Conditional Sequence-Structure Integration: A Novel Approach for Precision Antibody Engineering and Affinity Optimization

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Abstract

Antibodies, or immunoglobulins, are integral to the immune response, playing a crucial role in recognizing and neutralizing external threats such as pathogens. However, the design of these molecules is complex due to the limited availability of paired structural antibody-antigen data and the intricacies of structurally non-deterministic regions. In this paper, we introduce a novel approach to designing antibodies by integrating structural and sequence information of antigens. Our approach employs a protein structural encoder to capture both sequence and conformational details of antigen. The encoded antigen information is then fed into an antibody language model (aLM) to generate antibody sequences. By adding cross-attention layers, aLM effectively incorporates the antigen information from the encoder. For optimal model training, we utilized the Causal Masked Language Modeling (CMLM) objective. Unlike other methods that require additional contextual information, such as epitope residues or a docked antibody framework, our model excels at predicting the antibody sequence without the need for any supplementary data. Our enhanced methodology demonstrates superior performance when compared to existing models in the RAbD benchmark for antibody design and SKEPMI for antibody optimization.

1 Introduction

In the complex and crucial domain of protein design, antibody design stands out as a particularly challenging task due to the sophisticated structures and specific antigen-binding capabilities of antibodies. Antigens, molecules that trigger an immune response, are typically found on the surfaces of pathogens such as bacteria, viruses, and fungi and are specific to each pathogen. These antigens are crucial targets for antibodies, or immunoglobulins, distinct proteins produced by the immune system to recognize and neutralize these pathogens. As the primary defense mechanism of the body, antibodies play a pivotal role in the adaptive immune response, ensuring specificity and memory against pathogens encountered previously (Janeway et al., 2001).

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Antibodies are structurally similar to a Y-shape, comprising two identical heavy chains and two identical light chains, which together form a functional unit poised for antigen binding (Figure 1). The antigen-binding site is largely defined by the Complementarity-Determining Regions (CDRs) within these chains (Schroeder and Cavacini, 2010). The third CDR of the heavy chain (H3) exhibits remarkable variability, allowing antibodies to attach to many different types of harmful substances, thus determining the specificity of the immune response (Al-Lazikani et al., 1997).

The central task of antibody design, a crucial aspect of therapeutic development, involves the prediction of the variable region sequences of an antibody, which directly interact with antigens. This prediction is based on the detailed structure and sequence of a specific antigen. Achieving this level of specificity in antibody design is a complex task due to the immense diversity of possible antibody sequences and the intricate three-dimensional structures they can form. Consequently, traditional approaches involving complex physics-based calculations have become less efficient (Li et al., 2014a; Adolf-Bryfogle et al., 2018).

Advancements in computational techniques have opened new avenues in antibody design, particularly through the adoption of deep learning methods. These methods focus on enhancing the design accuracy by integrating both the sequence and the structural aspects of antibodies (Jin et al., 2021; Luo et al., 2022a; Kong et al., 2022a; 2023). However, these innovative models encounter substantial challenges, which often slow down the creation of accurate and widely applicable models. The key challenges are described below:

- **Limited availability of paired structural data**: The main obstacle in antibody design is the shortage of extensive antibody-antigen structural data for training deep learning models. For instance, the Structural Antibody Database (SAbDab) dataset Dunbar et al. (2014), a widely-used and comprehensive resource containing paired antibody-antigen structures, includes only about 5,000 samples. This lack of data limits the models' overall efficacy and applicability by making it more difficult for the deep learning models to learn from and generalize across a wide variety of antigens.

- **Impact of CDR flexibility on sequence prediction**: The structural flexibility of CDRs (Jeliazkov et al., 2018) presents a significant challenge in accurately predicting their sequences. Zheng et al. (2023) emphasize that in such flexible regions, there is a weaker correlation between residue identities and their structural context. This aspect is particularly problematic in methods attempting to design both the sequence and structure of antibodies simultaneously, often leading to errors and resulting in the generation of inaccurate sequences.

- **Dependency on contextual information**: Existing models in antibody design often rely on additional data, such as the structural arrangements of antibodies within their target environment (docked antibody frameworks) Luo et al. (2022b) or the specific shapes and conformations of antigenic epitopes Kong et al. (2023). Although this contextual information plays a vital role in enhancing the scalability and overall effectiveness of the aforementioned methods, it is often challenging to obtain.

To address the above challenges, we propose Aligned Integrated Design for Antibodies (AIDA), a novel approach that leverages the advancement of protein language models, which have shown promise in forecasting protein structures and aiding in protein design. At its core, AIDA is driven by an antibody language model (aLM) and employs a specialized protein encoder to capture the sequential and structural information of antigens. Importantly, it integrates antigen adapter modules into the aLM, facilitating efficient information transfer from the encoded antigen to the aLM, which is crucial for the conditional prediction of antibody sequences.

AIDA's emphasis on sequence prediction skillfully circumvents the structurally non-deterministic nature of antibodies. It capitalizes on pre-trained models, which have undergone extensive training on large unsupervised datasets, effectively addressing the data scarcity challenge in antibody design. The efficacy of AIDA was validated in the Rosetta Antibody Design (RAbD) benchmark (Adolf-Bryfogle et al., 2018), where it demonstrated superior performance in recovering antibody sequences, surpassing existing state-of-the-art models without the reliance on additional contextual information.

1.1 Related Works

Computational antibody design is an expanding field that uses various methods to predict antibody sequences for a given antigen. Traditional approaches often involve optimizing complex energy functions. Additionally, these approaches require accurate simulation of real-world protein interactions, which is extremely complicated (Pantazes and Maranas, 2010; Li et al., 2014b; Lapidoth et al., 2015; Adolf-Bryfogle et al., 2018; Warszawski et al., 2019). This complexity is due to the fact that the full nature of protein-protein interactions is too intricate to be captured entirely by statistical functions Graves et al. (2020). In response, deep learning has become increasingly prominent, branching into two main approaches: sequence-based and structure-sequence co-design methodologies.

Sequence-based models, such as the ones proposed by Liu et al. (2019); Saka et al. (2021); Akbar et al. (2022); Melnyk et al. (2023), focus on using deep learning to develop antibodies by modeling the one-dimensional sequence data. However, these methods can underperform as they disregard structural information. On the other hand, co-design methods, as seen in the works of Jin et al. (2021); Kong et al. (2022b; 2023); Luo et al. (2022c); Verma et al. (2023), address antibody design by using graph neural networks or diffusion models to develop antibody sequences and 3D structures simultaneously. Despite their use of structural data, these methods still face the challenges mentioned in §1.

Our model addresses these limitations by taking a middle ground between these approaches. We employ graph modeling to encode both the sequence and structural information of the antigen. Then, we utilize sequence modeling to decode this information into the corresponding antibody sequence, effectively balancing the need for structural data with the advantages of sequence prediction.

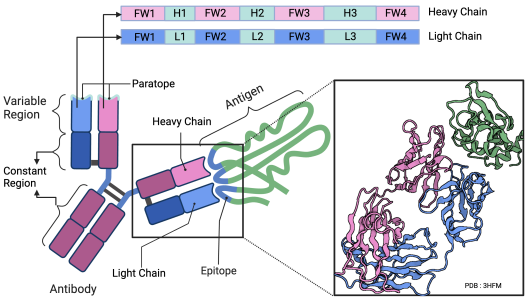

Figure 1: Schematic and structural representation of the antibody's typical Y-shaped formation, consisting of two identical heavy chains and two identical light chains. Each chain is composed of alternating framework regions (FW) and complementarity-determining regions (CDRs). There are three CDRs (H1, H2, H3 for the heavy chain and L1, L2, L3 for the light chain) that are instrumental in binding to specific parts of the antigen, and four framework regions (FW1, FW2, FW3, FW4) that support the overall structure. The paratope, formed by the CDRs, engages the antigen's epitope in a precise lock-and-key manner. The epitope is a specific part of an antigen that is recognized and bound by an immune system component. The right side of the figure showcases the three-dimensional configuration of an antibody-antigen complex (PDB: 3HFM), highlighting the interaction between the antibody (in pink and blue) and the antigen (in green), with a focus on how the paratope's CDRs closely contact with the antigen's epitope. Adapted from "Antigen Recognition by Antibodies", by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates.

Protein Structural Encoding The advancement of structure-based methodologies in computational biology has been significantly driven by innovations in encoding spatial characteristics of protein structures. Initially, these methodologies utilized 3D Convolutional Neural Networks (CNNs), as introduced by Derevyanko et al. (2018), and later incorporated Graph Neural Networks (GNNs), evidenced by the work of Gligorijević et al. (2021), Baldassarre et al. (2021), Jing et al. (2021), Wang et al. (2023), and Aykent and Xia (2022). This field has recently seen a surge in exploring the potential of pre-training structural encoders on extensive and unlabeled datasets. Pioneering contributions in this area, such as those by Hermosilla and Ropinski (2022); Chen et al. (2023); Guo et al. (2022), have adopted approaches such as contrastive learning, self-prediction, and denoising score matching. Additionally, Zhang et al. (2023) have proposed the Geometry-Aware Relational Graph Neural Network (GearNet), utilizing relational graph convolutional layers and edge message passing with augmentation functions, offering a novel perspective in self-supervised learning for protein structures. These developments are expanding the boundaries of what can be achieved in the encoding of protein structural information.

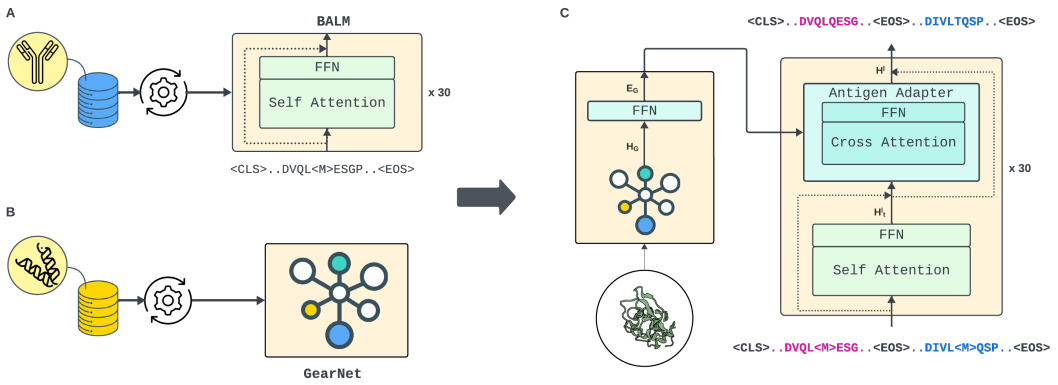

Figure 2: This diagram showcases our proposed encoder-decoder model for antibody sequence prediction, combining the strengths of two pre-trained networks. Panel A features BALM, a transformer-based model pre-trained on a vast dataset of single-chain antibodies using the MLM objective for sequence processing. In Panel B, GearNet is presented as a general-purpose protein structure encoder, pre-trained on the comprehensive AlphaFold dataset to encode structural data into graph form. Panel C unifies these components: GearNet's graph-encoded antigen information is channeled into BALM via an antigen adapter, using cross-attention mechanisms to translate intricate antigen structures into corresponding antibody sequences.

Protein/Antibody Language Models Protein language models (pLMs) such as ESM Lin et al. (2022) and ProtTrans Elnaggar et al. (2021), which have been pre-trained using the Masked Language Model (MLM) technique, have significantly enhanced our understanding of protein sequences. These advancements have motivated researchers to use similar methods in analyzing antibody sequences, leading to the creation of specialized models such as AbLang Tobias H. Olsen and Deane (2022), AntiBERTa Leem et al. (2022), AntiBERTy Ruffolo et al. (2021), and BALM Jing et al. (2023). AbLang, trained on the OAS database Olsen et al. (2022), focuses on filling in missing residues in B-cell receptor repertoire sequences. AntiBERTa, utilizing a 12-layer transformer architecture (Vaswani et al., 2023), provides a nuanced numeric representation of antibody sequences, capturing essential elements of antibody functionality, and is adaptable for paratope prediction tasks. AntiBERTy, on the other hand, groups antibodies into clusters that mimic the process of affinity maturation. Meanwhile, BALM stands out for its ability to predict both the function and structure of antibodies, exemplifying the significant role of machine learning in the field of immunology.

2 Method

In this section, we first outline the task formulation, followed by a detailed exposition of our proposed method, ensuring a logical flow from problem understanding to solution presentation.

2.1 Task Formulation

The objective is to predict antibody sequence b consisting of light and heavy chains l and h, respectively, given the input antigen information g. In this formulation, g is represented by a sequence-structure tuple $(s_i, \mathbf{x}_i)$ for $i = 1, \ldots, n$, where $s_i \in \mathcal{A}$, the set of all naturally occurring amino acids, and $\mathbf{x}_i \in \mathbb{R}^3$ is the coordinates of the alpha carbon atom of amino acid at position i. The task aims to learn parameters θ to maximize the conditional probability:

$$\max_{\theta} P(b_{\text{masked}} | g, b_{\text{known}}). \tag{1}$$

In specific cases, part of the antibody sequence, typically the framework, might already be identified, indicated as b_{known}. Our goal is to accurately predict the unspecified segments of the antibody sequence, referred to as b_{masked}. For the case of full antibody prediction, no section is known, hence $b_{\text{known}} = \emptyset$.

2.2 Architecture

Informed by our previous discussions, we elected to concentrate solely on the design of the antibody sequence. Our objective is to gain a deeper understanding of the antigen to create a complementary antibody sequence effectively. To achieve this, we adopted an encoder-decoder architecture.

The encoder in our framework is tasked with capturing the antigen's structural and sequential details comprehensively. The decoder, on the other hand, uses this information to produce the corresponding antibody sequence, systematically incorporating all essential aspects of the antigen. We utilized GearNet, a structural encoder pre-trained on the AlphaFold dataset (Figure 2A), for antigen encoding. This pre-training process equipped GearNet with a robust understanding of protein structures, making it adept at accurately encoding the information of antigens. The encoder function $\text{ENC}(g)$ produces H_g, which is in the shape of $n \times d_{\text{GearNet}}$, where n is the length of the antigen sequence and d_{GearNet} is the dimensionality of the encoded space. H_g is then passed through an adapter module, undergoing a linear transformation with weights W_{AdaptEnc} to produce E_g such that $E_g = W_{\text{AdaptEnc}} \cdot H_g$, and we parameterize the dimensionality of E_g with $d_{\text{AdaptEnc}} = 256$. The transformed representation E_g is then passed to the decoder, serving as the foundation for generating corresponding antibody sequences and translating the complex antigen information into a usable format for antibody design.

Our decoding component, the Bio-inspired Antibody Language Model (BALM), leverages a transformer-based self-attention mechanism with 30 layers and rotary positional encoding to understand the unique and conserved properties of antibodies (Figure 2B). Initially trained on a large dataset of unlabeled antibody sequences, BALM effectively captures contextual embeddings essential for inferring binding functions. Notably, BALM employs a unique antibody positional encoding method based on the IMGT numbering scheme (Lefranc et al., 2003), which provides a consistent framework for identifying amino acid positions, thereby enhancing its ability to generate meaningful embeddings.

In our methodology, the antibody sequence representation provided to BALM adopts a structure similar to ESM-2; it commences with a [CLS] token followed by the antibody's heavy chain sequence, a [EOS] token, the antibody's light chain sequence, and another [EOS] token. To adapt BALM for conditional generation crucial to our approach, we integrated antigen adapter layers after each self-attention layer within BALM (Figure 2C). This integration facilitates the efficient incorporation of the encoded antigen information into the decoding process. Each antigen adapter layer consists of a cross-attention layer followed by a feed-forward layer. In the cross-attention operation denoted as CrossAtt(Q, K, V), the output of each block in adapted BALM is given by:

$$H^l = W_{\text{FFN}} \cdot \text{CrossAtt}(H_t^l, E_g, E_g) + H_t \tag{2}$$

where l signifies the layer number, E_g represents the encoded antigen information, and W_{FFN} are the weights of the feed-forward layer, and H_t is the output from the previous feed-forward and self-attention layers. This refined structure ensures a synergistic interplay between the antigen's structural and sequential information, aligning with our objective of generating corresponding antibody sequences based on the encoded antigen information.

2.3 Training and Inference

During the training phase, our model utilizes the Causal Masked Language Modeling (CMLM) objective (Ghazvininejad et al., 2019), which facilitates the non-autoregressive generation of antibody sequences informed by antigen structure. A subset of tokens from the antibody sequence B is replaced with a [MASK] token, with the number of masked tokens uniformly sampled between 1 and $|B|$, where $|B|$ denotes the sequence length. To direct the model's learning toward the variable and critical CDRs rather than the more conserved framework regions, we apply Focal Loss Lin et al. (2018) as our training loss function. Focal Loss is mathematically formulated as:

$$FL(p_t) = -(1 - p_t)^{\gamma} \log(p_t) \tag{3}$$

where p_t is the model's estimated probability for the class label t and γ (In our training, $\gamma = 2$) is the focusing parameter that adjusts the rate at which easy-to-classify residues are down-weighted. This loss function is particularly effective in managing class imbalance and helps the model focus on the challenging CDR regions essential for our task.

Table 1: Comparison of AIDA with existing models (ReprogBert, Diffab, AbODE, dyMEAN) in single CDR design. Metrics: Amino Acid Recovery (AAR), Contact Amino Acid Recovery (CAAR), and Root Mean Square Deviation (RMSD). AIDA shows superior performance in H1, H2, H3 AAR, and CAAR.

	H1			H2			H3		
Model	AAR↑	CAAR↑	RMSD↓	AAR↑	CAAR↑	RMSD↓	AAR↑	CAAR↑	RMSD↓
ReprogBert	-	-	-	-	-	-	36.30%	-	2.47
Diffab	68.00%	60.02%	0.55	54.64%	42.77%	**0.41**	37.47%	20.88%	2.08
AbODE	70.50%	-	0.65	55.70%	-	0.73	39.80%	-	1.73
dyMEAN	76.55%	63.19%	0.56	69.52%	63.50%	0.48	43.20%	27.83%	**1.58**
AIDA	**80.56%**	**69.44%**	**0.47**	**71.25%**	**66.46%**	0.48	**46.41%**	**33.04%**	1.68
	L1			L2			L3		
Model	AAR↑	CAAR↑	RMSD↓	AAR↑	CAAR↑	RMSD↓	AAR↑	CAAR↑	RMSD↓
Diffab	45.88%	39.24%	0.55	54.68%	25.00%	**0.11**	43.99%	25.32%	**0.71**
dyMEAN	**74.11%**	**65.49%**	**0.48**	**81.98%**	**51.94%**	0.20	**51.93%**	33.33%	0.87
AIDA	67.01%	58.66%	0.51	78.09%	49.17%	0.65	47.03%	**62.07%**	1.63

During inference, we strategically place the [MASK] token at positions corresponding to the parts of the sequence we aim to predict, such as the H3 region. These masked positions are then predicted using our adapted BALM model. Unlike the iterative mask prediction strategy suggested in Ghazvininejad et al. (2019), which incrementally refines the sequences, our observations indicated no significant improvements with multiple iterations. Consequently, we opted for a single iteration of unmasking, which efficiently yields accurate sequence predictions without the need for iterative refinement.

The training of our model was conducted using the Adam optimizer on one NVIDIA A40 GPU, paired with an inverse square root learning rate scheduler. This scheduler featured a warm-up phase of 1,000 steps, after which the learning rate peaked at 10^{-4}. To preserve the integrity of the pre-trained models, we initially kept all pre-trained weights frozen during the first ten epochs. After this period, we unfroze the pre-trained weights and set their learning rate to a tenth of that of the newly added layers. Importantly, we initialized W_{FFN} in antigen adapters to zeroes. This weight initialization ensures that the newly added layers do not immediately disrupt the predictive capabilities of BALM, allowing the model to maintain its pre-trained performance while the new layers gradually adapt during the fine-tuning process. This approach allowed for end-to-end training, providing the model with the opportunity to adjust to the specific characteristics of our dataset gradually.

3 Experiment

In this section, we rigorously evaluate our proposed model through four experiments, benchmarking AIDA against established models in antibody design. The experiments include (1) Single CDR design (§3.1), (2) Multiple CDR design (§3.2), (3) Full antibody design (§3.3), and (4) Antibody Optimization (§3.4).

To thoroughly evaluate our model, we compared it against leading models in both sequence-based and co-design categories. In the sequence-based category, we included **ReprogBert** (Melnyk et al., 2023), which reprograms a pre-trained English BERT model for antibody design. Notably, ReprogBert utilizes IgFold (Ruffolo et al., 2023) for generating antibody structures and calculating Root Mean Square Deviation (RMSD). In the co-design category, our comparisons included **DiffAb** (Luo et al., 2022b), employing a diffusion process for simultaneous sequence and structure prediction, **AbODE** (Verma et al., 2023), modeling antigen-antibody interactions via graph Partial Differential Equations (PDE), and **dyMEAN** Kong et al. (2023), which features an adaptive multi-channel encoder for full atom modeling and a 'Shadow Paratope' technique for comprehensive antigen interaction analysis.

To better equip BALM for the specific requirements of our experiments and to enhance its understanding of the interplay between heavy and light chains in antibodies, we drew upon the strategies of Burbach and Briney (2023). Their work significantly boosted the performance of their aLM by focusing on training with natively paired heavy and light chain sequences. Motivated by this, we initiated a secondary pre-training phase for BALM, leveraging the OAS database to curate paired antibody sequences. These sequences were clustered based on a 50% sequence identity threshold, yielding a collection of approximately 100,000 non-redundant antibody sequences. For this pre-training stage, we implemented an MLM objective supplemented by entropy-guided masking, as recommended by

Table 2: Comparison of AIDA with existing models in multiple CDR design. Metrics: AAR, CAAR, RMSD. AIDA excels in AAR and CAAR for L3 and heavy chain CDRs, outperforming Diffab and dyMEAN overall.

	AAR↑								
Model	L1	L2	L3	H1	H2	H3			
Diffab	52.02%	56.03%	47.88%	68.97%	54.64%	39.82%			
dyMEAN	**75.89%**	**83.65%**	52.66%	76.13%	68.48%	37.51%			
AIDA	63.20%	75.4%	**61.49%**	**79.76%**	**70.23%**	**44.98%**			
	CAAR↑						Overall		
Model	L1	L2	L3	H1	H2	H3	AAR↑	CAAR↑	RMSD↓
Diffab	46.73%	28.06%	27.22%	61.85%	44.01%	24.31%	51.26%	40.35%	1.95
dyMEAN	**67.99%**	**53.61%**	35.26%	63.11%	62.52%	23.11%	60.36%	50.30%	1.35
AIDA	58.36%	44.72%	**46.30%**	**67.50%**	**65.74%**	**31.89%**	**63%**	**53.67%**	**1.01**

Jing et al. (2023). This pre-training phase is aimed at substantially enriching BALM's comprehension of antibody sequences and the complex relationship between heavy and light chains.

3.1 Single CDR Design

In this experiment, we tackled the challenge of predicting a single CDR, given the other domains of the light and heavy chains. We used a masking-unmasking technique, where the target CDR is initially masked, and the model then predicts its sequence. This process tests the model's ability to integrate contextual information from the known sections of the antibody's variable region to design the target CDR.

To train our model, we utilized the SAbDab dataset, which includes about 5,000 samples of paired antibodies and nanobodies. We clustered samples based on their CDR-H3 sequences using the MMseqs2 algorithm and the BLOSUM 62 scoring matrix, at a 40% sequence identity threshold. Sixty samples from the RAbD benchmark were reserved for testing, and clusters containing these test samples were excluded from the training and validation sets to prevent data leakage. From the remaining clusters, 10% were randomly selected for validation, with the rest used for training.

The model's predictive performance was assessed using three main metrics: Amino Acid Recovery (**AAR**), Contact Amino Acid Recovery (**CAAR**), and Root Mean Square Deviation (**RMSD**). AAR measures the accuracy of the predicted amino acid sequence, while CAAR evaluates the model's ability to predict residues that interact with the antigen. As our model does not directly predict protein structure, we utilized the dyMEAN structure prediction model, available on its official GitHub repository, to predict the complex tertiary structure for the generated antibody sequences. We then used RMSD to measure structural accuracy, calculating the average deviation between the backbone atoms of the predicted and actual protein structures post-alignment using the Kabsch algorithm. A lower RMSD indicates higher structural fidelity. By combining AAR and CAAR for sequence accuracy and RMSD for structural accuracy through dyMEAN predictions, we comprehensively evaluate our model's efficacy in replicating both the antibody sequences and their functional conformations.

Results As indicated in Table 1, our AIDA model demonstrated remarkable proficiency in predicting the sequence of a single CDR. This success highlights AIDA's ability to use context from conserved antibody regions and integrate targeted antigen information through adapter modules, enabling precise engineering of CDR regions critical for antigen recognition. Notably, AIDA outperformed models like DiffAb, AbODE, and dyMEAN in designing the heavy chain's third CDR (H3), showcasing its advanced sequence prediction capabilities. While AIDA excelled in both sequence-based and most structure-based metrics, it is important to consider potential inaccuracies from the external structure prediction tool used for evaluation.

3.2 Multiple CDR Design

In this experiment, we predicted the sequences of all six CDRs (three from the heavy chain and three from the light chain) simultaneously, given the antigen structure and the antibody framework sequence. This demonstrated AIDA's robustness in handling complex design tasks, integrating and processing intricate antigen information, and managing multiple CDRs. The evaluation followed the same setting as the single CDR design experiment (§3.1).

Table 3: Performance of AIDA in predicting the complete variable region of antibodies, including heavy and light chains and all CDRs, compared against dyMEAN. Metrics such as Amino Acid Recovery (AAR), Contact Amino Acid Recovery (CAAR), and Root Mean Square Deviation (RMSD) highlight AIDA's superior predictive capabilities in this extensive and complex task.

Model	AAR	CAAR	RMSD
dyMEAN	70.35%	40.02%	**1.11**
AIDA	**72.48%**	**45.15%**	1.21

Results The results in Table 2 show AIDA's exceptional capability in handling complex antibody design tasks. AIDA maintained consistent performance in multiple CDR design, with less dependency on known antibody sections compared to other methods like dyMEAN, which saw a significant drop in performance, especially in H3 design. AIDA's higher AAR and CAAR, along with significantly lower RMSD, underscore its superiority in accurate antibody sequence prediction.

3.3 Full Antibody Prediction (Whole Variable Region Prediction)

In this critical phase of our research, we extended the scope of AIDA's capabilities by challenging it to predict the entire variable region of antibodies. This includes both the heavy and light chains, encompassing all the CDRs and framework regions. Unlike the previous tasks that focused on specific CDRs, this task requires the model to generate a more extensive and complete sequence, reflecting the full complexity of an antibody's variable region. This experiment included similar settings as the single CDR (§3.1).

Table 4: Comparison of AIDA and dyMEAN in Antibody H3 Region Optimization: This table illustrates the performance of AIDA and dyMEAN in enhancing the binding affinity of the H3 region of antibodies. Metrics used for evaluation include the change in binding affinity ($\Delta\Delta G$) and the average number of modified residues (ΔL). The dyMEAN-n and AIDA-n variants indicate models restricted to modifying only n tokens. In contrast, dyMEAN and AIDA represent configurations where n tokens, ranging from 1 to the length of the H3 region, were randomly altered. For each sample, both models generated 100 sequences, with the best-performing sequence chosen for evaluation. These results highlight the models' effectiveness in achieving enhanced binding affinity with minimal sequence modifications.

Method	$\Delta\Delta G\downarrow$	$\Delta L\uparrow$
dyMEAN-1	-2.97	1.00
dyMEAN-2	-3.22	1.35
dyMEAN-4	-3.40	2.22
dyMEAN-8	-3.84	4.84
dyMEAN	-3.27	4.20

Method	$\Delta\Delta G\downarrow$	$\Delta L\uparrow$
AIDA-1	-3.47	0.82
AIDA-2	-4.46	1.47
AIDA-4	-5.24	2.27
AIDA-8	-3.48	4.12
AIDA	**-5.48**	4.10

Results Table 3 shows the results of the full antibody prediction experiment. Our model was compared against dyMEAN, the only other method capable of addressing this extensive task. Remarkably, AIDA surpassed dyMEAN in all sequential metrics for predicting the entire variable region of the antibody. This indicates AIDA's superior ability to model the interaction of antigens and antibodies.

3.4 Antibody Optimization

In our antibody optimization experiment, we aimed to enhance the binding affinity of antibodies to specific antigens, focusing on the H3 region. The models were trained on the SAbDab dataset, and SKEMPI V2.0 Jankauskaitė et al. (2018) was used for testing under the same settings as the single CDR design experiment (§3.1). Performance was assessed using two metrics: (1) the binding affinity change ($\Delta\Delta G$), determined through a GNN-based predictor Shan et al. (2022) as recommended by Kong et al. (2023), and (2) the average number of modified residues (ΔL), indicating the importance of minimal sequence alterations for improved affinity Ren et al. (2022).

To tailor our model for this experiment and control the number of modified residues, we masked n random tokens from the H3 region for AIDA to predict. We then used the dyMEAN structure

prediction model to predict the antibody-antigen complex structure. Both models generated 100 sequences for each sample, selecting the one with the best $\Delta\Delta G$ for metric calculation.

Results In Table 4, the results demonstrate AIDA's effectiveness in enhancing antibody binding affinity compared to dyMEAN. The evaluation, using $\Delta\Delta G$ and ΔL, shows that AIDA, particularly in its unrestricted form, significantly outperforms dyMEAN. AIDA achieves a notable improvement in binding affinity with $\Delta\Delta G$ = -5.48 while maintaining a reasonable degree of residue modification (ΔL = 4.10), highlighting its capability to optimize antibody sequences for higher affinity with minimal alterations.

3.5 Ablation Study

In our ablation study, we assess the necessity and value of the following components in the AIDA model: Focal Loss, the second paired pre-training process for BALM, CMLM training (replaced with a full masking strategy for training), and the antigen adapter (where we only fine-tuned BALM). The results (Table 5) across the H3, All CDRs, and Full Antibody design settings show that each component plays a crucial role in the model's performance. AIDA achieves the highest AAR and CAAR scores in H3 and Full Antibody settings, demonstrating the effectiveness of these components, particularly in challenging regions. Interestingly, CMLM performs best in All CDRs, suggesting advantages in general binding site prediction. Overall, the combination of these components is crucial for maximizing AIDA's accuracy and consistency across antibody regions.

Table 5: Ablations of different components in AIDA.

	H3		All CDRs		Full antibody	
Model	**AAR↑**	**CAAR↑**	**AAR↑**	**CAAR↑**	**AAR↑**	**CAAR↑**
AIDA	**46.41%**	**33.04%**	63.00%	53.67%	**72.48%**	**45.15%**
Focal	46.01%	31.86%	61.94%	52.62%	72.10%	43.26%
Paired Pretraining	45.32%	31.84%	63.23%	53.82%	71.58%	43.49%
CMLM	44.12%	30.37%	**64.14%**	**54.71%**	71.91%	43.54%
Antigen Adapter	43.10%	29.87%	61.15%	57.16%	72.07%	42.20%

4 Limitations and Future Work

In advancing computational antibody design with AIDA, we've identified key limitations. One major challenge in this field is the lack of computational metrics that accurately reflect antibody-antigen interactions, suggesting a significant area for future research.

Additionally, the scarcity of antigen-antibody paired data limits our model's predictive accuracy despite using pre-trained models and transfer learning. Future work could explore increasing sample numbers through wet lab experiments or data augmentation.

Finally, AIDA's precision is dependent on the structural models used for antigen encoding; inaccuracies here can affect the final design. However, our model's modularity allows for future improvements by incorporating advanced protein structure encoders focused on surface analysis and binding sites.

5 Conclusion

In conclusion, our study contributes significantly to the field of computational antibody design, tackling the prevalent challenges of data scarcity and structural flexibility in antibody regions. By introducing Aligned Integrated Design for Antibodies (AIDA), which utilizes an encoder-decoder architecture integrating both structural and sequence information of antigens, we have made noteworthy progress in antibody sequence prediction. Our proposed model exhibited enhanced performance over established methods such as dyMEAN and Diffab in different experiments, including predicting the single and multiple CDRs, the entire variable region of antibodies, and optimizing the antibodies' binding affinity. AIDA's focus on sequence prediction and its effective management of complex antigen information marks a meaningful step forward in the development of efficient and accurate methods for antibody design, opening new avenues for advancements in biomedical research and healthcare applications.

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