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Overview of quantitative imaging techniques[☆]

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2.1 Introduction

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Magnetic resonance imaging (MRI) was first adopted clinically because of the unprecedented ability to visualize soft tissues in the body. Beyond the ability to visualize these tissues, MRI can be used to measure quantitative properties that are indicators of the underlying biophysical processes. For example, diffusion, measured by the isotropic apparent diffusion coefficient (ADC), can determine if a tumor is responding to chemotherapy [1,2]. Relaxation parameters, such as R_2^* , can be used to measure liver iron in place of biopsy [3]. T_1 and T_2 relaxation measurements are used to assess cardiac function [4–6], and T_2 mapping is used for cartilage assessment [7]. Some quantitative MRI measurements are routinely used clinically, because they offer clinically actionable information, and more quantitative MRI methods are in the pipeline from research to clinical use due to their ability to detect changes in tissues.

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A quantitative MRI measurement is a map of tissue properties with a range of values and a unit. This differs from the majority of clinical MRI, which uses images that are weighted by a property and have no units (other than spatial dimensional information). Quantitative MRI measurements are made using a sequence to collect data, then a model is made to fit the data, and finally, the map of model parameter(s) is determined. The approaches to measure quantitative properties vary, and researchers continue to develop faster and more accurate methods.

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In this chapter, we will consider several quantitative MRI measurements of tissue properties and the different methods to measure these properties. The methods are grouped by their *modeling approach* (model-based or data-driven), the *sequence design* (one scan, one parameter or one scan, many parameters), and the *signal sources* (discrete images or continuous acquisitions). Table 2.1 presents an overview of several quantitative MRI methods and their categorization by modeling approach, sequence design, and signal sources. Finally, the limitations of these approaches are discussed, and some advanced methods, which arise from these limitations, are briefly presented. This chapter is not all encompassing: not all methods are presented, nor are all MR accessible tissue properties included. For any excluded

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Table 2–1 Overview of methods and their categorization by *modeling approach* (model-based or data-driven), the *sequence design* (one scan, one parameter or one scan, many parameters), and the *signal sources* (discrete images or continuous acquisitions).

Methods	Modeling approach	Sequence design	Signal sources	Reference(s)
T_1 inversion recovery	Model	1:1	Discrete	[8,9]
T_1 variable flip angle	Model	1:1	Discrete	[10]
T_1 Look-Locker	Model	1:1	Discrete	[11]
T_2 spin echo	Model	1:1	Discrete	[12]
T_2 multiecho	Model	1:1	Discrete	[13,14]
ADC	Model	1:1	Discrete	[15]
MOLLI (and variants) for T_1 , T_2	Model	1: n	Continuous	[16]
DESPOT1, DESPOT2, mcDESPOT	Model	1: n	Continuous	[17–19]
MRF for T_1 , T_2 , PD	Model	1: n	Continuous	[20,21]
MR multitasking for T_1 , T_2 , ADC	Model	1: n	Continuous	[22]
IR-bSSFP, IR TrueFISP for T_1 , T_2	Model	1: n	Continuous	[23,24]
MP-DESS for T_1 , T_2	Model	1: n	Continuous	[25]
DW-DESS for T_1 , T_2 , ADC	Model	1: n	Continuous	[26]
Diffusion tensor imaging	Data	1:1	Discrete	[27,28]
Diffusion kurtosis imaging	Data	1:1	Discrete	[29]

ADC, Apparent diffusion coefficient; *MOLLI*, modified Look-Locker inversion recovery; *DESPOT*, driven equilibrium single pulse observation; *MRF*, MR fingerprinting; *MR*, magnetic resonance; *IR*, inversion recovery; *bSSFP*, balanced steady-state free precession; *TrueFISP*, balanced steady state gradient recalled echo; *MP-DESS*, magnetization-prepared double-echo steady state; *DW-DESS*, diffusion-weighted double-echo steady state.

properties, such as chemical exchange saturation transfer, proton density fat fraction, magnetic resonance (MR) elastography, and flow, please refer to quantitative MRI [30].

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2.2 Modeling approach: model-based versus data-driven

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Our goal is to understand tissue properties using quantitative MRI, because these measurements of tissue properties can, or have the potential to, yield clinically actionable information. Philosophy 1 in Chapter 1 stated “Accept that MRI is incredibly complex,” and Philosophy 2 was “Model as much as you want.” In this chapter, we will first look at two different modeling approaches, model-based or data-driven, which are two different approaches to modeling the incredibly complex MRI signals.

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The Bloch equations are a good starting point for all models [12], including quantitative MRI. We start by considering all of the protons in a sample to be a single magnetic moment vector, aligned with the main magnetic field. (This is definitely “model as much as you want” in action; we’ve simplified all the protons to a single magnetic moment vector!) Then, using radiofrequency (RF) power, we tip this moment vector an amount (the flip angle) and characterize the return of the moment vector to its alignment with the main magnetic field.

While the magnetic moment vector is returning to its original position, it will also be precessing as described by the Larmor equation, $\omega = \gamma B$. This is described by Bloch equations:

$$\frac{d\mathbf{M}}{dt} = \mathbf{M} \times \gamma \mathbf{B} - \frac{M_x + M_y}{T_2} - \frac{M_z - M_0}{T_1} \quad (2.1)$$

where $\mathbf{M}$ is the magnetization vector, $\mathbf{B}$ represents the applied magnetic fields, M_0 is the equilibrium magnetization from B_0 , T_1 is the time constant characterizing the return to equilibrium magnetization along the z -axis, and T_2 is the time constant characterizing the return to equilibrium magnetization in the xy -plane. We can write these equations specifically to consider the magnetization components:

$$M_z = M_0 \left(1 - e^{-\frac{t}{T_1}} \right) \quad (2.2)$$

$$M_{xy} = M_0 e^{-\frac{t}{T_2}} \quad (2.3)$$

p0035 Practically speaking, we can only observe the RF signal that is in the transverse plane. With the Bloch equations, we can model the magnetic moment behavior for pulse sequence design and understand signals observed in the transverse plane. The spin-echo sequence is an example: the magnetic moment vector is tipped into the transverse plane, and the spins will dephase and return to the main magnetic field. However, if we apply an additional 180 degrees RF pulse at time t , this pulse will refocus the spins and create a strong, observable signal in the transverse plane at time $2t$. Typically, the time $2t$ is called the echo time, TE.

p0040 With the spin-echo sequence or another base sequence, there are several approaches to make a quantitative measurement using the model-based approach. The base sequence can be perturbed and repeated, or it can be modified with a magnetization preparation component. For example, to measure ADC, we can use a spin-echo base sequence with the addition of diffusion-weighting gradients to perturb the magnetization such that it is sensitive to water diffusion. We will discuss sequence design for the model-based approach in [Section 2.3](#).

p0045 The image data for these model-based approaches can be acquired using a one-sequence, one-parameter approach to obtain a quantitative map of a single parameter. Alternatively, a one-sequence, multiple-parameter approach can be used to obtain multiple quantitative parameter maps simultaneously. Both approaches are discussed in [Section 2.3](#). Another permutation to the model-based approach is the use of continuous data acquisition, such as for modified Look-Locker inversion recovery (MOLLI) [\[16\]](#), driven equilibrium single pulse observation (DESPOT) [\[17,18\]](#), and other sequences, which will be described more in [Section 2.4](#).

p0050 We contrast the model-based methods with the data-driven approach, which optimizes the model based on the data. The data-driven methods are more dependent on the implementation of the method than the model-based methods, and there can be more variability in the resulting parameters. The data-driven methods can discover novel relationships, and they are not predicated on the assumptions we make when using model-based methods [\[31\]](#). For example, data-driven methods can be used to design quantitative MRI

protocols, which may be useful when there is no relevant model [32]. However, the risk is that data-driven results may not correspond with the underlying biological and physical processes.

p0055 Data-driven methods require large data sets, while model-based methods can be implemented on images from a single acquisition. For example, diffusion tensor imaging (DTI) [27,28] expands on the principles of ADC to capture the fiber directions. Rather than acquiring two b-value images in three gradient directions, DTI requires a minimum of six gradient directions (and a higher number of images are almost always used) to calculate six independent model parameters. In the case of tractography via DTI, there are many viable solutions to a white matter bundle segmentation [33], and no solution that is obviously the physical result. Diffusion kurtosis imaging [29] further expands on DTI, resulting in 21 model parameters, which requires at least three distinct *b*-values and 15 unique gradient directions [29,34] to attempt to model crossing fibers.

p0060 Data-driven methods also include the use of machine learning methods [35,36], which are not covered in this chapter, but will be covered with a focus on MR fingerprinting (MRF) in Chapter 12. For the remainder of this chapter, we will focus on the model-based methods.

s0020 2.3 Sequence design

p0065 The end goal in quantitative MRI sequence design is to obtain one or multiple maps of tissue properties (again, to get clinically actionable information). To achieve this goal, a typical pipeline uses one sequence, perturbs one or more sequence parameters to generate multiple images, the model is fit to these images, and the result is a quantitative MRI map. This idea is explored in this section, and an example is shown in Fig. 2-1.

p0070 Early quantitative MRI was built on the groundwork laid by the NMR community. For example, T_1 relaxation time measurement via inversion recovery was developed by Hahn et al., and then used in MRI by Steen et al. four and a half decades later [8,9]. For ADC methods, Le Bihan built on the Bloch-Torrey equation [37] and Stejskal-Tanner single-pulsed field gradient encoding methods [38,39].

p0075 Model-based methods fit the acquired data using a physically or biologically derived model, and we can observe similarities in the models. This is especially so for T_2 , T_2^* , T_1 rho relaxation, and ADC, which are all simple exponential decay models. The model can be written as:

$$M_{xy} = M_0 e^{-a/b} \quad (2.4)$$

where M_{xy} is the acquired signal, M_0 is the initial magnetization, and the parameters a and b are defined by the method. For example, in the case of T_2 , $a = \text{TE}$ (echo time) and $b = T_2$, and for ADC, $a = b\text{value}$ and $b = 1/\text{ADC}$.

p0080 For the model-based methods, such as T_1 relaxation, a single parameter is varied through the experiment, and one image is obtained for each permutation. In Fig. 2-1, we illustrate this using data acquired in a phantom consisting of six samples with different T_1 and T_2 properties. Here, an inversion recovery spin echo acquisition is completed, where the

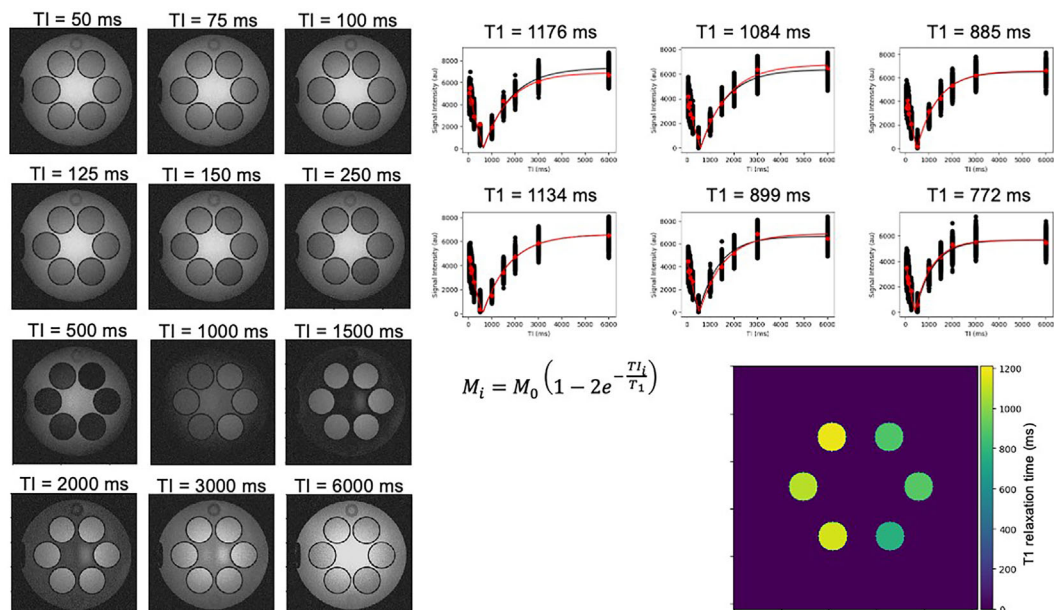


FIGURE 2.1 Demonstration of a one-sequence, one-parameter method using inversion recovery to measure T_1 values. A phantom containing 6 samples with different T_1 and T_2 relaxation times is imaged with 12 different inversion times. Regions of interest (ROIs) are identified in the tubes, and the signal model is fit to all voxels in these regions. (Each *black dot* is the signal from a single voxel in the ROI, and the *black line* is the fit using all *black dots*. The *red dots* are the mean value of the ROI, and the signal model fit to the mean values is shown in *red*.) Finally, the T_1 relaxation time (ms) for the region of interest is mapped (with the background masked and set to zero).

sequence parameters are the same in each acquisition, except for inversion time (TI). The TI array is 50, 75, 100, 125, 150, 250, 500, 1000, 1500, 2000, 3000, and 6000 ms, and the repetition time (TR) and TE are 10,000 and 14 ms. The inversion recovery model is fit to this data, and the T_1 relaxation time is calculated at each voxel. This approach considers one sequence, varies a single parameter (TI), and obtains one quantitative map (T_1 map).

Now, we consider Philosophy 3 from Chapter 1: “Parallel is better than serial.” The one-sequence, one-parameter approach can be slow, and even slower if we are serially acquiring multiple quantitative MRI parameters (see Chapter 1, Fig. 1–3). In addition, there are other challenges with serial acquisition, including errors due to patient motion or temporal delays, and the need to register any serially acquired maps. As a result, there has long been interest in one-sequence, multiple-parameter methods. Multiparametric acquisitions were proposed in the early days of clinical MRI, though they were signal-to-noise-ratio (SNR)-limited and still too slow for clinical adoption [40–42]. However, computational hardware advances and general improvements in SNR from increased field strength and reduced noise on MRI hardware made multiparametric acquisitions possible.

Rather than perturbing only a single variable in the sequence, the multiparametric acquisitions use a different sequence design that introduces multiple contrasts to the resulting images. As described in Chapter 1, we can rethink our approach to MRI and design sequences

that capitalize on all the factors that influence MRI signal to efficiently generate quantitative MRI maps. An example is shown in Chapter 1, Fig. 1.5, illustrating an arbitrary MRF-FISP sequence where the flip angle is continuously varied during the acquisition with a constant TR and TE. The resulting signal is constantly varying, and it is sensitive to both T_1 and T_2 properties. (Reconstruction of these signals is discussed more in [Section 2.4](#).)

p0095 These acquisitions using a single sequence typically build on steady-state sequence designs and include methods such as MRF [\[20\]](#), multicomponent driven equilibrium single pulse observation (mcDESPOT) [\[19\]](#), and MR multitasking [\[22\]](#). For an extensive summary of multiparametric quantitative MRI methods of the brain, the reader is referred to [\[43\]](#). In this chapter, MRF applications in neurological, cardiac, abdominal, musculoskeletal, pediatric imaging, and radiation oncology are covered in Chapters 17–22. The principles of the multiparametric acquisition can be applied to acquire different contrasts (i.e., there are many different acquisitions based on the MRF framework), as long as there is an orthogonality to the signal information.

p0100 There are several benefits of the one sequence, multiple parameter approach. First, as illustrated in Chapter 1, Fig. 1.3, the acquisition time is not as long as in the case of one sequence, one parameter, which would require sequential acquisitions of each parameter of interest. Second, the information from the multiple parameter maps is already colocated; there is no need for image registration. Third, the measurements are less sensitive to system imperfections [\[20\]](#). Fourth, the method is inherently robust to some motion artifacts [\[20,44\]](#), though not all (motion artifacts in MRF are addressed in Chapter 14). Finally, the acquired tissue properties may not be redundant, which will improve the ability to categorize tissues for diagnostic purposes, in particular for application to cancer diagnosis, characterization, and monitoring of treatment response [\[45–47\]](#).

s0025 2.4 Signal sources: discrete images or continuous acquisition

p0105 A primary difference between the single-parameter and multiparametric methods is the signal source, which we separate into two categories: discrete images or continuous acquisition.

p0110 Single-parameter methods use models fit to data from discrete timepoints, such as in [Eq. 2.4](#) and [Fig. 2.1](#). The discrete timepoints can be a series of steady-state images, or the experiment can be designed with a repetition time enabling full recovery (though this is impractical for any clinical setting). For example, T_1 can be determined using inversion recovery [\[8,9\]](#) or a faster approach using the variable flip angle method [\[10\]](#). In both cases, discrete images are used to fit the model and determine the T_1 relaxation time.

p0115 Multiparametric methods use continuous acquisitions in a transient state. The first uses of continuous acquisitions were for acceleration of single-parameter methods, such as with MOLLI [\[16\]](#) and inversion recovery balanced steady state free precession (IR-bSSFP), inversion recovery balanced steady state gradient recalled echo sequences like IR TrueFISP [\[23,24\]](#). Then, these single-parameter continuous acquisitions were modified for the acquisition of multiple parameters, as with the modification of DESPOT1, DESPOT2 [\[17,18\]](#), resulting

in mcDESPOT [19]. Some continuous acquisition transient state methods relied on balanced steady-state free precession (SSFP), such as the first implementation of MRF [20]. One drawback to bSSFP methods is off-resonance banding artifacts that can obscure important anatomy. This was overcome through unbalanced SSFP, as in FISP-MRF [21]. Other methods in this category include magnetization-prepared dual echo steady-state, MP-DESS [25], and MR multitasking [22]. For a complete review of multiparametric qMRI frameworks using continuous acquisitions, the reader is referred to Jara et al. (Table 2–1) [43].

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Continuous acquisition methods are typically faster than the discrete image methods, in part because they lend themselves to undersampling approaches. A high undersampling factor can be used, in which each individual image is low quality, but when examining the resulting signal over the continuous acquisition, a pattern is revealed, which results in the quantitative map. However, even with undersampling approaches, continuous acquisition methods generate substantially more data than discrete image methods. The reconstruction of quantitative maps from undersampled, continuous data can require substantial computational resources for dictionary-based [48] or AI-based reconstruction [49]. Our computational resources have improved dramatically since the discrete images methods were developed, as discussed in Chapter 1, Philosophy 4, “Search the whole space,” and computational resources no longer limit our approach. Advantages of continuous acquisition methods include reduced scan time, inherently colocated information that is robust to certain motion artifacts, and lower sensitivity to system imperfections, as described in Section 2.3.

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2.5 Advanced methods

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Current approaches to MRI can offer clinically actionable information, but there is much that we still do not understand about the body and how biological changes relate to MRI signal. At present, we generate quantitative property maps, and we try to estimate a biological phenomenon, for example, myelin water fraction, to tell us about brain development or degeneration [50]. Instead of using the intermediary step of quantitative property maps, could we instead directly image the biological phenomena? Current advanced MRI methods can delve into the understanding of biological phenomena on a subvoxel level.

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MRI information is grouped into voxels (approximately 1 mm^3 in volume), which are massive compared to the size of a cell (approximately $10 \text{ }\mu\text{m}$ in diameter). In the methods reviewed in this chapter, the resulting tissue measurement, from a single parameter or multiparametric method, is applied to an entire voxel. However, this is not the physical situation. First, it is possible that the voxel is placed over multiple tissues, and thus the measurement value is a combination of partial volumes from more than one tissue. Second, within a voxel, even over a single tissue, there is a world of cells, processes, and structures that are grouped together in the voxel. The tissue may have more than one relaxation or diffusion process that could be modeled. Additionally, in this chapter, we only considered single-component relaxation, while it is possible to consider multicompartiment relaxation due to partial volumes or multiple relaxation components in a single tissue. One method for

multicompartment relaxation mapping technique is based on extended phase graph formalism [51]. For an understanding of how to accurately represent the many processes at work in a tissue, we refer the reader to the work on microstructure modeling [52,53].

p0135 Finally, in this chapter, we did not discuss the use of machine learning. Machine learning can be used to obtain the quantitative maps from multiparametric methods using continuous acquisitions. For more information on this topic, we refer the reader to Chapter 12, “The Roles of Artificial Intelligence in MRF” and [54].

s0035 2.6 Conclusion

p0140 Quantitative MRI has immense potential to detect clinically meaningful changes in tissues, and over the last half-century, the capability of MRI methods has advanced such that this is now a reality. In this chapter, we discussed different quantitative MRI methods using the categories of *modeling approach* (model-based vs. data-driven), *sequence design* (one sequence, one parameter vs. one sequence, multiple parameters), and *signal sources* (discrete vs. continuous acquisitions). From these categories, the model-based, continuous acquisition of multiple parameters has great potential for impact in clinical use because different tissue properties can be obtained simultaneously. Since the early days of MRI, clinical use of quantitative mapping methods was limited due to the time required to acquire and process the data. Methods, such as MRF, enable clinical use of quantitative MRI [55]. The remainder of the book provides a deep dive into MRF methods.

st0050 References

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NON-PRINT ITEM

Abstract

Quantitative magnetic resonance imaging (MRI) methods produce tissue property maps used to diagnose and monitor disease states. In this chapter, we review quantitative MRI methods by considering *modeling approach* (model-based or data-driven), *sequence design* (one scan, one parameter or one scan, many parameters), and *signal sources* (discrete images or continuous acquisitions). Advantages and disadvantages of the approaches are discussed with a focus on model-based, multiparametric, continuous acquisitions.

Keywords: Quantitative MRI; models; data-driven; sequence design