

Chapter 6

Summary and Future Work

6.1 Summary

Three major contributions were made in this work:

- A small animal simultaneous PET/MRI system was developed to enable robust intratumoral imaging *in vivo*.
 - We developed image coregistration techniques that align simultaneously acquired PET and MRI images to subvoxel accuracy.
 - We characterized the interference effects between the PET and MRI instrumentation in the hybrid system. We showed that quantitative, dynamic PET/MRI studies can be performed with the hybrid PET/MRI system with minimal distortions to either the PET or MRI images.
 - A method was developed to enable the precise spatial coregistration of PET/MRI and DWBA images obtained from the same animal subject. This method was used to demonstrate that the hybrid PET/MRI system returns tumor images that are commensurate with intratumoral activity distributions in the underlying tissue.
- The diffusion MRI technique was adapted to monitor the response of the cancer nanotherapy CRLX101
 - We showed that diffusion MRI is sensitive to CRLX101 response within 2 days of treatment and before significant tumor size changes were observed.

- Model-based analysis of the diffusion MRI data was able to predict the antiproliferative effects of CRLX101 and the reduced antiproliferative effect of CPT-11 by comparison.
- PET and MRI techniques were developed to monitor the effects of the tumor-penetrating peptide iRGD
 - DCE-MRI was able to visualize increased vascular permeability and extracellular volume due to PAF-administration.
 - DCE-MRI did not show significant differences in vascular permeability and extracellular volume due to iRGD-administration.
 - PET/MRI studies showed that iRGD responses can be variable and may be tumor growth-dependent.

6.2 Future Work

6.2.1 Next Steps for Hybrid PET/MRI

Catana and Peng outlined a road map for the potential of hybrid PET/MRI [106, 142]. Since their discussions, the field of hybrid PET/MRI has grown substantially. In light of the current work, we elaborate on some of the points they raised and add to the PET/MRI roadmap .

6.2.1.1 Hardware

The major motivation for our work in sections 3.2 and 3.4 is the belief that the availability of high-resolution PET information to synergize with high-resolution information provided by anatomical and functional MRI will be an important motivator for the adoption of PET/MRI technology. Hardware for next-generation systems will be driven partly by this motivation. Increasing the number of detectors in the system and incorporating DOI capability to each PET detector will improve the sensitivity of the system, reduce parallax errors and enlarge the axial FOV. DOI can be implemented by placing PSAPD detectors on both ends of the scintillation crystal array. Decreasing the scintillation crystal size from $1.5 \times 1.5 \text{ mm}^2$ to $1 \times 1 \text{ mm}^2$ can improve the spatial resolution to close to 1 mm at the center of the FOV. The number of detector rings can be increased from 1 to 4. These

modifications can extend the axial FOV up to 6 cm (sufficient for whole body mouse scans) and improve the sensitivity of the system to 20%–30% [213]. The enlarged FOV will improve the time efficiency of small animal PET/MRI studies, as the animal can remain static during the whole study. Increased sensitivity of the PET system will be very important for combined dynamic PET/MRI studies since each time bin for these studies will contain low activity counts.

A major challenge towards this goal is to design PET detectors, and a system that house these detectors, that will fit within the confined space imposed by the MRI system. An obvious solution is to miniaturize all the parts that are found in the current system. However, the presence of more electronics in the same volume may amplify the shielding and temperature challenges (e.g. section 3.6) that underlie the current technology. These challenges can only be explored and met as the next system is being built. Methods developed in this and previous works will aid in evaluating new systems at each stage of development.

6.2.1.2 Software

Concurrent PET and MRI datasets can be used to improve the data quality of each separate dataset. Some active avenues of research in this area were outlined in section 2.3.3. One important line of research is the development of partial volume correction techniques for reconstructed PET images using MRI information. Current studies are restricted to phantom explorations and/or lack gold standard verification [288, 289]. The availability of datasets such as those in section 3.4) will be useful to verify these techniques in *in vivo* situations.

6.2.1.3 Applications

Widespread adoption of PET/MRI technology will be dependent on the utility of its applications. There is no doubt that PET and MRI information are synergistic, but as mentioned in section 2.3.3, it will be the necessity of near-simultaneous PET/MRI data acquisition that will drive hybrid system development.

Verification of Image-based Models. We used a diffusion MRI-based model of tumor growth to understand treatment response of a cancer nanotherapy. The model can be improved by introducing more measurable parameters, which PET/MRI can provide. For example, tumor glycolytic and pro-

liferation information from ^{18}F -FDG and ^{18}F -FLT images can be fed as the proliferative parameter in the logistic model [208]. Conversely, the robustness of parameters derived from a unimodality model (e.g. diffusion MRI only) can be verified with information obtained from the alternative modality (figure 6.1).

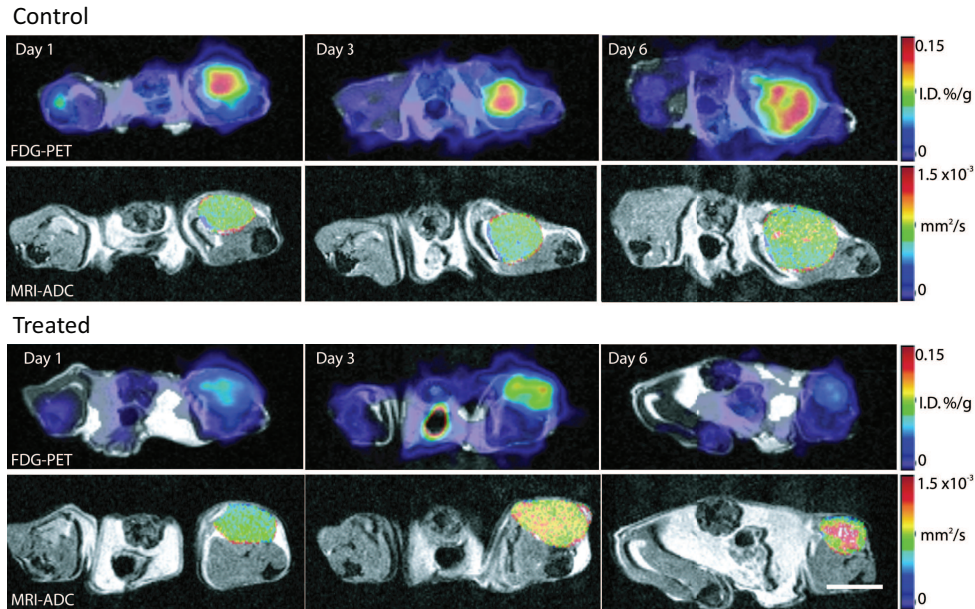


Figure 6.1: Simultaneous PET/MRI data can analyzed with image-based models. Availability of simultaneous PET/MRI data, such as the FDG-PET/diffusion MRI data shown here, can be integrated into multimodal models of tumor growth or be used to verify unimodal models. FDG-PET/diffusion MRI images were acquired in mice treated with cyclophosphamide or saline and followed over the course of a week. (Scale bar = 10 mm).

Improved PET and MRI quantification. Quantification of PET is challenging and is the subject of numerous investigations. In section 3.4 we showed that PET images from a small animal PET/MRI scanner return good quantitative images. This was aided by the fact that attenuation effects of tissue and bone in small animals on 511 keV photons are minimal. Robust quantitation of PET images in larger animals and patients requires good attenuation correction. Availability of temporally and spatially coregistered PET/MRI images will provide accurate anatomical maps (from MRI) that can be used to correct PET datasets. However, since MRI does not provide direct measures of photon attenuation, it will be important to determine optimal ways to convert the MRI data into attenuation maps.

Similarly, quantification of MRI signals can be complex. MRI image intensities can be mod-

ulated by several mechanisms, ranging from the intrinsic relaxation properties of the underlying tissue, the type of pulse sequence being used, to the presence of CA. In particular, quantification of “smart” MRI CAs that are sensitive to physiological changes *in vivo* would benefit from the availability of concurrent PET data. The PET data aids the interpretation of the MRI signal changes. An example of this concept has been shown by Frullano *et al.*, who developed a bimodal PET/MRI probe that is sensitive to pH [90]. PET imaging of this probe provided its concentration. This concentration information was then used to normalize the MRI relaxation information to determine pH.

In chapter 5, we demonstrated the utility of quantitative pharmacokinetic modeling to study physiological processes. Most kinetic models require an AIF to derive quantitative parameters. Spatially coregistered MRI images can guide ROI delineation for imaged-derived AIFs for PET (figure 5.2, [290]). Alternatively, bimodal CAs can be used in conjunction with the hybrid instrumentation to allow the AIF to be obtained using one modality (optimized to collect AIF data) while tissue information can be obtained with the other modality (optimized to collect information from the tissue).

Real time PET/MRI-guided imaging. The availability of near-perfect spatially coregistered PET/MRI images will allow one modality to guide image acquisition by the other modality in real-time. For example, rapid location of tumor metastases by PET can inform the choice of the specialized functional or anatomical MRI imaging sequence, which can vary depending of the location being imaged, to pursue in the same study session. Another area of study where real-time analysis of simultaneous PET/MRI can have a big impact is in the area of cardiology and peripheral vascular disease. PET or PET/MRI visible probes targeted to vascular inflammation or early atherosclerotic plaque formation can be located by PET, followed by high-resolution MRI of the anatomy around the highlighted region [186]. These types of studies are not only time efficient, but the combined imaging technique can be potentially more sensitive and specific than the single modality tests currently available.

Multimodal studies of uptake and response. The current work developed a PET/MRI strategy to follow the uptake and response of cancer nanotherapy where simultaneity of image acquisition

is important. Future studies can build upon the initial results presented here. In particular, PET insert-compatible DCE-MRI in combination of radiolabelled nanotherapies will allow us to further understand the interactions between tumor structure and drug uptake. Another realm of inquiry where multimodal PET/MRI will be useful is the monitoring of immunotherapy. Multimodal immunotherapy, such as the combination of *in vivo* cell and cytokine therapies, act synergistically in short time scales. Near-simultaneous PET/MRI will be useful here to monitor real-time biodistribution and interactions between these therapies at an organ-level scale.

6.2.2 Translational Considerations

In this work, we developed noninvasive imaging techniques to understand cancer nanotherapy uptake and response in the preclinical setting. Unimodal or multimodal preclinical imaging provide important links between basic biological studies and their clinical application. Ultimately, the success of these preclinical studies will be gauged by whether they can positively impact patient care. Simultaneous PET/MRI systems are being introduced in the clinic; the methods and imaging approaches developed here are directly applicable for use in these systems. The diffusion and DCE-MRI protocols described herein are currently being adopted for clinical trials. It will be very important in future studies to verify the applicability of these protocols in human patients. Concurrently, methods developed in this thesis can be used to match imaging information to volumetric microscale data (DWBA/histology) and to infer mechanistic insights (via image-based modeling), both of which can inform the basic development of next-generation therapies.

It is hoped that the techniques and advances described herein will contribute in some way towards the collective effort against cancer.