PET HARMONIZATION TOOLBOX
USER MANUAL

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The objective of this document is to provide instructions to perform quantitative harmonization experiments and processing on PET scanners.

The method is based on the paper Namias, M., Bradshaw, T., Menezes, V. O., Machado, M. A. D., & Jeraj, R. (2018). A novel approach for quantitative harmonization in PET. Physics in Medicine and Biology, 63(9), 1–12. https://doi.org/10.1088/1361-6560/aabb5f. The toolbox now supports uniformity and SUV QC from cylindrical phantom scans plus NEMA-phantom based harmonization with updated EANM/EARL standards.

Quantitative Harmonization in PET

The aim of these experiments is to determine the optimal reconstruction settings and minimum acquisition time to comply with EARL specifications (http://earl.eanm.org/cms/website.php?id=/en/projects/fdg_pet_ct_accreditation/accreditation_specifications.htm).

1. PRELIMINARY REQUIREMENTS

Please update the PET scanner calibration files:

- Detector gains
- Energy tables
- Position maps
- Coincidence timing

Update normalization tables (usually performed with a cylindrical phantom filled with 18F or 68Ge, also called crystal efficiency on some scanners) and absolute activity calibration (also called well-counter cross calibration on some scanners) to ensure optimal scanner performance / image quality during the experiments.

Also check the dose calibrator accuracy for F18 and the synchronization of the dose calibrator and scanner console clocks. Accuracy should be better than 5%, ideally under 2%.

2. CYLINDRICAL PHANTOM PREPARATION AND ACQUISITION

Objectives

To verify that absolute activity concentration measurements in homogeneous regions are accurate (cylindrical phantom).

To verify image uniformity.

To measure the scanner resolution (MTF) from the phantom edges.

To measure the Noise Power Spectrum (NPS).

To harmonize the scanner.

Materials

You will need:

- A fillable cylindrical phantom (NEMA 1994 phantom or similar) with 20 cm diameter. It is usually included with the PET system for routine calibration and QA.
- Ideally, a phantom holder (usually comes with the scanner). The phantom should be positioned on the holder and not on the scanner bed if possible. Philips scanners usually don´t allow to use the holders outside calibration mode.
- 70 MBq of 18F-FDG
- Dose calibrator (18F).
- Syringes, needles, Personal Protective Equipment (PPE), personal dosimeters, etc.
- Bubble level (spirit level).

Phantom Preparation and Image Acquisition

Phantom preparation.

- Measure the internal phantom volume. The typical NEMA NU-1994 phantom volume is 5640 ml.
- Calibrate 70 MBq of 18F-FDG (DO NOT USE 18F-FNa!) in a syringe.
- Activity =..... MBq specified or calibrated at ..... (hh:mm:ss)
- The reference time for the activity should be the estimated start of the PET acquisition. This means that there should be 70 MBq in the phantom at the time of the image acquisition. Register activity and measurement time.
- Fill the cylindrical phantom with distilled water. Remove 300-500 ml of water to be able to homogenize the activity.
- Add the activity into the phantom. Shake thoroughly to homogenize the activity. Fill the remaining volume and shake again. Leave no air bubbles.
- Measure residual activity. Activity = ... (MBq) measured at ..... (hh:mm:ss)

Phantom positioning

- If available, place the phantom on the phantom holder.
- Level the phantom with the help of the bubble level and the phantom holder.
- Align the phantom with the help of the positioning lasers.
- The phantom should be centered on the FOV, both vertically and horizontally.

- Verify that the phantom is leveled with the help of scout images. The following picture shows an example of bad phantom leveling:

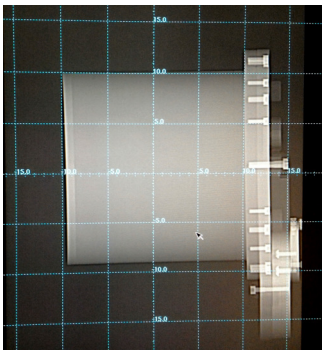
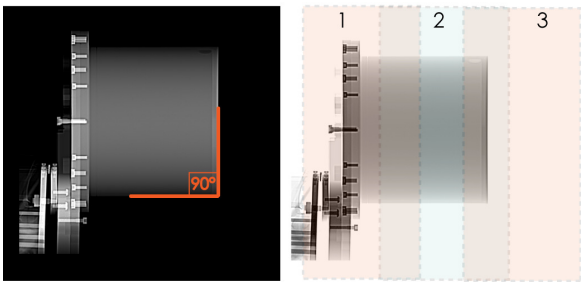


Image Acquisition

- Setup a PET/CT acquisition as usually done in clinical practice.
- Fill the injected and remaining activities (with their respective measurement times) on the scanner console.
- Setup two or three overlapping PET bed positions (use the default slice overlap used in the clinical protocols). 50 % overlap is the recommended value for normal axial FOV scanners (around 16 cm) with full acceptance angle, as it results in more uniform noise and resolution. Typical overlap values for large axial FOV scanners (Siemens TrueV, GE Discovery IQ, etc.) are lower than 50% since they use limited acceptance angles.
- The upper edge of the phantom (the one opposite to the holder) should be exactly in the center of the overlap region (between bed positions 2 and 3 or 1 and 2):



- Use the default CT protocol for attenuation correction.
- Acquisition time per PET bed: 20 minutes.
- Register the exact time of the PET acquisition start.
- Reconstruction settings: use the typical clinical recon settings and also setup an additional reconstruction without any type of filtering. Be sure to enable all quantitative corrections (attenuation, scatter, randoms, dead time, decay, normalization, etc.).
- Store the PET RAW data and CTAC series for future reconstructions if possible.
- Export all images in DICOM 3.0 format without compression, ideally from the scanner console.

Image analysis for harmonization

Image analysis will be performed using custom made MATLAB software.

Expected results

Image uniformity should be better than 10% for every slice and SUV errors should be under 5% for every slice (ideally under 3%).

2. IMAGE PROCESSING

Objetive

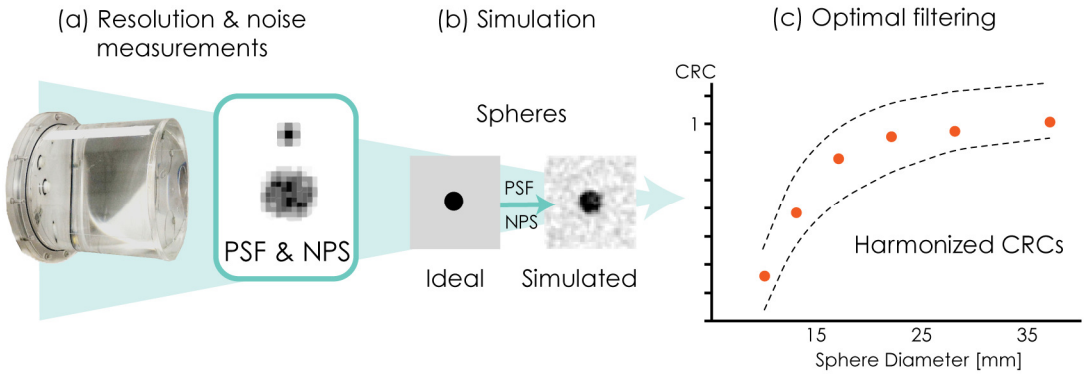
To determine CRCs for the NEMA IQ phantom spheres, by using simulation software.

Materials

You will need:

- The DICOM files of the cylindrical phantom
- The Harmonization Toolbox GUI (MATLAB software).

The overall workflow is as follows:

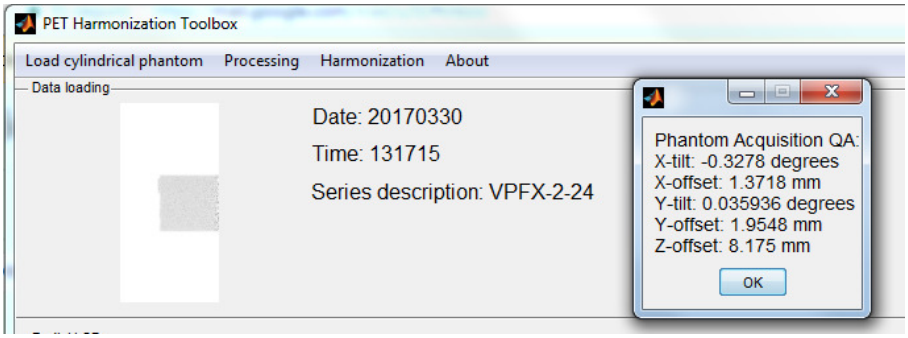


First, the resolution and noise power spectrum are estimated from the cylindrical phantom. This information is then used to simulate spheres that are used to estimate CRC values.

Image analysis

Image loading

- Open the Harmonization Toolbox GUI.
- Select "Load cylindrical phantom" from the menu.
- Select the directory containing the DICOM files of the cylindrical phantom.
- The software will load the slices and do a quality check to assess the positioning of the phantom. Currently, this is for informative purposes only.
- The toolbox will show the following information:

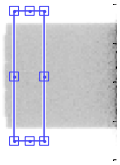


The date and time of the acquisition is shown, together with the series description. The message box shows the X&Y tilt and offsets and the Z-offset of the phantom. The X&Y offsets are the distances between the center of the phantom and the center of the PET FOV. The tilts are the angles between the phantom axis and the PET axis. The Z-offset is the distance between the top edge of the phantom and the center of the overlapping region of the PET FOVs.

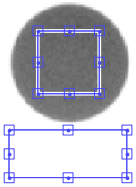
Image Processing

There are two options: manual and automatic processing. In automatic processing, the regions of interest to extract resolution and NPS estimates are automatically determined. This mode is suitable for all users. Under manual processing, the regions of interest are selected by the user and requires knowledge of the underlying method.

Manual radial LSF processing:

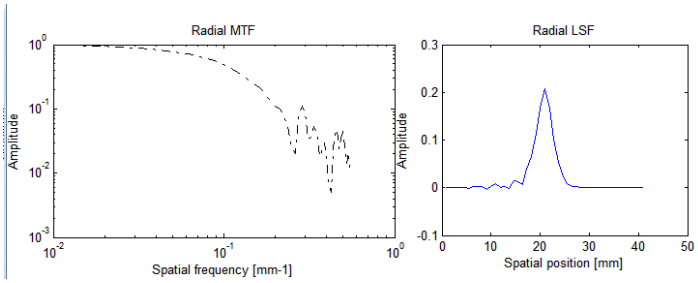


- Select an axial range close to the top edge of the phantom.
- Double click to continue.

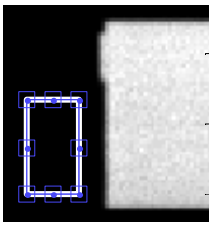


- Drag and select an ROI for the background, close to the active part of the phantom.
- Double click to accept.
- Drag and select an ROI for the foreground.
- Double click to accept.

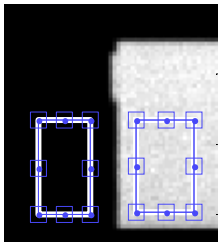
The radial LSF and MTF appear on the main screen of the GUI, together with an estimation of the FWHM:



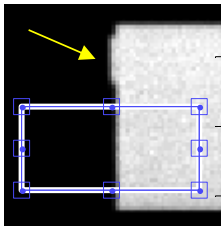
Manual axial LSF processing:



- Select an ROI representative of the background.
- Double click to continue.

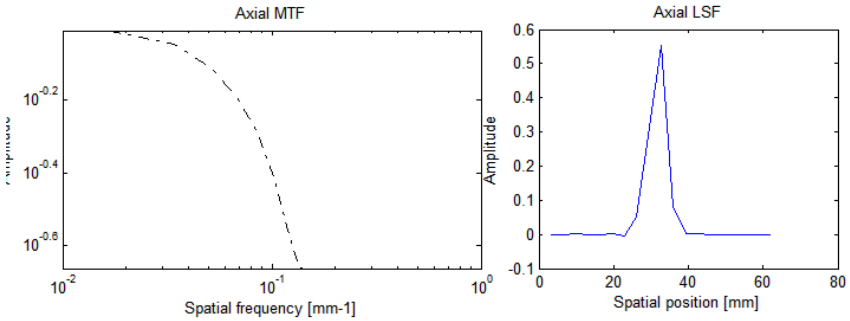


- Select an ROI representative of the background.
- Double click to continue.

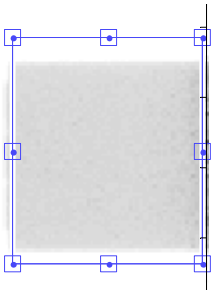


- Select an ROI representative of the saggital analysis range. ***Avoid*** holes in the top of the phantom if present (yellow arrow).
- Double click to continue.

The axial LSF and MTF appear on the main screen of the GUI:

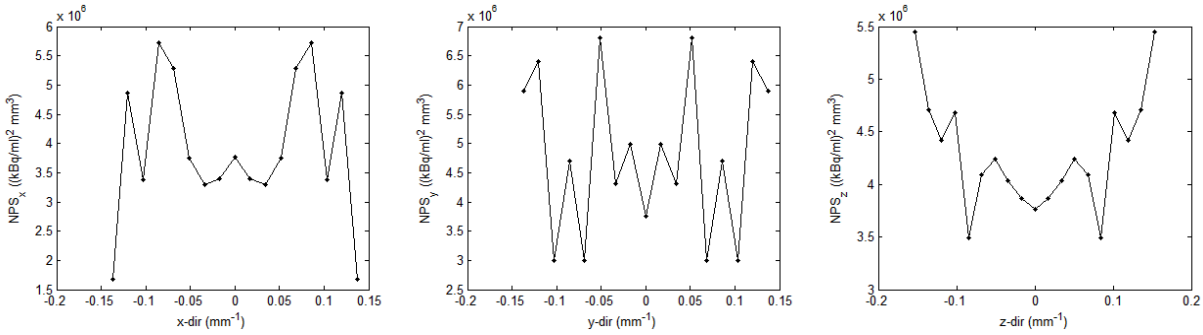


Manual NPS processing:



- Select the whole active axial range of the phantom.
- Double click to continue.

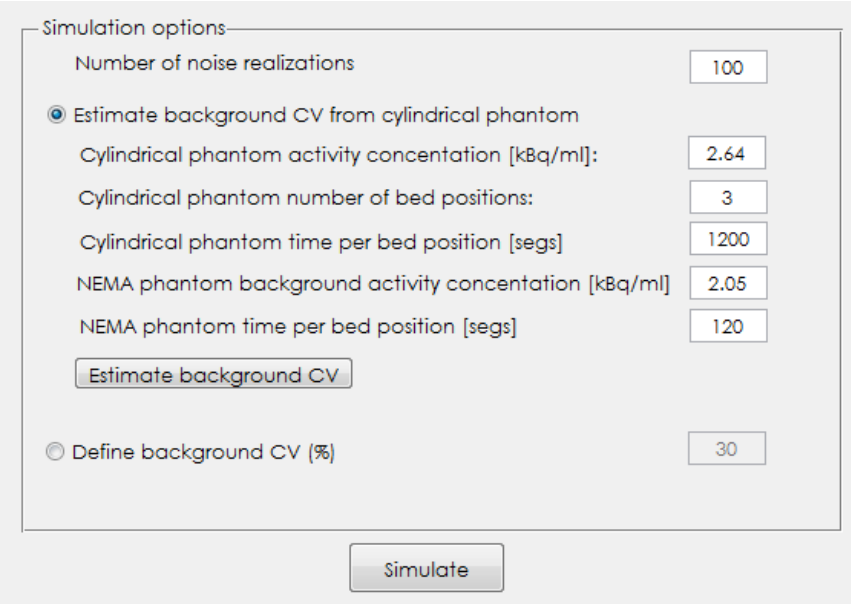
Three 1-D profile along the main frequency axis will be shown on the main GUI:



2. SIMULATION

Once the radial and axial LSFs and the NPS are estimated, the spheres can be simulated.

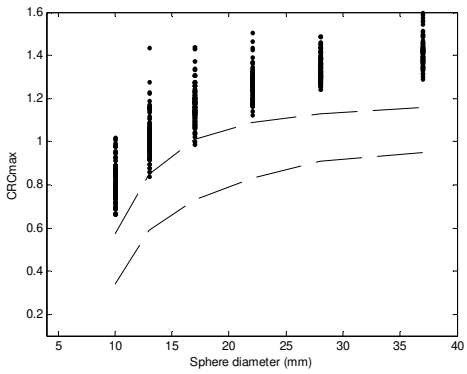
Select *Harmonization* →*Simulate spheres* from the main menu. A pop-up screen will appear:

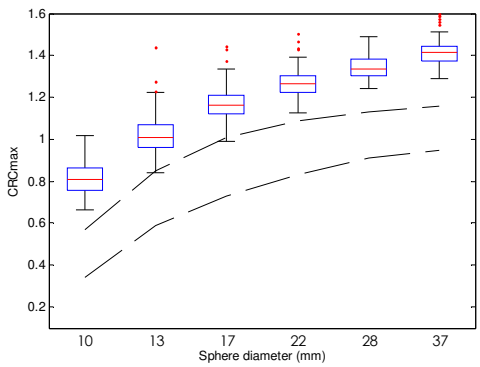


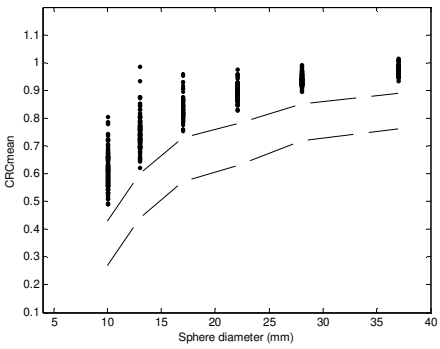
1. Select the number of noise realizations (default: 100)

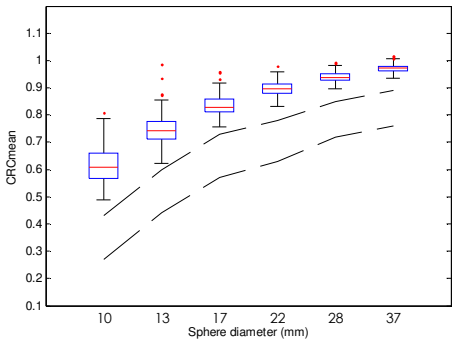
2. The background CV of the simulated NEMA phantom can be estimated from the cylindrical phantom (default) or can be set to an arbitrary value. If the first option is desired:
    a. Check that the information from the cylindrical phantom is correct (activity concentration, number of bed positions and time per bed).
    b. Select the parameters of the NEMA phantom to be simulated. Activity and time can be changed.
    c. Click "Estimate background CV". The estimated value will replace the lower left edit box value.
3. Click "Simulate". The simulation can take a few minutes depending on the number of noise realizations.

The simulated CRCs appear on pop-up figures, both as scatter-plots and box-plots:

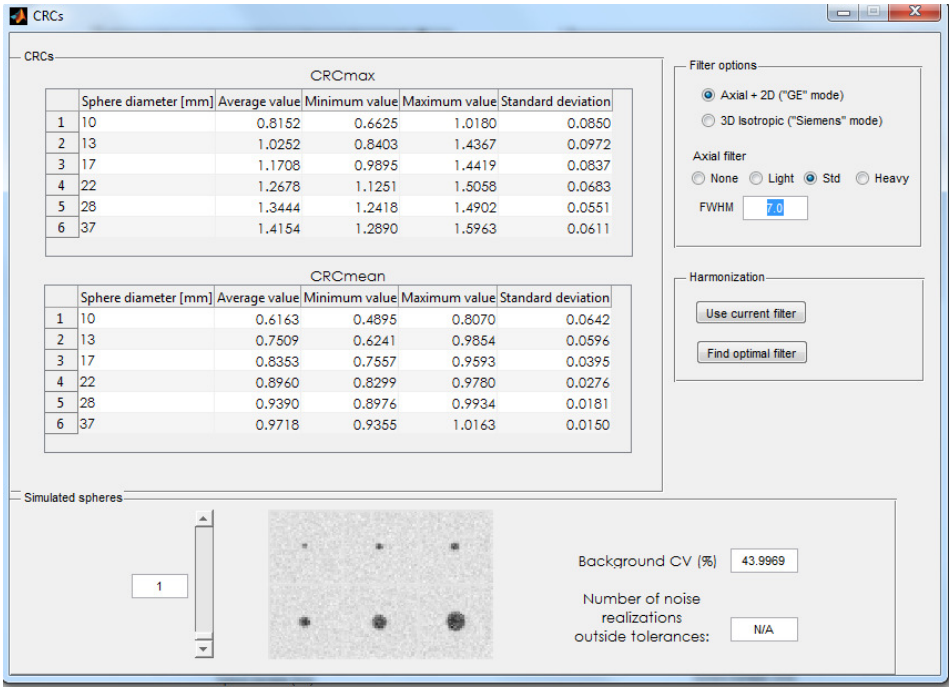








The CRC analysis windows also appears, showing the results in a tabular way:



Under the "Simulated spheres" panel, all the noise realizations can be visualized with the slider control.

3. HARMONIZATION FROM CYLINDRICAL PHANTOM

There are two options to harmonize the CRC values:

1) Manual search of the optimal filter parameters.

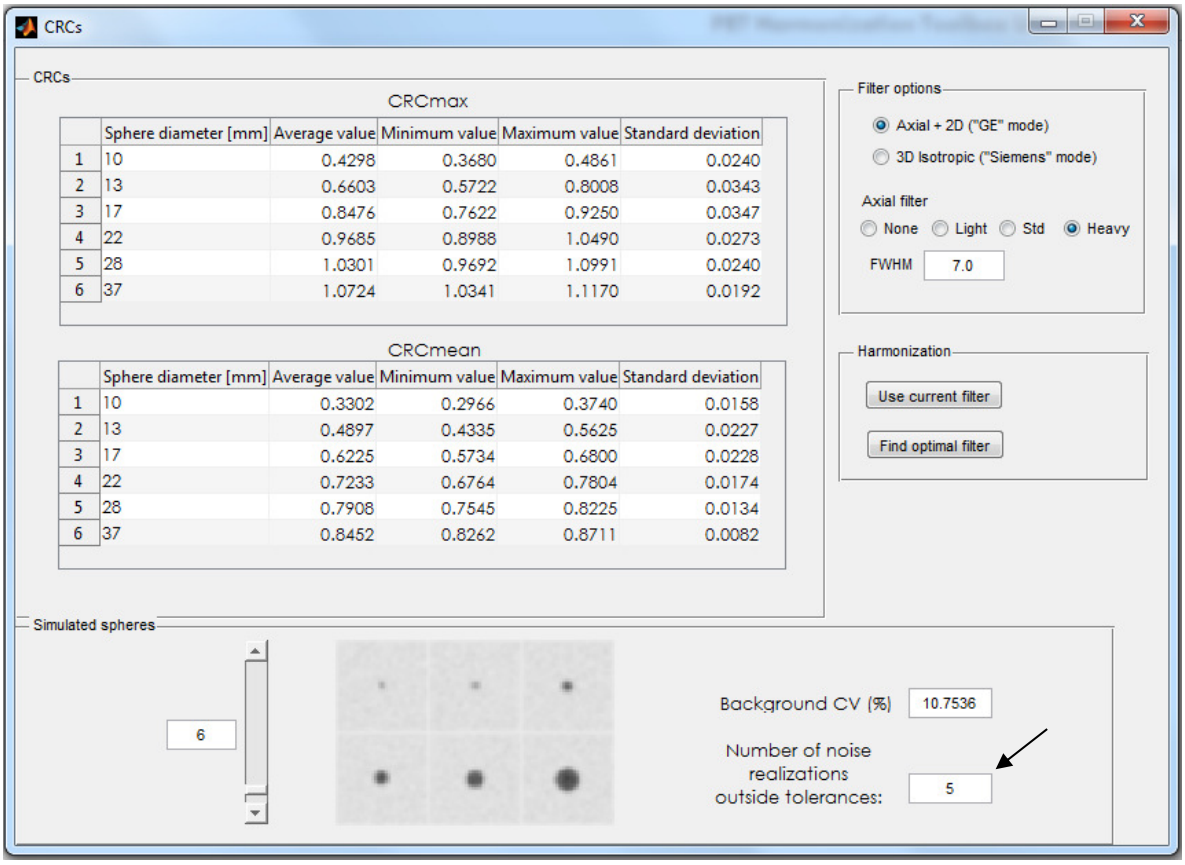
The filter settings can be manually changed in the "Filter options" panel. Two modes are available:

- "GE" mode: a 2D filter + an axial filter is used. The axial filter can have the following settings:
  - None
  - Light
  - Standard
  - Heavy
- "Siemens" mode: a 3D Gaussian isotropic filter is used.

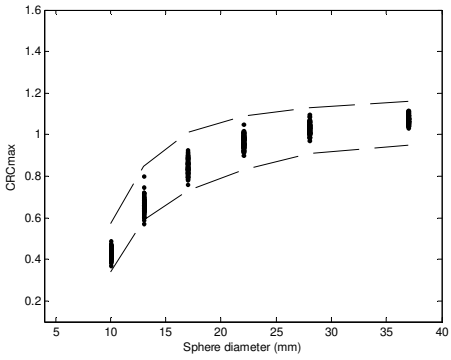
In "GE" mode, the "FWHM" edit box represents the 2D filter FWHM. In "Siemens" mode, the "FWHM" value represents the 3D FWHM value of the filter.

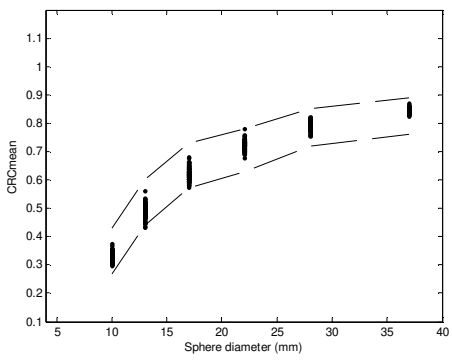
1. Select the mode (GE or Siemens).
2. If GE was selected, select the axial filter strength.
3. Select the FWHM value (in mm).
4. Press the "Use current filter" button.

New CRC figures appear, and the table is updated. The new background value is also shown:



Finally, the number of noise realizations outside tolerances are shown on the lower right of the screen.





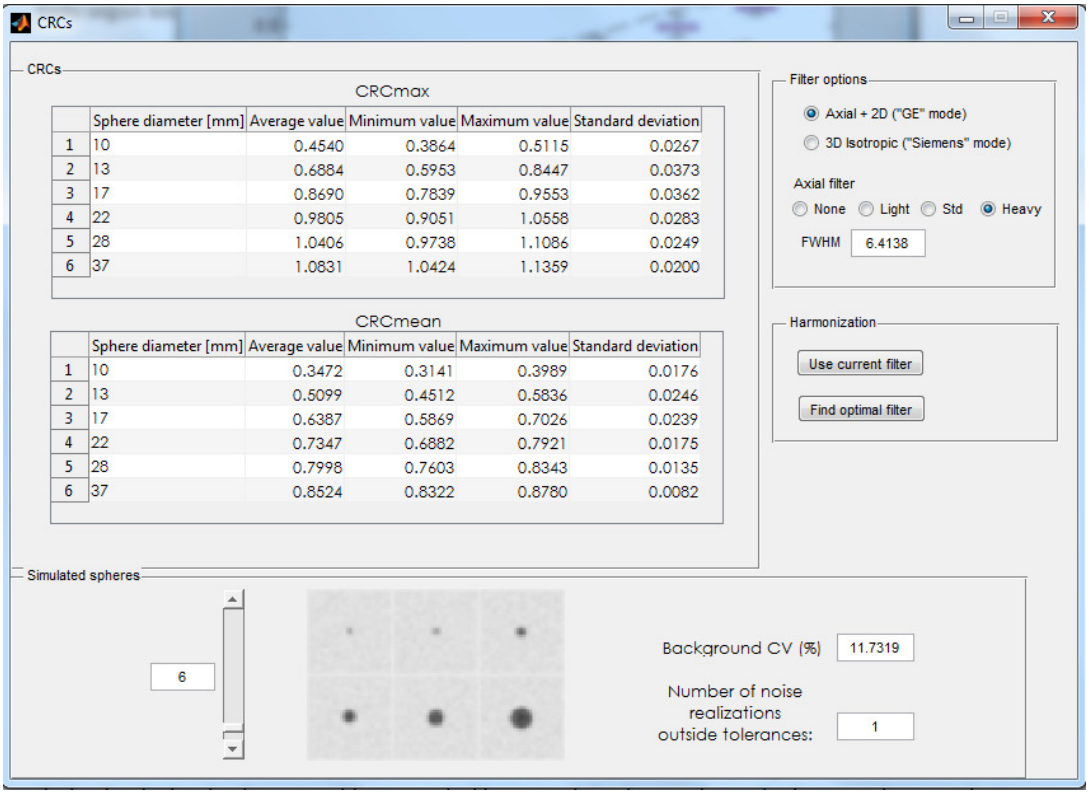
2) Filter optimization

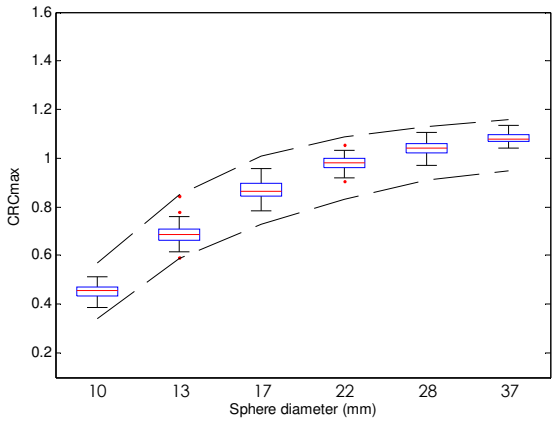
The filter mode should be set before using the filter optimization routine since it doesn´t change the axial filter (i.e.: it only optimizes the 2D filter in "GE" mode).

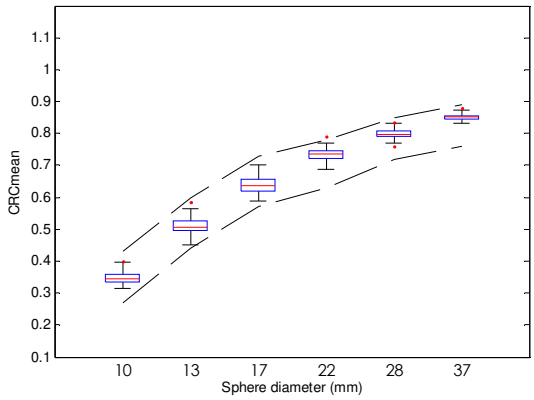
1. Select the mode (GE or Siemens).
2. If GE was selected, select the axial filter strength.
3. Press the "Find optimal filter" button.

Please be patient, the optimization process can take a few minutes.

The new results after optimization are shown on the GUI:







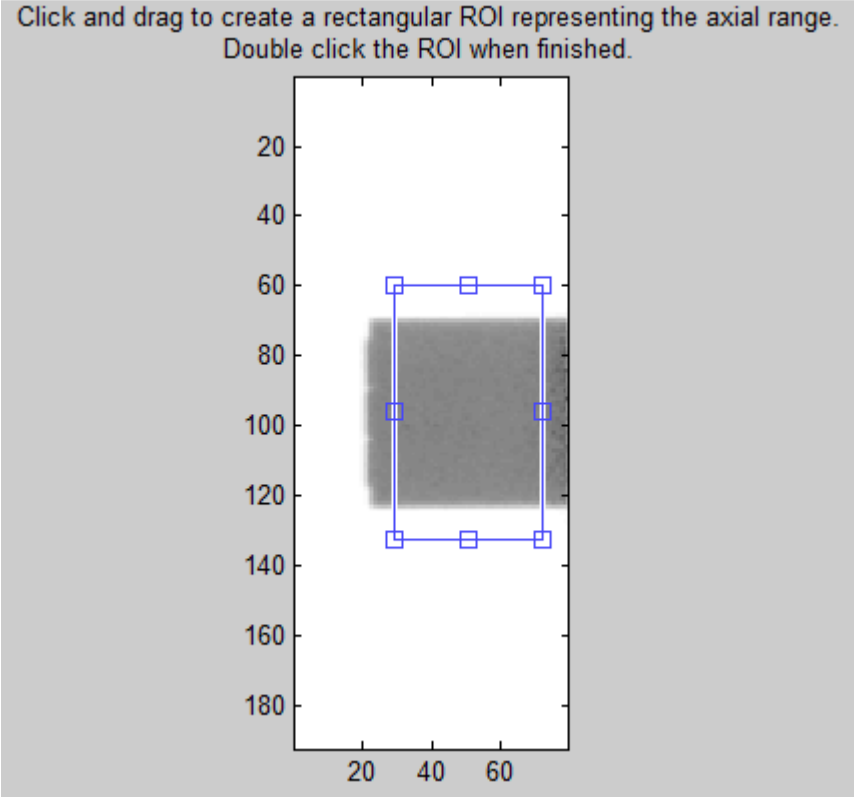
Sometimes it´s impossible to achieve perfect harmonization (i.e.: number of noise realizations outside tolerances = 0). Keep in mind that the EARL tolerances were designed for the mean values and not for a particular noise realization.

4. SUV AND UNIFORMITY QUALITY CONTROL

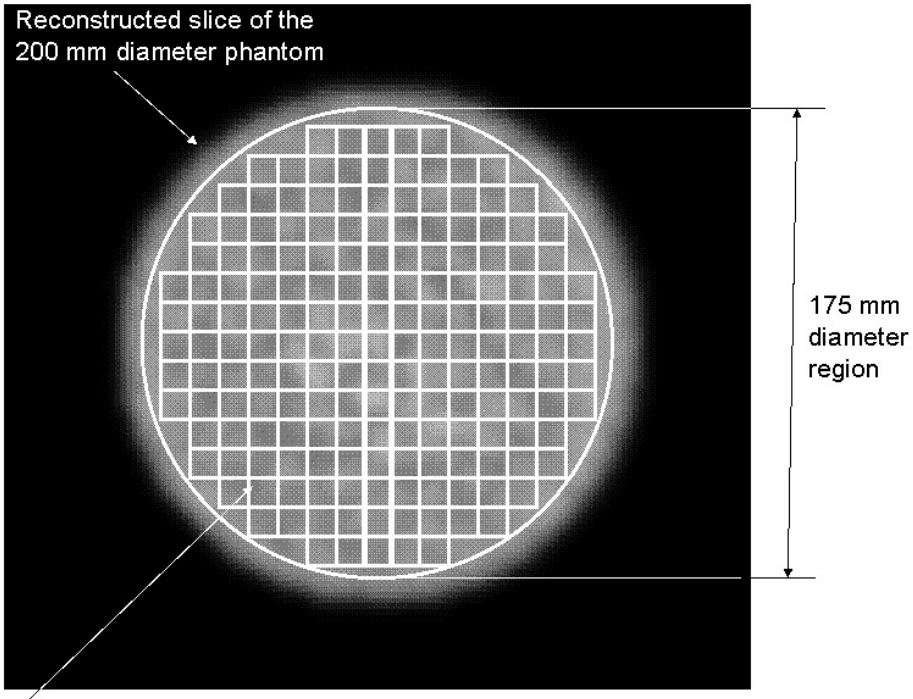
Select "Cylindrical Phantom Processing → Uniformity & SUV".

If the phantom was reconstructed without filters, you can specify the FWHM of a 3D Gaussian filter to apply before uniformity and SUV analysis. Setting a value of "0" will disable filtering.

A prompt to verify or correct the phantom activity appears, first in Bq and then in mCi, followed by the activity measurement time and internal phantom volume. A figure then appears to select the axial range for analysis:



The toolbox will then estimate non-uniformity and SUV bias according to https://www.iaea.org/publications/8002/quality-assurance-for-pet-and-petct-systems

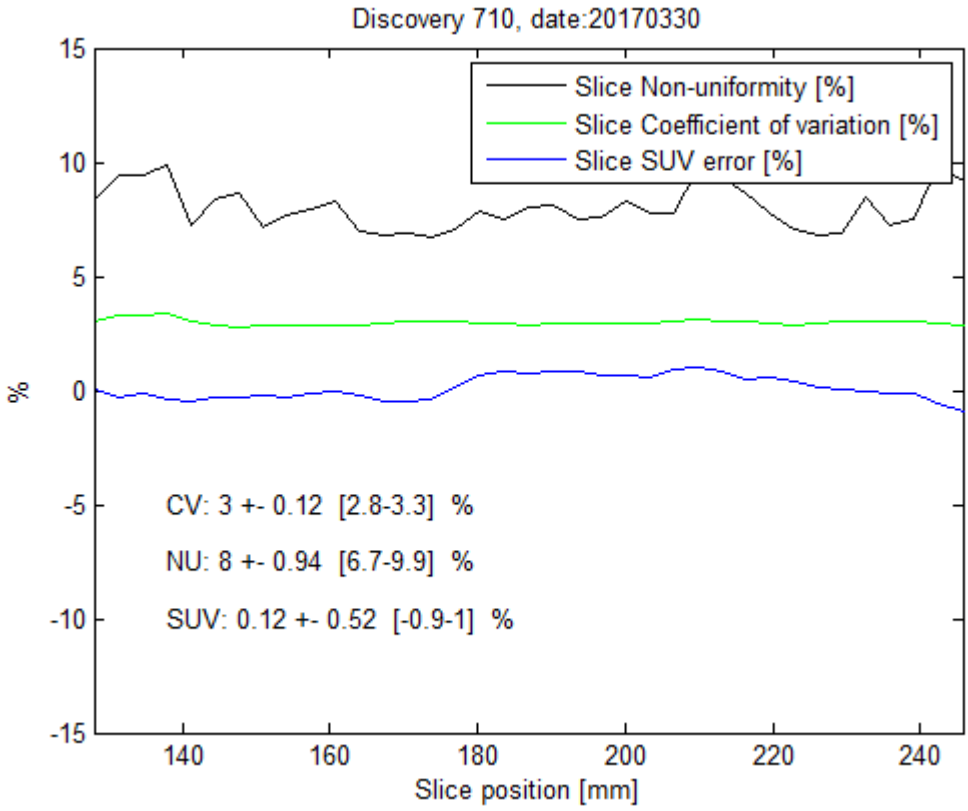


We define MAX(Ck), MIN(Ck) and AVE(Ck) as the maximum, minimum and average number of counts, respectively, with respect to any square region k within a given slice i. Non-uniformity in each slice shall be evaluated as:

$$NU_i = MAX\left\{ \begin{array}{l} 100\dfrac{MAX(C_k) - AVE(C_k)}{AVE(C_k)} \\ 100\dfrac{AVE(C_k) - MIN(C_k)}{AVE(C_k)} \end{array} \right\}$$

$$CV_i = 100\frac{SD_i}{AVE(C_k)}$$

Results are shown in a figure:



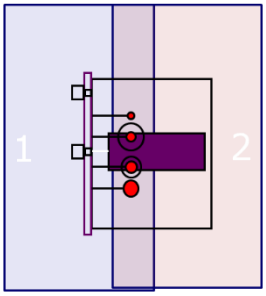
5. HARMONIZATION FROM NEMA IQ PHANTOM

The toolbox now supports CRC estimation from a NEMA phantom, following the methodology proposed by EANM/EARL (https://earl.eanm.org/).

2) Phantom preparation

Phantom preparation		**Checklist**
Fill a bottle with exactly 1000 ml of water.		
Calibrate two syringes with 20 MBq of ^{18}F-FDG calibrated at the expected time of the PET image acquisition. Phantom preparation usually takes between 30 and 60 min depending on the operator skills. It is usually better to overestimate the phantom preparation time.	**Syringe 1 (spheres)** Activity = _____ MBq at _____ hh:mm **Syringe 2 (background)** Activity = _____ MBq at _____ hh:mm	

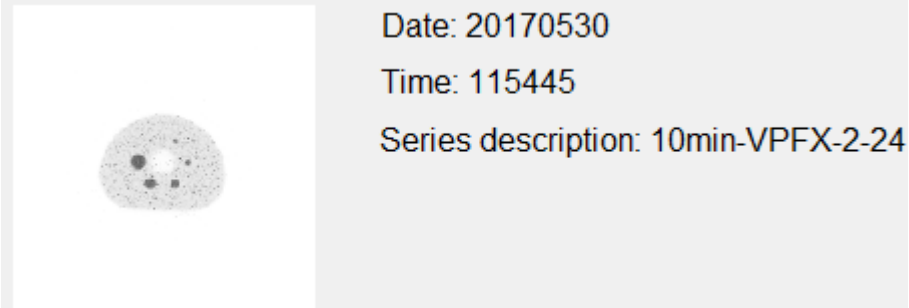
Place the lung insert filled with polystyrene balls and air (no water here!) in the phantom.		
Fill the background of the phantom with water. Leave around 500 ml of air.		
Add the content of syringe 1 into the calibrated 1000 ml bottle. Flush three times. Homogenize the content by shaking.		
Measure the residual activity at syringe 1	**Syringe 1 (spheres) – residual activity** Activity = _____ kBq at _____ hh:mm	
Fill all the spheres with the previous ^{18}F-FDG solution with the help of the special syringe. Be sure to avoid leaving air bubbles inside the spheres.		
Add the content of syringe 2 in the 9700 ml background compartment.		
Measure the residual activity at syringe 2	**Syringe 2 (background) – residual activity** Activity = _____ kBq at _____ hh:mm	
Homogenize the background compartment and fill the remaining water volume to remove air bubbles.		

Image acquisition		Checklist
Place the phantom in the scanner table.		
Center the phantom with the help of the lasers. The lung insert should be in the isocenter of the scanner.		
Start a new patient exam. In the injected activity field, input the activity of syringe 1, and the residual activity. In this way, the activity information will be stored in the DICOM header.		
Perform a scout view / topogram.		
Prescribe an overlapping two-bed acquisition, using the same overlap as in the cylindrical phantom experiment. The central plane of the spheres should be exactly in the middle of the overlap region.		
Prescribe a 10 minute per bed position (20 minutes total) PET scan, using the default clinical acquisition protocol. Perform a CT scan for attenuation correction. The PET acquisition will begin when the activity in syringe 1 (spheres) equals 20 MBq.	PET acquisition start time: _____ hh:mm:ss	
Please use an easily identifiable series name for each acquisition / reconstruction. Example: 20MBqx10min-acq#1-2i24s-nofilter.		
PET reconstruction settings: For EARL 1 standards, disable PSF modeling (SharpIR, TrueX, etc). For EARL 2 standards, enable PSF modeling (SharpIR, TrueX, etc). Use a combination of iterations and subsets between 50-60 (e.g.: 2 iterations and 24/28 subsets) without any type of post-filtering.	Recon settings: Algorithm name: _____ Iterations / subsets: _____ Pixel spacing [x, y, z]: _____ mm	

Be sure to enable all quantitative corrections (attenuation, scatter, randoms, dead time, decay, normalization, etc.). If TOF is available, please enable it. Aim at a pixel size close to 4 mm if possible.	TOF enabled: Yes / No	
Export all images in DICOM 3.0 format.		

2) Phantom analysis

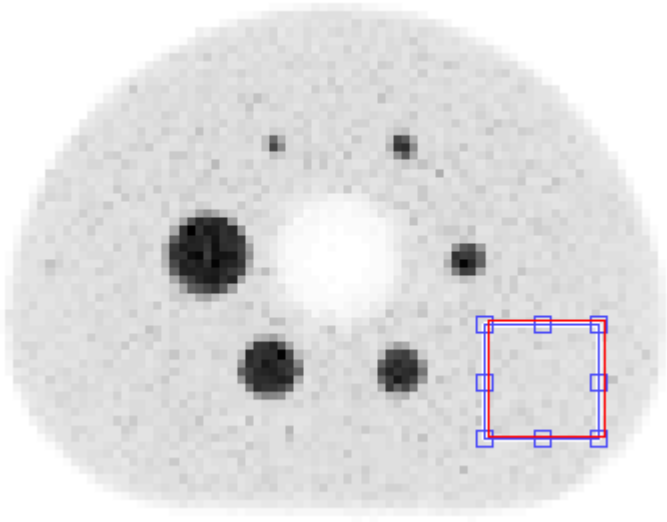
Go to "Load Nema Phantom". A MIP of the phantom should be displayed:



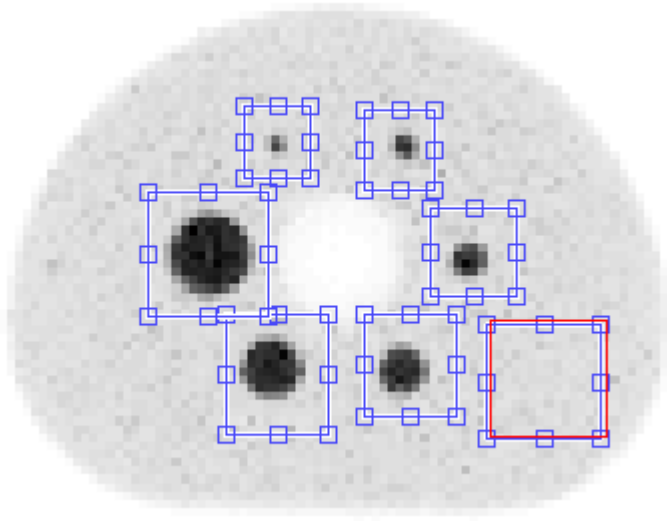
Go to "Harmonization from NEMA phantom". The toolbox will ask for confirmation of:

- Volume of the solution used to fill the spheres [ml]
- Activity used to fill the spheres [MBq]
- Activity reference time [hhmms]
- Start of image acquisition [hhmmss]

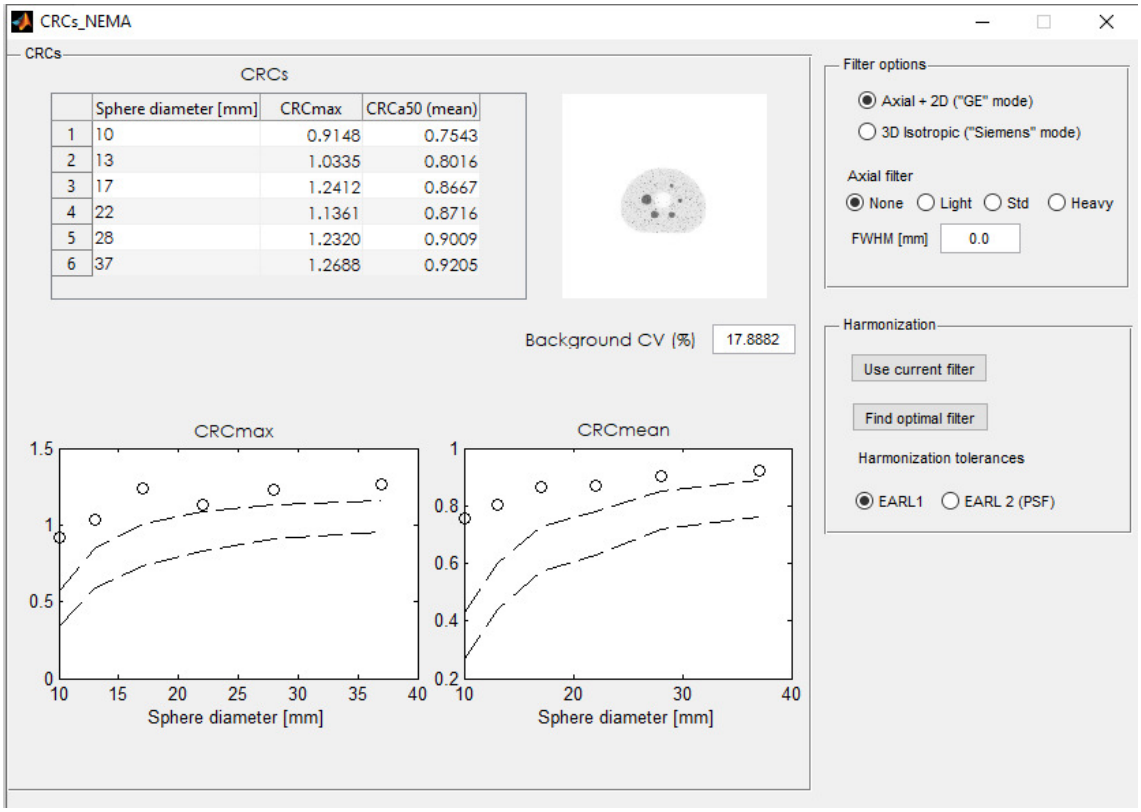
Then, draw a rectangular selection in the background (double click to confirm):



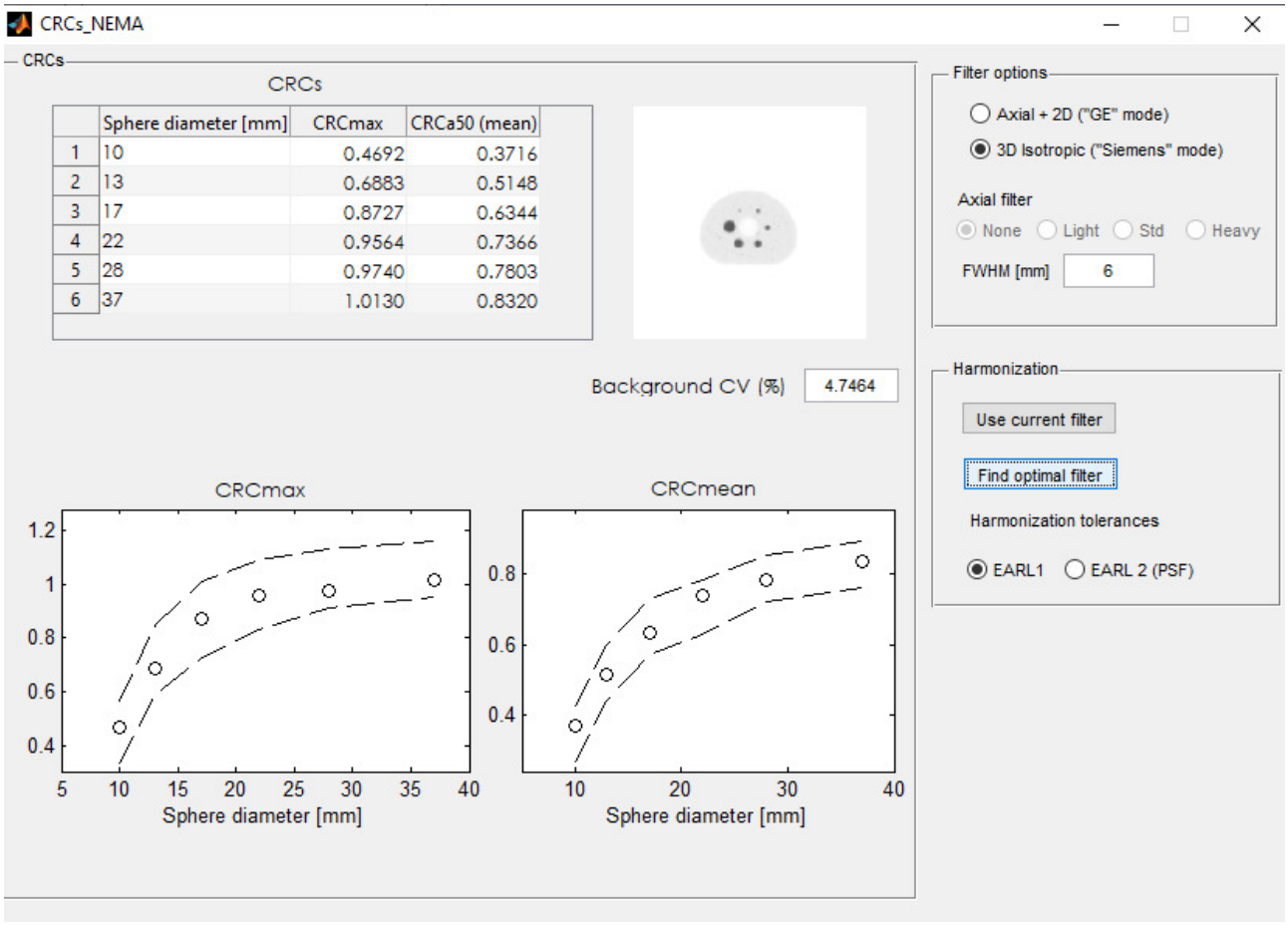
Next, draw rectangular ROIs enclosing the spheres, from smallest to biggest:



A window with CRC estimation appears:



The harmonization options are very similar to those of the cylindrical phantom utility. The user can now select EARL 1 (non-PSF) or EARL 2 (PSF) tolerances. For example, we could select 3D Isotropic filter ("Siemens" mode) and then click on "Find optimal filter" for EARL 1 tolerances:



The result should be 6 mm FWHM for the demonstration image included with the toolbox.