SARS-CoV-2 drug discovery based on intrinsically disordered regions

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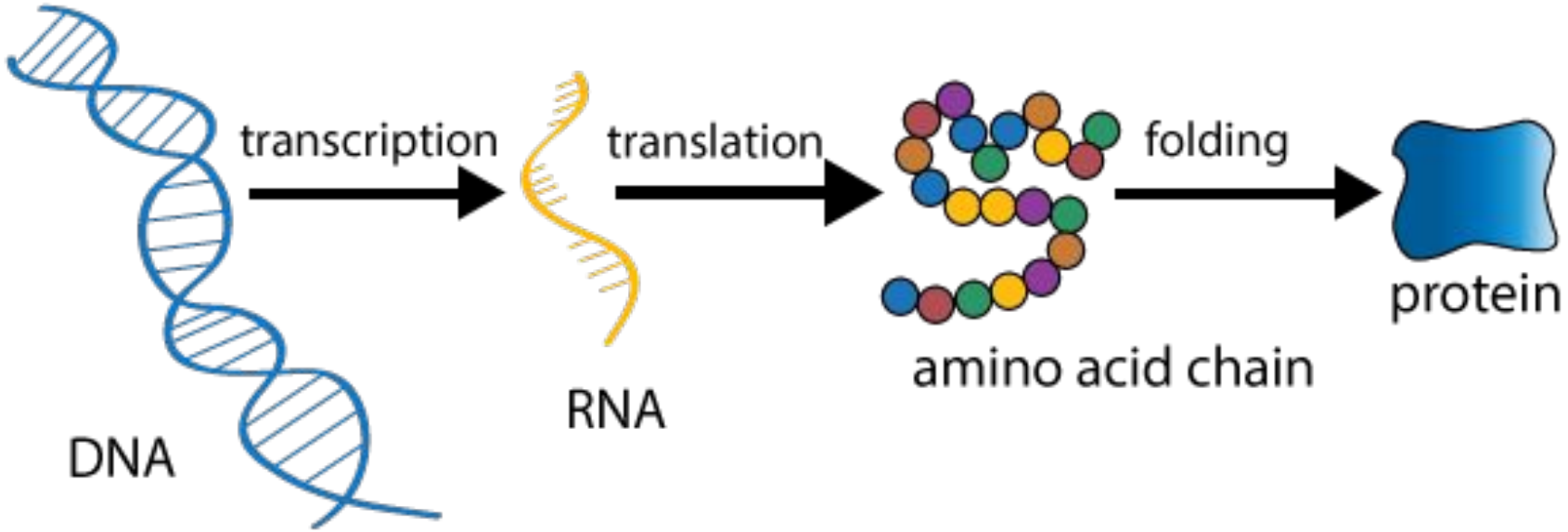
Agenda

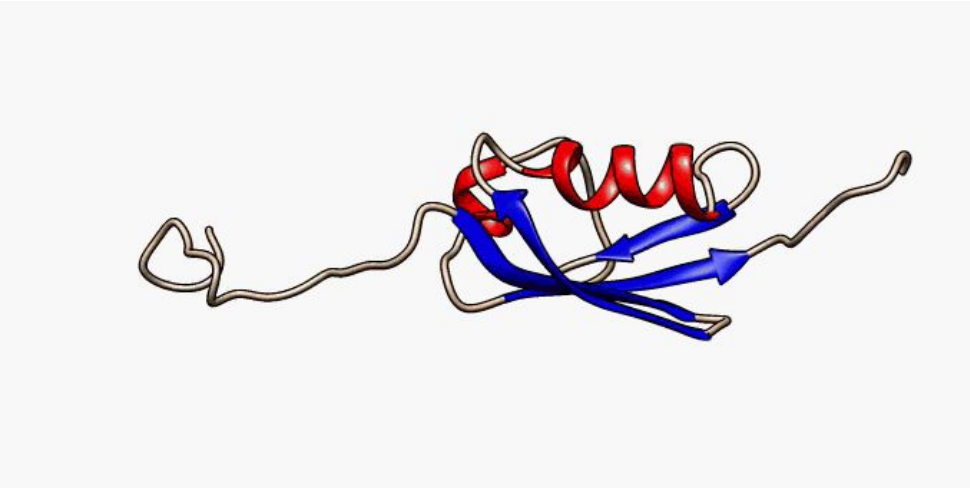
- Biological background
- SARS-CoV-2 therapeutic discovery
- Biomimicry-based drug discovery

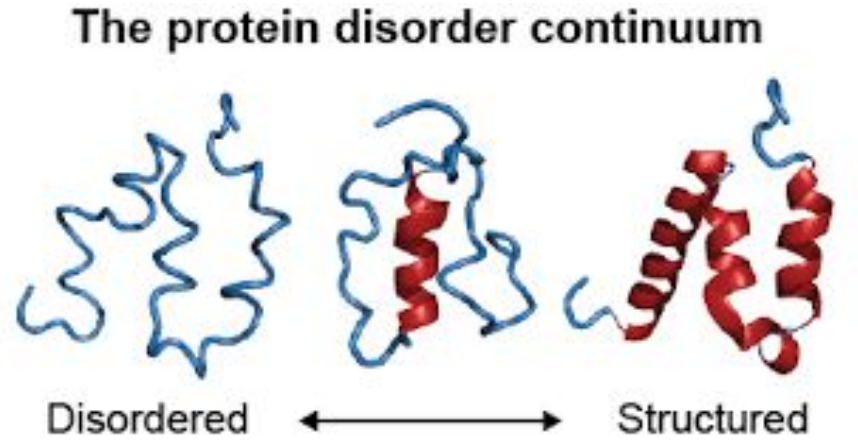
Background

Central dogma of molecular biology

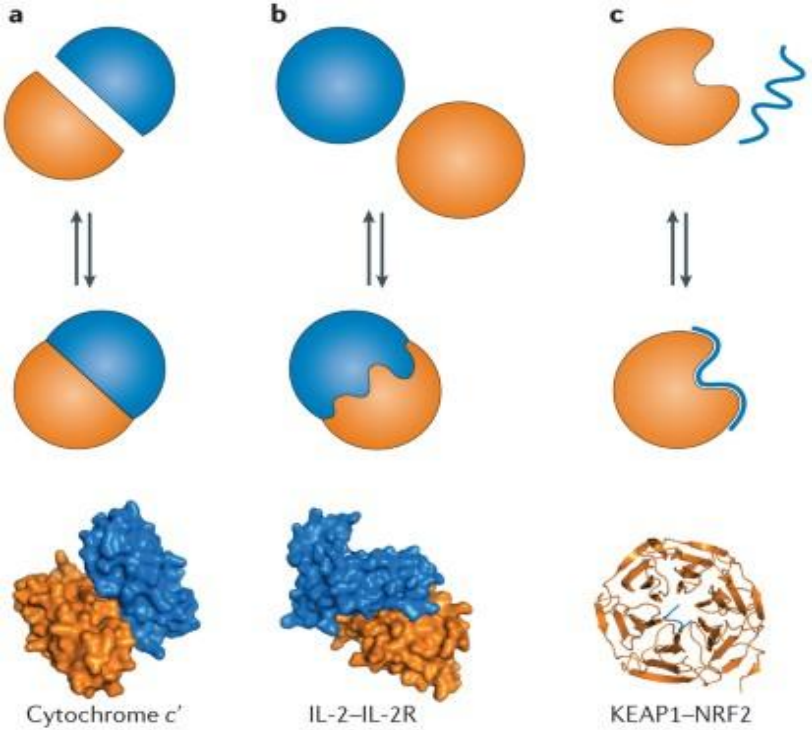


Intrinsically Disordered Proteins / Regions (IDPs / IDRs)





Drug Discovery



Why target IDRs?

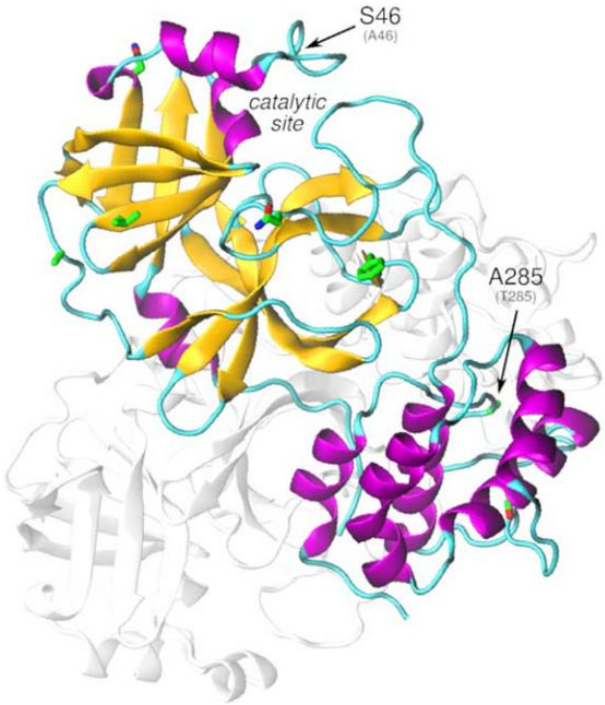
Common (33%)

Drug resistance

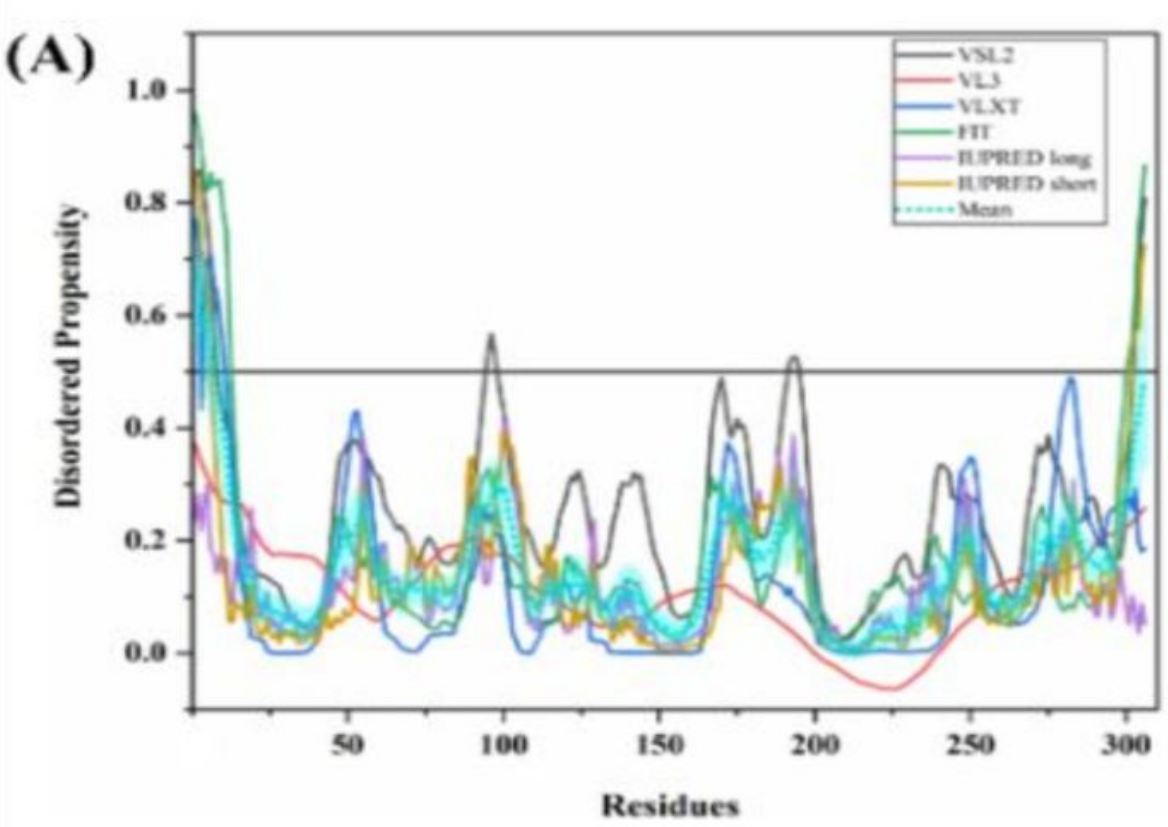
New opportunity

SARS-CoV-2 therapeutic discovery

The target: 3CL-protease



3CLpro disorder

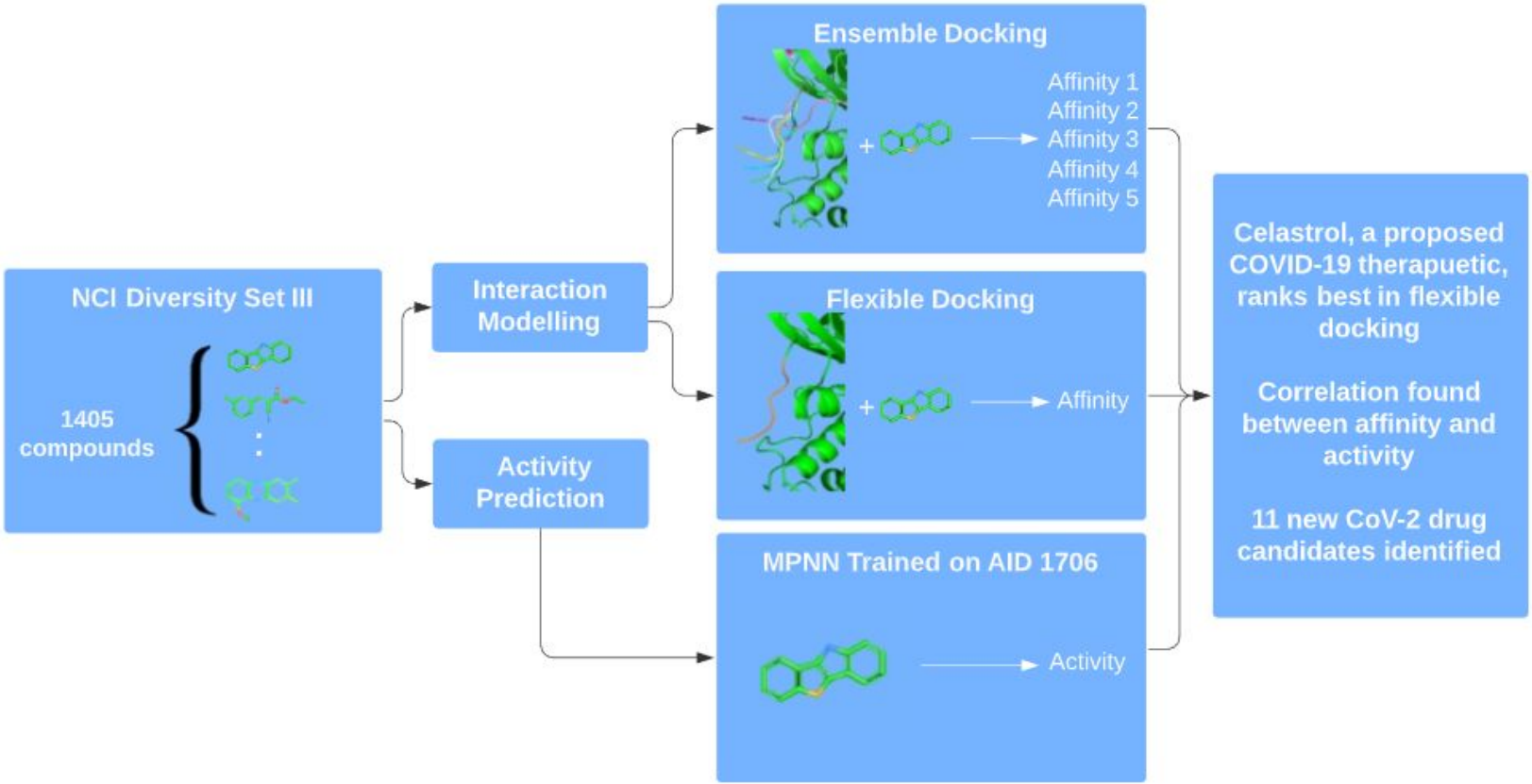


IDRs

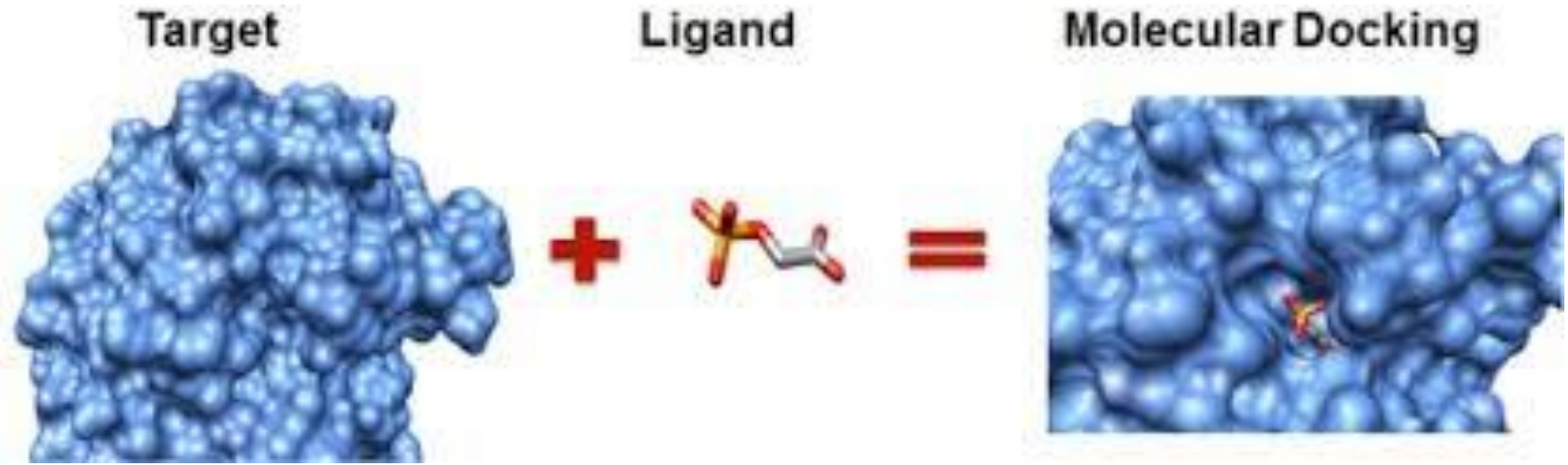
Residues 1-6*

Residues 302-306

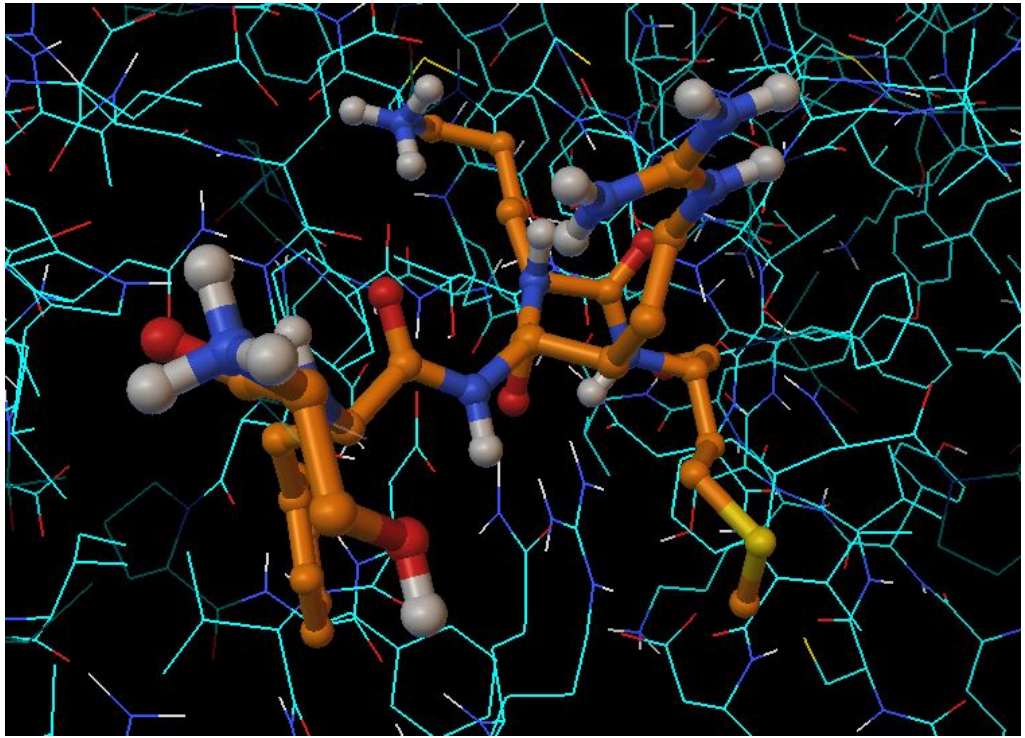
Our Approach



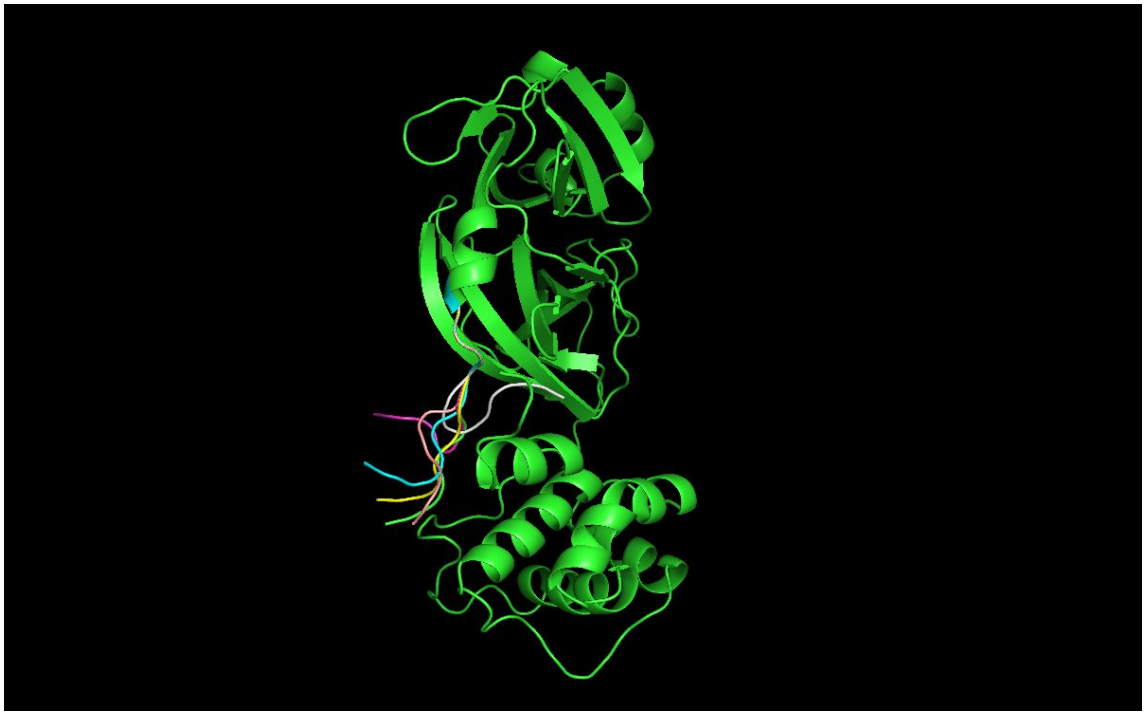
Interaction Modelling (Docking)



Independent Modification 1: Flexible side chains



Independent Modification 2: Ensemble docking



Results

Table 1. Binding affinity results from flexible docking (abridged)

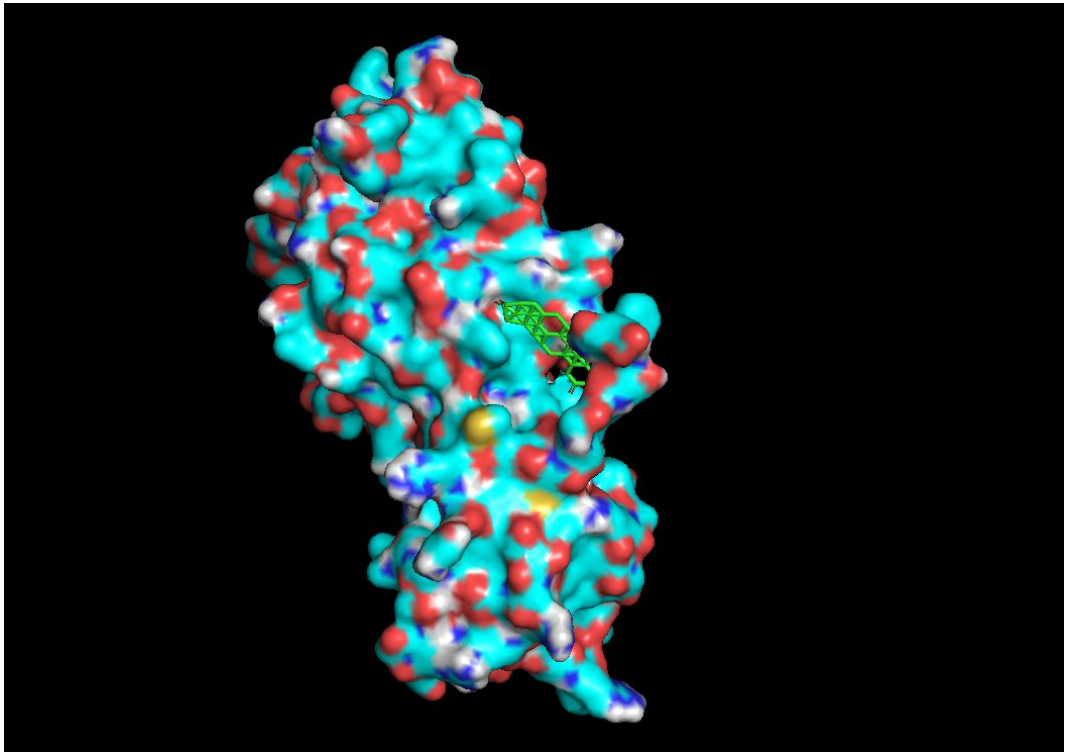
Molecule (NSC)	Binding Affinity (kcal/mol)
70931	-9.8
177862	-9.7
16437	-9.3
96541	-9.1
117987	-8.8
45527	-8.8
…	…

Results (cntd.)

Table 2. Binding affinity results from ensemble docking (abridged)

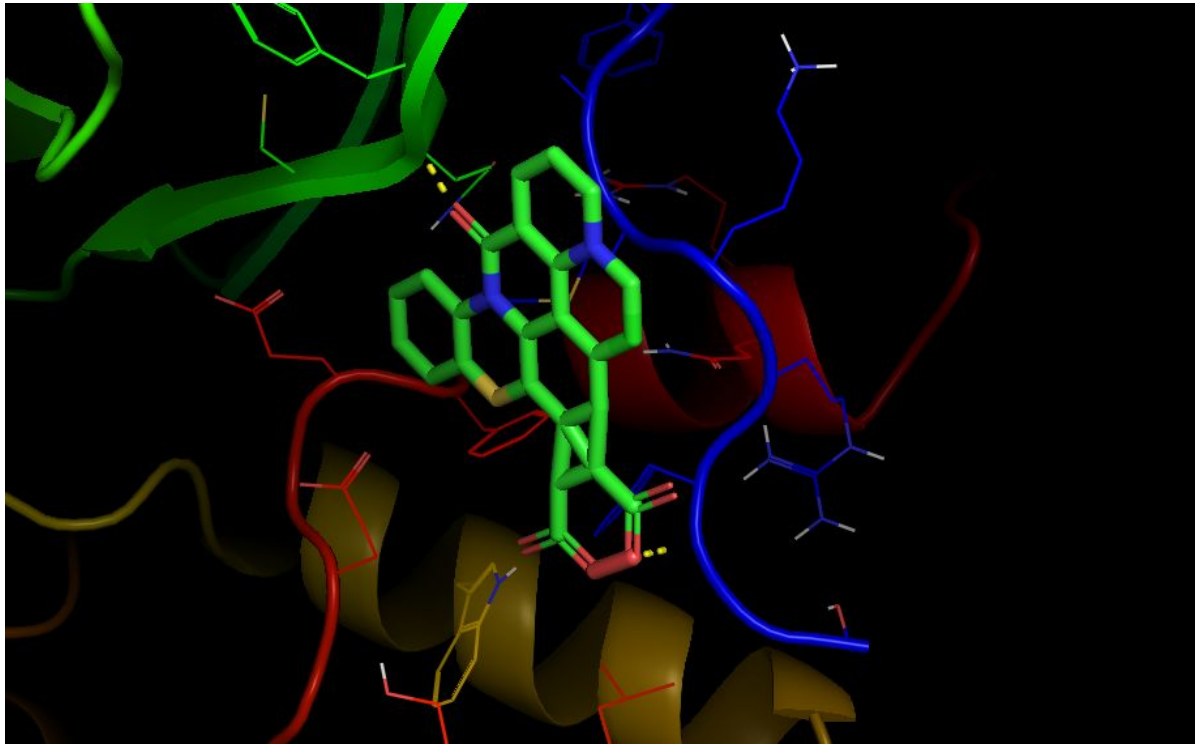
Molecule (NSC)	Best Binding Affinity (kcal/mol)
166259	-9.3
37641	-9.1
121868	-9.1
727038	-9.1
117987	-8.7
70931	-8.6
…	…

Visualizations



Molecule 70931 / Celastrol

Visualizations (cntd.)



Molecule 166259

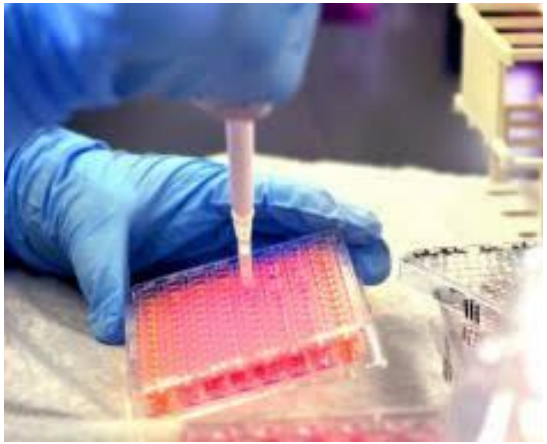
Cross-verification

In silico: docking

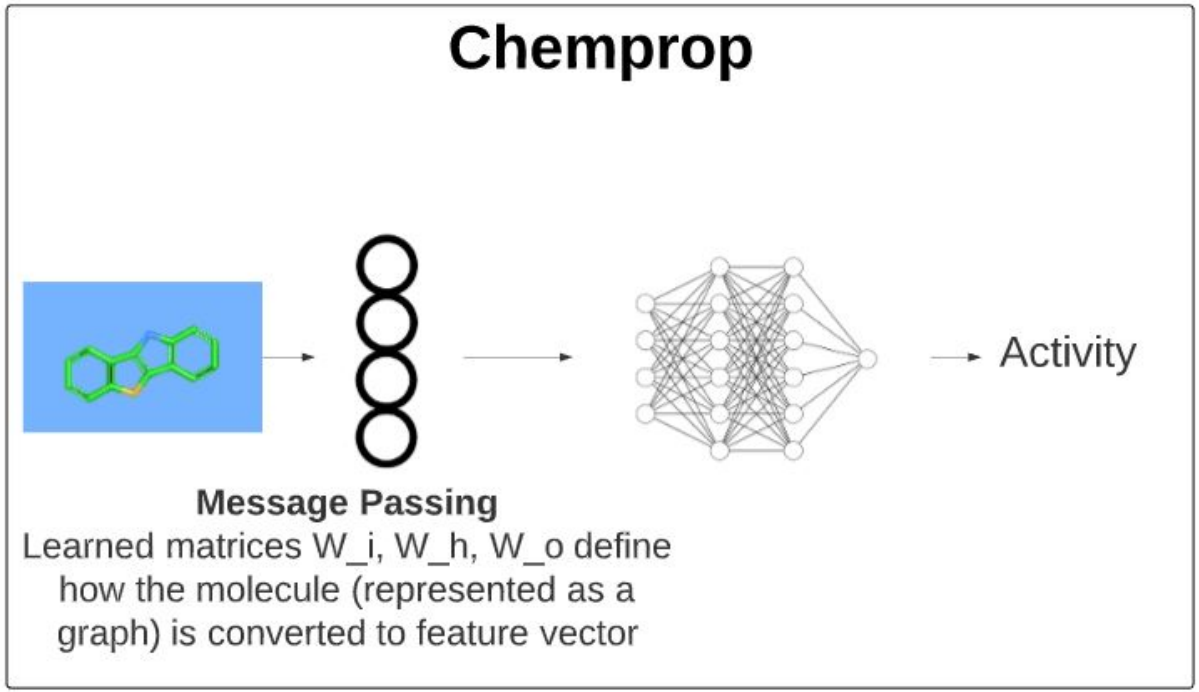
In vitro: AID 1706

In-vitro assay. Detects inhibition of SARS-CoV 3CL protease

N = 290,726



The model



Learns task-specific features, rather than fixed ones
Model is trained end-to-end

Results

Metrics + hyperparameters

80% train, 10% val, 10% test

Balanced training

Test AUC: .739

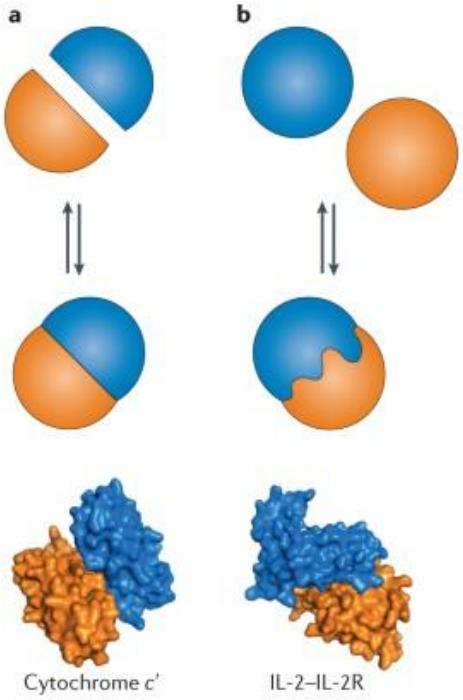
Results

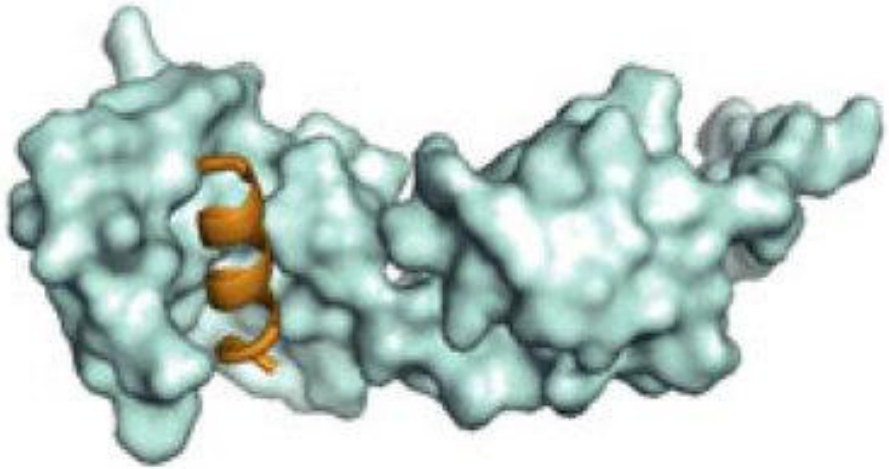
Table 4. Top 11 drug candidates in terms of affinity and activity.

Molecule (NSC)	Activity	Affinity	Active Bioassays
16437	.859	-9.3	Foot-and-mouth disease (FMD) virus
117987	.872	-8.8	
601359	.855	-8.4	Melanoma cell line, Malaria
13294	.825	-8.4	
127133	.908	-8.3	
61610	.823	-8.2	Malaria
107582	.877	-8.1	
128606	.920	-8.0	
211490	.808	-8.0	Hepatitis C virus, Human cytomegalovirus
679525	.894	-8.0	Orthopoxviruses, FMD virus
204232	.800	-7.9	DNA Polymerase Beta

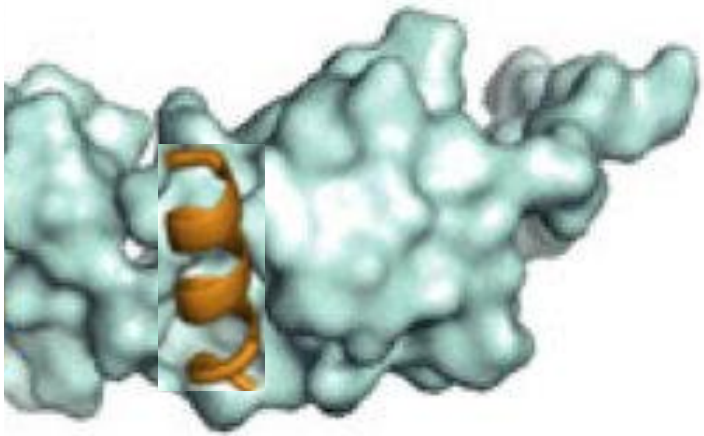
Biomimicry-based drug discovery

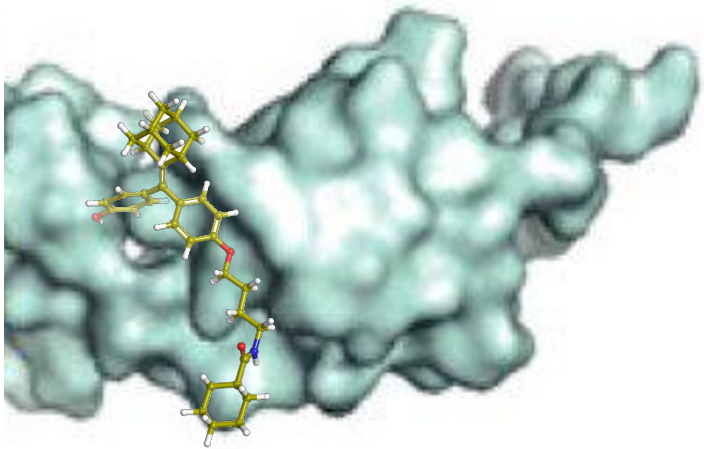
Molecular recognition features (MoRFs)



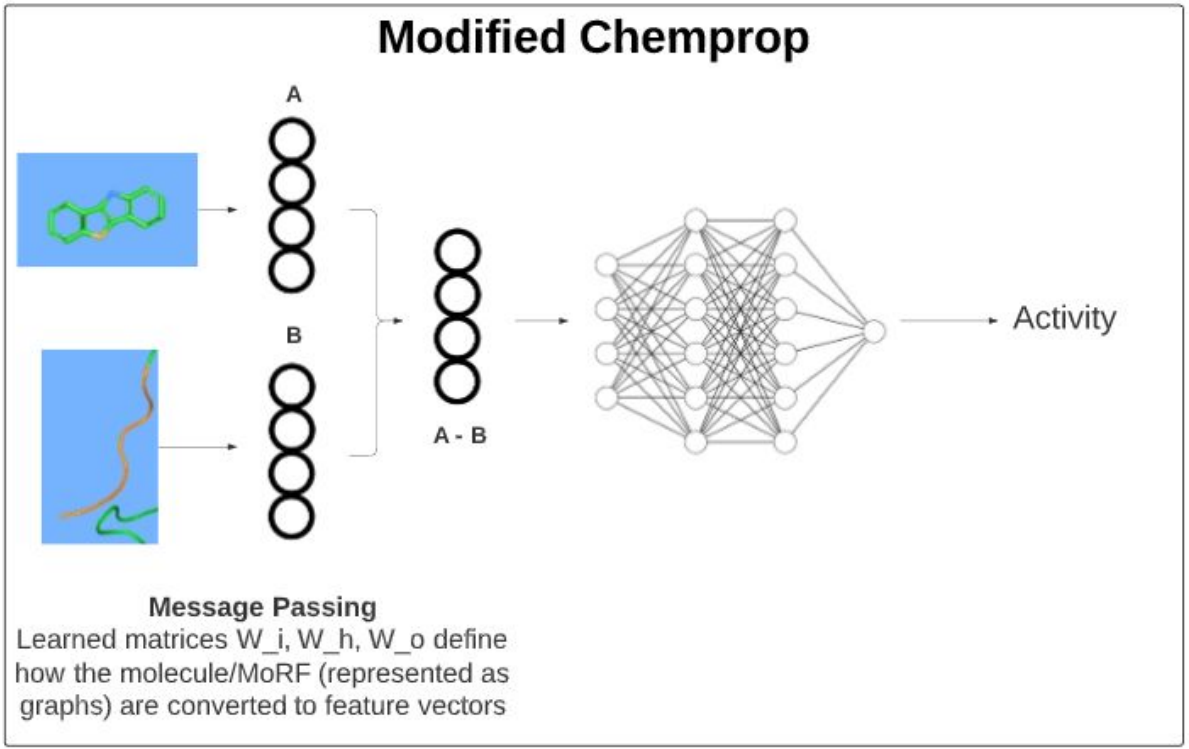


Biomimicry





The model


Modified Chemprop
A
B
A - B
Activity
Message Passing
Learned matrices W_i, W_h, W_o define how the molecule/MoRF (represented as graphs) are converted to feature vectors

Data

N = 7046

Each datapoint: ((ligand, MoRF), 0/1)

Bioassays 625185, 765185, 363

Total size = 7,045 | train size = 5,636 | val size = 704 | test size = 705

Results

Accuracy

Best validation AUC = 0.928 on epoch 29 (of 30).

Test AUC = 0.918

Previous work: .907

Pacific Symposium on Biocomputing

Mudide, Anish. et al. “SARS-CoV-2 Drug Discovery Based On Intrinsically Disordered Regions”, *Pac Symp Biocomput*, 2020.

Acknowledgements

Ning Xie and Ling Teng

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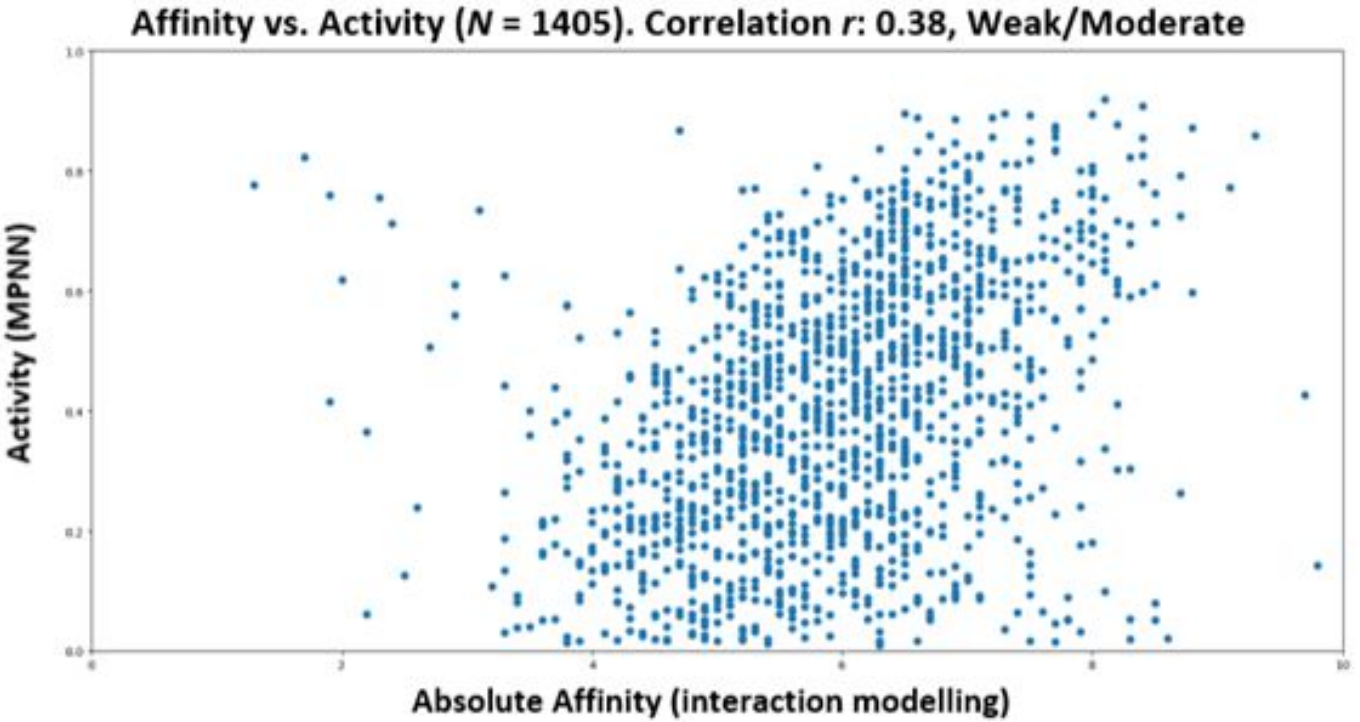
MIT PRIMES

My mom, dad and brother

Supplemental

Link between IDR affinity & 3CLpro inhibition score



Code

Molecular docking: https://github.com/Biomedical-Cybernetics-Lab2/IDR-SARS-CoV-2.

Modified chemprop for biomimicry: https://github.com/amudide/chemprop.

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