A Computational Neural Agent-Based Model for Analyzing Lung Tumor Growth in Human Lungs

PhD Dissertation Proposal

by

M.S. Angel Ernesto Picazo Castillo

Doctoral Advisors:

PhD Leopoldo Altamirano Robles , INAOE

Instituto Nacional de Astrofísica, Óptica y Electrónica

January, 2025

Santa María de Tonantzintla, Puebla, CP 72840

Contents

Abstract

Lung cancer is a leading cause of cancer-related mortality worldwide, driven by challenges such as high therapeutic resistance and late-stage diagnosis. These issues highlights the urgent need for innovative computational models capable of addressing the complexity of tumor evolution and its interactions with the surrounding microenvironment. This research proposes a *Neural Agent-Based Model (NABM)*, which integrates neural networks into agent-based simulations to model the growth and progression of lung cancer in a dynamic, adaptable, and therapy-responsive manner. The *NABM* enables agents to simulate cellular decision-making processes by responding to microenvironmental features such as nutrient availability, oxygen levels, and chemical signals. This approach provides a powerful tool for simulating the intricate interactions within the tumor microenvironment and predicting tumor behavior under various conditions, including therapeutic interventions. By incorporating deep learning, the model allows for the simulation of complex tumor dynamics and supports the exploration of advanced therapeutic strategies.

The contributions of this research include the integration of neural networks within an agent-based model, enabling agents to adapt, learn, and make decisions based on dynamic microenvironmental inputs. This advancement bridges the gap between traditional rule-based modeling and adaptive artificial intelligence, offering a more flexible and realistic approach. Additionally, the study introduces a dataset generated using probabilistic functions and parameterized microenvironmental characteristics, ensuring both flexibility and scalability across a variety of scenarios. Another key contribution is the development of a deep learning-based model capable of analizing elements of the cellular microenvironment and accurately predicting cellular actions. This significantly enhances our understanding of cellular responses to complex and dynamic environmental factors. Lastly, this work advances the modeling of cellular populations and cancer therapies, enabling the simulation of interac-

tions between cellular populations and therapeutic interventions, providing a valuable platform for evaluating and optimizing treatment strategies.

The expected results include improved accuracy in predicting lung cancer evolution, enhanced understanding of microenvironmental influences on tumor behavior, and the evaluation of therapeutic strategies. By bridging the domains of computational modeling and oncology, this work provides a potential foundation for future studies and applications aimed at mitigating the impact of lung cancer.

Keywords: *Lung Cancer, Agent-Based Simulation, Deep Learning, Computational Oncology, Deep Learning*

1 Introduction

Lung cancer remains a leading cause of cancer-related mortality worldwide, claiming millions of lives each year. Despite advancements in treatment, its diagnosis often occurs at an advanced stage, complicating intervention and significantly reducing survival rates. This disease is characterized by the uncontrolled growth of abnormal cells within the lung tissue, resulting in the formation of malignant tumors [1, 2, 3]. Early detection and accurate prediction of tumor growth and evolution are critical to improving patient outcomes, but these remain significant challenges in clinical practice [4].

Lung cancer is broadly categorized into two main types: non-small cell lung cancer (NSCLC), which accounts for approximately 85% of cases, and small cell lung cancer (SCLC), which constitutes the remaining 15% and is characterized by its aggressive growth and rapid metastasis. Treatments, including surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy, have shown varying levels of success. However, for many patients, survival rates remain unsatisfactory, underscoring the pressing need for innovative approaches [5, 6].

Recent advancements in artificial intelligence (AI) and computational modeling offer a promising path toward addressing these challenges. AI-driven techniques, particularly those leveraging deep learning, have demonstrated remarkable capabilities in analyzing medical images for the detection of lung cancer and predicting its type. [7, 8, 9] These methods have the potential to revolutionize diagnostic and therapeutic strategies by providing clinicians with actionable insights into tumor behavior and response to treatment [10, 11, 12].

To complement AI-based detection, computational models such as agent-based simulations (ABS) can capture the dynamic and nature of lung cancer at a cellular level [13, 14, 15]. These models offer a unique advantage by enabling the repre-

sentation of individual tumor cells as agents interacting with their microenvironment, responding to nutrient availability, oxygen levels, and therapeutic interventions. However, traditional ABS often rely on static rule-based approaches that lack adaptability to the complex and evolving nature of cancer.

This work proposes the development of a novel computational model that integrates neural networks into agent-based simulations, creating a dynamic model capable of learning and adapting to the intricate interactions within the tumor microenvironment. By combining the predictive power of deep learning with the flexibility of agent-based models, this work aims to provide a tool not only for early detection but also for predicting tumor evolution and evaluating the efficacy of therapies.

The significance of this work lies in its dual contribution: advancing the understanding of lung cancer progression and providing a computational approach for cancer research. From a computer science perspective, this project addresses the critical gap in existing models by introducing neural network-driven agents capable of autonomous decision-making. The resulting model will enable the simulation of tumor behavior under varying microenvironmental conditions. This integrated approach represents a step forward in cancer research, with implications for early detection and treatment optimization.

2 Background

2.1 An Overview about Lung Cancer

Lung cancer is a severe disease that originates in the tissues of the lungs, typically in the cells lining the airways. It is the leading cause of cancer-related deaths among men and women worldwide, responsible for approximately 1.8 million deaths annually, which accounts for 18.6% of all cancer-related deaths. In countries like China and India, the burden is particularly high due to elevated smoking rates and exposure to carcinogens, while in Mexico, around 8,000 deaths are reported yearly, making it the most lethal form of cancer in the country. Despite advances in diagnosis and treatment, lung cancer remains a global health challenge [4, **?**].

There are two main types of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC constitutes approximately 80-85% of cases and includes subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is the most common subtype, seen in both smokers and non-smokers [16, 12]. Squamous cell carcinoma is strongly associated with smoking, while large cell carcinoma, though less common, tends to grow rapidly. In contrast, SCLC accounts for 15-20% of cases and is characterized by its aggressive behavior and strong correlation with heavy smoking [6, 17, 18].

The primary risk factor for lung cancer is smoking, contributing to about 85% of cases. Other factors include exposure to secondhand smoke, carcinogens such as asbestos and radon, and genetic predispositions [1, 2, 3]. Symptoms often include persistent cough, shortness of breath, chest pain, unexplained weight loss, and fatigue. Diagnosing lung cancer requires a combination of imaging techniques such as chest X-rays and computed tomography (CT) scans, along with biopsies to confirm the presence of malignant cells[6, 2, 3].

Treatment strategies for lung cancer depend on the type and stage of the disease, as well as the patient's overall health. Surgical options, such as lobectomy or pneumonectomy, are common for early-stage cancer. Advanced stages often require systemic therapies like chemotherapy, which uses drugs such as cisplatin and paclitaxel, or targeted agents that attack specific molecular pathways. Radiotherapy and immunotherapy, particularly immune checkpoint inhibitors like pembrolizumab, are also employed, especially in advanced cases where surgery is not feasible[19, 11].

Tumor growth and progression in lung cancer are driven by complex molecular mechanisms involving oncogenes, tumor suppressor genes, and DNA repair genes. Oncogenes such as *MYC* and *RAS* promote uncontrolled cell proliferation and survival, often through mutations or overexpression. Tumor suppressor genes, like *TP53* and *BRCA1/BRCA2*, normally inhibit excessive growth, but their inactivation leads to unchecked cellular division. Defects in DNA repair genes exacerbate genetic instability, allowing mutations to accumulate and drive cancer progression. Additionally, the process of angiogenesis—where tumors stimulate the formation of new blood vessels—ensures a continuous supply of oxygen and nutrients, enabling sustained tumor growth and metastasis [20, 4].

Environmental factors play a crucial role in lung cancer initiation and progression. Carcinogens such as tobacco smoke, radiation, and certain chemicals induce genetic mutations that disrupt normal cellular processes. Chronic exposure to these agents increases the likelihood of malignant transformation. Moreover, viruses like the human papillomavirus (HPV) have been implicated in some lung cancers, highlighting the multifactorial nature of the disease [12, 11].

Efforts to combat lung cancer must focus on prevention, particularly reducing smoking rates and minimizing exposure to carcinogens. Early detection through regular screenings, especially for high-risk populations, is essential for improving outcomes. Advances in personalized medicine, including therapies targeting specific

genetic mutations, offer hope for more effective treatments. However, the aggressive nature of the disease and its global impact underscore the need for continued research and comprehensive public health strategies [18, 4, 11, 21].

2.2 Agent-Based Simulations (ABS): A Tool for Modeling Complex Systems

Agent-Based Simulations (ABS) are a powerful modeling methodology used to study complex systems by simulating the interactions of multiple autonomous entities, known as agents. These agents represent individuals, groups, or entities that interact with one another and their environment, making decisions based on predefined rules and their perception of their surroundings. This modeling approach enables the study of emergent behaviors that arise from simple interactions, which might not be evident in more traditional models [22].

Agents in an ABS are defined as entities capable of perceiving their environment, processing information, and acting based on internal rules. Each agent is autonomous, operating independently while adapting and learning from its interactions. This autonomy allows agents to represent diverse behaviors within a simulation, capturing the variability seen in real-world models. Furthermore, the interactions between agents and their environment often lead to emergent behaviors, where simple individual actions result in complex, system-wide phenomena. For instance, coordinated group movements, competitive dynamics, or the evolution of cooperation are all emergent properties frequently observed in ABS models.

The core strength of ABS lies in its ability to model systems from the ground up. Instead of imposing high-level dynamics on the system, ABS begins by defining the rules governing individual agents. This micro-level detail captures intricate interactions and provides insights into the macroscopic behaviors of the system. ABS

has been successfully applied in diverse fields, including economics (modeling markets and consumer behavior), sociology (studying social dynamics and migrations), ecology (esimulating species interactions), and biology (investigating cellular growth and morphogenesis) [22, 10, 23].

In biology, ABS has proven particularly valuable in exploring cellular processes and systemic behaviors. For example, these models can simulate cell growth and division, accounting for environmental factors such as nutrient availability and chemical signaling. In morphogenesis, ABS helps study how cells self-organize to form complex structures, elucidating the role of intercellular interactions in determining the final shape of tissues and organs. Additionally, in immunology, ABS enables the simulation of immune responses by modeling the interactions between immune cells and pathogens, providing insights into the mechanisms underlying effective immune defenses [24, 15, 25].

ABS is also instrumental in studying diseases such as cancer. By simulating the interactions between cancerous and healthy cells, researchers can investigate the factors influencing tumor growth, invasion, and metastasis. These models incorporate variables such as nutrient gradients, cell signaling pathways, and mechanical forces to recreate the tumor microenvironment, offering a dynamic view of disease progression. Beyond tumor dynamics, ABS is used to explore collective behaviors in microbial populations or cellular ecologies, shedding light on cooperative or competitive strategies that influence survival and adaptation [23, 24, 26, 15].

2.3 Integration of Neural Networks in Intelligent Agents

The integration of neural networks into intelligent agents has transformed their ability to learn and adapt to complex environments. By leveraging neural networks, agents can process vast amounts of data, recognize patterns, and make informed decisions, greatly enhancing their functionality and versatility.[10, 27]

2.3.1 What is a Neural Network?

An artificial neural network (ANN) is a computational model inspired by the human brain's structure and functionality. It consists of interconnected nodes, known as artificial neurons, which process and transmit information. These neurons are arranged in layers: an input layer that receives data, one or more hidden layers that process this information, and an output layer that provides results. The connections between neurons are weighted, and these weights are adjusted during training to optimize the network's performance.[28]

Key Components: Neural networks are built on the following fundamental elements:

- **Neurons:** Process incoming signals and generate outputs for subsequent layers.
- **Weights:** Define the strength and influence of connections between neurons.
- **Activation Functions:** Introduce non-linearity, allowing the network to model complex relationships in data.

2.3.2 Advantages of Neural Networks

Neural networks provide numerous benefits, making them essential tools in intelligent agent systems:

- **Learning Capability:** They excel at learning intricate patterns and relationships from extensive datasets, enabling adaptation to changing conditions.
- **Unstructured Data Handling:** ANNs are adept at processing unstructured data, such as images, audio, and text, which traditional models may struggle with.

- **Robustness:** Neural networks are resilient to noise and variations in input data, maintaining performance across diverse scenarios.
- **Generalization:** Once trained, they can accurately predict outcomes for new, unseen data, a crucial feature for real-world applications.

2.3.3 Incorporation into Agents

The integration of neural networks enhances intelligent agents' capabilities by allowing them to learn from experience and adapt their behavior dynamically. This synergy offers several key advantages:

- **Adaptive Learning:** Agents equipped with neural networks can continually refine their decision-making processes based on feedback and changing environments.
- **Complex Decision-Making:** Neural networks enable agents to analyze intricate scenarios, recognizing subtle patterns and making well-informed choices.
- **Environmental Interaction:** Neural networks allow agents to interpret and respond to environmental cues effectively, facilitating their application in fields like robotics and simulations.

2.3.4 Application Examples

The integration of neural networks has been successfully applied in various domains, including:

- **Autonomous Robotics:** Robotic agents employ ANNs for navigation, obstacle avoidance, and performing tasks in dynamic environments.

- **Gaming:** Neural networks enable agents to develop and refine strategies, competing effectively against humans or other agents.
- **Recommendation Systems:** Intelligent agents use ANNs to analyze user preferences and deliver personalized recommendations, enhancing user experience.

By incorporating neural networks, intelligent agents gain the ability to operate in complex, data-rich environments, making them more effective and adaptable across a wide range of applications.

2.4 The Microenvironment in Agent-Based Simulations

In agent-based simulations (ABS), the microenvironment represents the environment in which agents interact and make decisions. This concept is essential to understanding the dynamics that emerge within a simulated system, as the microenvironment can significantly influence agent behavior and the overall outcomes of the simulation. By defining the conditions in which agents operate, the microenvironment shapes their interactions, decisions, and evolution over time.

The microenvironment encompasses various physical, chemical, and biological factors that affect the agents. In biological contexts, for example, it may include conditions such as the availability of nutrients, the presence of other cell types, or environmental variables like temperature and pH levels. These characteristics directly influence the behavior, growth, and survival of agents. As a result, understanding the microenvironment is key to accurately modeling and predicting agent interactions and the outcomes of complex systems [14, 13].

Agents interact with their microenvironment through mechanisms that allow them to perceive their surroundings. Sensors or input methods enable agents to collect information about factors such as resource availability or environmental conditions. Based on this information, agents make decisions and take actions that align

with predefined behavioral rules. For instance, a cellular agent might proliferate if nutrients are abundant or migrate toward areas with higher resource concentrations. These actions are governed by rules that can vary from simple (moving toward a resource) to highly complex (forming collaborative structures with other agents). Behavioral rules often include specific conditions that must be met for an agent to execute particular actions, such as cell division or apoptosis.

Agents not only interact with their environment but also with each other, often leading to emergent behaviors at the system level. For example, in a tumor growth model, the interactions among cancer cells can drive tumor proliferation. Rules governing these interactions may involve competition for resources, cooperation to form structured assemblies, or communication via chemical signaling. This inter-agent communication, often mediated by chemical signals in biological systems, plays a crucial role in coordinating actions and responding to changes in the environment or other agents. Such coordination enables the formation of communities or complex structures within the microenvironment.

Agent-based simulations are widely used in biology to model phenomena such as tumor growth, immune responses, and cellular ecosystems. For instance, in modeling tumor growth, ABS can capture how cancer cells interact with their surroundings and other cell types, revealing insights into proliferation and invasion dynamics. In immunology, simulations help explore how immune cells detect and respond to pathogens, as well as their interactions within the immune system. Furthermore, in cellular ecology, ABS is employed to study interactions among diverse cell types within tissues or ecosystems, offering a better understanding of cooperative and competitive behaviors that drive tissue formation or ecological balance [15, 23, 24, 25, 26].

The integration of microenvironmental factors into ABS enhances the realism and predictive power of these simulations, providing valuable insights into complex biological systems. By capturing the interplay between agents and their surround-

ings, these models can simulate emergent phenomena and offer a deeper understanding of processes that are otherwise challenging to study experimentally.

3 Related work and State-of-the-art

Lung cancer presents a significant challenge in terms of diagnosis, treatment, and prognosis, emphasizing the urgent need for effective tools and approaches to understand and model tumor dynamics, as well as the interactions among diverse cellular populations involved in the disease. Current limitations demand detailed attention. On one hand, mathematical and computational models require greater precision to capture the complexity of the pulmonary tumor microenvironment and cancer progression over time, in addition to validation with representative clinical datasets. On the other hand, understanding the complex interplay between cellular populations is essential for developing novel therapeutic strategies and prognostic biomarkers.

In the state of the art, various approaches address these challenges and relate to this thesis proposal. Firstly, mathematical models for tumor growth have primarily focused on describing tumor size and cellular populations, often incorporating treatment effects. For instance, Jha et al. (2023) and Prelaj et al. (2023) developed mathematical models to describe the general dynamics of cancer, while Salgia et al. (2018) employed stochastic models to study small-cell lung cancer [29, 30, 31]. Other studies, such as Wang et al. (2016), applied particle swarm optimization to adjust parameters in tumor models [32]. Similarly, Rojas et al. (2022) characterized immunotherapy using Hamiltonian models, and Ghita et al. (2021) proposed a radiation therapy model for non-small cell lung cancer [33, 12]. However, these models treat the tumor as a whole and do not analyze cancer at the cellular level, leading to the omission of several critical biological aspects.

Agent-based simulations are another promising avenue for modeling cancer.

Tools like PhysiCell demonstrate great potential for simulating interactions among different cellular populations, providing a generic platform for cell-level simulations. PhysiCell enables the incorporation of cancer therapies but requires the addition of behavioral rules for other cell populations, complicating its use. Benson et al. (2024) used the Compucell platform for a 3D cancer model, yielding biological insights into cancer cell invasion [15]. Sreejithkumar et al. (2024) developed a 3D computational model for tumor growth, achieving realistic representations of the tumor microenvironment [34]. However, these approaches work at the cellular level but are not specialized for lung cancer, highlighting an area for future exploration [13, 21].

In the case of lung cancer, several models exist for cancer classification using various medical imaging techniques and machine learning models. Recent examples include Raza et al. (2023), who utilized an EfficientNet on CT scans, achieving 99% accuracy [35]. Sachdeva et al. (2024) applied different machine learning algorithms, such as Naive Bayes, K-nearest neighbors, and Decision Trees, with a maximum accuracy of 96% [36]. Nasra (2024) employed a ResNet50 architecture, reaching 99% accuracy, while Naseer et al. (2023) used a modified U-Net to segment and detect cancerous nodules, achieving 98.84% accuracy [37, 38]. However, none of these models address tumor growth dynamics, and no studies have been identified to date that tackle tumor growth in the human lung.

Agent-Based Models with Neural Networks

A novel and underexplored idea involves incorporating neural networks into agents for simulation, aiming to improve and analyze the decisions made by agents in their environment. Although not yet applied to biological contexts, this concept holds promise for enhancing simulation realism. For example, Wilterson et al. (2021) used neural networks in agents to model visuospatial attention for an object-catching task [10]. Hendrikse et al. (2023) implemented agents with neural networks to simulate

social interactions [27].

Table 1 summarizes key studies in the field, highlighting the authors, year of publication, type of model used, and major achievements [29, 30, 31, 32, 33, 12, 15, 34, 13, 21, 35, 36, 37, 38, 10, 27].

Table 1: Summary of the State of the Art in Tumor Modeling

Author(s)	**Year**	**Model Type**	**Achievements**
Jha et al.	2023	Mathematical Model	Developed models describing general cancer dynamics. Focused on tumor size and progression.
Van et al.	2023	Mathematical Model	Enhanced understanding of cancer progression using deterministic approaches.
Salgia et al.	2018	Stochastic Model	Studied small-cell lung cancer dynamics and stochastic behavior.
Wang et al.	2016	Particle Swarm Optimization	Applied optimization techniques to parameter adjustment in tumor models.
Rojas et al.	2022	Hamiltonian Model	Characterized immunotherapy using Hamiltonian dynamics.
Ghita et al.	2021	Radiation Therapy Model	Proposed a model for radiation therapy in non-small cell lung cancer.
Benson et al.	2024	Compucell ABM	Developed a 3D cancer model to study cell invasion dynamics.
Sreejithkumar et al.	2024	Computational Model	Created a realistic 3D tumor microenvironment representation.
Raza et al.	2023	EfficientNet	Applied EfficientNet to CT scans, achieving 99% accuracy for lung cancer classification.
Sachdeva et al.	2024	Machine Learning Algorithms	Used Naive Bayes, KNN, and Decision Tree for classification with up to 96% accuracy.
Nasra et al.	2024	ResNet50	Achieved 99% accuracy in lung cancer classification using ResNet50.
Naseer et al.	2023	Modified U-Net	Developed a U-Net for segmentation and detection of cancerous nodules, achieving 98.84% accuracy.
Wilterson et al.	2021	Neural Agents	Modeled visuospatial attention in agents using neural networks.
Hendrikse et al.	2023	Neural Agents	Simulated social interactions in agents using neural networks.

4 Research Proposal

We expect to develop a computational model that allows simulating and visualizing the dynamics of lung cancer, integrating interactions between different cell populations and cancer therapies. The results of this research could significantly contribute to early diagnosis, personalized treatment, and accurate prognosis of lung cancer, thus improving the quality of life of patients.

4.1 Problem Statement

Lung cancer remains one of the most prevalent and lethal forms of cancer worldwide, with its progression and response to therapy heavily influenced by the complex interactions between tumor cells and their microenvironment. These interactions involve dynamic processes, such as nutrient competition, cellular signaling, and environmental adaptation, which are difficult to predict using traditional experimental and computational approaches. While significant strides have been made in understanding these processes, many existing models fail to capture the natural mechanisms and behaviors that arise within the tumor microenvironment.

Current computational models often lack the flexibility to dynamically represent cellular responses to environmental factors such as oxygen gradients, nutrient availability, or chemical signals. Additionally, many models are static or overly simplified, providing limited insights into how tumor cells adapt to adverse conditions or develop resistance to therapies. The absence of robust and adaptable models hinders the ability to predict tumor growth, evolution, and the emergence of treatment-resistant phenotypes effectively [21, 4].

Furthermore, despite the recent advancements in deep learning and agent-based modeling, these two fields have yet to be fully integrated to address the challenges of modeling tumor dynamics. The potential of neural networks to learn and predict

complex behaviors remains largely untapped in the context of agent-based simulations. As a result, there is a pressing need for a computational model that combines the adaptability of neural networks with the dynamic nature of agent-based modeling to provide more accurate and scalable predictions of tumor behavior [26, 27, 15].

Algorithms and mathematical models reported generally represent the tumor growth problem considering only the tumor itself. This representation limits the variables that may impact in the tumor growth. Additionally, this perspective does not allow for analyzing the impact of the microenvironment in certain parts of the tumor. This perspective provides a narrow view when compared with more complex phenomena, such as therapy resistance, which is a major issue in the state of the art [39, 21, 25].

4.2 Motivation

Lung cancer remains one of the leading causes of mortality worldwide, claiming millions of lives each year. Its complex biology and multifaceted progression involve not only the intrinsic behavior of cancer cells but also their continuous interaction with the surrounding microenvironment. Understanding this interplay is crucial for developing effective therapeutic strategies and improving patient outcomes. The tumor microenvironment, including nutrient availability, oxygen gradients, chemical signaling, and interactions with immune cells, plays a pivotal role in regulating tumor growth, invasion, and resistance to therapy. Agent-based simulations (ABS) provide a robust and flexible framework to model these interactions at a cellular level. By simulating individual cells as autonomous agents, ABS captures their dynamic behavior and the feedback loops that drive tumor progression, offering insights beyond static experimental observations.

The integration of neural networks into agent-based simulations represents an advancement in computational modeling. Neural networks empower agents with

adaptive learning capabilities, enabling them to refine their responses to environmental stimuli based on prior experiences or complex input data. This approach allows to simulate highly intricate biological processes, such as the evolution of therapy resistance, the emergence of cooperative cellular behavior, or the intricate dance between tumor and immune cells. By leveraging neural networks, these simulations can reveal emergent patterns and behaviors that are difficult, if not impossible, to predict using traditional experimental techniques or mathematical models. The combination of ABS and neural networks thus opens the door to a deeper understanding of cancer dynamics, fostering innovation in both basic research and clinical applications.

4.3 Justification

Lung cancer presents an urgent need for innovative approaches to understand its progression and develop effective therapies. One of the most significant challenges in lung cancer treatment is the development of resistance by cancer cells to conventional therapies. This resistance, driven by complex interactions within the tumor microenvironment, often results in treatment failure and disease recurrence. Without a comprehensive computational model to study these dynamics, critical insights into how cancer cells adapt and survive therapeutic interventions may remain undiscovered [16, 12, 1, 2, 3].

Traditional experimental methods, while invaluable, are limited in their capacity to capture the adaptive behaviors of tumor cells within their microenvironment. These methods often lack the scalability and resolution required to explore the intricate interplay between cellular populations, nutrients, oxygen levels, and chemical signals. If we fail to integrate advanced computational models, our understanding of these processes will remain fragmented, delaying the development of novel strategies to overcome therapeutic resistance [17, 4, 11].

Agent-based simulations (ABS) enhanced with neural networks offer a powerful solution to address this challenge. By enabling agents to learn, adapt, and respond dynamically to their surroundings, these models provide a unique opportunity to study emergent behaviors that are otherwise difficult to predict.

By advancing an agent-based neural model for simulating lung cancer dynamics, this research bridges critical gaps in current methodologies. It provides a pathway to investigate adaptive cellular behaviors, understand resistance mechanisms, and ultimately contribute to the development of precision therapies.

4.4 Research Questions

- What are the behaviors of the main cellular populations involved in the lung cancer microenvironment?
- What are the physical and chemical stimuli provided by the lung cancer microenvironment to the cellular populations?
- How can deep learning models be designed to represent the behaviors of different cellular populations given the stimuli from the lung cancer microenvironment?
- How can neural networks be designed and integrated into agent-based models to enable agents to adapt and learn from their environment?

4.5 Hypothesis

We hypothesize that the integration of neural networks into an agent-based model can provide more accurate predictions of tumor growth and evolution. By enabling agents to learn from and adapt to their microenvironment, this approach enhances the capacity of the simulation to capture complex and emergent behaviors of tumor

cells. This computational model could outperform traditional modeling techniques by offering deeper insights into the dynamic interactions between cancer cells and their surroundings, ultimately contributing to a better understanding of tumor progression and therapeutic interventions.

4.6 Objectives

4.6.1 General Objective

To develop a computational agent-based model enhanced with neural networks to describe tumor growth dynamics in the human lung, including the interactions with therapeutic treatments .

4.6.2 Specific Objectives

1. To describe cellular-level interactions among the different cell populations involved in the lung cancer microenvironment and their response to therapies.
2. To design and implement a neural network capable of recognizing key microenvironmental elements in lung cancer and predicting cellular behaviors in response to these factors.
3. To establish a computational model that accurately represents the characteristics of the cellular microenvironment and its interactions with the cell populations
4. To develop an agent-based model that incorporates neural networks to mimic the behaviors of tumor cells and their interactions with the microenvironment.
5. To implement therapeutic strategies within the model, enabling the interactions between cellular populations and potential cancer treatments

6. To validate the integrated ecosystem by comparing its predictions with experimental data or established biological benchmarks.

4.7 Expected Contributions

This research is expected to contribute significantly to the field of computer science through the following advancements:

- **Development of a Deep Learning-Based Model:** Establishing a neural network model capable of recognizing the elements of a cell's microenvironment and predicting its actions. This contribution will enhance the understanding of cellular responses to complex and multiple environmental factors.
- **Representation of the Cellular Microenvironment:** Creating a computational model that accurately represents the characteristics of the cellular microenvironment, providing a platform for exploring interactions and dynamics in biological systems.
- **Integration of Neural Networks in an Agent-Based Model:** Implementing neural networks within an agent-based model to enable agents to adapt, learn, and make decisions based on dynamic microenvironmental inputs. This integration bridges the gap between rule-based modeling and adaptive artificial intelligence.
- **Modeling of Cellular Populations and Cancer Therapies:** Introducing a model to simulate the interactions between cellular populations and cancer therapies, including the representation of therapeutic effects on the cells. This contribution allows for the evaluation and optimization of therapy strategies.

4.8 Methodology

In this section, we present a methodology to be followed in order to achieve the objectives outlined in this project.

Activities

1. Literature review:
    - Review of lung cancer growth models and their simulation methodologies.
    - Study of agent-based models (ABM) and their application to cancer research.
    - Review of neural network architectures for decision-making in dynamic systems.
    - Identify and analyze existing datasets and microenvironment models relevant to lung cancer.
    - Evaluate state-of-the-art ABM tools and models, such as PhysiCell, for their suitability in modeling tumor progression.
    - Define specific objectives for integrating neural networks within agent-based models.
2. Development of the agent-based tumor growth model:
    - Define initial conditions for the tumor microenvironment, including oxygen, nutrients, pressure, space availability, and toxicity.
    - Represent the tumor microenvironment.
    - Develop rules and behaviors for individual tumor cells, including proliferation, movement, resting, and death.
    - Integrate neural networks into each agent for decision-making based on environmental factors.

- Simulate tumor growth dynamics over a fixed number of steps and validate the results against expected biological behavior.

3. Integration and visualization of simulation results:

    - Implement a visualization pipeline to generate real-time 2D and 3D plots of the tumor microenvironment parameters (e.g., oxygen, nutrients, pressure).
    - Create comparative graphs to evaluate the effects of different initial conditions and parameter settings on tumor progression.
    - Develop metrics to quantify tumor growth, cell proliferation rates, and agent behaviors over time.

4. Application and analysis of therapeutic strategies:

    - Simulate the effects of different therapies, such as hypoxia-inducing treatments or nutrient deprivation, on tumor growth.
    - Analyze the impact of various therapy protocols on cell behavior, survival rates, and overall tumor size.
    - Use simulation data to optimize therapeutic strategies and assess their effectiveness.

5. Validation and model refinement:

    - Compare simulation outputs with experimental or clinical data, if available.
    - Refine the agent behaviors and neural network models based on observed discrepancies.
    - Conduct sensitivity analysis to identify key parameters influencing tumor growth and agent decisions.

4.9 Work Plan

The following table presents the work plan for this project, detailing the activities and their timeline over the course of four years divided into three periods each year.

Activities	**Year 1**			**Year 2**			**Year 3**			**Year 4**		
	P1	P2	P3	P1	P2	P3	P1	P2	P3	P1	P2	P3
Literature review	✓	✓	✓	✗								
Define specific objectives for integrating neural networks within ABMs				✗								
Development of the agent-based tumor growth model				✗	✗	✗						
Integration and visualization of simulation results					✗	✗	✗					
Application and analysis of therapeutic strategies					✗	✗	✗					
Validation and model refinement							✗	✗	✗	✗	✗	✗
Publications						✗			✗			

Table 2: Work Plan for the Project

4.10 Publications Plan

We aim to publish two articles in scientific journals, which will present the results obtained up to that point during the thesis development. The first article will be based on one year of progress in the research, while the second article will encompass the results of the thesis by the end of the third year.

4.11 Scope and Limitations

The scope of this project encompasses the development of a computational model that integrates deep learning-based neural networks into agent-based simulations to predict and analyze tumor growth and evolution in lung cancer. This model aims to design neural networks capable of interpreting critical elements of the cellular microenvironment, such as nutrient availability, oxygen levels, and chemical signals, and predicting cellular responses based on these factors. Additionally, an agent-based model will be developed to simulate the behavior and interactions of individual tumor cells within their microenvironment, focusing on processes such as proliferation, migration, and apoptosis under varying environmental conditions. The ultimate goal is to provide a flexible and extensible computational tool that advances our understanding of tumor dynamics and serves as a platform for exploring therapeutic interventions.

Despite the ambitious goals of this project, several limitations must be acknowledged. First, the model relies on a simplified representation of the cellular microenvironment and behaviors, using a finite set of parameters and rules that may not fully capture the complexity of real biological systems. Furthermore, the accuracy of the model depends heavily on the availability and quality of experimental data, which are essential for training the neural networks and validating the simulation outcomes. Computational costs also pose a significant challenge, as the integration of deep learning into agent-based simulations requires substantial computational resources, potentially limiting the scale and resolution of the simulations.

Another limitation lies in the generalizability of the model. While ours is designed specifically for lung cancer, adapting it to other types of cancer or biological systems would require extensive modifications and revalidation. Finally, it is important to note that this project focuses on modeling tumor growth and evolution rather than directly predicting the efficacy of specific therapeutic interventions. Ad-

dressing these limitations will require careful consideration during the development process and may present opportunities for future work and refinement.

4.12 Development Tools

To conduct the experiments, the following resources are considered:

Software: The experiments will be conducted using the following software resources:

- Python 3: The primary programming language for algorithm development and implementation.
- PyTorch 1.8: A deep learning framework for neural network modeling and training.
- NumPy: For numerical computations and array manipulations.
- Pandas: For data manipulation and analysis.
- OpenCV: To process and analyze visual data.
- Matplotlib: For creating static, animated, and interactive visualizations.

Hardware: The computational experiments will be carried out on a PC with the following specifications:

- Storage: 1 TB.
- RAM: 32 GB.
- GPU: NVIDIA RTX 3060 with 6 GB RAM.
- CPU: AMD Ryzen 9 5900HX with Radeon Graphics

NVIDIA Academic Grant Program: The NVIDIA Academic Grant Program supports researchers conducting computationally intensive work in data science and related fields. This initiative provides access to high-performance computing resources, particularly leveraging NVIDIA's GPU architectures and software frameworks, to advance cutting-edge research [40]. More details about the program can be found at:
`https://goo.su/Z4u0g`.

Benefits of Utilizing the Grant Program for This Research: The proposed study involves deep learning and agent-based modeling, both of which require significant computational power for training neural networks and running large-scale simulations. By utilizing the resources provided by the NVIDIA Academic Grant Program, this research can benefit in the following ways:

- **Access to High-Performance GPUs:** Selected projects receive up to 32,000 hours on A100 40GB GPUs, significantly accelerating model training and simulation processes.
- **Optimized Frameworks for Data Science:** The grant program supports the use of RAPIDS, cuPy, cuDF, cuGraph, and Modulus, which enhance large-scale data processing, statistical analysis, and graph-based computations.
- **Scalability for Large Simulations:** The ability to run parallelized simulations with multiple GPUs allows for modeling tumor growth dynamics with high spatial and temporal resolution.
- **Advanced Graph Neural Networks (GNNs):** The program enables the exploration of graph-based deep learning architectures to improve cellular interaction modeling within the tumor microenvironment.
- **Integration with Physics-Informed Models:** NVIDIA's Modulus framework facilitates physics-based modeling, which could enhance the biological accuracy

of tumor progression simulations.

This program presents an excellent opportunity to enhance this research. We have submitted our application and are currently awaiting a response from the NVIDIA team, which is expected in June.

5 Preliminary Results

This research focuses on the development of a Neural Agent-Based Model that integrates deep learning-based neural networks into an agent-based simulation. A dataset was designed to capture biologically relevant cellular behaviors, serving as the foundation for neural agents capable of modeling cellular responses to dynamic and modifiable microenvironmental stimuli.

The microenvironment is represented as a 2D array, where each point is characterized by specific features that serve as inputs for the neural agents. These agents make decisions based on the microenvironment, with each action influencing both the microenvironment and neighboring cells, creating a complex, dynamic system of interactions.

Significant progress has been made in modeling the tumor microenvironment, establishing potential foundations for predicting cellular behavior through machine learning. At the end of the simulation, the complete state of the microenvironment and the final population count of the cells can be analyzed. This work aims to provide a comprehensive framework for understanding tumor growth and cellular interactions, leveraging the predictive capabilities of neural networks.

5.1 Dataset Creation

The creation of a this dataset has been a crucial aspect of this work, aiming to model cellular behavior within a dynamically changing microenvironment. The dataset is designed to represent six key features: oxygen, nutrients, pressure, available space, waste toxicity, and the oxygen gradient. These features are essential inputs for modeling cellular responses.

Weights for Cellular Actions

The weights assigned to the microenvironmental features represent the relative influence of each factor on the probabilities of cellular actions. The weights used for each action are as follows:

Table 3: Weights assigned to each cellular action

Action	Oxygen	Nutrients	Pressure	Space	Toxicity	Oxygen Gradient
Proliferation	0.6	0.5	-0.1	0.2	-0.2	0.1
Rest	0.4	0.4	0.4	0.2	-0.2	-0.2
Death	-0.5	-0.4	0.5	-0.4	0.4	-0.2
Movement	0.4	0.4	0.2	0.5	0.4	0.6

Dataset Generation Process

To train and evaluate the neural networks, a synthetic dataset was generated based on the input parameters of the microenvironment and their probabilistic relationships with cellular responses. For example, probability functions were employed to model the likelihood of specific cellular actions—such as proliferation or cell

death—depending on varying levels of environmental factors. These functions are derived from biological principles and, if experimental data were available, could be calibrated to reflect real-world observations.

The dataset generation process ensures diversity and representativeness by incorporating a wide range of environmental conditions and cellular states. Each data entry includes environmental features, agent states, and corresponding cellular responses, providing a comprehensive training set for the neural network. Moreover, the probabilistic approach enables the simulation of stochastic behaviors observed in biological systems, enhancing the biological realism and generalization capabilities of the model.

Probability Formulas

The probabilities of cellular actions are calculated using a formula that evaluates the weighted product of the microenvironmental features. To avoid negative values, the function $\min(0, z_j)$ is used where applicable. The formulas for each cellular action are as follows:

Proliferation

$$P_{\text{Proliferation}} = \frac{\min(0, z_{\text{Proliferation}})}{\sum_{k=1}^{4} \min(0, z_k)},$$

where:

$$z_{\text{Proliferation}} = 0.6 \cdot O_2 + 0.5 \cdot N + (-0.1) \cdot P + 0.2 \cdot S + (-0.2) \cdot T + 0.1 \cdot G,$$

and:

- O_2: Oxygen.
- N: Nutrients.

- P: Pressure.
- S: Available space.
- T: Toxicity.
- G: Oxygen gradient.

Rest

$$P_{\text{Rest}} = \frac{\min(0, z_{\text{Rest}})}{\sum_{k=1}^{4} \min(0, z_k)},$$

where:

$$z_{\text{Rest}} = 0.4 \cdot O_2 + 0.4 \cdot N + 0.4 \cdot P + 0.2 \cdot S + (-0.2) \cdot T + (-0.2) \cdot G.$$

Death

$$P_{\text{Death}} = \frac{\min(0, z_{\text{Death}})}{\sum_{k=1}^{4} \min(0, z_k)},$$

where:

$$z_{\text{Death}} = (-0.5) \cdot O_2 + (-0.4) \cdot N + 0.5 \cdot P + (-0.4) \cdot S + 0.4 \cdot T + (-0.2) \cdot G.$$

Movement

$$P_{\text{Movement}} = \frac{\min(0, z_{\text{Movement}})}{\sum_{k=1}^{4} \min(0, z_k)},$$

where:

$$z_{\text{Movement}} = 0.4 \cdot O_2 + 0.4 \cdot N + 0.2 \cdot P + 0.5 \cdot S + 0.4 \cdot T + 0.6 \cdot G.$$

Reasoning Behind: Min function

The $\min(0, z_j)$ function ensures that probability values remain non-negative, maintaining biological consistency. This approach ensures that only favorable combinations of features contribute positively to a specific cellular action, while unfavorable combinations are assigned a value of 0.

5.2 Dataset Generation Process

The dataset generation process follows these steps:

1. Generate random uniform values between [0, 1] for the microenvironmental features.
2. Compute the probabilities of each action using the formulas above.
3. Normalize the probabilities so that their sum equals 1.
4. Assign a class based on the action with the highest probability.
5. Repeat until a balanced number of samples per class is obtained.

Description of the Generated Dataset

The dataset contains:

- **Inputs:** Microenvironmental features (`Oxygen`, `Nutrients`, `Pressure`, `Available_Space`, `Toxicity`, `Oxygen_Gradient`).
- **Probabilities:** For each action (`Proliferation_Prob`, `Rest_Prob`, `Death_Prob`, `Movement_Prob`).
- **Classes:** Numeric and nominal values (`Class_Numeric`, `Class_Nominal`).

The final dataset consists of 2,500 samples evenly distributed across the four classes, ensuring balance.

5.3 Neural Network´s Training and Evaluation

A prototype neural network has been implemented to process the microenvironment data and predict cellular responses. This model utilizes a feed-forward architecture optimized for speed and accuracy, capable of handling multiple inputs such as nutrient gradients, oxygen levels, and and waste accumulation.

The neural network was trained using the generated dataset to predict cellular behavior based on the microenvironmental features. This section describes the architecture of the network, training process, and the evaluation of the neural network's performance.

Neural Network Architecture

The network was constructed as follows:

- **Input Layer:** Six neurons corresponding to the microenvironmental features (`Oxygen`, `Nutrients`, `Pressure`, `Available_Space`, `Toxicity`, `Oxygen_Gradient`).
- **Hidden Layers:**
  - First hidden layer: 64 neurons.
  - Second hidden layer: 32 neurons.
  - Third hidden layer: 16 neurons.
- **Output Layer:** Four neurons, output probabilities for each cellular behavior (`Proliferation`, `Rest`, `Death`, `Movement`).

Training Performance

During training, the model achieved a high degree of accuracy, stabilizing at 99% on the test set. The loss for both training and validation sets converged, indicating

the absence of overfitting. Figure 1 illustrates the loss evolution during training.

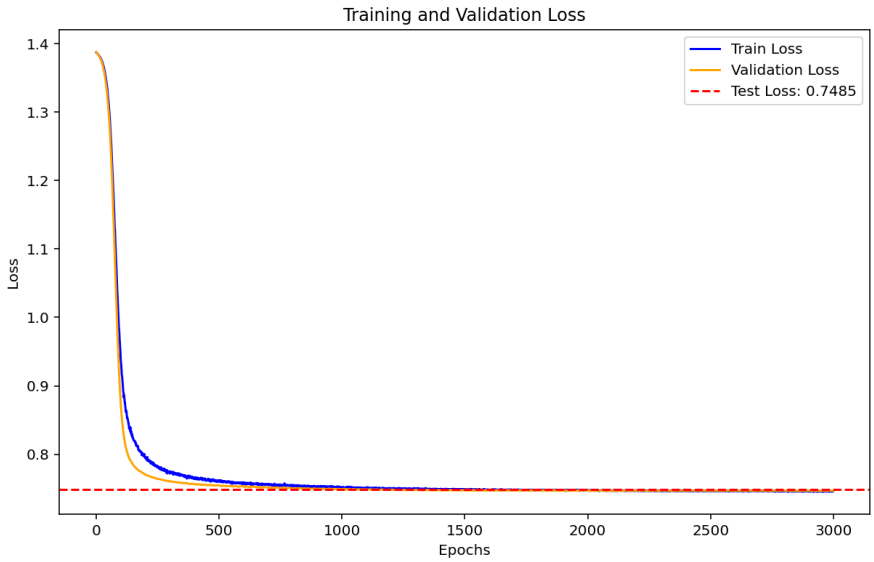


Figure 1: Training and validation loss over 3,000 epochs.

Evaluation Results

The final test accuracy was 99%. Table 4 summarizes the evaluation metrics for each class.

Table 4: Evaluation Metrics for Each Class

Class	**Precision**	**Recall**	**F1-Score**	**Support**
Proliferation	0.99	1.00	0.99	355
Rest	1.00	0.99	0.99	382
Death	0.99	1.00	1.00	377
Movement	1.00	0.99	0.99	386
Average	0.99	0.99	0.99	1,500

The confusion matrix in Figure 2 highlights the strong predictive capability of the model, with minimal misclassifications across all classes.

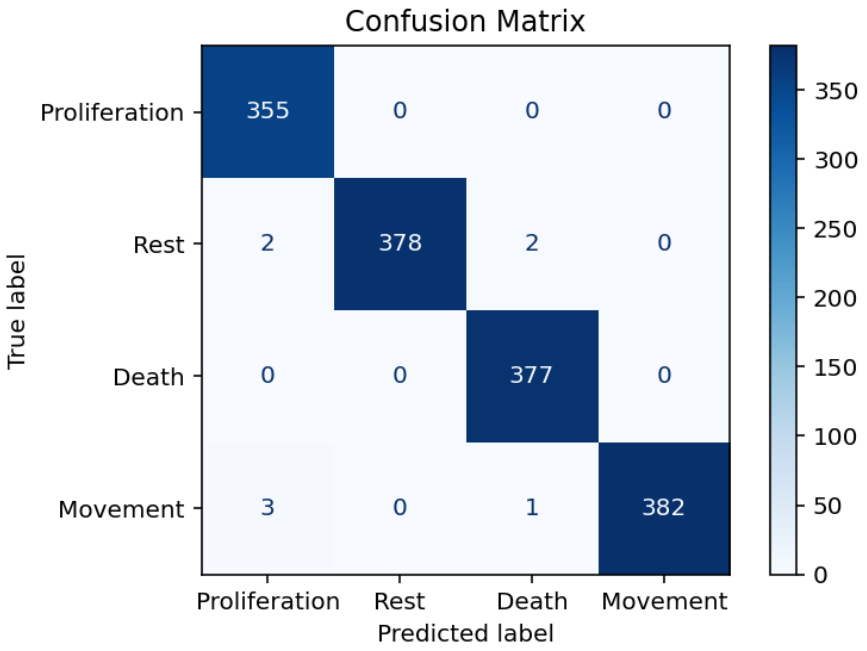


Figure 2: Confusion Matrix.

5.4 Microenvironment Design and Scalability

The microenvironment was designed to simulate a simplified but biologically relevant representation of the conditions influencing cellular behavior. By focusing on key environmental factors, such as **oxygen**, **nutrients**, **pressure**, **space**, **toxicity**, and the **oxygen gradient**, this model provides a flexible foundation for studying the interactions between cells and their surroundings. Below, we detail the guiding principles and scalability aspects used during the conducted ongoing experiments. For this experiment a microenvironment of 25x25 was designed with oxygen and nutrients in the center.

Key Design Principles

1. **Radial Symmetry for Gradual Changes:** The oxygen and nutrient distributions are modeled using a radial decay function ($\exp(-r^2)$), simulating a nat-

ural diffusion-like behavior. This allows for a biologically realistic gradient, promoting interactions that are spatially dependent.

2. **Dynamic Gradients:** The oxygen gradient is calculated directly from the oxygen distribution, ensuring that changes in the microenvironment automatically reflect in the calculated gradients. This approach enables adaptive responses in the simulation to mimic real-world biological processes.

3. **Layered Features:** Each feature (oxygen, nutrients, etc.) is stored as a separate layer in a multidimensional array. This modular design supports seamless additions or modifications of features without disrupting the existing model.

4. **Scalability and Generalization:** The microenvironment can easily adapt to incorporate additional features, such as **temperature**, **pH levels**, or **drug concentrations**, by simply appending new layers to the multidimensional array. The same methodology can be extended to represent larger or smaller environments by adjusting the `size` parameter of the microenvironment array.

Visual Representation of Features

The heatmaps generated for each feature provide immediate insights into their spatial distributions. These visualizations are not only essential for debugging but also offer to the user a clear understanding of how the microenvironment evolves over time. Below in Figure 3 we present the heatmaps that represent each feature of the microenvironment.

We can see in Figure 3 each feature. This values are easily modifiable for future experiments. In this case, oxygen and nutrient are available in the center, space is available, pressure and toxiciy are nule and the oxygen gradient is calculated.

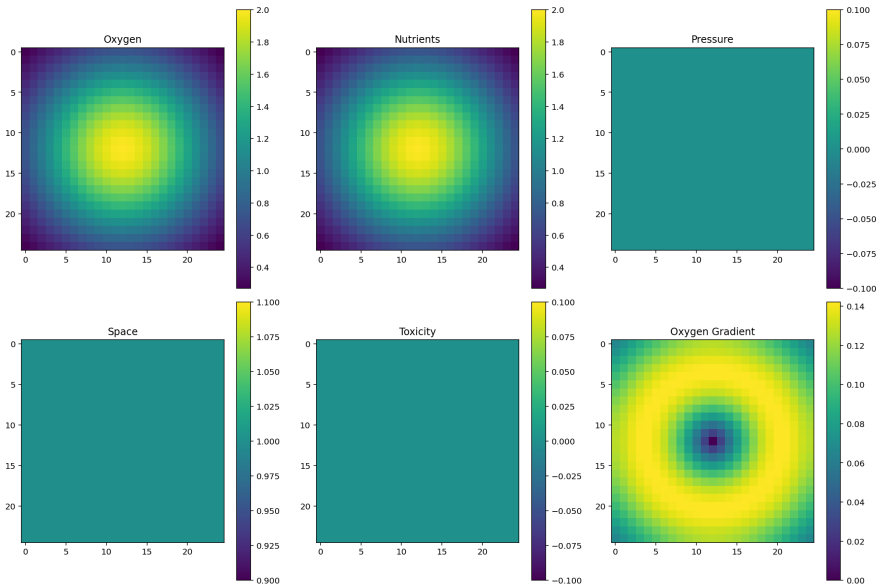


Figure 3: Micromicroenvironment´s heatmaps for each feature during the start of the simulation.

5.5 Neural Agent-based Ecosystem Results

The integration of neural networks into the agent-based model remains an ongoing effort. This involves establishing dynamic feedback loops, where the neural network not only predicts cellular responses but also adjusts the microenvironment based on those responses. For example, a cell's decision to proliferate will locally alter nutrient availability and waste accumulation, which also affects neighboring agents. The simulation's design emphasizes scalability, ensuring that large-scale cellular populations can be modeled efficiently. The following pseudocode summarizes the main steps of the simulation:

Pseudocode of the Neural Agent-based Ecosystem

Algorithm 1: Neural Agent-based Ecosystem

Data: Initial microenvironment, initial cell states (normal or cancer cells)

Result: Updated microenvironment, Cell states, and Cell´s Population

Initialize: Load microenvironment and Agents´ Neural Network;

Define: Initial number of cells and cells´ positions

foreach *step* $t = 1, \ldots, T$ **do**

Update Microenvironment:

- Update pressure.
- Update Oxygen Gradient.

Update Cell States:

- Evaluate environmental inputs for each cell.
- Calculate probabilities for proliferation, movement, rest, and death.
- Update cell states based on probabilities.

Adjust Environment:

- Modify the microenvironment based on cell actions (e.g., nutrient consumption, waste production).

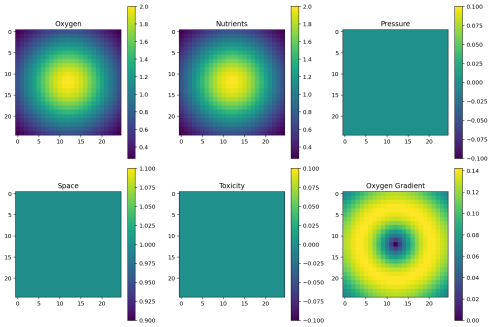
Update Microenvironment:

- Update all microenvironment´s features.
- Verify all features values are in range.

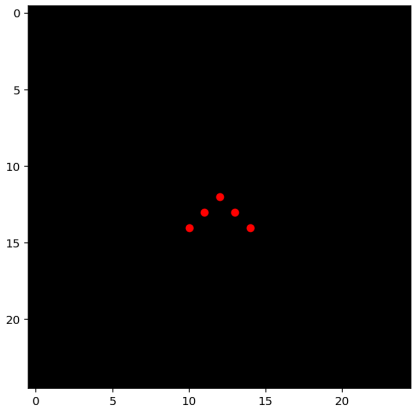
end

Visualization of Results

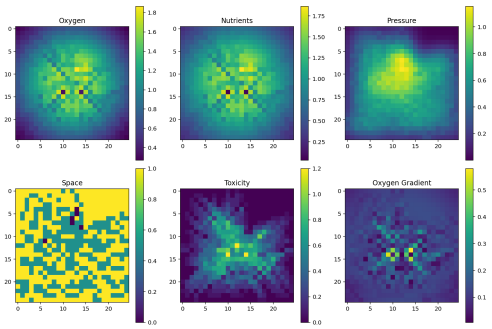
Below are the heatmaps of the microenvironment and cell states at key steps of the simulation (**steps 0, 10, 50, 100, 150, and 200**). Each pair of heatmaps shows the spatial distribution of environmental factors and cell states.



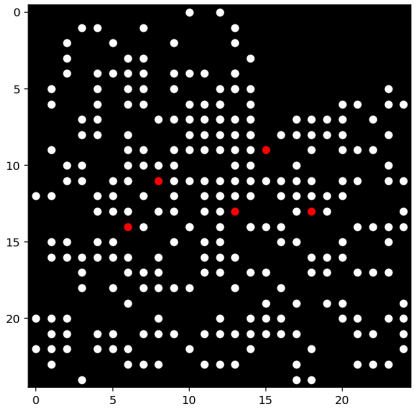
Microenvironment at initial Step



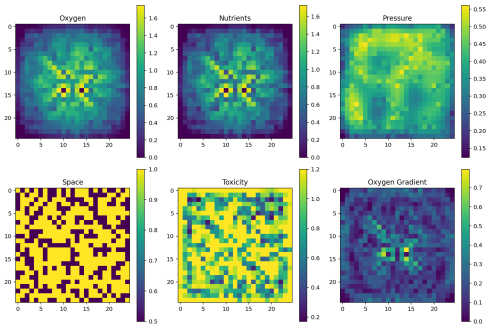
Cells at Initial Step



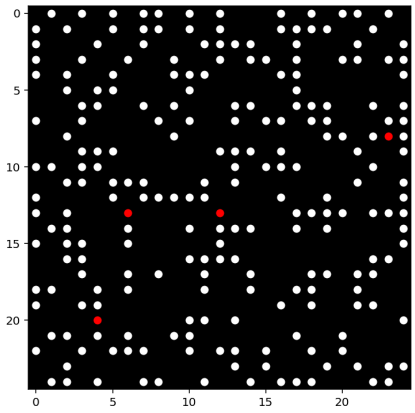
Microenvironment at Step 10



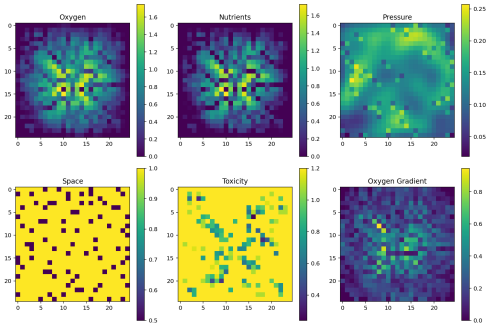
Cells at Step 10



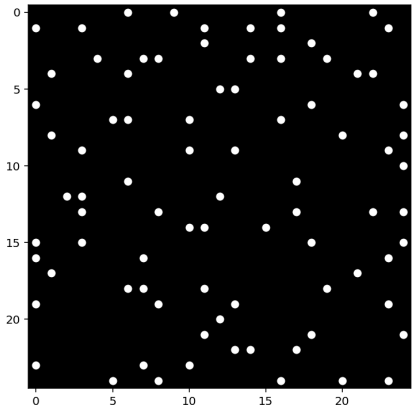
Microenvironment at Step 50



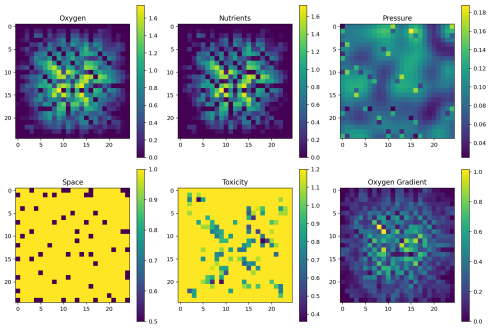
Cells at Step 50



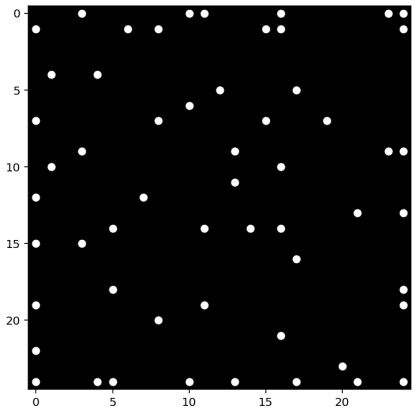
Microenvironment at Step 100



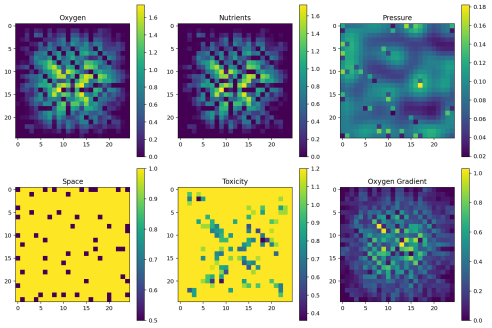
Cells at Step 100



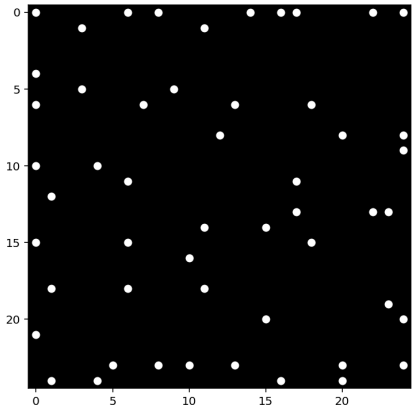
Microenvironment at Step 150



Cells at Step 150



Microenvironment at Step 200



Cells at Step 200

Cancer Cell Count Over Time

The following plot shows the number of live cancer cells throughout the simulation, providing insights into the dynamics of tumor growth or reduction.

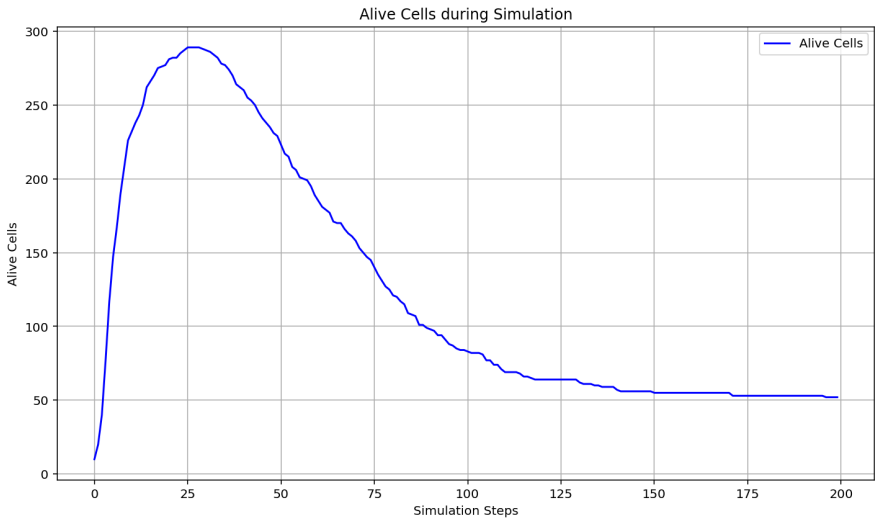


Figure 4: Number of Cancer Cells Over Time

5.6 Discussion

The Results demonstrates the adaptability of the microenvironment and cell interactions. The visualizations and statistics provide valuable insights into the spatiotemporal dynamics of cancer cell behavior under varying environmental conditions.

In general, this simulation does not provide additional oxygen or nutrients to the cells during the simulation runtime. This constraint aligns with scenarios where the tumor microenvironment experiences limited resources, contributing to the biological realism of the model. However, parameters such as the weight and volume of the cells could be further refined to improve the accuracy and precision of the results.

The results obtained from the simulation show coherence with known biologi-

cal behaviors. The interactions between cancer cells and their environment, such as proliferation, movement, and death, reflect patterns observed in experimental data. The integration of neural networks within the agent-based model enhances the ability of cells to make decisions based on environmental conditions, and the network functions adequately in this context.

Additionally, other tests were conducted using different initial numbers of cancer cells to evaluate the robustness of the model. These tests demonstrated consistent behavior in line with biological expectations, indicating the reliability of the model across varying initial conditions.

6 Conclusions

This research introduces an innovative computational approach by integrating neural networks into an agent-based model to simulate tumor growth and cellular interactions within a dynamic microenvironment. The current implementation demonstrates the adaptability of the microenvironment and the agents' ability to respond to changing environmental conditions. However, there are several areas for further refinement and exploration.

The parameters defining cell behavior, such as weight and volume, as well as the physical and chemical characteristics of the microenvironment, could be optimized to improve accuracy and better reflect biological reality. Additionally, incorporating more complex biochemical interactions, such as signaling pathways and metabolic constraints, would enhance the model's capacity to capture tumor evolution with greater fidelity.

The flexibility of the neural network architecture also presents opportunities for improvement. The current implementation can be expanded to incorporate alternative architectures such as *liquid neural networks, physics-informed neural net-*

works, and Kolmogorov-Arnold Networks (KAN). These approaches could improve the model's adaptability, predictive capabilities, and interpretability, allowing for a more detailed exploration of cellular decision-making processes.

This methodology is not limited to tumor modeling but can be extended to simulate other neural agents representing distinct cellular populations, such as *immune cells or healthy cells within the tumor microenvironment.* Additionally, therapies could be modeled as neural agents, dynamically interacting with tumor cells. While the selection of specific therapies for simulation is still under consideration, this approach opens new pathways for studying treatment strategies computationally.

6.1 Final Remarks

One of the primary challenges of this research is the validation of the model, as there is a limited availability of real-world datasets that accurately track tumor progression at a cellular level. However, comparisons can be made using existing murine tumor models, where tumor volume evolution has been documented over time. These comparisons would allow for an initial assessment of the model's accuracy and biological relevance.

Furthermore, we have applied for the NVIDIA Hardware Grant Program, which, if approved, would provide access to advanced computational resources for more complex simulations and large-scale experiments. Leveraging NVIDIA's hardware could significantly accelerate training times for neural networks, enabling more extensive hyperparameter tuning and real-time processing of tumor dynamics.

6.1.1 Scalability for Future Applications

Beyond the current model, several extensions could be explored to enhance the scalability and versatility of this approach:

1. **Expansion to 3D Simulations:** Introducing a third spatial dimension (z-axis) would enable the simulation of more biologically relevant structures, such as tumor spheroids or full tissue models.

2. **Heterogeneous Microenvironments:** Instead of a homogeneous distribution of microenvironmental factors, more complex spatial patterns could be introduced, incorporating tissue regions with variable oxygen, pressure, and nutrient levels to better replicate in vivo conditions.

3. **Dynamic Environmental Updates:** Over time, factors such as *pressure, toxicity, and oxygen diffusion* can be updated dynamically in response to cellular actions (e.g., proliferation increasing pressure or death increasing toxicity). This feature would enable longitudinal studies of tumor evolution and the effects of different therapeutic strategies.

4. **Integration of Adaptive Therapies:** By incorporating neural agents representing *adaptive therapies*, the model could simulate dynamic treatment strategies, such as personalized drug responses based on real-time tumor progression.

References

[1] W. H. Organization, "Cáncer de pulmón," accessed: December 10, 2024. [Online]. Available: https://www.who.int/es/news-room/fact-sheets/detail/lung-cancer

[2] A. C. Society, "Estadísticas importantes sobre el cáncer de pulmón," accessed: December 10, 2024. [Online]. Available: https://www.cancer.org/es/cancer/tipos/cancer-de-pulmon/acerca/estadisticas-clave.html

[3] "Tabaquismo y cáncer de pulmón — comisión nacional contra las adicciones — gobierno — gob.mx," accessed: December 10, 2024. [Online]. Available: https://www.gob.mx/salud/conadic/articulos/tabaquismo-y-cancer-de-pulmon

[4] A. Leiter, R. R. Veluswamy, and J. P. Wisnivesky, "The global burden of lung cancer: current status and future trends," *Nature Reviews Clinical Oncology*, vol. 20, pp. 624–639, 9 2023.

[5] U. C. for Disease Control and Prevention, "Información básica sobre el cáncer de pulmón — cáncer de pulmón — cdc," accessed: December 10, 2024. [Online]. Available: https://www.cdc.gov/lung-cancer/es/about/index.html

[6] "Cáncer de pulmón: Medlineplus en español," accessed: December 10, 2024. [Online]. Available: https://medlineplus.gov/spanish/lungcancer.html

[7] J. Alyami, A. R. Khan, S. A. Bahaj, and S. M. Fati, "Microscopic handcrafted features selection from computed tomography scans for early stage lungs cancer diagnosis using hybrid classifiers," *Microscopy Research and Technique*, vol. 85, 2022.

[8] N. K. Singh, R. Gupta, and S. Sahu, "Bio-inspired swarm-intelligent with machine learning framework for prediction and classification of lung cancer," in *Multidisciplinary Science Journal*, vol. 5, 2023.

[9] E. Kolokotroni, D. Abler, A. Ghosh, E. Tzamali, J. Grogan, E. Georgiadi, P. Büchler, R. Radhakrishnan, H. Byrne, V. Sakkalis, K. Nikiforaki, I. Karatzanis, N. J. McFarlane, D. Kaba, F. Dong, R. M. Bohle, E. Meese, N. Graf, and G. Stamatakos, "A multidisciplinary hyper-modeling scheme in personalized in silico oncology: Coupling cell kinetics with metabolism, signaling networks, and biomechanics as plug-in component models of a cancer digital twin," *Journal of Personalized Medicine*, vol. 14, 5 2024.

[10] A. I. Wilterson and M. S. Graziano, "The attention schema theory in a neural network agent: Controlling visuospatial attention using a descriptive model of attention," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 118, 2021.

[11] A. Lahiri, A. Maji, P. D. Potdar, N. Singh, P. Parikh, B. Bisht, A. Mukherjee, and M. K. Paul, "Lung cancer immunotherapy: progress, pitfalls, and promises," *Molecular Cancer*, vol. 22, 12 2023.

[12] M. Ghita, V. Chandrashekar, D. Copot, C. Billiet, D. Verellen, and C. M. Ionescu, "Lung tumor growth modeling in patients with nsclc undergoing radiotherapy," in *IFAC-PapersOnLine*, vol. 54, 2021.

[13] A. Ghaffarizadeh, R. Heiland, S. H. Friedman, S. M. Mumenthaler, and P. Macklin, "Physicell: An open source physics-based cell simulator for 3-d multicellular systems," *PLoS Computational Biology*, vol. 14, 2018.

[14] R. Heiland, D. Bergman, B. Lyons, G. Waldow, J. Cass, H. L. da Rocha, M. Ruscone, V. Noël, and P. Macklin, "Physicell studio: a graphical tool to make agent-based modeling more accessible," *GigaByte*, vol. 2024, 2024.

[15] T. O. Benson, M. A. Islam, K. Liu, and A. N. F. Versypt, "Agent-based modeling reveals impacts of cell adhesion and matrix remodeling on cancer collective cell migration phenotypes," *bioRxiv*, p. 2024.12.23.630172, 12 2024. [Online]. Available: https://www.biorxiv.org/content/10.1101/2024.12.23.630172v1https://www.biorxiv.org/content/10.1101/2024.12.23.630172v1.abstract

[16] Z. Wang, L. Zhang, J. Sagotsky, and T. S. Deisboeck, "Simulating non-small cell lung cancer with a multiscale agent-based model," *Theoretical Biology and Medical Modelling*, vol. 4, p. 50, 2007. [Online]. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC2259313/

[17] F. Bray, M. Laversanne, H. Sung, J. Ferlay, R. L. Siegel, I. Soerjomataram, and A. Jemal, "Global cancer statistics 2022: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *Ca*, vol. 74, pp. 229–263, 5 2024.

[18] R. L. Siegel, K. D. Miller, N. S. Wagle, and A. Jemal, "Cancer statistics, 2023," *Ca*, vol. 73, pp. 17–48, 1 2023.

[19] W. S. Hong, S. G. Wang, and G. Q. Zhang, "Lung cancer radiotherapy: Simulation and analysis based on a multicomponent mathematical model," *Computational and Mathematical Methods in Medicine*, vol. 2021, 2021.

[20] F. Yang, W. Wang, F. Wang, Y. Fang, D. Tang, J. Huang, H. Lu, and J. Yao, "scbert as a large-scale pretrained deep language model for cell type annotation of single-cell rna-seq data," *Nature Machine Intelligence 2022 4:10*, vol. 4, pp. 852–866, 9 2022. [Online]. Available: https://www.nature.com/articles/s42256-022-00534-z

[21] J. Smieja, "Mathematical modeling support for lung cancer therapy—a short review," 2023.

[22] D. L. Poole and A. K. Mackworth, "Artificial intelligence: Foundations of computational agents, 3rd edition," accessed: December 10, 2024. [Online]. Available: https://artint.info/3e/html/ArtInt3e.html

[23] K. M. Schneider, K. Giehl, and S. A. Baeurle, "Development and application of an agent-based model for the simulation of the extravasation process of circulating tumor cells," *International Journal for Numerical Methods in Biomedical Engineering*, vol. 39, 2023.

[24] J. Poleszczuk, P. Macklin, and H. Enderling, "Agent-based modeling of cancer stem cell driven solid tumor growth," *bioRxiv*, 12 2015. [Online]. Available: http://biorxiv.org/lookup/doi/10.1101/035162

[25] S. Zouhri and M. E. Baroudi, "Mathematical formalism for agent-based model of proteins interaction inside cancer cell," *Communications in Mathematical Biology and Neuroscience*, vol. 2023, 2023.

[26] J. D. Butner, D. Fuentes, B. Ozpolat, G. A. Calin, X. Zhou, J. Lowengrub, V. Cristini, and Z. Wang, "A multiscale agent-based model of ductal carcinoma in situ," *IEEE Transactions on Biomedical Engineering*, vol. 67, 2020.

[27] S. C. Hendrikse, J. Treur, and S. L. Koole, "Modeling emerging interpersonal synchrony and its related adaptive short-term affiliation and long-term bonding: A second-order multi-adaptive neural agent model," *International journal of neural systems*, vol. 33, 7 2023. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/37381917/

[28] M. R. Baig, T. V. Joseph, and N. Sadvilkar, *The Deep Learning Workshop: Learn the Skills You Need to Develop Your Own Next-Generation Deep Learning Models with TensorFlow and Keras.* Packt Publishing, 2020. [Online]. Available: https://books.google.com.mx/books?id=xgmvzQEACAAJ

[29] A. Jha, S. K. Sahani, A. Jha, and K. Sahani, "From equations to insights: Navigating the canvas of tumor growth dynamics," *MASALIQ*, vol. 3, 2023.

[30] A. Prelaj, E. G. Galli, V. Miskovic, M. Pesenti, G. Viscardi, B. Pedica, L. Mazzeo, A. Bottiglieri, L. Provenzano, A. Spagnoletti, R. Marinacci, A. D. Toma, C. Proto, R. Ferrara, M. Brambilla, M. Occhipinti, S. Manglaviti, G. Galli, D. Signorelli, C. Giani, T. Beninato, C. C. Pircher, A. Rametta, S. Kosta, M. Zanitti, M. R. D. Mauro, A. Rinaldi, S. D. Gregorio, M. Antonia, M. C. Garassino, F. G. de Braud, M. Restelli, G. L. Russo, M. Ganzinelli, F. Trovò, and A. L. G. Pedrocchi, "Real-world data to build explainable trustworthy artificial intelligence models for prediction of immunotherapy efficacy in nsclc patients," *Frontiers in Oncology*, vol. 12, 2023.

[31] R. Salgia, I. Mambetsariev, B. Hewelt, S. Achuthan, H. Li, V. Poroyko, Y. Wang, and M. Sattler, "Modeling small cell lung cancer (sclc) biology through deterministic and stochastic mathematical models," 2018.

[32] Z. Wang and Q. Wang, "Numerical simulation of a tumor growth dynamics model using particle swarm optimization," *Journal of Computer Science and Systems Biology*, vol. 09, 2016.

[33] A. Rojas-Domínguez, R. Arroyo-Duarte, F. Rincón-Vieyra, and M. Alvarado-Mentado, "Modeling cancer immunoediting in tumor microenvironment with system characterization through the ising-model hamiltonian," *BMC Bioinformatics*, vol. 23, 2022.

[34] V. Sreejithkumar, E. Schrom, and R. Germain, "3d extension of spatial patterning analysis of cellular ensembles (space) to extract parameters for dynamic tumor modeling," *Journal of Immunology*, vol. 212, 5 2024. [Online]. Available: https://journals.aai.org/jimmunol/article/212/1_Supplement/0245_4416/267696/3D-extension-of-spatial-patterning-analysis-of

[35] R. Raza, F. Zulfiqar, M. O. Khan, M. Arif, A. Alvi, M. A. Iftikhar, and T. Alam, "Lung-effnet: Lung cancer classification using efficientnet from ct-scan images," *Engineering Applications of Artificial Intelligence*, vol. 126, p. 106902, 11 2023.

[36] R. K. Sachdeva, P. Bathla, P. Rani, R. Lamba, G. S. P. Ghantasala, and R. S. R, "Lung cancer classification using machine learning," *2024 First International Conference on Innovations in Communications, Electrical and Computer Engineering (ICICEC)*, pp. 1–6, 10 2024. [Online]. Available: https://ieeexplore.ieee.org/document/10808741/

[37] P. Nasra, "Lung cancer classification using resnet50," *2nd International Conference on Intelligent Cyber Physical Systems and Internet of Things, ICoICI 2024 - Proceedings*, pp. 1201–1205, 2024.

[38] I. Naseer, S. Akram, T. Masood, M. Rashid, and A. Jaffar, "Lung cancer classification using modified u-net based lobe segmentation and nodule detection," *IEEE Access*, vol. 11, pp. 60 279–60 291, 2023.

[39] E. Raeisi, M. Yavuz, M. Khosravifarsani, and Y. Fadaei, "Mathematical modeling of interactions between colon cancer and immune system with a deep learning algorithm," *The European Physical Journal Plus 2024 139:4*, vol. 139, pp. 1–16, 4 2024. [Online]. Available: https://link.springer.com/article/10.1140/epjp/s13360-024-05111-4

[40] "Nvidia academic grant program. call for proposals data science," accessed: December 10, 2024. [Online]. Available: https://nvdam.widen.net/s/djf2gxbssk/her-grant-program-cfps-data-science-3424582-r3