MIDAS Signal Calibration

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Introduction

The MR acquisition is uncalibrated; therefore to provide comparison of individual image values between studies it is necessary to apply a signal normalization procedure. In addition, it is necessary to correct for spatially-dependent variations of the metabolite signal (bias field correction). Both of these operations are implemented in the MIDAS package using the SINORM program, which obtains the bias field correction and normalization factor from a MRI measurement.

This normalization procedure requires a signal reference, for which tissue water is used, but with different options available for obtaining this value from acquired MR images. This reference image is used with an optional calibration factor, “K”, or “K-factor”, to scale the fitted metabolite MRSI signal intensities to a number that is related to the concentration; however, this is not a quantitative measurement. The K-factor is derived from a phantom calibration measurement, and this document describes how this is obtained. Additional description of the normalization procedure itself can be found in the SINORM documentation.

It is important to note that there is a unique K value for each different combination of the MRI and MRSI acquisition, and for the processing protocols used for each image.

The K factor relates the metabolite signal to that obtained from tissue water, i.e., the procedure uses tissue water as an internal calibration standard. After scaling by this value, the metabolite results are in “institutional” units. In principle, the resultant normalized metabolite signal units could be converted to molar concentration units by accounting for both T1 and T2 relaxation effects; however, this quantitation step is not included in the SINORM processing.

The K value is obtained from an experimental calibration measurement in a phantom using a metabolite of known concentration. The acquisition must use the identical MRI and MRSI imaging and processing protocol as that to be used for the imaging study, with the exception that very long TRs are used for the MRI and the MRSI measurement, and a very short TE is used for the MRSI measurement, to minimize the relaxation weighting from the calibration. All other imaging parameters must be the same as that used for the subsequent study for which the K-factor is to be used.
The $K$-factor is then obtained by:

$$K = \left( C_{\text{Ref}} \ast MRI_{H_2O} \otimes srf_{SI} \right) / SI_{\text{Ref}}$$

where $C_{\text{Ref}}$ is the concentration of the fitted metabolite signal in the calibration phantom, $MRI_{H_2O}$ is the MRI signal intensity from a proton-density weighted image, $SI_{\text{Ref}}$ is the signal from the metabolite image for the phantom, and $srf_{SI}$ is the MRSI spatial response function.

The signal calibration is then performed as:

$$[\text{Met}] = I_{\text{Met}} \cdot K / I_{MRI\_PD}$$

Where $I_{\text{Met}}$ is the intensity of the metabolite image and $I_{MRI\_PD}$ is the MRI_PD image intensity after convolution with the SI spatial response function, i.e. at the SI resolution.

Additional information on the normalization procedure can be found in the help file for the SINORM program and in the MIDAS paper:


NOTES

The algorithm is as follows

- Convert MRI-resolution tissue segmentation maps to SI-resolution $\Rightarrow f_{GM}, f_{WM}, f_{CSF}$
- Create simulated water-reference SI based on tissue maps and accounting for estimated T1s, E, and water density, D:
  $$\text{Sim}_SI = f_{GM} \ast D_{GM} \ast E_{GM} + f_{WM} \ast D_{WM} \ast E_{WM} + f_{CSF} \ast D_{CSF} \ast E_{CSF}$$
- Read water-reference SI $\Rightarrow SI_{\text{Ref}}$
- Generate scaling image:
  $$\text{Scale} = SI_{\text{Ref}} / \text{Sim}_SI$$
  This image is smoothed heavily to account for local differences in M0 and T1, and on the assumption that the bias field is slowly varying.
- Scale Metabolite “Area” image
  $$\text{Met}' = K_{\text{Met}} \ast \text{Met\_Area} / \text{Scale}$$
  $$= K_{\text{Met}} \ast \text{Met\_Area} \ast \text{Sim}_SI / SI_{\text{Ref}}$$
  Resultant images are named with the full metabolite name, e.g. “NAcetylaspartate”.
- Scale Reference image (result is named “Water_SI”)
  $$\text{Water} = K_{H_2O} \ast SI_{\text{Ref}} / \text{Scale}$$
  $$= K_{H_2O} \ast SI_{\text{Ref}} \ast \text{smooth(SI\_Sim}_SI / SI_{\text{Ref})}$$

Calibration

$$\text{Met}_K = K_{\text{Met}} \ast \text{Met\_Area} / \text{Scale}$$
The Calibration Phantom

It is necessary to have a phantom with the following requirements:

- Relatively large and with no internal structure, such that a central homogeneous region can be selected from the MRSI study that in not influenced by B0 inhomogeneities or Gibbs ringing effects.
- Containing a metabolite at known concentration, for which the corresponding \textit{a priori} information is available for the FITT program. The spectrum should be simple, with a singlet resonance sufficiently well-separated from water to minimize fitting errors. To improve SNR it is recommended that the metabolite concentration be larger than typical in vivo concentrations. The FITT program likes to have NAA to use as a reference but Acetate is a suitable compound to use.

For Siemens’s users, the standard Acetate 0.1 M spectroscopy phantom can be used. This contains:
1) Sodium acetate (NaC2H3O2; Formula weight: 82.03 g; 8.2 g/1000 mL of H2O): 100 mM
2) Lithium acetate (C3H5O3Li; Formula weight: 96.01 g; 9.6 g/1000 mL of H2O): 100 mM

Alternatively, a phantom containing typical brain metabolites can also be used. The description that follows used a ‘braino’ phantom, made as follows:
Container: Sphere, 2.7L
Water: Distilled

1) Potassium Phosphate – monobasic (Sigma P0662) 50 mM
2) N-Acetylaspartate (Aldrich 441546) 12.5 mM
3) Creatine (Sigma C0780) 10 mM
4) Choline (Choline chloride, Sigma C1879) 3 mM
5) myo-Inositol (Sigma I5125) 7.5 mM
6) Glutamate (Sigma G1149) 12.5 mM
7) Taurine (Sigma T0625) 1.5 mM
8) Glutamine (Aldrich G3202) 6.25 mM
9) Lactate (Lithium Lactate, Aldrich 440469) 5 mM
10 Sodium Azide (Aldrich 199931) 0.1% 

pH adjusted to 1.0 using NaOH and HCl solutions.

Calibration Method

The general procedure is to take MRSI data using a phantom with a metabolite of known concentration, process this in the usual manner, including correction for any bias field in the fitted metabolite image, and then measure the ratio between the metabolite and proton-density MRI data. The detailed steps are as follows:

1. Run the MRI and MRSI MIDAS acquisition protocol on the calibration phantom. This should be identical to the protocol to be used for the subsequent human studies for which the derived calibration factor is to be used, though with a long TR and short TE acquisition. This is done to minimize the effect of relaxation parameters of the reference compound. E.g.:
   - Volumetric EPSI with TR = 10,000 ms, TE = 26 ms.
   - MRI acquisition with short TE and long TR, to obtain a proton density (PD) image. An example would be double-spin-echo, with TR=10,000 ms (or maximum allowed), with only the PD image needed.

2. Import all MRI and MRSI data in the normal manner. You may want to create a new MIDAS Project, e.g. “Calibration_3T”, to import the data into. This will create a new “Subject” or you could add another Study under an existing Subject. The MRI data can be imported with a MRI_PD label (for a single file), or under the MRI_T2 label, as is typically done for a multiecho acquisition (see Figure).
Screen shot of the MIDAS browser showing a project ‘Calibration_3T’ that has a subject ‘VG_Braino_101005’ and its MRI_PD and MRSI (SI and SI_Ref) data.

3. Run the Volumizer on the imported data in the usual manner.

4. Create a segmentation image corresponding to the MRI PD image. A tool is provided to create this image dataset, resulting in the image regions corresponding to the phantom object being categorized as 100% CSF.

This utility is `FakeSegMask`. This can be run by the following methods:

i) By running from the Utilities section of the MIDAS Toolbar: and selecting “Create Segmentation from Phantom Data”.

ii) By restoring and running the IDL save file for this program. Note the save filename is modified by the IDL version number, i.e. start a new IDL session and enter:

```
IDL> cd, getenv('midasbindir')
IDL> restore, 'FakeSegMask62.sav'  - Note, the ‘62’ needs to be replaced with your IDL version!
IDL> fakesegmask
```

The program may also be compiled and run directly from the IDL code, which is located in the “Normalization” directory.

When this program starts, it prompts you to select the MRI_PD node of the calibration study and opens up the MIDAS browser. The ‘fake’ segmentation image result will then be generated and automatically updated into the previously-created Study in the subject.xml file (see Figure). You may check this using the viewer or SID programs.

Screen shot of the MIDAS browser showing a project ‘Calibration_3T’ that has a subject ‘VG_Braino_101005’ and its MRI_T1, MRSI (SI and SI_Ref), MRI_PD and MRI_SEG data.

5. Apply the standard MIDAS MRSI processing protocol (see Figure) for that project to the acquired SI data
Screen shot of the MIDAS Tools showing the relevant processing tools to be applied on the MRSI calibration data (SI and SI_Ref).

There are some modifications from the standard processing, namely:

- The Automask program cannot be used (as there is no lipid); therefore a ‘brain’ mask for the spectral fitting must be created using the Mask program.
- The LITE process can be excluded since there is no subcutaneous lipid.
- The spectral fitting must include the metabolite of interest, e.g. acetate. If the phantom contains only acetate (not NAA, Cr, Cho), then the Cr and Cho metabolites should be excluded from the model [Use: Proc File Editor / Spectral Limits].

6. Run the normalization procedure, e.g. SINORM, in the usual manner, using $K$ factors of 1.0. This processing applies a scaling to the data, based on the PD MRI, and also applies a bias-field correction. The detailed procedure is as follows:

   a) Start the MRSI Normalization procedure

   b) The widget shown at right will appear.

   Note that if this is the first time this has been run for this project then the “$K_{\text{factor scaling}}$” parameters (see below) are value 1.0, which is shown in the grayed-out number to the right of the scaling factor.

   - Click Browse and select the Study. The program will find the MAPS node containing the FITT results. (Selection may also be made at the subject level, in which case the program will automatically find the default Study node if only one study is present.)

   - Check the TR, this is for the MRI PD data. The value was read from the data, but can be changed if needed.

   - Enter the T1 values for the MRI-observed water signal under the “CSF” entry. Note that the widget defaults to showing T1 values for gray matter, white matter, and CSF at the field strength at which the data were acquired; however, for this operation it is only the CSF value that will be used. The accuracy of the T1 value is not critical provided that the data was taken with a long TR, and in this situation it should be possible to use an estimate of the water T1 value.

   - Enter the proton density factors (i.e. water content) for the CSF. For this calibration procedure the CSF factor should be 1.000.
• Set the MRI/SI Scaling Factors (K) = 1. It is possible to use any K factor value here, but the value must be noted for use in the scaling factor calculation. Also make a note of the K_Factor_Scaling parameter, which appears in grey.

• Run the program and exit.

7. Using the SID program in MIDAStools, measure the signal intensity of the normalized metabolite image. An average value can be obtained to improve the measurement.

    a) Start the SID program (SID).
    b) Load the SI data (see Figure). The MAPS data should be opened automatically.
    After loading, check the data (e.g. see Figure).

    c) View and check the metabolite you are using for the calibration from the SID Ref List (see Figure). Note, this must the image after normalization, e.g. “NAcetylAspartate”, which is the scaled NAA area, and not “NAA_Area”, which is the unscaled result from the spectral fitting. Go to the slice corresponding to the center of the object (to minimize edge effects).
d) Obtain an average value over some central region. Go to SID Processing → choose Read Image Values (see Figure).

Select the checkbox corresponding to the metabolite image you are using for the calibration (e.g. NAcetylAspartate, see Figure).

Then enable the sum mode: In the SID Spectrum window, go to Processing → select Sum Region ON (Figure).
Now, in the SID Reference Image window, select a voxel located approximately at the center and sum over several voxels in that area (see Figure). Here, the aim is to choose a central region with good SNR and homogeneity and remote from any Gibbs-ringing artifacts.

At the end of summing, you will see a mean and standard deviation displayed in the Image Values window. Make a note of this mean value, which is the $Met$ given in the equation in Section 8 below.

8. Calculate the MRI-metabolite $K$ scaling factor as:

$$K = \frac{C_{met}}{Met} \times K'$$

where $K'$ is the $K$ value you used for the normalization in Step 6 above (e.g. value 1); $Met$ is the measured image value from step 7d, and $K$ is the final calibration factor.

Example:

$$C_{met} = 12500 \ \mu\text{M}, \text{ known NAA concentration in the phantom. See Note 1 below on the reason for using microMolar concentration units!}$$

$$Met = 0.005574,$$ obtained in step 7 above

$$K' = 1 \times 1000.$$ This is the combination of the metabolite K_factor (1.0) and K_factor_scaling (1000.0), that were used when the SINorm program was run on this data.

The new $K$ factor is, $K = (125000/0.005574) \times 1000.$

$$K = 2.24255 \times 10^{10} \quad \text{- see Note 2 below}$$

NOTE 1: The data scaling results in a data value that is of the same order as the units of concentration, or value of $C_{met}$. If mM range had been selected, i.e. 12.5 mM in the above example, then the resulting images would have small data values (e.g. 1.0 to 10.0 mM range). Unfortunately, this has been found to cause problems with look-up tables in some
display programs that may have been optimized for MRI, and which may convert image data to integer. Therefore, in the example we have used \( \mu \text{M units} \). For in vivo data the normalized tissue metabolite results will therefore be roughly in the 1000 to 10000 range.

Therefore, the use of \( \mu \text{M} \) for the concentration of the metabolite in the phantom is recommended.

NOTE 2: The scaling factors tend to be large numbers, and for this reason the program can make use of a “K_factor_scaling” parameter. This is set in the SINorm_parameters.txt file (see below) and can be changed by manually editing the value. In this example, it would be convenient to set the following parameters:

\[
\text{K\_Factor} = 22.4255 \\
\text{K\_Factor\_Scaling} = 1000000000
\]

9. Repeat the measurement and calculation for the MRI-Water_Reference_SI \( K \) factor:

In SID select the “Reference” SI image and in the “Read Image Values” function select the “Water_SI” data. This value can also be selected and done at the same time as the previous measurement for NAA, e.g.:

Now calculate the water reference scaling factor in the same way. Once again, we need to give some thought to the units. One suggestion is to use 110,000 mM proton concentration. Since the water reference SI image is not obtained in the same way as the fitted metabolite image, the scaling factors may differ considerably.

NOTE: Scaling of the water reference is not intended to be quantitative in any way! This function is only provided for convenience - in order to get the resultant numbers in a reasonable range, i.e 10,000 instead of something like \( 1 \times 10^{14} \).

10. Add the K factors to the Defaults File used by the SINorm program. If only the K-Factors need changing then this can be done from the SINorm program by editing the values and selecting “Save Defaults”. If the K\_Factor\_Scaling needs changing as well, then the file
needs to be edited. This file is “SINorm_parameters.txt”, and is located in the Project top-level directory, e.g.:

D:\Data\Normals_Study\ SINorm_parameters.txt

This file is automatically created the first time you run the SINorm program. The file is organized by MR instrument and the corresponding K_Factor value should be replaced with the value you have just derived. Example:

![Example of the SINorm_parameters.txt file](image)

Example of the SINorm_parameters.txt file, showing the K_factor and other settings for a study at 3 Tesla.

(NOTE: In a future release this information will eventually be stored in the Project.xml file.)

**Additional Considerations**

Both MRI and MRSI, for the calibration and the actual study, must be done in the same session so that the coil loading is the same for both measurements.

The calibration measurement is based on the ratio between two image intensities, therefore is not dependent upon signal intensity variations across the image; however, the same spatial variations must be present in the MRI and MRSI data. In the case of phased-array acquisitions, it is therefore necessary that no bias field correction be applied to the MRI, and it should be verified that the MRI and MRSI reconstructions result in the same receiver sensitivity distributions.

At higher fields (3T and above), it will also be necessary to account for differences in the signal excitation (i.e. transmitter B1 variations), since different pulse sequences and pulse shapes are typically used for the MRI and MRSI acquisitions. For this situation a separate procedure (SINORM2) is under development (as of 12/05).
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