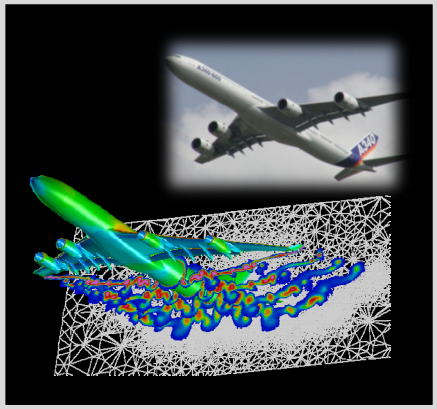

High Performance Computing

ADVANCED SCIENTIFIC COMPUTING

Prof. Dr. – Ing. Morris Riedel
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SHORT LECTURE 13

Systems Biology & Bioinformatics

November 21, 2019
Webinar

UNIVERSITY OF ICELAND
SCHOOL OF ENGINEERING AND NATURAL SCIENCES
FACULTY OF INDUSTRIAL ENGINEERING, MECHANICAL ENGINEERING AND COMPUTER SCIENCE

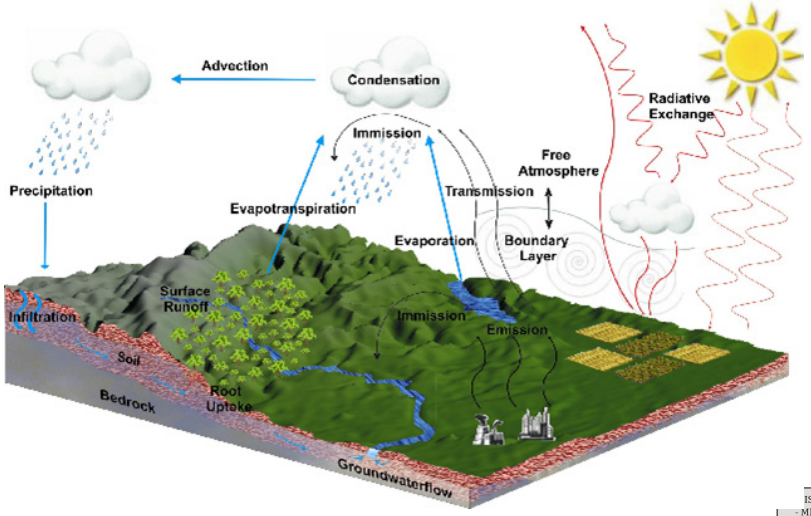
JÜLICH Forschungszentrum | JÜLICH SUPERCOMPUTING CENTRE

DEEP Projects

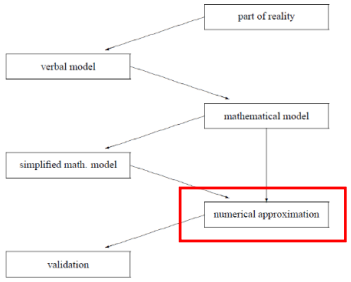
HELMHOLTZ RESEARCH FOR GRAND CHALLENGES

HAICU HELMHOLTZ ARTIFICIAL INTELLIGENCE COOPERATION UNIT

Review of Short Lecture 12 – Terrestrial Systems & Climate



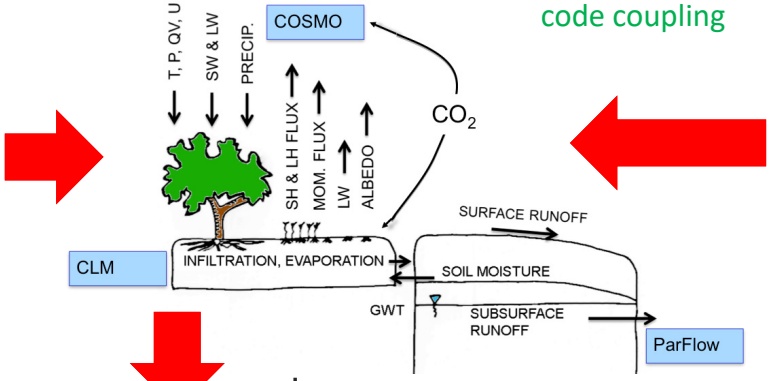
Physical system changes are accompanied by major state changes of land surfaces & ecosystems

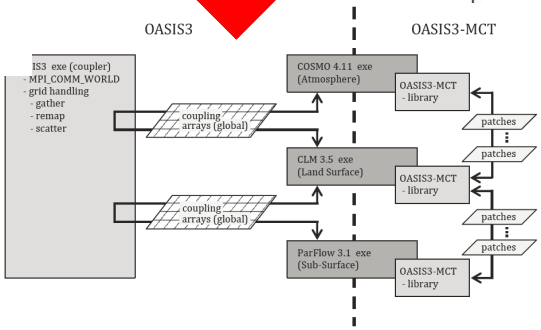


Solving Partial Differential Equations (PDEs) is often too complicated & computationally expensive or impossible to analytically compute driving the need for numerical approximation

modified from [1] SimLab Terrestrial Systems [2] F. Gasper et al.

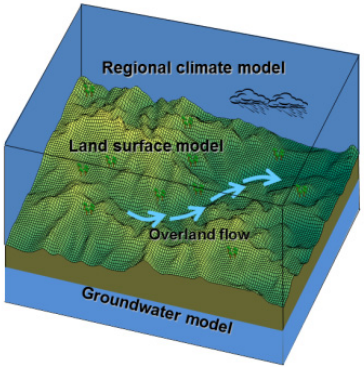
Towards reality: code coupling



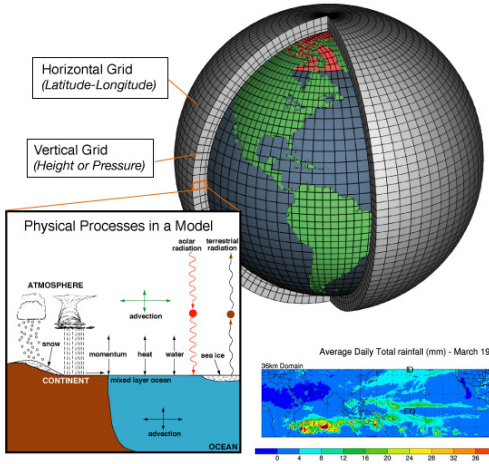


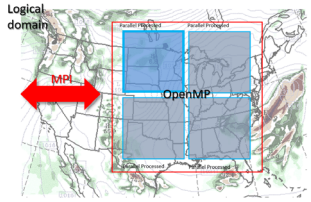
modified from [3] Wikipedia on 'Numerical Weather Prediction'

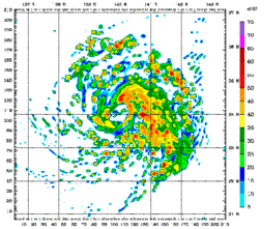
modified from [4] WRF – Code and Parallel Computing



Numerical Weather Prediction Example



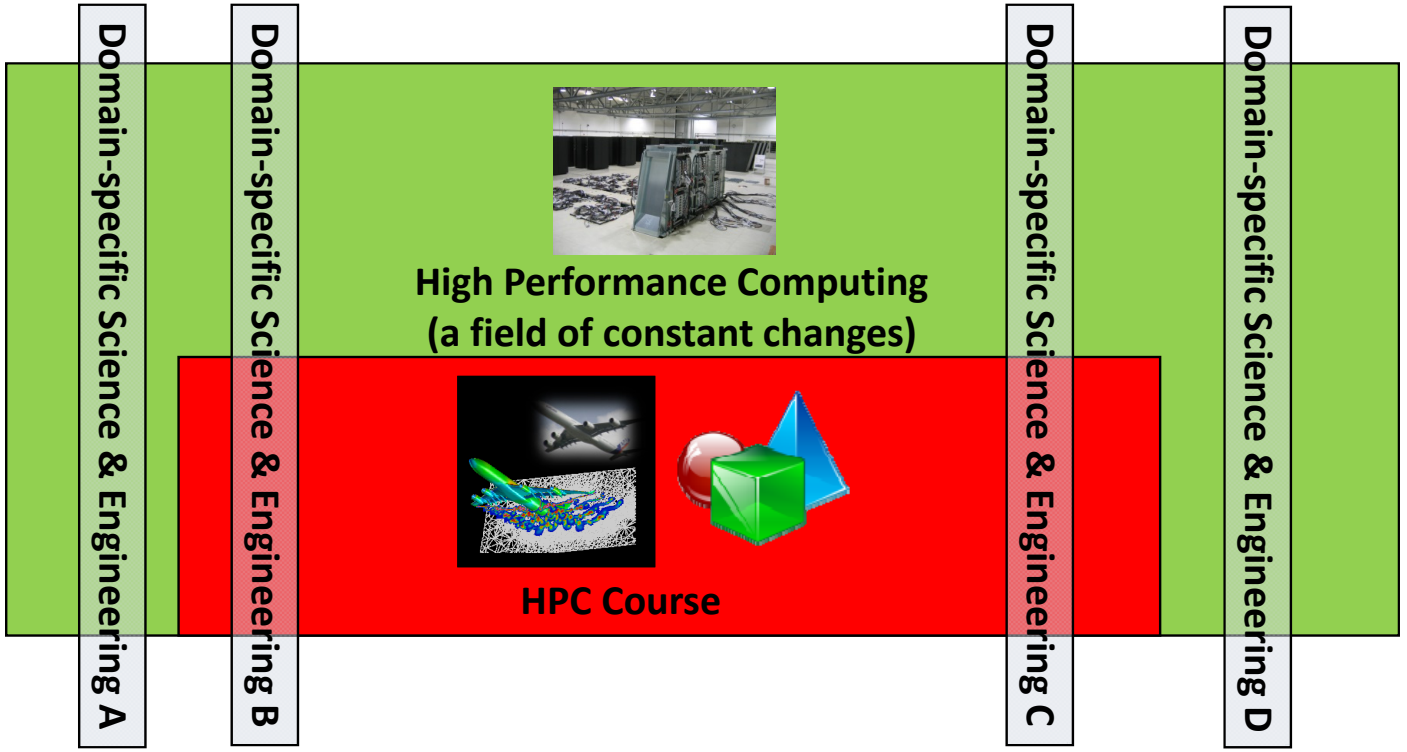




[5] Wikipedia on 'WRF'

HPC-A[dvanced] Scientific Computing (cf. Prologue) – Second Part

- Consists of techniques for programming & using large-scale HPC Systems
  - Approach: Get a broad understanding what HPC is and what can be done
  - Goal: Train general HPC techniques and systems and selected details of domain-specific applications



Outline of the Course

1. High Performance Computing
2. Parallel Programming with MPI
3. Parallelization Fundamentals
4. Advanced MPI Techniques
5. Parallel Algorithms & Data Structures
6. Parallel Programming with OpenMP
7. Graphical Processing Units (GPUs)
8. Parallel & Scalable Machine & Deep Learning
9. Debugging & Profiling & Performance Toolsets
10. Hybrid Programming & Patterns
11. Scientific Visualization & Scalable Infrastructures
12. Terrestrial Systems & Climate
13. Systems Biology & Bioinformatics
14. Molecular Systems & Libraries
15. Computational Fluid Dynamics & Finite Elements
16. Epilogue

+ additional practical lectures & Webinars for our hands-on assignments in context

- Practical Topics
- Theoretical / Conceptual Topics

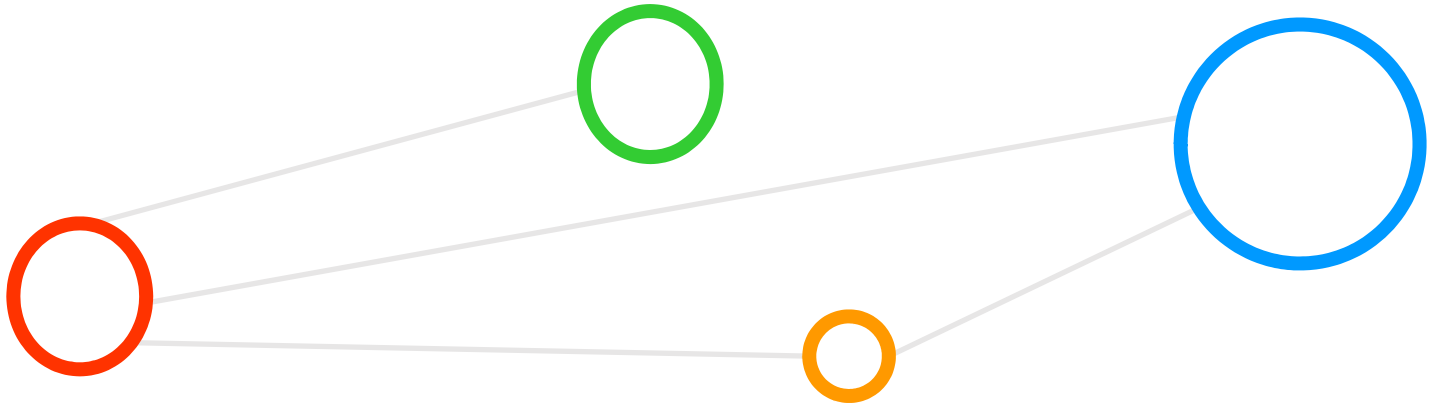
Outline

- Systems Biology
  - Motivation to Simulate Complex Systems & Basic Terminology
  - Scientific Case Protein Folding & Role of Specific Shapes
  - Role of Monte Carlo Methods & Repeated Random Sampling
  - SMMP Parallel Package Example to Simulate Proteins
  - Neuroscience Parallel Applications & NEST Parallel Code
- Bioinformatics
  - Motivation for Analysis of DNA Sequences & Terminology
  - Scientific Case Gene Sequencing & Role of Databases
  - Web Portals & BLAST Parallel Application Example
  - Drug Development using Scalable Computing Infrastructures
  - Human Brain Project Example for Challenges in Neuroscience

- **Promises from previous lecture(s):**
- ***Practical Lecture 0.2:*** **Lecture 12 & Lecture 13 provides more insights about selected applications in Terrestrial Sytems & some applications in Neuroscience**
- ***Lecture 5:*** **Lecture 13 will provide more details on using different & scalable parallel algorithms for systems biology & bioinformatics applications**
- ***Lecture 10:*** **Lecture 13 will provide more details on various systems biology & bioinformatics application codes that use parallel computing**
- ***Lecture 12:*** **Lecture 13 provides more details on general & so-called ensemble methods to estimate uncertainties that are often used in HPC**

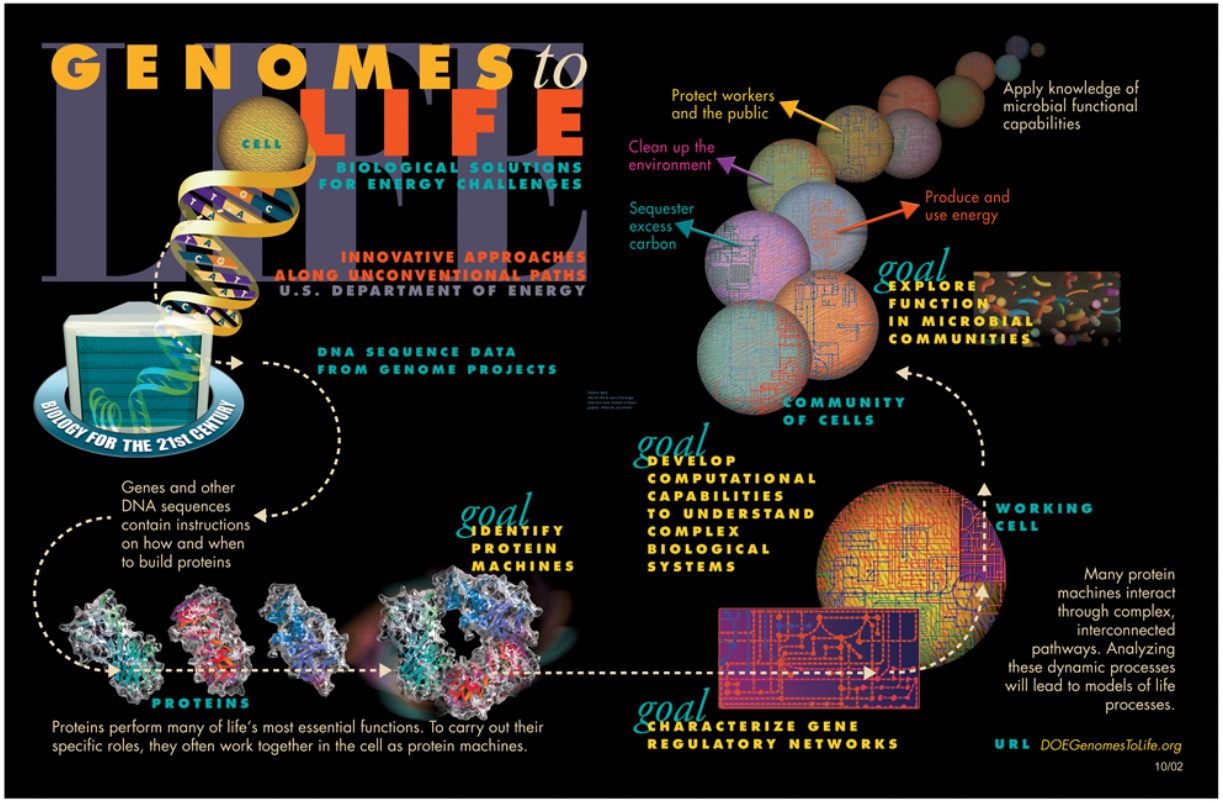
- **Note that this lecture is only a short lecture that usually needs a full course**
- **The goal is to understand selected HPC application fields & provide a few pointers to other advanced related university courses/topics/tutorials**

Systems Biology



Systems Biology – Motivation

- Focus
  - Study, model, and simulate a ‘complex biological system‘
  - E.g. understand and simulate small ‘Protein machines‘
  - E.g. understand and simulate models of life processes in cells (‘protein interactions pathways & joint work‘)



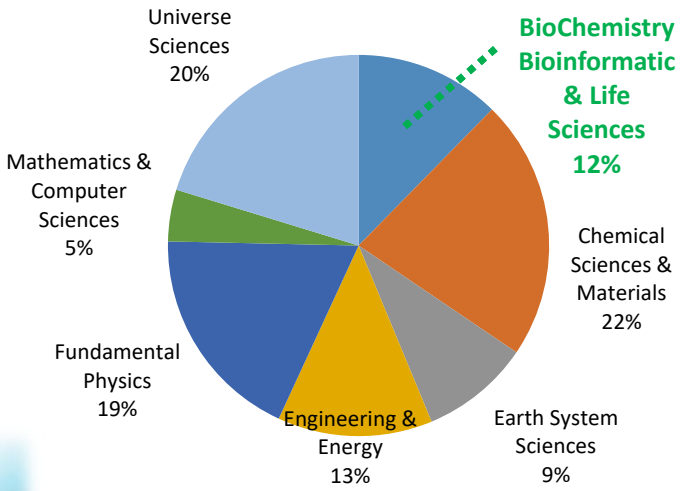
- **Systems biology is the computational and mathematical modeling of complex biological systems**
- **Modelling complex interactions within complex biological systems require powerful HPC systems**

modified from [6] Wikipedia on Systems Biology

Systems Biology – Complex Domain-Specific Terminology

- Selected terms (overlaps with many other domain-specific terminology)
  - Atoms, molecules, peptides, cells, tissue, energy fields, proteins, etc.
- Selected fields
  - Life sciences (broad), biochemistry, bioinformatics, biophysics, etc.
- Selected tasks
  - Analysis, sampling, monte carlo
- Importantance in HPC
  - Focus on the 'task at hand' in parallelization:
    Not get carried away by terminology

- **Modelling a complex biological systems requires an understanding of the complex terminology**
- **Working closely together with domain scientists ensures correct understanding & modelling ideas**

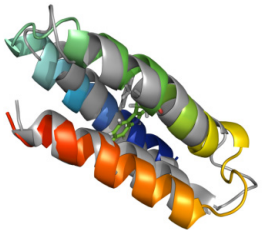


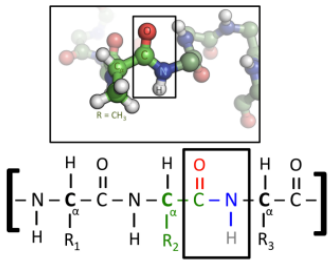
[7] PRACE Usage per community

Systems Biology – Domain-Specific Terminology – Proteins

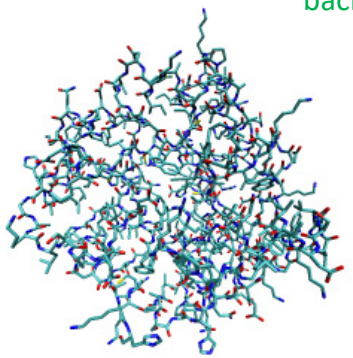
- Proteins
  - Large biological molecules that consist of one or more long chains of amino acid residues
  - Responsible for transporting molecules
  - Catalyzing and regulating biochemical reactions in the cell (or as antibodies for fighting infections)
  - E.g. 3D-structure of the 'protein triose-phosphate isomerase'

Function of a protein is closely related to its 3D shape

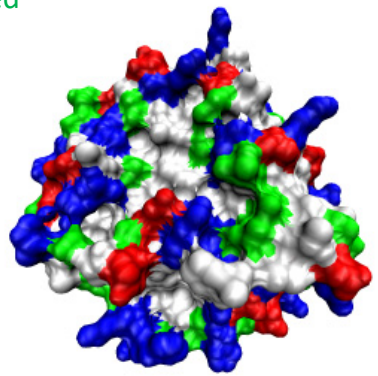




(all atom representation colored by atom type)



(simplified representation illustrating backbone conformation, colored by secondary structure)



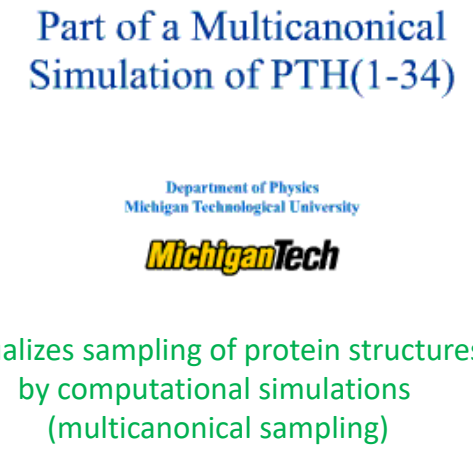
(Solvent-accessible surface representation colored by residue type – acidic residues red; basic residues blue, polar residues green, non-polar residues white)

(once linked in the protein chain, an individual amino acid is called a residue)

[8] Wikipedia on Protein

Systems Biology – Scientific Case Protein Folding (1)

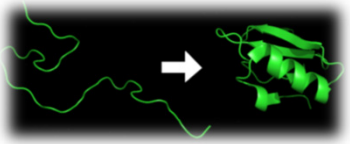
- Understanding ‘physics of the proteins‘
  - Only functional if they assume specific shapes
  - Important to explore how these structures emerge from a protein's chemical composition (sequence of amino acids as specified in the genome)
- Scientific impact
  - Lead to the rational design of novel drugs
  - Understanding of diseases that are caused by misfolding of proteins (e.g. protein mis-fold and aggregate conditions → neurological diseases)
  - Research on solutions for neurological diseases (e.g. Alzheimers)
- Computational simulations
  - Explore ‘sequence-structure relation’ – very complex problem
  - Extremely difficult for realistic protein models with high dimensionality and competing interactions



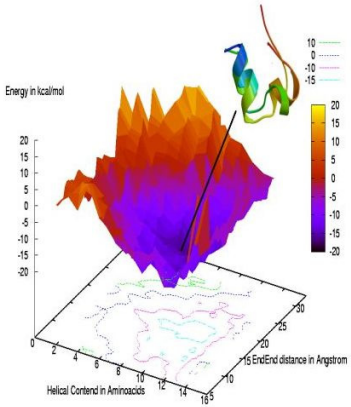
Visualizes sampling of protein structures by computational simulations (multicanonical sampling)

Systems Biology – Scientific Case Protein Folding (2)

- Need for ‘computational biophysical chemistry‘
  - Understand for a given protein the relation between its sequence of amino acids and the set of thermally accessible conformations
  - Comprehend the mechanism by which the protein folds into its native structure
- Complex systems (Protein folding is computationally hard)
  - All-atom models lead rough energy landscape
  - Probing the mechanism of folding in small proteins
  - Explore conditions under which proteins mis-fold and aggregate
  - Analysis of the energy landscape of molecules
  - Time intensive calculation of energy function → Potential for parallelization



[9] Protein Folding



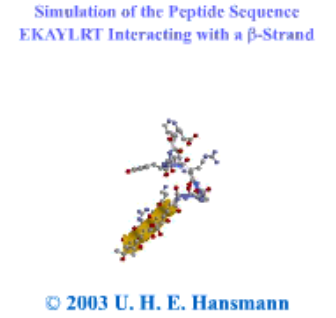
[10] A. Schug et al.

- **Understanding functions of proteins is a biological case of complex systems requiring HPC systems**

Systems Biology – SMMP Package Example (1)

- Approach
  - Time intensive calculation of energy function: parallelized calculation of the energy
  - Targets complexity through the development of numerical methods and techniques
  - Energy of a protein can be calculated by exploiting different force fields
  - Use various force fields to calculate the energy of a protein and protein-protein interactions
- Selected Features
  - Open source software package (some parts use MPI)
  - Contains various modern Monte Carlo algorithms
  - Contains more than 60 functions and subroutines

[11] Eisenmenger & Hansmann et al.



Structure of peptide (strand, alpha-helix, etc.) EKAYLRT depends on its environment

- **Simple Molecular Mechanics for Proteins (SMMP) is a parallel software tool for protein simulations**

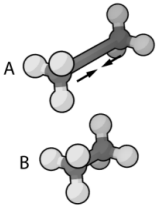
Systems Biology – SMMP Package Example (2)

- Example: Parallelization of ECEPP/3 force field *[12] J. Meinke et al.*
  - i and j are indices of atoms; r_{ij} is the distance between atom i and j,
  - L is the index of a dihedral angle in the protein chain.

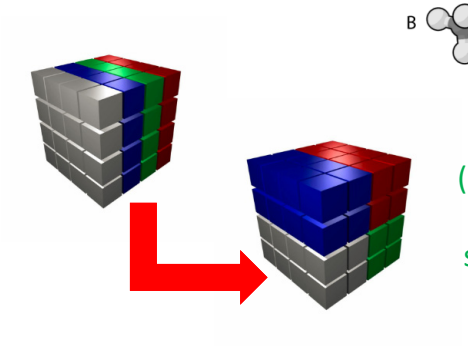
$$E_{\mathrm{ECEPP/3}} = \sum_{(i,j)} \frac{332 q_i q_j}{\epsilon r_{ij}} + \sum_{(i,j)} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) + \sum_{(i,j)} \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} \right) + \sum_{l} U_l (1 \pm \cos(n_l \xi_l)) \, ,$$

Energy function equation that needs to be calculated

(used to describe the potential energy of a system of particles (e.g. molecules and atoms)



[13] Wikipedia on 'force fields'

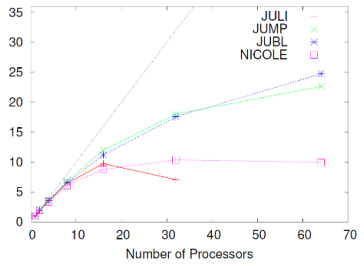


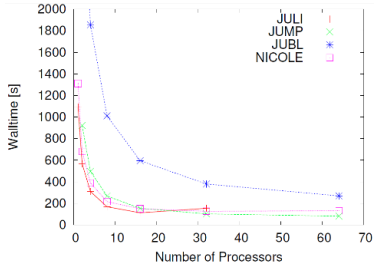
(default arrangement for 4x4x4 communicator)

(cubic arrangement of communicator scale much better)

(Monte Carlo simulation of Top7 protein – 50 sweeps)

- Selected parallelization approaches
  - Optimize MPI communicators for the energy calculation with a cubic arrangement
  - Use of sweeps of a Monte Carlo simulation (e.g. of the designed protein Top7, a 92 residue protein with 1477 atoms)





(maximum speedup 25x on JUBL – BlueGene/L System)

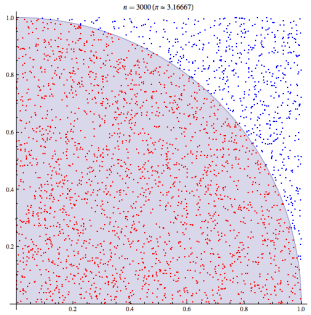
(significant reduction of used walltime)

Systems Biology – Monte Carlo Methods – Approach

- Method applicability
  - Useful when it is difficult or impossible to apply a deterministic algorithm
  - Define a domain of possible inputs
  - Generate inputs randomly from a probability distribution over the domain
  - Perform a deterministic computation on the inputs and aggregate the results

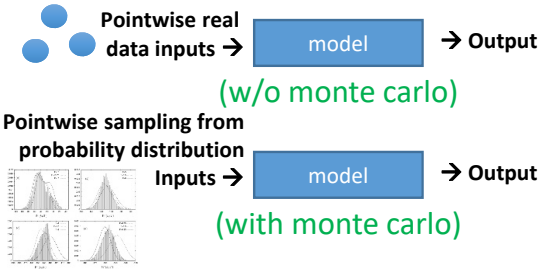
(origin related to techniques in playing & recording results in gambling casinos)

(also known as MC ensemble method)



(Example of approximating the value of pi – After placing many (30000) random sampling points, the estimate for pi is within 0.07% of the value – happens with an approximate probability of 20%)

- **Monte Carlo (MC) methods rely on repeated random sampling to obtain numerical results**
- **MC run simulations many times over to obtain the distribution of an unknown probabilistic entity**



(count the number of points inside the circle and the total number of points)

(the ratio of the two counts is an estimate of the two areas ~ pi/4)

(estimate of the two areas gives ~pi/4, so multiply with 4 to estimate pi)

[14] Wikipedia on Monte Carlo method

Systems Biology – Monte Carlo Methods – MPI Example

```
#include <math.h>
#include <mpi.h>
#include <gsl/sdl_rng.h>
#include "gsl-spring.h"

int main( int argc; char *argv[]) {
  int i, k, N;
  double u, ksum, Nsum, gsl_rng *r;
  MPI_Init(&argc,&argv);
  MPI_Comm_size(MPI_COMM_WORLD, &N);
  MPI_Comm_rank(MPI_COMM_WORLD, &k);

  r = gsl_rng_alloc(gsl_rng_spring20);

  for (i=0; i<10000; i++) {
    u = gsl_rng_uniform(r);
    ksum += exp(-u*u);
  }

  MPI_Reduce(&ksum, &Nsum, 1, MPI_DOUBLE,
          MPI_SUM, 0, MPI_COMM_WORLD);
  printf("MC estimate is %f\n", (Nsum/10000/N));
  MPI_Finalize();
  return 0;
}
```

modified from [15] MSMC

'simplified demo code'

- Include library for a parallel random number generator (PRNG) – Important part of MC!
- Initializes random number generator (with a specific type)
- Use 10000 variates on each processor to create 'local sum'
- Gsl_rng_uniform(r) function returns a double precision floating point number uniformly distributed in the range [0,1) (idea of probability distribution)
- Use MPI_Reduce to create 'global sum' and printout estimate

(MPI code prints out estimate of integral)

$$I = \int_0^1 \exp(-u^2) du$$

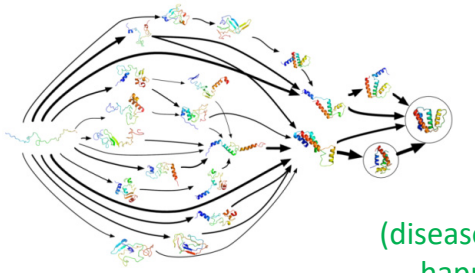
Systems Biology – Monte Carlo Methods – Example (1)

- Scientific case: Understanding protein folding & pathways
  - Proteins perform functions within living organisms (e.g. respond to stimuli)
  - Proteins differ in their sequence of amino acids, results in different foldings
  - Correct and unique 3D structure is essential to the functions of proteins

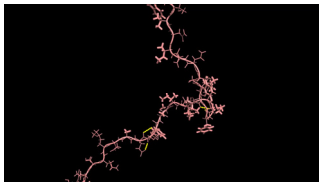
(Research 'folds' to find out what the protein does and how it does it)

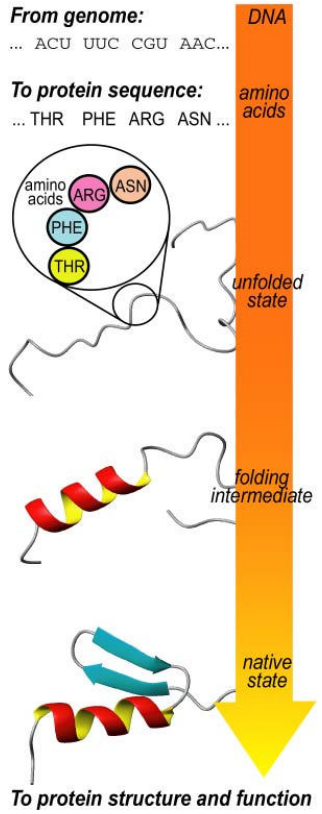
- Process of protein folding as a parallel computing application
  - Using Monte Carlo simulations
  - Simulations that use stochastic methods
  - to generate new configurations of a system
  - Initial conditions of particles, then Monte Carlo 'moves' that changes configurationof particles (if acceptance criteria is fulfilled)

(out of the astonomical number of possible ways to fold, a protein can pick one fold in microseconds)



(diseases may happen)





[17] S. Mohanty et al, JSC Simlab Biology *[16] Folding@Home*

- **The Monte Carlo 'method' is used in many parallel computing applications, e.g. also in finance**

Systems Biology – Parallel Neuroscience Application Example – Revisited

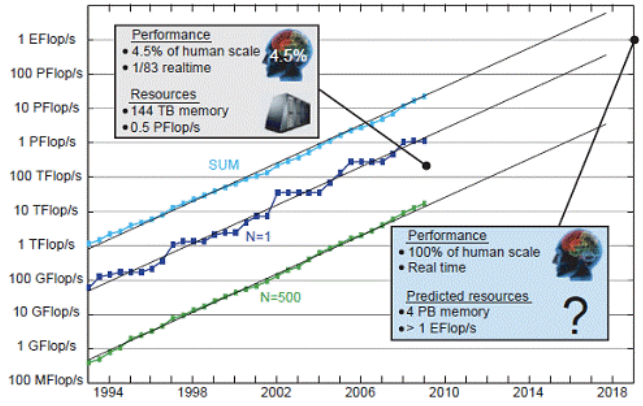
- Scientific case: understanding the function of the human brain
- Neuron/NEST code:
  - Parallel application codes to simulate biologically realistic neural networks (neurons + synapses)

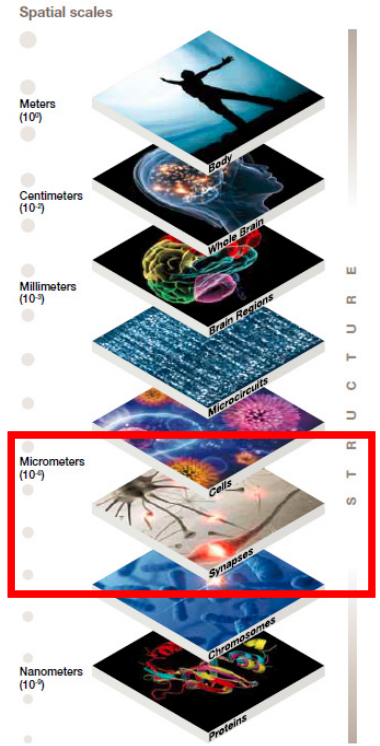
(the biggest supercomputers today just reach ~4.5% of human scale)

- Simulate models of the brain at different levels
  - Different 'granularity': Molecular, cellular, network level
  - Simulated brain will reach up to ~900 TB (Big Data!)

Simulated ~2 billion neurons

- 1 second biological time
- 40 minutes compute time (on K supercomputer)





[18] HBP Project

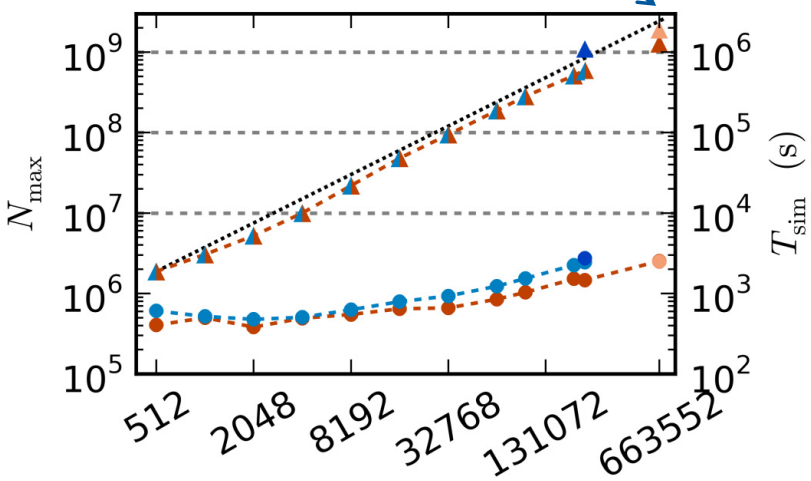
Systems Biology – Parallel Neuroscience Application Example – Revisited

- Simulations of spiking – parallel neural network models
  - Use parallelization (e.g. MPI cf. Lecture 3 and hybrid programming)

Human Brain Project

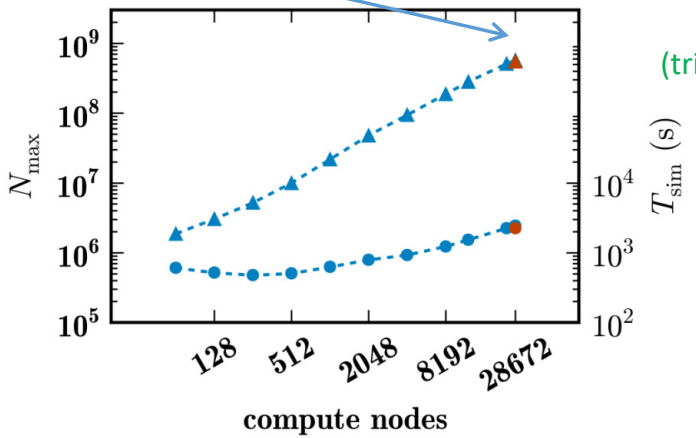
nest::

Largest spiking neural network simulation to date:
$1.86 \cdot 10^9$ neurons, $11.1 \cdot 10^{12}$ synapses



(11.250 synapses/neuron – light blue JUQUEEN, red: K computer)

550 Mio. Neurons, $5.5 \cdot 10^{12}$ synapses on 458752 cores

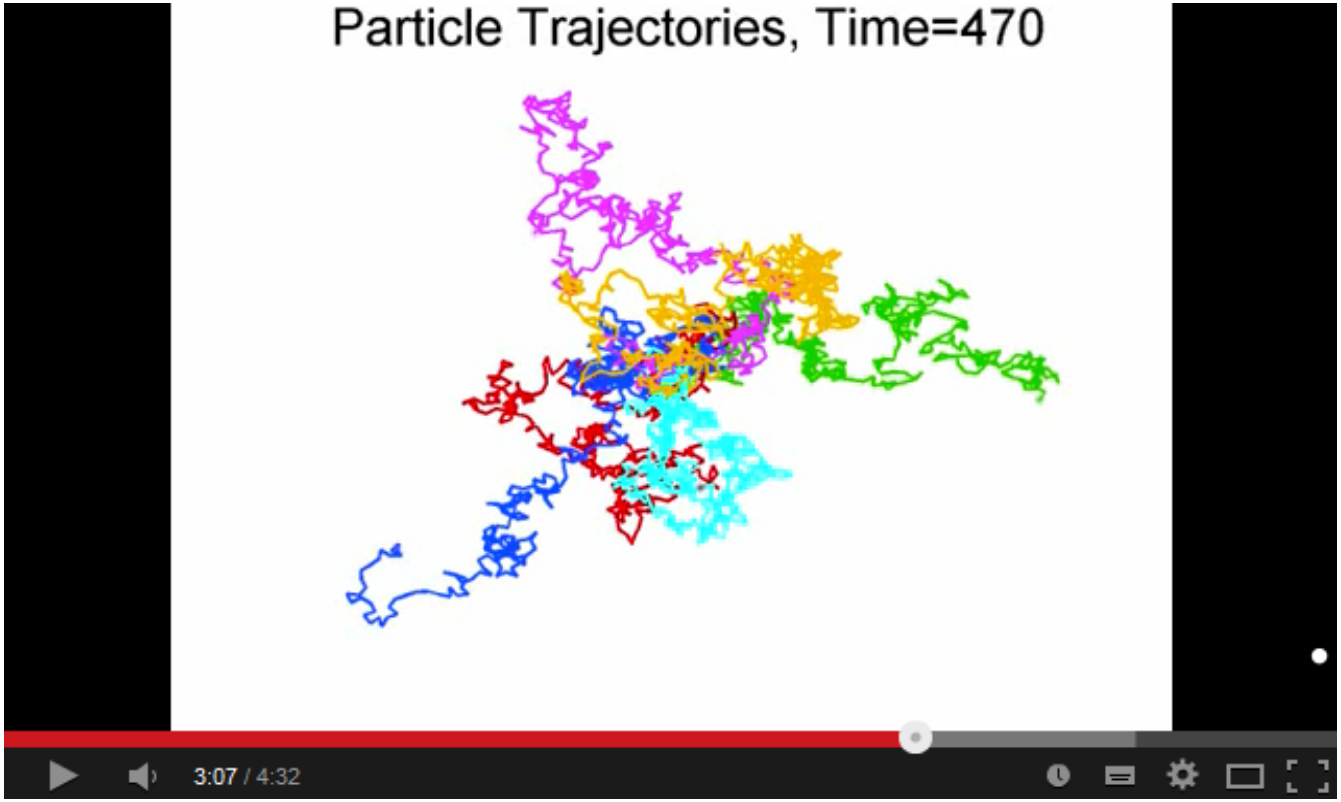


(blue: 8 threads, red: 16 threads per node)

(triangles: maximum network size, dots: simulation time)

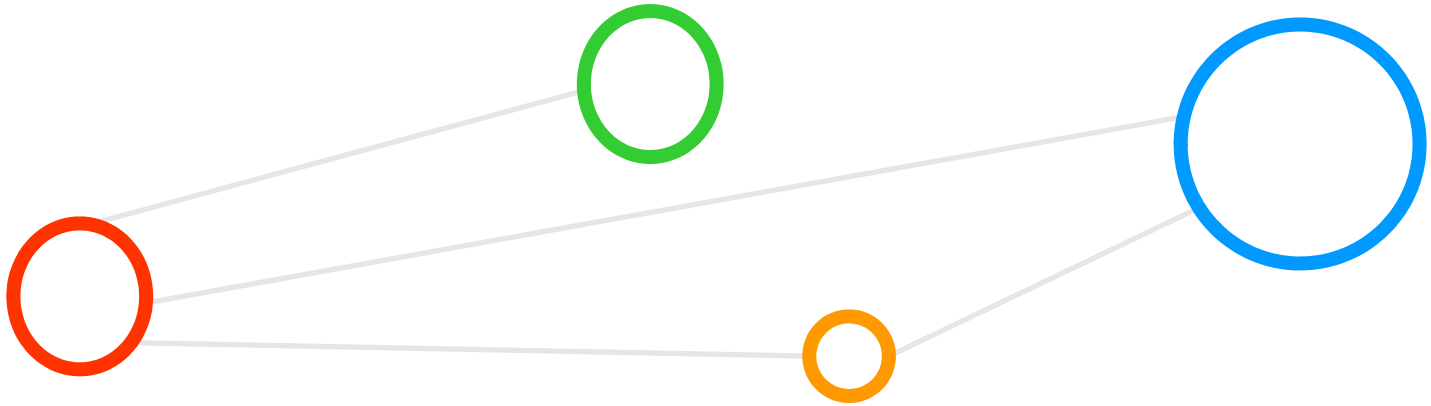
[18] HBP Project

[Video] Systems Biology – Important Monte Carlo Methods



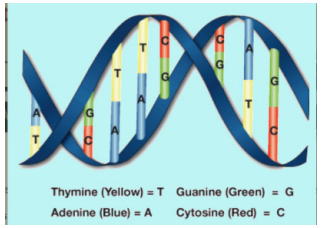
[19] YouTube Video, Monte Carlo Simulation

Bioinformatics



Bioinformatics – Motivation & BLAST Application Example

- Focus
  - Study and process biological datasets (cf. Systems Biology focus was ‘model complex systems‘)
  - Develop user-friendly tools & technologies
  - E.g. analysis of ‘DNA sequences‘
- Relationship to Systems Biology
  - Closely related with massive overlaps
  - Tools & techniques developed & exchanged
  - Datasets used in both fields from real biological systems
- BLAST Application Example
  - Scientific case: Infer functional and evolutionary relationships between gene sequences
  - General approach: Finds regions of local similarity between gene sequences
  - Two step method:
    1. Compare gene sequences to sequence databases (DBs)
    2. Calculate the statistical significance of matches



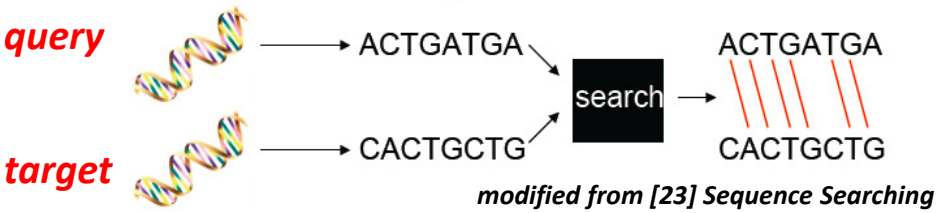
- **Bioinformatics develops methods & software tools for understanding biological datasets**
- **Interdisciplinary field combining computer science, statistics, mathematics and engineering**

- **The Basic Local Alignment Search Tool (BLAST) is one of the most known tools in comp. biology**
- **BLAST two step method: (1) Compares gene sequences to DBs (2) Calculates match significance**

modified from [22] Wikipedia on Bioinformatics ***[21] DNA sequences***

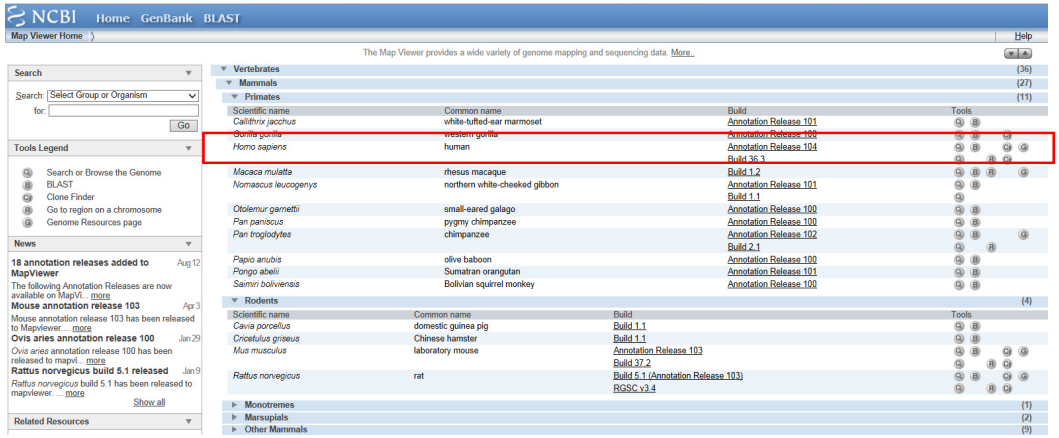
Blast Application in Computational Biology – Comparing Sequences

- Comparing sequences
  - Heuristic method → approximate solutions, exact is too compute-intensive
  - Finds similar sequences not by comparing either sequence in its entirety
  - Locates short matches between the two sequences to find similar ones
- Algorithm (many optimizations and variations exist)
  - Input A: Query sequence to search for
  - Input B: Sequence(s) to search against (target sequence)
    (Use of sequence DB here enables comparison with n sequences)
  - Output: Found sub-sequences in target/DB similar to subsequences in query



modified from [23] Sequence Searching

[24] NCBI GenBank Genomic BLAST databases

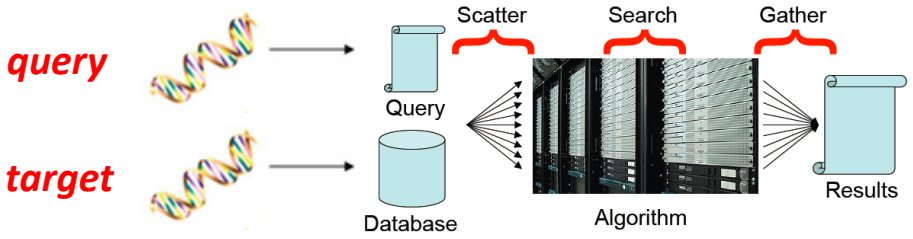


Blast Application in Computational Biology – Parallelization Approach

- Parallelization
  1. Apply a good parallelization method (e.g. domain decomposition or general parallelization approach)
  2. Write 'manually' good MPI (or OpenMP) code for (technical) communication between processors (e.g. across 1024 cores)
     - In this case the MPI implementation exists already: mpiBLAST
     - (practice: several different parallel implementations of BLAST exist)
- mpiBLAST as 'parallel computing application'
  - Open Source, parallel MPI implementation of BLAST

[25] MPI Blast

Master-worker scheme (cf. Lecture 3)



- **As the searches are independent from each other we can use parallel libraries to split the whole 'big search query' into smaller independent 'search tasks' computed in parallel**

- **As in many cases within parallel application development, commonly needed libraries or implementations of algorithms are already existing and should be re-used where possible**

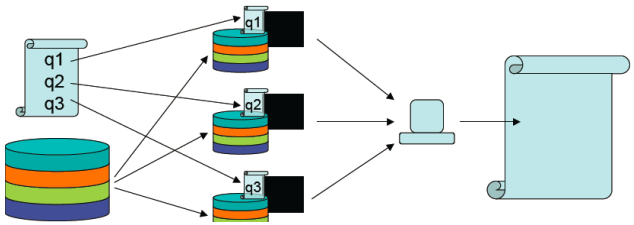
```
int main( int argc, char* argv[] ) {
  …
  MPI_Init(&argc, &argv);
  MPI_Comm_rank(MPI_COMM_WORLD, &rank);
  MPI_Comm_size(MPI_COMM_WORLD, &node_count);
  …
  MPI_Barrier(MPI_COMM_WORLD);
  …
  MPI_Finalize();
  …
}
```

mpiblast.cpp

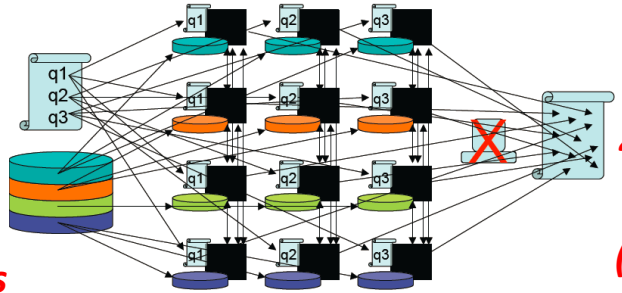
Blast Application in Computational Biology – Parallel I/O Approach

- I/O Approach
  - Integrate well technical code with 'problem-domain code' (e.g. target database data & data distribution)

'Distribute DB & Query fragments'



Knowing…
… system architecture
… parallel file system
… available memory
… MPI instead of files
… using communicators

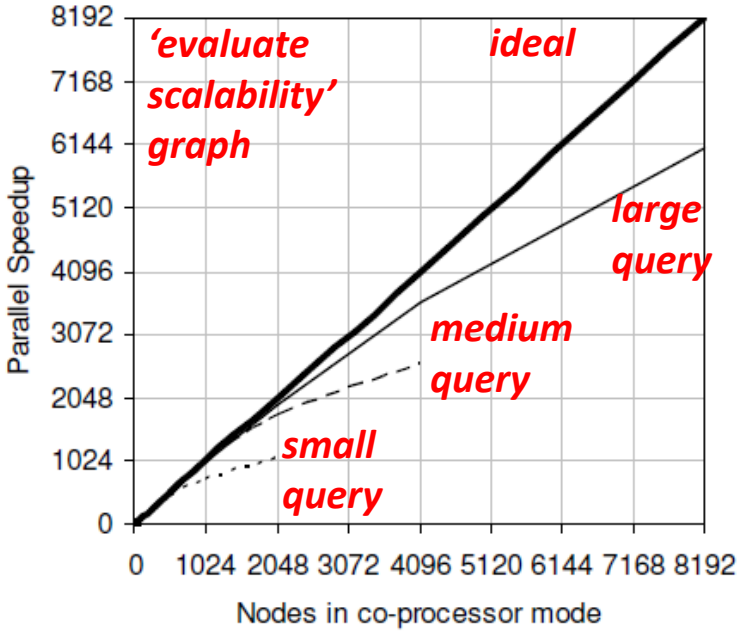


'not well integrated' → scalability limits (master bottleneck, IO, load imbalancing,…)

'optimizations' (e.g. think about I/O & network)

'well integrated' → truly scalable (parallel IO, multiple masters)

- **Achieving a speedup of 'processing some problem space data sets' is one of the major motivations of creating parallel computing applications that users can really experience**



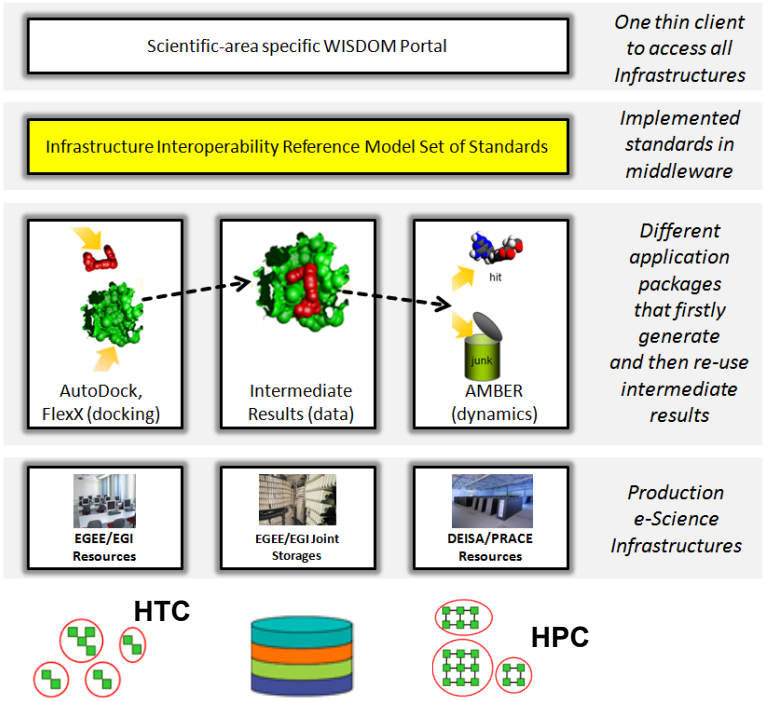
- **Optimizations in various forms and using a wide variety of different approaches can lead to significant improvements in speed-up of the parallel computing application**

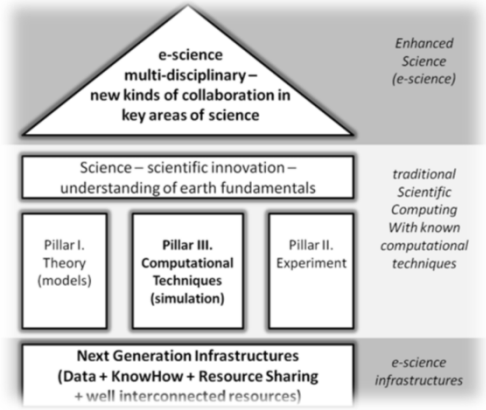
modified from [26] O. Thorsen et al., Parallel Genome Sequence Search

[23] Sequence Searching

Bioinformatics – Drug Development using Scalable Computing Infrastructures

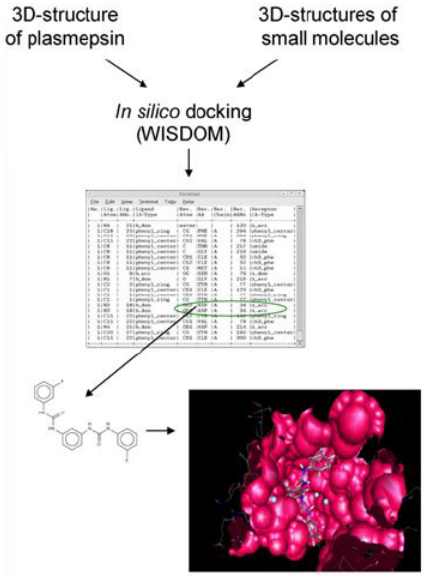
- Use of Interoperability of two different computing paradigms
  - E.g. use of HTC in EGI & HPC in PRACE infrastructures (cf. Short Lecture 11)





[27] M. Riedel et al., 'Research Advances by using interoperable e-Science Infrastructures', 2009

(Web-based portal make complex infrastructure access easy for biological domain scientists)

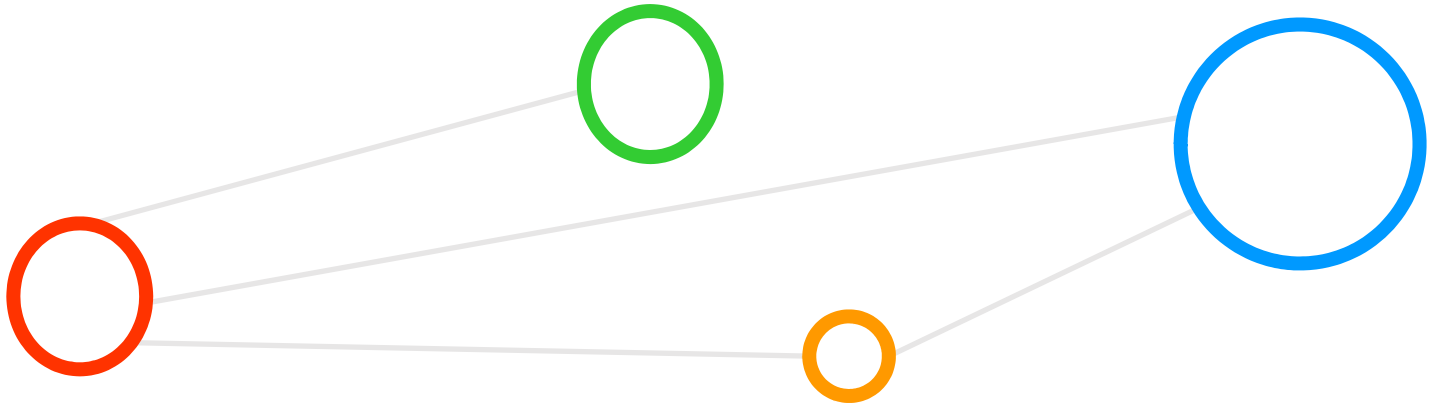


➢ **Lecture 14 will provide more pieces of information about molecular systems & libraries as well as selected parallel application methods**

[Video] Systems Biology & Bioinformatics in Neuroscience

[20] YouTube Video, Human Brain Project

Lecture Bibliography



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