Super-resolution based image enhancement for magnetic resonance imaging

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**NANYANG
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**SUPER-RESOLUTION BASED IMAGE ENHANCEMENT
FOR MAGNETIC RESONANCE IMAGING**

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SCHOOL OF CHEMICAL AND BIOMEDICAL ENGINEERING

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**SUPER-RESOLUTION BASED RESOLUTION ENHANCEMENT OF
MR IMAGES**

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ABSTRACT

Magnetic Resonance Imaging (MRI) is a versatile modality which is widely used for anatomical and physiological imaging in applications including oncology, neuroimaging, and cardiac angiography - to name a few. However, due to patient motion, hardware limitations and constraints on acquisition time, anisotropic images are acquired, sacrificing detail in through-plane. Multiplane super-resolution is a post-processing technique that uses data from multiplane anisotropic acquisition and reconstructs higher resolution MR images. However, certain gaps exist in the application of super-resolution in the context of MRI and research presented in this thesis attempts to address some of the unexplored areas in terms of clinical applications as well as applicability of current state-of-art super-resolution frameworks.

The focus of this thesis is on the application of super-resolution for resolution improvement of MR images and development of a novel super-resolution framework that broadens its applicability to other MR applications. For this, three main studies were performed. In the first study, super-resolution was employed to enhance DWI resolution in the context of prostate cancer assessment. In this study, MRI data of 25 patients were acquired, isotropically reconstructed using super-resolution and analysed. Since it is unclear how through plane affects prostate cancer assessment, impact of through plane resolution improvement on prostate cancer diagnosis has been investigated. From the study, super-resolution reconstructions have been found to have increased SNR, sharpness and reduced volumetric error compared to anisotropic acquisitions. These isotropic super-

resolution reconstructions have been also found to have increased accuracy for detection of clinically significant cancers and improved visualization in through-plane. In the second study, super-resolution reconstructions of DWI and super-resolution reconstructions of T2WI were fused to improve delineation of tumor and visualization. In this study, it was found out that fusion of super-resolution reconstructions of DWI and T2WI improved tumor coverage and visualization in through and oblique planes, which could potentially benefit targeted biopsy. In the third study, a novel SR framework, **DIRSR**, was designed and developed in which deformable registration is added to registration framework, along with rigid registration. Most super-resolution implementations use rigid registration, making the SR framework prone to artifacts in applications with non-rigid deformation/motion including lungs and heart. Using DIRSR, isotropic volumes were reconstructed from lung data and were evaluated. Results show significant improvement in alignment of images compared to Rigid-Registration SR frameworks. Reconstructions from DIRSR were also found to have increased sharpness and reduced error compared to Rigid-Registration SR framework and super-resolution using pre-registered inputs. In summary, the studies presented in the thesis indicate that SR techniques can be beneficial for clinical assessment and diagnosis, including MR guided biopsy.

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LIST OF ABBREVIATIONS

ADC	Apparent diffusion coefficient
CT	Computed tomography
DCE-MRI	Dynamic contrast enhanced MRI
DIRSR	Deformable image registration based super-resolution
DWI	Diffusion weighted imaging
EPI	Echo planar imaging
FID	Free induction decay
FWHM	Full width at half maximum
GRAPPA	A parallel imaging technique
mpMRI	Multi-parametric magnetic resonance imaging
MRI	Magnetic resonance imaging
MRUSFB	Magnetic resonance – ultrasound fusion biopsy
PET	Positron emission tomography
PRSR	Super-resolution with pre-registered inputs
RF	Radio frequency
SNR	Signal to noise ratio
SR	Super-resolution
SRR	Super-resolution reconstruction
T1WI	T1 weighted imaging

T2WI	T2 weighted imaging
TE	Echo time
TI	Inversion time
TR	Repetition time

LIST OF PUBLICATIONS

1. Deformable registration based super-resolution for isotropic reconstruction of 4D MRI volumes (*under resubmission*)
2. Super-resolution reconstruction of diffusion weighted magnetic resonance images for enhancement of prostate cancer assessment and intervention (*under review*)
3. **G. S. Chilla**, C. H. Tan, C. Xu, and C. L. Poh, "Diffusion weighted magnetic resonance imaging and its recent trend—a survey," Quantitative imaging in medicine and surgery, vol. 5, p. 407, 2015.
4. Van Reeth E., **Soujanya G.**, Sdika M., Cervenansky F., Poh C.L. MisoSR: Medical Image Isotropic Super-Resolution Reconstruction. 2015 Jun.
5. Y. Peck, P. He, **G. S. V. Chilla**, C. L. Poh, and D.-A. Wang, "A preclinical evaluation of an autologous living hyaline-like cartilaginous graft for articular cartilage repair: a pilot study," Scientific reports, vol. 5, 2015.

CHAPTER 1 - INTRODUCTION

Medical diagnosis and treatment has progressed from the early days of medicine where physicians have relied on visual, auditory or tactile cues to more accurate means of estimation using a combination of physical examination and findings from new medical technologies. Medical imaging forms an important role in not only aiding diagnosis but also in treatment and prognosis of pathologies. Some of the medical imaging modalities frequently used in hospitals includes X-Ray radiography, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Ultrasound Imaging. These modalities use different techniques to reconstruct visual images of the patient tissues, thus helping physicians to interpret structural or functional abnormalities.

The most commonly used X-ray radiography and CT imaging use electromagnetic X-radiation, an electromagnetic radiation in the wavelength order of Angstroms (10^{-8} cm), for clinical imaging. Fig. 1-1 shows electromagnetic waves and their corresponding wavelength ranges.

Fig. 1-1 Electromagnetic waves spectrum

These modalities capture the X-ray attenuation by tissues and use this attenuation profile to generate images. X-ray radiography is used frequently for investigating bone fractures, skeletal system related pathologies, dental practice, fluoroscopy, breast cancer screening and detection (mammography), investigation of thoracic and abdominal infections. Although X-ray imaging is fast, is only limited to 2 dimensions. CT imaging is more advanced and can obtain cross-sectional visualization of tissues by capturing attenuation profile at each point in tissues. The images are then reconstructed using advanced image reconstruction techniques like filtered back-projection. CT is widely used in preventive medicine and for investigations in oncology, orthopedics, lung infections and heart diseases. Both X-ray and CT involve the use of ionizing X-ray. Although the clinical X-ray dosages are lower, cumulative effects of X-ray can increase the risk of cancers and is particularly risky with unborn fetus. Therefore, benefits of X-ray based examinations in pregnant woman to radiation have to be weighed carefully against hazards. Therefore, keeping radiation dose '*As Low As Reasonably Achievable*' (ALARA principle) is a practice mandate for radiation safety in X-ray and CT imaging [1].

PET is a nuclear imaging method, where imaging is achieved through intravenously injected radioactive materials which generate γ -rays that interact with tissues [2]. PET is used for investigation of metabolic activity in tissues but has lower anatomical detail compared to CT and MRI. To address this shortcoming, PET-CT and PET-MRI are becoming more popular than stand-alone PET. Ultrasound imaging is a comparatively safer imaging modality. Unlike CT or PET where X-rays or radioactive materials are used, ultrasound uses inaudible sound waves in the range of 20 kHz and

higher for image generation. Though ultrasound images suffer from high noise and low contrast, ultrasound is used widely for real-time soft tissue investigations in body systems including heart. Ultrasound is most popular in Obstetrics and Neonatology to assess and check fetal growth and any fetal abnormalities.

Magnetic resonance imaging (MRI) is a multi-dimensional imaging modality that does not involve the use of ionizing radiation [3]. MRI relies on the inherent spin property of protons, which are widely available in tissues in the form of water in intracellular and extracellular fluids. Under very strong static magnetic field, MRI manipulates these spins through electromagnetic pulse (referred to as RF pulse) and external magnetic fields for image generation. Since MRI does not use radiation, it is safer than modalities involving ionizing radiation. MRI can be preferred to CT to avoid radiation when same data could be obtained from MRI. A key advantage is that MRI is able to achieve excellent soft tissue contrast and is able to acquire images at any planes. Hence it is used for anatomical imaging as well as to image inherent phenomenon in tissues, which can be referred to as functional imaging (fMRI). MRI is widely used in cancer assessment and diagnosis. Typical applications include investigations in neuro-oncology, gastrointestinal cancer, breast cancer, liver cancer and any soft tissue tumors [4]. It is widely used in investigating musculoskeletal damages. Neuroimaging however, is one of the biggest applications of MRI in investigations of brain, from neural tractography to functional imaging. MRI angiography and Cardiac MRI are few other applications of MRI. Although MRI does not have any radiation effects, due to the nature of magnetic fields, it is prohibitive for patients with conductive or ferromagnetic implants,

RF activation based implants like pacemakers, and cochlear implants, or implants susceptible to motion due to magnetic field or RF.

Due to hardware limitations and constraint on acquisition times however, anisotropic MR images are routinely acquired even though higher resolution isotropic images are more useful for diagnosis. Further, resolution varies across different sequences due to difference in acquisition methods and parameters. Sequences like Diffusion weighted Imaging (DWI) suffer inherent low resolution due to their imaging acquisition method (Echo Planar Imaging - EPI) compared to anatomical sequences like T2 weighted imaging (usually acquired with spin-echo sequences). There is an on-going important need to increase the resolution of MR images which will subsequently benefit clinical practice.

To this end, the research in this thesis focuses on image resolution enhancement of MRI using super-resolution techniques. The subsequent section 1.1, in this Chapter will describe the basics of MRI including MR physics, basic imaging sequences, image reconstruction and image quality. Next section 1.2 presents an overview of super-resolution, various super-resolution algorithms and resolution improvement of MR images through super-resolution. Problem statements and the objectives of the research are presented at the end of the Chapter.

1.1 Magnetic Resonance Imaging (MRI)

1.1.1 MR Physics

In quantum mechanics, atomic nuclei have associated spins, which gives rise to nuclear magnetic moment. Under usual conditions, the spinning particles randomly align themselves, canceling out each other and hence the net magnetization would be zero. However, when a strong external magnetic field B_0 is applied, greater numbers of spins align themselves parallel to the applied field (lower energy state) and the rest align themselves antiparallel (high energy state) to the field. Individual spins will still be in precession at a frequency referred to as Larmor frequency (of angular frequency ω_0), which is proportional to the applied magnetic field B_0 .

$$\omega_0 = \gamma B_0 \quad (1.1)$$

In equation (1.1), γ is the gyromagnetic ratio (a constant). The net magnetization, M , will be in the direction parallel to the applied field and can be referred to as a sum of a longitudinal and a transverse component. Fig. 1-2 (a) shows randomly aligned spins, which upon application of field B_0 , align themselves parallel or anti-parallel to the field, as shown in Fig 1-2 (b). Fig. 1-2 (c) shows the precession (dotted line) of net magnetization vector M and its longitudinal and transverse components – M_z and M_{xy} .

Fig. 1-2 Net magnetization M , before and after application of magnetic field B_0 , its longitudinal (M_z) and transverse (M_{xy}) components.

When a 90° RF signal of resonant frequency is transmitted, energy is absorbed and some of the lower energy spins are excited to a higher energy state causing a decrease in the longitudinal component of net magnetization and an increase in the transverse component at the same time. This 90° RF signal flips the net magnetization vector into transverse (xy) plane and as the spins return to their normal state, they emit a RF signal (captured in direction perpendicular to the applied magnetic field B_0) whose signal decays overtime

with energy release. This emitted RF signal is termed as free induction decay (FID). Fig. 1-3 (a) shows the motion of net magnetization vector M after it is flipped into transverse plane, along the dotted line and Fig. 1-3 (b) shows corresponding free induction decay signal S , over time t .

Fig. 1-3 (a) Net Magnetization vector motion and (b) corresponding free induction decay (FID) signal S , over time t .

However, application of gradients for spatial encoding (explained in section 1.1.2) dampens the signal much faster. Since this is undesirable for image acquisition, a dephasing and quickly rephasing gradients are added to frequency encoding gradient which slows down the signal decay. This results in an echo signal, as shown in Fig. 1-4.

Fig. 1-4 Dephasing and Rephasing gradients to slow down echo signal decay

T1, T2 and T2 relaxation times:* Recovery of longitudinal magnetization to its equilibrium state is referred to as T1 or spin-lattice relaxation which is marked by exponential increase of longitudinal magnetization over time. The recovery of transverse magnetization to its equilibrium state is referred to as T2 or spin-spin relaxation and is marked by exponential decrease of transverse magnetization component. However, the measured decay signal is not only due to spin-spin interactions but also because of the imperfections in the applied magnetic field as well as magnetic susceptibilities, which is referred to as T2* relaxation.

The relationship between T2 and T2* is given as

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \gamma\Delta B \quad (1.2)$$

where ΔB refers to the magnetic field inhomogeneity across voxel. T1 and T2 relaxation values are different for different tissues. Fig. 1-5 shows T1 relaxation and T2/T2* decay plots.

Fig. 1-5 Relaxation plot for T1 recovery and T2* relaxation

In general, the signal intensity of received RF is proportional to $(e^{-\frac{TE}{T_2^*}})$ and $(1 - e^{-\frac{TR}{T_1}})$, where TE is echo time, TR is repetition time and M_0 is the maximum magnetization before applying RF pulse, and can be given by

$$S \propto M_0(e^{-\frac{TE}{T_2^*}})(1 - e^{-\frac{TR}{T_1}}) \quad (1.3)$$

Although T1 and T2 relaxation times for a tissue is fixed, the tissue contrast parameters TE and TR can be altered to highlight differences in longitudinal or transverse relaxation in images.

Tissue contrast parameters, T1 and T2 weighted imaging: On application of the 90° RF pulse (i.e., flip angle of 90°), the magnetization vector recovers with the release of FID signal. This experiment is repeated until enough data is obtained for reconstruction. The time between successive applications of this 90° RF pulse is called repetition time, TR. TE or echo time is the time between application of RF pulse and peak of echo signal, allowing for T1 recovery.

If a shorter TR and shorter TE values are chosen, differences in longitudinal relaxation rate between two tissues are captured in image contrast, which is called T1 weighted image. If longer TR and longer TE are chosen, differences in transverse decay between two tissues are captured, creating a T2 weighted image. In case of short TE and long TR however, most of the magnetization would recover yet higher signal is obtained. Acquired image therefore would have contrast differences from differences in proton density, making it a proton density weighted image.

In T1 weighted images, fat has higher signal intensity than water as the realignment of longitudinal magnetization of fat is faster compared that of water. In T2 weighted images however, fluids like water have loosely packed structure and hence take

more time for maximum signal decay than fat and therefore have higher signal intensity [3].

1.1.2 Imaging & Image reconstruction

MR imaging can be achieved through several pulse sequences, each of which has its own advantage depending on the application. Spin echo sequences and fast scanning techniques like gradient echo are the most commonly used basic pulse sequences in MRI.

Basic pulse sequences: Spin echo (SE) is a basic pulse technique for MRI scanning. After the application of 90° pulse, a FID is formed which declines rapidly due to the dephasing of faster and slower spins from spin-spin interactions and magnetic inhomogeneity. After a time τ , 180° pulse is applied to refocus the faster spins. The spins start rephasing and after time τ , spins will completely rephase giving maximum signal again. This total time 2τ (time from application of 90° pulse to 180° pulse and time taken from application of 180° pulse to maximum echo time) is called Echo time, TE, in a spin-echo sequence. Once the echo from first 180° pulse is received, multiple 180° pulses can be applied in same order. The number of echoes received is equal to number of 180° pulses applied in one TR and is referred to as Echo train length or ETL. Conventional spin echo sequences can have a train of 180° refocusing pulses resulting in FIDs of decreasing amplitudes for each refocusing pulse. In each TR (or each “shot”), one row of MR image space (called k-space) is recorded and this is repeated with spatial encoding until each row in k-space is filled. Fast spin echo (FSE) or turbo spin echo (TSE) is a faster imaging pulse sequence

based on same SE principle. However, instead of filling one row of data in one TR, FSE fills multiple rows in one TR.

In Inversion recovery (IR) sequences, instead of a 90° pulse followed by a 180° pulse, 180° pulse is followed up with a 90° pulse with a time difference of TI, inversion time, between them. Unlike traditional T1 and T2 curves, since the initial flipping angle is 180° , recovery curve for IR follows $M_0 \left(1 - 2e^{\frac{-t}{T_1}}\right)$, reaching a null point at $T_1 = 0.693T_1$. This null point is used in tissue suppression techniques like fat suppression.

In gradient echo (GRE), instead of a 90° pulse, pulses of smaller flip angles are employed which allow for smaller TR value and consequently shorter scan times. The FID decay is initially accelerated by gradient application and then is immediately reversed by application of same strength but opposite polarity gradient to reverse the decay. This realigns the dipoles to give out echo [5].

These basic imaging sequences - spin echo (a) gradient echo (b) and Inversion recovery (c) can be seen in Fig. 1-6.

Fig. 1-6 Pulse sequence diagrams for (a) spin-echo sequence (b) Gradient echo sequence and (c) Inversion recovery sequence. TE, TR and TI denote echo time, repetition time and inversion time respectively.

Although FID is received from the techniques, these FID signals lack spatial information. As a result, spatial encoding using gradients is required to retrieve the positional information.

Spatial Encoding: For spatial encoding, gradients are applied for phase and frequency discrimination, in addition to selective slice excitation. For slice excitation, slice selective gradient (GSS), a rectangular slice selection profile, is applied whose frequency is given by $f = \gamma B_0$. This ensures that spin frequency differs varies across the length of body or z axis. Stronger gradients and narrower RF bandwidths are useful in selecting thinner slices. Once the slice is selected, gradients are applied across one of the axis perpendicular to slice select direction to modify Larmor frequencies of column spins perpendicular to axis of application. This frequency data is collected along the axis of frequency encoding gradient application. Phase encoding gradients (PEG) are applied to the remaining axis, where phase differences arise in spins due to gradient application. This gives the spatial positioning of spins in each row. Fig. 1-7 shows frequency and phase encoding for MR imaging.

Fig. 1-7 Spatial encoding in MR imaging. After slice selection pulse is applied, frequency encoding is applied in x direction changing frequency in spins (f_a , f_b and f_c) in the direction of the applied gradient. Phase encoding is applied in y direction to differentiate phase of same frequency spins.

From the slice selection, frequency and phase encoding, we get frequency and phase information, which is then shifted to zero frequency from its carrier frequency and separated into real and imaginary components. These real and imaginary components are digitised in k-space. The phase and magnitude images can be reconstructed in spatial domain from Fourier transformation of the real and imaginary components of k-space.

Echo planar imaging: Echo planar imaging (EPI) is a fast imaging technique based on the conventional sequences, which requires high strength gradients for scanning. In EPI, a continuous phase encoding (blipped/non-blipped) is applied in a conventional sequence (SE, GRE or IR), which is read-out in k-space in a rectilinear fashion. In multi-shot EPI, k-space data acquisition is done in interleaved segments. Echo planar Imaging is used in measuring diffusion changes inside tissues, which is known as diffusion weighted imaging [6].

1.1.2.1 Diffusion weighted imaging: Diffusion weighted imaging is a functional imaging technique which uses fast imaging techniques for faster signal acquisition before the signal decays. For generating diffusion weighting in an image, the readout signal is made dependent on applied diffusion gradients, added to conventional MR sequences. Fig. 1-8 shows diffusion weighting addition to a spin-echo sequence. Two diffusion gradients G , one dephasing and one rephasing, are added to spin-echo sequence, symmetric to the 180° RF pulse.

Fig. 1-8 Diffusion weighting for a spin-echo sequence. The gradients applied in readout are of equal amplitude G and duration δ but have opposite polarity and are applied at a time separation of Δ .

The second gradient reverses the proton phase shift induced by the first gradient. However, if there is any movement in the proton position, the second gradient will not completely reverse the changes induced by the first gradient, resulting in signal attenuation. This signal loss is given by Stejskal-Tanner equation

$$S(b) = S_0 e^{-bD} \quad (1.4)$$

where $S(b)$ is the received signal for a gradient value (or *b-value* ' b '), S_0 is the signal strength without any diffusion weighting and D is diffusion or 'Apparent Diffusion Coefficient' (*ADC*). Gradient value or b is directly proportional to magnitude of applied gradient G , their duration δ and application time Δ , which can be varied. A typical DWI

procedure will have multiple scans at different b values. A b value of 0 indicates no diffusion application and is devoid of any diffusion weighting in the image. Higher b values indicate higher diffusion weighting in the image. However, DWI has T1 and T2 contrast in the image and hence ‘ADC maps’, devoid of T1 and T2 contrast are derived according to following equation.

$$\text{ADC} \cong \left[\ln \frac{S(b_2)}{S(b_1)} \right] \cdot \frac{1}{b_1 - b_2} \quad (1.5)$$

In conditions like tumours, cellularity increases thereby restricting diffusion. They show as hypo-intense signal on DWI. In conditions like stroke as well, DWI shows signal changes as early as 30 minutes as compared to 8 hours on anatomical T2 weighted imaging (T2WI). Hence DWI is primarily used for such applications. Some of the other DWI applications include investigation of cancer in tissues like liver, kidneys, prostate, musculoskeletal system etc. [7].

1.1.3 Image quality

In MRI, image quality is highly dependent on scan parameters. However, image quality parameters are correlated and optimization involves trade-offs in other parameters. Briefly discussed below are the important image quality parameters.

Resolution: An MRI image is defined with both its in-plane and through-plane resolution. While MRI in-plane resolution can be obtained by dividing the field of view (FOV) with the matrix size, through-plane resolution of a volume can be given by its slice thickness.

Although high resolution is desired for increased image clarity and interpretation, it will require an increase in scan time, decrease in pixel size or decrease in SNR. In anisotropic scans, in-plane resolution is higher and through-plane resolution is lower and is usually widely used because of lower scanning time and higher in-plane resolution, even at the cost of through-plane resolution. In isotropic scans, imaged volumes have the same in-plane and through-plane resolution. However, isotropic scans usually have lower maximum achievable resolution than that of anisotropic volumes. Achievable resolution in MRI is also limited by type of scanning sequence – an EPI based diffusion weighted image has a typical lower resolution than a turbo spin-echo based T2WI.

SNR: Larger voxels maximize the signal captured and hence have higher SNR compared to smaller voxels. However, this means resolution is sacrificed. If the resolution has to be maintained the same, then the number of averages for image generation have to be increased, which will result in increased scan time.

Image Contrast: Image contrast is guided by the choice of scan parameters TE, TR, TI and flip angles employed. These impact T1, T2 or proton density weighting in MR images. The choice of these variables should be such that signal difference between different tissues is maximized.

Artifacts: MR images are also susceptible to several artifacts depending on the choice of parameters as well as scanning sequence. Aliasing is one of the common wrap-around artifacts usually seen in MR images with smaller FOV. Motion related, whether patient

motion or pulsation, including cardiac and breathing can cause blur or ghosting in images. Magnetic susceptibility artifacts are common in EPI based DWI which introduce geometric distortion into images, especially near air-tissue interfaces. In addition, MR imaging is also susceptible to artifacts like truncation, zipper and chemical shifts. Artifacts in MRI can be reduced using motion restricting techniques or breath-hold sequences, use of different imaging sequences, changing image quality parameters or other hardware adjustments. Some post-processing techniques are also available to reduce certain artifacts.

Spatial resolution: Spatial resolution is defined as the smallest distances between two point sources which the imaging source can resolve. Any imaging modality is limited in terms of spatial resolution as below a certain separation, the imaging modality cannot resolve the point sources anymore. Although the resolution of individual modalities is dependent on the quality and other factors of the imaging system itself, the maximum resolution of any optical imaging system will be fundamentally limited by diffraction of light. An imaging system which cannot resolve point sources will blur the corresponding points on the image to a certain size and shape. This response of imaging system to a point source is called Point Spread Function (PSF) and two point sources which are separated by at least a distance greater than full width at half maximum (FWHM) of the PSF profile can be resolved [8]. Fig. 1-9 shows how the resolvability of point sources decreases as the distance between them decreases.

Fig. 1-9 FWHM and resolvability of point sources

Although, techniques like super-resolution microscopy are able to break the diffraction limit, these rely on innovative image capturing methods to do so and are not applicable in modalities like MRI, whose imaging techniques are different from that of optical microscopy. Although hardware improvements can be done, they are often expensive and are limited in scope. Therefore, post-processing methods are commonly used in such cases to improve the resolution.

Interpolation techniques are the most commonly used resolution improvement techniques for natural image processing. Traditional interpolation techniques like linear, bilinear, cubic or quadratic interpolation rely on guessing a high resolution voxel using a kernel from set of low resolution voxels. Some of the newer adaptive interpolation techniques rely on image features for interpolation. However, these interpolation techniques rely on available data in the image to ‘guess’ high resolution voxel and do not add any new information nor recover any lost frequency information. Traditional

interpolation methods might also lead to blurring and can also introduce artifacts. Given the diagnostic value of medical images, post processing technique like super-resolution adds more value compared to the interpolation techniques.

1.2 Super-resolution

Super-resolution (SR) is a resolution improvement technique which was first applied to natural images and in video processing [9-12]. It has been shown to improve resolution of images while maintaining good signal to noise ratio through different approaches. Super-resolution has since been used to improve resolution of natural images, videos and medical images [13-15]. Super-resolution techniques can be broadly classified into single-frame super-resolution and multi-frame super-resolution. Single-frame super-resolution is based on machine learning where the learning kernel is trained to ‘see’ fine details from a large collection of high resolution images and their corresponding low resolution observations. In single-frame super-resolution, once the kernel is trained well, high resolution image is predicted from single image. Single frame super-resolution requires a large training database to generate high resolution images. Super-resolution can also use multiple images of same scene with sub-pixel shifts between them for a denser sampling grid, which is referred to as multi-frame super-resolution [13]. Multi-frame super-resolution works well when a large database of high resolution and corresponding low resolution observations are not available. This research focuses on multi-frame super-resolution so that resolution of images can be improved from fewer acquisitions without having to acquire large amount of data. For the remainder of this thesis, the term ‘super-resolution’ will refer to multi-frame super-resolution.

During image acquisition, high resolution scene is degraded by imaging system, resulting in the acquired low resolution images. Imaging system introduces distortion, blur, noise, artifacts etc. and super-resolution aims to reverse this degradation process. In super-resolution image acquisition model, an ideal high-resolution image X undergoes deformation or warping G_k , blurring B_k and down-sampling D_k . Deformation generally consists of translation, rotation and other kinds of distortion and blur can be modelled through the point spread function, PSF. Corresponding low resolution images Y_k are obtained along with the added noise, V_k . Mathematically this can be represented by

$$Y_K = D_k B_k G_k X + V_k \quad (1.6)$$

Combining and indicating deformation, blurring and down-sampling operators by a single global transformation operator W_k , equation (1.6) becomes

$$Y_K = W_k X + V_k \quad (1.7)$$

Global transformation matrix W_k has very small singular values and as a result, equation (1.7) cannot be inverted directly. Therefore, it is regarded as an inverse problem and iterative error minimization algorithms are employed to reconstruct high resolution images. Fig. 1-10 shows generic image degradation model, which forms basis for super-resolution.

Fig. 1-10 Image degradation model for super-resolution framework

1.2.1 Super-resolution algorithms

There are a number of different super-resolution algorithms including back-projection, deterministic regularized approach, statistical regularized approach and projection onto convex sets.

Back-Projection: One of the simplest algorithms for iterative high resolution estimation is back-projection. In this method, an initial high resolution estimate is used to obtain set of corresponding low resolution images by simulating the image acquisition model. Then, corresponding error between the low resolution acquisitions and the low resolution simulation is calculated. The high resolution estimate is updated using the back-projection kernel h^{BP} and error term. The iterative process is continued until the error function is minimized, to get optimal solution. In equation (1.8), X^n is the high resolution observation in n^{th} iteration, N are the total number of inputs and $\check{Y}$ is the low resolution image obtained from simulation.

$$X^{n+1} = X^n + h^{BP} * \sum_{k=1}^N (Y_k - \check{Y}_k) \quad (1.8)$$

Although Back-Projection is the simplest iterative estimation method to implement, it can have non-unique solutions.

Projection onto Convex Sets (POCS): In POCS, solution set is constrained through multiple closed convex sets that satisfy specific properties. The image is contained in this intersection and the estimation of high resolution image is done using projectors P_i that project a point onto the closed convex sets. Unlike Back-Projection, this method can be used to incorporate a priori knowledge for image reconstruction. Equation (1.9) shows POCS principle in iterative estimation.

$$X^{n+1} = P_m P_{m-1} P_{m-2} \dots P_3 P_2 P_1 * X^n \quad (1.9)$$

Even though POCS can constrain solution by incorporating priors, the solution still can be non-unique.

Deterministic regularized approach: In regularized approaches, prior information can be incorporated through regularizer terms for constraining solution. This regularizer term $\mathcal{R}$, can be chosen depending on the nature of the expected output, if known. For example, a regularizer that penalizes high frequencies can be used, if the expected high resolution image output is expected to be smoother. These approaches try to minimize the error and regularizer terms, balanced by regularizer weights λ . The generic iterative estimation in deterministic approaches is given in equation (1.10).

$$X^{n+1} = X^n + \alpha [\sum_{k=1}^N W_k^T (|Y_k - \check{Y}_k|) - \lambda \mathcal{R}(X^n)] \quad (1.10)$$

In the above equation, α corresponds to the optimization approach parameters and W_k^T is the transpose of global transformation operator W_k . Assuming the chosen prior is a convex function, deterministic regularized approaches converge to a unique solution although they cannot model new noise priors.

Stochastic regularized approach: In stochastic regularization, statistical approaches like Bayesian formulations are used for high resolution image estimation. Maximum a posteriori methods try to maximize the probability of a high resolution image X using Bayes theorem, given its low resolution observations Y_k , as given in equation (1.11).

$$X = \operatorname{argmax}(\ln(P(Y_k/X)) + \ln(P(X))) \quad (1.11)$$

In equation (1.11) the first term is the likelihood term $P(Y_k/X)$, which can be modelled using a zero-mean Gaussian distribution model. The second term ($P(X)$) is the prior term, which can be modelled using priors that deem fit for the application. Stochastic regularization approaches are more robust in modelling noise.

1.2.2 Super-resolution in MRI

In MRI, the image acquisition is done in k-space, followed by reconstruction in image space. Therefore, traditional image space sub-pixel shifts in super-resolution translate to

linear phase modulation in k-space. Hence, unless the input images have inherent tissue motion or were acquired with FOV shift, addition of new frequencies in the in-plane is limited. Although several studies noted increase in image quality due to decrease in noise and subsequent increase in SNR, traditional sub-pixel shift super-resolution is limited in MRI due to the Fourier shifting property for MR images. Therefore, traditional super-resolution formulation based on sub-pixel shift in in-plane do not add extra/missing information in in-plane and hence do not improve MRI resolution [8, 15, 16]. However, super-resolution has been implemented in MRI either through machine learning based single-frame SR [17-19] or using multi-plane SR for through-plane resolution improvement [20-22].

1.3 Objectives of research

1.3.1 Problem definition

Although isotropic MR images are highly desirable in clinical settings, these are not generally acquired because of hardware limitations as well as image quality constraints. As voxel size reduces, noise in the voxel increases. Consequently, SNR reduces, which is undesirable. Higher resolution isotropic images also take longer time to acquire, causing patient discomfort which is likely to cause patient motion during the scan. This patient motion can introduce artifacts into the image. In some cases, acquiring a higher resolution isotropic image with same resolution as that of maximum achievable in-plane resolution of anisotropic image is impossible due to hardware constraints. Therefore, anisotropic images with higher in-plane resolution (but lower through-plane resolution) are usually acquired in clinical settings, at the cost of sacrificing detail in through-plane.

Although super-resolution is inherently limited in improving in-plane resolution, it has been successfully employed for through-plane resolution improvement [22]. Images with sub-pixel shifts in through-plane have been used for reconstructing MR images with higher resolution in through-plane. Super-resolution has been employed in resolution improvement of both morphological MR sequence images like T1 weighted imaging (T1WI), T2WI and also for resolution improvement of non-morphological MR sequence images including DWI [8, 15].

However, it is worth noting that even though super-resolution has been applied for resolution improvement of non-morphological sequences like DWI, so far it has been limited to brain imaging, that too for resolving fiber tracts or estimating diffusion tensors. Such resolution improvement in DWI/DTI in these cases is not geared towards clinical applicability. Hence it is unclear if super-resolution would be beneficial in clinical situations such as cancer diagnosis and assessment.

Additionally, current super-resolution frameworks are only applicable to MR applications with rigid motion. Multiplane SR uses MR images from different acquisition planes and assume rigid motion between inputs. As a result, it is mainly applicable to clinical applications in which organ motion is minimal or otherwise rigid. Resolution improvement for lung, cardiac or thoracic images which are affected by breathing or cardiac motion, requires inputs to have no deformable motion in between to achieve high quality SR reconstructed images. Currently, this requires careful selection of images such that the images acquired at different planes at the same cardiac or breathing phase to

reduce their differences. This is tedious and requires careful image acquisition. Although pre-registration before applying SR could help in aligning the images, pre-registration of inputs could also cause loss of information in the acquisitions while adding additional step to pre-processing.

To address these research gaps, several studies were carried out with regards to the applicability of super-resolution in prostate cancer assessment and intervention as well as to address deformable motion in inputs for super-resolution based enhancement.

For prostate cancer assessment, DWI is an essential component for detecting and localizing lesions along with T2WI for anatomical detail. DWI correlated with T2WI has shown to improve specificity of lesion detection. Increasingly, MRI-ultrasound guided fusion biopsy (MRUSFB) systems also use MR images for targeting lesions. Although DWI would be an ideal choice for lesion localization, segmentation is done on T2WI as DWI suffers from inherent low resolution. In this thesis, part of the research focuses on improving DWI resolution for cancer assessment and intervention. In one study, DWI was isotropically reconstructed using super-resolution and its impact on prostate cancer assessment was studied. Another major study introduces a novel application for super-resolution, which could benefit targeted biopsy system. Using super-resolution based resolution improvement of DWI and T2WI, avenues for prostate cancer intervention were explored.

In second part of this thesis, research focuses on addressing current limitation of SR framework in resolution improvement of MR applications with deformable motion. A new super-resolution framework, that incorporates deformable image registration is developed and evaluated on 4D TWIST lung MR images.

1.3.2 Research objectives

The objective of this research is to improve resolution of MR images using super-resolution post-processing techniques. The super-resolution framework is built to have optimized PSF model and optimized registration model for MR images.

The first part of research aims to improve clinical assessment and diagnosis of prostate cancer by improving resolution of DWI and T2WI. To this end, anisotropic DWI images are isotropically reconstructed using a SR technique and impact of through-plane resolution improvement on prostate cancer assessment is evaluated. Investigation to determine optimal slice thickness of anisotropic T2WI acquisitions, which could be reconstructed with similar or better image quality as that of a standard 3 mm T2WI acquisition, was also carried out. Finally, DWI and T2WI were fused using super-resolution to improve tumor delineation and visualization, which could potentially benefit MRI-Ultrasound guided fusion biopsy.

The second part of the study presents research done to address current limitation of using rigid-registration models for SR. To this end, a deformable registration based super-resolution framework – DIRSR has been developed and evaluated on 4D TWIST lung MR images.

Original Contributions:

- Studying impact of super-resolution based resolution improvement in prostate cancer assessment and diagnosis using MRI data of phantom and 25 patients MRI data.
- Investigation of optimal slice thickness for super-resolution reconstruction of T2WI using T2WI of phantom and patient.
- Fusion of super-resolution reconstructed DWI and T2WI to improve targeted biopsy.
- Development of a novel **Deformable Image Registration Super-Resolution (DIRSR)** framework for MR applications with deformable motion.
- Isotropic reconstruction of lung volumes from inputs of different breathing phases using DIRSR.

1.3.3 Thesis organization

This introductory chapter has given a brief overview of MR physics, imaging, image quality and clinical applications. Super-resolution framework and various approaches for super-resolution reconstruction are also discussed.

Chapter 2 briefly gives an overview and literature survey on super-resolution in MRI, specifically in diffusion weighted imaging as well as 4D lung MRI.

Chapter 3 will present research on impact of DWI resolution improvement on prostate cancer assessment.

Chapter 4 presents research carried out to investigate optimal slice thickness of a T2WI for isotropic reconstruction through super-resolution, which could be of similar or better quality than standard clinical anisotropic acquisition.

Chapter 5 presents fusion of DWI and T2WI for targeted MRI-Ultrasound fusion biopsy, following the results from Chapter 3 and Chapter 4.

Chapter 6 presents DIRSR and its implementation on synthetic and multiplane acquisition of 4D TWIST lung MR images.

Thesis ends with Chapter 7, which briefly reviews work done in this thesis and presents future work.

CHAPTER 2 – LITERATURE REVIEW¹

In Chapter 1, basics of MR imaging and super-resolution have been discussed. As mentioned, super-resolution in MRI is limited in in-plane unless under specific conditions which involve manipulation of acquisition parameters or imaging method. In this chapter, super-resolution in the context of MRI will be reviewed.

Super-resolution in MRI has been an area of interest as these post-processing techniques allow reconstruction of better quality and high resolution MR images than conventional techniques like interpolation. A comprehensive review on super-resolution in MRI has been done by Van Reeth et al [8] in 2012. In this review article, the advantages, limitations and various strategies employed for super-resolution in literature have been discussed. It is mentioned that multi-orientation inputs give better reconstruction quality compared to parallel plane inputs although more inputs are unlikely to give a better reconstruction compared to fewer inputs. Author also notes that choice of SR approach is application and data dependent and that no method significantly outperforms other method in all aspects. A previous review article [15] also mentions that spatial domain SR application was widely preferred over frequency domain SR application, following the approach from non-MR applications in the 90s. In this chapter, several SR approaches and models are discussed in the context of MRI. These include single-frame and multi-frame super-resolution, several SR approaches, modelling of PSF

¹ A review article has been published on DWI, challenges involved and recent advancements. Chilla GS, Tan CH, Xu C, Poh CL. Diffusion weighted magnetic resonance imaging and its recent trend—a survey. *Quantitative Imaging in Medicine and Surgery* 2015;5(3):407-422.

and registration and applications of super-resolution in diffusion weighted imaging. The last section deals with current state-of-art super-resolution in a broader sense as well as additional pre-processing steps that should be adopted for SR reconstructions of DWI.

2.1 Single-frame and multi-frame super-resolution

As evident from the name, single-frame super-resolution refers to resolution improvement using a single input and multi-frame super-resolution refers to resolution improvement using multiple inputs. Unlike in natural and medical 2D images, traditional super-resolution methods using sub-pixel shift do not improve in-plane resolution. This is because in-plane shifts in spatial domain is equivalent to linear phase modulation in k -space. Resolution improvement in MRI through such sub-pixel shifts is similar to zero padding although such methods are reported to have reconstructions with increased SNR or decreased noise [15, 23]. In [16], authors stated that although new information is added in in-plane direction, it is relatively small and is not enough to justify application of SR for in-plane resolution improvement. In this sense, traditional sub-pixel shift based super-resolution might not be able to compete with single-image based resolution improvement strategies like interpolation, for example. However, single-frame super-resolution, which uses only single plane acquisition, has been used for through-plane resolution improvement, often through the means of using image priors or by employing machine learning methods in literature. In [20], authors have used a multi-atlas patch based framework to increase through-plane resolution of cardiac MR images. Part of the acquisition data was used for building atlases, which was then used to enhance through-plane resolution using expectation-maximization framework. Single-frame SR involving

non-local patch based estimation was also used for image reconstruction in [24]. In Ref. [25], single-frame SR was used to improve resolution of DTI images using MAP estimation approach, by incorporating a spatial prior. In this study, authors have also accounted partial volume effect in the reconstruction and have reported reduction in mean error and increase in FA values through proposed method. SR was applied for DW images in [18], where authors used a non-local patch based framework and a spatial prior constraint for resolution improvement.

Deviating from the sub-pixel shifted scans for traditional super-resolution, multi-frame SR in MRI usually employs at least two orthogonal plane inputs for resolution improvement. The concept behind multi-frame SR has been demonstrated in Fig. 2-1. Two anisotropic voxels from images of orthogonal directions, V_1 and V_2 , would contribute in reconstructing a higher resolution voxel V_{HR} . Although several studies have also used non-orthogonal acquisitions in multi-frame SR, the principle behind resolution improvement remains the same. Typically, most articles on SR are multi-frame approaches, that use at least two inputs for resolution improvement.

Fig. 2-1 Resolution improvement in super-resolution using orthogonal voxels V1 and V2. New higher resolution voxel V_{HR} is indicated in common area between V1 and V2 in grey shade with continuous black border.

2.2 Super-resolution approaches

As mentioned in Chapter 1, choice of SR method is dependent on the application. MAP and regularized SR are the most frequently used SR approaches recently, although POCS and IBP have been used in several studies as well.

Iterative back projection (IBP) has introduced by Irani and Peleg and has been since used in several studies [23, 26, 27] on MRI brain data. However, IBP suffers from non-uniqueness and non-inclusivity for priors. Similarly, POCS has also been used in studies [28-30] for its superior results in presence of inconsistent or noisy data although it cannot guarantee uniqueness of solution for reproducibility. Alternatives like MAP formulation and regularized SR are usually preferred in this case.

MAP formulations are statistical regularized approaches which allow inclusion of prior knowledge. In [31] Markov random field priors are used to model priors and then

reconstruct high resolution cardiac images using inputs that have been pre-registered using a deformable registration method. Similar study using MAP approach has been done on tongue MR images where the inputs have been pre-registered using both rigid and deformable registration [32]. Variations of total variation based regularization and non-local means approach into MAP were also employed in studies [33] and [34]. In super-resolution for diffusion weighted and diffusion tensor imaging, MAP formulation and ML estimation has been used to reconstruct high resolution volumes in studies, [25] and [35].

Deterministic regularization SR approaches have also been used widely for MRI resolution improvement. In recent years, total variation regularizers and self-similarity based regularizers are gaining practice in deterministic regularization approaches. In [24], authors used non-local patch based deterministic regularization based on structural similarities for a single-frame SR. Similarity and patch based approaches are also adapted in studies [19, 36-38]. Trilateral variation of total variation regularizer has been used in studies [39] and [40]. In [41], Feng et al., authors used non-local spatial similarity from high resolution priors in the reconstruction of high resolution images using a deterministic regularized approach. In this study, authors have used low-rank regularizer and total variation regularizer.

2.3 PSF modelling

For natural image processing, the blur operator B_k is a 2 dimensional operator but for MRI, the operator has to be 3 dimensional due to slice selection component in image acquisition. PSF in through-plane can be defined using slice excitation profile, which

theoretically is rectangular function in image space or a Sinc profile in Fourier space. However, due to hardware limitations, truncated Sinc function is used for slice selection, resulting in a non-rectangular slice selection. However from the study by Greenspan et al [23], a Gaussian PSF profile delivers optimal result compared to a box (rectangular) PSF function. In another study by Yan and Wu [27], where the authors tested Gaussian blur function in several dimensions, an anisotropic Gaussian PSF function delivered good results. Following the studies, anisotropic Gaussian PSF profile is widely used for recent applications in SR for MRI.

2.4 Registration in super-resolution

For a multi-frame SR where inputs do not have patient motion in between, registration is not necessary for super-resolution. However, in case of patient motion, spatial alignment between inputs is necessary. For SR applications with orthogonal inputs or inputs at an angle, registration helps with inter-slice inconsistency and inherent partial volume effects. In most reported studies, either multi-frame SR inputs are either pre-registered using deformable registration or inputs are carefully chosen to have minimal deformable motion in between and reconstructed using rigid registration super-resolution framework. As rigid registration is computationally less expensive and easier to implement, these methods are more popular for resolution improvement. A study on 2D cardiac images [28] has used rigid registration methods and has reported in-plane resolution improvement. In Ref. [8], author states that in-plane resolution is possible in the presence of non-controlled motion like patient motion for example. However, in this study, a 3D dataset consisting of n images is employed and resolution of n^{th} 2D image is improved using $(n-1)^{\text{th}}$ and $(n+1)^{\text{th}}$

image. Since deformable motion between these 2D images is negligible, motion could be assumed to be rigid. However, for registration of 3D volumes which have deformable motion in between inputs, deformable registration is necessary.

2.4.1 Super-resolution in the presence of deformable motion

Although super-resolution has widely been employed to increase resolution of MR images, rigid registration has been the standard registration model in the SR framework for most studies. Deformable registration methods are primarily used to register images of same acquisition plane and usually are computationally more intensive than rigid registration methods. Also, optimization of rigid registration methods is easier compared to deformable registration methods as they could be readily modelled to converge based on values of image metrics such as mean square error (MSE) or mutual information (MI), to stop registration. In contrast, deformable registration methods like demons registration usually run for fixed number of iterations before stopping registration. As such, if number of iterations in demons registration is set to a very low value, registration could prematurely stop. Conversely, setting the number of iterations to a very large value would not help to stop registration, even if convergence is reached prior to reaching the fixed iteration number. In addition, deformable registration itself is an active research area and there are only few invertible deformable registration methods for SR iterative estimation. Hence, rigid registration models are usually favoured for super-resolution framework. However, there have been few studies in which authors have used deformable registration to compensate non-rigid motion between input images, usually as a pre-processing step.

In a study on neonatal brain images, Shi et al. [42] have used affine registration followed by nonlinear diffeomorphic demons registration to align MR images (T1 weighted and T2 weighted) as a pre-processing step before super-resolution reconstruction. In [32], authors have used a affine registration followed by deformable (diffeomorphic demons) registration model in the pre-processing step for high resolution reconstruction of MR tongue images. Rahman et al. [31] have used demons registration along with a rigid registration model for registering and then reconstructing isotropic cardiac images using SR. In another study, Heinrich et al. [43] used a multi-modal deformable registration to reconstruct high-resolution lung MRI images using high resolution CT image as a prior.

Even though deformable registration has been employed, in most cases, it is a pre-processing step, before iterative estimation in super-resolution. However, any errors in pre-registration could result in accumulation of registration errors in iterative estimation of SR and loss of information from the original acquisitions. This challenge is addressed in this thesis in Chapter 6.

2.5 Super-resolution in Diffusion weighted imaging

As mentioned in Chapter 1, DWI is an MR imaging technique capturing degree of diffusion in tissues. Although DWI finds application in many areas including prostate cancer assessment, detection of liver lesions etc., DW images are of lower resolution than morphological sequences like T2WI. This is because of its imaging acquisition sequence and protocol which limits its ability to generate high resolution and high quality images.

Hardware limitations (rate of gradient changes, gradient amplitude) as well as limitations in field homogeneity can result in DW image distortion (EPI distortion) and lower image quality such as lower resolution and SNR compared to traditional sequences like T2WI. A typical high resolution DW sequence at 3T is 1 mm x 1 mm at a through-plane resolution of 3 mm or has isotropic resolution of 2 mm x 2 mm x 2 mm. Given DW images are often used adjunct to much higher resolution images like T2 weighted images (typically 0.5 mm x 0.5 mm x 0.5 mm), lower resolution of DW images poses significant problem. Recent advancements and current state-of-art DWI have been reviewed and published in [44].

Given limitations in hardware improvements, post-processing methods like super-resolution has been employed in DWI (or diffusion tensor imaging, DTI) for resolution improvement in literature with successful results. However, most of the applications are in brain tractography and diffusion tensor estimation for brain imaging. In [45] Nedjati-Gilani et al., employed super-resolution based reconstruction to recover fiber configurations from volume fractions using information from neighbourhood voxels. In 2012, Scherrer et al. [35] reconstructed high resolution isotropic volumes by combining multiple anisotropic diffusion images. They employed probabilistic approach for reconstruction and reported higher contrast, PSNR and sharpness in SR reconstructed volumes. Similar study was done in [46] and [47] by Poot et al., with lower through-plane resolution images. In [25] and [18], authors have proposed a single frame image super-resolution. In the former study, a spatial prior was employed for reconstruction whereas in the latter study, a patch-based framework constrained with a non-diffusion image is used for high resolution reconstructions. A study in 2014 [48] utilized dependency between

gradients for high resolution super-resolution reconstruction. Single-frame SR has also been used in [49] using coupled low resolution and high resolution patches. Multi-orientation super-resolution, not limiting to orthogonal datasets, was used for high resolution image reconstruction in [50] whereas in [51], authors combined compressed sensing with super-resolution for high resolution DWI data reconstruction. In all the studies pertaining to tractography, authors reported higher quality reconstructions and higher metrics like increase in FA (fractional anisotropy) values through super-resolution reconstruction. So far, all the applications of SR in DWI have been restricted to brain tractography investigations.

2.6 Current state-of-art super-resolution framework

Current state-of-art super-resolution techniques might use different super-resolution approaches based on the application, although popular ones tend to be regularized SR, MAP formulation approaches and POCS in some cases. Gaussian PSF is being used for blur modelling while for deformation modelling, rigid registration methods including affine registration and six-degree rigid registration methods are used.

For research presented in this thesis on MRI resolution improvement, a deterministic regularized super-resolution method was chosen for its convergence speed, uniqueness of solution and computational ease. Given the assumption of additive zero-mean Gaussian noise, both regularized super-resolution and statistical (MAP) super-resolution will lead to similar performance as stated in [8]. Following [23] and [27], an anisotropic Gaussian PSF is used as blur operator for better image reconstruction quality.

For regularization, a trilateral total variation regularizer is employed for smoother reconstructions and sharper edges, following study in Ref. [40].

Although DWI SR reconstruction is largely based on the same super-resolution framework as that of traditional MRI reconstruction, it requires several additional steps. Given that EPI is more prone to EPI based distortion, DWI-SR usually involves an additional pre-processing step for distortion correction. This distortion correction can be carried out using additional ‘field map’ acquisitions, obtained from MRI scanner. Several tools like FSL (FMRIB Software Library)[52] or Fieldmap toolbox in SPM [53] can be used for distortion correction using field maps. Several authors have also proposed q-space alignment (diffusion gradient alignment) along with the usual k-space alignment. Fig. 2-2 shows a typical super-resolution framework for DWI resolution enhancement involving two gradient inputs DWI_{b1} and DWI_{b2} in three orthogonal planes. In the figure, C, S, A refer to the coronal, sagittal and axial plane images and C', S' and A' are the corresponding distortion corrected images. Usually, the last step in DWI super-resolution consists of generating ADC maps from the high resolution outputs, which is used for quantitative as well as qualitative analysis.

Fig. 2-2 A super-resolution framework for high resolution DW image reconstruction

2.7 Discussion

As stated in this chapter, super-resolution has been successfully employed to improve the resolution of MR images, including DWI images. Clinically DWI is widely employed for detection and localization of lesions apart from stroke detection. Although resolution improvement translated into clinical evaluation could result in improved patient care, currently there is a lack of assessment in this direction. It is unclear if resolution improvement through super-resolution would be beneficial for prostate cancer assessment and research presented in this thesis takes a step towards that direction. Research on DWI resolution, presented in chapters 3-6, evaluates super-resolution for prostate cancer assessment and aims to improve current method of targeting in MRI-ultrasound fusion biopsy. Additionally, current super-resolution frameworks for MRI do not allow applications requiring deformable registration. As diagnoses in thoracic applications regularly involve tissues which deform non-rigidly, having super-resolution framework which deal with deformable registration models are essential. To address this, DIRSR framework is developed and evaluated on lung MR images, which is presented in chapter 6. The main advantage of DIRSR would be its tolerance against non-rigid deformation in input images. In summation, this research would address some of the current limitations in super-resolution in the context of MR imaging.

CHAPTER 3 – SUPER-RESOLUTION RECONSTRUCTION OF DIFFUSION WEIGHTED IMAGES FOR PROSTATE CANCER ASSESSMENT

In the previous two chapters, super-resolution in the context of diffusion weighted imaging and review of corresponding literature have been explained. This chapter presents a study on the investigation of super-resolution based resolution improvement of DWI for prostate cancer assessment. Prostate cancer assessment and the role of DWI in it have also been discussed in the first part of this chapter. The aim of this study is to investigate if DWI reconstructed using a super-resolution (SR) technique improves prostate cancer lesion delineation and visualization. The next two sections cover experiment methodology, evaluation criteria and results of the study. The chapter ends with a discussion on the value addition from this study, limitations and further discussion. (A journal paper has been submitted on this research work²).

3.1 Research problem

In Chapter 2, several studies which employed super-resolution for resolution improvement of diffusion weighted images were discussed. Although DWI has many applications, the studies in literature have been done only in the context of tractography and diffusion tensor estimation. Given the importance of DWI based assessment in many other

² Chilla; GS, Tan; CH, Reeth; EV, ChandraMohan; S, Lee; CH, Poh CL. Super-resolution reconstruction of diffusion weighted magnetic resonance images for enhancement of prostate cancer assessment and intervention. Submitted to Magnetic Resonance Imaging in Aug 2016

applications, an investigation of DW image super-resolution for prostate cancer assessment has been carried out.

Prostate cancer, one of the most common types of cancer in elderly men, is one of the top five cancers causing majority of cancer related deaths in the world [54]. Prostate cancer assessment is a multi-modal assessment involving blood PSA (prostate-specific-antigen) level measurements and digital rectal examinations as the first step. Based on the outcome (elevated serum PSA levels and tissue irregularities from rectal examination), patient is ordered for multi-parametric MRI scanning (mpMRI) and trans-rectal ultrasound (TRUS)/MRI guided biopsy. Although mpMRI initially not a part of assessment process, it is now being widely adopted for better localization, staging and targeting compared to random ultrasound guided biopsies. This is because ultrasound has lower image detail which can result in under-sampling or missed lesions [55]. A scoring system, PI-RADS has also been developed for mpMRI, which aims to improve detection, localization and staging. mpMRI scanning and biopsy are followed by histopathologic analysis of samples for confirmation of cancers.

mpMRI consists of morphological T2 weighted imaging (T2WI) and physiological imaging like diffusion weighed imaging (DWI) and dynamic contrast imaging (DCE). Even though high resolution T2 weighted imaging gives better tissue contrast and resolution in prostate cancer imaging, they have sub-optimal sensitivity and specificity in differentiating between malignant and other non-malignant tissues [56, 57]. This is in relation to the anatomy of glandular region of prostate gland. According to McNeal's

zonal compartment system, prostate gland is broadly divided into central and peripheral gland. Central gland is further divided into transitional zone and peri-urethral tissue while peripheral gland is divided into central zone and peripheral zone [58]. On T2WI, cancerous lesions in peripheral zone of prostate gland appear as areas of low intensity and can be differentiated from surrounding normal tissue which has higher signal intensity. However, due to low intensities of central and transitional zones on T2WI, it is difficult to differentiate malignant lesions from normal tissue using T2WI alone. In addition, there might be many factors contributing to lower signal intensity in peripheral zone, such as inflammation, haemorrhage, post-radiation therapy fibrosis and hormone deprivation therapy, which might lead to wrong diagnosis [59]. To overcome this limitation, sequences like diffusion weighted MRI and dynamic contrast enhanced (DCE) MRI are added to anatomical imaging sequence like T2 weighted imaging, to improve localization of malignancy [58, 60]. PI-RADS scoring relies heavily on visual assessment of DWI, T2WI and DCE images. Although ADC maps from DWI can be useful in improving specificity [61], their reproducibility is difficult to achieve [62] to rely on quantitative values independently and hence either grayscale or colour coded ADC maps are employed for visual assessment. Although parametric maps from DCE might be used sometimes, DCE usefulness is secondary compared to T2WI and DWI in mpMRI. Hence DWI and T2WI remain crucial techniques for the assessment of cancers.

Although visual assessment of DWI helps in lesion detection, DWI sequences suffer from lower spatial resolution. This poses difficulty when DWI is correlated to T2WI as T2WI usually have higher spatial resolution. A typical standard clinical DWI

acquisition (in a 3T MRI scanner) would have a resolution of $1.4 \times 1.4 \times 3 \text{ mm}^3$ whereas the T2WI has a resolution of $0.47 \times 0.47 \times 3 \text{ mm}^3$. This lower resolution of DWI limits its ability to diagnose extra-prostatic extension of lesions and when DWI is used with T2WI for lesion localization, overestimation from partial volume averaging could happen, which results in error. Even if the in-plane resolution cannot be improved, isotropic voxels at highest possible resolution could help in better lesion delineation, minimizing lesion overestimation as well as reducing errors. However, scan times are approximately 3-4 minutes or longer to acquire a DWI in one plane for a volume of resolution $1.4 \times 1.4 \times 3 \text{ mm}^3$. To increase through-plane resolution of the image maintaining the same SNR, number of voxels in the image has to be increased, which in turn would increase the acquisition time. In patients where endo-rectal coils are employed, these increased scan times are significant and would be uncomfortable to patient, which prohibit acquisition of higher resolution DWI. Increased acquisition time can also result in likelihood of motion related artifacts and patient discomfort. In this case, post- processing techniques like super-resolution can be used for resolution improvement. Given the success of SR in brain applications of DWI/DTI, a SR technique has been employed to investigate impact of SR based isotropic reconstruction of DWI in multi-modal prostate cancer assessment.

3. 1. 1 Objective of the study

The aim of the study is to elucidate whether super-resolution reconstruction improves prostate cancer lesion delineation and visualization.

3. 2 Methodology and justification

In this section, the first part explains the experiment methodology of MRI scanning and super-resolution software framework that has been employed for investigation. The second part of this section explains the evaluation method.

3.2.1 Materials

MRI Scanning:

For MRI scanning, a multi-modality prostate phantom and 25 patients were scanned. Details of the phantom and patient data are given below.

Phantom Data: The phantom employed for this scan is a commercially available MR compatible - 053-MM multi-modality prostate training phantom, which is manufactured by CIRS [63]. This phantom, as can be seen in Fig. 3-1, mimics the internal structure of male pelvis. It is an 11.5 cm x 7.0 cm x 9.5 cm acrylic container which include simulations of prostate, rectal wall, seminal vesicles and urethra. The phantom prostate is made of zerdine with dimensions of 5 cm x 4.5 cm x 4 cm and a volume of 53cc approximately. Although this phantom does not replicate typical ADC values in prostate using DWI, it shows contrast between prostate and urethra, which could be used for evaluation.

Fig. 3-1 CIRS Model 053-MM prostate phantom

Patient Data: 25 male patients who have been suspected for prostate cancer from earlier diagnoses (higher PSA levels from routine blood test and abnormalities from routine biopsy) are recruited for MRI scanning. The mean age for the patients group is 66.8 ± 7.5 years. Inclusion criteria was willingness to provide informed consent and exclusion criteria was patients' unwillingness, excessive patient motion in localizer scans and any other contraindications to MRI. Institutional ethics approval was obtained from institutional review board (IRB) and written informed consent was obtained from patients, prior to the scans. Further diagnosis and histo-pathology of samples for these 25 patients revealed acinar adenocarcinoma in 22 patients and is atypical/cancer- negative in 3 patients.

MRI Scanning: Both phantom Imaging and patient scans were done on a 3T Siemens Trio Tim MRI scanner (Siemens Healthcare, Erlangen, Germany). For the phantom scanning, T2WI, DWI and corresponding field maps were acquired in axial and sagittal planes using parallel imaging with an acceleration factor of 2 (GRAPPA). For patients, 16 channel

pelvic phased array coil was used. DWI is obtained using echo planar imaging and at a resolution of DWI is 1.406 mm x 1.406 mm x 3 mm with acquisition matrix of 128 x 128. For phantom scan, DWI was obtained at b values 0 and 1000 and for patient scans, DWI was obtained at b-values of 50 and 1000. T2WI were obtained using turbo spin echo sequence at a resolution of 0.469 mm x 0.469 mm x 3 mm with acquisition matrix of 384 x 384 in-plane matrix size. Field of view (FOV) for DWI, T2WI and field maps is 180 mm. While the T2WI volumes in each plane took about 4 – 4 ½ minutes for scanning, DWI volumes were acquired in 3 – 3 1/2 minutes.

Super-resolution framework:

The super-resolution processing framework for diffusion weighted images is shown in Fig. 3-2. The framework (modified from a previous work [39]) consists of additional distortion correction step and generation of ADC maps. Distortion arises from echo planar imaging sequences and can be corrected using the acquired field maps. Using FSL (FMRIB Software Library v5.0) [52], DW images of all b-values are corrected for distortion correction individually in each plane and are referred to as distortion corrected DW images. Then distortion corrected DW images of same b-value in axial and sagittal planes are used as inputs for the super-resolution reconstruction algorithm [40] written in C++ using the ITK library [64].

Fig. 3-2 Super-resolution framework for diffusion weighted images. b1 and b2 (DWI_{b1} and DWI_{b2}) are b-values, A and S represent Axial and Sagittal DW images, ‘A’, ‘S’ refer to the distortion corrected DW images and SRR b1 and SRR b2 are the super-resolution reconstructions for b-values of b1 and b2 respectively.

For super-resolution reconstruction of high resolution images, a deterministic regularized model was employed. A trilateral total variation regularizer model is used for its edge preserving and de-noising properties [65]. This regularizer penalizes L1 norm of the image gradient magnitude and is given in equation (3.1). Although L2 norm is robust for Gaussian noise, noise model is unclear for acquired images (In MRI, noise model is usually Non-Gaussian [66]). Although other methods such as L1-L2 mixed norms are available, for the studies in this thesis, we used L1 norm, which is known to be robust to outliers and can preserve image details [67, 68].

$$\lambda \Gamma_{TTV}(X) = \sum_{\substack{l=-P \\ m=-P \\ n=0 \\ l+m+n \geq 0}}^P \alpha^{|m|+|n|+|l|} ||X - S_{xyz}^{lmn} X||_1 \quad (3.1) *$$

In equation (3.1), S_{xyz}^{lmn} is 3D shift operator, which shifts X by l , m and n pixels in x , y and z axes respectively for gradient calculation. α is the neighborhood weighing factor

and P is the regularizer kernel size. Equation (3.2) shows the iterative estimation for SR reconstruction.

$$\dot{X}_{n+1} = \dot{X}_n + \frac{\gamma(\beta^n - 1)}{N} \left[\sum_{k=1}^N G_k^T B_k^T D_k^T (|Y_k - \dot{Y}_k^n|) - \lambda \Gamma_{TTV}(\dot{X}) \right] \quad (3.2) *$$

*Adapted from [39, 69]

Equation (3.2) shows data fidelity term and regularization terms, which are balanced by a regularizer weight λ . Deformation operator D_k , is modelled using a rigid registration method with six degrees of freedom (translation and rotation). Mean square error is used as metric for registration. Blur B_k is modelled using a 3D anisotropic Gaussian point spread function (PSF). In equation (3.2), $\dot{X}_n$ and Y_k denote the current high resolution estimate and the low resolution input images. Parameters γ, β, N denote step size, decreasing rate and number of inputs respectively and $G_k^T B_k^T D_k^T$ denote the transpose of the degradation operators, G_k , B_k and D_k .

An initial high resolution estimate $\dot{X}_0$, is calculated by up-sampling the average of mutually registered input volumes. In each iteration n , data fidelity term and regularization terms are computed and added according to equation (3.2) to get the high resolution estimate for next iteration $\dot{X}_{n+1}$. This iterative process is repeated until optimal solution is reached. Once the high resolution estimate of DWI for both b-values is obtained, ADC maps are generated using Stejskal-Tanner equation [6] in MATLAB [70].

$$D = \frac{1}{(b_2 - b_1)} (\ln S_1 - \ln S_2) \quad (3.3)$$

In equation (3.3), D is the apparent diffusion coefficient, and S_1 and S_2 are the intensities of DWI of b-values b_1 and b_2 at same spatial position.

Convergence criterion for runs was set at a tolerance of 0.01 and a maximum iterative runs of 15. Typical parameter values for α , β and γ are 0.75, 0.99 and 0.9 respectively. Regularization weight λ , was chosen based on visual analysis of volumes reconstructed with varying weights. The reconstructed DWI and ADC maps have isotropic resolution of 1.406 mm x 1.406 mm x 1.406 mm and enclose the common area between axial and sagittal inputs.

3.2.1 Evaluation

SR reconstructed images were evaluated visually, qualitatively and quantitatively. Visual evaluation from DWI and ADC colour maps intends to show improvement in through-plane and oblique planes. For visuals in oblique plane, anisotropic DWI volumes/ADC maps and SR reconstructed DWI volumes/ADC maps were rotated at an arbitrary plane of 30°, 60°, 90° around z, y and x axes respectively, as shown in Fig. 3-3. Phantom and example patient reconstructed images are shown in three orthogonal planes.

Fig. 3-3 Rotation plane for oblique visuals

Phantom Data Quantitative Evaluation: For anisotropic acquisitions and SR reconstructions, SNR and edge thickness were calculated in regular plane (axial) as well as in the other two orthogonal projections individually. Phantom prostate is manually segmented on both anisotropic acquisitions and SR reconstructions using ITK-SNAP [71]. Since the volume of prostate phantom is known to be 53cc, the difference in volume of prostate phantom from anisotropic acquisitions and SR reconstructions segmentations is calculated.

Patient Data Qualitative evaluation: Anisotropic acquisitions and SR reconstructions of patient data are evaluated through a ranking procedure. Three experienced radiologists (experience of 13, 3 and 2 years) evaluated the anisotropic acquisitions and SR reconstructions in axial plane (reconstruction plane) and two other orthogonal projections. Lesion visibility on DWI/ADC maps is ranked on a scale of 1-5 where 1 indicates lack of lesion visibility to a 5 indicating excellent structural outline and identifiability. This score given individually by three reviewers is averaged to get final score for the anisotropic

acquisitions and SR reconstructions for each patient in each plane. Higher final score for SR reconstruction indicates that reviewers prefer SR volume for its lesion visibility detail whereas higher score for anisotropic acquisition indicates that anisotropic acquisitions are preferred for that patient. If the final score for both volumes is equal, it is interpreted that there is no preferred volume (anisotropic acquisitions and SR reconstruction score is equal) for that patient. For second part of ranking, reviewers look for and indicate suspicious tumor sites that can be seen in one volume (SR reconstruction/regular acquisition) but are not observed on the other (anisotropic acquisition/ SR reconstruction). The suspicious sites indicated by reviewer, if any, are compared to corresponding histopathology, which is not yet revealed to the reviewer. This is to investigate if additional details from through-plane improvement in SR reconstructions improve lesion detection/visibility on DWI since DWI might not show all lesions in anisotropic volumes. In the third part of ranking, histopathology is revealed and the reviewer is asked to choose a volume (anisotropic acquisition/SR reconstruction) that provides more details to examine the lesion, provided that the lesion is caught on DWI/ADC. The reviewer can also indicate no difference if both volumes give same amount of detail for lesion examination.

3. 3 Results

A. Phantom data:

Visuals: From the SR reconstructions of phantom data, improvement in through-plane resolution can be noticed. Fig. 3-4 (a) shows axial plane and its orthogonal projections for anisotropic acquisitions (Acq-DWI) and SR reconstructions (SRR-DWI) at a b-value of 0.

In Fig. 3-4 (b), oblique planes of the volumes are shown, after a rotation of 30°, 60°, 90° around z, y and x axes respectively. In Fig. 3-4 (a) and Fig. 3-4 (b), first row shows the axial plane and the second and third rows show orthogonal projections in sagittal and coronal plane. The projections in sagittal and coronal plane of anisotropic acquisition are linearly interpolated for comparison with SR reconstruction. Improvement in through plane resolution as well as in oblique plane from isotropic reconstruction through SR can be noticed from the figures.

Fig. 3-4 Anisotropic acquisition (Acq-DWI) and SR reconstruction (SRR-DWI) of phantom DWI data in orthogonal planes (a) and in oblique planes (b). First row shows the axial plane and the second and third rows show orthogonal projections in sagittal and coronal plane. Slice positions may vary by $\pm 0.7\text{mm}$.

In Fig. 3-5, resolution improvement can be noticed at a slice where the phantom urethra leaves prostate. The separation, indicated by arrows, can be clearly observed in coronal plane of SR reconstruction whereas in anisotropic acquisition, separation is blurred. From the figure, it can be seen that SR reconstructions are sharper in through-plane compared to the anisotropic acquisitions.

Fig. 3-5 Separation of urethra from phantom prostate in last slice, indicated by arrows. First column shows the axial plane and the second and third columns show orthogonal projections in sagittal and coronal plane. Slice positions may vary by $\pm 0.7\text{mm}$.

Quantitative Evaluation:

SNR: Signal to Noise ratio (SNR) results can be seen in Fig. 3-6. Average SNR for SR reconstructions is significantly higher than regular acquisitions in in-plane (XY plane) as well as through-plane (YZ and XZ planes) for phantom. Statistical tests (paired t-test)

indicates that average SNR for SR reconstructions is significantly higher in XY, YZ and XZ planes (p-value of less than 0.0001, 0.0157 and 0.0016 respectively).

Fig. 3-6 Average SNR for anisotropic acquisitions (Acq-DWI) and SR reconstructions (SRR-DWI) in XY (axial), YZ (Sagittal) and XZ (coronal) planes.

Edge sharpness: Results from the edge length evaluation of phantom can be seen in Fig. 3-7 Sharper edge transitions (lower edge lengths) were observed for SR reconstructions than for regular acquisitions in in-plane as well as through-plane. For SR reconstructions, edge width difference is not significant in XY plane (p-value of 0.1326) but is extremely significant in XY and YZ planes (p-value of less than 0.0001).

Fig. 3-7 Average edge length in pixels of length 1.406 mm for anisotropic acquisitions (Acq-DWI) and SR reconstructions (SRR-DWI) in XY (axial), YZ (Sagittal) and XZ (coronal) planes.

Volume from segmentation of phantom prostate: From the manual segmentation of phantom prostate in anisotropic acquisitions and SR reconstructions, the error reduced to 1.3% in SR reconstructions compared to 6.6% in anisotropic acquisitions. The volume from SR reconstructions is 52.3 cc and volume from anisotropic acquisitions is 49.5 cc compared to the actual volume of 53cc approximately, indicating better volumetric approximation from SR reconstructions.

B. Patient data:

Visuals: From the visual interpretation of DWI and ADC colour maps of 25 patients' data, it is evident that SR reconstructions offer more detail in through-plane than anisotropic acquisitions.

Fig. 3-8 shows an example of patient data from anisotropic acquisitions (top row) and SR reconstructions (bottom row) in three orthogonal planes (a), (b) and (c). In the

figure, DWI (b-value of 50) are shown in grayscale whereas corresponding ADC maps are shown in colour, based on quantitative ADC values. Histo-pathology for this patient indicates acinar adenocarcinoma in mid-gland and base as well as prostatic intraepithelial neoplasia in left apex. Although quantitative values of ADC maps are not independently relied for prostate cancer diagnosis, colour maps in Fig. 3-8 show added detail especially in through-plane.

Fig. 3-8 DWI (b50) and ADC colour maps of anisotropic acquisition (top row) and SR reconstruction (bottom row) for patient 22. (a), (b) and (c) show DWI and ADC maps in axial, sagittal and coronal planes respectively.

In Fig. 3-9, oblique visuals of the same patient, when rotated 30°, 60°, 90° around z, y and x axes respectively, can be seen.

Fig. 3-9 DWI (b50) and ADC colour maps of anisotropic acquisition (top row) and SR reconstruction (bottom row), rotated at 30°, 60° and 90° in z, y and x axes, for patient 22. (a), (b) and (c) show DWI and ADC maps in axial, sagittal and coronal planes respectively.

3D model from segmentation: 3D Visualization of prostate gland (from segmentation) can be seen in Fig. 3-10. From the surface model shown in Fig. 3-10, although the

segmentation from regular acquisition is smoother, SR reconstructed volumes offer more information and details as there are more closely spaced slices available for segmentation. This continuity in SR reconstructed volumes gives better delineation of anatomical structures and lesions in three planes.

Fig. 3-10 Surface model of prostate gland from patient 21 using segmentation from ADC maps of regular acquisition (a) and super-resolution reconstructed ADC map (b) along two different planes.

Ranking:

As stated, patient data is ranked on lesion visibility, presence of suspicious sites on one volume (anisotropic acquisitions/SR reconstructions) that cannot be seen on the other (SR reconstructions/ anisotropic acquisitions) and volume preference for examination of lesion detail, once histopathology is revealed.

From lesion visibility rankings, SR reconstructed volumes and anisotropic acquisitions did not significantly differ. Difference in lesion visibility scores of volumes in XY, YZ and XZ planes indicated a p-value of 0.614, 0.771 and 0.146 respectively. This means that the lesion visibility difference/improvement is statistically not significant at $p \geq 0.05$.

Reviewers did notice suspicious sites on one volume that were not noticeable on the other. Given the DWI interpretation is largely visual and based on signal intensities, this was observed for both SR reconstructions and anisotropic acquisitions. In 3 cases, interpretation from SR reconstructions formed complete histo-pathological diagnosis which was not observed on anisotropic acquisitions. In contrast, anisotropic acquisition contributed to complete histo-pathological diagnosis in 1 case. In 2 different cases each, both SR reconstructions and anisotropic acquisitions contributed to part of histo-pathological diagnosis. Similarly, in 2 cases, both volumes contributed to complete false positives. However, anisotropic acquisitions also contributed to partial false positives in 2 cases. This translates to a sensitivity and specificity of 25% and 86.84% from interpretations of SR reconstructions and a sensitivity and specificity of 18.75% and 84.21% regular acquisitions respectively, excluding cancers that were shown on both volumes. This is when clinically non-significant cancers (Gleason score 3+3 or less) in sextants are excluded. Including clinically non-significant cancers, sensitivity and specificity are 30%, 91.18% and 20%, 85.29% for SR reconstructions and regular acquisitions respectively, not including tumor sites that are visible on both volumes. The complete list of true positives and false positives can be seen in in Table 3-1, with

corresponding histo-pathology for patient. Table 3-2 summarizes sensitivity, specificity and accuracy.

Table 3-1. True positive and false positive cases seen in regular acquisitions and SR reconstructed ADC/DWI. In all these cases, lesions were seen on one volume (regular/SR reconstructions) but not on the other (SR reconstructions /regular acquisitions), for the same patient.

Patient ID	Suspicious sites on regular acquisitions	Suspicious sites on SR reconstructions	Histo-pathology
3	Left apex	Left base	Left base atypical
8	-	Base	Left apex
10	Left/Right mid and base	-	Right mid-gland. left apex
11	Right apex	-	Right mid, Right base
15	-	Right mid, Right apex	Right apex, mid; *nodule in right apex
18	Right base; Left base	Right apex	Right All, Left apex
20	-	Left mid, left apex	Left mid, left apex
21	Right apex	-	Right apex
22	Left mid	Left base	Right mid-gland, right base, left mid-gland, left base; Prostatic intraepithelial neoplasia in left apex;
25	-	Right Base	Right base, left base

Table 3-2. Summary of True positive and false positive cases seen in regular acquisitions and SR reconstructed ADC/DW and corresponding sensitivity, specificity and accuracy values.

	Regular acquisitions	SR reconstructions
True positives	04 (03 significant)	06 (04 significant)
True negatives	29 (32 significant)	31 (33 significant)
False positives	05 (06 significant)	03 (05 significant)
False negatives	16 (13 significant)	14 (12 significant)
Sensitivity	20.00% (18.75%)	30.00% (25.00%)
Specificity	85.29% (84.21%)	91.18% (86.84%)
Positive predictive value	44.44% (33.33%)	66.67% (44.44%)
Negative predictive value	64.44% (71.11%)	68.89% (73.33%)
Total accuracy	61.11% (64.82%)	68.52% (68.52%)

In third part of the ranking, reviewers stated preference for the volume that gave more details to examine the lesions on DWI volumes, once histo-pathology was revealed. From the results, at least 2 of 3 reviewers felt that SR reconstructions offered more details to examine the lesion in 9 cases compared to only 3 cases in regular acquisitions, of which one case was cancer negative but had atypical left base. In the remaining cases, histo-pathology from 3 patients was cancer-negative while in the rest of the cases, there was no preference between SR reconstructions and regular acquisitions or DWI showed no visible tumour.

3.4 Discussion

In literature, super-resolution has been used for through plane resolution improvement of MRI. However, in the context of DWI, it has been only limited to tractography and tensor estimation applications so far. In this study, through-plane resolution improvement in the context of prostate cancer assessment has been investigated.

High resolution isotropic images have the advantage of continuity and therefore enable more accurate delineation of anatomical structures and lesions. However, the current highest isotropic resolution possible for DWI is 2 mm x 2mm x 2mm, which is lower than highest resolution possible for anisotropic scans (between 1.2 mm – 1.5 mm depending on scanner). If isotropic DWI images of 1.406 mm x 1.406 mm x 1.406 mm were to be acquired through scanner maintaining the same SNR, it would take 15 minutes of continuous scanning without any patient motion. In practice, it is difficult to scan for longer time without any patient motion or patient discomfort. For this study, it was not possible to acquire an isotropic volume of this resolution because of scanner limitations. However, with super-resolution, two individual anisotropic scans amounting to less than 4 minutes each can be used to reconstruct isotropic images. Thus super-resolution has the advantage of being able to generate isotropic volumes without going through longer scanning time.

It is important to note that although DWI is one of the crucial techniques of mpMRI in prostate cancer assessment, all lesions might not be captured on DWI. Therefore, PI-RADS scoring approach is used to increase detection and localization.

Current prostate cancer guidelines recommend multi-parametric MRI for detection and PI-RADS as accepted risk stratification method by MRI [72]. Results from patient data ranking suggested that DWI SR reconstructions showed lower false positives compared to that of regular acquisitions and offered much more detail in lesion examination than that of regular acquisitions. This could potentially impact DWI interpretation in multi-modal prostate cancer assessment. Phantom data evaluation suggested better SNR and sharper edge transitions in SR reconstructed volumes, which could benefit delineation of lesions positively. As acquisition of isotropic phantom volumes is not possible, comparison of metrics (SNR, Edge sharpness or other metrics such as MSE) with ground truth could not be carried out. Volumetric evaluation also showed much smaller error when compared to anisotropic acquisitions, suggesting that SR might be helpful in determining lesion boundaries with smaller error in through-plane. This could impact MRI fusion based percutaneous ultrasound guided biopsies [73], which is presented in Chapter 5.

In brain imaging studies, EPI distortion is quite large and hence it is necessary to correct brain DWI/DTI images for EPI distortion before they can be utilized. However, EPI distortion is low in prostate DWI and hence for clinical purposes, distortion correction might not always be employed. For research, analysis and further processing (including ADC map generation) though, distortion correction has to be carried out. This is because EPI distortion is different in different plane acquisitions and hence for multiplane SR reconstructions, it is important for different plane inputs to be consistent. Additionally, for ADC map generation, although two b-values (one high and one low) are required, it might be worth noting that in some cases ADC maps are generated using more

than 2 b-value DW images. In this study, DWI were acquired at only two b-values and hence to maintain consistency with scanner generated ADC maps (which were generated using two b-values), ADC maps of super-resolution reconstructions are also generated using two b-value DW reconstructions. Provided these are taken into account, super-resolution framework used for this study can be generalized for other body DWI applications.

However, there are some limitations for the study. As stated in previous chapters, super-resolution in MRI does not improve in-plane resolution and hence, there is no improvement in DWI correlation with T2WI in in-plane. In addition, considering that DW images do not always show lesions and thresholding based on quantitative ADC values is still under research, this study on 25 patients would not be conclusive enough to generalize it to a large cohort. Also, EPI sequences suffer from distortion, which can be seen from phantom scans in Fig. 3-4 and Fig. 3-5. Although distortion correction techniques can correct smaller distortion artifacts, larger distortion artifacts, as seen from phantom scans, can still transition into the SR reconstructions, affecting their quality.

Nonetheless, from the results of the study, through-plane resolution improvement can positively influence prostate cancer assessment and improvements in DWI Imaging will further enhance staging of significant disease. This study can be considered as a baseline to compare future developments of SR model in DWI, for prostate cancer assessment.

3.5 Chapter summary

From results of resolution improvement of phantom DWI data, super-resolution reconstructions showed improved visualization, increased SNR, sharpness and reduced volumetric error compared to anisotropic acquisitions. This translates to reduced error in volumetric analysis of tumour, if lesion were to be segmented on super-resolution reconstructed DWI. In addition, from the results of patient DWI data evaluation, super-resolution reconstructions are found to have more accuracy in estimation of clinically significant cancers. This could improve accuracy of lesion detection for prostate cancer assessment and potentially benefit clinical assessment.

CHAPTER 4 – INVESTIGATION OF OPTIMAL SLICE THICKNESS FOR SUPER-RESOLUTION BASED RECONSTRUCTION OF T2WI

In the Chapter 3, super-resolution reconstruction of DWI and its impact on prostate cancer diagnosis was investigated. In this chapter, super-resolution based isotropic reconstruction, which was carried out on T2 weighted images of different slice thicknesses is discussed. The aim of this study is to investigate optimal slice thickness of T2WI for isotropic SR reconstruction, which is of similar or better quality than the standard 3mm anisotropic acquisition. The anisotropic T2WI acquisitions of this optimal slice thickness would be the thickest volumes, which could maintain same image quality as that of standard 3mm anisotropic acquisition, upon SR reconstruction. To this end, isotropic volumes are reconstructed from anisotropic T2WI acquisitions of increasing slice thickness and evaluated.

4. 1 Research problem

Super-resolution has been applied to a number of morphological imaging sequences including T2WI. In a study of isotropic reconstruction of 4D lung sequences by Van Reeth et al. [74], authors have studied the impact of number of inputs and through-plane to in-plane resolution ratio on quality of an isotropic phantom reconstruction. TWIST sequence was used to acquire phantom scans with in-plane resolution fixed at 1.56×1.56 mm² while through-plane (slice-thickness) was varied. The through-plane to in-plane ratio for acquisitions was 2, 3, 4, 5 and 6, using which isotropic reconstructions were

carried out. Mutual information between these reconstructions (from inputs of ratios 2, 3, 4, 5, 6) and an isotropic reference was used to evaluate quality of reconstructions. From the results of the study, mutual information between SR reconstruction and isotropic reference was higher for inputs with lower through-plane to in-plane ratio, compared to inputs of larger through-plane to in-plane ratios. In this article, author states that for a given acquisition time, lower through-plane to in-plane ratio inputs lead to optimal reconstruction quality than increased number of inputs.

In mpMRI for prostate cancer diagnosis, T2WI is used for correlation of DWI as well as in PI-RADS scoring. T2WI also holds a major role in prostate cancer diagnosis, apart from DWI. However, at a resolution of $0.47 \times 0.47 \text{ mm} \times 3 \text{ mm}^3$, each acquisition takes approximately 4-5 minutes. In many cases, lower through-plane resolution of these images also necessitates acquisition of orthogonal plane acquisitions as well, to aid diagnosis. This increases acquisition time from 4-5 minutes to 8-15 minutes depending on the number of orthogonal plane acquisitions. In addition, when these T2WI are used for MRI-ultrasound guided biopsies, only one plane anisotropic acquisition is used due to lack of isotropic volume, which limits the ultrasound operators' ability to visualize anatomy in planes other than non-acquisition plane. Hence, reconstruction of isotropic volumes from anisotropic acquisitions in multiple planes can aid diagnosis as well as biopsy systems immensely.

4. 1. 1 Objective of the study

This study aims to investigate whether it is possible to reconstruct isotropic T2WI volume, which is of similar or better quality than the 3mm slice thickness standard acquisition, yet does not increase acquisition times significantly than multiplane 3mm anisotropic acquisitions. To this end, we acquire T2WI of a phantom at different slice thicknesses. We reconstruct isotropic volumes from inputs at each slice thickness and investigate quality of those reconstructions to choose optimal slice thickness for isotropic reconstruction that is of similar or better quality than a standard 3mm anisotropic acquisition. Following the results from phantom study, anisotropic T2WI data of patient were acquired, isotropic volumes were reconstructed and evaluated.

4. 2 Methodology and justification

4.2.1 Materials

Phantom Data:

The phantom which was used in Ref [74] by our lab previously was used in this study. The phantom is an acrylic box of dimensions 11.1 x 6.4 x 8.3 cm³ which contains three slanted plastic ladders immersed in saline water. Fig. 4-1 shows the coronal view of scanned phantom. In the figure, oppositely slanted grid structure can also be seen in sagittal view to the right corner.

Fig. 4-1 Coronal view of scanned phantom and grid structure (zoomed region in the right end) in sagittal view

MRI Scanning:

T2WI images of phantom were acquired in coronal, axial, and sagittal planes, using a turbo spin echo sequence. The in-plane resolution of all acquisitions is $0.47 \times 0.47 \text{ mm}^2$. Acquisitions have been repeated for different slice thicknesses from 3 mm to 6 mm with an increment of 0.5mm. This corresponds to 7 datasets of different slice thickness, each consisting of transversal, coronal and sagittal plane acquisitions. All datasets were acquired on a 3T Siemens Trio MRI scanner (Siemens Healthcare, Erlangen, Germany).

After qualitative and quantitative evaluation of phantom reconstructions, T2WI of a patient was acquired based on phantom evaluation results. Prostate T2WI data for one patient has been obtained at in-plane resolution of $0.47 \times 0.47 \text{ mm}^2$ and at slice

thicknesses of 3mm and 4mm in coronal and transversal planes. The 3mm transversal plane acquisition will be considered as control volume. The patient T2WI dataset is also acquired on a 3T Siemens Trio MRI scanner (Siemens Healthcare, Erlangen, Germany) using turbo spin echo sequence.

Super-resolution framework:

Super-resolution reconstruction of isotropic volumes from these T2WI has been carried out using ‘MisoSR’ framework [40], which was developed by our lab previously. This framework consists of a deformation G_k , blurring B_k and down-sampling D_k operators. Deformation has been modelled using a six-degree rigid registration methodology and anisotropic Gaussian PSF model was chosen for blur modelling. Trilateral total variation regularization was used for MisoSR, which was implemented in C++ using ITK toolkit [64].

Implementation:

At each slice thickness, using at least two of the anisotropic transversal (T), coronal (C) and sagittal (S) inputs, isotropic volumes were reconstructed using MisoSR. This corresponds to 4 reconstructions at each slice thickness – with coronal-transversal (CT) inputs, sagittal-transversal (ST) inputs, sagittal-coronal (SC) inputs and sagittal-coronal-transversal (SCT) inputs. Each reconstruction will be identified with the slice thickness of inputs and their orientation planes. For example, 50CT refers to the isotropic volume reconstructed using coronal and transversal plane inputs at a slice thickness of 5.0 mm. Similarly, a 45SCT corresponds to reconstructions from 4.5mm slice thickness sagittal

coronal and transversal inputs. In total there were 28 isotropic phantom reconstructions of resolution $0.47 \times 0.47 \times 0.47 \text{ mm}^3$.

For patient data, an isotropic T2WI is reconstructed using coronal and transversal plane inputs at 4mm slice thickness with in-plane resolution of $0.47 \times 0.47 \times 0.47 \text{ mm}^3$. Three orthogonal acquisitions were also acquired at slice thickness of 3mm, serving as a benchmark.

4.2.2 Evaluation

All the super-resolution phantoms reconstructions were evaluated qualitatively and quantitatively. Based on this, patient data is acquired and isotropically reconstructed. The primary plane of evaluation is in transversal plane as primary diagnosis of control volume (clinical acquisition plane of T2WI for prostate cancer diagnosis) is in transversal plane.

For qualitative visual analysis, two radiologists with an experience of more than 13 years have ranked isotropic reconstructions on a 5-point scale, individually in each plane, with a score of 5 being the highest. Scores given by reviewers were averaged to get mean qualitative score in each plane for SR reconstructions. In addition, two reviewers also ranked the isotropic volume and assigned score after evaluating the volume in all planes (combined 3-plane ranking, assigned after reviewing volume in three orthogonal planes). These scores are then averaged to obtain mean 3-plane score.

For quantitative analysis, mean signal to noise ratio (SNR) and mean edge sharpness were calculated. Mean SNR was calculated by averaging individual SNR values which was obtained at 10 different slice locations. Edge sharpness can be evaluated by fitting signal intensity $ES(x)$ across an edge x with center c , to a sigmoid function of the form $ES(x) = \frac{1}{(1+e^{(-a(x-c))})}$. The edge width is then computed with formula 4.4/a. Smaller the edge width, sharper is the edge transition. Mean edge width is computed by calculating average of 40 edge width measurements, taken at 4 spatial positions over 10 slices.

For evaluating quality of SR reconstructions in in-plane, anisotropic 3 mm transversal plane acquisition is chosen as control volume. Control volume is also qualitatively ranked and quantitatively evaluated using the above mentioned methods. All the SR reconstructed volumes were evaluated and optimal reconstruction was chosen based on the following criteria.

- Acquisition time
- In-plane (Transversal plane) metrics
 - Mean qualitative score
 - Mean SNR
 - Mean edge width
- Through-plane (Coronal & Sagittal plane) metrics
 - Mean qualitative score
 - Mean SNR
 - Mean edge width
- Mean 3-plane score

Patient scanning was done with same in-plane resolution $0.47 \times 0.47 \text{ mm}^2$ but at a slice-thickness determined from results of phantom data reconstructions. Patient data was visually evaluated.

4.3 Results

Phantom data: Ideally, an optimal SR reconstruction volume would have similar or better image quality than control volume in all the planes. However, no SR reconstruction has scored a ranking of 5 in qualitative analysis in in-plane, which was the mean qualitative score for control volume. However, a mean qualitative score 3 in in-plane is assumed to be minimum acceptable score for reconstructions, below which, they are not considered of good reconstruction quality. Of 28 SR reconstructions, only seven volumes scored 3 or more in all planes. These volumes are 30SCT, 30CT, 30ST, 35SCT, 35CT, 35ST and 40ST. It is interesting to note that except for 40ST, all these volumes that were scored 3 and above are reconstructed using inputs of slice thickness 3mm and 3.5mm and required at least one transversal plane input for good qualitative score. Given that transversal plane is the primary plane (in-plane) for analysis, it is not surprising that volumes which lacked a transversal input, i.e. sagittal-coronal (SC) reconstructions, did not score well. Only one isotropic volume 35 CT, reconstructed using 3.5 mm coronal and transversal inputs has scored at least a score of 3 in all planes and had superior metric values compared to that of control volume. Apart from 35CT reconstruction, only one volume - 40CT, had in-plane qualitative score above 3 and had SNR and edge sharpness metrics superior to that of control volume. The complete evaluation list and corresponding scores for all volumes are tabulated in Table 4-1.

Table 4-1. Evaluation results from phantom data reconstruction across various slice thicknesses inputs of different orientations. Volumes which scored 3 or more in all planes in qualitative ranking are highlighted in blue. Volumes which scored at least 3 in in-plane and had SNR and edge width metrics better than that of control volume are highlighted in yellow.

		In-plane (Tra)			Coronal plane			Sagittal plane			3-Plane
<i>Volume</i>	<i>Scan Time (s)</i>	<i>Mean Score</i>	<i>Mean SNR</i>	<i>Mean Edge width</i>	<i>Mean Score</i>	<i>Mean SNR</i>	<i>Mean Edge width</i>	<i>Mean Score</i>	<i>Mean SNR</i>	<i>Mean Edge width</i>	<i>Mean. score</i>
Control	74	5	133	13.6	1.75	135	2.34	2.25	204	2.23	2
30SCT	421	3.5	94	13.6	4.5	197	1.29	4.25	288	1.17	4.75
30CT	286	3.75	131	13.6	3.25	303	1.17	4.25	263	1.17	4.5
30ST	286	4.5	104	13.6	5	95	1.05	4.75	527	1.05	4.5
30SC	270	1.75	95	13.1	4.25	230	1.05	4.25	286	1.05	2.75
35SCT	446	3.25	104	13.5	5	160	1.29	4.25	1073	1.17	4.5
35CT	213	4.5	145	13.5	3.75	286	1.05	3.5	1050	1.05	3.5
35ST	307	4.75	99	13.6	4.25	97	1.17	4	1260	0.94	4.5
35SC	372	1.25	100	13	4.5	282	0.94	2.25	274	1.05	2.5
40SCT	303	3.75	107	13.5	3.75	102	1.41	2.75	131	1.05	2.5
40CT	224	3.25	135	13.6	2.75	535	1.05	2.75	613	1.05	3
40ST	161	4.25	116	13.6	3.75	62	1.05	3	241	0.94	3.5
40SC	221	1.75	100	12.6	1.75	556	1.29	2.5	63	1.29	1.75
45SCT	359	3.75	110	13.5	3	129	1.17	2.5	180	1.05	3.25
45CT	217	4	129	13.5	2.25	499	1.05	2.5	143	1.17	2.75
45ST	219	4.5	108	13.6	2.75	73	1.29	2.75	728	1.29	3
45SC	282	1	107	12.3	1.75	550	1.29	1	61	1.05	1
50SCT	299	4	104	13.5	3.5	118	1.17	2.5	65	1.41	3
50CT	153	2.75	144	13.5	2.5	556	1.29	2	204	1.29	2.25
50ST	216	4	110	13.7	3	76	1.17	1.75	1102	1.17	2.75
50SC	229	1	104	10.9	1.5	228	1.05	1.75	36	1.29	1.25
55SCT	360	3.75	113	13.5	2.75	85	1.41	3.75	76	1.41	3
55CT	216	3	155	13.5	1.25	338	1.29	1.5	55	1.17	2
55ST	283	4.25	117	13.6	3	61	1.05	2.5	936	0.94	2.25
55SC	221	1	124	11.2	2.25	649	0.94	2	45	1.29	1
60SCT	216	3.75	134	13.7	2.75	46	1.29	2.5	57	1.17	2.5
60CT	143	2.5	176	13.6	1.75	681	0.94	2.25	48	1.05	1.25
60ST	145	4.5	139	13.7	3	34	1.05	2.25	499	1.05	2.5
60SC	144	1.25	132	10	1.5	619	1.29	1.5	25	1.17	1.25

Fig. 4-2 shows control volume and corresponding 35CT and 40CT reconstructions of phantom. Although in the image, through-plane shows more details in 35CT and 40CT reconstructions than control volume, there are noticeable artifacts. In addition, in-plane degradation can be noticed from 35CT to 40CT reconstructions.

Fig. 4-2 Control volume, 35CT and 40CT reconstructions of phantom in transversal plane (first row), sagittal plane (second row) and coronal plane (third row).

In Fig. 4-3, control volume and corresponding 30CT reconstructions of phantom can be visually compared. 30CT had a better in-plane quality than 35CT and 40CT, suggesting reduction in in-plane quality with increase in slice thickness of inputs.

Fig. 4-3 Control volume and 30CT reconstruction of phantom in transversal plane (first row),
sagittal plane (second row) and coronal plane (third row).

Patient data: Based on the qualitative and quantitative results of phantom, isotropic 35CT and 40CT volumes are considered optimal to reconstruct an isotropic volume which will be similar to control volume (3mm slice thickness transversal volume). However, 3.5mm slice thickness volumes could not be obtained for the patient data. Hence only 4mm slice thickness coronal and transversal volumes were obtained. Given that visual analysis of phantom reconstructions was unsatisfactory, a 30CT volume was also reconstructed for patient data. The resolution of these isotropic volumes was $0.47 \times 0.47 \times 0.47 \text{ mm}^3$. Fig.

4-4 shows 3mm anisotropic transversal volume and corresponding 30CT and 40CT isotropic reconstructions in three planes.

Fig. 4-4 Control volume, 30CT and 40CT reconstructions of patient data in transversal plane (first row), sagittal plane (second row) and coronal plane (third row). Slice position might differ by ± 0.24 mm.

In the reconstructions shown in Fig. 4-4, 30CT reconstruction has higher image quality than 40CT reconstruction. However, quality of reconstructions did not improve significantly in sagittal plane unlike in phantom reconstructions. This could be due to the

fact that phantom is more homogenous and information from two orthogonal plane inputs can be used efficiently for reconstruction. However, patient data is more complex compared to phantom data. Although using third orthogonal input for SR reconstruction might add more information for patient data, this improvement could be masked by registration errors. To evaluate, a 30SCT volume is reconstructed from 3mm slice thickness three orthogonal inputs.

Fig. 4-5 Control volume and 30SCT reconstruction of phantom in transversal plane (first row), sagittal plane (second row) and coronal plane (third row). Slice position might differ by ± 0.24

mm.

Fig. 4-5 shows control volume and 30SCT reconstruction, which is reconstructed using coronal, sagittal and transversal inputs. As can be seen from the figure, although image quality improved in sagittal and coronal planes, detail was lost in in-plane.

4.4 Discussion

Although acquisition time for phantom scans in this study was short, for patient data scans, acquisition time is usually longer. For the patient data acquisition in this study, 3mm slice thickness scan took approximately 4 ½ minutes in each plane while for slice thickness of 4mm, acquisition time was 3 – 3 ½ minutes approximately. From results from phantom data evaluation, a 4mm slice thickness coronal and transversal plane inputs would result in a good quality reconstruction qualitatively as well as quantitatively. Although this would increase acquisition time by 50% compared to anisotropic 3mm transversal volume, isotropic volume could be reconstructed, which could not be acquired through scanner due to hardware limitations. However, despite the phantom data evaluation metrics, quality of reconstructions from patient data degraded as slice thickness increased. This suggests that smaller slice thickness inputs result in increasing resolution in through-plane without degrading in-plane image quality. In addition, as can be seen from Fig. 4-5, three plane inputs resulted in loss of in-plane detail. Considering maintaining in-plane quality of control volume is important for isotropic reconstruction, two plane reconstructions seem to be optimal choice for RS reconstructions. Based on results from phantom evaluation as well as patient data evaluation, for future studies, two plane orthogonal inputs of smaller slice thickness will be used for isotropic reconstruction of data.

4.5 Chapter summary

From the evaluation of phantom data reconstructions, volumes which were reconstructed from inputs with slice thicknesses between 3 mm and 4 mm showed good reconstruction quality. If only two inputs were used for reconstruction, one of the inputs is preferred to be in the same acquisition plane as that of control volume. However, when two inputs were used, there is no significant reduction in acquisition time when volumes of slice thicknesses 3 mm to 4 mm are acquired. From evaluation of patient data reconstructions, using input volumes of increasing slice thicknesses reduced in-plane image quality and introduced artifacts into reconstruction.

From the results, it is clear that in order to maintain good in-plane image quality in terms of visuals as well as metrics, thinner slice inputs and lower number of inputs have to be employed. It is also to be noted that there is no significant change in acquisition time between volumes of slice thickness varying by 0.5mm. Hence, from the study, it can be inferred that for optimal reconstructions, with quality (visual quality and quantitative metrics) similar to that of 3mm anisotropic acquisition, inputs of slice thickness 3 mm or 3.5 mm should be used.

CHAPTER 5 – FUSION OF SUPER-RESOLUTION RECONSTRUCTED DWI AND T2WI FOR IMPROVED TUMOR DELINEATION AND VISUALIZATION IN MPMRI

In the Chapter 3, super-resolution reconstruction of DWI and its impact on prostate cancer diagnosis was investigated. In Chapter 4, application of super-resolution for T2WI of prostate cancer images was studied across varying slice thicknesses. This chapter deals with fusion of super-resolution reconstructed DWI and T2WI for tumor delineation in mpMRI, which could potentially benefit modern biopsy systems.

5.1 Research problem

Current prostate cancer guidelines recommend multi-parametric MRI for detection and PI-RADS as accepted risk stratification method by MRI [72]. PI-RADS v2 assessment category is a 5-point scale procedure which is based on the findings from T2WI, DWI and DCE. mpMRI is now widely used to detect clinically significant cancers, aiding in assessment of prostate cancer.

Although ultrasound guided prostate biopsies are very popular for diagnosis of prostate cancer, random ultrasound biopsies can result in missed cancers. In case of persistent clinical suspicion with history of prior negative biopsy or in active surveillance cases, targeted biopsy is adopted. Cognitive fusion is one of the targeted biopsy methods where operator targets lesion location after reviewing of lesion from mpMRI. Direct MRI

guided biopsy is another, in which, biopsy is done in-bore, within MRI tube. For this, current MRI image is fused with a prior MRI image, which depicts lesion for targeting. However, cognitive fusion biopsy can introduce human error whereas direct MRI guided biopsy is time consuming and requires multiple MRI scans/sessions [75]. MRI-Ultrasound fusion biopsy (MRUSFB) systems seem to have advantage in these areas, where accuracy of mpMRI is utilized, along with a faster, real-time alternative of ultrasound scanning.

MRUSFB systems are more popular as they effectively fuse MRI with real time ultrasound and reconstruct 3D prostate model for targeted biopsy. The main advantage of MRUSFB systems is that they use localization information from MRI for accurate targeting. Yet the guided biopsy can be done in outpatient setting at lower cost compared to in-bore biopsies. Another advantage is that MRUSFB systems allow for both random and targeted biopsies, even in the same session. Some of the popular MRUSFB systems are Uronav (InVivo Corp, Philips Healthcare, Gainesville, FL), Artemis (Eigen, Grass Valley, CA) and Urostation (Koelis, La Tronche, France).

MRUSFB systems like Uronav (InVivo Corp, Philips Healthcare, Gainesville, FL) require prostate gland delineation from morphological MRI sequences, which is used for targeting the ultrasound probe. The gland is co-registered on MRI (T2WI) and ultrasound, and motion compensation from biopsy systems will provide quick-registration in case of patient or probe movement. Fused MRI images can also contain lesion information and biopsy sites which can be overlaid for accurate targeting. In current state-of-art targeted MR/Ultrasound biopsy systems, lesion segmentation from DWI can be overlaid onto

either axial 3D volumes or axial 2D volumes to improve lesion region of interest (ROI) planning that can subsequently be used with real time ultrasound imaging for targeted biopsy. As stated in Chapter 3, DWI is an important sequence for delineating clinical significant prostate cancer, especially for the depiction of peripheral zone lesions in the PIRADS classification [72]. Although DWI provides better localization of lesion, for targeted biopsy, lesions are segmented on T2WI rather than on DW images. This is due to resolution difference between T2WI and DWI. In addition, low through-plane resolution even on T2WI limits its use during real-time MRUSFB in planes other than the plane of image acquisition.

From results of study in Chapter 3, super-resolution based resolution improvement of DWI resulted in a higher positive predictive value as well as lower volumetric error, suggesting smaller error in determining lesion boundaries. In addition, super-resolution based resolution improvement in T2WI also showed improved through plane resolution in Chapter 4. Improved resolution of DWI and T2WI will have significant clinical impact in percutaneous MRI-ultrasound guided biopsies [73] in terms of improved visualization as well as lesion targeting through increased resolution. American Urological Association (AUA) and Society of Abdominal Radiology (SAR) also recommend usage of high-quality MRI in repeat biopsy patients with prior negative biopsy but persistent clinical suspicion as well as MRI guided targeted biopsy in patients with PI-RADS assessment category of 3-5 [76].

5. 1. 1 Objective of the study

The hypothesis behind fusion of super-resolution reconstructed DWI and T2WI is that fusion of SR reconstructed images enable more accurate visualization of tumor (from DWI) and anatomy (from T2WI) in through-plane as well as in oblique planes, which could benefit biopsy.

To this end, in this study, fusion of SR reconstructed DWI and T2 MRI was carried out and its potential benefits for MRI/ultrasound guided targeted biopsy are visually evaluated.

5. 2 Methodology and justification

5.2.1 Materials

MRI Data: The patient data of 25 subjects' scans, mentioned in Chapter 3, are used for this study. DWI images of b-values 50 and 1000, corresponding fieldmaps and T2WI images are used for fusion.

Implementation:

DW images are first undistorted with fieldmaps using FSL (FMRIB Software Library v5.0) [52]. Axial and sagittal plane DWI volumes of same b-value are then used to reconstruct isotropic reconstructions using the super-resolution framework shown in Fig. 3-2. These isotropic reconstructions have resolution of 1.406 mm x 1.406 mm x 1.406 mm. Similarly, T2WI in axial and sagittal planes are also used for reconstruction of isotropic T2W images using rigid registration super-resolution framework MisoSR [40].

Voxels in SR-T2WI have a resolution of 0.47 mm x 0.47 mm x 0.47 mm. T2WI do not require distortion correction as they are non-EPI sequences.

Co-registration of DWI and T2WI: To generate fusion images, anisotropic acquisitions of DWI (Acq-DWI) and T2WI (Acq-T2WI) and their corresponding super-resolution reconstructions, of DWI (SR-DWI) and T2WI (SR-T2WI) are used. Lower b-value DWI (b-50) of Acq-DWI and SR-DWI are registered to T2WI (Acq-T2WI and SR-T2WI). Lower b-value DWI carry higher amount of morphological information and with the increase in b-value, morphological information decreases and diffusion weighting increases in the image. Since T2WI carries morphological information, co-registration of T2WI with lower b-value DWI yields more accurate registration than registration with higher b-value DWI. However, b-0 DWI are not usually obtained clinically as lower b-value DWI is more prone to artifacts from vascular motion in patients.

Lesion data segmentation: Lesions can be more readily detected and visualized on higher b-value DWI, after which they are correlated with the other b-value DWI, ADC maps and T2WI for localization. For fusion, an expert radiologist segmented lesion data on a b-1000 DWI data of a patient. The patient has been confirmed with acinar adenocarcinoma in right midpole, right base and on left side (complete) of the prostate through prior biopsy and histology. The segmentation has been done on both Acq-DWI and SR-DWI.

Fusion: DWI datasets, of all b-values, are assumed to have no motion in between them. Hence, we use the same registration transform obtained from co-registration of b-50 DWI

datasets and T2WI to fuse all DW images. Following the same, the lesion segmentation images from b-1000 DWI datasets are overlaid onto T2WI. Brief overview of fusion process can be seen in algorithm 5-1.

Algorithm 5-1 – Fusion of DWI and T2WI

1. Super-resolution reconstruction of DWI and generation of ADC maps using methodology shown in Fig. 3-2.
 - a. EPI distortion correction of acquired DWI (Acq-DWI) using fieldmaps
 - b. super-resolution reconstruction of DWI (SR-DWI)
 - c. Generation of ADC maps.
2. Super-resolution reconstruction of T2WI(SR-T2WI)
3. Registration of b-value 50 DW image with T2WI
 - a. Acq-DWI with Acq-T2WI
 - b. SR-DWI with Acq-T2WI
 - c. SR-DWI with SR-T2WI
4. Lesion data segmentation on b-value 1000 DWI/ADC
 - a. Acq-DWI
 - b. SR-DWI
5. Fusion of lesion segmentation on DWI and T2WI
 - a. Acq-DWI lesion segmentation + Acq-T2WI
 - b. SR-DWI lesion segmentation + Acq-T2WI
 - c. SR-DWI lesion segmentation + SR-T2WI

5.2.2 Evaluation

Super-resolution based resolution improvement for DWI and T2WI has been established in literature and also in studies from Chapter 3 and Chapter 4. DWI-T2WI fusion images generated in this study are evaluated visually in in-plane and in through-plane. The visual comparison is between fusion images from (1) Acq-DWI/Acq-T2WI, where lesion segmentation from Acq-DWI is fused with Acq-T2WI (both anisotropic acquisitions) (2) SR-DWI/Acq-T2WI, where lesion segmentation from SR-DWI is fused with Acq-T2WI (SR reconstructed DWI and anisotropic T2WI) and (3) SR-DWI/SR-T2WI, where lesion segmentation from SR-DWI is fused with SR-T2WI (both SR reconstructions). These volumes, rotated 30°, 60° and 90° in z, y and x axes respectively, are also evaluated visually.

5.3 Results

Fig. 5-1 shows DWI-T2WI fusion images of anisotropic acquisitions and SR based reconstructions in three orthogonal planes. In the figure, first row shows acquisition plane (axial) and second and third rows show projections in sagittal and coronal plane. Fusion images from super-resolution reconstructions (SR-DWI and SR-T2WI) show improved visualization in sagittal and coronal planes compared to fusion images with Acq-T2WI.

Fig. 5-1 Lesion segmentation overlay (in red) on T2WI in axial (first column), sagittal (second column) and coronal (third column) planes for DWI and T2WI fusion images. Fusion images of SR reconstructed DWI and T2WI shows increased tumor coverage from segmentation in oblique planes.

In Fig. 5-2, oblique planes of the fusion images are shown, after a rotation of 30°, 60°, 90° around z, y and x axes respectively. Resolution improvement is evident in all oblique planes for super-resolution based fusion images.

Fig. 5-2 Lesion segmentation overlay (in red) on T2WI in axial (first column), sagittal (second column) and coronal (third column) planes in orthogonal oblique planes. Volumes from Fig. 5-1 are rotated 30°, 60° and 90° in z, y and x axes respectively. Fusion images from acquired DWI and acquired T2WI shows poor tumor coverage and visualization while SR reconstructed DWI and T2WI shows increased tumor coverage and improved visualization Fusion image of SR reconstructed DWI and T2WI shows increased tumor coverage from segmentation in oblique planes.

5.4 Discussion

In current state-of-art targeted MR/Ultrasound biopsy systems, although axial 3D volumes yield better SR reconstructed images in the sagittal and coronal planes, these are usually not as accurate as T2WI acquired in 2D in the sagittal and coronal planes separately. Therefore, in the clinical practice setting, the latter is still preferred. However, for the

purposes of image reconstruction for fusion biopsy systems where only one sequence is used for reformat, isotropic data sets are advantageous. Super resolution data sets allow this without the increased scan times of a 3D acquisition. High quality multi-planar reconstructed images of the prostate will enable fusion of MRI data with ultrasound and targeted biopsy will be hugely benefited with high resolution lesion segmentation overlay on high resolution T2WI, which also can be isotropically reconstructed using super-resolution. Super-resolution based segmentation-T2WI fusion has the advantage of better tumor coverage of suspicious sites from DWI, in different planes as well as increased through-plane resolution on T2WI, as can be seen from Fig 5-1 and Fig. 5-2.

5.4.1 Limitations of study

Even with the super-resolution reconstruction, resolution of DWI does not match the high resolution of T2WI (resolution after SR reconstruction: DWI - $1.41 \times 1.41 \times 1.41 \text{ mm}^3$; T2WI - $0.47 \times 0.47 \times 0.47 \text{ mm}^3$). Therefore, segmentation from SR-DWI is up-sampled to match resolution of SR-T2WI, potentially including neighbouring voxels into fused image. Current super-resolution based improvement methods in MRI only improve through-plane resolution, when there is no inherent motion in between input volumes. In addition, although fusion image (Fig. 5-2) of SR-T2WI and SR-DWI showed good through-plane morphology, lesion segmentation in through-plane is markedly different from the fusion images of Acq-DWI with Acq-T2WI and SR-T2WI. A future study in this direction would evaluate impact of lesion segmentation through SR approach on MRI/ultrasound guided biopsy in terms of localization and also any improvement in registration of SR-T2WI image with real-time ultrasound scanning.

Co-registration of DWI and T2WI can be a bottleneck for fusion images, even with lower-b DW images which carry more morphological information. EPI sequences are more prone to artifacts and distortion which can affect their registration with T2WI. In some cases, as seen in Chapter 3 for phantom scans, EPI distortions are very large and cannot be corrected completely. In such case, DWI based segmentations could be unreliable.

5.5 Chapter summary

Visual evaluation of fusion images of super-resolution reconstructed DWI and T2WI showed superior tumor coverage from DWI and improved anatomical detail from T2WI in all planes. This improvement of resolution in through-plane and oblique planes improved overall visualization and could benefit targeted MRI-ultrasound guided biopsy systems as well as targeted therapy, which are gaining ground in clinical practice.

CHAPTER 6 – DEFORMABLE REGISTRATION BASED SUPER-RESOLUTION (DIRSR) FOR MR APPLICATIONS

In the previous chapters of this thesis, rigid-registration based super-resolution has been employed for resolution improvement of T2WI and DW Images. Registration is an important component of multiplane super-resolution in aligning input images. In multiplane super-resolution, input images are registered, up-sampled and averaged to compute initial high resolution image. In the rigid registration SR framework used for DWI and T2WI resolution improvement in this thesis, transformation from registration is also used in error computation during iterative estimation. This is to ensure that the reconstructed high resolution image, when subjected to same degradation process (image acquisition model in SR), would result in images similar to that of input images. Given that there is no or very little motion between the input images, isotropic images of with good image quality could be reconstructed. However, in cases where inputs have non-rigid deformation between them, rigid-registration based SR models would not be able to deliver reconstructions of good image quality. Therefore, a deformable registration based super-resolution (DIRSR) has been developed for MRI applications in which there is non-rigid deformation during scanning (e.g. 4D MRI lung imaging). In this chapter, a deformable registration based SR framework is developed and this novel DIRSR framework is demonstrated and evaluated using 4D (3D+time) lung MR images.

6. 1 Research problem

MR is an important imaging modality that gives excellent tissue contrast and also allows functional imaging. Hence it is widely used in diagnosing and monitoring pathologies concerning musculoskeletal system, heart – to name a few. Although interpretation and analysis of rigid structures is easier across multiple modalities, organs like heart and lungs undergo non-rigid deformation during scan. Due to the conventional practice of acquiring anisotropic MRI images to save on acquisition time and to maintain good SNR, this non-rigid deformation could affect accurate estimation of extent of tumors for diagnosis and treatment, including radiotherapy. Cardiac and breathing cycles can also cause motion related artifacts in abdominal and pelvic scanning applications, like liver scans, although to a much lesser degree. Although breath-hold sequences and respiratory/cardiac triggering can be used to control motion, some motion might still persist, causing reduced image quality. Another aspect to consider is the patient motion in between scans. Since patient motion is not always rigid motion, same voxel might hold different spatial location information in acquisitions of different orientations, which cannot always be corrected by rigid registration methods. As super-resolution reconstructions use inputs from multiple orientations for detail addition in high-resolution estimate, these differences in spatial information could result in improper estimation of the High Resolution (HR) voxel, thereby introducing error into SR reconstructions.

For super-resolution reconstructions, accurate registration is one of the most important factors in SR process. Most of the current SR approaches use rigid registration as deformation parameter to align images, and it helps in reconstructing high resolution

images of good quality when there is no elastic deformation in scanned structures. In chapter 5, a higher resolution T2WI-DWI fusion image has been reconstructed to aid in visualization during targeted biopsy. This fusion image has been reconstructed using rigid registration based super-resolution technique. Since there is no non-rigid deformation in prostate MRI scans, the inputs could be aligned accurately using rigid registration methods. However, in thoracic and abdominal applications, rigid registration would not be able to align images accurately where there is non-rigid organ deformation during the scans. This is due to larger organ deformation arising from breathing cycles and cardiac cycles.

Several studies which used deformable registration for alignment of inputs have been discussed in literature review in Chapter 2. However, in these studies, deformable registration has been employed as a pre-processing step outside the super-resolution iterative reconstruction. Pre-registered inputs are often used for reconstructions and deformable registration has been employed in applications which require correction of smaller scale deformations. Since registration is crucial step in SR, where accumulation of registration errors can reduce quality of reconstructed image, pre-registration of inputs was carried out in these studies. However, deformable registration involves smoothening of the inputs and this could lead to loss in information, that were present in the original acquired data (unregistered original acquisitions). In addition, any registration errors present in the pre-registered inputs will be accumulated in iterative reconstruction of SR process. Hence registration being a part of super-resolution reconstruction framework could avoid further processing of input data and could also help in minimizing any

registration errors, if present, through minimizing error. This chapter presents development and evaluation of such deformable registration based SR framework for non-rigid deformation applications. A key challenge in achieving this framework is incorporating and optimizing an invertible deformable registration into SR model. This deformable SR framework is aimed at reconstructing isotropic MR volumes from inputs which have non-rigid deformation between them.

The proposed approach, **Deformable Image Registration based Super-Resolution** or **DIRSR**, employs diffeomorphic deformable registration method for alignment of inputs for SR reconstruction and does not require pre-registration of inputs. This framework has been implemented on 4D lung MR datasets using 12 synthetic datasets and 1 multi-plane patient acquisition in both free breathing and controlled breathing manoeuvres. Isotropic 3D lung volumes have been reconstructed using DIRSR from two orthogonal anisotropic 3D lung datasets, each at a different breathing phase from the other. The reconstructions have been evaluated against rigid-registration based super-resolution framework (**Rigid-Registration SR** - RRSR) and a super-resolution framework using pre-registered inputs (PRSR), visually and quantitatively.

6. 2 Methodology and justification

6.2.1 Materials

Super-resolution framework:

A generic super-resolution framework for non-EPI sequences, consisting of deformation G_k , blurring B_k and down-sampling D_k , with additive noise V_k , is shown in Fig. 6-1.

Fig. 6-1 Image degradation model for super-resolution framework

In the proposed framework - DIRSR, image acquisition model includes deformation which is modelled using registration transformation, blurring and down-sampling. Deterministic regularized approach was chosen where HR estimate is updated using error computed in each iteration. Registration modelling in DIRSR is two-fold: in the first level, inputs are registered using a multi-resolution six-degree rigid registration model. Rigid-registration aligned inputs are then registered through a multi-resolution diffeomorphic demons registration model [77]. For error computation, the registration transformation has to be invertible and hence for both rigid and deformable registration, an invertible registration model is chosen. For deformable registration, there are a number of deformable registration techniques such as Demons, B-splines, finite element deformable registration etc. [78]. However, for super-resolution, invertible registration models are needed in error computation and hence a diffeomorphic demons registration model was chosen since it offers invertibility. Diffeomorphic demons model has also been employed in several SR studies during pre-registration.

Diffeomorphic demons registration, proposed by Vercauteren et al. [77] is a diffeomorphic registration method based on demons algorithm. Diffeomorphic registration methods provide invertibility, which is important in preserving topology by preventing folding that can happen from using non-diffeomorphic deformable registration methods like demons. Several computational applications like DTI also require invertible registration methods in computing Jacobian of transformations for reorienting tensors.

Demons registration works by computing optical forces, regularization and updating transformation iteratively until convergence. Given an initial field s (which could be set to zero), a correspondence update field u is computed by minimizing correspondence energy using the equation 6.1.

$$u(p) = -\frac{F(p) - M \circ s(p)}{\|J^p\|^2 + \frac{\sigma_i^2(p)}{\sigma_x^2}} J^{p^T} \quad (6.1)$$

In equation (6.1), $F(\cdot)$ is the fixed image, $M(\cdot)$ is the moving image, $s(\cdot)$ is the field transformation that models mapping of points from fixed image space to moving image space, $p \rightarrow s(p)$. $M \circ s(p)$ is the linear map between moving image and the field transformation, which is also called product of M and s . $\sigma_i(p)$ is the weight on estimation of image noise given by $|F(p) - M \circ c(p)|$ where c is the desired registration, σ_x is the estimation of spatial uncertainty in correspondences and J^p is the Jacobian given by $-\nabla_p^T(M \circ s)$. Then the transformation field s is updated iteratively [79] using exponential map of u and convolution with a Gaussian kernel K_{diff} for a diffusion like regularization. The algorithm has been demonstrated in Fig. 6-2.

Fig. 6-2 Diffeomorphic demons registration with reference from [77]

In this research work, diffeomorphic demons model has been optimized by fixing initial deformation field as null, varying sigma for field smoothness and the number of iterations and then testing on lung images. These smoothness parameters (indicated and set through corresponding sigma value in ITK) control the registration through pushing the contours. Smoothness setting of deformation field is very crucial as smaller value results in larger fluidic deformations while a larger sigma value has too little effect on deformation. Since diffeomorphic demons has no control points and operates only on

minimizing correspondence energy in each iteration until specified number of iterations are run, deformation field sigma has to be chosen carefully. Once optimal deformation field sigma is chosen, update field sigma can be set to fine tune registration. In this work, deformable registration is optimized first before running super-resolution. As such, multiresolution levels were set to 3, number of iterations were set to 50 in each level and smoothness of deformation field and update field is set to 3 and 0 respectively. These parameters provided good registration within short amount of time.

In DIRSR, blur operator has been modelled by anisotropic Gaussian PSF model, following PSF studies in [23] and [27]. A total variation regularization was chosen for its image denoising properties, following [40]. Isotropic reconstruction was implemented using C++ and ITK toolkit [64].

The initial high resolution guess $\hat{H}_1$ is obtained by up-sampling the average of mutually registered (rigid registration followed by deformable registration) inputs. In each iteration, a low resolution simulation $\hat{L}_k$ is done by degrading the high resolution estimate $\hat{H}$ using the registration transformation, blurring and down-sampling – which is the image degradation model shown in Fig. 6-1. Error between the low resolution simulation $\hat{L}_k$ and its corresponding low resolution observation L_k (input) is calculated. A high resolution image of this error image can be obtained by inverting the image degradation model (up-sampling, inverting blur and registration transformation). Data fidelity term (DF) is obtained by adding this high resolution error images calculated from SR image degradation model, as can be seen from equation (6.2).

$$DF = \sum_{k=1}^N G_k^T B_k^T D_k^T (|L_k - \hat{L}_k|) \quad (6.2)$$

Total variation regularization term R prevents noise apparition in image by penalizing the norm of image gradients. Equation (6.3) shows calculation of regularization term using high resolution estimate $\hat{H}$. In equation (6.3), P is the kernel size, S_{xyz}^{lmn} is the shift operator which shifts $\hat{H}$ by l , m , n pixels in x , y , z directions respectively and α is a weighting coefficient.

$$R = \sum_{\substack{l=-P \\ m=-P \\ n=0 \\ l+m+n \geq 0}}^P \alpha^{|m|+|n|+|l|} ||\hat{H} - S_{xyz}^{lmn} \hat{H}||_1 \quad (6.3)$$

For high resolution image estimation in each iteration, data-fidelity and regularization terms are added, balanced by regularization weight λ . This process is repeated until convergence. Equation (6.4) shows computation of high resolution estimate in iteration n . In equation (6.4), γ and β are optimizer variables, which decide step length in each iteration.

$$\hat{H}_{n+1} = \hat{H}_n + \frac{\gamma(\beta^n - 1)}{N} [DF - \lambda R] \quad (6.4)$$

Although error estimation and high resolution image estimation is done in every iteration, registration of inputs only is carried out during the estimation of $\hat{H}_1$ and the registration transformations are saved and utilized during iterative estimation to avoid intensive

computation effort. Hence there is not much difference in computation times between standard rigid-registration SR frameworks and DIRSR. The reconstruction process of DIRSR is summarized in Algorithm 6-1.

Algorithm 6-1 – Regularized SR Reconstruction

6. Initialization
7. Repeat until convergence
 - a. For each input L_k ($k=1$ to N)
 - Determine low resolution estimate $\hat{L}_k$ from high resolution estimate $\hat{H}_n$ using image degradation model
 - Calculate error between original low resolution observation and its computation L_k and $\hat{L}_k$
 - Calculate high resolution error image using inverse degradation model and add to data-fidelity term
 - b. compute regularization term R for high resolution estimate $\hat{H}_n$
 - c. update high resolution estimate for next iteration $\hat{H}_{n+1}$ according to equation (6.4)

Convergence criterion for DIRSR runs was set at a tolerance of 0.01 and a maximum iterative runs of 15. Typical parameter values for α , β and γ are 0.75, 0.99 and 0.9 respectively. Regularization weight λ , was chosen based on visual analysis of volumes reconstructed with varying weights.

In DIRSR, error is computed between inputs and corresponding low resolution computations from HR estimate and hence, any registration errors in the initial HR estimate will be reduced as iterative estimation progresses. This is unlike in PRSR, where registration errors in inputs get accumulated in reconstructions.

For DIRSR and corresponding PRSR and RRSR evaluations methods, isotropic volumes of resolution that match the in-plane resolution of input volumes were reconstructed.

MRI Data:

To evaluate and demonstrate DIRSR, single-plane and multiplane 4-D MR scans of the thorax of lung cancer patients were acquired. These 4D MRI lung data have been acquired by our group for previous studies [80] and [74].

A fast gradient-echo 3-D dynamic sequence (TWIST) with parallel imaging algorithm (GRAPPA PAT 2) was employed for scanning. The datasets from a previous study [80] are used for creation of synthetic datasets in this work. These scans were carried out using a fast gradient-echo 3-D dynamic sequence (TWIST) with parallel imaging (GRAPPA PAT 2) on a 3 T MRI scanner (Siemens Magnetom Trio, Siemens Healthcare, Erlangen, Germany) using a 6 channels body matrix coil. The datasets were acquired from three healthy patients and three lung cancer patients in coronal plane. For each patient 4D MR datasets were acquired using controlled breathing manoeuvre as well as during free breathing. In control breathing mode, patient starts from maximum

exhalation and breathes in for 3 seconds which is followed by breathing out for 3 seconds, repeated for six times. The resolution of all these datasets is $2.81 \times 2.81 \times 4 \text{ mm}^3$ at an acquisition matrix of 128×128 and FOV of 360 mm. Acquisition of each volume took approximately 0.9s. Using these 6 controlled breathing and 6 free breathing datasets, multi-plane synthetic data was created as described in next section. Summary of these 4D acquisitions used for creation of synthetic datasets is shown in Table 6-1.

Table 6-1 Summary of lung datasets acquisitions

Dataset ID	No. of 3D volumes in controlled breathing dataset	No. of 3D volumes in free breathing dataset
1	30	30
2	30	30
3	30	30
4	60	60
5	45	45
6	45	45

Fig. 6-3 shows sample transition in one 4D dataset (change in anatomy over time). The change in lung length with breathing cycles can be particularly noticed in left lung across volumes. In the figure, volume V7 and V22 have minimal lung length compared to other volumes.

Fig. 6-3 Transition in 4D controlled breathing dataset for Patient 1, from volumes V1 to V22 over time t

The multiplane dataset used in this study was (from another previous study [74] by our group) was acquired during free breathing. The acquisition was also done using the same sequence (TWIST). Although three orthogonal plane datasets were acquired, following results from previous studies, only coronal and transversal planes were used for this study. Resolution of these 4D datasets is $2.1 \times 2.1 \times 7 \text{ mm}^3$ at an acquisition matrix of 128×128 and FOV of 269 mm. 4D dataset in each plane was acquired for 1 minute.

Preparation of synthetic data: To evaluate DIRSR performance for 4D datasets, synthetic data has been prepared from 12 single-plane 4D datasets of all patients. All the volumes

from patients were initially down-sampled to isotropic volumes of resolution $4 \times 4 \times 4$ mm³. The first volume in this dataset would serve as control volume for quantitative comparison of DIRSR and RRSR.

The down-sampled datasets are further down-sampled to a resolution of $4 \times 4 \times 5$ mm³— first volume of the dataset in axial plane and rest of the volumes in coronal plane. The first volume, down-sampled to a resolution of $4 \times 4 \times 5$ mm³ in axial plane, will be one of the two inputs for SR reconstructions. The rest coronal datasets (resolution - $4 \times 4 \times 5$ mm³) would serve as the second input in SR reconstructions. Following this, for a 4D dataset with n 3D volumes, there would be $n-1$ super-resolution reconstructions. Fig. 6-4 shows methodology of creating synthetic data.

Fig. 6-4 Preparation of synthetic data by down-sampling 4D datasets for the evaluation of DIRSR

6.2.2 Evaluation

The 3D datasets which were reconstructed using DIRSR, PRSR and RRSR were evaluated using three criteria.

1. *Alignment of inputs:* To evaluate the accuracy of non-rigid alignment, edge sharpness was measured using sigmoid fitting in coronal plane. Measurement position is chosen such that breathing phase difference between inputs is more pronounced, as shown in Fig. 6-5. Edge sharpness can be evaluated by measuring edge width using a sigmoid fitting function of the form

$$ES(x) = \frac{1}{(1+e^{(-a(x-c))})} \quad (6.5)$$

In the above equation, $ES(x)$ refers to the signal along the edge at voxel x and c is the location of edge centre. Edge width is defined as the length of edge rise from 10% to 90% of the signal intensity in pixels. It is equal to $4.4/a$. Smaller edge width indicates sharper edges as change in signal intensity takes place over fewer pixels.

2. *Image sharpness:* Although sigmoid fitting can measure edge width at chosen location, it does not completely measure sharpness of image. For this study, we measured image sharpness using second derivative methods by using a Laplacian operator. In this method, images are convolved with a Laplacian filter and the variance of the resulting image is measured [2]. Since SR reconstructed images are expected to have been corrected for noise, no smoothing of images was done before taking measurements. Higher the variance, sharper is the image.

3. *Mean square error (MSE)*: For synthetic datasets, isotropic 4mm control image is taken as reference and MSE is calculated for DIRSR reconstructions, PRSR reconstructions and Rigid-Registration (RRSR) reconstructions.

Fig. 6-5 Spatial location of edge width measurements

The stated evaluation criteria are charted against percentage change in lung length. This percentage change in lung length is calculated using the difference in length of lung between first input volume (which is a constant for all reconstructions) and the second input volume, at same spatial location in same orientation.

After SR reconstructions (from DIRSR, PRSR and RRSR), resolution of synthetic datasets is $4 \times 4 \times 4 \text{ mm}^3$ and resolution of multiplane acquisition dataset is $2.1 \times 2.1 \times 2.1 \text{ mm}^3$. All reconstructions from DIRSR were compared against reconstructions from RRSR framework and PRSR. RRSR framework is similar to DIRSR except for deformation operator, where only multi-resolution rigid registration is used for iterative reconstruction.

For PRSR reconstructions inputs are pre-registered using multi-resolution rigid registration followed by multi-resolution diffeomorphic demons registration. There is no further registration in PRSR. All reconstructions from DIRSR, PRSR and RRSR method resemble breathing phase of the first input of corresponding dataset.

6.3 Results

Synthetic data: Isotropic volumes were reconstructed from the controlled breathing synthetic lung MR volumes using DIRSR, PRSR and RRSR methods. Of 468 volumes reconstructed using synthetic data (using RRSR, PRSR and DIRSR), 7 reconstructions were unsuccessful due to improper alignment from rigid registration. Hence these 7 volumes were excluded from evaluation. Evaluation has been carried out using the remaining 461 reconstructions. The reconstruction of isotropic volumes of 4mm voxels with a matrix of 89 x 89 x 36 was done on a 3.2 GHz, 6 core processor. For RRSR reconstructions the computation time was approximately 1 ½ minute (converged in 12 iterations) and for DIRSR reconstructions, computation time was approximately 2 minutes (converged in 13 iterations), for a tolerance of 0.01. PRSR reconstructions took approximately 1 minute for convergence, excluding time required for initial pre-registration. Together in all patient datasets, the percentage change in lung length varied from -17.39% to 29.55% in the second input compared to the first input.

Fig. 6-6 Inputs (a) and (b) and their corresponding isotropic reconstruction from RRSR (c).

PRSR (d) and DIRSR (e) for synthetic data in three orthogonal planes.

Fig. 6-6 shows inputs and corresponding RRSR and DIRSR reconstructions for one dataset reconstruction. The inputs shown in the figure have a 20% lung length difference. From the figure, it is evident that RRSR reconstruction (c) could not align inputs well, compared to PRSR (d) and DIRSR (e) reconstructions. If inputs were well aligned, second input (b), would be deformed to match the first and then reconstructed as with the case in PRSR and DIRSR reconstructions.

Mean edge width from sigmoid fitting of RRSR reconstructions, PRSR reconstructions and DIRSR reconstructions is 15.37 ± 15.21 mm, 10.08 ± 11.98 mm and 8.82 ± 11.45 mm respectively. The difference in mean edge width between PRSR reconstructions and DIRSR reconstructions for 461 samples is statistically significant (p-value is 0.0496).

Fig. 6-7 shows mean edge width calculations for synthetic 4D data, across varying lung lengths. Sample sizes for each bin are 60 (-20% to -10 %), 158 (-10% to 0 %), 179 (0% to 10 %), 51 (10% to 20 %) and 13 (20% to 30 %) respectively. The difference between mean edge width for volumes reconstructed from inputs with percentage lung change between -10% to -10% and 0% to 30% is not significant. For volumes reconstructed from inputs with percentage lung change between -10% and 0% (sample size of 158), difference between mean edge width from DIRSR (8.78 mm) and PRSR (13.27 mm) is statistically significant ($p=0.0003$).

Mean Laplacian of reconstructions from RRSR, PRSR and DIRSR is 1388 ± 434 , 716 ± 262 and 1334 ± 425 respectively. Difference between mean Laplacian from PRSR reconstructions and DIRSR reconstructions is highly significant ($p < 0.0001$). Mean Laplacian measurements from reconstructions for synthetic data, across varying lung lengths, can be seen in Fig. 6-8. For all volumes reconstructed from inputs with percentage lung change between -20% and 30%, difference between mean edge width from DIRSR and PRSR is highly significant ($p < 0.0001$).

Fig. 6-7 Mean edge width from RRSR, PRSR and DIRSR across reconstructions from different breathing phases for synthetic data.

Fig. 6-8 Mean Laplacian from RRSR, PRSR and DIRSR across reconstructions from different breathing phases for synthetic data.

MSE values from reconstructions of RRSR, PRSR and DIRSR are $1.3 \pm 0.61\%$, $1.76 \pm 0.84\%$ and $1.21 \pm 0.71\%$ respectively. Difference between mean MSE from PRSR reconstructions and DIRSR reconstructions is highly significant ($p < 0.0001$). Results of MSE estimation can be seen in Fig. 6-9. For all volumes reconstructed from inputs with percentage lung change between -20% and 20% (samples sizes 60, 158, 179 and 51) difference between mean MSE from DIRSR and PRSR is highly significant ($p < 0.0001$). For volumes reconstructed from inputs with percentage lung change between 20% and 30% (samples size of 13), difference between mean MSE from DIRSR and PRSR reconstructions is significant ($p = 0.0066$).

Fig. 6-9 MSE from RRSR, PRSR and DIRSR across reconstructions from different breathing phases for synthetic data.

Multiplane patient data: 60 coronal volumes were reconstructed using one constant coronal input volume and varying axial inputs of different breathing phases using DIRSR and RRSR. The axial inputs have lung length difference between -19% and 11% decrease, compared to the input coronal volume. However, percentage lung length difference for most of the volumes falls between -6% to 3% compared to first input, for multiplane patient data. Isotropic resolution of output volumes was 2.1 mm with matrix of 128 x 97 x 120. For RRSR volumes which underwent 3 levels of 500-iteration rigid registration and 15 super-resolution iterations with 0.01 tolerance, computation time on a 3.2 GHz, 6 core processor was around 10 minutes. For DIRSR reconstructions with same parameters, computation time was around 12 minutes (addition of 3-level, 50-iteration deformable

registration). PRSR reconstructions took approximately 8 minutes, excluding time required for initial pre-registration.

Fig. 6-10 shows one example of input volumes and their corresponding RRSR, PRSR and DIRSR reconstructions for lung length difference of 2%.

Fig. 6-10 Inputs (a) and (b) and their corresponding isotropic reconstruction from RRSR (c).

PRSR (d) and DIRSR (e) for patient data in three orthogonal planes.

Mean edge width from reconstructions of RRSR is 12.87 ± 2.4 pixels, PRSR is 6.91 ± 0.7 pixels and DIRSR is 6.82 ± 1.28 pixels and is not statistically significant. Mean edge width calculations of DIRSR, PRSR and RRSR reconstructions across varying lung lengths, can be seen in Fig. 6-11. Sample size for less than -3% lung length change is 18, between -3% and 3% is 38 and above 3% is 4.

Fig. 6-11 Mean edge length from RRSR, PRSR and DIRSR reconstructions across inputs of different breathing phase differences for multiplane patient data.

Mean Laplacian of reconstructions from RRSR, PRSR and DIRSR is 194 ± 2.4 , 157 ± 9.25 , 237 ± 4.53 respectively and is highly significant ($p < 0.0001$). Mean Laplacian measurements from reconstructions for synthetic data can be seen in Fig. 6-12.

Fig. 6-12 Mean Laplacian from RRSR, PRSR and DIRSR across reconstructions from different breathing phases for multiplane patient data.

6.4 Discussion

In this study, we used diffeomorphic demons in super-resolution framework for high resolution reconstruction of volumes with non-rigid motion in between. With the proposed approach - DIRSR, we reconstructed isotropic reconstructions of 4D MR lung volumes using anisotropic 4D acquisitions, without any pre-registration. This framework has been applied on 4D lung MR dataset where images from different breathing cycles were used to increase through-plane resolution. Although deformable registration based super-resolution was also employed for isotropic reconstructions of medical images, to the best of our knowledge, it has not been applied on lung MR images. Compared to other

applications where deformable registration based SR is used, deformation in lungs is larger due to breathing cycles. This poses a greater challenge to reconstruct lung MR images from inputs of different breathing cycles.

Reconstructions from DIRSR were compared against reconstructions from rigid-registration based SR as well as SR reconstructions from pre-registered inputs. As expected, rigid-registration was not able to correct non-rigid deformation present in lung datasets. Our results show superior performance of DIRSR in reconstructing isotropic lung reconstructions from inputs of different breathing phases, compared to RRSR. From evaluation of non-rigid alignment (through sigmoid fitting) in both synthetic data and multiplane patient data reconstructions, DIRSR outperformed both RRSR and PRSR with mean edge width of 8.82 mm and 6.82 mm for synthetic data and multiplane patient data respectively. Image sharpness evaluation from Laplacian shows sharper reconstructions from DIRSR. In evaluation of reconstructions from synthetic data, MSE was lower for DIRSR reconstructions compared to both PRSR and RRSR reconstructions. DIRSR was also able to correct for artifacts that were present in some PRSR reconstructions, as can be seen from synthetic data reconstructions in Fig. 6-6. Fig. 6-13 reproduces sagittal plane shown in Fig. 6-6 for easier visualization.

Fig. 6-13 A PRSR reconstruction (left) and DIRSR reconstruction (right). DIRSR was able to correct for the registration errors that PRSR was not able to correct (in red).

Although we successfully employed deformable registration based super-resolution for resolution improvement of lung images, one main limitation is that deformable registration is only limited by number of iterations unlike rigid registration techniques which converge based on image metrics like mean square error or mutual information. As a result, rigid registration is more reliable compared to iteration limited deformable registration. Although with fixed number of iterations for registration we were able to reconstruct isotropic images, a more reliable method would be stopping registration through image metrics, similar to the case of rigid registration. Deformable registration should also be optimized before reconstructing isotropic volumes through DIRSR. The alignment of images can be checked manually.

From the results of synthetic data evaluation, Laplacian of rigid registration based super-resolution was 1388 ± 434 while for DIRSR, it is 1334 ± 425 . From these results, it

can be inferred that reconstructed volumes from DIRSR are less sharp than reconstructions from rigid registration SR. However, this is because DIRSR has additional smoothing from deformable registration. Hence replacing current registration methodology of DIRSR (Rigid registration + deformable registration) with deformable registration would ensure sharper reconstructions. However, current deformable registration methods are only iteration limited which can limit accuracy of registration. Hence these methods are not ideal to be relied upon completely for good quality reconstructions from super-resolution framework. However, with the current DIRSR framework, we achieved good quality reconstructions and were able to reconstruct isotropic lung volumes from inputs of different breathing phases.

6.5 Chapter summary

A novel deformable registration based super-resolution framework, DIRSR, has been developed for MRI applications that involve non-rigid/deformable motion in between scans such as in lung imaging. Evaluation of DIRSR on 4D lung datasets showed superior results compared to rigid registration SR frameworks in alignment of inputs with deformable motion. Compared to employing SR on pre-registered inputs (PRSR), DIRSR preserved image details and sharpness, while reducing artifacts that seem to be present in some reconstructions from PRSR. In conclusion, we found superior reconstruction quality as well as better volume alignment from DIRSR compared to super-resolution with pre-registered inputs. Following the results from our study, DIRSR would be further enhanced in future studies for potential benefit in volumetric analyses related to lung as well as in tumor estimation.

CHAPTER 7 – DISCUSSION AND CONCLUSIONS

7.1 Discussion of thesis work

The focus of this thesis is on the application of super-resolution technique for the resolution improvement of MR images. In literature, super-resolution has only been applied on DWI for tractography purposes in resolving tract fibers. In Chapter 3, resolution improvement of DW images using super-resolution has been carried out and the impact of resolution improvement on prostate cancer diagnosis has been investigated. Results from the investigation presented in Chapter 3, showed lower volumetric error and increased sensitivity and specificity from super-resolution based isotropic reconstructions of DW images.

Chapter 4 presents an investigation to determine optimal slice thickness of T2WI, which when isotropically reconstructed would provide similar or better quality image than that of the control – a standard 3mm transversal acquisition. From qualitative and quantitative evaluation of phantom data, reconstructions from coronal and transversal inputs of 3.5mm and 4 mm slice thicknesses were able to match quality of control volume in in-plane while offering higher resolution in through-plane. However, reconstructions of patient data from inputs of 4mm slice thickness were not able to match the quality of control volume. From visual analysis of patient data reconstructions, it could be deduced that increased slice thickness of inputs would degrade reconstruction quality in general. It was also observed that increase in number of inputs would also increase registration errors in reconstruction, thereby degrading image quality. Therefore, for isotropic reconstruction of T2WI, two orthogonal inputs of 3mm slice thickness were considered optimal, which

would preserve in-plane quality as well as improve resolution in through-plane. From the results of this study, it can be inferred that although isotropic reconstruction from thicker slices is possible, increasing slice thickness would degrade in-plane image quality. Hence for good image reconstruction quality, inputs of thinner slices should be preferred.

Chapter 5 focuses on a specific clinical application of super-resolution based resolution improvement, prostate cancer assessment and MRI-ultrasound guided biopsies. Recent advances in technology enable MRI-ultrasound fusion guided biopsies which are more efficient in targeting lesions or biopsy. Compared to the existing methods, ultrasound offers real-time imaging while MRI helps in guiding ultrasound probe as well as brings lesion information for targeting in these MRUSFB systems. However, lower resolution of MR images limits visibility in through-plane, for which a MRI fusion image was proposed in Chapter 5. Isotropic DWI reconstructions are co-registered with isotropic reconstructions of T2WI and segmented lesion information from isotropic DWI is overlaid onto isotropic T2WI reconstructions to obtain fusion images. The main advantage of these fusion images is that they carry lesion information as well as tissue morphology in high resolution, through super-resolution reconstructions. This has the potential to not only improve visualization in through-plane as well as oblique planes but also improve guidance for ultrasound probes.

In chapters 3-5, the focus of application in these chapters is on prostate cancer diagnosis and rigid registration super-resolution framework has been employed to increase the resolution of images. In prostate cancer application, there is negligible non-

rigid motion of tissue in between scans and hence super-resolution based isotropic reconstruction was possible. For applications as such, which have rigid motion, super-resolution frameworks based on rigid-registration fare well. However, for applications with deformable motion, rigid-registration based super-resolution frameworks fail in aligning inputs properly, thereby introducing errors into reconstructions. To allow for isotropic reconstruction of data from inputs which have deformable motion in between, a deformable registration model is incorporated into super-resolution framework in Chapter 6. This framework, referred to as DIRSR, is applied on lung inputs of different breathing phases. Even though the deformation was large in some inputs, DIRSR was able to correctly register images and reconstruct isotropic images from them. The proposed approach, DIRSR was evaluated against RRSR framework and super-resolution reconstruction using pre-registered inputs. DIRSR showed consistent performance in aligning the inputs with non-rigid motion while maintaining image quality.

Super-resolution frameworks used for studies in this thesis are based on rigid-registration based and deformable-registration and can be applied to isotropically reconstruct volumes from multi-plane MR input images. Apart from deformation, operators like blur and down-sampling in super-resolution are usually standard - Blur modelling is usually done using Gaussian PSF whereas for down-sampling, simple interpolation methods like linear interpolation or b-spline interpolation are commonly used. Although SR approaches differ depending on application and inclusion of prior data, tuning of registration and blur operators plays a key role in reconstructing images of high quality. However, there is also no clear agreement on the best approach for SR

reconstructions. In the studies carried out, deterministic regularized SR approach has been chosen, with total variation as regularization model which is known for its de-noising properties. MAP based SR can also be a good choice for the studies, which will be considered in future work. However, the focus of this thesis was application of super-resolution to MR data using rigid registration and deformable registration methods.

7.2 Limitations

Unlike in other applications, traditional super-resolution methodology does not enhance in-plane resolution of MR images significantly. This is due to MR image acquisition model, which relies on capturing image information in frequency or k-space. Hence, for MRI, super-resolution framework is modified to improve resolution from multi-plane acquisitions, where information from another plane acquisition is used to improve through-plane resolution. The focus of studies in this thesis, which used super-resolution methodology, has been on through-plane resolution improvement and isotropic reconstruction of volumes from two plane inputs.

For study on DWI resolution improvement and its impact on prostate cancer diagnosis in Chapter 3, it is important to note that DWI is only one of the important parts of multi-modal assessment. DWI might not always show lesions and hence the study on 25 patients would not suffice to summarize its impact on diagnosis quantitatively. A larger study involving much larger cohort would be required for this. Although resolution improvement does enhance details to examine the lesions and tissues, lesion visibility on DWI is beyond image enhancement factors. This study has been done to show that

resolution enhancement of DWI does improve lesion visibility, in case if lesion can be seen on DWI. It does impact diagnosis since evaluation of mpMRI in PI-RADS is largely based on visual assessment of images. For PI-RADS scoring, super-resolution reconstructions of T2WI and DWI might individually contribute in better classification, although this is yet a research question that needs to be studied.

For DIRSR, a diffeomorphic demons registration model was used, which runs for certain number of iterations. Although the alignment was good from visual evaluation, terminating registration by number of iterations is not an optimal way to run registration. However, unlike rigid registration methods, this is a problem posed by deformable registration methods. Deformable registration is still an active research area and hence with advances in this area, super-resolution reconstruction could be positively benefitted. Stopping criteria for deformable methods is currently dictated by number of iterations, which is not reliable indicator for accurate alignment. Lack of reliable convergence criteria in deformable registration SR methods hence requires manual intervention to evaluate proper registration, which is a bottleneck for deformable registration based super-resolution frameworks. This is one of the reasons why rigid registration methods, whose convergence can be dictated by more reliable estimators of alignment, are preferred. Although DIRSR achieved good reconstructions through the said method, accurate method would be convergence through image metrics rather than number of iterations.

7.3 Conclusion of thesis and future outlook

Super-resolution based resolution improvement for MRI has been shown to improve image resolution, as seen from studies in previous chapters. In chapter 3, super-resolution framework was tested on phantom data as well as 25 patients data, extending applicability of super-resolution to clinical applications. This study on resolution improvement of DWI and evaluation of its impact on prostate cancer assessment has shown that super-resolution based resolution improvement impacts clinical diagnosis positively. In chapter 4, optimal slice thickness of T2WI was investigated using phantom data and subsequent patient data acquisition, which could be reconstructed with a quality similar to that of standard clinical acquisition. From this study, we found that thinner-slice volumes and lower number of inputs result in good SR reconstructions.

Following results from chapters 3 and 4, in chapter 5, super-resolution enhanced DWI and T2WI were fused for better tumor delineation and coverage. In addition to improving visualization in orthogonal and oblique planes, these fusion images also provide DWI information. This has considerable application in MRI-Ultrasound fusion biopsy systems, whose practice has been gaining clinically for prostate cancer intervention. The objectives of enhancing assessment and intervention of prostate cancer has been achieved through these studies.

Chapter 6 deals with development of a deformable registration based super-resolution framework, DIRSR, for applications with non-rigid motion in between. The proposed framework while providing benefits of rigid-registration SR, such as good

image quality metrics, also provides good deformable alignment of images. Superior results from DIRSR over state-of-art SR framework using pre-registered inputs was demonstrated using inputs from 4D lung datasets, each of different breathing phase from the other. As such, DIRSR could replace the current state-of-art SR methodology of pre-registering inputs with deformable registration models before isotropic SR reconstruction. Hence the objective of developing a novel SR framework to address current challenge of SR reconstruction using inputs with deformable motion, a novel contribution to super-resolution in MRI, has been achieved.

Although the main focus of this work has been through-plane resolution improvement, a previous study in 2D cardiac images [28] used inherent non-rigid organ motion in between frames to increase in-plane resolution. On the same lines, there might be a possibility that DIRSR would be able to increase in-plane resolution. A future work in this direction would evaluate the possibility of improving in-plane resolution in inputs with non-rigid organ motion.

Apart from using inherent organ motion for in-plane resolution improvement, machine learning can be used for in-plane resolution improvement. Although training phase for machine learning techniques requires large amount of data, these techniques are very successful in other applications including detection, diagnosis (CAD) and in robotic surgeries [81-83]. Future studies would also consider using machine learning frameworks for simultaneous in-plane and through-plane resolution improvement of MR images.

Further, incorporating priors, from other MR sequences and multiple modalities, would also be of interest.

The main contribution from super-resolution reconstructions is image resolution enhancement through post-processing, that cannot be captured through scanners due to hardware limitations or limitations on acquisition time. Resolution improvement does impact clinical diagnosis and has positive implications on treatment as shown in this thesis. SR based fusion images, which were generated for MRUSFB systems in Chapter 5, would also help in bridging gap between available state-of-art methodologies and clinical needs. An immediate future work is to evaluate super-resolution based fusion images of DWI and T2WI real-time with ultrasound guided biopsy system to quantitatively evaluate the improvement from super-resolution based fusion images. Thereafter, in-plane resolution improvement of DWI to match that of T2WI would be considered for more accuracy in future work.

Another future work is enhancing the registration framework of DIRSR such that deformable registration converges based on image metrics rather than number of iterations. Current rigid registration methods allow convergence through a wide variety of image metrics like mean square error or variations of mutual information. Deformable registration and consequently DIRSR could benefit with similar convergence methodology. In addition, in-plane resolution improvement in MR images through machine learning methods could also help in reconstructing high resolution images through DIRSR, regardless of rigid/deformable motion in between organs. Modification

of DIRSR framework in such direction could potentially benefit clinical diagnosis and treatment and would positively affect biomedical imaging.

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