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Article

Significance of Tumor Growth Modeling in the Behavior of Homogeneous Cancer Cell Populations: Are Tumor Growth Models Applicable to Both Heterogeneous and Homogeneous Populations?

Divya Reddy, Dr. Alexander Zaslavsky, Dr. Todd Morgan, and Mr. Joe Rasmus
Williamston High School, Williamston, MI

SUMMARY

The ability to predict and slow the spread of cancer in the human body is a task that medical professionals have been trying to accomplish for many years. Being able to give factual basis to the use of certain growth models for application in not just heterogeneous, but also homogeneous cancer cell populations is imperative to treatment research as using mathematical analysis to predict the dynamics of tumor growth allows professionals to simulate how tumors might behave in the human body. This study follows the process of single-cloning and the growth of a homogeneous cell population in a superficial environment over the course of six weeks with the end goal of showing which of five tumor growth models commonly used to predict heterogeneous cancer cell population growth (Exponential, Logistic, Gompertz, Linear, and Bertalanffy) would also best exemplify that of homogeneous cell populations. We hypothesized that the Gompertz, Linear, and Bertalanffy models would provide the best fit to the homogeneous cancer (clonal) cell population growth data while models such as the exponential and logistic model, which are most commonly associated with the growth of heterogeneous cancer cell populations in natural environments (i.e. malignant tumors), would veer off the growth data. It was shown that Gompertz and Linear functions provided the best fit for this population, while exponential and Logistic functions fell slightly behind. The data collection and analysis for this research was performed through the University of Michigan Research Labs and Solver by Frontline Systems.

INTRODUCTION

Cancer has always been a burden to the health system as malignant tumors are notorious for slowly taking over the body due to their ability to evade apoptosis and reproduce indefinitely [1]. In 2020, the American Cancer Society estimates that there will be 191,930 new cases of prostate cancer and about 33,330 deaths resulting from the disease (2). Scientists have tried to identify the "most accurate" mathematical model to fit tumor growth. However, results are either inconclusive or vary greatly depending on the cell population as most studies only focus on the early stages of tumor growth. Similarly, though many studies have determined a model that best fit that set of tumor growth data, these findings were not applicable to other data sets as tumor growth can vary greatly depending on the tumor environment [3]. If a certain model fits better than others and behavioral patterns of tumor growth predicted by mathematical analysis can be generalized to all cell populations, scientists will have a better idea of the timeline of tumors in the human body. Treatment can then be developed to inhibit this behavior, effectively slowing down the spread of cancer and the growth of malignant tumors [3].

Major key concepts to be addressed in this research are the application of mathematical tumor growth models in association with homogeneous cancer cell populations, proliferation rates of cancer cell lines (specifically in the VcaP cell line), and the cell cloning procedure as a whole. The proliferation rate refers to the rate of growth of the cancer cell population or the malignant tumor itself. Proliferation could also refer to the reproduction rate of the cells. In this research, the proliferation rates among these cell lines was directly measured through cell counting as the increase in cell count over the course of the experiment would signify the overall proliferation rate of the population. Cell lines are specific cell samples from general cancer that are purchased for the research lab. For example, both VcaP and PC3 are cell lines of prostate cancer that are used for general research in urologic cancer labs. Cell cloning is the process of taking a cell line sample and diluting it to the point where you have a single cell isolated in its well (cell plate). Over time this cell will then reproduce infinitely and form a homogeneous cell population [4]. In this research, the proliferation rate of one prostate cancer homogeneous cell population was measured over a time period of six weeks and compared to five different tumor growth models (Exponential, Logistic, Gompertz, Linear, and Bertalanffy).

The exponential growth model yields a growth rate that is proportional to the cell population and is most commonly associated with the early stages of tumor proliferation [3]. However, this model has proven to be less accurate as tumor growth progresses in the body due to angiogenesis and

Model	Equation
Exponential	$V = aV$
Logistic	$V = aV(1 - \frac{V}{b})$
Gompertz	$V = aV - bV\,lnV$
Linear	$V = \frac{aV}{V+b}$
Bertalanaffy	$V = aV^{\frac{2}{3}} - bV$

Table 1: Five growth functions are being utilized. For each equation, a and b serve as parameters that are relative to the data set. V exemplifies the change in tumor size over time. In this case, V will be representing the cell population number at the given time [3, 9].

nutrition depletion. When graphing this model, the solution to the initial equation is used [5]. The solution is given by:

$$V(t) = V_0 e^{rt}$$

with t serving as the week the data was collected, r serving as a growth parameter, and V_0 serving as the initial cell population measurement. The model assumes that growth is proportional to the surface area and that there is a decrease in tumor volume due to cell death. The Logistic Delay growth model yields that the growth of a cancerous cell population is limited by some capacity relative to the tumor size. The logistic model assumes that the cell population increases linearly until zeroing out at carrying capacity for the said population and embodies a standard sigmoidal curve [3]. The Gompertz growth model is a generalization of the logistic model and is known to be the best example of breast and lung cancer in the human body [3]. The model had the original intent of displaying the human mortality curve, however, it proves to be applicable to the growth of organisms with a sigmoidal curve that is asymmetrical with the point of inflection [6]. It also predicts that as the tumor grows in size, its growth rate decelerates. The model shows that a tumor's rate of growth is the most significant at the early stages of growth when there are no means to detect the tumor clinically [7]. The linear growth model assumesthat a cell population grows at a constant rate, first exponentially then linearly over time. The model was also initially used to predict the growth rate of cancer cell populations when this type of research was moderately new [3]. The Bertalanffy growth model was created to exemplify organism growth and is known to provide the best example of tumor growth [3]. Each model has a specific tumor growth formula that can be applied to unique data sets in order to predict the future growth of a tumor or cancer cell population (Table 1).

The hypothesis of this study is that when a homogeneous cell population is monitored from its start in an artificial setting it will best resemble a constant rate of growth exemplified by the Linear, Gompertz, and Bertalanffy model as opposed to a constant growth rate given by the Exponential or Logistic growth model. This is because these two models are more commonly associated with early stages of heterogeneous tumor growth in a natural environment with limited resources. While some of the models studied here have proven to be good examples of specific cases heterogeneous tumor growth (i.e. the Gompertz Model is known for best predicting breast and lung cancer) the exponential and logistic models are known for being a good basic generalization of early heterogeneous tumor growth of varying types [3]. Along with that, we hypothesized that the Linear, Gompertz, and Bertalanffy growth models would be a better fit for the experimental data generated, as based on a previous study of superficial heterogeneous tumor growth, they seem to be significantly more flexible than the exponential model when it comes to fitting data points generated in lab environments [3]. These models are not commonly associated with general heterogeneous tumor growth [3]. Similarly, the Logistic model, though having about the same fit as the Gompertz and Linear model in the study mentioned, were still assumed to have a lacking fit since this study was focused on homogeneous growth and the Logistic model is, as previously mentioned, more commonly associated with the basic generalization of natural heterogeneous tumor growth [3]. Major issues to be addressed through this research include identifying what growth model best fits the early stages of growth of a homogeneous cell population in a superficial environment, as well as determining if those models differ from those more commonly associated with heterogeneous tumor growth in its early stages and in a natural environment with limited resources (i.e. exponential and logistic) [3]. In this study, growth data from a prostate cancer single-cell clone population was collected over a period of time starting from the formation of the cell population and the experimental data points' fit to the growth models being utilized (Exponential, Logistic, Gompertz, Linear, and Bertalanffy) to determine which model best described homogeneous cancer cell population growth in this context. The models utilized in this study were chosen based on their widespread use in measuring tumor growth in the human body [3, 6]. The two other commonly used models in tumor growth — Surface and Mendelsohn — were not utilized in this research due to the fact that these models commonly use tumor volume as a measurement and not cell population count. Since the measurement unit in this study is cell population count, it is important to only use models that are versatile when it comes to units of measurement [2]. The purpose of this research is to provide evidence as to which model fits best with the behavior of a homogeneous cell population and give reasoning as to why this outcome exists. No specific treatment is being imposed other than the cell cloning process itself and parameter generation for each model.

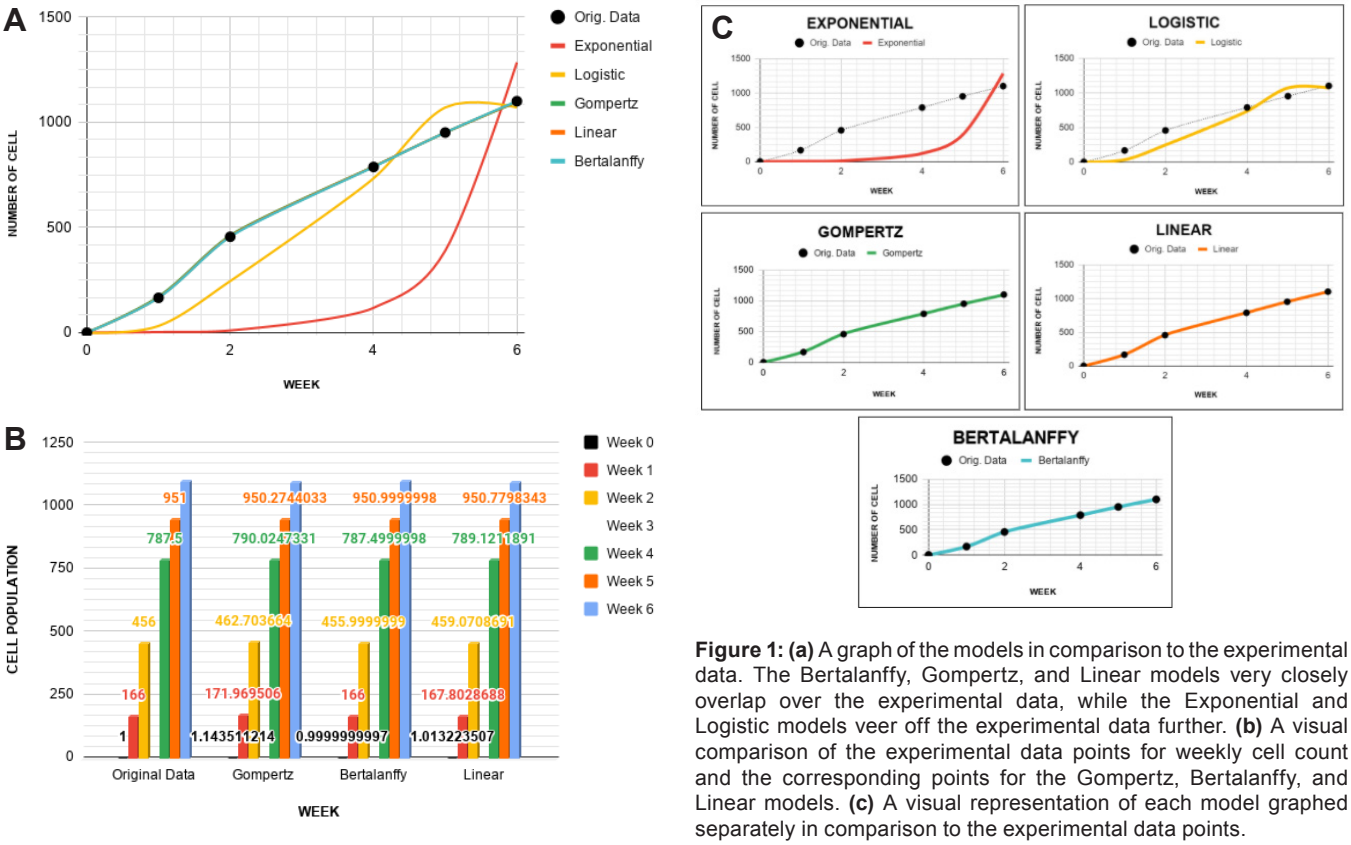

Figure 1: (a) A graph of the models in comparison to the experimental data. The Bertalanffy, Gompertz, and Linear models very closely overlap over the experimental data, while the Exponential and Logistic models veer off the experimental data further. **(b)** A visual comparison of the experimental data points for weekly cell count and the corresponding points for the Gompertz, Bertalanffy, and Linear models. **(c)** A visual representation of each model graphed separately in comparison to the experimental data points.

RESULTS

This experiment was conducted through first the procedure of single-cell cloning and then data optimization to generate an equation for each of the tumor growth models being studied from the original cell population data. A single cell was first taken from a VcaP prostate cancer cell line sample and left to incubate over six weeks with growth media that was changed in weekly intervals. Over this time, periodic cell population counts were taken weekly, and these data points were then optimized through Solver (Google Sheets) to generate the best fit equation for each tumor growth model being studied. In order to decide which model suited the homogeneous cell population best, the NMSE (Normalized Mean Square Error) and SSR (Sum of Least Squares) were taken for each model. The objective was to have a small SSR and NMSE, as that indicates the best fit. The AICc (Aikake's Information Criterion) for each model was also taken to help identify possible bias within the models, with a high AICc indicating potential bias.

We hypothesized that when a homogeneous cell population is monitored from its start it will best resemble a Linear, Gompertz, or Bertalanffy growth model as opposed to an Exponential or Logistic growth model, which are more commonly associated with heterogeneous tumor growth in its early stages and in a natural environment with limited resources [3]. After calculating the NMSE and AICc for each model, we concluded that while the Bertalanffy model had an NMSE and SSR of zero, indicating a perfect fit, it also had an abnormally high AICc pointing to potential bias having to do with sample size and eliminating it from the being a possible fit to the data. As expected, when considering both the NMSE and AICc, the Linear model had the lowest values, indicating a generally good fit and minimal bias. The Gompertz model followed, with the second lowest NMSE and AICc, and the logistic and exponential models followed after that (Table 2). The Bertalanffy, Gompertz, and Linear models were almost indistinguishable from each other due to their close fit to the experimental data (Figure 1B), however, the Exponential and Logistic Models showed high variation from the experimental data points (Figure 1A & C). It also needs to be mentioned that due to confounding variables data was unable to be collected for week three of this study, qualifying it as an erroneous data point for all figures and further discussion of results.

As stated before, the SSR, NMSE, and AICc for each model had a good amount of variation. While the Bertalanffy model had a perfect SSR and NMSE, it also had an abnormally high AICc, pointing to potential bias most likely having to do with a small set of data points. The Gompertz model was the best fit for the experimental data overall, as when considering the three forms of analysis together, the Gompertz model had the lowest overall values proving it to be a good fit with minimal bias. The Linear model was the second-best fit in terms of the overall analysis; however, it still fell behind the Gompertz in the sum of squared residual analysis. This is slightly surprising as even with having the second highest SSR, the linear model still had the best NMSE and AICc in the sense that both

Model	SSR	NMSE	AICc
Exponential	1021839.2	0.085281	80.27213
Logistic	80237.756	0.0066965	75.00594
Gompertz	105.20054	0.0000087799	35.18465
Linear	38904.237	0.0000018203	21.81120
Bertalanaffy	0	0	-170.6488

Table 2: The SSR, NMSE, and AIC c for each model. The ideal for each form of analysis is having a number relatively close to zero. In terms of the AICc positive or negative values do not hold any value over one another.

Model	a	b	r
Exponential	n/a	n/a	1.193
Logistic	-2.591×10^{-3}	2.185	n/a
Gompertz	1.144	2.103×10^{-2}	n/a
Linear	71522.726	70588.288	n/a
Bertalanaffy	-5.13×10^{-11}	-0.999	n/a

Table 3: The parameters for each model. The parameter of r comes from the exponential solution, not the initial function listed (Table 1).

values were the closest to zero when compared to those of the other models. The logistic and exponential models proved to be the worst fit for the data, both having high AICc and NMSE in comparison to the other models. It is also surprising that both the exponential and logistic models had the highest AICc after the Bertalanffy model as the exponential model only had one parameter (Table 2).

Going off that, the parameters generated for each model had a slight amount of variation as well (Table 3). Each model had two parameters of a and b, apart from the exponential model which only required one parameter of r, signifying growth rate. Though these parameters play no part in interpreting each model's actual fit to the data they still hold interest. While most of the parameters generated (for those of a and b) centered around zero, those of the linear model were substantially high which could be expected, as this is a commonality in similar experiments [3].

DISCUSSION

We hypothesized that when a homogeneous cell population is monitored from its start it will best resemble a Linear, Gompertz, or Bertalanffy growth model as opposed to an Exponential or Logistic growth model, which are more commonly associated with heterogeneous tumor growth in its early stages and in a natural environment with limited resources [2]. These findings support the original hypothesis in that the logistic and exponential models proved to be the worst fit for a homogeneous cell population, suggesting that there was a difference between the growth, model of a single-cell population, and the growth of a heterogeneous cell population. Many factors contribute to this including the fact that the single-clone population was artificially created and existed in a controlled environment. A heterogeneous cell population existing in the body would have different nutritional and environmental conditions that would alter the growth of the population overtime.

When interpreting which models exemplified a good fit to the data, it was also important to take note of the circumstances in which each model works best and how this could translate to potential bias. The best example of this with this set of data is the Bertalanffy model. Though it is always suspicious when a model has a perfect fit, it could be assumed that this model may have a "perfect" fit due to the small sample size of the study. The Bertalanffy model assumes that growth is proportional to surface area, and since the number of data points as well as timespan was very small in this study, it is safe to assume that the surface area of the cell population had minimal to no change over time even though the cell number itself rose. This was supported as even though the model did have a "perfect" fit to the data with an SSR and NMSE value of zero, the AICc of the model was significantly high. Since an AICc is meant to correct for sample size and parameter bias, it is reasonable to assume that the reason the Bertalanffy model had such an accurate fit to the data is that there were too few data points. Under those circumstances and the assumption of bias, the Bertalanffy model was rejected as a potential fit to this set of data as it would only be fair to take the equation under consideration with a large number of data points that simulate infinite time. That leaves both the Gompertz and Linear models as good representations of the data provided by the population. This is unsurprising as linear models were originally used to predict the growth of cell populations in early research, and the Gompertz model was also used for this purpose [3]. Both models are also quite versatile in terms of units, as they can estimate growth from both tumor volume measurements and quantitative cell population data. Both models also have the ability to work well with smaller sets of data such as that utilized in this study. This is because the Linear model generates a slope directly from the given data, so no matter the sample size the model will generally fit the points fairly well due to its flexibility [3]. Similarly, the Gompertz model follows the pattern of a function that is asymmetrical with the point of inflection. This makes the Gompertz function quite flexible, as it allows the function to fit any amount of data quite closely since the function does not have to be symmetrical with the data's point of inflection like in the Logistic model [3]. Along with the Logistic model, the Exponential model is quite inflexible when it comes to smaller sets of data as the function only has one parameter, allowing for very little change to the general function when inputting a small number of data points [3]. Both of these models had the highest AICc after Bertalanffy, suggesting that they had some form of bias. This most likely also had to do with limited sample size, since both functions are typically used with larger sets of data due to their inflexibility when it comes to small sets of data [3, 6]. We

also suspected that the reason the logistic and exponential models proved to not be a great fit is that the cell population being studied was not in an environment with a limited number of resources or space.

In terms of parameters, all numbers computed seem to fit the general data trends set by previous studies of this kind. For instance, in previous studies, the parameters of all of the model's used except Linear were centered around zero, while those of the Linear model all were significantly higher. The same trend can be seen in this study as the parameters of a and b in the linear model were significantly higher than those in the Gompertz, Bertalanffy, and Logistic models. Along with that, in considering the Gompertz model, most other studies dealing with the Gompertz model utilize a three-parameter equation of a, b, and, c (Figure 2). This equation is given by:

$$V = aV\,ln(\frac{b}{V+c})$$

The equation utilized in this study had two parameters only (Table 1) [9]. While this should not have had an impact on the fit of the model itself as both are functions of Gompertz, it would have increased the model's AICc as it deals directly with a higher number of parameters in correlation to bias [3]. The three-parameter equation was not utilized in this study due to variable constraints in Solver. The parameters of a, b, and r in each data set serve as "free number" parameters that are generated by a data optimization function to create an equation for each model that best fits the experimental data. However, these parameters should hypothetically fall into the following definitions for each growth model. For the exponential model, r should serve as the growth constant. For the Logistic model, a should serve as a growth constant and b should serve as a carrying capacity [3]. For this formulation of the Gompertz model, a and b truly serve as free parameter values [9]. For this formulation of the Linear model, a/b should give the initial exponential growth rate, and a should give the later constant growth rate. For the Bertalanffy model, a should serve as a growth constant, and b should serve as a constant of cell death [3]. For some of these models, specifically the Logistic and Bertalanffy models, these parameter definitions do not make sense. This again could be due to sample size bias as they both had a very high AICc when compared to models with an equal number of parameters such as the Linear and Gompertz models.

Boundaries that possibly inhibited the course of this study include time, material, and sample size. Travel to the lab was only possible once a week, which limited the number of observations and experiments that could be carried out as well as limited the amount of data that could be collected within a specific timeframe. This could provide for some unwanted bias in some models (i.e. Bertalanffy, Exponential, and Logistic) that rely heavily on large data counts [3]. Another boundary that exists in terms of this research is material. This hypothesis on more than one cell line or cell single clone population due to the limited amount of cancer lines available in cell culture at this given time.

In terms of uncontrollable factors in relation to this study, time and material constraints likely had an impact on the overall execution. Week three of data collection was considered an erroneous data point as independent circumstances did not allow data collection to happen; however, ideally that would not be the case. Similarly, time constraints only allowed for this set of data to have a small number of points, leading to a great deal of potential bias among equations that require a larger set of data such as the Bertalanffy, Logistic, and Exponential models. It is also generally known that larger sets of experimental data yield stronger results. Time constraints also limited the set of data that could be produced. Ideally, at least three single clones would be produced, and a large number of data points would be collected. However, there was only enough time to perform the study on one clonal population after deciding which cell line to use. The material available also played a factor in this. Along with that, ideally, data would also be taken on a daily basis rather than a weekly one, as that would provide more insight into the population's growth rate and would generate a larger set of data. This was not possible as transportation constraints only allowed data to be taken on a weekly basis. If these uncontrollable factors did not exist and the situation was ideal, then the models would probably show more accuracy, and models such as the Bertalanffy model would not have been rejected due to sample size bias. However, since the Gompertz and Linear models had a low AICc for this data set and had limited known bias under the circumstances of this experiment, we can still assume that these models still provide the best fit for homogeneous cell populations, while exponential and logistic models might be a better fit for heterogeneous cell populations under natural circumstances. For procedural improvements, the single-clone procedure itself was performed under proper circumstances and conditions, indicating that there was no bias with the experimental data set. In terms of data application and parameter optimization, proper methods and functions were utilized for each model. Apart from the minimal amount of data points, each function was applied with the proper method as well. For future research, using a much larger sample size both in terms of number of single-clone cell populations and time data points collected would be recommended, as well as the utilization of the VcaP cell line as it provides for a stable homogeneous cell population. By being aware of the differences in the growth between heterogeneous and homogeneous cell populations, as well as the growth functions that model each, cancer treatment research can be taken to the next level as scientists would be able to accurately predict the growth of tumors prior to their spread and not be limited by time or material. The findings of this research provide useful knowledge about the development of homogeneous cancer cell populations; however, they still leave room for additional research since not all cancer cell lines and growth functions were utilized.

MATERIALS AND METHODS

A VcaP prostate cancer cell line was used to create a homogeneous single clone population, and population counts were recorded weekly over a period of six weeks. Afterward, the raw data was applied to five different tumor growth functions with the goal of providing the best fit to the population growth.

Single Clone and Cell Counting Procedure

Through the process of the single clone procedure cells were cultured in RPMI-1640 supplemented with 10% FBS, 1% Penicillin/Streptomycin and 1% L-glutamine. Phosphate-buffered saline, and trypsin were utilized to clean holding flasks and detach cells for counting. The cell clone procedure was performed as follows. Growth media was aspirated out of the original flask holding the Vcap cells, and 10 mL of PBS was added to the flask. The PBS was aspirated, and one mL of trypsin was added to the flask in order to detach the cell from the flask wall. After three minutes, 5 mL of PBS was pipetted into the flask in an up and down matter to neutralize the trypsin creating a 6 mL cell solution within the flask. Three mL was taken from this cell solution and put into a test tube. The test tube was then inserted into a centrifuge and spun at 194 RCF for a total of 5 minutes in order to pellet the cells. After the cell was spun down fully, the solution above the cell pellet was aspirated out of the tube to just leave the pellet. 10 mL of PBS was pipetted into the tube in order to dilute the cell pellet. A 20 µL sample of test tube solution was then inserted into and counted using the hemocytometer. After a cell density and dilution factor was calculated for the sample, the test tube cell solution was diluted to the ratio of 100 cell/mL and pipetted into two 96-well plates. The plates were then studied under the microscope, and wells observed to only have one cell present were identified and marked. The plates were put in the incubator to rest. After one week, the plates were studied again and a single well (out of the ones initially marked) was chosen to continue the rest of the experiment. Only one well was chosen because in this experiment only one of the wells marked held a healthy cell population at the first weekly check. The cells of this well were transferred to a bigger flask every two weeks, so the cell population was not spatially limited in terms of cell density. Cell population counts were taken weekly.

A hemocytometer was used to take all cell population counts as well as provide the dilution factor for the initial single-clone process. Ink-counting was also utilized throughout this study for population count validation. The procedure for using the hemocytometer was as follows. First, 10 µl was taken from the cell suspension (post-trypsin) and pipetted into a small test tube. Ten µL of the solution was pipetted into each side of the hemocytometer plate. The plate was placed under the microscope and the number of cells in each of the four corner grids were counted and the hemocytometer formula for measured cell density was imposed to determine the initial dilution factor [8]. The formulas for measured cell density and initial dilution factor are given by:

$$Measured\ Cell\ Density = \frac{\frac{Number\ of\ Total\ Counted\ Live\ Cells}{Number\ of\ Grid\ Squares\ Counted} \times Dilution\ Factor}{Volume\ of\ Grid\ Square\ (mL)} = \frac{\frac{Number\ of\ Total\ Counted\ Live\ Cells}{4} \times Dilution\ Factor}{0.001(mL)}$$

After performing this formula for each side of the hemocytometer, the results from both sides were averaged [8]. For the initial cloning procedure, the cell was diluted to one-hundred cell per mL (or 1 cell per 100 uL). For the periodic cell counts after the cloning was completed, just the measured cell density (cell population count) formula was used and the result was recorded after being scaled to the proper volume. In the sample used, the initial dilution factor was 480 mL, meaning that in order to achieve 100 cell per mL, 480 mL needed to be added to the sample. To do this, only 1 mL of the initial 10 mL sample was taken, and 48 mL was added to that sample in order to reach the desired dilution of 100 cells per mL. For the periodic cell counts the dilution factor in the measured cell density formula was equal to one as the sample was not diluted, for the initial cloning procedure dilution calculation, it was equivalent to 10 as the cell pellet was diluted by 10 mL.

The hemocytometer was used to count the cell population of the VcaP single-cell population on a weekly basis for a six-week period. Counts were taken only during transfers of the population to larger plates and with small amounts of trypsin in order to limit potential confounding variables. Over the course of this experiment, the VcaP population was transferred four times and trypsinized for a total of seven. As the cell counts for the VcaP cell line were gathered over the experimental period, a graph was created to visually display the growth of the homogeneous cell population.

Throughout the course of the study, continued contact was made with the primary investigator, the lab manager, and the lab attendant of the research lab that housed the cell population.

Mathematical Modeling

After population counts were collected over a period of six weeks, the data was applied to five mathematical growth functions commonly used to model tumor growth in the human body: the Exponential model, the Gompertz model, the Logistic model, the Linear model, and the Bertalanffy model. Each function was applied to the data provided by the VcaP single clone cell population via optimization through Solver (Frontline Systems, Google Sheets), and the parameters for each differential equation was generated with the objective of a minimum sum of squared residuals given by:

$$SSR = (y_i - y)^2$$

with y_i representing the experimental data points, and y representing the corresponding data points on the model [3]. After the parameters were fitted the normalized mean square error (NMSE) and Aikake's information criterion (AICc) were

also computed using Google Sheets. These are given by:

$$NMSE = \frac{(y_i - y)^2}{\sum_i y_i^2}$$

$$AIC_C = n \ln\left(\frac{SSR}{n}\right) + \frac{2(K+1)n}{n-K-2}$$

with K being the number of parameters and n being the number of data points. Since models have a different number of parameters, the AICc was used to correct for smaller sample sizes as well as eliminate potential bias having to do with parameters. It is known that models with a higher number of free parameters will ultimately be able to fit the data better than those with fewer parameters. A higher AICc in comparison to the other models would signify that there is a potential bias in correlation to the data for that specific model. Models with a NMSE and/or AICc relatively close to zero were deemed to be the best fit. AICc is also meant to be interpreted in terms of absolute value, so positive or negative values hold no difference [3].

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