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3D Printed NMR Spectra: From 1D and 2D Acquisition to 3D Visualization

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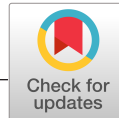*MSU Graduate Student*

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RESEARCH ARTICLE

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3D printed NMR spectra: From 1D and 2D acquisition to 3D visualization

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Abstract

Visualization of two-dimensional and relaxation NMR spectra can be difficult for students new to the subject. Educators have utilized 3D printing previously to demonstrate concepts such as potential energy surfaces and molecular orbitals, but this technology has yet to be used to create a visual model of NMR data. In order to address this, we have developed an approach for creating 3D printed models of two-dimensional and inversion recovery spectra, which can then be used as an innovative teaching tool. This was done by converting raw FT NMR data into a 3D data graph using *Mathematica*. This graph is then converted into stereolithography format and printed using a 3D printer. These physical models will allow students to better understand the complex information presented in these NMR spectra.

KEYWORDS
3D printing, data visualization, NMR relaxation, stereolithography, two-dimensional NMR

1 | INTRODUCTION

Advanced NMR methods have become more commonplace in the undergraduate chemistry curriculum.[1] It can be used as a standard technique in organic chemistry classes and inorganic courses as well as physical chemistry courses where both 2D NMR and relaxation are covered. There are also numerous NMR texts aimed at upper-level undergraduates and introductory graduate students to learn NMR in more depth (see reference[2] for examples). Innovative approaches to teaching 2D NMR have been published recently in the chemistry education literature,[3,4] in an effort to make a difficult topic more tractable to undergraduates and students new to the concepts. Time-dependent NMR can also readily be incorporated in the undergraduate curriculum.[5]

We developed an approach using 3D printing to visualize NMR data and assist in understanding the utility of 2D NMR for structure determination and T_1 data for NMR relaxation. We outline the overall process in a flowchart in Figure 1, and then provide more detail in the Supporting Information. An NMR spectrum is acquired initially, and peak intensities are extracted (either 1D or 2D). These data are then processed by *Python* (python.org), then converted to a 3D data graph in *Mathematica* (Wolfram, Champaign, IL) and finally exported to stereolithography (3D printing,.stl) format for 3D printing. 3D printing technology has become relatively commonplace on university campuses often in conjunction with the library or library services.[6] With its versatility and tactile nature, 3D printing has a wide variety of applications to chemical education, and provides an alternate way for learners to visualize the relevant information. In particular, some examples where 3D printing has been used for physical chemistry education include 3D printed potential energy surfaces,[7–9] orbitals,[10,11] and reaction progress by 3D visualization of spectroscopic data including 1D NMR.[12] Additionally, 3D printing can be used to assist students or learners with visual impairments, where the tactile nature can help with conceptualization of the data.

## 2 | RESULTS AND DISCUSSION

2.1 | 2D NMR and 3D printing

High-field NMR is an integral part of department instrumentation in chemistry, and indeed functioning NMR spectrometers for use by undergraduate students are required

for accreditation by the American Chemical Society.[13] This highlights the need to offer new and innovative ways for students unfamiliar with NMR to learn the techniques. For the 2D NMR aspect, a ^{1}H-^{1}H TOCSY (TOtal Correlation SpectroscopY) spectrum has been acquired initially. While COSY experiments offer simpler spectra to analyze, we felt a TOCSY spectrum would be more information-rich and engaging without being overwhelmingly complicated. The sample analyzed is thymidine (Figure 2), the 'T' nucleotide in DNA. As with choosing the TOCSY, we felt this molecule

offered the right amount of complexity for initial testing of our protocol. The sample was dissolved in one milliliter of 99.9% deuterium oxide (Cambridge Isotope Labs, Tewksbury, MA). The NMR experiments were performed using a Varian 400 MHz INOVA NMR spectrometer with VnmrJ 4.2 acquisition software. Sample temperature was maintained at 25°C. The TOCSY experiment used an MLEV17 spinlock of 80 ms, with four scans and 200 t1 increments. The spectral width was set for 4000 Hz with 1024 complex points, and a presaturation pulse was used for solvent suppression.
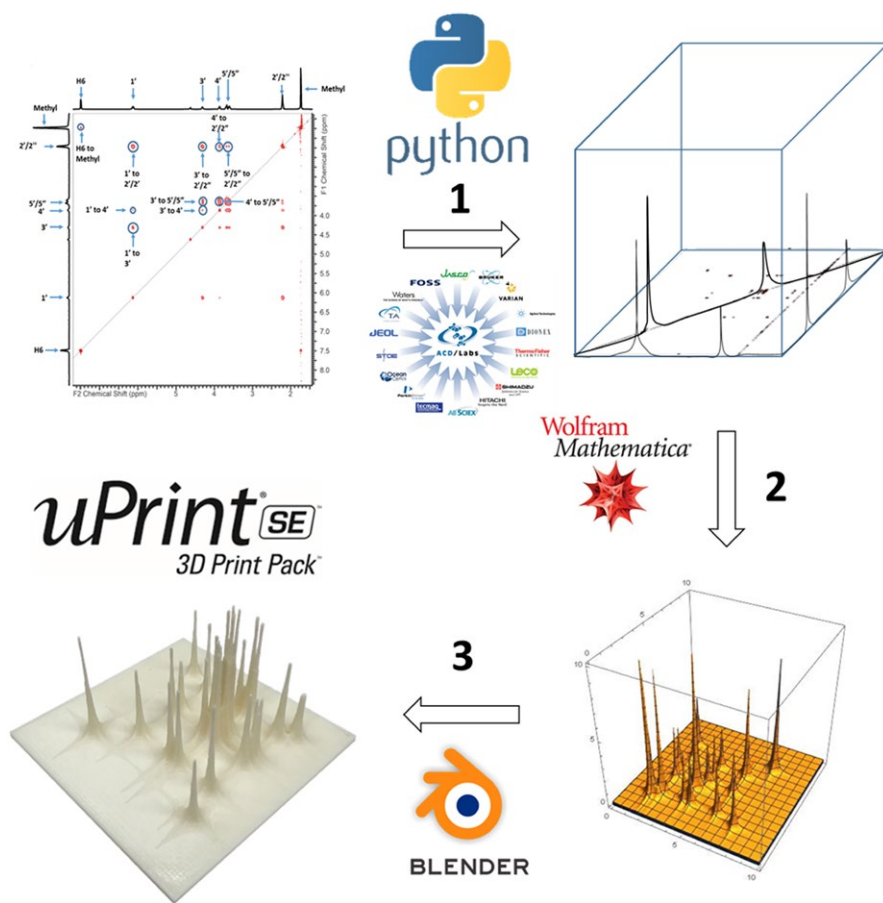
FIGURE 1 Flowchart visualizing how NMR data are converted to a 3D print.
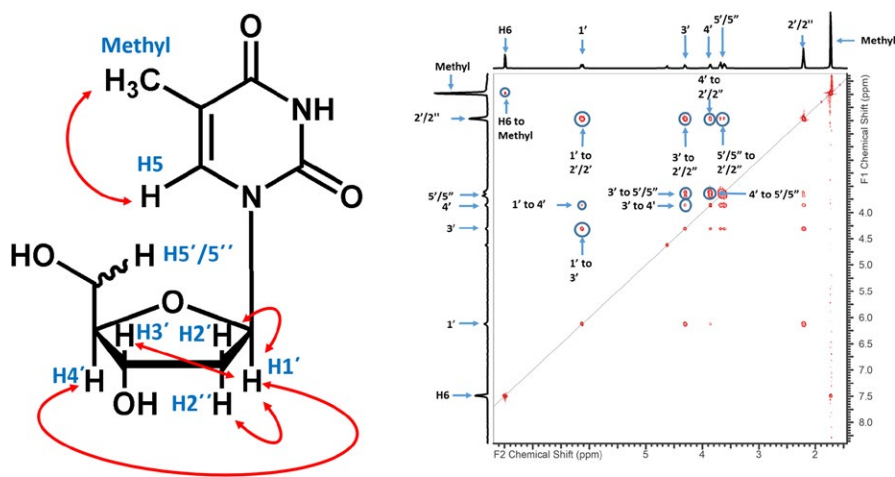
FIGURE 2 (Left) Thymidine molecule used for the TOCSY experiment. Blue labels indicate the coupled protons. The red arrows indicate several of the connectivites that are shown in the spectrum. (Right) TOCSY spectrum of thymidine as a contour plot, indicating the proton assignments. Note that there are some artefacts associated with the largest (methyl) peak on the diagonal

After we performed the NMR experiments, they were analyzed using ACD/Spectrus 2017.2.1 software (ACD/Labs, Toronto, Canada). Intensities of the 2D NMR peaks were extracted using the Spectrus Processor. The threshold in Spectrus can be adjusted and the peak picking function can be used to create a list of peaks to export, that represents only the peaks of interest. Alternately, a user could manually pick the peaks of interest. The chosen peaks and intensities are converted into a .txt file through the Export option in the program. The .txt file contains the three values that represent the 2D NMR data: F1, F2, and peak intensity. The specific data used for this work are provided in the Supplemental Information.

From there, a *Python* program (also provided in the Supporting Information) reads the numbers in the .txt file and creates an output that can be read by *Mathematica*. As a part of this process, the *Python* code does the following:

1. Sorts data by intensity and removes all peaks too small to be considered relevant.
2. Normalizes intensity by dividing all intensities by the maximum.
3. Takes the absolute value to create all positive peaks
4. Creates an individual Lorentzian (or Gaussian) function for each of the recorded peaks in *x*, *y*, and *z*.
5. Generates a mathematical function by converting the matrix into a single string

The result of this process is a command line (step 5, to be read in *Mathematica*), which is used to generate a 3D graph of the 2D NMR. The spectrum can be adjusted to fit the criteria required for the specified parameters, which in this case were a noise reduction value of 0.05, a max peak height of five, and a resolution of 100. These values can be changed to fit an instructor's specific needs. Once completed with the function, the model is symmetrized to fix artefacts by copying missing peaks to the other side of the diagonal and switching the *x* and *y* coordinates. *Mathematica* then allows a user to export a 3D graph as a .stl file, which can then be 3D printed directly. The figure generated by *Mathematica* can then be visualized in a program such as 3D View (Microsoft Corporation, Redmond,

WA) before 3D printing, to ensure the best quality printed spectrum for the user's needs. The 3D printer used for this paper (in conjunction with the Missouri State Library) is a model uPrint ES, but other models could certainly be used.

To optimize the physical 3D printed model, several iterations and adjustments might need to be performed on the 3D electronic figure. There likely needs to be a competition between spectral resolution and fragility of the print. If the peaks are thin to show NMR detail (eg, J-couplings) they are prone to breakage. The peaks can be artificially thickened by adjusting the Lorentzian parameters, but NMR information can then be lost. An additional option if losing resolution is not a concern is to use Gaussian functions rather than Lorentzians (Figure 4). While the Lorentzian function is technically more accurate, the Gaussian function is able to provide the same qualitative information, and makes the physical peaks sturdier.
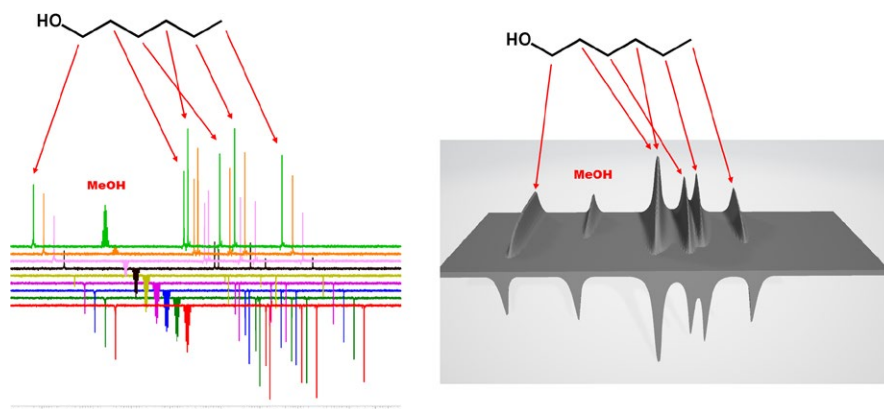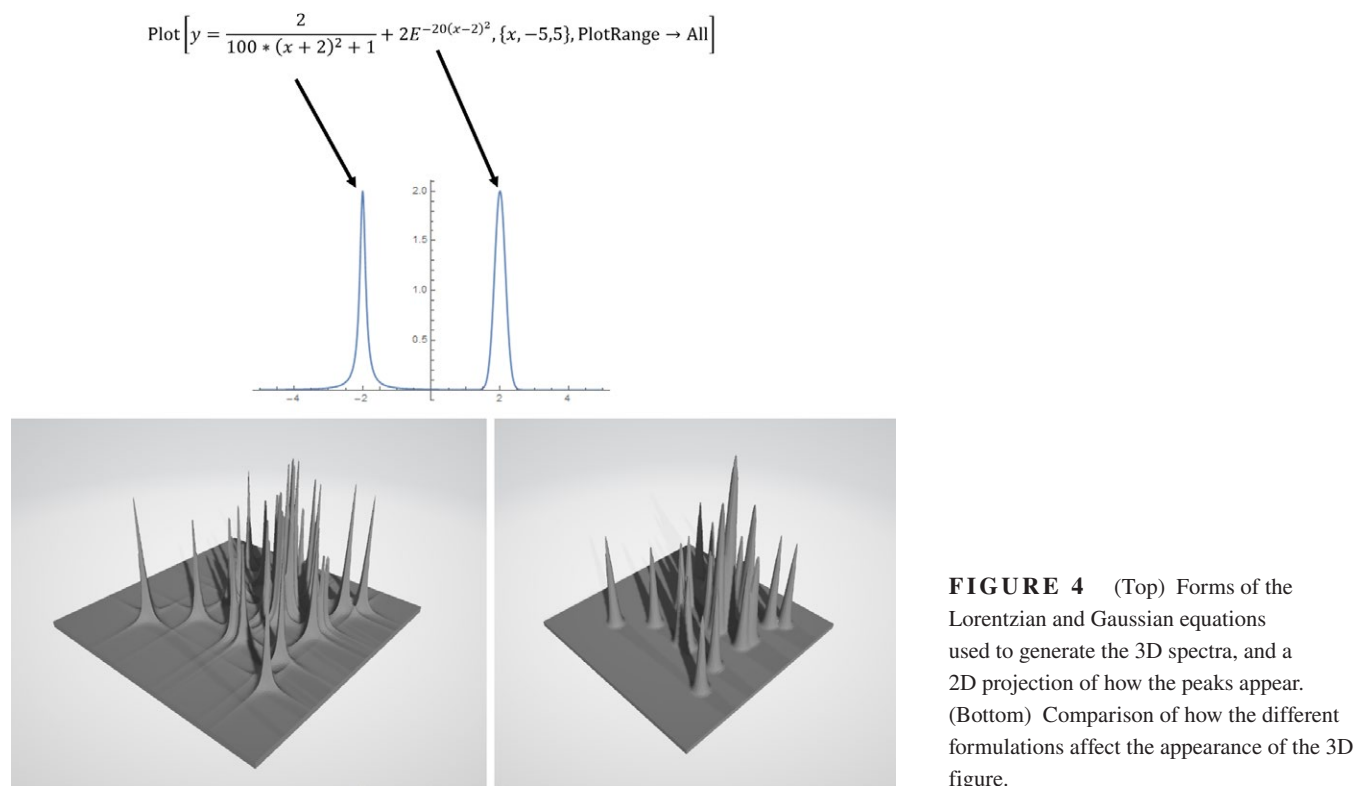
2.2 | T_1 NMR and 3D printing

A ^{13}C inversion recovery experiment was performed on 1-hexanol in deuterated methanol, following the work by Gasyna and Jurkiewicz published on the *Journal of Chemical Education*.[7] Per standard relaxation analysis, partially relaxed 1D spectra were plotted (Figure 5) as a function of variable time delay (τ). The intensities are fit with an exponential curve as a function of recovery time and peak intensity, and the T_1 values extracted. The goal is to use information from these spectra to create a 3D graphical format to visualize in *Mathematica*, and then 3D printed.

To create a 3D time-dependent NMR model (details in the Supporting Information), we decided to simplify the process as much as possible. The only parameters needed for this are the equilibrium peak intensity (M_0, obtained from a 1D or fully relaxed spectrum) and the T_1 values for the peaks that are to be displayed in the 3D print. The 3D figure (Figure 5) is then generated using Equation 1 below:

$$M_Z = M_0 \left(1 - 2e^{\tau/T_1}\right) \tag{1}$$
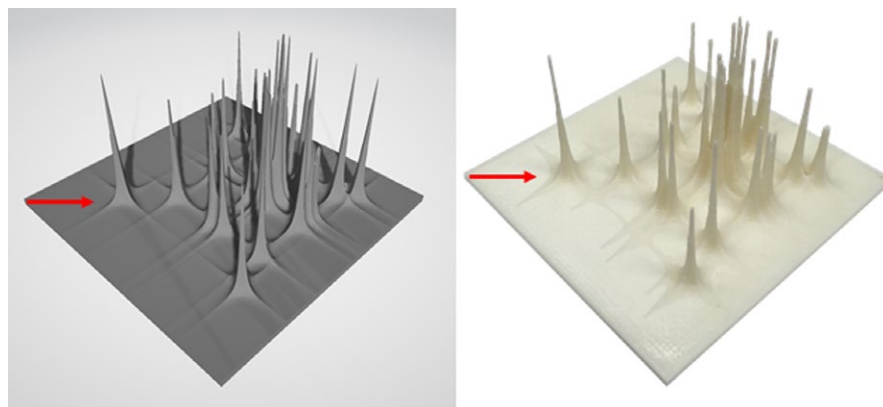
FIGURE 3 Comparison of the 3D Viewer visualized stacked plot of the TOCSY spectrum and the 3D printed spectrum. Arrow indicates the direction of the diagonal.

$$\text{Plot}\left[y = \frac{2}{100*(x+2)^2+1} + 2E^{-20(x-2)^2}, \{x, -5, 5\}, \text{PlotRange} \to \text{All}\right]$$

FIGURE 4 (Top) Forms of the Lorentzian and Gaussian equations used to generate the 3D spectra, and a 2D projection of how the peaks appear. (Bottom) Comparison of how the different formulations affect the appearance of the 3D figure.

FIGURE 5 (Left) ^{13}C Inversion recovery spectra for 1-hexanol in deuterated methanol. The carbons are specified according to the assignments in reference 5. (Right) Indication of the carbon peaks for the 3D graph of the inversion recovery experiment. The graph and its 3D print are intended to represent the spectra as shown but note that the carbons 2 and 4 have lost resolution. Note that the residual methanol solvent peak is included (at 49.15 ppm).

3 | CONCLUSION

Figure 2 shows the 2D TOCSY spectrum as it was acquired and processed. Figure 3 shows the 3D Viewer version next to the 3D printed version of the same spectrum. As can be seen, the relevant crosspeaks that appear in the 2D plane of the NMR spectrum are now able to be visualized as their 3D equivalent. Likewise, Figure 5 shows the inversion recovery experiment and Figure 6 shows a comparison of 3D View to the 3D printed model.

The 3D models generated by this work demonstrate how new technology can be used for innovative teaching options,

even on advanced topics such as 2D and relaxation NMR. Depending on the type of NMR experiment, the entire process could be completed within a day or so. A TOCSY or inversion recovery experiment on a relatively concentrated small molecule can take about 15-20 minutes. The data processing and computations in *Python* and *Mathematica* take about 5-20 minutes depending on computer speed. The 3D printing process can be (in our experience) between 2 and 12 hours, and prints were generated overnight without the need for supervision of the printing process. As an example, the Lorentzian 2D print took 4.75 hours, cost $24, used 3.45
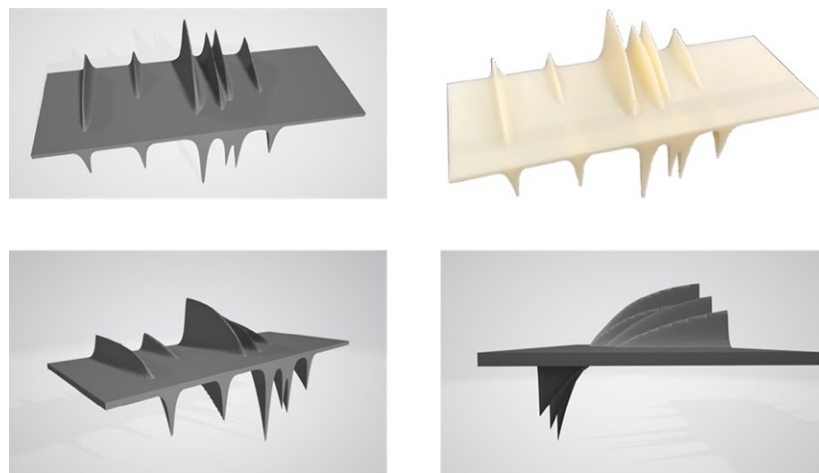
FIGURE 6 (Top) Comparison of 3D visualized inversion recovery and 3D printed version. (Bottom) Different orientations of the 3D figure, to display the exponential recovery of the magnetization.

cubic inches of filament, and 0.77 cubic inches of support material.

Future uses of this work can involve many types of 2D NMR experiments, such as COSY, NOESY, HSQC, or HMBC to name just a few. Solid-state NMR lineshape could be printed for visualization of spatial-dependent aspects of NMR spectra. 3D printed spectra could be used in conjunction with the computer processing to help aid students in understanding of the assignment and structure determination process, as well as basic programming. Additionally qualitative interpretation of interbond or internuclear distances could be achieved with the 3D printed peaks of differing magnitudes. Any instructor wishing to use this process can take a spectrum of the model molecule that most interests them, process the data in *Mathematica* and convert to a .stl file for 3D printing to supplement their personal instruction. Specific regions within the spectrum could be expanded, helping with the spectral clarity, resolution, and interpretation. More complex spectra (such as NOESY spectra or HSQC of biomolecules) could be broken up into quadrants to print separately. 3D printers with options for different colored filament could be used as a teaching enhancement for emphasis. In lieu of this option, the peaks of interest could be painted or otherwise colored. Finally, these models could be used in tandem with video tutorials that are available on YouTube or on the Bruker BioSpin website.[14]

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

The .stl and Python files are available at https://bearworks.missouristate.edu/articles-cnas/25/.