Magnetic Materials for Nuclear Magnetic Resonance and Magnetic Resonance Imaging

Elizaveta Motovilova and Shaoying Huang

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ABSTRACT

This chapter presents the applications of magnetic materials for nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI), including the history and latest developments. Magnetic materials are applied for MRI/NMR mainly in two ways. One is the use of permanent magnets for generating the main magnetic fields $B_0$ and the other is magnetic nanoparticles (MNPs) injected in the object under scan for contrast enhancement. The physics and techniques of these two main applications will be detailed. Discussions and future perspectives will be provided at the end of the chapter.

In this chapter, the physics of magnetic materials, especially those related to MRI/NMR, are introduced in detail in Section 3.1. It is followed by Section 3.2 which details the working principles of MRI and NMR. In Section 3.3, magnetic materials used to provide the main magnetic field for imaging are presented. Examples of MRI systems using permanent magnets for imaging are demonstrated. In Section 3.4, the other main application of magnetic materials for MRI, contrast enhancement using MNPs, is presented. The history, physics, design criteria, and classifications of MNPs are introduced in detail. Different types of contrast agents (CAs) are systematically introduced and compared.

3.1 INTRODUCTION OF MAGNETIC MATERIALS

Magnetism originates from magnetic moments $m$ of elementary particles, that is, electrons, protons, and neutrons, and from the way these magnetic moments interact with one another. The classical definition of a magnetic moment is given in terms of the current magnitude $I$ and the enclosing area $S$ of a planar loop (Figure 3.1) and expressed by the following equation:

$$ m = IS \quad (3.1) $$
Moving charged particles, for example, electrons orbiting around the nucleus in an atom, form electric currents and these currents produce so-called orbit magnetic moments.

There is another type of magnetic moment called spin magnetic moment, or simply spin. It is an intrinsic property of all elementary particles and cannot be understood from a classical point of view. One could imagine an electron as a negatively charged sphere which spins around its own axis and thus produces a magnetic moment. However, this model does not agree with the behaviors of spin obtained from experiments. In 1922, Otto Stern and Walter Gerlach demonstrated the quantum nature of an electron spin, and that experiment gave rise to the further development of the quantum theory which fully explains the nature of spin.

These electric currents produced by moving charged particles and the fundamental magnetic moments all together give rise to a magnetic field. All matter is magnetic to some degree because of the non-cooperative behavior of orbiting electrons in an atom. However, it is the collective interaction of the atomic magnetic moments that gives the variety of different types of magnetic behaviors observed for different materials.

In order to classify magnetic materials and understand the nature of magnetism, it is good to start with the interaction of different materials with an external magnetic field. The relationship between the external magnetic field $H$ and the magnetic induction $B$ inside an object is the following:

$$ B = \mu H $$

where $\mu$ is the magnetic permeability of the object. For vacuum, $\mu = \mu_0 = 4\pi \times 10^{-7} \text{ V} \cdot \text{s} / (\text{A} \cdot \text{m})$, and it is called the magnetic constant or permeability of free space. However, the situation is different for any other kind of matter. All substances exhibit magnetic properties to some degree and different phenomena can be observed depending on the properties of the substance and the applied magnetic field strength. When a material is subjected to an external field $H$, it is magnetized. The magnetization $M$ is a vector sum of all the magnetic moments $m_i$ within a given volume $V$

$$ M = \sum \frac{m_i}{V} $$

FIGURE 3.1  Magnetic moment of a planar current loop.
The magnetization $M$ and the external magnetic field $H$ are related by the following equation:

$$M = \chi_m H$$

(3.4)

where, $\chi_m$ is the magnetic susceptibility of the substance. It is dimensionless and shows the degree of magnetization, or in other words, how easily the substance can be magnetized. Magnetic susceptibility is an intrinsic property of a matter. It depends on factors such as the orientation of atoms in a molecule. The sign and value of $\chi_m$ determine the magnetic behavior of a matter.

Therefore, for an object placed in an external magnetic field, the actual magnetic induction inside the object is a sum of the external field and magnetization contributions

$$B = \mu_0 H + \mu_0 M = \mu_0 (H + M)$$

(3.5)

Furthermore, by substituting Equations 3.2 and 3.4 into Equation 3.5, the magnetic permeability $\mu$ can be expressed in terms of magnetic susceptibility $\chi_m$

$$\mu = \mu_0 (1 + \chi_m)$$

(3.6)

All materials can be classified depending on the sign and the magnitude of the magnetic susceptibility $\chi_m$. This approach is called the phenomenological classification of magnetic materials. It has been used for a long time to describe, rather than explain, different types of magnetic behavior naturally observed for pure elements and commonly used compounds. According to this classification there are three types of magnetic behavior: diamagnetism, paramagnetism, and ferromagnetism.

The most common types of magnetic materials at room temperature are diamagnetic and paramagnetic. Almost all the elements of the periodic table fall into these two categories (Figure 3.2). In our everyday life we usually refer to diamagnetic or paramagnetic materials as nonmagnetic. That is because their response to an external magnetic field is weak, that is, their magnetic susceptibility $\chi_m$ has a small magnitude. The difference in diamagnetic and paramagnetic materials is in the direction of the induced magnetization relative to the applied field, that is, positive or negative $\chi_m$.

Beyond the phenomenological classification, there are cases which do not fit in the three aforementioned classes. For this reason, people typically recognize two more forms of magnetism: antiferromagnetism and ferrimagnetism. In this section, these five types of magnetic behaviors are introduced in detail, especially the aspects related to MRI/NMR.

### 3.1.1 DIAMAGNETISM

Being placed in an inhomogeneous magnetic field, an object is either pulled into or pushed out of the area of the stronger magnetic field depending on its magnetic susceptibility. If the direction of the induced magnetization and direction of the external
Magnetic Materials for NMR and MRI

**Paramagnetic**

- Hydrogen (H)
- Lithium (Li)
- Beryllium (Be)

**Diamagnetic**

- Nitrogen (N)
- Oxygen (O)
- Neon (Ne)

**Ferromagnetic**

- Rare earth elements
  - Neodymium (Nd)
  - Samarium (Sm)
  - Europium (Eu)
  - Gadolinium (Gd)
  - Terbium (Tb)
  - Dysprosium (Dy)
  - Holmium (Ho)
  - Erbium (Er)
  - Thulium (Tm)
  - Yttrium (Y)
  - Lanthanum (La)
  - Cerium (Ce)
  - Praseodymium (Pr)
  - Neptunium (Np)
  - Plutonium (Pu)

**Antiferromagnetic**

- Helium (He)
- Carbon (C)
- Nitrogen (N)
- Oxygen (O)
- Neodymium (Nd)
- Samarium (Sm)
- Europium (Eu)
- Gadolinium (Gd)
- Terbium (Tb)
- Dysprosium (Dy)
- Holmium (Ho)
- Erbium (Er)
- Thulium (Tm)
- Yttrium (Y)
- Lanthanum (La)
- Cerium (Ce)
- Praseodymium (Pr)
- Neptunium (Np)
- Plutonium (Pu)

**Rare earth elements**

- Neodymium (Nd)
- Samarium (Sm)
- Europium (Eu)
- Gadolinium (Gd)
- Terbium (Tb)
- Dysprosium (Dy)
- Holmium (Ho)
- Erbium (Er)
- Thulium (Tm)
- Yttrium (Y)
- Lanthanum (La)
- Cerium (Ce)
- Praseodymium (Pr)
- Neptunium (Np)
- Plutonium (Pu)

**FIGURE 3.2** Periodic table of elements.
field are opposite to each other, the effective field will push the object toward the low field region (Figure 3.3), and this behavior is termed *diamagnetism*. Mathematically, this tendency of matter to oppose an external magnetic field is expressed by the negative sign of magnetic susceptibility for diamagnetic materials, with the average value of $\chi_m$ being of about $10^{-5}$.

Diamagnetism is a quantum mechanical effect. Diamagnetism originates from the orbital motion of electrons. All the electrons circulate in orbitals acting like current loops, as shown in Figure 3.1. They are paired in diamagnetic materials and therefore the net magnetic moment is zero. In the presence of an external magnetic field, the applied field aligns the electron paths and meanwhile generates currents in the loops that oppose the change of the field. This results in the repelling phenomenon for diamagnetic behavior. The electrons are rigidly held in orbitals by the charge of the protons and are constrained by the Pauli exclusion principle. Therefore, diamagnetism is generally weak in materials. In short, diamagnetic materials naturally do not have magnetization in the absence of a magnetic field and they are repelled by an externally applied magnetic field.

Generally speaking, all matters possess the diamagnetic property because diamagnetism originates from the orbital motion of electrons. For the same reason, diamagnetism is a property of *every* atom and molecule. However, this effect is so weak that, despite its universal occurrence, diamagnetism is usually masked by other effects, such as paramagnetism or ferromagnetism. It is difficult to observe truly diamagnetic phenomena. Usually substances that mostly display diamagnetic behavior and are generally thought of as nonmagnetic are said to be diamagnetic materials. Practically all organic compounds and the majority of inorganic compounds are examples of diamagnetic materials. The strongest diamagnetic materials are pyrolytic carbon and bismuth. Other notable diamagnetic materials include water, wood, diamond, living tissues (note that the last three examples are carbon-based), and many metals such as copper, gold, and mercury. Magnetic susceptibilities of some diamagnetic materials are shown at Table 3.1. It should be noted here that $\chi_m$ is temperature independent.

Probably the most interesting example of diamagnetism application is magnetic levitation. Due to the strong diamagnetism of pyrolytic carbon, it is easy to

**FIGURE 3.3** Schematic illustration of a diamagnetic sample behavior in an external magnetic field.
demonstrate the magnetic levitation effect with the help of neodymium (NdFeB) permanent magnets and a thin slice of pyrolytic carbon (Figure 3.4a). The most spectacular part of this experiment is that all the components are at room temperature and no special conditions are required.

As living organisms are diamagnetic, they can also exhibit magnetic levitation. However, because the magnitude of their magnetic susceptibility is much smaller compared to pyrolytic carbon or bismuth, these objects can levitate only in much stronger magnetic fields. In 2010, the Radboud University Nijmegen in the Netherlands demonstrated a live frog levitation (Figure 3.4b) in a 16 Tesla (T) magnetic field inside a bore solenoid (note that so far the maximum strength of a static magnetic field approved by the U.S. Food and Drug Administration (FDA) which can be used in medicine for human beings is 8 T). In 2009, NASA’s Jet Propulsion Laboratory in Pasadena, California, demonstrated a live mice levitation. This is a great step forward because mice are biologically closer to human beings than frogs.

TABLE 3.1
Diamagnetic Materials and Their Magnetic Susceptibilities

<table>
<thead>
<tr>
<th>Material</th>
<th>Water</th>
<th>Copper</th>
<th>Graphite</th>
<th>Lead</th>
<th>Diamond</th>
<th>Silver</th>
<th>Mercury</th>
<th>Bismuth</th>
<th>Pyrolytic Carbon</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \chi_m \times 10^{-5} )</td>
<td>-0.91</td>
<td>-1.0</td>
<td>-1.6</td>
<td>-1.8</td>
<td>-2.1</td>
<td>-2.6</td>
<td>-2.9</td>
<td>-16.6</td>
<td>-40.9</td>
</tr>
</tbody>
</table>


FIGURE 3.4 (a) Pyrolytic carbon levitating above NdFeB magnets and (b) live frog levitation.
However, the experiment required a superconducting magnet that makes the whole experiment more complicated.

### 3.1.2 Paramagnetism

Looking back at the periodic table in Figure 3.2, many chemical elements at room temperature are paramagnetic. For paramagnetic materials, the directions of the induced magnetization $M$ and the applied magnetic field $H$ are the same. Due to the effective field, the object is pulled toward the area with the higher magnetic field (Figure 3.5). In this case, the susceptibility has a positive sign and the magnitude is of the order of $10^{-3}$–$10^{-5}$, which is comparable to or slightly larger than that of diamagnetic materials.

Multiple theories have been proposed to explain paramagnetism in different types of materials. Some of them explain one specific type of material better, while others are valid for other types. Here we consider the Langevin model of paramagnetism. The origin of paramagnetism comes from the unpaired noninteracting electrons. In fact, in many atoms and in the vast majority of molecules, electrons are combined in pairs with their spins pointing in opposite directions obeying the Pauli exclusion principle, which results in a zero magnetic moment. The only magnetization left is from the orbital motion of such electrons pairs that gives rise to the diamagnetism considered in Section 3.1.1. However, some atoms have unpaired electron spins which results in nonzero permanent magnetic moments. In the absence of an applied magnetic field, these magnetic moments are randomly oriented resulting in a zero net magnetic moment. In the presence of an external magnetic field $H$, the magnetic moments inside paramagnetic objects align with the field, resulting in an attracting force as shown in Figure 3.5. However, after removal of the external magnetic field, paramagnetic objects do not retain their magnetization because without the alignment by the external force the internal magnetic moments disorient to achieve thermodynamic equilibrium. In short, paramagnetic materials naturally do not have a magnetization and they are attracted by an externally applied magnetic field. Elements from chromium to copper, iron, cobalt, nickel, and rare-earth that

![FIGURE 3.5 Schematic illustration of a paramagnetic sample behavior in an external magnetic field.](image-url)
sequence around gadolinium have this property. Their compounds and alloys are generally paramagnetic or even ferromagnetic.

There is always competition between the diamagnetic contribution from the core electrons and the paramagnetic contribution from the outer shell unpaired electrons, and the resulting magnetic behavior depends on the relative strength of these two. The competition can clearly be seen in s- and p-type metals* where the electrons are delocalized, that is, traveling as an electron gas. This results in weak paramagnetism or even diamagnetism. For example, in the case of gold, the orbital magnetic moments overshadow spin magnetic moments, resulting in the diamagnetic behavior of this metal. In the case of aluminum, the paramagnetic contribution happens to be slightly stronger than the diamagnetic one resulting in the weak attraction of aluminum to an external magnetic field. These small differences are difficult to detect and usually require sensitive analytical devices.

Stronger paramagnetic effects can be observed for d- and f-type elements† with strongly localized electrons. The high magnetic moments of lanthanides explains the reason that gadolinium, neodymium, and samarium are typically used for strong magnets.

It should be noted that paramagnetism, unlike diamagnetism, is temperature dependent. The randomizing thermal effect becomes significant at high temperature, making it hard to align the magnetic moments along the external magnetic field. This behavior was experimentally found and named as the Curie law

\[ \chi = \frac{C}{T} \]  

(3.7)

where \( C \) is the Curie constant which depends on material and \( T \) is the temperature in kelvins.

Figure 3.6 summarizes the behaviors of diamagnetic and paramagnetic materials with the change of an external magnetic field and temperature. As shown in Figure 3.6a and c the relationship between \( H \) and \( M \) is linear for both of the materials, the difference is only in the sign of the magnetic susceptibility, \( \chi_m \). However, the temperature behavior of \( \chi_m \) for these two types of materials differs significantly, as shown in Figure 3.6b and d. Magnetic susceptibility is a constant for a diamagnetic material, while it obeys the Curie law for a paramagnetic one.

Due to the absence of a strong permanent net magnetic moment, paramagnetic materials are not widely used. However, they have one interesting application: they can be used to achieve extremely low temperatures. The working principle is based on the adiabatic demagnetization effect. When a paramagnet is cooled to liquid-helium temperature (4 K, or –269°C) in the presence of a strong magnetic field, almost all the spins are aligned along the field. If the sample is thermally isolated and the field is gradually decreased, the temperature of the paramagnet

---

* s-elements are those which the outer electronic configuration of \( ns^1 \) or \( ns^2 \), p-elements are those which the outer electronic configuration of \( ns^2np^x \), where \( x = 1…6 \).

† The general outer electronic configuration of d-elements is \((n−1)d^nx^y\), where \( x = 1…10 \), \( y = 1,2 \); the general outer electronic configuration of f-elements is \((n−2)f^y(n−1)d^nx^2\), where \( x = 1…14 \), \( y = 0,1 \).
will decrease further. The reason is as follows. In the decreasing external field, magnetic moments inside the paramagnetic sample start to reorient back to the random arrangement. This reorientation consumes thermal energy of the system thus, with thermal isolation, the temperature of the system decreases further (<4 K). Praseodymium alloyed with nickel (PrNi5) has an extremely strong adiabatic demagnetization effect and is used to approach a temperature within one thousandth of a degree of absolute zero.

### 3.1.3 Ferromagnetism

The third type of magnetic behavior, according to the phenomenological classification, is called ferromagnetism. In contrast to diamagnetic and paramagnetic materials, ferromagnetic materials have large spontaneous magnetization even in the absence of an external magnetic field. This is the result of the cooperative ordering of spins. It should be noted that ferromagnetism can occur only in materials with paramagnetic properties, because it requires the presence of unpaired electron spins in atoms in order to produce a nonzero net magnetic moment.

The unique feature of ferromagnetic materials is that the relation between $M$ and $H$ is not linear. Moreover, the complicated relation between $M$ and $H$ for ferromagnetic materials is difficult to characterize by simple mathematical functions. Thus, it is usually obtained through a series of experiments by plotting the magnetization $M$ against the strength $H$ of the external magnetic field applied. A magnetic hysteresis loop is shown in Figure 3.7. Ferromagnetic materials can be easily magnetized, and in strong magnetic fields the magnetization reaches a certain limit called saturation magnetization $M_s$, as shown in Figure 3.7. Beyond this limit no further significant increase in magnetization occurs. It should be noted that saturation magnetization is an intrinsic property of a material, which does not depend on the shape or size of the material. Interestingly, with the gradual reduction of the applied field, the magnetization $M$ of a ferromagnetic material does not decrease by its original path, but at a slower rate. When $|H|$ reaches 0 A/m, $M$ is still positive. This positive magnetization is called remanence and denoted using $M_r$. Therefore, unlike dia- or paramagnetic materials, ferromagnetic materials retain a magnetization after the externally

---

**FIGURE 3.6** Typical behavior of diamagnetic and paramagnetic materials depending on an external magnetic field and temperature.

---

\[
\begin{align*}
\text{Diamagnetism} & \quad \chi < 0 \\
\text{Paramagnetism} & \quad \chi > 0 \\
\end{align*}
\]

\[\text{Slope} = \chi \quad \text{Slope} = \chi \]

\[\chi \approx 1/T\]

---

$M$ (a) (b) (c) (d)
applied magnetic field is removed, or in other words, they “remember” their history. This feature of ferromagnetic materials is exploited in magnetic memory devices such as magnetic tape, hard disk drives, and credit cards. When $|H|$ is reduced further (becomes negative and changes its direction), the magnetization becomes zero again at a certain value of magnetic field strength which is called the point of coercivity and denoted by $H_c$. This parameter indicates the strength of the reverse field needed to remove the residual magnetization from the material after the saturation. As the field strength increases further, the magnetization reaches the saturation magnetization in the opposite direction. To complete the entire cycle, $|H|$ along the negative direction can be moved gradually back to 0 A/m and then increased till $M$ reaches the positive saturation magnetization. As is shown in Figure 3.7, by changing the magnetic field strength $H$ and measuring the induced magnetization $M$ for ferromagnetic materials, a loop, called the magnetic hysteresis loop is formed, that characterizes the unique behavior of ferromagnetic magnetization.

Different ferromagnetic materials have different shapes and sizes of hysteresis loops. The form of this loop tells the properties of the material. The area inside the hysteresis loop shows the energy losses due to the change of the magnetization. This energy in converted into heat. The parameters $M_s$, $M_r$, and $H_c$ indicate important magnetization properties of the material. $M_r$ and $H_c$ indicate how easily the material can be magnetized/demagnetized; $M_s$ shows the amount of magnetization it can store. For example, the coercivity in pure iron is about 0.16 kA/m while in the neodymium magnet (NdFeB) it is more than 800 kA/m. It means that a 5000 times stronger field is required in order to demagnetize NdFeB compared to the amount of field needed to demagnetize iron. This is the reason that the neodymium magnet is the most widely used permanent magnet. Magnetic materials are classified as soft or hard depending on the ease of demagnetization, in other words, the classification is based on the value of their coercivity, or the shape of the hysteresis loop. Hard magnetic materials are those that retain their magnetism and are difficult to demagnetize; they have high $H_c$ and therefore a wide hysteresis loop. One the other hand, soft magnetic materials are those that are easy to magnetize and demagnetize; they have low
and a narrow hysteresis loop. The permanent neodymium magnet belongs to the first category. It has a broad hysteresis loop and a large coercivity. Due to its stability, NdFeB is used as a permanent magnet. Permanent magnets are used to supply the main magnetic field in some MRI systems for imaging. They are introduced in detail in Section 3.3.1. For other applications, sometimes, it is better to reduce energy losses during the hysteresis cycles. One of the examples is the transformer cores in stators and rotors for electrical machinery. In this case soft magnetic materials with a narrow hysteresis loop and small remanence magnetization are more suitable.

Another remarkable feature of ferromagnetic materials is the way magnetic moments are organized inside the material. When cooled below the Curie temperature all ferromagnetic materials consist of microscopic blocks (or the so-called domains) of atoms. The magnetic domain is a region within which the magnetization is in a uniform direction, meaning that individual atoms have the same direction of magnetic moment, as shown in Figure 3.8. However, the direction of magnetization of different domains may be different. Therefore, the magnetic field lines from different domains of a ferromagnetic material pass through each other in alternating directions and thus reduce the field outside the material. The domains are separated by thin layers of boundaries (also called walls) where the magnetization vector gradually changes its direction from the direction in one domain to that in the neighboring one, as shown in Figure 3.8d.

The formation of domains, alignment of magnetic moments of atoms in a domain, and formation of flux closure domains where the field lines are allowed to form a closed loop crossing the domains, are the results of energy minimization. The formation of a domain is done in order to reduce magnetostatic energy. Within a domain, when two nearby atoms both have unpaired electrons, it is favorable for the electrons to have their spins aligned because in this way they occupy different orbitals and thus the Coulomb repulsion is smaller and the exchange energy is minimized. The flux closure domains can only be formed when the magnetostatic energy saved is

![Figure 3.8](https://example.com/fig3.8.png)  
**FIGURE 3.8** Domain formation in a ferromagnetic sample (a) without field, (b) with some field applied, (c) with a strong linear field, and (d) a closer look at the domain wall formation.
greater than the energy cost for changing the local net magnetization. It takes two
types of energy to form a loop of field lines. One is called *magnetocrystalline anisotropy energy* that is the energy which magnetizes a material in directions other than the favorable “easy axis.” The other type is *magnetoelastic anisotropy energy* that is the energy needed due to magnetostriction, the energy for overcoming the mechanical stresses due to the change of the orientation of the molecule in the process of magnetization.

In the presence of an external field \( \mathbf{H} \), the favorable direction of magnetization is along \( \mathbf{H} \) and the magnetization of the material can be increased by the displacement or rotation of the domain walls. The material is so-called magnetized. Typically in the presence of a weak external magnetic field, the increase in the magnetization of the material is due to the displacement of boundaries, as can be seen in Figure 3.8b, c. In the case of a strong magnetic field, the increase is mostly due to the rotation of the domain and aligning along the favorable direction of the external magnetic field (Figure 3.8c). With an external magnetic field, the domain walls are orientated and the domains are aligned, producing a magnetic field. The new orientations of the domain walls and the domains are pinned and not easy to be re-orientated when the external magnetic field is removed. This is the reason that when a piece of ferromagnetic material is magnetized, it becomes a permanent magnet.

Going back to the periodic table in Figure 3.2, only three pure elements Fe, Co, and Ni are examples of ferromagnetic materials at room temperature, and all other ferromagnets are their products, alloys, and combinations. When these materials are heated up, the ordered domain structure is destroyed and they become paramagnetic. The temperature at which such transition occurs is called the Curie temperature, \( T_c \). Different materials have different Curie temperatures (Fe: \( T_c = 770^\circ\text{C} \), Co: \( T_c = 1131^\circ\text{C} \), Ni: \( T_c = 358^\circ\text{C} \)). There is a more general law of magnetic susceptibility temperature behavior called the Curie–Weiss law, which is valid for ferromagnetic materials in the paramagnetic state,

\[
\chi = \frac{C}{T - T_c}
\]  

(3.8)

This law is only valid for behavior of a ferromagnetic material above Curie temperature when it is paramagnetic and disordered. Below the Curie temperature the ferromagnetic material is ordered into domains. This magnetic ordering temperature is another key feature of ferromagnetic materials.

Moreover, when the size of a ferromagnetic material is very small, for example, a ferromagnetic nanoparticle (NP), ferromagnetism in the material becomes superparamagnetism. In superparamagnetic NPs, magnetization can randomly flip direction under the influence of temperature. Superparamagnetic NPs are one of the important types of NPs applied for CAs for MRI enhancement. More physics on superparamagnetic particles and their application for MRI enhancement are detailed in Section 3.4.6.

The phenomenological approach of classifying materials gives a general idea about different types of magnetic behavior but does not explain the physical mechanisms
of the phenomenon. Moreover, there are cases where it is not possible to fit materials to one of the three classes. For this reason, people typically recognize two more forms of magnetism: antiferromagnetism and ferrimagnetism.

### 3.1.4 Antiferromagnetism

Antiferromagnetic materials have properties of both ferro- and paramagnets. Antiferromagnets are similar to ferromagnetic materials in the way magnetic moments are organized: they are also magnetically ordered. However, unlike ferromagnets, in antiferromagnets all magnetic moments are aligned antiparallel to each other, as shown in Figure 3.9, resulting in a zero net magnetic moment like in paramagnets. This complex form of magnetic ordering occurs due to the specific crystal structure. Magnetic oxides are well-known antiferromagnets and they are composed of two interpenetrating and identical magnetic sublattices, typically called sublattice A and sublattice B. The interaction between spins in this system leads to the antiparallel spontaneous magnetization of these two sublattices.

To better understand the origin of this antiparallel alignment of magnetic moments, we consider MnO as an example below. As shown in Figure 3.10, the crystal structure consists of linear chains of $\text{Mn}^{2+}$ and $\text{O}^{2-}$ ions. Due to the fact that all 3rd orbitals of $\text{Mn}^{2+}$ are occupied with spin-up electrons, the only way of covalent bonding with $\text{O}^{2-}$ is by donating the spin-down electron of $\text{O}^{2-}$ to $\text{Mn}^{2+}$. In this case, a spin-up electron of oxygen is left behind. It can be donated to another $\text{Mn}^{2+}$ ion in the chain where this ion must have all spin-down electrons on the 3rd orbital. Such
type of indirect interaction (mediated by oxygen in this particular case) is called super-exchange interaction.

Like all ferromagnets, antiferromagnets also have the Curie–Weiss dependence but only above a certain critical temperature of magnetic ordering, called the Néel temperature ($T_N$). Figure 3.11a shows the susceptibility of antiferromagnetic materials versus temperature. Above the Néel temperature, an antiferromagnet becomes paramagnetic with randomly oriented magnetic moments and follows the Curie–Weiss law of the following form:

$$\chi = \frac{C}{T + T_N}$$

Figure 3.11b shows the spontaneous magnetization of sublattices A and B below $T_N$. As shown in Figure 3.11b, below the Néel temperature, the sublattices (A and B) have spontaneous magnetizations of the same amount but in opposite directions and thus cancel each other resulting in zero net magnetic moments of the bulk material. The small and positive susceptibility decreases with decreasing temperature. This enables antiferromagnets to respond to an external field in the same manner as paramagnets, and in the meantime, the magnets have a microscopic structure similar to that of ferromagnets.

In their paramagnetic state, antiferromagnets do not have a wide range of applications like ferromagnets. This is because of the absence of spontaneous magnetization. However, they can be a good toy system where theoretical models of more complex ferrimagnets can be tested. The only antiferromagnetic element at room temperature is chromium with the Néel temperature of 37°C.

### 3.1.5 Ferrimagnetism

Ferrimagnets are similar to both ferromagnets and antiferromagnets. They have a spontaneous magnetization below a certain temperature, even in the absence of
an external magnetic field, like ferromagnets. At the same time, in terms of magnetic ordering, they are related to antiferromagnets because of the super-exchange mechanism of coupling. This type of coupling exists in both ferrimagnetic and antiferromagnetic materials. Therefore, these two types of magnetic material are both composed of two sublattices which are antiparallelly aligned. Unlike antiferromagnetic materials, the magnetizations of the sublattices in a ferrimagnetic material are not identical in magnitude (Figure 3.12, cf. Figure 3.9). Therefore, they do not cancel each other resulting in the existence of a nonzero spontaneous net magnetization like that in ferromagnets. Figure 3.12 shows the spin arrangement in ferrimagnetic materials. In ferrimagnetic materials, the magnetizations of the sublattices are not identical and they do not necessarily vary monotonically with temperature, making the net magnetization behavior complicated. Figure 3.13a and b show the magnetization versus temperature curves of NiO–Cr₂O₃ and Li₀.₅Fe₁.₂₅Cr₁.₂₅O₄. In the case of the Li₀.₅Fe₁.₂₅Cr₁.₂₅O₄ compound as shown in Figure 3.13b, the net spontaneous magnetization decreases to zero even before the critical temperature, and changes to

![Figure 3.12](image-url)  
**Figure 3.12** Spin arrangement in a ferrimagnetic material.

![Figure 3.13](image-url)  
**Figure 3.13** Magnetization curves of A and B sublattices (dotted lines) and the net magnetization (solid line) in two different ferrimagnets (a) NiO–Cr₂O₃ and (b) Li₀.₅Fe₁.₂₅Cr₁.₂₅O₄.
the opposite direction. The temperature at which the magnetizations are exactly balanced is called the compensation point. There are structures which have more than two magnetic sublattices and the magnetization behavior there is even more complex with multiple compensation points.

The applications of ferro- and ferrimagnetic materials have a long history. The term ferromagnetism comes from the most common material which exhibits this property, iron (ferrum in Latin). Ferrimagnetism, in turn, originates from the name ferrites, compounds which demonstrate ferrimagnetic behavior. Ferrites are ferromagnetic transition-metal oxides that have been used for centuries. The very first magnetic material which was used for navigation compasses is lodestone and it contains a magnetic mineral, magnetite, which is ferrite. They are now widely used in high-frequency applications due to their high saturation magnetization and low electrical conductivity. Moreover, with the advancement in processing techniques, such as the ceramic processing technique, ferrites can be produced readily with precisely tuned properties for specific applications.

3.2 WORKING PRINCIPLES OF NMR AND MRI

The history of NMR and MRI dates back to the end of the eighteenth century. In 1895, Roentgen discovered the x-ray which enables the visualizing of the interior of the human body without surgical intervention. Today, besides NMR, there are different medical imaging modalities including x-ray radiography, x-ray computerized tomography (CT), ultrasound, and nuclear medicine. Imaging based on NMR is called MRI for short. In chemistry and physics communities, magnetic resonance is usually referred to as NMR while in the imaging community, the world “nuclear” is omitted because of the concerns of public relations.

NMR was discovered in 1946 by Felix Bloch [1] and Edward Purcell [2] independently. The two physicists shared the 1952 Nobel Prize in physics for “their development of new ways and methods for nuclear magnetic precision measurements.” In 1973, Paul Lauterbur reported the first MR image [3] using gradient fields in Nature. Table 3.2 shows the scientific contributions to MRI before the first image was reported. In the 1970s, most of the work was done in academia. In the 1980s, industry joined in and accelerated the development. As a result, the image quality has been improved dramatically, and MRI and MRI systems have become popular worldwide.

Compared to other modalities, MRI provides advantages of good contrast especially soft tissue contrast, non-invasiveness, no ionizing radiation, and arbitrary scan planes. Figure 3.14 shows MRI images of a human head. Sagittal, coronal, and axial refer to the slice orientation as illustrated. The MRI images in Figure 3.14 are acquired in a 3 T MRI scanner. As shown in the figure, anatomical details can be seen using MRI. More details can be seen with an increase in the main magnetic field of an MRI system, which motivates the research and development of MRI to increase the field to 4 T, 7 T, and so on. Besides anatomical imaging, metabolic information is available with MR, which enables noninvasive in vivo physiological studies. Next, the basic physics and imaging methods of MR will be introduced for the purpose of understanding the nature of the MR phenomenon and the imaging modalities.
**TABLE 3.2**
Scientific Contributions to MRI before the First MRI Image

<table>
<thead>
<tr>
<th>Year</th>
<th>Contributor</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1952</td>
<td>Herman Carr (Harvard University)</td>
<td>Produced 1D MRI image</td>
</tr>
<tr>
<td>1960</td>
<td>Vladislav Ivanov (Soviet Union)</td>
<td>Filed a document for a MRI device (USSR State Committee for Inventions and Discovery at Leningrad)</td>
</tr>
<tr>
<td>1970</td>
<td>Peter Mansfield (University of Nottingham)</td>
<td>Developed a mathematical technique that would allow scans to take seconds rather than hours and produce clearer images than Lauterbur had</td>
</tr>
<tr>
<td>1971</td>
<td>Raymond Damadian (State University of New York)</td>
<td>Reported tumors and normal tissue can be distinguished <em>in vivo</em> by NMR; this method is not effective and not practical</td>
</tr>
<tr>
<td>1972</td>
<td>Raymond Damadian</td>
<td>Created the world’s first MRI machine and filed a patent</td>
</tr>
<tr>
<td>1973</td>
<td>Paul Lauterbur (State University of New York)</td>
<td>Expended Carr’s technique and generated and published the first NMR 2D and 3D images (using gradients)</td>
</tr>
</tbody>
</table>

**FIGURE 3.14** MRI images of a human head. (a) Sagittal, (b) coronal, and (c) axial refer to the slice orientation as illustrated.
3.2.1 Spins

Atoms with an odd number of protons and/or odd number of neutrons possess nonzero nuclear spin angular momentum. A nonzero spin is associated with a nonzero magnetic moment and exhibits an MR phenomenon. In biological specimens, hydrogen (^1H) that has a single proton is the most abundant and the most sensitive. For imaging, polarizations, precession, and relaxations of spins take place, and signals are acquired and processed to construct an image. For the aforementioned processes to take place, three kinds of magnetic fields are needed, namely the main magnetic field ($B_0$), radiofrequency (RF) magnetic field ($B_1$), and linear gradient field ($G$). Figure 3.15 shows a cutaway view of a traditional MRI scanner with a patient lying in the bore. As shown in Figure 3.15, superconducting magnets, RF coils, and gradient coils are the hardware generating $B_0$, $B_1$, and $G$, respectively.

3.2.2 $B_0$ and Polarization of Spins

The main magnetic field, $B_0$, is applied for polarization of spins. As shown in Figure 3.16, in the absence of an external magnetic field, the spins are randomly oriented and there is no net magnetic moment macroscopically. When $B_0$ is applied along the $z$-direction, the spins are aligned and a net magnetic moment is created. This process is called polarization. Moreover, the nuclear spins exhibit resonance at a defined frequency called Larmor frequency, $\omega$. The Larmor frequency is linked to $B_0$ in the way below,

$$\omega = \gamma B_0$$  \hfill (3.10)
or alternatively

\[ f = \frac{\gamma}{2\pi} B_0 \]  

(3.11)

where \( \gamma \) is called gyromagnetic ratio which is the ratio of the magnetic dipole moment to the angular momentum of a particle, such as an atom, or a system (SI unit: \( \text{rad} \cdot \text{s}^{-1} \cdot \text{T}^{-1} \)). Different atoms have different gyromagnetic ratios. For \(^1\text{H} \), \( \gamma/2\pi = 42.58 \text{ MHz/T} \). Therefore, for a system with \( B_0 = 1 \text{ T} \), its Larmor frequency is 42.58 MHz.

The resonant frequency is in the RF frequency range at which RF signals are transmitted and received for imaging. \( B_0 \) is required to be homogeneous for imaging using the gradient field that will be introduced shortly. The homogeneity of fields is calculated using Equation 3.12 or Equation 3.13 that follows in parts per million (ppm). The main magnetic field in a MRI scanner in the hospital is generated by superconducting magnets.

\[
\text{Homogeneity} = \sum_i^n \frac{|B_i - B|}{B} \times 10^6
\]  

(3.12)

where \( B_i \) is the magnitude of the magnetic field on the \( i \)th node in the region of interest, \( B \) is that of the magnetic field at the center of the region, and \( n \) is the total number of nodes in the region.

\[
\text{Homogeneity} = \frac{B_{\max} - B_{\min}}{\bar{B}} \times 10^6
\]  

(3.13)

\( B_{\max} \) and \( B_{\min} \) are the maximum and minimum field in the region of interest, and \( \bar{B} \) is the average field in the region.
3.2.3 $B_1$ and Precession

The RF magnetic field, $B_1$, is the magnetic field of the RF signal that is tuned at Larmor frequency in an MRI system for imaging. Unlike $B_0$ that is applied in the $z$-direction, $B_1$ is applied on the $xy$-plane to excite the spins out of their equilibrium along the $z$-direction, as shown in Figure 3.17. In Figure 3.17, the spin is represented using its magnetization vector by a gray arrowed line. $B_1$-field is generated by RF coils around the bore. It applies a torque which rotates the spins by a prescribed angle dependent on the strength of $B_1$ and its duration. In a clinical scanner, the strength of $B_1$ is typically a small fraction of a Gauss and its duration is normally a few milliseconds. There are two ways to describe the behaviors of the spins when they are exposed to both $B_0$ and $B_1$, one using the laboratory frame shown in Figure 3.17a and b, the other one using a frame rotating at the Larmor frequency about the $z$-axis, as shown in Figure 3.17c. As shown in Figure 3.17a, when using a laboratory frame, the magnetization vector is tipped to the $xy$-plane following a conical spiral trajectory whereas in the rotating frame shown in Figure 3.17c, the spin is tipped with a trajectory on a plane that is perpendicular to the $xy$-plane. Figure 3.17b shows a top view of the precession in the laboratory frame.

**FIGURE 3.17** Effect of $B_1$ field. (a) 3D view of a spin in a laboratory frame; (b) top view of a spin in a laboratory frame; and (c) 3D view of a spin in a rotating frame.
3.2.4 Relaxation

For a 90-degree excitation, the spins can be excited and tipped to the \( xy \)-plane by \( B_1 \) generated by RF coils. When the excitation is turned off, relaxation of the spins back to the equilibrium occurs. During the relaxation, the magnitude of the magnetization of the spins which is the length of the magnetization vector does not remain constant over time. The \( z \)-component of the magnetization vector (\(|M_z|\)) increases while the component of the vector on the \( xy \)-plane (\(|M_{xy}|\)) decreases. Figure 3.18 shows the changes of the different components over time. There are two time constants characterizing the relaxation of the spins, \( T_1 \) and \( T_2 \). \( T_1 \) is called the longitu-
dinal recovery time constant and characterizes the recovery of the magnetization vector along the \( z \)-axis and \( T_2 \) is called the transverse decay time constant and characterizes the decay of the vector components on the \( xy \)-plane. \( T_1 \) is determined by the thermal interactions between the resonating protons and other protons and other magnetic nuclei in the magnetic environment called “lattice.” \( T_2 \)-decay is due to magnetic interactions that occur between spinning protons. \( T_2 \)-interactions do not involve a transfer of energy but only a change in phase, which leads to a loss of coherence between different spins. In humans, \( T_1 \) values of most tissues range from 100 to 1500 ms whereas \( T_2 \) values range from 20 to 300 ms. Relaxation time constants have distinct values for different tissues. They are important MR parameters for creating a tissue contrast. Images using \( T_1 \)- and \( T_2 \)-relaxation contrasts are called \( T_1 \)- and \( T_2 \)-insert spaceweighted images, respectively. \( T_1 \)- and \( T_2 \)-weighted images are where MNPs are applied for the enhancement of contrast. The details are presented in Section 3.4.

When the excitation is turned off and relaxation takes place, the rotating magnetization vectors on the \( xy \)-plane induce electromotive force (EMF) in an RF receiver coil oriented to detect the change of the magnetization on the \( xy \)-plane. Figure 3.19 shows a schematic diagram for RF receiver coils for signal detections. The receiver coil can be a transmission coil that is switched to a receive mode. Alternatively, it can be a separate RF coil only for receiving. The generated time signal is called free induction decay (FID). Figure 3.20 (3rd row) shows examples of FIDs. To construct an MRI image, a set of FIDs are recorded and processed.

![Figure 3.18](image_url)  
*FIGURE 3.18  Relaxation of a spin: (a) longitudinal relaxation characterized by time constant \( T_1 \) and (b) transverse relaxation characterized by time constant \( T_2 \).*
For an MRI scan, if the subject under scan is exposed to a homogeneous magnetic field, all spins possess the same resonant frequency. The transmit/receiver RF coil encompasses the whole region of interest. If only $B_0$ exists, it is impossible to excite a certain portion of the volume or distinguish the signals from different spatial locations. Linear gradient field ($G$) is added for spatial localization. Taking
the gradient in the x-direction ($G_x$), for example, the gradient field that is applied to the region under imaging is $G_x = G_x \hat{z}$. This equation means first, the gradient field is in the z-direction and second, its magnitude depends on the locations along the x-direction. Therefore, the total field at a location is $(B_0 + G_x x) \hat{z}$ which is in the z-direction as well. Based on Equation 3.10, the frequency of spins becomes a function of location in the x-direction, $\omega(x) = \gamma(B_0 + G_x x) = \omega_0 + \gamma G_x x$. Therefore, if the dimension of the region under imaging along the x-direction is $\Delta x$, the FID contains signals spanning over a frequency range of $\Delta \omega(\Delta x)$. For example, if $G_x = 1 \text{ G/cm}$, then for an object 5 cm wide in the x-direction, the frequency bandwidth is 21.26 kHz. On a whole body system, the gradient field strength is usually less than 1 Gauss/cm (10 mT/m).

The columns of Figure 3.20 show a comparison of imaging without and with gradient fields along the x-direction, respectively. The FID contains signal of a single frequency for the case without a gradient field, which can be seen clearly in the frequency domain after performing the Fourier transform. On the other hand, with a gradient field, the FID contains signals over a frequency band. After performing the Fourier transform, the signals in the frequency domain show the contributions from each frequency component which can be linearly mapped to a particular location along the x-direction because of the aforementioned way the gradient field is applied along the x-direction.

### 3.2.6 BLOCH EQUATION

The behavior of the magnetization vector $M$ is described by an empirical equation, the Bloch equation as shown below

$$\frac{dM}{dt} = M \times \gamma B - \frac{M_y x + M_z y}{T_2} - \frac{(M_z - M_0)z}{T_1}$$

(3.14)

where $M_0$ is the equilibrium magnetization arising from the main field, $B_0$, and $B$ includes $B_0$, $B_1$, and $G$.

If $B$ is static and homogeneous, $B = B_0 \hat{z}$, the solution for Equation 3.14 is as follows:

$$M(t) = \begin{bmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{bmatrix} = \begin{bmatrix} e^{-t/T_2} & 0 & 0 \\ 0 & e^{-t/T_2} & 0 \\ 0 & 0 & e^{-t/T_2} \end{bmatrix} \begin{bmatrix} \cos(\omega_0 t) & \sin(\omega_0 t) & 0 \\ -\sin(\omega_0 t) & \cos(\omega_0 t) & 0 \\ 0 & 0 & 1 \end{bmatrix} M^0$$

$$+ \begin{bmatrix} 0 \\ 0 \\ M_0(1 - e^{-t/T_1}) \end{bmatrix}$$

(3.15)

The x- and y-components of $M$ contain a factor of $e^{-t/T_2}$ which indicate the decay of the precessing magnetization in the $xy$-plane with a time constant $T_2$. The columns of Figure 3.20 show a comparison of imaging without and with gradient fields along the x-direction, respectively. The FID contains signal of a single frequency for the case without a gradient field, which can be seen clearly in the frequency domain after performing the Fourier transform. On the other hand, with a gradient field, the FID contains signals over a frequency band. After performing the Fourier transform, the signals in the frequency domain show the contributions from each frequency component which can be linearly mapped to a particular location along the x-direction because of the aforementioned way the gradient field is applied along the x-direction.
Simultaneously, there is a return to the equilibrium along the $z$-direction at a time constant of $T_1$. Equation 3.15 is a mathematical expression for relaxation.

When $B$ changes with time and gradient fields are applied, $B(r,t) = [B_0 + G(t) \cdot r]z$ the solution for the transverse magnetic field $(M = M_x + iM_y)$ is

$$M(r,t) = M^0(r)e^{-t/T_2(r)}e^{-i\omega t}\exp\left(-i\gamma \int_0^t G(\tau) \cdot r d\tau \right)$$  \hspace{1cm} (3.16)

### 3.2.7 SIGNAL AND MR IMAGING

The received time signal $s_r(t)$ is calculated based on the contributions of all processing transverse magnetization in the volume. It is written as follows:

$$s_r(t) = \int_{\text{vol}} M(r,t) dV$$  \hspace{1cm} (3.17)

Based on Equations 3.16 and 3.17, the expression for the signal can be written as follows:

$$s_r(t) = \iiint M^0(x,y,z)e^{-t/T_2(r)}e^{-i\omega t}\exp\left(-i\gamma \int_0^t G(\tau) \cdot r d\tau \right) dx dy dz$$  \hspace{1cm} (3.18)

For a 2D image, we are interested in imaging based on the integral over the slide centered at $z_0$ with a width of $\Delta z$. Therefore,

$$m(x,y) \equiv \int_{z_0-\Delta z/2}^{z_0+\Delta z/2} M^0(x,y,z) dz$$  \hspace{1cm} (3.19)

and when the relaxation term $e^{-t/T_2}$ is ignored

$$s_r(t) = \iiint m(x,y) e^{-i\omega t}\exp\left(-i\gamma \int_0^t G(\tau) \cdot r d\tau \right) dx dy$$  \hspace{1cm} (3.20)

Furthermore, to drop the factor $e^{-10\omega t}$, let

$$s(t) = s_r(t)e^{+i\omega t} = \iiint m(x,y)\exp\left(-i\gamma \int_0^t G(\tau) \cdot r d\tau \right) dx dy$$  \hspace{1cm} (3.21)

As can be seen in Equation 3.21, $s(t)$ provides information about $m(x, y)$, the transverse magnetization of interest. $m(x, y)$ is a function of the NMR parameters $\rho(x, y)$ (density), $T_1(x, y)$, and $T_2(x, y)$ which is the so-called image in MRI. If the spatial
localization is required only in the $x$- and the $y$-direction, Equation 3.21 can be further simplified as follows:

$$s(t) = \iiint m(x,y)\exp\left[-i\gamma\left(\int_0^t G_x(\tau)d\tau\right)x\right]\exp\left[-i\gamma\left(\int_0^t G_y(\tau)d\tau\right)y\right]dxdy$$ (3.22)

or

$$s(t) = \iiint m(x,y)e^{-i2\pi[k_x(t)x+k_y(t)y]}dxdy$$ (3.23)

where

$$k_x(t) = \frac{\gamma}{2\pi}\int_0^t G_x(\tau)d\tau \quad \text{and} \quad k_y(t) = \frac{\gamma}{2\pi}\int_0^t G_y(\tau)d\tau$$

Equation 3.23 is the signal equation stating the relation between the baseband signal $s(t)$ and the magnetization $m(x, y)$. The signal is a surface integration of the magnetization multiplied by a spatially dependent phase factor. The phase factor is linearly dependent on the spatial position when linear gradient fields are applied. In Equation 3.23, $s(t)$ is the 2D Fourier transform of $m(x, y)$, which can be expressed mathematically as

$$s(t) = M[k_x(t),k_y(t)]$$

With $k_x$ and $k_y$ as variables in the 2D Fourier transform space, the Fourier transform space is called the $k$-space. Based on Equation 3.23, imaging can be realized by acquiring a set of $\{s(t)\}$ in the $k$-space and applying the Fourier transform to the data. Figure 3.21 shows raw data in the $k$-space and the corresponding image in the physical domain before and after the Fourier transform, respectively.

### 3.3 Magnetic Materials Used to Supply the Main Magnetic Field in MRI

As shown in Figure 3.15 earlier, an MRI scan needs a main magnetic field, $B_0$. For imaging using gradient fields, $B_0$ is required to be homogeneous. For a human scanner, it is popular to use superconducting magnets for generating homogeneous $B_0$ over a volume that hosts human parts or a human body. Alternatively, $B_0$ can be generated using permanent magnets. This is the first application of magnetic materials for MRI. Normally, a scanner using permanent magnets and gradient fields has a small imaging volume, for example, a diameter of a few centimeters. For a human scanner, it requires a large chunk of permanent magnets that can have a weight of a few hundreds of tons. A magnet array can possibly supply $B_0$ with an increased image volume. However, the homogeneity is difficult to achieve. This problem has
recently been overcome by applying nonlinear imaging methods. In this session, we will review key aspects of permanent magnets that are associated with the application for MR imaging. Moreover, recent work on using permanent magnets to supply $B_0$ for imaging is presented.

### 3.3.1 Permanent Magnets

A magnet is a material or object that produces a magnetic field. A permanent magnet is an object made from a material that is magnetized and creates its own persistent magnetic field even in the absence of an applied magnetic field. It is made of ferromagnetic or ferrimagnetic materials. As we have introduced earlier in Sections 3.1.3 and 3.1.5, these two types of magnetic materials show spontaneous magnetizations, the magnetizations without an external magnetic field below Curie temperature. Examples of such kinds of materials are iron, nickel, cobalt, and alloys of rare-earth metals.

There are different types of permanent magnets. One type is naturally occurring ferromagnets, such as magnetite (or lodestone), nickel, cobalt, and rare-earth metals such as gadolinium and dysprosium (at a very low temperature due to their low Curie temperatures). They are used in the early experiments with magnetism. With the advance of technology, composites based on natural magnetic materials are produced, with improved magnetic field strength and mechanical properties. They are the second type of permanent magnets. The magnet field strength of this type of magnet can reach 1 T. One example is ceramic magnets that are made of the sintered composite of powdered iron oxide and barium/strontium carbonate ceramic.
They are inexpensive and can be easily mass produced. They are noncorroding but brittle. There are other examples such as injection-molded magnets which are the composite of various types of resin and magnetic powders, alnico magnets that are made by casting or sintering a combination of aluminum, nickel, and cobalt with iron and a small amount of other elements. Another example is flexible magnets that are composed of a high-coercivity ferromagnetic compound mixed with a plastic binder.

The third type is rare-earth magnets. Rare-earth magnets are the strongest type of permanent magnets made from the alloy of rare-earth elements that are the 15 metallic chemical elements with atomic numbers from 57 to 71 (as shown in Figure 3.2) and are ferromagnetic. Their magnetic field can exceed 1 T. The high magnetic field comes from the rare-earth elements (e.g., scandium, 21Sc, yttrium, 39Y) that have atoms that retain high magnetic moments in the solid state, which is a consequence of incomplete filling of the f-shell allowing up to seven unpaired electrons with aligned spins. The rare-earth elements show low Curie temperature above which the material loses magnetism. However, when they form compounds with transition metals (e.g., iron, nickel, and cobalt), the Curie temperatures of the compounds increase to higher than room temperature. There are mainly two types of rare-earth magnets, neodymium (Nd$_2$Fe$_{14}$B) and samarium (SmCo$_5$). Table 3.3 shows their magnetic properties. As introduced previously, remanence ($B_r$) measures the strength of the magnetic field, coercivity ($H_c$) is the resistance of the material to becoming demagnetized, energy product ($BH_{max}$) is the density of magnetic energy; and $T_c$ is Curie temperature. To supply the main magnetic field for MRI, high-field strength is preferred because it results in high signal-to-noise ratio (SNR) thus improving image quality. Rare-earth magnets have relatively high magnetic field strength, therefore they are widely used to supply $B_0$ for MRI.

### 3.3.2 Using Permanent Magnets to Generate Main Magnetic Field for Imaging

Multiple MRI systems are built using permanent magnets to provide $B_0$ field. Field homogeneity, image volume, and weight are crucial parameters for evaluate a magnet/magnet system. There are mainly two categories of a magnet system, those using the magnetic field between two poles and those using a magnet array.

#### 3.3.2.1 Magnet System Using the Magnetic Field between Two Poles

Within this category, the C-shaped permanent magnet (Texas A&M University, 1997) [4–6] is well known. The C-shaped permanent magnet was proposed in Reference 4.
detailed in Reference 5, and used in a desktop MRI imaging system in Reference 6. It provides a magnetic field of 0.21 T with homogeneity of 20 ppm within a cylindrical region of 0.5 in. in diameter times 0.75 in. in length.

Figure 3.22a and b shows a photo and the cross-sectional view (with dimensions) of the C-shaped magnet, respectively. As shown in Figure 3.22b, the C-shaped magnet consists of a rectangular C-arm connecting two iron necks, two NdFeB poles, and two round-shaped pole faces with an air gap in between. The size of the air gap is 7 in. × 4 in. Both the poles and the necks are cylindrical, the pole has a diameter of 7 in. and the necks are tapered from a diameter of 7 in. to one of 4 in. The tapered diameter of the neck at the junction to the C-arm is to reduce the iron volume, and,
in turn, to reduce the overall weight of the system. Both the dimensions of the neck and the C-arm are optimized so that the iron does not saturate and the reluctance does not increase dramatically. Pole faces are designed to re-focus magnetic field lines toward the C-gap.

The magnet poles were constructed using 330 pieces of NdFeB material in $1 \times 1 \times 0.5$ in. blocks. Each block is numbered, and the energy is measured. The magnets are stacked in groups of three in order to minimize energy variation. This resulted in several groups of magnetization energy, which are placed symmetrically around the pole pieces. The pole pieces are designed using numerical solutions, the 2D Pandira code from Los Alamos National Lab. Shimming is achieved by adjustment of the pole pieces and with four electrical shim coils. 20 ppm in homogeneity at 0.21 T from a cylindrical phantom 0.75 in. long by 0.5 in. in diameter is achieved.

Another example is the magnet built by the Institute of Electrical Engineering of the Chinese Academy of Sciences in Beijing [7]. Figure 3.23a and b shows the photo and the cross-sectional view of the magnet, respectively. The field strength is 0.19 T and the weight is 13 kg. As shown in Figure 3.23b, two iron pole faces, two rare-earth magnets, and an iron case form a magnetic circuit allowing the flow of the magnetic flux. The image volume is between the two pole faces. The distance between the pole faces is 4 cm and the homogeneity is about 50 ppm over 1 cm diameter of spherical volume (DSV). It is used in a tabletop MRI scanner developed in the Martinos Center for Biomedical Imaging, Massachusetts General Hospital [8].

3.3.2.2 Magnet Array
Within the category of magnet array, the Halbach array, especially the Halbach cylinder, is popular in the application for MRI.

3.3.2.2.1 Halbach Cylinder
The Halbach cylinder used widely in MRI is the one that provides a magnetic field pointing in the same direction, as shown in Figure 3.24a. Figure 3.24b shows the directions of the magnetization of the magnets forming the array. As shown in Figure 3.24b, the $i$th magnet is placed on a circle at an angle $\alpha_i = \frac{2\pi i}{n}$ and its magnetization is defined by an angle $\beta_i$ where $\beta_i = 2\alpha_i$, $i = 0, 1, 2, \ldots n - 1$, and $n$ is the number of magnets.

Ideally, the magnetic field inside the cylinder is uniform when the cylinder is infinitely long and the magnetization varies continuously. However, in reality, the length is finite, which introduces nonuniformity at two ends (called end effects). Moreover, continuously varying magnetization is not practical and is implemented by magnet blocks with rotated magnetization. This leads to inhomogeneity of the field inside the bore. For the application to MRI, homogeneity of the magnetic field is required in a desired volume. To eliminate the inhomogeneity, there are different shimming methods proposed in the literature.

In Reference 9, two strategies are applied for magnetic shimming. First, as shown in Figure 3.25a, the magnet bars are split into two parts with a gap in the longitudinal direction ($z$-direction) in order to increase the homogeneity in that direction. Figure 3.26 shows the simulated field profiles at different gap sizes ($\text{eps}$). As shown
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**FIGURE 3.23** Magnet built by the Institute of Electrical Engineering of the Chinese Academy of Sciences in Beijing. (a) Photo and (b) side view. (Adapted from Martinos Center for Biomedical Imaging, Massachusetts General Hospital. Available: http://iee.ac.cn/Website/index.php?ChannelID=2195.)

**FIGURE 3.24** Halbach cylinder. (a) Side view and (b) labeled side view.
in Figure 3.26, the homogeneity of field changes considerably with the change of the gap size. Figure 3.27 shows the volume with a field homogeneity of less than 100 ppm, based on Equation 3.13 versus the gap size. The optimal gap size is 0.77 mm where the homogeneous volume is 2640 mm³. The second strategy is using shimming array inside the Halbach array as shown in Figure 3.25b. The radius of the shimming ring array \( r_l \) and their location \( d_H \) are optimized for field homogeneity. The homogeneity is improved with the shimming arrays [9].

Shimming the magnetic field using inner magnet rings in a Halbach array is applied to magnet arrays in different portable MRI systems [10,11]. Figure 3.28 shows the 3D and the side view of the Halbach array presented in Reference 11, two cube arrays are inserted inside the Halbach array for eliminating the end effect. The location of the cube arrays is studied in Reference 11. If the location of the cube array is defined by \( D \) as shown in Figure 3.28b, the bandwidth of the resonance increases as \( D \) increases, as can be seen from Figure 3.29a, which is the result of an increase in field inhomogeneity. Besides shimming, the cube arrays inside the cylinder increase the average magnetic field strength of the magnet array. Figure 3.29b shows the
simulated magnetic field profiles (Bxy) of the magnet array with and without the shimming cube arrays.

3.3.2.2.2 Other Magnet Arrays

There are other magnet arrays proposed for generating $B_0$ for MRI/NMR. The array shown in Figure 3.30 is an example. It was invented by G. Aubert in 1991. As shown in Figure 3.30, two magnet arrays with the designed magnetization arranged a distance apart generate homogeneous magnetic fields along the z-direction. The volume where the field is homogeneous is affected by the discretization of the rings [12].

Using permanent magnets to generate $B_0$ for MR imaging is a low-cost approach compared to using superconducting magnets. However, this approach is limited by low magnetic field strength (thus low SNR), inhomogeneity or small imaging volume if the field is relatively homogeneous, and heavy for those magnet systems used for imaging humans. The advancement of nonlinear signal reconstruction recently relaxed the requirement on field homogeneity and thus, a less bulky permanent magnet array for imaging human or human parts becomes possible [10]. More developments along this direction can be expected in the near future for low cost and portable MRI systems.

FIGURE 3.26  Field profile along z-direction with different gap sizes (eps). (a) eps = 0 mm, (b) eps = 0.5 mm, (c) eps = 0.9 mm, and (d) eps = 1.3 mm.
FIGURE 3.27  Image volume with a field homogeneity of less than 100 ppm versus gap size.

FIGURE 3.28  (a) 3D model and (b) the side view of the Halbach array. (Adapted from Z. H. Ren et al., RF and Wireless Technologies for Biomedical and Healthcare Applications (IMWS-BIO), IEEE MTT-S 2015 International Microwave Workshop Series on, pp. 92–95, Taiwan, 2015. © 2015 IEEE.)
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### 3.4 MRI CONTRAST ENHANCEMENT USING MNPs

Using MNPs for MRI contrast enhancement is another important application of magnetic materials for MRI. Paramagnetic NPs have been used for *in vitro* diagnostics as CAs in MRI for more than four decades [13]. The *in vivo* applications, however, require them to play a more challenging role. They have to be highly specific, efficient, small enough to be transported within the blood stream, and at the same time, they should be able to attach to cells or even enter a cell. In order to fulfill the requirements of contrast enhancement, the materials used must be magnetically active. Paramagnetic materials, like different lanthanide, iron-based...
or ion like (gadolinium, manganese, and dysprosium) compounds have unpaired electrons and thus a positive susceptibility [14]. The large magnetic moment of paramagnetic NPs creates large magnetic field heterogeneity and thus shortening the $T_1$ (MRI positive) or $T_2$ (MRI negative) relaxation times. Iron oxides are well known and widely used MRI negative CAs, while Gd-based materials are used as MRI positive CAs.

The challenge in their in vivo application rises from the following problems: (a) NP agglomeration (NPs tend to agglomerate due to their high surface/volume ratio), (b) short half-life of the particles in blood circulation (if NPs agglomerate or adsorb plasma proteins, they are taken up by the macrophages of the mononuclear phagocyte system and are eliminated from the bloodstream before they can reach the target cells), (c) low efficiency of the intracellular uptake of the NPs, and (d) nonspecific targeting [15,16].

The transport of the CAs is typically done by intravenous administration, which determines the maximum size of the NPs. The reason is that for a successful delivery of NPs, they have to pass through the vascular capillary wall. Gd-based complexes are typically less than 10 nm in diameter which makes it relatively easy to deliver them. Iron oxide-based complexes can be up to 100 nm and their delivery to the targeted tissue is more problematic. Depending on the size, charge, and coating these NPs are metabolized by the reticuloendothelial system (RES), which consist of macrophages and monocytes, and accumulate in the lymph nodes, spleen, and liver. Particles with the size larger than 50 nm are generally taken up by liver cells [17]. If they are not entirely captured by the liver and spleen, they might be used as markers for imaging of inflammatory and degenerative disorders (like plaque or brain ischemia) [18,19]. Smaller particles generally have a longer circulation time and tend to

![FIGURE 3.30 Aubert’s magnet array.](image-url)
accumulate in the cells of the lymphatic system and bone marrow. The control of the NPs’ size, charge, and configuration of the coating gives a possibility to enhance the contrast of the imaging of different parts of the body.

The macrophages in normal tissues and in tumor lesions react differently with the magnetic particles. In healthy tissues, the macrophages uptake the particles and thus darken the image, whereas tumor lesions do not uptake the particles, leaving the lesion tissue bright in the MRI image. This is the reason MNPs are widely used for tumor detections. Figure 3.31 demonstrates the importance of injecting CAs. As shown in Figure 3.31a, from the $T_1$-weighted image without any contrast, one can notice only a vague area of edema (swelling). In Figure 3.31b in the $T_2$-weighted image, the edema is much more prominent and shows up bright on the image. However, the best way to see the actual tumor is to look at a $T_1$-weighted image with a contrast as shown in Figure 3.31 where the cancer tissue is much more obvious.

The following sections will cover the history and physics of MNPs used in clinical practice, their classification and differences, advantages and disadvantages, as well as future perspectives.

### 3.4.1 History

MRI CAs have become an indispensable and routine part of modern MRI technology. Currently, about 35% of MRI images are done with the use of CAs, and this percentage is expected to grow further with the development of more effective and specific contrast media. Although MRI provides high-resolution soft tissue contrast by means of noninvasive unenhanced imaging, in many cases CAs offer additional diagnostic information, and improve sensitivity and/or specificity. For example, in many instances of brain metastasis, the properties of the tumorous tissues and the surrounding edema are very similar. The use of CAs helps to differentiate between them, which might be otherwise indistinguishable. Continuous development of MRI hardware and the emergence of nanotechnology in the 1990s have driven the creation of new contrast media designs and led to increased sensitivity and SNR of the MRI images.

From the perspective of the clinical application, MRI CAs can be divided into two groups. Those which shorten the $T_1$ and $T_2$ relaxation times are called MRI
positive and negative CAs, respectively. In terms of chemical composition and magnetic properties, there are two main classes of contrast media: they are paramagnetic and superparamagnetic agents.

Paramagnetic metals, which include gadolinium, were well known for their relaxation effect in in vitro MRI studies for a long time. However, these metals were toxic in their ionic forms which prevented them from being used in humans. In 1981, it was proposed that in order to create a safe agent, the metal ion should be tightly bound by a chelate. The presence of the ligand does not affect the paramagnetic property of gadolinium ion significantly, but the toxicity is limited by achieving rapid and total renal excretion. That is when the forefather of the gadolinium-based contrast agents (GBCAs), Gd^3+ diethylenetriamine pentaacetate (Gd-DTPA, Magnevist®), was first described. Soon after this, in 1983, the first report of an animal model study using Gd-DTPA as a CA was published. In 1988, Magnevist received U.S. FDA approval for clinical contrast-enhanced imaging of the central nervous system (CNS). Gadolinium chelates are now the major class of CAs used in MRI clinical practice, with the total number of nine FDA-approved GBCAs up to date.

CAs based on Gd-chelates primarily affect T1 relaxation rates, resulting in positive lesion enhancement. At very high concentrations, they also affect the T2 relaxation rate, although in most clinical situations, T2-weighted scans are not appreciable. Administration of the Gd-based contrast agents can significantly improve lesion identification and characterization. Within the CNS, lesion enhancement occurs as a result of the disruption of the blood–brain barrier (BBB). In the case of extra-axial abnormalities and lesions outside the CNS, contrast enhancement is seen in the differences in tissue vascularity.

The research and development of new Gd-based contrast agents have been focused on the improvement of tolerance, the physiochemical properties, and relaxivity. The key safety factors are thermodynamics, solubility, selectivity, and kinetics. The affinity of the chelate for the metal ion must be high, which is associated with the thermodynamic binding constant of the complex (K_{eq}). The CA must be sufficiently soluble in order to prevent potential toxicity of gadolinium ion precipitation. The chelate must have high selectivity for the Gd ion in order to prevent a potential metal exchange with other endogenous ion, such as zinc (Zn) and copper (Cu).

CAs with low osmolality and viscosity are excreted almost completely from the body with a normal renal function, thus allowing a faster administration at higher doses. Other modification steps of Gd-based contrast agents include the development of nonionic (neutral) compounds instead of ionic (charged) ones, and the evolution from linear chelates to macrocyclic chelates.

For a long time CAs that principally affect T2 relaxation rates have not received much attention. This is explained by the fact that originally T2-weighted scans required longer imaging time and in most clinical cases, changes on T2-images had generally little contribution to the diagnosis. However, now with the fast spin echo techniques, T2-scanning time is no longer the issue. One of the most studied groups of intravenous T2 CAs is the iron NP group.

Discoveries of new MNPs that shorten T2 relaxation time push the development of T2 CAs further. Polymer-coated iron oxide particles have a long history of clinical applications.
use. For example, in the 1960s they were used for iron deficiency and anemia treatments [20]. Dextran polysaccharide has been typically used as a polymer coating of the core iron oxide. The reason for this is its well-known antithrombotic, volume expanding properties, and its affinity for iron oxides. Later a new NP termed “dextran magnetite” was developed that exhibited a much stronger magnetism than the paramagnetic particles used for anemia. This unusually strong magnetic behavior was called superparamagnetism. It was soon found that superparamagnetic iron oxides (SPIONs) could shorten the water relaxation time and thus could be used as CAs for MRI. One of the first controlled and reliable demonstrations of the $T_2$ relaxation time shortening due to the presence of SPIONs particles was performed by Oghushi in 1978 with dextran-magnetite particles [21]. After this discovery and experiment, the field of magnetic particles for $T_2$-weighted MRI images has continuously been developing, resulting in a range of CAs now being approved and widely used in clinics.

The first generation of MRI negative CAs was polydisperse SPIO (with one, two, or more crystals per NP and a broad size range in solution). After an intravenous injection of SPIO NPs, they can be easily detected by macrophages of the RES of the body and transported to the liver and/or the spleen, because these organs are responsible for blood purification [22–24]. These materials darken normal, but not metastatic liver tissue at $T_2$-weighted images, and therefore serve as contrast enhancing agents to detect cancerous lesions.

Quite soon it was discovered that the decrease of NP size can extend the circulation time in blood. The reason is that smaller NPs cannot be detected by the RES and in this case macrophages of lymph nodes uptake the NPs. Therefore, smaller MNPs act as a CA for hepatic metastases lymph nodes imaging. The size reduction was achieved by using monodisperse NPs (with only one crystal per NP in solution) [25,26].

The next generations of MNPs for MRI have been modified considerably and achieved significant number of improvements since the first polymer-coated iron oxides. Now they are more sophisticated and can be molecularly targeted to a specific biomolecule via attached antibody, peptide, or polysaccharide; serve as a label for cell tracking; or can be combined with fluorescent components and thus give additional optical information. The aforementioned CAs change the $T_1$ or $T_2$ relaxation only, therefore they are also called single mode CAs. However, in modern diagnostics, single mode CAs are not always sufficient and there is a new quickly growing field of dual mode $T_1$–$T_2$ CAs [27,28]. MNPs have gone through years of technological improvement, and preclinical and clinical testing. It has given us a diverse range of applications by far. In the future, even more developments can be foreseen in various areas in biology and medicine.

### 3.4.2 Physics of MRI CAs

MRI is a noninvasive technique used in radiology, which provides information on local biology, anatomy, and physiology with high spatial resolution by detection of the signals coming from proton relaxation in an external magnetic field. With the help of MRI 3D images of different types of tissues can be seen. In principle, it is
possible to track the relaxation of different elements, and the reason proton relaxation is typically studied is because of the abundance of protons in the human body and because different tissues have high contrasts in terms of proton density. There are two independent relaxation processes going on during the proton recovery to its original state, namely $T_1$ and $T_2$ relaxations. $T_1$ is the time of magnetic moment $m$ recovery in the direction of the $B_0$ field, and $T_2$ is the time of the loss of the signal in the transverse plane. These $T_1$ and $T_2$ times strongly depend on the tissue type and its physical properties, resulting in high tissue contrast in MRI images. Therefore, MRI scanners are particularly useful at providing highly detailed information about soft tissues. $T_1$ and $T_2$ independently provide different information of images and each has its own advantages and disadvantages, and thus are used to better visualize different types of substances. Certain substances have their own magnetic moment and generate local magnetic field ($B_1$) that changes the speed of proton relaxation ($T_1$ or $T_2$) significantly and therefore leads to the brightening or darkening of the image. A CA that predominantly affects $T_1$ relaxation time by reducing it and thus increases signal intensity on a $T_1$-weighted image is called an MRI positive CA. On the other hand, a CA that predominantly affects $T_2$ relaxation time, reducing it and thus decreasing signal intensity on a $T_2$-weighted image is called an MRI negative CA.

Although a profound review of the relaxivity theory is beyond the scope of this chapter, a basic conceptual understanding will help to appreciate the physics involved in CA enhancement phenomena.

A magnetic moment created by unpaired electrons can interact with surrounding water protons either directly or indirectly via its local magnetic field influence, and thus enhance the $T_1$ or $T_2$ relaxation times. Therefore, only magnetic ions with exceptionally slowly relaxing unpaired electrons are effective as MRI CAs, because they give the most profound enhancement. The quantum theory says that the ions with the highest spin quantum number have the most slowly relaxing electrons. Examples of such ions are gadolinium ($\text{Gd}^{3+}$), iron ($\text{Fe}^{3+}$), dysprosium ($\text{Dy}^{3+}$), and manganese ($\text{Mn}^{3+}$), as shown in Figure 3.32. However, this theoretically desirable

<table>
<thead>
<tr>
<th>Ion</th>
<th>Configuration</th>
<th>Magnetic moment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition metal ion</td>
<td>$^{24}\text{Cr}^{3+}$</td>
<td>3.88</td>
</tr>
<tr>
<td></td>
<td>$^{25}\text{Mn}^{3+}$</td>
<td>5.92</td>
</tr>
<tr>
<td></td>
<td>$^{26}\text{Fe}^{3+}$</td>
<td>5.92</td>
</tr>
<tr>
<td></td>
<td>$^{29}\text{Cu}^{2+}$</td>
<td>1.73</td>
</tr>
<tr>
<td>Lanthanide metal ion</td>
<td>$^{63}\text{Eu}^{3+}$</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>$^{64}\text{Gd}^{3+}$</td>
<td>7.94</td>
</tr>
<tr>
<td></td>
<td>$^{66}\text{Dy}^{3+}$</td>
<td>10.65</td>
</tr>
</tbody>
</table>

**FIGURE 3.32** Configuration and magnetic moment of some of the paramagnetic ions. (Adapted from H. B. Na, I. C. Song, and T. Hyeon, *Adv Mater*, 21, 2009, 2133–2148.)
High spin quantum number is not the only factor determining the efficacy of an MRI CA.

The interaction mechanism between water molecules and a CA is complex and can be divided into two parts, inner-sphere relaxation and outer-sphere relaxation. During the inner-sphere relaxation the formation or dissociation of a coordinate covalent bond between a water molecule and the CA occurs, leading to a chemical exchange and catalyzation of the water protons relaxation. The ability of a CA to bind a large number of water molecules and to perform a rapid exchange is a highly desirable feature because it allows a greater relaxation enhancement. Outer-sphere relaxation, in contrast, does not involve any direct bonding or chemical exchange mechanism, but it is associated with the relative rotational and translational diffusion of water molecules and CAs. The efficiency of the enhancement in this case depends on the mobility of the CA and the ease of approaching interaction with water molecules protons.

All these effects must be taken into consideration while designing CAs, especially those with functional coatings and complexes. For example, if there is a magnetic particle–ligand complex, the system will rotate and translate slower in space, decreasing the number of interactions. Moreover the distance between the magnetic core and the water proton will be increased, reducing the relaxation enhancement effect of the magnetic particle.

There is a mathematical description of the relaxation of water protons in the presence of a magnetic ion, called the Solomon–Bloemberger–Morgan equation:

$$1/t_c = 1/t_r + 1/t_s + 1/t_m$$

(3.24)

where $t_c$ is the total correlation time, $t_r$ is the correlation time of rotation, $t_s$ is the correlation time of electron relaxation, and $t_m$ is the correlation time of chemical exchange. Equation 3.24 describes the probability of contact (correlation time) between the CA and the water molecule proton. It should be noted that the component with the smallest magnitude will affect the total correlation time of interaction the most. A schematic view of the correlation parameters is shown in Figure 3.33. The relaxivities of

![FIGURE 3.33](image-url)
current commercial CAs are small compared to what is theoretically possible. The optimization of the correlation times can lead to a dramatic increase in relaxivity, and potentially can result in the values of relaxivities which are about an order of magnitude larger than those of the commercially available ones [30].

### 3.4.3 Design Criteria

The human body normally contains magnetic substances, for example, degradation products of hemoglobin, or molecular oxygen. However, there should be a significant concentration of such substances in the area of interest in order to get a profound disturbance of the local magnetic field and thus better contrast. That is the reason why the first and foremost criterion of an MRI CA is its ability to influence the parameters responsible for image contrast at low concentration. Second, a contrast media should possess some tissue specificity in vivo so that the CA is delivered to an area of a tissue or an organ in a higher concentration than to other locations in the body. Third, the CA must be substantially cleared from the targeted organ or tissue in a reasonable period of time (typically several hours after the imaging) in order to minimize potential toxicity, and eventually excreted from the body via renal or hepatobiliary routes. Fourth, MRI CAs must meet toxicity and tolerance criteria, and pass many other tests for chemical stability in vivo, potential mutagenicity, teratogenicity, and carcinogenicity. Finally, a commercial need for in vitro stability of the CA has to be satisfied. It must have a shelf life of at least several years.

All the criteria mentioned above stimulate the development of different types of MNPs used as CAs.

### 3.4.4 Classification of CAs

Although GBCAs are the most common class of MRI CAs to date, many other types of agents are appearing on the market. MRI CAs can be classified by their

- Magnetic properties
- Effect on the image intensity
- Chemical composition
- Administration route
- Applications

In terms of their magnetic properties, CAs are typically divided into two groups: paramagnetic and superparamagnetic. Most of the CAs now in clinical use are based on paramagnetic metal ions, such as gadolinium (Gd³⁺). Materials used in superparamagnetic CAs are iron-based, such as magnetite (Fe₃O₄) or maghemite (γ-Fe₂O₃). The most common way of describing existing CAs is to classify them into two categories, namely MRI positive CAs and MRI negative CAs. As mentioned previously, the difference between them is that positive CAs reduce $T₁$ relaxation times (increasing signal intensity and thus appearing bright on the $T₁$-weighted images), while negative CAs predominantly affect $T₂$ relaxation times (decreasing $T₂$ time and appearing dark on MRI images). GBCAs are the most studied and common
examples of MRI positive CAs. They are now routinely used in clinics. It should be noted as well that Gd is paramagnetic. SPIO NPs are, on the other hand, an example of MRI negative CAs.

The choice of type of CA, positive or negative, depends on the specific organ or disease suspected, as well as the pulse sequence used. Both types of CAs have certain advantages and disadvantages. For example, for gastrointestinal (GI) MRI positive CAs, ghosting artifacts due to respiratory or peristaltic motion is a problem. One of the solutions is to use breath holding pulse sequences and first order flow compensations. Another solution is to use a pharmaceutical which reduces bowel motion. On the other hand, GI MRI negative CAs do not have this ghosting problem due to the lack of signal in the bowel. However, metallic artifacts are seen when gradient echo sequences are used. Moreover their cost is generally higher and there are limited evaluations of safety on a large number of patients.

Properties, functions, and principles of work of these two types of CAs used now in clinical practice will be covered in the following sections. Some examples of novel CAs will be discussed as well.

3.4.5 MRI Positive CAs

Paramagnetic materials are used as positive CAs due to their ability to develop a magnetic moment in the presence of a magnetic field (inside the bore of the MRI scanner). This large induced magnetic moment enhances the relaxation of the water molecule protons in the vicinity of the agent and creates bright contrast on the $T_1$-weighted images. For a paramagnetic material to be an effective MRI positive CA, the electron spin-relaxation time must match the Larmor frequency of the protons, and this condition is better met for Gd$^{3+}$, Mn$^{2+}$, and Dy. The main problem with paramagnetic metal ions is their toxicity in their native form. Chelating ligands, such as diethylenetriamine pentaacetic acid, DTPA, are bound to the paramagnetic ion in order to prevent the lanthanide from binding to chelates in the body.

3.4.5.1 Gadolinium-Based CAs

The use of GBCAs to enhance the $T_1$-weighted images has been part of standard clinical practice for over two decades. There are now nine FDA-approved GBCAs, which can be classified into two groups on the basis of their chemical structure: linear and macrocyclic (Figure 3.34 and Table 3.4). In Table 3.4, several evolutional directions in the design of the CAs can be seen as well, from linear to macrocyclic, and from ionic to nonionic.

The most important consideration about GBCAs is their stability. Free Gd$^{3+}$ is toxic and thus the ability of the ligand to tightly bind to the Gd ion is an important safety consideration, especially after 2006 when an association between the development of nephrogenic systemic fibrosis (NSF) and the administration of Gd was noticed.

3.4.5.1.1 Stability of the GBCAs

The thermodynamic stability constant ($K_{\text{therm}}$) is a measure of stability: the higher the $K_{\text{therm}}$ constant the more stable the Gd complex. However, the thermodynamic
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[**Gd**(DTPA)(H$_2$O)$_2$–
(Magnevist: BSP)]

[**Gd**(DTPA-BMA)(H$_2$O)]
(Omniscan: GE Healthcare)

[**Gd**(DTPA-BMEA)(H$_2$O)]
(OptiMARK: Mallinckrodt)

[**Gd**(DTPA)(H$_2$O)]–
(Magnevist: BSP)

[**Gd**(HP-DO3A)(H$_2$O)]
(ProHance: Bracco)

[**Gd**(BOPTA)(H$_2$O)]–
(MultiHance: Bracco)

[**Gd**(BOpta)(H$_2$O)]–
(Vasovist: BSP)

FIGURE 3.34 Commercial Gd-based MRI CAs. (Adapted from E. Werner et al., Angew Chem Int Ed, 47(45), 2008, 8568–8580.)
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stability constant does not take the pH of the environment into account. Therefore, the conditional stability of a complex constant ($K_{\text{cond}}$), which is a measure of the stability of a complex at a physiologic pH, is considered a more relevant stability parameter [31]. Table 3.5 presents thermodynamic constants of the FDA-approved GBCAs.

There are a number of factors that affect the stability of the Gd complex in vivo. A number of endogenous metals, such as zinc, copper, calcium, and iron normally presented in vivo environment can act as destabilizers of the GBCA complex, leading to its dissociation into Gd ion and a ligand. This displacement of the Gd ion from its ligand by other metals via competitive ionic binding is called transmetallation. An in vitro comparison analysis of linear and macrocyclic GBCAs demonstrates that in the presence of competitor metals (Zn and Cu) macrocyclic agents (Dotarem and ProHance) remain essentially intact (<1% reaction), while the linear Gd-based complexes are more reactive [32]. A similar analysis in vivo also demonstrates a better performance of the macrocyclic GBCAs: up to 14 days after injection of GBCAs,

### TABLE 3.4
Currently Available GBCAs

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Chemical Name</th>
<th>FDA Approval</th>
<th>Structure</th>
<th>Ionicity</th>
<th>Clinical Use</th>
<th>Intra-Venous Injection (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dotarem</td>
<td>Gadoterate</td>
<td>2013</td>
<td>Macroyclic</td>
<td>Ionic</td>
<td>Multi-purpose</td>
<td>376.9</td>
</tr>
<tr>
<td>Gadavist</td>
<td>Gadobutrol</td>
<td>2011</td>
<td>Macroyclic</td>
<td>Nonionic</td>
<td>CNS, breast</td>
<td>604.72</td>
</tr>
<tr>
<td>Ablavar</td>
<td>Gadofosveset</td>
<td>2008</td>
<td>Linear</td>
<td>Ionic</td>
<td>Blood pool</td>
<td>244</td>
</tr>
<tr>
<td>Eovist</td>
<td>Gadoxetate</td>
<td>2008</td>
<td>Linear</td>
<td>Ionic</td>
<td>Liver</td>
<td>181.43</td>
</tr>
<tr>
<td>MultiHance</td>
<td>Gadobenate</td>
<td>2004</td>
<td>Linear</td>
<td>Ionic</td>
<td>Multi-purpose</td>
<td>529</td>
</tr>
<tr>
<td>OptiMARK</td>
<td>Gadoversetamide</td>
<td>1999</td>
<td>Linear</td>
<td>Nonionic</td>
<td>CNS, liver</td>
<td>330.9</td>
</tr>
<tr>
<td>Omniscan</td>
<td>Gadodiamide</td>
<td>1993</td>
<td>Linear</td>
<td>Nonionic</td>
<td>Multi-purpose</td>
<td>287</td>
</tr>
<tr>
<td>ProHance</td>
<td>Gadoteridol</td>
<td>1992</td>
<td>Macro cyclic</td>
<td>Nonionic</td>
<td>Multi-purpose</td>
<td>279.3</td>
</tr>
<tr>
<td>Magnevist</td>
<td>Gadopentetate</td>
<td>1988</td>
<td>Linear</td>
<td>Ionic</td>
<td>Multi-purpose</td>
<td>469.01</td>
</tr>
</tbody>
</table>

Source: Adapted from M. F. Tweedle, E. Kanal, and R. Muller, Suppl Appl Radiol, 43(5), 2014, 1–11.

### TABLE 3.5
Thermodynamic Constants of GBCAs

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Dotarem</th>
<th>Gadavist</th>
<th>Ablavar</th>
<th>Eovist</th>
<th>MultiHance</th>
<th>OptiMARK</th>
<th>Omniscan</th>
<th>ProHance</th>
<th>Magnevist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Macroyclic</td>
<td>Macroyclic</td>
<td>Linear</td>
<td>Linear</td>
<td>Linear</td>
<td>Linear</td>
<td>Linear</td>
<td>Linear</td>
<td>Macro cyclic</td>
</tr>
<tr>
<td>Log($K_{\text{therm}}$)</td>
<td>25.6</td>
<td>21.8</td>
<td>22.1</td>
<td>23.5</td>
<td>22.6</td>
<td>16.6</td>
<td>16.9</td>
<td>23.8</td>
<td>22.1</td>
</tr>
<tr>
<td>Log($K_{\text{cond}}$)</td>
<td>19.3</td>
<td>14.7</td>
<td>18.9</td>
<td>18.7</td>
<td>18.4</td>
<td>15</td>
<td>14.9</td>
<td>17.1</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Source: Adapted from M. F. Tweedle, E. Kanal, and R. Muller, Suppl Appl Radiol, 43(5), 2014, 1–11.
macrocyclic agents have the lowest level of residual Gd [33]. *Ex vivo* human data show that dissociation of the nonionic linear GBCAs is much more pronounced. Up to 30% of the nonionic linear agents was released in human plasma 2 weeks after administration, while for the ionic linear agents this number was reduced to about 2%, and for the macrocyclic GBCAs the percent of dissociation processes is 0% (Figure 3.35, adapted from Reference 31). The most credible and important data of *in vivo* human studies support the high stability of macrocyclic GBCAs. The

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**FIGURE 3.35** Amounts of Gadolinium ions released from 1 mM solutions of (a) all commercial GBCAs at 37°C in native human serum from healthy volunteers; (b) an enlarged section of the graph visualizing the data for the ionic linear and macrocyclic GBCAs. (Adapted from M. F. Tweedle, E. Kanal, and R. Muller, *Suppl Appl Radiol*, 43(5), 2014, 1–11.)
amount of Gd$^{3+}$ deposed in the bone of hip replacement patients after administration of Omniscan is four times more than that after ProHance administration [34]. However, recent studies on a sensitive in vivo animal model show that even at day 364 after the administration, a very small amount of Gd was still present in the skin of rats administered macrocyclic GBCAs, indicating that there is still a “low-risk” rather than “no-risk” of using GBCAs, especially for patients with a high risk of NSF (Table 3.6, [31]).

### 3.4.5.1.2 Relaxivity of the GBCAs
Relaxivity rates, another important property of the CAs, can be modified depending on the contrast medium ability to interact with proteins. It was found that interaction with proteins, most notably human serum albumin (HSA), noticeably increases the effective size of the Gd-ligand complex, and meanwhile reduces the molecular motion, thus shortening the $T_1$ relaxation time and greatly increasing signal intensity enhancement [35]. Figure 3.36 shows the relaxivity profiles of solutions containing 1 mM of either Gadavist or MultiHance in the absence and presence of 4% HAS [36]. For Gadavist, as well as for other nonprotein binding GBCAs, the presence of HSA has no effect on the relaxivity profile, whereas for MultiHance the presence of HSA results in a notable increase in relaxivity.

### 3.4.5.1.3 GBCAs Safety and NSF
Until 2006 GBCAs were considered as one of the safest CAs used in humans [37]. Over 200 million patients have been exposed to gadolinium since the late 1980s. Worldwide post-marketing surveillance studies have all demonstrated that nearly all drug reactions can be characterized as very mild (<2.5%) or moderately severe (<0.02%) [38]. However in 2006 Grobner et al. reported about the possible association between GBCAs and a new and rare disease, NSF [39]. NSF was first described in the medical literature in 2000. NSF causes fibrosis of the skin, connective tissues
like muscles, tendons, ligaments, and blood vessels throughout the body, leading to a thickening of the skin and severe decreasing of joints mobility. However, NSF has been reported only in patients with pre-existing chronic kidney disease and end-stage kidney disease. Due to the weak kidney function, the human body cannot clear itself of GBCAs and the extended presence of gadolinium may lead to irreversible health problems, possible confinement to a wheelchair, and even death. Table 3.7 shows an overview of worldwide unconfounded NSF cases for various GBCAs. A retrospective study with Omnisan in about 370 patients with severe renal insufficiency estimated the risk of NSF to be 4% [40]. It is still unknown what causes NSF, there is no cure for it so far, and skin biopsy is the only true means of diagnosis.

### Table 3.7

<table>
<thead>
<tr>
<th>Trade Name of GBCA</th>
<th>NSF Cases Global</th>
<th>Contrast Media Examinations Global (in Millions)</th>
<th>NSF Relative Frequency (Cases/1 Million Applications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omniscan</td>
<td>438</td>
<td>&gt;47</td>
<td>9.3</td>
</tr>
<tr>
<td>Magnevist</td>
<td>135</td>
<td>&gt;115</td>
<td>1.2</td>
</tr>
<tr>
<td>OptiMARK</td>
<td>7</td>
<td>&gt;9</td>
<td>0.8</td>
</tr>
<tr>
<td>Gadavist</td>
<td>1</td>
<td>&gt;6</td>
<td>0.7</td>
</tr>
<tr>
<td>ProHance</td>
<td>1</td>
<td>&gt;14</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Dotarem</td>
<td>1</td>
<td>&gt;21</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>MultiHance</td>
<td>0</td>
<td>&gt;11</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

3.4.5.2 Mn-Based CAs

Although the most of the research involving MRI positive CAs has been carried out by Gd\(^{3+}\)-based CAs, Mn\(^{2+}\) agents have recently received considerable attention. Manganese, being one of the first reported examples of paramagnetic CAs used in cardiac and hepatic MRI, is especially useful for the detection of anatomical structures and for the mapping of functional brain regions. However, there are several drawbacks which prevent it from being widely used and developed as a contrast media, for example, the toxicity of the Mn ion and the difficulty to find ligands capable of binding to the Mn ion [42].

3.4.5.3 Dy-Based CAs

According to the relaxivity theory of Dy\(^{3+}\), Dy\(^{3+}\)-based complexes are the most efficient agents to be encapsulated, due to their high magnetic moment. Incorporation of the amphiphilic Dy\(^{3+}\) complexes in the liposome bilayer yields a marked sensitivity enhancement, allowing for the MRI visualization of cellular epitopes, such as membrane transporters present at very low concentrations [43].

3.4.6 MRI Negative CAs

In terms of MRI negative CAs, the most studied and commonly used magnetic materials are magnetite (Fe\(_3\)O\(_4\)) and its oxidized form maghemite (γ-Fe\(_2\)O\(_3\)).

Magnetite is a black ferrimagnetic mineral which has both Fe\(^{2+}\) and Fe\(^{3+}\) and a saturation magnetization of 4.76 \times 10^5 A/m. Maghemite is a red brown ferrimagnetic mineral isostructural with magnetite, with all or most of the iron being trivalent. It is formed when the magnetite is oxidized and has the saturation magnetization of 4.26 \times 10^5 A/m [44]. Ferrites have an inverse spinel structure, where oxygen atoms form face centered cubic lattices and iron ions occupy tetrahedral (T\(_d\)) and octahedral (O\(_h\)) interstitial sites, as shown in Figure 3.37. Iron oxides have been intensively

![FIGURE 3.37 Ferrite’s crystal structure.](image-url)
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investigated by both chemists and materials scientists for 5 decades, resulting in a number of different synthesis methods [45].

Interestingly, magnetite is found in many bio-systems, from bacteria to human bodies. For example, in 1962 Lowenstam found magnetite in the radula teeth of chitons (marine molluscs) and proved its biological origin [46]. Before his discovery the formation of magnetite was thought to occur only under high temperature and pressure in volcanic or metamorphic rocks. For chitons the magnetite serves to harden the tooth caps, enabling the chitons to extract and eat endolithic algae from within the outer few millimeters of rock substrates. In 1975 Blackmore discovered a bacterium which is sensitive to the Earth’s magnetic field and called it magnetotactic bacterium [47]. Its organelles called magnetosomes contain magnetite crystalline particles of size 50–100 nm. These magnetosomes act just like a compass needle and force the bacteria to migrate along oxygen gradients in aquatic environments, under the influence of the Earth’s magnetic field. So it means that the bacteria are passively torqued even if they are dead. In both of the above examples the magnetite particles are formed by the organisms by a process called biomineralization. A good review of the formation of magnetite by living organisms is done by Arakaki et al. [48]. Remarkably, the structures formed by the biomineralization process often exhibit excellent physical and/or chemical properties which outperform artificial material, and moreover the conditions required for this are incredibly mild in comparison with common synthetic methods. That is why, in order to understand the key biological and chemical principles of biomineralization, molecular studies including genome sequence, mutagenesis, gene expression, and proteome analysis have been recently performed giving us a simple way to prepare functional protein–magnetic particle complexes and clues for the development of advanced nanomaterials. According to Thomas-Keprta et al. [49] there are six criteria that are unique for biologically produced magnetic crystals, such as a definite size range and width/length ratio, chemical purity, crystallographic perfection, arrangement of crystals in linear chains, unusual crystal morphology, and elongation of crystals in the [111] crystallographic direction. The simultaneous presence of all of them should constitute the evidence of the biological origin of the material. Surprisingly, recent observation of Martian meteorite ALH84001 by NASA researchers shows the presence of magnetite NPs which fulfill all six criteria. These findings lead to the hypothesis that they could be in fact microfossils of former Martian magnetotactic bacteria and that life on Earth could have been brought by meteorites from Mars where conditions could have been more favorable for the creation of life from non-living ingredients in the early history of the solar system [50].

Therefore, the biocompatibility and availability of different synthesis methods of iron oxide nanoparticles make them popular in biomedical studies and they are now considered the gold standard for MRI contrast imaging. They are commercially available and approved by the U.S. FDA for clinical applications.

3.4.6.1 The Effect of Size

It is necessary to keep in mind that some of the magnetic responses are structure-sensitive and some are relatively structure-insensitive. Susceptibility and coercivity are examples of the first category, while saturation magnetization is an example of
the second one [51]. The reduction of size in magnetic materials leads to profound changes in their intrinsic properties. Nano-sized magnetic materials are governed by laws which are different from those for the material in its bulk form, resulting in phenomena which were never detected before for their macro-size counterparts. For example, in large ferromagnetic particles (with size more than 1 µm) there are still many magnetic domains and the coercivity is relatively small forming a narrow hysteresis loop. However, for smaller particles (with size <1 µm) it becomes more energetically efficient to have a single domain and coercivity of ferromagnetic particles experience a dramatic increase with the reduction of the particle size, leading to the hysteresis loop broadening. If the particle size is reduced further to a certain critical value (to about 20 nm) or the so-called superparamagnetic radius, the particle becomes superparamagnetic (SPM) with a zero remanence, forming the $M$–$H$ curve without hysteresis, as shown in Figure 3.38. This superparamagnetic feature of nanoparticles is highly advantageous for biomedical applications because it means that there is no remanent magnetic moment after the removal of the external magnetic field. In other words there will be no aggregation of the magnetic particles in the blood vessels after a diagnostic measurement or a therapy [52].

**3.4.6.2 Surface Effects**

There are certain disadvantages associated with NP size reduction. With the decrease of the particle size, the surface to volume ratio increases introducing noticeable surface effects such as spin canting, spin glass behavior, and non-collinear spins. These effects result in crystal structure disorder, thus changing the magnetic properties of the particles. Subsequently, this results in an unfavorable saturation magnetization reduction [53]. The association between magnetization and size is quantified by the magnetic anisotropy constant ($K_u$). It measures the energy to be overcome in order to preserve the direction of the magnetic dipoles of the material. This constant is determined by crystal lattice symmetry, the surface coordination with the core of the NP, and the shape of it. Thus, it is different for different materials [52,54]. The lower the constant, the more size dependent the magnetization is, and therefore, the faster the

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**FIGURE 3.38** (a) Variation of coercivity ($H_c$) of MNPs with size, and (b) theoretical magnetization versus magnetic field curve for SPM and ferro- or ferrimagnetic NPs. (Adapted from A. Figuerola et al., *Pharmacol Res*, 62(2), 2010, 126–143.)
decrease of magnetization with size will be. Moreover, materials with high magnetic anisotropies have a significant magnetization even at very small particle sizes. This can be used in many biomedical applications [52]. It has been observed [55] that metal alloys have higher magnetization values than their oxide counterparts and thus can act as potentially more efficient CAs with higher image contrast and lower doses of MNPs.

3.4.6.3 Pharmacokinetics
Iron oxide-based NPs are highly biocompatible, they are metabolized in the hepatorenal system, added into body’s iron reserves, and finally become part of the red blood cells as hemoglobin [56].

Different surface coatings are used for iron oxide NPs in order to provide chemical stability during and after synthesis of the MNPs, prevent their agglomeration inside the body, and change NP recognition by human immune cells [57]. Typical surface coatings are dextran and its derivatives, albumin, silicon, PEG (polyethylene glycol), PEI (polyethylenimine), chitosan, co-polymer, liposomes, and starch. The resulting organic/inorganic complexes have a core–shell nanoarchitecture, which can be functionalized by adding various compounds. The chemistry of the magnetic core and surface of a core–shell SPIO NP dictates its function and working environment [58]. The design of the chemical nature and crystal lattice of the magnetic core enables the control of the magnetic response of the NPs by modifying the core size and chemical composition. On the other hand, the functionalization of the surface allows us to modulate the behavior of particles in solution. With the help of surface coatings homogeneous suspensions can be formed which remain stable in blood and aqueous environments [59]. Moreover, a study [60] shows that polymer (cyclodextran and F127) coatings can reduce NP size and attenuate their cluster behavior consistently from more than 300 nm down to 90 nm. Studies [59,61] show that polymer (PEG) coating of NPs can reduce the recognition and uptake of the NPs by the liver and spleen, and thus increase their circulation times.

3.4.6.4 Superparamagnetic Iron Oxide CAs
It is generally considered that when iron oxide NPs being in an aqueous environment have an overall hydrodynamic size larger than 40 nm they are called SPIO. If their hydrodynamic size is smaller than 40 nm they are called ultra-small superparamagnetic iron oxide (USPIO). Most of the magnetic NPs available on sale are SPIO NPs with the size ranging from 60 nm up to several micrometers.

The first clinical use of SPIO NPs as a contrast media was done for imaging liver tumors. After an intravenous injection of SPIO NPs they can be easily detected by the macrophages of the RES of the body and are therefore accumulated in the liver and in the spleen because these organs are responsible for blood purification. Healthy liver cells can uptake the particles, whereas diseased cells cannot, as schematically shown in Figure 3.39. In the presence of NPs the relaxation time $T_2$ is reduced, thus on $T_2$-weighted images only the change in the brightness of the normal cells will be seen. The use of SPIO as contrast media increases the characterization accuracy of lesions in hepatic cellular carcinoma (HCC) and focal nodular hyperplasia (FNH) patients [62].
On the other hand, USPIO NPs do not accumulate in the RES because they are too small for the RES to detect and therefore have a longer circulation time in the blood. They are able to pass across capillary walls, drain via the lymphatic circulation, and localize in lymph nodes independent of size or morphological features of the node. This tendency of USPIO NPs to passively target tumors, due to the enhanced permeation retention (EPR) effect of solid tumors, allows us to identify nodal metastases of less than 2 mm in diameter, which is under the threshold of detection of other imaging modalities [63,64].

For other kinds of tumors functionalized NPs with tumor specific antibodies are utilized. These functionalized complexes are actively targeted to the tumor and darken the tumor cells on T₂-weighted images [65].

### 3.4.6.5 Clinical Application of Iron Oxides

Although a number of SPIONs and USPIOs have been approved for clinical use in the past, as shown in Table 3.8, only one oral iron oxide CA Lumirem/Gastromark is available to date.
3.4.6.6 Toxicity
The requirement of millions of particles with very high saturation magnetization values limits the usage of MNPs as CAs. However, SPIO have much higher magnetic moments and thus require a lower dose for the MRI administration of CAs. For this reason, it reduces potential cellular toxicity. No serious adverse effect has been observed to date. The possibility of mild-to-moderate adverse effects is 3%–28%, with back pain being the most common one [59].

3.4.6.7 Theragnostics
The capability of SPIO NPs to incorporate a broad range of diagnostic and chemotherapeutic agents allows one to combine diagnostic and therapeutic approaches for complex simultaneous cancer detection and therapy [45]. A study [65] demonstrates multifunctional polyspartic acid nanoparticles (MPAN), containing the SPIO core and chemotherapeutic drug Doxorubicin. They act both as a $T_2$ MRI CA and an anti-tumor drug delivery system. This combination treatment has a great potential to advance and personalize medicine.

3.4.7 Multimodal ($T_1 + T_2$) Imaging
Today single-mode CAs are not always sufficient, and dual-mode CAs have recently been receiving a great amount of attention. These new contrast media combine the advantages of positive and negative MRI CAs, thus sharpening anatomical details and allowing improved accuracy for diagnosis.

Although the design and preparation of such complexes is a highly challenging task, there have been several techniques reported. For example, one study [55] shows a core–shell-type agent with FeCo core and single graphite shell. It has a relaxation rate $r_2$ six times higher than that of the commercially available CA Ferridex. In the study [66] silica layer of different thickness was used to separate $T_1$ ($\text{Gd}_2\text{O}_4\text{CO}_3$) and $T_2$ ($\text{MnFe}_2\text{O}_4$) contrast modes. A recent report [67] demonstrates three different approaches for dual-mode CAs’ preparation based on SPIO NPs, the polymer coating of which is combined with Gd ions. In general, these complex dual-mode contrast media exhibit outstanding relaxivity performance.
REFERENCES