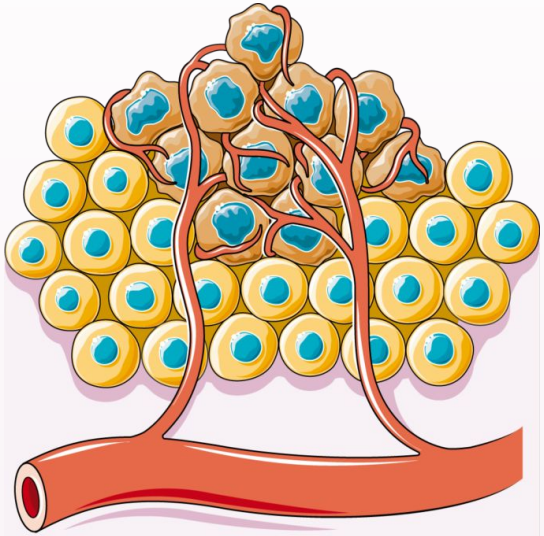


Param Hansa Center for Computational Oncology

OncoAngi

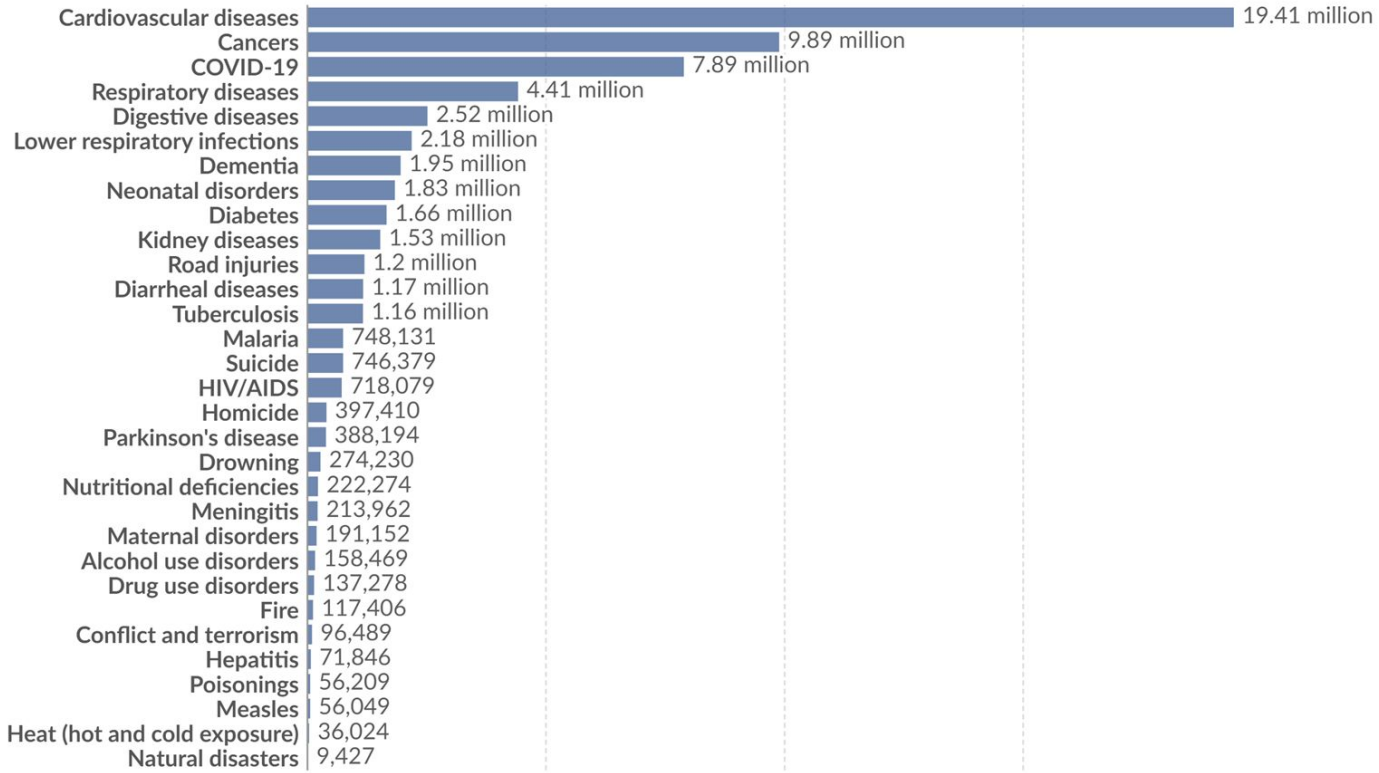
Abhishek Raje
Ashna Narain
Gopal Kulkarni
Pratosh Tiwari
Vikas Kumar

Code Credits:Ernesto Lima

5th July 2024

Causes of death, World, 2021

The estimated annual number of deaths from each cause. Estimates come with wide uncertainties, especially for countries with poor vital registration[1].

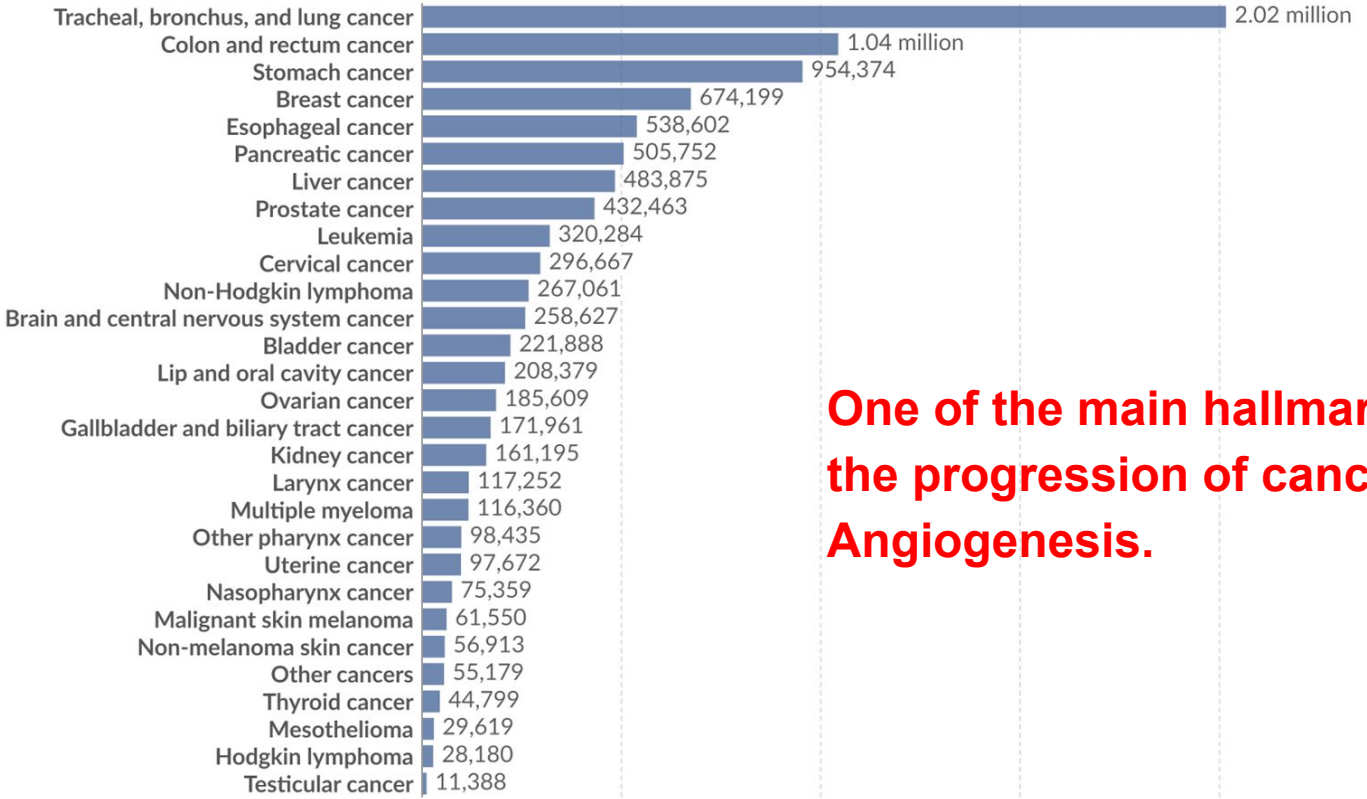


Data source: IHME, Global Burden of Disease (2024)

Cancer deaths by type, World, 2021

Total annual number of deaths from cancers across all ages and both sexes, broken down by cancer type.

Our World in Data



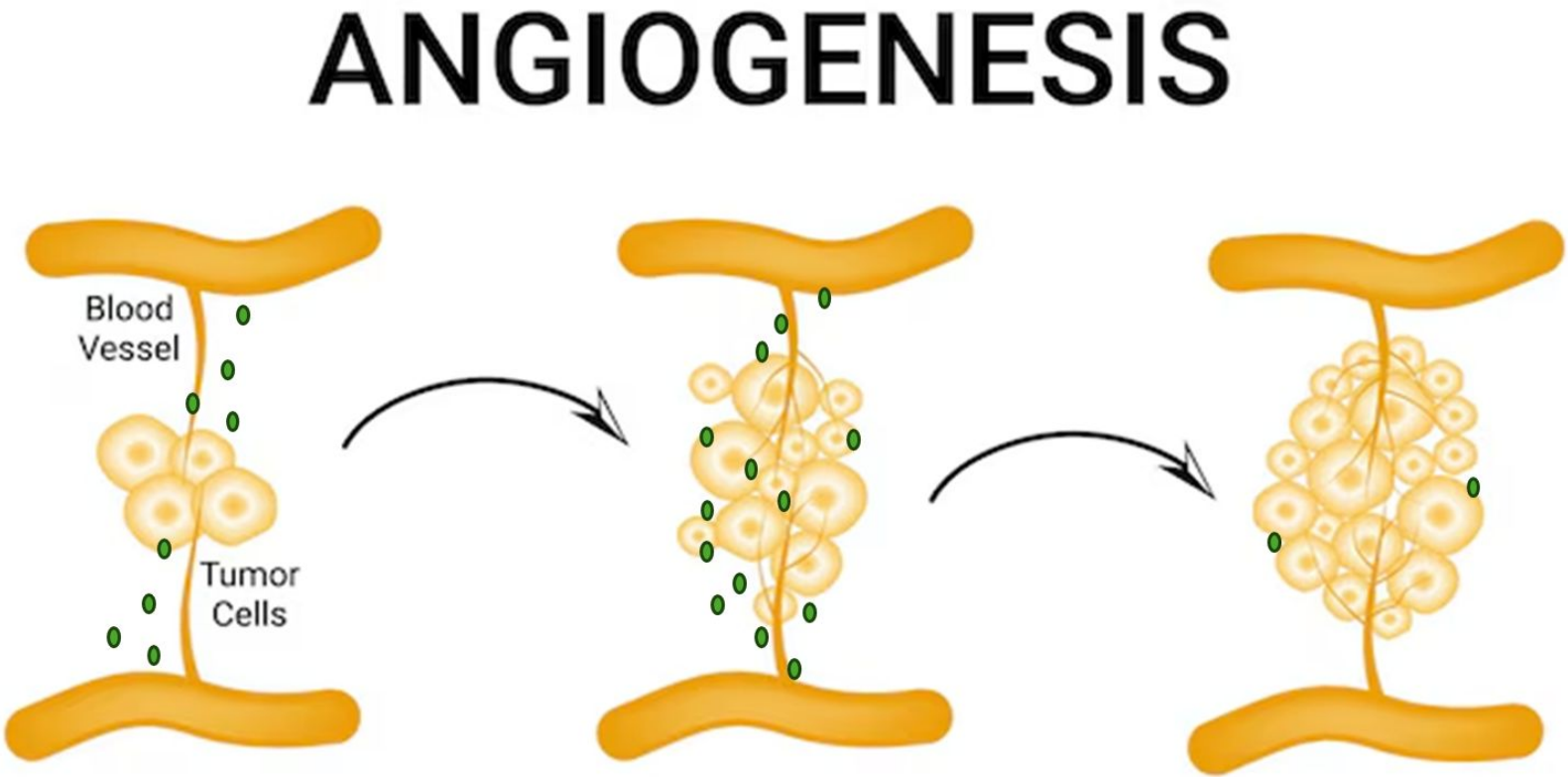
One of the main hallmarks of the progression of cancer is Angiogenesis.

Data source: IHME, Global Burden of Disease (2024)

OurWorldInData.org/cancer | CC BY

https://doi.org/10.1016/j.ctarc.2021.100422

Angiogenesis and Cancer Progress



- Angiogenic factors (VEGFs)

https://doi.org/10.1038/s41392-023-01460-1

Problem Statement

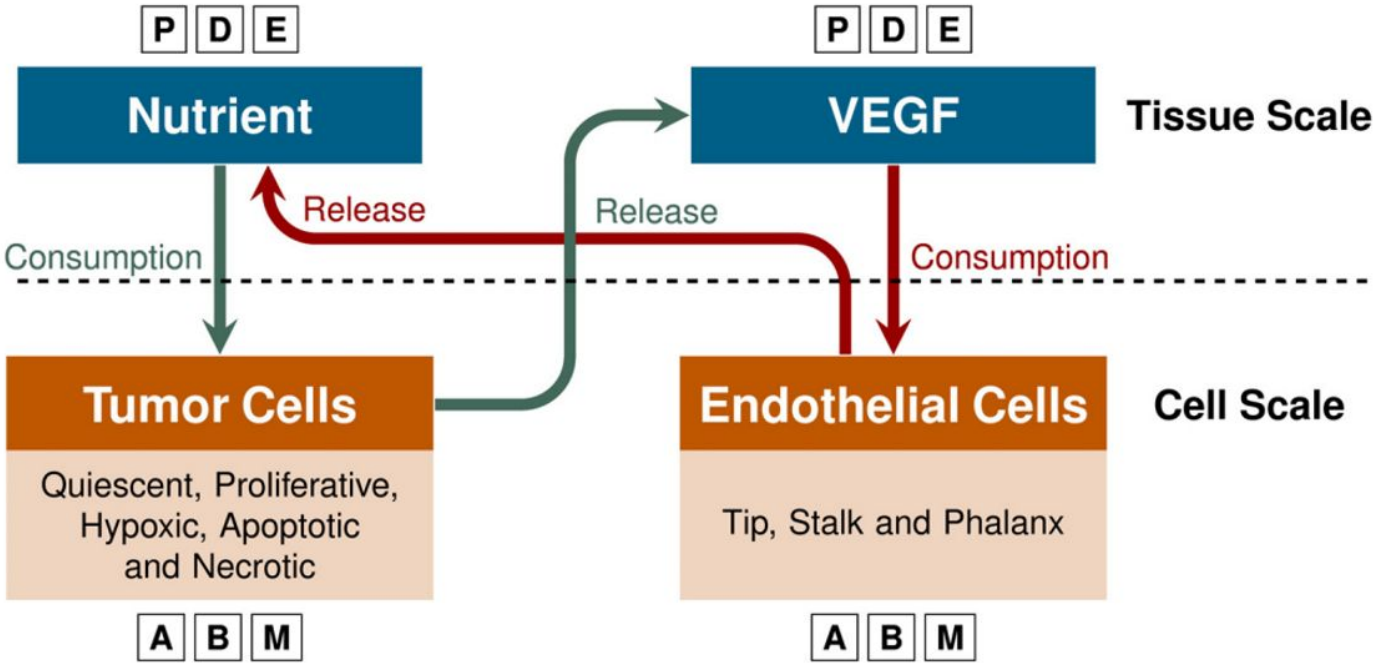
A multi-scale hybrid model that integrates angiogenesis into tumor growth to study the effect of cytotoxic-T cells on cancer cells under anti-angiogenic drug treatment.

Previous Objectives

- To simulate **tumor growth and immune cell interaction** with angiogenesis.
- To predict the **in vivo tumor responses to drugs** (Sunitinib) with different efficacies.
- To analyse **phenotypic behavior and dynamics** of tumor and endothelial cells with and without drug administration.

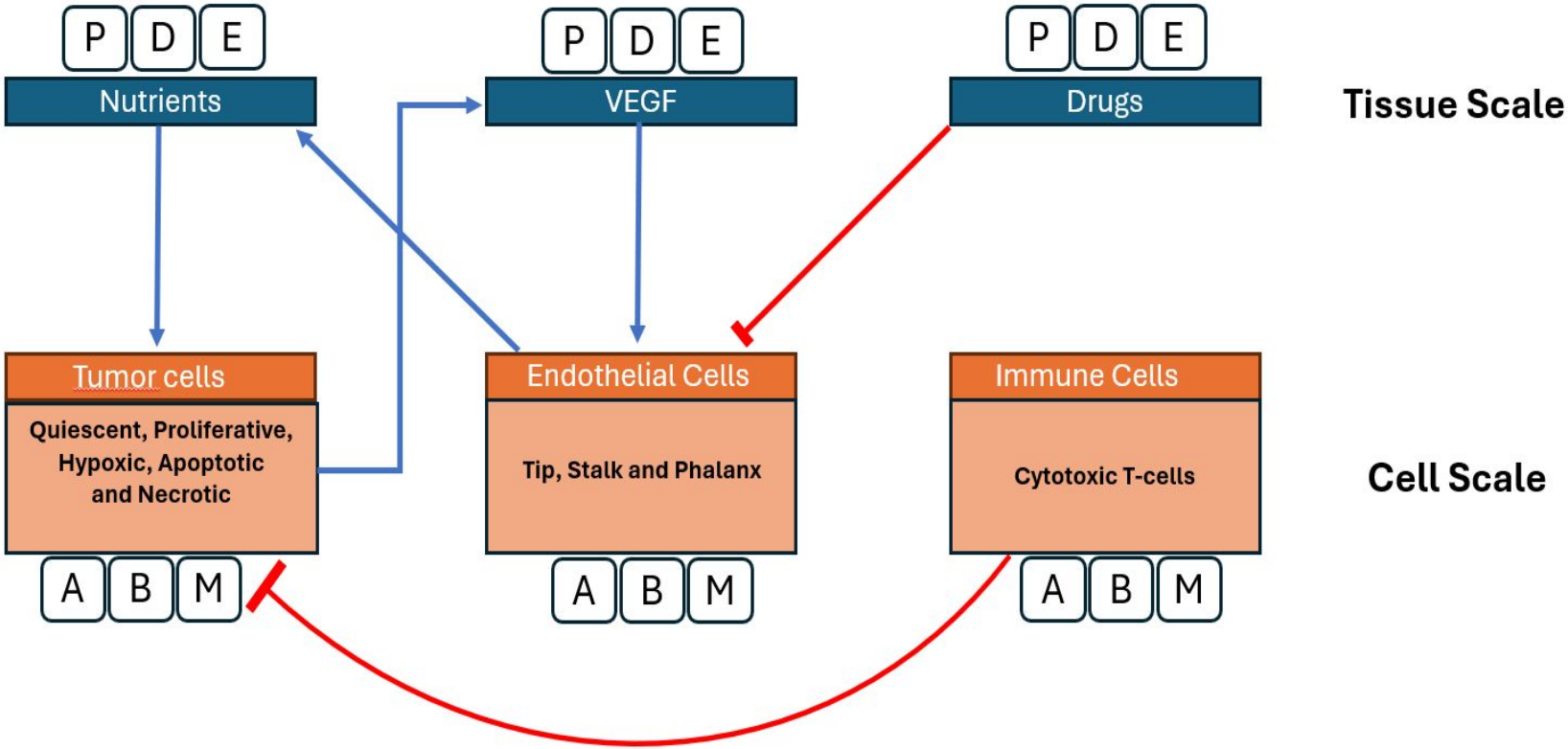
Model Development

Initial Model |



Caleb M. Phillips.et al, 2020

Our Model


P D E
Nutrients
P D E
VEGF
P D E
Drugs
Tissue Scale
Tumor cells
Quiescent, Proliferative, Hypoxic, Apoptotic and Necrotic
Endothelial Cells
Tip, Stalk and Phalanx
Immune Cells
Cytotoxic T-cells
Cell Scale
A B M
A B M
A B M

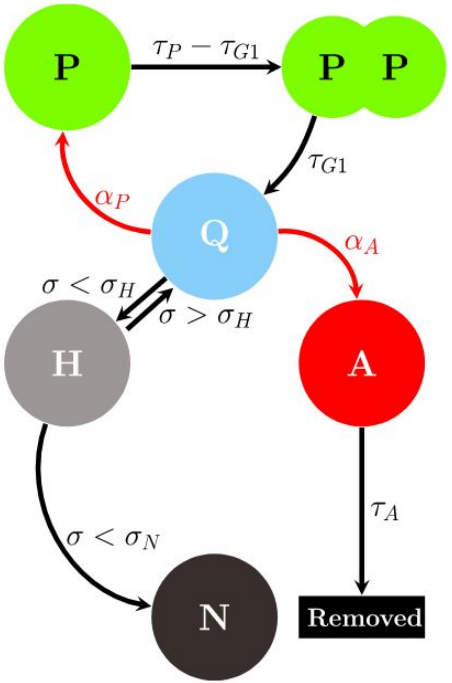
A set of rules to determine the migration of endothelial cells, branching of vessel sprouts, the interaction of cytotoxic T cells with tumor cells, and the tumor cells phenotypic switching behavior

Properties of the agents:

- Phenotypic switching of the cells
- Quiescence
- Apoptosis
- Necrosis
- Migration
- Proliferation

Caleb M. Phillips.et al,2020

Phenotypic Switching in Tumour Cells



Q **Quiescent cell:** cell in the phase *G*0 of the cell cycle

P **Proliferative cell:** cell undergoing mitosis

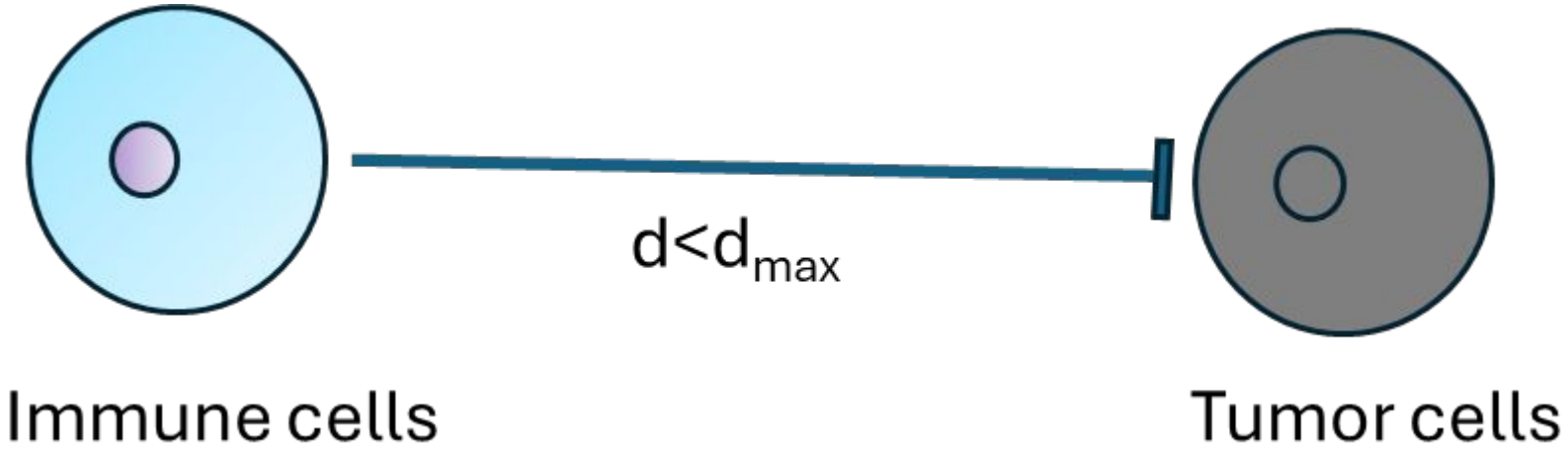
H **Hypoxic cell:** cell undergoing nutrient stress

A **Apoptotic cell:** cell undergoing a programmed cell death

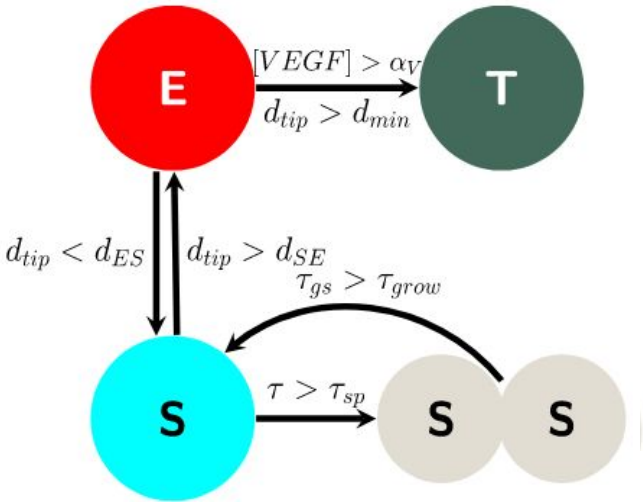
N **Necrotic cell:** cell undergoing nutrient shortage

T-Cell Contact Mediated Tumour Cell Apoptosis

In this model, when a T-cell encounters a tumor cell, it has a probability *p* of killing the tumor cell through apoptosis.



Phenotypic Switching in Endothelial Cells



E **Phalanx cell:** endothelial cell constituting the blood vessel wall

S **Stalk cell:** endothelial cell with increased proliferation

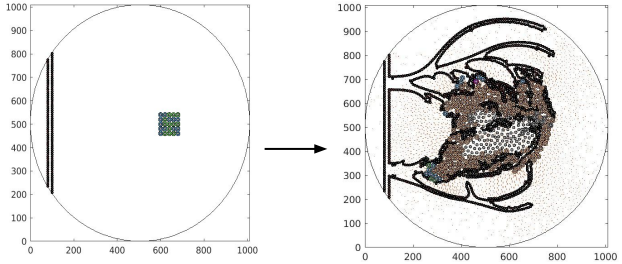
T **Tip cell:** endothelial cell with increased migration toward VEGF gradient

Model Simulation and Results

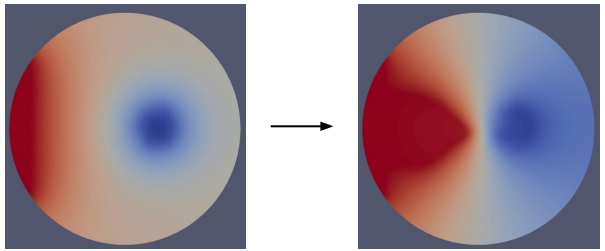
Model simulations without & with drug (Sunitinib)

Initial Model

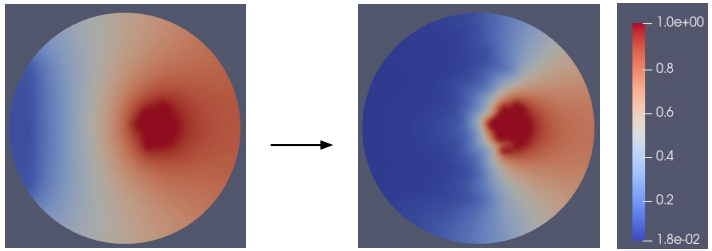
ABM



Nutrient

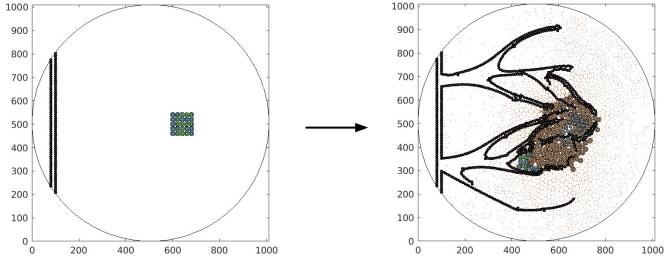


VEGF

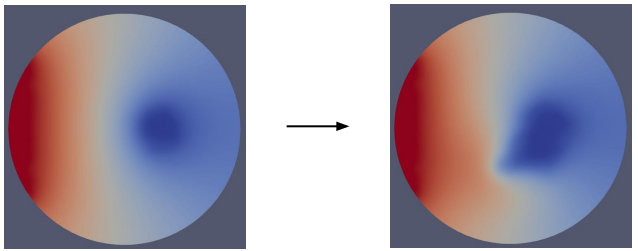


Drug

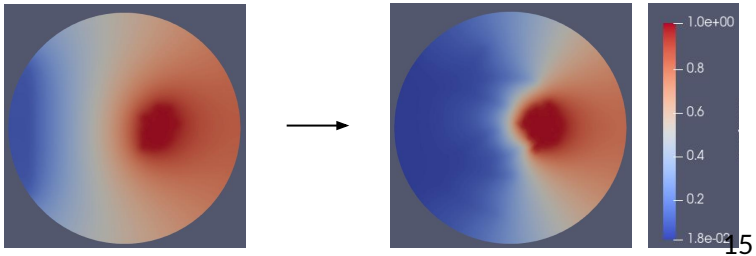
ABM



Nutrient



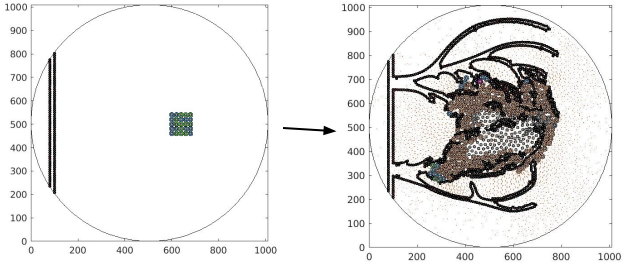
VEGF



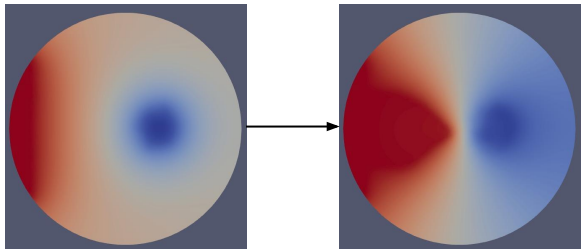
Model simulations without and with Immune cells

Initial Model

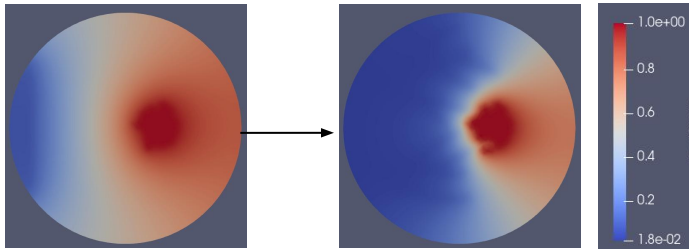
ABM



Nutrient

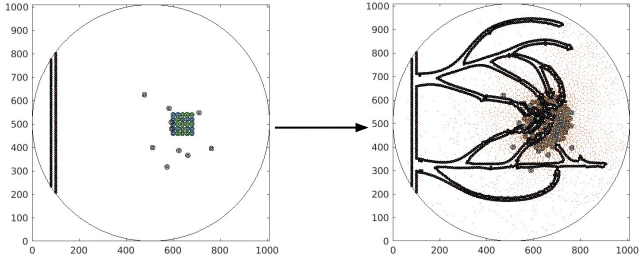


VEGF

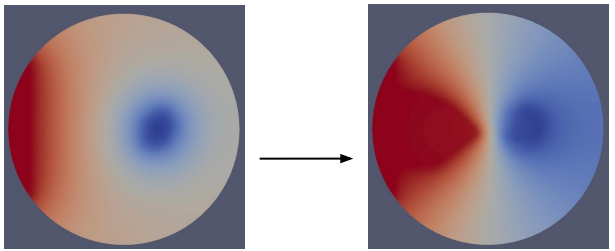


Cytotoxic T-Cells Integration

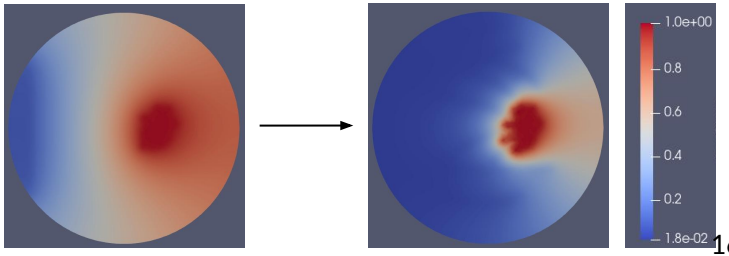
ABM



Nutrient



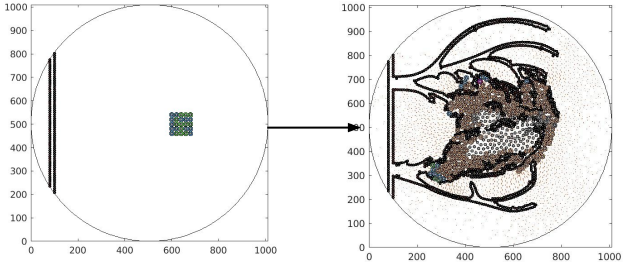
VEGF



Model simulations without and with Immune cells & Drug Integration

Initial Model

ABM



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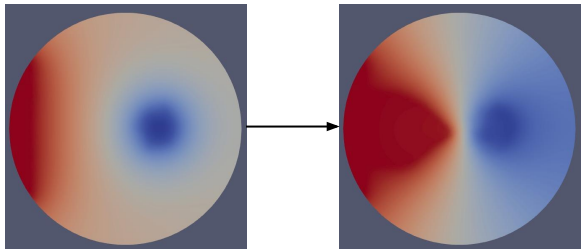
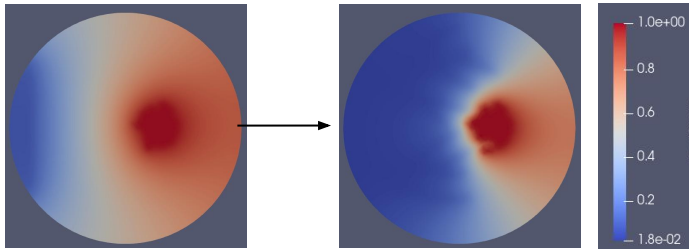
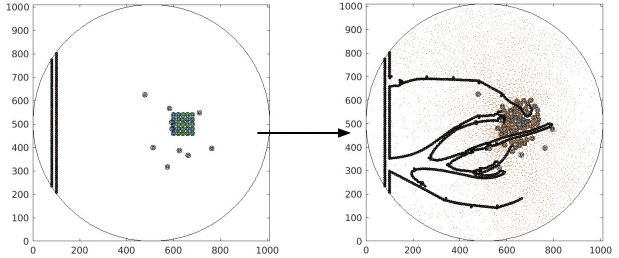


VEGF



Immune Cells & Drug Integration

ABM



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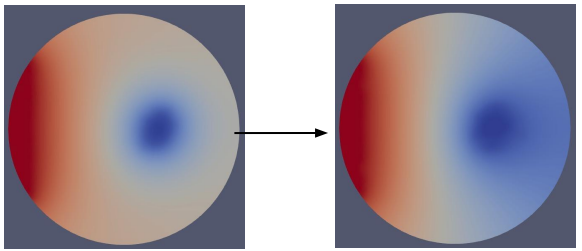
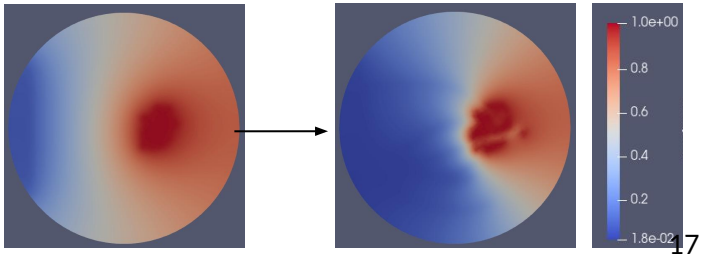


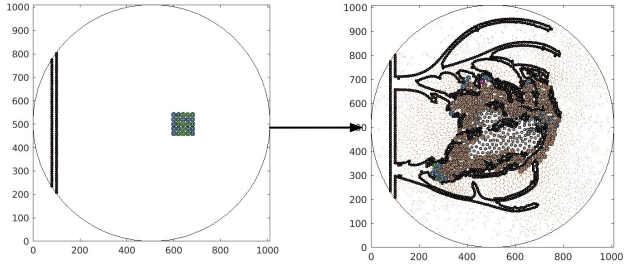
VEGF



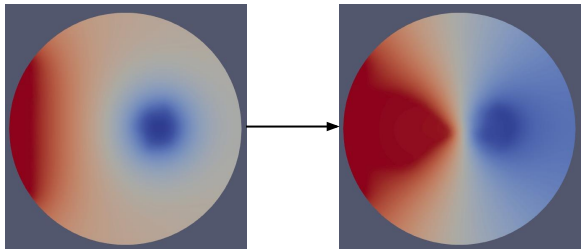
Model simulations without and with VEGF Threshold

Initial Model

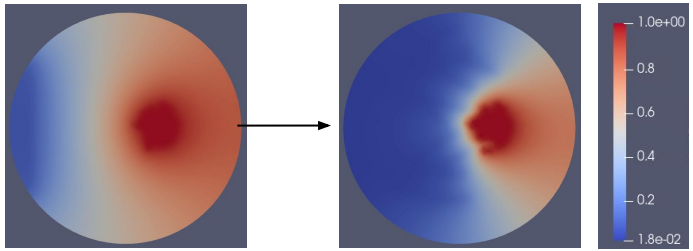
ABM



Nutrient

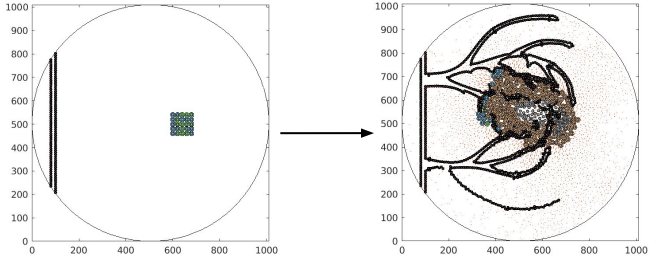


VEGF



VEGF Threshold Activating Drug Integratio

ABM



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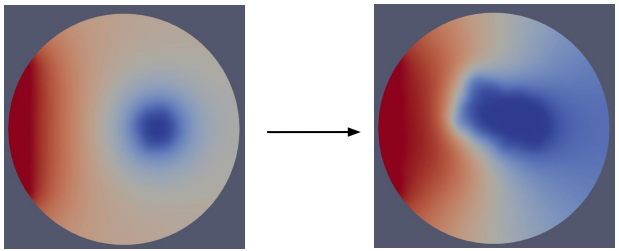

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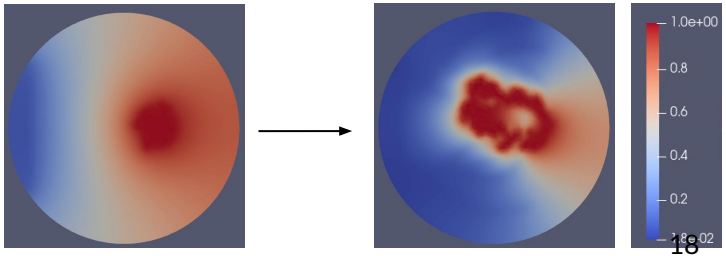
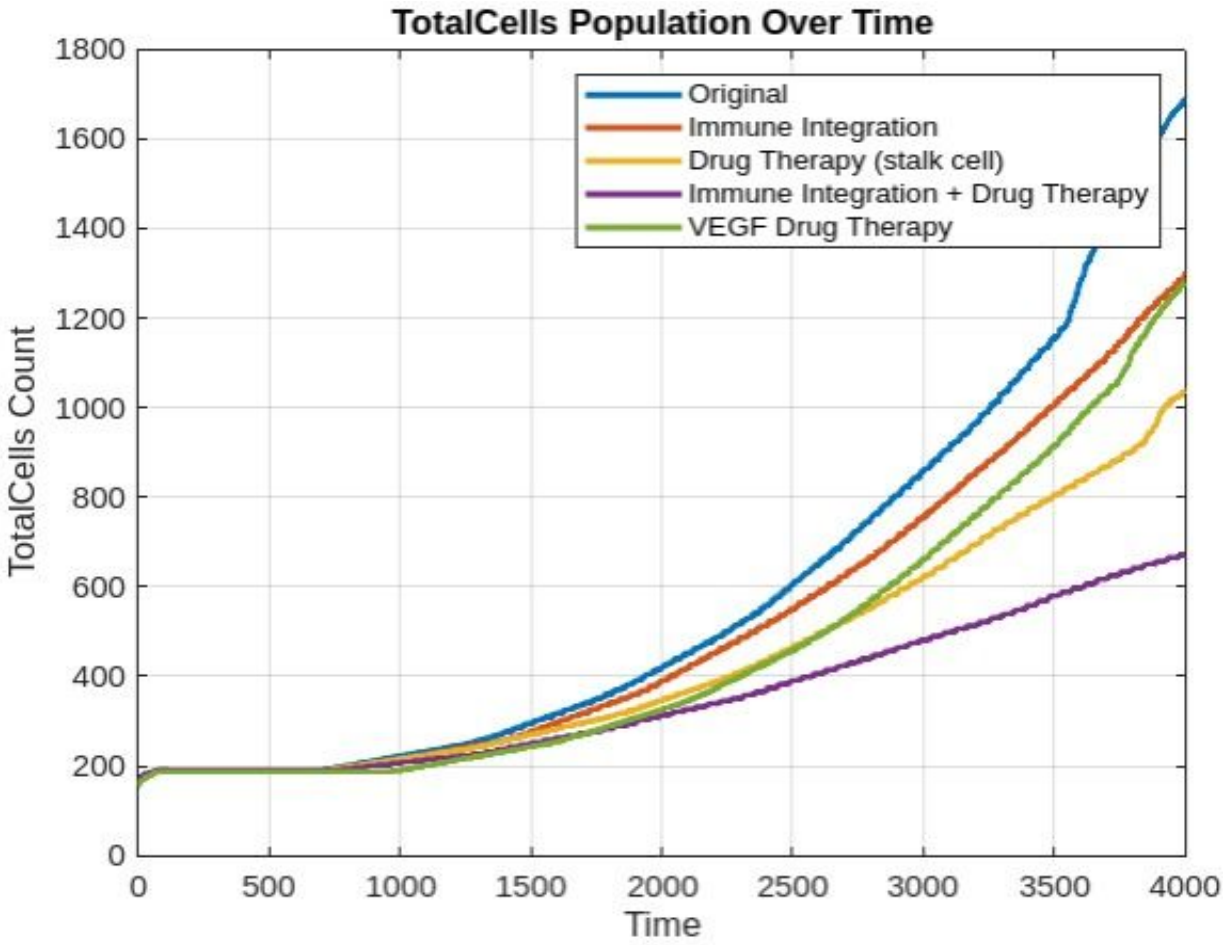
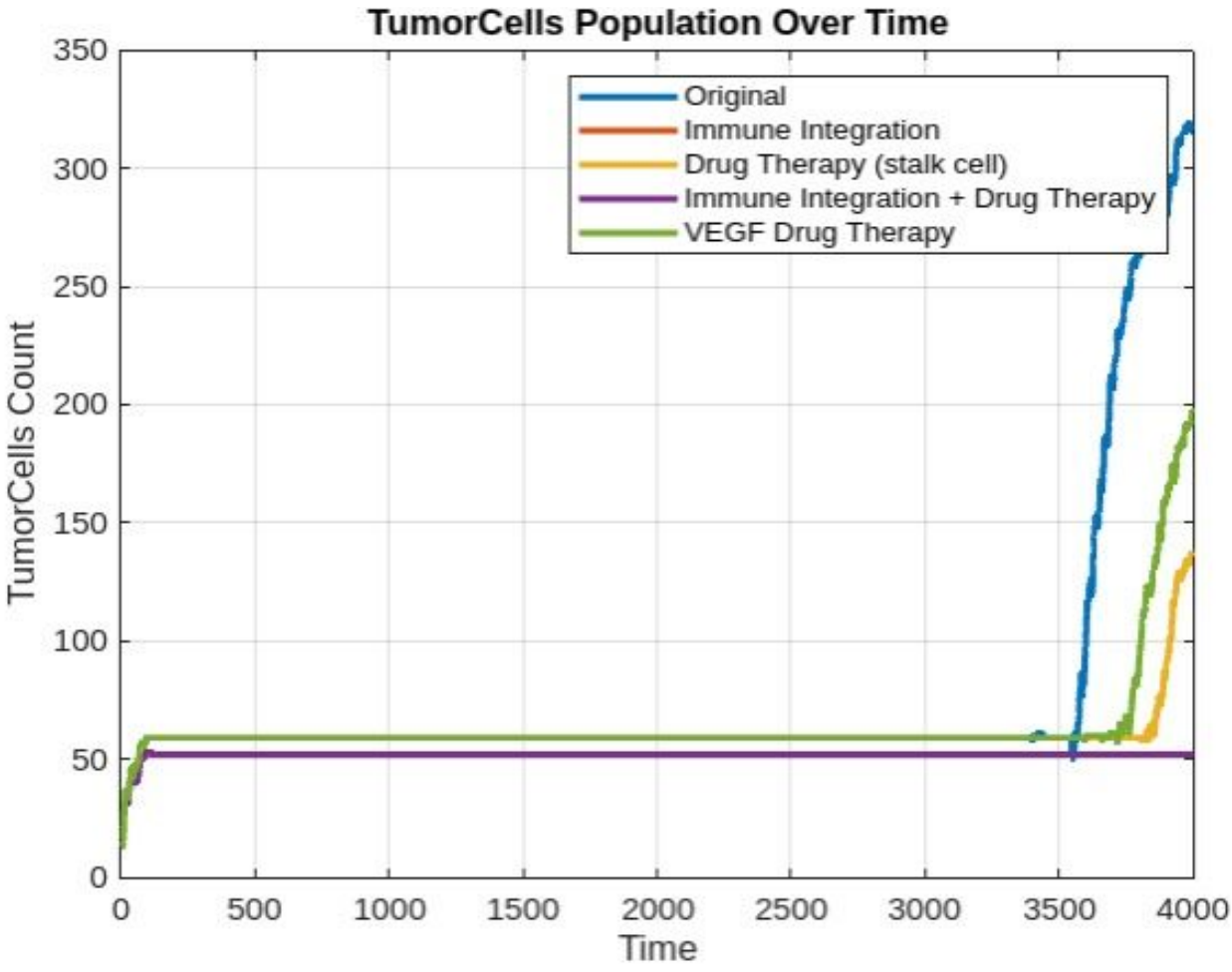


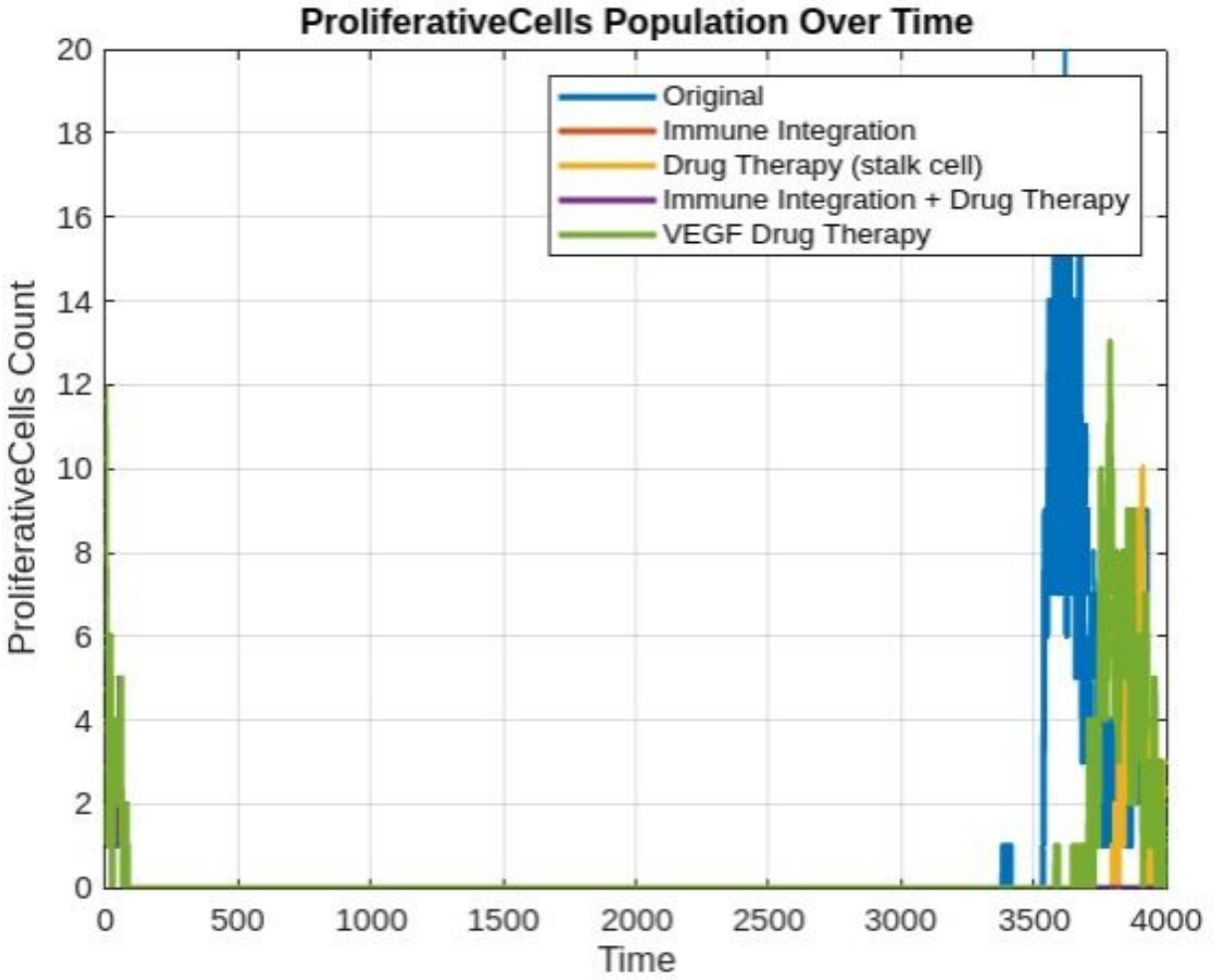
Comparative Population Analyses of Total Cell Population Over Time



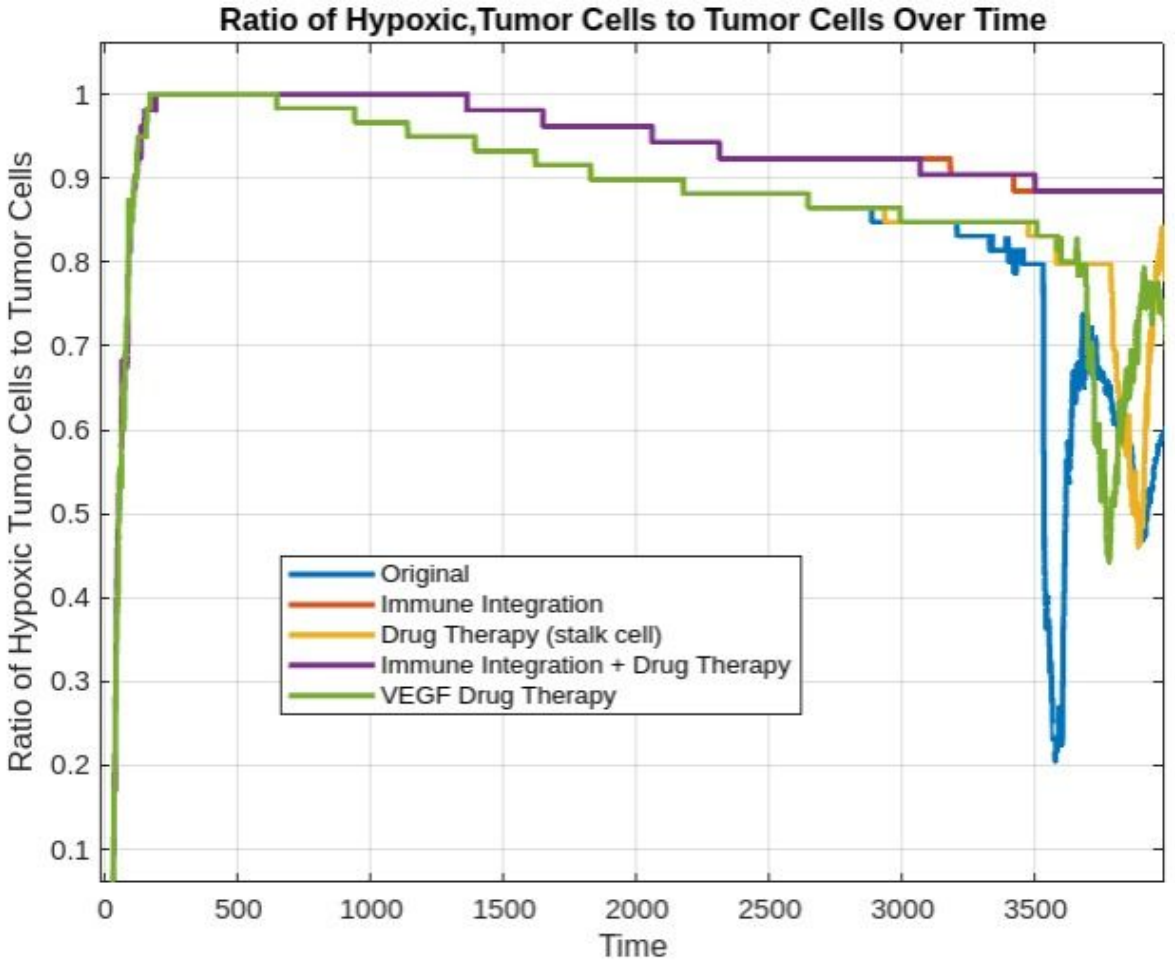
Comparative Population Analyses of Total Tumor Cell Population Over Time



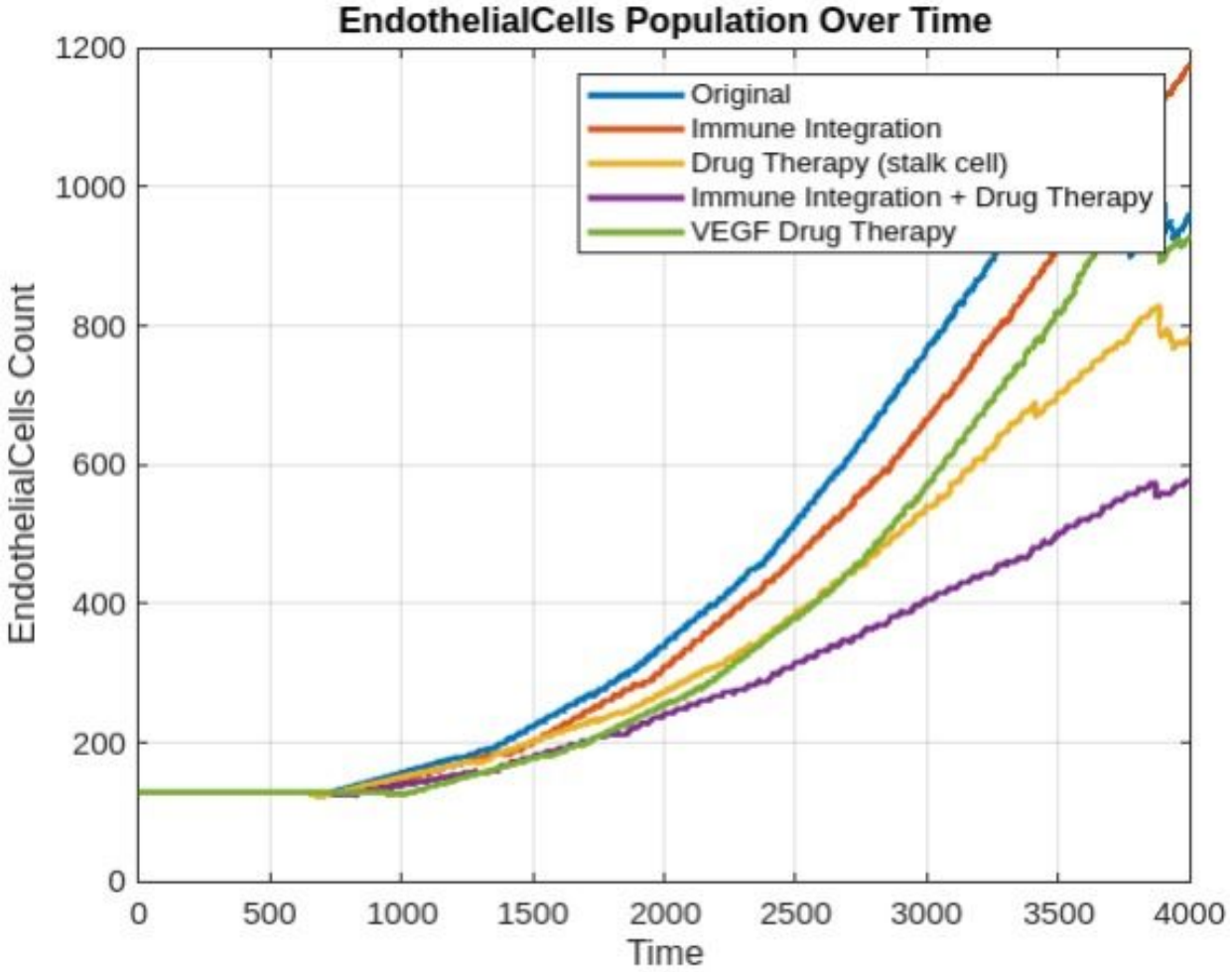
Comparative Population Analyses of Proliferative Tumor Cell Population Over Time



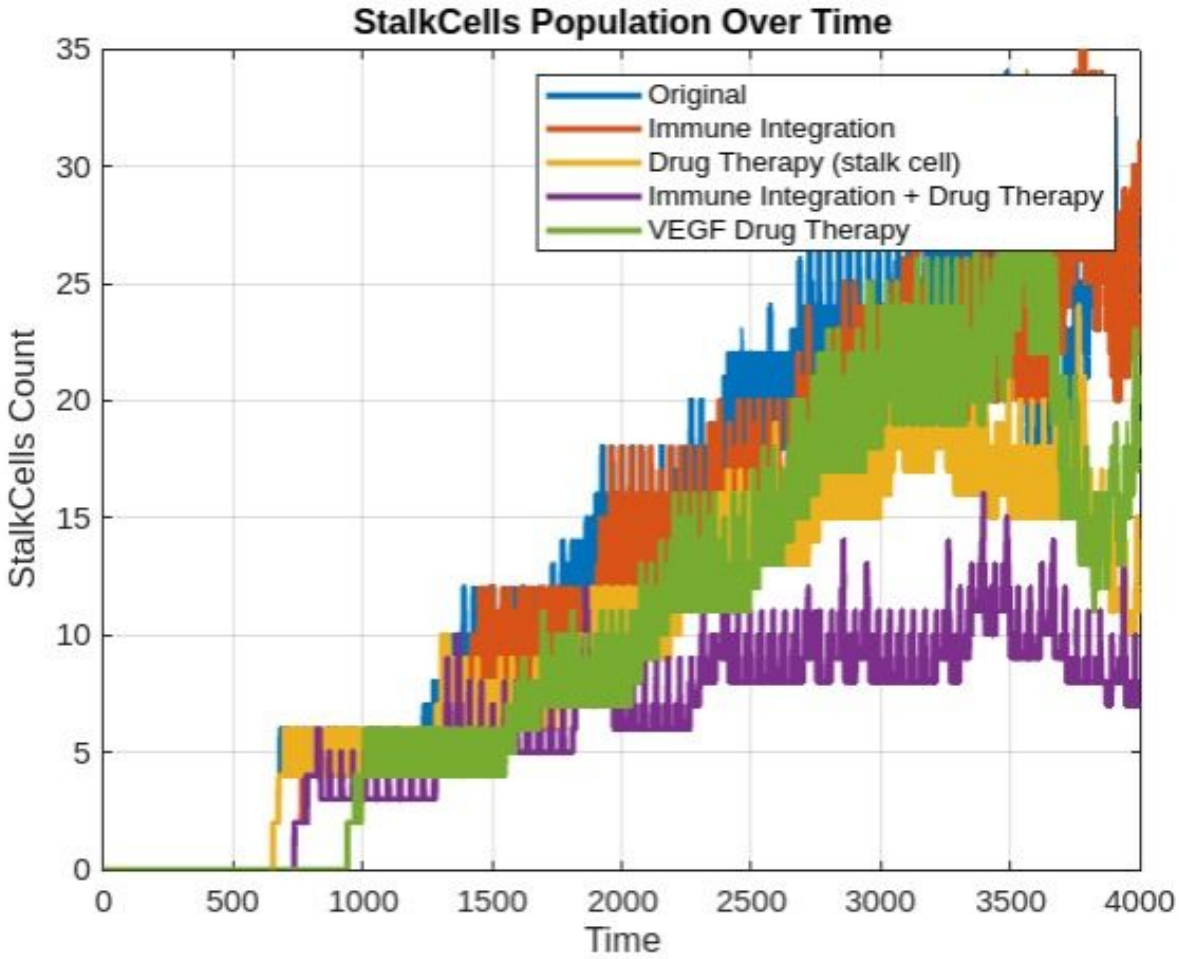
Comparative Population Analyses of Hypoxic Tumor Cell Population Over Time



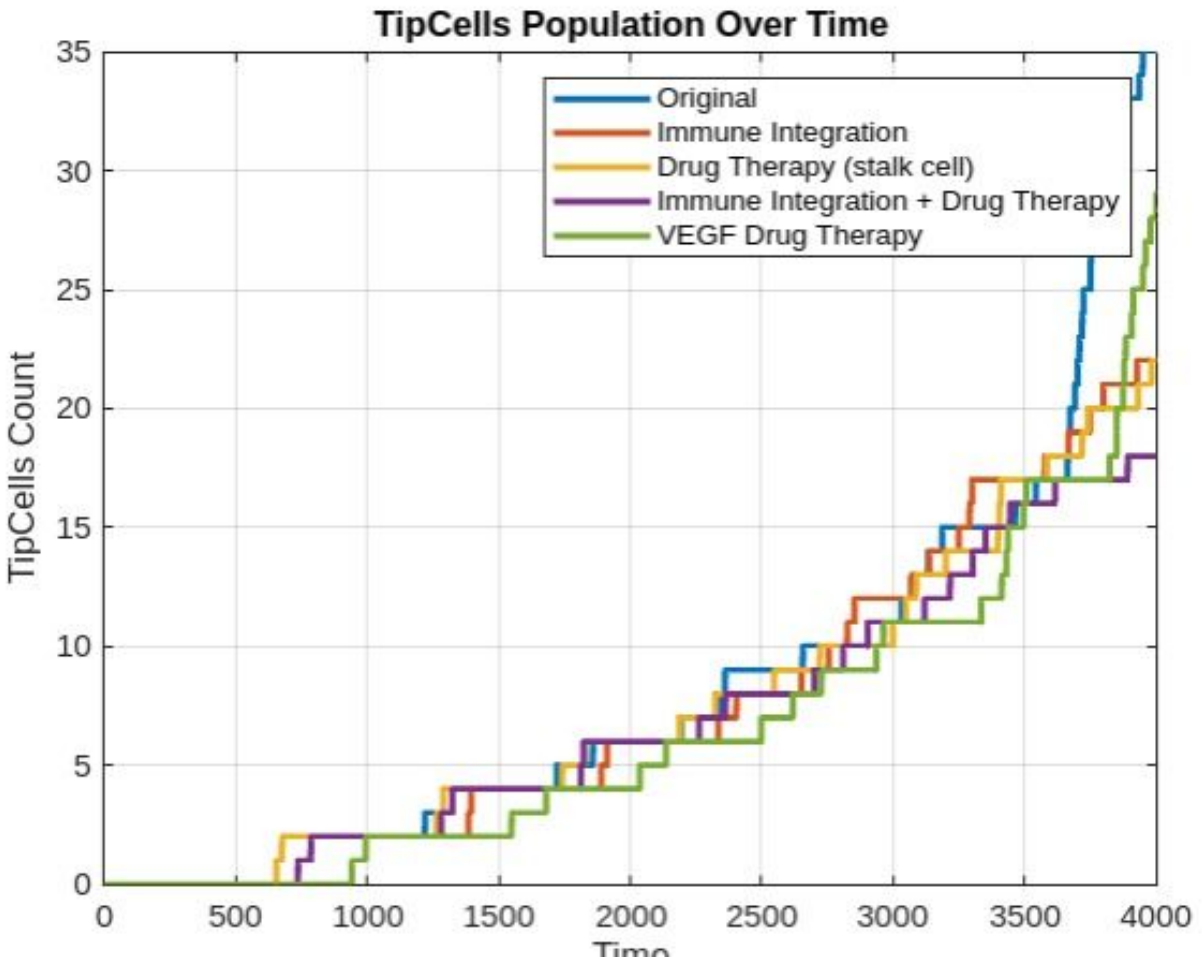
Comparative Population Analyses of Total Endothelial Cell Population Over Time



Comparative Population Analyses of Stalk Endothelial Cell Population Over Time

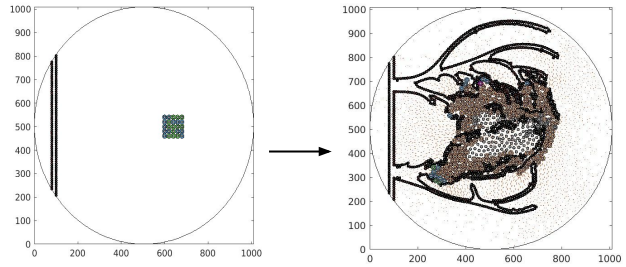


Comparative Population Analyses of Tip Endothelial Cell Population Over Time

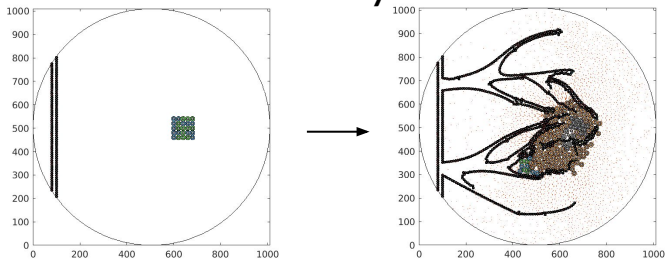


Inferences and Observations

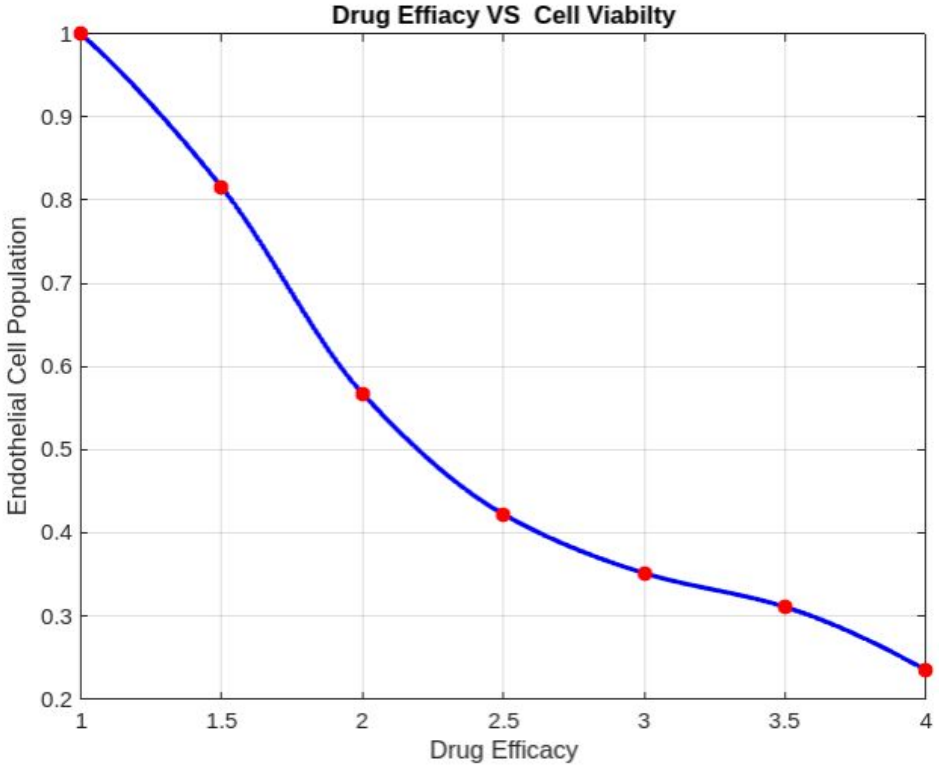
Effect of increasing drug efficacy on the endothelial cell population



Efficacy = 1

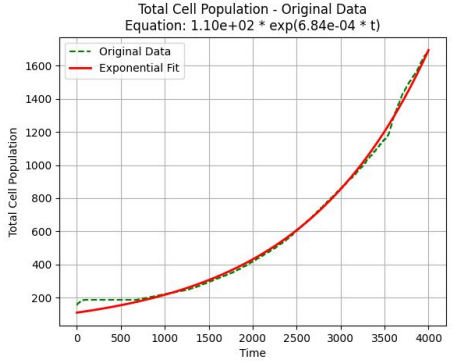


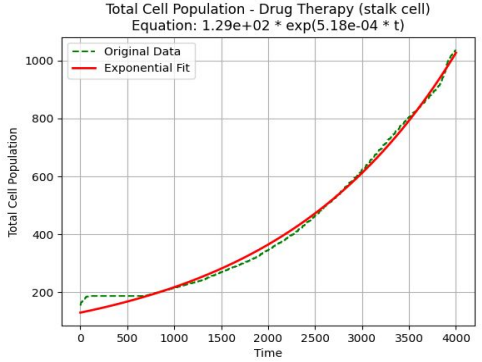
Efficacy = 1.5

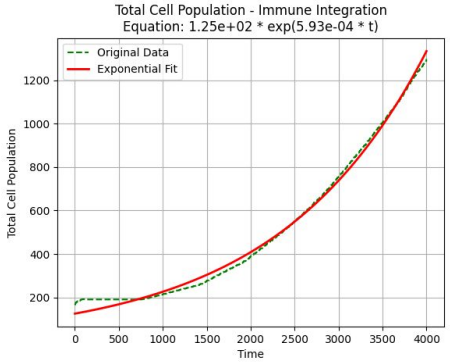


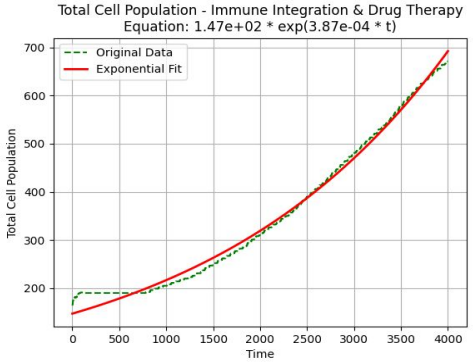
Synergy between Immunotherapy and Antiangiogenic drugs.

Synergy: The combined effect of two treatments or interventions is greater than the sum of their individual effects.









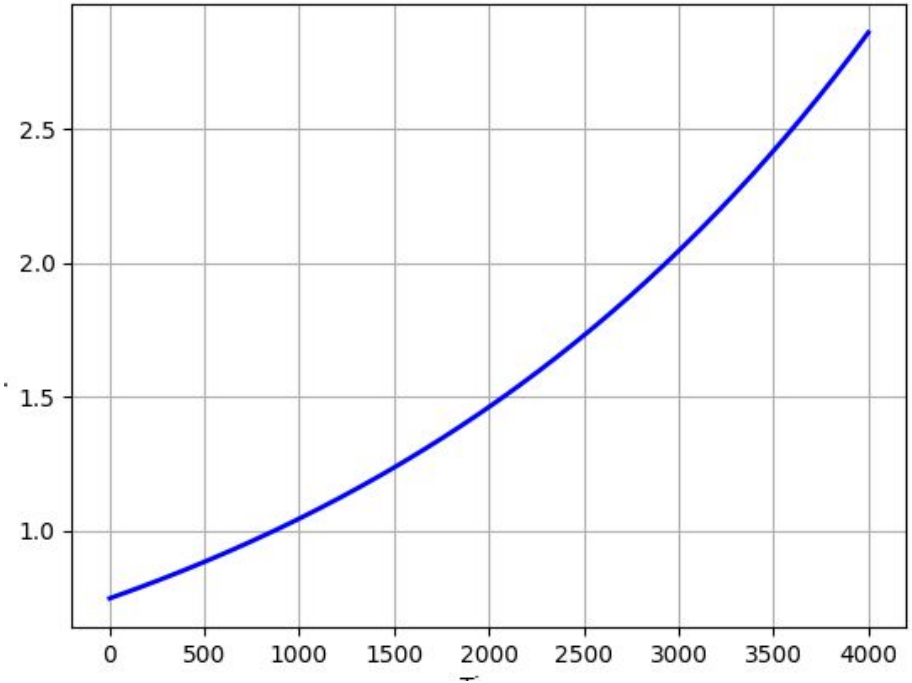
Synergy Modelling

Loewe Additivity Model:

$$S(t) = \frac{\text{ImmuneTherapy}(t) \cdot \text{DrugTherapy}(t)}{(\text{Immune\&DrugTherapy}(t))^2}$$

$$SynEffect = \frac{\int_0^t S(t)\,dt}{t}$$

$$SynEffect = 1.76$$



Conclusion:

- Contribution to a hybrid multiscale model tumor growth model for angiogenesis with immune cell and drug integration
- Reaction-Diffusion equations for nutrient and VEGF showed the dynamics of the gradient for combined therapy.
- Immune cells and anti-angiogenic drugs have synergistic effect on tumor size and cell population
- Potential therapeutic applications of the model to predict effect of drugs with immunotherapy.

Future Directions

- Parameter sensitivity analysis
- Integration of mesenchymal phenotype in the tumor cells to analyse EMT and metastasis of tumor cells.
- Effect of ECM heterogeneity on angiogenesis
- Development of a 3D model to capture spatial dynamics better
- In-Vivo validation of predicted synergy.

Thank You

https://www.memecreator.org/meme/what-are-you-studying-systems-biology/