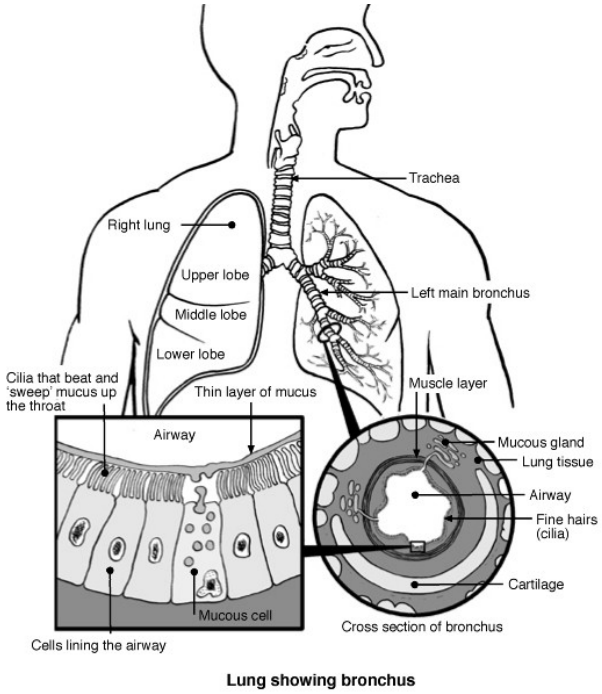


Figure 2: Schematic view of the bronchi, revealing epithelial cells where lung carcinomas arise. http://www.patient.co.uk/showdoc/21692519/

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

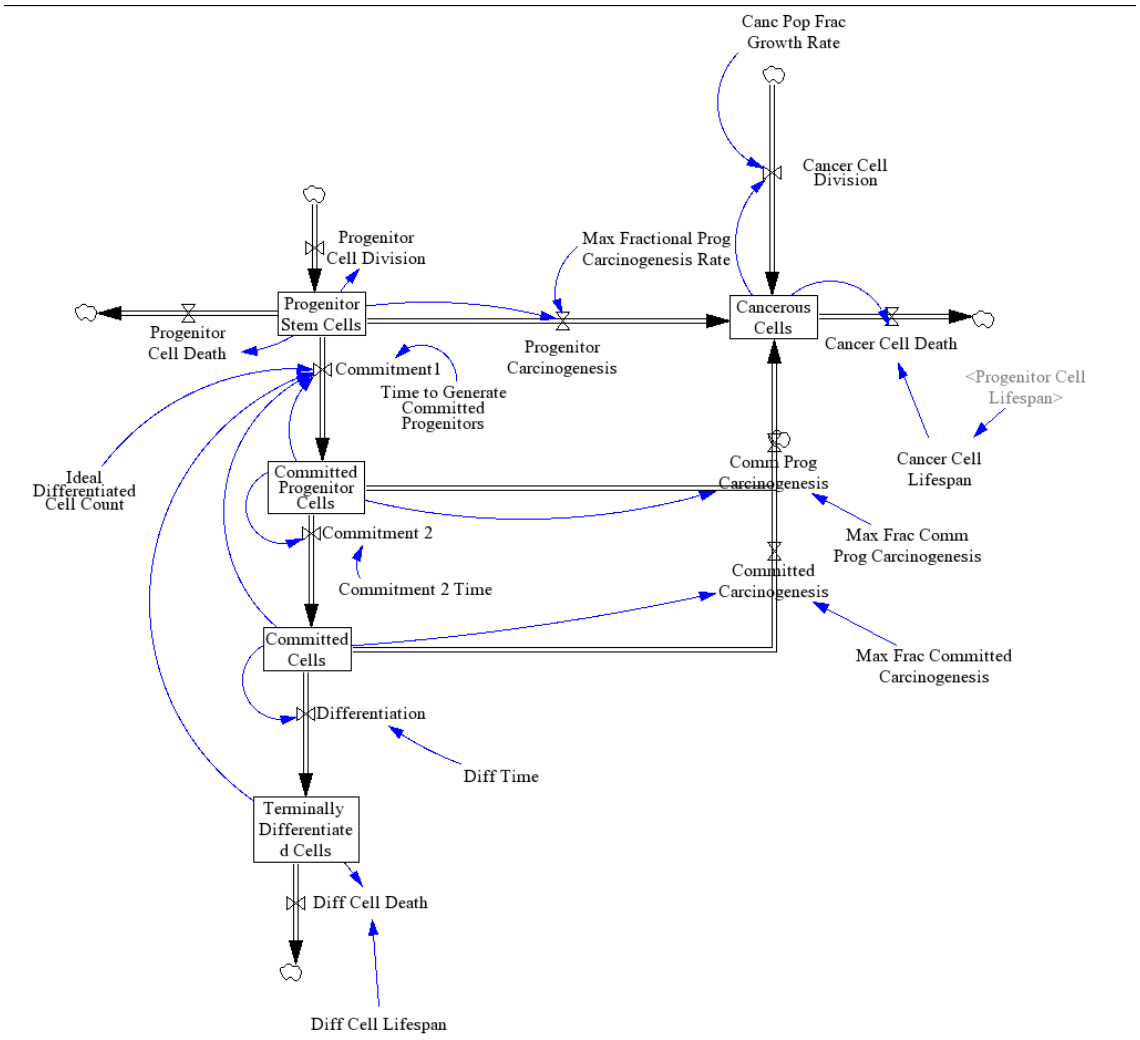


Figure 3: Tissue cell populations represented as stocks with flows into their normal and cancerous developmental fates.

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.

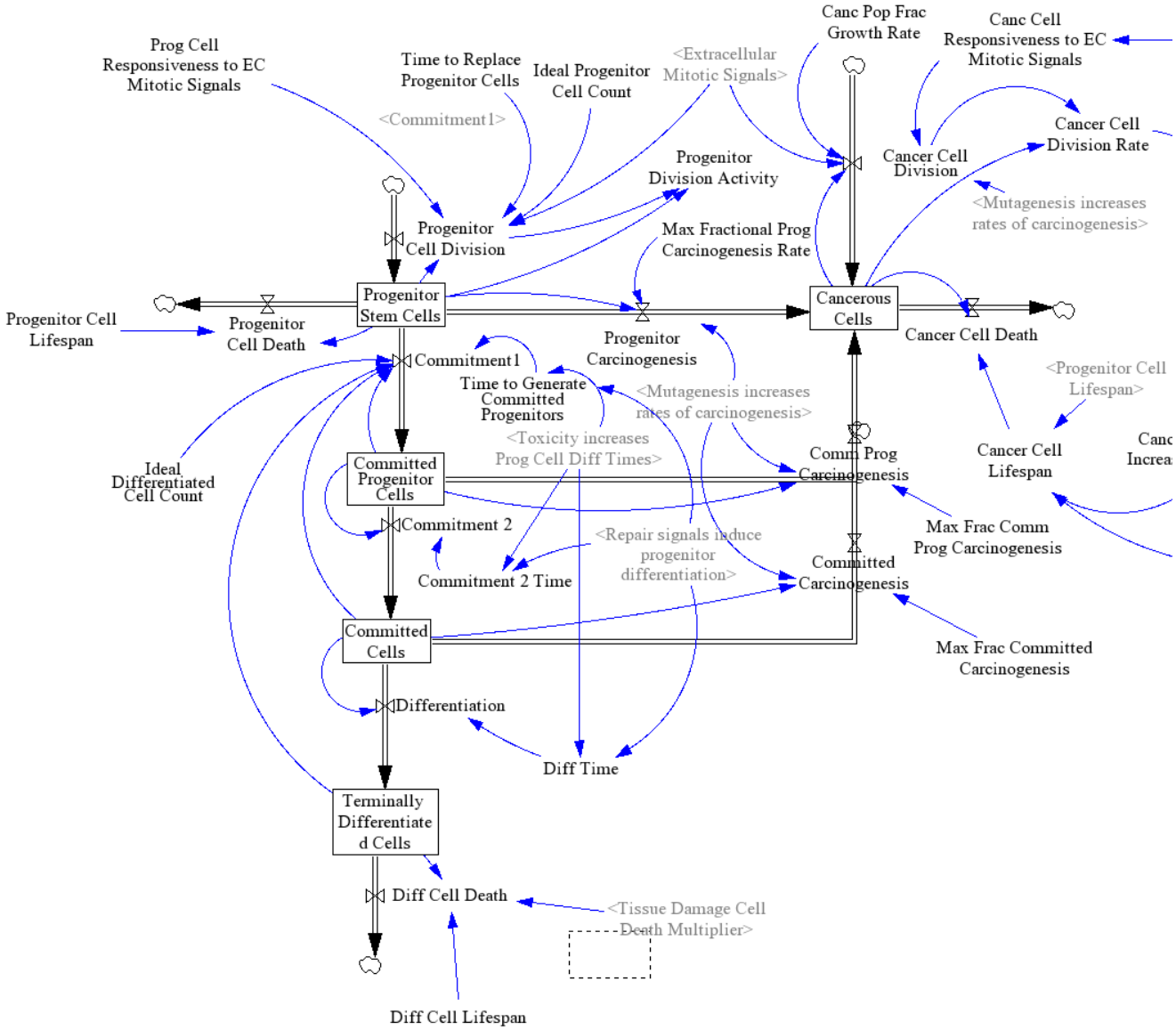


Figure 4: Responsiveness of tissue cell populations to extracellular mitotic and damage signals.

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.

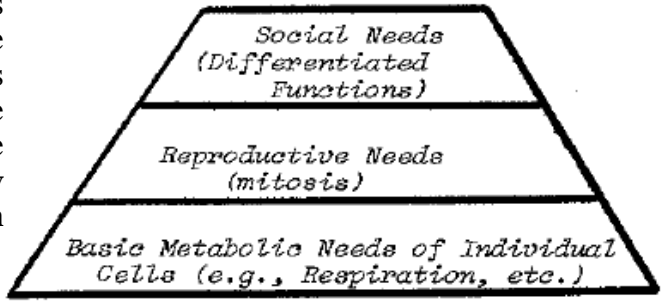


Figure 5: Richmond's hierarchy of cellular needs.

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.

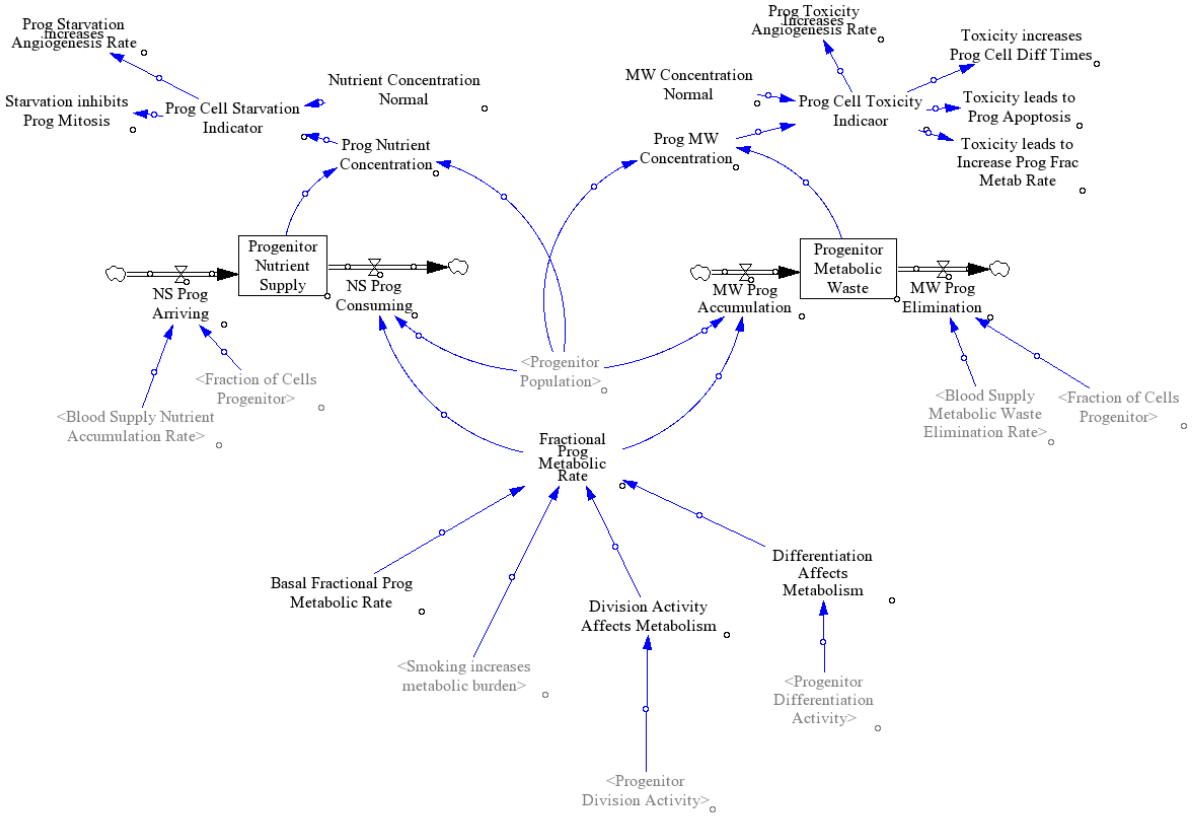


Figure 6: Structure of progenitor cell metabolism and waste elimination.

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.

Damage, Division and Repair

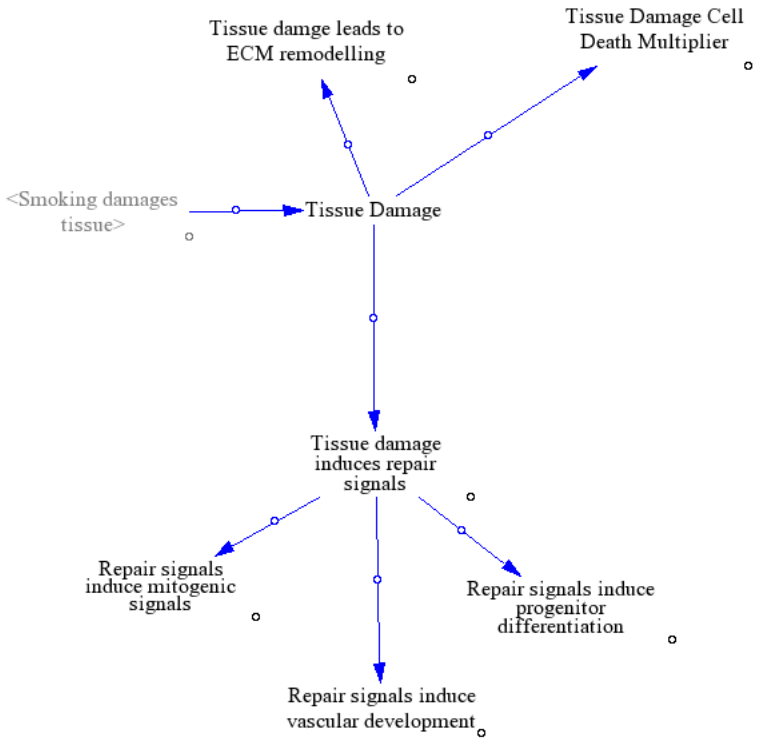


Figure 7: Causes and effects of tissue damage.

Developing a model of tissue damage and repair is vital to an understanding of lung cancer. In this model, damage to tissue results exclusively from the toxic effects of tobacco smoke. Tissue damage simultaneously triggers a cascade of differentiated cell death and repair pathway activation. The repair signals work to activate vascular development removing toxins and generating immune invasive ECM response (not yet fully modeled), and to induce mitosis and differentiation in progenitor cells so lost cells can be replaced before the organ is functionally compromised.

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.

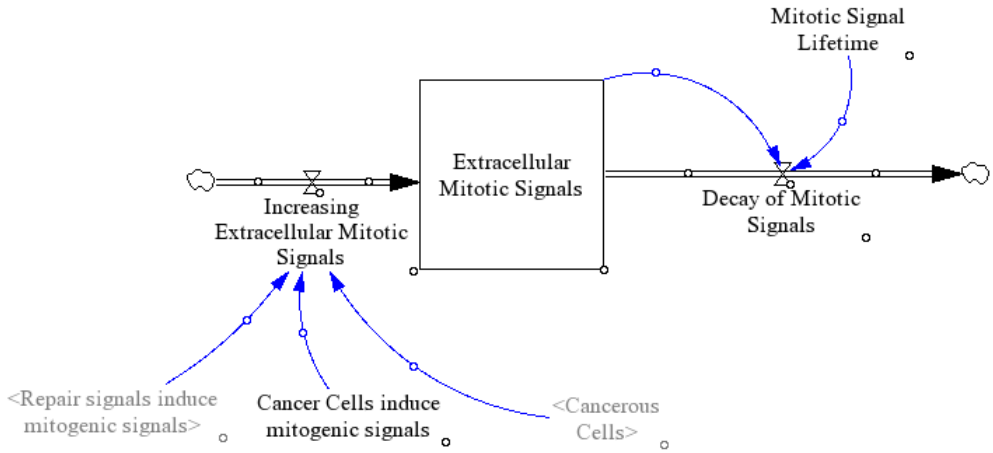


Figure 8: Mitotic signals generated in tissue repair and cancer.

Smoking

We model smoking as a recurring pulse whose magnitude depends on the effect of one cigarette and whose repeat time is based on the number of cigarretes consumed per day. We also take into account a fraction growth rate in cigarette consumption that would capture the often seen upsurge in a smoker's daily regimen over the course of a few years.

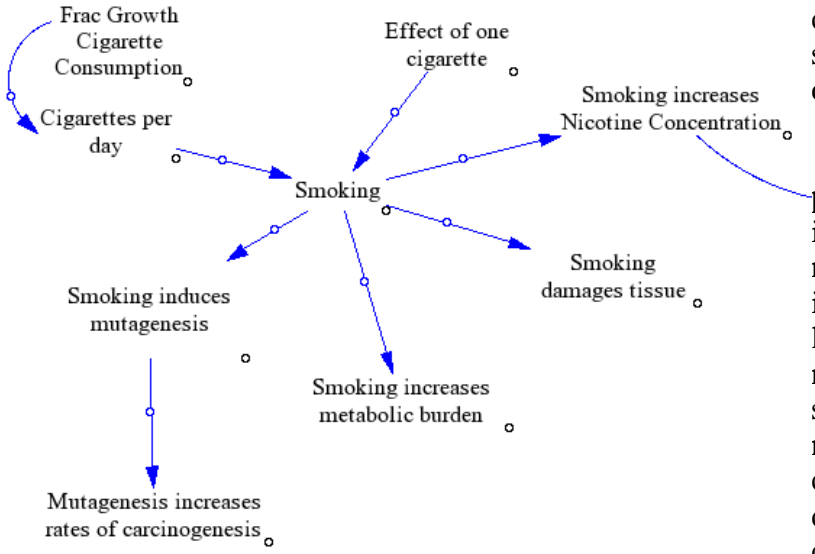


Figure 9: Cigarette smoking and its effects.

The model here posits four parallel processes with which nicotine 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 then induces GRP and neuromedin expression in surrounding cells that are developmentally plastic enough to do so – these are usually just cancer cells. Increased GRP and neuromedin expression will in turn make the cancerous cells more responsive to mitogenic signals and accelerate the disease progression.

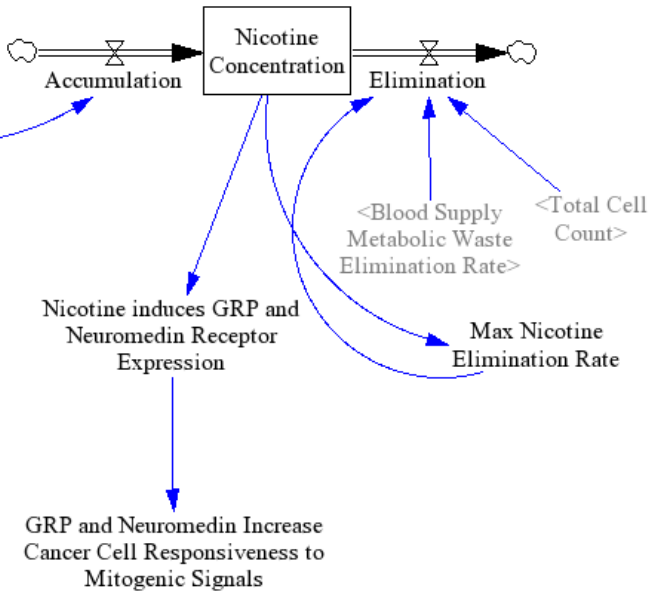


Figure 10: Autocrine stimuli from nicotine.

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.

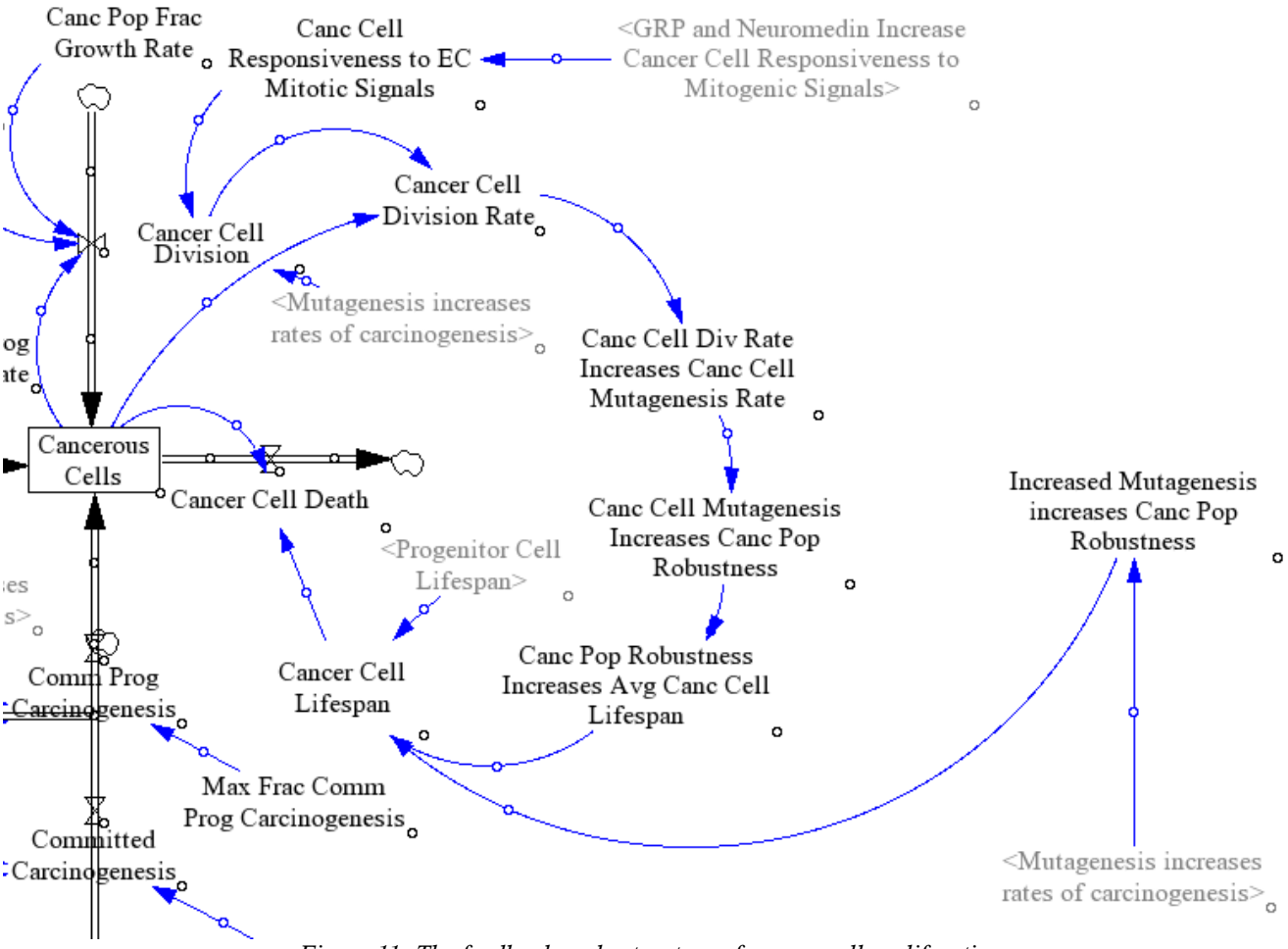
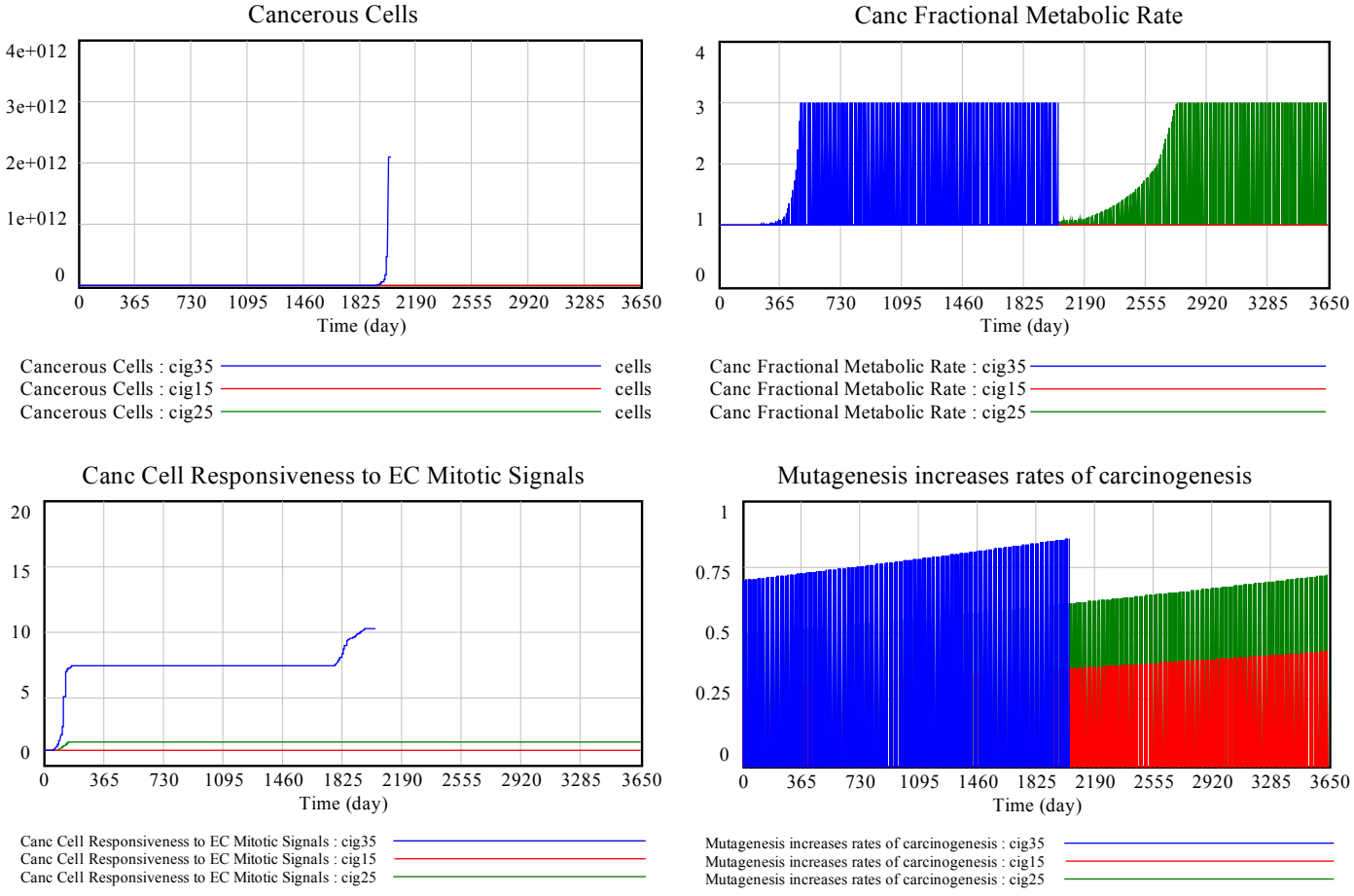


Figure 11: The feedback cycle structure of cancer cell proliferation.

Preliminary Simulation Runs

In this preliminary 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 ten 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 15, 25, and 35 per day and then examine the system and state variables. We find that the 15 and 25 per day smokers are slowly increasing their cumulative risk of developing a metastasis over the course of the 10 years and that the 35 per day smoker has already developing a terminal (at least in this microscopic segment of tissue) lung tumor.



Though we have recapitulated these basic relationships found in small-cell lung cancer and validated the correspondence between smoking and carcinogenesis in our model, much work remains before it can be used as a viable simulation tool. For one, the metabolic sectors need to be adjusted for each of the cell populations to reflect a more realistic accumulation-consumption relationship. For another, the effects of angiogenic and mitotic factors on each subtype of cells needs to be carefully considered. In addition, the wound healing processes and cytokine interactions of cancerous and normal cells need to be added to the model, and will possibly change the observed dynamics on a large scale.

The task is begun -- we have begun to build a systems theoretic view of cancer that intergrates the molecular, cellular, and physiological level insights from the past 25 years of cancer research. Using systems dynamics tools and leveraging well-known archetypes, we are formulating a structural view of current biological theory. We begin with this focus on the small-cell lung cancer problem, and hope to turn it into a useful tool for generic abstraction and systems level hypothesis generation in the study of cancer.

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