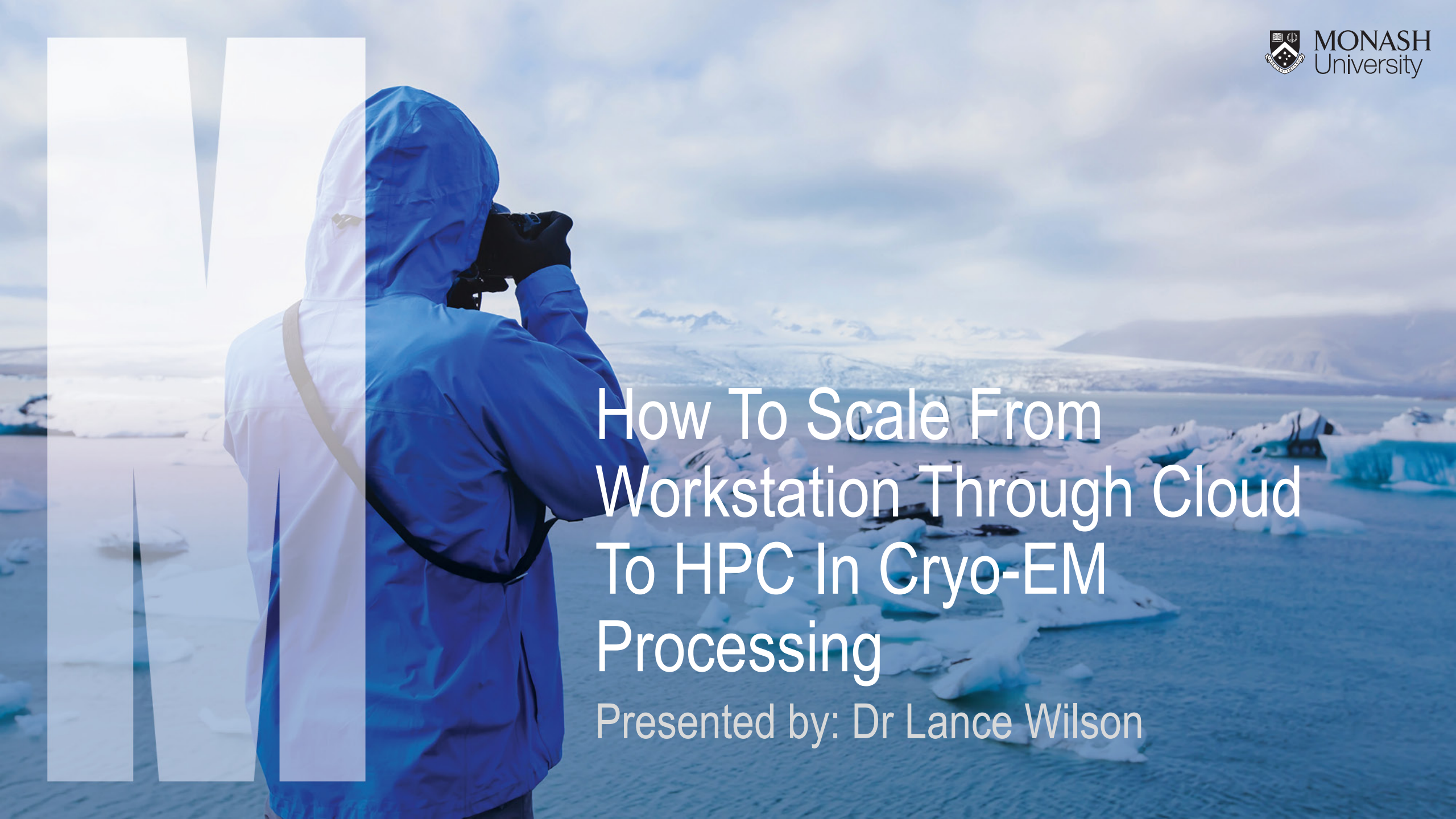

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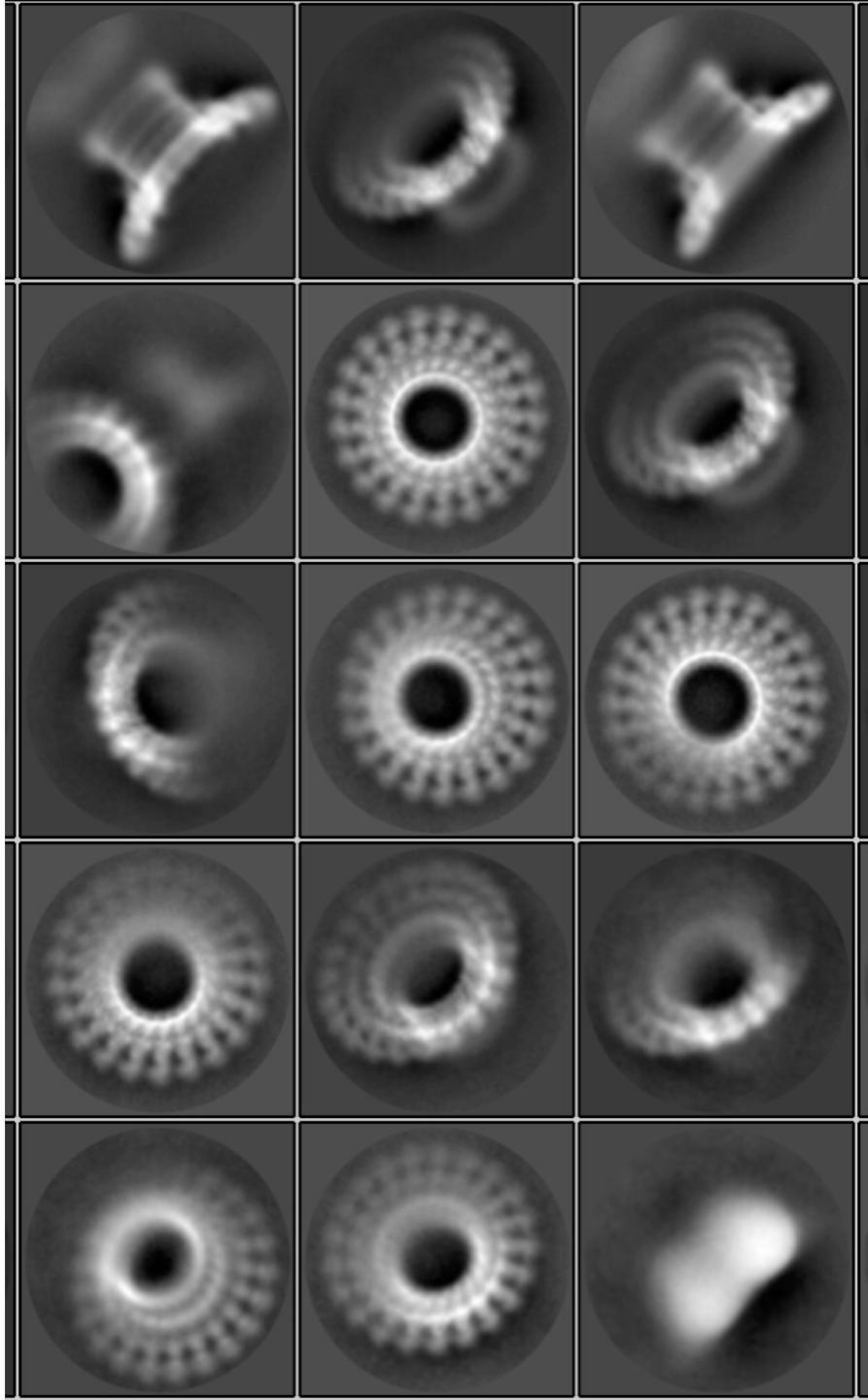
How To Scale From Workstation Through Cloud To HPC In Cryo-EM Processing

Presented by: Dr Lance Wilson

What will we discuss…

Presentation Outline

- Who am I? Where am I from?
- What is cryo-electron microscopy?
- How long does analysis take?
- What impact does hardware have?
- What options do you suggest?
- What processing opportunities exist?
- Next opportunity: Light sheet microscopy!



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Who am I and Where am I from?

The research context

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US Dept of State Geographer
© 2018 Google
Image U.S. Geological Survey
Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google Earth

OUR GLOBAL FOOTPRINT

100+
partner universities

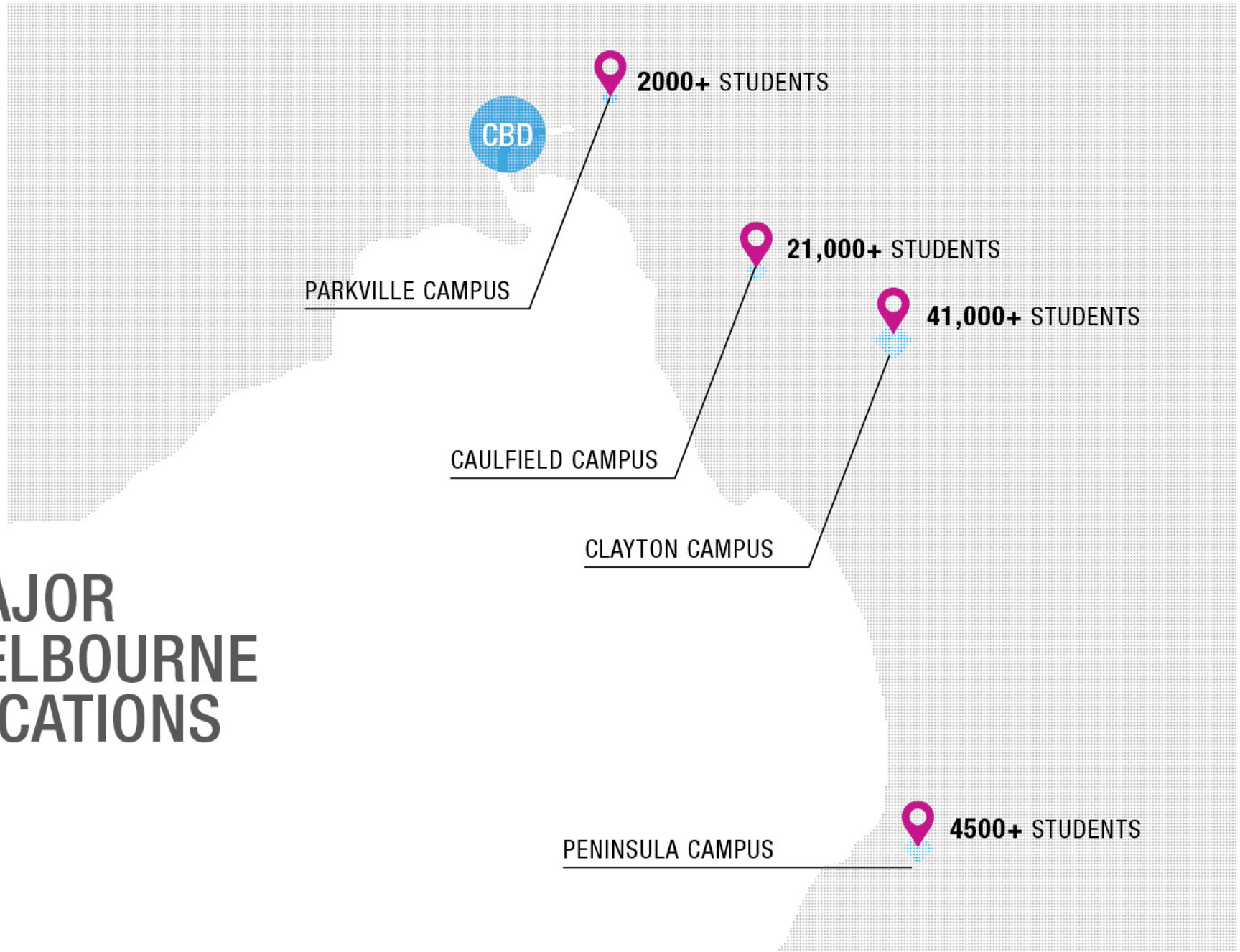
STUDY ABROAD EXPERIENCES

900+
INCOMING TO AUSTRALIA

4500+
OUTGOING TO PLACES AROUND THE WORLD

MONASH University

OUR AUSTRALIAN CAMPUSES



4 MAJOR MELBOURNE LOCATIONS

MONASH University

MASSIVE

… is a data processing engine for Australian science. It empowers researchers to unlock impactful research discoveries within scientific data.

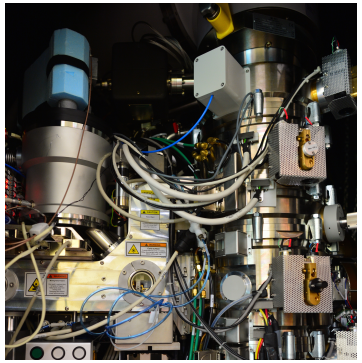
Integrative High Performance Computing

- usability by new HPC user communities over raw capacity;
- hardware suited to data processing;
- underpinning high performing wet, experimental and data-focused laboratories, with growing data processing needs;
- workflows that increase return on investment in instruments and experiments; and
- porosity and flexibility to serve specific requirements in growth usage areas, such as the life sciences, machine learning etc.

Professor Trevor Lithgow

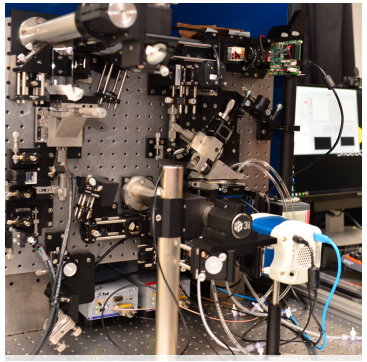
ARC Australian Laureate Fellow

Discovery of new protein transport machines in bacteria, understanding the assembly of protein transport machines, and dissecting the effects of anti-microbial peptides on anti-biotic resistant “super-bugs”



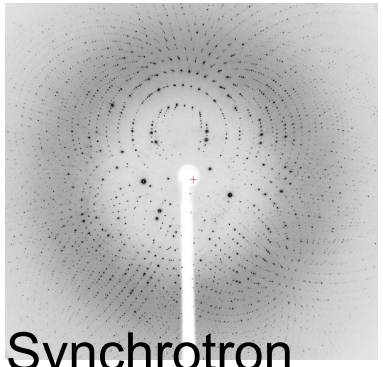
FEI Titan Krios

Nationally funded project to develop environments for Cryo analysis



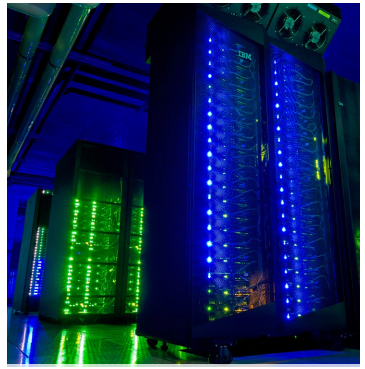
MMI Lattice Light Sheet

Nationally funded project to capture and preprocess LLS data



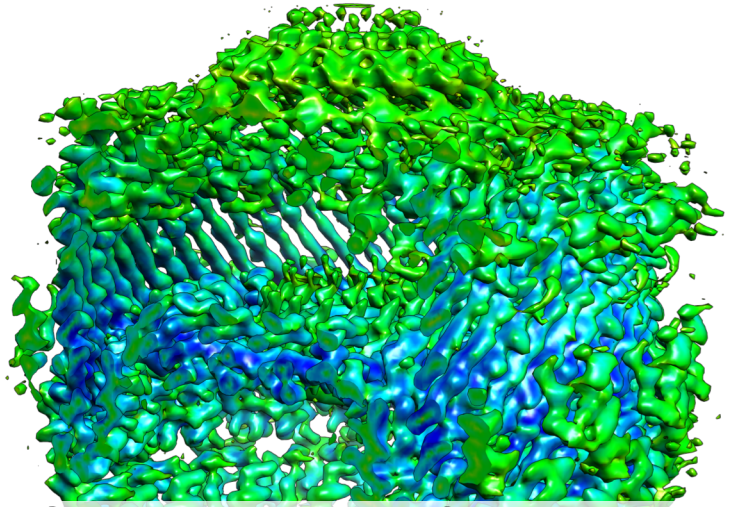
Synchrotron MX

Data Management, Integration between AS and MASSIVE M3



MASSIVE M3

Structural refinement and analysis



Chamber details from the nanomachine that secretes the toxin that causes cholera.

Research and data by Dr. Iain Hay (Lithgow lab)

How do we partner with researchers…

MASSIVE and Characterisation Virtual Laboratory

NCRIS National Research Infrastructure for Australia
An Australian Government Initiative

ardc australian research data commons
Built from ands nectar RDS

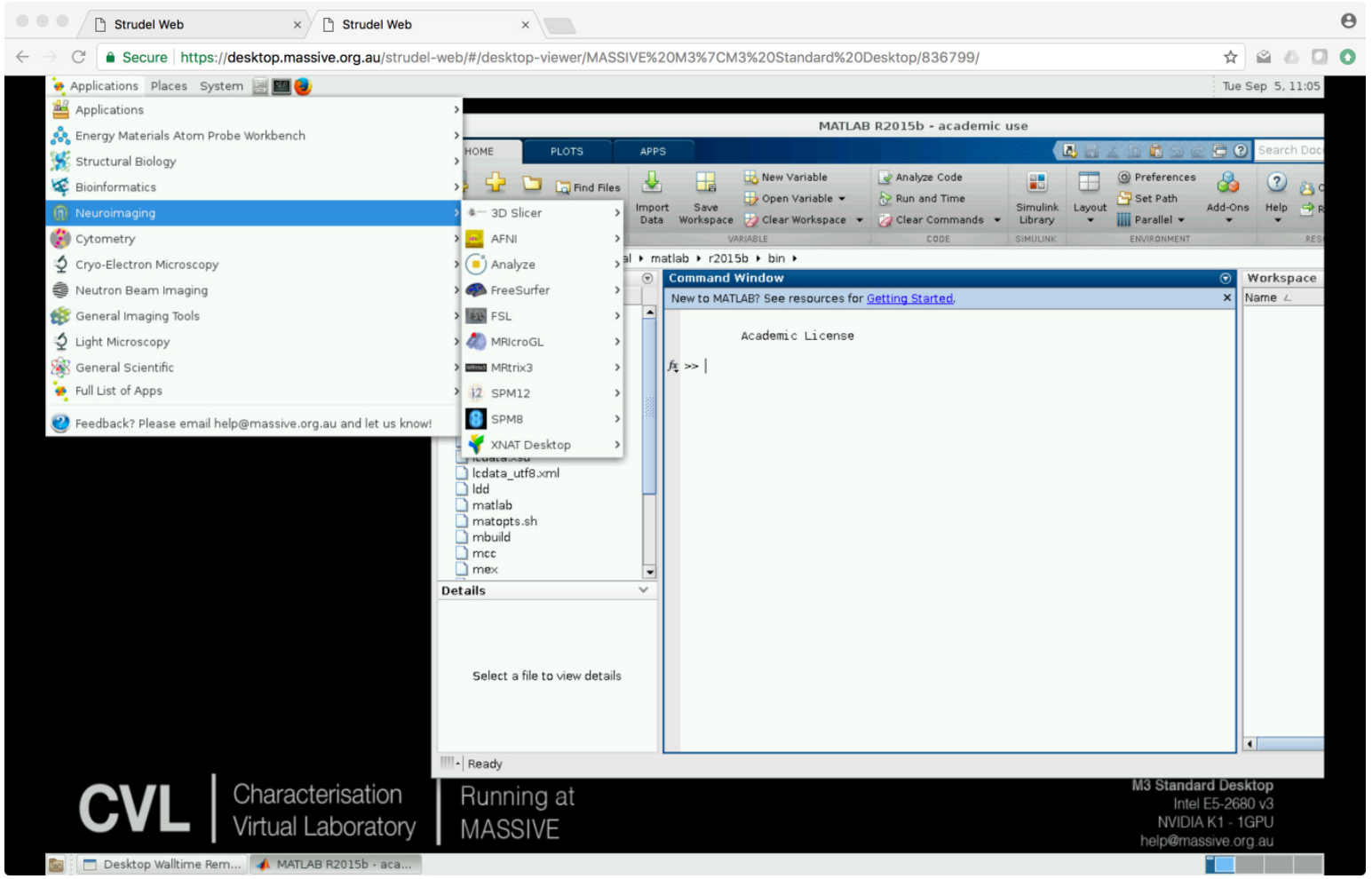
"Here is your CD of data…"

"Your data is moving up to a data management system in the cloud where you have access to a range of tools and services to start your data analysis"

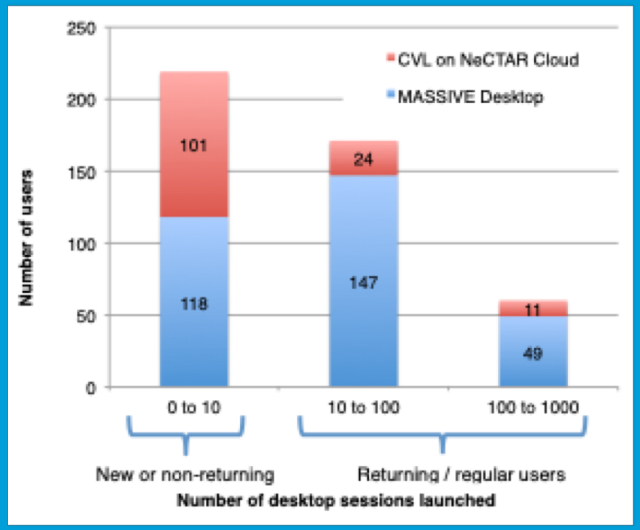
Monash University
ANSTO
National Imaging Facility
Microscopy Australia
The University of Western Australia
The University Of Queensland
The University of Sydney
University of Wollongong Australia

How do we complement/replace workstations…

Rich Online Workbenches



Atom Probe, **Structural Biology**, Bioinformatics, Cytometry, **Cryo-Electron Microscopy**, Neutron Beam Imaging, General Imaging Tool, Light Microscopy, General Scientific, X-ray



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Cryo-Em:
Titan Krios

Cryo-Em PC
Collect
movies,
Images,

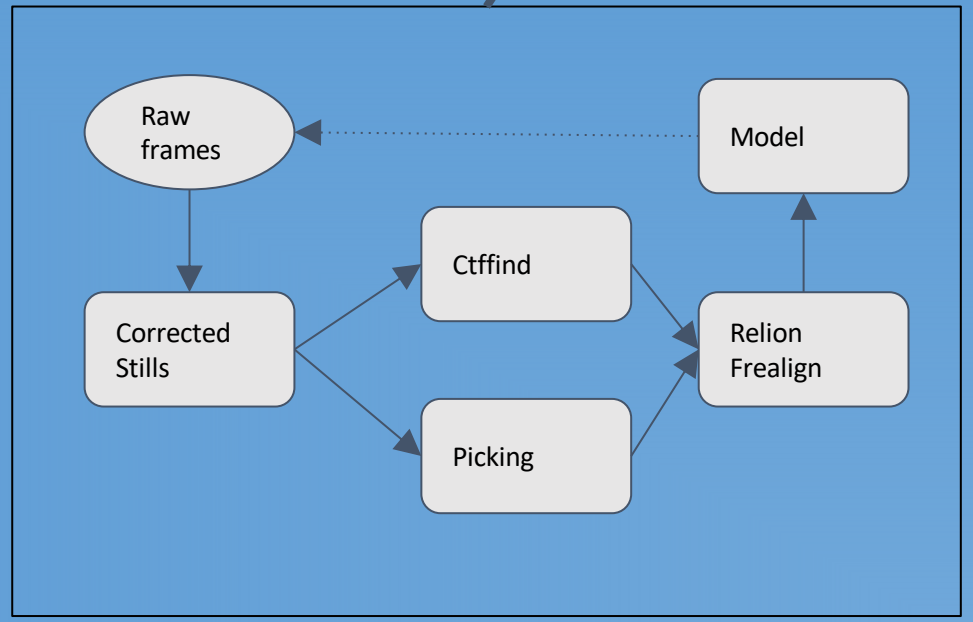
MyData
App

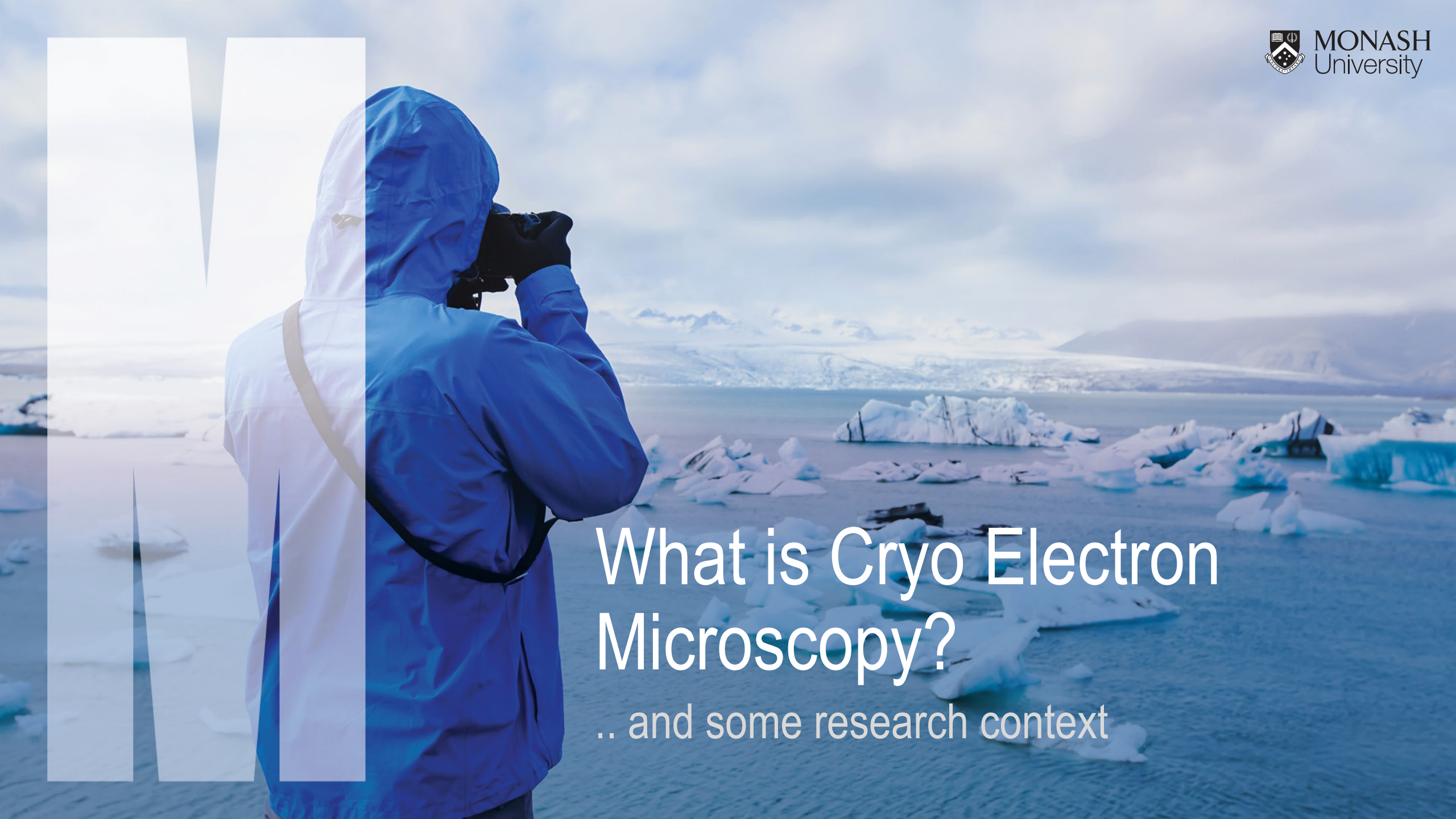
MyTardis
Data storage,
sharing

Publication
DOI, Reuse

MyData
App

Strudel
Desktop & Web





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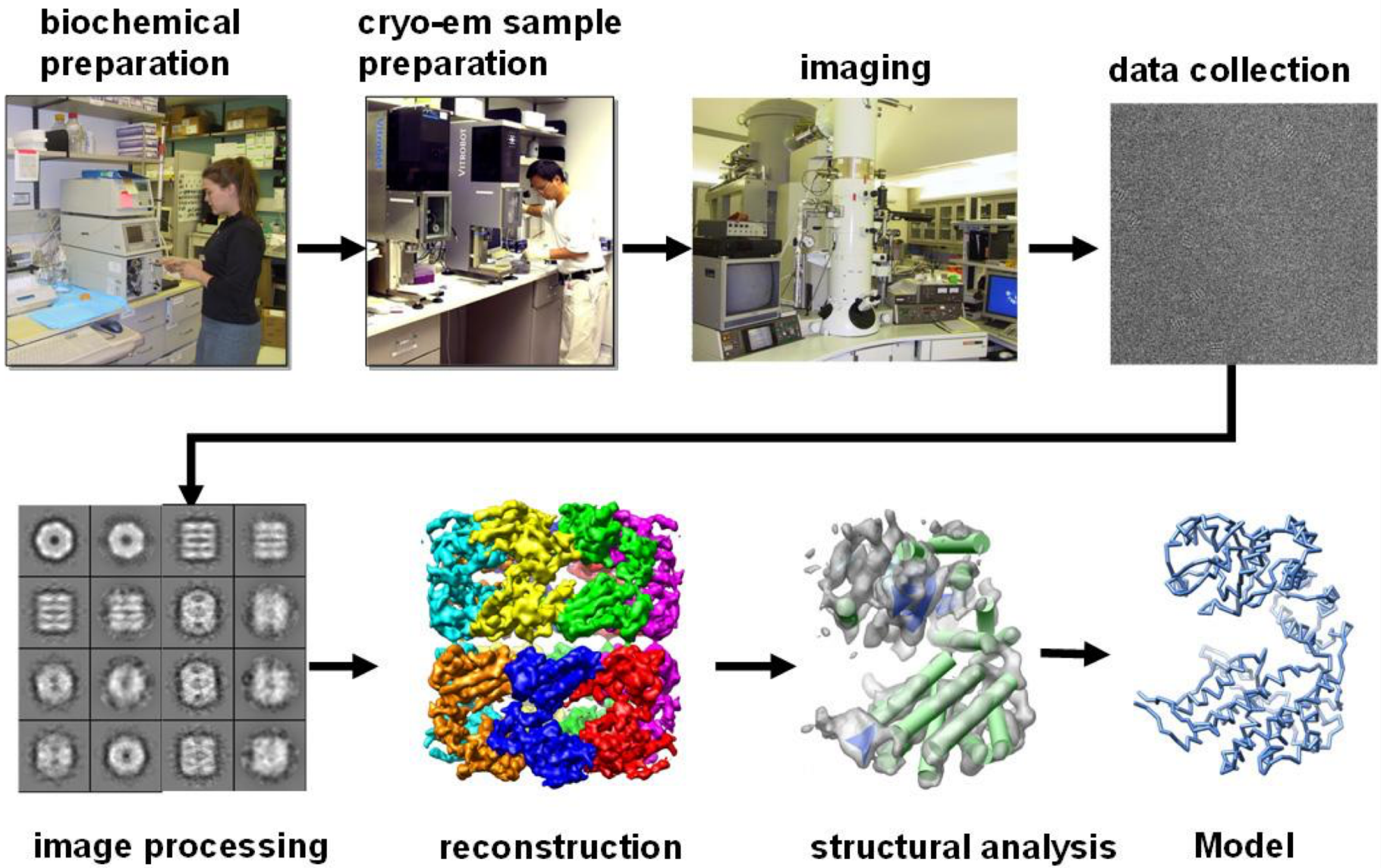
What is Cryo Electron Microscopy?

.. and some research context

Pipeline in Biological Cryo-EM



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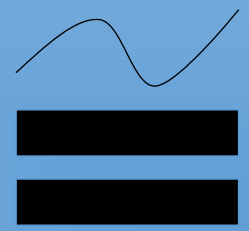
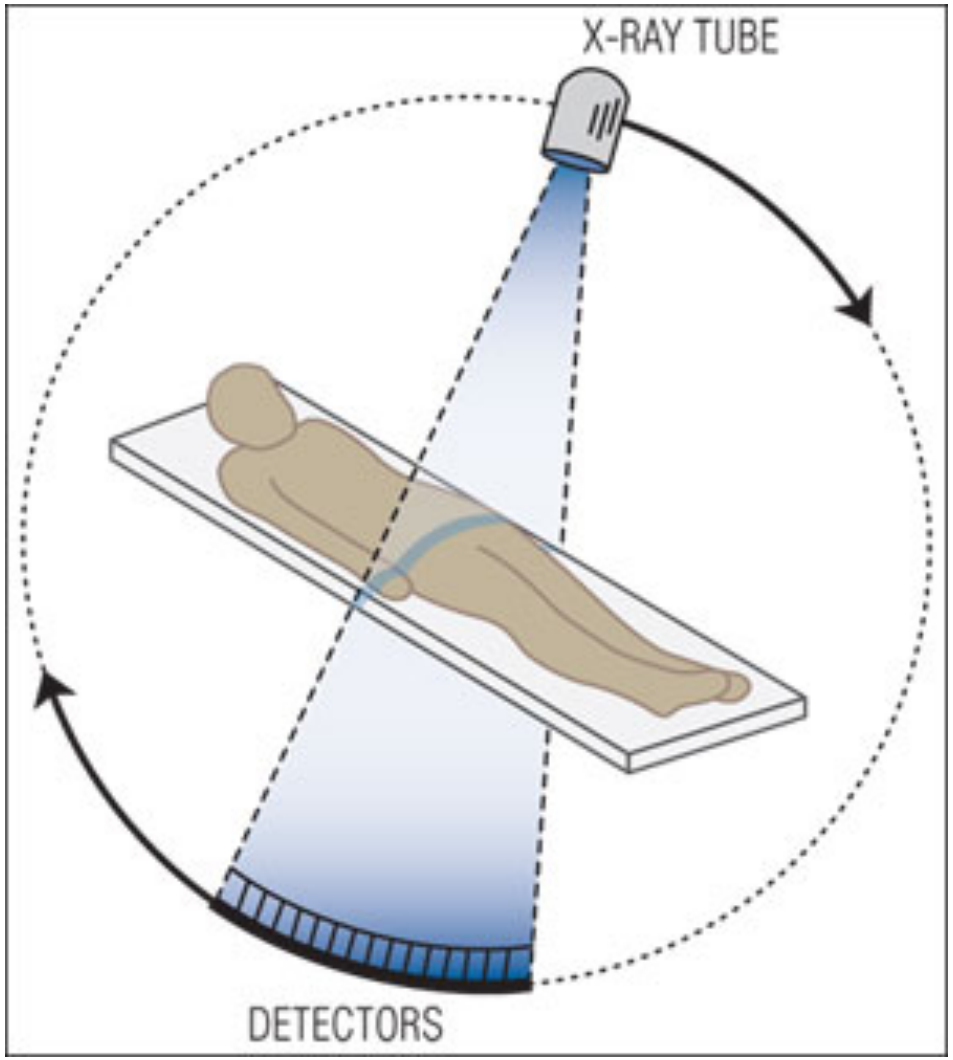
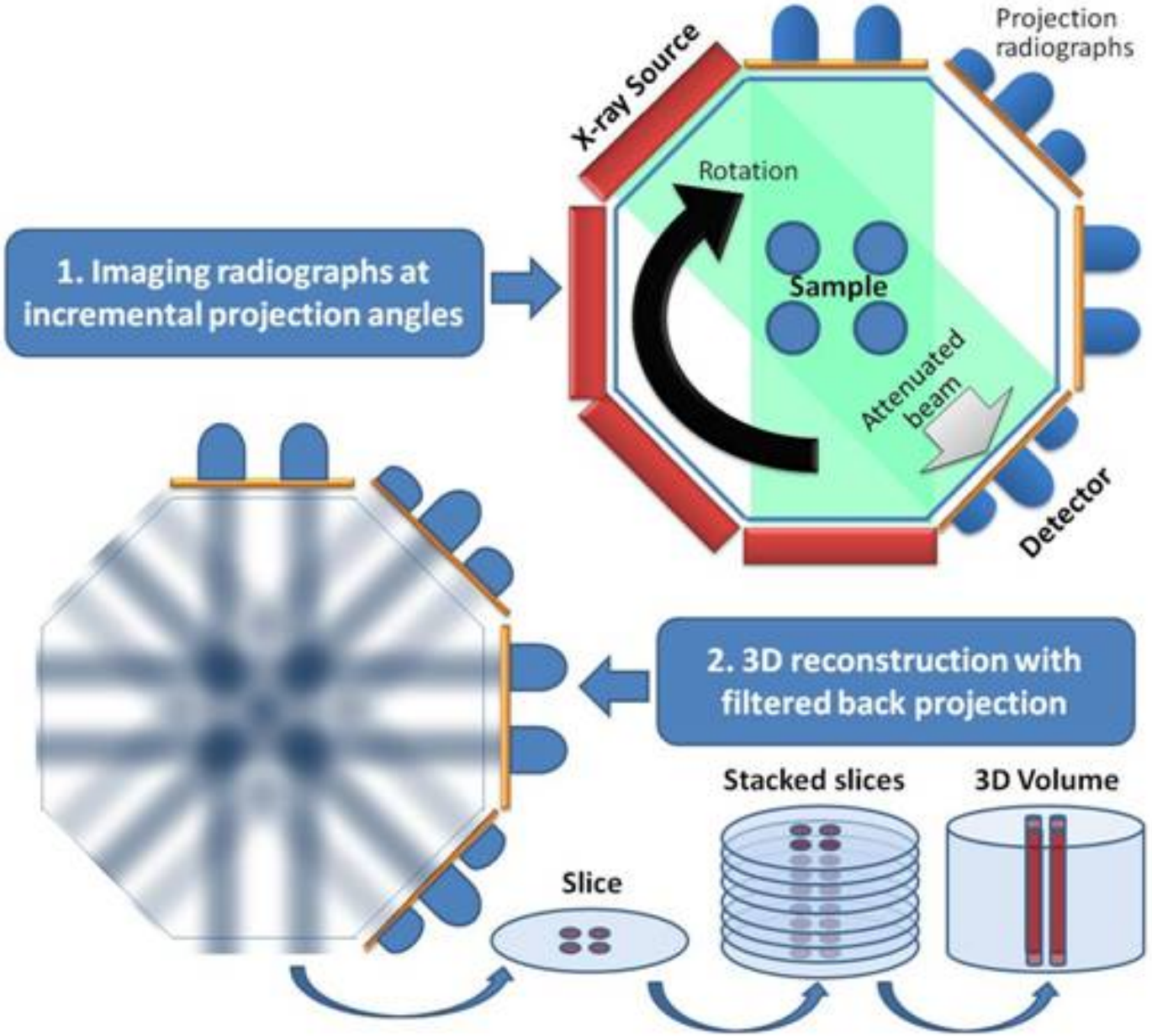
CryoEM  Computed Tomography + Photogrammetry

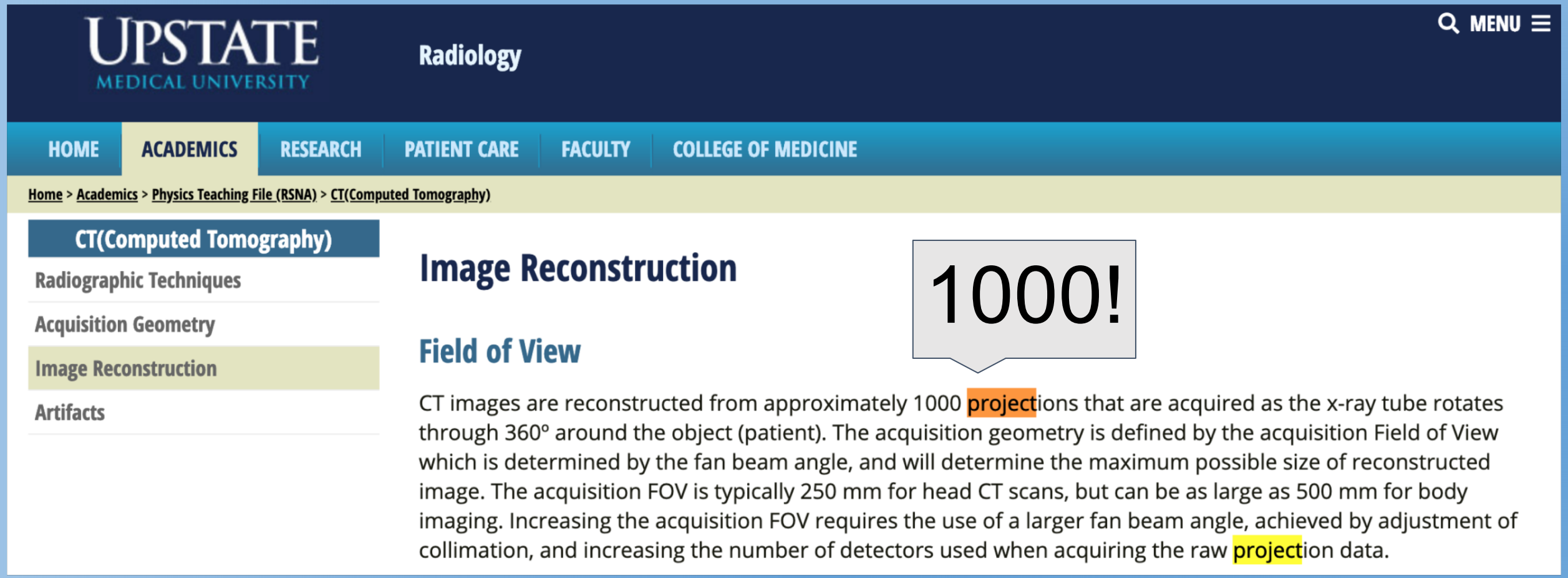




https://www.maximintegrated.com/en/app-notes/index.mvp/id/4682

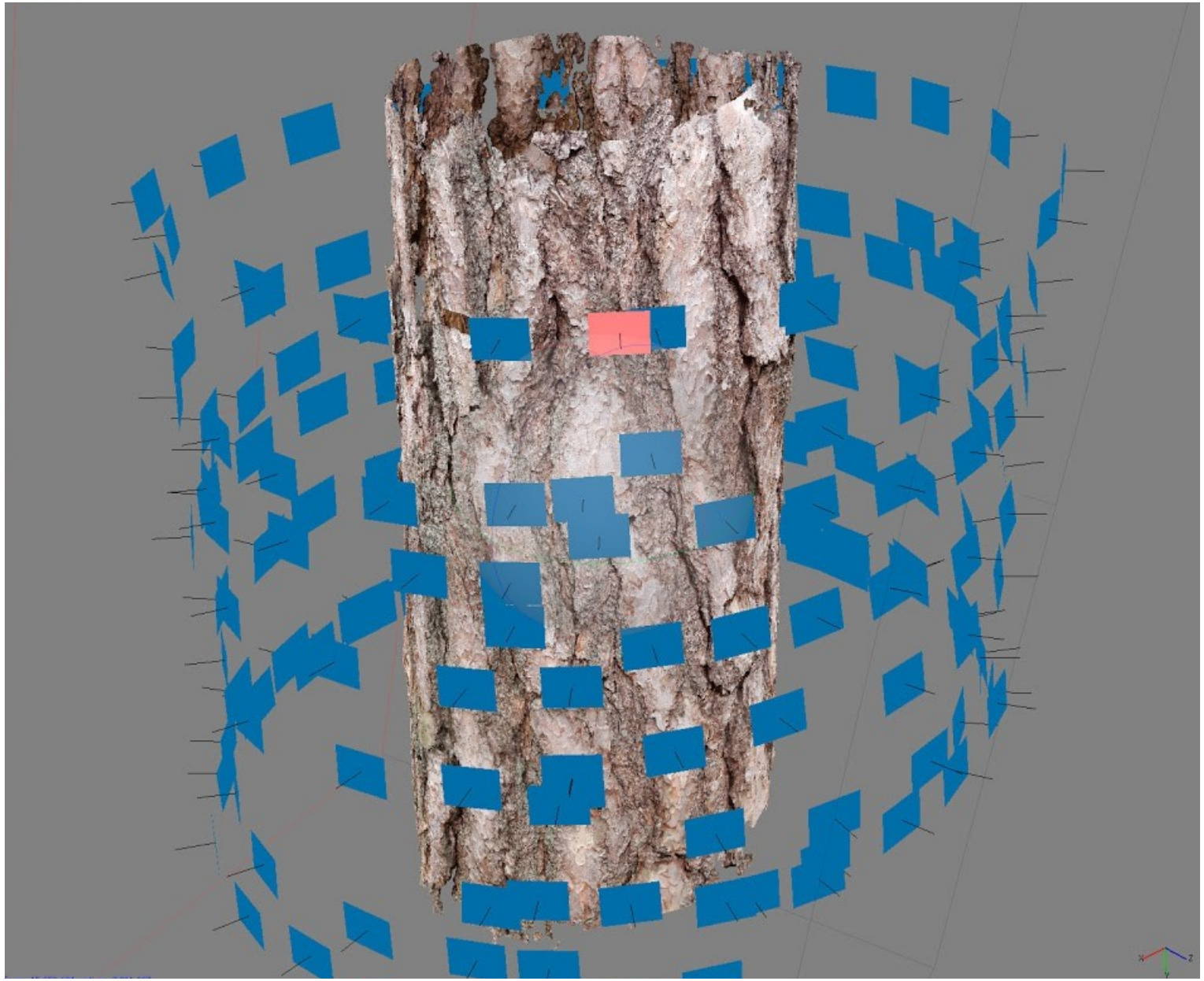
http://www.cmu.edu/me/xctf/xrayct/index.html

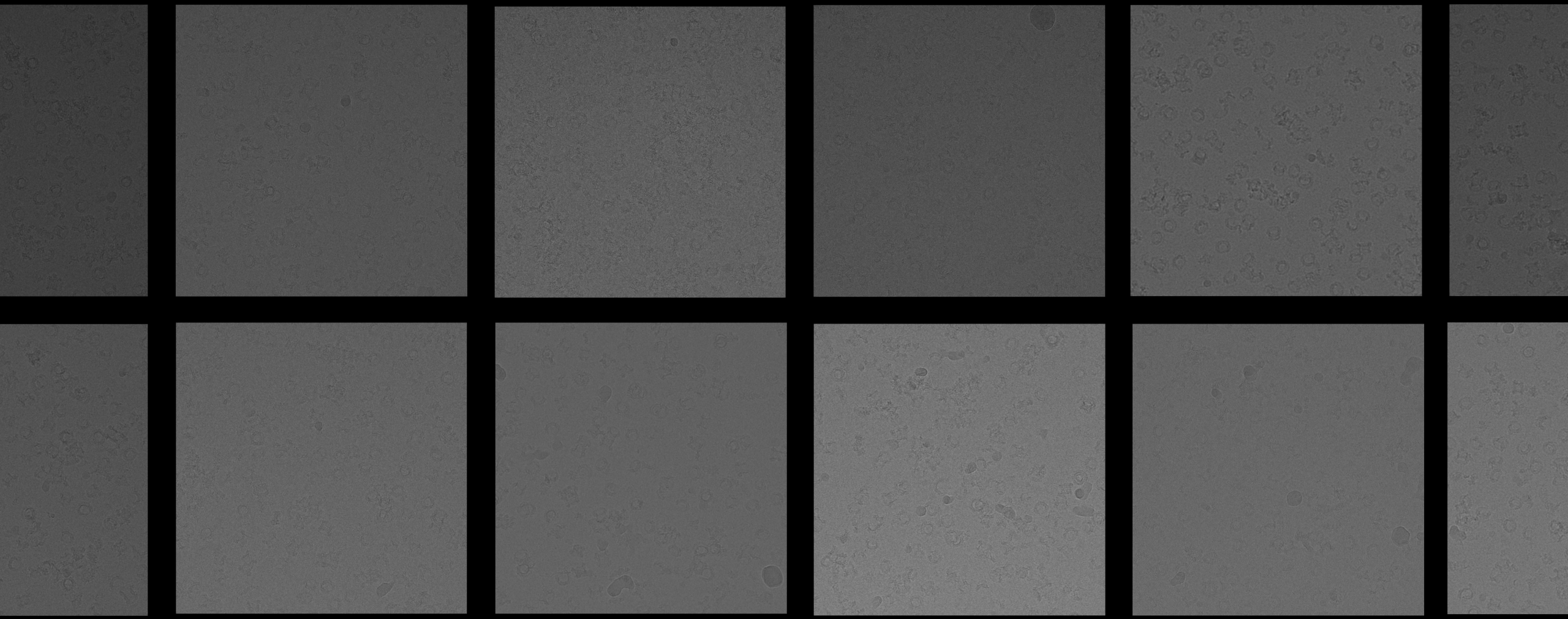
How many projections does a clinical CT use?

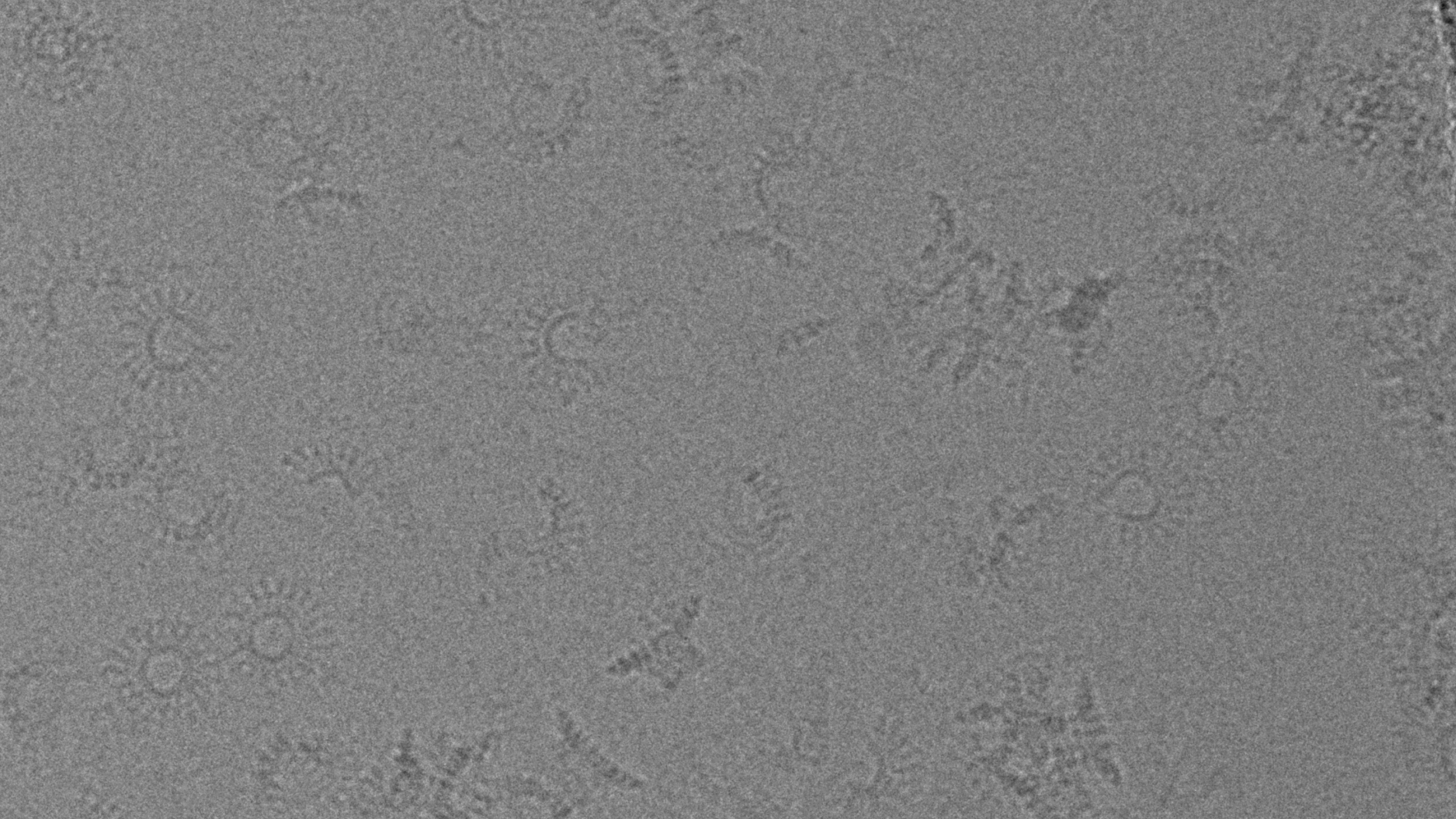


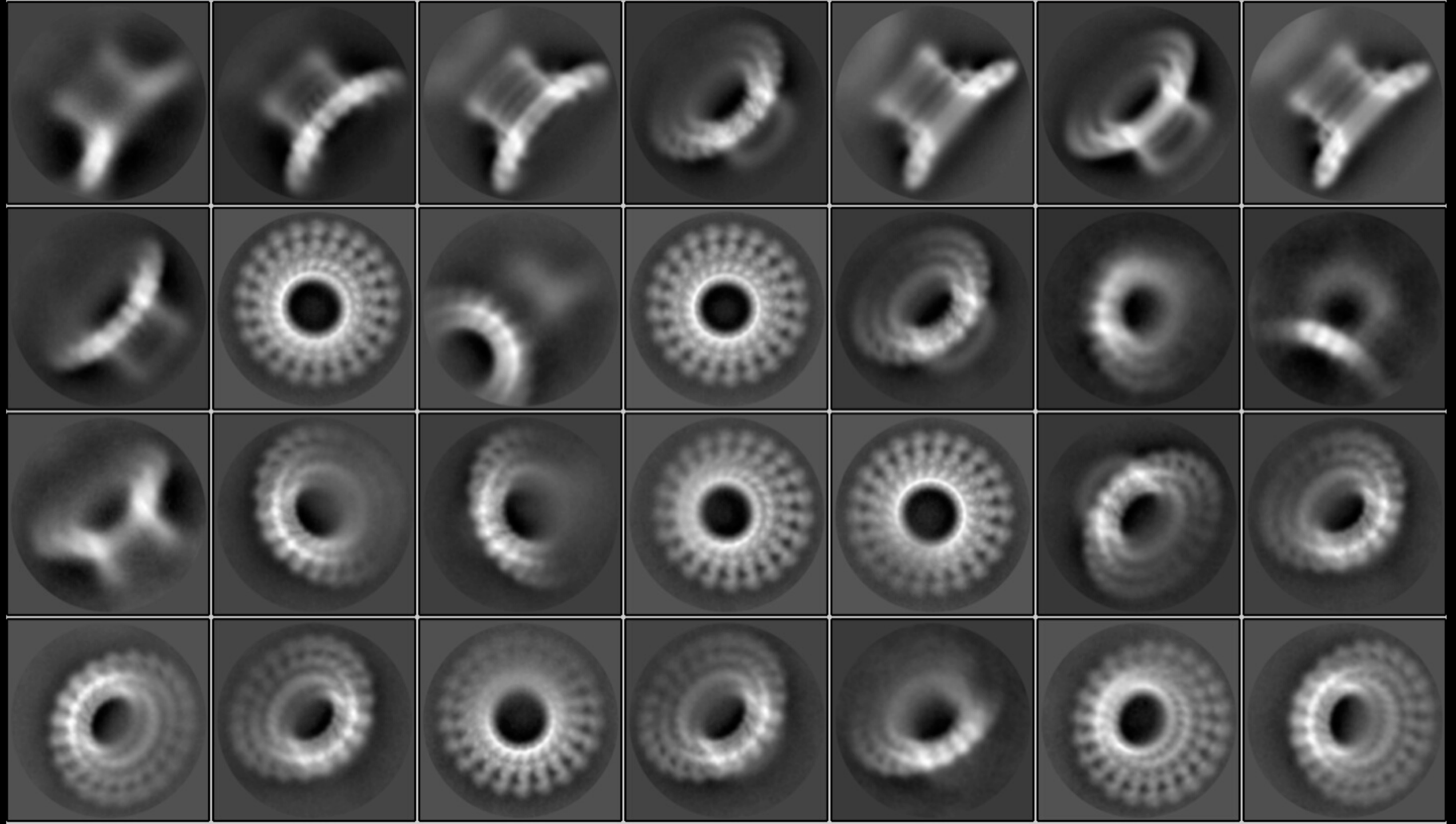
http://www.upstate.edu/radiology/education/rsna/ct/rec

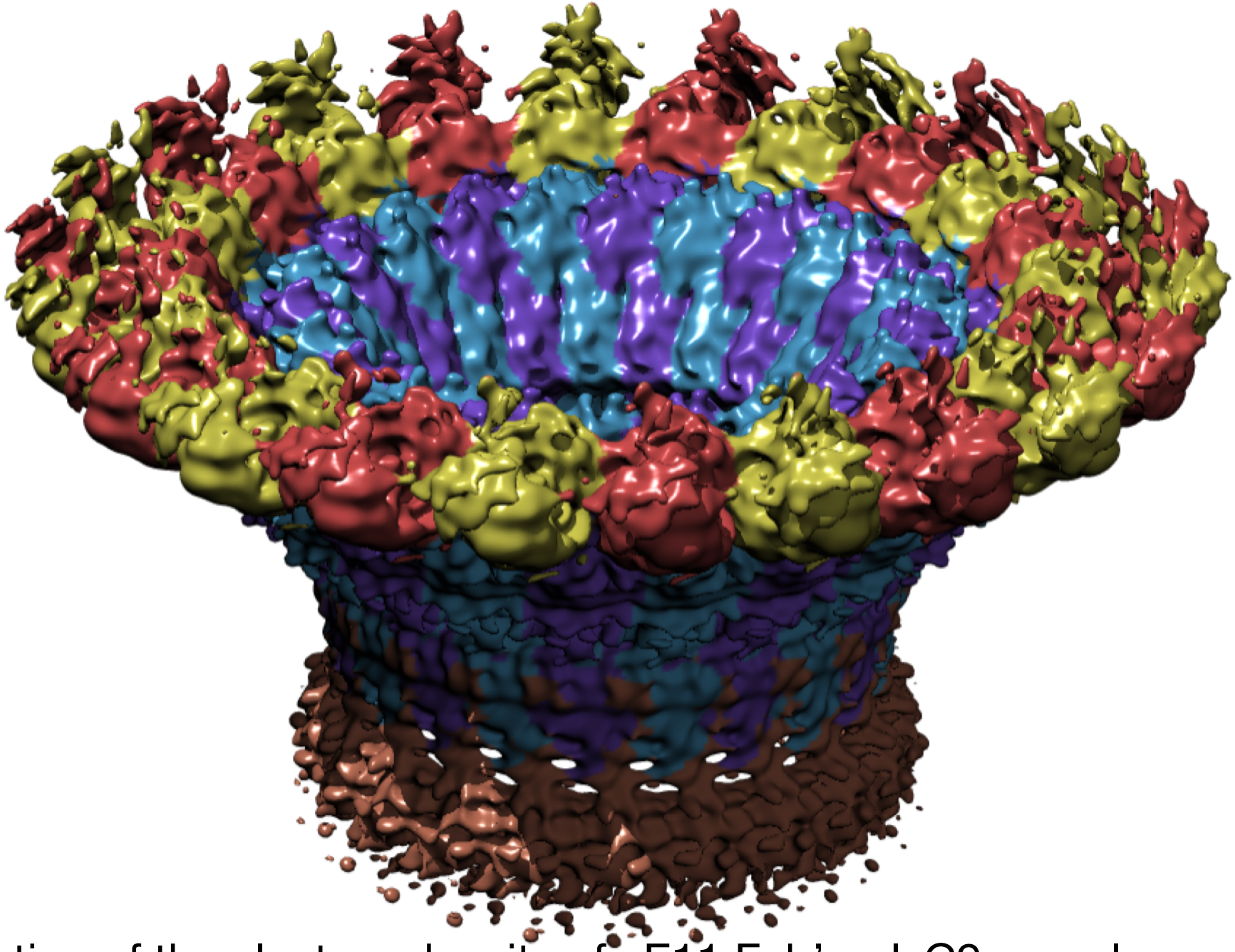
https://skfb.ly/TI89











3D reconstruction of the electron density of aE11 Fab’ polyC9 complex

What outcome are the scientists looking for?

Protein Data Bank in Europe
Bringing Structure to Biology

Examples: hemoglobin, BRCA

PDBe › 5k12

Electron Microscopy
1.8Å resolution

Cryo-EM structure of glutamate dehydrogenase at 1.8 A resolution

Source organism: *Bos taurus*

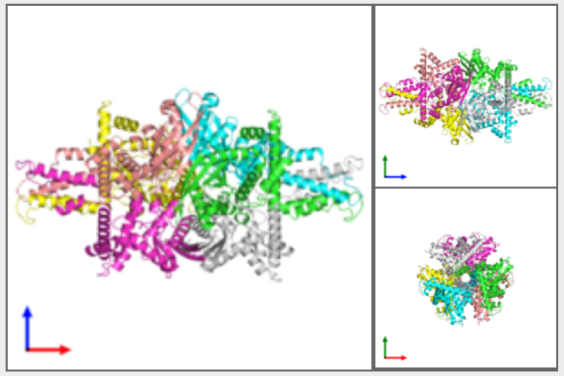
Primary publication:

Breaking Cryo-EM Resolution Barriers to Facilitate Drug Discovery.

Merk A, Bartesaghi A, Banerjee S, Falconieri V, Rao P, Davis MI, Pragani R, Boxer MB, Earl LA, Milne JL , Subramaniam S

Cell (2016)
PMID: 27238019

Released: 08 Jun 2016



Related structures: EMD-8194

http://www.ebi.ac.uk/pdbe/entry/pdb/5k12

Disease resistance and drug targets

Structural Basis for Linezolid Binding Site Rearrangement in the *Staphylococcus aureus* Ribosome

Matthew J. Belousoff,[a] Zohar Eyal,[b] Mazdak Radjainia,[c] Tofayel Ahmed,[d] Rebecca S. Bamert,[a] Donna Matzov,[b] Anat Bashan,[b] Ella Zimmerman,[b] Satabdi Mishra,[d] David Cameron,[a] Hans Elmlund,[c,e] Anton Y. Peleg,[a,f] Shashi Bhushan,[d,g] Trevor Lithgow,[a] Ada Yonath[b]

Infection & Immunity Program, Biomedicine Discovery Institute & Department of Microbiology, Monash University, Clayton, Australia[a]; Department of Structural Biology, Weizmann Institute of Science, Rehovot, Israel[b]; The Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy, Department of Biochemistry and Molecular Biology, Monash University, Victoria, Melbourne, Australia[c]; School of Biological Sciences, Nanyang Technological University, Singapore, Singapore[d]; Infection & Immunity Program, Biomedicine Discovery Institute & Department of Biochemistry and Molecular Biology, Monash University, Clayton, Australia[e]; Department of Infectious Diseases, Alfred Hospital, Prahran, Australia[f]; NTU Institute of Structural Biology, Nanyang Technological University, Singapore, Singapore[g]

ABSTRACT An unorthodox, surprising mechanism of resistance to the antibiotic linezolid was revealed by cryo-electron microscopy (cryo-EM) in the 70S ribosomes from a clinical isolate of *Staphylococcus aureus*. This high-resolution structural information demonstrated that a single amino acid deletion in ribosomal protein uL3 confers linezolid resistance despite being located 24 Å away from the linezolid binding pocket in the peptidyl-transferase center. The mutation induces a cascade of allosteric structural rearrangements of the rRNA that ultimately results in the alteration of the antibiotic binding site.

IMPORTANCE The growing burden on human health caused by various antibiotic

Received 27 March 2017 **Accepted** 17 April 2017 **Published** 9 May 2017

Citation Belousoff MJ, Eyal Z, Radjainia M, Ahmed T, Bamert RS, Matzov D, Bashan A, Zimmerman E, Mishra S, Cameron D, Elmlund H, Peleg AY, Bhushan S, Lithgow T, Yonath A. 2017. Structural basis for linezolid binding site rearrangement in the *Staphylococcus aureus* ribosome. mBio 8:e00395-17. https://doi.org/10.1128/mBio.00395-17.

https://doi.org/10.1128/mBio.00395-17

Disease resistance and drug targets

ChemPubSoc Europe

DOI: 10.1002/cmdc.201900042

CHEMMEDCHEM Communications

cryoEM-Guided Development of Antibiotics for Drug-Resistant Bacteria

Matthew J. Belousoff,[a] Hari Venugopal,[b] Alexander Wright,[c] Samuel Seoner,[c] Isabella Stuart,[a] Chris Stubenrauch,[a] Rebecca S. Bamert,[a] David W. Lupton,*[c] and Trevor Lithgow*[a]

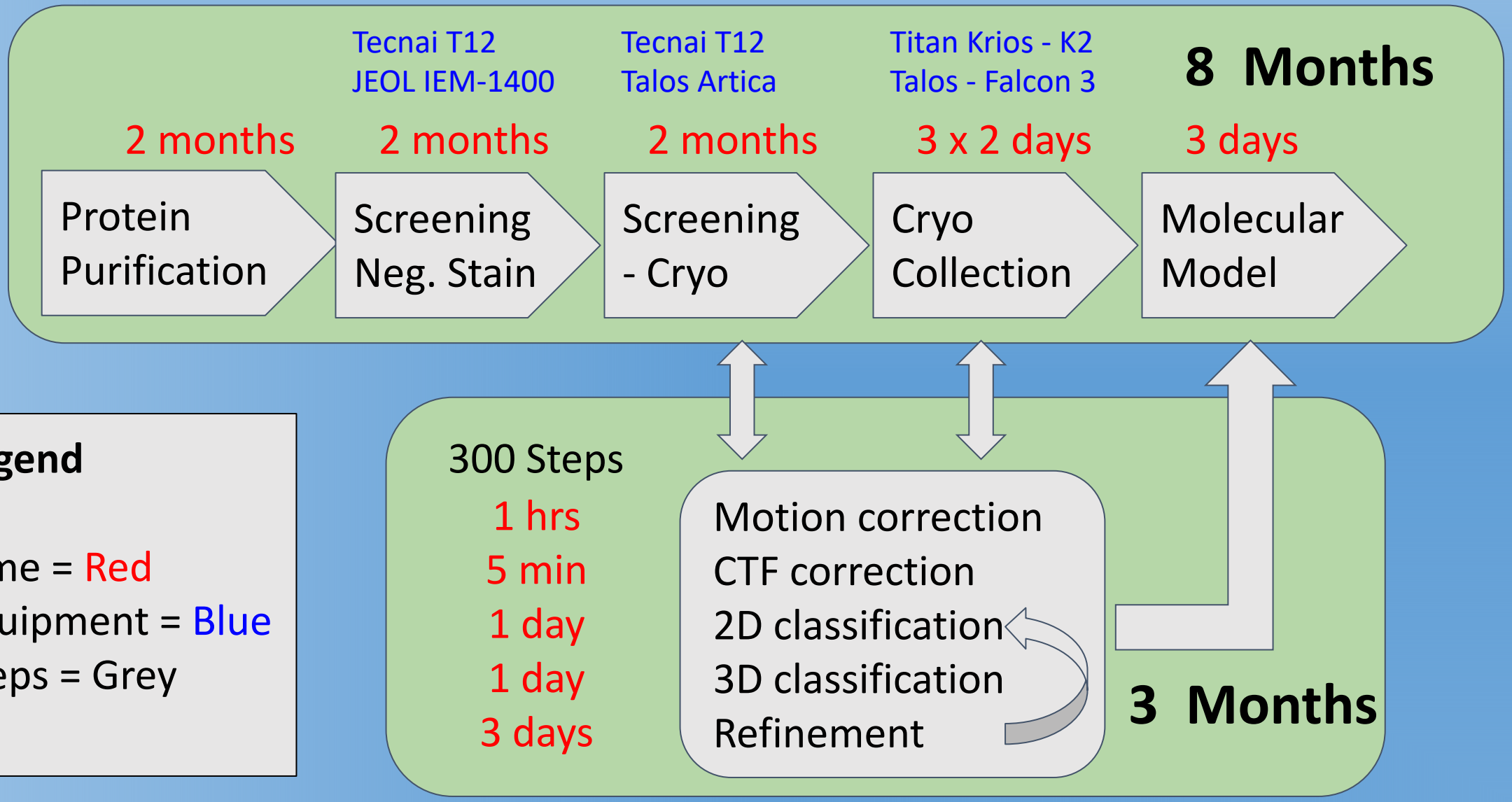
While the ribosome is a common target for antibiotics, challenges with crystallography can impede the development of new bioactives using structure-based drug design approaches. In this study we exploit common structural features present in linezolid-resistant forms of both methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) to redesign the antibiotic. Enabled by rapid and facile cryoEM structures, this process has identified (*S*)-2,2-dichloro-*N*-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (LZD-**5**) and (*S*)-2-chloro-*N*-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl) acetamide (LZD-**6**), which inhibit the ribosomal function and growth of linezolid-resistant MRSA and VRE. The strategy discussed highlights the potential for cryoEM to facilitate the development of novel bioactive materials.

dition to reaching resolution targets that allow unambiguous placement of small molecules, cryoEM is a solution-phase technique which may prove advantageous. Although cryoEM-guided design of novel ligands is underdeveloped, the interactions of known drugs with their targets have been examined with the *Plasmodium* 20S proteasome,[6] the GPCR family,[7] pathogenic ribosomes,[8] receptor-bound insulin,[9] and important HIV viral entry proteins,[10] to name a few examples. In 2017, Scheres, Baum, and co-workers exploited cryoEM to elucidate the mode of action that mefloquine uses to inhibit the *Plasmodium falciparum* ribosome, and then used this insight to develop a next-generation molecule with enhanced antiparasitic activity.[11] As part of our studies into mechanisms of antibiotic resistance, we examined one of the escape routes that *Staphylococcus aureus* uses to develop resistance to the ribosomal-interfering antibiotic, linezolid.[8a] These studies, and those of others [12] show that disparate mutations result in a common

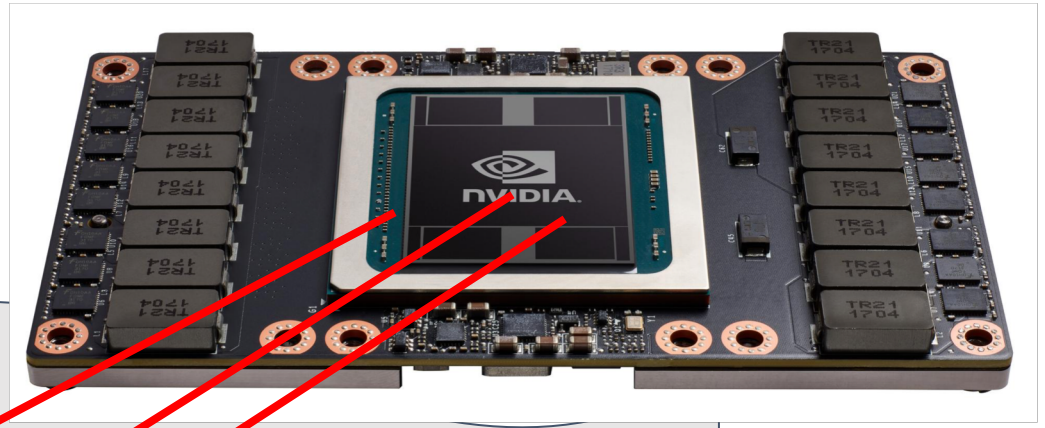
https://doi.org/10.1002/cmdc.201900042

What is a time taken for analysis of a single dataset set?

Paper Processing Time



How much are GPUs used in preprocessing?



Important quote:

"The structure determination task is further **complicated** by the **lack of information** about the relative orientations of all particles and, in the case of **structural variability** in the sample, also their assignment to a structurally unique class."

doi:10.1016/j.jmb.2011.11.010 *J. Mol. Biol.* (2012) **415**, 406–418

Contents lists available at www.sciencedirect.com

Journal of Molecular Biology

journal homepage: http://ees.elsevier.com.jmb

A Bayesian View on Cryo-EM Structure Determination

Sjors H. W. Scheres

MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 0QH, UK

Received 4 August 2011; received in revised form 27 October 2011; accepted 3 November 2011
Available online 12 November 2011

Edited by W. Baumeister

Keywords:
cryo-electron microscopy; three-dimensional reconstruction; *maximum a posteriori* estimation

Three-dimensional (3D) structure determination by single-particle analysis of cryo-electron microscopy (cryo-EM) images requires many parameters to be determined from extremely noisy data. This makes the method prone to overfitting, that is, when structures describe noise rather than signal, in particular near their resolution limit where noise levels are highest. Cryo-EM structures are typically filtered using *ad hoc* procedures to prevent overfitting, but the tuning of arbitrary parameters may lead to subjectivity in the results. I describe a Bayesian interpretation of cryo-EM structure determination, where smoothness in the reconstructed density is imposed through a Gaussian prior in the Fourier domain. The statistical framework dictates how data and prior knowledge should be combined, so that the optimal 3D linear filter is obtained without the need for arbitrariness and objective resolution estimates may be obtained. Application to experimental data indicates that the statistical approach yields more reliable structures than existing methods and is capable of detecting smaller classes in data sets that contain multiple different structures.

What are the major analysis steps?

2D Classification

3D Classification

Refinement

Hint: All use GPUs and are done repeatedly.

What is 2D Classification?

2D classification results are a way to visualize how your 2D images will cluster together into homogenous class averages without any model required.

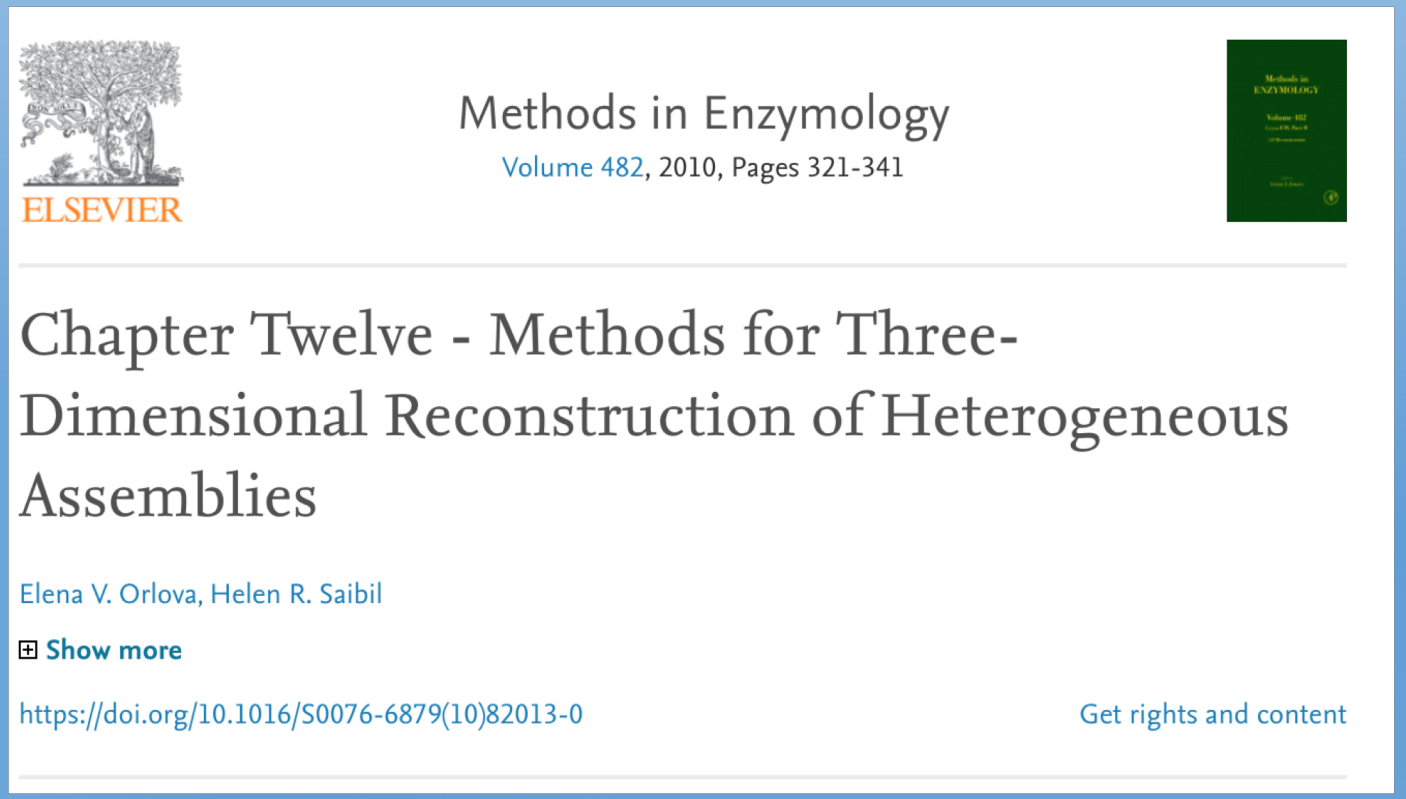
Source: https://github.com/cianfrocco-lab/Old-school-processing/wiki/2D-classification

2D Classification

The ML2D algorithm may be used to simultaneously align and classify single-particle images

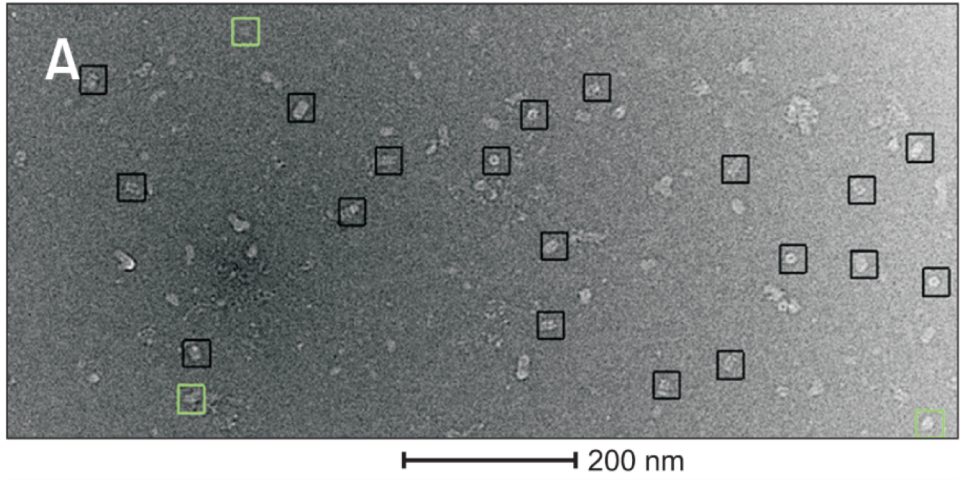
An intrinsic characteristic of the ML approach is that it does not assign images to one particular class or orientation. Instead, images are compared with all references in all possible orientations and probability weights are calculated for each possibility.

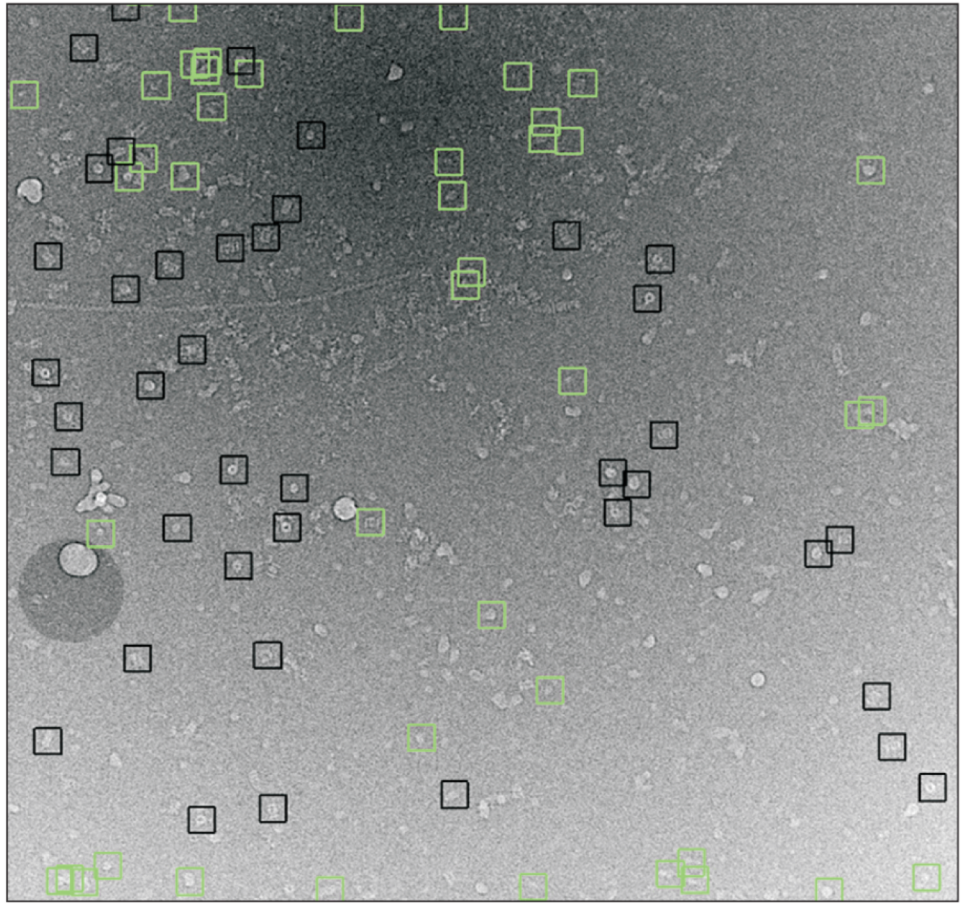
(Maximum Likelihood)

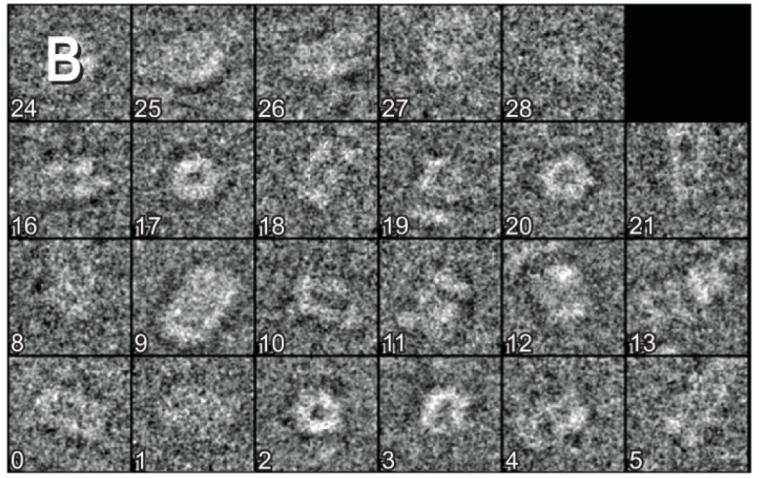


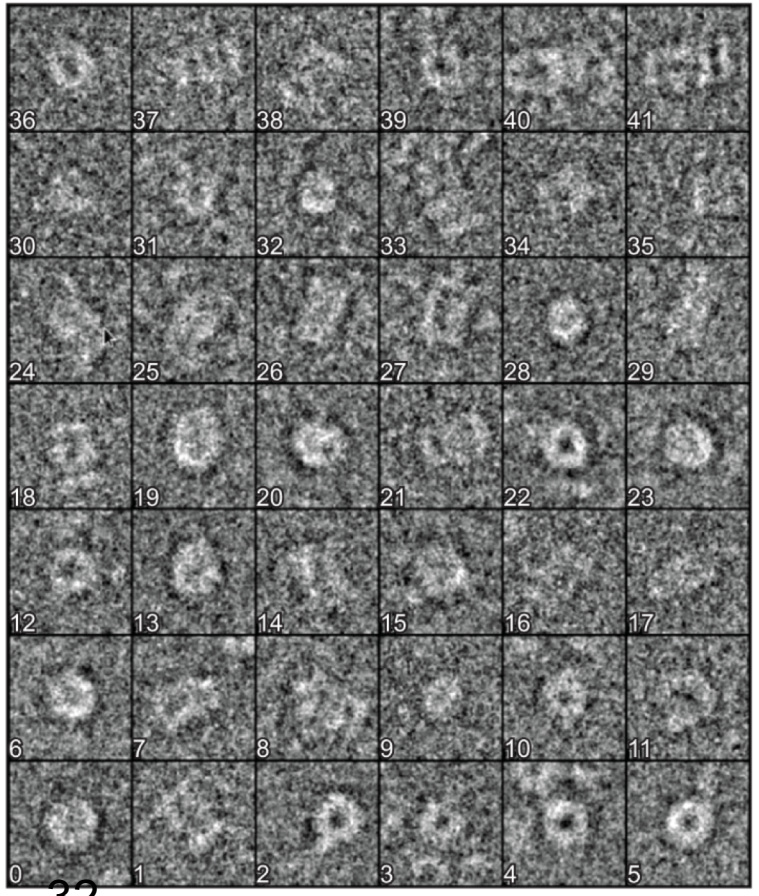
https://doi.org/10.1016/S0076-6879(10)82013-0

Particle picking for next step of classification in 2D





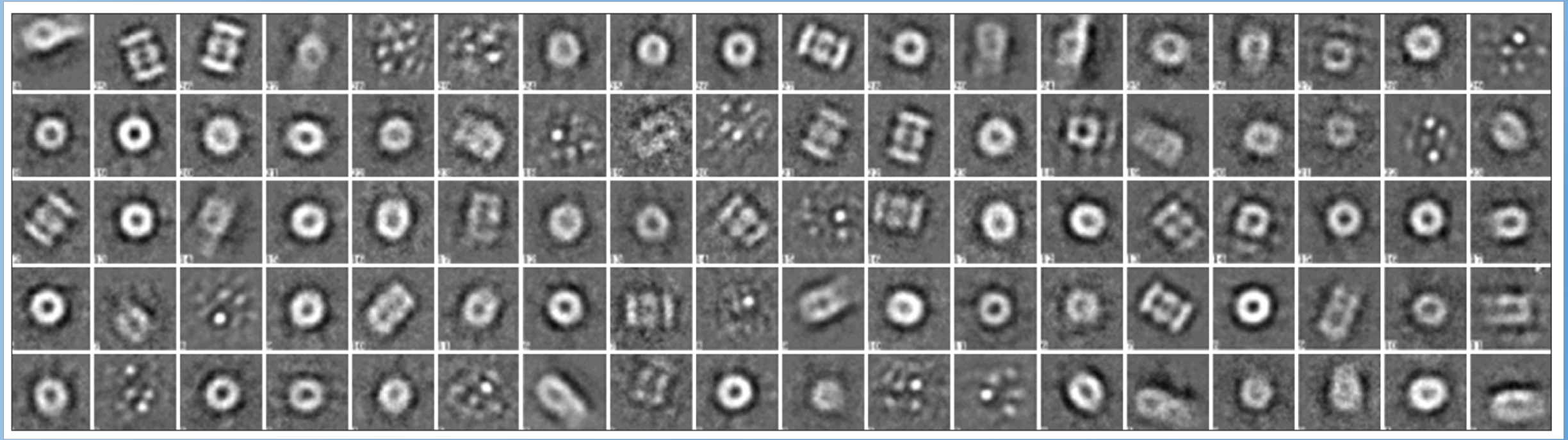




Boxed particles

Source: https://www.e-sciencecentral.org/articles/Table.php?xn=am/am-48-001&id=

Classification of selected particles in 2D



Source: https://www.e-sciencecentral.org/articles/Table.php?xn=am/am-48-001&id=

What is 3D Classification?

“The premise of 3D classification is to use an initial starting model to sort your particles into 3 or more groups. By using the 3D model, Relion uses maximum likelihood methods to create homogenous classes of particles that will belong to a given group.”

Source: https://github.com/cianfrocco-lab/Old-school-processing/wiki/Relion-3D-classification

What is a time taken for analysis of a single dataset set?

What is the problem? Antibiotics at crisis point

Slow time from lead compound to clinic Increasing prevalence of resistant bacteria in the clinic

UK AMR review: “Deaths by infection will be larger than both cancer and diabetes combined by 2050…..”

A big problem is Methicillin-resistant Staphylococcus aureus (MRSA) and Vancomycin-resistant Enterococci (VRE)…

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Eur Rev Med Pharmacol Sci. 2017 Oct;21(17):3974-3979.

Linezolid vs. vancomycin in treatment of methicillin-resistant staphylococcus aureus infections: a meta-analysis.

Li J[1], Zhao QH, Huang KC, Li ZQ, Zhang LY, Qin DY, Pan F, Huang WX.

Author information

Abstract

OBJECTIVE: This study aims to explore the treatment of methicillin-resistant staphylococcus aureus (MRSA) infection by using meta-analysis method.

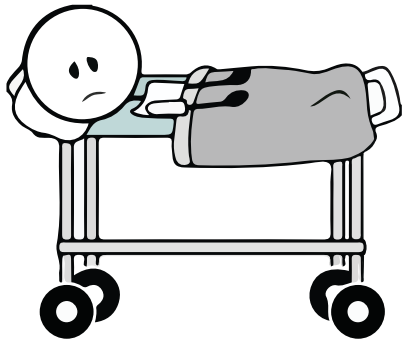
MATERIALS AND METHODS: Pubmed/Medline, ScienceDirect, CNKI and Wanfang database were comprehensively searched to obtain the randomized controlled trials (RCTs) on linezolid and vancomycin in the treatment of MRSA infections. We extracted features and information of included studies and selected appropriate effect models based on the heterogeneity test results. The funnel plot was used to analyze publication bias.

RESULTS: A total of seven RCTs including 5376 cases met the inclusion criteria. Meta-analysis showed that the clinical cure rate of linezolid group was higher than that of vancomycin group after treatment (OR = 1.85; 95% CI: 1.33-2.59, p<0.001) and follow-up (OR = 1.49; 95% CI: 1.17-1.91, p=0.001). In the microbiologically evaluable patients, end of therapy (EOT) MRSA clearance rate, and test of cure (TOC) MRSA clearance rate of linezolid were superior to those of vancomycin.

CONCLUSIONS: Based on the combined analysis of randomized controlled trials, the efficacy of linezolid should be better than that of vancomycin in the treatment of infections caused by MRSA, but conclusions still need to be further validated by more well-designed RCTs of a large sample.

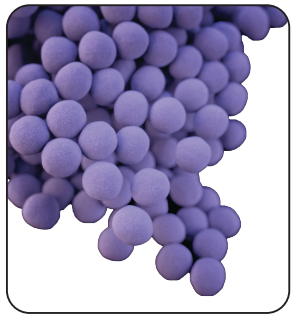
Patient to Microscope "Pragmatic Approach"

- Rational redesign of existing drug pharmaphacores
  - **Linezolid**
  - Virginiamycin (Synercid)
    - More tractable chemical synthesis of fully synthetic derivatives
  - Thiostrepton
    - Semi-synthetic modifications to help with drug solubility



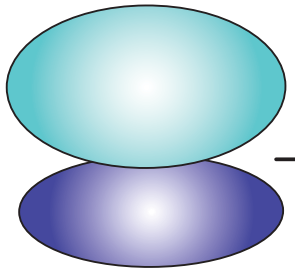
Australian patient contracts MRSA

Linezolid resistance



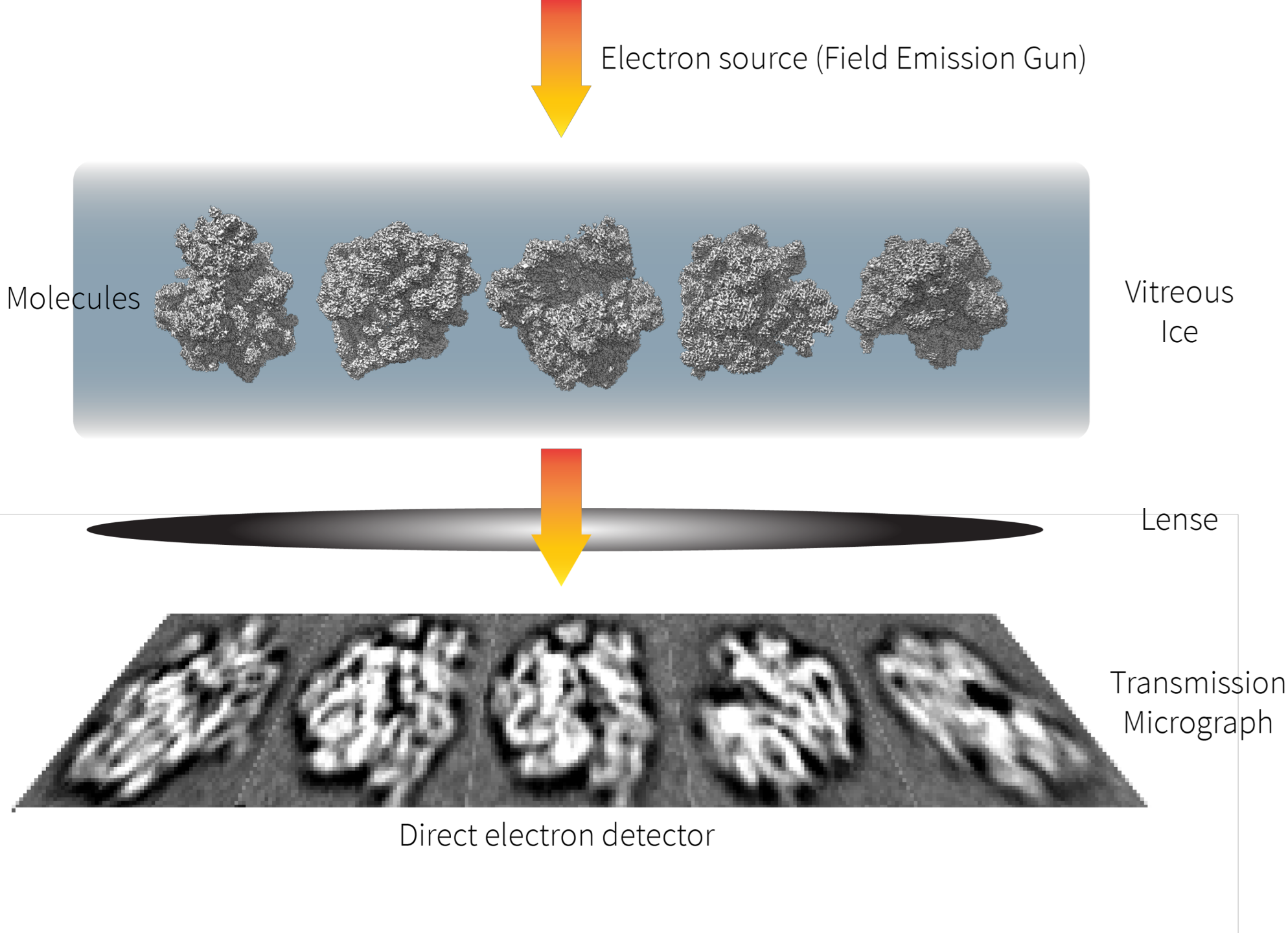
MDR-MRSA Isolated

Genome seqenced (Illumina)

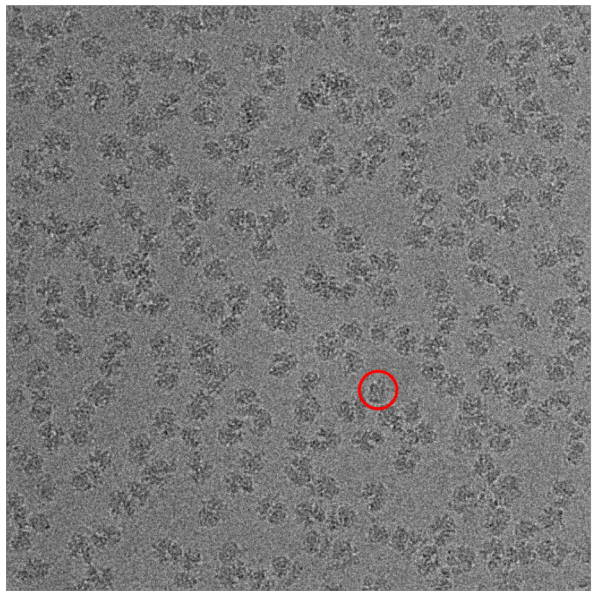


70S ribosomes Isolated

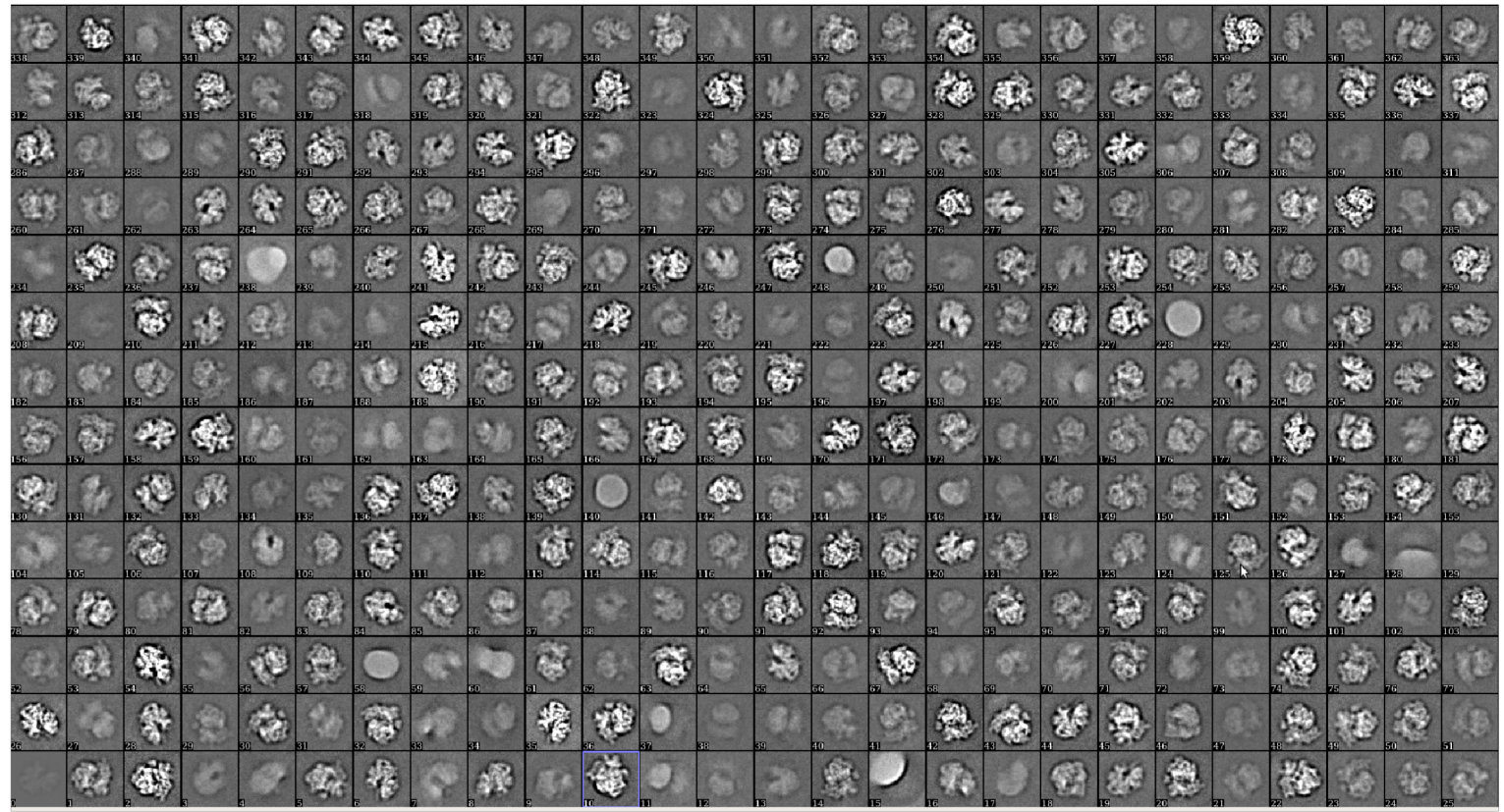
Ribosomes imaged on FEI Titan Krios


Electron source (Field Emission Gun)
Molecules
Vitreous
Ice
Lense
Transmission
Micrograph
Direct electron detector

TEM Micrograph

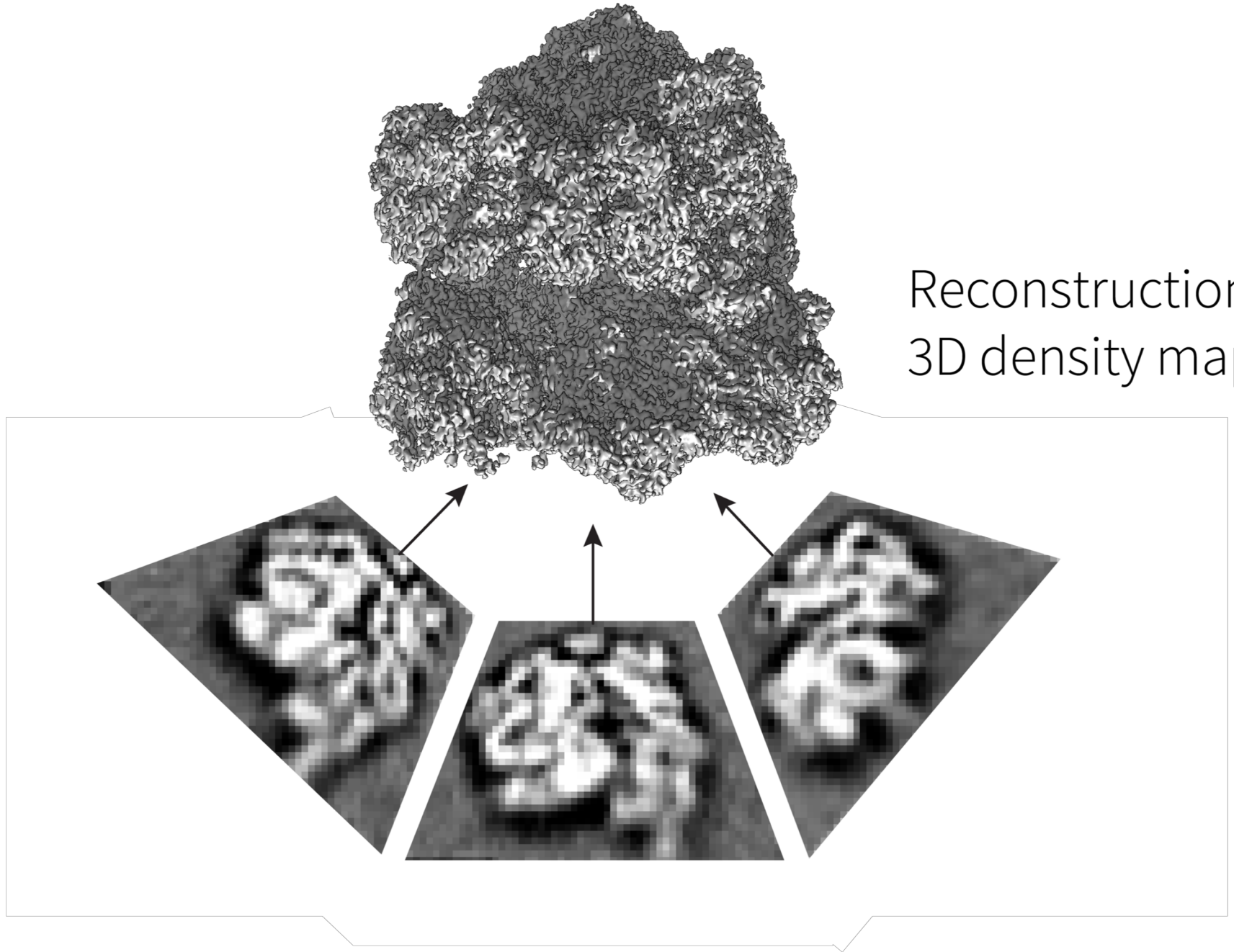


2D Particle Classes



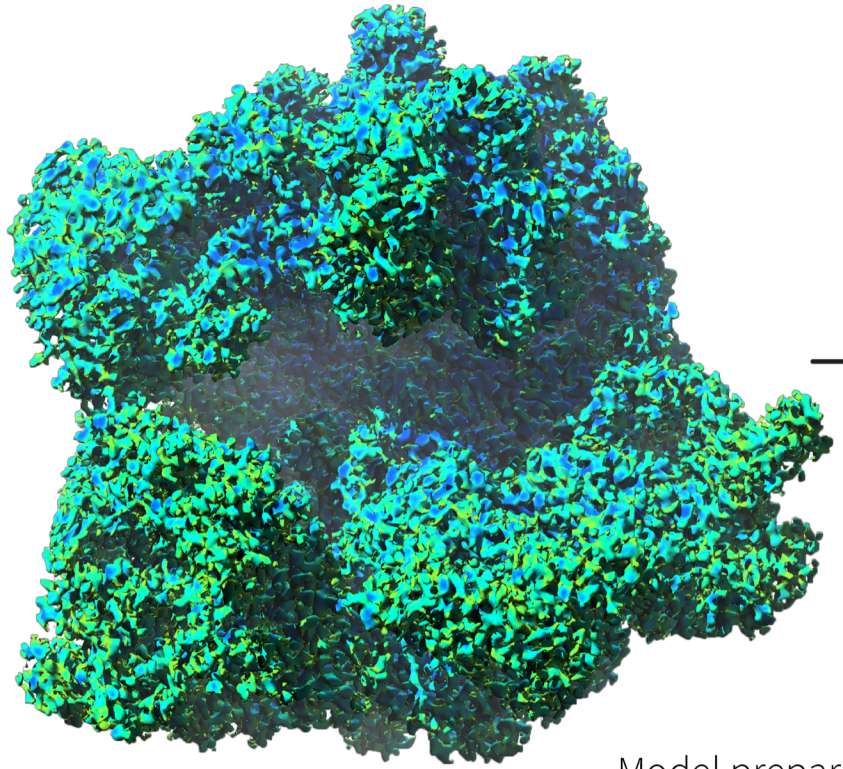
- CTF Correction of micrographs
- Particle extraction
- Classifcation of Particles

- ~300 - 500k particles collected

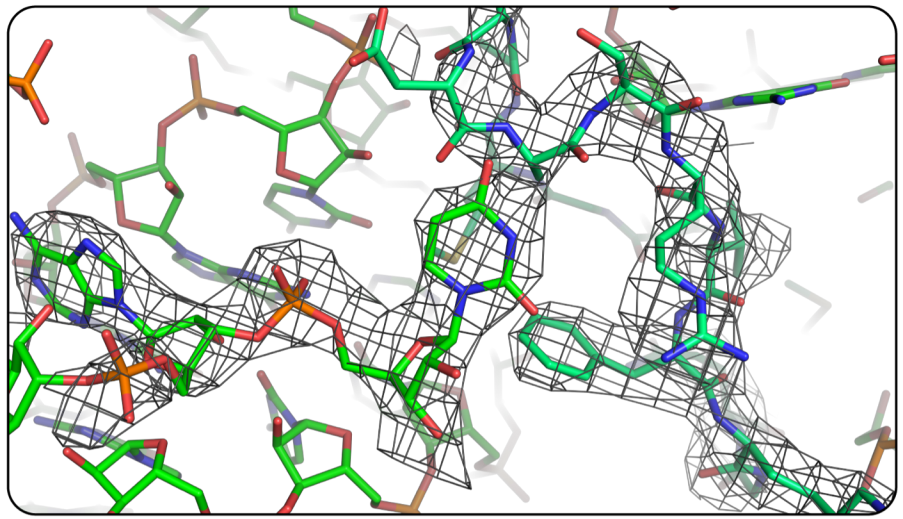


Reconstruction of
3D density map

Electron density map (70S)



Molecular modelling



Density map drawn @ 5 σ

- Model preparation (Rosetta / coot)
- Energy guided molecular dynamics (namd2)
- Manual model building (coot)
- Refinement (Phenix)

How long does an analysis take (and why?)?

2017

- ~1-4TB raw data set/sample ~2000-5000 files
- Pipeline analysis with internal & external tools
- Require large memory gpu > 8GB
- Require large system memory > 64GB
- Require cpu cores 200 - 400
- Parallel file reads and writes

2019

- ~1-10TB raw data set/sample ~2000-10000 files
- Require large memory gpu > 16GB
- Require large system memory > 18GB
- Require cpu cores 30 - 130
- Parallel file reads and writes and high ops local cache

Task	Submitted?	GPU?	Nodes	Time
Import	No			< 1 min
Motion Correction	Yes	Yes	3	20 min
CTF estimation	Yes	No	1	20 min
Manual Picking	No			?
Autopicking	Yes	Yes	2	40 min
Particle Extraction	Yes	No	1	10 min
2D Classification	Yes	Yes	2	10 min/iteration
3D Classification	Yes	Yes	1	10 min/iteration
3D Refine	Yes	Yes	2	5-10 min/iteration
Movie Refine	Yes	No	1	1 hour
Particle Polishing	Yes	No	1	1-2 hours
Mask Creation	No			5-30 min
Postprocessing	No			<1 min

How long do each of the steps take?

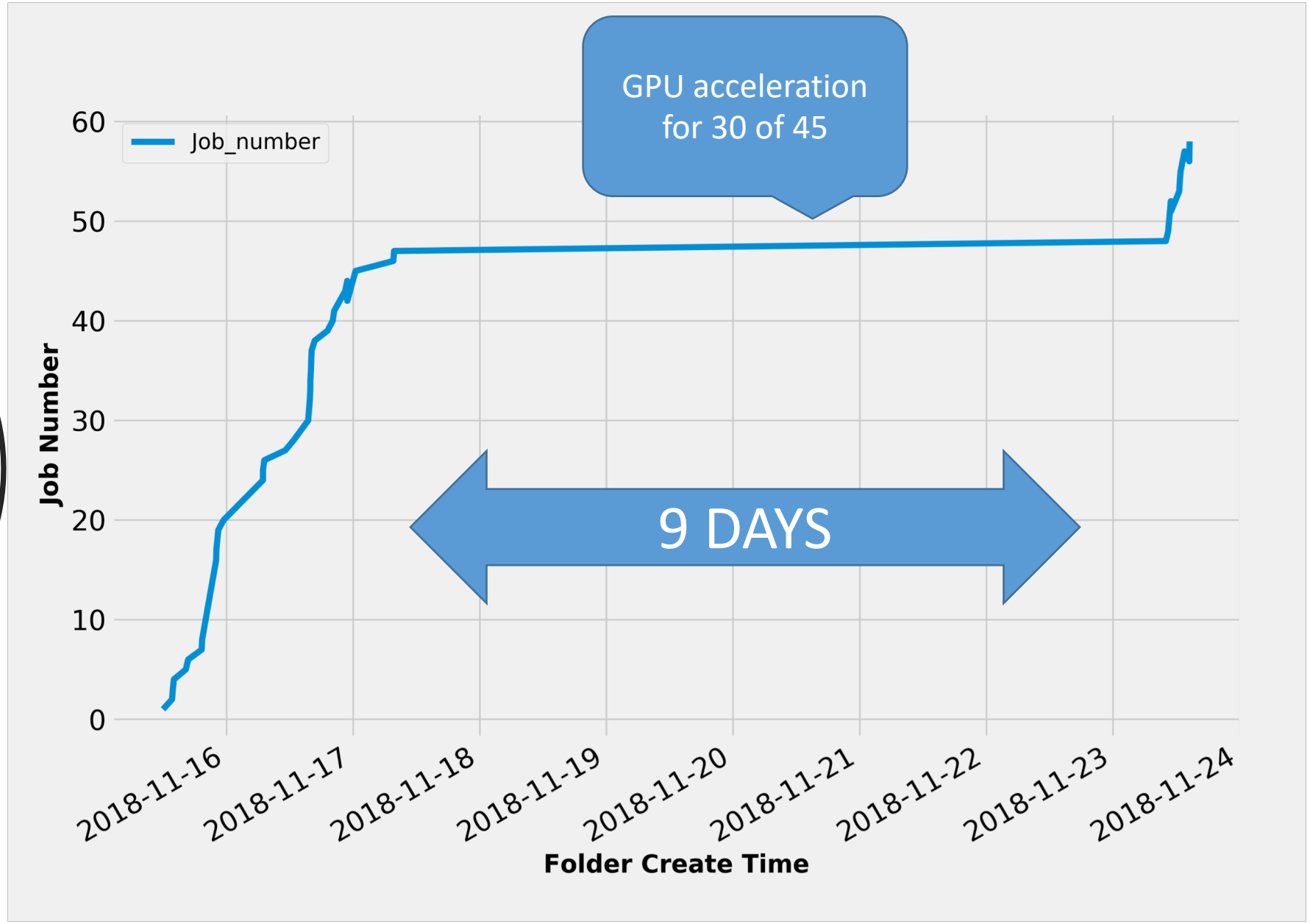
- 2,500 images
- 150,000 particles
- 260 pixels

Malaria Parasitic Protein

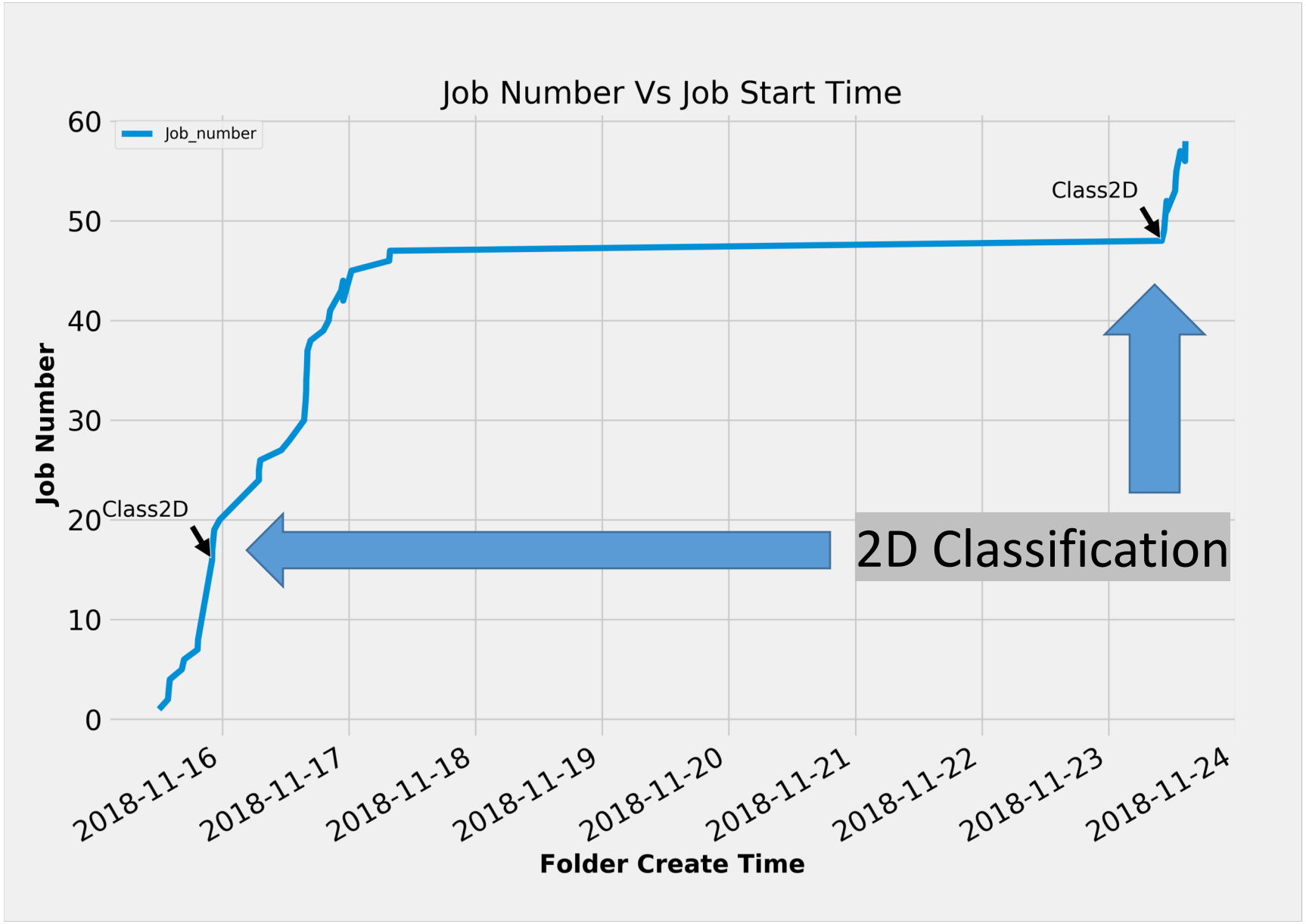
Protein used for metabolic recycling
~200 kDa *150 Å diameter*
Resolution = 2.6 Å
Particles Used in Reconstuction = 32 k

Unpublished Data

How long does an analysis take (and why?)?

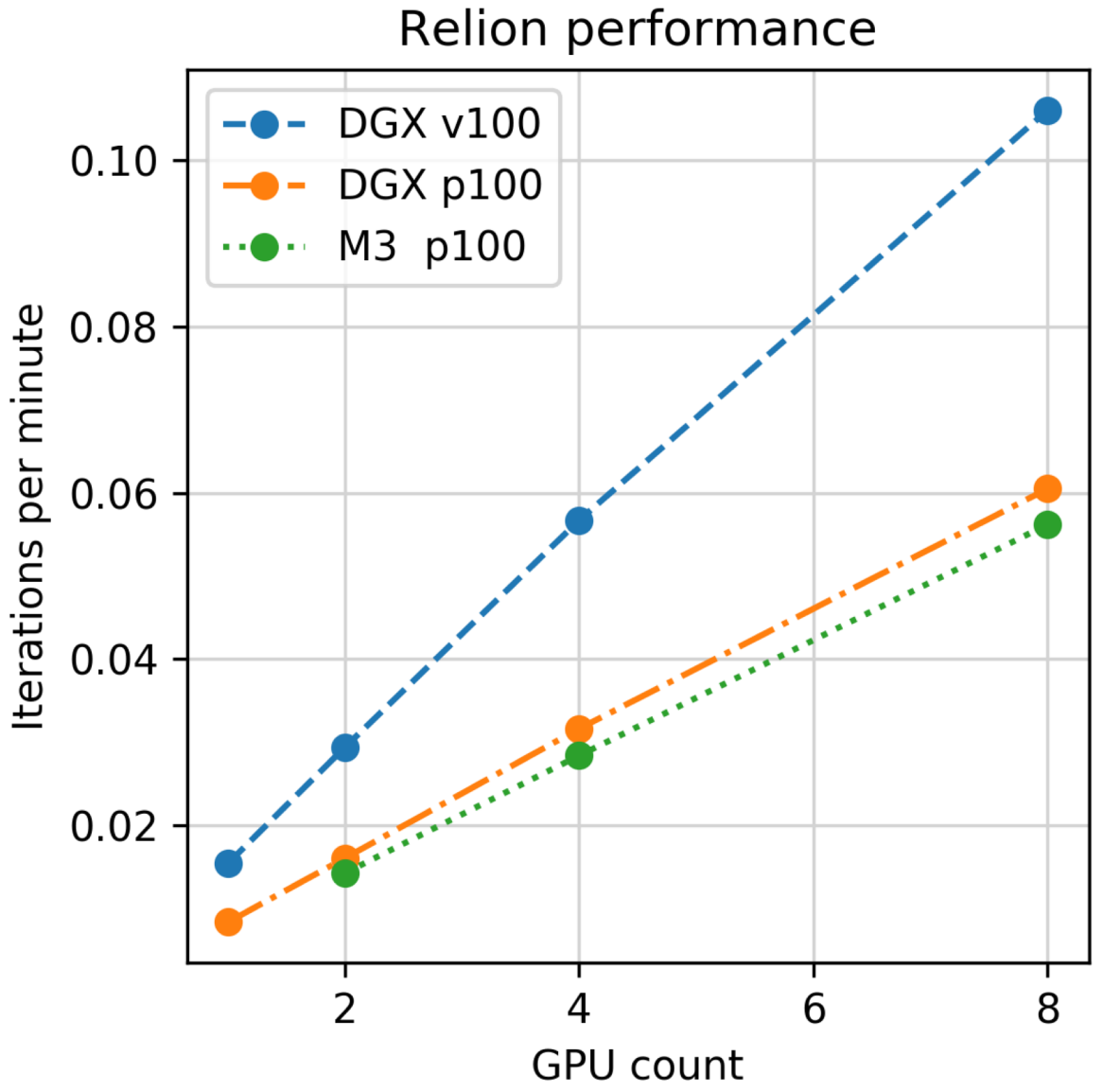


How long does an analysis take (and why?)?



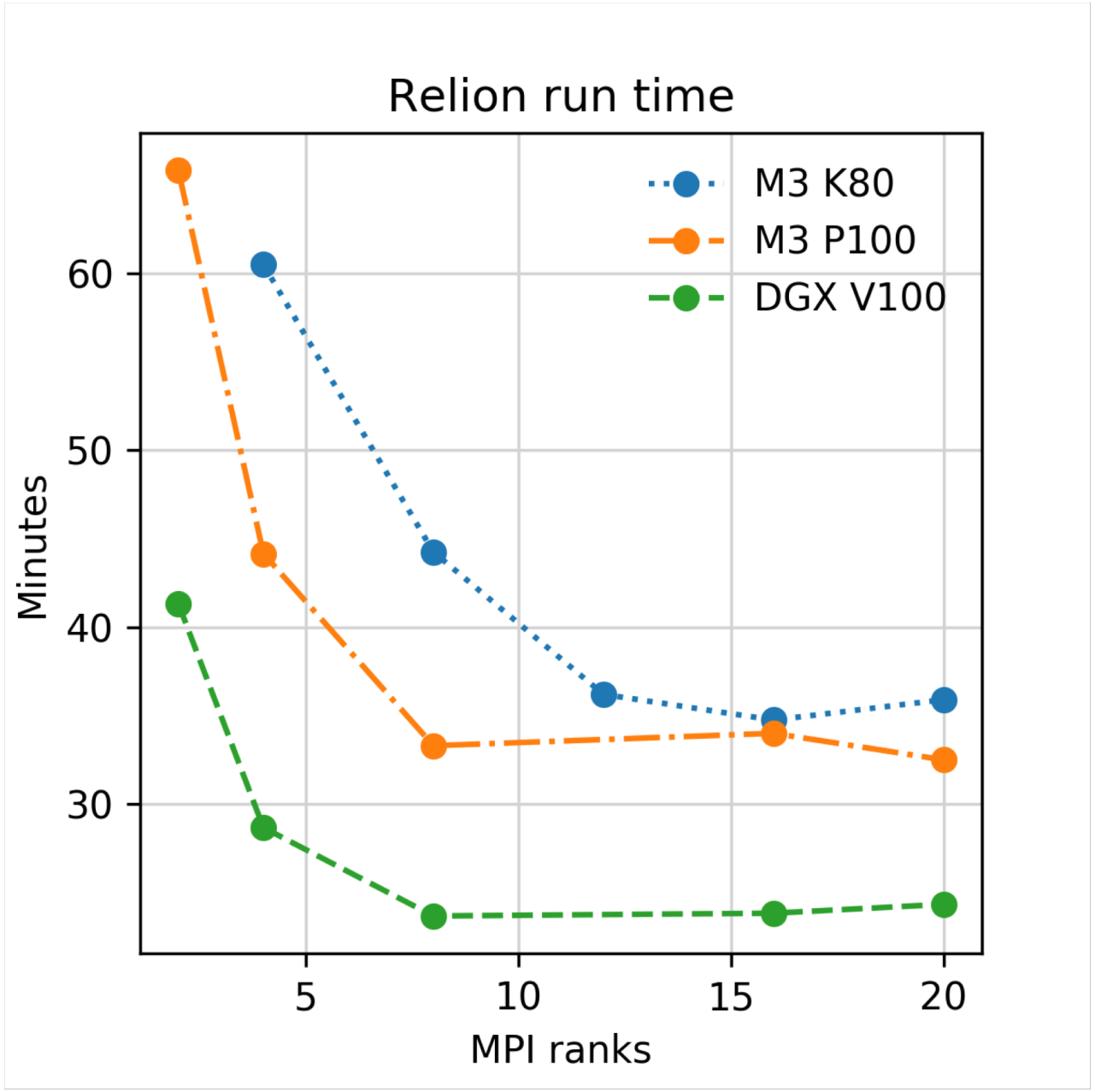
Does GPU architecture affect performance?

~ 2 x per generation (Kepler -> Volta)



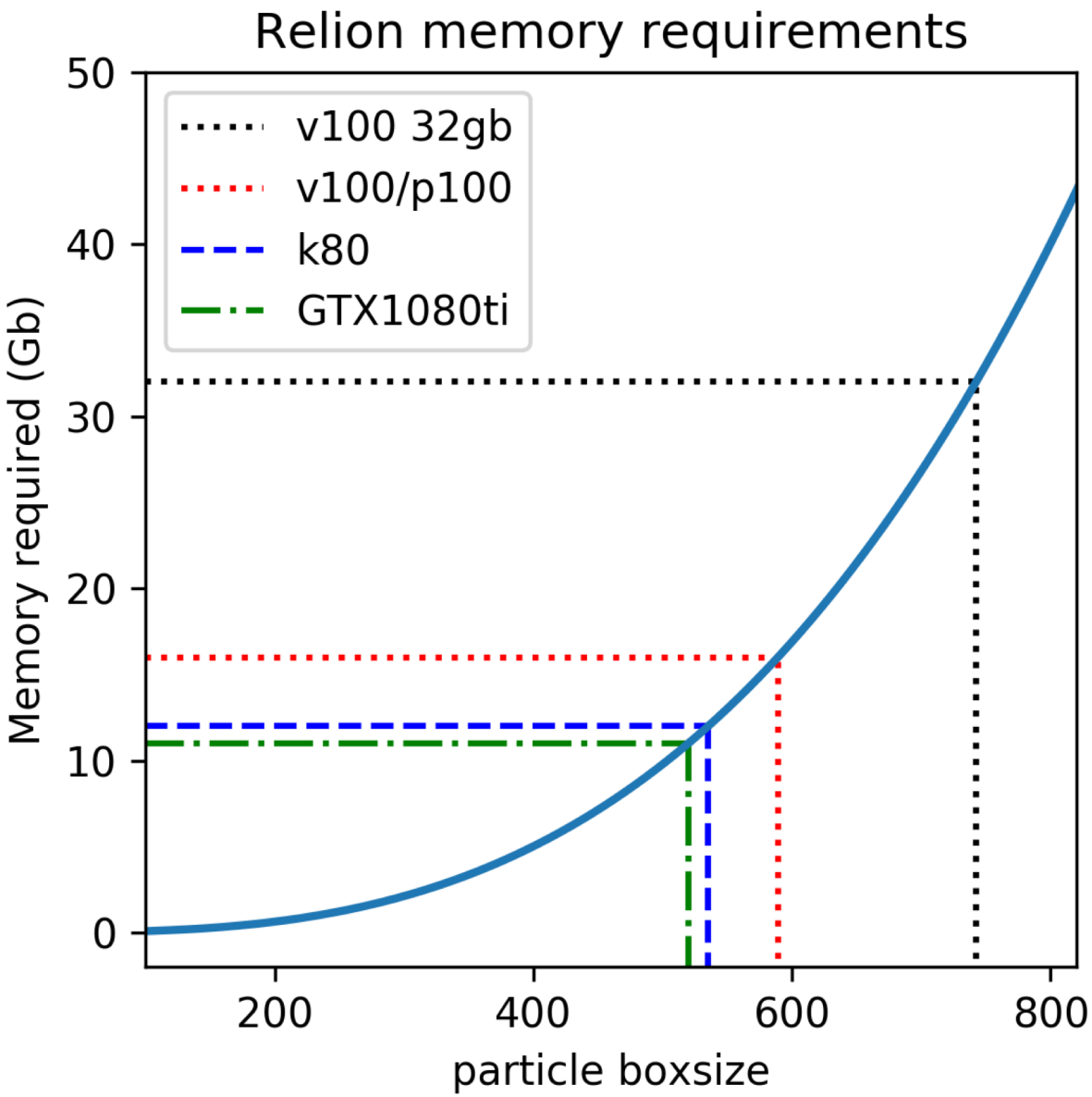
Does job layout matter between GPU architectures?

Volta peaks at lower MPI ranks, leaves more GPU Ram available



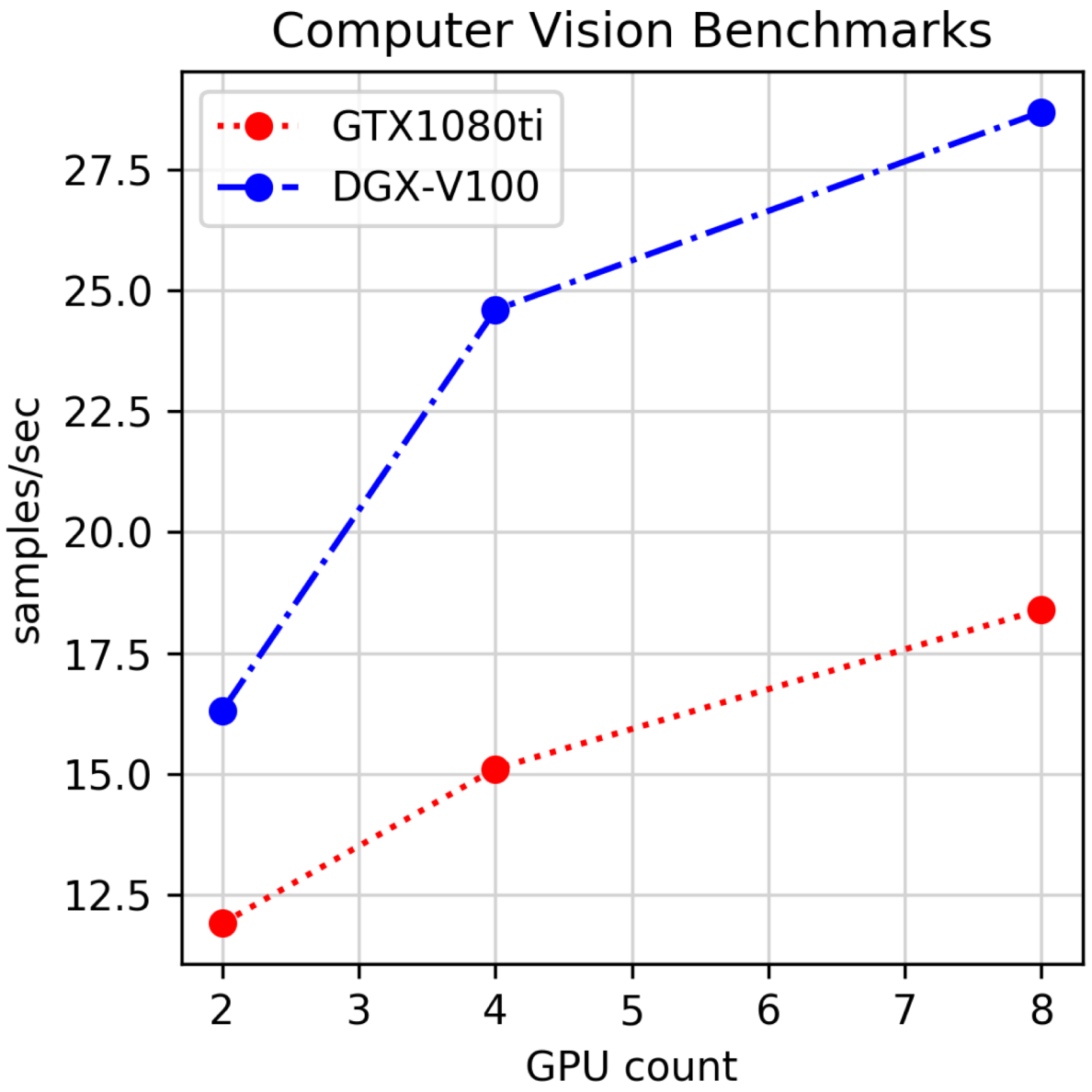
How does GPU Ram affect scientific outcomes?

K3 cameras produce 5k images



Workstation GPUs vs HPC GPUs?

~30% Faster, even faster for higher precision

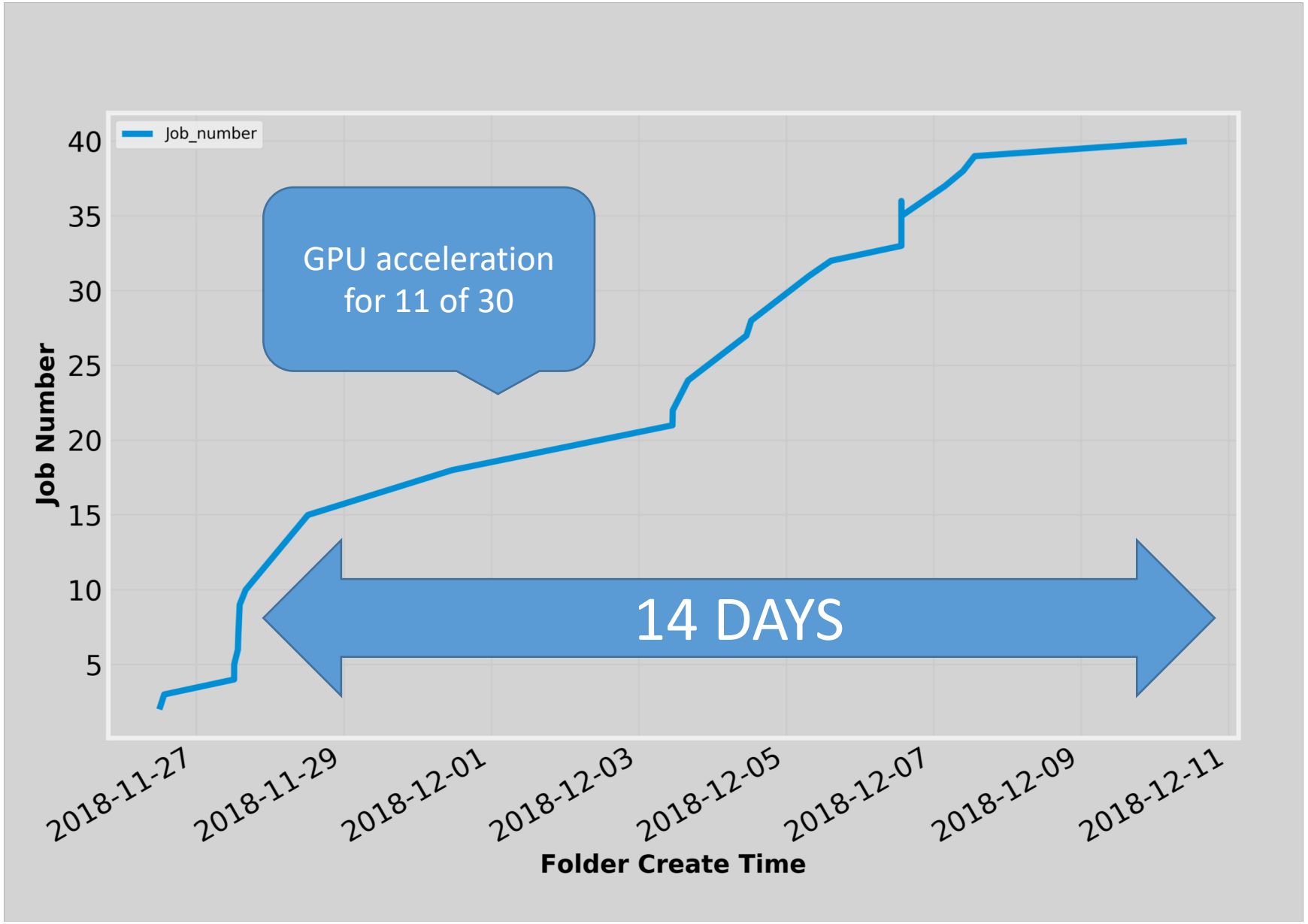


Methicillin Resistant Ribosome

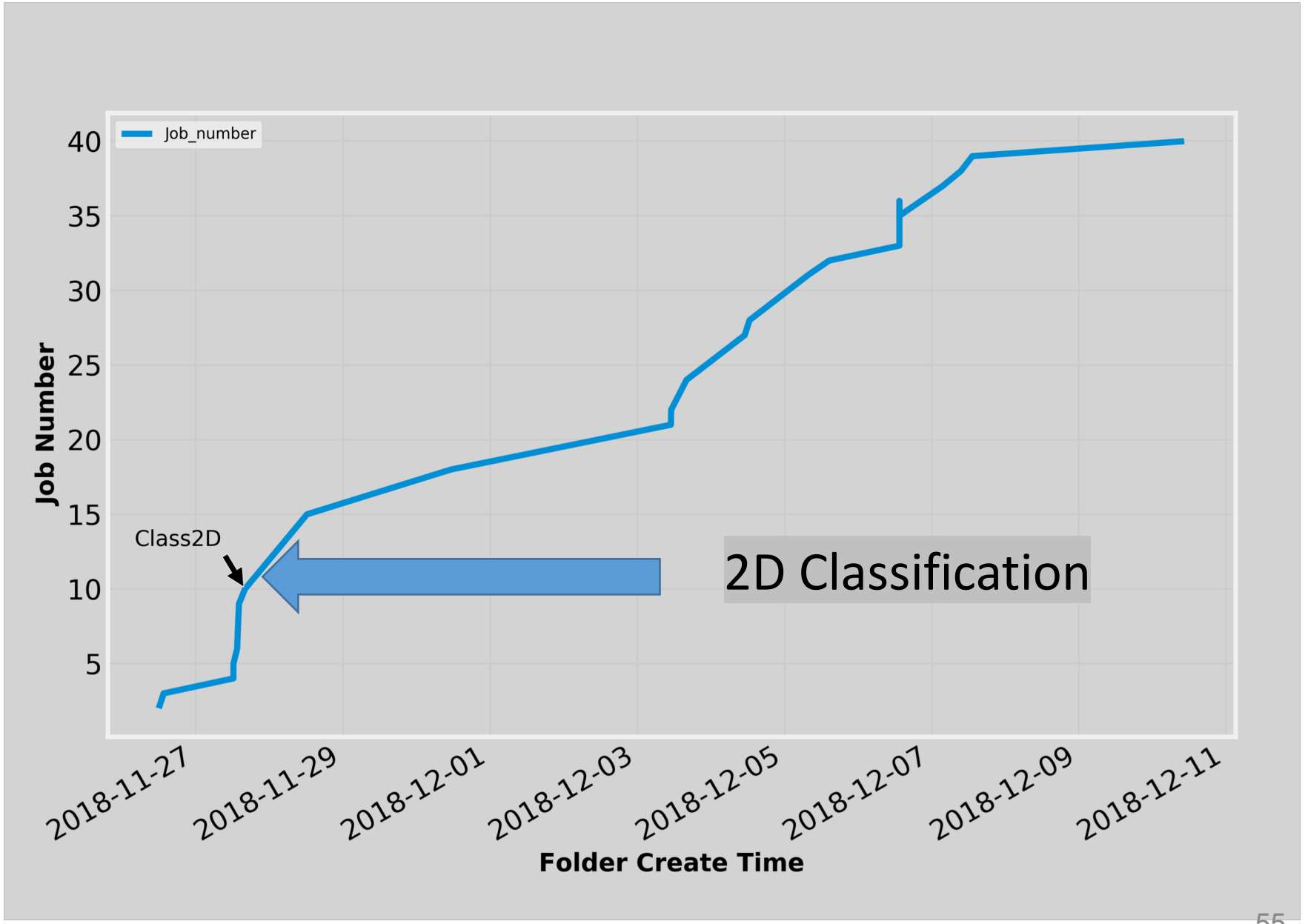
Nanomachine used for protein synthesis
In complex with new antibiotic - Tedizolid
~3.8 MDa *310 Å diameter*
Resolution = 3.1 Å
Particles Used in Reconstuction = 77 k

Unpublished Data

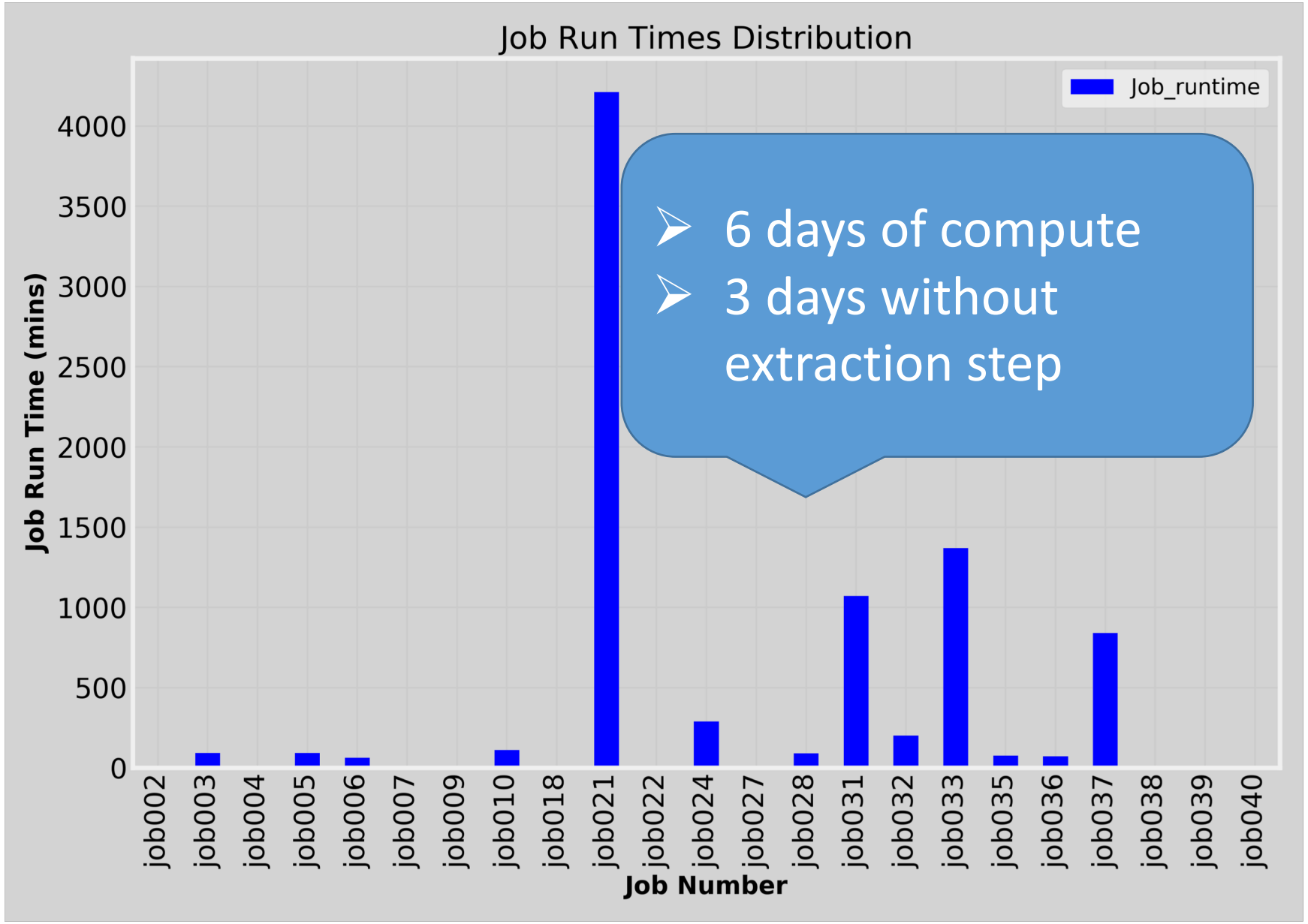
How long does an analysis take (and why?)?



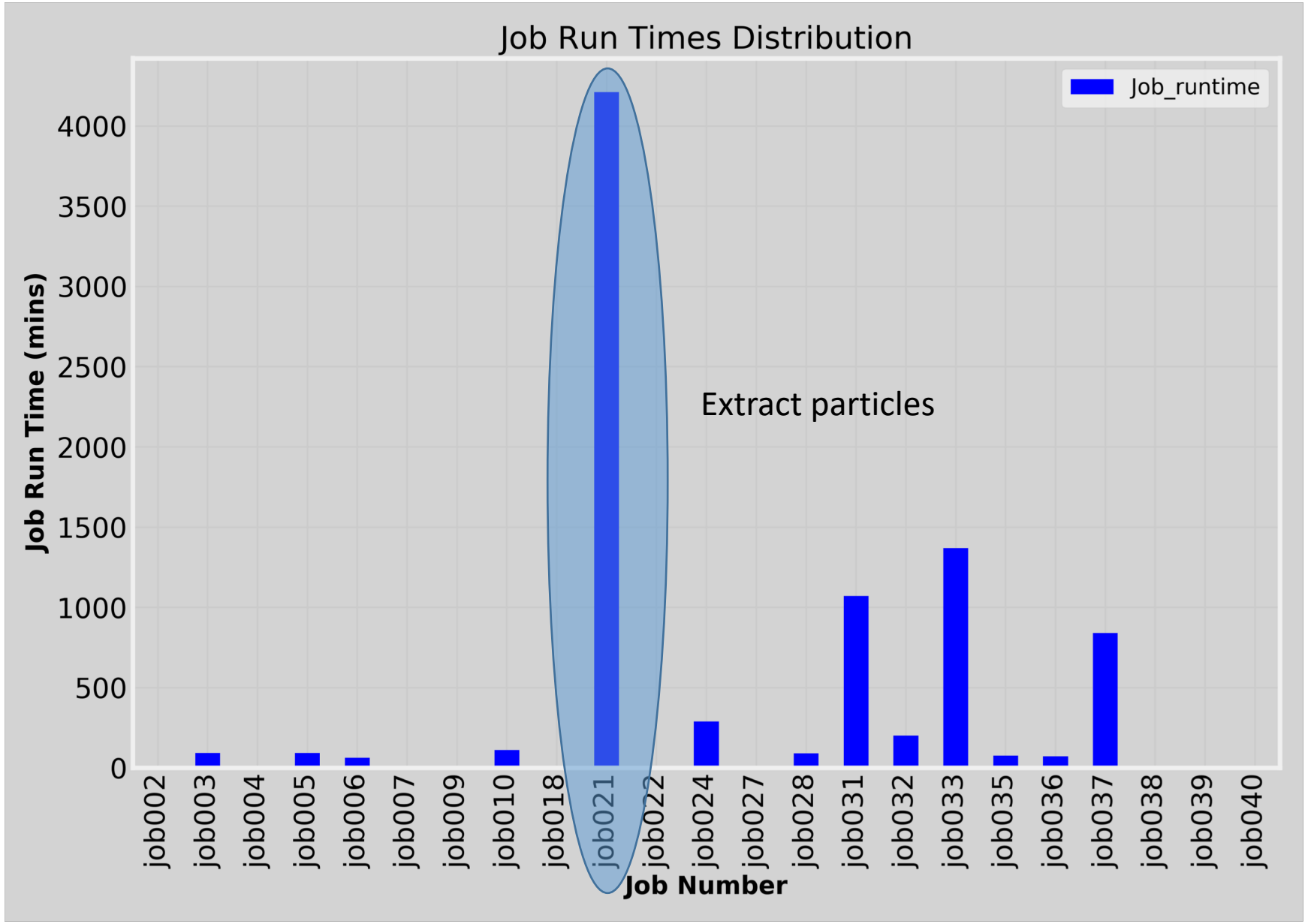
How long does an analysis take (and why?)?



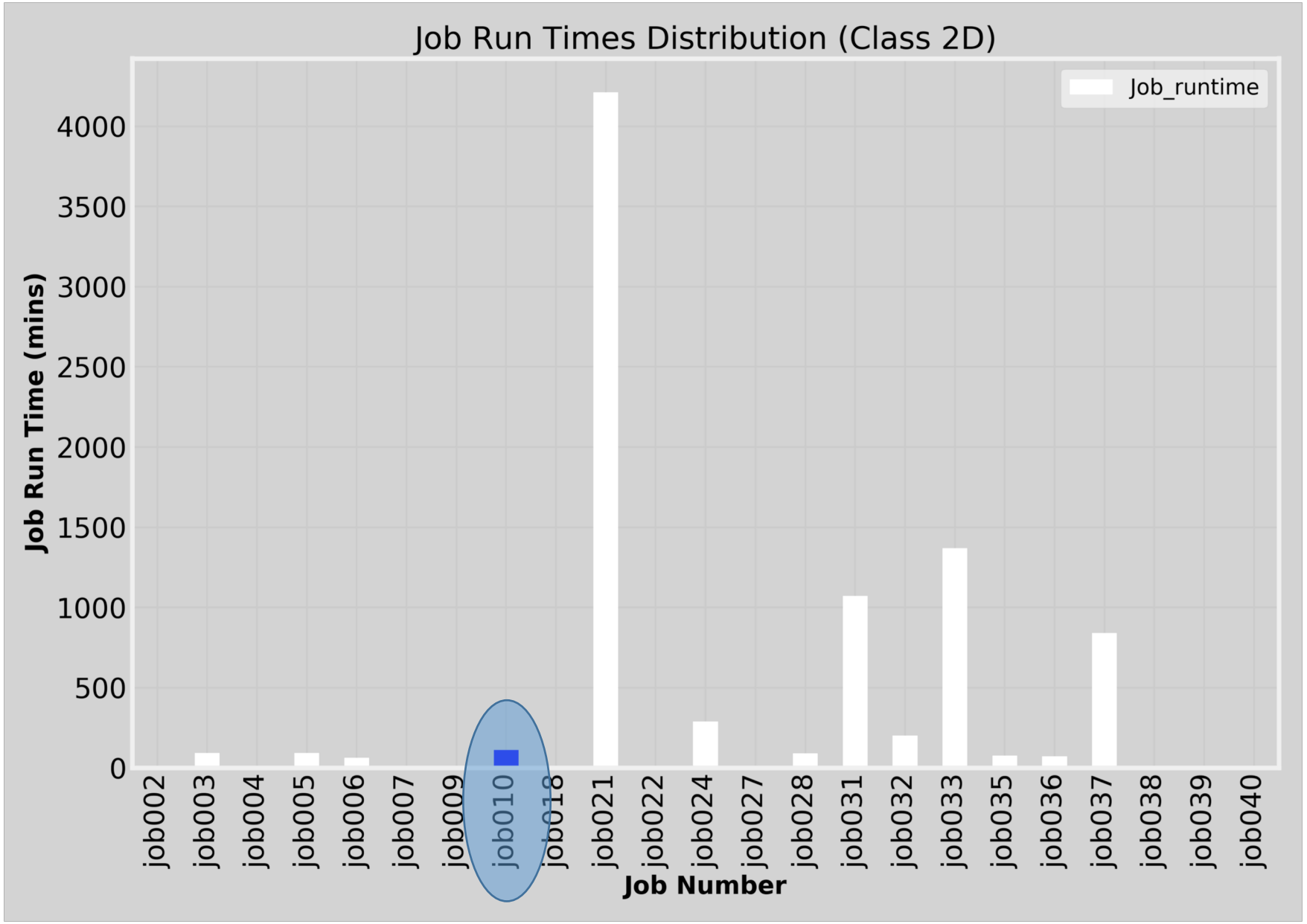
How long does each step take (and why?)?



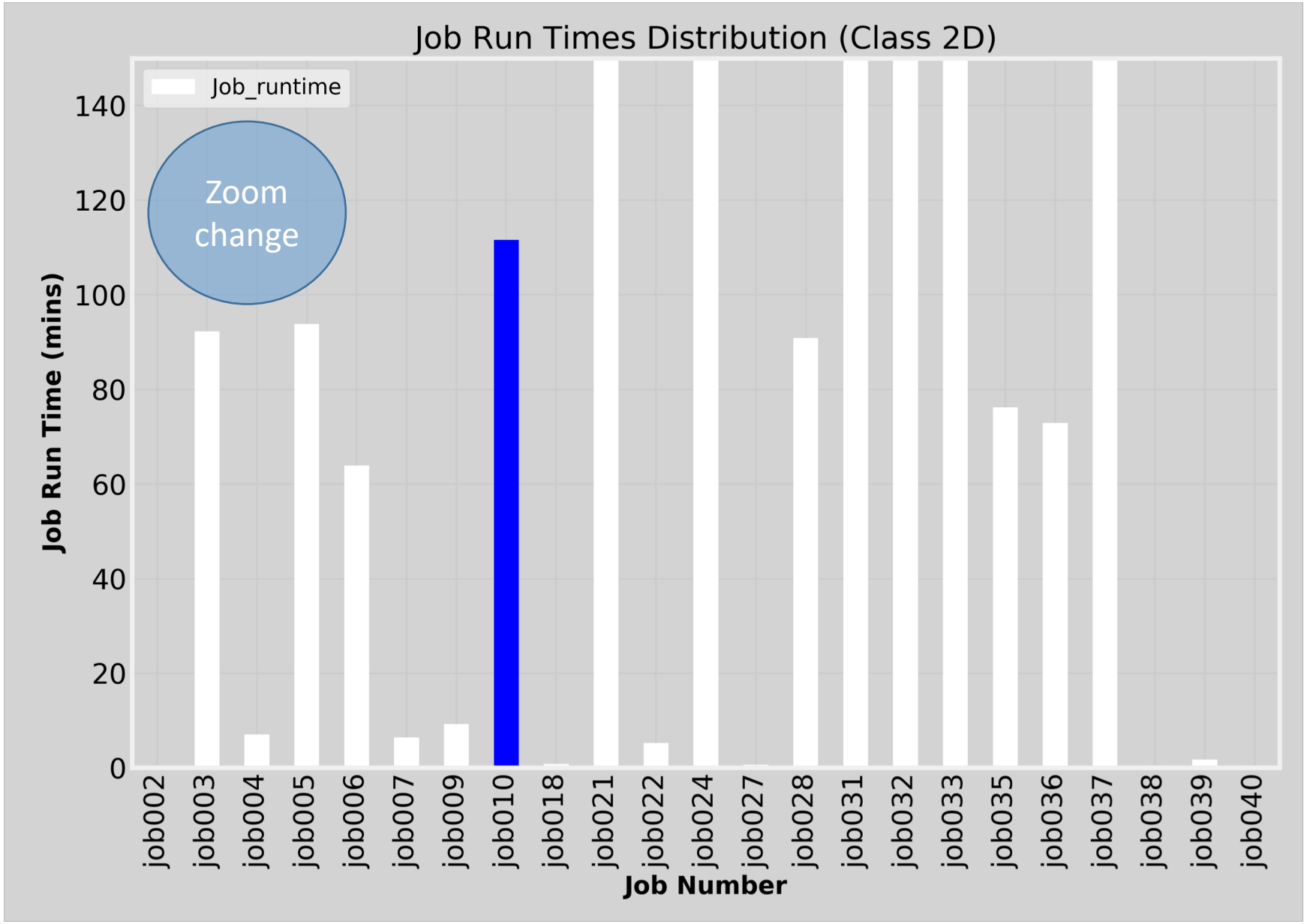
How long does each step take (and why?)?



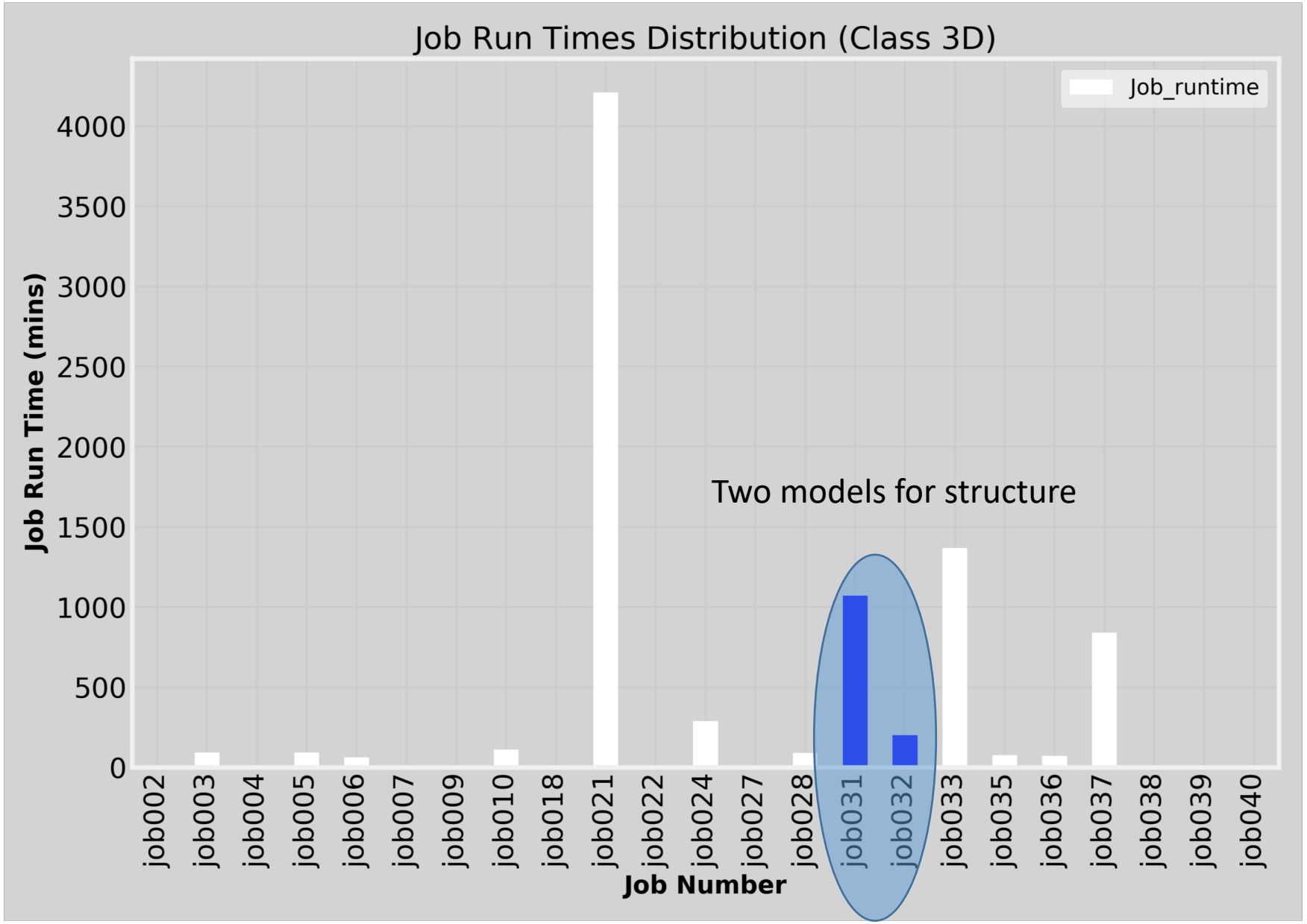
How long does each step take (and why?)?



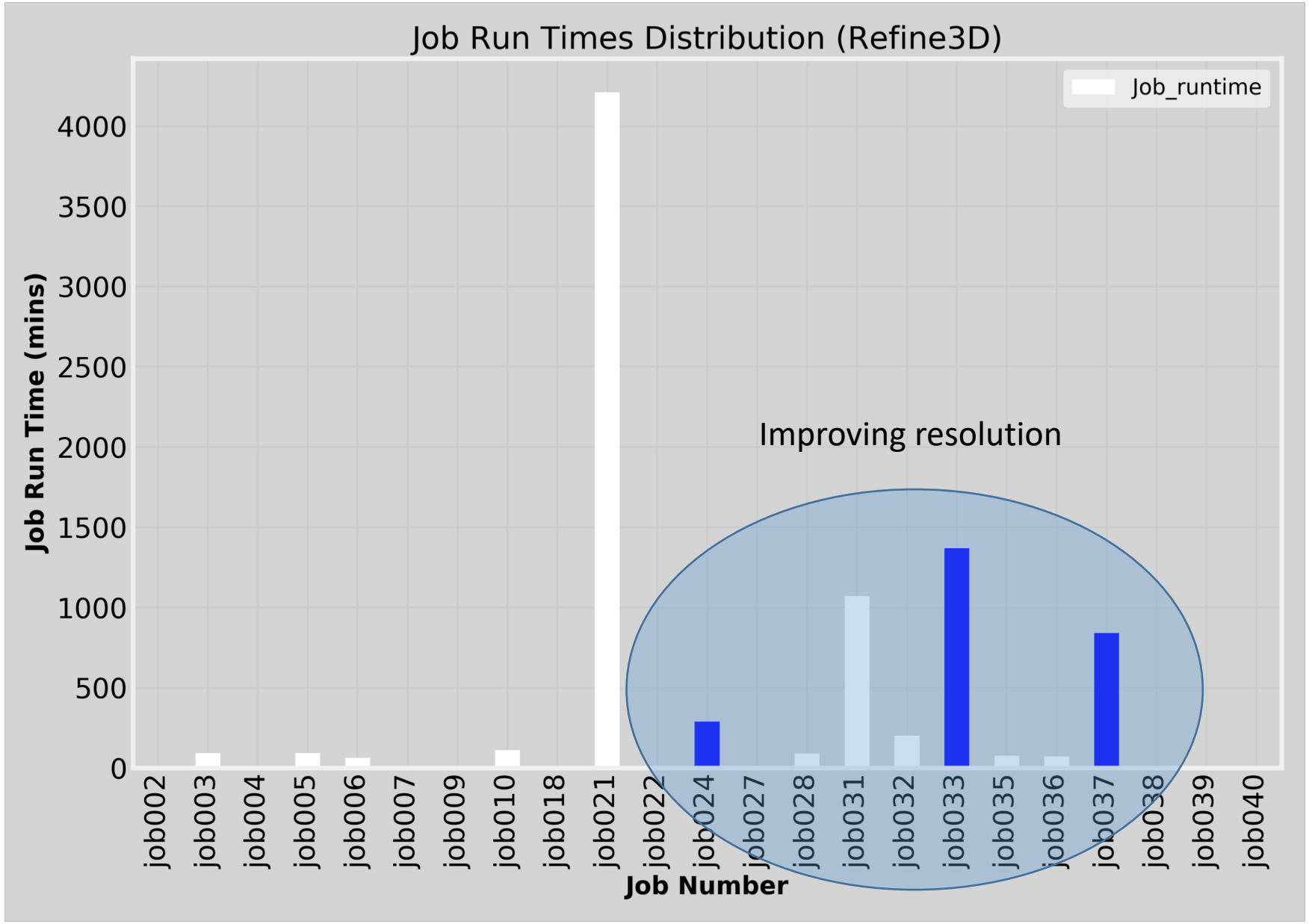
How long does each step take (and why?)?



How long does each step take (and why?)?



How long does each step take (and why?)?



MONASH University

How fast can we process this data?

… hardware choices, do they matter?

Hardware Configurations

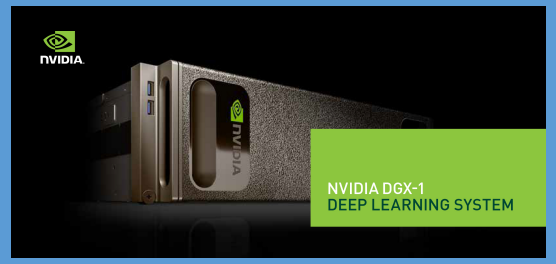
Workstation

8 Cores
64GB Ram
4 x GTX1070

Cloud (HPC)

Dual Socket
36 Cores
384GB Ram
3 x V100

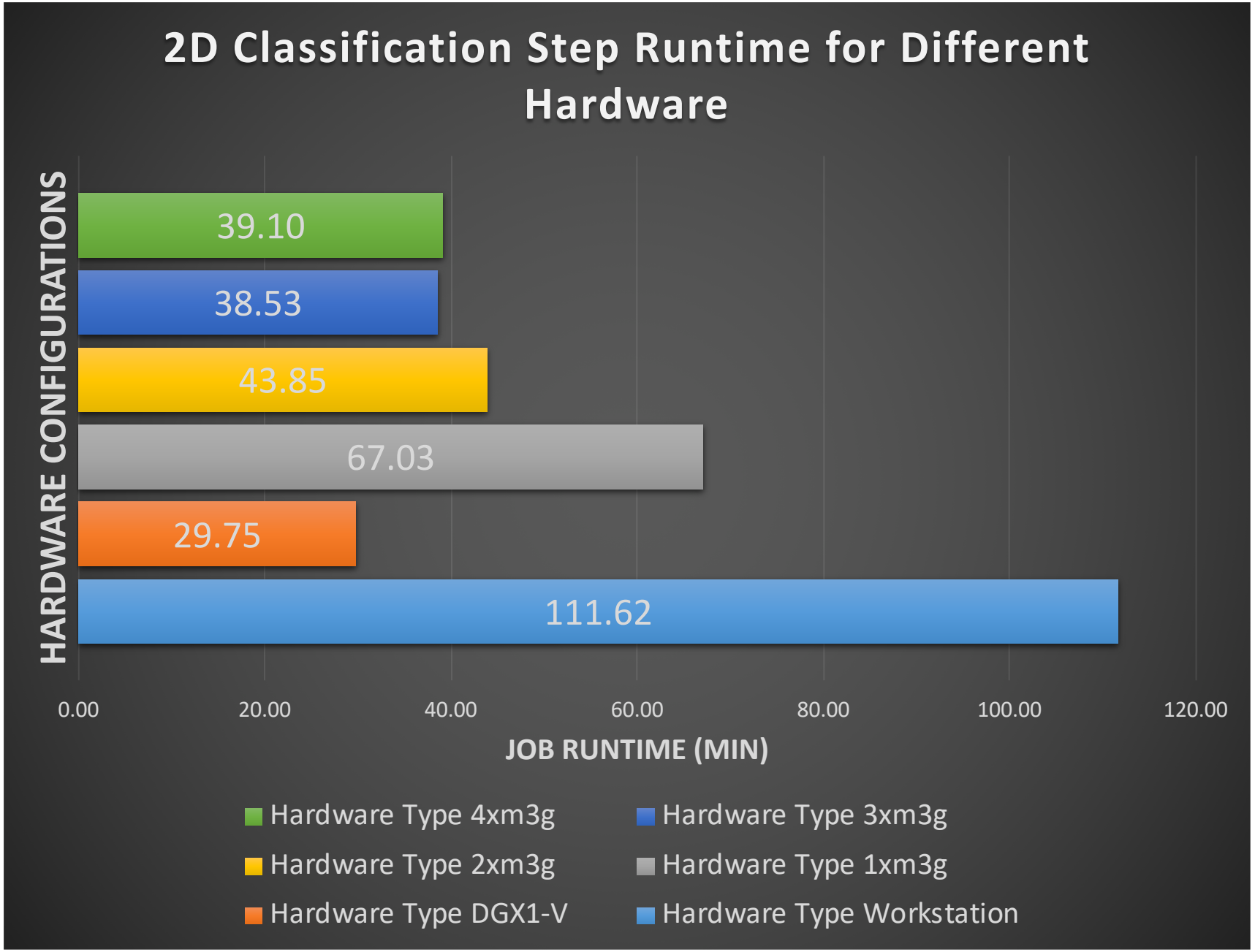
DGX-1V



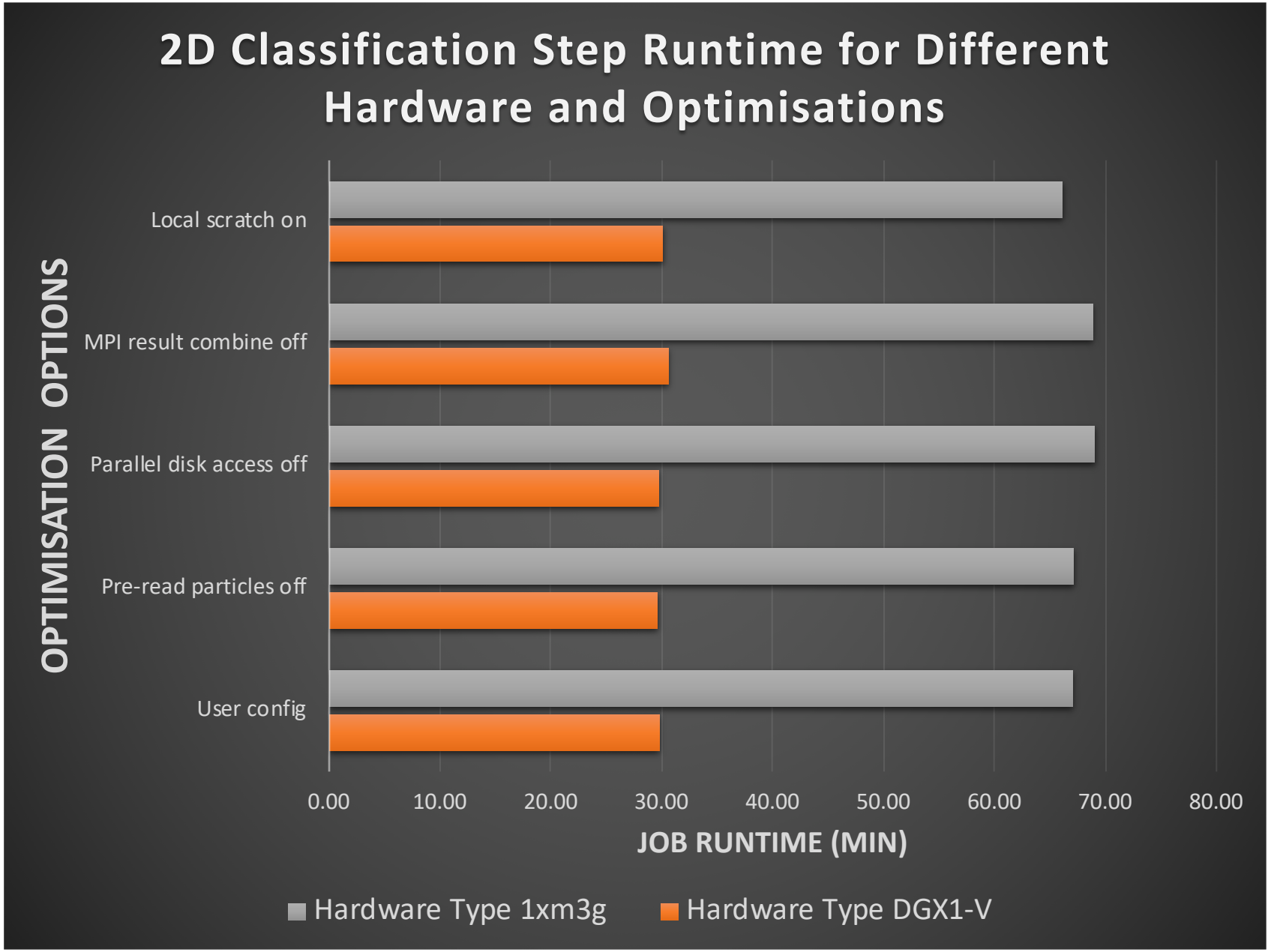
Dual Socket
40 Cores
512GB Ram
8 x V100

SSD + NAS | **SSD + Lustre** | **SSD**

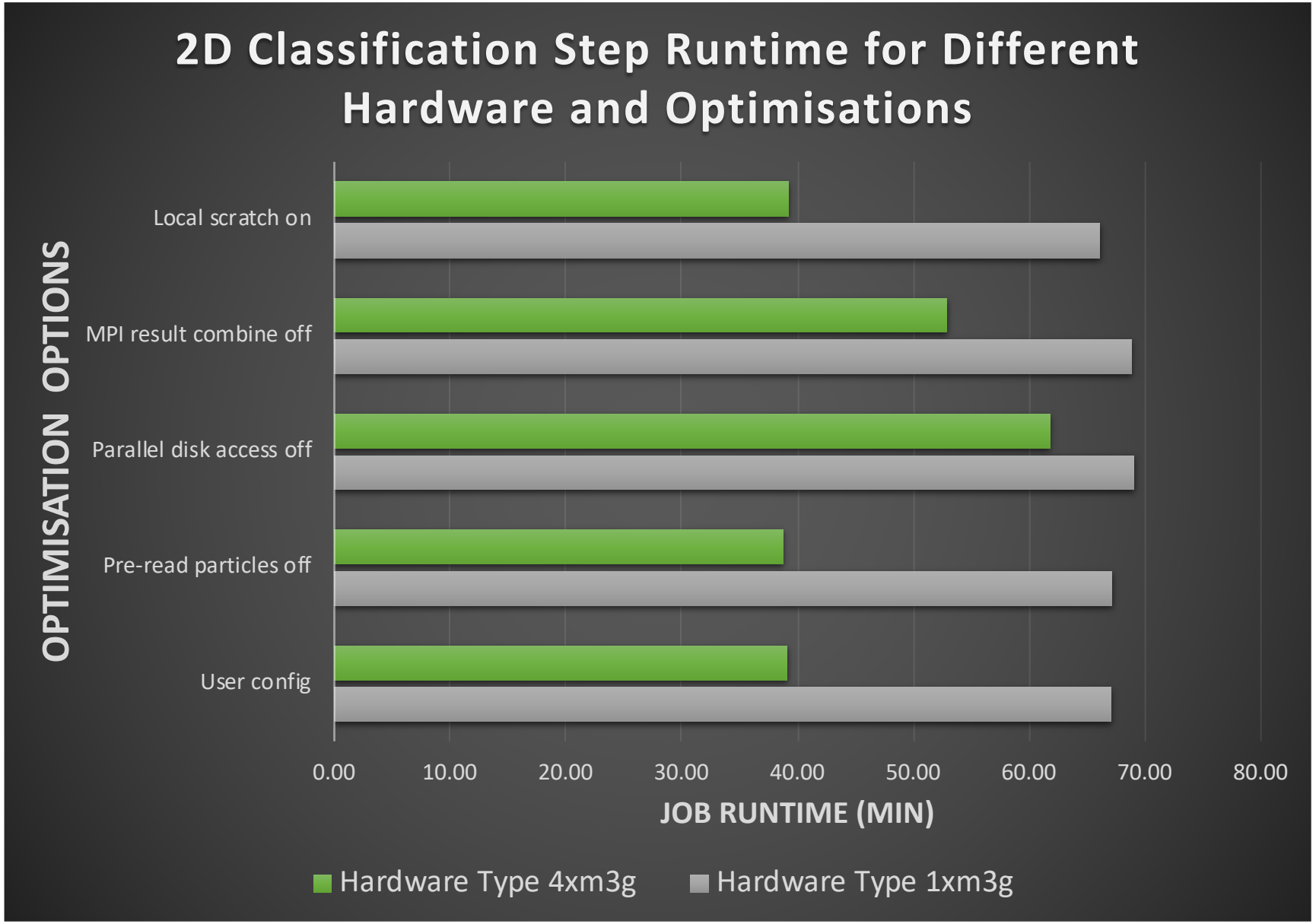
Can we process faster? (Is HPC the option)



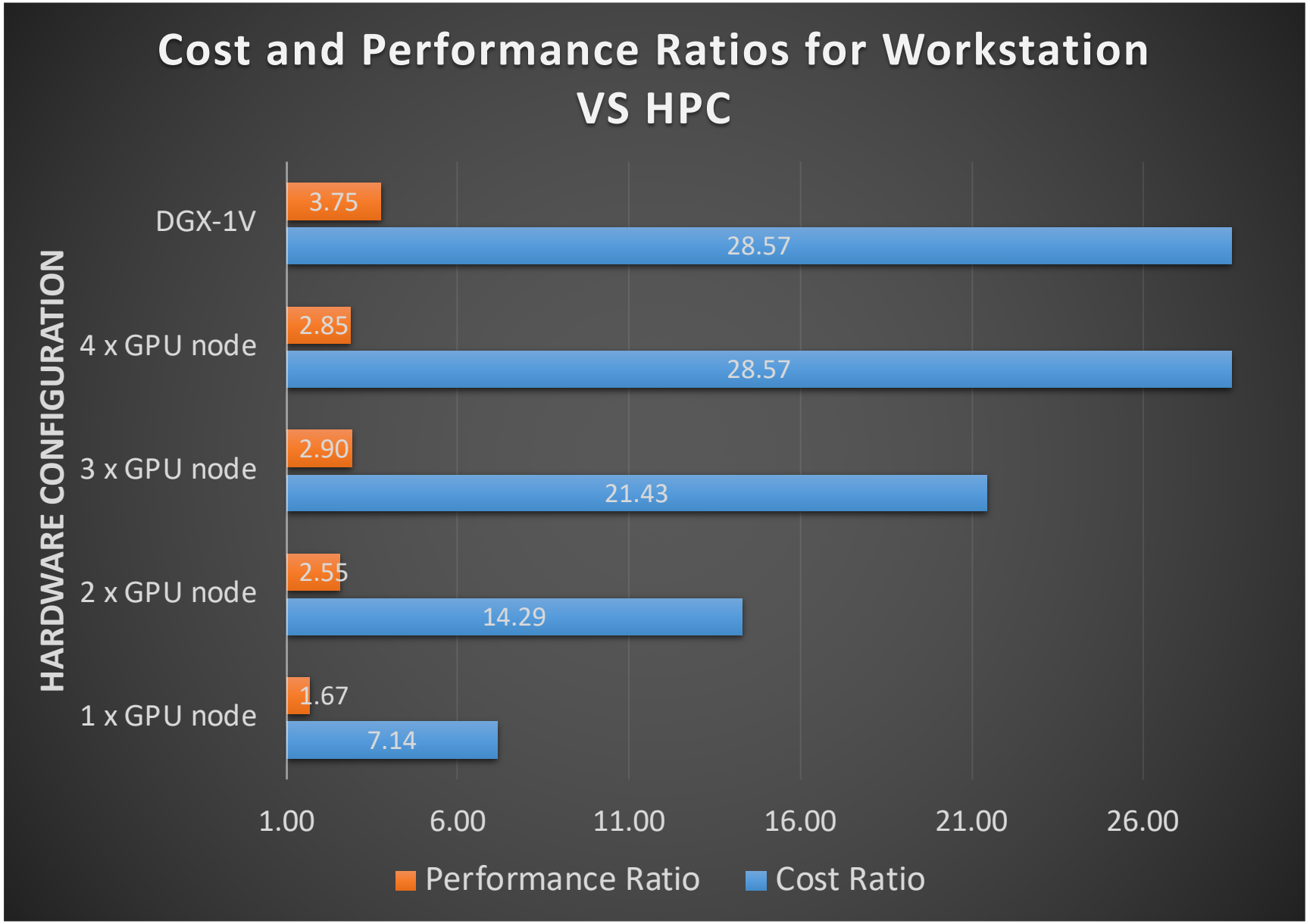
Can we process faster? (do options matter?)



Can we process faster? (do options matter?)



What is the ratio of cost to performance?



What retail options for compute exist?

Workstations + Software Support

How fast are the Relion developers machines?

- [lancew@m3-login1 job008]$ pwd
- /scratch/br76/relion3tut/relion30_tutorial_precalculated_results/Class2D/job008
- [lancew@m3-login1 job008]$ ls --full-time
- total 2884
- -rw-r--r-- 1 lancew br76 2777 2018-06-07 23:32:58.000000000 +1000 default_pipeline.star
- -rw-r--r-- 1 lancew br76 840 2018-06-07 23:32:58.000000000 +1000 job_pipeline.star
- -rw-r--r-- 1 lancew br76 448 2018-06-07 23:32:58.000000000 +1000 note.txt
- -rw-r--r-- 1 lancew br76 0 2018-06-07 23:32:57.000000000 +1000 run.err
- -rw-r--r-- 1 lancew br76 820224 2018-06-07 23:32:58.000000000 +1000 run_it025_classes.mrcs
- -rw-r--r-- 1 lancew br76 740401 2018-06-07 23:32:57.000000000 +1000 run_it025_data.star
- -rw-r--r-- 1 lancew br76 223301 2018-06-07 23:32:57.000000000 +1000 run_it025_model.star
- -rw-r--r-- 1 lancew br76 5916 2018-06-07 23:32:58.000000000 +1000 run_it025_optimiser.star
- -rw-r--r-- 1 lancew br76 458 2018-06-07 23:32:56.000000000 +1000 run_it025_sampling.star
- -rw-r--r-- 1 lancew br76 1234 2018-06-07 23:32:57.000000000 +1000 run.job
- -rw-r--r-- 1 lancew br76 307687 2018-06-07 23:32:58.000000000 +1000 run.out
- -rw-r--r-- 1 lancew br76 820224 2018-06-07 23:32:58.000000000 +1000 run_unmasked_classes.mrcs

DO MORE SCIENCE!
Have peace of mind, focus on what matters most, knowing your system is backed by a 3 year warranty and support.

PLUG AND PLAY
Exxact systems are fully turnkey, built to perform right out of the box so you avoid the drudgery of configuration and setup.

Why do these systems look attractive to researchers?

Suggested R

Entry-Level
Tensor Workstation

- 1x Intel Core i7-7820X
- 4x NVIDIA RTX 2080 Ti, RTX 2080 or GTX 1080 Ti
- 8x 16GB Memory
- 1x 256GB SSD (OS)
  2x 2TB SSD (Data)

STARTING AT **$9,599**

START YOUR ORDER

Mid-Range
Tensor Workstation

- 2x Intel Xeon Scalable (Silver)
- 4x NVIDIA RTX 2080 Ti, RTX 2080 or GTX 1080 Ti
- 12x 16GB Memory
- 2x 240GB SSD (OS)
  2x 2TB HDD (Data)

STARTING AT **$12,999**

START YOUR ORDER

High-End
Tensor Server

- 2x Intel Xeon Scalable (Gold)
- Up to 8x NVIDIA Tesla GPUs
- 12x 32GB Memory
- 1x 512GB M.2 SSD (OS)
  2x 2TB HDD (Data)

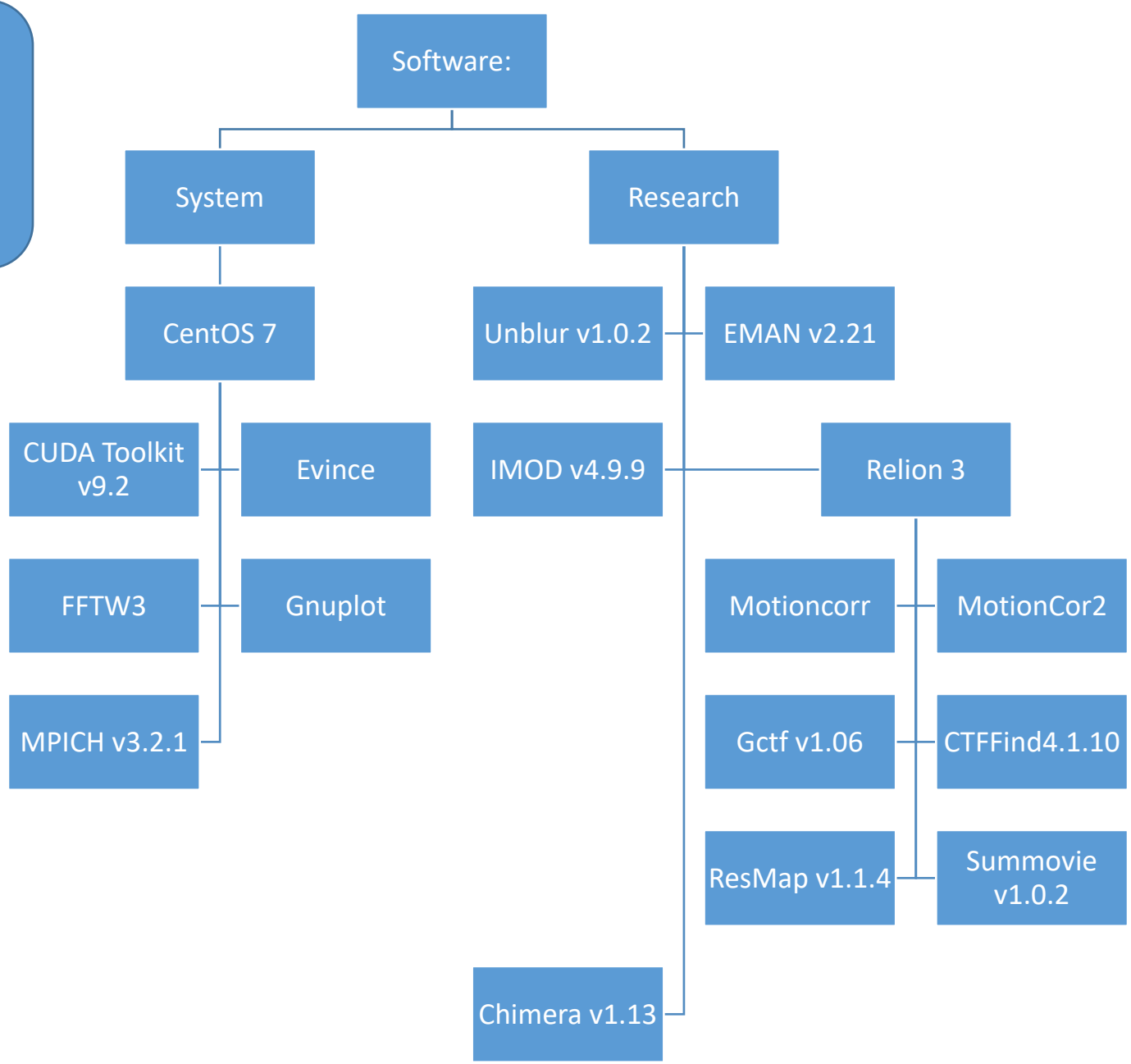
STARTING AT ***$22,999**

START YOUR ORDER

Source: https://www.exxactcorp.com/Relion-for-Cryo-EM-Solutions

PRECONFIGURED
“Relion 3.0 beta and v2.1 With example job submission scripts, benchmarks, a fully validated test suite, and the latest software patches for quick implementation.”

Why do these systems look attractive to researchers?



Source: https://www.exxactcorp.com/Relion-for-Cryo-EM-Solutions

Why do these systems look attractive to researchers?

4. Turn-key Systems.

All of our systems are delivered ready to use inmediately. We setup the Workstation parameters such as Networking, Users creation, Backup automated sytem,

Users configuration.

Networking, hostname, DNS's, etc....

Services.

Data migration

Virtual Machines Installations

Remote access configuration.

Automated Data Backup

Source: http://www.linuxvixion.com/wp-content/uploads/2016/04/linuxvixion-molecular-dynamics-2016-english.pdf

Amazon EC2 P3 Instance Product Details

Instance Size	GPUs - Tesla V100	GPU Peer to Peer	GPU Memory (GB)	vCPUs	Memory (GB)	Network Bandwidth	EBS Bandwidth	On-Demand Price/hr*	1-yr Reserved Instance Effective Hourly*	3-yr Reserved Instance Effective Hourly*
p3.2xlarge	1	N/A	16	8	61	Up to 10 Gbps	1.5 Gbps	$3.06	$1.99	$1.05
p3.8xlarge	4	NVLink	64	32	244	10 Gbps	7 Gbps		$7.96	$4.19
p3.16xlarge	8	NVLink	128	64	488	25 Gbps	14 Gbps		$15.91	$8.39
p3dn.24xlarge	8	NVLink	256	96	768	100 Gbps	14 Gbps		$18.30	$9.64

$25/hr

* - Prices shown are for Linux/Unix in the US East (Northern Virginia) AWS Region and rounded to the nearest cent. For full pricing details, see the Amazon EC2 pricing page.

Customers can purchase P3 instances as On-Demand Instances, Reserved Instances, Spot Instances, and Dedicated Hosts.

What are the cloud options? …and cost?

Source: https://aws.amazon.com/ec2/instance-types/p3/


Source: http://labphoto.tumblr.com/post/105112424006/cyanuric-triazide-or-2-4-6-triazido-1-3-5-triazine

What has changed in 2 years?

Mostly hardware …. And a little ML

Options for Computation (2017)

Workstation

Pro

Full user control

Con

Limited by single machine

Cloud

Pro

Scales easily

Con

Cost, complexity, data movement

HPC

Pro

Huge resources

Con

Tightly controlled, shared

Options for Computation (2019)

Workstation

Pro

Full user control

Con

Limited by single machine

Cloud

Pro

Scales ~~easily~~

Con

Cost, complexity, data movement

HPC

Pro

Huge resources, **purpose designed**

Con

Tightly controlled, shared

Containers

SYSTEM SPECIFICATIONS

GPUs	**8X Tesla V100**
Performance (Mixed Precision)	**1 petaFLOPS**
GPU Memory	**256 GB total system**
CPU	**Dual 20-Core Intel Xeon E5-2698 v4 2.2 GHz**
NVIDIA CUDA® Cores	**40,960**
NVIDIA Tensor Cores (on V100 based systems)	**5,120**
Power Requirements	**3,500 W**
System Memory	**512 GB 2,133 MHz DDR4 RDIMM**
Storage	**4X 1.92 TB SSD RAID 0**
Network	**Dual 10 GbE, 4 IB EDR**
Operating System	**Canonical Ubuntu, Red Hat Enterprise Linux**
System Weight	**134 lbs**
System Dimensions	**866 D x 444 W x 131 H (mm)**
Packing Dimensions	**1,180 D x 730 W x 284 H (mm)**
Operating Temperature Range	**5–35 °C**

SYSTEM SPECIFICATIONS

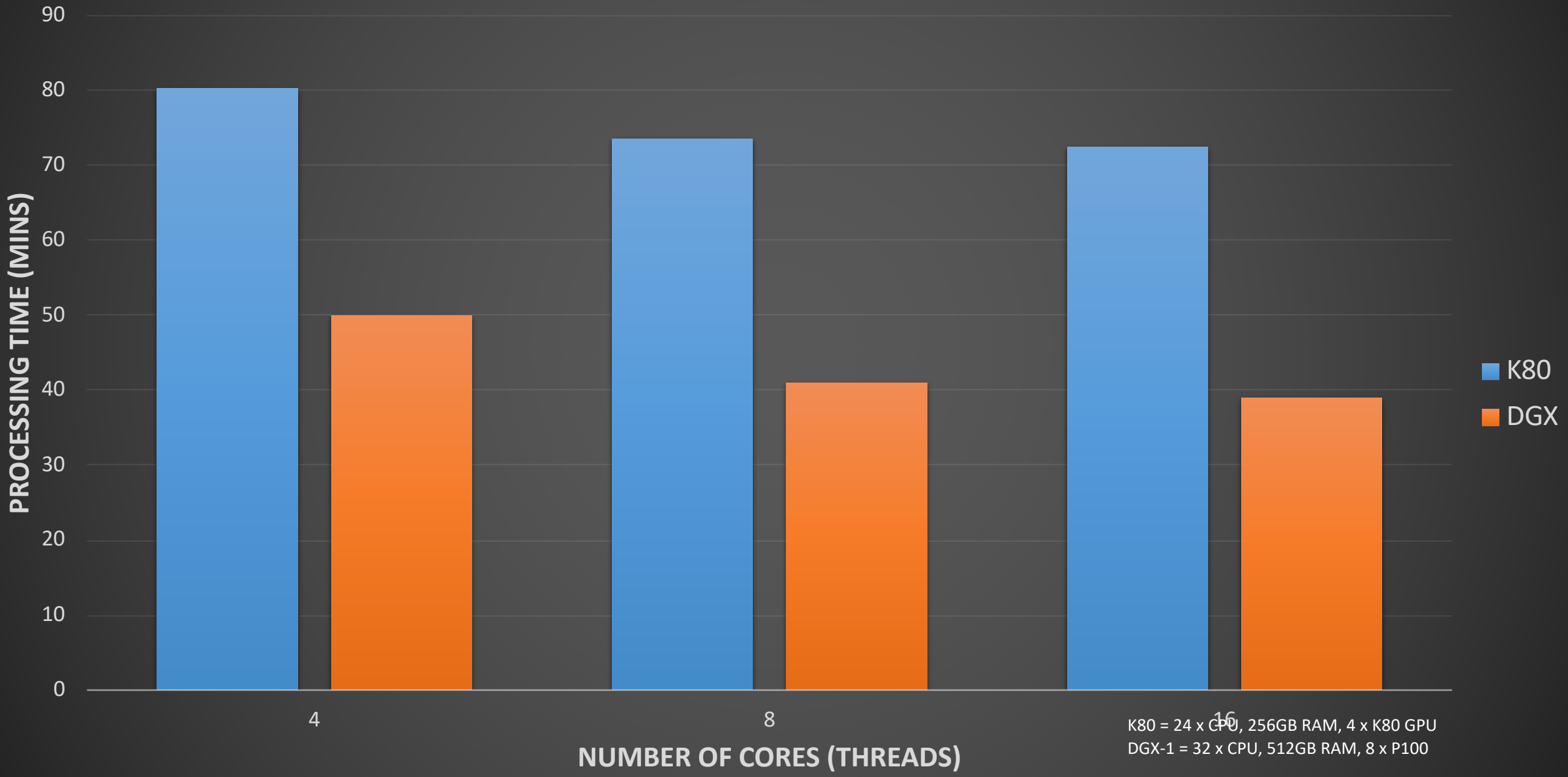
GPUs	**8X Tesla V100**	**8X Tesla P100**
TFLOPS (GPU FP16)	**960**	**170**
GPU Memory	**128 GB total system**	
CPU	**Dual 20-Core Intel Xeon E5-2698 v4 2.2 GHz**	
NVIDIA CUDA® Cores	**40,960**	**28,672**
NVIDIA Tensor Cores (on V100 based systems)	**5,120**	**N/A**
Maximum Power Requirements	**3,200 W**	
System Memory	**512 GB 2,133 MHz DDR4 LRDIMM**	
Storage	**4X 1.92 TB SSD RAID 0**	
Network	**Dual 10 GbE, 4 IB EDR**	
Software	**Ubuntu Linux Host OS See Software Stack for Details**	
System Weight	**134 lbs**	
System Dimensions	**866 D x 444 W x 131 H (mm)**	
Packing Dimensions	**1,180 D x 730 W x 284 H (mm)**	
Operating Temperature Range	**10–35 °C**	

SYSTEM SPECIFICATIONS

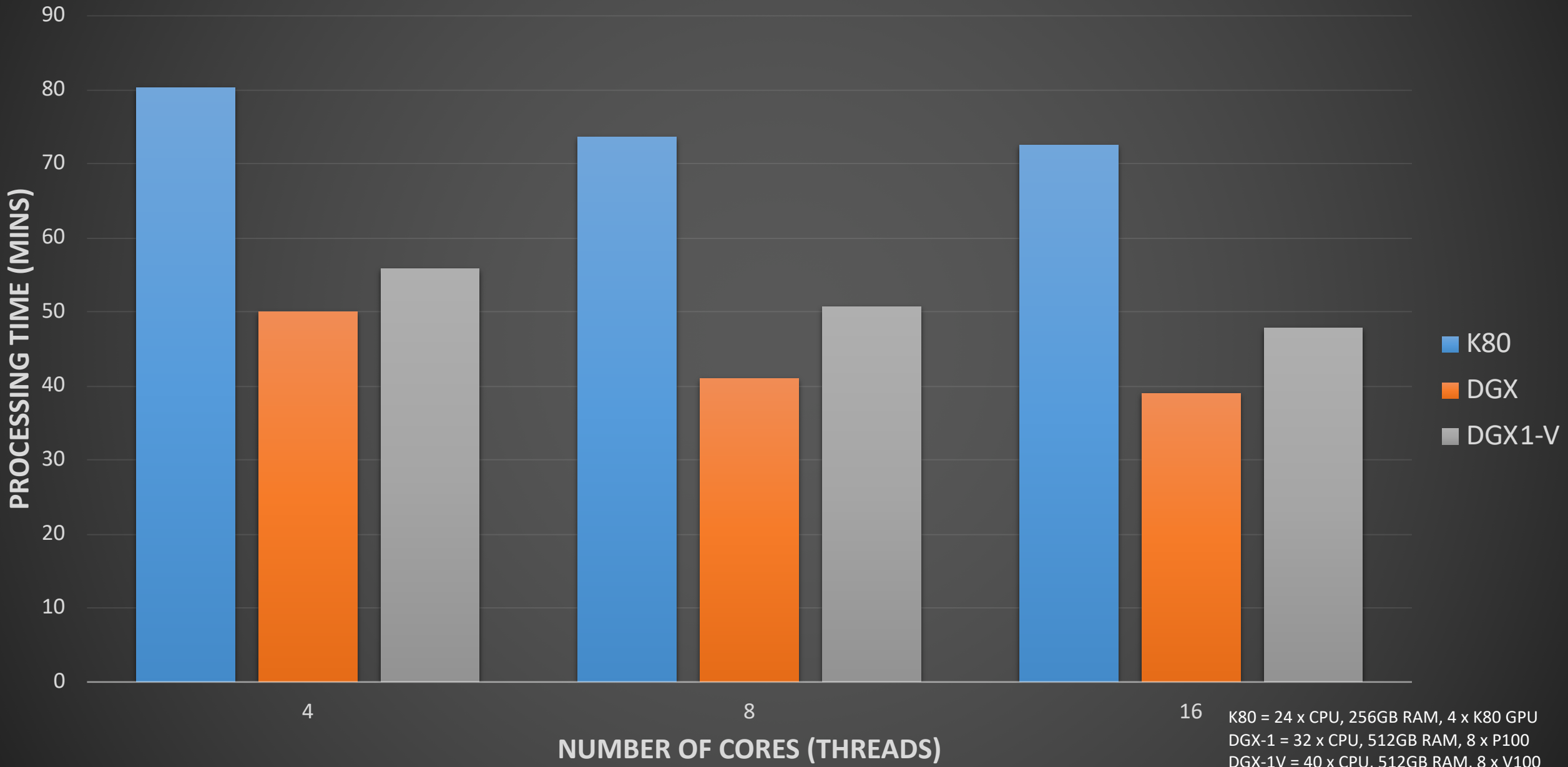
GPUs	**8x Tesla P100**
TFLOPS (GPU FP16 / CPU FP32)	**170/3**
GPU Memory	**16 GB per GPU**
CPU	**Dual 20-core Intel® Xeon® E5-2698 v4 2.2 GHz**
NVIDIA CUDA® Cores	**28672**
System Memory	**512 GB 2133 MHz DDR4**
Storage	**4x 1.92 TB SSD RAID 0**
Network	**Dual 10 GbE, 4 IB EDR**
Software	**Ubuntu Server Linux OS DGX-1 Recommended GPU Driver**
System Weight	**134 lbs**
System Dimensions	**866 D x 444 W x 131 H (mm)**
Packing Dimensions	**1180 D x 730 W x 284 H (mm)**
Maximum Power Requirements	**3200W**
Operating Temperature Range	**10 - 30°C**

P100 -> V100

Relion - 3D Classification Step (2017)

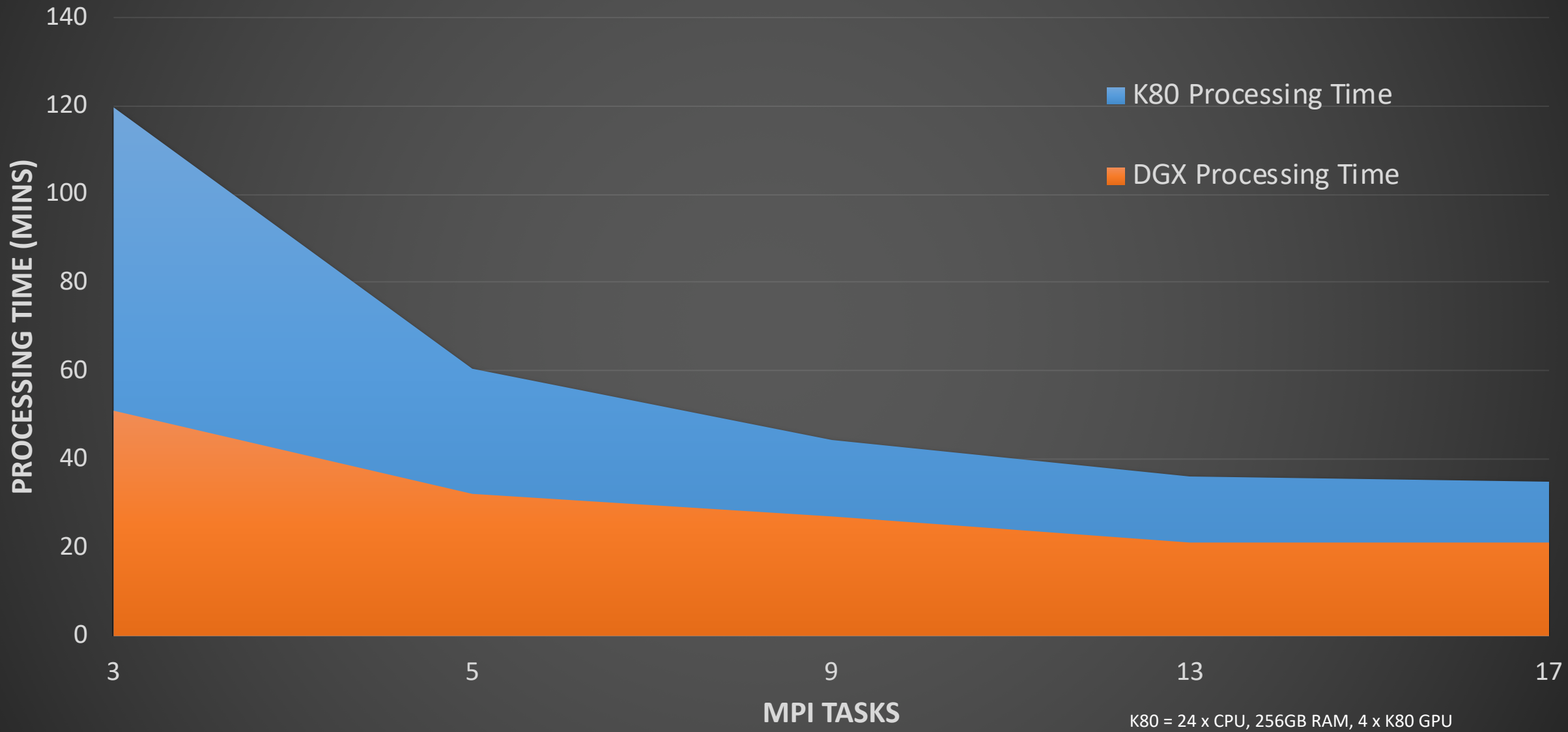


Relion - 3D Classification Step (2019)



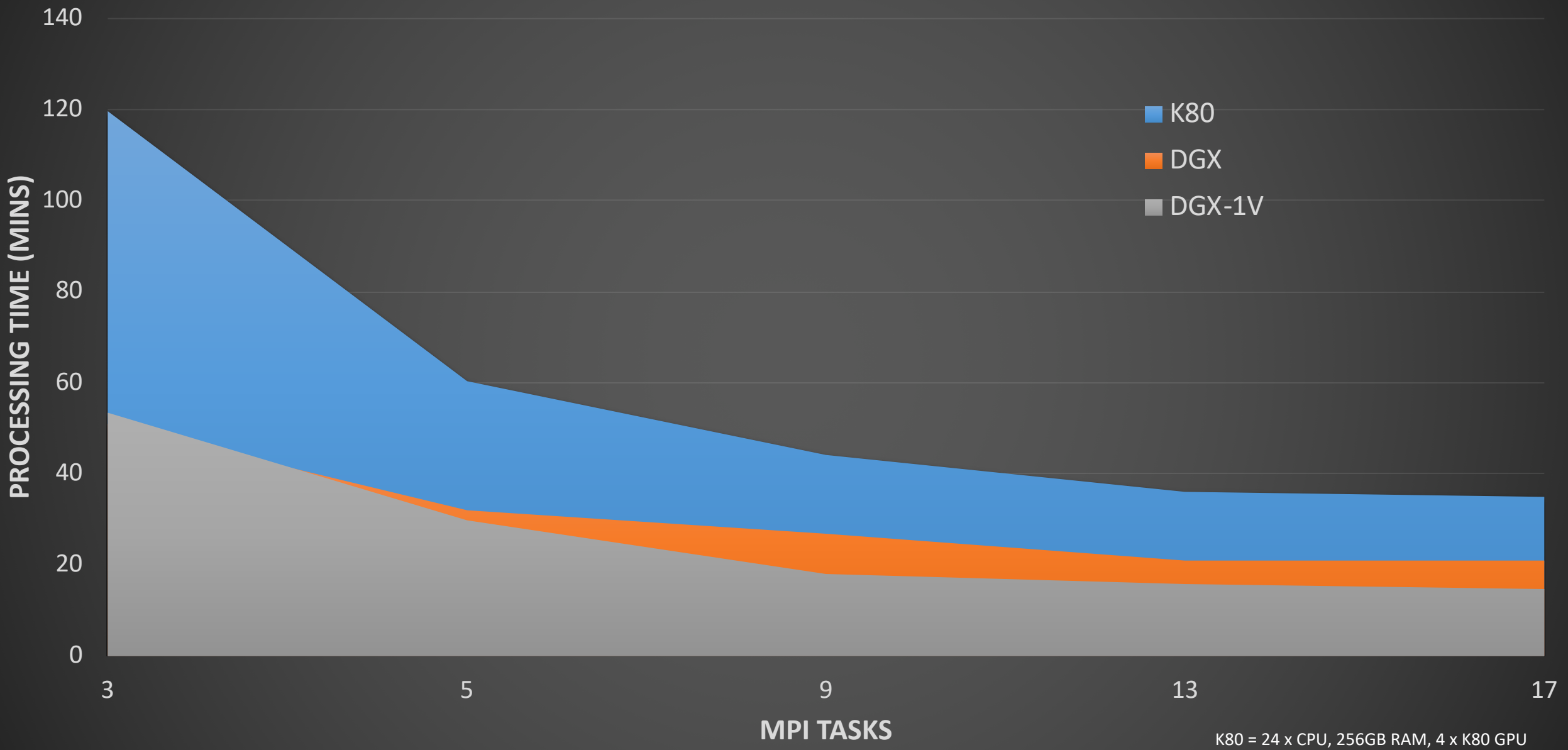
K80 = 24 x CPU, 256GB RAM, 4 x K80 GPU
DGX-1 = 32 x CPU, 512GB RAM, 8 x P100
DGX-1V = 40 x CPU, 512GB RAM, 8 x V100

Relion Class 3D - MPI Task Effects (2017)



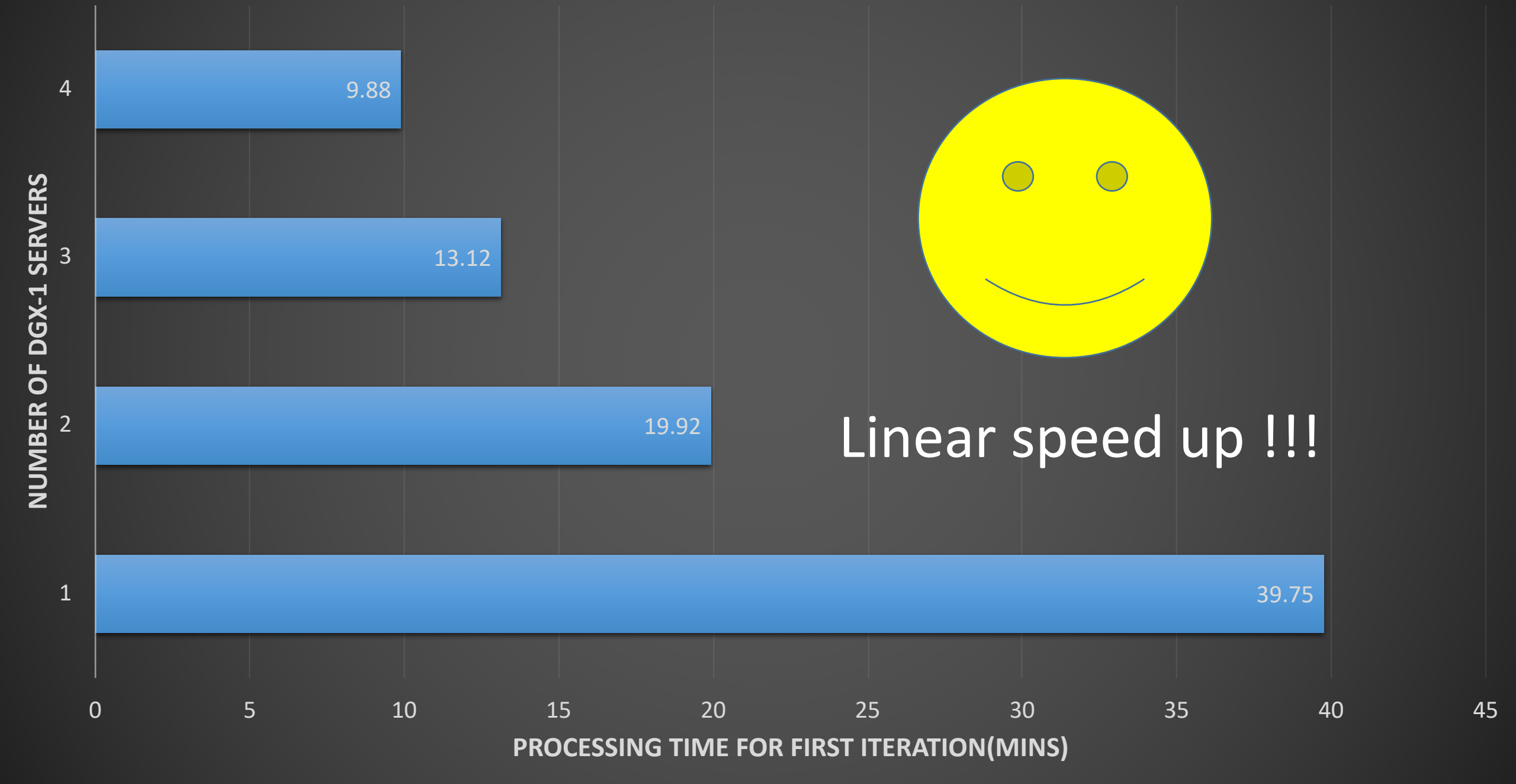
K80 = 24 x CPU, 256GB RAM, 4 x K80 GPU
DGX-1 = 32 x CPU, 512GB RAM, 8 x P100

Relion Class 3D - MPI Task Effects (2019)



K80 = 24 x CPU, 256GB RAM, 4 x K80 GPU
DGX-1 = 32 x CPU, 512GB RAM, 8 x P100
DGX-1V = 40 x CPU, 512GB RAM, 8 x V100

Iteration Processing Time VS Number of DGX-1 Servers



What has stayed the same in 2 years?

Mostly software …. Still a struggle

Software Dependencies

Ubuntu 18.04 LTS (Bionic Beaver) / Ubuntu Universe amd64 / openmpi-bin_2.1.1-8_amd64.deb

openmpi-bin_2.1.1-8_amd64.deb

Description

openmpi-bin - high performance message passing library -- binaries

Property	Value
Distribution	Ubuntu 18.04 LTS (Bionic Beaver)
Repository	Ubuntu Universe amd64
Package name	openmpi-bin
Package version	2.1.1
Package release	8
Package architecture	amd64
Package type	deb
Installed size	444 B
Download size	86.12 KB
Official Mirror	archive.ubuntu.com

bforsbe commented 5 hours ago Contributor

openmpi 2.0.2 is my go-to version, for future reference.

How to accelerate a solution with HPC?

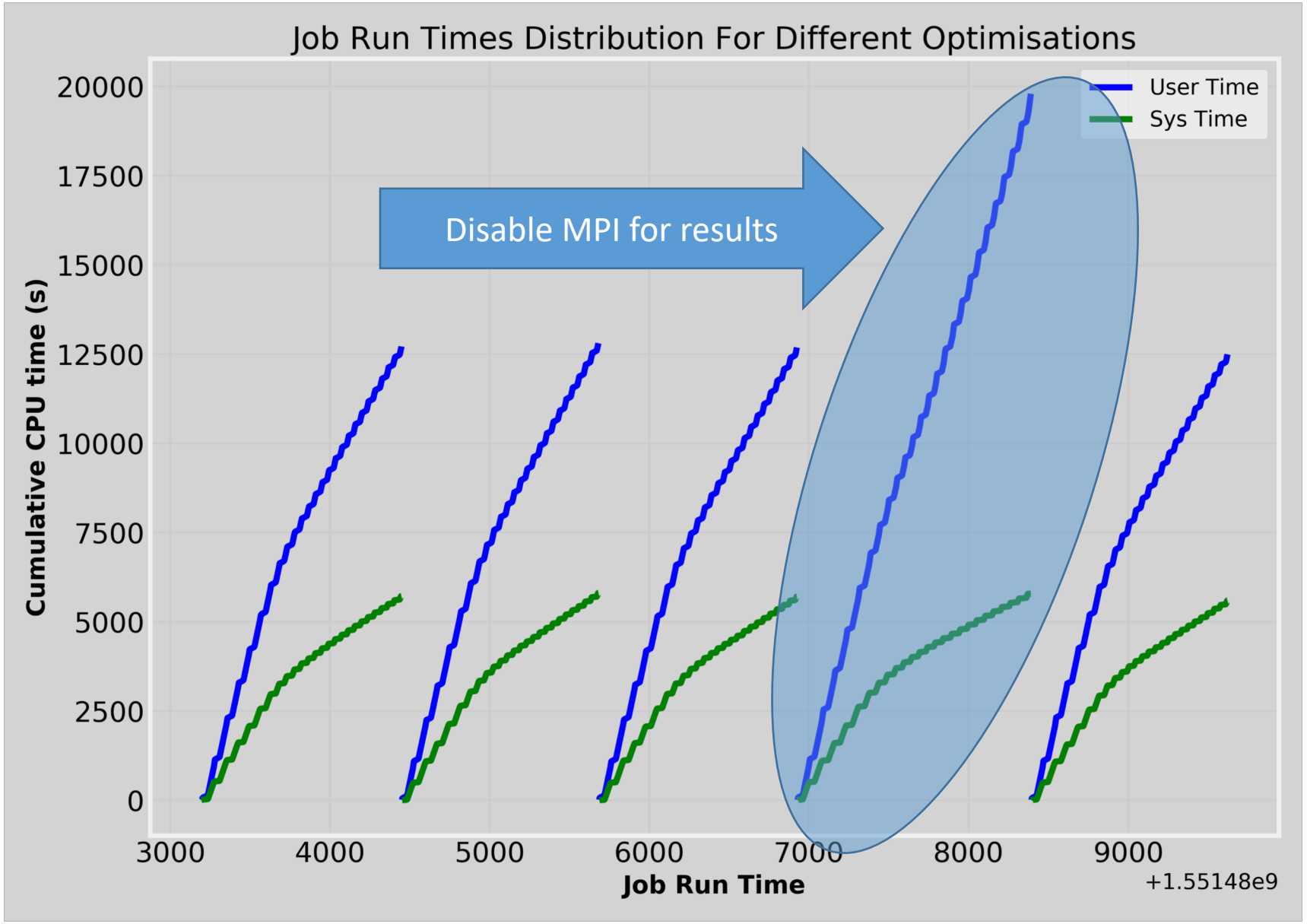
Using a real example (K2)

What are the optimisation options?

--j	The number of parallel threads to run on each CPU. **We often use 4-6.**
--dont_combine_weights_via_disc	By default large messages are passed between MPI processes through reading and writing of large files on the computer disk. By giving this option, the messages will be passed through the network instead. **We often use this option.**
--no_parallel_disc_io	By default, all MPI slaves read their own particles (from disk or into RAM). Use this option to have the master read all particles, and then send them all through the network. **We do not often use this option.**
--preread_images	By default, all particles are read from the computer disk in every iteration. Using this option, they are all read into RAM once, at the very beginning of the job instead. **We often use this option if the machine has enough RAM** (more than N*boxsize*boxsize*4 bytes) to store all N particles.
--scratch_dir	By default, particles are read every iteration from the location specified in the input STAR file. By using this option, all particles are copied to a scratch disk, from where they will be read (every iteration) instead. **We often use this option if we don't have enough RAM to read in all the particles, but we have large enough fast SSD scratch disk(s)** (e.g. mounted as /tmp).

Source: https://www3.mrc-lmb.cam.ac.uk/relion/index.php/Benchmarks_%26_computer_hardware

What are the optimisation options?



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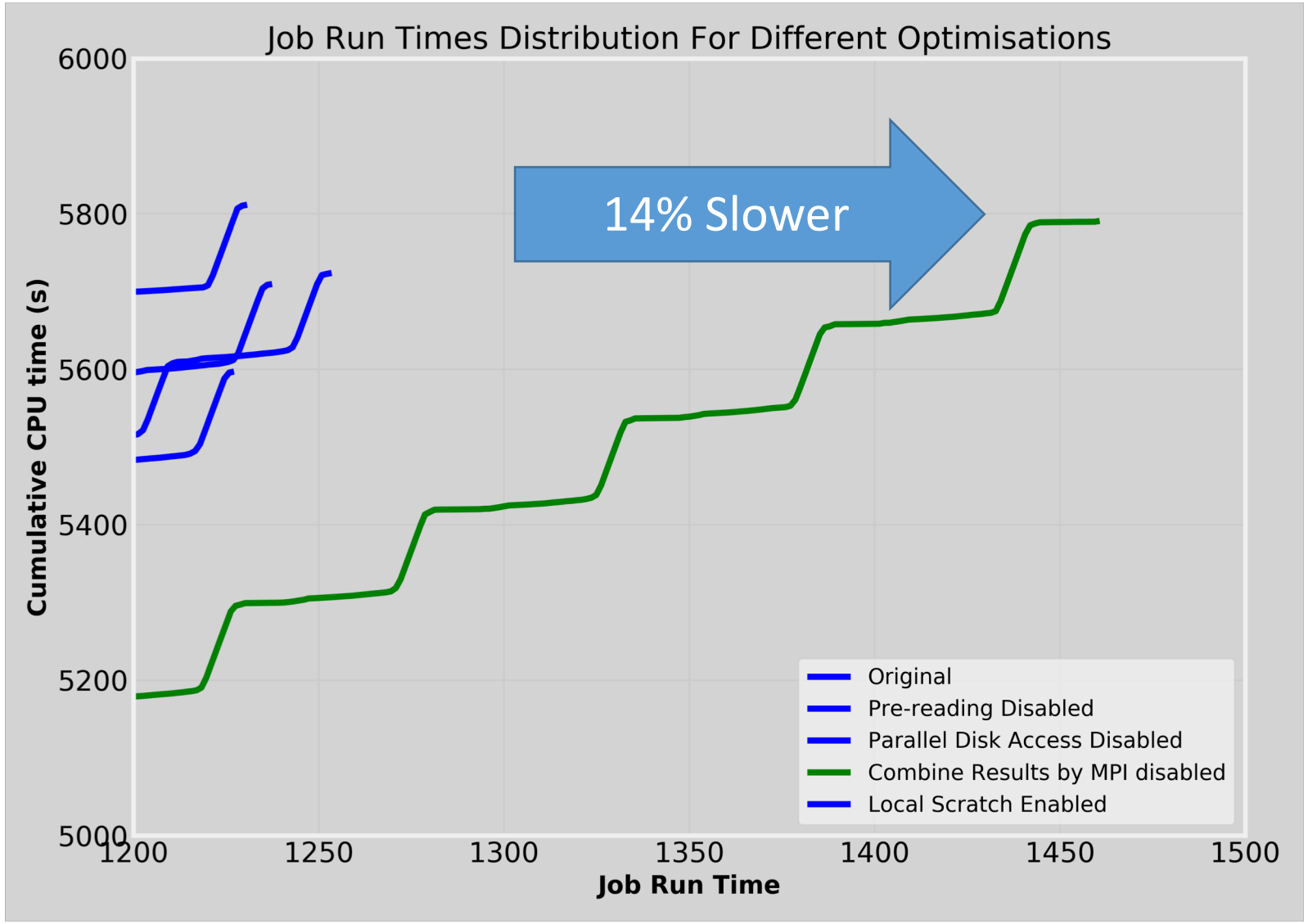
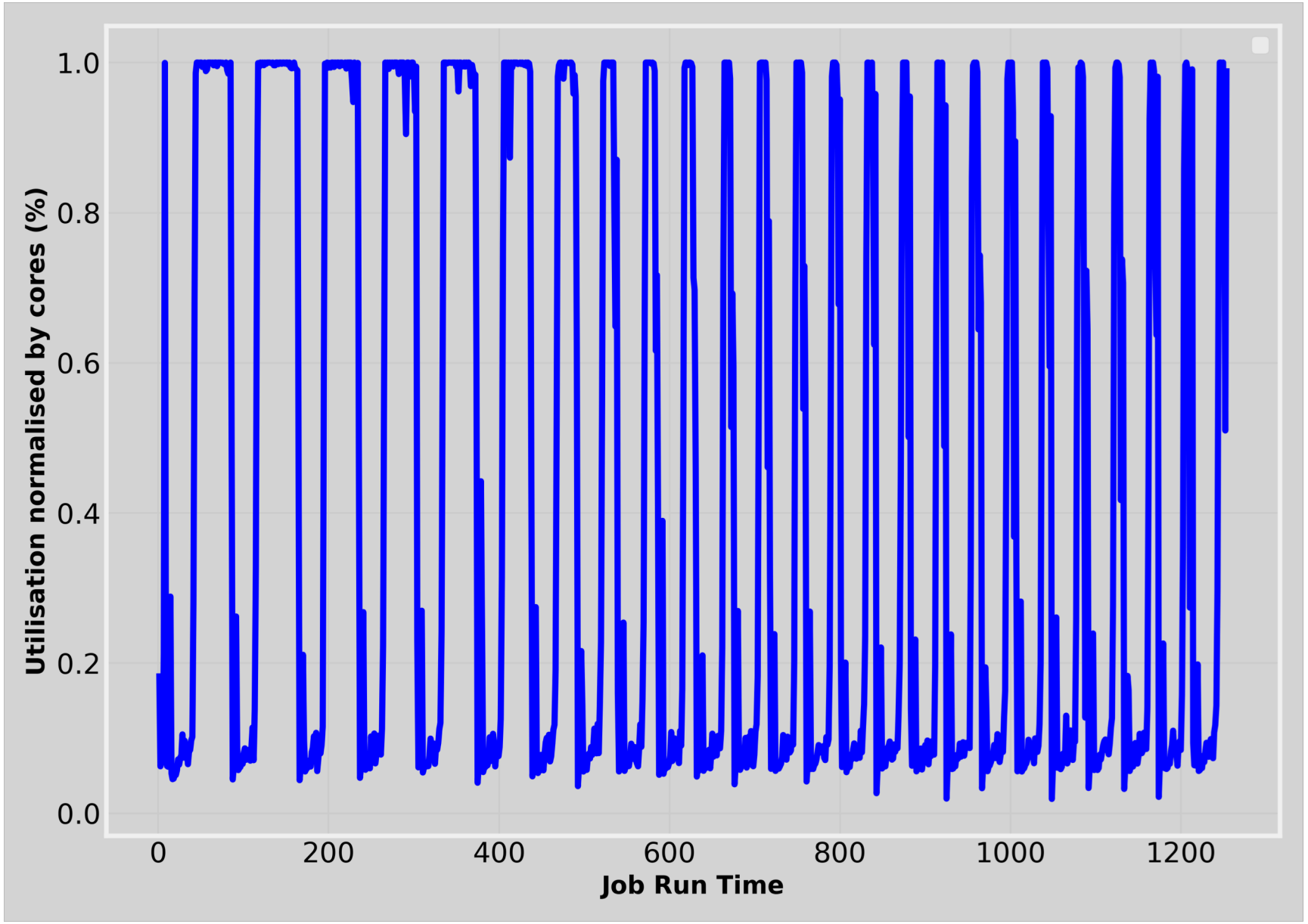


How are the CPUs used? … How many are needed?



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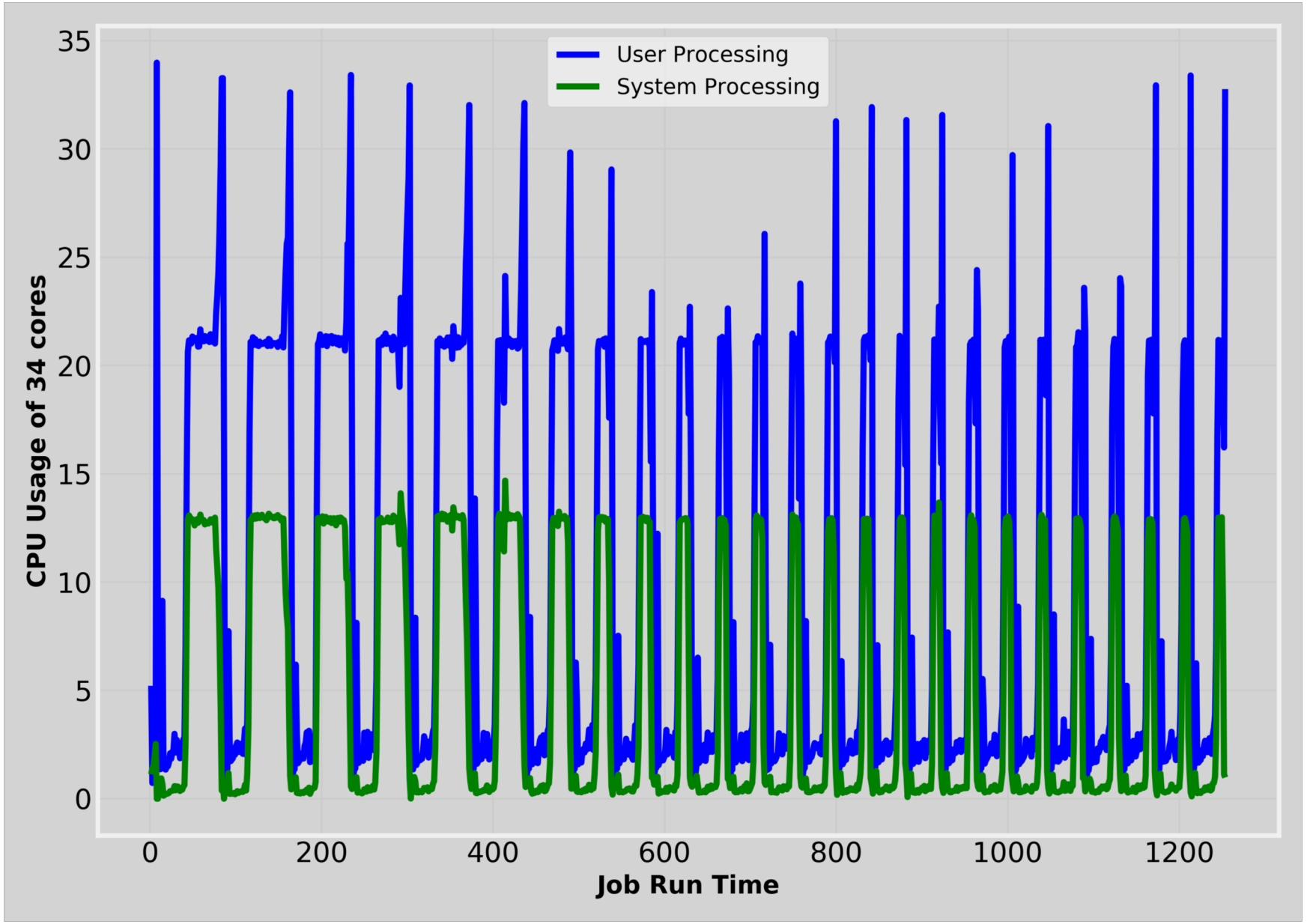

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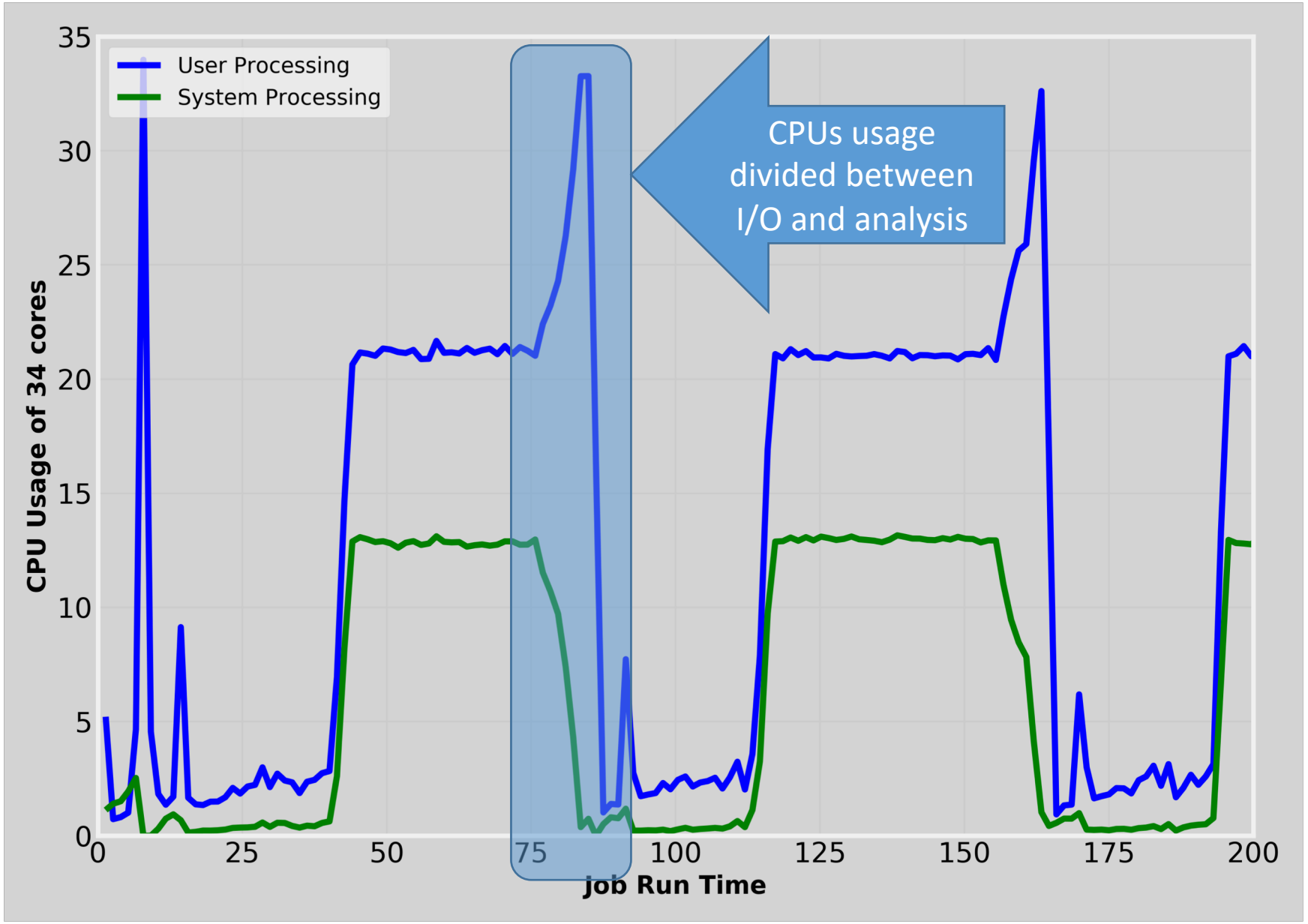


How efficient is the software…

GPU Performance Measurements

Utilization rates report how busy each GPU is over time, and can be used to determine how much an application is using the GPUs in the system.

GPU Percent of time over the past sample period during which one or more kernels was executing on the GPU.

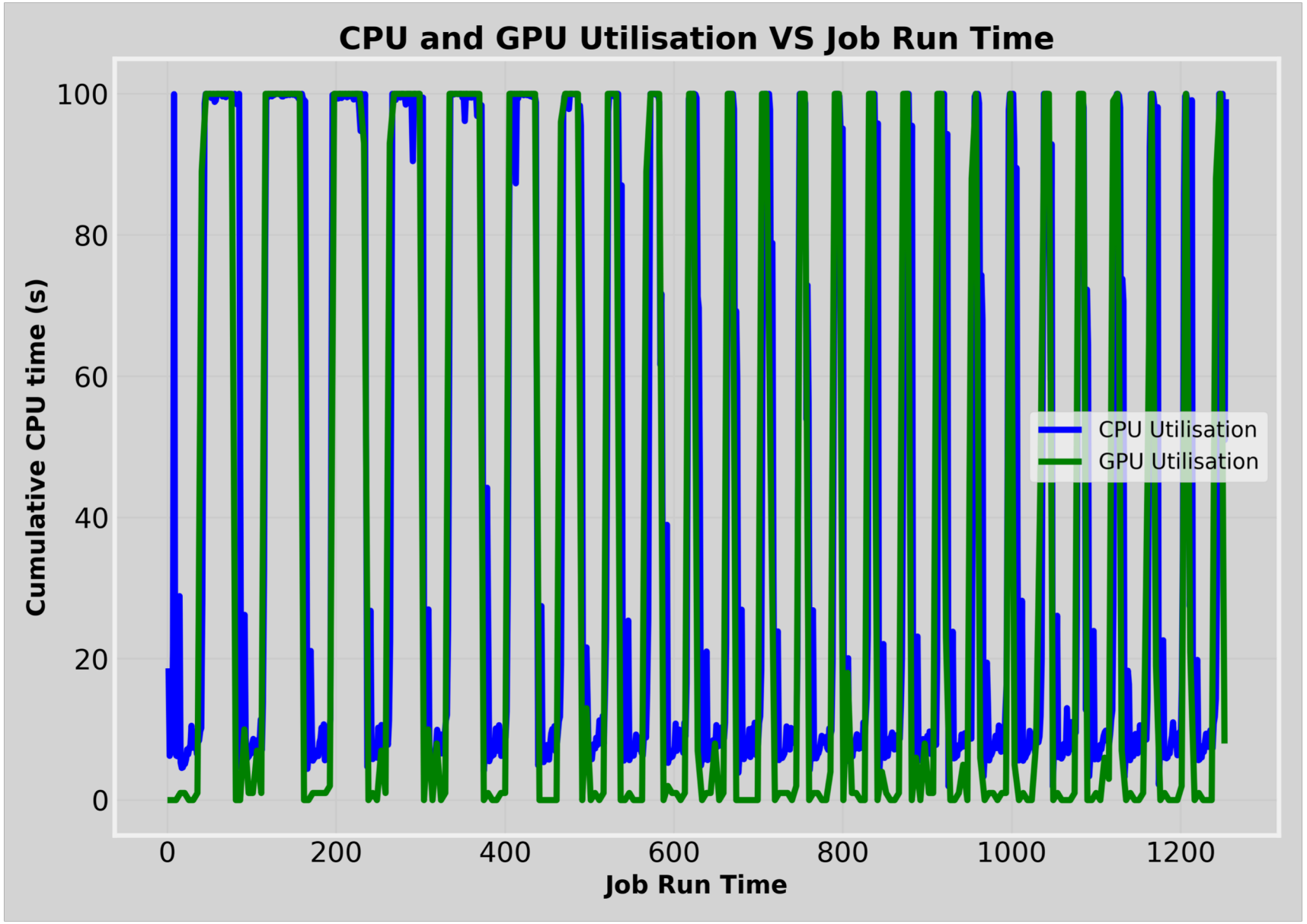
Memory Percent of time over the past sample period during which global (device) memory was being read or written.

PCIe Rx and Tx Throughput in MB/s

Latest generation GPU hardware enables very detailed performance metrics.

https://developer.download.nvidia.com/compute/DCGM/docs/nvidia-smi-367.38.pdf

What are the GPUs doing? … are they busy?



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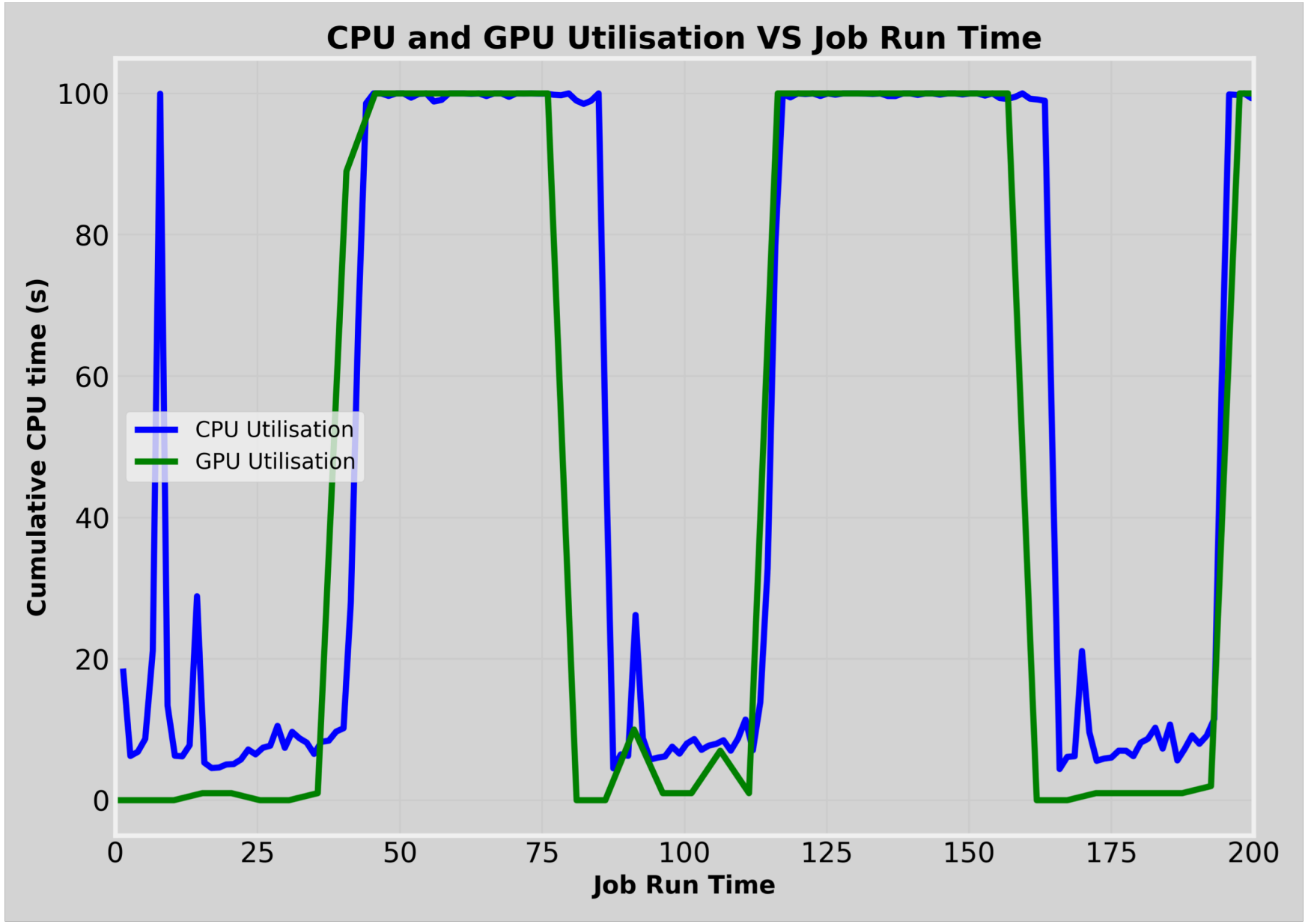

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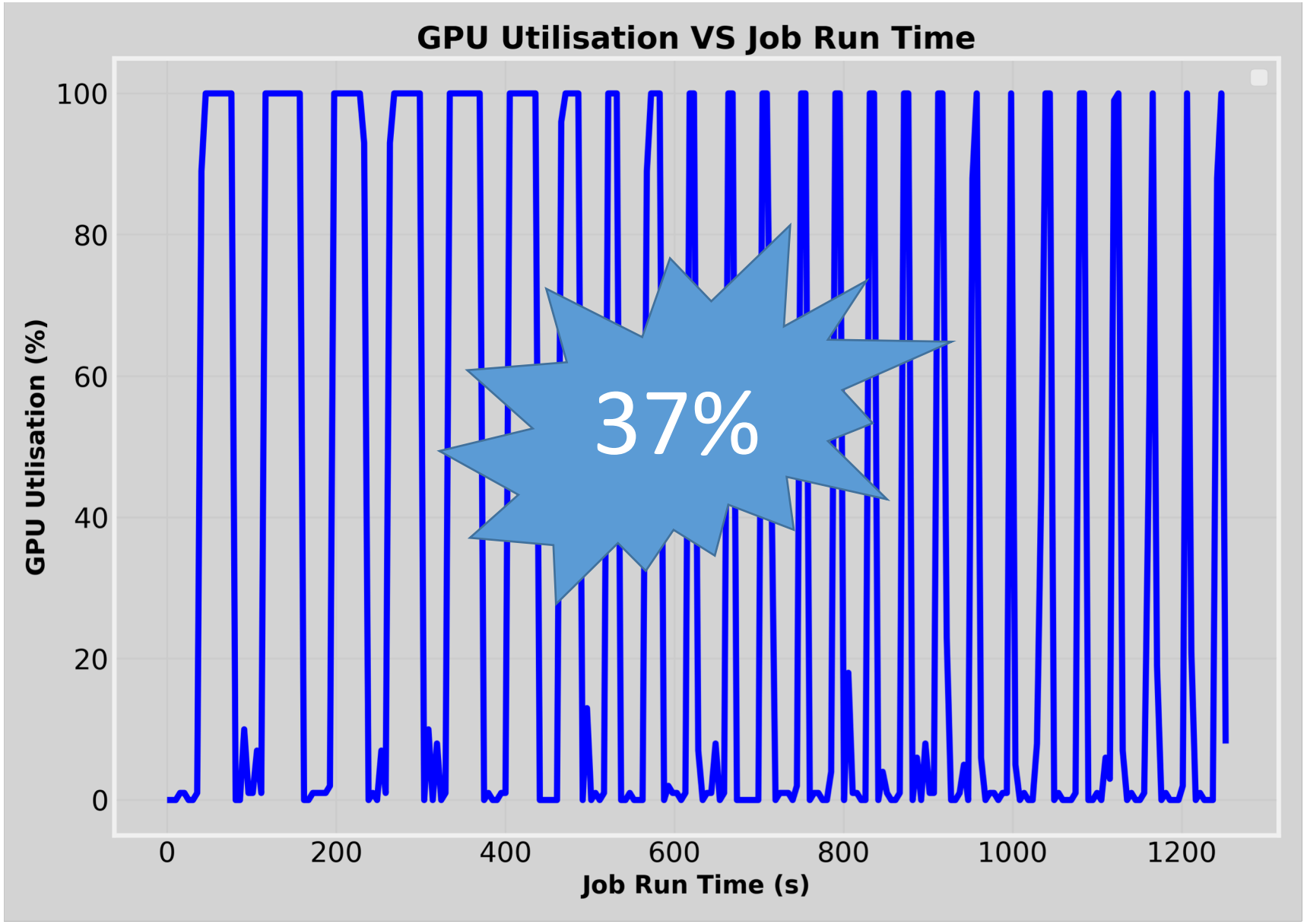
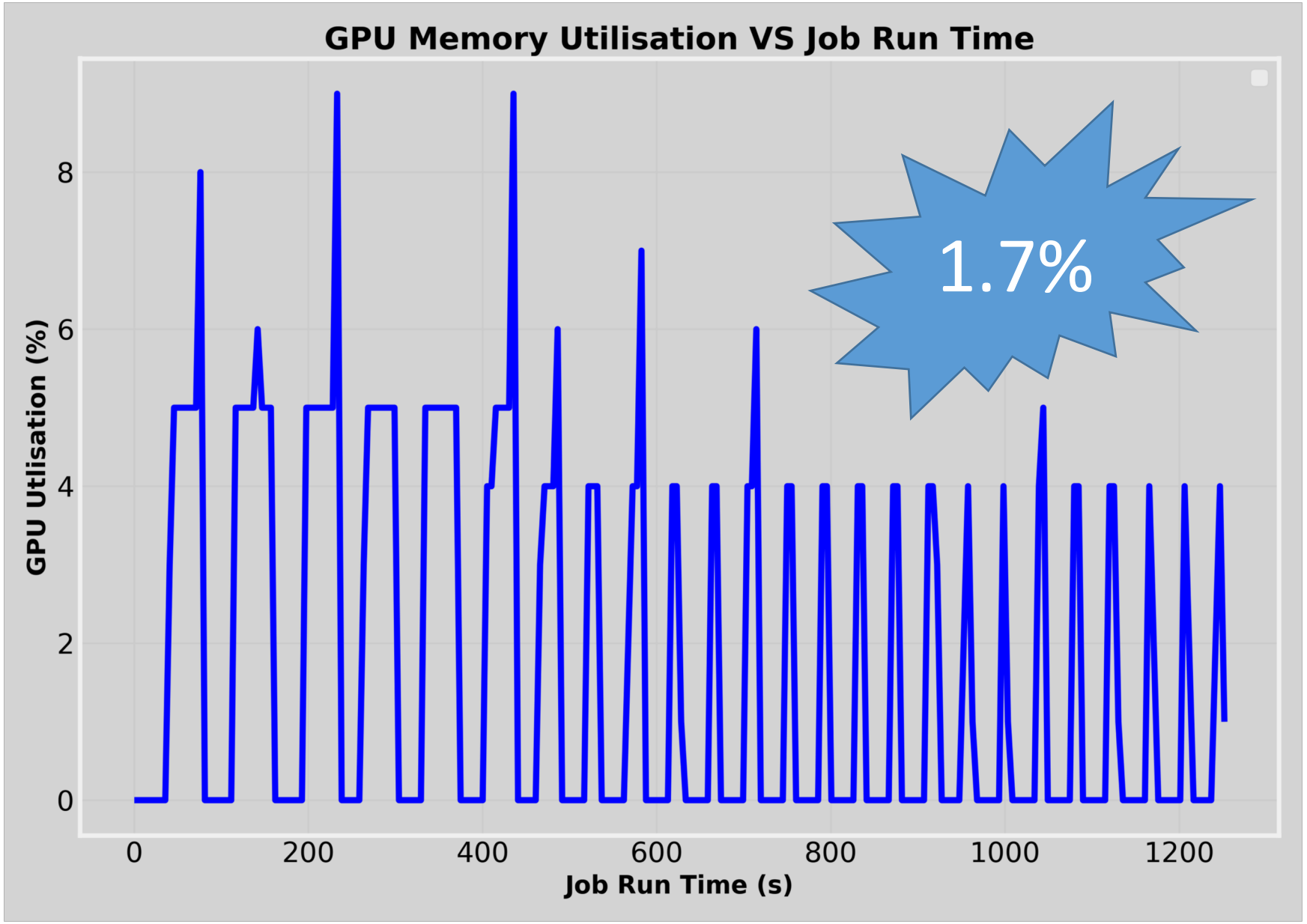


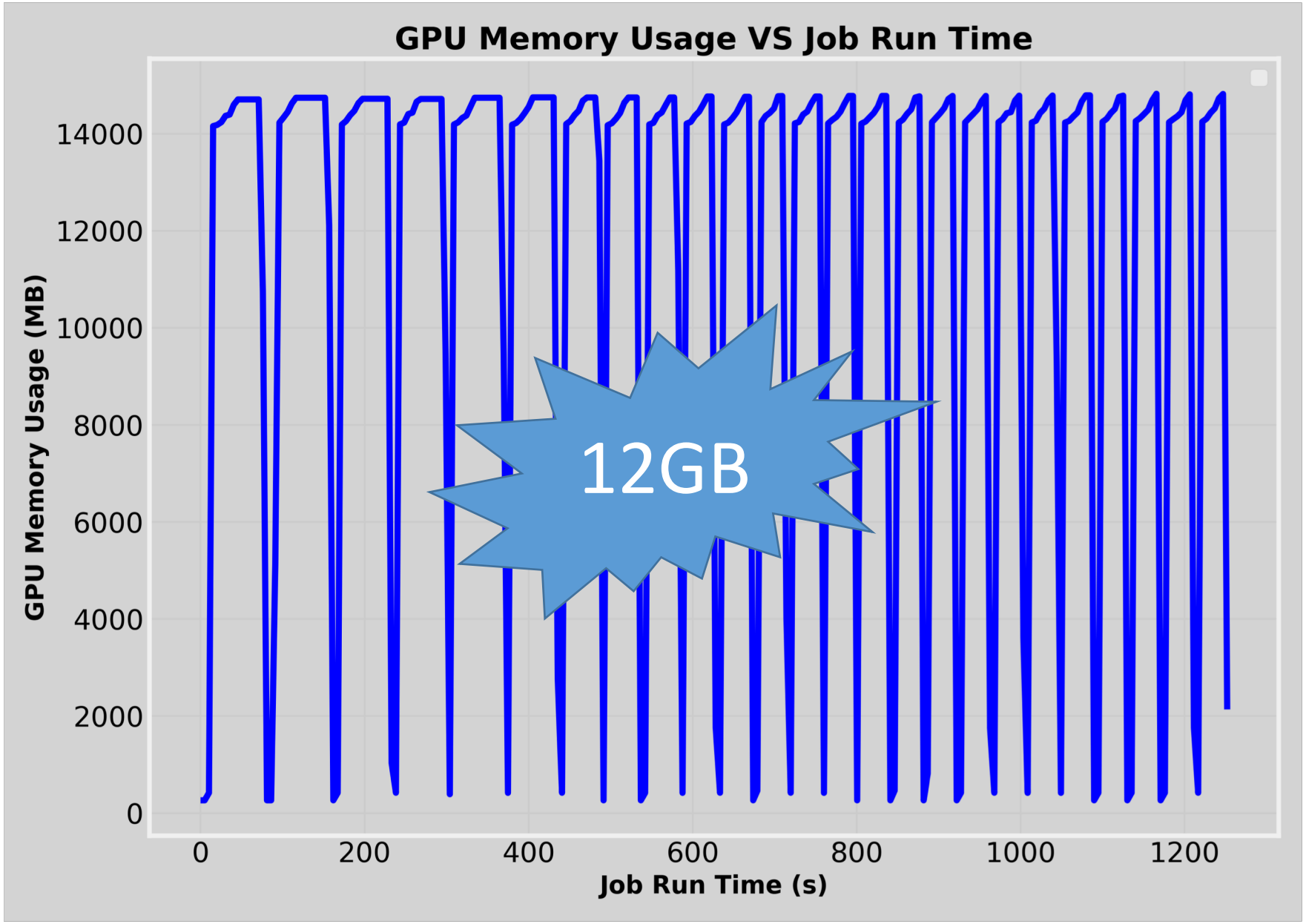
Relion3 Tutorial Dataset

What are the GPUs doing? … are they busy?



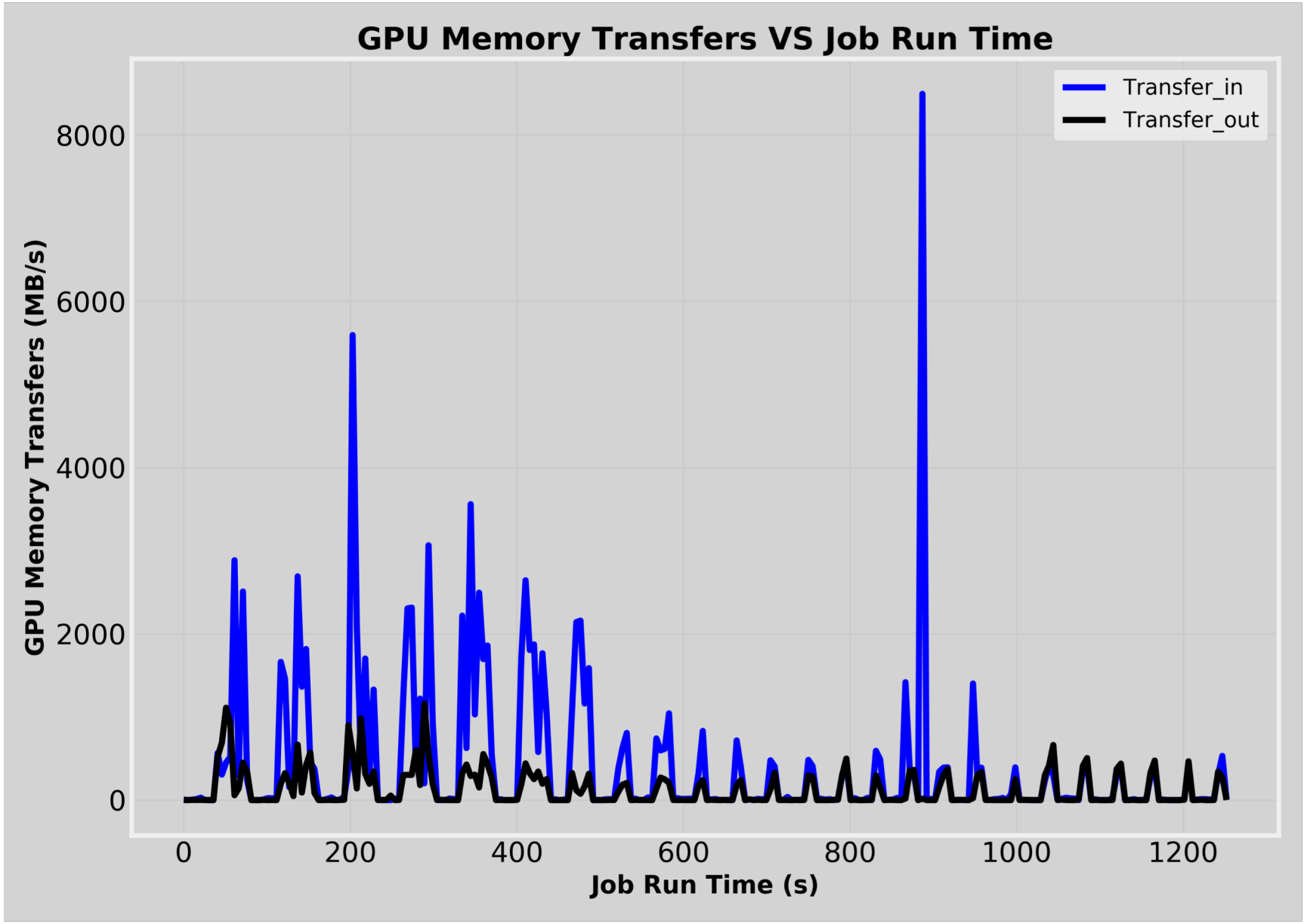
Relion3 Tutorial Dataset

What are the GPUs doing with memory?



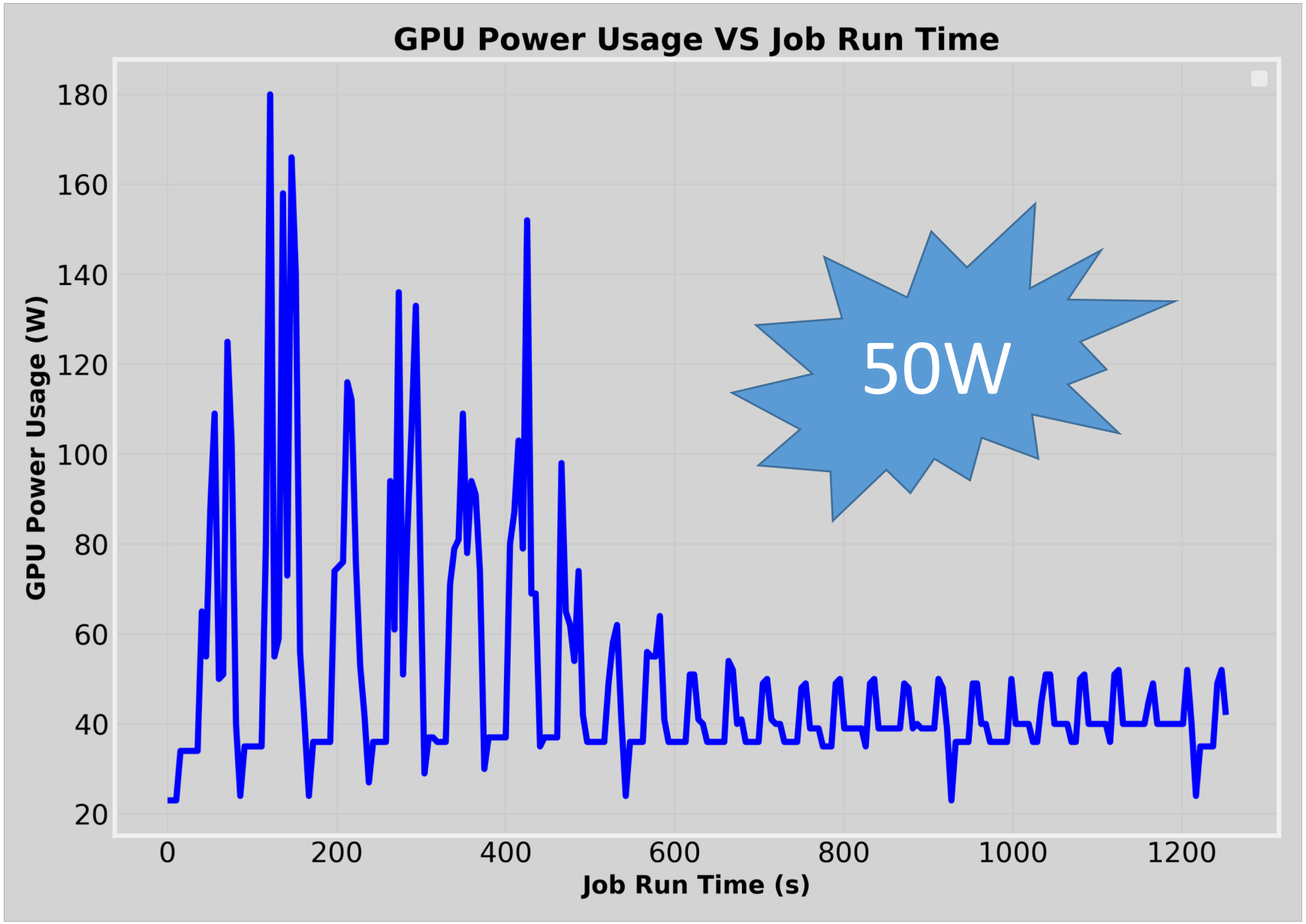
Relion3 Tutorial Dataset

How fast is data copied to memory?



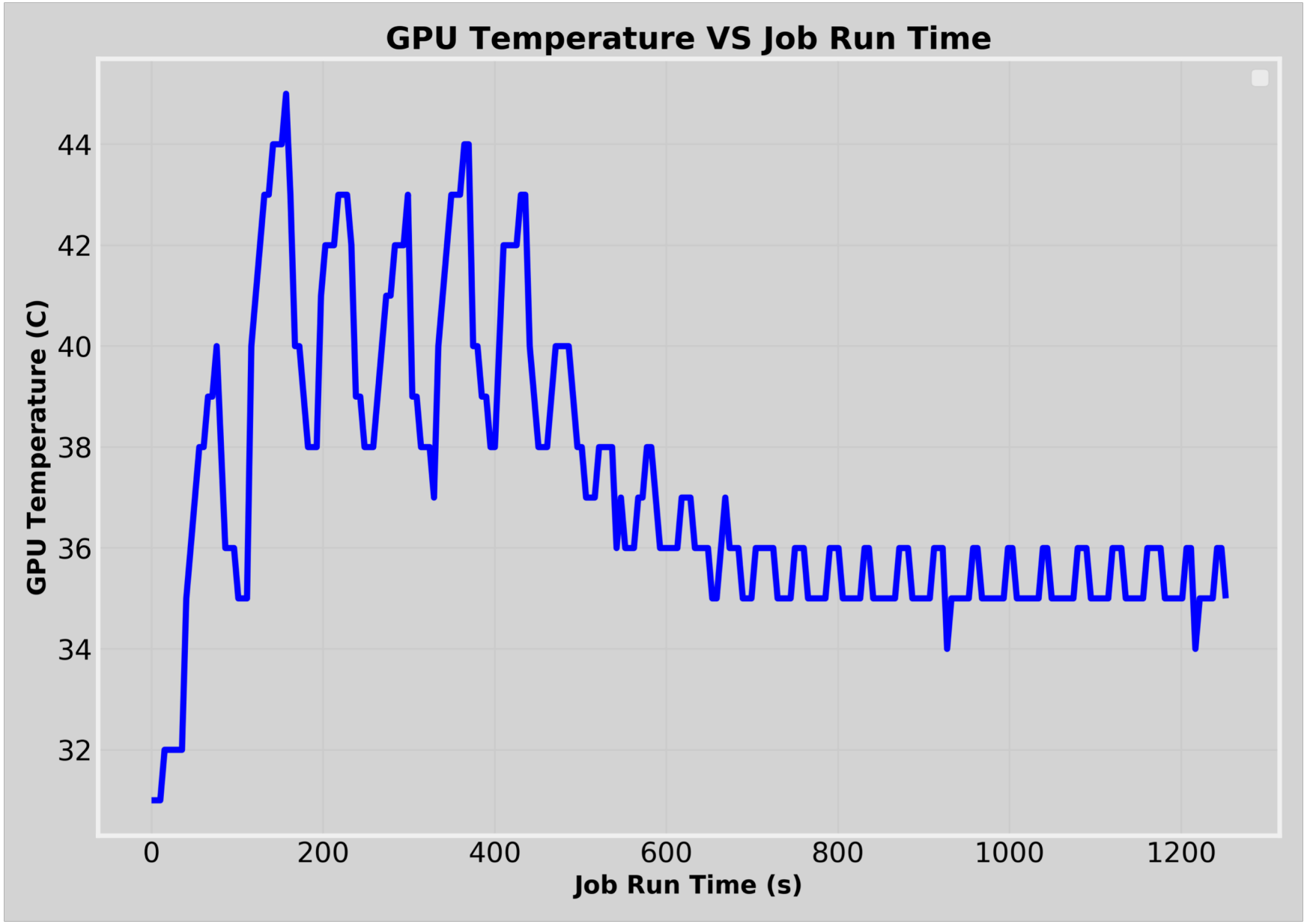
Relion3 Tutorial Dataset

How much power is consumed ? … global warming?



Relion3 Tutorial Dataset

How cooling is needed ? … global warming?



Relion3 Tutorial Dataset

Where are the opportunities for reducing “Time to Science”?

Where is development heading…

Relion 3 – CPU Vs GPU?

However, the GPU acceleration is only available for cards from a single vendor, and it cannot use many of the largescale computational resources available in existing centres, local clusters, or even researchers' laptops. In addition, the **memory available on typical GPUs limits the box sizes that can be used**, which could turn into a severe bottleneck for large particles. For relion-3, we have developed a new general code path where **CPU algorithms have been rewritten to mirror the GPU acceleration**, which provides dual execution branches of the code that work very efficiently both on accelerators as well as the single-instruction, multiple-data vector units present on traditional CPUs.

Limitations of memory

Increased performance from new CPUs

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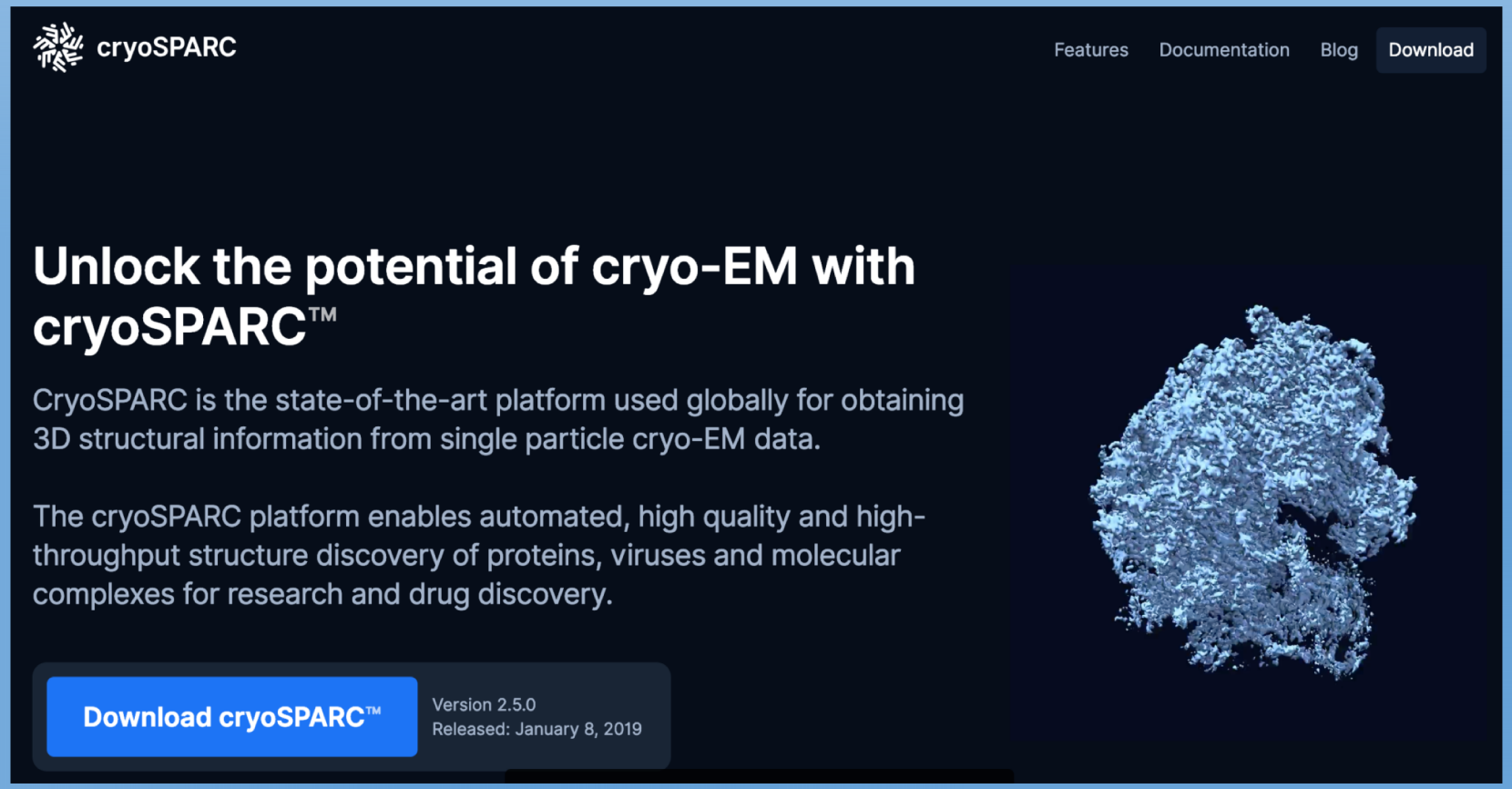
https://www.biorxiv.org/content/biorxiv/early/2018/09/19/421123.full.pdf

Opportunities for speed up

- ❑ Cryosparc
- ❑ Cryolo
- ❑ Preprocessing tools



Source: https://cryosparc.com/

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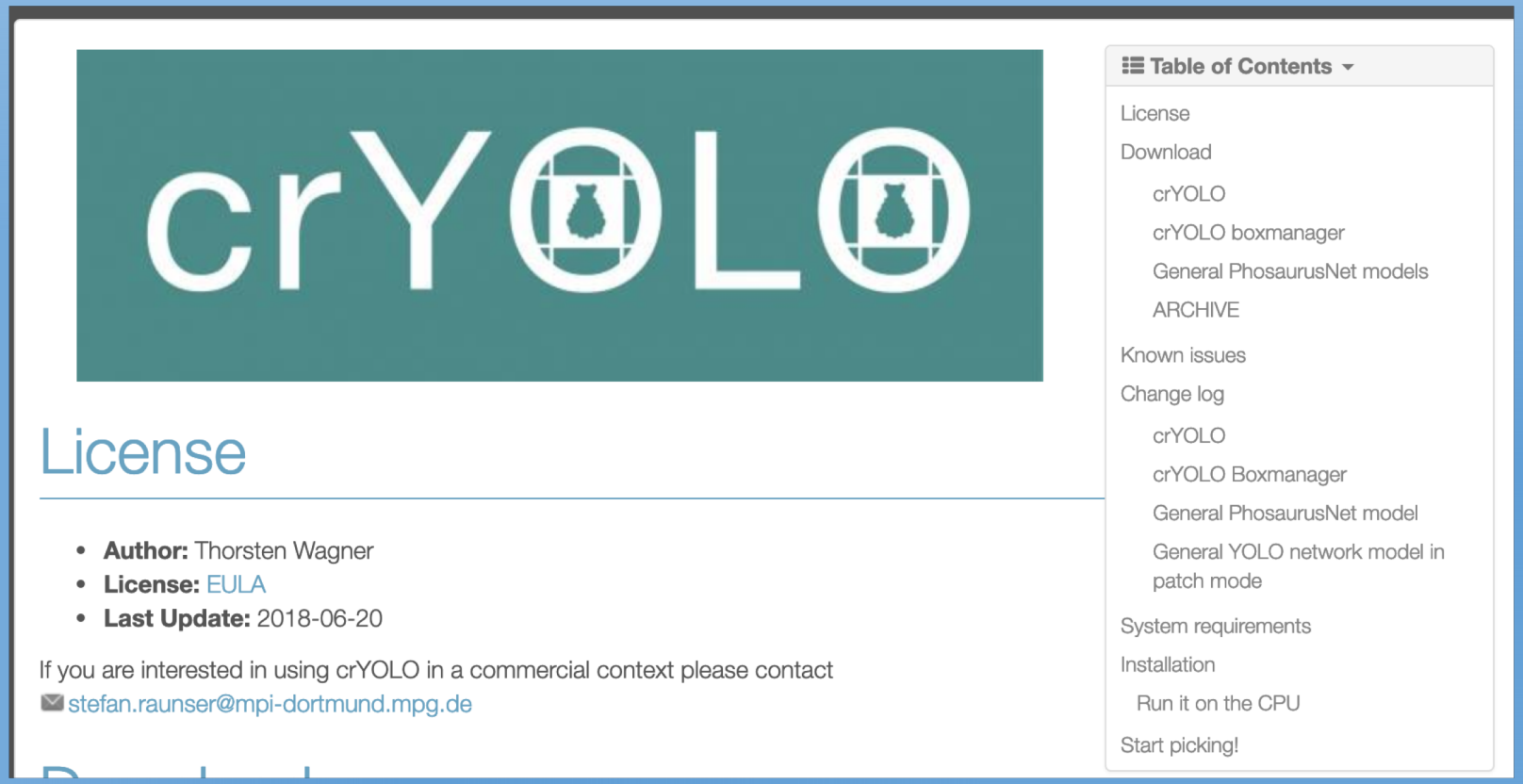

Source: http://sphire.mpg.de/wiki/doku.php?id=downloads:cryolo_1&redirect=1

Known issues

- Issue 0: Training on multiple GPUs sometimes lead to worse performance (higher loss). We currently recommend to train on single gpus.
- ~~Issue 1: crYOLO sometimes not exit properly after training finished. Has to be killed manually.~~
- ~~Issue 2: If you use automatic filtering with .tif files, you get an error like "OSError: cannot identify image file 'filtered_folder/another_folder/my_image.tif'". It will be fixed in the next release.~~
- ~~Issue 3: (Boxmanager) The visualization only shows the first filament when loading eman1 helical box files (start end coordinates). Will be fixed in the next release.~~
- ~~Issue 4: The filament mode will crash if crYOLO cannot identify a single particle in the image. Will be fixed in 1.2.2~~
- ~~Issue 5: If movies were aligned with cisTEM and picked with crYOLO, the box position are vertically flipped. Will be fixed in 1.2.2~~
- ~~Issue 6: crYOLO does overwrite the environmental variable "CUDA_VISIBLE_DEVICES" with 0 if no gpu is specified by the -g parameter. This leads to the behavior that crYOLO ignores previous settings in CUDA_VISIBLE_DEVICES. Will be fixed in 1.2.2~~
- ~~Issue 7: On K3 images crYOLO seems to add a offset toward the longer axis of the input image.~~
- ~~Issue 8: There is a logical error in filament tracing, which sometimes connects two parallel filaments.~~
- ~~Issue 9: Some people report an error when running cryolo prediction/training: "ImportError: numpy.core.multiarray failed to import". It will be fixed in 1.2.3.~~
- ~~Issue 10: On machines with many cores (e.g 64) an error during filtering might pop up: "[ERROR:0] 53: Can't spawn new thread"~~
- ~~Issue 11: If the -g parameter is not provided, crYOLO will use the memory of all GPUs. Will be fixed in 1.2.3.~~
- ~~Issue 12: The LineEnhancer depdenceny of crYOLO is still dependent from opencv. Workaround: In the crYOLO environment: conda install opencv~~
- Issue 13: After picking it can happen that some of the boxes are not fully immersed in the image.

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- ❑ Cryosparc
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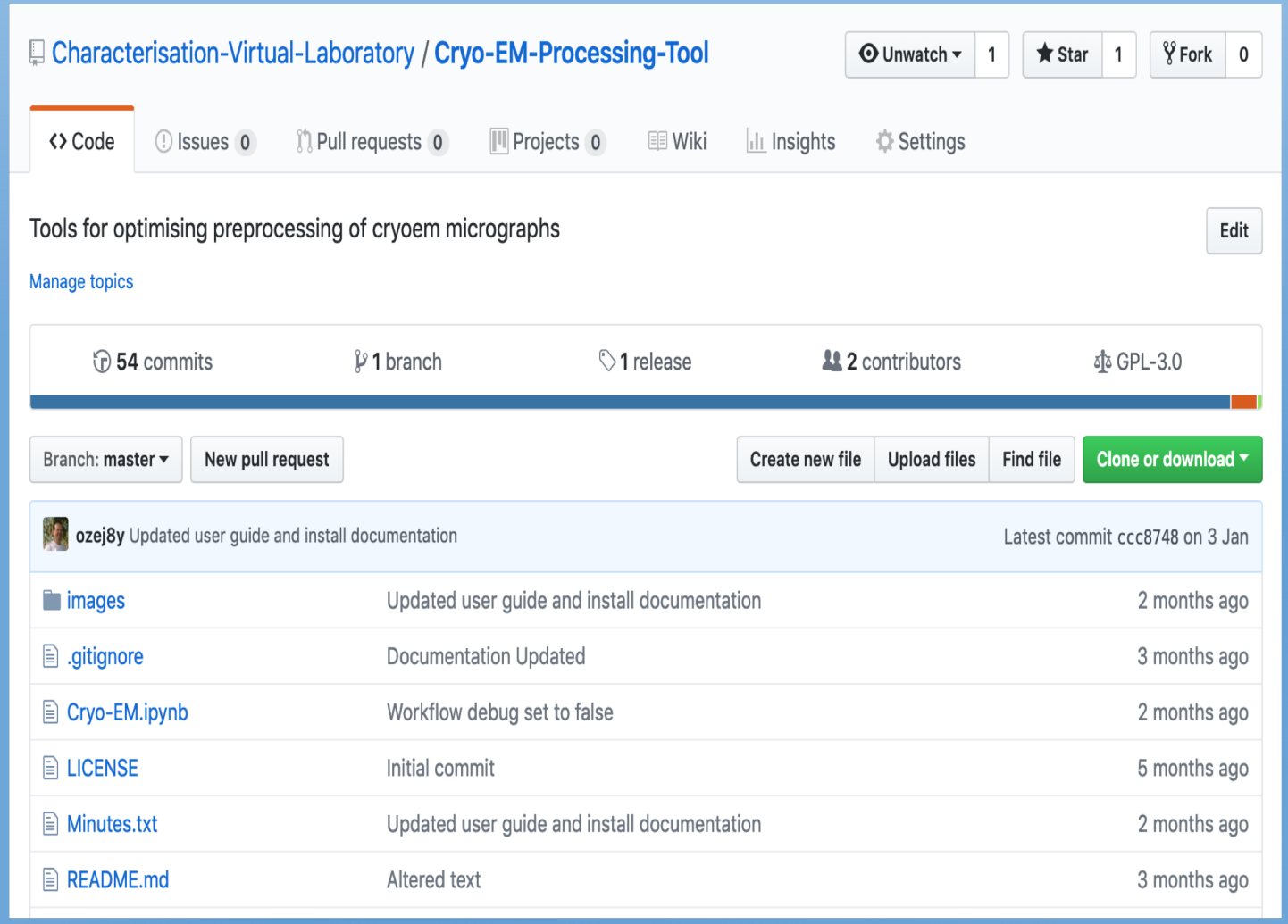
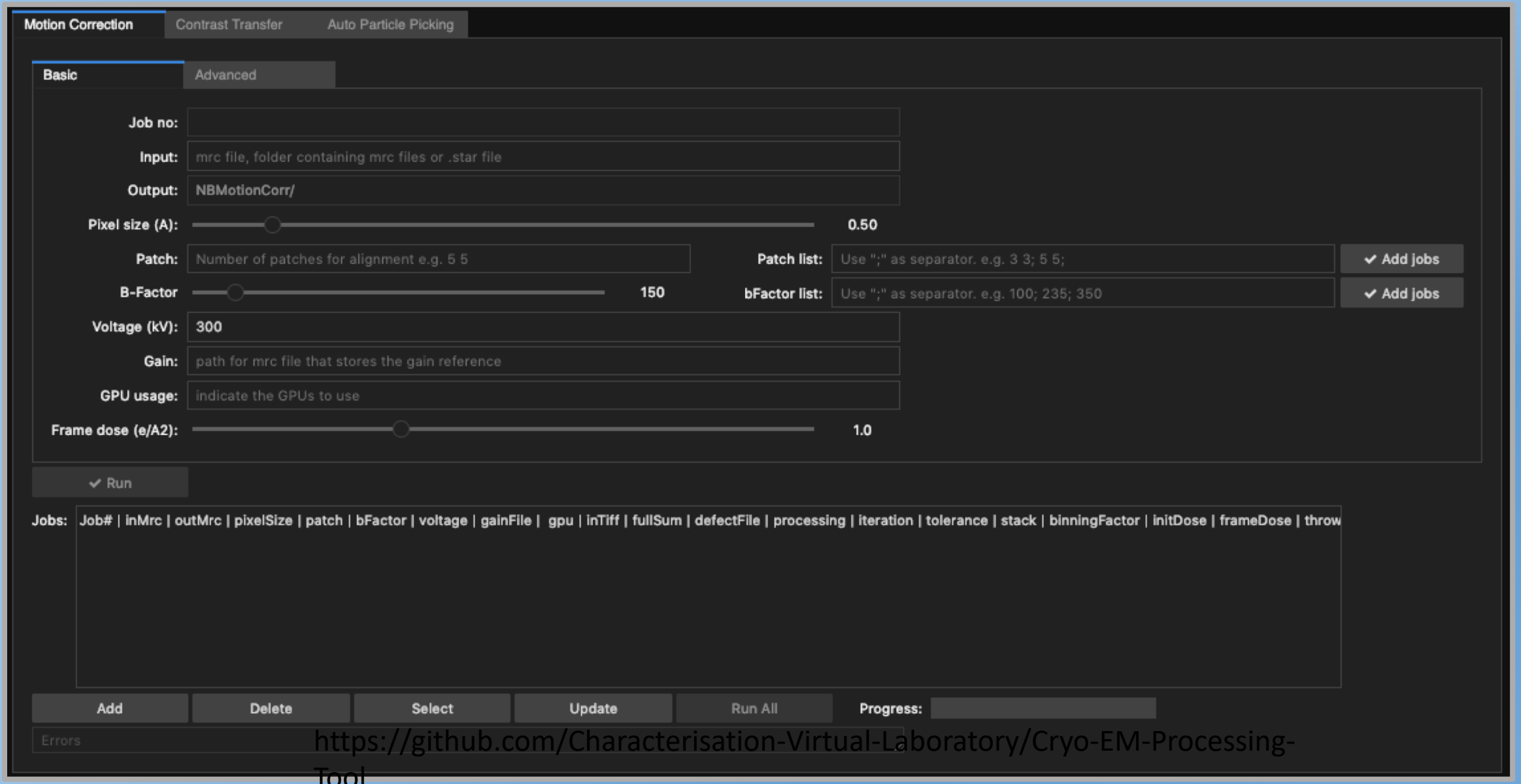


https://github.com/Characterisation-Virtual-Laboratory/Cryo-EM-Processing-Tool

Cryo-EM Processing Tool



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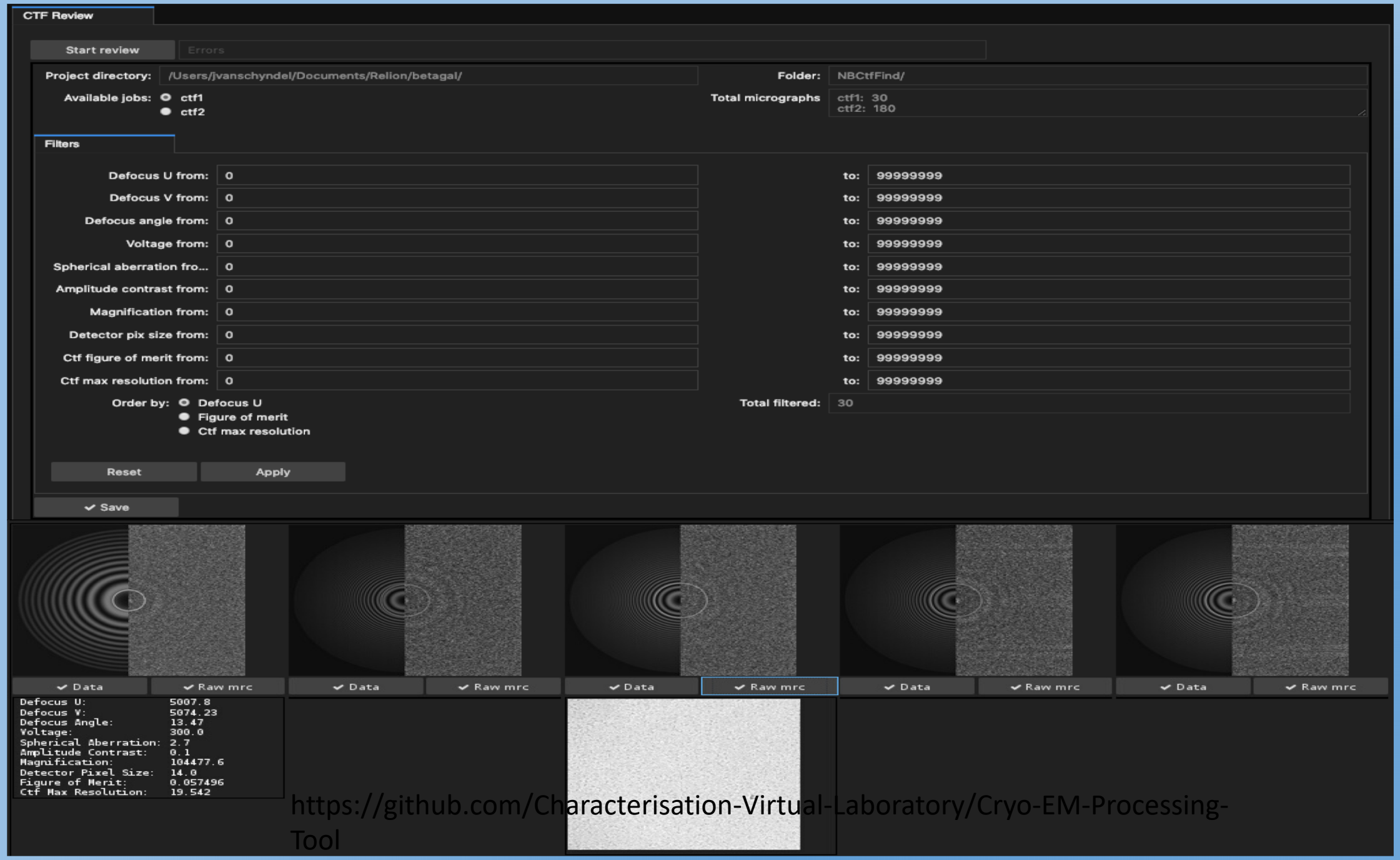

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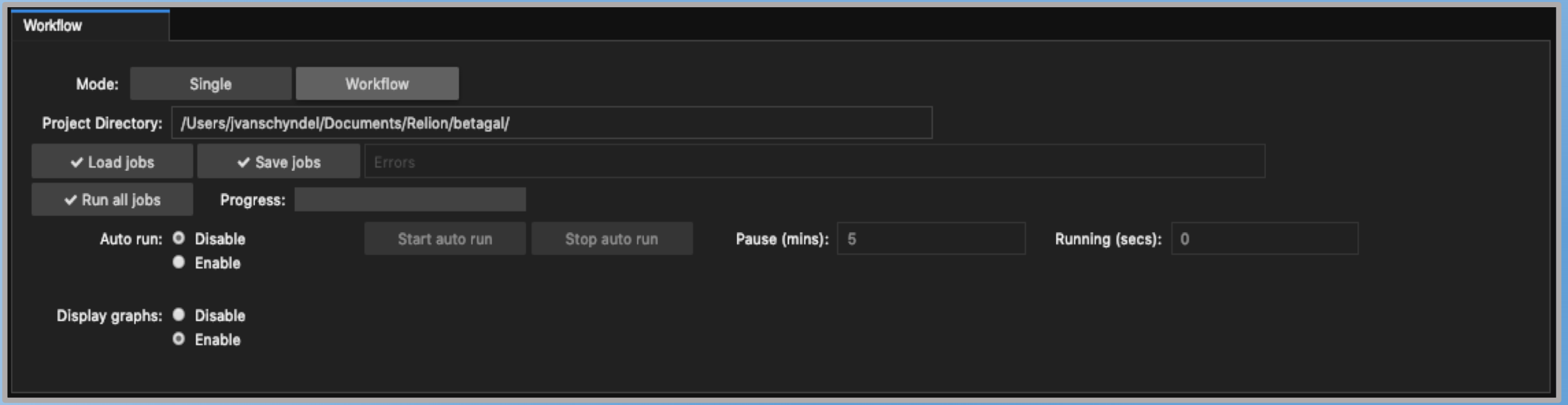

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Next Generation: 4D+ Volumetric Imaging

Lattice light sheet microscopy

RESEARCH ARTICLE

BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis

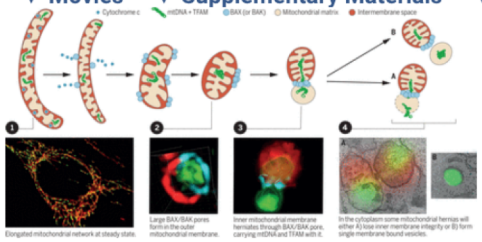
Kate McArthur[1,2,3,*], Lachlan W. Whitehead[1,2], John M. Heddleston[4], Lucy Li[1], Benjamin S. Padman[5], Viola Oorschot[6], Niall …

+ See all authors and affiliations

Science 23 Feb 2018:
Vol. 359, Issue 6378, eaao6047
DOI: 10.1126/science.aao6047

Figures

▼ Movies ▼ Supplementary Materials ▼ Additional Files



Schematic of apoptotic mitochondrial herniation.

Inset images show the key stages as captured by lattice light-sheet microscopy, structured illumination microscopy, and correlative light and electron microscopy.

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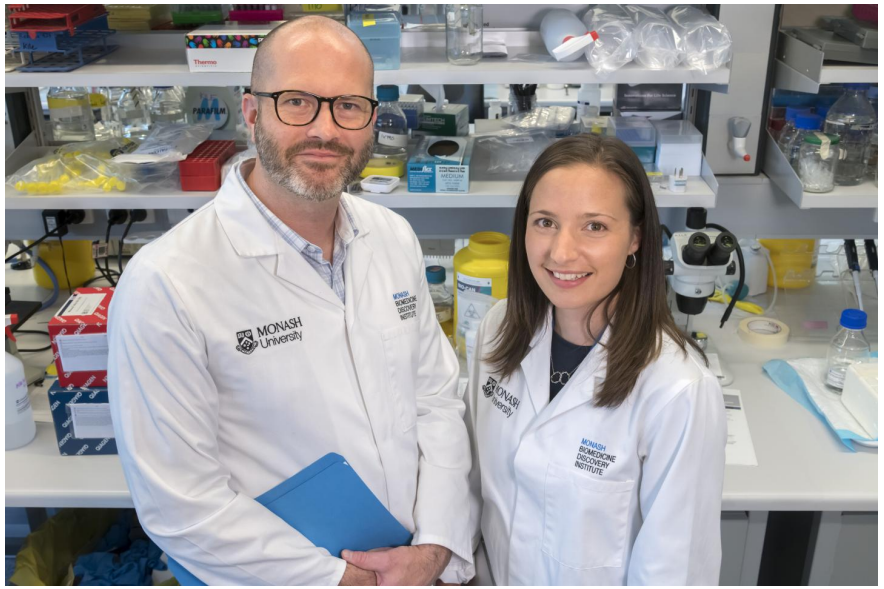
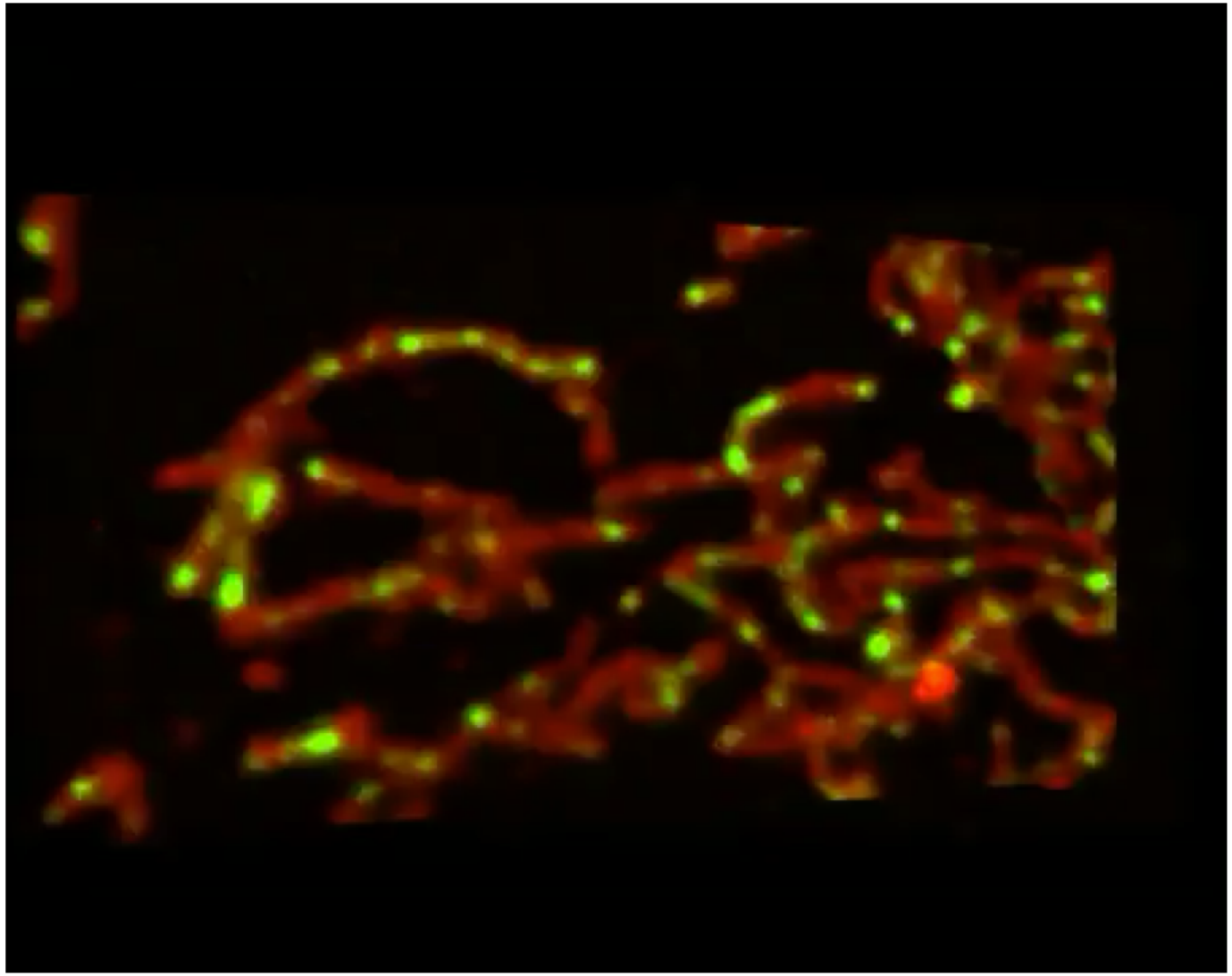
Mitochondrial DNA (green) escaping mitrochondria (red) during cell death.

Dr Kate McArthur (Monash BDI) and Dr Lachlan Whitehead (WEHI) and The Advanced Imaging Centre at Janelia Research Campus.



Credit: Steve Morton



Acknowledgments

Dr Matt Belousof
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Jafar Lie
Jay Van Schyndel

MASSIVE Partners
ARDC

MONASH University

THANK YOU

Final messages:

- ✓ HPC is the best option, if you have interactive queues.
- ✓ Cloud is good for one off analysis.
- ✓ Workstations make great training/learning platforms

For future questions: lance.wilson@monash.edu