Reinforcement Learning for Molecular Design
Guided by Quantum Mechanics

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Abstract
Automating molecular design using deep reinforcement learning (RL) holds the promise of accelerating the discovery of new chemical compounds. A limitation of existing approaches is that they work with molecular graphs and thus ignore the location of atoms in space, which restricts them to 1) generating single organic molecules and 2) heuristic reward functions. To address this, we present a novel RL formulation for molecular design in Cartesian coordinates, thereby extending the class of molecules that can be built. Our reward function is directly based on fundamental physical properties such as the energy, which we approximate via fast quantum-chemical methods. To enable progress towards de-novo molecular design, we introduce MolGym, an RL environment comprising several challenging molecular design tasks along with baselines. In our experiments, we show that our agent can efficiently learn to solve these tasks from scratch by working in a translation and rotation invariant state-action space.

1. Introduction
Finding new chemical compounds with desired properties is a challenging task with important applications such as de novo drug design and materials discovery (Schneider et al., 2019). The diversity of synthetically feasible chemicals that can be considered as potential drug-like molecules was estimated to be between \(10^{30}\) and \(10^{60}\) (Polishchuk et al., 2013), making exhaustive search hopeless.

Recent applications of machine learning have accelerated the search for new molecules with specific desired properties. Generative models such as variational autoencoders (VAEs) (Gómez-Bombarelli et al., 2018), recurrent neural networks (RNNs) (Segler et al., 2018), and generative adversarial networks (GANs) (De Cao & Kipf, 2018) have been successfully applied to propose potential drug candidates. Despite recent advances in generating valid structures, proposing truly novel molecules beyond the training data distribution remains a challenging task. This issue is exacerbated for many classes of molecules (e.g. transition metals), where such a representative dataset is not even available.

An alternative strategy is to employ RL, in which an agent builds new molecules in a step-wise fashion (e.g., Olivecrona et al. (2017), Guimaraes et al. (2018), Zhou et al. (2019), Zhavoronkov et al. (2019)). Training an RL agent only requires samples from a reward function, alleviating the need for an existing dataset of molecules. However, the choice of state representation in current models still severely limits the class of molecules that can be generated. In particular, molecules are commonly described by graphs, where atoms and bonds are represented by nodes and edges, respectively. Since a graph is a simplified model of the physical representation of molecules in the real world, one is limited to the generation of single organic molecules. Other types of molecules cannot be appropriately described as this representation lacks important three-dimensional (3D) information, i.e. the relative position of atoms in space. For example, systems consisting of multiple molecules cannot be generated for this reason. Furthermore, it prohibits the use of reward functions based on fundamental physical laws;
instead, one has to resort to heuristic physicochemical parameters, e.g. the Wildman-Crippen partition coefficient (Wildman & Crippen, 1999). Lastly, it is not possible to impose geometric constraints on the design process, e.g. those given by the binding pocket of a protein which the generated molecule is supposed to target.

In this work, we introduce a novel RL formulation for molecular design in which an agent places atoms from a given bag of atoms onto a 3D canvas (see Fig. 1). As the reward function is based on fundamental physical properties such as energy, this formulation is not restricted to the generation of molecules of a particular type. We thus encourage the agent to implicitly learn the laws of atomic interaction from scratch to build molecules that go beyond what can be represented with graph-based RL methods. To enable progress towards designing such molecules, we introduce a new RL environment called MolGym. It comprises a suite of tasks in which both single molecules and molecule clusters need to be constructed. For all of these tasks, we provide baselines using quantum-chemical calculations. Finally, we propose a novel policy network architecture that can efficiently learn to solve these tasks by working in a translation and rotation invariant state-action space.

In summary, our contributions are as follows:

- we propose a novel RL formulation for general molecular design in Cartesian coordinates (Section 2.2);
- we design a reward function based on the electronic energy, which we approximate via fast quantum-chemical calculations (Section 2.3);
- we present a translation and rotation invariant policy network architecture for molecular design (Section 3);
- we introduce MolGym, an RL environment comprising several molecular design tasks along with baselines based on quantum-chemical calculations (Section 5.1);
- we perform experiments to evaluate the performance of our proposed policy network using standard policy gradient methods (Section 5.2).

2. Reinforcement Learning for Molecular Design Guided by Quantum Mechanics

In this section, we provide a brief introduction to RL and introduce our novel RL formulation for molecular design in Cartesian coordinates.

2.1. Background: Reinforcement Learning

In the standard RL framework, an agent interacts with the environment in order to maximize some reward. We consider a fully observable environment with deterministic dynamics. Such an environment is formally described by a Markov decision process (MDP) \( M = (S, A, T, \mu_0, \gamma, T, r) \) with state space \( S \), action space \( A \), transition function \( T : S \times A \rightarrow S \), initial state distribution \( \mu_0 \), discount factor \( \gamma \in (0, 1] \), time horizon \( T \), and reward function \( r : S \times A \rightarrow \mathbb{R} \). The value function \( V^\pi(s_t) \) is defined as the expected discounted return when starting from state \( s_t \) and following policy \( \pi \) thereafter, i.e. \( V^\pi(s_t) = \mathbb{E}_\pi[\sum_{t'=t}^T \gamma^{t'-t} r(s_{t'}, a_{t'}) | s_t] \). The goal is to learn a stochastic policy \( \pi(a_t | s_t) \) that maximizes the expected discounted return \( J(\theta) = \mathbb{E}_{s_0 \sim \mu_0}[V^\pi(s_0)] \).

**Policy Gradient Algorithms** Policy gradient methods are well-suited for RL in continuous action spaces. These methods learn a parametrized policy \( \pi_\theta \) by performing gradient ascent in order to maximize \( J(\theta) \). More recent algorithms (Schulman et al., 2015; 2017) improve the stability during learning by constraining the policy updates. For example, proximal policy optimization (PPO) (Schulman et al., 2017) employs a clipped surrogate objective. Denoting the probability ratio between the updated and the old policy as \( r_t(\theta) = \frac{\pi(\theta(a_t | s_t))}{\pi_\theta(a_t | s_t)} \), the clipped objective \( J_{\text{CL}} \) is given by

\[
J_{\text{CL}}(\theta) = \mathbb{E} \left[ \min(r_t(\theta)\hat{A}_t, \text{clip}(r_t(\theta), 1 - \epsilon, 1 + \epsilon)\hat{A}_t) \right],
\]

where \( \hat{A}_t \) is an estimator of the advantage function, and \( \epsilon \) is a hyperparameter that controls the interval beyond which \( r_t(\theta) \) gets clipped. To further reduce the variance of the gradient estimator, actor-critic approaches (Konda & Tsitsiklis, 2000) are often employed. The idea is to use the value function (i.e. the critic) to assist learning the policy (i.e. the actor). If the actor and critic share parameters, the objective becomes

\[
J_{\text{AC}}(\theta) = \mathbb{E} \left[ J_{\text{CL}}(\theta) - c_1 J^V + c_2 \mathbb{E}[\pi_\theta(s_t)] \right],
\]

where \( c_1, c_2 \) are coefficients, \( J^V = (V^\pi(s_t) - V_{\text{target}})^2 \) is a squared-error loss, and \( \mathbb{E} \) is an entropy regularization term to encourage sufficient exploration.

2.2. Setup

We design molecules by sequentially drawing atoms from a given bag and placing them onto a 3D canvas. This task can be formulated as a sequential decision-making problem in a...
finite-horizon MDP with deterministic transition dynamics, where

- state \( s_t = (C_t, \beta_t) \) contains the canvas \( C_t = C_0 \cup \{ (e_i, x_i) \}_{i=0}^{t-1} \), i.e. a set of atoms with chemical element \( e_i \in \{ \text{H, C, N, O, } \ldots \} \) and position \( x_i \in \mathbb{R}^3 \) placed until time \( t-1 \), as well as a bag \( \beta_t = \{ (e, m(e)) \} \) of atoms still to be placed; \( C_0 \) can either be empty, \( C_0 = \emptyset \), or contain a set of atoms, i.e. \( C_0 = \{ (e_i, x_i) \} \) for some \( i \in \mathbb{Z}^+ \); \( m(e) \) is the multiplicity of the element \( e \);
- action \( a_t = (e_t, x_t) \) contains the element \( e_t \in \beta_t \) and position \( x_t \in \mathbb{R}^3 \) of the next atom to be placed;
- deterministic transition function \( T(s_t, a_t) \) places an atom through action \( a_t \) in state \( s_t \), returning the next state \( s_{t+1} = (C_{t+1}, \beta_{t+1}) \) with \( \beta_{t+1} = \beta_t \setminus e_t \);
- reward function \( r(s_t, a_t) \) quantifies how applying action \( a_t \) in state \( s_t \) alters properties of the molecule, e.g. the stability of the molecule as measured in terms of its quantum-chemical energy.

Fig. 2 depicts the rollout of an episode. The initial state \((C_0, \beta_0) \sim \mu_0(s_0)\) of the episode comprises the initial content \( C_0 \) of the canvas and a bag of atoms \( \beta_0 \) to be placed, e.g. \( C_0 = \emptyset \), and \( \beta_0 = C_4 \text{H}_2\text{NO}_2 \) sampled uniformly from a given set of bags. The agent then sequentially draws atoms from the bag without replacement and places them onto the canvas until the bag is empty.

2.3. Reward Function

One advantage of designing molecules in Cartesian coordinates is that we can evaluate states in terms of quantum-mechanical properties, such as the energy or dipole moment. In this paper, we focus on designing stable molecules, i.e. molecules with low energy \( E \in \mathbb{R} \); however, linear combinations of multiple desirable properties are possible as well (see Section 5.1 for an example). We define the reward \( r(s_t, a_t) = -\Delta E(s_t, a_t) \) as the negative difference in energy between the resulting molecule described by \( C_{t+1} \) and the sum of energies of the current molecule \( C_t \) and a new atom of element \( e_t \), i.e.

\[
\Delta E(s_t, a_t) = E(C_{t+1}) - [E(C_t) + E(e_t)],
\]

where \( E(e) = E(\{ (e, [0, 0, 0]^T) \}) \). Intuitively, the agent is rewarded for placing atoms so that the energy of the resulting molecules is low. Importantly, with this formulation the undiscounted return for building a molecule is independent of the order in which atoms are placed. If the reward only consisted of \( E(C_{t+1}) \), one would double-count interatomic interactions. As a result, the formulation in Eq. (1) prevents the agent from learning to greedily choose atoms of high atomic number first, as they have low intrinsic energy.

Quantum-chemical methods, such as the ones based on density functional theory (DFT), can be employed to compute the energy \( E \) for a given \( C \). Since such methods are computationally demanding in general, we instead choose to evaluate the energy using the semi-empirical Parametrized Method 6 (PM6) (Stewart, 2007) as implemented in the software package SPARROW (Husch et al., 2018; Bosia et al., 2019); see the Appendix for details. PM6 is significantly faster than more accurate methods based on DFT and sufficiently accurate for systems studied here. For example, the energy \( E \) of a systems containing 10 atoms can be computed within hundreds of milliseconds with PM6; with DFT, this would take minutes. We note that more accurate methods can be used as well if the computational budget is available.

3. Policy

Building molecules in Cartesian coordinates allows to 1) extend molecular design through deep RL to a much broader class of molecules compared to graph-based approaches, and 2) employ reward functions based on fundamental physical properties such as the energy. However, working directly in Cartesian coordinates introduces several additional challenges for policy learning.

Firstly, it would be highly inefficient to naively learn to place atoms directly in Cartesian coordinates since most molecular properties are invariant under symmetry operations such as translation and rotation. For instance, the energy of a molecule—and thus the reward—does not change if the molecule gets rotated, yet an agent that was not invariant under rotation would need to learn these solutions separately. To prevent this issue, we introduce internal representations for states (Section 3.1) and actions (Section 3.2) that are invariant under these symmetry operations as well.

Secondly, the action space contains both discrete (i.e. element \( e_t \)) and continuous actions (i.e. position \( x_t \)). This is in contrast to most RL algorithms, which assume that the action space is either discrete or continuous. As a result, policy exploration becomes much more challenging compared to graph-based approaches, even when working with internal coordinates. Furthermore, not all discrete actions are valid in every state, e.g. the element \( e_t \) has to be contained in the bag \( \beta_t \). These issues are addressed in Section 3.2, where we propose a novel actor-critic neural network architecture for efficiently constructing molecules in Cartesian coordinates.

3.1. State Representation

For each atom on the canvas\(^2 \) \( C \) we require a representation that is invariant under translation and rotation of the canvas. To achieve this, we employ SCHNet (Schütt et al., 2017; 2018b), a deep learning architecture consisting of

\(^2\)Short hand for \( \{ \text{C, 4), (H, 3), (N, 1), (O, 2) \} \).

\(^3\)We omit the time index when it is clear from the context.
continuous-filter convolutional layers that works directly on atoms placed in Cartesian coordinates. SchNet($\mathcal{C}$) produces an embedding of each atom in $\mathcal{C}$ that captures information about its local atomic environment. As shown in Fig. 4 (left), we combine this embedding $\tilde{\mathcal{C}}$ with a latent representation $\tilde{\beta}$ of the bag, yielding a state embedding $\tilde{s}$, i.e.,
\[ \tilde{s} = [\tilde{\mathcal{C}}, \tilde{\beta}], \quad \tilde{\mathcal{C}} = \text{SchNet}(\mathcal{C}), \quad \tilde{\beta} = \text{MLP}_\beta(\beta), \quad (2) \]
where MLP$_\beta$ is a multi-layer perceptron (MLP).

3.2. Actor

Action Representation Similar to the state representation, we require an action representation that is invariant to translation and rotation by construction. We address this issue by modeling the position of the atom to be placed in internal coordinates—a commonly used representation for molecular structures in computational chemistry—relative to previously placed atoms. If the canvas is initially empty, $\mathcal{C}_0 = \emptyset$, the agent randomly selects an element $e_0$ from $\beta_0$ and places it at the origin, i.e., $a_0 = (e_0, [0, 0, 0]^T)$. Once the canvas $\mathcal{C}_t$ contains at least one atom, the agent first decides on a focal atom, $f \in \{1, \ldots, n(\mathcal{C}_t)\}$, where $n(\mathcal{C}_t)$ denotes the number of atoms in $\mathcal{C}_t$. This focal atom represents a local reference point close to which the next atom is going to be placed (see Fig. 3). The agent then models the position $x \in \mathbb{R}^3$ with respect to $f$ in internal coordinates $(d, \alpha, \psi)$, where

- $d \in \mathbb{R}$ is the Euclidean distance between $x$ and the position $x_f$ of the focal atom;
- $\alpha \in [0, \pi]$ is the angle between the two lines defined by $(x, x_f)$ and $(x, x_{n1})$, where $x_{n1}$ is the position of the atom closest to $f$; if less than two atoms are on the canvas, $\alpha$ is undefined/unused;
- $\psi \in [-\pi, \pi]$ is the dihedral angle between two intersecting planes spanned by $(x, x_f, x_{n1})$ and $(x_f, x_{n1}, x_{n2})$, where $x_{n2}$ is the atom that is the second closest to the focal atom; if less than three atoms are on the canvas, $\psi$ is undefined/unused.

As shown in Fig. 3 (right), these internal coordinates can then be mapped back to Cartesian coordinates $x$.

Model

This action representation suggests a natural generative process: first choose next to which focal atom the new atom is placed, then select its element, and finally decide where to place the atom relative to the focal atom. Therefore, we assume that the policy factorizes as
\[
\pi_{\theta}(\psi, \alpha, d, e, f | s) = p(\psi | \alpha, d, e, f, s) \times p(e | f, s) p(f | s). \quad (3)
\]

We model the distributions over $f$ and $e$ as categorical, $\text{Cat}(h_f)$, where $h_f \in \mathbb{R}^{n(\mathcal{C})}$ and $h_e \in \mathbb{R}^{E_{\text{max}}}$ are the logits predicted by separate MLPs, and $E_{\text{max}}$ is the largest atomic number that can be selected. Further, $p(\psi | \alpha, d, e, f, s)$ is factored into a product of univariate Gaussian distributions $\mathcal{N}(\mu, \sigma^2)$, where the means $\mu_d, \mu_\alpha$ and $\mu_\psi$ are given by an MLP and the standard deviations $\sigma_d, \sigma_\alpha$ and $\sigma_\psi$ are global parameters. Formally,
\[
\begin{align*}
  h_f &= \text{MLP}_f(\tilde{s}), \\
  h_e &= \text{MLP}_e(\tilde{s}_f), \\
  \mu_d, \mu_\alpha, \mu_\psi &= \text{MLP}_\text{cont}(\tilde{s}_f, \mathbb{1}(e)),
\end{align*}
\]
where $\tilde{s}_f = [\tilde{\mathcal{C}}_f, \tilde{\beta}]$ is the latent state of the focal atom $f \sim \text{Cat}(h_f)$, $\mathbb{1}(e)$ is a one-hot vector representation of element $e \sim \text{Cat}(h_e)$, and $d \sim \mathcal{N}(d; \mu_d, \sigma^2_d)$, $\alpha \sim \mathcal{N}(\alpha; \mu_\alpha, \sigma^2_\alpha)$, and $\psi \sim \mathcal{N}(\psi; \mu_\psi, \sigma^2_\psi)$ are sampled from their respective distributions. The model is illustrated in Fig. 4.

Maintaining Valid Actions As the agent places more atoms onto the canvas during a rollout, the number of possible focal atoms $f$ increases and the number of elements $e$ to choose from decreases. To guarantee that the agent only chooses valid actions, i.e., $f \in \{1, \ldots, n(\mathcal{C})\}$ and $e \in \beta$, we mask out invalid focal atoms and elements by setting their probabilities to zero and re-normalizing the categorical distributions.

Learning the Dihedral Angle The sign of the dihedral angle $\psi$ depends on the two nearest neighbors of the focal atom and is difficult to learn, especially if the two atoms are nearly equally close to the focal atom. In practice, we therefore learn the absolute value $|\psi|$ instead of $\psi$, as well as the sign $\kappa \in \{+1, -1\}$, such that $\psi = \kappa |\psi|$. To estimate $\kappa$, we exploit the fact that the transition dynamics are deterministic. We generate embeddings of both possible

Figure 3. Construction of a molecule using an action-space representation that is invariant under translation and rotation. Left: Current state $s_t$ with content $\mathcal{C}_t$ and remaining bag $\beta_t$. Center: Action $a_t$ adds an atom from the bag (highlighted in orange) relative to the focus $f$ (highlighted in blue). The relative coordinates $(d, \alpha, \psi)$ uniquely determine its absolute position. Right: Resulting state $s_{t+1}$ after applying action $a_t$ in state $s_t$.
next states (for $\kappa = +1$ and $\kappa = -1$) and select the embedding of the atom just added, which we denote by $\tilde{s}_+$ and $\tilde{s}_-$. We then choose $\kappa = +1$ over $\kappa = -1$ with probability

$$ p_+ = \frac{\exp(u_+)}{\exp(u_+) + \exp(u_-)}, \quad (7) $$

such that $p(\kappa | \psi, \alpha, d, e, f, s) = \text{Ber}(\kappa; p_+)$, where $u_+ = \text{MLP}_e(\tilde{s}_+)$. We further motivate this choice in the appendix. Thus, the policy is given by $\pi_\theta(\kappa | \psi, \alpha, d, e, f, s) = p(\kappa | \psi, \alpha, d, e, f, s)p(\psi | e, f, s)p(e | f, s)p(f | s)$.

3.3. Critic

The critic needs to compute a value for the entire state $s$. Since the canvas is growing as more atoms are taken from the bag and placed onto the canvas, a pooling operation is required. Here, we compute the average over all atoms within the embedding $\tilde{s}$. Thus, the critic is given by

$$ V_\phi(s) = \text{MLP}_\phi \left( \frac{1}{n(C)} \sum_{i=1}^{n(C)} \tilde{s}_i \right), \quad (8) $$

where $\text{MLP}_\phi$ is an MLP that computes value $V$ (see Fig. 4).

3.4. Optimization

We employ PPO (Schulman et al., 2017) to learn the parameters $(\theta, \phi)$ of the actor $\pi_\theta$ and critic $V_\phi$, respectively. While most RL algorithms can only deal with either continuous or discrete action spaces and thus require additional modifications to handle both (Masson et al., 2016; Wei et al., 2018; Xiong et al., 2018), PPO can be applied directly as is. To help maintain sufficient exploration throughout learning, we include an entropy regularization term over the policy. However, note that the entropies of the continuous and categorical distributions often have different magnitudes; further, in this setting the entropies over the categorical distributions vary significantly throughout a rollout: as the agent places more atoms, the support of the distribution over valid focal atoms $f$ increases and the support of the distribution over valid elements $e$ decreases. To mitigate this issue, we only apply entropy regularization to the categorical distributions, which we find to be sufficient in practice.

4. Related Work

Deep Generative Models A prevalent strategy for molecular design based on machine learning is to employ deep generative models. These approaches first learn a latent representation of the molecules and then perform a search in latent space (e.g., through gradient descent) to discover new molecules with sought chemical properties. For example, Gómez-Bombarelli et al. (2018); Kusner et al. (2017); Blaschke et al. (2018); Lim et al. (2018); Dai et al. (2018) utilized VAEs to perform search or optimization in a latent space to find new molecules. Segler et al. (2018) used RNNs to design molecular libraries. The aforementioned approaches generate SMILES strings, a linear string notation, to describe molecules (Weininger, 1988). Further, there exist a plethora of generative models that work with graph representations of molecules (e.g., Jin et al. (2017); Bradshaw et al. 2019a; Li et al. (2018a; b); Liu et al. (2018); De Cao & Kipf (2018); Bradshaw et al. (2019b)). In these methods, atoms and bonds are represented by nodes and edges, respectively. While the generated molecules are shown to be valid (De Cao & Kipf, 2018; Liu et al., 2018) and synthesizable (Bradshaw et al., 2019b), the generative model is restricted to a (small) region of chemical space for which the graph representation is valid, e.g. single organic molecules.

3D Point Cloud Generation An additional disadvantage of string- and graph-based approaches is their neglect of information encoded in the interatomic distances. To this end, Gebauer et al. (2018; 2019) proposed a generative neural network for sequentially placing atoms in Cartesian coordinates. While their model conserves rotational invariance as well as local symmetries by construction, atoms are placed
on a 3D grid. Further, similar to aforementioned approaches, this model depends on a dataset to exist that covers the particular class of molecules for which one seeks to generate new molecules.

Reinforcement Learning Olivecrona et al. (2017), Guimaraes et al. (2018), Putin et al. (2018), and Popova et al. (2018) presented RL approaches based on string representations of molecules. They successfully generated molecules with given desirable properties but, similar to other generative models using SMILES strings, struggled with chemical validity. You et al. (2018) proposed a graph convolutional policy network based on graph representations of molecules, where the reward function is based on empirical properties such as the drug-likeness. While this approach was able to consistently produce valid molecules, its performance still depends on a dataset required for pre-training. Considering the large diversity of chemical structures, the generation of a dataset that covers the whole chemical space is hopeless. To address this limitation, Zhou et al. (2019) proposed an agent that learned to generate molecules from scratch using a Deep Q-Network (DQN) (Mnih et al., 2015). However, such graph-based RL approaches are still restricted to the generation of single organic molecules for which this representation was originally designed. Further, graph representations prohibit the use of reward functions based on fundamental physical laws, and one has to resort to heuristics instead. Finally, geometric constraints cannot be imposed on the design process.

5. Experiments

We perform experiments to evaluate the performance of the policy introduced in Section 3. While prior work has focused on building molecules employing molecular graph representations, we are interested in designing molecules in Cartesian coordinates. In particular, we want to answer the following questions: 1) can our agent learn to construct single molecules in Cartesian coordinates from scratch, 2) does our approach allow building molecules across multiple bags simultaneously, 3) are we able to scale to larger molecules, and 4) can our agent construct systems comprising multiple molecules?

To this end, we introduce a new RL environment called MOLGYM in Section 5.1. It comprises a set of molecular design tasks, for which we provide baselines using quantum-chemical calculations. See the Appendix for details on how the baselines are determined.

5.1. Tasks

We propose three different tasks for molecular design in Cartesian coordinates, which are instances of the MDP formulation introduced in Section 2.2: single-bag, multi-bag, and solvation. More formally, the tasks are as follows:

Single-bag Given a single bag, learn to design stable molecules. This task assesses an agent’s ability to build single stable molecules. The reward function is given by \( r(s_t, a_t) = -\Delta E(s_t, a_t), \) see Eq. (1). If the reward is below a threshold of \(-0.6\), the molecule is deemed invalid and the episode terminates prematurely with the reward clipped at \(-0.6\).\(^4\) We evaluate the offline performance of the agent in terms of the average return across 10 episodes.

Multi-bag Given multiple bags with one of them being randomly selected before each episode, learn to design stable molecules. This task focuses on the agent’s capabilities to learn to build different molecules of different composition and size at the same time. The same reward function as in the single-bag task is used. Offline performance is evaluated across 10 rollouts per bag. The optimal return is given by the average optimal return over all bags.

Solvation The task is to learn to place water molecules around an existing molecule (i.e. CO is non-empty). This task assesses an agent’s ability to distinguish intra- and intermolecular interactions, i.e. the atomic interactions within a molecule and those between molecules. These interactions are paramount for the accurate description of chemistry in the liquid phase. In this task, we deviate from the protocol used in the previous experiments as follows. Initially, the agent is provided with an H\(_2\)O bag. Once the bag is empty, the environment will refill it and the episode continues. The episode terminates once \( n \in \mathbb{N}^+ \) bags of H\(_2\)O have been placed on the canvas. By refilling the H\(_2\)O bag \( n - 1 \) times instead of providing a single H\(_2\)O\(_n\) bag, the agent is guided towards building H\(_2\)O molecules.\(^5\) The reward function is augmented with a penalty term for placing atoms far away from the center, i.e. \( r(s_t, a_t) = -\Delta E - \rho \|x\|_2 \), where \( \rho \) is a hyper-parameter. This corresponds to a soft constraint on the radius at which the atoms should be placed. This is a task a graph-based RL approach could not solve.

5.2. Results

We use the tasks specified in Section 5.1 to evaluate our proposed policy. More details on model architecture, hyper-parameters and computing resources are in the Appendix.

Learning to Construct Single Molecules In a toy experiment, we evaluate whether our policy is able to learn to construct small single molecules by training the agent on the single-bag task for the bags CH\(_3\)NO, CH\(_3\)O and C\(_2\)H\(_2\)O\(_2\), respectively. From Fig. 5 it can be seen that the agent is able to learn the rules of chemical bonding and interatomic distances from scratch. While on average the

\(^4\)\(\Delta E\) is on the order of magnitude of \(-0.1\) Hartree, resulting in a reward of around 0.25 for a well placed atom.

\(^5\)A comparison of the two protocols is given in the Appendix.
agent reaches 90% of the optimal return after only 12 000 steps, the snapshots in Fig. 5 (b) highlight that the last 10% determine chemical validity. As shown in Fig. 5 (b), the model first learns the atomic distances $d$, followed by the angles $\alpha$ and the dihedral angles $\psi$.

**Learning across Multiple Bags**  We evaluate whether our agent is able to learn how to design molecules across multiple bags. We select all formulas contained in the QM9 dataset (Ruddigkeit et al., 2012; Ramakrishnan et al., 2014) that have up to 5 atoms, resulting in a set of 11 bags. Despite their small size, the set of molecules features a diverse set of bonds (single, double, and triple) and geometries (linear, trigonal planar, and tetrahedral). From the average offline performance and from visual inspection of the generated molecular structures shown in Fig. 6, it can be seen that our agent is able to build different molecular structures at the same time. For example, it learned that a carbon atom can have varying number and type of neighboring atoms leading to specific bond distance, angles, and dihedral angles.

**Scaling to Larger Molecules**  To study our agent’s ability to construct large molecules we let it solve the single-bag task with the bags $\text{C}_3\text{H}_5\text{NO}_3$, $\text{C}_3\text{H}_8\text{O}$, and $\text{C}_4\text{H}_7\text{N}$. Results are shown in Fig. 7. After 154 000 steps of training, the agent achieved on average a return of 2.60 on $\text{C}_3\text{H}_5\text{NO}_3$ (maximum across seeds at 2.72, optimum at 2.79), 2.17 on $\text{C}_3\text{H}_7\text{N}$ (2.21, 2.27), and 1.98 on $\text{C}_3\text{H}_8\text{O}$ (2.04, 2.07). While the agent did not always find the most stable configurations, it was able to explore a diverse set of chemically valid structures (including bimolecular structures which are shown in the Appendix).

**Constructing Molecular Clusters**  In this experiment, we task the agent to place 5 water molecules around a formaldehyde molecule, i.e. $\text{C}_0 = \text{CH}_2\text{O}$ and $n = 5$. The distance penalty parameter $\rho$ is set to 0.01. From Fig. 8, we observe that the agent is able to learn to construct H$_2$O molecules and place them in the vicinity of the solute. A good placement also allows for hydrogen bonds to be formed between water molecules themselves and between water molecules and the solute (see Fig. 8, dashed circle). In most cases, our agent arranges H$_2$O molecules such these hydrogen bonds can be formed (see Fig. 8, solid circles). The lack of hydrogen bonds in some structures could be attributed to the approximate nature of quantum-chemical method used in the reward function. Overall, this experiment showcases that our agent is able to learn both intra- and intermolecular interactions, going beyond what graph-based agents can learn.

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6 Additional experiments on the solvation task are given in the Appendix.
Figure 7. (a) Average offline performance on the single-bag task for bags C$_3$H$_5$NO$_3$, C$_3$H$_8$O and C$_4$H$_7$N across 10 seeds. Dotted lines denote optimal return for each bag, respectively. Error bars show two standard errors. The plot is smoothed for better readability. (b) Selection of molecular structures generated by trained models for the bag C$_3$H$_5$NO$_3$. For the bags C$_3$H$_8$O and C$_4$H$_7$N, see the Appendix.

Figure 8. Average offline performance on the solvation task with 5 H$_2$O molecules across 10 seeds. Error bars show two standard errors. The plot is smoothed for better readability. The dotted line denotes the optimal return. A selection of molecular clusters generated by trained models are shown in solid circles; for comparison, a stable configuration obtained through structure optimization is depicted in a dashed circle.

6. Discussion

This work is a first step towards general molecular design through RL in Cartesian coordinates. One limitation of the current formulation is that we need to provide bags for which we know good solutions exist when placed completely. While having the possibility to provide such prior knowledge can be beneficial, we are currently restricted to designing molecules of known formulas. A possible solution to this limitation is to provide bags that are larger than necessary, e.g. generated randomly or according to some fixed budget for each element, and enable the agent to stop before the bag is empty.

Compared to graph-based approaches, constructing molecules by sequentially placing atoms in Cartesian coordinates greatly increases the flexibility in terms of the type of molecular structures that can be built. However, it also makes the exploration problem more challenging: whereas in graph-based approaches a molecule can be expanded by adding a node and an edge, here, the agent has to learn to precisely position an atom in Cartesian coordinates from scratch. As a result, the molecules we generate are still considerably smaller. Several approaches exist to mitigate the exploration problem and improve scalability, including: 1) hierarchical RL, where molecular fragments or entire molecules are used as high-level actions; 2) imitation learning, in which known molecules are converted into expert trajectories; and 3) curriculum learning, where the complexity of the molecules to be built increases over time.

7. Conclusion

We have presented a novel RL formulation for molecular design in Cartesian coordinates, in which the reward function is based on quantum-mechanical properties such as the energy. We further proposed an actor-critic neural network architecture based on a translation and rotation invariant state-action representation. Finally, we demonstrated that our model can efficiently solve a range of molecular design tasks from our MOLGYM RL environment from scratch.

In future work, we plan to increase the scalability of our approach and enable the agent to stop before a given bag is empty. Moreover, we are interested in combining the reward with other properties such as drug-likeliness and applying our approach to other classes of molecules, e.g. transition-metal catalysts.
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A. Quantum-Chemical Calculations

For the calculation of the energy $E$ we use the fast semi-empirical Parametrized Method 6 (PM6) (Stewart, 2007). In particular, we use the implementation from the software package SPARROW (Husch et al., 2018; Bosia et al., 2019). For each calculation, a molecular charge of zero and the lowest possible spin multiplicity are chosen. All calculations are spin-unrestricted.

Limitations of semi-empirical methods are highlighted in, for example, a recent work by Husch & Reiher (2018). More accurate methods such as approximate density functionals need to be employed especially for systems containing transition metals.

B. Learning the Dihedral Angle

We experimentally validate the benefits of learning $|\psi| \in [0, \pi]$ and $\kappa \in \{-1, 1\}$ instead of $\psi \in [-\pi, \pi]$ by comparing the two models on the single-bag task with bag CH$_4$ (methane). Methane is one of the simplest molecules that requires the model to learn a dihedral angle. As shown in Fig. 9, learning the sign of the dihedral angle separately (with $\kappa$) speeds up learning significantly. In fact, the ablated model (without $\kappa$) fails to converge to the optimal return even after 100\,000 steps (not shown).

![Figure 9. Average offline performance on the single-bag task for the bag CH$_4$ across 10 seeds. Estimating $\kappa$ and $|\psi|$ separately (with $\kappa$) significantly speeds up learning compared to estimating $\psi$ directly (without $\kappa$). Error bars show two standard errors. The plot is smoothed for better readability. The dotted line denotes the optimal return.](image)

C. Model Architecture

The model architecture is summarized in Table 1. We initialize the biases of each MLP with 0 and each weight matrix as a (semi-)orthogonal matrix. After each hidden layer, a ReLU non-linearity is used. The output activations are shown in Table 1. As explained in the main text, both MLP$_f$ and MLP$_c$ use a masked softmax activation function to guarantee that only valid actions are chosen. Further, we rescale the continuous actions $[\mu_d, \mu_\alpha, \mu_\psi] \in [-1, 1]^3$ predicted by MLP$_\text{cont}$ to ensure that $\mu_d \in [\mu_{\text{min}}, \mu_{\text{max}}], \mu_\alpha \in [0, \pi]$ and $\mu_\psi \in [0, \pi]$. For more details on the SchNet, see the original work (Schütt et al., 2018b).

| Operation | Dimensionality | Activation |
|-----------|----------------|------------|
| SchNet    | $n(C) \times 4, *$ | $n(C) \times 4 \times 64$ | *(cf. Table 5)* |
| MLP$_f$   | $\epsilon_{\text{max}}, 128, 32$ | linear |
| pool      | $32, n(C) \times 32$ | — |
| MLP$_c$   | $n(C) \times (64, 32), n(C) \times 96$ | — |
| select    | $n(C) \times 96, n(C) \times 128, n(C) \times 1$ | softmax |
| MLP$_\text{cont}$ | $n(C) \times 96, 96, 128, 3$ | tanh |
| pooling   | $2 \times 96, 2 \times 128, 2 \times 1$ | softmax |
| MLP$_\beta$ | $n(C) \times 96, 96, 128, 1$ | linear |

D. Experimental Details

D.1. Computing Infrastructure

All experiments were run on a 16-core Intel Xeon Skylake 6142 CPU @ 2.6GHz with 96GB RAM.

D.2. Hyperparameters

We manually performed an initial hyperparameter search on a single holdout validation seed. The considered hyperparameters and the selected values are listed in Table 2 (single-bag), Table 3 (multi-bag) and Table 4 (solvation). The hyperparameters used for SchNet are shown in Table 5. An overview of which bags from the QM9 dataset are used in each experiment is given in Table 6.

E. Baselines

Below, we report how the baselines for the single-bag and multi-bag tasks were derived. First, we took all molecular structures for a given chemical formula (i.e. bag) from the QM9 dataset (Ruddigkeit et al., 2012; Ramakrishnan et al., 2014). Subsequently, we performed a structure optimization using the PM6 method (as described in Section A) on the structures. This was necessary as the structures in this dataset were optimized with a different quantum-chemical method. Then, the most stable structure was selected and considered the optimal structure for this chemical formula; the remaining structures were discarded. Since the undiscounted return is path independent, we determined the return...
Table 2. Hyperparameters for the single-bag task. Adapted values for the scalability (large) experiment are in parentheses.

| Hyperparameter            | Search set     | Value (large) |
|---------------------------|----------------|---------------|
| Range $[d_{\text{min}}, d_{\text{max}}]$ (Å) | —              | [0.95, 1.80]  |
| Max. atomic number $c_{\text{max}}$       | —              | 10            |
| Workers                    | —              | 16            |
| Clipping $\epsilon$        | —              | 0.2           |
| Gradient clipping          | —              | 0.5           |
| GAE parameter $\lambda$    | —              | 0.95          |
| VF coefficient $c_1$       | —              | 1             |
| Entropy coefficient $c_2$  | {0.00, 0.01, 0.03} | 0.01          |
| Training epochs            | {5, 10}        | 5             |
| Adam stepsize              | $\{10^{-4}, 3 \times 10^{-4}\}$ | $3 \times 10^{-4}$ |
| Discount $\gamma$          | {0.99, 1.00}   | 0.99          |
| Time horizon $T$           | {192, 256}     | 192 (256)     |
| Minibatch size             | {24, 32}       | 24 (32)       |

Table 3. Hyperparameters for the multi-bag task.

| Hyperparameter            | Search set     | Value         |
|---------------------------|----------------|---------------|
| Range $[d_{\text{min}}, d_{\text{max}}]$ (Å) | —              | [0.95, 1.80]  |
| Max. atomic number $c_{\text{max}}$       | —              | 10            |
| Workers                    | —              | 16            |
| Clipping $\epsilon$        | —              | 0.2           |
| Gradient clipping          | —              | 0.5           |
| GAE parameter $\lambda$    | —              | 0.95          |
| VF coefficient $c_1$       | —              | 1             |
| Entropy coefficient $c_2$  | {0.00, 0.01, 0.03} | 0.01          |
| Training epochs            | {5, 10}        | 5             |
| Adam stepsize              | $\{10^{-4}, 3 \times 10^{-4}\}$ | $3 \times 10^{-4}$ |
| Discount $\gamma$          | {0.99, 1.00}   | 0.99          |
| Time horizon $T$           | {384, 512}     | 384           |
| Minibatch size             | {48, 64}       | 48            |

Table 4. Hyperparameters for the solvation task.

| Hyperparameter            | Search set     | Value         |
|---------------------------|----------------|---------------|
| Range $[d_{\text{min}}, d_{\text{max}}]$ (Å) | —              | [0.90, 2.80]  |
| Max. atomic number $c_{\text{max}}$       | —              | 10            |
| Distance penalty $\rho$ | —              | 0.01          |
| Workers                    | —              | 16            |
| Clipping $\epsilon$        | —              | 0.2           |
| Gradient clipping          | —              | 0.5           |
| GAE parameter $\lambda$    | —              | 0.95          |
| VF coefficient $c_1$       | —              | 1             |
| Entropy coefficient $c_2$  | {0.00, 0.01, 0.03} | 0.01          |
| Training epochs            | {5, 10}        | 5             |
| Adam stepsize              | $\{10^{-4}, 3 \times 10^{-4}\}$ | $3 \times 10^{-4}$ |
| Discount $\gamma$          | {0.99, 1.00}   | 0.99          |
| Time horizon $T$           | {384, 512}     | 384           |
| Minibatch size             | {48, 64}       | 48            |

Table 5. Hyperparameters for SchNet (Schütt et al., 2018a) used in all experiments.

| Hyperparameter            | Search set     | Value         |
|---------------------------|----------------|---------------|
| Number of interactions    | —              | 3             |
| Cutoff distance (Å)       | —              | 5.0           |
| Number of filters         | —              | 128           |
| Number of atomic basis functions | {32, 64, 128} | 64           |

F. Results

F.1. Single-bag Task

In Fig. 10, we show a selection of molecular structures generated by trained models for the bags C$_4$H$_9$N and C$_3$H$_8$O. Further, since the agent is agnostic to the concept of molecular bonds, it is able to build multiple molecules if it results in a higher return. An example of a bimolecular structure generated by a trained model for the bag C$_3$H$_8$O is shown in Fig. 11. Finally, in Fig. 12, we showcase a set of generated molecular structures that are not chemically valid.

![Figure 10](image_url) Selection of molecular structures generated by trained models for the bags C$_4$H$_9$N (a) and C$_3$H$_8$O (b).
### Table 6. QM9 bags used in the experiments.

| Experiment          | QM9 Bags Used                                                                 |
|---------------------|-------------------------------------------------------------------------------|
| Single-bag          | C₂H₂O₂, CH₃NO, CH₃O                                                        |
| Multi-bag           | H₂O, CHN, C₂N₂, H₃N, C₂H₂, CH₂O, C₂HNO, N₂O, C₃HN, CH₄, CF₄              |
| Single-bag (large)  | C₃H₅NO₃, C₄H₂N, C₃H₈O                                                    |

Figure 11. Bimolecular structure generated by a trained model for the bag C₃H₈O in the single-bag task.

**F.2. Solvation Task**

In Fig. 13, we report the average offline performances of agents placing 5 H₂O molecules around the solutes (i.e., C₀) acetonitrile and ethanol. It can be seen that the agents are able to accurately place water molecules such that they interact with the solute. However, we stress that more accurate quantum-chemical method need to be employed in the reward function to describe hydrogen bonds to chemical accuracy.

In Fig. 14, we compare the average offline performance of two agents placing in total 10 H and 5 O atoms around a formaldehyde molecule. One agent is given 5 H₂O bags consecutively following the protocol of the solvation task as described in the main text, another is given a single H₁₀O₅ bag. Their average offline performances are shown in Fig. 14 in blue and red, respectively. It can be seen that giving the agent 5 H₂O bags one at a time instead of a single H₁₀O₅ bag improves performance.

Figure 12. Selection of chemically invalid molecular structures generated by trained models for the bags C₃H₈O (a), C₃H₅NO₃ (b), and C₃H₇N (c).

Figure 13. Average offline performances across 10 seeds on the solvation task with n = 5 and the initial states being acetonitrile and ethanol. Error bars show two standard errors. The plot is smoothed for better readability. The dotted lines denote the optimal returns. A selection of molecular clusters generated by models trained on the H₁₀O₅ task are shown in circles.

Figure 14. Average offline performance for the solvation task with n = 5 (blue) and placing atoms from a single H₁₀O₅ bag (red). In both experiments, C₀ is formaldehyde. Error bars show two standard errors. The plot is smoothed for better readability. The dotted line denotes the optimal return. A selection of molecular clusters generated by models trained on the H₁₀O₅ task are shown in red solid circles; for comparison, a stable configuration obtained through structure optimization is depicted in a black dashed circle.