MRI – recent advances and new horizons

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In the past 10 years, a variety of innovative MRI approaches have been proposed for the noninvasive assessment of molecular or cellular events. While MRI is intrinsically a molecular imaging technique, it has to cope with its inherent low sensitivity and consequently has to be performed on a large number of nuclei. The assessment of specific molecular processes occurring at the cellular level requires generating or modulating magnetic resonance signals with exogenous probes to overcome this intrinsic lack of sensitivity. A variety of highly promising approaches will be reviewed to achieve this goal through the increase of the detected signal, the development of specific probes generating field-dependent relaxation properties and of the associated imaging hardware to make use of such contrast mechanisms. Recent developments drawing future perspectives will then be reported and their respective outcomes will be discussed.

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Aa **Sensitivity:** the signal-to-noise ratio obtained for a given probe amount per square root of time ($\text{min}^{-0.5}$).

X-nuclei: nuclei other than ^1H that have NMR properties (e.g., ^3He , ^{13}C , ^{31}P and ^{129}Xe).

MRI is intrinsically a molecular imaging technique as the underlying physical principles rely on absorption of an on-resonance radiofrequency wave specific to nuclei (e.g., ^1H , ^{13}C , ^{19}F and ^{129}Xe). For a given nucleus in a molecule, subtle variations in the resonant frequency (such as chemical shifts) can further refine the molecular signature allowing unambiguous identification through NMR spectroscopy. While a great advantage of MRI for *in vivo* imaging is the use of nonionizing radiations, MRI has to cope with its inherent low **sensitivity** and has consequently to be performed on a large number of nuclei. The most abundant magnetic nucleus detectable *in vivo* is the one of hydrogen (^1H) in free water, and thanks to large variations of relaxation properties with mobility, MRI provides exquisite endogenous contrasts between soft tissues. Nevertheless, the assessment of specific molecular processes occurring at the cellular level requires generating or modifying MR signals with exogenous probes to overcome this lack of sensitivity. This can be done directly by detecting **X-nuclei** (non- ^1H), or indirectly by influencing ^1H magnetization and/or relaxation with contrast agents (CAs). Ongoing developments are focusing on the design of efficient probes and associated detection methods. In the context of molecular MRI [1,2], the sensitivity to probe molecular markers in the low concentration range is the critical point. After reviewing multiple factors influencing sensitivity and specificity for preclinical and clinical imaging with currently available approaches, recent developments drawing future perspectives will be reported.

General MRI principles

To perform MRI, a magnetic field (B_0 ; usually strong and static) is required. It is exploited in three ways: to polarize nuclei, giving rise to a macroscopic magnetization; to detect the MR signal at the resonance frequency; and to make use of relaxation mechanisms.

The intrinsic nuclear magnetic moments align with B_0 resulting in a macroscopic nuclear magnetization. This magnetization is excited and detected at the Larmor frequency F_0 proportional to B_0 and to the observed nucleus gyromagnetic ratio γ , by means of a radiofrequency (RF) coil. Localization is performed through repeated measurements during which position is discriminated by slightly shifting the frequency through magnetic field spatial variations (the imaging gradients). The longitudinal relaxation time T_1 characterizes the time needed to reach thermal equilibrium through an exponential recovery. The transverse relaxation time T_2 characterizes the

loss of coherence of the MR signal (following an exponential decay) in a spin echo experiment; and the apparent transverse relaxation time T_2^* , which includes T_2 and susceptibility-induced effects characterizes the loss of coherence of the MR signal in a gradient-echo experiment.

Direct detection

Molecular MRI can be based on the direct detection of probes having an MR detectable signal, such as with ^1H (spectroscopy), fluorine (^{19}F) or carbon (^{13}C). In this case, an important notion to characterize the sensitivity is the signal-to-noise ratio (SNR), which depends on multiple parameters, including contribution of B_0 , imaging sequence, detection hardware, magnetization, and total time T_{acq} during which the **voxel** signal is recorded. For molecular MRI, either the total number N of nuclei within the voxel or its concentration is important. As they are linked through the voxel size V , SNR can be synthesized according to **Equation 3.1**:

$$\text{SNR} \propto \gamma N P I H \sqrt{T_{acq}} \quad (\text{Equation 3.1})$$

Where H accounts for hardware sensitivity (e.g., radiofrequency reception coil), P is the nucleus polarization and I depends on the imaging sequence and the contrast parameters (flip angle, relaxation and repetition times). This expression (**Figure 3.1**) already gives a general insight into how to increase SNR: by increasing T_{acq} (e.g., through repeated measurements), which is often limited *in vivo* by the processes investigated and patient motion or available time. It is useful, then, to define sensitivity S as the SNR that is obtained with a certain amount of probe or nuclei N , in a given acquisition time, as shown in **Equation 3.2**:

$$S = \frac{\text{SNR}}{(N \sqrt{T_{acq}})} \quad \text{Equation 3.2}$$

To improve sensitivity, it is possible to optimize detection, to increase polarization and the number of probes, and to maximize I through the use of efficient imaging sequences. The reader will find more details of the multiple types of MRI pulse sequences

Voxel: elementary volume of signal encoded.

Figure 3.1. NMR sensitivity.

NMR sensitivity depends on: the magnetization, which is the product of the nucleus gyromagnetic ratio (γ) to the number of nuclei per unit volume and to their polarization (P); reception coils (H); and imaging pulse sequence (I) and its effective acquisition time T_{acq} (shown in the schematic magnetic resonance pulse sequence as n times T_{obs} , the acquisition window).
RF: Radiofrequency.

Detection threshold: the concentration of probe (or amount/voxel size) that generates a change of four in signal-to-noise ratio or in contrast-to-noise ratio.

and of their relative efficiencies in traditional textbooks, but it is worth noting that for steady-state free-precession (SSFP; usually considered the most SNR-efficient sequence since the magnetization is rephased and reused from one repetition to the other), $I \approx 0.5\sqrt{T_2/T_1}$ [3], for $TR \ll T_1$, where TR is the repetition time.

To provide an order of magnitude, one can easily check that imaging a saline solution ($T_1 \sim T_2$) at clinical field (1.5 T) in a volume head coil with 3D SSFP provides a typical SNR of 80 with μl voxel sizes in a 1-min acquisition. A typical sensitivity of $1 \mu\text{mol}^{-1} \cdot \text{min}^{-0.5}$ is thus obtained on a standard clinical system. For preclinical imaging, approximately a factor of 1000 is gained through reduced coil size and increased magnetic field and approximately $1 \text{ nmol}^{-1} \cdot \text{min}^{-0.5}$ is typically obtained on a preclinical (7 T) small-animal system with an adequate RF coil. Using the Rose criterion with a **detection threshold** $SNRt = 4$, typical water detection threshold is $4 \mu\text{mol}$ in 1 min on clinical systems and 4 nmol in 1 min on preclinical systems. In terms of concentration, it converts to 4 M (mol/l) in a typical $1 \mu\text{l}$ voxel size, and to 4 M (mol/l) for a typical 1 nl voxel size, respectively. In the following, the typical 1 M sensitivity range will be considered. However, it is to be noted that a 10^3 gain, expressed in terms of concentration, is readily available through a 10^3 increased voxel size (1 ml or $1 \mu\text{l}$ for human or small animal, respectively).

Indirect detection through the use of contrast agents

Other molecular MRI approaches rely on the modification of water relaxation times with CA. Based on whether the CA increases principally the longitudinal recovery rate $R_1 = 1/T_1$ or the transverse relaxation decay rate $R_2 = 1/T_2$, they are classified as T_1 or T_2 agent, respectively. The contrast mechanisms are complex (see below and **Chapter 5**), but are usually synthesized by introducing the **relaxivity**, expressed in $\text{mM}^{-1} \cdot \text{s}^{-1}$ with a linear dependence on concentration $R_i = R_{i,0} + r_i c$ where $R_{i,0} = 1/T_{i,0}$ is the intrinsic relaxation time of the tissue, c is the local CA concentration, and r_i is the longitudinal or transverse relaxivity, $i = 1, 2$ or 2^* , respectively.

To illustrate the importance of SNR and of intrinsic relaxation parameters in the detection thresholds of CA, SNR variation (ΔSNR) can be analyzed in the low concentration range for a given tissue. In the case of a T_1 -weighted spoiled gradient-echo sequence using the optimal angle [4] and $TR \ll T_1$, one can easily derive $\Delta\text{SNR} = r_1 T_{1,0} \text{SNR} \times \delta c$. In the case of a T_2 -weighted sequence, $\Delta\text{SNR} = r_2 TE \times \text{SNR} \times \delta c$ is obtained and is

Relaxivity: the slope of the relaxation rate as a function of contrast agent concentration.

optimal when using $TE = T_2$ [4]. Hence the same variation $|\Delta SNR| = r_{i,0} SNR \times \delta c$ is obtained in the ideal cases of pure T_1 or pure T_2 agents, respectively. This emphasizes that the ability to detect a probe depends on the product of relaxivity to the relaxation time of the tissue of interest. For a T_1 agent with a typical $r_1 = 5 \text{ mM}^{-1} \cdot \text{s}^{-1}$, $T_{1,0} = 1 \text{ s}$ and $SNR = 40$ (obtained in $\sim 1 \text{ min}$ with typical voxel sizes), the detection threshold is $\delta c = 16 \text{ }\mu\text{M}$ for a Rose criterion at $\Delta SNR_t = 4$. For a T_2 agent with a typical $r_2 = 50 \text{ mM}^{-1} \cdot \text{s}^{-1}$, $T_{2,0} = 0.1 \text{ s}$, $SNR = 40$, the same detection threshold is obtained. As can be seen, there is already a 10^5 enhancement in the detection threshold using contrast modifications of water protons compared with direct detection.

Hence, to provide an efficient molecular imaging modality, MR sensitivity needs to be increased by orders of magnitude to be able to quantify events in the nano to pico-molar range [5]. A variety of highly promising approaches will be reviewed to achieve this goal through the increase of the detected signal, the development of specific probes generating field-dependent relaxation properties and of the associated imaging hardware to make use of such contrast mechanisms.

MRI signal detection hardware

One major advance in the past decade has been the generalization of multichannel receiver systems to detect the MRI signal. It allows the use of small RF coils array for detection [6], hence providing an increased sensitivity. Indeed, in MRI the signal of interest comes from the tiny imaged voxel while the noise originates from the entire volume detected by the coil, assuming the system follows the sample-noise dominating regime. In this noise regime, which is the ideal *in vivo* configuration, detection sensitivity H becomes independent of frequency or field strength B_0 , but highly dependent of the coil size in a $5/2$ coil radius r power law (the hardware sensitivity $H \propto r^{-5/2}$) [7]. Thus, there is a strong SNR gain close to the coil when its size is reduced, with a decreased sensitivity depth on the order of r . Typically, switching from a 35-cm volume head coil to current state-of-the-art 10-cm surface coils already allowed a sensitivity gain by approximately a factor of 20. It reaches almost 300 going from human to small-animal sizes (e.g., from 10 to 1 cm), allowing a voxel size decrease from the 1 mm down to $150 \text{ }\mu\text{m}$ in 3D. The side effect is the reduction in the 3D field-of-view of the coil, which can then be compensated for by using multiple coils to recover a full volume-of-interest with, however, a limited gain for in-depth tissue.

While the thermal noise coming from the sample sets the ultimate sensitivity attainable *in vivo*, in many situations the RF coil is the dominant

source of noise that constitutes a serious detection limit (e.g., at low MRI frequencies, or with small coil). For molecular MRI in such a configuration, cooling the RF coil circuit at cryogenic temperatures is a way to improve the sensitivity of NMR detection. Significant improvements, mainly in small-animal imaging, at clinical and higher field strength have recently been demonstrated [8,9].

Increasing polarization

Magnetization usually corresponds to thermal polarization, proportional to field strength B_0 , which is typically on the order of parts-per-million ($P/B_0 = 3.30 \text{ ppm} \cdot \text{T}^{-1}$ for ^1H at body temperature). Increasing the field strength is thus a natural option to increase polarization and sensitivity both for imaging and spectroscopic approaches, justifying the development of high-field MRI (>3 T for humans; >7 T for animals) for molecular imaging. Issues that limit the *in vivo* imaging at higher frequencies (e.g., RF propagation and power deposition) could be solved thanks to important developments in RF transmit technology and associated pulse sequences. However, there are also changes in relaxation times with a trend for longer T_1 [10], shorter T_2 and T_2^* and higher susceptibility effects at high field, all of them reducing the theoretical linear sensitivity dependence expected with field strength. The dissemination in research centers of recent equipments (e.g., 7 T for human) and the development of even higher field strength (17.6 T or 21.1 T for animal) will provide evaluation tools for molecular MRI approaches, allowing identifying optimal field strength to detect a given molecular probe at thermal polarization.

Another way to play on nuclear polarization is to artificially **hyperpolarize** the magnetic nuclei outside the MRI system, transport them and perform the acquisition after administration. In this configuration, and provided that the sample noise dominates, sensitivity is theoretically independent of field strength B_0 , allowing imaging at low or ultra-low field, hence benefiting from more favorable relaxation parameters. Multiple techniques can be used to hyperpolarize nuclei (optical pumping, brute force, dynamic nuclear polarization and the parahydrogen approach, a general review of these techniques can be found in [11]). They have variable efficiency to polarize nuclei, but can provide up to five orders of magnitude increase in polarization (with the physical limit of $P = 1$). This polarization is directly transposed to the detection sensitivity. However, in this situation the life time of this tremendous sensitivity gain is on the order of T_1 (seconds to minutes *in vivo* [12,13]), which constraints the

acquisition protocols and limits the applicability to relatively fast biological

Hyperpolarization: polarization levels of nuclear spin far beyond their thermal equilibrium where $P \sim 10^{-5}, 10^{-6}$.

processes. Additionally, the hyperpolarized state can only be used once, as it recovers to its thermal equilibrium, which is orders of magnitude lower, after the magnetization is flipped for detection. In this situation, the acquisition times T_{acq} is limited by relaxation times which prevent SNR increase through repeated measurements. To push this limit a little further, promising approaches can be used on specific molecules (e.g., in ^{13}C -enriched molecules) by storing the polarization in singlet state with longer T_1 [12]. Another promising approach, allowing for magnetization renewal and providing more flexibility in terms of labeling is the use of targeted cryptophane cages together with hyperpolarized xenon (Figure 3.2A) [13,14]. As xenon is easily dissolved in blood, there is an easy systemic access through the lung for continuous administration of the hyperpolarized gas. Xenon has a high affinity for the cryptophanes and they induce a strong chemical shift difference from the blood pool allowing specific detection of the cage. While xenon concentration delivered into cells lies in the micromolar range, approximately 10^3 detection amplification through chemical exchange saturation transfer can be obtained [13].

Increasing the number of probes using nano-objects

A general means to improve MR sensitivity for *in vivo* molecular imaging is to highly concentrate the number of probes. Tremendous development efforts have been made to synthesize large biocompatible objects that concentrate orders of magnitude of the atoms/CA of interest. They are usually concentrated in nano-objects, themselves able to be further concentrated by accumulation in emulsions, liposomes or cells. Typical particle sizes for injectable nano-objects lie in the range of 10–300 nm diameter [15,16], which transposes already to a four to nine orders of magnitude increase in the number of detectable probes concentration (particle concentration). These particles can be functionalized by the addition of specific ligands at the surface. The ability to detect a specific target in this configuration will depend on the affinity of the ligand to its target, the number of ligand at the surface, the particle size (limited by steric hindrance) and obviously the total number of probes. We will provide here the example of fluorine nanoparticles (NPs) [17] as an example of a X-nuclei probe directly detectable with MR while indirect detection with CA NPs will be covered in the next section.

The limited toxicity of fluorine-containing molecules such as perfluorocarbons (PFC) has been studied for few decades and some of them are already approved for human use. PFCs are slightly denser than water (up to twice), and concentrate a large number of fluorine nuclei per molecules (100% abundance of ^{19}F which is MR detectable). The advantage of using fluorine probes is the absence of the ^{19}F background *in vivo* signal, which makes the

detected signal fully specific to the probe of interest. This simplifies the estimation of sensitivity as it is directly transposable from ^1H imaging performances. Fluorine has a gyromagnetic ratio that is 94% of ^1H . At thermal polarization, an 89% reduction of sensitivity is expected per atom in the sample noise dominating regime. Considering the additional lower nucleus volume density N in liquid PFC (55%–60% that of hydrogen in water), a reduction of sensitivity of approximately 50% is expected (γNP) compared with ^1H in water. The sensitivity is then directly transposable from the sensitivity of water if all fluorine atoms resonate at the same frequency. The most efficient PFCs are the ones displaying symmetrical structures, such as in perfluoro crown-ether (PFCE) in which all ^{19}F nuclei are magnetically equivalent generating a single resonance line. However, the probe efficiency can be reduced by complicated spectra, such as in perfluorooctylbromide (PFOB), and more sophisticated imaging and spectroscopic approaches are then needed to increase sensitivity (Figure 3.2B) [18]. If expressed in terms of particle concentration, the detection threshold is directly increased proportionally to the number of atoms in a NP.

Making use of contrast agent effects

The nuclear magnetic relaxation properties of water, as influenced by a CA, are usually studied through **NMR dispersion (NMRD) profiles**, which give the relaxivities r_1 and r_2 versus the magnetic field B_0 . The theories describing these NMRD profiles have been comprehensively described for the two main types of CA (paramagnetic and superparamagnetic) and more insights on the physical principles can be found in **Chapter 5** and in [15,19]. One important parameter is the correlation time characterizing the motion responsible for relaxation (e.g., water mobility or CA rotational motion). In the design of CA, important developments have been made to influence the rotational motion while binding to a large molecule [15]. Additionally,

magnetic susceptibility is an important source of contrast in gradient-echo imaging. Susceptibility acts both on signal amplitude and phase. While the effects depend on local CA spatial distribution [15,20], they can be assumed to be proportional to concentration and molar susceptibility χ_m . Susceptibility effects will be reported here as equivalent ^1H frequency shifts $\chi_m \cdot f_0$, a parameter independent on the shape factor.

Figure 3.3 synthesizes the most interesting trends that can be encountered for

NMR dispersion profiles: describe the relaxation properties of a contrast agent as a function of magnetic field strength B_0 .

Magnetic susceptibility: usually given in part-per-million (ppm) to describe how a material is magnetized in a given magnetic field. For paramagnetic and diamagnetic material, the magnetization is proportional to the field: $\mu_0 M = \chi B_0$. The bulk magnetic susceptibility is highly influenced by paramagnetic and superparamagnetic materials that generate variations in the local magnetic field seen by the nuclei, leading to an important source of contrast in gradient-echo imaging.

Figure 3.2. Molecular imaging using other nuclei.

(A) Hyperpolarized Xe-biosensor **(B) Fluorine NP**

(A) Demonstration of the hyperpolarized (HP) Xe biosensor principle using chemical-exchange saturation transfer effect. A phantom comprising two compartments with avidin–agarose beads is used. Only the right compartment contains cryptophan cages binding to the beads. **(A,i)** Signal from HP ^{129}Xe around the beads and **(A,ii)** from the perfusion medium as imaged using their respective chemical shift. After continuous saturation of HP ^{129}Xe at the biosensor resonance, **(A,iii)** the bead's Xe signal is significantly depleted, allowing one to obtain **(A,iv)** an image from the Xe biosensor by difference. **(B)** *In vivo* targeted NP molecular imaging. **(B,i)** Anatomical, **(B,ii)** fluorine and **(B,iii)** combined image of a glioblastoma tumor model mouse. HYPER-CEST: Chemical exchange saturation transfer with hyperpolarization nuclei; NP: Nanoparticle. **(A)** Reproduced with kind permission from [14]. **(B)** Reproduced from [18] with kind permission from Springer Science and Business Media.

representative type of CAs: free and bound paramagnetic CAs, such as gadolinium-based MS-325 binding to albumin, and superparamagnetic iron oxides particles (SPIO), such as AMI-25. NMRD curves were obtained using reported fits and experimental data [21,22]. As can be seen, the r_1 profile for free-paramagnetic CA (small correlation time) displays a relaxivity close to approximately $5 \text{ mM}^{-1}\text{s}^{-1}$ that decreases monotonously. By contrast, the bound-paramagnetic as well as superparamagnetic CAs (higher correlation times) display a significant increase reaching a maximum relaxivity at a given frequency corresponding to approximately 0.5 T before decreasing at higher field. Interestingly, r_2 relaxivity for free-paramagnetic CA is similar to r_1 , while for bound-paramagnetic and superparamagnetic CAs, after a fast increase, a plateau is reached at approximately 1 T. The molar magnetization curve follows the Curie law for paramagnetic CA with a linear increase in bulk magnetization. The Langevin law is obtained for superparamagnetic CA with saturation reached at approximately 1 T.

The consequences for molecular MRI are multiple, and innovative methodologies have been proposed to make use of such field dependency. The first point is that bound-paramagnetic and superparamagnetic CAs as used as T_1 agents have an optimal efficiency in the low (<1.5 T) field range, and then act like T_2 agents at higher fields. The drastic relaxation enhancement in r_1 and r_2 between free and bound-paramagnetic CA is an elegant way to increase the specific detection of binding: using r_1 relaxivity, there is a difference free/bound up to approximately 3 T, but a higher efficiency is expected at approximately 0.5 T; using r_2 enhancement there is a difference at all field strength with a higher efficiency expected for field >0.5 T. Regarding bulk susceptibility effects, there is no difference between free and bound paramagnetic species. Assessing multiple types of image weightings (T_1 , T_2 , T_2^* and χ) would thus allow increasing the specificity through the possible differentiation of free/bound CA (see [Chapter 5](#) for the quantitative aspects). Another extremely promising approach relies on the adaptation to imaging of the hardware used to obtain the NMDR profiles, that is using [fast field-cycling](#) [23] technology in which an electromagnet is combined to an imaging system rendering possible to separate detection and relaxation fields. Delta-relaxation enhanced magnetic resonance (dreMR) [24] was proposed in which the magnetic field is varied in the range where r_1 -relaxivity slope is the largest for bound-paramagnetic CA (e.g., ~1.5 T). As the free-paramagnetic agent r_1 relaxivity is almost constant in this region, it appears as an appealing and

Fast field-cycling: technology allowing to switch rapidly (few ms) between different magnetic fields B_0 .

Figure 3.3. NMR dispersion profile and susceptibility effects.

Contrast agent effects for two molecular MRI candidates (Gd and iron oxide nanoparticle [NPIO] based): **(A)** longitudinal r_1 relaxivity, **(B)** transverse r_2 effects and **(C)** susceptibility effects. As can be seen, both Gd bound and NPIO display a maximum r_1 relaxivity in the low field range (below 1 T), and a r_2 relaxivity that saturates rapidly. Susceptibility effects are still increasing for Gd-based compounds, but are saturating for NPIO at low field. **(D)** The dreMR technique uses fast field-cycling technology for molecular imaging. **(D,i)** MS325 samples without and with albumin are **(D,ii)** imaged using standard sequences. **(D,iii)** The addition of a field-cycling magnet allows to specifically image bound contrast agents using longitudinal relaxivity changes. **(E)** The large transverse relaxivity of NPIO renders cell tracking possible *in vivo*. Lymphocyte-labeled tumor model on which strong signal decrease (white arrows) can be observed (magnetic resonance acquisition parameters and protocol are described in [27]). **(F)** The quantitative susceptibility technique can be performed at different magnetic fields to image superparamagnetic nanoparticles specifically. **(F,i)** *Ex vivo* mouse localization image with quantitative susceptibility maps on selected slices at 1.5 T and 3 T and difference allowing specific NPIO imaging with suppression of background.

Conc.: Concentration; dreMR: Delta-relaxation enhanced magnetic resonance; NMRD: NMR dispersion; QSM: Quantitative susceptibility map; PBS: Phosphate-buffered saline; RSA: Rat serum albumin; SPIO: Superparamagnetic iron oxide particle; USPIO: Ultra-small superparamagnetic iron oxide particle. **(D)** Reproduced from [24] with kind permission from John Wiley & Sons. **(F)** Reproduced from [25] with kind permission from Elsevier.

Figure 3.4. Detection thresholds for various molecular MRI approaches.

For direct NMR detection, sensitivity expressed in molar concentration is on the order of 1 M and a gain can be obtained by either: increasing field strength, reducing coil size or increasing voxel size. Hyperpolarized approaches can give up to a 10^6 sensitivity gain, and even higher (10^9) by using CEST amplification effect [12,13]. ^{19}F nanoparticles provides a 10^4 (10 nm diameter particles) to 10^8 (200 nm diameter particles) gain if sensitivity gain is expressed in terms of particle concentration. Combining a high field, reduced coil size and an increased voxel size (e.g., a factor 10 in volume that is equivalent to a factor 2.2 in each direction), can provide a significant gain in sensitivity. Indirect detection through the use of CA is already sensitive in the 10 μM range with standard CA, and μM range with an optimized CA binding to macromolecules (such as Gd-bound at ~ 0.5 T). If accumulated, T_1 -agents can exhibit quenching (see Chapter 5). However, combining this intrinsic efficiency with nanoparticles (such as iron oxide NPs) provides a direct 10^4 to 10^8 gains for 10 and 200 nm diameter particles, respectively, if expressed in terms of particle concentration; gains that could also be combined to a reduced coil size and increased voxel size to further enhance detection thresholds.

CA: Contrast agent; CEST: Chemical exchange saturation transfer; HP: Hyperpolarized; NP: Nanoparticle.

very specific way to differentiate bound to free CA. Extending these concepts, from the NMRD profiles, field-cycling could also be performed at lower field in the up-rise slope of r_1 using T_1 -contrast modulation, or in the up-rise slope of r_2 using T_2 -contrast modulation. Additionally, based on magnetization profiles that display highly nonlinear effects for superparamagnetic CA, it was shown that it can be used to differentiate them from the linear diamagnetic and paramagnetic substances [25]. With the field-cycling technology, it should be possible to perform

specific detection of superparamagnetic CA using MRI from magnetization measurement leading to a technique similar to the recently proposed magnetic particle imaging (MPI) [26]. To exploit the high potential of these approaches, more efficient molecular probes should be developed together with field cycling through whole-body resistive magnets, or with an additional coil allowing cycling the field directly within a superconducting magnet.

Conclusion

Figure 3.4 provides the order of magnitude for detection thresholds for *in vivo* preclinical and clinical molecular MRI with the various approaches presented here. The influences of the field, the reception coil and the voxel size has been included to show that they can give orders of magnitude increase in sensitivity, either through high-field systems, or through the limitation to smaller regions instead of whole body imaging, or through a reduction in spatial resolution. The latter is the easiest to perform and can rapidly provide orders of magnitude increase in sensitivity leading to low-resolution functional images that can be superimposed to anatomy provided by MRI. The limited sensitivity of direct NMR detection at thermal polarization can be overcome through the use of hyperpolarization and large particles, leading to sensitivities in the micromolar range that can be enhanced through longer T_1 and the use of saturation transfer. Indirect detection of CAs through their effects on water proton is already sensitive in the micromolar range with current contrast agents and even lower when considering the per particle efficiency (i.e., that may contain thousands of probes). This approach can be enhanced through the optimization of relaxation mechanisms and through modulation and mixing of contrasts allowing more specific detection. In the future, MR systems able to separate polarization, relaxation and detection of specially designed probes will lead to enhanced sensitivity and specificity for molecular MRI.

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M Poirier-Quinot and L de Rochefort contributed equally to this chapter.

Financial & competing interests disclosure

L de Rochefort has a patent pending on quantitative susceptibility mapping technology. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Summary

- The signal-to-noise ratio for direct NMR detection depends on multiple parameters: static magnetic field B_0 , imaging sequence, reception coils, polarization and the total time during which voxel signal is recorded.
- The contrast-to-noise ratio for exogenous contrast agent detection depends on signal-to-noise ratio, on relaxivity and on the intrinsic tissue relaxation parameters.
- Increase in NMR sensitivity can be obtained through high field or hyperpolarization, through optimization of reception coils, and through the use of large nanoparticles and amplification strategies such as cell internalization.
- Contrast agent relaxation parameters can be further optimized to obtain a significant increase in efficiency.
- MR systems and sequences able to separate polarization, relaxation and detection of specially designed probes will further lead to enhanced sensitivity and specificity for molecular MRI.

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