# MATH112B Final Project-Age Structured Modeling

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## 1 Introduction

For the Final Project of MATH112B, we have decided to study Project 7: **Age-structured modeling in cell biology**, which has the following boundary value problem for the age-density of the population [1]:

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(a)n \tag{1}$$

$$n(t,0) = \int_0^\infty b(a)n(t,a)\ da \tag{2}$$

In this model, $n(t,a)$ is the population density of age $a$ at time $t$, $b(a)$ is the birth rate, dependent on the age of individuals (age-specific fertility rate of women), and $\mu(a)$ is the death rate, also dependent on the age of individuals. $n(t,0)$ is the number of births at time $t$, or the boundary condition.

The dynamics of the model are given by [3]:

$$\frac{d}{dt}n(t,a) = \frac{\partial n}{\partial t} + \frac{da}{dt}\frac{\partial n}{\partial a} \tag{3}$$

As age passes at the same rate as time, we can say that $\dfrac{da}{dt} = 1$ and

$$\frac{d}{dt}n(t,a) = \frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} \tag{4}$$

In this case, as $\dfrac{\partial n}{\partial t} + \dfrac{\partial n}{\partial a} = -\mu(a)n$, we have a deterministic McKendrick–Von Foerster equation (DMF). Now, instead of using the PDE at (1), we can use it as an ODE:

$$\frac{d}{dt}n(t,a) = -\mu(a)n \tag{5}$$

Along the characteristic lines:

$$a(t) = t + c \tag{6}$$

We have the solution:

$$N(t) = N_0 e^{-\int_0^t \mu(s)\ ds} \tag{7}$$

With this, we can define a survival equation:

$$L(a) = e^{-\int_0^a \mu(s)\ ds} \tag{8}$$

which represents the fraction of individuals surviving from birth to age $a$ (survivorship). We can generalize $L$ to show the fraction of individuals that survive from age $a$ to age $b$ (survival rate) [4]:

$$L(a,b) = e^{-\int_a^b \mu(s)\ ds} \tag{9}$$

Following the characteristic lines, we have the solution for $n(t,a)$:

$$n(t,a) = n(t-a,0)L(0,a), a < t \tag{10}$$

$$n(t,a) = n(0,a-t)L(a-t,a), a > t \tag{11}$$

We assume the birth is proportional to the population, we should have an exponential growth or decline with respect to time, given by

$$n(t,a) = Cn'(a)e^{rt} \tag{12}$$

Where $n'(a)$ is the stable age distribution, and we assume $n'(0) = 1$ so that $n'(a)$ is the fraction of individuals with age $a$ that survive to age $a$ relative to age 0. Therefore:

$$n(t-a,0) = Cn'(0)e^{r(t-a)} = Ce^{r(t-a)} \tag{13}$$

Given that

$$n(t,a) = Cn'(a)e^{rt} \tag{14}$$

$$n(t,a) = n(t-a,0)L(0,a) = Ce^{r(t-a)}L(a) \tag{15}$$

We have stable age distribution:

$$Cn'(a)e^{rt} = Ce^{r(t-a)}L(a) \tag{16}$$

$$n'(a) = e^{-ra}L(a) \tag{17}$$

Now, rewriting the boundary condition of births given $n(t,a) = n(t-a,0)L(0,a)$, we have:

$$n(t,0) = \int_0^\infty b(a)n(t-a,0)L(0,a)\ da \tag{18}$$

Given $n(t,a) = Cn'(a)e^{rt}$:

$$n(t,0) = Cn'(0)e^{rt} = Ce^{rt} \tag{19}$$

Therefore, we have:

$$Ce^{rt} = \int_0^\infty b(a)Ce^{r(t-a)}L(0,a)\ da \tag{20}$$

With this, by dividing both sides by $Ce^{rt}$, we have the Lotka-Euler equation:

$$1 = \int_0^\infty b(a)e^{-ra}L(a)\ da \tag{21}$$

where $r$ being the intrinsic growth rate such that if $r > 0$ the population increases, otherwise it decreases. The steady-state density $n_{ss}(a)$ is proportional to $e^{-ra}L(a)$ [5].

We can also define the parameter $R_0 = \int_0^\infty b(a)L(a)\ da$, which, in this case, is the total number of female offspring produced by a mother over her lifespan. With this, it is possible to calculate the average generation time $T$ such that $e^{rT} = R_0$ ($T = \dfrac{ln(R_0)}{r}$), and the average age of reproduction is given by $T' = \dfrac{1}{R_0}\int_0^\infty ab(a)L(a)\ da$.

These structured-population PDEs can be applied in many scenarios, such as the incubation period of infected individuals in a SIR model ($I_{\text{asympt}} \to I_{\text{sympt}}$); blood cell aging; demographics; etc [5].

# 2 Mathematical and Numerical Analysis

For the computational work, we used the Sagemath and Mathematica environments. Firstly, using the presentation by Mahaffy given as reference, we plotted the functions $b(a)$, $\mu(a)$ and $L(a)$, and also calculated $R_0$ in Sage and $r, T$(average generation time) and $T'$(average age of reproduction) in Mathematica, as it is more practical for symbolic computations rather than numerical, such as the necessary steps in order to find an analytical solution for $r$ given (17).

## 2.1 Case Study 1: Example for Age-Structured Models

$$b(a) = \begin{cases} 0.3, 3 < a < 8 \\ 0, \text{otherwise} \end{cases}, \qquad \mu(a) = 0.02e^{0.25a}$$

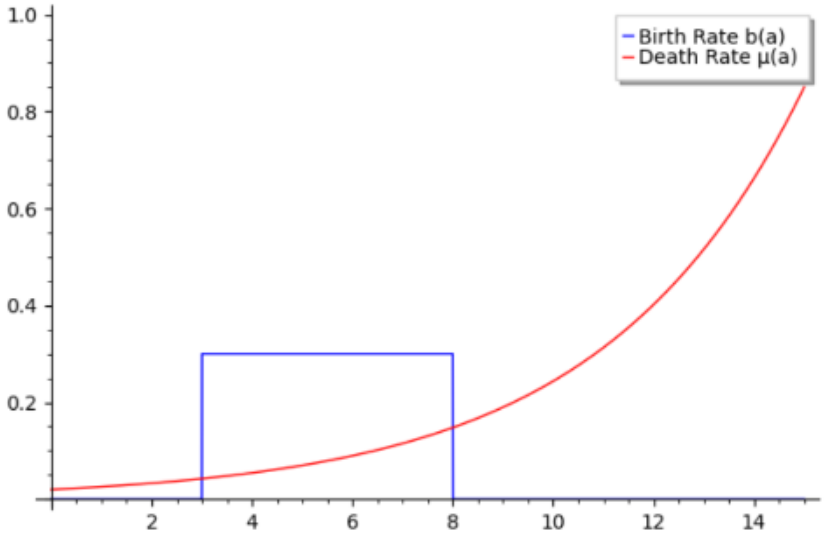


Figure 1: Birth an death rates

The survival function and basic reproduction number are given by:

$$L(a) = e^{-\int_0^a \mu(s)\ ds} = e^{-0.08(e^{0.25a}-1)}$$

$$R_0 = \int_0^\infty b(a)L(a)\ da = \int_3^8 0.3e^{-0.08(e^{0.25a}-1)}\ da = 1.16783$$

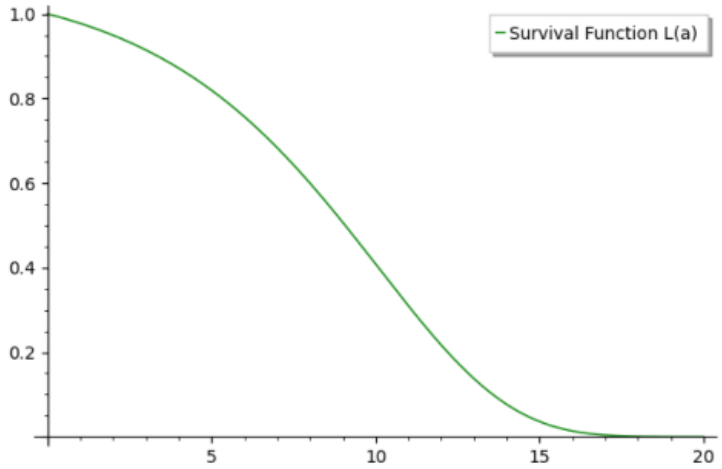


Figure 2: Survival rate

On average, each mother replaces herself with 1.16783 offspring. Now, to find the growth rate $r$:

$$1 = \int_3^8 e^{-ra} L(a) b(a)\ da$$

$$1 = \int_3^8 e^{-ra} (e^{-0.08(e^{0.25a}-1)})(0.3)\ da$$

$$r = 0.02926$$

With the growth rate, we may find the stable age distribution, as well as the average generation time as well as average age of reproduction:

$$n'(a) = e^{-ra} L(a) = e^{-0.02926a} e^{-0.08(e^{0.25a}-1)}$$

$$T = \frac{ln(R_0)}{r} = \frac{ln(1.16783)}{0.02926} = 5.3024$$

$$T' = \frac{1}{R_0} \int_0^\infty ab(a) L(a)\ da = \frac{1}{1.16783} \int_3^8 0.3ae^{-0.08(e^{0.25a}-1)}\ da = 5.33205$$

On average, a female individual will have on average 1.6783 female offspring, and the population grows around 3% per unit of time, given $r \approx 0.029$. A mother replaces herself with $R_0$ offspring in $T = 5.3024$ units of time, and the average age of reproduction is $T' = 5.33205$ units of time.

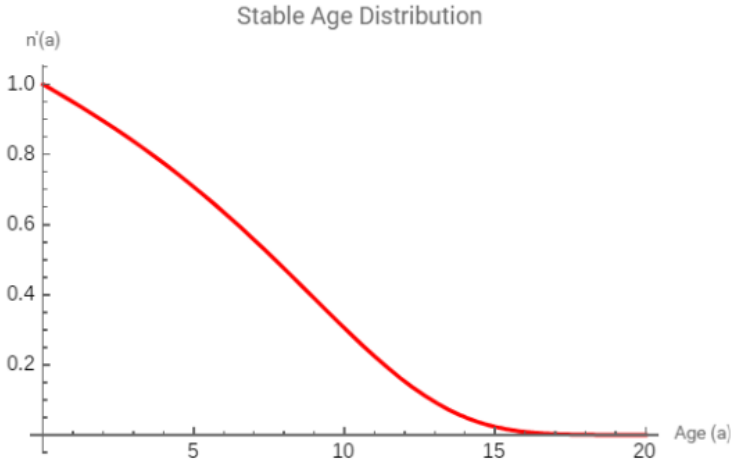


Figure 3: Stable age distribution

## 2.2 Case Study 2: Demographic Variability Among Individuals with and Among Clonal Bacteria Strains [7]

Diversity amongst individuals shapes ecological advancements. This is caused by changes in the environment, genotypic variation, or genotype-by-environment interactions. In this experiment, seven different strains of *Escherichia coli* are used to analyze the fitness of each strain in a highly controlled environment. As a result, this information reveals how genetic diversity affects the growth rate of each strain. For the purposes of this analysis, we will be focusing on only one of the seven strains. After analyzing the graphs provided in the research article (7), we obtained the following functions for the birth rate and the death rate for the bacterial strain MG1655-LM:

$$b(a) = \begin{cases} 2.0 + 0.01a, 0 \leq a \leq 30 \\ 2.4 - 0.0033a, 30 < a \leq 90 \end{cases}, \qquad \mu(a) = 0.0000125(a - 40)^2 + 0.02$$

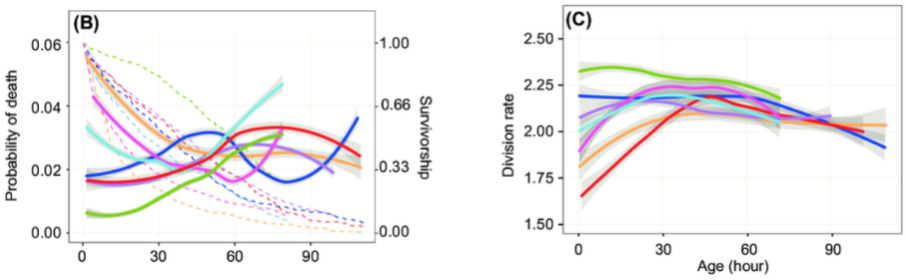


Figure 4: Data from the paper

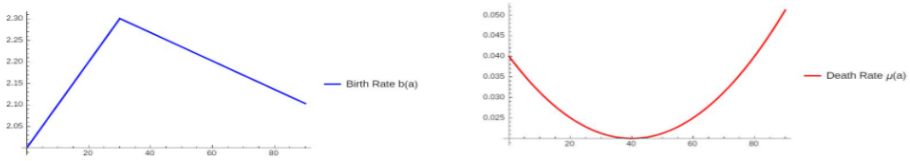


Figure 5: Birth an death rates

Now, we can use the death rate to find the survival function, and we get the following:

$$L(a) = e^{-\int_0^a \mu(s)\ ds} = e^{-0.04a+0.0005a^2-4.16667.10^{-6}a^3}$$

The survival function can now be used to find the basic reproduction number of each mother cell of the MG1655-LM strain.

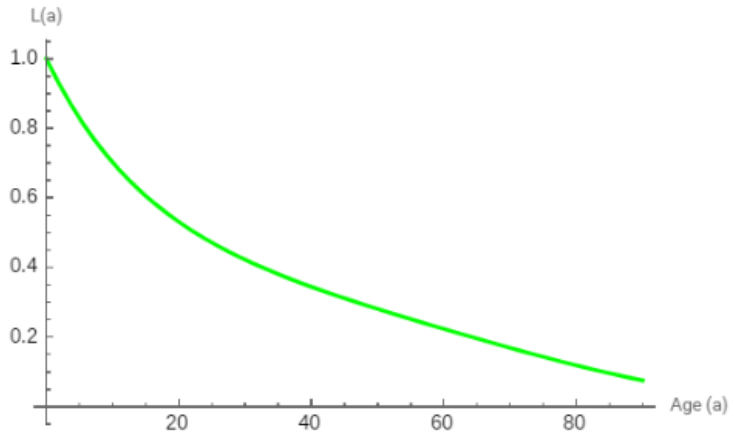


Figure 6: Survival rate

$$R_0 = \int_0^\infty b(a)L(a)\ da = 71.5414$$

So on average, each mother cell will divide on average around 71.5 times. In addition to finding the basic reproduction number, the survival function and birth rate are both used to find the overall growth rate, $r$. With the help of Mathematica, the overall growth rate is seen by the following:

$$1 = \int_0^{30} e^{-ra}L(a)b(a)\ da + \int_{30}^{90} e^{-ra}L(a)b(a)\ da$$

$$1 = \int_0^{30} e^{-ra}(e^{-0.04a+0.0005a^2-4.16667.10^{-6}a^3})(2+0.01a)\ da+$$

$$\int_{30}^{90} e^{-ra}(e^{-0.04a+0.0005a^2-4.16667.10^{-6}a^3})(2.4-0.0033a)\ da$$

$$r = 1.96548$$

Thus, since $r$ is positive the overall population is growing about 196% per unit of time. Since the growth rate has been found, we can obtain the steady-state age distribution of this strain's population:

$$n'(a) = e^{-ra}L(a) = e^{-1.96548a}e^{-0.04a+0.0005a^2-4.16667.10^{-6}a^3}$$

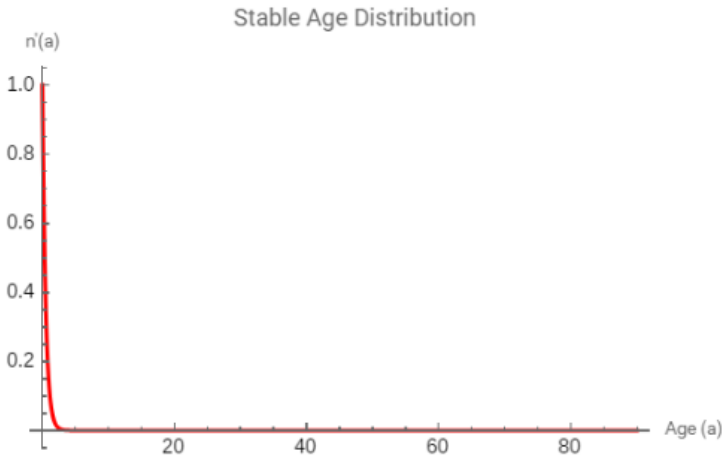


Figure 7: Stable age distribution

Lastly, we can use the survival function and birth rate to find the average age of reproduction, T'. The basic reproduction number, $R_0$, and the overall growth rate, $r$, are used to calculate the average generation time, T.

$$T = \frac{ln(R_0)}{r} = T = \frac{ln(71.5414)}{1.96548} = 2.17264$$
$$T' = \frac{1}{R_0}\int_0^\infty ab(a)L(a)\ da = 29.9504$$

We find that the mother replaces herself with 71.5 offspring per 2.17264-time units, and the average age of reproduction is 29.9504-time units. Overall, the differences in the growth rate of each strain allow us to see how genetic variability among individuals has an impact on their relative fitness. With no limitations on resources, all conditions for each strain were optimal. However, some strains would exhibit high cell lives and division rates, while other strains did not. So in the case of the MG1655-LM strain, it makes sense that it had an overall increased growth rate when placed in optimal conditions.

## 2.3 Case Study 3: Population Dynamics of CD4+ T Cell in Suspension and Collagen Culture Conditions

CD4+ T cells, or T helper cells, are a type of white blood cell that help coordinate the immune response. Specifically, CD4+ T cells secrete cytokines that stimulate other immune cells such as B cells and macrophages, which combats foreign substances like virus or bacteria. Therefore, studying the population dynamics of CD4+ T cells is critical to investigate immune system.

We found the data of estimated proliferation and death rate for CD4+ T cells by

the Flexible and dynamic Algorithm for Model Selection (FAMoS) [6]. Specifically, CD4+ T cells were extracted from the blood of healthy individuals and cultured in suspension or collagen for 0, 2, 4 and 7 days. At these time points, the distribution of the cells by their number of division is calculated, and then they used the FAMoS to estimate the generation-dependent proliferation and death rate per hour[6], which is shown in the table:

| Suspension | | | Collagen | | |
|---|---|---|---|---|---|
| Generation | Proliferation | Death | Generation | Proliferation | Death |
| 0 | 0.0394 | 0.0058 | 0 | 0.1980 | 0.0174 |
| 1 | 0.0042 | 0.0058 | 1 | 0.0107 | 0.0000 |
| 2 | 0.0213 | 0.0000 | 2 | 0.0071 | 0.0000 |
| 3 | 0.0791 | 0.0000 | 3 | 0.0278 | 0.0000 |
| 4 | 0.2020 | 0.0000 | 4 | 0.0984 | 0.0000 |
| 5 | 0.2020 | 0.2090 | 5 | 0.0984 | 0.1620 |
| 6 | 0.0268 | 0.2090 | 6 | 0.0984 | 0.1620 |
| 7 | 0.0268 | 0.0000 | 7 | 0.0000 | 0.1620 |
| 8 | 0.0028 | 0.0000 | 8 | 0.0000 | 0.1620 |
| 9 | 0.0028 | 0.0000 | 9 | 0.0000 | 0.1620 |

Table 1: Rates of proliferation and death

The following are the interpolated proliferation rate $b(a)$ and death rate $\mu(a)$ functions for CD4+ T cells in suspension culture and collagen culture, which is fitted by the cubic spline interpolation provided by *scipy.interpolatepackage* in python. However, the the piece-wise cubic polynomials are too complicated for solving the Lokta-Euler equation to get the numerical answer for the overall growth rate $r$.

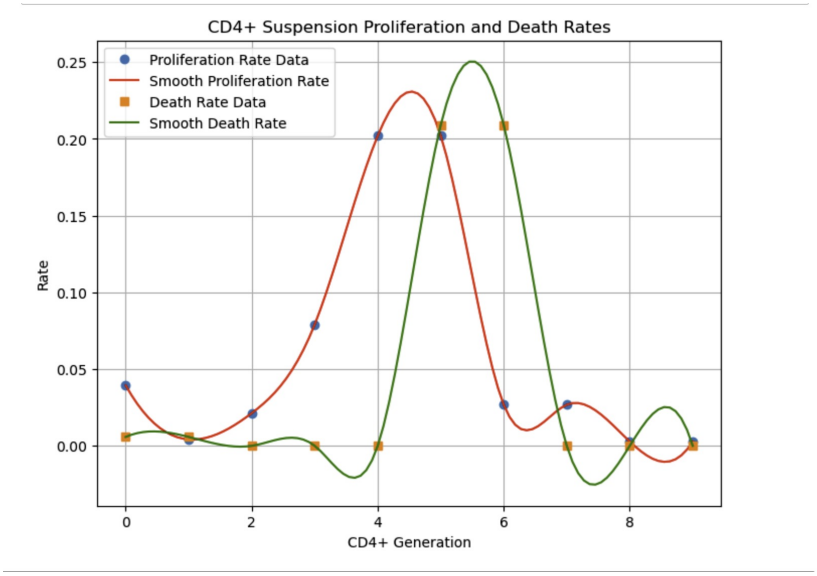


Figure 8: CD4+ T cell Proliferation and Death Rate in Suspension Culture

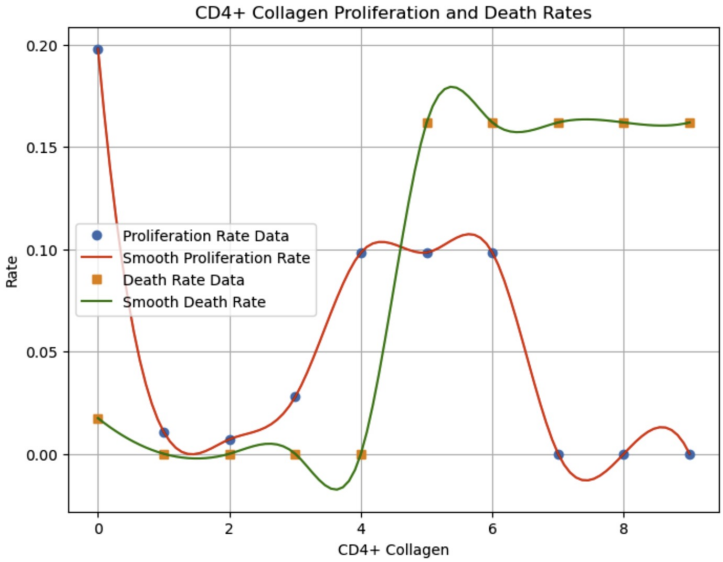


Figure 9: CD4+ T cell Proliferation and Death Rate in Collagen Culture

Therefore, we turned to quadratic regression provided by numpy.polyfit to get the proliferation rate $b(a)$ and death rate $mu(a)$ functions.

For CD4+ T cell cultured in Suspension, the birth and death rates calculated by quadratic regression are:

$$b(a) = -0.006495a^2 + 0.05561a - 0.004436, 0 < a < 9$$
$$\mu(a) = -0.005366a^2 + 0.0528a - 0.0417, 0 < a < 9$$

To calculate $L(a)$, we use *scipy.integrate* in python for integration and get:

$$L(a) = e^{-\int_0^a \mu(s)\ ds} = e^{a(0.001789a^2 - 0.0263991a + 0.0417)}$$

We use secant method implemented by *scipy.optimize* in python to numerically solve for $r$ from the Lokta-Euler Equation and get:

$$\int_0^\infty b(a)e^{-ra}L(a)\ da - 1 = 0$$
$$r = 0.189923$$

Therefore, the overall growth rate for CD4+ T cell in Suspension culture is around 19% per hour.

For CD4+ T cell cultured in Collagen, we perform the same numerical analysis:

$$b(a) = 0.000138a^2 + -0.011429a + 0.101373, 0 < a < 9$$
$$\mu(a) = 0.000395a^2 + 0.020037a - 0.018698, 0 < a < 9$$

$$L(a) = e^{-\int_0^a \mu(s)\ ds} = e^{a*(-0.000132a^2 - 0.010019a + 0.018698)}$$
$$\int_0^\infty b(a)e^{-ra}L(a)\ da - 1 = 0$$
$$r = 0.138334$$

Therefore, the overall growth rate for CD4+ T cell in Collagen culture is around 14% per hour.

$$r_{\text{suspension}} = 0.189923 > r_{\text{collagen}} = 0.138344$$

Therefore, CD4+ T cells grow slightly slower in Collagen culture, which agrees

with the conclusion in the paper[6]. The explanation for the slight difference in growth rates given by the paper is that the collagen matrix provides scaffolds that leads to 3D spacing of the cells. Thus, both the cells and extracellular factors cytokines are in lower concentration, leading to a slight reduction in proliferation capacity. In contrast, in Suspension cultures, the cells sediment the the bottom of the culture dish and thus have higher density for both cells and extracellular factors, which promotes proliferation[6].

# 3 Conclusion

From each example, we have derived the growth rate, $r$, for the presented biological cases above, demonstrating how the Lotka-Euler Equation has provided various parameters of insight regarding age-structured populations. After deriving the equation, we have obtained functions that provide insight into the growth or decline rate of a population. From there, we can deduce parameters such as a steady-state age distribution, average generation time, and the average age of reproduction, allowing for important information about the behaviors of the population to be revealed.

# 4 References


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