

# Accurate Contact/Distance Prediction by tFold

### tFold develop team:

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### **CASP14 Conference**

2020.12.03





# **Acknowledgement to CASP14 Organizers**

#### **CASP Organizers**



John MOULT President, University of Maryland, USA



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Andriy KRYSHTAFOVYCH University of California, Davis, USA



Torsten SCHWEDE University of Basel SIB Swiss Institute of **Bioinformatics** Switzerland



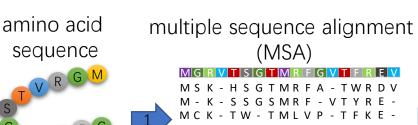
**Mava TOPF** Birkbeck, University of London, UK CSSB (HPI and UKE) Hamburg, Germany

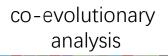
### **Contact-prediction Section Chair**



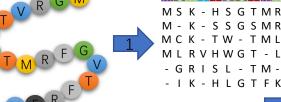
Affiliation: Toyota Technological Institute at Chicago

- Seq -> MSA MSA -> Feat Feat -> Cont
  - Cont -> Decoy





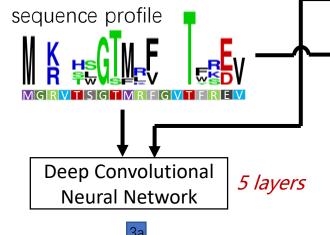




- G R I S L - T M - V G - T F S D -- I K - H L G T F K F T L T W S E V

1) Original model

# Contact-assisted de novo folding

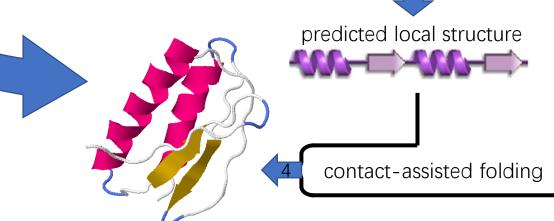


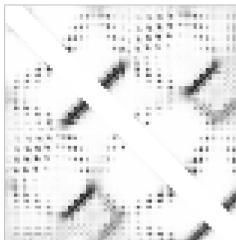
Deep Convolutional **Neural Network** 

60 layers



predicted contact







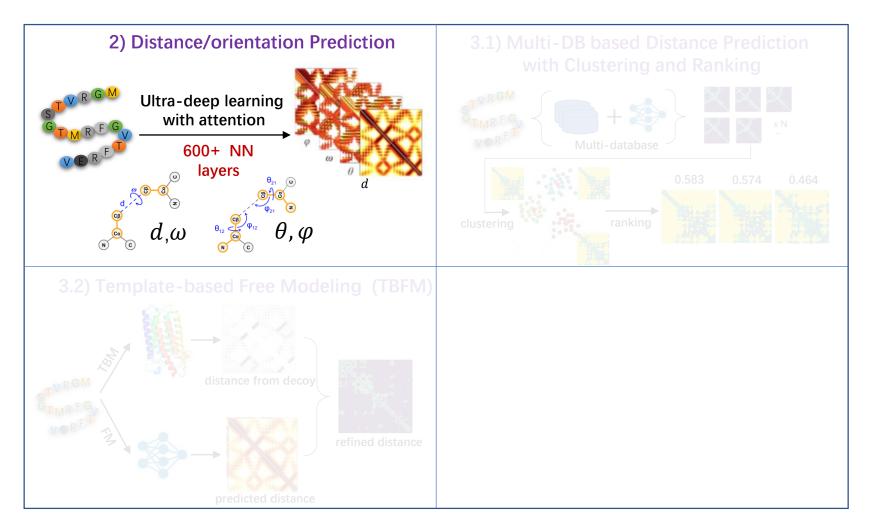
# Candidate issues of my previous work

- Contact V.S. distance/orientation
- Shallow network architecture

- Insufficient data usage
  - a. More input MSAs
  - b. More input decoys

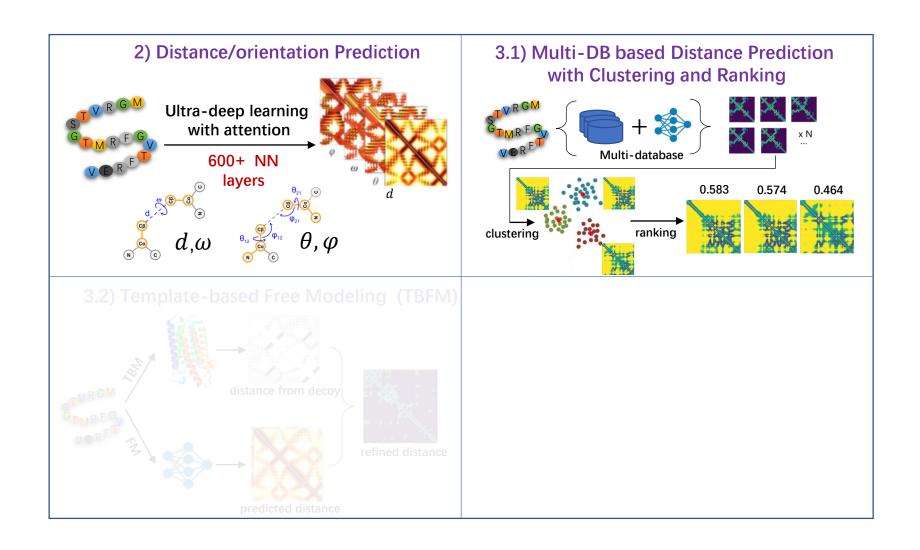


## New developments in tFold contact prediction



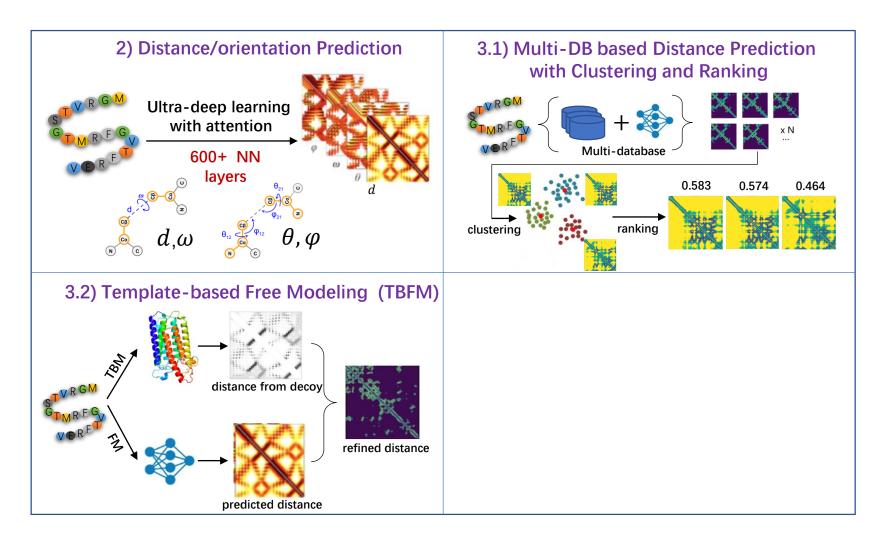


### New developments in tFold contact prediction



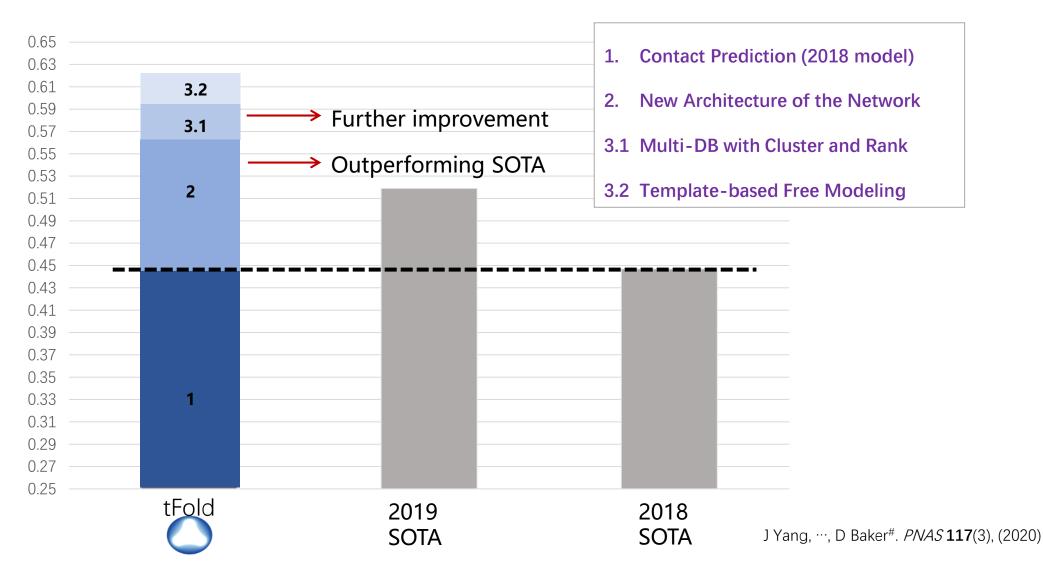


### New developments in tFold contact prediction





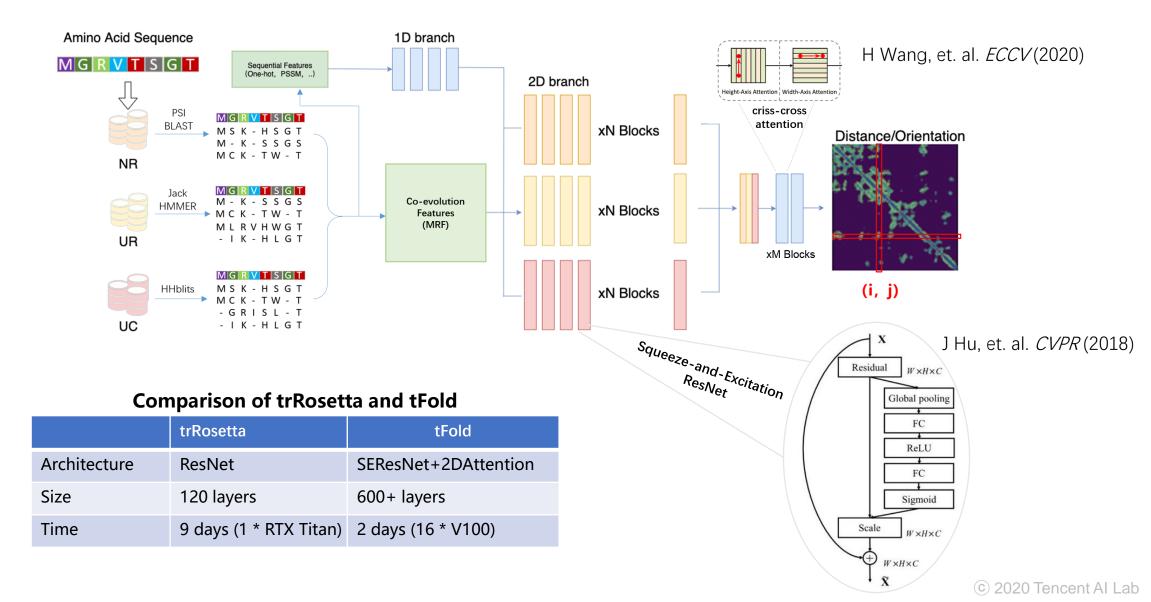
# **TopL Long Range Contact Precision**



Data draw using CASP13 targets

# tFold: Distance/Orientation Prediction with SEResNet+2DAttention with a Multi-input Multi-task Scheme







### **Ablation study of the Deep Learning model**

#### a) Data construction:

Construct MSAs from multi databases

• • •

#### b) Network architecture and loss design:

- SE ResNet module
- 2D Attention module
- Multi-task learning

• • •

### c) Training strategy:

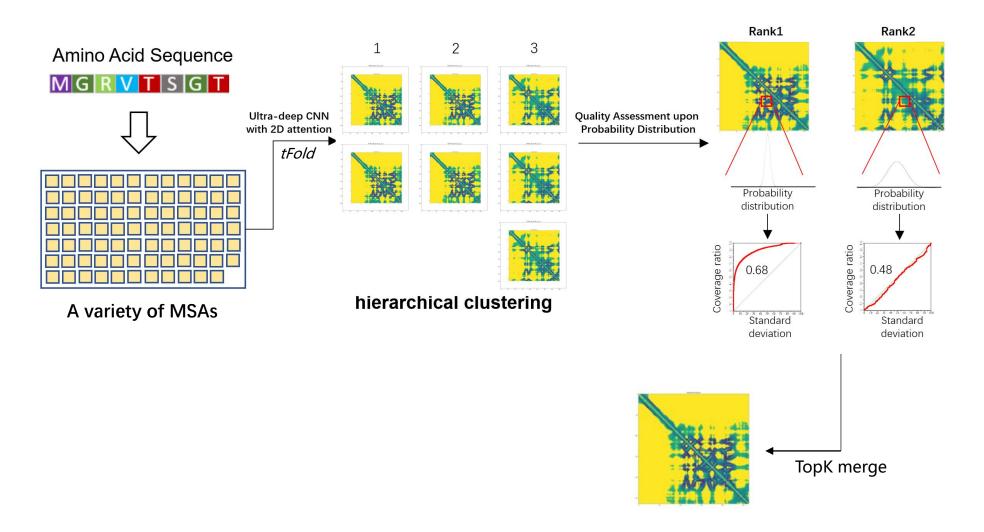
- Progressive training strategy
- 600+ layer ultra-deep network

• •

Model	CASP13 TopL long range contact				
Baseline model	51.32% ~ 2019 SOTA				
Baseline + a)	53.67%				
Baseline + a) + b)	55.15%				
Baseline + a) + b) + c)	56.37%				

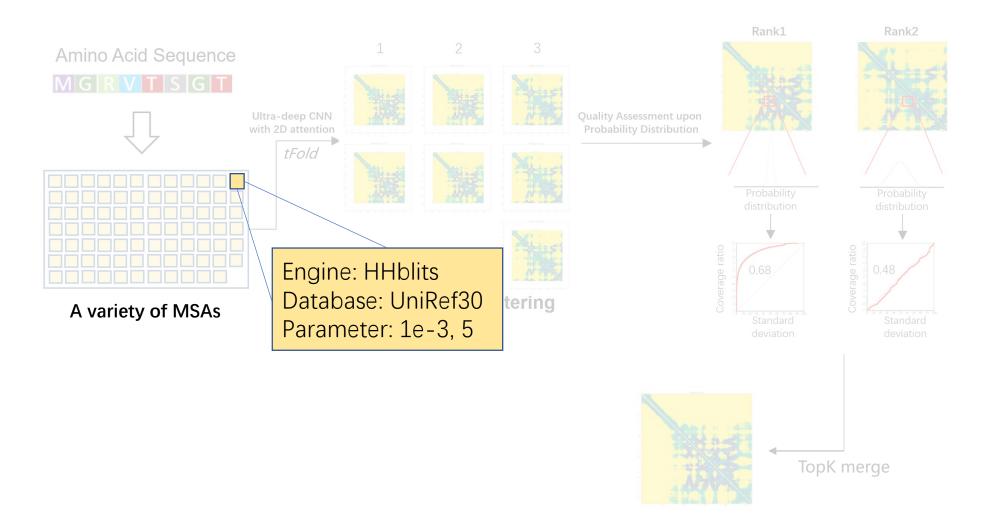






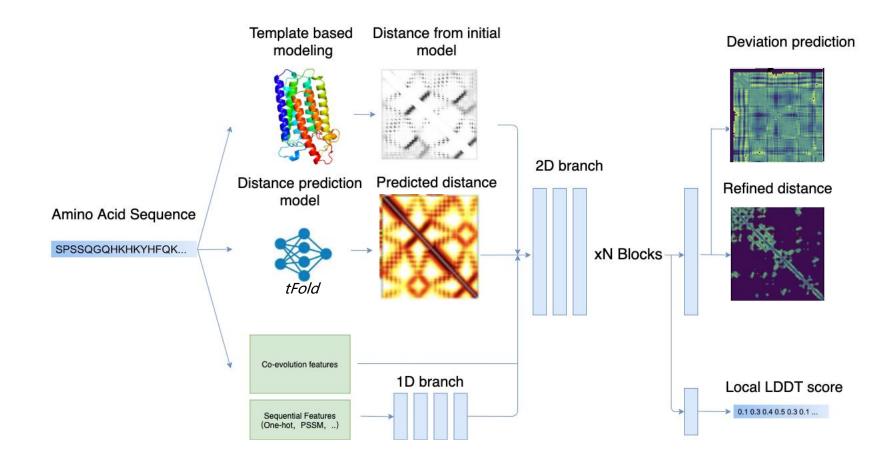
# tFold-CaT: Multi-DB based Distance Prediction with Clustering and Ranking





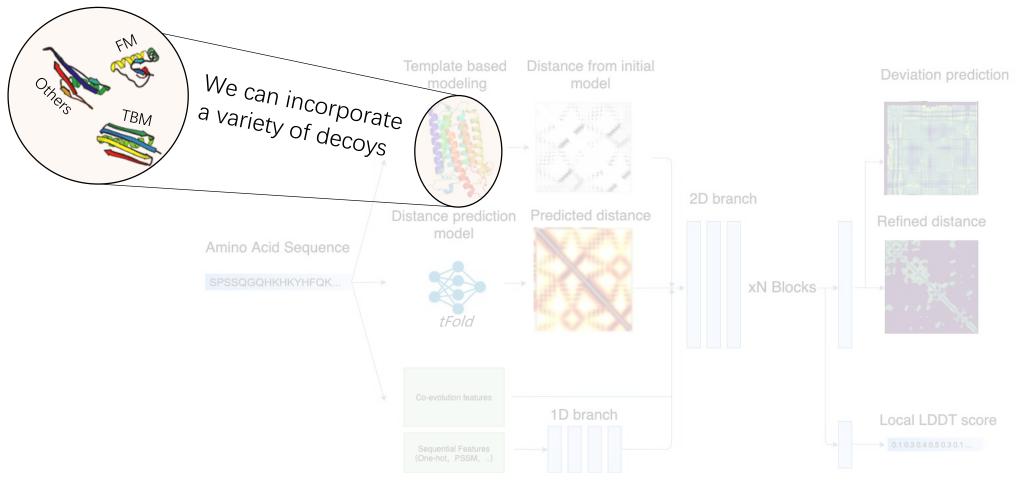


### tFold-IDT: Template-based Free Modeling (TBFM)





### tFold-IDT: Template-based Free Modeling (TBFM)





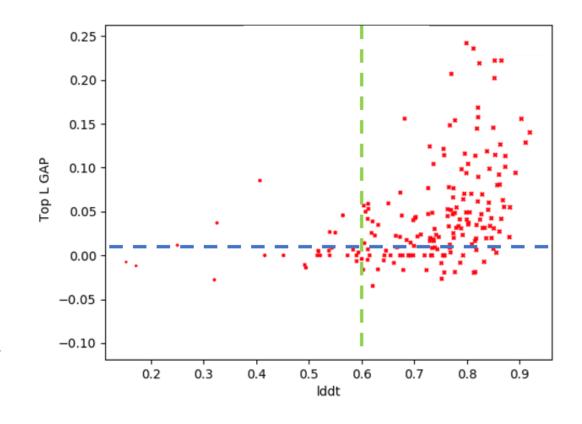
# The relationship between the decoy quality and the distance prediction enhancement

- High quality decoy significant enhance
- Low quality decoy

won't influence much

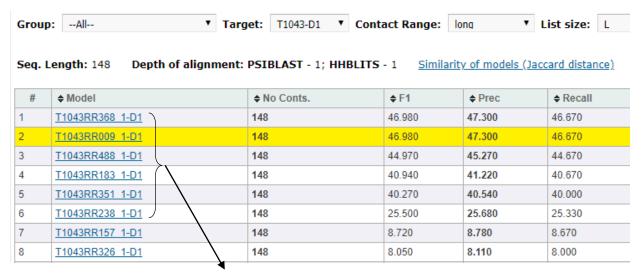


The robustness of our algorithm with respect of the decoy quality

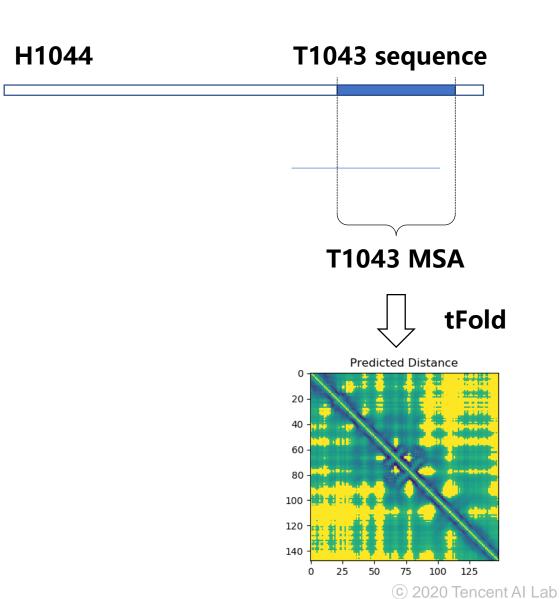




# What goes right and why?

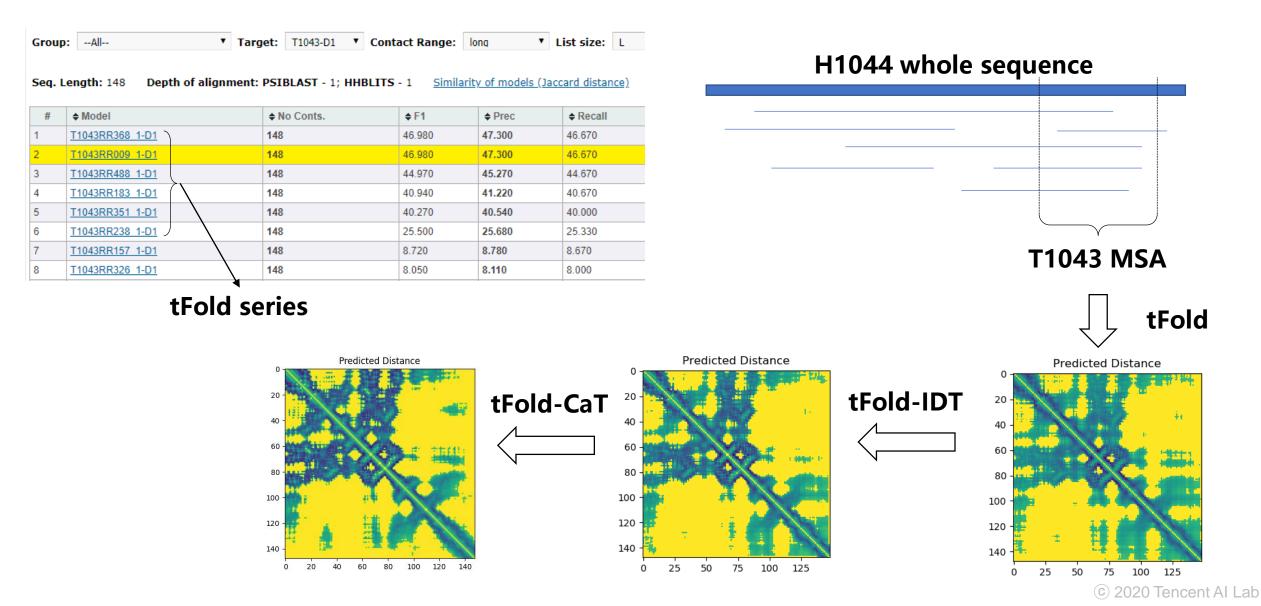


tFold series



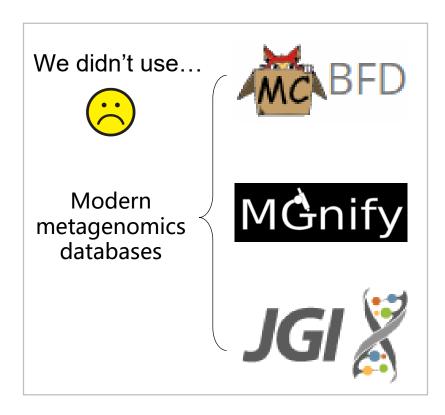


# What goes right and why?





### What goes wrong and why?



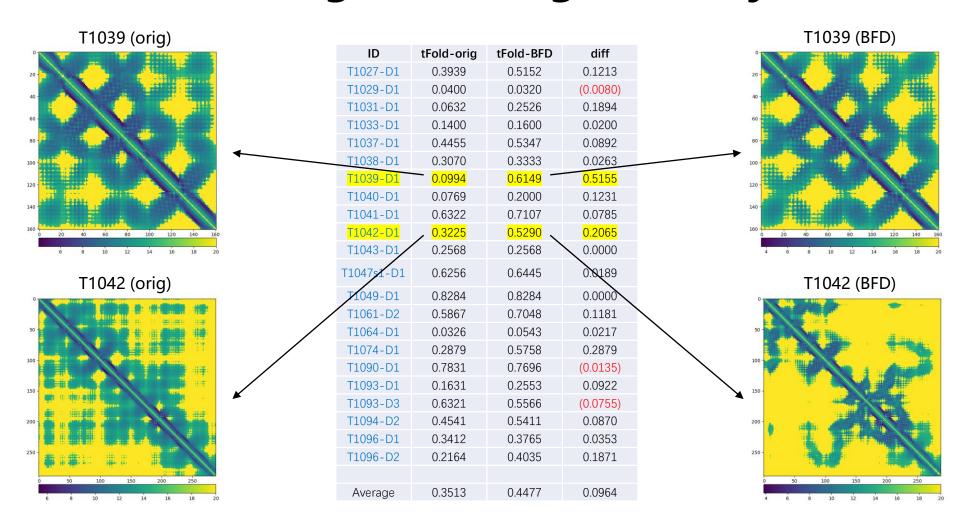
ID	TripleRes	tFold-orig	tFold-BFD	diff
T1027-D1	0.4343	0.3939	0.5152	0.1213
T1029-D1	0.0560	0.0400	0.0320	(0.0080)
T1031-D1	0.3789	0.0632	0.2526	0.1894
T1033-D1	0.1200	0.1400	0.1600	0.0200
T1037-D1	0.5767	0.4455	0.5347	0.0892
T1038-D1	0.2719	0.3070	0.3333	0.0263
T1039-D1	0.4596	0.0994	0.6149	0.5155
T1040-D1	0.4000	0.0769	0.2000	0.1231
T1041-D1	0.6901	0.6322	0.7107	0.0785
T1042-D1	0.4891	0.3225	0.5290	0.2065
T1043-D1	0.0473	0.2568	0.2568	0.0000
T1047s1-D1	0.4834	0.6256	0.6445	0.0189
T1049-D1	0.7388	0.8284	0.8284	0.0000
T1061-D2	0.7232	0.5867	0.7048	0.1181
T1064-D1	0.0652	0.0326	0.0543	0.0217
T1074-D1	0.3864	0.2879	0.5758	0.2879
T1090-D1	0.6138	0.7831	0.7696	(0.0135)
T1093-D1	0.0284	0.1631	0.2553	0.0922
T1093-D3	0.0566	0.6321	0.5566	(0.0755)
T1094-D2	0.6473	0.4541	0.5411	0.0870
T1096-D1	0.5569	0.3412	0.3765	0.0353
T1096-D2	0.4971	0.2164	0.4035	0.1871
Average	0. 3964	0.3513	0.4477	0.0964

			No. Domains		F1		Prec	
#	♦ Gr.#	♦ Gr. Name	♦ No Submit.	♦ No Total	<b>♦ Submit.</b>		<b>♦ Submit.</b>	▼ Total
1.	368	tFold-CaT_human	22	22	41.158	41.158	41.783	41.783
2.	488	tFold-IDT_human	22	22	39.374	39.374	40.504	40.504
3.	010	TripletRes	22	22	39.282	39.282	39.641	39.641
4.	125	PreferredFold	22	22	38.696	38.696	39.440	39.440
5.	024	DeepPotential	22	22	38.286	38.286	38.586	38.586
6.	009	tFold_human	22	22	36.821	36.821	38.056	38.056
7.	183	tFold-CaT	22	22	35.465	35.465	37.107	37.107
8.	351	tFold-IDT	22	22	34.774	34.774	36.516	36.516
9.	238	tFold	22	22	33.548	33.548	35.130	35.130

tFold-orig only uses metaclust50 (year 2018) as the metagenomics databases. tFold-BFD adds BFD (year 2019) as the additional metagenomics databases.



### What goes wrong and why?



tFold-orig only uses metaclust50 (year 2018) as the metagenomics databases. tFold-BFD add BFD (year 2019) as the additional metagenomics databases.



### Take home messages

- Distance/orientation matters.
- Deeper and attention-based network works.
- Sufficient data usage will increase the robustness:
  - a. More input MSAs
  - b. More input decoys



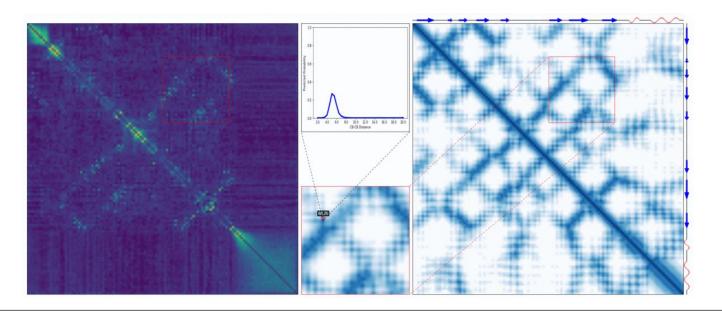
# Accurate De Novo Protein Structure Prediction by tFold Server

https://drug.ai.tencent.com/console/en/tfold

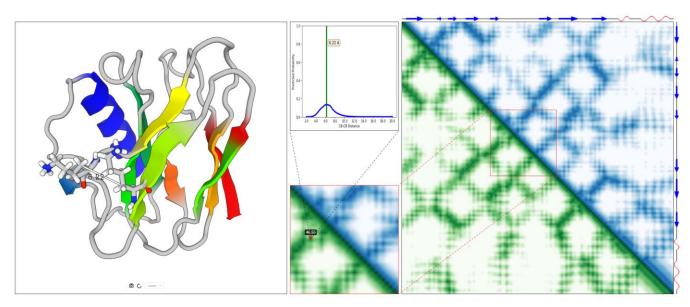
O iDrug	Protein Structure Prediction Histor	ry				中   EN User Guide Feedback 🜲 🛑 realbigws				
<ul> <li>◆ Protein Structure Pr</li> <li>⇒ Virtual Screening</li> <li>✓ Generative Chemistry</li> </ul>	Predicting the 3D structure of a protein from its amino acid sequence is called protein structure prediction, which is one of the most important goals pursued by bioinformatics and theoretical chemistry. Protein structure prediction is a very important tool in medicine (for example, drug design) and in biotechnolone we enzymes). In order to accurately predict protein structure, this module uses three innovative techniques to improve modeling accuracy. First, we developed a multi-source fusion technology to mine the co-evolutionary information in multiple sets of Multiple Sequence Alignments (MSA); then, with the help of residual network, we may significantly increase the prediction accuracy of some important 2D structural information such as the residue-residue distance and orientation matrix of the protein structure; finally, we effectively merge the structural information embedded in the 3D models generated by Free Modeling (TBM) approach, which greatly improves the final 3D Modeling accuracy.									
ADMET Prediction	Task Name									
₩ Synthetic Route Pla	Input AminoAcid Sequence Sequence	h								
	Select File  Click to Upload fastalt-d/seqfles file with a size less  Predict	is than 10MB								
	Recent History only display the last 10 records Create Time	s, you can also check the <b>all history</b> Status	Unique ID	Task Name	Progress	Actions				
	2020-11-23 22:38:47	completed	5VTE4uAv	PbSRD5A de novo folding		Check Delete				
	2020-11-23 22:36:57	completed	62uRsFB5	PbSRD5A de novo folding		Check Delete				
	2020-11-16 14:26:12	completed	4bwey2Kh	ttt		Check Delete				
	2020-11-12 22:47:09	completed	7J2eVktl	PbSRD5A de novo prediction		Check Delete				
	2020-11-12 19:25:24	completed	рохМесР9	protein test		Check Delete				
	2020-11-10 19:05:34	completed	vrVj1wgC	PbSRD5A test2		Check Delete				
	2020-11-07 14:10:39	completed	6jkGXjnv	test21		Check Delete				
<						*				

### From MRF to Distance



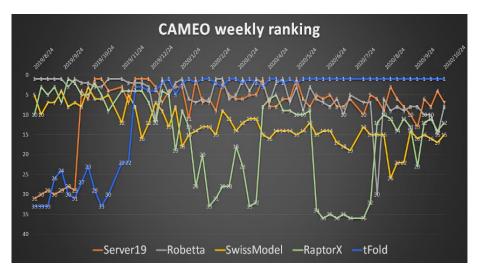


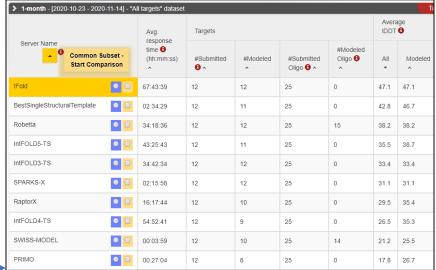
### From Distance to 3D model



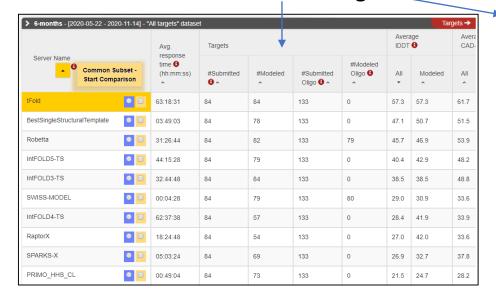


### **Excellent performance of tFold Server on CAMEO**





#### **Performance on hard targets**



<b>→ 3-months</b> - [2020-08-21 - 202	20-11-14] - "	All targets" datase	et					Ta
		Avg.	Targets				Average IDDT 3	
Server Name  Common S  Start Comp		response time (1) (hh:mm:ss)	#Submitted	#Modeled	#Submitted Oligo 😉 ^	#Modeled Oligo 😉	All 🕶	Modeled
tFold	• •	59:16:17	42	42	76	0	55.5	55.5
BestSingleStructuralTemplate	•	03:10:03	42	38	76	0	46.9	51.8
Robetta	•	29:58:37	42	42	76	47	46.6	46.6
IntFOLD5-TS	•	39:26:14	42	41	76	0	41.4	42.4
IntFOLD3-TS	•	32:26:40	42	42	76	0	37.8	37.8
RaptorX	•	14:58:13	42	38	76	0	37.3	41.2
IntFOLD4-TS	•	56:41:27	42	33	76	0	33.0	41.9
SWISS-MODEL	•	00:04:43	42	39	76	45	27.1	29.2
SPARKS-X	•	05:40:16	42	27	76	0	21.4	33.4
PRIMO_HHS_CL	•	00:51:16	42	35	76	0	21.3	25.5



Junhong Huang



Tao Shen



Junzhou Huang



Wei Liu



Jiaxiang Wu



Jianguo Pei



Ningqiao Huang



Haidong Lan







Liangzhen Zheng



Yuyi Liu



Zhenlei Xu



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Sheng Wang