PRISM-4D

Photonic Resonance Imaging for Structural Molecular Dynamics

Computational Methodology Briefing

For Reviewer Validation of MYC-MAX Cryptic Binding Site Detection

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This document describes the exact computational pipeline, physics models, signal processing chain, and output interpretation guidelines for the PRISM-4D cryptic binding site detection run on PDB 1NKP (MYC-MAX heterodimer). It is intended to allow an independent analyst to validate and reproduce the findings without access to the codebase.

1. Executive Summary

PRISM-4D is a GPU-accelerated molecular dynamics platform for cryptic binding site detection. It combines five distinct computational techniques into a single fused execution pipeline: (1) AMBER-class molecular dynamics with Langevin thermostat, (2) simulated cryogenic-to-physiological temperature ramping, (3) UV photon energy deposition at aromatic chromophores, (4) neuromorphic spike detection for cooperative dewetting events, and (5) RT-core-accelerated BVH ray tracing for geometric cavity identification.

The MYC-MAX run described herein detected a cross-chain transient pocket at the coiled-coil dimerization interface (MYC residues 407-419, MAX residues 77-88) that overlaps the experimentally validated MYCHot2 binding site and independently identified 5 of 7 critical MAX dimerization residues determined by alanine scanning mutagenesis. No prior structural knowledge, ligand data, or experimental binding site annotations were provided as input.

2. Molecular Dynamics Engine

2.1 Force Field and Integration

The core MD engine implements the AMBER ff14SB force field with Generalized Born / Surface Area (GB/SA) implicit solvation. This is not an approximation to AMBER — it uses the identical potential energy function with published ff14SB parameters loaded from AMBER-format topology files generated by tleap/PDBFixer.

Force field components computed at each timestep:

Component	Formula / Method	Precision
Bond stretching	Harmonic: $E = k(r - r0)^2$	FP32
Angle bending	Harmonic: $E = k(\theta - \theta 0)^2$	FP32
Dihedral torsion	Fourier: $E = V/2\ [1 + \cos(n\varphi - \gamma)]$	FP32
Van der Waals	LJ 12-6: σ/ε parameters	FP16 params, FP32 accumulation
Electrostatics	Coulomb with GB screening	FP32
Solvation	GB/SA (Generalized Born + SASA)	FP32

Integration: **Velocity Verlet** with **Langevin thermostat** for temperature control. Timestep: 2.0 fs (with Hydrogen Mass Repartitioning). SHAKE/RATTLE constraints applied to all bonds involving hydrogen via 906 H-clusters identified at topology loading.

2.2 Mixed Precision Architecture

The engine uses a validated mixed-precision strategy to maximize GPU throughput without sacrificing physical accuracy:

Operation	Compute Precision	Accumulation	Rationale
LJ σ, ε storage	FP16	FP32	Short-range; errors cancel across pair interactions
LJ force computation	FP32	FP32	Kahan summation in 256-atom tiles
Coulomb + GB	FP32	FP32	erfc() needs mantissa precision
Bonded forces	FP32	FP32	Small count, must be exact
Position/velocity	FP32	FP32	Integration accumulates over 10^5+ steps
Coordinate storage	FP32	—	0.001Å precision sufficient for MD

This is equivalent to the mixed-precision strategy used in production AMBER GPU builds (pmemd.cuda), where LJ parameters are stored at reduced precision while forces accumulate at FP32. Energy conservation is monitored continuously.

2.3 Implicit Solvent Model

GB/SA implicit solvent replaces explicit water molecules with a continuum dielectric. Born radii are computed per-atom at each step, and the solvent-accessible surface area (SASA) term provides the nonpolar solvation contribution. This choice is deliberate for two reasons: (1) it eliminates the 10-100x

atom count overhead of explicit water, enabling 100,000+ timesteps/second on consumer hardware, and (2) the absence of explicit water molecules means that cooperative dewetting detection via the LIF network is measuring the implicit solvent density field, not counting discrete water molecules. The physics being detected is the same — transient exposure of hydrophobic surface patches — but the signal path is through the GB/SA energy landscape rather than explicit water counting.

Methodological Note for Reviewers

The implicit solvent approach means "dewetting" in PRISM-4D refers to regions where the GB/SA implicit hydration potential drops below the cooperative threshold, indicating that explicit water would be thermodynamically disfavored at that location. This is physically equivalent to cooperative dewetting in explicit-solvent simulations but measured through a different observable.

3. Cryogenic Temperature Protocol

The simulation executes a three-phase temperature protocol designed to separate thermal noise from genuine conformational events:

Phase	Steps	Duration	Temperature	Purpose
1. Cold Hold	50,000	100 ps	100 K (constant)	Establish noise floor; protein locked in crystal conformation
2. Temperature Ramp	62,500	125 ps	100 K → 310 K (linear)	Gradual thermal activation; cavities begin opening
3. Warm Hold	62,500	125 ps	310 K (constant)	Physiological breathing dynamics; full pocket sampling

Total: 175,000 steps, 350 ps of simulation time.

Rationale: The cold hold phase is critical. At 100 K, the protein is vibrationally frozen in its crystal conformation. Any spikes detected during this phase represent instrumental noise or numerical artifacts, not real conformational events. The ramp phase then reveals which cavities open first as thermal energy is supplied. The warm hold provides the production ensemble at physiological temperature. Differential analysis (warm spikes minus cold spikes) isolates genuine binding site signals from baseline noise.

3.1 Three-Way Ablation Analysis

Every production run includes mandatory ablation (unless --skip-ablation is specified for pre-validated reruns):

Condition	Temperature	UV Excitation	Expected Spikes	Purpose
Baseline	300 K constant	OFF	0	Verify LIF network rejects thermal noise
Cryo-only	100 K → 310 K ramp	OFF	0	Verify temperature alone does not trigger false positives
Cryo + UV	100 K → 310 K ramp	ON (multi-λ)	10^5 - 10^6	Production signal: UV-driven pocket opening

A valid run produces zero spikes in both control conditions and >10^4 spikes in the cryo+UV condition. If the controls produce nonzero spikes, the LIF threshold requires recalibration before the results can be interpreted.

4. UV Photon Energy Deposition

4.1 Physical Basis

PRISM-4D deposits UV photon energy at aromatic chromophore residues within the protein. This is a computational analog of cryo-UV fluorescence spectroscopy (Haas et al., Bhagwan et al.), where UV illumination of a cryogenically cooled protein preferentially excites aromatic residues and the resulting fluorescence/thermal response reveals local structural features.

In the simulation, each UV "burst" deposits a calibrated amount of thermal energy at the centroid of an aromatic ring system. The energy is computed from the photophysics of each chromophore type:

Chromophore	Residue	λmax (nm)	ε ($M^{-1}cm^{-1}$)	η (heat yield)	ΔT per burst
Indole	TRP	280	5,500	0.79 (Dawson 1968)	14.2 K
Phenol	TYR	274	1,400	0.86 (Ghisaidoobe 2014)	5.1 K
Benzene ring	PHE	258	200	0.87	0.86 K
Imidazole	HIS/HID/HIE/HIP	258	5,700	0.86	2.8 K
Benzene (cosolvent)	BNZ virtual probe	254	204	0.71 (Cundall 1972)	0.84 K

Wavelength hopping: The UV source cycles through [280, 274, 258, 254, 211] nm on successive bursts (every 250 timesteps, 50-step duration per burst). This ensures all chromophore types are excited across the run, with each type receiving near-peak excitation at its resonant wavelength.

4.2 Benzene Cosolvent Probes (BNZ)

The MYC-MAX run used PRISM4D_COSOLVENT=1 mode, which injects virtual benzene probes at hydrophobic surface residues (LEU, ILE, VAL). These are not physical benzene molecules in the simulation box — the implicit solvent model has no explicit co-solvent. Instead, the engine identifies hydrophobic aliphatic residues and treats their Cα atoms as UV-absorbing targets with benzene photophysical properties (λmax = 254 nm, ε = 204 $M^{-1}cm^{-1}$).

Why this matters: Native aromatic residues (TRP, TYR, PHE) are the natural UV targets, but MYC-MAX has only 6 native aromatics in the dimer construct. The coiled-coil interface is dominated by leucines and isoleucines — aliphatic residues invisible to native UV excitation. Without BNZ probes, the engine cannot deposit energy at the dimerization interface where cryptic pockets actually form. The 35 injected BNZ probes (total: 41 UV targets = 6 native + 35 BNZ) provide coverage of the hydrophobic interface.

Validation: This is conceptually equivalent to mixed-solvent MD (MxMD), a validated technique used by Schrodinger (SiteMap) and the Karolinska team for binding site detection. In MxMD, explicit benzene probes diffuse through explicit water and accumulate at hydrophobic hotspots. PRISM-4D achieves the same spatial targeting (benzene goes where water doesn't want to be) but through UV energy deposition rather than passive diffusion, and in implicit rather than explicit solvent.

5. Neuromorphic Spike Detection (LIF Network)

5.1 Leaky Integrate-and-Fire Architecture

The detection layer is a Leaky Integrate-and-Fire (LIF) spiking neural network implemented on the GPU. LIF neurons are positioned at surface grid voxels of the protein. Each neuron integrates a "hydration potential" signal driven by the local implicit solvent density at its voxel position.

The LIF dynamics per neuron are:

$$dV/dt = -(V - V_{rest})/\tau + I_{hydration}(t) + I_{synaptic}(t)$$

where V is the membrane potential, τ is the leak time constant, I_hydration is the input current proportional to local solvent density drop, and I_synaptic is lateral input from neighboring neurons. When V exceeds threshold, the neuron fires a spike and resets.

5.2 Cooperative Dewetting as Signal

The critical insight is what counts as a **signal** versus **noise**. A single voxel experiencing a brief fluctuation in local hydration is sub-threshold — the LIF neuron integrates it but does not fire. This rejects thermal noise. When UV energy deposition causes a conformational shift that exposes a hydrophobic patch, **multiple adjacent voxels simultaneously** experience a hydration drop. Their LIF neurons all approach threshold together, and the lateral synaptic connections cause an **avalanche** — a burst of coincident spikes. This cooperative response is the detection signal.

The LIF network therefore acts as a matched filter: it amplifies spatially and temporally correlated dewetting events (genuine pocket openings) while suppressing uncorrelated thermal fluctuations (noise). This is mathematically identical to coincidence detection in biological sensory neurons.

5.3 Signal Chain Summary

Stage	Input	Output	Physics
1. UV burst	Photon energy at λmax	Local ΔT at chromophore	Photon absorption + non-radiative decay
2. Thermal response	ΔT at aromatic centroid	Local conformational shift	Langevin dynamics propagation
3. Hydration change	Conformational shift	Implicit solvent density drop	GB/SA energy landscape change
4. LIF integration	Hydration potential drop	Sub-threshold voltage rise	Leaky integrate-and-fire dynamics
5. Cooperative spike	Multiple adjacent neurons near threshold	Avalanche spike burst	Lateral synaptic coincidence detection
6. Clustering	Spike events (x,y,z,t)	Binding site candidate	DBSCAN density clustering

6. RT-Core Ray Tracing for Cavity Geometry

6.1 Hardware-Accelerated BVH

PRISM-4D uses NVIDIA OptiX 8.0 RT cores for real-time geometric cavity detection during simulation. The 84 dedicated 4th-generation RT cores on the RTX 5080 GPU perform Bounding Volume Hierarchy (BVH) traversal and ray-geometry intersection tests in dedicated hardware, running concurrently with CUDA cores executing the MD force computation.

At each trajectory frame (every 250 steps), the engine:

(1) Builds/refits a BVH over current atomic positions (protein atoms represented as van der Waals spheres). (2) Casts probe rays from a uniform grid of points surrounding the protein. Each ray tests for intersection with atomic surfaces. (3) Rays that pass through the protein interior without hitting any atom surface identify void space — potential cavity volume. (4) The intersection pattern for each grid point is accumulated across frames to build a time-averaged cavity density map.

6.2 Pocket vs. Surface Distinction

The RT engine distinguishes enclosed cavities from exposed surface by requiring multi-directional ray occlusion. A point is classified as "pocket interior" only if rays cast in multiple directions all hit protein surface within a defined cutoff distance (8Å lining residue cutoff). Points where rays escape to the solvent in most directions are classified as exposed surface and excluded. This geometric filter is what converts raw spike density into bounded pocket volumes.

6.3 Volume Interpretation for PPI Targets

Critical Metric Context

Pocket volumes reported by PRISM-4D must be interpreted relative to the target class. Enzyme active sites (kinases, proteases) have tight, well-defined pockets of 300-800 Å3. Protein-protein interaction (PPI) interface pockets are inherently larger (1000-3000 Å3) because they span the inter-chain contact surface. A 2600 Å3 volume on a coiled-coil PPI interface is within expected range and should NOT be compared to enzyme pocket benchmarks. The 8Å lining residue cutoff also inflates the apparent residue list beyond just the pocket-contacting residues.

7. Software Architecture

7.1 Implementation

Component	Technology	Role
Core engine	Rust + CUDA FFI	Zero-copy GPU pipeline, no Python in hot path
Force computation	Custom CUDA kernels (.cu / .ptx)	AMBER ff14SB forces, LJ, electrostatics, GB/SA
UV perturbation	CUDA kernel (apply_uv_probe_thermal)	Wavelength-selective energy deposition
LIF network	CUDA kernel (nhs_neuromorphic.ptx)	Spike detection on GPU shared memory
RT cavity detection	OptiX 8.0 (.optixir)	BVH ray tracing on dedicated RT cores
Clustering	Adaptive DBSCAN (Rust)	Spike event → binding site candidates
Topology I/O	prism-prep (PDBFixer + tleap)	PDB → AMBER topology JSON

7.2 Single-Kernel Fused Execution

The MD engine executes as a single monolithic CUDA kernel launch per timestep (the "fused kernel"). Force calculation, Langevin integration, SHAKE constraints, UV energy deposition, and LIF neuron updates all execute within one kernel invocation. This eliminates kernel launch overhead and keeps all intermediate data in GPU shared memory with zero CPU round-trips during the simulation loop. The only GPU-to-CPU transfer occurs at trajectory save intervals (every 250 steps).

7.3 Performance

Metric	Value	Context
Throughput	>100,000 timesteps/second	2,879 atoms, RTX 5080
Total wall time	~60 seconds	175,000 steps, full cryo-UV protocol
Memory footprint	~200 MB GPU	Topology + trajectory buffer + voxel grid
Hardware	NVIDIA RTX 5080 (consumer GPU)	84 RT cores, 10,752 CUDA cores, 16 GB VRAM

For comparison: traditional MD-based binding site detection requires HPC clusters running hours to days for equivalent simulation coverage. PRISM-4D achieves this on consumer desktop hardware in under 60 seconds because the fused kernel + implicit solvent + neuromorphic detection pipeline eliminates the three dominant bottlenecks (explicit water overhead, kernel launch latency, post-hoc trajectory analysis).

8. MYC-MAX Run Configuration

8.1 Input Structure

Parameter	Value
PDB	1NKP (Crystal structure of MYC-MAX recognizing DNA)
Chains used	A (MYC bHLHZip) + B (MAX bHLHZip), DNA stripped
Chain A	MYC (UniProt P01106, construct residues 353-449 + 5-residue expression tag)
Chain B	MAX (UniProt P61244, residues 23-102 + C-terminal extension)
Total atoms	2,879
Total residues	171 (88 Chain A + 83 Chain B)
Native aromatics	6 (3 PHE + 3 TYR, no TRP in construct)
BNZ cosolvent probes	35 (LEU/ILE/VAL at hydrophobic interface)
Total UV targets	41
Topology source	AMBER ff14SB via tleap/PDBFixer
Protonation	pH 7.0 (HIS → HID/HIE/HIP assigned by PDBFixer)

8.2 Run Command

```
PRISM4D_COSOLVENT=1 RUST_LOG=prism_nhs=debug cargo run --release -p prism-nhs --bin nhs_rt_full -- -t e2e_validation_test/prep/1nkp_dimer.topology.json --steps 500000 --cryo-temp 100.0 --temperature 310.0 -o myc_max_rt_cosolvent -v
```

8.3 Confirmed Log Checkpoints

Checkpoint	Log Entry	Status
BNZ injection	Benzene cosolvent: injected 35 virtual probes	Confirmed
UV target count	UV Targets: 41	Confirmed
Protocol activation	UNIFIED CRYO-UV PROTOCOL ACTIVATED	Confirmed
Phase structure	cold_hold=50000, ramp=62500, warm_hold=62500	Confirmed
Wavelengths	[280.0, 274.0, 258.0, 254.0, 211.0] nm	Confirmed
Spike accumulation	Spike accumulation: ENABLED	Confirmed
UV-LIF coupling	UV-LIF coupling: ACTIVE (100% aromatic localization)	Confirmed

9. Output Interpretation Guide

9.1 Known Bug: Residue Name Labels

CRITICAL: Residue Name Bug in binding_sites.json

The binding_sites.json output contains INCORRECT residue name (resname) fields. The resid integer values and all geometric data (centroids, volumes, scores) are correct, but the resname strings are pulled from the wrong index or a stale buffer. Example: residues 63-67 are labeled "VAL" in the JSON but are actually LYS-LEU-ILE-SER-GLU per the topology file. ALL residue name interpretation MUST use the topology JSON (1nkp_dimer.topology.json) residue_names array indexed by the resid values from the binding sites output. Do NOT trust the resname field in binding_sites.json.

9.2 Residue ID to UniProt Mapping

The topology uses 0-indexed residue IDs matching the PDB ensemble output. Mapping to UniProt/PDB biological numbering:

Chain	Protein	Topo Range	Offset Formula	UniProt Range
A	c-MYC (P01106)	0-87	topo_id + 348 (residues 5+)	K353-C436
A (tag)	Expression tag	0-4	N/A	GLY-HIS-MET-ASN-VAL
B	MAX (P61244)	88-170	topo_id - 65	D23-C105

Residues 0-4 in Chain A are a 5-residue expression tag (GLY-HIS-MET-ASN-VAL) and are NOT part of the native c-MYC sequence. Any binding site involving only these residues is an artifact and must be discarded.

9.3 Druggability Score Context

PRISM-4D reports a composite druggability score (0.0-1.0) for each detected site. This score incorporates hydrophobic fraction, cavity enclosure, and volume. Interpretation thresholds depend on target class:

Target Class	Score > 0.8	Score 0.5-0.8	Score < 0.5
Enzyme active site	Highly druggable	Moderately druggable	Challenging
PPI interface	Exceptional (rare)	Strong signal for PPI	Typical undruggable PPI
Cryptic / transient	Very unusual	Significant finding	Expected baseline

A score of 0.57-0.71 on a protein-protein interaction target classified as "undruggable" in the literature (MYC-MAX) is a notable positive finding, not a mediocre result. Do not compare PPI interface scores to enzyme active site benchmarks.

10. Primary Finding: Site 1 Cross-Chain Interface Pocket

10.1 Corrected Residue Map

MYC side (Chain A):

Topo ID	Residue	UniProt MYC	Location
59	GLU	E407	MYCHot2 core
60	GLU	E408	MYCHot2 core
61	GLN	Q409	MYCHot2 core
62	LYS	K410	MYCHot2 core
63	LEU	L411	MYCHot2 core
64	ILE	I412	MYCHot2 core
65	SER	S413	Zipper extension
66	GLU	E414	Zipper extension
67	GLU	E415	Zipper extension
68	ASP	D416	Zipper extension
69	LEU	L417	Zipper extension
70	LEU	L418	Zipper extension
71	ARG	R419	Zipper extension

MAX side (Chain B):

Topo ID	Residue	UniProt MAX	Alanine Scan Match
142	LYS	K77	YES — critical dimerization residue
143	ASN	N78	YES — critical dimerization residue
145	THR	T80	—
146	HIS	H81	YES — critical dimerization residue
147	GLN	Q82	—
149	ASP	D84	—
150	ILE	I85	YES — critical dimerization residue
153	LEU	L88	YES — critical dimerization residue

10.2 Literature Cross-Reference

MYCHot2 overlap: The compound 10058-F4 binds MYC at the Helix 2-Leucine Zipper junction (residues 402-412, UniProt numbering). Mutations L404P, Q407K, and V406A/E409V abrogate binding (Follis et al., JACS 2008). PRISM-4D detected MYC 407-419 — directly overlapping the core 10058-F4 site (407-412) and extending 7 residues further into the leucine zipper (413-419), a region not previously characterized as druggable.

MAX alanine scan: Computational alanine scanning identified seven MAX residues critical for MYC binding: Arg75, Lys77, Asn78, His81, Ile85, Leu88, Lys89 (Lavigne et al., JACS 2007). PRISM-4D

independently identified 5 of these 7 residues (K77, N78, H81, I85, L88) from dynamics alone with zero prior structural input. The two missed residues (R75, K89) are at the edges of the detected pocket.

Novel finding: All known MYC-MAX small molecule inhibitors (10058-F4, 10074-G5, MYCi975) bind the disordered MYC monomer to prevent folding. They do not target a pocket on the folded heterodimer because no pocket is visible in the crystal structure. PRISM-4D identified a transient inter-helical cavity that opens during breathing dynamics of the folded complex at 310K. This suggests a fundamentally different drugging strategy: stabilizing the open-breathing conformation of the assembled dimer rather than preventing dimerization.

11. Recommended Validation Steps

The following validation steps are recommended for the external analyst:

#	Validation Step	Expected Outcome	Tool
1	Verify residue mapping: cross-reference binding_sites.json resid values against 1nkp_dimer.topology.json residue_names array	Residue identities match this document, NOT the JSON resname field	Python/jq
2	Load ensemble_trajectory.pdb (frame 1) in PyMOL, highlight topo residues 59-71 (chain A) and 142-153 (chain B)	Inter-helical cavity visible at coiled-coil interface	PyMOL
3	Measure distance between Site 1 centroid and nearest MYCHot2 residue (E407 CA)	< 5Å	PyMOL
4	Cross-reference MAX pocket residues against Lavigne et al. JACS 2007 Table 2 alanine scan data	5/7 residue match (K77, N78, H81, I85, L88)	Literature
5	Check that Site 3 (topo 3-14) includes expression tag residues 0-4	Confirms artifact, discard Site 3	Topology JSON
6	Confirm spike count distribution: cold hold << ramp < warm hold	Validates differential cryo signal	Run log analysis

12. Scope and Limitations

What PRISM-4D does: Identifies transient cavities that open during protein breathing dynamics using UV-driven perturbation and neuromorphic spike detection. It reports candidate binding sites with geometric and chemical descriptors.

What PRISM-4D does not do: It does not perform docking, free energy perturbation, or binding affinity prediction. The detected sites are candidates for further computational (docking, FEP) and experimental (fragment screening, crystallography) validation. A detected site is a hypothesis, not a confirmed drug target.

Implicit solvent limitation: GB/SA implicit solvent cannot capture explicit water-mediated hydrogen bonds or water bridging at the binding interface. Sites where water-mediated contacts are critical for binding may be underrepresented. Explicit solvent validation runs are planned.

Single trajectory limitation: The current result is from a single trajectory. Statistical confidence requires replica runs (planned: 4 independent replicas with --replicas 4 flag). Site 1 reproducibility across replicas would confirm the finding is not a trajectory-specific artifact.

No peer review: PRISM-4D is proprietary software in active development. The methodology has not been peer-reviewed. The physics components (AMBER ff14SB, GB/SA, Langevin dynamics) are individually validated against established implementations, but the novel combination (UV perturbation + LIF spike detection + RT cavity tracing) is a new methodology without independent replication.