Agent-Based Simulation of CAR-T Cell Therapy Using BioDynaMo

BioDynaMo project description.

Author: *de la Torre Gonzalez, Salvador*

Google Summer of Code 2025 Program, CERN-HSF, CompRes

Mentors: Vassil Vassilev, Lukas Breitwieser

Size: 350 hours, medium difficulty

Overview

Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized immunotherapy, particularly in treating hematological malignancies. However, its effectiveness in solid tumors remains limited due to challenges such as poor tumor infiltration, immunosuppressive microenvironments, and T-cell exhaustion. Computational modeling has become a crucial tool for optimizing CAR-T therapy, as it allows researchers to predict outcomes, explore various treatment strategies, and guide experimental research.

This project aims to develop a scalable agent-based simulation of CAR-T therapy using BioDynaMo, a high-performance biological simulation platform. The model will focus on simulating CAR-T cell behavior, including migration, tumor engagement, and the impact of microenvironmental factors on CAR-T efficacy, helping researchers optimize CAR-T treatment strategies and better understand underlying biological processes.

Methodology Overview

The project will use an agent-based modeling (ABM) approach to simulate the interactions between CAR-T cells, tumor cells, and their microenvironment. The methodology involves the following steps:

- **Defining CAR-T cell agents**: These will be modeled with properties such as migration, proliferation, and cytotoxic activity, reflecting the key functions of CAR-T

cells in targeting and killing tumor cells.

- **Modeling tumor cells**: Tumor cells will be represented as agents with characteristics such as proliferation, immune evasion, and resistance mechanisms. These parameters will influence how the tumor behaves in the presence of CAR-T cells.

- **Simulating environmental factors**: Factors such as hypoxia, immunosuppressive cytokines, and regulatory T cells will be incorporated to model how the tumor microenvironment affects CAR-T cell function.

- **Running simulations**: The model will simulate different treatment scenarios, analyzing how varying parameters affect CAR-T cell efficacy and tumor progression.

- **Developing visualization tools**: Tools will be created to interpret the simulation results, helping researchers visualize tumor dynamics, CAR-T cell behavior, and treatment outcomes.

Background

- **CAR-T models and data in immunotherapy:** It is important to spot the main models and clinical results of CAR-T immunotherapy [12],[13],[14] in order to identify key parameters that can be used in simplified simulations and, in addition, allow us to compare our results with existing approaches. Several important papers describe CAR-T immunotherapy using Lotka-Volterra differential equations [1], [2]; which are highly relevant for understanding the dynamics of CAR-T cells and tumor interactions.
- **Simulations of tumor growth and response to immunotherapy:** It is crucial to examine tumor growth simulations and their response to immunotherapy [3],[4]. This helps us understand the expected behavior of tumors and the phenomena that should be taken into account in our model. *Cellular dynamics during epicutaneous immunotherapy using agent-based modeling* [5] focuses on Agent Based Simulations which makes it even more relevant to our approach.
- **BioDynaMo's capabilities**: It is important to review the examples and cancer simulations already created using BioDynaMo [6] to integrate similar models into our project. By doing so, we can learn how to safely model complex biological objects and interactions, such as those involved in tumor dynamics.
- **Biological Scientific papers related to oncology:** To further refine our model, we should explore biological phenomena and techniques relevant to oncology, such as hypoxia [7] (affecting both tumors and CAR-T cells), cytokines [8], apoptosis[11]and other factors [9], [10]

High-Level Implementation Plan

The **Implementation Plan** for the **Agent-Based Simulation of CAR-T Cell Therapy** using BioDynaMo follows a structured, multi-phase approach to simulate the dynamic interactions between CAR-T cells, tumor cells, and the surrounding microenvironment. The main goal is to create an agent-based model that can be used to optimize CAR-T therapy by considering

various factors that influence its effectiveness. Below, I'll break down each phase of the plan and the different properties that will be implemented.

Phase 1: Initial Setup & Simple T-cell Dynamics

Phase 1.1: Existing Models review

In the initial phase of the project, I will conduct a comprehensive review of existing literature to identify relevant studies and attempt to replicate their results. This step is crucial for ensuring that our project is on the right track and for providing a baseline for comparison with existing models, ultimately aiming to enhance the precision of our outcomes. While I have already referenced several well-known CAR-T models and experimental clinical data [1], [2],[12],[13],[14] in this proposal, it is important to revisit this process at the project's outset, as new publications may have emerged. Many relevant models rely on the dynamics of predator-prey systems, often using Lotka-Volterra differential equations, making them key candidates for our comparative analysis.

Phase 1.2: Simple T-cell Dynamics – Lotka-Volterra Model

The initial stage involves building a foundational model that simulates the basic dynamics of CAR-T cells and tumor cells using the **Lotka-Volterra predator-prey model**. In this model, CAR-T cells are treated as the "predator" population, while tumor cells are treated as the "prey."

Key Properties Implemented:

1. **Tumor Cells (Prey):**
    - **Proliferation Rate (r):** The rate at which tumor cells divide and reproduce. This is a crucial factor in modeling tumor growth.
    - **Carrying Capacity (K):** The maximum number of tumor cells that can be sustained by the environment. This simulates the concept of limited resources that tumors can use to grow.
    - **Death Rate due to CAR-T Attack (α):** This factor controls how effectively CAR-T cells kill tumor cells. A higher rate means the CAR-T cells are more efficient in eliminating tumors.
    - **Random Motility (D_tumor):** This parameter models the passive, random movement of tumor cells in the environment, simulating how they spread or infiltrate surrounding tissues.
2. **CAR-T Cells (Predator):**
    - **Initial CAR-T Cell Count (T0):** The number of CAR-T cells introduced into the system at the start of the simulation. This helps control the scale of the experiment.

- **Proliferation Rate (p):** The rate at which CAR-T cells multiply, particularly when they interact with tumor cells.

- **Engagement Efficiency (β):** This represents how effectively CAR-T cells bind to and destroy tumor cells upon contact.

- **Exhaustion Rate (E):** This factor simulates CAR-T cell exhaustion over time, representing the gradual loss of their cytotoxic capabilities.

- **Random Motility (D_CART):** Initially, CAR-T cells are modeled with random movement, which will later be refined to simulate chemotaxis (directed movement toward tumor cells).

The model will be set in a 2D or 3D grid environment, where CAR-T cells and tumor cells interact based on their defined behaviors. The goal is to observe the **predator-prey dynamics**:

- Tumor cells proliferate, attracting CAR-T cells.

- As CAR-T cells eliminate tumor cells, the tumor population decreases.

- With fewer tumor cells, CAR-T cells also diminish, allowing the tumor population to rise again.

Phase 1.3: Modeling Different Tumor Types

In this phase, the model will be extended to reflect the behavior of different types of tumors. Tumor cells will no longer just move randomly; instead, their movement and growth patterns will be altered to reflect the characteristics of specific cancers.

Key Properties Implemented:

1. **Tumor Migration and Dissemination:**

    - Tumor cells will now have a chance to migrate and form secondary tumors, simulating **metastasis** (the spread of cancer).

    - Some tumors, like **leukemia**, have cells that move freely, and the model will account for this behavior.

2. **Leukemia Models:**

    - For **leukemia**, the tumor cells will be modeled as free-moving agents that do not form solid masses but instead circulate freely within the system.

This phase will integrate existing tumor growth models from BioDynaMo to simulate different tumor types, enhancing the biological accuracy of the simulation.

Phase 2: Advanced CAR-T Cell Behavior & Tumor Interaction

Phase 2.1: Enhancing the Model

The second phase adds more biological complexity to the simulation by incorporating advanced CAR-T cell behaviors and improving tumor interactions.

Key Properties Implemented:

1. **Apoptosis:**
    - Both CAR-T cells and tumor cells will undergo **apoptosis** (programmed cell death), which reflects their natural lifespan. This will be an important factor in regulating the population of each type of cell.
2. **Exhaustion Rate (E):**
    - The exhaustion of CAR-T cells will be further refined. As CAR-T cells engage tumor cells, they will experience a decline in efficacy, and this will be modeled by adjusting the exhaustion rate.
3. **Motility (D_CART):**
    - The movement of CAR-T cells will be modified to reflect **chemotaxis**, meaning they will actively migrate toward the tumor cells based on signaling gradients in the environment (such as cytokines or tumor markers).
4. **Antigen Recognition Dynamics:**
    - CAR-T cells will recognize specific antigens on tumor cells, and the efficiency of antigen recognition and killing will be modeled.

Phase 2.2: Incorporating Hypoxia and Its Effects

Hypoxia, a condition of low oxygen, is a well-known factor that impacts both tumor growth and immune cell activity. This phase models how hypoxia influences both tumor and CAR-T cells.

Key Properties Implemented:

1. **Tumor Cells Under Hypoxia:**
    - **Tumor Growth:** Tumor growth will be slower under hypoxic conditions due to nutrient and oxygen deprivation. However, hypoxia will also promote **tumor**

cell dissemination, as tumor cells will search for new locations to grow.

2. **CAR-T Cells Under Hypoxia:**
    - The **proliferation rate** and **cytotoxic activity** of CAR-T cells will decrease under hypoxic conditions. This reflects the real-world impact of tumor oxygen depletion on immune function.
    - **Exhaustion effects** will become more pronounced under hypoxia, as CAR-T cells are less effective in such an environment.

This phase introduces a significant biological factor that could limit the success of CAR-T therapy, making the model more representative of real tumor environments.

Phase 3: Immune Evasion & Data Visualization

Phase 3.1: Immune Evasion Strategies

Tumors often employ **immune evasion strategies** to escape the immune system. This phase models some of these strategies, including the introduction of **cytokines** and **regulatory T cells** (Tregs) that can inhibit CAR-T cell function.

Key Properties Implemented:

1. **Regulatory T Cells (Tregs):**
    - Tregs suppress the immune response and will be modeled to interfere with CAR-T cell function, diminishing their efficacy in the tumor microenvironment.
2. **Cytokines:**
    - Immunosuppressive **cytokines** will be introduced into the model, reducing CAR-T cell activity and helping the tumor evade immune destruction.

Phase 3.2: Data Visualization and Performance Optimization

Data visualization tools will be developed to interpret the simulation results. This will help researchers assess how different treatment strategies perform under various conditions.

Key Properties Implemented:

1. **Visualization Tools:**
    - The simulation results will be visualized to show the dynamics of CAR-T cells, tumor cells, and the microenvironment over time.

    - These tools will allow for **spatial and temporal analysis**, helping researchers to easily know what to expect from a treatment and choose the best alternative for a patient.

2. **Performance Optimization:**

    - Since the simulations can be computationally demanding, performance optimization will ensure that large-scale simulations can be efficiently run on high-performance computing systems.

Phase 4: Empirical Comparison, Quality, and Documentation

Phase 4.1: Comparison with Experimental Data

Throughout the project, results will be compared with **experimental data** to ensure the model is accurate and biologically plausible. The hyperparameters of the model will be fine-tuned to match real-world observations as closely as possible.

Phase 4.2: Software Quality and Documentation

It is important to write readable and generalized code from the beginning; however, the aim of this phase is to refine the repository and create good documentation so that anyone can use and modify it.

New gadgets and considerations should be easy to add in the future, allowing the project to be adapted to simulate specific environments (for example using cart T in a patient under another parallel treatment as radiotherapy) or account for newly discovered interactions.

Phase 4.3: Analysis and Demonstrations

The final deliverable will be a **comprehensive scientific report** that showcases the findings of the simulation. This report will include:

- Recreate a few different scenarios and types of cancer to show **examples of usage**.
- Perform analysis and **extract information** from our simulations using statistical inference to validate their value and briefly comment on the discoveries.
- Conduct benchmarks between **several treatment strategies**.

Schedule

The final schedule can only be agreed between the mentors and the selected candidates once announced. However this is a realistic hypothetical schedule of how I would organize the derivables as a candidate.

Week	Activities	Deliverable
Week 1 (June 15-21)	**Phase 1.1**: Research and select papers for comparison. Set a solid foundation. Review initial BioDynaMo setup and ensure the environment is functioning for the project.	Selected papers, environment setup, and definitive project plan.
Week 2 (June 22-28)	**Phase 1.2**: Implement the basic agent-based model to simulate CAR-T and tumor dynamics. Early comparison with selected paper's results to validate direction.	Fully documented initial BioDynaMo simulation with CAR-T and tumor interactions (basic setup).
Week 3 (June 29 - July 5)	**Phase 1.2**: Refine model to include random motility for both CAR-T and tumor cells. Test basic interactions, update code documentation.	Updated BioDynaMo simulation with random motility and documentation.
Week 4 (July 6-12)	**Phase 1.3**: Extend the model to simulate different tumor types (e.g., leukemia and solid tumors). Implement tumor migration and basic growth.	Simulation of different tumor types with basic tumor dynamics.
Week 5 (July 13-19)	**Phase 2.1**: Introduce apoptosis dynamics for CAR-T and tumor cells. Test interactions, update documentation.	Apoptosis dynamics added to the simulation for both CAR-T and tumor cells, with detailed documentation.
Week 6 (July 20-26)	**Phase 2.1**: Incorporate CAR-T exhaustion. Refine the model with more complex tumor interactions (e.g., immune evasion).	Updated simulation with CAR-T exhaustion and immune evasion dynamics.
Week 7 (July 27 - Aug 2)	**Phase 2.2**: Begin modeling environmental factors like hypoxia (affecting both CAR-T and tumor behavior).	Model with hypoxia effects, including tumor growth under low oxygen and CAR-T cell activity.

Week 8 (Aug 3-9)	**Phase 2.2**: Implement chemotaxis for CAR-T cells (targeted movement toward tumors). Test hypoxia interaction with CAR-T chemotaxis.	Enhanced simulation with CAR-T chemotaxis and refined hypoxia interactions.
Week 9 (Aug 10-16)	**Phase 3.1**: Integrate immune evasion mechanisms (Tregs, immunosuppressive cytokines). Test overall model behavior.	Full immune evasion model with Tregs and cytokines affecting CAR-T efficacy.
Week 10 (Aug 17-23)	**Phase 3.2**: Develop analysis scripts for visualizing tumor reduction and CAR-T efficacy (graphs, spatial dynamics). Start preparing for performance optimization.	Working analysis scripts for tumor reduction and CAR-T efficacy visualization.
Week 11 (Aug 24-30)	**Phase 3.2**: Test and optimize model performance for large-scale simulations. Run benchmarks for treatment strategies and record results.	Performance benchmarks for different treatment strategies, optimization for large-scale simulations.
Week 12 (Sept 1-7)	**Phase 3.2**: Continue refining the model with feedback. Test the model with real-world data, adjust parameters.	Updated model with real-world data validation, fine-tuned parameters.
Week 13 (Sept 8-14)	**Phase 4.1**: Finalize data visualizations. Complete and refine analysis scripts for treatment strategy comparison.	Finalized data visualizations and analysis scripts for CAR-T and tumor dynamics.
Week 14 (Sept 15-21)	**Phase 4.2**: Start drafting the research-style report, summarizing the findings, including model details, data analysis, and performance benchmarks.	Draft of the research-style report with analysis and benchmarks.
Week 15 (Sept 22-28)	**Phase 4.3**: Finalize the report with a detailed explanation of findings, comparisons with experimental data, and treatment strategy results. Review and prepare for final submission.	Finalized report, fully written, including all analysis and findings.

Week 16 (Sept 29 - Oct 5)	**Phase 4.3**: Recovery week, to deal with unexpected delays in the process.	Recovery week to handle delays.
Week 17 (Oct 6 - Oct 12)	**Phase 4.3**: Submit the final report, all deliverables, and the fully documented codebase. Prepare the final project presentation.	Final report, deliverables, fully documented codebase, and presentation prepared.

Conclusion

By following this implementation plan, the project will create a robust, scalable simulation framework for CAR-T therapy that can help researchers optimize treatment parameters, explore new strategies, and ultimately improve the clinical outcomes of CAR-T therapy for various types of cancer. The insights gained from this project will help minimize the need for costly and time-consuming laboratory experiments.

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