# Geometric Algebra Approaches to Protein-Protein Docking


Azzam Alfarraj[1,2], Guo-Wei Wei[1,3,4]

[1] *Department of Mathematics, Michigan State University, MI 48824, USA*

[2] *Department of Mathematics, King Fahd University of Petroleum and Minerals, Dhahran 31261, KSA*

[3] *Department of Biochemistry and Molecular Biology, Michigan State University, MI 48824, USA*

[4] *Department of Electrical and Computer Engineering, Michigan State University, MI 48824, USA*


## INTRODUCTION

Protein-Protein docking is a method for predicting the preferred orientation of interactive proteins, when they are bound to form a stable complex. The most complete structural characterization is provided by X-ray crystallography but solving the structures of protein–protein complexes is often very difficult. Thus, it is desirable to develop computational docking methods that, starting from the coordinates of two unbound component molecules, can provide a model of acceptable accuracy for the structure of the bound protein-protein complex. Energy evaluation following Fast Fourier transforms (FFTs) enables sampling **billions** of putative complex structures and hence revolutionized rigid protein–protein docking. However, the number of degrees of freedom that must be considered when generating putative complexes makes the generation of new putative binding conformations **computationally expensive**. Hence, this challenge requires more efficient algorithms to improve the sampling process.

## Motivation for Geometric Algebra

Efficient acceleration, in current computational docking methods, is achieved in either the **rotational** or the translational subspace.
Geometric algebra presents a mathematical framework that performs rotations **efficiently** and compactly. Exploiting the **geometric product** along with **rotors** reduces the number of operations needed for rotations significantly, in comparison to the methods used currently in the literature which use rotation matrices.

## Geometric Algebra

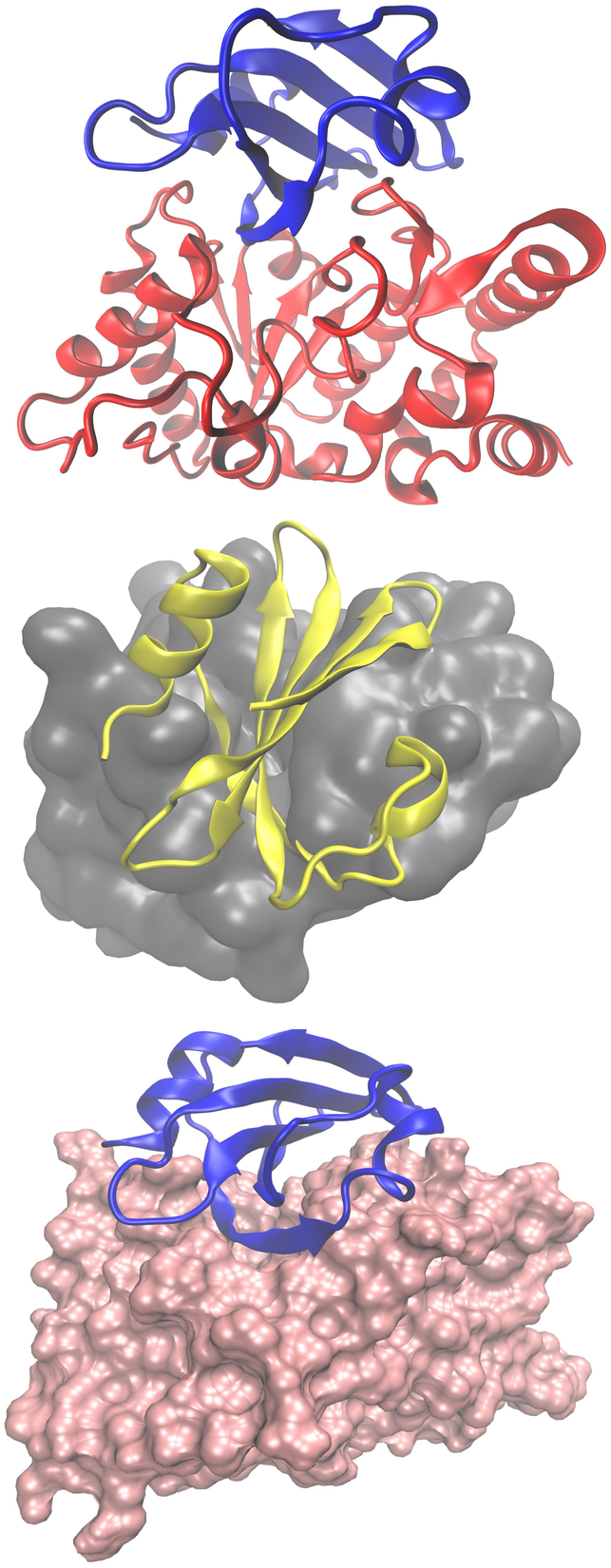
Geometric algebra (GA) is an extension of elementary algebra to work with geometrical objects, utilizing a **geometric product** that leads to higher-dimensional objects called **multivectors**.
GA overpasses in performing operations in a far more compact and efficient way. For example, Maxwell's equations are expressed in GA:

$$\left.\begin{aligned} \nabla \times H &= J + \partial D/\partial t \\ \nabla \times E &= -\partial B/\partial t \\ \nabla \cdot D &= \rho \\ \nabla \cdot B &= 0 \end{aligned}\right\} \equiv \nabla \mathcal{F} = \mathcal{J}$$

In our docking algorithm, we rotate the ligand using rotors as follows:

$$b = RaR^{-1}$$

$$\text{where} \qquad R = R_\psi R_\theta R_\phi = e^{-e_{12}\phi/2} e^{-e_{23}\theta/2} e^{-e_{12}\psi/2}$$



## Results

The GA-based docking method outperforms the FMFT docking method in execution time, lower binding energies, and higher cluster size when both are applied to enzyme–inhibitor 1udi (see figures):

**Execution Time:**

GA Time: 5 min 42 sec, FMFT Time: 6 min 31 sec

| Energy | | |
|---|---|---|
| Model # | GA | FMFT |
| 0 | -880.01 | -880.01 |
| 1 | -876.91 | -843.87 |
| 2 | -843.87 | -841.74 |
| 3 | -841.74 | -826.94 |

| Cluster Size | | |
|---|---|---|
| Model # | GA | FMFT |
| 0 | 305 | 303 |
| 1 | 205 | 214 |
| 2 | 120 | 89 |
| 3 | 94 | 61 |

## CONCLUSION

Geometric algebra has been widely used in physics, computer vision, image analysis but has not been used for protein-protein docking, where it has a great potential in reducing the cost of rotations. The proposed geometric algebra approach opens the doors for making the current docking methods more efficient, and can lead to new advances in other forefronts, such as protein design, enzyme optimization, antibody therapies, drug discovery, protein engineering, etc. Our work also inspires the development of advanced mathematics for biological sciences.

## REFERENCES


[1] Alfarraj, A., & Wei, G. W. (2022). Geometric algebra generation of molecular surfaces. *JRSI*, *19*(189), 20220117.

[2] Padhorny, D., Kazennov, A., Zerbe, B.S., Porter, K.A., Xia, B., Mottarella, S.E., Kholodov, Y., Ritchie, D.W., Vajda, S. and Kozakov, D. (2016). Protein–protein docking by fast generalized Fourier transforms on 5D rotational manifolds. PNAS, 113(30), E4286-E4293.

[3] Alfarraj, A., & Wei, G. W. Geometric algebra Approach for protein-protein docking. *In preparation.*


## Acknowledgement


This work was funded in part by King Fahd University of Petroleum and Minerals, NIH grants R01GM126189 and R01AI164266, NSF grants DMS-2052983, DMS-1761320, and IIS-1900473, and NASA grant 80NSSC21M0023.



https://users.math.msu.edu/users/weig/ weig@math.msu.edu azzam@msu.edu