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IN SILICO SCREENING OF SARS-CoV-2 RBD-TARGETING ANTIBODIES USING HDOCK AND PRODIGY

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Abstract

The receptor-binding domain of the SARS-CoV-2 spike protein is the primary target for neutralizing antibodies, yet its continuous evolution demands efficient computational strategies for antibody screening. This study screened 288 antibodies from the CoV-AbDab database using a combined workflow of HDOCK docking and PRODIGY affinity prediction, identifying five top-ranked candidates: P4A2, C1A-B3, COVOX-150, CC12.1, and 3G10. To further examine binding robustness, steered molecular dynamics (SMD) simulations were conducted for these five complexes, where non-equilibrium work (W_{pull}) and maximum pulling force (F_{max}) were obtained as mechanical stability indicators. Among the candidates, P4A2 exhibited the highest mechanical resistance to unbinding, consistent with its most favorable PRODIGY binding energy. Strong correlations were observed between SMD metrics and PRODIGY results (R = -0.95 for W_{pull} and -0.93 for F_{max}), highlighting the consistency of affinity ranking across independent computational methods. Together, these findings validate a cost-effective computational pipeline for prioritizing antibody candidates and identify P4A2, C1A-B3, and CC12.1 as promising leads for further experimental evaluation via ELISA, SPR, and extended molecular dynamics simulations.

Keywords: *HDOCK, monoclonal antibody, PRODIGY, protein-protein docking, RBD, SARS-CoV-2, SMD.*

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SÀNG LỌC *IN SILICO* CÁC KHÁNG THỂ CHO THỤ THỂ RBD CỦA SARS-CoV-2 BẰNG HDOCK VÀ PRODIGY

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Tóm tắt

Vùng liên kết thụ thể của protein gai SARS-CoV-2 là thụ thể chính của các kháng thể trung hòa; tuy nhiên, sự tiến hóa liên tục của virus đòi hỏi các chiến lược sàng lọc kháng thể hiệu quả dựa trên tính toán. Trong nghiên cứu này, 288 kháng thể từ cơ sở dữ liệu CoV-AbDab đã được sàng lọc bằng quy trình kết hợp giữa docking HDOCK và dự đoán ái lực PRODIGY, qua đó xác định 05 ứng viên tiềm năng nhất gồm: P4A2, C1A-B3, COVOX-150, CC12.1 và 3G10. Để đánh giá giữa các phương pháp, mô phỏng động lực học kéo định hướng phân tử đã được thực hiện cho 05 phức hợp này, từ đó thu được công không cân bằng (W_{pull}) và lực kéo cực đại (F_{max}) như các chỉ số đặc trưng cho độ ổn định cơ học của phức hợp. Trong số các ứng viên, P4A2 thể hiện khả năng liên kết mạnh nhất, phù hợp với năng lượng liên kết thuận lợi nhất do PRODIGY dự đoán. Sự tương quan giữa kết quả SMD và năng lượng PRODIGY (R = -0.95 đối với W_{pull} và -0.93 đối với F_{max}) cho thấy sự thống nhất giữa các phương pháp tính toán độc lập. Kết quả này khẳng định tính hiệu quả của quy trình sàng lọc in silico và xác định P4A2, C1A-B3 và CC12.1 là những ứng viên triển vọng cho các bước xác thực thực nghiệm bằng ELISA, SPR và mô phỏng động lực học phân tử ở thang thời gian dài hơn.

Từ khóa: *HDOCK, monoclonal antibody, PRODIGY, protein-protein docking, RBD, SARS-CoV-2, SMD.*

1. Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has emerged as one of the greatest global health challenges of the 21st century, prompting an urgent global demand for effective therapeutic and preventive strategies (Lai et al., 2020). Despite the widespread deployment of vaccines and the implementation of measures such as social distancing and mask-wearing, effective treatments for severe cases remain a pressing need. According to the Ministry of Health, as of 25th May, 2025, more than 777 million cases and over 7 million deaths have been recorded worldwide, while Vietnam has reported 641 sporadic cases across 39 provinces and cities since early 2025. In this context, antibody-based therapies-particularly monoclonal antibodies (mAbs)-have gained attention as a promising treatment approach (Taylor et al., 2021). These mAbs play a critical role not only in treating infections but also in protecting individuals with poor immune responses to vaccines and countering immune-evasive viral variants (Cowan et al., 2023). This strategy targets the Receptor Binding Domain (RBD) of the SARS-CoV-2 spike protein, which mediates viral entry through interaction with the human ACE2 receptor (Lan et al., 2020). Blocking this interaction is considered a promising strategy to neutralizing the virus and preventing infection (Iyer et al., 2020; Premkumar et al., 2020).

Monoclonal antibodies (mAbs) have emerged as powerful tools in both therapeutic and diagnostic applications for viral diseases, including COVID-19, due to their ability to specifically bind to viral proteins-such as the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein and inhibit viral entry (Wang et al., 2020). In the context of SARS-CoV-2, numerous antibodies targeting the spike RBD have been developed with varying degrees of neutralization potency and binding affinity. To support the development and analysis of such antibodies, several specialized databases have been established to provide comprehensive information on antibody sequences, three-dimensional (3D) structures, and their interaction properties. Key resources include the Observed Antibody Space (OAS), which hosts over one billion human and animal antibody sequences but lacks structural data (Olsen et al., 2022); IMGT/3D structure-DB, which offers standardized 3D structural data for complementarity-determining regions (CDRs) with limited utility for large-scale computational analysis (Kaas et al., 2004); and the Therapeutic Structural Antibody Database (Thera-SAbDab), a clinically oriented subset of SAbDab that compiles antibodies under development or in trials, though its data extraction capabilities remain somewhat constrained (Raybould et al., 2021). These databases play a crucial role in facilitating antibody discovery, optimization, and therapeutic evaluation against evolving viral threats.

In this context, computational docking methods offer an efficient strategy to pre-screen a large number of antibodies for their potential to bind strongly to the target RBD, significantly reducing experimental workload and cost. These docking algorithms simulate antibody-protein interactions based on structural data, enabling *in silico* estimation of binding orientation and energy. HDOCK (Yan et al., 2017) combines template-based and *ab initio* strategies. It automatically detects homologous complexes and applies template information when possible, while retaining the ability to perform global docking when no templates exist. HDOCK also employs a physics-based scoring function optimized for protein-protein interactions, and supports fully automated, large-scale docking without requiring prior definition of binding sites or constraints. However, currently available monoclonal antibodies face several limitations. Many have shown reduced neutralization potency against emerging SARS-CoV-2 variants due to mutations within the RBD, leading to potential immune escape (Cowan et al., 2023). Additionally, the high cost and complexity of large-scale mAb production pose challenges for accessibility in low- and middle-income countries like Vietnam. These challenges highlight the urgent need to discover novel

antibodies with improved binding characteristics and broader variant coverage through cost-effective computational approaches.

This study employed the HDOCK (Yan et al., 2017), a hybrid docking platform integrating template-based and *ab initio* strategies for protein-protein interaction prediction, to screen 288 antibodies against the RBD of SARS-CoV-2. Compared to other docking tools like HADDOCK, HDOCK offers enhanced efficiency for large-scale screening due to its automated template detection and optimized scoring function. The binding poses and docking score obtained from HDOCK were subsequently re-evaluated using the PRODIGY web server (Xue et al., 2016), which predicts the binding free energy (ΔG) and dissociation constant (K_d) of protein-protein complexes based on structural features. The goal of this study is to identify potential antibody candidates with strong binding affinity to the RBD of SARS-CoV-2, complementing existing therapies like bamlanivimab, etesevimab and REGN-COV2, as indicated by favorable docking scores, low predicted binding free energies, and dissociation constants in the picomolar to nanomolar range. These results provide a foundation for selecting promising antibodies for further investigation through molecular dynamics simulations and *in vitro* binding assays. In the context of Vietnam, where sporadic COVID-19 cases persist, this study supports the development of affordable antibody-based therapies tailored to local healthcare needs.

2. Materials and methods

2.1. Antibody dataset and target structure

A total of 288 antibody structures were collected from the coronavirus antibody database (CoV-AbDab. The filtering criteria for antibodies in this study are as follows: *Type: antibody, Binds to: SARS-CoV-2, Does not bind to: All, Neutralizing against: All, Not neutralizing against: All, Protein/Epitope: Spike protein - RBD, Origin: All, Heavy V gene: All, Heavy J gene: All, Light V gene: All, Light J gene: All.* The receptor binding domain (RBD) of the SARS-CoV-2 spike glycoprotein was extracted from the high-resolution crystallographic structure (PDB ID: 8DLK). The RBD region encompassing residues 401-421 and 442-501 was selected as the target binding site. These two non-contiguous segments correspond to key contact zones between RBD and the human ACE2 receptor, which form the functional core of the receptor-binding interface, as shown in structural studies (Lan et al., 2020). It showed in Figure 1.

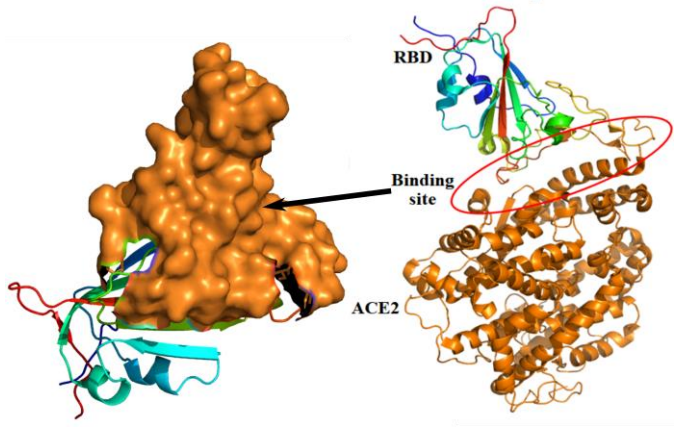

Figure 1. The 3D structure of PDB ID: 8DLK and the Receptor Binding Domain (RBD) of the SARS-CoV-2 spike glycoprotein

All structures were cleaned to remove water molecules, ligands, and ions, and were prepared for docking using standard preprocessing procedures, including chain selection and hydrogen addition, which were preprocessed using the PyMOL Molecular Graphics System, Version 1.8 (Schrödinger, LLC, 2015) for version of education.

2.2. Protein-Protein docking using HDOCK

Docking simulations were performed using the HDOCK V1.0 downloaded and installed on a local computer system (http://hdock.phys.hust.edu.cn/), which integrates template-based modeling and free docking for predicting protein-protein interactions. Each antibody was docked individually to the RBD's ACE2-interacting interface (residues 401-421 and 442-501). HDOCK V1.0 settings and parameters were used: Input format: PDB files for both antibody and RBD, search strategy: box binding site for RBD, output: Only the top-ranked model per antibody was selected based on HDOCK's scoring function, which optimizes for protein-protein interaction energy.

2.3. Binding affinity estimation using PRODIGY

To obtain a more reliable prediction of the binding free energy and binding affinity, each docked complex was submitted to the PRODIGY software (https://bianca.science.uu.nl/prodigy/) for estimation of binding free energy (ΔG) and dissociation constant (Kd). The analyses were performed using standard desktop systems running Ubuntu 22.04. The system uses structural features of the interface to estimate: Binding free energy (ΔG, kcal/mol), dissociation constant (Kd, M) at 300 K. Only the top-ranked binding mode from HDOCK was evaluated in PRODIGY for each antibody. This two-step approach (HDOCK followed by PRODIGY) allows for both spatial modeling and thermodynamic estimation of protein-protein interactions.

2.4. Steered molecular dynamics (SMD)

Steered molecular dynamics (SMD) (Li et al., 2012) simulations were performed for the five top-ranked antibody-RBD complexes to probe the unbinding process. In the SMD setup, the antibody was connected to a virtual (dummy) atom through a harmonic spring with spring constant k, while the dummy atom was pulled at a constant velocity v along the x-direction. The pulling force was computed as:

$$F = k\,(\Delta x - vt)$$

with $k = 600$ kJ/(mol.nm^2), $v = 5$ nm/ns.

The non-equilibrium work, W_{pull}, was used as the primary scoring function to rank the binding strengths of the complexes, as it provides a more reliable measure for SMD-based unbinding analysis [A new method]. The work was calculated as:

$$W_{pull} = \int_0^{x_{max}} \vec{F}.\overrightarrow{dx} = \sum_1^{N_{step}} \frac{(F_{i+1} + F_i)}{2}(x_{i+1} + x_i)$$

where N_{step} is the total number of steps used in simulation. For each antibody–RBD complex, five independent SMD replicates were performed under identical simulation conditions. The reported values of W_{pull} and F_{max} represent the average from these five replicates, ensuring statistical reliability and reducing the influence of stochastic fluctuations inherent to SMD.

3. Results and discussion

3.1. Docking results

The docking simulations using the HDOCK V1.0 yielded predicted interaction energies (E_HD) for 288 antibodies against the SARS-CoV-2 RBD. The docking scores ranged from -232.7 to -441.2, indicating a broad spectrum of binding propensities across the antibody set. Lower (more negative) docking scores values suggest stronger predicted interactions.

Among 288 docking configurations between the receptor-binding domain (RBD) of SARS-CoV-2 (extracted from PDB ID: 8DLK) and antibodies obtained from the antibody database, the docking scores (E_HD) ranged from -232.7 to -441.2. Thereby, 05 complexes with the lowest docking scores and dissociation constants (Kd) were selected for detailed analysis, which presented in Table 1. The ranking and positions of these complexes among the 288 configurations are as follows.

Table 1. HDOCK docking scores values, dissociation constant Kd, and PRODIGY-predicted energy of RBD-Ab complexes

Complex (RBD-Ab)	E_HD	Rank (out of 288)	Kd (M)	E_Pr (kcal/mol)
RBD - P4A2 (7WVL)	-311.6	67	8.20×10^{-15}	-19.2
RBD - C1A-B3 (7KFW)	-348.8	26	4.80×10^{-14}	-18.2
RBD - COVOX-150 (7BEI)	-347.1	27	9.20×10^{-14}	-17.8
RBD - CC12.1 (6XC2)	-329.6	36	4.90×10^{-14}	-18.1
RBD - 3G10 (8HN6)	-357.1	20	1.20×10^{-13}	-17.6

Detailed analysis of hydrogen bonds and non-covalent (nonbonded) contacts indicates that the stability and high affinity between the RBD and antibodies mainly depend on specific residues within the receptor-binding motif (RBM) of the RBD, as well as the complementarity determining regions (CDRs) of the antibodies.

Key RBD residues: Positions such as Tyr473, Leu455, Ala475, Asn487, Glu484, Tyr501, and Tyr505 consistently participate in forming hydrogen bonds and nonbonded contacts with multiple residues in the antibody CDR regions. These residues act as “hotspots”, playing a crucial role in forming a stable interaction network and enabling specific antibody recognition.

Hydrogen bonds: Hydrogen bonds are formed via polar and charged groups of RBD residues (Ser, Asn, Gln, Tyr, Glu) interacting with residues primarily including Tyr, Ser, Arg, and Asp on the antibodies. These bonds enhance specificity and stabilize the complex. For example, the RBD - P4A2 complex exhibits 10 prominent hydrogen bonds such as Tyr489-Thr206, Tyr501-Asn165, Lys417-Asp147. Meanwhile, RBD - C1A-B3 and RBD - CC12.1 establish between 14 to 16 hydrogen bonds, reflecting a dense network of interactions, especially at RBM residues.

Nonbonded contacts: Beyond hydrogen bonds, hydrophobic interactions and van der Waals contacts involving nonpolar residues such as Phe456, Phe486, Val503, and Gly416

also significantly contribute to strengthening the surface interactions between RBD and antibodies. The combination of hydrogen bonding and nonbonded contacts creates a binding environment that is both specific and stable.

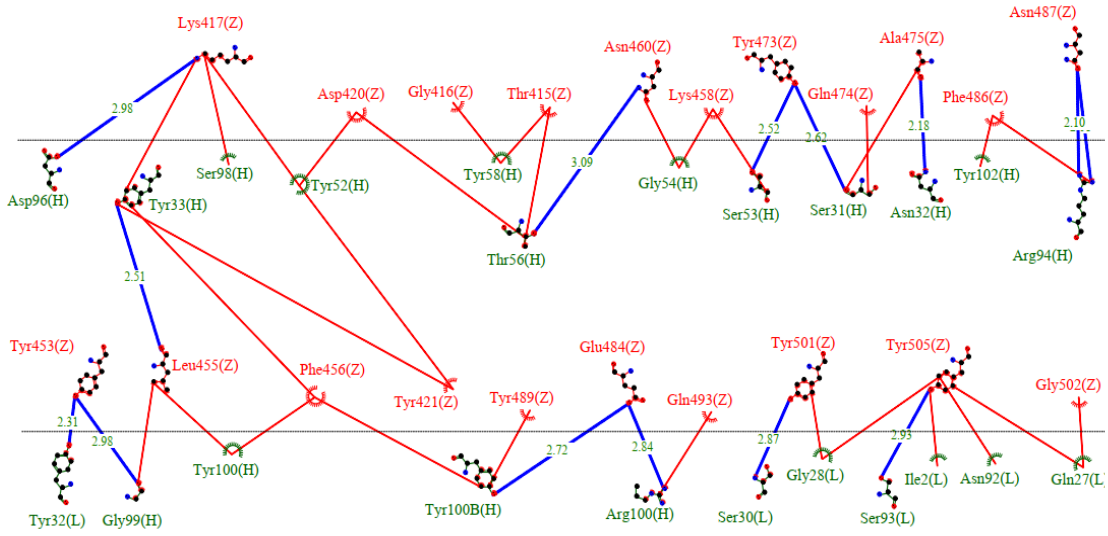

Figure 2. The hydrogen bonding network (dashed blue line), nonbonded contacts (NBCs) (dashed red line) of complex RBD-C1A-B3

Significance of docking scores Rankings: Although the RBD-3G10 complex has the lowest docking scores (-357.1) and ranks 20th among the 288 configurations, its Kd value is higher compared to other complexes. This suggests that overall stability beyond hydrogen bonding might depend on hydrophobic interactions and molecular packing. Conversely, the RBD-P4A2 (7WVL) complex, despite having a higher docking scores (-311.6) and ranking 67th, shows the lowest Kd (8.2 x 10^{-15} M), reflecting an optimized hydrogen bond network and highly specific interactions at the antibody recognition site. It showed in Figure 3.

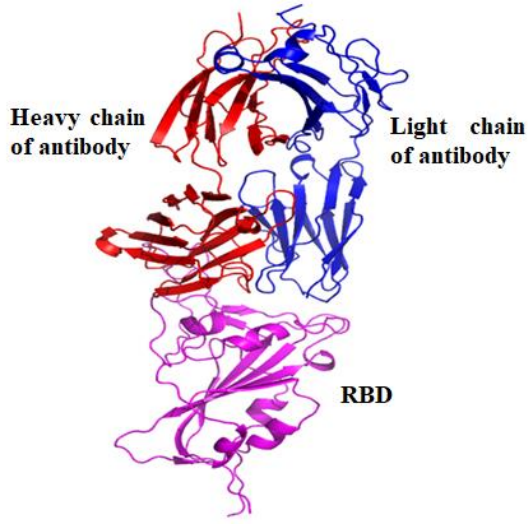

Figure 2. The RBD-C1A-B3 complex is visualized with the RBD domain shown in magenta, the heavy chain of the C1A-B3 antibody in red, and the light chain in blue

However, as HDOCK is a rigid-body docking platform and does not explicitly account for solvation or entropy effects, these values should be interpreted with caution and supplemented with thermodynamic analysis.

3.2. Predicted binding affinity from PRODIGY

PRODIGY was used to predict the binding free energy (ΔG) and dissociation constant (Kd) of each antibody-RBD complex. The predicted ΔG (energy_prodi) values varied between approximately -7.6 to -19.2 kcal.mol^{-1}, with corresponding Kd values (KD_prodi) ranging from 10 pM to 10 μM.

Notably, a group of antibodies demonstrated predicted binding affinities in the low nanomolar or even picomolar range, suggesting strong and potentially therapeutically relevant interactions. These predictions help prioritize antibodies for further structural or experimental validation.

3.3. Steered molecular dynamics results.

We additionally performed steered molecular dynamics (SMD) on the five prioritized antibody-RBD complexes to probe unbinding. From these runs we extracted non-equilibrium work and the maximum pulling force (F_{max}) for each complex. The results are showed in Table 2.

Table 2. The maximum pulling force (Fmax) and non-equilibrium work for each complex.

Complex (RBD-Ab)	F_{max} (pN)	W_{pull} (kcal.mol^{-1})	E_HD	E_Pr (kcal.mol^{-1})
RBD - P4A2 (7WVL)	2665.1 ± 132.6	1266.7 ± 61.4	-311.6	-19.2
RBD - C1A-B3 (7KFW)	1848.8 ± 64.0	627.5 ± 30.5	-348.8	-18.2
RBD - COVOX-150 (7BEI)	1616.5 ± 80.1	600.2 ± 29.7	-347.1	-17.8
RBD - CC12.1 (6XC2)	2028.6 ± 71.0	639.3 ± 21.8	-329.6	-18.1
RBD - 3G10 (8HN6)	1804.4 ± 53.7	565.6 ± 18.4	-357.1	-17.6

SMD provided additional insights into the mechanical stability of the top five antibody-RBD complexes. Among them, P4A2 exhibited the highest maximum pulling force (F_{max}) and non-equilibrium work (W_{pull}), indicating the strongest resistance to unbinding, consistent with its most favorable PRODIGY-predicted binding free energy. The remaining antibodies showed intermediate mechanical stabilities, with C1A-B3 and CC12.1 forming a moderately strong group, while COVOX-150 and 3G10 displayed lower F_{max} and W_{pull} values. These results highlight that while docking scores provide a useful initial filter, SMD and PRODIGY better capture differences in binding robustness. The overall consistency across methods supports the reliability of the computational pipeline and reinforces P4A2 as the strongest candidate for subsequent validation using ELISA, SPR, and longer-timescale MD simulations.

3.4. Correlation analysis

A strong negative correlation (R = -0.9) was observed between HDOCK docking scores (E_HD) and PRODIGY-predicted binding free energy (E_Pr), indicating that lower

docking scores correspond to more favorable binding energies or wild-type SARS-CoV-2 complexes (Figure 4). Similarly, a correlation of R = -0.9 was found between E_HD and the natural logarithm of the dissociation constant (ln(Kd)), suggesting that antibodies with stronger predicted interactions (lower E_HD) exhibit higher binding affinities (lower Kd). These findings align with previous studies validating HDOCK and PRODIGY against experimental binding data (Xue et al., 2016; Yan et al., 2017), which confirms the reliability of our computational approach. However, as HDOCK employs rigid docking, it may overlook conformational flexibility and solvation effects, potentially affecting prediction accuracy. Future studies should incorporate molecular dynamics simulations to account for these factors and further validate the prioritized antibodies.

A full correlation analysis across all 288 docking models was not included in the present study because PRODIGY requires high-quality and physically realistic interface geometries, whereas a portion of the large-scale docking outputs did not meet the required structural criteria for reliable affinity prediction. Interface refinement and full-panel correlation analysis will be conducted in a follow-up study to provide a more comprehensive statistical assessment.

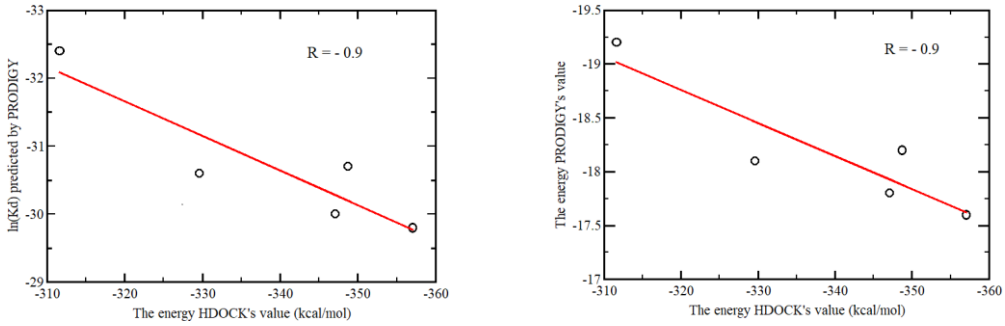

Figure 3. Correlation plots of HDOCK docking scores (E_HD) with (A) PRODIGY-predicted binding free energy (E_Pr, kcal/mol) (left). Natural logarithm of dissociation constant (ln(Kd)) (right) for RBD-AB complexes

In addition to the correlation between HDOCK docking scores and PRODIGY-predicted binding free energies, we also examined the relationships between the SMD-derived unbinding metrics and PRODIGY. A strong negative correlation was observed between the non-equilibrium work and the predicted binding energy with R = -0.95, indicating that complexes requiring higher mechanical work to dissociate also possess more favorable PRODIGY affinities. Similarly, the maximum pulling force showed a strong negative correlation with PRODIGY (R = -0.93), supporting the interpretation that mechanically robust complexes tend to exhibit stronger predicted binding (Figure 5). Although these correlations were calculated from the top five prioritized antibody-RBD complexes, the high magnitude of the correlation coefficients demonstrates a consistent trend across docking, SMD, and PRODIGY scoring. These results further reinforce the reliability of the computational workflow and affirm that P4A2, C1A-B3, and CC12.1 possess both strong mechanical resistance to unbinding and favorable predicted binding energetics.

Future work will include epitope mapping of the top-ranked antibodies and comparison with clinically approved antibodies as well as mutation hotspots across SARS-CoV-2 Variants of Concern, in order to evaluate the resilience of these candidates against viral evolution.

It should be noted that the correlations derived from the top five antibody-RBD complexes represent internal consistency within the prioritized subset rather than population-wide statistical behavior. These correlations therefore serve as a validation step for selecting high-confidence candidates, while future work will extend the analysis to the entire 288-complex dataset to assess global trends.

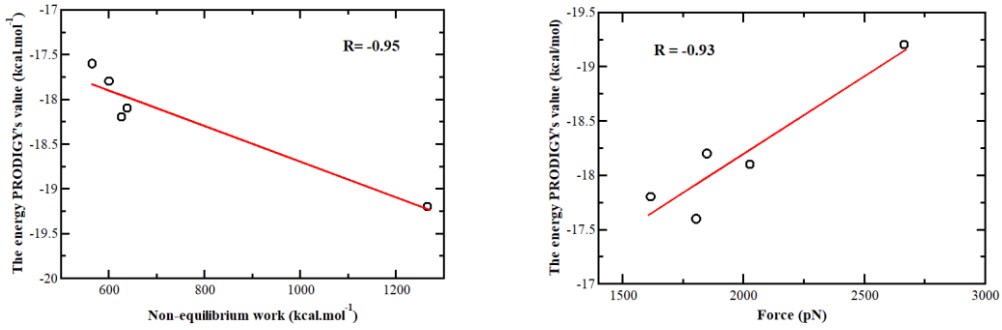

Figure 5. Correlation plots of PRODIGY-predicted binding free energy and non-equilibrium work (left), and F_{max} (right).

4. Conclusion

Although the present study focuses on known antibodies from CoV-AbDab, the novelty of this work lies in establishing a consistent and validated computational pipeline that integrates docking, affinity prediction, and SMD-based unbinding analysis, which can be applied to larger and more diverse antibody repertoires in future studies. Despite focusing on antibodies structurally characterized previously, the scientific contribution of this work lies in developing and validating a unified, reproducible, and computationally efficient screening pipeline. This workflow establishes the methodological foundation required for future large-scale screening of novel, engineered, or computationally generated antibody repertoires, thereby extending far beyond the scope of existing datasets. This study presents a reproducible and integrated computational workflow for screening antibody-RBD interactions, combining HDOCK docking, PRODIGY affinity estimation, and SMD-based mechanical stability analysis. From an initial set of 288 antibodies, five top-performing candidates were identified, with P4A2 emerging as the strongest binder based on docking scores, PRODIGY predictions, and SMD-derived W_{pull} and F_{max} values. The strong correlations between SMD metrics and PRODIGY binding energies further demonstrate the internal consistency and reliability of the screening approach. While the current analysis focuses on known SARS-CoV-2 antibodies from CoV-AbDab, the workflow establishes a solid foundation for larger-scale antibody discovery and refinement. Future work will expand correlation analysis to the full dataset, incorporate equilibrium molecular dynamics to capture structural flexibility, and validate computational predictions experimentally through ELISA and SPR assays. Overall, the results provide a robust basis for guiding experimental antibody development in a rapid and cost-effective manner.

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