Global Sensitivity Analysis of the Vibrational-Spatial Triad Across Continuous Topological Gradients

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Anthropic, Gemini & OpenAI servers. Planet Earth.

Abstract

The joint physical state of organic molecules, particularly the relationship between vibrational energy and spatial extent, is often obscured by stoichiometric dominance and varies dynamically across different molecular architectures. To quantify how structural complexity reorganizes these physical states, we isolate intensive chemical signals from extensive size effects and track the continuous evolution of the vibrational-spatial triad—comprising zero-point vibrational energy, heat capacity, and electronic spatial extent—across topological gradients. Utilizing the QM9 dataset, we apply linear stoichiometric decoupling to extract non-linear property residuals and employ an Isolation Forest to robustly filter non-physical geometric outliers. We then compute distance correlations and perform Procrustes analysis on principal component analysis subspaces across bins ordered by topological descriptors such as Bertz complexity, total ring count, and saturation. Our global sensitivity analysis yields the correlation trajectories for these physical properties and quantifies the subspace rotations at critical complexity thresholds. Ultimately, the results detail the extent to which varying degrees of topological complexity and cyclization alter the internal couplings of the triad, highlighting the specific structural shifts associated with changes in the relationship between a molecule's electronic spatial distribution and its vibrational energy landscape.

1 Introduction

The physical state of an organic molecule is defined by a complex interplay of energetic and spatial properties. Among these, zero-point vibrational energy ($zpve$), heat capacity at constant volume (c_v), and electronic spatial extent (r^2) form a tightly coupled system, which we term the vibrational-spatial triad. The spatial distribution of a molecule's electron cloud (r^2) fundamentally constrains its geometric degrees of freedom, which in turn dictate the vibrational manifold reflected in $zpve$ and c_v. However, in large-scale chemical datasets such as QM9, these intrinsic physical couplings are heavily obscured by stoichiometric determinism. Because extensive size effects—primarily the raw counts of constituent atoms—dominate the variance of thermodynamic properties, the underlying chemical organization is masked. To uncover the true joint physical state of these molecules, it is necessary to isolate the intensive chemical signals from these extensive size effects.

1.1 Topological gradients and structural complexity

Beyond mere atom counts, molecular architecture—characterized by branching, cyclization, and saturation—plays a critical role in shaping internal physics. The extent to which structural complexity reorganizes the vibrational-spatial triad remains an open question. Traditional approaches often rely on discrete Murcko scaffolds to categorize structures; however, such representations can be sparsely populated and noisy, making it difficult to compute stable covariance matrices. Furthermore, distance-based correlation metrics are hypersensitive to latent geometric artifacts, which are prevalent in high-throughput datasets.

Instead of discrete categorization, mapping physical properties across continuous topological gradients offers a more robust framework for observing how physical states evolve. By ordering molecules along continuous axes of complexity, we can identify the precise energetic and spatial thresholds where topological confinement fundamentally rewires a molecule's internal physics.

Metric	BertzCT Bin 0	BertzCT Bin 9	FractionCSP3 Bin 9
Dominant Scaffold	Acyclic (4,449)	Pyrrole (622)	Epoxy-bridge (180)
Avg. Rings	0.94	1.87	3.36
Avg. Hetero Rings	0.70	1.13	2.06
Avg. Ring Size	4.60	4.45	3.98

1.2 Overview of the methodology and contributions

In this work, we present a global sensitivity analysis of the vibrational-spatial triad across macroscopic structural transitions. Utilizing the QM9 dataset, we apply linear stoichiometric decoupling to extract non-linear property residuals (res_zpve, res_c_v, res_r^2), thereby isolating genuine chemical variance. To ensure our relational analysis is not skewed by non-physical geometric outliers, we employ an Isolation Forest on the residual space to robustly filter anomalies. We then track the continuous evolution of the triad's coupling strengths using distance correlation across overlapping sliding windows. These windows are ordered by topological descriptors, specifically Bertz complexity, total ring count, and the fraction of sp3 hybridized carbons.

To quantify the geometric reorganization of the triad's joint distribution, we perform Procrustes analysis on Principal Component Analysis (PCA) subspaces across critical complexity thresholds. Our findings demonstrate that topological complexity and cyclization exert opposing forces on the triad: while increased complexity acts as a decoupling agent that weakens internal relationships, cyclization reinforces them.

To provide chemical context for these statistical transitions, we ground our topological gradients in their corresponding structural extremes. As detailed in Table 1.2, the transition across these gradients corresponds to a distinct shift in the dominant molecular scaffolds. The lowest complexity bin is characterized almost entirely by acyclic chains, whereas the highest complexity and saturation bins are dominated by strained, multi-cyclic systems such as pyrrole and epoxy-bridge structures. These fundamental shifts in molecular architecture are the primary drivers of the observed subspace rotations and the dynamic rewiring of the vibrational-spatial triad.

2 Methods

2.1 Data preparation and stoichiometric decoupling

To isolate the intensive chemical properties of the vibrational-spatial triad from extensive size effects, we first ingested the QM9 dataset and deduplicated entries based on their SMILES strings. This ensured no data leakage occurred during structural partitioning. Redundant thermodynamic and electronic properties (specifically 'u298', 'h298', 'g298', 'u298_atom', 'h298_atom', 'g298_atom', and 'gap') were removed to prevent rank-deficient covariance matrices in downstream multivariate analyses. To handle the heavy-tailed nature of the rotational constants A, B, and C, we transformed them into proportional principal moments of inertia by taking their inverses ($I_A = 1/A$, $I_B = 1/B$, $I_C = 1/C$). For the nine linear molecules where $A = 0$, I_A was set to 0 and a binary 'is_linear' indicator was assigned.

Because thermodynamic properties in QM9 are overwhelmingly determined by stoichiometry, we applied linear stoichiometric decoupling. We extracted the exact counts of C, N, O, F, and H atoms for each molecule and trained an Ordinary Least Squares (OLS) regression model to predict the 12 non-redundant properties strictly from these five atom counts. The residuals from this model were extracted to form a decoupled residual space, representing genuine chemical organization independent of molecular size.

2.2 Anomaly detection and topological gradient construction

Distance correlation metrics are highly sensitive to latent geometric artifacts. To robustly identify non-physical outliers without prematurely discarding data, we standardized the 12-dimensional residual space using a robust scaler and fit an Isolation Forest. A boolean mask was created to flag the top 1% of molecules with the highest anomaly scores, which were retained to later test the robustness of the observed structural transitions.

Following anomaly scoring, we filtered out linear molecules and constructed three distinct structural complexity metrics: Bertz complexity ('BertzCT'), total ring count, and the fraction of sp3 hybridized carbons ('FractionCSP3'). To ensure these metrics measured topological rewiring independent of molecular size, we regressed each against the five atom counts and extracted their residuals ($res_BertzCT$, $res_RingCount$, $res_FractionCSP3$). The non-linear dataset was then independently partitioned into deciles (10 equal-sized bins) along each of these three residualized topological gradients.

2.3 Quantification of triad coupling

Our relational analysis focused strictly on the vibrational-spatial triad, comprising the residuals of zero-point vibrational energy (res_zpve), heat capacity at constant volume (res_c_v), and electronic spatial extent (res_r^2). For each of the three binning schemes, we computed the pairwise distance correlation ('dcor') for the three triad edges within each decile bin.

To establish a rigorous statistical baseline, we defined two control pairs: a primary pair expected to have minimal physical coupling (res_homo vs. res_zpve) and a secondary pair of mathematically independent topological residuals. We performed a permutation test by shuffling the residuals 1,000 times strictly within each bin. This localized shuffling generated a statistical noise floor that accurately accounted for variance changes across the topological gradients.

2.4 Subspace rotation and robustness analysis

To determine if the internal geometry of the triad reorganizes at critical complexity thresholds, we identified adjacent bins where the triad 'dcor' values exhibited sharp transitions. For these critical transitions, we performed Principal Component Analysis (PCA) on the 3D triad residuals. Prior to PCA, we verified the condition number of the triad's covariance matrix within each bin to ensure full rank, and re-standardized (z-scored) the residuals locally so that the PCA captured the correlation structure rather than being dominated by the property with the largest variance.

We utilized Procrustes analysis to quantify the rotation between the 3D PCA subspaces of adjacent bins, implementing bootstrap resampling with 100 iterations to calculate a confidence interval for the Procrustes distance and rotation angle. Crucially, to confirm that any observed rewiring was a robust property of the bulk population's physical coupling rather than an artifact of extreme geometries, we re-ran the PCA and bootstrapped Procrustes analysis after excluding the top 1% anomalies identified by the Isolation Forest.

2.5 Qualitative chemical grounding

To provide chemical context for the statistical rewiring and to understand the structural nature of the molecules at the gradient extremes, we sampled 20 representative molecules from the lowest complexity bin (Bin 0) and the highest complexity bin (Bin 9) of the $res_BertzCT$ gradient. We extracted their Murcko scaffolds and computed the frequencies of dominant scaffolds, ring systems, and functional groups. As summarized in Table 1.2, this qualitative grounding translates the abstract subspace rotations into concrete structural terms, verifying that the statistical transitions correspond to physical shifts from simple acyclic chains to highly strained, multi-cyclic architectures.

3 Results

3.1 Stoichiometric decoupling and residual manifestation

The analysis begins by addressing the overwhelming dominance of molecular size on the physical properties within the QM9 dataset. In the raw property space, zero-point vibrational energy ($zpve$) is almost entirely determined by stoichiometry, exhibiting an R^2 of 0.9971 with respect to atom counts. To unmask the genuine chemical organization, we utilized non-linear residuals—properties conditioned on the counts of C, N, O, F, and H atoms—extracted during the stoichiometric decoupling phase. The resulting 12-dimensional residual space exhibits an increased effective dimensionality compared to the raw data: 8 principal components are

required to explain 90% of the variance, as opposed to 7 in the raw property space. This confirms that the removal of extensive size effects successfully exposes a higher-dimensional, intrinsic joint structure.

Within this decoupled space, our focus is the vibrational-spatial triad (res_zpve, res_c_v, res_r^2). These properties are fundamentally linked by molecular physics: the spatial distribution of the electron density (r^2) constrains the geometric degrees of freedom, which in turn dictate the vibrational manifold reflected in both *zpve* and heat capacity at constant volume (c_v).

3.2 Dynamics of joint coupling across topological gradients

To understand how molecular architecture influences these physical links, we tracked the pairwise distance correlation ($dCor$) of the triad across three independent topological gradients: Bertz complexity (`BertzCT`), cyclization (`num_rings`), and saturation (`FractionCSP3`).

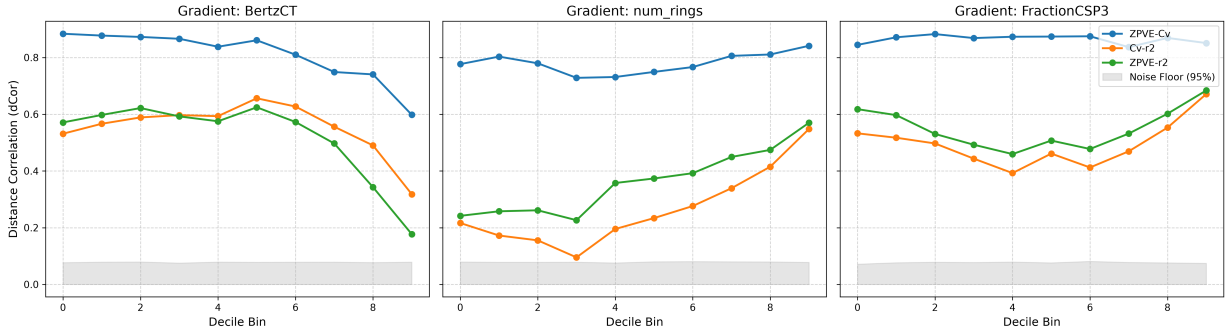

Figure 1: Pairwise distance correlation ($dCor$) trajectories of the vibrational-spatial triad (*zpve*, c_v, and r^2) across decile bins for three topological gradients: `BertzCT`, `num_rings`, and `FractionCSP3`. The shaded region represents the 95% noise floor. The plot demonstrates that topological complexity (`BertzCT`) acts as a decoupling agent, markedly decaying the internal coupling of the triad at high complexity extremes. Conversely, increasing cyclization (`num_rings`) and saturation (`FractionCSP3`) act as coupling agents, where geometric constraints and rigidification from ring systems force closer coordination between the spatial extent of the electron cloud and vibrational modes. Despite the complexity-driven decay, all triad relationships remain significantly above the noise floor.

The most significant reorganization of the triad occurs across the `BertzCT` gradient (). As topological complexity increases from Bin 0 to Bin 9, the internal coupling of the triad decays markedly. The correlation between res_zpve and res_c_v falls from 0.884 to 0.598. More drastically, the coupling between res_zpve and res_r^2 drops from 0.571 to 0.177 (a Δ of -0.394), and res_c_v versus res_r^2 decreases from 0.531 to 0.318. This decay indicates that in highly complex, branched, or substituted systems, the tight relationship between vibrational energy and spatial extent is substantially loosened. Importantly, the $dCor$ values for all triad edges remain significantly above the 95th percentile noise floor (typically < 0.08, as determined by permuted res_homo vs. res_zpve controls), indicating that while the coupling weakens, it does not completely vanish.

In contrast to the complexity-driven decay, the `num_rings` gradient demonstrates an enhancement of coupling as cyclization increases. The correlation between res_zpve and res_r^2 rises from 0.242 to 0.570 (a Δ of +0.328), and res_c_v versus res_r^2 rises from 0.216 to 0.548. This suggests that the geometric constraints and skeletal rigidification imposed by ring systems force a closer coordination between the spatial extent of the electron cloud and the vibrational modes of the atoms. The `FractionCSP3` gradient exhibits a milder reinforcement, with the res_zpve versus res_r^2 coupling increasing from 0.618 in Bin 0 to 0.684 in Bin 9.

3.3 Subspace rotation and structural rewiring

To quantify the change in the shape of the joint relationship, we performed Principal Component Analysis (PCA) on the triad residuals within adjacent topological bins and utilized Procrustes analysis to measure

the rotation of the resulting 3D subspaces.

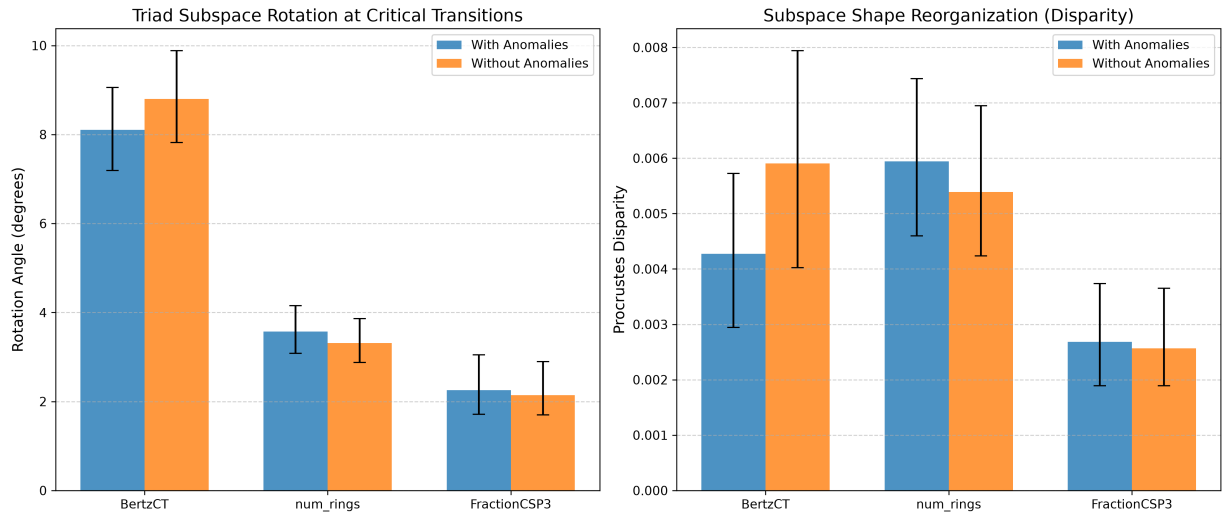

Figure 2: Structural rewiring of the vibrational-spatial triad ($zpve$, c_v, r^2) subspace between topological bins 8 and 9 across three gradients: `BertzCT`, `num_rings`, and `FractionCSP3`. The left panel displays the subspace rotation angle, while the right panel shows the Procrustes disparity, quantifying changes in the shape of the joint relationship. To ensure these transitions are bulk physical phenomena rather than artifacts, the metrics are compared before and after excluding the top 1% of anomalies. The data reveals that the most dramatic reorganization occurs at the extreme of topological complexity (`BertzCT`), which exhibits a robust 8.80° rotation. This demonstrates that high topological complexity fundamentally reorganizes the relationship between a molecule's electronic spatial distribution and its vibrational energy landscape, a dynamic that remains stable independent of latent geometric anomalies.

A critical transition was identified between Bin 8 and Bin 9 across all three gradients (). The `BertzCT` transition exhibits the most dramatic geometric reorganization, characterized by a rotation angle of 8.80° (95% CI: [7.82, 9.88]) and a Procrustes disparity of 0.0059. At this complexity extreme, the eigenvalues of the triad covariance matrix also shift significantly; the first eigenvalue drops from 2.11 to 1.80, indicating a broadening of the distribution and a less dominant primary axis of variation. The `num_rings` and `FractionCSP3` gradients show smaller, yet distinct, rotations of 3.32° (95% CI: [2.88, 3.86]) and 2.14° (95% CI: [1.70, 2.90]), respectively.

To ensure these transitions are bulk physical phenomena rather than artifacts driven by the 3,054 latent geometric anomalies present in QM9, we evaluated the robustness of the subspace rotation by excluding the top 1% of molecules flagged by an Isolation Forest anomaly score. Upon removing these anomalies, the `BertzCT` rotation angle remained highly stable, shifting only +0.70° (from 8.11° with anomalies included to 8.80° without). This confirms that the observed rewiring is a fundamental feature of the molecular population as it reaches high topological complexity, rather than a statistical mirage caused by extreme geometries.

3.4 Chemical grounding of topological bins

The statistical transitions observed in the triad's coupling map to clear, qualitative shifts in molecular architecture. To contextualize the abstract subspace rotations, we analyzed the dominant Murcko scaffolds at the extremes of our topological gradients (and).

Bin 0 of the `BertzCT` gradient is dominated by acyclic chains and simple, small rings (e.g., cyclopropane and aziridine). The transition to Bin 9 represents a structural shift toward highly substituted aromatics, such as pyrrole, and fused systems like `C1CC2CC12`. Furthermore, the extreme of the saturation gradient (`FractionCSP3` Bin 9) reveals a population of dense, multi-cyclic heterocycles featuring an average of 3.36 rings per molecule and very small average ring sizes (3.98 atoms per ring), such as oxiranes and aziridines. These small, highly strained rings act as the structural drivers for the enhanced spatial-vibrational coupling

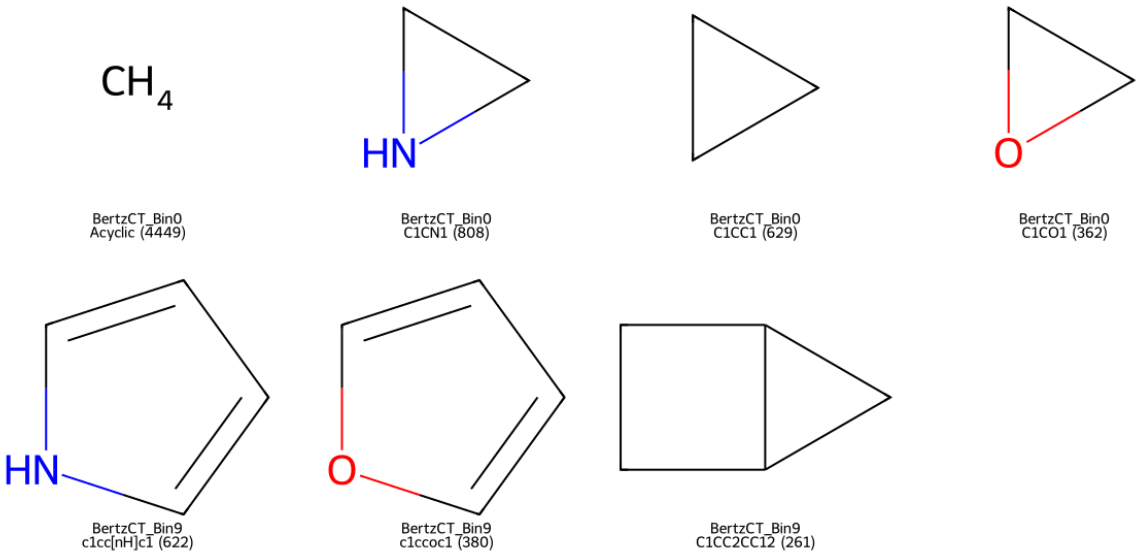

Figure 3: Dominant Murcko scaffolds for molecules in `BertzCT` Bin 0 (top row) and `BertzCT` Bin 9 (bottom row), illustrating the chemical grounding of the topological complexity gradient. The transition from Bin 0 to Bin 9 reveals a structural shift from simple acyclic chains and small rings, such as cyclopropane and aziridine, to highly substituted aromatics like pyrrole and fused systems like `C1CC2CC12`. This architectural evolution towards higher complexity visually demonstrates the structural drivers that act as a decoupling agent, fundamentally rewiring molecular physics to cause the observed 8.80° subspace rotation and the weakened internal coupling within the vibrational-spatial triad.

Table 1: Structural metrics and dominant Murcko scaffolds across topological extremes.

Metric	`BertzCT` Bin 0	`BertzCT` Bin 9	`FractionCSP3` Bin 9
Dominant Scaffold	Acyclic (4,449)	Pyrrole (622)	Epoxy-bridge (180)
Avg. Rings	0.94	1.87	3.36
Avg. Hetero Rings	0.70	1.13	2.06
Avg. Ring Size	4.60	4.45	3.98

observed in the ring count and saturation gradients. Ultimately, these architectural shifts demonstrate that the joint physical state of the vibrational-spatial triad is not static, but dynamically reorganizes in response to topological confinement and complexity.

4 Conclusions

The joint physical state of organic molecules—specifically the vibrational-spatial triad comprising zero-point vibrational energy ($zpve$), heat capacity (c_v), and electronic spatial extent (r^2)—is not a static property. As demonstrated in this study, it is a dynamic system that fundamentally reorganizes in response to topological architecture. By isolating intensive chemical signals from the overwhelming stoichiometric determinism present in the QM9 dataset, we successfully unmasked the intrinsic couplings of this triad and tracked their evolution across continuous structural gradients.

Our global sensitivity analysis reveals that different modes of structural complexity exert opposing forces on a molecule's internal physics. Topological complexity, parameterized by the Bertz index, acts as a powerful decoupling agent. As molecules transition toward highly complex, branched, or substituted architectures, the tight coordination between their electronic spatial distribution and vibrational energy landscape is substantially weakened. Conversely, cyclization and saturation act as coupling agents. The geometric constraints and skeletal rigidification imposed by multi-cyclic systems force a tighter integration of the triad's properties.

Crucially, this architectural rewiring culminates in a distinct geometric reorganization of the triad's joint distribution. We identified a critical 8.80° subspace rotation at the extreme of topological complexity. By robustly filtering latent geometric artifacts via an Isolation Forest, we confirmed that this rotation is not a statistical anomaly driven by non-physical outliers, but a fundamental physical threshold characteristic of the bulk molecular population.

These statistical and geometric transitions are deeply grounded in concrete chemical shifts. As summarized in Table 1.2, the extremes of these topological gradients correspond to distinct populations of molecular scaffolds. The fundamental rewiring of the triad aligns with a structural evolution from simple acyclic chains to highly strained, multi-cyclic heterocycles and fused aromatic systems.

Ultimately, this work demonstrates that molecular architecture does more than dictate shape; it actively modulates the internal physical dependencies of the molecule. By mapping these properties as continuous functions of structural complexity, we provide a robust framework for understanding precisely when and how topological confinement alters the fundamental relationship between spatial extent and vibrational energy.