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

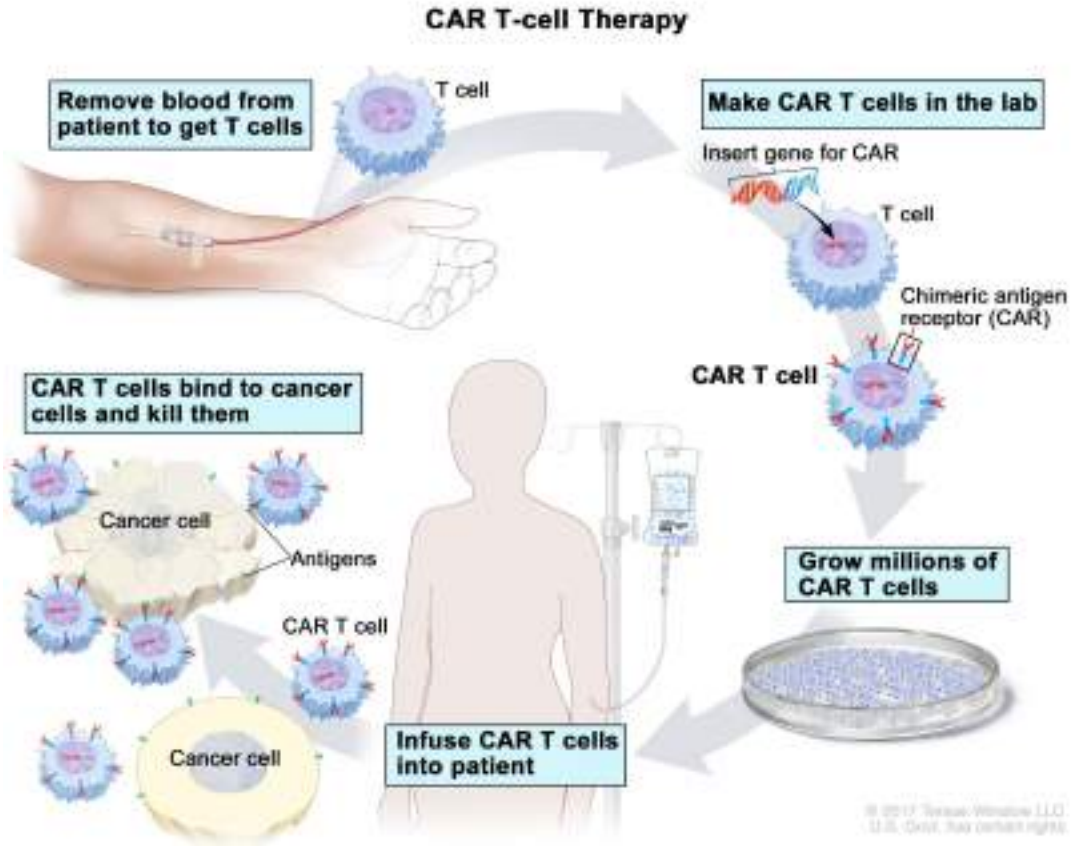
CompilerResearchCon 2026, Google Summer of Code project



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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.

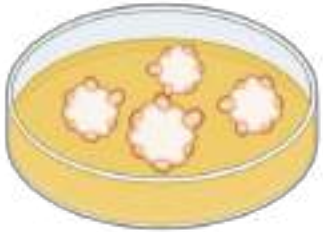
Image ref: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy

CAR-T Treatment Modeling: CARTopiaX

- CAR-T therapy is **effective against blood cancers** but remains **challenging** in **solid tumors**, where simulation models are scarce.
- **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*" (Luciana M. Luque et al. 2024)
- Purpose: Simulate tumor-immune interactions, **test hypotheses** and **evaluate** CAR-T **strategies** in silico, accelerating research and reducing wet-lab costs.
- New Goal: Extend and calibrate CARTopiaX to **reproduce state-of-the-art CAR T-cell experiments**, **demonstrating** it as a **flexible** and **robust framework.**

CARTopiaX

CARTopiaX repository



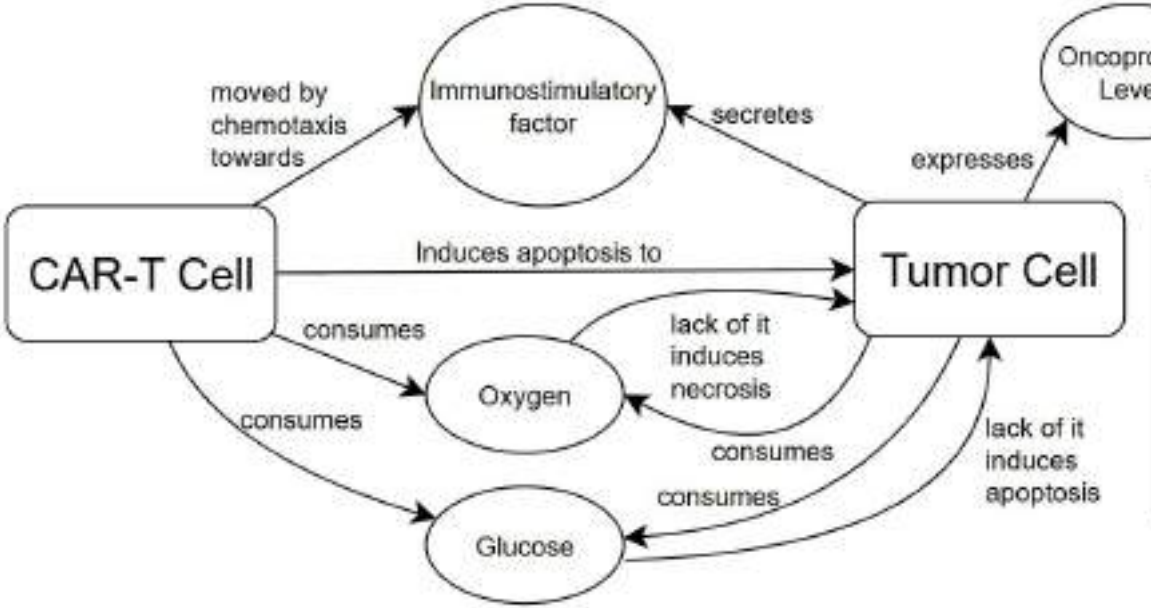
The Selected Paper: Evaluating CAR-T Cell Therapy in a Hypoxic 3D Tumor Model (Ando et al. 2019)

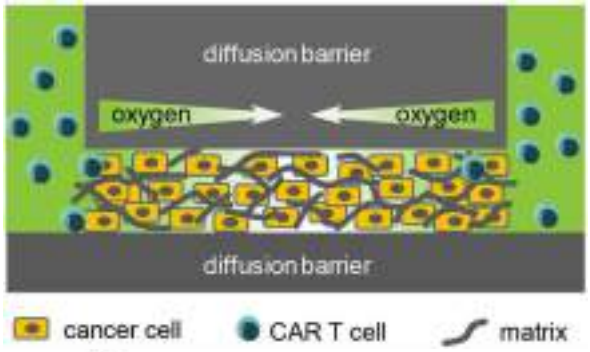
- Experimental Setup: **Ovarian cancer cells** forming a flat **cylinder**, comparing a **hypoxic environment** (created by a **polycarbonate cap**) **against normoxia** (no cap).
- Treatment Protocol: **CAR-T cell 20:1 effector-to-target (E:T) ratio** over **72 hours**.
- Limited T Cell Infiltration: Despite high tumor mortality, CAR-T cell **infiltration was negligible**.
- Hypothesis, Bystander Killing Mechanism: Peripheral CAR-T cells consume glucose and oxygen, causing **metabolic competition** that starves cancer cells in the tumor core and drives **cell death at a distance**.
- Aim: Extend CARTopiaX to **replicate their results** in silico and **analyze the causes** of tumor cell **death**.



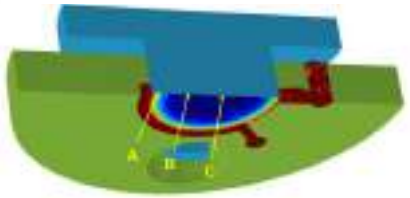
Ando Y, Siegler EL, Ta HP, Cinay GE, Zhou H, Gorrell KA, Au H, Jarvis BM, Wang P, Shen K. Evaluating CAR-T Cell Therapy in a Hypoxic 3D Tumor Model. Adv Healthc Mater. 2019 Mar;8(5):e1900001. doi: 10.1002/adhm.201900001. Epub 2019 Feb 8. PMID: 30734529; PMCID: PMC6448565.

The new model: cylindrical tumor mass





Represents the antigen expression of the tumor cell. Cells with higher oncoprotein levels are more proliferative but also more likely to be killed by CAR-T cells.

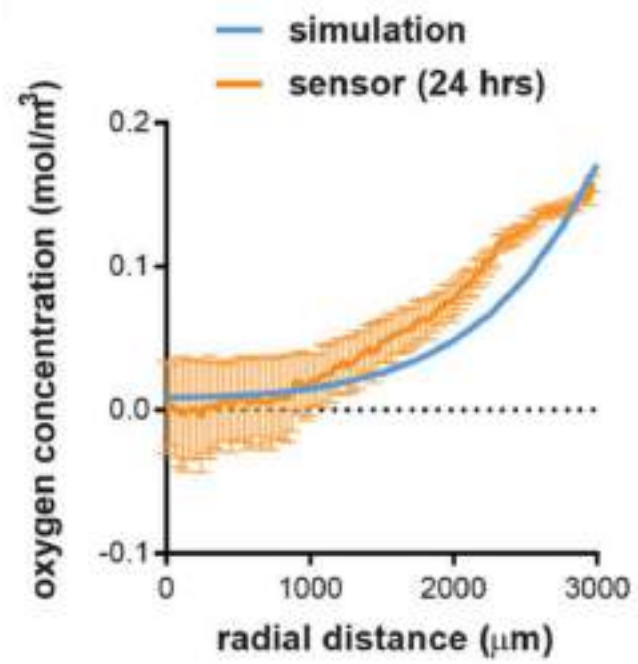


A **Bayesian calibration tool** (Optuna/TPE) was added to **fit model** parameters to experimental data while **minimizing costly simulations**.

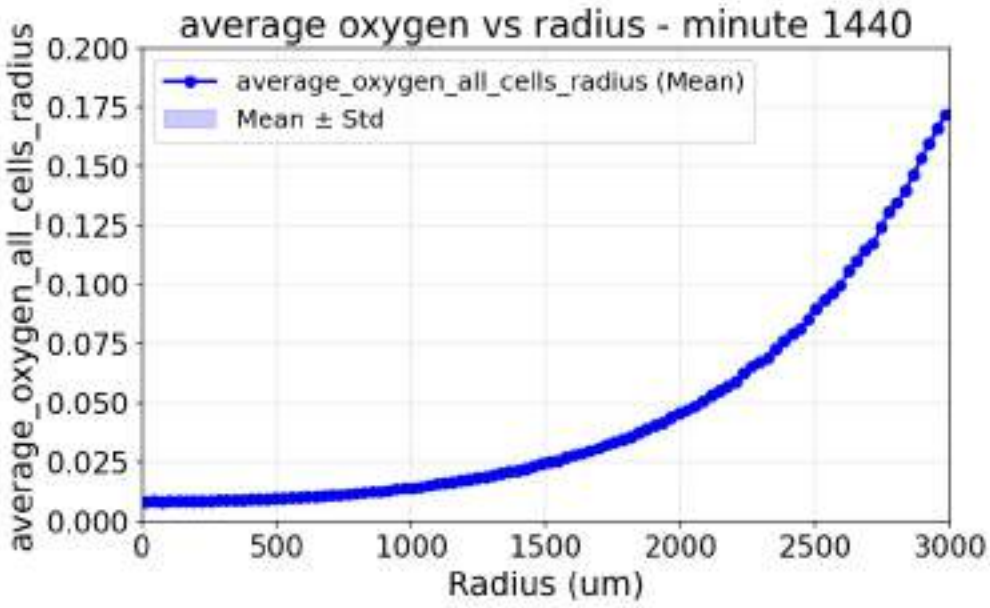
Image ref: https://pubmed.ncbi.nlm.nih.gov/30734529/

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

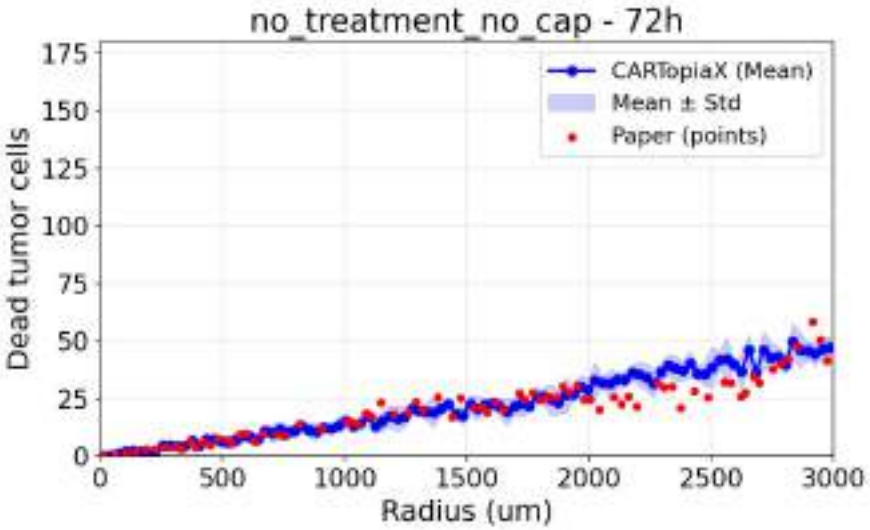
Paper's reported oxygen levels (orange). The authors also modeled them using a simple differential equation model (blue), but this is unrelated to CARTopiaX

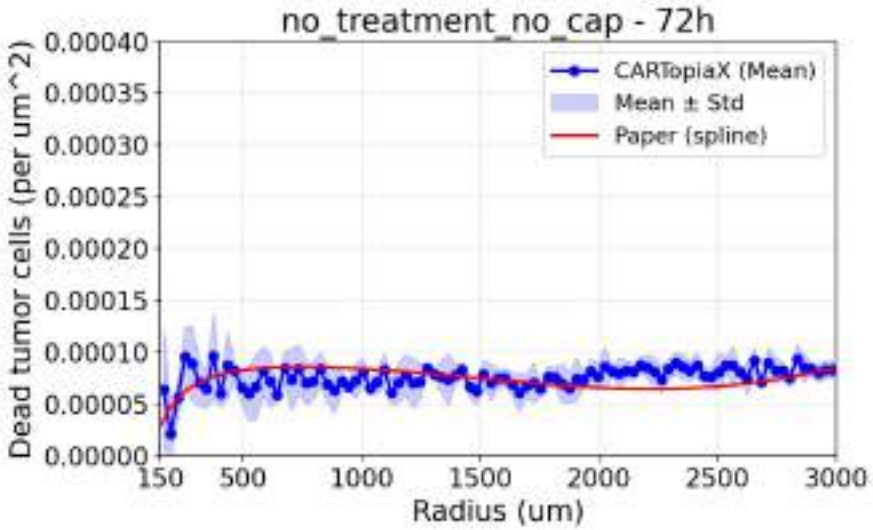


Decreasing oxygen that flows from the border of the cylinder (3000μm)



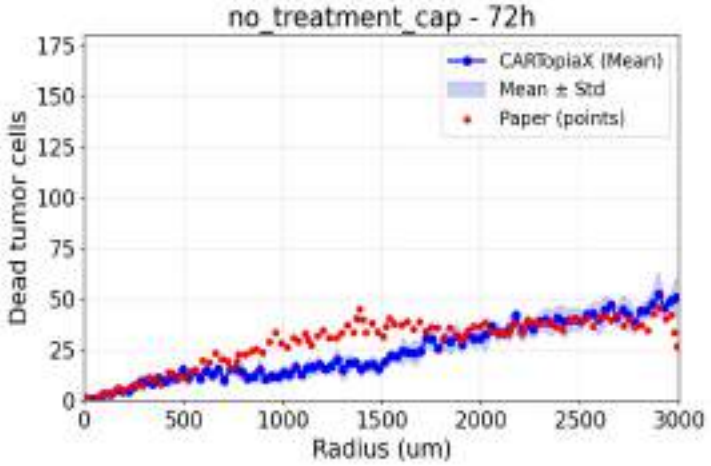
10 million cancer cells/mL, no treatment: without cap (normoxia)

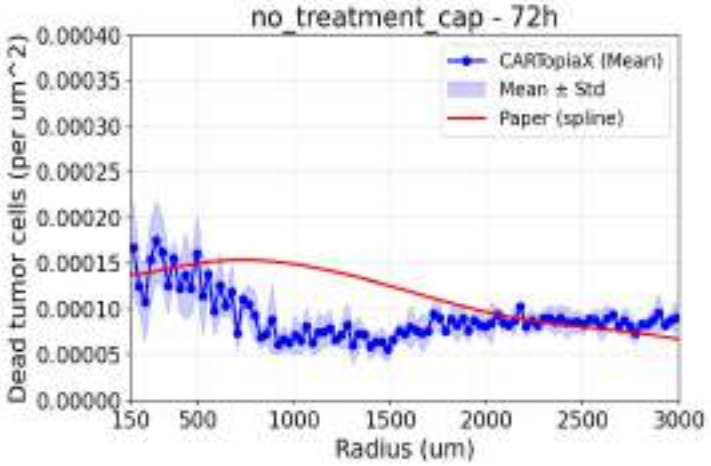




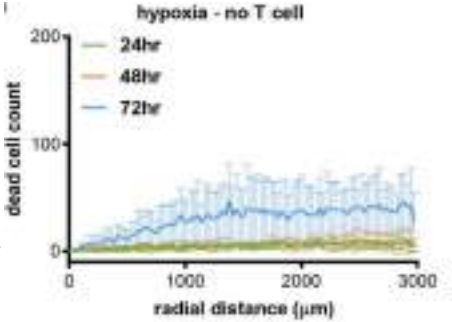
- Cell **death is uniform** because the environmental conditions are perfectly symmetric.
- Points at radii below 150 are omitted because the concentric rings are too small, resulting in very few data points, large variations, and a dividing area that tends to zero.

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



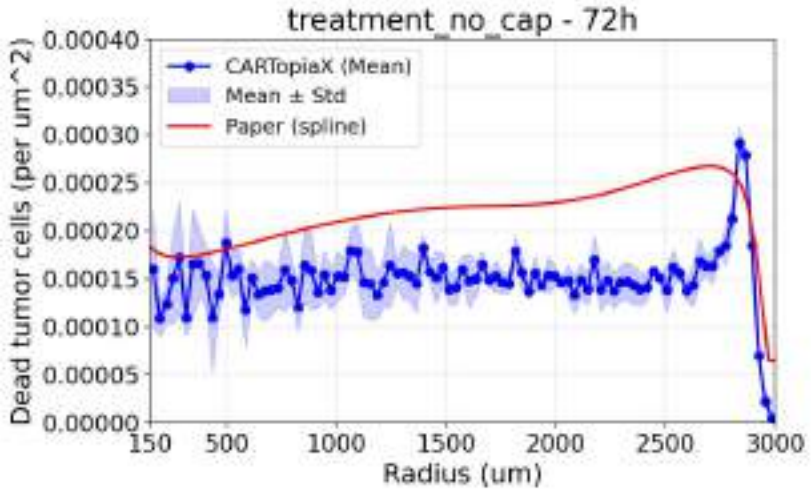


We focus on **key trends** due to high biological variability and **large error bars**.



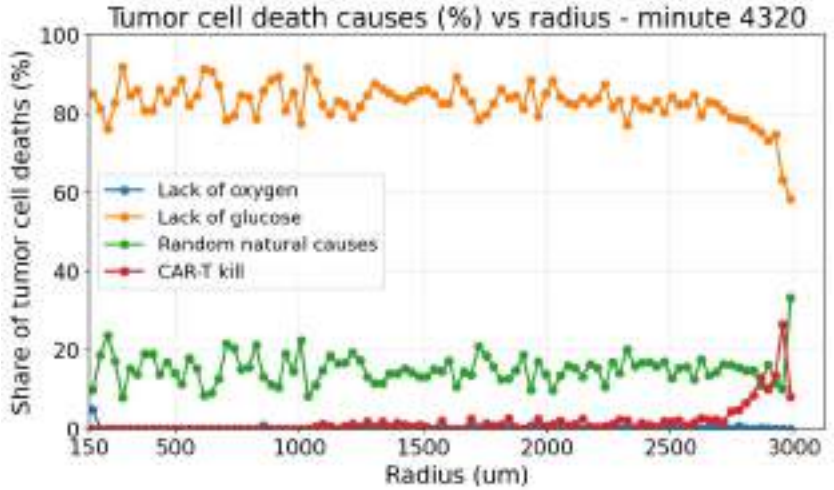
Since oxygen flows in from the edges, the cap creates a **hypoxic region in the center** of the cylinder, increasing cell death.

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

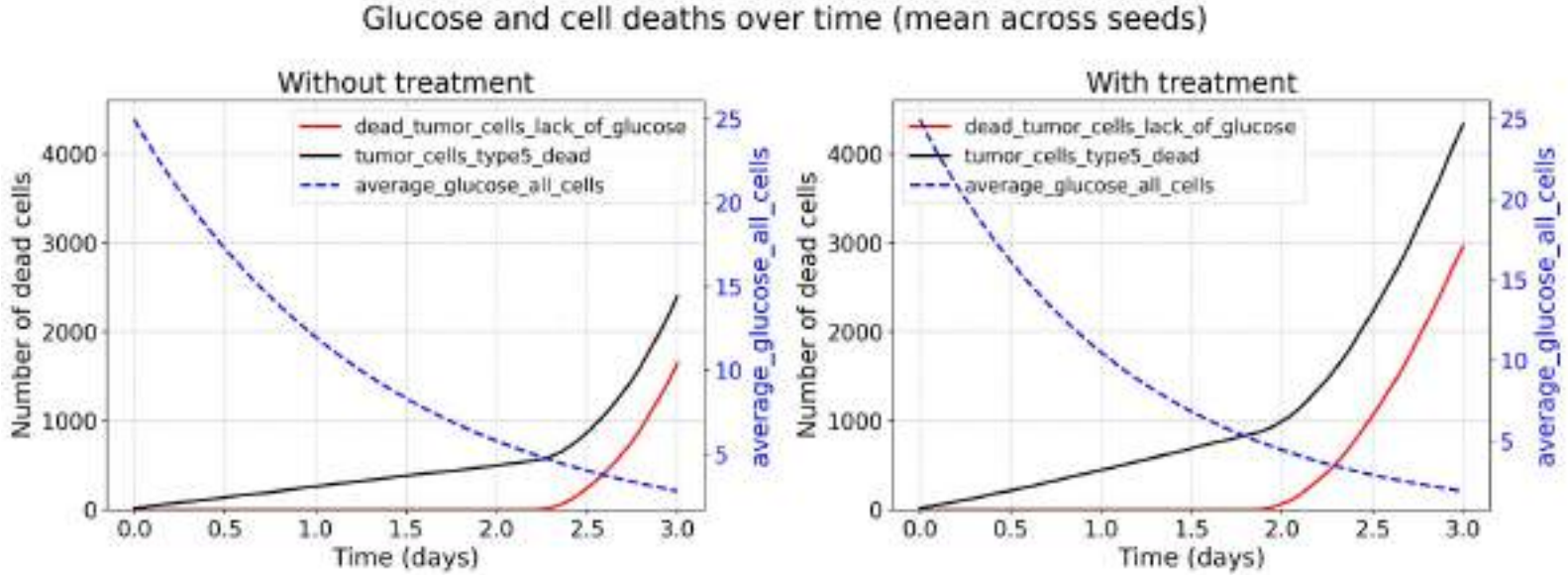


- **CAR-T cells barely infiltrate** the tumor, as reported in the paper, so very few cancer cells are killed directly by them.
- **Most cancer cell deaths** are caused by **glucose deprivation**.

- Cell **death is uniform** except at the edge, where CAR-T cells target and kill tumor cells.
- Unexpected emergent behavior: Cell **death drops** at radius 3000 as **CAR-T cells push** tumor cells toward the core.

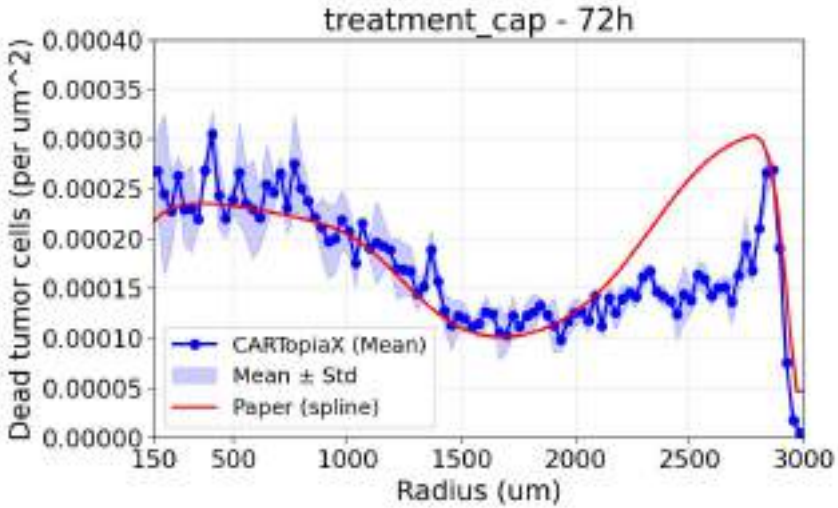


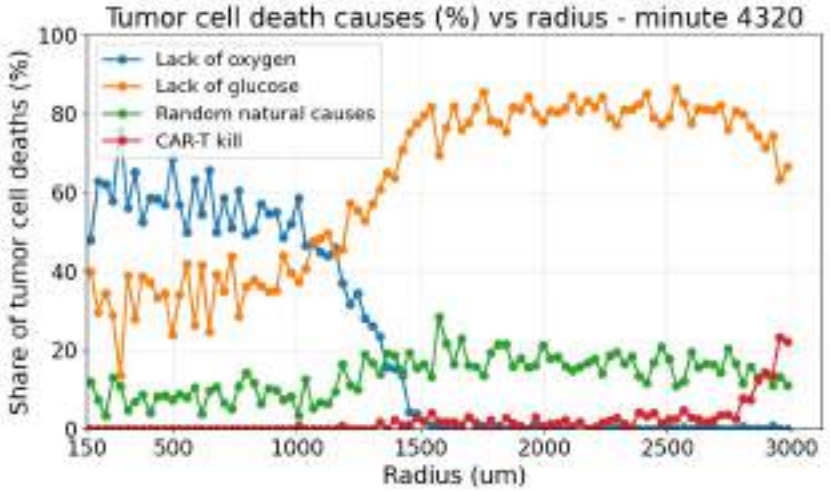
Glucose starvation kills cells



- Cells progressively **consume** the available **glucose**, **increasing mortality** over time.
- **CAR-T glucose consumption** worsens the situation causing what the authors call “**non-contact mediated CAR-T cell cytotoxicity**.”

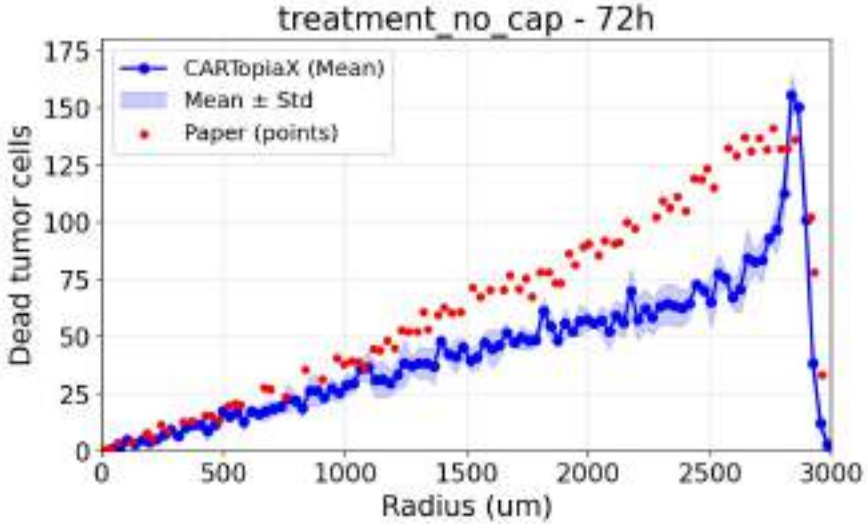
10 million cancer cells/mL, 20:1 treatment: with cap (hypoxia)

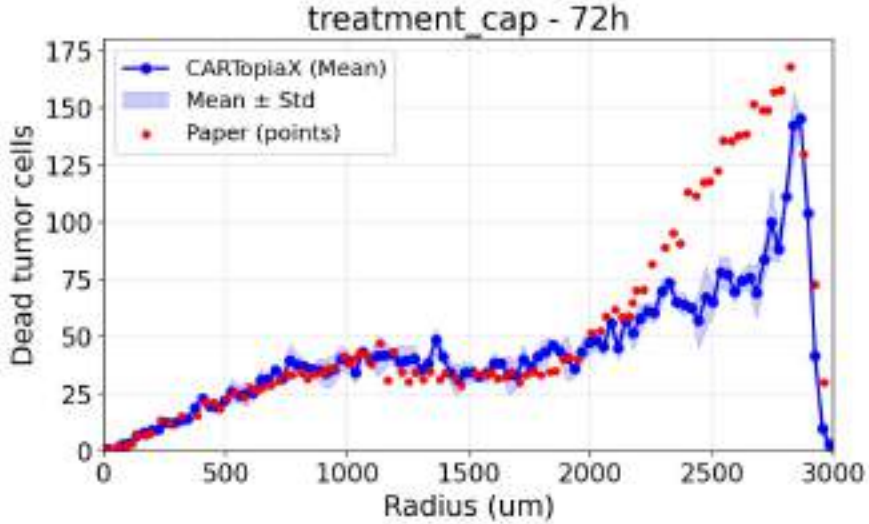




- Again, with the cap, more cells die in the **core** due to **oxygen deprivation**. **CAR-T cells also consume oxygen**, further exacerbating the situation at the center.
- At the **edges, CAR-T cells** push and kill cancer cells, as before.
- As a result, cell death increases both at the core and at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

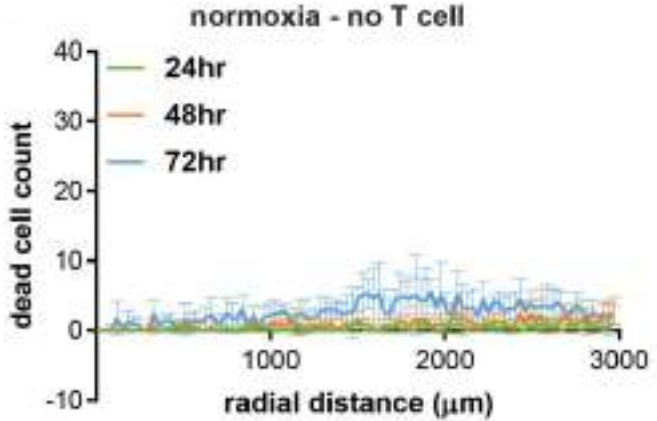
20:1 treatment: Cell deaths in the middle with vs. without the cap

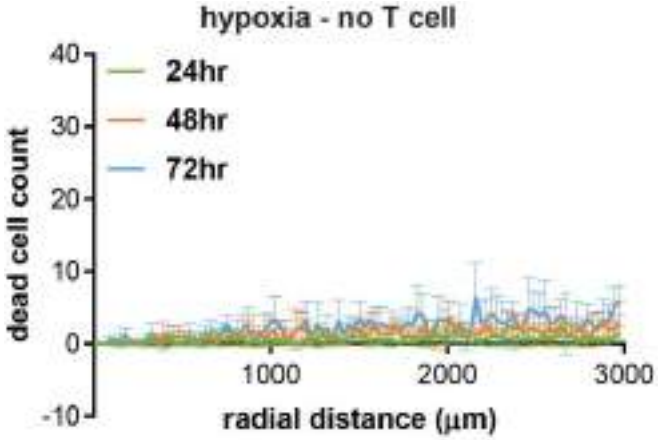




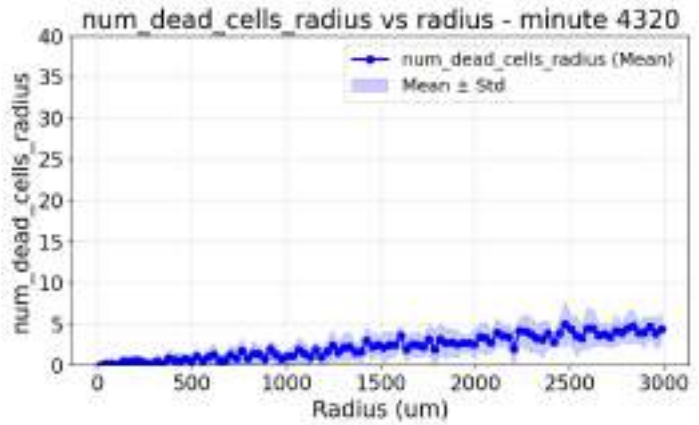
- Notice how **more cells die between radii 1400 and 2500** when there is **no cap**.
- Without the cap, **more oxygen is available**, allowing cells to **proliferate more** and consequently increasing cell deaths.
- This **does not happen at the core** because, with the cap, **oxygen** levels are **so 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**.

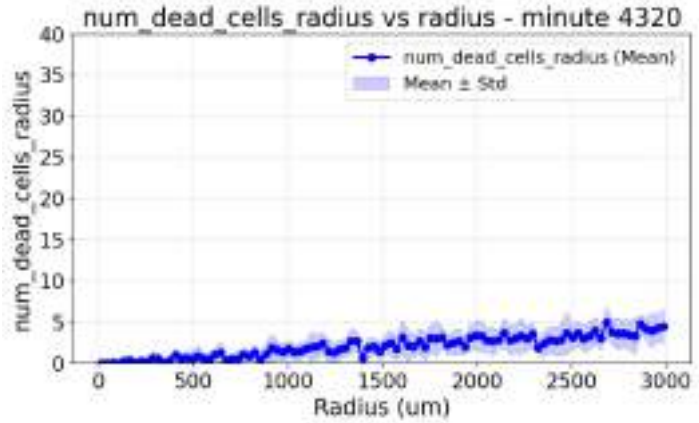
Density of 1 million cells/mL, no treatment





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**.





CARTopiaX achievements and future work

- Model extension: **New** tumor **geometry**, **glucose** diffusion, and cell **behaviors/mechanics** to reproduce a **new wet-lab scenario**.
- Bayesian calibration: Flexible automated **parameter fitting** with **fewer** costly **simulations**.
- Results: **Reproduced** key experimental **trends** and **emergent behaviors**.
- Key insight: The model offers an **in silico explanation** of **non-contact-mediated CAR-T cytotoxicity** and detailed cell death causes.
- Impact: **Flexible**, **fast**, **low-cost** platform for **CAR-T hypothesis testing**, providing **insights** into phenomena **difficult to measure in vitro**.
- Future work:
  - **Increase Monte Carlo runs** to reduce stochastic noise.
  - A manuscript presenting CARTopiaX in a **scientific journal**.

