

MAGNETIC RESONANCE STUDIES OF TRANSPORT IN MULTIPHASE
PHARMACEUTICAL DELIVERY AND MIXING SYSTEMS

by

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of the requirements for the degree

of

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DEDICATION

I dedicate this thesis to my family. Thank you for years of encouragement, humor, love and support.

Travis, you're a superb brother. I'm proud of the person you've become even though you're almost always in need of grooming. Thank you for all the times you have come to my rescue, babysitting last second so that I can run experiments or escape for a baby-free dinner.

Dad, you've always been there when I've needed you the most. You have allowed me to make my own decisions but somehow have the ability to give the timeliest advice. Your dedication to your work and to your patients makes me proud.

To my mom, possibly the feistiest *mama bear* this world has ever seen, thank you for your fierce protection, unconditional love and unwavering support. Thank you for reading aloud to me for countless hours as a child; buying me all the books I wanted so long as I could add up their total cost accurately; taking me hiking and skiing; sending me to France in high school; teaching me that engineers are cool; putting me through college debt free; coming to Bozeman to cook, clean and watch my baby so that I could work with less stress - I could write a dissertation about everything you have done for me...

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ABSTRACT

In this dissertation research utilizing magnetic resonance methods to noninvasively probe the dynamics and transport properties of novel engineering systems is presented. The systems investigated are an osmotic controlled release pharmaceutical tablet as well as two mixing and reaction devices, a Taylor-Couette device and a jet-in-tube mixer.

Magnetic resonance imaging of an osmotic controlled-release pharmaceutical tablet is used to measure water concentration as a function of tablet hydration time. A 1D mass transport model for tablet water hydration directly quantifies whether osmotic or diffusive processes dominate transport and is used to estimate transport coefficients for these processes.

Magnetic resonance velocity mapping of Couette and Taylor vortex flow regimes for single and two-fluid systems in a vertically oriented Taylor-Couette device are compared to simulations. For the single fluids, the magnetic resonance experiments and Fluent© computational fluid dynamics simulations show excellent agreement in determining the rotation rate at which the flow transitions from Couette to Taylor vortex flow and the corresponding critical wavelength of the unstable flow. In the two-fluid studies, immiscible fluids are axially stratified in the stable density, heavy fluid on bottom, configuration. In both simulation and experiment, the two-fluid interface is observed to remain in the Couette flow regime after the pure fluids away from the interface have transitioned to the Taylor vortex flow regime, thus indicating a stabilizing force, surface tension, at the interface.

A vertically oriented co-current jet-in-tube device with acetone as the jet fluid and water as the tube fluid, operated at low jet Reynolds numbers ($Re_{jet} \sim 17$), is used to produce a laminar positively buoyant jet, which transitions to an unstable mixing regime, characterized by vortex formation and breakdown in flow visualization experiments. Magnetic resonance velocity mapping and diffusion measurements at varying positions downstream of the jet exit are used to characterize the mixing due to vortex formation and breakup. The buoyancy driven instability which results from introducing the less dense acetone ($SG=0.79$) into the more dense water ($SG=1$) in opposition to gravity gives rise to significantly enhanced hydrodynamic dispersion of the two fluids. Non-equilibrium statistical mechanics concepts are introduced as a model for mixing by the formation and decay of coherent vortex structures generated by the buoyant instability.

INTRODUCTION

Magnetic resonance techniques are appealing for studying engineering systems for the same reasons that they are so valued in health care, namely because MR experiments are noninvasive and can be applied to opaque systems. The ability to image a pharmaceutical tablet as it hydrates without cutting into it or to measure fluid velocities in a mixing device without seeding the flow with tracer particles yields exact measurements of system dynamics. Furthermore, the information about molecular-level dynamics which can often be gleaned directly or indirectly from MR experiments contributes to a deeper understanding than measuring macroscopic system properties alone.

Average pharmaceutical R&D costs have been increasing much more rapidly than inflation. According to a 2003 study, pharmaceutical R&D spending grew at an annual rate of 9.4% above inflation during the 1970s and 7.4% above inflation during the 1980s [1]. On average it takes \$802 million and 11.8 years to develop a new pharmaceutical product [1] and more recent estimates have determined the cost to be closer to \$1 billion and the duration of development to be 12-15 years. According to Dr. David K. Rosen, head of development and commercial strategic alliances for Pfizer Global Research and Development, only three in 10 medicines will generate enough revenue to pay for the investment in the research and development for that medicine [2]. The combination of daunting risks and uncertain rewards, blockbuster drugs such as Lipitor going off patent and the marginal world economy, large drug makers are paring back research [3], and promising therapeutics are frequently unexplored because companies lack both the will

and the resources to undertake the effort - all of this at a time when quality R&D is of huge importance. The Obama administration has become so concerned about the slowing pace of industrial drug development that officials have decided to launch an NIH controlled drug development center to help create medicines [4].

Work has been done to identify the factors that are most strongly contributing to the continuing growth in R&D costs [5]. To paraphrase, many new medicines under development are aimed at treating more challenging chronic diseases and are thus requiring more complex technologies and intensive research to develop, to produce and to prove their safety and efficacy. As personalized medicine continues to emerge and develop, it's expected that the medicines and therapies required to treat chronic diseases will require increasingly novel and complex technologies. Furthermore, the costs associated with developing and manufacturing the biotechnology-derived products that personalized medicine often requires are even greater than the costs of developing and manufacturing medicines that have no biologically active components. These facts will further challenge the pharmaceutical industry to cut costs while developing the most innovative therapies ever.

Some stories of drug development and commercial process design hint that industrial R&D has been so focused on achieving an end product and satisfying Food and Drug Administration (FDA) regulations that intelligent design and scientific and engineering fundamentals are often neglected. As an example, Amgen's Epogen®, a recombinant protein which stimulates red blood cell production, was commercially produced in the same small-scale roller bottle reactors which were used during

development work [6]. Production increases consisted of adding another rack of roller bottle reactors. Between batches, the desired erythropoietin alpha protein from each roller bottle reactor had to be individually separated and purified, and the reactors discarded. Thus, the process was time-consuming, expensive and wasteful. However, since the scale-up from lab to commercial scale for many unit operations, *e.g.* batch centrifugation or affinity chromatography, are not well-understood, commercial production using development scale reactors is sometimes the only option. Thus, there is a significant need for basic research in the pharmaceutical and biomedical industry as well as in all industries. In a 1945 report to President Truman, Vannevar Bush, the Director of the Office of Scientific Research and Development, argued that the post-war research model in the U.S. should focus on basic research. “[Basic research] results in general knowledge and an understanding of nature and its laws. It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn [7].” In order to overcome its challenges, the pharmaceutical and biomedical industry will need to achieve a more optimal balance between applied and basic research.

The research presented in this thesis combines basic and applied research in order to quantify and better understand transport in a multiphase osmotic controlled-release pharmaceutical tablet as well as in two multiphase mixing devices used in pharmaceutical processes. In Chapter 4, MR imaging of the hydration of a gastrointestinal therapeutic system (GITS) tablet in combination with a simple 1D transport model allows for direct quantification of the transport processes. Order of magnitude diffusivity values for water in the two layers (drug and sweller layers) of the tablet are presented. The unique nature

of the MR signal intensity data allows the clear transition from diffusive to osmotic transport of water in the sweller layer to be directly measured. The data and analysis presented for tablet hydration provide important first steps toward development of realistic 3D water transport models which can be used to improve efficiency by minimizing the empirical studies associated with tablet formulation.

In Chapter 5, a vertical Taylor-Couette device is used to study axially stratified immiscible two-fluid Taylor vortex flow (TVF) via MR velocity mapping experiments and transient volume of fluid CFD simulations. Experiments and simulations consistently show that at rotation rates that produce unstable Taylor vortex flow in each of the pure fluids the interface undergoes purely azimuthal $v_\theta(r)$ flow with no secondary v_r or v_z flows. The apparently robust phenomena of a significant zero plateau in the secondary flows that form in TVF at the interface of two axially stratified fluids may have potential for pinning solid particles or biological cells between fluids using buoyancy forces. The ability to pin a biological cell or particle at the interface in order to treat portions with different reagents has the prospect of supplying new capabilities for cellular biology and offers new approaches to microreactor design.

In Chapter 6, the buoyancy driven instability which results from introducing acetone (SG=0.79) into water (SG=1) in opposition to gravity gives rise to significantly enhanced transverse mixing and hence hydrodynamic dispersion of the two fluids. For the first time, enhanced dispersion due to buoyancy driven instability is quantified as a function of fluid displacement observation time and position relative to the jet exit. Non-equilibrium statistical mechanics concepts are introduced as a model for mixing by the

formation and decay of coherent vortex structures generated by the buoyant instability. Pre-asymptotic transverse dispersion was shown to determine the transport length scale of these vortical mixing structures. The increased hydrodynamic dispersion arising from flow destabilizing buoyancy forces has potential for enhancing mixing in microfluidic devices.

NUCLEAR MAGNETIC RESONANCE THEORY

Magnetic resonance (MR) techniques are extremely powerful because they enable opaque samples to be probed noninvasively. This point is particularly evident in healthcare settings where magnetic resonance imaging (MRI) is used to identify joint and organ injuries, spot tumors, study brain function and more without making incisions or using other invasive medical procedures. In magnetic resonance microscopy (MRM), magnetic resonance techniques are applied to small (typically 5 mm – 3 cm diameter) samples in order to noninvasively probe fluid motion and transport, characterize porous media and determine chemical composition in both natural and engineered systems and processes. This information is useful to scientists and engineers so that they can better understand and potentially control dynamical systems.

Basics Concepts of NMR

Quantum Mechanics and Nuclear Magnetization

The focus of the following nuclear magnetic resonance (NMR) introduction will be on proton NMR as the proton is the sole MR active nuclei used in the experiments which will be described in this dissertation. In order to understand why the proton nucleus is MR-active, it is helpful to first remember what a hydrogen atom looks like (Fig. 2.1). A hydrogen atom has a single electron in its electron orbital and its nucleus consists of a single proton. In the hydrogen atom, both the proton and electron possess a property called “spin” which causes them to precess or spin about their own axes in order to keep their respective charges balanced. Since a moving charge or current creates a

magnetic field, the proton nucleus possessing angular momentum $\mathbf{J}$ creates a very small magnetic field with a magnetic moment μ . It is the magnetic moments or “spins” of magnetic resonance active nuclei such as proton nuclei that are manipulated in nuclear magnetic resonance experiments. Spin angular momentum is quantized and the spin angular momentum quantum number I of the proton nucleus is $1/2$.

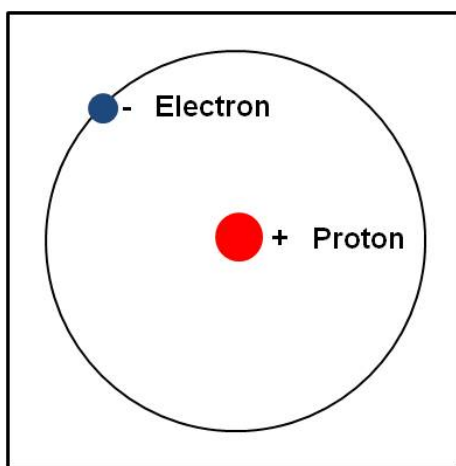


Figure 2.1. Hydrogen atom.

In the absence of an applied magnetic field, the proton spins in a sample, for instance a water sample, are randomly oriented. In nuclear magnetic resonance a static magnetic field $\mathbf{B}_0$ causes the spins of the sample to align either parallel or anti-parallel to $\mathbf{B}_0$ as shown in Fig. 2.2.

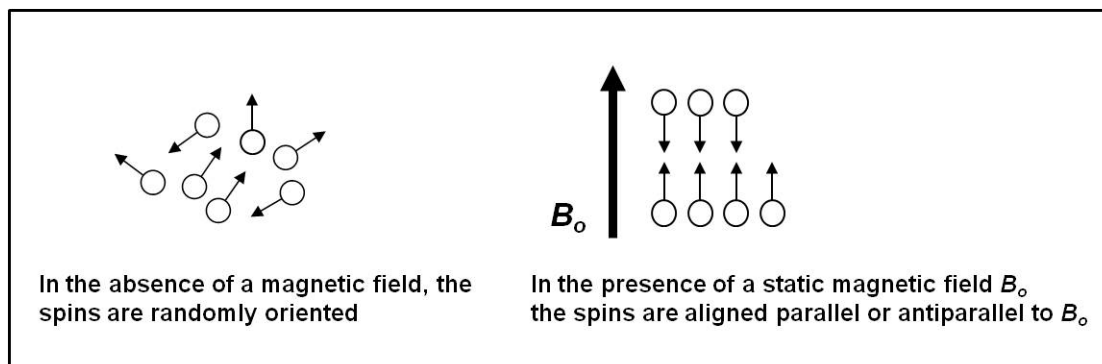


Figure 2.2. Effect of a static magnetic field $\mathbf{B}_0$ on spins.

The interaction of the magnetic dipole moment μ with the magnetic field $\mathbf{B}_0$ is known as the Zeeman Interaction. The equation $2I+1$ determines how many spin angular momentum states or energy levels exist for a spin experiencing the Zeeman interaction. For the proton nucleus $I = 1/2$ and there are two possible angular momentum states $m = -1/2$ which is the higher energy state and $m = +1/2$ which is the lower energy state, with the spins aligned parallel to the magnetic field $\mathbf{B}_0$. The Zeeman Interaction can be captured for a single nucleus mathematically through linear algebra. For instance, the angular momentum component along the z-axis for a single nucleus in the basis state $|z\rangle$ is described by the eigenvalue equation,

$$A_z|z\rangle = \lambda|z\rangle \quad (2.1)$$

where the diagonal matrix A_z is the angular momentum operator along the z-axis, $|z\rangle$ is the eigenvector of the basis state and λ is the eigenvalue or observable behavior of the single magnetic moment μ interacting with $\mathbf{B}_0$. For $I = 1/2$, the spin-up eigenvector is $|+z\rangle = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$, the spin-down eigenvector is $|-z\rangle = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$ and A_z is

$$A_z = \begin{bmatrix} 1/2 & 0 \\ 0 & -1/2 \end{bmatrix}$$

As an example, solving (2.1) for the observable λ when the spin system is in the spin-up state yields $\lambda = \langle +z|A_z|+z\rangle = \frac{1}{2}$. (Note: $\langle +z|$ is the row vector conjugate to $|+z\rangle$).

The angular momentum operators A_x and A_y along the x and y axes, respectively for a spin-1/2 nuclei are

$$A_x = \begin{bmatrix} 0 & 1/2 \\ 1/2 & 0 \end{bmatrix}, \quad A_y = \begin{bmatrix} 0 & -i/2 \\ i/2 & 0 \end{bmatrix}.$$

The energy or Hamiltonian operator describing the Zeeman interaction for $\mathbf{B}_0$ oriented along the z-axis is

$$H = -\gamma\hbar B_0 A_z. \quad (2.2)$$

Planck's constant $\hbar = 1.0546 \cdot 10^{-34}$ J sec/rad, can be dropped and the Hamiltonian energy operator will have units of angular frequency, unless energy units are specifically required.

For a spin experiencing the Zeeman Hamiltonian, there is a very slight preference for the spins to be aligned parallel to $\mathbf{B}_0$ in the lower energy “spin up” position than in the higher energy “spin down” antiparallel position. At thermal equilibrium, the ratio of the number of spins in the lower energy state N^+ to the number of spins in the higher energy state N^- is described by Boltzmann's Distribution

$$\frac{N^+}{N^-} = \exp\left[\frac{\Delta E}{kT}\right] = \exp\left[\frac{\gamma B_0 \hbar}{kT}\right]. \quad (2.3)$$

Here, γ is the gyromagnetic ratio, an intrinsic property of the MR active nuclei being probed where $\gamma = \mu/J$ (for hydrogen $2.675 \cdot 10^8$ rad/T sec or 42.57 MHz/T), k is Boltzmann's constant $1.3805 \cdot 10^{-23}$ J/K and T is absolute temperature in Kelvin.

Whatever the angular momentum quantum number I , the energy difference between the energy levels m is always $\Delta E = \gamma B_0 \hbar$. For $I = 1/2$, the energy difference between the two spin states as a function of B_0 is shown in Fig. 2.3.

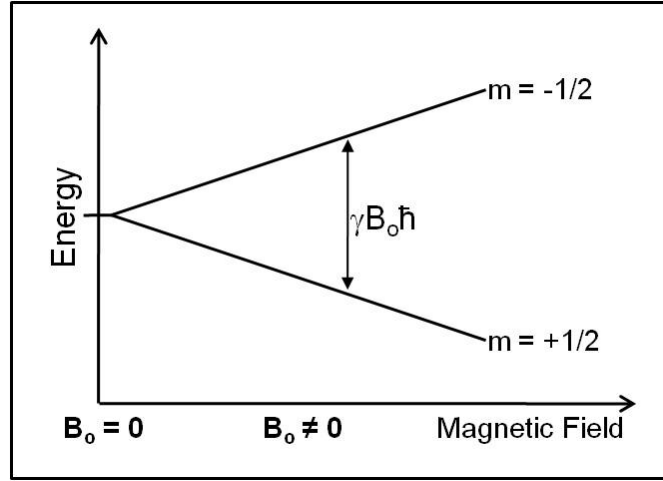


Figure 2.3. Energy difference between the angular momentum spin states as a function of $\mathbf{B}_0$.

For a nuclear spin under the influence of the $\mathbf{B}_0$ field and H constant with time

(2.2) the evolution operator $U(t)$ is

$$U(t) = \exp(-iHt/\hbar) = \exp(i\gamma B_0 A_z t). \quad (2.4)$$

The Zeeman interaction evolution operator describes a clockwise rotation about the z -axis by an angle $\gamma B_0 t$. That is, in addition to introducing energy levels, the static magnetic field $\mathbf{B}_0$ also exerts a torque $\mathbf{T} = \boldsymbol{\mu} \times \mathbf{B}_0$ on the spins. This torque causes the spins to precess about the z -axis. The frequency of the precession ω_0 , called the Larmor or resonance frequency, is

$$\omega_0 = \gamma B_0. \quad (2.5)$$

The energy difference between the spin states ΔE of Boltzmann's Distribution is related to ω_0 as $\Delta E = \omega_0 \hbar$. The Larmor frequency of spins in NMR experiments is typically in the high frequency (HF) to ultra high frequency (UHF) radiofrequency (rf) range of the electromagnetic spectrum, *i.e.* at 7T, $\omega_0=300$ MHz. However, Earth's Field NMR (EFNMR) utilizes the Earth's magnetic field as the $\mathbf{B}_0$ field, which is many orders

of magnitude smaller than conventional NMR superconducting magnetic field strengths at a mere 50 microtesla. The Larmor frequency of proton nuclei in EFNMR is in the audio frequency range.

Additionally, the mathematics of quantum mechanics and statistics shows that there is no a priori phase coherence of an ensemble of spins in thermal equilibrium. Phase coherence comes from the off-diagonal operator A_x which gives rise to a transverse magnetization component. In order for there to be detectable nuclear magnetic resonance signal, precessing transverse magnetization is essential.

At this point, quantum mechanics has provided an explanation for the alignment and precession of nuclear spins in a static magnetic field $\mathbf{B}_0$. The quantum mechanics description is appropriate for a single nuclear spin in isolation. Of course, experimentally the magnetic resonance signal arises from large *ensembles* of many spins in which the different nuclei occupy different basis states. Hence a classical mechanics perspective will adopted from here on in which the nuclear magnetization will be described in terms of ensemble averages or the net behavior of a large number of spins.

Resonant Excitation and the Rotating Reference Frame

Consider the effect of an oscillating magnetic field of amplitude B_1 and frequency ω applied transverse to a set of equivalent spins in thermal equilibrium in the longitudinal magnetic field $\mathbf{B}_0$. The Hamiltonian operator in the laboratory, i.e. stationary, reference frame, may be written

$$H_{lab} = -\gamma B_0 A_z - 2\gamma B_1 \cos \omega t A_x. \quad (2.6)$$

Now, making a coordinate transformation to the reference frame rotating with frequency $\omega=\omega_0$, the rotating field B_1 appears stationary. This transformation is advantageous because it renders the Hamiltonian operator time independent, greatly simplifying the evolution operator. Additionally, in the rotating frame of reference, the net magnetization arising from all the nuclear spins in a sample can be represented as a stationary vector, which greatly aids visualization of the behavior of a large ensemble of nuclear spins undergoing various electromagnetic disturbances.

In the rotating frame, the Hamiltonian (2.6) becomes

$$H_{rot} = -\gamma(B_0 - \omega/\gamma)A_z - \gamma B_1 A_x. \quad (2.7)$$

At resonance $\omega=\omega_0$ the longitudinal field vanishes, rendering the effective field along the rotating frame x-axis. The reduction of the longitudinal field is key to how the relatively weak rf field is able to affect the magnetization of the nuclear spins in the presence of the much stronger $\mathbf{B}_0$ field. The effective field arising from the oscillating B_1 rf pulse exerts a torque on the nuclear spins. Consequently, the spins are disturbed from their thermal equilibrium position and they precess about the x-axis. Radiofrequency excitation will be described further from the classical mechanics perspective.

The Semi-Classical Mechanics Perspective

For the purposes of the research presented in this thesis, it is useful to consider the semi-classical perspective, as the semi-classical picture provides methods for visualizing and understanding the ensemble behavior of a large group of spins, e.g. there are on the order of 10^{23} spins in any particular sample. The net effect of all the spins in the presence

of $\mathbf{B}_0$ is that there will be an excess of spins aligned parallel to $\mathbf{B}_0$ precessing at the Larmor frequency as shown in Fig. 2.4.

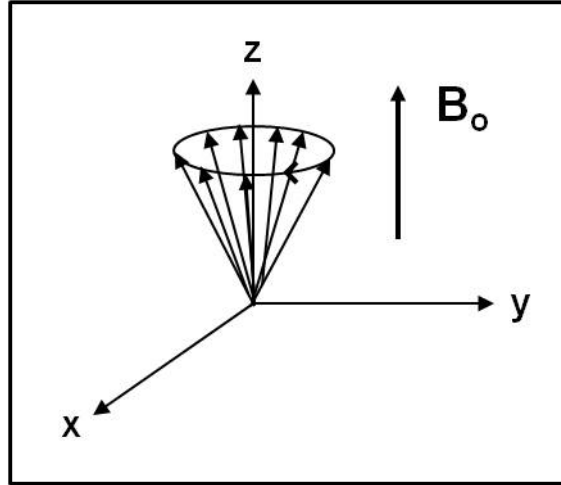


Figure 2.4. Orientation and precession of nuclear spins at thermal equilibrium in a stationary magnetic field $\mathbf{B}_0$ aligned with the z-axis.

In the semi-classical description, the net sample magnetization vector $\mathbf{M}$ is simply the sum of all of the magnetic moment vectors $\boldsymbol{\mu}$ in the sample

$$\mathbf{M} = \sum \boldsymbol{\mu}. \quad (2.8)$$

As previously mentioned, there is only a slightly larger percentage of the spins aligned parallel to $\mathbf{B}_0$ (Boltzmann's Distribution). Therefore, the net magnetization $\mathbf{M}$ arising from the sample will be small in magnitude, i.e. $\mathbf{M} \ll \mathbf{B}_0$ and aligned parallel to $\mathbf{B}_0$ in its thermal equilibrium position $\mathbf{M}_0$. The net effect of all the spins precessing about the z-axis, is that the net magnetization vector $\mathbf{M}$ precesses about z at the Larmor frequency.

The sample magnetization vector $\mathbf{M}$ is the critical component of MR experiments. Now that $\mathbf{M}$ has been established, it can be manipulated in order to glean useful

information about a sample. The process of exciting $\mathbf{M}$ and obtaining an MR signal will be discussed in subsequent sections. A rotating frame of reference (designated as x' , y' and z') will be adopted so that vector notation can be used to visualize the sample magnetization $\mathbf{M}$. In the rotating frame of reference, when the coordinate system is rotating at the Larmor frequency ω_0 , $\mathbf{M}$ appears to be stationary as shown in Fig. 2.5.

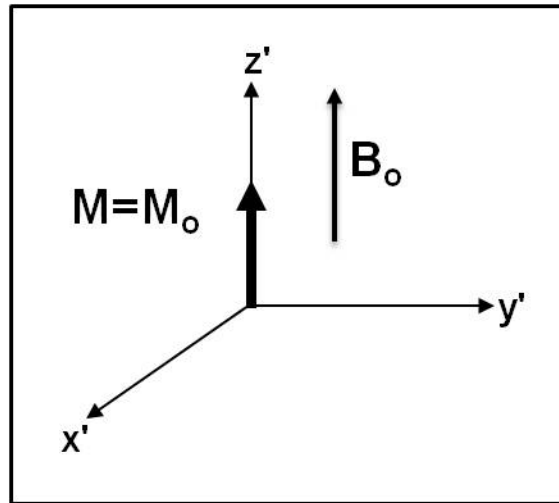


Figure 2.5. Thermal equilibrium position of net magnetization vector $\mathbf{M}$ in the presence of $\mathbf{B}_0$ in the rotating reference frame.

Excitation & Detection

In NMR experiments, a radiofrequency (rf) coil holds the sample. The rf coil acts as both a transmitter of rf energy pulses and as a receiver of the signal arising from the sample magnetization. Applying an oscillating magnetic field perpendicular to the net sample magnetization $\mathbf{M}$ causes $\mathbf{M}$ to be excited from its equilibrium position if the applied field oscillates at the Larmor frequency. The $\mathbf{B}_1$ magnetic field is applied as a radiofrequency energy pulse with amplitude B_1 oscillating at ω_0 . It is necessary that the sample be irradiated with rf energy at the Larmor frequency because this is the energy

that the hydrogen nuclei in the sample can absorb based on the energy difference ΔE between the two spin states of hydrogen spins. A typical NMR experiment utilizes an oscillating rf field of amplitude B_1 and duration t_p to excite spins from the lower energy state to the higher energy state. The net effect of rf excitation is to tip $\mathbf{M}$ from its equilibrium position through an angle $\theta = \gamma B_1 t_p$ by providing the energy needed to cause “spin up” spins to transition to the higher energy “spin down” position, and vice versa. For example, for $\theta = 90^\circ$ the rf pulse excitation will result in there being an equal number of spins in each spin state so that $\mathbf{M}$ is tipped into the transverse plane as shown in Fig. 2.6.

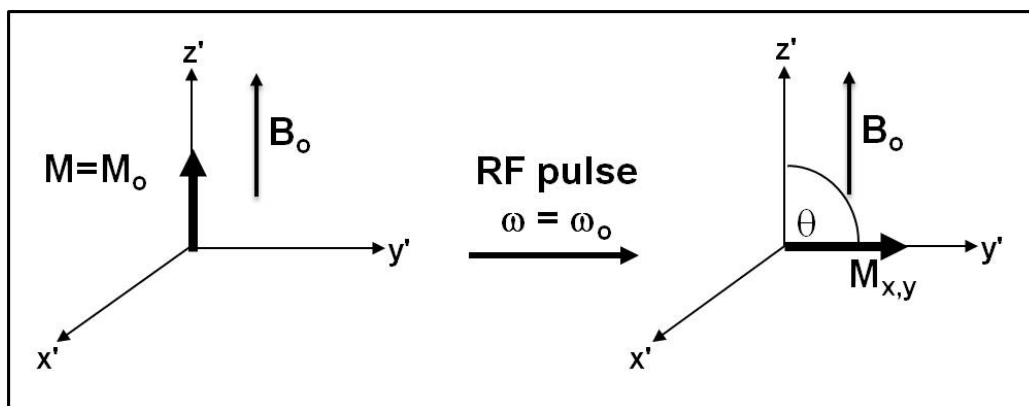


Figure 2.6. Application of a $\theta = 90^\circ$ radiofrequency pulse tips the net magnetization vector $\mathbf{M}$ from its thermal equilibrium position $\mathbf{M}_0$ into the transverse plane so that there is now a transverse magnetization vector $\mathbf{M}_{x,y}$.

Once tipped into the transverse plane, the sample magnetization vector $\mathbf{M}$ continues to precess at the Larmor frequency about the z' axis. This oscillating magnetic field induces a voltage in the radio frequency coil. This voltage is known as the free induction decay (FID) signal because its amplitude decays over time due to the effects of relaxation processes which shall be addressed in some detail shortly. The FID signal is depicted in Fig. 2.7. Note that following a 90° rf pulse, the FID signal is proportional to

the population difference between the two spin states as it is the precession of the net magnetization vector $\mathbf{M}$ which gives rise to the NMR signal.

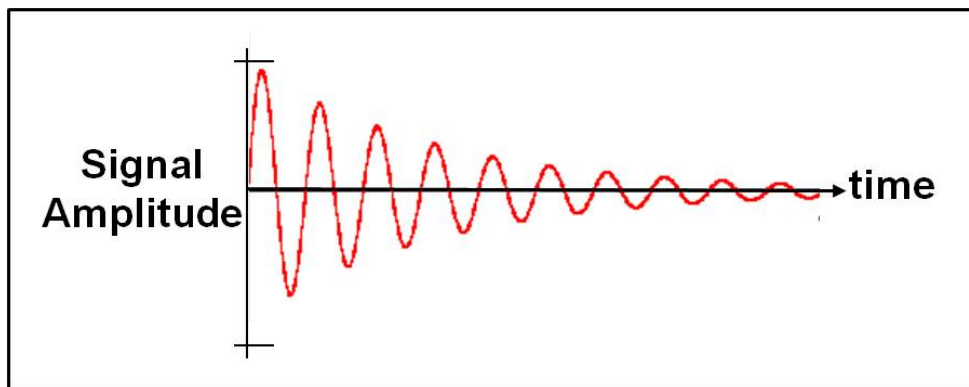


Figure 2.7. Free Induction Decay signal.

Relaxation Processes

Following radiofrequency excitation, the hydrogen nuclei proceed to release rf energy, the magnetization vector relaxes back to the equilibrium position and the FID signal decays due to relaxation processes. There are two relaxation processes that act on the net sample magnetization when it is not in the equilibrium state. The first is “longitudinal” or “spin-lattice” relaxation which is denoted by the time constant T_1 . The second is called “transverse” or “spin-spin” relaxation and is denoted by the time constant T_2 .

T_1 Longitudinal Spin-Lattice Relaxation. Longitudinal spin-lattice relaxation will be considered first. Immediately following the rf pulse, all of the sample magnetization is in the transverse plane and there is no longitudinal sample magnetization. At this point, the sample begins releasing the energy it absorbed during rf excitation. Specifically, the nuclear spins of the sample release the energy to their surrounding

environment, the “lattice.” As spins release energy, they return to the lower energy spin-up position in which they are aligned parallel to $\mathbf{B}_0$. As this happens, the ratio of spins in the spin up position to those in the spin down position is returning to the Boltzmann distribution, and the net magnetization vector returns to its thermal equilibrium position $\mathbf{M}_0$ aligned in the longitudinal direction with $\mathbf{B}_0$. The phenomenological description of the spin-lattice relaxation process is given by the equation

$$\frac{dM_z}{dt} = \frac{-(M_z - M_0)}{T_1}, \quad (2.9)$$

with solution

$$M_z(t) = M_z(0)e^{-t/T_1} + M_0(1 - e^{-t/T_1}). \quad (2.10)$$

The time constant, for longitudinal relaxation, T_1 , is typically 0.1-10 seconds for protons in liquids at ambient temperature [8].

T_2 Transverse Spin-Spin Relaxation. The second relaxation process, spin-spin relaxation, describes how the transverse magnetization resulting from the application of the rf excitation pulse, evolves over time. During this relaxation process, spins exchange energy with other spins, hence “spin-spin” relaxation. T_2 relaxation results primarily from the spins, *i.e.* magnetic moments, imparting slight fluctuating magnetic fields on one another through magnetic dipole-dipole interactions. As a result of this energy exchange due to spin-spin coupling, the magnetic field varies locally and since the precession frequency ω is a function of the local magnetic field, the spins begin precessing at different frequencies. As the spins precess at different frequencies, they

spread out from one another or *dephase* in the transverse plane causing the net transverse magnetization vector $\mathbf{M}_{x,y}$ to shrink as shown in Fig. 2.8.

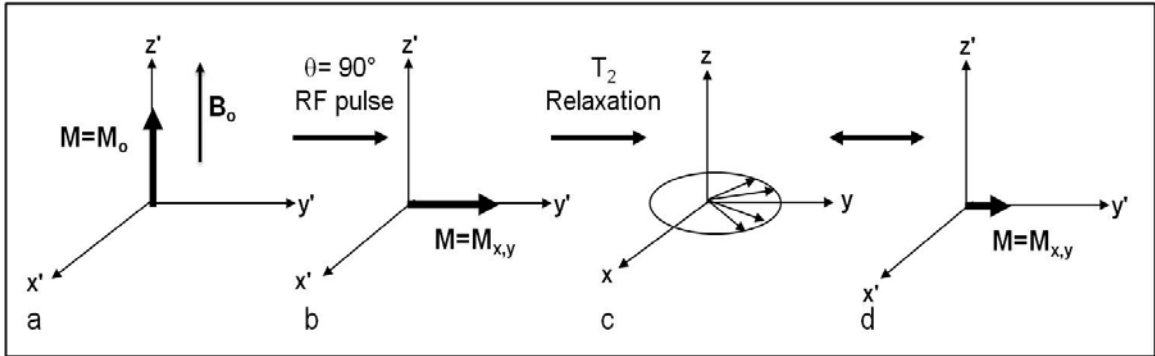


Figure 2.8. T_2 Relaxation Process. a.) The net sample magnetization vector is in thermal equilibrium $\mathbf{M}_0$. b.) Immediately following a 90° rf excitation pulse, the sample magnetization vector is in the transverse plane and the spins are in phase. Therefore, the transverse magnetization vector $\mathbf{M}_{x,y}$ is at its maximum magnitude. c.) T_2 relaxation processes begin to cause individual spins to dephase which has the effect of d.) shrinking the magnitude of the net transverse magnetization vector $\mathbf{M}_{x,y}$.

A reversible process which contributes to the loss of transverse magnetization through the loss of phase coherence is T_2^* . T_2^* relaxation results from macroscopic inhomogeneities in the magnetic field surrounding the sample. The additional line width broadening caused by magnetic field inhomogeneities dephasing the transverse magnetization can cause severe distortion in NMR microscopy and can also result in the FID signal decaying at a much faster rate than by pure T_2 relaxation effects alone. Great care is taken to ensure that the magnetic field surrounding the sample in NMR experiments is as homogeneous as possible and special shim coils are used to impart fine corrections to the magnetic field in the region of the sample. However, some variation in $\mathbf{B}_0$ persists even after shimming. Fortunately, phase coherence loss due to magnetic field inhomogeneities is reversible and can be undone as long as spins do not diffuse to a significantly different magnetic field environment during the time between refocusing

180° rf pulses. Various methods for recovering coherence losses due to inhomogeneities exist. However, the Hahn Spin Echo method is probably the most utilized, and will be detailed as an introductory NMR experiment.

The phenomenological description of transverse relaxation is given by the equation

$$\frac{dM_{x,y}}{dt} = \frac{-M_{x,y}}{T_2}, \quad (2.11)$$

with solution

$$M_{x,y}(t) = M_{x,y}(0)e^{-t/T_2}. \quad (2.12)$$

The exponential decay of the transverse magnetization as represented by the phenomenological equation for T_2 relaxation applies for relatively weak T_2 relaxation as is the case for spins residing in liquids. In order to accurately model T_2 relaxation in solids and macromolecules, more complex equations are required.

The Bloch Equations

The precession of the spin magnetization vector $\mathbf{M}$ can be described in terms of the time rate of change of angular momentum through the following equation

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B}. \quad (2.13)$$

Where the magnetic force, $\mathbf{B}$, acting on $\mathbf{M}$ can arise from a number of sources including:

- 1.) From a large static magnetic field, $\mathbf{B}_0$.
- 2.) From an electromagnetic field generated by an rf coil, $\mathbf{B}_1$.
- 3.) From fluctuating magnetic fields generated by the motion of magnetic nuclei, e.g. dipole-dipole interactions.

In a typical NMR experiment several of these forces may be acting on $\mathbf{M}$ at the same time. Combining equations (2.9), (2.11) and (2.13) in the rotating frame yields the set of relationships known as the Bloch equations [9]

$$\frac{dM_x}{dt} = \gamma M_y \left(B_o - \frac{\omega}{\gamma} \right) - \frac{M_x}{T_2} \quad (2.14)$$

$$\frac{dM_y}{dt} = \gamma M_z B_1 - \gamma M_x \left(B_o - \frac{\omega}{\gamma} \right) - \frac{M_y}{T_2} \quad (2.15)$$

$$\frac{dM_z}{dt} = -\gamma M_y B_1 \frac{-(M_z - M_o)}{T_1}. \quad (2.16)$$

The phenomenological Bloch equations are useful in describing the effects of magnetic forces, $\mathbf{B}$, on the net magnetization vector, $\mathbf{M}$, which are critical in designing and interpreting NMR experiments.

Dipolar Interactions and the Visibility of Fine Details

The line width of a chemical shift peak at half height in an NMR chemical spectrum is proportional to $1/\pi T_2$. In liquids, the T_2 time is long and the line width may be 8 or 9 orders of magnitude smaller than the Larmor frequency [8] owing to the fact that there are significant separation distances between magnetic moments, which minimizes dipole-dipole interactions. This means that very fine features and relatively small chemical shift displacements can be distinguished in liquid chemical shift spectra. In solids, strong dipolar interactions between spins destroy the transverse magnetization phase coherence within microseconds after its formation, which leads to a significantly broadened line width and the loss of fine features. The extremely short T_2 relaxation times of solids also limit the range of MR experiments that can be applied.

Chemical Shift

The electron clouds surrounding atomic nuclei shield the nuclei from applied magnetic fields. The result of magnetic shielding is that atomic nuclei in different molecular electron environments will experience differing effective magnetic fields. Since the Larmor frequency is a function of the effective magnetic field, the Larmor frequencies for atomic nuclei located in different molecular environments will vary, thus labeling nuclei in different electron environments with a “chemical fingerprint.” This phenomenon, known as *chemical shift*, is the basis of chemical spectroscopy. Chemical shift spectra can be used for the valuable purposes of identifying and quantifying the chemical constituents present in the sample.

In addition to chemical spectroscopy, chemical shift also allows for chemical selective excitation through which rf pulses can be applied in such a manner that only nuclei with a specific Larmor frequency or chemical shift are excited. However, chemical shift can lead to severe artifacts in NMR imaging. In NMR imaging experiments, the Larmor frequency is made to be a function of position through the application of a magnetic field that varies linearly with position. If there are nuclei of significantly different chemical environments located within the same spatial pixel(s) of an image, they will appear to be displaced due to the difference in their Larmor frequencies, *i.e.* their chemical shift. An example of such an imaging artifact, which is sometimes called *pixel shift*, is shown in Fig. 2.9. In this image, frequency encoding was performed in the horizontal direction so that the nuclei in the same horizontal position appear horizontally shifted between the oil and water.

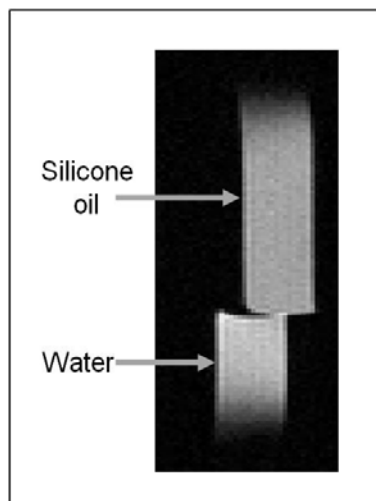


Figure 2.9. Chemical shift artifact shown for silicone oil and water in a test tube.

To minimize chemical shift artifacts, the spectral width can be increased in order to increase the range of allowable frequencies within each pixel. Or phase encoding rather than frequency encoding imaging techniques can be used to eliminate chemical shift artifacts altogether, but this is very time consuming as will be covered in the NMR imaging section.

Signal Detection and Transformation

The Receiver. The FID signal is very small (on the order of μV) and is proportional to the transverse magnetization that exists in the sample. Fortunately, modern electronics are capable of amplifying this signal to a level where it can be digitized. Generally a pre-amplifier is placed as close to the rf probe as possible. This is so that the weak signal can be boosted before being transmitted down a cable to the spectrometer console [10].

Digitization and Sampling. An analog to digital converter or ADC is used to convert the NMR signal from a voltage to a binary number which can be stored in computer memory. The ADC samples the signal at regular intervals, resulting in the representation of the FID signal as discrete data points. Therefore, the ADC output is an approximation of the actual waveform it samples. Increasing the ADC's number of bits and its sampling frequency improve this approximation, but both the number of bits and sampling frequency are limited technically. At present, ADCs with between 16 and 32 bits are commonly used in NMR spectrometers [10] and the maximum sampling frequency f_{max} is between 200 kHz and 2MHz.

The Nyquist theorem [11], a fundamental principle in Fourier transform spectrometry, states that a time domain FID must be sampled at a frequency that is at least twice the maximum frequency in the signal bandwidth $f_{sampling} \geq 2f_{maxsignal}$ in order that the signal appear at its correct frequency in the spectrum obtained by Fourier transformation of the time-domain waveform. Therefore, the Nyquist condition requires that the dwell time τ_{dwell} , the time between each data point sampled, is $\tau_{dwell} \leq \frac{1}{2f_{maxsignal}}$. The use of quadrature detection allows both positive and negative frequencies to be distinguished so for a dwell time of τ_{dwell} the range of frequencies from $-f_{maxsignal}$ to $+f_{maxsignal}$ is represented correctly.

The Nyquist condition presents a problem since a typical NMR frequency is on the order of hundreds of MHz but there are no ADCs available which are capable of digitizing an NMR FID with the degree of accuracy needed. However, although the NMR frequency is high compared to maximum digitizer sampling frequencies, the range

of frequencies covered in a typical spectrum is rather small. As an example, the 10 ppm of a proton spectrum recorded at 250 MHz cover just 2500 Hz. Therefore, by taking the NMR signal and subtracting a reference frequency ω_{ref} (typically the basic frequency set as the center point of the frequency spectrum) the resulting frequency of the waveform to be digitized is much lower than the NMR frequency, and is now readily sampled and digitized. This procedure is known as *downmixing*.

Quadrature Detection. It is through quadrature detection that positive and negative frequencies can be distinguished. Practically, the phase of the signal is determined through heterodyne mixing. In the heterodyne mixing process, the NMR signal coming from the rf probe is split into two components that are phase shifted by 90° relative to one another and fed to two separate *mixers*. The mixers perform mathematical operations on the phase shifted signals, effectively deducing the $S_x(\mathbf{i})$ and $S_y(\mathbf{j})$ components of the transverse magnetization. These two outputs are digitized separately and become the real and imaginary components, respectively of the complex time domain signal. The laboratory frame magnetization as a function of time t immediately following an rf excitation pulse is

$$M(t) = [M_o \cos \omega_o t \mathbf{i} + M_o \sin \omega_o t \mathbf{j}] \exp\left(-t/T_2\right). \quad (2.17)$$

Recall that through complex number notation cosine and sine functions are replaced by exponential functions. The laboratory frame magnetization and signal as a function of time t following an rf excitation pulse in complex number notation can be written as

$$M(t) = M_o \exp(i\omega_o t) \exp\left(-t/T_2\right) \quad (2.18)$$

$$S(t) = S_o \exp(i\Delta\omega t) \exp\left(-t/T_2\right). \quad (2.19)$$

Here S_o is the signal amplitude immediately following the rf pulse, a number proportional to M_o and $\Delta\omega = \omega_o - \omega_{\text{ref}}$ is the offset frequency. The NMR signal is measured in the time domain as an oscillating, decaying electromagnetic field or voltage induced by the magnetization in free precession. Equation (2.19) shows mathematically that $S(t)$, the FID signal, will be purely exponential if $\omega_{\text{ref}} = \omega_o$.

Fourier Transformation. Fourier transformation of the FID signal transforms the signal from the time domain to the frequency domain. Fourier transformation of the real S_x and imaginary S_y components of the time domain signal yields the absorption and dispersion spectra, respectively. Typical chemical spectra are presented as absorption spectra, in which the peaks resulting from Fourier transformation of the real FID signal have the shape of a Lorentzian function and the center of the Lorentzian peak corresponds to the frequency of $\Delta\omega = \omega_o - \omega_{\text{ref}}$.

Introductory NMR Practicalities and Experiments

RF Excitation

Radiofrequency energy pulses of amplitude B_1 and frequency ω_o , *i.e.* the Larmor frequency, are used to excite the sample magnetization $\mathbf{M}$ from thermal equilibrium into the transverse x-y plane where its oscillation induces a detectable FID signal. The tip angle θ that an rf pulse affects on $\mathbf{M}$ is determined through the equation $\theta = \gamma B_1 t_p$ where t_p is the duration of the rf pulse, typically between 50 μs and a few ms. Application of rf

pulses not only has the effect of rotating the nuclear spins from their thermal equilibrium position, but also brings the spins in-phase. The phase of rf pulses used in an NMR experiment can be changed at will. The equations of quantum mechanics which describe the degree of “single quantum coherence” (for $I=1/2$ spins) of an ensemble of nuclear spins are covered in some detail in Sec. 2.1 of [8] and will not be presented here. Suffice it to say that phase coherence occurs when spins have been excited from their thermal equilibrium position and decays quickly due to T_1 and T_2 relaxation. Varying the angle θ and phase ϕ of an rf pulse affects the rotation of the sample magnetization vector $\mathbf{M}$. Sec. 10.8 of [12] presents the details of the mathematics to determine the effects of an rf pulse of angle θ and phase ϕ on the sample magnetization. Systematic variation of the rf pulse phase is an important NMR technique, referred to as *phase cycling*. Through phase cycling, a pulse sequence is repeated many times with a systematic variation of the relative phases of the pulses within the sequence so that only signal from the spins that experienced each of the applied rf pulses is retained. Phase cycling is critical to MR experiments because it allows the signal from spins that have experienced all rf pulses exactly as intended to be added coherently while unwanted interference signals, *e.g.* signal arising from spins that did not experience one or more of the applied rf pulses as intended, is eliminated.

The amplitude of the rf pulse B_1 is controlled by setting the attenuation for the constant amplitude power coming from the rf amplifier before it is sent to the rf coil surrounding the sample. The range of frequencies or bandwidth excited by a particular rf pulse is inversely proportional to t_p . For example, a 50 μs rf pulse excites a large

(relative to the range of Larmor frequencies present in a sample) bandwidth of 20 kHz. Such a pulse is commonly referred to as a *hard pulse*, and a pulse of narrow bandwidth such as a 2 ms duration pulse corresponding to a 500 Hz bandwidth, is known as a *soft pulse*. Soft pulses are used for selective excitation in which a small specific range of frequencies are excited. Soft pulses are used in chemical shift selective excitation and slice selection to excite a specific chemical component or a specific region of a sample, respectively. The shape of rf pulses is also controlled. For instance, it is often desired for slice selective experiments that the acquired signal comes from a rectangular region of the sample. According to the mathematics of Fourier transforms for band limited functions, the shape of the rf pulse applied in the time domain must have the shape of a sinc function in order that a rectangular region of the sample is selected in the frequency domain, *i.e.* the Fourier transform of a sinc function is a hat function.

Signal Averaging

NMR experiments are inherently low sensitivity owing to the fact that at room temperature, only a tiny fraction more spins reside in the spin up position versus the spin down position as described by the Boltzmann Distribution (2.3). It is customary to improve the signal-to-noise ratio *SNR* by adding the signal from N successive experiments. Successive addition is effective because the signals add coherently while the noise averaging is random and hence incoherent. As a result, the *SNR* improves as $N^{1/2}$. Since the number of experiments N is proportional to the time t required to run the experiment, the *SNR* increases as $t^{1/2}$. This means that the duration of the entire experiment, *i.e.* including all N experiments, must be quadrupled in order to double the

SNR. Obviously, time considerations limit the utility of running additional experiments to improve *SNR*. T_1 relaxation time is the primary time consideration since it is necessary to wait for a recovery time $T_R \sim 3-5T_1$ to allow the nuclear spin system to relax back to thermal equilibrium between successive averages in order to retain full signal strength.

Inversion Recovery

The rf pulse sequence called “Inversion Recovery,” depicted in Fig. 2.10 (a), is used for measuring T_1 relaxation times as well as for the selective suppression of unwanted spin signals. In the “Inversion Recovery” sequence, the first 180° rf pulse inverts the sample magnetization vector. Spin lattice T_1 relaxation acts on $\mathbf{M}$ over time t_{inv} , the time at which the 90° pulse is used to inspect any longitudinal magnetization that remains. The inversion time at which the signal is minimized corresponds to the T_1 relaxation time since the sample magnetization will cross over through zero magnetization when $\mathbf{M}$ has relaxed for $t=T_1$.

The signal amplitude versus time is shown in Fig. 2.10 (b) and is described by

$$\mathbf{M}(t) = M_o \left[1 - 2\exp\left(-t/T_1\right) \right]. \quad (2.20)$$

Setting the left hand side of (2.20) equal to zero and solving for t , it is clear that the zero magnetization cross over occurs at $0.6931T_1$. This method can be used to minimize unwanted signal when a sample contains spins with varying T_1 relaxation times. The undesired spins’ signal can be suppressed by applying a 180_x pulse at $0.6931T_1$ before the beginning of a standard pulse sequence, *e.g.* an imaging sequence.

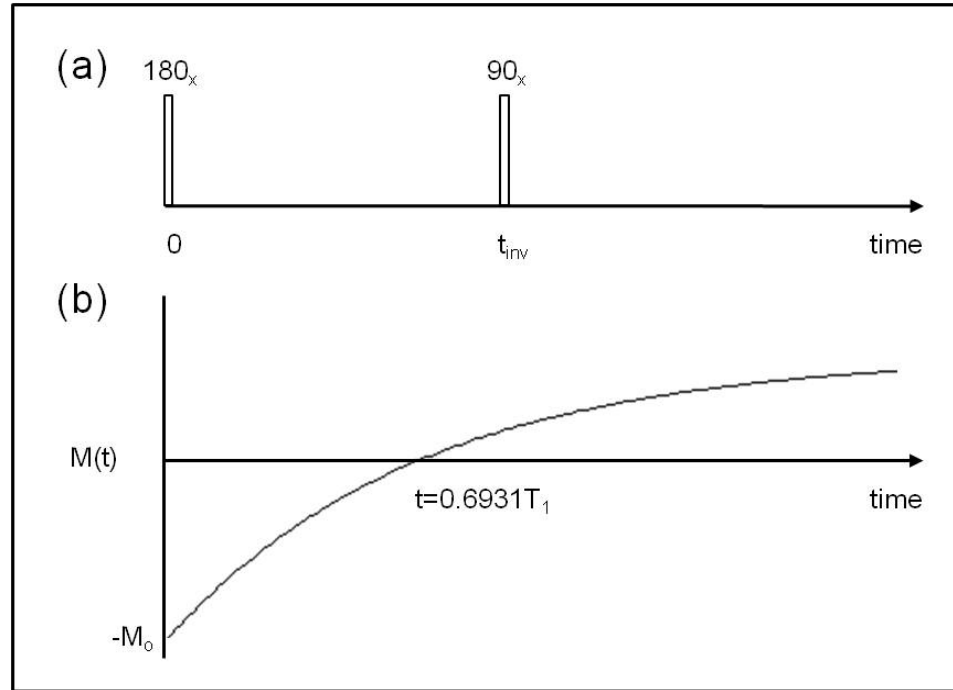


Figure 2.10. (a) Inversion recovery pulse sequence and (b) plot of signal amplitude as a function of time.

The Hahn Spin Echo

Loss of phase coherence due to magnetic field inhomogeneity, *i.e.* T_2^* relaxation, is recoverable because it is not random – it's a function of the spread of the B_0 field across the sample ΔB_0 . Probably the most common method of recovering phase coherence that is lost via T_2^* relaxation is the Hahn spin echo method, named for Erwin Hahn [13], who recognized that this loss of phase coherence was inherently reversible. Application of a 180_y° rf pulse following a delay time τ after the 90_x° pulse will cause the spins to come back into phase at time 2τ as shown in Fig. 2.11. The time at which the spins come back into phase, 2τ , is known as the echo time T_e .

- 1.) The spins are in thermal equilibrium immediately before the 90_x rf pulse.
- 2.) The 90_x rf pulse rotates the sample magnetization vector into the transverse plane.

- 3.) The NMR signal decays as the spins dephase due to inhomogeneities in the polarizing magnetic field ΔB_0 causing the spins to precess at different Larmor frequencies.
- 4.) Immediately following the 180_y rf pulse applied at $t=\tau$, the spin precession direction has effectively been reversed
- 5.) At $t=2\tau$, the spins have come back into phase, and the resulting refocused signal is referred to as the “Spin Echo” signal.

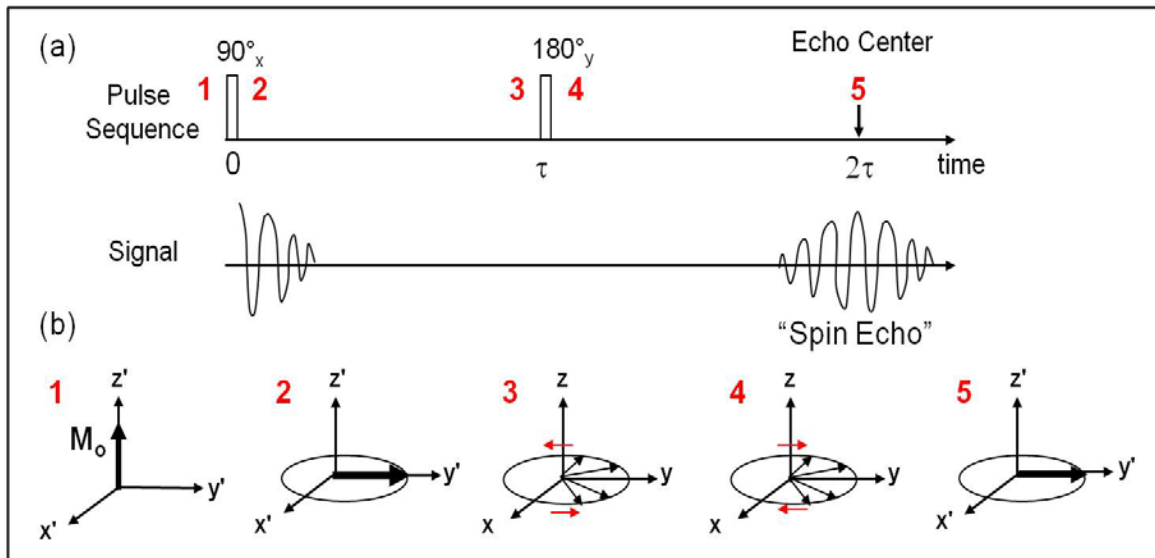


Figure 2.11. (a) Hahn spin echo pulse sequence and echo signal. Note that the 180_y pulse inverts the phase of each spin packet precessing at a specific frequency, effectively reversing the direction of precession of the spin packets. (b) Evolution of the sample magnetization undergoing the Hahn spin echo pulse sequence.

An analogy to runners on a track is commonly used to explain the Hahn spin echo experiment. In this analogy, runners are initially lined up together at the starting point, *i.e.* they're in phase. At $t=0$, the runners are set racing around the track and they begin to spread out. Runners in different lanes correspond to groups of spins precessing at different frequencies. At $t=\tau$, the whistle is blown, signaling the runners to reverse

direction while maintaining the same running pace, *i.e.* precession frequency. At $t=2\tau$, the runners will be lined up once again, having come back in phase.

The Carr-Purcell-Meiboom-Gill Echo Train

The phase coherence recovered in the Hahn spin echo is subsequently lost for $t > 2\tau$. However, successive recoveries are possible if a train of additional 180° rf pulses are applied [14]. Meiboom and Gill then modified this sequence to use quadrature 180_y pulses in order to avoid the cumulative effects of small turn angle errors [15].

Eventually, the echo signal will decay to zero due to non recoverable spin-spin relaxation T_2 . The T_2 relaxation time can be determined through the Carr-Purcell-Meiboom-Gill CPMG sequence (Fig. 2.12) by plotting the echo amplitude as a function of the 2τ time according to the phenomenological equation

$$M_y(2\tau) = M_o \exp\left(-2\tau/T_2\right). \quad (2.21)$$

Additionally, adding multiple echo signals obtained from a CPMG train of 180° rf pulses can improve the signal-to-noise ratio without increasing overall experiment times.

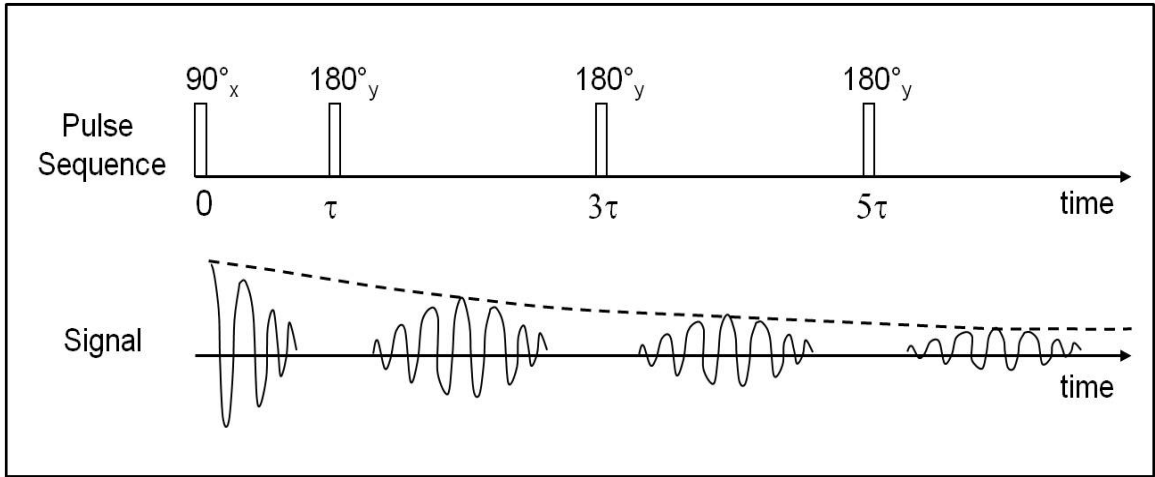


Figure 2.12. CPMG pulse sequence and spin echo signals at $2n\tau$ (n refers to the n^{th} 180°_y pulse of the pulse train) modulated by T_2 relaxation. The time at which the relaxation envelope has decayed completely and subsequent 180° rf pulses no longer recover any signal is the T_2 relaxation time.

Stimulated Echo

In many materials, the transverse relaxation time T_2 is much shorter than T_1 , thus limiting potential experiments. Through the stimulated echo, transverse magnetization can be stored along the z-axis where it is protected from loss of phase coherence due to T_2 relaxation. The stimulated echo sequence, depicted in Fig. 2.13, supplies extra time to allow a sample to evolve, *e.g.* to undergo diffusive translational motion.

In Fig. 2.13, at $t=0$, the standard 90_x rf pulse is applied to excite the sample magnetization into the transverse plane. Then at $t=\tau$, another 90_x rf pulse is applied, which has the effect of rotating the y-component of transverse magnetization along the z-axis, a state in which only T_1 relaxation will occur. Any x-magnetization at $t=\tau$ is unaffected by the second 90_x rf pulse and remains in the transverse plane. Application of a homogeneity spoiling “homospoil” magnetic field, destroys this remaining transverse magnetization without affecting the magnetization which has been stored along the z-

axis. Finally at $t=T$, a third 90_x rf pulse is applied, which returns the longitudinally stored transverse magnetization to the transverse plane, and the desired echo signal will form at time τ after the final rf pulse.

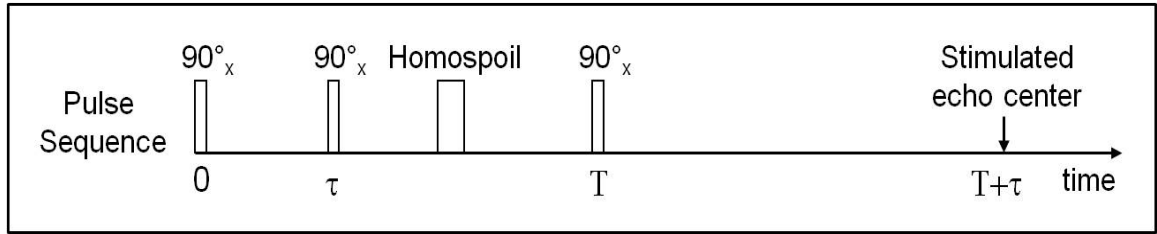


Figure 2.13. Stimulated echo pulse sequence.

Imaging

Linearly Varying Magnetic Field Gradients

The fact that the Larmor precession frequency is so sensitive to magnetic field strength is the basis of nuclear magnetic resonance, and this feature is exploited routinely in NMR experiments. In the case of NMR imaging, magnetic fields that vary linearly across the sample, often referred to simply as “gradients” are applied independently of the much larger polarizing $\mathbf{B}_0$ field. In this way, the Larmor frequency is made to vary linearly as a function of spatial position $\mathbf{r}$ as

$$\omega(\mathbf{r}) = \gamma \mathbf{B}_0 + \gamma \mathbf{G} \cdot \mathbf{r}. \quad (2.22)$$

The magnetic field gradient $\mathbf{G}$ can be applied in any direction.

When the reference frequency ω_{ref} is chosen to be the resonance frequency ω_0 , as it usually is, the offset frequency is

$$\Delta\omega = \omega(\mathbf{r}) - \omega_0 = \gamma \mathbf{G} \cdot \mathbf{r}. \quad (2.23)$$

k-space, Frequency Encoding and Phase Encoding

In NMR imaging, the signal is sampled in the time domain and is then Fourier transformed into the frequency domain. The time domain is referred to as reciprocal space or “k-space” and the frequency domain is known as the direct or real space. The convention of representing the time domain signal as a function of $\mathbf{k}$ rather than time has precedence in wave scattering experiments. The major difference between NMR experiments and the classical scattering techniques is that the NMR signal is a complex number and contains both magnitude and phase information whereas scattering techniques provide only intensity data.

Through the application of magnetic field gradient pulses, position is encoded into the phase of the signal as a function of $\mathbf{k}$. Where the wave vector $\mathbf{k}$ is defined as

$$\mathbf{k} = \frac{\gamma \mathbf{G} \delta}{2\pi}. \quad (2.24)$$

A gradient applied for a time interval δ causes a spread in frequencies as a function of position and leads to an accumulated phase shift $\phi(\mathbf{r}) = [\omega(\mathbf{r}) - \omega_0]\delta$ with respect to the reference frequency chosen to be the resonance frequency ω_0 . The resulting phase shift of spins at position $\mathbf{r}$ following a gradient pulse $\mathbf{G}$ of duration δ is then $\phi(\mathbf{r}) = \gamma \mathbf{G} \cdot \mathbf{r} \delta$.

Recalling that the signal generated by the precessing sample magnetization is a complex number (2.18), the phase shift created by the gradient pulse leads to the NMR signal, which is the multiplication of the unperturbed NMR signal with the phase factor $\exp(i\phi(\mathbf{r}))$. The total signal arising from all the spins within the sample of spin density $\rho(\mathbf{r})$ obtained by integrating the phase factors over the entire sample volume is

$$S(\delta) = \iiint \rho(\mathbf{r}) \exp(i\gamma \mathbf{G} \cdot \mathbf{r} \delta) d\mathbf{r}. \quad (2.25)$$

Or written in wave vector notation

$$S(\mathbf{k}) = \iiint \rho(\mathbf{r}) \exp(i2\pi \mathbf{k} \cdot \mathbf{r}) d\mathbf{r}. \quad (2.26)$$

Fourier transformation of the signal $S(\mathbf{k})$ gives the image or density of the spins $\rho(\mathbf{r})$

$$\rho(\mathbf{r}) = \iiint S(\mathbf{k}) \exp(-i2\pi \mathbf{k} \cdot \mathbf{r}) d\mathbf{k}. \quad (2.27)$$

Of course, in practice, the signal is digitized and thus sampled at discrete equidistant steps and a Fast Fourier Transform FFT is performed on the signal rather than the full analytical Fourier transform.

There are two methods for traversing k-space to acquire the position-dependent NMR signal. The first method called *phase* encoding was just presented. For phase encoding a magnetic field gradient of amplitude G is applied for a time δ and the signal is acquired after the gradient is turned off. Only one data point is acquired for each gradient application and the sample magnetization must be given full recovery time to relax back to thermal equilibrium between each successive round of excitation, gradient pulse application and signal detection. Therefore, phase encoding is prohibitively time consuming. Since the signal is acquired in the presence of a homogeneous magnetic field, *i.e.* there are no gradients present during signal acquisition, the NMR signal retains its chemical signature. This feature can be exploited to generate an image in which each voxel contains individual spectra representing the local chemical environment, a method

known as Chemical Shift Imaging (CSI). Phase encoding also finds applications for solid-like samples as it is used to overcome line broadening issues.

The second method for sampling k-space to acquire the NMR signal is known as *frequency encoding*. In frequency encoding a gradient of constant amplitude G , sometimes called the *read* gradient, is applied during signal acquisition and data points are acquired at regular time intervals Δt . The time between data points in frequency encoding is called the *dwell time* τ_d . Frequency encoding saves time because an entire line of k-space is sampled for each round of excitation, gradient pulse application and signal detection versus only one point for phase encoding. The disadvantage to frequency encoding is that the presence of the gradient during signal acquisition masks the chemical spectral information. Recall the chemical shift artifact described previously. Figure 2.14 depicts the phase and frequency encoding methods.

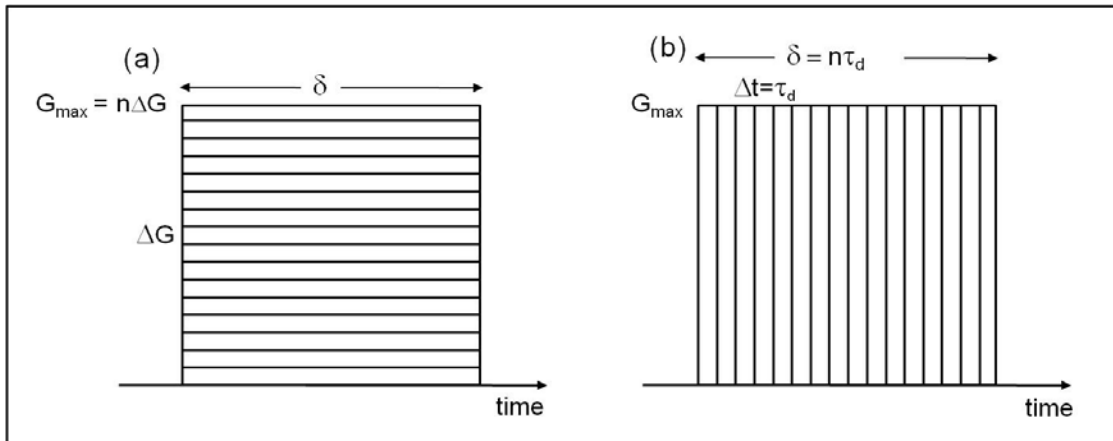


Figure 2.14. Comparison of (a) Phase encoding (b) frequency encoding. In the phase encoding scheme (a), the gradient of duration δ and maximum amplitude $G_{\max}$ is split into n equal steps. The signal is acquired n times (here $n=16$) following each gradient application of strength $i\Delta G$ where i is varied from 1 to n . For the frequency encoding method (b), the maximum gradient amplitude $G_{\max}$ is maintained at this constant level and the total duration δ is split into 16 equal steps Δt . The signal is sampled in the presence of the gradient n times (here $n=16$) following time steps of duration $i\Delta t$ where i is varied from 1 to n .

The increment traversed in k-space between data point sampling determines the field of view (FOV) in real space through the equation

$$FOV = \frac{n-1}{2} \frac{2\pi}{\gamma \mathbf{G}_{max} \delta}. \quad (2.28)$$

For n gradient steps (*phase* encoding) or n time steps (*frequency* encoding) there are n different k values, and the image of spin density $\rho(\mathbf{r})$ possesses a resolution of n points as a consequence of the data sampling procedure. It is important that the appropriate combination of n , G_{max} and δ be chosen for the object being imaged as ambiguous assignment of position will occur if the maximum phase angle encoded into the signal exceeds 2π .

Slice Selection

A *soft* rf pulse applied simultaneously with a linearly varying magnetic field gradient allows for selective slice excitation. The range of frequencies contained in an excitation pulse is inversely proportional to the pulse duration t_p . Recalling that $\omega(\mathbf{r}) - \omega_o = \gamma \mathbf{G} \cdot \mathbf{r}$, it is clear that in the presence of a magnetic field gradient $\mathbf{G}$, the frequency is a function of position. Therefore, the duration of a soft rf pulse can be tuned so as to select a *slice* of spins that has been tagged for selection by a *slice* gradient. The shape of the rf pulse determines the shape of the slice of spins that is selected. Since the shape of an rf pulse applied in the reciprocal domain, *i.e.* k-space, is the Fourier transform of the shape selected by the pulse in the frequency domain, in order to select a rectangular slice of the sample, the rf pulse shape needs to be a sinc function, as described previously.

The Typical Imaging Experiment

For the sake of keeping NMR imaging experimental times reasonable, typical NMR images are two-dimensional with slice selection being employed in the 3rd dimension. Usually, one of the two dimensions is imaged using phase encoding methods and is called the *phase* direction, and the second of the two dimensions is imaged using frequency encoding and is referred to as the *read* direction.

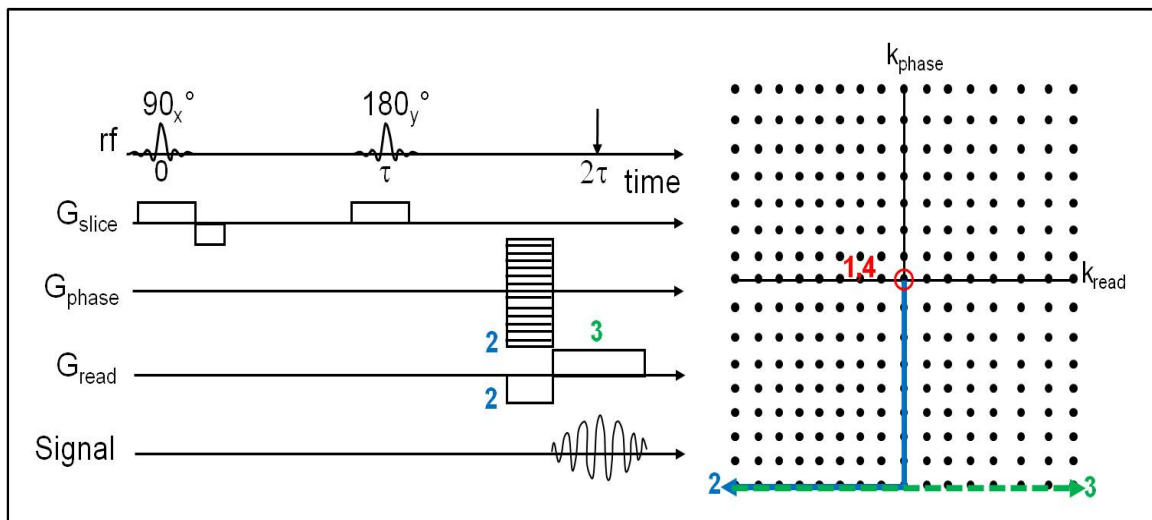


Figure 2.15. Typical NMR imaging pulse sequence with slice selection, frequency and phase encoding in three orthogonal directions and the k-space raster sampled for such a sequence.

Figure 2.15 presents a typical NMR imaging experiment as well as a map for how this sequence directs the sampling of k-space. At $t=0$, a *soft* 90° rf pulse with a sinc function shape applied simultaneously with a slice gradient excites spins that have the range of Larmor frequencies corresponding to those encoded by G_{slice} into the transverse plane. The *soft* sinc-shaped 180° rf pulse inverts the phase of the spins within the selected rectangular slice of the sample due to the presence of the slice gradient G_{slice} , this of course, leads to the formation of the echo signal centered at $t=2\tau$. The first phase

encoding gradient level and negative lobe of the read encoding gradient (labeled “1” in Fig. 2.15) encode the phase of the NMR signal for position in two dimensions and direct k-space mapping from the center of k-space to the left, bottom quadrant. The NMR signal is then sampled in the presence of the positive read gradient and an entire line of k-space is traversed while sampled (labeled “3” in Fig. 2.15). Then during the recovery time following signal acquisition, relaxation processes return the signal to the center of k-space (labeled “4” in Fig. 2.15). The entire process is repeated until all of k-space, *i.e.* the entire 16 x 16 matrix, has been sampled. The k-space raster is then Fourier transformed into an image of spin density in the frequency domain.

Rapid Imaging Techniques

When measuring transient phenomena with MR imaging sequences, long experimental times will not be sufficient to accurately quantify the dynamic process and it is necessary to use a sufficiently rapid acquisition method so that the entire **k**-space raster can be sampled within a duration short compared to the changes occurring in spin density or the local molecular velocities. The most rapid image acquisition methods are Echo Planar Imaging (EPI) [16, 17] and Fast Low-Angle SHot (FLASH) imaging [18], which have acquisition times of ~40msec and ~100msec, respectively [8].

EPI is the fastest pulse sequence available. In EPI, the entirety of image-encoding is performed following a single radiofrequency excitation pulse, and the phase encoding of each line is achieved by adding a constant-amplitude short-duration gradient lobe after each frequency-encode gradient reversal. EPI cannot be applied to samples with short

T_2^* relaxation times, *e.g.* due to variation in susceptibility in heterogeneous samples. It is useful for rapidly measuring dynamics in rather homogeneous fluid samples.

In FLASH imaging, small tip angles are employed for the imaging sequence so that there is a constant reservoir of sample magnetization which can be used to sample **k**-space and it is not necessary to wait the recovery time between each image encoding cycle. Typical flip angles are 5-10°. In reducing the flip angle, the total image acquisition time is reduced at the expense of the signal-to-noise ratio and hence spatial resolution since larger voxel sizes are required.

ADVANCED MAGNETIC RESONANCE TOPICS

Relaxation and Molecular Motion

In Chapter 2, semi-classical quantum mechanical descriptions of the T_1 and T_2 relaxation processes were given in which relaxation was described phenomenologically as decaying exponentially. In practice, this description is accurate for spins in rapidly tumbling molecules but for slow molecular motions, this description breaks down. Furthermore, the phenomenological approach does not provide any insight into how the relaxation times depend on the magnitude of spin magnetic moment interactions or molecular-level rotational motion. Nor does it indicate when exponential relaxation behavior is applicable.

The relaxation behavioral regimes are broadly divided into “rapid” and “slow” motion. The rapid motion regime is applicable to most molecules in the liquid state and the slow motion regime applies to highly viscous liquids and polymers, for example. In spin- $\frac{1}{2}$ nuclei such as protons, the dominating interaction which causes spin relaxation arises from the dipolar Hamiltonian H_D , whereas in higher spin systems quadrupolar interactions are significant. The focus of the discussion presented here will be on the effects of the H_D on relaxation.

Dipolar Interactions, Molecular Motion and Relaxation

The magnetic moment arising from a nuclear spin dipole exerts a strong influence on its neighbors via the magnetic field produced by this magnetic moment acting on the magnetic moments of remote spins. The math associated with calculating the dipolar

Hamiltonian is beyond the scope of this dissertation and can be found elsewhere [8].

Suffice it to say that the complicated dipolar Hamiltonian has extreme significance in

nuclear spin systems, and its magnitude is of order $\frac{\mu\gamma^2\hbar}{4\pi r^3}$ where μ the magnitude of the magnetic moment and r is the distance between a pair of spin dipoles. Small r values, on the order of a few Å, and limited molecular mobility, for instance in a solid material, lead to particularly strong dipolar interactions.

Molecular tumbling at the Larmor frequency causes transitions between spin states, inducing the equilibrium sample magnetization $\mathbf{M}_0$ as well as causing relaxation of the free induction decay signal. In solids, molecules and their corresponding MR-active nuclei are essentially fixed so that there is minimal molecular mobility. This, combined with the strength of the dipolar interactions, leads to rapid dephasing of the transverse magnetization and T_2 relaxation times on the order of a few microseconds.

Here, the effects of molecular tumbling on relaxation are considered for liquids or the “rapid” motion case. Originally, this theory was described by Bloembergen, Purcell and Pound, and is thus referred to as BPP theory [19]. BPP theory assumes that the autocorrelation function of the molecular fluctuations that cause relaxation is proportional to e^{-t/τ_c} where τ_c is the correlation time of the molecular rotational motion. Specifically, the autocorrelation function of molecular position as a function of time is used to determine the rate at which two spins lose memory of their previous positions due to random rotational motion, and τ_c is the time scale for this loss of memory. The Fourier transform of the molecular position autocorrelation function is termed the spectral density function. Spectral density functions $J^{(q)}(\omega)$ represent the amount of energy available for

transitions between the different spin energy states for the spatial tensor component, q , and at a specific frequency, ω . Using an isotropic rotational diffusion model to represent the fluctuations in dipolar interactions, the $J^{(q)}(\omega)$ are given by [9]

$$\begin{aligned} J^{(0)}(\omega) &= \frac{24}{15r^6} \frac{\tau_c}{1 + \omega^2 \tau_c^2} \\ J^{(1)}(\omega) &= \frac{4}{15r^6} \frac{\tau_c}{1 + \omega^2 \tau_c^2} \\ J^{(2)}(\omega) &= \frac{16}{15r^6} \frac{\tau_c}{1 + \omega^2 \tau_c^2}. \end{aligned} \quad (3.1)$$

The relevant frequencies for fluctuations in energy that cause transitions between the spin states are the Larmor frequency ω_0 and twice the Larmor frequency $2\omega_0$. This is because ω_0 is simply the energy difference between the two spin states. BPP theory provides the following equations for T_1 and T_2 relaxation due to the dipolar interactions between a pair of like proton spins ($I=1/2$)

$$\frac{1}{T_1} = \frac{9}{8} \left(\frac{\mu\gamma^2\hbar}{4\pi r^3} \right)^2 [J^{(1)}(\omega_0) + J^{(2)}(2\omega_0)] \quad (3.2)$$

$$\frac{1}{T_2} = \frac{9}{8} \left(\frac{\mu\gamma^2\hbar}{4\pi r^3} \right)^2 \left[\frac{1}{4} J^{(0)}(0) + \frac{5}{2} J^{(1)}(\omega_0) + \frac{1}{4} J^{(2)}(2\omega_0) \right]. \quad (3.3)$$

Note the presence of the H_D magnitude squared in both equations, thus the strong effects of dipolar interactions on relaxation are clear. Also, the $J(0)$ term shows up in (3.3), the equation describing T_2 relaxation, only. This term arises from the spins that look stationary relative to other spins and represents the magnetic moment of a stationary spin impacting the local magnetic field of its neighbors. Since there is no energy available for spins to transition energy levels at $\omega=0$, $J(0)$ impacts T_2 only. The $J(\omega_0)$ and $J(2\omega_0)$

terms account for energy release to the lattice, *i.e.* T_1 relaxation, as well as dipolar interactions which destroy phase coherence, *i.e.* T_2 relaxation.

Evaluating the effects of rotational motion on the correlation time τ_c in relation to the Larmor frequency ω_0 , when $1/\tau_c \gg \omega_0$, *e.g.* τ_c is on the order of picoseconds, $T_1 \sim T_2$. Extremely short rotational motion correlation times such as this apply to small molecules in the liquid state. Since the spectral line width is proportional to $1/T_2$, as the T_2 time increases, the line width decreases and finer details are apparent in the chemical spectra. For $1/\tau_c \ll \omega_0$, rotational tumbling is very slow and thus the correlation time is long. The lack of molecular motion means that there is no means by which the strong dipolar interactions between the spins can be averaged out so that $T_2 \ll T_1$. This is the relaxation behavior characteristic of solids, which are difficult to study using MR techniques because the FID decays within a few microseconds.

Relevance to Imaging Controlled Release Pharmaceutical Tablets. In Chapter 4, the proton spins of water molecules hydrating controlled release pharmaceutical tablets are imaged as a function of water hydration time. The tablet is made up of highly-compressed powders, which makes for short distances r between MR-active nuclei (relative to the distances separating nuclei in liquids) and limits molecular tumbling. Thus, the water protons in the tablet experiences solid-like relaxation processes due to their rotational motion being hindered in the tablet matrix. The restricted rotational motion leads to strong dipolar interactions between the proton spins on the tablet molecules as well as on the water molecules within the tablet. These dipolar interactions are so strong for the proton nuclei on the tablet components that the signal from these

protons relaxes before signal acquisition using an echo time of 2.81 ms. Therefore, the measured signal arises from the proton spins on water molecules only.

Measuring Translational Motion

In the previous chapter, the fact that the Larmor frequency is sensitive to the local magnetic field was exploited to label the phase of the transverse magnetization and thus the position of MR-active nuclei for the purpose of MR imaging experiments. Here, these same principles will be used to spatially label nuclei at one instant of time, and then to check the labeling at a later time to determine whether the nuclei have moved. Diffusion, velocity and dispersion can be measured via pulsed gradient NMR techniques. The mathematical theory and experimental methods for measuring translational motion via pulsed gradient NMR experiments are described in the subsequent sections.

The Conditional Probability Function

In general, the motion of a molecule i can be characterized by some time-dependent displacement $\mathbf{r}_i(t)$. This function will often vary in a random way from molecule to molecule, and in NMR, a large number of molecules contribute to the signal, therefore it is necessary to use statistics to describe translational motions in molecular ensembles. One statistical method commonly used is probability. For example, consider the conditional probability that a molecule initially at position $\mathbf{r}$ will have a displacement $\mathbf{r}'$ after a time t . Descriptions of relative motion correlate the positions of $\mathbf{r}'_i(t)$ and $\mathbf{r}_j(0)$ for $i \neq j$ as well as $i = j$. Descriptions of self motion are much simpler than those of relative motion. Therefore, it is desirable to measure the self-correlation function, $P_s(\mathbf{r}|\mathbf{r}', t)$ for

$i=j$ only, which describes the conditional probability that a specific molecule initially at $\mathbf{r}$ will have moved to position $\mathbf{r}'$ after a time t . Fortunately, NMR motion-encoding experiments are sensitive to self motion rather than relative motion given that the individual nuclei are tagged by their characteristic Larmor frequencies.

Unrestricted Self-Diffusion and the Propagator

For the case of self-diffusion, there is no concentration gradient driving force, unlike the classical description of diffusion through Fick's Law with $\mathbf{J}$, the particle flux, and D , the diffusion coefficient,

$$\mathbf{J} = -D\nabla C. \quad (3.4)$$

However, a Fick's Law description of self-diffusion is possible [8]. The spatial derivatives in Fick's equations refer to the coordinate $\mathbf{r}'$ so ∇' is used to make this clear when writing Fick's Law in terms of P_s

$$\mathbf{J} = -D\nabla' P_s \quad (3.5)$$

where $\mathbf{J}$ is the conditional probability flux. Since the total conditional probability is conserved, continuity applies and

$$\nabla' \cdot \mathbf{J} = -\frac{\partial P_s}{\partial t}. \quad (3.6)$$

Combining equations (3.5) and (3.6) leads to the partial differential equation sometimes referred to as Fick's second law,

$$\frac{\partial P_s}{\partial t} = D\nabla'^2 P_s, \quad (3.7)$$

where D is the molecular self-diffusion coefficient. Solving (3.7) using the initial condition

$$P_s(\mathbf{r}|\mathbf{r}', 0) = \delta(\mathbf{r}' - \mathbf{r}),$$

which simply means that at $t=0$ the system is perturbed by a unit impulse force, and the boundary condition for unrestricted self-diffusion

$$P_s \rightarrow 0 \text{ as } \mathbf{r}' \rightarrow \infty$$

yields

$$P_s(\mathbf{r}|\mathbf{r}', t) = (4\pi Dt)^{-3/2} \exp\{|\mathbf{r}' - \mathbf{r}|^2/4Dt\}. \quad (3.8)$$

Here, $(\mathbf{r}' - \mathbf{r}) = \mathbf{R}$ is the net displacement of the particle during time t , sometimes called the *dynamic* displacement.

A useful function, sometimes called the *average propagator* or simply the *propagator*, $\bar{P}_s(\mathbf{R}, t)$ is defined using this concept of dynamic displacement,

$$\bar{P}_s(\mathbf{R}, t) = \int P_s(\mathbf{r}|\mathbf{r} + \mathbf{R}, t) \rho(\mathbf{r}) d\mathbf{r}. \quad (3.9)$$

The average propagator gives the average probability for any particle to have a displacement $\mathbf{R}$ over time t . For unrestricted self-diffusion, a Markov process that retains no memory of starting position, P_s is independent of $\mathbf{r}$. Thus, for unrestricted self-diffusion, the average propagator is common to all molecules and the over bar notation can be dropped. Then

$$P_s(\mathbf{R}, t) = (4\pi Dt)^{-3/2} \exp\left(-|\mathbf{R}|^2/4Dt\right). \quad (3.10)$$

$P_s(\mathbf{R}, t)$ is a normalized Gaussian function of displacement $\mathbf{R}$ with variance of $2Dt$. As time advances the location of an individual molecule becomes less certain. The Gaussian nature of diffusion makes clear its inherent randomness. This solution, equation (3.10), is

the *fundamental solution* to the 3D diffusion equation, (3.7). It can be derived from probability theory, conservation laws or using Fourier transforms.

When diffusion is superposed on a flow moving with velocity $\mathbf{v}$, an advection-diffusion equation results from adding the term $\nabla' \cdot \mathbf{v}P_s$ to the right-hand side of equation (3.7)

$$\frac{\partial P_s}{\partial t} = \nabla' \cdot \mathbf{v}P_s + D\nabla'^2 P_s. \quad (3.11)$$

If $\mathbf{v}$ is constant, then the solution is

$$P_s(\mathbf{R}, t) = (4\pi Dt)^{-3/2} \exp\left(-|\mathbf{R} - \mathbf{v}t|^2 / 4Dt\right). \quad (3.12)$$

The propagator (3.12) is a normalized Gaussian function of dynamic displacement $\mathbf{R}$ as it was for pure self-diffusion. The mean dynamic displacement is $\mathbf{v}t$. The variance or width of the propagator is $2Dt$.

It is the net dynamic displacement $\mathbf{R}$ which is measured in pulsed gradient NMR. Using the propagator formalism and the pulsed gradient NMR experiment, diffusive motion as well as applied velocity can be measured. In practice, NMR measurements of $\mathbf{R}$ are limited to 100 Å-several mm and timescales of a few milliseconds to a few seconds.

The Pulsed Gradient Spin Echo Experiment for Motion Encoding

The pulsed gradient spin echo (PGSE) nuclear magnetic resonance experiment, first demonstrated by Stejskal and Tanner in 1965 [20], provides a noninvasive means of measuring translational motion. In this method, magnetic field gradient pulses of

duration $\delta \ll \Delta$ are used to modulate the phase of the transverse magnetization of the spins, thus encoding the net displacement of the spins within the phase of the signal. Therefore, the modulation of phase is directly related to the dynamic displacement, $\mathbf{R}$ over the experimental observation time Δ .

To distinguish the different magnetic field gradients, motion encoding gradients will be designated $\mathbf{g}$ whereas position encoding gradients are designated $\mathbf{G}$. The narrow-pulse PGSE NMR sequence is depicted in Figure 3.1. At time $t = 0$, a 90° rf pulse excites the net sample magnetization from its thermal equilibrium position oriented along the z-axis into the transverse plane. Shortly thereafter, a magnetic field gradient pulse $\mathbf{g}$ is applied for duration δ , causing the spins to dephase in the transverse plane and imparts a phase shift of $\gamma\delta\mathbf{g}\cdot\mathbf{r}$ to the spins as a function of their position $\mathbf{r}$. The application of a 180° rf pulse flips the spins, effectively reversing the direction of the spin precession. A second magnetic field gradient pulse, with the same magnitude and duration as the first but with effectively opposite direction, due to the 180° rf pulse reversing the phase direction, is applied. The net phase shift following this pulse is $\gamma\delta\mathbf{g}\cdot(\mathbf{r}'-\mathbf{r})$. If spins have not moved during time Δ , the second gradient pulse has the effect of rephasing the spins in the transverse plane and there will be no net phase shift remaining. If spins have moved during the time Δ , there will be a net phase shift $\phi(\mathbf{R})$ remaining,

$$\phi(\mathbf{R}) = \gamma\delta\mathbf{g} \cdot \mathbf{R}. \quad (3.13)$$

The observation time Δ should be large compared to the gradient duration time δ . Typical values for δ are 100 μs to 5 ms and for Δ are 1 ms to 1 s.

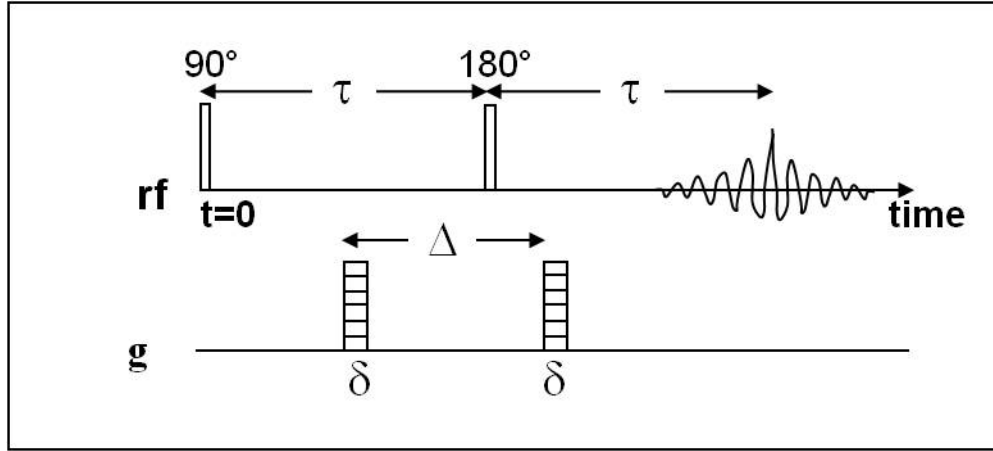


Figure 3.1. Schematic of the pulsed gradient spin echo NMR experiment.

The spin echo signal of the PGSE experiment in Fig. 3.1 is detected in the absence of magnetic field gradients therefore the different chemical components of a mixture can be spectrally resolved using this experimental method, assuming that there is detectable signal from each component of the mixture. For instance, experiments to measure diffusion coefficients for an equimolar mixture of benzene and butanol had two spectral peaks with different diffusion coefficients for each peak [21].

Average Propagator Method. Defining the *echo signal* $S(\mathbf{g})$ as the amplitude of the echo at its center and the normalized echo signal as $E(\mathbf{g})=S(\mathbf{g})/S(0)$, to account for T_2 relaxation effects on the echo signal, the total NMR signal is

$$E(\mathbf{g}) = \int \rho(\mathbf{r}) \int P_s(\mathbf{r}|\mathbf{r}', \Delta) \exp[i\gamma\delta\mathbf{g} \cdot (\mathbf{r}' - \mathbf{r})] d\mathbf{r}' d\mathbf{r}. \quad (3.14)$$

The echo signal (3.14) is an ensemble average in which each phase term $\exp(i\gamma\delta\mathbf{g} \cdot \mathbf{R})$ is weighted by the probability for a spin to begin at $\mathbf{r}$ and move to $\mathbf{r}'$ during time Δ . This probability is identically $\rho(\mathbf{r})P_s(\mathbf{r}|\mathbf{r}', \Delta)$.

The wave vector $\mathbf{q}$, which is analogous to the wave vector $\mathbf{k}$ of MR imaging, is used for descriptions of MR motion encoding, and is defined as

$$\mathbf{q} = \frac{\gamma \mathbf{g} \delta}{2\pi}. \quad (3.15)$$

The $\mathbf{q}$ wave vector, has units of inverse length and is conjugate to displacement.

Since NMR is inherently sensitive to self-motion, the phase shifts of (3.14) depend only on the dynamic displacement $\mathbf{R}$, the substitution $\mathbf{r}' = \mathbf{r} + \mathbf{R}$ can be made. Rewriting (3.14) in terms of $\mathbf{q}$ and $\mathbf{R}$ results in

$$E(\mathbf{q}) = \int \bar{P}_s(\mathbf{R}, \Delta) \exp(i2\pi \mathbf{q} \cdot \mathbf{R}) d\mathbf{R}. \quad (3.16)$$

Thus, (3.16) expresses a Fourier relationship between $E(\mathbf{q})$ and the average propagator, $\bar{P}_s(\mathbf{R}, \Delta)$. Acquisition of the signal in the $\mathbf{q}$ -domain followed by Fourier transformation of $E(\mathbf{q})$ enables the imaging of the ensemble average probability that spins will move a distance $\mathbf{R}$ over time Δ , $\bar{P}_s(\mathbf{R}, \Delta)$, just as signal acquisition in $\mathbf{k}$ -space and Fourier transformation of that signal enabled the imaging of the spin density, $\rho(\mathbf{r})$.

Phase Shift Method. The relative phase of the NMR signal is a measure of the motion of MR-active nuclei. Equation (3.13) shows the phase to be a function of displacement for the PGSE sequence depicted in Fig. 3.1. In general, the phase shift accumulated at time t subject to a position dependent Larmor frequency is

$$\phi(\mathbf{r}, t) = \int_0^t \boldsymbol{\omega}(t') \cdot \mathbf{r}(t') dt' = \gamma \int_0^t \mathbf{g}^*(t') \cdot \mathbf{r}(t') dt'. \quad (3.17)$$

Here $\mathbf{g}^*(t')$ is the effective gradient. Now consider the Taylor series expansion of spin position as a function of time t ,

$$\mathbf{r}(t) = \mathbf{r}(0) + \mathbf{v}t + \frac{1}{2}\mathbf{a}t^2 + \dots \quad (3.18)$$

Where $\mathbf{v}$ is the velocity and $\mathbf{a}$ is acceleration. Combining equation (3.17) and (3.18) we obtain

$$\begin{aligned} \phi(\mathbf{r}, t) &= \gamma \int_0^t \mathbf{g}^*(t') \cdot \left[\mathbf{r}(0) + \mathbf{v}t + \frac{1}{2}\mathbf{a}t^2 + \dots \right] dt' \\ &= \gamma \left[\mathbf{r}(0) \cdot \int_0^t \mathbf{g}^*(t') dt' + \mathbf{v} \cdot \int_0^t t' \mathbf{g}^*(t') dt' + \frac{1}{2} \mathbf{a} \cdot \int_0^t t'^2 \mathbf{g}^*(t') dt' + \dots \right]. \end{aligned} \quad (3.19)$$

The integrals of (3.19) are the successive moments of the effective gradient $\mathbf{g}^*(t')$, which can be manipulated at will. By choosing a specific time dependence for $\mathbf{g}^*(t')$ the echo signal can be made sensitive to position, velocity or acceleration. The phase modulated echo signal is then

$$\begin{aligned} S(t) = \exp \left(i\gamma \mathbf{r}(0) \cdot \int_0^t \mathbf{g}^*(t') dt' + i\gamma \mathbf{v} \cdot \int_0^t t' \mathbf{g}^*(t') dt' + \frac{1}{2} i\gamma \mathbf{a} \cdot \int_0^t t'^2 \mathbf{g}^*(t') dt' + \dots \right). \end{aligned} \quad (3.20)$$

In (3.20) the concept of $\mathbf{q}$ -space no longer applies since the Fourier dependence of the echo signal is no longer apparent.

The PGSE pulse sequence displayed in Fig. 3.1 has an effective gradient with a zeroth moment $\mathbf{m}_0 = \int_0^t \mathbf{g}^*(t') dt' = 0$. The zeroth moment is required to be zero so that the final phase shift depends only on the motion and not on the starting position of the MR-active nuclei. For a flow with uniform motion without acceleration, the PGSE pulse sequence displayed in Fig. 3.1 has an effective gradient with a first moment $\mathbf{m}_1 =$

$\int_0^t t' \mathbf{g}^*(t') dt' = \delta \mathbf{g} \Delta$ so that the net accumulated phase $\phi = \gamma \delta \mathbf{g} \Delta \mathbf{v}$. Since the phase is measured, and γ , δ , $\mathbf{g}$ and Δ are known values, the velocity can be calculated.

Practical Considerations

It is important to consider some fundamental limits to measuring motion. The limit to the maximum velocity v_{max} that can be measured along the longitudinal axis of the NMR magnet bore is determined by $v_{max} \leq l/T_e$ where l is the height of the radiofrequency coil active region and T_e is the echo time. Spins must remain in the active region of the radiofrequency coil for long enough time that excitation, gradient application and signal detection can occur before the spins flow out of the active region. Furthermore, MR-active nuclei must be exposed to the $\mathbf{B}_0$ magnetic field for a time of $\sim 5T_1$ in order to come to thermal equilibrium prior to the application of the NMR pulse sequence. The limit to the smallest average velocity which can be measured is limited by the T_1 relaxation time and self-diffusion. In order to differentiate small average velocities from random diffusive motion, long observation times must be employed. The longest observation times are afforded by using stimulated echoes sequences in which the sample magnetization is stored in the direction of $\mathbf{B}_0$ so that only T_1 relaxation is occurring. Thus, the smallest average velocities v_{min} which can be measured are $v_{min} \sim (D/T_1)^{1/2}$.

The Stejskal-Tanner Relation

The goal of this section is to show how the normalized echo signal, $E(\mathbf{q})$ is used to evaluate self-diffusion using the conditional probability function as first demonstrated for the PGSE experiment by Stejskal [22]. Defining the z-axis as the direction of the

magnetic field gradient pulse g and combining equations (3.10) and (3.16) for one dimension yields

$$E(q) = \int_{-\infty}^{\infty} (4\pi D\Delta)^{-1/2} \exp\left(-Z^2/4D\Delta\right) \exp(i2\pi qZ) dZ. \quad (3.21)$$

The Fourier transform of a Gaussian function is $\exp(-2\pi^2 q^2 \sigma^2)$ where $\sigma^2 = 2D\Delta$ is the variance. Thus, the Fourier transform with respect to time Δ of (3.21) is

$$E(q) = \exp(-4\pi^2 q^2 D\Delta). \quad (3.22)$$

For a finite pulsed gradient duration δ a reduced observation time $\Delta_r = \Delta - \delta/3$ is used in place of Δ . For diffusion experiments, pulsed gradients of varying amplitude are applied and the echo signal attenuates as a function of the gradient amplitude. The straight line that results from plotting $\log(E)$ versus $\gamma^2 \delta^2 g^2 (\Delta - \delta/3)$ is known as the *Stejskal-Tanner* plot. The slope of this line is the diffusion coefficient D !

Some practical points complete the discussion of the Stejskal-Tanner experiment. A quality Stejskal-Tanner diffusion measurement will utilize at least eight data points to create the Stejskal-Tanner plot. Additionally, the normalized signal amplitude decay should be between 20-30% between the first and final data points. (Recall that the data points vary as a function of pulsed gradient amplitude, typically). If the signal attenuation between the first ($q=0$) and final points is less than 20% or more than 30%, the experiment should be repeated with a higher or lower gradient increment, respectively. The pulsed gradient duration δ can also be tuned slightly to achieve the optimal signal attenuation.

The rationale for using the signal that has only attenuated to 30% of the signal intensity at $\mathbf{q}=0$ comes from performing a Maclaurin series expansion on the amplitude of the signal's ensemble average phase shift, $\overline{\exp(i2\pi\mathbf{q} \cdot \mathbf{R})}$

$$E(q) \approx 1 - \frac{1}{2!} (2\pi q)^2 \overline{Z^2} + \frac{1}{4!} (2\pi q)^4 \overline{Z^4} + \dots \quad (3.23)$$

where, Z is the component of displacement along the gradient direction defined by $\mathbf{q}$.

The expansion makes clear that whatever the form of the transport process, Gaussian or otherwise, the initial signal decay, which corresponds to low $\mathbf{q}$, will always be dominated by the ensemble average mean squared displacement or variance $\overline{Z^2}$ [23]. Thus, the initial signal decay captures the variance, *i.e.* full-width at half maximum, and renders the methods of Stejskal and Tanner described above valid for Gaussian and non-Gaussian transport processes.

Velocity Imaging

Velocity imaging is a powerful tool for determining local molecular ensemble behavior in heterogeneous systems, providing, in principle, a resolution of order 10 μm for the position dimension $\mathbf{r}$, and 0.1 μm for the displacement dimension $\mathbf{R}$. In velocity imaging experiments, position and displacement are simultaneously encoded in order to obtain velocity maps. The imaging gradients $\mathbf{G}$ encode for spatial position $\mathbf{r}$ and the PGSE gradients $\mathbf{g}$ encode for displacement $\mathbf{R}$.

The signal modulated in both $\mathbf{k}$ - and $\mathbf{q}$ -space is described by

$$S(\mathbf{k}, \mathbf{q}) = \int \rho(\mathbf{r}) \exp[i2\pi\mathbf{k} \cdot \mathbf{r}] \int P_s(\mathbf{r}|\mathbf{r}', \Delta) \exp[i2\pi\mathbf{q} \cdot (\mathbf{r}' - \mathbf{r})] d\mathbf{r}' d\mathbf{r}. \quad (3.24)$$

The effect of the spatially resolved PGSE experiment is that each pixel of the image contains the contrast $E(\mathbf{q}, \mathbf{r})$. Where $E(\mathbf{q}, \mathbf{r})$ is the normalized average signal contribution from the pixel at position $\mathbf{r}$, given by

$$E(\mathbf{q}, \mathbf{r}) = \int \bar{P}_s(\mathbf{R}, \Delta) \exp[i2\pi \mathbf{q} \cdot \mathbf{R}] d\mathbf{R}. \quad (3.25)$$

Therefore, the position and displacement encoded signal (3.23) is defined as

$$S(\mathbf{k}, \mathbf{q}) = \int \rho(r) E(\mathbf{q}, \mathbf{r}) \exp[i2\pi \mathbf{k} \cdot \mathbf{r}] d\mathbf{r}. \quad (3.26)$$

The essence of equations (3.24-3.26) is that the average propagator $\bar{P}_s(\mathbf{R}, \Delta)$ for each pixel $\mathbf{r}$ of the image is measured.

A pulse sequence combining imaging and motion encoding is depicted in Fig. 3.2. This pulse sequence uses two-dimensional position encoding and in the third spatial dimension, a slice of the sample is excited. Concurrently with position encoding, the PGSE experiment is run so that the final result of the combined experiments is an image that displays the average distribution of displacements $\mathbf{R}$ or average distribution of velocities $\mathbf{R}/\Delta$ in each pixel.

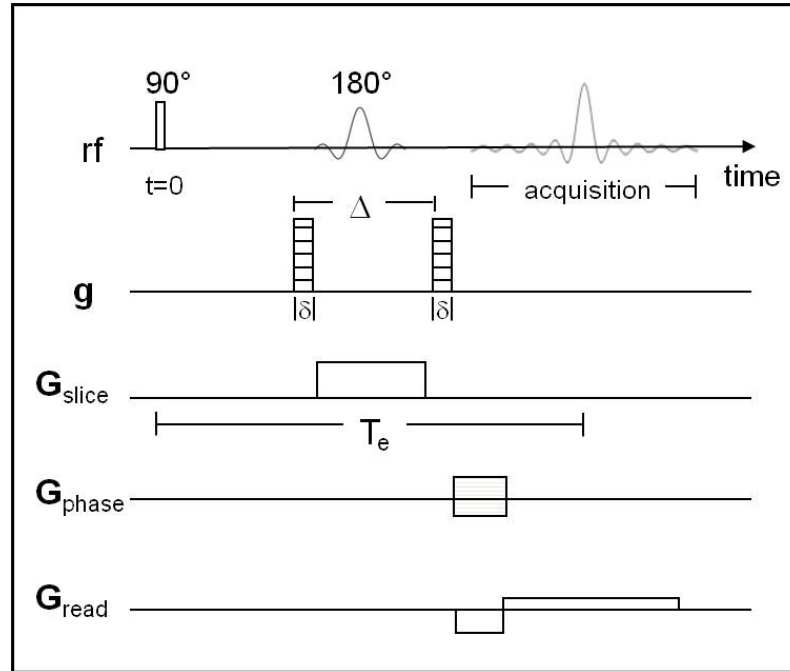


Figure 3.2. Pulse sequence combining position and displacement encoding for velocity imaging.

Relevance to Measuring Multiphase Mixing. In chapters 5 and 6 of this dissertation, velocity imaging experiments similar to the one displayed in Fig 3.2 are employed to spatially resolve two-fluid motion in a Taylor-Couette device and in a jet-in-tube mixer, respectively. The velocity imaging pulse sequence used measured signal at only two q-space positions, so that average velocity for each pixel of the image was determined through the phase shift or *Fukushima* method [24] as opposed to measuring the signal at more than two q-space locations in order to calculate the average propagator for each pixel and thus obtain a distribution of velocities for each pixel of the velocity image. This latter method is loosely referred to as the *Callaghan* method [8].

Velocity-Compensated Pulsed Gradient Spin Echo Experiment

In the velocity-compensated or double PGSE experiment, displayed in Fig. 3.3, the motion-encoding pulsed gradient pair of the standard single PGSE experiment, Fig. 3.1, is applied twice.

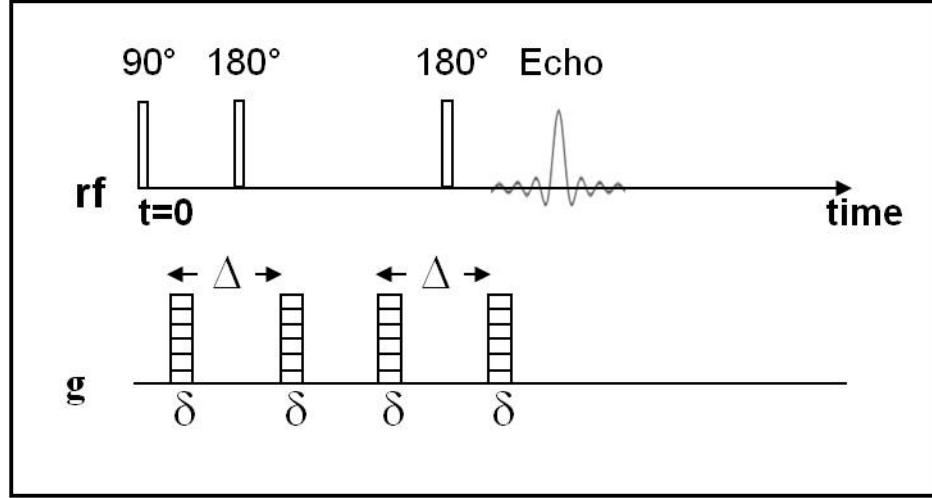


Figure 3.3. Double PGSE pulse sequence for measuring incoherent motion.

The effect of repeating the motion-encoding gradient pair is that the phase shifts acquired due to coherent flow during the first time interval Δ are cancelled during the second time interval Δ . In the double PGSE experiment, both the zeroth moment

$$\mathbf{m}_0 = \int_0^t \mathbf{g}^*(t') dt'$$

and the first moment $\mathbf{m}_1 = \int_0^t t' \mathbf{g}^*(t') dt'$ are equal to zero.

Therefore, the double PGSE sequence encodes for fluctuations in the motion, *i.e.*

incoherent random motion, over the timescale 2Δ . It is important to note that the second

$$\mathbf{m}_2 = \int_0^t t'^2 \mathbf{g}^*(t') dt'$$

moment $\mathbf{m}_2 = \int_0^t t'^2 \mathbf{g}^*(t') dt'$ for the single PGSE experiment (Fig. 3.1) is not equal to zero. Thus, the single PGSE experiment measures both coherent and incoherent motions.

By comparing results from both single and double PGSE experiments, coherent and

stochastic motion components of the overall flow can be separated.

Relevance to Quantifying a Buoyancy Driven Flow Instability. In Chapter 6, single and double PGSE Stejskal-Tanner experiments are employed to measure the dispersion coefficients which result from the buoyancy-driven instability of acetone and water mixing in a jet-in-tube mixer. Through the use of both single and double PGSE experiments, the purely stochastic diffusion behavior can be separated from the coherent motion contributions to the effective diffusion coefficient for an acetone-water fluid system as it transitions from unmixed two-fluid laminar flow, to an unstable mixing flow regime that is driven by buoyancy forces and eventually to a well-mixed solution. This data lead to understanding that the transverse flows resulting from the buoyancy driven instability were not chaotic and random but primarily coherent.

Restricted Diffusion and Structural Imaging

The translational motion of molecules containing MR-active nuclei in a heterogeneous structure will be restricted by the boundaries. For instance, the diffusion of water flowing within a pipe experiences a barrier to diffusion at the pipe wall. This restricted motion, means that the propagator $P_s(\mathbf{R}, \Delta)$ describing the probability distribution of displacements, may not be Gaussian and will have a time dependence characteristic of the length scales and the local molecular self-diffusion coefficient. The time dependent behavior of $P_s(\mathbf{R}, \Delta)$ has potential for elucidating the sample microstructure.

Consider a heterogeneous sample with pore length a in the direction parallel to the direction of gradient application. At very short observation times, $\Delta \ll a^2/2D$, most molecules will experience unrestricted self-diffusion and $E(\mathbf{q})$ will not depend on

structure. At long observation times, $\Delta \gg a^2/2D$, the majority of molecules will experience restricted diffusion as they encounter the pore boundaries. The echo signal $E(\mathbf{q})$ will reflect the boundary structure as it is the power spectrum of the reciprocal lattice of the sample in the long time limit.

In the long time limit, $\Delta \rightarrow \infty$, the molecule has lost all memory of its starting position and can be located anywhere within the structure. This means that in the long time limit $P_s(\mathbf{R}, \Delta \rightarrow \infty)$ reduces to $\rho(\mathbf{r}')$, and plugging this result into the echo signal equation (3.14), written with respect to $\mathbf{q}$, gives

$$\begin{aligned} E(\mathbf{q}) &= \iint \rho(\mathbf{r})\rho(\mathbf{r}')\exp[i2\pi\mathbf{q} \cdot (\mathbf{r}' - \mathbf{r})]d\mathbf{r}'d\mathbf{r} \\ &= \int \rho(\mathbf{r}) \exp[-i2\pi\mathbf{q} \cdot \mathbf{r}]d\mathbf{r} \int \rho(\mathbf{r}') \exp[i2\pi\mathbf{q} \cdot \mathbf{r}']d\mathbf{r}' \\ &= S^*(\mathbf{q})S(\mathbf{q}) = |S(\mathbf{q})|^2. \quad (3.27) \end{aligned}$$

Therefore, the long time limit echo signal attenuation $|S(\mathbf{q})|^2$ is the power spectrum or the squared modulus of the reciprocal lattice. The measured signal is the reciprocal space spectrum of displacements, and periodicities that may occur in the signal are a result of the sample's structure.

The fact that in the long time limit, the echo attenuation is the power spectrum enables the analogies to optics [25] that result in the potential for measuring structure in heterogeneous samples. Valuable information about the sample can be obtained from analyzing the data in $\mathbf{q}$ -space. The measured power spectrum can be interpreted by comparing it with a model of the sample in reciprocal space. Essentially, the structure of the material being characterized is hypothesized and its reciprocal power spectrum is

calculated. Then, this physical model is compared to the measurement, and this process is iterated until a model that is a “good fit” to the data is found. More simply, the signal attenuation versus $\mathbf{q}$ plot is often interpreted simply by considering this plot to be a *diffraction pattern*. Coherences in the plot arise due to uniform structures in the sample, and taking the inverse of the wave vector $\mathbf{q}$ at the location of a coherence feature provides the approximate length-scale of the uniform structure. That is, uniform structural features associated with the pore length a are observable when the value of $q \sim a^{-1}$. The presence of a coherence feature depends on the uniformity of structure in the sample. A sample lacking structural uniformity may not be well-suited for this method as the presence of coherence features depends on coherence of structures in the sample.

One major advantage of $\mathbf{q}$ -space imaging is that the $\mathbf{k}$ -space imaging gradients, which limit resolution to $\sim 10\mu\text{m}$, are not employed. Thus, the range of spatial resolution is extended significantly. This is a tremendous result and porous structures [26, 27], emulsion droplet sizes [28, 29] and vortice length-scales [30] $\sim 1\text{-}16\mu\text{m}$ have all been probed using $\mathbf{q}$ -space structure determination.

A note of caution is appropriate here as the $\mathbf{q}$ -space method of structure determination is inherently *ill-posed*, *i.e.* there is not one unique model that fits the data. This is an example of an *Inverse Problem* where there are multiple models that fit the data, and thus multiple physical explanations for the measured power spectrum of the material. Thus, the experimentalist must consider which physical explanation is most probable given the physical system.

MAGNETIC RESONANCE IMAGING AND RELAXOMETRY TO STUDY WATER
TRANSPORT MECHANISMS IN A COMMERCIALY AVAILABLE
GASTROINTESTINAL THERAPEUTIC SYSTEM (GITS) TABLET

Introduction

Gastrointestinal therapeutic system (GITS) tablets utilize osmotic pressure and polymer swelling to deliver active pharmaceutical ingredients in a controlled, steady and reproducible manner. Typically, these tablets consist of two layers - a drug layer and a water-swellaable polymer layer, which are compressed to form a tablet core (see Fig. 4.1 and Fig. 4.2). The core is coated with a hard cellulosic membrane that is permeable to water but impermeable to species present in gastrointestinal fluid as well as to the drug and excipients, which form the tablet core. Therefore, as the tablet is immersed in the fluid of the GI tract, water hydrates the tablet rendering the drug layer a suspension or slurry and causing the polymer layer to swell. The coating contains one or more delivery ports through which the swelling polymer layer “pumps” out the drug suspension after sufficient tablet hydration. The first osmotic pump system which was commercialized for oral drug delivery was developed by Felix Theeuwes in the mid-1970’s [31]. Since that time, a variety of osmotically controlled oral drug delivery systems have been developed, and these form a major segment of drug delivery products today [32, 33].

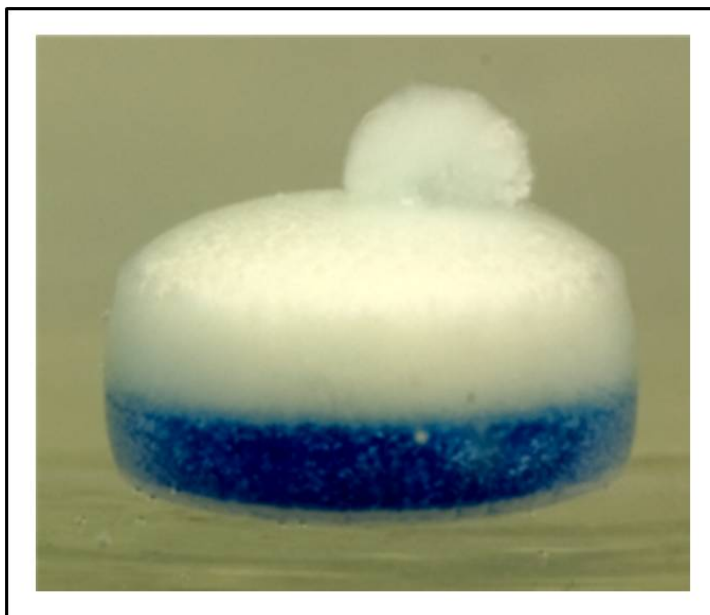


Figure 4.1. Digital picture of a hydrating GITS tablet.

In vitro and in vivo drug release (dissolution) testing are probably the most common analytical methods for characterizing the performance of pharmaceutical tablets. Other common methods of characterizing the performance of controlled-release (CR) dosage forms include infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and x-ray diffractometry (XRD). These methods can provide information about the physiochemical behaviors of both the active pharmaceutical ingredient (API) and the excipients of a formulation, and may help to identify processing constraints and how the excipients affect drug release and tablet performance. However, these methods provide no direct information about the microstructural changes within the tablet or the transport mechanisms that may be impeding or promoting drug release.

Confocal laser scanning microscopy (CLSM) has been used to study particle deformation during tablet compression [34] and to measure the distribution of drug within solid dosage forms during hydration [35]. Albeit non-invasive, CLSM requires

that the material being probed be fluorescent and therefore requires a model fluorescent sample in place of the true dosage form.

The standard analytical methods for characterizing tablets do not directly provide information on the morphological and compositional changes in the tablet that occur during the drug release process. In order to efficiently formulate and optimize CR dosage forms, an analytical method which noninvasively permits the *in situ* measurement of the microstructural changes which occur during tablet hydration, swelling and drug release in a real (not an altered model) system would be extremely useful.

Magnetic resonance imaging (MRI) is a non-invasive method which does not require a “model” sample. ^1H MRI can measure water concentration if the T_2 times of the water are longer than the echo time of the MRI sequence and if all other protons in the sample, *i.e.* protons that are not from water molecules, have much shorter T_2 times, as is the case in the sample used for this study. Therefore, the MRI techniques used here provide spatially resolved images of the penetration of water into the tablet with resolution on the order of hundreds of microns.

Nuclear magnetic resonance (NMR) and MRI have previously been used for pharmaceutically relevant applications to study the hydration of polymers such as hydrogel formation and polymer swelling [36-39], the diffusion and kinetics of water uptake in tablets [40-43] and the microstructural transformation in degradable bioceramics [44]. MR imaging of tablets in deuterated dissolution medias has been used to follow drug solubilization and release and/or the spatial distribution and dynamics of protonated excipients [39, 45]. MRI was used to qualitatively evaluate GITS tablets

which showed different release patterns of drug during quality control testing [46] and recently a benchtop-MRI system was used to characterize and compare various formulations for Isradipine push-pull tablets [47]. In this work, these studies have been extended to quantify the transition from diffusive to osmotic transport.

Materials and Methods

Commercially available 4mg Cardura XL (Pfizer™) GITS tablets were used for the study. These bilayer osmotic tablets are often referred to as “push-pull” tablets and consist of a drug-containing (Doxazosin Mesylate) “pull” layer and an osmotic water-swellable polymer “push” layer. The solubility of doxazosin at 25°C is 0.008g/100g water [48]. The Cardura XL GITS tablets used here contained the strong osmotic agent, NaCl, in the sweller layer. The layers are bonded together through tablet compression to form a single tablet-shaped core which is enclosed by a semipermeable coating with a single laser-drilled delivery port as depicted in Fig. 4.2. The Cardura XL tablets used are approximately 9 mm in diameter and 5 mm thick and have mass 290-300 mg.

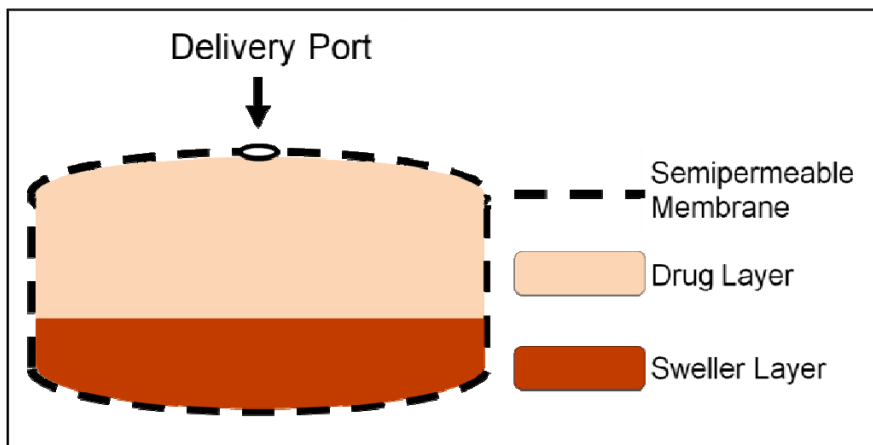


Figure 4.2. Cross-sectional schematic of an osmotic bilayer gastrointestinal therapeutic system (GITS) tablet.

Deionized water was used to hydrate the tablet. When a GITS Cardura XL tablet is placed in an aqueous environment, due to the presence of osmotic excipients in both of the tablet's layers, diffusive and osmotic processes transport water into the tablet. A suspension of the poorly water soluble drug and excipients forms in the drug layer while the water swellable polymer in the "push" layer begins to expand. As the "push" layer expands, the drug suspension is released through the delivery orifice [49]. The highly engineered GITS tablet releases drug at an approximately steady rate for 12-18 hrs under physiological conditions (Fig. 4.4).

Dissolution (Drug-Release) Studies

The release rate of doxazosin mesylate was determined by using a USP Apparatus II dissolution apparatus with a paddle rotation rate of 75rpm. Dissolution was performed using standard physiologic conditions as well as the conditions at which the MR imaging experiments were conducted.

The dissolution medium was either de-aerated simulated gastric fluid (SGF), without enzyme, at pH 1.2 and 37°C (standard conditions), SGF without enzyme, at pH 1.2 and 20°C or deionized water (DI H₂O) at 20°C (MR imaging conditions). The sample aliquots were quantified using HPLC with spectrophotometric detection. Preparation for the dissolution test began by adjusting the paddle height to 2.5 ± 0.2 cm from the bottom of the vessels as required by the USP. Dissolution medium was placed into the dissolution vessel and the temperature was equilibrated to the specified temperature. With paddles rotating, placement of one previously weighed tablet was made into the dissolution vessel. An automated sampling system was used to collect

samples at pre-determined times. A 10 μ m full flow filter was fitted to the sample sippers, and the sampler was programmed to withdraw 1-mL at each time point. Time points of 1, 2, 3, 4, 5, 6, 7, 8, 12 and 18 hours were collected. The doxazosin concentration was analyzed for each time point. The results are shown in Fig. 4.4.

Magnetic Resonance Imaging Studies

Deionized water at ambient temperature, 20°C, was used as the dissolution media for these initial MR imaging studies in order to prevent complicating image interpretation with the presence of salts, sugars, etc. Temperature control on the NMR spectrometer currently limits the study to 20°C.

In ^1H MRI experiments the nuclear magnetic moments of hydrogen atoms in a sample are spatially labeled via linearly varying magnetic fields $\mathbf{G}$ so that the position of the spins $\mathbf{r}$ can be encoded via the precession (Larmor) frequency ω : $\omega(\mathbf{r}) = \gamma(\mathbf{B}_0 + \mathbf{G}(\mathbf{r}))$ where $\mathbf{B}_0$ is the static magnetic field. If the recovery time T_r of the experiment is 1.5 times longer than the spin-lattice relaxation time T_1 of the water inside the GITS tablet and the echo time T_e is chosen to be significantly shorter than the spin-spin relaxation time T_2 of the water in the tablet and longer than the T_2 of any other protons (such as those on polymer excipients) then Fourier transformation of the acquired signal produces a spatial distribution of water density within the tablet. The details of magnetic resonance theory and imaging methods can be found elsewhere [8, 50].

The sample was placed in a 500 mL deionized water reservoir to prevent drug saturation of the fluid surrounding the tablet and to accurately reflect the conditions of the

dissolution study for comparison. The spectrometer compatible tablet holder and experimental setup are depicted in Fig. 4.3.

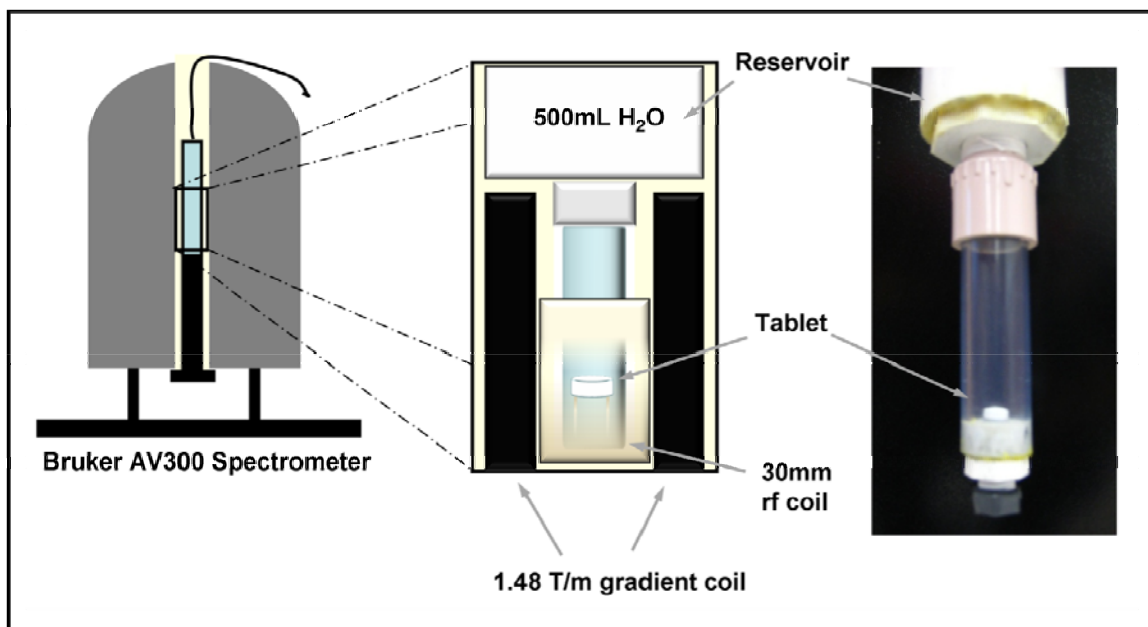


Figure 4.3. Experimental set up. The tablet holder is placed in the bore of the Bruker Avance III 300 MHz wide vertical bore spectrometer so that the tablet lies in the active region of the 30 mm radio frequency (rf) coil.

A Bruker Avance III 300 MHz wide vertical bore spectrometer, a 3D gradient coil (1.48 T/m) and a 30 mm ¹H probe were used for the imaging studies. The gradient coil temperature was maintained at 20°C throughout the imaging experiments. A standard slice selective spin-echo sequence with an echo time T_e of 2.81 msec and a recovery time T_r of 1 sec were used. Each image consisted of 20 averages obtained over approximately 43 minutes with a slice thickness of 2 mm and an in-plane resolution of 312 x 234 μm^2 .

Magnetic Resonance Relaxometry Studies

Relaxometry studies were conducted in a Bruker DRX 250 MHz vertical bore spectrometer equipped with a 10 mm ¹H probe. Tablets were soaked in 500mL of

deionized water on the bench top, then gently dried and placed completely in the active region of the probe. A Carr-Purcell-Meiboom-Gill (CPMG) [14] one-dimensional pulse sequence and Laplace inversion [51] were used to determine the distribution of T_2 relaxation times present in the tablets for a range of hydration times. The T_1 relaxation times of the tablets were determined using a 90° pulse experiment to determine the T_r at which full signal recovery had occurred.

Transport Modeling

For this study, the simplest transport model was chosen to reflect the order of magnitude of the diffusivities, and in particular, elucidate differences in timescales and identify when changes in the mechanism of transport occurs. A one-dimensional mass conservation model was used in order to identify the dominant transport mechanisms and to estimate effective transport coefficients for flux of water into the GITS tablet. This simple transport model was chosen because GITS tablets have been shown to have zero-order release kinetics and are minimally affected by environmental factors such as pH or convection [31, 52]. Specifically, doxazosin GITS tablets have been shown to perform independently of stir rate in the range of 50-100 rpm and are unaffected by pH in the range of 1.2-7.5 [49].

Approximating the 3D tablet as a 1D rod is the first step in showing the significant data MR images can provide regarding the transport mechanisms in real tablet systems. The 1D mass conservation transport equation for the water concentration c in the tablet as a function of position x and time t is

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + \frac{N}{l} \quad (4.1)$$

The transport has been broken into two mechanisms: molecular diffusion with effective diffusivity D and osmotic pressure driven flux, $N = K\Delta\pi$. The osmotic flux occurs across a membrane of thickness l and with permeability coefficient K considering only the osmotic pressure driving force $\Delta\pi$ [53].

In the diffusion dominated transport regime, $D \frac{\partial^2 c}{\partial x^2} \gg \frac{N}{l}$, equation (4.1) can be simplified as

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \quad (4.2)$$

For pure water surrounding the tablet at $t = 0$, the boundary conditions and initial conditions are:

$$c(0, t) = c(L, t) = 1 \quad (4.2a)$$

$$c(x, 0) = f(x) \text{ where } f(x) = 1, \quad x \leq 0 \text{ or } x \geq L \\ f(x) = 0, \quad 0 < x < L. \quad (4.2b)$$

Equation (4.2) is a partial differential equation which can be solved using Fourier series methods. However, solving equation (4.2) using non-homogeneous boundary conditions (4.2a) is very cumbersome. To avoid this, the reference was changed in order to make the boundary conditions homogenous. The shifted reference boundary conditions (4.2a*) and initial condition (4.2b*) were used to determine a Fourier series solution.

$$c(0, t) = c(L, t) = 0 \quad (4.2a^*)$$

$$c(x, 0) = f(x) \text{ where } f(x) = 0, \quad x \leq 0 \text{ or } x \geq L \\ f(x) = -1, \quad 0 < x < L \quad (4.2b^*)$$

Setting $c(x,t)=F(x)G(t)$ and using Separation of Variables, two ordinary differential equations (ODEs), one for $F(x)$ (4.3) and one for $G(t)$ (4.4), were obtained in place of the partial differential equation (2).

$$\frac{\partial^2 F(x)}{\partial x^2} - AF(x) = 0 \quad (4.3)$$

$$\frac{\partial G(t)}{\partial t} - ADG(t) = 0 \quad (4.4)$$

Here A is an arbitrary constant. Looking for non-trivial solutions to (4.3) which satisfy the boundary conditions, it was determined that $A < 0$. For $A < 0$, the general solution to (4.3) is

$$F(x) = C_1 \cos \sqrt{A} x + C_2 \sin \sqrt{A} x.$$

Applying the boundary conditions forces $F(0)=C_1=0$ and $F(L) = C_2 \sin \sqrt{A} L = 0$.

Setting $C_2=0$ results in only the trivial solution. However, requiring that $(\sin \sqrt{A} L) = 0$ dictates that

$A = \frac{n^2 \pi^2}{L^2}$ for $n=1,2,\dots$ and the solution $F_n(x) = \sin \frac{n\pi x}{L}$ for $n=1,2,\dots$ satisfies the B.C.s and equation (4.3).

Using the result that $A = \frac{n^2 \pi^2}{L^2}$, equation (4.4) was solved by separating and integrating the first order ODE. The general solution to (4.4) is

$$G_n(t) = B_n e^{-\frac{n^2 \pi^2 D}{L^2} t} \text{ for } n=1,2,\dots \quad (4.5)$$

where B_n is the constant of integration which remains from separating and integrating (4.4).

Hence,

$$c_n(x, t) = F_n(x)G_n(t) = B_n \sin \frac{n\pi x}{L} e^{-\frac{n^2\pi^2 D}{L^2}t} \quad (4.6)$$

are solutions to the diffusion equation (4.2) which satisfy the boundary conditions. The $c_n(x, t)$ are the eigenfunctions of the problem, corresponding to the eigenvalues $\lambda_n = \frac{n\pi}{L}$.

Next, the solution to (4.6) which satisfies the initial condition was determined by considering the series of eigenfunctions,

$$c(x, t) = \sum_{n=1}^{\infty} B_n \sin \frac{n\pi x}{L} e^{-\frac{n^2\pi^2 D}{L^2}t}. \quad (4.7)$$

Applying the initial condition to (4.7) the series expansion of equation (4.6), the following relationship was found

$$c(x, 0) = \sum_{n=1}^{\infty} B_n \sin \frac{n\pi x}{L} = f(x).$$

This makes clear that the initial condition will only be satisfied if the B_n 's are coefficients of the Fourier sine series. B_n was then determined by solving the equation

$$B_n = \frac{2}{L} \int_0^L f(x) \sin \frac{n\pi x}{L} dx$$

with $f(x) = -1$. The particular Fourier series solution to (4.2) with the prescribed boundary and initial conditions is then

$$c(x, t) = \sum_{n=1}^{\infty} F_n(x)G_n(t) = \sum_{n=1}^{\infty} \frac{2}{n\pi} (\cos(n\pi) - 1) \sin \frac{n\pi x}{L} e^{-\frac{n^2\pi^2 D}{L^2}t}. \quad (4.8)$$

Now to account for the true physical initial and boundary conditions, we add one to equation (4.8) *i.e.* perform a shift of reference so that the final Fourier series solution is

$$c(x, t) = 1 + \sum_{n=1}^{\infty} \frac{2}{n\pi} (\cos(n\pi) - 1) \sin \frac{n\pi x}{L} e^{-\frac{n^2\pi^2 D}{L^2}t}. \quad (4.9)$$

Equation (4.9) can be fit to the experimentally obtained $c(x,t)$, and D can be determined.

In Appendix A, the MatLab code that was used to estimate D is presented.

In the osmotic pressure dominated transport regime, $\frac{N}{l} \gg D \frac{\partial^2 c}{\partial x^2}$, diffusion was assumed to be negligible so that a simple first order in time ODE remains to be solved

$$\frac{\partial c}{\partial t} = \frac{N}{l} = \frac{K\Delta\pi}{l}. \quad (4.10)$$

The osmotic pressure driving force $\Delta\pi = P^o - P^{tab}$ was approximated using Van't Hoff's Law [54]

$$\Delta\pi = P^o - P^{tab} = \frac{RT}{\underline{V}_w^l} \ln(\gamma_w x_w) \quad (4.11)$$

Here P^o is the pressure outside the tablet, P^{tab} is the pressure inside the tablet, R is the ideal gas constant, T is temperature, $\underline{V}_w^l$ is the molar specific water volume, γ_w is the water activity coefficient and x_w is the mole fraction of water. Assuming that the solution of water inside the tablet is ideal, $\gamma_w = 1$ and substituting $x_w = 1 - x_s$ into equation (4.11) results in

$$\Delta\pi = \frac{RT}{\underline{V}_w^l} \ln(1 - x_s). \quad (4.12)$$

Where x_s is the mole fraction of solute in the tablet. In the dilute limit as $x_w \rightarrow 1$, $x_s \ll 1$.

The MacClaurin series expansion approximation for the term $\ln(1 - x_s)$ was determined to be $-x_s$. Plugging this result into (4.12) results in

$$\Delta\pi = -\frac{RT}{\underline{V}_w^l} x_s. \quad (4.13)$$

For a dilute ideal solution approximation, the osmotic pressure is related to x_s the mole fraction of solute in the tablet sweller layer. Substituting $x_s = 1 - x_w$ into equation (4.13) enables $\Delta\pi$ to be written in terms of normalized water concentration $c = \frac{x_w}{V_w^l}$,

$$\Delta\pi = -\frac{RT}{V_w^l} (1 - x_w) \sim -\frac{RT}{V_w^l} + RTc. \quad (4.14)$$

Plugging (4.14) into equation (4.10) and separating and integrating generates a solution of the form $c(t) = c_o e^{\beta t}$ with $\beta = \frac{KRT}{l}$. Exponential curve fitting to experimental data can be used to estimate β .

Results and Discussion

Dissolution Profile

Dissolution studies (Fig. 4.4) showed that the time required for 100% drug release under standard dissolution conditions is approximately 12-18 hours. During the drug delivery process, the drug is released at an approximately constant (apparent zero order) rate through the single delivery port at the top of the tablet. Using the MR imaging experimental conditions (DI H₂O, 20°C) for dissolution testing resulted in 65% drug released after 18 hrs. The paddle mixing rate was maintained at 75 rpm for all dissolution studies in order to prevent inaccurate drug release measurements. MR images were obtained under stagnant conditions, without mixing. The drug release profile obtained using SGF at 20°C, shows that the difference in the release profiles is due to the effects of temperature on diffusion rates [55]. As expected, drug release was found to be

independent of the dissolution media used [49]. The dissolution performance of the tablets was found to be extremely reproducible under all conditions tested.

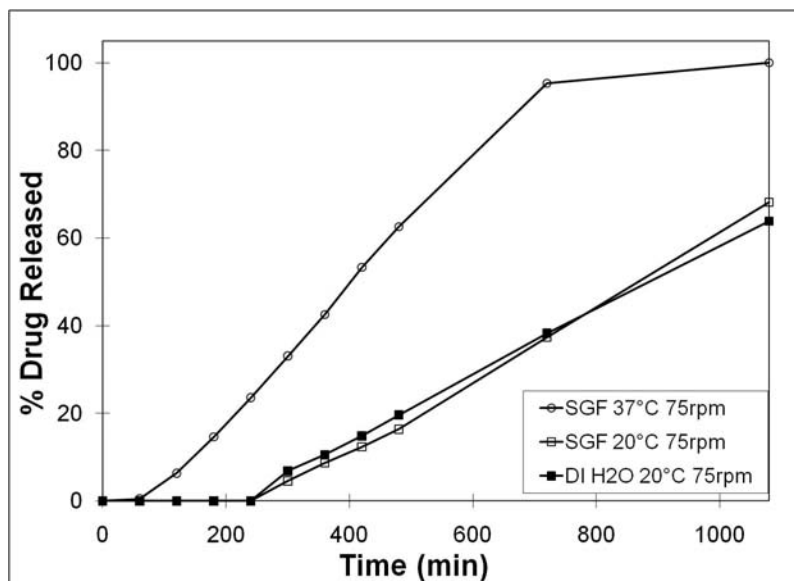


Figure 4.4. Drug release profiles obtained using standard dissolution conditions (SGF, 37°C) and using the conditions present in the MR imaging experiments (DI H₂O, 20°C).

Magnetic Resonance Images

Three separate experiments on different tablets (trials) were conducted over a 16 hour time period. The results from ‘trial 3’ are shown in Fig. 4.5. The ‘trial 3’ images were selected because this trial had the best time resolution of 20 images taken over the 16 hr. time period. The images for all trials are similar as reflected in the subsequent data analysis and transport modeling which incorporates data from all three trials.

The T_1 relaxation of the bulk water ($T_{1bulk} \geq 3$ s) surrounding the tablet is longer than the experiment T_r of 1 sec. Therefore, in that region the image intensity does not directly reflect water density as it is T_1 weighted and hence the observed signal intensity is lower than in regions of the tablet with $T_1 \ll T_r$, which do accurately represent water density.

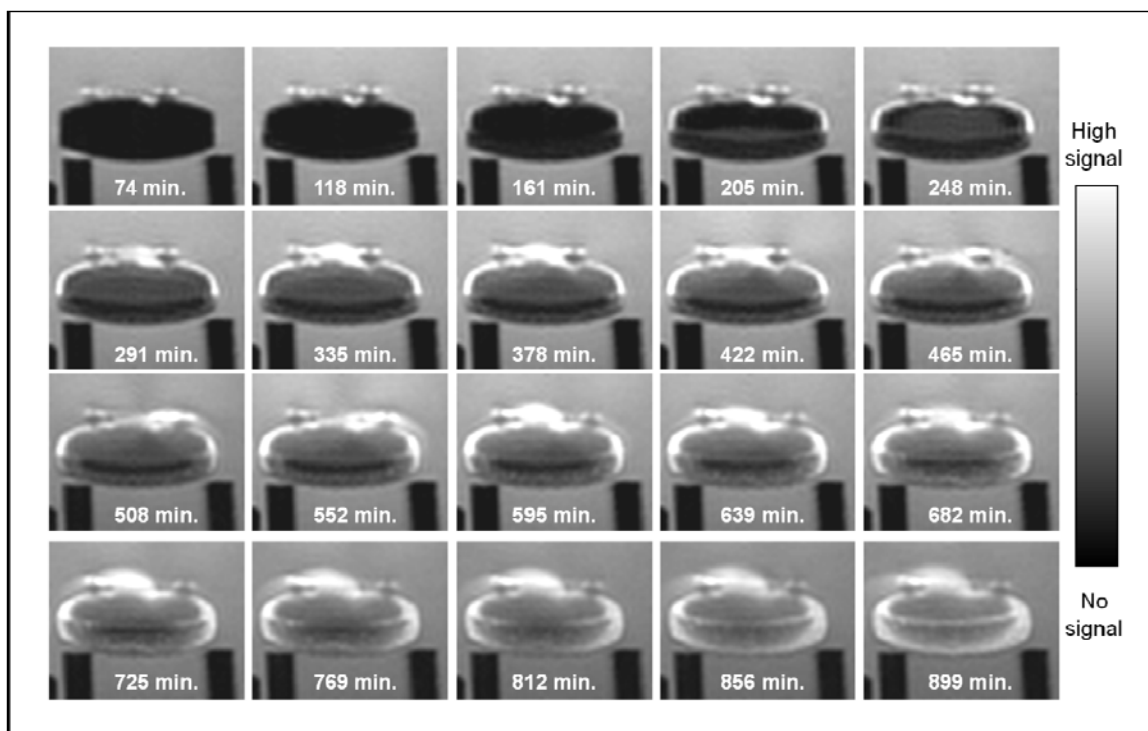


Figure 4.5. Images of the trial 3 Cardura XL tablet over a 16-hr time period. The signal intensity for each image is averaged over a 43 minute time period. The gradual increase in signal intensity inside the tablet is due to tablet hydration. For all images, the slice thickness is 2 mm and the in plane resolution is $312 \times 234 \mu\text{m}^2$.

Qualitatively, the images shown in Fig. 4.5, show higher signal intensity in the drug layer than in the sweller layer, at early times. Additionally, the signal intensity of the water within the membrane surrounding the drug layer is far greater than that for the water in the membrane surrounding the sweller layer at early times. The transport analysis presented in the section: Estimating Effective Diffusion and the Rate of Osmotic Transport, provides explanation of which transport process, diffusion or osmosis, dominates in the individual drug and sweller layers as a function of hydration time. Currently, it is unclear why the drug layer hydrates more rapidly than the sweller layer at early times. Relaxometry and imaging studies on the individual tablet excipients as a function of hydration time would provide the data necessary to explain the hydration

behavior of the separate tablet layers. Furthermore, evaluating 1D hydration of the tablet layers separately as well as the hydration behaviors for tablets of varying formulations may provide insight towards understanding whether the layer formulation affects the hydration behavior of the membrane surrounding the specific layer. Chapter 7 of this thesis outlines in more detail future studies aimed at answering some of the unresolved questions from this work.

In Fig. 4.6, MR images taken at three different times are compared to the optical images of GITS tablets soaked for the corresponding time period. Within the tablet layers, the MR images show an increase in signal intensity over time due to increasing water concentration within the tablet as it hydrates. Corresponding features in the images include the drug suspension deposited on the upper surface of the tablet, clear distinction between the drug and sweller layers, and swelling of the sweller layer.

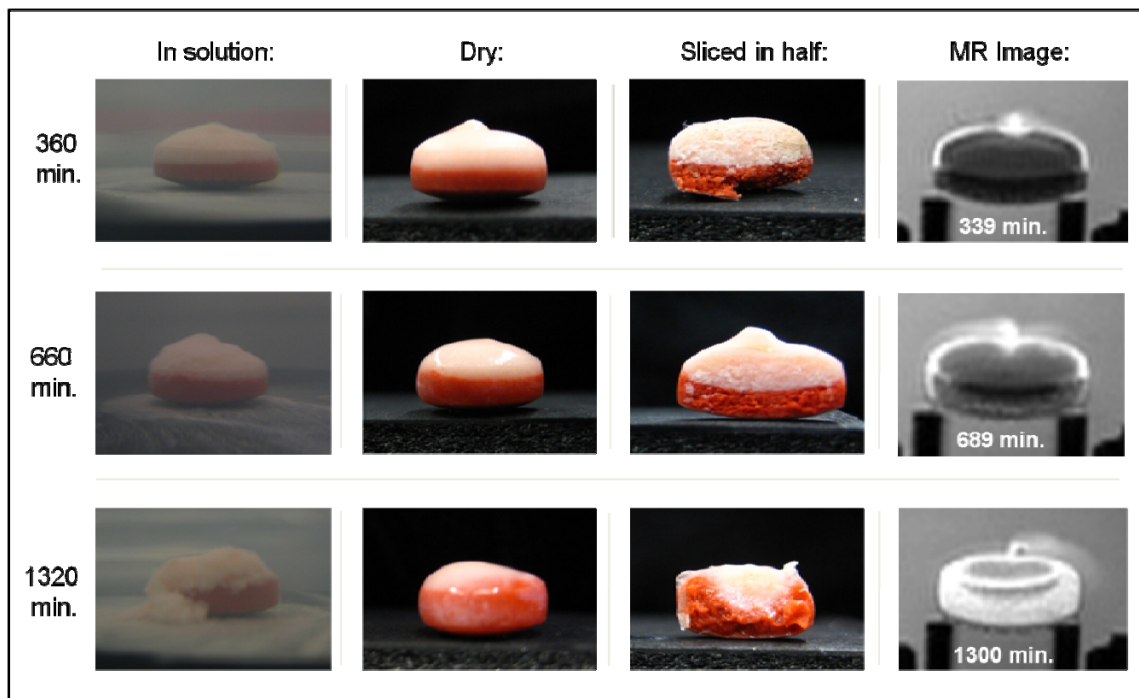


Figure 4.6. Comparison of the trial 1 Cardura XL tablet MR images (far right) to digital images of a tablet (in 500 mL of deionized water in a glass beaker) corresponding to the same hydration times. Images from left to right: Tablet hydrating in beaker of water; tablet after removing it from the water; cross-section of tablet after slicing it in half longitudinally; MR image of tablet placed in MR tablet holder at corresponding hydration time.

Relaxation Times and the Impact on Imaging

In order to use the MR images to investigate water transport in the drug and sweller layers of the tablet, it is necessary to determine that the image intensities accurately reflect water concentration in these regions. A study of the relaxation times, T_2 and T_1 , in the tablet throughout the 16 hr hydration period allowed a high degree of confidence that this was the case.

Spin-spin T_2 relaxation results from the spins, *i.e.* magnetic moments, in a molecule imparting slight magnetic fields on one another through magnetic dipole-dipole interactions. T_2 relaxation is extremely dependent on molecular motion. Generally, in

liquids, there is sufficient molecular mobility, through rotational diffusion, to motionally average dipole-dipole interactions so that the T_2 time is relatively long. In small pore materials, such as within the Cardura XL tablet, the water molecules are restricted and bound to surfaces, which limits molecular motion, and can generate surface relaxation dependent on pore size or surface:volume ratio [8, 50]. The motionally restricted water molecules in small pore materials thus exert strong dipolar interactions on their neighbors and experience significant susceptibility gradients, which causes rapid loss of transverse phase coherence and short T_2 times.

In Fig. 4.7, distributions of T_2 relaxation times are presented for tablets hydrated for 1, 4, 8 and 16 hr. For all hydration times, the two primary measured relaxation populations are at approximately 10ms and greater than 40ms. We currently interpret these distinct populations as belonging to distinct regions in space, within which the spins could be in fast exchange with the rigid polymers in that region. The very short T_2 signal, *i.e.* fast T_2 relaxation time, (< 1 ms) is from protons located on the rigid polymer molecules of the tablet, as evidenced by measurement of the T_2 distribution of a dry tablet, and these protons will therefore not contribute to the image signal acquired using a T_e of 2.81 ms, but they will influence the T_2 of the water due to the fast exchange with the surrounding water. As a specific region is hydrated then the relative population exchange between the relaxation sites on the polymers will decrease and the relaxation time of water in that region will increase.

The very short T_2 signal, *i.e.* fast T_2 relaxation time, (< 1 ms) is from protons located on the rigid polymer molecules of the tablet, as evidenced by measurement of the

T_2 distribution of a dry tablet, and these protons will therefore not contribute to the image signal acquired using a T_e of 2.81 ms.

Between the 1 hr (60 min) and 4 hr (240 min) hydration time points, the short T_2 (~9 ms) population broadens and yet remains approximately constant in net area. However, the longer T_2 relaxation time population significantly increases in area. Based on the images in Fig. 4.5, the longer T_2 relaxation time population is the water in the drug layer as this is the region where signal increases in the images during the first four hours.

Between the 4 hr (240 min) and 8 hr (480 min) hydration times, the net area associated with the longer T_2 relaxation time population remains fairly constant. Referencing the images of Fig. 4.5, the drug layer signal remains fairly constant between 4 hr (240 min) and 8 hr (480 min), which provides additional support for the conclusion that the longer T_2 relaxation time population is the water within the drug layer. For all the T_2 values present, the 2.81 ms echo time used in the MR images would result in no T_2 -weighting in the drug layer and only slight T_2 weighting in the sweller layer.

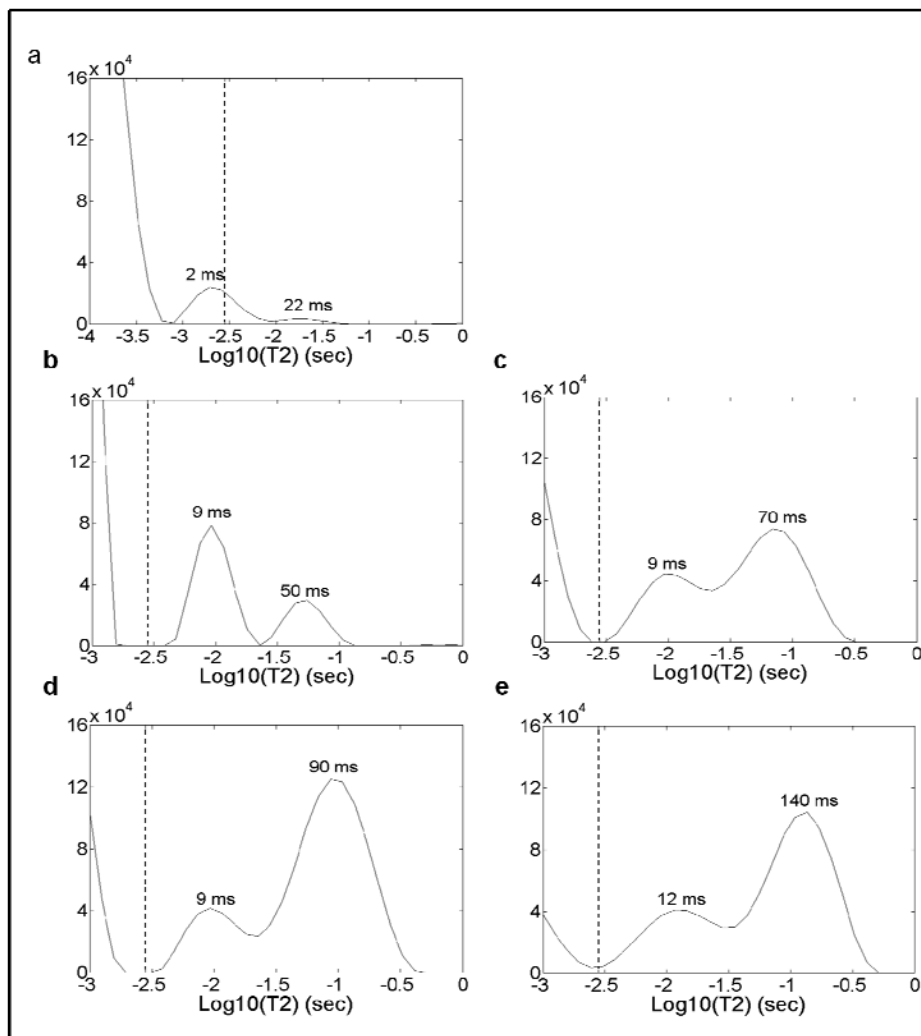


Figure 4.7. Log scale T_2 relaxation time distributions in the Cardura XL tablet (a) dry and at hydration times (b) 1 hr (c) 4 hrs (d) 8 hrs and (e) 16 hrs. The dashed line in each distribution marks the 2.81 ms echo time used in the 2D MR imaging experiments.

Understanding whether T_1 -weighting is occurring within the tablet region of the MR images with a $T_r = 1$ s is important as it is assumed for subsequent analysis and modeling that the signal intensity in the tablet reflects water concentration. Table 4.1 shows approximate T_1 relaxation times for tablets hydrated for 1-16 hr. The approximate T_r at which signal intensity remained steady for free water was approximately 5 s, so there is definitely T_1 weighting of the bulk water signal. However, this is of no concern

as we do not need to measure water concentration in the surrounding bulk water. For a tablet hydrated for 1 hr, $T_1 \approx 600$ ms and for a tablet hydrated for 8-16 hrs, $T_1 \approx 200$ ms. This analysis indicates that a small amount of T_1 -weighting of the signal from within the tablet was present at early times in the tablet imaging studies, but that T_1 -weighting was not significant at hydration times beyond six hours. The longer T_1 at early hydration times is probably due to the heavier weighting of the overall tablet signal by the polymer which will have long T_1 values. Therefore, the T_1 -weighting of the water is likely to be even less than the small amount these values suggest, indicating a direct correlation between signal intensity and water concentration is valid.

Table 4.1. Bulk T_1 relaxation times for the water within the tablet at the specified tablet hydration time.

Hydration Time (hr)	T_1 time (ms)
1	600
2	400
3	400
4	400
5	400
6	400
7	200
8	200
12	200
16	200

Estimating Effective Diffusion and the Rate of Osmotic Transport

For each image acquired over the 16-hr hydration time, signal intensity data for a 624 μm wide and 9 mm long horizontal region was selected from each layer of the tablet (top left image in figures 4.8 and 4.9). The signal intensity data for each image, *i.e.* time point, was normalized to the average signal intensity of the surrounding water, as it was

assumed that the T_1 -weighting of the bulk water was stable over the duration of the experiment. The plots of spatially and temporally varying signal intensity reveal the transport behavior of water in the drug (Fig. 4.8) and the sweller (Fig. 4.9) layers. The signal intensity profiles for each of the three trials show the same behavior.

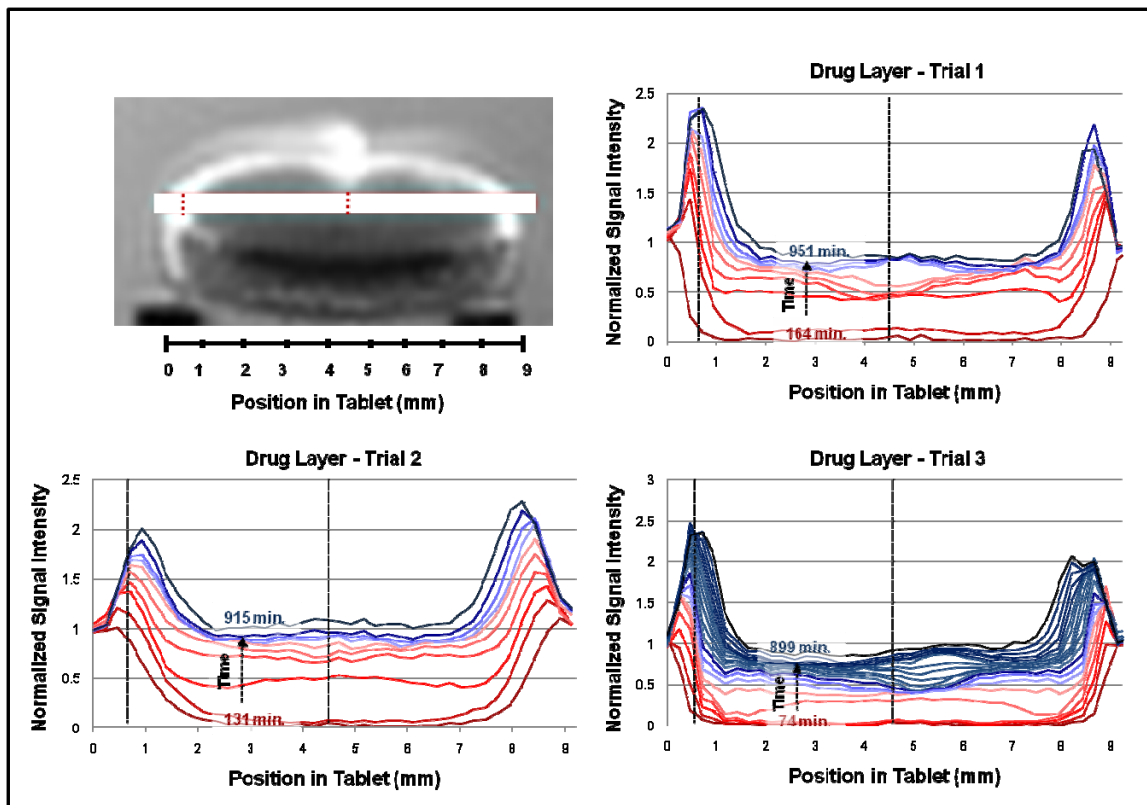


Figure 4.8. Signal intensity profiles for the drug layers for each of the three trials show similar behavior. Each line of data corresponds to the line through the drug layer (top left) for each image, or time point. The dashed line at position 4.5 mm corresponds to the data analyses shown in Figure 4.11. Note the signal intensity variation with time in the membrane, dashed line at position 0.7 mm.

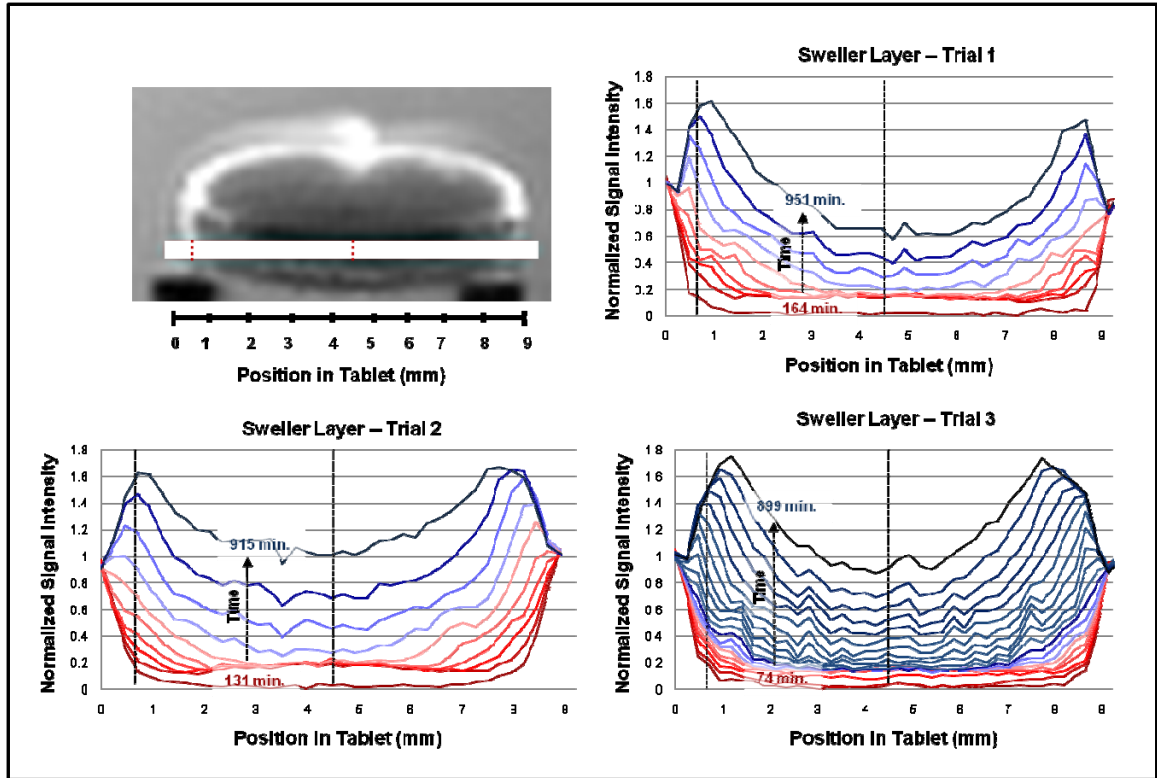


Figure 4.9. Signal intensity profiles for the sweller layers for each of the three trials show similar behavior. Each line of data corresponds to the line through the sweller layer (top left) for each image, or time point. The dashed line at position 4.5 mm corresponds to the data analysis shown in Figure 4.12. Note the signal intensity variation with time in the membrane, dashed line at position 0.7 mm.

The 1D time-dependent diffusive model equation (4.2) yields the concentration profiles shown in Fig. 4.10 for a diffusivity value of $D = 1.8 \times 10^{-10} \text{ m}^2/\text{s}$. For reference, the free diffusivity of water at 20°C is $2.1 \times 10^{-9} \text{ m}^2/\text{s}$ [56].

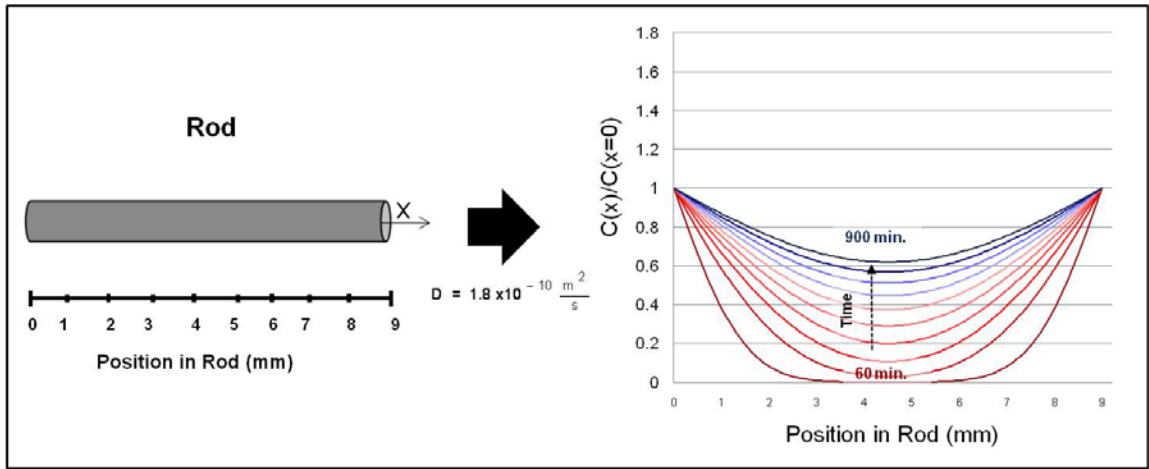


Figure 4.10. The model signal intensity profile was generated using the 1D diffusion model, equation (4.9), for a time period of 60-900 minutes. The model provides a basis with which to interpret the diffusive behavior of the osmotic GITS tablets and to estimate effective diffusivity of water within the drug and sweller layers.

Signal intensity for a region (area = $624 \times 234 \mu\text{m}^2$) located in the center of each layer of the tablet (dashed lines located at $x = 4.5 \text{ mm}$ in Figures 4.8 & 4.9) was used to estimate the effective diffusivity of water in both the drug (Fig. 4.11) and sweller (Fig. 4.12) layers. In the drug layer (Fig. 4.11) between 200-350 min., hydration appears to be rapid, observable by a steep increase in signal intensity after an initial slow hydration regime. For the duration of the MR imaging experiments, the drug layer follows a diffusion process comparable to the generated diffusion model with diffusivity values lying in the order of magnitude $D \approx 3.3 \times 10^{-10} \text{ m}^2/\text{s}$ to $D \approx 8.3 \times 10^{-10} \text{ m}^2/\text{s}$.

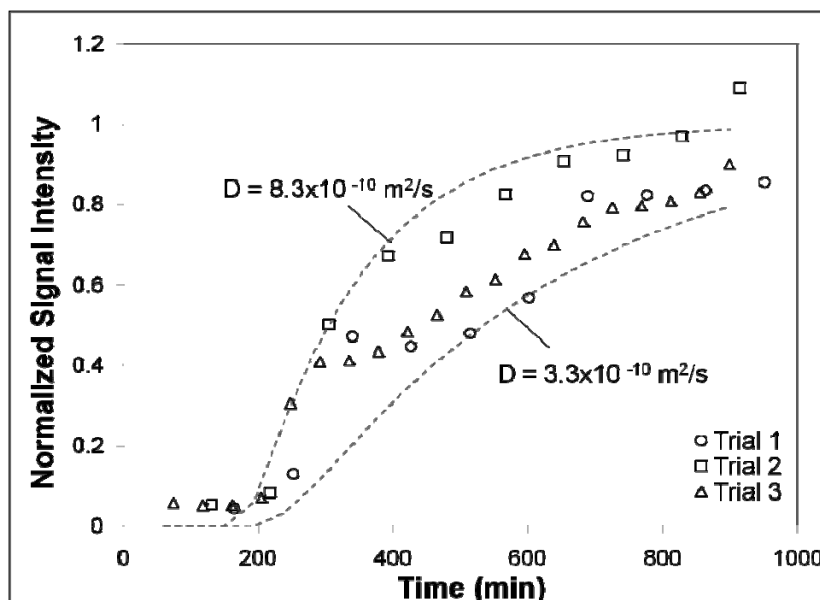


Figure 4.11. Diffusive transport in the drug layer. The data shown is taken from a pixel (area: $624 \times 234 \mu\text{m}^2$) in the center of the drug layer (dashed line at 4.5 mm in Figure 4.8). Comparing this behavior to the diffusion model (dashed lines), the diffusivity for the water moving into the drug layer appears to lie in the range of $D = 3.3 \times 10^{-10} \text{ m}^2/\text{s}$ to $D = 8.3 \times 10^{-10} \text{ m}^2/\text{s}$.

During the initial hydration of the tablet ~ 600 min (10 hr), movement of water into the sweller layer (Fig. 4.12) exhibits similar behavior to that of the diffusion model with a diffusivity value around $D \approx 8.3 \times 10^{-10} \text{ m}^2/\text{s}$. From 600 min on, the sweller layer shows a rapid increase in signal intensity that is not consistent with a purely diffusive process. A physical mechanism such as flux increase due to osmotic pressure changes [47] is indicated. When water first transports into the sweller layer, the driving transport mechanism is the chemical potential difference due to the water concentration gradient (water diffusing into a porous solid). At around $t = 600$ min, enough of the sweller layer matrix is solubilized that the water, polymer and osmotic agent in the sweller layer can be described as a concentrated solution. At this point, as indicated by the exponential increase in the water concentration (see [Transport Modeling](#)), the driving transport

mechanism is the chemical potential due to the osmotic pressure between two different solutions across a membrane. This interpretation is consistent with the increase in the number of molecules in the shorter T_2 relaxation time distribution and the increasing value of T_2 for that distribution (Fig. 4.7) for times longer than 600 minutes. As mentioned earlier, the increase in T_2 is consistent with the increase in the rotational mobility of the water and the polymers, and the decrease in the relative population of polymer to water to contribute to proton exchange for the water molecules that occurs as a solution forms.

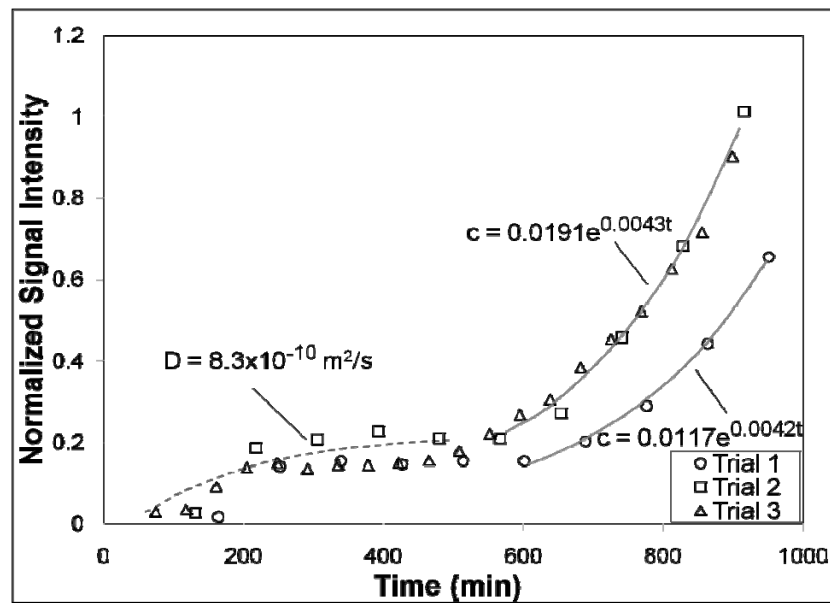


Figure 4.12. Diffusive and osmotic transport in the sweller layer. The data shown is taken from a single pixel in the center of the sweller layer (dashed line at 4.5 mm in Figure 4.8). The diffusion model (dashed line) estimates the diffusivity for the water moving into the polymer sweller layer during the first 600 min is approximately $D = 8.3 \times 10^{-10} \text{ m}^2/\text{s}$. The sweller layer behavior after $t = 600$ min suggests an osmotic transport mechanism. The increase in signal intensity at $t \geq 600$ min was approximated using an exponential model (solid lines) and the equations for the exponential increase in signal intensity are shown.

The data indicates an exponential increase in signal intensity for $t \geq 600$ min. Exponential models approximating the behavior of the water in the sweller layer during this osmosis-dominated mass transport regime are shown in Fig. 4.12. The rate coefficient $\beta = KRT/l \sim 0.0043 \text{ s}^{-1}$ is similar for all trials. The model's ability to quantify osmotic transport is limited due to the Van't Hoff's Law approximation, which is valid only for low solute concentrations, but clearly shows that osmotic transport is occurring. MR imaging studies in which water transport is limited to one dimension, systematically varying formulation and a more detailed thermodynamic analysis of the osmotic pressure driving force are necessary to fully quantify the diffusive and osmotic transport coefficients.

Conclusions

A short echo time ($T_e = 2.81 \text{ ms}$) MRI technique for imaging the hydration of a GITS tablet was implemented, and three separate imaging trials were conducted. A simple 1D transport model allowed for direct quantification of the transport processes. The data from the three trials was consistent and order of magnitude diffusivity values for water in the drug layer were determined from the 1D diffusion model: $3.3 \times 10^{-10} \text{ m}^2/\text{s} \leq D_{\text{drug}} \leq 8.3 \times 10^{-10} \text{ m}^2/\text{s}$. Water diffusivity in the sweller layer was $8.3 \times 10^{-10} \text{ m}^2/\text{s}$ so that the diffusion behavior in both layers appeared similar. The unique nature of the data allowed the clear transition to osmotic transport in the sweller layer to be directly measured. Data and analysis presented here provide important first steps toward

development of realistic 3D transport models. This work was published in the International Journal of Pharmaceutics [57].

PULSED GRADIENT SPIN ECHO (PGSE) NUCLEAR MAGNETIC RESONANCE (NMR) MEASUREMENT AND SIMULATION OF TWO-FLUID TAYLOR VORTEX FLOW (TVF) IN A VERTICALLY ORIENTED TAYLOR-COUPETTE DEVICE

Introduction

For more than a century, scientists, mathematicians and engineers have studied the vast array of flows arising from the Couette flow device. The Couette was originally designed by the French physicist, Maurice Couette, and consists of two coaxial cylinders with one or both of the cylinders rotating and the space between the cylinders filled with a viscous fluid [58]. In 1923, Geoffrey I. Taylor showed that a hydrodynamic instability occurs when the rotation rate of the inner cylinder Ω_{inner} exceeds a critical rotation rate Ω_c [59]. Taylor observed that for a given fluid when the inner cylinder rotation rate exceeded this critical value, pairs of counter-rotating, evenly spaced toroidal vortices appeared along the axial direction of the cylinder. This flow is known as Taylor-Couette flow or Taylor vortex flow (TVF). In this paper, the stable one dimensional flow that occurs below the Ω_c will be referred to as *Couette flow* and the unstable three dimensional flow which occurs above Ω_c will be called *Taylor vortex flow*.

A large number of different and incredibly diverse flows occur as the inner and outer cylinders' Reynolds numbers $Re_i = R_i(R_o - R_i)\Omega_i/\nu$ and $Re_o = R_o(R_o - R_i)\Omega_o/\nu$, respectively are varied. Fascinatingly, the Taylor-Couette device produces numerous patterned flow regimes that are not laminar or turbulent and that vary as a function of fluid properties, system geometry and rotation rate. In Figure 5.1, a stability map presenting the wide ranging number and types of flow obtained experimentally for a

Taylor-Couette device of radius ratio $\eta=0.883$ is presented [60]. An impressive array of theoretical and experimental studies have been conducted on these flows [61-63].

Taylor-Couette hydrodynamic instabilities in single fluids have been imaged previously using magnetic resonance microscopy MRM [30, 64-68].

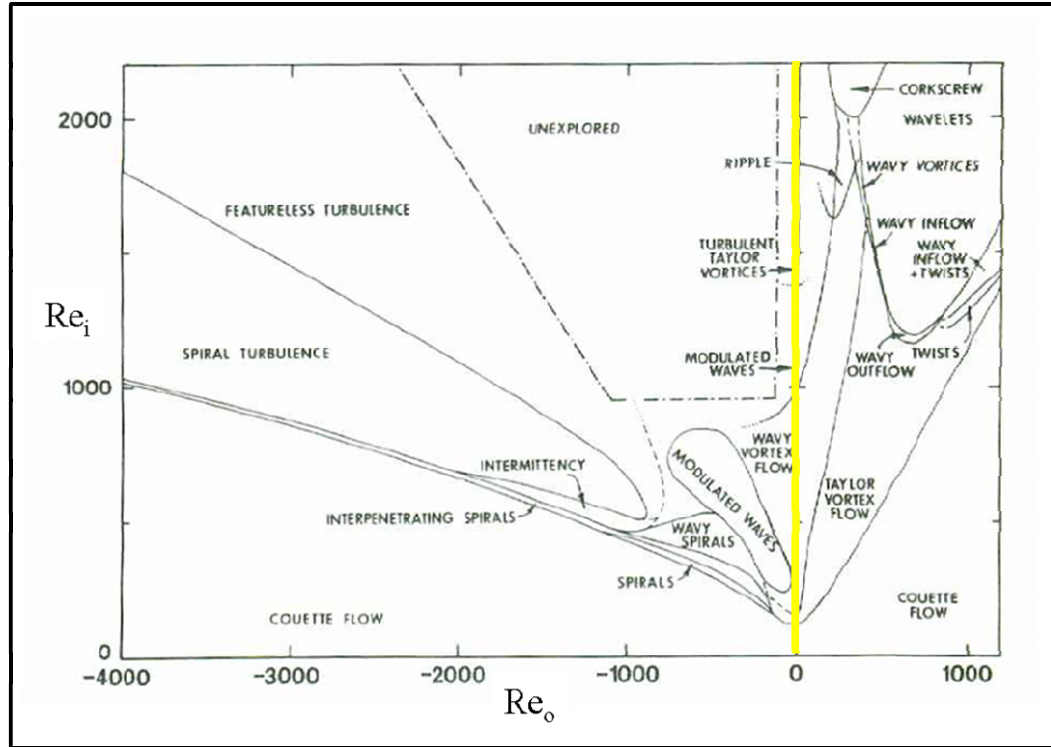


Figure 5.1. Experimental stability diagram the flows arising in a Taylor-Couette device of $\eta=0.883$ as a function of inner cylinder Reynolds number Re_i and outer cylinder Reynolds number Re_o [60]. (Permission to use granted by C.D. Andereck and H. L. Swinney). The highlighted region indicates the Reynolds numbers used in the studies presented here.

The majority of previous theoretical and experimental studies involving two-fluid flows in a Taylor-Couette device have utilized horizontal orientations, radial stratification of the two-fluids and rotation of both the inner and outer cylinders of the Couette [69, 70]. In many liquid-liquid Taylor-Couette flow studies of Taylor vortex flow reactors, axial flow is incorporated [71-74]. Stability analysis of two immiscible fluids radially

stratified between concentric cylinders with the outer cylinder fixed and the inner cylinder rotating was performed to analyze the effects of different viscosities, densities and surface tension on the stability of Couette flow [75]. Recently, radial stratification of two immiscible fluids in a vertically oriented Taylor-Couette device [76] has been studied. Only two studies have been identified that investigated pairs of axially stratified immiscible fluids in a vertically oriented Couette with only the inner cylinder rotating [77, 78]. However, small aspect ratios $\Gamma=d/h$, ranging from 4 to 6, were used in the Toya *et al* [77] study and thus had a significant impact on the wavelength of the Taylor vortex flow cells. In the work conducted by Sathe *et al* [78], simulations and experiments were carried out under dispersed droplet conditions, *i.e.* very high Re_i . The experiments and simulations presented here are for a Taylor-Couette device with a fixed outer cylinder and low rotation rates of the inner cylinder. For the two-fluid experiments and simulations, the fluids are axially stratified and the inner cylinder rotation rates produce the Couette and Taylor vortex flow regimes, which do not result in dispersion or emulsification of the fluids. Nuclear magnetic resonance (NMR) pulsed gradient spin echo (PGSE) experiments allowed for the imaging of all three velocity components v_r , v_θ and v_z and the resulting velocity maps and lengths of waveforms were compared to computational fluid dynamics (CFD) simulations. The location of the two-fluid interface and the wavelengths of the flow features were compared between the two-fluid experiments and simulations.

Materials and Experimental Methods

Materials

The fluids used in the TVF experiments were deionized water with kinematic viscosity of 1 cSt, a silicone oil with kinematic viscosity of 1.65 cSt (SG= 0.853) and a silicone oil with kinematic viscosity of 0.65 cSt (SG=0.764) [Clearco Products, Bensalem, PA]. In the two-fluid experiments, the densest fluid, water, was always placed below the less dense silicone oils to prevent instabilities due to buoyancy forces from complicating the system dynamics.

Experimental Apparatus

The Rheo-NMR Couette (Magritek, New Zealand) has a 1.05 mm gap width d between the inner and outer cylinders. The ratio of the inner cylinder radius $R_i = 2.5\text{mm}$ to the outer cylinder radius $R_o = 3.55\text{mm}$ is $\eta=0.70$. The ratio of the height of the fluid column to the gap width, aspect ratio $\Gamma=d/h$, is approximately 50. Inner cylinder rotation rates Ω_{inner} ranged from 3-14 rps. The outer cylinder was stationary. The upper boundary of the fluid was a free interface and the lower boundary was stationary, see Fig. 5.2.

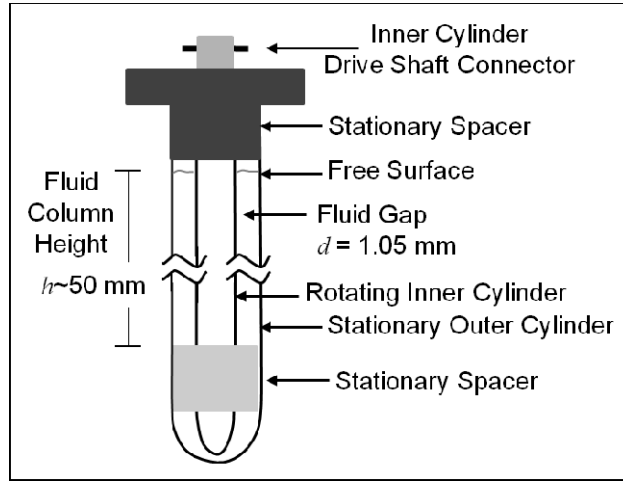


Figure 5.2. Schematic of the Taylor-Couette device used for MRM experiments.

Magnetic Resonance Velocity Imaging Experiments

A Bruker DRX 250 MHz vertical wide bore spectrometer, a 3D gradient coil (1.728 T/m) and a 10 mm ^1H radiofrequency (rf) probe maintained at 20°C were used to obtain MRM velocity maps of the fluids in the Couette.

To obtain MRM velocity maps, both position-encoding and velocity-encoding gradients are applied, see Figure 5.3. The PGSE gradient pair $\mathbf{g}$ encodes for displacement and the imaging gradients $\mathbf{G}$ encode for spatial resolution [8]. It is important to emphasize that the velocities measured in dynamic imaging experiments are ensemble, volume and time averaged. Averaging is both inherent in the MR experiment and necessary for increasing the signal to noise ratio SNR . Voltage signals which provide data at each position of the resultant velocity map are acquired by averaging the signals for each $\mathbf{g}$ value over the entire experiment duration. Fourier transformation of the acquired signal, as discussed below, results in a velocity volume averaged over the dimensions of the velocity map voxel (156 μm x 78 μm x 1mm for single fluid

experiments and $78\mu\text{m} \times 78\mu\text{m} \times 1\text{mm}$ for two-fluid experiments) and the displacement observation time ($\Delta=3.69\text{ms}$ for single fluid experiments and $\Delta=3.98\text{ms}$ for two-fluid experiments). Since the ensemble average velocity is obtained for each voxel, that velocity is inherently averaged over the volume of the imaging voxel and time-averaged over the observation time Δ . Multiple measurements are made to sample all of the reciprocal image space, $\mathbf{k} = \gamma \mathbf{G} t_G / 2\pi$, where γ is the gyromagnetic ratio and t_G is the duration of the position encoding gradient $\mathbf{G}$, and at least two points in the reciprocal displacement space, $\mathbf{q} = \gamma \mathbf{g} \delta / 2\pi$, where δ is the duration of the motion encoding gradient $\mathbf{g}$. Since data is sampled regularly over the entire experiment duration which varied from approximately 1-7 hrs depending on the spatial resolution, the repetition time T_R and the number of averages, the final velocity map represents the stationary ensemble average of all displacements over this entire time.

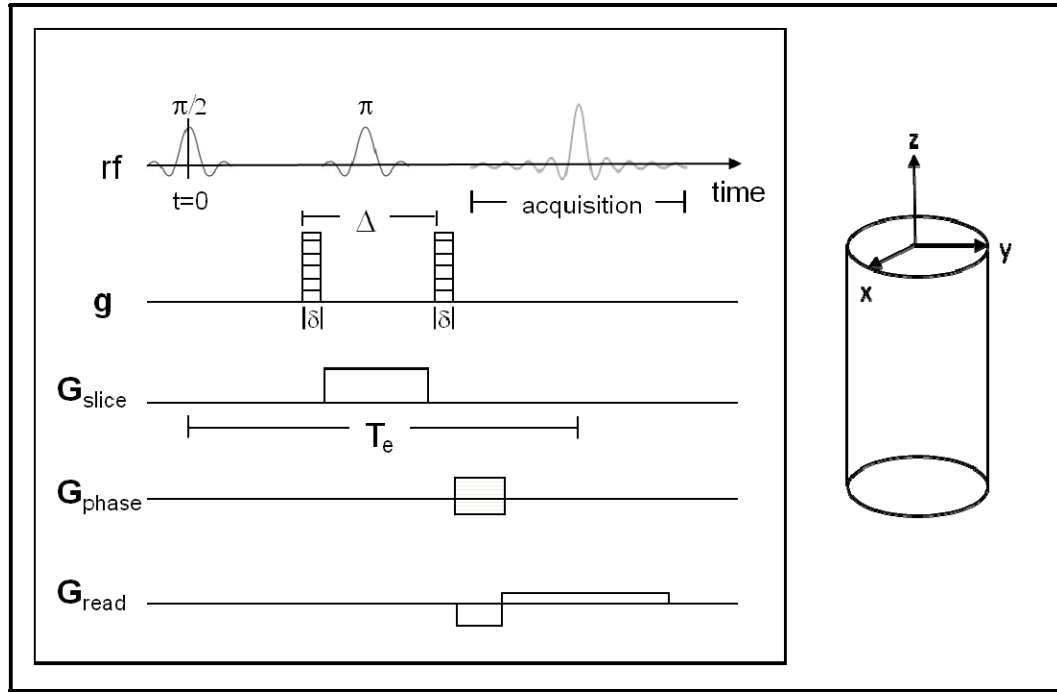


Figure 5.3. MRM velocity map pulse sequence schematic. The slice selective gradient G_{slice} was applied in the x direction so that a (y,z) cross section through the center of the T-C flow cell is selected. The read encoding gradient G_{read} was applied in the axial (z) direction. The PGSE gradient pair $\mathbf{g}$ was applied alternately in all three directions - radial (y), axial (z) and azimuthal (x) - to obtain the three velocity components.

The signal obtained from the experiment represented in Figure 5.3 is modulated by both the motion-encoding $\mathbf{g}$ and position-encoding $\mathbf{G}$ gradients and is described mathematically as

$$S(\mathbf{g}, \mathbf{G}) = \int \rho(\mathbf{r}) E_{\Delta}(\mathbf{g}, \mathbf{r}) \exp(i\gamma \mathbf{G} t_G \cdot \mathbf{r}) d\mathbf{r}. \quad (5.1)$$

The Fourier transform of (5.1) will yield $\rho(\mathbf{r}) E_{\Delta}(\mathbf{g}, \mathbf{r})$ where $\rho(\mathbf{r})$ is the spin density in the imaging voxel of finite volume $d\mathbf{r}$ and $E_{\Delta}(\mathbf{g}, \mathbf{r})$ is the Fourier transform of the local velocity profile, which in terms of the wave vector $\mathbf{q}$ is

$$E_{\Delta}(\mathbf{q}, \mathbf{R}) = \bar{P}_s(\mathbf{R}, \Delta) \exp(i2\pi \mathbf{q} \cdot \mathbf{R}) d\mathbf{R}. \quad (5.2)$$

$P_s(\mathbf{R}, \Delta)$ is the volume averaged conditional probability that a spin will move a distance $\mathbf{R}$ during time Δ , thus providing the velocity, $\mathbf{v}=\mathbf{R}/\Delta$.

Specifically for the velocity maps presented in this paper, the slice gradient G_{slice} is applied in the x direction so that a (y,z) cross section through the center of the Couette flow cell is selected, Fig. 5.3. The read gradient G_{read} is applied in the z direction. In order to minimize outflow from the slice during motion encoding, the first 90° rf pulse excites the entire sample and slice selection occurs with the 180° pulse.

For the single fluid velocity maps presented in this paper, the following experimental parameters were used: echo time $T_e=9.4$ ms, $T_R=2.5-3.5$ s, total experimental time approximately 1 hr; slice thickness of 1 mm, voxel size = $156 \times 78 \times 1000 \mu\text{m}^3$, corresponding to Field of View = 20 mm x 10 mm x 1 mm and 128 x 128 points position sampling gradient values; the PGSE motion-encoding gradients vary as a function of rotation rate and velocity encoding direction; $\delta = 1$ ms, observation time $\Delta=3.69$ ms.

For the two-fluid velocity maps presented in this paper, increased spatial resolution was used in order to better capture the two-fluid interface so that its wave and fluid dynamical behavior could be compared to simulations. The experimental parameters for the two-fluid experiments are as follows: echo time $T_e = 10$ ms, $T_R = 3$ s, total experimental time approximately 4 hr; slice thickness of 1 mm, voxel size = $78 \times 78 \times 1000 \mu\text{m}^3$, corresponding to Field of View = 20 mm x 10 mm x 1 mm and 256 x 128 position sampling gradient values; the PGSE motion-encoding gradients vary as a function of rotation rate and velocity encoding direction, $\delta = 1$ ms, observation time $\Delta = 3.98$ ms.

Due to the significant chemical shift in the Larmor frequency, 4.6 ppm, between water and the two silicone oils used in the two-fluid experiments, a distortion occurs at the two-fluid interface in the read encoding, *i.e.* axial, direction of the two-fluid velocity maps. If there are nuclei of significantly different chemical environments located within the same spatial pixel(s) of an image, they will appear to be shifted in space due to this chemical shift.

In addition, for the two-fluid radial direction velocity maps, two velocity maps were taken at each inner cylinder rotation rate: one in which the slice was centered with respect to Larmor frequency of the water and one in which the slice was centered with respect to the Larmor frequency of the silicone oil. The two images were then combined to obtain the two-fluid radial direction velocity maps shown in Figures 5.5 and 5.6.

Computational Fluid Dynamics Simulations

Computational fluid dynamics (CFD) simulations, using ANSYS Fluent© software [79], were calculated for comparison to the experimental data. A two-dimensional axisymmetric cylindrical finite volume model with no slip stationary boundary conditions at the outer cylinder wall and bottom boundary was used. In order to model the air-liquid interface at the top of the Couette, a zero-shear stress boundary condition was specified at that interface. The fluid density and viscosity were specified independently. Steady state simulations were used and determine the rotation rate at which the Taylor vortex instability first occurred in the single fluids.

In order to capture the multiphase dynamics for axially stratified fluid pairs undergoing TVF, a time dependent “Volume of Fluid” model which solves the continuity equation for the volume fraction ϕ of each phase and a single momentum equation for both phases in each cell was used [79]. The momentum equation, shown below, depends on the volume fractions through ρ and μ .

$$\frac{\partial(\rho\mathbf{v})}{\partial t} + \nabla \cdot (\rho\mathbf{v}\mathbf{v}) = -\nabla P + \nabla \cdot [\mu(\nabla\mathbf{v} + \nabla\mathbf{v}^T)] + \rho\mathbf{g} + F_{vol}$$

The surface tension σ between the two fluids was incorporated into the momentum equation as a surface tension volume force F_{vol} [80], which for a two phase system is defined as

$$F_{vol} = \sigma \frac{\rho\kappa\nabla\phi_1}{\frac{1}{2}(\rho_1 + \rho_2)}.$$

Here ρ is the volume averaged density, $\rho = \phi_2\rho_2 + (1 - \phi_2)\rho_1$ and κ is the curvature.

The curvature can be defined in terms of the divergence of the unit normal $\hat{n}$, which is defined as

$$\hat{n} = \frac{\nabla\varphi_1}{|\nabla\varphi_1|}, \text{ thus}$$

$$\kappa = \nabla \cdot \frac{\nabla\varphi_1}{|\nabla\varphi_1|}.$$

In the two-fluid simulations a surface tension σ of 15 mN/m was used.

Stability Theory and Dimensional Analysis

The Taylor vortex flow MR velocity image data presented in this work, provides direct visualization of the axisymmetric disturbance velocities [59, 63, 81], which perturb the linearized Couette flow solution, and have the following form [62]

$$v_r(r, z) = v_r(r) \cos kz e^{st}$$

$$v_\theta(r, z) = v_\theta(r) \cos kz e^{st}$$

$$v_z(r, z) = v_z(r) \sin kz e^{st}. \quad (5.3)$$

Here s is the eigenvalue or growth rate corresponding to the dimensional axial wave number k , which is only one component of the Fourier spectrum of disturbances. The wavelength corresponding to a specific Fourier mode can be computed as $\lambda=2\pi/k$.

In linear stability analysis, the Navier Stokes equations are linearized and the Couette flow solution $V_d(r)$ is perturbed. Appendix D presents the linear stability analysis of the Couette solution for a single pure fluid. A solution of the linearized Navier Stokes and continuity equations using axisymmetric disturbance velocities of the form (3) anticipates the existence of a final flow solution that is periodic in z , the Taylor

vortex flow solution. In linear stability analysis, the fastest growth rate, *i.e.* largest positive real eigenvalue s , is determined in order to determine the dominant Fourier mode that causes the Couette flow to go unstable. The wavelength of the dominant Fourier mode identified through linear stability analysis should correspond to the critical wavelength determined experimentally.

The dimensionless Taylor number is a ratio of inertial to viscous forces similar to a Reynolds number but specific to the Taylor-Couette device geometry. The Taylor number that arises from solving the axisymmetric linear stability problem for a Taylor-Couette device with a stationary outer cylinder [82] is

$$T = \frac{2\eta^2}{1 - \eta^2} \frac{\Omega^2 d^4}{\nu^2}$$

Here Ω is the inner cylinder rotation rate in rev/s (rps) and ν the kinematic viscosity of the fluid. The dimensionless axial wave number α of the Taylor vortex flow pattern measured in units of $1/d$ is defined as $\alpha = 2\pi d/\lambda$. Where λ is the wavelength or vertical length Δz of a pair of Taylor vortices. The critical Taylor number T_c and critical wave number α_c are defined as the Taylor number and wave number at which the flow transitions from stable *Couette flow* to unstable *Taylor vortex flow*.

Results and Discussion

Single Fluid Experiments and Simulations

Each of three fluids was separately studied in the Couette device by mapping the velocities for a range of rotation rates. Incrementing Ω_{inner} by 0.1 rps, the inner cylinder

rotation rate at which instability onset occurs in the single fluids at ambient temperatures $T=20-22^{\circ}\text{C}$ was determined. In the 1.65 cSt silicone oil for all rotation rates up to and including $\Omega_{inner} = 7.9$ rps, stable 1-D Couette flow is observed. For stable 1-D flow there is no velocity component observed in the axial (z) or radial (r) directions and the azimuthal (θ) direction velocity is a function of the radial variable r only, see Figure 5.4 (a). At $\Omega_{inner} = 8$ rps the transition to Taylor vortex flow is observed. Figure 5.4 (b) shows the azimuthal (θ), axial (z) and radial (r) direction 1.65cSt silicone oil velocity maps clearly indicating the expected features of Taylor vortex flow. Figure 5.4 (c) and (d) show the velocity maps at the onset of TVF for water and 0.65 cSt silicone oil, respectively. The transition is first observed at 4.7rps for water and at 3.2rps for 0.65 cSt silicone oil.

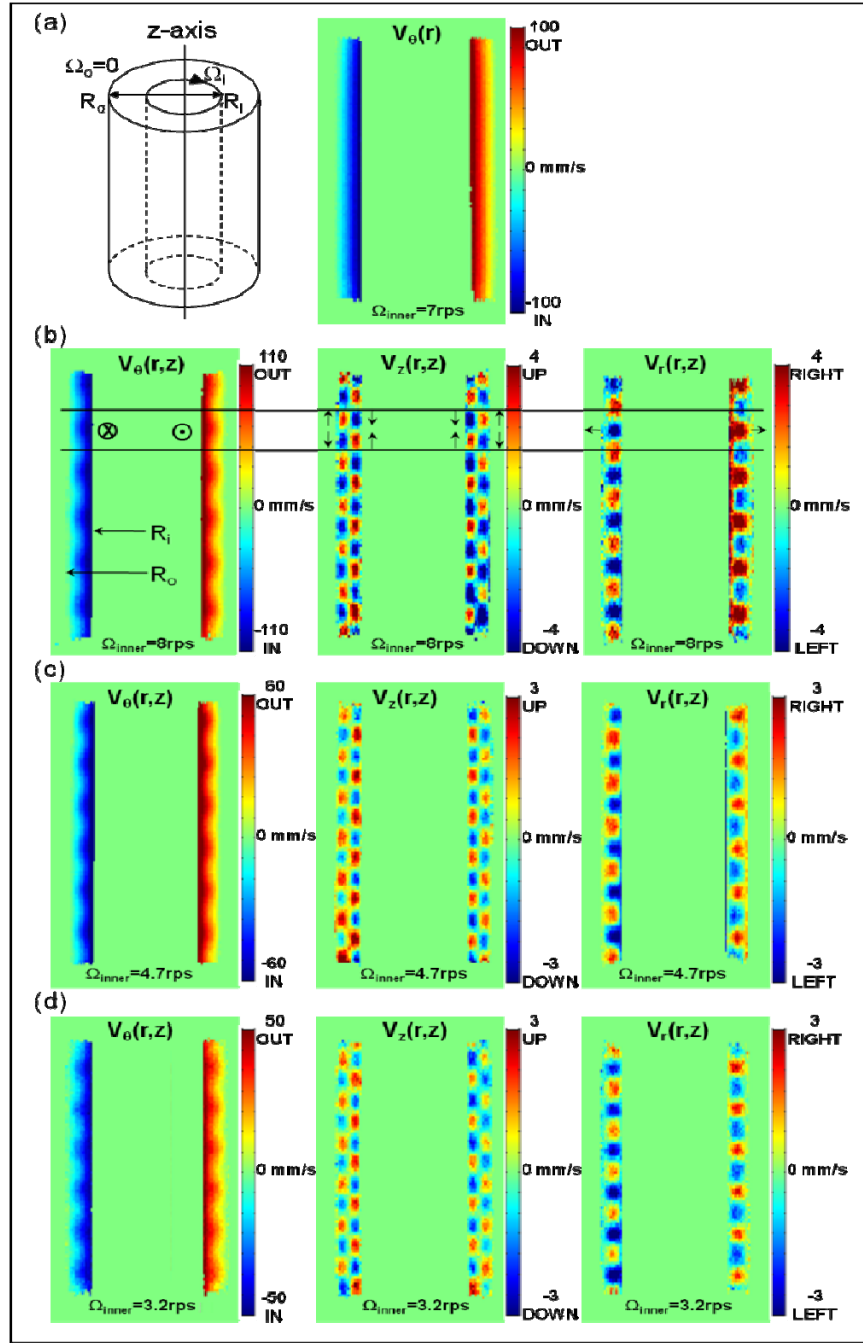


Figure 5.4. Experimentally determined pure fluid instability onset. (a) Couette device geometry and azimuthal (θ) direction velocity map corresponding to laminar one-dimensional Couette flow in 1.65 cSt silicone oil at $\Omega_{inner}=7\text{ rps}$. Azimuthal (θ), axial (z) and radial (r) direction velocity maps at the onset of TVF in (b) 1.65 cSt silicone oil at $\Omega_{inner}=8\text{ rps}\pm 0.2\text{ rps}$ at 20°C , (c) 1 cSt water at $\Omega_{inner}=4.7\text{ rps}\pm 0.2\text{ rps}$ at 22°C and (d) 0.65 cSt silicone oil at $\Omega_{inner}=3.2\pm 0.2\text{ rps}$ at 22°C .

The arrows on Figure 5.4 (b) show the direction of fluid motion. In the azimuthal $v_\theta(r,z)$ velocity map, the left hand fluid column is flowing out of the plane of the page and the right hand fluid column is flowing into the plane of the page.

In the radial $v_r(r,z)$ velocity map, there are large magnitude narrow jetting radial flows towards the outer stationary wall and smaller magnitude wider radial flows towards the inner rotating wall. The horizontal lines show how the two counter-rotating vortices in all three directions are grouped. Two sets of axial vortices correspond to each wavelength λ of the oscillatory azimuthal flow. At higher inner cylinder rotation rates, see Fig. 5.5 (c) and 5.6 (c), the axial direction vortice pairs appear to pinch outwards towards the outer wall of the Couette, due to the increasing influence of the radial direction jetting flows at higher rotation rates causing asymmetry prior to transition to wavy flow regimes.

The onset of instability for the three fluids was also determined using Ansys Fluent© CFD simulations with a rotation rate resolution of 0.05 rps. In Table 5.1 the rotation rates at which instability onset occurs as determined by the simulations are presented and compared to those observed experimentally. The onset of instability in the 1.65 cSt silicone oil was determined to occur at $\Omega_{\text{inner}} = 8.0$ rps. For water, the onset of instability occurred at $\Omega_{\text{inner}} = 4.85$ rps, and for 0.65cSt silicone oil, instability onset occurred at $\Omega_{\text{inner}} = 3.15$ rps. Using the axial direction velocity maps at instability onset, the critical wavelengths λ_c were determined by measuring the trough-to-trough length Δz of the sinusoidal waves in the θ direction velocity maps. The critical wavelengths are

also presented in Table 5.1. The critical rotation rates and wavelengths as determined by simulations agree well with those determined experimentally.

Table 5.1. Critical rotation rate (rev/sec), wavelength (mm), axial wave number and Taylor number determined experimentally and via simulation for 0.65cSt silicone oil, water and 1.65cSt silicone oil.

	0.65cSt Silicone Oil	Water	1.65cSt Silicone Oil
Ω_{inner} at instability onset (Experiment)	3.0-3.2 rps	4.5-4.7 rps	7.9-8.1 rps
Ω_{inner} at instability onset (Simulation)	3.1-3.2 rps	4.8-4.9 rps	8.0-8.1 rps
λ at instability onset (Experiment)	2.2 mm	2.1 mm	2.2 mm
λ at instability onset (Simulation)	2.1 mm	2.1 mm	2.1 mm
Critical axial wave number α_c (Experiment)	3.0	3.1	3.0
Critical axial wave number α_c (Simulation)	3.1	3.1	3.1
Critical Taylor number T_c (Experiment)	2011-2289	1912-2086	2165-2276
Critical Taylor number T_c (Simulation)	2148-2289	2176-2267	2220-2276

For a Taylor-Couette device with a stationary outer cylinder, Roberts [82] determined T_c and α_c as a function of η . For $0.65 < \eta < 0.75$, the T_c is between 2383.96 and 2102.17 and the α_c is between 3.1425 and 3.1355 [82]. For the Taylor-Couette device used in these studies $\eta=0.7$ and the critical Taylor and wave number results fall in or near the expected ranges based on Roberts' work (Table 5.1).

Two-Fluid Experiments and Simulations

In the two-fluid experiments, water was placed in the lower portion of the vertically oriented Couette and the less dense silicone oil was placed atop the water so that the two-fluids were axially stratified in a stable density configuration. Figure 5.5 shows velocity images of 1.65 cSt silicone oil and 1 cSt deionized water with Ω_{inner} increasing from left to right. At $\Omega_{\text{inner}}=7\text{rps}$, TVF is present in the water $T=4627$ but not in the 1.65 cSt silicone oil $T=1699$ as can be seen by the absence of any axial or radial

velocity components in the oil. At $\Omega_{\text{inner}} = 8$ rps, there are secondary flows present in both the fluids. There is clearly a significant velocity gradient between the two-fluids as the viscosity of the oil resists and damps fluid motion more strongly than the viscosity of the water. Figure 5.6 shows velocity images of 0.65cSt silicone oil and 1cSt deionized water with Ω_{inner} increasing from left to right. At $\Omega_{\text{inner}} = 4$ rps, TVF is present in the 0.65 cSt silicone oil $T=3567$ and faint signs of TVF onset at the lower boundary of the Taylor-Couette device are present in the water $T=1511$. At $\Omega_{\text{inner}} = 5$ rps, secondary flows are present in both the fluids. Again, there is clearly a significant velocity gradient between the two-fluids.

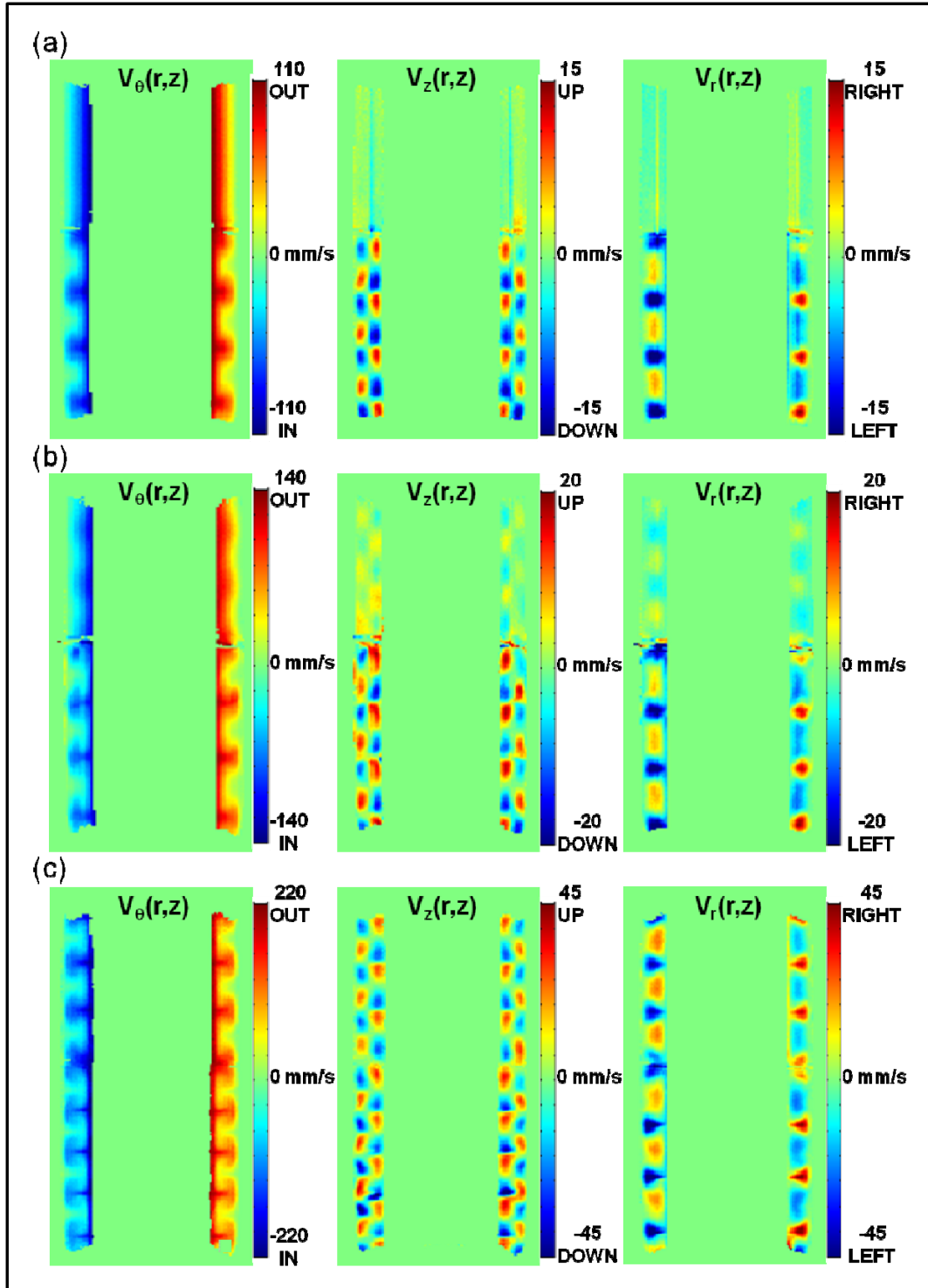


Figure 5.5. Experimental two-fluid velocity maps. Azimuthal (θ), axial (z) and radial (r) velocity maps for an axially stratified two-fluid system - 1.65 cSt silicone oil (top) and water (bottom) at increasing inner cylinder rotation rates Ω_{inner} (a) 7 rps (b) 8 rps and (c) 14 rps.

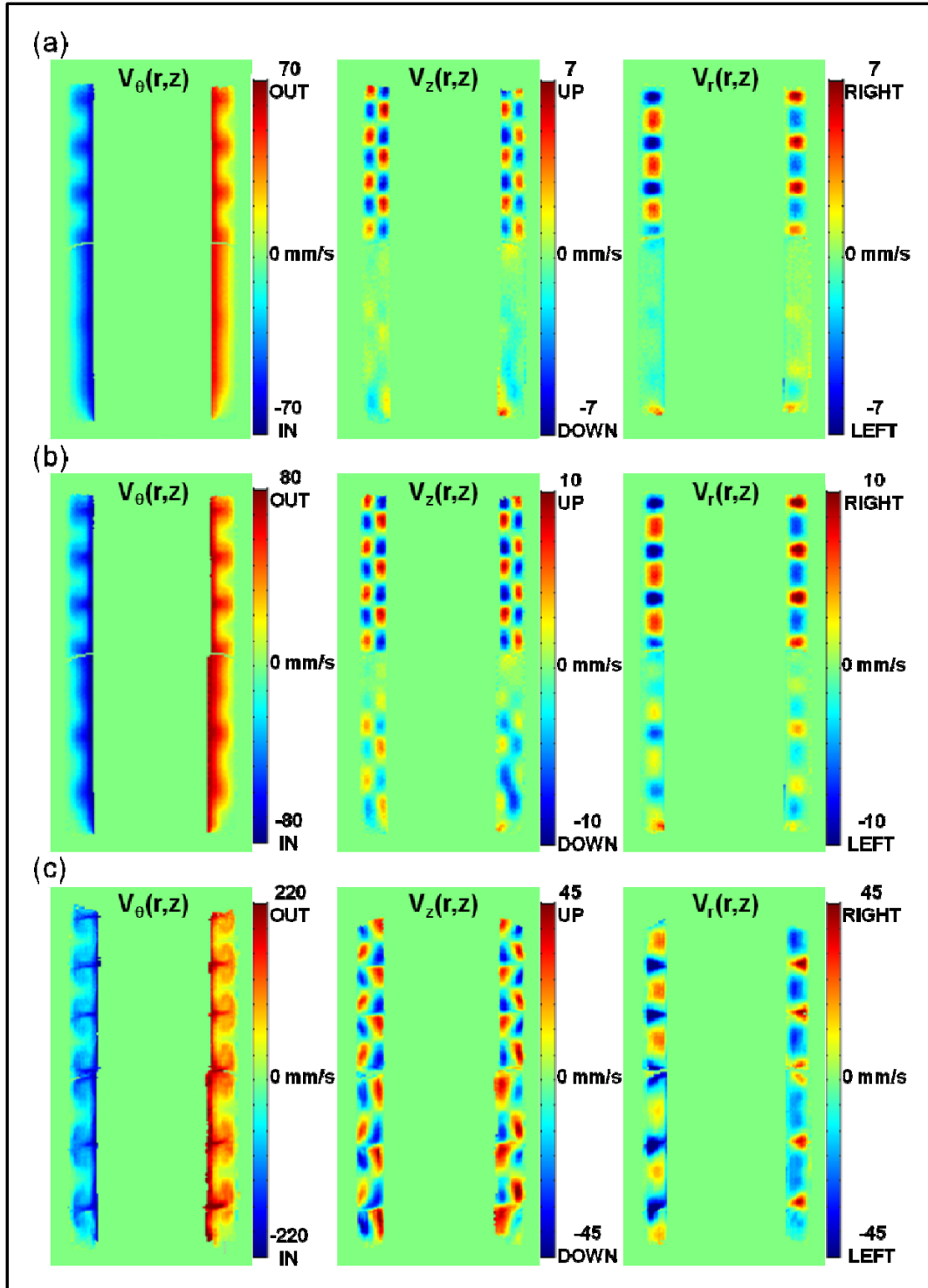


Figure 5.6. Experimental two-fluid velocity maps. Azimuthal (θ), axial (z) and radial (r) velocity maps for an axially stratified two-fluid system - 0.65 cSt silicone oil (top) and water (bottom) at increasing inner cylinder rotation rates Ω_{inner} (a) 4 rps (b) 5 rps and (c) 14 rps.

Chemical shift artifacts are seen clearly at the two-fluid interface in the θ direction velocity maps shown in figures 5.5 (a), 5.5 (b), 5.6 (a) and 5.6 (b). However, in the θ direction velocity maps at 14 rps, Fig. 5.5 (c) and 5.6 (c), the chemical shift artifact is less apparent.

At rotation rates far away from TVF onset for both fluids, interesting features can be seen in the two-fluid velocity maps. The radial direction velocity maps for the 14 rps rotation rate, presented in figures 5.5 (c) and 5.6 (c) show that the interface falls at the center of a radial out flowing jet, *i.e.* a jet that flows at a high velocity magnitude outward from the rotating inner cylinder to the stationary outer cylinder. The interface splits the out flowing jet into two jets, and a region of zero velocity in the radial direction occurs between them. In the axial direction velocity map, the interface has zero axial direction velocity, and it falls between an axial vortice pair that collides at the inner cylinder. That is, a down flowing axial vortice collides with an up flowing axial vortice at the inner cylinder, and between these counter rotating flows there is a no-flow region. A similar stagnation effect was seen at the interface of a density stratified, immiscible oil-water pair contained in a horizontal rotating cylinder [83]. In these experiments [83], the oil wetted the cylinder surface, surrounding the water and formed two major flow cells, an upper cell which moved rapidly with the rotating cylinder; and a lower cell which was counter rotating and slow. The water rotated with the cylinder as a single circular flow cell and its flow was very slow except for near the cylinder boundary, indicating a similar interfacial damping. Renardy and Joseph [75] found that surface tension stabilizes short-

wave interfacial disturbances for radially stratified immiscible fluids in a Taylor-Couette device with a fixed outer cylinder.

Figure 5.7 shows the transient CFD simulations of the azimuthal (θ), axial (z) and radial (r) direction velocity maps for the 1.65 cSt oil and water system ($\Delta t=0.001$ s and $t=20$ s) and the 0.65 cSt oil and water system ($\Delta t=0.001$ s and $t=7$ s) at 14 rps for the right-hand side of the Taylor-Couette device (rotating inner cylinder at on the left and stationary outer cylinder on the right). (Note that the simulations were conducted using a fluid column height in the axial z -direction of $h=50$ mm. However, an axial distance of only $z=13.5$ mm is displayed in all the figures shown here as this corresponds to the imaging window of the MR velocity mapping experiments). The experimental data confirms the simulation results are valid by reproducing the same features discussed above. An interesting feature that is indicated experimentally and supported by the simulations is the layer of purely azimuthal $v_\theta(r)$ flow between the two vortices that form either side of the interface. This is due to surface tension damping the TVF instability. Qualitatively, in both experiments and simulations, the wave containing the two-fluid interface is longer than the pure fluid waves. This appears to be related to the purely azimuthal flow, *i.e.* no secondary flow, layer that forms at the interface.

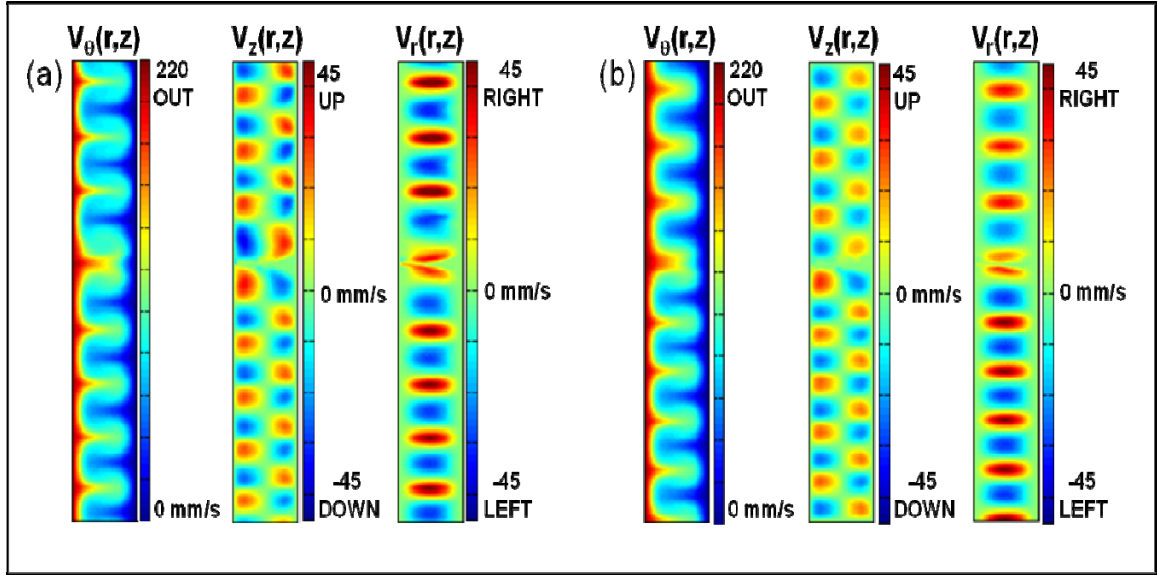


Figure 5.7. Single column two-fluid transient simulations of the Azimuthal (θ), axial (z) and radial (r) direction velocity maps at $\Omega_{inner}=14\text{rps}$ for a stratified two layer system consisting of (a) 0.65 cSt silicone oil and water and (b) 1.65 cSt silicone oil and water.

Figure 5.8 compares side-by-side the experimental and simulation velocity maps for the 1.65 cSt silicone oil and water system at the 14 rps inner cylinder rotation rate. Appendices B and C describe the methods of data analysis used for experiments and simulations, respectively. The lengths of the water and 1.65cSt silicone oil waves as well as the length of the wave containing the interface from the simulation are shorter than those from the experiment. The simulations for this two-fluid system at 14 rps were rerun using a refined mesh.

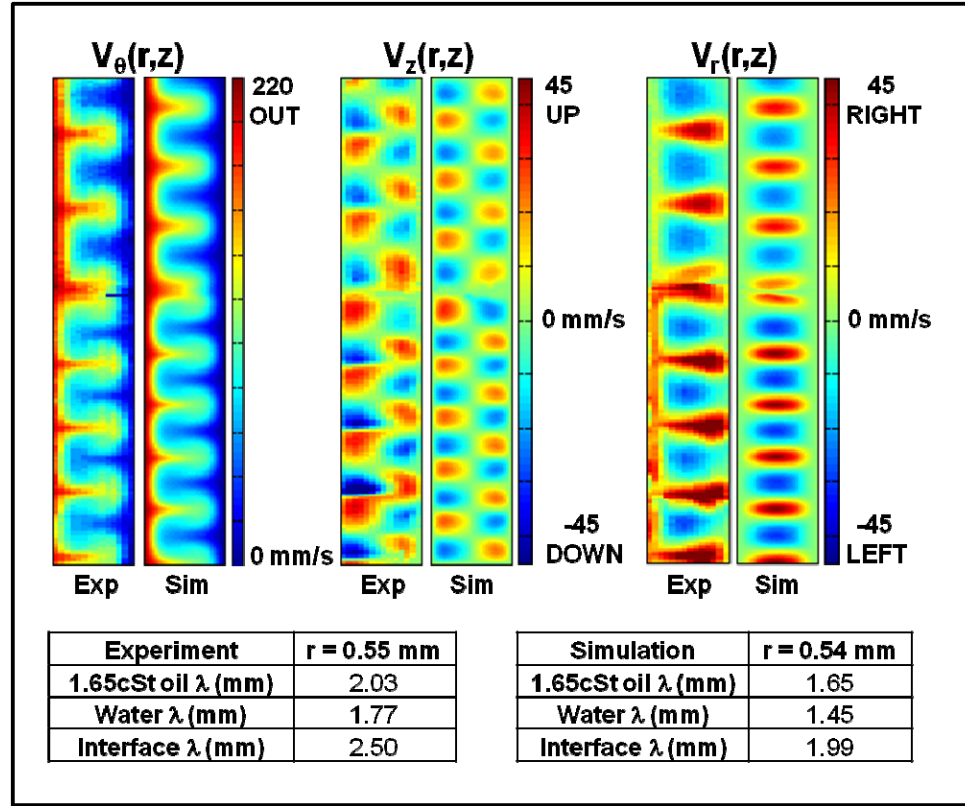


Figure 5.8. Comparison of experimental and simulated azimuthal, axial and radial direction single column velocity maps for the 1.65cSt oil and water two-fluid system at $\Omega_{inner}=14 \text{ rps}$.

Figure 5.9 compares the experimental velocity maps and wavelengths to those of the refined mesh simulations. For this simulation, the discretization time was $\Delta t = 0.001 \text{ s}$ and the total elapsed time was $t = 50 \text{ s}$. The quantitative agreement between experiment and simulation is quite good, especially considering the hysteretic nature and sensitivity to initial conditions of these flows [84, 85]. Similar discrepancies between experimental and simulation wavelengths were found for the 0.65cSt silicone oil and water system at 14 rps, and mesh refinement improved the agreement.

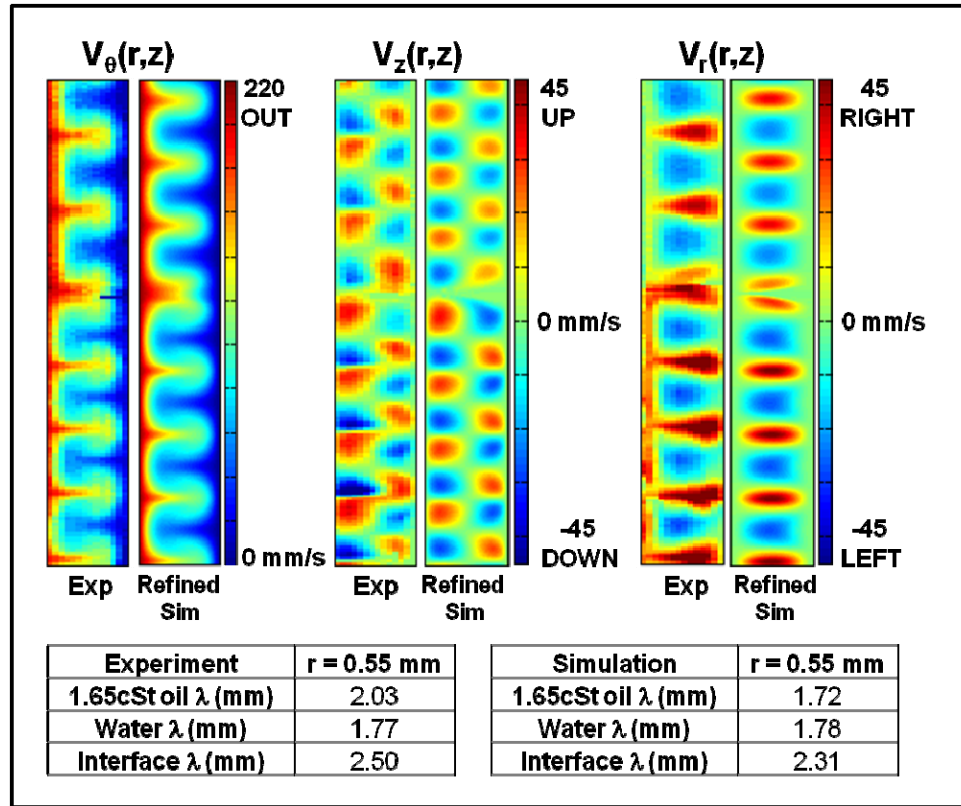


Figure 5.9. Comparing (a) experiment and (b) simulation with refined mesh axial direction velocity maps, velocity profiles and wavelengths for the 1.65cSt oil and water two-fluid system at $\Omega_{\text{inner}}=14 \text{ rps}$.

Another attempt to improve the wavelength agreement between experiment and simulation relied on using the refined mesh transient solution of Fig. 5.9 as the starting point for a steady state model. The motivation for this was that this would be a better representation of experiment since the experimental velocity maps were averaged for several hours, and for experiments the inner cylinder rotation rate was ramped up slowly from zero to 14 rps. There was almost no change in the simulation wavelengths after 50,000 steady state iterations.

In Figure 5.10, the single fluid column comparison of the 1.65cSt silicone oil and water system experiments and simulations at 7 rps, Fig. 5.10 (a), and 8 rps, Fig. 5.10 (b),

are presented. At 7 rps, Fig. 5.10 (a), the 1.65cSt silicone oil $T=1699$ is still in the stable Couette flow regime, as expected, and this is clear in both experiment and simulation as there are no radial or axial velocity components. The water $T=4627$ is in the unstable TVF regime as reflected in both experiment and simulation. In both the experiment and simulation at 7 rps, just above the interface in the oil, faint vortices can be seen. This observation indicates that the flow is perturbed at the interface and that the instability moves from the interface into the viscous oil. There is a significant difference in the wavelength of the water Taylor vortices for the experiment and the simulation.

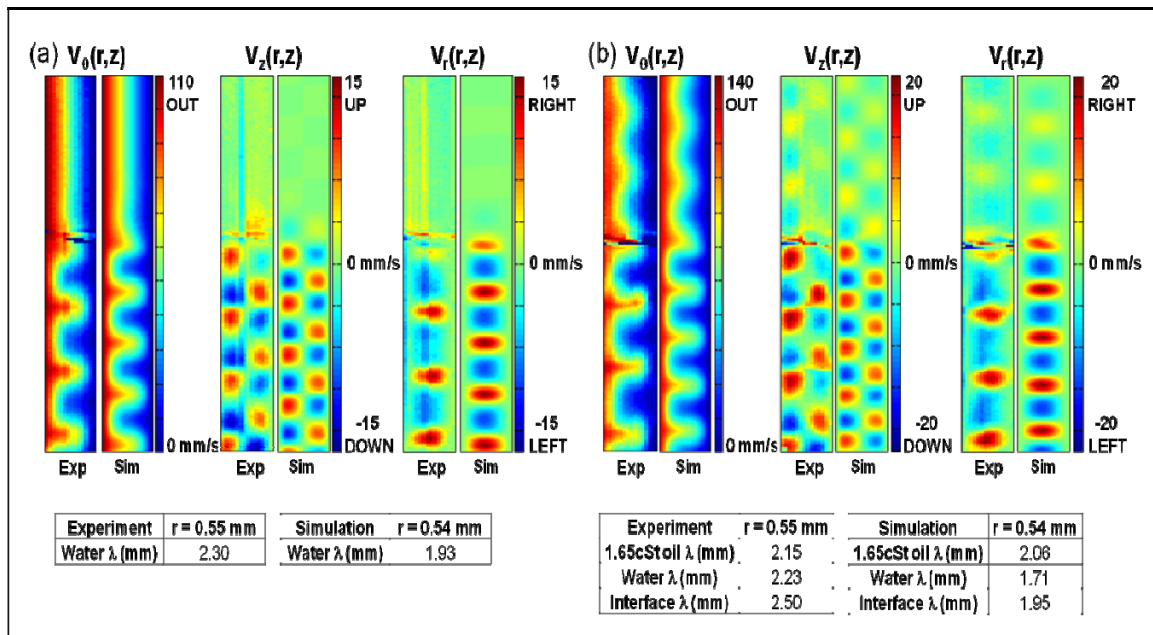


Figure 5.10. Comparison of experiments to transient simulations of two-fluid axially stratified flow for 1.65cSt oil and water at (a) 7 rps and (b) 8 rps.

At 8 rps, Fig. 5.10 (b), both the 1.65cSt silicone oil $T=2220$ and the water $T=6043$ are experiencing TVF. In the radial direction simulation velocity map, the initial splitting of the out flowing radial jet can be seen. In the 8 rps velocity maps from the experiments, the chemical shift artifact at the interface makes it difficult to see interfacial details. The

wavelengths of the Taylor vortices in the water, in particular, are not a good match between experiments and simulations. Given that the wavelength is known to be strongly affected by initial conditions [84, 85], it is not surprising that there are wavelength discrepancies since for the experiments the inner cylinder rotation rate was ramped slowly from zero to the operational rotation rate, and for the simulations, the inner cylinder rotation was a sudden start at the operational rotation rate. However, the general flow features are remarkably well reproduced by the simulations.

Steady State Simulations of Two-fluid TVF. Initially, simulations of the two-fluid systems undergoing Taylor vortex flow were conducted using steady state models. These simulations were mistakenly simulated using a rotating rather than stationary bottom spacer (see to Fig. 5.2). The resulting simulated velocity maps show the same features as expected based on experiments. Namely, the two-fluid interface splits a radial out flowing jet into two jets, and a region of zero velocity occurs in both the radial and axial direction velocity maps at the location of the interface. The steady state rotating bottom spacer velocity map simulations for 1.65cSt silicone oil and water at 14 rps are shown in Fig. 5.11. Upon realizing that the bottom spacer had been simulated as rotating when it was known to be stationary in experiments, the steady state simulations were re-run using a stationary bottom spacer boundary condition. Figure 5.12 displays the corresponding solution for 1.65 cSt silicone oil and water at 14 rps. Observe that the interface now splits a low velocity radial inflowing jet, *i.e.* flow is towards the rotating inner cylinder, which is in direct contradiction to every two-fluid experiment conducted to date. To confirm that this simulation was not a fluke, it was repeated and the same

result obtained. Additionally, 1.65 cSt silicone oil and water steady state simulations at 7 and 8 rps and 0.65 cSt silicone oil and water steady state simulations at 4, 5 and 14 rps using the stationary boundary condition were run. All of these showed the interface to be splitting an inflowing instead of an outflowing radial jet.

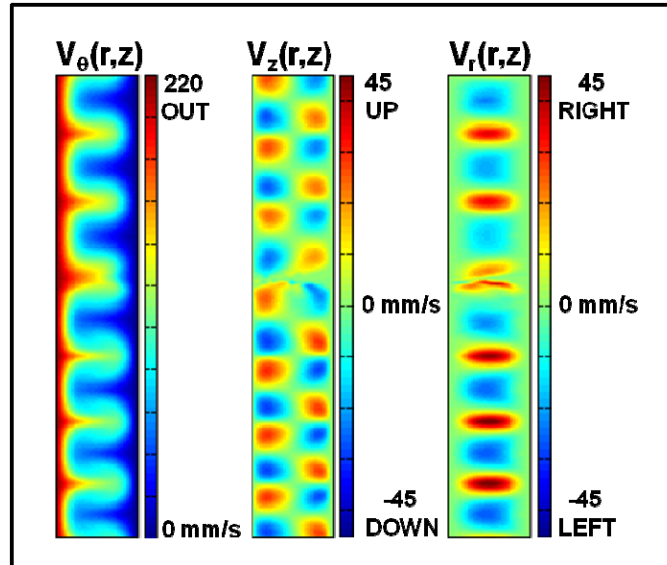


Figure 5.11. Steady state simulations of 1.65cSt silicone oil and water for and inner cylinder rotation rate of 14 rps. The bottom spacer boundary condition was set as rotating at 14 rps.

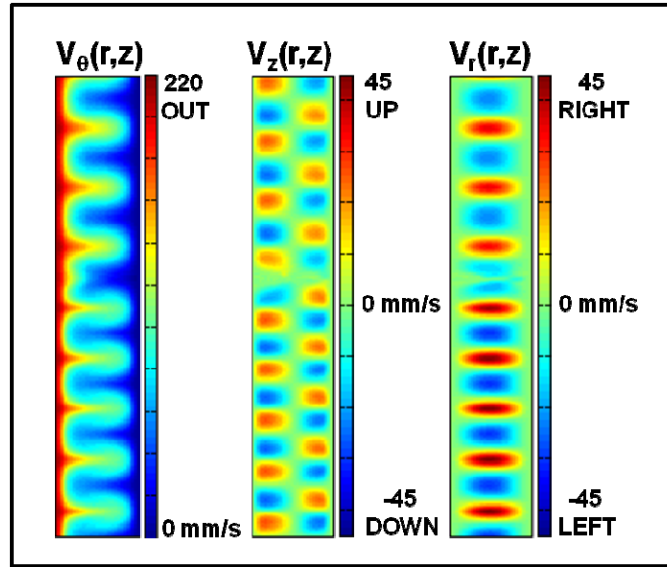


Figure 5.12. Steady state simulations for 1.65cSt silicone oil and water for an inner cylinder rotation rate of 14 rps. The bottom spacer boundary condition was set to be stationary.

Since the two-fluid TVF experiments could not be accurately reproduced via steady state simulations using the stationary bottom boundary condition, the switch to time-dependent simulations was made. Consultation of the Fluent Theory Guide [79] revealed that the volume of fluid model is generally used to compute transient solutions. “A steady-state VOF calculation is sensible only when your solution is independent of the initial conditions and there are distinct inflow boundaries for the individual phases [79].” It was not obvious that a steady state solution for the two-fluid Taylor vortex flow would be insufficient, and this was determined only *a posteriori*.

It is interesting that the steady state solution using a rotating bottom boundary condition produced the same qualitative flow features as those captured experimentally. This is likely a result of the Taylor vortex hydrodynamic instability being non-unique.

Conclusions

Axially stratified immiscible two-fluid velocity mapping experiments and transient volume of fluid simulations at rotation rates that produce unstable Taylor vortex flow in both fluids show that the interface undergoes purely azimuthal $v_\theta(r)$ flow with no secondary v_r or v_z flows. Good qualitative comparison between experiments and simulations provide mutual validation of the two approaches for studying vertically stratified two-fluid Taylor vortex flow. The wavelength discrepancies between experiments and simulations confirm the sensitivity of TVF to initial conditions.

The apparently robust phenomena of a significant zero plateau in the secondary flows that form in TVF at the interface of two axially stratified fluids may have potential for pinning solid particles or biological cells between fluids using buoyancy forces. The ability to pin a biological cell or particle at the interface in order to treat portions with different reagents has the prospect of supplying new capabilities for cellular biology [86-88] and offers new approaches to microreactor design. This work was submitted to the journal, *Experiments in Fluids*, in January 2011.

HYDRODYNAMIC DISPERSION DUE TO A BUOYANCY DRIVEN FLOW INSTABILITY

Introduction

Motivation

Characterization of a jet-in-tube reactor (Fig. 6.2) was initially motivated by collaboration with Bend Research, Inc (BRI). Many drug compounds are poorly-water soluble, and dissolution is often the rate-limiting step to drug absorption by the human body [89]. Low drug compound solubility leads to poor bioavailability. Increasing the drug content of a formulation to compensate for the low bioavailability can lead adverse physiological effects (AEs). Thus, methods to enhance solubility and bioavailability without increasing drug loading are critical.

There are technologies to mitigate the problem of low solubility such as spray dried dispersions (SDDs) [90, 91], lipid systems and self-assembled nanoparticles. These technologies reduce poor solubility and bioavailability by optimizing the chemical environment so as to maximize drug absorption. This is accomplished by the formation of the amorphous drug/polymer nanostructures and small aggregates of these structures [92]. These structures constitute a stable amorphous, high-energy form of drug that can rapidly dissolve due to their small size. In the case of nanoparticles, the surface area of poorly water-soluble drug particles is greatly increased, which also contributes to solubility enhancement and improved bioavailability. Scientists and engineers at BRI use a jet-in-tube reactor to precipitate self-assembled nanoparticles containing active

pharmaceutical ingredient (API) as well as inactive delivery and stability enhancing ingredients [93].

Jets and Plumes

Free boundary flows are frequently encountered in natural and engineered systems. The boundary free flow resulting from momentum input alone is termed a “jet,” and the flow arising from only a buoyancy force is called a “plume.” Characteristics of buoyant jet flow, such as stability, depend on the dimensionless Froude and Reynolds numbers. The Froude number characterizes the ratio of inertial forces to buoyancy forces acting on the jet fluid and the jet Reynolds number characterizes the ratio of inertial to viscous forces acting on the jet fluid. They are defined as

$$Fr = \frac{U}{\sqrt{g'R}} \quad (6.1)$$

and

$$Re = \frac{UR}{\nu}. \quad (6.2)$$

The jet radius R is the characteristic length and g' is the reduced gravity which for a positively buoyant jet is defined as $g' = g(\rho_{tube} - \rho_{jet})/\rho_{jet}$. U is the characteristic velocity of the jet, defined here as the average velocity $U = Q/\pi R^2$ where Q is the volumetric flow rate of the fluid in the jet, and ν is the kinematic viscosity of the jet fluid.

Turbulent buoyant jets are frequently encountered in nature and in waste disposal systems for their ability to dilute waste by turbulent entrainment and dilution and have thus been the focus of many of the buoyant jet studies [94-99]. The majority of studies

conducted on laminar buoyant jets have relied on thermal rather than compositional buoyancy driving forces [100, 101]. The destabilizing effects of thermal buoyancy on laminar buoyant jets was studied and very small amounts of buoyancy were found to destabilize the flow [102]. Very low Reynolds number ($Re \sim 10^{-1}$ - 10^{-4}) compositionally buoyant plumes were investigated by emitting a lower density fluid into a higher density fluid from a point source. In particular, the ability of the lower density fluid to entrain the higher density fluid was studied [103]. Compositionally and thermally buoyant jets of varying Froude numbers Fr (6.1) were studied by Anwar [104]. For $Fr < 5^{1/2}/2$, it was found that the motion in the jet is laminar and becomes unstable a certain distance above the nozzle, and that the length of the laminar region is dependent on the jet Reynolds number Re (6.2) [104]. Positively buoyant jets are those driven by both momentum and buoyancy in the upward direction, *i.e.* opposite gravity. A laminar positively buoyant jet which results from pumping a lighter fluid out of a 500 μm diameter jet into a slow moving heavier fluid with both fluids flowing counter to gravity is studied here.

The experiments presented here investigate the breakup of a positively buoyant jet for laminar flow conditions in a jet-in-tube mixer and quantify the resulting transverse and longitudinal hydrodynamic dispersion. The data provide the potential to characterize the dominant contribution to the hydrodynamic dispersion arising from the buoyant breakup of the jet which occurs on a time scale much shorter than that of the Taylor-Aris contribution to the hydrodynamic dispersion. The main experiments, which will be the focus of the publication of this work, were conducted with water as the outer (tube) fluid at a volumetric flow rate of 90 mL/hr, $Re_{tube} = 10$ and acetone as the (inner) jet fluid at a

volumetric flow rate of 10 mL/hr, $Re_{jet} = 17$ and $Fr_{jet} = 0.55$. For experiments in which water was used in the jet as well as the tube, the same volumetric jet flow rate was used, 10 mL/hr, yielding $Re_{jet} = 7$ and $Fr = \infty$ since there are no buoyancy forces present.

The research presented in this chapter began on a far simpler experimental system than that which motivates the study. The characterization work described in this chapter was performed on laminar jets ($Re_{jet} \sim 17$), of lower velocity than those used industrially (Re_{jet} of order 100-1000). The flows in these laminar jets are dominated by buoyancy forces rather than inertial forces. The quantification of mixing in the hydrodynamic instability driven breakup of the buoyant laminar jet is of importance in natural plumes in the environment [105] as well as of fundamental interest in fluid dynamics [106].

Theory of Stochastic (Diffusive) Processes

A brief review of the theory of stochastic processes, in particular of Brownian motion theory, is appropriate as these methods will be drawn on heavily in analyzing the time-dependent hydrodynamic dispersion coefficients measured for the buoyancy-driven instability that occurs in the acetone-water system. In Chapter 3, it was explained how pulsed gradient spin echo (PGSE) NMR experiments are used to measure self-diffusion. Specifically, self-diffusion refers to the random molecular motion which arises due to thermal energy for a single molecular species, *i.e.* there is no chemical potential driving force. The first experimental observation of the effects of molecular motion is attributed to the botanist, Robert Brown, who observed the jittery motion of pollen grains floating in water. The random motion of particles suspended in a fluid is referred to as *Brownian motion*, and is now understood to occur as a result of the fluid molecules being in

constant motion and colliding with the particle. Einstein [107] and Sutherland [108] made the connection between this molecular motion and thermal energy. The *Stokes-Einstein-Sutherland Relation* relates the diffusion coefficient D_p of a Brownian particle (diameters of 1-5 μm) to its radius R_o and its mobility in a solvent of viscosity μ at temperature T ,

$$D_p = \frac{kT}{6\pi\mu R_o}. \quad (6.3)$$

Here k is Boltzmann's constant $1.3805 \cdot 10^{-23}$ J/K. The denominator of (6.3) is the friction or drag coefficient, $f=6\pi\mu R_o$, for the particle in the Stokes flow regime.

The Langevin equation is an equation of motion with both deterministic and random components. For a particle with velocity $\mathbf{u}$, the Langevin equation is written as [109, 110],

$$m \frac{d\mathbf{u}}{dt} = -f\mathbf{u} + \mathbf{R}(t). \quad (6.4)$$

The particle drag force, $-f\mathbf{u}$, is deterministic whereas $\mathbf{R}(t)$ is a random force, which describes a stochastic process that changes randomly over time. The motion of a particle, $\mathbf{u}(t)$, is stochastic as well since it is generated by the stochastic $\mathbf{R}(t)$ driving force.

Dividing through by the particle mass m and plugging the initial condition $\mathbf{u}(0) = \mathbf{u}_o$ into (6.4) the explicit solution to the Langevin equation is found to be [109]

$$\mathbf{u}(t) = \mathbf{u}_o e^{(-\gamma t)} + e^{(-\gamma t)} \int_0^t e^{(\gamma t')} \frac{\mathbf{R}(t')}{m} dt'. \quad (6.5)$$

Here $\gamma=f/m$ and $\mathbf{R}(t)$ now represents the velocity fluctuation for the fluid molecules. For Brownian motion, it is assumed that $\mathbf{R}(t)$ is a Gaussian white noise process with average $\overline{\mathbf{R}(t)} = 0$ and time correlation function $\overline{R(t)R(t')} = \Gamma\delta(t - t')$,

where Γ is the amplitude of the noise. In the case of large Brownian particles relative to the surrounding fluid molecules, the force $\mathbf{R}(t)$ acting on the particle results from a great many collisions of the fluid molecules so that the Gaussian property is expected to be valid by the central limit theorem. Furthermore, the time constant for the motion of the fluid molecules will be much shorter than the characteristic time of the much larger Brownian particle. This separation in time scales is characteristic of Brownian motion.

Given (6.5) and $\overline{R(t)R(t')} = \Gamma\delta(t - t')$, the time correlation function for the velocity fluctuation of the Brownian particle is found to be [109]

$$\overline{u(t_1)u(t_2)} = \left(u_o^2 - \frac{\Gamma}{2\gamma}\right)e^{-\gamma(t_1+t_2)} + \frac{\Gamma}{2\gamma}e^{-\gamma|t_1+t_2|}. \quad (6.6)$$

The equilibrium behavior of (6.6) is determined by taking the limit as $t_1, t_2 \rightarrow \infty$, for $\tau = t_1 - t_2$ finite. The Brownian particle velocity fluctuation correlation behavior is

$$\overline{u(\tau)u(0)} = \frac{\Gamma}{2\gamma}e^{-\gamma\tau}. \quad (6.7)$$

This is the classic exponential velocity fluctuation decay of Brownian motion where τ is the correlation time of the velocity fluctuations of the particle. Transport processes that exhibit this behavior are referred to as Ornstein-Uhlenbeck processes [111]. However, this result was first derived by G.I. Taylor for turbulent mixing in 1921 [112].

Evaluating the short and long time limits of the mean squared particle displacement or average displacement variance $\overline{z^2(t)}$ provides important understanding about the time-dependence of simple diffusion. For a Brownian particle, the displacement $z(t)$ is simply the time integral of its velocity and the average displacement variance is

$$\overline{z^2(t)} = \frac{2\overline{u^2}}{\gamma} \left(t + \frac{1}{\gamma} e^{-\gamma t} - \frac{1}{\gamma} \right). \quad (6.8)$$

Defining the correlation time $\tau_c = 1/\gamma$ and taking the limit of (6.8) as $t \rightarrow 0$ ($t \ll \tau_c$) the short time limit average variance is

$$\overline{z^2(t)} = \gamma \overline{u^2} t^2, \quad (6.9)$$

and the limit of (6.8) as $t \rightarrow \infty$ ($t \gg \tau_c$), i.e. the equilibrium behavior, of the displacement variance is found to be

$$\overline{z^2(t)} = \frac{2\overline{u^2} t}{\gamma}. \quad (6.10)$$

Recognizing that $\overline{u^2}$ is the mean squared velocity from Maxwell's relation for the kinetic theory of gases in one-dimension,

$$\overline{u^2} = \frac{k_B T}{m},$$

and plugging this result into (6.10), it is evident that $\overline{u^2}/\gamma = D$ and

$$\overline{z^2(t)} = 2Dt. \quad (6.11)$$

A subtlety worth noting is that D , the diffusion coefficient of the Brownian particle, is the ratio of the fluid molecules' velocity fluctuation to the dissipation of the particle's motion due to the fluid's viscosity and the amplitude of the noise correlation Γ is proportional to the friction coefficient on a per mass basis γ and the thermal energy $k_B T$, thus relating the fluctuation and the dissipation [109]. Application of the theory of Brownian motion is not limited to actual Brownian particles. In general, Brownian motion theory applies to any system with a fluctuating motion of a mode in a macroscopic dynamical system [109]. Brownian motion theory has been applied to turbulent motion [112, 113], porous

media [114], polymer dynamics [115], colloidal hydrodynamics [116], Taylor-Aris hydrodynamic dispersion [117] and a myriad of other applications.

For diffusive behavior in the short time limit, theory predicts that variance scales as t^2 with time and the diffusion coefficient is a linear function of time, as depicted in Fig. 6.1 (solid line). This short time limit behavior is termed *ballistic* motion. In the long time limit, variance is linear with respect to time and the diffusion coefficient asymptotes to a constant value as shown in (6.11), Fig. 6.1 (solid line). Systems experiencing periodic dynamics due to a potential such as in the caging of fluid molecules in a dense fluid [118] or a damped Brownian harmonic oscillator [119] exhibit a maximum in the pre-asymptotic regime as illustrated with the dash line of Fig. 6.1.

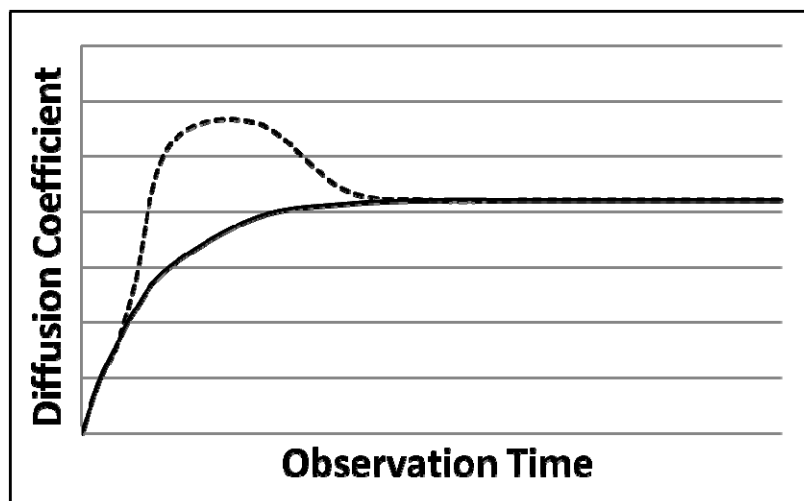


Figure 6.1. Simple diffusion (solid line). At short times, the diffusion coefficient scales linearly with time and at long times, the diffusion coefficient is time independent. Time-dependent pre-asymptotic diffusion (dashed line).

A focus of this chapter is measurement via dynamic PGSE NMR of hydrodynamic dispersion coefficients to characterize the breakup of an acetone jet in water due to a buoyancy driven instability. In the “Results and Discussion” section of

this chapter, time-dependent transverse (to the flow direction) hydrodynamic dispersion coefficients are presented as a function of position downstream of the jet exit into the water. A pre-asymptotic maximum was found for the time-dependent dispersion coefficient obtained for a 2 mm thick slice centered 66 mm past the jet exit. The measurement of the time-dependent pre-asymptotic dispersion coefficient $D(t)$ via PGSE NMR is significant because using the Green-Kubo relations $D(t)$ can be defined in terms of a time correlation function as the time integral of the velocity autocorrelation function (VACF) $\Psi(t)$ [120]. The VACF is the normalized self correlation function of advective velocities $\mathbf{v}$

$$\psi(t) = \frac{\overline{\mathbf{v}(0)\mathbf{v}(t)}}{\overline{\mathbf{v}^2}}. \quad (6.12)$$

The pre-asymptotic dispersion coefficient is defined as

$$D(t) = \overline{\mathbf{v}^2} \int_0^t \psi(t') dt'. \quad (6.13)$$

Thus, in using PGSE NMR to measure $D(t)$ the VACF is characterized. At the end of this chapter, the observation time at which pre-asymptotic dispersion is maximized is used to calculate a characteristic transport length for the breakup of the acetone jet. Dynamic PGSE NMR experiments have previously been found to provide length scale characterization of porous media due to the protons in water sampling the pore structure via molecular diffusion [26, 27] and advection [121, 122]. Advection has also been used to characterize the length scale of coherent vortical structure using PGSE NMR [30]. The non-equilibrium statistical mechanics theory of dispersion has recently been used to interpret the unique features of the pre-asymptotic dispersion regime as measured via

PGSE NMR in order to determine the characteristic transport length scale in open-cell foams [123, 124]. In this context, a non-equilibrium statistical mechanics model of the VACF in terms of its memory function $K(t)$ is shown to qualitatively provide a model for the measured pre-asymptotic dispersion behavior. This provides a new modeling approach based on non-equilibrium statistical mechanics for mixing in hydrodynamic instability driven flows which have coherent flow structures [106].

Materials, Experimental Apparatus and Flow Visualization

The vertical jet-in-tube mixer was operated with laminar flows running opposite gravity (Fig. 6.2). That is, the jet was positively buoyant since momentum and buoyancy forces both acted in the upward direction. Water was used as the tube fluid. (CuSO_4 -doped water and deuterated water were used for a handful of experiments). Either acetone or water was used as the jet fluid (acetonitrile was used as the jet fluid for one set of exploratory experiments). There is a significant difference in density, 21%, between acetone $SG_{\text{acetone}}=0.79$ and water $SG_{\text{water}}=1$.

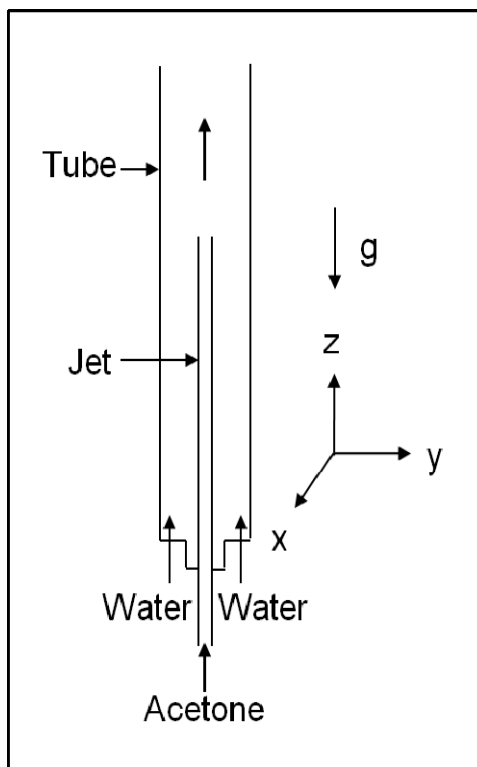


Figure 6.2. Schematic of the jet-in-tube device.

The polyether ether ketone (PEEK) jet had an inner diameter of 500 μm and the tube was made of glass with inner diameter equal to 3.3 mm. To prevent the jet from vibrating and to center the jet as much as possible within the tube, two ~ 20 mm long centering devices constructed of Delrin, were constructed to fit tightly around the outside of the jet. The centering devices had six grooves for the tube fluid to flow through, and an outer diameter of ~ 3.3 mm so that they were secure against the inside of the glass tube. (The jet-in-tube device used and the centering devices were constructed by Doug Millard of Bend Research, Inc). The acetone was pumped to the jet using a Harvard Apparatus 22 syringe pump with a 100 mL glass syringe. The water was pumped to the tube using a Pharmacia LKB-500 High Precision pump.

Digital images of the water-water and acetone-water jet-in-tube flows were taken for the jet-in-tube device operating on the bench top. The jet fluid was dyed with crystal violet to aid the visualization of the flow path and features.

Magnetic Resonance Experiments

A Bruker DRX 250 MHz vertical wide bore spectrometer, a 3D gradient coil (1.728 T/m) and a 5 mm ^1H radiofrequency (rf) probe maintained at 20°C were used for all magnetic resonance experiments conducted.

Chemical Selective Propagator Experiments

A slice selective PGSE velocity probability distribution, *i.e.* propagator, MR experiment with a chemical selective excitation pulse was implemented to measure flow velocity in the z-direction. The pulse sequence is illustrated in Fig. 6.3. The excitation pulse was made to be chemically selective as depicted in Fig. 6.4 in order to separate the dynamics of the jet fluid from the tube fluids' dynamics. A slice selective Gaussian-shaped refocusing pulse is employed to select a 2 mm thick slice in the axial direction. Displacement encoding pulsed gradients of duration $\delta=0.44\text{ms}$ were applied in the z-direction, *i.e.* the direction of flow. A displacement encoding observation time $\Delta=5\text{ ms}$ was used. An eight-part phase cycle was employed and spoiler gradients were applied in the x-direction before and after the refocusing pulse to minimize artifacts while maximizing the signal-to-noise ratio.

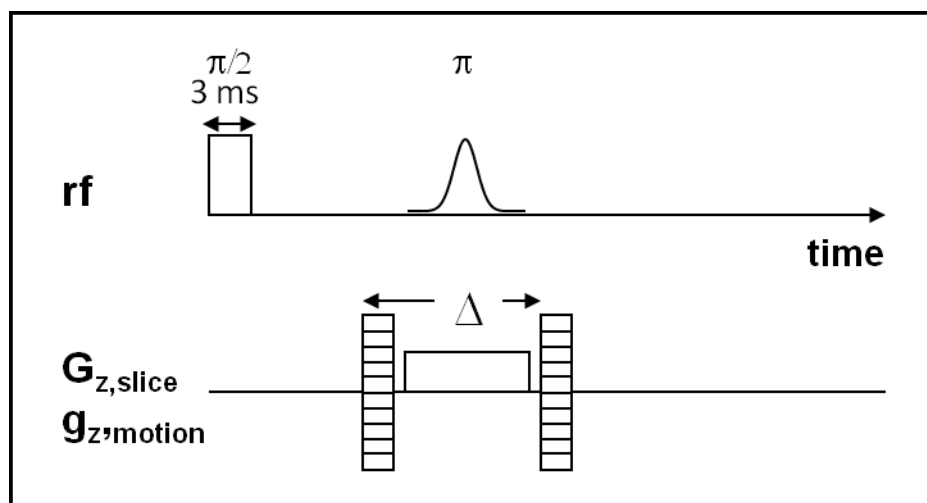


Figure 6.3. Pulse sequence for the slice and chemical selective PGSE propagator experiment.

A chemical shift selective propagator experiment was implemented in order to measure separately the dynamics of the acetone in the jet and the water in the tube. In addition to needing to differentiate the solvent dynamics from the water dynamics, it was also necessary to use chemical shift techniques to simply resolve the dynamics of the jet fluid. There was so much more signal from the large volume of tube fluid, water, that the dynamics of the jet fluid could not be resolved until the 90° rf excitation pulse was modified to be chemical shift selective. In order to make the excitation pulse chemical selective, the spectrometer's basic frequency was set as the Larmor frequency of acetone, thereby tuning the spectrometer to the solvent's frequency. Then, a rectangular excitation pulse of long duration, 3 ms, so that in the reciprocal, *i.e.* frequency, domain it selected a sinc-shaped region of narrow bandwidth, 426 Hz. The combination of tuning the spectrometer to the solvent's resonance frequency and setting up the excitation pulse so that it just selected the solvent peak in the frequency domain, made it possible to selectively excite the solvent protons.

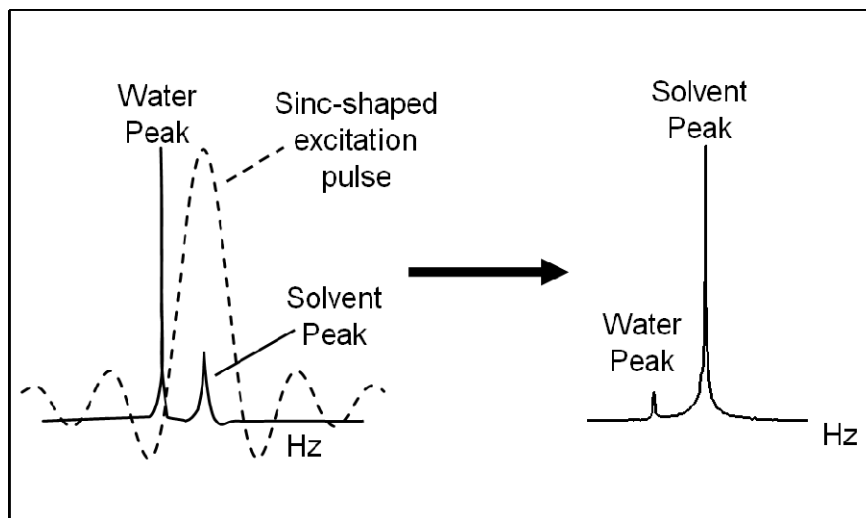


Figure 6.4. Frequency-domain illustration of the effects of a chemical selective excitation pulse.

In order to use chemical shift advantageously to measure the differing dynamics of the jet and tube fluids, the tube fluid was chosen to be deionized water and the jet fluid an organic solvent with sufficiently good chemical shift to resolve the jet fluid using a chemical selective 90° excitation pulse. Acetone and acetonitrile are two such organic solvents [125].

NMR “Invisible” Tube Fluid Propagators Experiments

Another method to distinguish the jet flow from the tube flow was to use a fluid in the tube that either experienced such rapid signal decay or contained no proton, ^1H , nuclei so that the tube fluid would be effectively NMR invisible and all signal would arise from the jet fluid only. Doping the water flowing in the tube with CuSO_4 to a concentration of 400mM CuSO_4 (SG=1.04) caused its signal to decay via T_2 relaxation so rapidly that there was no signal from the tube fluid for a 20 ms echo time. Another NMR invisible tube fluid, 99.8% deuterium oxide or deuterated water, D_2O , was used for several

experiments. Deuterium, ^2H , is NMR invisible when using a proton, ^1H probe. Therefore, there was no signal from the tube fluid in these experiments. The disadvantage to using 99.8% D₂O is the expense, \$489/1000g from Cambridge Isotopes in February 2010.

Separate experiments using CuSO₄-doped water and deuterated water as the tube fluid are presented in the Results and Discussion section. The slice selective PGSE pulse sequence from Fig. 6.3 was modified so that the excitation pulse was 50 μs long providing broadband frequency excitation, Fig. 6.6, for these experiments, thus eliminating the chemical selection as it was unnecessary when using the “NMR invisible” tube fluids.

Velocity Mapping Experiments

Spatially resolved maps of x and z-direction velocities were made using the PGSE velocity mapping sequence shown in Fig. 6.5. The excitation and refocusing rf pulses were both 2 ms sinc pulses with slice selection on the refocusing 180° pulse only. In the single PGSE motion-encoding experiment, the net accumulated phase $\phi = \gamma \delta \mathbf{g} \Delta \mathbf{v}$ is captured in the measured signal. Since the phase is measured, and γ , δ , $\mathbf{g}$ and Δ are known values, the velocity can be calculated.

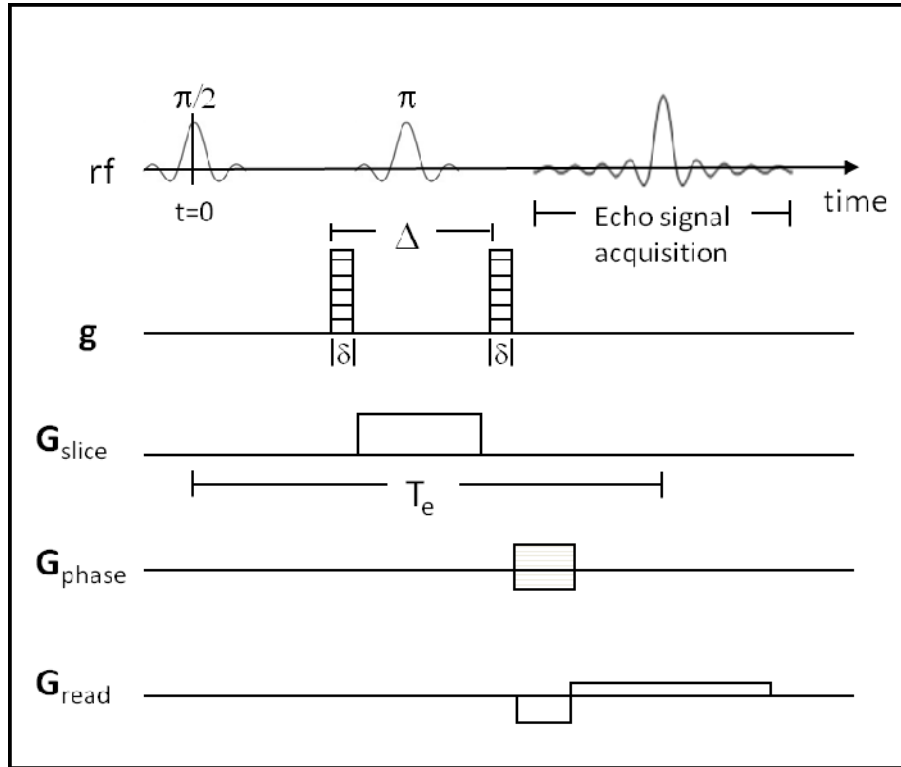


Figure 6.5. Single PGSE motion-encoding pulse sequence for velocity mapping.

All the velocity maps presented have a $45\mu\text{m}^2/\text{pixel}$ in plane resolution over a 1 mm thick slice, recovery time $T_R=2.5$ s, displacement encoding pulsed gradient duration $\delta=0.94$ ms, displacement encoding observation time $\Delta=4.142$ ms. The z-direction velocity maps have 40 averages, which corresponds to a total experiment time of approximately 7 hr. For the x-direction velocity mapping experiments, the number of averages used was varied.

Stejskal-Tanner Diffusion Experiments

In PGSE diffusion experiments, pulsed gradients of varying amplitude are applied and the echo signal attenuates as a function of the gradient amplitude and proton spin

motion. The straight line that results from plotting $\log(E)$ versus $\gamma^2 \delta^2 g^2 (\Delta - \delta/3)$ for a single constant diffusion coefficient is known as the *Stejskal-Tanner* plot [20, 22]. The slope of this line is the effective diffusion coefficient D . Slice selective single PGSE NMR diffusion experiments (Fig. 6.6) using 16 q -points, pulsed gradient duration $\delta=0.44$ ms and varying displacement observation times Δ were conducted. These experiments were not chemical selective, therefore a 50 μ s rectangular-shaped excitation pulse was used.

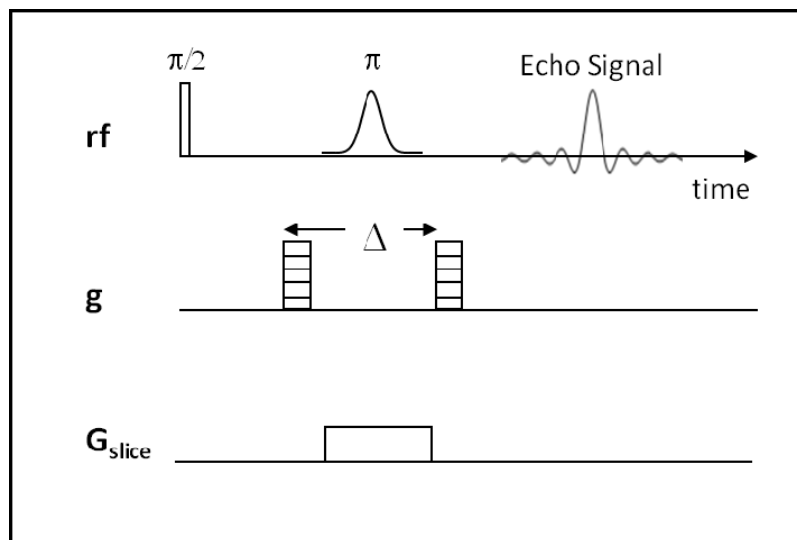


Figure 6.6. Slice selective single PGSE motion-encoding pulse sequence.

In an idealized diffusion-free laminar flow, the velocity gradients arising due to shear stress cause molecules that begin their flow history in close proximity on adjacent streamlines to gradually separate. Reversing the laminar flow would return the molecules to their initial positions, thus cancelling their separation. This reversible, coherent separation differs from that which occurs with the spreading due to the stochastic sampling of velocities as self-diffusion causes molecules to cross streamlines, *i.e.* Taylor-

Aris hydrodynamic dispersion [117, 126]. This incoherent spreading is irreversible. PGSE NMR makes it possible to separate the effects of coherent spreading and stochastic dispersion through the double PGSE experiment, which has the same effect as flow reversal [23, 127]. The double PGSE pulse sequence shown in Fig. 6.7 uses its second pair of pulsed gradients to cancel the phase shifts that occur due to coherent flow during the first pulsed gradient pair application [8]. The double PGSE experiment measures the stochastic fluctuations in motion over the timescale 2Δ [23, 127].

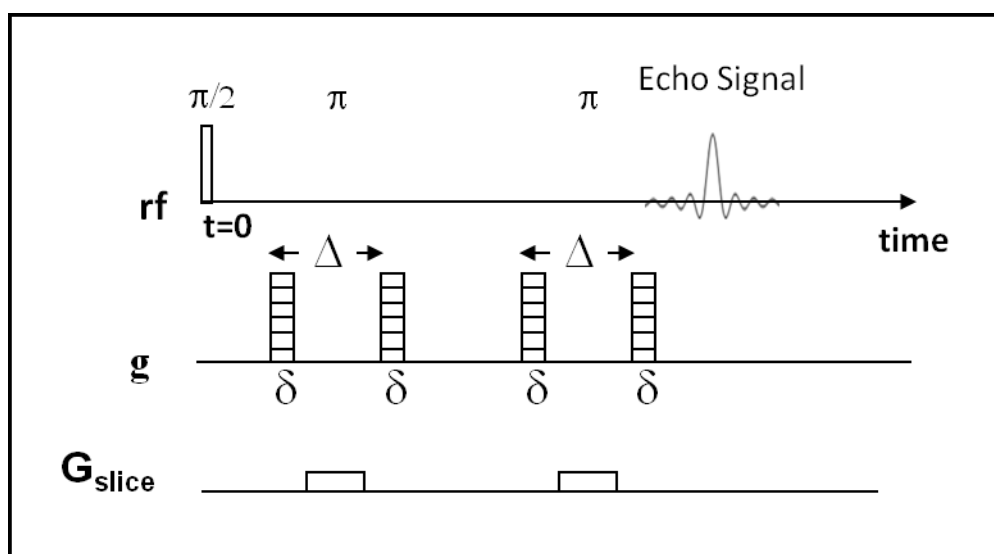


Figure 6.7. Slice selective double PGSE motion-encoding pulse sequence.

The water-water system experiments consisted of 32 averages, taking ~ 13 min for an experiment. Due to the fluctuating motions for the acetone-water system, particularly at 66 mm and 80 mm past the jet exit, the diffusion data was far noisier than that for the water-water system so 128 averages, 52 min, were used for the acetone-water diffusion experiments.

Results and Discussion

Bench top Flow Visualization

For the digital images displayed in Fig. 6.8, the jet fluid was dyed with crystal violet to aid the visualization of the jet fluid flow path. Under the laminar flow conditions used in this study, when present, buoyancy forces dominate the inertial forces which arise from pumping the fluids. The buoyancy forces cause the acetone to accelerate out of the jet into the surrounding water. Figure 6.8 (b) shows a digital image of the buoyancy driven instability for acetone flowing from the jet at 10 mL/hr and water flowing at 90 mL/hr. For comparison, Fig. 6.8 (a) shows a digital image of water flowing from the jet at 10 mL/hr and water flowing in the tube at 90 mL/hr. The water-water system is stable and laminar over the entire 100 mm region past the jet exit and only slight spreading of the jet is apparent. This is due to the fact that the only mixing mechanism present is Taylor dispersion which occurs over the timescale, $R^2/D \sim 20$ min. In contrast the buoyant jet is unstable and significant mixing is evident over the 100 mm region past the jet exit. The observed flow regime transitions for the buoyancy driven instability shown in Fig. 6.8(b) are:

- Laminar flow (0-50 mm). The acetone is confined to a thin, threadlike region, and no mixing of the two fluids is observed. When this image is magnified, the interface between the acetone and the water can be seen to be wobbly.
- Jet breakup (50-60 mm). The acetone jet disintegrates into discrete vortex-like packets of fluid.

- Growth (60-70 mm). The vortices grow possibly due to entrainment of water [103].
- Vortex collision and bursting (70-90 mm). Drag forces and the diminishing magnitude of the buoyancy force due to the two miscible fluids mixing away density gradients cause the larger vortices farther downstream of the jet to decelerate. Then smaller, faster vortices closer to the jet to run into the large decelerated vortices. This collision bursts the vortices, thus mixing the acetone and water.
- (100 mm +). The acetone and water are increasingly well mixed with increasing distance from the jet and there are no clear flow structures remaining.

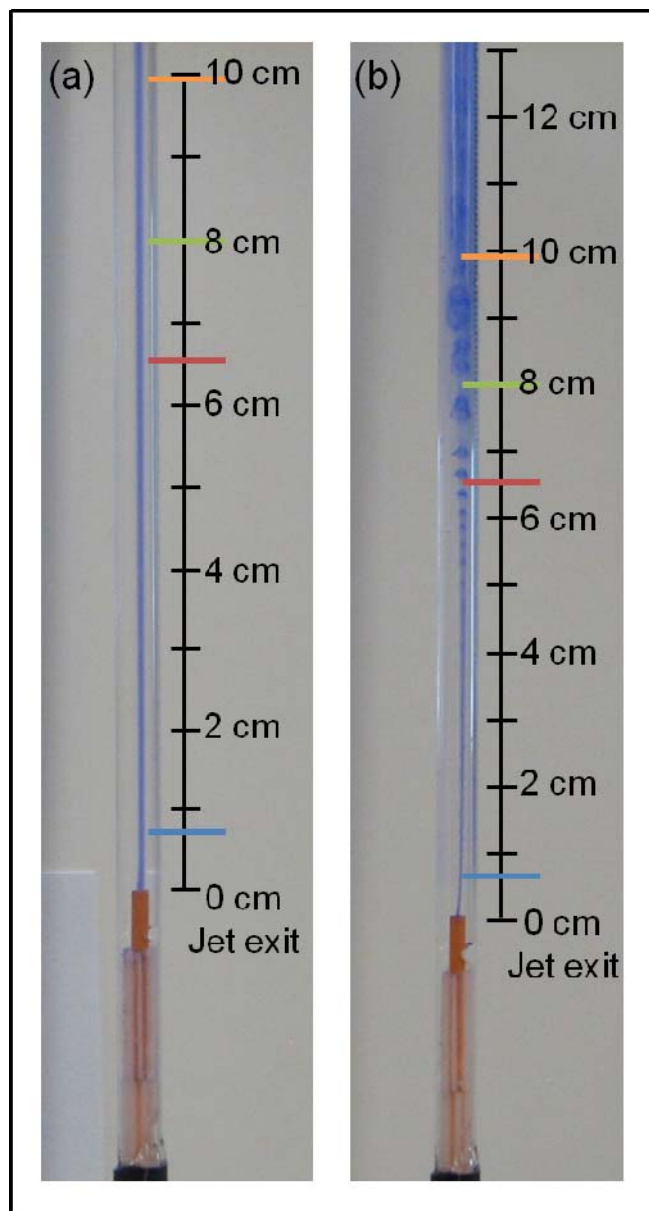


Figure 6.8. Digital images of the jet-in-tube mixing device with crystal violet dissolved in the jet fluid to aid flow visualization for (a) volumetric flow rates of 10 mL/hr water exiting the jet and 90 mL/hr water as the surrounding tube flow and (b) volumetric flow rates of 10 mL/hr acetone exiting the jet and 90 mL/hr water in the tube. The colored lines at 7 mm, 66 mm, 80 mm and 99 mm past the jet exit highlight the positions at which MR velocity mapping and dispersion experiments were run.

Chemical Selective Propagators

Axial direction acetone selective propagators for 10 mL/hr acetone flowing from the jet and 90 mL/hr water flowing from the tube are displayed in Fig. 6.9 (a). (As an aside, these propagators are the best acetone selective propagators measured out of dozens of experiments. This is mostly due to the acetone selective rf excitation pulse being exceptionally well-tuned to the acetone peak). Four propagators of varying slice position relative to the jet exit are displayed on two plots to aid visualization. For acetone flowing at 10 mL/hr in the 500 μm inner diameter jet, $Re_{jet} \sim 17$, and by definition the flow is laminar. The velocity probability obtained from the 2 mm slice positioned over the jet, triangles in Fig. 6.9 (a), is the characteristic Poiseuille flow hat-shaped function [128], which shows that in the jet there is an equal probability for all velocities from 0 to the maximum velocity $v_{max} \sim 28$ mm/s. Just 3.5 mm past the jet, squares in Fig. 6.9 (a), the acetone selective propagator shows that the acetone has accelerated out of the jet due to the effects of buoyancy forces. At this position, the propagator has retained its hat-shape, indicating that molecular diffusion or other mixing mechanisms in the transverse direction are not yet significant, and thus the proton spins have not had enough time to randomly sample streamlines with different velocities, the phenomenon known as Taylor-Aris dispersion [126]. For flow in the glass tube, the timescale for Taylor dispersion in the water-water system is $R^2/D \sim 20$ min where $R = 1.65 \times 10^{-3}$ m is the radius of the glass tube and $D = 2.1 \times 10^{-9}$ m²/s is the molecular diffusion coefficient for water. In the acetone-water system the Taylor dispersion time scale is ~ 10 min since the molecular diffusion coefficient for acetone is $D = 4.4 \times 10^{-9}$ m²/s. The low magnitude velocity peak

(near zero) is signal from the water. Despite having used an acetone-selective experiment, signal from the water protons is present. Proton exchange between the acetone and water molecules as the two fluids mix is likely the primary cause for the presence of the water peak.

By 44 mm past the jet exit, diamonds in Fig. 6.9 (b), the acetone is already decelerating relative to its maximum velocity at the 3.5 mm slice position. The shape of the distribution is Gaussian-like, indicating some randomizing transport process is occurring. Again, the velocity peak closest to zero is due to proton exchange between the two fluids. Protons initially on acetone molecules during the excitation pulse have exchanged positions with protons on water molecules so that the dynamics of the water are being convoluted with those of the acetone. At 88 mm past the jet exit (circles in Fig. 6.9), the acetone velocities have slowed significantly so that now the acetone and water velocity distributions overlap, and the dynamics are not readily distinguished.

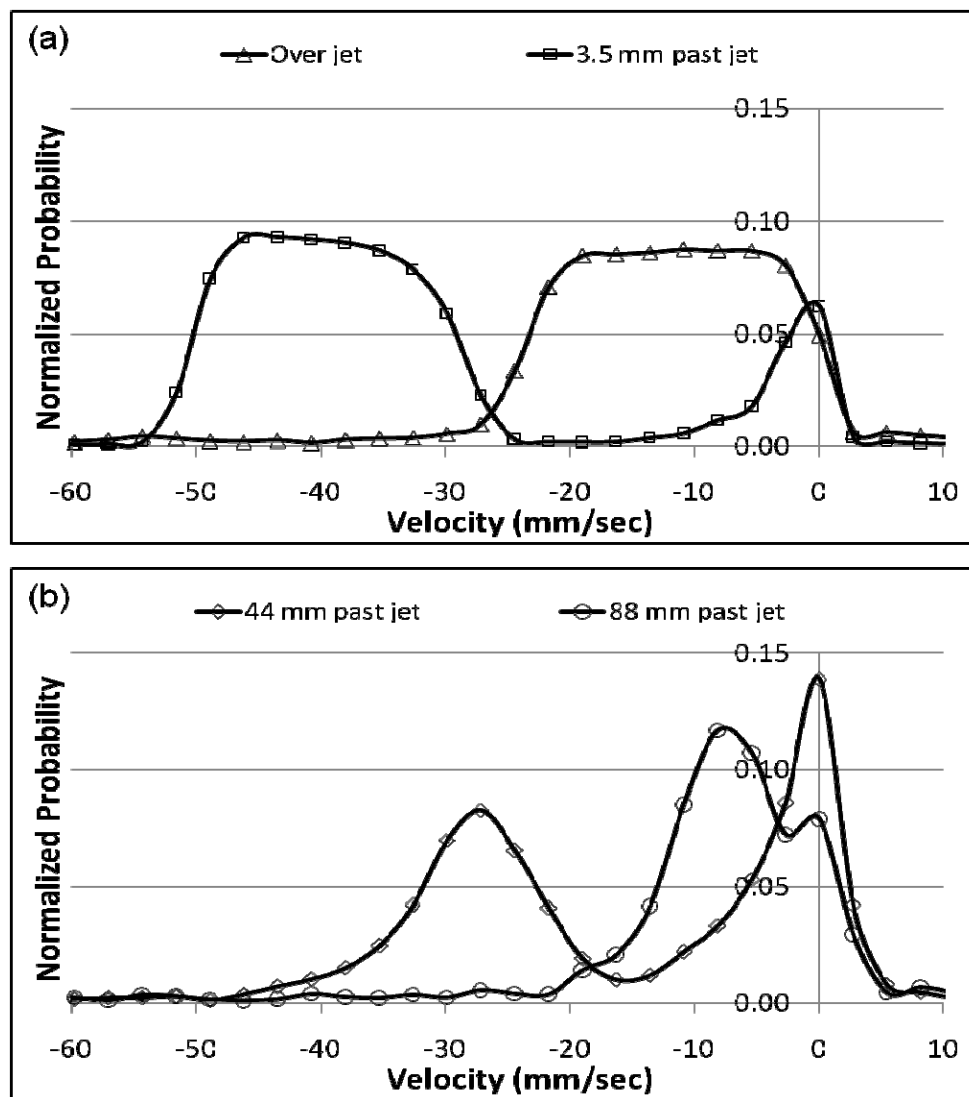


Figure 6.9. Acetone selective z-direction propagators as a function of position past the jet exit for a jet flow of 10 mL/hr acetone and a tube flow of 90 mL/hr water.

The chemical selective propagator experiment was found to have limited applicability for measuring velocities at slice positions past the jet exit since the acetone and water exchange protons when in contact. Chemical selection requires a physical boundary between the different chemical species in order to avoid proton exchange. However, the chemical selective experiments did make it possible to see the acetone signal, which was previously hidden by the water signal because the water was in such

large excess compared to the acetone, and provided insight into the progression of the acetone dynamics while acetone and water mixing occurred.

Thermodynamic Considerations

Two two-fluid systems, acetone-water and acetonitrile-water, were tested in the jet-in-tube system, Fig. 6.10, with the organic solvent flowing through the jet and the water flowing in the tube. Both acetone ($MW=58.08$ g/mol) and acetonitrile ($MW=41.05$ g/mol) are completely miscible in water. The specific gravities of acetone and acetonitrile are equal, $SG=0.79$. Therefore, the buoyancy forces caused by the density difference between acetone and water in the acetone-water system and between acetonitrile and water in the acetonitrile-water system are equal.

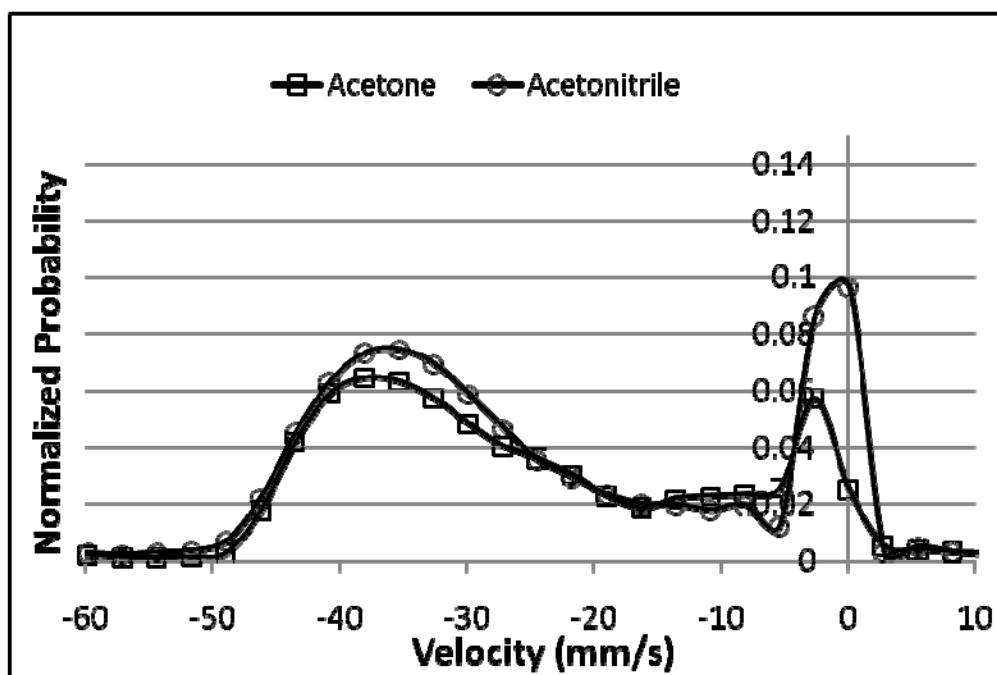


Figure 6.10. Acetone selective (squares) and acetonitrile selective (circles) axial (z) direction propagators for a 2 mm slice centered 1 mm past the jet exit. The peaks at velocities near zero arise due to proton exchange between the acetone and water molecules.

The goal of these experiments was to consider the effects of mixing thermodynamics and how they might be contributing to the bulk fluid motions measured in the propagator experiments. For each two-fluid system, volumetric flow rates of 10 mL/hr for the jet and 90 mL/hr for the tube were used. For the acetone-water system, this resulted in a solution with acetone mole fraction $x_{\text{acetone}} = 0.027$ and for the acetonitrile-water system the solution had an acetonitrile mole fraction $x_{\text{acetonitrile}} = 0.037$.

For the low organic solvent concentrations used, the final solutions can reasonably be assumed to be ideal [129, 130] for thermodynamic calculations. The Gibb's Free Energy of mixing per mole of solution was calculated for an ideal solution [131]

$$\Delta G_{\text{mix}} = RT(x_1 \ln x_1 + x_2 \ln x_2)$$

Where R is the ideal gas constant 8.314 J/mol K, T is temperature in K, x_1 is the solvent mole fraction and x_2 is the mole fraction of water. For the acetone-water system, $\Delta G_{\text{mix}} = -298$ J/mol and for the acetonitrile-water system $\Delta G_{\text{mix}} = -385$ J/mol. The difference in ΔG_{mix} for the two two-fluid systems is simply due to slightly lower mole fraction of acetone in the acetone-water system compared to the mole fraction of acetonitrile in the acetonitrile-water system, and this reflects a slightly different chemical potential between the two-fluid systems.

The enthalpy of mixing ΔH_{mix} for the two two-fluid systems was calculated using calorimetric data [132] for acetone-water and acetonitrile-water solutions. The available calorimetric data was plotted and then a best fit parabolic equation was determined for the dilute solution. This equation was then used to calculate $\Delta H_{\text{mix}} = -246$ J/mol of x_{acetone}

= 0.027 solution and $\Delta H_{mix} = 0.9$ J/mol of $x_{acetonitrile} = 0.037$ solution. Figure 6.11 shows the ΔH_{mix} versus solvent mole fraction plots for acetone-water and acetonitrile-water solutions, respectively. Clearly, the acetone-water mixing is exothermic and the acetonitrile-water system is slightly endothermic.

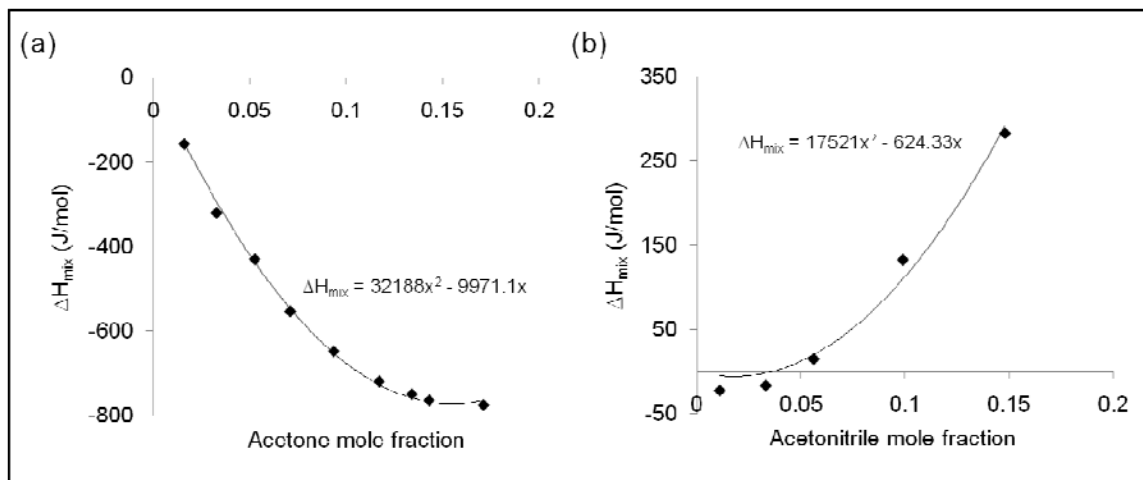


Figure 6.11. (a) Acetone-water solution enthalpy of mixing versus acetone mole fraction and (b) acetonitrile-water solution enthalpy of mixing versus acetonitrile mole fraction.

This thermodynamic data taken in light of the overlaid acetone and acetonitrile chemical selective propagators, Fig. 6.10, indicates that buoyancy is the primary force behind the flow instability since the propagators match up so closely even though the enthalpy of mixing values are very different. The change in density in the acetone-water system due to exothermic effects is small compared to the 21% difference in density between acetone and water. The chemical potential driving force, *i.e.* ΔG_{mix} , between the acetone and water and the acetonitrile and water also contributes to mixing, particularly transverse mixing. Future experiments matching density while varying chemical potential could provide further insight into chemical potential mixing but these were not attained in this work.

NMR “Invisible” Fluid Propagators

Propagator experiments were conducted using 400mM CuSO₄ in water (SG=1.04) as the tube fluid, Fig. 6.12 (a), in order to relax the signal from the tube fluid so quickly that it did not contribute to the propagator measurement, thus yielding a measurement of the jet fluid velocity distribution only. Additionally, propagator experiments using 99.8% D₂O (SG=1.1) as the tube fluid, Fig. 6.12 (b), were conducted. Since the deuterium, ²H, nuclei resonate at $\omega_0=38$ MHz in the 5.9 T magnet they are not detectable by the 250 MHz proton, ¹H, probe. The resulting propagator thus provides a measurement of the jet fluid velocity distribution only. For both the 400 mM CuSO₄ in water (Fig. 6.12 (a)) and 99.8% D₂O (Fig. 6.12 (b)) tube fluid experiments, deionized water was used as the jet fluid.

Since the same volumetric flow rates of deionized water, 10 mL/hr, were used for both sets of experiments, the velocity distribution for the 2 mm thick slice positioned over the jet (blue squares), *i.e.* the velocity distribution for the water inside the jet, has the same hat-function shape characteristic of Poiseuille flow in both Fig. 6.12 (a) and (b). For laminar, Poiseuille flow in a jet with inner diameter equal to 500 μ m and volumetric flow rate equal to 10 mL/hr, the average velocity will be $v_{avg}=14$ mm/s and the maximum velocity is $v_{max}=2v_{avg}=28$ mm/s. The maximum velocity for the water within the jet for both two-fluid systems is ~ 28 mm/s as expected. For positions downstream of the jet exit, where the water has exited the jet and is interacting with the NMR “invisible” tube fluid, the propagator width, *i.e.* the range in velocities, differs between the two experiments. Notice in particular, the 7 mm past the jet position (green triangles) in Fig.

6.12 (a) and the 9 mm past the jet position (green triangles) in Fig. 6.12 (b). For both propagators, the jet fluid has accelerated relative to its average and maximum velocities experienced at the 1 mm past the jet position (red triangles). At the farthest position past the jet exit for the H₂O-400 mM CuSO₄ system $v_{avg} \sim 20$ mm/s and $v_{max} \sim 30$ mm/s and for the H₂O-D₂O $v_{avg} \sim 25$ mm/s and $v_{max} \sim 33$ mm/s. The difference in velocities between the two systems is due to the difference in the buoyancy forces acting on the water. Since the 400 mM CuSO₄ solution has a specific gravity of 1.04, the buoyancy forces acting on the water are lower in this two-fluid system than in the H₂O-D₂O system of Fig. 6.12 (b) as the specific gravity of D₂O is 1.1. Propagator experiments using 200 mM CuSO₄ water (SG=1.02) as the outer fluid (not shown) were also conducted. Due to the smaller buoyancy force, the H₂O-200 mM CuSO₄ system propagator experiments showed a smaller range in velocities at the same position relative to the jet exit than the H₂O-400 mM CuSO₄ experiments.

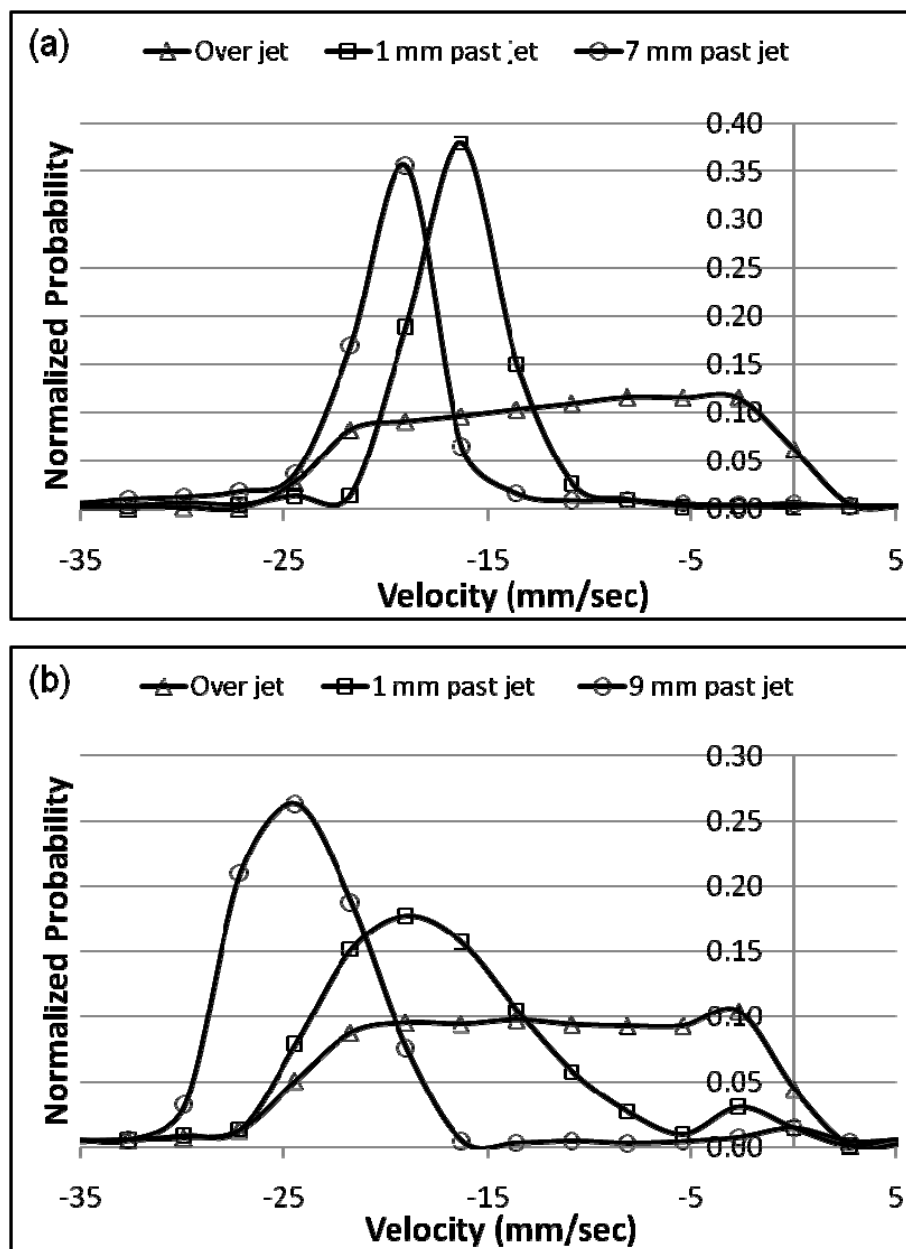


Figure 6.12 Axial (z) direction velocity distributions for the (a) water-400 mM CuSO_4 system and (b) water-99.8% D_2O system. Each propagator experiment was averaged over a 2 mm slice at the specified axial location relative to the jet and observation time $\Delta=5$ ms.

The NMR “invisible” tube fluid experiments were useful for two primary reasons.

First, these experiments confirmed that the buoyancy force was the primary driving force behind the flow instability observed in the bench top experiments and that the propagator measurement was sensitive to small changes in the density difference between the jet fluid and the tube fluid. Second, the NMR “invisible” fluid experiments confirmed that the chemical shift selective propagator experiment for the acetone-water and acetonitrile-water two-fluid systems was far from perfect and that a significant amount of signal from the water tube fluid was contributing to the propagator experiment which was intended to measure only the acetone (or acetonitrile) dynamics.

Velocity Maps

Longitudinal (xz plane) x-direction velocity maps for the water-water jet-in-tube system are presented in Figure 6.13 for a jet flow of 10 mL/hr water, $Re_{jet}=7$. For the x-direction velocity map with the center located 7 mm past the jet exit, Fig. 6.13 (a), secondary flows due to entrance effects are present near the jet. At only 4 mm past the jet exit, these secondary flows no longer remain, and the system is in well-developed stable laminar flow. Looking farther downstream from the jet exit, Fig. 6.13 (b)-(d), the longitudinally oriented x-direction velocity maps show no secondary flows for the water-water system, as is expected for this low Reynold’s number flow.

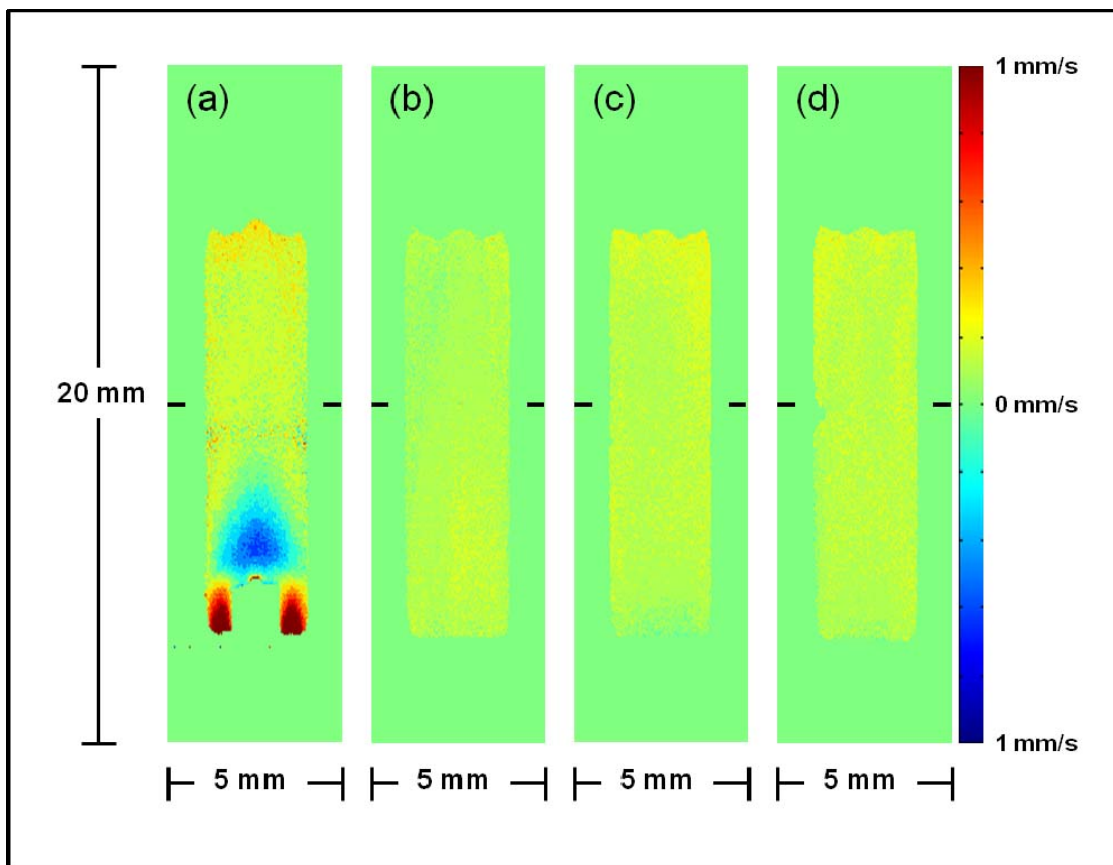


Figure 6.13. X-direction (into and out of the plane of the page) MR velocity maps for water flowing in both the jet (10 mL/hr) and tube (90 mL/hr). The center of the image (black lines on each velocity map) in (a) corresponds to 7 mm past the jet exit (b) corresponds to 66 mm past the jet exit (c) corresponds to 80 mm past the jet exit, and in (d) corresponds to 99 mm past the jet exit. Aside from some entrance effects seen around the jet in the velocity map of (a), there are no secondary flows seen in the water-water jet-in-tube flow system. Resolution=1000x45x45 μm^3 .

For the acetone flowing at 10 mL/hr from the jet and water flowing at 90 mL/hr as the tube fluid, the x-direction velocities around the jet flow's exit into the tube, Fig. 6.14 (a), are higher in velocity magnitude and persist farther downstream than those for the water-water system. The more intense secondary flows seen in the acetone-water system at the jet exit are due to the effects of the buoyancy forces causing the acetone to accelerate out of the jet as seen in the chemical selective propagator experiments shown

in figures 6.9 and 6.10. The center of the velocity map shown in Fig. 6.14 (b) is 66 mm past the jet exit and secondary flows are evident and intense. For figures 6.14 (c) and (d), with center points 80 mm and 99 mm past the jet exit, respectively, secondary flows remain, however, by 99 mm past the jet exit, they are less intense as the acetone and water become well mixed (see Fig. 6.8 (b)).

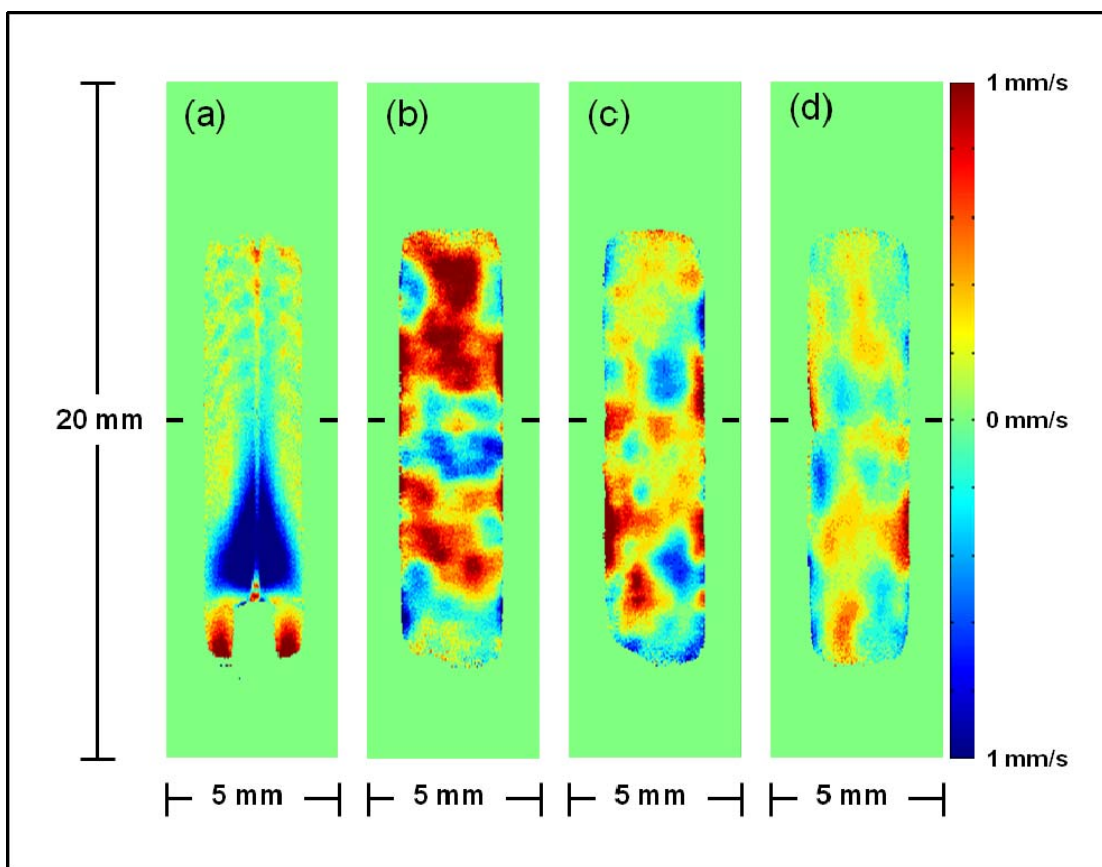


Figure 6.14. X-direction (into and out of the plane of the page) MR velocity maps for acetone flowing in the jet (10 mL/hr) and water flowing in the tube (90 mL/hr). The center of the image (black lines on each velocity map) in (a) corresponds to 7 mm past the jet exit (b) corresponds to 66 mm past the jet exit (c) corresponds to 80 mm past the jet exit, and (d) corresponds to 99 mm past the jet exit. Resolution=1000x45x45 μm^3 .

Axial (z-direction) velocity maps for the water-water (Fig. 6.15) and acetone-water (Fig. 6.16) systems at varying positions relative to the jet exit continue to illustrate

the significant differences between the two systems due to the buoyancy-driven instability. As stated previously, for laminar, Poiseuille flow in a 500 μm jet with a volumetric flow rate of 10 mL/hr, the maximum velocity is 28 mm/s. The water-water and acetone-water velocity maps averaged over a 1 mm slice positioned over the jet, Fig. 6.15 (a) and Fig. 6.16 (a) respectively, measure the anticipated maximum velocity, 28 mm/s, and are indistinguishable. This is as expected since the volumetric flow rates for both systems are matched, and no buoyancy forces act on the acetone-water system before the acetone exits the jet. At all positions characterized past the jet exit, the axial flow is unchanging for the water-water system. Furthermore, the water flow from the jet into the tube water decelerates immediately after exiting the jet and a steady-state Poiseuille tube flow is achieved merely 7 mm past the jet exit. The water-water flow is parabolic as shown in the velocity profiles presented in Fig. 6.17.

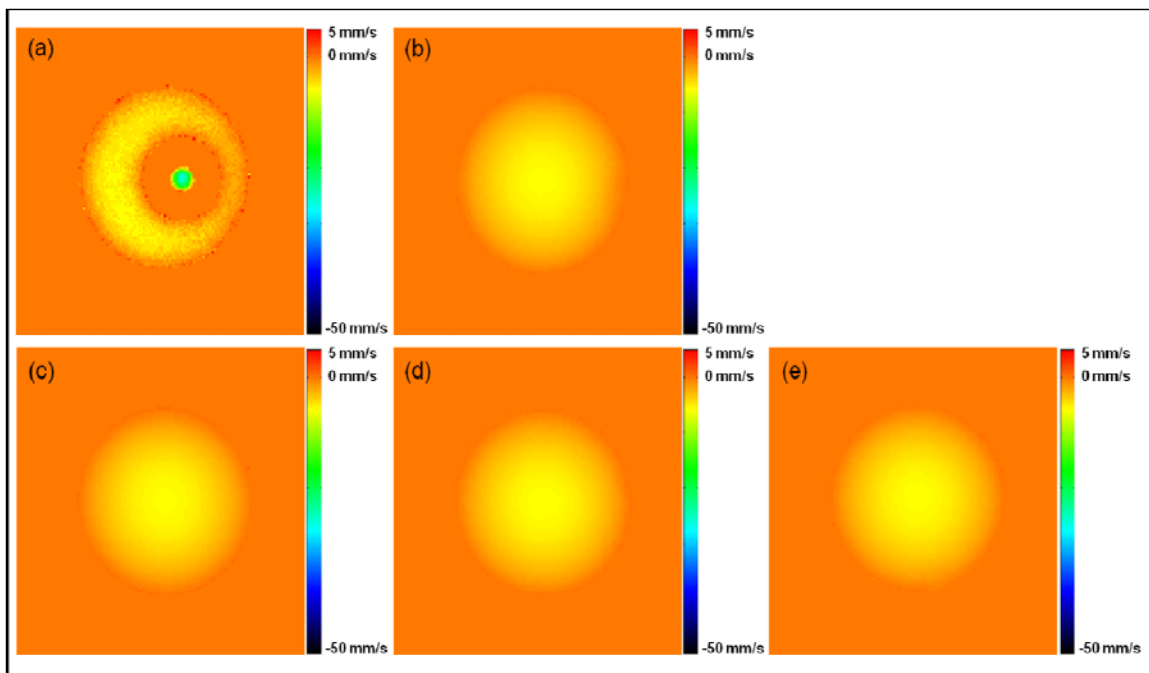


Figure 6.15. Axial z-direction velocity maps and velocity profiles taken from the center column of the corresponding velocity map for water flowing in the jet 10 mL/hr and water flowing in the tube 90 mL/hr. For each velocity image, z-direction velocities for a 1 mm thick slice centered at the z-position a) 7 mm past the jet exit (blue line in Fig. 4) and b) 93 mm past the jet exit. In the profiles, open squares are the experimental data and open circles are the Poiseuille model data for the same maximum velocity. Velocity map resolution = $45 \times 45 \times 1000 \mu\text{m}^3$.

Conversely, the acetone-water z-direction velocity maps illustrate an extremely dynamic system. In Fig. 6.16 (b), the velocity map for the 1 mm slice positioned 7 mm past the jet exit, the acetone from the jet has accelerated due to the action of buoyancy forces, and maximum velocities of nearly 60 mm/s are measured. At 66 mm past the jet exit $v_{\text{max}} \sim 22$ mm/s, at 80 mm $v_{\text{max}} \sim 20$ mm/s and at 99 mm $v_{\text{max}} \sim 13$ mm/s, figures 6.16 (c)-(e) respectively. Thus, the acetone-water system z-direction flows decelerate as the system becomes increasingly well mixed forming a solution of uniform density [103].

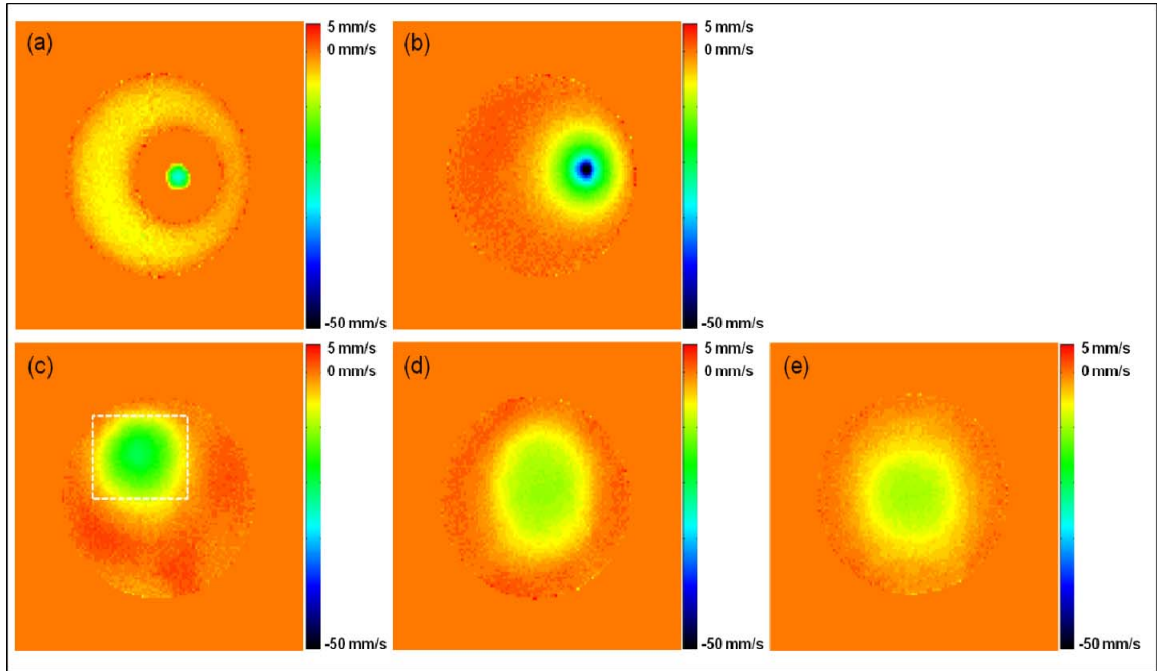


Figure 6.16. Axial z-direction velocity maps for acetone flowing in the jet 10 mL/hr and water flowing in the tube 90 mL/hr. For each velocity image, z-direction velocities are averaged over a 1 mm thick slice centered at the z-position (a) over the jet (b) 7 mm past the jet exit (c) 66 mm past the jet exit (d) 80 mm past the jet exit and (e) 99 mm past the jet exit. Resolution= $45 \times 45 \times 1000 \mu\text{m}^3$.

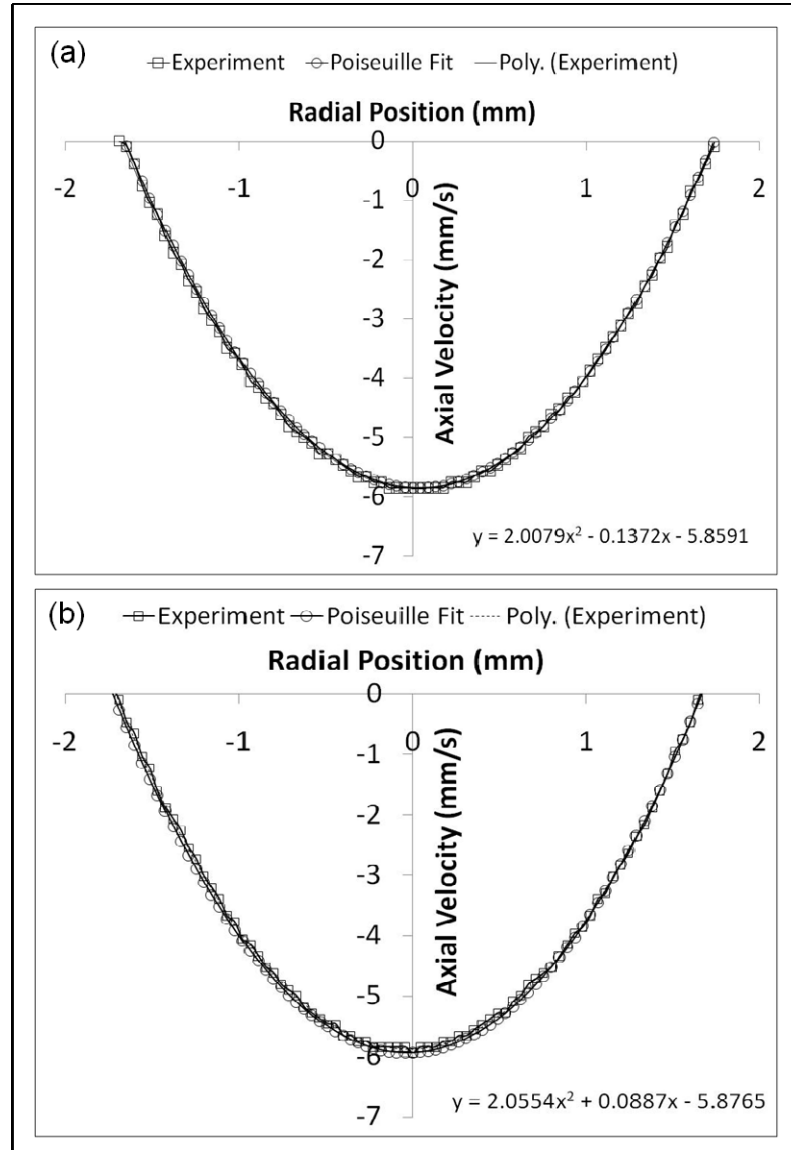


Figure 6.17. Axial (z-direction) velocity profiles for the water-water jet-in-tube system. The center lines of the velocity maps presented in Fig. 6.10 (b) and (e) respectively, were selected so that the profile in (a) is positioned 7 mm past the jet exit and (b) is positioned 99 mm past the jet exit.

Hydrodynamic Dispersion Coefficients

Figure 6.8 highlights the positions at which flow and effective diffusion measurements were taken. These positions were purposely chosen in order to measure

and compare the flow dynamics as the flow transitions into the different flow regimes of the buoyancy driven instability, Fig. 6.8 (b). At the 7 mm position, the laminar region of flow was characterized. At 66 mm past the jet exit, the acetone jet has disintegrated into discrete fluid packets and these are growing. At 80 mm past the jet exit, the expanded fluid packets are colliding and bursting so that there is considerable mixing. Finally at 99 mm past the jet exit, the acetone and water are well-mixed.

The molecular self-diffusion coefficients for pure water and pure acetone were measured at $T=20^{\circ}\text{C}$ in an NMR test tube. The molecular self-diffusion coefficient for pure water at $T=20^{\circ}\text{C}$ was measured to be $D_{\text{water}}=2.1 \times 10^{-9} \text{ m}^2/\text{s}$, which agrees with the accepted value [56] and serves as a calibration. The molecular self-diffusion coefficient for pure acetone at $T=20^{\circ}\text{C}$ is $D_{\text{acetone}}=4.4 \times 10^{-9} \text{ m}^2/\text{s}$. Diffusion experiments were conducted on a well-mixed solution of acetone and water with a volume ratio of 1:9 acetone:water at $T=20^{\circ}\text{C}$. There was only one spectral peak present after Fourier transforming, thus indicating that the signal from the large volume fraction of the water dominated the acetone signal. The measured molecular diffusion coefficient for the water in acetone for the well-mixed solution is $D_{\text{water_acetone}}=1.8 \times 10^{-9} \text{ m}^2/\text{s}$. Acetone-water mixtures take up less volume than the sum of their individual components at $T=20^{\circ}\text{C}$ [133, 134]. Thus, the slight reduction in the molecular diffusion coefficient for water in the mixture versus water in water is a result of the mixture constricting due to hydrogen bonding, thus hindering diffusion.

As expected, based on the laminar flow observed and measured for all water-water experiments, Fig. 6.8 (a), Fig. 6.13 and Fig. 6.15, the diffusion values measured

for the water-water system were the same as that for stationary water at $T=20^{\circ}\text{C}$, $D_{\text{water}}=2.1 \times 10^{-9} \text{ m}^2/\text{s}$ [56]. For the water-water jet-in-tube system, dispersion coefficients were measured in the x and y directions at the specified slice positions and at observation times up to 200 ms. For all the experiments conducted, the dispersion coefficient values measured for the water-water system ranged from $1.79 \times 10^{-9} \text{ m}^2/\text{s}$ to $2.52 \times 10^{-9} \text{ m}^2/\text{s}$ near the molecular diffusion of water. Figure 6.18 is a plot of dispersion coefficients for the water-water system as a function of observation time Δ in the x-direction averaged over a 2 mm thick slice centered 66 mm past the jet exit. Both single and double PGSE diffusion coefficients are displayed, and the fact that they are exactly the same shows that in the water-water system, the motion in the transverse direction is due to purely stochastic molecular self-diffusion.

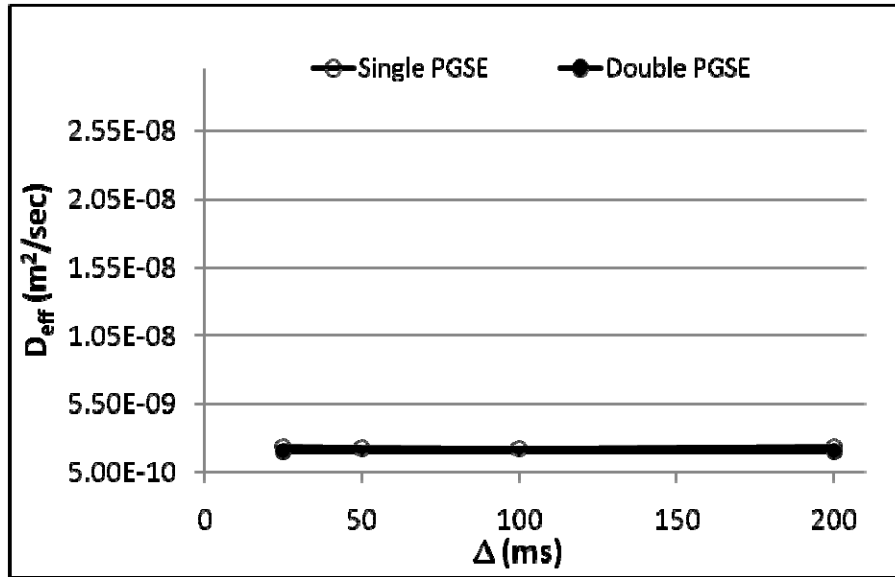


Figure 6.18. Single and double PGSE determined effective diffusion coefficients as a function of observation time Δ for the 2 mm slice centered 66 mm past the jet exit in the water-water system.

Effective single and double PGSE diffusion coefficients for the acetone-water system as a function of slice position and observation time Δ are shown in figures 6.19

(x-direction) and 6.20 (y-direction). The experiments used to determine each effective diffusion value were averaged 128 times, and most of the effective diffusion values presented result from averaging the values from two or three separate experiments. In preliminary work, experiments were conducted using 32 and 128 averages. The experiments which were averaged 32 times yielded significantly noisier Stejskal-Tanner plots and resulted in somewhat larger magnitude diffusion coefficients than those obtained using 128 averages. This behavior is indicative of larger velocity fluctuations generating NMR dephasing as observed in turbulent flows [135].

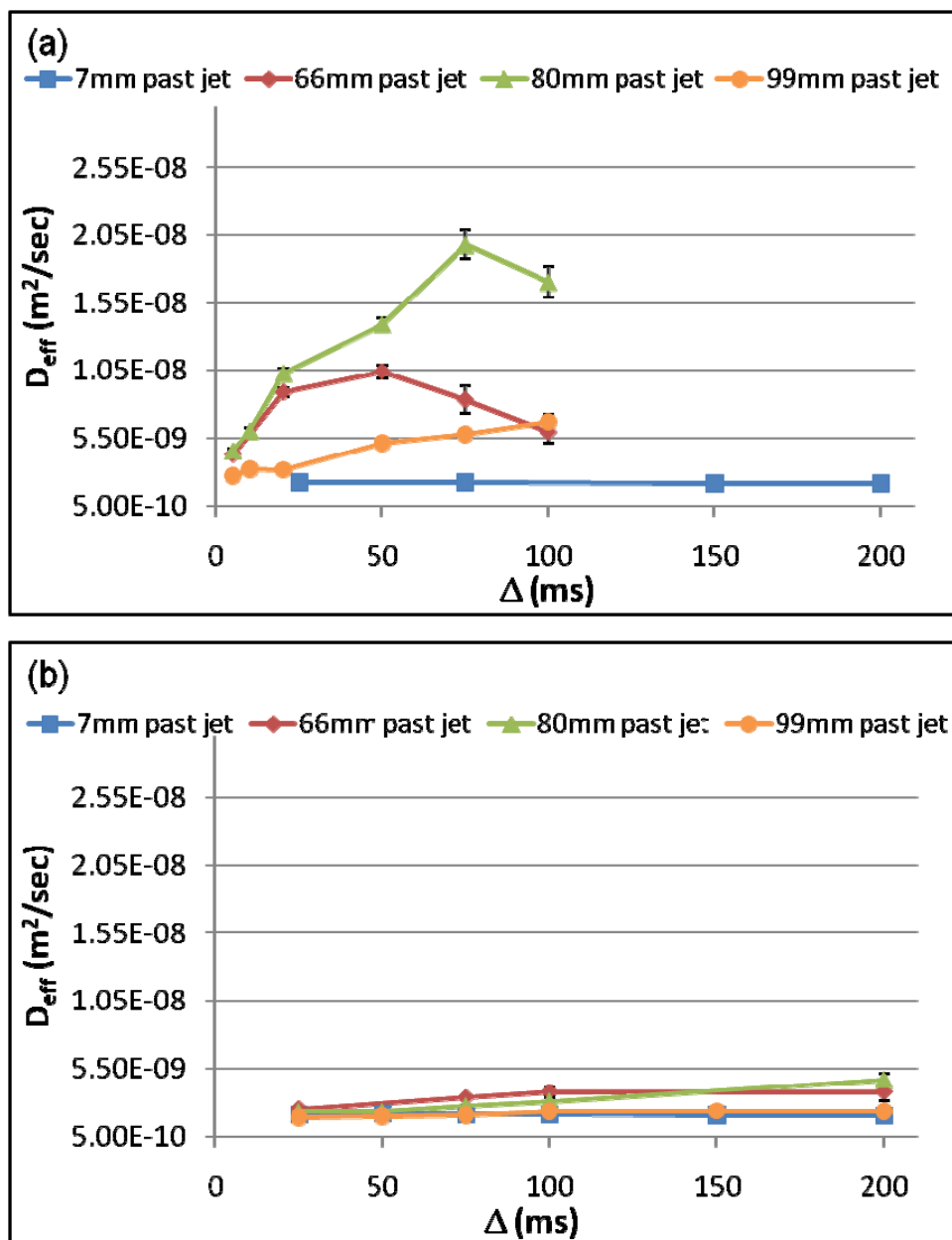


Figure 6.19. (a) Single and (b) double PGSE determined x-direction effective diffusion coefficients as a function of observation time Δ for a 2 mm slice centered at varying positions past the jet exit for the acetone-water system.

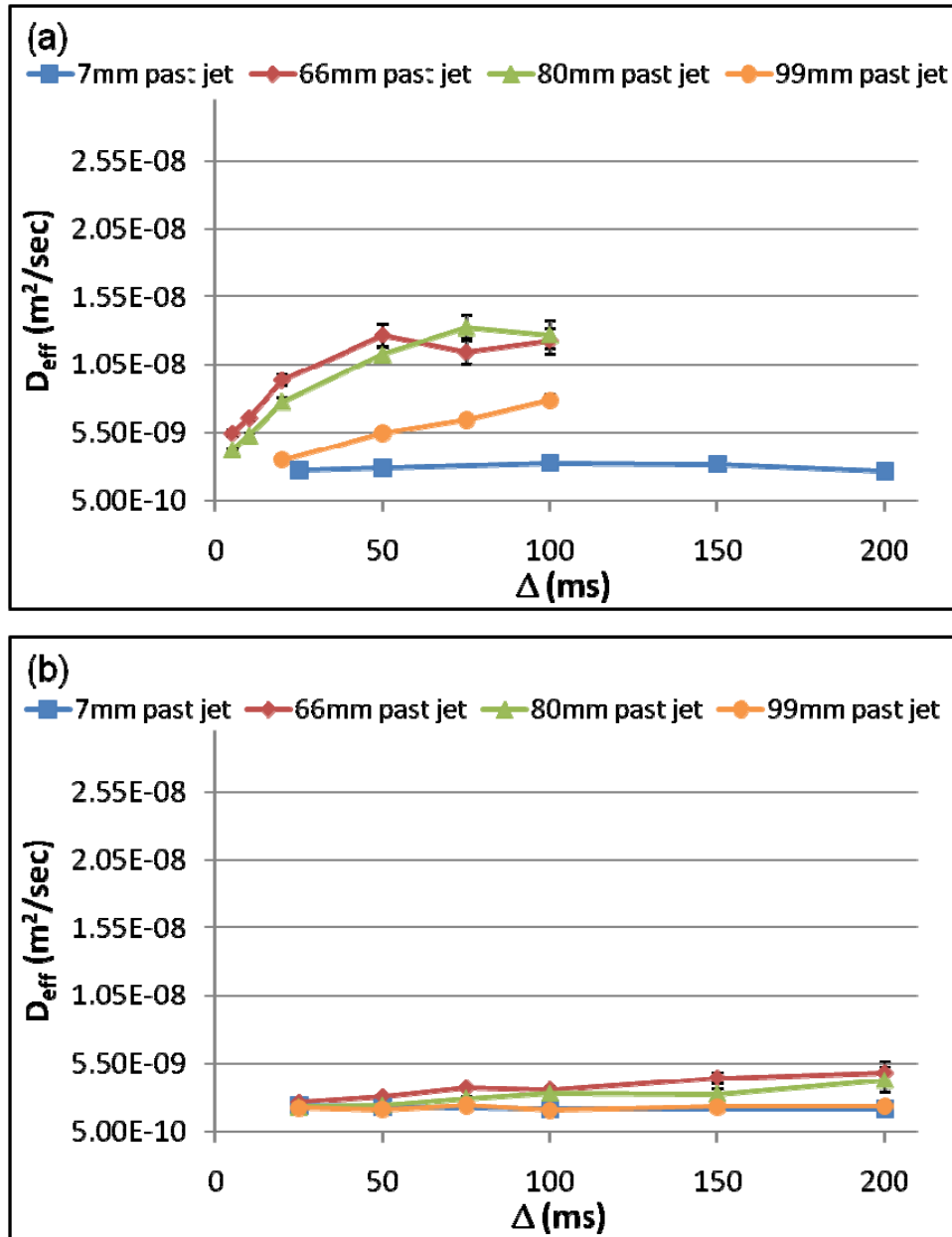


Figure 6.20. (a) Single and (b) double PGSE determined y-direction effective diffusion coefficients as a function of observation time Δ for a 2 mm slice centered at varying positions past the jet exit for the acetone-water system.

Comparing the single PGSE data, Fig. 6.19 (a) and Fig. 6.20 (a), which captures both coherent and incoherent flow effects, to the double PGSE data, Fig. 6.19 (b) and Fig. 6.20 (b), which measures only contributions that are random or incoherent, it appears that

the transverse dispersion arises primarily from refocusable coherent flow. The x-direction velocity maps presented in Fig. 6.14 make clear that there are velocities in the transverse direction, and these lead to the transverse dispersion measured at 66 mm, 80 mm and 99 mm past the jet exit. The buoyancy force driven breakup of the acetone jet causes the secondary flows that enhance diffusion, *i.e.* dispersion, and these secondary flows have deterministic (refocusable) and random (non-refocusable) components.

The single PGSE effective diffusion data, Fig. 6.19 (a) and 6.20 (a), show the transverse dispersion for the acetone-water system to be strongly position dependent. At 7 mm past the jet exit (blue squares in Fig. 6.19 and Fig. 6.20), in both the x and y-directions, the single and double PGSE experiments give approximately the same effective diffusion coefficient value for all Δ , essentially the molecular diffusion value of water. At this position there are no transverse velocities (Fig. 6.14 (a)) so the only mechanism for transverse motion is molecular diffusion. Single PGSE dispersion is significantly enhanced and clearly time dependent at the 66 mm past the jet exit (red diamonds in Fig. 6.19 (a) and 6.20 (a)) and 80 mm past the jet exit (green triangles in Fig. 6.19 (a) and 6.20 (a)) due to transverse mixing, which resulted from the jet breaking up into vortex-like structures which, grow, collide and burst. For the 66 mm position in figures 6.19 (a) and 6.20 (a) a maximum in $D_{\text{eff}}(t)$ is found at 50 ms. After 50 ms, in Fig. 6.19 (a) the 66 mm x-direction $D_{\text{eff}}(t)$ curve decreases, approaching the long time asymptotic constant diffusion coefficient value. In Fig. 6.20 (a) the 66 mm y-direction $D_{\text{eff}}(t)$ data (red diamonds) is not decreasing towards its long time asymptotic value as rapidly as seen in the x-direction, Fig. 6.19 (a). This difference in $D_{\text{eff}}(t)$ behavior is due

to the jet being slightly off center in the tube thus causing asymmetries in the flow. The single PGSE time-dependent dispersion coefficients for the 80 mm position are approximately equal to (Fig. 6.20 (a)) or greater than (Fig. 6.19 (a)) those measured at the 66 mm position. Again, the differences in the dispersion coefficient in the x and y-directions are due to the flow asymmetries caused by the jet being slightly off center. The double PGSE $D_{eff}(t)$ values measured at 66 mm past the jet exit (red diamonds in Fig. 6.19 (b) and Fig. 6.20 (b)) and 80 mm past the jet exit (green triangles in Fig. 6.19 (b) and Fig. 6.20 (b)) are increased over those measured at the 7 mm position. This increase is due to non-refocusable random fluctuations in the transverse direction velocities, which occur at the 66 mm and 80 mm positions. Figure 6.8 (b) shows that by 99 mm past the jet exit, the acetone and water are becoming well-mixed and the solution looks almost uniform. The single PGSE dispersion values at 99 mm past the jet exit (orange circles Fig. 6.19 (a) and 6.20 (a)), are smaller than those measured at 66 mm and 80 mm past the jet exit, and interestingly show a linear in time dispersion coefficient dependence, which is characteristic of ballistic motion. The double PGSE diffusion data, Fig. 6.19 (b) and 6.20 (b), lies on top of that measured at 7 mm, indicating that the ballistic motion observed in the single PGSE experiment is almost entirely refocusable and that fluctuations in the transverse velocities are not as significant as they were at the 66 mm and 80 mm positions. Thus, at 99 mm past the jet exit, the incoherent motion (double PGSE) contribution to $D_{eff}(t)$ is from molecular diffusion almost exclusively.

Additional analysis of the x-direction velocity maps (b), (c) and (d) from Fig. 6.14 contributes to the interpretation of the x-direction dispersion coefficients, Fig. 6.19. The

absolute-values of the velocity maps from Fig. 6.14 (b), (c) and (d) are shown from left to right in Fig. 6.21 (a). The dashed box in each image highlights the 2 mm thick slice over which the transverse hydrodynamic dispersion coefficients of Fig. 6.19 were measured. For each of these velocity maps, the modulus of the average velocity $|v_{avg}|$ was calculated. They were found to be 0.43 mm/s, 0.26 mm/s and 0.17 mm/s for the 66 mm, 80 mm and 99 mm past the jet positions, respectively. Using these $|v_{avg}|$, velocity variance maps, $(|v_{avg}| - |v_{pixel}|)^2$, as shown in Fig. 6.21 (b) were plotted for each velocity map of Fig. 6.21 (a). The MatLab code used to determine $|v_{avg}|$ and to create the variance maps is presented in Appendix E. The variance maps are essentially maps of the intensity of the x-direction velocity fluctuations. The variance maps illustrate that overall, the velocity fluctuations are maximized in the left-most map of Fig. 6.21 (b), which contains the slice centered 66 mm past the jet exit and minimized in the right-most map containing the slice centered 99 mm past the jet exit. However, considering just the 2 mm slices used for dispersion measurements, it is found that the slice 80 mm past the jet exit has larger $|v_{avg}|=0.30$ mm/s, maximum absolute velocity $|v_{max}|=1.26$ mm/s and maximum variance $(|v_{avg}| - |v_{pixel}|)^2_{max}=0.92$ mm²/s² than the slice centered 66 mm past the jet exit (Fig. 6.24). Table 6.1 displays $|v_{avg}|$, $|v_{max}|$ and $(|v_{avg}| - |v_{pixel}|)^2_{max}$ for the 66 mm, 80 mm and 99 mm slice positions. This data trends as expected based on Fig. 6.19 (a), which shows that hydrodynamic dispersion is maximized at the 80 mm slice position and decreases substantially at the 99 mm slice position.

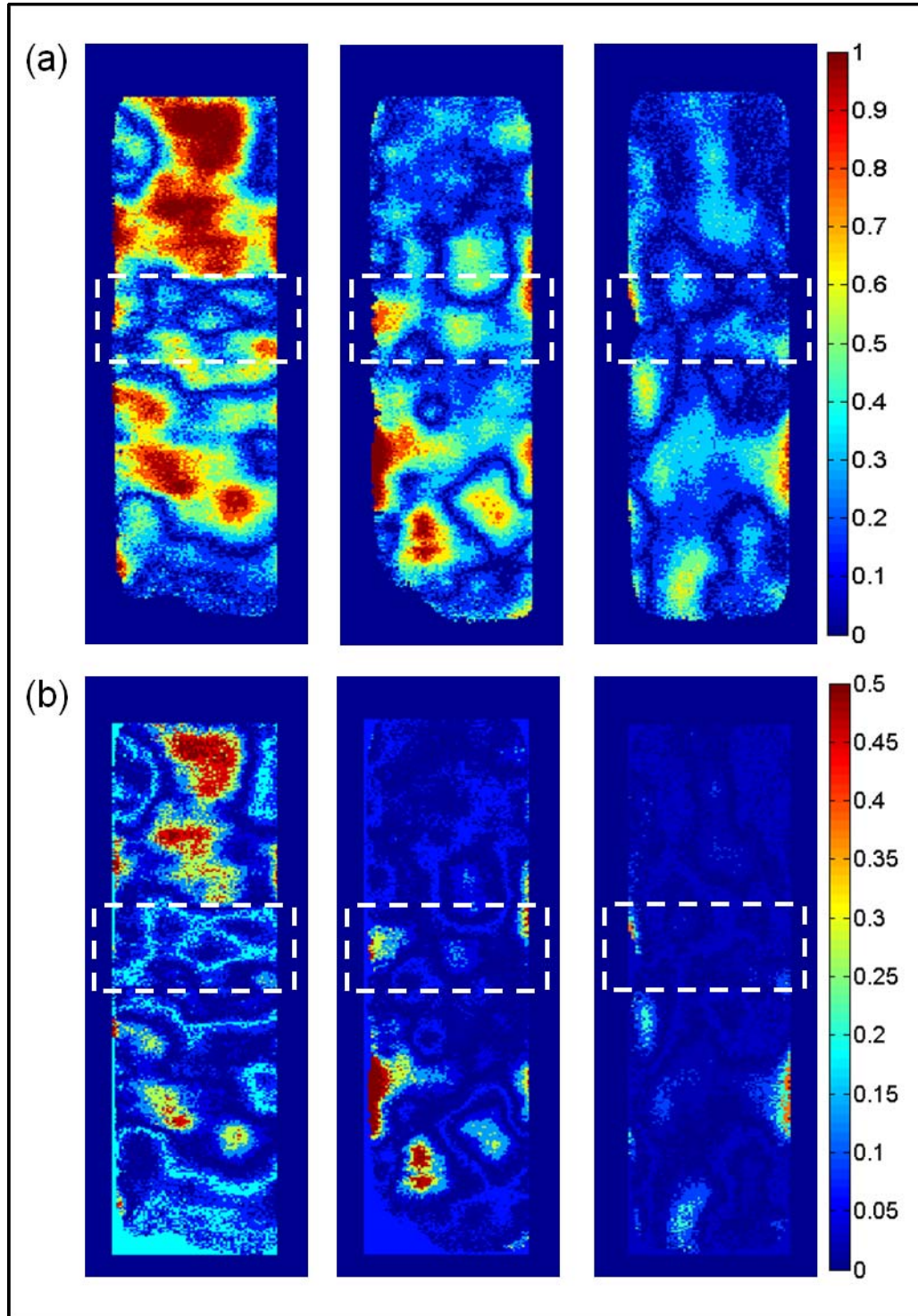


Figure 6.21. (a) Absolute-valued x-direction velocity maps and their corresponding (b) variance maps. From left to right, the center of the highlighted box in each image corresponds to the slice used for the dispersion measurements 66 mm, 80 mm and 99 mm past the jet exit.

Table 6.1. Velocity and variance values taken from the 2 mm thick slice regions highlighted in the dashed boxes of the velocity and variance maps of Fig. 6.21 (a) and (b).

	66 mm	80 mm	99 mm
$ v'_{avg} $ (mm/s)	0.26	0.3	0.14
$ v'_{max} $ (mm/s)	1.1	1.26	0.94
$(v'_{avg} - v'_{median})^2_{max}$ (mm/s) ²	0.7	0.92	0.64

Figure 6.22(a) presents the z-direction double PGSE dispersion coefficients for the acetone-water system as a function of slice position and observation time Δ . For all positions studied some time-dependence of the effective diffusion coefficients is observed. The extreme increase in dispersion seen for the 66 mm and 80 mm positions occurs in large part because the discrete fluid packets, which formed from the buoyancy force driven breakup of the acetone jet, grow, collide and burst, thus randomizing the flow in this region. These collisions and bursts lead to turbulent-like velocity fluctuation induced mixing and hence, enhanced axial dispersion. The z-direction double PGSE effective dispersion coefficients for the water-water system are shown in Fig. 6.22 (b) for comparison.

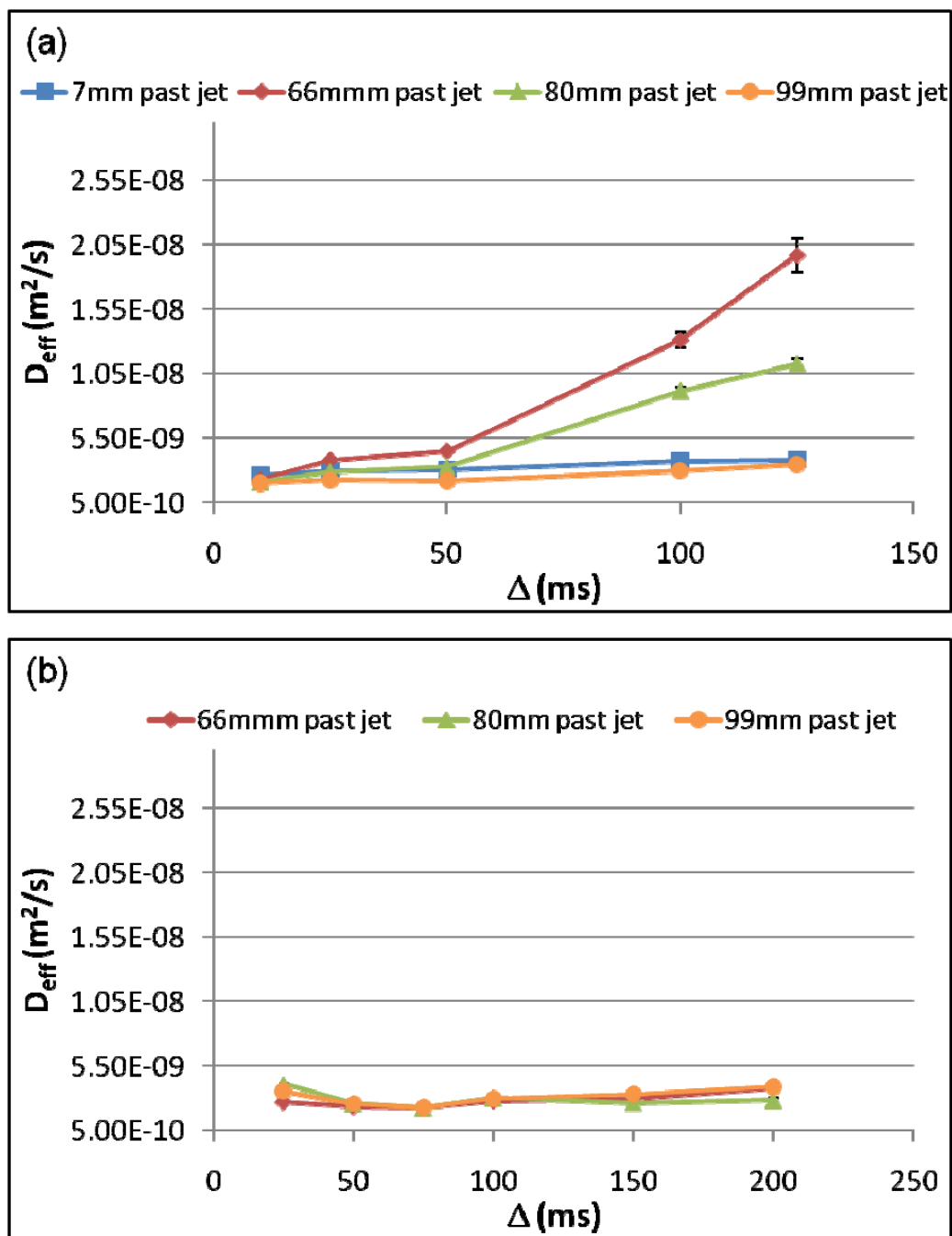


Figure 6.22. Double PGSE z-direction effective diffusion values as a function of observation time Δ for a 2 mm slice centered at varying positions past the jet exit for the (a) acetone-water system and the (b) water-water system.

Pre-asymptotic Dispersion Maxima to Characterize Transport Length Scale

A pre-asymptotic maximum is measured in the time-dependent x-direction hydrodynamic dispersion coefficient data for the 66 mm past the jet slice position, Fig. 6.23. The observation time corresponding to this maximum, 50 ms can be used as a characteristic time for determining a dynamic transport length scale [136] of the dominant mixing flow structure at this position.

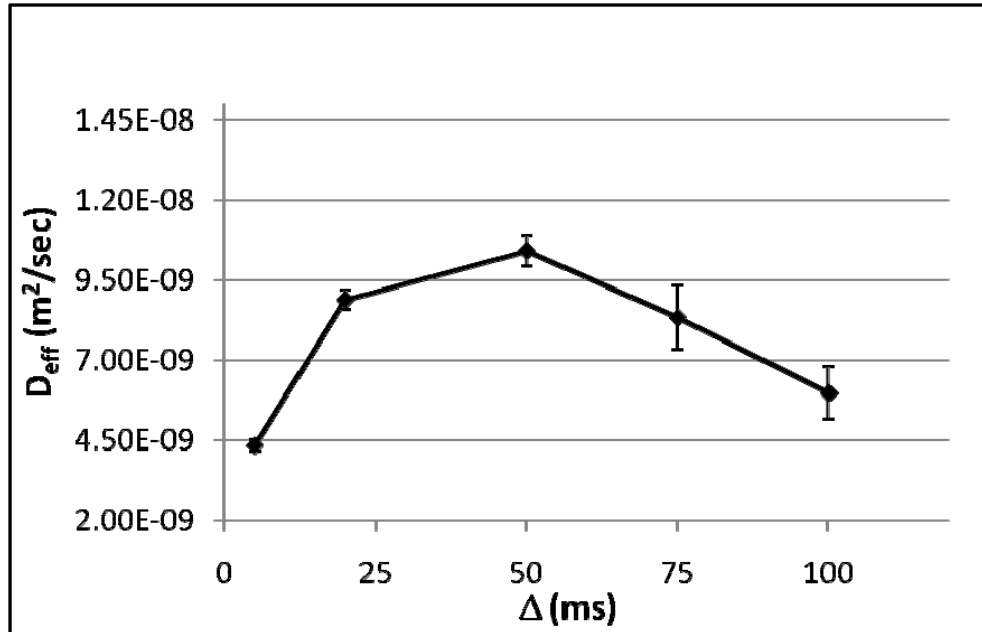


Figure 6.23. The acetone-water system time-dependent transverse hydrodynamic dispersion coefficient for a 2 mm thick slice centered 66 mm past the jet exit.

A characteristic velocity for sampling of the flow instability structure, analogous to the velocity for sampling the porous media structure demonstrated in references [123, 124], is required to determine the dynamic transport length. It is not entirely obvious what system velocity should be used as the characteristic velocity in calculating the dynamic transport length scale. Three velocities considered relevant were the average

transverse direction velocity $\overline{v_x}$ for the 2 mm long slice over which the dispersion was measured (see Fig. 6.24), the average axial direction velocity $\overline{v_{zfast}}$ obtained from fast flowing region highlighted in Fig. 6.16 (c) and the average velocity of the entire Fig. 6.16 (c) velocity map. Since $\overline{v_x} = 0.26$ mm/s, $\overline{v_{zfast}} = 7.9$ mm/s and $\overline{v_z} = 3.3$ mm/s it is anticipated that advection in the longitudinal direction dominates the sampling of the flow instability mixing structures by the fluid molecules. Beyond this, it is difficult to state for certain which velocity $\overline{v_{zfast}}$ or $\overline{v_z}$ should be used, especially as they are the same order of magnitude. The breakup of the fast-moving acetone jet occurring at this 66 mm position has coherent structure that is observable in the bench top digital images of Fig. 6.8 (b), which indicates that the acetone dynamics dominate the overall fluid dynamical behavior. However, the slow-moving water is in great excess (by volume and mass) of the acetone and its contribution to the system dynamics should not be excluded. A compromise is to simply present a length-scale range for the characteristic transport length. Thus, the characteristic length-scale of the dominant transport structure at the 66 mm position is $165 \mu\text{m} \leq l \leq 400 \mu\text{m}$.

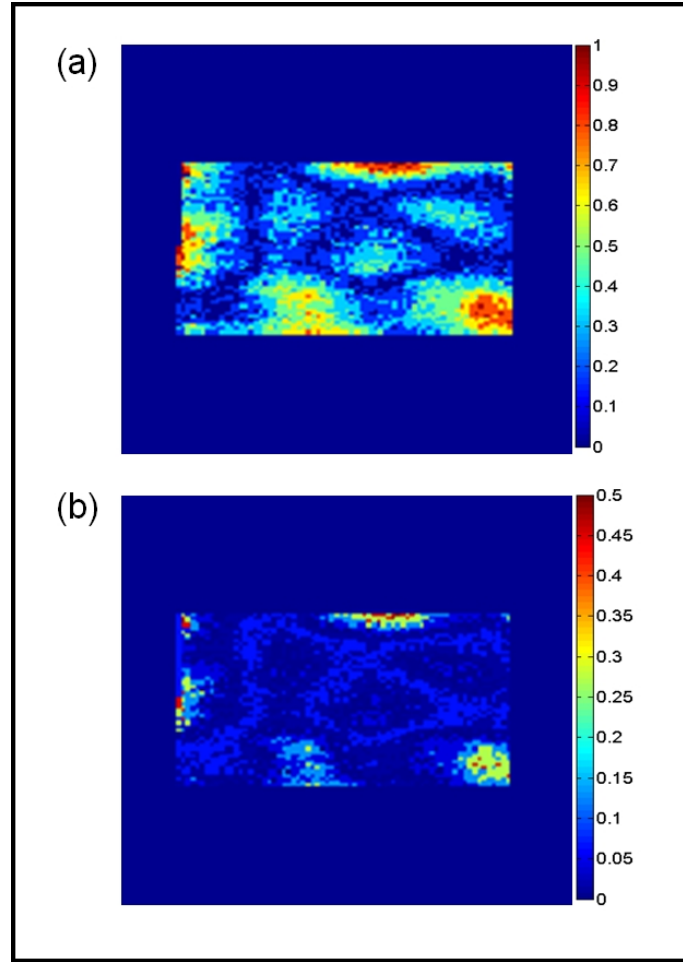


Figure 6.24. (a) Absolute-valued x-direction velocity map and its corresponding (b) variance map for the 2 mm thick slice over which the 66 mm past the jet exit position dispersion measurements were made.

To model the observed behavior of the effective diffusion, or hydrodynamic dispersion, the theory of non-equilibrium statistical mechanics is used. The time rate of change of the VACF can be expressed in terms of all of its previous values convoluted with the memory function, $K(t)$ [109, 118-120],

$$\frac{d\Psi}{dt} = - \int_0^t K(t-t')\psi(t')dt'. \quad (6.14)$$

This is known as the memory function equation. Short time dynamical behavior of dense fluids has been modeled using molecular dynamics simulations to evaluate the time variation of $\Psi(t)$ [120, 137]. Figure 6.25 displays a simplified representation of the results of [137]. For a dense fluid, $\Psi(t)$ shows time-dependence suggestive of a damped Brownian harmonic oscillator, exhibiting a strong oscillation and dipping into negative values. This behavior arises from the tagged molecule being confined in a cage formed by its immediate neighbors. In effect, the $\Psi(t)$ versus t plot shows the tagged molecule colliding with the cage and being deflected causing a reversal of velocity, which is responsible for the negative lobe of the velocity autocorrelation function. This effect is sometimes called *backscattering*.

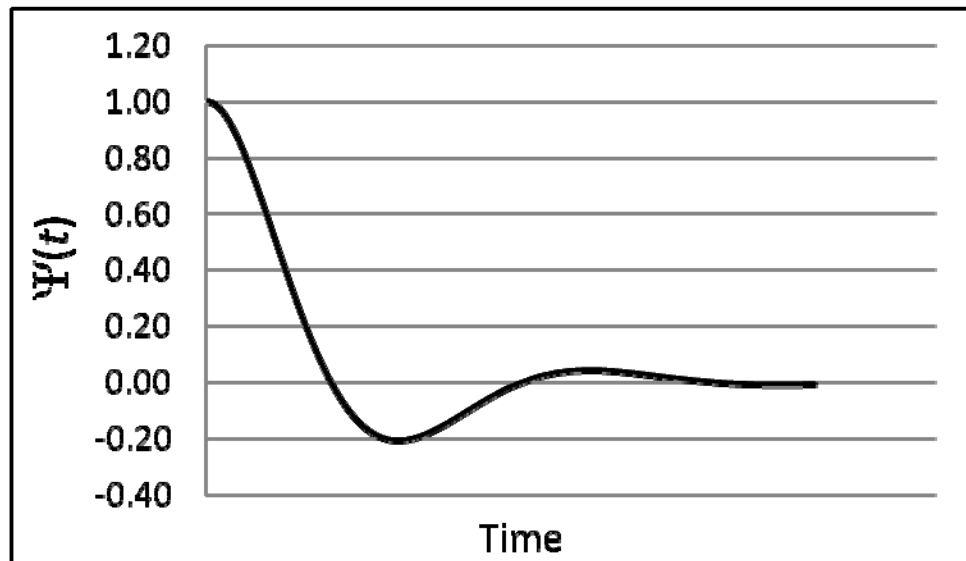


Figure 6.25. Time-dependence of $\Psi(t)$ for a dense fluid.

The relevance of Fig. 6.25 is that the backscattering effect illustrated yields a minimum in $\Psi(t)$, which corresponds to the maximum in $D(t)$ (6.13). Interpreting the pre-asymptotic dispersion behavior measured in the jet-in-tube system in the context of $\Psi(t)$ contributes to the hypothesis that at 66 mm past the jet, there is a coherent transport

structure, *e.g.* a decaying vortice, that forms the confining cage with characteristic transport length scale l .

Using an exponential memory function, $K(t) = \omega_v^2 \exp(-t/\tau)$, [118, 119] $\omega_v^2 = K(0)$ is the initial value of the memory function as well as a restoring force. The exponential memory function generates a velocity autocorrelation function [120]

$$\Psi(t) = \left(\cos \varpi t + \frac{1}{2\varpi\tau} \sin \varpi t \right) \exp\left(-\frac{1}{2\tau}\right), \quad (6.15)$$

where τ is the relaxation time to long asymptotic dynamics and the frequency of

oscillation $\varpi = \sqrt{\omega_v^2 - \frac{\tau^2}{4}}$. The damped oscillation of (6.15) qualitatively captures the diffusive randomization (exponential decay derived in equation (6.7)) and the advective sampling of the confining vortice boundaries (oscillatory motion) which results from the breakup of the positively buoyant acetone jet. The measured maximum in the time-dependent pre-asymptotic hydrodynamic dispersion coefficient at the 66 mm slice position clearly indicates backscattering effects during mixing by a buoyancy-driven hydrodynamic instability. The non-equilibrium statistical mechanics theory of dispersion [138] can be used to model mixing in hydrodynamic instabilities and to characterize a dynamics based length-scale of mixing.

Conclusions

The buoyancy force which results from introducing acetone (SG=0.79) into water (SG=1) in opposition to gravity is highly destabilizing to the laminar jet flow, and the resulting unstable flow gives rise to significantly enhanced hydrodynamic dispersion of

the two fluids. For the first time, enhanced dispersion due to buoyancy driven instability is quantified as a function of fluid displacement observation time and position relative to the jet exit. Non-equilibrium statistical mechanics concepts are introduced as a model for mixing by the formation and decay of coherent vortex structures generated by the buoyant instability. Pre-asymptotic transverse dispersion was shown to determine the characteristic time to sample the vortice length scale, which was then used to calculate a characteristic transport length scale of these vortical mixing structures. Measurement and evaluation of $D(t)$ using different jet and tube diameters, fluids of varying density and viscosity and varied flow rates is of future interest for testing the sensitivity of this technique. Furthermore, the increased hydrodynamic dispersion arising from flow destabilizing buoyancy forces has potential for enhancing mixing in microfluidic devices.

FUTURE RESEARCH DIRECTIONS

Osmotic Controlled-Release Tablet MR Imaging

There is abundant potential for improving osmotic controlled-release tablet development and formulation through improving knowledge of how tablet excipients in varying amounts affect the transport of water into the tablet and the transport of solids out of the tablet. The MR tablet imaging and water transport model presented in this thesis demonstrated the direct correlation between the MR signal intensity within the studied tablet and water concentration.

In order to expand on the initial tablet imaging and water transport modeling work, collaboration between the MSU MR research group and Bend Research, Inc. (BRI) has been proposed. The work plan includes development of three or four swellable core technology (SCT) tablets all containing the same API but with varying excipients and excipient concentrations. Specifically, hygroscopic polymers of varying molecular weight and hence different viscosity will be used, and the amount of the osmotic agent, sodium chloride, will also be varied. BRI will conduct drug dissolution studies on each formulation under physiologic and MR imaging conditions. These tablet formulations will then be studied via MR imaging during tablet hydration. MR imaging of water hydrating the tablet from all three directions as well as imaging of tablet hydration limited to one dimension will be conducted. The purpose of the 1D hydration study will be to determine whether differences in the transport properties can be detected through the MR imaging method. If so, the diffusive and osmotic transport coefficients for each

formulation will be quantified. For both 1D and 3D tablet hydration, transport coefficients will be estimated so that the differences in the transport coefficients between the 1D model and 3D tablet can be quantified and it can be determined whether the 1D water transport model combined with the 3D imaging provides acceptable estimates of transport coefficients. The drug dissolution data will be used to connect the water transport properties to the drug release performance as a function of time. The overarching goal of this work is to make osmotic controlled-release tablet design and formulation less empirical and more efficient.

Some suggested technical and experimental improvements of the original MR tablet imaging work are as follows:

- 1.) Include a test tube of deionized water in the tablet MR imaging window so that this water can serve as the control for normalizing the signal intensity within the tablet.
- 2.) Build a magnet-compatible tablet holder equipped with temperature control so that these tablet imaging studies can be conducted at physiological temperature, $T=37^{\circ}\text{C}$.
- 3.) Conduct bulk T_1 and T_2 relaxation time measurements as a function of hydration time prior to tablet imaging experiments in order to find out what relaxation and echo times should be used to avoid T_1 -weighting of water signal from within the tablet and to ensure that the minimum echo time available for the imaging experiments is appropriate for measuring signal from the solid-like tablets with their strong dipolar interactions.

- 4.) For 2D imaging experiments, set up the field of view and number of points sampled in each dimension so as to achieve isotropic resolution in the 2D plane.

Two-Fluid Taylor Vortex Flow Studies

One potential follow-up study for the two-fluid Taylor vortex flow work would be to match the initial, *i.e.* startup, conditions exactly between experiment and simulation and see what, if any, impact that has on the wavelength matching. For instance, the experiments could be repeated with the rotation rate suddenly started at the operational rotation rate in order to match the startup conditions of the simulations presented in this thesis.

Additional simulations and experiments (if possible) to evaluate how flow at the interface evolves as the inner cylinder rotation rate is increased are of particular interest. Do the two fluids at the interface transition from Couette flow, which has only a $v_\theta(r)$ velocity, directly to an emulsification regime in which one fluid is being dispersed as droplets into the other? Or is there some intermediate interfacial mixing which is not quite emulsification that occurs between these two regimes?

A fundamental direction for the two-fluid Taylor vortex flow would be to conduct bifurcation and linear stability analyses for the axially stratified two-fluid systems studied in this thesis. A bifurcation analysis examining the effects of surface tension on the steady-state interfacial velocities would be especially interesting. Linear stability analysis has been previously conducted for the flow of two immiscible fluids that are

radially stratified between the concentric cylinders of a Taylor-Couette device with the outer cylinder stationary and the inner cylinder rotating [75]. In Renardy and Joseph's work [75], the interface was assumed to be flat, which greatly simplifies the analysis as would the assumption of a flat interface for the stability analysis of two fluids that are axially stratified.

An aggressive and challenging new body of work would be to identify a biological system consisting of a single biological cell and two fluid reagents and to design a microfluidic Taylor-Couette device with gap size slightly larger than the cell's outer diameter. The denser of the two fluids would be placed in the lower portion of the vertically oriented Taylor-Couette device and the less dense in the upper portion. At the interface, a biological cell, ideally of intermediate density between those of the two reagents, would be placed so that it could be simultaneously subjected to the different reagents. Then a series of MR imaging and velocity imaging studies as well as biological assays would be run on the system with the overall goal of this work being to determine whether the axially stratified two-fluid Taylor vortex flow reactor is an effective microfluidic device for delivering biochemical reagents to cells with subcellular spatial selectivity, *i.e.* exposing different regions of the cell to different biochemical agents. Initial studies aimed at selective chemical treatment of cellular microdomains were conducted by the Whitesides' group at Harvard [86, 88]

Buoyancy Driven Mixing and Dispersion

The so-called “jet-in-tube” project began with the intention of improving the understanding of the microscale mixing which occurs in the high Reynolds number jet-in-tube flows used for nanoparticle precipitation reactions [139]. Based on current in-house MR experimental capabilities, which constrained the studied flows to low velocities, *i.e.* low jet and tube Reynolds’ numbers, a very different body of work emerged than what was originally intended. Future work aimed at studying flows closer to those occurring in nanoparticle precipitation reactions would likely prove equally surprising and rewarding.

A reasonable initial goal might be to increase both the jet and the tube flow velocities by an order of magnitude, *e.g.* from 10 mL/hr to 100 mL/hr for the jet flow and from 90 mL/hr to 450 mL/hr or 900 mL/hr for the tube flow. Pumps capable of delivering these flows in a steady, pulsation-free manner and with a volume large enough to supply flow for 5-10 h for long time signal averaging will need to be purchased. At least one of the pumps will need to be solvent, *e.g.* acetone, compatible. In order to increase jet-in-tube flow velocities, rapid MR motion encoding pulse sequences, *e.g.* $\square\square\square\square\square\square\square\square\square$ [140, 141], would likely need to be programmed, tested and fine-tuned for this specific experimental system, and at some point, pre-magnetization of the jet-in-tube fluids may also need to be considered.

Measurement and evaluation of the time-dependent hydrodynamic dispersion coefficients $\mathbf{D}(t)$ using different jet and tube diameters, fluids of varying density and viscosity and varied flow rates is of substantial interest for improving understanding of

what variables are most important for mixing enhancement. This body of work would also contribute to testing the limits of using the time-dependent pre-asymptotic dispersion maxima to determine the characteristic transport length scale.

APPENDICES

APPENDIX A

MATLAB CODE OF 1D DIFFUSION MODEL

The following MatLab code calculates water concentration as a function of position x in a 9 mm diameter sample for $n=10$ different time t points where $0 < t < 900$ minutes. This code uses equation (4.9) to calculate water concentration. The water concentration is plotted as a function of position for the $n=10$ time points.

```
*****
*****
```

```
% function [U] = calcdiff( loop, t)
```

```
clear all
```

```
close all
```

```
loop=10000;
```

```
c1=10;
```

```
U=zeros(1,c1);
```

```
%D is the diffusion coefficient. Vary D to get the best fit to the
data. D for free water=0.126 mm2/min.
```

```
D=1.1e-2; %mm^2/min
```

```
L=9; %mm
```

```
x=(0:0.05:9); %(mm) discretized 9mm into 0.05mm intervals
```

```
n=10;
```

```
t=60:(900-60)/(n-1):900; %(min) discretized time
```

```
%Shift plot. Effectively adds 1 to the concentration everywhere -
shifts the reference.
```

```
V=1/loop;
```

```
H=0;
```

```
U2=[];
```

```
for i=1:length(t)
```

```
    U=0;
```

```
    for m=1:loop
```

```
        a=(-2/m/pi()*(1-cos(m*pi())))*sin(m*pi()*x/L)*exp(-
D*(m*pi()/L)^2*(t(i)-H))+V;
```

```
        U=U+a;
```

```
    end
```

```
U2(i,:)=U;
```

```
plot(x,U,'r') %plot water concentration versus tablet position for 10
time points
```

```
hold on
```

```
end
```

```
*****
```

The following MatLab code calculates the water concentration at the center point

($x=4.5$ mm) of a 9 mm diameter tablet every 60 minutes out to 900 minutes. This code

uses equation (4.9) and $x=4.5$ to calculate water concentration. The water concentration is plotted as a function of time. Vary D , the diffusion coefficient in this code, and perform a least squares analysis between this model data and experimental data to find the D that gives the best fit to the experimental data.

```
clear all
%close all
%clc

loop=10000;
c1=10;
U=zeros(1,c1);
x=4.5;
% D is the diffusion coefficient. Vary D to get the best fit to the
data. D for free water=0.126 mm2/min.
D=5e-2; %mm2/min
L=9; %mm
n=20;
t=60:(900-60)/(n-1):900; %(min) discretized time.

%shift plot
%(For drug layer bounds, V=0.0001, H=150)
V=1/loop;%effectively adds 1 to the concentration everywhere - shifts
the reference
H=150; %effectively shifts the time (min)

for i=1:length(t)
    for m=1:loop
        a(m)=(-2/m/pi()*(1-cos(m*pi())))*sin(m*pi()*x/L)*exp(-
D*(m*pi()/L)^2*(t(i)-H))+V;
    end
    b(i)=sum(a);
end

plot(t,b,'o')
hold on
```

APPENDIX B

METHODS FOR ANALYZING THE EXPERIMENTAL
COUETTE AND TAYLOR VORTEX FLOW DATA

The raw experimental data was generated using the PGSE velocity mapping pulse sequence, “ABDWISE.pc.ppg,” on the DRX 250 spectrometer using Paravision 3.0.2 software to control the experiments. It was first analyzed in Prospa, where the velocity map was generated. Then a matrix of data was exported from Prospa and modified in Excel so that a data matrix containing the velocity information from a single fluid column of the T-C device could be readied for Fourier transform analysis and plotting in MatLab.

- **FTP**

- o The raw experimental data must be transferred from the spectrometer computer to a hard drive or network that is accessible to the computer being used for data analysis. Use a file transfer program (FTP) to move the data to an accessible location.

- **Prospa V2.2.19**

- o Open Prospa.
 - Import the raw data that was just transferred via the FTP.
NMRI→importData
 - Point the Working directory to the location where the raw data is stored.
 - Type: LittleEndian
 - Size 1: number of points sampled in first spatial dimension
 - Size 2: number of points sampled in first spatial dimension
 - Size 3: number of velocity encoding gradients used (i.e. q points).
 - Select “Load” button. Should see data load in Prospa’s “2d Plot” window.
 - In the CLI window, enter the command: `A=trans(mat2d, yx)` . This command transposes x and y so that the data is oriented correctly.
 - Fourier transform the spatial data. NMRI→nDFourier Transform
 - Input matrix: 3D A (unless another name was specified when the data was loaded during data importation)
 - Type: FTEcho in the 2 spatial dimensions
 - Type: None in the 3rd dimension (no Fourier transformation in the q dimension).
 - Make sure w=size 1, h=size 2 and d=size 3 from importData step.
 - Data smoothing is optional. If smoothing is not desired simply select the “Transform” button. To smooth data,
 - o Select “Filter parameters” button. Under the Filter menu, select “Gaussian.” Adjust the p1 and p2 parameters as desired. The test button allows you to see the Gaussian shape which results from varying p1 and p2. To use a specific equation, hit the “Save” button and close the “Filter Designer” GUI.

- o In the nD Fourier Transformation window select “Gaussian” filters for the w and h size domains (i.e. the spatial domains)
 - o Select “Transform” button. Should see the Fourier transformed data in Prospa’s “2d Plot” window.
- Generate the spatially resolved velocity map.
NMRI→makeVelocitymap
 - q-space matrix: same name as the FT data in Prospa’s “2d Plot” window. (e.g. Aft)
 - q-dimension: z
 - 2D velocity map: vel
 - 2D intensity map: int
 - Calculation threshold: 1e5 (good starting value, vary this number so that the noise in the velocity map is minimized without chopping off real data).
 - Zerofill: 128 by default (this is fine)
 - Max. gradient (T/m): enter the value of the increment between velocity encoding gradients from PGSE experiment
 - Large delta (s): enter Δ from PGSE experiment
 - Small delta (s): enter δ from PGSE experiment
- Store the velocity map as a data matrix.
 - Right click on the velocity map and select “Copy plot data to matrix.”
 - Give the data matrix a name, e.g. “vel,” and select “Copy”
- Export the velocity map as a data matrix. In the main Prospa window go to File→Export Data→2D
 - Ascii
 - Real
 - Matrix to save: vel
 - File name: specify lab notebook information for the original experiment, whether the data was smoothed and the calculation threshold used.
- **Excel 2007**
 - o Open Excel
 - Open the Prospa velocity data matrix that was just exported. Office button→Open→double click the matrix file
 - The Text Import Wizard will open. Select original data type: “delimited” and delimiters: “space.” The column data format is “general.”
 - o Once opened, the velocity map matrix needs to be modified so that it is comparable to the Taylor vortex flow simulation data supplied by Jim Mullin from BRI (i.e. keep data from only one fluid column, delete all the

zero velocities resulting from the glass walls and the marker fluid velocities). The following steps can also be done in MatLab, but it is faster to modify the data set in Excel.

- Delete all the zero velocity data. Delete the marker fluid velocity data. Keep only the rows of positive-valued velocity data (for azimuthal direction velocity maps) as this is directly comparable to the simulation data.
- Save the spreadsheet as a .xls file. This spreadsheet can be opened in MatLab for further analysis.

- **Open MatLab 7.10.0 R2010a**

- o File→Import Data→select the desired. xls file.
- o Rename the file something short and simple such as “dat.”
- o Double click on “dat” so that the experimental velocity data is visible in MatLab’s Variable Editor window.

APPENDIX C

METHODS FOR ANALYZING THE SIMULATED
COUETTE AND TAYLOR VORTEX FLOW DATA

The raw Fluent CFD simulation data is sent as text (.txt) files from Jim Mullin of Bend Research, Inc. (BRI). The data is first opened in Excel where it is sorted and unit conversions are performed. The Excel spreadsheet is saved as a .xls file that is then imported into MatLab where the short function, “creatmatrix.m,” is run to make a data matrix of velocity where the columns correspond to the radial positions and the rows are the axial positions.

- **Excel 2007**

- o Open Excel. Then, open the desired text file – may have to switch the files type to “all files” in order to see the .txt files.
 - Office button→Open
- o Select original data type: “delimited” and delimiters: “comma” as you proceed through the steps for opening the file in the “Text Import Wizard” GUI. The column data format is “general.”
- o The “y-coordinate” specifies the radial position and the “x-coordinate” specifies the axial position of the fluid in the Taylor-Couette device. Both coordinates have dimensions of meters.
 - Select the “y-coordinate” data column→Sort & Filter→Sort Smallest to Largest.
 - Then select the “x-coordinate” data column→Sort & Filter→Sort Smallest to Largest.
 - Now add a column of data to the left of the “y-coordinate.” Call it “radial coor. (mm)” and multiply the y-coordinate data by 1000 to convert the units from m to mm. Right click→Format Cells→Number→Number-2 decimal places. Repeat this step for the x-coordinate data and call this new column “axial coor. (mm).”
 - Repeat this procedure for all the columns of velocity data. Convert the velocity units from m/sec to mm/sec by multiplying all of the velocity data by 1000.
- o Only about 14 mm of the 50 mm long fluid column from the Taylor-Couette experiments is in the active region of the radiofrequency coil. For the sake of comparison, it is appropriate and useful to select an axial region of simulation data that is approximately 14 mm long and located about 17 mm above the bottom of the T-C device. Ideally, I would simply hide the data I don’t want to use, but it shows up in MatLab so it must be deleted.
 - Select the rows of data spanning from axial coor. (mm) =0 to 17 mm and delete them. Right click→Delete.

- Leave the rows of data spanning from axial coor. (mm) = 18 to 32 mm.
 - Select the rows of data spanning from axial coor. (mm) = 33 to 50 mm and delete them. Right click→Delete.
 - o Much of the data in this spreadsheet will not be useful when opened in MatLab to do the contour plots and Fourier transform analysis. Therefore, delete the unnecessary columns. The columns to delete are: nodenumber and absolute-pressure.
 - o Now arrange the data so that the first column is the axial coor. (mm), second column is the radial coor. (mm), third column is swirl vel. (mm/sec), fourth column is axial vel. (mm/sec), etc. The creatmatrix.m file that will be used in MatLab requires that the data be arranged in this way.
 - o Now save the Excel spreadsheet.
 - Office button→Save as→Save as Type .xls (.xlsx files do not import into the MatLab version I use correctly).
 - o Now this spreadsheet can be opened in MatLab for further analysis.
- **MatLab 7.10.0 R2010a**
 - o Open Matlab. Set the current directory so that it points to the location where the creatmatrix.m file is saved.
 - o File→Import Data→select the desired. xls file.
 - o Rename the file called “data” which pops up in the MatLab workspace. Call it “list.” This is required for the creatmatrix.m file to work properly.
 - o Double click on “list” so that all of the simulation data is visible in MatLab’s Variable Editor window.
 - o At this point, it might be best to precisely determine the length of the fluid column in the experiment that is being compared to the simulation data. Then any excess simulation data can be deleted in the Variable Editor window of MatLab so that the velocity maps of both the experimental and simulation data have the same dimensions.
 - o In the MatLab Command Window enter: `A=creatmatrix(list);`
 - o The creatmatrix.m macro takes the 3rd column of “list” (should be r, θ or z direction velocity data) and builds a data matrix “A” that is the radially and axially varying velocity map. It spits out the velocity map image using the command “imagesc.” The imagesc function scales image data to the full range of the current colormap and displays the image.

The creatmatrix.m function is copied below.

```
function[datmat]=creatmatrix(list)
```

```
% This m.file takes an excel spreadsheet (list) containing axial  
position in the first column, radial position in the second column, and
```

a value (e.g. a velocity) at the corresponding z,r coordinate in the third column and rearranges this data into a matrix which MatLab can plot. This m.file is to be used to convert Taylor-Couette simulation data into matrices.

```
list1=list(:,1);
x=length(list(:,1));

    i=1;
    p=0;
    while(p==0)

        p=list1(i+1)-list1(i);
        i=i+1;

    end %m:number of columns in final matrix
m=i-1;
n=x/m; %number of rows in final matrix
vel=list(:,3); % stores velocity data from the 3rd column of the list
as a vector
datmat=vec2mat(vel,m);
imagesc(datmat)
colorbar('EastOutside')

*****
```

APPENDIX D

LINEAR STABILITY ANALYSIS SET UP FOR THE
PURE FLUID COUETTE SOLUTION

The Physical Situation

A Newtonian incompressible fluid contained in a Couette viscometer device consisting of two coaxial cylinders with the inner cylinder rotating and the outer cylinder stationary (Fig. D.1).

The boundary conditions are:

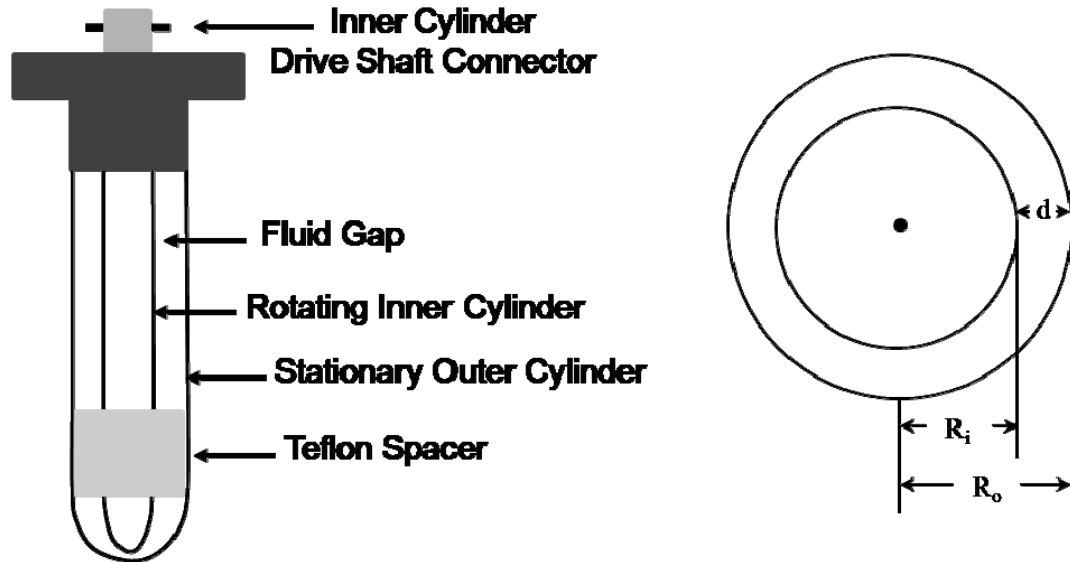


Figure D.1. Schematic of the Couette device used in magnetic resonance velocity mapping experiments. The fluid to be investigated was placed in the 1.05 mm gap between the coaxial cylinders.

Dimensional Analysis of the Continuity and Navier-Stokes Equations

Dimensional analysis of the mass balance (*i.e.* continuity equation) and momentum balance (*i.e.* Navier-Stokes equations) for an incompressible Newtonian fluid.

Variables & Units Defined

$R_o \equiv$ Outer cylinder radius [m]

$R_i \equiv$ Inner cylinder radius [m]

$$\eta \equiv R_i/R_o$$

$$\Omega_o \equiv \text{Outer cylinder rotation rate [rev/s]}$$

$$\Omega_i \equiv \text{Inner cylinder rotation rate [rev/s]}$$

$$\omega_o \equiv \text{Outer cylinder angular rotation rate} \equiv 0 \text{ (for the system studied in this work) [rad/s]}$$

$$\omega_i \equiv \text{Inner cylinder angular rotation rate} \equiv 2\pi\Omega_i \text{ [rad/s]}$$

$$R_i\omega_i \equiv \text{Inner cylinder linear velocity of rotation} \equiv 2\pi\Omega_i R_i \text{ [m/s]}$$

$$d \equiv R_o - R_i \equiv \text{gap length [m]}$$

$$\mu \equiv \text{viscosity [kg/m s]}$$

$$\rho \equiv \text{density [kg/m}^3\text{]}$$

$$\nu \equiv \mu/\rho \equiv \text{kinematic viscosity [m}^2\text{/s]}$$

$$P \equiv \text{Pressure} \equiv [\text{kg/ m s}^2]$$

$$\mathbf{g} \equiv \text{gravitational acceleration constant [m/s}^2\text{]}$$

For an incompressible Newtonian fluid, the continuity (D.2) and Navier-Stokes (D.3) equations are:

$$\nabla \cdot \mathbf{v} = 0, \quad (\text{D.2})$$

$$\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} - \nu \Delta \mathbf{v} + \frac{1}{\rho} \nabla P - \mathbf{g} = 0. \quad (\text{D.3})$$

Non-dimensionalizing Scales

$$d \equiv \text{length scale}$$

$$d^2/\nu \equiv \text{time scale}$$

$$R_i\omega_i \equiv \text{velocity scale}$$

$$\rho d^3 \equiv \text{mass scale}$$

Dimensionless Variables (The * denotes the dimensionless variable)

$$\mathbf{v}^* = d\nabla \rightarrow \nabla = \frac{\nabla^*}{d}$$

$$\Delta^* = d^2\Delta \rightarrow \Delta = \frac{\Delta^*}{d^2}$$

$$t^* = \frac{t\nu}{d^2} \rightarrow t = \frac{t^*d^2}{\nu}$$

$$\mathbf{v}^* = \frac{\mathbf{v}}{R_i\omega_i} \rightarrow \mathbf{v} = \mathbf{v}^* R_i\omega_i$$

$$P^* = \frac{Pd}{\rho\nu R_i\omega_i} \rightarrow P = \frac{P^*\rho\nu R_i\omega_i}{d}$$

$$\mathbf{g}^* = \frac{\mathbf{g}d^2}{\nu R_i\omega_i} \rightarrow \mathbf{g} = \frac{\mathbf{g}^*\nu R_i\omega_i}{d^2}$$

Plugging in $\nabla, \Delta, t, \mathbf{v}, P$ and $\mathbf{g}$ as a function of their dimensionless variables $\nabla^*, \Delta^*, t^*, \mathbf{v}^*, P^*$ and $\mathbf{g}^*$ into the continuity and Navier-Stokes equations gives

$$\frac{R_i \omega_i}{d} \nabla^* \cdot \mathbf{v}^* = 0,$$

$$\frac{\nu R_i \omega_i}{d^2} \left(\frac{\partial \mathbf{v}^*}{\partial t^*} + (\nu R_i \omega_i d) \mathbf{v}^* \cdot \nabla^* \mathbf{v}^* - \Delta^* \mathbf{v}^* + \nabla^* P^* - \mathbf{g}^* \right) = 0.$$

Dividing the continuity equation by $\frac{R_i \omega_i}{d}$ dividing the N-S equation by $\frac{\nu R_i \omega_i}{d^2}$ results in the dimensionless equations:

$$\nabla^* \cdot \mathbf{v}^* = 0, \quad (\text{D.4})$$

$$\frac{\partial \mathbf{v}^*}{\partial t^*} + \text{Re}(\mathbf{v}^* \cdot \nabla^* \mathbf{v}^*) - \Delta^* \mathbf{v}^* + \nabla^* P^* - \mathbf{g}^* = 0. \quad (\text{D.5})$$

where $\text{Re} = \frac{R_i \omega_i d}{\nu}$ is the Reynold's number for the Couette geometry using the specified dimensionless variables.

The corresponding dimensionless boundary conditions are:

$$r^* = \frac{R_i}{d} = \frac{\eta}{1 - \eta}, \quad v_\theta^* = 1 \quad r^* = \frac{R_o}{d} = \frac{1}{1 - \eta}, \quad v_\theta^* = 0. \quad (\text{D.6})$$

Solving the Dimensionless Continuity and Navier Stokes Equations

Now, the dimensionless N-S and continuity equations will be solved in order to determine the laminar steady-state velocity profile for a Newtonian, incompressible fluid in the Couette device. (Note: For convenience, the $*$ -notation for dimensionless equations

has been dropped. All equations and boundary conditions presented from here on are dimensionless).

For the laminar flow of a Newtonian, incompressible fluid contained in the gap of a Couette device with only a rotating inner cylinder $v_z = 0$ as there is no driving force to cause axial flow. Furthermore, it is expected that solutions will only be a function of the radial coordinate r since there is circular symmetry around the cylinder (θ -direction) and translational symmetry along the cylinder (z -direction). Solving the cylindrical coordinate continuity equation

$$\nabla \cdot \mathbf{v} = \frac{1}{r} \frac{\partial}{\partial r} (rv_r) + \frac{1}{r} \frac{\partial}{\partial \theta} (v_\theta) + \frac{\partial}{\partial z} (v_z) = 0$$

determines that $v_r = C/r$. Since there can be no flow across the cylinder walls at R_i and R_o , the radial velocity at these positions is zero. Therefore, $C=0$ and $v_r = 0$ everywhere.

Using the postulates: $v_z = 0$, $v_r = 0$ and $v_\theta = v_\theta(r)$ the cylindrical coordinate N-S equation reduces to:

$$\frac{\text{Re } v_\theta^2}{r} = \frac{\partial P}{\partial r}.$$

Integrating gives

$$P(r) = \text{Re} \int \frac{v_\theta(r)^2}{r} dr$$

the pressure field which counters the “centrifugal force” of the rotational motion of the inner cylinder. This integral is not evaluated further as it not needed in the subsequent analysis.

The axial direction N-S equation reduces to:

$$0 = \frac{-\partial P}{\partial z} - \rho g$$

which is the hydrostatic effect, the effect of gravity on pressure. For the problem at hand, only the theta-direction equation of motion is needed, and this integral is not evaluated.

The azimuthal direction N-S equation simplifies to:

$$0 = \frac{d}{dr} \left[\frac{1}{r} \frac{d}{dr} (r v_\theta) \right]. \quad (\text{D. 7})$$

Separating and integrating twice shows that $v_\theta(r)$ has the form:

$$v_\theta(r) = Ar + \frac{B}{r}. \quad (\text{D. 8})$$

The constants A and B are determined by plugging the dimensionless boundary conditions (D.6) into (D.8):

$$A = -\frac{\eta(1-\eta)}{(1-\eta^2)}, \quad B = \frac{\eta}{(1-\eta)(1-\eta^2)}.$$

Then the dimensionless azimuthal velocity distribution is:

$$v_\theta(r) = \frac{\eta}{(1-\eta^2)} \left[-(1-\eta)r + \frac{1}{(1-\eta)r} \right]. \quad (\text{D. 9})$$

This is an exact steady state solution of the continuity and Navier-Stokes equations, known in fluid dynamics as the *Couette solution*. The steady state of a dynamical system occurs when there are no changes in time, and is referred to as an equilibrium state.

Linear Stability Analysis of the Couette Solution

Generally, we are concerned with the dynamics of nonlinear processes. Nonlinear differential equations are those which contain a term or terms that do not fulfill the linearity criteria, *i.e.* the criteria of addition and scalar multiplication. Very few nonlinear

differential equations can be treated analytically. However, information regarding the stability of a steady state can be determined by restricting attention to the region *very close* to the steady state and considering only the effect of infinitesimal disturbances through the methods of linear stability analysis [142].

The flow dynamics in the immediate neighborhood of an equilibrium state are determined by linearization. Through linearization methods, a differential linear operator $\mathcal{L}$ is determined. Defining the eigenvector $\mathbf{U}$ belonging to the eigenvalue $\lambda = \sigma + i\omega$, the eigenvalue problem is $\mathcal{L}\mathbf{U} = \lambda\mathbf{U}$. Solving for the eigenvalues determines the stability of an equilibrium state, in this case, of the Couette solution, to some infinitesimal disturbance. Specifically, the real component σ of eigenvalues determines stability. If all the real parts of the eigenvalues of $\mathcal{L}$ are negative, then the steady state solution is stable to the disturbance. If even one eigenvalue of $\mathcal{L}$ has a positive real component, then the steady state is unstable to the disturbance.

The process of linearizing nonlinear differential equations while subjecting them to an infinitesimal disturbance and solving the resulting eigenvalue problem is known as linear stability analysis (LSA). In the subsequent sections, linear stability analysis will be performed about the *Couette* equilibrium solution.

Linearizing the Continuity and Navier-Stokes Equations

In the Navier-Stokes equations, the convective term, $\mathbf{v} \cdot \nabla \mathbf{v}$, is nonlinear. Perturbation methods [143] can be used to linearize the convective term in order to investigate the local stability of the Couette solution.

Defining the velocity perturbation vector $\mathbf{U} = (u_r, u_\theta, u_z)$, the pressure perturbation variable q and the perturbation amplitude $\varepsilon \ll 1$, the perturbation series expansion of the velocity and pressure components of the Couette solution can be written as $\mathbf{v} = \mathbf{v}^0 + \varepsilon \mathbf{U}$ where $\mathbf{v}^0$ is the vector representation of the Couette solution and $Q = P + \varepsilon q$ $\mathbf{v}^0 = (v_r = 0, v_\theta(r), v_z = 0)$. Plugging the $\mathcal{O}(\varepsilon)$ expansions for $\mathbf{v}$ and Q into the dimensionless continuity (D.4) and Navier-Stokes (D.5) equations results are:

perturbed continuity equation

$$\frac{1}{r} \frac{\partial}{\partial r} [r(v_r + \varepsilon u_r)] + \frac{1}{r} \frac{\partial}{\partial \theta} (v_\theta + \varepsilon u_\theta) + \frac{\partial}{\partial z} (v_z + \varepsilon u_z) = 0,$$

perturbed radial direction Navier-Stokes equation

$$\begin{aligned} & \frac{\partial(v_r + \varepsilon u_r)}{\partial t} + \text{Re} \left[(v_r + \varepsilon u_r) \frac{\partial(v_r + \varepsilon u_r)}{\partial r} + \frac{(v_\theta + \varepsilon u_\theta)}{r} \frac{\partial(v_r + \varepsilon u_r)}{\partial \theta} \right. \\ & \quad \left. + (v_z + \varepsilon u_z) \frac{\partial(v_r + \varepsilon u_r)}{\partial z} - \frac{(v_\theta + \varepsilon u_\theta)^2}{r} \right] + \frac{\partial(P + \varepsilon q)}{\partial r} \\ & \quad - \frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r(v_r + \varepsilon u_r)) \right) - \frac{1}{r^2} \frac{\partial^2(v_r + \varepsilon u_r)}{\partial \theta^2} - \frac{\partial^2(v_r + \varepsilon u_r)}{\partial z^2} \\ & \quad + \frac{2}{r^2} \frac{\partial}{\partial \theta} (v_\theta + \varepsilon u_\theta) = 0, \end{aligned}$$

perturbed azimuthal direction Navier-Stokes equation

$$\begin{aligned}
& \frac{\partial(v_\theta + \varepsilon u_\theta)}{\partial t} + \text{Re} \left[(v_r + \varepsilon u_r) \frac{\partial(v_\theta + \varepsilon u_\theta)}{\partial r} + \frac{(v_\theta + \varepsilon u_\theta)}{r} \frac{\partial(v_\theta + \varepsilon u_\theta)}{\partial \theta} \right. \\
& \quad \left. + (v_z + \varepsilon u_z) \frac{\partial(v_\theta + \varepsilon u_\theta)}{\partial z} + \frac{(v_r + \varepsilon u_r)(v_\theta + \varepsilon u_\theta)}{r} \right] + \frac{1}{r} \frac{\partial(P + \varepsilon q)}{\partial \theta} \\
& \quad - \frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r(v_\theta + \varepsilon u_\theta)) \right) - \frac{1}{r^2} \frac{\partial^2(v_\theta + \varepsilon u_\theta)}{\partial \theta^2} - \frac{\partial^2(v_\theta + \varepsilon u_\theta)}{\partial z^2} \\
& \quad - \frac{2}{r^2} \frac{\partial}{\partial \theta} (v_r + \varepsilon u_r) = 0,
\end{aligned}$$

perturbed axial direction Navier-Stokes equation

$$\begin{aligned}
& \frac{\partial(v_z + \varepsilon u_z)}{\partial t} + \text{Re} \left[(v_r + \varepsilon u_r) \frac{\partial(v_z + \varepsilon u_z)}{\partial r} + \frac{(v_\theta + \varepsilon u_\theta)}{r} \frac{\partial(v_z + \varepsilon u_z)}{\partial \theta} \right. \\
& \quad \left. + (v_z + \varepsilon u_z) \frac{\partial(v_z + \varepsilon u_z)}{\partial z} \right] + \frac{\partial(P + \varepsilon q)}{\partial z} - \frac{1}{r} \frac{\partial}{\partial r} (r(v_z + \varepsilon u_z)) \\
& \quad - \frac{1}{r^2} \frac{\partial^2(v_z + \varepsilon u_z)}{\partial \theta^2} - \frac{\partial^2(v_z + \varepsilon u_z)}{\partial z^2} - g = 0.
\end{aligned}$$

Using $\mathbf{v}^0 = (v_r = 0, v_\theta(r), v_z = 0)$ and $\mathbf{U} = (u_r, u_\theta, u_z)$, and retaining only the terms that are $\mathcal{O}(\varepsilon)$ and dividing through by ε , the infinitesimally perturbed and linearized continuity and cylindrical N-S equations are:

linearized continuity equation

$$\nabla \cdot \mathbf{U} = \frac{1}{r} \frac{\partial}{\partial r} (r u_r) + \frac{1}{r} \frac{\partial u_\theta}{\partial \theta} + \frac{\partial u_z}{\partial z} = 0, \quad (\text{D. 10})$$

linearized radial direction Navier-Stokes equation

$$\frac{\partial u_r}{\partial t} + \text{Re} \left[\frac{v_\theta}{r} \frac{\partial u_r}{\partial \theta} - \frac{2v_\theta u_\theta}{r} \right] + \frac{\partial q}{\partial r} - \frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r u_r) \right) - \frac{1}{r^2} \frac{\partial^2 u_r}{\partial \theta^2} - \frac{\partial^2 u_r}{\partial z^2} = 0, \quad (\text{D.11})$$

linearized azimuthal direction Navier-Stokes equation

$$\begin{aligned} \frac{\partial u_\theta}{\partial t} + \text{Re} \left[u_r \frac{\partial v_\theta}{\partial r} + \frac{v_\theta}{r} \frac{\partial u_\theta}{\partial \theta} + \frac{u_r v_\theta}{r} \right] + \frac{1}{r} \frac{\partial q}{\partial \theta} - \frac{\partial}{\partial r} \left(\frac{1}{r} \frac{\partial}{\partial r} (r u_\theta) \right) - \frac{\partial^2 u_\theta}{\partial \theta^2} - \frac{\partial^2 u_\theta}{\partial z^2} \\ - \frac{2}{r^2} \frac{\partial u_r}{\partial \theta} = 0, \quad (\text{D.12}) \end{aligned}$$

linearized axial direction Navier-Stokes equation

$$\frac{\partial u_z}{\partial t} + \text{Re} \left[v_\theta \frac{\partial u_z}{\partial \theta} \right] + \frac{\partial q}{\partial z} - \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_z}{\partial r} \right) - \frac{1}{r^2} \frac{\partial^2 u_z}{\partial \theta^2} - \frac{\partial^2 u_z}{\partial z^2} = 0. \quad (\text{D.13})$$

The corresponding boundary conditions are:

$$\begin{aligned} \text{at } r = R_i, \quad v_\theta = R_i \Omega_i \text{ and } v_r = v_z = u_\theta = u_r = u_z = 0, \\ \text{at } r = R_o, \quad v_\theta = v_r = v_z = 0 \text{ and } u_\theta = u_r = u_z = 0. \quad (\text{D.14}) \end{aligned}$$

The Linearized Eigenvalue Problem

Assuming that the first unstable flow regime arising from an infinitesimal disturbance to the Couette solution is axisymmetric in θ , *i.e.* independent of θ , all the terms differentiated with respect to θ are dropped from equations (D.10)-(D.13). The axisymmetric assumption is valid for a Couette device with a stationary outer cylinder and for the transition to unstable Taylor vortex flow from the Couette equilibrium state, [144] which is the transition that was studied in the experiments presented in this thesis.

To proceed, it is necessary to make an educated guess as to the forms of $\mathbf{U}$ and q . Since equations (D.10)-(D.13) are constant coefficient with respect to t and z , exponential

solutions in t and z are expected, and we've assumed that the velocity vector $\mathbf{U}$ and pressure perturbation variable q have the form of a complex Fourier series [63, 142].

$$\begin{aligned} u_r &= \sum_{n \in \mathbb{Z}} u_{r_n}(r) e^{\lambda t} e^{i\alpha_n z} \\ u_\theta &= \sum_{n \in \mathbb{Z}} u_{\theta_n}(r) e^{\lambda t} e^{i\alpha_n z} \\ u_z &= \sum_{n \in \mathbb{Z}} u_{z_n}(r) e^{\lambda t} e^{i\alpha_n z} \\ q &= \sum_{n \in \mathbb{Z}} q_n e^{\lambda t} e^{i\alpha_n z}. \quad (\text{D.15}) \end{aligned}$$

where $\alpha_n = 2\pi n/h$ is the axial wave number and h is the height of the fluid column in the Couette device.

Plugging the Fourier series forms for u_r , u_θ , u_z and q (D.15) into equations (D.10)-(D.13) and then differentiating and dividing through by $e^{\lambda t} e^{i\alpha_n z}$ for the axisymmetric in θ assumption, the linearized equations (D.10)-(D.13) then become

Continuity equation:

$$\frac{1}{r} \frac{d}{dr} (r u_{r_n}(r)) + i\alpha_n u_{z_n}(r) = 0 \quad (\text{D.16})$$

Radial direction equation:

$$\frac{2Re v_\theta(r)}{r} u_{\theta_n}(r) - \frac{dq_n}{dr} + D u_{r_n}(r) = \lambda u_{r_n}(r) \quad (\text{D.17})$$

Azimuthal direction equation:

$$-Re \left[\frac{dv_\theta(r)}{dr} + \frac{v_\theta(r)}{r} \right] u_{r_n}(r) + D u_{\theta_n}(r) = \lambda u_{\theta_n}(r) \quad (\text{D.18})$$

Axial direction equation:

$$-i\alpha_n q_n + Du_{z_n}(r) + \frac{u_{z_n}(r)}{r^2} = \lambda u_{z_n}(r) \quad (\text{D.19})$$

Where the linear operator $D = \frac{1}{r} \frac{d}{dr} \left[r \frac{d}{dr} \right] - \alpha_n^2 - \frac{1}{r^2}$.

Now the aim is to reduce the number of equations that make up the eigenvalue problem. The continuity equation (D.16) can be used to eliminate $u_{z_n}(r)$ and combining α_n^2 times the radial equation (D.17) with $i\alpha_n d/dr$ of the axial equation (D.19) enables the simplification of equations (D.17) and (D.19) to one equation

$$\begin{aligned} \lambda \left[\frac{1}{r} \frac{d}{dr} \left[r \frac{d}{dr} (u_{r_n}(r)) \right] - \frac{u_{r_n}(r)}{r^2} - \alpha_n^2 u_{r_n}(r) \right] + \left[\frac{3}{r^4} - \alpha_n^2 \frac{2}{r^2} - \alpha_n^4 \right] u_{r_n}(r) \\ + \left[\frac{-3}{r^3} + \alpha_n^2 \frac{2}{r} \right] \frac{du_{r_n}(r)}{dr} + \left[\frac{3}{r^2} + 2\alpha_n^2 \right] \frac{d^2 u_{r_n}(r)}{dr^2} - \frac{2}{r} \frac{d^3 u_{r_n}(r)}{dr^3} \\ - \frac{d^4 u_{r_n}(r)}{dr^4} + \frac{2\alpha_n^2 Rev_\theta(r)}{r} = 0. \quad (\text{D.19}) \end{aligned}$$

Equation (D.18) can be used to eliminate $u_{r_n}(r)$ from (D.20). Then the eigenvalue problem has been reduced to a single equation, which written in terms of the differential operator D is [145]:

$$(\lambda - D)^2 Du_{\theta_n}(r) - \frac{4A\alpha_n^2 Re^2 v_\theta(r)}{r} u_{\theta_n}(r) = 0 \quad (\text{D.21})$$

where

$$A = -\frac{\eta(1-\eta)}{(1-\eta^2)}.$$

This eigenvalue problem (D.21) is 6th order with non-constant coefficients and in general must be solved numerically. Using some rough but clever approximations,

Roberts [146] was able to approximate (D.21) as a constant coefficient differential equation. Using $R_i=1$ and assuming a narrow gap d , $R_o=1+d$ and $2A \approx 1/d$. Continuing with the narrow gap approximations [145], $d/dr \sim 1/d$ is large whereas $r \sim 1$ so approximating the differential operator D as $Du_\theta = \frac{d^2 u_\theta}{dr^2} - \alpha^2 u_\theta$ is a justifiable simplification. Further simplification comes from replacing v_θ/r by its average value, $1/2$. Finally, assuming $u_\theta \propto \sin[\beta(r-1)]$, where $\beta = m\pi/d$ is the radial wave number, it is found that

$$-(\lambda + (\beta^2 + \alpha^2))^2 (\beta^2 + \alpha^2) + \frac{\alpha^2 \text{Re}^2}{d} = 0. \quad (\text{D.22})$$

Solving (D.22) for λ gives,

$$\lambda = -(\beta^2 + \alpha^2) \pm \frac{\alpha \text{Re}}{\sqrt{d(\beta^2 + \alpha^2)}}. \quad (\text{D.23})$$

Thus, rough estimates of the eigenvalues of perturbations to Couette flow as a function of the Reynolds number and axial and radial wave numbers can be made using (D.23).

At sufficiently high Reynolds number, the energy supplied to the gap fluid by the rotating inner cylinder overcomes the fluids' ability to dissipate that energy and the Taylor vortex flow instability results. Figure D.2 is a plot of the eigenvalues for varying axial and radial wave numbers α and β , respectively for $\text{Re}=80$. The eigenvalues shown in Fig. D.2. are mostly negative and these correspond to dynamic modes which decay due to the effects of viscous dissipation. For sufficiently large Reynolds number Re , the positive second term of (D.23) becomes large enough to overcome the negative first term in (D.23) and eigenvalues for several axial wave numbers $\alpha \geq 6$ become positive for the radial mode $m=1$. Thus, at such a Reynolds number the inertia caused by the rotating

inner cylinder dominates viscous energy dissipation and the Couette flow becomes unstable.

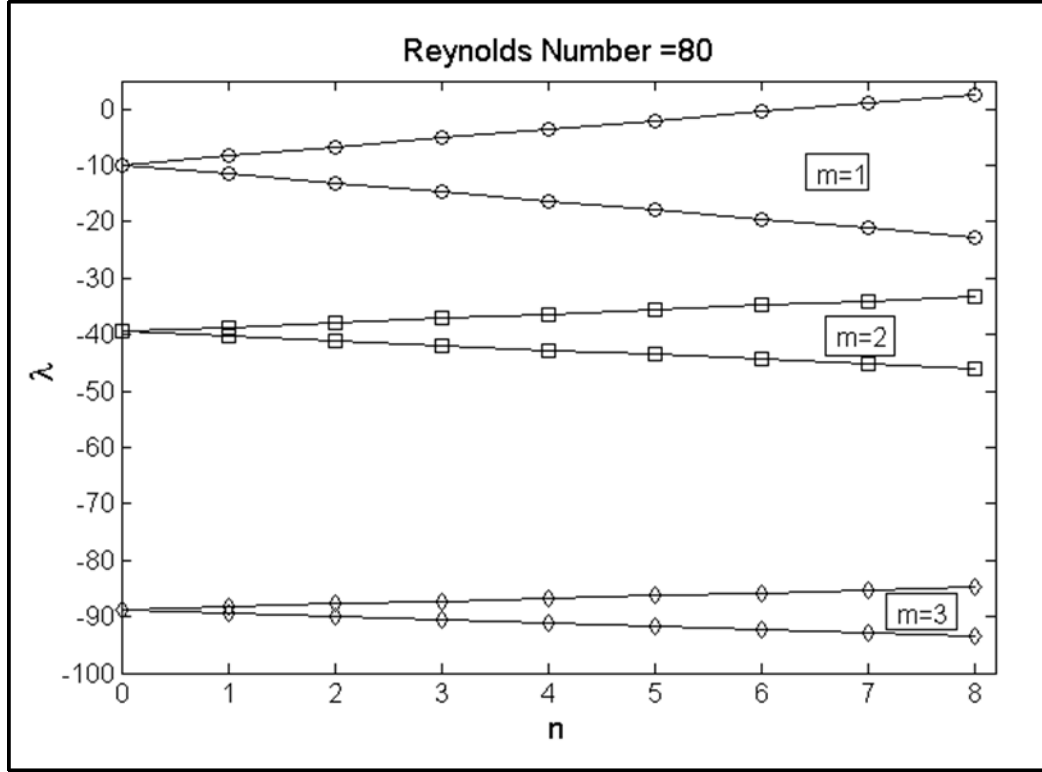


Figure D.2. Rough approximations of the eigenvalues of perturbations to Couette flow for $R_0=2$, ($d=1$) and $h=50$ at $Re=80$. The eigenvalues are plotted as a function of the axial n and radial m modes. Observe that the eigenvalue at the top of the plot has just gone unstable for the axial modes $n \geq 6$.

APPENDIX E

MATLAB CODE USED TO MAKE
VELOCITY VARIANCE MAPS

```

function[avg]=variancematrix(data)

% This m.file takes a matrix of velocity values from Prosopa (data) and
% calculates the average velocity. It plots the velocity map and
% calculates a variance value for each pixel and plots a corresponding
% variance map.

[m,n]=size(data);

avg=0;
c=0;
for i=1:512
    for k=1:128
        c=c+1;
        avg=avg+data(i,k);
    end
end

avg=avg/c
vel=zeros(m,n);
var=zeros(m,n);
for i=1:512
    for k=1:128
        vel(i,k)=data(i,k);
        var(i,k)=(avg-data(i,k))^2;
    end
end
figure
imagesc(vel)
figure
imagesc(var)
colorbar('EastOutside')

```

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