

# Hybrid Computational Modelling of Human Voltage-Gated Sodium Channels for Isoform-Specific Therapeutic Design

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## Introduction

Voltage-gated sodium channels are membrane proteins that open and close in response to voltage changes to allow Na<sup>+</sup> influx in excitable cells, enabling action potentials, muscle contraction, and electrical signaling.

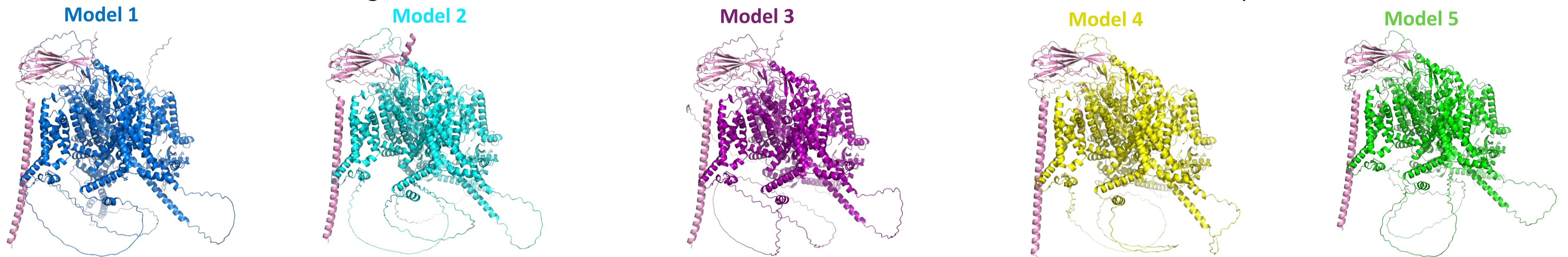
## AIM

Apply a hybrid modelling strategy that combines artificial intelligence and physics-based refinement to build a realistic 3D models of NaV channels

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## AI MODEL GENERATION WITH ALPHAFOLD3

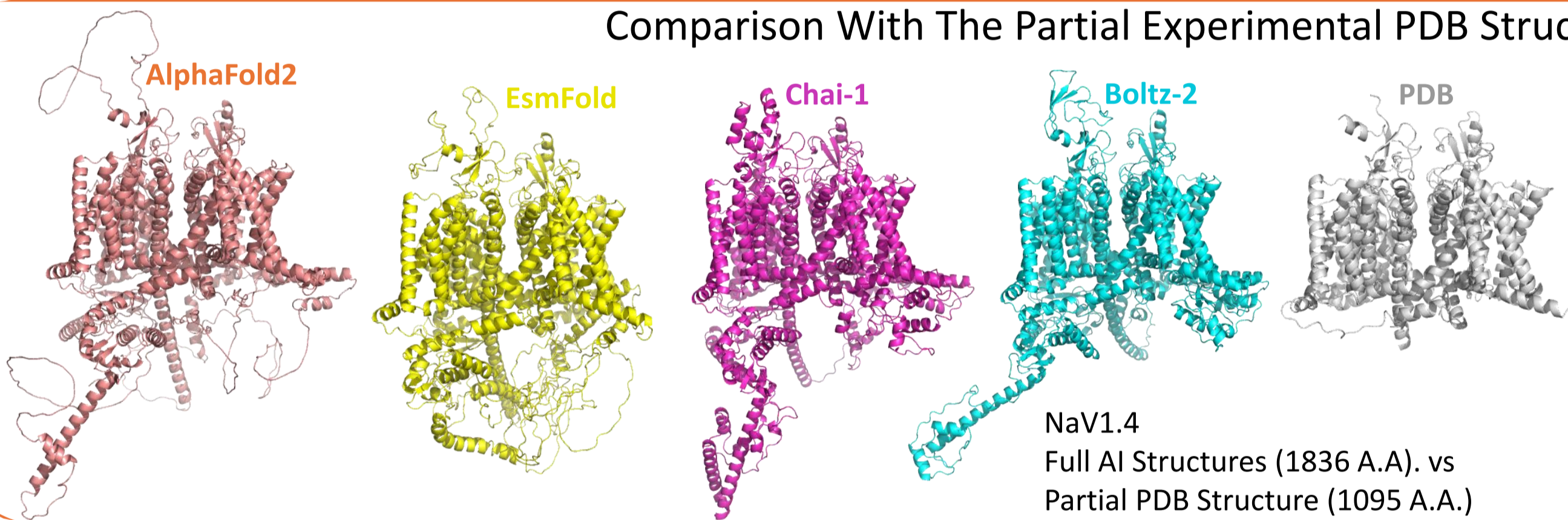
Five Full-Length Human NaV Channel Models Of Each Isoform Generated With UniProt Sequence



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## STRUCTURAL COMPARISON AGAINST MULTIPLE REFERENCES

Comparison With The Partial Experimental PDB Structure As Reference



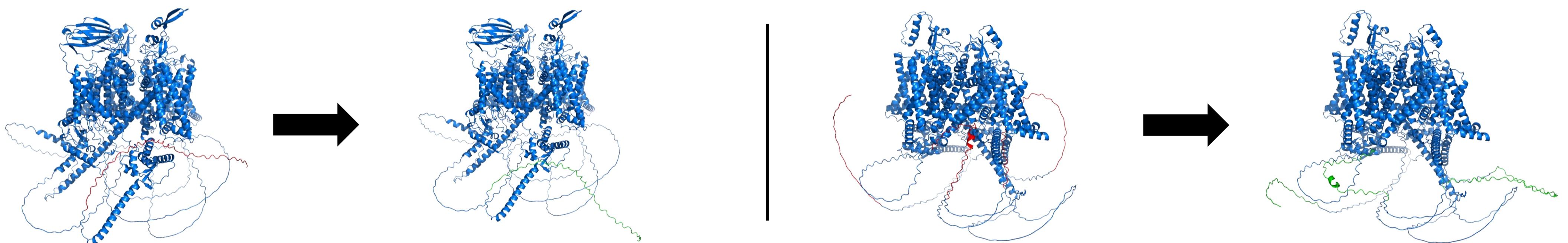
	AlphaFold3	AlphaFold2	EsmFold	Chai-1	Boltz-2
NaV1.1	1.3	1.3	3.6	2.3	1.9
NaV1.2	1.1	1.2	3.3	2.1	1.8
NaV1.3	0.8	1.4	3.1	2.5	1.2
NaV1.4	1.0	1.2	3.6	2.5	1.8
NaV1.5	0.9	1.5	6.3	2.6	1.9
NaV1.6	1.3	1.5	3.8	2.6	1.8
NaV1.7	0.8	1.2	3.6	2.3	1.6
NaV1.8	0.8	1.4	3.2	1.9	1.5

Average of RMSD Values (Å)

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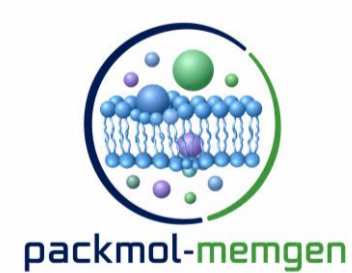
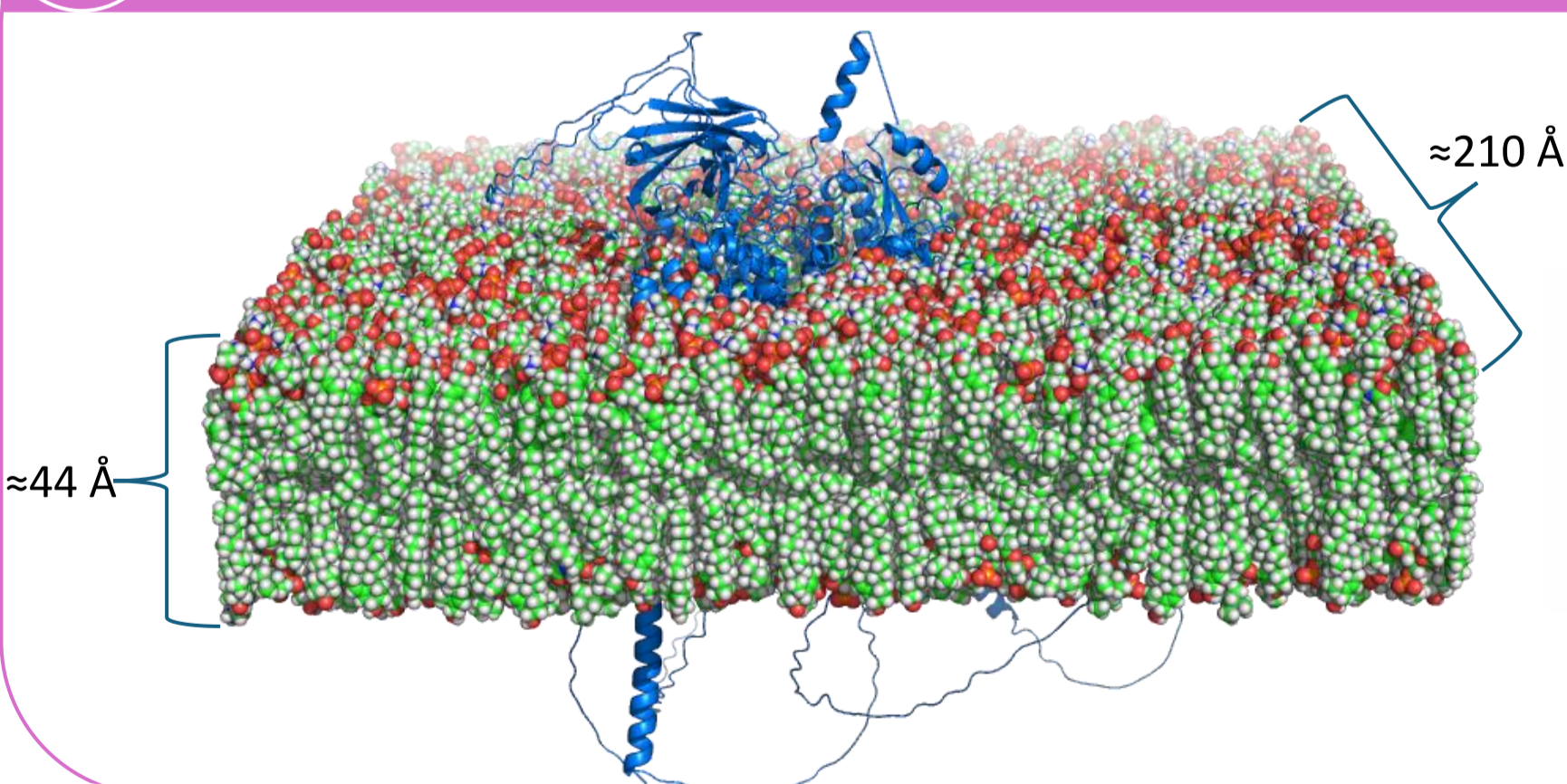
## MANUAL LOOP ADJUSTMENT IN PYMOL

Loop Regions Inspected and Refined Based on Structural Assessment and Biological Knowledge



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## EMBEDDING INTO A REALISTIC HETEROGENEOUS HUMAN-LIKE MEMBRANE



### Membrane Composition

Phosphatidylcholine	28%
Phosphatidylethanolamine	16%
Sphingosine	15%
Cholesterol	32%
Phosphatidylserine	5%
Phosphatidic acid	1%
Phosphatidylinositol	3%

### Advantages

Realistic physical and chemical environment:

- Orientation
- Diffusion
- Binding
- Conformational Changes

Interpretation Improvement of:

- Molecular Dynamics
- Binding Studies

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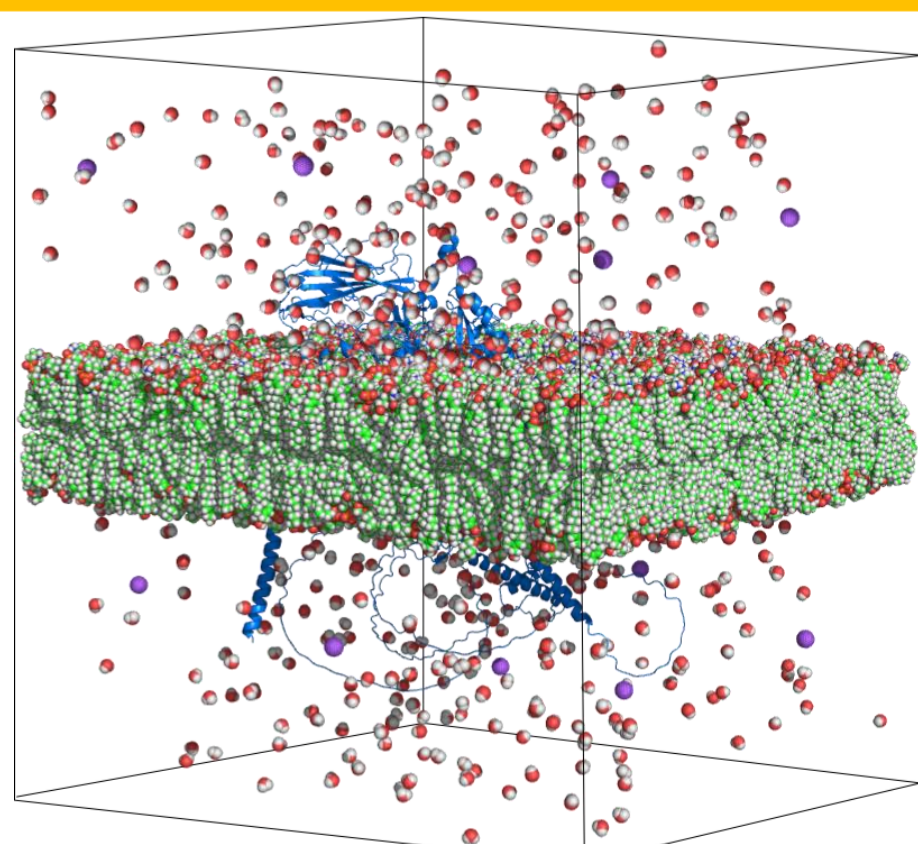
## MOLECULAR DYNAMICS REFINEMENT

All-Atom MD Simulations to Refine Structure and Assess Stability and Dynamics

### Force Fields

Lipid17  
(lipids)

ff14SB  
(proteins)



Explicit Water  
(TIP3P)

Analysis  
- RMSD  
- RMSF  
- Channel Opening

