

Mutant Nav1.5 (SCN5A, rsid) — MSM Pipeline

Martini 3 CG · HREMC · Independent Local Matrices

SIM

HREMC Simulation

12 replicas \times 1,000 frames = 12,000 total
 $\lambda = 1.0 \rightarrow 0.5$, 1,000 cycles, 100 ns/replica

λ schedule:
1.0, 0.939, ..., 0.5

B/N

Bottleneck Identification

Low pairs: (1 \leftrightarrow 2) 6.2%, (6 \leftrightarrow 7) 4.2%
Overall acceptance: 16.0%

Block 1
Rep {0,1}
2,000 fr

Block 2
Rep {2,3}
2,000 fr

Rep {4,5,6} excluded
Block 3
Rep {7-11}
5,000 fr

island between (4 \leftrightarrow 5) & (6 \leftrightarrow 7)

S1

Step 1: Feature Extraction

24,349 features \times 9,000 frames
BB distances, Q , dihedrals, R_g , inter-domain

S2

Step 2: TICA (PCA-whitened)

57 PCA \rightarrow 20 TICs, $\tau = 10$ frames
TIC 1: 144 ns, TIC 2: 60.1 ns

Whitened SVD
solves $d \gg N$

S3

Step 3: k-Medoids Clustering

FasterPAM, $k = 200$, silhouette = 0.276
Pop. range: 10–110, all non-empty

S4

Step 4: Count Matrices (per-block)

$C^{(b)}(\tau=10)$, strict block boundaries
SCCs: 52, 55, 158 — all retained

All 3 blocks
included

S5

Step 5: Transition Matrices

Blocks 1+2+3 aggregated \rightarrow SCC: 200 states
 T^{rev} , T^{nonrev} ; CK test $L_2 \leq 0.033$

0 states dropped
(full SCC=200)

S6

Step 6: Stationary Distribution

$\pi^T \mathbf{T} = \pi^T$, $H/H_{\text{max}} = 0.987$
90% mass in 163 / 200 states

$\|\pi T - \pi\|_2 < 10^{-16}$

S7

Step 7: Free Energy Landscapes

$\Delta G = -k_B T \ln \pi_i$, $T = 310$ K
B1: 0–4.5, B2: 0–4.0, B3: 0–4.6 $k_B T$

12 \times 2D FES contour maps + 1D profiles
 π , \mathbf{T} , eigenvalues, CK test

vs WT: Slowest ITS 377.7 ns (WT: 306.2 ns)
 $H/H_{\text{max}} = 0.987$ (WT: 0.972); SCC 200 (WT: 197)