PharmacoMatch: Efficient 3D Pharmacophore Screening via Neural Subgraph Matching

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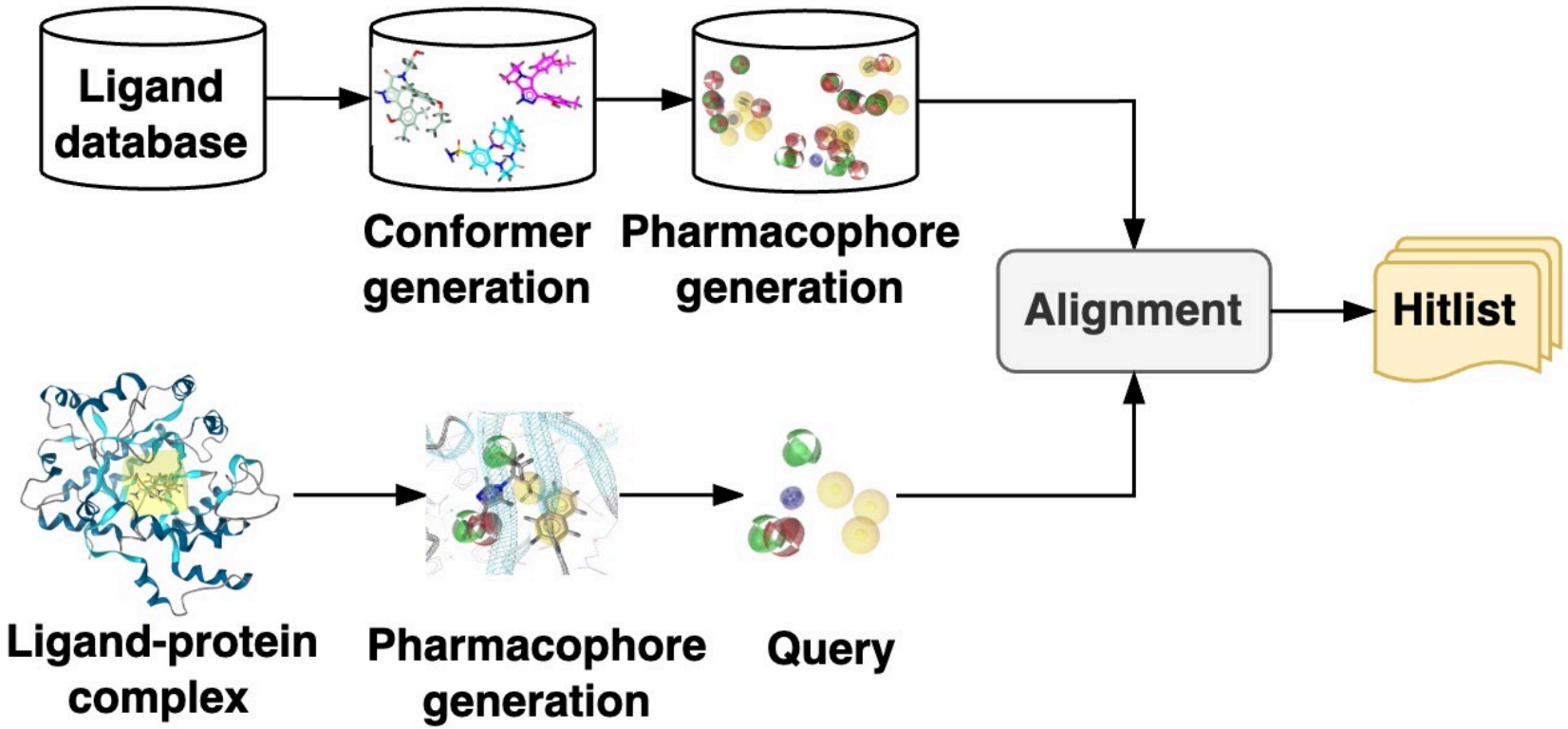
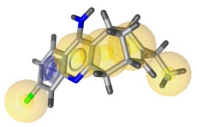
Pharmacophore Screening





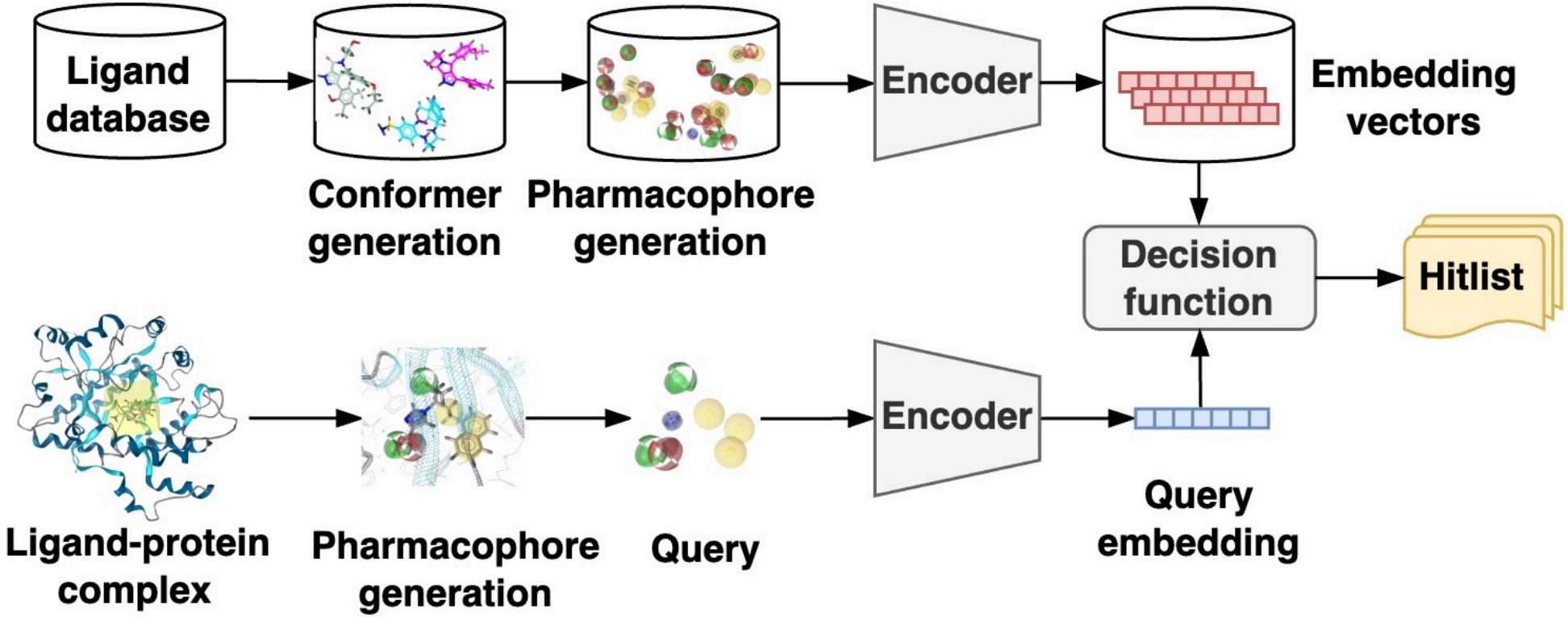
3D Pharmacophore screening works with alignment algorithm

😔

Alignment does not scale well with large molecular databases

Can we train a model to speed up the alignment?

Overview: PharmacoMatch



- Conceptualization of pharmacophore matching as representation learning problem
- Model training via self-supervised learning strategy
- Virtual pre-screening with learned embeddings is efficient and scalable

Pharmacophore Matching

Pharmacophore representation

$$P = \{(\mathbf{r}_i, d_i) \in \mathbb{R}^3 \times \mathcal{D}\}_i$$

- Pharmacophore P
- Cartesian coordinates $\mathbf{r}_i$
- Descriptor d_i
- Descriptor set $\mathcal{D}$

$$G(P) = (V_P, E_P, \lambda_P)$$

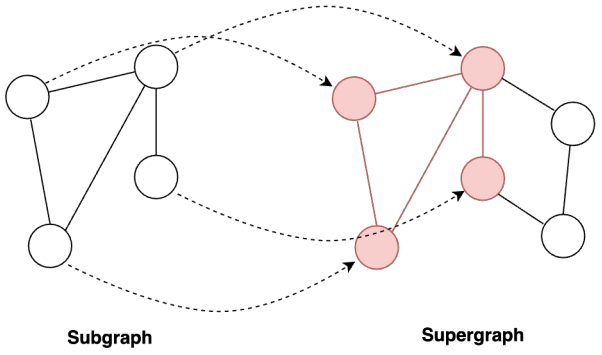
- Complete graph G
- Node set $V_P = \{v_1, ..., v_{|P|}\}$
- Edge set $E_P = V_P \times V_P$
- Label set $\mathcal{L} = \mathcal{D} \cup \mathcal{R}$
- $\mathcal{R} = \{\|\mathbf{r}_i - \mathbf{r}_j\|_2 \mid 1 \leq i, j \leq |P|\}$
- Labeling function $\lambda_P : V \cup E \to \mathcal{L}$
- Node attributes $\lambda_P(v_i) = l_i$
- Edge attributes $\lambda_P(e_{ij}) = \|\mathbf{r}_i - \mathbf{r}_j\|_2$

Subgraph isomorphism

$$G_1 = (V_1, E_1, \lambda_1),\ G_2 = (V_2, E_2, \lambda_2)$$
$$G_1 \simeq G_2 \text{ iff } \exists f : V_1 \to V_2 \text{ s.t.}$$

- $\forall (u, v) \in E_1 : (f(u), f(v)) \in E_2$
- $\forall v \in V_1 : \lambda_1(v) = \lambda_2(f(v))$
- $\forall (u, v) \in E_1 : \lambda_1((u, v)) = \lambda_2((f(u), f(v)))$

$$G_Q = (V_Q, E_Q, \lambda_Q),\ G_T = (V_T, E_T, \lambda_T)$$
$$G_H = (V_H, E_H, \lambda_H) \text{ s.t. } V_H \subseteq V_T,\ E_H \subseteq E_T$$
$$\mathcal{H} = \{G_H \mid G_H \simeq G_Q\}$$
$$G_Q \lesssim G_T \text{ iff } \mathcal{H} \neq \varnothing$$

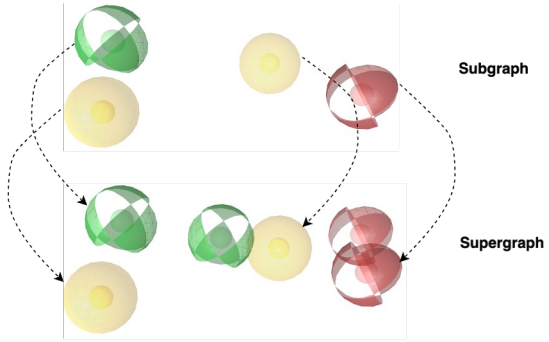


Pharmacophore matching

$$P_H \subseteq P_T \text{ iff } \exists g : P_Q \to P_H \text{ s.t.}$$

- $\forall i \in P_Q : d_i = d_{g(i)}$
- $\|\mathbf{r}_i - \mathbf{r}_{g(i)}\|_2 < r_T$
- r_T tolerance sphere radius

$$G_Q = G(P_Q),\ G_H = G(P_H),\ G_T = G(P_T)$$
$$\lambda_Q((u, v)) \approx \lambda_H((f(u), f(v)))$$



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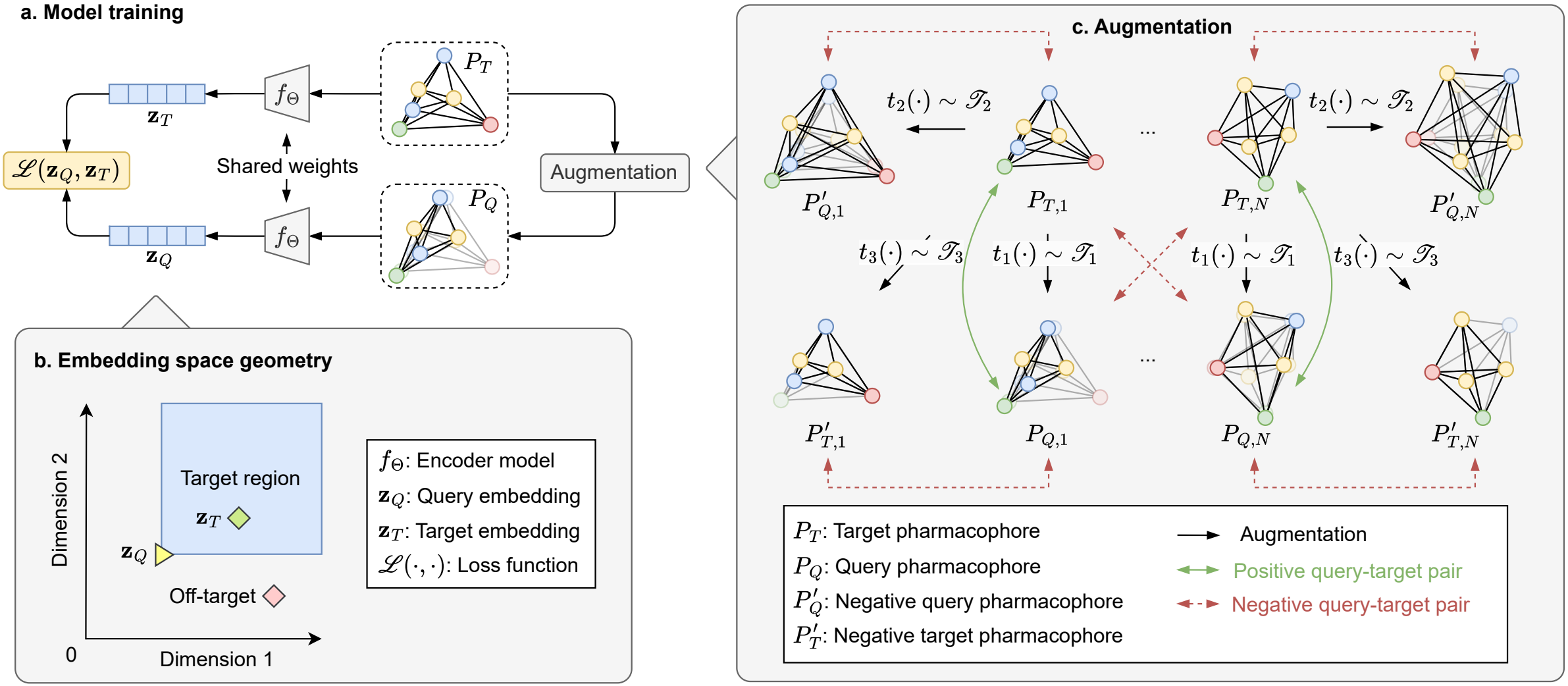
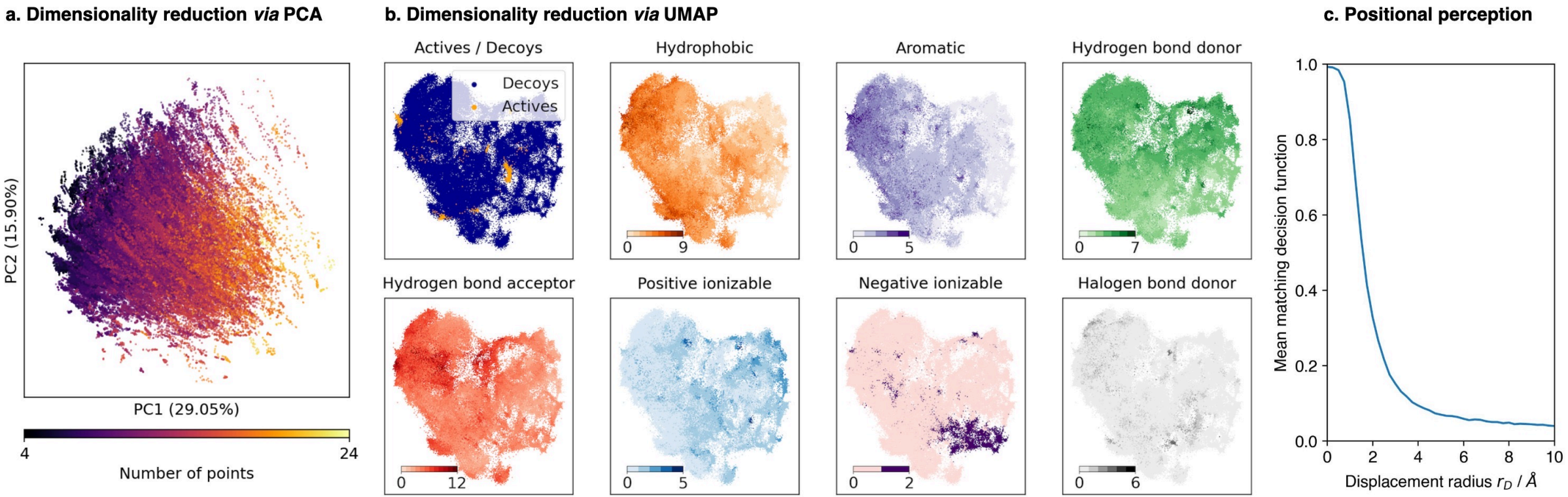
Order embedding loss encodes query target relationship:

$$\mathcal{L}(\mathbf{z}_Q, \mathbf{z}_T) = \sum_{(\mathbf{z}_Q, \mathbf{z}_T) \in Pos} E(\mathbf{z}_Q, \mathbf{z}_T) + \sum_{(\mathbf{z}_Q, \mathbf{z}_T) \in Neg} \max\{0, \alpha - E(\mathbf{z}_Q, \mathbf{z}_T)\}$$

Self-Supervised Model Training

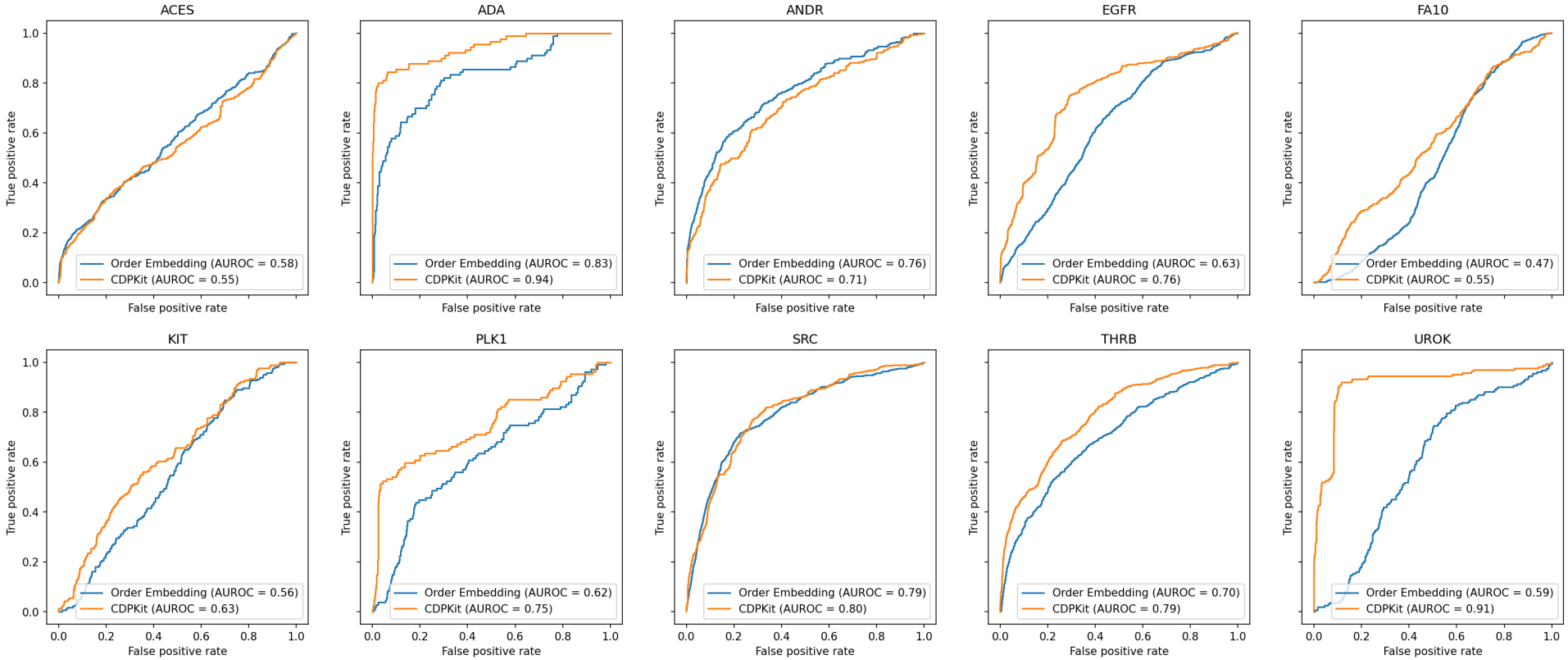


Results – Embedding Visualization



- Embedding space is structured according to graph size
- Pharmacophore feature types are represented
- 3D positional information is included

Results – Screening



	DEKOIS2.0					*LIT-PCBA*					Runtime
	AUROC	BEDROC	$EF_{0.5\%}$	$EF_{1\%}$	$EF_{5\%}$	AUROC	BEDROC	$EF_{0.5\%}$	$EF_{1\%}$	$EF_{5\%}$	per ligand (s)
PharmacoNet	**62.5**	12.3	4.4	4.2	2.9	-	-	-	3.1	-	$5.2 \cdot 10^{-3}$
PharmacoMatch (ours)	60.9	**15.1**	**5.5**	**4.9**	**3.2**	57.4	5.0	6.0	**3.5**	2.2	$\mathbf{3.3 \cdot 10^{-6}}$

Runtimes per Pharmacophore:

- Embedding time
  $67 \pm 7\ \mu s$
- Alignment time
  $66 \pm 6\ \mu s$
- Matching time:
  $0.3 \pm 0.09\ \mu s$

Summary

- Scaling pharmacophore screening to large libraries is challenging
- Pharmacophore screening can be formulated as a contrastive representation learning problem
- The learned representations can be used for efficient pre-screening

https://github.com/molinfo-vienna/PharmacoMatch

https://openreview.net/forum?id=27Qk18IZum

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