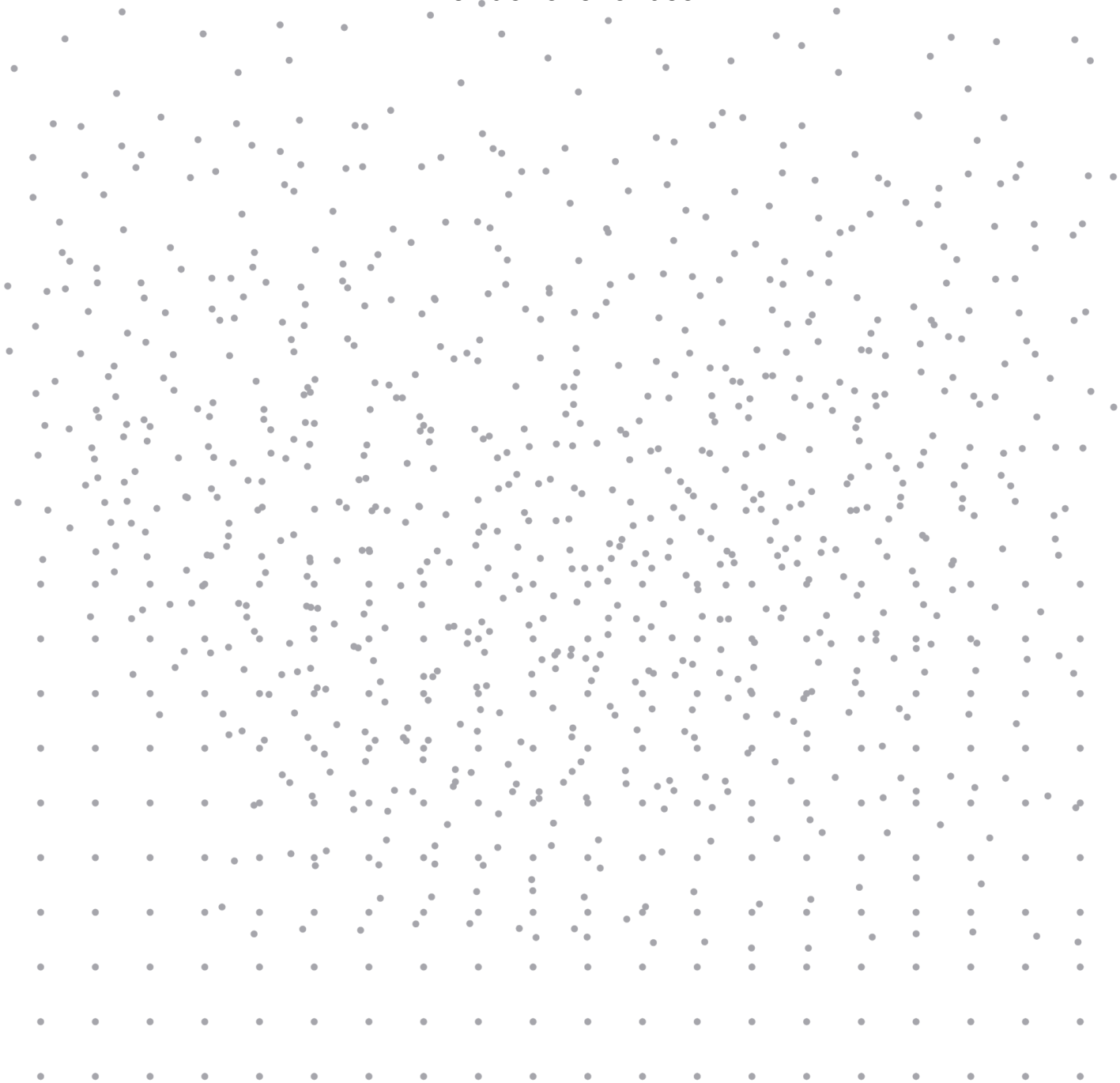
Capillary Function

Instructions for use



Cercare Medical

Application version: `release-2022-03-01-01`, build date: `2022-04-04`

Contents

1 Regulatory symbols **2**

2 Terms and definitions **2**

3 General warnings and cautions **2**

4 Incidents and adverse events **3**

5 About Capillary Function **3**

6 About Cercare Medical Neurosuite **3**

7 Introduction **4**

8 Indications for use **4**

9 Device description **4**

10 Requirements **5**
10.1 Hardware acceleration 5

11 Performance **5**
11.1 Guarantees 5

12 Installation **5**

13 Usage **5**
13.1 Overview of generated series 5
13.2 Settings View 7
13.3 Motion Correction 15
13.4 Enable MR PWI DCE population-based AIF 15
13.5 Vasculature removal 16
13.6 Mean intensity curve view 16
13.7 AIF selector view 17
13.8 Keyboard shortcuts 19

14 MR DSC Perfusion Processing **19**
14.1 Notes on advanced perfusion markers 20

15 MR DCE Perfusion Processing (EU ONLY) **21**

16 Warnings and alerts **22**

17 CT Perfusion Processing **23**

18 References **25**

19 Appendix A: Overview of Capillary Function outputs **26**
19.1 MR DSC and CT Perfusion 26
19.2 MR DCE (EU ONLY) 28
19.3 MR DWI 29

1 Regulatory symbols

Cercare Medical A/S
Inge Lehmanns Gade 10
DK-8000 Aarhus C
Denmark

This device is CE-marked according to
the Medical Device Directive 93/42/EEC

Capillary Function

Medical Device

2 Terms and definitions

Defined terms are spelled with uppercase first letters to signify their importance.

Table 1: Terms, abbreviations and definitions

Term/abbreviation	Definition
AIF	Arterial input function
CF	Capillary Function
CMN	Cercare Medical Neurosuite
CT	Computed Tomography
CTP	CT Perfusion
DICOM	Digital Imaging and Communications in Medicine
DSC	MR Dynamic Susceptibility Contrast
GPU	Graphics Processing Unit
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
RTH	Relative Transit Time Heterogeneity

3 General warnings and cautions

Capillary Function is designed to assist physicians in their daily work.

⚠ (US only) Federal law restricts this device to sale by or on the order of a physician.

⚠ Use of contrast material in conjunction with Capillary Function is at the user's discretion. Any use of contrast material should be consistent with that material's approved labelling.

(US only) Refer to the U.S. Food and Drug Administration's website (www.fda.gov) for information on contrast material uses, warnings and precautions.

⚠ Use of contrast material in conjunction with Capillary Function is at the user's discretion. Any use of contrast material should be consistent with that material's approved labelling.

(US only) Refer to the U.S. Food and Drug Administration's website (www.fda.gov) for information on contrast material uses, warnings and precautions.

⚠ Caution when using MR DCE:
Cercare Medical A/S Capillary Function is only compatible with MR DCE sequences that are interpretable by the steady state formula.

Literature shows that quantitative inter-patient comparison of DCE derived parameter maps should not be performed when based upon fixed pre-bolus T1 values.

Using Cercare Medical A/S Capillary Function with MR DCE sequences with a flip angle below 15 degrees may in certain cases cause artefacts in derived images.

⚠ Cercare Medical A/S offers no guarantees on the correctness, quality, or legality of the medical images on which the software bases its calculations. This includes, but is not limited to, incorrect DICOM headers not set by Cercare Medical Neurosuite. User caution is advised when using the software.

4 Incidents and adverse events

In case of indicents or adverse events connected to the use of CF, please contact Cercare Medical A/S immediately at **support@cercare-medical.com**.

5 About Capillary Function

CF is a software module developed and distributed by Cercare Medical A/S for use with CMN for medical image processing.

6 About Cercare Medical Neurosuite

CMN is a cross platform, desktop application for performing analysis of MR and CT image series.

The application is available for Windows and Linux, but screenshots in this manual may be from other platforms. MN functionality is equivalent across all supported platforms.

7 Introduction

This document contains instructions for use including installation for the software CF manufactured by Cercare Medical A/S. The document is intended for users of the software.

8 Indications for use

CMN and associated modules, including the CF module, is an image processing software package to be used by trained professionals, including physicians and medical technicians.

The software package runs on standard off-the-shelf computer or a virtual platform, such as VMware, and can be used to perform image viewing, processing, and analysis of images. Data and images are acquired through DICOM (Digital Imaging and Communications in Medicine) compliant imaging devices.

CMN provides viewing capabilities, whereas the Capillary Function module provides analysis capabilities for functional and dynamic imaging datasets acquired with CT Perfusion (CTP), and MRI including a Diffusion Weighted MRI (DWI) Module and a Dynamic Analysis Module (dynamic contrast-enhanced imaging data for MRI and CT).

The Capillary Function module is used for visualization and analysis of dynamic imaging data, showing properties of changes in contrast over time. This functionality includes calculation of parameters related to tissue flow (perfusion) and tissue blood volume. In addition, the Capillary Function module's DWI technology is used to visualize local water diffusion properties from the analysis of diffusion-weighted MRI data.

9 Device description

CF, when added to the installed CMN, provides further functionalities for reading, writing, visualizing, and studying medical images.

CF provides perfusion post-processing technologies, where dynamically acquired perfusion CT or MRI series can be processed to yield information relevant for assessment of the hemodynamic status of a patient.

CF generates hemodynamic markers, which can be used for management of diseases with possibly compromised hemodynamic function, such as ischemic stroke and tumors.

The generated output maps can be viewed by standard DICOM image viewers. In addition, CF includes the possibility for post-processing diffusion-weighted imaging (DWI) MRI data. Post-processing of DWI data results in maps reflective of local water diffusion properties. The post-processed DWI-derived maps can be viewed in standard DICOM image viewers. CF thus works with the following technologies:

- CT (Computed Tomography)
- MRI (Magnetic Resonance Image)

Comparative performance testing was performed for CMN with CF with respect to the RAPID software (K172477) through bench testing including simulated digital phantoms and retrospective clinical data. Whereas the latter was primarily used for visual inspection due to the relative nature of most perfusion image biomarkers, rigorous testing was conducted through digital phantoms where the true parameter combinations were known. The simulated phantom data included variations of hemodynamic parameter combinations, while simultaneously simulating various experimental conditions such as patient motion, signal-to-noise ratios, and diffusion gradient schemes. Both so-called structured digital phantoms and more human-like phantom testing and analyses were conducted and performance quantified through comparison of absolute bias, correlation coefficients, and multi-scale structural similarity index obtained for both devices. The established acceptance criteria were reached in all tests conducted.

10 Requirements

CF is distributed as part of CMN. System requirements for CF are the same as for CMN. Please refer to “2.3080 Instructions for use Cercare Medical Neurosuite” for details.

10.1 Hardware acceleration

CF can optionally make use of Graphics Processing Unit (GPU) hardware acceleration during parts of its calculations. Hardware acceleration requires the presence of an OpenCL enabled graphics card. If no compatible graphics card is detected, calculations are performed in software utilizing solely CPU processing, which overall results in slower speed. Current generation GPUs can speed up calculations by as much as a factor of 10 depending on the exact graphics card model. Please refer to Table 2 for details about graphics card compatibility.

Table 2: Supported hardware acceleration frameworks

Processing mode	Acceleration framework	Minimum version supported
capillary-function	OpenCL	1.0

11 Performance

In this section, the expected performance of the application is briefly discussed.

11.1 Guarantees

No guarantees about specific performance numbers are made since performance is highly dependent on factors such as:

- Input image resolution
- Hardware performance
- Network speeds
- Data transfer speeds
- Size of input series

12 Installation

CF is automatically installed as part of CMN.

13 Usage

The following sections detail how to use the CF module.

13.1 Overview of generated series

As a processing module in CMN, CF generates several image series based on an original perfusion input series.

The following sections enumerate and describe all output series that can be generated by CF. Please refer to section 19 for definitions of CF outputs and Section 14.1 for a description of how to use the non-standard perfusion series in clinical work.

CF supports different algorithms for calculating certain images with similar clinical interpretations (eg. the ”rBCV” image can be interpreted similarly to the ”rCBV Basic” image, although the underlying algorithms are different). When multiple images with the same interpretation are available for generation by CF, only one of those will be generated, namely the one determined by Cercare Medical to provide the highest level of safety. If needed, generation of alternative, similar images can be enabled via the CMN GUI settings or by CMN command line switches.

⚠ Please note:
The following are non-standard perfusion derived series:

- rCMRO2
- COV
- CTH
- Delay
- OEF
- rLeakage
- Lack of information (probability)

Please consult the literature referenced in section “References” for detailed documentation of possible interpretations of each non-standard series.
A warning icon is displayed in the image area when a non-standard series is loaded into the viewer.

⚠ Please note:
When processing perfusion MR series the included perfusion data is truncated. In practice, this means that only data recorded up to 20 seconds before and 40 seconds after the measured minimum intensity are included in perfusion calculations per default, albeit these thresholds may be adjusted. Truncation is performed to mitigate the risk of unreasonably long processing times in the case of very long (temporal) sequences.

Table 3: Overview of CF output series

Series name	**Series abbreviation**	**Series description**
Relative cerebral blood flow	rCBF	The relative cerebral blood flow.
Relative cerebral blood volume	rCBV	The relative cerebral blood volume.
Time point of residue function max value	Tmax	The time point at which the residue function attains its maximum value.
Relative model-based cerebral metabolic rate of oxygen	rCMRO2 Model-based	The relative model-based relative cerebral metabolic rate of oxygen.
Coefficient of variance	COV	Coefficient of Variance also referred to as relative transit time heterogeneity ‘RTH’ in scientific and clinical literature.

Capillary transit time heterogeneity	CTH	Capillary Transit-time heterogeneity. A measure of the dispersion in intra-voxel capillary transit times. Unit: seconds.
Delay	Delay	Delay from site of measurement of the arterial input function concentration time-curve and site of measurement of the tissue concentration-time curve. Unit: seconds.
Mean transit time	MTT	Mean Transit Time of the passage of blood through a voxel. Unit: seconds.
Relative leakage	rLeakage	Extravasation of contrast agent in a particular voxel, i.e. leakage from the vascular compartment to the extravascular compartment.
Model-based oxygen extraction fraction	OEF (model-based)	Model-based oxygen extraction fraction.
Time To Peak	TTP	Time to peak of the concentration-time curve.
Minimum Intensity Projection	MinIP	Intensity value filtering on lowest intensity values on MR perfusion series.
Maximum Intensity Projection	MaxIP	Intensity value filtering on highest intensity values on CT perfusion series.
Lack of information (probability)	LOI Probability	Measure of the lack of information. I.e. a value larger than e.g. 0.05 means that there is very little information in the particular voxel.
Mean intensity and AIF curves	Mean intensity and AIF curves	A line chart with mean intensity and AIF curves in a single image. The image is based on the same data as the Mean Intensity Curve View in the Cercare Medical Neurosuite viewer.

13.2 Settings View

The settings view is reached by clicking the globally available “Settings” icon in the upper right-hand corner of the application. It provides access to various settings which are used to customize the functionality of CMN.

13.2.1 Processing settings group

The processing settings group enables the user to change some parameters used by CF when processing image series.

13.2.1.1 Select GPU for OpenCL computations

To speed up processing, CF makes use of GPU accelerated calculations. The checkboxes located on the right-hand side of the processing settings group (see Figure 1 lists the names of available OpenCL capable devices. The top checkbox “Auto Select GPU” lets CMN attempt to choose the most suitable device. The remaining checkbox labels contain the name of an OpenCL capable device. In the case shown on Figure 1, a GPU by the name “GeForce GTX 1050” was found. Multiple device names may be available. For manual GPU selection simply check a box and press save.

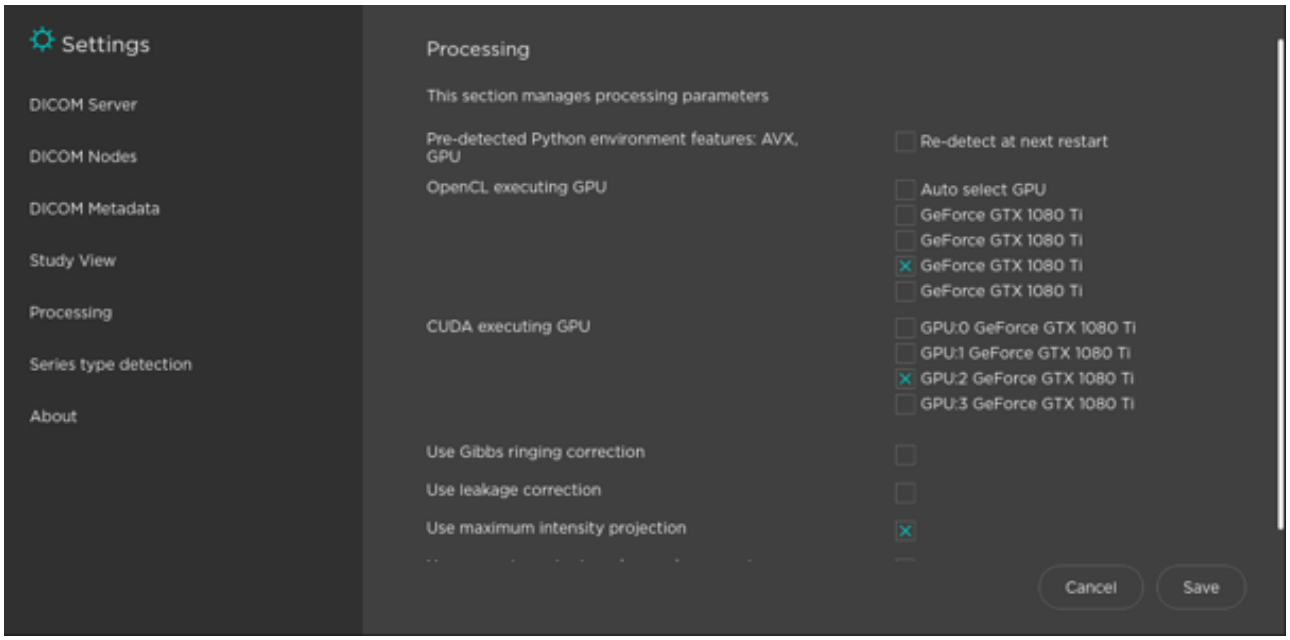


Figure 1: Processing settings group

13.2.1.2 Use leakage correction

When this checkbox is checked, leakage correction is applied when performing processing of perfusion series. This leads to the derived series “Leakage” being generated, see Table 3. Please note that leakage series will not be created for MR PWI DCE series (already leakage corrected) and CTP series (based in the assumption that CTP is not used in leakage sensitive use cases).

13.2.1.3 Define processing constants

To allow users to control certain image processing steps a series of control handles are available in the application. An overview of these controls is presented in Figure 3, albeit not all settings are included. Descriptions of the individual settings are provided below.

> ⚠ Be aware that changing these manual constants may result in changes to the images and other results generated by the product.

13.2.1.3.1 Use leakage correction

Type: Checkbox.
Default value: Inactive.
Relevance: Relevant for the CF module.
Description: In certain pathologies, the blood brain barrier may become permeable to contrast agent, which in turn in principle breaks down the assumed vascular model. In such cases, a two-compartment model should be employed, with one compartment representing the vasculature and the other representing the accessible extra-vascular, extra-cellular compartment. Activating the leakage correction check box thus formally adds a transfer term between these two compartments. For more information, see [**?**] for documentation of the ‘standard’ DSC MRI/CT perfusion vascular model and [**?**] for documentation of the DSC MRI/CT perfusion vascular model including correction for contrast agent extravasation. These references can be located under Section 18.

13.2.1.3.2 Use maximum intensity projection

Type: Checkbox.
Default value: Active.

Relevance: Relevant for the CF module.
Description: By enabling the 'Use maximum intensity projection' check box, so-called maximum intensity projection and minimum intensity projection images will be generated for perfusion input data, depending on whether the perfusion data under consideration are DSC MRI data (minimum intensity projection images are generated) or CT perfusion (maximum intensity projection images are generated). The minimum and maximum intensity projection images are calculated as the minimum or maximum intensity over time for each voxel, respectively.

13.2.1.3.3 Use manual constants (advanced users only)

Type: Checkbox.
Default value: Inactive.
Relevance: All modules depending on the settings altered in the advanced settings menu.
Description: By activating the check box, several advanced settings appear just under the check box. In the settings menu, these settings are indented compared to the general settings to provide a separation between 'standard' and 'advanced' settings. The advanced settings are described individually below.

13.2.1.3.4 CTP pre bolus cutoff (s)

Type: Text field.
Default value: 20.
Relevance: Relevant for the CF module.
Description: The CT Perfusion (CTP) pre-bolus cutoff determines a time period (in seconds) before the valley peak of the mean intensity curve to include in the perfusion analysis calculations (inverse of Figure 2). Hence, dynamic acquisitions before this cutoff value are not included in the perfusion analysis.

13.2.1.3.5 CTP post bolus cutoff (s)

Type: Text field.
Default value: 40.
Relevance: Relevant for the CF module.
Description: The CT Perfusion (CTP) pre-bolus cutoff determines a time period (in seconds) after the valley peak of the mean intensity curve to include in the perfusion analysis calculations (inverse of Figure 2). Hence, dynamic acquisitions after this cutoff value are not included in the perfusion analysis.

13.2.1.3.6 CTP post bolus cutoff (s)

Type: Text field.
Default value: 40.
Relevance: Relevant for the CF module.
Description: The CT Perfusion (CTP) pre-bolus cutoff determines a time period (in seconds) after the valley peak of the mean intensity curve to include in the perfusion analysis calculations (inverse of Figure 2). Hence, dynamic acquisitions after this cutoff value are not included in the perfusion analysis.

⚠ The truncation of the dynamic series before and/or after the peak intensity should be considered with some caution, since strong truncation (low numbers in the pre/post cutoff text fields) can likely result in severely degraded images. The default thresholds supplied for this functionality has not been observed to induce image degrading but speeds up processing time for large perfusion series substantially.

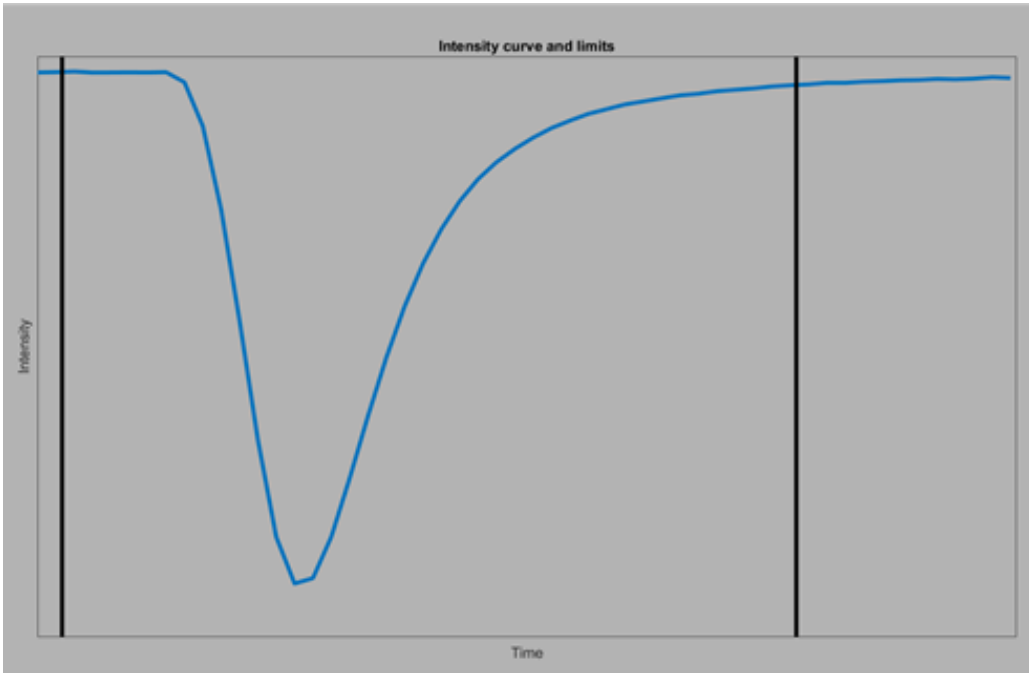


Figure 2: Illustration of the pre-bolus (left vertical bar) and post-bolus (right vertical bar) on a model intensity-time curve where the bolus results in an intensity decrease

13.2.1.3.7 DSC pre bolus cutoff (s)

Type: Text field.
Default value: 20.
Relevance: Relevant for the CF module.
Description: The MR Dynamic Susceptibility Contrast (DSC) pre-bolus cutoff determines a time period (in seconds) before the peak of the mean intensity curve to include in the perfusion analysis calculations (see Figure 2). Hence, dynamic acquisitions before this cutoff value are not included in the perfusion analysis.

> ⚠ The truncation of the dynamic series before and/or after the peak intensity should be considered with some caution, since strong truncation (low numbers in the pre/post cutoff text fields) can likely result in severely degraded images. The default thresholds supplied for this functionality has not been observed to induce image degrading but speeds up processing time for large perfusion series substantially.

13.2.1.3.8 DSC post bolus cutoff (s)

Type: Text field.
Default value: 40.
Relevance: Relevant for the CF module.
Description: The MR Dynamic Susceptibility Contrast (DSC) pre-bolus cutoff determines a time period (in seconds) before the peak of the mean intensity curve to include in the perfusion analysis calculations (see Figure 2). Hence, dynamic acquisitions before this cutoff value are not included in the perfusion analysis.

> ⚠ The truncation of the dynamic series before and/or after the peak intensity should be considered with some caution, since strong truncation (low numbers in the pre/post cutoff text fields) can likely result in severely degraded images. The default thresholds supplied for this functionality has not been observed to induce image degrading but speeds up processing time for large perfusion series substantially.

13.2.1.3.9 DCE pre bolus cutoff (s)

Type: Text field.
Default value: 30.
Relevance: Relevant for the CF module.
Description: The MR Dynamic Contrast Enhanced (DCE) pre-bolus cutoff determines a time period (in seconds) before the peak of the mean intensity curve to include in the perfusion analysis calculations (inverse of Figure 2). Hence, dynamic acquisitions before this cutoff value are not included in the perfusion analysis.

> ⚠ The truncation of the dynamic series before and/or after the peak intensity should be considered with some caution, since strong truncation (low numbers in the pre/post cutoff text fields) can likely result in severely degraded images. The default thresholds supplied for this functionality has not been observed to induce image degrading but speeds up processing time for large perfusion series substantially.

13.2.1.3.10 DCE post bolus cutoff (s)

Type: Text field.
Default value: 1200.
Relevance: Relevant for the CF module.
Description: The MR Dynamic Contrast Enhanced (DCE) pre-bolus cutoff determines a time period (in seconds) after the peak of the mean intensity curve to include in the perfusion analysis calculations (inverse of Figure 2). Hence, dynamic acquisitions after this cutoff value are not included in the perfusion analysis.

> ⚠ The truncation of the dynamic series before and/or after the peak intensity should be considered with some caution, since strong truncation (low numbers in the pre/post cutoff text fields) can likely result in severely degraded images. The default thresholds supplied for this functionality has not been observed to induce image degrading but speeds up processing time for large perfusion series substantially.

13.2.1.3.11 Remove vasculature

Type: Check box.
Default value: Active.
Relevance: Relevant for the CF module, but only for CT perfusion.
Description: Activating the checkbox results in vasculature removal from the final output images based on area under the curve similarity to the arterial input function, i.e. if a particular voxel has an area under the concentration curve similar to the arterial input function area under the curve, that voxel is de-activated in the resulting derived perfusion maps. The similarity measure can be changed via the 'Vascular threshold' setting.

13.2.1.3.12 Vascular threshold

Type: Text field.
Default value: 0.4.
Relevance: Relevant for the CF module, but only for CT perfusion.
Description: If the 'Remove vasculature' setting is enabled, voxels with area under the curve greater than the area under the arterial input function curve multiplied by the vascular threshold are considered blood vessels and are masked out from the derived perfusion maps.

13.2.1.3.13 b value threshold

Type: Text field.
Default value: 0.
Relevance: Relevant for all modules as it is related to the automatic series type detection.

Description: The ‘b value threshold’ setting sets a lower threshold for which to label a series as a diffusion weighted MRI series.
Note: This is only one rule implemented to detect diffusion MRI series.

13.2.1.3.14 inversion time upper threshold

Type: Text field.
Default value: 1000 – the unit is milliseconds.
Relevance: Relevant for all modules as it is related to the automatic series type detection.
Description: The ‘inversion time upper threshold’ sets an upper threshold for which to label a series as a T2FLAIR MRI series. A DICOM header value higher than the upper threshold means that a given series will not be labeled as a T2FLAIR MRI series.
Note: This is only one rule implemented to detect T2FLAIR MRI series.

13.2.1.3.15 inversion time lower threshold

Type: Text field.
Default value: 0 – the unit is milliseconds.
Relevance: Relevant for all modules as it is related to the automatic series type detection.
Description: The ‘inversion time upper threshold’ sets an upper threshold for which to label a series as a T2FLAIR MRI series. A DICOM header value higher than the upper threshold means that a given series will not be labeled as a T2FLAIR MRI series.
Note: This is only one rule implemented to detect T2FLAIR MRI series.

13.2.1.3.16 tr upper threshold MR_PWI_DSC

Type: Text field.
Default value: 2500 – the unit is milliseconds.
Relevance: Relevant for all modules as it is related to the automatic series type detection.
Description: The ‘tr upper threshold MR_PWI_DSC’ setting sets an upper threshold for the repetition time for which to label a series as a DSC MRI series. A DICOM header value higher than the upper threshold means that a given series will not be labeled as a DSC MRI series.
Note: This is only one rule implemented to detect DSC MRI series.

13.2.1.3.17 tr lower threshold MR_PWI_DSC

Type: Text field.
Default value: 600 – the unit is milliseconds.
Relevance: Relevant for all modules as it is related to the automatic series type detection.
Description: The ‘tr lower threshold MR_PWI_DSC’ setting sets a lower threshold for the repetition time for which to label a series as a DSC MRI series. A DICOM header value lower than the lower threshold means that a given series will not be labeled as a DSC MRI series.
Note: This is only one rule implemented to detect DSC MRI series.

13.2.1.3.18 te upper threshold MR_PWI_DSC

Type: Text field.
Default value: 50 – the unit is milliseconds.
Relevance: Relevant for all modules as it is related to the automatic series type detection.
Description: The ‘te upper threshold MR_PWI_DSC’ setting sets an upper threshold for the repetition time for which to label a series as a DSC MRI series. A DICOM header value higher than the upper threshold means that a given series will not be labeled as a DSC MRI series.
Note: This is only one rule implemented to detect DSC MRI series.

13.2.1.3.19 te lower threshold MR_PWI_DSC

Type: Text field.
Default value: 15 – the unit is milliseconds.
Relevance: Relevant for all modules as it is related to the automatic series type detection.
Description: The 'te lower threshold MR_PWI_DSC' setting sets a lower threshold for the echo time for which to label a series as a DSC MRI series. A DICOM header value lower than the lower threshold means that a given series will not be labeled as a DSC MRI series.
Note: This is only one rule implemented to detect DSC MRI series.

13.2.1.3.20 Resampling size x axis

Type: Text field.
Default value: 128.
Relevance: Relevant for the CF module.
Description: The 'Resampling size x axis' setting defines the spatial resampling in number of pixels for the image width employed in perfusion processing calculations. Only spatial downsampling will be performed, i.e. a resampling in x value of 128 in conjunction with an actual image resolution of 100 will *not* result in image resampling during perfusion processing.

The idea behind spatial resampling is to improve signal to noise ratio, while at the same time speeding up processing speed.
Note: Arterial input function selection is performed on the originally sampled data, since the vessel signal-to-noise ratio is usually very good due to the high blood volume and high concentration of contrast altering tracer.

13.2.1.3.21 Resampling size y axis

Type: Text field.
Default value: 128.
Relevance: Relevant for the CF module.
Description: The 'Resampling size y axis' setting defines the spatial resampling in number of pixels for the image height employed in perfusion processing calculations. Only spatial downsampling will be performed, i.e. a resampling in y value of 128 in conjunction with an actual image resolution of 100 will *not* result in image resampling during perfusion processing.

The idea behind spatial resampling is to improve signal to noise ratio, while at the same time speeding up processing speed.
Note: Arterial input function selection is performed on the originally sampled data, since the vessel signal-to-noise ratio is usually very good due to the high blood volume and high concentration of contrast altering tracer.

13.2.1.3.22 Do resample spacing between slices

Type: Text field.
Default value: Inactive.
Relevance: Relevant for the CF module, but only for CT perfusion.
Description: Some CT perfusion images may be sampled very fine in the slice direction (for example 1 mm slice distance). Given the quite low signal-to-noise ratio of CT perfusion raw images due to the low blood volume in brain tissue, the derived images for such a series in its native resolution may be of quite low quality. The 'Do resample spacing between slices' setting provides a handle for improving this by resampling the slice distance to the value provided by the 'Resample spacing between slices (mm)' setting.
Note: Only spatial downsampling will be performed.

13.2.1.3.23 Resample spacing between slices (mm)

Type: Text field.
Default value: 3 – unit is in mm.
Relevance: Relevant for the CF module, but only for CT perfusion.
Description: The interslice distance to resample a 3D image volume to in the case the 'Do resample spacing between slices' settings is enabled, see that setting for additional information.

13.2.1.3.24 Minimum number of frames for perfusion calculation

Type: Text field.
Default value: 18.
Relevance: Relevant for the CF module.
Description: The 'Minimum number of frames for perfusion calculation' setting sets the minimum number of temporal samples for labeling a series as a perfusion series. This value is checked for all imported series in order to detect the type of the series. The interslice distance to resample a 3D image volume to in the case the 'Do resample spacing between slices' settings is enabled, see that setting for additional information.
Note: This is only one rule implemented to detect perfusion series.

13.2.1.3.25 Base line length

Type: Text field.
Default value: 5.
Relevance: Relevant for the CF module.
Description: The default length of the baseline used in perfusion image analysis when converting the intensity-time curve for each voxel to the corresponding concentration-time curve. The baseline length is used to obtain a good measure of the voxelwise image intensity before bolus arrival to reduce noise in the determination of the pre-bolus image intensity. The baseline length is in the vast majority auto detected, and only in extremely rare cases is the default baseline length relevant.

13.2.1.3.26 Temporal subsampling level

Type: Text field.
Default value: 4.
Relevance: Relevant for the CF module.
Description: During parametric deconvolutional perfusion image processing, the results may benefit from finer sampling of the residue function – in particular close to the initial part of the curve, since this part is very relevant for the flow determination. The parametric deconvolution approach adaptively employs subsampling during processing to provide the best possible derived images, given the raw data.

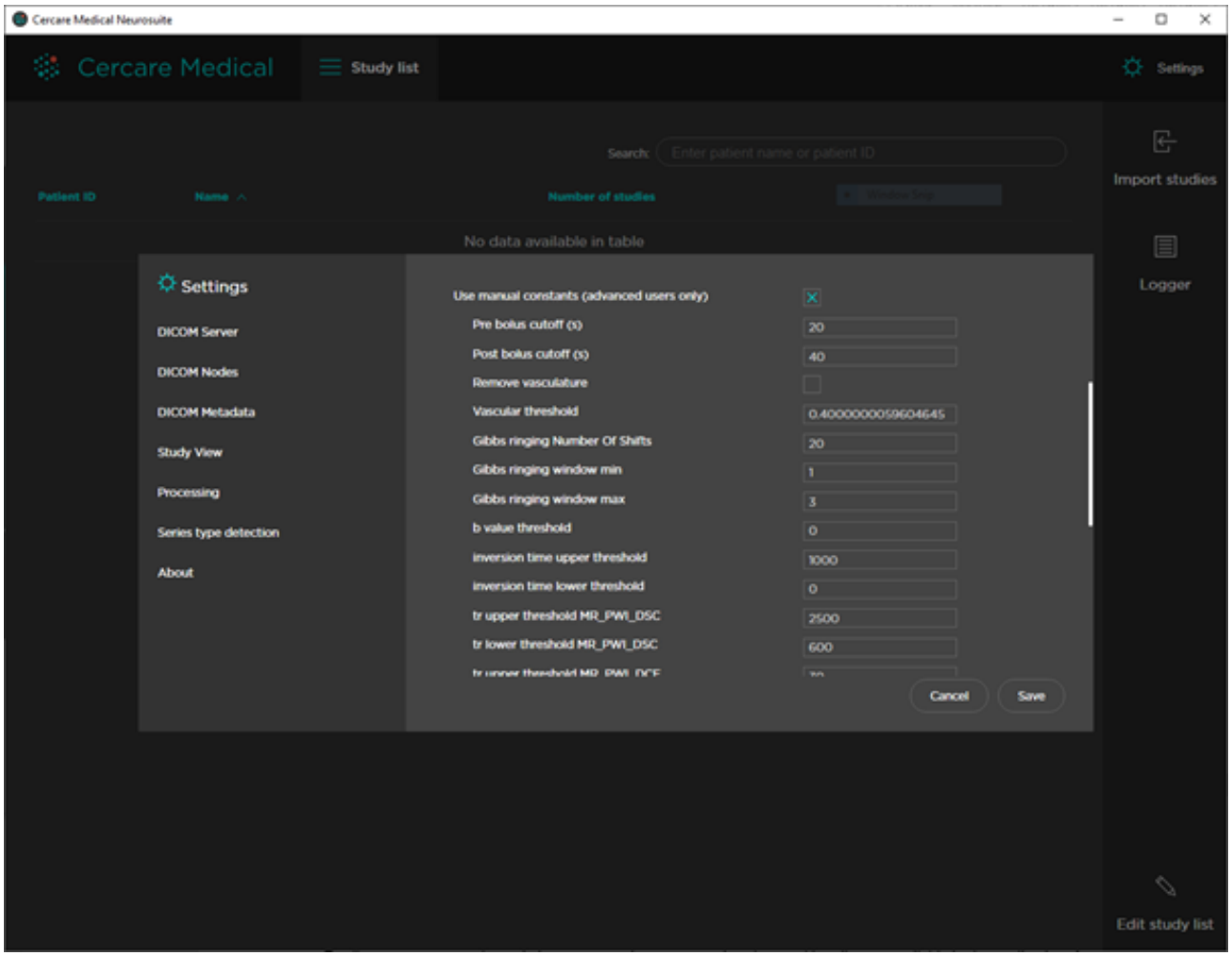


Figure 3: Manual processing constants

13.3 Motion Correction

By default, motion correction is applied to perfusion series. Because of the relatively long recording time compared to other series types, the volumes within a perfusion series tend to move around relative to each other. To mediate this spatial movement, each volume is registered to a single volume within the series, thereby removing any spatial displacement between the volumes.

It is important to note that motion corrected perfusion series does not contain the first volume of the source series. For CT perfusion series, the last volume is removed as well. This is due to these volumes usually being of such poor quality that motion correction and processing of that volume is irrelevant.

13.4 Enable MR PWI DCE population-based AIF

It is possible to use population-based AIF for MR DCE perfusion calculations. This is simply done by checking the checkbox shown in Figure 4. When this setting is enabled an additional set of maps are created based on population-based AIF.

Figure 4: Population-based AIF

13.5 Vasculature removal

It is possible to enable automatic removal of vasculature on CT perfusion series by enabling the “Remove vasculature” checkbox in the settings dialog under Processing -> “Use manual constants (advanced users only)”. Enabling “Remove vasculature” masks voxels with a high blood flow from images derived from the CT perfusion series based on thresholding. Series that have had their vasculature removed contain the “vasculature-removed” marker as part of their description.

13.6 Mean intensity curve view

To verify the quality of perfusion series loaded, the application provides an overview of the mean intensity in form of a curve. The Mean Intensity Curve View is illustrated in Figure 5 below.

The Mean Intensity Curve view is accessed by clicking the “Intensity curve” button in the button bar on the right-hand side of the Study View.

If there is no perfusion series in the selected study or if intensity data has not yet been calculated by the application yet, clicking the button will yield an informative message telling the user that no intensity data is currently available.

Once open, the Mean Intensity Curve View shows the average measured intensity values over the first perfusion series in the study measured over the caption time within the identified brain mask area. That means time is shown along the x-axis, while measured intensities are shown along the y-axis.

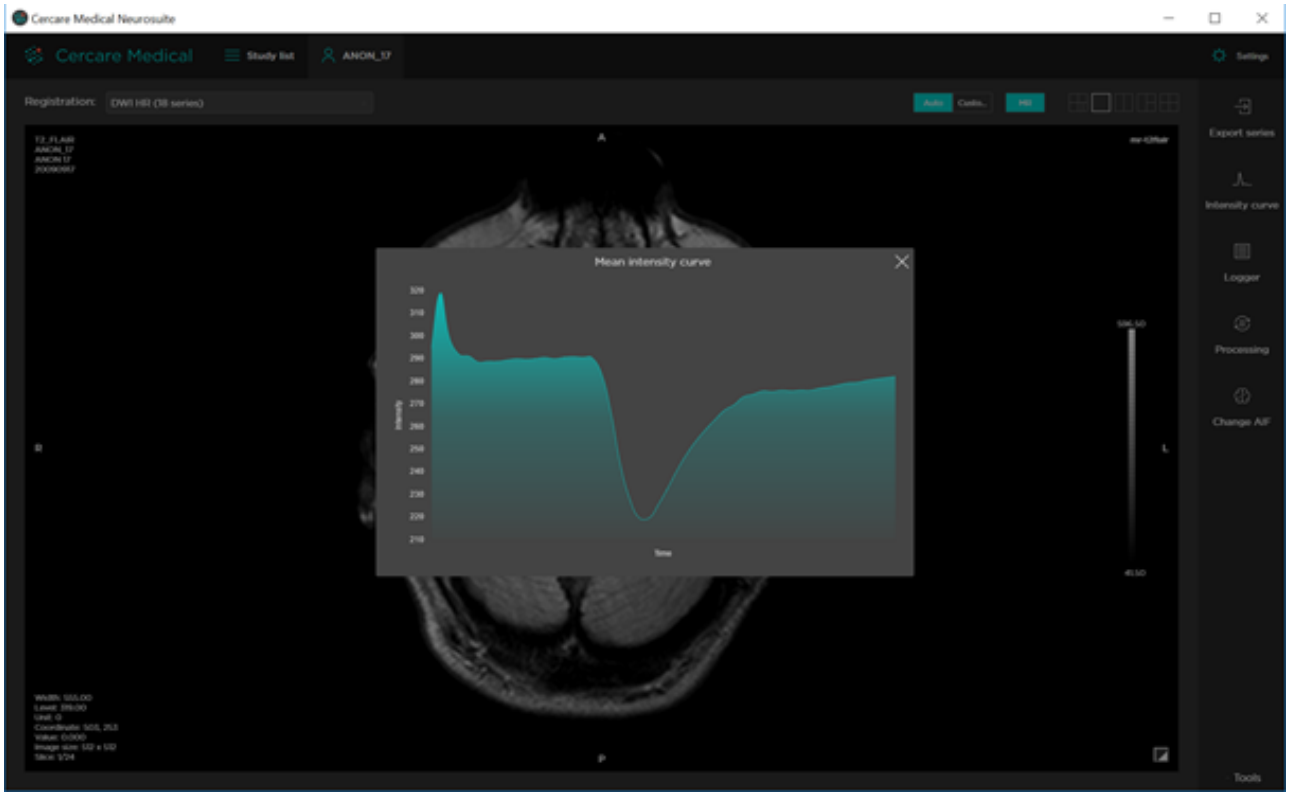


Figure 5: The mean intensity curve view

The measured minimum intensity is subtracted from all displayed values, ensuring that the minimum value is placed at the bottom of the curve view. Additionally, the curve display is scaled such that the maximum measured intensity is placed just below the upper edge of the curve view.

13.7 AIF selector view

The AIF selector view is reached through the study view by clicking on the “Change AIF” button in the sidebar panel. This view allows the user to inspect the automatically picked voxels the “Auto AIF” selector has selected to be used as reference points for calculating the derived series of the PWI series. These points are estimations of artery positions in the image.

The automatically picked voxels are shown as blue dots in the image viewer, and associated intensity curves are shown in the right bottom corner in blue. Voxels in the currently visible slice are highlighted with a brighter shade of blue then voxels in other slices.

13.7.1 Selecting custom voxels

The AIF selector can, in addition to showing the automatically selected AIF voxels, also show manually selected AIF voxels. It allows the user to select these voxels to create a custom AIF selection, that can be used as the basis for a new computation. See Figure 7.

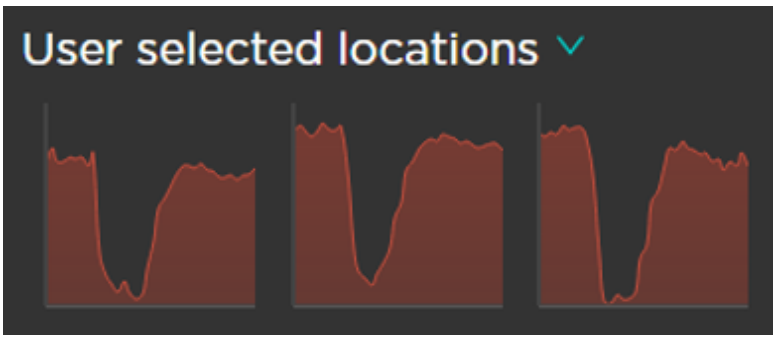


Figure 6: Click a graph in the grid view to remove it from current selection

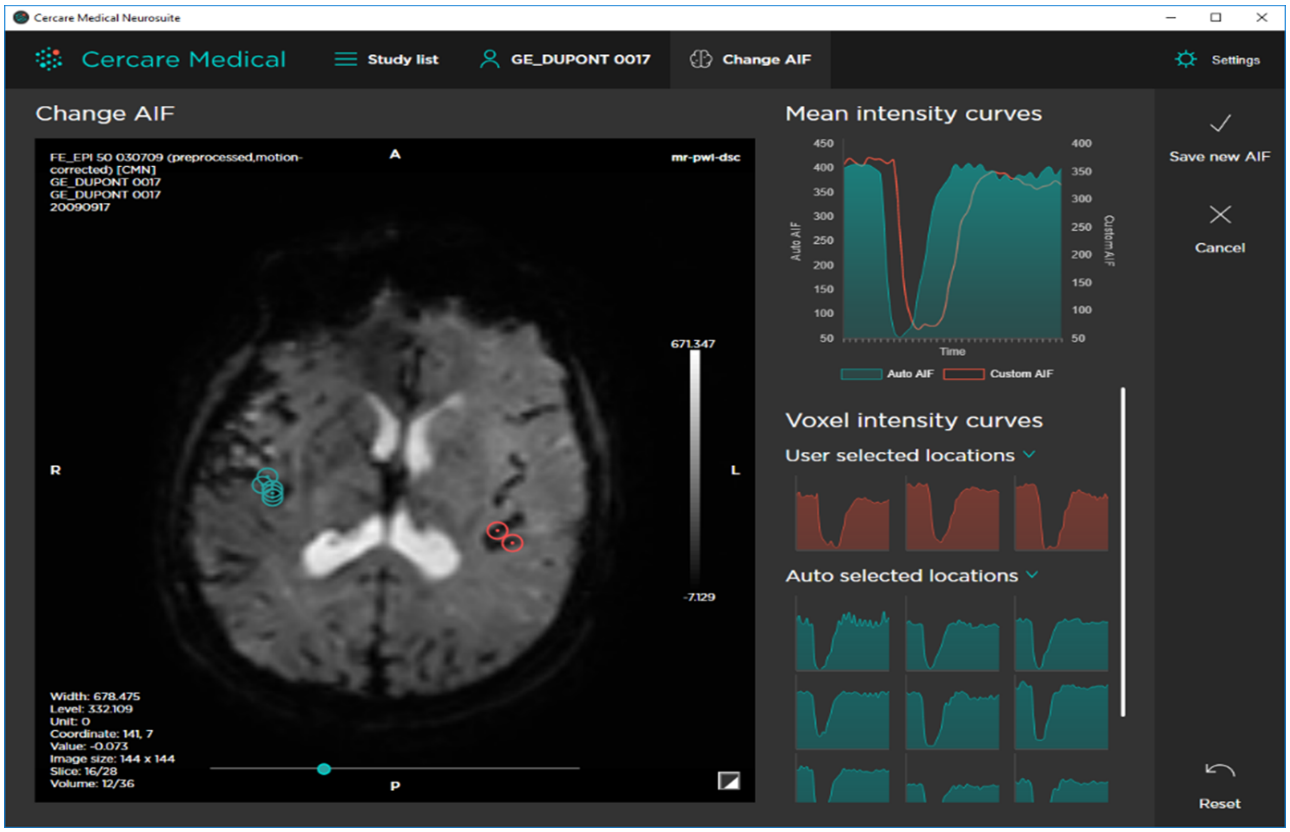


Figure 7: Demonstration of inserted voxels

To select a voxel, click on the image viewer in the position where the selection is wanted. This will place a red circle around the voxel with a single red dot in the center, indicating the center of the selected voxel. A maximum of 9 voxels can be selected at a time. Only voxels selected within the current slice is shown on screen, i.e., AIF voxels in other slices are only shown once that slice is displayed in the viewer.

Each selected voxel will generate a corresponding intensity graph shown in the side panel in the grid view, see Figure 6. When hovering a graph in the grid view the voxel paired with the graph will be highlighted in the image viewer. When hovering a user selected AIF graph in the grid view, the selected graph will also show the "Remove curve" overlay on the graph. This is to indicate that clicking a graph in the grid view will remove the corresponding voxel from the current selection.

A preview of the mean intensity curve of all auto selected and user selected voxels is presented in the graph view in the side panel above the grid view. The curve representing the user selected voxels will update as voxels are added or deleted.

13.7.2 Saving Custom Voxels

To save the user selected voxels press the "Save new AIF" button in the side bar panel. This will stop any currently running processing based on older custom voxel selection as well as deleting all derived series based on these. A new processing job with the new voxel selection will be scheduled such that new derived series can be calculated.

To exit the AIF selector without saving the selected voxels press the "Cancel" button in the sidebar panel and no changes will be made to existing series based on any previous custom voxel selection.

13.8 Keyboard shortcuts

CMN supports multiple keyboard shortcuts, depending on the current active view. This section lists the shortcuts available for the relevant views within the CF module.

13.8.1 AIF view

The Supported shortcuts for the AIF view are:

Table 4: Supported shortcuts for the AIF view

Shortcut	Action
Arrow up	Next image in volume
Arrow down	Previous image in volume
Arrow right	Next volume in series
Arrow left	Previous volume in series
Space	Toggle jet coloring of the topmost image series

14 MR DSC Perfusion Processing

Given an MR PWI DSC series, CF generates several derived series. This is depicted in Figure 8. As can be seen in the figure, the raw PWI DSC series is processed by the pre-processing pipeline first, to adjust for possible patient movement during the scan and to apply any necessary cropping of volumes to decrease processing time. Note that cropping might be automatically increased due to removal of abnormally bright volume(s) within the baseline samples. The result of this pre-processing is then fed to the CF pipeline, which creates twelve distinct derived series. It is noted that some markers cannot be quantified and are thus relative within a patient. These markers are prepended with an ‘r’, such as ‘rCBV’ for relative cerebral blood volume.

Some series are common output series from DSC perfusion post-processing (MinIP, TTP, rCBV, rCBF, MTT, and Delay), while others are not. Potential usage of the non-standard series in a clinical workflow is described in Section 14.1.

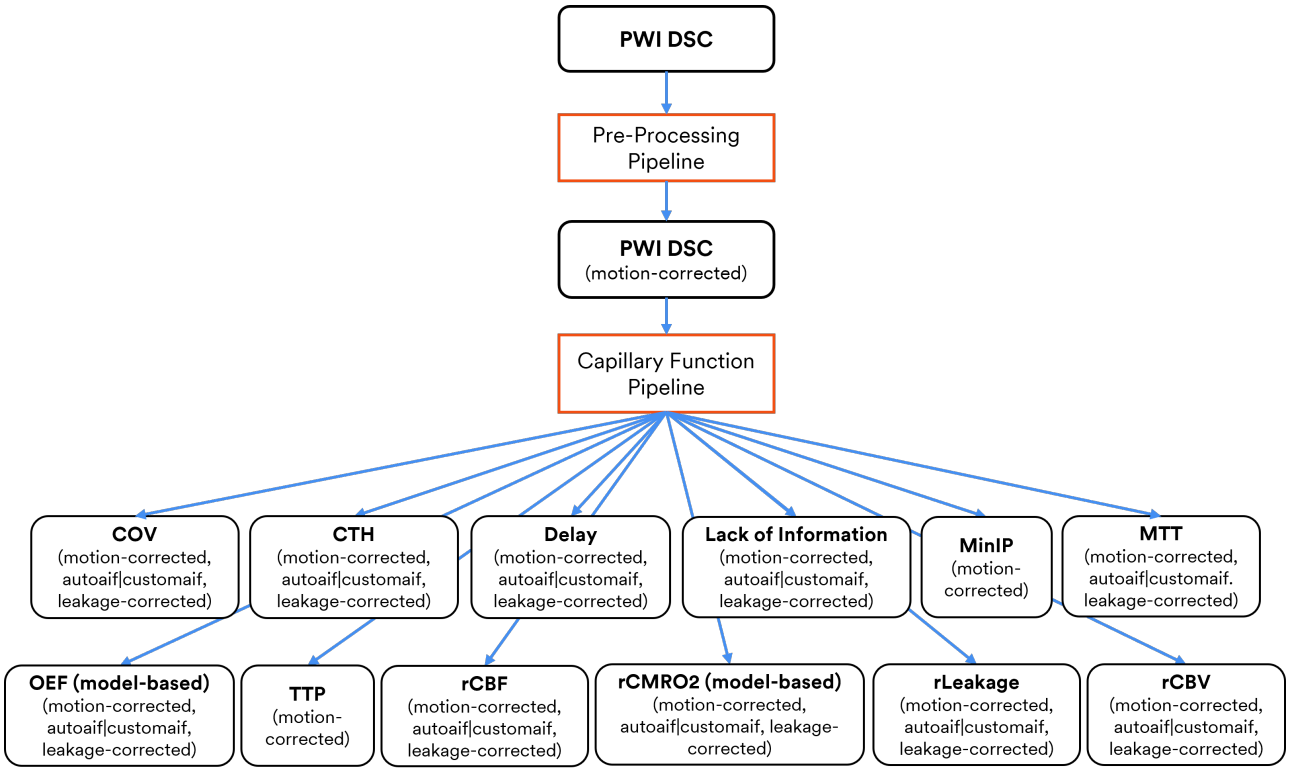


Figure 8: MR PWI DSC processing

14.1 Notes on advanced perfusion markers

The output series CTH, COV, OEF(model-based), and rCMRO2(model-based) are non-standard perfusion series calculated during post-processing of DSC perfusion data. The CTH parameter, is a measure of the heterogeneity of the transit times within each voxel, in complete analogy with the mean transit time (MTT) denoting the mean of the transit times within each voxel. Naturally, the individual transit times cannot be measured in an DSC MRI or CTP measurement, but the distribution of transit times can be estimated via the residue function, which in turn enables quantification of mean and heterogeneity of that distribution. The formal details and implementation details can be found in e.g. [**?**, **?**], whereas publications illustrating the potential usefulness in different diseases can be found in [**?**, **?**, **?**, **?**].

The availability of an estimate of the transit time distribution, also enables estimation of oxygen extraction fraction from DSC MRI or CTP, as detailed in [**?**] and implemented in [**?**] in a leakage-free model and [**?**] in a model including correction for leakage. Since this parameter is based on a computational model, it is denoted 'OEF(model-based)' in order to avoid potential confusion with other means of quantifying oxygen extraction, such as positron emission tomography (PET).

In practice, it might be observed that the OEF parameter is increased in areas with compromised perfusion (reduced blood flow for instance), which might be interpreted as the tissue attempting to extract as much oxygen from the blood as possible. This, in turn, gives rise to an estimate of a relative metabolic rate of oxygen since the combination of delivery (rCBF) and extraction (OEF) provides an estimate of the potential metabolism.

This parameter is denoted 'rCMRO2(model-based)' to reflect the non-quantitative nature of the parameter and to distinguish the parameter from the CMRO2 parameter obtainable via e.g. ^{15}O-PET imaging. The rCMRO2(model-based) parameter can thus be used to visually assess the concerted effect of rCBF and OEF(model-based) in areas with suspected perfusion deficits. For instance, in a condition reducing the perfusion in one hemisphere, the rCMRO2(model-based) map might be used to visually compare effects on metabolism between hemispheres, i.e. whether an increased OEF(model-based) is enough to compensate for a reduction in rCBF.

The COV parameter (also referred to as relative transit time heterogeneity 'RTH' in scientific and clinical literature), can be viewed as describing a dissociation between MTT and CTH. Scientific studies based on vascular network simulation models have illustrated that MTT and CTH vary co-dependently under normal circumstances, i.e. reducing MTT in a healthy passive, compliant network automatically reduces CTH as well. In disease, however, patho-physiological conditions such as vessel thickening, increase of vessel stiffness, or vascular constriction might result in the network being incapable of adjusting to e.g. reduction in perfusion pressure, which result in a dissociation of CTH and MTT, which will be detectable via the COV parameter map.

Finally, the output map entitled 'Lack of Information' is a measure of the extent to which the information content in each voxel is sufficient for estimating hemo-dynamic parameters. This should only be used as an optional check for data adequacy, with high values (larger than e.g. 0.05) denoting that care should be taken in interpreting the results under such a voxel. For standard quality perfusion acquisitions, values of the 'Lack of Information' parameter above zero are observed in the cerebrospinal fluid and eyes, where very limited signal intensity changes occur during a perfusion data acquisition.

In addition, CF includes the option to switch to a leakage correction model, where extravasation of contrast agent out of the vasculature is corrected for. The associated parameter measuring the relative magnitude of the correction term is denoted relative Leakage (rLeakage). Further reference to the model and its implementation is available in [**?**], whereas results from different clinical conditions are available in [**?**, **?**, **?**].

15 MR DCE Perfusion Processing (EU ONLY)

⚠ DCE is not cleared for clinical use in the US.

Given an MR PWI DCE series, CF generates several derived series. This is depicted in Figure 9. As can be seen in the figure, the raw PWI DCE series is processed by the pre-processing pipeline first, to adjust for possible patient movement during the scan and to apply any necessary cropping of volumes to decrease processing time. The result of this pre-processing is then fed to the CF pipeline, which creates five distinct derived series.

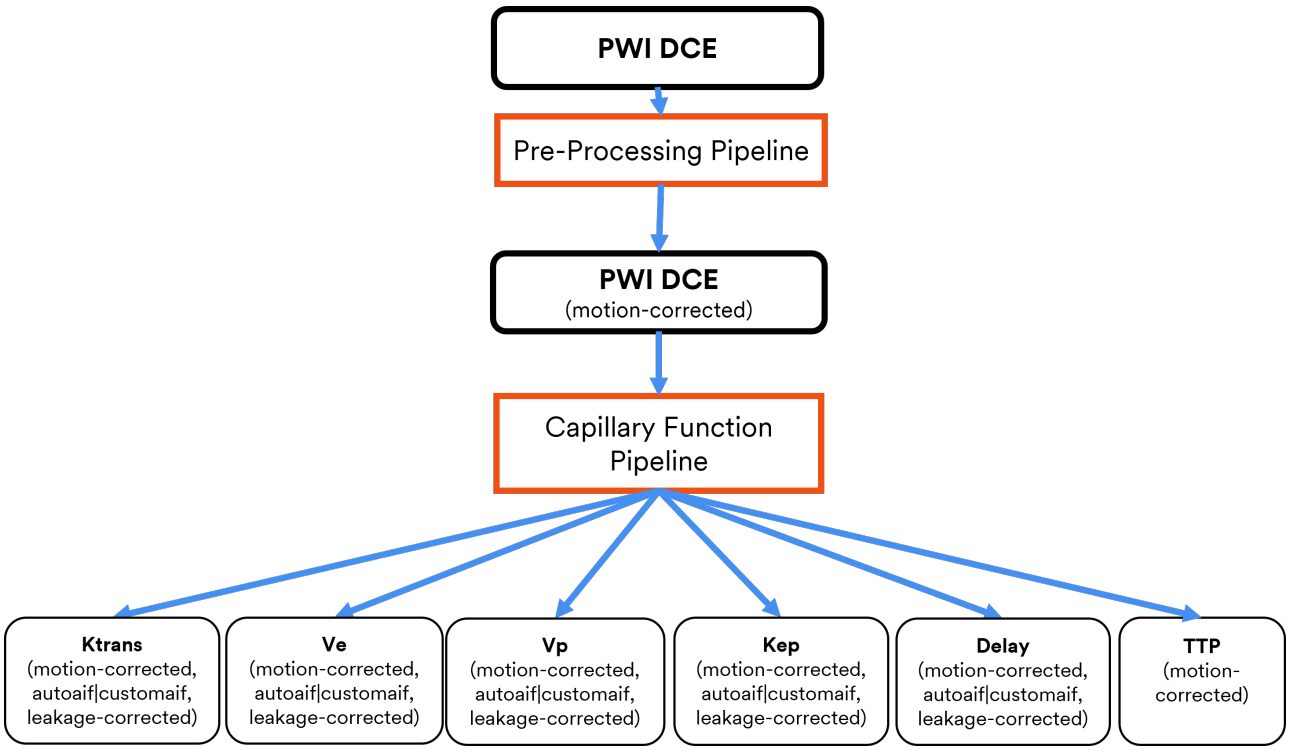


Figure 9: MR PWI DCE processing

The MR DCE perfusion concentrations are calculated using the steady state formula. In short, only MR DCE sequences that are interpretable by the steady state formula should be used. When calculating each voxel concentration, the assumption of fixed relaxion rate (T1) for all voxels are used. In other words, the T1 value are not calculated using variable flip angle or saturation recovery techniques but instead set to a fixed value.

16 Warnings and alerts

The study view's warning bar becomes visible when a warning is associated to the particular series currently loaded, or to the entire series (Figure 10).

Figure 10: Warning bar

Click "See all warnings" to open the warning overview dialogue (Figure 11).

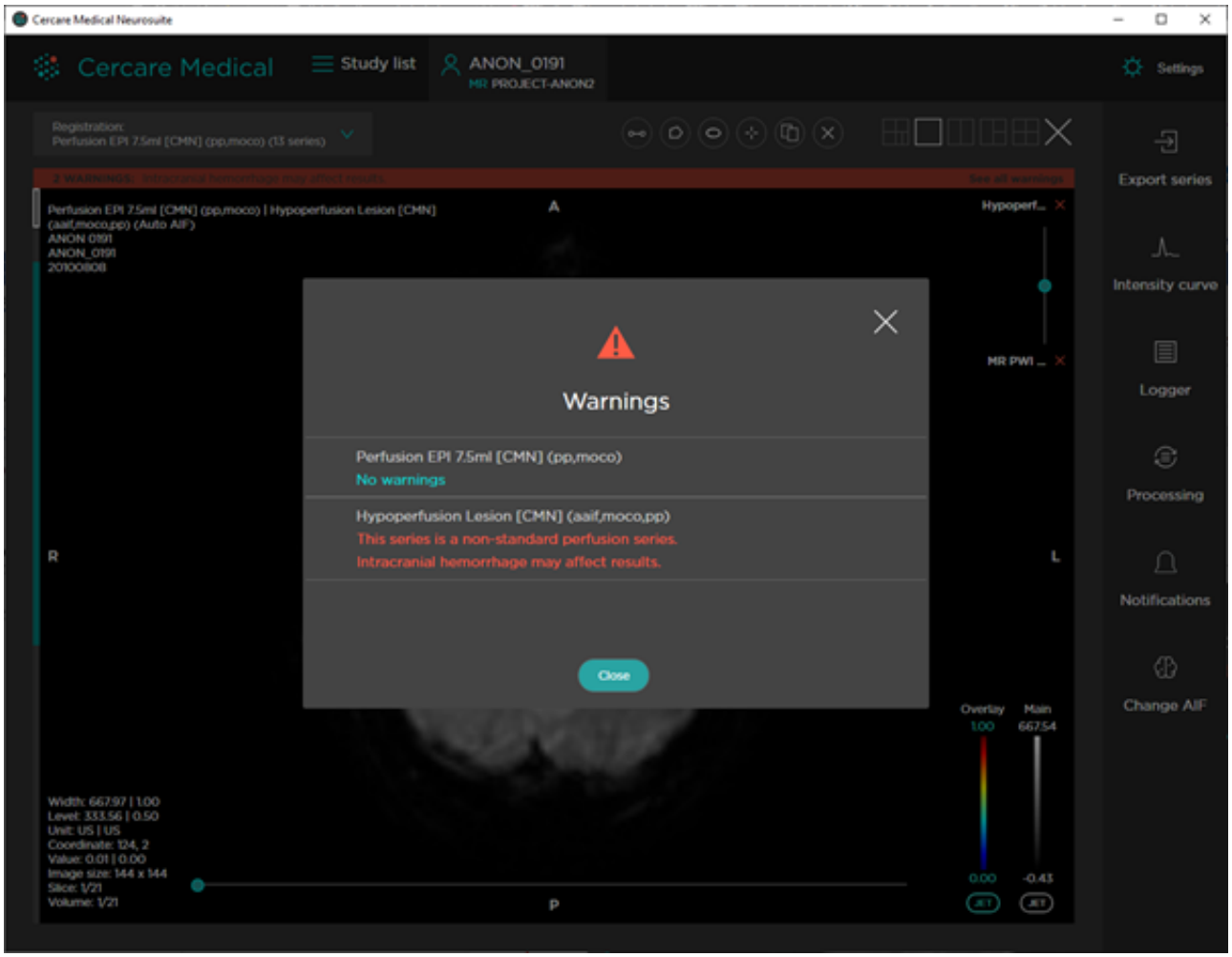


Figure 11: Warning dialogue

Possible warnings generated by the Capillary Function module:

Warning message	**Additional description**
Literature suggests that stroke patients of 80 years or older have reduced benefit of treatment	
This series is a non-standard perfusion series	See section 17.1 Notes on advanced perfusion markers

17 CT Perfusion Processing

Given a CT Perfusion series, CF generates several series. This is shown in Figure 12. Like the MR PWI DSC processing, the first step is to perform pre-processing of the raw series, to remove errors that can occur because of the patient moving while being scanned (particularly a problem for CT perfusion scans), and to perform volume cropping. Following completed pre-processing and writing of the pre-processed series to disk, the CF pipeline is given the new series to process.

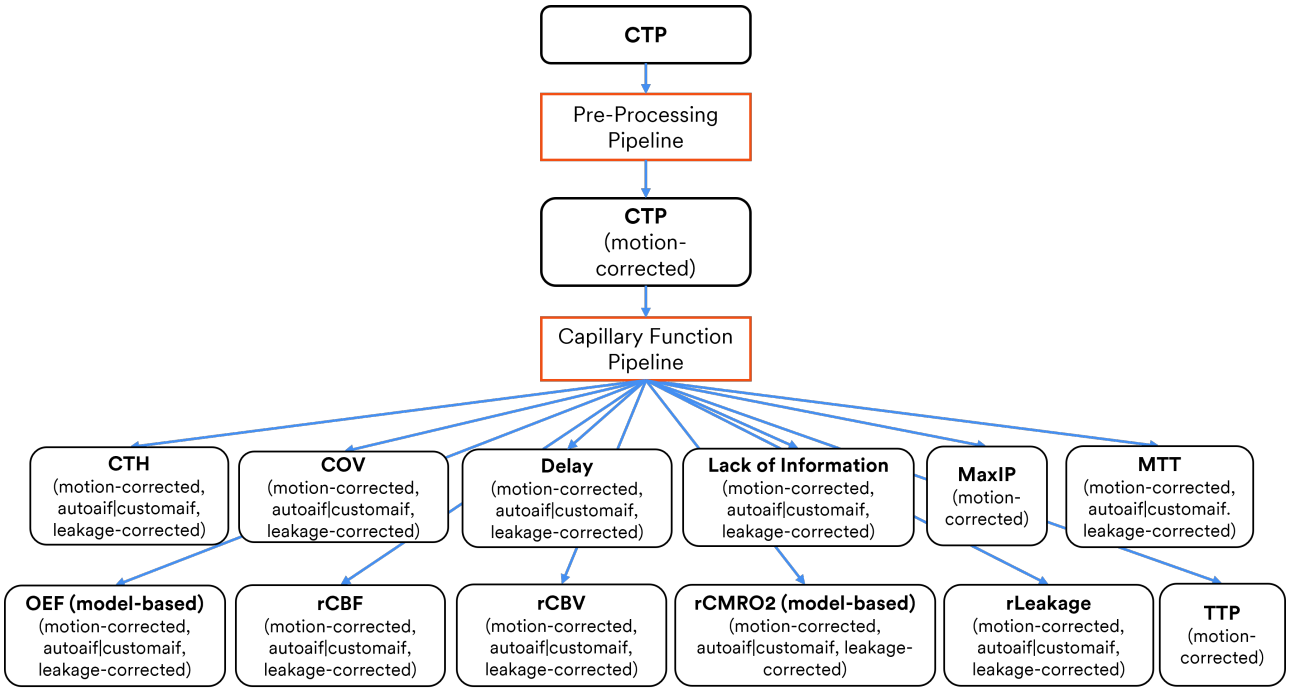


Figure 12: CT Perfusion processing

18 References

19 Appendix A: Overview of Capillary Function outputs

19.1 MR DSC and CT Perfusion

Given MR DSC or CT perfusion series, CF outputs the maps described in the following table.

Note: Outputs from the common SVD based deconvolution algorithm are provided by CMN with a ”Basic” suffix in the DICOM series description field. The SVD based rCBF image for instance, is provided under the description ”rCBF Basic”.

Table 5: CF output maps for MR DSC or CT perfusion series

Parameter	SVD	Parametric	Units	Notes
rCBF	Maximum of impulse response function **Mathematical formula:** CBF = max(R)	Parameter estimated during fitting procedure **Mathematical formula:** Parameter in the model and hence not applicable	Relative	Similar interpretation
rCBV	Area under the residue function **Mathematical formula:** $CBV = \frac{dt}{2}\sum_{i=1}^{N_t-1} R(t_i) + R(t_{i-1})$	Area under the residue function **Mathematical formula:** Same as SVD	Relative	Similar interpretation
MTT	Calculated as rCBV/rCBF via the central volume theorem **Mathematical formula:** $MTT = \frac{rCBV}{rCBF}$	Mean value of the transit time distribution **Mathematical formula:** $MTT = \int_0^\infty th(t)\,dt$	Seconds	Similar interpretation

Tmax	Time point at which the residue function attains its maximum value **Mathematical formula:** Tmax = argmax(R)	Parameter estimated during fitting procedure (entitled delay) **Mathematical formula:** Parameter in the model and hence not applicable	Seconds	The interpretations of the Tmax and delay parameters are not exactly the same. The delay parameter is a measure of the temporal shift required for the AIF to best fit the concentration-time curve of a particular voxel. While both parameters estimate some form of delay of bolus for each voxel, *care should be taken in directly comparing Tmax and delay parameters.* Especially thresholding in connection with stroke lesions should be avoided.
CTH	Not available	Standard deviation of the transit time distribution **Mathematical formula:** $CTH = \sqrt{\int_0^\infty (t - MTT)^2 \, h(t) \, dt}$	Seconds	Unique for the parametric algorithm
COV	Not available	CTH relative to MTT, i.e. RTH = CTH/MTT **Mathematical formula:** $COV = \frac{CTH}{MTT}$	Unitless	Unique for the parametric algorithm
OEF(model-based)	Not available	Model-based oxygen extraction fraction available from the residue function in conjunction with a passive diffusion extraction model **Mathematical formula:** $OEF = 1 - \int_0^\infty \left(1 - e^{-kt}\right) h(t) \, dt$	Unitless	Unique for the parametric algorithm
rCMRO2(model-based)	Not available	Model-based relative metabolism of oxygen, calculated as CMRO2 = CBF x OEF **Mathematical formula:** $CMRO2 = CBF \cdot OEF$	Relative	Unique for the parametric algorithm

rLeakage	Not available	Parameter estimated during fitting procedure **Mathematical formula:** Parameter in the model and hence not applicable	Relative	Unique for the parametric algorithm
Lack of Information	Not available	Measure of the lack of information. I.e. a value larger than e.g. 0.05 means that there is very little information in the particular voxel. **Mathematical formula:** See text around Eqs. (15)-(17).	Unitless	Unique for the parametric algorithm

19.2 MR DCE (EU ONLY)

Given MR DCE series, CF outputs the maps described in the following table.

Table 6: CF output maps for MR DCE series

Parameter	SVD	Parametric	Units	Notes
Ktrans	Not available	K^{trans} is the volume transfer constant for contrast agent between blood plasma and EES. The parameter is estimated during model fitting. **Mathematical formula:** Parameter in the model and hence not applicable.	Relative	
Ve	Not available	V_e is the fractional volume of EES and reflects the amount of available space within the tissue interstitium for accumulation contrast agent. The parameter is estimated during model fitting. **Mathematical formula:** Parameter in the model and hence not applicable.	Unitless	
Vp	Not available	V_p is the plasma volume. **Mathematical formula:** Parameter in the model and hence not applicable.	Unitless	

Kep	Not available	K_{ep} is the rate constant for contrast reflux from EES back into the vascular system. K_{ep} is not a fully independent parameter, since it is the ratio between K^{trans} and V_e. **Mathematical formula:** $K_{ep} = \frac{K^{trans}}{V_e}$	Relative	

19.3 MR DWI

It is noted that CF applies a correction for B1 magnetic field inhomogeneities on diffusion weighted images. The so-called zero-gradient image (also known as the B0 or B=0 image) is used as the target for iteratively adapting a slow varying filter, which effectively reduces such inhomogeneities. The filter is subsequently applied to the isoDWI image (see the table below). This ensures that the ADC image is unaltered, as it must be since this quantity is not dependent on the static magnetic field. The algorithm implemented is the so-called N4ITK bias field correction algorithm [**?**].

Given MR DWI series, CF outputs the maps described in the following table.

Table 7: CF output maps for MR DFW series

Parameter	SVD	Parametric	Units	Notes
isoDWI	The isoDWI is the average of all diffusion gradient direction images within a diffusion shell. That is, given a b-value of e.g. b=1.000 s/mm^2, all gradient directions with that particular b-value are averaged pixel-wise.	**Mathematical formula:** $isoDWI\,(b) = \frac{1}{N_d(b)} \sum_{i=1}^{N_d(b)} DWI\,(i)$ Where N_d(b) is the number of directions for b-value *b*, and DWI is the 3D MRI image stack pertaining to image *i*.	Relative	The units are the same as the units of the raw diffusion weighted images (typically not specified).
Zero-gradient image	The image where the gradient strength b is zero is handled as a special case.	**Mathematical formula:** Not applicable, since it is typically just a single 3D image stack. The image is denoted B0.	Relative	The units are the same as the units of the raw diffusion weighted images (typically not specified).

ADC	The apparent diffusion coefficient (ADC) is calculated based on the classical Stejskal-Tanner diffusion experiment equation, and represents the mean diffusion coefficient in each voxel.	**Mathematical formula:** $ADC\,(b) = -\frac{1}{b}\log\left(\frac{isoDWI_{(b)}}{B0}\right)$ Where b is the b-value and isoDWI(b) and B0 are provided above.	μm^2/second	