

CARTopiaX: Extending a Next-Generation Platform for Computational Cancer Biology

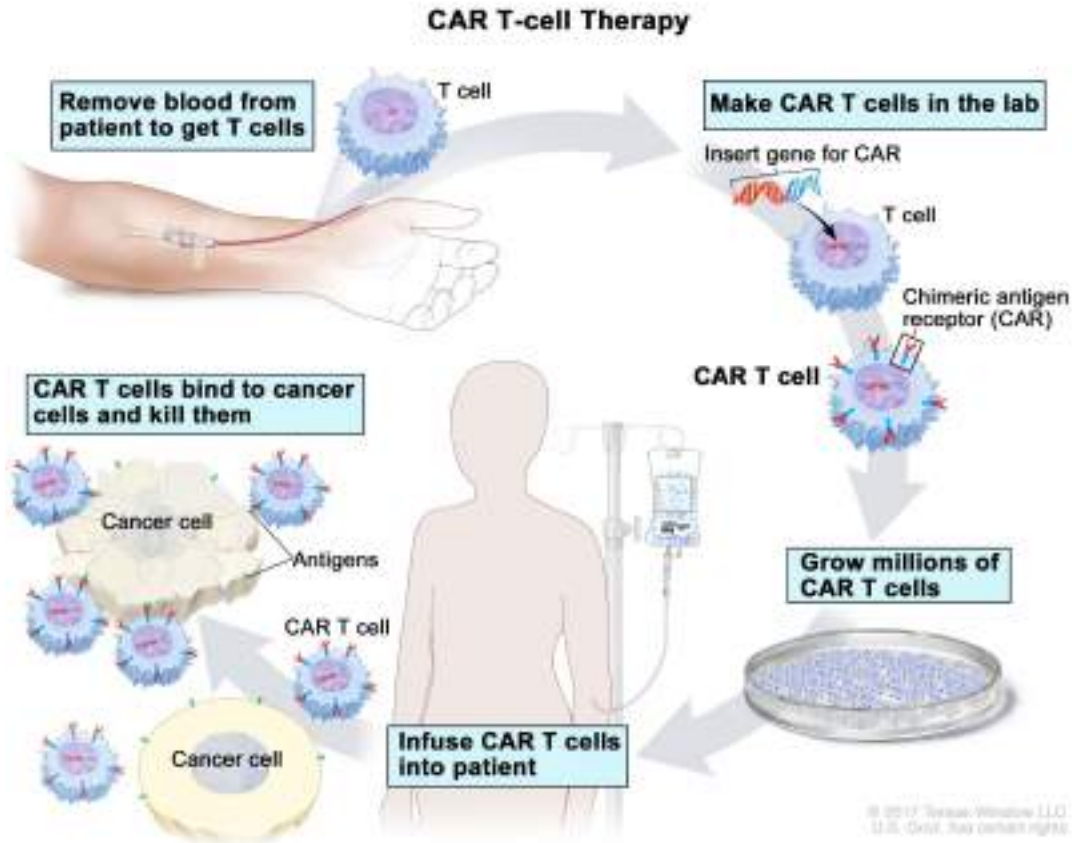
Wrap-up of Google Summer of Code Project 2026



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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 Treatment Modeling: CARTopiaX

- While CAR-T therapy is **highly effective in hematological cancers** (e.g., leukemia) and supported by numerous mathematical models, it still **struggles in solid tumors**, where robust simulation **models remain scarce** despite their importance for optimizing treatment strategies.
- **CARTopiaX** is an **agent-based model** (ABM) built on [BioDynaMo](#), implementing the **mathematical framework** proposed in Nature [paper](#) “*In silico study of heterogeneous tumour-derived organoid response to CAR T-cell therapy*” (2024)
- It provides a platform for simulating **tumor–immune interactions**, **testing hypotheses** and **evaluating CAR-T treatment strategies in silico**.
- Goal: Extend and calibrate CARTopiaX to **reproduce state-of-the-art CAR T-cell experiments**, **demonstrating** it as a **flexible** and **robust framework** for in silico hypothesis testing that **accelerates research** and **reduces reliance on costly wet-lab** experiments.



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The Selected Paper: Evaluating CAR-T Cell Therapy in a Hypoxic 3D Tumor Model

- Experimental Setup: The study utilized HER2+ SKOV3 **ovarian cancer cells** in a 3-D GelMA hydrogel, comparing a **hypoxic environment** (created by a **polycarbonate cap**) **against normoxia** (no cap).
- Treatment Protocol: **Anti-HER2 CAR-T cell** efficacy was evaluated at a **20:1 effector-to-target (E:T) ratio** over a total experimental duration of **72 hours**.
- Limited T Cell Infiltration: Despite high tumor mortality, CAR-T cell infiltration into the 3-D hydrogel bulk was negligible, with most immune cells remaining at the edges.
- Key Finding, Bystander Killing Mechanism: **Tumor death at a distance (in the core)** was driven by metabolic competition; activated **CAR-T cells at the periphery** rapidly consume glucose and oxygen, **starving the already stressed cancer cells in the center**.
- Aim: Extend CARTopiaX to **replicate their results** in silico.



Ando Y, Sieglar EL, Ta HP, Cinay GE, Zhou H, Gorrell KA, Au H, Jarvis BM, Wang P, Shen K. Evaluating CAR-T Cell Therapy in a Hypoxic 3D Tumor Model. *Adv Healthc Mater*. 2019 Mar;8(5):e1900001. doi: [10.1002/adhm.201900001](https://doi.org/10.1002/adhm.201900001). Epub 2019 Feb 8. PMID: 30734529; PMCID: PMC6448565.

The new model: cylindrical tumor mass

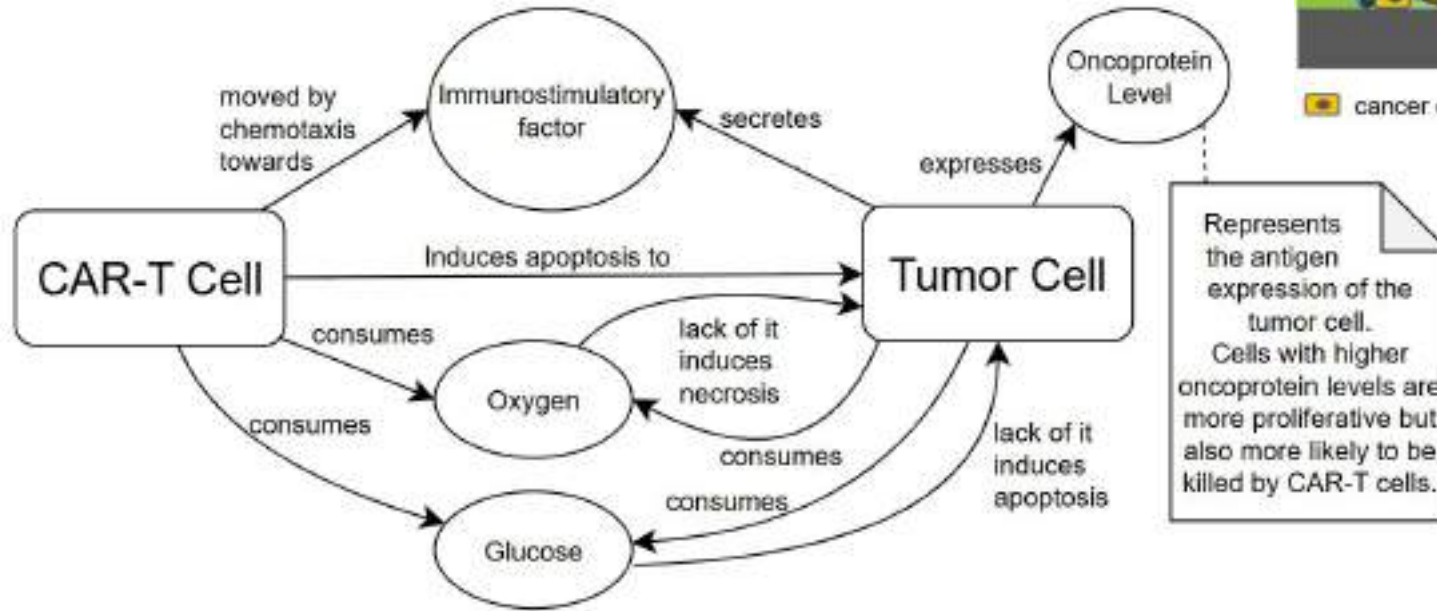
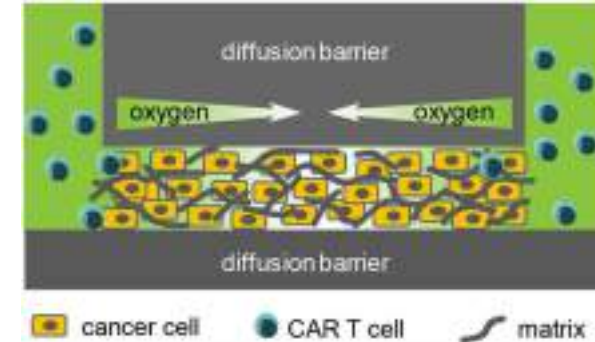
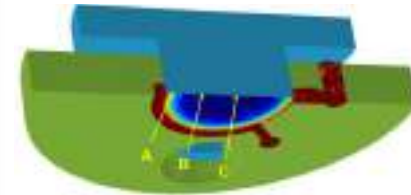
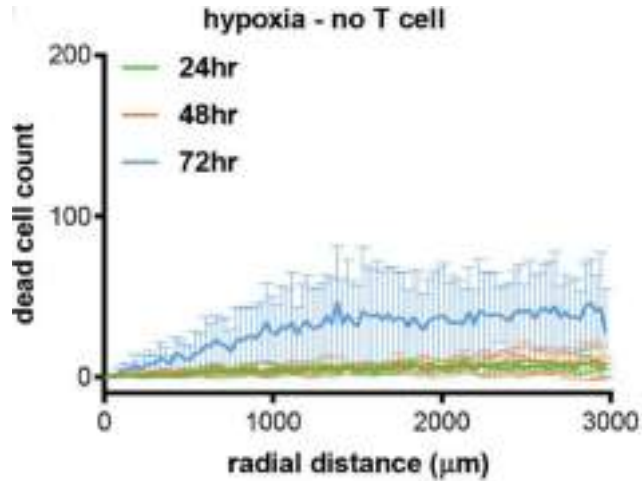
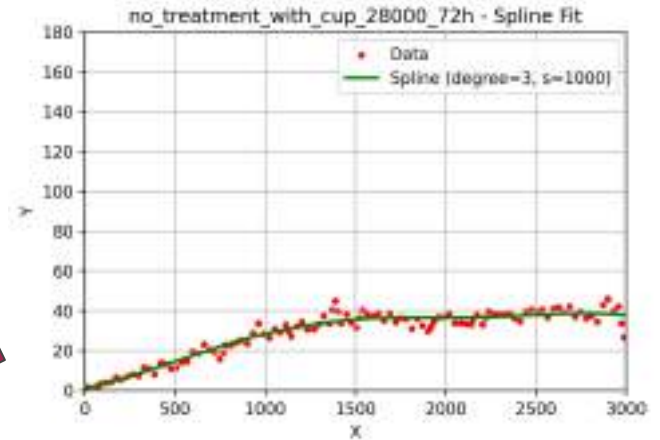
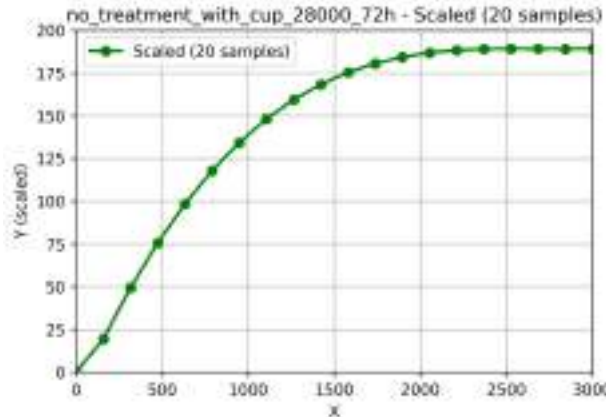
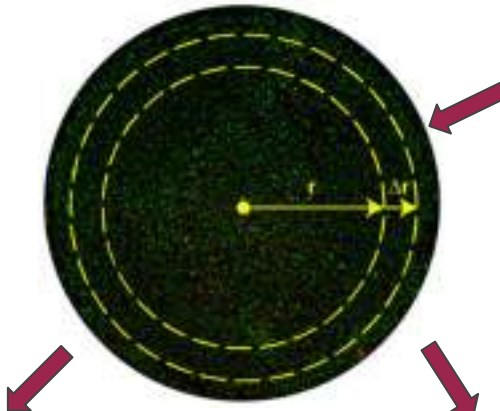


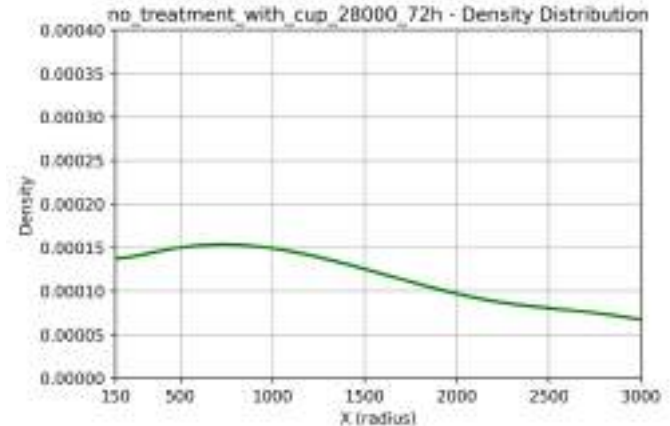
Image ref:

<https://pubmed.ncbi.nlm.nih.gov/30734529/>

Data obtention

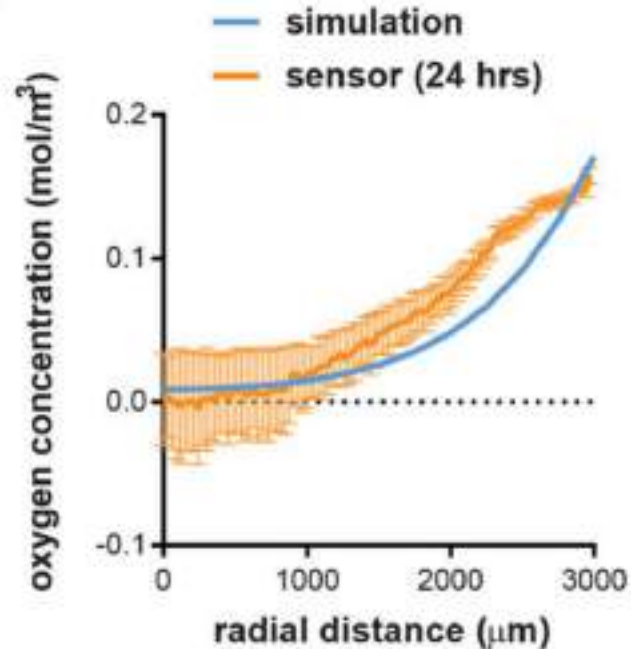


Area normalization
of the absolute
numbers to study
trends

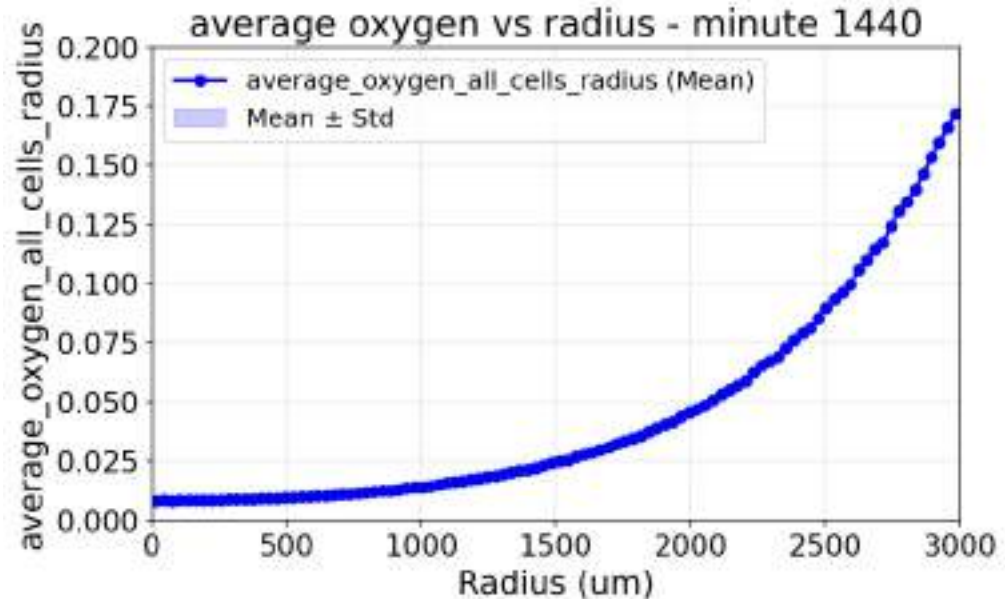


Density of 10 million cells/mL, with cap (hypoxia), no treatment

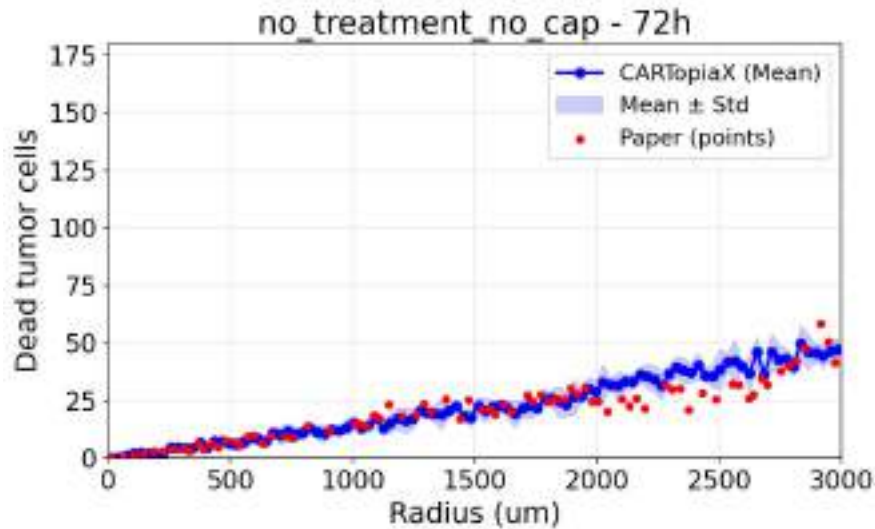
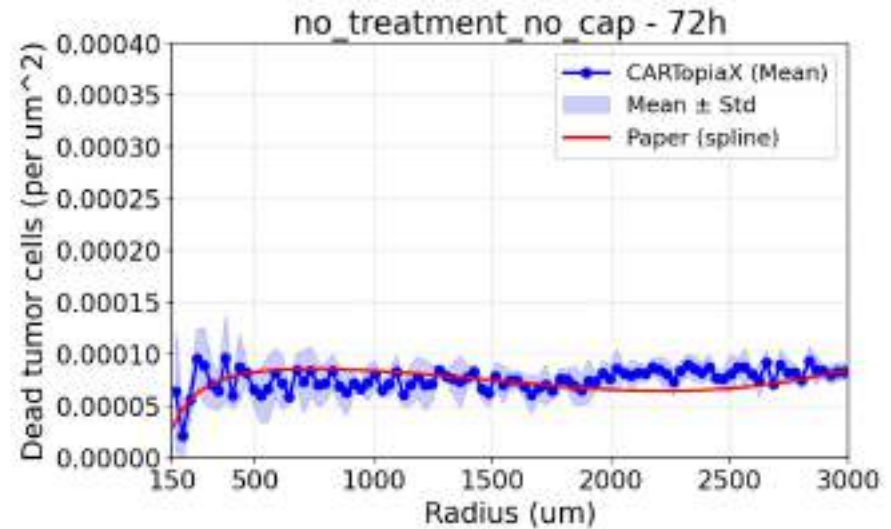
Paper's reported oxygen levels (orange).
The authors also modeled them using a
simple differential equation model (blue),
but this is unrelated to CARTopiaX



**Decreasing oxygen that flows
from the border of the cylinder
(3000 μm)**

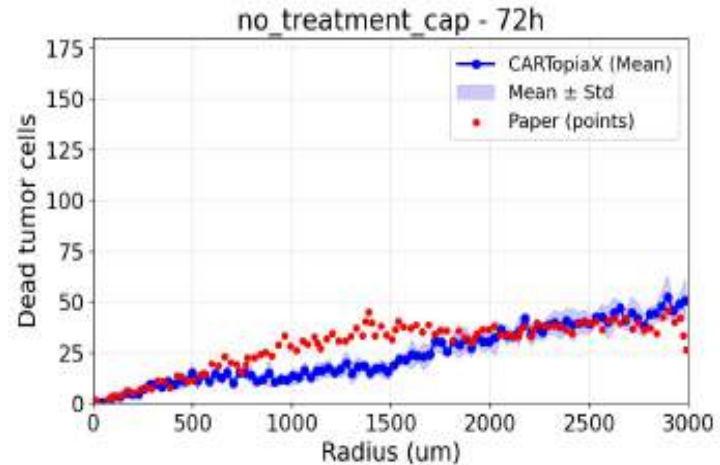
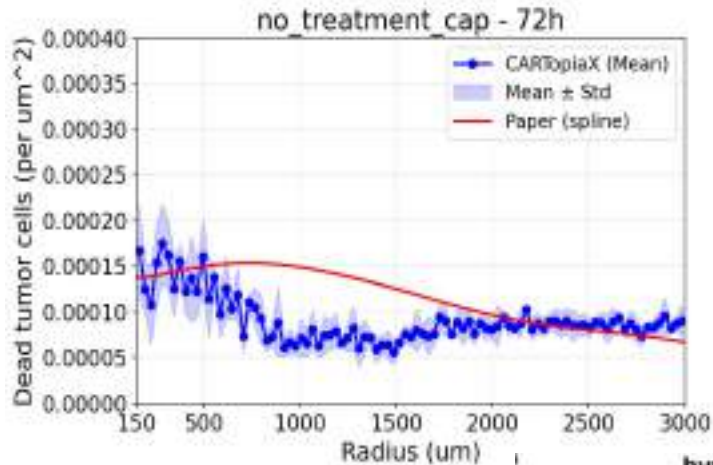


10 million cancer cells/mL, no treatment: without cap (normoxia)



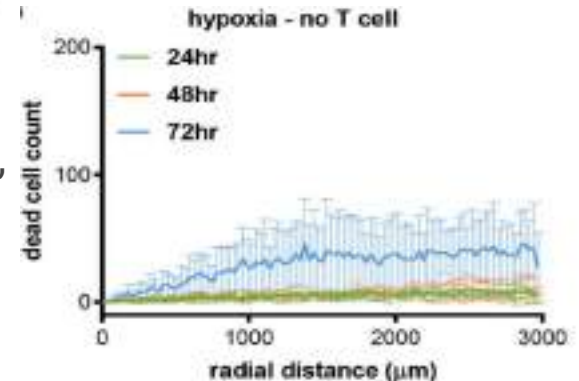
- Cell **death is uniform** because the environmental conditions are perfectly symmetric.
- Points at radii below 150 are omitted because the concentric rings are too small, resulting in very few data points, large variations, and a dividing area that tends to zero.

10 million cancer cells/mL, no treatment: with cap (hypoxia)

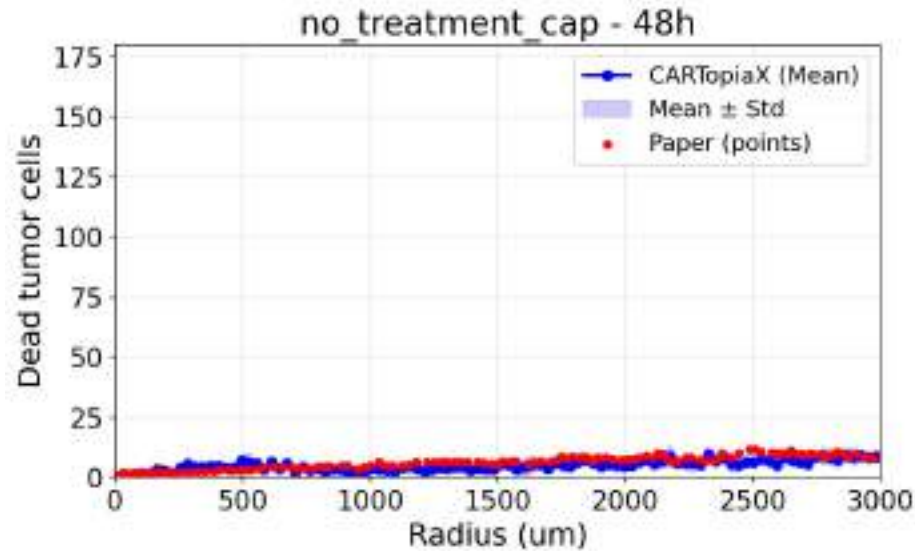
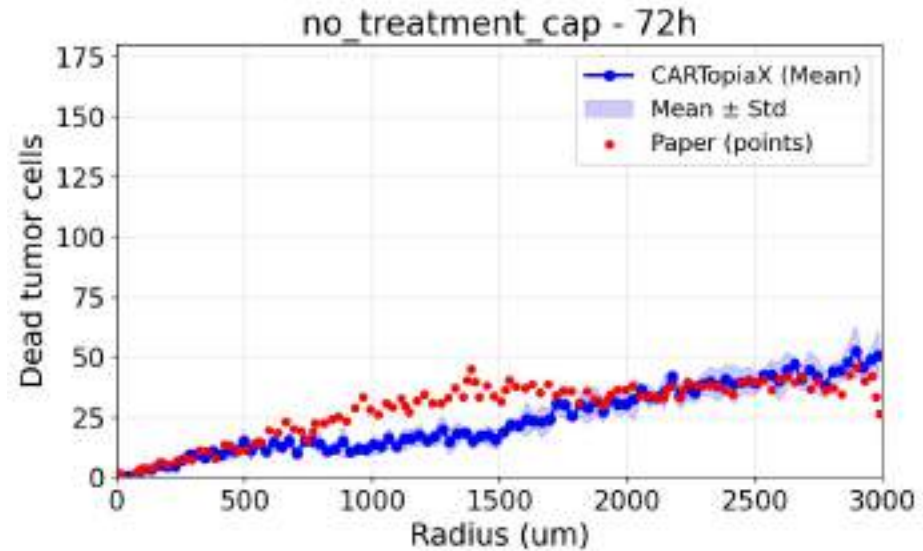


We focus on reproducing the key trends, as the biological process is highly stochastic and the **error bars** in the paper are very **large**.

- Since oxygen flows in from the edges, the cap creates a **hypoxic region in the center** of the cylinder, increasing cell death.



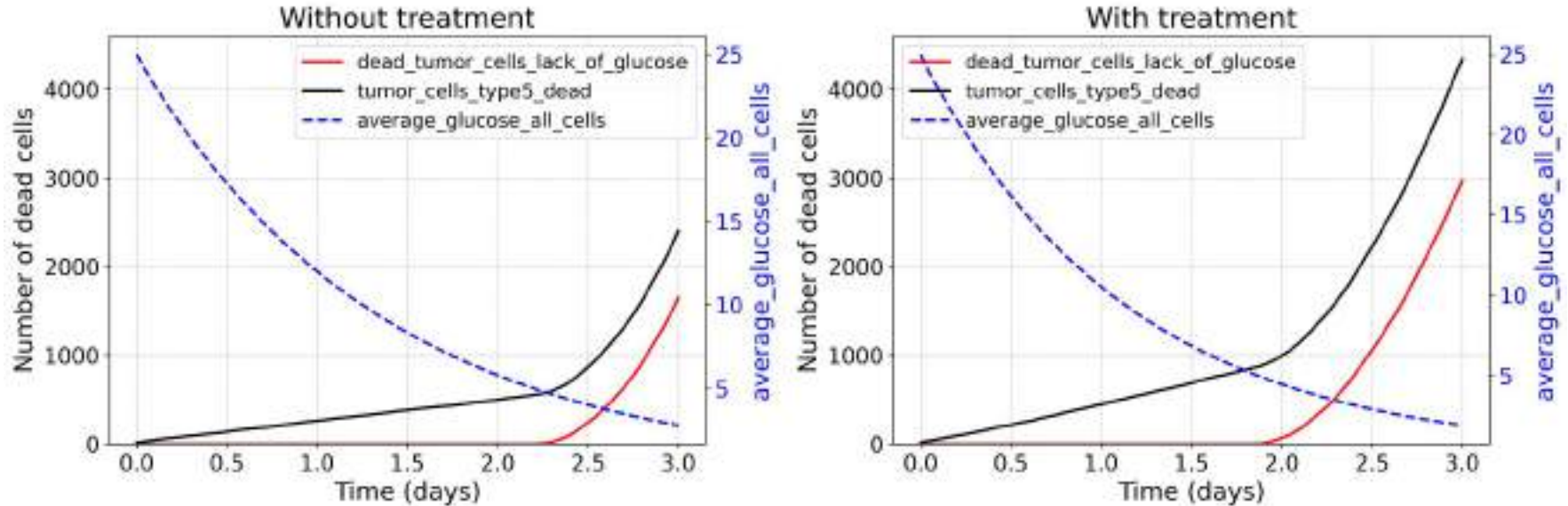
Glucose starvation kills cells



- The device used by the researchers contains **medium with glucose** to feed the cells. Since it is **not replaced**, this explains why **many more cells are dead by day 3** than by day 2.

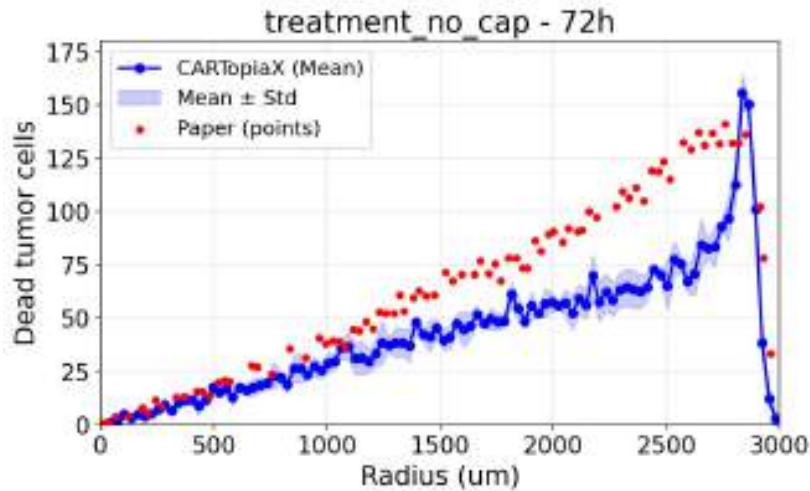
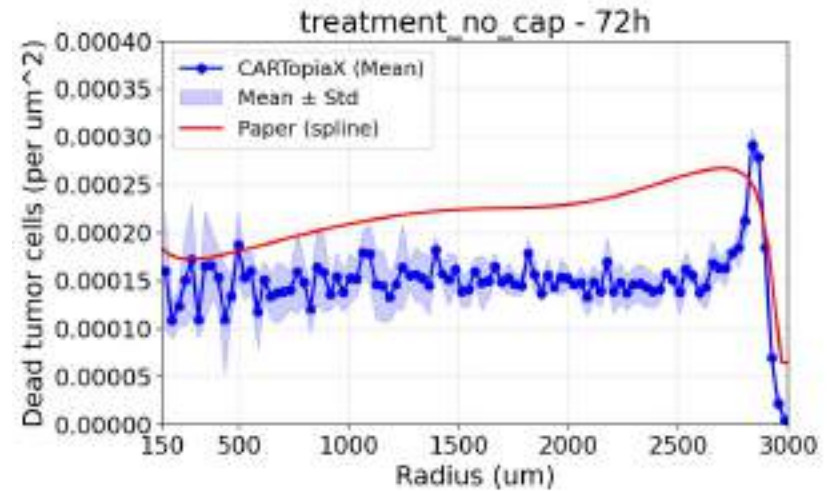
CAR-T cells starve cancer cells

Glucose and cell deaths over time (mean across seeds)



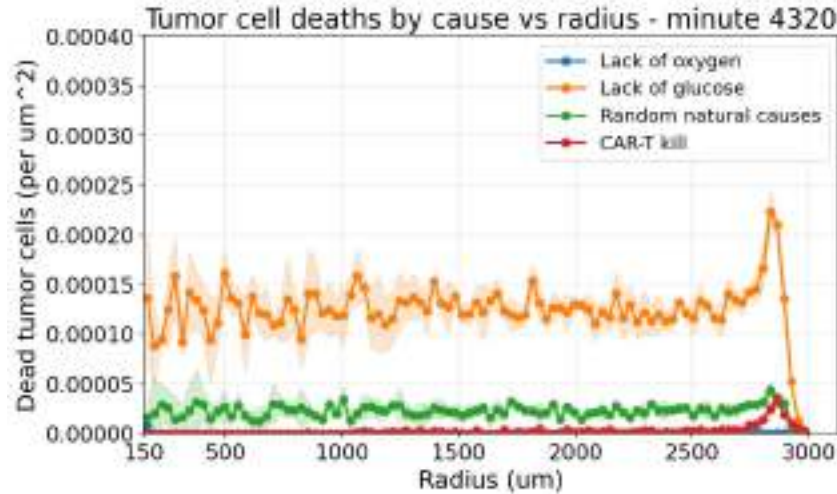
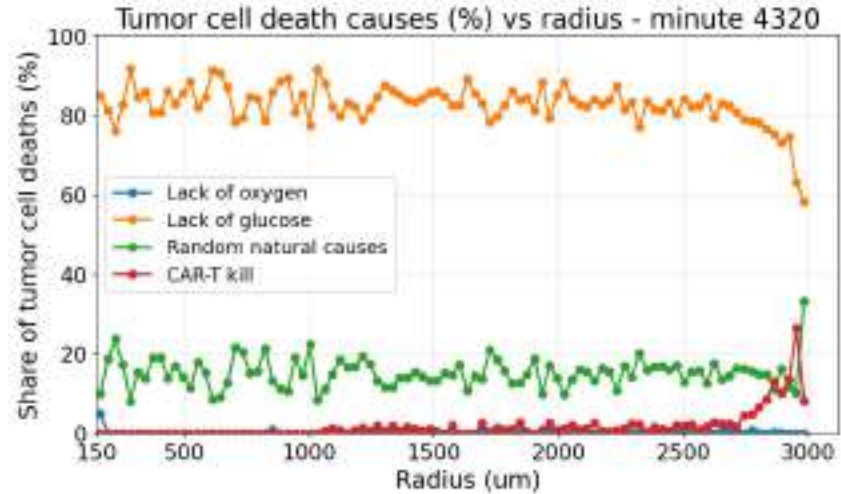
- When treatment is added, **CAR-T cells also consume glucose**, which increases what the authors call “**non-contact mediated CAR-T cell cytotoxicity.**”

10 million cancer cells/mL, 20:1 treatment: without cap (normoxia)



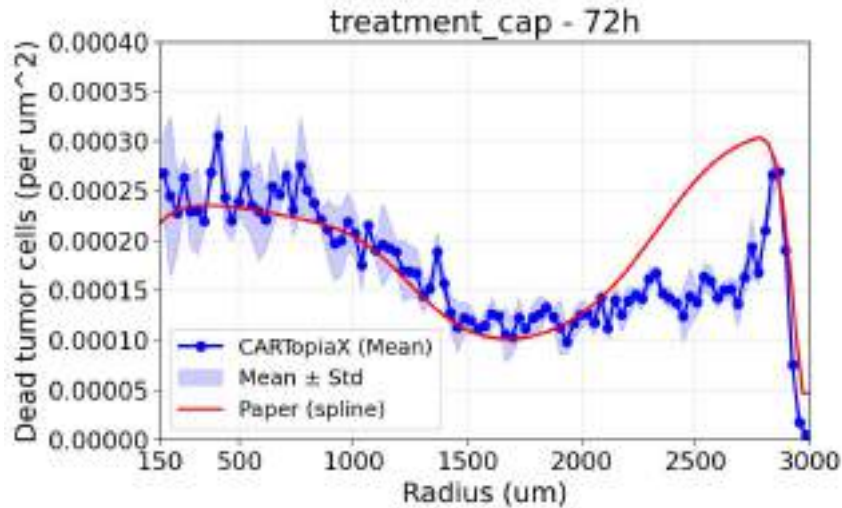
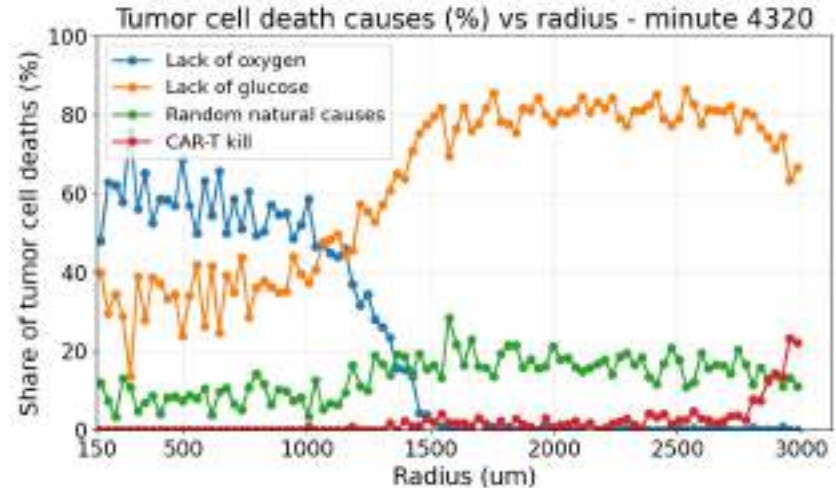
- Cell **death is uniform** except at the edge, where CAR-T cells target and kill tumor cells.
- Unexpected emergent behavior: cancer cell deaths drop at a radius of 3000 because a large number of **CAR-T cells** enter at the edges and **push tumor cells toward the center**.

10 million cancer cells/mL, 20:1 treatment: without cap (normoxia)



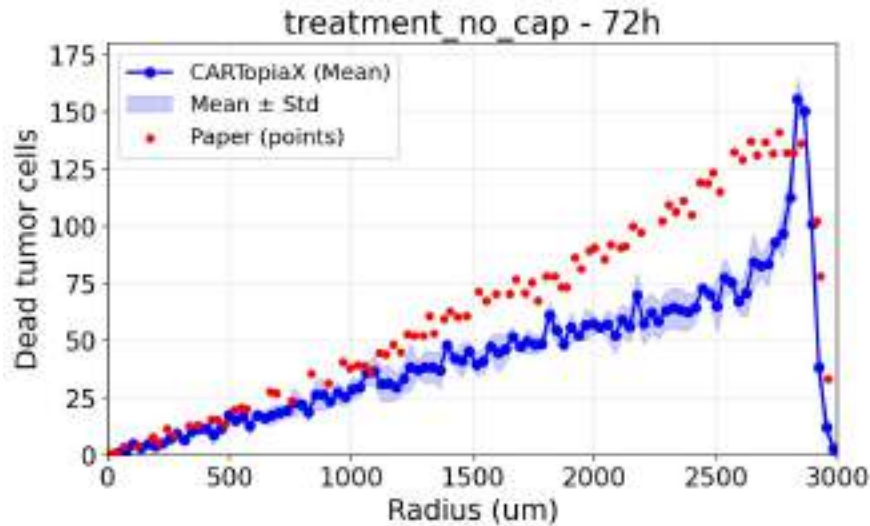
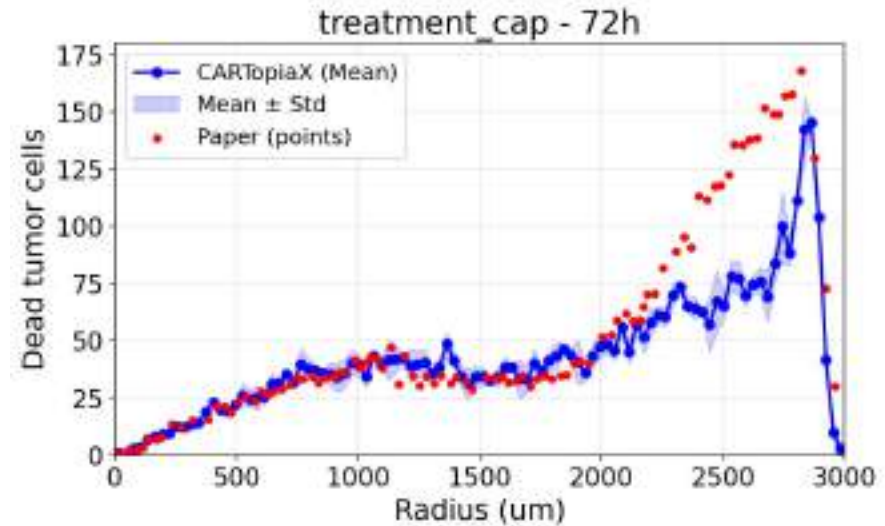
- **CAR-T cells barely infiltrate** the tumor, as reported in the paper, so very few cancer cells are killed directly by them.
- **Most cancer cell deaths** are caused by **glucose deprivation**, which is exacerbated by **glucose consumption by CAR-T cells**.

10 million cancer cells/mL, 20:1 treatment: with cap (hypoxia)



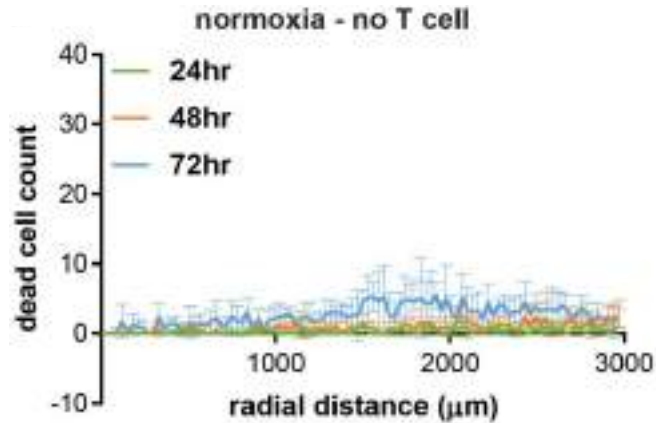
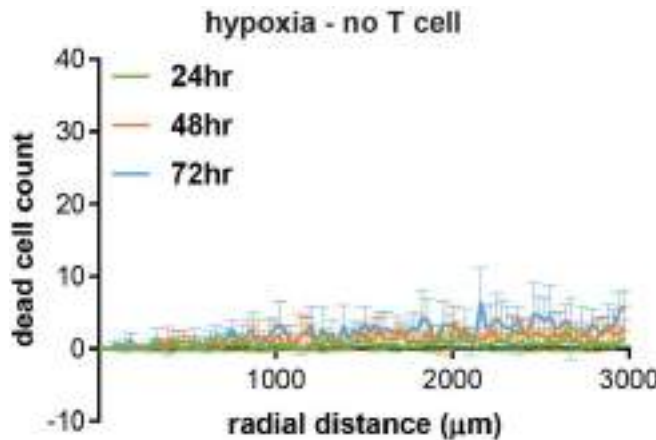
- Again, with the cap, more cells die in the **core** due to **oxygen deprivation**. **CAR-T cells also consume oxygen**, further exacerbating the situation at the center.
- At the **edges**, **CAR-T cells** push and kill cancer cells, as before.
- As a result, cell death increases both at the core and at the edges, resulting in a **U-shaped cell density profile**, with a drop at radius 3000 due to the CAR-T cells pushing cancer cells inward.

20:1 treatment: Cell deaths in the middle with vs. without the cap

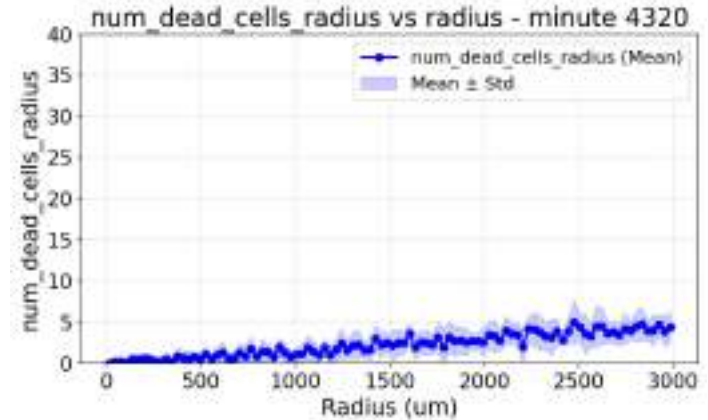
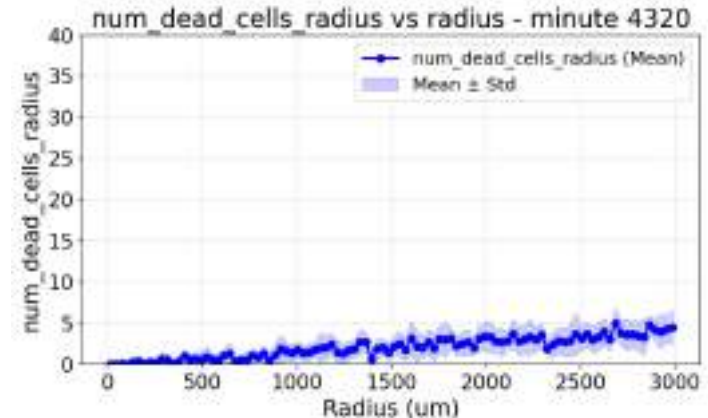


- Notice how **more cells die between radii 1400 and 2500** when there is **no cap**.
- Without the cap, **more oxygen is available**, allowing cells to **proliferate more** and consequently increasing cell deaths.
- This **does not happen at the core** because, with the cap, **oxygen levels are so low** that cells not only stop proliferating but also **die much more frequently**.
- At the **edges**, **oxygen levels are sufficiently high** in both cases, so cell death rates remain **similar**.

Density of 1 million cells/mL, no treatment



Very few cells are present. Therefore, both the normoxic (without cap) and hypoxic (with cap) conditions **are effectively normoxic**, resulting in **no significant differences**. In addition, since there are far fewer cells, they do not run out of glucose.



Automated Model Calibration with Bayesian Optimization

- Problem: many **parameters can't be measured in the lab** or are **not found in the biological literature**, and each simulation is expensive, so a grid search is not feasible.
 - New in the repository: a calibration tool that automatically **estimates the parameters** that best reproduce experimental data.
 - How it works: **Bayesian optimization** (Optuna, TPE). A probabilistic surrogate learns from past trials and proposes promising parameters, **minimizing costly simulations**.
 - Robust to noise: each candidate is averaged over multiple **Monte Carlo runs**.
 - Flexible loss: time series, radial profiles, or a custom error.
- 

CARTopiaX achievements and future work



- CARTopiaX was **extended to replicate a new wet-lab scenario**, with:
 - a completely **new tumor geometry**
 - **glucose** as a new diffusing substance, whose lack limits proliferation and can starve cells to death
 - new cell **behaviors** and **mechanics**
- A new **Bayesian optimization tool** calibrates parameters against experimental data while minimizing the number of simulations.
- The **key trends of the paper** were reproduced, including emergent behaviors that were not explicitly programmed.
- The model **offers an in silico explanation** of the “**non-contact mediated**” **CAR-T cytotoxicity** (glucose and oxygen competition). It uses data that is hard to measure in the lab, such as death causes per radius.
- CARTopiaX proves to be a **flexible platform** for **fast, low-cost hypothesis testing** of CAR-T therapies providing insights that cannot always be obtained experimentally in a lab.
- Future work
 - **Run more simulations** per scenario (current graphs use ~5 runs) to reduce stochastic noise.
 - A **manuscript** presenting CARTopiaX is in preparation for **a scientific journal**.