Current Clinical and Medical Education

Received 19 Mar 2024 | Revised 20 Mar 2024 | Accepted 24 Apl 2024 | Published Online 2 May 2024

Published By: Vision Publisher

ISSN 2942-0792

CCME 02 (5), 33-48

Original Article

Nuclear Magnetic Resonance (NMR): Principle, Applications, Types, and Uses in Metabolite Identification and Medical Biotechnology

Zahraa Sabah Abdel Zahra[1]

[1]Department of Applied Medical Physics, Hilla University College, Iraq

Abstract: The field and laboratory applications of nuclear magnetic resonance (NMR) for assessing the damage potential of drilling, completion, and production fluids are numerous. Enhanced oil recovery, drilling, completion, and other applications use NMR to assess emulsion droplet size and behavior in the pore space. When compared to other methods, nuclear magnetic resonance (NMR) has shown to have the most promise for advancing exploration and production in unconventional gas fields, and its usage in both laboratory and field scales allows for the evaluation of unconventional gas resources. Geosteering, logging while drilling, and other field uses of NMR in exploration and drilling were also covered. The presentation concluded with an overview of the possible future paths of NMR tool development, including the use of multi-dimensional NMR and the improvement of the signal-to-noise ratio of the data acquired during drilling operations (logging).

One way to test metabolites is with nuclear magnetic resonance (NMR). This technique can pick up on things like amino acids, ketone bodies, lipoproteins, and even some inflammatory markers. Metabolic disorders like diabetes, infectious diseases, neuropsychiatric diseases like Parkinson's and Alzheimer's dementia, and the vast field of cancer are among the many areas where nuclear magnetic resonance (NMR) has found use. The discipline of NMR metabolomics is expanding rapidly as researchers work towards the ultimate aim of personalized medicine: the ability to detect diseases earlier, tailor treatments to individual patients, and track how well treatments are working. Lipoproteins in serum, for instance, can be analyzed with the help of nuclear magnetic resonance (NMR), which provides a plethora of information. Particle size and density allow for the separation and quantification of the four lipoproteins: HDL, LDL, IDL, and VLDL. There are four sizes for HDL and six sizes for LDL, for instance. Plus, you can measure the proportions of each of their parts. Phospholipids, triglycerides, apolipoproteins, cholesterol, and free cholesterol are all part of this group. An improved understanding of disease mechanisms and diagnostic accuracy can be achieved by studying lipoprotein profiles, which are changed in a variety of disorders and are crucial to metabolic activities.

Keywords: NMR, Principle, Types, Applications, Medical Biotechnology

Corresponding Author: Zahraa Sabah Abdel Zahra†, Department of Applied Medical Physics, Hilla University College, Iraq

Introduction: For a deeper grasp of the reservoir and its characteristics, precise determinations of fluid and rock parameters are required. A range of logging tools can be used to retrieve most of these properties in field applications. Unfortunately, with the current state of well log technology, it is not possible to obtain precise data for crucial petrophysical variables as permeability and capillary pressure curves [1]. For this reason, it is crucial to conduct evaluations of oil and gas reservoirs using laboratory-scale measurements in order to precisely ascertain reserves and possible recovery methods. This highlights the need of combining results from both the lab and the field. Logging tools can conduct field-scale measurements of formation fluids using low-field NMR, and laboratory-scale measurements taken with benchtop instruments can be used to cross-validate the field-scale measurements and expand them for future research [1,2]. An operating Larmor frequency of ϋ = 2 MHz may be used for both laboratory and field-scale measurements; however, a stronger magnetic field might be used for lab-scale experiments, opening up a wider variety of possible uses. Current industry technology allows for the acquisition of longitudinal relaxation time (T 1), transverse relaxation time (T 2), fluid diffusion coefficient (D), and 2D nuclear magnetic resonance (NMR) (e.g., T 1 -T 2 T 2 -D). The drilling mud filtrate may prevail to a depth of tens of centimeters, known as the flushed zone, during the examination. Nevertheless, as we will see in the section titled "4 NMR Applications in Field Scale:" the obtained signal could readily distinguish between the fluid phases, enabling reliable interpretation of the NMR logging data. Logging while drilling (LWD), cased and open hole, and stationary data acquisition methods are also possible. Service providers including Schlumberger, Baker Hughes, and Halliburton have created and developed a number of NMR logging technologies. At 2 MHz with a minimum echo duration of 0.2 ms, Schlumberger's CMR-Plus has the highest operating frequency of any industry product [3-5]. Halliburton offers the XMR, the deepest exploration tool (102 cm) that operates between 0.547 and 1.183 MHz with a minimum echotime of 0.2 ms. In addition, they created a LWD tool known as MRIL-WD that operates at a lower frequency (0.5 MHz with a minimum echo time of 0.5 ms).

Static magnetic field B0 to induce polarization through the sample, RF radiation applied at Larmor frequency, and a coil to detect the emitted oscillating NMR signal are the main components for NMR benchtop basic experiments at the laboratory scale. Typically, the two coils are the same. In order to gain more versatility and a wider range of uses for NMR data, larger-scale studies are conducted in the lab. With the use of lithium ion battery electrolytes, chemical structure under in-situ combustion conditions, upstream and downstream, nuclear magnetic resonance (NMR) has demonstrated its reliability in the energy sector. But nuclear magnetic resonance (NMR) is still a young area of study in the energy sector, and it offers a number of promising avenues for further investigation [6, 7]. Depending on the parameters of the studies, a broad variety of magnetic field strengths can be used to take readings in the lab. The classification is based on the strength of the magnetic field and the typical experiments performed in each category [8]. The cryogenically cooled superconducting components of high-field NMRs produce a strong magnetic field with great sensitivity, making them ideal for application in chemistry, particularly for the elucidation of molecular and solid structures.

Research on porous media (rock core relaxation and diffusion) and engineering systems makes extensive use of it. Also, certain low-field magnets are tiny and portable [9]. Petrophysics and enhanced oil recovery (EOR) are the primary areas where nuclear magnetic resonance (NMR) is used in petroleum engineering for research conducted on a laboratory scale. Because it accurately determines porosity, pore size distribution, fluids saturation, and permeability—all without invasive procedures—NMR petrophysical core analysis is a powerful and dependable technique for routine core analysis (RCA) [10-12]. Additionally, NMR can be used to measure wettability, capillary pressure, and clay mineral analysis as part of special core analysis (SCA) investigations.

Uses for improved oil recovery

A variety of processes, including drilling and enhanced oil recovery (EOR) activities, can be better understood with the use of nuclear magnetic resonance (NMR) (Kenyon 1997). To assess the efficacy of the EOR therapies, various NMR measures can be employed. To record the alterations to the rock porosity system caused by EOR treatment, the standard method use T2 distribution. T2 can also be used to track the saturation levels of the fluids in EOR trials, which improves the design and assessment of EOR techniques [13, 14]. By utilizing T2 methodology, one may evaluate oil saturations over time, as well as track the remaining oil saturation for various EOR procedures in the reservoir (via NMR logging) and in controlled laboratory settings.

In addition, the non-invasive NMR pulsed field gradient (PFG) approach can be used to determine the diffusion coefficient for many fluids. This information is useful for early EOR treatment stage method selection based on the pore network. One way to test compounds for potential use in EOR treatments is by employing diffusion measurements to evaluate pore coupling. For instance, in cases where the reservoir's connection is inadequate, chemicals can be employed to enhance the pores' connectivity; [15-17] however, fluids with a high injection pressure requirement should not be included. When developing and testing various fluid systems for EOR applications, knowing the apparent diffusion coefficient is a great way to have a better idea of how the oil and water distribute across porous surfaces.

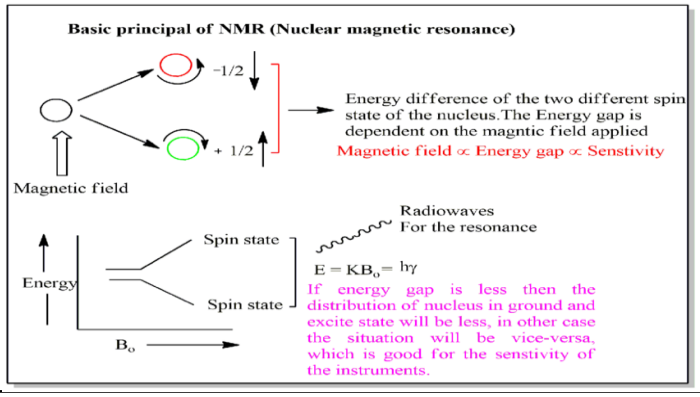
The use of nuclear magnetic resonance (NMR) in the lab and in the reservoir (via NMR logging) allows for the assessment of oil saturations at various times and the monitoring of remaining oil saturation for various EOR procedures. In laboratory settings [18, 19], low-field NMR measurements can be employed to assess EOR treatments for both conventional (light and heavy oil) and unconventional (shale oil) reservoir types.

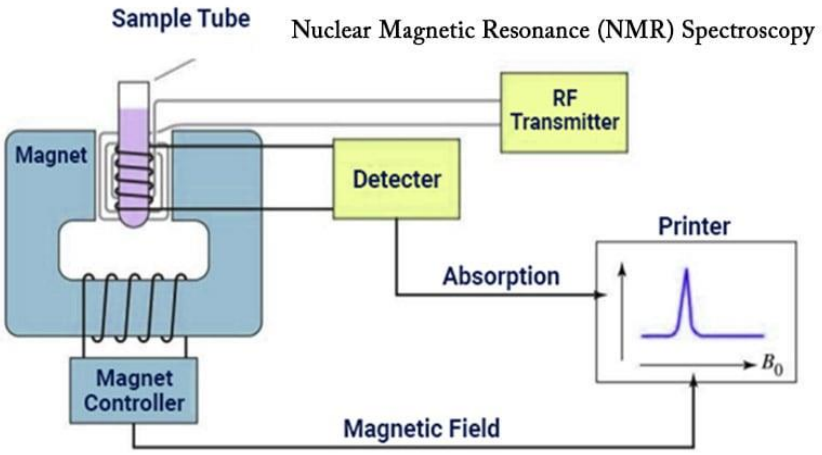
Screening several chemicals for EOR applications, including CO2, surfactants, and polymer flooding, is the main goal of NMR experiments. In most cases, the saturation profile with respect to distance or in conjunction with the treated rock samples is generated from the distribution of T 2 relaxation time. Getting the T 2 relaxation time profiles both before and after the treatment can give you a decent idea of the saturation distribution and how much oil is still there [20-24]. Chemical elective imaging, complete signal suppression, and paramagnetic doping are some of the methods that can be employed to ascertain the oil saturation. Rock type, composition, and chemical type are among the many variables that go into deciding which method is best [25].

Using nuclear magnetic resonance (NMR) to assess EOR operations has several benefits, one of which is the ability to optimize EOR performance through comprehensive and continuous monitoring of remaining oil saturation. Chemical enhanced oil recovery (cEOR) procedures can be followed using nuclear magnetic resonance (NMR) imaging of the surfactant's adsorption-induced changes in pore surface wettability [26, 27]. Conversely, desktop NMR devices are primarily designed for use with tiny core samples, typically ranging from 2 to 4 inches in diameter [28]. This can limit their ability to analyze longer core samples. To get around the capillary end effect and get more accurate results from coreflooding investigations, large core samples (6-20 inches) are usually used. We had to chop the core samples into little pieces and create composite cores during the chemical flooding because these long samples cannot be used for NMR experiments.

To further understand the oil recovery mechanisms for various surfactants, the NMR technique was used to track the oil-AS contact. In addition, by identifying the blocked pores that the injected chemicals can use to displace the oil, NMR analysis aids in evaluating the injectivity issues that arise during AS flooding. Eight core samples with high permeability (120-1200 mD) were utilized to track the oil saturation during water flooding and sulfonate-based NS injection utilizing a low-field NMR technique [29].

Fundamentals of Nuclear Magnetic Resonance (NMR) Thermoanalysis: According to nuclear magnetic resonance (NMR) theory, all nuclei have an electrical charge and a large number of them have spin. The use of an external magnetic field allows for the transfer of energy from the base energy to a higher energy level, often through a single energy gap [30-33]. The energy is transferred at a wavelength that is corresponding to radio frequencies, and it is also released at the same frequency when the spin goes back to its base level. An NMR spectrum for the relevant nucleus is obtained by measuring and processing the signal that corresponds to this transfer.





To maximize oil output, we measured oil recovery during CO2 injection and tried out various soaking durations during huff-n-puff (HnP). Using the T 2 relaxation time as a basis, the NMR approach was employed to generate the profiles of free fluid (FF), capillary bound fluid (CAF), and clay-bound fluid (CBF). Using low-field NMR measurements, the fluid displacements across various pore sizes and system pressures were studied. In the first and second cycles of CO 2 injection, the free fluid and a majority of the capillary-bound fluid were retrieved from the small and medium pores, according to the NMR data. In contrast, the clay-bound fluid did not undergo any modifications. On the whole, the saturation profiles for the free, capillary bound, and clay-bound fluids were provided by the floods and NMR measurements, which helped optimize the CO 2 injection.

steps in the polymer flooding process can benefit from NMR. These include characterizing the polymer, tracking its passage through the porous media, and detecting any plugging that may occur. Nucleotide MR analysis allows one to evaluate the alterations in the chemical composition of polymers. In addition, NMR measurements can be taken in-situ to assess gelation characteristics including gel strength and gelation time. Since nuclear magnetic resonance (NMR) is a non-destructive test that permits rapid and accurate measurements, it is an attractive tool for investigating polymer flooding processes. Research on the use of NMR in EOR operations is relatively new, and there have only been a few of studies done thus far. Additionally, additional research is necessary to fully understand how oil and injected fluids interact during polymer flooding. When it comes to EOR activities, the NMR approach will be crucial in revealing how the rocks and fluids behave.

Also, NMR logging is employed to ascertain the in-situ oil saturation on a reservoir scale. The rapid data collecting rate of nuclear magnetic resonance (NMR) allows for the generation of continuous profiles of oil saturation. In addition, nuclear magnetic resonance (NMR) logs can track the injection of chemicals and show where the chemical and oil saturations are distributed. So, for all chemical EOR pilot testing, NMR logging is typically advised to be done. Further improvement of oil recovery operations can be achieved by combining the NMR method with coreflooding trials; this will allow for a more accurate evaluation of the residual oil saturation, which can then be supplemented with field pilots.

Different Forms of Nuclear MR Imaging

Chemical analysis makes use of solid-state NMRs to identify structural changes brought about by phase transitions and other solid-state processes. Magic angle spinning (MAS) is the most common method used in solid-state nuclear magnetic resonance (NMR). By narrowing the wider lines of the NMR, this magic angle improves the sample's resolution, which in turn yields isotropic values and spinning sidebands that identify the nuclei's CS, allowing for more exact structural assessment in solid materials.

Nuclear Magnetic Resonance Imaging of Phosphorus:

To investigate the chemical and structural makeup of various samples, solid-state nuclear magnetic resonance (NMR) makes use of isotopes like phosphorus. Orthophosphate diesters, polyphosphate, phosphonates, orthophosphate monoesters, and orthophosphates were among the phosphorus compound classes that were discovered.

Nuclear Proton Magnetic Resonance

One of the first and most common atoms utilized in nuclear magnetic resonance spectroscopy is the proton. It can also be referred to as hydrogen-NMR (1H-NMR), and it reveals details about the surrounding environment and the various hydrogen types in the molecule. The primary materials' 1H-NMR spectra reveal a narrow chemical shift (CS) range for the typical molecule under investigation. A wide variation in the magnitude of the coupling constant was noted, with this CS ranging from +14 to -14 ppm.

^{29}Silicon Magic Angle Spinning Nuclear Magnetic Resonance

An important element, silicon has a natural occurrence of 4.70 percent with the half spin nucleus of its 29Si isotope, which is utilized in ^{29}Si-NMR. This spectroscopic method is only one more tool in the toolbox for studying organic molecule structures. It has a low resonance frequency because its magnetic moment value is slightly low. From +50 to -200 ppm, 29Si-NMR changes are most prominent. From +50 to -200 ppm, ^{29}Si-NMR changes are most prominent.

^{19}Fluorine Magic angle Spinning Nuclear Magnetic Resonance

With the exception of the 19F isotope, naturally occurring fluoride isotopes are present at extremely low concentrations. The sole stable fluorine isotope present in significant amounts is F-19. The 19F MAS NMR technique makes advantage of it because of its high quantity and excellent nuclear properties.Among the most accessible NMR nuclei is the 19F nucleus, and the 19F-NMR technique is much faster than the 1H-NMR approach [33]. The spin of fluorine is half-nucleus. It has a binding energy of 147,801 keV and typically has nine electrons surrounding its nucleus in molecules. Fluorine is very reactive to NMR measurements with an exceptionally wide CS range because of the sensitivity of 19F-NMR spectroscopy to its CS, which allows for the analysis of precise details of the local surroundings.

^{27}Aluminum Magic Angle Spinning Nuclear Magnetic Resonance

The nuclear spin of ^{27}Aluminum MAS-NMR is 5/2, and its natural abundance is 100%. Across a wide range of CS, the aluminum nucleus responds strongly, producing wide lines. Finding the presence of aluminum and studying the likely structural alterations of the many aluminum kinds are the primary uses of this NMR. Previous research has employed 27Al-NMR to see how the setting glass carbomer cement changes from Al (IV) to Al (VI).

Advantages of Nuclear Magnetic Resonance Spectroscopy

1. **Noninvasiveness**

Noninvasiveness is the hallmark of nuclear magnetic resonance (NMR). Thanks to nuclear magnetic resonance (NMR), it is now feasible to study living cells and tissues without causing any harm to the material. The most obvious benefit of NMR for in vivo research is that imaging and spectra may be acquired without sample destruction.

2. **Lack of Ionizing Radiation**

The fact that NMR does not use ionizing radiation is another big plus. In vivo investigations employing ionizing radiations are being conducted using a variety of methods. Thanks to nuclear magnetic resonance (NMR), researchers and subjects are no longer exposed to radiation, which poses health risks to everyone involved. Instead of using radioactive chemicals, nuclear magnetic resonance (NMR) makes use of stable isotopes like carbon-13 to quantify metabolic fluxes. In addition to reducing the risk of radiation exposure to both subjects and observers, nuclear magnetic resonance (NMR) technology does away with the disposal of radioactive tests and other potentially contaminated items. In this way, NMR can guarantee worker safety and cut down on experimental expenses by eliminating the need to dispose of radioactive materials.

3. **Detailed Structural Analysis**

Over the period, NMR has played a major responsibility in determining the mechanisms and chemical connections at a molecular level. This technique has helped to obtain information regarding the minute details about the physical and chemical characteristics of structures.25 NMR can also analyze the parameters of CS, and it can give details on the local bonding environment around a particular atom, which could be calculated for the extended period of times with NMR [34]. It utilizes the pseudo wave function to get information about large compound structures.27 NMR has the

capability to assist studies of biochemical processes conducted in vivo, which is not efficiently achieved with other imaging techniques. Lee et al28 proposed that NMR is a better-quality technique as compared with X-ray diffraction in determining the archaeological bone structure.

Medicinal Biotechnology Applications

Artifacts limit the usefulness of CT scans of the head, whereas nuclear magnetic resonance (NMR) imaging of the brain has no such limitations. One medical use of nuclear magnetic resonance (NMR) is the detection of malignancies, hematomas, and other diseases in children.31 Because MS is so difficult to diagnose, nuclear magnetic resonance (NMR) has emerged as the gold standard for MS testing. Some tissues, such bone, which has a low water content [35], cannot release strong signals to generate images for nuclear magnetic resonance (NMR), but this technique is ideal for other parts of the body, including the brain, where it creates clear and detailed images demonstrating the separation of gray and white matter.

Furthermore, NMR appears to be successful in the early detection of breast cancer. A radiologist from Cleveland claims that when there are numerous cysts in the breast, a mammography will not be able to tell the difference between a little cancer and a spot, but nuclear magnetic resonance (NMR) imaging can.34 Additionally, the NMR method provides excellent pictures of adipose tissues, and a substantial amount of fat produces stunning pictures [35]. Furthermore, NMR allows for thorough structural examination of blood vessel surfaces and irregularities, which is very promising for the detection of vascular disorders.

The goal of dental treatment is to restore lost tissue as closely as possible while preserving the patient's own tissue. Mechanical testers, physical testers, rheologists, and biocompatibility testers are just a few of the characterization instruments used to study these dental biomaterials. Fortunately, nuclear magnetic resonance spectroscopy (NMR spectroscopy) is a wonder tool for delving into the complex chemical reactions of materials. Gas ionomer cement (GIC) [36], resin composites, dental bone cements, and periodontal membranes materials have all been the subject of substantial NMR spectroscopy research. Through the use of nuclear magnetic resonance spectroscopy, Prosser et al. demonstrated that tartaric acid inhibits the early gelation of cement in GIC by reacting with glass more rapidly than polyacid.

Cement production causes the leaching out of Al ions in the glass from its surface layer, as shown by solid-state NMR spectroscopy, and the cross-linking of Al in the GIC setting is particularly important.37 The biocompatibility, strength, and remineralization property of a newly synthesized antimicrobial polymeric dental restorative material were examined using NMR (1H- and 13C-NMR) spectroscopy in an experimental setting.38 The field of proteomics has made tremendous strides in dentistry, which has greatly improved the diagnosis and treatment of oral disorders as well as the study of molecular alterations that occur during the use of dental materials for the restoration or rebuilding of soft and hard oral tissues [37]. Zhou et al. investigated 1H-NMR-based metabolomics to identify inflammatory chemicals in saliva samples as potential indicators for orthodontically induced external apical root resorption. Clinical dentistry and early dental diagnosis are two areas that can greatly benefit from NMR spectroscopy, which is highlighted in this paper. Multiple biochemical signatures were identified in both the control and sarcoidosis patient saliva, according to another study on salivary metabolomics. Omic technologies, such as nuclear magnetic resonance (NMR), allow for the exploration of additional biomarkers in human saliva, which has attracted researchers as a diagnostic oral fluid due to its noninvasiveness, ease of collection, and low cost.

Clinical Metabolomics and Customized Medicine via Nuclear Magnetic Resonance

When trying to make sense of nuclear magnetic resonance (NMR) and its potential use in clinical metabolomics and personalized medicine, it's helpful to remember the method's limitations and strengths in these contexts [38]. Keeping this in mind, we will look at the ways this analytical technique has been employed effectively and positively in various projects and studies, as well as ways to improve upon its shortcomings. It is common to criticize NMR for being too insensitive and having poor resolution when compared to other analytical methods, especially MS. The reality remains that, even with all the advancements in technology over the past few years, the conventional metabolomics platforms can only identify and quantify hydrophobic metabolites at concentrations in the micromolar range when using nuclear magnetic resonance (NMR). In addition, specifically in 1D-NMR, the resolution might be severely compromised due to signal overlapping caused by the lack of preparatory separative procedures for NMR analysis. Although the

resolution is substantially improved by multi-dimensional NMR techniques, sensitivity is still NMR's biggest drawback [39]. It is clear that this method can only see a tiny fraction of the metabolome because many metabolites in biofluids have concentrations that are either below or near the NMR detection limit. The part of the metabolome that can be seen and measured by NMR is frequently of critical importance, so this limitation should be balanced out. On the other hand, dependable metabolomics analysis should not be reduced to detecting a [40] maximum number of metabolites, and there may be multiple of them.

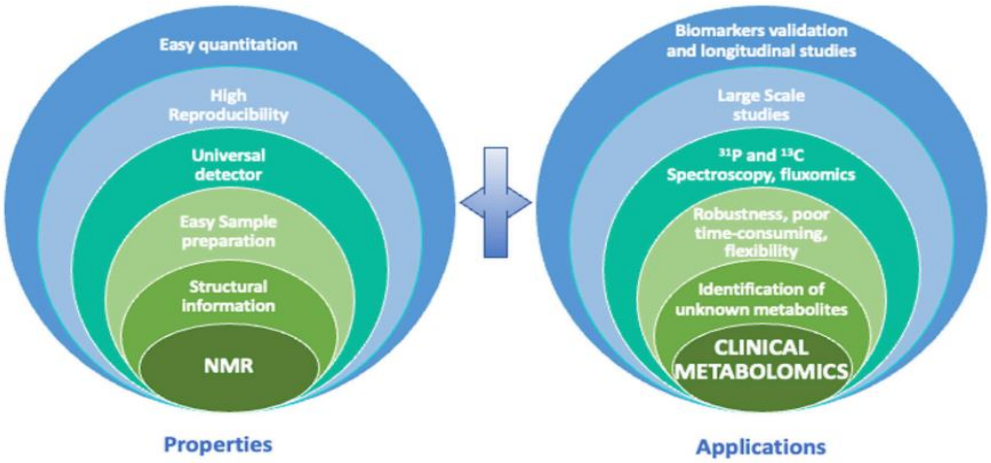


Figure 3. Properties of NMR that allow specific advantages for clinical metabolomics.

Identification of Metabolite

Methodological advancements and the creation of two-dimensional techniques (e.g., COSY, TOCSY, HSQC) could allow for a greater detection and quantification capacity for metabolites. Nuclear magnetic resonance metabolomics: recent and future advancements delves more into these breakthroughs. Combining Nuclear Magnetic Resonance with Mass Spectrometry in Clinical Metabolomics demonstrates how these two analytical platforms work well together, and it's interesting to note that NMR might also be utilized to assist MS quantification [41]. Furthermore, nuclear magnetic resonance (NMR) is the method most often cited for its ability to reveal organic molecule structures. The identification of metabolites. For any metabolomics investigations to be accurate and relevant, accurate metabolite identification is obviously crucial at multiple levels. It has been possible to assign metabolites by comparing the NMR data between samples and reference spectra, thanks to the development of metabolites databases and automated comparison techniques within the previous decade. We can mention HMDB, which is likely the most comprehensive metabolite database, BNL-NMR, BMRB, Metabolight, and a few commercial platforms and software that enable the identification and quantification of metabolites, such as the Bruker IVDr platform and ChenomX software©. Automated identification and search systems, ranging from simple to highly complicated, are a part of several of these databases [42], which are linked to boost their effectiveness [43]. Adding more metabolites spectra and data and developing more powerful algorithms for the automation of metabolite identification and quantification are obvious ways to improve these spectrum databases and the tools for comparison, identification, and quantification.

Get Your Sample Ready

Analytical techniques, particularly NMR and MS, aren't always a good fit for the complex biological samples used in clinical metabolomics. The complexity of the analyses is increased due to the introduction of a substantial risk of variability, which necessitates the adaptation of pre-analytical methods, such as protein precipitation [44]. Spectral approaches have been developed in NMR that minimize the preanalytical processes and the modification of samples. For example, CPMG pulse sequences suppress protein signals and pre-saturation pulse sequences suppress water signals. Consequently, NMR is faster and less prone to introducing unwanted experimental variability at this level. This method is more versatile and can quickly analyze not only classical biofluids (such as blood, urine, saliva, and cerebrospinal fluid) but also biopsies, cells, feces, and bronchoalveolar lavage fluid No chromatographic techniques are required, which increases the method's flexibility. Liquid samples are typically required for metabolomics research because of the analytical platforms used. Not only is this step not always easy to accomplish, but it can also cause problems with reproducibility and waste time. These limitations would be mitigated by directly observing solid or

semi-solid samples [45]. Metabolite measurements in live cells or tissues are now possible with the use of high-resolution magic angle spinning (HRMAS) nuclear magnetic resonance spectroscopy, which has been used to identify hundreds of chemicals. Although the resolution is not as good as in traditional high-resolution liquid NMR, this novel application has the potential to be very useful in clinical settings, especially as a quick diagnostic tool (for biopsy analysis, it only takes about 10–15 minutes). The approach's invasiveness can now be reduced thanks to recent advancements in miniaturization, which bodes well for its potential clinical applications [46].

A Lipidomics Approach Based on Nuclear Magnetic Resonance

A vast class of macromolecules known as lipids fall within the metabolites category because of their molecular weight. It is common practice to classify lipids into subgroups such as sterols, glycerolipids, phospholipids, ceramides, sphingolipids, acyl-carnitines, and lipoproteins. They are essential to the functioning of many biological systems because to their various roles as energy stores, signal molecules, protein transporters, and, of course, plasma membrane components [47, 48]. Lydic and Goo (2018) and Guo et al. (2020) found that lipid dysregulation is commonly associated with several diseases and pathological states, including cancer, diabetes, and cardiovascular disorders. Lipidomics emerged as a separate area due to the immense relevance of lipids as a result of their physicochemical specificities, large number, and crucial biological role; lipidomics had previously been a part of metabolomics . The nature of the lipids, the abundance of isomers and isobaric lipids, the physicochemical qualities, and the complexity of the samples are all major obstacles to lipid analysis. The substances included in the samples also vary greatly in concentration. The current analytical method for lipidome analysis is mass spectrometry, often in conjunction with gas or liquid separative techniques. This is particularly true in light of the devices that offer additional separation via ion mobility, For a long time, NMR's insensitivity and lack of resolution meant that it could only be used for basic research in lipidomics, such as 1) identifying biologically relevant lipid structures, 2) investigating plasma membrane structure and composition with 13C-labeled precursors and 31P NMR, and 3) tracking how pathological states affect lipid metabolism. Newer studies have shown that nuclear magnetic resonance (NMR) can supplement mass spectrometry (MS) and be helpful in classical lipidomic analysis. To quantitatively and selectively [49, 50] monitor phospholipid classes, one could use 31P spectroscopy. Furthermore, quantitative investigations of lipids from the various main classes can still be conducted using proton NMR, even though it does not provide fine lipid separation like MS. So far, this method has shown promise in clinical lipidomics in a number of studies, and for semi-automated profiling, dedicated workflows and tools (like Lipspin) have been developed.

Advances in two-dimensional nuclear magnetic resonance (NMR) have opened up new avenues for lipid identification and resolution enhancement. From chylomicrons to Very Low-Density Lipoproteins (VLDL), lipoproteins are a family of supramolecular lipid transporters categorized by density [51]. Measurement of these particles, and more especially their distribution profile across subclasses, is crucial in various pathological states, including cardiovascular diseases, metabolic syndrome neuropathologies, and degenerative diseases.

An Approach to Fingerprinting and Its Clinical Biology Applications

Metabolomics has produced many potential methods, but fingerprinting is perhaps the most widely used so far. This type of metabolomics study is one that does not have a priori metabolite identification but instead identifies spectral or chemical patterns that may be associated with a disease or other condition. Clearly, this method is not at odds with biomarker identification and quantification; rather, it takes a broader picture of the metabolome and how it may change over time or as a result of disease. Instantly apparent is the potential diagnostic use of fingerprinting. On the other hand, just like in clinical biology, it's very clear that this kind of application necessitates high throughput analyses, consistency in results, robustness, and standardization of analytical methodologies. In fact, these are among of NMR's strongest points [52, 53]. NMR works wonderfully for fingerprinting because of its adaptability to studying big cohorts. Developing specialized procedures and methodologies is clearly necessary for this strategy, which encounters several obstacles, particularly when it comes to multivariate analysis of the raw data. Metabomic fingerprints have the potential to be highly beneficial in a preventative framework, which is crucial in the individualized treatment approach, in addition to the diagnostic models they can produce. Indeed, tracking patients' metabolomic profiles on a regular basis would definitely help spot abnormalities that may be associated with the start of certain diseases earlier. There is also the matter of whether or whether NMR-based metabolomics has the potential to become a tool in clinical practice [54], as well as how it stacks up against the methods already employed in clinical

biology. Although there are many case studies that show how metabolomics could be useful in therapeutic settings, there is still a long way to go before the field can be considered fully established. The only way to fill this need is for metabolomics to catch up to the quality, robustness, and reproducibility requirements expected in clinical biology, and NMR will undoubtedly play a significant part in this. While the identification of novel biomarkers is undeniably a primary goal of metabolomics in clinical practice, the comprehensive nature of this method suggests that it has much more to offer in the areas of disease understanding, progression prediction, patient stratification, treatment assessment and adaptation, and treatment evaluation and adaptation [55]. Once clinical metabolomics has mastered and standardised its data processing processes and analysis, it will surely give crucial information for enhancing patient care, rather than competing with current techniques. With its analytical capabilities, resilience, and automation simplicity, nuclear magnetic resonance (NMR) is undeniably a technology platform that will join other devices in supplying doctors with the data needed for patient monitoring and diagnosis. To round things up, we should also mention in vivo Magnetic Resonance Spectroscopy (MRS), which involves targeted nuclear magnetic resonance (NMR) spectroscopy conducted inside an MRI machine [56]. This method is unique in that it permits study of the human metabolome while the subject is still alive. Although in vivo and imaging applications of classical high-resolution NMR spectroscopy are of great therapeutic interest, they have not been included in this study. To ensure that nuclear magnetic resonance (NMR) continues to be a potent analytical tool in metabolomics, we will outline in the sections that follow the ways in which its limits have been and will be overcome, as well as the methodological and technological developments that will enable NMR to progress in the coming years. Additionally, we will look at how this method works well with other analytical tools and why that synergy could be the key to unlocking the metabolome's mysteries.

The Use of Nuclear Magnetic Resonance and Mass Spectrometry in Clinical Metabolomics

The great promise of nuclear magnetic resonance spectroscopy in clinical metabolomics was laid out in the preceding section. It is notoriously difficult to conduct sensitive NMR metabolomics due to the method's inherent insensitivity and the fact that most 1D 1H experiments on complicated biological materials experience non-negligible signal overlap. This restricts its usefulness in a number of domains, including tailored healthcare. Indeed, signal overlap further complicates the already challenging process of metabolite identification and, by extension, the subsequent finding of biomarkers. This is why, as mentioned earlier, mass spectrometry-based metabolomics has surpassed nuclear magnetic resonance spectroscopy in most metabolomics studies. In addition to their many benefits, MS methods are not without their limitations [57], such as an inconsistent and unreliable result or the difficulty in determining which biomarkers match to the many features seen in MS spectra. These limitations should not be disregarded in clinical research, as reliable and reproducible methods for comparing results across laboratories are necessary for the identification of biomarkers of a specific disease or the response to a therapeutic intervention. The complementarity of NMR spectroscopy and MS-based metabolomics methods has been extensively discussed over the last fifteen years in an effort to circumvent the limitations of each method and make the most of their combined strengths.

Fusion of Nuclear Magnetic Resonance and Mass Spectrometry Equipment

Various methods of hardware hyphenation have been recently detailed, but combining nuclear magnetic resonance (NMR) with liquid chromatography (LC-NMR) and then with mass spectrometry (MS) (LC-NMR-MS) has been done for a long time, particularly in the examination of natural products. Both pharmaceutical research and drug metabolism have discovered this method to be effective. For example, made it possible to identify paracetamol metabolites and endogenous chemicals in human urine by combining HPLC-NMR with an ion-trap MS. This triple-hyphenated technique resolved the NMR signal overlap problem by effectively identifying phenylacetylglutamine, which could not be done with 1 H NMR alone. However, according to [56], one of the most important steps in identifying the sample's paracetamol-glucuronide conjugate isomers was the nuclear magnetic resonance analytical component. The metabolism of fluorinated new drug candidates or drug intermediates was investigated in urine samples of animal models using LC-NMR-MS in conjunction with 19F NMR spectroscopy, without the need for special radiolabeling. The technological challenges of integrating methods with orthogonal analytical needs have likely contributed to the community's declining interest in LC-NMR-MS during the last decade (Silva Elipe, 2003). The Use of Mass Spectrometry and Nuclear Magnetic Resonance in the Exploration of Metabolic Processes The

success of NMR and MS-based metabolomics procedures integrating datasets has outweighed the success of hyphenating their respective hardware. Combining NMR with MS-based metabolomics has many benefits, the most apparent of which is the increased metabolic coverage and, by extension, the increased likelihood of discovering novel biomarkers. In fact, nobody in the metabolomics field has ever claimed that their method provides a comprehensive picture of the metabolic environment. Several studies provided strong [57] evidence in favor of this view by illustrating the interplay between the various platforms utilized for metabolite identification using a Venn diagram. Human serum metabolome studies are well-known as an example. The authors identified 3,764 compounds using five analytical platforms: NMR spectroscopy, LC-ESI-MS/MS, GC-MS, DFI-MS, and TLC-GCFID. Of these, only 200 were detected by two or more systems often. Quantitative data for a subset of the identified metabolites rounded out the work; while there were some platform-specific discrepancies, overall, the results were in agreement. Additionally, a NIST standard reference material for human plasma and its use in clinical laboratories were investigated using GC-MS, LC-MS, and NMR in combination. Although there was some overlap between LC-MS and NMR identifications, NMR was able to detect small sugars that were not directly accessible by LC-MS, and 353 metabolites were identified in total. The analytical technique with the most unique identifications was GC-MS with 65. In a study that mirrored the Human Serum Metabolome, researchers employed a combination of NMR, FIA-MS, GCMS, and LC-HRMS to examine the skeletal muscle metabolome of mice. They found 132 discriminant metabolites, however only 17 of them were detected by several analytical platforms. The article's analytical approach was designed to be easily modified for use in human clinical trials, [58] which is an important consideration. Finally, three analytical platforms were used to evaluate the therapeutic treatment's effect on human gastric cancer cells through lipidomics and metabolomics: NMR spectroscopy, GC-MS, and LC-MS. This highlights the significance of utilizing various platforms when conducting a study with the goal of capturing the metabolome in its entirety, or of selecting the right platform with care when only a subset of the metabolome is of interest, due to the fact that different analytical platforms have different sample preparation requirements and can only access a subset of the metabolome.

Harnessing the Power of NMR and MS to Assist in Metabolite Identification

Biomarkers are of great importance for understanding the roles they play in specific diseases, and as metabolic coverage and sensitivity increase, there will be more to discover. When it comes to identifying biomarkers, the complementary information gathered by NMR and MS-based techniques is a huge plus. This is particularly true when high resolution MS (HRMS) is used to get precise mass measurements from parent compounds and their fragments, complementing the structural information gathered by 1D and 2D NMR spectroscopy. Several comprehensive methods for integrating the two have been put forth, including SUMMIT MS/NMR and NMR/MS translator. The first one uses high-resolution mass spectrometry [59-62] (HRMS) data to predict NMR spectra and suggest potential chemical formulas and scaffolds from complicated samples. The experimental HSQC NMR spectra of each sample metabolite are compared to these predicted spectra after deconvolution. Since NMR/MS Translator begins with 1D and 2D NMR acquisition, allowing putative annotations to be established by comparing experimental NMR spectra to databases, it might be considered as the inverse of SUMMIT MS/NMR. Last but not least, the authors used this strategy to discover hitherto unrecognized metabolites in human urine. The same team has also proposed using the SUMMIT MS/NMR method on analytes that were still unidentified after using the NMR/MS translator method [63]. Biomarker identification in clinical research could benefit from automation of some processes in these two methods, although this has not yet seen widespread implementation.

How Nuclear Magnetic Resonance (NMR) Contributes to Medical Physics in the Pathophysiology of Cancer

The complex and diverse disease of cancer remains a significant challenge to global health. Early and accurate cancer detection is crucial for effective cancer therapy and better patient outcomes. Nuclear magnetic resonance (NMR) is a vital tool in medical physics that helps with early identification, describing [64], and following up on different types of cancer. This article delves into the ways nuclear magnetic resonance (NMR) is enhancing our comprehension of cancer biology and explores the particular ways this method is being used for cancer diagnosis.

Nuclear magnetic resonance spectroscopy is a painless way to study and image atomic nuclei because it uses their inherent magnetic properties. In medical physics and cancer detection, the proton (hydrogen) nucleus is the one that is most studied. Radiofrequency (RF) pulses and strong magnetic fields are used in nuclear magnetic resonance (NMR) to elucidate the molecular composition, structure, and dynamics of biological materials.

Nuclear Magnetic Resonance (NMR) for Cancer Detection

Imaging with Magnetic Resonance (MRI): Nuclear magnetic resonance imaging (NMR-MRI) is a key tool in the fight against cancer. Breast, brain, prostate, and liver cancers can all be better diagnosed and staged with the help of magnetic resonance imaging (MRI). The ability to see soft tissues in three dimensions with great clarity [65] is made possible by this. To better understand the tumor's size, location, and tissue involvement, it provides doctors with fine-grained visuals.

The metabolic patterns of both healthy and cancerous tissues can be studied using nuclear magnetic resonance spectroscopy. Imaging using Spectroscopy for the Study of Tissues. By analyzing the quantities of metabolites such as citrate, choline, and lactate, NMR spectroscopy can differentiate [66, 67] between benign and cancerous cells. For the detection of prostate cancer, this approach is quite advantageous.

Diffusion-Weighted Imaging (DWI): DWI use nuclear magnetic resonance (NMR) principles to quantify the diffusion of water molecules in tissues. Limited diffusion is a common consequence of cancer cells' increased cell density and altered cell membranes. The aggressiveness of tumors and the presence of benign or malignant lesions can be determined with the help of DWI.

Some molecular and metabolic processes within cancer cells can be visualized using advanced nuclear magnetic resonance (NMR) techniques, such as chemical exchange saturation transfer (CEST) imaging and hyperpolarized NMR. Through the use of these methods, new insights into tumor metabolism and potential [68] treatment targets can be revealed.

Innovations in NMR technology have increased its significance in cancer diagnoses. Thanks to the enhanced picture resolution offered by ultra-high field MRI equipment, smaller lesions can be recognized. Thanks to hyperpolarization techniques, nuclear magnetic resonance (NMR) has become a fast and sensitive tool for real-time metabolic imaging.

Problems, though, remain. Modern nuclear magnetic resonance (NMR) equipment and expertise may be out of reach in certain healthcare facilities. In addition to specialized training for interpreting NMR data, additional standardization and validation may be required before NMR may be integrated into traditional clinical practice.

When it comes to cancer diagnostics, NMR is the way to go. Developing portable and cost-effective NMR cancer screening equipment is the focus of continuing research. Recent advances in machine learning and artificial intelligence have made it possible to automate the examination of nuclear magnetic resonance (NMR) data, which speeds up the diagnostic process. When combined with other imaging modalities such as computed tomography (CT) and positron emission tomography (PET) [69-73], nuclear magnetic resonance (NMR) may also allow for a comprehensive evaluation of cancer.

Among medical physicists, Nuclear Magnetic Resonance (NMR) has become an indispensable tool for cancer detection. Its uses, such as magnetic resonance imaging (MRI), spectroscopy, diffusion-weighted imaging (DWI), and molecular image analysis (MDA), allow for the early detection, precise characterization [74-77], and ongoing monitoring of cancerous lesions. As technology advances and becomes more accessible, nuclear magnetic resonance (NMR) will play an increasingly crucial role in enhancing cancer diagnosis. In the long run, this will lead to improved outcomes for cancer patients and more tailored treatment regimens.

CONCLUSION

Nuclear magnetic resonance (NMR) is a potent tool for studying the behavior of rocks, fluids, and rock-fluid interactions in porous environments. The oil and gas sector views it as a research trend because of this. An effective method for cross-validating data from rock cores and logs is to use 1D and 2D NMR measurements, which may be done both in a lab and on-site. The acquired signal inversion, experimental parameters, and pulse sequences were all thoroughly explained. The use of nuclear magnetic resonance (NMR) in the petroleum industry shows great promise, particularly for petrophysically characterizing reservoir features. In both conventional and unconventional fields, nuclear magnetic resonance (NMR) is a powerful technique for petrophysically characterizing reservoir fluids and rocks in laboratory core analysis and field logging instruments. Factors such as wettability, fluid saturation capillary pressure, permeability, pore size distribution, and porosity are involved in this.

Taking into account all of the possible benefits of the NMR approach, it is safe to say that it has become the method of choice for any kind of diagnosis, treatment planning, treatment maintenance, and observing the behavior of foreign materials' interactions with the human body. Many believe that more discoveries are on the horizon due to the fact that NMR is still an evolving technology.

Noninvasive nuclear magnetic resonance (NMR) medical applications are currently gaining a lot of attention. There are primarily two methods. The first uses 31P NMR spectroscopy as an analytical tool to detect and quantify the most prevalent phosphate metabolites in different tissues. By tracking changes in intracellular cytoplasmic pH and levels of these metabolites under different ischemia and hypoxia settings, one can detect metabolic disorders inherited in a person and track their metabolic response to stress. The second main strategy is a totally different way of using nuclear magnetic resonance (NMR) imaging. It makes use of 1H, the nucleus that is most abundant in living things (mostly in water and lipids), to generate NMR pictures of any part of the body. With the use of non-uniform magnetic fields applied over a body section, hydrogen nuclei in various elemental volumes can be tagged with distinct frequencies. The signals from these tags can then be analyzed to create an image of the section. When imaging soft tissues, nuclear magnetic resonance (NMR) imaging is superior to computed tomographic scanning.

This is supported by the many NMR-based papers, research, and results, which continue to advance this method. The topic of NMR's future in metabolomic investigations has been raised by the recent advancements in mass spectrometry coupled with liquid or gas chromatography, a more sensitive and higher resolution technology. As a result, NMR has progressively taken a "second" seat. Nevertheless, metabolomics has encountered new demands and obstacles due to its use in personalized medicine and clinical research. These include, but are not limited to, the need to analyze large cohorts, stratify and follow patients longitudinally, and identify and quantify biomarkers. With its many strengths and possibilities, NMR is well-equipped to meet all of these demands. Indeed, NMR spectroscopy has emerged as a frontrunner in clinical metabolomics and personalized medicine, thanks to numerous recent methodological and instrumental advancements that aim to increase sensitivity and resolution and show how well it complements mass spectrometry. Another obstacle that metabolomics is encountering is the transfer of research from the lab to the clinic. We believe that nuclear magnetic resonance (NMR) is a powerful analytical tool that can help us overcome this obstacle and move closer to a more individualised approach to healthcare. In light of the many encouraging points raised in this review, it is certain that NMR spectroscopy will continue to play an important role in clinical metabolomics for the foreseeable future.

REFERENCES

1. Ehrlich R, Howard JJ, Kenyon WE (1995) Determination of porosity types from NMR data and their relationship to porosity types derived from thin section. J Pet Sci Eng 13:1–14.
2. Brautaset A, Ersland G, Graue A, Stevens J and Howard J, (2008). Using MRI to study in situ oil recovery during CO2 injection in carbonates. In: Int. Symp. Soc. Core Anal. Abu Dhabi, UAE, 29 Oct. - 2 Novemb. 2008 SCA paper 2008–41
3. Broche LM, Ross PJ, Davies GR, MacLeod M-J, Lurie DJ (2019) A whole-body fast field-cycling scanner for clinical molecular imaging studies. Sci Rep 9:10402.
4. Cheng Y, Chen S, Eid M, Hursan G, Ma S, (2017) Determination of permeability from NMR T1/T2 ratio in carbonates. In: SPWLA 58th annual logging symposium Coates, Marschall, D., Mardon, D., Num, R., (1997) A new char- acterization of bulk-volume irreducible using magnetic resonance. Log Anal. 39(01)
5. Coman R, Thern H, Kischkat T, (2018) Lateral-motion correction of NMR logging-while-drilling data. In: SPWLA 59th annual log- ging symposium 2018.
6. Connolly PRJ, Vogt SJ, Iglauer S, May EF, Johns ML (2017) Capillary trapping quantification in sandstones using NMR relaxometry. Water Resour Res 53:7917
7. Demas V, Prado PJ, Hürlimann MD, Song YQ, Fantazzini P, Bortolotti V, (2008) Compact magnets for magnetic resonance. In: AIP conference proceedings. AIP, pp. 36–39.
8. DePavia L, Heaton N, Ayers D, Freedman R, Harris R, Jorion B, Kovats J, Luong B, Rajan N, Taherian R, Walter K, Willis D, Scheibal J, Garcia S, (2003) A next-generation wireline NMR logging tool. In: All Days. SPE, Denver, Colorado, p. 7

9. Diehl B (2008) Principles in NMR spectroscopy. In: Holzgrabe U, Wawer I, Diehl BBT (eds) NMR spectroscopy in pharmaceutical analysis. Elsevier, Amsterdam, pp 1–41.
10. Freedman R, Heaton N, Flaum M, Hirasaki GJ, Flaum C, Hürlimann M (2003) Wettability, saturation, and viscosity from NMR measurements. SPE J 8:317–327.
11. Gamal H, Elkatatny S, Adebayo A (2021) Influence of mud filtrate on the pore system of different sandstone rocks. J Pet Sci Eng 202:108595.
12. Ge X, Myers MT, Liu J, Fan Y, Zahid MA, Zhao J, Hathon L (2021) Determining the transverse surface relaxivity of reservoir rocks: a critical review and perspective. Mar Pet Geol 126:104934.
13. Ghomeshi S, Kryuchkov S, Kantzas A (2018) An investigation into the effects of pore connectivity on T NMR relaxation. J Magn Reson 289:79–91.
14. Elsayed M, El-Husseiny A, Kwak H, Hussaini SR, Mahmoud M (2021b) New technique for evaluating fracture geometry and preferential orientation using pulsed field gradient nuclear magnetic resonance. SPE J.
15. Enwere MP, Archer JS, (1992) NMR imaging for water/oil displacement in cores under viscous-capillary force control. In: SPE/DOE enhanced oil recovery symposium. Society of Petroleum Engineers
16. Gladden LF, Mitchell J (2011) Measuring adsorption, diffusion and flow in chemical engineering: applications of magnetic resonance to porous media. New J Phys 13:035001.
17. Hosseinzadeh S, Kadkhodaie A, Yarmohammadi S (2020) NMR derived capillary pressure and relative permeability curves as an aid in rock typing of carbonate reservoirs. J Pet Sci Eng 184:106593
18. Glorioso JC, Aguirre O, Piotti G, Mengual, JF, (2003) Deriving capillary pressure and water saturation from NMR transversal relaxation times. In: Proc. SPE Lat. Am. Caribb. Pet. Eng. Conf. 418–430.
19. Hollingsworth KG, Johns ML (2003) Measurement of emulsion drop- let sizes using PFG NMR and regularization methods. J Col- loid Interface Sci 258:383–389.
20. Isah A, Adebayo AR, Mahmoud M, Babalola LO, El-Husseiny A (2021a) Drainage mechanisms in gas reservoirs with bimodal pores – a core and pore scale study. J Nat Gas Sci Eng 86:103652
21. Heaton N, Jain V, Boling B, Oliver D, Degrange J-M, Ferraris P, Hupp D, Prabawa H, Torres Ribeiro M, Vervest E, Stockden I, (2012) New generation magnetic resonance while drilling. In: All Days. SPE.
22. Jackson JA, Burnett LJ, Harmon JF (1980) Remote (inside-out) NMR. III. Detection of nuclear magnetic resonance in a remotely produced region of homogeneous magnetic field. J Magn Reson 41:411–421
23. Kanfar MF, (2012) Real-time integrated petrophysics: geosteering in challenging geology and fluid systems.In: Soc. Pet. Eng. – SPE Saudi Arab. Sect. Young Prof. Tech. Symp. 2012, YPTS 2012 45–54.
24. Kwak HT, Wang J, AlSofi AM, (2017) Close monitoring of gel based conformance control by NMR techniques. In: Day 2 Tue, March 07, 2017. SPE. D
25. Lalanne B, Rebelle M, (2014) A review of alternative methods to classify rock-types from capillary pressure measurements. In: All Days. IPT
26. Makeen YM, Shan X, Lawal M, Ayinla HA, Su S, Yelwa NA, Liang Y, Ayuk NE, Du X (2021) Reservoir quality and its control- ling diagenetic factors in the Bentiu Formation, Northeastern Muglad Basin, Sudan. Sci Rep 11:18442 Mitchell J, Fordham EJ (2014) Contributed Review: Nuclear magnetic resonance core analysis at 0.3 T. Rev Sci Instrum 85:111502.
27. Prammer MG, Drack E, Goodman G, Masak P, Menger S, Morys M, Zannoni S, Suddarth B, Dudley J, (2000a). The magnetic resonance while-drilling tool: theory and operation. In: proceedings of SPE annual technical conference and exhibition. Society of Petroleum Engineers, pp. 281–288.
28. Raheem ON, Fernandes MO, Thomas NC, Hashem MH, Alfazazi U, Sulemana NT, (2017) Using nmr t2 to predict the drainage capillary curves pc-sw in carbonates reservoirs. In: Soc. Pet. Eng.- SPE Reserv. Characterisation Simul. Conf. Exhib. RCSC 2017:1–34.
29. Pan J, Liao G, Su R, Chen S, Wang Z, Chen L, Chen L, Wang X, Guo Y (2021) 13C solid-state NMR analysis of the chemical structure in petroleum coke during idealized in situ combustion conditions. ACS Omega 6:15479–15485.

30. Shikhov I, Li R, Arns CH (2018) Relaxation and relaxation exchange NMR to characterise asphaltene adsorption and wettability dynamics in siliceous systems. Fuel 220:692–705.

31. Heidari Z (2018) Effect of internal magnetic-field gradients on nuclear-magnetic-resonance measurements and nuclear-magnetic-resonance-based pore-network characterization. SPE Reserv Eval Eng 21:609–625. https:// doi. org/ 10. 2118/ 18

32. Thrane LW, Seymour JD, Codd SL (2019) Probing diffusion dynamics during hydrate formation by high field NMR relaxometry and diffusometry. J Magn Reson 303:7–16

33. Hursan G (2017) Laboratory and downhole wettability from NMR T1/T2 ratio. Petrophysics 58:352–365

34. Amiel, A., Tremblay-Franco, M., Gautier, R., Ducheix, S., Montagner, A., Polizzi, A., et al. (2019). Proton NMR Enables the Absolute Quantification of Aqueous Metabolites and Lipid Classes in Unique Mouse Liver Samples. Metabolites 10, 9.

35. Ardenkjaer-Larsen, J. H., Fridlund, B., Gram, A., Hansson, G., Hansson, L., Lerche, M. H., et al. (2003). Increase in Signal-To-Noise Ratio of > 10,000 Times in LiquidState NMR. Proc. Natl. Acad. Sci. 100, 10158–10163. doi:10.1073/pnas.1733835100

36. Duckett, S. B., and Mewis, R. E. (2013). "Improving NMR and MRI Sensitivity with Parahydrogen," in Hyperpolarization Methods in NMR Spectroscopy. Editor L. T. Kuhn (Berlin, Heidelberg: Springer Berlin Heidelberg), 75–103.

37. Beger, R. D., Schmidt, M. A., and Kaddurah-Daouk, R. (2020). Current Concepts in Pharmacometabolomics, Biomarker Discovery, and Precision Medicine. Metabolites 10, 129. doi:10.3390/metabo10040129

38. Beirnaert, C., Meysman, P., Vu, T. N., Hermans, N., Apers, S., Pieters, L., et al. (2018). Speaq 2.0: A Complete Workflow for High-Throughput 1D NMR Spectra Processing and Quantification. PLoS Comput. Biol. 14, e1006018. doi:10.1371/journal.pcbi.1006018

39. Bruzzone, C., Bizkarguenaga, M., Gil-Redondo, R., Diercks, T., Arana, E., García de Vicuña, A., et al. (2020). SARS-CoV-2 Infection Dysregulates the Metabolomic and Lipidomic Profiles of Serum. iScience 23, 101645. doi:10.1016/ j.isci.2020.101645

40. Catapano, A. L., Graham, I., De Backer, G., Wiklund, O., Chapman, M. J., Drexel, H., et al. (2016). 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Atherosclerosis 253, 281–344. doi:10.1016/ j.atherosclerosis.2016.08.018

41. Debik, J., Euceda, L. R., Lundgren, S., Gythfeldt, H. v. d. L., Garred, O., Borgen, E., et al. (2019). Assessing Treatment Response and Prognosis by Serum and Tissue Metabolomics in Breast Cancer Patients. J. Proteome Res. 18, 3649–3660. doi:10.1021/acs.jproteome.9b00316

42. Elliott, P., Vergnaud, A.-C., Singh, D., Neasham, D., Spear, J., and Heard, A. (2014). The Airwave Health Monitoring Study of Police Officers and Staff in Great Britain: Rationale, Design and Methods. Environ. Res. 134, 280–285. doi:10.1016/j.envres.2014.07.025

43. Doeswijk, T. G., Smilde, A. K., Hageman, J. A., Westerhuis, J. A., and van Eeuwijk, F. A. (2011). On the Increase of Predictive Performance with High-Level Data Fusion. Analytica Chim. Acta 705, 41–47. doi:10.1016/j.aca.2011.03.025

44. Gogiashvili, M., Nowacki, J., Hergenröder, R., Hengstler, J. G., Lambert, J., and Edlund, K. (2019). HR-MAS NMR Based Quantitative Metabolomics in Breast Cancer. Metabolites 9, 19. doi:10.3390/metabo9020019

45. Féraud, B., Govaerts, B., Verleysen, M., and de Tullio, P. (2015). Statistical Treatment of 2D NMR COSY Spectra in Metabolomics: Data Preparation, Clustering-Based Evaluation of the Metabolomic Informative Content and Comparison with 1H-NMR. Metabolomics 11, 1756–1768. doi:10.1007/s11306- 015-0830-7

46. Gowda, G. A. N., and Djukovic, D. (2014). Overview of Mass Spectrometry-Based Metabolomics: Opportunities and Challenges. Methods Mol. Biol. 1198, 3–12. doi:10.1007/978-1-4939-1258-2_1

47. Hermkens, N. K. J., Eshuis, N., van Weerdenburg, B. J. A., Feiters, M. C., Rutjes, F. P. J. T., Wijmenga, S. S., et al. (2016). NMR-Based Chemosensing via P-H2 Hyperpolarization: Application to Natural Extracts. Anal. Chem. 88, 3406–3412. doi:10.1021/acs.analchem.6b00184

48. Jacob, M., Lopata, A. L., Dasouki, M., and Abdel Rahman, A. M. (2019). Metabolomics toward Personalized Medicine. Mass. Spec. Rev. 38, 221–238. doi:10.1002/mas.21548

49. Karaman, İ., Nørskov, N. P., Yde, C. C., Hedemann, M. S., Bach Knudsen, K. E., and Kohler, A. (2015). Sparse Multi-Block PLSR for Biomarker Discovery when Integrating Data from LC-MS and NMR Metabolomics. Metabolomics 11, 367–379. doi:10.1007/s11306-014-0698-y

50. Gouilleux, B., Marchand, J., Charrier, B., Remaud, G. S., and Giraudeau, P. (2018). High-throughput Authentication of Edible Oils with Benchtop Ultrafast 2D NMR. Food Chem. 244, 153–158. doi:10.1016/ j.foodchem.2017.10.016

51. Millard, P., Cahoreau, E., Heuillet, M., Portais, J.-C., and Lippens, G. (2017). 15NNMR-Based Approach for Amino Acids-Based 13C-Metabolic Flux Analysis of Metabolism. Anal. Chem. 89, 2101–2106. doi:10.1021/acs.analchem.6b04767

52. Lane, A. N., Higashi, R. M., and Fan, T. W.-M. (2019). NMR and MS-based Stable Isotope-Resolved Metabolomics and Applications in Cancer Metabolism. TrAC Trends Anal. Chem. 120, 115322. doi:10.1016/j.trac.2018.11.020

53. Ouldamer, L., Nadal-Desbarats, L., Chevalier, S., Body, G., Goupille, C., and Bougnoux, P. (2016). NMR-Based Lipidomic Approach to Evaluate Controlled Dietary Intake of Lipids in Adipose Tissue of a Rat Mammary Tumor Model. J. Proteome Res. 15, 868–878. doi:10.1021/ acs.jproteome.5b00788

54. Nelson, S. J., Kurhanewicz, J., Vigneron, D. B., Larson, P. E. Z., Harzstark, A. L., Ferrone, M., et al. (2013). Metabolic Imaging of Patients with Prostate Cancer Using Hyperpolarized [1-13C]Pyruvate. Sci. Transl. Med. 5, 198ra108. doi:10.1126/scitranslmed.3006070

55. Leenders, J., Grootveld, M., Percival, B., Gibson, M., Casanova, F., and Wilson, P. B. (2020). Benchtop Low-Frequency 60 MHz NMR Analysis of Urine: A Comparative Metabolomics Investigation. Metabolites 10, 155.

56. Powers, R. (2014). The Current State of Drug Discovery and a Potential Role for NMR Metabolomics. J. Med. Chem. 57, 5860–5870.

57. Nagana Gowda, G. A., Gowda, Y. N., and Raftery, D. (2015b). Massive Glutamine Cyclization to Pyroglutamic Acid in Human Serum Discovered Using NMR Spectroscopy. Anal. Chem. 87, 3800–3805. doi:10.1021/ac504435b

58. Psychogios, N., Hau, D. D., Peng, J., Guo, A. C., Mandal, R., Bouatra, S., et al. (2011). The Human Serum Metabolome. PLOS ONE 6, e16957.

59. Robinette, S. L., Ajredini, R., Rasheed, H., Zeinomar, A., Dossey, F. C., Dossey, A. T., et al. (2011). Hierarchical Alignment and Full Resolution Pattern Recognition of 2D NMR Spectra: Application to Nematode Chemical Ecology. Anal. Chem. 83, 1649–1657. doi:10.1021/ac102724x

60. Sliz, E., Kettunen, J., Holmes, M. V., Williams, C. O., Boachie, C., Wang, Q., et al. (2018). Metabolomic Consequences of Genetic Inhibition of PCSK9 Compared with Statin Treatment. Circulation 138, 2499–2512. doi:10.1161/ CIRCULATIONAHA.118.034942

61. Puig-Castellví, F., Pérez, Y., Piña, B., Tauler, R., and Alfonso, I. (2018). Comparative Analysis of 1H NMR and 1H-13C HSQC NMR Metabolomics to Understand the Effects of Medium Composition in Yeast Growth. Anal. Chem. 90, 12422–12430. doi:10.1021/acs.analchem.8b01196

62. Tilgner, M., Vater, T. S., Habbel, P., and Cheng, L. L. (2019). High-Resolution Magic Angle Spinning (HRMAS) NMR Methods in Metabolomics. Methods Mol. Biol. 2037, 49–67. doi:10.1007/978-1-4939-9690-2_4

63. Scarfe, G. B., Wright, B., Clayton, E., Taylor, S., Wilson, I. D., Lindon, J. C., et al. (1999). Quantitative Studies on the Urinary Metabolic Fate of 2-Chloro-4- Trifluoromethylaniline in the Rat Using 19F-NMR Spectroscopy and Directly Coupled HPLCNMR-MS. Xenobiotica 29, 77–91. doi:10.1080/ 004982599238821

64. Robinson JN, Coy A, Dykstra R, Eccles CD, Hunter MW, Callaghan PT. Two-dimensional NMR spectroscopy in Earth's magnetic field. J Magn Reson 2006;182(2):343–347

65. Dubinnyi MA, Lesovoy DM, Dubovskii PV, Chupin VV, Arseniev AS. Modeling of 31P-NMR spectra of magnetically oriented phospholipid liposomes: a new analytical solution. Solid State Nucl Magn Reson 2006;29(4):305–311

66. Frydman L, Harwood JS. Isotropic spectra of half-integer quadrupolar spins from bidimensional magic-angle spinning NMR. J Am Chem Soc 1995;117:5367–5368

67. Knight MJ, Webber AL, Pell AJ, et al. Fast resonance assignment and fold determination of human superoxide dismutase by high- resolution proton-detected solid-state MAS NMR spectroscopy. Angew Chem Int Ed Engl 2011;50(49):11697–11701

68. Davis PL, Crooks LE, Margulis AR, Kaufman L. Nuclear magnetic resonance imaging: current capabilities. West J Med 1982;137(4):290–293

69. Yesinowski JP, Mobley MJ. Fluorine-19 MAS-NMR of fluoridated hydroxyapatite surfaces. J Am Chem Soc 1983;105:6191–6193

70. Koutcher JA, Sawyer RC, Kornblith AB, et al. In vivo monitoring of changes in 5-fluorouracil metabolism induced by metho- trexate measured by 19F NMR spectroscopy. Magn Reson Med 1991;19(1):113–123

71. Budinger TF. Image analysis in critical care medicine. Crit Care Med 1982;10(12):835–840

72. Prosser HJ, Richards CP, Wilson AD. NMR spectroscopy of dental materials. II. The role of tartaric acid in glass-ionomer cements. J Biomed Mater Res 1982;16(4):431–445

73. Pires RA, Nunes TG, Abrahams I, Hawkes GE. The role of aluminium and silicon in the setting chemistry of glass ionomer cements. J Mater Sci Mater Med 2008;19(4):1687–1692

74. Bienek DR, Frukhtbeyn SA, Giuseppetti AA, Okeke UC, Skrtic D. Antimicrobial monomers for polymeric dental restoratives: cytotoxicity and physicochemical properties. J Funct Biomater 2018;9(1):E20

75. Khurshid Z, Zohaib S, Najeeb S, Zafar MS, Rehman R, Rehman IU. Advances of proteomic sciences in dentistry. Int J Mol Sci 2016;17(5):E728

76. Zhou J, Hu H, Huang R. A pilot study of the metabolomic profiles of saliva from female orthodontic patients with external apical root resorption. Clin Chim Acta 2018;478:188–193

77. Duchemann B, Triba MN, Guez D, et al. Nuclear magnetic resonance spectroscopic analysis of salivary metabolome in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2016; 33(1):10–16