RPT-TEC

Sept 2022

MIRDcalc and MIRDfit: MIRD tools for pharmokinetic modelling and dosimetry

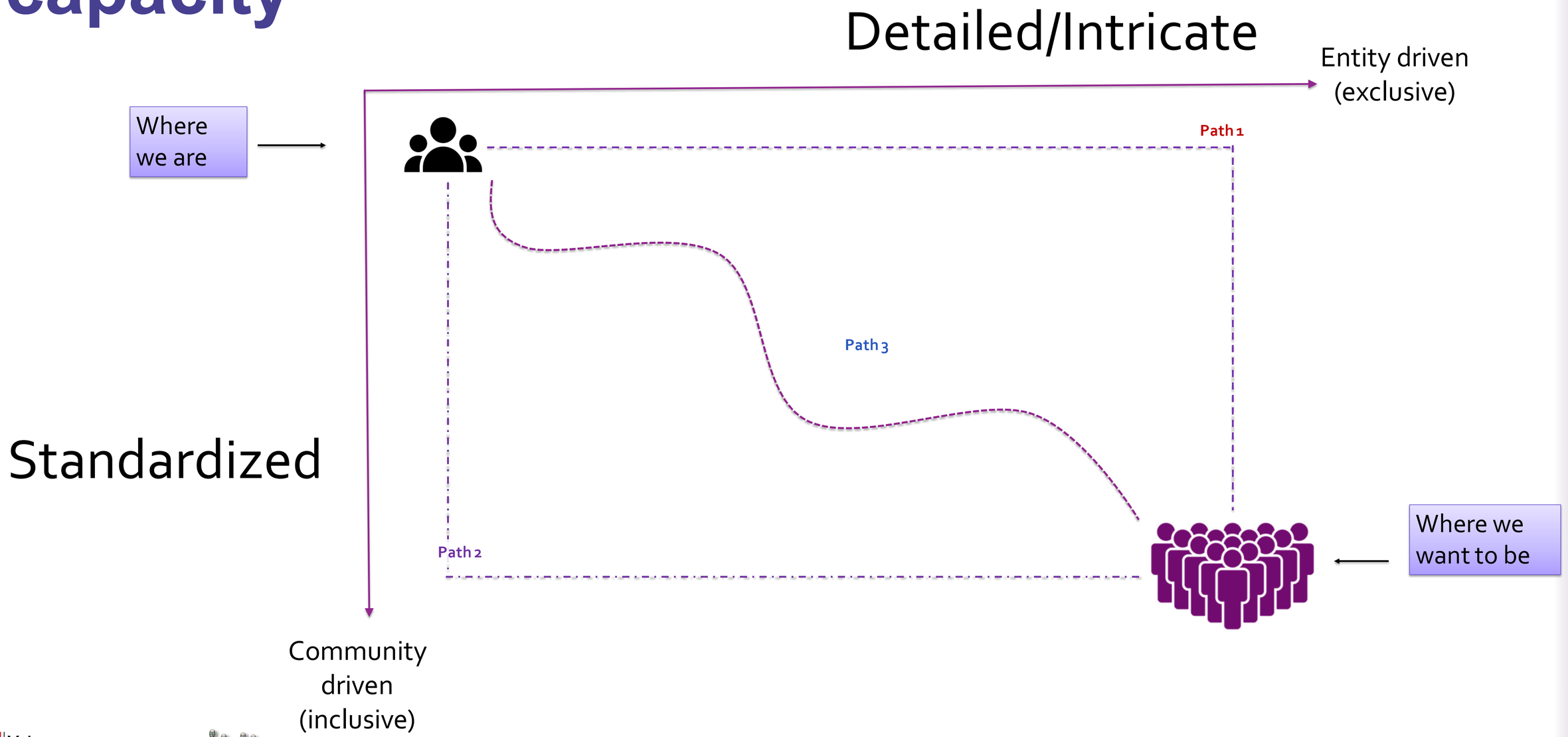
Presenter: Adam Kesner, PhD, DABR

Deputy Service Chief of Molecular and X-Ray Imaging Physics
Memorial Sloan Kettering Cancer Center
kesnera@mskcc.org

Presentation overview

- Topics
  - Standardization and error propagation via MIRDsoft.org tools
    1. MIRDcalc: TIAC->dosimetry
    2. MIRDfit: data points -> TIAC
  - Perspectives on organ level dosimetry
  - Perspectives on standardization
  - Closing remarks

Current status of personalized dosimetry capacity



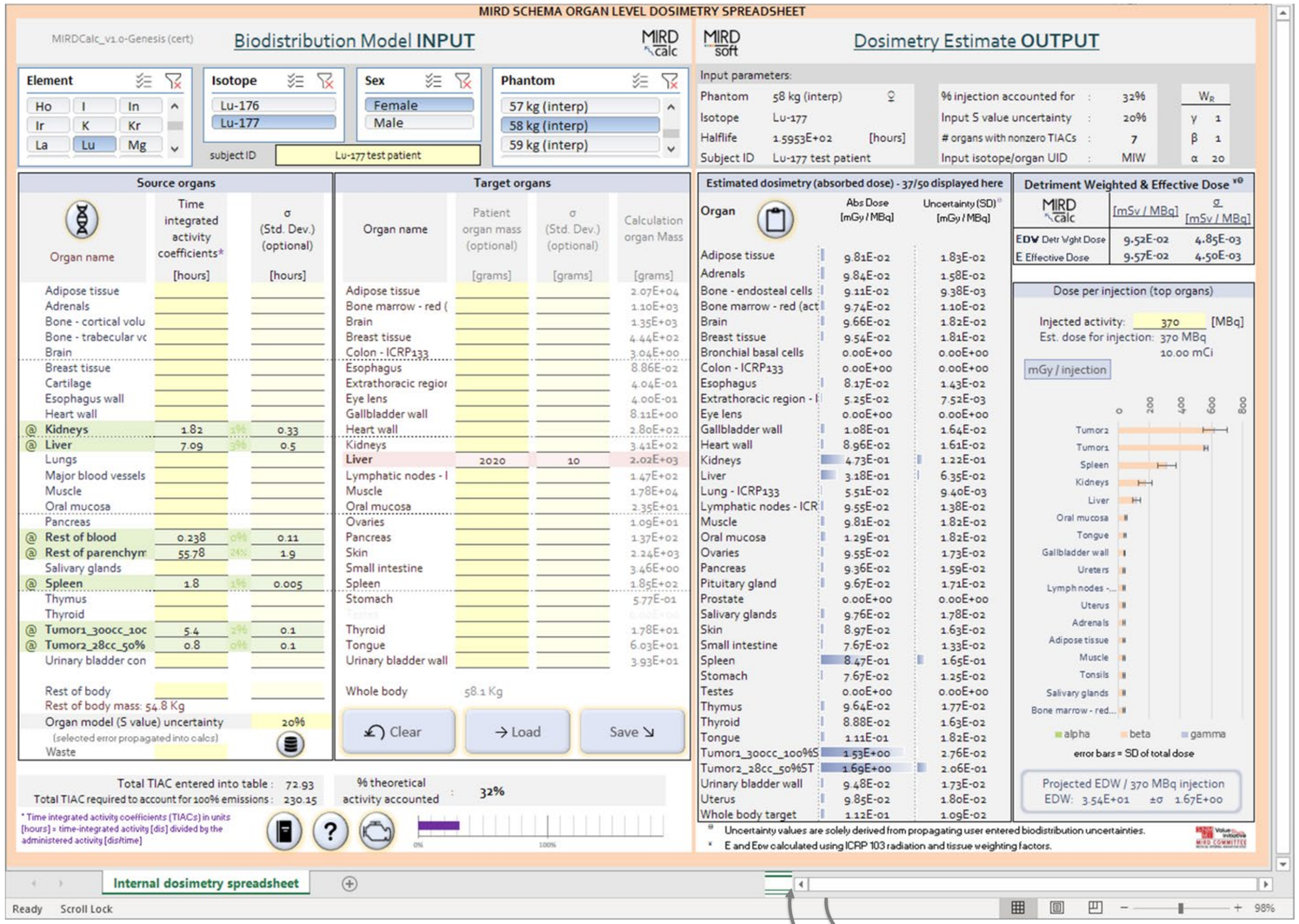
Introduction to MIRDsoft.org

- The SNMMI MIRD committee initiative to make a suit of free dosimetry-supporting software tools
- Collaborative project
  - MIRDcalc grant
    - NIBIB - U01, Bolch (UF)/Kesner(MSK)
  - MIRDcell grant
    - NCI - R01, Howell (Rutgers)
- Project hosted on www.MIRDsoft.org
  - Software dissemination
  - Community platform

Introduction to MIRDsoft.org

- Available now
  - **MIRDcalc v1 – organ-level internal dosimetry**
  - MIRDcell v3 – cell-level dosimetry
- Coming soon
  - **MIRDfit – biodistribution fitting/statistical analysis**
  - MIRDct – CT dosimetry
  - MIRDmc – voxel & mesh Monte Carlo dosimetry

MIRDcalc screenshot

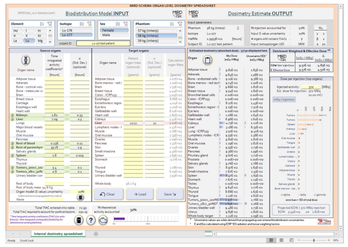


Data base with S values (protected, versioned)

$$D(r_T) = \sum_{r_S} \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S)$$

Dose calculation	Quality control	Error calculation
Effective dose calculations	Risk index	Formatted reporting

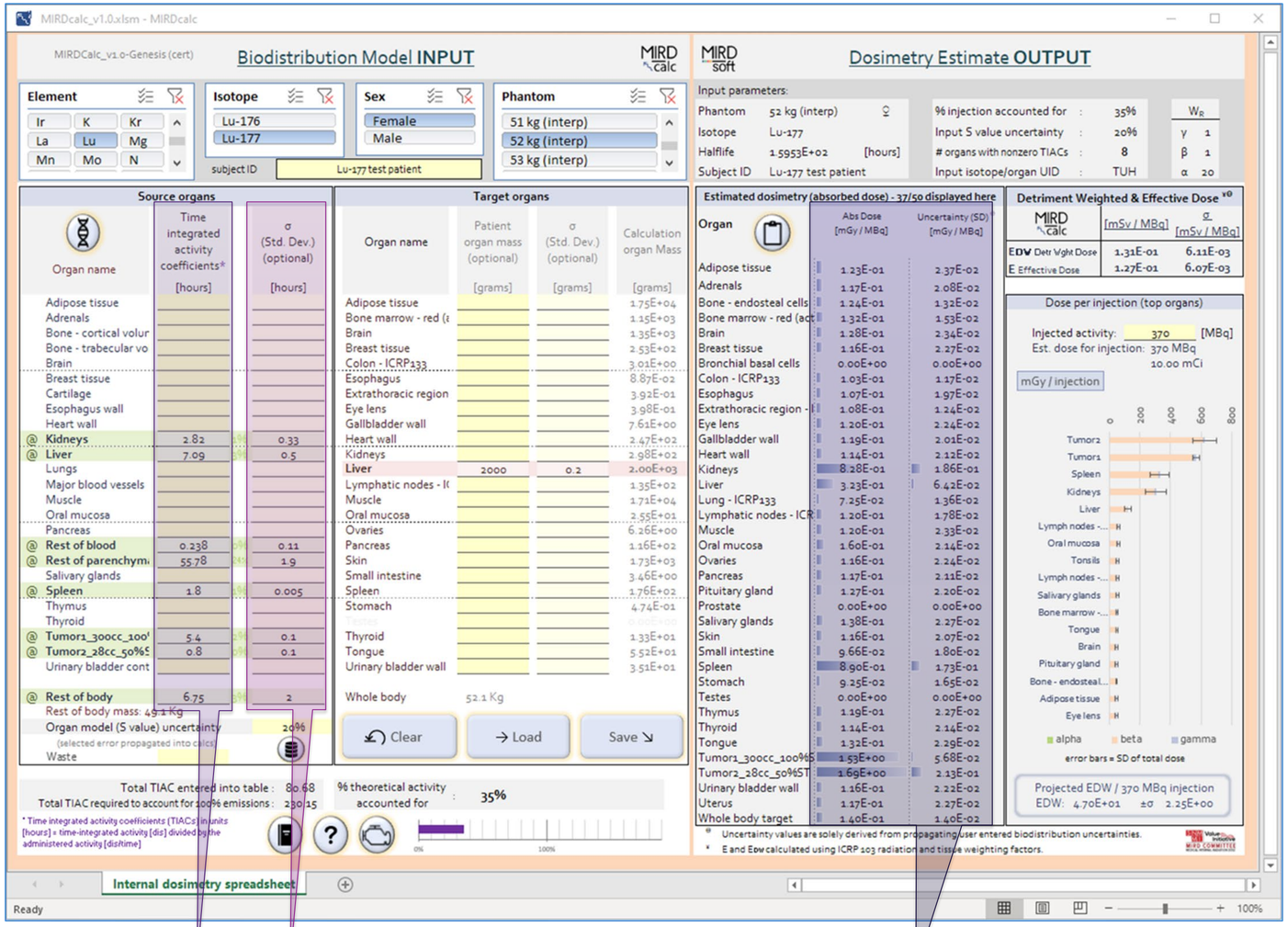
MIRDcalc



- **Innovations**
  - 81 source regions, 48 target regions, 333 isotopes
  - Single screen user interface
  - Real time processing
  - Graphical quality control checks
  - Modern ICRP phantoms
    - Well documented
  - Spectrum of phantom models (m/f, pediatric to adult, 1 kg steps)
  - Dynamic source regions
    - Rest of body
    - Rest of blood
    - Rest of parenchyma
  - (New) blood model
  - **<u>Uncertainty propagation</u>**
  - Tumor dosimetry module
  - Output: Organ dose, effective dose, detriment weighted dose, risk index
  - Thorough case documentation
    - Highly detailed output text files
    - Default screen capture
  - Command line execution
    - Supports batch processing, possibly 3rd party
  - And more…

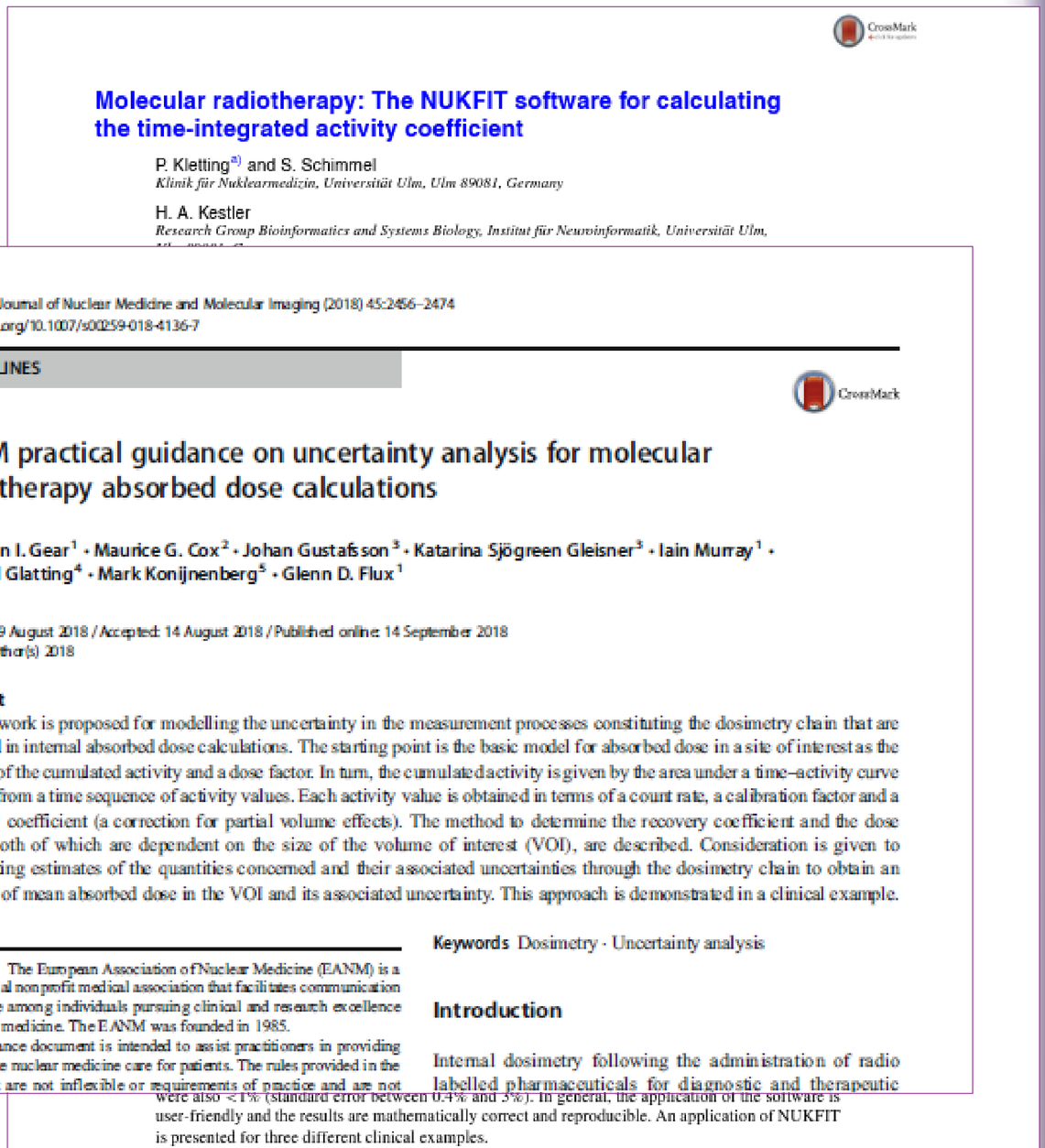
MIRDcalc dosimetry software

- MIRDcalc has capacity to propagate uncertainty



Uncertainty estimation in time-activity curve fitting

- Pharmacokinetic modelling used to transform raw measurements into biodistribution input for dosimetry calculations
  - Time integrated activity coefficients (TIACs – area under the curve) used to define sources of radiation
  - Uncertainty in time point measurements can mathematically propagate into uncertainty in TIACs
- Existing software
  - SAAM-II
  - NUKFIT
- Existing guidance document
  - EANM Procedural Guidelines for Uncertainty Analysis



Molecular radiotherapy: The NUKFIT software for calculating the time-integrated activity coefficient

P. Kletting[a)] and S. Schimmel
Klinik für Nuklearmedizin, Universität Ulm, Ulm 89081, Germany

H. A. Kestler
Research Group Bioinformatics and Systems Biology, Institut für Neuroinformatik, Universität Ulm,

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:2456–2474
https://doi.org/10.1007/s00259-018-4136-7

GUIDELINES

EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations

Jonathan I. Gear[1] · Maurice G. Cox[2] · Johan Gustafsson[3] · Katarina Sjögreen Gleisner[3] · Iain Murray[1] · Gerhard Glatting[4] · Mark Konijnenberg[5] · Glenn D. Flux[1]

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Abstract
A framework is proposed for modelling the uncertainty in the measurement processes constituting the dosimetry chain that are involved in internal absorbed dose calculations. The starting point is the basic model for absorbed dose in a site of interest as the product of the cumulated activity and a dose factor. In turn, the cumulated activity is given by the area under a time–activity curve derived from a time sequence of activity values. Each activity value is obtained in terms of a count rate, a calibration factor and a recovery coefficient (a correction for partial volume effects). The method to determine the recovery coefficient and the dose factor, both of which are dependent on the size of the volume of interest (VOI), are described. Consideration is given to propagating estimates of the quantities concerned and their associated uncertainties through the dosimetry chain to obtain an estimate of mean absorbed dose in the VOI and its associated uncertainty. This approach is demonstrated in a clinical example.

Keywords Dosimetry · Uncertainty analysis

Preamble The European Association of Nuclear Medicine (EANM) is a professional non profit medical association that facilitates communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985.
This guidance document is intended to assist practitioners in providing appropriate nuclear medicine care for patients. The rules provided in the document are not inflexible or requirements of practice and are not

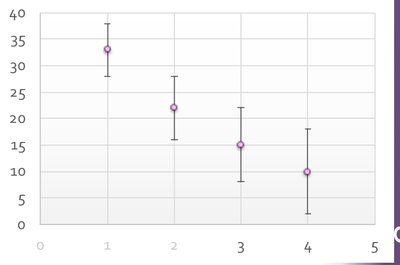
Introduction

Internal dosimetry following the administration of radio labelled pharmaceuticals for diagnostic and therapeutic

were also <1% (standard error between 0.4% and 5%). In general, the application of the software is user-friendly and the results are mathematically correct and reproducible. An application of NUKFIT is presented for three different clinical examples.

Review of curve fitting procedures

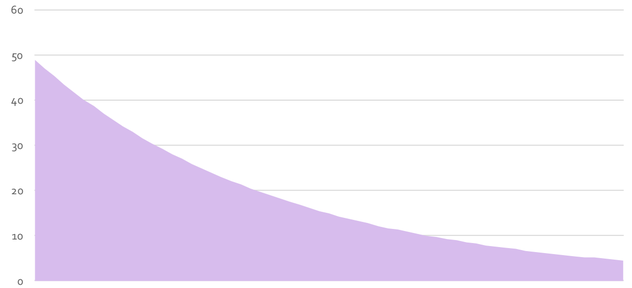
x	f(x)	u(x)
1	33	5
2	22	6
3	15	7
4	10	8
n	…	…



Given calibrated measurements:

1. Select (exponential) modelling equation
2. Curve parameters determined by iterative fitting approach
   - Least squares approach using non-linear regression to minimize objective function
3. Time-integrated activity coefficient derived from integration
4. Uncertainties are obtained by Gaussian error propagation, taking the variances and covariances of the fit parameters into account
5. Additional statistics can be determined, and used in selection of “best model”
   - R^2,Akaike information criterion, Akaike corresponding weights, Weighted residuals

$$AUC = \int_0^\infty A_1(e^{-(\lambda_1+\lambda_{phys})t} - e^{-(\lambda_2+\lambda_{phys})t})dt = \frac{A_1}{\lambda_1+\lambda_{phys}} - \frac{A_1}{\lambda_2+\lambda_{phys}}$$



TIAC = 1.23 ± ± 0.006

Variance-covariance table

	bo	b1	b2
bo	1.014933	0.009028	0
b1	0.009028	0.000103	0
b2	0	0	1E+16

Fit metric comparison legend

	👎	👍
R^2	0.7	1.0
AICc	Max	Min
w_{AICc}	Min	Max
$r_{model/trapezoidal}$	±25%	0%

Review of curve fitting procedures

- Microsoft solver output

Title: Model5Fit

Weight	SD for Y	SD for X's	Observations	Parameters		
Absolute	N	N	4	3	1	1	N

ANOVA

Source	Sum Sq.	Degr. Fred.	Mean Sq.	F calc.	Crit. F(.05)	
Model	5299.666346	2	2649.833173	11385.93616	199.5	
Residual	0.232728617	1	0.232728617			
Total	5299.899075	3				

Chi Square Statistics

ChiSq. Calc	Crit. ChiSq.(.05)Inf.	Crit. ChiSq.(.05)Sup.	Passed F
0.232728617	0.00393214	3.841458821	0.62950794	Ok

R	Low. CI(.95)	Up. CI(.95)	R^2	R^2 adj	
0.999978044	0.9858773	0.999999966	0.999956088	0.999868

Parameters Statistics (from linearized Variance-Covariance Matrix)

Par.	Value	Std. Err.	Z calc.	Crit. Z(.05)	Low. CI(.95)
b0	48.99751939	1.007438849	48.63572558	1.959963985	
b1	0.396995227	0.010150499	39.1109069	1.959963985	
b2	39.11467473	100000000	3.91147E-07	1.959963985	

Parameters Statistics and Wald Test (from Fisher Information Matrix)

Par.	Value	Std. Err.	Z calc.	Crit. Z(.05)	Low. CI(.95)
b0	48.99751939	1.008125899	48.60257973	1.959963985	
b1	0.396995227	0.01015934	39.07687147	1.959963985	
b2	39.11467473	100000000	3.91147E-07	1.959963985	

Chi^2 Joint Confidence Parameters Statistics

Par.	Value	Low. CI(.95)	Up. CI(.95)	Passed Prob.	Check
b0	48.99751939	46.18124073	51.81379805	0	Ok
b1	0.396995227	0.368619674	0.42537078	0	Ok
b2	39.11467473	-279548309.2	279548387.4	1	No

Variance-Covariance Table for Parameters

	b0	b1	b2
b0	1.014933034	0.009028016	0
b1	0.009028016	0.000103033	0
b2	0	0	1E+16

Hessian Variance-Covariance Table for Parameters

	b0	b1	b2
b0	1.016317828	0.009043782	0
b1	0.009043782	0.000103212	0
b2	0	0	1E+16

Correlation Table for Parameters

	b0	b1	b2
b0	1	0.882848583	0
b1	0.882848583	1	0
b2	0	0	1

Ratio Objects/Parameters	Check
1.333333333	No

Observation Statistics (CI based on Z Statistic)

Y	Ycalc	Low. Regr. Conf. Band (.95)	Up. Regr. Conf. Band (.9	
22.59288635	22.55376416	20.39588962	24.71163869	0.127776
10.31188916	10.38159246	9.127913392	11.63527152	-0.36426
4.813540079	4.778690652	3.339608914	6.21777239	0.287323
2.197005332	2.199651397	0.583119636	3.816183158	-0.03406

Cut Point

Non-Weighted Residuals Statistics

Mean	Standard Deviation
0.000405563	0.050365072

Collinearity Tests for the Jacobian Matrix

Jacobian Correlation Matrix

	b1	b2
b1	1	

Condition Number for the Correlation Matrix

Value	Check

Variable	Tolerance	VIF	Check
b0	0.960349328	1.04128776	Ok
b1	0	1E+300	No

Durbin Watson Statistic for Autocorrelation of Residuals

Note: DW tests do not apply directly to residuals from regression throug

Durbin Watson Bounds Test

DW	DWcritInf(.05)	DWcritSup(.05)	4-DWcritSup(.05)	4-DWcrit

Box Pierce Ljung Q' Test for Autocorrelation Of High Order

Autoregressive Order	Q'	ChiSqcrit(.05)	Check(.05)	Passed F
1	3.828275665	5.991464547	Ok	0.050394752	

Residuals Runs Test

Res. +	Res. -	Runs	Low Crit. Runs (.05)		Up. Crit. Runs (.05)	
2	2	4	2	4	No	1

Breush-Pagan Test for Homoscedasticity of Residuals

Breush-Pagan MSS/2	ChiSqcrit(.05)	Check(.05)	Passed Prob.
0.067579832	3.841458821	Ok	0.794893693

Koenkar-Evans NR2	ChiSqcrit(.05)	Check(.05)	Passed Prob.
0.164065213	3.841458821	Ok	0.685441021

Error Sum of Squares (RSS or SSE)	n	p	dF	Error Me
0.232728617	4	3	1	0.232728617	0.241209772

R	R^2	R^2 adj
0.999978044	0.999956088	0.999868264

PRESS	1.240506393
MEP	0.310126598
R^2 prediction	0.999765938
SDEC	0.241209772
SDEP	0.556890113

AIC (Akaike Information Criterion)	-5.376706402
AICc (Adjusted Akaike Information Criterion)	65535
HQC (Hannan Quinn Criterion)	-9.416900842
HQCc (Adjusted Hannan Quinn Criterion)	
BIC (SBC-Schwarz Baynesian Criterion)	-7.217823318
BICc (SBCc-Adjusted Schwarz Baynesian Criterion)	

Models Comparison using Information Criterion (Replace IC)

	IC	IC
Min IC	65535	65535	65535
Weight Sum	2	1	1
Probability	0.5	0.5	
Evidence Ratio	1	1	

Log-Likelihood Section

Log-Likelihood Function	-2.759989654

Log-Likelihood Tests for Nested Models (Replace RSS and NPar values)

	RSS	NPar		Test Value	dF	Crit. Ch
Restricted Model	0.232728617	3		Lagrange Multipl		
Unrestricted Model	0.232728617	3		Likelihood Ratio		
Ratio	1		Wald Statistic	0	0	#NUM!

F Test for Models Comparison (Replace Residual Mean Square and dF)

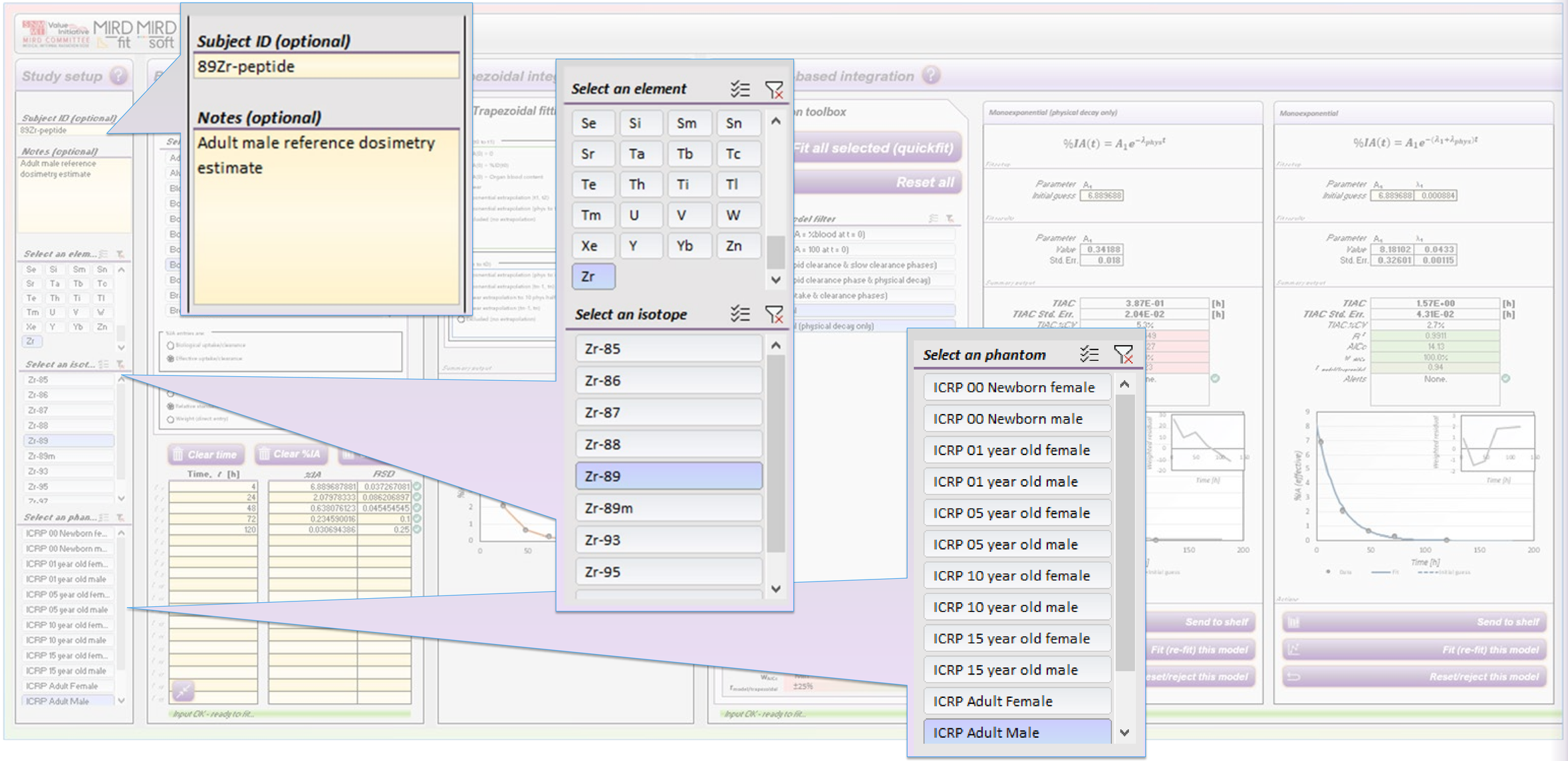
Residual Sum of Squares #1	dF #1	Residual Sum of Squares #2			
0.232728617	1	0.232728617	1	1	647.7890115

Extra Sum F Test for Significance of Extra Parameters in Nested Models (

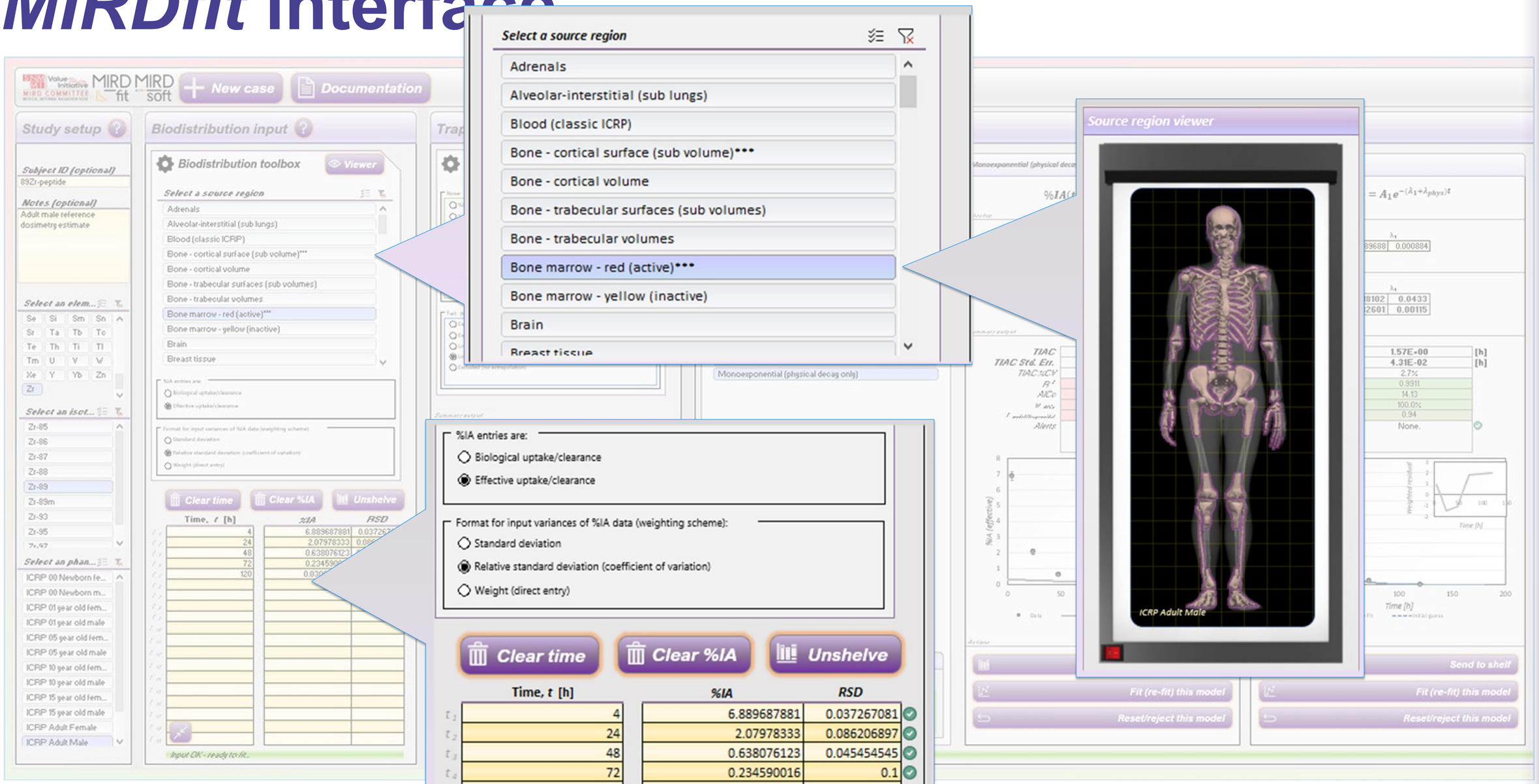
Reduced Model	Residual Sum Of Squares	Reduced Model dF		Full Mod	
0.232728617	1	0.232728617	1	#DIV/0!	#NUM!	#DIV/0!

MIRDfit interface

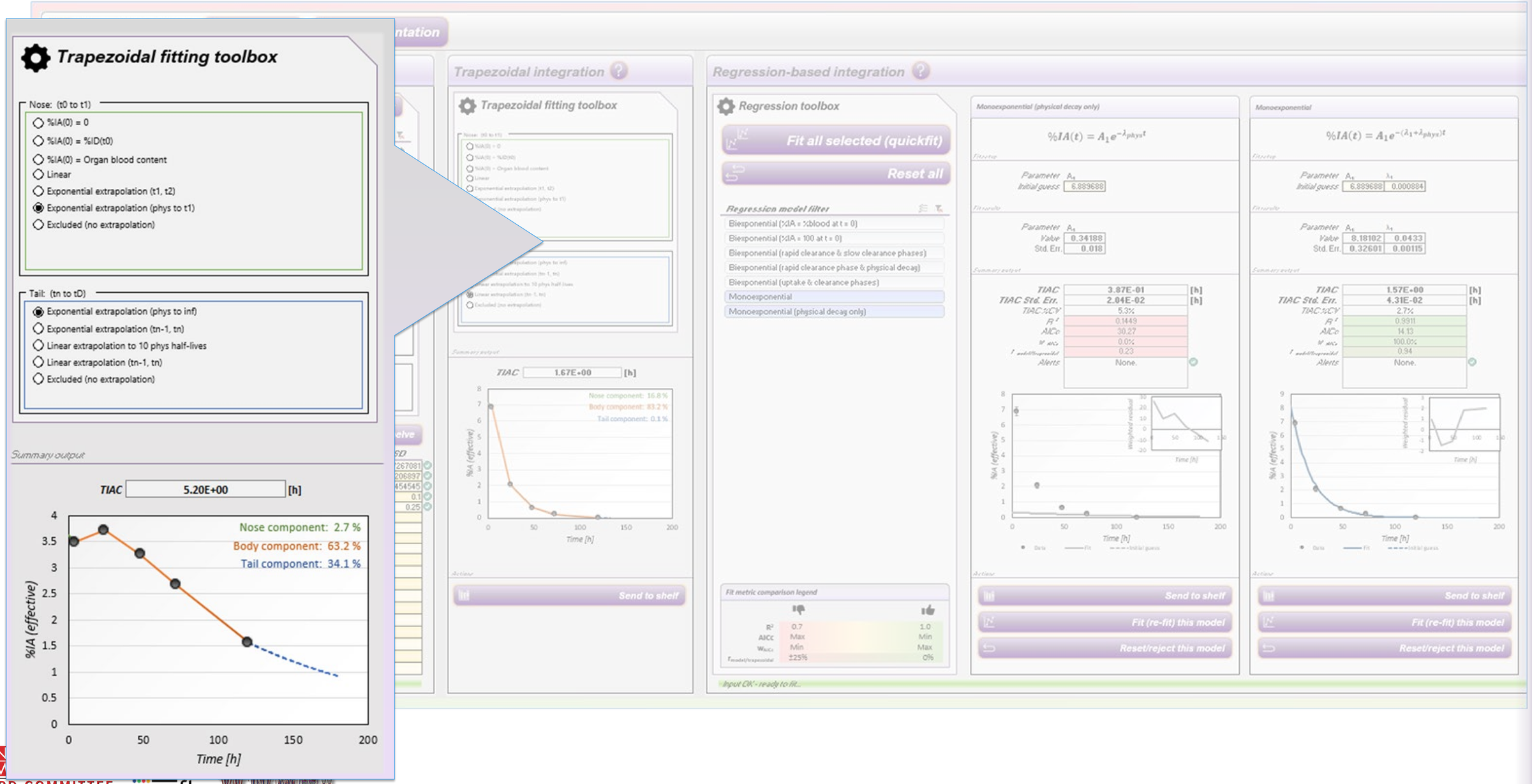
MIRDfit interface



MIRDfit interface



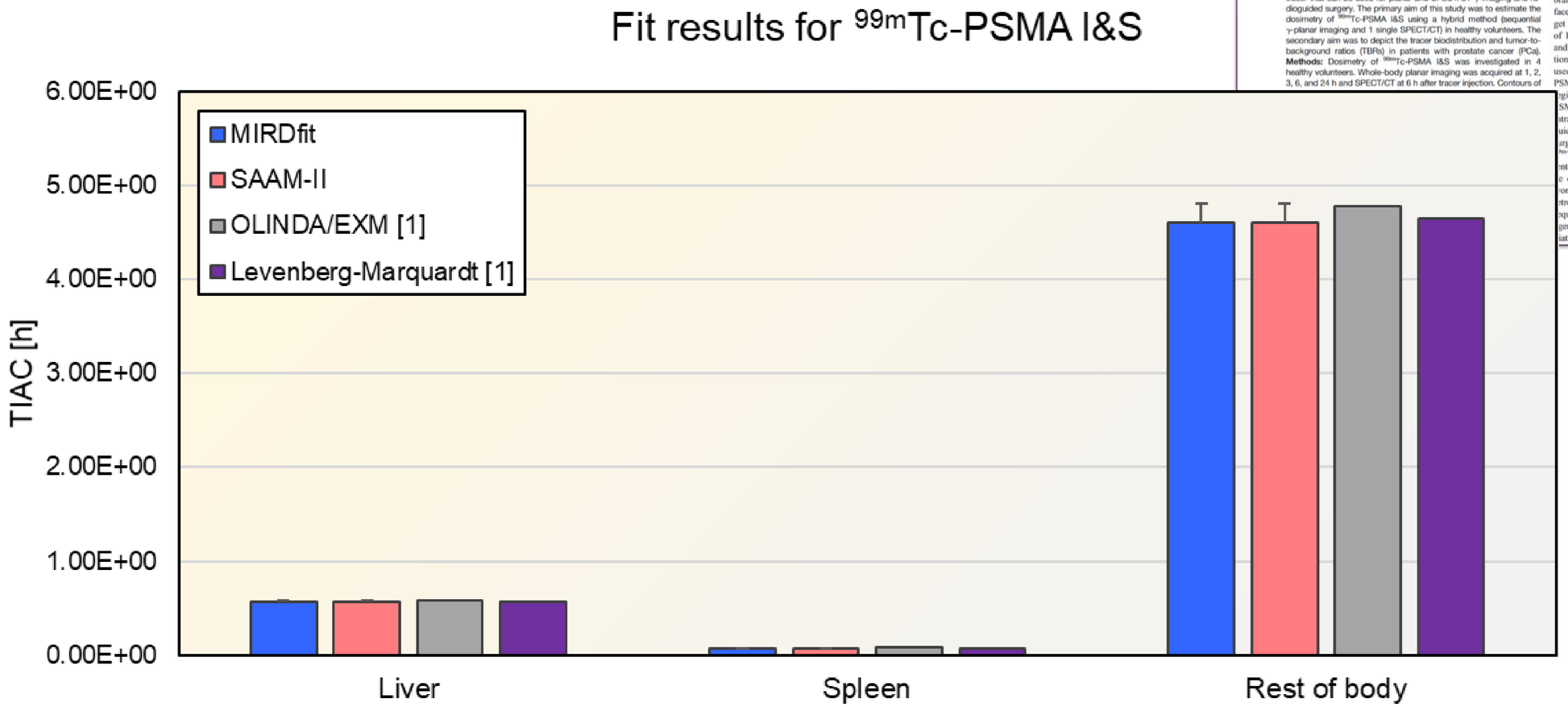
MIRDfit interface

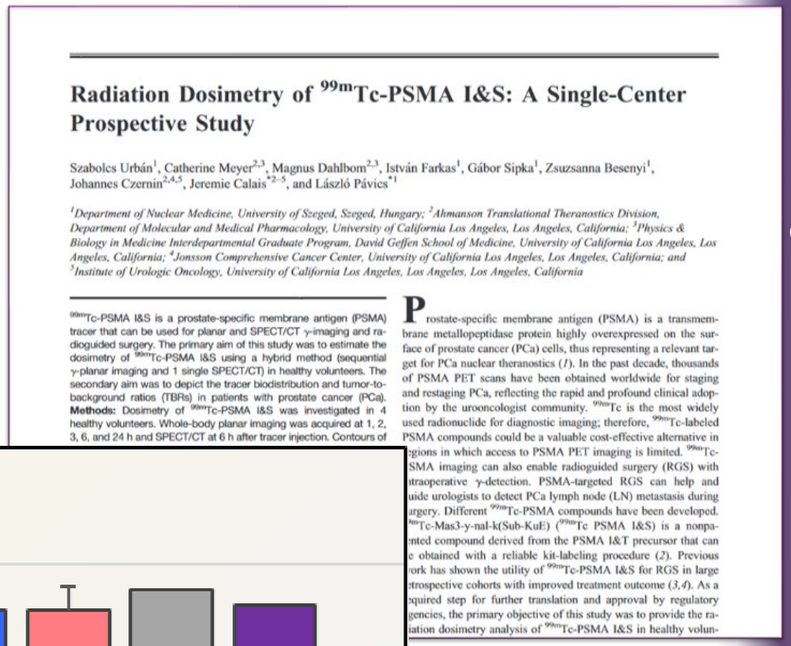


MIRDfit interface

MIRDfit performance

- Within 1% agreement with SAAM-II in testing





Radiation Dosimetry of ^{99m}Tc-PSMA I&S: A Single-Center Prospective Study

Szabolcs Urbán[1], Catherine Meyer[2,3], Magnus Dahlbom[2,3], István Farkas[1], Gábor Sipka[1], Zsuzsanna Besenyi[1], Johannes Czernin[2,4,5], Jeremie Calais[*2–5], and László Pávics[*1]

[1]*Department of Nuclear Medicine, University of Szeged, Szeged, Hungary;* [2]*Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, University of California Los Angeles, Los Angeles, California;* [3]*Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California;* [4]*Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, California; and* [5]*Institute of Urologic Oncology, University of California Los Angeles, Los Angeles, Los Angeles, California*

^{99m}Tc-PSMA I&S is a prostate-specific membrane antigen (PSMA) tracer that can be used for planar and SPECT/CT γ-imaging and radioguided surgery. The primary aim of this study was to estimate the dosimetry of ^{99m}Tc-PSMA I&S using a hybrid method (sequential γ-planar imaging and 1 single SPECT/CT) in healthy volunteers. The secondary aim was to depict the tracer biodistribution and tumor-to-background ratios (TBRs) in patients with prostate cancer (PCa). **Methods:** Dosimetry of ^{99m}Tc-PSMA I&S was investigated in 4 healthy volunteers. Whole-body planar imaging was acquired at 1, 2, 3, 6, and 24 h and SPECT/CT at 6 h after tracer injection. Contours of

Prostate-specific membrane antigen (PSMA) is a transmembrane metallopeptidase protein highly overexpressed on the surface of prostate cancer (PCa) cells, thus representing a relevant target for PCa nuclear theranostics (*1*). In the past decade, thousands of PSMA PET scans have been obtained worldwide for staging and restaging PCa, reflecting the rapid and profound clinical adoption by the urooncologist community. ^{99m}Tc is the most widely used radionuclide for diagnostic imaging; therefore, ^{99m}Tc-labeled PSMA compounds could be a valuable cost-effective alternative in regions in which access to PSMA PET imaging is limited. ^{99m}Tc-PSMA imaging can also enable radioguided surgery (RGS) with intraoperative γ-detection. PSMA-targeted RGS can help and guide urologists to detect PCa lymph node (LN) metastasis during surgery. Different ^{99m}Tc-PSMA compounds have been developed. ^{99m}Tc-Mas3-γ-nal-k(Sub-KuE) (^{99m}Tc PSMA I&S) is a nonpatented compound derived from the PSMA I&T precursor that can be obtained with a reliable kit-labeling procedure (*2*). Previous work has shown the utility of ^{99m}Tc-PSMA I&S for RGS in large retrospective cohorts with improved treatment outcome (*3,4*). As a required step for further translation and approval by regulatory agencies, the primary objective of this study was to provide the radiation dosimetry analysis of ^{99m}Tc-PSMA I&S in healthy volun-

[1] Urban et al. *J Nucl Med* 2021 Aug 1;62(8):1075-1081. doi: 10.2967/jnumed.120.253476

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  - Perspectives on standardization
  - Closing remarks

Anatomy of a dinner preparation workflow

- Several methods have been proposed

Complexity spectrum

Anatomy of a dosimetry workflow

- Several methods have been proposed

Complexity spectrum

Lookup table.
One size for all

- ICRP 53, ICRP 80, ICRP 106,…

- Regulatory approved package insert for one size fits all radiopharmaceutical therapies

Organ level dosimetry

MIRD formalism

Voxel level dosimetry
(in house or commercial software)

Point kernel Monte Carlo

Patient specific – derived from patient biodistribution

Perspectives on organ level dosimetry

Lookup table.
One size for all

Organ level dosimetry

Voxel level dosimetry
(in house or commercial software)

- Patient specific
- Integrates millions of points of data (image voxels)
- Can be accomplished with accessible (free) software
- Flexible to accommodate variations in equipment, resources
- Relatively easier to standardize
- Models systems beyond voxels (blood, bone marrow, whole body, tumor)
- Output organ level dose (current standard for contextualizing dosimetry)

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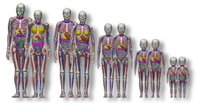
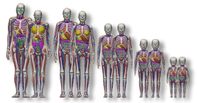


Perspectives on standardization

- Not all dose is equal
  - Equipment, expertise, resources, and values differ across the global healthcare community
  - Community is best served if we account for these differences
- 20th century models of innovation are often siloed. 20th century dosimetry practices have failed to establish footing in clinical workflows
- 21st century brings new opportunities to standardize dosimetry across the community.
- We have examples of simple, standardized dosimetry protocols working in close fields: Y90 microspheres
  - Accessible
  - Treatment has been a gateway for:
    - Innovation in image based dosimetry,
    - Nuclear medical physicists working and billing for dosimetry
  - Provides example of simple models evolving (BSA -> partition)



Perspectives on standardization

- RPT-TEC models should be be derived from diverse data from multiple regions/centers if it is to be relevant across regions/centers
- Can follow trial designs to collect data from multiple centers and process with central workflow

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Closing remarks

- MIRDsoft tools are created in an effort to create easy to use, easily accessible, vetted software for dosimetry community.
  - Inspired by existing tools (Olinda, IDAC, Nukfit, ….)
  - Vetted and endorsed by the SNMMI MIRD committee
- MIRDcalc and MIRDfit provide (new) option for integrating uncertainty into dosimetry calculations
  - We have the tools, how best to use them (ie input)
- MIRDcalc pamphlet coming soon (final stages of submission)
  - Pamphlet + benchmark/software comparison compendium with 1000+ cases
- MIRDcalc not currently FDA approved

- MIRDsoft.org and/or MIRDsoft.org model can be used for collecting dosimetry/adverse event data in the future…

Acknowledgements

- **MSKCC MIRDcalc team**
  - Lukas Carter
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  - Yitian Wang
  - Laura Dinwinddie
  - Robert Dawson
  - Cameron Kofler
  - Jared Baggett
  - Wyatt Smither
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  - John Humm (MSK)
  - Joe O'Donoghue (MSK)
  - Daniel Lafontaine (MSK)
  - Jazmin Schwartz (MSK)
  - Simone Krebs (MSK)
  - Heiko Schoder (MSK)
  - Derek Jokisch (Marion)
  - Roger Howell (Rutgers)
  - Darrell Fisher (Versant)
  - George Sgouros (Hopkins)
  - Bill Erwin (MD Anderson)
  - Bud Wendt (MD Anderson)
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  - NIH U01 EB028234 (Kesner/Bolch)
  - NIH P30 CA008748 (MSK)

Overview of internal dosimetry protocols

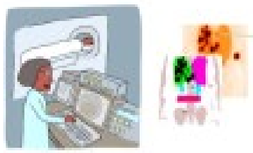
Data Collection

Biodistribution Summary

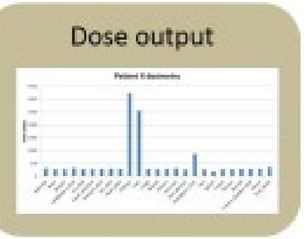
Radiation Dose Calculations

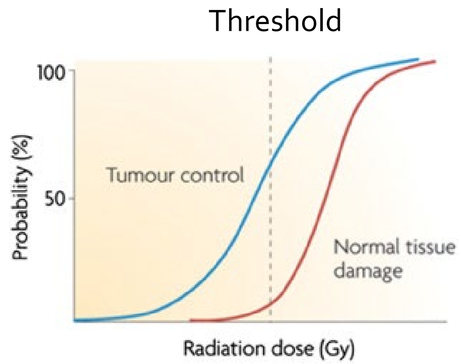
Dose Reporting

Dose contextualizing



Modelling (TIACs)	Assumptions	Dosimetry calculation
curve fitting model/method	phantom model	calculation method
bladder voiding model	mass phantom-patient extrapolation	software
integration limits	choice for interpolating blood, urine, remainder	weighting factors
	2D/3D/4D (interspecies) interpolation	reporting

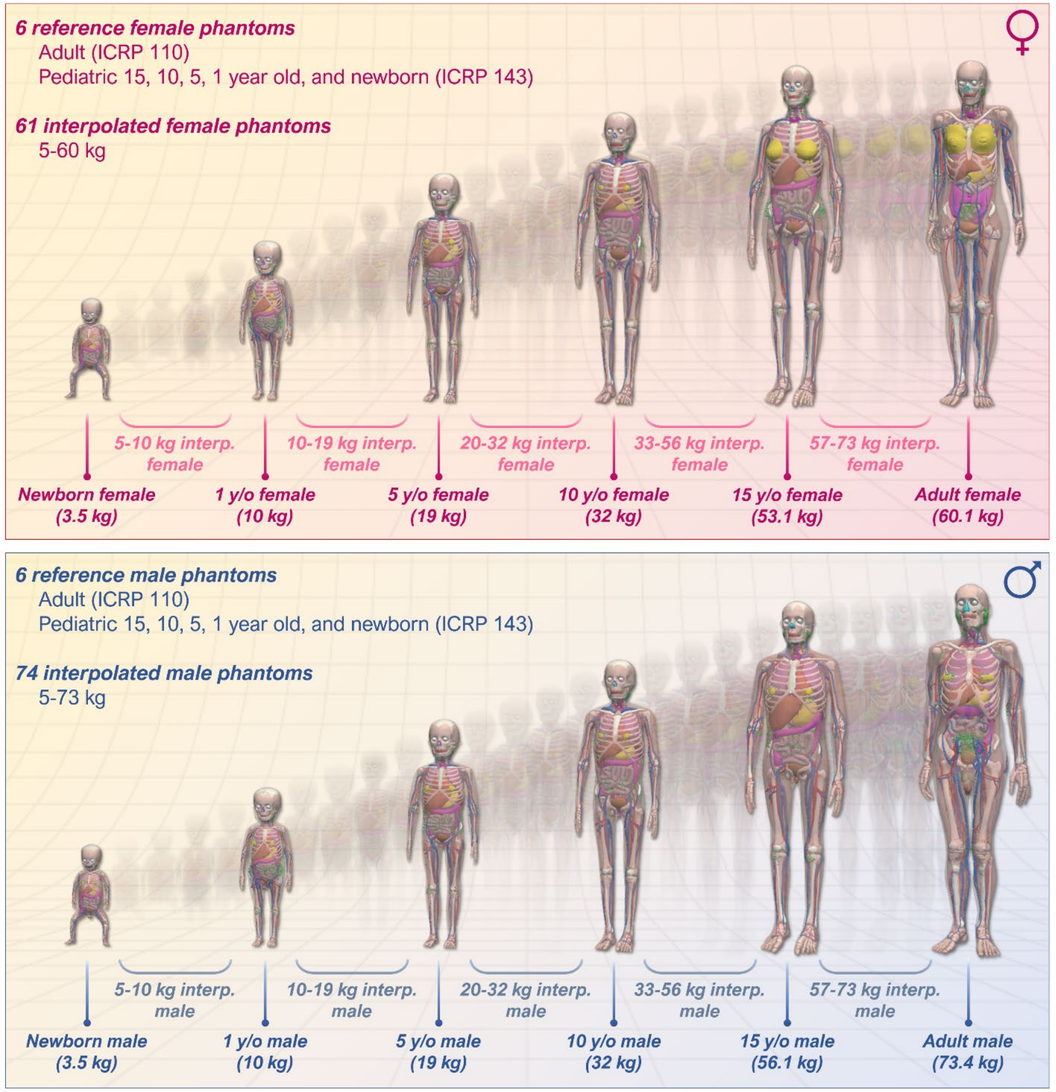




Biodistribution summary is a common point in dosimetry calculation and protocols

MIRDcalc phantoms

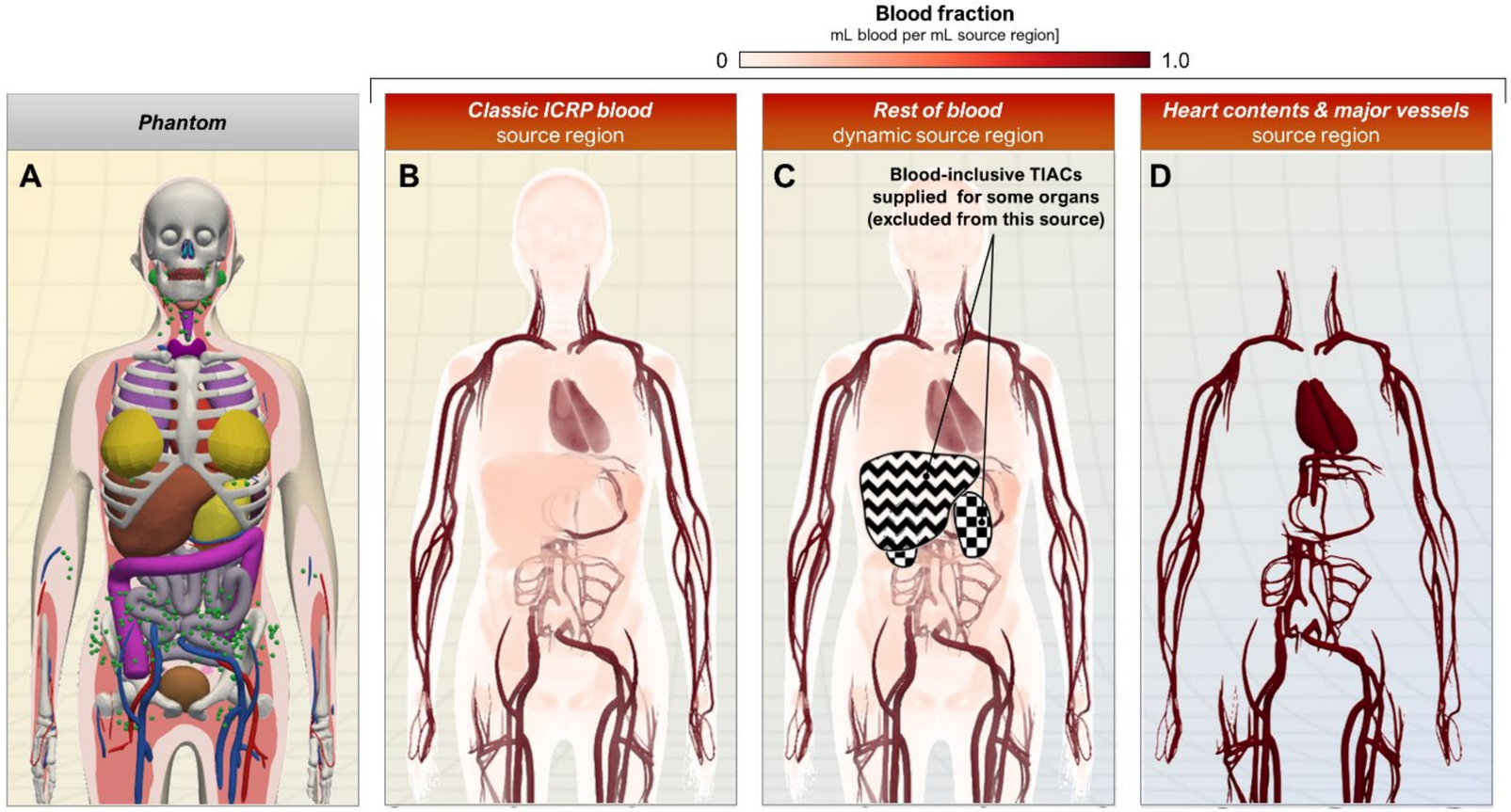
- Phantom models
  - ICRP reference phantoms (reports 110 and 143)
    - Newborn (m/f)
    - 1 year-old (m/f)
    - 5 year-old (m/f)
    - 10 year old (m/f)
    - 15 year old (m/f)
    - Adult (m/f)
  - Additional source regions generated
    - Heart contents
    - Major blood vessels
  - MIRDcalc interpolation feature
    - Organ masses interpolated linearly relative to whole body mass
    - S values interpolated log-log



Visualization of MIRDcalc phantom library

MIRDcalc blood model

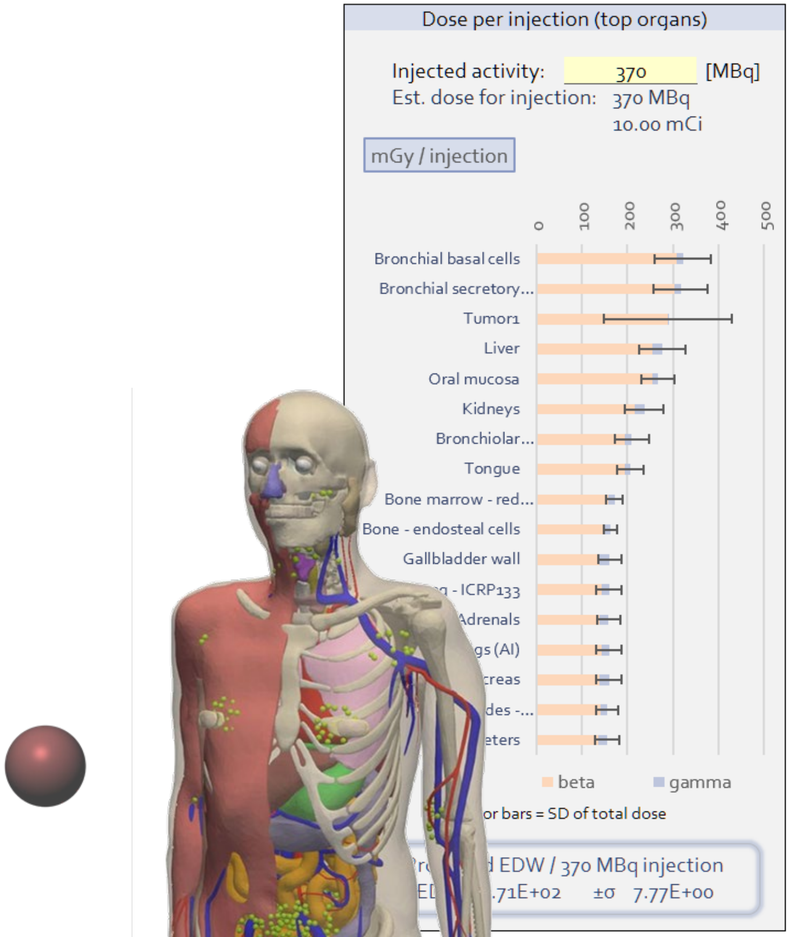
- User can use multiple blood source regions



MIRDcalc blood source options

MIRDcalc tumor dosimetry

- MIRDcalc tumor dose model
  - Spherical tumor model
    - Olguin et. al, PMB, 2020
  - Model parameters
    - Sphere volume (optional uncertainty)
    - TIAC (optional uncertainty)
    - Tissue composition (bone/soft tissue)
  - Dosimetry semi-integrated with organ dosimetry
    - Self dose (no cross dose)
    - Integrated TIAC accounting



MIRDcalc validation

- Example comparison with other software
  - Fluorodeoxyglucose (18F-FDG), ICRP 128 distribution