RC Short Course: AlphaFold 3 on Alpine

Research Computing
UNIVERSITY OF COLORADO BOULDER

AlphaFold 3 on Alpine

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- Website: www.rc.colorado.edu/rc
- Documentation: https://curc.readthedocs.io
- Helpdesk: rc-help@colorado.edu
- Survey: http://tinyurl.com/curc-survey18

Slides
https://github.com/ResearchComputing/alphafold3_short_course

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Meet the User Support Team

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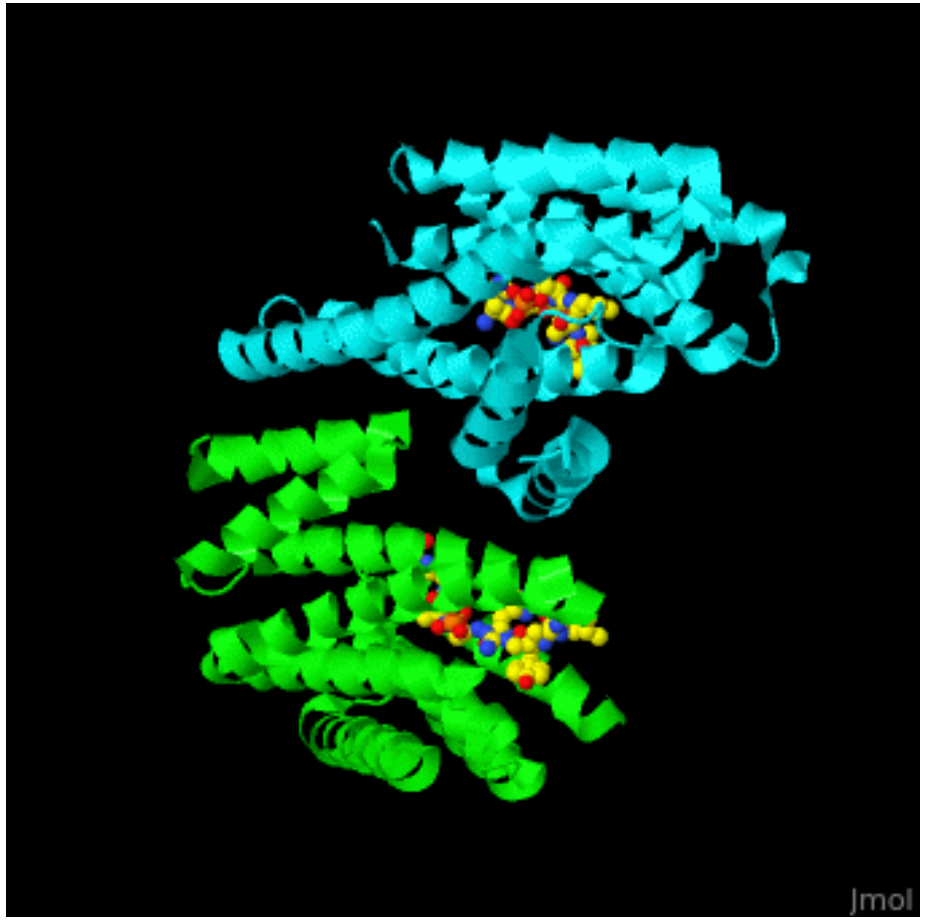
Background: The Protein Folding Problem

- What a protein does (it's biological function) depends on its 3D structure
- Figuring out the what shapes a protein folds into has been a grand challenge in biology for 50+ years
- Can we predict a protein's 3D structure based on its 1D aa sequence?

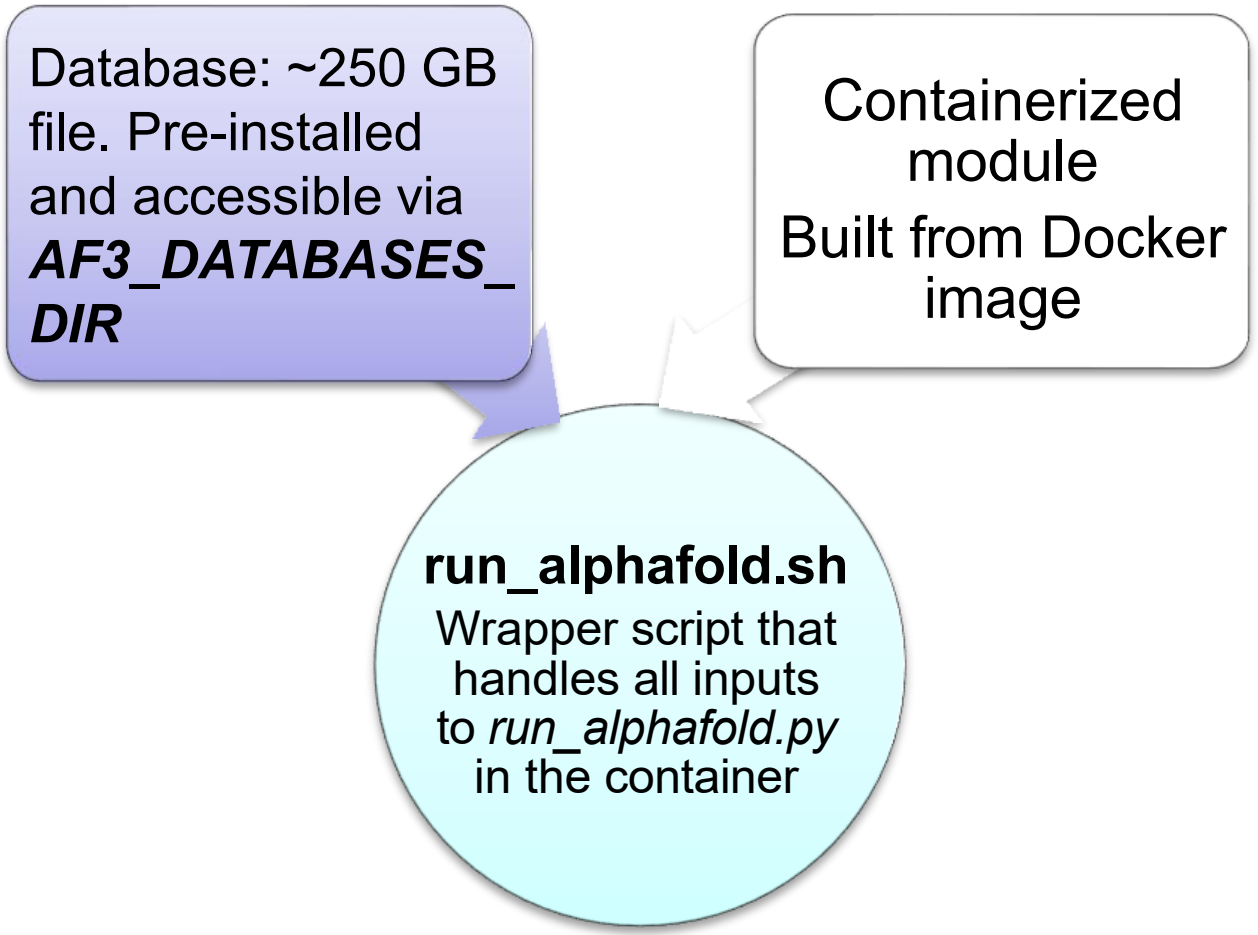


Notable changes to AlphaFold 3

- The model parameters are a separate download with licensing issues.
- The main run_alphafold.py script can now be executed in 2 phases, the CPU/time intensive database search, followed by the GPU-based model inference.
- The database has shrunk from 2+ TB to ~600 GB.
- The input file format has changed to a custom JSON format, instead of FASTA file.
- Overall performance appears to be improved, qualitatively.

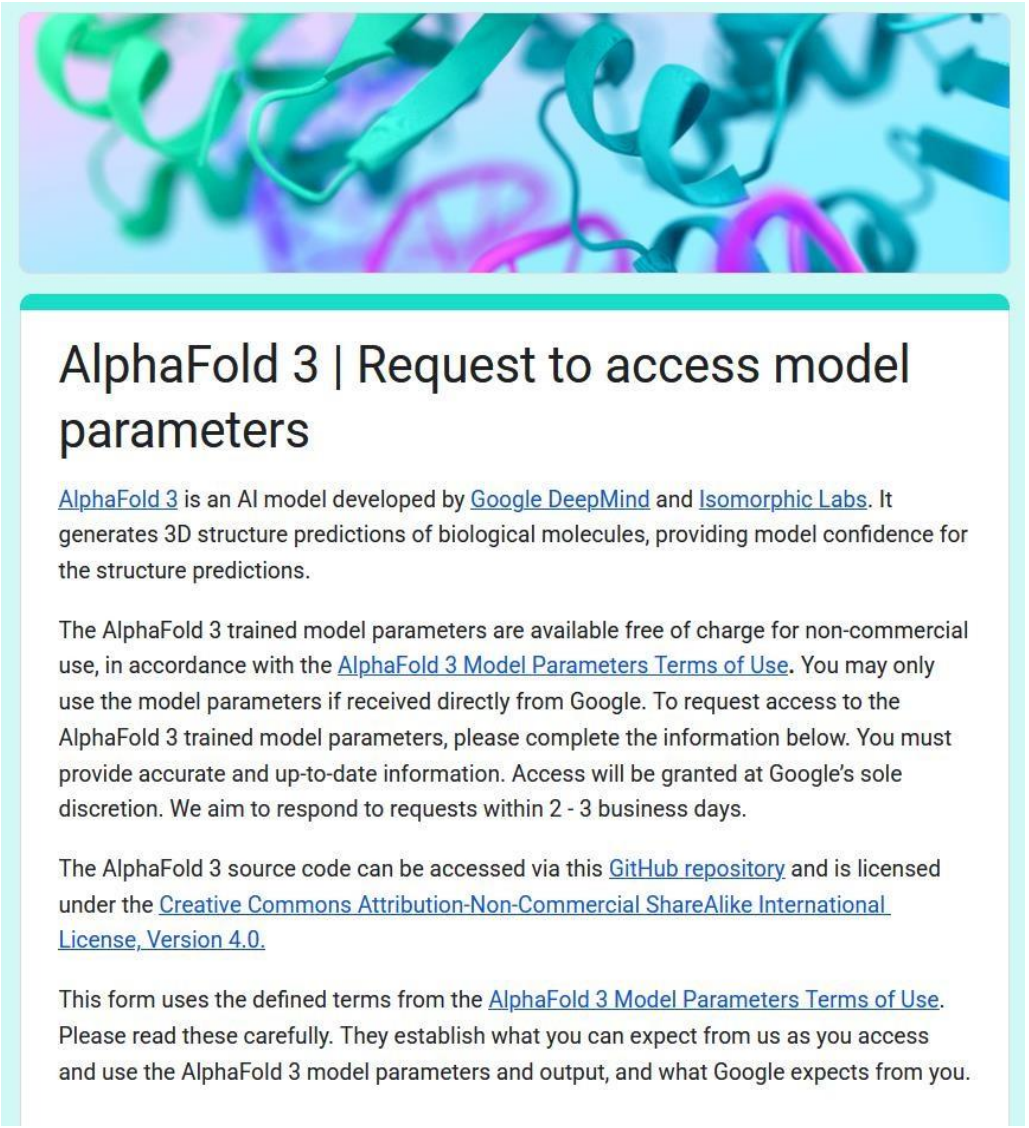
AlphaFold 3 Installation

- No customization of the Python code
- The wrapper:
  - Chooses the number of copies of jackhmmer/nhmmer processes to run in parallel based on the number of cores assigned to the job.
  - These are hard-coded to run with 8 threads each.



Model Parameters

- We opted to have users download their own copy of the model parameters.
- We provide a page with links and guidance on submitting the Google form to request their own copy.
  - So far, no user has reported an issue obtaining their own copy following the guidance here.



AlphaFold 3 Inputs

- The input **JSON** file format is the biggest change for users.
  - Documentation on the format is available.
  - There aren't very many examples online.
  - DeepMind does not provide any sort of validation tool for the format.
    - Error messages for bad inputs are not terribly helpful.
- You can provide inputs in one of two ways:
  - Single input file: **--json_path** flag followed by the path to a single JSON file.
  - Multiple input files: **--input_dir** flag followed by the path to a directory of JSON files.

AlphaFold 3 Module

- Loading the module (**ml alphafold/3.0.0**):
- creates a shortcut to the AlphaFold 3 script
- sets environment variables used by the wrapper script:
  - **AF3_IMAGE**: Path to the AlphaFold 3 container image
  - **AF3_CODE_DIR**: Directory containing the AlphaFold 3 codebase
  - **AF3_DATABASES_DIR**: Location of the required AlphaFold 3 reference databases
- redirects temporary files to **/scratch/alpine/$USER**
  - Can be overridden by resetting TMPDIR after you load the module:

AlphaFold 3 Module

```
------------------------------------------------------------------------
   /curc/sw/alpine-modules/udep/bio/alphafold/3.0.0.lua:
------------------------------------------------------------------------
setenv("AF3_RESOURCES_DIR","/curc/sw/install/bio/alphafold/3.0.0")
setenv("AF3_IMAGE","/curc/sw/install/bio/alphafold/3.0.0/alphafold3.sif")
setenv("AF3_CODE_DIR","/curc/sw/install/bio/alphafold/3.0.0/alphafold3-3.0.0")
setenv("AF3_EXAMPLES","/curc/sw/install/bio/alphafold/3.0.0/examples")
setenv("AF3_DATABASES_DIR","/gpfs/alpine1/datasets/bioinformatics/alphafold3")
setenv("TMPDIR","/scratch/alpine/mokh8410")
set_shell_function("run_alphafold","bash /curc/sw/install/bio/alphafold/3.0.0/ru
n_alphafold.sh \"$@\"","bash /curc/sw/install/bio/alphafold/3.0.0/run_alphafold.
sh $*")
help([[AlphaFold 3.0.0 (Containerized)

This module provides access to AlphaFold 3 (DeepMind) via a Singularity containe
r.
Users must supply the DeepMind-provided model parameters separately.

Usage:

1. MSA Search (CPU):
   sinteractive --partition=al40 --nodes=1 --ntasks=8 --time=1:00:00
   ml purge && ml alphafold/3.0.0
```

AlphaFold 3 Workflow

- AlphaFold 3 runs in two stages:
  - Stage 1 (MSA Search): CPU and I/O-intensive; uses jackhmmer and hhmsearch.
  - Stage 2 (Inference): GPU-intensive; performs structure prediction.
- To better utilize limited GPU resources, these stages can be split using flags:
  - --norun_inference → Run only the MSA/data pipeline (Stage 1)
  - --norun_data_pipeline → Run only the inference step (Stage 2)

Running Your Prediction

- Example input files and scripts are in **/curc/sw/install/bio/alphafold/3.0.0/examples**.
- Loading the module stores this path in **AF3_EXAMPLES**.
- Copy the folder to a location where you have write permissions

```
$ls $AF3_EXAMPLES
alphafold3_alpine_cpu.sh  alphafold3_alpine_gpu.sh
alphafold3_alpine.sh  fold_protein_2PV7
```

Running Your Prediction

```
#!/bin/bash

#SBATCH --nodes=1
#SBATCH --time=30:00
#SBATCH --partition=al40
#SBATCH --qos=normal
#SBATCH --gres=gpu:1
#SBATCH --job-name=af3_test
#SBATCH --output=af3_test_%j.out
#SBATCH --ntasks=8
#SBATCH --mail-type=ALL
#SBATCH --mail-user=<your email address>

# Load the AlphaFold 3 module
module purge
module load alphafold/3.0.0

# Set input JSON, output directory, and model parameter path
export INPUT_FILE=/path/to/input/json
export OUTPUT_DIR=/path/to/output
export AF3_MODEL_PARAMETERS_DIR=/path/to/alphafold3/params

# Run AlphaFold 3
run_alphafold --json_path=$INPUT_FILE --output_dir=$OUTPUT_DIR --model_dir=$AF3_MODEL_PARAMETERS_DIR
```

Performance Considerations

- The number of cores/threads used during MSA steps is hardcoded and so AF cannot use more than 8 CPU cores.
- Requesting more cores will **not** improve performance and you may end up waiting longer for your job to start.

```
I1005 11:40:25.187402 23318643615296 subprocess_utils.py:68] Launching subprocess
"/hmmer/bin/jackhmmer -o /dev/null -A /tmp/tmpb0qmrgip/output.sto --noali --F1 0.0005 --F2 5e-05 --F3 5e-
07 --cpu 8 -N 1 -E 0.0001 --incE 0.0001 /tmp/tmpb0qmrgip/query.fasta
/root/public_databases/uniref90_2022_05.fa"
I1005 11:42:28.693908 23318639412800 subprocess_utils.py:97] Finished Jackhmmer in 123.506 seconds
```

Visualizing Outputs

- AlphaPickle: https://github.com/mattarnoldbio/alphapickle
- PyMol (free for education): https://pymol.org/
- AlphaFold Protein Structure Database website provides a great resource for learning how to interpret visualizations: https://alphafold.ebi.ac.uk/entry/Q9Y223#help

Thank you!

Survey and feedback

http://tinyurl.com/curc-survey18