

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
<input type="checkbox"/>	<input checked="" type="checkbox"/> The exact sample size ( <i>n</i> ) for each experimental group/condition, given as a discrete number and unit of measurement
<input checked="" type="checkbox"/>	<input type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
<input checked="" type="checkbox"/>	<input type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/> A description of all covariates tested
<input checked="" type="checkbox"/>	<input type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
<input checked="" type="checkbox"/>	<input type="checkbox"/> A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
<input checked="" type="checkbox"/>	<input type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i> ) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
<input checked="" type="checkbox"/>	<input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
<input type="checkbox"/>	<input checked="" type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i> ), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	We modeled mutations and predicted the corresponding change in binding affinity values for antibody-antigen complexes from the SAbDab database (accession date 19 May 2022) using FoldX (version 5) and Rosetta Flex ddG (Rosetta version 2020.08+release.cb1caba).
Data analysis	We built the EGNN deep learning models in Python v3.7.10 using PyTorch v1.8.0 and PyTorch Geometric v1.6.3. The code is available at <a href="https://github.com/oxpig/Graphinity">https://github.com/oxpig/Graphinity</a> . We visualized the data using Python v3.9.1, matplotlib v3.9.2, seaborn v0.13.2, PyMOL v2.3.0, and PowerPoint v16.95.4. Colors were selected in part using ColorBrewer 2.0 ( <a href="https://colorbrewer2.org">https://colorbrewer2.org</a> ).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

## Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The synthetic  $\Delta\Delta G$  datasets and links to download the corresponding PDBs can be found at <https://github.com/oxpig/Graphinity>.

The AB-Bind database is available at <https://github.com/sarahsirin/AB-Bind-Database>. The SKEMPI v2.0 database is available at <https://life.bsc.es/pid/skempi2>.

Source data for Figures 2-4 is available with this manuscript and at <https://github.com/oxpig/Graphinity>.

## Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender

Population characteristics

Recruitment

Ethics oversight

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://nature.com/documents/nr-reporting-summary-flat.pdf)

## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	<p>We created synthetic change in binding affinity datasets using PDBs from SABDab. The final datasets consisted of 942,723 FoldX mutations from 1471 antibody-antigen complexes and 20,829 Flex ddG mutations from 1302 antibody-antigen complexes.</p> <p>The synthetic FoldX dataset size was determined as the number of mutations that could be generated through exhaustive mutagenesis of interface positions from a clustered dataset (90% length-matched CDR sequence identity cutoff) of solved antibody-antigen complex structures. The synthetic Flex ddG dataset was subsampled from the synthetic FoldX dataset at ca. 16 mutations per antibody-antigen complex. The Flex ddG dataset size was restricted by computational requirements.</p> <p>The sufficiency of these datasets was analyzed through developing models on subsampled datasets. Performance plateaued as the full dataset size was reached.</p> <p>Analyses were also conducted on existing experimental databases, AB-Bind and SKEMPI 2.0.</p>
Data exclusions	<p>We clustered the SABDab PDBs based on 90% length-matched CDR sequence identity and carried forward one PDB from each cluster for interface mutagenesis. We excluded mutations where the WT amino acid was 'X', the chain identifier was a number, the antibody and antigen were &gt; 4 Å apart and the FoldX Interaction Energy calculation or Rosetta Flex ddG mutation modeling failed.</p>
Replication	<p>The FoldX software is deterministic.</p>
Randomization	<p>This study is centered on the development and validation of models for predicting change in antibody-antigen binding affinity. The quantitative data is formatted as the difference in binding affinity between the wild-type and mutant complexes (<math>\Delta\Delta G</math>) and does not test for a causal relationship between groups. As such, randomization was not applicable to this study.</p>
Blinding	<p>This study is centered on the development and validation of models for predicting change in antibody-antigen binding affinity. The quantitative data is formatted as the difference in binding affinity between the wild-type and mutant complexes (<math>\Delta\Delta G</math>) and does not test for a</p>

## Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

### Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging