CARTopiaX: an Agent-Based Simulation of CAR T-Cell Therapy built with BioDynaMo and ROOT

ROOT Users Workshop 2025, UPV-Valencia

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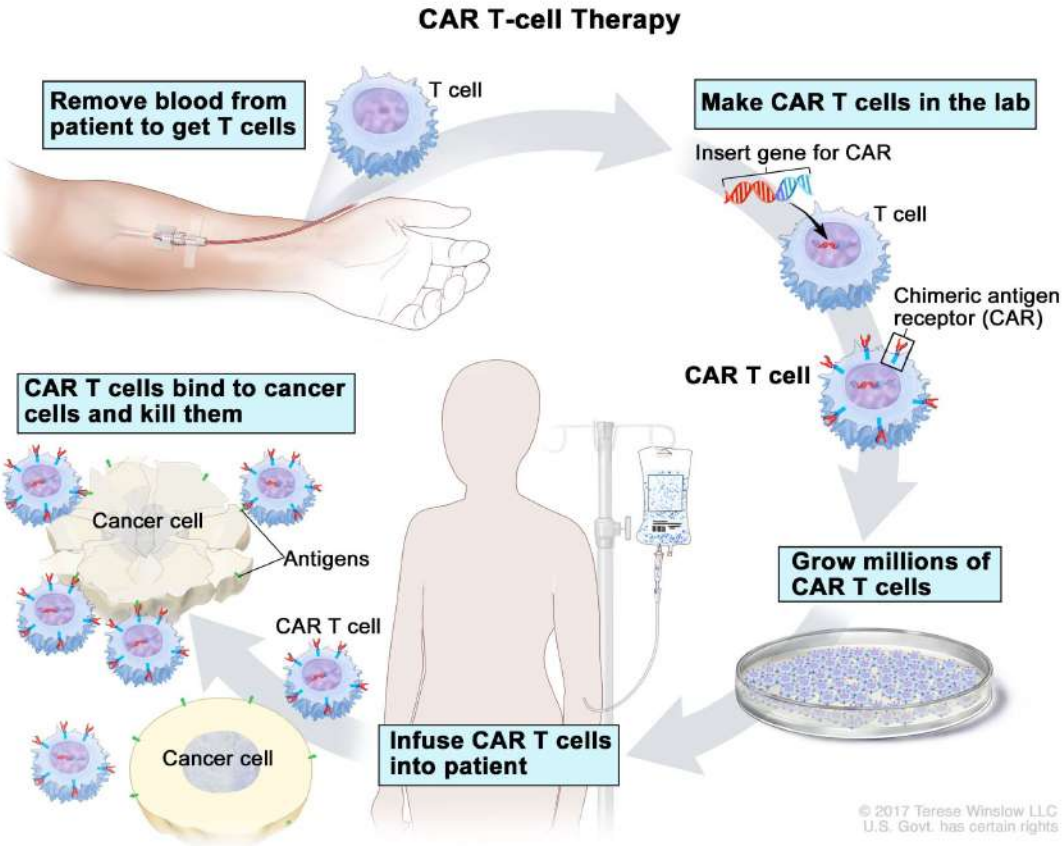
CAR T-cell Therapy

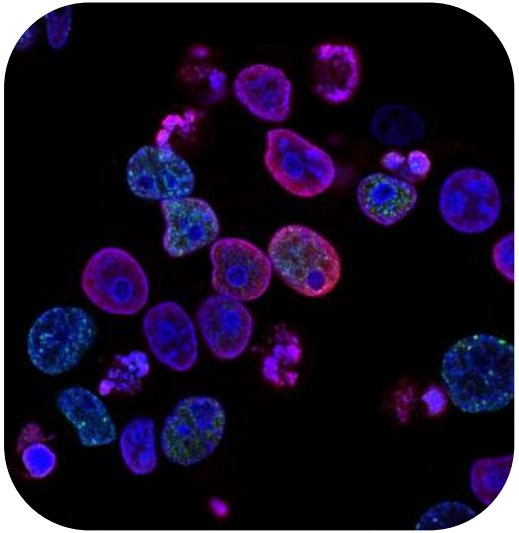


CAR T-cell therapy: A type of immunotherapy that engineers T-cells to recognize and kill cancer cells.

Image ref: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy

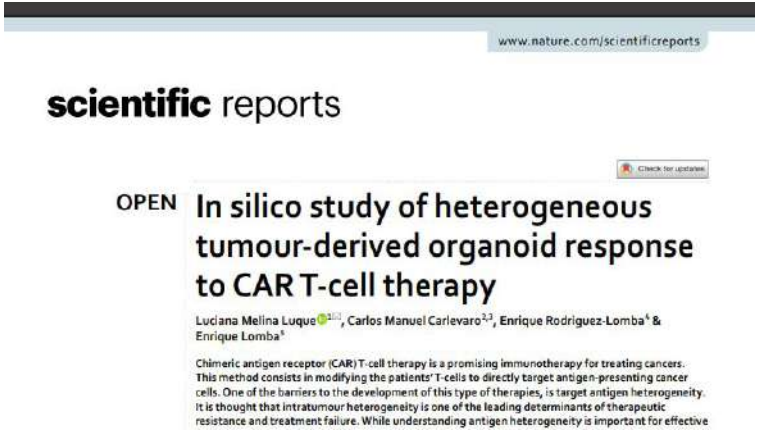
CAR T-cell Therapy: the Challenge

- It has been proven effective in **leukemia** and other **blood** cancers.
    - In the literature, many **robust models**, typically based on differential equations, simulate CAR T treatment in blood cancers.
- However, CAR T still **remains limited in solid tumors** due to unique tumor microenvironmental factors.
    - Researchers need models to try different treatment techniques and scenarios in order to improve CAR T performance. However, **very few models** exist for these types of cancers, and much less data is available.



State-of-the-art model

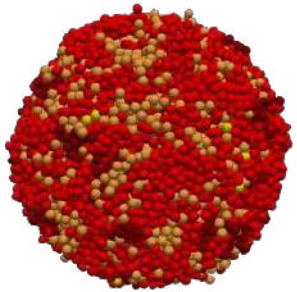
- "*In silico study of heterogeneous tumour-derived organoid response to CAR T-cell therapy*" (*Nature*) presents an ABM simulating **CAR T-cell therapy in tumor-derived organoids**.
- **Agent-Based Modeling (ABM)** is a computational approach in which individual entities, such as **cells, are represented as autonomous agents** with defined **behaviors and interactions**. This makes it particularly suitable for studying the **complex local dynamics** of solid tumor microenvironments.

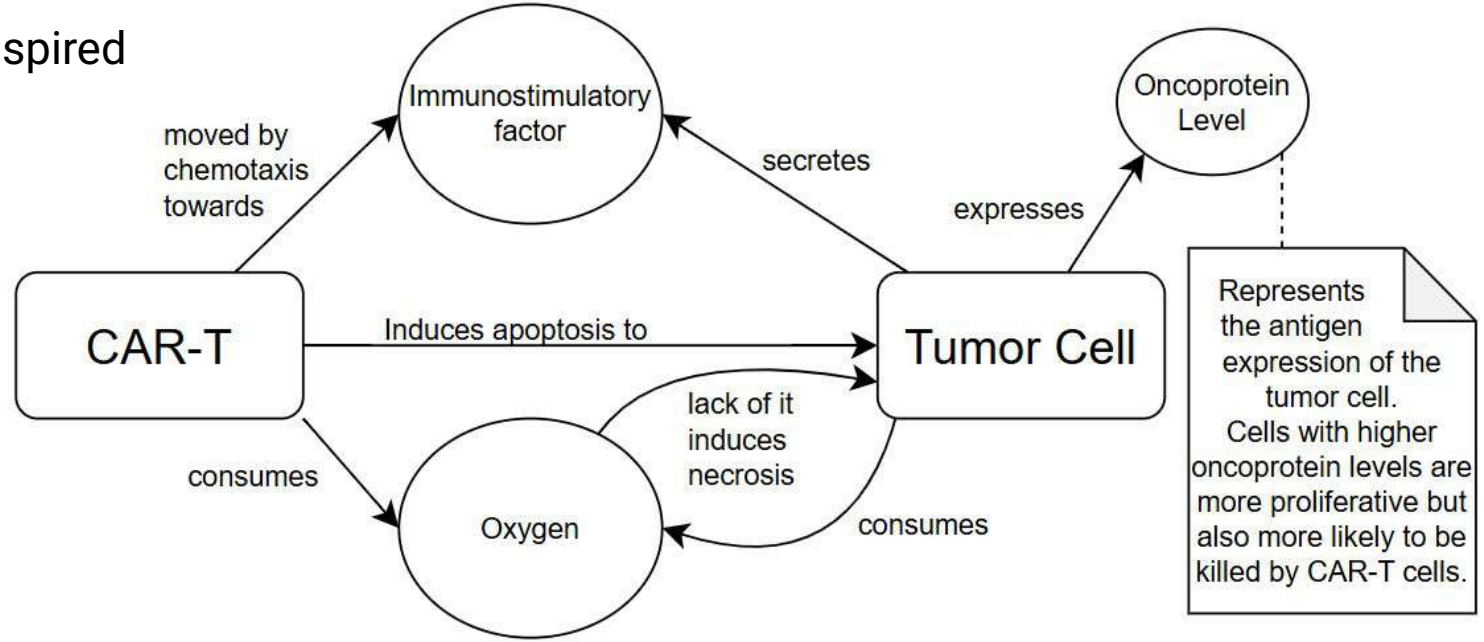


Luque, L.M., Carlevaro, C.M., Rodriguez-Lomba, E. *et al.* In silico study of heterogeneous tumour-derived organoid response to CAR T-cell therapy. *Sci Rep* 14, 12307 (2024). https://doi.org/10.1038/s41598-024-63125-5

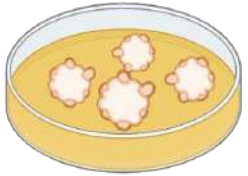
Model Overview

- Solid tumor inspired by **Carcinoma (liver cancer)** data.





- Model calibrated to replicate experimental observations from **wet-lab studies**.
- Enables evaluation of multiple <u>therapeutic strategies</u> **without the cost or time of laboratory experiments**.
- Captures complex cell **microenvironmental interactions**.

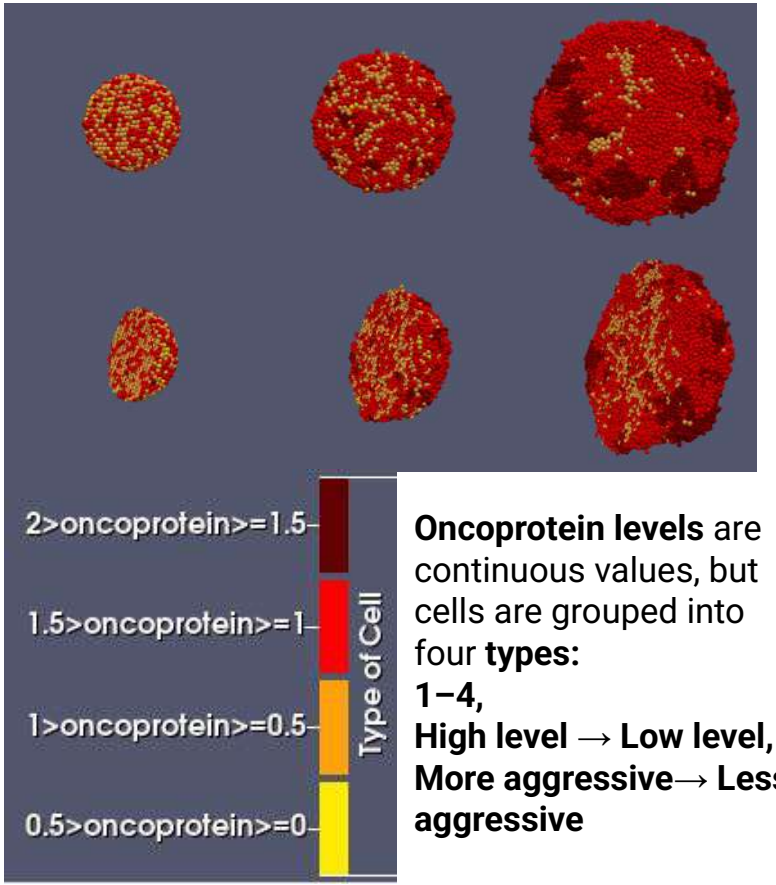


CARTopiaX: CAR T ABM on BioDynaMo

- Although Luciana Melina Luque et al. present a significant advancement from the biological perspective, we observe that aspects such as execution **performance, code readability**, **extensibility,** and **maintainability** could still be improved.
- Our goal was to improve this model by developing **CARTopiaX**: an agent-based simulation using the mathematical framework from the *Nature* paper to **replicate its results** while leveraging **BioDynaMo** and **ROOT capabilities**.
- **BioDynaMo** is a high-performance **open-source platform** for **large-scale**, **high-performance** and **modular** biological modeling built on the ROOT framework for **efficient** simulation and data management.

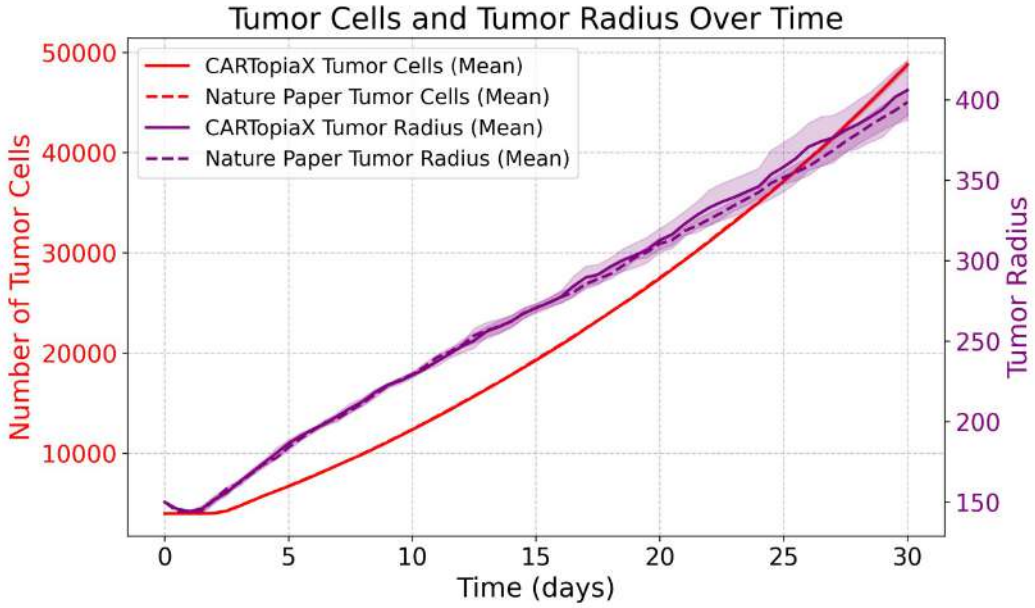
BioDynaMo:
https://doi.org/10.1093/bioinformatics/btab649, https://doi.org/10.1145/3572848.3577480

30-day evolution of a 150 μm radius tumor with no CAR T-cell treatment

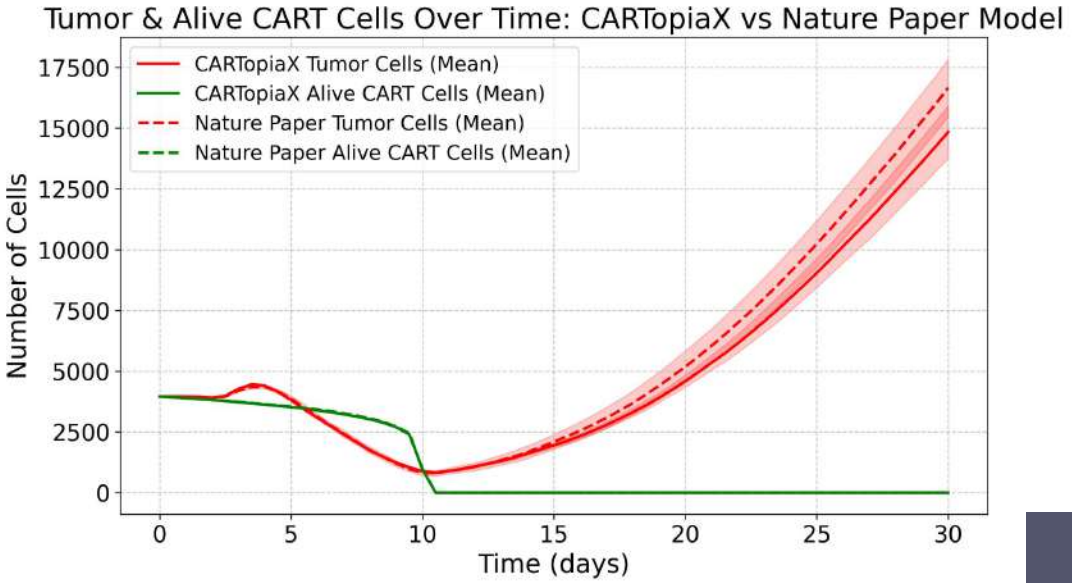


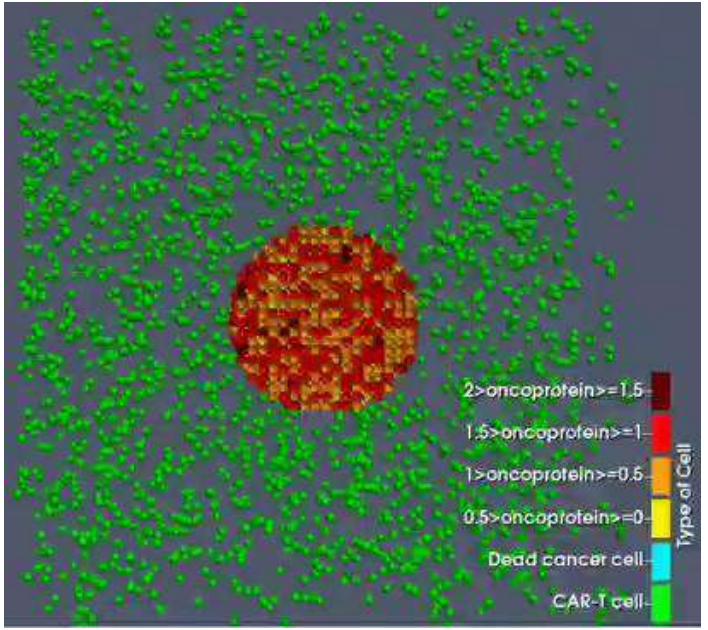
Oncoprotein levels are continuous values, but cells are grouped into four **types:**
1–4,
High level → Low level,
More aggressive→ Less aggressive

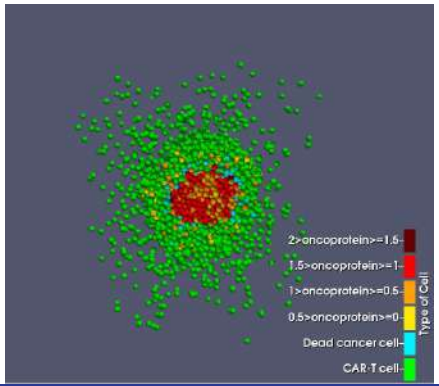
- All graphs compare CARTopiaX results with the Nature paper model, demonstrating a **successful replication**.
- All simulations in this presentation were **run five times** to ensure statistical validity.
- The lines represent the **average results**, and the shaded areas indicate the **standard deviation**.



One dose of scale 1:1, 30-day evolution



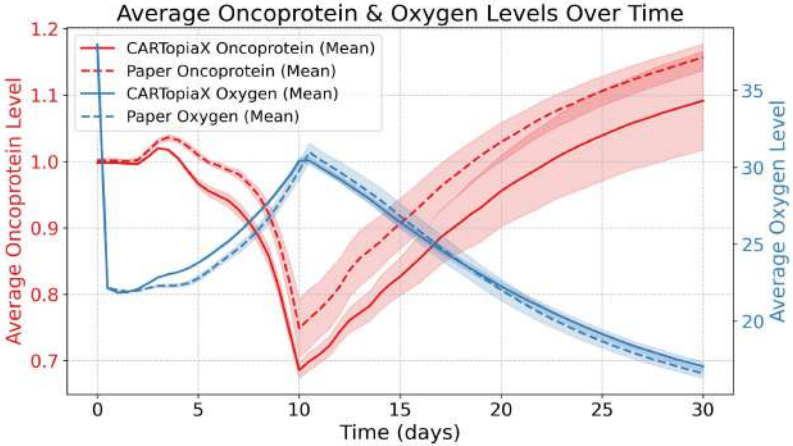


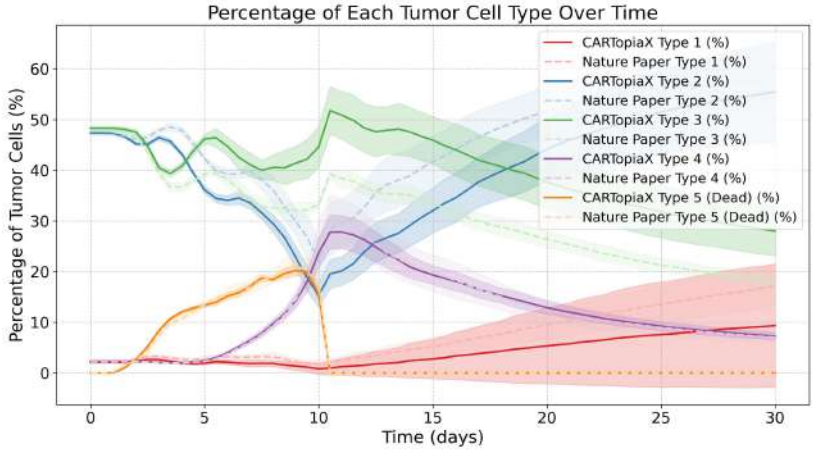


[Visualization of a sliced tumor with CAR-T cells (in green) in ParaView]

- A single dose containing the **same number of CAR T cells as tumor cells** is administered on day 0.
- **Dead and resistant** cells form a **shield** around the solid tumor, hindering CAR T-cell infiltration and therefore its effectiveness.

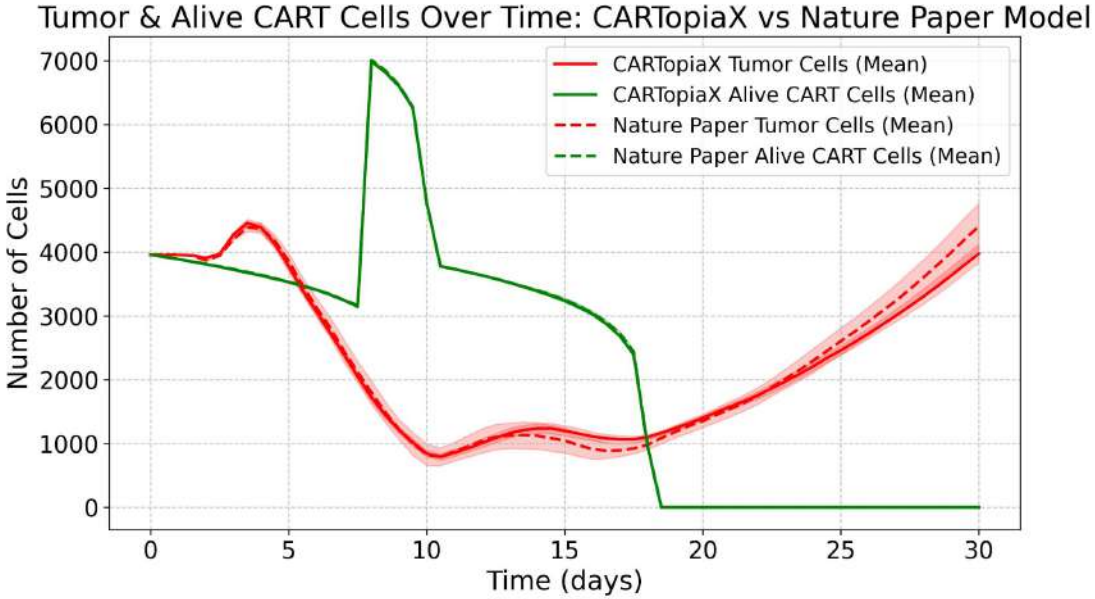
One dose of scale 1:1, 30-day evolution

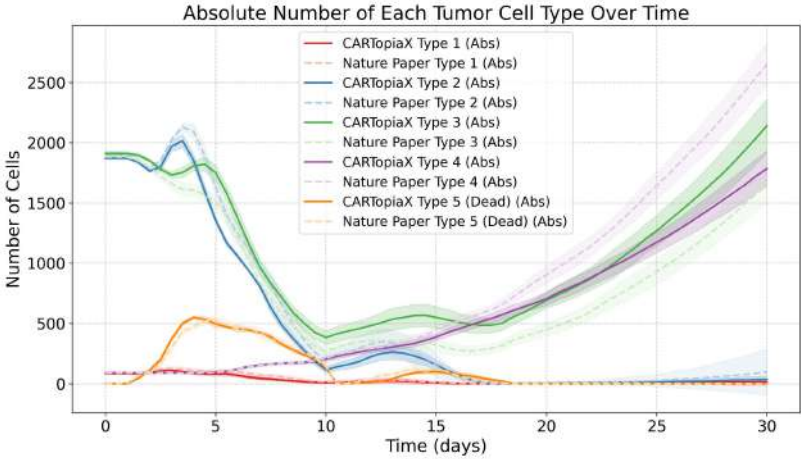


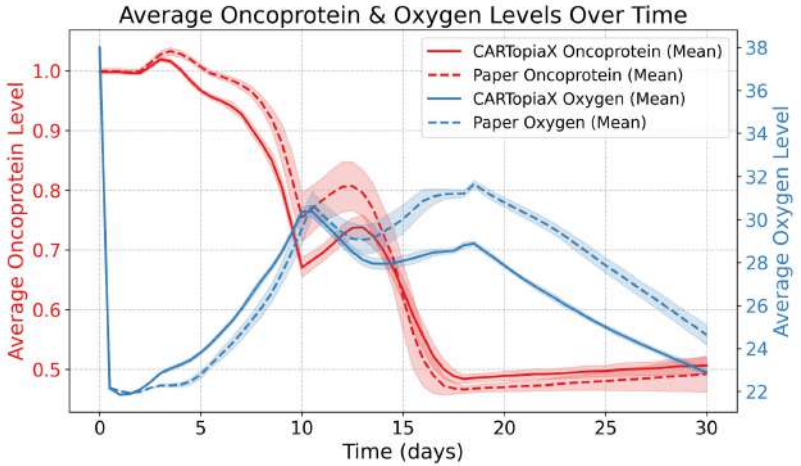


- Even though the graphs of CARTopiaX and the *Nature* paper model do not always overlap, this is due to substantial known **differences in their modeling approaches and stochastic nature**. What matters is that the overall **behaviors are accurately replicated**, as scientists are primarily interested in these **peaks** and **trends** when **designing treatments**.
- CAR T-cells are **administered on day 0** and die stochastically **until at most day 10**.
- Before day 10: CAR-T cells are still present.
  - **Oxygen** levels **increase** as both CAR T and tumor cells die, leading to lower overall oxygen consumption.
  - The average **oncoprotein level and Type 1 and 2 cells decrease rapidly**, since CAR T-cells preferentially kill the most aggressive cancer cells.
- After day 10: CAR T-cells are completely gone.
  - **Oxygen levels decrease** again as the tumor resumes growth.
  - **Oncoprotein levels rise, and Type 1 and 2 cells increase** their proportion in the tumour at the expense of Type 3 and 4, as high-expressers proliferate faster.

Two doses with scale 1:1, 30-day evolution

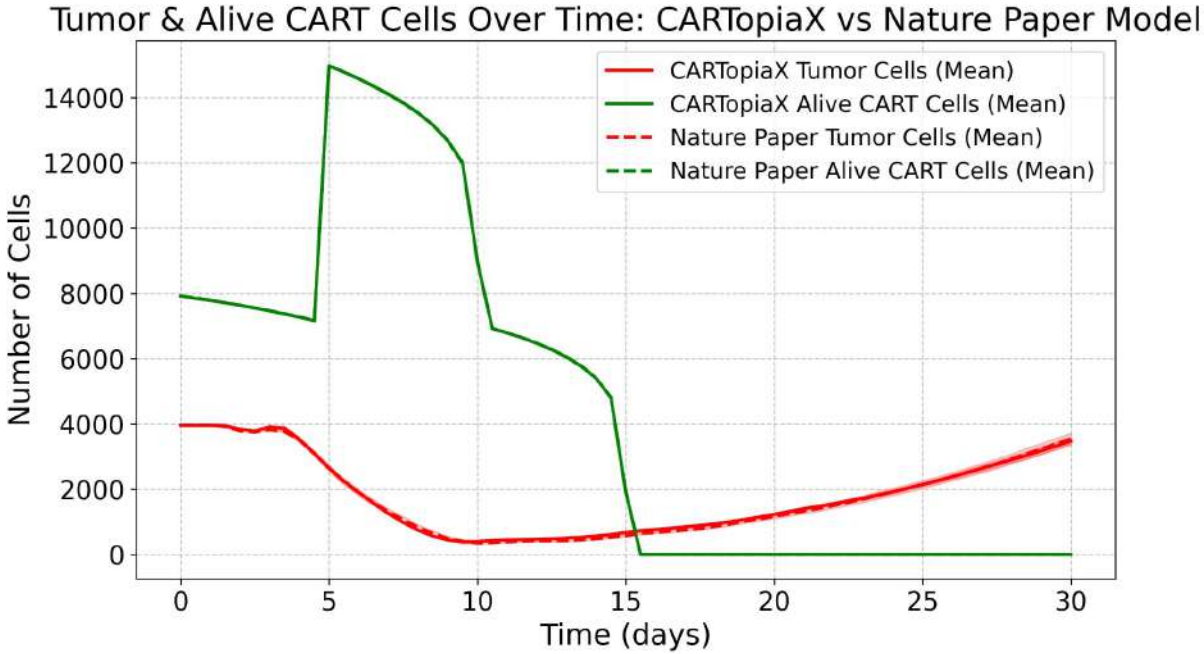






- **Two-Dose** Treatment: Administration of CAR T-cells in each dose **equal to the number of cells in the initial tumor**, delivered on **day 0** and **day 8**.
- On **day 30** there are around **4000 tumor cells** ->this treatment is much **more effective** than applying a single 1:1 dose on day 0 (which resulted in ~15000 cells) .

Example of replicated result: Less is better, increasing cellular dosage does not always increase efficacy

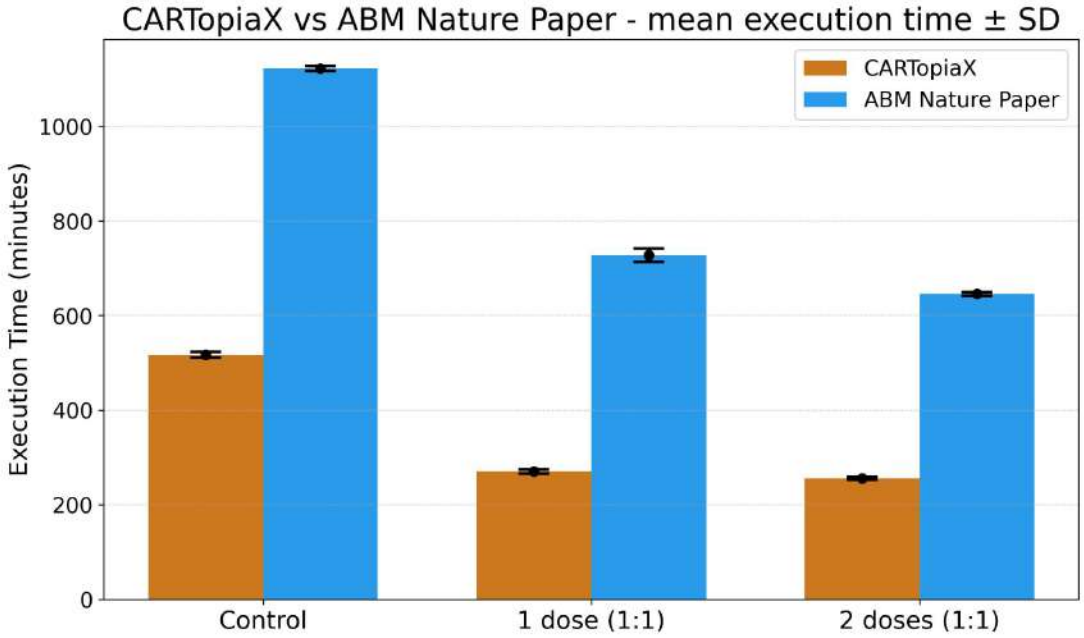


- **Two-Dose** Treatment: Each dose contains CAR T-cells in a quantity **twice the initial tumor cell count**, delivered on **day 0** and **day 5**.
- By day 30, the **number of tumor cells is roughly the same as before**, despite using **twice the amount of CAR T**-cells.

Increasing CAR T-cell dosage does **not necessarily improve** tumor killing and can **increase toxicity**. The model suggests two doses at a 1:1 CAR T-to-cancer cell ratio, balancing effectiveness and safety while minimizing inactive ‘free’ CAR T-cells.

Preliminary Performance Comparison:

- Time comparison for a **30-day** simulation with **3957 initial cancer cells** and:
  - No CAR-T treatment.
  - 1 Dose of 3957 CAR-T cells on day 0.
  - 2 Doses of 3957 CAR-T cells on days 0 and 8.
- Simulations were run **5 times varying the seed**.
- Hardware used: AMD Ryzen 5 3600, 6 cores / 12 threads, 16 GB RAM



➢ CARTopiaX runs more than **twice as fast** thanks to BioDynaMo and ROOT capabilities, and we expect even greater gains once profiling and parameter tuning are applied.

CARTopiaX achievements and future work

- Faster simulations: Quickly run scenarios to enable rapid iteration, robust analysis and **faster hypothesis testing**.
- Clean, readable code: Built with C++ best practices, making it **easy to understand**, **maintain** and **adapt** for new experiments.
- Extensible design: A modular structure supports easy customization, encourages collaboration, and fosters a **growing open-source ecosystem** for **exploring new scenarios** and **adding relevant elements** in CAR T research.

➢ After developing CARTopiaX during **2025 Google Summer of Code**, our intention is to **extend the model** and address new **biologically relevant questions** of interest to researchers.

Thank you for your attention

Questions are welcome.

Salvador
de la Torre Gonzalez

CARTopiaX