Molecular & Cellular Imaging: From the Bench to the Bed

Lecture title: Basic Relaxation Mechanisms & Contrast Agent Design

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Target audience: M.D. and Ph.D. researchers with an interest in molecular imaging concepts, applications and clinical translation.

Outcome objectives:
- Review basics of paramagnetic relaxation theory
- Review basic designs of biologically responsive agents
- Demonstrate why water exchange rates are so important in CA design
- Compare chemical features of T_1, T_{2exch}, and CEST agents
- Illustrate *in vivo* examples of responsive contrast agents
- Discuss obstacles for translation of new agents to the clinic

Background: MRI contrast agents play an important role in clinical medicine. Gadolinium-based agents in particular have gained the most favor among clinicians because they provide positive image contrast in most MR sequences, are easily administered and rapidly excreted, and have been proven safe at clinically acceptable doses over the past ~25 years. All current clinically approved agents vary only in the chemical structure of the ligand that surrounds or encapsulates the Gd^{3+}; all are low molecular weight, water soluble molecules that distribute throughout all extracellular space before being excreted largely via the kidneys. Scientific interest in new types of contrast agents has grown considerably over the past decade or more even though there has been little investment in development of new agents by industry. Newer MR methods such as APT, CEST and hyperpolarization offer considerable potential for providing new insights into metabolism *in vivo* but responsive Gd^{3+}-based agents remain the focus in many research labs. So, one of the challenges faced by the MR research community is to continue pushing for investments and regulatory approval of newer types of contrast agents that can provide specific diagnostic tests for clinicians.

Basic Theory: The design of Gd^{3+}-based responsive MR contrast agents is typically based either on a change in *q*, the number of inner-sphere water molecules, or a change in molecular reorientation as governed by the rotation correlation time, τ_R. The rate at which water molecules exchange between an inner-sphere water coordination site on the Gd^{3+} (or other lanthanide ion) and tissue water is rarely considered in the design of responsive agents. This rate is overlooked as a potential variable perhaps for a couple of reasons. First, measuring water exchange rates is not a simple procedure, usually requiring careful temperature-dependent

measures. Second, our scientific understanding of how to fine-tune water exchange rates using simple chemical principles is poor so designing new agents with specific water exchange rates is difficult if not impossible. Nevertheless, one can easily argue that water exchange may be *the key parameter* one should consider in any new molecular design.

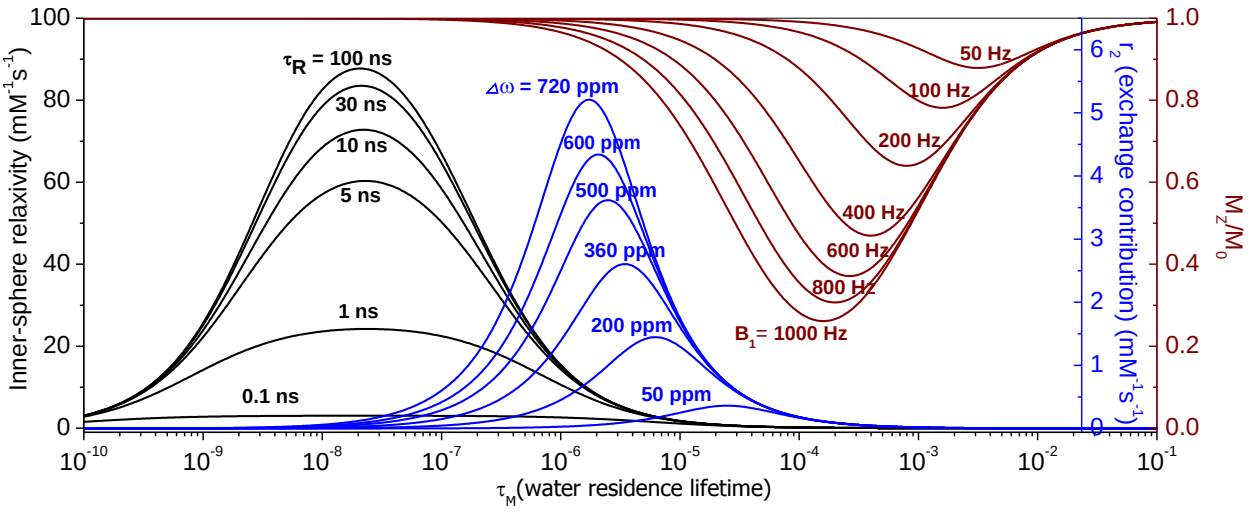

Figure 1. Simulated curves showing the effect of water residence lifetime (τ_M) of inner-sphere bound water on the r_1^{IS} for a Gd^{3+} complex, r_{2exch}, and CEST effect for various lanthanide complexes as a function of τ_R, $\Delta\omega$, and B_1, respectively, at 3T.

Take-home lessons: In this lecture, the impact of water exchange rates on three classes of lanthanide-based MRI contrast agents, T_1-based relaxation agents, T_2 exchange line-broadening agents, and chemical exchange saturation transfer (CEST) agents will be discussed and examples of *in vivo* applications of such agents will be presented.