Relaxometry: Two-Dimensional Methods

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1 INTRODUCTION

There is an extensive literature on the use of high-resolution nuclear magnetic resonance (NMR) for the determination of the structure and dynamics of biopolymers in dilute solution where fast molecular motion ensures well-resolved resonance lines. However, the requirement for well-resolved resonances excludes the majority of complex, aggregated, multicomponent and multiphase biopolymer systems as well as low water content rubbery and glassy-state biopolymer systems of importance to, for example, the food or pharmaceutical industries. Of course, high-resolution solid-state NMR methods open a useful window on low water content, solid-like polymer systems but most complex biopolymer systems, such as food, have intermediate or high water contents and the sample would be destroyed by the fast magic angle spinning routinely used to separate resonance lines in high-resolution solid-state NMR. Moreover, both liquid- and solid-state high-resolution methods fail to show how water is distributed between the various components and microphases comprising complex biopolymer systems. Yet, this microscopic and macromolecular distribution of water is critical in determining structure–function relationships and, in the case of food materials, their processing and storage response. The same is true in porous materials such as rock cores, porous glasses, and soil, where the microscopic distribution of water and other fluids, such as oil, in the porous matrix is of interest.

Of course, low-resolution, time-domain NMR relaxometry and diffusometry can provide useful information in even the most complex material but, traditionally, these methods have been limited to simple measurements of either the transverse or longitudinal proton relaxation characteristics or water diffusivity. Quite recently, however, this situation has changed dramatically with the advent of two-dimensional cross-correlation relaxation and diffusion methods,\textsuperscript{1,2} made possible by the development of a fast algorithm for two-dimensional inverse Laplace transformations.\textsuperscript{3} Such multidimensional time-domain methods have enormous potential for characterizing complex systems and it is likely that they will, eventually have an impact similar to the earlier development of multidimensional NMR spectroscopy.\textsuperscript{4} Not just in academic research laboratories but as quality control measurements in industrial settings. As we shall see, the potential of multidimensional relaxometry has only begun to be explored and there remain many aspects that require further development and research in both two-dimensional and three-dimensional cross-correlation protocols.

2 METHODOLOGY

2.1 $T_1$–$T_2$ Relaxation Spectra

The measurement of a longitudinal relaxation time ($T_1$) with an inversion recovery pulse sequence or a transverse relaxation time ($T_2$) with a Carr-Purcell pulse sequence, Meiboom-Gill modification (CPMG) sequence are among the simplest of NMR measurements that can be performed on a low-field bench-top spectrometer. If the sample is characterized by a single relaxation time and a suitably long recycle delay is used to avoid saturation, the relaxation times are simply extracted by fitting the data to a single exponential model, whereby

\begin{equation}
M(t) = M_\infty[1 - 2\exp(-t/T_1)]
\end{equation}

for the inversion recovery and CPMG sequences, respectively.

The observed signal, $M(t)$ is now a Laplace transform of the probability $P(T_1)$ or $P(T_2)$ and these normalized distributions, which can be called relaxation time spectra are obtained by inverse Laplace transformation of the signal, $M(t)$. Algorithms, such as WINDXP\textsuperscript{\textregistered} and UPEN,\textsuperscript{4,5} are available to perform this inversion and output the relaxation time spectra. Figure 1 shows a typical example, in this case, the $T_2$ proton spectrum of parenchyma apple tissue. The distribution in Figure 1 does not, however, show the whole story because protons with the same $T_2$ but different $T_1$ values are not resolved. The obvious solution is to extend the measurement to two dimensions by associating the first-time dimension, $t_1$, with the inversion recovery part of the pulse sequence and the second-time dimension, $t_2$, with the CPMG part of the sequence, and to independently vary $t_1$ and $t_2$ so that the observed signal becomes a two-dimensional matrix, $M(t_1, t_2)$ such that

\begin{equation}
M(t_1, t_2) = M_\infty\int dt_1 P(T_1)[1 - 2\exp(-t_1/T_1)]
\end{equation}

\begin{equation}
M(t_1, t_2) = M(0)\int dt_2 P(T_2)\exp(-t_2/T_2)
\end{equation}

\begin{equation}
M(t_1, t_2) = M_\infty\int dt_1 \int dt_2 P(T_1, T_2) \times [1 - 2\exp(-t_1/T_1)]\exp(-t_2/T_2)
\end{equation}
2 RELAXOMETRY: TWO-DIMENSIONAL METHODS

Figure 1 The $T_2$ proton spectrum of parenchyma apple tissue acquired at 23.4 MHz with a CPMG pulse sequence and a pulse spacing of 200 µs. The four peaks arise from water in the vacuole, cytoplasm, and extracellular and cell wall compartments, with the longest $T_2$ corresponding to the vacuolar water.

where $P(T_1, T_2)$ is now the two-dimensional relaxation time spectrum, which is obtained from $M(t_1, t_2)$ by a two-dimensional inverse Laplace transformation. This approach was made possible by the pioneering work of Song and coworkers at Schlumberger-Doll Research, who devised a very fast computer algorithm for performing this two-dimensional inversion. Figure 2 shows the $T_1-T_2$ relaxation time spectrum of the same apple tissue as Figure 1 and illustrates how the extension to two dimensions has succeeded in resolving many more peaks. Other examples will be presented in the section “Applications”.

The smallest value of $T_2$ that can be measured in a $T_1-T_2$ sequence is, of course, limited by the shortest CPMG 90–180◦ sequence is, of course, limited by the shortest CPMG pulse spacing of 200 µs. Note the exchange cross-peaks in a $T_1-T_2$ spectrum. In the simplest cases where each proton pool is associated with unique values of $T_1$ and $T_2$ and there is no exchange of magnetization, the ideal $T_1-T_2$ spectrum comprises one peak for each proton pool. However, in most multicomponent, microstructured systems there is exchange of proton magnetization between the various proton pools, compartments, or pores in the sample. This can occur by actual proton chemical exchange, as between water protons and exchangeable polymer or solute protons or, in the case of longitudinal magnetization, by proton exchange and dipolar cross relaxation. In microstructured systems, molecular diffusion processes can transfer magnetization between adjacent pores or microdomains. Such magnetization transfer introduces exchange cross-peaks into the $T_1-T_2$ spectrum. More specifically, if there is exchange between proton pools labeled “a” and “b,” then four peaks are predicted at the corners of a square at locations $(s_1^+, s_2^+)$, $(s_1^-, s_2^+)$, $(s_1^+, s_2^-)$, and $(s_1^-, s_2^-)$ where

$$s_{i+/-}^i = -1/2(R_{ai} + k_{ai} + R_{bi} + k_{bi})$$

$$\pm 1/2((R_{ai} + k_{ai} + R_{bi} + k_{bi})^2$$

$$- 4((R_{ai} + k_{ai})(R_{bi} + k_{bi}) - k_{ai}k_{bi}))^{1/2}$$

are the effective relaxation rates. Here $R_{ai}$ refers to the intrinsic relaxation rate on site $a$ for longitudinal ($i = 1$) or transverse ($i = 2$) magnetization and $k_{ai}$ is the corresponding exchange rate, with analogous terms for site $b$. In practice, experimental imperfections, noise and suboptimum regularization in the inverse Laplace transform mean that the exchange cross-peaks in a $T_1-T_2$ spectrum may not form a perfect square. We shall see examples where the exchange square is distorted, and it can then be difficult to distinguish...
exchange cross-peaks from those arising from nonexchanging proton pools. Replacement of H2O with D2O can help in this regard since this eliminates the exchangeable proton peaks as well as the proton exchange mechanism, while leaving only longitudinal dipole–dipole cross relaxation.

More information is obtained by associating the two time dimensions with other relaxation processes. The T2–store–T2 sequence associates both time dimensions with a CPMG measurement of the transverse relaxation, but allows exchange of magnetization between the various proton pools by storing the magnetization in the longitudinal direction for a variable store time, t3. The pulse sequence is therefore CPMG(t1)−90−τ1−CPMG(t2). If the store time, t3, is very short so there is no time for exchange, the T2–T2 spectrum reduces to a one-dimensional CPMG relaxation time spectrum along the diagonal. However, as the store period, t3, is increased, off-diagonal peaks appear in the spectrum connecting diagonal peaks a and b whenever the store time equals the exchange lifetime. Examples can be seen in Figures 6 and 7 and will be discussed in the section “Aqueous BSA Solutions and Gels”. Of course, in the fast exchange regime, only a single peak on the diagonal appears at the weighted average T2.

The complementary diagonal sequence T1–store–T1 has also been developed. Here the magnetization is stored for a variable time, t3, as transverse magnetization. An inversion recovery sequence weights the first-time dimension with T1 and, in principle, another inversion recovery or saturation recovery sequence could be used to weight the second-time dimension with T1. However, the need to repeat the sequence for each t1 and t2 time point would render this approach impractically slow. To speed up the acquisition, the T1 value in the second-time dimension is therefore measured with a single shot, multiple read-out sequence involving a series of 90° pulses creating a chain of free induction decays. If the initial magnetization is phase alternated between +M(0) and −M(0) on two successive scans, the decay of magnetization in the second dimension becomes

\[ M[(n-1)t_2] = 2M(0)\exp(-t_2/T_1)\cos\alpha P(T_1) \sin^2(t_2/\tau_2) \]  

where \( \tau_2 \) is the time interval between the \( \alpha \) degree pulses, so that \( t_2 = (n - 1)\tau_2 \). The T1–store–T1 pulse sequence is therefore 180°−t1−(90°−[t1−180°−\tau_1m−90°]−[\alpha−A\alpha]m), where the subsequence (90°−[t1−180°−\tau_1m−90°]m) stores transverse magnetization for an exchange time 2\( \pi \) before returning it to positive and then negative longitudinal magnetization on alternate scans.

The T1–store–T1 sequence complements the T2–store–T2 sequence in many ways. In the T1–store–T1 sequence, exchange of transverse magnetization during the store period cannot occur by dipolar interactions, so a cross-peak that only appears in the T2–store–T2 spectrum but not in the T1–store–T1 spectrum must be exchanging magnetization through the dipolar mechanism. In other types of samples, such as porous rocks, diffusion through internal magnetic field gradients created by discontinuities in the magnetic susceptibility, can severely affect the T2–store–T2 spectrum especially at high B0 fields, but not the T1–store–T1 spectrum, at least at short store times.

### 2.3 Diffusion Weighted Relaxation

A number of 2D methods have been developed that correlate relaxation processes with diffusion, using either fixed or pulsed field gradients. The T1-D and T2-D methods use combined saturation recovery pulse gradient echo (PGSE) or PGSE-CPMG pulse sequences respectfully where the diffusion dimension is created by varying the wave vector, q, which is \((2\pi)^{-1/2} G \delta \) usually by increasing the gradient amplitude, G, at fixed gradient pulse duration, \( \delta \). The observed signal for the T2-D spectrum is therefore,

\[ M(t_1, t_2) = M_\infty \int d\mathbf{D} \int dt_2 P(D, t_2) \exp(-bD) \exp(-t_2/T_2) \]

where the variable, b, is \( \delta^2 G \), and there is an analogous equation for the T1-D spectrum. T2-D spectra are, of course, especially useful for separating water peaks from those of other more slowly diffusing molecules such as oil and sugar. Figure 3 shows a typical T2-D spectrum, in this case for intact parenchyma tissue of avocado, where the two oil peaks are clearly resolved from those of the water peaks.

Pulsed gradient methods can, of course, also be combined with other 2D relaxation experiments such as T2–store–T2 by adding a propagator dimension to the T2 exchange experiment. The basis of this approach is the Fourier relationship between the displacement propagator, \( P(R, \Delta) \), and the echo attenuation, \( S(q, \Delta) \), such that

\[ P(R, \Delta) = \int dq S(q, \Delta) \exp(-iq.R) \]

where \( R \) is the displacement and \( \Delta \) is the diffusion time, which is the store time in the T2 exchange experiment. Using a combined Fourier 2D inverse Laplace transformation a 2D T2–T2 spectrum can be obtained for each displacement distance, \( R \). This is especially useful in porous matrices where it can be used to determine whether changes in \( T_2 \) values during the store time interval arise from intra- or inter pore transport.

A T2-D spectrum can also be acquired by working in the constant field gradient created, for example, either by deshimming the magnet or by placing the sample in the stray field of the magnet. This obviates the need for expensive gradient controllers and amplifiers and is particularly suited to low-cost industrial quality control. The method introduces diffusion weighting by associating the first dimension with a stimulated echo where the total echo time, (TE), to the stimulated echo is held constant and the time, \( t_1 \), between the first and second 90° pulses is varied for the first dimension. The stimulated echo is followed by a train of 180° pulses giving \( T_2 \) weighting. The data, \( M(t_1, t_2) \), are therefore given as

\[ M(t_1, t_2) = \int d\mathbf{D} \int dt_2 P(D, t_2) \exp(-t_2/T_2) \]

where \( t_2 \) is the TE after the stimulated echo. Equation (10) shows that the spectrum, \( P(D, t_2) \), can be extracted using a double inverse Laplace transform with respect to the variables \( b \equiv \gamma^2 G^2 t_1^2 (TE - 4t_1/3) \) and \( t_2 \). There are, however,
some subtleties involved in this procedure to take account of the possibility that with a strong gradient the radiofrequency pulses may become slice selective and echo shapes may be distorted. These problems can, of course, be avoided at the expense of using pulsed gradient methods.

2.4 Applications

In this section, we illustrate the power of 2-D relaxometry by reference to samples of increasing structural and compositional complexity. As we shall see, assigning the relaxation time peaks to particular proton pools is a recurring difficulty that can become extreme with the most complex processed food samples. We therefore begin by illustrating the problem of peak assignment with a "simple" aqueous sucrose solution.

2.4.1 Aqueous Sucrose Solutions

Figure 4 shows the proton $T_1$–$T_2$ spectrum of a saturated sucrose solution at 299 K acquired at 23.4 MHz with a CPMG 90–180° pulse spacing of 200 µs. Four peaks are clearly resolved but several techniques are required to assign them to particular proton pools. Peak 1 can be assigned to the pool of exchangeable hydroxyl protons both on water and sucrose. This was proved with a variety of additional experiments that involved varying the proton exchange rate, the spectrometer frequency, the CPMG pulsing rate, the sucrose concentration, and finally by replacing the water with D$_2$O. However, assigning the remaining three peaks to particular sucrose CH protons required chemical-shift-resolved $T_1$–$T_2$ spectroscopy on a high-resolution NMR spectrometer.

Fourier transformation of the echo envelopes from each spin echo of the CPMG sequence yields a frequency spectrum and allows chemical shift separation of the nonexchanging sucrose peaks. A separate $T_1$–$T_2$ spectrum can then be extracted.
for each chemically resolved peak in the proton frequency spectrum. This has been done at 300 MHz for a 20% sucrose solution in D2O without sample spinning and also for the oil–water peaks in cheese.

2.4.2 Aqueous BSA Solutions and Gels

An aqueous biopolymer solution or a gel represents the next level of complexity. Figure 5 shows the $T_1-T_2$ proton spectrum of a 2.5% w/w native bovine serum albumin (BSA) solution at 298 K acquired at 100 MHz with a CPMG pulse spacing of 100 µs with peak assignments. Peaks 2–4 in Figure 5 are nonexchanging or very slowly exchanging BSA protons though it is not possible without much higher field NMR to assign them to proton pools on the BSA. These assignments were based on a number of experiments with different BSA concentrations, spectrometer frequencies, and $T_2$-store-$T_2$ spectra at increasing store times. For example, Figure 6 shows a typical $T_2$-store-$T_2$ spectrum for a 24% BSA solution acquired at 23.4 MHz with a store time of 100 ms. The exchange cross-peaks appearing at this particular store time are labeled CP. Clearly these types of experiments give considerable insight into cross relaxation and magnetization transfer mechanisms in such biopolymer systems over a wide concentration range but are of limited value unless the BSA proton peaks 2–4 can be chemically assigned, and this remains a considerable challenge.

It is noteworthy that 2D NMR relaxometry has real potential for determining microphase composition in mixed biopolymer systems or biopolymer systems exhibiting microdomain structure. Thermal denaturation of a 24% BSA solution creates a gel comprising interconnected microdomains, some of which are protein rich and some protein poor, and Figure 7 shows the $T_2$-store-$T_2$ spectrum at 100 MHz with a very long store time of one second. The two diagonal peaks labeled domain 1 and domain 2 arise from water and exchangeable protons in the protein-poor and protein-rich domains respectively. But it is noteworthy that water diffusion between microdomains during the long store time of one second creates off-diagonal cross-peaks, labeled (DCP), as indicated. This type of spectrum not only allows the protein concentration in each domain to be determined from the relative peak areas but also gives information about average domain size because the diffusion exchange peaks appear only when the store time equals the mean exchange lifetime and water diffuses a distance $(6D_{\text{store}})^{1/2}$ in this time, which therefore gives the mean domain size.

Figure 5 The $T_1-T_2$ proton spectrum of a 2.5% BSA solution at 298 K acquired at 100 MHz with a CPMG pulse spacing of 200 µs. Peak 1 arises from the exchangeable water and BSA protons and peaks 2–4 from nonexchanging BSA protons.

Figure 6 The $T_2$-store-$T_2$ proton spectrum of a 24% BSA solution at 298 K acquired at 23.4 MHz with a CPMG pulse spacing of 200 µs and a store time of 100 ms. Note the appearance of exchange cross-peaks (labeled CP) at this store time.

Figure 7 The $T_2$-store-$T_2$ proton spectrum of a 24% thermally denatured BSA gel at 298 K acquired at 100 MHz with a CPMG pulse spacing of 100 µs and a store time of 1 s. The peaks labeled domain 1 and 2 arise from water in the two microdomains in this phase-separated gel. Peaks labeled DCP are diffusive cross-peaks between the microdomains.
size. To our knowledge, this is the first example where a direct NMR measurement of water diffusion has been made without the use of field gradients.\textsuperscript{15}

The relaxation times of the biopolymer peaks do, of course, reflect their chain dynamics and this aspect has been explored more explicitly in a comparison of the effects of thermal and high-pressure gelation of starch granules.\textsuperscript{16} The $T_1-T_2$ spectra revealed dramatic changes as a type A starch granule (waxy maize starch) is gelatinized by high pressure at room temperature and by how the resulting gel has a radically different dynamic and microstructural state to the gel formed by thermal treatment at atmospheric pressure.

2.4.3 Cellular Tissue

2D relaxometry is particularly useful for studying water compartmentation in cellular plant tissue and, as the $T_1-T_2$ spectrum for parenchyma apple tissue in Figure 2 nicely illustrates, separate peaks can, in many samples, be resolved from water in the vacuole, cytoplasm, and cell wall region. In addition, the spectrum in Figure 2 reveals peaks from proteins, starch granules, and cell wall biopolymers such as pectins, and hemicelluloses. Such spectra are therefore sensitive to the physiological state of the tissue and a number of reports have appeared where 2D techniques are used to monitor the subcellular changes associated with such conditions as mealiness and watercore in apples,\textsuperscript{17} browning in pears,\textsuperscript{18} and the ripening of avocado.\textsuperscript{19} Processing effects have also been reported. These include the effects of high pressure and thermal treatments on carrot\textsuperscript{20} and potato\textsuperscript{16} as well as freezing effects on peas.\textsuperscript{21} Much less work has been done on mammalian tissue though water compartmentation in rat myocardium has been studied by the $T_1$-D and $T_1-T_2$ methods.\textsuperscript{22}

2.4.4 Processed Foods

Processed foods present the next level of compositional and microstructural complexity. An early exploratory paper\textsuperscript{23} presented a broad survey of $T_1-T_2$ spectra for a variety of food materials including egg white and egg yoke, hydrocolloids such as salad cream and even cake as an example of a complex solid foam of protein, polysaccharide, and fat with a water content of 28%. The three overlapping peaks in the cake spectrum (Figure 8) were not assigned but it was noted that, at the very least, such spectra could be used as quality control “finger-prints” to monitor processes such as staling that determine food shelf-life. Dairy products including milks, yogurt, cream, and cheeses have been studied in the context of water- or oil-saturated porous rocks.\textsuperscript{3} and high-pressure gelation of starch granules.\textsuperscript{25} The first applications of $T_1-T_2$ relaxometry were made on brine-saturated porous rocks\textsuperscript{3} and included a detailed discussion of the regularization method used to find a balance between the residual fitting errors in the 2D inverse Laplace transformation and the known noise amplitude. This is controlled by a regularization parameter, $\alpha$, which should ideally be optimized for each application.

The effect of diffusion through internal gradients created by susceptibility discontinuities across interfaces has been studied in the context of water- or oil-saturated porous rocks.\textsuperscript{27} Such internal gradients can be studied by dividing the CPMG sequence into two parts. The second part of the 2D sequence is acquired with a variable number of echoes and a short pulse spacing, $\tau$, so it measures pure transverse relaxation without the complications of diffusion through internal gradients. On the other hand, the first part is sensitized to diffusion through internal gradients by varying the 180° pulse spacing, $\tau_1$, using different numbers of echoes in a fixed total acquisition time, $t_1$. The resulting echo attenuation is given as,

$$M(t_1, 2\pi\tau) = \frac{1}{3} \left\{ \int F(DG_{av}^2, T_2) \exp\left[-(t_1 + 2\pi\tau)/T_2\right] \right\} \times \exp\left[-(\gamma^2 D G_{av}^2 t_1^2/3)/D T_2 d(DG_{av})\right]$$

where 2D inverse Laplace inversion gives the distribution, $F(DG_{av}^2, T_2)$, of the average internal gradient, $G_{av}$, (weighted by the diffusion coefficient, $D$) and the transverse relaxation time. In porous rocks the $T_2$ distribution is related to the pore size distribution so the spectrum, $F(DG_{av}^2, T_2)$ shows the distribution of internal gradients for different pore sizes. As already mentioned, these explicit studies of the internal gradients are complemented by the $T_1$–store–$T_1$ sequence, where the role of internal gradients is greatly diminished, especially at short store times.
2D relaxometry is also proving valuable in other kinds of porous matrix. 2D exchange methods have been used to study the pore structure in cement and a combination of $T_1 - T_2$ relaxometry with differential interference contrast optical microscopy has recently been used to compare the pore structures of hydroxyethyl methacrylate-based synthetic hydrogels used in conventional contact lenses with three silicone hydrogels primarily developed for continuous wear contact lenses. It was shown that both types of hydrogels have a connected network of nanopores but that, in addition, the silicone hydrogels contain pores on the micron scale that enhance their permeability. Relaxation time peaks from the nonexchanging polymer protons also appeared at short $T_2$ values in the $T_1 - T_2^*$ spectrum and reflected the flexibility of the polymer network. The very different $T_1 - T_2$ spectra characterizing the three silicone hydrogels was particularly noteworthy and reflects the different biphasic structure of the polymer network in these materials.

3 CONCLUSIONS

It is hoped that this brief description of 2D relaxometry serves to show its considerable potential for characterizing complex systems on low-cost bench-top relaxometers. Even where relaxation time peaks cannot be assigned, the spectrum can still act as a “finger-print” for characterizing sample changes and this approach should find increasing industrial application in process and quality control. The pulse sequences described here are by no means the only ones that can be developed, especially if a third dimension is added to the pulse sequence, and we have seen the beginning of this type of 3D development in the propagator resolved $T_1 - T_2$ spectra referred to earlier. The spectral densities contributing to the longitudinal relaxation time $T_1$ often impart a dispersive dependence on the magnetic field strength, so that the implementation of the $T_1 - T_2$ or $T_1 - T_1$ sequences on a field cycling relaxometer would be of particular interest. Early attempts at field cycled $T_1 - T_2$ spectra have been made but only on model sucrose and BSA solutions. Most recently a $T_1 - T_2$ map of cross-linked natural rubbers has been acquired in the strongly inhomogeneous magnetic field of a single-sided NMR MOUSE. To the author’s knowledge, 2D relaxation methods have not yet been extended to relaxation in the rotating frame, characterized by $T_{1\text{rho}}$. Novel combinations such as $T_2 - T_{1\text{rho}}$ and $T_{1\text{rho}} - T_{1\text{rho}}$ can therefore be anticipated in the near future. Although this article has focused on relaxation processes, very similar concepts apply in low-field multidimensional “D–D” diffusion methods such as DEXSY and the interested reader will find Refs. useful introductions to these diffusion methods.

4 RELATED ARTICLES

Diffusion Measurements by Magnetic Field Gradient Methods; Diffusion in Porous Media; Dynamics of Water in Biological Systems: Inferences from Relaxometry; Molecular Motions: $T_1$ Frequency Dispersion in Biological Systems; Multidimensional Spectroscopy: Concepts; Relaxometry of Tissue; Relaxation Theory: Density Matrix Formulation; Relaxation Measurements in Whole Body MRI: Clinical Utility.

5 REFERENCES

Biographical Sketch