Chapter 8

Summary and Outlook

The thesis is summarized in this concluding chapter, and some directions for future research are suggested.

8.1 Summary

The goal of this thesis was to contribute to the research field of encoding with nonlinear magnetic fields in MRI, a topic of increasing interest that has only received scant attention in the past. The conducted work has been part of PatLoc, a research direction that combines nonlinear encoding with parallel imaging, initiated by Prof. Dr. Jürgen Hennig within the INUMAC project. PatLoc offers new options to improve the encoding efficiency, to reduce peripheral nerve stimulation and to develop other interesting applications such as those that arise from advances in shimming methodology with nonlinear phase preparation, with many more applications expected to arise (see chapter 3.2); research in this field is still at the beginning.

During the course of this thesis the theoretical foundations of PatLoc encoding and image reconstruction were elaborated. Efficient reconstruction algorithms were developed, and the effectiveness of several encoding and reconstruction strategies was theoretically discussed and assessed by evaluating imaging results.

The algorithms were applied to simulated data, but also to experimental data. The experimental part resulted from team work, in total conducted by not fewer than ten researchers, mainly members of the Freiburg MR-Physics group, but also employees from industrial partners. The experiments required:

- Design and manufacturing of hardware for the generation of NB-SEMs and integration into existing MR scanner environments.
- Development and implementation of useful encoding strategies.
- Data acquisition and pre-processing.

G. Schultz, *Magnetic Resonance Imaging with Nonlinear Gradient Fields*,
DOI 10.1007/978-3-658-01134-5_8, © Springer Fachmedien Wiesbaden 2013

In this thesis, only those topics were presented with significant own contributions that have resulted (or will result) at least in a co-authorship of a publication or a co-inventorship of a patent application.

Generalizing Parallel Imaging For this work, it has been extremely useful to realize that PatLoc generalizes state-of-the-art imaging technology that makes use of parallel reception devices. Parallel imaging has been the subject of intensive research activities for more than ten years now, and therefore mature know-how was available on which this thesis could be based on, even though not much knowledge had been generated up to that point on nonlinear encoding. The generalization to nonlinear encoding favored the adoption of a rather abstract theoretical point of view; this approach facilitated the detection of principles that are common to conventional imaging and PatLoc imaging, and the analysis of effects which are specifically caused by the nonlinearities and/or non-bijectiveness of the encoding fields. While writing this thesis and reviewing existing reconstruction methods, it became apparent that this abstract point of view also sheds new light onto conventional image reconstruction by revealing connections between established methods like SENSE and GRAPPA or between gridding reconstruction and the general matrix approach (see chapter 2).

The theoretical background of encoding with nonlinear fields was elaborated in chapter 4. A generalized k-space concept was introduced that loses its meaning as the Fourier space of the encoded object. The advantage of the introduced concept is that it leads to a separation of the temporal degrees of freedom (k-space trajectory) and the spatial degrees of freedom (SEM geometries). Despite the nonlinearity of the SEMs, the encoding process is still described as a linear operator that allows application of linear image reconstruction methods. Image reconstruction reduces therefore to a simple matrix inversion and image properties can be calculated easily with linear algebra. Unfortunately, this approach normally only works in 1D. In higher dimensions, the matrix to be handled is huge, in 2D almost as large as one million entries along each of the two dimensions. Therefore, it was essential to develop efficient reconstruction algorithms. Due to the inverse nature of the reconstruction a high degree of accuracy is required for the formulation of adequate reconstruction methods. It could be shown that, in this regard, the requirements can be less demanding for the determination of fundamental image properties; an acceptable accuracy is often ensured with approximate methods. For example, image resolution can be predicted well with the concept of local k-space.

In this thesis, the possibilities of PatLoc were explored by analyzing encoding strategies of increasing complexity, thereby developing a number of methods for accurate image reconstruction. To focus on the essentials, only static anatomical imaging was dealt with (thus excluding for example cardiac imaging), where a 2D slice was excited with the standard z-gradient.

Encoding and Reconstruction with Two SEMs The most basic 2D situation one might think of when dealing with NB-SEMs is an experiment where the x- and y-gradients are replaced by a PatLoc coil that generates two orthogonal quadrupolar SEMs. There is evidence (see Appendix A.4) that these fields represent a first natural generalization from linear SEMs toward arbitrarily-shaped NB-SEMs.

Such a setup was put into practice (see chapter 3.3); this had the advantage that conventional sequences could be reused, thus allowing to purely focus on the additional spatial degrees of freedom that come along with PatLoc imaging. Image properties that depend on the time-courses of the applied SEMs, such as image contrast, are not affected compared to conventional imaging as long as the same sequence parameters are used. In standard imaging, the most basic sequence is a Cartesian trajectory. This sequence was adapted for PatLoc imaging. Encoding and reconstruction with this trajectory was analyzed in detail in chapter 5. The same experimental setup was then driven with a non-Cartesian (radial) trajectory and formed the subject matter of chapter 6.

It is remarkable that for the Cartesian trajectory, image resolution and noise propagation can be described by simple analytical expressions, thus allowing a precise analysis of this basic PatLoc experiment. The main result was that the application of NB-SEMs basically leads to a spatial relocalization of the magnetization in the Fourier domain of the signal data. The non-bijectiveness of the encoding has the positive effect of an intrinsic acceleration, however, also aliasing is observed. This artifact is resolved in PatLoc by supplementing SEM encoding with RF-sensitivity encoding. Undersampling typically results in reduced noise amplification in PatLoc compared to Cartesian SENSE because aliased locations are distributed over the image and not along a single direction. It could also be shown that the nonlinearities of the SEMs lead to image distortions and intensity modulations. These SEM-dependent effects are corrected by rewarping the image and multiplying the final image with an intensity correction factor, thus introducing variations in image resolution and SNR.

These effects are therefore directly related to variations of the gradient strength of the SEMs. This property can be exploited to improve the encoding efficiency by increasing the gradient strength in a ROI. Due to the fact that magnetic fields are the strongest near the coil surfaces, the encoding information can be enhanced most efficiently at the periphery of the imaging volume. This could be verified also with the quadrupolar design that showed a higher spatial resolution at the periphery of the imaging volume compared to standard imaging and a lower resolution at the center, which is useful for example in cortical imaging.

Image properties are determined by the SEM geometry to a high degree, but also the trajectory and the chosen reconstruction method can have a significant influence. Three different reconstruction approaches were discussed for Cartesian as well as non-Cartesian trajectories:

1. Direct Reconstruction in the image domain.
2. Direct Reconstruction in the PatLoc k-space domain.
3. Iterative reconstruction using the CG method.

It turned out that all reconstructions could be formulated in a way that is similar to the corresponding counterparts in PI. Methods which are based on k-space, such as GRAPPA, can be applied to subsampled PatLoc data without any modification. In the image domain, Cartesian SENSE must be slightly modified to account for the nonlinearities of the SEMs (intensity-correction, rewarping). An interesting difference between the two methods is that aliasing can be resolved in the image domain, whether resulting from subsampling or from the non-bijectiveness of the SEM encoding. In the k-domain, it is, however, a much more intricate process to resolve the ambiguities that are caused by the non-bijectiveness of the SEMs.

Not much less efficient than those direct methods is iterative CG reconstruction because, with two SEMs, the time-domain reconstruction algorithm can be accelerated by applying the nuFFT in the forward operation. Almost no compromise regarding image quality has to be made with such a nuFFT-based reconstruction. In extreme cases of vanishing gradients, an implementation that uses the nuFFT of type 3 with a homogeneous distribution of image voxels should be preferred to the nuFFT of type 1/2 with an inhomogeneous distribution. This is different for direct reconstruction, which does not profit from using a homogeneous reconstruction grid.

To be precise, the number of required elementary computations is the least for the Cartesian direct method with $\mathcal{O}(N^2 \log N^2)$, where $N \approx 256$ describes the problem size, followed by $\mathcal{O}(k^2 N^2 \log N^2)$, $k \ll N$, for the fastest direct non-Cartesian method to $\mathcal{O}(lk^2 N \log N)$ for iterative nuFFT reconstruction, where l describes the number of iterations and where $k \ll N$ is larger for the nuFFT of type 3 than for the nuFFT of type 1/2. Direct image space reconstruction is therefore faster than any of the presented iterative algorithms. However, the dependency on the problem size N is the same, and even equivalent to the FFT; this ensures that the reconstruction times do not differ by several orders of magnitude and can compete with the fastest image reconstruction algorithms used in standard MRI.

In most situations, the faster methods guarantee a similar image quality than the more computation-intensive methods. Only at locations with heavy SEM-encoding deficiencies (vanishing local gradients) significant differences may occur. It has been shown that radial imaging trajectories are less problematic than Cartesian trajectories because the isotropic shape of the radial PSF reduces pronounced Gibbs ringing artifacts that emanate from regions with vanishing gradients. Iterative reconstruction makes more efficient use of the additional information provided by the RF sensitivities than the direct methods and are therefore superior, especially for subsampled trajectories; for example, a star-shaped undersampling artifact, resulting from radial quadrupolar encoding, could be reduced significantly with iterative reconstruction. With respect to image quality, the unaccelerated iterative time-domain algorithm may serve as a "gold standard" reconstruction technique.

It can be concluded that the presented direct reconstruction methods are typically a good choice, also under strongly nonlinear and non-bijective imaging conditions. They are very fast and do not suffer from the problem of having to define a proper stopping criterion. In extreme cases, however, iterative image reconstruction can be superior to direct reconstruction.

Encoding and Reconstruction with More than Two SEMs The last encoding strategy that was analyzed marked an important step toward more flexible encoding. When only two SEMs are available combinations of those can be formed, but tight restrictions on the achievable field geometry exist.

For example, with pure quadrupolar encoding, the superimposed field still has a quadrupolar geometry. With more than two SEMs, driven to its extreme, the effective magnetic encoding field can take a great variety of shapes and can change from one instant of time to the next almost without restriction.

The experimental setup did not provide such flexible encoding, but it allowed superposition of the two quadrupolar SEMs with the standard linear gradient fields. The resulting field is also a quadrupolar field, whose center, however, is not bound to one location, thus eliminating the problem of extreme encoding deficiencies. Signal encoding and image reconstruction was investigated with 4D-RIO, a particularly efficient sequence.

A problem with multi-dimensional trajectories, such as 4D-RIO, is that direct inversion of the encoding matrix with a complexity of $\mathcal{O}(N^6)$ is intractable, and iterative CG-based reconstruction cannot be accelerated with a nuFFT and therefore requires $\mathcal{O}(lN^4)$ elementary operations. Image reconstruction is therefore a challenging problem for multi-dimensional PatLoc trajectories. Reconstruction time can be reduced significantly by exploiting the highly-parallelizable structure of the reconstruction. Even further acceleration is possible by making the problem sparser. For example, it was shown that a large class of multi-dimensional sequences, among them 4D-RIO, form generalized image projections that are sparse in the frequency domain if adequately filtered, thereby reducing the numerical complexity to $\mathcal{O}(lkN^3)$, with $k \ll N$. With this method, the computation time does not increase for longer signal readouts. For high-resolution 2D-imaging applications, the additional speedup is typically well above one order of magnitude, and reconstruction time is brought down to the range of seconds, fast enough to be applicable during the examination, provided that the imaging hardware is equipped with processing units that are specialized for parallel computing.

With the iterative CG method high-quality images from 4D-RIO phantom and in vivo data could be reconstructed. However, successful reconstruction required extremely well-calibrated data, thus showing a very high sensibility to systematic errors of the used signal model.

The performed analysis has shown that multi-dimensional encoding offers more degrees of freedom for trajectory design than encoding with only two SEMs. At the same time, the imaging problem becomes more complex, but it could be shown that tools are available that help to get the problems under control. Especially helpful in this regard is the local k-space concept, which has proven useful in estimating spatial encoding properties such as local image resolution or in assessing if the encoding strategy ensures that the bulk part of the relevant signal energy is acquired.

Overall Assessment Table 8.1 lists several reconstruction algorithms that were discussed in this thesis and compares their numerical complexity with the range of encoding strategies that are compatible with the corresponding algorithm. The table clearly shows a rule that often appears in practice: The smaller the scope of a method, the more optimization is possible concerning computing time. In practice, this means that the Cartesian reconstruction can be performed in the range of milliseconds whereas the iterative time-domain method requires at least several minutes to reconstruct a single 2D image on a modern desktop PC equipped with a GPU. As a rule of thumb, image reconstruction is fast and also robust as long as only two SEMs are used to encode a 2D slice; the situation becomes much more challenging for multi-dimensional encoding strategies, where some problems could be solved already, yet by far not all.

Within the scope of this thesis, only three encoding strategies could be analyzed in detail. Bringing the results of these three examples together can only explain a small part of what can actually be done with PatLoc. However, the encoding strategies were chosen with care and give an overview of the implications that PatLoc may have on MRI. Nevertheless, caution must be taken when generalizing to other trajectories without a closer analysis. A goal of this thesis was to provide insight and tools for future research in this direction.

The presented material appears to be a good starting point for further generalizations, for example, to nonlinear encoding also during RF transmission, a topic that is part of a separate PhD project that has been termed *ExLoc* by Hans Weber. The general approach taken in this thesis may also serve to quantify further specializations such as the briefly discussed imaging with nonlinear phase-preparation that has generated useful applications already like reduced field-of-view imaging or the elimination of balanced SSFP banding artifacts.

Despite its extent, this thesis has only treated *static* effects; it has largely been disregarded that MRI is a *dynamic* process, where temporal effects play

Table 8.1: Reconstruction algorithms: numerical complexity and scope of applicability ($N \approx 256, k \ll N, l \approx 20-40$)

property \ method	direct Cartesian	direct non-Cartesian	iterative nuFFT
operations required $\mathcal{O}(\cdot)$	$N^2 \log N^2$	$k^2N^2 \log N^2$	$lk^2N^2 \log N^2$
number of SEMs	2	2	2
direct/iterative	direct	direct	iterative
works with undersampling	+	-	+
trajectory	Cartesian	non-Cartesian	non-Cartesian
	iterative frequency-domain	**iterative time-domain**	**matrix inversion**
operations required $\mathcal{O}(\cdot)$	lkN^3	lN^4	N^6
number of SEMs	arbitrary	arbitrary	arbitrary
direct/iterative	iterative	iterative	direct
works with undersampling	+	+	+
trajectory	generalized projection	arbitrary	arbitrary

a fundamental role. However, a variety of new options also for dynamic encoding become available with PatLoc imaging, especially when multiple magnetic fields are used for signal encoding. As an example may serve a comparison of conventional Fourier imaging with 4D-RIO. The results have shown that static image properties, such as image resolution or SNR, are similar over an extended region; however, the temporal evolution of the applied magnetic fields is very different. Therefore, physiological reactions like PNS will be different. Another example is the separation of signal echoes with a quadratic field that allows dynamic shimming during the acquisition of a single slice. This thesis may have shown the capabilities of PatLoc imaging for spatial encoding; however, these examples illustrate that a great potential also lies in the temporal domain, an aspect that needs to become a focus of future research.

8.2 Ongoing and Future Research

In the course of the PatLoc project, a novel type of gradient hardware has been built, sequences with interesting properties have been realized, adequate reconstruction methods have been implemented and initial medical applications have been developed. This work is currently being continued and future research will also follow these four directions: hardware design, sequence design, image reconstruction and medical applications.

Hardware Design A high-performance PatLoc coil for in vivo imaging is currently under development. The coil will be similar to the existing PatLoc hardware, but with significantly improved specifications. The industrially manufactured new system will allow a fair comparison with state-of-the-art gradient hardware, and it will be possible to evaluate the imaging results also from a clinical perspective. One drawback will, however, persist: As before, the new system will be equipped with a very limited amount of SEM channels. We have therefore begun to develop also other PatLoc coils with completely different geometries. Sebastian Littin has recently completed construction of a three-channel planar surface coil [[103]]. The next step has to be and will be the development of a much more flexible gradient coil. Christoph Juchem has recently shown that impressive improvements for $B0$-homogeneity can be achieved with a flexible shimming system [79]. Initial steps toward a flexible gradient system have been undertaken by Stefan Wintzheimer [203]. This system has interesting properties, however, there is much room for improvement. The insight we have gained so far in the PatLoc project will enable us to build a gradient system that is as powerful, but much more flexible than our current hardware implementations.

Sequence Design In this thesis, 2D PatLoc imaging modalities were considered, where slice selection was performed with the linear z-gradient. Very interesting encoding strategies have recently been tested or are being elaborated in the PeXLoc [54, 152] and ExLoc [[191]] projects, where the implications of NB-SEM encoding during RF transmission on the magnetization are explored.

The current PatLoc hardware requires that all developed sequences define time-courses of a maximum of six independent gradient channels. A flexible gradient design will particularly have implications to sequence design. A more flexible system will have many more channels that can all be controlled independently from each other, thus increasing the complexity, most probably to a degree which will be difficult to be handled without the introduction of new concepts.

The local k-space concept [[42]] may help to design appropriate trajectories. In its current form the local k-space distribution only gives a vague estimate of how much aliasing is to be expected, but generally it provides an excellent measure of how the acquired spatial information is distributed over the ROI (thus defining for example image resolution in the ROI). It will be crucial in the future to extend this concept also along the temporal dimension to be able to reliably assess the temporal encoding efficiency and other dynamic properties of the trajectory such as the resulting image contrast or the probability to cause PNS. Novel performance measures also need to be developed that allow one to assess if the trajectory can meet other requirements; for example, the hardware constrains magnetic field amplitudes, as well as spatial and temporal derivatives thereof, and encoding strategies have to be designed such that inevitable calibration errors can be tolerated by the method that is used for image reconstruction. The definition of such performance measures will be essential to facilitate the design of useful PatLoc encoding strategies in the future.

Image Reconstruction In this thesis, unconstrained linear image reconstruction was shown to be effective in PatLoc imaging. This is especially the case when only two SEMs are involved; in this regard, only occasionally, the presentation has remained vague. For example, evidence still has to be provided that a direct reconstruction is not only partially, but also entirely, feasible in PatLoc k-space, including non-Cartesian trajectories. Also, it is yet not fully clear why iterative reconstruction yields better results with a nuFFT of type 3 than with a nuFFT of type 1/2. These few problems need to be solved in the future, but much more challenging are the unsolved problems of multi-dimensional encoding. It has been shown that the time-domain reconstruction can be applied almost universally, most often resulting in images of high quality. The method can also easily incorporate model refinements. However, the time-domain reconstruction has shown to be problematic with regard to several aspects that need to be tackled in the future.

1. The time-domain algorithm could already be accelerated by more than a factor of 1000 compared to an initial implementation; yet, it is currently still not fast enough to be useful in the clinical routine.

2. Artifacts like Gibbs ringing or those resulting from undersampling, amplified by weak SEM encoding, may not be suppressed sufficiently by linear unconstrained image reconstruction.
3. For multi-dimensional PatLoc trajectories, image reconstruction requires very accurate knowledge of the applied encoding fields in order to yield images of sufficient quality.

It will be an important aspect of future work to further accelerate the computing time by optimizing parallel computing implementations and by further exploiting any encoding sparsity. This thesis has shown that a close analysis of a specific encoding strategy can lead to accelerations of reconstruction time up to several orders of magnitude. For the success of imaging with NB-SEMs, it will be essential to achieve orders-of-magnitude acceleration also under general conditions of imaging with matrix gradient coils that have a multitude of encoding elements.

Problems associated with weak encoding gradients can be circumvented by ensuring sufficient encoding over the whole excited volume. However, this reduces the encoding efficiency, and therefore improvements in this regard are important and are currently being pursued in a collaboration with Dr. Florian Knoll from the University of Graz, where it could be shown that nonlinear image reconstruction with regularization using total generalized variation effectively eliminates the star-shaped artifact that occurs in quadrupolar radial PatLoc imaging up to very high undersampling factors. It will also be tested to what extent nonlinear signal modeling and nonlinear reconstruction will help to reduce the calibration problem, one of the most urgent problems that need to solved in the near future.

Medical Applications The aim of this thesis was not to develop medical applications, but to elaborate fundamental theoretical principles of MR signal encoding with nonlinear magnetic fields, to contribute solutions to technical problems, and to develop practical image reconstruction methods. Up to this point, also the whole PatLoc project was rather technologically-oriented. Notwithstanding, we have already demonstrated that the increased encoding efficiency at the periphery has implications to cortical imaging. Other applications like reduced field-of-view imaging and advantages for dynamic shimming have been evaluated, showing the potential of PatLoc for a variety of medical applications.

With state-of-the-art gradient hardware, magnetic field gradients are generated homogeneously across a large volume, in human systems allowing to faithfully image large portions of the human body. Very often, diagnostic or functional information is required only from small ROIs. With nonlinear fields encoding can be focused onto the location of interest with flexible volume coverage. Thus, organ-specific applications will profit most from the additional degrees of freedom offered by PatLoc imaging. Reduced scan-time, mitigation of problems like acoustic noise or PNS are just a few examples that are noted here. However, it has to be admitted that the range of possibilities that multi-dimensional encoding strategies offer are not yet foreseeable at the current stage of research, and it will be exciting to observe what medical applications will eventually be developed. Undoubtedly, there is work for many future PhD students in this interesting research field that involves nonlinear encoding fields.

I am very happy to see that a new large project, RANGEmri[1], lead by Dr. Maxim Zaitsev, has recently been funded by the European Research Council. This will guarantee that the work performed in PatLoc will be continued in Freiburg for at least five additional years with radically fresh ideas about technological and methodological advancements and prospective diagnostic and functional applications in such different medical areas like neuroscience, neurology and oncology.

[1] Acronym for *Rapid Adaptive Nonlinear Gradient Encoding for Magnetic Resonance Imaging*.