Fostering student engagement and collaboration with real-life scenarios in and out of the classroom

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Career Readiness of College Graduates

- "Career Readiness" has been defined by the National Association of Colleges and Employers (NACE) as the attainment and demonstration of requisite **competencies** that prepare college graduates for a successful transition into the workplace:
- teamwork and collaboration; leadership
- critical thinking and problem-solving skills
- ability to leverage existing digital technologies ethically and efficiently to solve problems, complete tasks, and accomplish goals
- Communication skills
- Equity and inclusion

Involving students in research projects

Outside of the classroom

- As Independent Research Projects – Math 299, 399,499
- Presenting at State Conferences
- Virginia Academy of Sciences
  - Fall undergraduate meeting
  - Spring annual meeting
- CNU PAIDEIA research symposium
- CNU CUPOLA research online journal for undergraduates

In the classroom

- Differential Equations class
- Mathematical Modeling class
- Assigning group projects
- Group in class work – using SIMIODE scenarios
- Developed student project on 3-species Lotka-Volterra model with Dr. Brucal-Hallare; published in CODEE

SIMIODE DEMARC – Modeling Scenarios Developer Workshop (Summer 2021)

- With Dr. Brucal-Hallare we developed four modeling scenarios implementing our previous experience working with undergraduate students on research projects
- **The good kind of virus: Oncolytic viruses vs cancer cells**, SIMIODE; 6-017-T-OncolyticViruses; https://www.simiode.org/resources/8471critical thinking and problem-solving skills
- **Fitting the Lotka-Volterra model to time series data with gauseR package**, SIMIODE; 6-067-T-LotkaVolterra, https://www.simiode.org/resources/8555.
- **Should cancer therapy start before or after surgery?** SIMIODE, 1-150-T-CancerTherapy; https://www.simiode.org/resources/8479
- **Analyzing an efficient wireless power transmission system**. SIMIODE, 3-092-T-WirelessPower; https://www.simiode.org/resources/8515

- In this project, students explore oncolytic virotherapy using systems of differential equations and numerical simulations.
- The first activity guides the students in simulating the dynamics between the uninfected cancer cells x(t), the oncolytic virus-infected cancer cells y(t), and the oncolytic viruses v(t); the model consists of three differential equations.
- The second activity builds upon the previous model and guides the students in exploring the dynamics between x(t),y(t),v(t), and the immune system cells z(t); the model consists of four differential equations.
- The numerical simulation uses a Python code administered via an internet-based environment called Glow Script.

The good kind of virus: Oncolytic viruses vs cancer cells

Activity I: Simulating virotherapy on cancer cells

It is very important to understand each term that comprise the equations in a mathematical model.

$$\begin{cases} \frac{dx}{dt} = \alpha x - \beta xv \\ \frac{dy}{dt} = \beta xv - \delta y \\ \frac{dv}{dt} = N\delta y - \gamma v \end{cases}$$

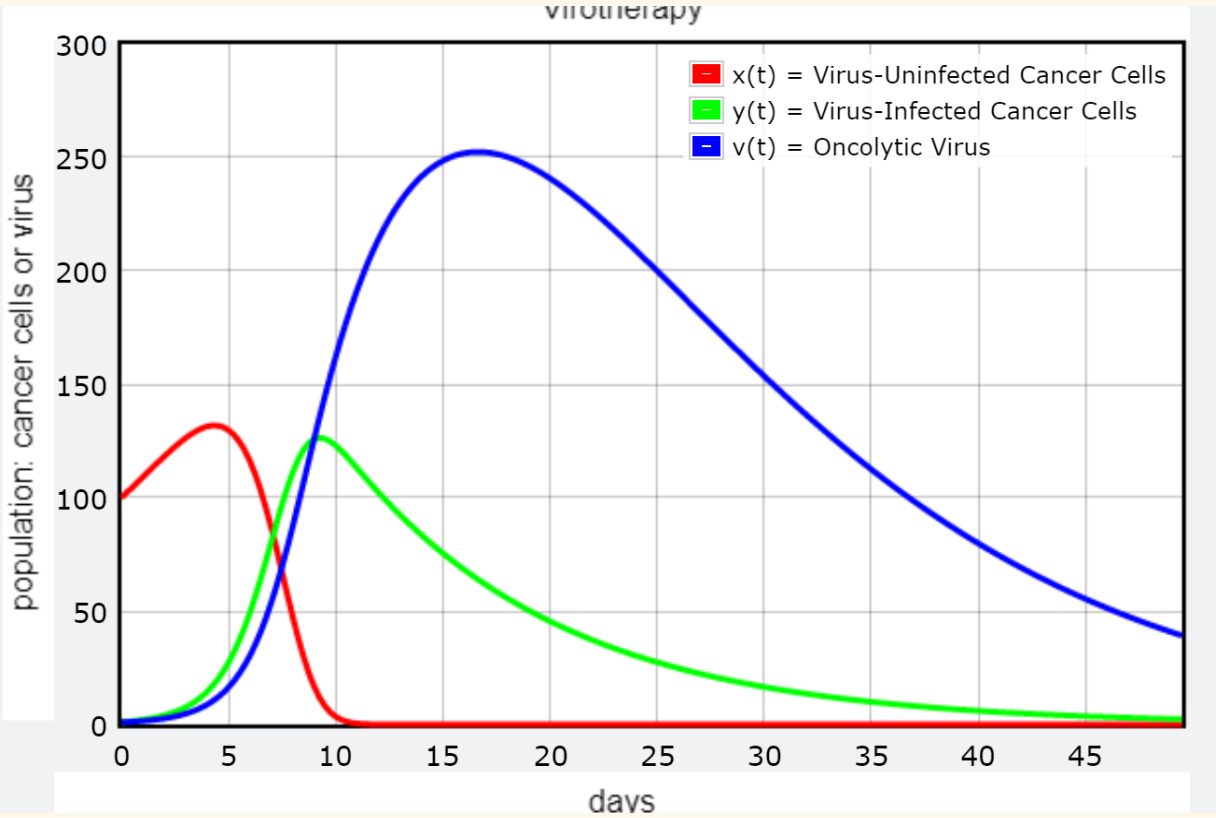
Initial conditions: $x(0), y(0), v(0)$

Term	Rate description	Hints
αx		Set $\beta = 0$ in the first equation. Does the resulting equation look familiar?
βxv		This term appears in the first equation, with a negative sign. It also appears in the second equation for $\frac{dy}{dt}$ but it does not involve y.
δy		Set $\beta = 0$ in the second equation. Why is this term negative?
$N\delta y$		N is the replicating number of the oncolytic virus. Remember that a virus relies on the host cell for its survival!
γv		Why is this term negative?

Answers

αx	growth rate of the cancer cells that are not infected by the oncolytic virus
βxz	infection rate of the cancer cells by the oncolytic virus
δy	death rate of oncolytic virus-infected cancer cells to include natural death and virus-induced death
$N\delta y$	growth rate of oncolytic virus due to infecting cancer cells
γv	death rate of the oncolytic virus

Study time-evolution graph for the populations x(t),y(t),v(t) with the given initial values



- Provided Python code in GlowScript
- Easy for the students to use and modify the program without the need to install any programing language on their computers; only a web-browser is needed
- Implemented calculus concepts for min/max and inflection points when analyzing the graphs
- Used concepts of concavity and increasing/decreasing of a function

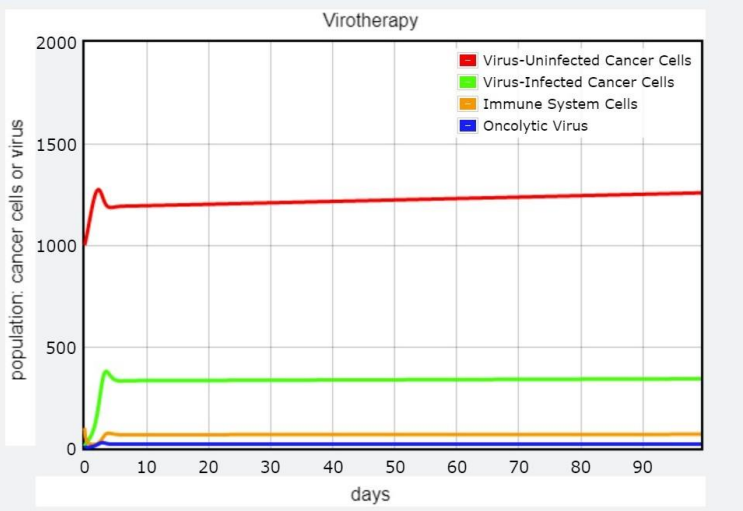
Activity II: Simulating virotherapy with immune system effects

- In experiments, viral therapy was not initially successful
- Immune cells recognize the infected cancer cells and destroy them before the virus could replicate to its full potential
- Effect of the immune system effect was included in the model
- Suppression of the immune system was also included

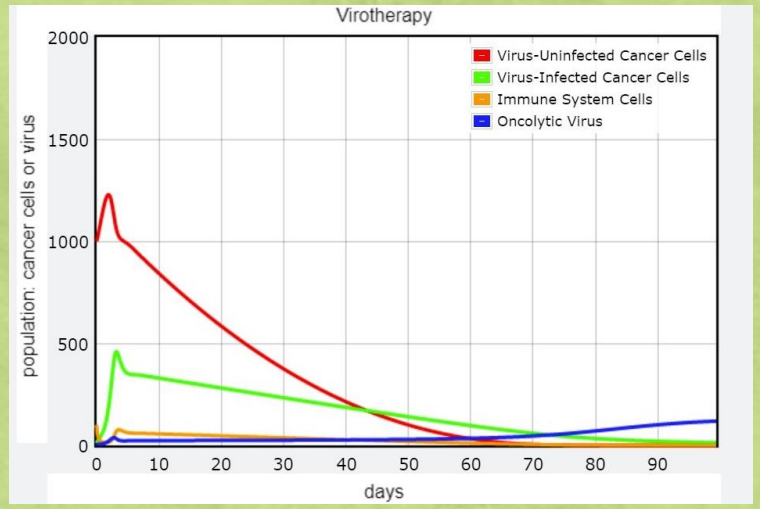
$$\begin{cases} \frac{dx}{dt} = \alpha x - \beta xv \\ \frac{dy}{dt} = \beta xv - syz - \delta y \\ \frac{dz}{dt} = syz - \omega z^2 - ez \\ \frac{dv}{dt} = N\delta y - nvz - \gamma v \end{cases}$$

- Simplified version of a model from Chou, C.S. and A. Friedman, Introduction to Mathematical Biology: Modeling, Analysis, and Simulations. 2010. Springer. 172 p.

syz	stimulation rate of immune cells by infected cells
ωz^2	clearing rate of immune cells
nvz	killing rate of the virus by immune cells
ez	death rate of immune cells due to immune-suppressor drug; $0 \leq e \leq 1$

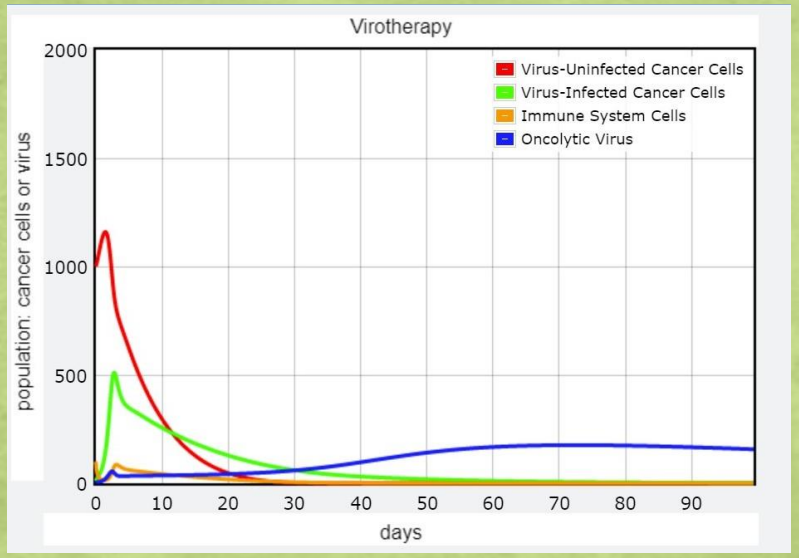


No chemotherapy for immune system suppression applied ($e = 0$).

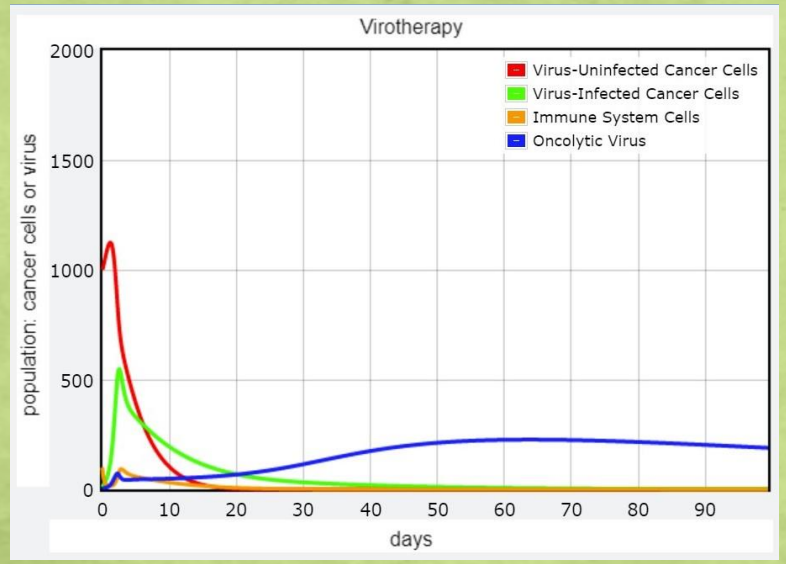


Chemotherapy to suppress the immune system applied ($e = 0.5$).
Cancer cells replicating number $N = 4$.

- Without and with immune system suppressant



Chemotherapy applied $e = 0.5$.
Virus replication number $N = 6$.



Virus replication number further increased to $N = 8$.

- Effect of the virus replication number N

- When the parameter **s** is increased it means that immune cells are recognizing the infected cancer cells more readily. The effect of increased **s** is a much larger number of immune cells, lots of increased cancer death, and decrease in infected cancer cells as well as lower amount of free virus particles.
- Increasing **β** decreases the number of cancer cells alive (infected, immune, and regular), increases death rate of cancer cells, and overall number of virus particles not in cells.
- Increasing **e** would mean either higher dose or adding another different drug that suppresses the immune system;
- Increasing **e** only works up to 1; anything above that has no effect on the cancer-immune system interactions under virotherapy.
- Increasing **e** kills cancer cells faster over time but also increases amount of virus particles in the body, lowers significantly immune cell count.

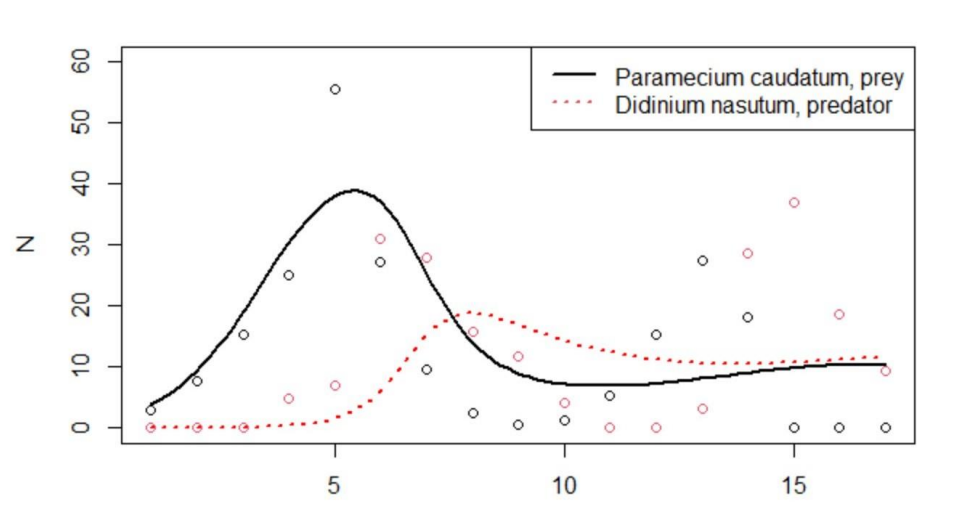
Mathematical Modeling

- While the complexity of oncolytic dynamics is well known, it is difficult to measure the contribution of each component of the oncolytic system
- Models can provide informed hypotheses for experimental testing and identify potential targets for clinical manipulation of the oncolytic response.
- Mathematical modeling of the treatment responses represents an attractive avenue towards narrowing the set of possibilities that should be tested in preclinical models and in the clinical setting.
- Shows that mathematics can be a powerful tool in furthering biological understanding
- Here we show how mathematical models can be used to test different assumptions by varying the models' parameters.
- They provide deeper insights into questions that **cannot be addressed by clinical or experimental studies alone.**

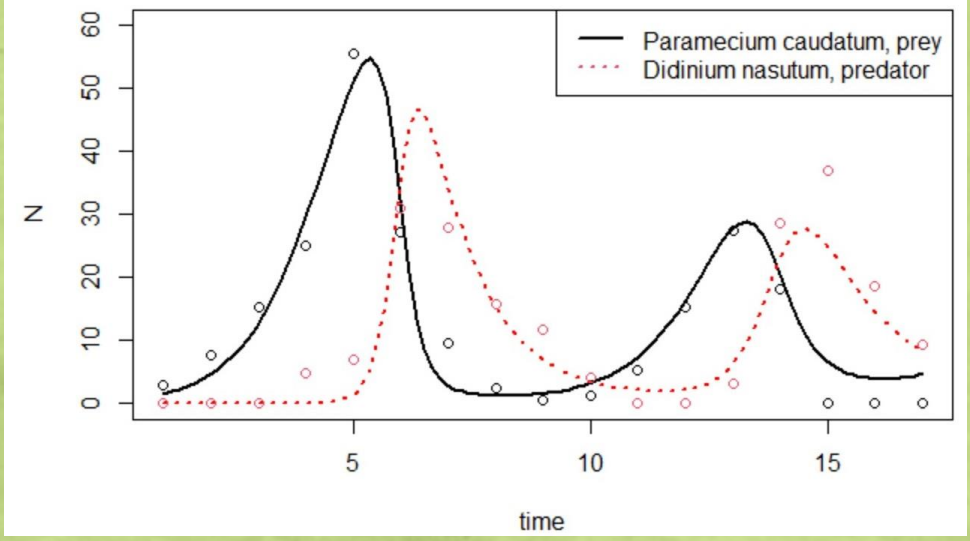
- This modeling scenario guides students through the process of **fitting the Lotka-Volterra model of two differential equations to a real time series observational data**.
- Uses the capabilities of R and R studio, and the gauseR package - a collection of tools specialized for fitting the Lotka-Volterra models to time series data.
- Students start the modeling scenario by fitting the **logistic growth** model to a given set of data while they are provided with the R code.
- Next, they are guided through the process of fitting the Lotka-Volterra model to a time series data of **predator-prey** and of **two competing species**.
- Students learn how to **extract the model parameters and make predictions for the future behavior** of the interacting species using the fitted mathematical model

Fitting the Lotka-Volterra Model to Time Series Data with gauseR Package

Model Fitting in R



Without optimizer



With optimizer

$$\begin{cases} \frac{dN}{Ndt} = r + aN + bP \\ \frac{dP}{Pdt} = e + cP + dN \end{cases}$$

- Data from Gause's lab experiments on prey-predator systems
- Lotka-Volterra is highly sensitive to smallest parameter changes
- Optimizer is needed for obtaining a model of best fit
- gauseR package has a build-in optimization-function (*optim*)

How these projects were extended beyond the classroom

Collaborative Research Experience for Undergraduates

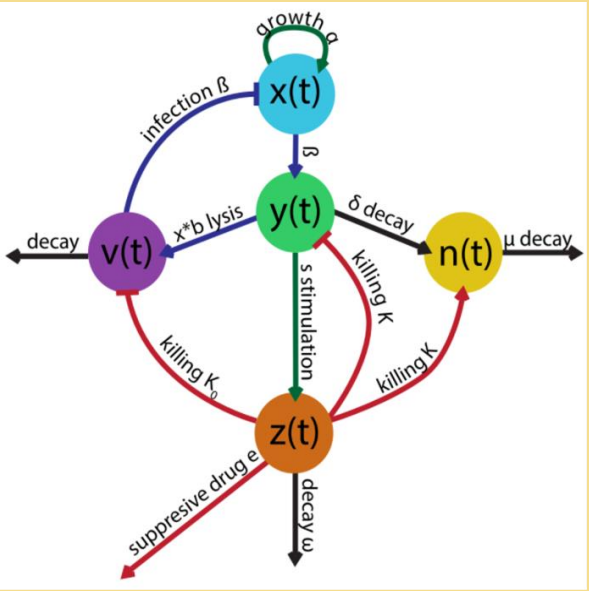
- CURM Grant - NSF supported through the Center of Undergraduate Research in Mathematics
- These projects were the foundation from where our research groups started
- Students extended them further
- 9 students, grouped by interests in a group of 3
- Interdisciplinary approach – from different STEM majors

With Dr. Brucal-Hallare from Norfolk State Uniersity

Group 1: Mathematical Modeling: Effect of Virotherapy on Cancer Tumors

- Literature review
- Analytical Approach – finding equilibria and their stability
- We derived the equation for the rate of change of the radius of the tumor
- Numerical simulations using "real-data" obtained from observational/clinical studies
- Sensitivity analysis of the model with respect to the model parameters

$$\begin{cases} \frac{dx}{dt} = \alpha x - \beta x v \\ \frac{dy}{dt} = \beta x v - k y z - \delta y \\ \frac{dz}{dt} = s y z - \omega z^2 - e z \\ \frac{dn}{dt} = k y z + \delta y - \mu n \\ \frac{dv}{dt} = b\delta y - k_0 v z - \gamma v \end{cases}$$

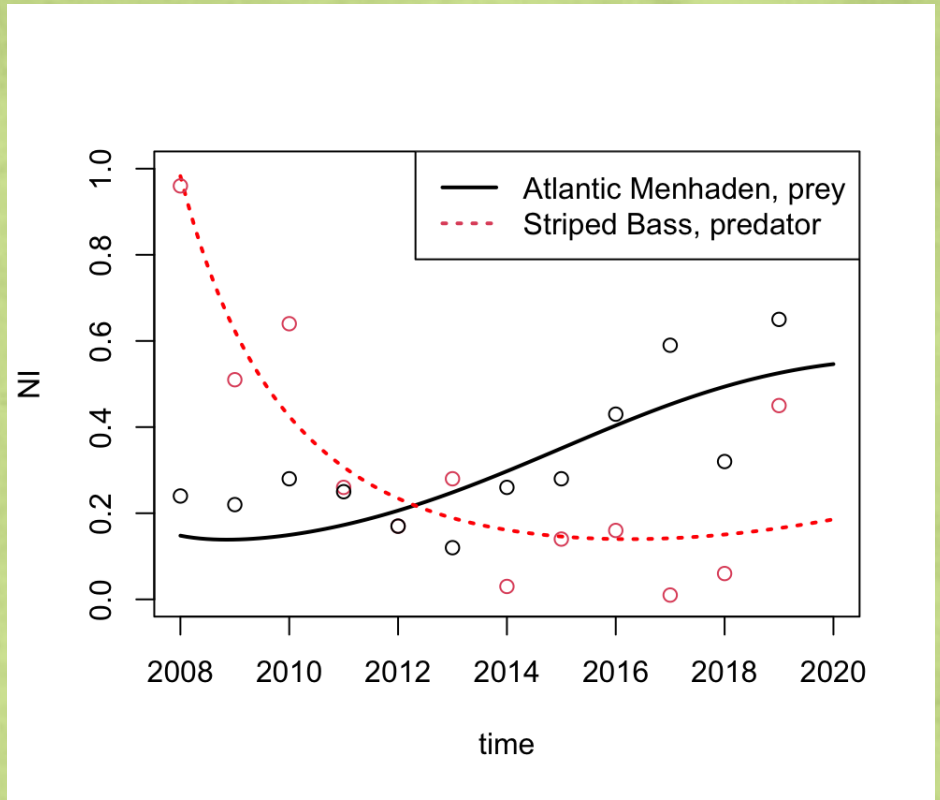


$$\frac{dR}{dt} = \frac{R}{\theta_0}(\alpha x + syz - \omega z^2 - ez - \mu n)$$

$$\text{where } \theta_0 = x_0 + y_0 + z_0 + n_o$$

Group 2:Bioeconomic Harvesting in a PredatoroPrey System: A Case Study in the Chesapeake Bay Fisheries

- Extended the R-project to a real data from the Chesapeake Bay fisheries on menhaden (prey) and striped bass(predator)
- For the found model parameters we predicted the long-term behaviors
- Related it to the equilibrium and its stability
- Extended the research further to ask how to balance the sustainability of the ecosystem while making the harvesting economically optimal

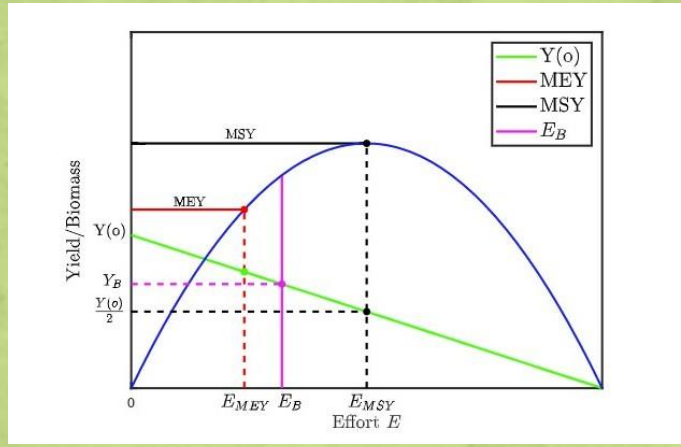


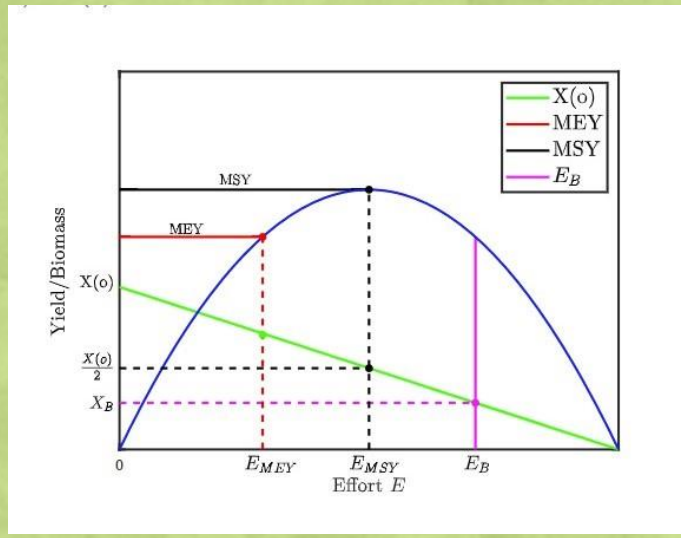
Study on different policy approaches in respect to harvesting effort

Harvesting Effort E
(as an independent variable)

- Maximum Sustainable Yield (MSY) E_{MSY}
- Maximum Economic Yield (MEY) E_{MEY}
- Bioeconomic equilibriums (E_B)
- Connecting the three concepts – E_{MSY}, E_{MEY}, E_B
- Optimal Harvesting Control

Harvesting the prey only






Collaboration for Undergraduate Research in Mathematics
CURM @ (CNU + NSU)
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Calvin Klein

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Thank you!

Questions?