Non-Uniqueness of Multiexponential Time-Activity Curves in Few-Timepoint Theranostic Workflows Can Increase Dosimetric Error

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Balfour D[1], Sage J[1], Willaime JMY[1] and Boukerroui D[1].

1. Mirada Medical Ltd., Oxford, UK

Aim and Introduction:

Recent literature has shown interest in reducing the number of timepoints in theranostic workflows. Many such studies use parametric, multiexponential time-activity curve (TAC) models to obtain the time-integrated activities (TIAs) required for dosimetry. Such methods then have more parameters than measurements. Mathematically, this leads to an infinity of possible curves that can solve the fitting problem, each with a different TIA. A unique curve is selected randomly by the solver or determined by some prior information, but it is not commonplace for the choice to be explicitly discussed or analysed.

The non-uniqueness of the solution in situations where there are fewer timepoints than model parameters is demonstrated here and its impact on TIA estimation is assessed.

Materials and Methods

A curve stripping TAC fitting method [1] was adapted and solutions analytically derived for a 3 timepoint workflow. The TAC was modelled as a 4-parameter bi-exponential decay consisting of rapid and slow washout terms since these contribute most to dosimetric accuracy.

With only 3 measurements, 1 parameter remained underdetermined. A prior, $\rho \in]0,1[$, was introduced to characterise this unknown: it represented the ratio of contributions between the two washout terms at the second timepoint.

The physical assumptions of the model, such as ensuring the rapid washout curve decayed faster, were analysed to obtain constraints on the range of valid values for ρ, parameterising the family of valid solutions. The equivalent range of valid TIA values was then calculated.

To demonstrate on realistic data, 2 [Lu-177]-DOTATATE theranostic patients [2] were segmented and locally rigidly registered to produce a set of activity measurements for the liver at 3 timepoints.

For comparison, the TIA was also estimated using trapezoidal integration extrapolated with physical-only decay.

Results

The family of valid TACs was determined by identifying the upper and lower bounds on ρ. All curves between these bounds are plausible.

Patient 1 had liver TIA values between 18.4 and 19.6 MBq·h/ml, (6.1% maximal underestimation) and patient 2 had TIA values between 23.9 and 24.5 MBq·h/ml (2.7% maximal underestimation). By comparison, the trapezoidal TIAs were 18.76 and 18.79 MBq·h/ml, respectively.

Conclusions

Curve non-uniqueness in parametric TAC integration is a source of error not usually accounted for in uncertainty analysis. Robust means to select a unique curve is required to ensure accurate dosimetry. This can be achieved using good-quality statistical priors.

References

[1] Jackson et al. (2020) https://doi.org/10.1002/mp.14243

[2] Uribe et al. (2021) https://doi.org/10.2967/jnumed.121.262748

Table 1: **Constrained range of ρ for both liver TACs & the corresponding TIA ranges.**

Patient	*Min. ρ*	*Max. ρ*	*Min. TIA [MBq·h/ml]*	*Max. TIA [MBq·h/ml]*	*Maximal underestimation [%]*	*Trapezoidal TIA [MBq·h/ml]*
1	10^-6	0.123	18.42	19.55	6.1%	18.76
2	10^-6	0.021	23.89	24.54	2.7%	18.79