Optimizing Radioligand Dosage: A DNA Damage-Based Framework to Maximize Tumor Control and Minimize Normal Tissue Damage

Shahin Ghaseminejad[1], Glen Bauman[2], Ting-Yim Lee[1]

[1]Department of Medical Biophysics, Western University, Robarts Research Institute, and Lawson Research Institute, London, ON

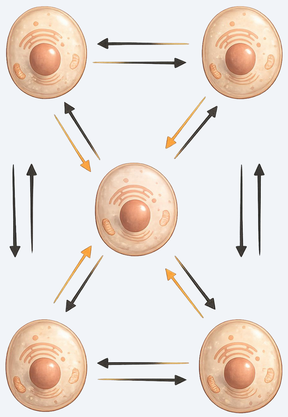
[2]Department of Radiation Oncology, London Health Sciences Centre, London, ON

Introduction

- Radioligand therapy (RLT) selectively targets cancer cells while sparing normal tissue.[1]
- In RLT, a major limitation is the **one-size-fits-all dosing** strategy, where administered activity is not tailored to each patient's in vivo biodistribution.

• Personalized RLT should account for:

- ✓In vivo radioligand distribution, particularly **random uptake** among tumor clones.
- ✓**Cross-fire** and **bystander** effects.
- ✓Linear energy transfer (**LET**).
- ✓**DNA lesions** rather than absorbed dose[2].
- ✓Tumor Control Probability (**TCP**).



Crossfire and bystander effects

The proposed framework translates cellular absorbed dose into DNA lethal lesions in patient-specific tumor models to optimize personalized radioligand dosing.

Methods

❖ Monte Carlo multi-cell model and random distribution of activity:

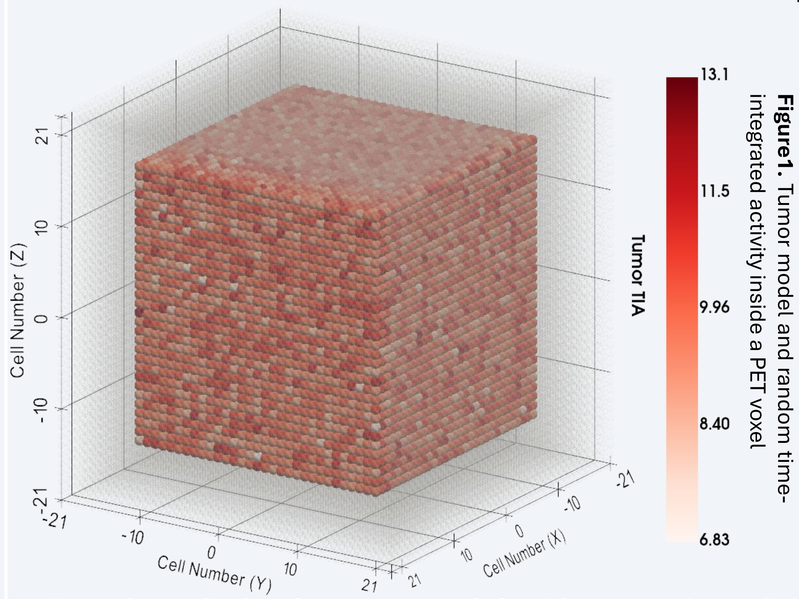


Figure1. Tumor model and random time-integrated activity inside a PET voxel

- A **patient-derived tumor model** with approximately 30,000 cells (red) surrounded by six layers of healthy cells (grey) was modeled in a PET voxel using TOPAS[3]
- 3D Time-integrated activity (**TIA**) maps were generated by sampling from a normal distribution (**patient-derived mean**, CV = 30%).

❖ Cell Dose Kernel (CDK):

Absorbed dose to neighboring cells at various distances from activity in a central cell. The CDK was convolved with TIA Maps to obtain cell-wise absorbed dose maps.

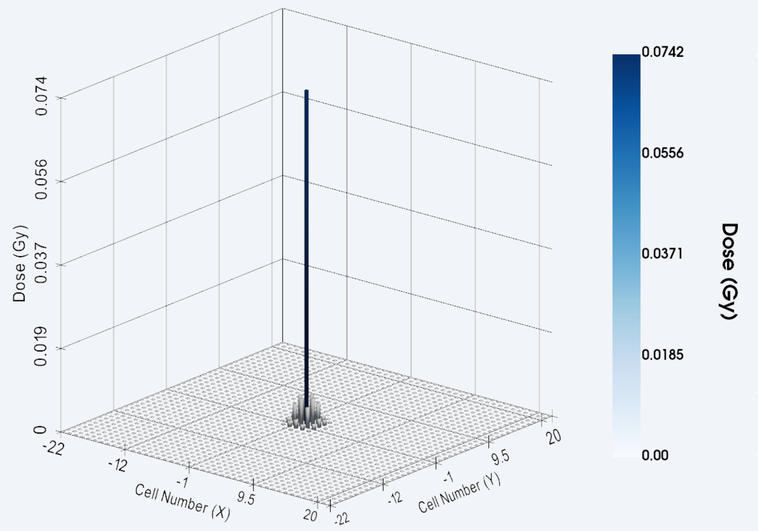


Figure2. ^{225}Ac Cell Dose Kernel (CDK)

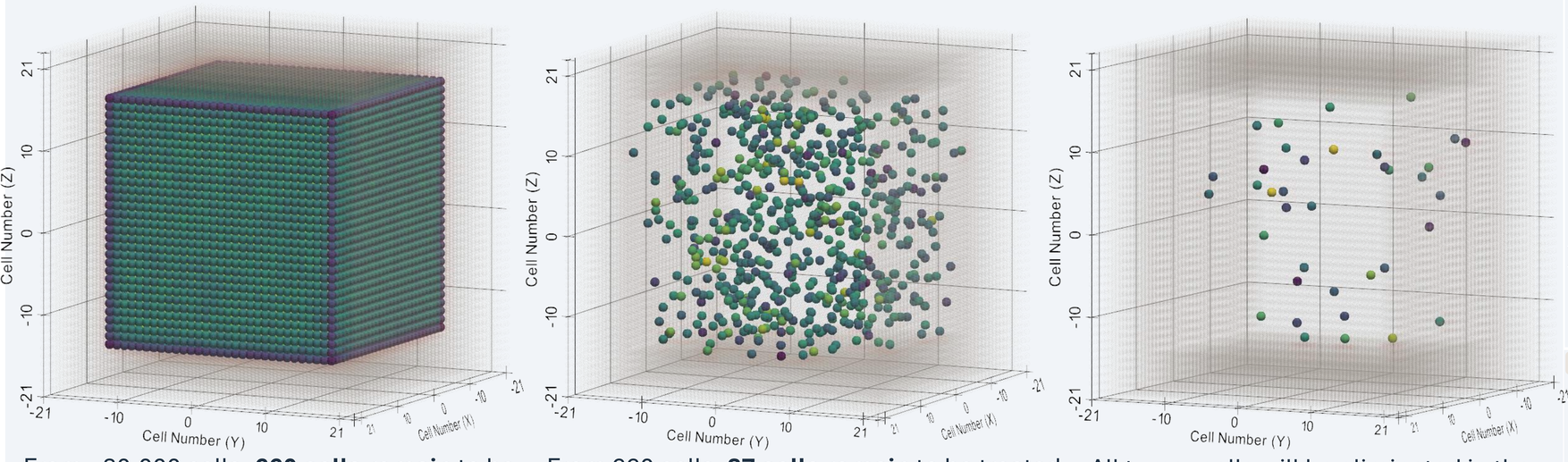
- A modified linear-quadratic (LQ) model was used to **calculate DNA Lethal Lesions (LLs)** and the **Tumor Control Probability (TCP),** accounting for radiation quality, dose rate, and DNA repair.

$$DNA\ Lethal\ Lesions, \lambda = \alpha D + G\beta D^2 \qquad TCP = e^{-N_o(e^{-\lambda})}$$

Results

Lethal Lesion 3D maps, survival fraction, and TCP in an optimized treatment plan.

^{225}**Ac** – Cycle1 – **2 MBq** → ^{225}**Ac** – Cycle2 – **100 KBq** → ^{225}**Ac** – Cycle3 – **15 KBq**



From ~30,000 cells, **660 cells remain** to be treated in the next cycle. $TCP = 0\%$

From 660 cells, **37 cells remain** to be treated in the next cycle. $TCP = 0\%$

All tumor cells will be eliminated in the last cycle. $TCP = 99.78\%$

Conclusion

- The framework is capable of **estimating the number of lethal lesions induced by radioligands inside tumor cells, as well as surrounding healthy cells.**
- Given the tumor model, TIA distribution, and treatment schedule for TCP ≈ 100%, the framework determines the radioligand dose for each cycle, accounting for the **radiation type**, **cross-fire and bystander effects**, **tumor size**, and **stochastic radioligand uptake**.
- Future work includes applying the framework voxel-by-voxel for the entire tumor volume to achieve a patient-specific treatment plan.

Acknowledgments

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References

1- Mittra Es et. al. Cancer Medicine. 2024;13(3):e6780.doi:10.1002/cam4.6780

2- Nickoloff, J. A.et al. 2020;31(1):1-6. doi: 10.3390/genes11010099

3- B. Faddegon et al. Phys Med. 2020;191(2):125. doi: 10.1016/j.ejmp.2020.03.019

Sghase5@uwo.ca