Qeios

Peer Review

# Review of: "AlignAb: Pareto-Optimal Energy Alignment for Designing Nature-Like Antibodies"

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1. Methodological Innovation

The primary limitation of this work lies in its reliance on existing methods without substantial methodological innovation. The BERT pre-training follows standard protocols from protein language models, while the diffusion model architecture closely resembles previous work. The preference optimization component essentially applies existing DPO methodology to the antibody domain. To strengthen the innovation aspect, the authors should:

- Consider developing novel architectures specifically tailored for antibody design
- Explore new loss functions that better capture the unique characteristics of antibody-antigen interactions
- Investigate the possibility of end-to-end training approaches that could improve the integration of the three stages

2. Technical Details

Several technical aspects require further clarification and justification. The choice of reward weights (1:3 ratio) appears arbitrary without theoretical or experimental justification. The temperature scaling strategy, while effective, lacks rigorous analysis of its impact on diversity and stability. The independent training of three stages might be suboptimal compared to potential joint optimization approaches. The authors should:

- Provide theoretical analysis justifying parameter choices
- Develop more sophisticated adaptive strategies for temperature scaling
- Consider end-to-end training alternatives
- Include sensitivity analysis for key hyperparameters



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3. Experimental Validation

The experimental validation, while extensive in some aspects, has notable gaps. The absence of comprehensive ablation studies makes it difficult to assess the contribution of individual components. The lack of failure case analysis limits our understanding of the method's limitations. Additionally, the evaluation of generated sample diversity is insufficient. To address these issues, the authors should:

- Conduct detailed ablation studies for each major component
- Include analysis of failure cases and their potential causes
- Provide quantitative metrics for assessing the diversity of generated antibodies
- Compare with a broader range of baseline methods

4. Presentation and Organization

While the overall presentation is clear, several improvements would enhance the paper's accessibility and impact. The methodology section would benefit from a clear flow diagram illustrating the interaction between different components. The related work section needs a more systematic comparison with existing methods, potentially through a comprehensive comparison table. The visualization of results could be more intuitive and informative. Suggested improvements include:

- Adding a detailed methodology flow diagram
- Including a systematic comparison table in the related work section
- Improving the visualization of experimental results
- Providing more detailed analysis of limitations and future directions

## Declarations

**Potential competing interests:** No potential competing interests to declare.