Chapter 1

Modeling Pre-invasive Bronchial Epithelial Lesions

Pathologists diagnosing lung cancer in a patient must consider the global architecture of the bronchial tissue, as well as the local architecture of cells and the appearance of individual cells. In order to obtain more detailed information on the condition of the bronchial tissue, a bronchoscopy is performed on the patient and a tissue sample of the lesions is obtained. The pathologist obtains a two-dimensional (2-D) photograph of the sample extracted from a region of the tissue containing abnormal cells.

Often an abnormal cell will die naturally without forming a cancer so the pathologists are concerned only with identifying the cells that will eventually develop into a cancer. Since cancer treatment is very aggressive and traumatic for the patient, pathologists want to be fairly certain that the abnormal cells present in the sample will lead to cancer before recommending treatment. When the sample contains large amounts of abnormal cells or none at all the diagnosis is simple; however, in many cases there are just a few abnormal cells in the sample and diagnosis is difficult.

As part of the PIMSIPS Workshop, two members of the Cancer Imaging Lab of the British Columbia Cancer Research Centre, Drs. Carole Clem and Martial Guillaud, presented a model of pre-invasive bronchial epithelial lesions. This model presupposes a large number of parameters designed to accurately reflect the biological process. The two researchers asked the following ques-
Suppose a 2-D cross-section of tissue from the model is presented. What information can be determined about the original lesion? In particular, is it possible to predict the structure of the three-dimensional (3-D) lesion accurately enough to determine whether the lesion will progress towards cancer? (Figure 1).

The lung tissue can be seen as divided into three layers: the basal layer, where stem cells divide; an intermediate layer, which thickens as more abnormal cells are present; and the epithelial layer, which is the top layer where cells flatten and die. The tissue is about 10 cells thick. In a normal tissue, a stem cell divides and gives birth to two identical cells. One of the new daughter cells stays in the basal layer and will become a new stem cell, while the other daughter cell differentiates and will slowly move toward the epithelial layer where it will die. A clone is the set of cells that are descendants of the same stem cell. On occasion, abnormalities may occur in a cell. Most of the times, the body has mechanisms that will simply stop the life cycle of such a cell; however, there are a few cases in which the abnormal cell does not die and the cell and its clone multiply out of control.

Flexible fiber-optic bronchoscopy is an important diagnostic technique used for lung cancer. The flexible fiber-optic bronchoscope consists of fiber-optic light bundles for light transmission and auxiliary channels for passing instruments. The flexible video-chip bronchoscope has a small number of glass fibers to deliver the light distally, but the image is recorded directly by a video-chip at the distal end of the bronchoscope [22]. Until recently, the only diagnostic tool available to localize pre-malignant cellular alterations and early bronchial cancer was conventional white light fiber-optic bronchoscopy (FOB). Because only the relatively thick or polyploid lesions are visualized by FOB, only 29% of these lesions were visible to an experienced endoscopist [21], [18]. In an effort to overcome these problems, the Cancer Imaging Laboratory at the British Columbia Cancer Agency (BCCA), Vancouver, has developed the Lung Imaging Fluorescence Endoscopic Device (LIFE) which utilizes differences in tissue autofluorescence to detect precancerous and CIS lesions at a much higher rate.

**Figure 1:** Example of 3-D lesion and 2-D cross-section from the model.
CHAPTER 1. BRONCHIAL EPITHELIAL LESIONS

than FOB [15], [16].

The instrument is introduced in the patient’s lung orally. To obtain a epithelium biopsy, a 1 cm needle attached to a catheter is placed through the mucosa using the bronchoscope. Using suction, cells are collected for cytologic evaluation. The sample will contain a vertical cross-section of the lung tissue including cells from the three layers. From this sample, 2-D biopsies of the lesion are obtained from which the pathologists must predict whether the lesion will evolve into a malignant tumor or if it will at least not evolve towards cancer.

Recently, new technology has allowed the ready detection of pre-invasive neoplastic bronchial lesions, which are believed to be the possible precursors of malignant tumors. The natural history of lung cancer development from the initial genetic event through other multiple genetic changes, cell-cell, cell kinetics, and cell-host interaction is not completely understood. New techniques (microdissection and PCR amplification) and tools (quantitative cytology and quantitative histology) are elucidating this neoplastic development process. These techniques are generally dealing with snapshots (biopsies, bronchial fragments) of a continuously evolving (changing) epithelium. Current understanding suggest that as pre-invasive neoplastic epithelial tissue becomes more likely to develop into an invasive neoplasia, the amount of genetic changes and genetic heterogeneity in the tissue also increases. While it is still impossible to measure the complete genetic makeup of individual cells in a biopsy or tissue section, it is possible to measure a few selected genetic changes. However, it is still impossible to determine the genetic relationship of all the cells in a pre-invasive neoplastic lesion during the development into invasive cancer. Unfortunately, this is what would be required to completely understand the evolution of normal epithelium into invasive neoplasia. The only feasible alternative is to develop models, which try to simulate the initial stages of the neoplastic process and most importantly to try to simulate the development pathway from normal tissue to abnormal lesion. The simulated development of an abnormal lesion (clonal or multiclonal) requires a model, which takes into account not only the individual cell, but also the whole architecture of the tissue.

2 Model Characteristics

A graphical computer model of the 3-D architecture of bronchial epithelial lesions was developed by Dr. Clem in order to refine hypotheses concerning the progressive spatial disorganization of the bronchial epithelium during the pre-invasive neoplastic process.

There are two main parts in this model. First, there is a static model which simulates the physical arrangement of cells in normal and pre-invasive neoplastic tissue of the bronchial epithelium, and, secondly, a dynamic part which allows the simulation of the continuously interacting nature of living tissue using the 3-D representation obtained from the static model as a starting point.

In the static part, the positions, sizes, shapes and orientations of the nuclei are used as a basis for the 3-D modeling of the architecture. The representation also takes into account the spatial arrangement of the nuclei, with several cell layers modeled. The nuclei are modeled by tri-axial spheroids. The sizes of the major and minor axes of each nucleus are deduced from cytomorphometric analysis. A homogeneous three-dimensional Poisson point process is used to simulate the candidate-positions of nuclei. This point process is layered to take into account the different intensities on the different layers (basal, intermediate and superficial). In addition, the model generates a random angle of orientation of each nuclear axis. Each newly generated nucleus is inscribed in a suitable rectangular parallelepiped with faces parallel to the planes defined by the spheroid axes. If this parallelepiped has an intersection with a parallelepiped of any earlier generated nucleus, the newly generated candidate-position with its nucleus is deleted.

In order to determine whether the model's behaviour has an acceptable range of accuracy for its intended purpose, the system computes the values of 2-D parameters from several computer "sec-
tions" through the simulated 3-D image. An iterative process is used, based on statistical comparison between the 2-D parameters computed and those used from real (2-D) histological sections. If the t-test showed a statistically significant difference between the obtained values and the expected ones, the corresponding values are modified and the process is repeated until no statistically significant differences are found.

The dynamic part of the model can be seen as a tissue growth process applied to the 3-D representations obtained from the static model. Before applying this growth process, an initialization procedure is used in order to define the different cell types that can be found in the tissue (stem or differentiated cells). The simulated tissue can be considered as a closed volume where no cell, even if it is submitted to a force which pushes it out of the box, can go out except by passing into the lumen. Each cell is defined by some internal states which include its capacity of division, its position in the tissue, its age, its displacement capacity, its lifetime and its cell type. Under normal conditions, only the stem cells are able to divide and only the differentiated cells can migrate from basal layer to lumen. At each time step, several events may occur: a stem cell can divide and a new cell can appear; the volume of a stem cell can increase; a differentiated cell can move towards the lumen; a collision between two cells can occur; a cell can die; a nucleus can enter into pyknosis. All these events induce local and global modifications of the tissue architecture and require the model to check the structural stability of the tissue at each time step. Furthermore, all these processes, in order to occur, require an analysis of the local environment of the cell which is involved in one of these events.

The analysis of the local environment of a cell requires the detection of any small changes on the position of a cell and its neighbours. The Gabriel Graph is one of the most commonly used distance mathematical methods for cluster detection. It is sensitive enough to noisy conditions while giving most information necessary for the analysis of the local environment. Simulations of different diffusion patterns of abnormal cells within the bronchial epithelium during the pre-invasive neoplastic process have been obtained as well [4], [5], [6], [7].

3 Assumptions

As with any tractable mathematical model, there were a number of assumptions made about the biopsy procedure and cell behaviour:

1. The cross-section consists of a vertical plane of the lung tissue. That is, the cross-section goes from the basal layer to the epithelial layer.
2. Any given lesion starts with only one abnormal cell, since the probability of an abnormal cell forming from a normal cell is extremely small.
3. The cross-section is taken in the lesion detected by bronchoscopy and will therefore (with high probability) be near the site where the lesion began.
4. Normal cells are formed at the basal layer through cell division of stem cells. They then have a tendency to "drift" towards the epithelial layer. As a simplification to the problem, we will assume that the stem cells will always remain static at the basal layer and the new cells will be the ones moving upwards. This assumption is valid since mother and daughter cells are identical.
5. When a cell reaches the epithelial layer it dies.
4 The General Approach

Clearly there are a large number of parameters to consider in solving this problem. In particular, any mathematical system must form a simpler model that accurately describes Clem's model. To this end, we decided to begin by modeling a 2-D process (that is, we effectively assumed lesions are formed in a 2-D lung). We then studied the difficulty of taking a 1-dimensional cross-section and determining the structure of the 2-D process. In this report we assume that cells divide with a fixed probability and that cells cannot move once they are formed (that is, there is no lateral or upward movement).

2 The 2-Dimensional Model

We will be working with the integer lattice with all points having non-negative coordinates. There will be an initial abnormal cell at position (0, 0). Given an abnormal cell at position \((i, j)\), an abnormal cell will occur at position \((i + 1, j)\) with fixed probability \(p (0 < p < 1)\) and independently at position \((i, j + 1)\) with the same fixed probability \(p (0 < p < 1)\). Since the total height of a cross-section in the 3-D case is at most ten, we will only allow cells to occupy lattice positions \((i, j)\) such that \(0 \leq i + j < 20, 0 \leq i, j < 10\). That is, we restrict to a height of 10 along the diagonal (i.e. the points \((0, 0), (1, 1) \ldots (9, 9)\)).

A configuration for \(p = 0.6\) is illustrated in Figure 2. Notice that since there are only a finite number of configurations of abnormal cells, it would be possible to enumerate all configurations and assign each a probability (as a function of \(p\)). A cross-section of a configuration (the only information we assume is available) will be the line of slope 1 passing through the point \((0, 0)\). As a practitioner, the reproduction rate of abnormal cells, \(p\), will be of interest. Therefore, one problem that we wish to address here is the following:

*Given a cross-section of a configuration generated using some probability \(p\), find an interval \([p_L, p_U]\) such that 90% of the time, in repeated experiments, similar intervals will contain the true value \(p\); that is, find an approximate 90% confidence interval for the parameter \(p\).*

Notice that we can view a cross-section as a sequence of 0's and 1's of length 10 where the first element is always 1 and represents the abnormal cell at \((0, 0)\). The sequence for the cross-section in Figure 2 would be 1101000000 since there are abnormal cells at positions \((0, 0), (1, 1)\) and \((3, 3)\).
Mathematically, a cross section can be denoted by \((X_0, X_1, \ldots, X_9)\) where \(X_i = 0\) if a normal cell is in position \(i\) on the cross section and \(X_i = 1\) if an abnormal cell is in position \(i\).

1 Experimental results

The model described above was developed and run through computer simulations for various values of \(p\). It is hypothesized (and verified through experimental results) that at \(p = .64\) [13] there is a threshold effect – any smaller \(p\) results in mainly small configurations whereas any larger \(p\) results in most configurations having some cells that reach the last level. Our analysis, described in the following paragraphs, confirms this conjecture.

Using Monte Carlo simulation methods, generating 1000 2-D lattices for each value of \(p\) between .1 and .9, incrementing by .1, we were able to determine the (approximate) probability of an abnormal cell being at a particular lattice point in the cross-section, for all points in the diagonal slice under consideration; that is, we were able to find the marginal distributions of the random variables \(X_i, i = 0, 1, \ldots, 9\). The joint distribution of these indicator random variables would require many more simulations, as there are \(2^{10}\) sample points to consider in the joint distribution. Therefore, a suitable test statistic should be sought in order to make inferences about the parameter \(p\).

Our strategy for estimating \(p\) was to choose as a test statistic the last grid point along the cross-section that was occupied (i.e. the position of the right-most 1 in a cross-sectional sequence, or \(\max (i : X_i = 1)\)). The rationale for choosing this value as a test statistic was that it was evident from running simulations and also intuitively that the last grid point was very sensitive to the true value of \(p\). Therefore, given this information, estimation of the parameter \(p\) may be relatively precise. Furthermore, this is a single (univariate) random variable, which can be studied thoroughly using simulation. The choice of a test statistic at this point is highly intuitive, and verification that the test statistic is “good” (that is, a function of a complete and sufficient statistic, unbiased, optimal in terms of variance) has not been formally investigated.

Again using Monte Carlo simulation based on 1000 trials, for values of \(p\) between .1 and .9, incrementing by .1, we obtained frequency histograms of the test statistic (comprising the last grid point along the cross-section) (Figure 3). Table 1 shows the results obtained after running the simulation 1000 times.

<table>
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<tr>
<th>(p)</th>
<th>lvl 0</th>
<th>lvl 1</th>
<th>lvl 2</th>
<th>lvl 3</th>
<th>lvl 4</th>
<th>lvl 5</th>
<th>lvl 6</th>
<th>lvl 7</th>
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<th>lvl 9</th>
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</tr>
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<td>100</td>
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<td>41</td>
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<td>8</td>
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<td>1</td>
<td>2</td>
<td>9</td>
<td>970</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Table of frequencies of the test statistic (last grid point along the cross-section) after 1000 simulations.

Using these results, we attempted to estimate the value of \(p\) used in the sample cross section (Figure 2). A natural method to use with this amount of information is the method of maximum
likelihood. From the list of frequencies, we found the (approximate) maximum likelihood estimate of \( p \) to be 0.6 (that is, the probability function of the test statistic is maximized at \( p = 0.6 \)). This "perfect" estimate is, of course, in light of the fact the we have no histograms for any other values of \( p \) between 0.5 and 0.7. We also found an approximate 90% confidence interval for \( p \) using these histograms: \([0.4, 0.8]\). Again, the interval would be slightly different (more precise) if simulations for more values of \( p \) were performed.

2 Extensions

There are a number of extensions to this model that warrant further investigation. First, we hope to calculate, for a probability \( p \), the probability of a particular configuration occurring, explicitly. Using this information, the joint distribution of \((X_0, X_1, \ldots, X_9)\) can be obtained, and the entire sample cross-section may be used to estimate \( p \) (we would in this case maximize the joint probability function of \((X_0, X_1, \ldots, X_9)\)). This may also allow us to arrive, either explicitly or numerically, at the exact probability distribution of the proposed test statistic (last grid point along the cross-section), and therefore exact estimates and confidence intervals for given confidence levels. The rigorous investigation of the proposed test statistic mentioned earlier would also be possible.

If the above explicit solutions are unfeasible to establish, a next step would be to investigate the distribution of the proposed test statistic for a much finer partition of the interval \((0, 1)\) and to establish much more precise estimates. Next, we will investigate models in which cells are allowed
to move (first vertically and then laterally).

3 Modelling Lesions as Contact Processes

The model proposed above could be seen as a discrete time Markov chain. Hence, we could modify this to be defined over continuous time. Markov chains in continuous time are defined by giving the rates

\[ q(x, y) = p(x, y)Q \]

at which jumps occur from state \( x \) to state \( y \), where \( Q \) is a constant representing the total jump rate and \( p(x, y) \) the transition probability at each point of a Poisson process with rate \( Q \).

The finite dimensional distributions of the process at \( state_{[x]} \) at time \( t \) is described by the probabilities \( P(state_{[x]} = i_1, ... state_{[x]} = i_n) \), for each choice of a finite number of sites \( x_1, ..., x_n \) and of possible states \( i_1, ..., i_n \). The total configuration at time \( t \) is described by giving the state of each site \( x \). An initial distribution for the process which does not change in time is called a stationary distribution [17].

If there is a stationary distribution which concentrates on configurations that have infinitely many sites in each possible state then we say that coexistence occurs. In most cases in which coexistence occurs there will be a translation invariant stationary distribution where \( P(state_{[x]} = i) \) is a constant \( u[i] > 0 \) that we will call the density of type \( i \) [17]. Clustering occurs if for each \( x \) and \( y \) the probability of seeing one type of particle at \( x \) and a different type of particle at \( y \) converges to 0 as \( t \) tends to infinity [17].

The contact process model was first introduced by Harris in 1974. In this model, each site in the square lattice is either occupied (in state 1) or vacant (in state 0) and follows the conditions:

(i) An occupied site becomes vacant at a rate \( \delta \); and

(ii) a vacant site becomes occupied at a rate equal to the fraction of the four nearest neighbours that are occupied. [14].

Much research has been done on these types of models [[17], [8],[9], [10],[1]], but perhaps the most important result on contact process is the Complete Convergence Theorem:

When the contact process does not die out then it will converge to the stationary distribution that is the limit starting from all 1’s [11].

An immediate consequence of this is that the only stationary distributions for the process are:

(i) the limit starting from all 1’s,

(ii) the trivial stationary distribution which assigns probability one to the all 0’s configuration, and

(iii) \( p \) times (i) plus \( (1 - p) \) times (ii) [11].

An interesting modification to this model was presented by Durrett and Levin in 1994 when they proposed that the behaviour of stochastic spatial models could be determined from the properties of the mean field ODE [12].

Going back to our model, we will rephrase it in terms of a modification to the contact process model. We will define our diamond lattice (square lattice rotated 45 degrees) to be at most 10 cells in the diagonal since that is a characteristic of the lung tissue. Each site in the diamond lattice is either occupied by an abnormal cell (in state 1) or vacant (in state 0) and follows the conditions:

(i) a vacant site becomes occupied at a rate equal to \( \lambda \) times the fraction of the four nearest neighbours that are occupied, and
(ii) an occupied site becomes vacant at a rate equal to \( \delta \) times the fraction of the four nearest neighbours that are vacant, where \( \delta \leq \lambda < 1 \) is the rate at which abnormal cells split and \( 0 \leq \delta < 1 \) is the small probability of an abnormal cell being displaced from the site by a healthy cell. The reason for these constraints is that we are interested in the problem where both normal and abnormal cells coexist (at least in the early stages). It is easy to see that if \( \delta \geq 1 \) the process would die out, i.e., there would be total recovery; and if \( \lambda \geq 1 \) then the abnormal cells would take over the entire tissue.

In practice, the vacant sites are not actually vacant but occupied by healthy cells that can be displaced by abnormal ones. However, since we are currently only concerned about the growth of abnormal cells, considering the healthy sites vacant simplifies the problem considerably. Condition (ii) is necessary since there is a very small probability that a healthy cell may displace an abnormal cell. When this occurs, since we are not allowing cells to drift in any direction on the plane, the new cell will be pushed out of the 2-D plane. Hence, for this simple 2-D model, this situation is resolved by setting \( \delta = 0 \); i.e., once a site is occupied by an abnormal cell, it will never become vacant. However, the condition \( \delta > 0 \) must be considered when introducing drift and when building the 3-D model.

Let \( S_0 = \{ \text{finite subsets of } \mathbb{Z}^2 \} \). If \( A \in S_0 \) is the original set of abnormal cells, then let \( \xi^A_t \) be the set of sites occupied by abnormal cells at time \( t \). We can rewrite the above as Markov processes \( (\xi^A_t)_{t \geq 0} \) and their jump rates are given by

\[
\begin{align*}
A &\to A \cup \{x\} (x \notin A) \text{ at rate } \lambda |\{y \in A : ||y - x|| = 1\}|, \\
A &\to A \setminus \{x\} (x \in A) \text{ at rate } \delta |\{y \in A : ||y - x|| = 1\}|,
\end{align*}
\]

where \( ||x|| \) is the distance from \( x \) to \( 0 \); i.e., the rate at which a site becomes occupied by an abnormal cell is dependent on the cardinality of the set of sites occupied by abnormal cells adjacent to the current site.

Note that if \( \delta = 0 \) and \( \lambda = 1 \), then our model is a finite version of Richardson's growth model presented in [19]. There Richardson showed that if \( B(t) \) is the set of sites occupied at time \( t \), then \( B(t)/t \) clusters to a limiting shape, which is roughly but not exactly circular. Since we assumed that the process started with a single abnormal cell at the origin, then we are only interested in the process \( \xi^\emptyset_t \).

Hence, we can represent our model using a partial differential equation to describe the stochastic process. We will consider the following equation:

\[
\frac{\partial n}{\partial t} = \sigma \Delta n + \lambda n + \mu_y \frac{\partial n}{\partial y}
\]

where \( n \) represents the number of abnormal cells in the region of interest. We quickly summarize the various parts of the equation.

The term:

\[
\frac{\partial n}{\partial t} = \sigma \Delta n
\]

represents the diffusion equation, and models the random movement of the abnormal cells in the tissue over time, where \( \sigma \) is the diffusion constant. The birth rate of the abnormal cells is controlled by the parameter \( \lambda \). Clearly this term allows the number of abnormal cells spawned at any given time to grow linearly with the current number of abnormal cells.
Since there is a natural upwards drift of the cells in the tissue, we use the term:
\[
\frac{\partial n}{\partial y}
\]
to model this phenomenon. Notice that this term depends on the distribution of the cells in the vertical direction, since we can expect more cells to drift upwards if there are more cells clustered near the basal layer of the tissue than elsewhere.

To model other aspects of the biological processes occurring in the diseased tissue, additional terms are required. For example, the term:
\[
\mu_x \frac{\partial n}{\partial x}
\]
can be added to model the lateral drift of the cells; the rate can be controlled through the parameter \( \mu_x \).

Finally, we need to apply suitable boundary conditions. For instance, we could set the Dirichlet conditions:
\[
\begin{align*}
  n(0) &= 1 \\
  n(10) &= 0
\end{align*}
\]
at the bottom and top respectively of the cell layer. This makes sense physically since in this simple model we only allow one abnormal cell at the basal layer, and assume that once cells reach the top layer they die. The boundary conditions to model the sides of the region are more complicated. A possible solution would be to use moving boundary conditions at these edges, so that as the lesion expands the boundaries would also expand.

4 Conclusions and Future Work

The growth of cancer cells involves many different processes which can only be captured by a complex model. However, simplified models provide a great deal of insight into the fundamental processes involved. In this workshop we proposed two simple models – one discrete stochastic model and one PDE model – to solve a 2-D simplification of the original problem.

It is worth mentioning that, after the PIMSIPS workshop, we came across a model of skin cancer, presented for the first time by Williams and Bjerknes, that follows a similar approach to ours. In their model, each site is either occupied (in state 1) or vacant (in state 0) following the conditions:

(i) an occupied site becomes occupied at a rate \( \delta \) times the fraction of the four nearest neighbours that are occupied, and

(ii) a vacant site becomes occupied at a rate equal to the fraction of the four nearest neighbours that are occupied.

Letting \( B(0) \) be a finite set and \( B(t) \) be the set of lattice points occupied at time \( t \), if \( B(t) \) is ever the empty set then it will remain so for all time, in which case we say the model dies out [20]. In other papers, Bramson and Griffeath showed that if \( B(t) \) does not die out, then \( B(t)/t \) has a limiting shape [2], [3]. The main difference between this model and ours is that, by the nature of the problem, skin cancer growth was modelled only as sidewise splitting on the basal layer in such a way
that the surface folded onto a torus. On the other hand, our lung cancer model is very constrained since we are modelling all three layers as cross-sections of the bronchial epithelium, which forces the model to be restricted to a finite height along the diagonal. However, the model of Williams and Bjerknes gives veracity to ours since their approach, similar to ours, is plausible and well studied.

Our next step is to add both horizontal and vertical drift to the 2-D discrete model. This will make it more natural to model as a stochastic process as well as make it closer to the experimental observations. There is also a natural extension to using a 3-D lattice for the discrete model. In the partial differential equation model we will require another independent variable to handle movement of cells in the third dimension. Hence, if $\mu_x$ and $\mu_z$ are the rates of lateral drift at which cells move along the $x$- and $z$-axis, respectively, then

$$\frac{\partial n}{\partial t} = \sigma \Delta n + \lambda n + \mu_y \frac{\partial n}{\partial y} + \mu_x \frac{\partial n}{\partial x} + \mu_z \frac{\partial n}{\partial z}$$

By combining analytic techniques with computer simulations we hope to produce a model that is useful in modelling the growth of cancer cells and predicting the existence of lung cancer at an early stage.

5 Acknowledgments

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