Chapter 7

Conclusions and future directions

The first and primary aim of this thesis was to develop a general computer simulation program for FMRI with the following properties:

- The ability to produce realistic anatomical simulated MR images of any brain (or any other object) for a variety of different scanning conditions;
- The ability to produce realistic time-dependent sequences of simulated MR images including the effects of physiological activations due to some external stimulus;
- The ability to model realistic image related artefacts (mainly due to rigid-body motion of the object and magnetic field inhomogeneities).

The development of the simulator was done in three distinct stages: the model development, software implementation and the evaluation of this software, each of which was described in chapters 3-5 respectively.

The second aim of this thesis was to use the newly developed simulator and apply it in investigation of some of the motion-related issues in FMRI as well as in some interesting applications in image acquisitions.

The conclusions regarding the simulator and its use, together with suggestions for future research, are discussed below.

7.1 Development of the simulator

The development of a computer program that can simulate generation of functional MRI images is a very complex task. The first reason for the complexity of the task is the difficulty of *capturing all of the realistic scanner effects into one model*. There are many factors that influence the generation of MR images: scanner environment, subject's brain structure and MR characteristics, subject's behavior which can change from experiment to experiment. Chapter 3 presents how a range of these factors have been incorporated into a single model. The model of the simulator is based on Bloch equations which are adapted and solved in order to generate MR images and also to capture some of the most prominent features in MRI and FMRI data such as: magnetic field inhomogeneities, rigid-body motion of the head, BOLD signal, eddy currents and noise.

The second reason for the complexity of the simulator development task is the *computational demand* of simulators of this kind. In order for the simulations to be realistic it is crucial to have as many of the factors influencing the FMRI data included in the simulations as possible. Incorporating these factors creates a huge demand on the computational memory and time. This problem has prevented many of the simulators developed in the past from simulating realistic 3D images and also modelling some of the very common but more complex artefacts (e.g. spin history). Chapter 4 describes the method used in this research to implement the previously described model (in Chapter 3) in a computationally efficient way. It is shown how various computational speed ups are used (including the use of semi-analytical results and parallelisation techniques) in order to make the simulations memory- and time-efficient. With the described way of implementing the model, it is possible to do simulations of a 2D image within minutes, simulations of a 3D image within an hour and long FMRI sequences within a day. The simulator now is several orders of magnitude faster than the version that was not computationally optimised. This is one of the biggest achievements of the work described in this thesis.

The third reason for the complexity of the simulator development task is the difficulty in *evaluating software* of this kind. In order to evaluate each of the software features it is crucial to have experimental data to compare the simulated data with. However, it is impossible to fully control the experimental data, which contains many un-planned factors that are part of the scanning process. The validation process done in this thesis is presented in Chapter 5 and is done so that both the implementation and the modelling side of the software are evaluated. Experiments were devised which were focused specifically on validating the motion model of the software.

Currently the simulations do contain some limitations. BOLD activation is modelled purely through changes in T_2^*, which neglects any other changes induced by varying Cerebral Blood Volume and Cerebral Blood Flow, such as flow-induced signal artefacts [28] or changes in vascular occupancy [50]. Also, the simulator can not fully model spin-echo sequences (including stimulated echoes) or implement general RF pulses. Thus, areas for future improvement of the current simulation would be to incorporate true spin-echo modelling and allow for more general RF pulses, including fully numerical Bloch simulation during the RF pulse.

The software presented in this thesis, named POSSUM (Physics-Oriented Simulated Scanner for Understanding MRI), is planned to be released as part of the FSL software package (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/) in the forthcoming year. In addition, POSSUM is part of an international collaboration (between the University of Oxford, the Montreal Neurological Institute at McGill University and the University of Hawaii) which aims to build a very comprehensive FMRI simulation environment named MIDAS (MR Imaging Data

Acquisition Simulator) [54]. More details can be found at http://www.fmrib.ox.ac.uk/analysis/research/possum/.

7.2 Applications of the simulator

In this thesis five different applications of the simulator were investigated.

Firstly, the simulator was applied in testing a motion correction algorithm - MCFLIRT (Section 6.2). The MCFLIRT algorithm showed very good performance when tested with various types of simulated data. It was found that four stages of optimisation when estimating the motion parameters, with the fourth stage using sinc interpolation, performed significantly better than the three stage option which is the current default in MCFLIRT. In addition to this, it was found that the final transformation is significantly more accurate when applied using the sinc interpolation than when applied using the trilinear interpolation which is the current default option in MCFLIRT. This application of the simulator, together with some future tests, will result in an improved motion correction tool.

In Section 6.3 the simulator was applied used to investigate the performance of ICA as a tool for quantifying motion-related artefact. The results found that the ICA method was reliable in estimating some of the effects of motion (rotation about z-axis) for various levels of motion. These results are, however, not quite enough to make a more general conclusion about the performance of ICA. It would be interesting to take this research further and test the performance of ICA with simulated data that contains various other effects (such as B_0 inhomogeneities – motion interaction of second type i.e. when the motion involves rotation about the x or y-axis).

The third application was presented in Section 6.4 and it involved evaluation of the impact of stimulus correlated motion (SCM) artefacts in FMRI data.

The results demonstrated that stimulus correlated motion affects the data significantly more than stimulus uncorrelated motion. The results also demonstrated that the areas of distortion due to the B_0 inhomogeneities were particularly badly influenced in SCM-affected images. In these areas many of the erroneous activation appeared. These results are a confirmation of the results so often seen in practice and are well know. However, what would possibly be an interesting application of the simulator is to be implemented as a first step in motion correction of FMRI data as a kind of “predictor” of where the erroneous activation might occur (for a given brain, field map and a motion sequence) which would then serve to distinguish between “real” and “false” activations.

The fourth application (Section 6.5) was in the field of eddy currents artefacts. With the use of the simulator it was demonstrated that using a standard affine registration method is not sufficient to correct for strong eddy current effects. It was also shown that by using the doubly-refocused pulse sequence, the level of eddy currents is substantially reduced compared to the more widely used single spin-echo approach. These results are very promising, and based on them it is possible to say that further simulation work using the simulator may help to devise better schemes to align DW images in the presence of higher order eddy current fields.

Finally, the last application done in this thesis (Section 6.6) presents the application of the simulator in direct neuronal current imaging. The results in this application were obtained by considering the influence of one neuronal current and they found that: the maximum signal change due to the neural current happens when the timing of this current overlaps the center of the k-space; the signal splitting when the phase encode direction is along x-axis (coronal slices) is seen to be along x-axis; the signal splitting when the phase encode direction is along z-axis (coronal slices) is seen to be along the x-z diagonal. These results were a very close match with the results obtained experimentally by Pell et.al.[60]. These are promising results, lending support to the belief that further simulation work using this software may help when investigating complex neuronal current models (e.g. the effect when a number of randomly oriented neuronal currents would have on the signal when they act together). This would be very useful for the further experiments in direct neuronal current imaging, as building phantoms is a highly difficult and costly task which could be helped by the use of simulations as an extra tool.

7.3 Future development of the simulator

The research presented in the previous chapters leaves many promising avenues open for future research. This section looks at some of the future directions in the development of the simulator.

Spin-echo modelling An obvious limitation of the simulator is that it can not fully model spin-echo sequences (including stimulated echoes). This limitation exists because, de-phasing of the spins is averaged over each voxel i.e. each voxel is characterised by only one magnetisation vector. This magnetisation vector decays exponentially following the T_2^* decay and can not exhibit "re-phasing". In order to be able to model re-phasing, the model of the voxel magnetisation needs to be more complex. For example, one way would be to model each voxel as a collection of isochromats. Magnetisation vector for each of the isochromats satisfies Bloch equation and the total sum of these vectors would in this case be able to simulate re-phasing which is necessary to obtain the spin-echo and the T_2 decay. A downfall with this approach is that it is very computationally expensive as each of these magnetisation vectors also needs to be followed through the pulse sequence (i.e. Bloch equation needs to be solved for at every point for all of them). The computational demands of the simulator are already quite high and with this extra work the simulations quickly become un-realistic. A way to overcome this and still be able to model the spin-echo is an open problem and an obvious useful future direction for the simulator development.

General RF pulses Another possibility for future work is to implement general RF pulses. At the moment RF pulses are implemented with a use of a slice profile and are assumed to happen instantaneously. This approach prevents investigation of the motion effects during the RF pulse. It can be improved by including fully numerical Bloch simulation during the RF pulse.

RF inhomogeneities An additional improvement to the simulator is modelling RF inhomogeneities. This is a part of an on-going work which has not yet been fully implemented and validated within the simulator. However, the model has already been developed. Inhomogeneities in the RF field are modelled separately in the simulator for the receiving RF coil and the transmitting RF coil. Inhomogeneity in the receiving RF coil impacts received signal strength and is modelled with an extra multiplier $\psi_r(\mathbf{r}_0)$ in Eq. [3.19]:

$$S(t) = \sum_{j\in\Lambda} \sum_{\mathbf{r}_0\in\Omega} \psi_r(\mathbf{r}_0) s_j(\mathbf{r}_0, t) \, . \tag{7.1}$$

Inhomogeneity in the transmitting RF coil impacts the strength of the flip angle and is modelled with an extra multiplier $\psi_t(\mathbf{r}_0)$ in the equation for the flip angle:

$$\alpha(\mathbf{r}_0, t_{0-}) = \psi_t(\mathbf{r}_0) W(\omega(\mathbf{r}_0, t_{0-}) - \omega_{RF}) \, . \tag{7.2}$$

Values of $\psi_r(\mathbf{r}_0)$ and $\psi_t(\mathbf{r}_0)$ range from zero (maximal inhomogeneity) to one (no inhomogeneity). They are specified for every object voxel through user specified files. RF inhomogeneities are currently being implemented into the simulator.

More advanced pulse sequences Theoretically, the simulator can simulate any gradient-echo sequence. However, the current implementation has been done for the standard 2D gradient-echo sequence and the standard EPI sequence. A further improvement of the simulator would be to extend the implementation of the simulator so that it can simulate other gradient-echo type sequences such as spiral EPI, partial k-space EPI, 3D EPI, FLASH and SSFP. The work would mainly involve extending the pulse sequence generator and reconstruction algorithms.

Parallel imaging An additional area of improvement is including the possibility of parallel imaging in the simulator. Besides the image contrast, imaging speed is probably the most important consideration in clinical magnetic resonance imaging (MRI). Unfortunately, current MRI scanners already operate at the limits of potential imaging speed. In recent years, the greatest progress in further increasing imaging speed has been the development of parallel MRI (pMRI).

Parallel MRI works by taking advantage of spatial sensitivity information inherent in an array of multiple receiver surface-coils to partially replace time-consuming spatial encoding, which is normally performed by switching magnetic field gradients. In this way, only a fraction of phase-encoding steps have to be acquired, directly resulting in an accelerated image acquisition while maintaining full spatial resolution and image contrast. Besides increased temporal resolution at a given spatial resolution, the time savings due to pMRI can also be used to improve the spatial resolution in a given imaging time. Furthermore, pMRI can diminish susceptibility-caused artifacts by reducing the echo train length of single- and multi-shot pulse sequences.

The way the parallel MR imaging can be done in the simulator is by including the coil model in the simulator. Each coil has their own sensitivity map which needs to be incorporated into the existing RF model of the simulator. The simulator can then be run for each of the coils independently and the output needs to be reconstructed using algorithms developed specially for parallel MR imaging.

Respiratory and cardiovascular changes In addition to the above mentioned improvements which are mainly concerned with improving the scanning properties, it would also be useful to look at the ways of improving the physiological noise model by adding the respiratory and cardiovascular induced changes. However, the exact way of how respiratory and cardiovascular induced changes influence MR parameters is not completely known and is part of current research by a few world groups e.g. Montreal Neurological Institute, McGill University. Some suggestions exist that the main changes occur in the T_2^* and the phase of the magnetic field and this could be easily modeled in the simulator by modifying the T_2^* and B_0 variations in time.

7.4 Final remarks

In this thesis, a novel FMRI simulator is presented. The simulator, for a given gradient echo pulse sequence, a segmented object with known tissue parameters, and a motion sequence produces realistic simulated images and FMRI time series. The way the Bloch equations are solved, by tracking and updating the magnetisation vector through time for every object voxel, allows the changes that occur during the acquisition of one TR to be modelled and then carried through to the acquisition of the next TR, making it possible to simulate the BOLD response (through T_2^* changes), the spin history effects, motion during the readout periods and interactions that motion-related artefacts have with B_0 inhomogeneities.

The simulator has the capability to turn on or off various subject- and scanner-related effects, which is not possible in real scanning and therefore has a wide range of applications. These applications include the simulation and removal of various artefacts, both in MRI and FMRI. Furthermore, by generating the "ground truth", the FMRI simulator can be used for evaluation and validation of software tools for FMRI analysis methods (e.g. motion correction, registration, statistical analysis of images, etc.). Specifically, the simulator can be used to model the full effects of rigid-body motion artefacts on FMRI data and on FMRI statistics.

Using simulation-based methods is a very cost-effective method of evaluating complex systems. However, until recently this was not possible due to the computational requirements. With the development of processing power and with the development of methods such as the one presented in this thesis, simulation-methods have the potential of becoming a very important tool in the field of neuroimaging.