PhUSE 2014

Paper DH06

Do you like what you see? - Understanding data in magnetic resonance imaging studies

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ABSTRACT

As diagnostic methods evolve and new measures find their way into clinical trials statistical programmers are faced with more complex data. Magnetic resonance imaging (MRI) data can become difficult to interpret for non-specialists: Results may be calculated from the actual electronic image using sophisticated computational algorithms. These procedures often involve external vendors and therefore create logistical challenges. Programmers also need a basic understanding of underlying physical principles in MRI to be able to understand the meaning of the results used in the final statistical analysis. This paper will cover the overall workflow from MRI data generation and assessment, the further processing procedures at an external reader site to final analysis.

INTRODUCTION

Magnetic resonance imaging (MRI) allows visualizing tissue structures with high contrast and in several planes. It makes structures visible which cannot be evaluated with other methods e.g. X-rays. A classic approach to analyze images is the use of standardized scoring systems. From a statistical programming perspective scoring data can be analyzed without extra-ordinary efforts since the methodology is straightforward, well-documented and all potential outcomes can be anticipated. Although there are scoring systems used in MRI (e.g. Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS)) [1], [3]), new techniques were developed in the past years that use the advanced technical properties of MRI images. As opposed to scores which normalize the evaluator´s subjective diagnostic finding to a fixed numerical or categorical scale, these new techniques use computational algorithms to analyze actual image data. Since these techniques require special expert knowledge a whole new industry has been built in this area and serves as third party vendor in clinical trial settings.

A case-study in Rheumatoid Arthritis will show why these techniques create new challenges for statistical programmers. It is also a good example why it is important for programmers to know about the complete data generation process.

DATA WORKFLOW IN STUDIES INVOLVING EXTERNAL VENDORS

At first glance the workflow of MRI data in a clinical study is similar to other data assessed on-site and analysed by a third party. Laboratory data is a good example: The sample is taken on-site, transferred to the external vendor, processed in some way and the result is transferred to the sponsor for statistical analysis.

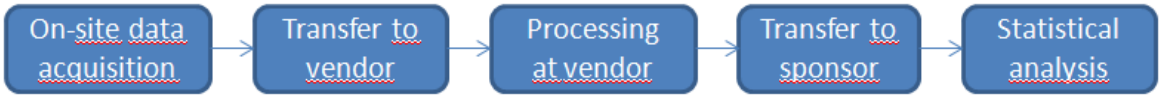

Figure 1. Data workflow in a typical clinical study setting

Analysing lab data is pretty much straight forward: Processes have been established for years, vendors are used to put thousands of samples per day through their machines and have an interest in getting results out to sponsors in a standardized way. Moreover, there are normal ranges available for almost all parameters to internally validate results for consistency.

In MRI studies, the situation is different. Let´s walk through the complete process in an MR Imaging study to understand where the data is coming from and why it needs to be handled differently. First of all we´ll take a look at how an MRI image is produced and what is measured in an advanced MRI study.

HOW DOES AN MRI SCANNER WORK?

The underlying physical principles of the MRI scanning technique are highly complicated and many of the effects used to finally acquire an MRI image can only be explained by use of quantum physics (many radiologists are also physicists by training). I will focus on the really basic aspects that help to understand the setup of an MRI image. A more detailed summary can be found in [2].

Our body is made up by atoms and a large amount of these are hydrogen atoms or protons. That is because our body mainly consists of water and fat. Protons have an interesting feature: in terms of classical physics, they can be seen as little spinning tops. The spin produces a magnetic field and makes protons behave like very little magnets. Let´s assume a patient is positioned within an MRI scanner which forms a strong magnetic field (from 0,5 to up to 7 Tesla) around the area to be imaged. The protons in this area are now exposed to the strong magnetic field and due to their intrinsic magnetic properties, line up in the longitudinal direction of the external magnetic field and start to precess, like a spinning top which not only spins about its own axis but also wobbles about the vertical axis. This can happen parallel or anti-parallel to the external magnetic field and the amounts of magnetic fields from parallel and anti-parallel aligned protons would even out. A small amount of protons however, does not have a “partner proton” with the opposite alignment and therefore an overall magnetization can be detected (Figure 1). This amount of protons is the important part which is used in MRI imaging to detect the actual imaging signal.

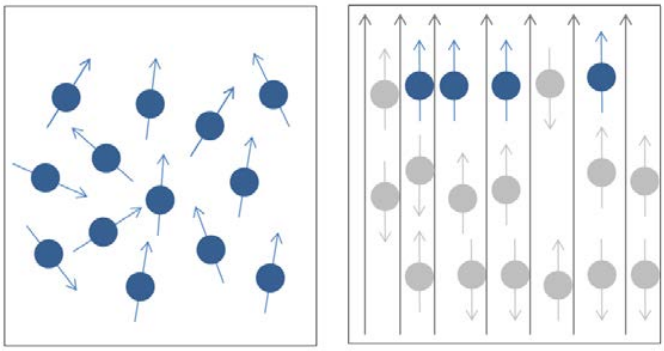

Figure 1: Random position of protons (left), parallel and anti-parallel alignment of spin-axes after applying an external magnetic field.

Protons in the strong magnetic field of the MRI apparatus can be influenced by applying a radio frequency (RF) pulse at a certain frequency, otherwise known as the Lamor frequency. Protons can absorb energy at the Lamor frequency. They start to spin in phase and the spin axes of some of them get flipped. The vector of the resulting magnetic field is no longer in longitudinal (z-) direction but also flipped by 90° (xy-direction). When the RF pulse is switched off, protons release energy as electromagnetic wave and return to equilibrium state in z-direction. The vector of the magnetic field in xy-direction decays as spins get out of phase and the longitudinal component recovers when spins re-align in z-direction. The time needed for the magnetic field to recover in z-direction is called longitudinal relaxation time (T1). It depends on the mobility of protons. Protons in tissues with a high amount of water (= high mobility of protons) have longer relaxation times than those in fat based tissues. This effect is used in T1-weighted images to assess tissues with high amounts of water (e.g. cysts, liquor, blood) or post-contrast imaging.

The time for decay of the magnetic field in xy-direction (T2) is independent from T1 and occurs 5-10 times faster. It is an intrinsic property of each tissue and is used in T2-weighted images to detect e.g. edema, white matter lesions and zonal abnormalities in prostate and uterus.

Regardless of the used technique, protons emit a signal when they return to equilibrium. This signal is detected by the MRI machine and forms the image information. So, what an MRI basically measures is the amount of protons in every point of the body. Other than suggested by the actual two-dimensional image the MRI image is not made up of pixels but volume pixels or “voxels” showing the intensity of the proton signal detected in a defined volume of the body. Depending on weighting the resulting image of the same body region can look completely different (Figure 2).

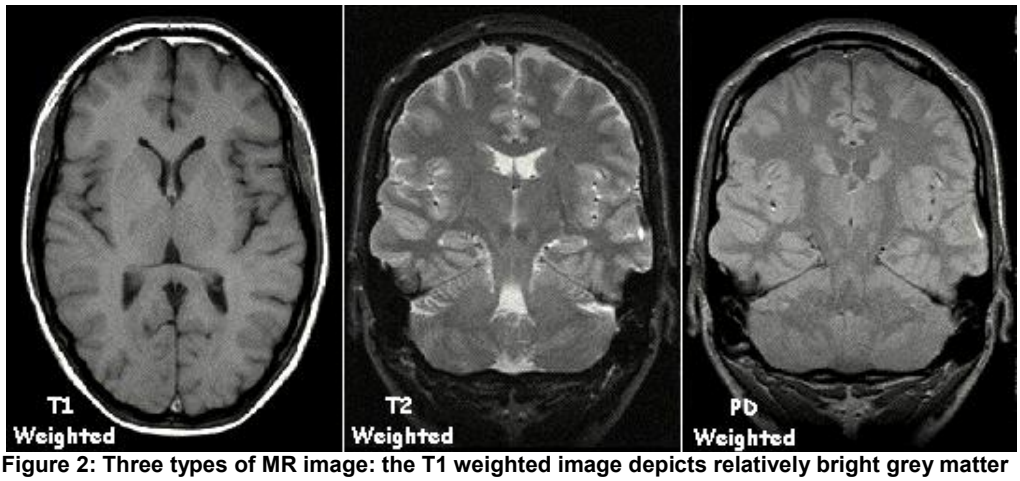

Figure 2: Three types of MR image: the T1 weighted image depicts relatively bright grey matter and dark cerebrospinal fluid; the T2 weighted image highlights the CSF, while the PD (proton-density) weighted image shows little contrast between tissues.[2]

As described in the section above, MR images can look very different depending on weighting during image acquisition. In addition, tissue structures can also be investigated using Gadolinium-based intravenous contrast agents. These agents allow excited protons to relax faster, hence tissue structures with higher concentration of contrast agent can be separated easily from tissues with lower concentration.

A special application is dynamic contrast enhanced MRI (DCE-MRI)[4]. This method involves the acquisition of sequential images in rapid succession every few seconds during and after the intravenous administration of contrast agent.

In our case-study, this effect is used to measure the enhancement of contrast agent in the synovial compartment of joints in subjects with rheumatoid arthritis (RA). In a healthy joint the enhancement of contrast agent is lower than in a joint affected by RA. In addition, the severity of inflammation can be measured by assessing the time course of contrast enhancement. The result of a DCI-MRI study is shown below:

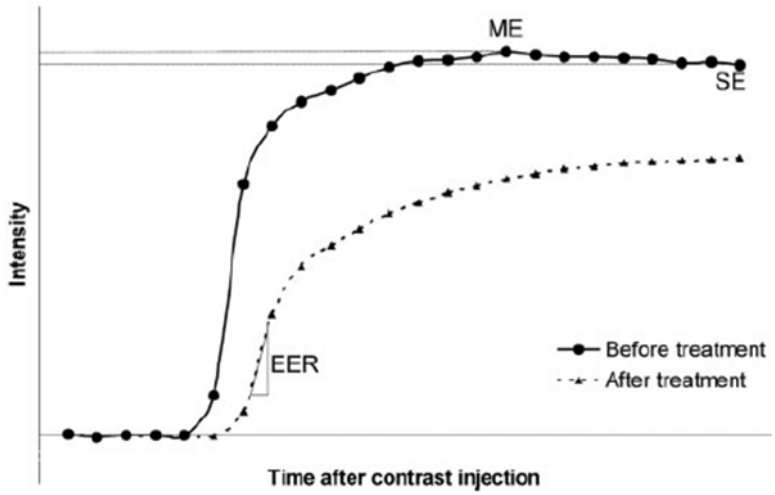

Figure 3: Enhancement curve from a series of DCE-MRI images of a patient with RA showing early (initial) enhancement rate (EER, IRE), the maximum enhancement (ME) and the late (static) enhancement (SE). Enhancement is reduced after treatment.[5]

MRI ACQUISITION AND PROCESSING BY CENTRAL READER

As opposed to the use of standardized scoring systems, the actual results of DCE-MRI studies are not generated at the investigator´s site or captured on case report forms. Investigators, however, produce the images and send them to a central reader. At the central reader site, all images of the time series are reviewed separately and joint regions of interest (ROI) are identified by literally marking the joint capsule on the image (Figure 4). In theory, the ROI should be the same in all images and the intensity of the signal should change as the contrast agent enhances in the ROI.

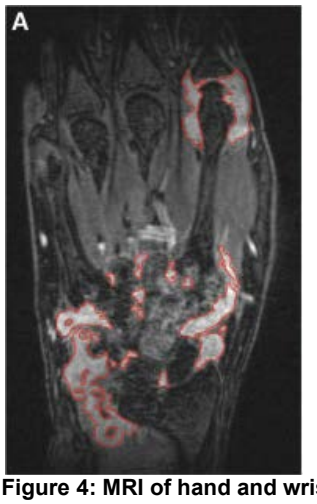

Figure 4: MRI of hand and wrist with marked region of interest.[5]

The next step of the central reading procedure is the evaluation of all voxels (volume pixels) in the ROI by a computational algorithm. This algorithm not only measures the change of the enhancement signal over time, but also the overall "behavior" of the enhancement. Some voxels in the image show an enhancement which is stable during the measurement ($N_{plateau}$). Other voxels show an initial enhancement which is not stable over time. These voxels are counted as $N_{washout}$. Let´s assume we want to calculate the combined initial rate of enhancement (IRE, corresponds to EER in figure 3.) for metacarpocarpal (MCP) joints 2-5. The respective formula would look like this:

$$IRE^{MCP2-5,precise} = \frac{\sum_{j=2}^{5} I^{MCPj,precise} * \left({N_{plateau}}^{MCPj,precise} + {N_{washout}}^{MCPj,precise} \right)}{N_{vox}^{MCP2-5,precise}}$$

with

$$N_{vox}^{MCP2-5,precise} = \sum_{j=2}^{5} {N_{plateau}}^{MCPj,precise} + {N_{washout}}^{MCPj,precise}$$

where

I - Mean Initial Rate of Enhancement (IRE) in the volume ROI
j – Joint number
$N_{plateau}$ – Number of voxels with plateau pattern of enhancement in the volume ROI
$N_{washout}$ – Number of voxels with wash-out pattern of enhancement in the volume ROI
MCP – MCP joints

The maximum rate of enhancement (ME) is calculated analogously by replacing *Mean Initial Rate of Enhancement (IRE) in the volume ROI* with *Mean Maximum Enhancement (ME) in the volume ROI.*
It is obvious that the overall number of voxels (N_{vox}) plays a special role in the formula above. Since N_{vox} forms the denominator a result of zero for N_{vox} should result in a missing result for IRE or ME. The table below shows a simplified example of derived results sent to the sponsor for further analysis.

Acq. Date	Mean ME	Std. Dev. ME	Mean IRE	Std. Dev. IRE	N-plateau	N-washout	N-plateau + N-washout	ME normalized*	IRE normalized*
Baseline	1.59	0.23	0.010	0.01	609	185	794	1262	7.94
Day 1	1.59	0.37	0.011	0.02	590	313	903	1436	9.93
Day 2	1.63	0.28	0.015	0.02	119	132	251	410	3.77
Day 7	1.72	0.40	0.024	0.03	118	89	207	356	4.97
Baseline	1.59	0.23	0.008	0.01	531	85	616	979	4.93
Day 1	1.46	0.16	0.004	0.001	376	103	479	701	1.92
Day 2	1.43	0.09	0.002	0.001	39	23	62	88	0.12
Day 7	1.47	0.13	0.003	0.001	31	4	35	52	0.11
Baseline	1.79	0.19	0.038	0.02	10	65	75	134	2.85
Day 1	2.06	0.39	0.041	0.02	10	56	66	136	2.71
Day 2	2.00	0.24	0.037	0.01	10	51	56	112	2.47
Day 7	2.14	0.36	0.054	0.03	9	61	70	150	3.78

The overall evaluation takes place at the central reader site and as mentioned earlier, there are no normal ranges available for this kind of MRI measurements. The data transfer should therefore also include all raw data needed to reproduce the analysis result. Depending on the therapeutic area there may be many variables and variable names and labels are often cryptic. Therefore, it can be very difficult to relate variable names to derivations. The table above just shows the final result for IRE and ME but more than 60 variables were available in the data transfer file and were used in derivations. The external vendor needs to provide a concise data specifications document with a complete description of all raw variables and how they are used in derivations. The documentation should also describe handling of missing data as well as imputation algorithms. This is of major importance if any of the variables is used as denominator (see the formula for IRE above). Specification documents should be available as early as possible, at least before the first data transfer takes place. Ideally, the vendor should also provide a test dataset with real patient data. Development of programs can start using test data before the first study data extract is sent. In blinded trials this is the only way to pre-develop programs since results or MRI study data are also blinded.

DISCUSSION

The procedures at the central reader site are kind of a black box for programmers. On one hand, programming rarely sees the raw images used to get to the final result. This is not really an issue, since the same is true for lab assessments. However, for lab results normal ranges are available and help to understand whether a result is reliable or not. In MRI, there are no such ranges for the signal intensity in specific tissues, hence programmers cannot use normal ranges to validate the received data. Since all data for later use in the statistical analysis are based on raw data from the actual images, it is important to have a clear description available on image acquisition, data handling and evaluation at the reader site. These procedures can be part of different documents, e.g. the protocol or statistical analysis plan. Central reader procedures are often provided by the external vendor. Programmers should have a basic knowledge of the underlying physical principles in MRI and basic terminology in order to be able to understand these documents. The following points provide some guidance on what information should be provided and what statistical programmers should consider upfront in clinical trials utilizing MRI.

1. Image Acquisition and transfer to the central reader

The very first step in an DCE-MRI trial is the proper acquisition of MRI images. Since there are no normal ranges for the signal intensity, images should be acquired using the same technique across all sites, subjects and visits to minimize variability. Overall MRI procedures should be clearly described in the protocol. At least the examined body sites, schedule of MRI acquisition and handling procedures should be mentioned. The protocol should also outline the general workflow of data evaluation especially when an external vendor is involved. Details on MRI methodology, image acquisition protocol, data handling and shipment, validation, and other methods should be outlined in a

separate imaging charter. The imaging charter mainly guides investigators and ensures that the same MR imaging technique is used across sites.

2. Central reader procedures

In general, DCE-MRI analyses in RA can be done per joint, joint groups or combining several joint groups. Resulting datasets can get huge depending on the number of joints analysed separately. Also, labeling of variables can be misinterpreted easily, e.g. variables with raw values can get confused with derived results.

Therefore, technical specifications should be available for central reader procedures and clearly describe evaluation algorithms including all formulas and derivation rules. Data transfer specifications should list all variables provided in final deliverables from the central reader. If variable names provided in the transfer dataset are part of a derivation they should be related to derivation rules or formulas used.

Central reader procedures may also involve missing data handling rules or imputation rules. These should be described as well in the specifications document.

3. Request test data

Programmers should insist to receive a dummy dataset, ideally before the central review starts. This is of special importance in blinded trials where results may not be available before database-lock. A test dataset should consist of real-life data for all variables to be able to test programs and to check derivation rules. It should also describe the underlying raw data and the outcome of the central reader procedure.

4. Quality check of data transfers

In any case, it should be verified whether missing data points are due to missing images. This is normally a task for data management. However, the transfer of images from sites to the central reader is often independent from data management activities. Investigators upload their images directly to the vendor´s server and the vendor is taking care of completeness of the images sent and proper blinding, if applicable. Moreover, although an image has been uploaded does not mean that it is (completely) evaluable. The image quality may not be sufficient to retrieve all needed data and this may also be a reason for missing data points. So, all activities to check data quality of the transferred results are related to verify that the assessed raw data has been evaluated correctly. Datasets should be scanned for missing data points and if missing data algorithms have been applied correctly. Due to the lack of normal ranges, raw data cannot be checked for consistency apart from identifying isolated outliers. The provided documentation should therefore enable programmers to reproduce all results provided in the data transfer, at least those used in the statistical analysis.

CONCLUSION

The introduction of more advanced methods to analyze MRI data has introduced a couple of challenges in statistical programming. The actual data used for the final statistical analysis is delivered by external vendors who have a special expertise in analyzing raw images using sophisticated computational algorithms. The overall imaging procedure and external analysis should therefore be described in detail. However, without at least a basic knowledge about MRI and related technical terms it is almost impossible to understand the documentation as well as the meaning of the transferred data. Overall consistency and completeness of data deliverables cannot be ensured by data management since third party vendors directly interact with sites. Quality assurance activities are moved to statistical programmers who need to involve themselves earlier study processes to ensure they will have all tools available to understand where the data is coming from and what it means.

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