Chapter 35

Analysis Protocols for MRI Mapping of Renal T_1

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Abstract

The computation of T_1 maps from MR datasets represents an important step toward the precise characterization of kidney disease models in small animals. Here the main strategies to analyze renal T_1 mapping datasets derived from small rodents are presented. Suggestions are provided with respect to essential software requirements, and advice is provided as to how dataset completeness and quality may be evaluated. The various fitting models applicable to T_1 mapping are presented and discussed. Finally, some methods are proposed for validating the obtained results.

This chapter is based upon work from the COST Action PARENCHIMA, a community-driven network funded by the European Cooperation in Science and Technology (COST) program of the European Union, which aims to improve the reproducibility and standardization of renal MRI biomarkers. This analysis protocol chapter is complemented by two separate chapters describing the basic concept and experimental procedure.

Key words Magnetic resonance imaging (MRI), Kidney, Mice, Rats, T_1 mapping, Processing, Fitting

1 Introduction

The computation of T_1 maps from MR datasets represents an important step towards the precise characterization of kidney disease models in the small animal. Although some concepts pertaining to T_1 mapping are relatively general, there are some important points that need to be observed specifically for each different acquisition strategy. In this section we will describe in more detail the three main classes of data fitting procedures corresponding to saturation recovery, inversion recovery, and variable flip angle protocols.

This analysis protocol chapter is complemented by two separate chapters describing the basic concept and experimental procedure, which are part of this book.

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2 Materials

2.1 Software Requirements

The method described in this chapter does require the following software tools:

1. For Bruker users, the availability of a Bruker post-processing station with Bruker Paravision fitting tools (“ISA Tools”) installed, or if an independent console is not available, the scanner console. It may not always be possible or practical to alter the vendor-proposed routines to adapt to a particular use case.
2. A programming environment capable of applying fitting models, such as MATLAB® including the curve fitting toolbox (MathWorks, <https://www.mathworks.com/products/matlab.html>), Octave (<https://www.gnu.org/software/octave/>), ...
3. An image processing software (e.g., Image J, we recommend using Fiji, which is ImageJ with a wide range of plugins already included, <https://fiji.sc/>, open source), as a practical tool for the image quality check or for measuring the SNR.
4. For region based approaches, analysis can be done in the R language [1].
5. To speed up computation time, it may be necessary to use optimized compiled code executables or to take advantage of parallel computing.

2.2 Source Data: Format Requirements and Quality Check

2.2.1 Input Requirements

To be able to calculate T_1 maps, multiple images with different repetition times, inversion times or flip angles are needed. It is necessary to have access to some scan parameters, including matrix size and number of slices, scaling information (offset and slope), and the values of the repetition times, inversion times or flip angle. Additional time delays may also be required. In the case of protocols with multiple acquisitions, the receiver gain should also be accessible. Consistency in the acquisition parameters is paramount, especially the parameter that is varied, which should sample the same interval for each animal in the study. The completeness of the data needs to be verified ahead of the processing, by checking that the matrices have the expected size and dimensionality, or in the case of multiple protocols datasets, by ensuring that each expected protocol has indeed been acquired.

2.2.2 Physiologic Motion Check

Physiological motion is an important source of image error. Because it is difficult to avoid entirely in vivo, even in the presence of triggered acquisitions, it represents an important determinant of the dataset quality. The amount of physiologic motion can be assessed visually or via quantitative estimators (see below). Frames displaying high respiratory motion may be either discarded altogether, or they may be weighted differently in the fitting procedure.

Fig. 1 Illustration of physiologic respiration-based noise. Left: original image. Middle: same image with a different windowing applied. Respiratory noise is evident as a signal smeared in the phase-encoding direction (vertical) only in the image with a strong windowing applied. Different amounts of noise may be tolerated depending on the final intended use of the data. Right: image with T_1 map overlay on the kidneys (color scale in ms)

In the simplest cases (especially with cartesian sampling schemes), respiratory motion can be identified as high intensity regions in the air surrounding the animal, corresponding to smeared projection of the signal along the phase-encoding direction (Fig. 1). Such motion may not be immediately visible and instead require to enhance the image windowing. Varying degrees of physiologic motion may be tolerated depending on the application. Automated methods can be put in place, to selectively remove frames where the noise level in the air region surrounding the animal exceeds a certain limit, in a retrospective fashion [2].

2.2.3 Acquisition Geometry Check

The geometry of the acquisition also needs to be set and verified prior to processing.

1. Verify the slice position and orientation to ensure that an optimal delineation of the kidneys is possible. A coronal orientation is often chosen, because it enables to have large regions of interest that depict all the anatomical regions of the kidney in a single image.
2. Visually check image centering to ensure that the dataset can be exploited.

2.2.4 Acquisition Parameters Consistency Check (Multiple Scans Case Only)

Regardless of the technique which is applied, it is preferable to acquire a single protocol where the parameter of interest varies.

1. Assume that the acquisition parameters are the same for all acquired images and move on to the next step.

If such a protocol is not available on the system, the same scan has to be acquired several times while varying the parameter of interest. This is the case typically for T_1 mapping with variable flip angle approach.

2. Check that all parameters (other than the varied parameter of interest) have stayed the same.

**2.2.5 Receiver Gain
Consistency Check
(Multiple Scans Case Only)**

1. Check that the receiver gain setting is identical for each scan when merging data from separate protocols.
2. If the receiver gain is not the same: contact the manufacturer to obtain receiver gain amplification tables.
3. Use the receiver gain amplification tables to calculate correcting factors.
4. Apply the correction factors to set each image at a common amplification level.

This exposes the user to noise compression or amplification and should only be used as a last resort.

**2.2.6 Data Intensity
Scaling Consistency Check
(Multiple Scans Case Only)**

The data should also be rescaled to the same intensity mapping. This ensures comparability of data coming from different datasets. For Bruker-generated data, it is recommended to use the absolute mapping option in the reconstruction options. If this has not been done during acquisition, additionally for Bruker-generated data, at the console, the user must:

1. Duplicate the processing.
2. Activate “Prototype Reconstruction”.
3. Set output mapping to “User Scale”.
4. Set parameters “Output Slope/Output Offset” accordingly to the setting of the first scan of the series. The setting of the first scan of the series can be checked in the “Single Parameter” parameter editor.

3 Methods

3.1 Data Exclusion

1. Check that all data points have sufficient signal to noise (SNR of 5 or higher).
2. If not all data points have high SNR then consider the necessity to only use data points with sufficient signal to noise (see next two steps).
3. For variable repetition time protocols, eliminate the data points at low repetition times (TR) that have insufficient SNR.
4. For inversion recovery protocols eliminate the data points close to the zero-crossing that have sufficient signal to noise.

3.2 Data Coregistration

To improve dataset quality, coregistration of images can be implemented to correct for respiratory motion, if such tools are available. The elastix package [3], MATLAB’s built-in `imregtform` function, SPM [4], or AIR [5] (among others) can be used toward that objective.

3.3 Model Fitting

With contemporary computing hardware, fast fitting of the model to the signal intensity magnitude images can be performed on each pixel of the initial dataset. A region-based approach (wherein the fitting procedure is applied to ROI averages), can also be applied, but by construction it will lack the ability to examine the local spatial variations of tissue T_1 .

3.3.1 Fitting Data for Saturation Recovery Experiments

1. Select an appropriate fitting equation. For the VTR protocol, the following equation is applicable (under the assumption of a perfect pulse) [6]:

$$S = S_0 \left(1 - e^{-TR/T_1} \right) + \varepsilon \quad (1)$$

where S is the signal magnitude, S_0 is the maximal available signal magnitude (including amplification factors), TR is the repetition time, T_1 is the longitudinal relaxation time, and ε is an additive noise component with Rician distribution.

2. If S_0 is known, linearize the fitting equation. A plot of $\ln(1 - S/S_0)$ against TR yields a straight line of slope $-1/T_1$ from which T_1 can be extracted with linear regression (*see Note 1*).
3. If the longest TR is significantly longer than T_1 , please refer to **Note 3**.
4. If S_0 is not known, Eq. 1 can be fitted with nonlinear regression.
5. Initialize the fit with appropriate starting values for S_0 (*see Note 2*), using the signal obtained at the longest TR (*see Notes 3 and 4*).
6. Initialize the fit with appropriate starting values for T_1 (*see Note 2*) using the value obtained by linear regression if applicable (*see item 2*).
7. Perform the fit with the Levenberg-Marquardt, the trust region or the maximum likelihood algorithms (*see Note 5*).

3.3.2 Fitting Data for Inversion Recovery Experiments

1. Select an appropriate fitting equation. For the inversion-recovery protocol, the following equation is applicable (assuming perfect pulses and absence of relaxation during pulses) [6, 7]:

$$S = \left| S_0 \left(1 - 2e^{-TI/T_1} \right) + \varepsilon \right| \quad (2)$$

where S is the signal magnitude, S_0 is the maximal available signal magnitude (including amplification factors), TI is the inversion time, T_1 is the longitudinal relaxation time, and ε is an additive noise component with Rician distribution.

2. If S_0 is known, linearize the fitting equation. A plot of $\ln((S_0 - S)/(2 \cdot S_0))$ against TI yields a straight line of slope $-1/T_1$ from which T_1 can be extracted with linear regression (*see Note 1*).

3. Optionally, apply a corrective formula to account for the perturbation in recovery caused by the small angle imaging pulses (*see* **Note 6**):

$$\frac{1}{T_1} = \frac{1}{T_1^*} + \frac{\ln(\cos(\theta))}{\tau} \quad (3)$$

4. Optionally, the following equation is also applicable (assuming perfect pulses and absence of relaxation during pulses) [2, 8–11] and adds a saturation-correcting factor (*see* **Notes 7** and **8**):

$$S = S_0 \left(1 - \beta \cdot e^{-TI/T_1^*} \right) \quad (4)$$

5. If S_0 is known, linearize fitting Eq. 4. A plot of $\ln(1 - S/S_0)$ against TI yields a straight line of intercept $\ln(\beta)$ and of slope $-1/T_1^*$ from which T_1^* can be extracted with linear regression. The actual T_1 is subsequently recovered from the values of T_1^* and β as follows:

$$T_1 = T_1^* \cdot (\beta - 1) \quad (5)$$

6. If S_0 is not known, Eqs. 2 and 4 can be fitted with nonlinear regression using S_0 , T_1 and β as adjustable parameters and if applicable the correction of Eq. 5.
7. Initialize the fit with appropriate starting values (*see* **Note 2**) for S_0 , using the signal obtained at the longest TI (*see* **Notes 3** and **4**).
8. Initialize the fit with appropriate starting values (*see* **Note 2**) for T_1 using the value obtained by linear regression if applicable (*see* **Note 4**), or using the graphical procedure outlined in **Note 9**.
9. If the longest TR is significantly longer than T_1 , please refer to **Note 10**.
10. Perform the fit with the Levenberg-Marquardt, the trust region or the maximum likelihood algorithms (*see* **Note 5**).

3.3.3 Fitting Data for Variable Flip Angle Experiments

1. If only two flip angles are available, use the following simplified equation involving α_1 and α_2 the two flip angles used, β the ratio image obtained between the two flip angles, and TR the repetition time TR [12] to compute the T_1 :

$$T_1 = \frac{TR}{\ln \left(\frac{\beta \cdot \sin(\alpha_2) \cdot \cos(\alpha_1) - \sin(\alpha_1) \cdot \cos(\alpha_2)}{\beta \cdot \sin(\alpha_2) - \sin(\alpha_1)} \right)} \quad (6)$$

2. In the more general case, the following equation is applicable (*see* **Notes 11** and **12**):

$$S(\theta) = S_0 \cdot \sin(\theta) \cdot ((1 - E_1)/(1 - E_1 \cdot \cos(\theta))) \quad (7a)$$

where

$$E_1 = \exp(-TR/T_1) \quad (7b)$$

3. Determine T_1 using linear regression on the linear form of Eqs. 7a and 7b [13]:
Plot $S(\theta)/\sin(\theta)$ against $S(\theta)/\tan(\theta)$.
4. Retrieve the slope of the plot from the linear regression. This is E_1 (definition in Eq. 7b).
5. Compute the T_1 estimate directly as $-1/\ln(E_1)$.
6. Retrieve the intercept of the plot from the linear regression. This is $S_0(1 - E_1)$. The S_0 value is estimated by dividing the intercept value that was found by $1 - E_1$ (using for E_1 the value obtained previously).
7. Alternately, determine T_1 using a nonlinear fitting procedure.
8. Initialize the fit with starting values (*see Note 2*) for S_0 and T_1 obtained using the linearization described previously (*see Note 4*).
9. Perform the fit with the Levenberg-Marquardt, the trust region or the maximum likelihood algorithms (*see Note 5*).

3.4 Visual Display

T_1 maps can be shown as gray-scaled or color-coded maps. T_1 maps from the region of interest can be superimposed after coregistration on a morphological image or on an image acquired with the T_1 mapping protocol to better illustrate anatomical location. Window scales, usually run from $T_1 = 0$ to $T_1 = 3000$ ms, should be provided with the map and should be kept constant between figures.

3.5 Quantification

The fitting algorithm is usually applied on a voxel-by-voxel basis to yield a T_1 map. Mean T_1 is then calculated by averaging T_1 values within a region of interest. It is recommended to define a region of interest for each anatomical subregion of the kidney, as the pathology of interest can affect differently these subregions [14]. Typical ROIs are cortex, outer medulla and inner medulla, using morphological images as references to draw these ROIs. Provided sufficient spatial resolution is available, finer structures such as the outer and inner stripes of the outer medulla [15], or the corticomedullary junction [7], may be distinguished. It is also common to report T_1 changes relative to baseline or to the contralateral kidney.

3.6 Results

Validation

3.6.1 Evaluation of Analysis Errors and Variability Using Synthetic Data

Synthetic datasets of various complexities should be generated to test the validity of the processing solution. Artificial noise can be added to assess the stability of the fitting procedure. T_1 of the numeric phantom should match the expected T_1 . This approach is, however, limited by the signal equation, which may or may not recapitulate the real situation complexity. Hence, the use of physical phantoms can also be recommended (*see* procedure outlines in the chapter by Irrera P et al. “Dynamic Contrast Enhanced (DCE) MRI-Derived Renal Perfusion and Filtration: Experimental Protocol”).

3.6.2 Comparison with Reference Values from the Literature

Relatively few studies have reported T_1 values for kidney acquired in animal models at high magnetic fields (4.7 T and higher). Typical ranges for normal kidney tissue are $T_1 = 1000\text{--}1700$ ms at magnetic field strengths of 7 or 9.4 T [14–16], with significant differences reported between mouse strains [16]. Acute kidney injury and unilateral nephrectomy have been reported to increase T_1 values in kidney, up to $T_1 = 1944$ ms at 7 T for severe acute injury [15] and well above $T_1 = 2000$ ms at 9.4 T for unilateral nephrectomy [14].

4 Notes

1. The accurate estimation of S_0 is, not trivial. Indeed, in Eqs. 1 and 2, signal evolution is asymptotic and even at very high TR or TI values, the signal only approaches the actual S_0 value. Furthermore, in these protocols, TR or TI directly affect the acquisition duration. Hence, the precision of the estimation of S_0 directly affects scan duration. In the linearization approach, the available precision on S_0 dictates the precision with which T_1 is recovered (error propagation). Hence with this approach, increased acquisition time is needed to improve the precision of the measurement. If the duration of the experiment is a concern (dynamic studies, animal models of severe diseases, difficult anesthesia), it may be preferable to leave S_0 as free parameter and to use a nonlinear fitting procedure.
2. In nonlinear fitting algorithms it can be advantageous to provide starting points that are close to the final values. Indeed, this allows to decrease the number of iterations required to reach convergence, and hence can limit the computation time. Furthermore, using starting values close to the true values also helps identifying the global minimum rather than a distant local minimum. Hence, strategies can be adopted to provide as accurate as possible initial estimates for the free parameters of the nonlinear fitting procedure.

3. In some cases, an initial S_0 estimate for fitting initialization can be obtained from the highest signal available (at the latest saturation or inversion recovery delays for instance). This estimate will only be precise if the longest delay that is sampled is sufficiently long.
4. The outlined strategies for determining reasonable starting values may not work in all cases. For instance, in the presence of high experimental noise or in the case of poorly controlled acquisition conditions, the initial estimates may prove unreliable. In this case, reasonable starting values for the T_1 may be alternately obtained from the literature. Special care should be taken to select literature reference values from studies where similar magnetic field strength, protocol type and experimental disease models were used.
5. Careful comparison of the performance of the fitting algorithms should be conducted on datasets obtained on the disease model and hardware setup used in the study. The various algorithms may be compared in terms of computation speed and goodness-of-fit figures of merit such as the root-mean-squared error before a final choice is made.
6. In inversion recovery protocols, the T_1 relaxation process is sampled several times after an inversion RF pulse using small gradient echo shots, EPI readouts or FISP readouts. Thus, the natural longitudinal recovery is perturbed by the application of the imaging RF pulses of flip angle θ and separated by a repetition interval τ . The effect can be accounted for by correcting T_1^* , the apparent T_1 resulting from the fit, using the expression given in Eq. 3 [17–19].
7. With inversion-recovery protocols followed by multiple shots, it would be preferable to use long delays between the imaging RF pulses, to drive down the saturation effect of the fast repeating gradient echo excitation RF pulses. This is not always practical, since short delays are required to fit a large number of imaging shots within a single inversion recovery interval. This is linked to the requirement that no transverse magnetization remains at the end of an imaging shot once the subsequent imaging shot is acquired, that is, that the condition of spoiled magnetization is applicable. The generally accepted condition is thus to ensure that $\tau \gg T_2^*$. Thus, although not ideal, it is acceptable to shorten the repetition time between imaging RF pulses, to reach an optimal situation where the two conflicting constraints of having both a large number of imaging shots per inversion recovery and a sufficiently good spoiling of magnetization between consecutive imaging shots are met. Similarly, it can be advantageous to work at low flip angle, to minimize the perturbation to the natural magnetization recovery relative to

the ideal case when no imaging RF pulses are applied after the inversion RF pulse. This comes at a disadvantage of having a smaller signal to noise ratio. However, this may be preferable when exactness of the recovered T_1 is important. In conclusion, the selection of the most appropriate fitting equation should be guided by careful examination of the specific acquisition protocol that was used, and of values of the imaging delays, flip angles, and typical expected tissue magnetic properties in the disease model at hand.

8. More complete correction schemes can be applied in the case of Look–Locker protocols. In particular, the delay between the inversion RF pulse and the first imaging RF pulse may be different than the delay between subsequent sequential imaging RF pulses. The imperfections in the inversion profile may also be modelled in the equation. Expressions taking this delay into account are available. Furthermore, in inversion recovery protocols, some variants may be segmented. For instance, partial k-space segments can be acquired by groups of imaging shots at several times post inversion. The various individual shots in a segment are used to reconstruct an image at a single inversion delay (the delay between the inversion RF pulse and the half of the imaging segment). Imaging segments may be separated by arbitrary delays. Expressions are available to take into account these delays [20–22].
9. In the case of inversion recovery protocols, a simpler method may be used to provide a reasonable estimate of T_1 to be used as starting point. Indeed, the signal has the typical shape where the image magnitude first drops down to zero, then comes back up (*see* Fig. 2). This is due to the fact that the image magnitude is gotten from the transverse component of the magnetization, without discerning whether the magnetization is below or above the transverse plane. This offers a graphical way to determine rapidly the T_1 by identifying the point at which the signal is minimal. The recovery delay at which this condition is verified is an approximation of the time when the longitudinal magnetization crosses the transverse plane. The precision of this estimate will be improved if the sampling of inversion times is dense around this point. The delay of the zero-crossing is equal to $T_1 \times \ln(2)$. Hence the true T_1 can be identified by dividing the zero crossing delay by $\ln(2)$. This can be useful to obtain a rapid estimate of the T_1 during parameter optimization. This computation can be performed very simply at each voxel by identifying the index of the signal vector where the smallest signal intensity is obtained. This strategy is, however, limited when only few points are available along the regrowth or when the signal to noise is low. Both cases can

Fig. 2 Inversion recovery plot depicting the graphical method to identify T_1 . An estimate of T_1 is obtained by identification of the inversion time yielding the smallest available signal, and dividing this value by $\ln(2)$. Although this quantification is not optimally accurate, it may prove useful in determining sufficiently close values to serve as a good initialization point for nonlinear fitting procedures

alter the accuracy of the estimation of the delay time yielding zero crossing.

10. Depending on the acquisition conditions, images are available at TI (or TR) $\gg T_1$. In that case, Eqs. 1 and 2 collapse to $S = S_0$. Such images can be used to normalize the data, and the nonlinear fitting procedure can be carried out on S/S_0 rather than S . By suppressing the free parameter S_0 from the fitting procedure, the numeric stability of the fit is improved, at the expense of the longer acquisition time required for the acquisition of the TI $\gg T_1$ protocol. This approach is also subject to the problem of error propagation from the S_0 estimation into the T_1 term exposed previously.
11. The true signal behavior may differ significantly from this expression, especially if the applied flip angle is not homogeneous. In that case, a corrective, smoothly spatial-varying $\zeta(B_1^+)$ term may need to be applied to account for excitation radiofrequency field heterogeneity. The effectively obtained flip angles, θ_{eff} , are in that case a modulation of the prescribed

flip angle series, θ , such that $\theta_{\text{eff}} = \zeta(B_1^+) \cdot \theta$. The evaluation of the ζ field is not trivial, and becomes especially important at higher field strengths. Post-processing methods based on large scale features in the image such as low pass filtering, or fitting of slowly spatially varying functions, can be proposed, but only extract the combined effects of transmit (B_1^+) and receive (B_1^-) heterogeneities [23]. The modulation fields can be subtracted out before performing the fit, provided that the reception field is sufficiently homogeneous. Of note, this assumption is quite difficult to validate, especially at high field strengths or when single receive RF coil elements are used as the detection circuitry.

12. Alternately, a reference T_1 map acquired with a Look–Locker protocol at lower spatial resolution and short acquisition time can be used to correct B_1 heterogeneity. Indeed, such protocol is much less prone to B_1 heterogeneity artifacts, hence the T_1 it provides can be assumed to be precise [19]. This low spatial resolution reference T_1 map is fed into a separate fit of Eq. 7a expressed as function of $\theta_{\text{eff}} = \zeta(B_1^+) \cdot \theta$ rather than merely θ , and letting ζ as free parameter. Finally, the modulation map ζ determined in that way can be injected back into Eq. 7a, this time letting T_1 and S_0 as free parameters to be determined, and operating at the full spatial resolution of the VFA dataset. This approach enables a more precise quantification of T_1 because the B_1^+ and B_1^- effects are effectively separated out into the ζ and the S_0 maps, respectively. However, this approach is more complex and requires to acquire separate reference T_1 map, increasing the overall scan time duration.

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