AI-Assisted and Physics-Refined Modeling of Human Voltage-Gated Sodium Channels for Selective Target Discovery

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Introduction

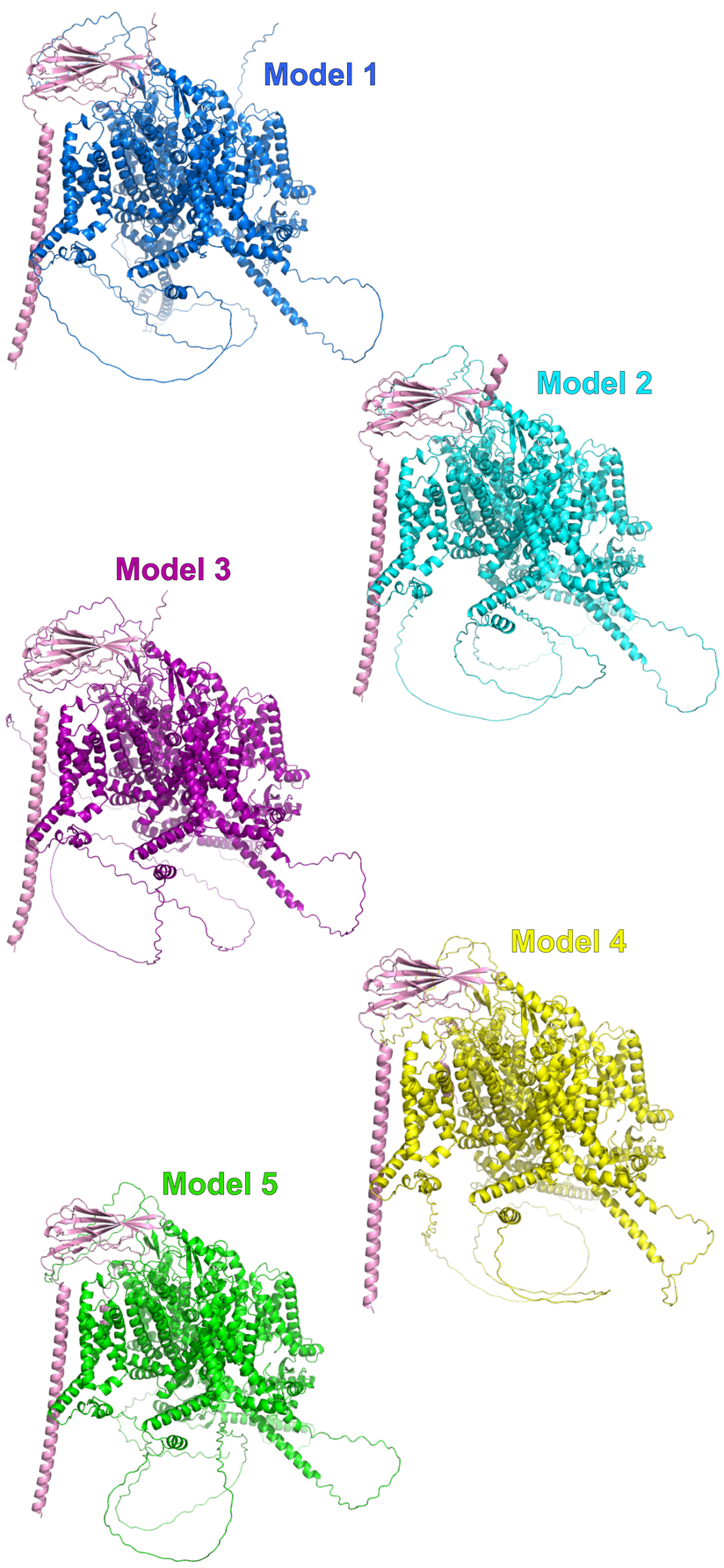
Voltage-gated sodium channels are membrane proteins that open and close in response to voltage changes to allow Na^+ influx in excitable cells, enabling action potentials, muscle contraction, and electrical signaling.

AIM

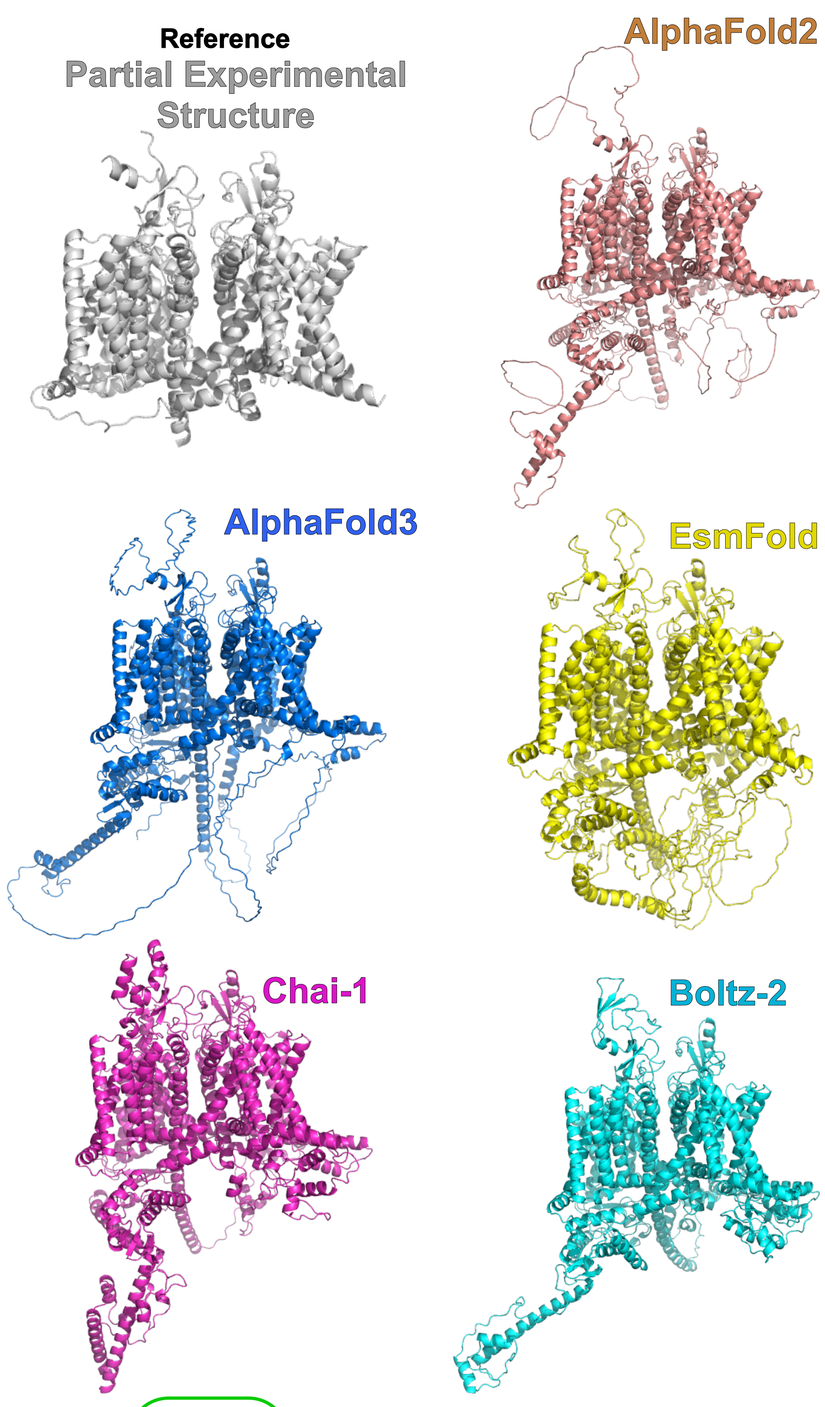
Apply a hybrid modelling strategy that combines artificial intelligence and physics-based refinement to build a realistic 3D models of NaV channels

1 AI MODEL GENERATION WITH ALPHAFOLD3

Generation of Five Full-Length Human NaV Channel Models of Each Isoform



2 STRUCTURAL COMPARISON

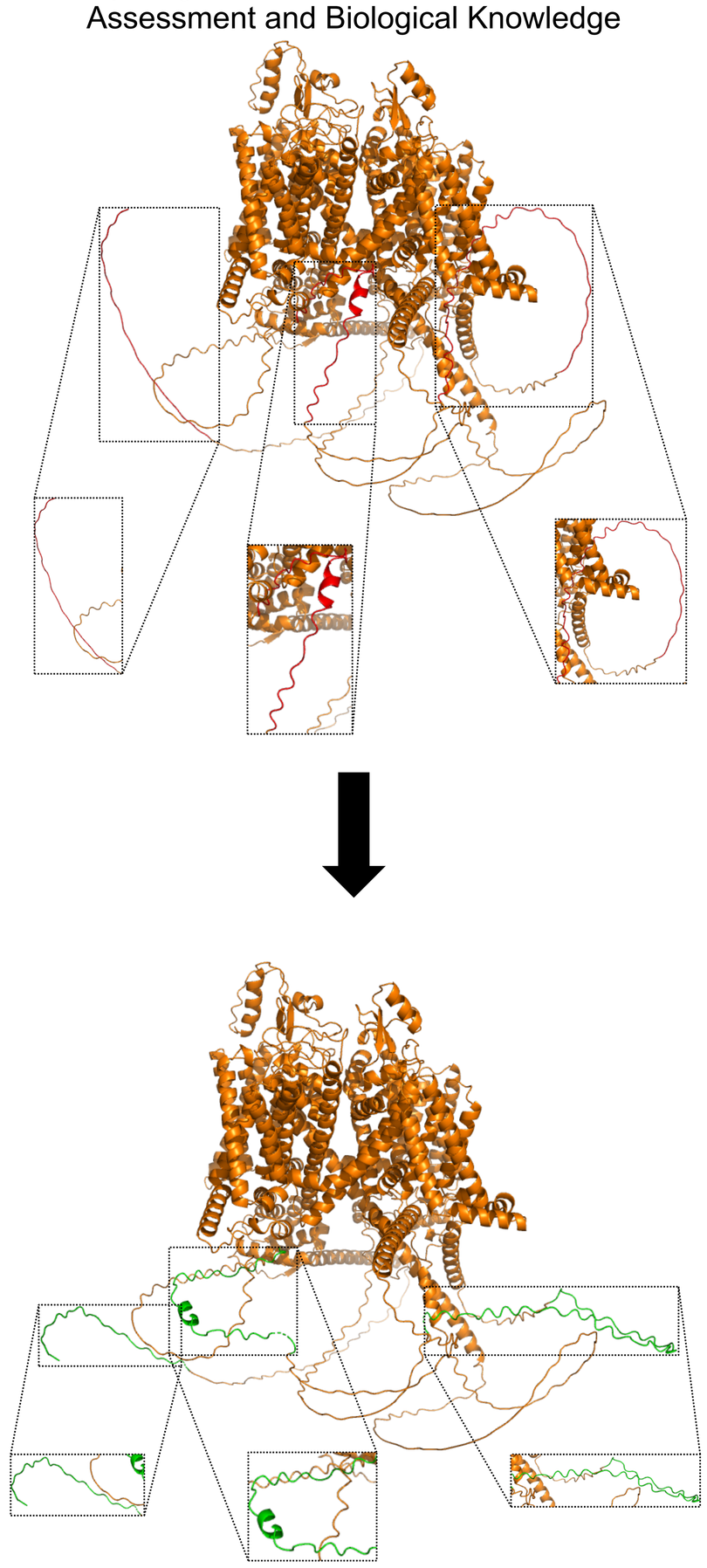


	AlphaFold3	AlphaFold2	EsmFold	Chai-1	Boltz-2
NaV1.1	1.3	1.3	3.6	2.3	1.9
NaV1.2	1.1	1.2	3.3	2.1	1.8
NaV1.3	0.8	1.4	3.1	2.5	1.2
NaV1.4	1.0	1.2	3.6	2.5	1.8
NaV1.5	0.9	1.5	6.3	2.6	1.9
NaV1.6	1.3	1.5	3.8	2.6	1.8
NaV1.7	0.8	1.2	3.6	2.3	1.6
NaV1.8	0.8	1.4	3.2	1.9	1.5

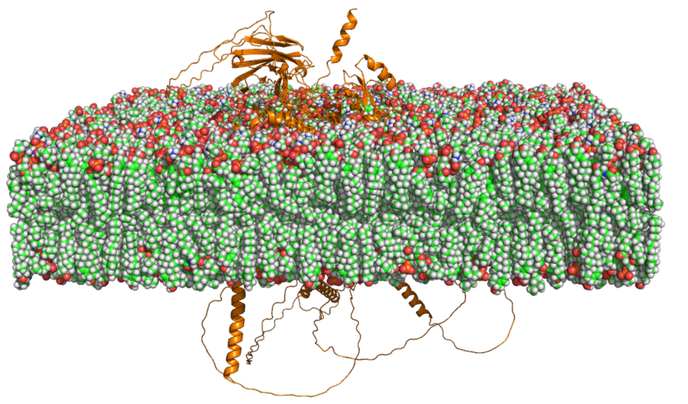
Average of RMSD Values (Å)

3 MANUAL LOOP ADJUSTMENT IN PYMOL

Loop Regions Refined Based on Structural Assessment and Biological Knowledge



4 HUMAN-LIKE MEMBRANE GENERATION



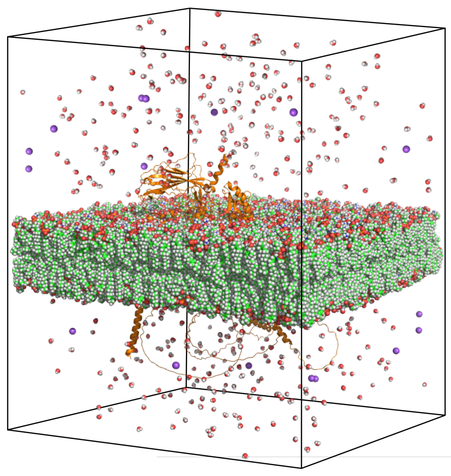
Thickness ≈ 44 Å / Length ≈ 210 Å / Width ≈ 210 Å

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

5 MOLECULAR DYNAMICS REFINEMENT

Force Fields

- **Lipid17** (lipids)
- **ff14SB** (proteins)



- Explicit Water (TIP3P)
- Analysis - RMSD -RMSF
- 1000 ns
- MDs in Progress

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