



VIRTUAL GASTROINTESTINAL TRACT VIGOR++

Deliverable: 3.2

Description of the Image Analysis Toolbox 2

Partner: TUD

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Summary

This document gives a description of image analysis toolbox II that was developed for VIGOR++. The tools aid in the assessment of Crohn's disease activity. Particularly, improvements are made to the existing toolbox and new tools are created for enabling quantitative assessment of the vascularization. The toolbox is presented here as deliverable 3.2 of the VIGOR++ project.

Introduction

The image analysis toolbox II contains algorithms encoded in MATLAB to sustain quantitative measurement of Crohn's disease features. The algorithms deal with the following MRI analysis problems: (1) improved identification of the bowel wall; (2) improved MRI data registration and (3) quantitative characterization of the vascularization. The next sections shortly describe the developed algorithms in the context of the tasks in WP3: Image analysis.

Description of the algorithms

T3.1 Identification of the bowel surface

The colonic wall thickness is typically increased with active Crohn's disease. A first step to enable automated measurement of the thickness (see below) is to identify the bowel surface in the MR-images. This is a challenging problem, because the shape varies sharply, the lumen is regularly narrowed into stenotic parts and the contrast between wall and lumen is space variant. A semi-automated method that overcomes most of these problems was already contained in image analysis toolbox I (D3.1). This algorithm was improved to also cope with the varying signal from the space variant bowel content.

Initially, a centerline is manually drawn by an expert through a part of the bowel suspected of Crohn's activity. Subsequently, a so called level-set representation evolves to match the bowel surface. The level-set is steered by the image information (transitions in intensity) while smoothness constraints restrict its shape. Additionally, it deals with heterogeneities in the lumen by incorporating intensity measurements along the path through the lumen. The method proved capable to segment healthy as well as diseased bowel parts, as can be seen in figure 1.

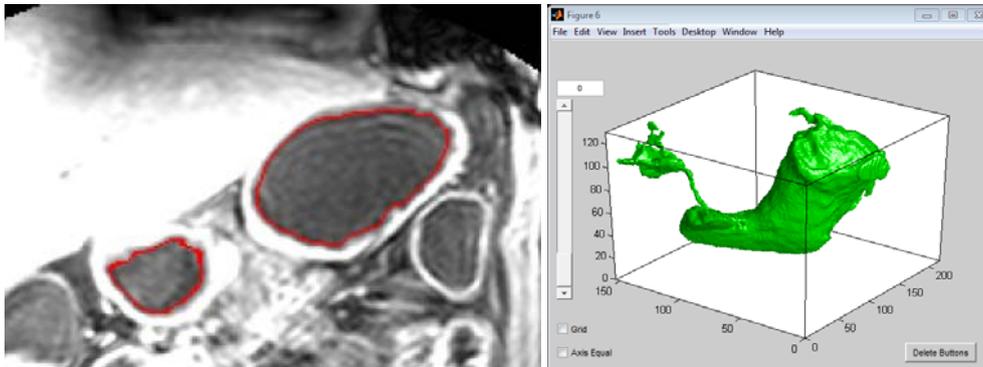


Fig. 1. Example of the bowel surface segmentation; left: original data with superimposed in red the segmented lumen boundary; right: 3D surface representation of the segmented lumen.

Due to possible imperfections during patient preparation, the lumen itself may consist of water, air and faecal residue. The newer version of the algorithm is able to handle these lumen heterogeneities as well. It does so by assigning a certainty that if a voxel would be lumen than it must be one of the three materials. The outcome can be seen in figure 2.

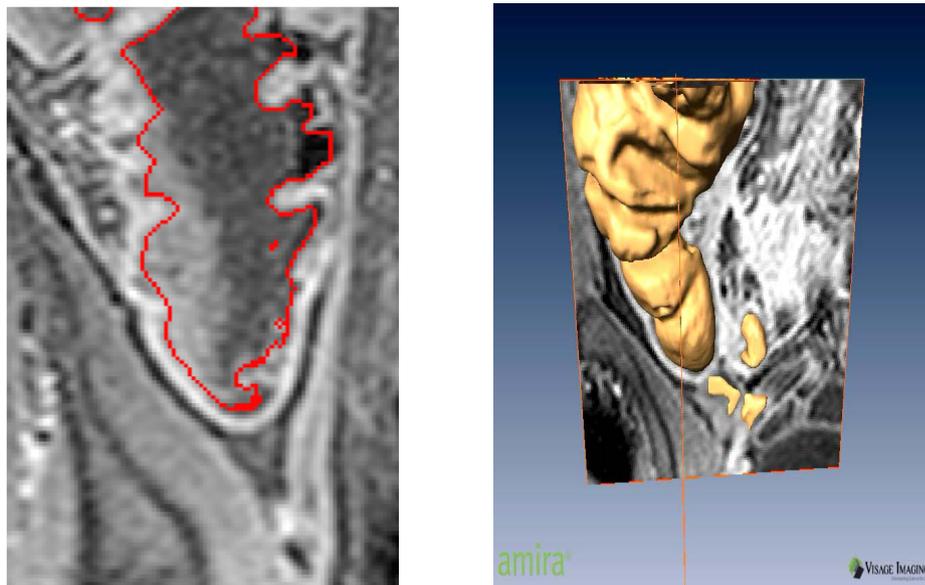


Fig. 2. Example of the bowel surface segmentation in the presence of inhomogeneous lumen content: left original data with superimposed in red the segmented lumen boundary, right 3D surface representation.

The segmentation requires a predefined constant that specifies the ratio between the intensity of water and faecal residue intensity. This is necessary as the algorithm then knows whether the segmentation approaches the water-faecal residue interface or the



water-bowel wall interface. In the first case, the segmentation propagates through the interface. In the second case, it stops.

The outcome of the algorithm is a level set function that implicitly contains the segmentation of the inner bowel surface. The level set function will be used as an initialization for the outer wall-segmentation algorithm. A small example script is given below showing the function description and how the method can be executed :

```
%[U_lev]=BSS3DnetMedical(I_sub,x_path,px,py,pz,lx,ly,lz,n_iter,a_s1,a_s2,alpha,d_ani,delta_t,o_b);  
%  
% Input:  
% I_sub: Region of interest in a T1_weighted image of a piece of bowel  
% x_path: image coordinates of points on the centerline  
% px,py,pz: coordinates top left voxel of ROI  
% lx,ly,lz: dimensions of the ROI in voxels  
% x_path: image coordinates of points on the centerline  
% n_iter: number of iterations for the level set algorithm  
% a_s1,a_s2: smoothness constraint  
% alpha: ratio between the intensity of water and faecal residue  
% d_ani: the anisotropy in the size of voxel  
% delta_t: step size  
% o_b: binary number that indicates whether a patient lied in a prone  
or supine position  
%  
% Output:  
% U_lev: Level function  
% T_surface: Segmentation of the inner bowel surface  
%  
% Example Algorithm  
% load ExampleROISmallBowel.mat  
% [U_lev,T_surface] = BSS3DnetMedical (I_sub,x_path,50)  
% overlay(I_sub,T_surface)
```

T3.2 MRI data registration.

The Time Intensity Curves (TICs) obtained from Dynamic Contrast Enhanced MRI (DCE-MRI), are expected to contain important information on the degree of inflammation of the bowel wall. However, respiratory and peristaltic motions complicate an easy analysis of such curves since spatial correspondence over time is lost. Therefore, a combined retrospective gating and registration procedure was developed to spatially align the MRI data over time. After this registration step the time intensity curves from bowel segment can be extracted.

Furthermore, the post-contrast MR images facilitate measurement of colonic wall thickness, which is typically increased with active Crohn's disease. As such, these images contain complementary information to DCE MRI. A non-rigid registration procedure was devised to spatially align (i.e. create spatial correspondence) the DCE data to the post-contrast MR images.

Preliminary algorithms to perform the abovementioned registrations were already included in Image Analysis Toolbox I. The current deliverable improves the previous

version with respect to accuracy, provides validation experiments and contains a new non-rigid registration method for pre- and post-contrast scans

Extensions in Image Analysis Toolbox II

Fine tuning of DCE image registration

We compared different approaches to perform gated analysis of the DCE data, including gating to expiration, inspiration and random breathing phases. It was found that the expiration phase based method is the best procedure for registration (see Table.1). Also, we tested different parameter settings (e.g. grid size for the transformation, see Fig.3) of the registration procedure and fixed those settings.

Table 1 (Mean square error) MSE differences after fitting a bi-exponential model to TIC's in various ROI's, averaged over all subjects. The first column indicates the bowel section in which the ROI was placed: TI = Terminal Ileum, CA = Colon Ascendens, TC = Transverse Colon, SIG = Sigmoid colon.

The first four rows are averages over diseased areas, the last 4 rows are over normal bowel regions. #1 are averaged MSE differences from original data; #2 are the averaged MSE differences from gated data; #3 shows averaged MSE differences after registering *all* data to the expiration phase atlas; #4-#6 result from gating and registration to random, inspiration and expiration phases, respectively.

Case	Original data#1	E-Phase #2	E-Phase all#3	R-Phase #4	I-Phase #5	E-Phase #6
TI(diseased, n=26)	0.0060	0.0039	0.0031	0.0034	0.0028	0.0027
CA(diseased, n=8)	0.0122	0.0052	0.0053	0.0039	0.0031	0.0021
TC(diseased, n=1)	0.0103	0.0136	0.0027	0.0030	0.0025	0.0016
SIG(diseased, n=1)	0.0021	0.0020	0.0020	0.0020	0.0019	0.0013
TI(normal, n=26)	0.0107	0.0046	0.0032	0.0030	0.0025	0.0016
CA(normal, n=8)	0.0137	0.0084	0.0026	0.0025	0.0020	0.0012
TC(normal, n=1)	0.0840	0.0579	0.0067	0.0082	0.0056	0.0042
SIG(normal, n=1)	0.0133	0.0120	0.0095	0.0104	0.0080	0.0089

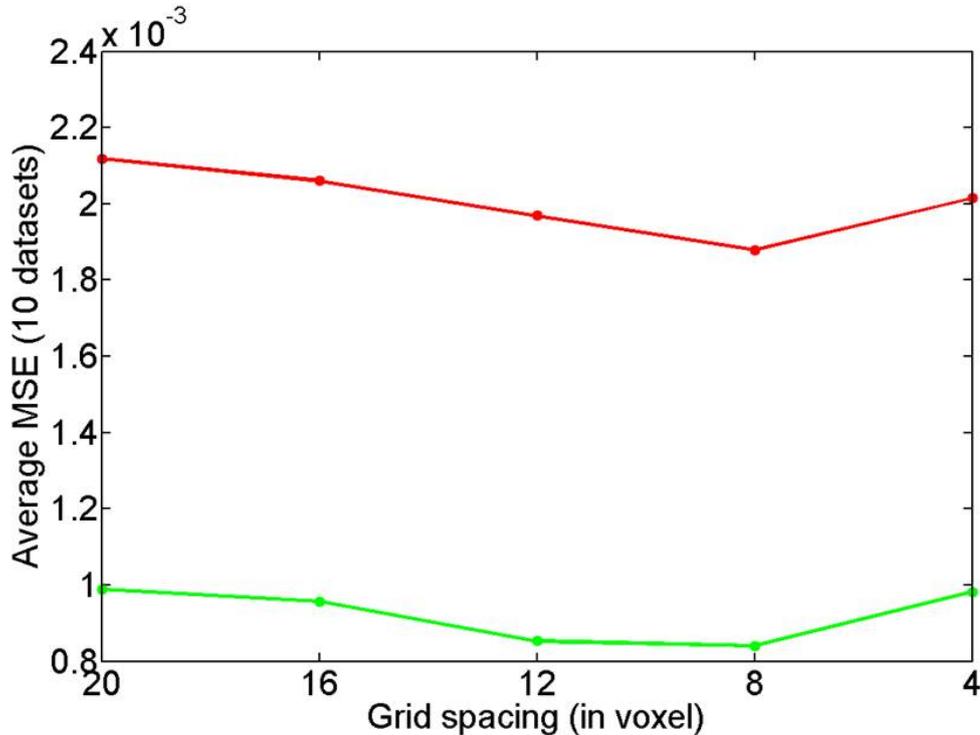


Fig. 3. Averaged MSE (over 10 datasets) after fitting a bi-exponential model to TIC's as a function of the selected B-spline node spacing.

TICs of ROIs in original, gated and registered data are compared in Fig.4(b)-(d). The red region contains inflammatory bowel wall; the green region contains healthy tissue and is added for comparison. Notice the particularly smooth TICs of the registered data in Fig.4(d). Clearly, the red curve demonstrates the largest intensity enhancement. This may reflect that the inflammation information could be distinguished by the TICs after our registration procedure. Accordingly, we also found that the intensity enhancement has good correlation with the crohn's disease endoscopic index of severity (CDEIS, see for more details Deliverable 7.1).

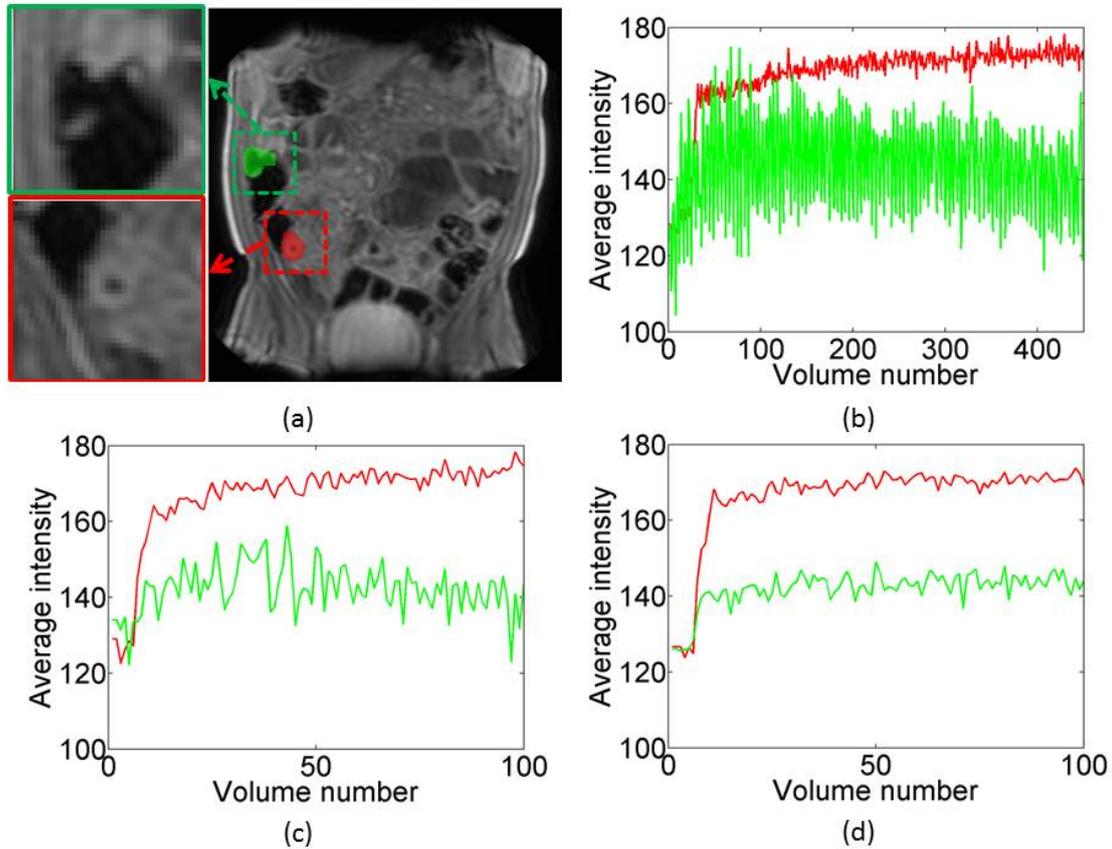


Fig. 4. The TICs from two ROI's (a): green is a region deemed health, red is considered to contain Crohn's disease activity. Furthermore, (b) - (d) show the TICs of original data, expiratory gated data and registered data (notice the reduced number of volumes in the gated dataset).

The abovementioned algorithms are packaged in one main MATLAB function. The code uses a publically available image registration toolbox: Elastix[1]. The function description in MATLAB code is:

```
function MMR(inDir,outDir)
%load Dicom image from path
[imnew,x,y,z,info]=Load_Dicom4D(inDir);
Resolution=[x,y,z];
%save the original image
im=make_nii(imnew,Resolution);
imname=strcat(outDir,'Raw.nii');
save_nii(im,imname);
%Build the expiration atlas
[BreathOut,AverageImg,AllTransX,index]=BreathOut_Atlas(imnew,Resolution);
%Export nii for Elastix
Export_nii(BreathOut,Resolution,outDir);
%save the atlas
```



```
Ave=make_nii(AverageImg,Resolution);  
Average=strcat(outDir,'Average.nii');  
save_nii(Ave,Average);  
system('4D-nonrigid-new.bat')
```

The acronym 'MMR' stands for Mono-Modality Registration. It has two input variables: 'inDir' is a DCE-MRI DICOM file directory; 'outDir' is the directory of the gated and registered images (also in DICOM format). Firstly, the data is loaded from 'inDir'. Secondly, the expiration atlas image is calculated and saved. The expiration phase images are selected and saved as well. Thirdly, both atlas image and expiration images are registered using the 'elastix' toolbox. Finally, the registered results are saved in 'outDir'.

Pre- to post-contrast image registration

Registration of pre to post-contrast registration is important as it also provides information about the relative contrast enhancement (RCE). RCE is an important feature for distinguishing Crohn's disease, since it has good correlation with CDEIS (see more details in Deliverable 7.1). The registration algorithm is based on [2] by using the modality independent neighborhood descriptor (MIND). The registration result is compared with a mutual information (MI) based procedure in Fig.5.

The algorithm of this procedure is written in Matlab as well:

```
function Im_out = MIND_Registration(precontrast, postcontrast)
```

The input 'precontrast' is the fixed image and 'postcontrast' is the moving image. Im_out is the output of registered post-contrast data.

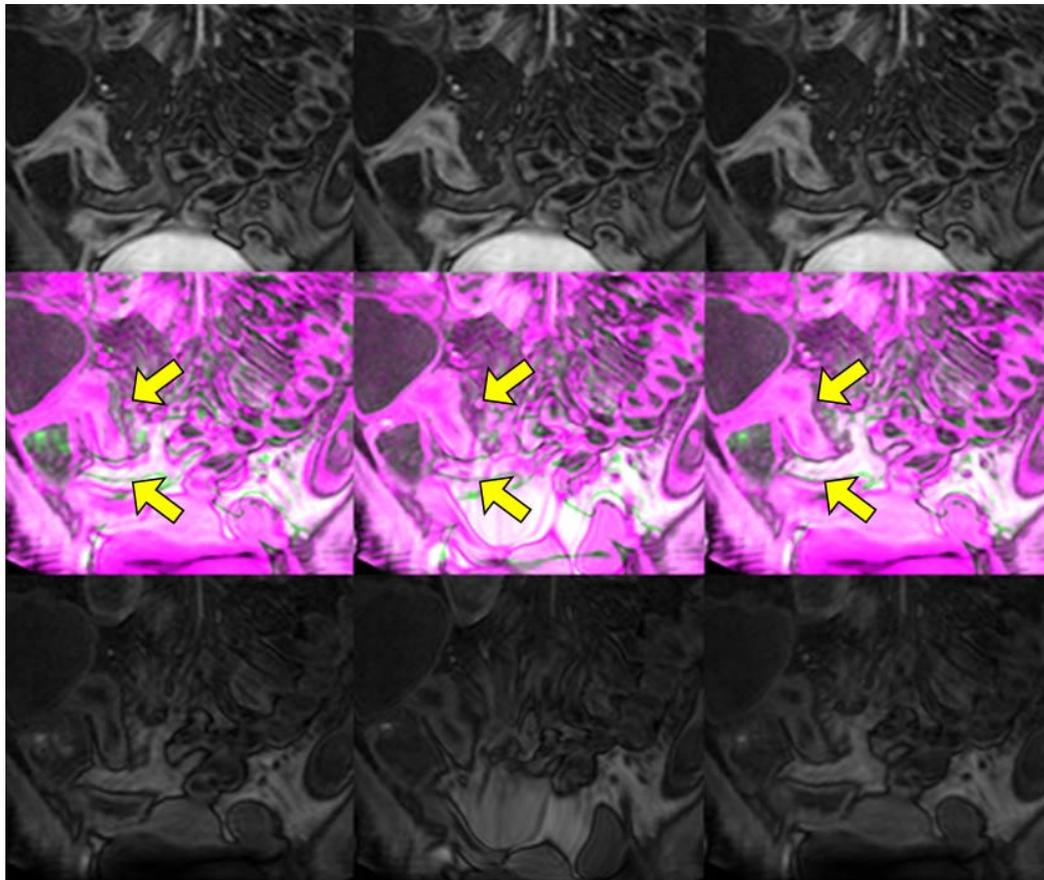


Fig. 5. Example of the pre- to post-contrast image registration. The post image (top row) is encoded in the red and blue channels (middle row); the pre-contrast image (bottom row) in the green channel (middle row). The left column is without registration, the centre column is after registration using MI and right is after registration using MIND. Notice those positions pointed to by yellow arrows. The MIND based method clearly shows a better result than the MI based method.

T3.3 Colon wall segmentation

A method was developed for colon wall segmentation that assumes an accurately segmented colon surface (see T3.1). The method uses a graph based approach to find the outer surface. Edges with a high negative gradient are assigned a low cost, hence a minimum cut is obtained at the outer surface since the wall generally has a higher intensity than the neighboring structures. Two regularization terms are introduced as well. One term states that the distance between the inner and outer surface should be a smoothly varying function, which is necessary because the bowel exterior may exhibit a similar intensity as the bowel wall. An example is illustrated in figure 6.

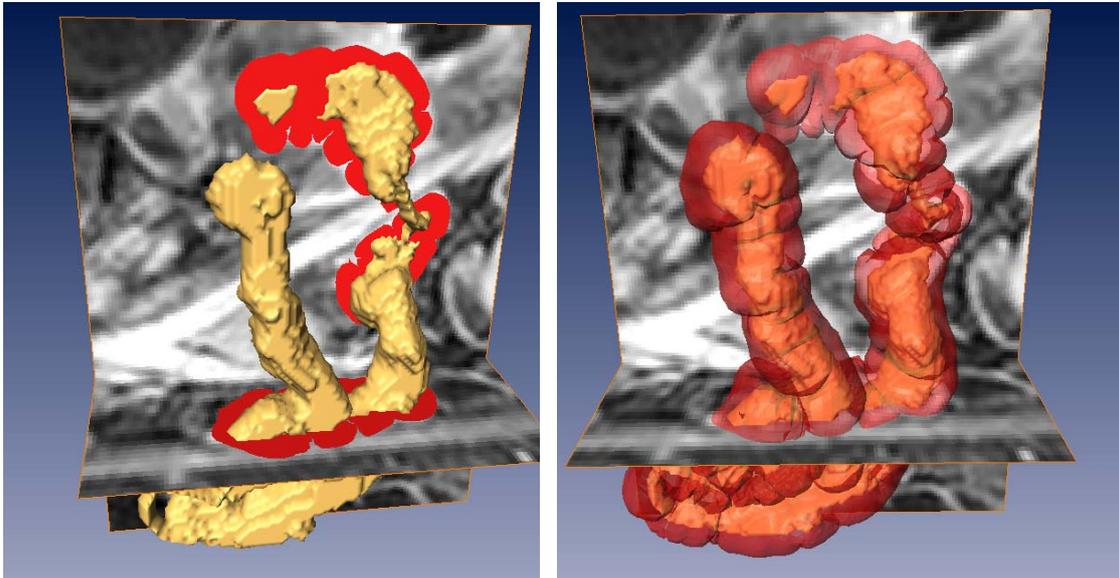


Fig. 6. The left figure illustrates a slice through a ROI extracted from a T1-weighted post-contrast MR-volume. The segmentation of the bowel wall is superimposed in red, a surface rendering of the lumen surface is displayed in yellow. The right figure gives a 3D visualization of the bowel wall

The second constraint, prohibits the merging of adjacent pieces bowel wall into one large piece as shown in figure 7. The spaghetti like orientation of the medial axis of the bowel necessitates such a constraint.

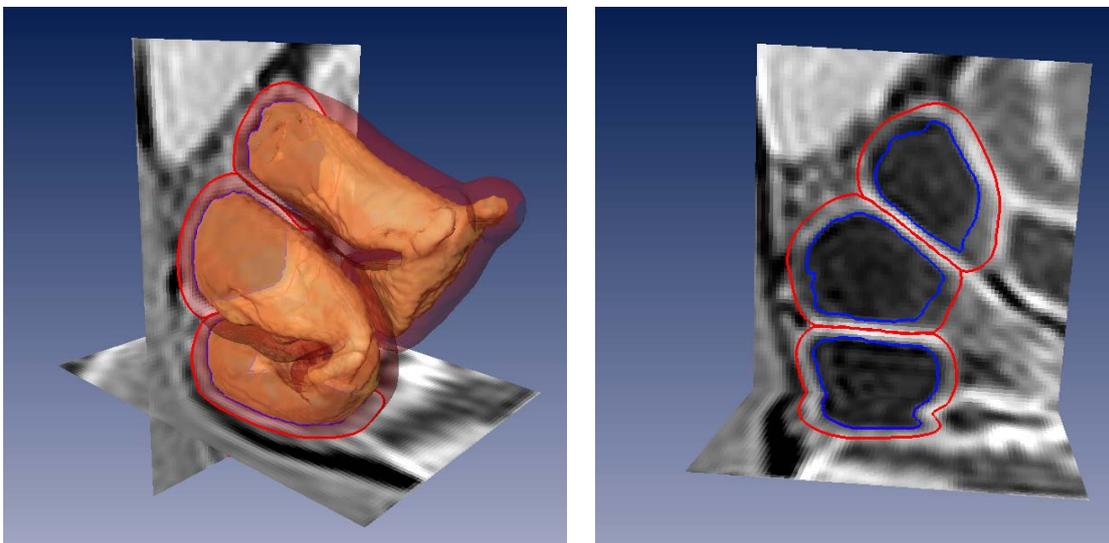


Fig. 7. This figure shows that the outer surface segmentation algorithm does not merge neighboring/adjacent pieces of bowel wall

The algorithm requires the following input variables, namely a region of interest in a T1 weighted MRI image and the level set function:

1. Use the level set function to generate a triangulated surface
 $[float(N,3), int(M,3)]$ `isosurface(float(lx,ly,lz) == 0)`
 $float(lx,ly,lz)$; An array containing the levelset function
 $float(N,3)$; An array containing the coordinates of the vertices of the triangulated surface
 $int(M,3)$; An array specifying the connections between the vertices of the triangulated surface
 $N = int(1)$; the number of triangle vertices
 $M = int(1)$; the number of edges

2. This triangulated surface will function as a reference surface and a starting point of the deformable model. Propagate each triangle vertex with a velocity specified by the cost function
 $[float(N,3), int(M,3)]$ `adjustdeformablesurface(float(lx,ly,lz), float(N,3), int(M,3), float(k,1))`
 $float(lx,ly,lz)$; An array containing the image intensities
 $float(N,3)$; An array containing the coordinates of the vertices of the triangulated surface
 $int(M,3)$; An array specifying the connections between the vertices of the triangulated surface
 $float(k,1)$; A vector containing values of the model parameters

3. Transform the surface into a rasterized label field
 $T = surfacetolabelfield(I, float(N,3), int(M,3))$
 $float(N,3)$; An array containing the coordinates
 $I = float(lx,ly,lz)$; float specifying the image intensities. This array is used to specify the sampling characteristics of the rasterized grid
 $T = int(lx,ly,lz)$; binary image depicted the outer surface
 $float(N,3)$; An array containing the coordinates of the vertices of the triangulated surface
 $int(M,3)$; An array specifying the connections between the vertices of the triangulated surface

T3.4 Quantitative characterization of the wall structure

The MRI regions of bowel wall thickening may present several types of mural stratification patterns corresponding to different stages of the disease. Automated procedures were applied in the statistical modeling of disease activity workpackage (WP4). As such they were included in D4.2 Pattern Analysis Toolbox II.

T3.5 Quantitative characterization of the vascularization

In Crohn's Disease, the degree of vascularization and perfusion are higher, which is expected to result in elevated signal enhancement, compared to normal tissue. Conventionally, these aspects are modelled through a parametric, pharmacokinetic model (e.g., Tofts' model), that is fit to Dynamic Contrast Enhanced MRI data (DCE-MRI).

In order to perform pharmacokinetic modelling a reliable pre-contrast T_1 -map of a region of interest is needed first. We acquire the T_1 -map by a short Look-Locker (LL) MRI scan right before the actual DCE-MRI scan. The data provided by this LL scan is then passed on to a fitting algorithm, which yields a T_1 -map as output.

Secondly, time-concentration curves (TCCs) can be derived from the DCE MRI scan using the pre-contrast T_1 -map. The TCC's describe the concentration of contrast agent over time.

The third step is extracting an Arterial Input function (AIF) from the DCE-MRI data, which is defined as the concentration of contrast agent in an artery nearby the tissue of interest. This artery must be selected manually by the user.

Finally, the fourth step is fitting Tofts' model, using the AIF and the TCCs as input. The output consists of four volumes of the patient, indicating these quantities:

- Fractional volume of plasma, v_p [-]
- Fractional volume of interstitial space, v_e [-]
- Diffusion rate constant, K_{ep} [1/s]
- Volume transfer rate constant, K_{trans} [1/s]

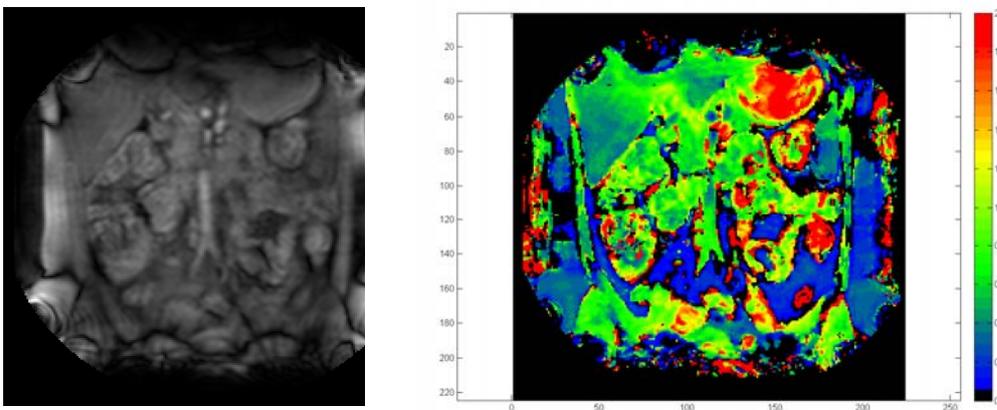


Fig. 8. Raw LL data (actually one phase of a single slice), and the T_1 -map created from this data.

List of functions

All four steps described in subsection 3.5 have been implemented in Matlab. An overview of the functions is given below, including the inputs required and output provided by each function.

Look-Locker fitting algorithm



This function takes the data scanned with the Look-Locker sequence and produces a T_1 -map:

```
function T1_LL = DCEanalysis_T1_LL(I_LL, info_LL)
% Required input:
%   Intensity maps:
%   I_LL: 4-D matrix, nRows * nCols * nSlices * nPhases, double
%   Dicom headers:
%   info_LL: 1-D cell, 1 * 3
%   {1} header.FlipAngle: scalar, double
%   {2} header.RepetitionTime: scalar, double
%   {3} header.TriggerTime: 2-D matrix, nSlices * nPhases, double
%
% Provided output:
%   T1-map, created from LL data:
%   T1_LL: 3-D matrix, nRows * nCols * nSlices, double
```

DCE intensity to concentration conversion

This function takes the data scanned with the DCE sequence (i.e. the TICs) and the pre-contrast T_1 -map, and computes the time-concentration curves.

```
function TCC = DCEanalysis_DCE_3T(I_DCE, info_DCE, T1_precontrast)
% Required input:
%   Intensity maps:
%   I_DCE: 4-D matrix, nRows * nCols * nSlices * nTimePoints, double
%   Dicom headers:
%   info_DCE: 1-D cell, 1 * 2
%   {1} header.FlipAngle: scalar, double
%   {2} header.RepetitionTime: scalar, double
%   T1-maps:
%   T1_precontrast: 3-D matrix, nRows * nCols * nSlices, double
%
% Provided output:
%   Time-Concentration curves:
%   TCC: 4-D matrix, nRows * nCols * nSlices * nTimePoints, double
```

Extracting the Arterial Input Function

This function takes the (registered) DCE data, as well as a mask indicating the location of a nearby artery, to compute the AIF.

```
function AIF = DCEanalysis_AIF(TCC, AIF_mask)
% Required input:
%   Time-Concentration curves:
%   TCC: 4-D matrix, nRows * nCols * nSlices * nTimePoints, double
%   Arterial Input Function segmentation:
%   AIF_mask: 3-D matrix, nRows * nCols * nSlices, boolean
%
% Provided output:
```



```
% Arterial Input Function:  
% AIF: 1-D vector, 1 * nTimePoints, double
```

Pharmacokinetic model fitting algorithm

This function fits Tofts' model to the time-concentration curves, using the AIF. It outputs four PK-parameters, as described above.

```
function [Ktrans, Kep, ve, vp] = DCEanalysis_PKmodel(TCC, AIF, time)  
% Required input:  
% Time-Concentration curves:  
% TCC: 4-D matrix, nRows * nCols * nSlices * nTimePoints, double  
% Arterial Input Function:  
% AIF: 1-D vector, 1 * nTimePoints, double, double  
% Time points of the DCE data:  
% time: 1-D vector, 1 * nTimePoints, double, double  
%  
% Provided output:  
% Pharmacokinetic parameter maps  
% Ktrans: 3-D matrix, nRows * nCols * nSlices, double  
% Kep: 3-D matrix, nRows * nCols * nSlices, double  
% ve: 3-D matrix, nRows * nCols * nSlices, double  
% vp: 3-D matrix, nRows * nCols * nSlices, double
```

T3.6 Characterization of microscopy images

The microscopy images from each patient are visually assessed on inflammation activity and presence of fibrostenosis. However, there appeared to be no added value of an automatic procedure to evaluate the microscopy images. Consequently, no procedures to do so are in Image Analysis Toolbox II.

Conclusion

This document describes the MRI analysis algorithms, that are part of image analysis toolbox II of VIGOR++. Several aspects are improved compared to image analysis toolbox I; others are new:

- The semi-automatic bowel surface segmentation algorithm produces robust segmentation results in the presence of varying bowel content.
- The colon wall segmentation utilizes the bowel surface segmentation as initialization to find points on the outer surface.
- The registration algorithms now match pre-contrast, DCE and post-contrast MRI images. Additionally, the parameter settings of the algorithms were carefully checked.



- Furthermore, procedures were developed for quantitative assessment of the vascularization of the bowel wall.

References

[1] Klein, S., Staring, M., Murphy, K., Viergever, M., Pluim, J.: elastix: a toolbox for intensity based medical image registration. *IEEE Trans. Med. Imaging* 29, 196–205(2010).

[2] Heinrich, M.P., Jenkinson, M., Bhushan, M., Matin, T., Gleeson, F.V., Brady, S.M., Schnabel, J.A., 2012. MIND: Modality independent neighbourhood descriptor for multi-modal deformable registration. *Med Image Anal*, 16, 7:1423-35.