Modeling the Dynamics of Chromosomal Alteration Progression in Cervical Cancer: A Computational Model

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Introduction

Cervical cancer is a complex disease that is characterized by unpredictable genetic alterations of cells. Computational modeling has the potential to simulate the growth and behavior of cervical cancer within a tissue. This computational model allows for the transformation of individual cells between healthy, precursor lesion and cancerous states, with different mutation rates and reproductive rates for each state. The model provides data on the day-to-day growth of cancer within a tissue and the progression of a cell from healthy to cancerous. The results of this study suggest how cancer cells become dominant over time within a system and outgrow healthy tissue. Overall, this computational model can provide a valuable tool for understanding the behavior of cervical cancer and developing new treatment strategies.

Results

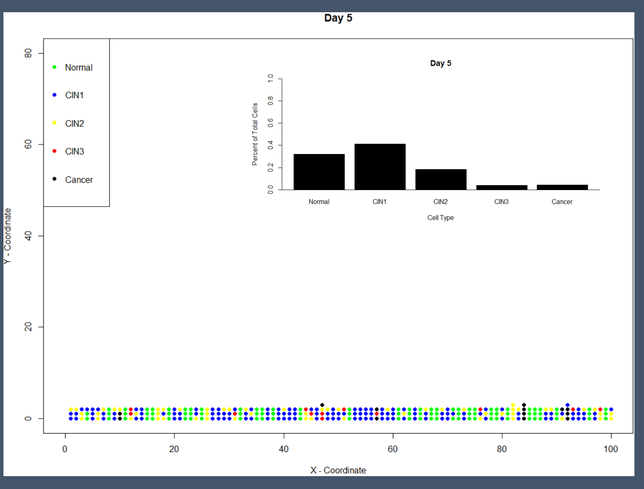

Figure One (1): This graph is taken on day 5 of a 50-day run for the model. Approximately 40% of cells are "CIN1", 30% of cells are "Normal" and about 20% of cells are "CIN2"

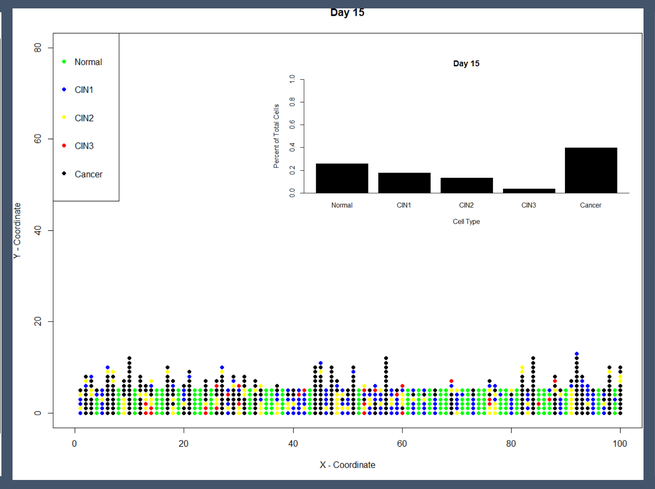

Figure Two (2): This graph is taken on day 15 of a 50-day run for the model. Approximately 40% of cells are "Cancer", 25-30% of cells are "Normal" and about 20% of cells are "CIN1"

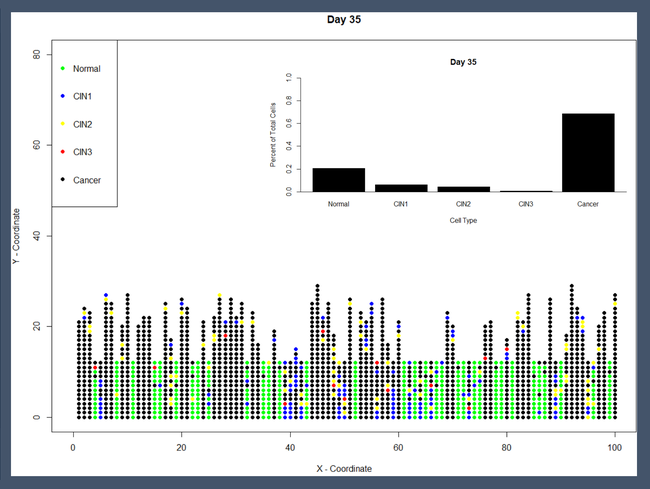

Figure Three (3): This graph is taken on day 35 of a 50 day-run for the model. Approximately 70% of cells are "Cancer", 20% of cells are "Normal"

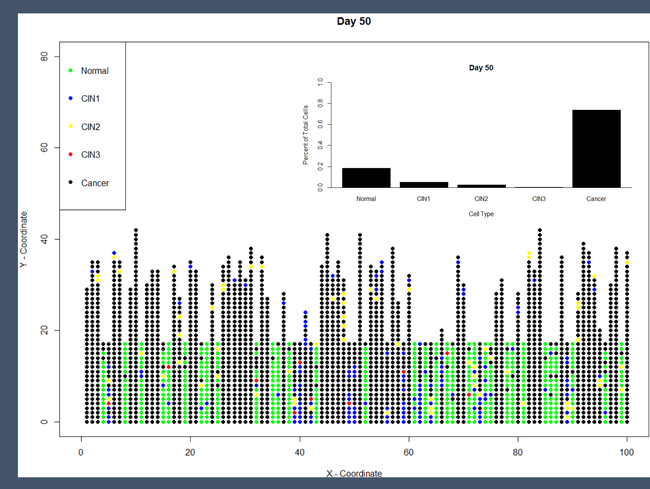

Figure Four (4): This graph is taken on day 50 of a 50 day-run for the model. Approximately 80% of cells are "Cancer", 20% of cells are "Normal"

Figure One (1) was taken on day 5 of the 50-day run. This figure shows that there is an influx of "CIN1" cells, which are precursor cells. These precursor cells have a faster reproduction rate than "Normal" cells and are also more prone to becoming cancerous. Figure Two (2) was taken on day 15 of the 50-day run. While looking at the results of Figure Two (2), we see that the influx of "CIN1" cells in Figure One (1) led to an increased prevalence of "CIN2" and "Cancer" cells. We can also observe in Figure Two (2) that there is a slight difference within the number of cells in each column. Columns that have varying heights are representative of the number of cells within those columns and tell us information about their reproduction rate. Columns that have a high percentage of lesion or cancerous cells are taller than columns with a high percentage of healthy cells. Figure Three (3) was taken on day 35 of the 50-day run. This figure demonstrates the way cancer can dominate a system. The columns which had predominantly lesion and cancer cells in Figure Two (2) showed significantly increased reproduction rates, as observed in Figure Three (3). There is also a variance of growth between columns which are cancerous. This variance can be indicative of the mutations occurring to individual cells within the column. If enough mutations occur to a precursor or cancerous cell than there will be a shortened cell division cycle. This can be seen from Figure Three (3) and Figure Four (4) in which the predominantly black columns have different heights in comparison to one another. Green columns are all approximately the same height because those cells are not undergoing the same number of mutations each day. Every time a cell replicates there are mutations, and these mutations increase the chance of a cell obtaining a damaged gene set. Given that Cancer cells and Lesion cells are reproducing at a much quicker rate, their mutations also compile at a much quicker rate. This can lead to a cell's gene set becoming "Damaged" or "Broken", which in turn also increases that individual cells reproductive rate. This model demonstrates the mechanism behind why cancer cells become successful and dominate a system over time.

Methods

In order to simulate the growth of cells, a Cell Array was created. Each column within the Cell Array is a characteristic describing a cell. Each row signifies a unique cell. The original sample size of the model is 100 cells. These cells on day one are all assigned to be "Normal." Each cell also has a randomized value of P, and the value of P is randomized by two dice. The cell's P value will signify whether a cell starts the everyday loop as a "Normal" or "CIN1" cell. After the original set up of the Cell Array, the program enters the "Everyday" for loop. The first loop is the number of days that this model will run. Within the first loop is another loop, which goes through each cell and adjusts it based on its variable values. A cell can only linearly progress throughout the states. For example, a normal cell cannot change into a cancerous cell without going through the precursor stages first. A cell can exemplify behaviors of another cell type through its reproduction rate. Within the daily loop there is a function (add.cell) sent to the cell when it is ready to divide. Each cell type is assigned a designated number of days between division. Reproduction rates of an individual cell can increase based on the number of mutations to a cell's gene set. Precursor lesion or cancer cells will divide at faster rates than a normal cell, barring mutations to its gene set. A cancer cell will divide everyday, while precursor lesions will divide every other day. Normal cells will divide every three days. This function creates two identical cells. When the new cell is created, it is reattached to the Cell Array. The next function a cell receives (gene.mutations) will adjust the values for the cell's genes. The genes included within the Cell Array are crbp, rb, p53, and egfr. The values of these genes are important when assigning the reproduction type of the cell. When the next function (Rep.function) is sent, a cell's genes values are considered. A cell is then classified into one of three groups: "Normal", "Damaged", and "Broken." If a cell is classified as having a damaged or broken gene set, then it will reproduce at a rate faster than its rate assigned for type of cell. For example, a "Normal" cell divides every three days. If this cell's gene set is classified as "Broken," then this cell will start dividing every day. This process reflects the damage to a cell's tumor suppressant genes, resulting in an increase in the cell's reproduction rate. The last function (mutation.track) tracks all of the mutations occurring to a specific cell. The returned value for this function is used within the reproduction function to determine the damage done to a cell's gene set. For visualization purpose, a normal cell is green, a CIN1 cell is blue, a CIN2 cell is purple, a CIN3 cell is red, and a Cancer cell is black. The everyday loop can be run for as long as desired. For our purposes, we ran the everyday loop for 50 days. The loop will terminate once the value T is equivalent to last day of the loop.

Discussion

The results of this study provide valuable insights into the growth patterns of different cell types in a controlled environment. The findings suggest that over time there is a clear shift in the growth patterns of cells, with the prevalence of the "CIN1" cell type in the initial stages giving way to the growth of cancer cells over time. The observations made in Figures One to Four indicate that the growth of cancer cells is accompanied by a reduction in the number of "Normal" cells. This can be linked to the increased reproduction rate within Cancer cells. Mutations and damage to a cell's tumor suppressant genes allow for increased reproduction rates of individual cells. The more times a cell divides the more mutations it gathers, enhancing the quick reproduction rates of cancerous and precursor cells even more. The comparison between Figure One and Figure Four highlights the potential for cancer cells to displace healthy cells and dominate their environment, a phenomenon that is often observed in cancer progression in the body. The topography difference between the two graphs highlights why reproduction rate is paramount. Let's compare two columns and their change within the 50 days. Specifically, let's look at column X = 10 and column X = 11. In Figure One, the two columns have the same number of cells. By day 15, we already observe a clear difference between the two columns. The generally healthy column is growing at a fraction of the cancerous column. By day 35, the cancerous column has almost doubled the healthy column. On day 50, the cancerous column (X = 10) has vastly outgrown the healthy column (X = 11). It is worth noting that the growth patterns observed in this study are limited to a controlled environment and may not necessarily reflect the growth patterns observed in a human body. However, the findings provide a useful starting point for further research into the mechanisms underlying cancer growth and the factors that influence the progression of Cancer cells. This model has the capability to grow into an even more accurate depiction of Cancer growth and could be modified by loosening the controlled environment and adding in more cell types. This model may be useful tool for future research understanding the phenomenon that is cancer and why Cancer cells out compete healthy cells, including testing the potential efficacy of new treatments for Cancer.

Parameters

Parameter	Value
Cell Reproduction Rate	"Normal" – 3 days "CIN1" – 3 days "CIN2" or Gene Set "Damaged" – 2 days "CIN3" – 2 days "Cancer" or Gene Set "Broken" - Everyday
Mutation Rate	If Cell is not reproducing – 5% Chance of mutation everyday If Cell is Reproducing – 100% of a mutation
Life Span of Cell	20 Days
Number of Cells on Day One	100 Cells
Mutation Value	Mutations vary from the Integers -2 to 1

Acknowledgements

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References

Cabrera-Becerril, Augusto, et al (2017). Modeling the dynamics of chromosomal alteration progression in cervical cancer: A computational model. Plos One. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0180882.