An Analysis of NMRD profiles and ESR lineshapes of MRI Contrast Agents

Xiangzhi Zhou

Bio-physical Chemistry
Department of Chemistry
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Abstract

To optimize contrast agent in MRI scan region, e.g. to enhance paramagnetic relaxation in the MRI scan fields (0.1T-3T), one possible way is to slow down the tumbling of the paramagnetic complex. The effect of slowing down the reorientational motion of the complex to increase relaxivity is obvious and this strategy has already been employed in producing MRI contrast agent that can bind to specific proteins. An example is MS-325 binds to human serum albumin (HSA). The slow down effects on the ligands around paramagnetic ion, and on the zero field splitting (ZFS) interaction are under studies and the physics behind is still not clear. In this thesis, a generalized Solomon-Bloembergen-Morgan (GSBM) theory together with stochastic Liouville approach (SLA), is applied to investigate the mechanism behind the slow down effects. Two gadolinium complexes, MS-325+HSA and Gd(H₂O)₈³⁺+glycerol are studied by means of NMRD and ESR experiments.

GSBM is a second order perturbation theory with closed analytical form. The computation based on this theory is fast, but it has its limitation and in the case of Gd(S=7/2) the ZFS strength times its correlation time (Δₜ · τₙ) should be less than 0.1. In comparison, the SLA is an "exact" theory that can evaluate the validity of GSBM calculation. However, the calculation in SLA is time consuming due to the large matrix it constructed. The major model used in GSBM is a two dynamic model, characterized by transient ZFS Δₜ and static ZFS Δₘ and their corresponding correlation time τₙ and τₙ, while in SLA the model is only described by Δₜ and τₙ. A combined NMRD and ESR analysis is used to understand the details of ZFS interaction. Both models can reproduce experimental NMRD profiles and model parameters are similar; for ESR linewidths the model parameters are quite different. The fitting results indicate the NMRD profiles are less sensitive to the detail expression of ZFS correlation function. In order to interpret both NMRD and ESR experiments with identical parameters, a more complex ZFS interaction model should be developed.

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GSBM is a second order perturbation theory with closed analytical form. The computation based on this theory is fast, but it has its limitation and in the case of Gd(S=7/2) the ZFS strength times its correlation time ($\Delta_t \cdot \tau_f$) should be less than 0.1. In comparison, the SLA is an "exact" theory that can evaluate the validity of GSBM calculation. However, the calculation in SLA is time consuming due to the large matrix it constructed. The major model used in GSBM is a two dynamic model, characterized by transient ZFS $\Delta_t$ and static ZFS $\Delta_s$ and their corresponding correlation time $\tau_f$ and $\tau_R$, while in SLA the model is only described by $\Delta_t$ and $\tau_f$. A combined NMRD and ESR analysis is used to understand the details of ZFS interaction. Both models can reproduce experimental NMRD profiles and model parameters are similar; for ESR linewidths the model parameters are quite different. The fitting results indicate the NMRD profiles are less sensitive to the detail expression of ZFS correlation function. In order to interpret both NMRD and ESR experiments with identical parameters, a more complex ZFS interaction model should be developed.
List of Papers

1. Xiangzhi Zhou, Peter Caravan, R.B. Clarkson and Per-Olof Westlund, 
   On the philosophy of optimizing contrast agents. An analysis of $^1$H NMRD profiles and ESR lineshapes of the Gd(III) complex MS-325+HSA.  

2. Xiangzhi Zhou and Per-Olof Westlund,  
   $^1$H NMRD Profiles and ESR lineshapes of Gd(III) complexes: A Comparison between the generalized SBM and the Stochastic Liouville approach.  

3. Xiangzhi Zhou and Per-Olof Westlund,  
   The Viscosity and Temperature dependence of X-band ESR lineshapes of Gd(III) Aqueous Complex.  

4. Xiangzhi Zhou and Per-Olof Westlund,  
   The Viscosity and Temperature dependence of $^1$H $T_1$-NMRD of the Gd(H$_2$O)$_8^{3+}$ Complex.  
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A Liouville Space
Chapter 1

Introduction

1.1 Spin Relaxation

For a spin system without external magnetic field, the orientation of spin is random and irregular, there is no net magnetic field in this spin system from a macroscopic point of view. When an external magnetic field is applied on, for example, a spin system with spin number 1/2, there will be two different spin states coming up: "spin up" and "spin down". The number of spins in each state will have a Boltzmann distribution\[1\]

\[
\frac{n_1}{n_2} = e^{-(E_1 - E_2)/k_BT} \tag{1.1}
\]

after the system reaches equilibrium, where \(n_1\) and \(n_2\) are the number of spins in state up and down, \(E_1\) and \(E_2\) are the energy of each states, \(k_B\) is Boltzmann constant and \(T\) is the system temperature. The difference between \(n_1\) and \(n_2\) will cause a net magnetic field in the spin system.

If the above equilibrium is disturbed, for example by applying a magnetic field in the direction which is perpendicular to the original static field, the equilibrium will be destroyed and a new equilibrium state will be established if the new field stays there all the time. But what will happen if we take this new magnetic field away? From our instinct we say the spin system will go back to its original equilibrium state. The process going back to equilibrium is the so called relaxation.

Suppose the spin system is in a very ideal condition, in which the interaction between spin and original magnetic is the only interaction in the system, thus the original magnetic field is the driving force to make disturbed spin system back. Unfortunately it will not stop at the equilibrium
CHAPTER 1. INTRODUCTION

point that we expected, but goes on to another side, then back and forth, like a harmonic oscillation never stops if no "friction" exists.

But the above nonstop vibration will never happen, in fact the spin system will finally goes back to its original equilibrium. So there must be some mechanism acting as "friction" forcing it to stop at the equilibrium point. The lattice dynamic(Temperature) and the fluctuating local magnetic fields are the sources of "friction". There are many local magnetic fields caused by other spins and orbitals, and the most important, those local fields are fluctuating with the random movement of atoms and molecules where those spins and orbitals are located.

The local fluctuating field gives relaxation to the spin system. We can use a interaction Hamiltonian to express the interaction between spins. Assume the interaction Hamiltonian at a certain time $t$ is $\hat{H}_{inte}(t)$, the time correlation function can be defined as

$$G(\tau) = \langle \hat{H}_{inte}(t) \hat{H}_{inte}(t + \tau) \rangle. \quad (1.2)$$

Due to the irregular fluctuation of the interaction Hamiltonian, the correlation function will approach zero after a certain time. The integration of the normalized time correlation function along time axis is defined as the correlation time. Fourier transform the above time correlation function, we will get the Spectral Density function in frequency domain. The frequency we are interested in is the spin Larmor frequency. Usually zero frequency and double Larmor frequency are also considered, but they are less efficient for the relaxation mechanism.

1.2 MRI Contrast Agent

Nuclear spin relaxation time could be affected in the vicinity of paramagnetic ions, and those ions which shorten the proton spin relaxation time in aqueous solutions are extensively studied due to their application as contrast agents in Magnetic Resonance Imaging(MRI).

The unpaired electrons of paramagnetic ions have larger magnetic dipole moments than proton, thus the local magnetic fields are enhanced and influence the proton spin relaxation time. In this thesis, for proton spin relaxation, only proton spin-electron spin dipole-dipole(DD) interaction is considered because the DD interaction is the dominant factor that causes the proton spin-lattice relaxation. The lanthanide metal, gadolinium($S=7/2$), which contains 7 unpaired electrons in its 4f orbital, is the most widely used MRI contrast agent element in clinical application.
1.3. **STOCHASTIC LIOUVILLE EQUATION**

Although Gd(III) has strong paramagnetic enhancement, free gadolinium ion exhibits low in vivo stability and is deposited in lung and kidney, causes necrosis in liver and spleen and blocks different calcium channels in human cells[2]. The method to reduce the Gd ion toxicity is to incorporate it into polybasic organic ligands and form stable chelates or complexes[3]. These compounds have good stability and renal clearance in human body. For example, when the ligands such as DTPA are chelated to Gd ion, the whole Gd-DTPA complex has no detectable dissociation in the body and is excreted intact[4]. Early Gd related contrast agents were extracellular agents which were only simple chelates of Gadolinium. Extracellular agents have no specific targets and are distributed evenly upon injection, which is often used in the detection of tumors in brain and breast.\(^1\)

Later blood pool agents were developed to enhance the vascular structure. The receptor-induced magnetization enhancement (RIME) strategy[5] gives a method which involves targeting a small Gd(III) complex to a particular protein, in which the Gd(III) complex tumbles at a rotational rate similar to that of the target big molecule because of the binding. MS-325 is a typical pool agent which has strong binding to human serum albumin (HSA).

In this thesis two Gd complexes (MS-325 and Gd(H\(_2\)O\(_8\))\(^{3+}\)) are studied and the mechanism of optimizing relaxivity of these two complexes are investigated.

1.3 **Stochastic Liouville Equation**

The probability of the spin in each state and the coherence between different states could be illustrated by density operator[6]. The matrix corresponding to the density operator is called the density matrix. In quantum spin systems, the time evolution of the density operator can be calculated by the quantum mechanical equivalent Liouville equation

\[
\frac{d}{dt}\sigma(t) = -\frac{i}{\hbar}[H(t), \sigma(t)] = -iL(t)\sigma(t)
\]

(1.3)

where \(H(t)\) is the Hamiltonian describing the whole spin system, \(L(t)\) is the corresponding Liouville operator, and \(\sigma(t)\) is the density operator. This equation is also called density operator equation[7], which is useful for calculating the dynamics of the spin system. In this thesis, this equation is the starting point of studying the relaxation of the spin systems.

\(^1\)Malignant tumors have their own blood supply network once they reach a certain size. In a MRI scan, a contrast agent injected into the bloodstream can detect a tumor by highlighting its blood vessel network.
Since the spin system is subject to random external perturbations, this differential equation is also called stochastic Liouville equation (SLE). SLE could be solved exactly when the perturbation Hamiltonian is well defined, or approximately especially when the perturbation is weak and rapid [8]. In this thesis, the approximate solution is applied on proton spin system as well as the electron spin system. However, the approximation is not always valid in the electron spin system, where the perturbation is larger and slower, therefore the exact method should be applied on studying the dynamics of electron spin system.

In this thesis, the SLE are solved within the frame of Liouville superoperator formalism. The approximate method (Redfield theory) will be presented first. Then the exact method (stochastic Liouville approach) will be briefly introduced. The limitation of the approximate method is discussed in detail in the enclosed Paper 2.

1.4 Relaxation related Experiments

Proton spin relaxivity measured as a function of magnetic field is called NMR dispersion (NMRD) experiment. Proton T1 NMRD profiles are informative tools to explore the dynamics of molecules, especially those complexes containing paramagnetic ions which drastically change the proton relaxation time in certain range of proton Larmor frequency. In the range 0.01-50 MHz, NMRD profiles could be measured by field cycling relaxometer. The electromagnet in the relaxometer could generate magnetic field from the earth magnetic level up to 1 Tesla, thus convenient measurements could be accomplished in a single experiment. However, low field means low sensitivity and resolution, in which the relaxation time actually is a weighted value for all the protons in different groups. At the proton Larmor frequency higher than 50 MHz, relaxation time could be measured on standard NMR spectrometers equipped with superconducting magnets. At frequencies higher than 600 MHz, a problem of too much protons may arise for cryo-probe, which causes radiation damping [9] and the inversion recovery method can not be used. Nevertheless, the saturation recovery method can be used instead, but the reliability of the results should be considered.

NMRD experiment is an indirect way to study the electron spin system. More direct information could be obtained by Electron Spin Resonance (ESR) measurements on the interested paramagnetic complex. Although for many paramagnetic ions ESR experiment is not applicable because their fast relaxation makes the ESR lineshapes too broad, gadolinium...
is an exception. The X-band ESR spectra of Gd usually have linewidths ranging from 100-700 Gauss. Since the ESR lineshape/linewidth indicates the electron spin-spin relaxation, it provides direct dynamic information of the electron spin system. However, attention should be paid due to that the X-band ESR spectrum of Gd ion is Gd concentration dependent[10].
Chapter 2

Redfield Theory

Relaxation in a spin system, can be treated both classically and quantum mechanically. For a spin system which has a solvable time-independent Hamiltonian and a small perturbative time-dependent Hamiltonian, the time dependent perturbation theory is an ideal way to calculate the time dependent quantum energy levels and eigenstates. The Redfield theory, also referred as Wangsness-Bloch-Redfield (WBR) theory [11]-[14], is a time dependent perturbation theory, developed to describe the time evolution of the density operator [6] of the spin system.

In this chapter, I am going to give a general introduction of the Redfield theory using Liouville space super operator formalism. The generalized SBM (GSBM) theory [15]-[18] will be derived within the frame of Redfield theory and Liouville formalism. The purpose of this chapter is to simplify the Liouville equation

\[
\frac{d}{dt} \sigma(t) = -i(L_0 + L_1(t))\sigma(t) \tag{2.1}
\]

into a Redfield equation:

\[
\frac{d}{dt} \sigma(t) = -iL_0\sigma(t) + R\sigma(t) \tag{2.2}
\]

where \( L_0 \) is the Liouville superoperator, \( L_1(t) \) is the perturbation Liouvillean supposed to be weak and fast, \( R \) is the Redfield superoperator which gives the relaxation, and \( \sigma(t) \) is the density operator.

2.1 WBR Theory on Nuclear Spin System

Here we focus on nuclear spin system and the lattice around, starting with the Liouville-Von Neumann equation which describes the motion of the en-
CHAPTER 2. REDFIELD THEORY

tire spin lattice system
\[
\frac{d}{dt} \sigma(t) = i(L_I + L_L + L_{IL}) \sigma(t)
\]
(2.3)
in which \( L_I \) is the nuclear spin Liouvillean, \( L_L \) the lattice Liouvillean and \( L_{IL} \) the spin-lattice interaction Liouvillean.

In interaction picture the above equation can be expressed as
\[
\frac{d}{dt} \sigma^*(t) = iL_{IL}^* \sigma^*(t)
\]
(2.4)
where
\[
\sigma^*(t) = e^{-i(L_I + L_L)t} \sigma(t)
\]
(2.5)
\[
L_{IL}^*(t) = e^{-i(L_I + L_L)t} L_{IL} e^{i(L_I + L_L)t}
\]
(2.6)

We can resolve this equation (Eq. 2.4) of motion by cumulant expansion:
\[
\sigma^*(t) - \sigma^*(0) = \sum_{n=1}^{\infty} (-i)^n \int_0^t dt_1 \cdots \int_0^{t_{n-1}} dt_n L_{IL}^*(t_1) \cdots L_{IL}^*(t_n) \sigma^*(t_n)
\]
(2.7)

If we truncate the terms higher than second order and write the total density operator as a direct product of nuclear spin density operator \( \sigma_I^*(t) \) and lattice density operator \( \sigma_L^{eq} \), the equation can be written by
\[
\frac{d}{dt} \sigma_I^*(t) = - \int_0^\infty d\tau T_{RL} \{ L_{IL}^*(t) L_{IL}^*(t - \tau) \sigma_L^{eq} \} \sigma_I^*(t)
\]
(2.8)

Finally this equation can be transformed back to Schrödinger picture from interaction picture and the equation of motion of the nuclear spin density operator is obtained:
\[
\frac{d}{dt} \sigma_I(t) = [-iL_I + R] \sigma_I(t)
\]
(2.9)
where the relaxation superoperator \( R \) is
\[
R = - \int_0^\infty d\tau T_{RL} \{ L_{IL} e^{-i(L_I + L_L)\tau} L_{IL} \sigma_L^{eq} \}
\]
(2.10)
2.1. WBR THEORY ON NUCLEAR SPIN SYSTEM

2.1.1 Nuclear Spin Lattice Interaction

The Hamiltonian describing the interaction between nuclear spin and lattice can be written as

\[ H_{IL} = \sum_{n=-1,0,1} (-1)^n I_n^1 T_n^1 \]  

(2.11)

where \( I_n^1 \) is nuclear spin operator and \( T_n^1 \) is lattice operator which can be written as contraction of a rank one irreducible spherical tensor operator \( S_1^q \) for electron spins and a rank two irreducible spherical tensor operator \( F_2^q \) for the reorientation of the spin-spin vector

\[ T_n^1 = (-1)^{n+1} \sqrt{3} \sum_{q=-1,0,1} \left( \frac{1}{q} \frac{2}{n-q} \frac{1}{-n} \right) S_1^q F_2^{n-q} \]  

(2.12)

where

\[ F_2^q = -\sqrt{10} k D_0^2(\Omega) \]  

(2.13)

in which \( D_0^2(\Omega) \) is the Wigner rotation matrix element\[19\] and \( k \) is the interaction constant

\[ k = \frac{\mu_0 \hbar \gamma_I \gamma_S}{4\pi r_{IS}^3} \]  

(2.14)

where \( \gamma_I \) and \( \gamma_S \) are magnetogyric ratio for nuclear and electron, \( r_{IS} \) is the distance between nuclear spin and electron spin. Now we can rewrite the relaxation superoperator using the interaction Hamiltonian and decompose the nuclear spin system and the lattice system\[18\][20]

\[ R = -\sum_n K_n(n\omega_I) T_n^1 T_n^{1\dagger} \]  

(2.15)

where the spectral density \( K_n(n\omega_I) \) is the Fourier-Laplace transformation of the correlation function of the lattice operator

\[ K_n(n\omega_I) = \int_0^\infty \text{tr}_L \{ T_n^1 \exp(iL_L t) T_n^1 \sigma_L \} \exp(-i\omega_I t) dt \]  

(2.16)
2.1.2 Relaxation of Proton Spin (I=1/2)

In Liouville space, one basis set is using Irreducible Spherical Tensor Operators (ISTO)[19]. For nuclear spin, the operator is $O^\Lambda$. The Redfield matrix could be constructed in this basis set[20]:

$$O^\Lambda_R O^\Lambda = - \sum_n \sum \sum\text{Re}\{K_{n,-n}(n \omega_I)}\} (2I + 1)(I + 1)(2\Gamma + 1) \sqrt{(2\Lambda + 1)(2\Lambda' + 1)} \left((-1)^{\Lambda+1+\Gamma} - 1\right) [1 - (-1)^{\Lambda'+1+\Gamma}]$$

$$\left(\begin{array}{ccc} \Lambda & 1 & \Gamma \\ -\lambda & n & \gamma \end{array}\right) \left(\begin{array}{ccc} \Gamma & 1 & \Lambda' \\ \gamma & n & -\lambda' \end{array}\right) \left\{ \begin{array}{ccc} \Lambda & 1 & \Gamma \\ I & I & I \end{array}\right\} \left\{ \begin{array}{ccc} \Gamma & 1 & \Lambda' \\ I & I & I \end{array}\right\}$$

(2.17)

where $\left(\begin{array}{ccc} \Lambda & 1 & \Gamma \\ -\lambda & n & \gamma \end{array}\right)$ is a 3$j$-symbol and $\left\{ \begin{array}{ccc} \Lambda & 1 & \Gamma \\ I & I & I \end{array}\right\}$ is a 6$j$-symbol[19].

For proton spin (I=1/2) the spin-lattice relaxation time $T_1$ is

$$\frac{1}{T_1} = O^\Lambda_{0}^\dagger R O^\Lambda_{0} = -2\text{Re}\{K_I(\omega_I)\}$$

(2.18)

Thus far, the equations for proton spin $T_1$ has been formulated, but the lattice Liouvillean including electron spin Liouvillean has not yet been given.

2.2 WBR Theory on Electron Spin System

2.2.1 Electron spin Liouvillean

In previous section, the electron spin system is regarded as a part of lattice around nuclear spin system. In this section, the electron spin system will be described and Redfield theory will be applied on it. For electron spin $S \geq 1$, Zero Field Splitting (ZFS) is the main interaction which affects the electron spin relaxation. The electron spin Liouvillean can be expressed as the sum of electron spin Zeeman Liouvillean and ZFS Liouvillean

$$L_S = L^Z_{\text{Zeeman}} + L^Z_{\text{ZFS}}.$$  (2.19)

2.2.2 Zero field splitting

Zero field splitting is the phenomenon of the separation of multiplet sublevels of electron spin in the absence of an external magnetic field. ZFS is caused by crystal field effects, either by electron-electron dipolar interaction, or
by spin-orbit interaction. In the case of transition metal complexes, the spin-orbit coupling between unpaired electrons dominates ZFS.

ZFS influences the spin energy levels, and further the spin relaxation and ESR lineshape, so it is important to have a reasonable ZFS Hamiltonian expression. The electron spin ZFS Hamiltonian is expressed by a scalar contraction of irreducible spherical tensor operators

\[ H_{\text{ZFS}}(t) = \sum_{n(-2,-1,0,1,2)} (-1)^n F^2_{-n}(t) S^2_n \]  

(2.20)

where \( F^2_{-n}(t) \) is a stochastic time dependent second rank tensor function and \( S^2_n \) is an irreducible spherical standard electron spin operator. If we introduce 3 different frames: Principal frame(P), Laboratory frame(L) and macro Molecular fixed frame(M), we can rewrite the ZFS function \( F^2_{-n}(t) \) in detail:

\[ F^{2(L)}_{-n}(t) = \sum_k \sum_m f^2_{k} D^2_{km}[\Omega_{MP}(t)]D^2_{m-n}[\Omega_{LM}(t)] \]  

(2.21)

where \( f^2_{k} \) are the components of ZFS tensor. The time dependence of the Euler angles \( \Omega_{MP}(t) \) is due to local distortion of the ligand field symmetry. And the time dependence in \( \Omega_{LM}(t) \) is caused by the reorientation of the macromolecule and is expected to be slower than the relaxation of the electron spin system. Due to the influence from macromolecule the ZFS interaction can not give a zero averaged value, so the ZFS interaction could be split into two parts: static part

\[ F^{2(L)\text{Static}}_{-n}(t) = \sum_k \sum_m f^2_{k} S^2_{km} D^2_{m-n}[\Omega_{LM}(t)] \]  

(2.22)

and transient part

\[ F^{2(L)\text{Transient}}_{-n}(t) = \sum_k \sum_m f^2_{k} \left(D^2_{km}[\Omega_{MP}(t)] - S^2_{km}\right) D^2_{m-n}[\Omega_{LM}(t)] \]  

(2.23)

where \( S^2_{km} \) is the partial average \( \langle D^2_{km}[\Omega_{MP}(t)] \rangle \).

The ZFS fluctuating with time as transient ZFS is the dominant mechanism for the electron spin relaxation for \( S \geq 1 \). The amplitude of static ZFS and its contribution to the electron spin relaxation is still not clear. Usually, for a homogeneous system in which the metal ions are surrounded by water molecules, the static term of ZFS is averaged to zero. For low symmetry
complexes, the static ZFS is present under the condition that the average symmetry of the paramagnetic site is less than octahedral. The static ZFS interaction is modulated by the reorientational motion and influences primarily the energy level fine structure.

The simplified Hamiltonians of static ZFS and transient ZFS that can be used in Redfield theory can be expressed by

\[ H_s^{ZFS} = \Delta_s^{ZFS} D_{00}^2(\Omega_{LM})S_0^2 \]  
(2.24)

and

\[ H_t^{ZFS} = \Delta_t^{ZFS} D_{00}^2(\Omega_{MP})S_0^2 \]  
(2.25)

where \( S_0^2 \) is a standard second rank electron spin operator, and \( D_{00}^2 \) are the reduced Wigner rotation matrix elements.

### 2.2.3 Redfield Equation of Electron Spin System

Redfield theory used on electron spin system follows the same way as it used on nuclear spin system. Starting again from the Liouville-Von Neumann equation which describes the motion of the entire electron spin system

\[ \frac{d}{dt} \sigma_S(t) = i(L_S^{Zeeman} + L_S^{ZFS})\sigma_S(t) \]  
(2.26)

in which \( \sigma_S(t) \) is the density matrix of the electron spin system.

In interaction picture the above equation can be expressed as

\[ \frac{d}{dt} \sigma^*_S(t) = iL_s^{*ZFS} \sigma^*_S(t) \]  
(2.27)

where

\[ \sigma^*_S(t) = e^{-i(tS^{Zeeman})} \sigma_S(t) \]  
(2.28)

\[ L_s^{*ZFS}(t) = e^{-i(tS^{Zeeman})} L_s^{ZFS} e^{i(tS^{Zeeman})} \]  
(2.29)

This equation of motion can be resolved by cumulant expansion:

\[ \sigma^*_S(t) - \sigma^*_S(0) = \sum_{n=1}^{\infty} (-i)^n \int_0^t dt_1 \cdots \int_0^{t_{n-1}} dt_n L_s^{*ZFS}(t_1) \cdots L_s^{*ZFS}(t_n) \sigma_S(t_n) \]  
(2.30)
If truncating the terms higher than second order, the equation can be written by

\[ \frac{d}{dt} \sigma^*_S(t) = - \int_0^\infty d\tau \text{Tr}_S \{ L^*_S L^*_ZFS(t) \{ \sigma^*_S(t) - \sigma^*_S(t - \tau) \} \sigma^*_S(t) \} \]  

(2.31)

This equation can be transformed back to Schrödinger picture from interaction picture and the equation of motion of the electron spin density operator is obtained:

\[ \frac{d}{dt} \sigma_S(t) = [-iL^Z_{\text{Zeeman}} + R] \sigma_S(t) \]

(2.32)

where the relaxation superoperator \( R \) is

\[ R = - \int_0^\infty d\tau \text{Tr}_S \{ L^*_S L^*_ZFS e^{-iL^Z_{\text{Zeeman}}\tau} \} \]

(2.33)

After applying the Redfield theory, the electron spin Liouvillean could be written as

\[ L_S = L_{Z_{\text{Seeman}}} - iR \]

(2.34)

Now we use the ZFS Hamiltonian in Eq.(2.20) and rewrite the relaxation operator

\[ R = - \sum_n \sum_{n'} \int_0^\infty d\tau \text{Tr}_S \{ F^2_{n,n'} \} \{ [S^2_{n'}, e^{-iL^Z_{\text{Zeeman}}\tau} S^2_n] \} + \text{Tr}_S \{ F^2_{n,n'} \} \}

(2.35)

where the correlation functions \( \text{Tr}_S \{ F^2_{n,n'} \} \) and \( \text{Tr}_S \{ F^2_{n,n'} \} \) are the same, and \( e^{-iL^Z_{\text{Zeeman}}\tau} S^2_n \) is \( e^{-i\omega S\tau} S^2_n \), then the relaxation operator can be simplified as

\[ R = - \sum_n \int_0^\infty d\tau \text{Tr}_S \{ F^2_{n,n'} \} \{ [S^2_{n'}, S^2_n] + [S^2_n, S^2_{n'}] \} e^{-i\omega S\tau} \]

(2.36)

If a super operator \( S^2_n \) is defined

\[ S^2_n = [S^2_{n'}, \ldots] \]

(2.37)
and a spectral density $K_n(n\omega_S)$ is defined by the Fourier-Laplace transformation of the correlation function $Tr_S\{F^2_{-n}F^2_{-n}\}$

$$K_n(n\omega_S) = \int_0^\infty d\tau Tr_S\{F^2_{-n}F^2_{-n}\} \exp(-in\omega_S\tau) \quad (2.38)$$

the relaxation super operator of electron spin system is finally given by

$$R = -\sum_n K_n(n\omega_S)S^2_n\sigma^2_n \quad (2.39)$$

The correlation function $Tr_S\{F^2_{-n}F^2_{-n}\}$ depends on the explicit expression of the ZFS Hamiltonian, but if we assume that it has the simplest exponential decay where the correlation time is $t$ and the amplitude is $f^2$, then the spectral density is

$$K_n(n\omega_S) = \int_0^\infty f^2 \exp(-\tau/t) \exp(-in\omega_S\tau) d\tau = f^2 \frac{t - in\omega_st^2}{1 + (n\omega_st)^2} \quad (2.40)$$

This spectral density has real and imaginary parts. More complicated models of spectral densities will be given in next section.

In Liouville space, if we choose the direct product of Zeeman states as the basis, the relaxation superoperator $R$ could be expressed by

$$R_{\alpha\alpha'\beta\beta'} = \sum_n (-1)^n \{\delta_{\alpha'\beta'} \sum_\gamma \langle \beta' | A_n | \gamma \rangle \langle \gamma | A_{-n} | \alpha' \rangle K(\beta' - \gamma)
+ \delta_{\alpha\beta} \sum_\gamma \langle \alpha | A_n | \gamma \rangle \langle \gamma | A_{-n} | \beta \rangle K(\gamma - \beta)
- 2\langle \alpha | A_n | \beta \rangle \langle \beta' | A_{-n} | \alpha' \rangle J(\alpha - \beta)\} \quad (2.41)$$

where $K(n) = J(n) + iQ(n)$; $J(n)$ and $Q(n)$ are real and imaginary parts of electron spin spectral density.

Now the relaxation time can be extracted from this Redfield matrix. But first, the matrix has to be transformed to a more convenient ISTO basis, because the above matrix is expressed in direct product of Zeeman basis $|S, m + \sigma\rangle\langle S, m|$. Assuming matrix $O$ represents basis $\hat{O}_{s}^\Sigma$ and $Z$ represents the old basis, the transformation matrix $T$ between the two basis $O$ and $Z$ is

$$O = TZ \quad (2.42)$$

Thus the Redfield matrix $R$ can be transformed to a new matrix $M$ with new basis by

$$M = TRT^{-1} \quad (2.43)$$
2.2. WBR THEORY ON ELECTRON SPIN SYSTEM

From certain elements of $M^{-1}$, the electron spin-spin and spin-lattice relaxation times could be obtained.

In real calculation when consider both static ZFS and transient ZFS, the static ZFS interaction which splits Zeeman levels will be considered either as a part of the electron spin Liouvillean or enter into the electron spectral density in relaxation matrix.

2.2.4 Electron spin spectral density

We can include both transient ZFS and static ZFS into electron spin spectral density (Model 2), or only include transient ZFS (Model 1) and add the static ZFS to electron spin Liouvillean.

Model 1

In this pseudo-rotation model\cite{21}\cite{22}, due to the slow tumbling of the complex, the complex is assumed not rotating, but distorting. The principal axis system of the complex is randomly changing, which can be modeled as a distortional diffusion. The transient ZFS tensor is defined in its own principal axis, first transformed to molecular frame (M) by $D_{km}^2[\Omega_{MP}(t)]$, then to laboratory frame (L) by $D_{m-n}^2[\Omega_{LM}(t)]$. The spectral densities of this isotropic pseudo-rotation model is defined as

$$J_n(n\omega_{S}(m_I)) \equiv \frac{\Delta^2}{5} \sum_k |D_{kn}^2(\Omega_{LM})|^2 \frac{\tau_k}{1 + (n\omega_{S}(m_I)\tau_k)^2}$$

with the dynamic frequency shift $Q_n$ defined by

$$Q_n(n\omega_{S}(m_I)) \equiv -\frac{\Delta^2}{5} \sum_k |D_{kn}^2(\Omega_{LM})|^2 \frac{\tau_k^2 n\omega_{S}(m_I)}{1 + (n\omega_{S}(m_I)\tau_k)^2}$$

The correlation times are then given as

$$\frac{1}{\tau_{0}} = \frac{1}{\tau_{\perp}}$$

$$\frac{1}{\tau_{\pm1}} = \frac{5}{6\tau_{\perp}} + \frac{1}{6\tau_{\parallel}}$$

$$\frac{1}{\tau_{\pm2}} = \frac{1}{3\tau_{\perp}} + \frac{2}{3\tau_{\parallel}}$$

The dynamics reflects the symmetry breaking motions in the first coordination sphere of the paramagnetic ion. If only one water molecule is coordinated to Gd-ion and other ligands are atoms from the macromolecule,
the "spinning" motion is expected to reflect the flickering/wagging motion of the water molecule, the correlation time $\tau_\parallel$ of the "spinning" of water molecule is expected to be in the range of 1-5 ps. The flexibility of the complex due to the other ligands may be expected to be slower which depends on the binding intensity between the complex and the macromolecule. The correlation time of this "perpendicular" motion is characterized by $\tau_\perp$.

**Model 2**

In this simplified model the spectral density is a combination of transient ZFS spectral density and static ZFS spectral density. The dynamic description of the transient ZFS is described by one correlation time $\tau_f$. In addition we assume that the coordination sphere is permanently disturbed resulting in a static ZFS which is modulated by the rotational diffusion motion of the paramagnetic complex. The correlation time of the motion of the static ZFS interaction is assumed as $\tau_R$, the same as the reorientation correlation time of the nuclear spin-electron spin vector. This simple model was first suggested by Dwek[23] for biochemical systems. The electron spin spectral densities are given in this case by:

$$ J_n(n\omega_s) = \frac{\Delta_t^2}{5} \frac{\tau_f}{1 + (n\omega_s\tau_f)^2} + \frac{\Delta_s^2}{5} \frac{\tau_R}{1 + (n\omega_s\tau_R)^2} $$  \hspace{1cm} (2.49)

with the dynamic frequency shift $Q_n$ defined by

$$ Q_n(n\omega_s) = -\left( \frac{\Delta_t^2}{5} \frac{\tau_f^2 n\omega_s}{1 + (n\omega_s\tau_f)^2} + \frac{\Delta_s^2}{5} \frac{\tau_R^2 n\omega_s}{1 + (n\omega_s\tau_R)^2} \right) $$  \hspace{1cm} (2.50)

### 2.3 GSBM theory

The essential part of GSBM theory is applying Redfield theory on electron spin system, using Liouville formalism, which has been done in previous section. Now we come back to the expression of $T_1$ for the proton spin Eq. (2.18) and calculate the spectral density $K_1(\omega_I)$. If the Lattice Liouvillian is written as the sum of electron spin Liouvillian and reorientation Liouvillian

$$ L_L = L_S + L_R $$  \hspace{1cm} (2.51)

and the decomposition approximation is applied which denote the lattice density operator as the direct product of electron spin density operator and reorientation density operator, we get

$$ K_1^{DD}(\omega_I) = s_{-1} + 3s_0 + 6s_1 $$  \hspace{1cm} (2.52)
where

\[
s_\sigma = \int_0^\infty Tr_S\{S_\sigma^1 \exp(iL_st)S_\sigma^1 \sigma_S\} \exp(-i\omega t - 1/\tau_R)tdt \tag{2.53}\]

If we define a super operator \(M\) as

\[
M = -iL_S + 1(i\omega_I - \frac{i}{\tau_R}) \tag{2.54}
\]

we get

\[
s_\sigma = \int_0^\infty Tr_S\{S_\sigma^1 \exp(-Mt)S_\sigma^1 \sigma_S\}dt = Tr_S\{S_\sigma^1 M^{-1}S_\sigma^1 \sigma_S\} \tag{2.55}\]

If change to ISTO base \(\{Q^\Sigma\}\) we get

\[
s_\sigma = \frac{S(S+1)}{3} Tr_S\{Q_\sigma^1 M^{-1}Q_\sigma^1\} \tag{2.56}\]

In GSBM theory the electron spin Liouvillean \(L_S\) is expressed by \(L_S = L_S^{\text{Zeeman}} - iR\). Of course \(L_S\) could have other expressions if Redfield theory is not applied on electron spin system. For other expressions the construction of final matrix is very similar, but that is beyond the scope of this section. One complete electron spin Liouvillean will be discussed in next chapter.

### 2.4 ESR lineshape

Here I give a short derivation of ESR lineshape function. \(L_S\) represents electron spin Liouvillean, and it has different expressions when using different approaches. Starting with Liouville equation of motion for electron spin system

\[
\frac{d}{dt}\sigma(t) = -iL_S\sigma(t) \tag{2.57}
\]

and Fourier-Laplace transform both sides

\[
\int_0^\infty \frac{d\sigma(t)}{dt}e^{-i\omega t}dt = -\sigma(0) + i\omega I(\omega) \tag{2.58}
\]

\[
\int_0^\infty [-iL_S]\sigma(t)e^{-i\omega t}dt = [-iL_S]I(\omega) \tag{2.59}
\]

we get the expression of lineshape function as

\[
I(\omega) = [i\omega + iL_S]^{-1}\sigma(0) = N^{-1}\sigma(0) \tag{2.60}
\]
Here $N$ is very similar to the matrix $M$ we constructed in previous section. There is one element $tr_S\{Q^1_-N^{-1}Q^1_-\}$ in matrix $N^{-1}$ gives the electron spin-spin relaxation and the ESR lineshape. This general ESR lineshape function only depends on the specific expression of the electron spin Liouvillean.
Chapter 3

Stochastic Liouville Approach

Redfield theory requires the truncation of higher order terms in cumulant expansion. Although it is safe to use for nuclear spin system, however, this approximate theory introduces errors when applied on some electron spin systems. So a more general theory, the so called stochastic Liouville approach (SLA), or slow-motion theory, was developed by Wennerström and co-workers [24]-[26] in 1980s. This theory gives complete Liouville description of the lattice outside nuclear spin system, thus it doesn’t have the disadvantages of time-dependent perturbation approaches such as Redfield theory. I’m just going to give a short introduction of SLA, interested readers can refer to related articles [24]-[28].

Redfield theory applied on nuclear spin system has already safely given us the expression of the nuclear spin-lattice relaxation time in Eq.(2.18):

\[ \frac{1}{T_1} = -2Re\{K_1(\omega_f)\} \]  

(3.1)

in which the spectral density \(K_1(\omega_f)\) is the Fourier-Laplace transform of the nuclear spin-electron spin dipole-dipole correlation function. This correlation function could be simplified by dividing the lattice into two subsystems: electron spin system and reorientational system if these two systems are not coupled to each other. In this chapter the coupled case will be discussed first, and then the decoupled case will be presented.
CHAPTER 3. STOCHASTIC LIOUVILLE APPROACH

3.1 Coupled Case

The spectral density $K_1(\omega_I)$ Eq.(2.16) is:

$$K_1(\omega_I) = \int_0^\infty tr_L \{ T_1^{\dagger} \exp(iL_L t) T_1 \sigma_L \} \exp(-i\omega_I t) dt$$ (3.2)

Next step is to figure out the lattice dynamics and give the expression of the lattice Liouvillean $L_L$, which should include the electron spin Liouvillean and the reorientation Liouvillean:

$$L_L = L_S + L_R$$ (3.3)

in which $L_R$ is the Markov operator describing the motion of molecular principal axes relative to the laboratory principal axes and the electron spin Liouvillean is denoted by complete electron spin Liouvlleans:

$$L_S = L_S^{Zeeman} + L_{ZFS} + L_D$$ (3.4)

where $L_S^{Zeeman}$ is the electron spin Zeeman Liouvillean, $L_{ZFS}$ Liouvillean and $L_D$ is the Markov operator describing the reorientation of the ZFS tensor principal axes relative to molecular principal axes, which is modulated by the ligand geometry (the ligand frame around the the paramagnetic ion). When static ZFS is considered, the lattice Liouvillean could be written as

$$L_L = L_S^{Zeeman} + L_{ZFS}^r + L_{ZFS}^s + L_D + L_R$$ (3.5)

Now a complete orthogonal basis spanning the Liouville space should be constructed. The basis is formed by direct product of eigenoperators of electron spin system $L_S$, distortional diffusion $L_D$ and reorientational diffusion $L_R$:

$$\{ |O_i\rangle \} = \{ |A, B, C\rangle \} \otimes \{ |L, M\rangle \} \otimes \{ |\Sigma, \sigma\rangle \}$$ (3.6)

where

$$|A, B, C\rangle = \sqrt{\frac{2A+1}{8\pi^2}} D_{B,C}^A(\Omega_{LM})$$ (3.7)

$$|L, M\rangle = \sqrt{\frac{2L+1}{8\pi^2}} D_{0,M}^L(\Omega_{PM})$$ (3.8)
3.2. **DECOUPLED CASE**

\[
|\Sigma, \sigma\rangle = Q^\Sigma_{\sigma} = \sum_{m} \sqrt{2^{2\Sigma+1}} \begin{pmatrix} S & S \\ m+\sigma & -m \end{pmatrix} (-1)^{S-m-\sigma} |S, m+\sigma\rangle |S, m\rangle
\]

(3.9)

In Liouville space one may construct a supermatrix \( M = -iL_L + (i\omega_I)E \) and the elements of \( L_L \) are \( L_{ij} = (O_i|L_S|O_j) \), \( E \) is a unit matrix. Finally the spectral density is

\[
K^{DD}_1(\omega_I) = c^*M^{-1}c
\]

(3.10)

where vector \( c \) projects the relevant matrix elements of the inverted matrix \( M^{-1} \).

### 3.2 Decoupled Case

The decomposition approximation can be applied on the proton spin-electron spin dipole-dipole correlation function when the electron spin correlation function is statistically independent of the reorientational dynamics\[22]\[29\]. This approximation is credible if the electron spin relaxation takes place on a different time scale than the reorientational motions. Thus the dipole-dipole correlation function can be decoupled into a product of reorientational correlation function and electron spin correlation function:

\[
K_1(\omega_I) = \int_0^\infty tr_S \{ S_1^{++} \text{exp}(iL_ST)S_1^{++}\Sigma_S \text{exp}((-i\omega_I - 1/\tau_R)t) dt
\]

(3.11)

Here I use the Pseudo-Rotation model\[22\] to describe the electron spin system. The electron spin Liouvillean is

\[
L_S = L_S^{Zeeman} + L_{\Delta, t}^{ZFS} + i\Gamma_{PR}
\]

(3.12)

where \( L_S^{Zeeman} \) is electron spin Zeeman Liouvillean, \( L_{\Delta, t}^{ZFS} \) is transient ZFS Liouvillean and \( \Gamma_{PR} \) is the Markov operator describing the distortional motion of the ligand frame which modulates the transient ZFS interaction. In this model, the ZFS interaction is characterized by transient ZFS \( \Delta_t \) and the corresponding correlation time \( \tau_f \).

Now we construct a complete orthogonal basis of the lattice, which is formed by direct product of eigenoperators of electron spin and distortional diffusion:

\[
\{|O_i\rangle = \{|L, M\rangle \otimes \{|\Sigma, \sigma\rangle \}
\]

(3.13)
In Liouville space one may construct a supermatrix $\mathbf{M} = -i\mathbf{L} + \left(i\omega_I + \frac{1}{r_i}\right)\mathbf{E}$ and the elements of $\mathbf{L}$ are $L_{ij} = \langle O_i|L_S|O_j \rangle$, $\mathbf{E}$ is a unit matrix. Finally the spectral density is

$$K^{DD}(\omega_I) = c^*\mathbf{M}^{-1}c \quad (3.14)$$

where vector $c$ projects the relevant matrix elements of the inverted matrix $\mathbf{M}^{-1}$. 
Chapter 4

Summary of Papers

4.1 Paper 1 — GSBM theory on MS-325+HSA

The GSBM theory is applied to describe the paramagnetically enhanced water proton spin-lattice relaxation rates of the aqueous systems containing a Gd complex MS-325 in the presence and absence of human serum albumin (HSA). The reorientational time, $\tau_R$ of MS-325 is short, around 100 ps, but when MS-325 binds to HSA, $\tau_R$ becomes 100 time longer, around 10000 ps. Altering the reorientational motion has drastically increased the relaxivity of MS-325 (about 8 times larger at proton Larmor frequency 20MHz for observed NMRD), which is so obvious that increasing reorientational correlation time of the complex by binding to large molecules has become the major topics of optimizing MRI contrast agents. Figure 4.1 is the schematic picture of MS-325 binding to HSA.

In this paper two dynamic models of electron spin relaxation are presented, characterized by transient and static ZFS interactions. Proton NMRD profiles and X-, Q-, U- and W-band ESR spectra of MS-325+HSA are analysed by fitting the GSBM parameters to experimental data in order to describe the effect of MS-325 binding to a macromolecule.

The NMRD and ESR fitting are consistent for Gd-aqua complex, Gd-DTPA and MS-325 since same set of parameters can explain both NMRD and ESR results, however, problem arises when MS-325 associates with HSA. A reasonable explanation for the discrepancy is because the electron spin-spin relaxation time is sensitive for slow motions whereas the $T_1$-NMRD profile is dominated by the electron spin-lattice relaxations rates where slow motions are less important.

This paper suggested a more detail analysis of the X-band ESR spectra
Figure 4.1: Schematic picture of MS-325 binding to HSA. Big molecule represents HSA and small one represents the complex MS-325. The reorientational correlation time $\tau_R$ of free MS-325 is about 100ps, when it binds to HSA, $\tau_R$ is around 10000 ps.

The advantage of GSBM theory comparing with SBM theory\cite{30}-\cite{32} is it takes into account the multi-exponential electron spin relaxation effects using closed analytical forms. The differences between SBM and GSBM because of multi-exponential electron spin relaxation and static ZFS-interaction are clearly shown in this paper. The SBM picture and the GSBM picture predict the same trends but differ in the microscopic parameters describing the electron spin relaxation rates.
4.2 Paper 2 — Comparison between GSBM and SLA

This paper compares the GSBM with the Stochastic Liouville approach (SLA) in order to determine the validity of the closed analytical expressions of the $T_1$ NMRD profiles and the ESR lineshape functions in GSBM theory.

Regardless the decomposition approximation, SLA is considered as a complete theory using full lattice Liouvillean and giving exact solution of the Liouville equation. Based on the simple one dynamic model of ZFS interaction, both approaches give the same results at all fields in NMRD profiles and a very small divergence is observed for X- and W-band ESR lineshapes when the magnitude of the perturbation term times the correlation time set to $\Delta_{ZFS} \tau_f \leq 0.1$. A conclusion can be drawn that within the perturbation regime as defined above, the relatively simple GSBM theory is a reliable tool in analysing both NMRD profiles and ESR spectra.

The experimental X-band ESR spectrum of the Gd(III) complex MS-325+HSA could not be reproduced by GSBM theory. However, in SLA, a parameter set with $\Delta_t=0.038$ cm$^{-1}$ and $\tau_f=150$ ps could somewhat reproduce the experimentally unsymmetrical lineshape. These parameters in SLA indicate a slow-motion effect caused by a slow modulation of the ZFS interaction. The characteristic correlation time of this slow modulation is in the range of 150 ps which therefore is not due to the reorientational motion of the whole MS-325+HSA complex. The physics behind this rather long ZFS correlation time is still not clear. In order to analyse this X-band spectrum we need the SLA and probably a more complex dynamic model of the ZFS interaction, which includes more than two different time scales.

Figure 4.2 displays the experimental X-band ESR spectrum of MS-325+HSA together with the lineshape from SLA calculation.

4.3 Paper 3 — ESR linewidth of Gd-aqua complex

In this paper, X-band ESR spectra of Gd-aqua complex in various weight concentration of glycerol have been recorded at four temperatures. Figure 4.3 displays the Gd aqua complex, whose hydration shell, in this paper, is assumed to be intact.

The interpretation of the ESR-linewidth is preformed using both SLA and GSBM theory. The SLA uses a one dynamic model of the zero-field splitting whereas the GSBM uses a two dynamic model, which is the model
II in Paper 1. This two dynamic GSBM model is similar to the approach developed by Rast et al. [33]-[35]. In this paper, both models can reproduce the variation of the linewidth with respect to viscosity. In the SLA model both the ZFS interaction and the correlation time vary with the glycerol content. In the two dynamic GSBM model only the correlation times are viscosity dependent.

In GSBM, the parameters from ESR linewidth fitting reveal that increasing the glycerol concentration mainly influences the two correlation times $\tau_f$ and $\tau_R$. The parameters also show that with increasing temperature, transient ZFS $\Delta_t$ is increasing and static ZFS $\Delta_s$ is decreasing, which means the symmetry of the complex is increased because of the fast distortional motion of the first hydration shell.

In SLA, the one dynamic model reveals that the transient ZFS parameter changes with glycerol concentration: $\Delta_t$ is decreasing with the increasing viscosity. This could be explained by that adding glycerol actually makes the hydration shell more rigid and tight, thus reduces the strength of transient ZFS interaction. $\Delta_t$ is increasing with the increasing temperature, and this
Figure 4.3: Schematic picture of Gd aqua complex. The hydration shell contains 8 water molecules and in this paper, it is assumed to be intact.

trend is the same as that from the GSBM theory.

However, using the parameters from ESR linewidth fitting, the two models give different NMRD profiles. The main discrepancy is in the electron spin-lattice relaxation process. These findings emphasize the importance of getting the description of the electron spin-lattice relaxation process right.

Also the NMRD profiles using parameters from ESR linewidth fitting, are not the same as the experimental NMRD profiles. A combined ESR and NMRD analysis probably need a much more detailed description of the ZFS time correlation function.

4.4 Paper 4 — NMRD profiles of Gd-aqua complex

With the same samples (glycerol weight concentration from 0% to 40%) as in Paper 3, water proton $T_1$ NMRD profiles of Gd-aquo complex have been recorded at three temperatures to check the viscosity and temperature dependence of the $^1$H NMRD profiles.

The analysis is performed using both the GSBM theory and the SLA approach. The theoretical backgrounds in Paper 3 and Paper 4 are quite much the same, but in Paper 3 the focus is on electron spin system and in Paper 4, the focus is on proton spin-lattice relaxation with the presence of paramagnetic Gd ions. The ZFS interaction models are the same as those in
Paper 3: one is the one dynamic SLA model and another is the two dynamic GSBM model.

Figure 4.4: Schematic picture of Gd aqua complex with glycerol molecules surrounded by water molecules, where glycerol molecules have no direct contact with Gd aqua complex. The left bottom one is Gd aqua complex, others are glycerol molecules surrounded by water molecules. In Paper 4 the hydration shell of Gd ion is supposed to be disturbed by glycerol molecules when the glycerol concentration is higher than 20%.

Both one dynamic SLA model and two dynamic GSBM model can reproduce the NMRD profiles. They give similar fitting parameters and the fitted GSBM parameters are within the Redfield limit. Both models’ $\tau_f$ and $\tau_R$ roughly decrease with increasing temperature and increase with increasing viscosity. These trends of correlation times were also shown in the ESR fitting in Paper 3. In the NMRD analyses, the transient ZFS also more or less increases with increasing temperature, which is the same as the results from Paper 3. However, with increasing viscosity, the transient ZFS decreases first and then increases, showing a minimum value at about 20 w/w% glycerol content. This is probably due to the hydration shell was disturbed by the intrusion of glycerol molecules. A schematic picture depicting that the glycerol molecules have no direct contact with Gd aqua complex is shown in Figure 4.4. When glycerol content is higher than 20 w/w%, it is supposed that there are not enough water molecules around glycerol and thus glycerol will interfere with Gd aqua complex.

The GSBM fitting also shows that the contribution from static ZFS is negligible for NMRD fitting. This is because the NMRD profiles are not so
sensitive to the exact model of ZFS interaction. Again, in this paper, the parameters from NMRD fitting can not reproduce the experimental ESR lineshape. A universal model of ZFS interaction for both NMRD and ESR is needed for future work.
Chapter 5

Conclusions

In this thesis the GSBM theory has been further developed and applied on gadolinium (S=7/2) complexes. The receptor-induced magnetization enhancement (RIME) strategy is studied in the case of MS-325 binding to HSA; another strategy is slowing down the tumbling of the Gd complex to enhance its relaxivity, which is studied in the case of Gd-aqua complex with the presence of glycerol. The extracted long reorientational correlation time and the resulted drastically increased relaxivity in interested magnetic field region, using GSBM theory for both MS-325+HSA and Gd(H₂O)₃⁺+glycerol, clearly show the effect of slow-down motion of Gd complexes. The MRI contrast agent MS-325 binding to HSA is a good example of RIME strategy in clinical application. However, increasing viscosity is another way to gain insight of the relaxivity enhancement mechanism of Gd complexes.

GSBM theory is a second perturbation theory, and it is reliable to use under the condition that the ZFS interaction strength times corresponding correlation time is less than 0.1. This conclusion was drawn when GSBM theory compares with the complete theory SLA. The unsymmetrical X-band ESR lineshape in the experiment is beyond the scope of GSBM theory, and it can be explained by SLA that the wave-like X-band spectrum is caused by slow distortional motion of the ligand field, but the physics behind is still not clear.

The NMRD profiles and ESR lineshapes of Gd(H₂O)₃⁺ with different glycerol content are also studied by means of the two dynamic GSBM model and the one dynamic SLA model. Although both theories can explain the experiments, the model parameters extracted from theories for NMRD and ESR experiments are different. Both models give similar parameters in NMRD fitting, but the parameters describing ESR linewidths are different.
These differences are due to that the $T_1$ NMRD profiles, compared to the ESR lineshapes, are less sensitive to the detailed shape of the ZFS correlation function.
Appendix A

Liouville Space

In quantum mechanics, eigenfunctions of Hamiltonian $|n\rangle (n = 1, 2, \ldots )$ constitute orthogonal bases of a linear space, which is Hilbert space. Any wavefunction can be regarded as a vector in this space. For a given quantum number $I$ in spin system, there are $2I + 1$ states, differing by the quantum number $m (m = -I, -I + 1, \ldots , I)$. The states can be written as $|I, m\rangle$ or $|m\rangle$ if $I$ is known.

Sometimes for the convenience of calculation, another linear space is constructed by the direct product of two Hilbert spaces, and the new space is called Liouville space. In the case of spin system, the base is $|I, m\rangle \langle I, n|$ and there are $(2I + 1)^2$ states in this space. In spin system, a complete and orthogonal set of basis operators $|\Sigma, \sigma \rangle$ can be defined in spin Liouville space

$$|\Sigma, \sigma \rangle = O^\Sigma_{\sigma} = \sqrt{2\Sigma + 1} \sum_m (-1)^{m-I} \left( \begin{array}{ccc} I & I & \Sigma \\ m + \sigma & -m & -\sigma \end{array} \right) |I, m + \sigma\rangle \langle I, m|$$

(A.1)

where $\left( \begin{array}{ccc} I & I & \Sigma \\ m + \sigma & -m & -\sigma \end{array} \right)$ is a 3j-symbol[19]. The above $(2I+1)^2$ operators are called Irreducible Spherical Tensor Operators(ISTO).

In Liouville space, the Liouville operator is defined by its corresponding Hamiltonian in Hilbert space:

$$L = (1/h)[H, \ldots ]$$

(A.2)

Using the ISTO, the Liouville matrix could be constructed in Liouville space by

$$O^{\Sigma}_{\nu'} L O^{\Sigma}_{\sigma} = Tr\{O^{\Sigma}_{\nu'} [H, O^{\Sigma}_{\sigma}]\}$$

(A.3)
The expression of the matrix elements depends on the definition of the specific Hamiltonian $H$.

However, the Liouville space could be expanded to include not only spin operator, but also other operators such as Markov operators which describe the distortional motion of the ZFS tensor or the reorientation of the molecules. The new Liouville space is just the direct product of the basis of its sub-spaces.
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Bibliography


