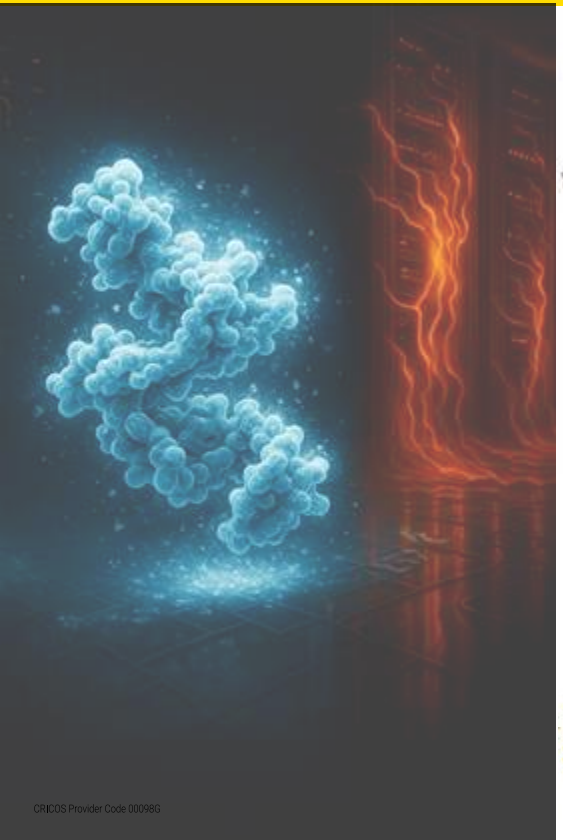
Frozen Samples, Melting Servers:

The CryoEM and AlphaFold data explosion

Research Data Experience Seminar – 2025 July 9th

Dr Daniel Luque & Dr Keiran Rowell



Structural Biology Facility

RESEARCH TECHNOLOGY SERVICES

COMPUTE DATA COMMUNITY

AlphaFold – AI workloads backed by large biodatabases

SBF nodes:

- **k099** & **k100** (Slarti & Bartfast)
  - 4x**H200 GPU** (141 GB VRAM), 7.3&5.1/11 TB local NVMe
- **k095** (Trillian) & Zaphod (DevOps test server)
  - 4x**A100 GPU** (40 GB VRAM), 4.9/5.3 TB local NVMe

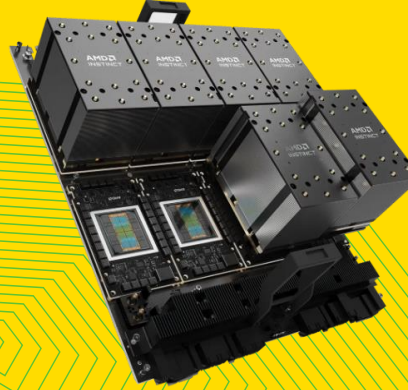
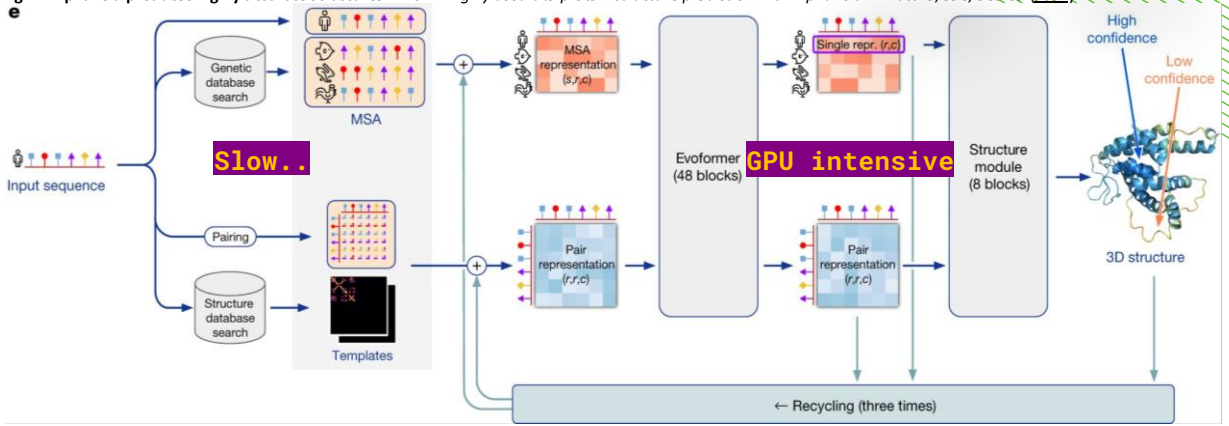
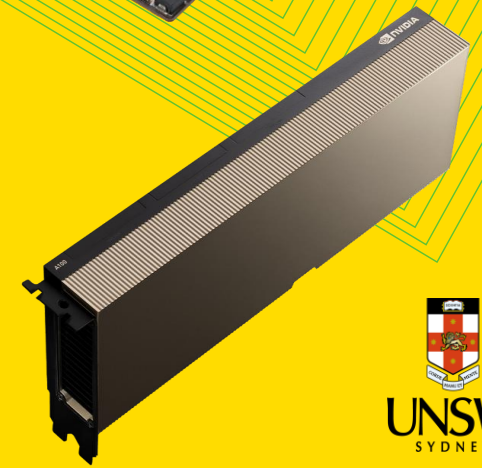


Fig. 1: AlphaFold produces highly accurate structures – from *"Highly accurate protein structure prediction with AlphaFold"* - Nature, **596**, 583-89 (2021).





Google DeepMind

Brainfloat-16 (bfloat16)

Float32 vs Float16 vs BFloat16? : https://newsletter.theaiedge.io/p/float32-vs-float16-vs-bfloat16

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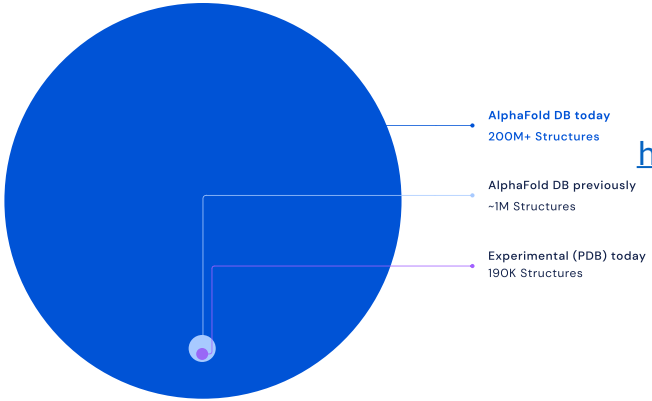
AlphaFold – I/O matters – 4 TB DBs – mind your nanoseconds

200,000 experimentally resolved structures **2.5 *billion* genetic sequences**



MC BFD

https://bfd.mmseqs.com/

VAST

WEKA

& &

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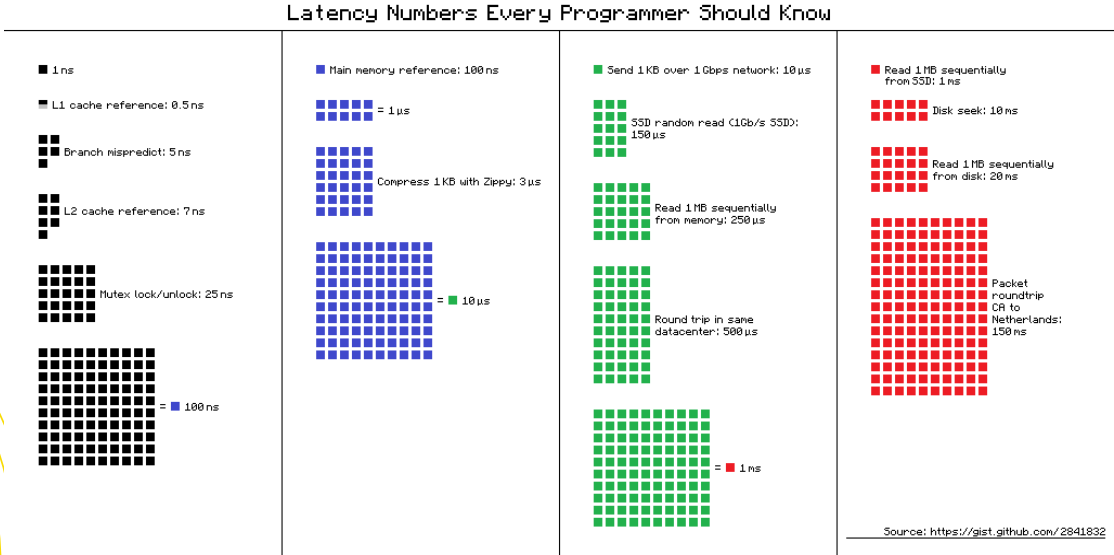
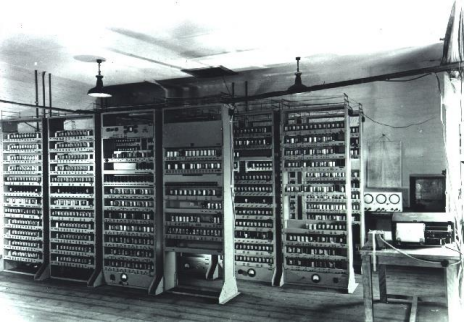
PURE STORAGE

www.rcsb.org (Protein DataBank)

https://news.sherlock.stanford.edu/publications/sherlock-goes-full-flash

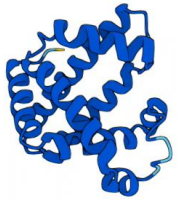


It was ever thus... biomolecules &



Wikimedia Commons: EDSAC I, June 1948.
Copyright Computer Laboratory, University of Cambridge. Reproduced by permission.

Science Museum Group Collections: The original model of the myoglobin molecule.
Copyright The Board of Trustees of the Science Museum, London



AlphaFold Protein Structure Database:
Myoglobin, AF-P02168-F1-v4, 2022-11-01, AlphaFold2.0

JOHN C. KENDREW

Myoglobin and the structure of proteins

Nobel Lecture, December 11, 1962

But, as already indicated, the amount of computation required increases very rapidly with the resolving power. Even at the first stage of the analysis we made use of an electronic computer, EDSAC I, which though small and slow by modern standards was at the time one of the very few such instruments in operation in the world; it is significant that these early Fourier syntheses of the myoglobin data were, to the best of my belief, the first crystallographic computations ever carried out on an electronic computer and initiated a practice which later (and incidentally after a time lag of several years) became universal among crystallographers. At each stage of the myoglobin analysis the computers employed were among the most rapid available at the time, and we are now using very fast and large computers such as EDSAC II and IBM 7090; most proteins are larger than myoglobin, and will need even bigger computers. There are also problems of data collection and data handling.

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Incidentally, **John Lennard-Jones** (KBE, FRS) founding Dir. of the **Mathematical Laboratory** in Cambridge
->
Department of Computer Science and Technology
->
built **EDSAC** under second Dir. **Maurice Wilkes** (FRS, FREng)

AlphaFold – benchmarking – node-local vs scratch

```
Completed at: 15-May-2025 11:52:41
Duration    : 1h 4m 23s
CPU hours   : 6.4
Succeeded   : 14

real→   64m27.471s
user→   155m48.017s
sys→17m1.646s

                    Resource Usage on 15/05/

Job Id: 6515259►
Queue: MWAC
Walltime: 01:04:30  (requested 02:00:00)
Job execution was successful. Exit Status 0.►

|              |            GPUs
| Node  GPU ID | Requested    Used    Efficienc
| k095     1   |         1     0.0      0%

|Total         |         1     0.0     0.0%

|              |            CPUs
| Node         | Requested    Used    Efficienc
| k095         |         6    2.68     45.0%

fastalocalk095.pbs.o6515259  300,1          Bot
```

```
Completed at: 15-May-2025 12:06:08
Duration    : 1h 17m 54s
CPU hours   : 7.8
Succeeded   : 14

real→   77m57.965s
user→   152m18.542s
sys→7m39.276s

                    Resource Usage on 15/05/20

Job Id: 6515260►
Queue: MWAC
Walltime: 01:18:00  (requested 02:00:00)
Job execution was successful. Exit Status 0.►

|              |            GPUs
| Node  GPU ID | Requested    Used    Efficiency
| k099     1   |         1     0.05      5%

|Total         |         1     0.05     5.0%

|              |            CPUs
| Node         | Requested    Used    Efficiency
| k099         |         8    2.05     26.0%

fastalocalk099.pbs.o6515260  301,1          Bot
```

```
Completed at: 15-May-2025 12:10:51
Duration    : 1h 22m 33s
CPU hours   : 8.2
Succeeded   : 14

real→   82m36.938s
user→   155m12.017s
sys→17m14.130s
Cgroup memsw limit exceeded:►

                    Resource Usage on 15/05/2

Job Id: 6515261►
Queue: MWAC
Walltime: 01:22:39  (requested 02:00:00)
Job execution was successful. Exit Status 0.►

|              |            GPUs
| Node  GPU ID | Requested    Used    Efficiency
| k095     2   |         1     0.0      0%

|Total         |         1     0.0     0.0%

|              |            CPUs
| Node         | Requested    Used    Efficiency
| k095         |         6    2.09     35.0%

<stasharedk095.pbs.o6515261 310,1          Bot
```

```
Completed at: 15-May-2025 12:04:19
Duration    : 1h 16m 5s
CPU hours   : 7.6
Succeeded   : 14

real→   76m9.014s
user→   149m22.560s
sys→6m57.215s

                    Resource Usage on 15/05/20

Job Id: 6515262►
Queue: MWAC
Walltime: 01:16:10  (requested 02:00:00)
Job execution was successful. Exit Status 0.►

|              |            GPUs
| Node  GPU ID | Requested    Used    Efficiency
| k099     2   |         1     0.05      5%

|Total         |         1     0.05     5.0%

|              |            CPUs
| Node         | Requested    Used    Efficiency
| k099         |         8    2.05     26.0%

<stasharedk099.pbs.o6515262 308,1          Bot
```

Credit Josh Caley: computational systems officer @ SBF

Job batching is super important!

Single input search

```
1 c4/1c6a0b 6660576.kman.restech.unsw.edu.au
NFCORE_PROTEINFOLD:BOLTZ:MSA:MMSEQS_COLABFOLDSEARCH
(input_seqs_1) COMPLETED 0 2025-07-01 21:01:02.408 1h 45m
1h 45m 15s 686.4% 240.4 GB 268.4 GB 52.6 MB 88.5 MB
```

Batch search (21 proteins)

```
1  93/9c23a7  6660292.kman.restech.unsw.edu.au
NFCORE_PROTEINFOLD:BOLTZ:MSA:MMSEQS_COLABFOLDSEARCH
(input_seqs_1)  CACHED  0 2025-07-01 18:38:12.660 1h 52m
1h 51m 20s 585.1% 241.2 GB 428.6 GB 93.2 MB 623.3 MB
```

Credit Tom Litfin: senior research associate @ SBF

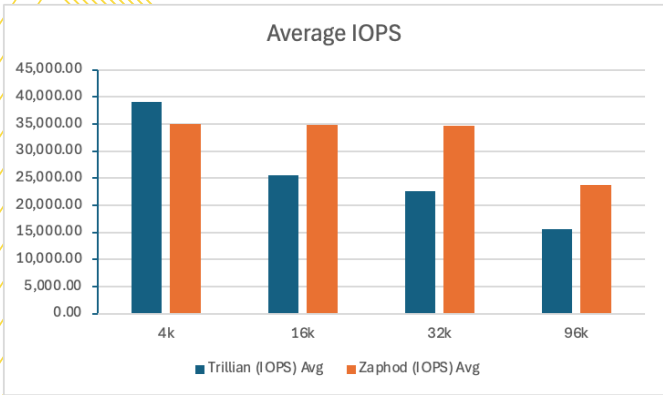
Mass scratch *vs* local

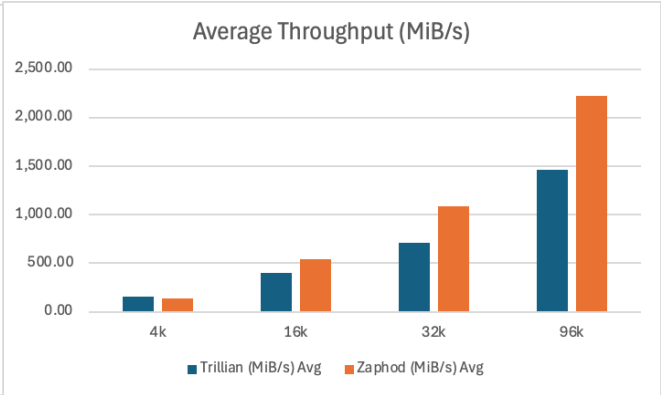
Disk striping

MDADM (Trillian) *vs*

ZFS (Zaphod)

```
--direct=1
--rw=randread
--bs=${BLOCK_SIZE}
--iodepth=256
--runtime=120
--numjobs=4
```





Credit N.: computational systems officer @ SBF

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GPU accelerated sequence alignment

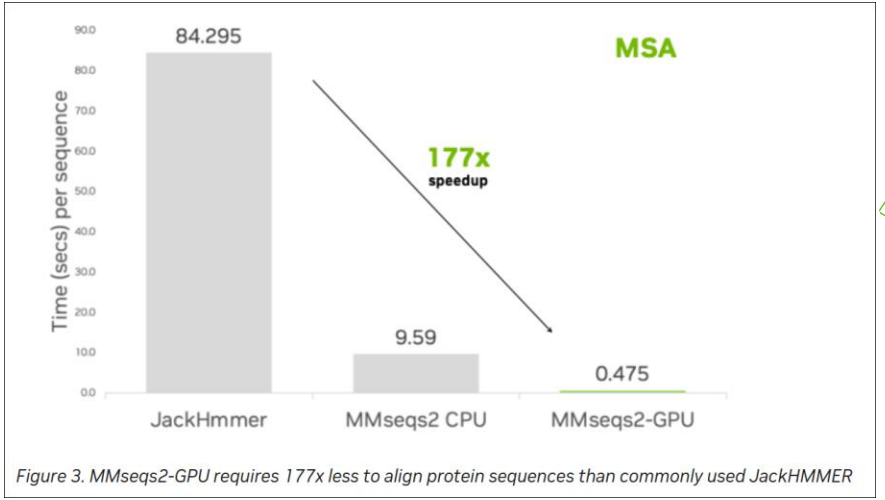

Figure 3. MMseqs2-GPU requires 177x less to align protein sequences than commonly used JackHMMER

NVIDIA dev blog 2024-11-13: https://developer.nvidia.com/blog/boost-alphafold2-protein-structure-prediction-with-gpu-accelerated-mmseqs2/

(b) For single-batch processing, **MMseqs2-GPU delivers the fastest speed at lowest cloud compute cost, being 71 times faster** than MMseqs2 k-mer at **0.05 times the cost.**

(c) **Faster folding speeds *at no accuracy cost*.** On 20 CASP14 targets, ColabFold leveraging MMseqs2-GPU (green) results 3 and 23 times faster than ColabFold using MMseqs k-mer (orange) or AlphaFold2 using JackHMMER (violet), respectively.

(d) **All methods reach similar TM score** (~0.70±0.05).

MMseqs2-GPU (L40S) · MMseqs2-GPU (8xL40S) · MMseqs2 (k-mer) · MMseqs2 (gapless) · BLASTP · PSI-BLAST

mmseqs.com mmseqsDownUnder?

bioRxiv 2024-11-15 "*GPU-accelerated homology search with MMseqs2*" Felix Kallenborn, Alejandro Chacon, Christian Hundt, Hassan Sirelkhatim, Kieran Didi, Christian Dallago, Milot Mirdita, Bertil Schmidt, Martin Steinegger

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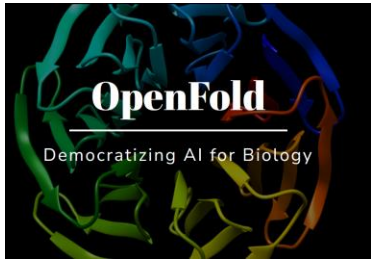
AlphaFold – algos & scale – method always beats hardware

HPC & Hyperscalers: Batch, $O(N^2)$ VRAM, $O(N^3)$ time, fixed DBs, 1000s calcs, fast I/O

'Evo'formers (GPU+CPU+DBs)

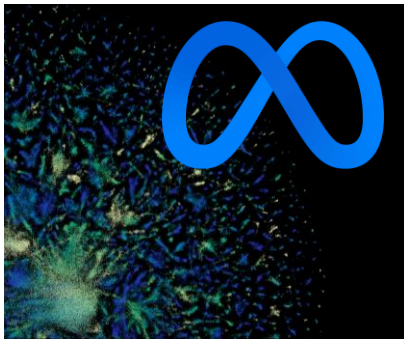
(Alpha|Open|RoseTTA|Boltz)Fold



Google DeepMind

Protein-LMs (GPU)

ESMFold, ProtTrans



We can't keep GPUs busy! They are *so fast*

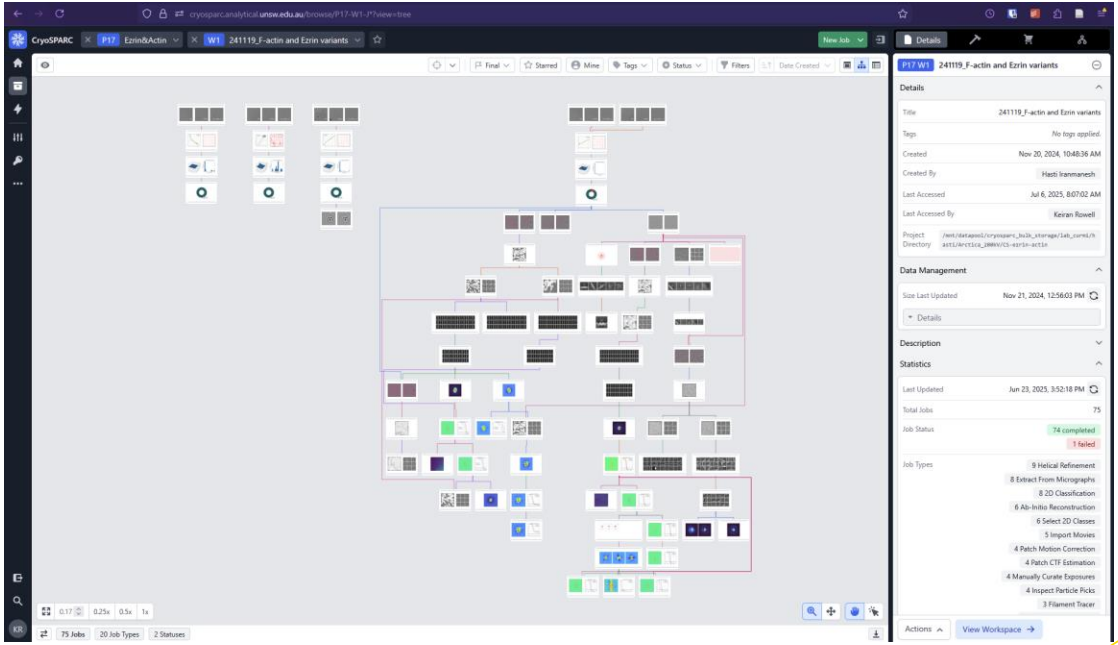
- GPU calculations x50 faster than CPU. 2 hrs vs 5 days
- **ESMFold** is pure GPU. **AlphaFold** GPU+CPU+DB retrieval.
  - 613 proteome 8 hrs vs 22 days. 4,622 protoeome 10 days vs ?? (2 years)

Sequence alignment is the rate limiting step!

(Applies to genomics too)

Domain experts *want* a single pane of glass

Interfaces rolled out by the SBF @UNSW



Master: Proxmox HA 3-node cluster
Workers: Crysoparcuser workers – rack mount GPU
Workstations: Custom CryoEM software & support – A'Tuin 4xA6000
Data storage: Current: DDN -> TrueNAS (replica on ResTech server)
Planned: IBM ESS flash + HDD back-up. TrueNAS as replica?

cryosparc.analytical.unsw.edu.au

Proteinfold

Structural Biology Facility

Computationally predict protein structures

Samplesheet

/srv/scratch/z3374843/Melb_Bioinf_Meetup/monomer_sequences

Acceptable inputs

- **Directory containing Fasta file(s):** /srv/scratch/z3141592/my_experiment
- **Amino acid sequence:** NLYIQWLKDGGPSSGRPPPS

Warning! Please ensure your input data (e.g., FASTA file or run name) does not contain sensitive data. Katana is **NOT** suitable for sensitive or highly sensitive data. You should use the UNSW Data Classification scheme to classify your data and learn about managing your research data by visiting the Research Data Management Hub.

Run Name

AF2_monomer_sequences

Alphanumeric and "_" only

Method

Alphafold2

- **AlphaFold2.3** High Accuracy, Slower - Paper
- **ESMFold** Medium/Low Accuracy, Fastest (No Evolutionary Sequence Calculations) - Paper
- **RoseTTAFold-All-Atom** High Accuracy, Slower; optimised for atomic-level modeling - Paper

Mode

Monomer

- Only applies to AlphaFold2.3 and ESMFold
- Monomer_ptm for AlphaFold2.3 only

MSA Search Database

Full

- **Full** High Accuracy, Slower
- **Reduced** Optimised for speed

Facility Citation

doi.org/10.26190/4KQF-M552

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Launch

* The Proteinfold session data for this session can be accessed under the data root directory.

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Access:
control lists

Portal:
OpenOnDemand
HTML / JS (?)

Pipeline:
nf-core/proteinfold

Collab:
CRG (Barcelona)
SBF (UNSW)
BioCommons (Aus)

kod.restech.unsw.edu.au/pun/sys/dashboard/batch_connect/sys/sbf_proteinfold/

Questions / Discussion