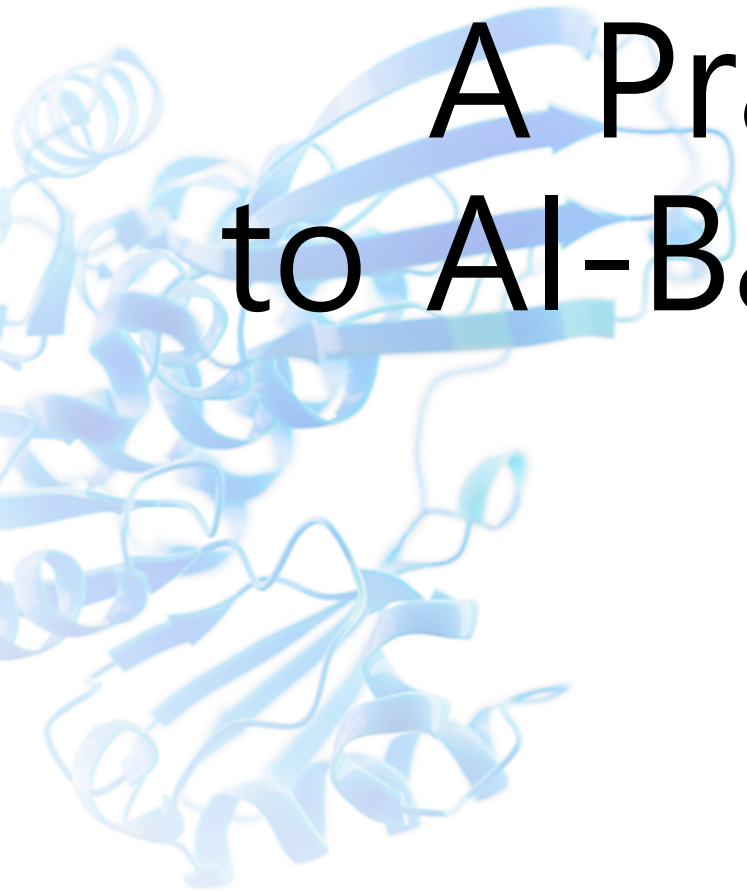
한국응용생명화학회
The Korean Society for Applied Biological Chemistry



A Practical Introduction to AI-Based Protein Structure Prediction

2025-11-28

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Korea Institute of Science and Technology

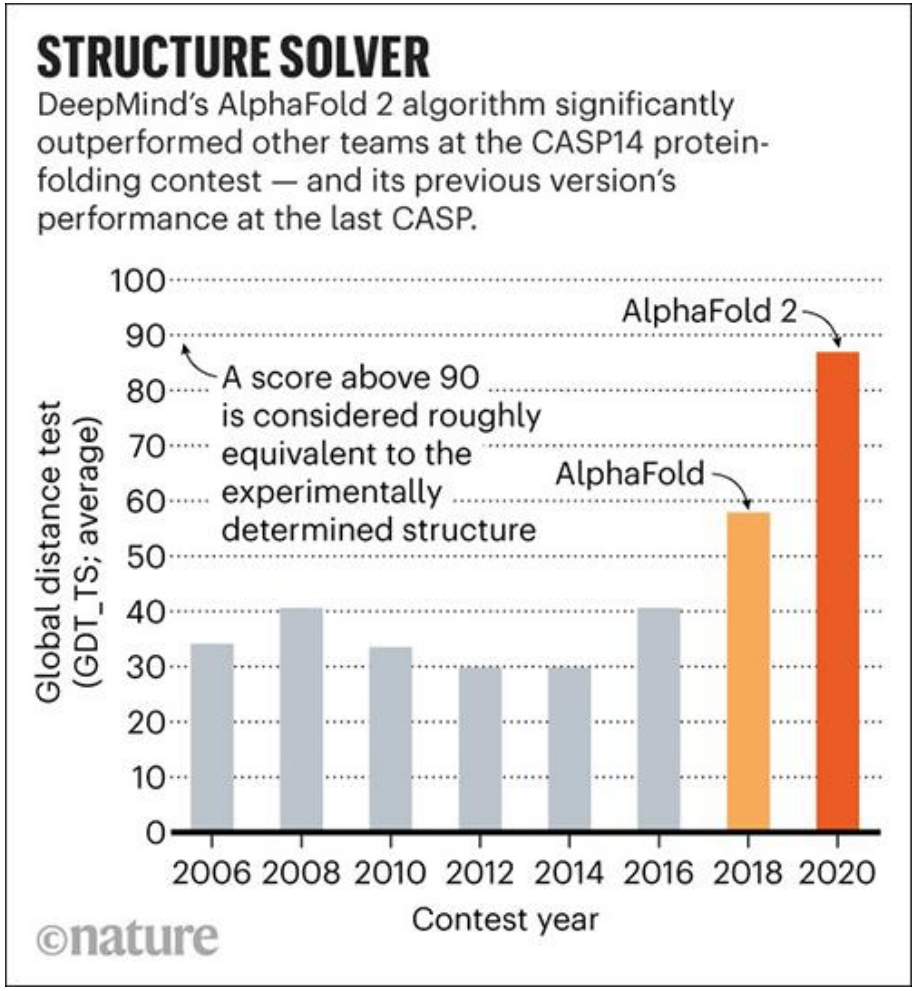
Contents

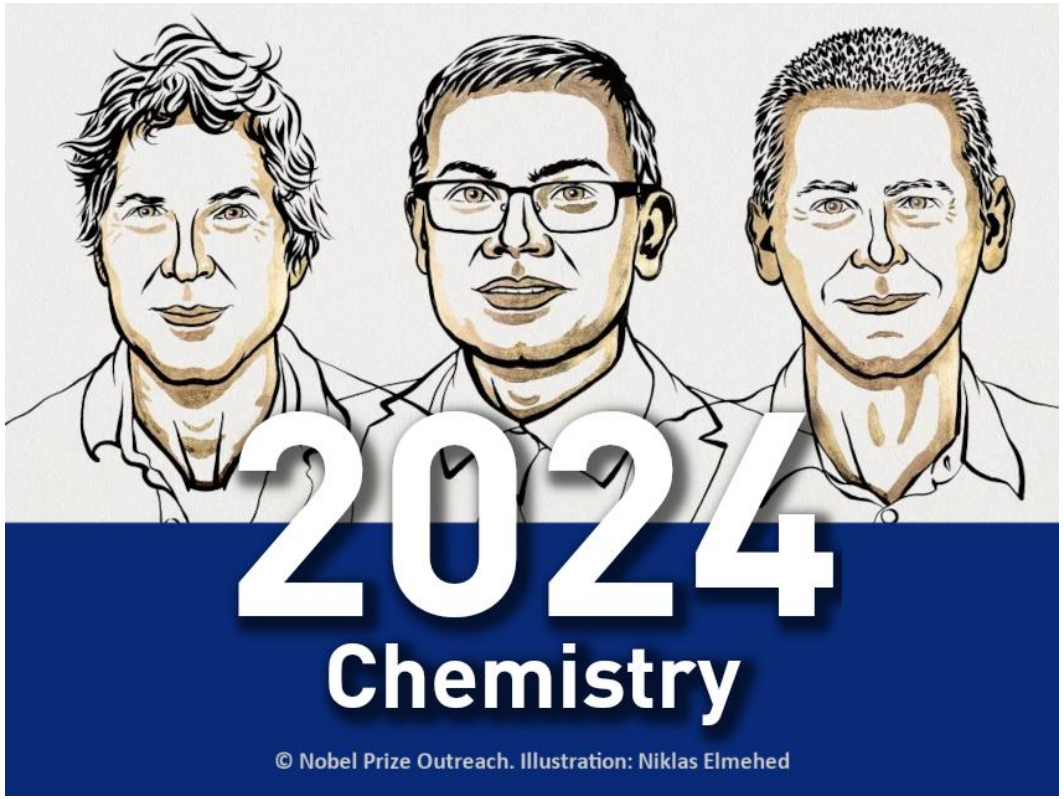
- Introduction
  - Overview of Alphafold
  - 연구 활용 사례 (Glutamine binding protein)

- Cloud-based 환경에서 단백질 구조예측 사용하기
  - Alphafold server 사용하기
  - Other Cloud models

- On-premises 환경에서 Alphafold3 사용하기
  - Docker로 Alphafold3 환경 구성하기
  - input json 파일 작성
  - docker 명령어 작성
  - Alphafold3 예제

Alphafold

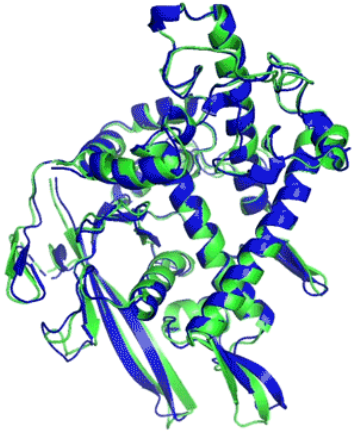




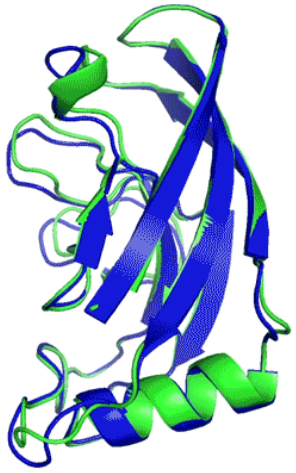
50년 이상의 난제 "단백질 폴딩 문제"
단백질 서열로 3D 구조 예측 어려움

Alphafold 3 등장 배경

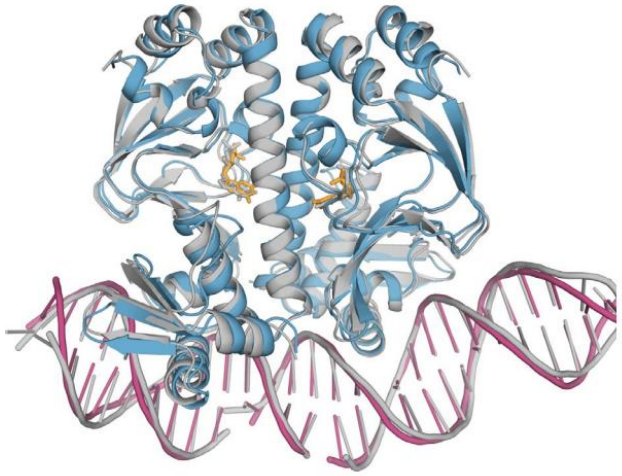
- Alphafold 2의 등장(2020), 단백질 단일 사슬 구조예측도가 혁신적으로 향상
- 단백질과 이종 분자(리간드, 핵산(DNA/RNA), 이온)와의 상호작용 구조 예측이라는 과제가 남아 있었음



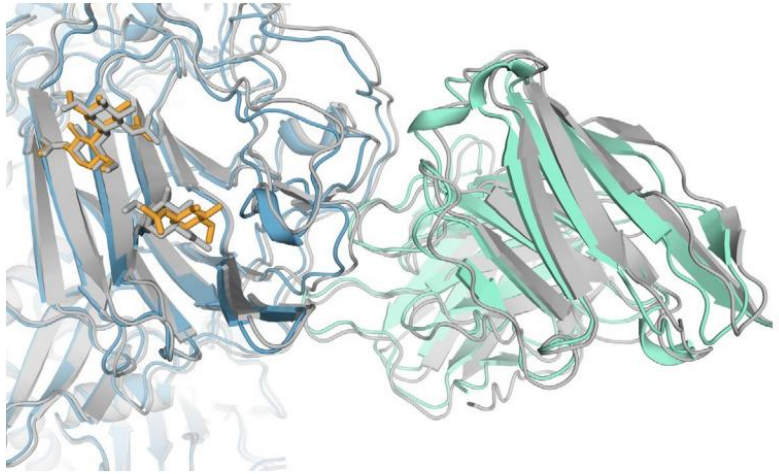
T1037 / 6vr4
90.7 GDT
(RNA polymerase domain)



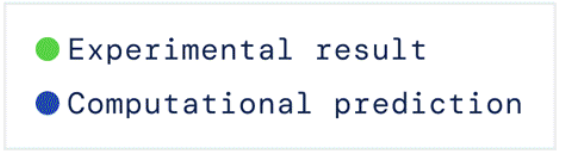
T1049 / 6y4f
93.3 GDT
(adhesin tip)



Bacterial CRP/FNR family transcriptional regulator protein bound to DNA and cGMP



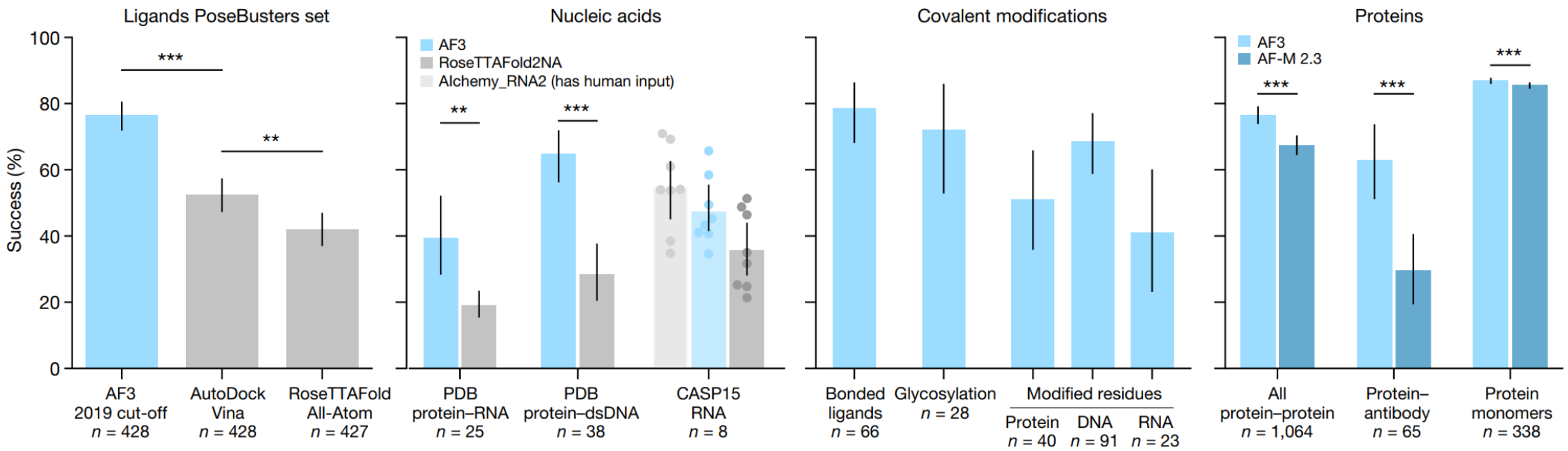
Human coronavirus OC43 spike protein, 4,665 residues, heavily glycosylated and bound by neutralizing antibodies



Abramson et al., *Nature* 630, 493–500 (2024).

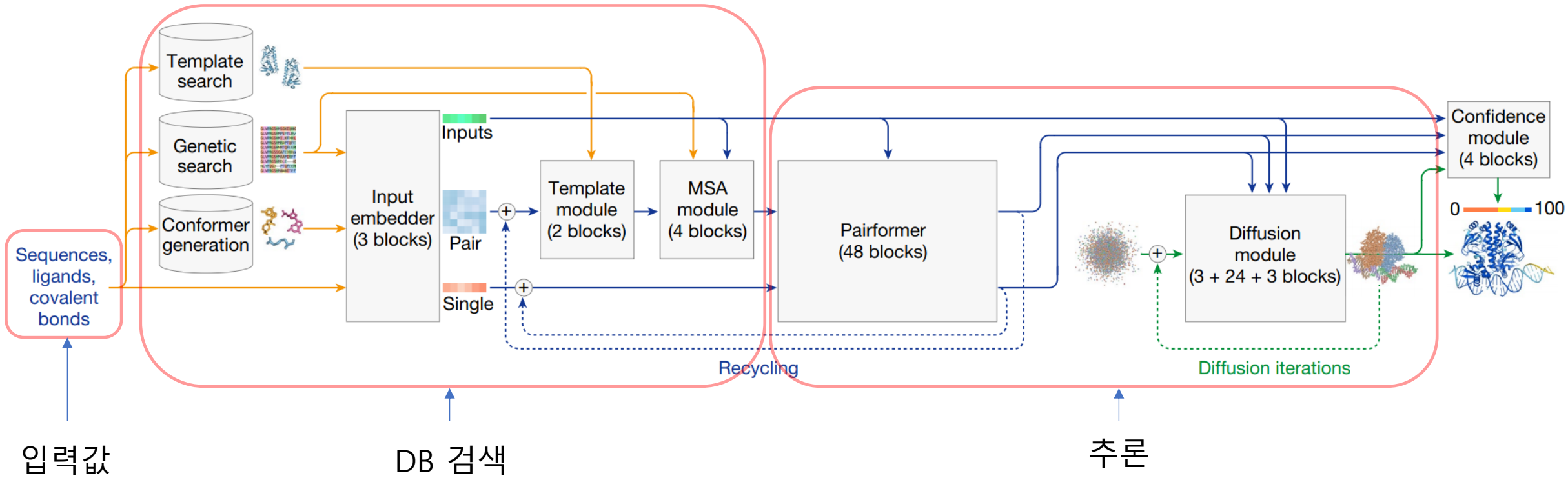
Alphafold 3의 성능 및 특징

- 예측 정확도 향상
- 단백질-단백질과 단백질-이종 분자(리간드, 핵산(DNA/RNA), 이온)간 복합체 모델링 가능
- Post-translational modification (PTM) 가능
- 항원-항체 상호작용 모델링 가능



Abramson et al., *Nature* 630, 493–500 (2024).

Alphafold 3의 기본 작동 구조



Abramson et al., *Nature* 630, 493–500 (2024).

Alphafold의 연구 활용 사례

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Check for updates

Enhancing protein structural properties through model-guided sequence optimization

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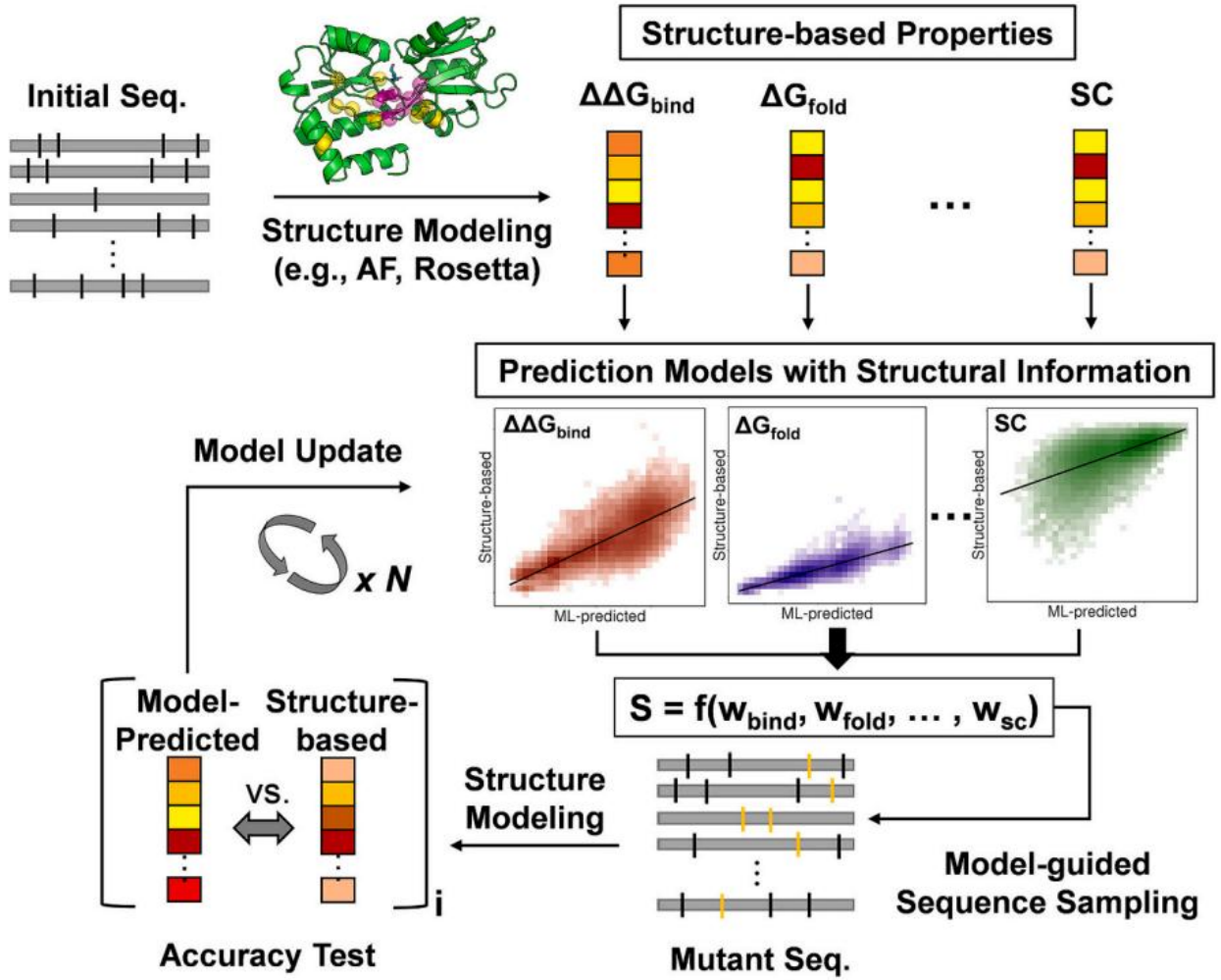
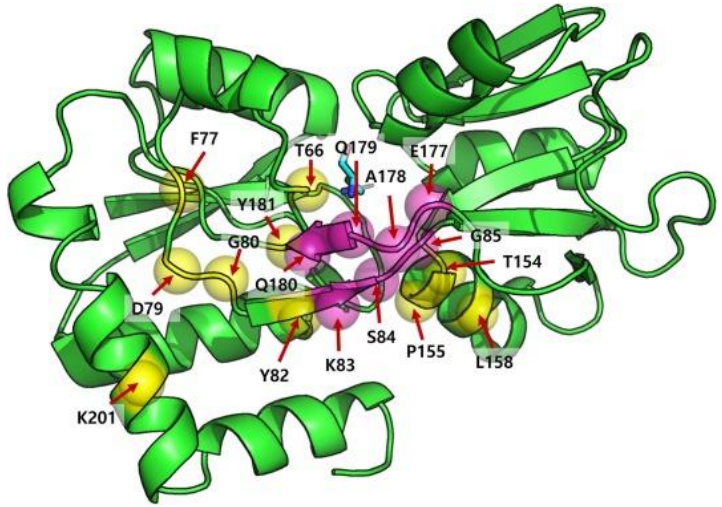
Alphafold의 연구 활용 사례



Overview of the sequence optimization workflow for improving protein structural properties

Mutation sites selected in glutamine-binding protein



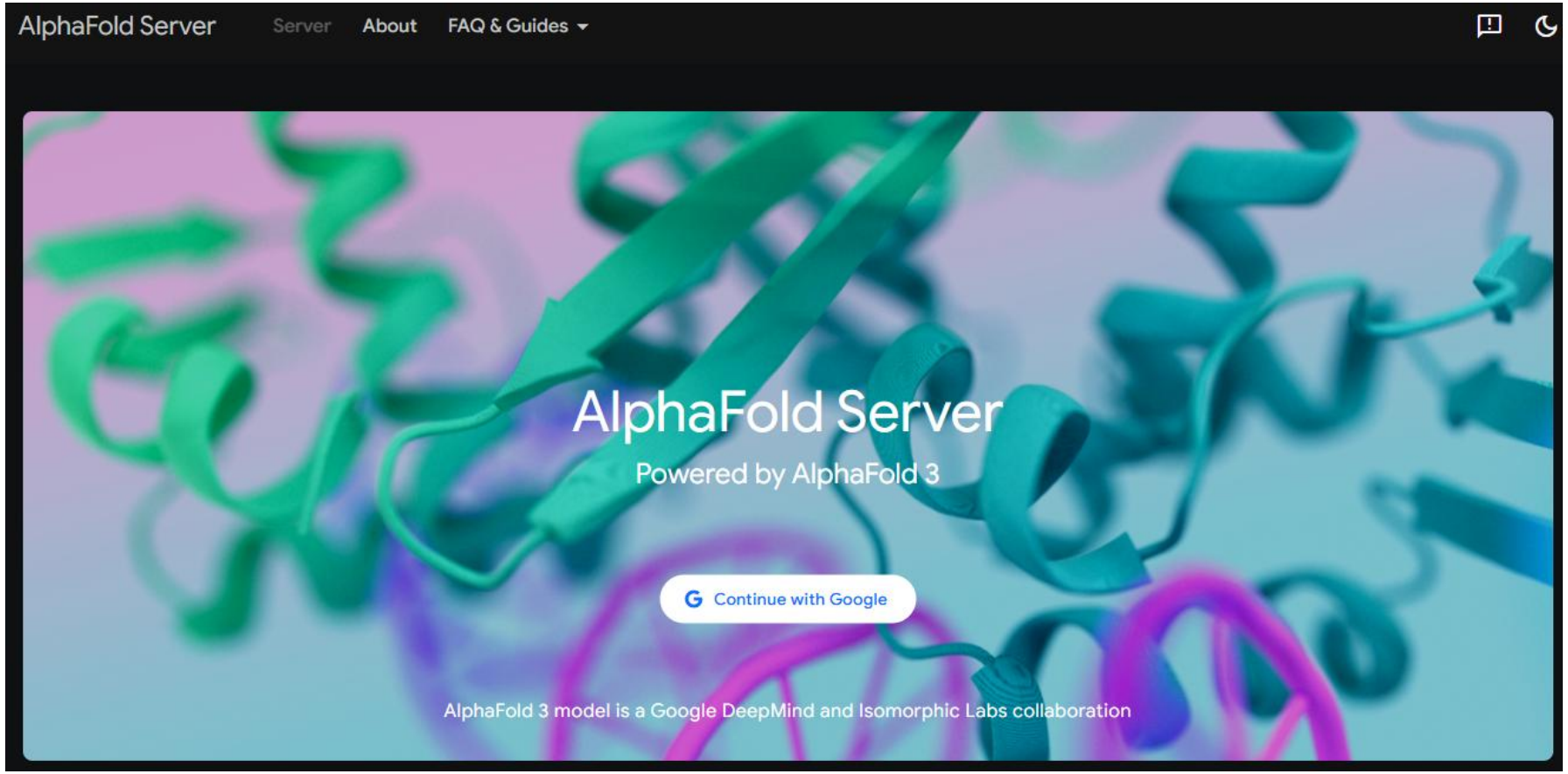
Potential structural determinants and additional scoring metrics associated with the observed thermal stability (T_m) values.

Scores	Description	Pearson's r	*p*-value
SMINA score (AF3-SMINA)	SMINA local minimization score for AF3 -predicted model	−0.814	0.002
Total Score (AF3-Rosetta)	Rosetta total score for relaxed AF3-pre dicted model	−0.687	0.014
omega (AF3-Rosetta)	Rosetta omega term for relaxed AF3-pr edicted model	−0.637	0.024
Normalized interface energy (AF3-Rosetta)	Rosetta interface energy for relaxed AF 3-predicted model	−0.583	0.038
Total Score (Rosetta, binding site fixed)	Rosetta total score for relaxed Rosetta model structure fixing binding site geo metry	−0.527	0.059
ProGen2 score (Sequence)	ProGen2 sequence likelihood score	0.508	0.067
fa_atr (AF3-Rosetta)	Rosetta Lennard-Jones attractive potent ial for relaxed AF3-predicted model	−0.445	0.099

Alphafold 3 사용하기

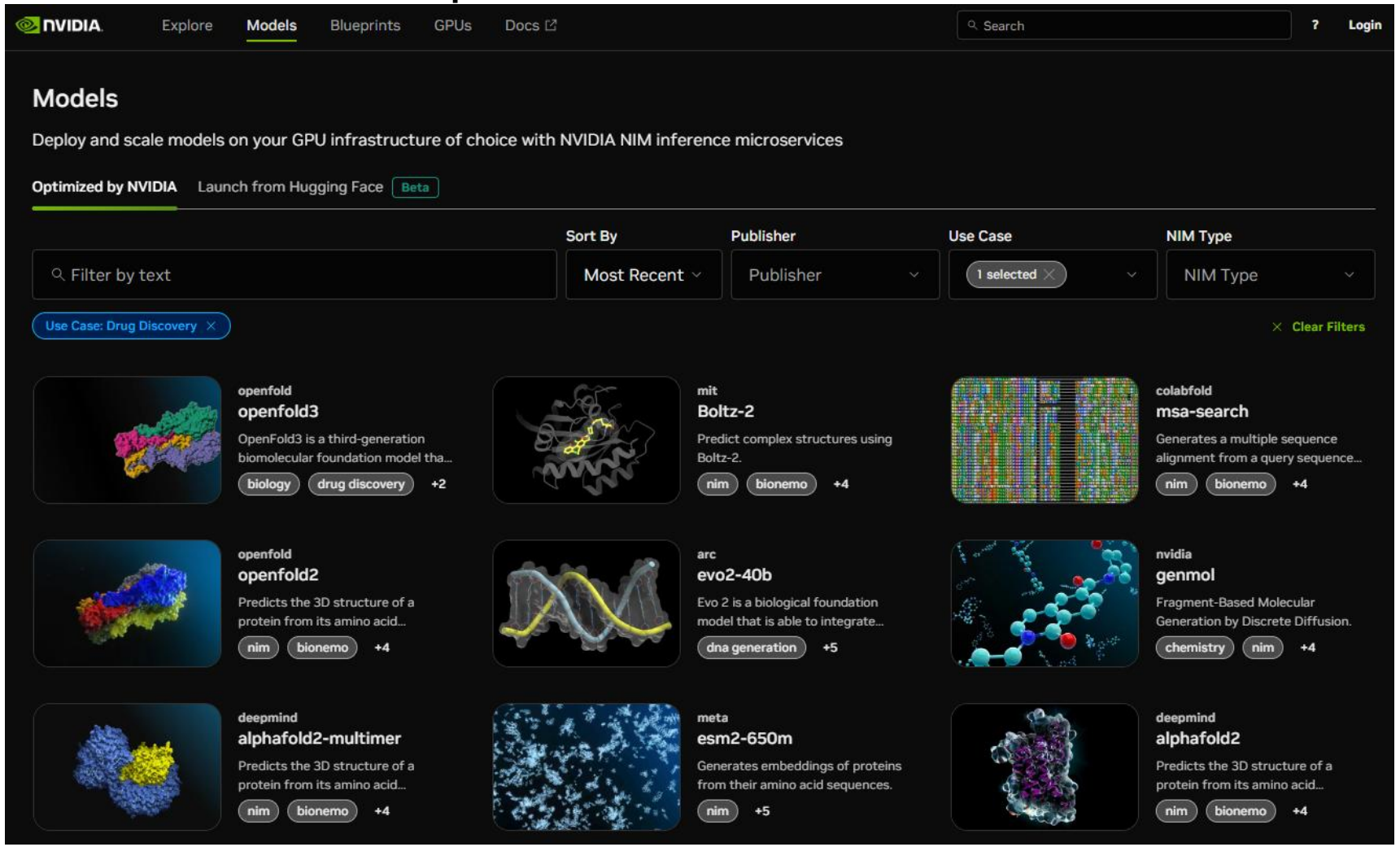
Cloud 환경에서 단백질 구조예측 사용하기

- Alphafold server : https://alphafoldserver.com/



Cloud 환경에서 단백질 구조예측 사용하기

- NVIDIA models : https://build.nvidia.com/models



Alphafold3 사용하기
- On-premises 환경

On-premises 환경에서 Alphafold3 사용하기

- Alphafold3 github URL
  - https://github.com/google-deepmind/alphafold3

- 권장사양
  - GPU : RTX 3090 or 4090 VRAM 8-12GB
  - CUDA : 12.6
  - Modern Multi-core CPU
  - System RAM : 32GB
  - HDD for DB : 630GB

가상화 환경

- **도커(Docker)**? - 컨테이너 기반 가상화 플랫폼
  - 응용 프로그램과 그 종속성을 격리된 환경인 **컨테이너**로 패키징하여 실행하는 기술
  - 응용 프로그램을 **서로 다른 환경**에서도 일관되게 실행
  - **가볍고 빠르며 확장성이** 좋아서 개발 및 **배포** 프로세스를 **간소화**하는 데 사용된다.

On-premises 환경에서 Alphafold3 사용하기

준비물

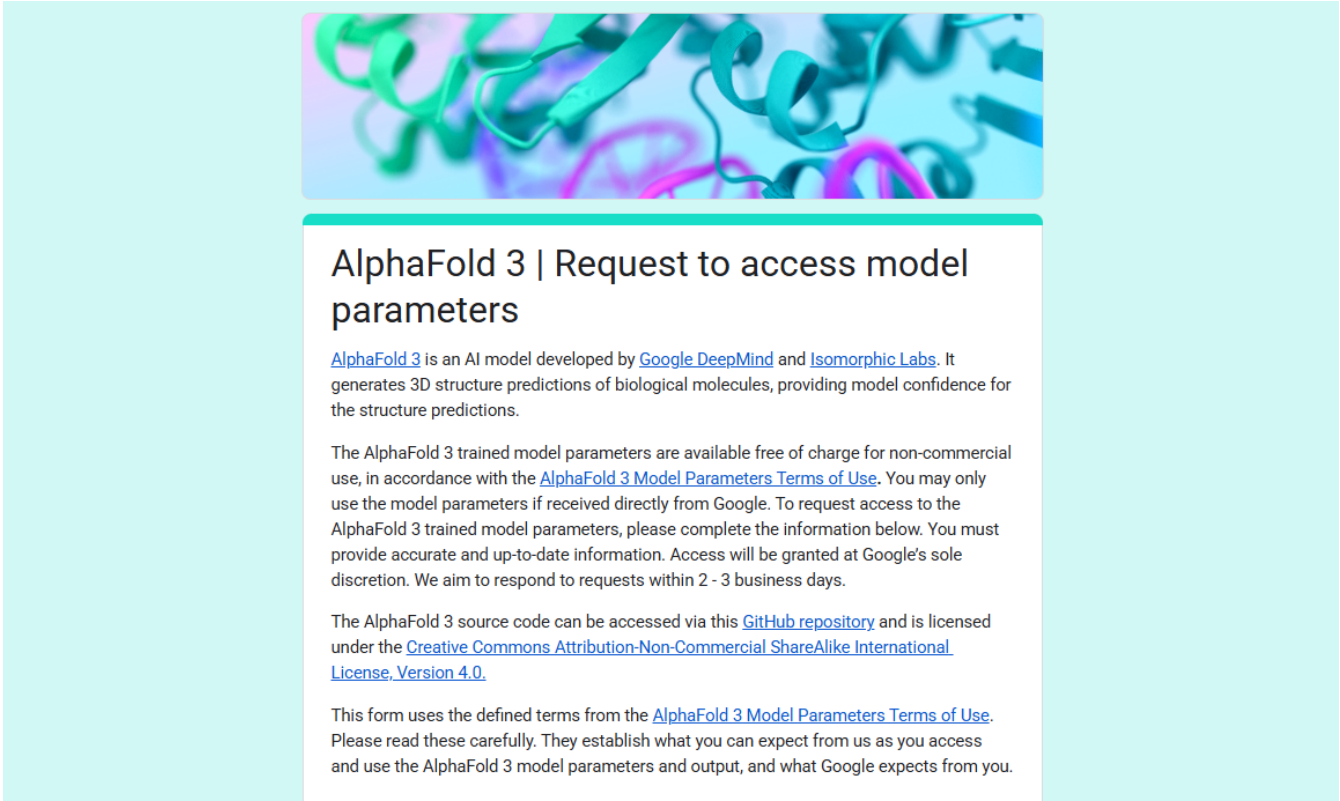
- Database
  - BFD, PDB, Mgnify, UniProt, UniRef, Rfam, NT, RNACentral 등
- Model parameter
  - Apply form link : https://forms.gle/svvpY4u2jsHEwWYS6
- Docker images
  - Alphafold3 실행환경과 알고리즘이 담겨있는 가상화 이미지
- JSON 파일
  - 서열, smile, PTM, MSA 등 예측을 위한 정보가 담겨있는 파일
- Docker command
  - DB 경로, Model parameter 경로, 작업 경로, 결과물 경로를 지정하여 Docker 환경에서 Alphafold3를 실행하는 명령어

On-premises 환경에서 Alphafold3 사용하기

- Database
  - Link : https://storage.googleapis.com/alphafold-databases/v3.0
  - BFD, PDB, Mgnify, UniProt, UniRef, Rfam, NT, RNACentral 등 데이터베이스
    - pdb_2022_09_28_mmcif_files.tar.zst
    - mgy_clusters_2022_05.fa
    - bfd-first_non_consensus_sequences.fasta
    - uniref90_2022_05.fa
    - uniprot_all_2021_04.fa
    - pdb_seqres_2022_09_28.fasta
    - rnacentral_active_seq_id_90_cov_80_linclust.fasta
    - nt_rna_2023_02_23_clust_seq_id_90_cov_80_rep_seq.fasta
    - rfam_14_9_clust_seq_id_90_cov_80_rep_seq.fasta
  - Database download
    - shell> bash fetch_databases.sh <download path>

On-premises 환경에서 Alphafold3 사용하기

- Model parameter
  - Alphafold3 model parameter
  - Apply form link : https://forms.gle/svvpY4u2jsHEwWYS6
  - Form 작성후 심사후 download



AlphaFold 3 | Request to access model parameters

AlphaFold 3 is an AI model developed by Google DeepMind and Isomorphic Labs. It generates 3D structure predictions of biological molecules, providing model confidence for the structure predictions.

The AlphaFold 3 trained model parameters are available free of charge for non-commercial use, in accordance with the AlphaFold 3 Model Parameters Terms of Use. You may only use the model parameters if received directly from Google. To request access to the AlphaFold 3 trained model parameters, please complete the information below. You must provide accurate and up-to-date information. Access will be granted at Google's sole discretion. We aim to respond to requests within 2 - 3 business days.

The AlphaFold 3 source code can be accessed via this GitHub repository and is licensed under the Creative Commons Attribution-Non-Commercial ShareAlike International License, Version 4.0.

This form uses the defined terms from the AlphaFold 3 Model Parameters Terms of Use. Please read these carefully. They establish what you can expect from us as you access and use the AlphaFold 3 model parameters and output, and what Google expects from you.

On-premises 환경에서 Alphafold3 사용하기

- JSON 파일
  - Sequence (Protein, DNA, RNA), Ligand, bonds 등 예측을 위한 정보가 담겨있는 파일
  - https://github.com/google-deepmind/alphafold3/blob/main/docs/input.md

The top-level structure of the input JSON is:

```
{
  "name": "Job name goes here",
  "modelSeeds": [1, 2],  # At least one seed required.
  "sequences": [
    {"protein": {...}},
    {"rna": {...}},
    {"dna": {...}},
    {"ligand": {...}}
  ],
  "bondedAtomPairs": [...],  # Optional.
  "userCCD": "...",  # Optional, mutually exclusive with userCCDPath.
  "userCCDPath": "...",  # Optional, mutually exclusive with userCCD.
  "dialect": "alphafold3",  # Required.
  "version": 4  # Required.
}
```

On-premises 환경에서 Alphafold3 사용하기

- Docker command
  - DB 경로, Model parameter 경로, 작업 경로, 결과물 경로를 지정하여 Docker 환경에서 Alphafold3를 실행하는 명령어

```
docker run -it \
    --volume $HOME/af_input:/root/af_input \
    --volume $HOME/af_output:/root/af_output \
    --volume <MODEL_PARAMETERS_DIR>:/root/models \
    --volume <DB_DIR>:/root/public_databases \
    --gpus all \
    alphafold3 \
    python run_alphafold.py \
    --json_path=/root/af_input/fold_input.json \
    --model_dir=/root/models \
    --output_dir=/root/af_output
```

Docker로 Alphafold3 환경 구성하기

- Docker로 Alphafold3 환경 구성하기
  - Docker image 생성
    - shell> git clone https://github.com/google-deepmind/alphafold3.git
    - shell> cd alphafold3
    - shell> docker build -t alphafold3 -f docker/Dockerfile .

  - Docker images pulling
    - shell> docker pull suppak/alphafold3:clean

Alphafold3 실행을 위한 json 파일 작성하기

- On-premises 환경에서 Alphafold3 사용하기
  - https://github.com/suppakoko/alphafold3_class/examples

- af3cli – json file 작성 도구
  - https://github.com/SLx64/af3cli
    - shell> git clone https://github.com/SLx64/af3cli.git

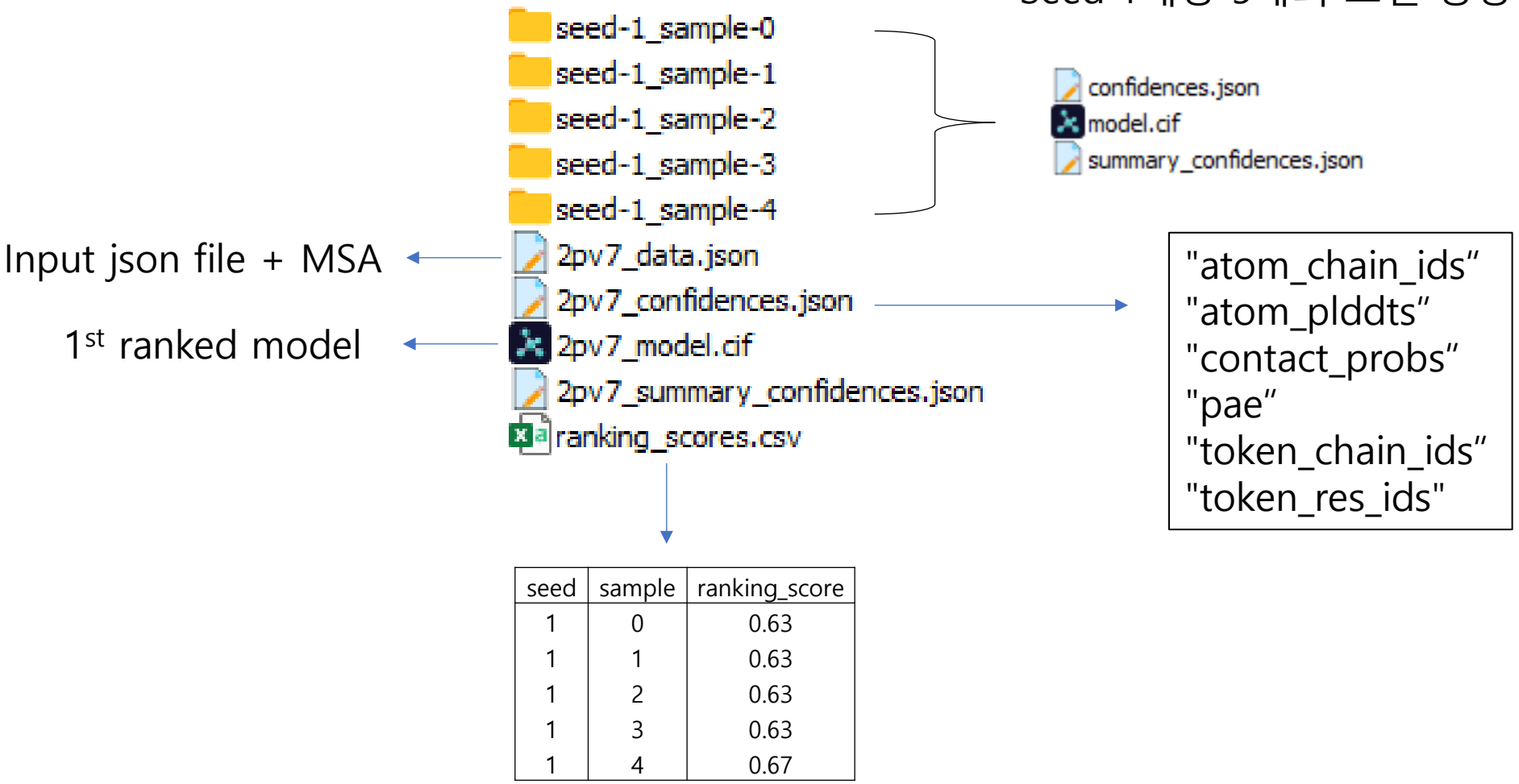
Alphafold3 실행을 위한 docker 명령어 작성하기

- On-premises 환경에서 Alphafold3 사용하기

  - https://github.com/suppakoko/alphafold3_class/blob/main/Docker/docker_command_example.txt

Alphafold3 실행 결과

- root/af_output/



seed	sample	ranking_score
1	0	0.63
1	1	0.63
1	2	0.63
1	3	0.63
1	4	0.67

Alphafold3 실행 결과

- summary_confidences.json

	A	B
A	0.76	1.04
B	1.03	0.76


```
"chain_iptm": [ 0.63, 0.63 ],
"chain_pair_iptm": [
 [ 0.68, 0.63 ],
 [ 0.63, 0.68 ]],
"chain_pair_pae_min": [
 [ 0.76, 1.04 ],
 [ 1.03, 0.76 ]],
"chain_ptm": [ 0.68, 0.68 ],
"fraction_disordered": 0.09,
"has_clash": 0.0,
"iptm": 0.63,
"ptm": 0.62,
"ranking_score": 0.67
```


pLDDT (Predicted Local Distance Difference Test)
"Is this loop or helix **shaped correctly**?"

> 90 : Very high confidence (side-chains are reliable).
70–90 : High confidence (backbone is reliable).
50–70 : Low confidence (caution needed).
< 50 : Very low confidence (likely intrinsically disordered or unstructured).

ipTM (Interface Predicted Template Modeling Score)
"Do these two proteins **actually bind** like this?"

> 0.8: High confidence (very likely a real binder with correct pose).
0.6–0.8: Moderate confidence (likely interacts, but exact orientation might vary).
< 0.5: Low confidence

PAE (Predicted Aligned Error)
"Are these **two domains actually sitting next to each other**, or are they floating apart?"

Scale: 0 to ~30 Å.
< 5 Å (Dark Blue/Green): The two residues are locked together rigidly
> 15 Å (White/Red): The relative position is uncertain

pTM (Predicted Template Modeling Score)
"Is the **overall shape** of this protein correct?"

> 0.7: High confidence (the fold is likely correct).
> 0.5: Correct topology (the general shape is right).
< 0.5: Failed prediction (random coil or incorrect fold).

Alphafold3를 이용한 예제

- On-premises 환경에서 Alphafold3 실제 사용하기

감사합니다

Q & A