MRI has become a very important tool for clinical diagnosis of disease as well as in biomedical studies for the noninvasive three-dimensional imaging of living subjects and specimens. It can distinguish between various parts of soft tissue water based on differences in the longitudinal relaxation time ($T_1$), the transverse relaxation time ($T_2$), the apparent transverse relaxation time ($T_{2*}$) and the water concentration.

Since the clinical introduction of MRI in the early 1980s, it became obvious that the need of exogenous molecules was crucially needed to locally enhance the signal in presence of low intrinsic contrast. Similar to opaque agents used in x-ray computed tomography (CT), the use of MRI agents would substantially improve the sensitivity and specificity of this new technique. Unlike the differential attenuation measured by CT, the contrast agents (CAs) in this case would alter multiple MR parameters. The MR signal resulting changes will be induced by significant variation of the relaxation times $T_1$, $T_2$, and $T_{2*}$ of the water in the vicinity of CAs leading to $T_1$- (or $T_2$, $T_{2*}$-) weighted image contrast.

While both organic and inorganic molecules can act as MRI CAs, agents containing metal atom such as gadolinium(III) (Mody et al., 1999), manganese(II) and iron(III) (Koblinsky et al., 2000) are almost exclusively chosen due to their excellent magnetic properties. These free metal ions can however be very toxic to biological systems. Hence, they require being complexed by chelating agents to form nontoxic compound while maintaining the needed magnetic properties.

The gadolinium(III) complex diethylenetriaminepentaacetic acid (DTPA, gadopentetate dimeglumine, or Magnevist™) is the most commonly used clinical agent to delineate diseased tissue based on the uptake rate or vascular eakage (Weinmann et al., 1984). Over these past two decades, MR CAs have evolved towards increasing specificity and function by rendering the resulting agent targeted to specific tissues and organs (Brasch et al., 1992; Weinmann et al., 2003).

Blood pool agents for MR angiography are in the other hand based on much larger macromolecule CAs (Hoffmann et al., 1999; Fink 2007; Kramer et al., 2007) designed to recirculate in the blood for an extended period either through protein-binding (Caravan et al., 2002, Cavagna et al., 2002), through the use of polymeric complexes (Schuhmann-Giampieri et al., 1991; Cavagna et al., 1994; Corot et al., 2000; Misselwitz et al., 2001) or through the use of dendrimers obtained by complete synthetic cascade polymers (Weiner et al., 1994). Their large size prevents their extravasations through the endothelium of normal tissue. Their entering into interstitial space is slow enough to prevent the accumulation of detectable amounts before complete excretion from the body. These compound have also been used to visualize myocardial necrosis (Muhler et al., 1995; Kroft et al., 1999) and viability (Schmiedl et al., 1987) as well as to detect tumors (Daldrup et al., 1997; Kiessling et al., 2007). We will illustrate through examples the effect of the inclusion of a polyethylene glycol on the solubility, plasma half-life and biodistribution of blood agents.

The use of superparamagnetic iron oxide nanoparticles (SPIO) can aid in distinguishing various internal structures (neovascularization and edema) and type of tumors. It enables the early detection and monitoring of early stages of tumor development in the brain (Rousseau et al., 1998), the lymph nodes (Harisinghani et al., 1997; Wunderbaldinger et al., 2002; Stets et al., 2002), the liver (stark et al., 1988; Hahn et al., 1990; Sugarbaker et al., 1990) and the splenic tumor (Tanimoto et al., 2001). Similar to the previously described Gd-based nanoparticles, polyethylene glycol can be used to sterically stabilize small unilamellar vesicles enabling the differentiating between colon carcinoma cells and healthy tissue in rats (Pauser et al., 1997).
On a much smaller scale and readily accessible approach, manganese can be used efficiently in biomedical research to later contrast tissue contrast. In fact, it was the first paramagnetic element suggested for enhancing imaging contrast in a phantom by Lauterbur in his landmark paper in 1973. It was subsequently tested successfully on differentiating tissue contrast from various organs by the same group (Mendonca-Dias et al., 1983). Yet, only one chelated form manganese dipyridoxyl diphosphate (MnDPDP, Teslascan, Amersham, Princeton, NJ, USA) has found clinical and FDA approval so far (Federle et al., 2000). The clinical usefulness of MnDPDP (termed also mangafodipir trisodium) has been exclusively aimed for imaging the hepatobiliary system through slow dissociation of Mn to be taken up by hepatocytes followed by biliary excretion (ToF et al., 1997; Jung et al., 1998; Reimer et al., 2004).

In the other hand, manganese Mn$^{2+}$ acting as a calcium analogue has become a very popular and powerful contrast agent for small animal MRI over this past decade. The associated approach termed as Manganese Enhanced MRI (MEMRI) (Koretsky et al., 2004) based on the confined presence of Mn$^{2+}$ in specific tissues can provide highly localized contrast brightening changes either through passive or active redistribution. Although, little is known about the manganese uptake mechanisms and dynamics of transport, MEMRI has seen the emergence of a wide variety of applications. We will review how MEMRI can be broadly used to visualize the 3D brain neuro-architecture (Watanabe et al., 2002; Wadghiri et al., 2004), the functional mapping of neuronal activity (Lin et al., 1997; Tindemans et al., 2003; Xin et al., 2005) as well as the neuronal circuitry through track tracing of neuronal projection (Pautler et al., 1998, Cross et al., 2008; Bertrand et al., 2010).

Although the main focus of this part of the course will be in the brain, the examples shown will be used to highlight the practical implication of administration routes on Mn$^{2+}$ biodistribution, the mechanisms of tissue uptake and redistribution as well as the characterization of intra-neuronal transport though track-tracing dynamic studies and the impact of the physiological status of the subject being studied.

References


