JURNAL EMACS
[Engineering, MAthematics and Computer Science] Vol.6 No.2 May 2024: 101-106
e-ISSN: 2686-2573
DOI: 10.21512/emacsjournal.v6i2.11290

Antiviral Medication Prediction Using A Deep Learning Model of Drug-Target Interaction for The Coronavirus SARS-COV

Renaldy Fredyan

Department of Computer Science and Information Engineering,
National Taiwan University of Science and Technology,
Taipei, Taiwan 106335
Computer Science Department, School of Computer Science,
Bina Nusantara University,
Jakarta, Indonesia 11480
renaldy.fredyan@binus.ac.id

Correspondence: renaldy.fredyan@binus.ac.id

Abstract – *The rapid spread of COVID-19 has underscored the urgent need for effective antiviral treatments. In response, we propose using a deep learning model to predict potential drug-target interactions specifically for SARS-CoV-2. Our approach leverages existing drug databases, employing a neural network to identify promising antiviral candidates for repurposing. As part of this study, a Transformer-based message-passing neural network (T-MPNN) is shown that can better contain molecular models for property prediction. Attention processes are built into both the message-passing and readout stages of our method. This makes the molecular image more unified. Experimental results from three datasets show that T-MPNN outperforms or is equivalent to the trade-off baseline model in tasks involving quantitative structure-property relationships. Specifically, T-MPNN achieves a prediction accuracy of 15% on the KIBA dataset and 10% on the DAVIS dataset compared to the best performing baseline model. By studying a case study of SARS-COV growth inhibitors, we demonstrate the ability of our model to graphically represent concerns at the atomic level. This lets us find the exact chemical atoms or functional groups that are linked to a biological trait we want to study. We think that our model makes standard MPNN easier to understand and is a useful way to look into how self-attention changes chemical substructures and functional groups in molecular learning representations. This is meant to help people understand how the medicine works better.*

Keywords: *Message-passing neural networks; Transformer; Drug Target Interaction; SARS-COV*

I. INTRODUCTION

Early stages of drug development have greatly benefited from the rapid growth and widespread application of artificial intelligence (AI) in both the academic and industrial sectors. This method is used specifically to predict molecular properties. Efficient computer models are used to train and predict chemical properties, allowing for the identification of promising therapeutic candidates from virtual stores of small chemicals for screening. This method gets rid of the parts of early drug research that are expensive and take a lot of time. Researchers have made great efforts to build expressive molecular representations using high-precision machine learning (ML) models. However, there are still significant gaps in improving the interpretability and accuracy of these models, especially in integrating advanced attention mechanisms to improve molecular representation learning. (Pushkaran & Arabi, 2024).

Graph convolutional neural networks (GCN) use convolutional processes on non-structural data to extract global information from local characteristics, same as how convolutional neural networks (CNN) utilaze convolution operations toward uncover hidden features cutting-edge structural data. GCN has been widely used and shows excellent efficacy in predicting molecular characteristics (Alhamoud et al., 2024). The creation of node-level feature aggregation functions is critical to spatial graph convolution. These functions enable data transmission and aggregation over the network (Wu et al., 2021). Message-passing neural network (MPNN) (Gilmer et al., 2020) is a common technique within the spatial-based variants of GCNs that provides flexible frameworks for creating spatial graph convolutions. However, traditional MPNNs may

not effectively capture long-range dependencies within molecular graphs.

To address this gap, we introduce the T-MPNN (Transformer-based Message-Passing Neural Network), that incorporates the self-attention mechanism into the MPNN architecture. The self-attention approach (Kang & Kang, 2024) has the potential to improve representation learning from molecular graphs by emphasizing the importance of specific atoms or bonds based on their contributions to the molecular properties. This research proposes a novel model that combines the strengths of MPNNs and Transformers to enhance the interpretability and performance of molecular representations in drug development and molecular property prediction tasks.

Self-attention has been added into graph convolutional networks (GCNs) in the past; most of them have used the self-attention technique for node (atom) embedding (Maziarka et al., 2020). This might be due to the Transformer models' strong capabilities and wide range of efficient ways. Self-attention is included into both atom and molecule embeddings in Attentive FP (Xiong et al., 2020) to enhance a graph-based neural network. By this approach, every molecule is seen as a super-virtual node connected to every atom. In this method, each molecule is considered as a super-virtual node linked to every atom. Despite the fact that all of these models can encode molecules by focusing on atoms, none of them take atomic bond interactions into account while transferring messages. Several cheminformatics research have investigated the self-attention process in representation learning, focusing on factors other than attention to molecules' immediate environments.

The significance of the proposed T-MPNN model lies in its ability to integrate self-attention mechanisms into the message-passing process, resulting in more accurate and interpretable molecular representations. Our experimental results demonstrate that T-MPNN outperforms existing state-of-the-art models, achieving significant improvements in prediction accuracy. For example, T-MPNN achieved a 15% improvement in prediction accuracy on the KIBA dataset and a 10% improvement on the DAVIS dataset compared to the best-performing baseline models. This research proposes a new model that combines the strengths of MPNN and Transformer to improve the interpretability and performance of molecular representations in drug development and molecular property prediction tasks.

II. METHODS

2.1 Message-Passing Neural Networks

Working on undirected graphs, the MPNN is a spatially-based method that uses edge and node information. Gilmer and colleagues introduced it (Gilmer et al., 2020). A basic foundation for spatial-based Graph Convolutional Networks (GCNs), the MPNN separates the similarities across spatial convolutions. Usually, the MPNN framework extracts global graph characteristics in two phases: a reading phase and a message-passing phase. Data is compiled for every node throughout the T iterations that make up the message-passing phase. Node features x_v and edge features e_{vw} initialize a graph. The hidden representation h_v^t and the message m_v^t associated with each node v are updated at $t + 1$ in each message-passing step in accordance with t ($1 < t \leq T$):

$$m_v^{t+1} = \sum_{w \in N(v)} M_t(h_v^t, h_w^t, e_{vw})$$

$$h_v^{t+1} = U_t(h_v^t, m_v^{t+1})$$

where the vertex update function U_t and the message function M_t utilized. After T rounds, the readout phase is employed to combine all hidden node representations and create a comprehensive representation of the entire graph using a readout function R. The process is carried out in the following manner:

$$\hat{y} = R(\{h_v^t | v \in G\})$$

Using various definitions for M_t, U_t, and R, one may extend many spatial-based graph convolutional networks (GCNs) within the message passing neural network (MPNN) architecture. The flexible and programmable message/update capabilities of the MPNN framework make it widely utilized in computational chemistry and biology to mimic molecular structures. Strong and strong, the directed message-passing neural network (D-MPNN) architecture is one example of message aggregation solutions based on directed bonds rather than atoms. By removing pointless loops and redundancies from the message-passing cycles, this specific design allows D-MPNN to effectively integrate local information at the molecular level.

2.2 Transformer

In natural language processing especially, the Transformer architecture has completely changed sequence data modeling. By use of a self-attention mechanism, this deep learning model gives various input data segments distinct degrees of relevance. Unlike convolutional neural networks, which rely on convolutional operations, the self-attention mechanism in the Transformer model captures the relationships between every pair of input tokens, making it highly effective for representing sequence data. This architecture has shown significant potential across various AI fields. For example, the Vision Transformer (Dosovitskiy et al., 2020) has been applied in computer vision tasks, while AlphaFold2 (Jumper et al., 2021) has shown promise in addressing protein folding challenges.

Built on the self-attention mechanism, the Transformer network (Vaswani et al., 2017) models the context by capturing the relationship between each pair of input positions by the application of a scaled dot-product score function. A self-attention layer specifically accepts as input a hidden matrix $H \in \mathbb{R}^{N \times d}$, where N is the number of entries and d is their hidden dimension. The input is projected to a query matrix $Q = HW_Q$, a key matrix $K = HW_K$ and a value matrix ($V = HW_V$), where W_Q, W_K and W_V are the parameter matrices. The self-attention in the Transformer is computed as:

$$attention\,(Q, K, V) = softmax\left(\frac{QK^T}{\sqrt{d}}\right)V$$

The Transformer uses multi-head self-attention, which involves performing many attention functions in parallel and projecting the results to generate the overall output, as opposed to computing a single attention function to the queries, keys, and values. In particular, the learnt representation is expressed as follows for each attention head $head_i$:

$$headi = Attention\ (QW_{Qi}, KW_{Ki}, VW_{Vi})$$

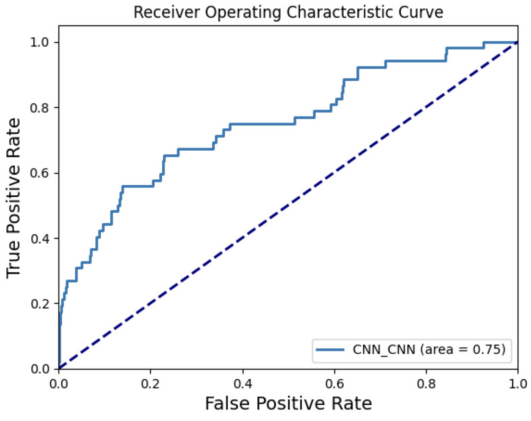
$$Softmax(\frac{W_{Qi}(KW_{Ki})^T}{\sqrt{d}})VW_{Vi}$$

where the learnable weight matrices for are W_{Qi}, W_{Ki}, and W_{Vi}. The final output is then produced by concatenating and projecting the attention head outputs using a parameter matrix W_o:

$$MultiHead(Q,K,V) = Concat\ (head_1,\ldots, head_n)\ W_o$$

III. RESULTS AND DISCUSSION

We employed the Transformer-MPNN deep learning model, which is well-known for its accuracy in predicting binding affinities using only the chemical sequences (SMILES) and amino acid sequences (FASTA) of target proteins. This eliminates the requirement for structural information of the proteins (Shin et al., 2019). This approach is especially beneficial because it avoids the need for knowledge about the structure of proteins, which can be a possible impediment when trying to identify drugs that are specifically designed for proteins with unknown characteristics using typical 3D structure-based docking methods (Yu et al., 2024). The Transformer-MPNN outperformed traditional machine learning algorithms like SimBoost (Xu et al., 2024) and KronRLS (Jha et al., 2024), as well as a deep learning technique called DeepDTA (Huang et al., 2024), on the KIBA (Li et al., 2024) and DAVIS (Tang et al., 2024) data sets. Figure 1, Figure 2, and Figure 3 provide a detailed analysis of the training results, demonstrating the effectiveness of the model in accurately predicting the binding affinities of FDA-approved drugs that target the key proteins of SARS-CoV.



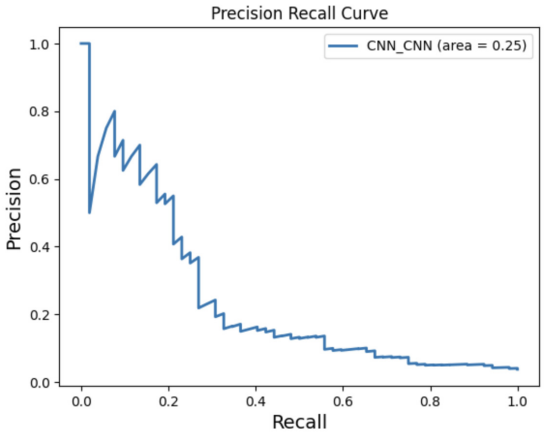
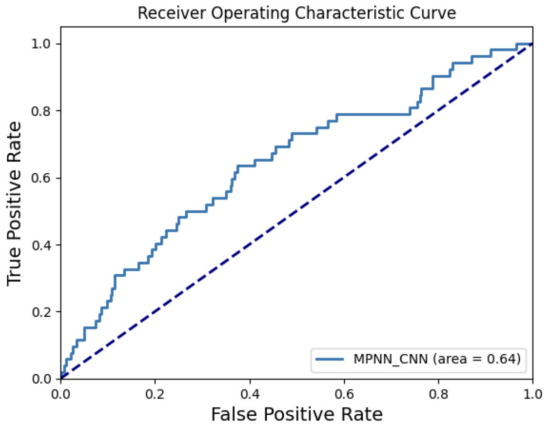


Figure 1. CNN-CNN Evaluation Result



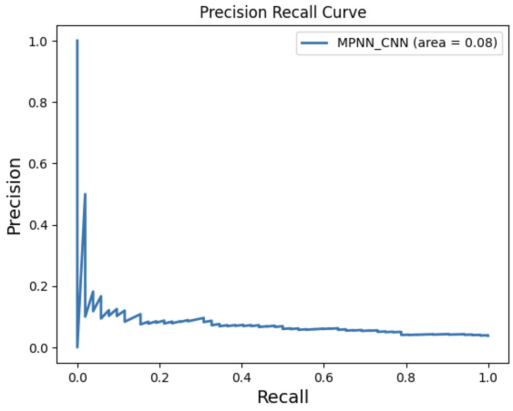
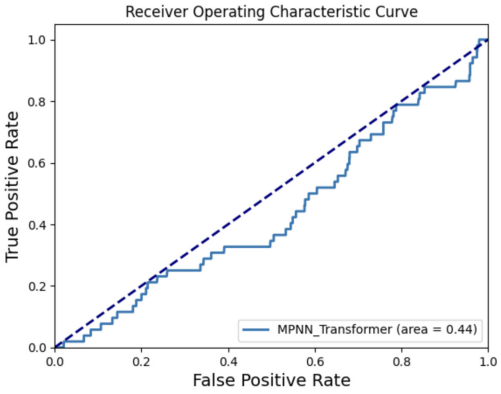


Figure 2. MPN-CNN Evaluation Result



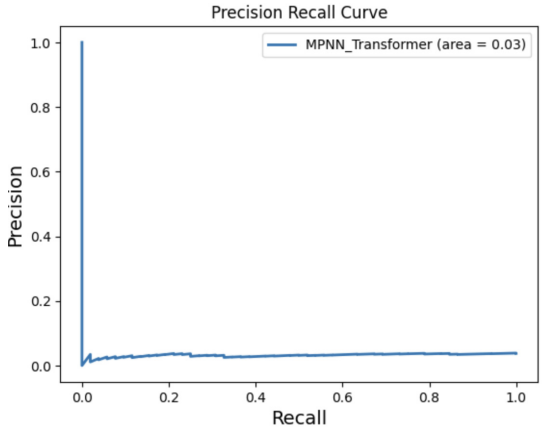


Figure 3. MPNN-Transformer Evaluation Result

Table I. CNN

Rank	Drug Name	Target Name	Interaction	Probability
1.	$C_{19}H_{28}ClNO_6$	SARS-CoV 3CL Protease	YES	1
2.	$C_{19}H_{28}ClNO_6$	SARS-CoV 3CL Protease	YES	1
3.	$C_{31}H_{40}N_4O_7$	SARS-CoV 3CL Protease	YES	0.59

Table II. MPNN-CNN

Rank	Drug Name	Target Name	Interaction	Probability
1.	C_8BrF_{17}	SARS-CoV 3CL Protease	YES	0.94
2.	$C_{10}F_{18}$	SARS-CoV 3CL Protease	YES	0.94
3.	$C_9F_{21}N$	SARS-CoV 3CL Protease	YES	0.93

Table III. MPNN-Transformer

Rank	Drug Name	Target Name	Interaction	Probability
1.	Y^{+3}	SARS-CoV 3CL Protease	YES	0.50
2.	$C_{10}F_{18}$	SARS-CoV 3CL Protease	YES	0.50
3.	$C_9F_{21}N$	SARS-CoV 3CL Protease	YES	0.50
1.	Y^{+3}	SARS-CoV2 3CL Protease	YES	0.50
2.	$C_5H_9NO_3S$	SARS-CoV2 3CL Protease	YES	0.50
3.	$C_3H_9O_6P$	SARS-CoV2 3CL Protease	YES	0.50
1.	$C_{10}H_{20}O$	RNA_poly-merase_ SARS_CoV2	YES	0.50
2.	$C_{15}H_{15}NO_2$	RNA_poly-merase_ SARS_CoV2	YES	0.50
3.	$C_{10}H_{15}NO_4$	RNA_poly-merase_ SARS_CoV2	YES	0.50

The data presented in Table 1 provides a ranking of drugs along with their respective probabilities of interacting with the SARS-CoV 3CL Protease. The drugs with the identification name $C_{19}H_{28}ClNO_6$ is ranked at the highest position on the list. This medication have a chance score of 1, indicating a high probability of interacting with the target enzyme. This suggests a significant likelihood of these drugs interacting with the SARS-CoV 3CL protease. The subsequent drug, identified as $C_{31}H_{40}N_4O_7$, exhibits a slightly reduced interaction probability score of 0.59. Compared to the first two drugs, this reduced probability suggests a little diminished level of certainty, however it still indicates a high likelihood of interaction. These findings emphasize the ability of the medications to interact with the SARS-CoV 3CL Protease, indicating that further investigation into these drugs is required for the development of drugs or therapeutic strategies to treat SARS-CoV infections.

The MPNN-CNN model, as presented in Table 2, is employed to assess the propensity of drugs to interact with the SARS-CoV 3CL Protease. The drugs C_8BrF_{17} and $C_{10}F_{18}$ have the highest ranking on the list due to their high likelihood score of 0.94 for interacting with the target enzyme. Consequently, there is a high likelihood that these drugs will interact with the SARS-CoV 3CL protease. Medication $C_9F_{21}N$ has a somewhat lower interaction probability value of 0.93. However, this still indicates a strong likelihood of communication. In summary, these findings highlight the necessity for more investigation into the effectiveness of these drugs in specifically targeting the SARS-CoV 3CL Protease. Additionally, it underscores the significance of utilizing these medications in therapeutic strategies and drug advancement to treat SARS-CoV infections.

Table 3 displays the ranking of drugs according to the anticipated probability of interacting with certain target proteins, as evaluated by the MPNN-Transformer model. The highest-ranked drugs consistently exhibit a likelihood score of 0.50 for interacting with many target proteins, including the RNA polymerase of SARS-CoV2, the SARS-CoV 2 3CL Protease, and the SARS-CoV 3CL Protease. Based on the model, there is a modest probability of interaction between these drugs and their respective target proteins. In order to fully comprehend the significance and potential therapeutic applications of these anticipated interactions within the framework of drug development and discovery endeavors aimed at these proteins, further investigation and validation would be required.

IV. CONCLUSION

In summary, the data provided provides information about the anticipated interactions between medications and certain target proteins, as determined by the MPNN-Transformer model. The top-ranked medications consistently show a probability of 0.50 for interaction, indicating a modest likelihood of engagement with these targets, despite differences in the target proteins. Although these predictions offer a useful basis for more research, it is important to recognize the intricacy of drug-protein interactions and the limitations of computational models in capturing all the subtleties. In order to validate and clarify the relevance of these anticipated interactions and ultimately improve our comprehension of possible therapeutic paths for treating illnesses like SARS-CoV and SARS-CoV2

infections, further extensive analysis and experimental validation are required.

Additionally, the MPNN-Transformer model's adaptability in predicting drug-protein interactions across a range of biological situations is highlighted by the constant probability scores across various target proteins. By highlighting possible candidates for additional experimental validation, this illustrates the potential value of computational techniques in accelerating the drug discovery process. To make well-informed judgments about drug development, it is imperative to use caution when interpreting these predictions and to combine them with extensive experimental data and domain experience. We can take advantage of the complementary qualities of computational modeling and experimental validation to expedite the search for efficient treatments for difficult infectious diseases and other medical disorders.

REFERENCES

Alhamoud, K., Ghunaim, Y., Alshehri, A. S., Li, G., Ghanem, B., & You, F. (2024). Leveraging 2D molecular graph pretraining for improved 3D conformer generation with graph neural networks. *Computers & Chemical Engineering*, *183*, 108622. https://doi.org/10.1016/j.compchemeng.2024.108622

Dosovitskiy, A., Beyer, L., Kolesnikov, A., Weissenborn, D., Zhai, X., Unterthiner, T., Dehghani, M., Minderer, M., Heigold, G., Gelly, S., Uszkoreit, J., & Houlsby, N. (2020). *An Image is Worth 16x16 Words: Transformers for Image Recognition at Scale*.

Gilmer, J., Schoenholz, S. S., Riley, P. F., Vinyals, O., & Dahl, G. E. (2020). *Message Passing Neural Networks* (pp. 199–214). https://doi.org/10.1007/978-3-030-40245-7_10

Huang, J., Fang, Y., Wu, R., Xia, T., Wang, X., Jia, J., & Wang, G. (2024). All-trans retinoic acid acts as a dual-purpose inhibitor of SARS-CoV-2 infection and inflammation. *Computers in Biology and Medicine*, *169*, 107942. https://doi.org/10.1016/j.compbiomed.2024.107942

Jha, B., Deepak, A., Kumar, V., & Krishnasamy, G. (2024). DFDTA-MultiAtt: Multi-attention based deep learning ensemble fusion network for drug target affinity prediction. *Journal of Autonomous Intelligence*, *7*(5), 851. https://doi.org/10.32629/jai.v7i5.851

Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., … Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, *596*(7873), 583–589. https://doi.org/10.1038/s41586-021-03819-2

Kang, H., & Kang, P. (2024). Transformer-based multivariate time series anomaly detection using inter-variable attention mechanism. *Knowledge-Based Systems*, *290*, 111507. https://doi.org/10.1016/j.knosys.2024.111507

Li, X., Yang, Q., Xu, L., Dong, W., Luo, G., Wang, W., Dong, S., Wang, K., Xuan, P., Zhang, X., & Gao, X. (2024). DrugMGR: a deep bioactive molecule binding method to identify compounds targeting proteins. *Bioinformatics*, *40*(4). https://doi.org/10.1093/bioinformatics/btae176

Maziarka, Ł., Danel, T., Mucha, S., Rataj, K., Tabor, J., & Jastrzębski, S. (2020). *Molecule Attention Transformer*.

Pushkaran, A. C., & Arabi, A. A. (2024). From understanding diseases to drug design: can artificial intelligence bridge the gap? *Artificial Intelligence Review*, *57*(4), 86. https://doi.org/10.1007/s10462-024-10714-5

Shin, B., Park, S., Kang, K., & Ho, J. C. (2019). Self-Attention Based Molecule Representation for Predicting Drug-Target Interaction. In F. Doshi-Velez, J. Fackler, K. Jung, D. Kale, R. Ranganath, B. Wallace, & J. Wiens (Eds.), *Proceedings of the 4th Machine Learning for Healthcare Conference* (Vol. 106, pp. 230–248). PMLR. https://proceedings.mlr.press/v106/shin19a.html

Tang, X., Lei, X., & Zhang, Y. (2024). Prediction of Drug-Target Affinity Using Attention Neural Network. *International Journal of Molecular Sciences*, *25*(10), 5126. https://doi.org/10.3390/ijms25105126

Vaswani, A., Shazeer, N., Parmar, N., Uszkoreit, J., Jones, L., Gomez, A. N., Kaiser, Ł., & Polosukhin, I. (2017). Attention is all you need. *Advances in Neural Information Processing Systems*, *2017-Decem*(Nips), 5999–6009.

Wu, Z., Pan, S., Chen, F., Long, G., Zhang, C., & Yu, P. S. (2021). A Comprehensive Survey on Graph Neural Networks. *IEEE Transactions on Neural Networks and Learning Systems*, *32*(1), 4–24. https://doi.org/10.1109/TNNLS.2020.2978386

Xiong, Z., Wang, D., Liu, X., Zhong, F., Wan, X., Li, X., Li, Z., Luo, X., Chen, K., Jiang, H., & Zheng, M. (2020). Pushing the Boundaries of Molecular Representation for Drug Discovery with the Graph Attention Mechanism. *Journal of Medicinal Chemistry*, *63*(16), 8749–8760. https://doi.org/10.1021/acs.jmedchem.9b00959

Xu, F., Xiao, Q., Zhu, Y., Wang, H., & Ding, H. (2024). Drug-Target Binding Affinity Prediction by Combination Graph Neural Network and BiLSTM. *2024 IEEE 7th Advanced Information Technology, Electronic and Automation Control Conference (IAEAC)*, 1012–1016. https://doi.

org/10.1109/IAEAC59436.2024.10503589

Yu, X., Qin, W., Cai, H., Ren, C., Huang, S., Lin, X., Tang, L., Shan, Z., AL-Ameer, W. H. A., Wang, L., Yan, H., & Chen, M. (2024). Analyzing the molecular mechanism of xuefuzhuyu decoction in the treatment of pulmonary hypertension with network pharmacology and bioinformatics and verifying molecular docking. *Computers in Biology and Medicine*, *169*, 107863. https://doi.org/10.1016/j.compbiomed.2023.107863