

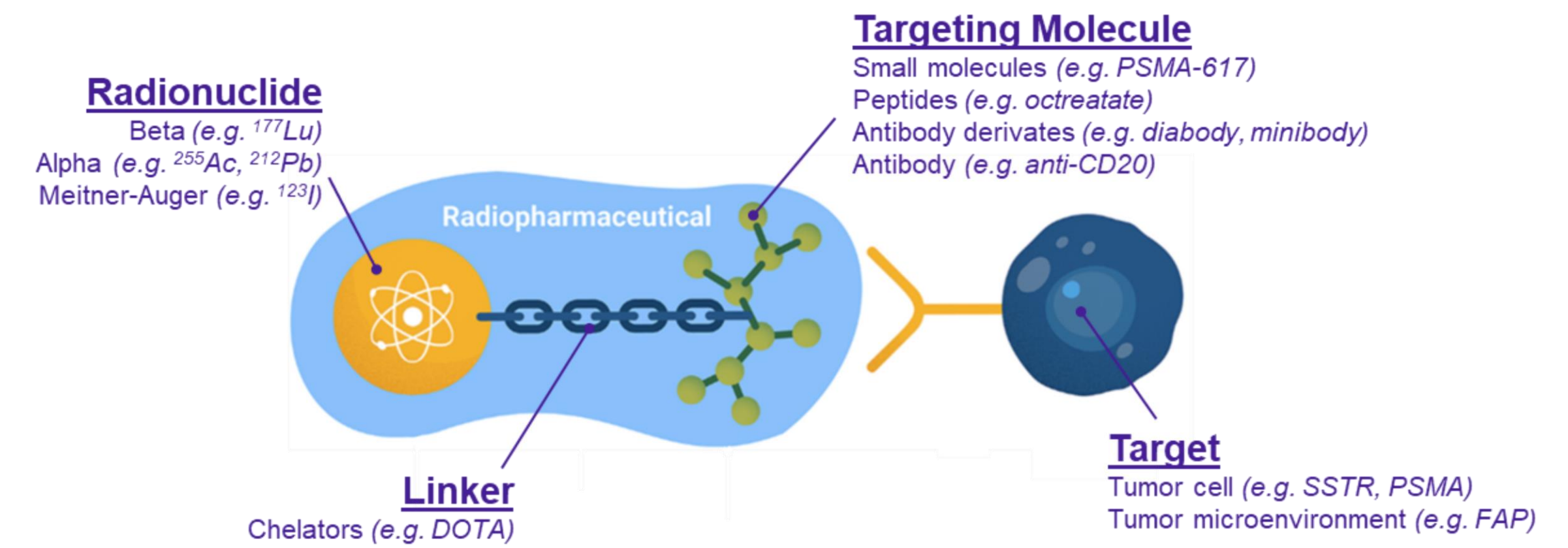
Modeling Targeted Radionuclide Therapy: General Approach to Optimize Dose Selection



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Introduction

Targeted Radionuclide Therapy (TRT) has emerged as a promising cancer treatment modality, offering significant advantages over existing approaches. This therapy combines radioactive compounds emitting cytotoxic radiation with target-specific molecules, such as small molecules, peptides, or antibodies. The targeting moiety selectively binds to and accumulates on the intended target site, allowing for localized delivery of the therapeutic radiation.

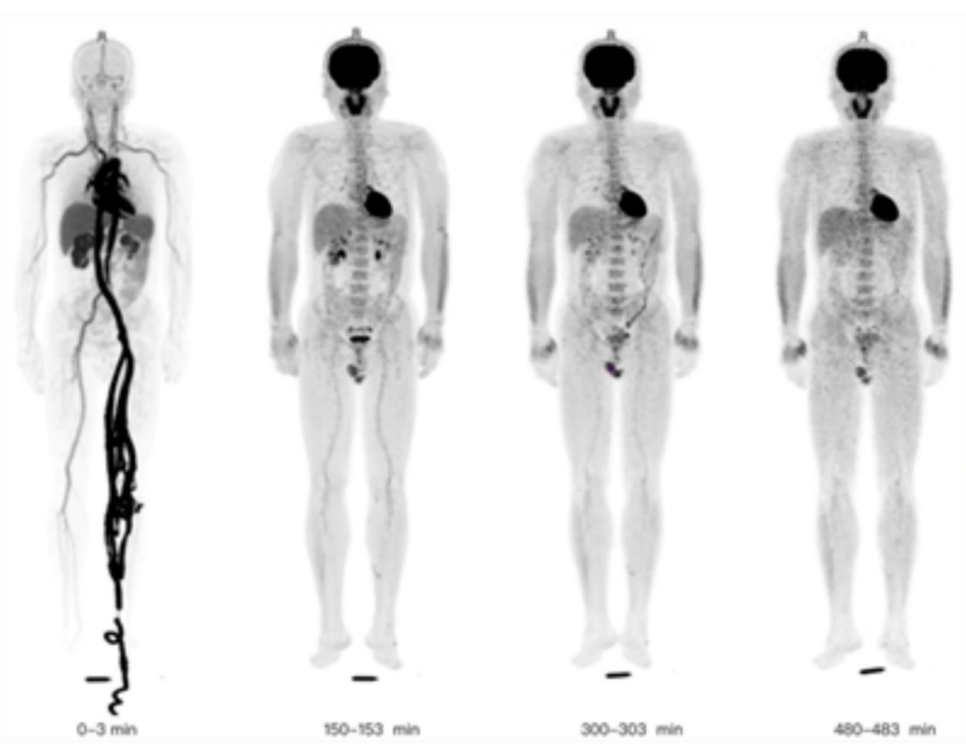


Problematic

How can the complex pharmacokinetics of Targeted Radionuclide Therapy (TRT) be effectively characterized and addressed in population pharmacokinetic (popPK) models to meet regulatory requirements for dosing justification during drug development?

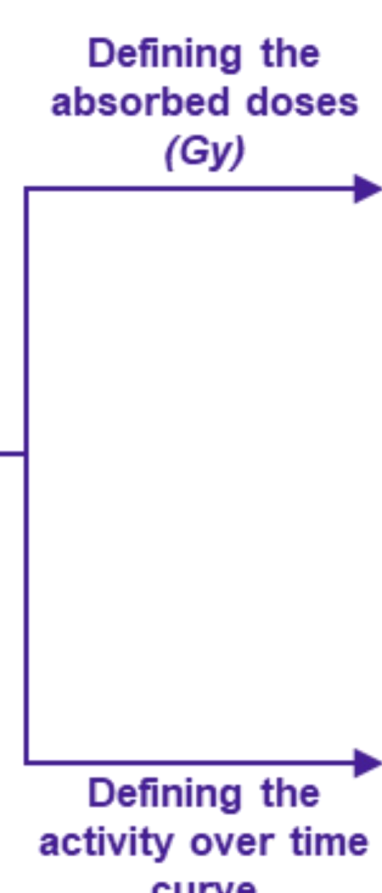
1. Dosimetry Analysis

The data presented are adapted from Siebinga et al., 2023 [1]

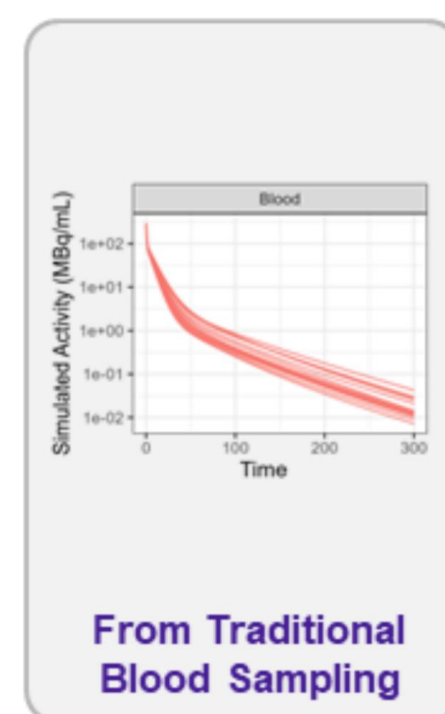
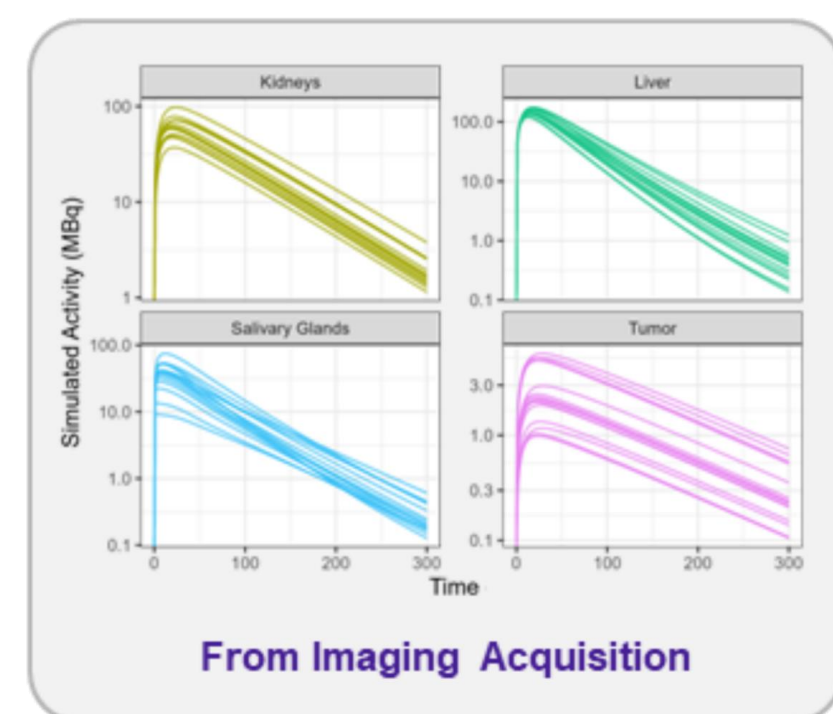


Quantitative imaging using SPECT/CT scan: allows to monitor the traffic of the radiopharmaceutical in the body over time

Dosimetry Analysis using dedicated software (e.g., Olinda)



Tissue	Absorbed Dose (mGy/MBq)
Brain	0.017
Kidneys	2.9
Liver	0.15
Lungs	0.10
Pancreas	0.031
Red Marrow	0.065
Spleen	0.15
Thyroid	0.24



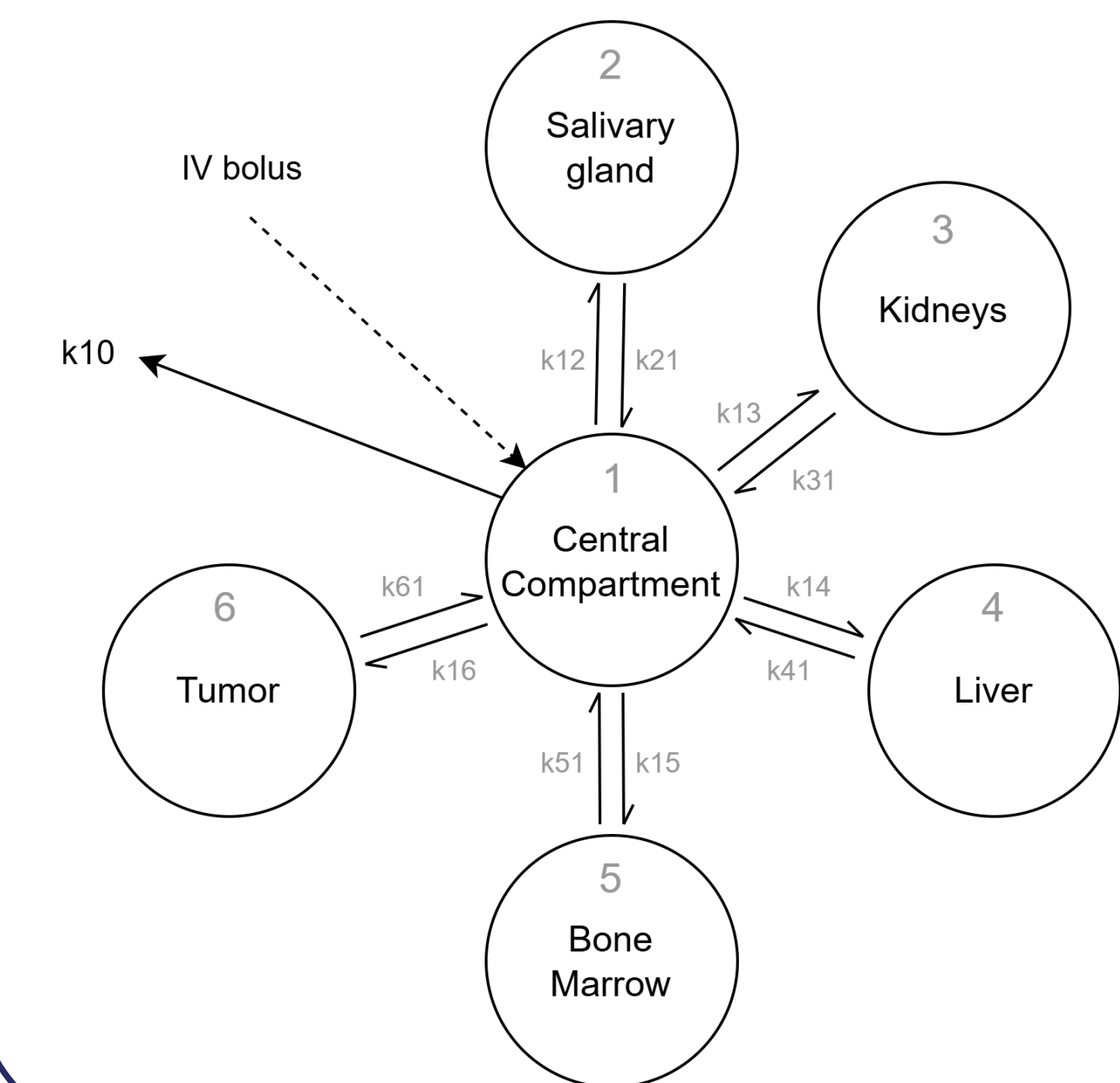
2. Understanding Dual Half-Lives

- Initial non-compartmental analysis (NCA) allows the estimation of the **observed half-lives and organ-specific accumulation of the radiopharmaceutical**
- This observed half-lives corresponds to the **effective half-life** of the radiopharmaceutical, that combines radionuclides physical decay and biological clearance of the targeting molecule
- Direct modeling of uncorrected data confounds these effects and complicates interpretation → Apply **decay correction to normalize measurements to the time of injection** and ensure **accurate PK parameter estimation**.

Decay-corrected data =

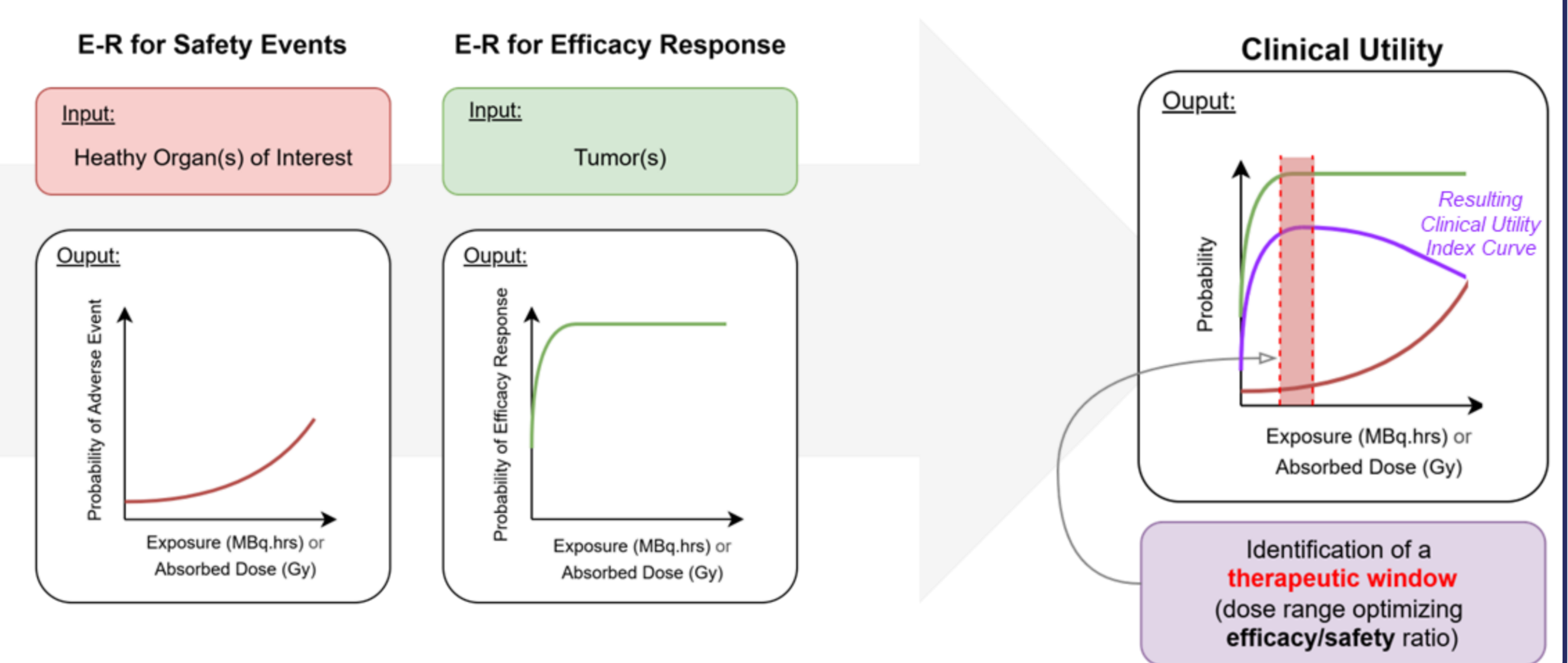
$$\text{Original data} \times e^{\ln(2) \times \left(\frac{\text{Time elapsed between Injection and Measurement}}{\text{Physical Half-Life}} \right)}$$

3. PopPK Dosimetry Modeling



- Comprehensive popPK model that integrates **data from imaging**
- Each organ of interest is represented as a **separate compartment connected to a central compartment**
- Enables **modeling (and therefore prediction) of the full biodistribution of the radiopharmaceutical** within the body, where efficacy is linked to the tumor compartment and safety to the organ compartments

4. Exposure-Response Relationship



Conclusion

This stepwise approach begins with graphical exploration and non-compartmental analysis to extract key information, followed by the development of a multicompartment model using empirical parameters. This strategy enables accurate prediction and simulation of radioactivity uptake in all compartments, allowing absorbed dose calculations with the MIRD method.

By enabling dose estimation from a single optimized SPECT/CT scan, this approach improves patient management and operational efficiency. Ultimately, it supports robust dosing strategies and advances the personalization of TRT therapy.

Disclaimer

This poster is for informational purposes only. Readers are kindly requested to cite the original work when referencing the concepts, data, or methodologies presented herein.

References

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