

RPT-TEC

Sept 2022

MIRDcalc and MIRDfit: MIRD tools for pharmokinetic modelling and dosimetry

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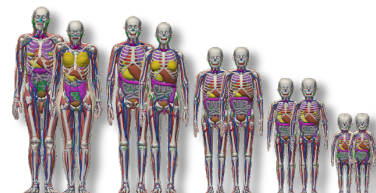
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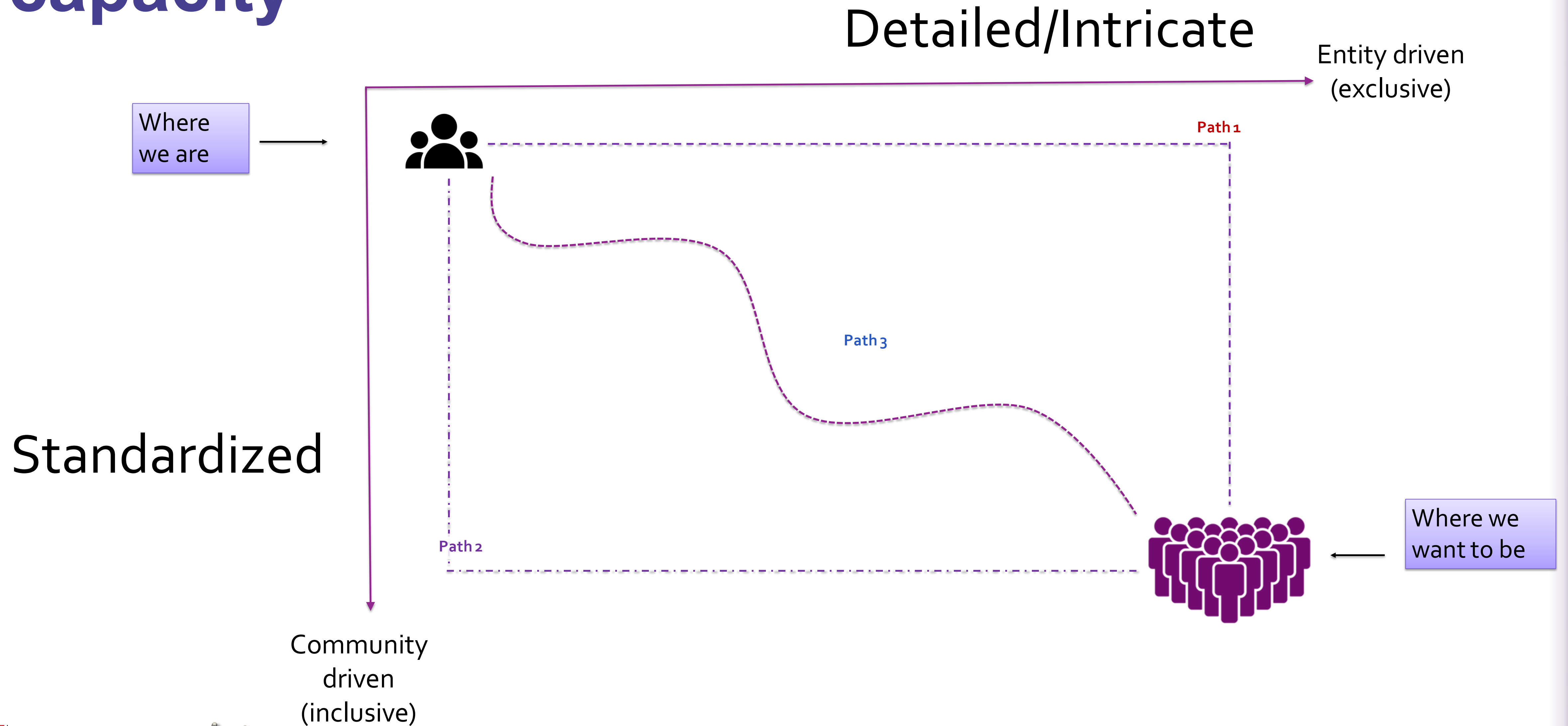


Presentation overview

- 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

MIRD SCHEMA ORGAN LEVEL DOSIMETRY SPREADSHEET

MIRDCalc_v1.0-Genesis (cert) **Biodistribution Model INPUT** MIRDcalc MIRDsoft **Dosimetry Estimate OUTPUT**

Element: Ho, Ir, La, Lu, Mg, In, K, Lu, Lu-176, Lu-177, Sex: Female, Male, Phantom: 57 kg (interp), 58 kg (interp), 59 kg (interp), subject ID: Lu-177 test patient

Source organs			Target organs			
Organ name	Time integrated activity coefficients* [hours]	σ (Std. Dev.) (optional) [hours]	Organ name	Patient organ mass (optional) [grams]	σ (Std. Dev.) (optional) [grams]	Calculation organ Mass [grams]
Adipose tissue			Adipose tissue			2.07E+04
Adrenals			Bone marrow - red (1.10E+03
Bone - cortical volu			Brain			1.35E+03
Bone - trabecular vc			Breast tissue			4.44E+02
Brain			Colon - ICRP133			3.04E+00
Breast tissue			Esophagus			8.86E-02
Cartilage			Extrathoracic regio			4.04E-01
Esophagus wall			Eye lens			4.00E-01
Heart wall			Gallbladder wall			8.11E+00
@ Kidneys	1.82	1%	Heart wall			2.80E+02
@ Liver	7.09	5%	Kidneys	2020	10	3.41E+02
Lungs			Liver			2.02E+03
Major blood vessels			Lymphatic nodes - l			1.47E+02
Muscle			Muscle			1.78E+04
Oral mucosa			Oral mucosa			2.35E+01
Pancreas			Ovaries			1.09E+01
@ Rest of blood	0.238	0%	Pancreas			1.37E+02
@ Rest of parenchym	55.78	24%	Skin			2.24E+03
Salivary glands			Small intestine			3.46E+00
@ Spleen	1.8	1%	Spleen			1.85E+02
Thymus			Stomach			5.77E-01
Thyroid			Thyroid			1.78E+01
@ Tumor1_300cc_10c	5.4	3%	Tongue			6.03E+01
@ Tumor2_28cc_50%	0.8	0%	Urinary bladder wall			3.93E+01
Urinary bladder con						
Rest of body			Whole body	58.1 Kg		
Rest of body mass: 54.8 Kg						
Organ model (S value) uncertainty		20%				
(selected error propagated into calcs)						
Waste						

Total TIAC entered into table: 72.93
Total TIAC required to account for 100% emissions: 230.15
% theoretical activity accounted: 32%

Estimated dosimetry (absorbed dose) - 37/50 displayed here

Organ	Abs Dose [mGy / MBq]	Uncertainty (SD) [mGy / MBq]
Adipose tissue	9.81E-02	1.83E-02
Adrenals	9.84E-02	1.58E-02
Bone - endosteal cells	9.11E-02	9.38E-03
Bone marrow - red (act	9.74E-02	1.10E-02
Brain	9.66E-02	1.82E-02
Breast tissue	9.54E-02	1.81E-02
Bronchial basal cells	0.00E+00	0.00E+00
Colon - ICRP133	0.00E+00	0.00E+00
Esophagus	8.17E-02	1.43E-02
Extrathoracic region -	5.25E-02	7.52E-03
Eye lens	0.00E+00	0.00E+00
Gallbladder wall	1.08E-01	1.64E-02
Heart wall	8.96E-02	1.61E-02
Kidneys	4.73E-01	1.22E-01
Liver	3.18E-01	6.35E-02
Lung - ICRP133	5.51E-02	9.40E-03
Lymphatic nodes - ICR	9.55E-02	1.38E-02
Muscle	9.81E-02	1.82E-02
Oral mucosa	1.29E-01	1.82E-02
Ovaries	9.55E-02	1.73E-02
Pancreas	9.36E-02	1.59E-02
Pituitary gland	9.67E-02	1.71E-02
Prostate	0.00E+00	0.00E+00
Salivary glands	9.76E-02	1.78E-02
Skin	8.97E-02	1.63E-02
Small intestine	7.67E-02	1.33E-02
Spleen	8.47E-01	1.65E-01
Stomach	7.67E-02	1.25E-02
Testes	0.00E+00	0.00E+00
Thymus	9.64E-02	1.77E-02
Thyroid	8.88E-02	1.63E-02
Tongue	1.11E-01	1.82E-02
Tumor1_300cc_100%5	1.53E+00	2.76E-02
Tumor2_28cc_50%5T	1.69E+00	2.06E-01
Urinary bladder wall	9.48E-02	1.73E-02
Uterus	9.85E-02	1.80E-02
Whole body target	1.12E-01	1.09E-02

Detriment Weighted & Effective Dose ¹⁰

MIRDcalc	[mSv / MBq]	σ [mSv / MBq]
EDW Detr Wght Dose	9.52E-02	4.85E-03
E Effective Dose	9.57E-02	4.50E-03

Dose per injection (top organs)

Injected activity: 370 [MBq]
Est. dose for injection: 370 MBq
10.00 mCi

mGy / injection


Projected EDW / 370 MBq injection
EDW: 3.54E+01 ±σ 1.67E+00

Internal dosimetry spreadsheet



Data base with S values (protected, versioned)

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

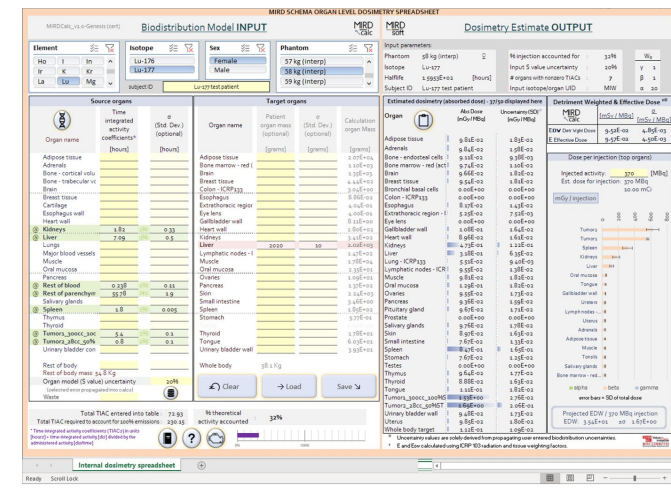


Dose calculation Quality control Error calculation

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
- **Uncertainty propagation**
- 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

The screenshot displays the MIRDcalc software interface, divided into two main sections: 'Biodistribution Model INPUT' and 'Dosimetry Estimate OUTPUT'.

Biodistribution Model INPUT:

- Element:** Lu (Lanthanum)
- Isotope:** Lu-176, Lu-177
- Sex:** Female
- Phantom:** 52 kg (interp)
- subject ID:** Lu-177 test patient

Source organs (Time integrated activity coefficients σ):

Organ name	Time integrated activity coefficients* [hours]	σ (Std. Dev.) (optional) [hours]
Adipose tissue		
Adrenals		
Bone - cortical volur		
Bone - trabecular vo		
Brain		
Breast tissue		
Cartilage		
Esophagus wall		
Heart wall		
@ Kidneys	2.82	0.33
@ Liver	7.09	0.5
Lungs		
Major blood vessels		
Muscle		
Oral mucosa		
Pancreas		
@ Rest of blood	0.238	0.11
@ Rest of parenchym.	55.78	1.9
Salivary glands		
@ Spleen	1.8	0.005
Thymus		
Thyroid		
@ Tumor1_300cc_100%	5.4	0.1
@ Tumor2_28cc_50%5	0.8	0.1
Urinary bladder cont		
@ Rest of body	6.75	2
Rest of body mass: 49.1 Kg		
Organ model (S value) uncertainty		20%
Waste		

Target organs:

Organ name	Patient organ mass (optional) [grams]	σ (Std. Dev.) (optional) [grams]	Calculation organ Mass [grams]
Adipose tissue			1.75E+04
Bone marrow - red (t			1.15E+03
Brain			1.35E+03
Breast tissue			2.53E+02
Colon - ICRP133			3.01E+00
Esophagus			8.87E-02
Extrathoracic region			3.92E-01
Eye lens			3.98E-01
Gallbladder wall			7.61E+00
Heart wall			2.47E+02
Kidneys			2.98E+02
Liver	2000	0.2	2.00E+03
Lymphatic nodes - (l			1.35E+02
Muscle			1.71E+04
Oral mucosa			2.55E+01
Ovaries			6.26E+00
Pancreas			1.16E+02
Skin			1.73E+03
Small intestine			3.46E+00
Spleen			1.76E+02
Stomach			4.74E-01
Testes			0.00E+00
Thyroid			1.33E+01
Tongue			5.52E+01
Urinary bladder wall			3.51E+01
Whole body	52.1 Kg		

Dosimetry Estimate OUTPUT:

Input parameters: Phantom 52 kg (interp), Isotope Lu-177, Half-life 1.5953E+02 [hours], Subject ID Lu-177 test patient.

Estimated dosimetry (absorbed dose) - 37/50 displayed here:

Organ	Abs Dose [mGy / MBq]	Uncertainty (SD) [mGy / MBq]
Adipose tissue	1.23E-01	2.37E-02
Adrenals	1.17E-01	2.08E-02
Bone - endosteal cells	1.24E-01	1.32E-02
Bone marrow - red (act	1.32E-01	1.53E-02
Brain	1.28E-01	2.34E-02
Breast tissue	1.16E-01	2.27E-02
Bronchial basal cells	0.00E+00	0.00E+00
Colon - ICRP133	1.03E-01	1.17E-02
Esophagus	1.07E-01	1.97E-02
Extrathoracic region -	1.08E-01	1.24E-02
Eye lens	1.20E-01	2.24E-02
Gallbladder wall	1.19E-01	2.01E-02
Heart wall	1.14E-01	2.12E-02
Kidneys	8.28E-01	1.86E-01
Liver	3.23E-01	6.42E-02
Lung - ICRP133	7.25E-02	1.36E-02
Lymphatic nodes - ICR	1.20E-01	1.78E-02
Muscle	1.20E-01	2.33E-02
Oral mucosa	1.60E-01	2.14E-02
Tonsils	1.16E-01	2.24E-02
Pancreas	1.17E-01	2.11E-02
Pituitary gland	1.27E-01	2.20E-02
Prostate	0.00E+00	0.00E+00
Salivary glands	1.38E-01	2.27E-02
Skin	1.16E-01	2.07E-02
Small intestine	9.66E-02	1.80E-02
Spleen	8.90E-01	1.73E-01
Stomach	9.25E-02	1.65E-02
Testes	0.00E+00	0.00E+00
Thymus	1.19E-01	2.27E-02
Thyroid	1.14E-01	2.14E-02
Tongue	1.32E-01	2.29E-02
Tumor1_300cc_100%5	1.53E+00	5.68E-02
Tumor2_28cc_50%5T	1.69E+00	2.13E-01
Urinary bladder wall	1.16E-01	2.22E-02
Uterus	1.17E-01	2.27E-02
Whole body target	1.40E-01	1.40E-02

Detriment Weighted & Effective Dose σ :

MIRD Calc	[mSv / MBq]	σ [mSv / MBq]
EDW Detr Wght Dose	1.31E-01	6.11E-03
E Effective Dose	1.27E-01	6.07E-03

Dose per injection (top organs):

Injected activity: 370 [MBq]
Est. dose for injection: 370 MBq, 10.00 mCi

Bar chart showing dose per injection (mGy / injection) for various organs. The y-axis ranges from 0 to 800 mGy. The x-axis lists organs: Tumor2, Tumor1, Spleen, Kidneys, Liver, Lymph nodes, Oral mucosa, Tonsils, Lymph nodes, Salivary glands, Bone marrow, Tongue, Brain, Pituitary gland, Bone - endosteal, Adipose tissue, Eye lens.

Projected EDW / 370 MBq injection: EDW: 4.70E+01 \pm 2.25E+00

TIAC σ_{TIAC}

Absorbed dose $\pm \sigma_{Dose}$



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

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GUIDELINES



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

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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.

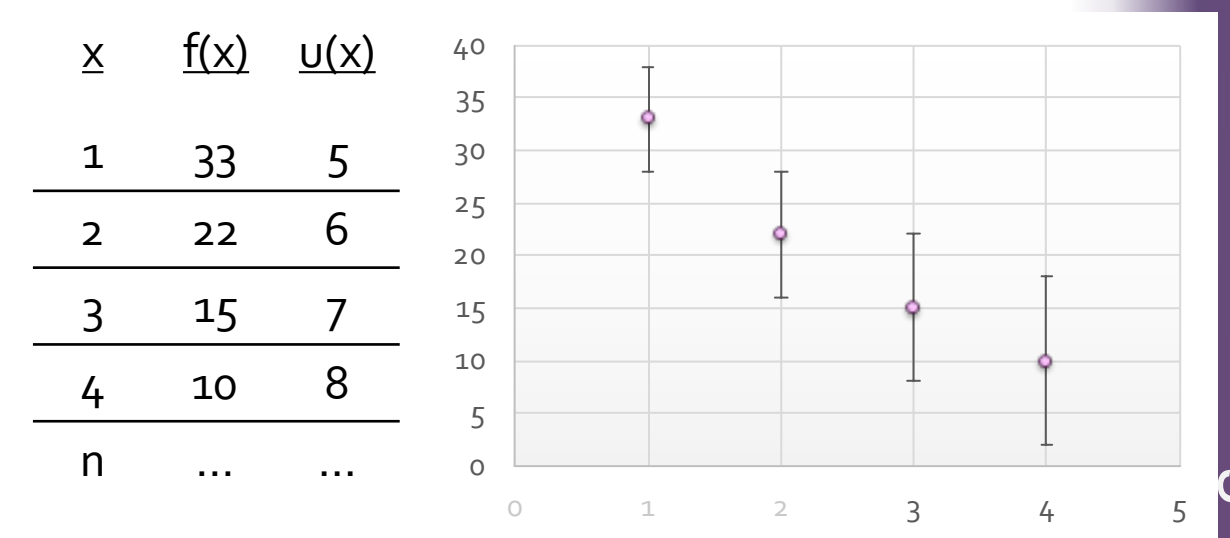
This guidance document is intended to assist practitioners in providing appropriate nuclear medicine care for patients. The rules provided in the document are not inflexible or requirements of practice and are not

Introduction

Internal dosimetry following the administration of radio-labelled pharmaceuticals for diagnostic and therapeutic purposes were also < 1% (standard error between 0.4% and 3%). 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.



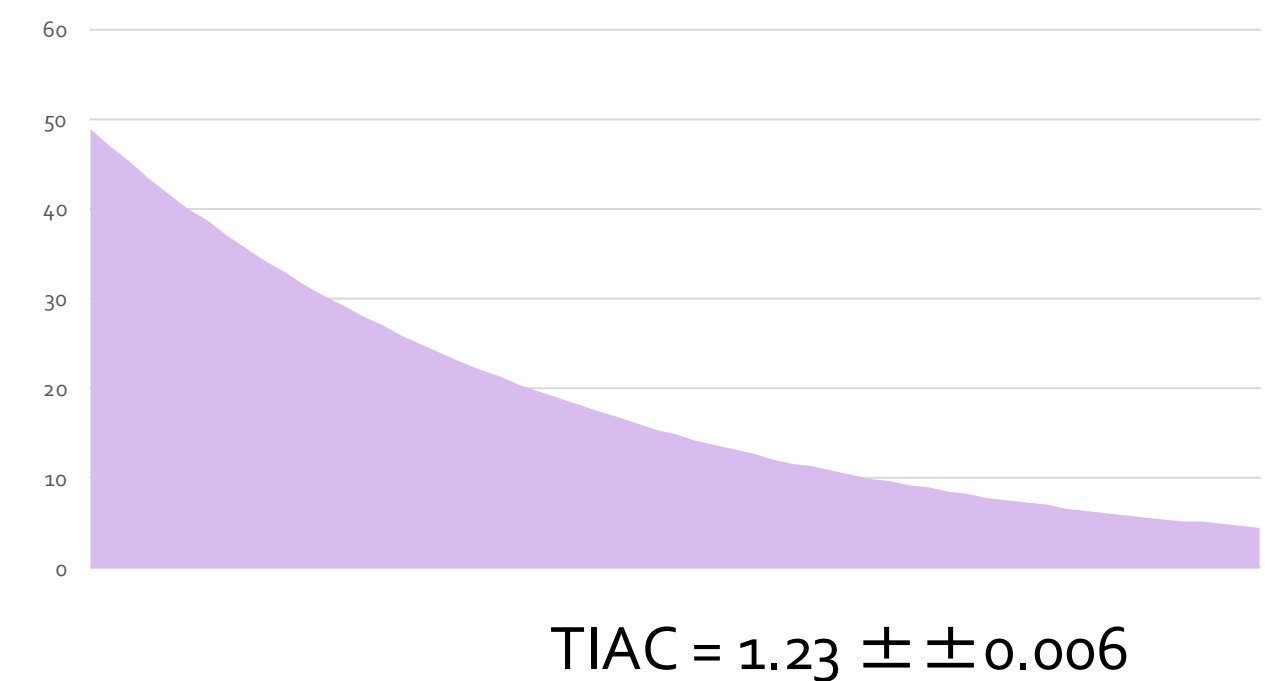
Review of curve fitting procedures



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

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



Variance-covariance table

	b0	b1	b2
b0	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 Absolute	SD for Y N	SD for X's N	Observations 4	Parameters 3	Observations 1	Parameters 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	Ok				
R	Low. CI(.95)	Up. CI(.95)	R^2	R^2 adj			
0.999978044	0.9858773	0.99999966	0.999956088	0.999868264			
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 (.95)				
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 through							
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)							
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							
HQc (Adjusted Hannan Quinn Criterion)							
BIC (SBC-Schwarz Bayesian Criterion) -7.217823318							
BICc (SBCc-Adjusted Schwarz Bayesian 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 Ratic		
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	dF #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 Model Residual Sum Of Squares	Full Model dF	#DIV/0!	#NUM!	#DIV/0!	
0.232728617	1	0.232728617	1				



MIRDfit interface

+
New case

Documentation

Study setup ?

Subject ID (optional)
89Zr-peptide

Notes (optional)
Adult male reference dosimetry estimate

Select an elem...

Se	Si	Sm	Sn
Sr	Ta	Tb	Tc
Te	Th	Ti	Tl
Tm	U	V	W
Xe	Y	Yb	Zn
Zr			

Select an isot...

- Zr-85
- Zr-86
- Zr-87
- Zr-88
- Zr-89
- Zr-89m
- Zr-93
- Zr-95
- Zr-97

Select an phan...

- ICRP 00 Newborn fe...
- ICRP 00 Newborn m...
- ICRP 01 year old fem...
- ICRP 01 year old male
- ICRP 05 year old fem...
- ICRP 05 year old male
- ICRP 10 year old fem...
- ICRP 10 year old male
- ICRP 15 year old fem...
- ICRP 15 year old male
- ICRP Adult Female
- ICRP Adult Male

Biodistribution input ?

Biodistribution toolbox Viewer

Select a source region

- Adrenals
- Alveolar-interstitial (sub lungs)
- Blood (classic ICRP)
- Bone - cortical surface (sub volume)***
- Bone - cortical volume
- Bone - trabecular surfaces (sub volumes)
- Bone - trabecular volumes
- Bone marrow - red (active)***
- Bone marrow - yellow (inactive)
- Brain
- Breast tissue

SIA entries are:

- Biological uptake/clearance
- Effective uptake/clearance

Format for input variances of SIA data (weighting scheme):

- Standard deviation
- Relative standard deviation (coefficient of variation)
- Weight (direct entry)

Clear time
Clear %IA
Unshelve

Time, t [h]	%IA	RSD
4	6.889687881	0.037267081
24	2.079783333	0.086206897
48	0.638076123	0.045454545
72	0.234590016	0.1
120	0.030694386	0.25

Input OK - ready to fit...

Trapezoidal integration ?

Trapezoidal fitting toolbox

Nose: (t0 to t1)

- %IA(t) = 0
- %IA(t) = %ID(t0)
- %IA(t) = Organ blood content
- Linear
- Exponential extrapolation (t1, t2)
- Exponential extrapolation (phys to t1)
- Excluded (no extrapolation)

Tail: (tn to tD)

- Exponential extrapolation (phys to inf)
- Exponential extrapolation (tn-1, tn)
- Linear extrapolation to 10 phys half-lives
- Linear extrapolation (tn-1, tn)
- Excluded (no extrapolation)

Summary output

TIAC 1.67E+00 [h]

Actions

Send to shelf

Input OK - ready to fit...

Regression-based integration ?

Regression toolbox

Fit all selected (quickfit)

Reset all

Regression model filter

- Biexponential (%IA = %blood at t = 0)
- Biexponential (%IA = 100 at t = 0)
- Biexponential (rapid clearance & slow clearance phases)
- Biexponential (rapid clearance phase & physical decay)
- Biexponential (uptake & clearance phases)
- Monoexponential
- Monoexponential (physical decay only)

Summary output

TIAC	3.87E-01	[h]
TIAC Std. Err.	2.04E-02	[h]
TIAC:WCV	5.3%	
R ²	0.1449	
AICc	30.27	
W AICc	0.0%	
T model/rejected	0.23	
Alerts	None.	✔

Actions

Send to shelf

Fit (re-fit) this model

Reset/reject this model

Input OK - ready to fit...

Monoexponential (physical decay only)

%IA(t) = A₁e^{-λ_{phys}t}

Fit setup

Parameter A₁
Initial guess 6.889688

Fit results

Parameter A₁
Value 0.34188
Std. Err. 0.018

Summary output

TIAC	1.57E+00	[h]
TIAC Std. Err.	4.31E-02	[h]
TIAC:WCV	2.7%	
R ²	0.9911	
AICc	14.13	
W AICc	100.0%	
T model/rejected	0.94	
Alerts	None.	✔

Actions

Send to shelf

Fit (re-fit) this model

Reset/reject this model



MIRDfit interface

The screenshot displays the MIRDfit software interface with several key components:

- Study setup:** Includes fields for Subject ID (optional) and Notes (optional).
- Element Selection:** A menu to "Select an element" with a grid of elements (Se, Si, Sm, Sn, Sr, Ta, Tb, Tc, Te, Th, Ti, Tl, Tm, U, V, W, Xe, Y, Yb, Zn, Zr).
- Isotope Selection:** A menu to "Select an isotope" listing isotopes from Zr-85 to Zr-95.
- Phantom Selection:** A menu to "Select a phantom" listing various ICRP models (e.g., ICRP 00 Newborn female, ICRP 01 year old female, ICRP 05 year old female, ICRP 10 year old female, ICRP 15 year old female, ICRP Adult Female, ICRP Adult Male).
- Data Table:** A table with columns for Time, t [h], %IA, and RSD.

Time, t [h]	%IA	RSD
4	6.889687881	0.037267081
24	2.07978333	0.086206897
48	0.638076123	0.045454545
72	0.234590016	0.1
120	0.030694386	0.25
- Model Parameters:** Shows parameters for a Monoexponential model, including A1 and lambda1 values and standard errors.
- Summary Output:** Displays calculated values for TIAC, TIAC Std. Err., TIAC %CY, and other metrics.
- Graphs:** Plots of %IA (effective) vs Time [h] and Weighted residual vs Time [h].
- Buttons:** Includes "Fit all selected (quickfit)", "Reset all", "Send to shelf", "Fit (re-fit) this model", and "Reset/reject this model".



MIRDfit interface

The screenshot displays the MIRDfit software interface, which is used for internal radiation dose calculations. The interface is divided into several functional areas:

- Study setup:** Includes fields for Subject ID (optional) and Notes (optional).
- Biodistribution input:** Features a 'Biodistribution toolbox' with a 'Select a source region' dropdown menu. A callout box provides a detailed view of this menu, listing regions such as Adrenals, Alveolar-interstitial (sub lungs), Blood (classic ICRP), Bone - cortical surface (sub volume)***, Bone - cortical volume, Bone - trabecular surfaces (sub volumes), Bone - trabecular volumes, Bone marrow - red (active)***, Bone marrow - yellow (inactive), Brain, and React tissue.
- Input Variance Selection:** A callout box shows options for '%IA entries are:' (Biological uptake/clearance, Effective uptake/clearance) and 'Format for input variances of %IA data (weighting scheme):' (Standard deviation, Relative standard deviation (coefficient of variation), Weight (direct entry)).
- Data Table:** A table with columns for Time, t [h], %IA, and RSD. The data points are:

Time, t [h]	%IA	RSD
4	6.889687881	0.037267081
24	2.07978333	0.086206897
48	0.638076123	0.045454545
72	0.234590016	0.1
120	0.030694386	0.25
- Source region viewer:** A callout box shows a 3D anatomical model of a human skeleton with a specific region highlighted. The model is labeled 'ICRP Adult Male'.
- Summary output:** Displays various metrics including TIAC, TIAC Std. Err., TIAC:NCY, R', AICc, W enc, T subfit/residual, and Alerts.
- Fit and Model Management:** Includes buttons for 'Fit (re-fit) this model' and 'Reset/reject this model'.



MIRDfit interface

Trapezoidal fitting toolbox

Nose: (t0 to t1)

- %IA(0) = 0
- %IA(0) = %ID(t0)
- %IA(0) = Organ blood content
- Linear
- Exponential extrapolation (t1, t2)
- Exponential extrapolation (phys to t1)
- Excluded (no extrapolation)

Tail: (tn to tD)

- Exponential extrapolation (phys to inf)
- Exponential extrapolation (tn-1, tn)
- Linear extrapolation to 10 phys half-lives
- Linear extrapolation (tn-1, tn)
- Excluded (no extrapolation)

Trapezoidal integration

Trapezoidal fitting toolbox

Regression-based integration

Regression toolbox

Fit all selected (quickfit)

Reset all

Regression model filter

- Bisponential (%IA = %blood at t = 0)
- Bisponential (%IA = 100 at t = 0)
- Bisponential (rapid clearance & slow clearance phases)
- Bisponential (rapid clearance phase & physical decay)
- Bisponential (uptake & clearance phases)
- Monoexponential
- Monoexponential (physical decay only)

Monoexponential (physical decay only)

$$%IA(t) = A_1 e^{-\lambda_{phys}t}$$

Parameter A_1
Initial guess: 6.889688

Parameter A_1
Value: 0.34188
Std. Err.: 0.018

TIAC	3.87E-01	[h]
TIAC Std. Err.	2.04E-02	[h]
TIAC:CY	5.3%	
R ²	0.1449	
AICc	30.27	
W _{AICc}	0.0%	
T _{model/residual}	0.23	
Alerts	None.	

Monoexponential

$$%IA(t) = A_1 e^{-(\lambda_1 + \lambda_{phys})t}$$

Parameter A_1 λ_1
Initial guess: 6.889688 0.000884

Parameter A_1 λ_1
Value: 8.18102 0.0433
Std. Err.: 0.32601 0.00115

TIAC	1.57E+00	[h]
TIAC Std. Err.	4.31E-02	[h]
TIAC:CY	2.7%	
R ²	0.9911	
AICc	14.13	
W _{AICc}	100.0%	
T _{model/residual}	0.94	
Alerts	None.	

Summary output

TIAC: 5.20E+00 [h]

Nose component: 2.7%
Body component: 63.2%
Tail component: 34.1%



MIRDfit interface

Regression toolbox

Fit all selected (quickfit)

Reset all

Regression model filter

- Biexponential (%IA = %blood at t = 0)
- Biexponential (%IA = 100 at t = 0)
- Biexponential (rapid clearance & slow clearance phases)
- Biexponential (rapid clearance phase & physical decay)**
- Biexponential (uptake & clearance phases)
- Monoexponential
- Monoexponential (physical decay only)

Fit metric comparison legend

R ²	0.7	1.0
AICc	Max	Min
W _{AICc}	Min	Max
f _{model/trapezoidal}	±25%	0%

Monoexponential (physical decay only)

$$%IA(t) = A_1 e^{-\lambda_{phys}t}$$

Fit setup

Parameter A_1
Initial guess: 6.889688

Fit results

Parameter A_1
Value: 0.34188
Std. Err.: 0.018

Summary output

TIAC	3.87E-01	[h]
TIAC Std. Err.	2.04E-02	[h]
TIAC %CV	5.3%	
R ²	0.1449	
AICc	30.27	
W _{AICc}	0.0%	
f _{model/trapezoidal}	0.23	
Alerts	None.	

Actions

Send to shelf

Fit (re-fit) this model

Reset/reject this model

Monoexponential

$$%IA(t) = A_1 e^{-(\lambda_1 + \lambda_{phys})t}$$

Fit setup

Parameter A_1 λ_1
Initial guess: 6.889688 0.000884

Fit results

Parameter A_1 λ_1
Value: 8.18102 0.0433
Std. Err.: 0.32601 0.00115

Summary output

TIAC	1.57E+00	[h]
TIAC Std. Err.	4.31E-02	[h]
TIAC %CV	2.7%	
R ²	0.9911	
AICc	14.13	
W _{AICc}	99.9%	
f _{model/trapezoidal}	0.94	
Alerts	None.	

Actions

Send to shelf

Fit (re-fit) this model

Reset/reject this model

Biexponential (rapid clearance phase & physical decay)

$$%IA(t) = A_1 e^{-(\lambda_1 + \lambda_{phys})t} + A_2 e^{-\lambda_{phys}t}$$

Fit setup

Parameter A_1 λ_1 A_2
Initial guess: 3.444844 0.02652 3.444844

Fit results

Parameter A_1 λ_1 A_2
Value: 8.33385 0.04578 0.06577
Std. Err.: 0.33622 0.00152 0.02451

Summary output

TIAC	1.60E+00	[h]
TIAC Std. Err.	4.44E-02	[h]
TIAC %CV	2.8%	
R ²	0.9964	
AICc	29.56	
W _{AICc}	100.0%	
f _{model/trapezoidal}	0.96	
Alerts	None.	

Actions

Send to shelf

Fit (re-fit) this model

Reset/reject this model

$A_1 e^{-(\lambda_1 + \lambda_{phys})t}$

λ_1 0.000884

λ_1 0.0433

λ_1 0.00115

1.57E+00 [h]

4.31E-02 [h]

2.7%

0.9911

14.13

100.0%

0.94

None.

200

Send to shelf

Fit (re-fit) this model

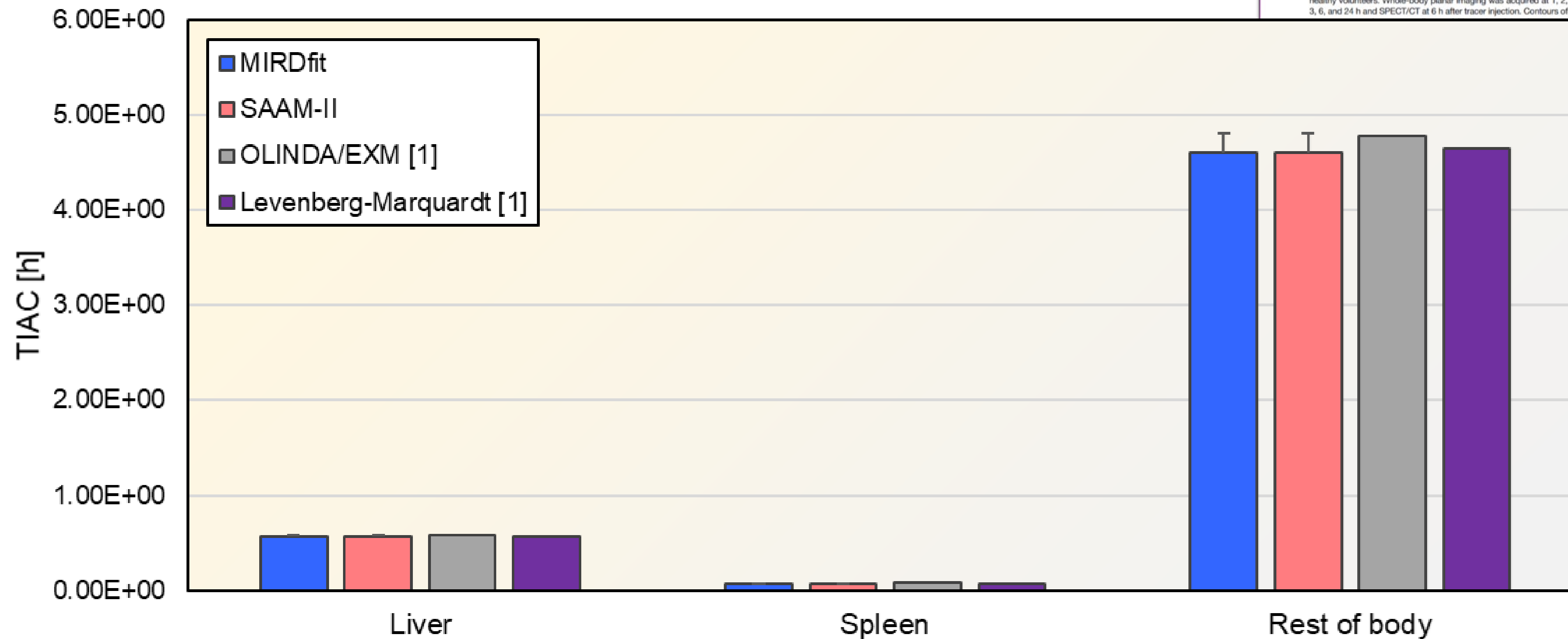
Reset/reject this model



MIRDfit performance

- Within 1% agreement with SAAM-II in testing

Fit results for ^{99m}Tc -PSMA I&S



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

Szabolcs Urbán¹, Catherine Meyer^{2,3}, Magnus Dahlbom^{2,3}, István Farkas¹, Gábor Sipka¹, Zsuzsanna Besenyi¹, Johannes Czernin^{2,4,5}, Jeremie Calais²⁻⁵, and László Pávics^{2,1}

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^{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 metalloproteinase 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 non-pa... 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 prospective 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...



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



Anatomy of a dinner preparation workflow

- Several methods have been proposed

Complexity spectrum



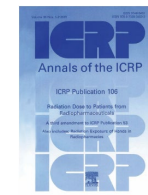
Anatomy of a dosimetry workflow

- 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

- 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)

Voxel level dosimetry
(in house or commercial software)



Presentation overview

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



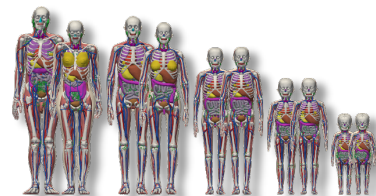
Perspectives on standardization

- 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 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



Presentation overview

- Topics
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 1. MIRDcalc: TIAC->dosimetry
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 - Perspectives on standardization
 - Closing remarks

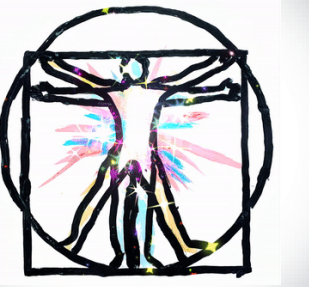


Closing remarks

- 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...



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- Lukas Carter
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- Wes Bolch (MIRDcalc co-PI)
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- Bonnie President
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- Yitian Wang
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- Cameron Kofler
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- Wyatt Smither

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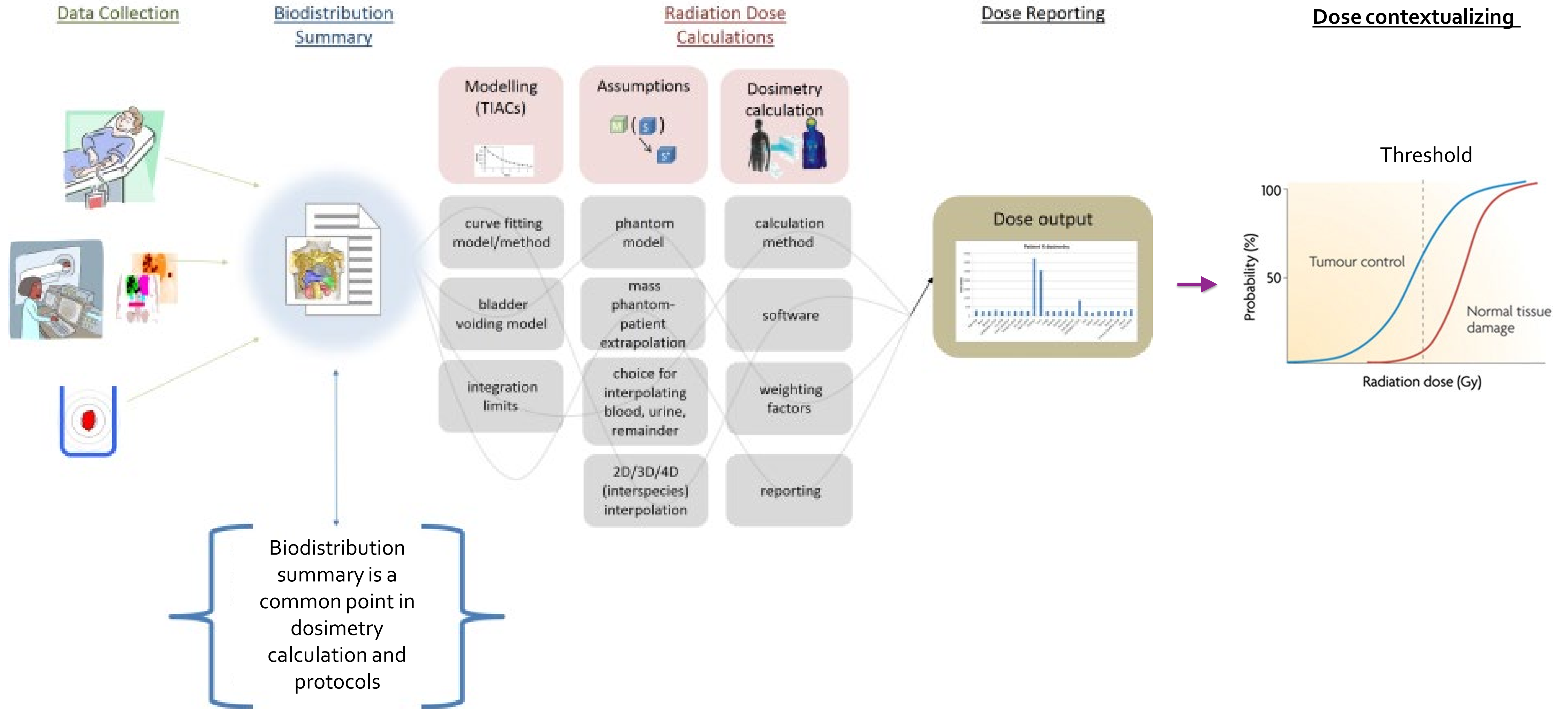
- Pat Zanzonico (MSK)
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- Joe O'Donoghue (MSK)
- Daniel Lafontaine (MSK)
- Jazmin Schwartz (MSK)
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SNMMI MIRD committee

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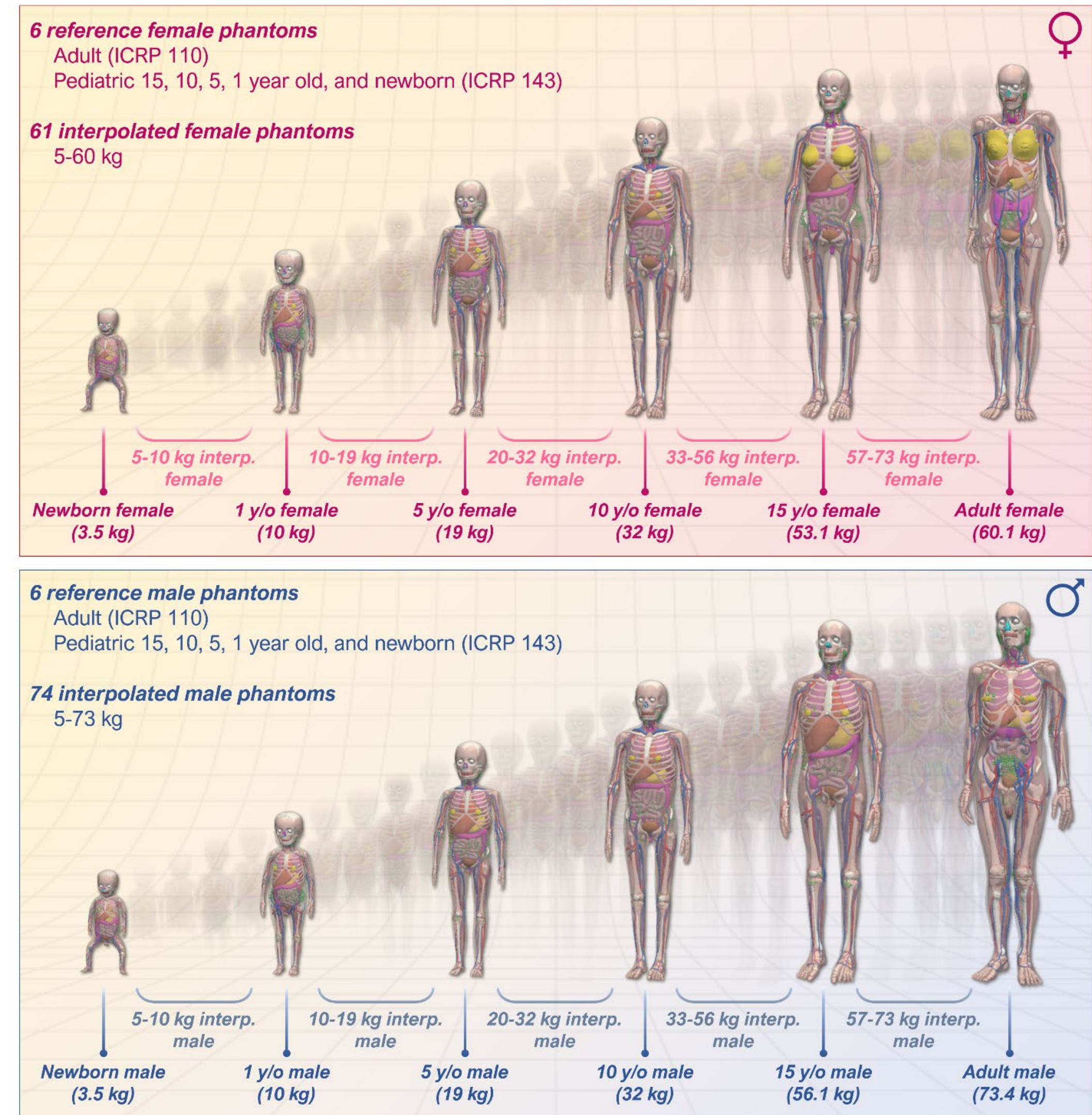
- NIH U01 EB028234 (Kesner/Bolch)
- NIH P30 CA008748 (MSK)

Overview of internal dosimetry protocols



MIRDcalc phantoms

- Phantom models
 - ICRP reference phantoms (reports 110 and 143)
 - Newborn (10) year old (m/f)
 - 1 year-old (15) year old (m/f)
 - 5 year-old (15) year old (m/f)
 - Adult (10) year old (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

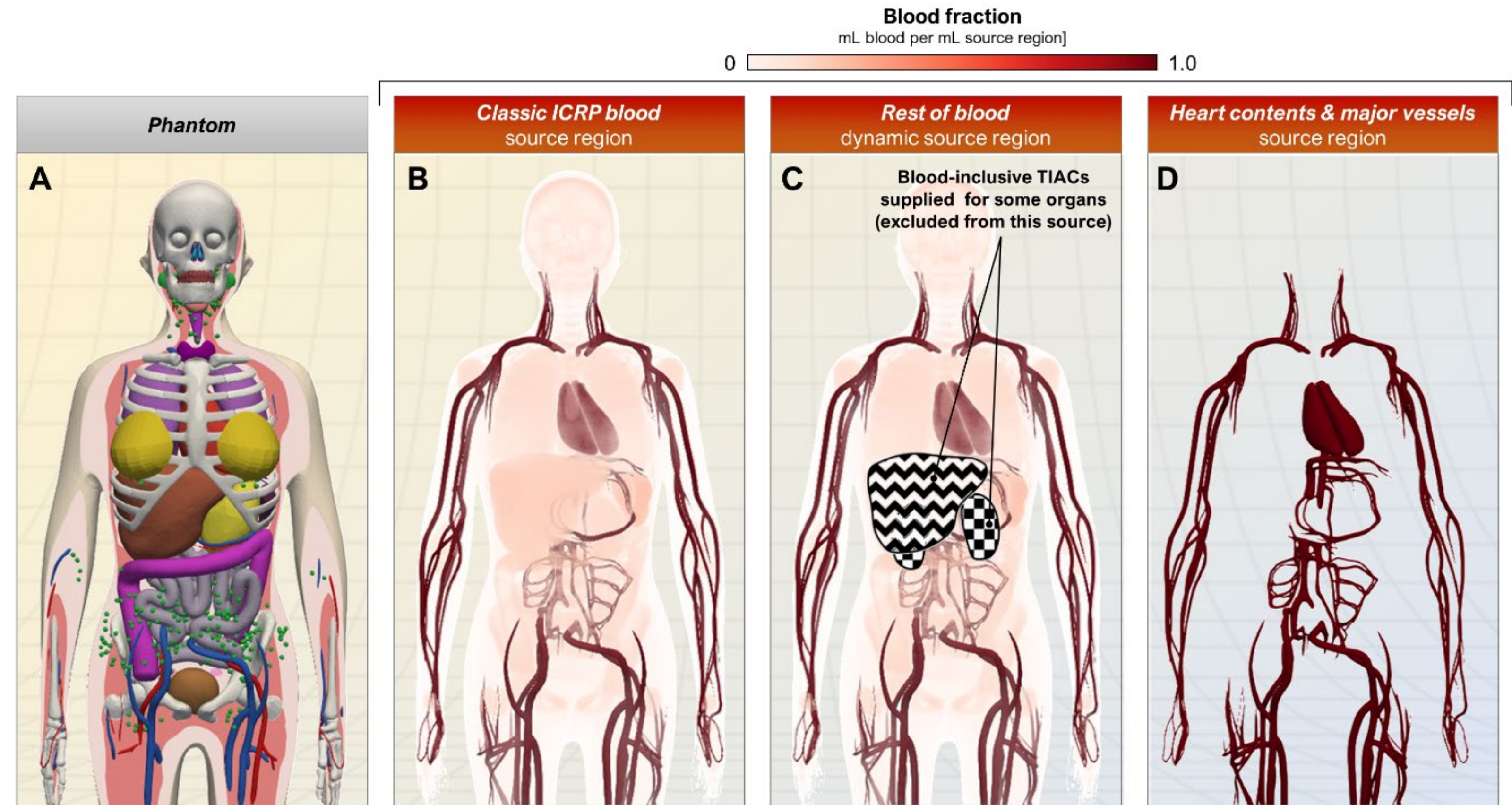


Visualization of MIRDCalc phantom library



MIRDcalc blood model

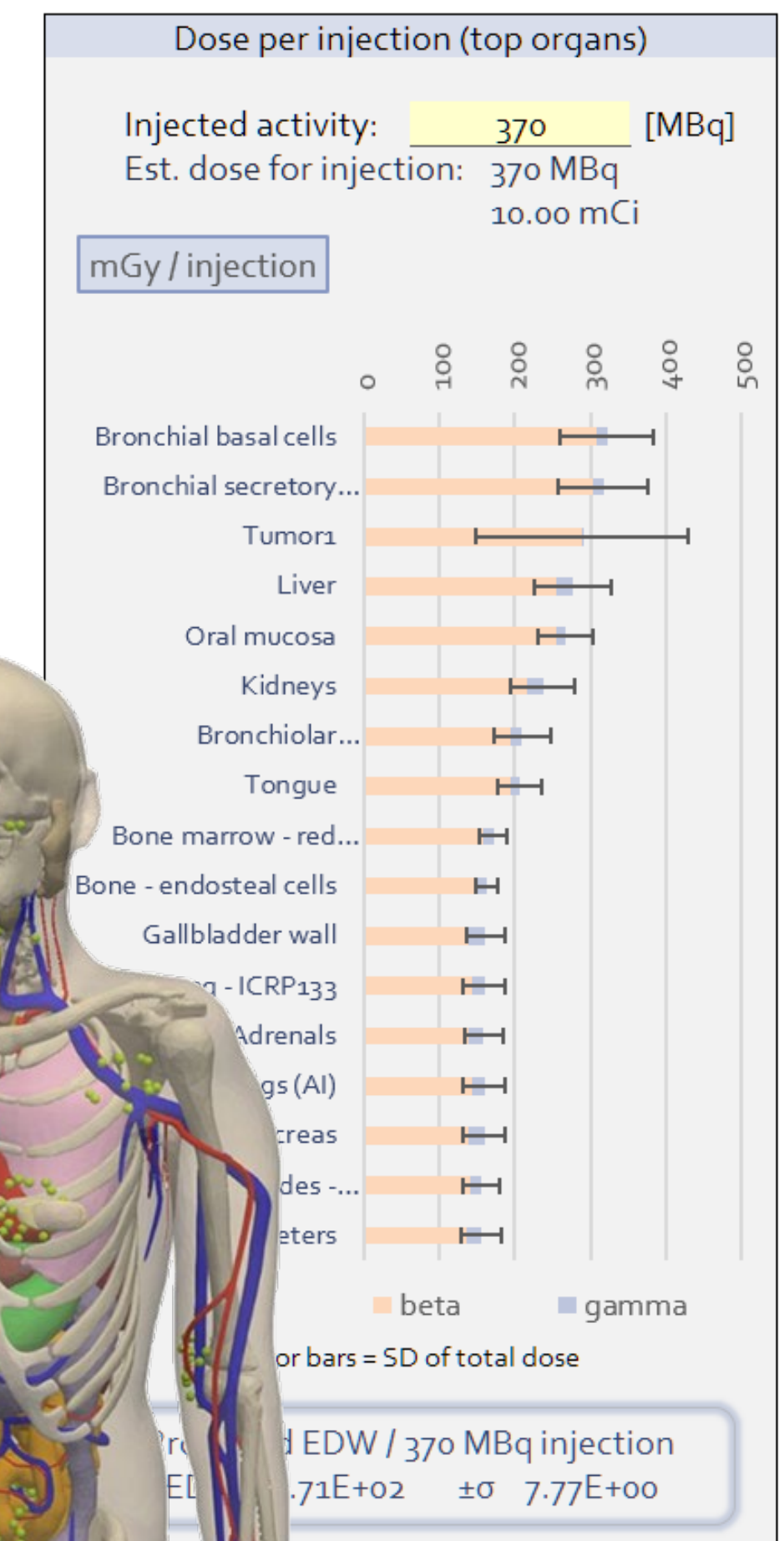
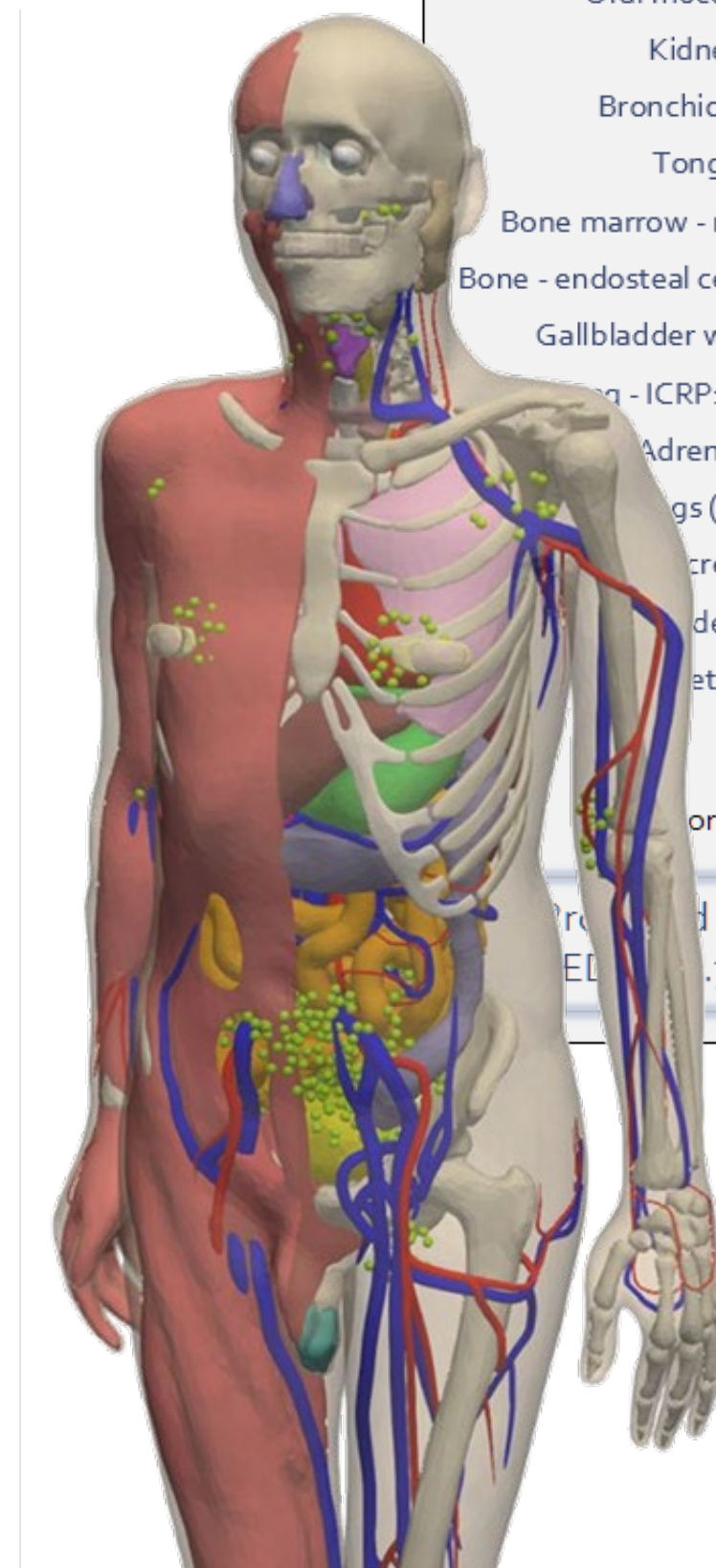
- User can use multiple blood source regions



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

