MRI Contrast Agents: Revealing the Body

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Abstract

Magnetic Resonance Imaging (MRI) has proven an invaluable, non-invasive window into the human body, using a strong magnetic field to produce 3D images of tissues. To enhance visualization, contrast agents are used in many MRI examinations. These chemical compounds bind to water molecules, manipulating the relaxation times of hydrogen atoms within tissues. For over 30 years, gadolinium-based agents have remained the clinical standard, but alternative compounds containing metals widely present in nature and the body could offer new advantages. Drawing from a biblical view of scientific discovery, the author details the chemical and physical mechanisms governing existing contrast agents and highlights ongoing research in iron-based contrast agents, bioresponsive “smart” compounds, and emerging concepts such as polymodal imaging and theranostics. These approaches not only present advancements in the early diagnosis and precise treatment of disease, but illuminate the intricate design of the physical body.

1 Introduction

MRI contrast agents are chemical compounds that could be administered to a patient for the MRI examination to facilitate the diagnosis. They have been key to enhancing imaging exams for over thirty years, as they enable better visualization of specific areas of the body. These contrast agents are predominantly made with the element gadolinium, which is relatively low-risk to the patient's health and leaves the body quickly, but efforts to develop better alternatives continue. Research in this area is aimed at minimizing side effects, environmental issues, and economic problems associated with the production and use of contrast agents. Furthermore, advances in medicine and technology are revealing new possibilities in MRI diagnostics and contrast agents in the very early detection of diseases, and in the precise monitoring of treatment after diagnosis.

In this article, I will explain both the chemical and physical background behind how these contrast agents operate in the body and will discuss ongoing scientific research that may change future methods and improve treatments for patients.

My research in this area has focused on developing alternatives to traditional MRI contrast agents using iron-based compounds. I have long been fascinated by the many roles that iron plays in the human body, a fascination that began first as a teenager with my interest in chemistry and all its complexity. I was intrigued by how the microscopic structure of matter gives rise to the properties we observe in everyday life, such as texture, color, taste, smell, and even toxicity. Learning how these underlying chemical processes shape the physical world has been greatly fulfilling for me. Sadly, this passion also drew me to look to the scientific heroes, to men and their discoveries, an attraction that resulted in the denial of my faith in God's hand over creation. My admiration for these "great scientists," icons of culture and technological process, strongly influenced the path of my career, as I embraced their biographies, convictions, and quotations. In the world of academia, among the renowned leaders and prestigious universities I brushed against, such attitudes were common. But the people I had looked up to eventually fell short. When they failed to provide the meaning I had hoped for, I was left feeling disappointed and without a clear sense of purpose in my work or in life. But God (as Dr. Ken Mays wrote in his book [May23]) never forgot about me. He was patiently waiting for me to cease my vain endeavors and come to Him, that he might use my fleshly existence for His glory. I finally accepted His Lordship—not just over my life but over my scientific efforts. God used the testimony of Dr. Joey Kim at The Master's University (TMU) to impact me deeply. I decided to visit TMU and was blessed to enjoy fellowship with other believing scientists like Dr. Matthew McLain. Following their encouragement, my prayer and hope in publishing my research is to draw others to worship not the human explorers, but the divine Creator.

2 MRI Technique

2.1 Physical Background

MRI, or Magnetic Resonance Imaging, is a medical imaging technique that creates detailed pictures of the inside of the body. It works by taking a series of cross-sectional images (similar to slices) that can be combined to show tissues and organs in great detail. Doctors use MRI to help diagnose many conditions, including brain injuries, heart and blood vessel problems, and other diseases [WKM06].

MRI machines use a very high static magnetic field—about 10,000 times higher than the Earth's natural magnetic field—and radio waves to create detailed pictures of the inside of the body. The machine detects signals from hydrogen atoms in the body's water and uses a computer to turn those signals into images of organs and tissues. Most of the device seen in the MRI room is the source of a magnetic field created by a special magnet. In such a magnet, called a superconductor, electrons flow practically without resistance, but extremely low temperatures are required. In order for such a magnet to work effectively, it is cooled with liquid helium to a temperature of 4 K (-454 °F). Liquid helium, in turn, is surrounded by liquid nitrogen at a temperature of 77 K (-321 °F), which allows the helium to be kept in the device for a longer time. The patient has no contact with such cold and can safely undergo the necessary tests at normal room temperatures.

The MRI technique analyzes the behavior of hydrogen atoms in the water molecules in our body [Lau73]. Depending on the patient's age, water constitutes 45% (in older people) to 80% (in infants) of body weight [HH26]. Water moves differently in various types of body tissue. This mobility affects a property called relaxation time, which describes how hydrogen atoms in water respond after being disturbed by the MRI scanner's magnetic field. The MRI machine measures these relaxation times. Because relaxation times vary across tissues, the scanner can distinguish between them and produce images that show the shapes and boundaries of organs and tissues [WKM06].

2.2 Features and Applications

The MRI technique has many positive features, which is why it is so frequently used in medical diagnostics. First, exposure to the magnetic field is believed to have no side effects. So far, it has not been found that placing a human in such a high magnetic field is harmful. However, metal implants present in the body, such as those used in orthopedic treatment, may be an obstacle. There is also a serious risk of interference with electronic devices implanted in patients' hearts (for example, pacemakers). Therefore, people who have such a device should not undergo MRI examinations. In every case however, an MRI must be recommended and ordered by a healthcare provider.

Another important feature of MRI is its non-invasiveness and ability to obtain a full, three-dimensional image of the body and its internal structures. No incision or insertion of instruments is necessary for the radiologist to view the inside of the body. Moreover, these images enable examination with very high resolution, even at the scale of one millimeter, which is practically impossible with most other tomography techniques. Also unique is the possibility of examining soft tissues such as the brain and elements of the nervous and digestive systems, as well as dynamic analysis of blood flow in the circulatory system (so-called angiography). So far, no other diagnostic technique combines so many valuable features for recognizing changes in the body and also for tracking the course of treatment.

3 MRI Contrast Agents

3.1 Role and Classification: Positive, Negative

Despite so many advantages and the wide application of MRI, there are situations when the image of the examined area of the body is not clear enough, and therefore an unequivocal diagnosis cannot be made. In such situations, patients are administered a contrast agent, most often in the form of intravenous infusion. Approximately 30–40% of MRI examinations are performed with contrast agents [CWPM22].

At the molecular level, a contrast agent is a chemical compound with magnetic properties. This compound consists of paramagnets, which serve to additionally change the relaxation times of hydrogen atoms, as mentioned in the previous section [LHS+17]. As a result, some structures in the image increase in visibility during the examination. One group of contrast agents brightens the images of the places where they appeared—these are called positive contrast agents. Alternatively, negative contrast agents are used to make parts of the images darker. As a result, contrast examination leads to clearer, higher contrast images, better diagnosis, and more effective treatment of the patient. It is worth adding that the contrast agent administered to the patient quickly leaves the body, usually in the urine. For example, one of the classic MRI contrast agents Dotarem® is at least half removed from the body two hours after administration.

3.2 Chemical Structure

Positive contrast agents are most often compounds of the chemical element gadolinium [CEML99]. This atom is surrounded by a molecular shell holding it like a crab's claws, which chemists refer to as a *chelate*, a term that originates from the Greek word for "claw." Thanks to this chelate, gadolinium can safely pass through the body without causing much harm [HAG+12]. At the same time, the chelate makes it easier for the gadolinium to reach the examination area. Selected chelates can cross the blood-brain barrier, which allows for better brain imaging [YC12]. Others, intended for the digestive system, can help better visualize pathological changes in liver cells.

On the other hand, negative contrast agents are **s**uper**p**aramagnetic **i**ron **o**xide **n**anoparticles (SPIONs). These are tiny iron particles additionally surrounded by sugar-based molecules (for example, dextrans) [Wan11]. These iron particles are so small that they are not visible to the naked eye, but they form a stable yellow-brown mixture. They are used, for example, to examine damage to cells in the bowel.

3.3 Mechanism of Action, Relaxivity

As mentioned earlier, MRI contrast agents are tiny magnets. Their role at the molecular level is to interact with water molecules in the body, which causes the measured relaxation times to change. The relaxation process itself is accelerated, therefore the relaxation times of these water molecules are shorter and, as a result, they appear brighter with positive contrast agents and darker with negative contrast agents.

Another property of contrast agents is that they bind particularly strongly to water molecules, which is why in MRI images they can especially highlight areas of high water content that are affected by disease, e.g. tumors or lesions. Let's take a closer look at how contrast agents behave if we could see them at a very high magnification (Figure 1) [Lau87].

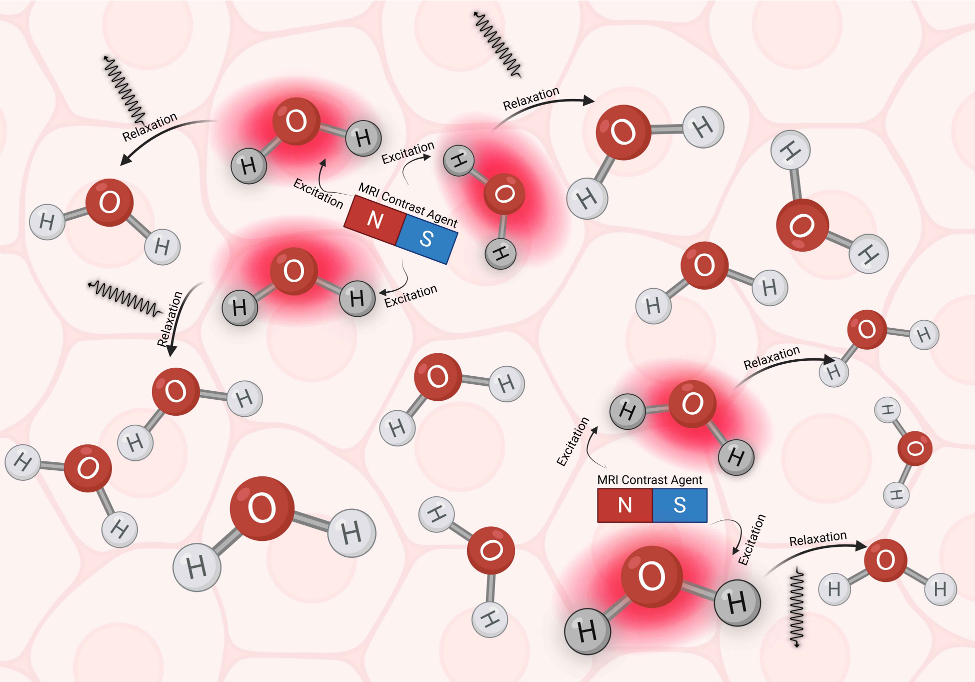

Figure 1: Schematic view of the interactions of water molecules in the human body and magnetic MRI contrast agents as a general overview of the mechanism. Created in BioRender. Kuźnik, N. (2026) `https://BioRender.com/iebsmsy`.

Positive contrast agents are magnetic ions, mainly gadolinium, that are enclosed with a biocompatible molecular structure called the chelate. The chelate acts as a protective "cage," allowing the agent to circulate safely in the body (Figure 2). However, this enclosure is not completely sealed, so water molecules can still come into close contact with the magnetic center. This partial accessibility is important because it allows water molecules to interact directly with the magnetic ion. These interactions significantly alter the relaxation times of nearby water protons, which is what the MRI scanner detects. As a result, the affected regions appear brighter on the image, producing strong contrast.

The effectiveness of a contrast agent is described by a property called relaxivity, which measures how much the relaxation time changes for a given concentration of the agent. Higher relaxivity means the agent produces a greater enhancement in image contrast [THM02]. This amount is important because it is necessary to select the dose for the patient.

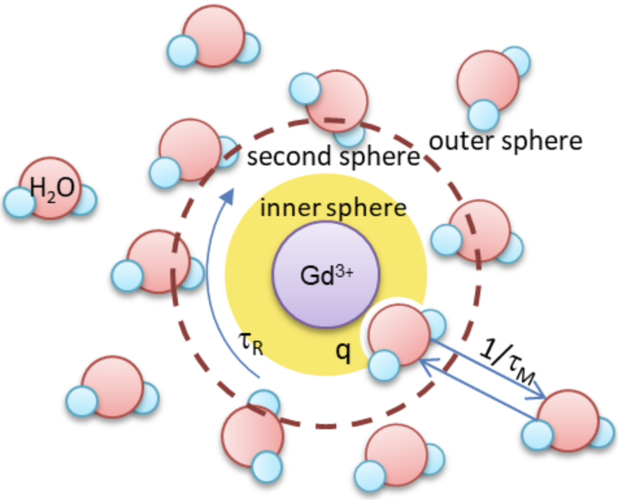

Figure 2: Detailed mechanism of the action of the positive MRI contrast agents. (Image source: Anna Kastelik-Hryniewiecka, used with permission.)

What else contributes to changing (shortening) the relaxation time? As shown in Figure 2, it also depends on the relaxation rate of the electrons themselves in the magnetic center (τ_S) and how quickly water molecules will stay attached to this center. This length of time is called the residence time of water molecules (τ_M) and involves a temporary bonding to the magnetic metal. Both of these factors (τ_S

and τ_M) depend primarily on what metal is used, and only to a small extent on the surrounding material that covers the magnet. This shell is generally water-friendly (or hydrophilic) and able to form hydrogen bonds, although certain aspects of the shell can be customized to target specific cells. In other words, different contrast agents are designed differently, depending on where they need to go in the body. For example, contrast agents for blood need to mix well with water, since blood is mostly water. On the other hand, contrast agents for liver cells are more hydrophobic since liver cells interact more with fats and proteins.

More generally, the shell also affects how quickly the whole particle rotates, called the correlation time of rotation (τ_R). Larger particles rotate more slowly, which improves their performance in MRI. However, their size must be limited so they can still travel through the body and be removed afterward. One way around this limitation is that some contrast agents can temporarily bind to large proteins in the blood, such as albumin. When this happens, the small agent effectively becomes part of a much larger structure, which slows its rotation. This leads to a much stronger MRI effect, because slower rotation improves how the agent interacts with nearby water molecules. This improvement is known as receptor-induced magnetization enhancement (RIME) [Car09].

Negative contrast agents for MRI behave in a simpler way. They affect nearby water molecules through their magnetic field [KK95], and this effect becomes weaker with distance. Therefore, these contrast agents must have a strong magnetic effect such as superparamagnetic particles, and furthermore, their coating should attract water molecules and allow them to approach closely In practice, this is achieved by coating the particles (such as SPIONs) with hydrophilic sugar chains, which not only brings the water molecules closer to the contrast agent but also greatly reduces their toxicity to humans.

3.4 Medical Routine and Side Effects

Before giving a contrast agent for an MRI, a doctor will first carefully evaluate whether it is needed. During a consultation, the doctor will interview the patient, recognize the symptoms, ask whether the patient has been previously administered contrast agents and ask whether any allergic reaction has occurred. The patient's kidney health is also important, because it is through the kidneys that the typical positive contrast agent is eliminated. To check your kidney's health, the doctor will likely recommend testing your creatinine level before administering a contrast agent. A normal blood creatinine test confirms good kidney function and minimizes potential issues.

Like any foreign substance or drug introduced into the body, MRI contrast agents may cause side effects. Reading the medication leaflet that always accompanies the recommended contrast agent can give an idea of possible side effects, which may include allergic reactions, nausea, or headaches. However, the doctor and the person directly performing the contrast examination will supervise the patient, so any concerning symptoms should be reported to them.

One rare side effect of gadolinium-based MRI contrast agents is called Nephrogenic Systemic Fibrosis (NSF) [Gro06]. This mostly occurs in patients with renal dysfunction and causes the skin to become thick, hard, red, or itchy, sometimes forming small lumps. At the molecular level, it is argued that this disease results from the release of gadolinium from the contrast agent (from the chelate) when it stays in the body for too long due to kidney failure. The released gadolinium interferes with calcium, which plays an important role in healthy functioning of the body. In recent years, doctors have identified a broader set of effects called 'gadolinium deposition disease', which describes how gadolinium can build up in the body. Research is ongoing to better understand these effects and find ways to prevent and treat them [HGC19].

3.5 Outlook of Scientific Research: Non-Gadolinium Contrast Agents, Bioresponsive, Polymodal, Theranostics

MRI contrast agents have been successfully used around the world for over thirty years. The measures used in the past have been replaced by more effective and safe ones. However, scientific research in this area is still intensively conducted [WGRRC19, PAC14, Mor17]. Side effects of approved contrast agents are monitored, but ecological and geopolitical factors also come into play. Gadolinium, which is found in most contrast agents, is not widespread in nature, so its release in patients' urine raises concerns about its impact on marine life [KH00]. The cost and access to raw materials containing gadolinium is another reason that turns some scientists' eyes to other more widespread and cheaper metals [Eur]. For example, iron and manganese are elements also naturally present in the body as microelements. Their magnetic properties and electron relaxation time, as mentioned in Section 3.3, are slightly less effective than those of gadolinium. However, it has been shown in some preliminary studies that it is possible to design the chelates with these metals in such a way that they match the properties of gadolinium [SDR02, KW16, DLT12].

I myself have always been astonished by the versatility of iron forms in human organisms. The iron-containing protein called hemoglobin is well-known for carrying oxygen through the body, but there are other forms crucial to life such as myoglobin and cytochromes. One of iron's specific features lies in the intensity and diversity of color hues in its compounds. For instance, the color of our blood comes from iron and changes according to the oxygenation level.

In my research, I have been blessed to design and study new MRI contrast agent candidates based on these iron compounds. As mentioned, the contrast effect of these alternatives is not yet comparable to traditional gadolinium compounds, so there is little motivation for pharmaceutical companies to undertake costly and lengthy clinical studies. But other advantages of iron, such as being widely available, occurring naturally in the body, having additional useful functions, and having lower production costs, may drive interest in gadolinium alternatives. Thus in ten years, if you are administered a red or violet MRI contrast agent, ask your doctor if it contains iron!

Initially, my coworkers and I investigated the possibility of siderophores as a new type of MRI contrast agent. These are natural, very stable iron(III) complexes [KSGO^{+}14, KJO^{+}14]; however, their potential proved to be rather limited. Subsequently, we studied the possibility of tracking enzymes activity using MRI, which can provide information about the progress of therapy given to a patient. For this purpose, we designed iron complexes with a sugar attached that was released upon contact with an enzyme called β-galactosidase. We confirmed this concept by performing MRI imaging of solutions containing such substances [Lau73, KCM^{+}12]. In other words, we designed a "smart" contrast agent that responds to biological activity instead of just passively showing tissue, which might be useful for monitoring the progress of therapy in a non-invasive way.

More recently, however, our research has evolved toward extending the functionality of MRI by combining it with the even more advanced PET technique, which enables the diagnosis of cancer at an early stage of its development. Our studies were based on contrast agents built from superparamagnetic iron oxide nanoparticles (SPIONs) for MRI, into which we incorporated ^{89}Zr nuclide in order to obtain simultaneous PET images. Our ambition was to precisely target cancer cells that express PD-L1, a protein used by tumors to evade the immune system [KHJB+22]. So far, our studies have encountered various challenges, but they fit within the emerging possibilities based on recent discoveries in immunotherapy, which aims to stimulate the immune system to independently combat cancer cells.

The second direction of scientific research, which we also explored, involves the design of bioresponsive contrast agents, previously also called smart contrast agents, which are those that react to biological changes in cells caused by disease-specific conditions [MM09]. For example, cancer cells have a lower, more acidic pH, and due to their greater metabolism, they consume more energy resources such as glucose, oxygen, etc. Traditional imaging techniques like CT and MRI (apart from PET) are unable to detect such chemical changes. However, chemical compounds introduced into the body, such as bioresponsive contrast agents, are designed to activate only in the presence of disease-specific signals (like low pH). So, let's imagine that the patient is given an inactive (mute) contrast agent that initially does not change the MRI image. But when it reaches the cell area with a lowered pH, such a particle changes its properties, exposes the magnetic nucleus (as described in Section 3.3) and thus the MRI image reveals the diseased area clearly. Therefore, it can be said that the bioresponsive contrast agent responded or reacted to the biological factor resulting from the lesion. Many such compounds have already been tested and they have shown promising properties, although various problems continue to arise, e.g. getting the agent into the right place (it may be difficult for it to cross cell membranes) or the strength of the signal change (the MRI contrast may not be strong enough to clearly see the reaction). Nevertheless, this idea is interesting and its success could help diagnose disease lesions at very early stages.

The reader must have noticed that there are many imaging diagnostic techniques in this article and in modern medical facilities. These techniques are used in various situations and are usually complementary. For example, MRI is used to image soft tissues, computed tomography (CT) shows the skeletal system, and PET enables the precise examination, above all, of cancer cells. Complex situations will often require obtaining images from two or more techniques. Since most of these imaging techniques use contrast agents (generally called molecular probes), the next trend in scientific research are exploring molecular probes for two or more tomographic techniques, called bi- or polymodal probes [WS18, MBSBS10]. Polymodal probes therefore contain all the elements that are necessary for a given technique, e.g. an MRI/PET/CT probe should contain a paramagnetic element (e.g. gadolinium), a positron-generating nucleus (e.g. ^{89}Zr) and high atomic weight elements (e.g. iodine). A molecular probe has even been created for six imaging techniques, demonstrating the possibilities of design of polymodal molecular probes [RCK+15]. However, the research also shows the weaknesses and challenges of this concept consisting in the difficulties of dose selection and the practical usefulness of such probes. It is also an engineering challenge to combine several techniques with one device, although some SPECT/CT combinations are already available in common medical practice.

Another area of exploration is called theranostics, which is an emerging concept in medicine that combines treatment (*thera*py) with real-time monitoring of how that treatment is working (diag*nostics*). Because MRI contrast agents are already used to visualize structures inside the body, researchers are exploring ways to pair them with therapeutic compounds so that a single agent can both treat a condition and allow clinicians to track its progress [JHN18, KS24].

These approaches are still largely in the early research stage, but studies have shown that it is possible to link drugs—such as antibiotics or anticancer agents—to MRI contrast agents. Another promising direction involves combining contrast agents with sensitizers used in therapies like photodynamic or thermal treatment. In these therapies, a substance is introduced into the body that absorbs energy from a laser and converts it into heat. When the targeted tissue is exposed to the laser, the sensitizer generates localized heat that can destroy diseased cells.

By combining these sensitizers with an MRI contrast agent, clinicians can monitor exactly where the treatment is occurring and observe changes in the tissue over time, such as the extent and progression of tissue destruction.

4 Summary

As described at the beginning of this article, MRI is a non-invasive technique, and this article has focused on contrast agents, which are chemical substances that are administered to make specific tissues or conditions easier to see in an MRI image. Because contrast agents are chemicals, they interfere with the normal chemistry within a human body. However, in most cases, they are very safe, and side effects are generally rare and mild. Nevertheless, scientific research is constantly being carried out to better understand the effects of contrast agents, further reduce side effects, lower the dose, improve organ targeting, and enhance their ability to detect diseases at very early stages. It is possible that, as the development of MRI hardware progresses and its sensitivity increases, the need for contrast agents may decrease. On the other hand, the possibilities offered by the combination of MRI, CT, PET, SPECT and other imaging techniques provide multidimensional diagnostic information. Some of these techniques, e.g. PET, even require special pharmaceuticals (in this case, those that are a source of positrons), so combining their functions with MRI could be highly beneficial. Finally, the possibility of conducting therapy and its simultaneous monitoring using MRI technology in theranostics is perhaps a new step in medicine that will enable more precise treatment and better selection of drugs.

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