

making functional MRI easy



nordicBrainEx

Tutorial – Dynamic Contrast Enhanced (DCE) Module

Please note that this tutorial is for the latest released nordicBrainEx.
If you are using an older version, please upgrade.

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1 Loading of DCE data

To start the Dynamic Contrast Enhanced (DCE) analysis, one structural and one DCE series have to be chosen. If the DCE type is unknown, right-click to set the type (Figure 1). It is possible to select several structural series, but only one DCE dataset for each analysis. To open DCE settings, right-click and select *Edit DCE Settings*. For more details about the DCE settings, see section 5 DCE settings on page 16.

Hit *Next* to start analysis.

The screenshot shows the software interface with two main tables and a sidebar. The top table lists patient information, and the bottom table lists series information. A context menu is open over the series table, showing options to set the type to DCE.

Patient name	Patient ID	Birth date	Sex	Inserted date	Series count
Glioma#01	0	19000101	M	2016.10.18 09:02:48	68
JD-104 DTI, DSC, DCE	1	19000101	M	2016.10.18 11:23:39	35
JD-105 DTI, DSC, DCE	1	19000101	F	2016.10.18 11:36:33	18
JD-108 DTI, DSC, DCE	1	19000101	M	2016.10.12 14:12:39	5
JD-110 DTI, DSC, DCE	1	19000101	M	2016.10.13 11:31:34	3
JD-113 BOLD, DTI, DCE, DSC	1	19000101	M	2016.10.17 13:42:05	8
NNL 4 - AVM - DTI, BOLD motor, language	1	19000101	F	2016.10.17 13:49:36	6
TD-02 DSC, DCE, ASL, DWI	td-02	19000101	M	2016.10.17 12:48:46	4
TD-03 DSC, DCE, ASL	td-03	19000101	F	2016.10.17 13:16:07	12
TD-04 DSC, DCE, ASL	td-04	19000101	M	2016.10.17 13:24:05	25

Series ID	Type	Modality	Series description	Protocol name	Date	Images	Settings
301	Structural	MR	3DT1TFE ISO	3DT1TFE ISO SENSE	2012.05.24	190	
501	DTI	MR	32DTI b800	32DTI b800 SENSE	2012.05.24	2380	
701	DCE	MR	10_DCE_fa10_GD	10_DCE_fa10_GD SENSE	2012.05.24	2438	Set type >
1001	DSC	MR	10_DSC PWI	10_DSC PWI SENSE	2012.05.24	1200	Reset settings
1002	Other	MR	3D snapshots of DTI Fiber-tracts		1900.01.01	5	Edit DCE Settings
1101	Structural	MR	3DT1TFE ISO GD	3DT1TFE ISO GD SENSE	2012.05.24	190	

The context menu for series 701 shows the following options:

- BOLD
- DCE
- DSC
- DTI
- Dynamic
- Other
- Structural
- Add type...

The sidebar on the right contains the following controls:

- Next >
- Search name or ID
- Date:
 - Any
 - Today
 - Yesterday
 - < 1 week
 - < 1 month
- Sex:
 - Any
 - Male
 - Female
 - Other
- Tools:
 - Refresh

Figure 1: To start DCE analysis, select one structural and one DCE series. To set the type to DCE, right-click and select the correct type from the list. To open DCE settings, select *Edit DCE Settings*. Hit *Next* to start analysis.

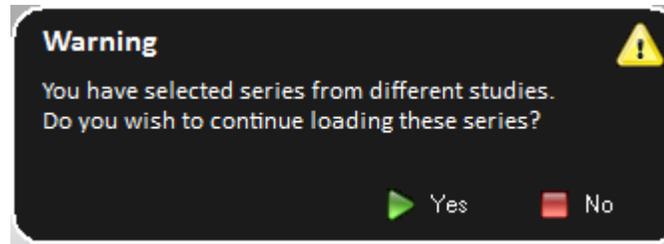


Figure 2: If you select series from different studies (time points), you will get a warning. Select yes, if you do want to load series from different studies.

If you select series from different studies (time points) when loading data, you will get a warning (Figure 2). This is to assure that any loading of series from different studies is only done if intended.

2 Coregistration

An important step in the analysis is coregistration of the DCE series to the structural series. This will ensure that DCE maps used as overlays are displayed in the correct position. Please see ‘Tutorial –Visualization and Interaction’ for details about the coregistration.

3 Interacting with the results

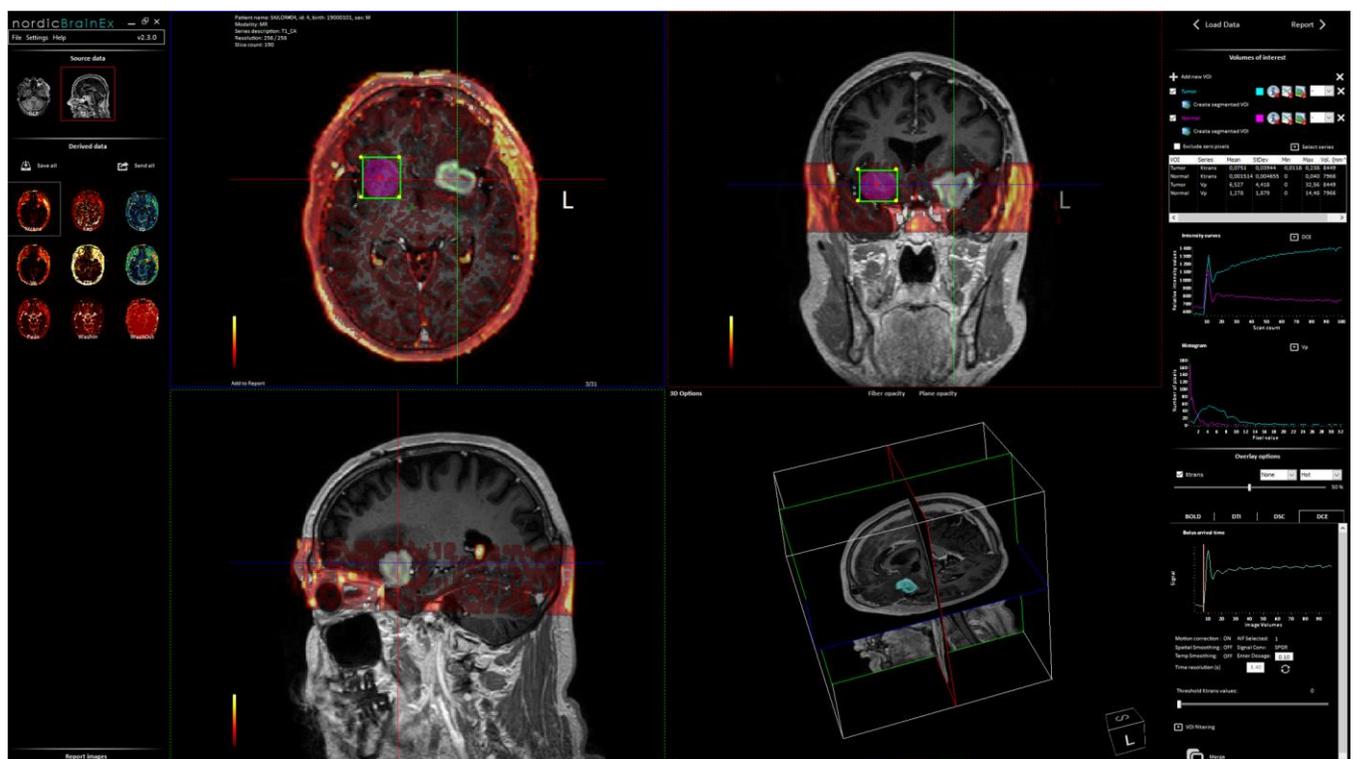


Figure 3: DCE analysis is done and the K^{trans} map is added as an overlay. VOIs are added in the tumor tissue the contralateral normal appearing tissue, and the mean K^{trans} value is measured. The intensity curve and histogram of the VOI is displayed.

When the DCE analysis is completed, the DCE maps are generated and shown as thumbnail in the left side of the panel. Add any map as overlay or underlay to investigate the output (Figure 3).

3.1 Bolus arrival time and analysis settings

The bolus arrival time is calculated automatically by the program, but can be edited by sliding the orange line along the time curve. Click  to use the new time position (Figure 4).

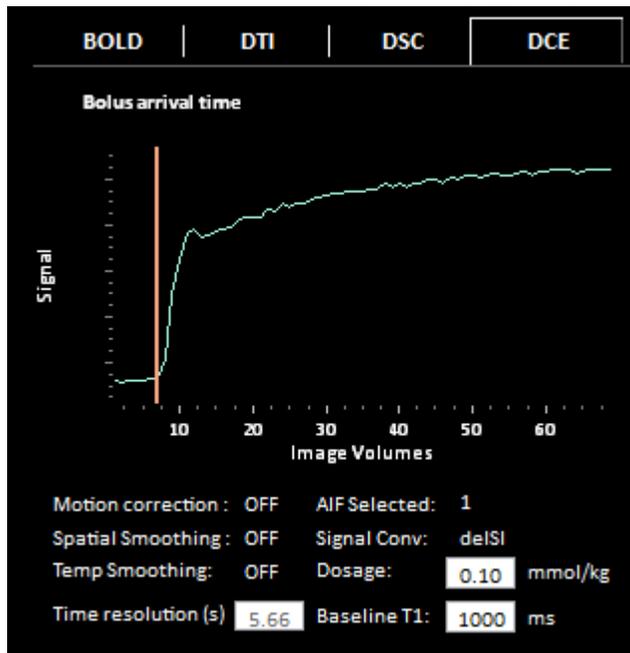


Figure 4: The bolus arrival time is automatically calculated, but can be changed by sliding the orange line along the time curve. Use  to recalculate to update with the new position.

Below the signal curve, the applied analysis settings for the DCE analysis are shown. Motion correction, spatial and temporal smoothing, selection of AIF type and signal conversion can be changed in the DCE settings (right-click on the DCE thumbnail on the left side of the window, see section 5 on page 16). The time resolution is automatically extracted from the DCE series' DICOM tags, but can also be edited by the user. If the time resolution is not present in the DICOM tags, the user must enter the time resolution to continue the analysis. DCE analysis with varying time resolution is not supported. The dosage (given in mmol/kg) and the baseline T1 (given in msec) can be edited by the user. The default value for the dosage is 0.10 mmol/kg and for baseline T1 it is 1000 msec. Care should be taken if these parameters are changed. Click  to re-do the calculations if any parameter values are changed (Figure 4).

3.2 General use

- Display DCE output maps as overlays or underlays:
 - Right-click on the thumbnail

- Using the Volume-of-Interest (VOI) tool to:
 - Measure statistical values on the parametric maps (Figure 5).
 - Display histogram and intensity curves (Figure 5).
- VOI statistics, intensity curves and histograms are displayed by selecting the icons next to the VOI name in the VOI list (Figure 5).
- Change K^{trans} overlay threshold (Figure 6) to remove low K^{trans} values from the visualized overlay.

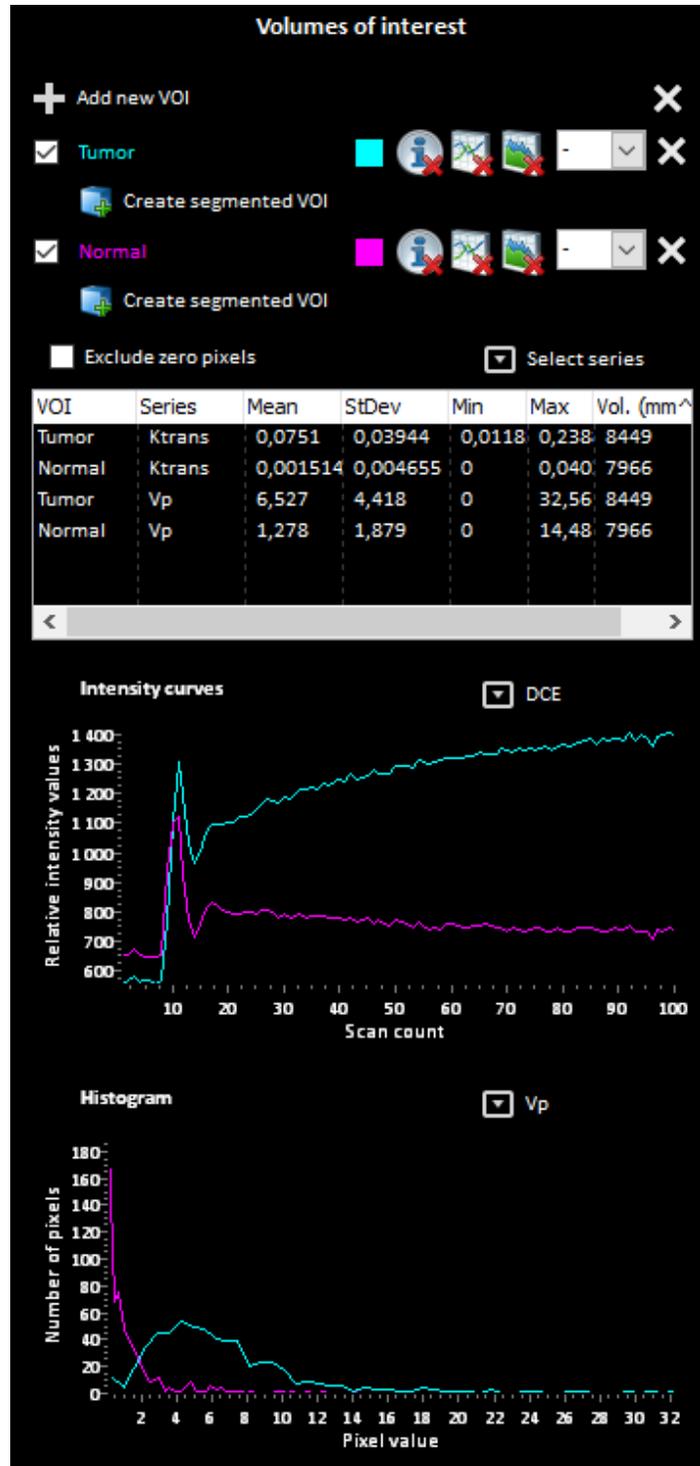


Figure 5: Two VOIs are added, one in tumor tissue and one in normal appearing tissue. The statistical values are measured in the two regions, and the intensity curves for the dynamic series and histograms for one parametric map (here Vp) for the two VOIs are displayed.

3.3 Merge K^{trans} for export to neuronavigation

Similar to for BOLD, DTI and DSC results, it is possible to save the K^{trans} result in a format that can be used in neuronavigation systems using *Merge*. Settings for merge export can be defined when choosing *Settings* and then *Export results as...* in the upper left corner of the *Visualization* interface. The K^{trans} maps can then be exported in a format compatible with viewing on certain neuronavigation systems.

- *Color export*
This will export the output map as separate DICOM image series that can be viewed together with the structural volume on various neuronavigation workstations.
- *White pixels on greyscale*
This will export the output map as DICOM image series where the activated regions are shown as white pixels in the structural dataset.

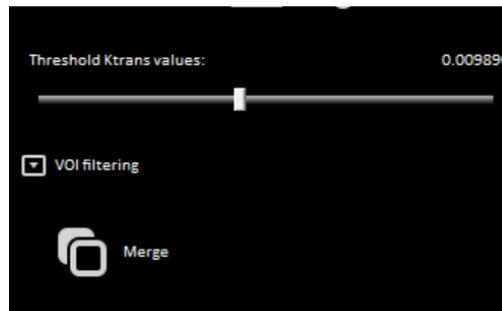


Figure 6: K^{trans} threshold can be changed in the DCE tab. Here, one can also use VOI filtering and merge to neuronavigation.

In order to do so, adapt your workflow to the following steps:

1. Do DCE analysis and add the K^{trans} map as overlay.
2. Change the threshold of the overlay by sliding on the K^{trans} threshold slider (Figure 6).
3. Locate the area(s) of interest and add VOIs.
4. Select VOI filtering and use include/exclude on VOI(s) to locate the region relevant for merge (it is possible to skip this step).
5. Verify the output in real time in the MPR.
6. Select *Merge* to create a new series.
7. Stop VOI filtering to continue.

While in VOI filtering mode, some of the application's functionality is blocked. To access all functionality, VOI filtering mode must be stopped (hit 'Stop', see).

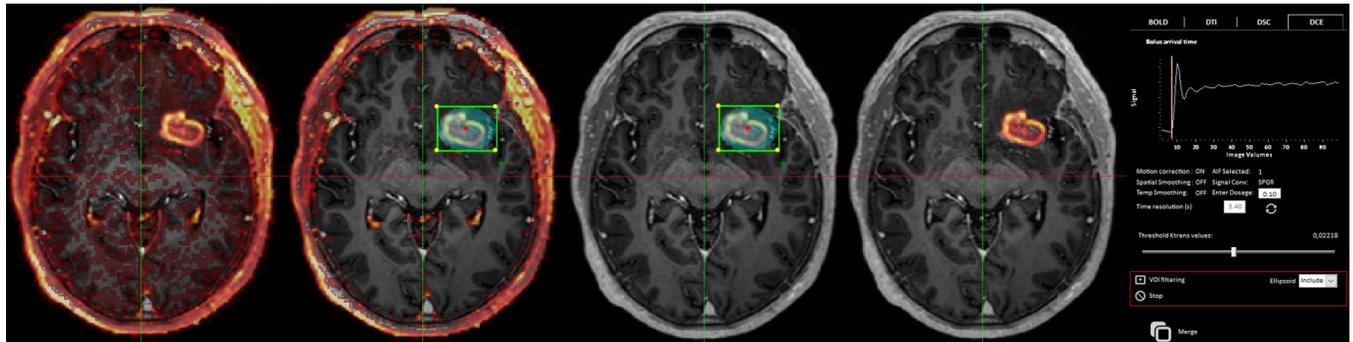


Figure 7: Merge K^{trans} for neuronavigation: Step 1: add the K^{trans} map as overlay. Step 2: Threshold the CBV. Step 3: Locate the area of interest and create a VOI. Step 4: Select VOI filtering to include/exclude regions. Step 5: Verify the output in real in the MPR. Step 6: Select Merge to create new series.

Note that multiple VOIs can be included or excluded to include/exclude multiple regions from the merged series.

3.4 Saving DCE data

There are several different ways of saving the DCE data.

- Save the derived maps to the database:
 - Right-click on the thumbnail and select *Save*
 - Right-click on the thumbnail and select *Save and send* to send it to a remote entity (e.g. PACS)
- Create a new DICOM series with DCE maps as overlay (see Figure 8):
 - Add a DCE map (e.g. K^{trans}) as an overlay
 - Right-click in MPR and select *Create snapshot*, *Slice selection* or *Slice all*.
 - This will create a new secondary capture slice package that can be saved to the database and sent to PACS.
- If choosing *Merge* in the *Interaction panel*, the selected K^{trans} map overlaid on the structural datasets can be merged into a new DICOM series.
- By right clicking on any of the three planes of the current volume in the MPR, choosing
 - *Create snapshot* will open the *Slice editor window* of the current slice.
 - *Create snapshot of MPR* will open the *Slice editor window* of the three current planes of the MPR, as well as the visualized activations in the 3D viewer.
 - *Copy* will copy the current slice to the clipboard, so it can be pasted into other programs (like word etc.).

See Figure 8.

- In the *Slice editor window* (See ‘Tutorial – Visualization and Interaction’), accessed by right clicking on any of the three planes in the MPR and choosing *Slice selection* (and clicking on *Slice*) or *Slice all*, slices can be:
 - Saved to the database

- Saved and sent to a remote entity (for example PACS)
 - Added to report (Select ‘View slices’ by right-clicking on the new thumbnail after saving to database)
 - Saved as AVI-file (Select ‘View slices’ by right-clicking on the new thumbnail after saving to database)
- *Send*, accessed by right clicking on series’ thumbnail in the *Data panel* will send the series to a remote entity (for example PACS). Read more about saving sessions in ‘Saving data to database and PACS’ in ‘Tutorial – Handling Image data’.
- *Add to report* (bottom left of any plane in the MPR) can be chosen to add the current slice to Report (see ‘Report’ in ‘Tutorial – Visualization and Interaction’).
- *Saving the session* can be done by choosing *File -> Save Session*. This will save the entire session (all loaded and acquired datasets) to the database. The session name that you entered will appear in the session table on the Select patient data window. Read more about saving sessions in ‘Saving, loading and sending a Session’ in ‘Tutorial – Handling Image data’.



Figure 8: Slice selection from the axial MPR has been selecting, displaying the VOIs and the VOI statistics, as well as the histogram for the K^{trans} and the intensity curves for the DCE dynamic series for the two VOIs. This frame can be send to PACS by selecting 'Save and send'.

3.5 Spike detection

Spike detection is a quality check by visual inspection of the dynamic series, which can be performed by the user. The user can exclude those slices or volumes from the analysis which contain spikes. The spike detection is normally done if there are "outliers", i.e. images/slices where the signal-to-noise ratio is low or when the results of the DTI analysis have not induced the expected results. In that case you can have a closer look at the dynamic series and exclude spike slices or volumes.

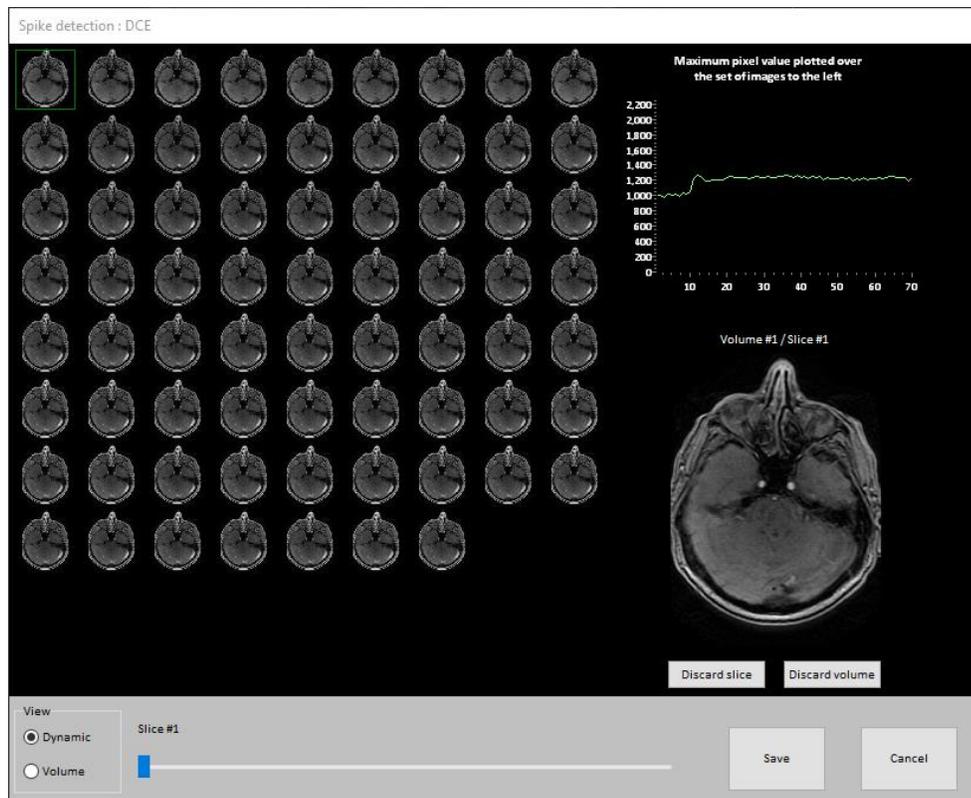


Figure 9: The spike detection interface for DCE in nordicBrainEx.

The spike detection interface (see Figure 9) can be opened by right-clicking on the DCE series' thumbnail in the Data panel of the Visualization interface and selecting *Spike detection*.

The DCE series can be displayed dynamically (all volumes for one selected slice or as a volume (all slices for a chosen volume)). Use the slider to easily change the slice/volume. The curve in the upper right corner shows the maximum pixel value of all the images to the left. If you have a slice/volume with high pixel values, this will show on the curve. If you have detected a spike slice, click on the slice in order to mark it, and then choose *Discard slice*, or *Discard volume* if you want to discard the entire volume at the specific time point. The following border colors are used in the Spike detection interface:

- A *green* border indicates the current slice/volume.
- A *yellow* border indicates that a slice/volume is marked to be discarded.
- A *red* border indicates that this slice/volume has been saved as discarded in a previous session.

Slices/volumes can be restored by choosing *Restore slice* or *Restore volume* (please note that after you re-run the analysis, the slices/volumes cannot be restored without re-loading the data). When you have marked all slices/volumes you would like to discard, click on Save. You will first be prompted with a warning telling you that discarding slices will modify the pixel values, and then a question if you want to re-run the analysis. If answering yes, the analysis will be redone without the discarded slices. All marked slices will then be replaced by the average of the corresponding slice from the two neighboring volumes.

4 Parametric maps

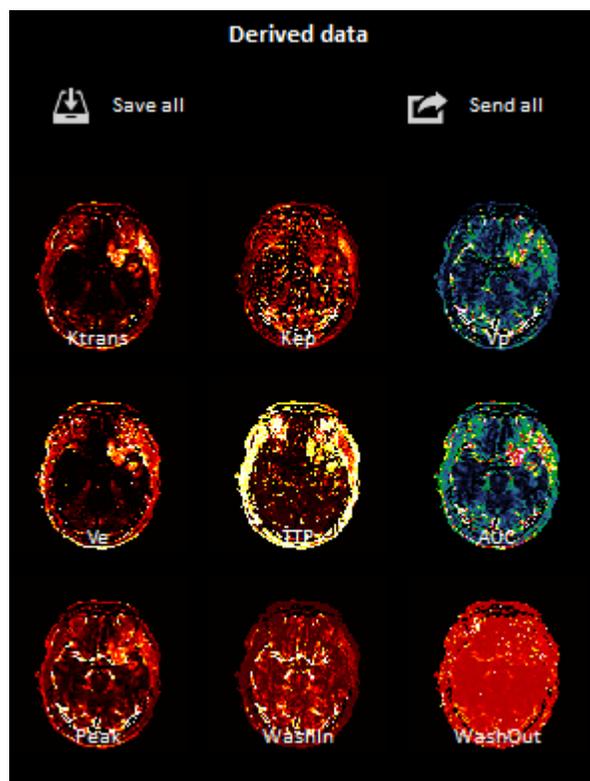


Figure 10: The parametric maps are displayed under derived data on the left side of the visualization screen. Right-click to interact (view as underlay / overlay, save to database, view slices etc.).

4.1 Calculation of parametric maps

The resulting parametric maps appear as icons on the left side of the screen under “Derived Data” (Figure 10). Parametric maps that can be obtained in nordicBrainEx include tissue plasma volume (V_p), extravascular volume fraction (V_e), rate constants (K^{trans} and k^{ep}), peak of the concentration curve ($E_{max}/peak$), time to peak (TTP), area under the curve (AUC), wash-in and wash-out.

DCE MRI analysis is the commonly used term to describe the analysis of the transient effect of a contrast agent (CA) on the measured signal intensity (or change in relaxation rate in the case of MRI) in the tissue of interest following a rapid bolus injection of the CA. The effect of the agent is analyzed using an appropriate kinetic model, describing the time-dependent distribution where the CA in tissue. The contrast agents currently used in DCE analysis are most commonly small molecular weight agents (like Gd-DTPA and similar chelates), which are renally excreted with a half-life in blood limited by the glomerular filtration rate (GFR) of the kidneys. The kinetics of these agents in tissue can generally be described by a so-called two-compartment exchange (TCx) model (Sourbron S, 2009) (Tofts PS1, 1999).

The two-compartment exchange model is illustrated in Figure 11 below.

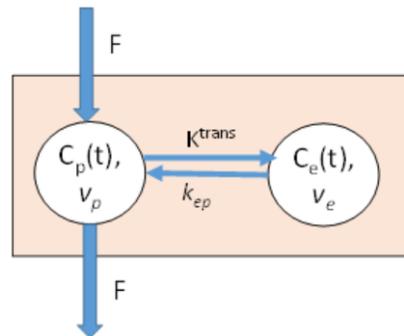


Figure 11: Two-compartment exchange (TCx) model describing the capillary passage, and extravasation of contrast agent (CA) in tissue. The CA enters the capillary volume due to tissue blood flow, F , and is initially distributed in the tissue plasma volume, V_p , but is gradually equilibrated to the extravascular, extracellular space (EES), with volume fraction V_e at a rate determined by the rate constants K^{trans} and k_{ep} , where $K^{trans} = k_{ep} \cdot V_e$.

In general, the TCx model has too many free parameters, yielding unstable results when applied to pixel-wise dynamic MRI data (Sourbron SP, 2011), and different simplifications and assumptions are therefore commonly applied to obtain stable results, as described in more detail below.

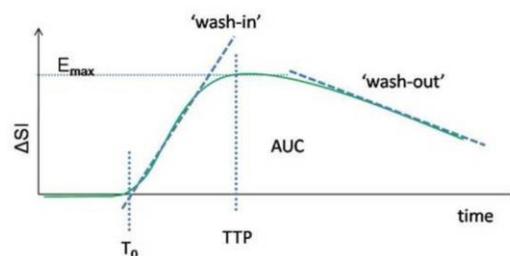


Figure 12: Typical dynamic dose-response following rapid contrast injection in a two-compartment exchange system, and corresponding curve parameters. E_{max} is the peak of the curve, AUC is the area under the dynamic response curve and TTP is the time to peak enhancement. In *nordicBrainEx*, the entire curve is used for the AUC estimation.

In case of very slow leakage, large EES or too short total sampling time, the wash-out phase can be ill defined. Also, the wash-in phase can often be bi-phasic with an initial steep slope (perfusion driven) followed by a reduced wash-in rate (K^{trans} driven).

This model assumes rapid flow (perfusion) relative to the sampling rate of the MRI sequence so that the CA transit time through tissue is essentially instantaneous. Under these conditions, it can be shown that the total CA in tissue is given by:

$$C_t(t) = K^{trans} \int_0^t C_p(\tau) e^{-k_{ep}(t-\tau)} d\tau + v_p C_p(t) \quad (1)$$

where C_p is the CA concentration in plasma and C_t is the total tissue CA concentration. Eq. 1 is a so-called convolution integral, describing the CA kinetics (CA concentration change) in tissue following a bolus of CA initially present in the arterials feeding the tissue. In DCE-MRI, $C_p(t)$ is determined from a well-defined artery (arterial input function, AIF) feeding the tissue of interest.

If the arterial input function (AIF) can be measured, then the equation describing the selected kinetic model (Eq. 1) can be solved using standard numerical methods. In nordicBrainEx, the AIF can be determined using pre-defined (population) AIFs (Matthias J.P. van Osch, 2003). The AIF contains signal from whole blood whereas the kinetic model assumes that we measure the plasma concentration of contrast agent. We therefore also need to scale the AIF signal according to the blood hematocrit (H_{ct}) since $AIF = (1-H_{ct}) C_p$. The H_{ct} is specified in nordicBrainEx as 0.45.

4.2 Estimation of concentration time curves (CTC)

The kinetic models used for MRI-DCE analysis explicitly assume that the CA concentration (C) is known. In MRI, the CA concentration cannot be measured directly and must be derived from the observed change in MR signal intensity (SI) in response to the presence of the CA in tissue. One common assumption is that the change in $1/T1$ relaxation rate is proportional to C, which is valid as long as there is a fast water exchange between water protons in tissue and the paramagnetic center of the CA. Given this assumption, C can be estimated (in relative units) if the change in $1/T1$ relaxation rate can be estimated.

The conversion from signal change to a change in relaxation rate (and thereby to concentration) is dependent on the MR image acquisition sequence. nordicBrainEx supports conversion from signal change to relaxation rate change for images acquired with Spoiled gradient echo (GRE) sequences. The relationship between SI and relaxation rates is explicitly given by the following expression:

$$SI = k \frac{\sin(\alpha)(1-e^{-\frac{TR}{T1}})}{1-\cos(\alpha)e^{-\frac{TR}{T1}}} e^{-\frac{TE}{T2^*}} \quad (2)$$

where k is an (unknown) constant, α is the flip angle, TR is the repetition time, $T1$ and $T2^*$ are the relaxation times and TE is the echo time. $T2^*$ is not known (the acquisition is heavily $T1$ weighted), but assuming that $T2^* \ll TE$, $e^{-\frac{TE}{T2^*}} \approx 1$ (Haase, 1990). Using two measurements, a baseline measurement and measurement with bolus present, the unknown constant k is eliminated from the equations and the change in $T1$ relaxation rate can be estimated.

With strongly T1-weighted sequences it is often assumed that the change in $1/T1$ is approximately proportional to the change in SI. Using this assumption, relative change in $1/T1$ (and hence C) can be estimated directly from the relative change in SI (either in absolute units or as a percent change). This conversion is also available in the DCE module and is typically used if the exact details of the MR sequence used are not known or a sequence is used where the signal response cannot be expressed in a simple analytical form (e.g. non steady-state sequences).

5 DCE settings

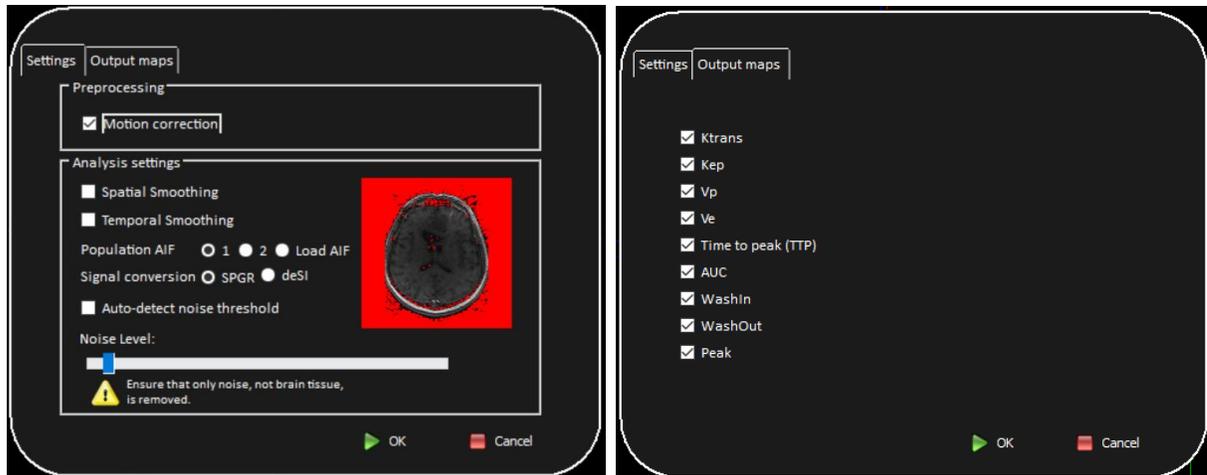


Figure 13: In DCE settings, the user can decide which preprocessing and analysis settings to use, and which output maps to display.

DCE settings (Figure 13) can be opened from the loading frame by right-clicking on the DCE series, or from the visualization interface by right-clicking on the DCE source data thumbnail. In the DCE settings, the user can decide which preprocessing and analysis settings to use, and which output maps to display.

5.1 DCE settings

The settings for DCE are global settings, meaning that changes done at one time will be saved and applied to all future analysis until the settings again are changed.

5.1.1 Motion correction

When checked this turns on motion correction of the DCE image series, meaning that all the image volumes are coregistered to the first image volume. These parameters are saved internally so that the user can display them at a later stage by right-clicking on the icon of the perfusion series and choose *Motion Correction Results*. The coregistration is performed using an iterative method based on a measure of similarity. Step sizes are calculated from the gradients of the similarity measure (the mutual information metric), and once the step size of the rotation and translation parameters is small enough, the iteration process is halted, and the estimated rotation and translation parameters are applied to the source volume using a cubic interpolation approach. Due to the limited geometrical resolution of such image series only in-plane rotations and translations for axial slices are done.

5.1.2 Spatial and temporal smoothing

Smoothing is performed on a data set to create an approximating function that attempts to capture important patterns in the data, while leaving out noise or other fine-scale structures/rapid phenomena. Spatial smoothing is computed by replacing value of a voxel with the mean value of immediate neighboring voxels (27 voxels, of which 26 are neighboring voxels in a 3x3x3 window). Temporal smoothing is computed on the dynamic time series, each value at time point is replaced with the mean value of voxels occurring within neighbourhood.

5.1.3 Population Arterial Input Function (AIF) selection

Two pre-defined AIF curves (one with a sharper peak than other) are available. AIF-1 (one with the sharper peak) is the default option, if results are not satisfactory, data can be re-analyzed with AIF-2. For more details on the usage of AIF in DCE maps computation see section 4.1, page 13.

5.1.4 User selected AIF

Module also provides an option for the user to select AIF function from the data. Following steps should be followed to export the intensity curve from the data.

- Selected a VOI around the region is as shown in Figure 14(a).
 - Tips: use scatter VOI with the DCE series as underlay to identify a good AIF.
- Intensity curve based on the above VOI can be now computed using the intensity curve button from the VOI as shown in Figure 14(b).
- This intensity curve can be saved as a text file as shown in Figure 14(b).
- From the settings screen this intensity curve can be loaded using Load AIF option, which will be used as user selected AIF as shown in Figure 14(c).

Although intensity curves from any dataset can be used as AIFs using this option, however preferably intensity curves from the same dataset should be used for better results. It is recommended to use this option, only if both the above population AIFs are not giving satisfactory results.

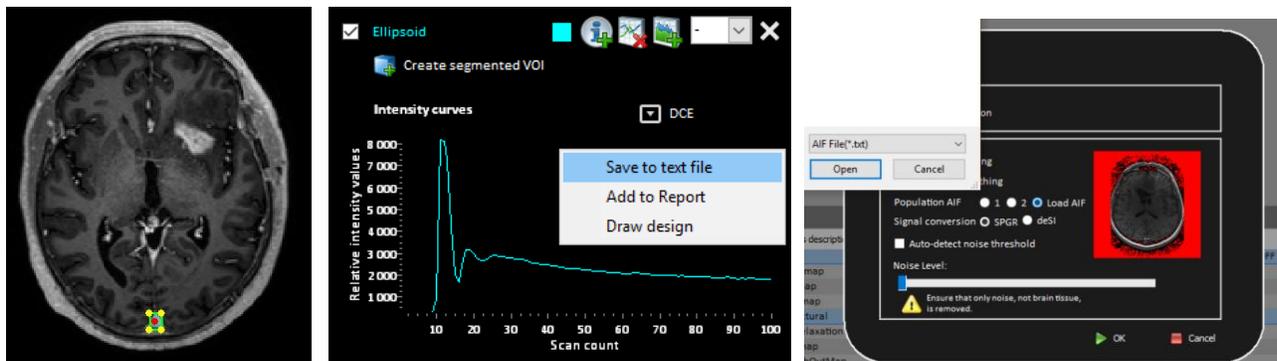


Figure 14: (a) VOI select on a DCE series; (b) intensity curve of DCE from the selected VOI and save to text file option; (c) Load AIF, section of dialog box with an option to load a text file. Note: VOI position is for illustration purposes and should not be used as a AIF location reference.

5.1.5 Signal conversion

Two options of signal conversion Delta SI and SPGR (Spoiled gradient echo sequences) are available with SPGR as the default option. For more details on signal conversion see section 4.2 page 15.

5.1.6 Auto-detect noise threshold

If checked, an automatic noise threshold is performed, and if unchecked, the user can set the noise threshold manually using a slider (Figure 15). The noise threshold is used to extract the brain region from the background, it does not affect the performance of the algorithm.

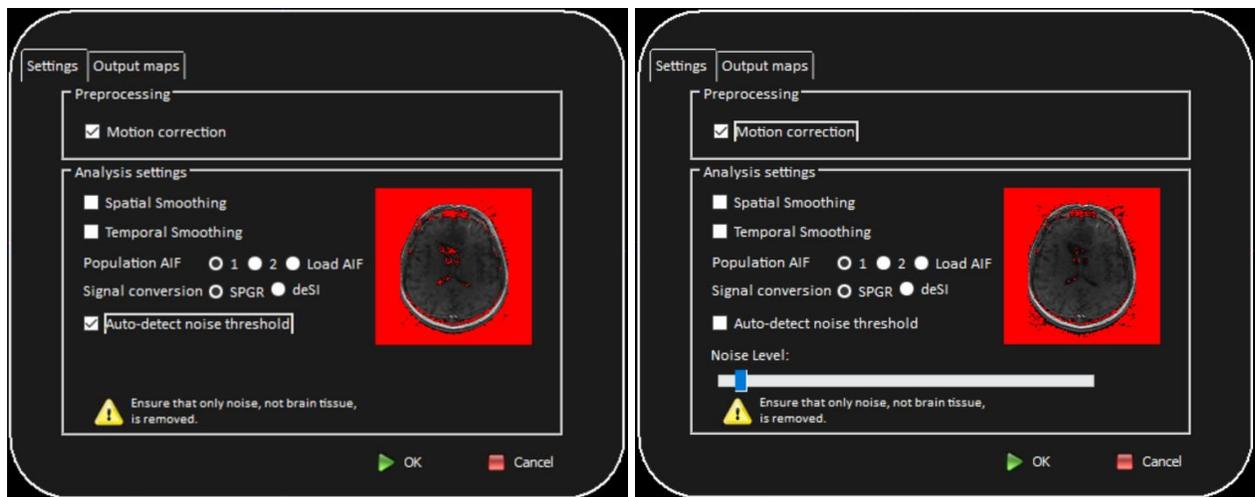


Figure 15: Noise-threshold can either be detected automatically, or the level can be changed using a slider.

5.2 Output maps

In the *Output maps* tab (Figure 13), the user can select which output maps to display. Details on how these parametric maps are calculated are given in section 4 Parametric maps.

6 References

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Sourbron SP, B. D. (2011). On the scope and interpretation of the Tofts models for DCE-MRI. *Magn Reson Med.*, 66(3), 735-45.

Tofts PS1, B. G. (1999). Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging*, 10(3), 223-32.