Understanding the origin and role of driver mutations in the case of Acute Myeloid Leukemia using a simulation study

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ABSTRACT

Cancer is a leading cause of death worldwide, with millions of new cases diagnosed each year. Understanding how those cancers arise within individuals is a major challenge. Here we focus on Acute Myeloid Leukemia (AML) a type of blood cancer in the bone marrow that involves the formation of abnormal myeloid cells in an individual. Each year, 190,000 cases are diagnosed worldwide, of which 147,000 die. (*Acute Myeloid Leukemia*, n.d.) In this paper, we aim to better understand the origin of AML and the role of driver mutations at the individual level. We build a Birth-Death model to explore the role of mutation along with cell birth rate, cell death rate, and tissue size. Each simulation is individual-specific, which allows us to consider stochasticity across individuals. We show that initial cell birth rate and cell death rate only play a minor role in cancer progression, even if there is a large inter-individual variance. On the contrary, we show that driver mutation rates play a more critical role in causing Acute Myeloid Leukemia. All in all, our paper highlights large variability in cancer progression across individuals and the major role of driver mutations in causing AML. This simulation model could be used to study other types of cancers.

Introduction

Cancer is the uncontrolled growth of cells in an individual. It is a disease that showcases evolution analogous to a pathogenic disease. Cancerous cells evolve under constraints like immunity and space. Tumors are a cluster of cancerous cells.

There are two kinds of tumor: a malignant tumor and a benign tumor. The latter stays in the same place, making it easy to remove, and the former metastasizes to different locations within an individual, which is particularly hard to treat. A malignant tumor is not homogeneous in terms of composition, the tumor can show intratumor heterogeneity as well as inter-tumor heterogeneity between the metastasized cancer. The tumor heterogeneity can lead to new biological characteristics displayed by the tumor or tumor cells, for instance, the speed of division, the degree of malignancy, and the sensitivity to external stimuli. Tumor heterogeneity can be classified into two kinds based on space and time: Spatial Heterogeneity and Temporal Heterogeneity. Spatial Heterogeneity pertains to tumor heterogeneity rising due to space whereas temporal heterogeneity arises with time due to exposure to drugs or various other therapies. Tumor heterogeneity can render many previous treatments and therapies useless for an individual which could lead to difficulty in handling cancer in cases of recurrence (Zhu, 2021). Like bacteria grow resistant to antibiotics with time, tumors can develop mechanisms to evade the immune system and present-day treatments.

The process of cancer evolution can be elegantly represented by cancer models: Darwinian cancer models and non-Darwinian cancer models. Darwinian cancer models include Linear, Branch, convergent, and parallel evolution models. Different models are used to represent different types of cancer, for instance: A linear model could be used to show breast cancer evolution while branch evolution could be used to represent colorectal cancer evolution.

In addition to the types of cancer each model can represent uniquely (Volz, 2013), they also vary based on their principle.

Here we study Acute Myeloid Leukemia (AML), which is a type of cancer that affects the bone marrow and blood cells and can account for the decreased cell count of white blood cells, red blood cells, or platelets. The bone marrow consists of the red marrow and the yellow marrow, the yellow marrow is made of adipose tissue while the red marrow is the house of blood stem cells. Stem cells are undivided and undifferentiated cells that can give rise to different kinds of cells on differentiation, and these blood stem cells differentiate to give rise to either myeloid stem cells or lymphoid stem cells. The myeloid stem cells give rise to red blood cells, granulocytes, and platelets while the lymphoid stem cells give rise to white blood cells. (*Acute Myeloid Leukemia Treatment - NCI*, 2022) However, in AML, the myeloid stem cell, instead of becoming a granulocyte, a red blood cell, or a platelet, becomes a myeloblast which is an abnormal cell also commonly called a leukemia cell. AML is the clonal expansion of defective immature blast cells. In severe congenital neutropenia, the level of granulocytes goes down as they are involved in the defense mechanism. To counterbalance this defect, patients, primarily children, are administered recombinant granulocyte colony-stimulating factor (GCSF) (Kimmel, 2013). The curious question for many researchers is the role of GCSF in giving impetus to the development of Secondary AML (sAML) with an intervening disorder-secondary myelodysplastic syndrome (A, 2020). This growth factor's detailed study could give answers to the question of where AML originated from. The role of GCSF and other factors causing the evolutionary transition to sAML can be detailed using two perspectives: the population genetics perspective and the population dynamics perspective. The latter is based on the accumulation of driver mutations over a span of time. The reason why driver mutations are chosen as a part of the study is that the accumulation of such mutations allows cancer to grow and invade an individual, however, other mutations like passenger mutations usually have no such effect. Therefore, in the paper, we explore the role of driver mutations in the origin of AML and their bearing on the birth rate and death rate over time.

Here we build a Birth-Death model used to study the time taken by driver mutation to cause AML in a population based on various parameters: birth rate, death rate, and maximum population size. Using the model, the quantity of driver mutations can be ascertained that could affect the risk and the timing of Acute Myeloid Leukemia in an individual. Our goal is to start from a normal population of cells and apply different parameters to check at what point in time and after how many driver mutations AML appears in a patient. We analyze the results of each simulation by counting the total cell number at the end of the simulations which would help determine the threshold value of cancer cells required for a patient to be diagnosed with AML. In addition, we can analyze the effects of the changing values of the parameters on mutations that impact the evolutionary process of cancerous cells in Acute Myeloid Leukemia.

Methodology

The research paper aims to find out the origin of AML in an individual, and how driver mutations affect the same. To explore this question, the first step is to understand the parameters that affect the growth of a tissue. Ordinarily, without any mutations in an individual, the organism's cells will divide and die at an optimum rate that we name the birth rate and death respectively which eventually affect the number of cells in a cohort of cells in the organism's body.

However, sometimes a mutation can appear. A mutation is a modification in the genetic material of the cell which in turn changes the behavior of the cell in an environment which is the body of the person. Things go out of control when the cells show different birth and death rates due to aberrance in cell division and apoptosis, caused by mutations. The unusual consequence of this deviance leads to the uncontrollable growth of cells which is ultimately what leads to cancer, thereby making the role of mutations critical in understanding the origin of cancer.

Here we model this process using a birth-death model, accounting for the accumulation of mutations (Figure 1). In looking at Figure 1, one can see that the birth and death rates are changing with the accumulation of driver mutation. The research aims to find out the origin of Acute myeloid cancer in an individual. In Acute Myeloid Leukemia, blood cells increase to abnormal amounts. Here, the aim is to find out the number of driver mutations causing

the shift to full-fledged cancer in an individual, and at what time the driver mutations pass the threshold for an individual to acquire AML.

```python
if 0<x[t,c]<P-1:
    #IF THERE IS BIRTH
    birth=np.random.rand()<=g*x[t,c]
    #IF THERE IS DEATH
    death=np.random.rand()<=d*x[t,c]
    x[t+1,c]=x[t,c]+1*birth-1*death
    #the evolution stops
else:
    x[t+1,c]=x[t,c]

if x[t+1,c] > threshold_cancer: ## Check if simulation successful
    simulation_successful = 1

if simulation_successful==True:
    if x[t,c]< threshold_cancer:
        time_successful.append(t)
```

Figure 1: Extract of the algorithm simulating tissue growth, accounting for cell mutation, written in Python 3.0

The research methodology is a direct one as observed in Figure 1: the number of cells and the number of mutations is kept track of using matrices, therefore obviating the need for extracting datasets from databases. The matrices would be used further to study the role of the mutable nature of birth and death rates affecting the cell population of cancerous cells. In Figure 1 the number of cells in a population is appended to matrix x.

Equation 1: $g = a + y[t+1,c] * bi$
Equation 2: $d = b * math.exp(-y[t+1,c])$

The equations (1) and (2) are used to update birth rate and death rate respectively.

After understanding the concept of cell growth in a population of cells, the next step is to take into consideration the driver mutations. In equations (1) and (2), the variables a and b are the initial birth rate and initial death rate that keep changing with the accumulating number of driver mutations over a while.

Consequently, if the number of cancerous cells passes a certain threshold value, the patient will be diagnosed with cancer. With that conditional statement being established, to check the correlation between the defined parameters and the actual cancer patients, a heatmap is generated. The gradient in the heatmap would give an insight into how strong or weak the correlation is. With the same set of parameters, the next step is to keep track of at what point in the cancer evolution the cancer cell number passes the threshold.

The final part of the research methodology is to track the origin of Acute Myeloid Leukemia in an individual. In simpler terms, the aim is to record the point when the cohort of cancer cells passes the threshold which would in turn be the point of origin of Acute Myeloid Leukemia as seen in Figure 1. In Figure 1, the number of cells getting accumulated under the changing birth rate and death rate over time exceeds a certain number of cells which is stored

in the variable- threshold_cancer. Whenever this number is exceeded in the simulation, that particular iteration is considered to be a case of Acute Myeloid Leukemia, and that simulation is recorded as 1 or True as seen in line in $simualtion\_successful = 1$ in Figure 1.

Results

Our birth-death model enables us to simulate the growth of a population of cells through time. In normal conditions, defined as equal birth and death rates, and no accumulation of driver mutations, we obtain populations as plotted in Figure 2. The figure shows that without mutations' effects on cell growth and death, cell division is on average stable. The increase and decrease are random and staggered. This is in accordance with stochastic population growth and represents a normal tissue, without AML.
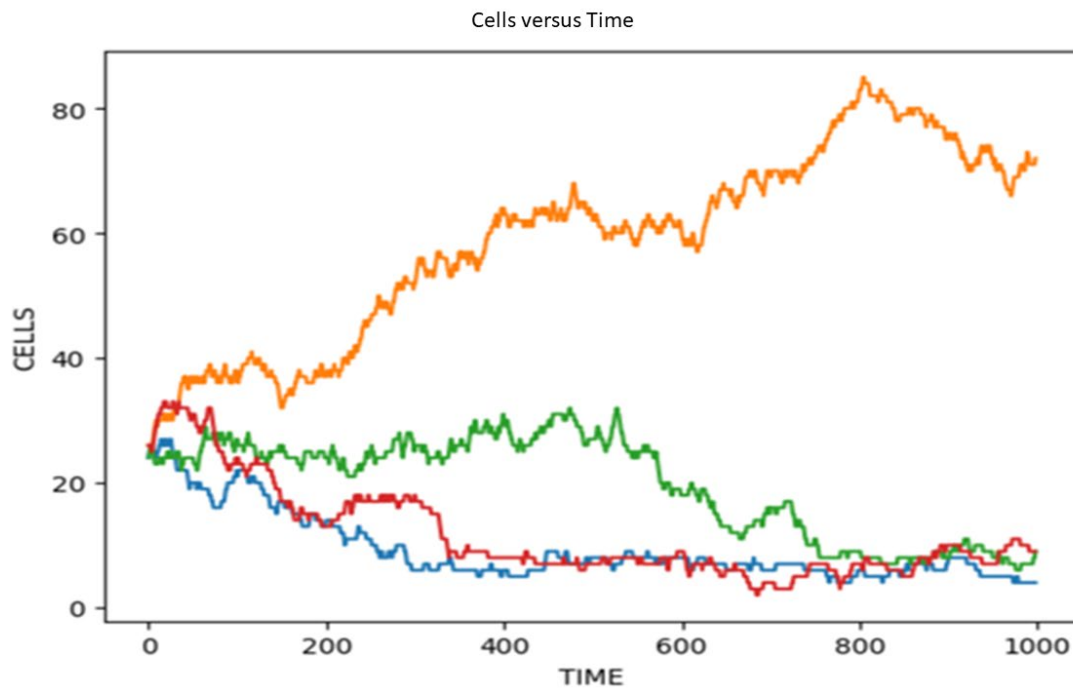

Figure 2: Changing cell population size with constant and equal -initial birth rate and death rate, and no accumulation of driver mutations. Each color represents one simulation. All simulations are independent. Birth rate = 0.01, Death rate = 0.01. We do not let cells accumulate mutations here.

Using our model, we further look at the cell population size when driver mutations are introduced. An example can be seen in Figure 3. As opposed to the previous figure, these simulations show a steady increase in the number of cells (Figure (3a)). Similarly in Figure (3b), The change in the number of mutations in a cohort of individuals is drastically increasing with time.

(3a)　　　　　　　　　　　　　　　　(3b)
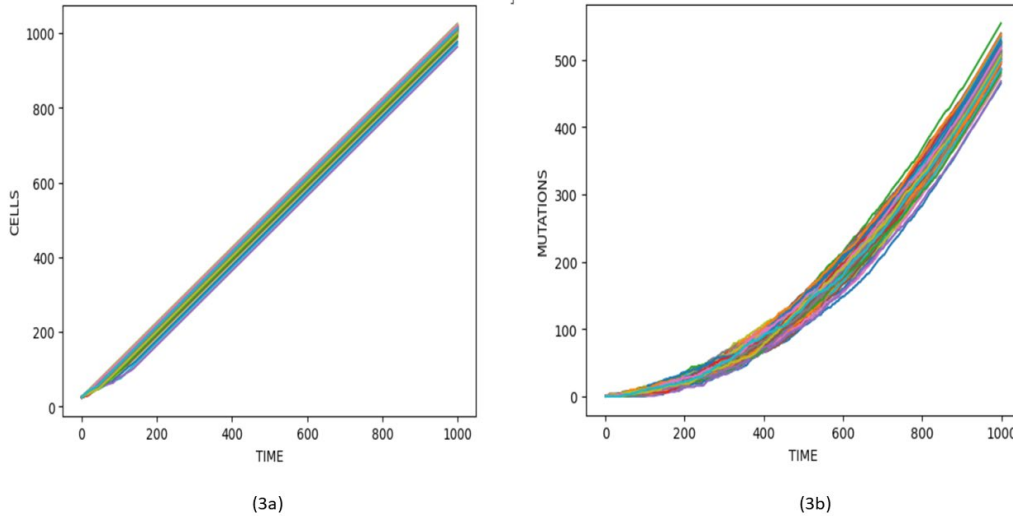
Figure 3: Simulations with a high mutation rate. (3a) With changing birth rate and death rates, the number of cells in a cohort of individuals is measured against time. (3b) The driver mutations accumulated over time are plotted for a cohort of individuals.

On looking back at Figure 3 represents cell growth in a population with accumulating driver mutations. The cell population is only increasing, which indicates abnormal cell growth. One of the hallmarks of any cancerous cell is abnormal cell division. Therefore, with time, these cells could in turn lead to cancer- Acute Myeloid Leukemia. Our simulation framework displays the expected characteristics. We now want to further investigate the extent to which the birth rate, the death rate, and the accumulation of driver mutations contribute to the origin of AML. We first explore the role of birth rate and mutation rate in cancer progression. We chose a set of birth rates to test (0 to 0.1), and a set of mutation rates (0 to 0.1). For each pair of parameters, we simulate 100 cell populations. We then compute the proportion of simulations that reach the cancer stage (defined as threshold cells). Results are presented in the form of a heatmap in Figure 4.
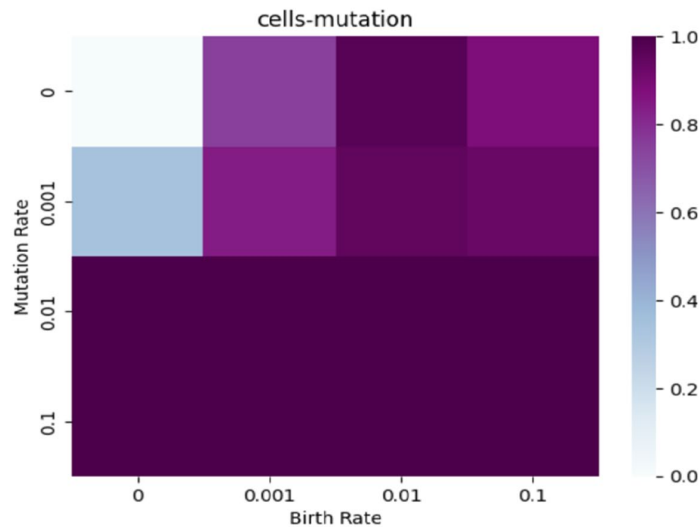
Figure 4: Effect of mutation rate and birth rate on the proportion of simulations that reach cancer stage: Darker color means a large proportion of simulations reached the cancer threshold and lighter color means a small proportion of simulations reached the threshold.

On analysis, we can see that at the top left corner in Figure 4, the shade of the heatmap is lightest and the corresponding value from the scale is 0.0, which implies when there is no cell division or mutation the probability of acquiring a cancer is zero, which stands logically correct. If there are not any cells forming and there is no mutation happening then the chances of developing cancerous properties are impossible. In the bottom left corner, the shade is the darkest even when the birth rate varies: '0','0.001', '0.01', and '0.1'. It implies that if the mutation rate is maximum then even if the birth rate is 0 the chances of acquiring cancer is cent per cent. This gives an important result: the mutation rate plays a more pivotal role in determining the possibility of acquiring cancer than the birth rate. The effect of mutation rate becomes even more intense after the bi value crosses halfway through values 0.001, and 0.01 irrespective of what the rate of birth is.

We will now understand the effect of birth rate and mutation rate on the aspect of time. We chose a set of birth rates to test (0 to 0.1), and a set of mutation rates (0 to 0.1). For each pair of parameters, like Figure 4, we simulate 100 cell populations. Now instead of computing the proportion of simulations that reach the cancer stage, we track the time when a patient acquires AML. Results are shown in the form of a heatmap in Figure 5.
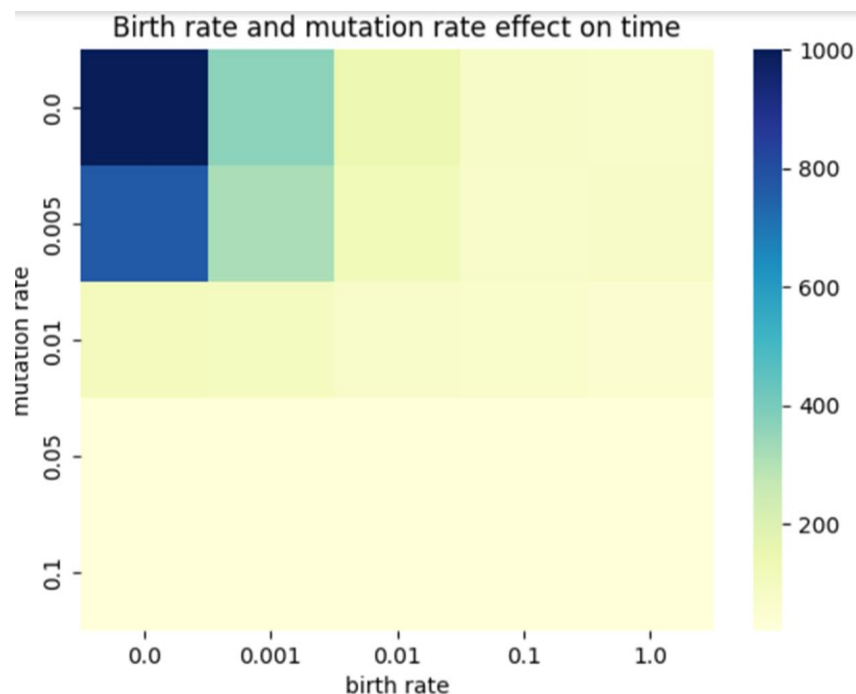
Figure 5: Effect of mutation rate and birth rate on the timing at which simulation reaches the cancer threshold. A darker color means a longer time to reach the cancer threshold and a lighter color means a smaller time to the threshold.

As it can be observed from Figure 5. when there is no cell division and mutation happening that is when both the values are set to zero, the corresponding time taken to observe the onset of cancer is 1000, which is the maximum value, making the acquisition of cancer in an individual nearly impossible. In contrast, however, when the value of mutation is extremely high (0.1 or higher) the individual will acquire cancer quite early on.

Finally, we observe the role of death rate and mutation rate in cancer progression. We chose a set of death rates to test (0 to 0.1), and a set of mutation rates (0 to 0.1). For each pair of parameters, we simulate 100 cell populations. We then compute the proportion of simulations that reach the cancer stage. Results are presented in the form of a heatmap in Figure 6.
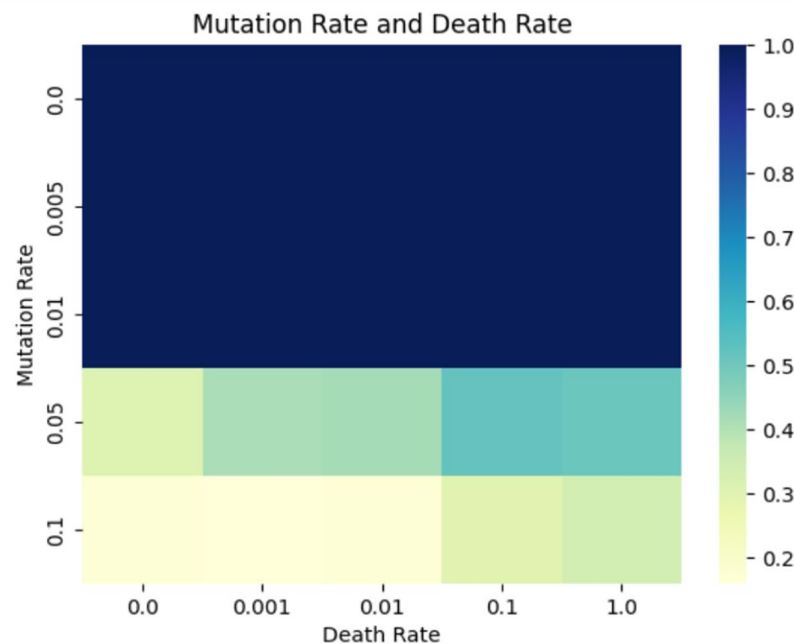
Figure 6: Mutation rate and death rate heatmap

In contrast to the effect of mutation rate-birth rate, the effect of mutation rate on Acute Myeloid Leukemia diagnosis is quite the opposite. The chances of acquiring this type of cancer by an individual with no mutation and no cell death are definite according to the heatmap. A person with no cell death and a high mutation rate shows almost negligible chances of acquiring Acute Myeloid Leukemia

Discussion

After successfully representing the effect of different parameters on the progression of cancer, when studying birth rate and mutation rate together, it can be deduced that mutation rate has a more profound effect on an individual to acquire AML (Figure 4). Even, in the case of the pair of parameters: death rate and mutation rate, the role of mutation rate in AML progression is more critical (Figure 6). Since the mutation rate is driving the progression of AML more strongly than the birth rate, the higher the mutation rate the shorter the time it would take for an individual to acquire AML. This conclusion is supported by Figure 5.

For further studies, the mathematical model used for Acute Myeloid Leukemia cases can be extended to different types of cancer types like multiple myeloma, breast cancer, and prostate cancer. The parameters involved in the study can be tweaked based on the type of cancer that is being researched. In addition to this, the reason why the origin of different types of cancer can be of interest is that different cellular and biological origins lead to very different histological and molecular characteristics of cancer, therefore studying the origin of not just AML, but cancer types like prostate can render information as to how to treat a particular cancer type without any undue treatment. For instance, the origin of skin carcinoma from hair follicle bulge stem cells. (L., 2013) However, in real-life settings, there are other factors that come into the picture, for instance, the role of oncogenic signaling also plays an important role in determining the origin of cancer, along with the biological and cellular origin. With that being said, the population's perspective on cancer, in particular, states that the increasing number of driver mutations supports the change of neutropenia to Acute Myeloid Leukemia by changing the normal cell population to cancerous, as observed and recorded in the simulations, in an individual. Within these number of such simulations, (Kimmel, 2013) it can be

observed that the accumulated number of driver mutations should be adequate enough to transition into blood cancer-Acute Myeloid Leukemia, and the point at which the transition takes place is the point of origin of cancer that has been the main catch of the algorithm in the birth-death simulation model as seen in Figure 1. The reason to focus on the point of origin and the transition phase to cancer is because according to statistics, the percentage of people developing Clonal Hematopoiesis (Link, 2019) after congenital Neutropenia is almost a solid 50%, making the role of driver mutations involved in the stochasticity of the development of Acute Myeloid Leukemia critical. In addition to this, these driver mutations not only lead to cancer but can also create tumor heterogeneity over time. The tumor, which is a cluster of such cancerous cells, can metastasize to different locations, and these mutations can further alter the biological and molecular properties such that the original tumor and the metastasized tumor are almost non-identical. The biggest concern, however, with such changes is that the treatment for the original tumor would be of no use for the metastasized tumor. The concern around malignant tumors is quite explanatory as around 90% (Seyfried, 2013) of cancer deaths are due to metastasis. This property of malignant tumors raises the question of the route that needs to be adopted to mitigate the issue.

Conclusion

In recent years, the rising cases of cancer death are due to malignant cancer, and the increase in the development of immunity against cancer treatment is due to tumor heterogeneity. Interestingly, the same trend is observed in one of the deadliest blood cancers- Acute Myeloid Leukemia. Therefore, the importance of tracing the evolutionary pattern of cancer becomes critical in understanding which treatment is best for an individual diagnosed with particular cancer. The research idea is to build an algorithm to track the origin of Acute Myeloid Leukemia with the simultaneous increase of driver mutations. The mathematical model in the code tackles the effect of these mutations on parameters like birth rate, death rate and population size to understand at which point the abnormal cell growth pattern starts to get exhibited. The time is recorded using the simulations which are depicted in the form of a heatmap to check the strength of the correlation between the aforementioned parameters and the occurrence of Acute Myeloid Leukemia. In the simulation carried out, the effect of the mutation rate is way higher than the birth rate on a person being diagnosed with Acute Myeloid Leukemia. And the opposite trend is observed with the set of parameters: death rate and mutation rate. The effect of death rate on the chances of acquiring Acute Myeloid Leukemia is more profound than the effect of mutation rate. The role of mutation rate on the diagnosis of cancer stands ambiguous with the given simulations, however, the trend of Acute Myeloid Leukemia diagnosis with changing birth rate and death rate makes logical sense- both have opposite effects on the diagnosis. The role of mutation rate can be studied in-depth with larger and more realistic values taking into account other different kinds of mutation-neutral mutations and passenger mutations with the respective locations of these mutations.

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