



“The Freedom To Discover”

Impact of HPC on Life Sciences
Bhanu Rekepalli, PhD (BioTeam)
Bio-IT World Conference & Expo'15

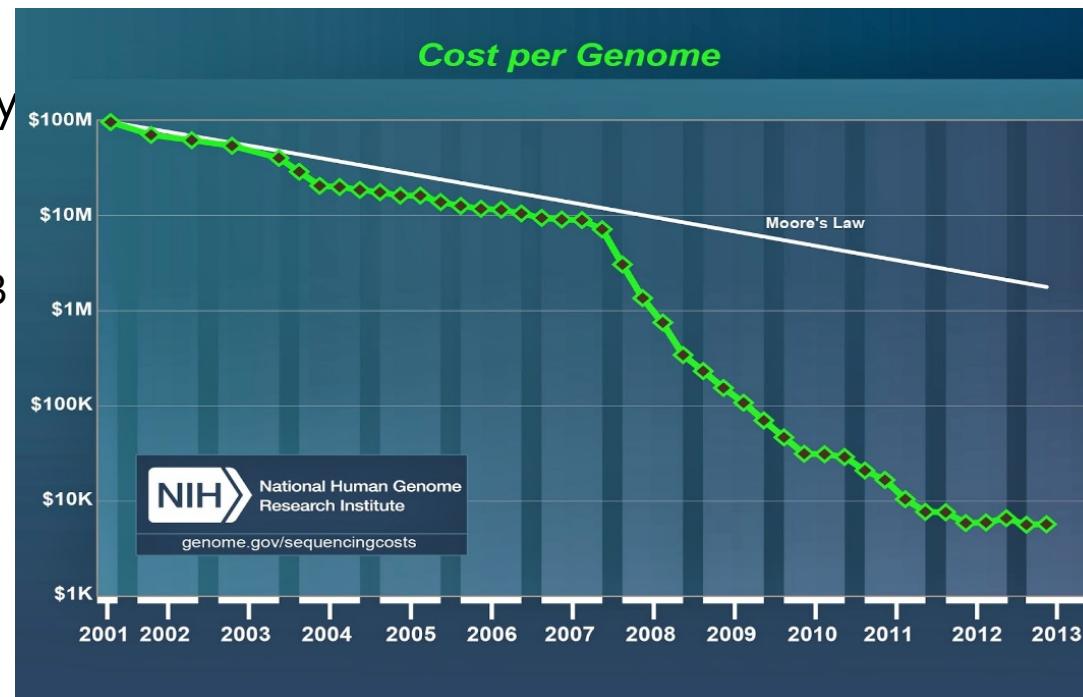
Outline

- Life Sciences data problem
- HPC architectures and Trends
- Parallel software Trends
- Large Scale Bioinformatics Applications
- Performance Numbers
- Science Highlights
- Future Horizon

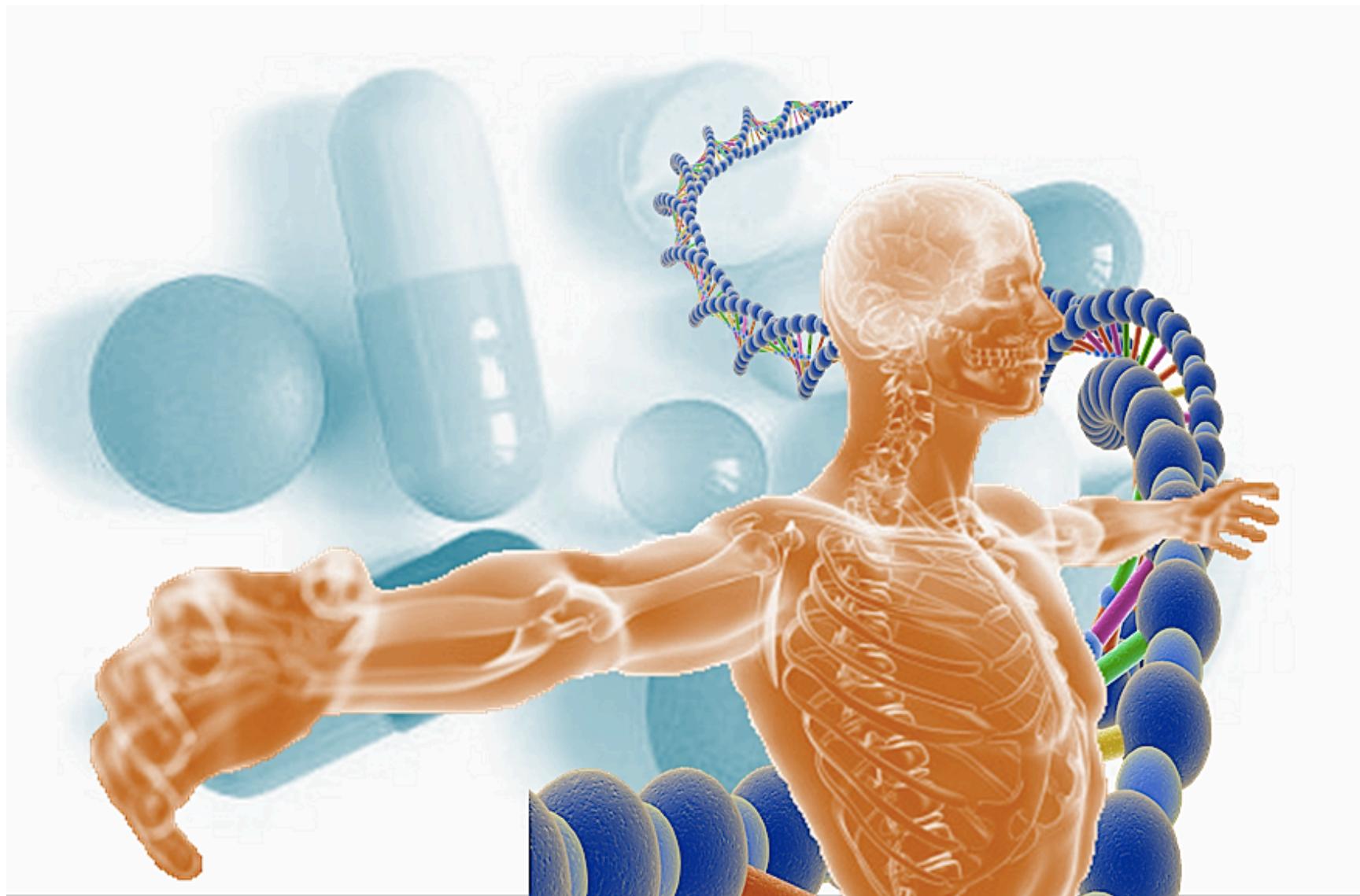
The genomics data problem

- Advances in next-generation sequencing techniques are producing complete genomes at faster rates than data analysis can process
- Data is managed by community centered databases (updated routinely)
 - e.g., GenBank, EMBL, NR, PDB
- **Challenge:** Bioinformatics research requires high-throughput processing and analytic tools to sustain the exponential growth in the genomic data

*Add the fact that HPC
Is difficult to utilize*



Personalized Medicine



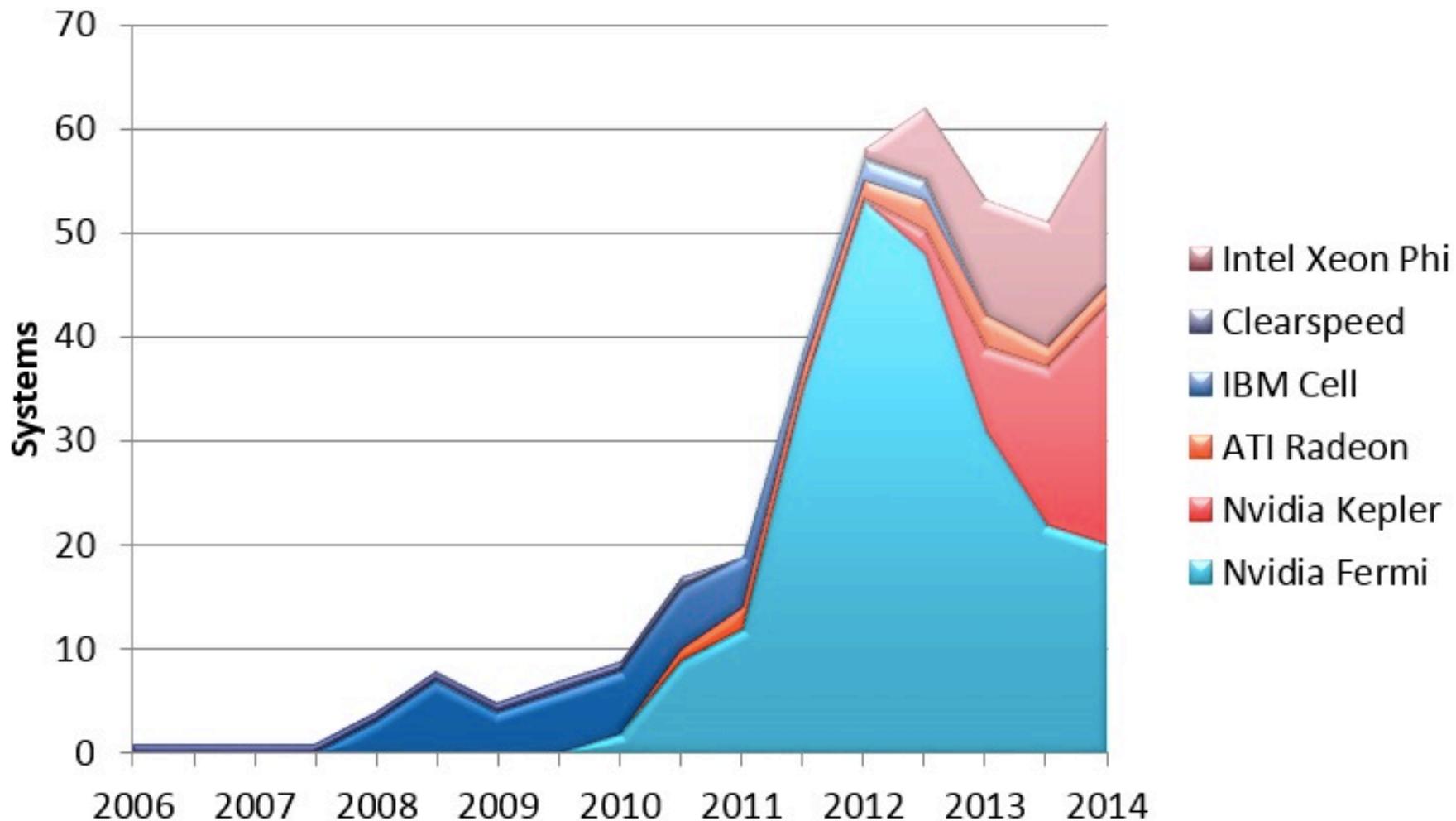
Solutions: Large-scale Computing

- Cloud Computing
- High Performance Computing Architectures
 - Conventional
 - Hybrid
 - High Memory
 - Special Purpose
- User-friendly Interfaces to Supercomputers

RANK	SITE	SYSTEM	CORES	RMAX (TFLOP/S)	RPEAK (TFLOP/S)	POWER (KW)
1	National Super Computer Center in Guangzhou China	Tianhe-2 (MilkyWay-2) - TH-IVB-FEP Cluster, Intel Xeon E5-2692 12C 2.200GHz, TH Express-2, Intel Xeon Phi 31S1P NUDT	3,120,000	33,862.7	54,902.4	17,808
2	DOE/SC/Oak Ridge National Laboratory United States	Titan - Cray XK7 , Opteron 6274 16C 2.200GHz, Cray Gemini interconnect, NVIDIA K20x Cray Inc.	560,640	17,590.0	27,112.5	8,209
3	DOE/NNSA/LLNL United States	Sequoia - BlueGene/Q, Power BQC 16C 1.60 GHz, Custom IBM	1,572,864	17,173.2	20,132.7	7,890
4	RIKEN Advanced Institute for Computational Science (AICS) Japan	K computer, SPARC64 VIIIfx 2.0GHz, Tofu interconnect Fujitsu	705,024	10,510.0	11,280.4	12,660
5	DOE/SC/Argonne National Laboratory United States	Mira - BlueGene/Q, Power BQC 16C 1.60GHz, Custom IBM	786,432	8,586.6	10,066.3	3,945
6	Swiss National Supercomputing Centre (CSCS) Switzerland	Piz Daint - Cray XC30, Xeon E5-2670 8C 2.600GHz, Aries interconnect , NVIDIA K20x Cray Inc.	115,984	6,271.0	7,788.9	2,325
7	Texas Advanced Computing Center/Univ. of Texas United States	Stampede - PowerEdge C8220, Xeon E5-2680 8C 2.700GHz, Infiniband FDR, Intel Xeon Phi SE10P Dell	462,462	5,168.1	8,520.1	4,510
8	Forschungszentrum Juelich (FZJ) Germany	JUQUEEN - BlueGene/Q, Power BQC 16C 1.600GHz, Custom Interconnect IBM	458,752	5,008.9	5,872.0	2,301
9	DOE/NNSA/LLNL United States	Vulcan - BlueGene/Q, Power BQC 16C 1.600GHz, Custom Interconnect IBM	393,216	4,293.3	5,033.2	1,972
10	Government United States	Cray CS-Storm, Intel Xeon E5-2660v2 10C 2.2GHz, Infiniband FDR, Nvidia K40	72,800	3,577.0	6,131.8	1,499

Top500 Supercomputers

Accelerators



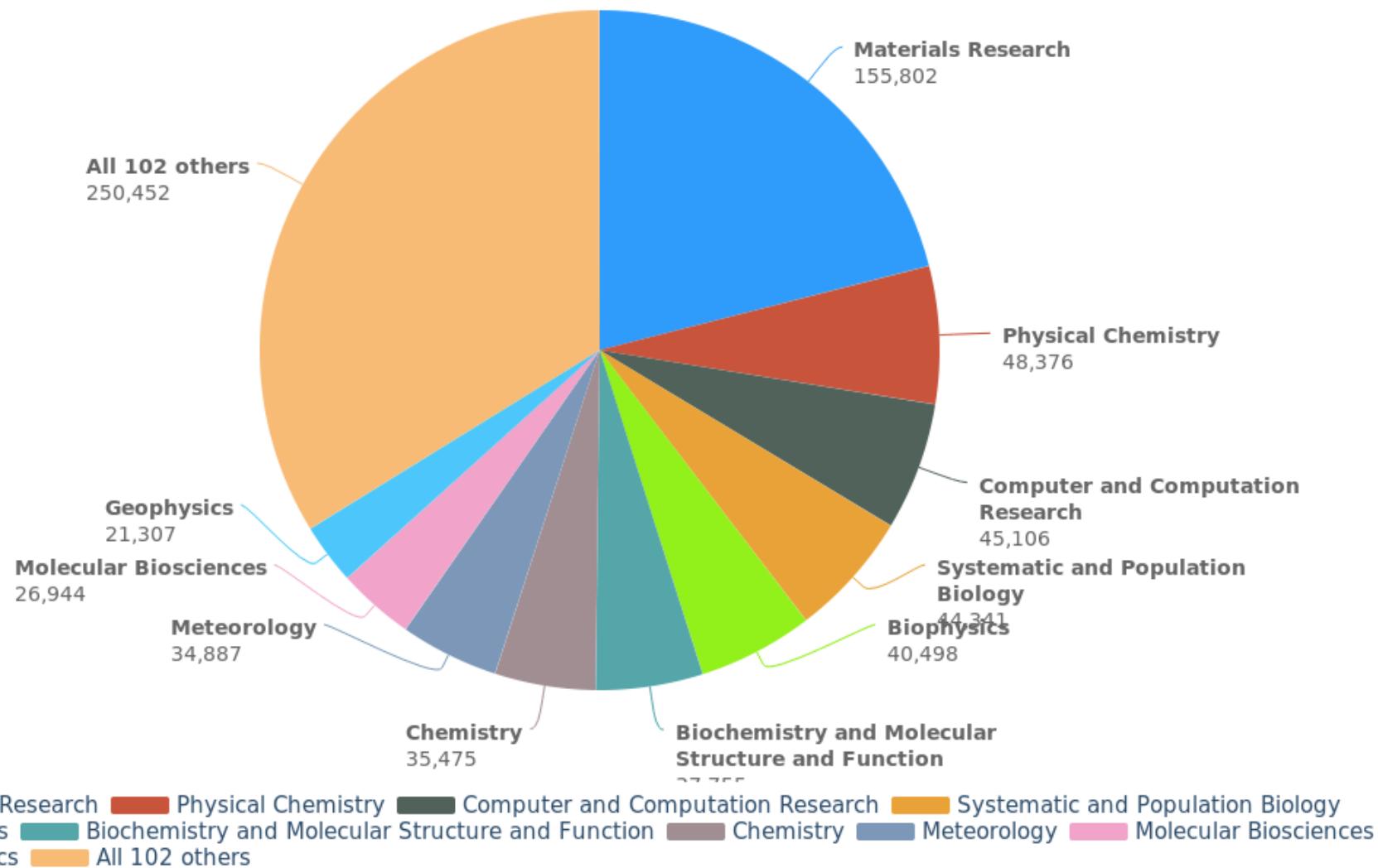
Name	Status	CPUs	Peak TFlops
Stampede  User Guide	✓ Healthy	102400	9600.0
Comet  User Guide	✓ Healthy	47616	2000.0
SuperMIC  User Guide	✓ Healthy	7200	925.0
Gordon Compute Cluster  User Guide	✓ Healthy	16384	341.0
Darter  User Guide	✓ Healthy	23168	248.9
Trestles  User Guide	✓ Healthy	10368	100.0
Blacklight  User Guide	✓ Healthy	4096	36.0

DOE Supercomputers

- Collaborative DOE Office of Science program at ORNL and ANL
- Mission: Provide the computational and data resources required to solve the most challenging problems.
- 2-centers/2-architectures to address diverse and growing computational needs of the scientific community
- Highly competitive user allocation programs (INCITE, ALCC).
- Projects receive 10x to 100x more resource than at other generally available centers.
- LCF centers partner with users to enable science & engineering breakthroughs (Liaisons, Catalysts).



Distribution by Field of Science



Design Challenges

Current and future performance requirements in the life sciences require a computational solution to:

- Scale well on:
 - Smaller compute resources typically found in scientific research labs and academics
 - Enterprise class large scale resources of today and the near future
- Perform well on:
 - Conventional compute resources (x86 and Power)
 - Many-Core resources such as the Intel Xeon Phi coprocessors and Nvidia GPGPU accelerators
 - Hybrid solutions employing a mixture of conventional and accelerator resources.



Parallelization of Bio-codes

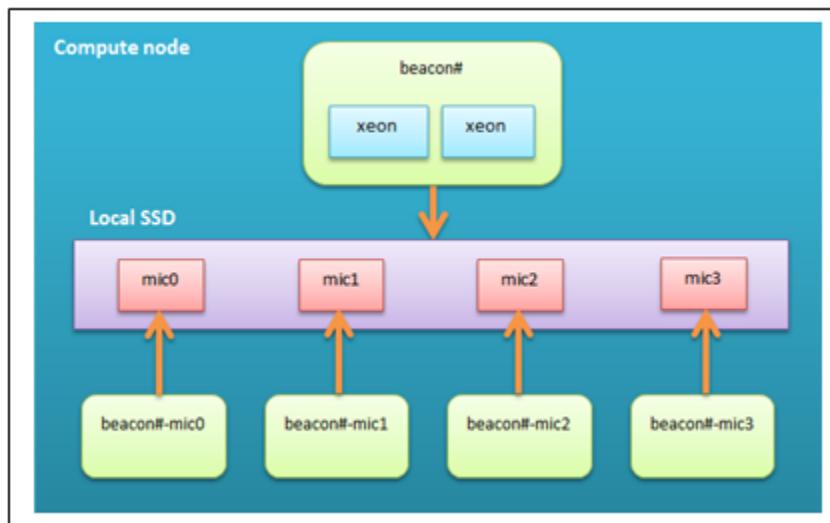
Parallel Informatics codes is:

- ✓ Fully compliant with Original algorithm
- ✓ Scalable: Exposing parallelism allows for
 - Replication Groups
 - Database distributions
 - Efficient utilization of highly threaded architectures
- ✓ High-throughput: rapid processing of large volumes of data
 - Capitalize on increased scalability
 - Fully utilize the extent of a computational resource



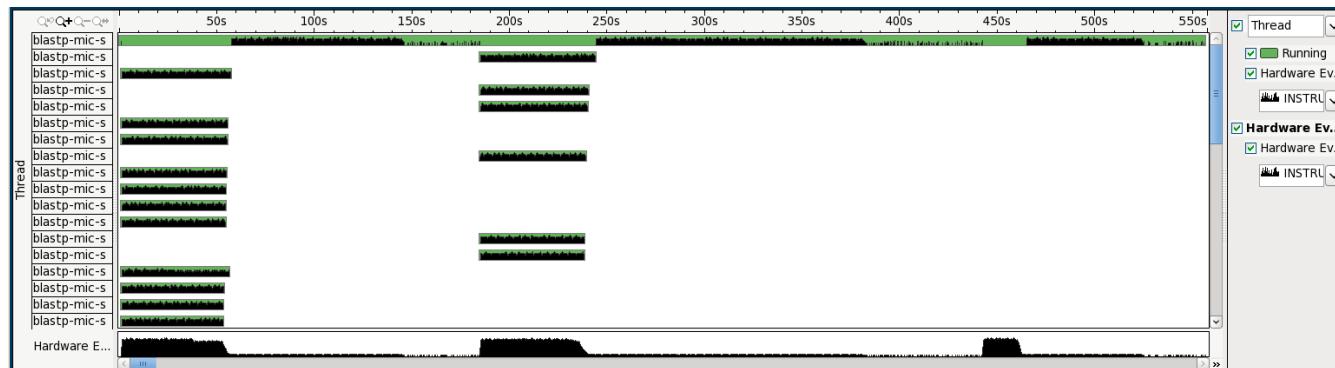
Intel Xeon Phi Terminology

- A many integrated core (MIC) for massive parallelism
- Programming models
 - Native – all code on MIC
 - Offload – main code on CPU, other on MIC
 - Symmetric – both CPU and MIC using message passing
 - Upload – main code on MIC, other on CPU



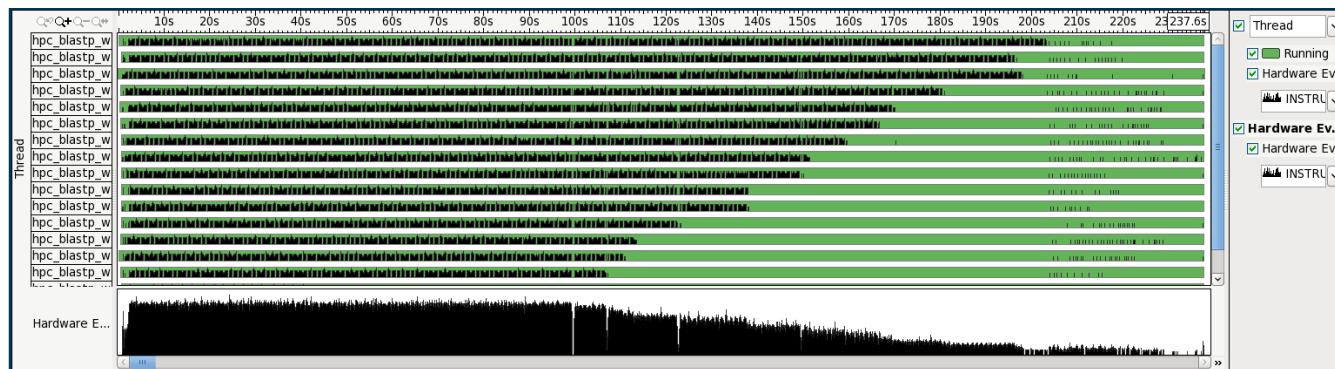
Performance Analysis:

The HPC-BLAST approach enables dramatic improvements in thread concurrency
 Intel® VTune™ 2013 concurrency analysis: 16 threads. NCBI-BLAST v.s. HPC-BLAST



NCBI-BLAST

- Green bars show running threads
- Clear serialization halting performance



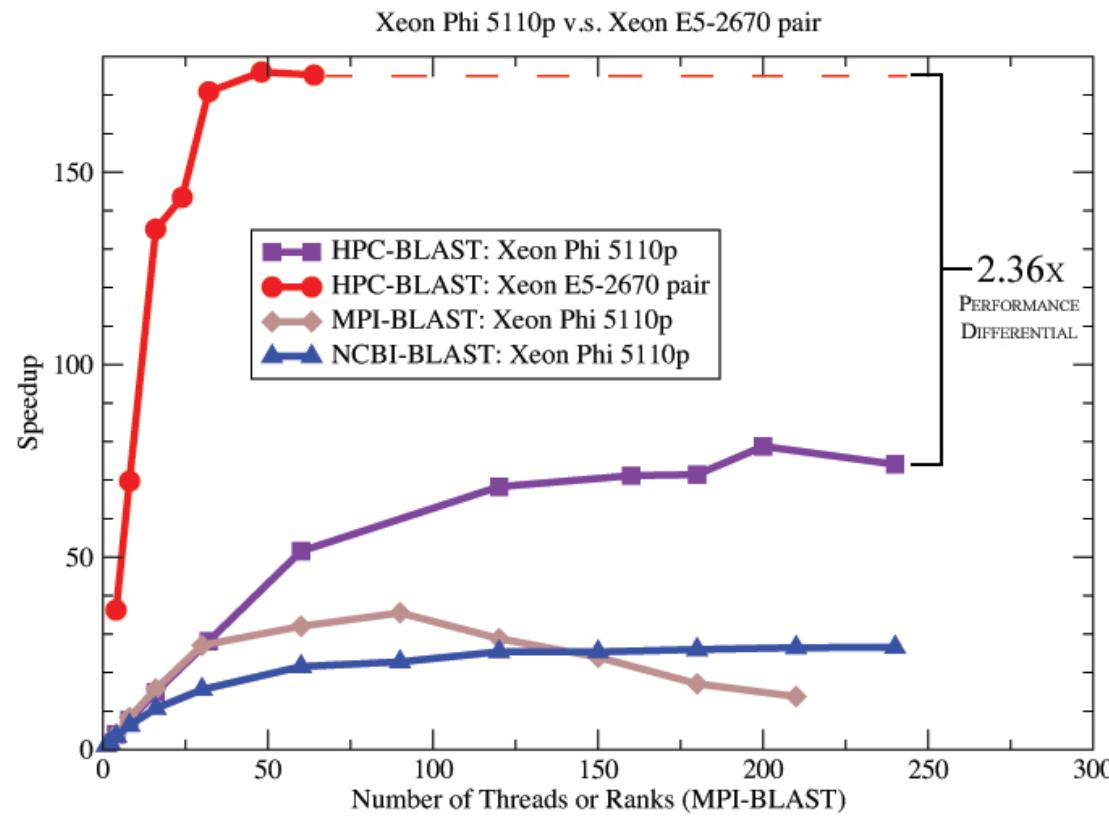
HPC-BLAST

- Concurrency is dramatically improved
- First pass at threading model implementation. Improvements continue with optimization!

Cost Effectiveness

The HPC-BLAST approach enables cost effective results in the life sciences

Relative Performance: Comparison of BLAST implementations



Resource + HPC-BLAST	Cost (USD, approximate)
Xeon E5-2670 (pair)	\$6,000
Xeon Phi 5110p	\$1,500

$$\frac{\text{Xeon E5-2670 pair performance}}{\text{Xeon 5110p performance}} = 2.36$$

$$\frac{\text{Xeon E5-2670 pair cost}}{\text{Xeon 5110p cost}} = 4$$

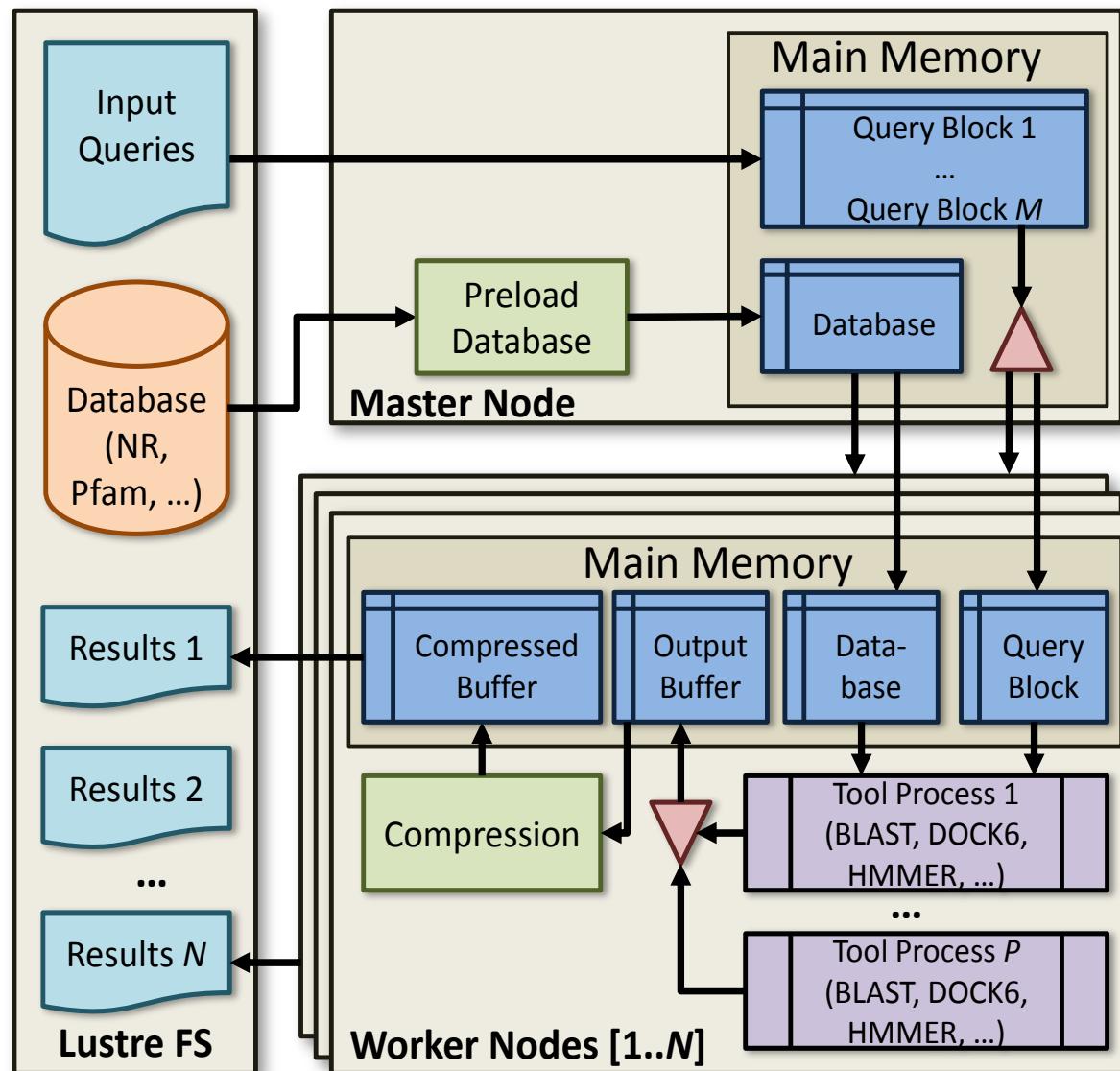
Pair of Xeon Phi 5110p + HPC-BLAST:
Xeon E5-2670 level performance
Half the price

HPC-BLAST enables more life science research results for less investment

Highly Scalable Parallel Wrapper

- HSP-wrap
- Software framework for scaling life science informatics applications to HPC environments via task parallelism
 - Bioinformatics and chemoinformatics domains
 - Portable → written in C/C++ and MPI
 - Load balance, parallel output, fault-tolerance, check-pointing
- Successfully ported tools
 - BLAST, HMMER, MUSCLE
 - DOCK6, AutoDock Vina, LINUS

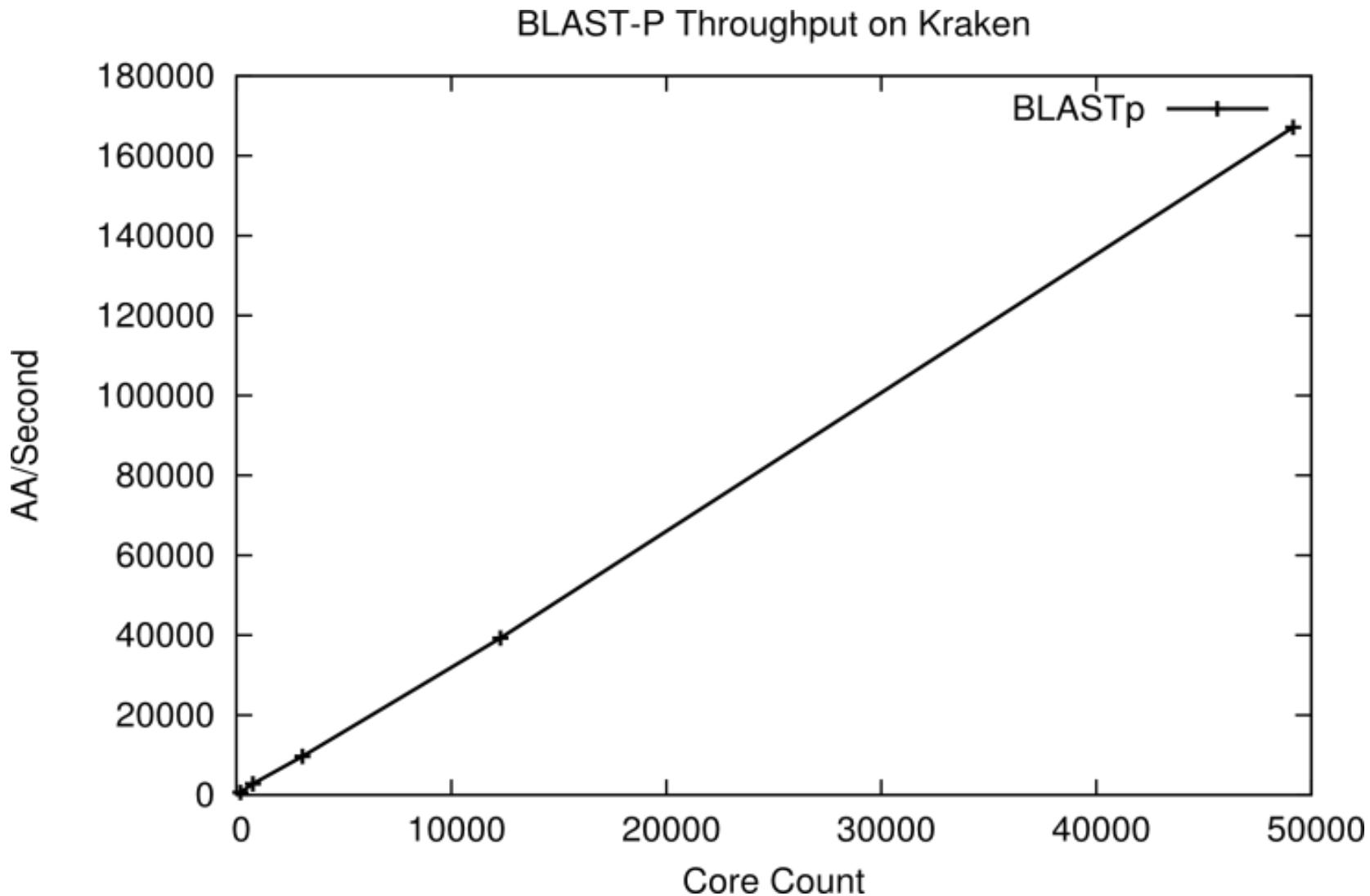
HSP-wrap: architecture



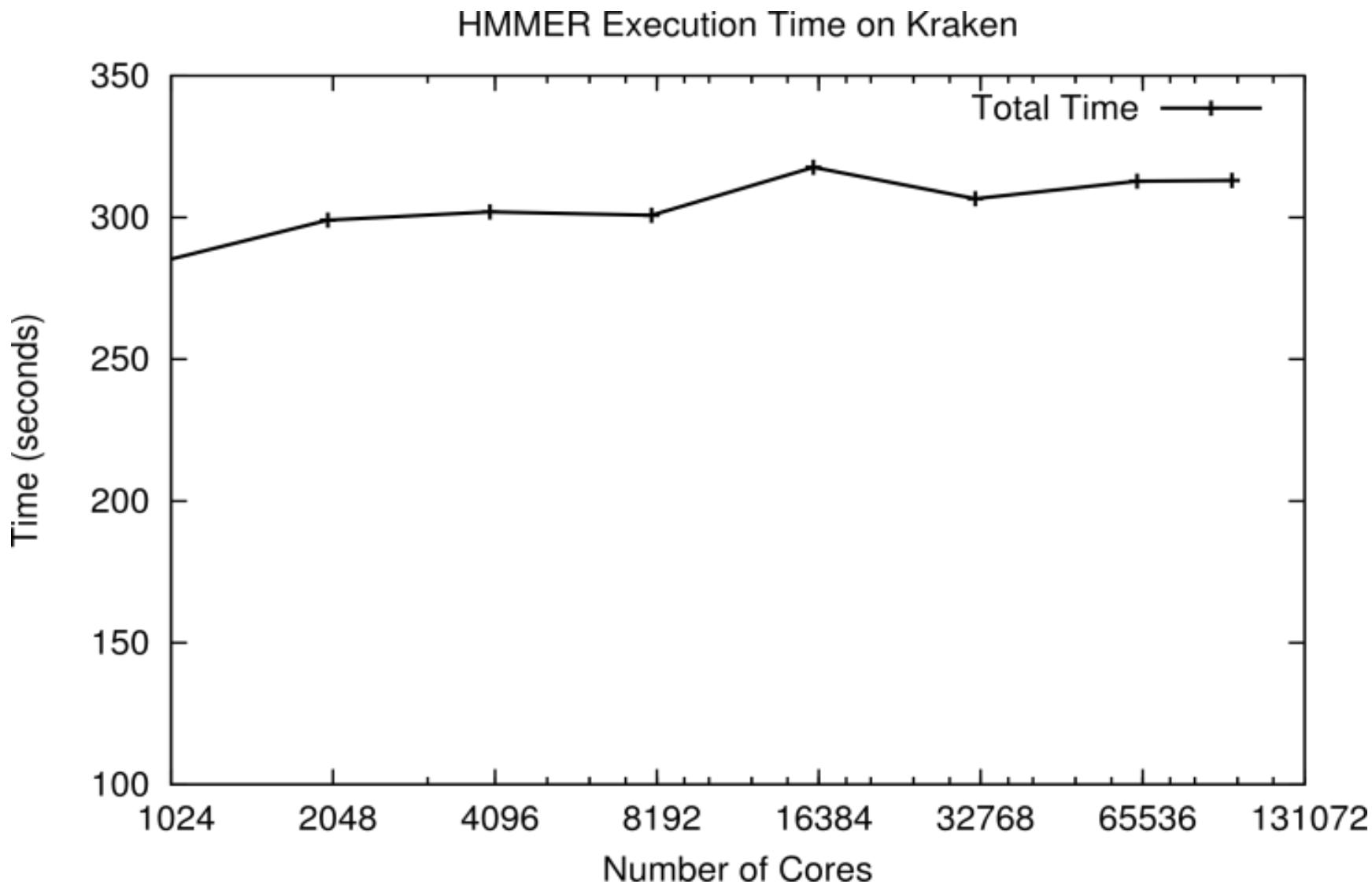
HSP-wrap: memory management

- stdiowrap – module for file management
- Function interposition to standard I/O calls
 - Minimal modification to original code (if any)
 - Input file management
 - Files are mapped to main memory on-demand
 - Tracks parallel reads
 - Output file management
 - Double buffered parallel support
 - Minimizes number of data transfers

BLAST Scaling Results



HMMER Scaling Results



Highly Scalable Parallel BLAST to Speedup Genomic Data Analysis on Titan

Bhanu Rekepalli, University of Tennessee, and Richard Casey, Colorado State University

The Challenge

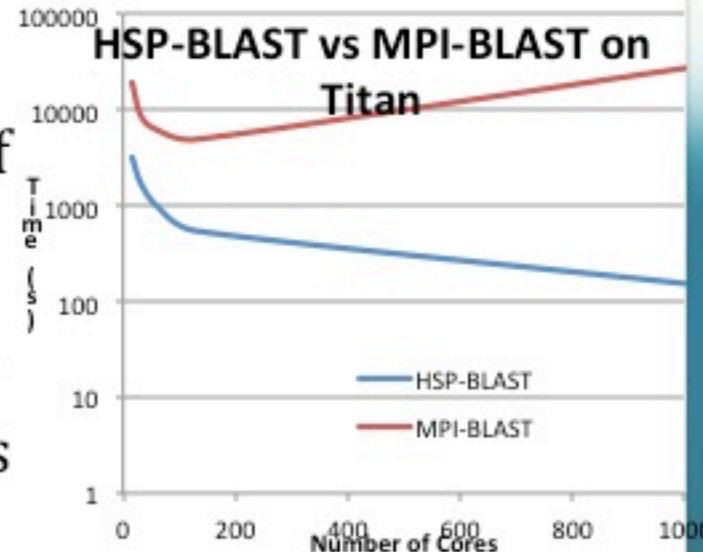
- Improve speed and scaling of downstream sequence analysis tools used to metagenomics data analysis of various micro-biomes

The Success

- Algorithmic and I/O improvements of NCBI-BLAST using HSP module versus the MPI-BLAST

Implications for Future Research

- The speedups achieved reduce the computational time needed for novel biological knowledge discovery from years to days on Titan supercomputer



Speedups achieved on Titan

With Algorithmic, I/O improvements and code optimizations we generated results for metagenomics sample set with 100 million sequences in few hours compared to months of computation using MPI-BLAST

This research used resources of the Oak Ridge Leadership Computing Facility at the Oak Ridge National Laboratory, which is supported by the Office of Science of the U.S. Department of Energy under Contract No. DE-AC05-00OR22725

Highly Scalable Parallel Docking to Speedup Drug Discovery

Bhanu Rekepalli, University of Tennessee, and Yuri Peterson, Medical University of South Carolina

The Challenge

- Improve speed and scaling of molecular docking tools used to search compounds and reduce the computational time needed for novel drug discovery
 - Libraries such as ZINC and PubChem contain millions of vendor and academic compounds and are growing rapidly

The Success

- Algorithmic and I/O improvements of the MPI version of Dock6

Research Speedup

- The speedups achieved reduce the computational time needed for novel drug discovery from years to days, significantly reducing the time to market of new drug

Boosting Bioenergy and Overcoming Recalcitrance

Molecular Dynamics Simulations

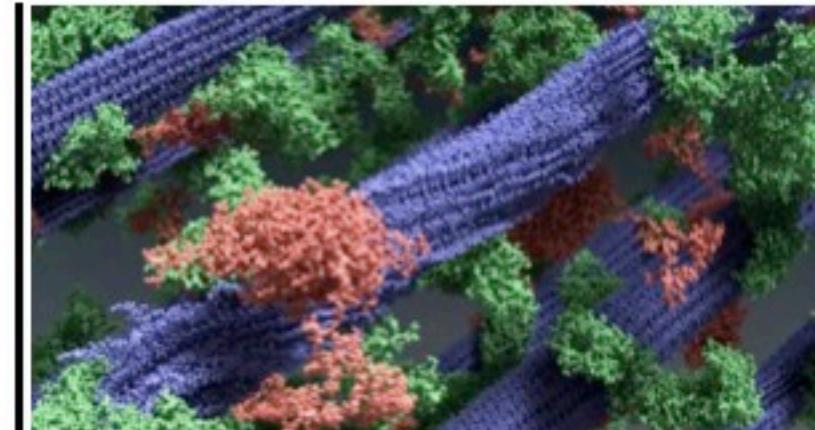
INCITE Program
Jeremy Smith, UTK & ORNL
Allocated hours: 78 Million
Used Hours: 72 Million

Science Objectives and Impact

- Optimize biomass pretreatment process by understanding lignin-cellulose interactions on a molecular level
- Overcome biomass recalcitrance caused by lignin and the tightly ordered structure of cellulose
- Improve efficiency of the biofuel production process and make ethanol less costly

Application Performance

- **2012:** Used GROMACS on Jaguar to monitor interactions of 3 million atoms that included crystalline and non-crystalline cellulose, lignin, and water
- **2013:** Now run accelerated GROMACS that can take advantage of Titan's GPUs, making the application 10 times bigger and much longer. Current simulations monitor 30 million atoms.



Interaction between cellulose fibril (blue) and lignin (pink and green) molecules.
Vizualization by M. Matheson (ORNL)

Science Results

Published paper in *Biomacromolecules* in August 2013

- Discovered amorphous cellulose is easier to break down because it associates less with lignin
- Phenomenon is not a result of direct interaction between lignin and cellulose, but is a water-mediated effect

Impact

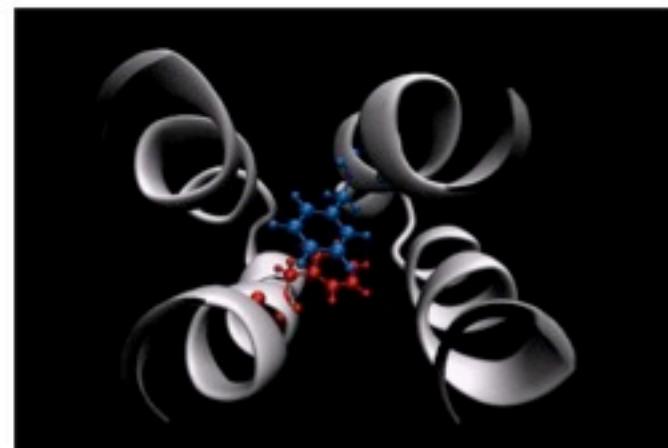
- Sheds light on the physical interactions that occur during pretreatment process.

Discovery and characterization of a trans-membrane molecular switch

Director's Discretion
PI – Jerome Baudry
12,350,000 hours allocated
2,700,000 hours used YTD

Science Objectives and Impact

- Previous simulations of the *E. coli* Tsr chemoreceptor dimer led to the discovery of the phenylalanine (Phe396) rotameric switch; however, the functional receptor in the bacterial cell unit is a trimer of dimers. Simulating the trimer requires petaflop computing.
- Simulate the chemoreceptor in trimer of dimer configuration to study the role of trimer arrangement in signal amplification originating from Phe396 molecular switch.
- Understanding the role of molecular switch in signal transduction has potential applications in drug design and biotechnology.



The flipping conformations in a pair of phenylalanine residues (Phe396, blue and red molecules) act as a molecular switch essential to the signaling mechanism of an *E. coli* chemoreceptor. Research indicates this type of molecular switch is widespread in nature (Ortega et al., 2013 *Nature Communications*). Image credit: Davi Ortega

OLCF Contribution

- Evolves almost 400,000 atoms in trimer of dimer simulation.
- Simulates system in 2 microseconds, which requires roughly 10x as many time steps as the average molecular dynamics simulation.
- 1.4 million core hours on Titan to date for this task.

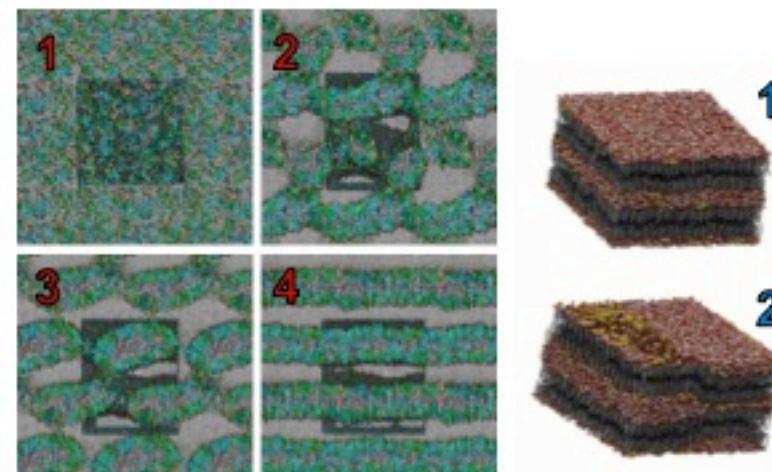
Science Results

- Ongoing simulations have already revealed previously unknown behavior of the trimer: “zipping” of dimers along the charged amino acid residues.
- Phe396 rotameric switch is shown to be active within the trimer.
- Upon completion of this simulation the detailed molecular mechanism within the chemoreceptor trimer of dimers is anticipated.
- D. Ortega, *Nature Communications* (December 2013)

Assembling and sustaining the “acid mantle” of the human skin barrier

Science Objectives

- To elucidate how acidity (pH) regulates the assembly of the lipid matrix of the skin's outer layer from constituent lipids: ceramide (wax), fatty acids and cholesterol.
- To calculate the (difficult to measure) water content in the lipid matrix using molecular simulations
- To predict the safety of chemical substances, in particular pH-sensitive ones, across the skin's outer layer



Sequence of self-assembly of stratum corneum layers (left) and of pH-driven adhesion between layers (right)

OLCF Contribution

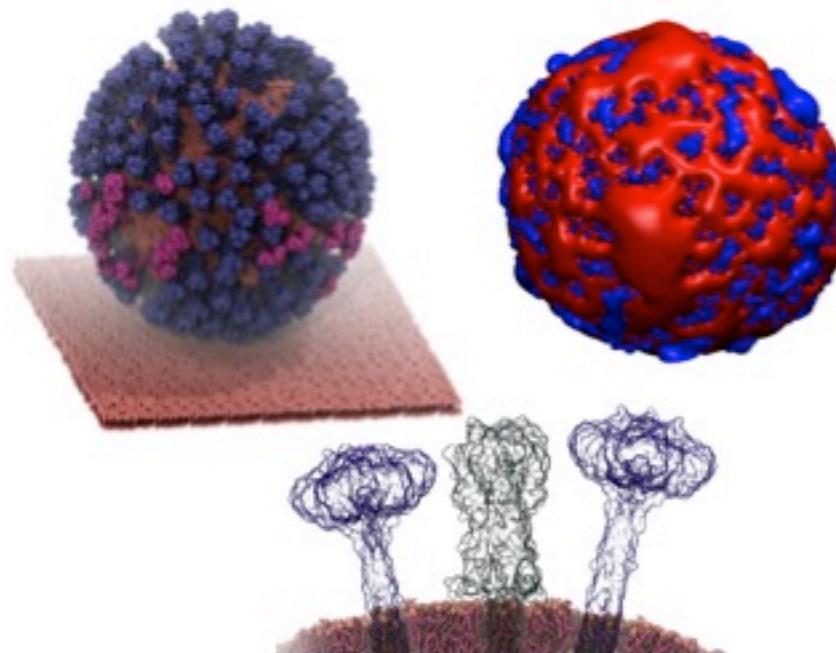
- OLCF Titan's hybrid compute nodes provided unprecedented throughput: up to 15 microseconds of simulated time were obtained on each model system
- GPU speedup surpassed expectations (+115% or more during this project vs. +88% based on 14/16 cores ratio)
- OLCF liaisons and user support provided accurate and timely information vital to optimizing code performance

Science Accomplishment and Impact

- We showed the self-assembly into a multilamellar structure starting from polydisperse solutions of lipid molecules, without the requirement for a pre-existing template
- Inner body-like, neutral pH favors fully detached lamellae, while strongly acidic pH destroys lamellar structure: the slightly acidic pH of outer skin maintains a connected multilamellar matrix
- We developed a transferable protocol to simulate the formation of biological tissue at the molecular level

Biochemistry of influenza virus

Avian influenza type A is a major pandemic threat. Two membrane glycoproteins, hemagglutinin (HA) and neuraminidase (NA), play important roles in mediating critical interactions with host-cell surface receptors that contain terminal sialic-acid moieties. Modeling NA and HA as crowded membrane-bound proteins embedded in the viral envelope provides new insights into the biology of influenza.



Top left: influenza particle suspended over epithelial cell membrane.
Top right: electrostatic potential of the viral model. Bottom: two NA flanking single HA and embedded within a viral envelope membrane

Atomistic model was built of the entire influenza virus lipid envelope (~15 million atoms) with NA and HA glycoproteins distributed over the viral surface in a physiologically relevant manner.

The electrostatic potential of this model was subsequently calculated using the parallel Adaptive Poisson Boltzmann Solver (APBS) software.

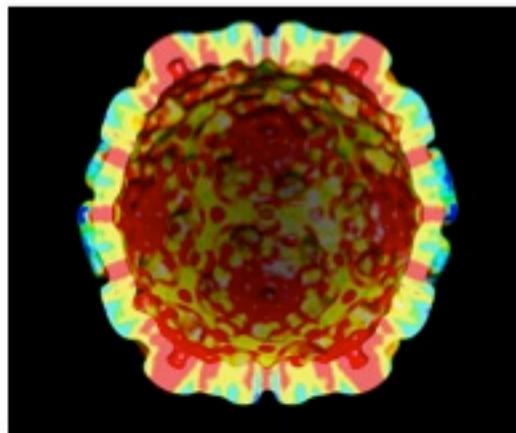
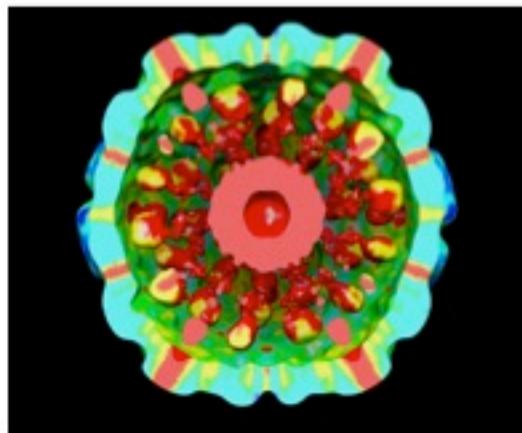
Even after segmenting into 448 regions, each calculation still required the full 64 GB available on the Gordon nodes

Source: Rommie Amaro (UCSD)
Used by permission. 2013

Heterogeneity in virus structure

Cryo-electron microscopy and three-dimensional image reconstruction are the techniques of choice for determining the structure of macromolecular complexes that resist crystallization. Using a novel maximum likelihood estimator (MLE) approach, it is also possible to determine heterogeneity of the structure and gain insight into the viral maturation process

Cross-sections of the HK97 reconstructions for particles with (left) and without protease (right). Variance is indicated by color and image-specific color maps are used (blue is low and red is high)



The MLE approach is both computationally and memory intensive. Early work using this algorithm was hampered by access to local resources that only have 16 GB of memory per node. The software is written in MATLAB and parallelized using the Matlab Distributed Computing Server (MDCS).

After porting to software to Gordon, MLE algorithms are being applied to first novel biological calculation (Hong Kong 97 virus)

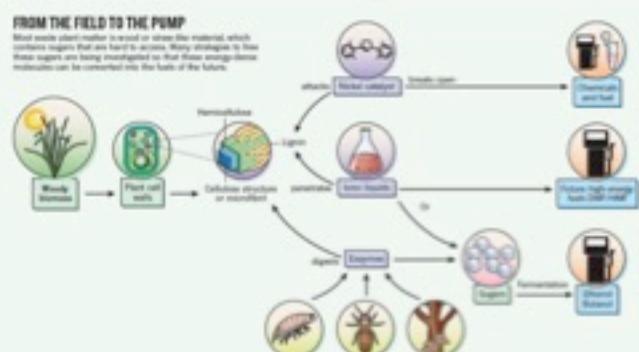
Source: Peter Doerschuk (Cornell), Jack Johnson (TSRI) Used by permission. 2013

Pittsburgh Supercomputing Center's Blacklight (SGI Altix® UV 1000) Massive Coherent Shared Memory Computer

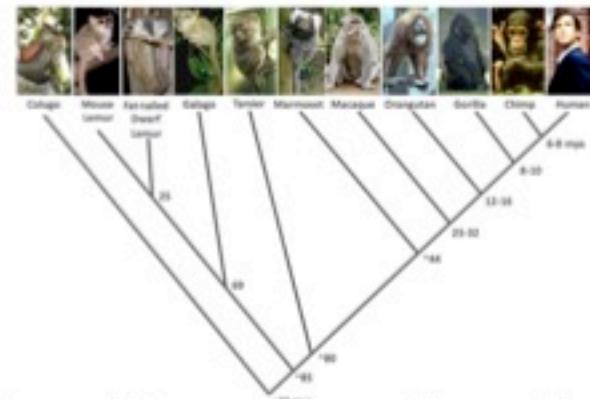
- 2×16 TB of cache-coherent shared memory, 4096 cores
 - *ideal for genome sequence assembly*
 - High bandwidth, low latency interprocessor communication
- SUSE Linux operating system
 - excellent for portability: supports OpenMP, C, C++, Java, Perl, Python, p-threads, MPI, UPC
 - *rapid algorithm development*



Blacklight: Flexible large shared memory for de novo assembly applications



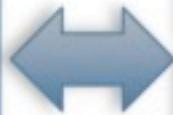
Reprinted by permission from Macmillan Publishers Ltd: [Nature 474](#), S12-S14, copyright 2011.



Metagenome/Plant Genome Assembly

16 TB

16 TB



2 x 16 TB RAM x 2048

cores:

Extreme-scale Shared
Memory

8 x 4 TB RAM x

512 cores:

Very Large Memory +
Throughput

Large Transcriptome Assembly



32 x 1 TB RAM x

128 cores:

Large Memory + High
Throughput

Creating Genetic Tools to Help Feed the World

PSC expertise + large shared memory computers helping unlock genetic secrets of important global food sources

Wheat

- One of top 3 crops that together make up 60% of world food intake
- Extremely large and complicated genome
- **Assembled Ae. tauschii wheat genome on Blacklight**



Whiteleg shrimp

- Rapidly growing food source contributes to global food security
- 3 million tons farmed annually worth over \$11 billion
- **Assembled shrimp transcriptome on Blacklight**



How PSC helped

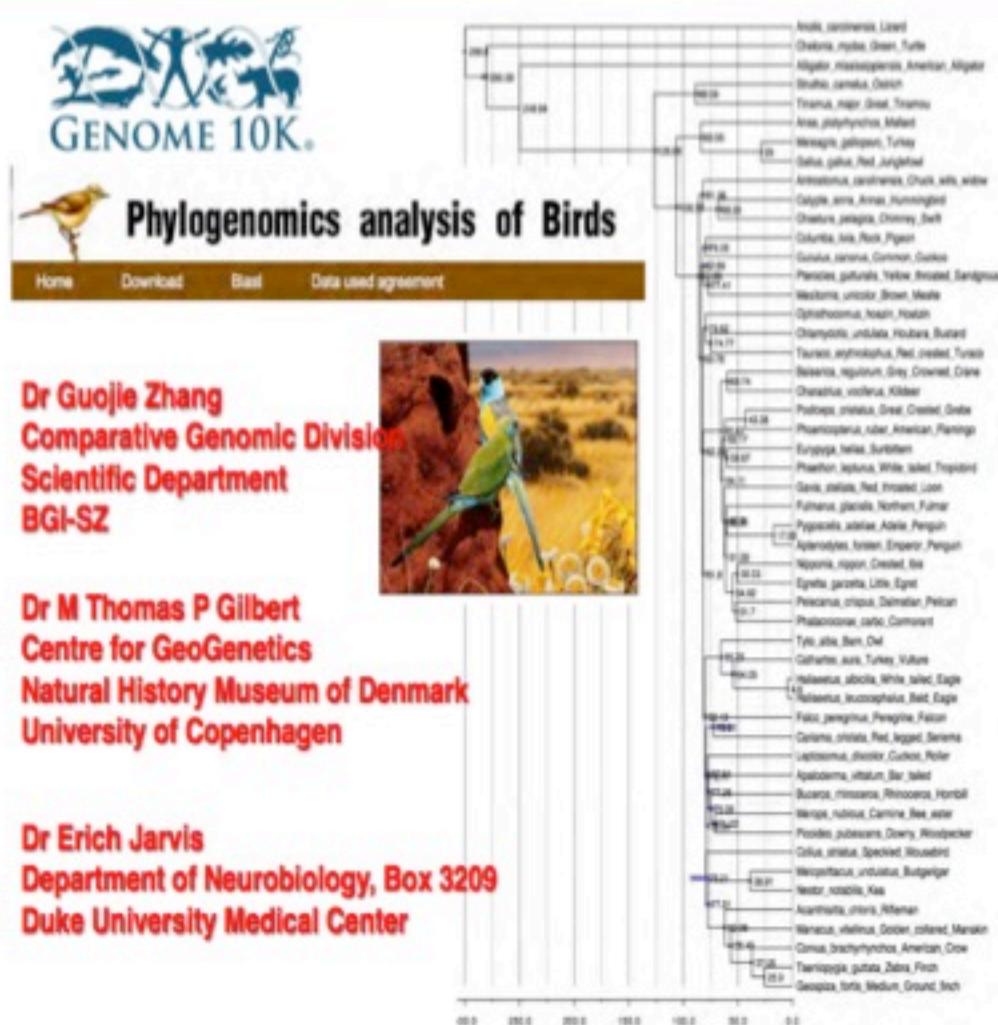
- Improved state-of-the-art genome analysis software
- Blacklight enabled assembly of massive genomes at 10x lower cost than previous methods (fewer sequence libraries required)
- Helped researchers perform sequence assemblies of many important species
- New genetic information obtained will help design crops that can better resist challenges like climate change and disease

"[PSC] not only provided us assistance in running our ... software ..., but also ... has provided scientific insights about issues that we encountered. ... Based on our great experience, we are the advocates of XSEDE, and especially PSC, on our campus."

-- Noushin Ghaffari, Bioinformatics Scientist,
Texas A&M

JICS-SI Projects Success

- Massive phylogeny has been achieved with the help of JICS Nautilus supercomputer
- Journal paper has been submitted and is under review in Science



Anton @ PSC



- Anton is a special purpose supercomputer for molecular dynamics simulation of biomolecular systems and is around 2 orders of magnitude faster than current state-of-the-art general purpose HPC resources.
- Anton was designed by D.E. Shaw Research (DESRES) in New York.

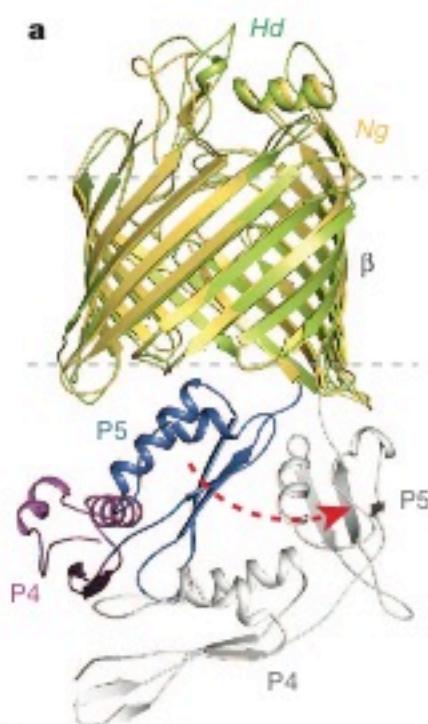
PSC in collaboration with DESRES has been hosting an Anton for access by the US biomedical research community since October of 2010.

- More than 229 research projects from 120 PIs have so far been completed on the machine.
- >78 publications (3 Nature, 7 PNAS, 9 BJ) have resulted from work conducted on the machine.
- A new RFP for time on Anton is currently underway – please apply at www.psc.edu.

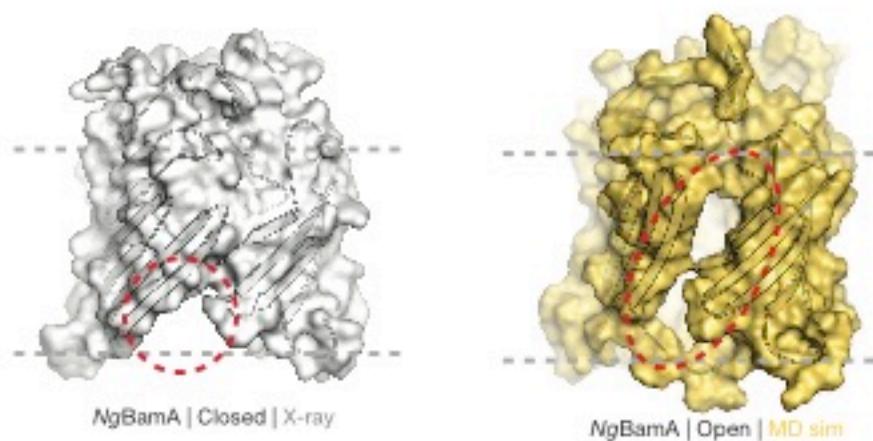


Anton Science Highlights: Membrane Protein Assembly

Structural insight into the biogenesis of β -barrel membrane proteins



Figures from Noinaj et al.,
(2013) Nature



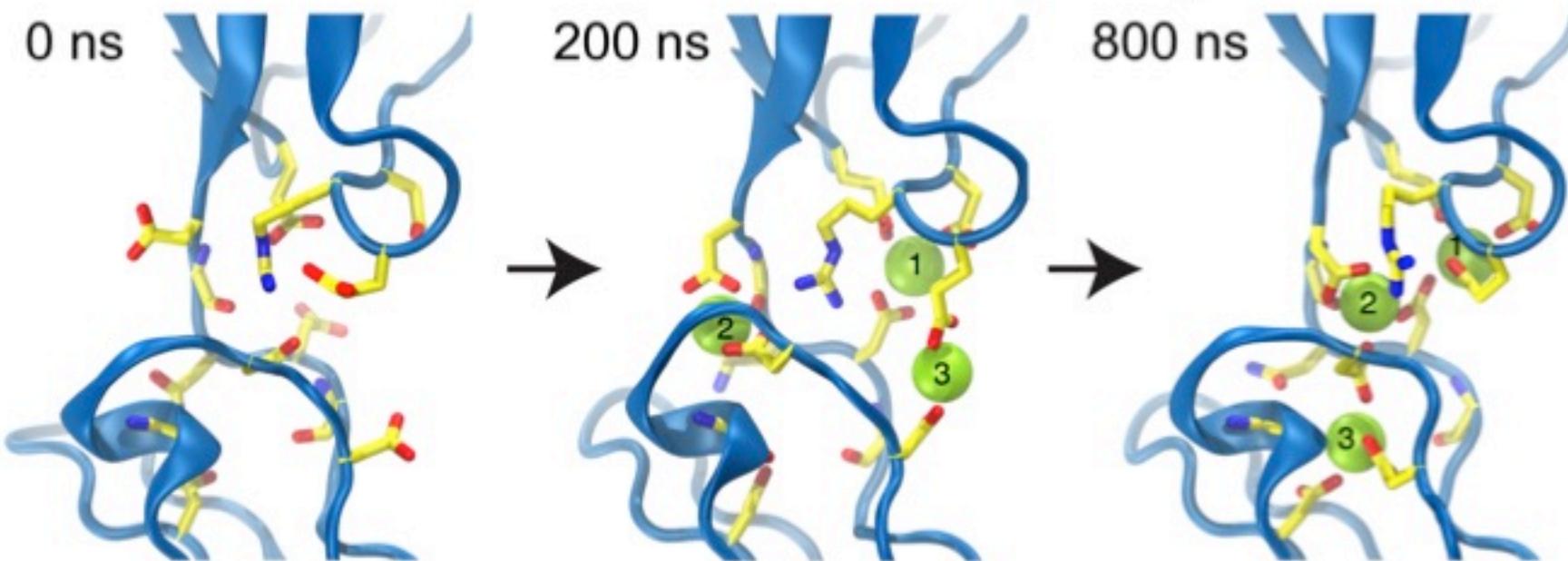
This study reports the structure of BamA, the central component of the β -barrel assembly machine complex. Anton simulations were used to study the functional properties of BamA, in particular its effect on membrane stability.

Noinaj et al. (2013), Nature, 501:385-387



Anton Science Highlights: Inner Ear Proteins

Characterization of key amino acids involved in hearing to better understand causes of deafness (Corey, Harvard)

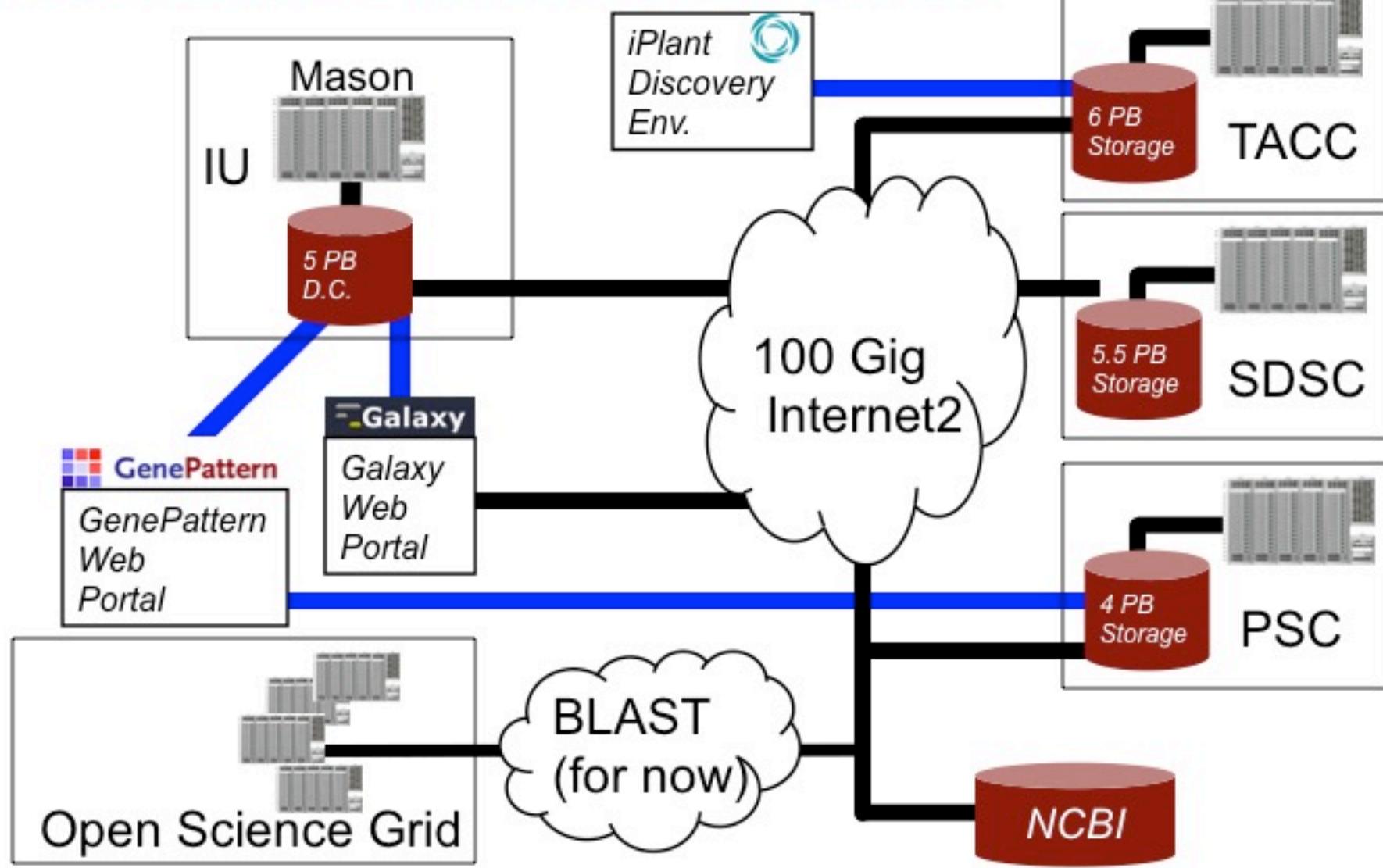


Calcium ions (green) binding to cadherin-23 (blue, binding site in colored stick), a protein essential to hearing. The sequence shows the progression of binding during the simulation. The final calcium-bound structure agrees well with the crystallographic structure.



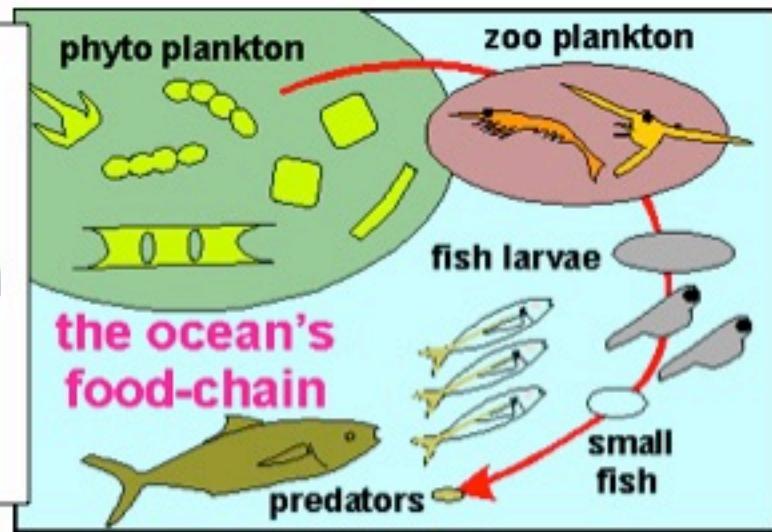
Sotomayor et al, Nature, 2012

NCGAS as a Virtual Instrument



NCGAS Science Stories

Transcriptomes of zooplankton
Calanus finmarchicus correlate
climate change with decrease in
zooplankton and fisheries
decline

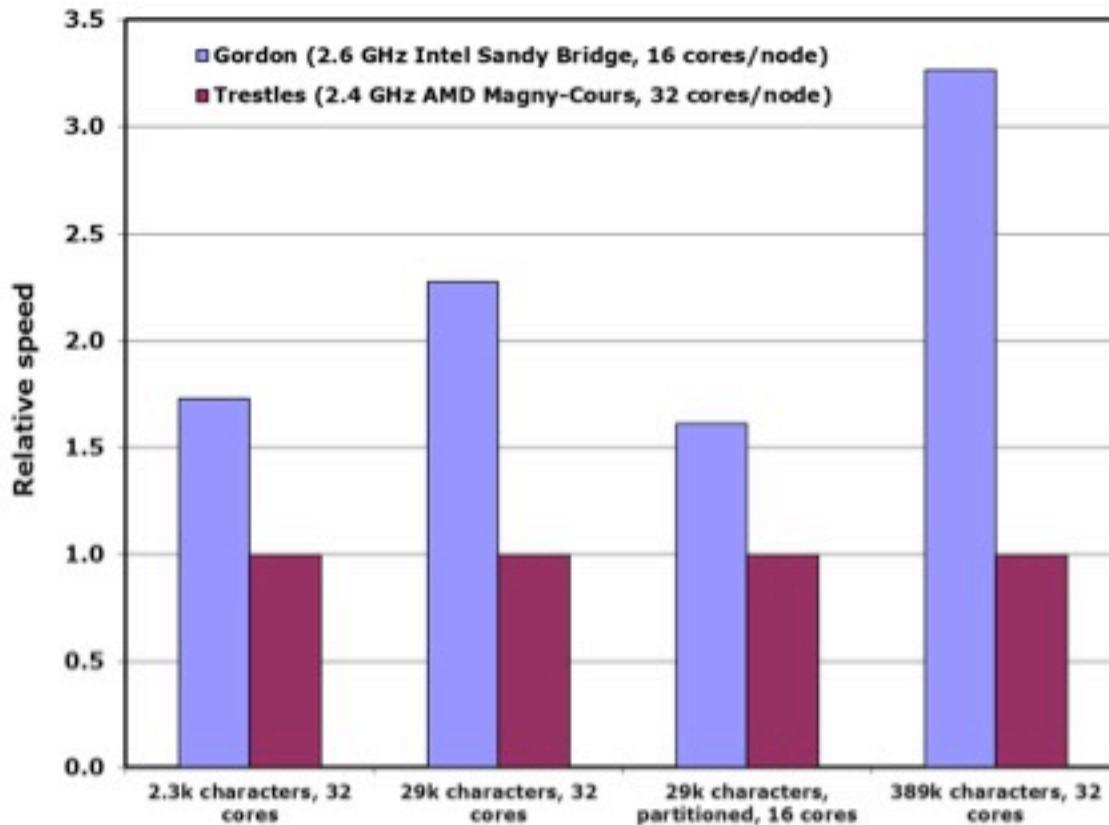


Study of complete RNA
collection of fruit fly uncovers
unprecedented complexity in
Drosophila melanogaster,
identifying thousands of new
genes, transcripts, and proteins



Phylogenetic tree construction

MrBayes 3.1.2 is used extensively via the CIPRES Science Gateway for Bayesian inference of phylogenetic trees. The hybrid parallel version running at SDSC uses both MPI and OpenMP.



Source: Wayne Pfeiffer (SDSC) Used by permission. 2013



CIPRES has allowed over 4000 biologists world-wide to run parallel tree inference codes via a simple-to-use web interface. It is arguably the most successful XSEDE Science Gateway. Applications can be targeted to appropriate architectures.

Gordon provides a significant speedup for unpartitioned data sets over the SDSC Trestles system. This is essential since phylogenetic tree codes can take up to a week to finish even on Gordon.

Environmental Disturbance Studies Linking Microbial Phenotypic Diversity to Mat Ecosystem

Sean Norman, University of South Carolina

The screenshot shows the PoPLAR portal homepage. At the top, there's a navigation bar with links for Home, Tools, My Workbench, My Profile, Help, and How to Cite Us. The main content area has a heading 'Missing Results? Check out the [PoPLAR Help](#), and we may be able to help.' Below this is a 'Log in' section with fields for 'Username' and 'Password', and 'Forgot Password?' links for both. There's also a 'Report an issue' link. At the bottom, there are logos for XSEDE, UT, JICS, NICS, and SDSC.

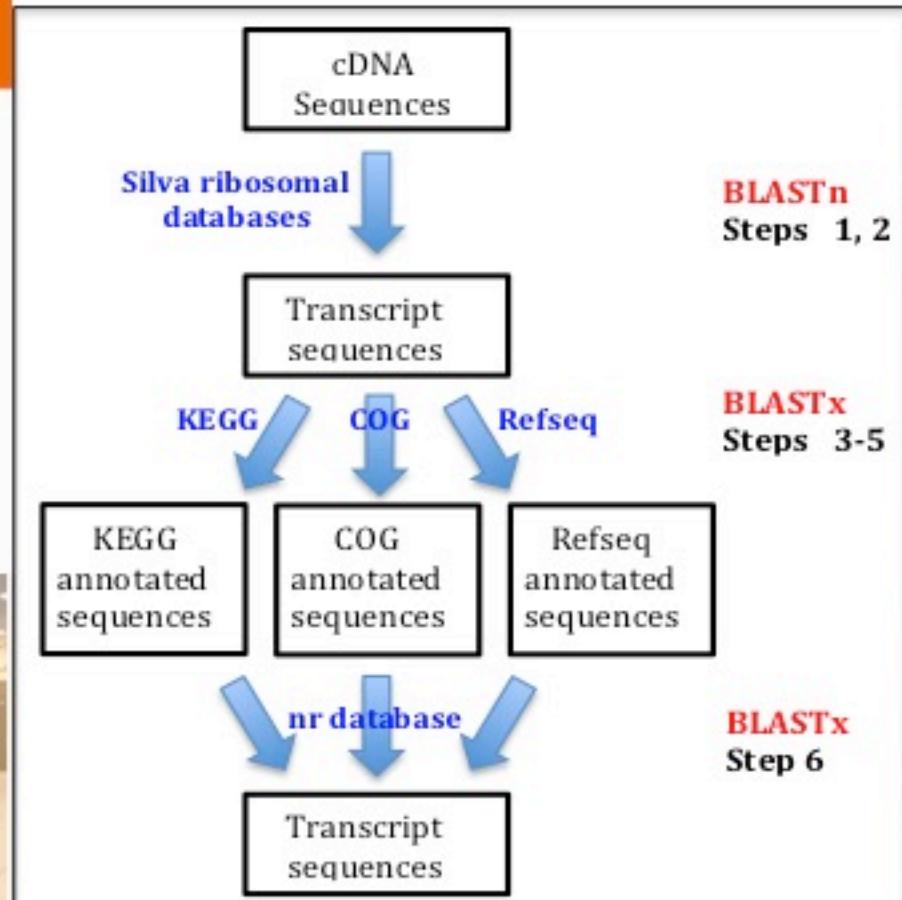


Figure 2. Bioinformatic workflow for metatranscriptomic annotation for each sample.

Evolution of Medical practices



Thank You



Bhanu Rekepalli, PhD
Sr. Scientific Consultant & PI
BioTeam Inc
Cell: 865-230-1605