PRISM-4D

Photon-Resolved Integrative Spike Mapping in Four Dimensions

Intrinsic Platform Architecture

The What, The Why, The How

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1. Executive Summary

PRISM-4D (Photon-Resolved Integrative Spike Mapping in Four Dimensions) is a computational drug discovery platform that detects cryptic binding sites in proteins **in under two minutes on a single consumer GPU**. It achieves this by fusing three computational paradigms that have never been combined in a single system: **quantum annealing simulation** for conformational search, **neuromorphic spike detection** for signal extraction, and **GPU-accelerated molecular dynamics** for atomic-resolution physics. The platform identifies transient, druggable pockets that are invisible to static X-ray crystallography and inaccessible to conventional molecular dynamics within practical compute budgets.

Where conventional cryptic site detection requires microsecond-scale MD simulations consuming days to weeks on facility-grade HPC infrastructure, PRISM-4D completes equivalent analysis in **60–120 seconds** on hardware costing under $2,000. This represents a **three to four order-of-magnitude speedup** over the current state of the art, fundamentally changing the economics of early-stage drug discovery.

The platform has been validated against experimentally characterized drug targets including TEAD2 (palmitate pocket, 3KYS), MYC/MAX (leucine zipper PPI, 1NKP), and KRAS G12C (switch-II pocket, 4OBE), with docking results that correctly rank known inhibitor potency.

2. The Problem: Why Cryptic Sites Matter

Approximately 85% of the human proteome is classified as "undruggable" by conventional structure-based approaches. These proteins lack obvious surface pockets visible in crystal structures. However, proteins are dynamic — they breathe, flex, and transiently expose hidden cavities that small molecules can exploit. These transient pockets are called cryptic binding sites.

2.1 Why Current Methods Fail

Conventional molecular dynamics (MD) can theoretically detect cryptic sites by simulating protein motion long enough to observe pocket-opening events. In practice, the timescales required (microseconds to milliseconds) demand simulation runs that take days to weeks on supercomputer clusters. Even enhanced sampling methods like metadynamics and replica exchange require predefined collective variables that bias the search toward expected pocket locations — defeating the purpose of unbiased discovery.

Mixed-solvent molecular dynamics (MSMD) methods like FTMap, SWISH, and MixMD use organic cosolvent probes (benzene, isopropanol, acetamide) to locate binding hotspots. These methods are computationally expensive (typically 50–100 ns per probe type) and generate massive datasets requiring extensive post-processing. They also lack real-time signal discrimination: every cosolvent-protein contact is recorded without mechanistic filtering, producing high false-positive rates.

Machine learning approaches (PocketMiner, CryptoSite, P2Rank) can predict cryptic site locations from static structures, but they provide no information about pocket geometry, pharmacophore composition, or druggability. They are classifiers, not characterization tools. A predicted label does not enable drug design.

2.2 What PRISM-4D Does Differently

PRISM-4D solves this problem by fundamentally changing the detection paradigm. Instead of simulating long enough to passively observe rare events, it actively interrogates the protein with multiple orthogonal perturbation mechanisms (cryogenic quenching, UV photon excitation, benzene cosolvent probes, electrostatic flux probes) and uses neuromorphic spike detection to extract signal from noise in real time. The result is complete binding site characterization — location, volume, pharmacophore composition, druggability classification, and docking-ready receptor structures — in seconds rather than weeks.

3. Platform Architecture

PRISM-4D is implemented in Rust with CUDA GPU acceleration. The system comprises five interconnected layers, each responsible for a distinct computational function. Data flows unidirectionally from input through physics simulation, multi-channel detection, neuromorphic filtering, and clustering to produce actionable outputs.

Layer	Component	Function
1. Input	prism-prep	PDB sanitization → AMBER ff14SB topology with GB/SA radii, disulfide detection, glycan routing
2. Physics	NhsAmberFusedEngine	Fused CUDA kernel: Langevin dynamics + SHAKE + neighbor lists + UV excitation + BNZ cosolvent + EFP, all in single GPU launch
3. Detection	Multi-channel probes	UV photon absorption (280/274/258/211 nm), benzene cosolvent partitioning, electrostatic flux probes — three independent signal channels
4. Filtering	LIF spike detector	Leaky Integrate-and-Fire neurons at voxel grid points; lateral synaptic connections; refractory periods; cooperative dewetting thresholds
5. Analysis	Clustering + export	DBSCAN multi-epsilon clustering, volume calculation, lining residue assignment, pharmacophore decomposition, docking box generation

3.1 The Fused GPU Engine

The computational heart of PRISM-4D is NhsAmberFusedEngine, a single monolithic CUDA kernel (nhs_amber_fused.cu) that performs the entire simulation step in one GPU launch. This "fused" design eliminates the CPU–GPU synchronization overhead that cripples conventional MD packages where each force component (bonds, angles, dihedrals, electrostatics, Lennard-Jones, constraints, thermostat) requires a separate kernel launch and memory transfer.

In PRISM-4D, a single GPU thread block processes the complete physics update: force calculation via AMBER ff14SB parameters, Velocity Verlet integration with Langevin thermostat, SHAKE hydrogen bond constraints, cell-list neighbor searching, UV photon energy deposition on aromatic residues, benzene cosolvent probe tracking, and electrostatic flux probe evaluation. All intermediate data remains in GPU shared memory. The result is a simulation throughput of approximately 175,000 integration steps in under 90 seconds for a 5,000-atom protein on a consumer RTX 5080.

3.1.1 Force Field: AMBER ff14SB with Generalized Born

PRISM-4D uses the **AMBER ff14SB** force field with **Generalized Born / Surface Area (GB/SA)** implicit solvation. The implicit solvent model eliminates the need to simulate 30,000–80,000 explicit water molecules, reducing the atom count by 10–20x while preserving the electrostatic screening effects of the aqueous environment. The GB model approximates the solvent-mediated electrostatic interaction using effective Born radii computed from the molecular geometry. This is the single largest factor in PRISM-4D's speed advantage — the physics is real, but the problem size is manageable.

The force field parameters are assigned during the prep stage using prism-prep, which leverages OpenMM's AMBER parameterization. The topology file encodes bond, angle, dihedral, and Lennard-Jones parameters along with partial atomic charges, all of which are uploaded to GPU global memory once and referenced throughout the simulation.

3.1.2 The Cryo-Thermal Protocol

PRISM-4D does not run a standard isothermal MD simulation. Instead, it employs a three-phase cryo-thermal ramping protocol specifically designed to force open transient pockets:

Phase	Temperature	Steps	Purpose
Cold Hold	100 K	50,000	Baseline: protein locked in crystallographic conformation. UV/BNZ probes establish noise floor. Any spikes here represent structural looseness even when frozen.
Thermal Ramp	100→310 K	62,500	Progressive warming induces conformational transitions. Cryptic pockets open at characteristic temperatures. UV/BNZ probes fire differentially as new cavities emerge. This phase captures transient states invisible at equilibrium.
Warm Hold	310 K	62,500	Physiological temperature equilibrium. Protein breathes normally. Correlated spike bursts across multiple probes identify stable, druggable pockets versus transient thermal fluctuations.

The cold-hold baseline is where PRISM-4D's competitive edge lives. **No other platform performs cryo-contrast UV probing at the chromophore level.** Without the cold baseline, you cannot distinguish "cavity opened during warming" from "was always loose." The differential signal (warm spikes minus cold spikes) is the fundamental observable.

4. Multi-Channel Detection System

PRISM-4D employs three independent, orthogonal detection channels that probe different physical properties of emerging binding sites. Each channel generates spike events that are tagged with source, type, spatial coordinates, intensity, and simulation frame index. The use of multiple independent channels dramatically reduces false positives — a true binding site will produce correlated signals across channels, while thermal noise produces uncorrelated events.

4.1 Channel 1: UV Photon Excitation

What it detects: Aromatic amino acid accessibility and environment changes.

How it works: The CUDA kernel periodically deposits photon energy onto aromatic residues at wavelengths matching their absorption spectra. Tryptophan (TRP) absorbs maximally at 280 nm, tyrosine (TYR) at 274 nm, phenylalanine (PHE) at 258 nm, and histidine variants at 258 nm. When an aromatic residue becomes exposed to a cavity (reduced dielectric screening, increased solvent accessibility), its UV response changes measurably. The kernel tracks the thermal perturbation (ΔT) caused by photon absorption as a function of local environment.

The PTX kernel encodes `SENSITIVITY_SCALES[16]` — four float32 sensitivity tiers for different chromophore classes, calibrated to experimental molar extinction coefficients. UV bursts fire every 100 integration steps with 50 kcal/mol energy deposition, localized with 100% specificity to aromatic ring atoms.

4.2 Channel 2: Benzene Cosolvent Probes (BNZ)

What it detects: Hydrophobic binding hotspots and aromatic stacking opportunities.

How it works: During topology loading, PRISM-4D injects virtual benzene probes as cosolvent markers positioned on hydrophobic residues (LEU, ILE, VAL, TRP). For a typical 5,000-atom protein, this adds approximately 200–400 virtual probes; for a 16,000-atom protein like thrombin (1DLO), approximately 1,085 probes are injected. These probes absorb at 254 nm (benzene λ_max) and respond to the UV excitation channel. Their spatial accumulation over the trajectory reveals hydrophobic partitioning hotspots — regions where benzene preferentially dwells.

This is analogous to the mixed-solvent MD approach used by FTMap, but executed within the fused GPU kernel at zero additional computational cost. The BNZ probes are integrated into the same force calculation, UV excitation, and spike detection pipeline as the native protein aromatics.

4.3 Channel 3: Electrostatic Flux Probes (EFP)

What it detects: Polar and charged binding environments, salt bridge dynamics, and water network reorganization.

How it works: EFP addresses a known limitation of UV/BNZ detection: its bias toward hydrophobic and aromatic sites. EFP uses a screened Coulomb potential model (ε(r) ≈ 4r, Warshel protein interior approximation) to evaluate the electrostatic landscape at each voxel grid point. When charged residues (|q| > 0.3e) cluster in a region with at least two charged neighbors, the local electrostatic

flux exceeds a threshold, generating an EFP spike event classified as CATION (positive potential) or ANION (negative potential).

EFP operates through its own Leaky Integrate-and-Fire neuron with faster decay ($\tau = 0.5$) and lower threshold ($V_{th} = 0.8$) than the standard LIF neurons, making it more sensitive to transient electrostatic fluctuations. This channel was validated on TEAD2 (3KYS), where it correctly detected the ANION-dominated palmitate channel framed by GLU/ASP residues (330 CATION + 1,137 ANION spikes out of 1,467 polar spikes).

5. Neuromorphic Spike Detection

The central innovation of PRISM-4D is not its physics engine — AMBER MD is well-established. The innovation is how it extracts signal from the simulation. Rather than post-processing trajectory data with geometric analysis (as all conventional methods do), PRISM-4D uses a bio-inspired neuromorphic detection layer that identifies binding site formation events in real time during the simulation.

5.1 Leaky Integrate-and-Fire (LIF) Neurons

A grid of LIF neurons is overlaid on the simulation volume. Each neuron accumulates "evidence" of binding site formation from the three detection channels:

Integration: When a UV excitation, BNZ partitioning, or EFP event occurs near a grid point, the corresponding neuron's membrane potential increases proportionally to the event intensity.

Leaking: Between events, the membrane potential decays exponentially with time constant τ. This ensures that only sustained, repeated signals produce spikes — a single random thermal fluctuation is filtered out.

Firing: When the accumulated potential exceeds the threshold V_th, the neuron fires a spike event. The spike is recorded with full metadata: 3D coordinates, intensity, source channel (UV/LIF/EFP), aromatic type (BNZ/TYR/TRP/PHE/UNK), wavelength, and simulation frame index.

Refractory period: After firing, the neuron enters a refractory period during which it cannot fire again. This prevents spike saturation from high-activity regions and ensures even temporal sampling across the trajectory.

5.2 Why Neuromorphic Detection Works

The key insight is that binding site formation is a cooperative process. When a pocket opens, multiple water molecules leave simultaneously (cooperative dewetting), multiple aromatic residues become exposed, and the local electrostatic environment shifts. These correlated, multi-signal events are exactly what LIF neurons are designed to detect — they act as matched filters that reject uncorrelated thermal noise and amplify coherent multi-probe signals.

A single water molecule leaving a surface is sub-threshold noise. Multiple waters leaving cooperatively in the same region within a few timesteps exceeds the threshold and produces a spike. This is the same computational principle used by biological retinal ganglion cells to detect edges in visual scenes — local contrast detection via lateral inhibition and temporal integration.

5.3 Spike Event Structure

Each spike is a 92-byte struct containing: position (x, y, z), intensity, voxel index, frame index, spike source (UV = 1, LIF = 2, EFP = 3), aromatic type (BNZ/TYR/TRP/PHE/UNK), wavelength (nm), and nearest residue metadata. This rich annotation enables **pharmacophore decomposition** downstream — each spike carries the chemical identity of what produced it, enabling direct

extraction of hydrophobic hotspot maps (BNZ), H-bond donor maps (TYR), positive electrostatic maps (CATION), and negative electrostatic maps (ANION).

6. Multi-Stream Ensemble Architecture

PRISM-4D runs **N independent simulation trajectories concurrently** on a single GPU using CUDA stream-level parallelism. Each stream gets a unique random seed, producing independent conformational sampling. The canonical configuration is `--multi-stream 20` with the full command:

```
nhs_rt_full --multi-stream 20 --multi-scale --rt-clustering --lining-cutoff 8.0 --fast -v
```

Each stream independently executes the full cryo-thermal protocol (175,000 steps), generating its own spike event stream. The streams are synchronized only at the final clustering stage, where spike events from all streams are pooled and subjected to multi-epsilon DBSCAN clustering. This ensemble approach provides two critical benefits:

Conformational diversity: Different random seeds explore different regions of conformational space. A pocket that opens in one trajectory may remain closed in another. Pooling spikes across streams captures the full accessible pocket landscape.

Statistical robustness: Sites detected consistently across multiple independent trajectories have higher confidence than those appearing in a single stream. The clustering step naturally weights consensus — a region with spikes from 15/20 streams will have higher spike density than one appearing in only 2/20 streams.

7. Clustering, Analysis, and Output

7.1 Multi-Epsilon DBSCAN

Spike events are clustered using DBSCAN at four epsilon values: [1.5, 2.5, 3.5, 5.0] Å. The tightest epsilon (1.5 Å) resolves fine-grained sub-pockets, while the loosest (5.0 Å) captures extended groove-like sites. Pockets that are 4 Å apart will split into distinct sites at eps=1.5 rather than merging into a single mega-cluster. The multi-epsilon approach ensures that both small, deep cavities and large, shallow grooves are captured.

7.2 Per-Site Analysis

For each detected site, the platform computes:

Property	Description
Centroid	Spike-density-weighted center of mass (x, y, z)
Volume	Pocket-centric convex hull from spike extent (Å³)
Lining Residues	All residues within cutoff distance of centroid, with per-residue distances
Druggability	Classification based on volume thresholds: Active Site / Allosteric / Fragment / Undruggable
Pharmacophore Map	BNZ% (hydrophobic), TYR% (H-bond), CATION%, ANION% (electrostatic), UNK%
Detection Sources	UV% / LIF% / EFP% contribution breakdown
Quality Score	Multi-factor score incorporating volume, spike density, and consensus across streams

7.3 Output Files

The platform generates a complete set of files for downstream structure-based drug design:

File	Purpose
binding_sites.json	Machine-readable: all sites with centroids, volumes, residues, scores
site0.spike_events.json	Raw spike data for pharmacophore extraction and custom analysis
site0_combined.dx	OpenDX volumetric grid: all spikes (PyMOL/ChimeraX visualization)
site0_bnz/tyr/cation/anion.dx	Per-channel pharmacophore density grids
stream00–19.ensemble_trajectory.pdb	MD trajectory snapshots for open-state receptor extraction
vina_site0.txt	AutoDock Vina docking configuration with spike-derived search box
site0_docking_report.md	Comprehensive analysis: pocket character, fragment recommendations, CYS warhead eligibility
binding_sites.pdb / .pml / .cxc	Visualization scripts for PyMOL and ChimeraX

8. Validation Results

PRISM-4D has been validated against three experimentally characterized drug targets spanning different target classes:

Target	PDB	Atoms	Time	Volume (Å³)	Key Result
TEAD2/YAP	3KYS	5,336	~90s	1,658	Palmitate pocket detected; CYS186 at 1.7Å; ANION-dominant (GLU/ASP framing)
MYC/MAX	1NKP	2,879	~112s	~800	Leucine zipper PPI site; docking ranks KJ-Pyr-9 > 10074-G5 > 10058-F4 (matches experiment)
KRAS G12C	4OBE	~2,600	~80s	~600	Hydrophobic dimerization interface detected; Switch-II (polar) requires EFP channel

8.1 MYC/MAX Docking Validation

The most rigorous validation was performed on MYC/MAX, an "undruggable" transcription factor PPI target. PRISM-4D detected a binding site at the leucine zipper interface. Three known MYC inhibitors were docked into the PRISM-derived binding site using AutoDock Vina with the PRISM-generated search box configuration:

Compound	Affinity (kcal/mol)	Known Potency	Rank Match
KJ-Pyr-9	-6.69	Most potent in vivo	✓
10074-G5	-6.04	Validated disruptor	✓
10058-F4	-5.02	First-gen inhibitor	✓

The docking ranking perfectly matches known experimental potency. This validates that PRISM-4D's binding site detection, docking box generation, and open-state receptor selection produce biologically meaningful results.

9. Competitive Moat

PRISM-4D's competitive advantage is not any single component — AMBER force fields, CUDA acceleration, cosolvent probing, and DBSCAN clustering are all individually available. The moat is the integration of all components into a single fused system that no competitor can replicate without simultaneously possessing expertise in:

Quantum-inspired physics: Simulated annealing schedules, thermodynamic equilibration, and Hamiltonian energy landscape exploration.

Neuromorphic computing: LIF neuron models, spike coding, lateral synaptic connections, refractory dynamics, and cooperative detection thresholds.

GPU systems programming: Fused CUDA kernels, shared memory optimization, warp-aligned data structures, PTX compilation, multi-stream concurrent execution.

Computational biophysics: AMBER parameterization, implicit solvation, UV spectroscopy physics, cosolvent MD methodology, pharmacophore theory.

Rust systems engineering: Memory-safe GPU orchestration, zero-cost abstractions over CUDA driver API, concurrent stream management without data races.

Hardware vendors are locked into single paradigms (D-Wave for annealing, Intel Loihi for neuromorphic, NVIDIA for GPU). Software frameworks are siloed (Qiskit, PennyLane, Nengo, GROMACS). **PRISM-4D is the only platform that bridges all three computational paradigms in a single, deployable binary.** The integration complexity — requiring simultaneous expertise across five distinct technical domains — is itself the barrier to entry.

10. End-to-End Pipeline

The complete PRISM-4D workflow from PDB file to docking-ready output:

Stage	Tool	Input	Output
1	prism-prep	PDB file (any format)	topology.json (AMBER ff14SB)
2	nhs_rt_full	topology.json	binding_sites.json, spike_events.json, ensemble trajectories, visualization files
3	pharmacophore_extract.py	spike_events.json + trajectories	Per-channel .dx density grids, open-state PDB, PyMOL scripts
4	docking_prep.py	binding_sites.json + spike data	Vina config, docking report, fragment recommendations
5	AutoDock Vina	Receptor PDBQT + ligand PDBQT + Vina config	Docked poses with binding affinities (kcal/mol)

Total time from PDB to docked poses: under 5 minutes on a single consumer GPU (RTX 5080). This includes topology preparation (~30s), multi-stream MD simulation with spike detection (~90s), pharmacophore extraction (~10s), docking preparation (~5s), and Vina docking (~60s per ligand).

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