Mechanistically Coupled PBPK Modeling for Analysis and Optimization of ^{177}Lu-PSMA Therapies

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INTRODUCTION

- PSMA-targeting radiopharmaceutical (RP) therapies (RPTs) are effective treatments for metastatic castration-resistant prostate cancer (mCRPC), yet administered activity remains fixed despite substantial inter-patient variability.
- Physiologically based **pharmacokinetic** (PBPK) models predict RP biodistribution; while radiobiological **pharmacodynamic** (PD) models describe radiation-induced tumor response.
- Although both modeling approaches have been developed for RPT in mCRPC, PBPK models assume static tumor biology, whereas radiobiological PD models assume predetermined changes in RP uptake across treatment cycles.
- In reality, RP pharmacokinetics and tumor response are dynamically coupled: treatment-induced changes in tumor burden alter RP uptake, thereby influencing subsequent tumor response.
- Mechanistic coupling of PBPK and PD is therefore needed to predict how tumor response feeds back on RP uptake and absorbed dose across treatment cycles.

RESEARCH OBJECTIVE

We aimed to couple PBPK and PD models for ^{177}Lu-PSMA therapies to capture the bidirectional feedback between pharmacokinetics and tumor response, quantifying cycle-dependent changes in uptake and absorbed dose to inform multi-cycle regimen optimization.

METHODS

PBPK/PD model coupling

- Multi-scale ^{177}Lu S-value formalism spanning single-cell to macroscopic tumors
- Rule-based tumor eradication criterion
- Power-law relationship describing treatment-induced reductions in tumor PSMA receptor density consistent with allometric scaling of PSMA expression[4]:

$$R_{den} = R_{den,0} \times \left(\frac{V_{tumor}}{V_{tumor,0}}\right)^{1/4}$$

Model simulations

- Representative patient with mean mCRPC population characteristics
- Fixed hot-to-cold ligand ratio consistent with ^{177}Lu-PSMA-617, scaled linearly with IA

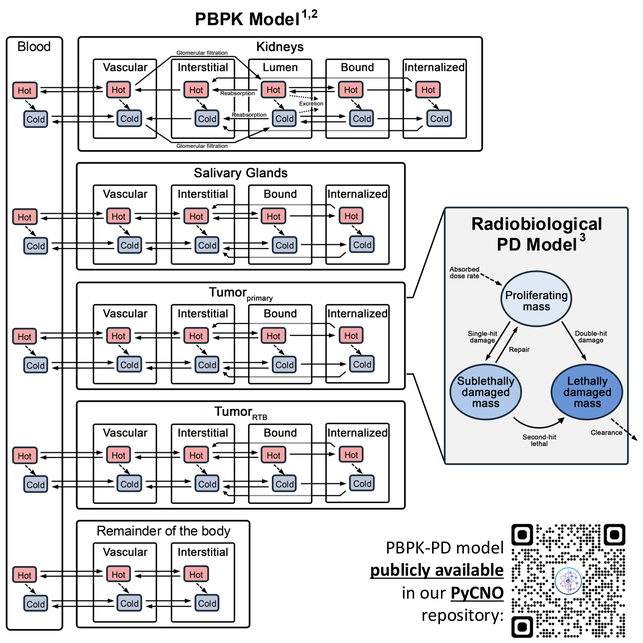

Figure 1. Structure of the coupled PBPK/PD model. Solid arrows denote transport (PBPK) and cell-state transitions (PD). Dashed arrows indicate radioactive decay (PBPK) and coupling of the PD model to the primary tumor compartment via absorbed dose rate (PD).

Table 1. Simulated clinical trial and model-informed treatment schedules.

Treatment regimen	Administration protocol	Cumulative IA
Standard of care	6 cycles of 7.4 GBq every 6 weeks	44.4 GBq
FLEX-MRT	12 cycles of 7.4 GBq every 6 weeks	88.8 GBq
OPTIMAL-PSMA	7.5 GBq on days 1, 3, & 15; 8-week break; then 7.5 GBq every 10 weeks × 3 cycles	45.0 GBq
LPS-BOOST	7.4 GBq on days 1, 8, 50, 57, 99, 141	44.4 GBq
Two-fraction	7.4 GBq followed by 37.0 GBq at week 6	44.4 GBq
Single-fraction	44.4 GBq day 1	44.4 GBq

KEY INSIGHTS INTO OPTIMAL TREATMENT STRATEGIES

Coupled model predicts progressive reductions in TAC

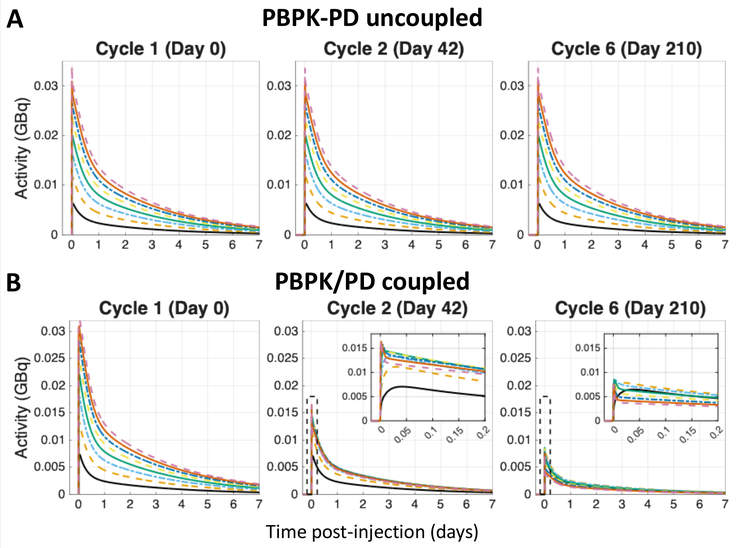

Figure 2. Simulated tumor time-activity curves (TACs) for standard ^{177}Lu-PSMA therapy (IA: 3.7 to 29.3 GBq) using the A) uncoupled and B) coupled PBPK/PD model.

Larger injected activities (IA) yield greatest shrinkage in early cycles

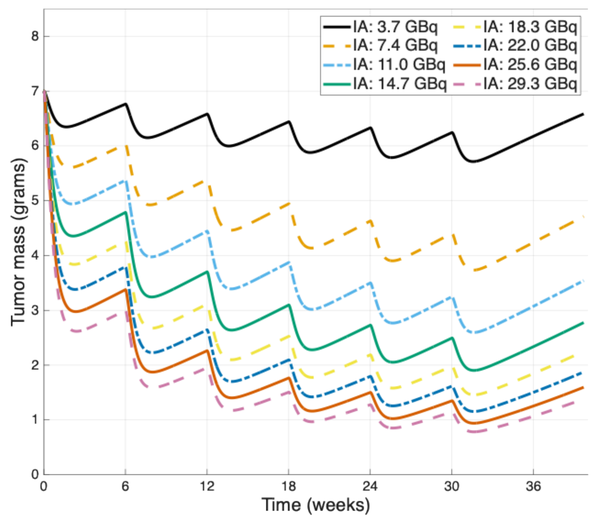

Figure 3. Tumor mass dynamics for an initial 7-gram tumor simulated using the coupled PBPK/PD model across standard 6-cycle regimens.

Cycle 1 induces the biggest "hit", with later cycles blunted due to reduced PSMA content and binding

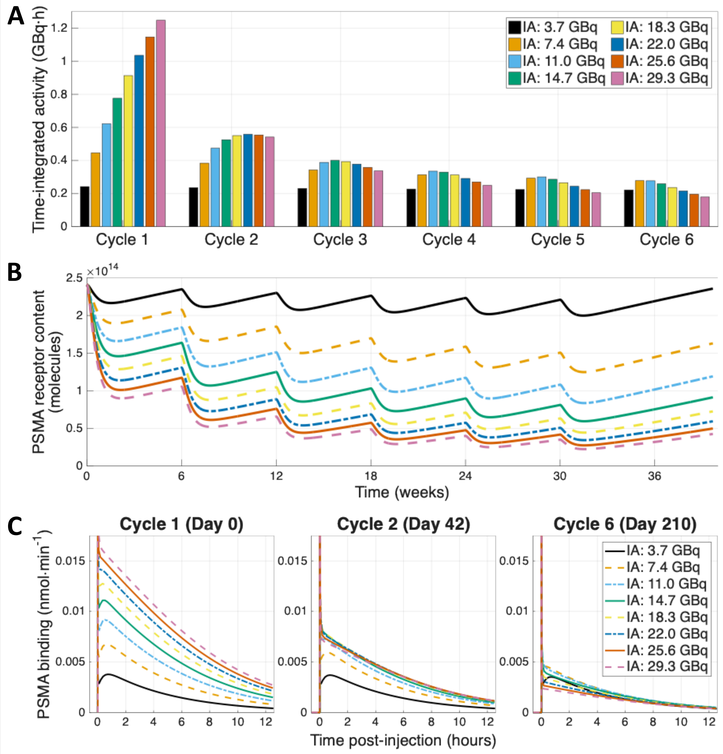

Figure 5. A) Cycle-specific tumor time-integrated activity. B) Total tumor PSMA receptor content across the simulated treatment schedules. C) ^{177}Lu-PSMA binding rate.

Optimal ^{177}Lu-PSMA treatment should focus on maximizing IA in early cycles

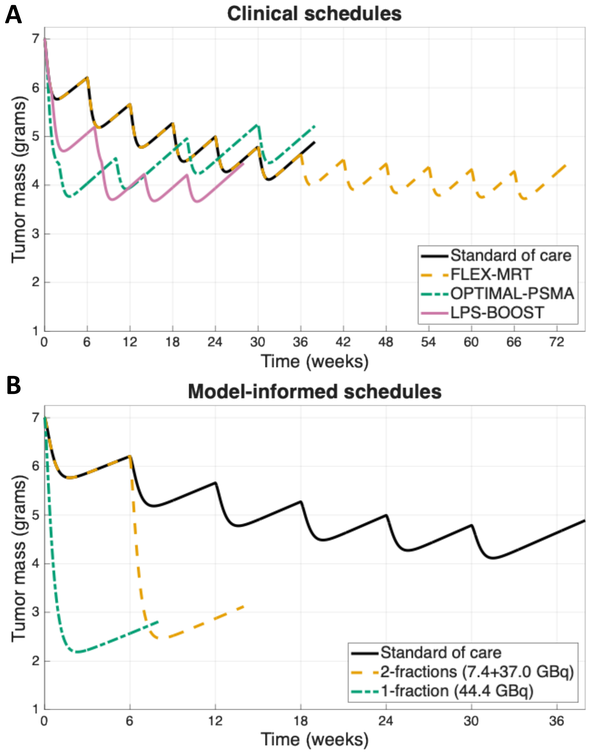

Figure 5. Simulated tumor response to A) ongoing clinical trial protocols and B) model-informed treatment schedules.

CONCLUSIONS AND FUTURE WORK

- The coupled PBPK/PD model captures feedback between tumor response and pharmacokinetics, predicting reduced tumor TAC in subsequent treatment cycles.
- Simulations indicate that the first treatment cycle provides the greatest therapeutic benefit, supporting investigation of upfront activity intensification.
- This framework represents a critical step toward computational nuclear oncology frameworks, including theranostic digital twins and model-informed optimization of RPT.
- Future work will validate the model using clinical datasets & quantify patient-specific variability in model parameters.

REFERENCES

[1]Kletting et al. *PLOS ONE.* 2016; [2]Fele-Paranj et al. *EJNMMI Radiopharm Chem.* 2024; [3]Zaid et al. *J Nucl Med.* 2025; [4]Perez-Garcia et al. *Nat Phys.* 2020

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