Multiscale Topology-enabled AI for Drug Discovery

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Introductions

Drug discovery is critical to modern healthcare but is hindered by traditional methods like molecular docking, free energy perturbation, and empirical modeling, which are time-consuming, costly, and often limited in scope. Deep learning has emerged as a transformative tool, enabling accurate predictions of protein structures and complex patterns while driving a shift toward data-driven approaches. Transformer-based models like ChatGPT demonstrate the promise of self-supervised learning, addressing the scarcity of labeled data in drug discovery. However, challenges remain in adapting these models to capture stereochemical intricacies in protein-ligand interactions. Addressing these limitations could revolutionize drug discovery, making it faster, more accurate, and cost-effective.

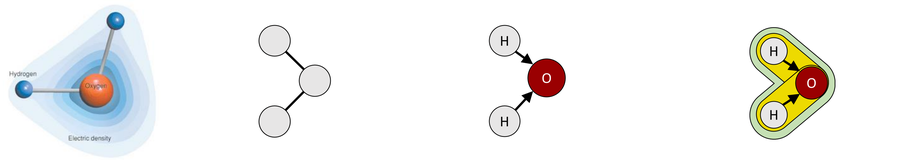
Methods

- **Hyperdigraph**

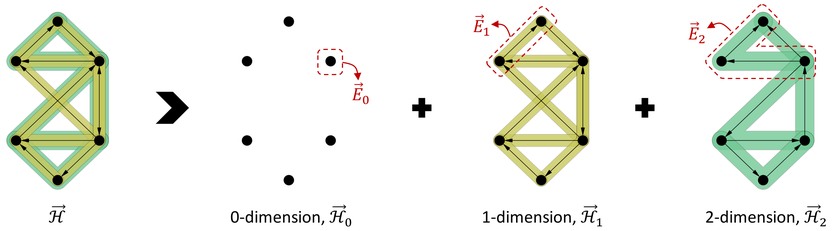
Definition 1: The hyperdigraph on finite vertex set $\boldsymbol{V}$ is defined by

$$\vec{\mathcal{H}} = (V, \vec{E}), \vec{E} = \{e: [k] \to V, [k] = \{0, 1, \dots, k\}\}$$

$\boldsymbol{E}$ is a set of directed hyperedges. A k-directed hyperedge is a sequence including $k+1$ distinct elements in $\boldsymbol{V}$.



(a) Water molecule (b) Graph representation (c) Digraph representation (d) Hyperdigraph representation



- **Hyperdigraph Laplacian**

The chain complex $C_*(V;\mathbb{K}) = C_p(V;\mathbb{K})_{p\geq 1}$ with the boundary operator $\partial_k: C_k(V;\vec{\mathcal{H}}) \to C_{k-1}(V;\vec{\mathcal{H}})$ given by

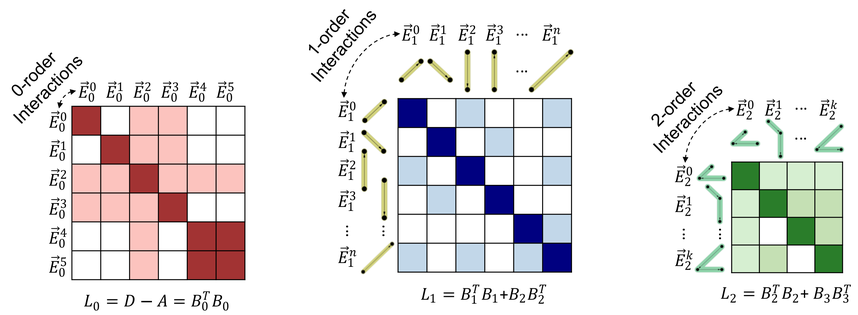
$$\partial_k(x_0, x_1, \dots, x_k) = \sum_{i=0}^{k} (-1)^n (x_0, \dots, \hat{x_i} \dots, x_k), \qquad n \geq 1.$$

The infimum chain complex defined by

$$\Omega_k(\vec{\mathcal{H}};\mathbb{K}) = \{x \in C_k(\vec{\mathcal{H}};\mathbb{K}) | \partial_k x \in C_{p-1}(\vec{\mathcal{H}};\mathbb{K})\}$$

Definition 2: The hyperdigraph Laplacian, $\Delta_k^{\vec{\mathcal{H}}}: \Omega_k(\vec{\mathcal{H}};\mathbb{K}) \to \Omega_k(\vec{\mathcal{H}};\mathbb{K})$ of $\vec{\mathcal{H}}$ is defined by

$$\Delta_k^{\vec{\mathcal{H}}} = \partial_k^* \circ \partial_k + \partial_{k+1} \circ \partial_{k+1}^*, k \geq 1 \quad \textbf{or} \quad L_k^{\vec{\mathcal{H}}} = B_k^T B_k + B_{k+1} B_{k+1}^T, k \geq 1$$



Topological Transformer

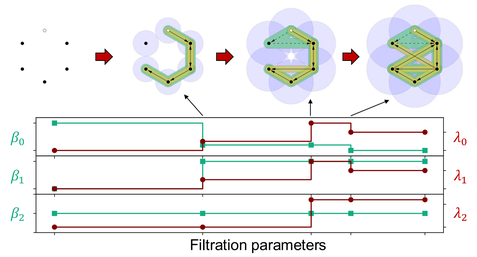
- **Persistent hyperdigraph Laplacian**

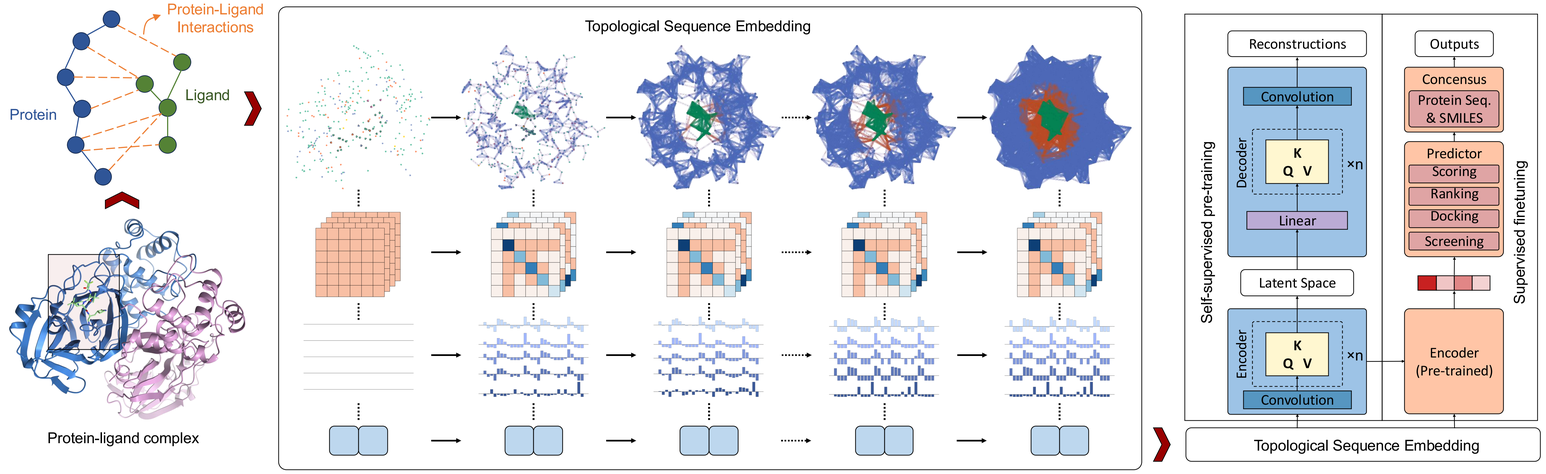
Consider the order set $(S, \leq)$, a filtration of hyperdigraph is a covariant functor $\mathcal{F}: (S, \leq) \to \boldsymbol{Hyper}$ from the category $(S, \leq)$ to the category of hyperdigraph.

Definition 3: For each $a \leq b \in S$, the kth (a,b)-persistent hyperdigraph Laplacian of $\mathcal{F}$ is defined by

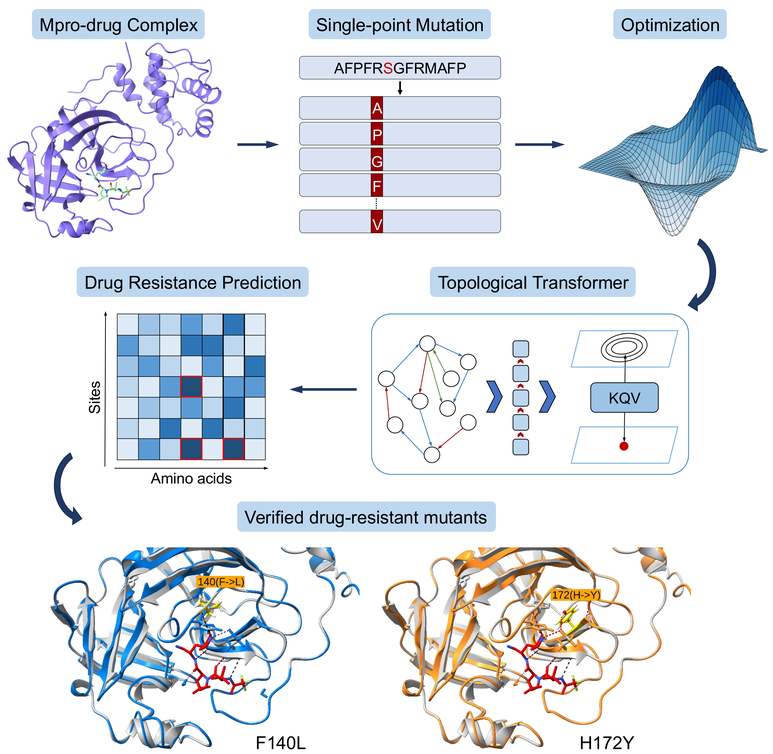
$$\Delta_k^{a,b} = (\partial_k^a)^* \circ \partial_k^a + \partial_{k+1}^{a,b} \circ (\partial_{k+1}^{a,b})^*, \qquad k \geq 0$$

$$L_k^{a,b} = (B_k^a)^T B_k^a + B_{k+1}^{a,b} (B_{k+1}^{a,b})^T, \qquad k \geq 0$$



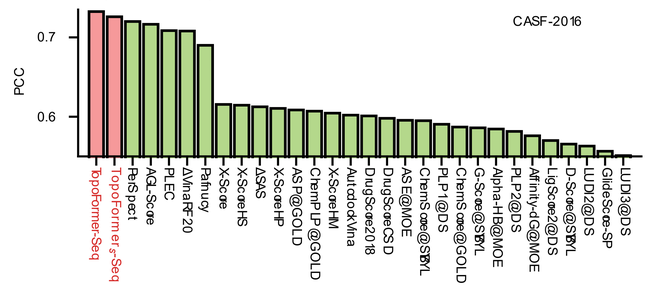


Drug Resistance Predictions



Binding Affinity Predictions

- Achieved the best performance in binding affinity prediction on the PDBbind database, including the CASF-2007, CASF-2013, and CASF-2016 benchmarks.[1]



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References

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