
ORACLE
INTERNET2
Webcast Series
UC Davis researchers advance medicine with Oracle high performance computing
Discover the benefits of high performance computing for research
Tuesday, December 8 at 12 p.m. ET

Webinar series: Powering the research community

- **Igniting Research with Oracle High Performance Computing**
  - Tuesday , Nov. 10 at 12 p.m. ET
- **UC Davis Researchers Advance Medicine with Oracle High Performance Computing**
  - Tuesday, Dec. 8 at 12 p.m. ET
- **Accelerating Science with CERN**
  - Tuesday, Jan. 26 at 12 p.m. ET
- **Paying only for what you use**
  - February 2021

ORACLE
Cloud Infrastructure

INTERNET 2®

UC DAVIS HEALTH

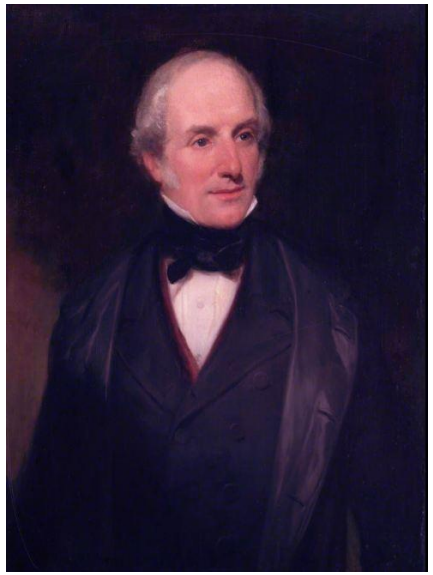
Igor Vorobyov, PhD

Assistant Professor, Departments of Physiology and Pharmacology, University of California, Davis.

- **PhD,** University of Louisville
- **Postdoctoral**
  - University of Maryland
  - University of California, Davis
  - University of Southern California

Prescription drugs can cause cardiac arrhythmia

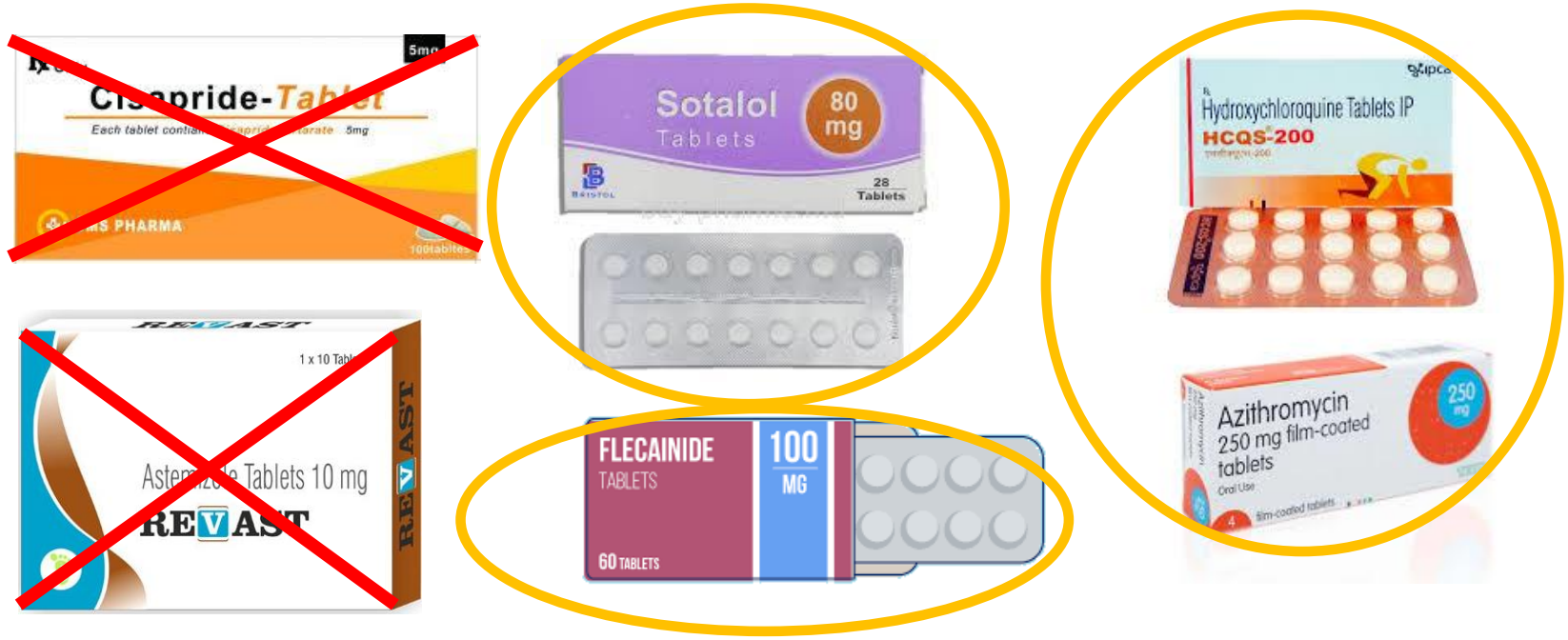
"Poisons and medicine are often the same substance given with different intents"
Peter Mere Latham (1789-1875)



- Up to 3% of prescription drugs carry arrhythmia risks.
- Cardiotoxicity account for 22-28% US post-market drug withdrawals.
- Up to 50-70% of small molecule leads are eliminated early in drug development due to potential for causing arrhythmias.
- This impedes drug development and greatly increases its $$$.
- Multiple drug classes are affected: most anti-arrhythmics, some antibiotics, anti-cancer drugs, allergy medications, GI drugs, COVID-19 medications etc.

Drug induced arrhythmia – a major regulatory problem

- In 1990s-2000s some drugs were withdrawn and some got limited distribution.



- These drugs can cause Torsades de Pointes (TdP) arrhythmias

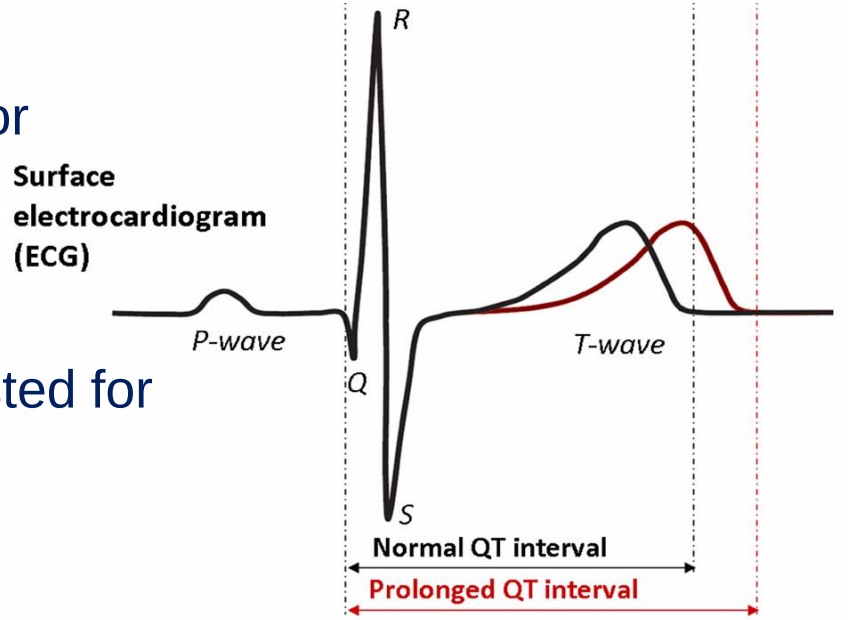
TdP arrhythmia often results in sudden cardiac death.

https://www.fda.gov/drugs/regulatory-science-action/impact-story-improved-assessment-cardiotoxic-risk-drug-candidates-comprehensive-vitro-proarrhythmia

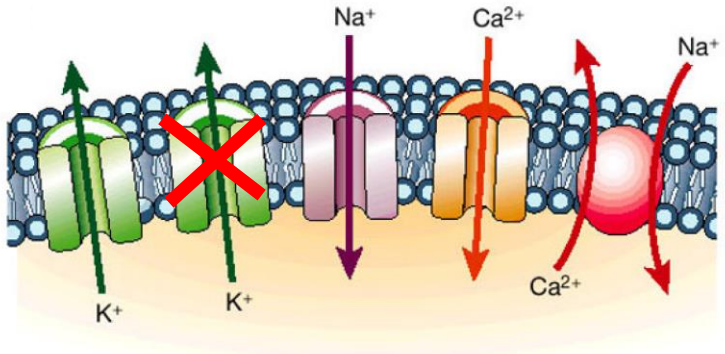
Drug induced arrhythmia – a major regulatory problem

- In 2005 two key international guidances were developed to solve this problem.

1) During clinical trials drugs are tested for QT interval prolongation on ECG



2) During pre-clinical testing drugs are tested for hERG channel inhibition



hERG channel moves K^+ ions across cardiac cell membranes and drives heart electrical activity to the resting state.

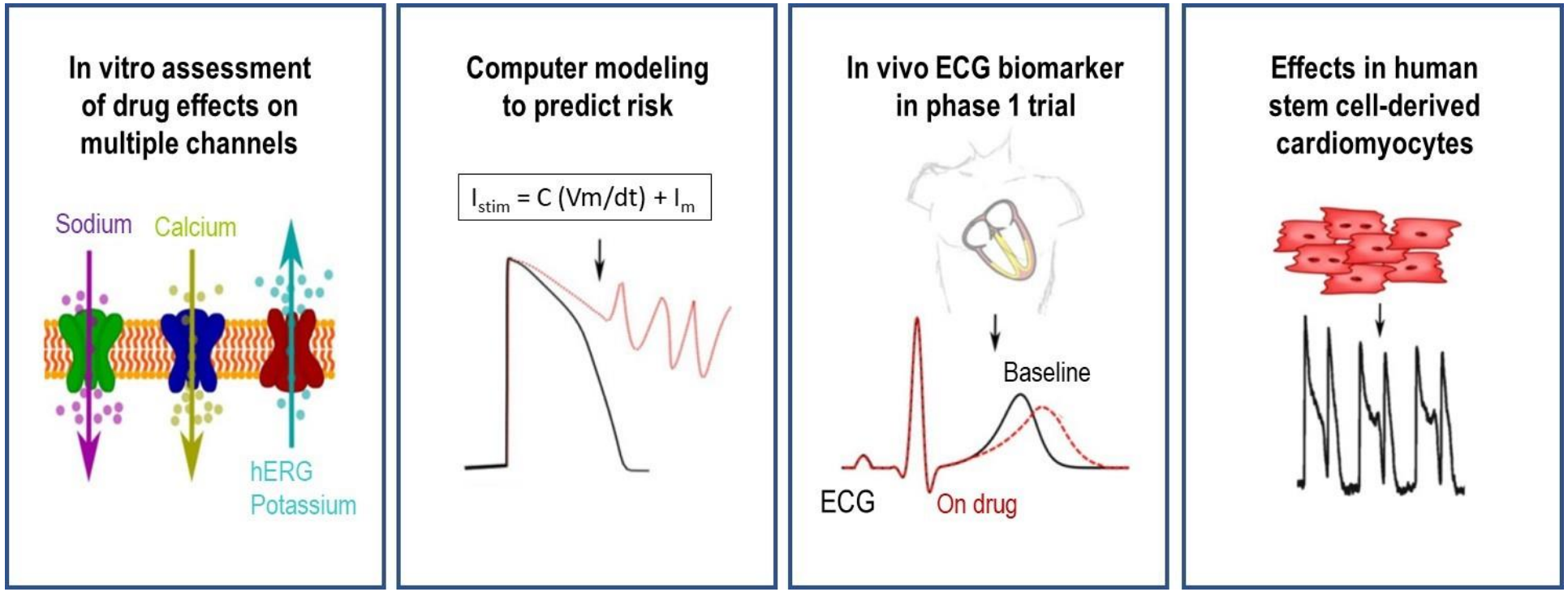
hERG channel is a promiscuous drug anti-target.

- No hERG blocking and QT prolonging drugs can enter the market.

Not all hERG blockers cause arrhythmia

- QT prolongation and hERG block are not selective criteria for drug-induced arrhythmia**.**
- Many hERG blocking drugs are cardiac safe. Grapefruit juice can cause QT prolongation.
- This can lead to abandonment of safe and effective drug candidates.

Comprehensive in vitro Pro-arrhythmia assay (CiPA) initiative.



It is a combination of experimental and computational techniques developed and used by multiple research groups in US and around the world. http://cipaproject.org/about-cipa/#1

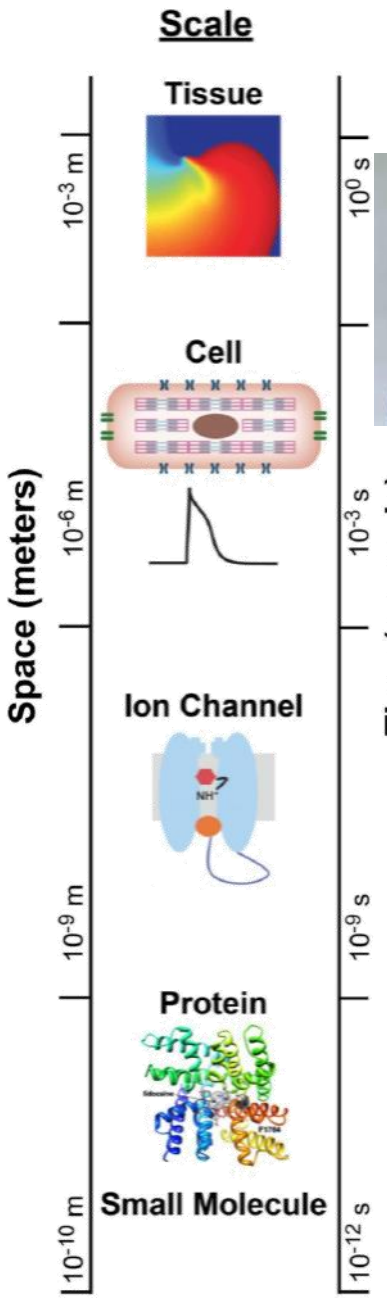
However, CiPA initiative does not provide a ready-to-go recipe on how to predict drug-induced pro-arrhythmia from drug chemical structure.

https://www.fda.gov/drugs/regulatory-science-action/impact-story-improved-assessment-cardiotoxic-risk-drug-candidates-comprehensive-vitro-proarrhythmia

In silico safety pharmacology

UC DAVIS HEALTH

NIH National Heart, Lung, and Blood Institute



UC Davis modeling team leaders

Prof. Colleen Clancy
Physiology

Prof. Vladimir Yarov-Yarovoy
Physiology

Prof. Tim Lewis
Mathematics

UC Davis experimental team leaders

Prof. Fernando Santana
Physiology

Prof. Jon Sack
Physiology

Prof. Heike Wulff
Pharmacology

Prof. Crystal Ripplinger
Pharmacology

Collaborators

Prof. Sergei Noskov
U. Calgary

Prof. Slava Bekker
ARC

Prof. Kazuharu Furutani
Tokushima Bruni U.

Researchers & trainees

Dr. Pei-Chi Yang
Project scientist

Dr. Kevin DeMarco
Postdoc

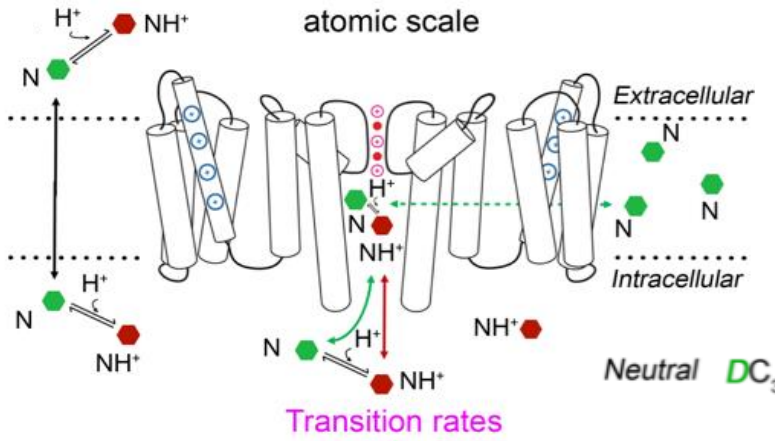
Dr. Parya Aghasafari
Postdoc

Mr. John Dawson
Grad. student

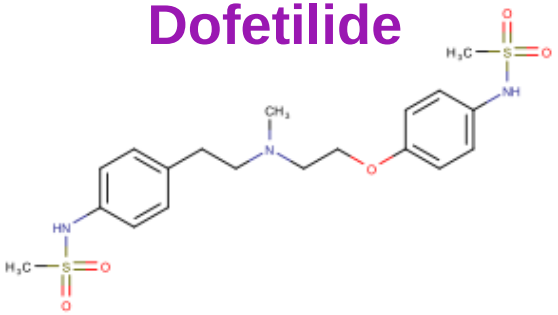
Goal: to predict drug-induced arrhythmogenicity from drug chemical structure using a multi-scale modeling pipeline guided by experiments.

Clancy et al. Ann Biomed Eng. 2016, 44: 2591

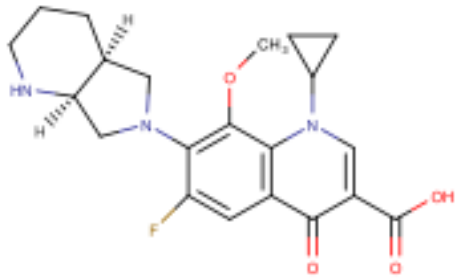
In silico pipeline to predict cardiotoxicity: from atom to rhythm

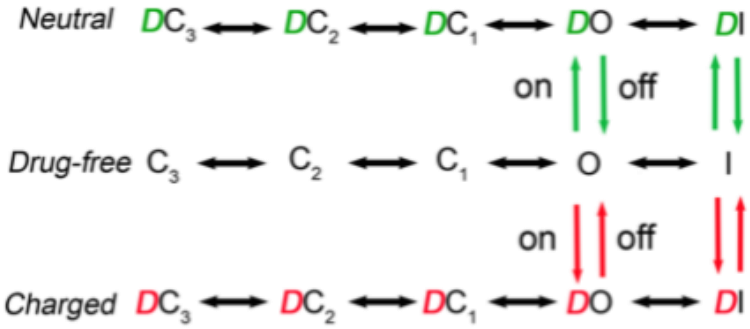


Dofetilide



Moxifloxacin

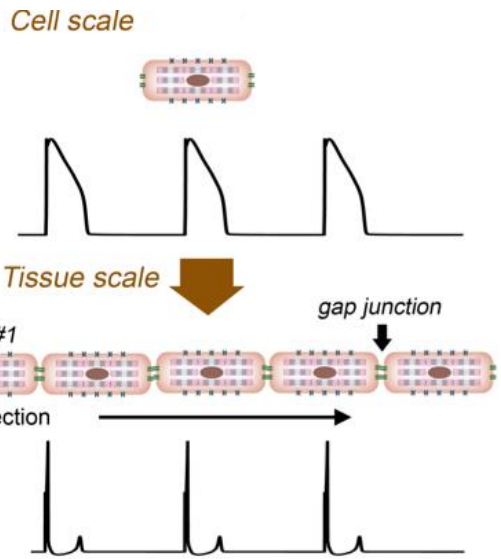




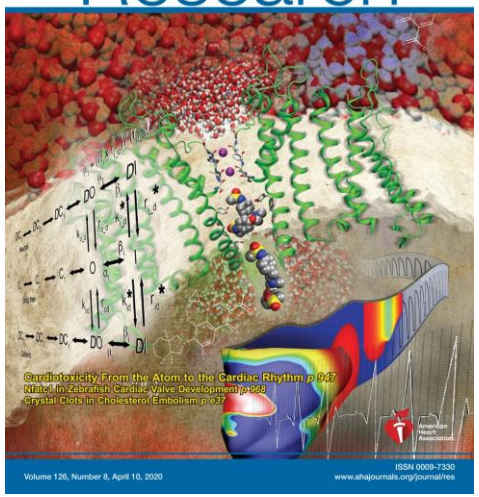
Atom

Function

Heart Rhythm

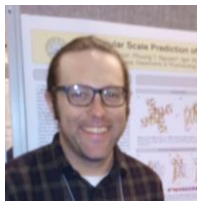


Pseudo ECG



Professor Colleen Clancy

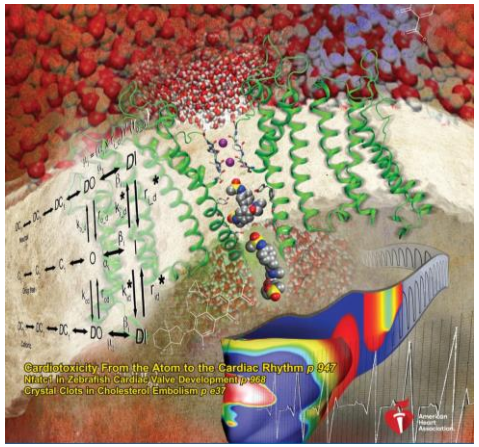
Dr. Pei-Chi Yang



Dr. Kevin DeMarco

Yang et al Circ Res 2020, 126(8): 947

Why use our multi-scale safety pharmacology pipeline?



- ✦ Move beyond hERG block and QT prolongation paradigm for cardiac drug safety testing.
- ✦ Translate microscopic drug – protein interaction data into their clinical effect on heart rhythm.
- ✦ Incorporate sex differences in drug testing.
- ✦ Include co-morbidities (e.g., heart failure, myocardial infarction) in drug testing.
- ✦ Account for patient specific genetic variations (mutations, polymorphism) for personalized medicine approach.
- ✦ Predict arrhythmia risks for chemically similar drugs.
- ✦ Rehabilitate promising drug candidates and repurpose existing medications.
- ✦ Develop new cardiac-safe and efficient treatments.
- ✦ Reduce costs of drug development and save human lives!

High-performance computing (HPC) are crucial for the pipeline

✦ **Atomistic molecular dynamics (MD) simulations are computationally demanding.**

1/1,000,000 second long simulation ~ 500,000,000 energy & force computations.

50 days for NAMD 2.14 on Nvidia Tesla P100 GPU for a 130,000 atom system

NAMD Scalable Molecular Dynamics

GROMACS FAST. FLEXIBLE. FREE.

NVIDIA CUDA

✦ **Functional cardiac tissue simulations can be also computationally demanding**

1D tissue of 165 cells running for 50 min: 1-2 days on a 12-core Intel Xeon CPU.

intel Intel® Software Development Tools

GCC

intel inside™ Xeon®

✦ **Machine learning simulations also run the best on GPUs.**

PYTORCH

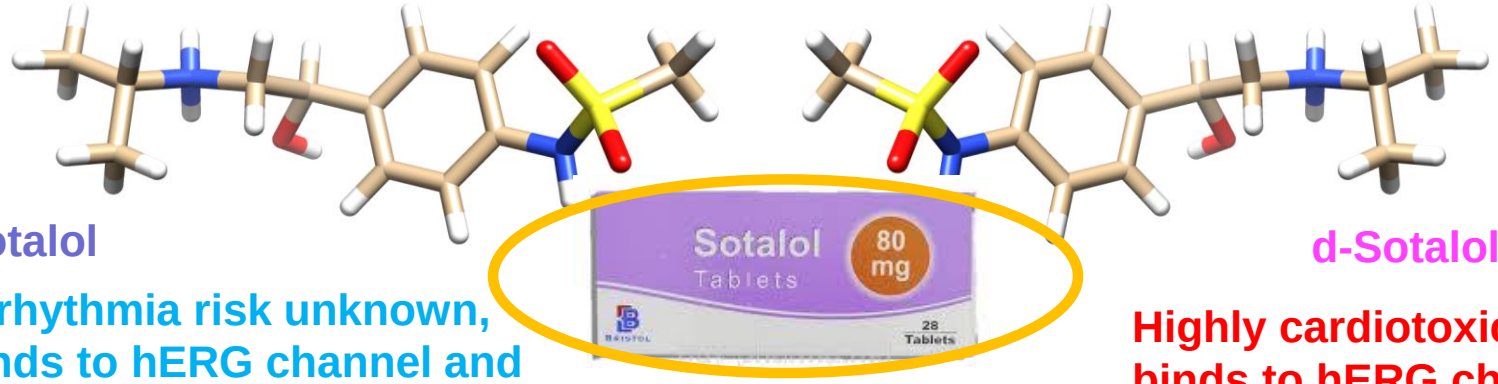
jupyter

Oracle cloud HPC for the safety pharmacology pipeline

- ✦ State of the art hardware and software is available
- ✦ Different instances and customized images.
- ✦ Flexible storage options (file, block etc.)
- ✦ Our data are secure and can be easily retrieved when needed
- ✦ No queue waiting time, can run instantaneously
- ✦ Different components of a multi-scale pipeline can run simultaneously
- ✦ We can easily automate our simulations using provided scripts
- ✦ Multiple sources of help and support

Extension to multi-target block in safety pharmacology pipeline

Many hERG blocking and QT prolonging drugs bind to other cardiac proteins, which may modify their pro-arrhythmia proclivities (also investigated through CiPA initiative)



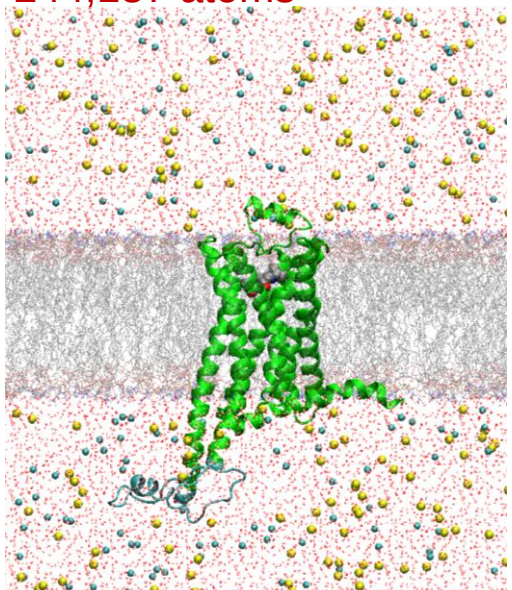
l-Sotalol

Arrhythmia risk unknown, binds to hERG channel and β adrenergic receptor

d-Sotalol

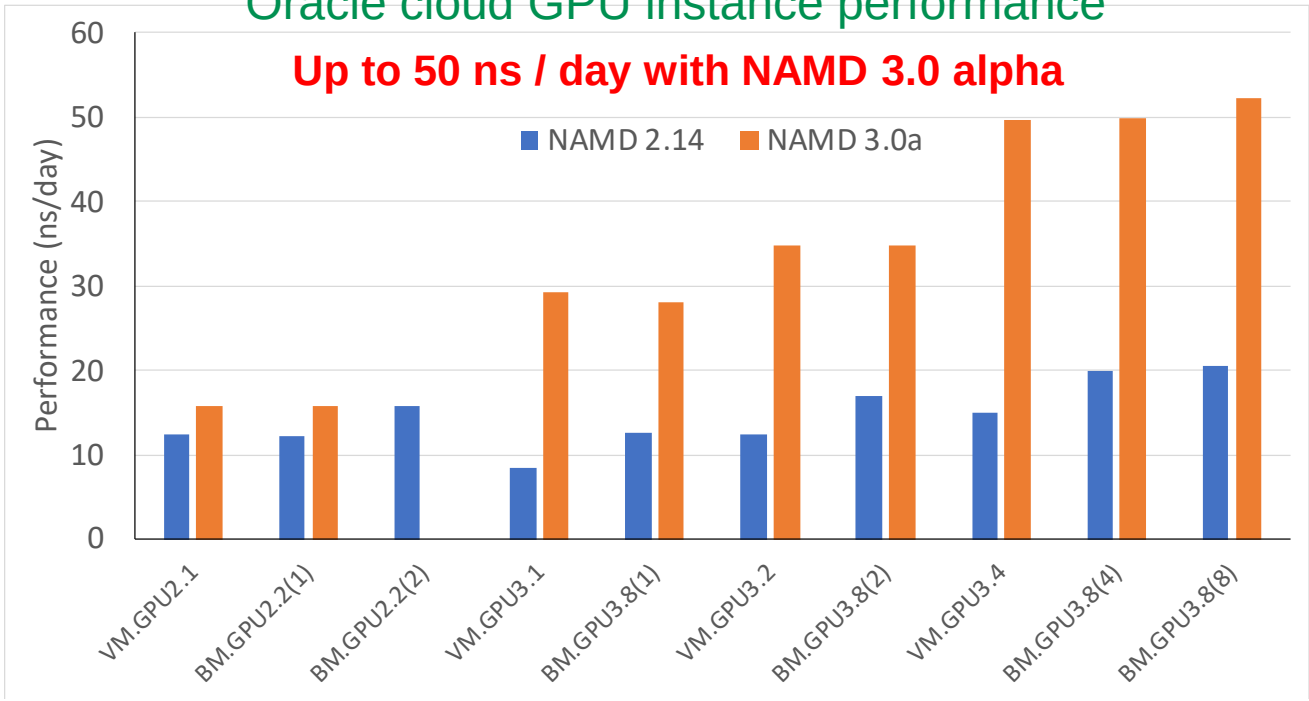
Highly cardiotoxic, binds to hERG channel only

β_1 adrenergic receptor with docked l-sotalol(+) 244,187 atoms

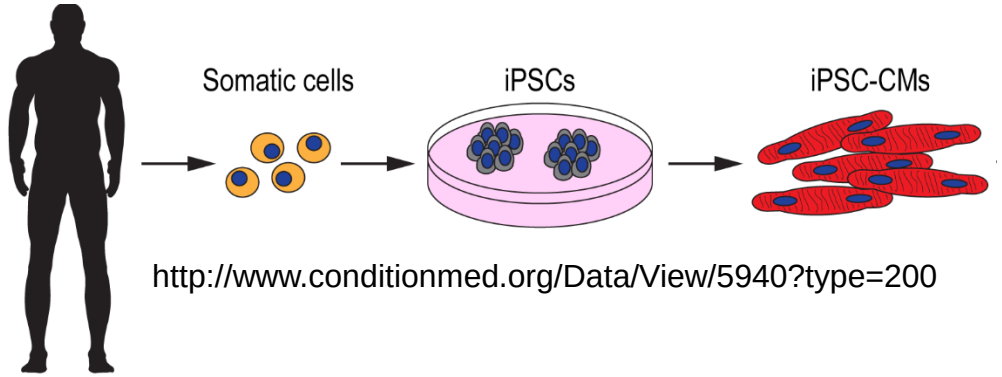


Oracle cloud GPU instance performance

Up to 50 ns / day with NAMD 3.0 alpha



Personalized safety pharmacology data science pipeline

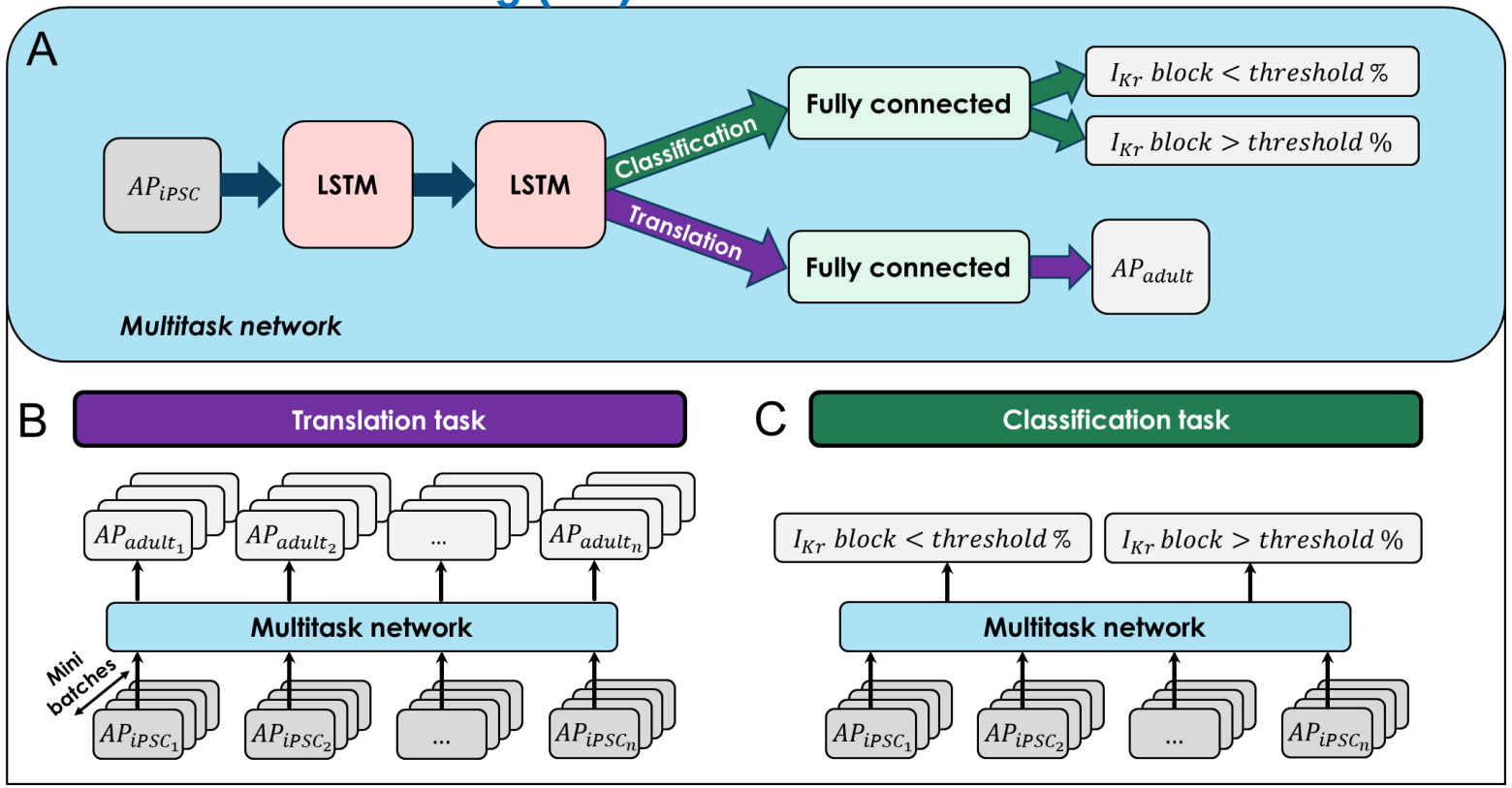


http://www.conditionmed.org/Data/View/5940?type=200

Induced pluripotent stem cells (iPSC) have immature phenotype.

Goal: translate to mature cells and identify ones with hERG block

Machine learning (ML) iPSC multitask network architecture



Oracle cloud data science platform: 740 s. Local resources: 1500 s.

Conclusions

- Multi-scale modeling and simulations can provide atomic-detail structural and dynamic information for cardiac ion channel – drug interactions and their effects on heart rhythm.

- Our prototype multi-scale safety pharmacology pipeline was able to correctly predict arrhythmogenic risks of two hERG blocking drugs, dofetilide and moxifloxacin.

- Oracle cloud HPC resources allow us to scale-up our pipeline and use it to investigate multi-target block, mutagenesis data, translate data between different models using data science platform.

Acknowledgments

University of California, Davis:

Prof. Colleen Clancy, Dr. Pei-Chi Yang, Dr. Kevin DeMarco, John Dawson, Dr. Parya Aghasafari, Mao-Tsuen Jeng, Gonzalo Hernandez, Brightany Li, Dr. Divya Kernik, Dr. Steffen Docken

Prof. Tim Lewis, Emily Meyer, Adam Rose, Dr. Stephanie Dodson

Prof. Vladimir Yarov-Yarovoy, Prof. Jon Sack, Prof. Kazuharu Furutani**,** Dr. Phuong T. Nguyen, Dr. Jan Mally, Aiyana Emigh & other lab members

Prof. Luis Fernando Santana, Prof. Heike Wulff, Prof. Crystal Ripplinger

American River College: Prof. Slava Bekker

University of Calgary (Canada): **Prof. Sergei Y. Noskov** & his lab members

Oracle for Research team:

Alison Derbenwick Miller, Bryan Barker, Rajib Ghosh, Wendy Niemann, Sanjay Basu, William Sanders, Julie Blankinship, Elise Crainshaw, Megan Jaskiewicz, Sue Klemens, Cathy Humrich, Jim Zemaitis

Internet2 team

Computing: **Oracle for Research**, XSEDE, PSC (Anton 2), NCSA (Blue Waters), TACC

$$$ Funding: UC Davis, NIH NHLBI, NIH Common Fund, American Heart Association

Thank you!!!

Rajib Ghosh

Global Senior Solutions Architect
Oracle for Research

How Oracle HPC benefits researchers

State-of-the-art hardware and software is available

- Oracle provides Bare metal and HPC shapes (Dedicated physical machines)
- High performance GPU shapes (NVIDIA Pascal P100, Volta V100 and Ampere A100)
- Scalable HPC clusters with instance pool and fast RDMA networking

Different instances and customized images

- Bare metal and Virtual GPU shapes for parallel computation
- Oracle Molecular Dynamics images - NAMD / GROMACS / GATK
- Oracle HPC Published benchmarks

Flexible storage options (file, block etc.)

- Object storage - Store high volume research data securely
- File system storage – Allows researcher to share data across projects
- Block storage – Petabyte scale price-performance shared storage for computation
- Local NVMe – High performance local storage for bare metal machines

Our data are secure and can be easily retrieved when needed

- 256 bit AES encryption for data at rest
- Data encryption with researcher keys
- Data in transit encryption

How Oracle HPC benefits researchers

No queue waiting time, can run instantaneously

- Oracle cloud HPC and GPU clusters automatically scale on demand
- Scaling is based on CPU / GPU utilization metrics unlike on-premise systems

Different components of a multi-scale pipeline can run simultaneously

- Bare metal GPU machines have both CPU and GPU footprint
- Multiple components of MD pipeline can execute and scale in parallel on the same machine

Easily automate our simulations using provided scripts

- Oracle cloud marketplace NAMD and GROMACS images provide configurable scripts
- Oracle for Research provides command line and Terraform based automation scripts
- Oracle HPC group provides standard performance benchmarks

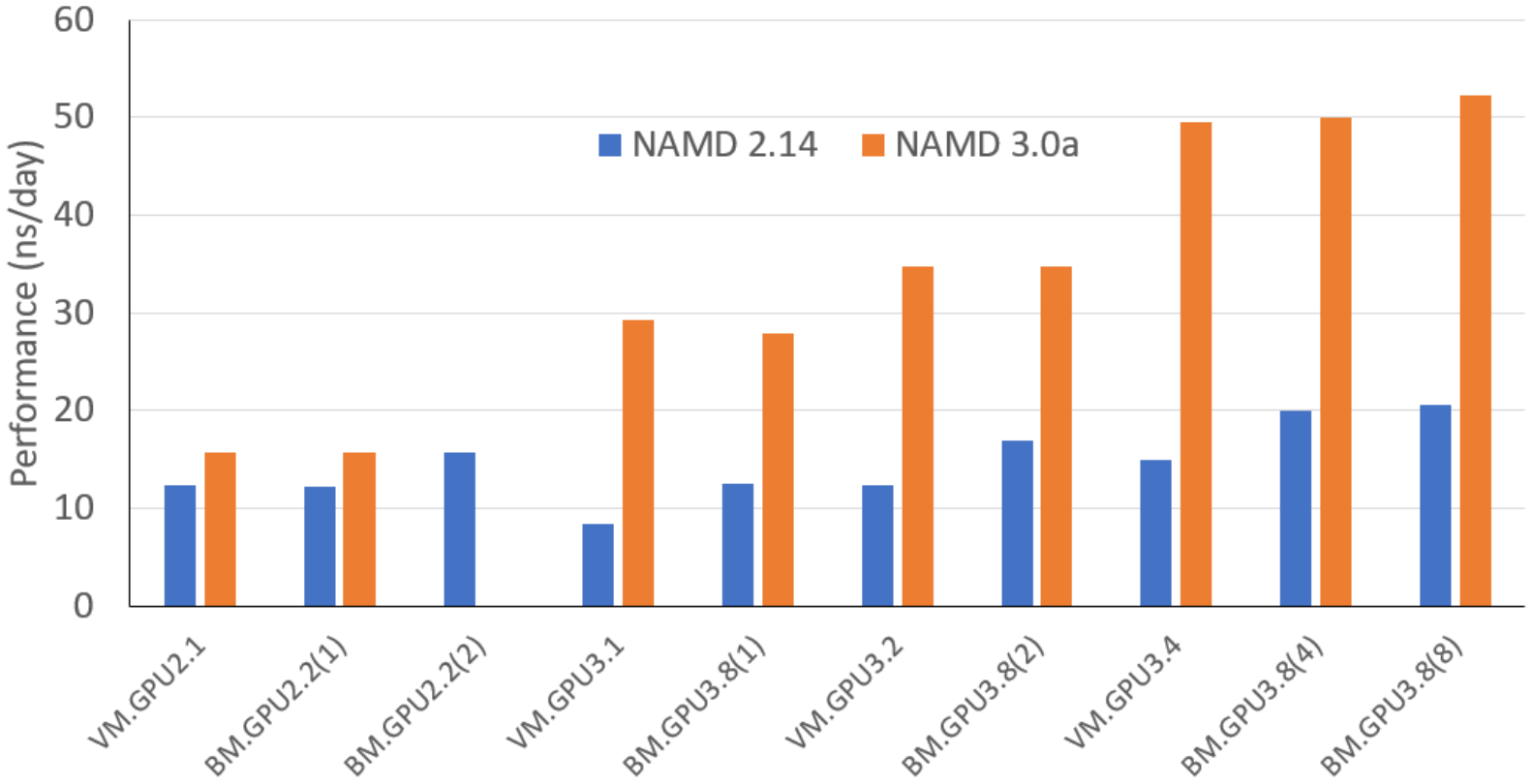
Multiple sources of help and support

- Oracle for Research architecture guidelines
- OCI HPC runbooks and research sandbox images
- Researcher office hours and technology talks
- Oracle for Research Github pages and blogs

Bigger workloads, better performance

NAMD 3.0 alpha

- GPU specific streamlined code paths with GPU accelerated Oracle Bare metal GPU 3.x compute
- Suited for 10K ~ 1M atoms MD simulations on Volta GPU (Courtesy: NAMD3.0a GPU-accelerated build)
- NAMD 3.0 alpha are geared for a single GPU-accelerated computational use-case



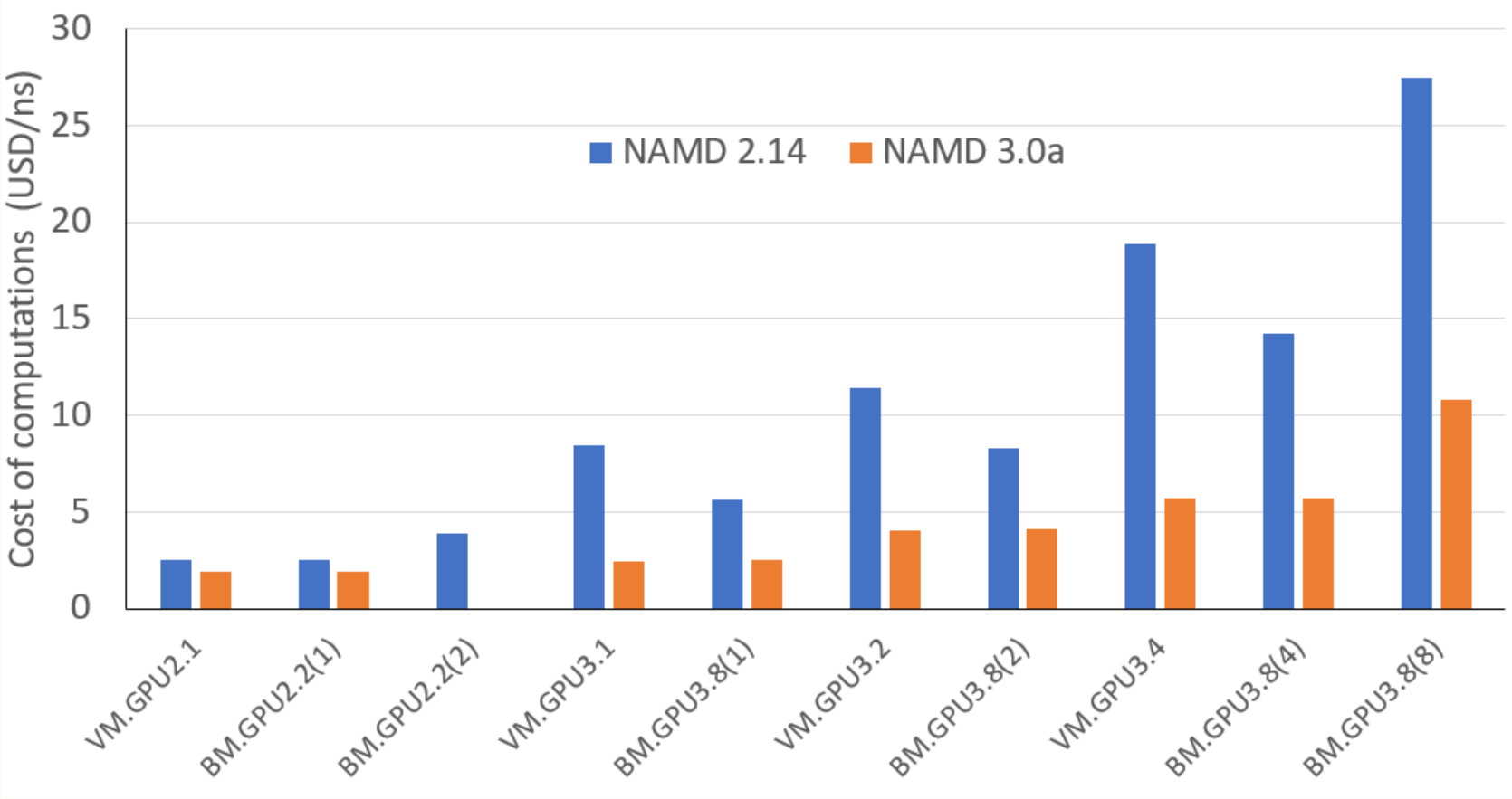
Conclusion

- NAMD 3.0 alpha showed 2.5x times performance gain as it is optimized for Volta (BMGPU3.x scenario)
- Both Virtual and Bare metal GPU performance are comparable
- Performance gains did not scale linearly with GPU cores
- Future versions of NAMD 3.x with multi-GPU acceleration capability has a higher performance potential

Overall Conclusion

- Oracle BM GPU shapes stretches its limits to perform better for high computation intensive research

Bigger workloads, more cost savings



Conclusion

- NAMD 3.0 alpha takes advantage of GPU acceleration and lowers cost
- GPU costs go up at a lower scale for higher computations
- Optimal cost when appropriate # of GPUs are used

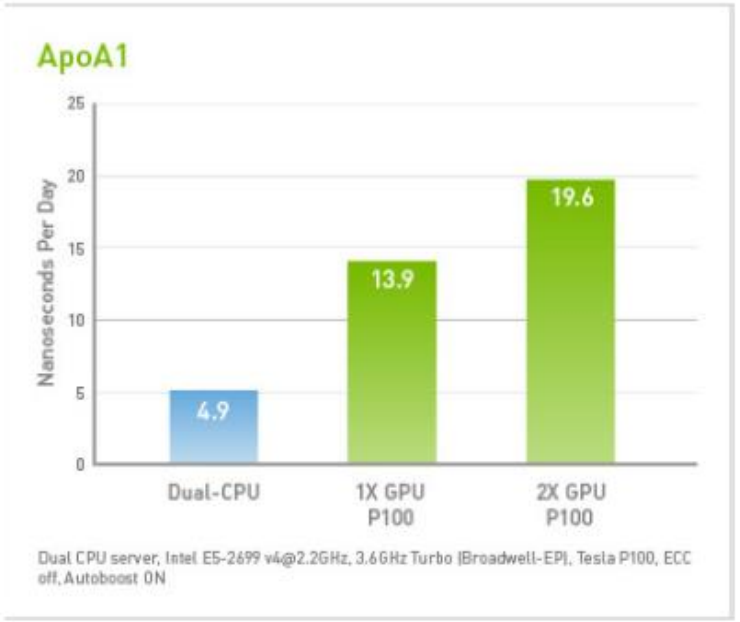
Overall Conclusion

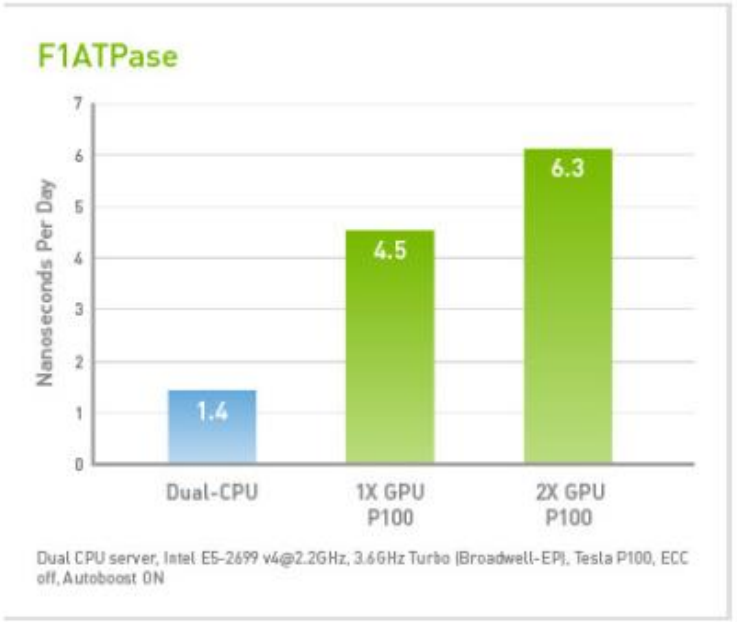
- $$ savings scales high with higher computational workloads

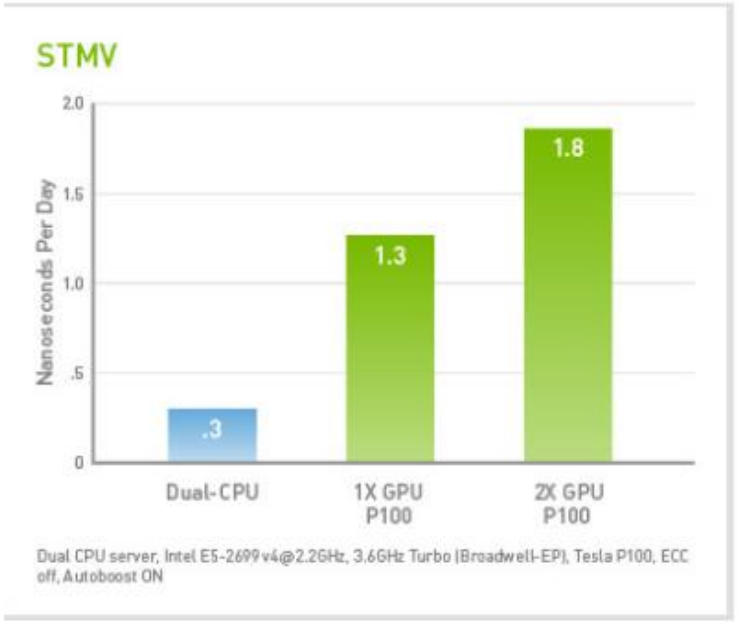
NVIDIA Published NAMD Performance Benchmarks

EXPECTED PERFORMANCE RESULTS

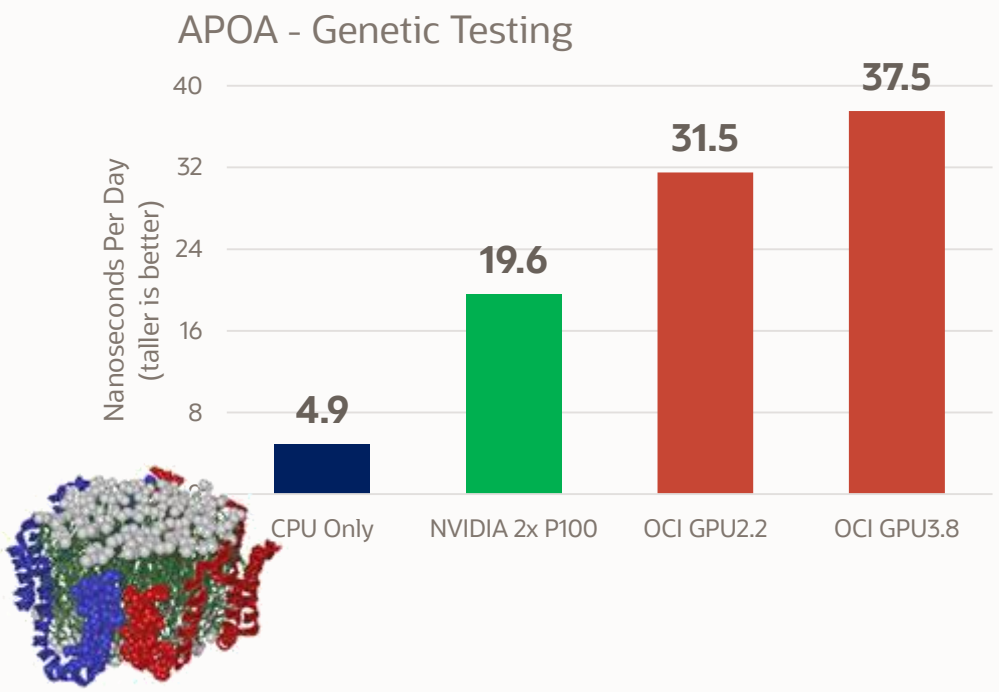
See the reference results below for different system configurations with dual-socket CPU and NVIDIA Tesla boards for 0 to 2 nodes connected with 4xEDR InfiniBand.

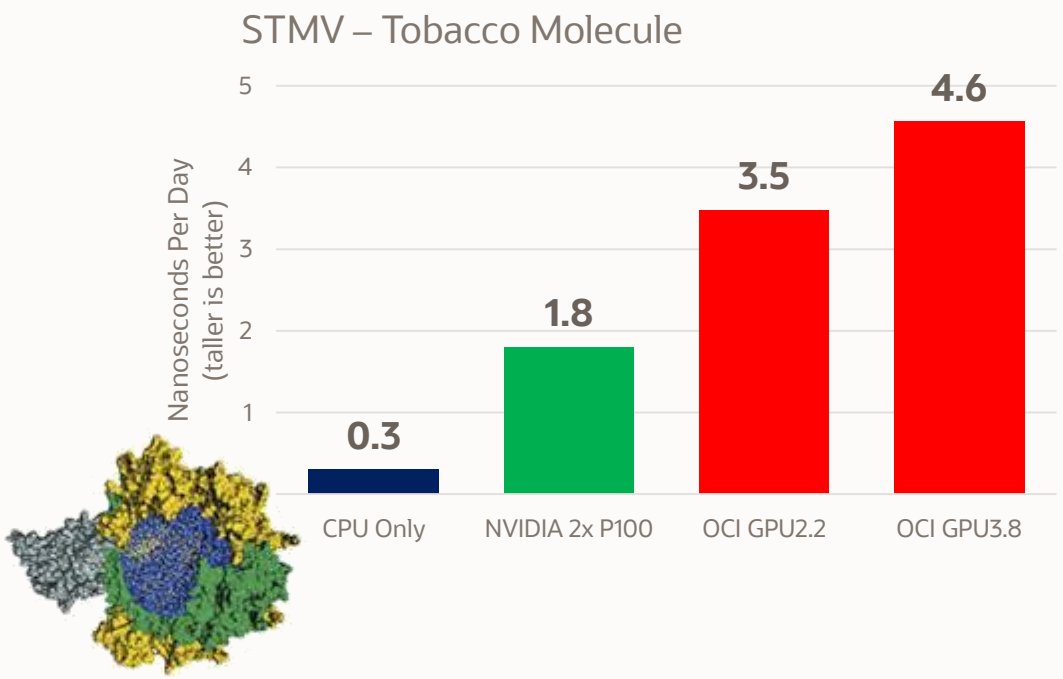






OCI Outperforms NVIDIA Benchmarks





Supported Research Areas

Research Area	Oracle Technologies
Genome sequencing Drug discovery Molecular dynamics Protein folding RNA Sequencing	• Large scale MD simulations on GPU Clusters • Genomic images on Oracle Linux platforms • Medical imaging Deep learning libraries • GPU enabled parallel computation libraries • Oracle Data science platform
Agro and farm research	• Data cleaning with Oracle R algorithms • Spatial analysis and visualization tools • Oracle database machine learning
Materials science and Engineering	• Oracle visualization and analytics • GPU ray-tracing based visualization • Singularity container architectures
Geo-tagging and environmental studies	• Geo-tagging AI and visual models • Federated learning and shared prediction models • ARCGIS AI and kinetica –in-memory analytics

Resources

Cloud Architecture

HPC and Machine learning

Technology How-To's

Researcher Publications

Oracle for Research Blogs

Technology Talks

Contact

Website: oracle.com/oracle-for-research/

Github: github.com/OracleforResearch

Twitter: @OracleResearch

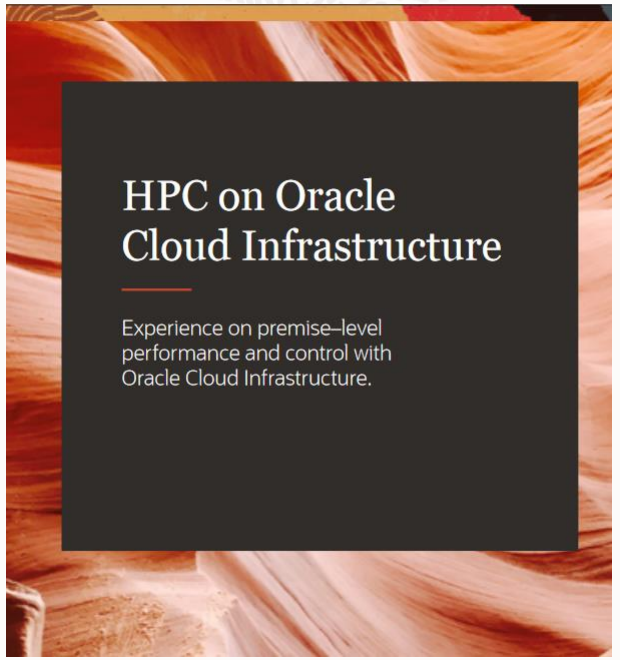
Email: OracleForResearch_ww@oracle.com
OracleForResearchTech_ww@oracle.com

Questions and Answers

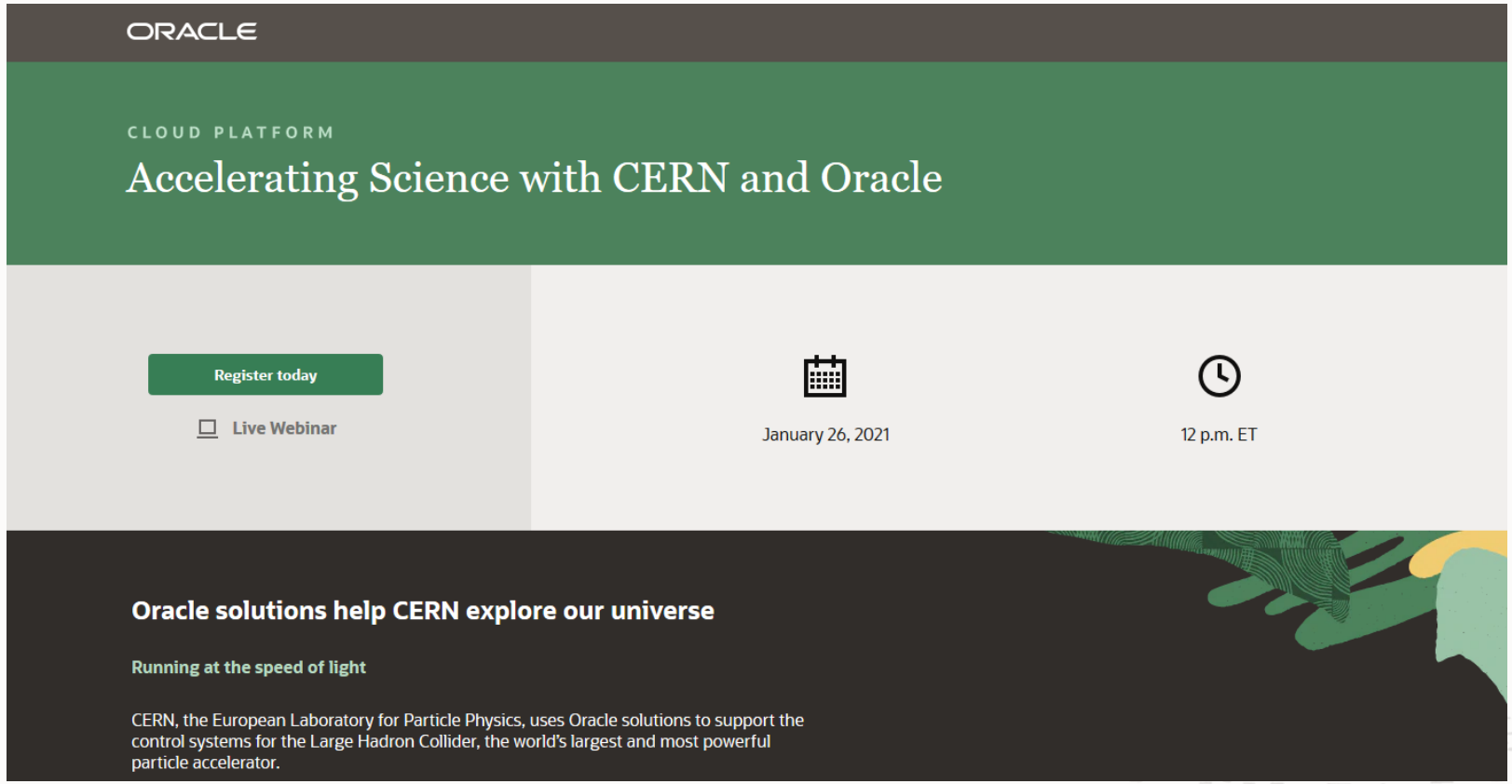
Use the chat function to ask a question

Try it!

- Oracle Cloud Free Tier-get started with no time limits: oracle.com/cloud
- Explore true costs of cloud, with better performance: oracle.com/economics
- Business brief: HPC on Oracle Cloud Infrastructure
- Oracle for Research: oracle.com/oracle-for-research/
- Visit the Internet2 Oracle channel for more resources



Next event: Jan. 26 at 12 p.m. ET



Register at: oracle.com/goto/internet2

Thank you

We'll see you on January 26 for *Accelerating Science with CERN and Oracle*


ORACLE