In 1609, Italian polymath Galileo Galilei built what is considered the first compound light microscope, thus opening the microscopic world for scrutiny. This led to Robert Hooke’s discovery of the biological cell (Figure 1 A&B) and van Leeuwenhoek’s observations of living cells in 1674. These observations gave birth to the cell doctrine on which modern biology is founded.

In 2009, 400 years after Galileo’s invention, the magnetic resonance (MR) microscope (Figure 1C-E) is evolving into a useful tool for cellular imaging and investigation of tissue microstructure. In an age where a number of microscopy techniques are readily available this may seem a small feat but in the following we will explain why we are convinced that this technique is important, and its further development worth pursuing.

Modern neuroimaging relies - for a large part - on MR-techniques either alone or in combination with other imaging modalities. While the image quality produced by current MR-systems is impressive, the image resolution is still very coarse (about 1000 µm) compared to the scale of biological tissue structures (about 10 µm). One way of making the MR signal reflect tissue structures on the cellular scale includes sensitizing it to water self-diffusion. This has been found to make MR imaging very effective for detection of ischemic tissues e.g. in stroke. However, even with the sensitivity obtained in this manner, the specificity of the diagnostic method is lacking and the underlying mechanisms remain unclear. In the same manner, the diffusion-based tractographic methods used to produce synthetic maps of brain fiber trajectories from MR data are unvalidated and their precision remains difficult to assess. It is in answering questions such as these the MR-microscope holds promise. In an effort to shed light on these and other questions, our collaboration has focused on using MR-microscopy to visualize (Figure 1E and Figure 2) and study MR-characteristics of individual mammalian cells (alpha-motor neurons, ~50 µm in diameter) in situ. This result was chosen for the front cover of NeuroImage for the July 2009 edition (Figure 2).
tissue components, regional tissue response to exposure to neuroactive substances (figure 3A) and high resolution investigations of brain tissue structure and the data processing methods used to visualize it from MR data (Figure 3B). MR-microscopy has obvious strengths in the study of biological tissue because, unlike other current microscopy methods, MR-microscopy employs a technique (magnetic resonance) which is one of the current imaging standards for disease diagnosis in the clinic. As such, MR-microscopy is capable of revealing the origins of MR signal - as well as alterations in that signal associated with disease pathology - at the cellular level. This information is crucial for the continued development of imaging-assisted differential diagnosis as microscopy studies will reveal exactly how and to what extent the MR signal changes as a result of specific disease states. Therefore the MR-microscope is a tool suitable for both the study of biological phenomena and the improvement of MR techniques already in use in the clinic.

A strong motivating factor for further research in this field is the prospect that, by using a combination of MR-microscopy and advanced mathematical modeling, we may become able to extract quantitative measures directly related to tissue microstructure far exceeding those which are possible using current techniques. Such techniques would be related to histological methods, but would not require stains, and - very importantly - could perhaps one day be performed in vivo. Such a method (call it virtual biopsy or MR-histology) would provide insight into a number of pathologies where tissue microstructure is known to change or degrade – one example being Alzheimer’s disease. Our ability to investigate the normal brain would also increase by such methods for instance by improving our understanding of how the brain’s microstructure is affected by external factors such as chronic stress, development, aging and learning.

By its invention 400 years ago, the optical microscope made possible a wealth of new scientific endeavors. While it is probably not fair to expect the MR-microscope to cause scientific breakthroughs comparable to those produced by the light microscope, it is certainly reasonable to say that the MR-microscope is now at a stage comparable to the stage of the light microscope at the time of Robert Hooke: We have a new tool that allows us to investigate many important topics that have so far been impossible to study using MRI. It is our hope that the MR-microscope may prove just as useful in the work of improving MR-based neuroimaging and diagnostics.

References

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