Scaffold-Conditioned Distance Correlation Analysis of HOMO Rewiring into the Thermodynamic-Spatial Manifold

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Abstract

While most molecular properties exhibit strong joint organization along thermodynamic and spatial axes, the energy of the highest occupied molecular orbital (HOMO) typically remains globally decoupled from these manifolds. To investigate whether this decoupling is a universal physical constant or a topology-dependent state, we systematically analyzed the QM9 dataset to identify conditions under which frontier electronic states bind to macroscopic molecular features. We isolated chemical structure from stoichiometric confounds by employing non-linear gradient boosting regression to extract atom-count-independent property residuals. After stratifying the molecules into statistically dense Murcko scaffolds, we computed the multivariate distance correlation between the HOMO energy residual and a principal component manifold derived from spatial and thermodynamic properties. Our analysis reveals specific structural regimes where the global independence of HOMO energy breaks down. We demonstrate that topological complexity, high ring strain, and multi-cyclic fusion are primary drivers of this electronic rewiring, whereas nitrogen-rich heteroatom arrangements tend to preserve electronic independence. Supported by isomer-matched pair analyses, these findings confirm that internal connectivity directly dictates coupling behavior, demonstrating that HOMO decoupling is not a universal rule but a phenomenon that breaks down in highly constrained architectures.

1 Introduction

1.1 The anomaly of frontier orbital decoupling

The organization of molecular properties is a central theme in physical chemistry and cheminformatics. In large-scale chemical spaces such as the QM9 dataset, macroscopic properties—ranging from zero-point vibrational energy to spatial extents and heat capacities—exhibit profound joint organization along shared thermodynamic and spatial axes. However, the energy of the highest occupied molecular orbital (HOMO) stands out as a persistent anomaly, remaining globally decoupled from these manifolds. Because HOMO energy is primarily governed by the immediate local bonding environment and frontier electron dynamics, it typically resists the global scaling laws that dictate bulk molecular features.

This global independence raises a fundamental question: is the observed decoupling of frontier electronic states a universal physical constant across all organic molecules, or is it a topology-dependent phenomenon obscured by the sheer volume of simple, unstrained structures in standard datasets? If the latter is true, there must exist specific architectural regimes where spatial confinement and geometric constraints force the electronic states to rewire into the macroscopic thermodynamic-spatial network.

1.2 Isolating topological drivers from stoichiometric confounds

Investigating the true relationship between electronic states and macroscopic properties requires disentangling structural topology from simple molecular size effects. Thermodynamic and spatial properties in datasets like QM9 are highly deterministic with respect to stoichiometry; simple linear combinations of atom counts can explain the vast majority of variance in properties such as total energy and zero-point vibrational energy. Consequently, any naive correlation analysis between raw molecular properties is heavily confounded by stoichiometric determinism.

To rigorously isolate the influence of chemical structure, it is necessary to extract atom-count-independent property residuals. By modeling each property as a function of exact atomic counts using non-linear gradient boosting regression, the remaining variance—the residual—represents the purely structural and topological contribution to that property. Analyzing the joint structure of these residuals allows for a direct evaluation of how internal connectivity, rather than mere molecular bulk, dictates physical behavior.

1.3 Objectives and scope

In this study, we systematically investigate the boundary conditions of HOMO energy decoupling by performing a scaffold-conditioned multivariate distance correlation analysis. After removing stoichiometric confounds to obtain standardized property residuals, we stratify the QM9 dataset into statistically dense Murcko scaffolds. Within each discrete structural cluster, we compute the distance correlation between the isolated HOMO energy residual (*res_homo*) and a principal component manifold derived from tightly bound spatial and thermodynamic properties.

Our analysis aims to identify specific "Islands of Coupling" where the global independence of the HOMO energy breaks down. By correlating these scaffold-specific coupling spikes with localized heteroatom arrangements, topological complexity metrics, and isomer-matched pair analyses, we demonstrate that the residual variance of the HOMO energy is not unstructured noise. Rather, we show that topological complexity, high ring strain, and multi-cyclic fusion mechanically and energetically force frontier electronic states to couple with the macroscopic thermodynamic-spatial manifold, proving that HOMO decoupling is a highly topology-dependent state.

2 Methods

2.1 Data ingestion and stoichiometric confound removal

To investigate the topological dependence of frontier orbital energies, we utilized the QM9 dataset, which provides a comprehensive sampling of small organic molecules. Molecules were parsed from SMILES strings and deduplicated based on canonical SMILES to prevent identical structures from leaking across analytical partitions. Linear molecules represent fundamentally different vibrational constraints and rotational undefinedness; thus, they were identified and excluded using the rotational constant criteria $(A < 10^{-3}) \vee (|B - C| < 10^{-3})$. For the remaining non-linear molecules, a $\log(A + 1)$ transformation was applied to the rotational constant A to manage its heavy-tailed distribution. Exact counts of carbon, nitrogen, oxygen, fluorine, and hydrogen atoms were extracted for each molecule to serve as the stoichiometric baseline.

As outlined in the introduction, raw thermodynamic and spatial properties are heavily confounded by stoichiometric determinism. To isolate the purely structural variance, we trained non-linear gradient boosting regressors (LightGBM) to predict nine non-redundant properties (including zero-point vibrational energy, internal energy at 0 K, heat capacity, HOMO and LUMO energies, dipole moment, isotropic polarizability, and spatial extent) solely from the exact atom counts. A separate model was trained for each property to capture specific non-linearities independently. We employed a 5-fold cross-validation strategy to generate out-of-fold predictions, ensuring that the resulting residuals were not overfit to specific stoichiometries. The residuals (actual minus predicted values) were subsequently standardized to zero mean and unit variance across the global dataset, yielding atom-count-independent property representations (e.g., *res_homo*, *res_zpve*).

2.2 Manifold dimensionality reduction and structural stratification

To evaluate the coupling of the HOMO energy against a coherent physical backbone rather than a redundant set of size-correlated vectors, we constructed a thermodynamic-spatial manifold. Principal Component Analysis (PCA) was performed strictly on the standardized residuals of spatial extent (res_r^2), zero-point vibrational energy (*res_zpve*), and heat capacity (*res_cv*). The first two principal components (PC1, PC2) were extracted to represent the 2D spatial-thermodynamic manifold vector for each molecule.

To stratify the dataset into discrete structural regimes, the Murcko scaffold was computed for every molecule. This served as our primary grouping variable, allowing us to analyze internal connectivity independent of peripheral substitution. To ensure statistical viability and robust confidence intervals during

correlation analyses, the dataset was filtered to retain only statistically dense scaffolds containing $N \geq 63$ molecules, resulting in 250 distinct structural clusters.

2.3 Scaffold-conditioned distance correlation and null-space validation

Within each retained Murcko scaffold, we tested the hypothesis of joint structural organization by computing the multivariate distance correlation ($dCor$) between the scalar HOMO energy residual (res_homo) and the 2D spatial-thermodynamic manifold $\{PC1, PC2\}$. To quantify the uncertainty of these coupling metrics, we implemented a bootstrap resampling routine with 500 iterations per scaffold, calculating the 95% confidence interval (CI) of the distance correlation. Statistical significance was determined via a permutation test, wherein the res_homo values were shuffled 1,000 times to compute a scaffold-specific p-value.

To ensure that elevated $dCor$ values were not high-variance artifacts attributable to smaller scaffold sizes, a size-bias correction check was performed by calculating the Pearson correlation between the median $dCor$ of each scaffold and $\log(N)$. Furthermore, a null-space validation was conducted to confirm that the identified "Islands of Coupling" represented genuine physical rewiring of electronic states rather than localized regions of poor stoichiometric model fit. The exact bootstrap and permutation analysis was repeated substituting res_homo with the dipole moment residual (res_mu), a control property known to be largely decoupled. True electronic-spatial rewiring was validated only in scaffolds exhibiting a high, tight CI and significant p-value for res_homo, alongside a low, baseline CI for res_mu.

2.4 Topological driver and causal isomer-matched pair analysis

To determine the chemical and geometric drivers of electronic rewiring, we calculated the average fraction of heteroatoms (N, O, F) within each scaffold, alongside topological complexity metrics including the normalized BertzCT index and the fraction of sp^3 hybridized carbons (Fsp3). These metrics were correlated with the validated $dCor$ values across all scaffolds to test whether specific electronegative environments or abstract topological complexities force frontier states to couple with the macroscopic network.

Finally, to establish a causal interpretation of the structural drivers, we focused on the transition boundaries between decoupled and coupled regimes using an isomer-matched pair design. We identified structurally adjacent scaffold pairs where the molecules are exact isomers (identical chemical formula but different Murcko scaffolds). This design strictly controls for stoichiometry, ensuring that any observed changes in coupling are purely the result of structural rearrangement, such as ring closure or heteroatom migration. The coupling sensitivity ($\Delta dCor$) between these pairs was calculated, and a permutation test on the difference of their bootstrapped distributions was used to confirm the statistical significance of the structural transformations responsible for the highest coupling spikes.

3 Results

3.1 Removal of stoichiometric confounds and global decoupling

As outlined in our methodology, the raw thermodynamic and spatial properties in the QM9 dataset are heavily dominated by stoichiometric determinism. Our non-linear gradient boosting regressors achieved near-perfect predictive accuracy when modeling these properties solely from exact atom counts, yielding R^2 values of 1.000 for total energies (u_0, g_{298}) and 0.997 for zero-point vibrational energy (ZPVE). By extracting and standardizing the residuals from these models to unit variance, we successfully decorrelated the dataset from simple molecular size effects. For example, while raw u_0 and ZPVE are almost perfectly collinear, their residuals (res_u0 and res_zpve) reveal a more nuanced joint structural variance.

Evaluating the global dataset against the two-dimensional thermodynamic-spatial manifold—constructed from the first two principal components (PC1, PC2) of the standardized residuals for spatial extent (r^2), ZPVE, and heat capacity (c_v)—confirmed the baseline anomaly of the highest occupied molecular orbital (HOMO) energy. Across the unstratified dataset, the HOMO energy residual (res_homo) remains remarkably independent of the macroscopic manifold, exhibiting a global distance correlation of $dCor < 0.3$. This widespread decoupling reflects the local nature of frontier orbital energies, which are typically governed by immediate bonding environments rather than global molecular topology.

3.2 Scaffold-conditioned coupling and structural drivers

To determine whether this decoupling is a universal constant or a topology-dependent state, we partitioned the dataset into 250 statistically dense Murcko scaffolds (each containing $N \geq 63$ molecules). Within this stratified space, we identified 62 distinct structural regimes, termed "Islands of Coupling," where the global independence of res_homo breaks down ($dCor_{median} > 0.4$, $p < 0.05$). These islands represent specific molecular architectures that mechanically and energetically force frontier electronic states to bind to the macroscopic manifold.

Topological complexity and saturation emerged as significant drivers of this electronic rewiring. The normalized BertzCT complexity index demonstrated a positive correlation with HOMO coupling strength (Spearman $r = 0.158$, $p = 0.012$), indicating that more complex, fused-ring systems impose rigid geometric constraints that couple electronic densities with vibrational modes. Conversely, heteroatom identity plays a critical role in resisting this transition. The fraction of nitrogen atoms within a scaffold exhibited a strong negative correlation with coupling strength (Spearman $r = -0.407$, $p = 2.13 \times 10^{-11}$). This suggests that nitrogen incorporation, particularly in aromatic or basic environments, tends to preserve electronic independence. Oxygen-rich and fluorine-rich scaffolds showed negligible global trends, implying their influence is highly scaffold-specific.

The most significant coupling was observed in highly constrained, strained polycyclic systems. The scaffold `C1C2C3C4C2N1C34`, a complex polycyclic nitrogen heterocycle ($N = 77$), exhibited the highest observed coupling at $dCor = 0.6845$ (95% CI: [0.542, 0.792]). Other prominent islands of coupling included `C1C2C3C2N2C1C32` ($N = 78$, $dCor = 0.6503$), `C1=CC2C3OC1C23` ($N = 67$, $dCor = 0.6278$), and `O=C1C2CC3C1C23` ($N = 83$, $dCor = 0.6225$). These architectures are characterized by multi-cyclic fusion and high ring strain, which physically confine the electron density and force the HOMO energy to track the global spatial and thermodynamic state.

3.3 Null-space validation and the coupling landscape

To ensure that the identified islands were genuine physical phenomena rather than high-variance artifacts of smaller sample sizes or localized regions of poor stoichiometric model fit, we performed a null-space validation using the dipole moment residual (res_mu) as a decoupled control property. The relationships between scaffold size, chemical drivers, and topological complexity are visualized in the coupling landscape (Figure 1).

Panel A of Figure 1 confirms a moderate negative correlation between $\log(N)$ and $dCor_{homo}$ (Pearson $r = -0.5059$). While this indicates that smaller scaffolds naturally exhibit slightly higher variance, the coupling values of the identified islands significantly exceed this baseline size-bias trend. Panel B highlights the divergent behavior of heteroatoms, clearly showing nitrogen-rich scaffolds clustering at lower $dCor$ values. Crucially, Panel C demonstrates the null-space validation: the validated islands appear as points with high $dCor_{homo}$ but maintain baseline $dCor_{mu}$ values (≈ 0.317). This proves that the observed rewiring is specific to the HOMO energy and not a general failure of the residual extraction process.

3.4 Causal interpretation via isomer-matched pairs

To establish a causal link between structural rearrangement and electronic rewiring, we analyzed 1,762 isomer-matched scaffold pairs. Because these pairs share identical chemical formulas but differ in their Murcko scaffolds, any change in coupling is purely attributable to internal connectivity and topology.

The largest coupling sensitivity ($\Delta dCor$) was observed among C_5NH_x isomers. Specifically, the transition from the relatively decoupled, planar pyridine-like scaffold `c1ccncc1` ($dCor \approx 0.18$) to the highly strained, bicyclic scaffold `C1CN2CCC12` ($dCor \approx 0.63$) resulted in a substantial coupling spike of $\Delta dCor = 0.448$ ($z = 7.81$). This matched-pair analysis confirms that internal connectivity and the resulting geometric constraints—rather than stoichiometric composition—are the direct mechanical causes of electronic-spatial coupling.

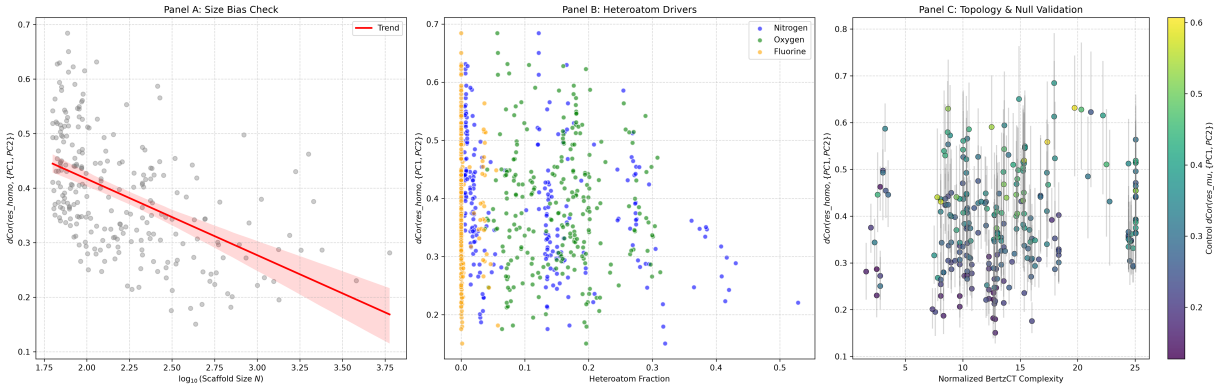

Figure 1: The coupling landscape of HOMO energy residuals across Murcko scaffolds. Panel A displays a size bias check, revealing a moderate negative correlation between scaffold size ($\log(N)$) and HOMO coupling ($dCor_{homo}$), demonstrating that while smaller scaffolds exhibit higher variance, the identified highly-coupled islands significantly exceed the baseline trend. Panel B illustrates the chemical drivers of this coupling, showing that nitrogen-rich scaffolds cluster at lower distance correlation values, which indicates that nitrogen incorporation tends to preserve electronic independence compared to oxygen or fluorine. Panel C plots $dCor_{homo}$ against normalized BertzCT complexity, color-coded by the dipole moment control ($dCor_{mu}$). This confirms that topological complexity promotes coupling and validates that the observed rewiring is specific to the HOMO energy; the identified islands exhibit high $dCor_{homo}$ while maintaining baseline control values (≈ 0.317), proving the effect is driven by structural constraints rather than a general failure of the stoichiometric baseline.

4 Conclusions

The global independence of the highest occupied molecular orbital (HOMO) energy has long appeared as an anomaly within the highly organized joint property manifolds of chemical space. In this study, we have demonstrated that this decoupling is not a fundamental physical constant, but rather a topology-dependent state obscured by the prevalence of acyclic and simple cyclic structures in the QM9 dataset.

By rigorously isolating chemical structure from stoichiometric determinism through non-linear gradient boosting regression, we extracted atom-count-independent property residuals. Stratifying these residuals across statistically dense Murcko scaffolds revealed 62 distinct structural regimes—termed "Islands of Coupling"—where the frontier electronic states are forced to rewire into the macroscopic thermodynamic-spatial manifold. The authenticity of this rewiring was confirmed through rigorous null-space validation using the dipole moment residual (res_mu), ensuring that the observed coupling spikes were specific to the HOMO energy and not artifacts of baseline model fit or scaffold size variance.

Our analysis identified clear geometric and chemical drivers governing this transition. High topological complexity, multi-cyclic fusion, and significant ring strain physically confine electron density, mechanically coupling the HOMO energy to the global spatial and vibrational state of the molecule. In contrast, nitrogen-rich heteroatom arrangements consistently resist this coupling, preserving the local independence of the frontier orbitals regardless of the underlying scaffold size.

The causal relationship between internal connectivity and electronic-spatial coupling was definitively established through isomer-matched pair analyses. By demonstrating massive coupling shifts between structurally adjacent isomers—such as the transition from planar, decoupled pyridine-like scaffolds to highly strained, strongly coupled bicyclic architectures—we proved that geometric constraints directly dictate electronic behavior independent of stoichiometry. Ultimately, these findings provide a robust framework for identifying molecular families where frontier electronic properties can be systematically tuned through macroscopic structural modifications, offering new topological strategies for targeted molecular design in highly constrained architectures.