STRUCTURE-BASED DRUG DESIGN VIA SEMI-EQUIVARIANT CONDITIONAL NORMALIZING FLOWS

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ABSTRACT

We propose an algorithm for learning a conditional generative model of a molecule given a target. Specifically, given a receptor molecule that one wishes to bind to, the conditional model generates candidate ligand molecules that may bind to it. Our problem is formulated mathematically as learning conditional distributions between two 3D graphs. The distribution should be invariant to rigid body transformations that act *jointly* on the ligand and the receptor; it should also be invariant to permutations of either the ligand or receptor atoms. Our learning algorithm is based on a continuous normalizing flow. We establish semi-equivariance conditions on the flow which guarantee the aforementioned invariance conditions on the conditional distribution. We propose a graph neural network architecture which implements this flow, and which is designed to learn effectively despite the vast differences in size between the ligand and receptor. We evaluate our method on the CrossDocked2020 dataset, displaying high quality performance in the key ΔBinding metric. We also demonstrate how the learned density may be usefully employed to define a scoring function.

1 INTRODUCTION

We consider a central problem in drug design: the problem of generating diverse ligands that may bind with receptors. In this paper, we model molecules as 3D graphs, that is graphs whose vertices (i.e. atoms) correspond to points in $\mathbb{R}^3$. Given this, our problem may be formulated mathematically as learning conditional distributions of the form $p(G|\hat{G})$, where G and $\hat{G}$ are two 3D graphs: G represents the ligand, and $\hat{G}$ represents the receptor.

We present a method for learning such conditional distributions based on continuous normalizing flows. A critical aspect of the problem is to learn a distribution which respects the correct invariances. Specifically, there must be an invariance to rigid motions which is a kind of "conditional invariance" which is expressed jointly in terms of G and $\hat{G}$. We are also interesting in capturing invariance to permutations of either the ligand or receptor atoms. Our main theoretical result is that this conditional invariance can be satisfied by a novel form of *semi-equivariance* of the normalizing flow. We then empirically demonstrate the utility of our technique in structure-based drug design given a target receptor.

Ragoza et al. (2022) is a pioneering work in this area, which uses a conditional VAE on an image-like discretized 3D atomic density grid; a post-sampling step converts this grid structure into molecules using an atom fitting algorithm. A more recent class of works (Luo et al., 2021; Liu et al., 2022; Peng et al., 2022; Drotár et al., 2021) use an auto-regressive approach. Luo et al. (2021) derive a model which captures the probability that a point 3D space is occupied by an atom of a particular chemical element. Liu et al. (2022) propose the GraphBP framework, which eliminates the need to discretize space; to place a new atom, they generate its atom type and relative location while preserving the equivariance property. Peng et al. (2022) include bond distributions and the corresponding bond prediction during the generation process. (Schneuing et al., 2022; Lin et al., 2022) employ a diffusion model, while Schneuing et al. (2022) develop an equivariant approach. By contrast, (Li et al., 2021; Thomas et al., 2021; Fialková et al., 2021; Fu et al., 2022) use approaches based on reinforcement

learning. Other works include fragment-based ligand generation, in which new molecular fragments are sequentially attached to the growing molecule (Powers et al., 2022); abstraction of the geometric interaction features of the receptor–ligand complex to a latent space, for generative models such as Bayesian sampling (Wang et al., 2022b) and RNNs (Zhang & Chen, 2022); and use of experimental electron densities as training data for the conditional generative model (Wang et al., 2022a).

We train our method on the CrossDocked2020 dataset (Francoeur et al., 2020) and attain high quality performance, in terms of both chemical validity and ΔBinding. Furthermore, an advantage of the normalizing flow formalism is that it gives an explicit form for the learned density; we show how this density may be used effectively to define a scoring function.

2 Semi-Equivariant Conditional Normalizing Flows

2.1 Notation and Goal

Notation A 3D graph is given by $G = (N, V, E, A)$, where N is the number of vertices; V is the list of vertices; E is the list of edges; and A is the set of global graph properties, i.e. properties which apply to the entire graph. The vertex list[1] is $V = (\mathbf{v}_i)_{i=1}^N$ where each vertex is specified by a vector $\mathbf{v}_i = (\mathbf{x}_i, \mathbf{h}_i)$; in which $\mathbf{x}_i \in \mathbb{R}^3$ is the position of the vertex, and $\mathbf{h}_i \in \mathbb{R}^{d_h}$ contains the properties of the vertex. The edges in the graph G are undirected, and the edge list E is specified by a neighbourhood relationship. Specifically, if η_i is the set of vertex i's neighbours, then we write $E = (\mathbf{e}_{ij})_{i<j:j\in\eta_i}$. The vector $\mathbf{e}_{ij} \in \mathbb{R}^{d_e}$ contains the properties of the edge connecting vertices i and j. Finally, the graph properties are given by K individual properties, i.e. $A = (\mathbf{a}_1, \ldots, \mathbf{a}_K)$.

Rigid Transformations The action of a rigid transformation $T \in E(3)$ on a graph G is given by $TG = (TN, TV, TE, TA)$ where $TV = (T\mathbf{v}_i)_{i=1}^N$ with $T\mathbf{v}_i = (T\mathbf{x}_i, \mathbf{h}_i)$. The other variables are unaffected by T; that is $TN = N$, $TE = E$, and $TA = A$.

Permutations The action of a permutation $\pi \in \mathbb{S}_N$ on a graph G with $N(G) = N$ is given by $\pi G = (\pi N, \pi V, \pi E, \pi A)$ where $\pi V = (\mathbf{v}_{\pi_i})_{i=1}^N$ and $\pi E = \left(\mathbf{e}_{\pi_i \pi_j}\right)_{i<j:j\in\eta_i}$. The other variables are unaffected by π; that is, $\pi N = N$ and $\pi A = A$.

Goal We assume that we have both a receptor and a ligand, each of which is specified by a 3D graph. We denote the receptor as $\hat{G} = (\hat{N}, \hat{V}, \hat{E}, \hat{A})$ and the ligand as $G = (N, V, E, A)$. Our goal is to learn a conditional generative model: given the receptor, we would like to generate possible ligands. Formally, we want to learn $p(G|\hat{G})$. We want our generative model to respect two types of symmetries, expressed mathematically as:

$$p(TG|T\hat{G}) = p(G|\hat{G}) \;\forall T \in E(3) \quad \text{and} \quad p(\pi G|\hat{\pi}\hat{G}) = p(G|\hat{G}) \;\forall \pi \in \mathbb{S}_N,\, \hat{\pi} \in \mathbb{S}_{\hat{N}} \tag{1}$$

The first condition says that if we transform both the ligand and the receptor with the same rigid transformation, the probability should not change. The second condition says that permuting the order of either the ligand or the receptor should not affect the probability.

General Approach We design our generative model $p(G|\hat{G})$ by using a Markov decomposition:

$$p(G|\hat{G}) = p(N, V, E, A|\hat{G}) = p(N|\hat{G}) \cdot p(V|N, \hat{G}) \cdot p(E|N, V, \hat{G}) \cdot p(A|N, V, E, \hat{G}) \tag{2}$$

In this paper, we focus on the first two terms on the right-hand side of the equation: the Number Distribution $p(N|\hat{G})$ and the Vertex Distribution $p(V|N, \hat{G})$. The latter two terms may also be specified (e.g. see Appendix C), but are not the focus of our investigation in this paper. The conditional probabilistic approach is illustrated in Figure 3 in the Appendix.

2.2 Two Flavours of EGNNs

In order to incorporate the relevant invariance properties, it will be helpful to use Equivariant Graph Neural Networks, also known as EGNNs (Satorras et al., 2021b). We now introduce two separate flavours of EGNNs, one which applies to the receptor alone, and a second which applies to the combination of the receptor and the ligand.

[1] We use lists, rather than sets, so as to make the action of permutations clear.

Receptor EGNN This is the standard EGNN which is described in (Satorras et al., 2021b), applied to the receptor. As we are referring to the receptor, we use hatted variables:

$$\hat{\mathbf{m}}_{ij}^{\ell} = \hat{\phi}_e(\hat{\mathbf{h}}_i^{\ell}, \hat{\mathbf{h}}_j^{\ell}, \|\hat{\mathbf{x}}_i^{\ell} - \hat{\mathbf{x}}_j^{\ell}\|^2, \|\hat{\mathbf{x}}_i^{0} - \hat{\mathbf{x}}_j^{0}\|^2, \hat{\mathbf{e}}_{ij}, \{\hat{\mathbf{a}}_k\}) \qquad \hat{b}_{ij}^{\ell} = \sigma(\hat{\phi}_b(\hat{\mathbf{m}}_{ij}^{\ell})) \qquad \hat{\mathbf{m}}_i^{\ell} = \sum_{j \in \hat{\eta}_i} \hat{b}_{ij}^{\ell} \hat{\mathbf{m}}_{ij}^{\ell}$$

$$\hat{\mathbf{x}}_i^{\ell+1} = \hat{\mathbf{x}}_i^{\ell} + \hat{\phi}_x(\hat{\mathbf{m}}_{ij}^{\ell}) \sum_{j \neq i} \frac{(\hat{\mathbf{x}}_i^{\ell} - \hat{\mathbf{x}}_j^{\ell})}{\|\hat{\mathbf{x}}_i^{\ell} - \hat{\mathbf{x}}_j^{\ell}\| + 1} \qquad \hat{\mathbf{h}}_i^{\ell+1} = \hat{\mathbf{h}}_i^{\ell} + \hat{\phi}_h(\hat{\mathbf{h}}_i^{\ell}, \hat{\mathbf{m}}_i^{\ell}) \tag{3}$$

The particular Receptor EGNN is thus specified by the functions $\hat{\phi}_e, \hat{\phi}_b, \hat{\phi}_x, \hat{\phi}_h$.

Conditional EGNN It is possible to design a joint EGNN on the receptor and the ligand, by constructing a single graph to capture both. The main problem with this approach is that the receptor can be much larger (by 1-2 orders of magnitude) than the ligand. As a result, this naive approach will lead to a situation in which the ligand is "drowned out" by the receptor, making it difficult to learn about the ligand. We therefore take a different approach: we compute summary signatures of the receptor based on the Receptor EGNN, and use these as input to an EGNN on the ligand. Our signatures will be based on the feature variables $\hat{\mathbf{h}}_j^{\ell}$ from each layer $\ell = 1, \ldots, \hat{L}$. These variables are invariant to rigid body transformations by construction; furthermore, we can introduce permutation invariance by averaging, that is by using $\hat{\mathbf{h}}_{av}^{\ell} = \Sigma_{j=1}^{\hat{N}} \hat{\mathbf{h}}_j^{\ell} / \hat{N}$. Thus, the receptor at layer ℓ of the ligand's EGNN is summarized by the signature $\hat{\mathbf{g}}^{\ell}$ which depends on both $\{\hat{\mathbf{h}}_{av}^{\ell}\}$, as well as the time t of the normalizing flow ODE (to be introduced shortly in Section 2.4):

$$\hat{\mathbf{g}}^0 = \phi_g^0\left(\hat{\mathbf{h}}_{av}^1, \ldots, \hat{\mathbf{h}}_{av}^{\hat{L}}, t\right) \qquad \text{and} \qquad \hat{\mathbf{g}}^{\ell} = \phi_g^{\ell}\left(\hat{\mathbf{g}}^{\ell-1}\right) \quad \ell = 1, \ldots, L \tag{4}$$

The Conditional EGNN is then specified by a form similar to the equations in (3), but in which the functions $\phi_e, \phi_b, \phi_x, \phi_h$ (now non-hatted, as we are referring to the ligand) each have an additional dependence on the receptor signatures $\{\hat{\mathbf{g}}^{\ell}\}_{\ell=1}^{L}$. Further details are in Appendix A.

2.3 The Number Distribution: $p(N|\hat{G})$

Construction Given the invariance conditions described in Equation (1), we propose the following distribution. Let $\boldsymbol{\zeta}_N$ indicate a one-hot vector, where the index corresponding to N is filled in with a 1. Based on the output of the receptor EGNN, compute

$$p(N|\hat{G}) = \boldsymbol{\zeta}_N^T F_2\left(\Sigma_{i=1}^{\hat{N}} F_1(\hat{\mathbf{h}}_i^L)/\hat{N}\right) \tag{5}$$

where F_1 and F_2 are multilayer perceptrons, and the last layer of F_2 is a softmax of size equal to the maximum number of atoms allowed. Since we use the $\hat{\mathbf{h}}_i^L$ vectors (and not the $\hat{\mathbf{x}}_i^L$ vectors), we have rigid motion invariance, as $T\hat{\mathbf{h}}_i^L = \hat{\mathbf{h}}_i^L$. Since we use an average, we have permutation invariance.

Loss Function The loss function is straightforward: it is simply the negative log-likelihood of the number distribution, i.e. $L(\theta) = \mathbb{E}_{G,\hat{G}}[-\log p(N|\hat{G};\theta)]$.

2.4 The Vertex Distribution: $p(V|N,\hat{G})$ via Continuous Normalizing Flows

General Notation Define a vectorization operation on the vertex list V, which produces a vector $\mathbf{v}$; we refer to this as a *vertex vector*. Recall that $V = (\mathbf{v}_i)_{i=1}^N$ where $\mathbf{v}_i = (\mathbf{x}_i, \mathbf{h}_i)$. Let

$$\mathbf{x} = \texttt{concat}(\mathbf{x}_1, \ldots, \mathbf{x}_N) \qquad \mathbf{h} = \texttt{concat}(\mathbf{h}_1, \ldots, \mathbf{h}_N) \qquad \mathbf{v} = \texttt{concat}(\mathbf{x}, \mathbf{h}) \tag{6}$$

The vertex vector $\mathbf{v} \in \mathbb{R}^{d_v^N}$ where $d_v^N = (d_h + 3)N$. We denote the mapping from the vertex list V to the vertex vector $\mathbf{v}$ as the vectorization operation $\texttt{vec}(\cdot)$: we write $\mathbf{v} = \texttt{vec}(V)$ and $V = \texttt{vec}^{-1}(\mathbf{v})$. We have already described the action of rigid body transformations T and permutations π on the vertex list V in Section 2.1. It is easy to extend this to vertex vectors $\mathbf{v}$ using the $\texttt{vec}$ operation; we have $T\mathbf{v} = \texttt{vec}(T\texttt{vec}^{-1}(\mathbf{v}))$ and $\pi\mathbf{v} = \texttt{vec}(\pi\texttt{vec}^{-1}(\mathbf{v}))$.

Given the above, it is sufficient for us to describe the distribution $p_{vec}(\mathbf{v}|\hat{G})$ from which the vertex distribution $p(V|N,\hat{G})$ follows directly, $p(V|N,\hat{G}) = p_{vec}(\texttt{vec}(V)|\hat{G})$. Note that we have suppressed N in the condition in $p_{vec}(\cdot)$, as $\mathbf{v}$ is a vector of dimension d_v^N, so the N dependence is already implicitly encoded.

Complex-to-Ligand Mapping and Semi-Equivariance Let γ be a function which takes as input the complex consisting of both the ligand G and receptor $\hat{G}$, and outputs a new vertex list V' for the ligand G:

$$V' = \gamma(G, \hat{G}) \tag{7}$$

We refer to γ as a *Complex-to-Ligand Mapping*. A rigid body transformation $T \in E(3)$ consists of a rotation and translation; let the rotation be denoted as T_{rot}. Then we say that γ is *rotation semi-equivariant* if

$$\gamma(T_{rot}G, T\hat{G}) = T_{rot}\gamma(G, \hat{G}) \quad \text{for all } T \in E(3) \tag{8}$$

γ is said to be *permutation semi-equivariant* if

$$\gamma(\pi G, \hat{\pi}\hat{G}) = \pi\gamma(G, \hat{G}) \quad \text{for all } \pi \in \mathbb{S}_N \text{ and } \hat{\pi} \in \mathbb{S}_{\hat{N}} \tag{9}$$

Note in the definitions of both types of semi-equivariance, the differing roles played by the ligand and receptor; as the equivariant behaviour only applies to the ligand, we have used the term semi-equivariance.

Conditional Flow Let γ be a Complex-to-Ligand Mapping. If $\mathbf{v}$ is a vertex vector, define $G_{\mathbf{v}}$ to be the graph G with the vertex set replaced by $\texttt{vec}^{-1}(\mathbf{v})$. Then the following ordinary differential equation is referred to as a *Conditional Flow*:

$$\frac{d\mathbf{u}}{dt} = \texttt{vec}\left(\gamma(G_{\mathbf{u}}, \hat{G})\right), \quad \text{with } \mathbf{u}(0) = \mathbf{z} \tag{10}$$

where the initial condition $\mathbf{z} \sim \mathcal{N}(0, \mathbf{I})$ is a Gaussian random vector of dimension d_v^N, and the ODE is run until $t = 1$. $\mathbf{u}(1)$ is thus the output of the Conditional Flow.

Vertex Distributions with Appropriate Invariance We now have the necessary ingredients to construct a distribution $p_{vec}(\mathbf{v}|\hat{G})$ which yields a vertex distribution $p(V|N, \hat{G})$ that satisfies the required invariance conditions. The following is our main result (proof in Appendix B):

Theorem (Invariant Vertex Distribution)**.** *Let $\mathbf{u}(1)$ be the output of a Conditional Flow specified by the Complex-to-Ligand Mapping γ. Let the mean position of the receptor be given by $\hat{\mathbf{x}}_{av} = \frac{1}{\hat{N}}\sum_{i=1}^{\hat{N}} \hat{\mathbf{x}}_i$, and define the following quantities*

$$\alpha = \frac{N}{N + \hat{N}} \quad \Omega_{\hat{G}} = \begin{bmatrix} \mathbf{I}_{3N} - \frac{\alpha}{N}\mathbf{1}_{N\times N} \otimes \mathbf{I}_3 & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{d_h N} \end{bmatrix} \quad \omega_{\hat{G}} = \begin{bmatrix} -(1-\alpha)\mathbf{1}_{N\times 1} \otimes \hat{\mathbf{x}}_{av} \\ \mathbf{0} \end{bmatrix} \tag{11}$$

where $\otimes$ indicates the Kronecker product. Finally, let $\mathbf{v} = \Omega_{\hat{G}}^{-1}\left(\mathbf{u}(1) - \omega_{\hat{G}}\right)$. Suppose that γ is both rotation semi-equivariant and permutation semi-equivariant. Then the resulting distribution on $\mathbf{v}$, that is $p_{vec}(\mathbf{v}|\hat{G})$, yields a vertex distribution $p(V|N, \hat{G}) = p_{vec}(\texttt{vec}(V)|\hat{G})$ that satisfies the invariance conditions in Equation (1).

Designing the Complex-to-Ligand Mapping For the Complex-to-Ligand Mapping, we choose to use the Conditional EGNN; that is, $V' = \gamma(G, \hat{G})$ is given by $v_i' = (\mathbf{x}_i^L, \mathbf{h}_i^L)$, the output of the EGNN's final layer. In practice, we use a slightly modified version of the foregoing, that is $v_i' = (\mathbf{x}_i^L - \mathbf{x}_i, \mathbf{h}_i^L)$, which we have found to converge well empirically. The rotation semi-equivariance of γ (both versions - ordinary and modified) follows straightforwardly from the rotation semi-equivariance of EGNNs and the rotation invariance of the receptor signatures $\{\hat{\mathbf{g}}^\ell\}_{\ell=1}^L$. Similarly, the permutation semi-equivariance follows from the permutation equivariance of EGNNs and the permutation invariance of the receptor signatures.

Loss Function The loss function and its optimization are implemented using standard techniques for continuous normalizing flows (Chen et al., 2018b; Grathwohl et al., 2018; Chen et al., 2018a). If the feature vectors contain discrete variables, then techniques based on variational dequantization (Ho et al., 2019) and argmax flows (Hoogeboom et al., 2021) can be used, for ordinal and categorical features respectively. This is parallel to the treatment in (Satorras et al., 2021a). Issues related to ODE stiffness naturally arise in this scenario, and are treated using various techniques from the literature (Finlay et al., 2020; Kelly et al., 2020; Yang & Karniadakis, 2020; Onken et al., 2021).

3 APPLICATIONS TO TARGET-AWARE MOLECULE GENERATION

3.1 SETTING

We now apply the theory we have developed to the problem of target-aware structure based molecule generation. The design of new molecules is an important topic, with applications in medicine, biochemistry, and materials science. Recently there have been quite a number of promising directions for applying machine learning techniques to this problem, including those which produce a generative model of molecules. Many approaches have focused on the unconditional setting, in which the goal is simply to produce molecules without regard for a more specific purpose; such techniques can, for example, effectively produce "drug-like" molecules. By contrast, we are interested in the conditional setting. In particular, we are interested in learning a conditional distribution of the form $p(G|\hat{G})$, which tells us which ligands better match a given receptor. Specifically, we assume that we are given a target receptor molecule; the aim is then to generate ligand molecules that may successfully bind to this receptor. This kind of conditional generative model is very useful in the context of drug design, in which one often has a target (receptor) in mind, and the goal is then to find drugs (ligands) which will bind to the target. Note that our approach of using a *probabilistic* generative model, from which one can generate multiple samples, is quite important from a practical perspective. This is because not all ligand candidates will be equally suitable experimentally, due to considerations such as toxicity; thus, it is important to generate multiple candidates. Furthermore, given a both a receptor and a ligand, the conditional probability $p(G|\hat{G})$ provides a useful indicator of the quality of the binding interaction between the two molecules, which can be used as a kind of scoring function. In what follows, we will explore both the generation and scoring aspects of the learned conditional distribution $p(G|\hat{G})$.

3.2 EXPERIMENTAL SETUP

Molecular Dataset Datasets with a large number of receptor-ligand complexes are critical to our endeavour. Many models have relied on the high quality PDBbind dataset which curates the Protein Data Bank (PDB) (Liu et al., 2017); however, for the training of generative models, this dataset is relatively small. CrossDocked2020 (Francoeur et al., 2020) is the first large-scale standardized dataset for training ML models with ligand poses cross-docked against non-cognate receptor structure, greatly expanding the number of poses available for training. The dataset is organized by clustering of similar binding pockets across the PDB; each cluster contains ligands cross-docked against all receptors in the pocket. Each receptor-ligand structure also contains information indicating the nature of the docked pair, such as root mean squared deviation (RMSD) to the reference crystal pose and Vina cross-docking score (Trott & Olson, 2010) as implemented in Smina (Koes et al., 2013). The dataset contains 22.5 million poses of ligands docked into multiple similar binding pockets across the PDB. We use the authors' suggested split into training and validation sets (Francoeur et al., 2020). This dataset contains docked receptor-ligand pairs whose binding pose RMSD is lower than 2Å. Based on considerations of training duration, we keep only those data points whose ligand has 30 atoms or fewer with atom types in {C, N, O, F}. We also keep only data points with potentially valid ligand-protein binding properties, i.e. whose ligands do not contain duplicate vertices and whose predicted Vina scores (Trott & Olson, 2010) are within distribution. The refined datasets consist of 132,863 training data points and 63,929 validation data points.

Features The ligand features that we wish to predict include the atom type $\in$ {C, N, O, F} (categorical); the stereo parity $\in$ {not stereo, odd, even} (categorical); and charge $\in \{-1, 0, +1\}$ (ordinal). The receptor features that are used are computed with the Graphein library (Jamasb et al., 2022). The vertex features include: the atom type $\in$ {C, N, O, S, "other"} where "other" is a catch-all for less common atom types[2] (categorical); the Meiler Embeddings (Meiler et al., 2001) (continuous $\in \mathbb{R}^7$). The bond (edge) properties include: the bond order $\in$ {Single, Double, Triple} (categorical); covalent bond length (continuous $\in \mathbb{R}$). The receptor overall graph properties ($\hat{A}$) contain the weight of all chains contained within a polypeptide structure, see (Jamasb et al., 2022).

Training Training the model takes approximately 18 days using a single NVIDIA A100 GPU for 39 epochs. We proactively stopped the training procedure when the negative log-likelihood (NLL)

[2]Specifically: Na, Mg, P, Cl, K, Ca, Co, Cu, Zn, Se, Cd, I, Hg.

Validity	
Ours	GraphBP
99.87%	99.75%

Bond Length Distribution			
	Ref. Mols.	Ours	GraphBP
mean	1.42	1.45	1.65
std	0.08	0.10	0.95

(a) Ligand validity and bond length distribution

ΔBinding	
Ours	GraphBP
35.7%	22.76%

Predicted Affinity Distribution			
	Ref. Mols.	Ours	GraphBP
mean	5.09	4.56	4.31
std	1.16	1.05	1.03

(b) ΔBinding and predicted affinity distribution

Table 1: Comparison of molecule validity and ΔBinding between proposed method and GraphBP.

term reached a low improvement rate between epochs. We train with the Adam optimizer, weight decay of 10^{-12}, batch size of 128, and learning rate of 2×10^{-4}. To improve the stability of the continuous flow model and to deal with ODE stiffness issues we use the ODE regularization term described in (Finlay et al., 2020) with a value of 10^{-3}; and perform gradient clipping, where the clipping term is set by calculating a moving average of 50 steps of the normalizing flow's gradient-norm. This is parallel to the treatment in (Satorras et al., 2021a). We use dopri5 (Runge-Kutta 4(5) of Dormand-Prince) as the ODE solver with relative (rtol) and absolute (atol) error tolerance values of 10^{-4}.

3.3 Results

We first evaluate the utility of our technique as a conditional generative model. Given a receptor, we generate ligands which may successfully bind to that receptor. To show that our method is competitive as a generative model we compare against Liu et al. (2022) – one of the recent works that showed promising results in similar settings. We then demonstrate the utility of our technique for indicating the nature of the interaction of ligands with their corresponding binding site. The trained model provides the conditional probability, $p(G|\hat{G})$, which defines the likelihood of a binding event occurring given a ligand, based on the presence of a specific target receptor.

Conditional Generative Model We perform inference using the method suggested in the baseline (Liu et al., 2022). Given a receptor, we sample from the learned distribution, which generates the ligands' vertices; we then then apply OpenBabel (Hummell et al., 2021) to construct bonds. Evaluation follows the standard procedure (Ragoza et al., 2022; Liu et al., 2022). First, the receptor target is computed by taking all of the atoms in the receptor that are less than 15Å from the center of mass of the reference ligand. We then generate 100 ligands for each reference binding site in the evaluation set, and compute statistics (i.e. validity and ΔBinding, see below) on this set of samples. As in (Ragoza et al., 2022; Liu et al., 2022), 10 target receptors for evaluation; each target receptor has multiple associated ligands, leading to 90 (receptor, reference-ligand) pairs. We train the baseline technique (Liu et al., 2022) on our filtered dataset. More specifically, the training continues for 100 epochs, using the hyperparameters given in the paper, with one exception: we set the atom number range of the autoregressive generative process according to the atom distribution of the filtered dataset.

Validity The validity is defined as the percentage of molecules that are chemically valid among all generated molecules. A molecule is valid if it can be sanitized by RDKit; for an explanation of the sanitization procedure, see (Landrum, 2016). As shown in Table 1(a), our model produces ligands with a validity of 99.87%, surpassing the baseline, GraphBP. We also compute the distribution of bond distances of the two methods, and compare this to distribution of the reference ligands; see Figure 1. Our method's distribution is considerably closer to the reference distribution than GraphBP; some non-trivial fraction of the time, GraphBP produces unusual, very high bond distances. (In fact, we have discarded values higher than 10Å on the GraphBP plot so as to display the distributions on similar scales.) This impression is reinforced in Table 1(a) which compares the mean and standard deviation of these distributions.

Binding Affinity A more interesting measure than validity is ΔBinding, which measures the percentage of generated molecules that have higher predicted binding affinity to the target binding site than the corresponding reference molecule. To compute binding affinities, we follow the proce-

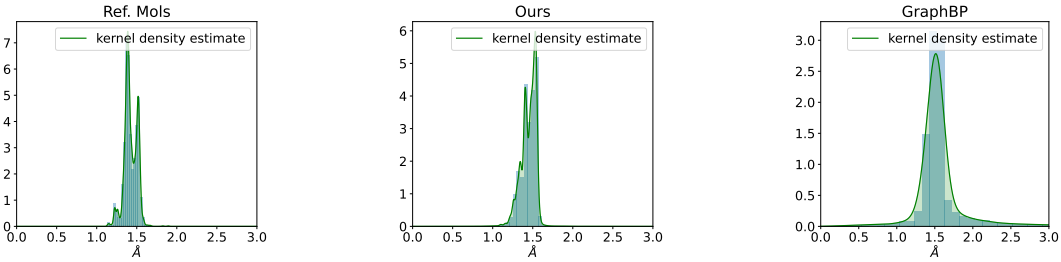

Figure 1: Normalized histogram of relative distances between atoms

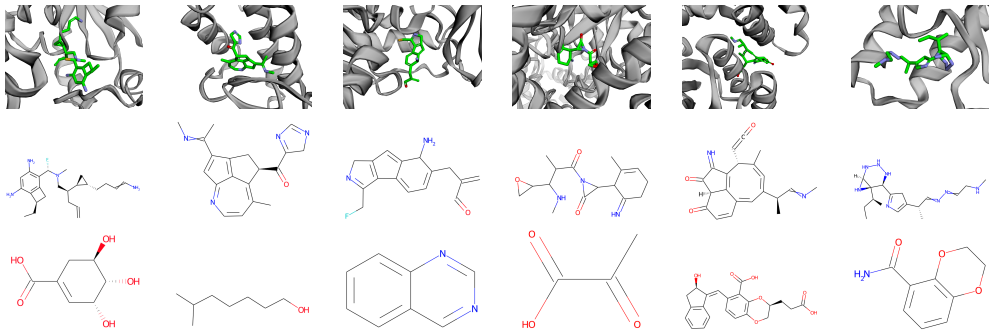

Figure 2: Comparison between generated 3D molecules for target binding-site and reference molecules. Receptor IDs, left to right: 1zyu, 2qu9, 2hw1, 3lcg, 3zt3, 5lvq. Top: generated ligand (colour) + receptor. Middle: generated ligand chemical structure. Bottom: reference ligand chemical structure.

dure used by GraphBP. Briefly, we refine the generated 3D molecules by Universal Force Field (UFF) minimization (Rappé et al., 1992); then, Vina minimization and CNN scoring are applied to both generated and reference molecules by using gnina, a molecular docking program (McNutt et al., 2021). As can be seen in Table 1(b), our result improves significantly on the baseline. Raw GraphBP attains ΔBinding = 13.45%. By playing with the minimum and the maximum atom number of the baseline autoregressive model, we were able to improve this to 22.76%; however, note that this results in a reduction in validity from 99.75% to 99.54%. Our method attains ΔBinding = 35.7%, which is a relative improvement of 56.81% over the better of the two GraphBP scores.

Qualitative Results We show examples of generated ligands in Figure 2, along with their chemical structures. Note that the structures of the generated molecules differ substantially from the reference molecules, indicating that the model has indeed learn to generalize to interesting novel structures.

Binding Likelihood The CrossDocked2020 dataset (Francoeur et al., 2020) includes quantitative measures indicating the quality of the binding of each docked receptor-ligand structure: (i) root mean squared deviation (RMSD) to the reference crystal pose; (ii) Vina cross-docking score (Trott & Olson, 2010) as implemented in Smina (Koes et al., 2013). Scoring functions that represent and predict ligand-protein interactions are important for applications in structure-based drug discovery (e.g. energy minimization, molecular dynamics simulations, and hit identification/lead optimization (DeWitte & Shakhnovich, 1996; McInnes, 2007; Charifson et al., 1999)), and particularly important for molecular docking where one seeks to predict the probability that binding occurs given a specified orientation and conformation (i.e. pose) of a ligand with respect to a target receptor (Su et al., 2018; Wang et al., 2003; Kitchen et al., 2004; Warren et al., 2006; Cheng et al., 2009; Huang & Zou, 2011; Trott & Olson, 2010; Cheng et al., 2012). We show how the conditional probability of our model may also be used as such an indicator. As we have seen in Section 2, our method is not trained on either of the binding quality indicators (Vina / RMSD), but instead is the result of learning a conditional probability distribution from ligand-receptor pairs; therefore it may be viewed as a complementary scoring method. Specifically, given the conditional probability $p(G|\hat{G})$ from the trained model, its negative log-likelihood (NLL) may be used a scoring method. Such an approach can be considered as a member of the family of knowledge-based methods (Muegge, 2000; Gohlke et al., 2000; Durrant & McCammon, 2011; Huang & Zou, 2011; Ballester & Mitchell, 2010; Hassan

Vina Score ↑			
	0 < Vina < 5	5 < Vina < 9	9 < Vina < 15
NLL ↓	-77.83	-144.30	-180.37

RMSD ↓			
	0 < RMSD < 1	1 < RMSD < 1.5	1.5 < RMSD < 2
NLL ↓	-137.70	-135.72	-130.67

(a) Ligand-receptor Vina score and RMSD vs average negative log-likelihood (NLL).

NLL under rigid transformation ↓						
			Rotation $\theta_x \sim U(-\frac{\pi}{u}, \frac{\pi}{u}), \theta_y \sim U(-\frac{\pi}{2u}, \frac{\pi}{2u}), \theta_z \sim U(-\frac{\pi}{u}, \frac{\pi}{u})$			
				$u = 20$	$u = 10$	$u = \frac{20}{3}$	$u = 5$
Translation $\tau \sim U\left([-t, t]^3\right)$			-134.34	-132.18	-124.15	-110.45	-91.94
	$t = 2$Å		-133.98	-130.80	-122.49	-109.22	-90.75
	$t = 5$Å		-129.28	-126.28	-118.57	-104.94	-86.02
	$t = 10$Å		-113.99	-111.80	-103.74	-91.15	-71.83
	$t = 15$Å		-88.85	-87.26	-76.85	-66.19	-45.89

(b) Average negative log-likelihood (NLL) under varying degrees of 3D rigid body transformations (translation and rotation) of ligand pose. $\theta_x, \theta_y, \theta_z$ are rotational Euler angles and $\tau \in \mathbb{R}^3$ is translation factor.

Table 2: Binding Likelihood. ↓ (↑) indicates stronger binding for lower (higher) values.

et al., 2018; Wójcikowski et al., 2019) which are constructed from entirely non-physical statistical potentials derived from known receptor-ligand complexes.

Vina and RMSD We split the 63,929 validation data points into three different groups according their Vina scores: (a) Vina $\in [0, 5]$ (b) Vina $\in (5, 9]$ (c) Vina $\in (9, 15]$. We randomly sample 10,000 receptor-ligand complexes from each group. Using the trained model, we calculate the average NLL for each group separately, where lower NLL indicates better conditional likelihood. The results in Table 2(a) show good correspondence between the Vina scores (higher values describe better affinity) with the binding likelihood outcomes of our model (lower NLL is better).

We then repeat this experiment, but using RMSD values instead of Vina scores. Again, we divide the validation set into three groups according to their RMSD values: (a) RMSD $\in [0, 1]$ (b) RMSD $\in (1, 1.5]$ (c) RMSD $\in (1, 2]$ (all values in Angstroms). Again, we see a good correspondence between the RMSD values (lower values describe a better connected complex) with the binding likelihood outcomes of our model (lower NLL is better).

Rigid Transformations The nature of binding between receptor and corresponding ligand is affected by the position of the ligand in the binding site. The ligand pose for each ligand-receptor pair in the validation data points was refined using the UFF force-field and then optimized with respect to the receptor structure using the Vina scoring function. We randomly select 10,000 validation data points and apply a rigid body transformation solely to the minimized ligand pose. Any such changes to the ligand pose with respect to the binding site potentially affect and reduce the binding affinity. The results in Table 2(b) show the NLL under varying degrees of rigid transformations. The more significant the transformation, the lower the binding likelihood (i.e. the higher the NLL) gets.

4 Conclusions and Directions for Future Work

We have presented a method for learning a conditional distribution of a ligand given a receptor. The method, which is based on a continuous normalizing flow, has provable invariance properties based on semi-equivariance conditions on the flow. We have demonstrated the usefulness of the method empirically; the method, which improves upon competing methods in the ΔBinding measure, promises the potential to generate previously undiscovered molecules with high binding affinity. We further show that the conditional probability model can be used as a kind of scoring function for ligand-receptor complexes. Such an approach can be considered as a member of the family of knowledge-based methods which are constructed from entirely non-physical statistical potentials derived from known receptor-ligand complexes.

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A THE CONDITIONAL EGNN

The receptor at layer ℓ of the ligand's EGNN is summarized by the signature $\hat{\mathbf{g}}^\ell$ which depends on both $\{\hat{\mathbf{h}}^\ell_{av}\}$ and the ODE time t:

$$\hat{\mathbf{g}}^0 = \phi^0_g\left(\hat{\mathbf{h}}^1_{av}, \ldots, \hat{\mathbf{h}}^{\hat{L}}_{av}, t\right) \qquad \text{and} \qquad \hat{\mathbf{g}}^\ell = \phi^\ell_g\left(\hat{\mathbf{g}}^{\ell-1}\right) \quad \ell = 1, \ldots, L \tag{12}$$

Note that there are $L+1$ separate functions $\{\phi^\ell_g\}_{\ell=0}^L$.

These invariant receptor signatures $\{\hat{\mathbf{g}}^\ell\}_{\ell=1}^L$ are then naturally incorporated into the Conditional EGNN as follows:

$$\mathbf{m}^\ell_{ij} = \phi_e\left(\mathbf{h}^\ell_i, \mathbf{h}^\ell_j, \|\mathbf{x}^\ell_i - \mathbf{x}^\ell_j\|^2, \|\mathbf{x}^0_i - \mathbf{x}^0_j\|^2, \hat{\mathbf{g}}^\ell, t\right) \qquad b^\ell_{ij} = \sigma(\phi_b(\mathbf{m}^\ell_{ij}, \hat{\mathbf{g}}^\ell)) \qquad \mathbf{m}^\ell_i = \sum_{j=1}^N b^\ell_{ij}\mathbf{m}^\ell_{ij}$$

$$\mathbf{x}^{\ell+1}_i = \mathbf{x}^\ell_i + \left(\sum_{j\neq i} \frac{(\mathbf{x}^\ell_i - \mathbf{x}^\ell_j)}{\|\mathbf{x}^\ell_i - \mathbf{x}^\ell_j\| + 1}\right)\phi_x(\mathbf{m}^\ell_{ij}, \hat{\mathbf{g}}^\ell) \qquad \mathbf{h}^{\ell+1}_i = \mathbf{h}^\ell_i + \phi_h(\mathbf{h}^\ell_i, \mathbf{m}^\ell_i, \hat{\mathbf{g}}^\ell) \tag{13}$$

The particular Conditional EGNN is thus specified by the functions $\{\phi^\ell_g\}_{\ell=0}^L, \phi_e, \phi_b, \phi_x, \phi_h$.

B PROOF OF THE INVARIANT VERTEX DISTRIBUTION THEOREM

In this section, we prove the Invariant Vertex Distribution Theorem presented in Section 2.4. We begin with two lemmata, after which the proof of the theorem is presented.

Lemma 1. *Let the mean position of the receptor be given by $\hat{\mathbf{x}}_{av} = \frac{1}{\hat{N}}\sum_{i=1}^{\hat{N}}\hat{\mathbf{x}}_i$, and define the following quantities*

$$\alpha = \frac{N}{N+\hat{N}} \qquad \Omega_{\hat{G}} = \begin{bmatrix} \mathbf{I}_{3N} - \frac{\alpha}{N}\mathbf{1}_{N\times N}\otimes\mathbf{I}_3 & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{d_h N}\end{bmatrix} \qquad \omega_{\hat{G}} = \begin{bmatrix} -(1-\alpha)\mathbf{1}_{N\times 1}\otimes\hat{\mathbf{x}}_{av} \\ \mathbf{0}\end{bmatrix}$$

where $\otimes$ indicates the Kronecker product. Given the following mapping:

$$\mathbf{v} = \Omega^{-1}_{\hat{G}}\left(\mathbf{u} - \omega_{\hat{G}}\right) \tag{14}$$

Let the inverse mapping be denoted by $\Gamma^1_{\hat{G}}$, i.e. $\mathbf{u} = \Gamma^1_{\hat{G}}(\mathbf{v})$. For any rigid transformation $T \in E(3)$, which consists of both a rotation and a translation, denote the transformation consisting only of the rotation of T as $T_{rot} \in O(3)$. Then

$$\Gamma^1_{T\hat{G}}(T\mathbf{v}) = T_{rot}\Gamma^1_{\hat{G}}(\mathbf{v}).$$

Furthermore, for any permutations $\pi \in \mathbb{S}_N$ and $\hat{\pi} \in \mathbb{S}_{\hat{N}}$, then

$$\Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v}) = \pi\Gamma^1_{\hat{G}}(\mathbf{v}).$$

Proof: The mapping $\mathbf{u} = \Gamma^1_{\hat{G}}(\mathbf{v})$ is given by

$$\mathbf{u} = \Omega_{\hat{G}}\mathbf{v} + \omega_{\hat{G}} \tag{15}$$

Let us denote the parts of $\mathbf{u}$ corresponding to the coordinates and the features as $\mathbf{x}^\mathbf{u}$ and $\mathbf{h}^\mathbf{u}$, respectively; and use similar notation for $\mathbf{v}$. Then we have that

$$\mathbf{h}^\mathbf{u} = \mathbf{h}^\mathbf{v} \tag{16}$$

and

$$\mathbf{x}^\mathbf{u} = \left(\mathbf{I}_{3N} - \frac{\alpha}{N}\mathbf{1}_{N\times N}\otimes\mathbf{I}_3\right)\mathbf{x}^\mathbf{v} - (1-\alpha)\mathbf{1}_{N\times 1}\otimes\hat{\mathbf{x}}_{av} \tag{17}$$

Breaking down this last equation by vertex gives

$$\begin{aligned}\mathbf{x}^\mathbf{u}_i &= \mathbf{x}^\mathbf{v}_i - \frac{\alpha}{N}\sum_{j=1}^N \mathbf{x}^\mathbf{v}_j - (1-\alpha)\hat{\mathbf{x}}_{av} \\ &= \mathbf{x}^\mathbf{v}_i - (\alpha\mathbf{x}^\mathbf{v}_{av} + (1-\alpha)\hat{\mathbf{x}}_{av}) \\ &= \mathbf{x}^\mathbf{v}_i - \bar{\mathbf{x}}^\mathbf{v}\end{aligned} \tag{18}$$

where $\mathbf{x}_{av}^{\mathbf{v}}$ is the average coordinate position of $\mathbf{x}^{\mathbf{v}}$, and $\bar{\mathbf{x}}^{\mathbf{v}}$ indicates the average of all vertices in the entire complex, i.e. taking both the ligand and the receptor together.

Now, let us examine what happens when we apply the rigid transformation T to both $\mathbf{v}$ and the receptor $\hat{G}$; that is, let us examine

$$\tilde{\mathbf{u}} = \Gamma^1_{T\hat{G}}(T\mathbf{v}) \tag{19}$$

In the case of the features $\mathbf{h}$, they are invariant by design; thus

$$\begin{aligned} \mathbf{h}^{\tilde{\mathbf{u}}} &= \mathbf{h}^{\mathbf{Tv}} \\ &= \mathbf{h}^{\mathbf{v}} \\ &= \mathbf{h}^{\mathbf{u}} \end{aligned} \tag{20}$$

where the last line follows from Equation (16). In the case of the coordinates, the transformation is as follows:

$$\mathbf{x}_i^{T\mathbf{v}} = R\mathbf{x}_i^{\mathbf{v}} + t \tag{21}$$

where $R \in O(3)$ is the rotation matrix, and $t \in \mathbb{R}^3$ the translation vector, corresponding to rigid motion T. As we apply T to the receptor $\hat{G}$, this has the effect of applying this transformation to each of the receptor vertices, and hence to their mean and the mean of the entire complex:

$$\hat{\mathbf{x}}_{av}^{T\hat{G}} = R\hat{\mathbf{x}}_{av}^{\hat{G}} + t \quad \Rightarrow \quad \bar{\mathbf{x}}^{\mathbf{Tv}} = R\bar{\mathbf{x}}^{\mathbf{v}} + t \tag{22}$$

Thus, following Equation (18), and substituting $T\mathbf{v}$ and $T\hat{G}$ in place of $\mathbf{v}$ and $\hat{G}$, we get

$$\begin{aligned} \mathbf{x}_i^{\tilde{\mathbf{u}}} &= \mathbf{x}_i^{T\mathbf{v}} - \bar{\mathbf{x}}^{T\mathbf{v}} \\ &= R\mathbf{x}_i^{\mathbf{v}} + t - (R\bar{\mathbf{x}}^{\mathbf{v}} + t) \\ &= R\left(\mathbf{x}_i^{\mathbf{v}} - \bar{\mathbf{x}}^{\mathbf{v}}\right) \\ &= R\mathbf{x}_i^{\mathbf{u}} \end{aligned} \tag{23}$$

Combining Equations (20) and (23), we have that

$$\tilde{\mathbf{u}} = T_{rot}\mathbf{u} \tag{24}$$

Since $\mathbf{u} = \Gamma^1_{\hat{G}}(\mathbf{v})$ and $\tilde{\mathbf{u}} = \Gamma^1_{T\hat{G}}(T\mathbf{v})$, we have shown that $\Gamma^1_{T\hat{G}}(T\mathbf{v}) = T_{rot}\Gamma^1_{\hat{G}}(\mathbf{v})$, as desired.

In the case of the permutations, let us now set

$$\tilde{\mathbf{u}} = \Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v}) \tag{25}$$

It is easy to see that $\hat{\pi}$ has no effect; the only place the receptor enters is through the quantities $\hat{N}$ and $\hat{\mathbf{x}}_{av}$, both of which are permutation-invariant. For the features, we now have

$$\begin{aligned} \mathbf{h}^{\tilde{\mathbf{u}}} &= \mathbf{h}^{\pi\mathbf{v}} \\ &= \pi\mathbf{h}^{\mathbf{v}} \\ &= \pi\mathbf{h}^{\mathbf{u}} \end{aligned} \tag{26}$$

That is, the features are simply reordered according to π. With regard to the coordinates, we have that

$$\begin{aligned} \mathbf{x}_i^{\tilde{\mathbf{u}}} &= \mathbf{x}_i^{\pi\mathbf{v}} - \bar{\mathbf{x}}^{\pi\mathbf{v}} \\ &= \mathbf{x}_{\pi(i)}^{\mathbf{v}} - \bar{\mathbf{x}}^{\mathbf{v}} \\ &= \mathbf{x}_{\pi(i)}^{\mathbf{u}} \end{aligned} \tag{27}$$

The coordinates are also therefore simply reordered according to π. Summarizing, we have that

$$\tilde{\mathbf{u}} = \pi\mathbf{u} \tag{28}$$

This is exactly equal to

$$\Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v}) = \pi\Gamma^1_{\hat{G}}(\mathbf{v})$$

which concludes the proof. □

Lemma 2. *Let $\mathbf{u}(1)$ be the output of a Conditional Flow specified by the Complex-to-Ligand Mapping γ which is rotation semi-equivariant and permutation semi-equivariant. This Conditional Flow maps the initial condition $\mathbf{z}$ to $\mathbf{u}(1)$; let the inverse mapping be denoted by $\Gamma^2_{\hat{G}}$, i.e. $\mathbf{z} = \Gamma^2_{\hat{G}}(\mathbf{u}(1))$. Then*

$$\Gamma^2_{T\hat{G}}(T_{rot}\mathbf{u}) = T_{rot}\Gamma^2_{\hat{G}}(\mathbf{u})$$

Furthermore, for any permutations $\pi \in \mathbb{S}_N$ and $\hat{\pi} \in \mathbb{S}_{\hat{N}}$, then

$$\Gamma^2_{\hat{\pi}\hat{G}}(\pi\mathbf{u}) = \pi\Gamma^2_{\hat{G}}(\mathbf{u})$$

Proof: Our first goal is to show that $\Gamma^2_{T\hat{G}}(T_{rot}\mathbf{u}) = T_{rot}\Gamma^2_{\hat{G}}(\mathbf{u})$. Let us define $F_{\hat{G}}$ to be the inverse of $\Gamma^2_{\hat{G}}$, and let $\mathbf{u} = F_{\hat{G}}(\mathbf{z})$. Then

$$\begin{aligned}
\Gamma^2_{T\hat{G}}(T_{rot}\mathbf{u}) = T_{rot}\Gamma^2_{\hat{G}}(\mathbf{u}) \quad &\Leftrightarrow \quad F^{-1}_{T\hat{G}}(T_{rot}F_{\hat{G}}(\mathbf{z})) = T_{rot}F^{-1}_{\hat{G}}(F_{\hat{G}}(\mathbf{z})) \\
&\Leftrightarrow \quad F^{-1}_{T\hat{G}}(T_{rot}F_{\hat{G}}(\mathbf{z})) = T_{rot}\mathbf{z} \\
&\Leftrightarrow \quad F_{T\hat{G}}(T_{rot}\mathbf{z}) = T_{rot}F_{\hat{G}}(\mathbf{z}) \qquad (29)
\end{aligned}$$

Thus, it is sufficient to show that $F_{T\hat{G}}(T_{rot}\mathbf{z}) = T_{rot}F_{\hat{G}}(\mathbf{z})$. For convenience, we shall set

$$\mathbf{u}(1) = F_{\hat{G}}(\mathbf{z}) \quad \text{and} \quad \tilde{\mathbf{u}}(1) = F_{T\hat{G}}(T_{rot}\mathbf{z}) \qquad (30)$$

In this case, $\mathbf{u}(1)$ is defined by the ODE

$$\frac{d\mathbf{u}}{dt} = \texttt{vec}\left(\gamma(G_{\mathbf{u}}, \hat{G})\right) \quad \text{with } \mathbf{u}(0) = \mathbf{z} \qquad (31)$$

whereas $\tilde{\mathbf{u}}(1)$ is defined by the ODE

$$\frac{d\tilde{\mathbf{u}}}{dt} = \texttt{vec}\left(\gamma(G_{\tilde{\mathbf{u}}}, T\hat{G})\right) \quad \text{with } \tilde{\mathbf{u}}(0) = T_{rot}\mathbf{z} \qquad (32)$$

Now, let us define $\breve{\mathbf{u}}(t) = T^{-1}_{rot}\tilde{\mathbf{u}}(t)$, so that $\tilde{\mathbf{u}}(t) = T_{rot}\breve{\mathbf{u}}(t)$. In this case, we have that:

1. $\breve{\mathbf{u}}(0) = T^{-1}_{rot}\tilde{\mathbf{u}}(0) = T^{-1}_{rot}T_{rot}\mathbf{z} = \mathbf{z}$.
2. $\frac{d\tilde{\mathbf{u}}}{dt} = T_{rot}\frac{d\breve{\mathbf{u}}}{dt}$.
3. $\texttt{vec}\left(\gamma(G_{\tilde{\mathbf{u}}}, T\hat{G})\right) = \texttt{vec}\left(\gamma(G_{T_{rot}\breve{\mathbf{u}}}, T\hat{G})\right) = T_{rot}\texttt{vec}\left(\gamma(G_{\breve{\mathbf{u}}}, \hat{G})\right)$, where the last equality is from the definition of rotation semi-equivariance of γ.

Plugging the above three results into the flow for $\tilde{\mathbf{u}}$ in Equation (32) yields

$$\begin{aligned}
T_{rot}\frac{d\breve{\mathbf{u}}}{dt} &= T_{rot}\texttt{vec}\left(\gamma(G_{\breve{\mathbf{u}}}, \hat{G})\right) \quad \text{with} \quad \breve{\mathbf{u}}(0) = \mathbf{z} \\
\Rightarrow \quad \frac{d\breve{\mathbf{u}}}{dt} &= \texttt{vec}\left(\gamma(G_{\breve{\mathbf{u}}}, \hat{G})\right) \quad \text{with} \quad \breve{\mathbf{u}}(0) = \mathbf{z} \qquad (33)
\end{aligned}$$

But this is precisely identical to the flow described in Equation (31); thus, we have that

$$\breve{\mathbf{u}}(t) = \mathbf{u}(t) \quad \text{for all } t \qquad (34)$$

But $\tilde{\mathbf{u}}(t) = T_{rot}\breve{\mathbf{u}}(t)$ so that $\tilde{\mathbf{u}}(t) = T_{rot}\mathbf{u}(t)$, and in particular $\tilde{\mathbf{u}}(1) = T_{rot}\mathbf{u}(1)$. Comparing with Equation (30) completes rigid motion part of the proof.

Let us now turn to permutations; the proof is similar, but we repeat it in full for completeness. Our goal is to show that $\Gamma^2_{\hat{\pi}\hat{G}}(\pi\mathbf{u}) = \pi\Gamma^2_{\hat{G}}(\mathbf{u})$. Let us define $F_{\hat{G}}$ to be the inverse of $\Gamma^2_{\hat{G}}$, and let $\mathbf{u} = F_{\hat{G}}(\mathbf{z})$. Then

$$\begin{aligned}
\Gamma^2_{\hat{\pi}\hat{G}}(\pi\mathbf{u}) = \pi\Gamma^2_{\hat{G}}(\mathbf{u}) \quad &\Leftrightarrow \quad F^{-1}_{\hat{\pi}\hat{G}}(\pi F_{\hat{G}}(\mathbf{z})) = \pi F^{-1}_{\hat{G}}(F_{\hat{G}}(\mathbf{z})) \\
&\Leftrightarrow \quad F^{-1}_{\hat{\pi}\hat{G}}(\pi F_{\hat{G}}(\mathbf{z})) = \pi\mathbf{z} \\
&\Leftrightarrow \quad F_{\hat{\pi}\hat{G}}(\pi\mathbf{z}) = \pi F_{\hat{G}}(\mathbf{z}) \qquad (35)
\end{aligned}$$

Thus, it is sufficient to shows that $F_{\hat{\pi}\hat{G}}(\pi\mathbf{z}) = \pi F_{\hat{G}}(\mathbf{z})$. For convenience, we shall set

$$\mathbf{u}(1) = F_{\hat{G}}(\mathbf{z}) \quad \text{and} \quad \tilde{\mathbf{u}}(1) = F_{\hat{\pi}\hat{G}}(\pi\mathbf{z}) \tag{36}$$

In this case, $\mathbf{u}(1)$ is defined by the ODE

$$\frac{d\mathbf{u}}{dt} = \texttt{vec}\left(\gamma(G_{\mathbf{u}}, \hat{G})\right) \quad \text{with } \mathbf{u}(0) = \mathbf{z} \tag{37}$$

whereas $\tilde{\mathbf{u}}(1)$ is defined by the ODE

$$\frac{d\tilde{\mathbf{u}}}{dt} = \texttt{vec}\left(\gamma(G_{\tilde{\mathbf{u}}}, \hat{\pi}\hat{G})\right) \quad \text{with } \tilde{\mathbf{u}}(0) = \pi\mathbf{z} \tag{38}$$

Now, let us define $\breve{\mathbf{u}}(t) = \pi^{-1}\tilde{\mathbf{u}}(t)$, so that $\tilde{\mathbf{u}}(t) = \pi\breve{\mathbf{u}}(t)$. In this case, we have that:

1. $\breve{\mathbf{u}}(0) = \pi^{-1}\tilde{\mathbf{u}}(0) = \pi^{-1}\pi\mathbf{z} = \mathbf{z}$.
2. $\frac{d\tilde{\mathbf{u}}}{dt} = \pi\frac{d\breve{\mathbf{u}}}{dt}$.
3. $\texttt{vec}\left(\gamma(G_{\tilde{\mathbf{u}}}, \hat{\pi}\hat{G})\right) = \texttt{vec}\left(\gamma(G_{\pi\breve{\mathbf{u}}}, \hat{\pi}\hat{G})\right) = \pi\texttt{vec}\left(\gamma(G_{\breve{\mathbf{u}}}, \hat{G})\right)$, where the last equality is from the definition of permutation semi-equivariance of γ.

Plugging the above three results into the flow for $\tilde{\mathbf{u}}$ in Equation (38) yields

$$\begin{aligned} \pi\frac{d\breve{\mathbf{u}}}{dt} &= \pi\texttt{vec}\left(\gamma(G_{\breve{\mathbf{u}}}, \hat{G})\right) \quad \text{with} \quad \breve{\mathbf{u}}(0) = \mathbf{z} \\ \Rightarrow \quad \frac{d\breve{\mathbf{u}}}{dt} &= \texttt{vec}\left(\gamma(G_{\breve{\mathbf{u}}}, \hat{G})\right) \quad \text{with} \quad \breve{\mathbf{u}}(0) = \mathbf{z} \end{aligned} \tag{39}$$

But this is precisely identical to the flow described in Equation (37); thus, we have that

$$\breve{\mathbf{u}}(t) = \mathbf{u}(t) \quad \text{for all } t \tag{40}$$

But $\tilde{\mathbf{u}}(t) = \pi\breve{\mathbf{u}}(t)$ so that $\tilde{\mathbf{u}}(t) = \pi\mathbf{u}(t)$, and in particular $\tilde{\mathbf{u}}(1) = \pi\mathbf{u}(1)$. Comparing with Equation (36) completes the proof. □

Theorem. *Let $\mathbf{u}(1)$ be the output of a Conditional Flow specified by the Complex-to-Ligand Mapping γ. Let the mean position of the receptor be given by $\hat{\mathbf{x}}_{av} = \frac{1}{\hat{N}}\sum_{i=1}^{\hat{N}}\hat{\mathbf{x}}_i$, and define the following quantities*

$$\alpha = \frac{N}{N+\hat{N}} \qquad \Omega_{\hat{G}} = \begin{bmatrix} \mathbf{I}_{3N} - \frac{\alpha}{N}\mathbf{1}_{N\times N} \otimes \mathbf{I}_3 & \mathbf{0} \\ \mathbf{0} & \mathbf{I}_{d_h N} \end{bmatrix} \qquad \omega_{\hat{G}} = \begin{bmatrix} -(1-\alpha)\mathbf{1}_{N\times 1} \otimes \hat{\mathbf{x}}_{av} \\ \mathbf{0} \end{bmatrix} \tag{41}$$

where $\otimes$ indicates the Kronecker product. Finally, let

$$\mathbf{v} = \Omega_{\hat{G}}^{-1}\left(\mathbf{u}(1) - \omega_{\hat{G}}\right) \tag{42}$$

Suppose that γ is both rotation semi-equivariant and permutation semi-equivariant. Then the resulting distribution on $\mathbf{v}$, that is $p_{vec}(\mathbf{v}|\hat{G})$, yields a vertex distribution $p(V|N, \hat{G}) = p_{vec}(vec(V)|\hat{G})$ that satisfies the invariance conditions in Equation (1).

Proof: The Conditional Flow maps from the Gaussian random variable $\mathbf{z}$ to the variable $\mathbf{u}(1)$. As this flow is a normalizing flow, it is invertible, so let us denote the inverse mapping by Γ^2:

$$\mathbf{z} = \Gamma^2_{\hat{G}}(\mathbf{u}(1)) \tag{43}$$

Note that the dependence on the receptor $\hat{G}$ is denoted using a subscript, as the invertibility does not apply to the receptor, but only to the ligand. Equation (42) maps from the variable $\mathbf{u}(1)$ to the variable $\mathbf{v}$; let us denote its inverse mapping by Γ^1:

$$\mathbf{u}(1) = \Gamma^1_{\hat{G}}(\mathbf{v}) \tag{44}$$

In this case, we have that

$$\mathbf{z} = \Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v})) \equiv \Gamma_{\hat{G}}(\mathbf{v}) \tag{45}$$

Now, our goal is to show that the following condition holds:

$$p(TV|N, T\hat{G}) = p(V|N, \hat{G}) \quad \text{for } T \in E(3) \tag{46}$$

Using the p_{vec} notation, this translates to

$$p_{vec}(T\mathbf{v}|T\hat{G}) = p_{vec}(\mathbf{v}|\hat{G}) \tag{47}$$

Now, from Equation (45), the fact that Γ is invertible, and the change of variables formula, we have that

$$p_{vec}(\mathbf{v}|\hat{G}) = p_{\mathbf{z}}(\Gamma_{\hat{G}}(\mathbf{v}))|\det J_{\Gamma_{\hat{G}}}(\mathbf{v})| \tag{48}$$

where $p_{\mathbf{z}}(\cdot)$ is the Gaussian distribution from $\mathbf{z}$ is sampled; and $J_{\Gamma_{\hat{G}}}(\cdot)$ is the Jacobian of $\Gamma_{\hat{G}}(\cdot)$. Since $\Gamma_{\hat{G}} = \Gamma^2_{\hat{G}} \circ \Gamma^1_{\hat{G}}$, this can be expanded as

$$p_{vec}(\mathbf{v}|\hat{G}) = p_{\mathbf{z}}(\Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v})))|\det J_{\Gamma^2_{\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))||\det J_{\Gamma^1_{\hat{G}}}(\mathbf{v})| \tag{49}$$

using the chain rule, and the fact that determinant of a product is the product of determinants. Plugging this into Equation (47), we must show that

$$\begin{aligned} & p_{\mathbf{z}}(\Gamma^2_{T\hat{G}}(\Gamma^1_{T\hat{G}}(T\mathbf{v})))|\det J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{T\hat{G}}(T\mathbf{v}))||\det J_{\Gamma^1_{T\hat{G}}}(T\mathbf{v})| \\ = \quad & p_{\mathbf{z}}(\Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v})))|\det J_{\Gamma^2_{\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))||\det J_{\Gamma^1_{\hat{G}}}(\mathbf{v})| \quad \text{for } T \in E(3) \end{aligned} \tag{50}$$

A rigid transformation $T \in E(3)$ consists of both a rotation and a translation. For brevity, denote the transformation consisting only of the rotation of T as $T_{rot} \in O(3)$. Now, from Lemma 1, we have that

$$\Gamma^1_{T\hat{G}}(T\mathbf{v}) = T_{rot}\Gamma^1_{\hat{G}}(\mathbf{v}) \tag{51}$$

From Lemma 2, we have that

$$\Gamma^2_{T\hat{G}}(T_{rot}\mathbf{u}) = T_{rot}\Gamma^2_{\hat{G}}(\mathbf{u}) \tag{52}$$

Combining Equations (51) and (52) gives that

$$\begin{aligned} p_{\mathbf{z}}(\Gamma^2_{T\hat{G}}(\Gamma^1_{T\hat{G}}(T\mathbf{v}))) &= p_{\mathbf{z}}(\Gamma^2_{T\hat{G}}(T_{rot}\Gamma^1_{\hat{G}}(\mathbf{v}))) \\ &= p_{\mathbf{z}}(T_{rot}\Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v}))) \\ &= p_{\mathbf{z}}(\Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v}))) \end{aligned} \tag{53}$$

where the last line follows from the rotation invariance of the Gaussian distribution.

Note that

$$\begin{aligned} J_{\Gamma^1_{T\hat{G}}}(T\mathbf{v}) &= \frac{\partial}{\partial \mathbf{v}}\left(\Gamma^1_{T\hat{G}}(T\mathbf{v})\right) \\ &= \frac{\partial}{\partial \mathbf{v}}\left(T_{rot}\Gamma^1_{\hat{G}}(\mathbf{v})\right) \\ &= T_{rot}\frac{\partial}{\partial \mathbf{v}}\left(\Gamma^1_{\hat{G}}(\mathbf{v})\right) \\ &= T_{rot}J_{\Gamma^1_{\hat{G}}}(\mathbf{v}) \end{aligned} \tag{54}$$

Now, T_{rot} can be represented by the $d_v^N \times d_v^N$ block diagonal matrix given by

$$T_{rot} = \begin{bmatrix} \mathbf{1}_{N\times 1} \otimes R & 0 \\ 0 & \mathbf{I}_{d_h N} \end{bmatrix} \tag{55}$$

where $R \in O(3)$, the top-left block corresponds to the coordinates $\mathbf{x}$ and the bottom-right block corresponds to the feature $\mathbf{h}$. Thus,

$$\begin{aligned} \det\Big(J_{\Gamma^1_{T\hat{G}}}(T\mathbf{v})\Big) &= \det\Big(T_{rot}J_{\Gamma^1_{\hat{G}}}(\mathbf{v})\Big) \\ &= \det(T_{rot})\det\Big(J_{\Gamma^1_{\hat{G}}}(\mathbf{v})\Big) \\ &= \det(R)^N \det(\mathbf{I}_{d_h N})\det\Big(J_{\Gamma^1_{\hat{G}}}(\mathbf{v})\Big) \\ &= \pm\det\Big(J_{\Gamma^1_{\hat{G}}}(\mathbf{v})\Big) \end{aligned} \tag{56}$$

where the second line follows from the fact that the determinant of a product is the product of determinants; the third line from the fact that the determinant of a block diagonal matrix is the product of the determinants of the blocks; and the fourth line from the fact that the determinant of a rotation matrix is ± 1.

To simplify $J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{T\hat{G}}(T\mathbf{v}))$, note that

$$\begin{aligned}\Gamma^2_{T\hat{G}}(\mathbf{u}) &= \Gamma^2_{T\hat{G}}(T_{rot}T_{rot}^{-1}\mathbf{u}) \\ &= T_{rot}\Gamma^2_{\hat{G}}(T_{rot}^{-1}\mathbf{u}) \end{aligned} \tag{57}$$

where we have used Equation (52). Thus,

$$\begin{aligned} J_{\Gamma^2_{T\hat{G}}}(\mathbf{u}) &= \frac{\partial}{\partial \mathbf{u}}\left(\Gamma^2_{T\hat{G}}(\mathbf{u})\right) \\ &= \frac{\partial}{\partial \mathbf{u}}\left(T_{rot}\Gamma^2_{\hat{G}}(T_{rot}^{-1}\mathbf{u})\right) \\ &= T_{rot}J_{\Gamma^2_{T\hat{G}}}(T_{rot}^{-1}\mathbf{u})T_{rot}^{-1} \end{aligned} \tag{58}$$

We wish to plug in $\mathbf{u} = \Gamma^1_{T\hat{G}}(T\mathbf{v})$. Note that from Equation (51), $\Gamma^1_{T\hat{G}}(T\mathbf{v}) = T_{rot}\Gamma^1_{\hat{G}}(\mathbf{v})$. Thus,

$$\begin{aligned} J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{T\hat{G}}(T\mathbf{v})) &= J_{\Gamma^2_{T\hat{G}}}(T_{rot}\Gamma^1_{\hat{G}}(\mathbf{v})) \\ &= T_{rot}J_{\Gamma^2_{T\hat{G}}}(T_{rot}^{-1}T_{rot}\Gamma^1_{\hat{G}}(\mathbf{v}))T_{rot}^{-1} \\ &= T_{rot}J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))T_{rot}^{-1} \end{aligned} \tag{59}$$

where in the second line we substituted Equation (58). Taking determinants gives

$$\begin{aligned} \det\left(J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{T\hat{G}}(T\mathbf{v}))\right) &= \det\left(T_{rot}J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))T_{rot}^{-1}\right) \\ &= \det\left(T_{rot}^{-1}T_{rot}J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))\right) \\ &= \det\left(J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))\right) \end{aligned} \tag{60}$$

where in the second line, we used the fact that permuting the order of a matrix multiplication does not affect the determinant.

Combining Equations (53), (56), and (60), we finally arrive at:

$$\begin{aligned} & p_{\mathbf{z}}(\Gamma^2_{T\hat{G}}(\Gamma^1_{T\hat{G}}(T\mathbf{v})))|\det J_{\Gamma^2_{T\hat{G}}}(\Gamma^1_{T\hat{G}}(T\mathbf{v}))||\det J_{\Gamma^1_{T\hat{G}}}(T\mathbf{v})| \\ = \quad & p_{\mathbf{z}}(\Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v})))|\det J_{\Gamma^2_{\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))||\det J_{\Gamma^1_{\hat{G}}}(\mathbf{v})| \end{aligned} \tag{61}$$

which is exactly Equation (50). Thus, we have shown that $p(TV|N, T\hat{G}) = p(V|N, \hat{G})$, as desired.

Let us turn now to the permutation case, which is quite similar. Similar to Equation (50), we need to show

$$\begin{aligned} & p_{\mathbf{z}}(\Gamma^2_{\hat{\pi}\hat{G}}(\Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v})))|\det J_{\Gamma^2_{\hat{\pi}\hat{G}}}(\Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v}))||\det J_{\Gamma^1_{\hat{\pi}\hat{G}}}(\pi\mathbf{v})| \\ = \quad & p_{\mathbf{z}}(\Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v})))|\det J_{\Gamma^2_{\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))||\det J_{\Gamma^1_{\hat{G}}}(\mathbf{v})| \quad \text{for } \pi \in \mathbb{S}_n \text{ and } \hat{\pi} \in \mathbb{S}_{\hat{N}} \end{aligned} \tag{62}$$

From Lemmata 1 and 2, we have that

$$\Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v}) = \pi\Gamma^1_{\hat{G}}(\mathbf{v}) \quad \text{and} \quad \Gamma^2_{\hat{\pi}\hat{G}}(\pi\mathbf{u}) = \pi\Gamma^2_{\hat{G}}(\mathbf{u}) \tag{63}$$

Thus

$$\begin{aligned} p_{\mathbf{z}}(\Gamma^2_{\hat{\pi}\hat{G}}(\Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v}))) &= p_{\mathbf{z}}(\Gamma^2_{\hat{\pi}\hat{G}}(\pi\Gamma^1_{\hat{G}}(\mathbf{v}))) \\ &= p_{\mathbf{z}}(\pi\Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v}))) \\ &= p_{\mathbf{z}}(\Gamma^2_{\hat{G}}(\Gamma^1_{\hat{G}}(\mathbf{v}))) \end{aligned} \tag{64}$$

where the last line follows from the permutation-invariance of the Gaussian distribution $p_{\mathbf{z}}(\cdot)$.

In a manner parallel to the derivation of Equation (54), we can show that

$$J_{\Gamma^1_{\hat{\pi}\hat{G}}}(\pi\mathbf{v}) = \boldsymbol{\pi} J_{\Gamma^1_{\hat{G}}}(\mathbf{v}) \tag{65}$$

where $\boldsymbol{\pi}$ now indicates the permutation matrix associated with the permutation π. Thus, we have that

$$\det\left(J_{\Gamma^1_{\hat{\pi}\hat{G}}}(\pi\mathbf{v})\right) = \det(\boldsymbol{\pi})\det\left(J_{\Gamma^1_{\hat{G}}}(\mathbf{v})\right) = \pm\det\left(J_{\Gamma^1_{\hat{G}}}(\mathbf{v})\right) \tag{66}$$

where we have used the fact that a permutation matrix has determinant of ± 1. Similarly, in a manner parallel to the derivation of Equation (59), we can show that

$$J_{\Gamma^2_{\hat{\pi}\hat{G}}}(\Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v})) = \boldsymbol{\pi} J_{\Gamma^2_{\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))\boldsymbol{\pi}^{-1} \tag{67}$$

so that

$$\begin{aligned}
\det\left(J_{\Gamma^2_{\hat{\pi}\hat{G}}}(\Gamma^1_{\hat{\pi}\hat{G}}(\pi\mathbf{v}))\right) &= \det\left(\boldsymbol{\pi} J_{\Gamma^2_{\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))\boldsymbol{\pi}^{-1}\right) \\
&= \det\left(\boldsymbol{\pi}^{-1}\boldsymbol{\pi} J_{\Gamma^2_{\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))\right) \\
&= \det\left(J_{\Gamma^2_{\hat{G}}}(\Gamma^1_{\hat{G}}(\mathbf{v}))\right)
\end{aligned} \tag{68}$$

Combining Equations (64), (66), and (68) yields Equation (62); completing the proof. □

C THE EDGE AND PROPERTIES DISTRIBUTIONS

The Edge Distribution Given the invariance conditions described in Equation (1), we propose a distribution which displays *conditional independence*: $p\left(E = (\mathbf{e}_{ij})_{i<j:j\in\eta_i} | N, V, \hat{G}\right) = \prod_{i<j:j\in\eta_i} p(\mathbf{e}_{ij}|N, V, \hat{G})$. We opt for conditional independence for two reasons: (1) The usual Markov decomposition of the probability distribution with terms of the form $p(\mathbf{e}_{ij}|\mathbf{e}_{<ij}, N, V, \hat{G})$ implies a particular ordering of the edges, and is therefore not permutation-invariant. (2) V is a deterministic and invertible function of the flow's noise vector $\mathbf{z}$; thus, conditioning on V is the same as conditioning on $\mathbf{z}$. If E is a deterministic (but not necessarily invertible) function of $\mathbf{z}$, then conditional independence is correct.

To compute $p(\mathbf{e}_{ij}|N, V, \hat{G})$, we use a second Conditional EGNN. The key distinction between this network and the Conditional EGNN used in computing the vertex distribution is the initial conditions. In the case of the vertex distribution, the initial conditions are $\mathbf{x}_i^1 = \mathbf{0}$ and $\mathbf{h}_i^1 = \mathbf{0}$. In the current case of the edge distribution, we are given V (we are conditioning on it); thus, we take the initial conditions to be $\tilde{\mathbf{x}}_i^1 = \mathbf{x}_i(V)$ and $\tilde{\mathbf{h}}_i^1 = \mathbf{h}_i(V)$. In other words, the initial values are given the vertex list V itself.

Given this second Conditional EGNN, we can compute the edge distribution as

$$p\left(\mathbf{e}_{ij}|N, V, \hat{G}\right) = \mathbf{e}_{ij}^T \,\texttt{MLP}\left(\tilde{\mathbf{m}}_{ij}^L\right) \tag{69}$$

in the case of categorical properties (where MLP's output is a softmax with d_e entries); analogous expressions exist for ordinal or continuous properties. It is straightforward to see that this distribution satisfies the invariance properties in Equation (1). The corresponding loss function is a simple cross-entropy loss (or regression loss for non-categorical properties).

The Property Distribution We propose the following distribution. We use a standard Markov decomposition: $p(A|N, V, E, \hat{G}) = \prod_{k=1}^K p\left(\mathbf{a}_k|\mathbf{a}_{1:(k-1)}, N, V, E, \hat{G}\right)$. Let

$$\boldsymbol{\xi}_h = \frac{1}{N}\sum_{i=1}^N \texttt{MLP}\left(\tilde{\mathbf{h}}_i^L\right) \qquad \boldsymbol{\xi}_e = \frac{1}{|E|}\sum_{i<j:j\in\eta_i} \texttt{MLP}\left(\mathbf{e}_{ij}\right) \qquad \boldsymbol{\xi}_{a,k} = \texttt{MLP}\left(\sum_{j=1}^{k-1} W_j \mathbf{a}_j\right) \tag{70}$$

where the matrices $W_1, \ldots W_K$ all have the same number of rows. Then we set

$$p\left(\mathbf{a}_k \,\middle|\, \mathbf{a}_{1:(k-1)}, N, V, E, \hat{G}\right) = \mathbf{a}_k^T \texttt{MLP}\left(\texttt{concat}\left(\boldsymbol{\xi}_h, \boldsymbol{\xi}_e, \boldsymbol{\xi}_{a,k}\right)\right) \tag{71}$$

in the case of categorical properties; analogous expressions exist for ordinal or continuous properties. Note that the only item which changes for the different properties k is the vector $\boldsymbol{\xi}_{a,k}$. It is easy to see that this distribution satisfies the invariance properties in Equation (1). The corresponding loss function is a simple cross-entropy loss (or regression loss for non-categorical properties).

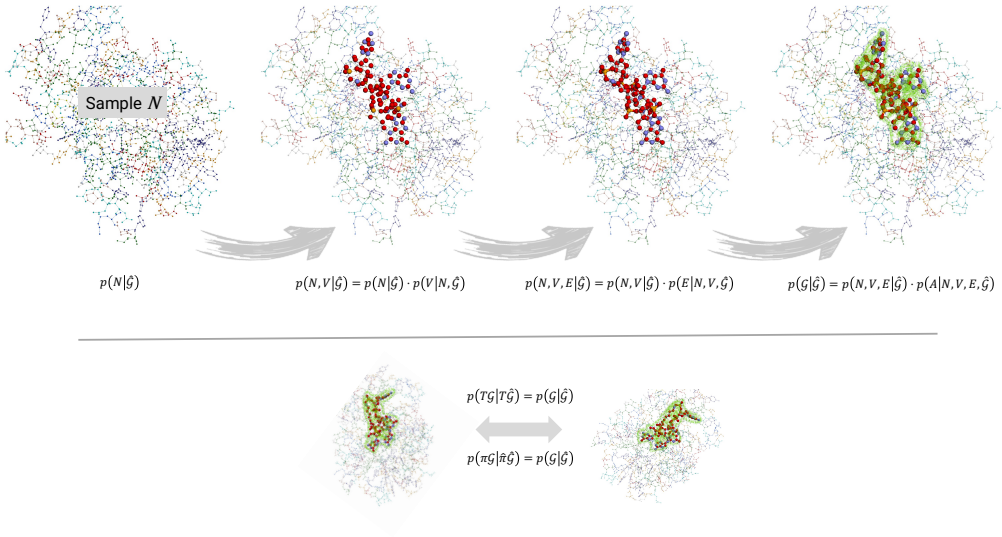

Figure 3: An illustration of the conditional probabilistic method. Top row: given a receptor (on the leftmost side), denoted as $\hat{\mathcal{G}}$, we wish to conditionally sample a second 3D graph, which we refer to as the ligand (represented by the enlarged vertices and edges), denoted as $\mathcal{G}$. The Markov decomposition of the conditional distribution, which ultimately allows us to obtain the conditional probability $p(\mathcal{G}|\hat{\mathcal{G}})$, is illustrated by its successive stages from left to right. Specifically: N is the number of vertices; V is the list of vertices; E is the list of edges; and A is the set of global graph properties (light green marking). Bottom row: we illustrate the invariance to rigid motions applied jointly to both graphs and permutations applied to each of the graphs separately.