The University of Texas at Austin
Oden Institute for Computational Engineering and Sciences

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Navigating uncertainty to build trust in digital twins

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Digital twin definition

"A Digital Twin is a set of virtual information constructs that mimics the structure, context, and behavior of an individual/unique physical asset, is dynamically updated with data from its physical twin throughout its lifecycle and informs decisions that realize value."

- AIAA Institute Position Paper, 2020

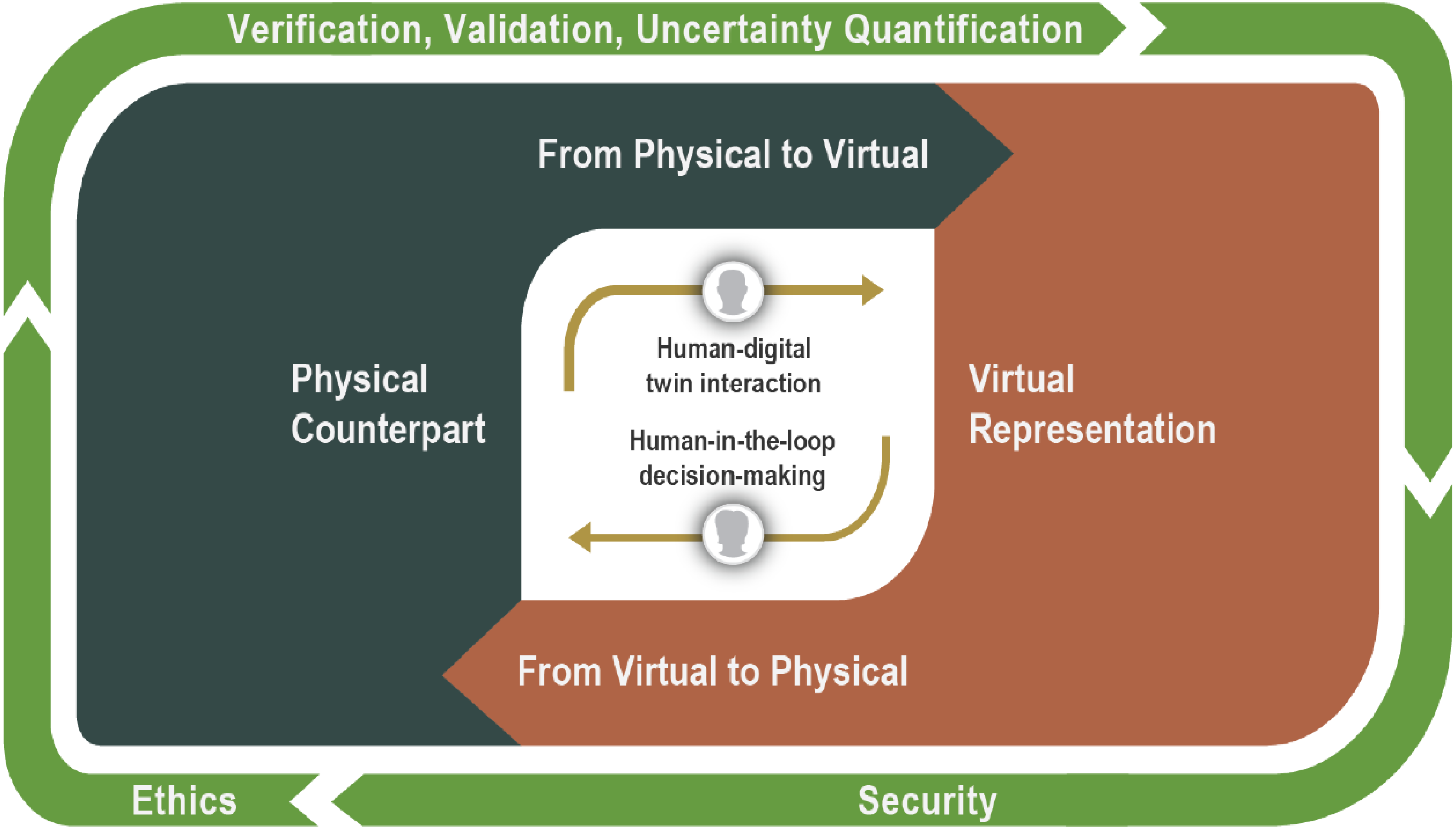
"A digital twin is a set of **virtual information constructs** that **mimics the structure, context, and behavior of a natural, engineered, or social system** (or system-of-systems), is **dynamically updated** with data from its physical twin, has a **predictive capability**, and **informs decisions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

- NASEM report, 2023

National Academies of Sciences, Engineering, and Medicine, 2023. Foundational Research Gaps and Future Directions for Digital Twins

Digital twins

- figure from "National Academies of Sciences, Engineering, and Medicine, 2023. Foundational Research Gaps and Future Directions for Digital Twins"



Interdisciplinary team

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Chengyue Wu (MDACC)

Guillermo Lorenzo (CCO, UT Austin; University of Pavia, Italy)

Building trust in digital twins is key for safety critical applications

A digital twin should be able to

- provide interpretable decisions through explainable underlying models with uncertain parameters
- quantify the effects of multiple sources of uncertainty and account for risk in decision-making
- be computable on actionable (possibly real-time) time scales

and ensure security, address ethical concerns, …

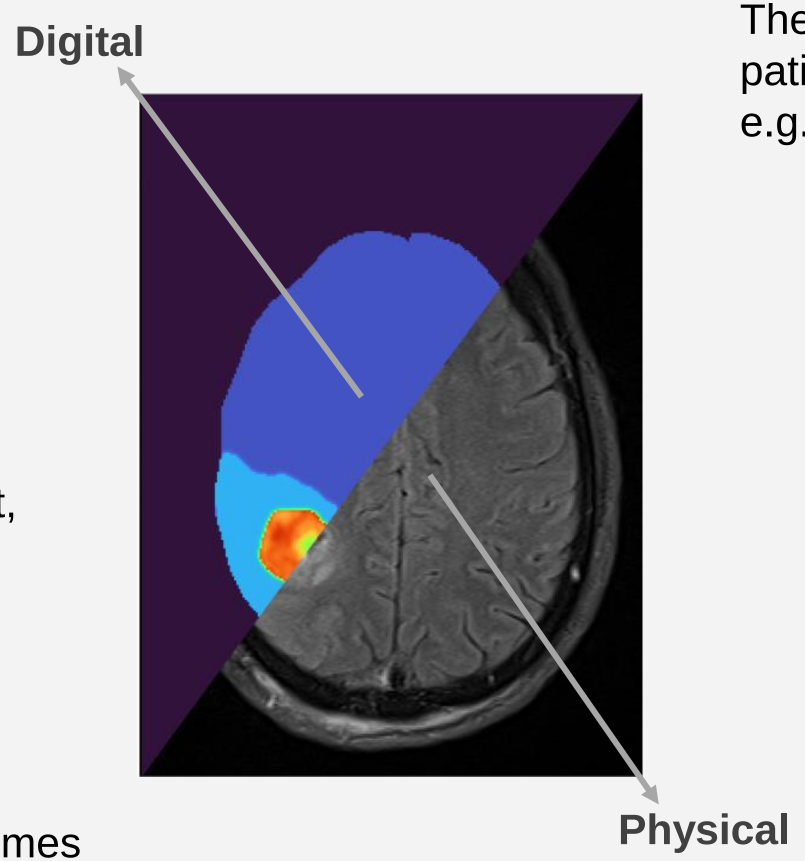
MATHEMATICAL ABSTRACTION

of a cancer patient-twin system

Digital State
Configuration of the computational models comprising the digital twin
e.g., mechanistic model parameters, tumor dynamics

Quantities of Interest
Quantities for monitoring the patient, estimated via model outputs
e.g., tumor cell count, time to progression, tumor shape

Reward
Quantifies overall patient outcomes
e.g., treatment efficacy, toxicity



Control inputs
Therapy decisions that influence the patient condition
e.g., MRI studies, treatment regimens

Physical State
State of the patient
e.g., anatomy, physiological state

Observational data
Available information describing the state of the patient
e.g., tumor size, cell density, perfusion, vasculature, tumor metabolism

Joint work between the Willcox Research Group and the Center for Computational Oncology at the Oden Institute

Chaudhuri, A, et al. “Predictive Digital Twin for Optimizing Patient-Specific Radiotherapy Regimens under Uncertainty in High-Grade Gliomas.” *Frontiers in Artificial Intelligence* 6: 1222612, 2023.

Interpretable decisions

are made possible through explainable models

- We achieve interpretability by placing biology/physics-based models at the core of the digital twin.
  - Choice of computational models offers different levels of complexity and fidelity.

- Explainable surrogate models, such as projection-based reduced order models play a critical role in reducing computational effort and retain a clear interpretable connection to the underlying physics-based models.

Logistic tumor growth model representing tumor dynamics and treatment

$$\frac{dN(t)}{dt} = \rho N(t)\left(1 - \frac{N(t)}{K}\right); \quad N(0) = N_{\text{initial}}$$

governing equation

$$S(u_t) = S_{\text{C}}\exp\left(-\alpha u_t - \frac{\alpha}{10}u_t^2\right)$$

radiotherapy treatment effect: surviving fraction

$$N_{\text{post-treatment}} = S(u_t)N_{\text{pre-treatment}}$$

discrete treatment events

Uncertainty quantification (UQ)

Continuous assessment of uncertainty in model predictions and decisions is necessary to build appropriate confidence in the digital twins.

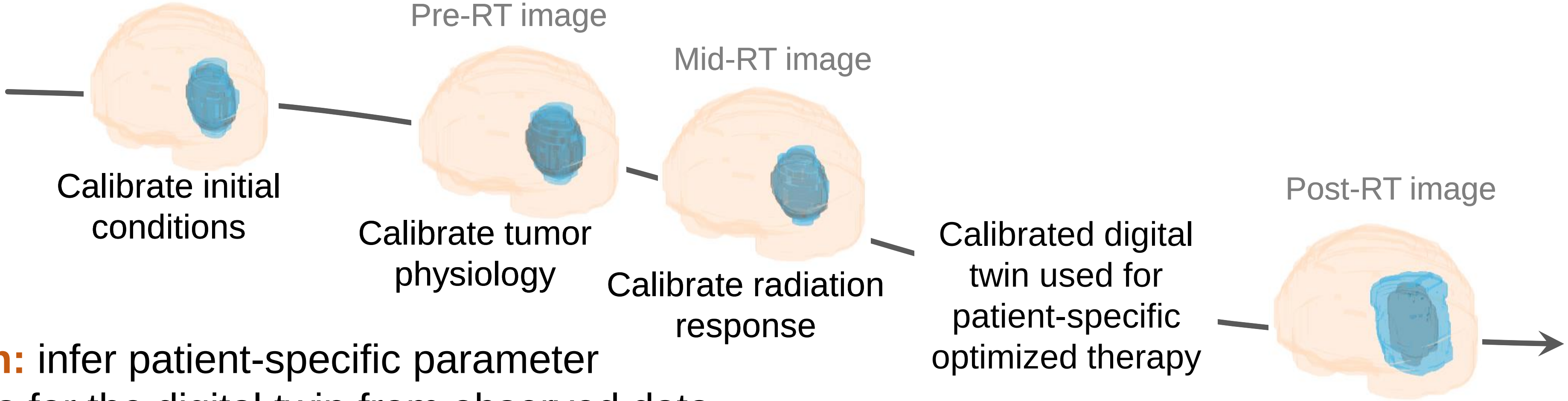
We develop predictive digital twins based on probabilistic graphical models to encode uncertainty.

Kapteyn, MG, Pretorius, JVR, and Willcox, KE. “A probabilistic graphical model foundation for enabling predictive digital twins at scale.” *Nature Computational Science* 1.5 (2021): 337-347.

Chaudhuri, A, et al. “Predictive Digital Twin for Optimizing Patient-Specific Radiotherapy Regimens under Uncertainty in High-Grade Gliomas.” *Frontiers in Artificial Intelligence* 6: 1222612.

Creating and evolving a cancer patient predictive digital twin

Predictive digital twins consist of **three phases to account for uncertainty** throughout a patient's treatment



Calibration: infer patient-specific parameter distributions for the digital twin from observed data

Chaudhuri, Anirban, et al. "Predictive Digital Twin for Optimizing Patient-Specific Radiotherapy Regimens under Uncertainty in High-Grade Gliomas." *Frontiers in Artificial Intelligence* 6: 1222612, 2023.

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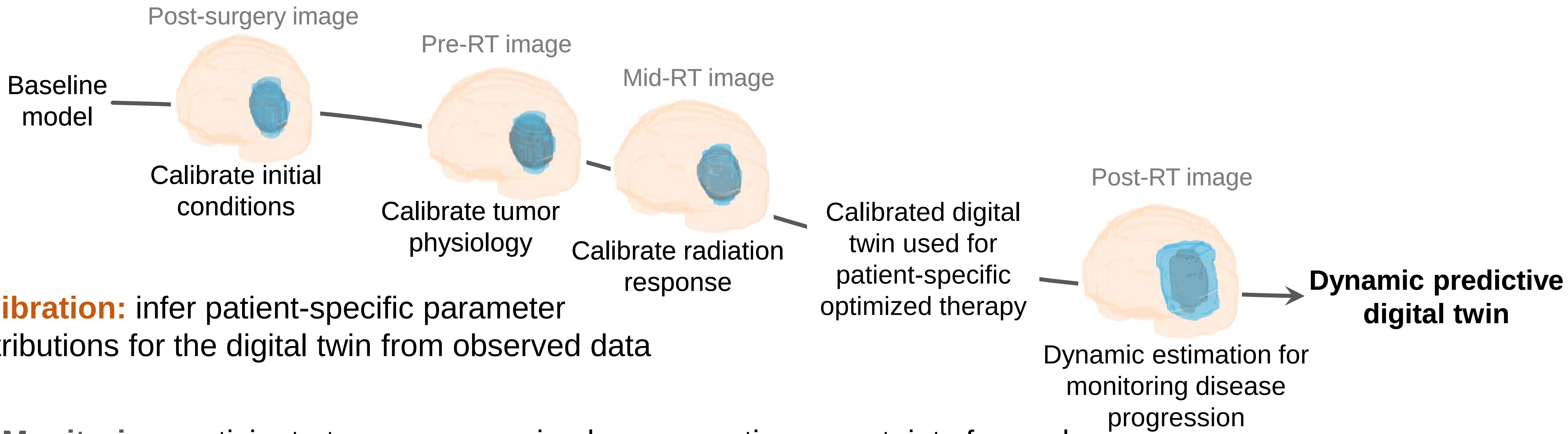

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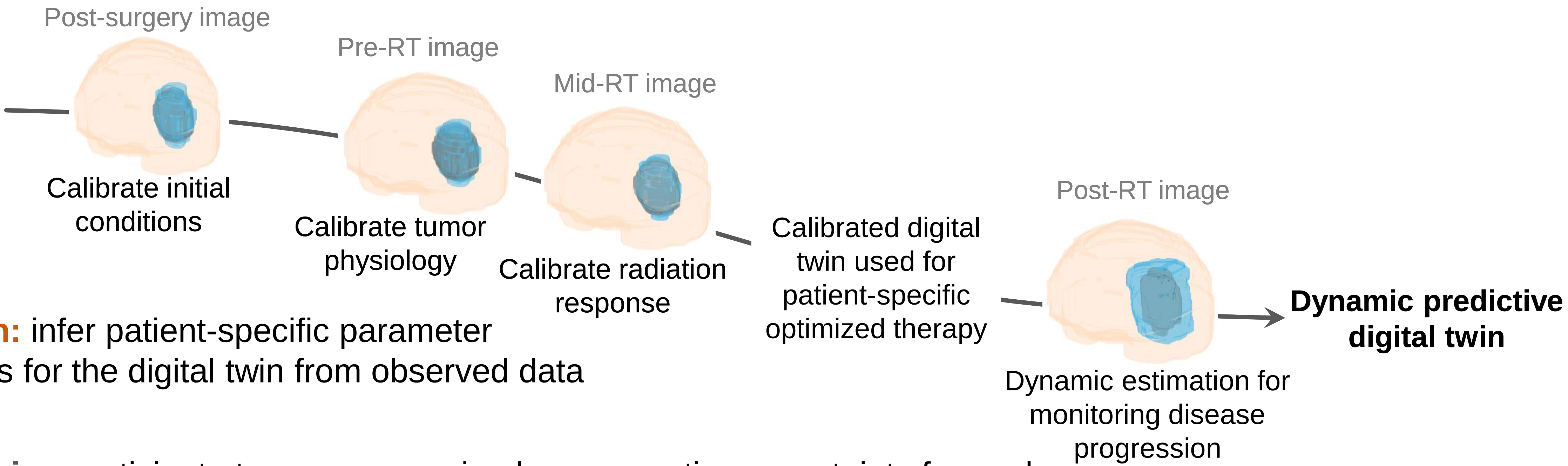


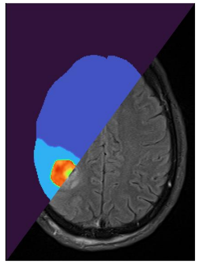
Calibration: infer patient-specific parameter distributions for the digital twin from observed data

Monitoring: anticipate tumor progression by propagating uncertainty forward

Optimize therapy: use predictive digital twin to choose optimal patient-specific treatment plan under uncertainty

Chaudhuri, Anirban, et al. "Predictive Digital Twin for Optimizing Patient-Specific Radiotherapy Regimens under Uncertainty in High-Grade Gliomas." *Frontiers in Artificial Intelligence* 6: 1222612, 2023.

Quantifying uncertainty in mechanistic tumor growth model representing tumor dynamics and treatment



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$$N_{\text{post-treatment}} = S(u_t) N_{\text{pre-treatment}}$$

discrete treatment events

Patient-specific model parameters

$N(t)$: tumor cell count

ρ: proliferation rate

K: carrying capacity

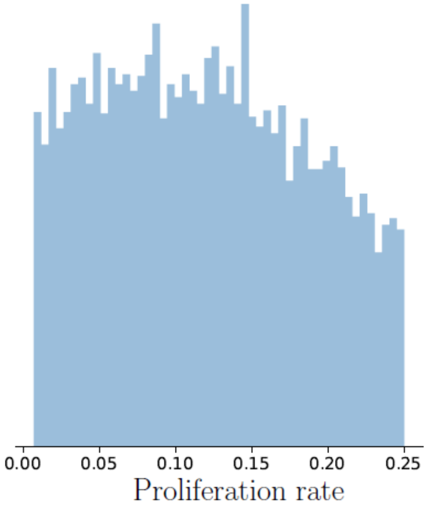
N_{initial}: initial tumor burden

α: radiosensitivity parameter

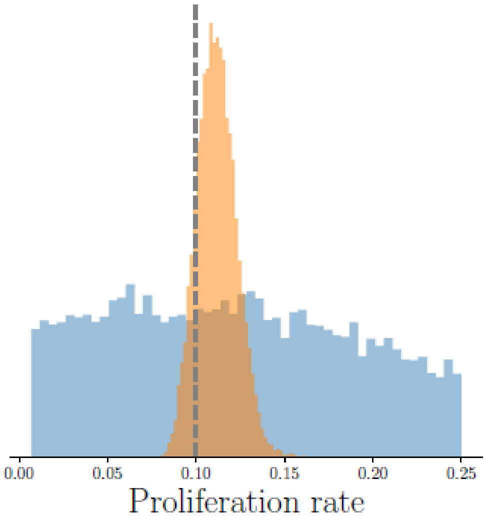
S_{C}: chemotherapy effect

u_t: dose of radiotherapy at time t

Probabilistic parameters use priors derived from clinical data of a population of patients



Patient-specific posterior distributions



Patient-specific tumor modeling

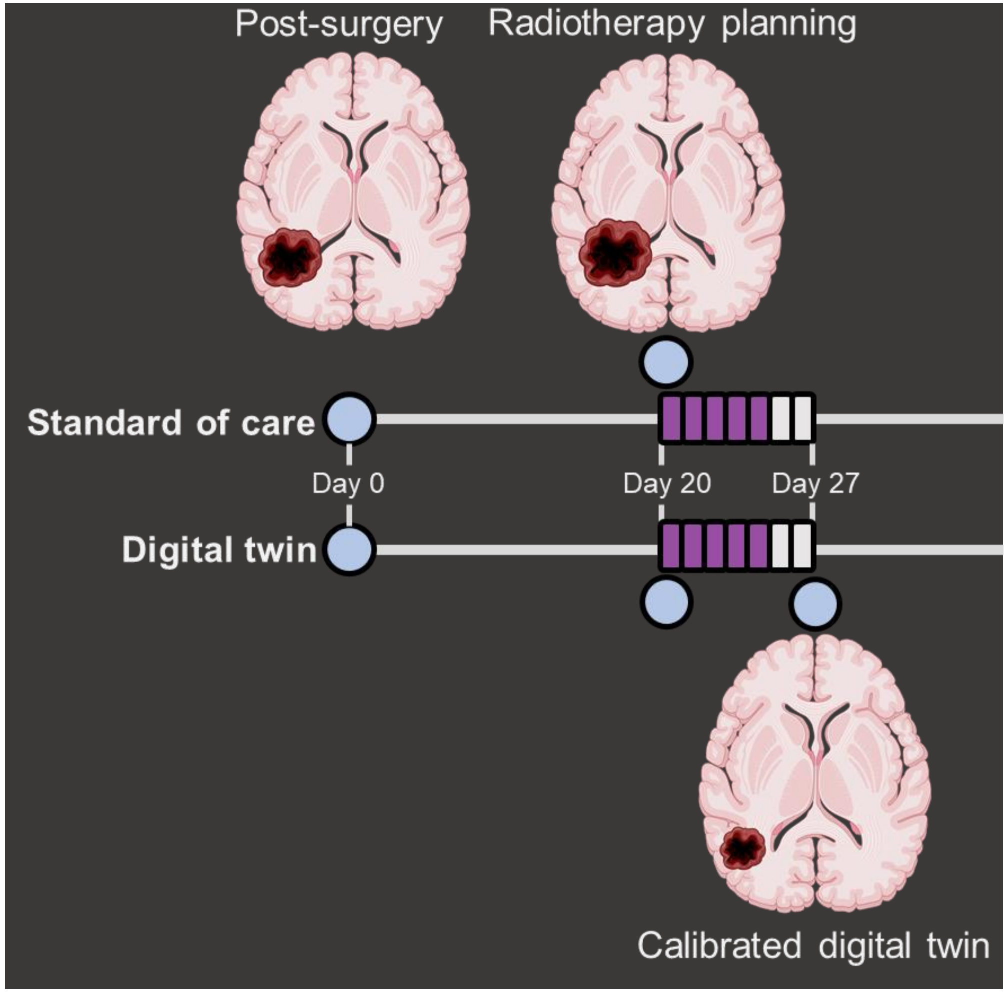
via Bayesian model calibration

Model parameters to be inferred:

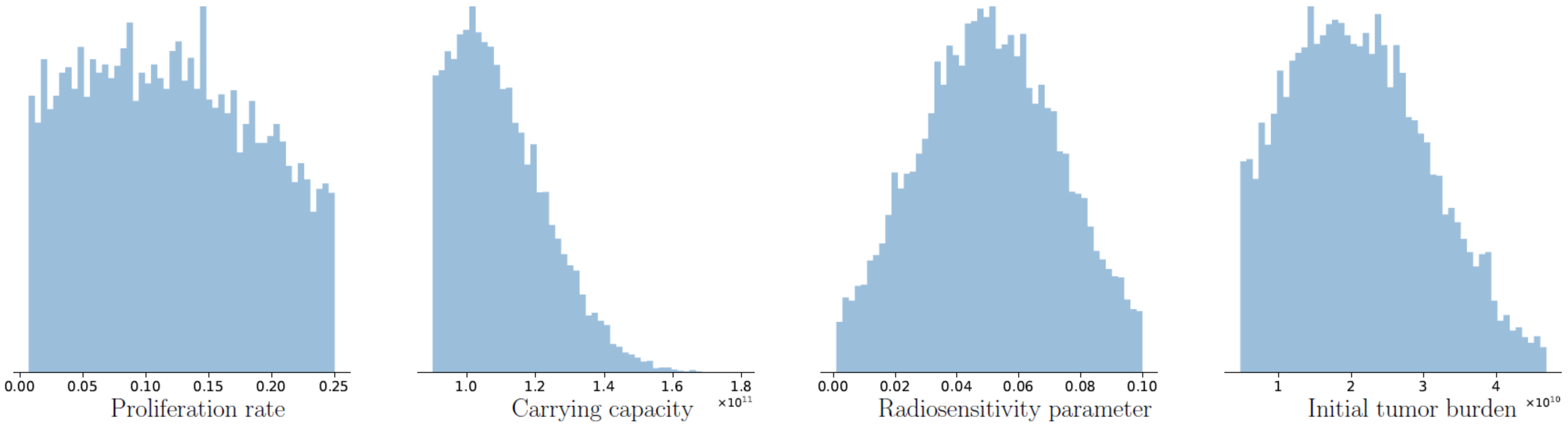
$\theta \coloneqq \{\rho, K, \alpha, N_{\text{initial}}\}$

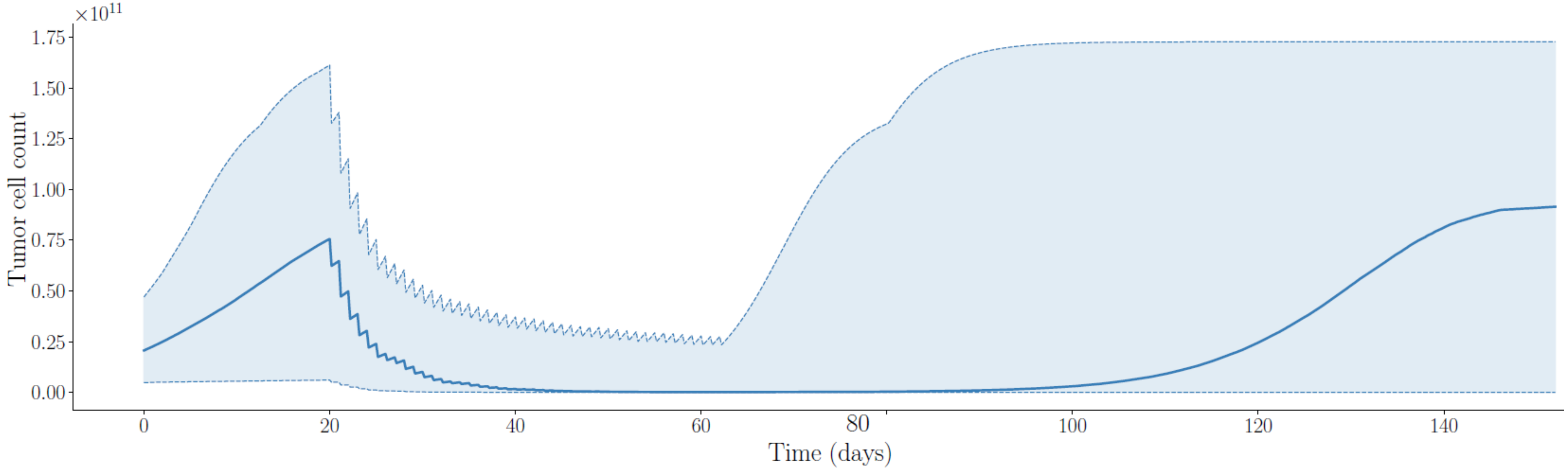
- Priors obtained from clinical data of a population of patients

We use a **Bayesian formulation** that combines prior knowledge with observed data to quantify uncertainty in the patient-specific model parameters.



Patient priors from clinical data of a population of patients

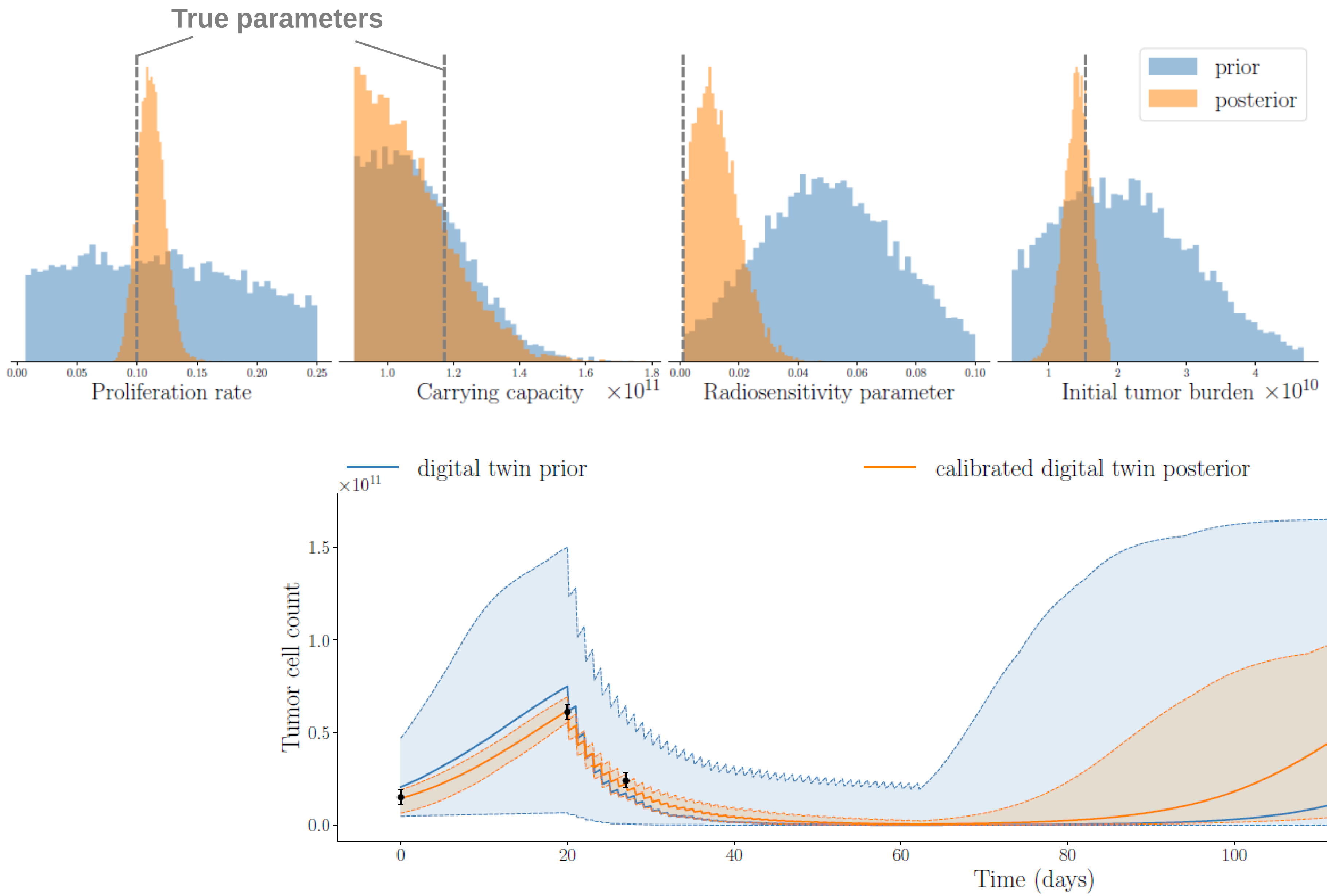




Patient 1: Calibrated digital twin

Patient 1 true parameters:

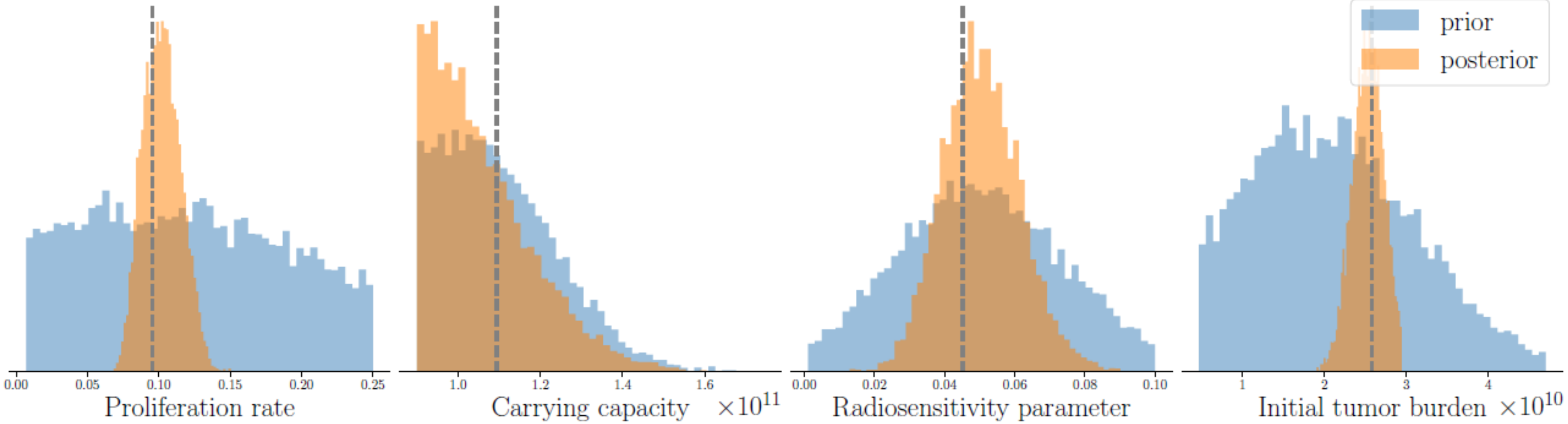
Proliferation Rate: 1.14e-01
Carrying Capacity: 1.17e+11
Radiosensitivity parameter: 1.05e-03
Initial Tumor Burden: 1.54e+10

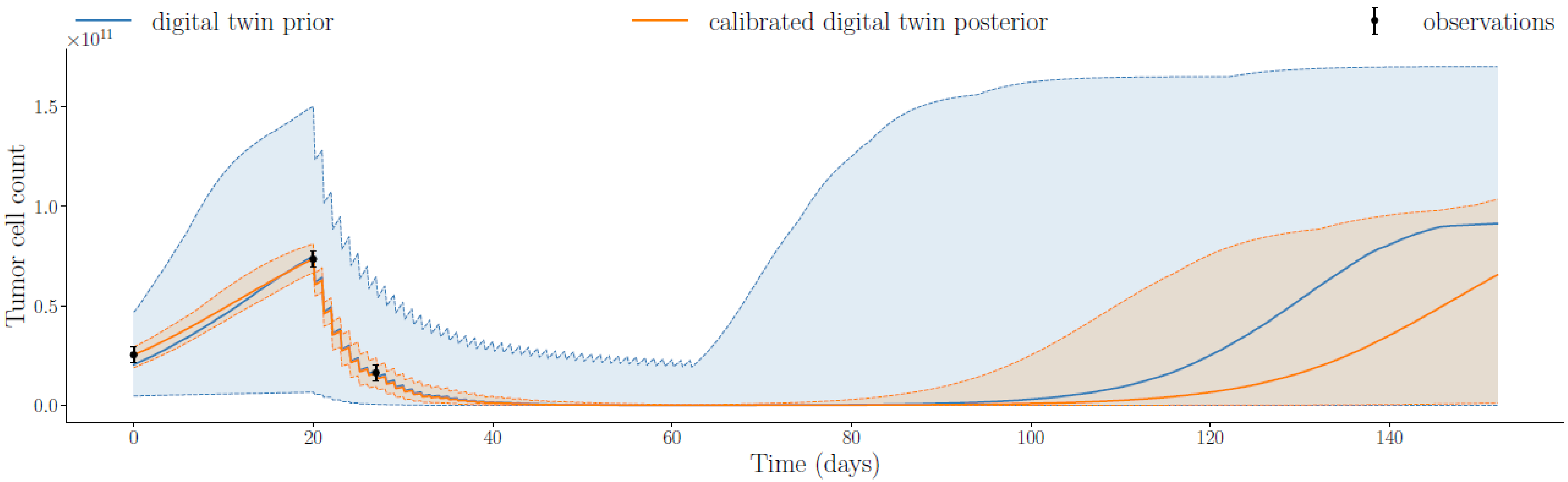


Patient 2: Calibrated digital twin

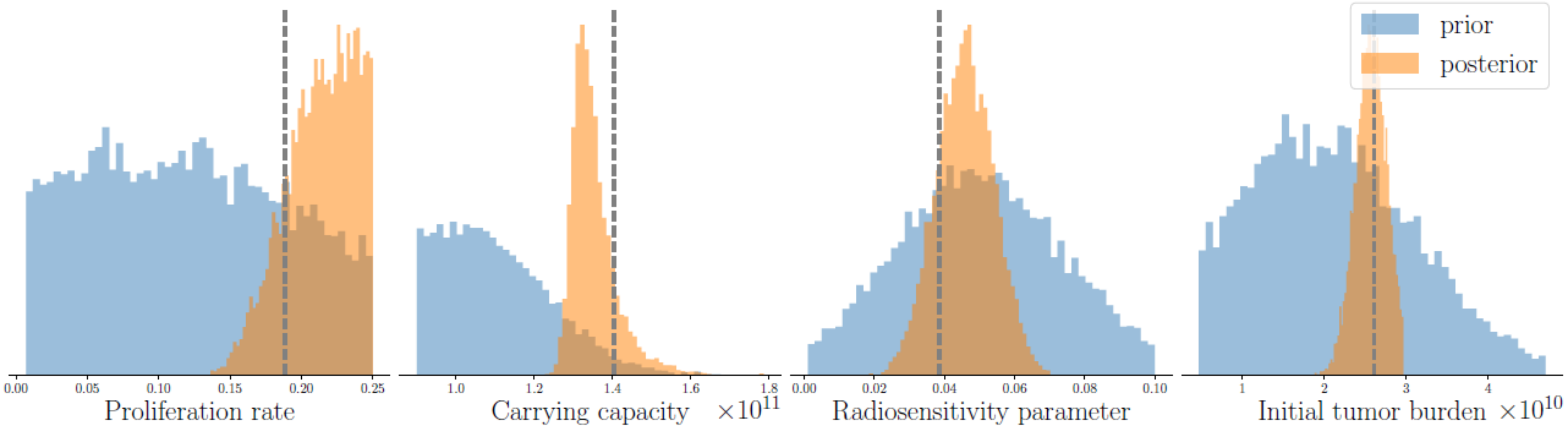
Patient 2 true parameters:

Proliferation Rate:	1.09e-01
Carrying Capacity:	1.09e+11
Radiosensitivity parameter:	4.58e-02
Initial Tumor Burden:	2.60e+10



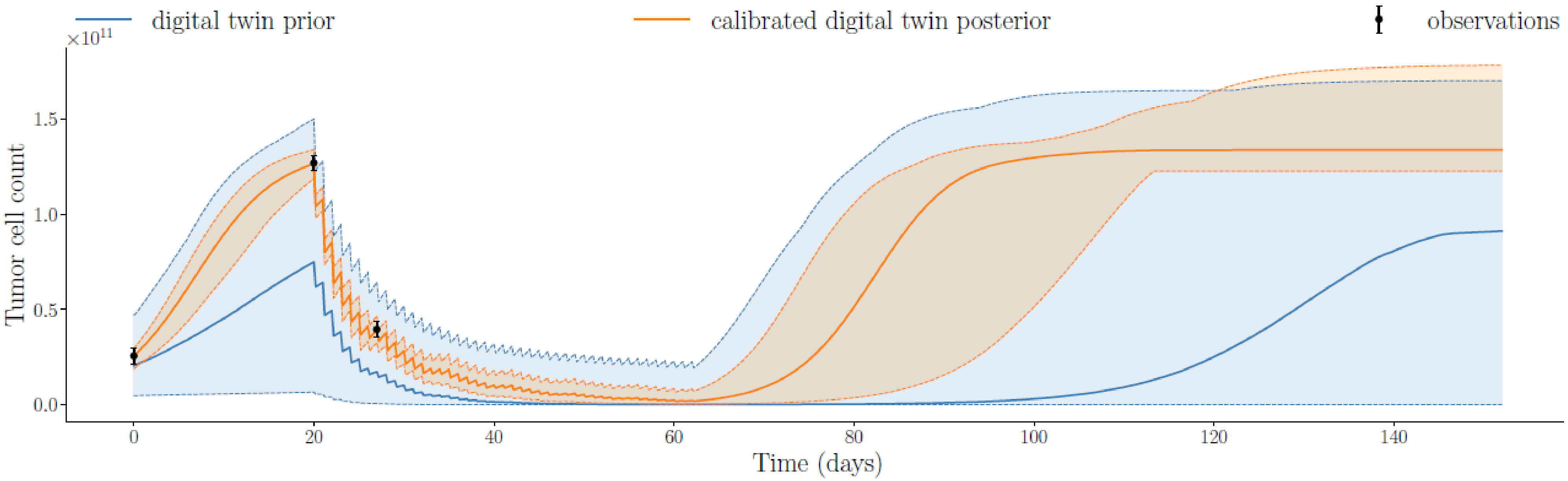


Patient 3: Calibrated digital twin



Patient 3 true parameters:

Proliferation Rate: 2.25e-01
Carrying Capacity: 1.40e+11
Radiosensitivity parameter: 3.90e-02
Initial Tumor Burden: 2.62e+10



Data handling and storage issues

when dealing with uncertainty

- Large amounts of information might need to be stored depending on the digital twin architecture, types of methods used to calibrate uncertain parameters, and the underlying model parameterization.

- "Fit-for-purpose" UQ when architecting a digital twin requires careful consideration of
  - accuracy of quantified uncertainty
  - computational efficiency of the UQ method
  - computational model
  - data storage capacity
  - data handling efficiency

Risk-informed optimal decisions

can be certifiable depending on the risk measure

Two notions of certifiability in risk-based decisions:

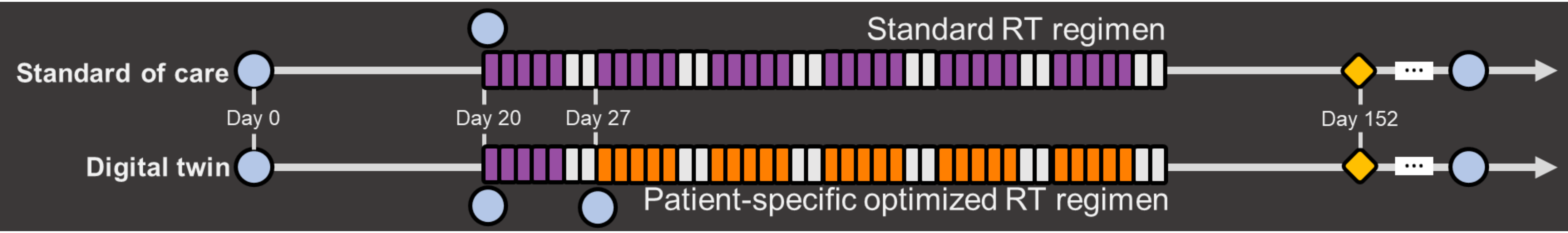
- **data-informed conservativeness**: decisions should be risk-averse against near-failure and catastrophic failure events
  (taking into account magnitude of failure)
- **optimization convergence and efficiency**: decisions using risk measure that preserve convexity of underlying functions can be certifiably optimal

Superquantile is a risk measure that satisfy these certifiability conditions.

Chaudhuri, A., Kramer, B., Norton, M., Royset, J.O. and Willcox, K., 2022. Certifiable risk-based engineering design optimization. *AIAA Journal*, *60*(2), pp.551-565.

Patient-specific treatment plans

Multi-objective optimization under uncertainty (OUU)



Risk-aware clinical decision-making: minimize risk and dose with constraint on total dose

$$\boldsymbol{u}^* = \arg\min_{\boldsymbol{u}\in\mathcal{U}} \mathcal{R}(M(\boldsymbol{u},\theta)) + \lambda\|\boldsymbol{u}\|_1$$
$$\text{s.t. } 5\|\boldsymbol{u}\|_1 \leq D_{\max},$$

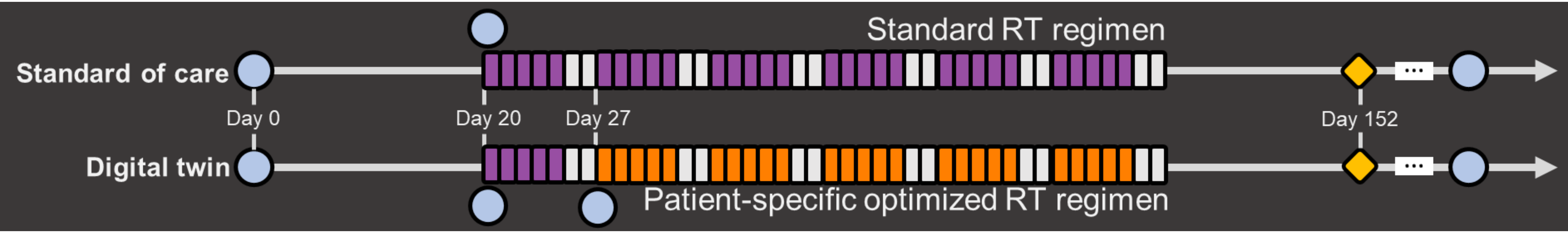
Control action ($\boldsymbol{u} \in \mathcal{U} \subseteq \mathbb{R}_+^w$)
Radiotherapy dose; carried out 5 days/week over $w = 5$ treatment weeks

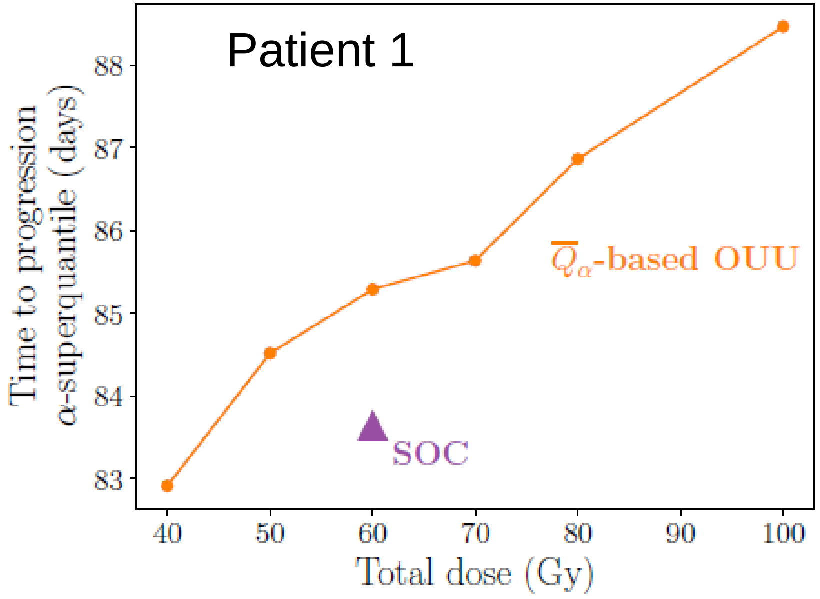
Quantity of interest ($M(\boldsymbol{u}, \theta)$): time to progression (TTP) beyond a threshold cell count N_{th}

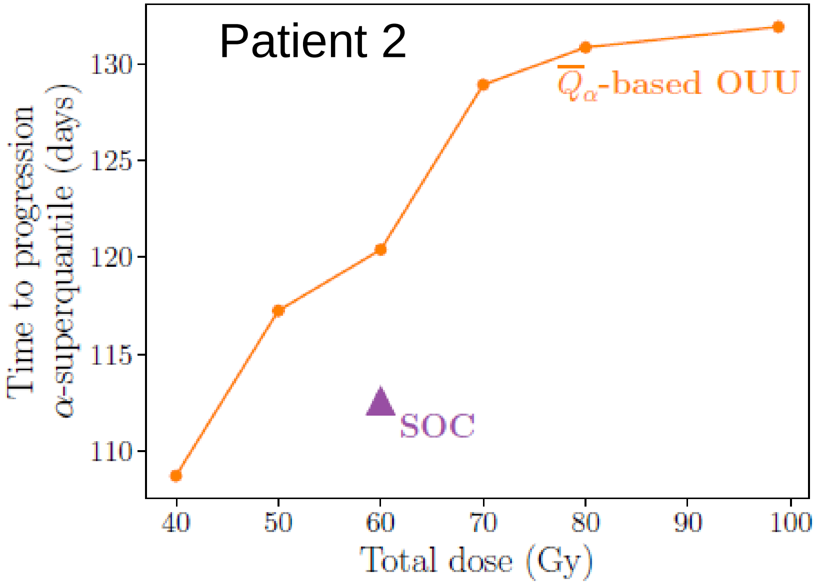
Risk measure ($\mathcal{R}$): α-superquantile

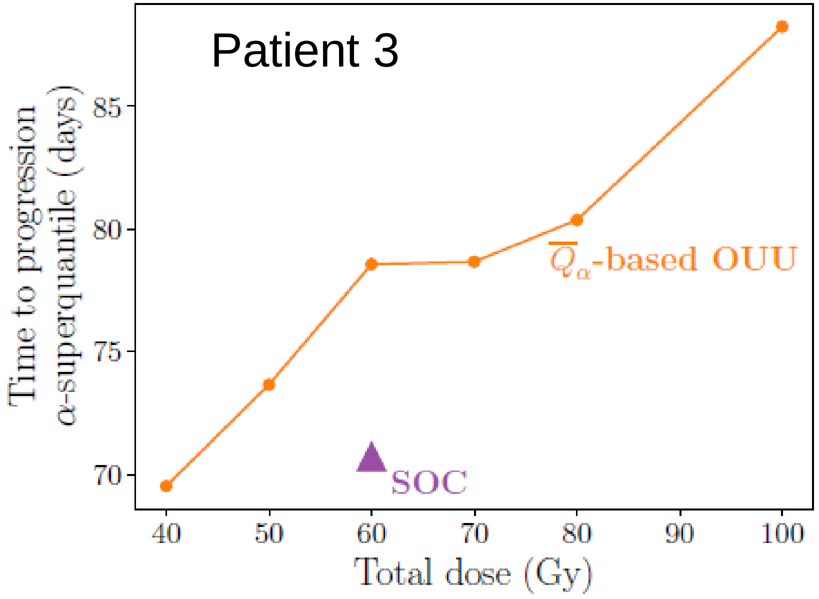
Leads to a *suite of optimal treatment regimens* with varying levels of trade-offs between competing clinical objectives: **(i) maximizing tumor control and (ii) minimizing toxicity from radiotherapy**

Patient-specific treatment plans with trade-off between tumor control and toxicity



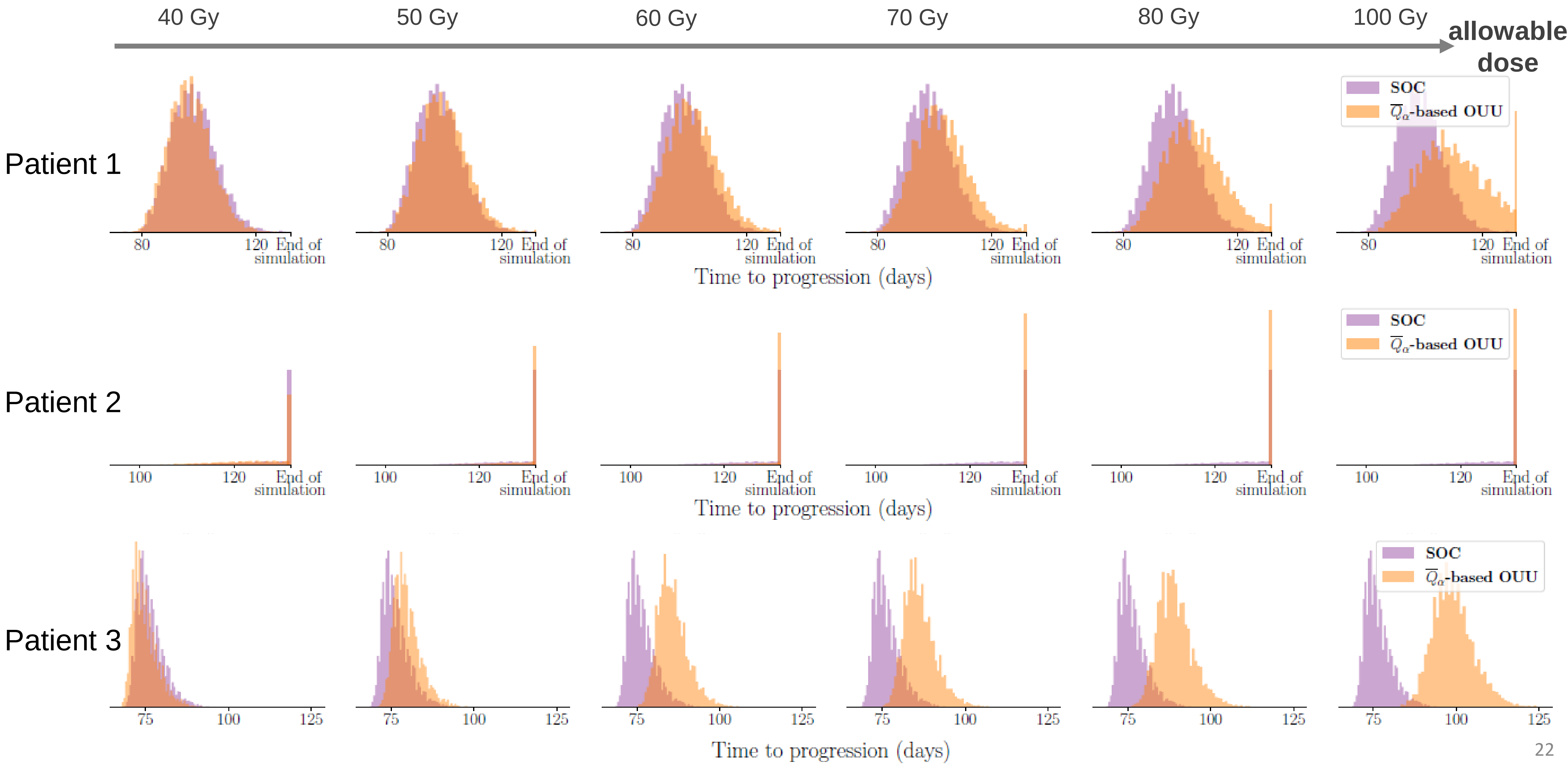




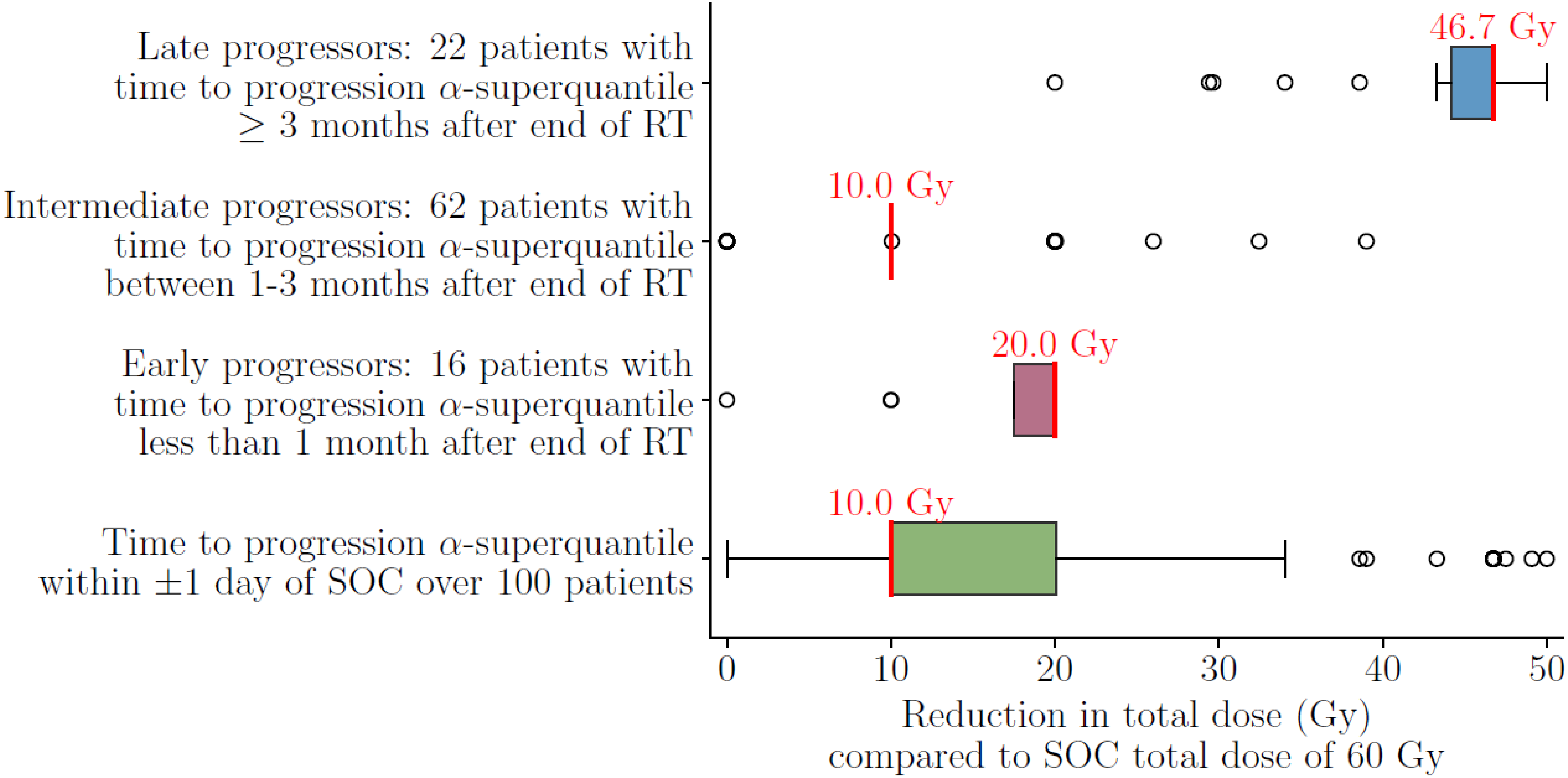


Suite of patient-specific treatment plans allows flexibility to consider the patient's and the treating physician's preferences

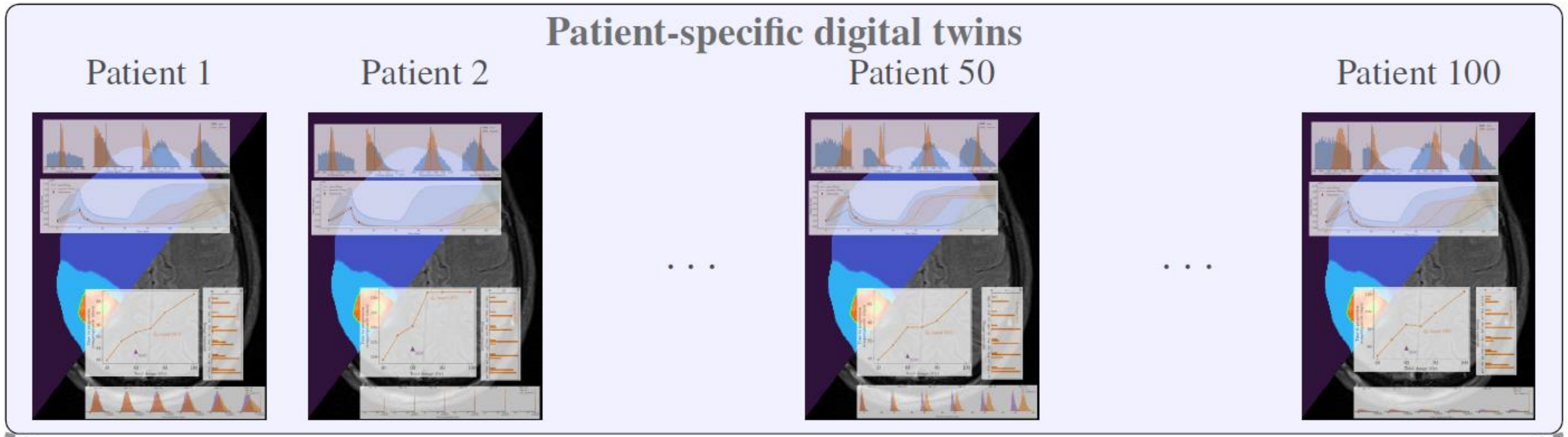
Time-to-progression distributions

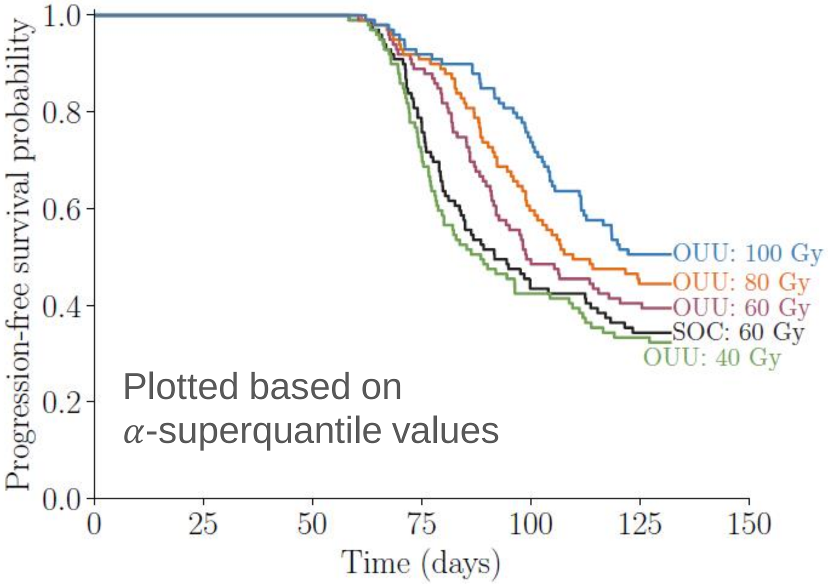


Optimal treatment regimen options with similar tumor control as standard-of-care (SOC), but reduced RT dose to mitigate toxicity effects



Making optimal decisions at the individual level improves survivability across the cohort of patients





Kaplan-Meier survival analysis over 100 patients

Estimator of survival probability from lifetime data (probability that life is longer than time t)

$$\hat{S}(t) = \prod_{i:t_i \le t} \left(1 - \frac{d_i}{n_i}\right)$$

t_i: time at which at least one event has happened

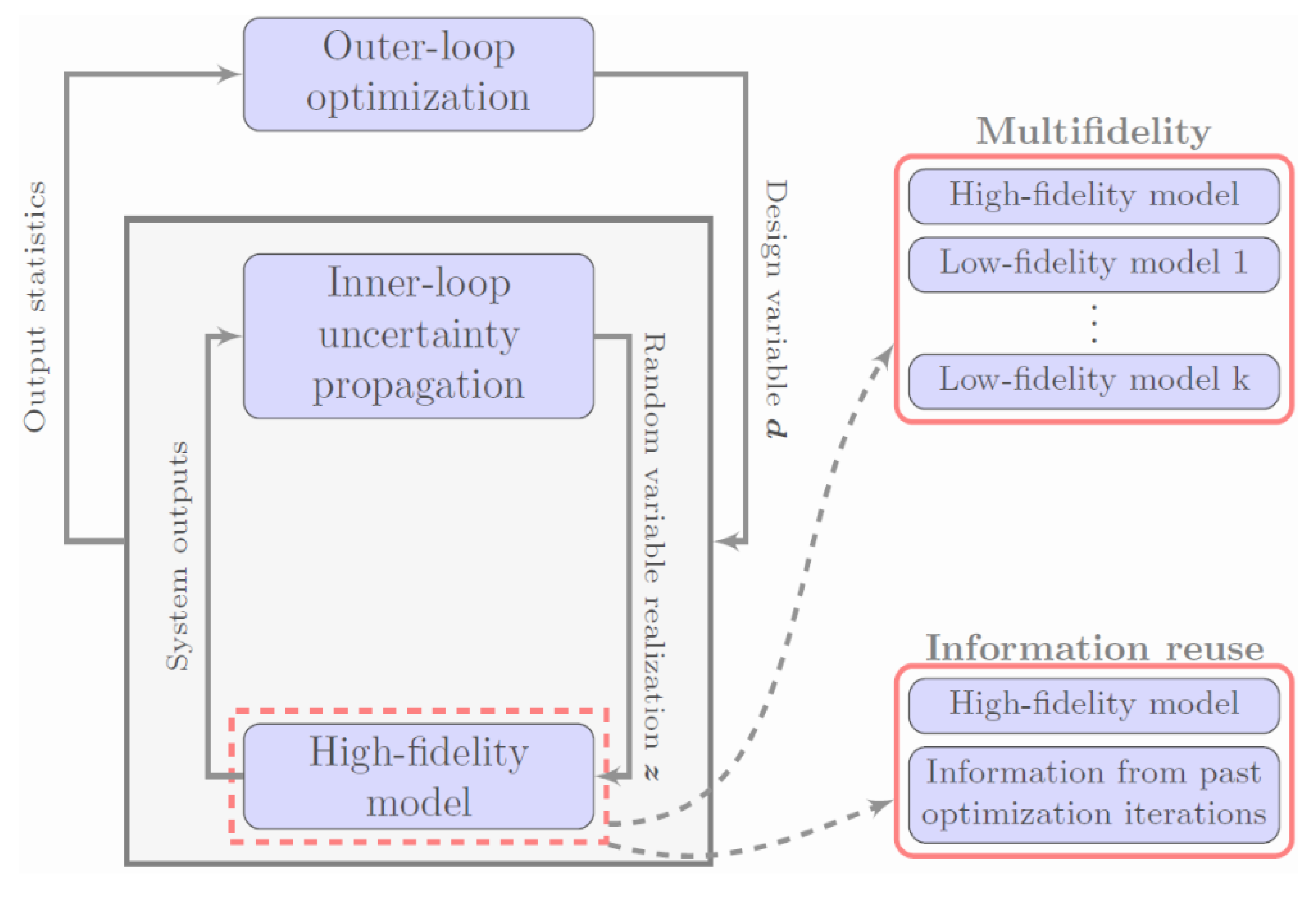
d_i: number of events at time t_i

n_i: number of survivors up to time t_i

Computability in actionable time-scales

makes a digital twin usable in practice

- Scalable methods are required for digital twins.
- Surrogate models play a key role: projection-based reduced order models, Gaussian process
- Models spanning range of fidelities and computational cost can reduce the overall computational effort associated with decision-making through digital twins.



Human-twin interaction

- Need to effectively communicate the uncertainty in predictions and decisions to the clinician
- Interpretable decisions are necessary for users to trust the digital twin

Predictive digital twins as a step towards risk-aware, personalized medicine requires significant efforts towards addressing clinician-twin interactions.

- Making digital twin findings accessible to the clinicians
- Clinical adoption will depend on understanding and trust in digital twin decisions under uncertainty
- Handling and transmitting patient data from physical to digital twin
- Privacy and security issues

Navigating uncertainty in digital twins

to build trust through

- interpretability of decisions based on explainable models with uncertain parameters
- uncertainty quantification and risk-informed decision-making
- ensuring computability in actionable time-scales

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