WILLCOX RESEARCH GROUP

INSTITUTE FOR COMPUTATIONAL ENGINEERING & SCIENCES
ODEN

Towards Predictive Digital Twins with Applications to Precision Oncology

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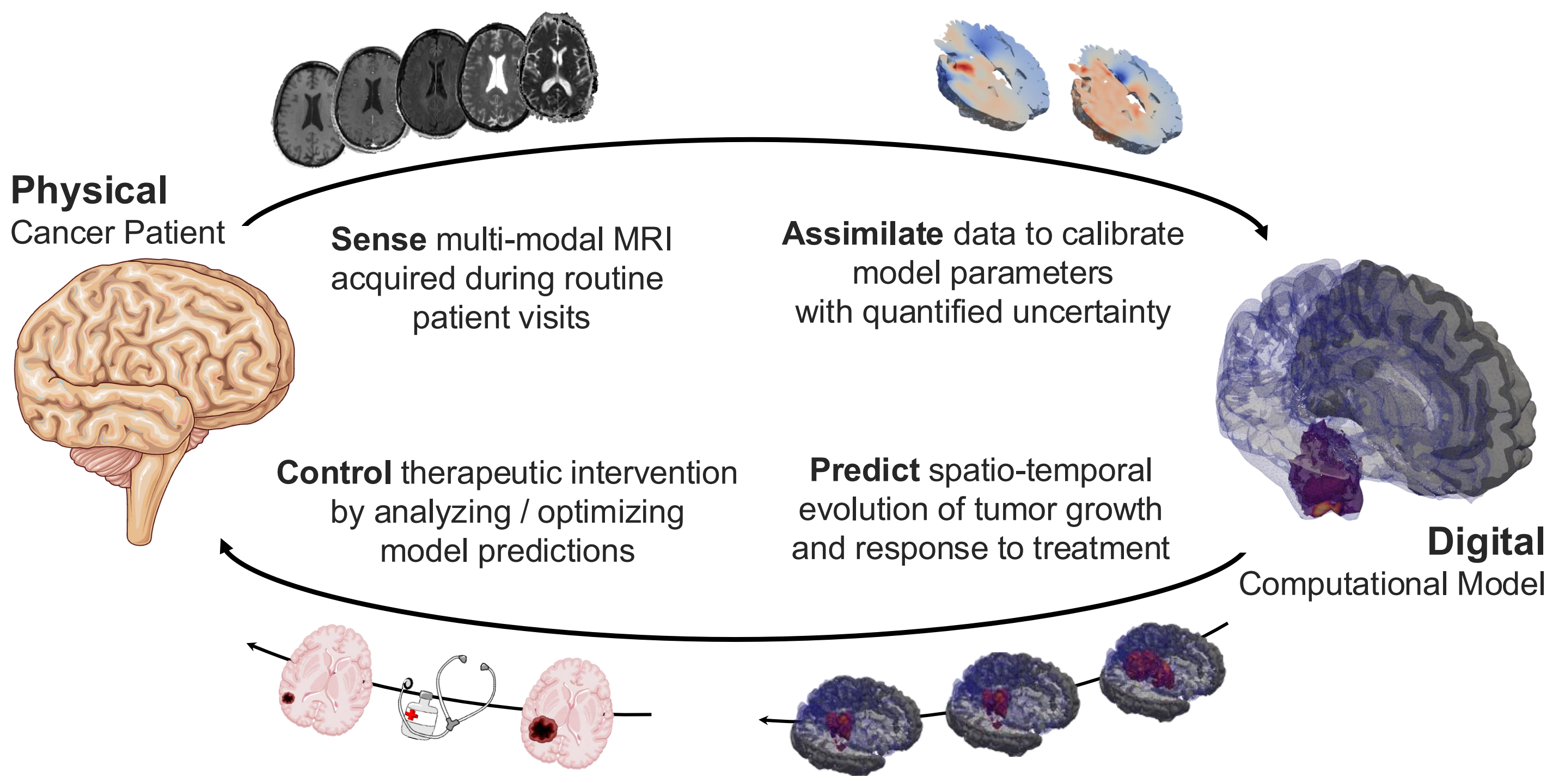
TEXAS

What is a Digital Twin?

> "A digital twin is a set of virtual information constructs that mimics the structure, context, and behavior of a natural, engineered, or social system (or system-of-systems), is **dynamically updated** with data from its physical twin, has a **predictive capability**, and **informs decisions** that realize value. The **bidirectional interaction** between the virtual and the physical is central to the digital twin."
>
> [NASEM, 2023]



Physical
Cancer Patient

Sense multi-modal MRI acquired during routine patient visits

Assimilate data to calibrate model parameters with quantified uncertainty

Digital
Computational Model

Predict spatio-temporal evolution of tumor growth and response to treatment

Control therapeutic intervention by analyzing / optimizing model predictions

Quantifying uncertainty in predictive models is critical for for **establishing trust** and enabling **risk-informed decision making.** In contrast to one-size-fits-all approaches that mitigate risk at the population level, **digital twins enable personalized modeling** thereby potentially improving individual outcomes and requires **patient-specific modeling and optimization.**

Key Idea: Improving decision making for the individual will improve outcomes at the population level.

Scalable Bayesian Inference for Patient-Specific Modeling

Realizing digital twins in biomedicine requires **scalable** and **efficient** methods to **integrate patient data** with **mechanistic models** of disease progression. We develop an end-to-end data-to-decisions methodology that integrates **MRI data** with mechanistic models of tumor growth to **forecast progression.** The methodology is demonstrated on a **virtual** patient and **validated on clinical data** showing relevance to real cases.

We model **tumor invasion** into healthy tissue and **proliferation** of exiting tumor with a semi-linear parabolic partial differential equation model.

$$\frac{\partial u}{\partial t} - \underbrace{\nabla \cdot (D(\boldsymbol{x}) \nabla u)}_{\text{infiltration}} - \underbrace{\kappa(\boldsymbol{x}) u(1-u)}_{\text{proliferation}} = \underbrace{f(u)}_{\text{treatment}} \quad \text{in } \Omega \times (t_0, t_f)$$

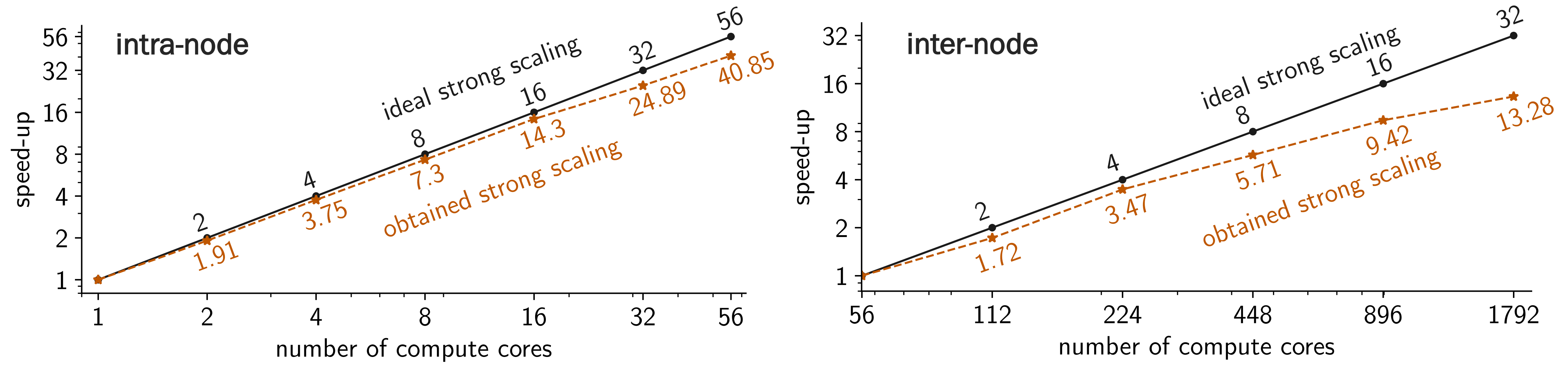
We pose model calibration as a **Bayesian inverse problem** where we seek the **posterior** distribution. Due to the high computational cost associated in the PDE setting, we leverage the **Laplace approximation** to the posterior.

Forward model
$$\mathcal{F}(m) = \mathcal{B}(u(m)), \text{s.t. } \underbrace{r(u(m), m) = 0}_{\text{residual form of PDE}}$$

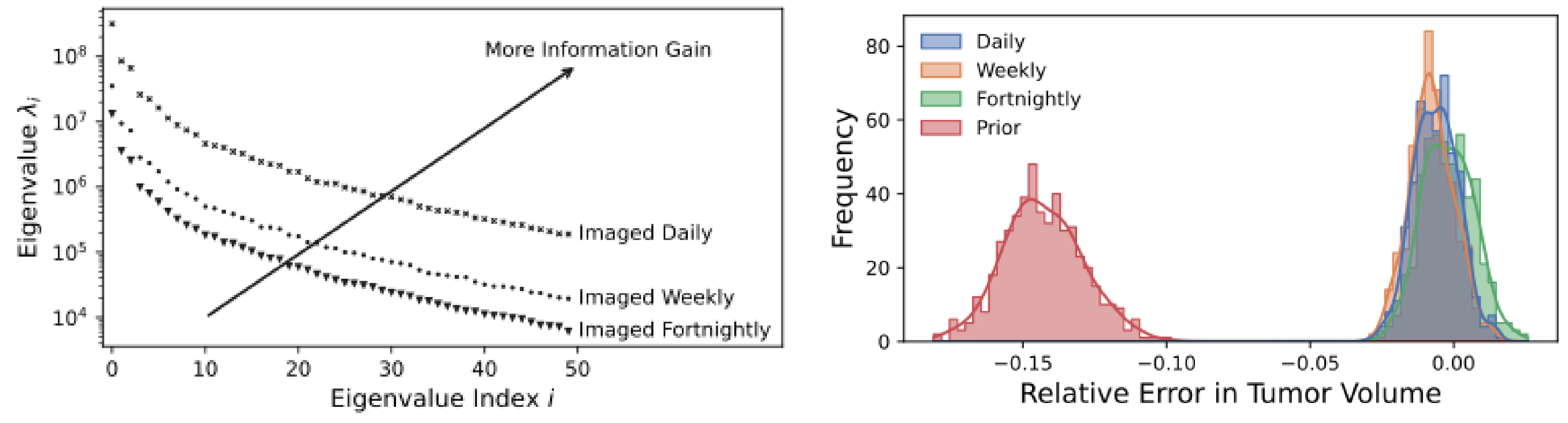
Posterior
$$d\nu_{\text{post}} \propto \exp\left\{ \underbrace{-\frac{1}{2}\|\mathcal{F}(m) - \boldsymbol{d}\|^2_{\Gamma^{-1}_{\text{noise}}}}_{\text{misfit}} - \underbrace{\frac{1}{2}\|m - m_{\text{pr}}\|^2_{\mathcal{C}^{-1}_{\text{prior}}}}_{\text{prior}} \right\}$$

Laplace approximation
$$\nu^{\mathcal{L}}_{\text{post}} \sim \mathcal{N}(m_{\text{MAP}}, \mathcal{H}^{-1}_{\text{MAP}})$$

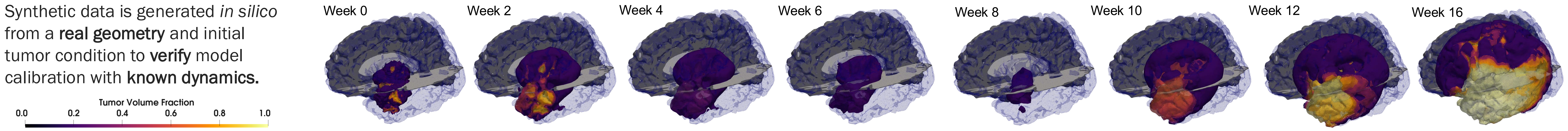
High-performance computing enables simulation and insight on **clinically relevant timelines.** We achieve suitable **strong scaling** intra-node and competitive scaling inter-node.



Model calibration is performed for **various imaging schedules** assessing the **impact of additional imaging** on **prediction quality.** The spectrum of prior-preconditioned Hessian quantifies **information gain.** Posterior predictive distributions for relative error in tumor volume reveals **balance between model performance and data quantity.**

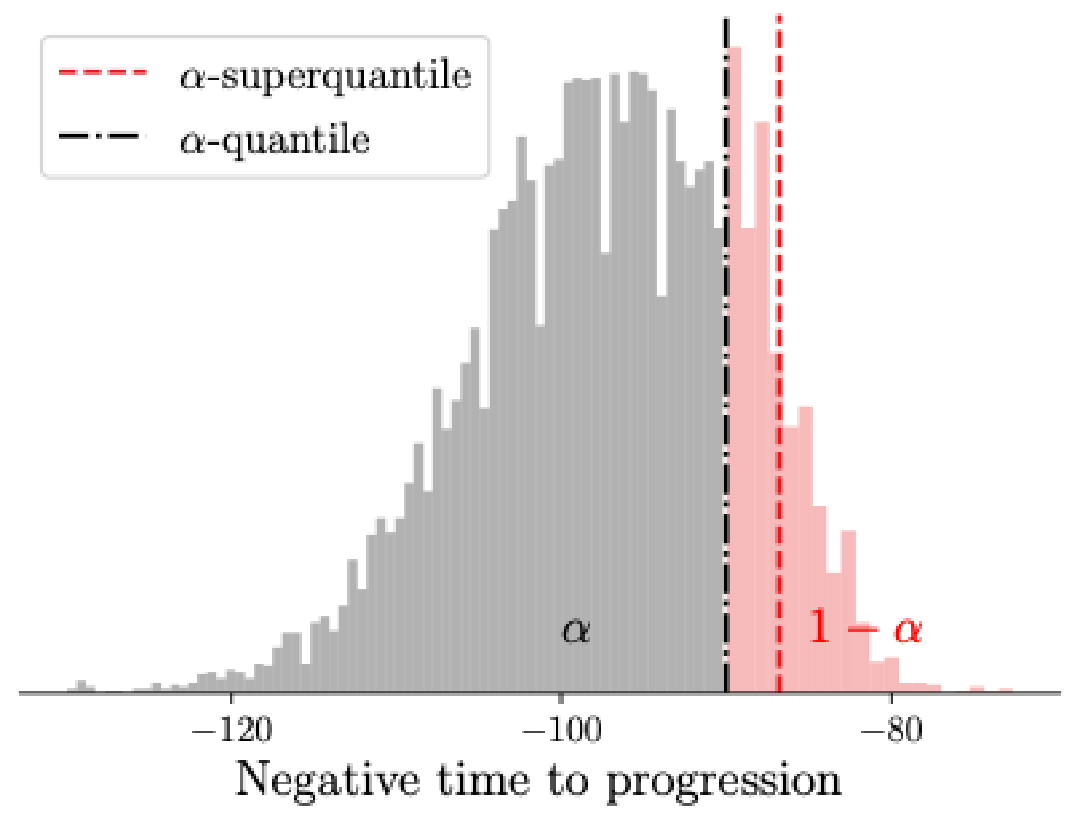


Synthetic data is generated *in silico* from a **real geometry** and initial tumor condition to **verify** model calibration with **known dynamics.**



Optimizing Patient-Specific Radiotherapy Schedules

Patient-specific **therapy planning** should account for uncertainties in the underlying biology. Bayesian approaches provide a mathematically rigorous foundation to quantify uncertainty which are in turn used to solve a **risk-based formulation.** Optimized treatment is tailored to the individual to **reduce toxicity and tumor burden.**

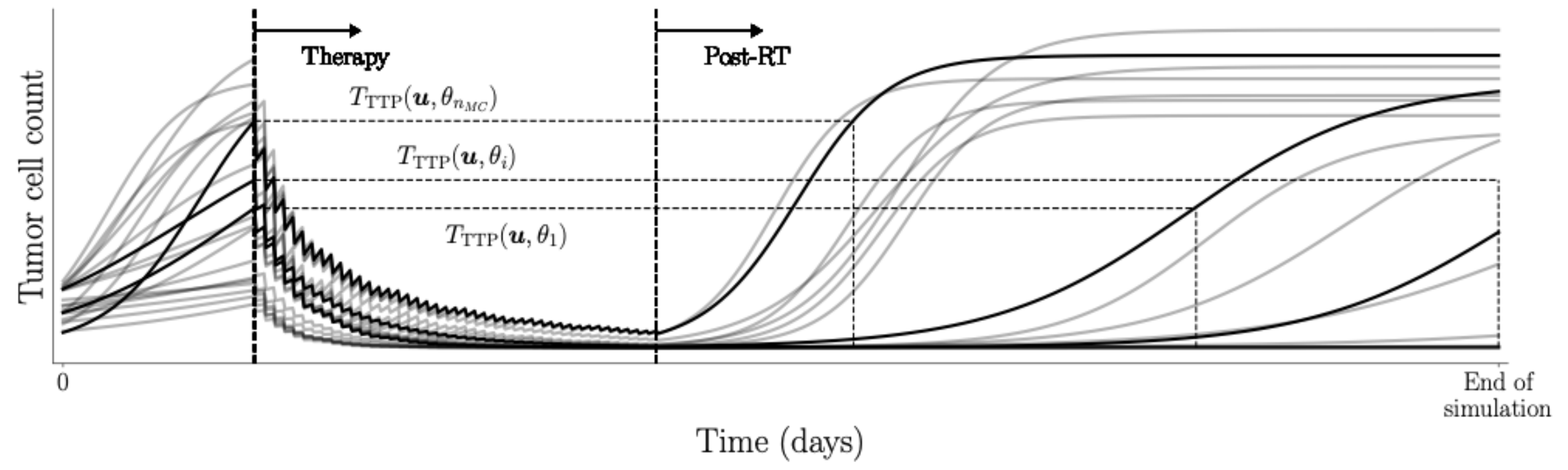


We maximize **time to progression (TTP)** in a risk-based formulation regularized to promote sparsity and **reduce toxicity** in the adapted plan, and subject to a **dosage constraint.**

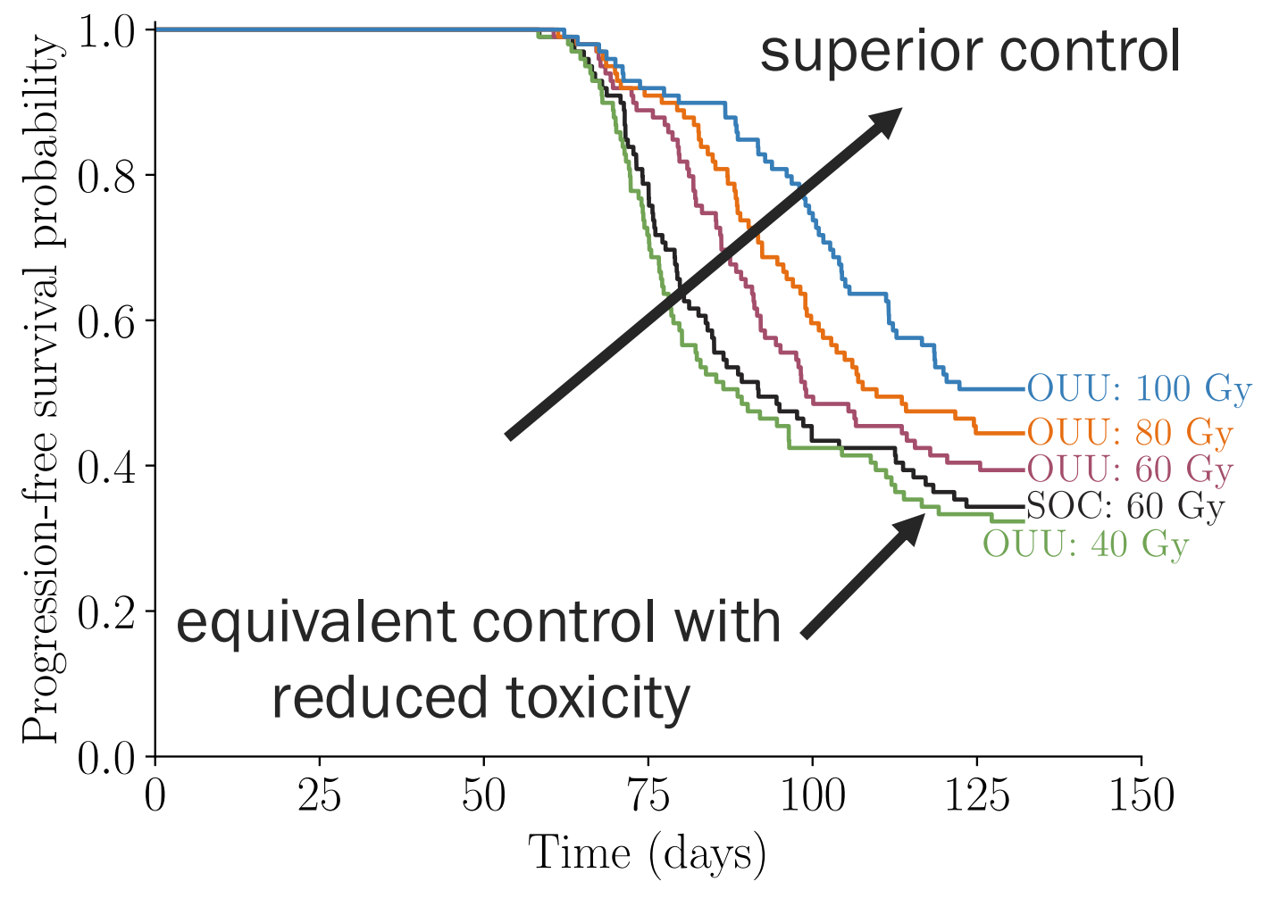
$$\boldsymbol{z}^* = \underset{\boldsymbol{z} \in \mathcal{Z}_{\text{ad}}}{\arg\min}\, \rho(Q(u); \boldsymbol{z}) + \lambda \|\boldsymbol{z}\|_1$$

$$\text{s.t. } \sum_i z_i \leq z_{\max}$$

Proposed dose schedules are assessed by computing **statistical estimates** of the **time-to-progression (TTP)** from the posterior predictive distribution.

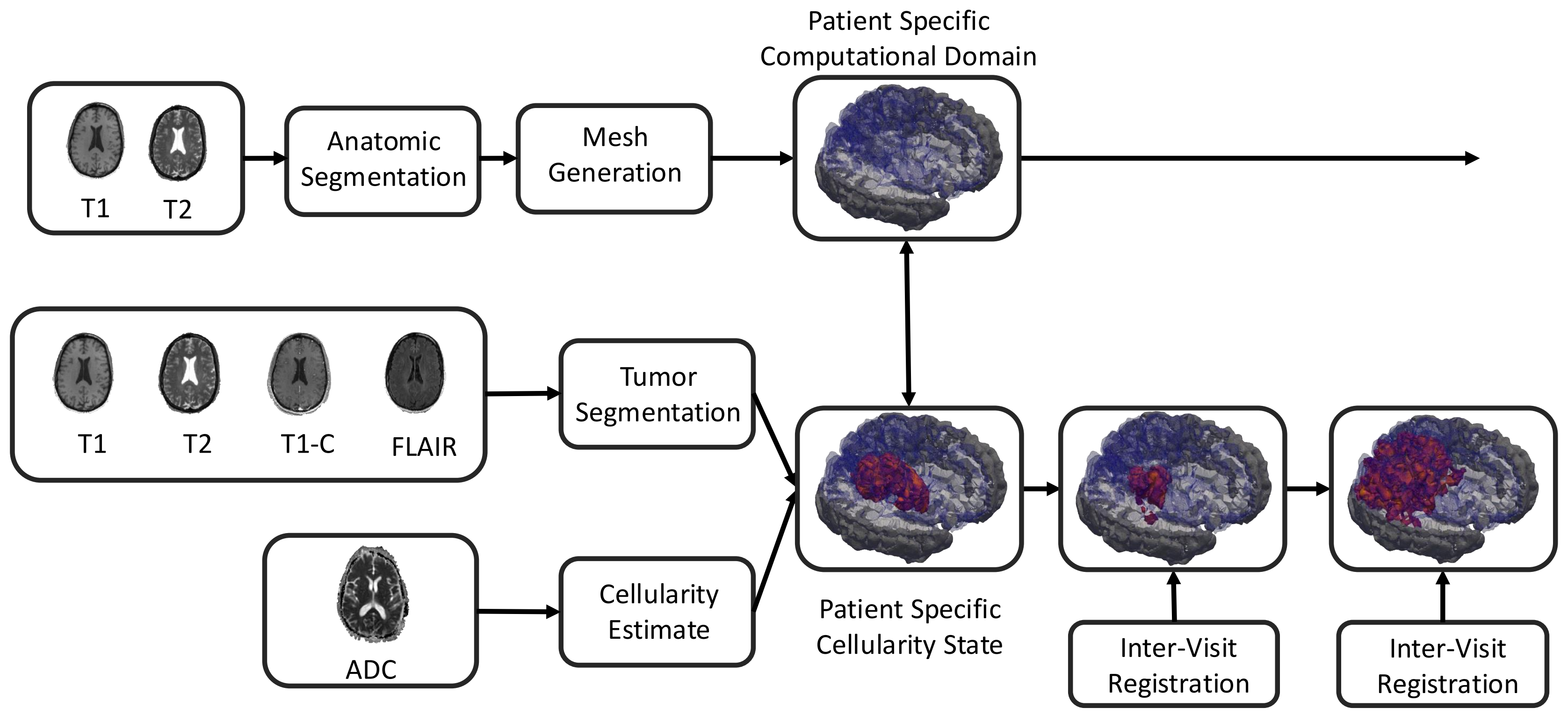


Statistical analysis of the **survival curves** demonstrates that optimal scheduling is **significantly better** for the **same amount** of applied radiation. Statistically **equivalent control** can be achieved with **reduced toxicity.**



Personalized Computational Representation

Personalized modeling starts at the level of computational domains **tailored to the individual**, capturing patient-specific anatomical features. Anatomic segmentation and mesh generation for **patient-specific geometry**, **cellularity estimation**, and **longitudinal registration.** Tumor volume fraction is estimated by combining tumor segmentations with cellularity estimates from apparent diffusion coefficient (ADC) images.



Patient Specific Computational Domain

T1

T2

Anatomic Segmentation

Mesh Generation

T1

T2

T1-C

FLAIR

Tumor Segmentation

ADC

Cellularity Estimate

Patient Specific Cellularity State

Inter-Visit Registration

Inter-Visit Registration

Interested in more?

Optimizing Radiotherapy Scheduling Under Uncertainty

`TumorTwin`
Framework for Digital Twins

Scalable Bayesian Inference

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