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Divide and correlate: mapping electronic correlations in proteins *via* local cut-wise reconstruction

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We introduce a scalable method to quantify electronic correlations in insulin using mutual information (MI), characterizing interatomic and inter-residue interactions. A cut-wise strategy, based on the locality and decay of electronic correlations, combines localized density functional theory (DFT) calculations on 51 overlapping spherical cuts to reconstruct global MI matrices. The approach accurately reproduces key biochemical features and aligns with full-protein DFT results, enabling efficient quantum correlation analysis for large biomolecules. This framework supports future applications in protein–ligand modeling, pharmacophore design, and quantum-enhanced drug discovery.

Understanding electronic interactions in biomolecular systems is essential for explaining protein folding and enzymatic activity.¹ These interactions determine structural stability and functional specificity, influencing numerous cellular processes.^{2,3} However, the quantum mechanical nature of electron correlation poses challenges for computational modeling, particularly for large systems like proteins.⁴

Classical force fields and semi-empirical methods offer scalable modeling solutions but often neglect critical quantum effects, limiting their accuracy in describing subtle intra- and intermolecular interactions.⁵ This limitation is especially relevant in drug design and protein modeling, where precise interaction profiles can determine the success of lead optimization.^{6–8} *Ab initio* quantum chemistry methods, in contrast, provide high-accuracy, first-principles solutions, but their exponential scaling restricts applications to small molecules or fragments.^{9,10}

Quantum information theory has emerged as a tool to quantify electronic correlations between orbitals and molecular fragments.¹¹ It has been applied in molecular orbital theory and tensor network approaches like the density matrix

renormalization group (DMRG), revealing entanglement patterns that govern reactivity and bonding.^{12–14} Building on this, atomic mutual information (AMI) quantifies shared electronic information between atoms without assuming specific chemical interactions, offering high-resolution insight into connectivity and interaction strength.¹⁵ A key observation in these previous studies is that mutual information is primarily local, opening up opportunities to quantify electron correlation in extensive systems within localized fragments, rather than necessitating *ab initio* computations at the full molecular level.

In this study, we apply AMI to insulin, a 51-residue peptide hormone critical for blood glucose regulation.^{17,18} Its size and structural complexity make it an ideal benchmark for testing a divide-and-conquer approach, where overlapping fragments are analyzed using Density Functional Theory (DFT) and assembled to reconstruct a global AMI-based correlation map,^{19,20} which can still be benchmarked with a full-molecular DFT computation.

Our work demonstrates the feasibility of applying AMI to realistic protein systems and highlights its potential as a quantum-informed tool for analyzing protein structure, interaction networks, and chemical environments. These insights provide a foundation for future applications in protein–ligand analysis and rational drug design, bridging the gap between high-accuracy quantum modeling and scalable computational approaches.

Our method extends prior work on quantum entanglement and electronic correlations in small biomolecules to the full insulin protein. Starting from von Neumann entanglement entropy measures, we estimate the atomic mutual information (AMI) I_{AB} between two atoms A and B from the quantum mutual information of the respective orbitals i and j on both atoms

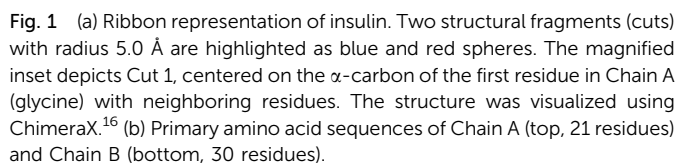
$$I_{AB} = \sum_{i \in A} \sum_{j \in B} I_{ij}. \quad (1)$$

For computational economics, the orbital-wise quantum information indices I_{ij} are typically computed at the Hartree–Fock mean-field or Kohn–Sham DFT level. It is conceptually

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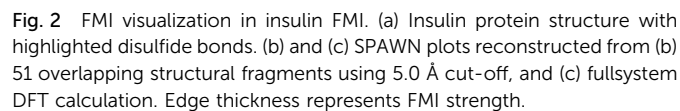


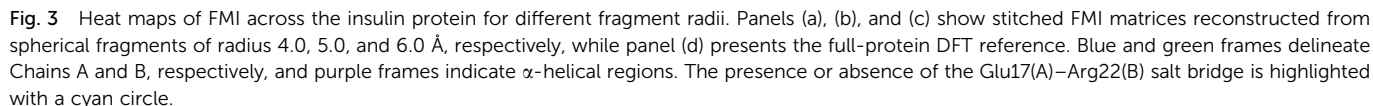

$$I_{XY} = \sum_{A \in X} \sum_{B \in Y} I_{AB}. \quad (2)$$

The three-dimensional structure of insulin, along with the defined structural cuts, provides the foundation for the cut-wise quantum mechanical analysis of electron correlation. Fig. 1 shows a ribbon representation of the insulin structure, highlighting its two-chain (A and B) and overall tertiary fold. The figure illustrates how the protein was segmented into 51 overlapping spherical fragments centered on α -carbon atoms, with two representative cuts marked. Each cut encapsulates a chemically meaningful region while maintaining sufficient overlap to reconstruct global electronic correlations. As each individual sphere is defined by a radial cutoff from its central α -carbon, individual fragments may include residues that are not directly connected through peptide bonds in that individual cut. For instance, AlaB30 is not directly bonded to the Chain A residues in Cut 1 in Fig. 1. Although counterintuitive, including spatially proximal but non-covalently connected residues helps stabilize the overlapping contributions. The corresponding sequence in Fig. 1(b) maps Chain A (21 residues) and Chain B (30 residues), providing a direct reference for fragment positioning.

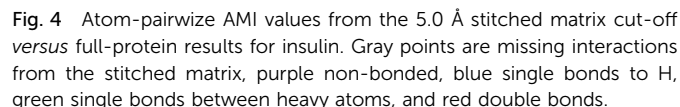
$$AMI_{ij}^{(\text{stitched})} = \frac{1}{N_{ij}} \sum_{k \in \mathcal{C}_{ij}} AMI_{ij}^{(k)}, \quad (3)$$

To evaluate the accuracy and completeness of the fragment-based FMI reconstruction, we compared heat maps derived from stitched and full-protein DFT calculations (Fig. 3).





Despite the overall similarity between stitched and full DFT matrices, the recovery of certain long-range interactions depends on fragment size. To assess this sensitivity, we repeated the cut-wise procedure using cutoff radii of 4.0 and 6.0 Å in addition to the 5.0 Å case. The 4.0 Å fragments fail to capture the Glu17(A)–Arg22(B) salt bridge, whereas both the 5.0 Å and 6.0 Å fragment sets recover this interaction (circle in Fig. 3), producing stitched FMI matrices that closely match the full-protein DFT reference. This behavior reflects the increased probability that these residues are simultaneously included within a single cut. Minor variations in the color gradients between the matrices arise from the energy minimization applied during fragment preparation, further details are provided in the SI. Expanding the fragment radius from 5.0 Å to



Regarding computational gains, DFT scales polynomially in the number of basis orbitals $t = \alpha L^\beta$, with t the computational wall time to complete a DFT computation, L the total number of atomic orbitals in the computation, and α and β method-dependent constants. The relevant variable in each computation is the number of residues N , as the total number of orbitals L in each fragment is proportional to the number of residues $L = N\ell$ with ℓ the average number of orbitals per residue. With these parameters in place, we can define a speedup factor as

in which N denotes the total number of residues ($N = 51$ for insulin), and $f_r = N_r/N$ denotes the relative fraction of residues for fragments of size r (see Table 1 for the case of insulin).

Table 1 Computation timings and scalings for the full insulin protein (right column) and cut-wise approach with $r = 4.0\text{--}6.0$ Å computed at the ω B97M-V/6-31G(d) level of theory using ORCA (more details in the SI)

	4.0 Å	5.0 Å	6.0 Å	Full protein
(Average) N	5.3	8.1	10.1	51
(Average) f_r	10%	16%	19%	100%
(Average) L	712	1068	1335	6424
(Average) t [s]	977	2091	3011	41 794
Full t [s]	49 830	106 632	153 556	41 794

The parameter β reflects the polynomial scaling of DFT, ranging from the theoretical $\beta = 4$, to $\beta = 3^{21}$ or even lower²² towards $\beta \rightarrow 1$. We will observe speedups whenever $\beta > 1$ and the radius of the spheres is sufficiently small. In the SI, we report details on the $r = 4.0\text{--}6.0$ Å computations at the ω B97M-V/6-31G(d) level of theory using ORCA,²³ leading to a quasi quadratic $\beta = 1.9$. As can be inferred from Table 1, our benchmark insulin protein is too small to observe a speedup, mostly due to the effective low β and relatively large residue fraction f_r . Extrapolating from this analysis, it can be anticipated that the locality of quantum correlations will become useful for proteins in the ~ 100 kDa range, where a speedup of $\times 10\text{--}20$ can be expected depending on the radius of the fragment. Furthermore, whenever only a small and finite number $\nu \ll N$ of spheres need to be computed, the speedup increases to $N\tau = 1/(\nu f^\beta)$.

We have shown that AMI and FMI provide an effective framework for quantifying electronic correlations in proteins at multiple spatial scales. Using a divide-and-conquer approach grounded in quantum locality, we mapped interatomic and inter-residue correlations in insulin with accuracy comparable to full-system DFT. FMI captures covalent bonds, disulfide bridges, hydrogen bonds, and secondary structure elements like α -helices, revealing both classical and subtle non-classical correlations. The agreement between FMI and fragment overlap maps highlights the nearsightedness of electronic interactions in proteins and supports the role of spatial locality in governing correlation strength. Extending AMI to realistic biomolecules enables quantum-informed exploration of protein–ligand interactions, pharmacophore modeling, and drug discovery.

Mostafa Javaheri Moghadam: data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); software (equal); supervision (supporting); validation (equal); visualization (lead); writing – original draft (lead); writing – review and editing (equal). Rebecca Mulder: data curation (supporting); investigation (supporting); software (equal). Stijn De Baerdemacker: conceptualization (lead); formal analysis (supporting); funding acquisition (lead); methodology (supporting); supervision (lead); validation (equal); writing – review and editing (equal).

Conflicts of interest

There are no conflicts to declare.

Data availability

All generated datafiles are available on the Dataverse server at the University of New Brunswick,²⁴ and the codes can be found at <https://github.com/QuNB-Repo/Insulin>.

Supplementary information (SI) is available. See DOI: <https://doi.org/10.1039/d5cc04161a>.

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