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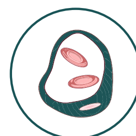

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Editorial

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Application of Magnetic Resonance Technologies to Cell Biology

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Since the discovery of Electron Paramagnetic Resonance (EPR) spectroscopy in 1944 [1], and the realization of the Nuclear Magnetic Resonance (NMR) signal [2,3], the capabilities and applications of Magnetic Resonance (MR) technologies has continued to advance throughout the 1970s at an enormous rate particularly accelerated by Fourier transform [4] and multidimensional methods [5]. At about the same time during the 70s, nuclear Magnetic Resonance Imaging (MRI) techniques were being realized and developed. Beyond the 1980s MR technologies were mixed with other technologies and evolving to become indispensable tools for drug discovery, design and diagnostics.

Early on it was recognized that MR techniques can offer a variety of unique advantages such as being completely non-destructive and non-invasive. Thus, MR can be utilized with inanimate samples or living organisms with no detrimental effects. MR can provide chemical and physical information for the solution (e.g. intra or extra cellular fluid), semi-solid (e.g. cellular membranes or tissues) and solid (e.g. immobilized or membrane bound proteins) states of matter. Recently, developed is the application to semi-solids that can be advantageous and/or necessary for intact tissues or whole cells [6]; metabolites or components are in their "native" environment i.e. potentially time consuming and disrupting/degrading extractions, or chemical modifications are not required in order to obtain valuable information.

One drawback of MR technologies is that they are sampled intensive requiring μM to mM concentrations translating to μg to mg quantities of material. A number of methods have been proposed to overcome the mass demand with the most significant for general applications being the invention of cryogenically helium cooled detection systems that substantially reduce thermal noise ultimately improving the signal-to-noise ratio. A second drawback recognized with larger proteins and macromolecular assemblies (>40 kDa) is the loss of signal due to broad line-widths and increased spectral complexity. There have been efforts to address this issue; however, these efforts are limited in scope and application.

MR is a technique that detects electrical currents induced by precessing nuclear magnetic moments. Nuclei with non-zero spin moments are MR active and in principle are detectable. Each individual type of spin-active nucleus has a unique precessional frequency dependent upon the strength of the static magnetic field, the magnetic properties of the isotope and the local electronic environment of the nucleus. The applications and significance have exploded because the exact precessional frequency (i.e. the chemical shift) is influenced by the local electronic environment of the nuclei and thus, MR can readily distinguish (for example) a ^{1}H nuclei that is chemically bound to different nuclei (e.g. carbon vs. nitrogen, etc.), is chemically bound to different oxidation states of the same nuclei (e.g. methyl vs. methylene carbon), and are in identical bonding environments (e.g. methyl ^{1}H nuclei) but in different electronic environments induced by surrounding functional groups (e.g. aromatic vs. carbonyl groups). Equally important, if a nucleus is influenced by another spin active nucleus either through a bond connection or in spatial proximity, a correlation exists that may be detectable. In this way atomistic properties can be determined [7]. Detailed atomistic characterization of molecules culminated in the structural elucidation of proteins by the mid 1980s [8]. In addition to the typical static structural information, one can also detail dynamic processes with rates in the range from 10^{-2} to 10^{-10} sec^{-1}. MR data can be further separated based upon relaxation, diffusion or spatial location. MR technologies can discriminate among large molecules like proteins and small molecules within the same sample. The relaxation mechanism plays an important role in distinguishing among small drug molecules and large proteins.

Pharmaceuticals have a diverse range of mechanisms for eliciting biological responses. Determining the biological target requires extensive micro-biological investigations. NMR can play a role within these investigations in particular by identifying the pharmacophore. Identifying the pharmacophore is an important aspect for drug discovery and understanding the mechanism of action as it assists with "intelligent" design of drugs through modifications that change binding characteristics (e.g. modifying the pharmacophore region) or solubility/permeability properties (e.g. modifying sites distant from the pharmacophore).

An important application, although commonly overlooked, is the accurate quantitative information that can be obtained without the need for laborious calibrations [9]. Under quantitative conditions and for all practical purposes with semi-solid or solution state samples, NMR spectroscopy has the unique distinction of having a uniform molar response for all nuclei of the same type i.e. all ^{1}H nuclei have the same integrated intensity and thus, a single calibrated (internal or more significantly external) standard can be used for accurate quantitation especially valuable for quality assurance/quality control (QA/QC) applications.

Analysis of soluble metabolites and metabolic flux can help ascertain the effects of a particular compound or extract on an organism. NMR is a suitable method for such analyses as it allows simultaneous detection of a variety of primary and secondary metabolites. NMR can resolve complex metabolomic samples by "isolating" compounds based on (for example) nuclei such as ^{1}H, ^{13}C, ^{15}N or ^{31}P providing spectral fingerprints with compound specificity and quantitative accuracy. The stability of the NMR instrument allows for repeated measures (often years apart) of samples with accurate

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reproducibly. The numerous advantages of NMR have been a major driver for developing NMR based metabolomics methodologies. The most commonly cited disadvantage is the lack of sensitivity. This is a major hindrance especially for low abundance metabolites that could be overwhelmed by highly abundant ones. Furthermore, in some applications such low level metabolites may be of high value. Approaches for simplifying sample matrices through chemical or physical separation have been developed to circumvent this issue.

In contrast to the molecular level details, MRI can provide 3D images of macroscopic matter *in vivo* leading to a variety of clinical applications. For example, during *in vivo* testing and diagnostic stages, MRI is capable of producing 3D images that can be used to monitor changes in brain activity in response to application of a pharmaceutical via MRI techniques, indirectly monitor the effects of a compound on tumours, or directly monitor the bio-distribution and bio-accumulation of a pharmaceutical by tagging it with an MRI contrast agent.

For the aforementioned reasons MR techniques provide valuable information on pharmaceuticals (therapeutics, diagnostics or the recently coined "theranostics"), small molecules, metabolites, peptides, proteins, complex mixtures, and molecular assemblies such as lipid bilayers or tissues. Together the MR technologies of NMR and MRI can cover a wide range of drug development from discovery through to clinical testing.

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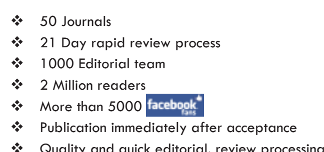
- More than 5000 
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