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Mapping the biological world

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Relaxation and relaxation constants is a rather complicated topic, both to explain and to understand. There are two main relaxation constants important for MRI: T1 and T2.

T2* which is also often mentioned in this context is not a time constant, it is a capricious global parameter representing a fluctuant time or time range.

An excursion into scientific history

This is not the place to go into the science of relaxation; a textbook is better suited for this [1]. Here I will just tell a bit about the history and background of relaxation times in biomedicine.

It all began in 1953 with Eric Odeblad. He was the first to describe relaxation times in biological systems. His first paper on the topic was entitled “Some preliminary observations on the proton magnetic resonance in biological samples” and published in Acta Radiologica Stockholm in early 1955 [2].

Odeblad had found that different tissues had distinct relaxation times, most likely due to water content but also to different bindings to lipids. Soon others joined in the new research field: Studies in blood, plasma and red blood cells, followed by T1- and T2-measurements of living frog muscle, the relaxation of water in living animals and in the arms of living humans.

Research groups in Brooklyn and in Baltimore got involved in the early 1970s. They measured relaxation times of excised normal and cancerous rat tissue, and the leader of the Brooklyn group stated that tumorous tissue had longer relaxation times than normal tissue and promoted these findings as the ultimate technology to screen for cancer [3].

However, already some months later the Baltimore group stated that independent verification on the same NMR instrument could not be provided; the results were not reproducible [4].

Later, the New York Times pointed out major discrepancies between what was claimed by the researchers from Brooklyn and what was actually accomplished, "discrepancies sufficient to make the author [Raymond Damadian] appear a fool if not a fraud." [5]

The summary of a paper published in 1975 – 42 years ago – by the group of Donald Hollis stated [6]:

> “The direct use of NMR T1 measurements for cancer diagnosis is clearly not feasible because of the lack of specificity … classification of tumors in this manner does not seem realistic.”

Shortly afterwards clinical MR imaging arrived and relaxation time measurements were considered very important during its first years. All machines were programmed to create true T1 and T2 images (T1- and T2-mapping), based on reliable and reproducible spin-echo (SE) and inversion-recovery (IR) sequences.

After absolute T1 and T2 values had been used unsuccessfully by researchers, combinations of T1 and T2, histogram techniques, and sophisticated three dimensional display techniques of factor representations were used. At that time, these approaches were called ‘electronic contrast agents’, today ‘fingerprinting’ or ‘biomarkers’.

However, soon it became clear that relaxation time values were not the claimed invaluable addition to diagnostics, and these applications were skipped in the early 1990s.

> “A spin-echo sequence with 24 echoes (Carr-Purcell-Meiboom-Gill sequence) was evaluated to determine the usefulness of magnetic resonance (MR) in detecting and typing brain tumors. ... T2 values calculated from an eight-point fit, however, did not allow discrimination of different tumors, nor did they allow differentiation between tumor, inflammatory tissue, and demyelination.” [7]

It was the time when the *Relaxation Times Blues* arrived [8], and Ian Young, one of the leading and influential scientists in MRI summed up the trials and errors in a short history of MRI as follows:

> "Sadly, the many attempts that were made to correlate pathology and relaxation behavior have yielded none of the precise numerical relationships that were hoped for in the early days of MRI, so that this line of investigation ... has now been abandoned." [9]

A grant-creating perpetuum mobile?

It is rare that a method appears, disappears, and then re-appears again as is the case of tissue characterization based on relaxation time constants. Yet some years later these obsolete methods were dug out again, grants were given to answer questions which had been discarded 25 years earlier [10, 11]. New pulse sequences and algorithms were developed – researchers tried their luck again.

Still, there is no easily explainable causality nor any evidence of a straight connection between these numbers and a distinct pathology. There is no unique signature of distinct malignancies or other pathologies in tissue relaxation times, be it in ex vivo or in vivo measurements. Many people believe that numbers (or, more fashionable, data) are the truth but they do not understand how the numbers were acquired and what they stand for. Nature doesn't care about numbers. Believing in such postulations many years after they have been dismissed is a sign of scientific naiveté.

What's wrong in relaxation time mapping and applications: the precondition and presumption that a difficult biological structure such as a tissue or tissue changes in the human body can be quantified and qualified with NMR proton relaxation parameters.

Quantity and quality are being confused; it's so easy counting something – which doesn't mean that one can classify or characterize with numbers what one counts. The components and chemical and electrical processes in a tiny volume element, no matter how small it is, are far too complex and fickle to be expressed in bare figures. More so, on closer inspection, "objective" procedures, "objectively" defined range values as well as "objective" quality indicators for measurements often prove to be biased and interest-driven. There is no precise numerical fingerprinting based on relaxation constants in biomedicine.
It is helpful to once look into a microscope and to see how complex and complicated tissue structures are, both in normal and in pathological tissues – and in not-normal, but not (yet) pathological tissues.

In the end, it is not necessarily the errors or procedural "confounders" connected to the most elaborate and sophisticated data acquisition that make typing of normal and pathological tissues or grading of diseases impossible – but rather the complexity of tissue composition and the overlapping of relaxation time values of heterogeneous volume elements examined and processed into a single number or number range.

Nowadays lessons are rediscovered that became clear 25 years ago … and finally admitted, though diplomatically beating around the bush:

> "In conclusion, our question, whether native T1 mapping in cardiac MR imaging can differentiate between healthy and diffuse diseased myocardium, must be answered with 'yes' and 'no', since the native myocardial T1 relaxation time allows discriminating between groups of patients with certain diffuse myocardial pathologies and a group of healthy individuals, but does not allow differencing between healthy and diffuse diseased myocardium in individual subjects." [12]

Researchers also came to realize that novel methods for faster data acquisition deliver crude estimations but not accurate data. The higher the magnetic field, the larger seems to be the spread of T1 and T2 relaxation time estimations.

> "A vast extent of methods and sequences has been developed to calculate the T1 and T2 relaxation times of different tissues in diverse centers. Surprisingly, a wide range of values has been reported for similar tissues (e.g. T1 of white matter from 699 to 1735 ms and T2 of fat from 41 to 371 ms), and the true values that represent each specific tissue are still unclear, which have deterred their common use in clinical diagnostic imaging." [13]

Exceptions from the rule

Few isolated cases allow tissue discrimination based on relaxation time alterations, but they are the exception. One needs massive changes of relaxation time constants, as well as large homogeneously altered

volumes to be able to use such data for diagnostic purposes. The data you get is not fake, it is not necessarily false, no, worse: it's half-true.

Does this mean that relaxation time maps cannot be used at all? Here are some insights into my own experiences: We started creating maps of relaxation constants and proton density as well as derivatives of these maps, called "synthetic images", in the early 1980s and presented the idea of synthetic MR images and simulating entire MR exams in the early 1980s at a conference in the United States. In 1994 we finally published the image simulation software MR Image Expert for teaching and research purposes. More than 12,000 copies of MR Image Expert were licensed since then.

The simulations were based on the three main contrast parameters in MRI: T1, T2, and proton density acquired with time-consuming, but precise data acquisitions and exact calculations – with "clean" basic pulse sequences: inversion recovery and spin echo. For a reliable T1 determination one needs between 15 and 30 IR measurements, for T2 we usually used 24 echoes of a SE echo train. They allowed the creation of outstandingly good simulations of MR images – but still simulations.

In general, from a scientific point of view, MR imaging is a crude and not very exact technology. Thus, in most cases, relaxation time mapping and derivatives of it – such as synthetic images – cannot be used to quantify exact tissue data (e.g., relaxation constants or proton density in tissues) since the calculated or estimated relaxation constants and proton density values are unreliable – and impracticable in diagnostic routine; they are not accurate and not conclusive.

The only way to exploit relaxation time values would be situations when the values change drastically under specific physiological or pathological circumstances. This can be the case before and after the application of an MR contrast agent. There are uses for such rough estimations.

An area of application of relaxation times measurements might be the follow-up of massive T1 changes after the injection of a targeted contrast agent, such as Mn-DPDP and the comparison of plain and contrast-enhanced tissue, e.g., in heart diseases. Here imprecise measurements might be of diagnostic value. However, such indications are limited because increasingly different and simpler MR techniques exist that may lead to the wanted result.

In one of the next columns I will try to discuss the non-scientific and non-medical reasons why these measurements returned and why they will stay with us for some time.

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Some side effects of the great gadolinium scare

Peter A. Rinck

This is a slightly different follow-up of the gadolinium scandal. I believe that I have put on the table in earlier columns and in our MR textbook all facts I know and feel publishable. [1] There are numerous publications about the topic containing "fake news," among them papers by certain authors that have to be digested *cum grano salis* as described earlier [2] because they try to whitewash themselves or make money.

Many feel competent enough to offer their humble opinion about gadolinium-based contrast agents (GBCA), not only radiologists and physicians of every shade and color, but also physicists and chemists, as well as want-to-be experts such as journalists and movie actors. Of particular interest may be the U.S.A., where lawyers mix up ethical and moral values with personal financial advantages.

They all incense fear and lead to confusion. Patients are increasingly becoming uneasy and worried. I am receiving letters like this one:

> "I am trying to find alternatives to gadolinium as I don't think the risk is worth it. Would the newer MRI machines with bigger magnets, more sensitive detectors, more computing power, and techniques to enhance the images, thinner slices, higher resolution, be good enough to detect a 3 mm to 4 mm in size or smaller acoustic neuroma tumor on the hearing nerve? How small of a tumor (mm) can a 3-Tesla MRI detect without gadolinium contrast?"

For some time, there is a witch hunt going on ...

For some time now, there has been a witch hunt going on in the U.S.A. against the Italian company Bracco and its contrast agent MultiHance (gadobenate, gadobenic acid), a compound superior to all of the competitors: far better relaxivity and higher contrast, enhancing both in the central nervous system and liver.

As I have already stated earlier:

> "Gadobenic acid (MultiHance) as well as gadoxetic acid (Primovist) are excreted by both the kidneys and the liver, although the percentage of liver excretion is far higher for gadoxetic acid. Still, MultiHance is the best-enhancing contrast agent on the market. As far as I am aware, there were no direct cases of nephrogenic systemic fibrosis with MultiHance, but there were a small number of 'confounding' cases with combinations of Omniscan. There is no scientific or statistically based reason to damn MultiHance and to promote Primovist for liver examinations, as the European Medicines Agency has now done." [3]

There is an increasing animosity against the European Medicines Agency (EMA) and their decisions; some companies say their precautionary measures are not based on facts and that the EMA used controversial "experts." There are also rumors about partial outside influence. I believe there has been a strong will from some to kill MultiHance.

Agencies such as the EMA and the U.S. Food and Drug Administration (FDA) differ in regulating the use of gadolinium-based contrast agents. The FDA's Medical Imaging Drugs Advisory Committee met on 8 September 2017 and finally stated:

> "To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. We have also received reports of adverse events involving multiple organ systems in patients with normal kidney function. A causal association between these adverse events and gadolinium retention could not be established." [4]

Among others, the committee invited the testimony of U.S. movie star Chuck Norris and his wife Gena, who suffers from rheumatoid arthritis. After three MRI examinations five years ago, Norris and his wife Gena claim that she now has "gadolinium depo-

sition disease" and, according to an article in the U.S. news magazine Newsweek, are suing for $10 million in damages, first and foremost directed at Bracco. [5]

According to reports, Gena Norris suffered from symptoms that include burning sensation in various parts of the body.

The term "gadolinium deposition disease" was introduced by Dr. Richard C. Semelka in 2016. [6] It's a syndrome whose symptoms are headache, cognitive disturbance, skin hyperpigmentation, and arthralgia – which according to the authors are clinical manifestations of presumed gadolinium toxicity in patients with normal renal function.

Semelka also proposed the application of Ca-DTPA and Zn-DTPA to reduce or eliminate gadolinium deposition disease symptoms. Meanwhile, a clinical study to prove this was suspended. [7] The idea is chemically sound – but the gadolinium has to be reachable and removable. If clustered as an insoluble phosphate deposit, it is rather unlikely that it will be caught and removed.

After at least 400 million doses of GBCAs have been injected into humans since the 1980s, there is no convincing evidence of systematic symptoms after recommended application, other than NSF in patients with impaired renal function. To repeat the statement of the FDA: "A causal association between these adverse events and gadolinium retention could not be established."

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