

MCTS aided by

GCN

Deep Reinforcement Learning for Molecular Inverse Problem of Nuclear Magnetic Resonance Spectra to Molecular Structure

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in its top 3 guesses for molecules with <10 heavy atoms. We believe that the proposed

framework is a significant step in solving the inverse design problem of NMR spectra.

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C pectroscopy in general has played a significant role in diverse applications, such as drug discovery, protein structure determination, and material discovery. Nuclear magnetic resonance (NMR) spectroscopy is one of the most crucial and versatile methods for chemical characterization. It is an analytical technique based on the nuclei's magnetic properties that have either an odd mass number or an even mass number with an odd atomic number. Nuclei with nonzero spin S would always have a nonzero magnetic dipole moment, $\vec{\mu}$. NMR relies on this for the nuclei to respond to electromagnetic waves as perturbations in the presence of an external magnetic field. In addition to small organic molecules, NMR spectroscopy is a critical method to obtain highresolution information about proteins, DNA, and RNA.^{1,2} It can also be used to obtain knowledge of energy minima and barriers by observing conformational dynamics of proteins.³ This can be pivotal in the process of drug discovery.

The ¹³C NMR spectra measure the properties of individual nuclei and consist of peaks that correspond to each carbon atom present in the molecule. The peak position (chemical shifts) and the peak splits (spin-spin coupling) are dependent on the local environment of that atom. Usually in laboratories, experts manually identify the molecular structure from the NMR spectra using highly specific domain knowledge. To date, most computer-based methods to verify the structure of a sample from its NMR spectra rely on matching the spectral data with a database of already known spectra.^{4,5} These methods restrict the usage to identifying only those molecules that are stored in the database.

The problem under consideration here is a nonlinear inverse problem. The forward model y = f(x), in this context, refers to the task of calculating the NMR spectra y, given a molecule x. Whereas, the inverse problem refers to drawing conclusions about an unobserved molecule x from its experimentally observed NMR spectra y. One of the first attempts in the literature at recognizing and modeling this problem as an inverse problem was done by Jonas⁶ (Figure 1).

Molecular Structure

The forward problem f for NMR spectra is relatively wellstudied with many methods ranging from quantum mechanical calculations and density functional theory⁷ to deep learning^{8,9} to solve the task. Other empirical methods, such as featurizing the neighborhood of a nuclei and then matching it against a database of known motifs to predict its shift, are also common.^{10,11}

Recently, there have been many significant studies on the use of modern deep learning and RL methods to solve problems in chemical sciences ranging from prediction of properties of molecules to *de novo* molecule generation with optimized properties.^{12,13} There are various high-throughput combinatorial methods to generate organic molecules with desired properties that are well-known and essential in the process of drug discovery.^{14–18} In such a workflow, it would be of great help to have a framework to verify the structures of samples generated *in situ* based on easily acquirable spectral data in a high-throughput manner.

In this work, an effort has been made to determine the structure of a molecule given its NMR spectra and molecular

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Figure 1. Schematic representation of the forward and inverse problem of NMR spectra. As an example, 2-methylbutane and its NMR spectra are given. Each carbon and its corresponding peak is indicated by the same color.



Figure 2. Monte Carlo tree search: A heuristic search algorithm where each node in the tree is a state of the environment. One of these four steps is taken at each step to navigate the search space. 1. Selection: New bonds are added to the root based on UCT values until a leaf node is reached. 2. Expansion: A new node is added to the leaf node after environment checks the validity of new node. 3. Rollout: Value neural network evaluates the value of the newly added node. 4. Back-propagation: The tree then back-propagates the new information to update the UCT values of all the nodes until the root node.



Figure 3. Training methodology. An example search tree while in the training mode on how subgraph isomorphism is used to make a data set for the neural networks to train on. The target molecule is shown on the top left. Assuming that the current state in the environment is *n*-butane, we see a possible state of the search tree. Each node in the tree is also accompanied by an illustration showing how it is a subgraph of the target molecule. Because this can be evaluated when the training mode is on, this is used to return intermediate reward r(s, a) = 1 when the current state is subgraph isomorphic to the target state; otherwise r(s, a) = 0.

formula. There have been a few endeavors to solve this inverse problem. Zhang et al.¹⁹ used a tree-based search framework with a SMILES generator to predict the structure from computationally generated ¹H NMR spectra. Their method included help from computationally expensive DFT calculations to guide the tree and was able to predict the structure for six out of nine given spectra. In a work by Jonas,⁶ a graph neural network is trained on molecular graphs with imitation learning. The NMR spectra is incorporated as per-node information in the molecular graph, and the molecule is built iteratively by adding edges based on the probabilities returned by the neural network. The work was tested on molecules with up to 32 heavy atoms.

In this work, we use a combination of online Monte Carlo tree search $(MCTS)^{20}$ and a set of offline trained graph convolutional networks²¹ to navigate through the chemical space and find the correct molecular structure of a given target ¹³C NMR spectra.

Letter



Figure 4. (a) Target state of cyclohexane and current state of 2methylbutane along with their splitvectors. (b) Target state of 4hydroxy-3-methylpentan-2-one and current state of 3-methylpentan-1-ol along with their splitvectors.

To reiterate, the problem is defined in the following way: given ¹³C NMR spectra of a molecule consisting of each carbon's shift and split values and the molecular formula, identify the structure of the molecule. The process of solving the problem is modeled as a Markov decision process (MDP) wherein the molecule is built iteratively from scratch by adding atoms and bonds to the current structure at each step. In this section, different components and details about the proposed framework are explained. The first part contains information about the data set used. The Letter gives details of the reinforcement learning algorithm used followed by information about the neural networks that aid the RL algorithm. Finally, the last paragraph of this section introduces a novel methodology of training prior and value networks.

We use nmrshiftdb2,²² which is a database for organic structures and their experimentally observed ¹³C NMR spectra.

In this work, we consider only organic molecules that have less than 10 non-hydrogen atoms (C, O, N, and F). Charged molecules and radicals are also excluded. Thus, the data set comprises a total of 2134 molecules with experimentally obtained chemical shift and split values of ¹³C NMR spectra.

In this subsection, we attempt to define the state space and action space for the MDP comprehensively. This is followed by information about the agent which chooses the appropriate actions at a particular state. Choosing an accurate and appropriate measure of reward is essential for any RL algorithm to perform well. We use a forward NMR prediction model to formulate a reward function defined at the end of this subsection.

- The current state in the search process is represented as a Molecular Graph.
- Each atom in the target molecule is present in the current state as a node. The graph of the current state has n s + 1 components, where *n* is the total number of atoms in the target molecule and *s* is the number of atoms present in molecule of the current state. Out of these n s + 1 components, one is a connected component representing the molecule of the current state, and the rest of the n s components are individual atoms that may join the current molecule by addition of new bonds later on. Here, a component is a subgraph which does not have any outgoing edges to the rest of the graph.
- Featurization of the target NMR: Each NMR peak is assigned to a carbon in the beginning when the state consists only of individual nodes and no edges. The node feature of an atom consists of the one-hot encoding of the atomic number of the element that the node represents and the current valency of that atom that is available for further addition of bonds. A Gaussian, with the peak of the assigned shift centered at the chemical shift value and $\sigma = 2$, is discretized into 64 bins. This feature is then appended to the node feature.
- Because this work uses ¹³C NMR spectra as an input, it is certain that the target molecule contains at least one carbon atom. Hence, without the loss of generality, we choose to start building our molecule from a molecular



Figure 5. An example run for the target molecule CC1=CC=NO1 with nmcts = 1000. $\pi_{tree}(a_i|s_j)$ represents the probability of taking action a_i according to the policy returned by the MCTS search with state s_j as the root. In the figure, each state s_j is also accompanied by the splitvector of that state.



Figure 6. (a) Accuracy over 5-fold cross-validation with nmcts = 1000. (b) Effect of nmcts (number of traversal from the root to leaf in MCTS search) on the various metrics of accuracy. (c) Histogram of time taken for the model to run on each molecule for nmcts = 1000. (d) Effect of nmcts on the time taken by the system to predict a molecule.

state containing a single carbon atom; that is, S_0 is just a carbon atom.

In this work, we formulate a fixed-dimension action space in which each action signifies the addition of an edge between any two nodes in the graph. The environment ensures the validity of these actions by checking for the following conditions:

- At least one of the end points of the newly added edge must belong to the subgraph containing the molecule of the current state.
- The addition of this new edge must obey the chemical rules of valency for each atom. If the valency due to connection with other heavy atoms is not enough to complete its octet, it is implicitly assumed that the rest of the valency is satisfied by hydrogens. These hydrogens are not taken as nodes in the molecular graph.
- The edge must not lead to formation of a ring with four or three atoms.
- The edge must not lead to a bond within an already present ring. (Note that this restriction does not prevent the formation of bicyclo and spiro compounds. It just guides the formation so that the smaller ring is formed before the larger ring. Doing so proved to be helpful in the initial experiments because this helps prune some redundant branches of the tree search.)

Because the problem is formulated as a Markov decision process, we are left to decide on a planning algorithm that would use some prior knowledge about the problem and explore various branches of the search tree before taking action a on a state s. A typical RL algorithm has two components: an agent, and an environment. The task assigned to the "agent" is to choose an action given the current state. On the other hand, the role of the "environment" is to simulate the action which was chosen by the agent and return the reward for the action which was taken.^{23,24} One such algorithm is Monte Carlo tree search (MCTS) (Figure 2). MCTS performs one of the four following steps repeatedly:

(1) **Select:** In this stage of MCTS, the tree is traversed from the root according to the UCT (upper confidence bound for trees) values at each level until it reaches a leaf node. The UCT value at any state is calculated based on the following formula:

UCT(s, a) = Q(s, a) +
$$c^* \pi_{\text{model}}(a|s)^* \frac{\sqrt{N(s) + 1}}{n(s, a) + 1}$$

where *s* is the current state, Q(s, a) the mean action value estimate $Q(s, a) = \frac{W(s, a)}{n(s, a)}$, W(s, a) the cumulative of all returns R(s', a') until the leaf node, $\pi_{\text{model}}(a|s)$ the prior probability by the policy network, N(s) the number of times state *s* has been



Figure 7. Target molecule and Top3 guesses as returned by the agent along with the reward and their predicted spectra for cases when the Top1 guess is the correct guess.

reached, n(s, a) the number of times action *a* was taken from state *s*, and *c* the constant with which one can manipulate the exploration versus exploitation ratio. The form of the UCT value used in this work is inspired by Moerland et al.,²⁵ which was proved to improve the performance of cases with asymmetric trees.

(2) **Expand:** Once a leaf node $s_{L'}$ is reached by the tree search, the tree is expanded by addition of a new leaf node s_{L} . The environment simulates this action and ensures its validity and also returns an intermediate reward.

(3) **Roll-out:** In a typical MCTS, the initial value of the new leaf node is estimated using a series of random rollouts from the leaf node s_L . Because of computational limitations, this work uses a value neural network, $V_{\text{model}}(s)$, to estimate the value function.

(4) **Back propagation:** After estimating the value of the newly added leaf node, R(s, a) of the whole backward trace is updated through back-propagation which in turn updates the UCT value of intermediate nodes belonging to this trace.

$$R(s_i, a_i) = r(s_i, a_i) + \gamma R(s_{i+1}, a_{i+1})$$

The above four steps are repeated for nmcts number of times. Then, a real action a_i is taken by the environment based on the policy of the tree. The tree's policy probability is determined by the visitation count of all the actions at the root node s_0 .

While the inverse problem is defined as the task to determine the molecular structure from the spectra, it naturally follows that the forward problem is that of calculating the NMR spectra given the molecule and its structure. Here, a forward NMR prediction model⁸ is used for the following:

(1) For intermediate reward: Typical MCTS applications also have an intermediate reward returned by the environment for each action. The step reward is calculated based on how close the current state is to the target molecule. The forward model predicts the NMR spectra of the current state, and the reward is defined by



(a) Example 1: Top3 ranked guesses by the framework for experimentally observed NMR spectra of Cc1c(O)c(=O)oc1=O



(b) Example 2: Top3 ranked guesses by the framework for experimentally observed NMR spectra of Cc1cc(=O)ccc1=O

Figure 8. Target molecule and Top3 guesses as returned by the agent along with the reward and their predicted spectra for cases when the Top1 guess is the incorrect guess.

$$r(s, a) = r(s') = 2\left(\frac{1}{2} - WS(s')\right)$$

 $WS(s') = first Wasserstein distance = l_1(S_T, S_C)$

$$l_{1}(u, v) = \int_{-\infty}^{\infty} |U - V|$$

where U and V are the CDFs for the distribution of some random variables u and $v_r^{26} S_T$ is the NMR spectra of the target molecule, and S_C is the NMR spectra of the current molecule. The reward r(s') is returned as explained above whenever the current state s' is known to be a terminal state. Otherwise, r(s') = 0 is returned.

(2) For the Scoring Function: Each episode performed by the agent returns one prediction of what the target molecule is. Because MCTS has some element of randomness, all guesses made by the agent are not the same. In such cases, after running the agent for a predetermined fixed number of times, all the unique guesses are ranked against each other by the means of the reward function discussed above. Then, the guess which returns the highest reward is taken as the final prediction.





(a) Accuracy when the model is trained of molecules with < 7 atoms and tested on molecules with < 10 atoms.



Figure 9. (a) Accuracy when the model is trained on molecules with <7 atoms and tested on molecules with <10 atoms. (b) Time taken for a molecule when it is guessed correctly and incorrectly (nmcts = 1000).

There are three modules of neural network used in this work:

Graph Featurizer: This module uses a message passing neural network,^{21,27} which provides a formulation for supervised learning on graph structured data. Consider a **molecular graph** G(V, E) with node features x_v (having information about the current state and also the target NMR spectra) and edge features e_{vw} . The features of each node at time step t are represented as h_v^t , initialized to x_v at t = 0. The features of nodes are updated for 3 time steps using messages m_v^{t+1} in the following way:

$$\begin{split} m_{v}^{t+1} &= \sum_{w \in N(v)} M_{t}(h_{v}^{t}, h_{w}^{t}, e_{vw}) \\ h_{v}^{t+1} &= U_{t}(h_{v}^{t}, m_{v}^{t+1}) \\ F_{v} &= g(x_{v}, h_{v}^{t}) = x_{v} + h_{v}^{t}, \quad \forall \ v \in V \end{split}$$

where N(v) is the set of neighboring nodes of v. M_t and U_t are the message function and vertex update function, respectively. The function g is simply taken to be vector addition in this work. F_v is the final atomic feature for the node which has information about the atomic properties, the local environment, and also the target NMR shift value that was assigned to this node. The feature (F_v) generated here will be further used by the policy neural network $\pi_{model}(als)$ and value network $V_{model}(s)$.

Policy Head: N nodes form $\binom{N}{2}$ pairs, each representing a possible edge. For each of these pairs, let the feature vector of the pair be the concatenation of the feature vector of the two nodes concerned. This pair's feature vector is then passed through two fully connected layers to obtain a 3-tuple representing the possibility of single, double, and triple bond between this pair.

Value Head: All the node features received from the graph featurizer are then sum-pooled to attain a molecule-level feature vector which has information about both the current molecule and the target NMR. This molecule level feature is then passed through two fully connected layers to finally predict the value $V_{model}(s)$ of the current state.

While in the training mode, the environment has access to not only the NMR spectra but also the structure of the target molecule. This can be used to guide the tree by giving a strong positive reinforcement in the form of r(s, a) (Figure 3). The tree policy (derived from visitation counts of the actions) and approximation of Q(s, a) hence obtained is used as the training data set for the prior policy neural network $\pi_{model}(a|s)$ and value network $V_{model}(s)$. When any action a at state s leads it to state s', i.e., $s \xrightarrow{a} s'$, then

$$r(s, a)$$
: = 1 iff $S(s_t, s')$, else 0

where $S(s_t, s')$ is Boolean function that returns True iff s' is subgraph isomorphic to the s_t . This work employs rdkit²⁸ to check whether the state s' is a subgraph of the target molecule s_t . With training mode on, the model was run on a system with an Intel Xeon E5-2640 v4 processor and Nvidia GeForce GTX 1080 Ti GPU for 23 h to collect experience and train the neural networks. Five models were trained on different crossvalidation training sets.

Each shift value in the data set is accompanied by a split value as well. The split value is a categorical variable that belongs to one of $\{S, D, T, Q\}$, and it is dependent on the number of hydrogen atoms that are attached to the carbon. A quaternary carbon (no hydrogen attached) leads to a singlet (S) split; a tertiary carbon (one hydrogen attached) leads to a doublet (D) split; a secondary carbon (two hydrogens attached) leads to a triplet (T) split; and a primary carbon (three hydrogens) leads to a quartet (Q) split. Let splitvector be the vector that stores the information about the number of carbons of each split kind in the current state. Because the only action possible in the modeled MDP is that of addition of an edge (decreases the number of implicit hydrogens), note the following two invariant properties:

- The sum of values in the splitvector would remain constant for states with only 1 connected component because the total number of carbons cannot increase.
- With addition of bonds, the kind of split made by a particular carbon can only move in the direction

$$S \leftarrow D \leftarrow T \leftarrow Q$$

As a consequence of this, certain states can be flagged as terminal states if it is known that they can never lead to the target molecule based on the following criteria:

- When the number of quaternary carbons in the current state becomes lower than the number of quartet splits in the target spectra.
- When the number of singlet carbons in the current state becomes more than the number of singlet splits in the target spectra and so on.

For example, in Figure 4 a, the agent can safely terminate search through this branch because once a duplet has formed in the current state, that carbon can never be transformed back to triplet or quartet and we know that the target molecule does not have any duplet or singlet carbon. Similarly, in Figure 4b, the agent can safely terminate because the number of quartets in the current state has gone below the number of quartets in the target molecule and there is no way to produce new quartet carbon atoms. These chemistry-guided conditions greatly prune the search tree and prevent the tree from exploring branches that can lead to the incorrect structure.

The forward model used in this work was trained on nmrshiftdb2 data set²² as included in the original work by Jonas and Kuhn.⁸ The mean absolute error obtained for the prediction of the shiftvalue per peak for the predictor was 1.374 ppm.

The total data set of 2134 molecules was randomly split into 5 equal groups. In each of the five experiments, one of the groups was chosen as the hold-out test data set and the model was trained on the remaining four groups. For each molecule, the agent made a number of guesses depending on how many episodes it ran. There were 20 processes initiated, with each of them running an episode. An example of one such episode run is illustrated in Figure 5. As shown in Figure 6a, on average, the agents guessed the correct structure of the molecule of the target spectra 93.8% of the time. All the guesses of the agent are then ranked based on the scoring function discussed in the earlier section. The Top1 ranked structure among the guesses was the target structure 57.2% of the time. The accuracy for Top3, Top5, and Top7 of the scored guesses can be seen in Figure 6a. Figure 7 shows the Top3 guesses made by the framework ranked by the criterion mentioned earlier for a couple of examples where the Top1 ranked molecule is the correct target structure, and Figure 8 shows examples where the Top1 ranked molecule is not the correct target structure.

nmcts is the number of times that the search tree is traversed from the root to leaf node to explore different branches before making a true action in the current state. As expected, it can be observed in Figure 6b that the net accuracy improves as nmcts increases.

It is also seen that the trend for Top1 accuracy is not the same as others, and it actually decreases with increase in nmcts. This can be explained by the fact that the increasing nmcts increases the exploration of the chemical space, and more potential candidates are scored against the current structure. This downward trend reveals that a better scoring function would improve the TopN accuracy of the agent because it would be able to rank the candidate guesses in a more accurate way.

Figure 6 d shows the distribution of time taken for each molecule with varying nmcts. As expected, we observe an increase in time taken for the agent to make all its guesses for a target NMR spectrum.

Even when the agent has the correct structure among its guesses, sometimes the scoring function ranks it lower than other guesses made, which reduces accuracy. Because the scoring function is dependent on the pretrained forward model, a more capable forward model is expected to increase the accuracy of the framework. In the event that a better, albeit computationally expensive scoring function is deviced, the overall practical accuracy can still be improved while being even more time efficient. This can be done by scoring only the TopN guesses of the agent with the time intensive scoring function. As can be seen in Figure 6b, the target spectra's correct molecular structure is present in the Top7 of the guesses >85% of the time for all the runs with nmcts > 200. In such a scenario, we can determine the correct structure for an NMR spectra by scoring only 7 structures while the MCTS search takes less than 100 s for most of the molecules.

In another experiment, molecules with <7 non-hydrogen atoms were filtered from the data set. After running the agent on these filtered set of molecules with training mode on, the agent was tested on 200 randomly sampled molecules with \geq 7 and <10 heavy atoms. The result of this experiment is plotted in Figure 9a. However, the system performs well on the class of data that it was never exposed to before, guessing the correct structure 86.5% of the time.

The histogram of the time taken for the agent to run all the episodes for a molecule can be seen in Figure 6c. On average, it takes \sim 330 s for the agent to make all its guesses for a target NMR spectra. All episodes are run within 300 s for 71.8% of the molecules and within 600 s for 88.5% of the molecules. It is observed in Figure 9b that the mean time taken for all the episodes for a molecule that is guessed correctly is \sim 305 s, whereas the mean time for molecules that are guessed incorrectly is ~780 s. This difference of distribution can be used to have more reliable predictions and improve the potential practical use-case of this framework. Stopping the search at a threshold time can improve accuracy for predicted molecules while also saving computational expense. When the framework makes predictions for all the molecules, i.e., without any threshold time, the correct structure is among the guesses made for 94.8% of the molecules. Having a threshold time of 300 s leads to the framework making predictions for 72% of the molecules and timing-out for the rest of the molecules. The correct structure is among these guesses for 99% of the molecules. Similarly, when the threshold is set to 1000 s, the framework makes predictions for 94% of the molecules. The correct structure is among the guesses 97% of the time.

This Letter provides a framework using graph convolution networks and reinforcement learning to solve the inverse molecular problem of NMR spectra. The work also introduces a novel method to train the policy and value networks a priori in guided MCTS runs (training mode on) and demonstrates the utility of Monte Carlo tree searches in navigating the chemical space. Unlike other prior attempts to solve this problem like the one by Jonas⁶ in which the model makes a prediction only 50% of the time (even though their work is tested on molecules with 32 heavy atoms), or the work by Zhang et al.¹⁹ in which the model is tested only on 9 handpicked target spectra, this model shows good promise by predicting the correct structure among its Top3 guesses ~80% of the time. Additionally, it is observed that the proposed framework performs better than brute-force checking in an enumerated database of known molecular structures. On average, it is seen that the framework calls the forward model for less than 7% of the molecules in OM9 which have the same molecular formula as the target structure, while still identifying the molecule correctly. More information on comparison of the framework against brute-force enumeration is provided in the Supporting Information. Still, there are various avenues for improvement for future work. Because the RL algorithm is dependent on the forward model for its intermediate reward, a better scoring function would potentially improve the prediction accuracy. ¹³C NMR is just one of the many spectroscopy techniques that are widely used. For example, ¹H NMR spectroscopy has a higher signal-to-noise ratio owing to the significantly larger abundance of spin-active isotope. Infrared spectroscopy sheds light on the vibrational transitions in a molecule and is considered to be complementary to NMR spectroscopy for characterizing small organic molecules. A promising extension of work presented in this Letter would be to incorporate other spectral data and leverage different kinds of information to elucidate the correct structure of an unknown molecule. Finally, we believe that the proposed work is a crucial step in high-throughput synthesis, where swift and efficient verification of structures generated can make the whole process of drug discovery more robust and reliable.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpclett.2c00624.

Tabular form of data points used to plot graphs in this work and additional analysis comparing this work against enumerated databases (PDF)

Transparent Peer Review report available (PDF)

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Notes

The authors declare no competing financial interest. The source code along with instructions for the work presented in this Letter can be found at https://github.com/ devalab/SpectraToStructure.

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