# Joint Design of Protein Surface and Backbone Using a Diffusion Bridge Model

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Paper Link

Code Link

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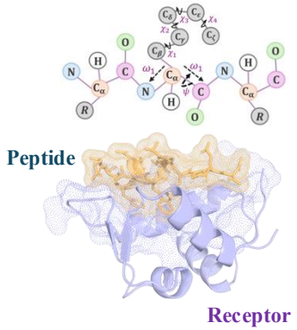
NEURAL INFORMATION PROCESSING SYSTEMS

## Background



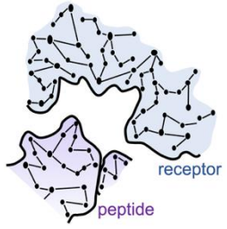

**Peptide backbone**

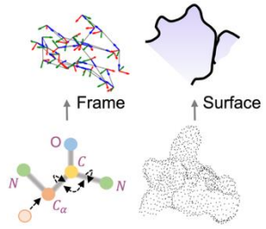
- Four key atoms $N^*, C_\alpha^*, C^*, O^* \rightarrow$ rigid frame.
- Rotation matrix $r_n$ , translation vector $m_n$.

**Side-chain atoms**

- Torsion angles $\chi \in [0,2\pi)^4$.

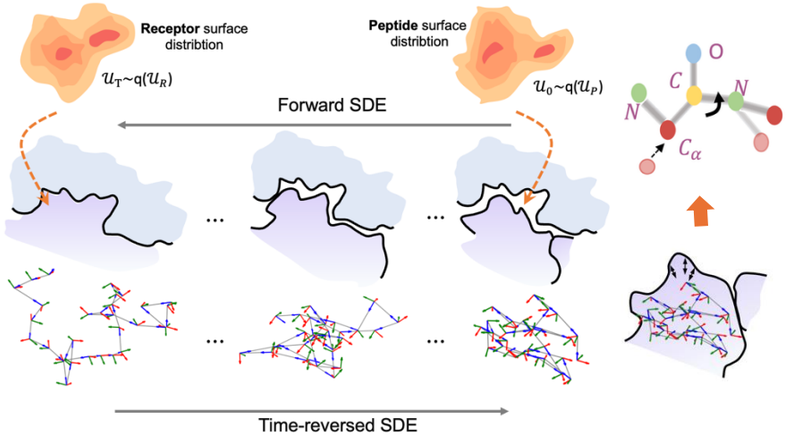
## Challenges & Problems




- PPI interfaces depend on surface complementarity & hydrophobic patterns.
- Most methods: backbone or full-atom generation, but rarely **joint** surface + structure with receptor context.
- Goal: generate ligand (peptide) surfaces and backbones **complementary** to a target receptor.

## Method




- Use receptor surface as **informative prior** (not Gaussian noise).
- Denoising Diffusion Bridge Model (DDBM) maps receptor surface → ligand surface.
- **Doob h-transform** constructs a diffusion bridge between receptor and ligand endpoint distributions $P_0, P_T$.

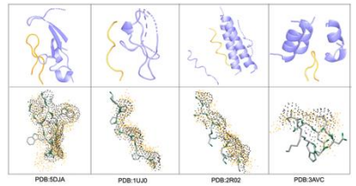
### Surface-Frame Matching Networks

- Backbone via **SE(3) diffusion** over frames (translations + torsions).
- **Surface–Frame Matching Network** for bidirectional info flow.
- Multi-modal diffusion completes full peptide (surface + side-chains).

## Experiments

### Surface-Structure Joint-Design

| | $Div_{stru}$ (↑) | Aff. % (↑) | Stab. % (↑) | RMSD Å(↓) | BSR (↑) |
|---|---|---|---|---|---|
| ProteinGenerator | 0.54 | 13.47 | 23.48 | 4.35 | 24.62 |
| RFDiffusion | 0.38 | 16.53 | 26.82 | 4.17 | 26.71 |
| Chroma (RIA) | 0.59 | 17.96 | 16.69 | 3.97 | 74.12 |
| PPFLOW | 0.53 | 17.62 | 17.25 | 2.94 | 78.72 |
| PepGLAD | 0.32 | 10.47 | 20.39 | 3.83 | 19.34 |
| PepFlow w/Bb | 0.64 | 18.10 | 14.04 | 2.30 | 82.17 |
| PepFlow w/Bb+Seq | 0.50 | 19.39 | 19.20 | 2.21 | 85.19 |
| PepFlow w/Bb+Seq+Ang | 0.42 | 21.37 | 18.15 | 2.07 | 86.89 |
| PepBridge w/Bb+surf | 0.60 | 20.07 | 21.75 | 2.04 | 84.62 |
| PepBridge w/Bb+Seq+surf | 0.62 | 22.07 | 20.71 | 2.18 | 84.91 |
| PepBridge w/Bb+Seq+Ang+surf | 0.59 | 19.16 | 25.02 | 2.19 | 83.90 |




- PepBridge (Bb+Seq+Surf) achieves top with low Cα-RMSD.
- Joint surface–backbone co-design improves binding-site coverage and stability over backbone-only baselines.

### Visualization

Visualized examples show PepBridge generating ligand surfaces and backbones that tightly complement receptor pockets at the binding interface.

### Side-Chain Packing

Modeling **interface geometry** with a diffusion **bridge** + SE(3) backbone yields complementary, stable designs.

| | Angle MAE °(↓) | | | | Angle Accuracy %(↑) | | |
|---|---|---|---|---|---|---|---|
| | $\chi_1$ | $\chi_2$ | $\chi_3$ | $\chi_4$ | All residues | Core residues | Surface residues |
| SCWRL4 | 29.79 | 30.12 | 52.38 | 62.03 | 45.93 | 66.25 | 34.59 |
| DLPacker | 28.35 | 32.62 | 54.69 | 59.60 | 49.00 | 68.03 | 39.56 |
| AttnPacker | 29.61 | 28.83 | 47.66 | 53.64 | 47.53 | 71.65 | 38.90 |
| DiffPack | 26.29 | 29.57 | 47.64 | 56.85 | 55.86 | **79.62** | 41.31 |
| PepFlow w/Bb+Seq+Ang | 27.61 | **25.60** | 48.20 | 54.02 | 54.29 | 70.47 | 44.06 |
| PepBridge (ours) | **25.96** | 26.76 | **46.81** | **52.95** | **56.71** | 73.79 | **46.17** |

### Ablation study

| Ablations | $Div_{stru}$ (↑) | $Div_{surf}$ (↑) | Aff. % (↑) | Stab. % (↑) | RMSD Å(↓) | BSR (↑) | Con. (↑) |
|---|---|---|---|---|---|---|---|
| PepBridge | **0.59** | **0.46** | **19.16** | **25.02** | **2.19** | **83.90** | **0.43** |
| -bridge/+vanilla diffusion | 0.42 | 0.39 | 15.97 | 17.72 | 3.18 | 46.21 | 0.31 |
| -bridge/+CFG diffusion | 0.39 | 0.41 | 16.38 | 19.32 | 3.46 | 57.39 | 0.36 |
| -surface context | 0.51 | – | 16.17 | 15.37 | 4.21 | 31.37 | – |
| -surface&frame matching | 0.42 | 0.35 | 14.82 | 22.41 | 3.71 | 54.71 | 0.25 |