In Silico Model for Tumor Diagnosis Based on Bloodstream Penetrating Extracellular Vesicles

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Introduction

Extracellular Vesicles (EVs) are a common biomarker to detect tumors [1]. EVs are tiny lipid-bound particles, 30 nm to 5 µm in size, released by cells into the extracellular space [1]. By modeling the flow of EVs in tissue and bloodstream in silico, we are able to derive the progress of a tumors size, even for very small tumors with a size of 50 µm [2]. In comparison – human hair is up to 100 µm.

- Lack of research in EV transportation through barriers of tissue.
- The use of in silico models as cost-effective alternatives to in vivo or in vitro experiments.

System Model

- Realistic model with distinct zones: the artery, vein, capillary network (Ω_c), tumor area (Ω_t), and healthy tissue (Ω_h)
- Several core equations, that define how EVs behave
  1. Penetration rate: Release of EVs to the blood
  2. Boundary conditions:
     - Capillary-tissue interface
     - Tumor-healthy-tissue interface
     - Partially absorbing condition
  3. Dynamic equations
     - Advection-Diffusion equation
     - Navier-Stokes-Gleichungen
- Diagnostic metric: EV flux over the venule cross section into the bloodstream is quantified by:

$$R_s = \iint_{\text{VCS}} c(\mathsf{r}, t)\, u_n(\mathsf{r}, t)\, ds$$

indicating tumor presence and size via bloodstream EV concentration.

Results

- COSMOL Multiphysics was used for the computational modeling
- Strong buildup of EVs in tumor regions due to dense tissue structure and lower diffusion rates, leading to significant barriers for capillary access.
- Inverse relationship between tumor size and the rate at which tumor-derived EVs enter the bloodstream. Shown in Figure 3.
- Small tumors (200 µm) release EVs rapidly
- Larger tumors (600 µm) produce weaker signals, with peak amplitudes reduced by 60% and slower rise times.

Conclusion

- This in silico framework offers a promising way for non-invasive cancer detection using circulating EV profiles, with potential sensitivity down to 50 µm, which is below the threshold of conventional imaging modalities.
- The temporal evolution of EV release is presented as a new diagnostic dimension beyond static imaging, enabling early detection.
- In future work, different EV sizes should be considered. Also in vivo and in vitro studies are needed to validate the results.

Figure 1

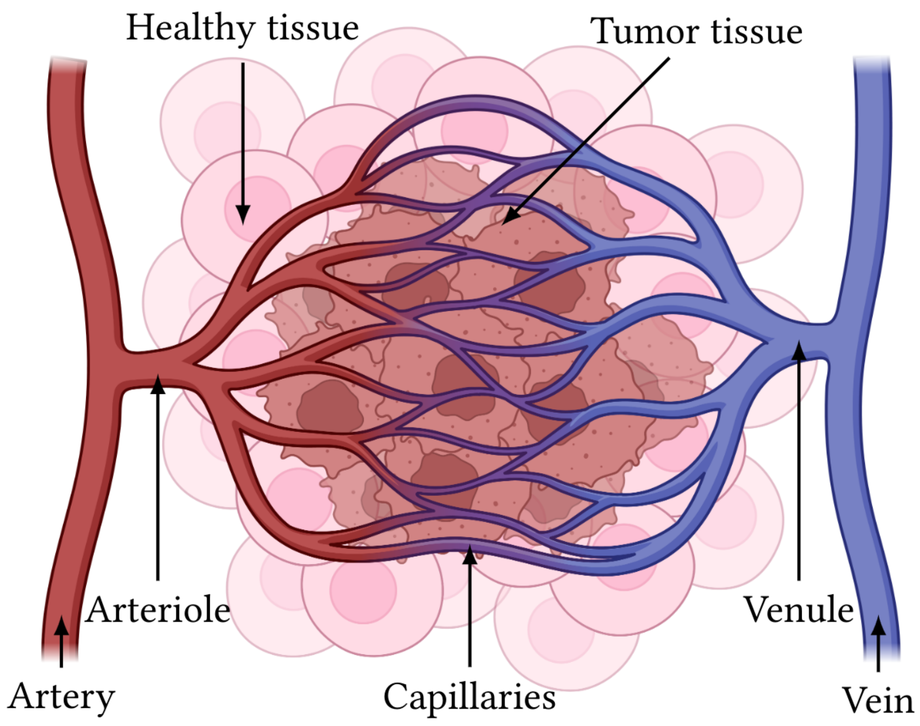


Figure 2

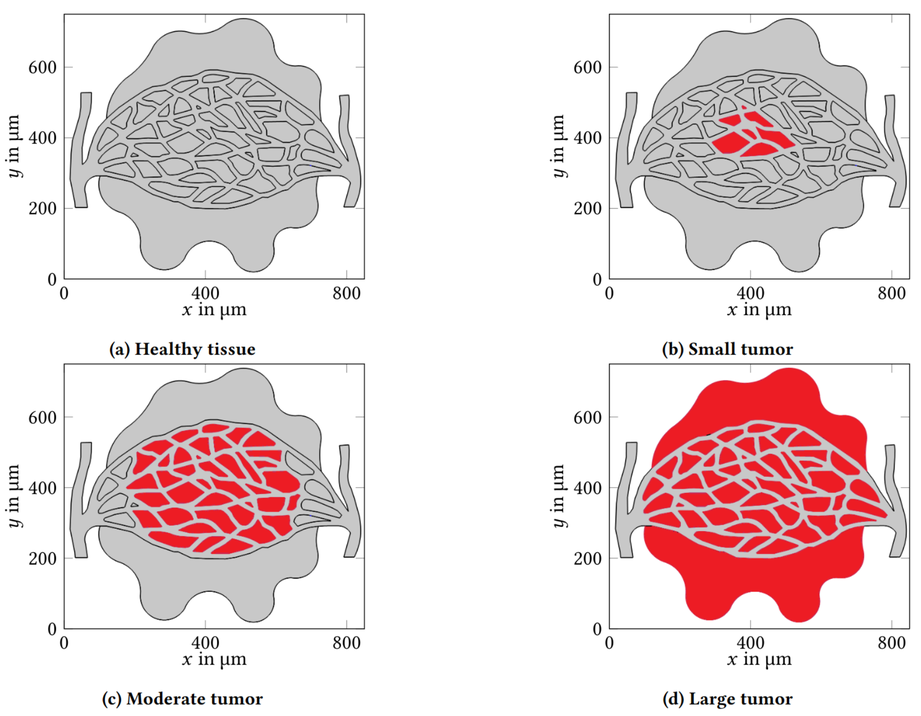
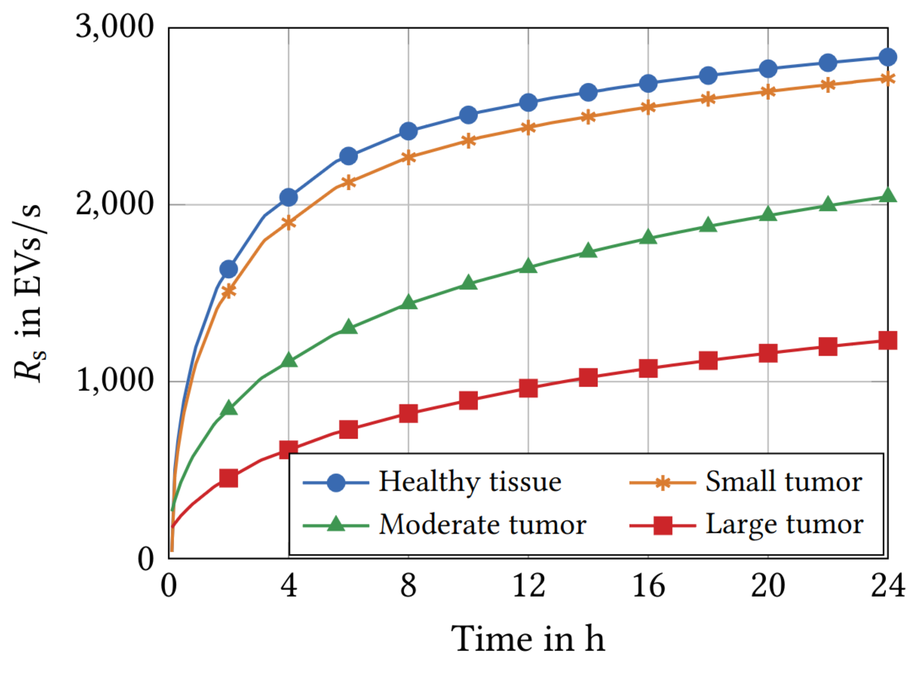


Figure 3



Quellen

[1] Doyle, L. and Wang, M. 2019. Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. Cells. 8, 7 (Jul. 2019), 727. DOI: https://doi.org/10.3390/cells8070727.

[2] Zoofaghari, M. et al. 2023. In Silico Model for Tumor Diagnosis based on Bloodstream Penetrating Extracellular Vesicles. Proceedings of the 10th ACM International Conference on Nanoscale Computing and Communication. (Sep. 2023), 129–135. DOI: https://doi.org/10.1145/3576781.3608719.