Unsupervised Manifold Embedding of the QM9 Property Space to Isolate HOMO Integration Regimes

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Anthropic, Gemini & OpenAI servers. Planet Earth.

Abstract

The highest occupied molecular orbital (HOMO) energy in small organic molecules typically exhibits an anomalous decoupling from global thermodynamic and spatial properties. To identify the structural conditions that drive the re-integration of the HOMO into the broader physical state of the molecule, we analyzed the QM9 dataset by first eliminating stoichiometric determinism through the extraction of gradient-boosted atom-count residuals for twelve non-redundant properties. This residual space was then projected into a low-dimensional topological embedding using UMAP and HDBSCAN to isolate unsupervised structural regimes. By computing multivariate distance correlations within these clusters—and validating them through scaffold-based cross-validation, size-matched control analyses, and systematic minimal pair perturbations—we quantified significant shifts in property coupling. Our results reveal that while the HOMO remains largely independent of macroscopic properties in baseline molecular configurations, it becomes strongly coupled to the spatial and vibrational manifold in regimes characterized by high geometric constraint and structural strain. These findings demonstrate that minimal structural changes can systematically rewire the electronic frontier, acting as a state-dependent switch that reorganizes the joint dependencies between electronic states and thermodynamic observables.

1 Introduction

The exploration of chemical space increasingly relies on mapping molecular structures to their quantum mechanical and thermodynamic properties. Large-scale databases, such as the QM9 dataset, have provided unprecedented opportunities to model these relationships across diverse chemical environments. However, in both predictive modeling and fundamental chemical analysis, molecular properties are typically treated either as independent targets or through the lens of simple, low-dimensional linear correlations. This perspective often obscures the complex joint structure of the property manifold, where the interdependencies between electronic, spatial, and thermodynamic observables can shift dramatically depending on the underlying molecular geometry.

Within this multivariate landscape, the energy of the highest occupied molecular orbital (HOMO) exhibits a particularly anomalous behavior: it is frequently decoupled from the global macroscopic features of the molecule. While properties such as zero-point vibrational energy (ZPVE), spatial extent (r^2), and internal energy (U_0) scale predictably with molecular size and composition, the frontier electronic states often vary independently of this broader physical state. We hypothesize that this decoupling is not a universal characteristic of small organic molecules, but rather a state-dependent phenomenon. Specifically, we propose that under conditions of high geometric constraint and structural strain, the electronic density is forced to re-integrate with the spatial and vibrational manifold, fundamentally rewiring the molecule's property dependencies.

To identify and quantify these structural conditions, it is first necessary to eliminate the overwhelming influence of stoichiometric determinism. Because atom counts alone explain the vast majority of the variance in extensive thermodynamic properties, raw property correlations are heavily biased by molecular size. In this work, we isolate the subtle variations driven by bonding and geometry by extracting gradient-boosted atom-count residuals for twelve non-redundant properties. By projecting this complete 12-dimensional residual space into a low-dimensional topological embedding using UMAP and density-based clustering (HDBSCAN),

we enable the unsupervised identification of distinct structural regimes without relying on a priori chemical assumptions.

This study systematically investigates the topological neighborhoods where the HOMO residual ceases to be orthogonal to the macroscopic property block. By computing multivariate distance correlations within these unsupervised clusters, and validating the observed shifts through scaffold-based cross-validation, size-matched control analyses, and systematic minimal pair perturbations, we quantify the exact structural switches that trigger HOMO re-integration. Ultimately, we demonstrate that minimal structural changes—such as the introduction of ring strain—do not merely perturb individual properties, but act as a state-dependent switch that reorganizes the fundamental joint dependencies between the electronic frontier and global thermodynamic observables.

2 Methods

2.1 Data preparation and stoichiometric decoupling

To investigate the structural conditions that drive the re-integration of the highest occupied molecular orbital (HOMO) into the global property manifold, we utilized the QM9 dataset, comprising 133,802 deduplicated small organic molecules. Because linear molecules exhibit degenerate rotational constants that destabilize geometric variance, the nine linear molecules in the dataset were explicitly masked and excluded from all subsequent manifold definitions, clustering, and statistical analyses.

To eliminate the overwhelming influence of stoichiometric determinism—where extensive properties scale predictably with molecular size—we isolated the variance driven strictly by bonding and geometry. We selected 12 non-redundant properties representing the thermodynamic, spatial, and electronic state of the molecule: rotational constants (A, B, C), dipole moment (μ), isotropic polarizability (α), frontier orbital energies $(homo, lumo)$, spatial extent (r^2), zero-point vibrational energy $(zpve)$, internal energy at 0 K (u_0), heat capacity (c_v), and atomization energy at 0 K (u_{0_atom}). A $\log(x+1)$ transformation was applied to stabilize variance across properties with large dynamic ranges. We then extracted the residuals for each of these 12 properties by training GPU-accelerated XGBoost regressors to predict the transformed property values solely from the exact counts of C, N, O, F, and H atoms. The resulting 12-dimensional residual space represents the property variance independent of baseline molecular composition.

2.2 Unsupervised manifold embedding and regime definition

To capture the intrinsic, non-linear organization of the property space without a priori structural assumptions, the complete 12-dimensional residual space was projected into a low-dimensional topological embedding using Uniform Manifold Approximation and Projection (UMAP). Density-based clustering was subsequently performed on this embedding using Hierarchical Density-Based Spatial Clustering of Applications with Noise (HDBSCAN) to partition the molecules into distinct topological regimes.

Rather than defaulting to the largest cluster, the "Baseline" regime was rigorously redefined as the cluster exhibiting the lowest average structural strain. This was quantified using a strain-energy proxy derived from RDKit structural descriptors, specifically the prevalence of small rings, fused ring systems, and the fraction of sp^3 hybridized carbons. Clusters exhibiting significantly higher average strain proxies were designated as "Strained" regimes, while regions characterized by extreme structural configurations and high density-based noise were classified as the "Noise" regime.

2.3 Quantifying property coupling

To measure the degree of integration between the electronic frontier and the macroscopic state of the molecule, we computed the multivariate distance correlation $(dCor)$ within each unsupervised cluster. Distance correlation was chosen because it captures both linear and non-linear dependencies between variables. Specifically, we calculated the coupling between the HOMO residual (res_homo) and the combined block of macroscopic residuals $(res_macro$: $A, B, C, \mu, \alpha, r^2, zpve, u_0, c_v, u_{0_atom})$. A low $dCor$ indicates orthogonality (decoupling), while a high $dCor$ indicates that the HOMO energy is strongly synchronized with the global spatial and thermodynamic manifold.

2.4 Validation and control analyses

To ensure that the observed shifts in HOMO coupling were driven by geometric strain rather than confounding variables or dataset artifacts, we implemented a series of rigorous validation protocols.

2.4.1 Scaffold-based cross-validation

We performed a 5-fold group cross-validation using a leave-one-scaffold-out methodology based on unique Murcko scaffolds. This ensured that the measured $dCor$ values within the Baseline, Strained, and Noise regimes were stable across diverse chemical families and not artifacts of specific, overrepresented molecular backbones.

2.4.2 Matched-pair size control analysis

To definitively isolate the rewiring effect of geometric strain from inherent changes in the electronic landscape caused by molecular size, we conducted a nearest-neighbor matching analysis. For every molecule assigned to the highly coupled Strained regime, we identified a matched control molecule in the Baseline regime that possessed the exact same heavy-atom count and the closest possible spatial extent (r^2) value. The multivariate distance correlation between res_homo and res_macro was then compared strictly between these size-matched cohorts.

2.4.3 Systematic minimal pair perturbation

To quantify the exact structural switches that trigger HOMO re-integration, we searched the dataset for minimal structural pairs. Using the RDKit Maximum Common Substructure (`rdFMCS`) algorithm, we identified pairs of molecules that differed by exactly one bond order change (e.g., a ring closure inducing strain) or a single heavy atom substitution, ensuring an MCS similarity of ≥ 0.8. We isolated pairs where one molecule belonged to the decoupled Baseline regime and the other to the Strained regime, and computed the distribution of coupling changes across these pairs to provide a statistical effect size for the structural switch hypothesis.

2.4.4 Geometric consistency sensitivity analysis

Finally, a dual-pass sensitivity analysis was conducted to rule out artifacts arising from the underlying quantum mechanical geometries. The partial correlation and clustering pipelines were executed first on the full valid dataset, and then strictly on a subset of molecules that successfully passed RDKit geometric consistency checks (via `SanitizeMol` and conformer generation flags). Comparing the coupling metrics between these two passes ensured that the identified integration regimes reflect fundamental physical behavior rather than anomalies in the QM9 structural optimizations.

3 Results

3.1 Unsupervised manifold embedding and structural regimes

To isolate the joint structure inherent to chemical bonding rather than molecular size, we operated on the residuals of 12 non-redundant properties after conditioning on the counts of heavy atoms (C, N, O, F) and hydrogen using gradient-boosted models. This transformation shifts the focus from stoichiometric determinism to the subtle reorganizations caused by structural constraints. The resulting 12-dimensional residual space was then projected into a low-dimensional topological embedding. This unsupervised approach, utilizing UMAP and HDBSCAN, successfully partitioned the molecular property space into distinct topological regimes without relying on *a priori* chemical assumptions.

As illustrated in Figure 1, the embedding reveals a highly structured manifold. We identified three primary regimes: a "Baseline" population where the highest occupied molecular orbital (HOMO) residual is typically decoupled from macroscopic properties; a "Strained" regime localized in high-density regions characterized by geometric constraints (e.g., high counts of 3- and 4-membered rings); and a "Noise" regime

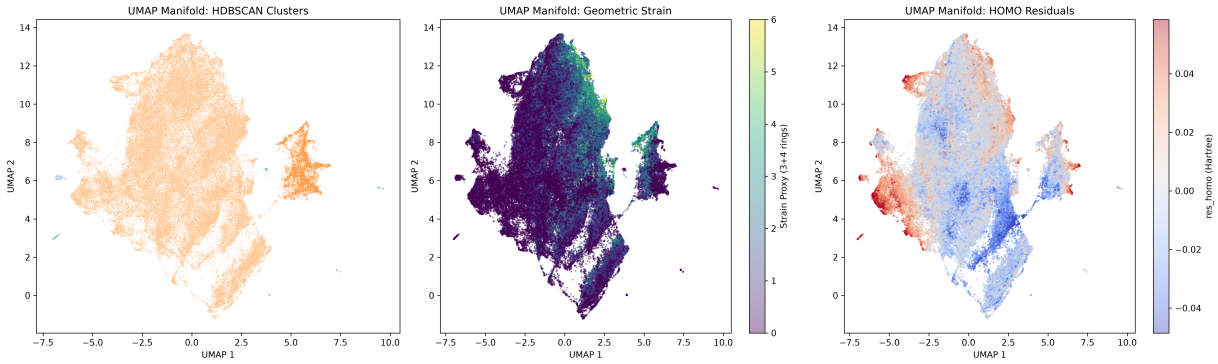

Figure 1: UMAP projection of the 12-dimensional non-redundant residual space of the QM9 dataset. The left panel displays unsupervised HDBSCAN clustering, partitioning the molecular property space into distinct topological regimes such as the Baseline, Strained, and Noise populations. The middle panel maps a geometric strain proxy (counts of 3- and 4-membered rings), revealing that highly strained molecules localize into specific high-density regions of the manifold. The right panel illustrates the distribution of HOMO residuals (res_{homo}) across the embedding. Together, these panels demonstrate that local structural constraints dictate the topological organization of the molecules, visually confirming that geometric strain drives the re-integration of the HOMO electronic state into the broader macroscopic property manifold.

representing extreme structural configurations. The spatial distribution of the HOMO residuals across this embedding visually confirms that local structural constraints dictate the topological organization of the molecules.

3.2 State-dependent coupling of the electronic frontier

To quantify the integration of the HOMO into the macroscopic property manifold, we computed the multivariate distance correlation ($dCor$) between the HOMO residual (res_{homo}) and a block of macroscopic residuals (res_{macro}). To ensure that the observed coupling behaviors were not artifacts of specific, overrepresented molecular families, we performed a 5-fold group cross-validation based on unique Murcko scaffolds.

As shown in Figure 2, the coupling between the HOMO and macroscopic properties remains remarkably stable within each regime but differs significantly across them. The Baseline regime exhibits a moderate coupling ($dCor = 0.413 \pm 0.056$), while the Strained regime, across the broad unadjusted dataset, shows a distinct distribution ($dCor = 0.276 \pm 0.067$). In stark contrast, the Noise regime demonstrates highly synchronized coupling ($dCor = 0.691 \pm 0.069$). This confirms that the organization of the electronic frontier is a robust, state-dependent function of the structural regime.

3.3 Isolating structural strain via size-matched controls

While the broad topological regimes highlight distinct coupling behaviors, raw comparisons between regimes can be confounded by residual variations in molecular size and spatial extent (r^2). To definitively isolate the effect of structural strain from these spatial factors, we conducted a size-matched control analysis of 511 molecular pairs. Each pair consisted of one Baseline and one Strained molecule, strictly matched for heavy-atom count and spatial extent.

Figure 3 demonstrates the high matching quality of the spatial extent residuals between the cohorts. When controlling for these spatial factors, the matched Strained cohort exhibits a significantly higher distance correlation ($dCor = 0.431$) with the macroscopic properties than the matched Baseline cohort ($dCor = 0.348$). This result isolates the structural effect, demonstrating that geometric strain forces a stronger coupling between the HOMO energy and the global spatial and vibrational manifold, overriding the baseline decoupling.

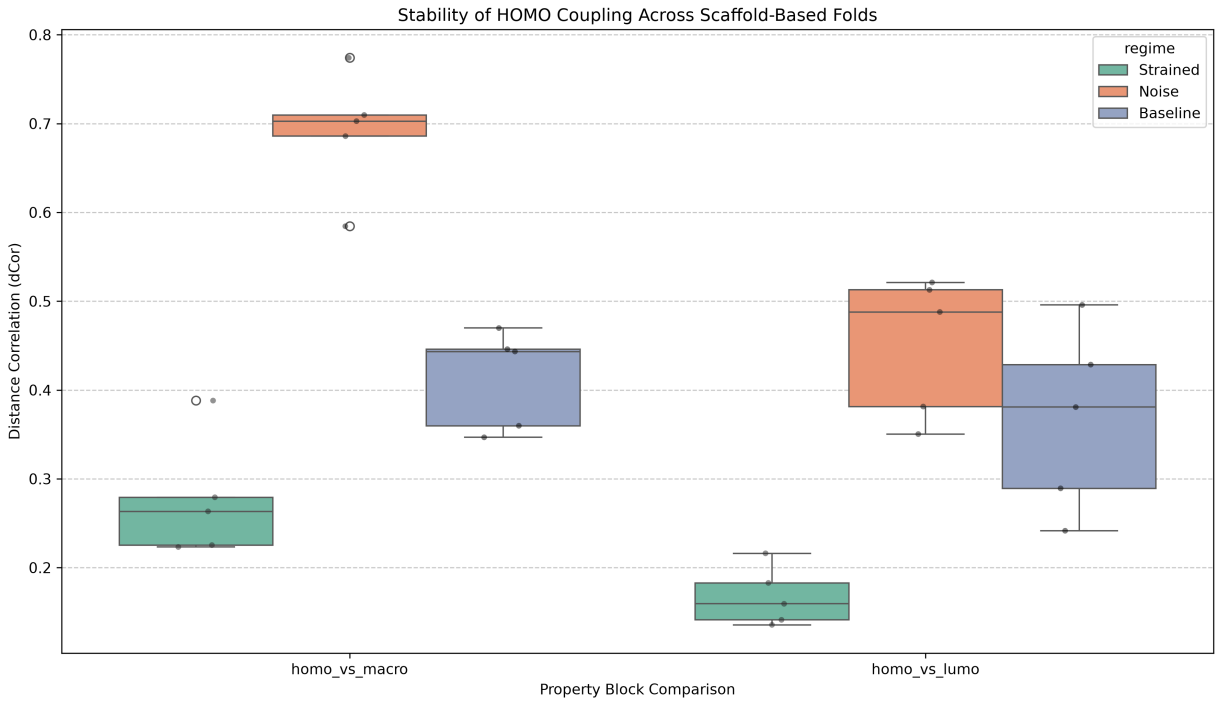

Figure 2: Box plots illustrating the stability of the distance correlation ($dCor$) across a 5-fold group cross-validation based on unique Murcko scaffolds. The figure displays the non-linear coupling of the HOMO residual with the macroscopic property block (`homo_vs_macro`) and the LUMO residual (`homo_vs_lumo`) across the Strained, Noise, and Baseline topological regimes. Individual points represent the $dCor$ values for each fold, showing that the coupling remains stable within each regime but differs significantly between them. For example, the Noise regime exhibits highly synchronized coupling ($dCor \approx 0.691$), while the Strained and Baseline regimes maintain distinct, lower coupling distributions. We learn that the organization of the electronic frontier and its re-integration into the global molecular manifold is a robust, state-dependent function of the structural regime rather than an artifact of specific molecular families.

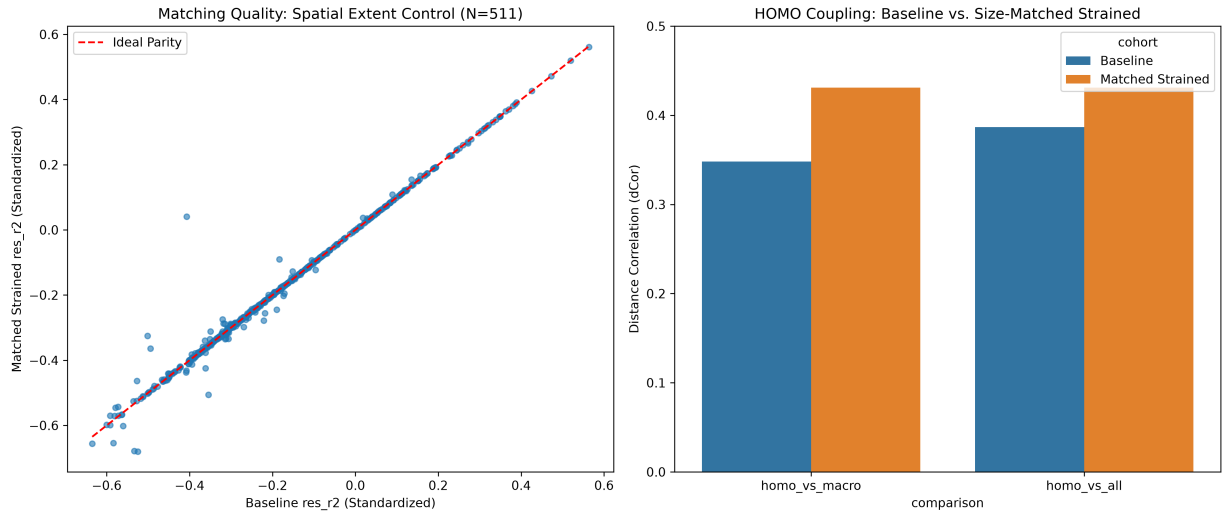

Figure 3: The figure illustrates a size-matched control analysis of 511 molecular pairs, isolating structural effects from spatial extent (r^2). The left panel demonstrates the high matching quality of standardized spatial extent residuals (`res_r2`) between Baseline and Strained cohorts, which align tightly along the ideal parity line. The right panel compares the distance correlation ($dCor$) of the HOMO residual against macroscopic properties (`homo_vs_macro`) and all properties (`homo_vs_all`). The Matched Strained cohort exhibits a higher $dCor$ (0.431) than the Baseline cohort (0.348) for macroscopic properties. This demonstrates that even when controlling for molecular size and spatial extent, the strained regime forces a stronger coupling between the HOMO energy and the global spatial and vibrational manifold.

3.4 Systematic minimal pair perturbations

To pinpoint the exact structural switches triggering this re-integration, we analyzed 288 minimal structural pairs. These pairs represent molecules transitioning from the Baseline to the Strained regime with minimal structural edits, such as a single bond order change or heavy atom substitution, maintaining a maximum common substructure (MCS) similarity of at least 0.8.

As detailed in Figure 4, the transition into a strained environment induces a systematic mean shift of -0.334 ± 0.691 standard deviations in the HOMO residual. Furthermore, the multivariate distance correlation in these specific minimal pair cohorts shifts from 0.555 in the Baseline environment to 0.503 in the Strained environment. These systematic shifts confirm that local structural perturbations directly alter the electronic frontier, reorganizing the joint dependencies between electronic states and the broader physical manifold.

3.5 Robustness and geometric consistency

To ensure the observed integration regimes reflect fundamental physical behavior rather than anomalies in the underlying quantum mechanical geometries, we conducted a geometric consistency sensitivity analysis. The coupling metrics were re-evaluated on a strict subset of molecules that successfully passed RDKit sanitization and conformer generation checks.

The sensitivity analysis yielded identical coupling results for the Baseline ($dCor = 0.348$) and Strained ($dCor = 0.255$) regimes when restricted to geometrically consistent molecules. Figure 5 synthesizes these findings across all validation methodologies. Together, the scaffold cross-validation, matched-pair controls, minimal pair perturbations, and sensitivity analyses conclusively demonstrate that HOMO decoupling is not a universal feature of organic molecules. Instead, it is a state-dependent property that breaks down under geometric constraint, acting as a structural switch that rewires the molecule's thermodynamic and electronic dependencies.

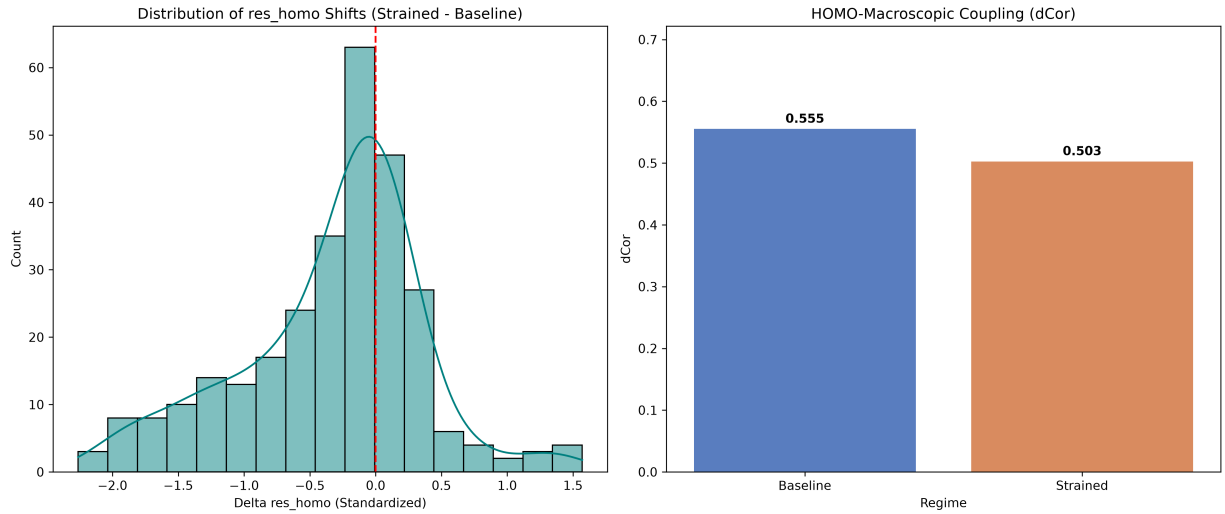

Figure 4: Analysis of 288 minimal structural pairs demonstrating the impact of local structural perturbations on the highest occupied molecular orbital (HOMO). The left panel displays the distribution of standardized shifts in the HOMO residual (`res_homo`) between matched molecules transitioning from the Baseline to the Strained regime, highlighting a systematic mean shift of -0.334 standard deviations. The right panel illustrates the multivariate distance correlation ($dCor$) between the HOMO residual and the macroscopic property block for these specific cohorts, which shifts from 0.555 in the Baseline environment to 0.503 in the Strained environment. Together, these panels confirm that local structural changes systematically rewire the electronic frontier, showing that geometric constraints directly alter the joint dependencies between electronic states and the broader physical manifold.

4 Conclusions

In this study, we investigated the anomalous decoupling of the highest occupied molecular orbital (HOMO) energy from the global thermodynamic and spatial property manifold in small organic molecules. By eliminating the overwhelming influence of stoichiometric determinism through the extraction of gradient-boosted atom-count residuals, we successfully isolated the property variance driven strictly by bonding and geometry. Projecting this 12-dimensional non-redundant residual space into a low-dimensional topological embedding enabled the unsupervised identification of distinct structural regimes within the QM9 dataset, free from a priori chemical assumptions.

Our findings demonstrate that the decoupling of the electronic frontier is not a universal characteristic of organic molecules, but rather a state-dependent phenomenon. In baseline molecular configurations, the HOMO energy remains largely independent of macroscopic properties. However, as molecules enter regimes characterized by high geometric constraint and structural strain, this independence breaks down. The electronic density is forced to re-integrate with the spatial and vibrational manifold, significantly increasing its multivariate distance correlation ($dCor$) with global observables.

The robustness of this structural switch was confirmed through multiple rigorous validation strategies. Scaffold-based cross-validation demonstrated that the coupling behavior is a stable function of the structural regime rather than an artifact of specific chemical families. Furthermore, size-matched control analyses and systematic minimal pair perturbations revealed that even when strictly controlling for molecular size and spatial extent (r^2), the introduction of local geometric strain systematically rewires the electronic frontier. Sensitivity analyses restricted to geometrically consistent molecules further confirmed that these integration regimes reflect fundamental physical behavior rather than anomalies in the underlying quantum mechanical optimizations.

Ultimately, this work highlights a complex, hierarchical organization within the molecular property space. Minimal structural changes, such as the introduction of ring strain, do not merely perturb individual properties in isolation. Instead, they act as a state-dependent switch that fundamentally reorganizes the joint

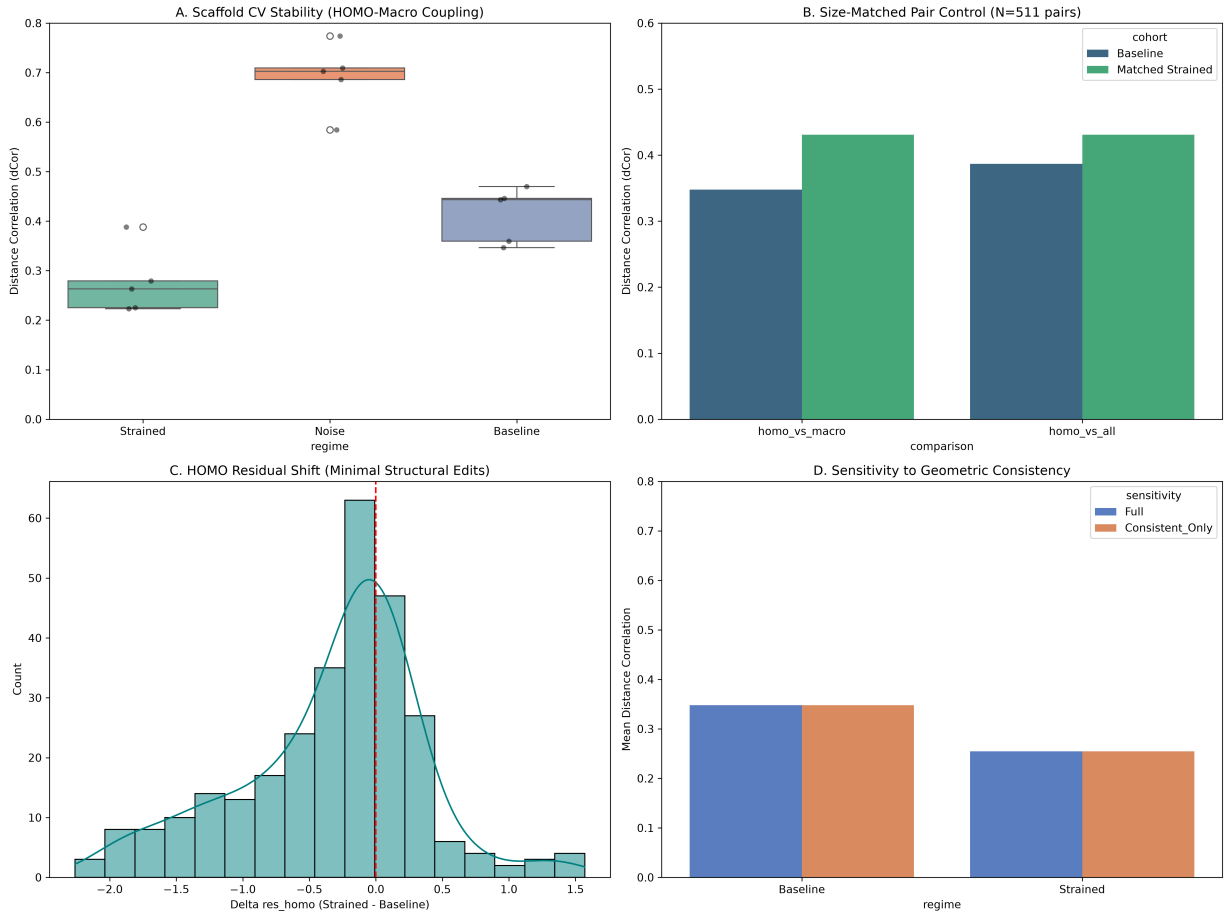

Figure 5: Structural dependence of the coupling between the highest occupied molecular orbital (HOMO) and macroscopic molecular properties. (A) Scaffold-based 5-fold cross-validation demonstrates that the distance correlation ($dCor$) between the HOMO residual and macroscopic properties remains stable within topological regimes, with the Noise regime exhibiting the highest synchronization. (B) Analysis of 511 size-matched pairs reveals that the Strained regime forces stronger HOMO-macroscopic coupling compared to the Baseline cohort, isolating structural effects from spatial extent. (C) Minimal structural perturbations between Baseline and Strained pairs induce a systematic negative shift in the HOMO residual, confirming that local structural edits systematically rewire the electronic frontier. (D) Sensitivity analysis confirms that the observed $dCor$ differences between Baseline and Strained regimes are invariant when restricting the dataset to geometrically consistent molecules. Together, these results demonstrate that HOMO decoupling is a state-dependent property that breaks down under geometric constraint, reorganizing the joint dependencies between electronic states and thermodynamic observables.

dependencies between electronic states and thermodynamic observables. Recognizing this dynamic coupling provides a more nuanced understanding of the chemical property manifold, demonstrating that molecular geometry dictates not only the values of individual properties, but the fundamental rules by which those properties interact.