# Age-Structured Modeling in Cell Biology

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# Overview of the Age-Structured Model

McKendrick-Von Foerster equation & Birth boundary condition:

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

$$n(t,0) = \int_0^\infty b(a)n(t,a) \ da$$

- $b(a)$: birth rate
- $\mu(a)$: death rate
- $n(t, a)$: population density of age $a$ at time $t$
- $n(t,0)$: total number of births at time $t$

The right-side of the PDE indicates that the only loss of population is through death, which gets more likely as age increases.

# Derivation of McKendrick–Von Foerster equation

The Age-Structured Model serves as a tool that allows us to study and analyze the dynamics of a population. More specifically, it can help us identify the overall growth rate of an age-structured population in demography or cell biology. Abide by chain rule, the dynamics of the system satisfy the following equation:

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

Population is denoted by *n(t,a)* as a function of time *t*, and age *a*. Given that age passes at the same rate as time– da/dt=1, we can rewrite the equation above as:

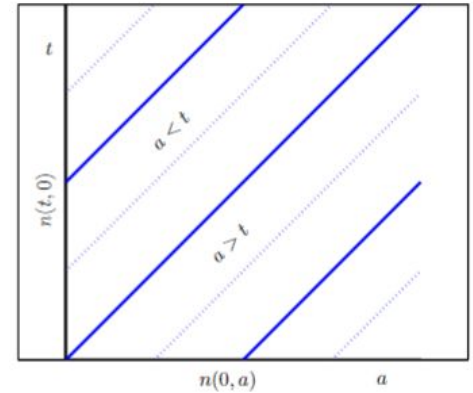$$\frac{d}{dt}n(t,a) = \frac{\partial n}{\partial t} + \frac{\partial n}{\partial a}$$

# Solving for n(t,a) by characteristic lines

The PDE of our system follows the deterministic McKendrick–Von Foerster equation (DMF), rewritten as the following ODE:

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

Along the characteristic line:

$$a(t) = t + c$$



Which has the following solution: $N(t)$ (total population at time $t$)

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

# Solving for n(t,a) – Survival Equation

We define the Survival Equation:

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

Generalizing to calculate the proportion of individuals surviving from age *a* to age *b* (survival rate):

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

From the previous slide, we follow the characteristic lines to obtain the solution:

$$a < t: \qquad n(t,a) = n(t-a,0)L(0,a),$$
$$a > t: \qquad n(t,a) = n(0,a-t)L(a-t,a)$$

# Solving for n(t,a)

Since birth is proportional to the population, we expect an exponential growth or decay depending on the growth rate *r*:

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

Where *n'(a)* is the fraction of individuals still surviving at age a, *C* depends on initial conditions.

In this case, we are considering *a < t*, therefore,

$$n(t, a) = n(t - a, 0)L(0, a)$$

# Introduction to the Lotka-Euler Equation

Assuming the fraction of individuals surviving at birth is 1, *n'(0)=1*

Using the prior definitions of *n(t,a)*, we can find *n'(a)*:

$$Cn'(a)e^{rt} = Cn'(0)e^{r(t-a)}L(a) = Ce^{r(t-a)}L(a)$$

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

Rewriting the boundary condition for births using what we got above, we have:

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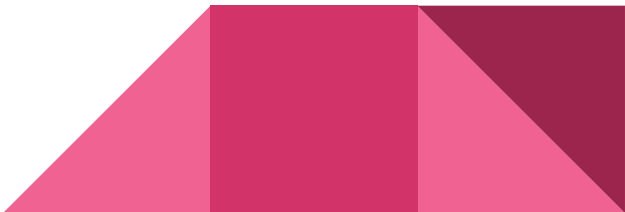
$$n(t,0) = \int_0^\infty b(a)n(t-a,0)L(0,a) \, da$$

# Introduction to the Lotka-Euler Equation (Cont.)

$$Cn'(0)e^{rt} = Ce^{rt} = \int_0^\infty b(a)Cn'(0)e^{r(t-a)}L(a)\ da = \int_0^\infty b(a)Ce^{r(t-a)}L(a)\ da$$

Dividing the equation above by $Ce^{\wedge}\{rt\}$ on both sides, we have that:

$$Ce^{rt}\ /Ce^{rt} = \int_0^\infty b(a)Ce^{rt}e^{-ra}L(a)\ da\ /Ce^{rt}$$

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

This is the Lotka-Euler equation.

# Lotka-Euler Equation - Interesting Parameters

Having defined the full Lotka-Euler equation, we can find some interesting parameters, such as:

- $R_0$ = total number of female offspring produced by a mother over her lifespan
- $T$ = average generation time
- $T'$ = average age of reproduction

$$R_0 = \int_0^\infty b(a)L(a) \ da \qquad T' = \frac{1}{R_0} \int_0^\infty ab(a)L(a) \ da$$
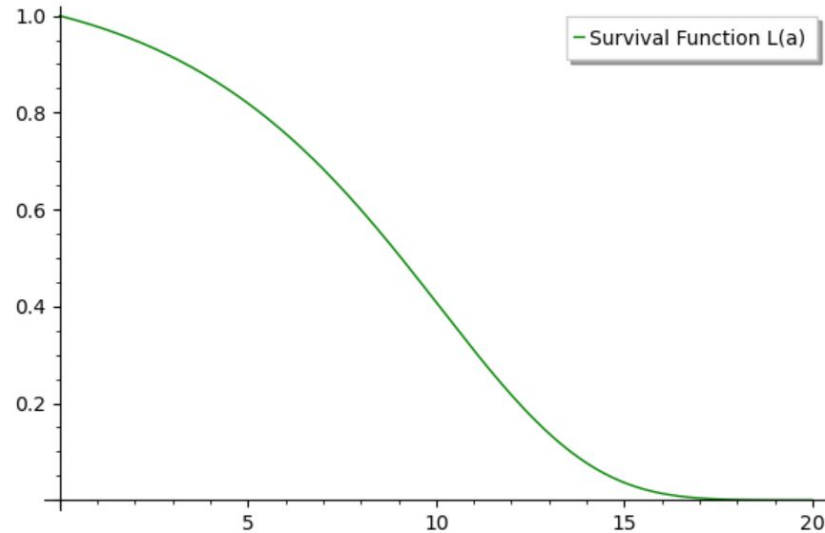
$$T = \frac{ln(R_0)}{r}$$

# Case 1: Math 636 - Mathematical Modeling: Age-Structured Models

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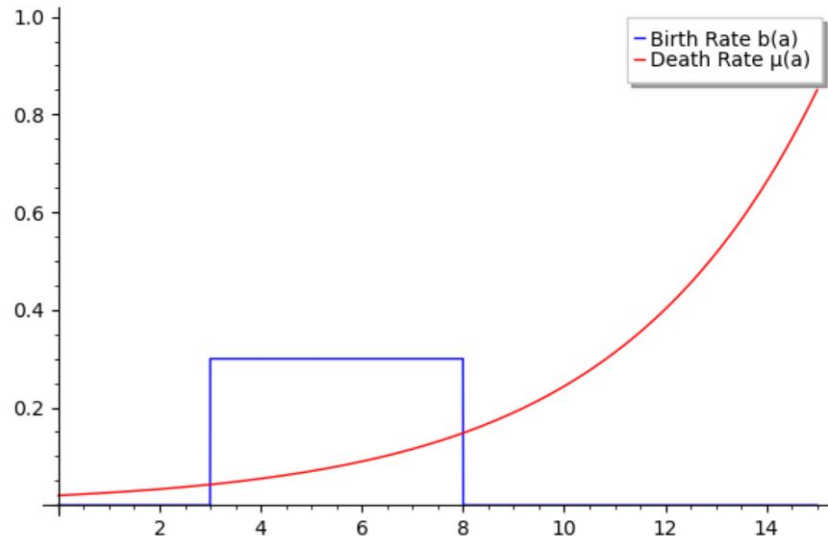
# Mathematical Deductions

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

# Overall Growth Rate Conclusion

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

$$1 = \int_3^8 e^{-ra} (e^{-0.08(e^{0.25a} - 1)})(0.3) \; da$$
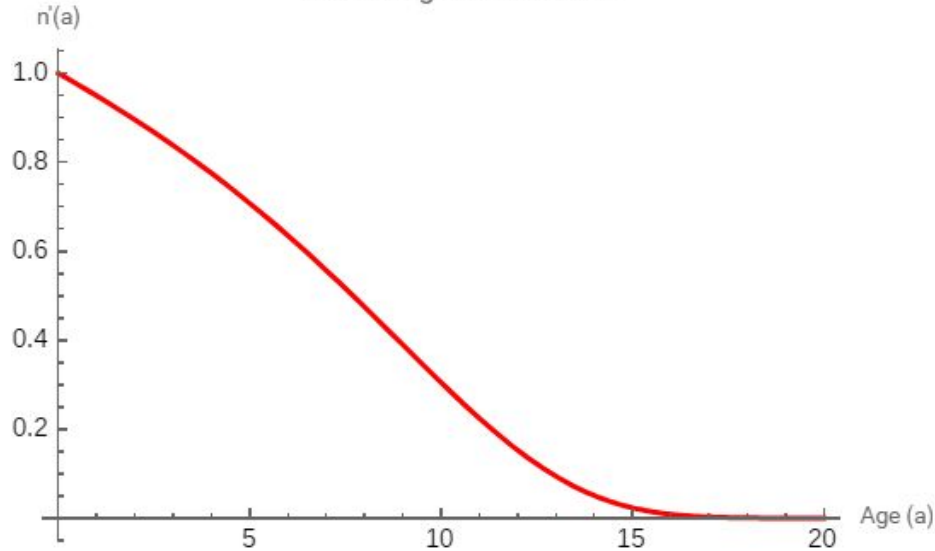
$$r = 0.02926$$

Since *r* is positive, the overall population is growing about 3% per unit of time.

# Mathematical Deductions

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

Stable Age Distribution

# Mathematical Deductions (Cont.)

Basic reproduction number

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

Mother replaces herself with $R_0$ offspring every $T$ units of time

$$T = \frac{ln(R_0)}{r} = \frac{ln(1.16783)}{0.02926} = 5.3024$$
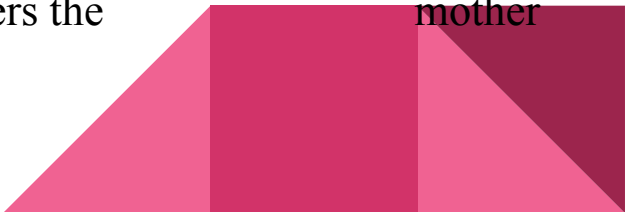
Average age of reproduction

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

# Case 2: Demographic Variability Among Individuals with and Among Clonal Bacteria Strains

Diversity amongst individuals shapes ecological advancements. This is caused by changes in the environment, genotypic variation, or by genotype by environment interactions. Seven different strains of *Escherichia coli* were used in the experiment. We focused on the MG1655-LM strain.

The purpose of the experiment was to analyze the fitness of each strain when the cells are not given a limitation of nutrients and do not have have any external factors.

They used microfluidic technologies on *E. coli* to simulate a highly controlled environment to see how the seven strains of *E. coli*. To analyze the fitness of each strain, the machine tracked the number of cells over a period of time, the lifespan of the mother cells, and the timing and number of divisions. Once the cell wall starts to disintegrate, a chemical enters the                    mother cell to signify its death (emits red signal).
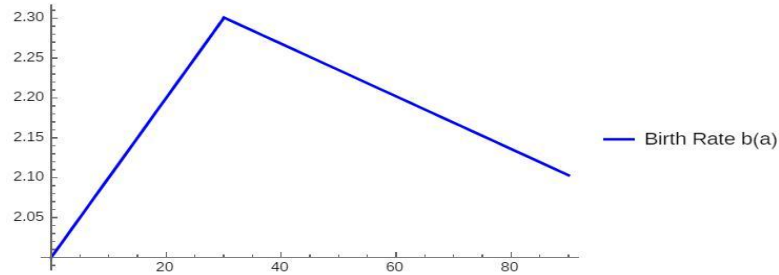
# Graphs
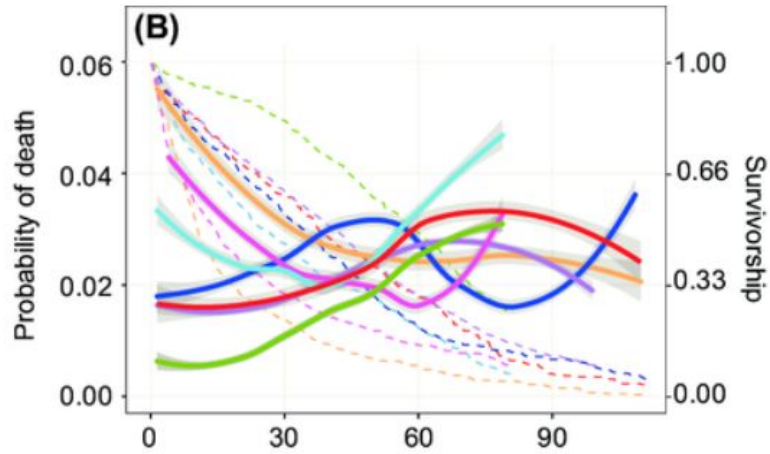


MG1655-LM, N = 505 Cells
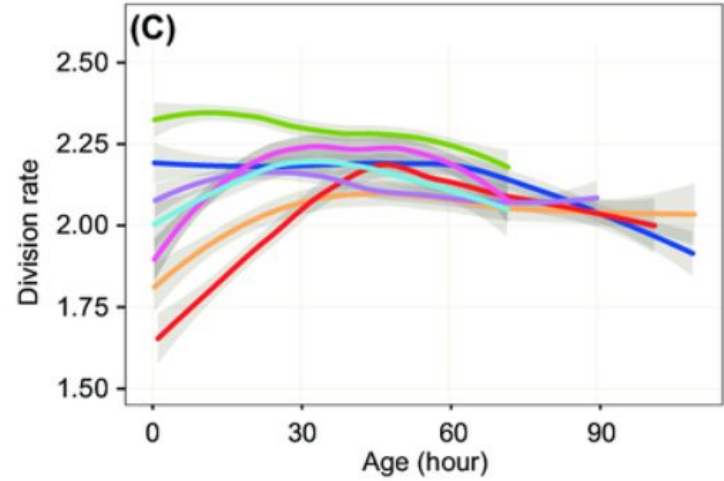
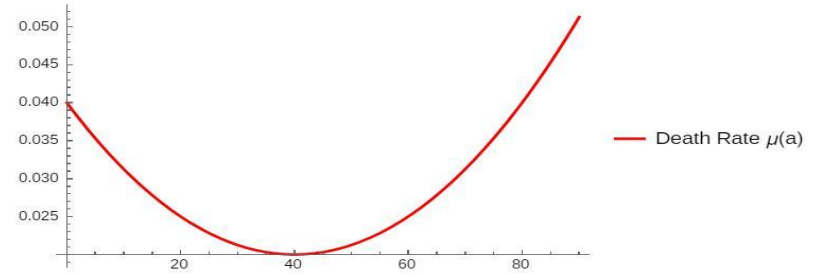# Mathematical Deductions

From the Probability of Death graph (B) and Division Rate graph (C), we used a computational software to extract and estimate the functions for the MG1655-LM strand. We obtain the following equations for the birth and death rates:
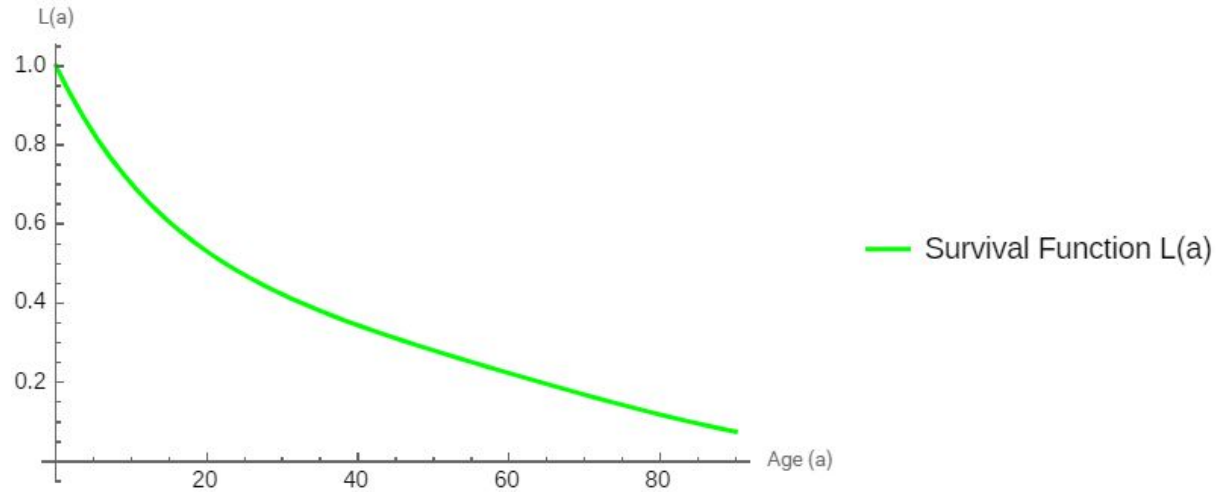


$$b(a) = \begin{cases} 2.0 + 0.01a, & 0 \le a \le 30 \\ 2.4 - 0.0033a, & 30 < a \le 90 \end{cases}$$

$$\mu(a) = 0.0000125(a - 40)^2 + 0.02$$

# Mathematical Deductions

$$L(a) = e^{-\int_0^a \mu(s)\ ds} = e^{-0.04a + 0.0005a^2 - 4.16667 \cdot 10^{-6} a^3}$$

# Overall Growth Rate Conclusion

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

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

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

$$r = 1.96548$$

Since $r$ is positive, the overall population is growing about 196% per unit of time.

# Mathematical Deductions

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



Stable Age Distribution
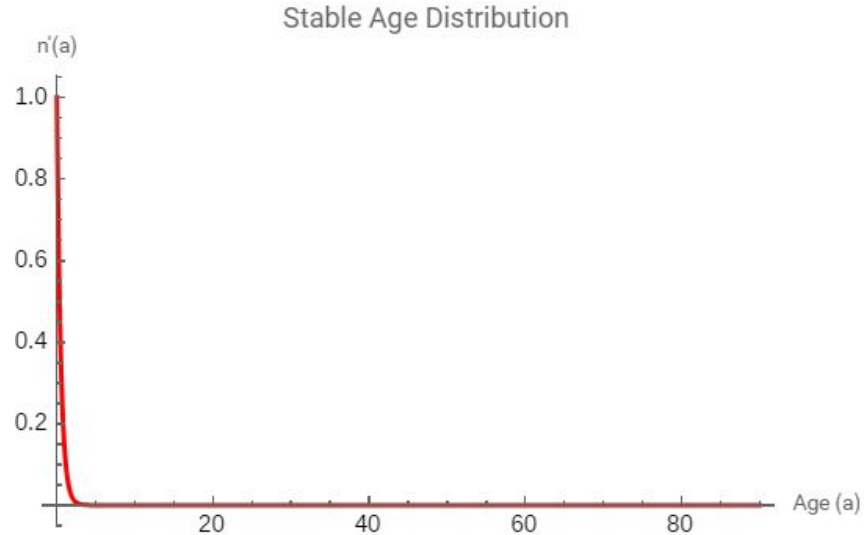
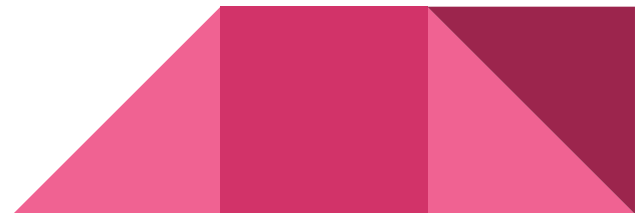# Mathematical Deductions (Cont.)

Basic reproduction number

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

Mother(s) replaces herself with $R_0$ offspring every $T$ units of time

$$T = \frac{ln(R_0)}{r} = T = \frac{ln(71.5414)}{1.96548} = 2.17264$$

Average age of reproduction

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

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

- CD4+ T cells, also known as T helper cells, are a type of white blood cell
- Help coordinate the immune response
- CD4+ T cells secrete cytokines that stimulate other immune cells like B cells and macrophages
- Proliferation and survival of CD4+ T cells is critical for maintaining a robust immune response
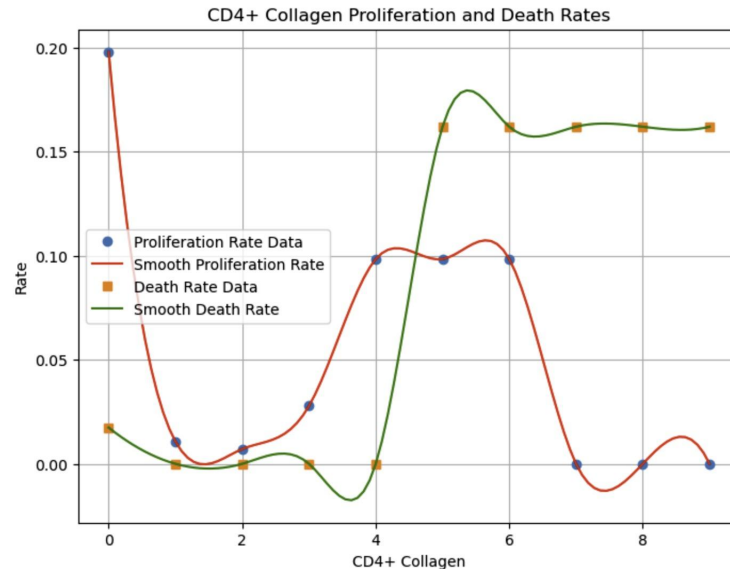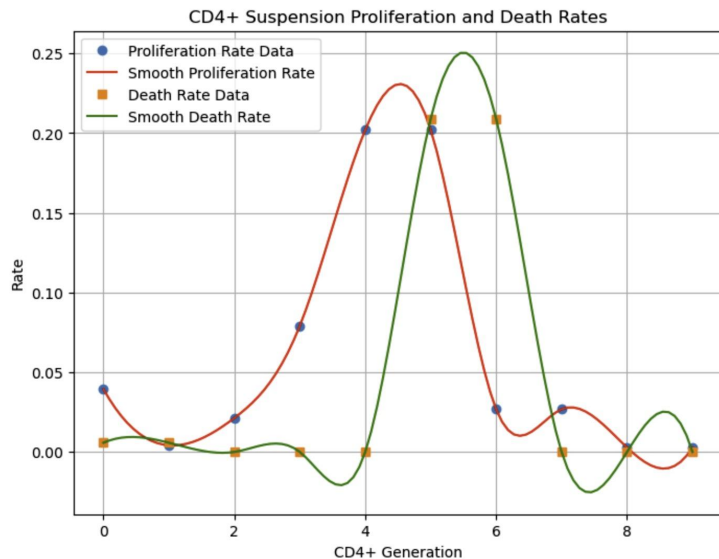
# CD4+ T Cell Proliferation and Death Rates Estimation from Experimental Data

- CD4+ T cells labeled with fluorescent dye (PKH) that dilutes with each cell division
- Cultured in
  - 2D suspension
  - 3D collagen matrix
- Dye dilution profiles measured by flow cytometry at 0, 2, 4, and 7 days
- Proliferation and death rates estimated by fitting a mathematical model to experimental dye dilution data using the FAMoS algorithm.

| | CD4+ suspension | proliferation rate | death rate | CD4+ collagen | proliferation rate.1 | death rate.1 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0.0394 | 0.0058 | 0 | 0.1980 | 0.0174 |
| 1 | 1 | 0.0042 | 0.0058 | 1 | 0.0107 | 0.0000 |
| 2 | 2 | 0.0213 | 0.0000 | 2 | 0.0071 | 0.0000 |
| 3 | 3 | 0.0791 | 0.0000 | 3 | 0.0278 | 0.0000 |
| 4 | 4 | 0.2020 | 0.0000 | 4 | 0.0984 | 0.0000 |
| 5 | 5 | 0.2020 | 0.2090 | 5 | 0.0984 | 0.1620 |
| 6 | 6 | 0.0268 | 0.2090 | 6 | 0.0984 | 0.1620 |
| 7 | 7 | 0.0268 | 0.0000 | 7 | 0.0000 | 0.1620 |
| 8 | 8 | 0.0028 | 0.0000 | 8 | 0.0000 | 0.1620 |
| 9 | 9 | 0.0028 | 0.0000 | 9 | 0.0000 | 0.1620 |

# Interpolated Proliferation Rate *b(a)* and Death Rate *μ(a)*



The interpolated function is too complicated for numerically solving the Lotka-Euler equation.
Quadratic Regression for Proliferation Rate *b(a)* and Death Rate *μ(a)*

# Calculation for Overall Growth Rate r for CD4+ T Cells in Suspension Culture

For CD4+ T cell cultured in Suspension:

$$b(a) = -0.006495a^2 + 0.05561a - 0.004436, 0 < a < 9$$

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

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

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

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

Solving for r using secant method, we get:

$$r = 0.189923$$

# Calculation for Overall Growth Rate r for CD4+ T Cells in Collagen Culture

For CD4+ T cell cultured in Collagen:

$$b(a) = 0.000138a^2 + -0.011429a + 0.101373, 0 < a < 9$$

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

$$L(a) = e^{-\int_0^a \mu(s)\ ds} = e^{a*(-0.000132a^2 - 0.010019a + 0.018698)}$$

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

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

Solving for r using secant method, we get:

$$r = 0.138334$$

# Conclusion: CD4+ T cells grows better in 2D Suspension Culture

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

**Explanations Provided in the Literature:**

2D suspension cultures:

- Cells sediment to bottom of culture dish due to gravity
- High cell density and interactions
- Ample access to nutrients and cytokines in media

3D collagen cultures:

- Collagen matrix provides scaffold for 3D spacing of cells
- Cells are more dispersed, lower local cell density
- Extracellular factors like cytokines may be more limited

# References

- Math 636 - Mathematical Modeling: Age-Structured Models, Joseph M. Mahaffy (Reference given)
- FAMoS: A Flexible and dynamic Algorithm for Model Selection to analyse complex systems dynamics, Gabel, Et Al (https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1007230)
- Jouvet, Lionel, et al. "Demographic Variability and Heterogeneity among Individuals within and among Clonal Bacteria Strains." Nordic Society Oikos, 20 Nov. 2017. (https://nsojournals.onlinelibrary.wiley.com/doi/full/10.1111/oik.04292)
- Euler-Lotka equation. https://en.wikipedia.org/wiki/Euler%E2%80%93Lotka_equation.
- Von Foerster equation. https://en.wikipedia.org/wiki/Von_Foerster_equation.
- Lab 3: Age-structured populations: https://kevintshoemaker.github.io/NRES-470/LAB3.html