Theoretical aspects on the use of single-time-point dosimetry for radionuclide therapy

Johan Gustafsson and Jan Taprogge

1 Medical Radiation Physics, Lund, Lund University, Lund, 221 85, Sweden
2 Joint Department of Physics, Royal Marsden Hospital, Sutton, United Kingdom
3 The Institute of Cancer Research, London, United Kingdom

* Author to whom any correspondence should be addressed.
E-mail: johan_ruben.gustafsson@med.lu.se

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Abstract

Objective. This study considers the error distributions for time-integrated activity (TIA) of single-time-point (STP) methods for patient-specific dosimetry in radionuclide therapy. Approach. The general case with the same pharmaceutical labelled with different radionuclides for imaging and therapy are considered for a mono-exponential time-activity curve. Two methods for STP dosimetry, both based on the combination of one activity estimate with the population-mean effective decay constant, are investigated. The cumulative distribution functions (CDFs) and the probability density functions for the two methods are analytically derived for arbitrary distributions of the biological decay constant. The CDFs are used for determining 95% coverage intervals of the relative errors for different combinations of imaging time points, physical decay constants, and relative standard deviations of the biological decay constant. Two examples, in the form of kidney dosimetry in $^{177}$Lu-DOTA-TATE therapy and tumour dosimetry for Na$^{131}$I therapy for thyroid cancer with dosimetry based on imaging of Na$^{124}$I, are also studied in more detail with analysis of the sensitivity with respect to errors in the mean biological decay constant and to higher moments of the distribution. Main results. The distributions of the relative errors are negatively skewed, potentially leading to the situation that some TIA estimates are highly underestimated even if the majority of estimates are close to the true value. Significance. The main limitation of the studied STP dosimetry methods is the risk of large underestimations of the TIA.

1. Introduction

Dosimetry-based treatment planning for radionuclide therapy (RNT) potentially allows for personalized treatments (Stokke et al 2017), but the procedure is sometimes argued to be inconvenient for the patient and resource-consuming for the hospital. Hence, an important step for the clinical acceptance of dosimetry in RNT is to simplify current dosimetry procedures while maintaining sufficient accuracy in absorbed-dose estimates in relation to the clinical requirements. Absorbed-dose estimates are generally presumed to require serial imaging over several days following administration, with the consequential need for patients to return to the hospital after they have been discharged and for the department to schedule imaging studies at multiple predefined time points.

A number of studies have investigated the possibility of reducing the number of imaging time points with respect to absorbed-dose estimation (Jentzen et al 2008, Del Prete et al 2018, Willowsom et al 2018, Seo et al 2019, Chicheportiche et al 2020, Freedman et al 2020). These studies have demonstrated the feasibility of reducing the number of imaging time points with a low impact on absorbed-dose estimates. Several studies have suggested the use of a single imaging time point in combination with population-based pharmacokinetic parameters to estimate the time-integrated activity (TIA) in, and the absorbed-dose to, a target (Bockisch et al 1993, Hänscheid et al 2018,

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Madsen et al 2018, Jackson et al 2020, Devasia et al 2021. In the simplest case, a mono-exponential function is considered and the TIA calculated from a combination of the activity at one time point and the mean effective half-life for the population (Hänsscheid et al 2018, Madsen et al 2018).

There are high hopes that the single-time-point (STP) dosimetry methods will simplify the absorbed-dose estimation process and thereby make dosimetry in RNT more accessible (Hänsscheid and Lasmann 2020). Several authors have shown that a single SPECT/CT image can provide adequate absorbed-dose estimates for kidneys in $^{177}$Lu-DOTA-TATE therapy and radiiodine therapy for benign thyroid disease, respectively (Bockisch et al 1993, Hänsscheid et al 2011, 2018, Sundlöv et al 2018, Zhao et al 2019). However, results in other studies have shown that simplified dosimetry protocols for $^{177}$Lu-DOTA-TATE were less reliable when compared to more complicated imaging schedules (Del Prete et al 2018, Willowson et al 2018, Sandström et al 2020) and the generalizability to other organs has been questioned (Hou et al 2021). Furthermore, the accuracy of STP dosimetry for hyperthyroid patients has been questioned in some studies (Berg et al 1996, Amato et al 2016) and Jentzen et al (2008) showed that a single Na$^{124}$I PET image was not sufficient to assess bio-kinetics in lesions of thyroid cancer patients. Conclusions about the accuracy and usefulness of STP dosimetry are often governed by several factors which vary between studies, such as the dosimetry method used as reference, the details of the STP measurement scheme, and the acceptance limit for errors in individual patients.

In light of the disagreement found in the literature, and to complement the empirical results gathered, there is a need to study the theoretical properties of STP dosimetry methods. To pursue this, we have derived expressions for the distribution of errors in STP dosimetry. The aims of this paper are to present exact details of the STP measurement scheme, and the acceptance limit for errors in individual patients.

2. Theory

2.1. General framework

Assume that the activity in an organ or lesion of a therapeutic radiopharmaceutical, $A_t(t)$ as a function of time $t$, follows a mono-exponential function according to

$$A_t(t) = A_t^0 \exp(-\lambda t).$$

(1)

$\lambda = \lambda_b + \lambda_p$ is the effective decay constant, in turn governed by the biological decay constant $\lambda_b$ and the physical decay constant $\lambda_p$, and $A_t^0$ is the activity at time $t = 0$. The radionuclide used for therapy will henceforth be referred to as the therapeutic radionuclide. The therapeutic radionuclide is, in some cases, replaced by or mixed with a complimentary radionuclide with better imaging properties for the assessment of biokinetics before (pre-therapeutic dosimetry) or during the therapy (peri-therapeutic dosimetry), respectively (Stokke et al 2017). For example, Na$^{123}$I (Camps et al 1996) or Na$^{124}$I (Jentzen et al 2008) have been used for pre-therapeutic assessment of the biokinetics of Na$^{131}$I for the treatment of benign thyroid disease or differentiated thyroid cancer. $^{111}$In-DOTA-TATE was often added to $^{99}$Y-DOTA-TATE for post-treatment imaging and dosimetry (Cremonesi et al 1999). This complimentary radionuclide is henceforth referred to as the imaged radionuclide. For the use of a separate imaged radionuclide, it must be assumed that the biological behaviour of the pharmaceutical is unaffected by the change of radionuclide. Hence, the activity as a function of time for the imaged radionuclide follows

$$A_d(t) = A_d^0 \exp(-kt),$$

(2)

where $k = \lambda_b + \lambda_p$ is the effective decay constant with $\lambda_p$ being the physical decay constant for the imaged radionuclide and $A_d^0$ is the activity in the source region at time $t = 0$ for the imaging administration. Note that the biological decay constant is assumed to be equal for (1) and (2).

For a given patient, the initial activities $A_t^0$ and $A_d^0$ are related so that

$$A_t^0 = CA_d^0,$$

(3)

where $C$ is the ratio of injected activities for the therapy and for the imaging. The biological decay constant varies between patients and is unknown for each individual. Hence, from the perspective of estimation of TIA it can be considered as a stochastic variable characterized by a mean $E[\lambda_b] = \lambda_b$ and a variance $V[\lambda_b]$. The physical decay constants can be assumed to be known exactly. The mean biological decay constant, therefore, propagates to a mean effective decay constant according to $\bar{\lambda} = \lambda_b + \lambda_p$ and $\bar{k} = \lambda_b + \lambda_p$...
The TIA in the organ or lesion during therapy is
\[
\tilde{A} = A^0 = A_A^0 = \frac{A_d(t) \exp \left[ (\lambda_b + \frac{m}{\lambda_b}) t \right]}{\lambda_b + \frac{m}{\lambda_b}} = \frac{CA_d(t) \exp \left[ \frac{m}{\lambda_b} t \right]}{\lambda_b + \frac{m}{\lambda_b} \lambda_b t}.
\]
(4)

For the following discussion, all parameters will be related to the mean biological decay constant. Define \( m = \lambda_p/\lambda_b, n = k_p/\lambda_b, \; h = \lambda_b t, \; \text{and} \; \xi = \frac{\lambda_p}{\lambda_b}. \) Hence
\[
\tilde{A} = CA_d(h/\lambda_b) \exp \left[ \frac{(\xi + n) h}{\lambda_b} \right], \tag{5}
\]
where \( E[\xi] = 1 \) and \( \sigma^2 = V[\xi] = V[\lambda_b]/E[\lambda_b]^2. \) The parameter \( h \) is the time normalized to \( 1/\lambda_b \) and will henceforth be referred to as normalized time. The parameter \( m \) represents the ratio of the physical decay constant for the therapeutic radionuclide to the mean biological decay constant, or, equivalently, the ratio of the mean biological half-life to the physical half-life of the therapeutic radionuclide. The parameter \( n \) represents the ratio of the physical decay constant for the imaged radionuclide to the mean biological decay constant, or, equivalently, the ratio of the mean biological half-life to the physical half-life for the imaged radionuclide. Hence, the ratio \( n/m \) represents the ratio of physical decay constant for the imaged radionuclide to the physical decay constant for the therapeutic radionuclide, or, equivalently, the ratio of the physical half-life for the therapeutic radionuclide to the physical half-life for the imaged radionuclide. The TIA can be estimated from one measurement of \( A_d(h/\lambda_b) \) according to
\[
\tilde{A}_{\text{est}} = CA_d(h/\lambda_b) q, \tag{6}
\]
where \( q \) is an approximation of \( \exp \left[ \frac{(\xi + n) h}{\lambda_b} \right] \) that is independent of \( \xi. \) The relative error of this estimate is
\[
\varepsilon(\xi) = \frac{\tilde{A}_{\text{est}}}{\tilde{A}} - 1 = q \exp \left[ -(\xi + n) h \right] \lambda_b (\xi + m) - 1. \tag{7}
\]

2.2. The Madsen method
The Madsen method for a mono-exponential time-activity curve (Madsen et al 2018) can be defined by setting
\[
q = \frac{\exp \left[ (1 + n) h \right]}{\lambda_b (1 + m)}. \tag{8}
\]
This is in turn equivalent to setting \( \lambda_b = \tilde{\lambda}_b \) in (4) and leads to a relative error
\[
\varepsilon_M(\xi) = \exp \left[ (1 - \xi) h \right] \frac{\xi + m}{1 + m} - 1. \tag{9}
\]
In contrast to the original publication by Madsen et al, (9) is derived from the assumption that different radionuclides may be used for imaging and therapy, but the resulting expression for the relative error is the same and is independent of the physical decay constant of the imaged radionuclide. Their conclusions about the optimal imaging time point \( t = 1/\tilde{\lambda}_b \), equivalent to \( h = 1/(1 + m) \), remains valid for the case with different radionuclides for imaging and for therapy.

2.3. The Hänscheid method
Hänscheid et al (2018) derived an approximate expression for the TIA that is independent of the effective half-life. One possible generalization of the method to the case where different radionuclides are used for imaging and therapy is
\[
q = \frac{\exp \left( f \right)}{f} \frac{1 + n}{1 + m} \frac{h}{\lambda_b}, \tag{10}
\]
where \( f \) is a constant that determines the interval for which the approximation is valid. The equations by Hänscheid et al correspond to \( f = \ln(2) \) and \( m = n \) (the same imaged and therapeutic radionuclides), resulting in \( q = 2t/\ln(2) \). Hence, for the special case of the same radionuclide being used for both imaging and therapy, \( q \) does not depend on the mean biological decay constant. However, the approximation is only valid for a certain interval of \( t \) relative to the effective half-life, which in turn makes the choice of \( f \) dependent on the mean biological decay constant. More background to (10) is provided in the appendix. The expression for the relative error becomes
\[
\varepsilon_H(\xi) = \exp \left[ -(\xi + n) h \right] (\xi + m) \frac{1 + n \exp \left( f \right)}{1 + m} \frac{h}{f} - 1. \tag{11}
\]
Only the case \( f = \ln(2) \) will be considered in the current study.
2.4. Error distributions

Both $\varepsilon_M$ and $\varepsilon_H$ have a maximum at $x = \frac{1}{h} - m$ equal to

$$\varepsilon_M\left(\frac{1}{h} - m\right) = \frac{1}{h(m+1)} \exp\left[(1+m)\frac{1}{h} - 1\right] - 1$$

and

$$\varepsilon_H\left(\frac{1}{h} - m\right) = \exp\left[(m-n)\frac{1}{h} - 1\right] \frac{1 + n}{1 + m} \exp\left(\frac{f}{f}\right) - 1.$$

For errors below the maxima, the probability of obtaining an error below a value $y$ is

$$\Pr[\varepsilon(x) < y] = \Pr(\varepsilon < x_1) + \Pr(\varepsilon > x_2) = \Pr(\varepsilon < x_1) + 1 - \Pr(\varepsilon < x_2),$$

where $x_1$ is the solution to the equation $\varepsilon(x) = y$ for $x < \frac{1}{h} - m$ and $x_2$ is the solution for $x \geq \frac{1}{h} - m$. For the Madsen method

$$x_1 = -\frac{1}{h} W_0(-h(y+1)(1 + m) \exp[-(m+1)\frac{1}{h}]) - m,$$

$$x_2 = -\frac{1}{h} W_{-1}(-h(y+1)(1 + m) \exp[-(m+1)\frac{1}{h}]) - m,$$

where $W_0$ and $W_{-1}$ are the principal and lower branches of the Lambert $W$ function, respectively. Hence, the cumulative distribution function (CDF) of the relative error for the Madsen method is

$$G_M(x) = 1 + L\left(\frac{1}{h} W_0(-h(x+1)(1 + m) \exp[-(m+1)\frac{1}{h}]) - m\right),$$

and

$$G_H(x) = 1 + L\left(\frac{1}{h} W_{-1}(-h(x+1)(1 + m) \exp[-(m+1)\frac{1}{h}]) - m\right).$$

The probability density function (PDF) of the relative error for the Madsen method is

$$g_M(x) = \frac{G_M'(x)}{m} = \frac{\frac{1}{h} W_0(-h(x+1)(1 + m) \exp[-(m+1)\frac{1}{h}]) - m}{\left(1 + m\right) \exp[-(m+1)\frac{1}{h}]}.$$
different ratios of and studied. The case approximately 73 h, would lead to
life is typically shorter for the imaging case. Hence, values of
Meares2000,T olmachev2008
percentiles from the CDFs
95% coverage intervals were formed for the Madsen and Hänscheid methods by calculating the 2.5th and 97.5th
3.1. Coverage intervals
3. Material and methods
2.5. Sensitivity to errors in estimated mean biological decay constant
In practice, the mean biological decay constant for a population is not known exactly and an estimated mean
biological decay constant is used for calculating the TIA. If the mean biological decay constant in (4) is replaced
by a biological decay constant (in general different from the mean biological decay constant and ξ and the
constants , and are redefined accordingly, the rest of the derivations follow without changes. Hence, (17)–
(20) are still valid also when the assumed biological decay constant is different from the mean biological decay
constant, but with a modified distribution for ξ. In particular, .

Figure 1. Illustration of PDFs and CDFs for the relative errors for the Madsen and Hänscheid methods. Top row: , Bottom row: , and .

3.1. Coverage intervals
95% coverage intervals were formed for the Madsen and Hänscheid methods by calculating the 2.5th and 97.5th
percentiles from the CDFs ((17) and (18)) as function of normalized time and standard deviation of ξ. The therapeutic
radionuclide is typically chosen to have a physical half-life at the same time scale as the biological processes, i.e. for a biological
decay constant of a few days, the physical half-life should also be in the order of a few days (Wessels and
Meares 2000, Tolmachev 2008). For example, a mean effective half-life for kidneys in [177Lu]Lu-DOTA-TATE
therapy of around 50 h (Heikonen et al 2016, Sandström et al 2020), corresponding to a mean biological half-life of
approximately 73 h, would lead to . Therefore, values of , and are valid (corresponding to
different ratios of to ) were investigated. If a different radionuclide is used for imaging than for therapy, the half-
life is typically shorter for the imaging case. Hence, values of (i.e. same imaged and therapeutic radionuclide) and
are valid (i.e. the half-life for the therapeutic radionuclide is twice the half-life for the imaged radionuclide) were
studied. The case is representative of for example [177Lu]Lu-DOTA-TATE and [177Lu]Lu-PSMA per-
therapeutic dosimetry, where imaged and therapeutic radionuclides are identical (Sundlöv et al 2017, Violet et al
2019). Another example where is the use of [111In]In-DOTA-TOC to assess biokinetics before or during
therapy with [90Y]Y-DOTA-TOC (Cremonesi et al 1999). The case of corresponds to the use of 124I for pre-
therapeutic dosimetry of 131I (Jentzen et al 2008). A log-normal distribution was assumed for ξ, which was motivated
by the observation that pharmacokinetic parameters are often well-described by this distribution (Lacey et al 1997,
Hou et al 2021). The range of normalized times studied was set from 0.05 to 1.0 to cover measurement times of
approximately one to two effective half-lives for the selected values of . CVs of the biological decay constant from
5% to 100% were investigated.

3.2. Comparison with propagation through a linearized model
The mean and standard deviations in relative errors from propagation through linearized versions of (9) and
(11), i.e. using normal analytical uncertainty propagation (Joint Committee for Guides in Metrology 2008), were
compared with the corresponding parameters calculated directly from the distributions of the relative errors for
the Madsen and Hänscheid methods. Equations for means and standard deviations from linearized models are
given in the supplemental material (S1 to S6) available online at stacks.iop.org/PMB/67/025003/mmedia.
The intervals were studied as a function of normalized time for discrete values of \( \sigma = 0.2, \sigma = 0.5, \) and \( \sigma = 0.8; m = 0.25, m = 0.5, \) and \( m = 1; \) and \( n = m \) and \( n = 2m. \) The discrete values of \( \sigma \) investigated here represent the range of \( \sigma \) observed in literature (Liu et al. 2014, Heikkonen et al. 2016, Sarnelli et al. 2019). The first and second moments obtained directly from the probability distributions ((17)–(20)) were calculated using the relationship

\[
E[\varepsilon(\xi)^2] = k \left( - \int_{-\infty}^{0} x^{k-1}G(x)\,dx + \int_{0}^{\infty} x^{k-1}(1 - G(x))\,dx \right)
\]

(21)

for the raw moments, where \( G \) is the CDF for either the Madsen method or the Hänscheid method. The standard deviation was obtained as \( \sqrt{E[\varepsilon(\xi)^2] - E[\varepsilon(\xi)]^2}. \) A log-normal distribution was assumed for \( \xi \) and the integrals in (21) were evaluated numerically using the \( \text{Qromb} \) function of the IDL programming language (Harris Geospatial Solutions, Boulder, CO, USA), which uses Romberg integration (Press et al. 1992).

The examples were also evaluated with respect to the ability of the mean \( \pm 2 \) standard deviations to indicate a 95% coverage interval for the relative error (Joint Committee for Guides in Metrology 2008). The 2.5th and 97.5th percentiles were calculated from the CDFs and compared with the intervals given by the mean and standard deviation from (21) and from (S1) to (S6).

3.3. Clinical examples

3.3.1. Kidney dosimetry for \(^{177}\text{Lu}\)/DOTA-TATE

The 30 kidney half-lives from the first cycle of \(^{177}\text{Lu}\)/DOTA-TATE presented by Garske et al. (2012) were analyzed. The biological decay constants were calculated from the presented half-lives and the mean of left and right kidney formed. The mean, relative standard deviation, skewness, and excess kurtosis for the corresponding values of the biological decay constant were computed, resulting in 0.008 85 h\(^{-1}\), 1.8%, –0.34, and –0.60, respectively. This combination of mean biological decay constant and physical half-life of the radionuclide corresponds to a value of \( n = m = 0.49. \) The fractions of the estimated TIs that would be within 10%, 5%, and 1% were calculated from a distribution from the Johnson family with mean 1 and standard deviation, skewness and kurtosis as for the sample. A Johnson distribution was used due to the ability to gradually change the skewness and kurtosis for distributions in this family. In order to assess the sensitivity of the result to the shape parameters, intervals of skewness and kurtosis around the initial parameters, \( \pm 0.85 \) and \( \pm 1.7 \), corresponding to \( \pm 2 \) standard errors for skewness and kurtosis respectively for a sample size of 30 (Fisher 1930), were also investigated. Mathematically impossible combinations of skewness and kurtosis were excluded. Furthermore, the fractions were computed for the log-normal and normal distributions for the specified mean and standard deviation, which are special cases of Johnson distributions. The computations of parameters for the Johnson distributions from the moments of the distributions were performed using the code by Hill et al. (1976).

The sensitivity to errors in the mean biological decay constant was also studied for a log-normal distribution of the biological decay constant based on the standard error of the mean for the used standard deviation and a sample size of 30, resulting in 3.4%. One thousand random relative errors for the mean biological decay constant were drawn from a Gaussian distribution and the effect on the distribution of errors for the Madsen method was studied through the 2.5th percentile, median and 97.5th percentile for an imaging time point 75 h post-injection, which is close to the theoretically optimal time point (Madsen et al. 2018). The values of \( m, \sigma, \) and \( h \) were updated according to the relative error for the mean biological decay constant. The fact that the normalized time changed in proportion to the change in mean biological decay constant means that the imaging time point was kept fixed in terms of non-normalized time \( t \). Since the relative error for the Hänscheid method does not depend on the mean biological decay constant if \( n = m \) and \( t \) is fixed (see (10) and (11)), the sensitivity to errors in the estimated mean biological decay constant was not evaluated for the Hänscheid method.

3.3.2. Lesion dosimetry for \(^{131}\text{I}/\)I therapy based on measurement of \(^{124}\text{I}/\)I

Mean biological decay constant and the associated relative standard deviation for lesions in therapies with \(^{131}\text{I}/\)I were calculated from the mean and standard deviation reported by Liu et al. (2014), resulting in 0.0144 h\(^{-1}\) and 69.5%, respectively. This combination of mean biological decay constant and radionuclide half-lives corresponds to values of \( n = 0.48 \) and \( m = 0.25 \). Similarly as for the example for \(^{177}\text{Lu}\)/DOTA-TATE, the fractions of estimated TIs that would be expected to lie within 10%, 5%, and 1% were calculated assuming activity estimates based on imaging with \(^{124}\text{I}/\)I. The base skewness and excess kurtosis were calculated from the corresponding parameters for a log-normal distribution (2.42 and 11.9) since the corresponding sample parameters were not available. In order to keep in line with the DOTA-TATE example, a sample size of 30 was assumed for the range of distribution parameters investigated \((\pm 0.85 \) and \( \pm 1.7 \)).

The sensitivity to errors in the mean biological decay constant was investigated as for the example for \(^{177}\text{Lu}\)/DOTA-TATE, with a standard deviation of the estimated mean biological decay constant of 12.7%. Both methods were studied for an imaging time point of 56 h post-administration. This imaging time point is
close to the optimum as described by Madsen et al. (2018) for the used mean effective half-life and is close to the optimum for \( m = 0.25 \) and \( n = 2m \) for the Hänscheid method as studied in section 3.1.

4. Results

4.1. Coverage intervals

The 2.5th percentile for the Madsen method as function of \( h \) and \( \sigma \) is shown in figure 2. The corresponding results for the Hänscheid method are shown in figure 3. The regions in which the 2.5th percentile is above −10% and the 97.5th percentile is below 10% for each \( m \) and \( n \) are indicated by the solid line. The region mainly follows the −10% isoline for the 2.5th percentile, except for some combinations of \( h \) and \( \sigma \) for the Hänscheid method when \( n \neq m \). That is, if an absolute error up to 10% for at least 95% of cases is considered acceptable in the sense that both the absolute values of the 2.5th and 97.5th percentiles are below 10% in an absolute sense, the main limiting factor is the number of cases in which the TIA is underestimated.

4.2. Comparison with propagation through a linearized model

Plots of the mean and standard deviation for the relative error calculated using the CDFs in (17) and (18) and the approximate expressions in (S1) to (S6) are shown in figure 4 for the Madsen method and figure 5 for the Hänscheid method for \( n = m \). The plots are similar for \( n = 2m \), and the results are shown in the supplemental material (figure S1). For the lowest relative standard deviation of the biological decay constant (20%), there is close agreement between the mean and standard deviations calculated directly from the CDFs and the mean and standard deviations using the linearized models for both the Madsen and Hänscheid methods. As the standard deviation increases for the biological decay constant, there are increasingly larger differences. In particular, the linearized models give a standard deviation of 0 for \( h = 1/(1 + m) \), which is not replicated by the standard deviations calculated from the CDF. There are also deviations for the calculated means between the models, especially for the case with the highest standard deviation of the biological decay constant (80%).

The 95% coverage intervals calculated from the CDFs are compared with intervals estimated from the mean and standard deviations derived from the CDFs and from the linearized models in figure 6 for the Madsen method and in figure 7 for the Hänscheid method for \( n = m \). Plots for the Hänscheid method for \( n = 2m \) are shown in the supplemental material (figure S2). The linearized models generally underestimate the width of the coverage intervals, as does standard deviation based intervals from the non-linear models albeit to a lesser degree. In particular, the 2.5th percentiles are lower when calculated from the CDF than when estimated from the moments.

4.3. Clinical examples

4.3.1. Kidney dosimetry for \([^{177}Lu]\)Lu-DOTA-TATE

The fractions of estimated TIA s that are within a relative error of 10%, 5%, and 1% for the \([^{177}Lu]\)Lu-DOTA-TATE clinical example are shown in figure 8, where the curves for the distributions of the biological decay constant are also indicated. For both the Madsen method and the Hänscheid method, there are relatively large intervals in which the fraction of estimates within 10% is close to 100%.
The sensitivity to errors in the estimated mean biological decay constant for the Madsen method at 75 h post-injection is illustrated in figure 9. The variability between distributions is low for this example, which is also reflected in a low variability for the 2.5th percentile, median, and 97.5th percentile.

4.3.2. Lesion dosimetry for $^{131}$I based on imaging with $^{124}$I
The fractions of estimated TIAs that are within a relative error of 10%, 5%, and 1% for the thyroid lesion dosimetry example are shown in figure 10. The dispersion of curves for the biological decay constant are also indicated. Compared with the DOTA-TATE example in figure 8 the errors are generally larger, with a majority of
distributions for the biological decay constant not reaching a fraction of estimates within 10% above 80%. However, there are some combinations of skewness and kurtosis that reach higher fractions.

The sensitivity to errors in the mean biological decay constant for the Madsen method are shown for an imaging time point of 56 h p.i. in figure 11(a). The corresponding results for the Hänscheid method are shown in figure 11(b). The variability between distributions and percentiles for different mean biological decay constants is larger than for the $^{177}$Lu-DOTA-TATE example and the shapes of the distributions of percentiles differ between the Madsen and Hänscheid methods.

5. Discussion

This paper has studied the theoretical properties of two methods for STP dosimetry in RNT that have gained increasing interest in recent years, namely the Madsen (Madsen et al 2018) and the Hänscheid methods.
Most previous studies on STP dosimetry methods have focused on the application for a specific cohort of patients and were often limited to small sample sizes. Absorbed-dose estimates from the simplified methods were compared with the estimates from a reference method using additional measurements (Del Prete et al 2018, Sundlöv et al 2018, Sandström et al 2020). Those studies have come to different conclusions about the applicability of these methods, even for the same radiopharmaceutical. Therefore, in the present study, the theoretical aspects of how a distribution of biological half-lives propagate to a distribution of errors in TIA were investigated. An understanding of the theoretical properties is essential to ensure the methodology is suitable for clinical practice and to identify scenarios where STP dosimetry may lead to clinically significant over- or under-exposures of patients.

A fundamental observation is that there are maximum positive relative errors that can result from the Madsen method and Hänscheid method. This may lead to markedly skewed error distributions, as illustrated in Figure 1, especially when the imaging time point is placed close to the optimum. The existence of a maximum positive relative error and the prominent negative skewness of the error distributions may lead to a significant underestimation of the TIA for some patients, which could limit the applicability of these methods, while at the same time a large fraction of TIA is close to the true value. This leads to the typical limitation of STP dosimetry methods being the fraction of underestimated TIA, as demonstrated in figures 2 and 3. The tendency for STP methods to underestimate rather than overestimate TIA has been observed in a previous study by Hou et al (2021).
Furthermore, this observation is in line with the underestimated absorbed doses observed by Sandström et al (2020), who concluded that STP dosimetry is unsuitable for use in RNT. Nevertheless, reasonable accuracy can be achieved in certain imaging time intervals even for relatively large standard deviations of the biological decay constant and especially for larger values of the physical decay constants studied. When used in the framework of personalized treatment planning, a significant underestimation of the absorbed doses to target tissues or organs-at-risk may lead to over- or under-treatment of patients. In such cases, more imaging time points would be necessary in order to achieve a sufficient accuracy of the estimated TIA or a mixed scheme with full dosimetry at the first cycle and simplified acquisition schemes at later time points would need to be employed (Jentzen et al 2008, Del Prete et al 2018, Willowsom et al 2018).

The comparison between mean relative errors and standard deviations as calculated through (17) and (18) versus the calculation using linearized models in figures 4 and 5 demonstrates much of the problems of analyzing STP dosimetry methods. There are marked differences between the different calculation methods both with respect to the mean and standard deviation for the CVs of 50% and 80%. Even for the case of 20% there are differences around the optima between the exact and linearized models that may be worth noting. For example, while the linearized model for the Madsen method predicts a standard deviation of 0 if $h = 1/(1 + m)$, the exact model calculates a standard deviation of 1.7% for this time point if $m = 0.25$. The same is true for the comparison of coverage intervals in figures 6 and 7, where the mean ± 2 standard deviations does not capture the 95% intervals calculated directly from the CDFs. Hence, approximate methods for studying the relative errors

Figure 9. The sensitivity to errors in the mean biological decay constant for the $^{177}$Lu-Lu-DOTA-TATE example using the Madsen method with imaging at 75 h post-injection. The two upper plots show the dispersion in the PDF and CDF resulting from a variable assumed mean biological decay constant with the dashed line indicating the distribution for the base parameters. The lower plot shows the distribution of the 2.5th percentile, median and 97.5th percentile with the vertical dashed lines indicating the percentiles for the base distribution.

Figure 10. The fractions of estimates that are within 10%, 5%, and 1% for different assumptions of the distribution of biological decay constants for pre-therapeutic tumour dosimetry using Na$^{124}$I in therapy with Na$^{131}$I. The dashed lines are for a log-normal curve with mean 1 and standard deviation 0.69 and the dotted lines are for a normal distribution with these parameters. The shaded areas are for Johnson distributions with the same mean and standard deviations but varying skewness and kurtosis. The rightmost plot shows the dispersion of biological decay constant distributions considered.
do not seem to be appropriate and more refined methods, such as those considered in the current paper, are necessary.

One of the differences between the current study and previous studies in the field is that the parameter investigated is the biological decay constant rather than the effective decay constant directly (Hänscheid et al 2018, Madsen et al 2018, Hou et al 2021). For a specific estimation of T1A, there is no difference between working with the biological decay constant or the effective decay constant and the relative errors in (9) and (11) could just as well have been formulated for the latter. However, in a framework that allows for different radionuclides for imaging and for therapy, the biological decay constant is the common parameter and therefore convenient to work with. Furthermore, many of the used distributions of the biological decay constant, e.g. the log-normal distribution, would in principle be invalid if assumed for the effective decay constant since they would imply a non-zero probability for the effective half-life to be larger than the physical half-life. If the relative standard deviation is low, these considerations are of little practical consequence (i.e. the probability of obtaining an effective decay constant smaller than the physical decay constant is negligible even if it is non-zero). However, as the standard deviation increases, the effect gradually grows in importance, as exemplified in figure 12. The different curves are for a fixed relative standard deviation of the effective decay constant of 25%, but for different physical decay constants \( m = 0 \) to \( m = 2 \), i.e. relative standard deviations of the biological decay constant from 25% to 75% (log-normal distributions). The 2.5th percentile and the 97.5th percentile are plotted as a function of \( h(1 + m) \), which is equivalent to scale the time relative to \( 1/\lambda \) rather than \( 1/\lambda_b \). For the 2.5th percentile there are substantial differences between the plots for different physical decay constants, which illustrates the need to account for biological decay constant and physical decay constant separately in the general

Figure 11. Variability in distributions caused by uncertainty in the estimated mean biological decay constant for the radioiodine example. Sub-figure (a) shows the Madsen method and subfigure (b) shows the Hänscheid method.
case, rather than combing them in an effective decay constant only. This exemplifies that STP dosimetry may not be suitable when large inter-patient variability is expected with respect to the biological retention.

For the general survey of coverage intervals in figures 2 and 3, relative standard deviations of $\sigma = 0.05$, to $\sigma = 1.0$ were considered. For the clinical example of $^{177}$LuLu-DOTA-TATE with a relative standard deviation of $\sigma = 0.18$, a good agreement was found between the two simplified methodologies and the actual TIA. Nevertheless, for a larger relative standard deviation of $\sigma = 0.69$, observed by Liu et al (2014) with Na$^{[131]}$I, agreement was found to be worse. The results show that the relative standard deviation of the biological half-life partially governs the applicability of STP dosimetry and the choice of the optimal imaging time point, but also that other properties of the biological decay constant distribution may influence the accuracy of estimated TIA.

With respect to the differences between methods, most applications of STP dosimetry methods have been for kidneys in $^{177}$LuLu-DOTA-TATE therapy using a rather late imaging time point of around 100 h (Hänscheid et al 2018, Sundlöv et al 2018, Sandström et al 2020, Devasia et al 2021), which corresponds to approximately two mean half-lives for the radiopharmaceutical. In this context, it can be worth noting that if $f = \ln(2)$, as in the original formulation of the Hänscheid method, and $h = 2 \ln(2) / (1 + n)$ (twice the mean half-life for the imaged radionuclide), then the relative errors are the same for the Madsen and Hänscheid methods. The same is true for the case $h = \ln(2) / (1 + n)$ and is a simple consequence of (8) and (10) coinciding for these combinations of $f$ and $h$. The bias for the Hänscheid method at other imaging time points is reflected in for example figure 8, where the dips around 70 h compared with around 50 h and 100 h for the 5% and 1% curves can be explained by the increasing bias at time points between one and two mean effective half-lives.

The sensitivity to errors in the mean biological decay constants for the two examples is investigated in figures 9 and 11. However, it should be noted that these results are for a particular example in terms of mean decay constants, standard deviations, physical half-lives, and imaging time points. The current paper does not seek to give a full description of how the uncertainty in mean decay constant affects the error distributions, but figure 11 indicates that the effect can be rather substantial if the uncertainty is large. Likewise, figures 8 and 10 suggest that it is not only the second moment (i.e. the variance) of the biological decay constant that affects the error distribution, but that higher moments, e.g. the skewness and kurtosis, may also be important to consider when discussing the applicability of STP dosimetry methods. Nevertheless, the results suggest that a good estimate of mean biological half-life is crucial for STP dosimetry. At present, mean biological decay constants are often based on small sample sizes and this could potentially introduce large uncertainties on the estimated absorbed doses.

The major limitation of the current study is its theoretical nature, and the transition from theoretical reasoning to practical implementation should always be performed with care. Hence, the current study is not meant as, and can never be, a substitute for validation studies based on patient samples. Furthermore, the uncertainty in the estimated activity is ignored in the analysis, which in a real-life situation would add another source of variability to the uncertainty propagation (Gustafsson et al 2015, Gear et al 2018). Still, we expect the
presented theory to be helpful in planning, analyzing, and understanding data from STP dosimetry methods and their relation to standard methods. Understanding the uncertainty introduced by relying on population averages for kinetic parameters should be relevant for any person using STP dosimetry methods, and this paper demonstrates how propagation of the full distribution of biological decay constants to a distribution of errors in TIA may be necessary in order to understand the deviations that can occur. In particular, the highly skewed distributions that can result cause the main limitation of the methods studied herein to be the risk of substantial underestimation rather than the symmetric risk of both over- and underestimations that is often assumed. While this may not be an issue that prohibits all use of STP dosimetry methods, the risk needs to be considered.

6. Conclusions

The validity of STP dosimetry methods does not only depend on the biological variability between patients, but also on the relation between the biological decay constant, the physical decay constant, and the imaging time point. It is important to consider these parameters in combination when assessing the accuracy of such methods, as well as the shape of the distribution of biological decay constants. When using STP dosimetry methods, one should be aware of the risk of substantially underestimating the TIA. The CDFs in (17) and (18) can be used as a first indication of the applicability of such methods for a particular combination of parameters.

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Appendix. Generalization of the Händscheid method

The original formulation of the Händscheid method (Händscheid et al. 2018), formulated for the case in which the same radionuclide is used for imaging and therapy, is based on the approximation

\[ 2\pi T_{\text{eff}} \approx 2t, \quad (A.1) \]

where \( T_{\text{eff}} \) is the effective half-life. This approximation is valid within 10% in the interval \( 0.75T_{\text{eff}} < t < 2.5T_{\text{eff}} \). It can be noted that equality holds in (A.1) for \( t = T_{\text{eff}} \) and \( t = 2T_{\text{eff}} \), i.e.

\[ 2\pi T_{\text{eff}} = 2t \Leftrightarrow t = T_{\text{eff}} \text{ or } t = 2T_{\text{eff}}. \]

In terms of the notation used in the current paper, (A.1) corresponds to

\[ \frac{\exp[(\xi + m)h]}{\lambda_b(\xi + m)} \approx \frac{2}{\ln(2)}h. \quad (A.2) \]

In particular, the approximation is valid for the mean biological decay constant, i.e.

\[ \frac{\exp[(1 + m)h]}{\lambda_b(1 + m)} \approx \frac{2}{\ln(2)}h. \quad (A.3) \]

If different radionuclides are used for imaging and therapy and a general proportionality with proportionality constant \( d \) is used as approximation, the expression becomes

\[ \frac{\exp[(1 + n)h]}{\lambda_b(1 + m)} \approx dh. \quad (A.4) \]

The expression is exact for

\[ \frac{\exp[(1 + n)h]}{\lambda_b(1 + m)} = dh \]

\[ \Leftrightarrow h_1 = -\frac{1}{1 + n}W_{\eta} \left( -\frac{1 + n}{d(1 + m)} \right) \]

\[ \text{or } h_2 = -\frac{1}{1 + n}W_{\eta}^{-1} \left( -\frac{1 + n}{d(1 + m)} \right), \quad (A.5) \]
The equation can be forced to have a solution at \( h_0 = f/(1 + n) \) if
\[
f = -W_0\left(-\frac{1 + n}{d(1 + m)}\right) \implies d = \frac{1 + m \exp(f)}{1 + n} f.
\]

If \( f = \ln(2) \) then \( h_1 = \ln(2)/(1 + n) \) and \( h_2 = 2 \ln(2)/(1 + n) \) as in the original method, but other choices are also possible, e.g. \( f = 1 \) gives \( h_1 = h_2 = 1/(1 + n) \).

**ORCID iDs**

Johan Gustafsson  [https://orcid.org/0000-0002-1022-8370](https://orcid.org/0000-0002-1022-8370)
Jan Tjaproke  [https://orcid.org/0000-0001-9947-2857](https://orcid.org/0000-0001-9947-2857)

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