SOCIETY OF NUCLEAR MEDICINE
AND MOLECULAR IMAGING
MIRD COMMITTEE

MIRD soft

MIRD fit

Biodistribution fitting and integration software

User Manual

Version 1.0

Memorial Sloan Kettering Cancer Center

UF UNIVERSITY of FLORIDA

Legal Notice

1 TABLE OF CONTENTS

2 SOFTWARE OVERVIEW 4

2.1 MIRDfit 4
2.2 Acknowledgements 4

3 INSTALLATION 5

3.1 Downloading 5
3.2 Requirements 5
3.3 Installing 5
3.4 Uninstalling 5
3.5 Troubleshooting 5

4 MIRDFIT SOFTWARE 6

4.1 General overview of software use 6
4.2 MIRDfit innovations 6
4.3 MIRDfit quick-step instructions for use 6

5 DETAILED INSTRUCTIONS FOR TIAC CALCULATIONS 8

5.1 General input instructions 8
5.2 Inputs for TIAC calculation 8
5.2.1 Element, isotope 8
5.2.2 Phantom 8
5.2.3 Biodistribution input 9
5.3 Trapezoidal model 9
5.4 Regression 10
5.4.1 Fit functions 11
5.4.2 Saving dosimetry calculations 11
5.5 Interface map 12

6 ADDITIONAL ITEMS 15

6.1 Operating system 15
6.2 Tips and Tricks 15
6.2.1 "Dose to blood" 15
6.3 Feedback 16

2 SOFTWARE OVERVIEW

2.1 MIRDFIT

MIRDfit is an organ-level biodistribution fitting and time-activity integration tool designed to support organ-level dosimetry calculations for estimating radiation dosimetry from internally distributed radionuclides.

Users are encouraged to read manual thoroughly. All input parameters can/will affect output dosimetry estimates; therefore, a full understanding of input design is required by the user.

2.2 ACKNOWLEDGEMENTS

MIRDfit is part of a grant supported project from the United States National Institute of Biomedical Imaging and Bioengineering, grant 5-U01-EB028234: "MIRDfit – A Community Tool for Deriving and Reporting Patient Organ Doses in Nuclear Medicine, Computed Tomography, and Hybrid Imaging". Principle Investigators: Wes Bolch (University of Florida) and Adam Kesner (Memorial Sloan Cancer Center).

Major project contributors include: Justin Brown (UF), Lukas Carter (MSKCC), Sean J. Domal (UF), John L. Humm (MSKCC), Derek Jokisch (FMU), Ryan Kerslake (MSKCC), Cameron B. Kofler (UF), Daniel Lafontaine (MSKCC), Juan C. Ocampo Ramos (MSKCC), Edmond Olguin (UF), Bonnie N. President (UF), Trung Tran (UF) and Pat Zanzonico (MSKCC).

We acknowledge guidance and support from the Society of Nuclear Medicine and Molecular Imaging Committee on Medical Internal Radiation Dose, and the SNMMI organization.

3 INSTALLATION

3.1 DOWNLOADING

MIRDfit is freely available on the MIRDsoft.org website: www.mirdsoft.org

3.2 REQUIREMENTS

The MIRDfit software is built within the Microsoft Excel environment and compiled using XLS padlock. MIRDfit software requires a windows PC with Microsoft Windows 7 (32- or 64-bit) or later, and Microsoft Office 2013 or later installed.

3.3 INSTALLING

The MIRDfit installation file can be downloaded from www.MIRDsoft.org.

To install the software, launch installation file and follow instructions. Software will automatically install to the location "C:\MIRDsoft\MIRDfit\MIRDfit_v1.0\".

User's may need permissions and firewall exceptions from their site administrators to complete installation.

3.4 UNINSTALLING

To uninstall MIRDfit, use the MIRDfit uninstaller "C:\MIRDsoft\MIRDfit\MIRDfit_v1.0\uninsooo.exe"

3.5 TROUBLESHOOTING

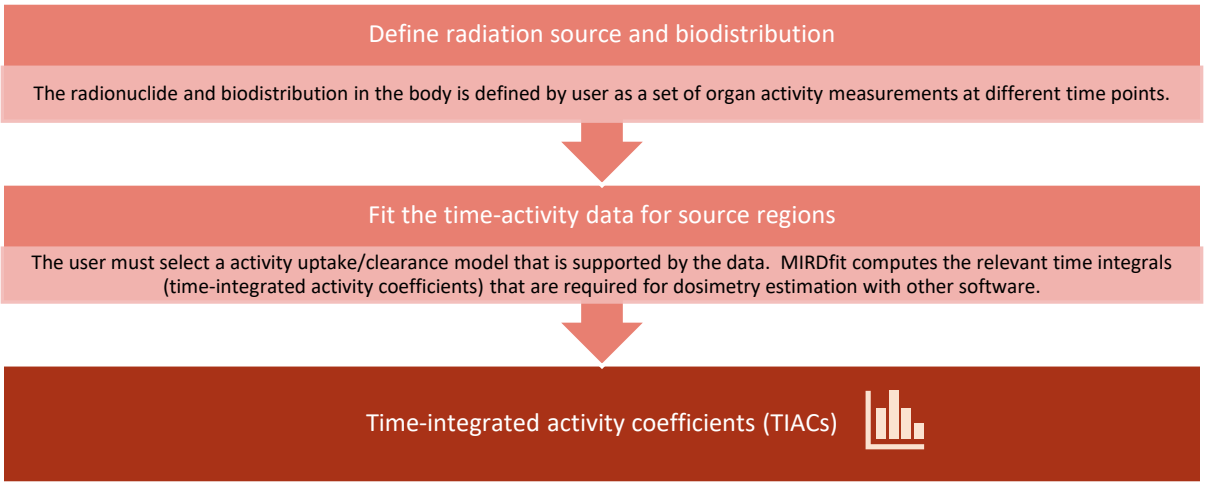
We are collecting feedback from users and will post troubleshooting advice as it is collected. These items will be posted on our website:

https://mirdsoft.org/MIRDfit-software-use-notes

4 MIRDFIT SOFTWARE

4.1 GENERAL OVERVIEW OF SOFTWARE USE

MIRDfit is biodistribution fitting software for TIAC estimation, designed to be used as an extension to the MIRDcalc dosimetry software tool. It shares some similarities with other available fitting/regression programs – the general workflow consists of a few basic steps:



4.2 MIRDFIT INNOVATIONS

MIRDfit was built with an aim of providing a user-friendly TIAC estimation software that offers objective metrics for selection of appropriate fit models and supports consideration of uncertainty in dose estimation. Several notable features include:

- Nuclear medicine-appropriate fit equations
- Objective metrics for best fit selection
- TIAC uncertainty calculation
- Quality control measures
- Data archiving
- Integration with MIRDcalc dosimetry tool
- User-friendly Excel interface

4.3 MIRDFIT QUICK-STEP INSTRUCTIONS FOR USE

In this handbook, instructions for performing TIAC estimation. A quick overview of steps required for internally distributed isotope dose estimation is provided below:

MIRDfit Quick-Step Usage Summary

1. Select ***Element/Isotope***
2. Select a ***Phantom*** or enter a custom source region list
3. Enter biodistribution (percentage of administered activity [%IA] in source regions over time)
    - (optional) Enter estimated uncertainty in %IA for the source region
4. Fit one or more models using the ***Regression*** module, as supported by number of observations
5. TIAC automatically generated on interface [units mGy/MBq]
    - If more than one model fit, choose best model guided by fit metrics and knowledge of biological system
    - Send the best model to the ***Shelf*** (saved results)
6. Select ***Export to file (MIRDcalc format)*** to export case as a *.csv (comma-delimited) format file
7. (Optional) import the saved file into MIRDcalc for dose calculation

Note - An elemental understanding of the fundamentals of dosimetry is strongly encouraged for proper use of this software. Many of these concepts are presented in the MIRDcalc software/manual.

5 DETAILED INSTRUCTIONS FOR TIAC CALCULATIONS

In MIRDfit, TIACs are calculated based on user biodistribution input.

5.1 GENERAL INPUT INSTRUCTIONS

MIRDfit has two types of input fields: multiple choice slicers and text fields.

Slicers – the MS Excel platform supports multiple choice selections via slicers. The user may select fields from the presented slicers.

Text fields – all yellow fields on the interface are editable. All non-yellow fields are not.

5.2 INPUTS FOR TIAC CALCULATION

MIRDfit TIAC estimation works by computing the analytic integral of a fit function based on optimized parameter estimates obtained through non-linear regression. The user supplies the patient specific biodistribution (as %ID at discrete times), ultimately generating a set of organ level TIAC estimates for the given phantom model and patient specific biodistribution.

The process for generating estimates are as follows:

5.2.1 Element, isotope

The selection of element and isotope loads the database information (decay constants) which are non-adjustable parameters in the fit equations.

5.2.2 Phantom

Selection of a phantom loads a list of source regions for which the user may have activity measurements. MIRDfit has pre-loaded region lists for each of the International Commission on Radiological Protection (ICRP) reference phantoms. These particular phantoms are also available in MIRDcalc for dose calculations.

In case the user has additional source regions to fit, or if the user intends to compute TIACs for a different series of phantoms (e.g., that may possess different source regions), these regions may be specified by choosing the *User-defined source regions* phantom from the list.

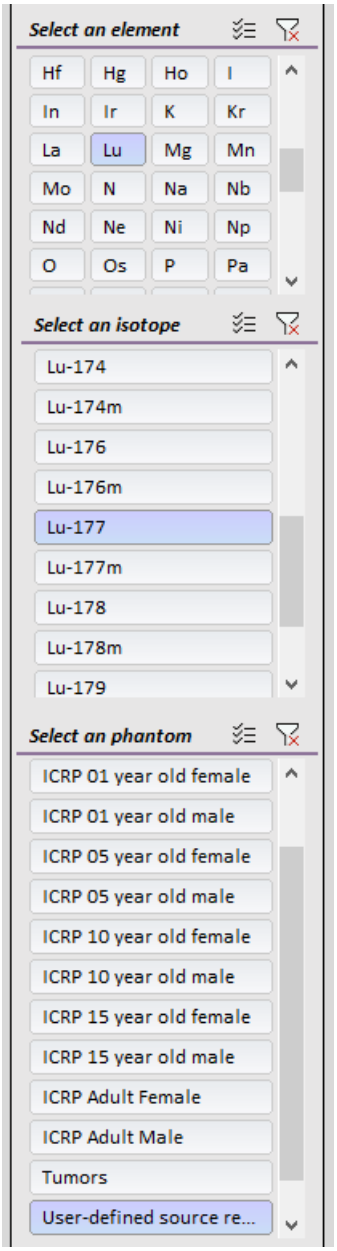


Figure 1: Study setup

5.2.3 Biodistribution input

MIRDfit provides biodistribution-specific TIAC estimates. To accomplish this, the percentage of administered activity in the different source regions over time, must be input into the software.

In MIRDfit, the biodistribution is defined for a given source region (Fig. 2, red box) by assigning percentage of administered activity [%IA] at discrete time points [h] post-administration. The user must specify whether the %ID measurements represent biological uptake/clearance (i.e., decay corrected back to time of administration) or effective uptake/clearance (i.e., not decay-corrected); this must be done by selecting the appropriate option in the green box of Fig. 2.

Optionally, the user may enter uncertainties associated with the %IA at each time point. This optional input requires the user to choose a variance input format for weighted least squares regression. The uncertainty in each observation may be entered as an absolute standard deviation, a relative standard deviation (coefficient of variation), or, a weighting factor may be entered directly (Fig. 2, green box). This option sets how weights for each observation (%IA data point) are assigned. For example, if the absolute standard deviation of the %IA at each time point are known, select the standard deviation option. If a variance input is not supplied for every data point, a default 10% relative standard deviation will be assigned. If no uncertainty entry is supplied.

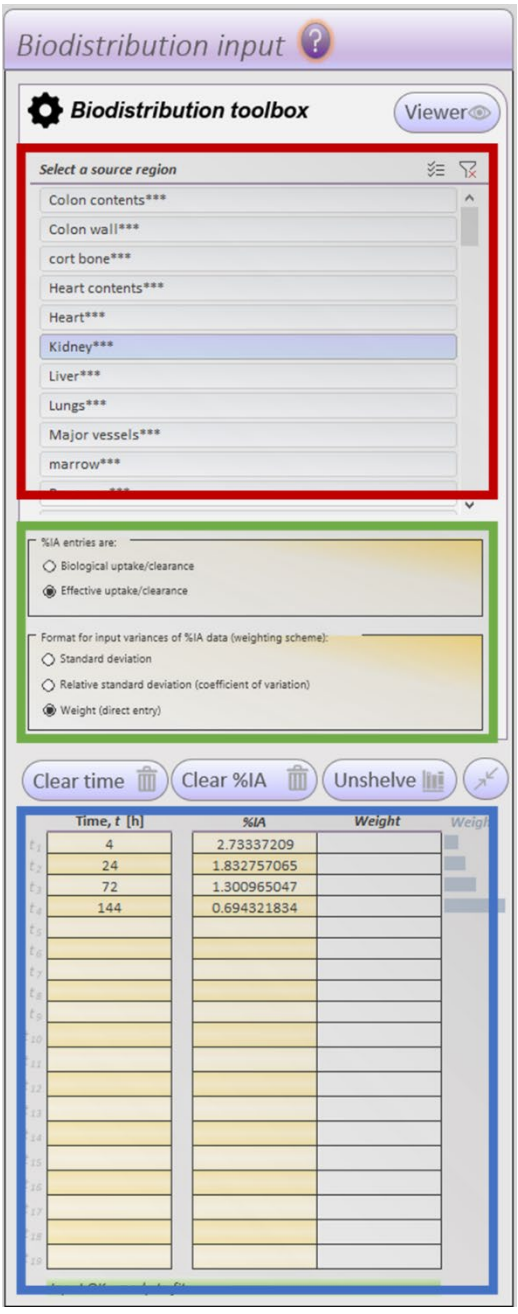


Figure 2: Biodistribution input.

5.3 TRAPEZOIDAL MODEL

The trapezoidal integration option is provided mainly as a QC measure for comparison with fitting results. Based on experience with a radiopharmaceutical, a user may develop knowledge about the uptake/clearance kinetics and may apply that knowledge to estimate the behavior before/after the measurement interval. If the user's estimate is vastly different than a fitted result, that may be an indication of, e.g., poor model fit, inappropriate initial guesses for parameters, etc.

To use the trapezoidal integration functions, first, choose an option for modeling uptake/clearance before the initial time point (i.e., the 'nose' of the time-activity curve). Then, choose an option for modeling uptake/clearance after the last measured time point (i.e., the 'tail' of the time-activity curve).

5.4 REGRESSION

This module performs weighted least squares fitting of various models to the time-activity data. The following objective function is minimized:

$$o_{WLS} = \sum_{i=1}^{n} w_i[d_i - m_i]^2$$

where d_i is the value of the i^{th} datum, m_i is the corresponding model estimate. The weight, w_i, is assumed to be the inverse of the variance of the datum unless weights are supplied directly via the "Weight (direct entry)" option.

1. Choose a model(s) of interest from the list of suitable models. Models are only available if the number of degrees of freedom supports an estimate of uncertainty (i.e. # of observations ≥ # model parameters + 1).
2. Enter initial guesses for parameters for each model (optional). If none are supplied, MIRDfit will make the guesses.
3. Choose the Fit all selected option to autofit the selected models. Alternatively, models may be fit individually using the Fit (re-fit) button in the bottom model Actions pane.
4. Critically evaluate the fit results. MIRDfit offers guidance on model discrimination based on the maximal Akaike weight (wAICc). The wAICc estimates the probability a particular model is the best for all models selected and fit by the user. The model with the maximal wAICc will be highlighted in green.
5. Other QC metrics in addition to wAICc should be evaluated to ensure an appropriate model is selected:
    - R^2: Close to 1
    - Corrected Akaike information criterion (AICc): Minimum over all fit models
    - Distribution of weighted residuals: Random (inspect inset line charts)
    - Ratio of fitted model TIAC to trapezoidal estimation (rmodel/trapezoidal): Close to 1
    - Visual inspection: No evident bias
    - Correlation of parameters: All off-diagonal elements of parameter correlation matrix between -0.8 and +0.8.

    The user may make adjustments to the initial parameter estimates and re-fit the model using the buttons in the model's Actions pane.
    The user may reset a model, excluding it from the set of models under comparison.
6. Select the most suitable model. The ***Send to shelf*** button (in the Actions pane of a model tab) stores the fitting results of the selected model.
7. If no models fit well, the trapeziodal estimate may be selected using the ***Send to shelf*** button in the Trapezoidal fit module.

8. If multiple models are supported by the data, the TIAC and standard error may be determined by inference. Essentially, this performs a weighted average of multiple models, weighted using the Akaike weight.

5.4.1 Fit functions

Radiopharmaceutical biokinetics are usually adequately described by simple combinations of exponential functions. The nuclear medicine-appropriate exponential models included in MIRDfit are given below:

Function	Description	Example use case
$\%IA(t) = A_1 e^{-\lambda_{phys} t}$	Physical decay only	No biological clearance
$\%IA(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t}$	Monoexponential (biological clearance with physical decay)	General use
$\%IA(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} + A_2 e^{-\lambda_{phys} t}$	Biexponential (1st phase, biological clearance with physical decay; 2nd phase, physical decay only)	General use
$\%IA(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} + A_2 e^{-(\lambda_2+\lambda_{phys})t}$	Biexponential (1st phase, rapid biological clearance with physical decay; 2nd phase, slow biological clearance with physical decay)	General use
$\%IA(t) = A_1 (e^{-(\lambda_1+\lambda_{phys})t} - e^{-(\lambda_2+\lambda_{phys})t})$	Biexponential (1st phase, uptake with physical decay; 2nd phase, biological clearance with physical decay)	Regions with initial uptake period (function constrained though origin)
$\%IA(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} + (100 - A_1) e^{-(\lambda_2+\lambda_{phys})t}$	Biexponential (1st phase, rapid biological clearance with physical decay; 2nd phase, slow biological clearance with physical decay)	Whole body, whole blood (i.v. administration), stomach contents (oral administration)
$\%IA(t) = A_1 e^{-(\lambda_1+\lambda_{phys})t} + (\%_{blood} - A_1) e^{-(\lambda_2+\lambda_{phys})t}$	Biexponential (1st phase, rapid biological clearance with physical decay; 2nd phase, slow biological clearance with physical decay)	Well-perfused organs (i.v. administration)

5.4.2 Saving dosimetry calculations

There are two ways to select or save the dosimetry output:

1. User may copy the dosimetry data to the clipboard by clicking the copy button  . One copied, the user may paste the tab delimited data in an external document (e.g. notepad, excel, word…).
2. The user may click the ***Export shelf*** button. This creates a comma delimited MIRDfit save file automatically saved to "C:\MIRDsoft\MIRDfit\MIRDfit_v1.0\MIRDfit_output \". This file can be reviewed by user and has a more robust accounting of input/output of case. This file can also be used to reload case at a later time (see section **Error! Reference source not found.**).

5.5 INTERFACE MAP

The full input/output interface is displayed to the user in a single screen. A screenshot with numbered info-points is displayed below along with a tabulated description (*vide infra*):

Description of Info-points

1	CASE SETUP: Create a new case, or load existing results.	2	NAVIGATION PANEL: These buttons autoscroll to different modules within MIRDfit.
3	NAVIGATION PANEL: These buttons autoscroll to different modules within MIRDfit.	4	ELEMENT SELECTION: Click to filter radionuclides by element.
5	PHANTOM SELECTION: Click a phantom to load its source region list. Two special user-configurable phantoms are available: 1) User-defined, and 2) Tumors. These source regions can be configured in the ***User organs*** tab accessible from the navigation panel.	6	SOURCE REGION SELECTION: User may click this button to change the input region.
7	%IA DECAY CORRECTION OPTION: If the source region time-activity data represent biological clearance (i.e., if they have been decay-corrected back to time of administration), then select ***Biological uptake/clearance***. Otherwise, select ***Effective uptake/clearance***.	8	VARIANCE MODE: Choose a format for specifying variance associated with the observations.
9	BIODISTRIBUTION HELPER BUTTONS: The right and middle buttons clear the biodistribution input cells. The ***Unshelve*** button is used to re-load the time-activity data for an organ that has already been shelved.	10	TIMES POST-ADMINSTRATION: Input the time in hours, post-administration.
11	%IA: Input the percentage of administered activity in the source region at the given time. Do NOT enter as a fraction of 1 (i.e., for 50%, enter 50, NOT 0.5).	12	UNCERTAINTY: Input the uncertainty in the %IA of each observation. This is an optional input.
13	FIT READY INDICATOR: The indicator bar will show red if input is inappropriate or incomplete.	14	TRAPEZOIDAL NOSE OPTION: Select an extrapolation option for the 'nose' of the time-activity curve – this indicates how the %IA vs. time on the interval spanning the time of administration to the first measured time point is defined.
15	TRAPEZOIDAL TAIL OPTION: Select an extrapolation option for the 'tail' of the time-activity curve – this indicates how the %IA vs. time on the interval spanning last measured time point to infinity is defined.	16	TRAPEZOIDAL TIAC: Display TIAC result based on the user's assumptions for (15) and (16)
17	TRAPEZOIDAL PLOT	18	REGRESSION HELPER BUTTONS: ***Fit all models*** will fit all regression models currently displayed on the interface. ***Reset all*** clears the fit results.
19	MODEL SELECTION: Models that have sufficient degrees of freedom to compute an uncertainty estimate (# observations - # adjustable parameters) ≥ 1) will be displayed in this pane. One or more models may be chosen to fit.	20	INITIAL PARAMETER GUESS: Enter an initial guess for the adjustable parameters in the model. This is optional. If no guess is entered, MIRDfit will provide an initial guess.
21	OPTIMIZED PARAMETERS: The results for optimized parameters (and standard error) will be output here.	22	TIAC and QC METRICS OUTPUT: The results for the TIAC, TIAC uncertainty, and quality control metrics for the fit are displayed here. The metrics should be compared among the models fit to ascertain the model that best supports the data.
23	REGRESSION PLOT: The input time-activity data and model fit are superimposed.	24	WEIGHTED RESIDUALS PLOT: A line chart of the weighted residuals for each observation is provided. An acceptable fit should yield a random distribution.
25	MODEL ACTIONS PANE: The buttons here can be used to fit or refit an individual model, accept the result (***Send to***	26	MODEL INFERENCE: If multiple models reasonably support the data, they may be averaged together, weighted by their Akaike weights.

	shelf), or reject this result (removing it as a candidate model for use in model inference)		
27	SHELF HELPER BUTTONS: Shelved data may be exported to the clipboard, or, saved as a MIRDcalc-format file for dose calculation in MIRDcalc.	28	SHELF: Archived results

6 ADDITIONAL ITEMS

6.1 OPERATING SYSTEM

Only PCs running Microsoft Windows 7 or later, with Microsoft Office installed are supported.

MIRDfit is not supported in Mac environments/virtual machines.

6.2 TIPS AND TRICKS

6.2.1 "Dose to blood"

'Dose to blood', computed as equilibrium dose from non-penetrating radiations, has historically been used as a surrogate for dose to the active marrow, but has largely been replaced by more advanced models for quantifying marrow dose (see P488 of Stabin et al: https://jnm.snmjournals.org/content/jnumed/63/3/485.full.pdf) except for the treatment of differentiated thyroid cancer, for which this concept is still in use (see Lassmann M, Hänscheid H, Chiesa C, Hindorf C, Flux G, Luster M. EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. Eur J Nucl Med Mol Imaging. 2008;35:1405-1412) and for biodosimetric purposes (e.g. see Eberlein U, Scherthan H, Bluemel C, et al. DNA Damage in Peripheral Blood Lymphocytes of Thyroid Cancer Patients After Radioiodine Therapy. J Nucl Med. 2016;57:173-179.).

The input for "dose to blood" calculations is usually the activity concentration in blood samples (e.g., %ID/g) rather than MIRDfit's required input units of %ID. Such calculations can be accomplished in MIRDfit via the following procedure:

1) *Select the "User-defined" phantom source region list, and create an entry called "Unit mass of blood" or similar.*
2) *Express the activity of the blood samples in units of %IA for 1g of whole blood by scaling the measured activity concentration*
    a. *This is numerically equivalent to the activity concentration in whole blood, in units of %IA/g*
3) *MIRDfit will report the TIAC [h] for 1g of whole blood*
    a. *This is numerically equivalent to the TIAC concentration in units of h/g*
4) *The dose coefficient for the blood, in units of Gy/MBq of activity administered, follows as the product of (2) with the equilibrium absorbed dose constant for non-penetrating radiations: TIAC/g * g-Gy/MBq-h = Gy/MBq*

6.3 FEEDBACK

MIRDfit is built as a community tool. We welcome cooperation and interest to make it better.

We are hoping our MIRDfit tool is useful to users throughout the community. Any and all feedback is welcome and will be taken under consideration for future development. Please email any comments or suggestions to contact@mirdsoft.org.