4 MR Permeability

Indications for Use

The MR Permeability application is designed to visualize T1 Weighted Dynamic Contrast-Enhanced (DCE) 3D datasets and assist in analyzing the tissue response. The MR Permeability application supports any related conditions for which permeability analysis is indicated as part of patient management, such as conditions involving the prostate and the brain.

Intended Use

The Philips IntelliSpace Portal is intended to be used and operated only in accordance with the safety procedures and operating instructions given in this "Instructions for Use" for the purpose for which it was designed. The purpose for which the equipment is intended is given below. However, nothing stated in this "Instructions for Use" reduces user's and operator's responsibilities for sound clinical judgement and best clinical procedure.

The IntelliSpace Portal processes clinical images from different modalities and enables advanced visualization of the images. When used by qualified personnel, it provides useful diagnostic information. IntelliSpace Portal can be used remotely by multiple users with compatible devices.

Use and operation of this equipment is subject to the law in the jurisdiction(s) in which the equipment is being used. Both users and operators must only use and operate the equipment in such ways as do not conflict with applicable laws, or regulations which have the force of law.

Indications for Use of the MR Permeability package are:

- MR Permeability facilitates the radiologist in visualizing and post-processing dynamic contrast-enhanced datasets. It is an optional package within IntelliSpace portal.
- MR Permeability can be used by the radiologist to assess the micro-vascular properties by computing vascular permeability (Ktrans), tracer efflux rate (Kep), extravascular volume fraction (Ve), plasma fraction (Vp), and Area under the curve (AUC) from T1 images of brain and prostate. The applied pharmacokinetic modeling is based on the Tofts model.
- The results are presented back to the user in the form of a parametric map, a table of results and in a graph.
- MR Permeability facilitates the visualization of areas with increased permeability.
- MR Permeability facilitates the visualization of variations in permeability.
- MR Permeability is a software tool for visualizing and post processing dynamic contrast-enhanced 3D datasets, acquired to visualize areas with abnormal vascularity.

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Overview

The MR Permeability package allows the analysis of a contrast bolus passing through the tissue. The package assesses the permeability differences between tissues according to the Tofts Model.

The purpose of the package is twofold:

1. Generating parametric maps

   The package generates parametric maps (in color or grayscale and with or without an underlay) that reflect different parameters describing the time intensity curve per pixel.

2. Detailed analysis of parametric maps calculated by the Permeability package

   Based on Regions Of Interest (ROI's) in different parts of the area under examination, numerical results can be calculated and presented in graphs.

Valid imaging series

MR Permeability has the following acquisition requirements.

Three series are required as follows:

- A Dynamic Contrast-Enhanced (DCE) series with 20 dynamics or more is needed, typically with high temporal resolution and flow artifact reduction.
- Two reference series.

To calculate the baseline T1 relaxation time per pixel (baseline T1 map), two T1-FFE reference series with different flip angles (for example, 5 and 15 degrees) are required.

The two reference series should be identical to the DCE series in terms of, for example, field of view, orientation, resolution, slice thickness, number of slices.

The two reference series should fulfill the following criteria:

- They should not be a dynamic series.
- TR about 10 ms (should be identical for reference series 1 and reference series 2).
- TE about 2 ms (should be identical for reference series 1 and reference series 2).
- Reference series 1 has a flip angle of 5 degrees.
- Reference series 2 has a flip angle of 15 degrees.

In exceptional cases a single reference series can also be used. But in that case the TR and the TE of the reference series and the DCE series have to be identical. They still need to have different flip angles.

Perfusion model for result calculation

The pharmacokinetic calculation is done on a pixel-by-pixel basis using a 2-compartment model. The calculation is based on the Extended Tofts Model (ETM):

$$C(t) = v_{\mathrm{p}}\, C_{\mathrm{a}}(t) + K^{\mathrm{trans}}\, e^{-tk_{\mathrm{ep}}} * C_{\mathrm{a}}(t)$$

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where:

C(t)	Contrast concentration in tissue
v_p	Fractional value of blood plasma (also referred to as Volume fraction of plasma space)
$C_a(t)$	Arterial Input Function (Contrast concentration in feeding artery) see explanation in the section below
K^{trans}	Transfer constant between blood plasma and extravascular extracellular space (EES)
k_{ep}	Rate constant between EES and blood plasma

For more details refer to “Quantitative MRI of the Brain” by Paul Tofts; Ch 10: T1-W DCE-MRI: T1-Weighted Dynamic Contrast-Enhanced MRI (pages 341–364).

For the population average AIF a bi-exponential analytical model is used (this is a mathematical equation instead of, for example, a list of numbers), which makes the model suitable for any temporal resolution. Furthermore, the bi-exponential Weinmann plasma curve is used, which means that the model shape is very simple and does not incorporate recirculation effects after the first bolus passage (this may be seen in other more complicated models as described by, for example, Fritz-Hansen or Parker).

Arterial Input Function (AIF)

The calculation of permeability characteristics can be done based on a model based AIF or based on a manual AIF.

The **model based AIF** can have 3 different bi-exponential shapes. The different shapes are controlled by the user selected **injection duration** which is a property of the injection preset and can be set to:

- short (less than 5 s)
- medium (from 5 to 10 s)
- long (longer than 10 s)

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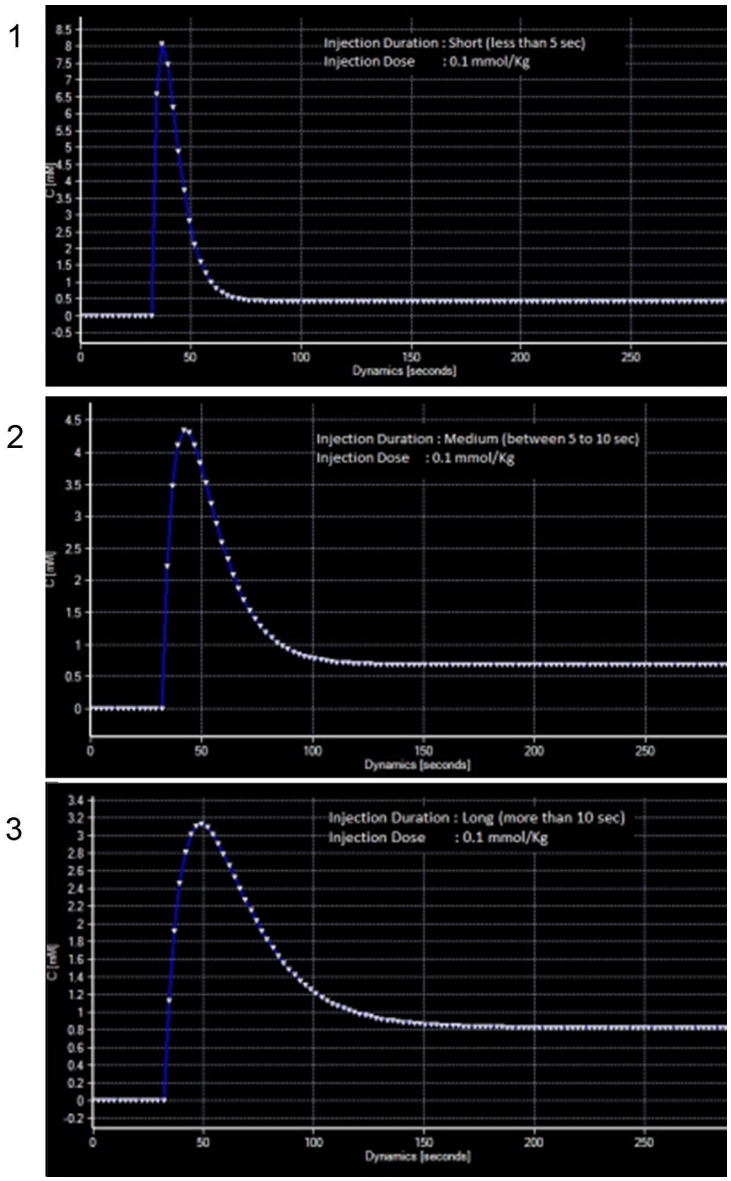

Fig. 24: The 3 different bi-exponential shapes used for the model based AIF: 1 - short, 2 - medium, 3 - long.

The values in the Philips injection presets serve as an example and are based on a common contrast agent Gd-DTPA, a commonly used injection dose of 0.1 mmol/kg, typical medium injection duration (between 5 s and 10 s) and a normal hematocrit value of 45%. However every hospital has to define their own injection protocols, that match their contrast agents and injection characteristics.

The **manual AIF** requires manual placement of a square of 7x7 pixels on a user selectable vessel. Based on a user selected collection of about 5 pixels out of the 7 x 7 matrix that in shape and timing best match an expected AIF, the system will determine an average AIF function to calculate the permeability characteristics.

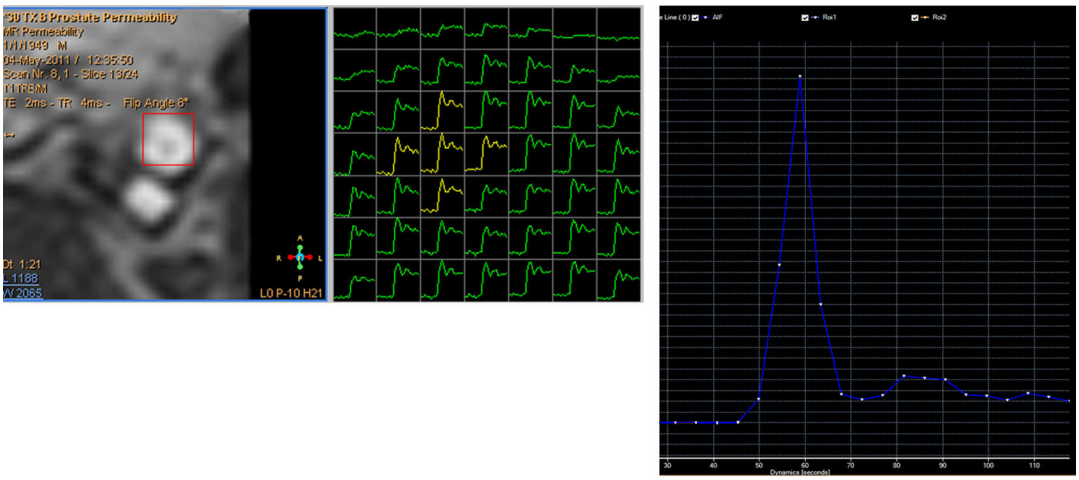

Fig. 25: Defining the Manual AIF. Left: ROI over the feeding artery and the corresponding curves of each pixel. Right: Average AIF.

Other properties affecting the results

Other hospital dependent injection properties affecting the calculation of permeability characteristics are the **contrast relaxivity** which depends on the contrast agent in use, and the **injection dose**. Since the **contrast relaxivity** is field strength and contrast agent dependent, per field strength and contrast agent a different injection preset is required if applicable. The hematocrit value is a patient dependent parameter, that has a default value of 45%.

User Interface

Screen layout

The MR Permeability package has a default layout of four viewports with toolbar, control panel and task guidance. The viewports display the following views:

- Source image in the middle of the imaging volume.
- In real-time calculated Parametric Permeability maps.
- Table Viewer (numerical results) and Anatomical Viewer.
- Graph Viewer (graphical results) and Anatomical Viewer.

Switch between Graph Viewer, Table Viewer and Anatomical Viewer

1. Click the 'Graph Viewer' tab to switch to the Graph Viewer.
2. Click the 'Anatomical Viewer' tab to switch to the Anatomical Viewer.
3. Click the 'Table Viewer' tab to switch to the Table Viewer.

More information on the Graph Viewer and the Table Viewer can be found in the section “Results” on page 69.

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More information on the Anatomical Viewer can be found in the section “Workflow” on page 61.

Task Guidance

The MR Permeability package provides a task guidance in the left part of the screen.

Follow the steps of the task guidance to make optimal use of the package.

The following workflow description is based on this task guidance.

Toolbar

Color LUT (Look-Up Table)

- To select the color look-up table for the maps.

  Possible settings are: 'Blue to Red', 'ASIST' and 'Gray'.

Color LUT	Minimum value				Maximum value
Blue to Red	Blue	Green	Yellow	Orange	Red
ASIST	Black	Light blue	Green	Yellow/ Orange	Red
Gray	Black		Gray		White

The ASIST LUT is a LUT specifically designed for acute stroke imaging. The Acute Stroke Imaging Standardization Group - Japan (ASIST-Japan) is a group that conducts medical research projects dedicated to the standardization of brain computed tomography (CT) and magnetic resonance imaging (MRI) in the clinical setting of acute cerebral stroke.

Layout

To select another screen layout, click  **Layout** and select a layout option. You can also edit the current layout and save it as a preset using the **More** menu. Custom layouts that you have saved as presets are also available in the **Layout** list.

Follow Mouse

Once enabled, this function displays real-time results for the current voxel (indicated by the current position of the cursor).

Select Reference Series

By default, during analysis suited reference series are automatically detected and used. The function 'Select Reference Series' allows to use other series as reference series if required.

1. Click 'Select Reference Series' from the 'More' drop-down menu in the toolbar.

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2. Then browse to the series you would like to use as reference series (Reference 1 and Reference 2) and click **OK** to confirm.

NOTICE

By default, the application uses the reference series with minimum and maximum available flip angle to compute the permeability maps.

According to literature, it is best to use reference series with flip angle of 5° and 15°. More information can be found in the article: Optimizing the Precision in T1 Relaxation Estimation Using Limited Flip Angles By Henry Z. Wang e.a. MRM 5, 399-416 (1987).

Viewing Tools

 **Mirror**

This function mirrors the image(s) (Right <-> Left)

 **Flip**

This function flips the image(s) (Up <-> Down)

 **Rotate Clockwise**

This function rotates the image(s) clockwise

 **Rotate Counter-Clockwise**

This function rotates the image(s) counter-clockwise

Workflow

Launch the MR Permeability package

▷ In the 'Directory' tab of the activity bar:

1. Select a suitable permeability series.
2. Click ’MR Permeability’.

The MR Permeability package opens.

Scroll through images

Through dynamics

1. In the image viewport, drag to the left or to the right.

Through slices

1. In the image viewport, drag up- or downwards.

Through maps

1. In the map viewport, drag to the left or to the right.

Analysis

In the Analysis list in the task guidance panel, select one of the following methods:

- Model based AIF

  For additional information see section “Co-Registration Inspection” on page 50.

- Manual AIF

Optional: Define Manual AIF

Manual AIF allows applying the manual AIF method in the result calculation, instead of the model based AIF that is performed depending on the injection parameters.

1. Select 'Manual AIF' from the 'More' drop-down menu in the toolbar.

   The 'Define AIF' window opens.
   Moreover the analysis step 'Define AIF ...' will be added to the Task Guidance as part of the step 'Analysis' allow to easily access the 'Define AIF' window.

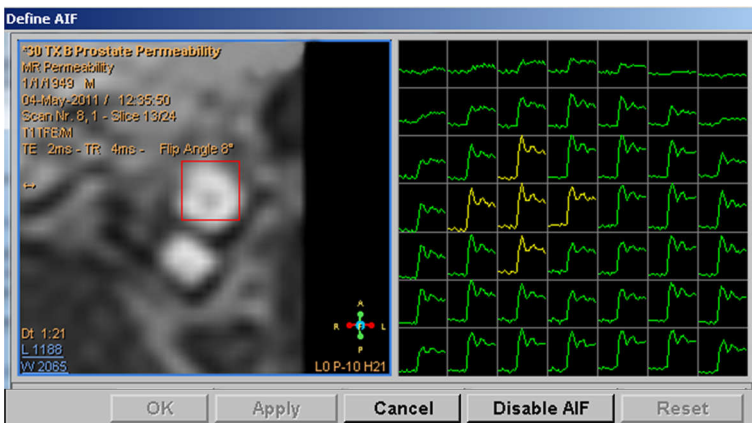

Fig. 26: 'Define Manual AIF' window. The left part of the window shows the anatomical image with the red box for vessel definition. The right part shows the corresponding Time-Intensity diagrams of each pixel.

2. Navigate to the slice with the vessel relevant for Manual AIF definition.
3. Zoom, pan and window the slices so that this vessel is clearly visible.
4. Drag the red box over this vessel.

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The display of the curves will automatically be updated.

5. Click the pixels where the curve shape best represents the expected AIF (i.e. high amplitude and/or steep upslope).

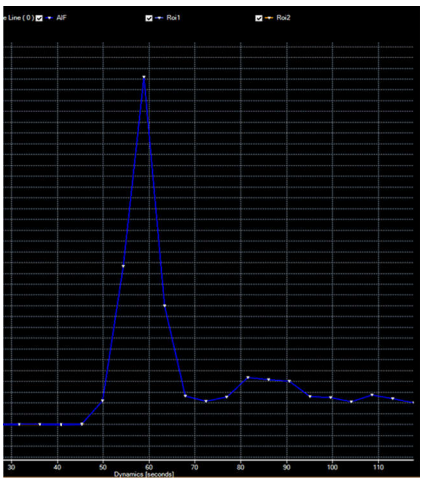

Fig. 27: Average AIF of selected pixels: contrast concentration curve reconstructed from the above selected signal intensity curves (yellow after selection).

6. Click 'Apply' to confirm this selection and in such a way start the calculation.
   Clicking 'OK' accepts the selection.
   Clicking 'Cancel' leaves the window without any change.
   Clicking 'Disable AIF' disables the manual AIF calculation and uses the model based AIF calculation instead.
   Clicking 'Reset' resets the position of the red box to its previous position.

NOTICE

Unreliable AIFs should be avoided to guarantee that the analysis works within its limitations. In particular, AIF with strong shape distortion should be avoided.

The Tofts model designed is based on a proper AIF.

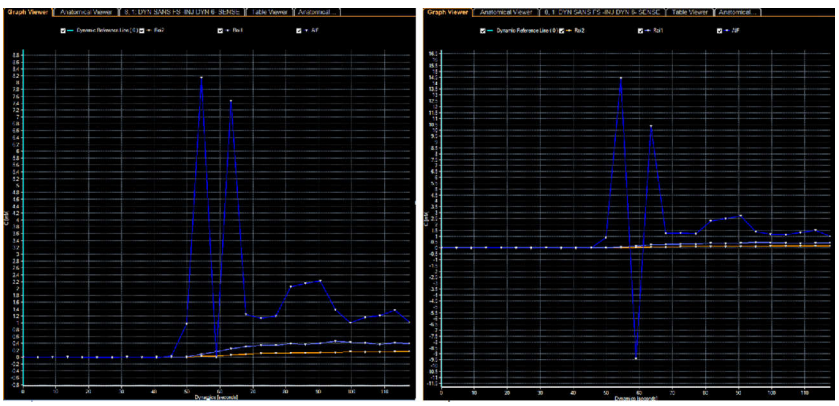

Fig. 28: Example of unreliable AIFs.

Select Input Parameters

1. Select an injection preset from the drop-down menu in the Task Guidance.

   If a suitable injection preset is not yet available, an injection preset needs to be created. See the "More" functions description in section “Toolbar” on page 60 for details.

WARNING

Verify that the selected preset matches the injection conditions during acquisition.

NOTICE

The Blood T1 values used for the calculations are different depending on the used magnetic field strengths.

The table gives the used values. More information can be found in the following article: Blood longitudinal (T1) and transverse (T2) relaxation time constants at 11.7 Tesla. Ai-Ling Lin e.a. Magn Reson Mater Phy; DOI 10.1007/s10334-011-0287-2.

Magnetic Field Strength (Tesla)	Blood T1 value (millisecond)
1.0	1345 ms
1.5	1412 ms
3.0	1613 ms
7.0	2149 ms

You can select what injection protocol is used depending on the tissue which was scanned. The preset details of each protocol can be viewed and edited with the 'view' option.

Create New Preset ...

This function allows to create analysis presets that match the injection protocols used.

During the analysis, you can select the preset corresponding to the current injection characteristics via the Task Guidance function "Select Input Parameters".

For ease of use, these presets can be saved under a user defined name. However, it is recommended to create a new preset only when necessary.

1. Click 'Create New Preset ...' from the More drop-down menu in the toolbar.
2. Enter a name for this preset.
3. Select the *Magnetic Field Strength* of the used MR system in Tesla.
4. Enter the *Contrast relaxivity* in s^{-1} x $mmol^{-1}$.
5. Enter the *Injection dose* in mmol/kg.
6. Set the *Injection duration* to *short*, *medium* or *long*.

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Select *Short* when the bolus takes less than 5 s; select *Medium* when the bolus takes 5 s to 10 s; select *Long* when the bolus is longer than 10 s.
With 'Manual AIF' the injection duration is not applicable. Instead the 'Manual AIF' is used for the calculation.

7. Enter the *Hematocrit* in %.

Delete Presets ...

This function allows to delete injection protocol presets.

 **Apply Spatial Smoothing**

- To spatially smooth the resulting maps.

Possible settings are: None (no smoothing), Weak, Medium or Strong.

Spatial smoothing smoothes the maps and the original images. In such a way, spatial smoothing has an effect on the numerical results.

 **Apply Temporal Smoothing**

- To temporally smooth the resulting maps.

  Possible settings are: None (no smoothing), Weak, Medium or Strong.

Select the Desired Maps

You can select the maps for real-time calculation and display, and for the generation of new imaging series.

1. Click the checkbox of a map to select/deselect this map.

   The display of the real-time calculated maps will be updated accordingly.

Display T1 and Delay Maps

- To display T1 and Delay maps in the maps viewport.

Select Series for Anatomical Viewer

Upon startup of the package, the Anatomical Viewer is empty. However an additional imaging series in the Anatomical Viewer might help during navigation through the data set and in order to draw ROIs.

Any type of imaging series can be loaded into the anatomical viewer. The orientation of the series in the Anatomical Viewer is always identical to the orientation of the source image and the map. This might require the calculation of real-time Multiple Planar Reformats.

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NOTICE

When you load an imaging series with an orientation different to the source image into the Anatomical Viewer, the series in the Anatomical Viewer will be a real-time Multiple Planar Reformat (MPR).

Always be aware that the imaging parameter of this series determine the image quality of the resulting MPR. Low resolution imaging series will result in blurry MPRs and might hamper the workflow.

To load an imaging series into the Anatomical Viewer

1. Click the **Anatomical Viewer** tab to switch to the **Anatomical Viewer**.
2. Right-click the **Anatomical Viewer** and click **Select Series** from the right mouse menu.
3. Click on a series in the **Select Series** window and click **OK** to confirm the selection.
4. You can also load a series by dragging and dropping a series.

Tip

When you save a layout, the series displayed in the viewer at that time is saved with the layout. When you reload the layout for another case, the same series is also reloaded in the viewer. You can save a layout using the More menu in the task guidance panel.

Select Underlay

You can select an MR series as underlay of the parametric maps allowing for better allocation.

In order to optimize the display you can also adjust the opacity of the overlaying parametric maps.

NOTICE

MR series are suitable source images. Secondary captures are not suitable because they are lacking in general geometry information.

The underlay is automatically reformatted to the geometry of the overlay. The resolution is determined by the resolution of the overlay in the preview viewer.

Select Underlay

1. Select an option:
   - **None**

     The parametric maps will be displayed without underlay.
   - **Source as Underlay**

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The source series will be displayed as underlay.

- **Select Other Underlay**

  Browse to the series you would like to use as underlay and click **OK** to confirm. You can also load a series by dragging and dropping a series.

Tip

When you save a layout, the series displayed in the viewer at that time is saved with the layout. When you reload the layout for another case, the same series is also reloaded in the viewer. You can save a layout using the More menu in the task guidance panel.

NOTICE

A warning is displayed if the selected series does not match the geometry, which may cause the anatomical image to be mispositioned.

NOTICE

There can be a mismatch between underlay and overlay also in the Anatomical viewer if there was any patient motion between the acquisitions of these series.

Adjust the opacity of the overlay

1. Drag the slider to adjust the opacity of the parametric maps.

You may also drag the right mouse button in the color maps to change the opacity of the overlay.

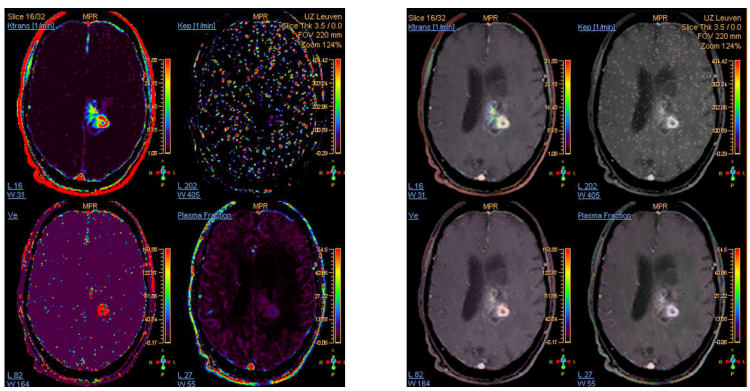

Fig. 29: Left: 100% opacity of the parametric maps. Right: 20% opacity of the parametric maps.

NOTICE

The image registration is disabled which may cause undesired results.

Draw ROI

1. If desired, draw a ROI to focus on a specific area.

   For information on how to draw, modify, and rename a ROI, see section “Draw ROI” on page 15.

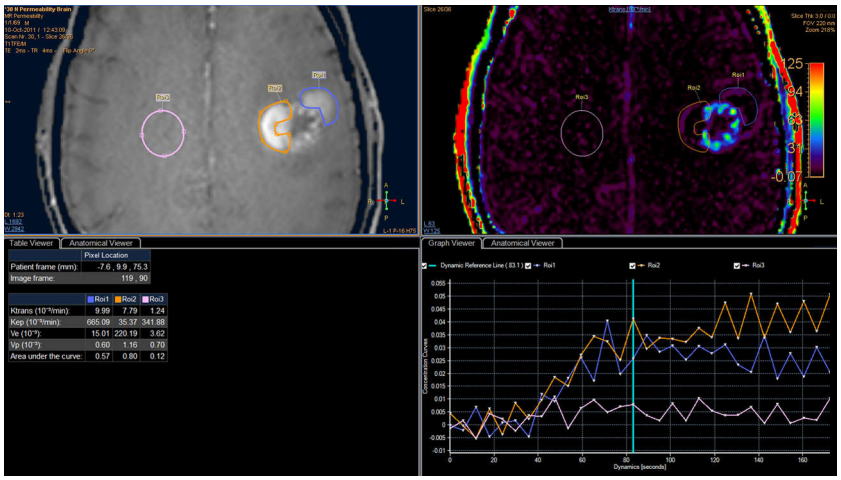

Fig. 30: Different ROI types with numerical and graphical results.

2. If the current series is a brain scan, you can display a mirror line and create contra-lateral ROIs automatically. If desired, select the following options in the task guidance panel:
   - **Show mirror line**
   - **Create contra-lateral ROI automatically**
3. If desired, you can remove the last drawn ROI. Do one of the following:
   - Press Ctrl+Z.
   - Right-click the ROI and then click **Delete Last Drawn ROI** in the shortcut menu.

More options

You can enable/disable the display of curves in the Graph Viewer.

1. Check the checkbox 'Roi1', 'Roi2' or any 'Roi' in the Graph Viewer to enable the display of the related graph.
2. Uncheck the checkbox 'Roi1', 'Roi2' or any 'Roi' in the Graph Viewer to disable the display of the related graph.

Generate Series

You can generate a new imaging series containing the parametric maps and results as defined in the previously described workflow.

1. To generate a standard DICOM-compatible series, select **Generate Series** using the Secondary Capture option from the drop-down list, and then click the button.
2. Enter the name of the new imaging series in the **Name** box.

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3. To generate a series as RGB images (high resolution color maps), select **Generate Series** using the Secondary Capture RGB option.

Register Data While Saving

Once enabled, this function performs registration when generating actual maps. In such a way image quality will most likely improve in the maps.

NOTICE

If the input data is unregistered, there can be a mismatch between the previewed and generated maps as the generated maps are calculated after registering the input.

Results

NOTICE

Various factors like inaccurate definition of AIF, patient motion, temporal resolution, and bolus injection conditions influence permeability values.

NOTICE

From synthetic validation studies it has been shown that for small extracellular extravascular space and large transfer constant of diffusable tracer from the vessel to the EES, the fitted results are not accurate. Therefore note that in parametric area the measured results should be interpreted with caution.

The package calculates the following results:

Graphical and numerical results

- The graphical results present a **Time-Intensity Diagram** (intensity versus time).

  In 'Follow Mouse' mode, the graph correlates to a specific pixel and shows the intensity value (intensity) over the time for this pixel.
- The results will be provided as **parametric maps** and in a **table of results**.

  Scrolling through the maps, the type of the map is indicated in the map’s series type field.

NOTICE

Please note that the pixel location remains in the table viewer, even after moving out of the image frame.

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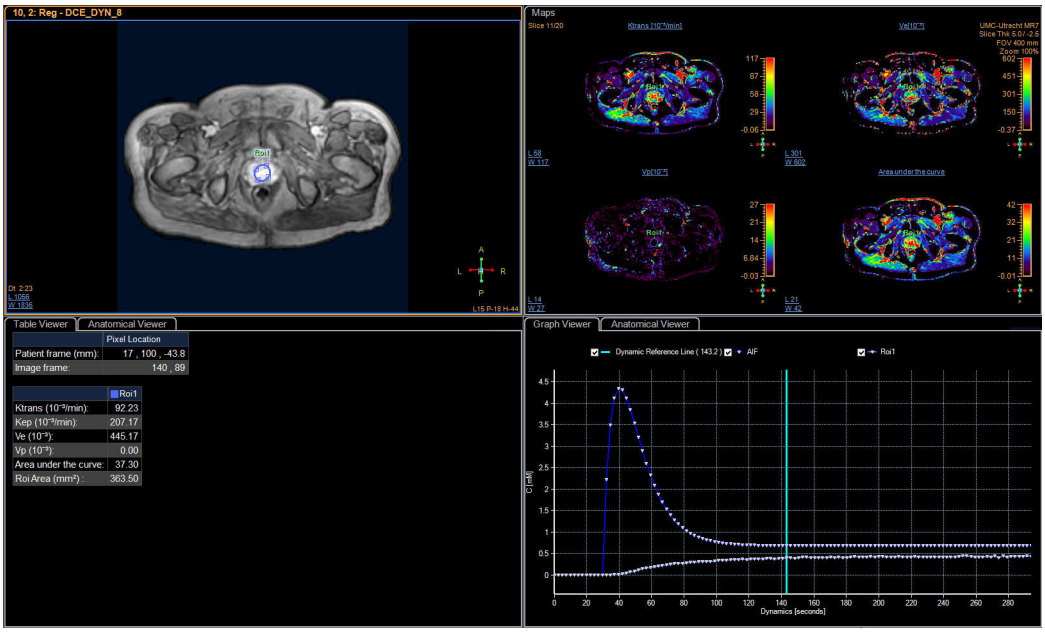

Fig. 31: Results screen: source image and maps with ROIs, Table Viewer and Graph Viewer. The dynamic reference line indicates the currently shown dynamic

NOTICE

If you hide the dynamic reference line, you can display it again by right-clicking in the Graph view and selecting it from the context menu.

To draw a windowing ROI, right-click a map and then click **Draw Windowing ROI**. The color scale of the map is recalculated to display maximum color heterogeneity inside the ROI. You can draw windowing ROIs on each map independently.

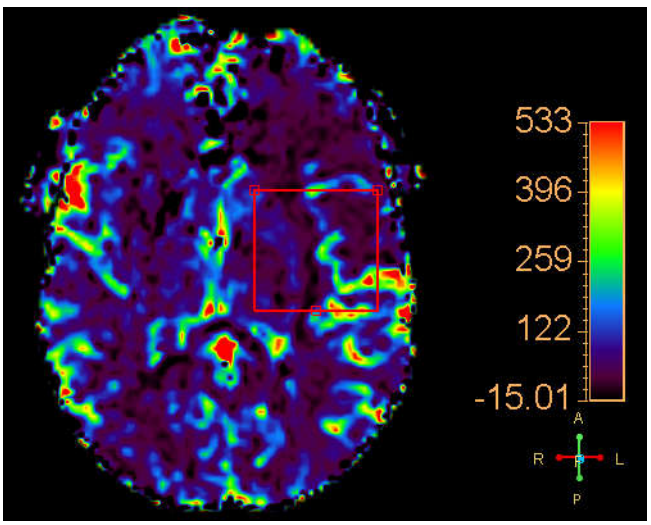

Fig. 32: Drawing a windowing ROI

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Measurement Type Selection

To change the type of measurement for all parametric maps, right-click the results summary table and select an option.

- **Region Parameters (Factory default)**: The application calculates T1 parameters using the time intensity curve for the drawn ROI and displays the values in the Table Viewer.
- **Mean Voxel Parameters**: The application calculates the mean of all the voxels inside the ROI of the output parameters and displays the values in the Table Viewer.

  The table heading is updated based on the selected type.

Show ROI Statistics

You can right-click the results summary table and choose to show ROI voxel statistics (or) select from the **More** menu.

An additional numerical results table is displayed as a floating window and displays Maximum, Minimum, Median, Average and Standard deviation of the quantitative parameters for the ROI voxels within the parametric maps.

When the number of columns in the Table Viewer exceeds thr default width, or number of rows exceeds default height, the auto scroll is visible to allow the user to scroll to see all the columns and rows.

To export table results:

1. Select **Copy to Clipboard** an open either Microsoft Word or Excel and paste the contents from your clipboard into the application.
2. Select secondary capture. A dialog box is displayed allowing you to select a file name, file format, and destination. You can save the series in DICOM format, or in non-DICOM format. If you select a non-DICOM format, you should additionally select a file system destination for exporting the table results.

Parameters

K^{trans}

- Transfer constant between blood plasma and Extravascular Extracellular Space (EES), also called vascular permeability

k_{ep}

- Rate between EES and blood plasma (also called Tracer Efflux Rate)

v_e

- Extravascular Volume fraction (Leakage space)
- Defined as K^{trans} / k_{ep}

v_p

- Plasma Volume fraction (Vp)

AUC

- Area Under the Curve of all time curves

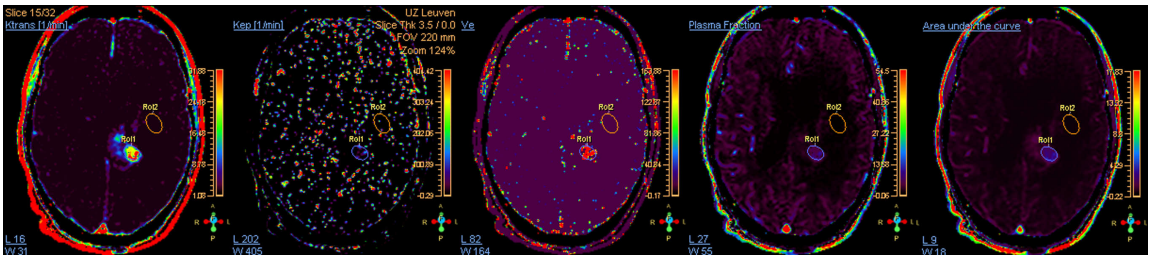

Fig. 33: Result maps of the Permeability package.: K^{trans}, k_{ep}, v_e, v_p, Area under the curve.

T1 and Delay map

The T1 and the Delay map are added for quality control purposes.

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