

# High End Computing Context for Genomes to Life

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*Director*

Computers, Computation, and Math Center

January 22, 2002

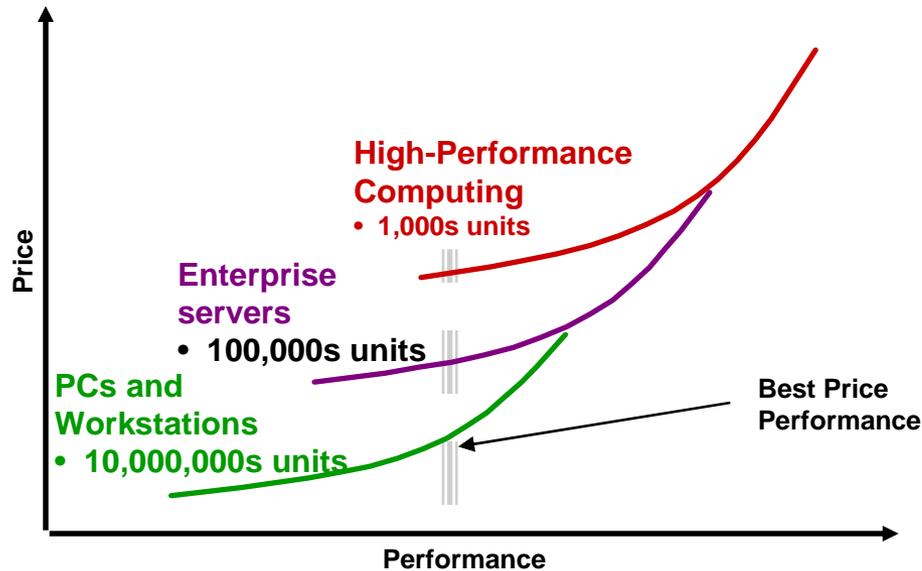
# What's Happening with High End Computing ?

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- High-volume building blocks available
  - Commodity trends reduce cost
- Assembling large clusters is easier than ever
  - Incremental growth possible
- HPC market is small and shrinking (relatively)
- Performance of high-volume systems increased dramatically
- Web driving market for scalable clusters
  - Hot market for high-performance interconnects

(Commodity, Commodity, Commodity)

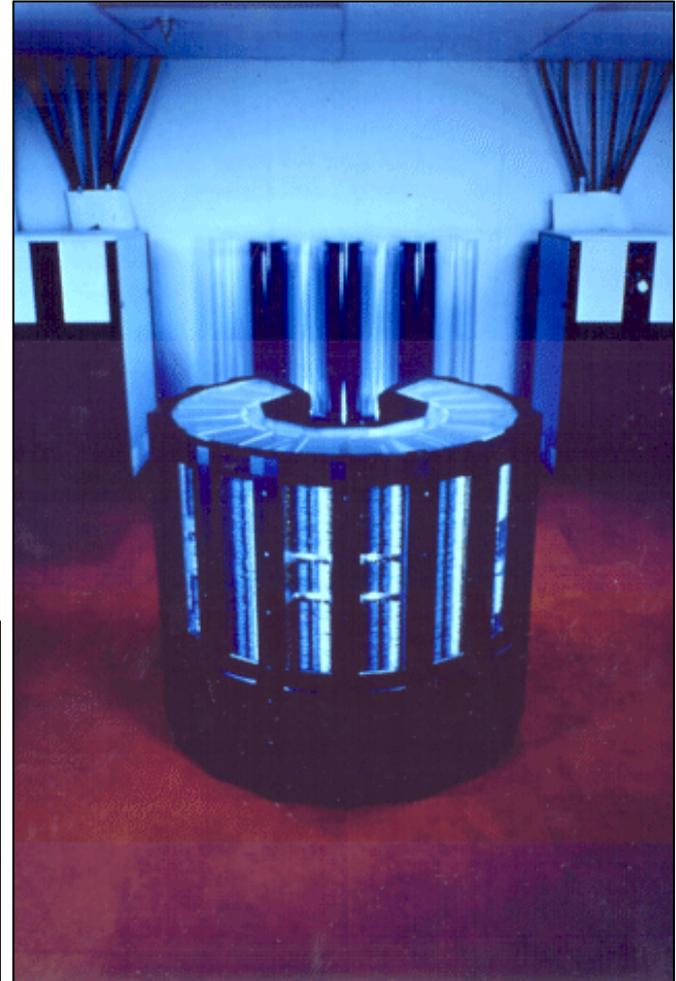
# Commodity Value Propositions



- Low cost to drive down the cost of simulation
- Flexible and adaptable to changing needs
- Manage and operate as a single distributed system

High Volume Technologies Give Favorable Price-Performance

# Cray-1



# nCUBE-2 Massively Parallel Processor (1024)

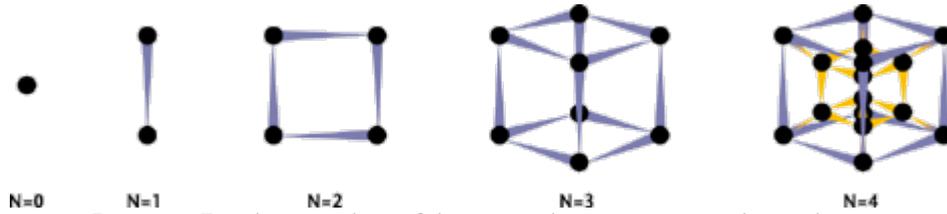
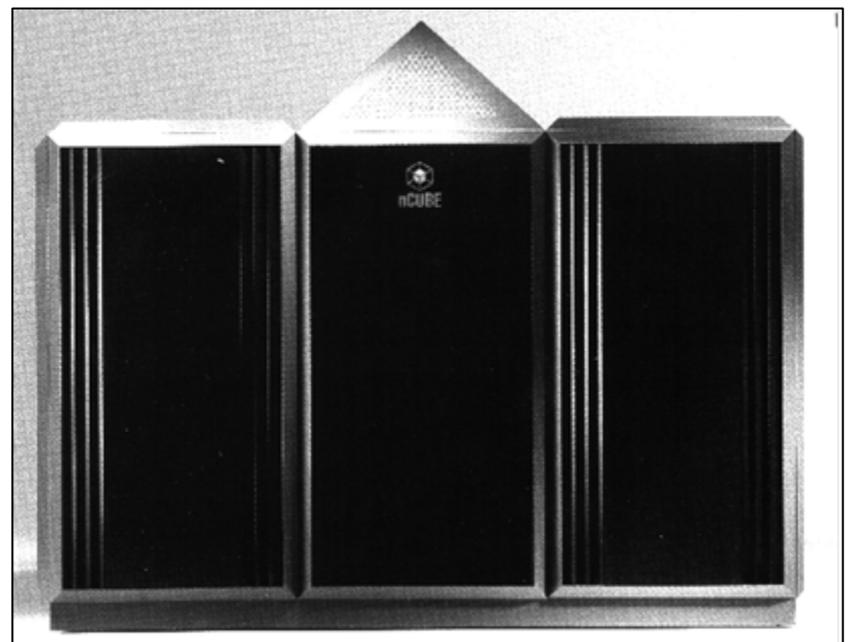
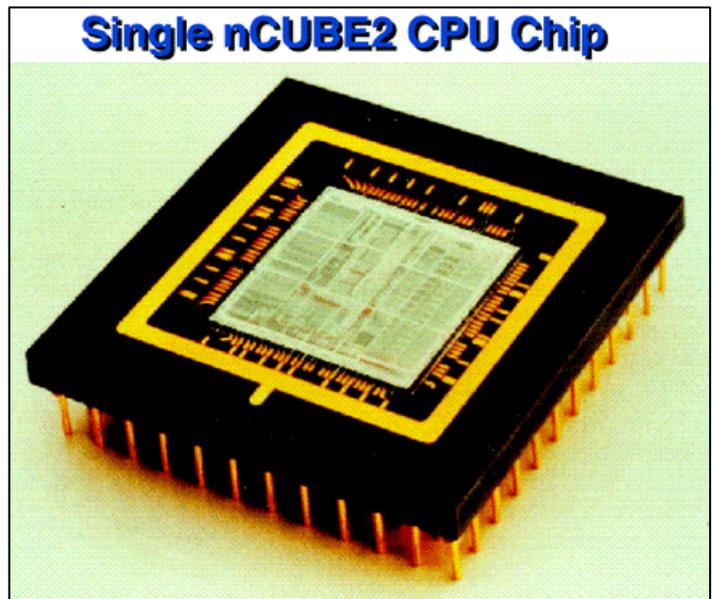


Figure 1: Two hypercubes of the same dimension, joined together, form a hypercube of the next dimension. N is the dimension of the hypercube.



# Intel Paragon

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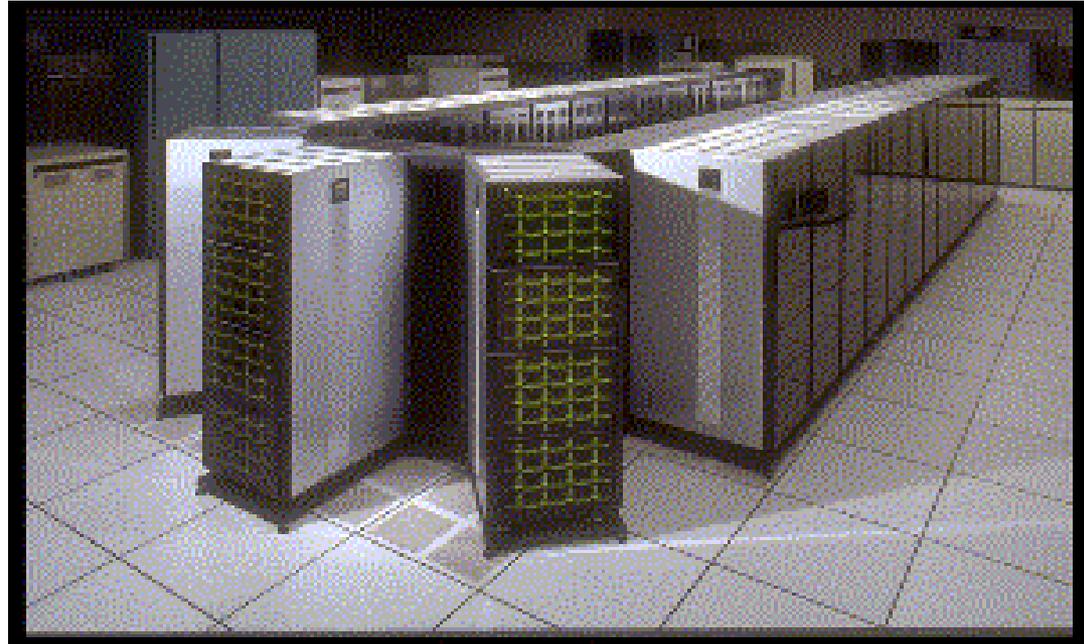
1,890 compute nodes

3,680 i860 processors

143/184 GFLOPS

175 MB/sec network

SUNMOS lightweight kernel



# High Performance Computing at Sandia: Hardware & System Software



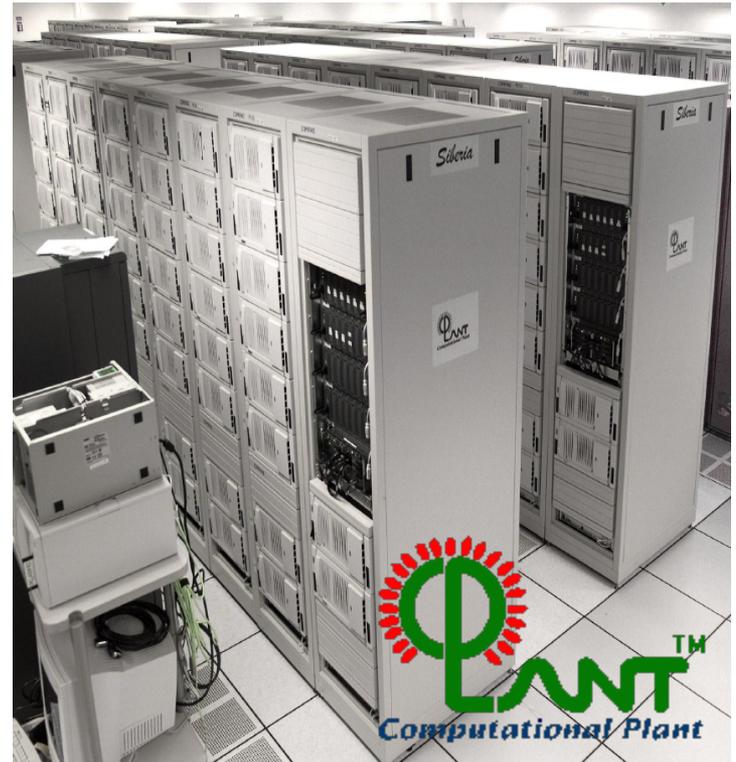
## ASCI Red: The World's First Teraflop Supercomputer

9,472 Pentium II processors

2.38/3.21 TFLOPS

400 MB/sec network

Puma/Cougar lightweight kernel OS



## Cplant™: The World's Largest Commodity Cluster

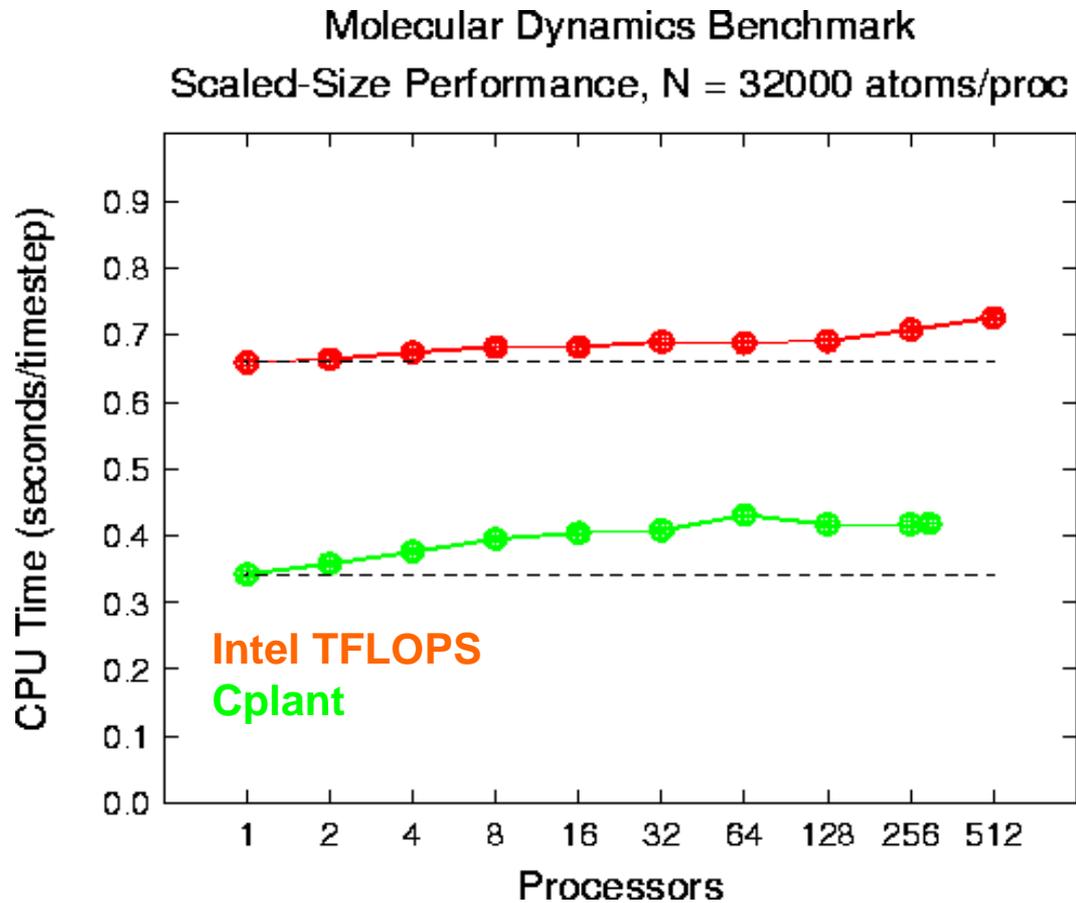
~2,500 Compaq Alpha Processors

~2.7 Teraflops

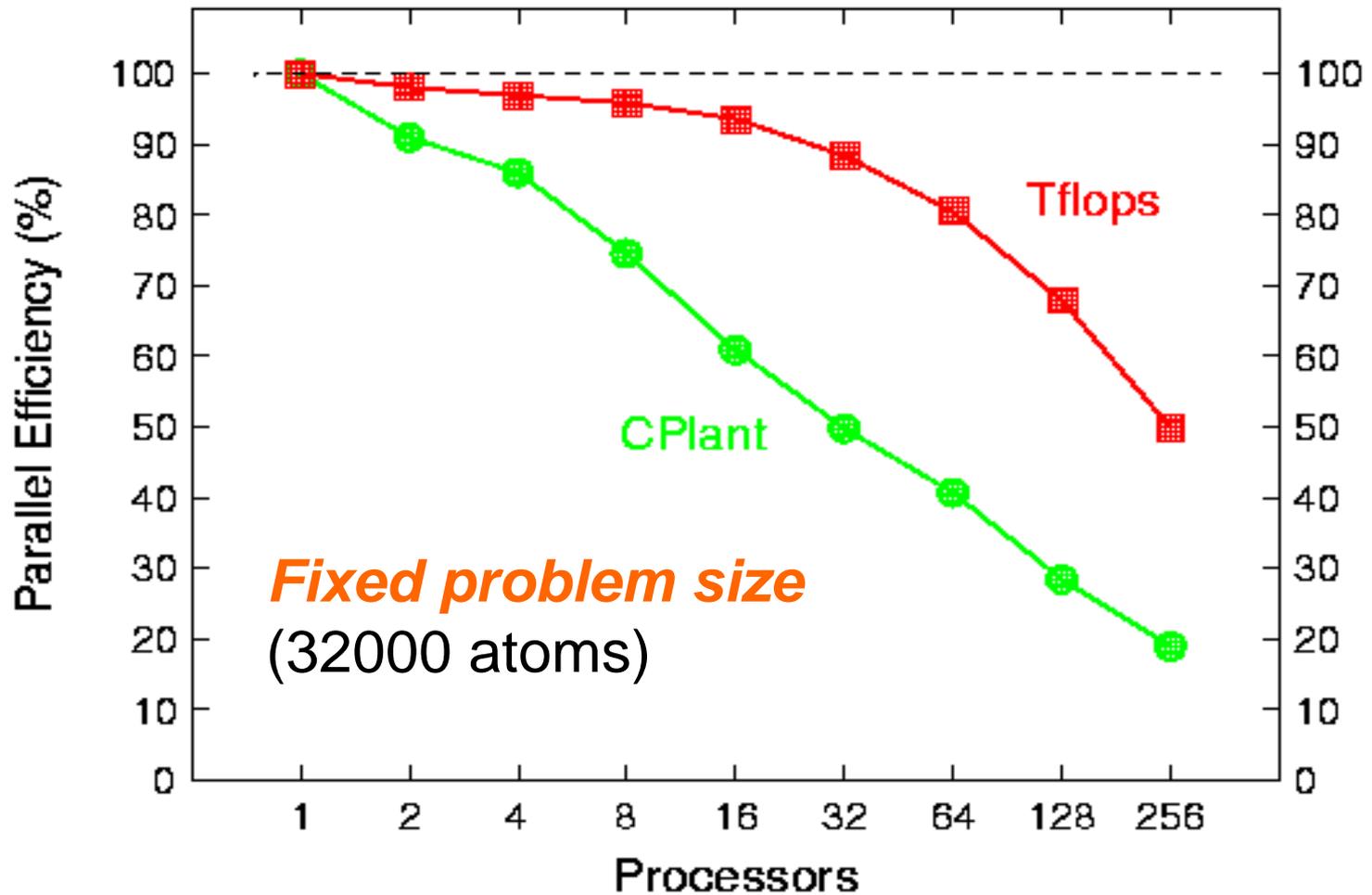
Myrinet Interconnect Switches

Linux-based OS (Portals)

# Cplant Performance Relative to ASCI Red



# Molecular Dynamics Benchmark (LJ Liquid)



# Distributed & Parallel Systems

Distributed systems

heterogeneous

Internet  
 Legion\Globus  
 Beowulf  
 Berkley NOW  
 Cplant  
 ASCI Red  
 Tflops

Massively parallel systems

homogeneous



Gather (unused) resources  
 Steal cycles  
 System SW manages resources  
 System SW adds value  
 10% - 20% overhead is OK  
 Resources drive applications  
 Time to completion is not critical  
 Time-shared

Bounded set of resources  
 Apps grow to consume all cycles  
 Application manages resources  
 System SW gets in the way  
 5% overhead is maximum  
 Apps drive purchase of equipment  
 Real-time constraints  
 Space-shared

# Communication-Computation Balance for Past and Present Massively Parallel Supercomputers

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<i>Machine</i>	<i>Balance Factor</i> (bytes/s/flops)
Intel Paragon	1.8
Ncube 2	1
Cray T3E	.8
ASCI Red	.6
Cplant	.1

*But Does Balance Matter for Biology?*

# *Biology*

## A Field With Increasing Impact on High End Computing

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Why is it important to high-end computing ?

What effect is it having ?

# High-Throughput Experimental Techniques Are Revolutionizing Biological and Health Sciences Research

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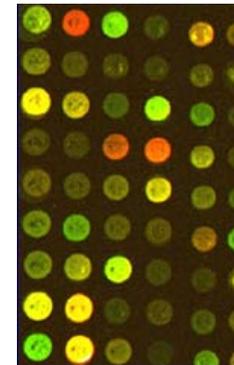
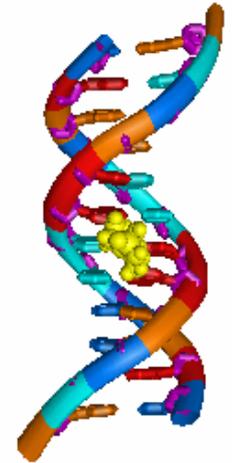
DNA Sequencing

Gene Expression Analysis With  
Microarrays

Protein Profiling via High Throughput  
Mass Spectroscopy

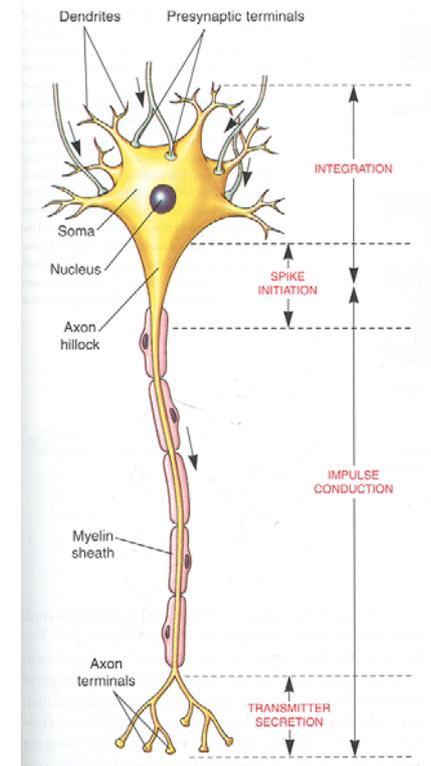
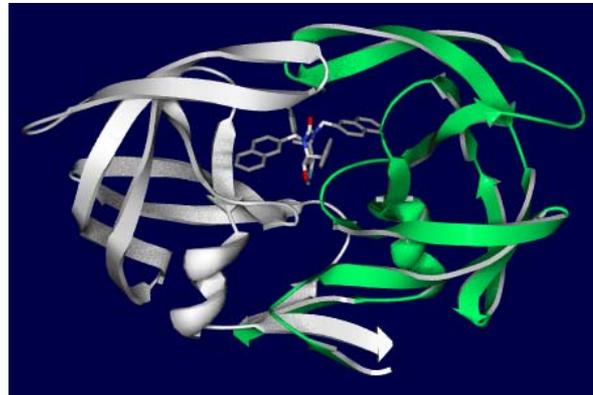
Protein-Protein Interactions

Whole-Cell Response



# The Ultimate Goal of "Systems Biology" Is Driving A Broad Range of Computing Requirements

- Bioinformatics: Accumulating data from high-throughput experiments followed by pattern discovery & matching.
- Molecular Biophysics & Chemistry
- Modeling Complex Systems (e.g. Cells)



# Computing-for-the-Life Sciences: The Lay of the Land

*The Implications of the New Biology for High-End Computing are Growing*

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IT market for life sciences forecast to reach \$40B by 2004, e.g.

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**Celera** builds 1<sup>st</sup> tera-cluster for biotechnology- speeds up genomics by 10x

**IBM, Compaq:** \$100 million investments in the life sciences market

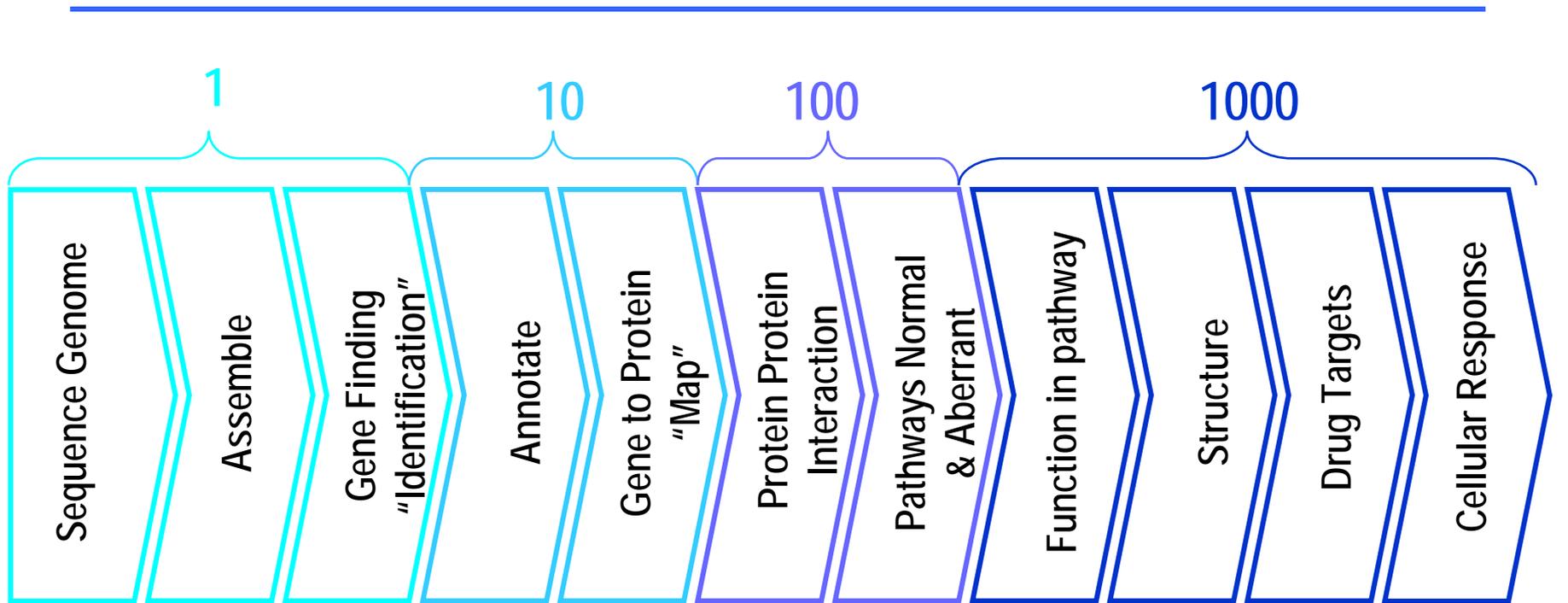
**NuTec** 7.5 Tflops IBM cluster (US, & Europe-planned)

**GeneProt** Large-Scale Proteomic Discovery And Production Facility: 1,420 Alpha processors.

**Blackstone** Linux/Intel Clusters (Pfizer, Biogen, AstraZeneca, & 10-15 more on the way)

# Computing For Life Sciences at the Terascale

## Consider One Example: In Silico Pharmaceutical Development ?



“Trivially Parallel”



“Massively Parallel”

Bioinformatics

Molecular Biophysics

Complex Systems

# Definitions

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## Molecular Biophysics

- Biological molecular-scale physical and chemical challenges and phenomena (e.g. structural biology, docking, ion channel problem.)

## Bioinformatics

- Informatics challenges (I/O, data mining, pattern matching, parallel algorithms etc.) presented by high-throughput biology and opportunities of application of terascale computing

## Complex Systems

- Developing models (most likely computationally intensive) of complex biological systems (e.g. cells):
- Volume methods, Circuit Models (Biospice, Bio-Xyce)), stochastic dynamics (e.g. Mcell), informatics (e.g. AFCS) 5) unit op's/rule-based interactions, reductionism (as last resort)

# Definitions

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## Distributed Resource Management & Problem Solving Environments

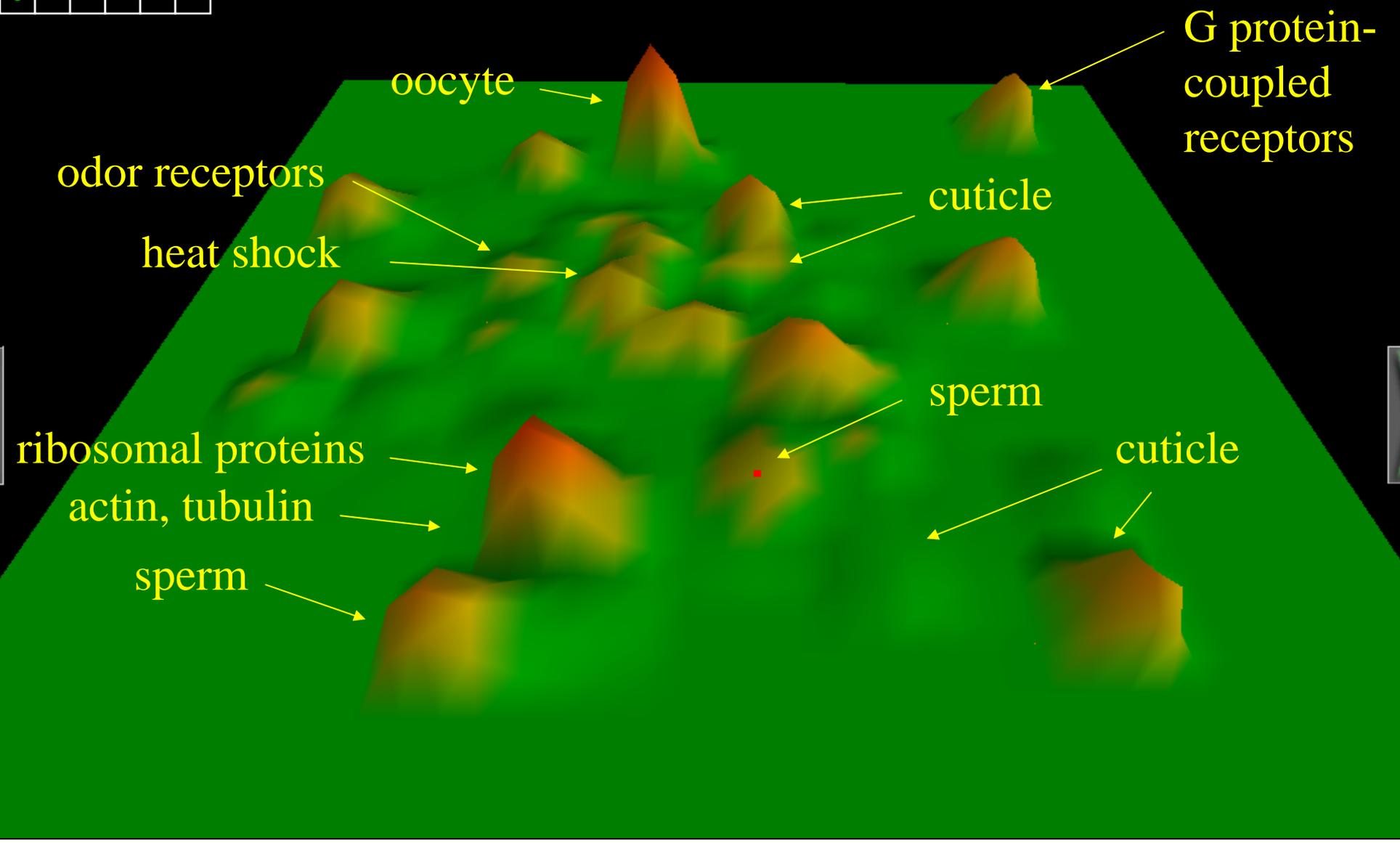
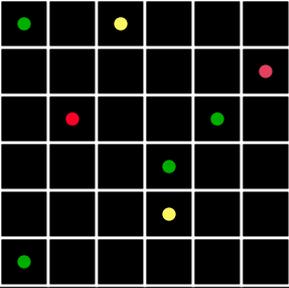
- Developing understanding & collaborations to establish a role in developing the tools & environment to enable the use of terascale computing to produce rapid understanding of complex biological systems through the combined approaches of
  - high-throughput experimental methods
    - data
    - parallel I/O
    - system software
    - meta OS
  - simulation & complex system modeling
  - integrated understanding
- People, data, software, hardware, algorithms distributed geographically, organizationally & institutionally- The **Bio-Grid**

# Some Examples

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(from Sandia's experience)

# VXInsight™ Analysis of Microarray Data

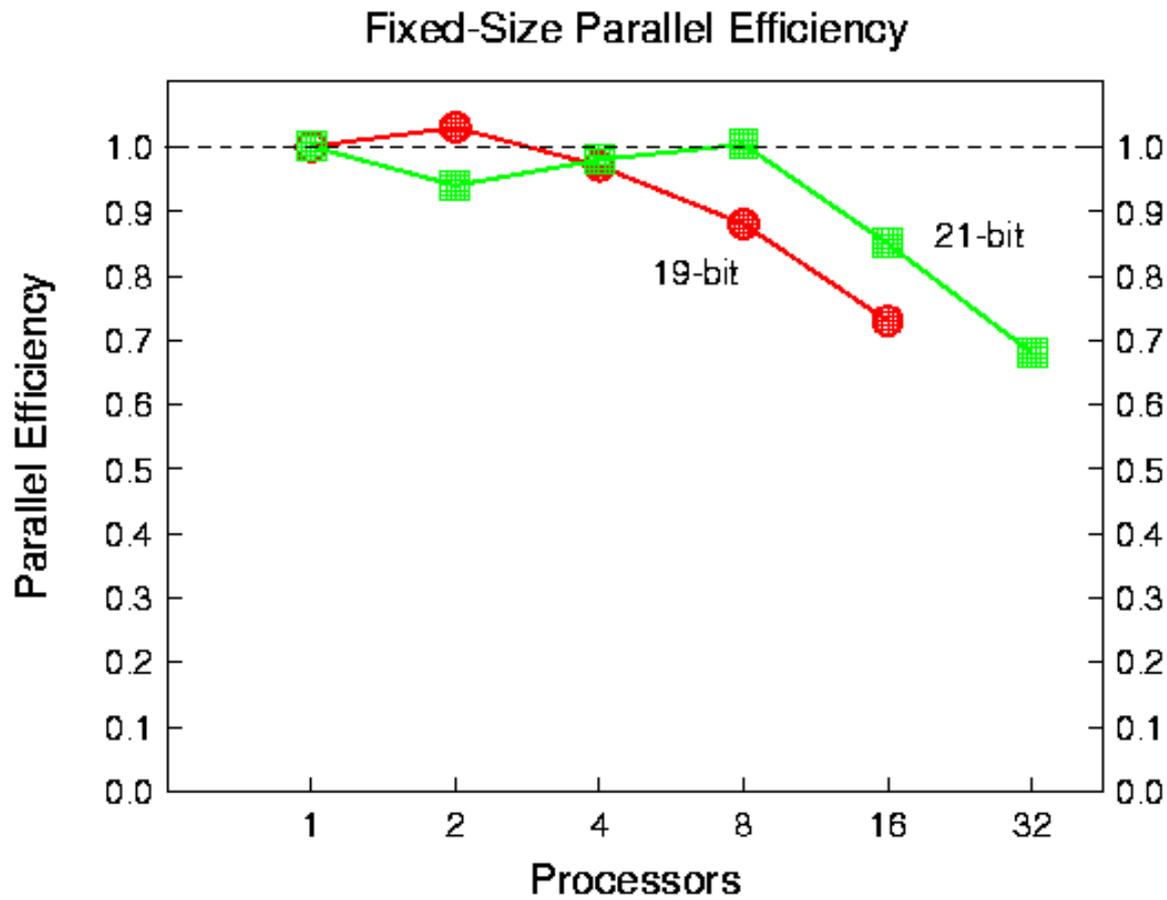


# GeneHunter

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- Popular linkage analysis code from Whitehead Institute:
  - does multipoint analysis (coupled marker effects)
- Computation/memory is exponential in size of pedigree,
  - linear in number of markers.
  - 15 person pedigree -> 24 bits -> vectors of length  $2^{24}$
  - CPU days on a workstation
- Ideal for explosion of genetic marker data (e.g. SNPs).
  - Our project: a distributed-memory parallel GeneHunter.
  - run on Cplant
  - extend scale of run-able problems, both in memory and CPU

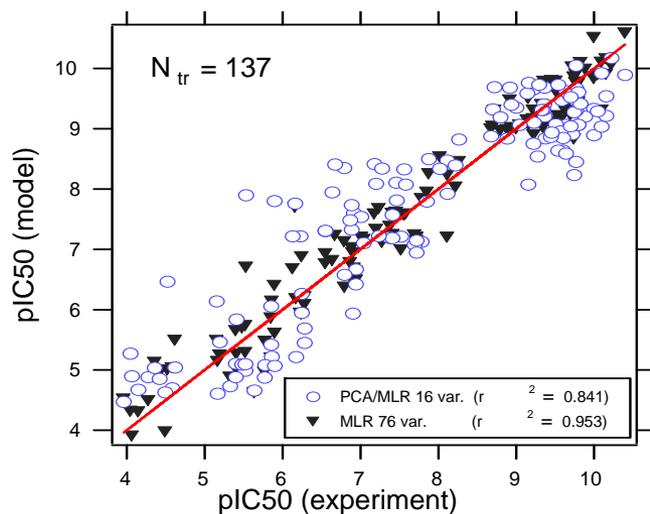
# Gene Hunter: Parallel Performance Results



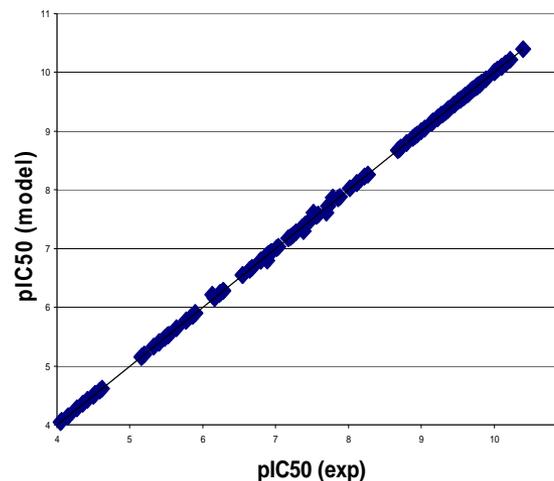
# New Database Methods for Structure-Property Relationships

## *QSAR Equation with Signature*

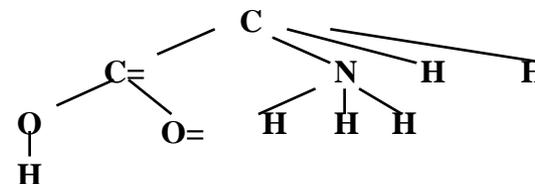
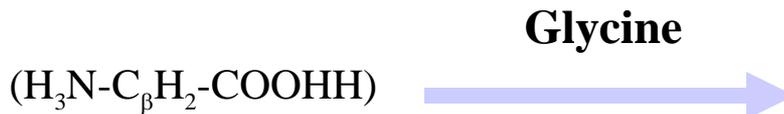
### HIV-1 protease inhibitors binding affinities (pIC50)



Typical QSAR (Molconn-Z descriptors)



Signature descriptors  
(extended connectivity index)



# Computational Molecular Biophysics

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## Molecular Simulation

### Molecular Dynamics (MD)

NVT, NVE

Grand Canonical MD

Reaction-ensemble MD

### Monte Carlo (MC)

Grand Canonical MC

Configurational Bias MC

Gibbs-ensemble MC

Transition state theory

## Molecular Theory

Classical Density Functional Theory

## Electronic Structure Methods

Local Density Approximation (LDA)

Quantum Chemistry (HF etc.)

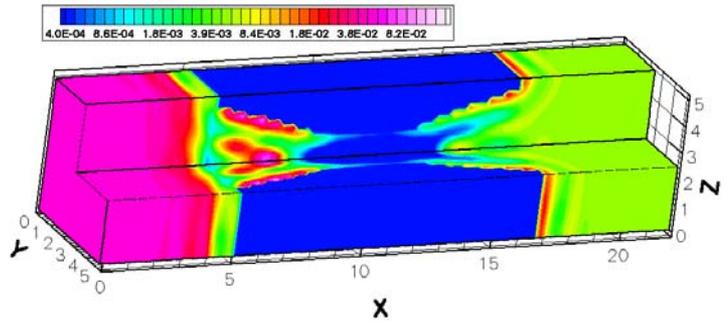
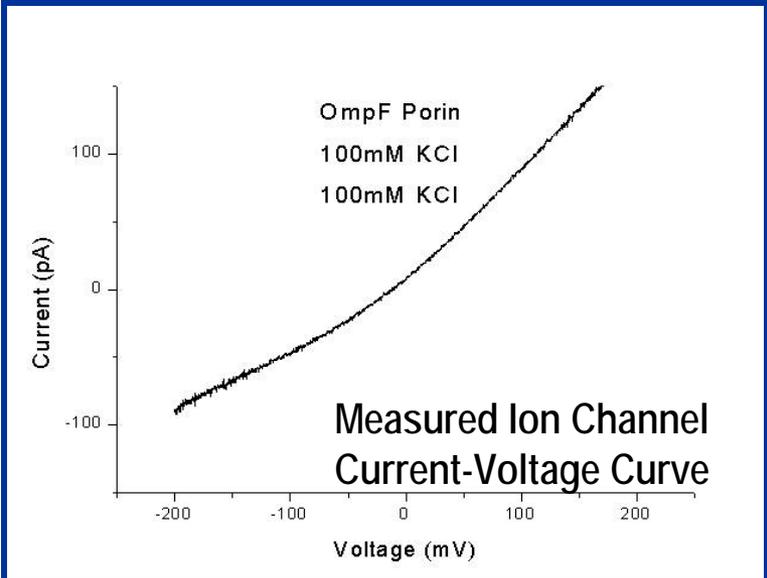
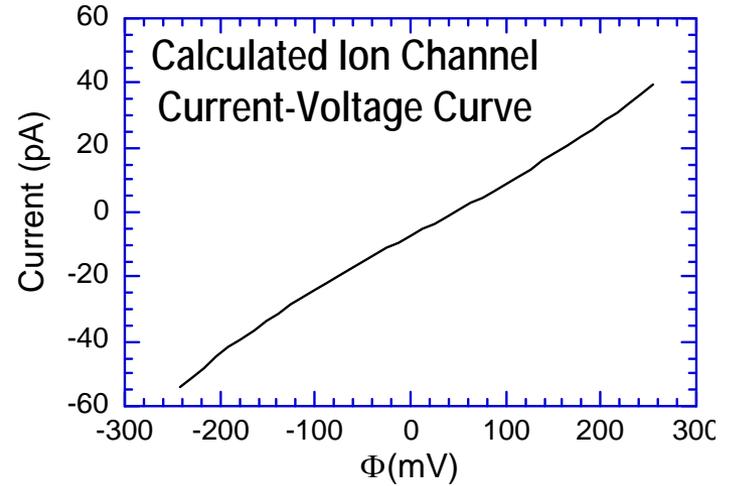
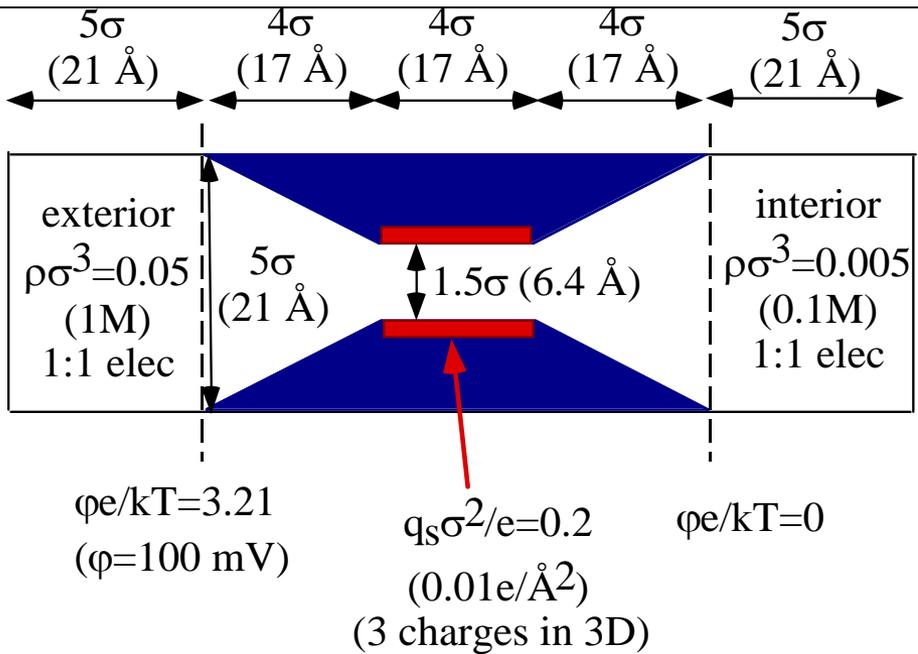
## Mixed Methods

Quantum-MD (Car-Parinello)

Quantum-CDFT

Brownian Dynamics-CDFT

# Ion Channel Model & Initial Results



# Virtual Cell Project

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NCRR-funded center within the UConn Health Center,  
Center for Biomedical Imaging Technology

National Resource for Cell Analysis & Modeling (Virtual Cell)

<http://www.nrcam.uhc.edu/>

## Sandia's Contributions

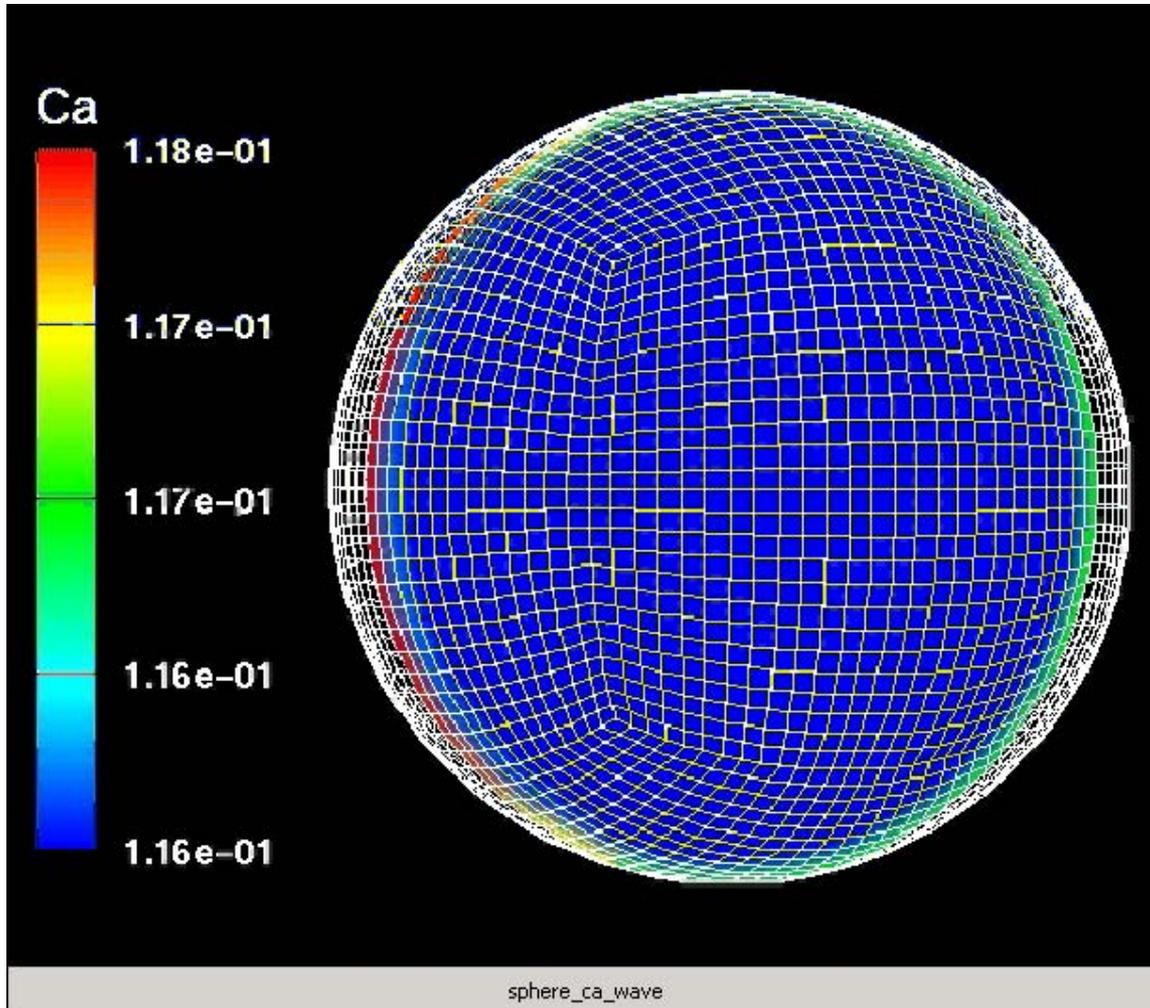
- efficient parallel implementation
- solving systems of stiff linear PDE's
- converting digitized images in 3d to meshable geometry



# Virtual Cell Collaboration

First Fully 3-D Simulation of the  $\text{Ca}^{2+}$  Wave Transport and Reaction During Fertilization of the *Xenopus Laevis* Egg

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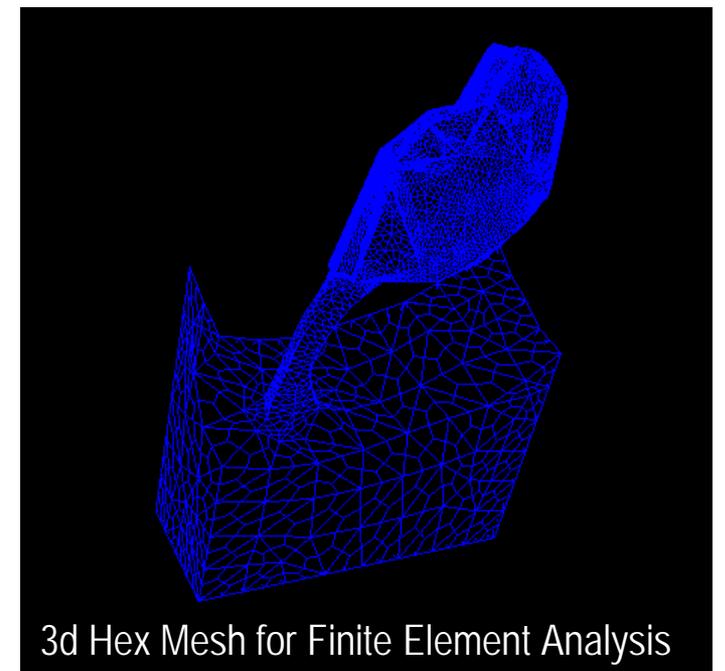
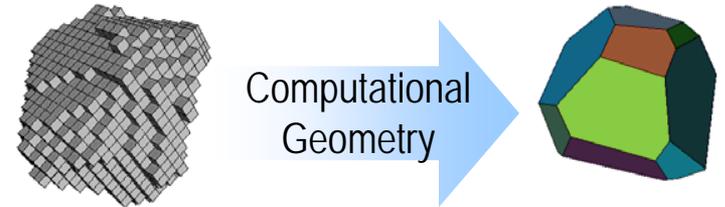
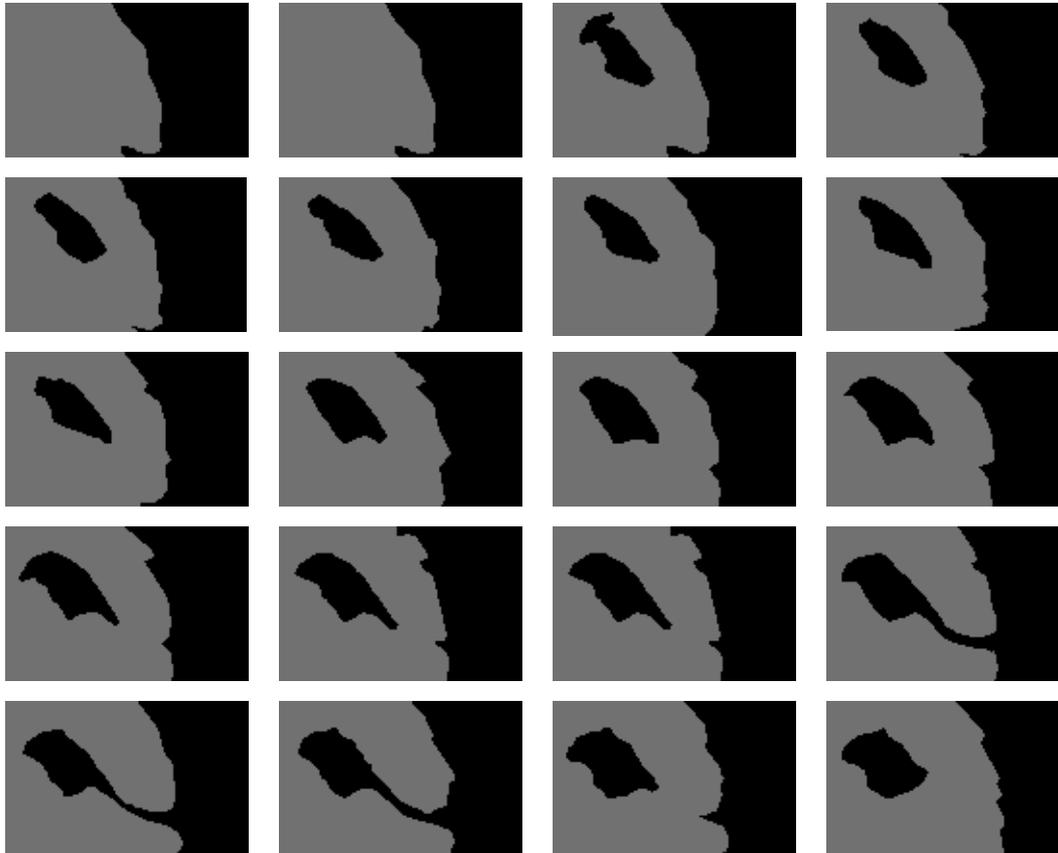
Meshed with Sandia's **CUBIT** technology and solved with Sandia's **MP-SALSA** massively parallel diffusion, transport, and reaction finite element code.

*Wjc*

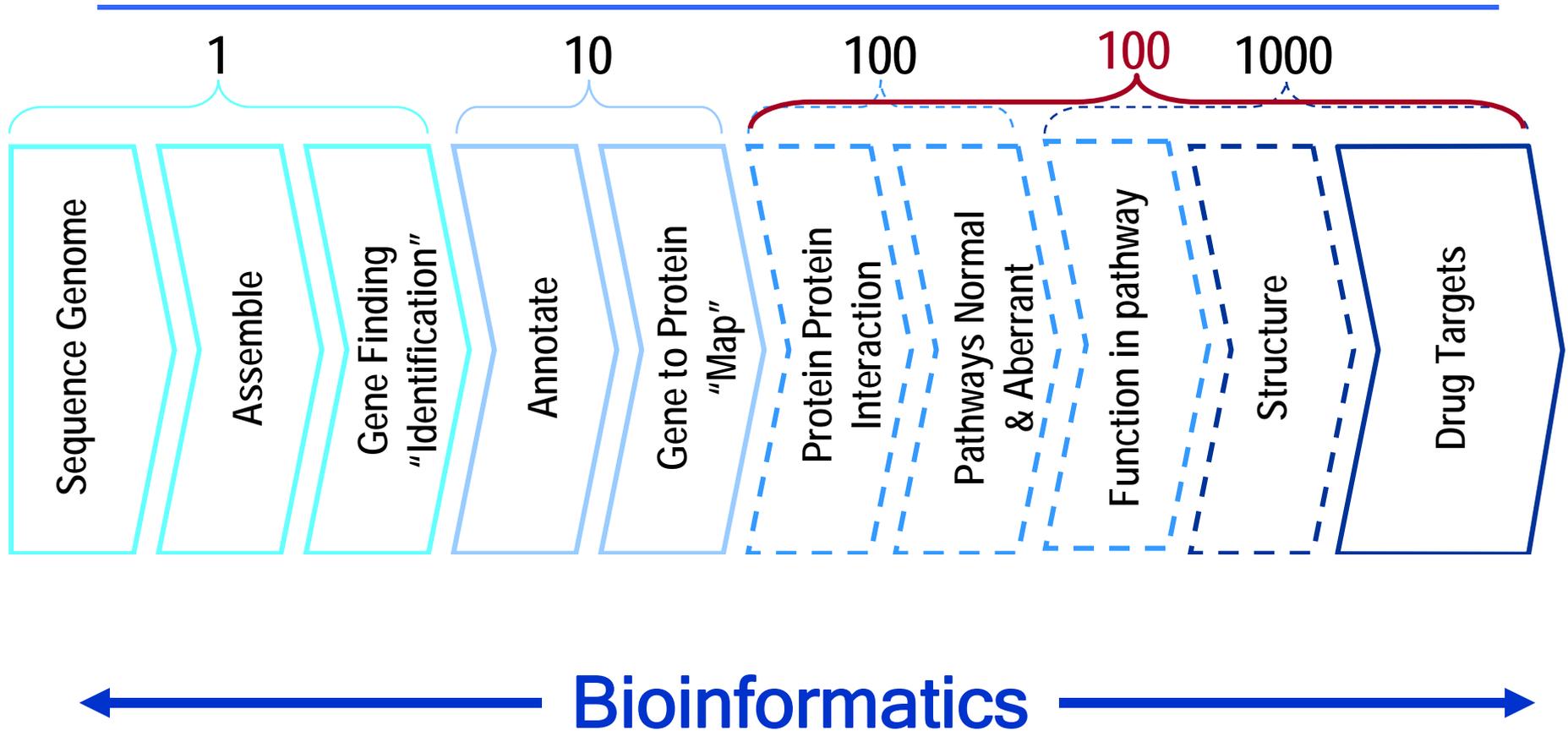
*Bill@sandia.gov*

# Meshing of Mitochondrial Cristae for 3-D ADP/ATP Transport Study Within Mitochondria

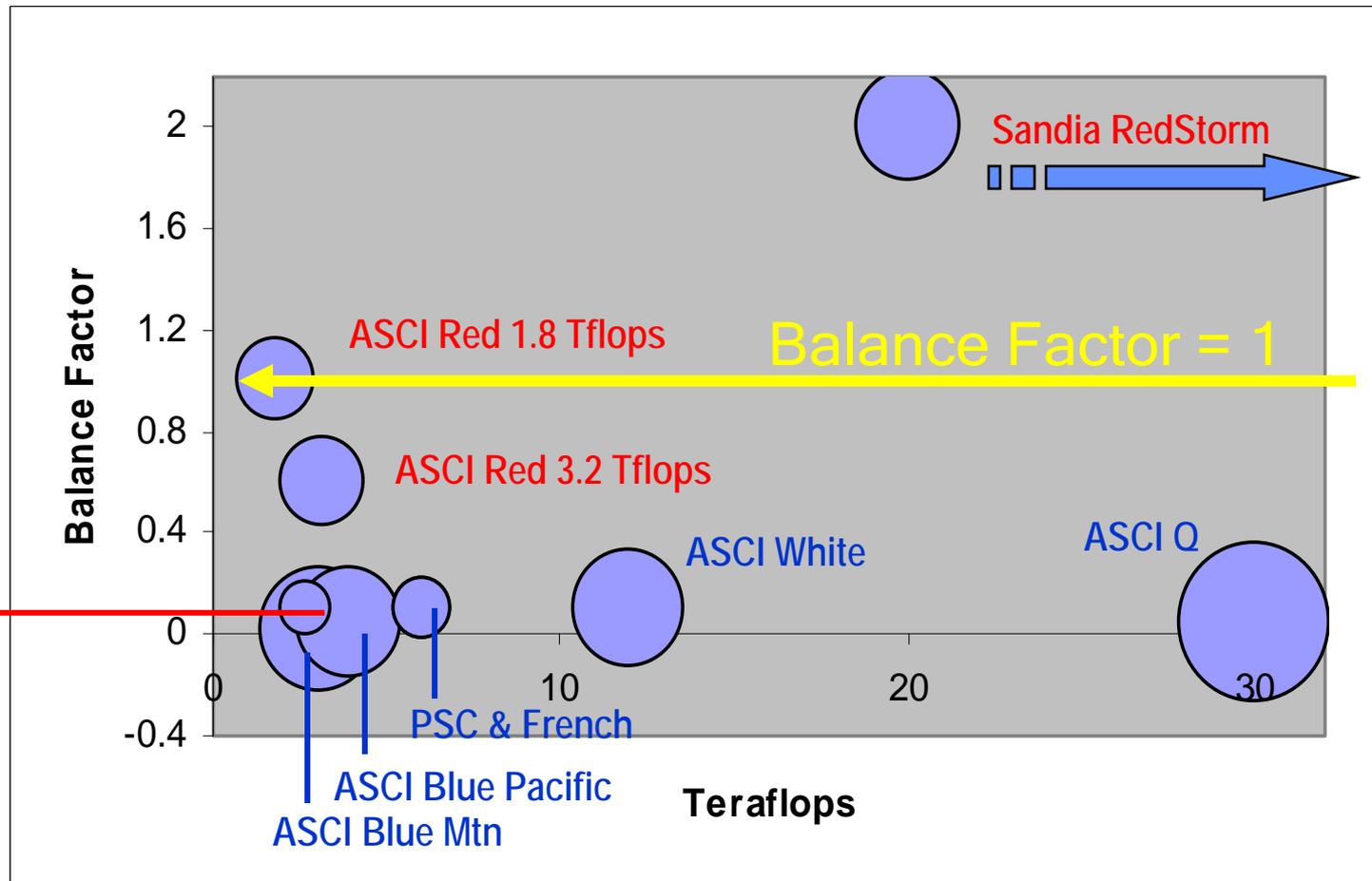
3d Mitochondria Cristae Geometry from Confocal Microscopy



# Another Possible Scenario



# Terascale Supercomputers To Date



# Big Pharma (& Biotech) Are Increasingly Driving The High-End Computing Market.

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Annual Sales (est.)	\$300B
Historic Growth Rate	10-14%
R&D Expenditures	\$62B (\$26.4B in US)

**\$4.6B external R&D to understand human genome**

11% of sales in 1980

20% of sales in 2000

- 70% of patented drugs come off patent in the next 4 years.
- 80% average drop in sales revenue when patent expires.
- \$600M average drug development cost.
- Diminishing pool of easy targets.

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# Speeding up Informatics - Parallel BLAST framework

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Idea: Create a tool for running large parallel BLAST jobs  
(genome vs genome) on distributed memory cluster

Problems with current approach:

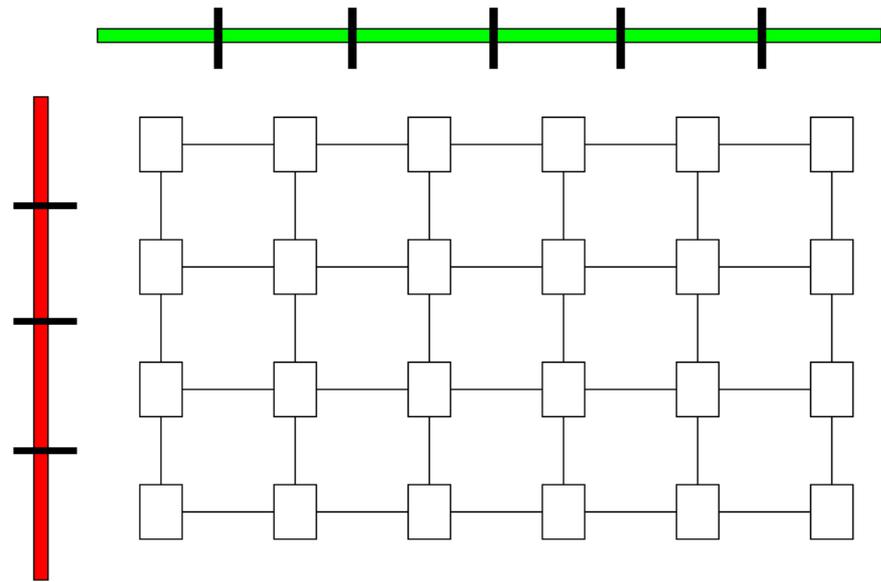
- tens of 1000s of LSF jobs:
- can't control or schedule them, users don't know progress
- full database on every proc
- I/O is not managed

Goals for parallel tool:

- scalable parallel performance
- minimize and measure memory/proc  $\leftrightarrow$  \$\$
- minimize and measure time in I/O
- feedback & monitoring for users
- design framework for more than BLAST

# Basic Idea

Large query file & database = many strings.



One file chunk per column, one per row.

BLAST ->  $N^2$  subsets of work to do => reduced memory per proc.

Others have looked at this as well

# Our Implementation of the Idea

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Master scheduler:

runs on 1 proc

breaks up sequence analysis problem into  $M \times N$  pieces

schedules slave jobs intelligently

Slave codes:

run on all procs

BLAST (or other tools)

pre- and post-processors

PVM or MPI:

launch slave job on particular proc

messages back to master

detect when slave is finished

# Scheduler Intelligence

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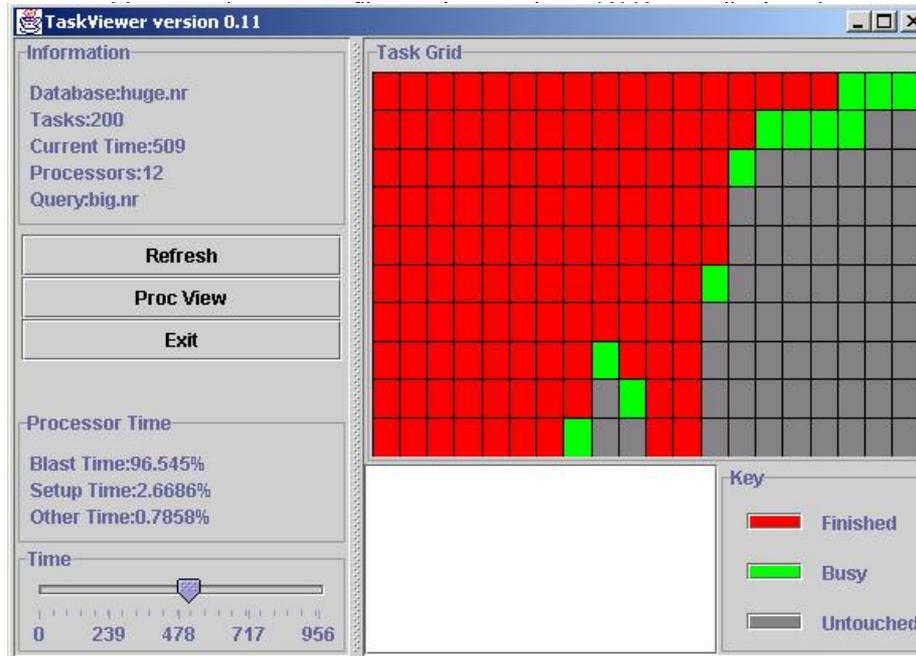
Query and DB pre-processing have to be run before BLAST sub-job.

Give a proc a new BLAST sub-job that doesn't require additional I/O.

Slaves can write to local disk to minimize I/O.

4 procs in a ES40 box can share files & loaded memory (via UBC).

# User monitoring



Timeline on job history on compute farm.

Stats on parallel performance, load-balance, individual jobs & procs.

Add instrumentation of BLAST for memory/CPU stats.

# Advantages

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## Reduced memory use per processor:

each BLAST task uses small portion of database and query files  
can be as small as desired

User feedback – JAVA app.

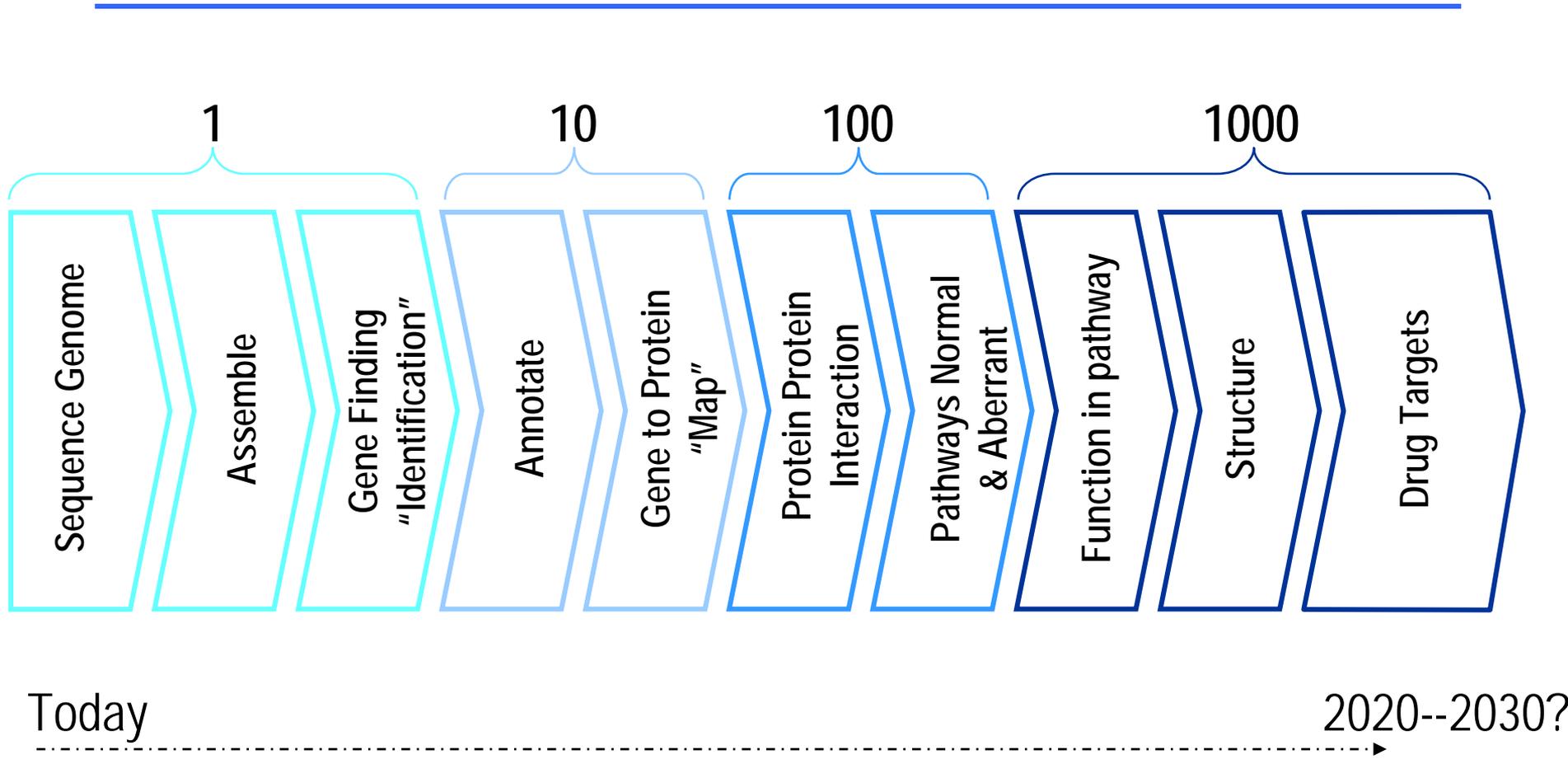
## Parallel efficiency & scalability:

fine granularity of BLAST sub-jobs -> load-balance  
overall throughput should be much greater and not dependent on high degree of user  
sophistication

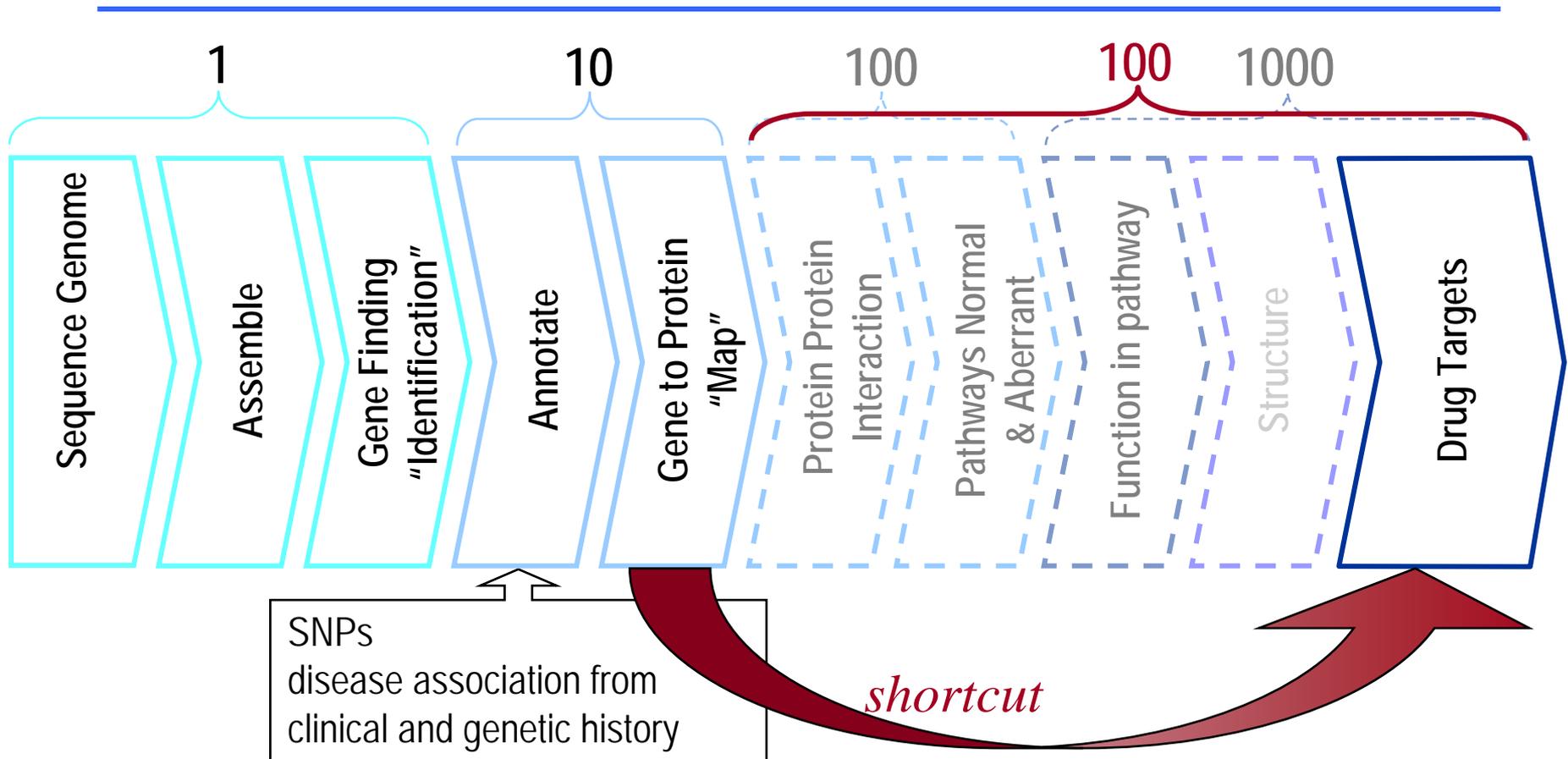
## Reduced I/O:

local vs NFS disks  
 $\sqrt{P}$  effect

# There May Be Other Ways to Attack This Problem: *Current Timeline?*

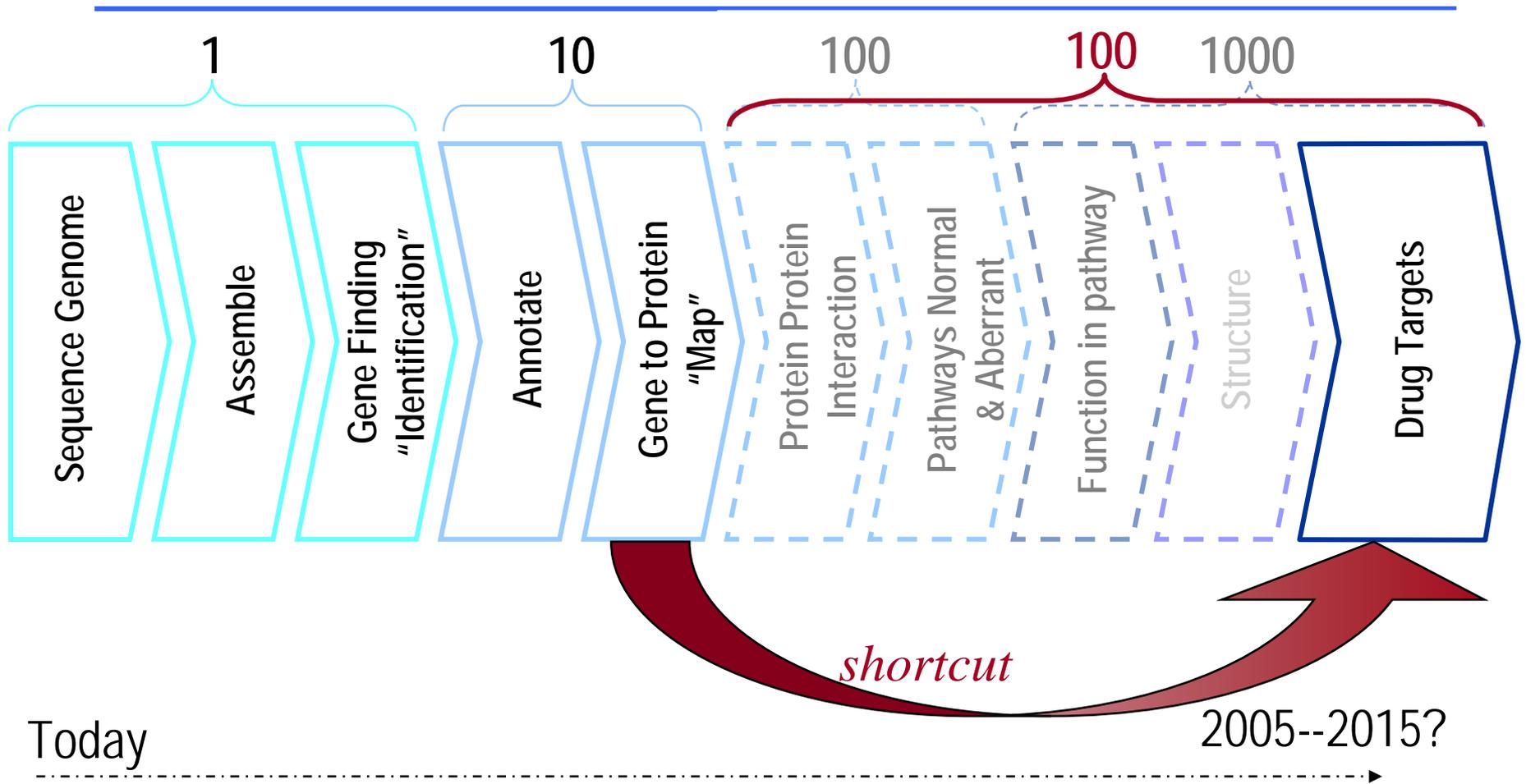


# ...High-Throughput Experiments May Create a *Shortcut*



*Existing clinical data and tissue banks  
could be CRITICAL because ...*

# Computing Power Needs May Decrease with Clinical Collaborations



# Summary

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There are bigger problems in GtL and similar efforts than any computer can handle now or in the next 10 years

However, we need to develop the computational tools and Frameworks that take us

from genomics to proteomics

and beyond to

Whole cell/ whole organism response

This will require a uniquely challenging juxtaposition of  
high-throughput experimental methods  
grid-based bio-informatics  
sophisticated simulation of info and energy flows,  
of structure and function, and of environmental reactions