Token-Level Guided Discrete Diffusion For Membrane Protein Design

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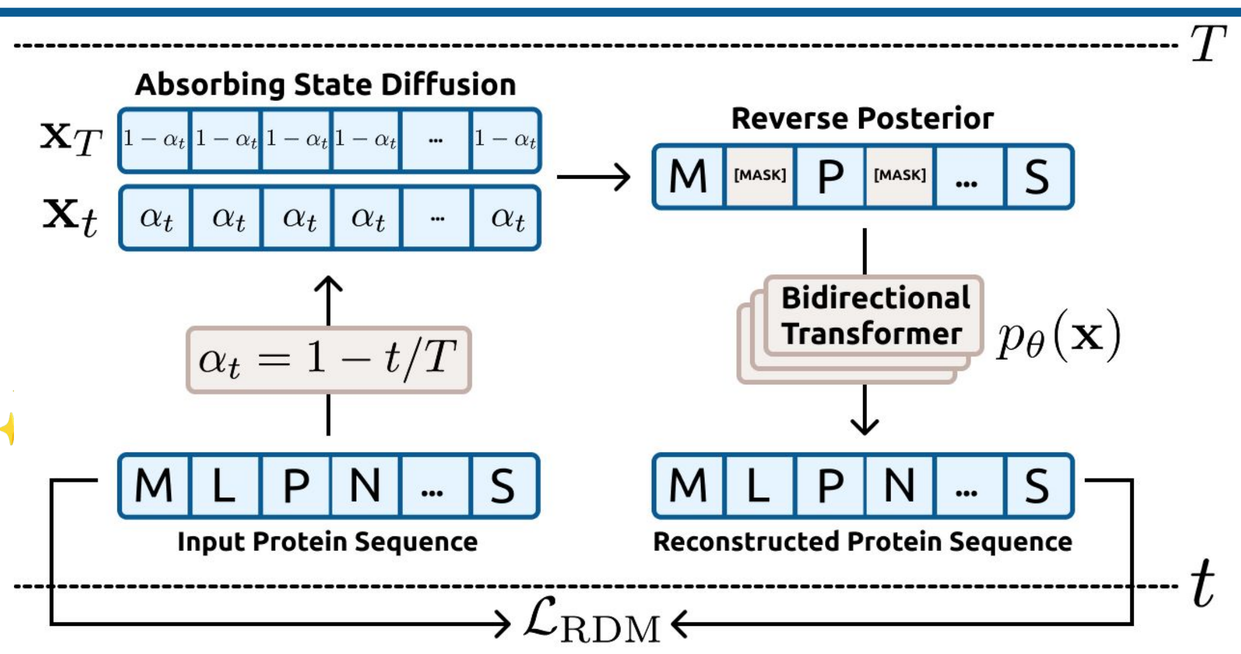
Motivation

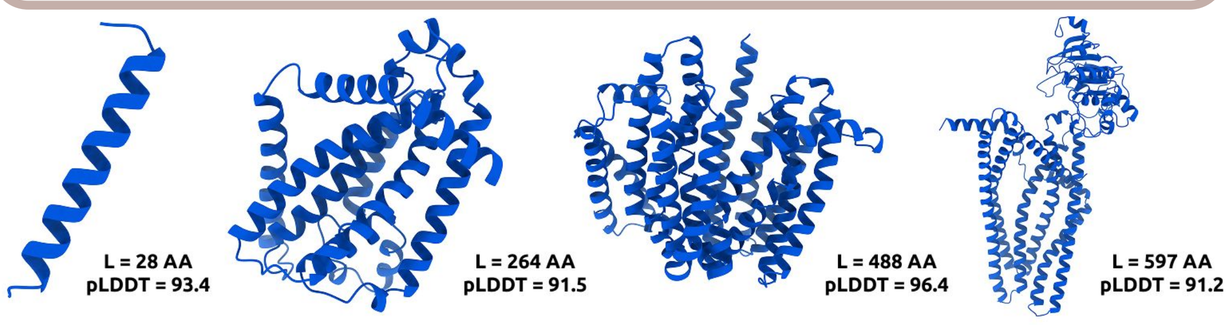
Membrane proteins regulate signaling and transport, rendering them **prime targets for therapeutic intervention**. However, they are challenging to design:

- Structure-based membrane protein design methods are severely limited by the **scarcity of high-resolution membrane protein structures** (~1% of the PDB).
- Autoregressive language models **struggle to capture the long-range** dependencies of interleaved transmembrane and soluble regions.
- Existing diffusion guidance strategies **lack the token-level precision** required to solubilize exposed loops while strictly preserving critical transmembrane domains.

Membrane Diffusion LM Architecture

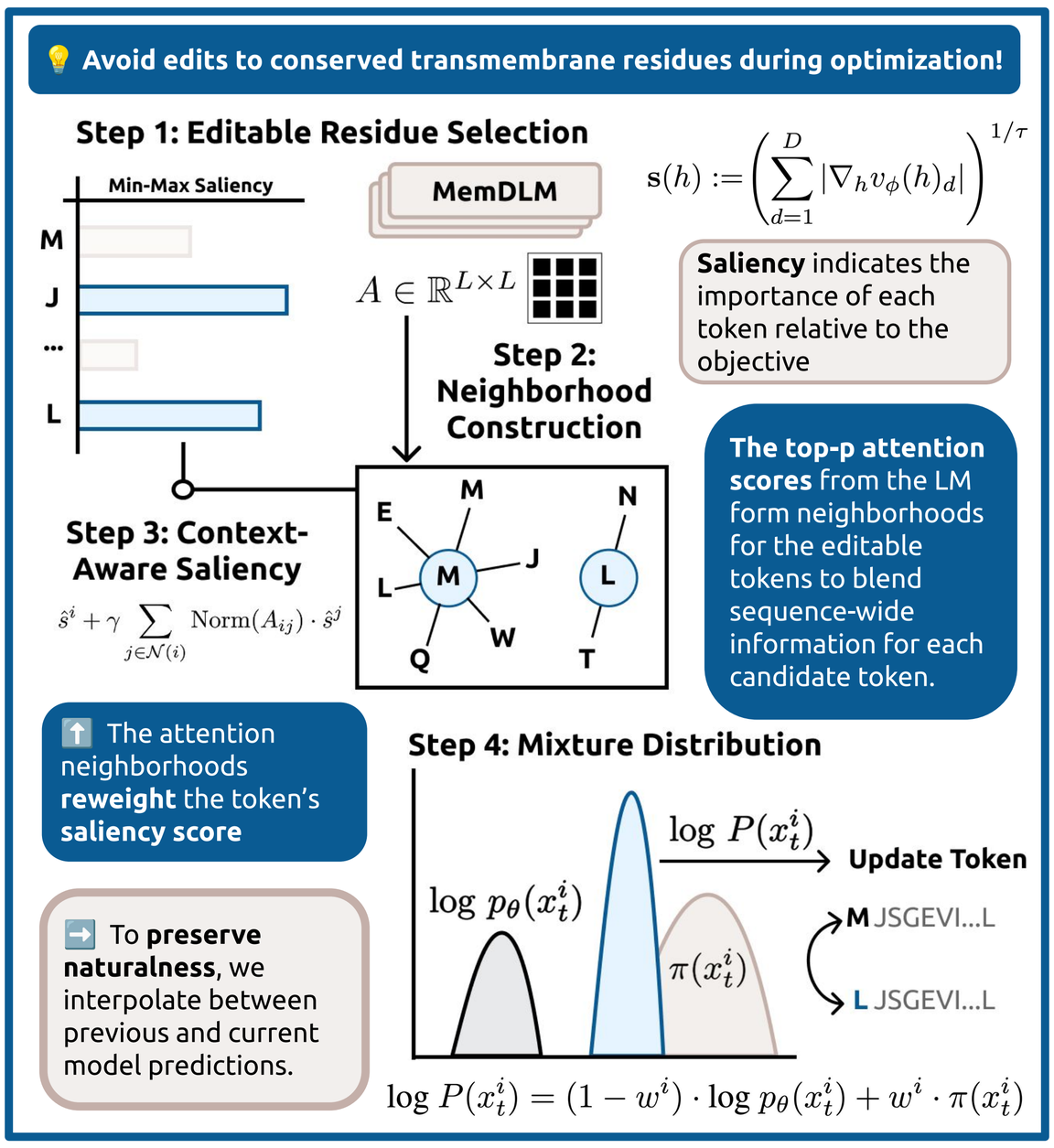


- We fine-tune the EvoFlow protein LM on a **reparameterized diffusion model (RDM) training objective**, forcing our model to learn denoising over higher masking rates
- During inference, the trained MemDLM can ***de novo* generate high-quality, plausible membrane protein sequences** from a fully masked prior



Per-Token Discrete Classifier Guidance

💡 **Avoid edits to conserved transmembrane residues during optimization!**

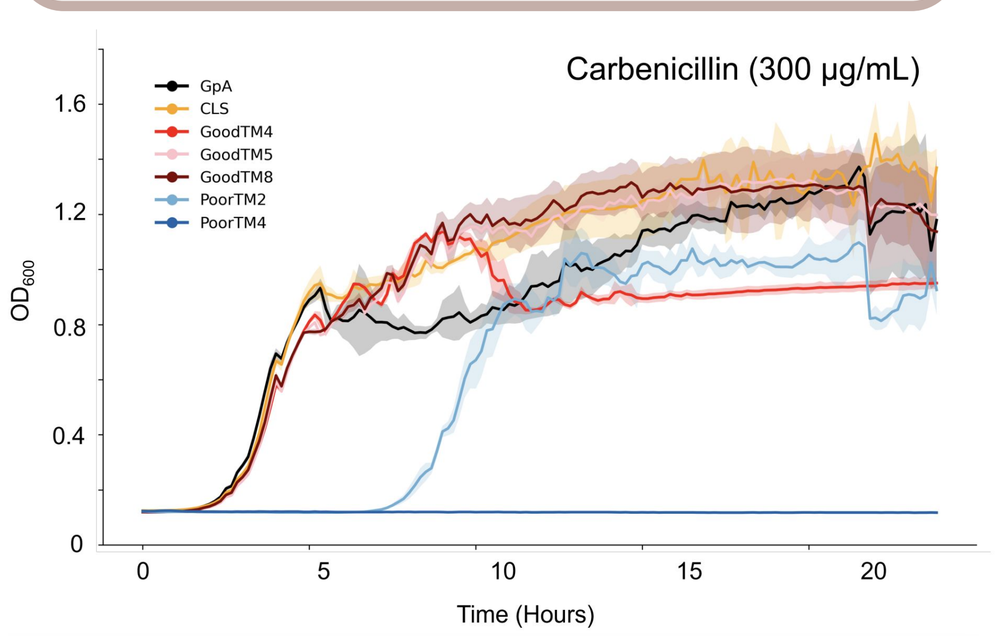


Unconditional Sequence Generation

	pLDDT (↑)	TMRD	PPL (↓)	Entropy (↑)
Test Set	76.637±10.676	0.294±0.219	5.707±3.435	3.918±0.253
ProGen2	54.998±19.235	0.048±0.153	126.646±1415.166	2.622±1.290
DPLM	62.318±20.669	0.310±0.264	**6.323**±10.317	3.179±0.812
MemDLM	**67.410**±14.828	**0.311**±0.250	6.344±3.278	**3.743**±0.326

⬆️ **MemDLM** more effectively **captured the underlying distribution** of membrane protein sequences

⬇️ In the TOXCAT β–lactamase growth assay, MemDLM-generated sequences exhibit **growth kinetics similar to natural** membrane proteins



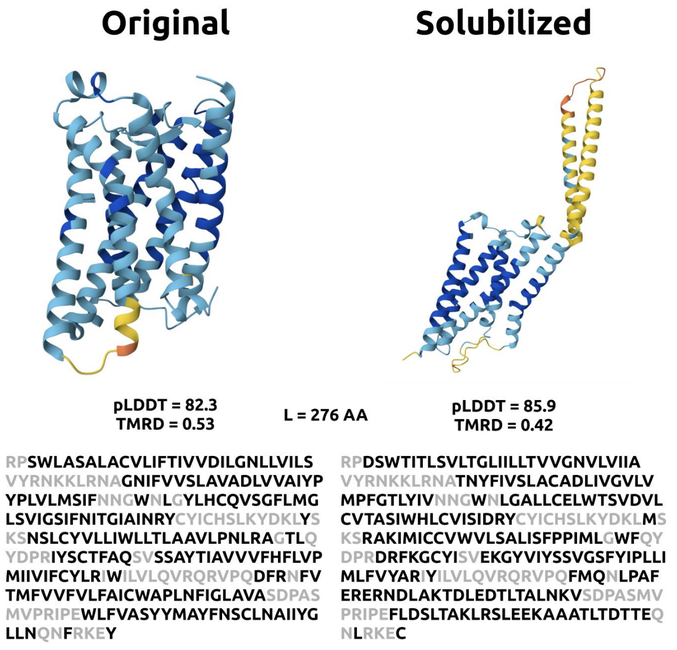
Motif Scaffolding & Representation Learning

Model	Solubility (↑)	Membrane Localization (↑)
ESM-2-650M	0.9383	0.6011
Fine-Tuned ESM-2	0.9375	0.6000
MemDLM	0.9375	0.5964

	Motif	pLDDT (↑)	PPL (↓)	BLOSUM (↑)	Entropy (↑)
Test Set	Insol	76.637±10.676	5.707±3.435	–	3.918±0.253
	Sol	76.637±10.676	5.707±3.435	–	3.918±0.253
EvoDiff	Insol	**64.058**±19.229	9.841±4.091	2.176±1.587	3.841±0.268
	Sol	64.036±19.145	4.632±3.271	-0.188±1.134	**3.841**±0.268
MemDLM	Insol	62.762±21.212	**8.748**±14.777	**2.964**±1.559	**3.876**±0.341
	Sol	**70.112**±16.912	**3.242**±2.362	**0.512**±1.556	3.803±0.321

MemDLM **scaffolds** over transmembrane and soluble motifs and **encodes important membrane protein features** in its learned latent space

Solubilization & Scaffold Retention



Metric	Test Set	MemDLM
pLDDT (↑)	76.637±10.676	62.979±17.906
TMRD (↓)	0.294±0.219	0.181±0.192
PPL (↓)	5.707±3.435	8.472±4.879
BLOSUM (↑)	–	0.495±2.346
Entropy (↑)	3.918±0.253	3.870±0.268

- PET solubilizes targeted transmembrane residues while retaining a sequence scaffold
- Solubilized sequences have positive BLOSUM scores, indicating PET's edits are evolutionarily conserved

Conclusions

Our results establish MemDLM as the first experimentally validated, classifier-guided discrete diffusion framework for membrane protein design, operating without structural templates. Per-Token Guidance (PET) enables solubilization while preserving functional TM scaffolds, offering controllability unattainable by traditional diffusion guidance methods. Benchmarking against SOTA models (DPLM, EvoDiff), MemDLM demonstrates superior motif scaffolding and *de novo* generation quality. Finally, the TOXCAT-β-lactamase assay shows our designs successfully insert into membranes , establishing MemDLM as a versatile platform for engineering programmable membrane protein therapeutics.

Acknowledgments

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Read the full paper!

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