# Divide and Cluster: The DIVINE Framework for Deterministic Top-Down Analysis of Molecular Dynamics Trajectories

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**ABSTRACT**

We present DIVIsive *N*-ary Ensembles (DIVINE), a deterministic, top-down clustering framework designed for molecular dynamics (MD) trajectories. DIVINE constructs a complete clustering hierarchy by recursively splitting clusters based on *n*-ary similarity principles, avoiding the need for $O(N^2)$ pairwise distance matrices. It supports multiple cluster selection criteria, including a weighted variance metric, and deterministic anchor initialization strategies such as NANI (N-ary Natural Initiation), ensuring reproducible and well-balanced partitions. Testing DIVINE up to a 305 μs folding trajectory of the villin headpiece (HP35) revealed that it matched or exceeded the clustering quality of bisecting *k*-means while reducing runtime and eliminating stochastic variability. Its single-pass design enables efficient exploration of clustering resolutions without repeated executions. By combining scalability, interpretability, and determinism, DIVINE offers a robust and practical alternative to conventional MD clustering methods. DIVINE is publicly available as part of the MDANCE package: https://github.com/mqcomplab/MDANCE.

## INTRODUCTION

Molecular dynamics (MD) simulations have become an important tool in the exploration of structure and dynamics of biomolecular systems at atomic resolution.[1,2] With the rise of GPU acceleration and broader access to high-performance computing, it is now routine for simulations to reach micro- to millisecond timescales.[3–5] These simulations generate massive, high-dimensional datasets comprising millions of conformational snapshots, which require careful and robust post-processing techniques to extract chemically meaningful information. A central task in this process is clustering, which involves the identification of discrete structural states, estimation of their populations, and visualization of their structural relationships.[6–10]

Traditional clustering pipelines used in MD analysis generally fall into two main categories: partitional methods such as *k*-means, and hierarchical methods, such as hierarchical agglomerative clustering (HAC). *k*-means is widely popular due to its computational efficiency and scalability. However, it assumes convex clusters and can be quite sensitive to initialization, which limits its applicability on high-dimensional MD trajectories.[11,12] To address some of these issue, we previously developed *k*-means *N*-ary Natural Initiation (NANI), a deterministic initialization scheme that improves cluster compactness and reproducibility.[13] However, the problem of strict convex partitioning remains an inescapable feature of every *k*-means implementation.

HAC, on the other hand, constructs a dendrogram by iteratively merging the most similar frames, allowing the identification of arbitrarily shaped clusters. However, its $O(N^2)$ time and memory complexity from the need to compute and store all pairwise distances make it impractical for large MD datasets.[7,14] To address this, we proposed Hierarchical Extended Linkage Method (HELM), a hybrid clustering protocol that uses *k*-means NANI for efficient pre-clustering, followed by agglomerative merging.[15] While this approach retained much of HAC's flexibility without a full distance matrix, it still relies on an agglomerative (bottom-up) strategy.

As an alternative, divisive clustering offers a top-down framework. It starts with the entire dataset as a single cluster, which is recursively split.[16] This strategy naturally captures global structure and crucially avoids ever constructing a full pairwise distance matrix if splits and decisions are made based on cluster-wise properties. A notable example is the bisecting *k*-means[17,18] (referred to as BKM in this paper), which iteratively splits the cluster with the biggest inertia (sum of squared errors) or largest number of frames using a standard *k*-means (with $k = 2$). While efficient, common implementations produce only a flat partition unless explicitly modified to retain intermediate splits. Moreover, the reliance on random or *k*-means++ initialization compromises reproducibility and requires multiple runs to properly assess clustering stability.

Another example is DIvisive ANAlysis (DIANA)[19], a classical top-down method. DIANA selects the cluster with the largest diameter (i.e., the most internally dissimilar cluster) and splits it by isolating a "splinter" group.[20] While conceptually appealing, DIANA also requires an $O(N^2)$ dissimilarity matrix making it not feasible for large-scale MD data. To our knowledge, no MD analysis-specific library currently implements a fully divisive clustering approach for millions of conformational frames.

In this work, we present DIVisive *N*-ary Ensembles (DIVINE), a deterministic top-down clustering framework designed for large-scale MD simulations. DIVINE begins with all frames in a single cluster and recursively splits them using *n*-ary similarity principles, enabling efficient $O(N)$ cluster evaluations without

requiring pairwise comparisons.[13,15,21–31] We incorporate three criteria for selecting clusters to split (mean squared deviation (MSD), radius, and weighted MSD) and three anchor-selection strategies (NANI-based, outlier-based, and DIANA-like splintering). Every step in DIVINE is completely deterministic, ensuring that identical inputs produce exactly the same outputs.

We benchmark DIVINE on a folding trajectory of the villin headpiece (HP35), comparing its performance against scikit-learn's BKM[17]. Our results demonstrate that DIVINE produces interpretable, memory-efficient hierarchical clustering in a single pass, with clustering quality, measured by standard validation metrics like Calinski–Harabasz[32] and Davies–Bouldin[33] indices, matching or exceeding BKM, while offering superior runtime stability and full reproducibility. Compared to conventional divisive clustering methods, DIVINE preserves the hierarchical structure and scales efficiently. It enables rapid screening over different cluster counts, making it a powerful addition to MD analysis pipelines. DIVINE is publicly available as part of the MDANCE package: https://github.com/mqcomplab/MDANCE.

## THEORY AND IMPLEMENTATION

### Clustering Framework Overview

DIVINE begins by treating the entire trajectory (consisting of N frames) as the initial cluster. It then proceeds iteratively: at each step, one cluster is selected for division and is then split into two subclusters. The process continues until a termination criterion is met.

Two stopping modes are supported: (a) end = "points", which continues until every cluster contains a single frame (i.e., an exhaustive hierarchy down to singletons), and (b) end = "k", which stops when a specified number of clusters $k$ is reached. Users may choose end = 'k' for a predetermined clustering or end = 'points' to extract the full dendrogram and then decide an optimal $k$ by analyzing clustering metrics.

To suppress formation of unwanted, low-population clusters, we introduce an optional threshold parameter that enforces a minimum size for valid subclusters. If a proposed split results in any subcluster with fewer than threshold x N frames, that split is skipped. This prevents overfragmentation as we treat extremely rare outlier clusters as noise.

### Cluster Selection Criteria

At each iteration, DIVINE must decide which cluster to split. We provide three selection criteria via the split parameter:

*MSD (Mean Squared Deviation):* Selects the cluster with the greatest internal dispersion as measured by the MSD of its frames. The MSD is the average of the pairwise squared distances computed in linear time ($O(N)$) using a cluster summary representation. A higher MSD indicates a structurally diverse cluster and thus a strong candidate for further subdivision. This criterion is similar in spirit to DIANA's diameter but uses all points collectively rather than just the single furthest pair, making it less sensitive to an isolated outlier.

*radius*: Selects the cluster with the largest radius, defined as the maximum distance between the cluster's medoid (most representative frame) and any other frame within the cluster. The medoid is determined using complementary MSD (cMSD), a measure of the frame's contribution to the overall cluster dispersion. For

each frame in the cluster, cMSD is computed as the MSD of all other frames when that frame is excluded. The frame whose exclusion results in the largest increase in dispersion (i.e., the highest cMSD) is considered the most central to the cluster and is selected as the medoid. The radius is then defined as the largest distance between this medoid and any other frame in the cluster.

*weighted_MSD*: Choose the cluster maximizing MSD x m (where m is the cluster's size). This weighted variance criterion biases the selection toward large clusters that are also dispersed. By incorporating cluster size into the decision metric, this directs the focus toward larger clusters that account for a greater share of the system's total structural variation.

**Anchor Frame Selection**

Once a cluster is selected for splitting, DIVINE now chooses two anchor frames to seed the resulting subclusters. We implemented multiple anchor selection strategies:

*NANI*: This mode leverages the *k*-means NANI algorithm to identify two high-quality initial centers for splitting. NANI selects diverse frames from high-density regions of the dataset, ensuring the chosen medoids are both well-separated and representatives of underlying structural modes. In DIVINE, we run *k*-means NANI with $k = 2$ and use the strat_all initialization mode. Other NANI init_type variants (strat_reduced, comp_sim, div_select), as well as stochastic options (random, *k*-means++), are also supported.

*outlier_pair*: This strategy selects a structurally distinct frame (A) as an outlier based on cMSD. Specifically, the frame with the lowest cMSD. It then identifies the frame (B) in the cluster that is farthest from A. Together, A and B span the approximate diameter of the cluster and serve as anchors for the split. Each frame is assigned to the closer of the two. Although simple and intuitive, this method may produce highly imbalanced splits if either A or B is an isolated outlier, resulting in a trivial subcluster.

*splinter_split*: This DIANA-inspired approach is a variant of outlier_pair, with a slightly different logic for defining the split. It first identifies an outlier frame A (as in outlier_pair) and then computes the medoid M of the remaining frames. Each frame is then assigned to the closer of the two anchors.

Due to their sensitivity to outliers, both outlier_pair and splinter_split are followed by an additional refinement step to enhance the quality and stability of the resulting partition.

**Partition Refinement**

After generating an initial split using any of the anchor selection strategies, DIVINE applies a refinement step to improve cluster compactness and boundary definition. In the current implementation, this refinement is applied by default for the outlier_pair and splinter_split methods, while it is inherently integrated into the NANI-based approach through its *k*-means execution.

The refinement procedure involves performing standard *k*-means (with $k = 2$) clustering on the cluster, using the medoids of the two original subclusters as the initial seeds. This additional step helps reassign borderline conformations based on proximity to the refined medoids, helping to improve cluster boundaries and reduce unbalanced partitions.

**Clustering Quality Evaluation**

DIVINE continuously tracks clustering quality metrics as a function of the number of clusters. After each split, we record the Calinski–Harabasz index (CHI) and Davies–Bouldin index (DBI) for the current partitioning level. CHI, also known as the variance ratio criterion, evaluates the ratio of inter-cluster dispersion to intra-cluster compactness.[32] Higher CHI values indicate more compact and well-separated clusters. On the other hand, DBI measures the average similarity between the most similar clusters, based on the ratio of internal spread to the distance between cluster centroids.[33] Lower DBI values reflect higher-quality clustering. Since DIVINE builds the hierarchy in a single run, these metrics are computed and stored incrementally at each stage, yielding a complete profile of clustering quality across a range of *k*. This allows us to identify natural stopping points or optimal values of *k* by analyzing trends in CHI and DBI without needing to rerun the algorithm at different *k*.

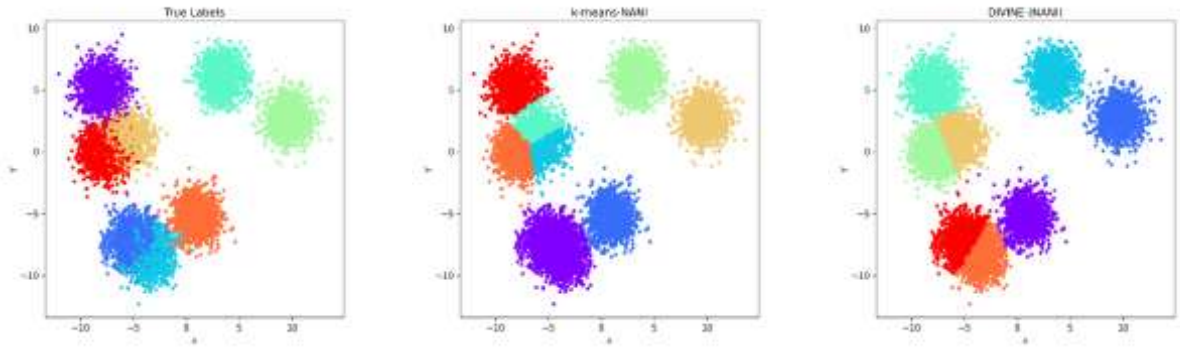


**Figure 1.** DIVINE clustering on a Synthetic 2D Benchmark Dataset. Clustering results are shown for a simple, low-dimensional 2D dataset with clearly separated clusters: ground truth labels (left), *k*-means NANI (center), and DIVINE using NANI for anchor selection (right). Each color represents a distinct cluster. While both methods broadly recover the true cluster structure, DIVINE achieves better separation and cluster consistency. This illustrative example provides a controlled benchmark for visual comparison but does not reflect the complexity of molecular dynamics data, which typically involve high-dimensionality and conformational noise. As such, we performed a more rigorous validation using a biomolecular system.

## SYSTEM AND PROTOCOLS

**HP35 Folding Trajectory:** Our primary test system is a 305 μs molecular dynamics simulation of a fast-folding villin headpiece subdomain variant (Nle/Nle double mutant), performed at 360 K by D. E. Shaw Research.[34] The trajectory comprises approximately 1.5 million frames saved every 200 ps. This system is a 35-residue protein featuring three helical segments: helix 1 spans residues 4–10, helix 2 includes residues 15–19, and helix 3 covers residues 23–32. To prepare the data, we discarded the first 5,000 frames to exclude initial equilibration and aligned the remaining frames to the 5,000$^{th}$ frame. For structural comparison, we selected the backbone atoms following prior studies: the N atom of residue 1; the N, Cα, and C atoms of residues 2 through 34; and the N atom of residue 35. To reduce data volume, we applied a 10-frame sieving interval, giving us a final set of 151,104 frames for clustering.

To contextualize DIVINE's performance, we also applied scikit-learn's BKM algorithm, on the same HP35 dataset. We tested two cluster selection strategies: biggest inertia and largest cluster as well as two

initialization settings random and *k*-means++. As noted earlier, because scikit-learn's BKM does not natively preserve the hierarchy of splits, we had to run the algorithm for each desired number of clusters (with 3 independent runs for each setting to gauge variability). This allowed us to compare the internal metrics with that of DIVINE.

## RESULTS AND DISCUSSION

### Cluster Selection Strategies

Since each iteration in DIVINE begins by selecting a cluster to split, we first evaluated different strategies for making this choice. DIANA selects the cluster with the largest diameter (i.e., the most dissimilar pair of points), but as discussed earlier, this approach is highly sensitive to outliers and can lead to fragmented or structurally uninformative splits. BKM uses either the largest cluster (by size) or the one with the biggest inertia (sum of squared errors). While this reduces direct sensitivity to individual outliers, it still introduces a bias toward larger clusters and may overlook smaller, yet heterogeneous, clusters.

To address these limitations, we explored metrics that capture dispersion more explicitly while remaining computationally efficient. We first implemented two measures: MSD and radius, that can be evaluated in linear time with respect to cluster size. MSD estimates the average pairwise squared distance, while radius measures the maximum distance from the cluster medoid to any member. Both can identify clusters with high internal variance. However, our initial tests revealed a consistent pattern: MSD and radius frequently prioritized dispersed and noisy clusters early in the hierarchy. As shown in Table S1 these splits produced long tails of high-MSD small clusters branching from a dominant supercluster.

To reduce this bias, we introduced the weighted_MSD criterion, which multiplies the cluster's MSD by its size. This adjustment steers selection toward large, heterogeneous clusters rather than small, high-variance ones. As a result, the early stages of the hierarchy exhibit more balanced cluster populations and fewer trivial outlier branches.

In Fig. 2, we compare the performance of these selection strategies using both CHI and DBI. Both MSD and radius, with the largest_cluster variant of BKM consistently yielded lower CHI and higher DBI scores, indicating less compact and less separated clusters. In contrast, weighted_MSD outperformed these methods and matched or exceeded BKM's biggest_inertia method across the full range of k. Error bars are shown only for BKM, as its reliance on random initialization leads to run-to-run variability. Based on these observations, we adopted weighted_MSD as the default splitting criterion for DIVINE and biggest_inertia for BKM to be used for further analyses.

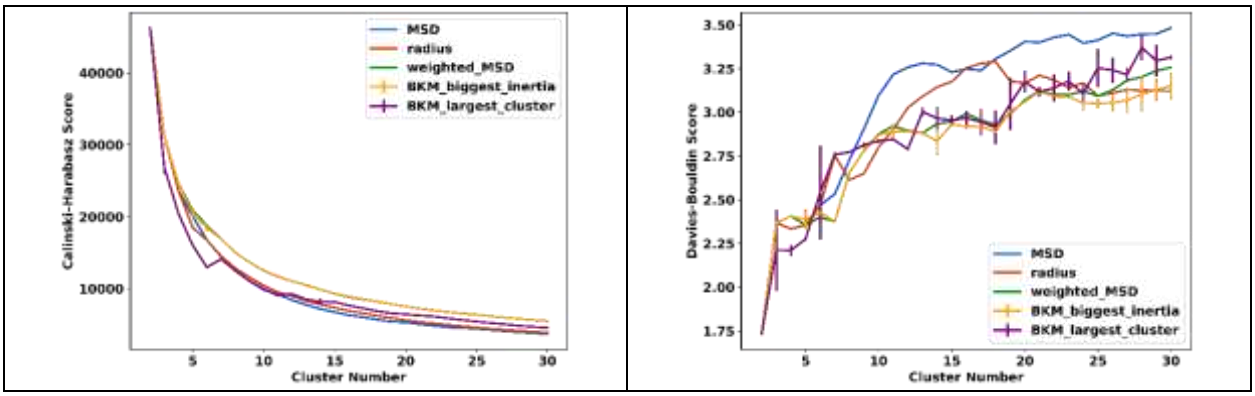


Figure 2. Change in Calinski-Harabasz and Davies-Bouldin indices for HP35 after DIVINE clustering from $k = 1$ to 30, comparing performance across different cluster selection strategies.

In addition to choosing a good splitting metric, we also found it useful to require a minimum split size to guard against trivial splits. As described in Theory, we introduced a threshold parameter requiring that both resulting subclusters contain at least a minimum fraction of the total frames, or else that split is rejected, and the next top cluster is chosen for splitting. However, we note that an aggressive threshold can eventually prevent any split when cluster sizes become naturally small. In fact, with a 5% threshold, DIVINE could only split up to about 10 clusters on HP35 before all remaining splits would violate the size rule. Interestingly, under that condition, the three split criteria all led to the same final 10 clusters (Table S2). In summary, a moderate threshold can improve cluster balance, but it should be set based on the intended number of clusters. For all main runs, we disabled this threshold criterion unless otherwise noted, to allow the hierarchy to fully emerge for screening purposes.

**Anchor Strategies and Refinement**

After selecting a cluster to split, DIVINE determines the anchor frames that define the initial subdivision. These anchors serve as seeds that represent the emerging subclusters, and their selection strongly influences the quality and shape of the resulting hierarchy. DIVINE provides three deterministic anchor strategies: NANI, outlier_pair, and splinter_split each reflecting a different principle of cluster initialization.

In Fig. 3, we report CHI and DBI values obtained from each strategy across a range $k = 1$ to 30. Based on DBI alone, splinter_split appears favorable, especially at low k, suggesting the formation of compact, well-separated clusters. However, CHI reveals a different trend: splinter_split consistently underperforms, with flat CHI scores across the screening range, indicating limited improvement in between-cluster separation.

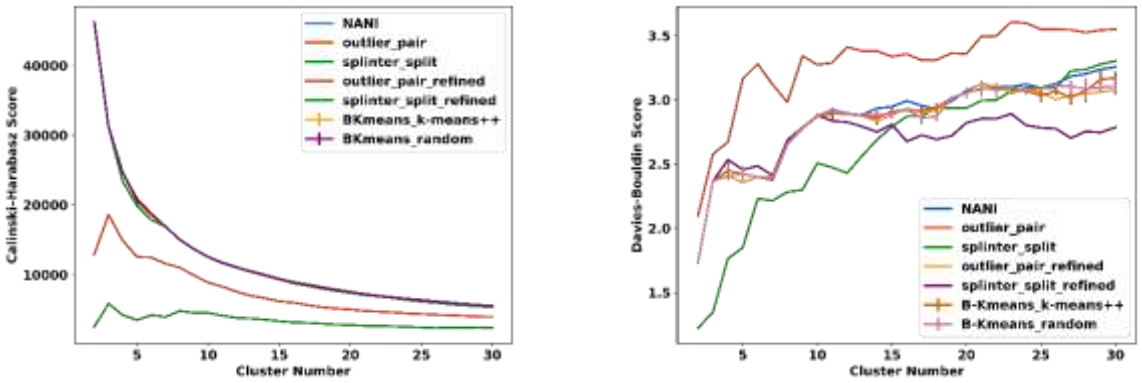

**Figure 3.** Change in Calinski-Harabasz and Davies-Bouldin indices for HP35 after DIVINE clustering from $k = 1$ to 30, comparing performance across different anchor methods.

To explain this discrepancy, we examined the cluster populations and MSDs at $k = 7$ (Table S2). The results showed that splinter_split produced a dominant cluster containing over 94% of the frames, while the remaining clusters accounted for less than 2% each. These small clusters typically exhibited high internal MSD, suggesting that they were isolated based on outlier frames rather than structural significance. A similar trend was observed for outlier_pair, although the imbalance was slightly less extreme.

To mitigate this, we applied a refinement step for the outlier-based anchors. After the initial outlier_pair or splinter_split division, we performed a *k*-means (with $k = 2$) refinement using the medoids as initial centers (see Theory). These refined versions (shown as outlier_pair_refined and splinter_split_refined in the plots) yielded significantly better results. As shown in Fig. 3, both refined anchors show marked CHI gains, especially at moderate k, and maintain or slightly improve DBI scores that match NANI and the BKM variants. Table 1 confirms improved population balance: the largest cluster drops below 50%, and several secondary clusters grow beyond 5%, making the resulting clusters more interpretable.

In contrast, the NANI strategy yielded well-balanced clusters without the need for refinement. At $k = 7$, the largest cluster contained ~43% of frames, with the remainder distributed among clusters ranging from ~6% to ~24%. These ratios fall within the ranges reported in previous studies[13,15] and support our choice of NANI as the default anchor strategy in DIVINE.

**Table 1.** Cluster populations MSDs of each cluster at k = 7 from DIVINE runs using the NANI and the refined variants of outlier_pair and splinter_split as anchors.

| NANI | | outlier_pair | | splinter_split | |
|---|---|---|---|---|---|
| **Population** | **MSD** | **Population** | **MSD** | **Population** | **MSD** |
| 6347 | 88.16 | 6372 | 88.35 | 6371 | 87.98 |
| 7681 | 87.81 | 7667 | 87.77 | 7662 | 88.10 |
| 10569 | 38.73 | 10571 | 38.75 | 11796 | 80.72 |
| 11774 | 80.73 | 11745 | 80.64 | 13354 | 74.63 |
| 13401 | 74.74 | 13405 | 74.76 | 13403 | 40.29 |
| 36677 | 16.89 | 36688 | 16.90 | 32312 | 15.45 |
| 64656 | 9.30 | 64657 | 9.30 | 66207 | 8.94 |

**Cluster Number Selection**

Beyond evaluating clustering quality across anchor strategies, a central motivation for divisive algorithms like DIVINE lies in their inherent ability to facilitate cluster screening. By constructing the full hierarchy in a single run, DIVINE enables users to identify the most informative number of clusters, without requiring separate runs for each target *k*. To assess this capability, we evaluated how well each anchor strategy supports the selection of *k*, not only by examining absolute metric performance, but also by analyzing how reliably they indicate where to partition the tree into meaningful clusters.

Our approach involved two levels of analysis. First, we identified global optima, the values of *k* at which CHI reaches its maximum or DBI reaches its minimum within the screened range. These points represent

the optimal number of clusters according to each metric. Second, we examined local optima by computing the second finite-difference derivatives of the CHI and DBI curves. Distinct peaks or dips in these second-derivative profiles highlight regions where splitting becomes more stable, and where further increases in splits contribute less to overall improvement. These inflection points can reveal meaningful and interpretable cluster counts, even if they do not correspond to the global extremum.

Table 2 summarizes the optimal number of clusters based on these metrics. All DIVINE strategies showed global CHI maxima at $k = 5$ and secondary peaks at $k = 6$, suggesting consistent identification of major conformational states. For DBI, both NANI and outlier_pair reached minima at $k = 5$, while splinter_split achieved its minimum at $k = 7$, reflecting its tendency to delay consolidation. Second-derivative trends were more revealing: all DIVINE anchors showed inflection points at $k = 7$. In contrast, BKM strategies exhibited scattered and inconsistent inflection points across runs, highlighting the challenges of reproducible model selection under stochastic initialization.

**Table 2.** Preferred numbers of clusters for HP35, identified using global and local optima from CHI and DBI metrics following DIVINE clustering.

| metric\anchor | DIVINE NANI | DIVINE outlier_pair | DIVINE splinter_split | BKM* *k*-means++ | BKM* random |
|---|---|---|---|---|---|
| Max. CH | 5 | 5 | 5 | 5/5/5 | 5/5/5 |
| 2nd Max. CH | 6 | 6 | 6 | 6/6/6 | 6/6/6 |
| Min. 2nd Der. CH | - | - | - | - | - |
| 2nd Min. 2nd Der CH | - | - | - | - | - |
| Min. DBI | 5 | 5 | 7 | 5/7/5 | 5/7/5 |
| 2nd Min DBI | 7 | 7 | 5 | 7/6/7 | 6/6/6 |
| Max 2nd Der. DBI | 7 | 7 | 7 | 7/28/7 | 22/7/29 |
| 2nd Max 2nd Der. DBI | 18 | 14 | 16 | 14/7/27 | 20/18/17 |

*BKM results shown as triplicate runs (*k*-means++ and random initializations).

Based on this analysis, we selected $k = 7$ for structural investigation. Fig. 4 shows the overlaps of the best representative frames from each of the seven clusters identified by DIVINE using NANI anchors and weighted_MSD, capturing distinct structural motifs within the HP35 folding trajectory. These same states were identified in previous studies using a *k*-means NANI clustering of the system, highlighting consistency across methods and reliability of DIVINE.

**Figure 4:** Overlaps of best representative structures from the seven clusters of HP35 after performing DIVINE using NANI as anchors and weighted_MSD as cluster selection strategy. Helices 1, 2, and 3 are colored green, cyan, and yellow, respectively.[35]

**Scalability and Performance**

To evaluate full runtime performance, we benchmarked all methods on two datasets (Table 3): a 150k frame subset and the full 1.5 million-frame trajectory of HP35. On the smaller dataset, all DIVINE anchor variants were completed in less than 40 seconds. In comparison, BKM with *k*-means++ and random initialization took 152.6 and 144.8 seconds, respectively, which are approximately four times longer compared to the DIVINE methods.

**Table 3:** Runtime (s) to complete a DIVINE screening ($k = 30$) with each anchor method

| anchor | ~151k frames | ~1.5m frames |
|---|---|---|
| NANI | 34.75 | 283.38 |
| outlier_pair | 33.39 | 312.06 |
| splinter_split | 37.29 | 559.25 |
| BKM_*k*-means++ | 205.47 | 1418.26 |
| BKM_random | 139.95 | 1324.40 |

As we screen the full 1.5 million HP35 trajectory, the differences become even more significant. NANI and outlier_pair anchors were completed at around six minutes. Even the more computationally demanding splinter_split anchor finished in under 10 minutes. In contrast, BKM required over 23 minutes (1418.26 seconds) using *k*-means++ initialization, and 22 minutes (1324.40 seconds) for the random variant. However, BKM's slower performance is partly due to implementation limitations. As mentioned, standard libraries like scikit-learn do not expose the internal clustering hierarchy, so unless the actual code is modified, the entire process must be repeated for each target value of *k*. While this is a technical detail, it highlights one of the advantages of DIVINE: it generates and retains all partitions in a single pass, enabling fast and reproducible screening even at large scales.

## CONCLUSIONS

We presented DIVINE, a deterministic, top-down clustering algorithm for MD trajectory analysis. DIVINE builds a complete, reproducible clustering hierarchy in a single pass by iteratively splitting clusters using cluster-wise metrics and robust anchor selection. Unlike conventional methods, DIVINE avoids pairwise

distance matrices, random seeds, and repeated runs, enabling rapid and memory efficient exploration of the conformational landscape.

The algorithm selects clusters for division based on dispersion and size-driven criteria, including MSD, radius, and weighted MSD, and supports multiple anchor strategies: NANI-based initialization, outlier-pair anchoring, and a DIANA-inspired splintering scheme. More importantly, DIVINE records quality metrics at each step of the hierarchy, enabling users to evaluate clustering performance globally across a range of cluster counts without rerunning the algorithm.

Our benchmarks on the HP35 trajectory demonstrate that DIVINE matches or surpasses bisecting *k*-means (with *k*-means++) in clustering quality, while significantly reducing runtime and eliminating variability across runs. We were able to complete the screening of the full 1.5 million HP35 frames in under six minutes on a single CPU core while producing well-separated and balanced clusters. The default combination of weighted MSD for cluster selection and NANI-based anchors consistently yielded stable partitions that reflected meaningful and previously reported structural states.

Methodologically, DIVINE's core strength lies in its divisive, top-down construction of the hierarchy. Unlike agglomerative or partitional methods, which are limited to either bottom-up heuristic or flat partitioning, this divisive strategy enables the global structural information to guide each recursive splitting. This allows a clearer representation of the system's conformational landscape, particularly in cases where dominant modes span large portions in the trajectory. This also enables DIVINE to leverage global structural information before committing to local partitions, allowing for a more coherent and chemically meaningful decomposition of an MD trajectory.

## SUPPORTING INFORMATION

Tables with the cluster populations and MSD values and structural overlap visualizations for top cluster frames from the HP35 system (PDF.)

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## DATA AND SOFTWARE AVAILABILITY

The code for DIVINE can be found here: https://github.com/mqcomplab/MDANCE.

Conflict of Interest: The authors declare no competing financial interests.

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