Searching For A New Drug on Computational Grid

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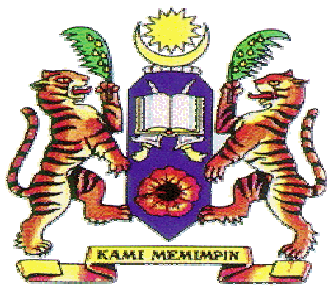
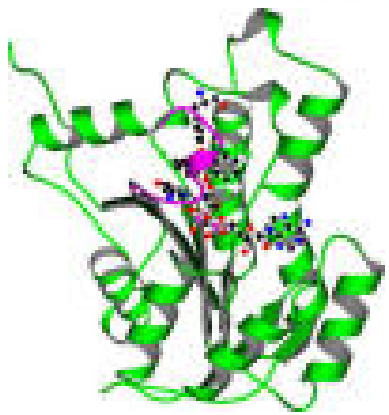


GGF7, Tokyo, Japan. 6th March, 2003

Introduction

- Drug discovery
  - Complex and expensive undertaking.
  - ~$800mil (Tuft Center)
  - 12-15 years.
- Effort to cut down the research timeline and cost
  - by reducing wet-lab experiments
  - use computer modelling.

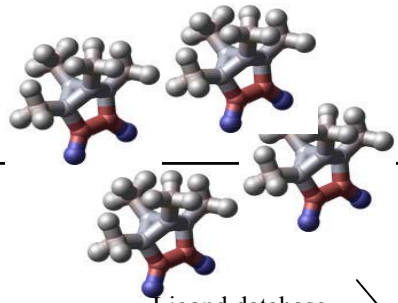


Outline:

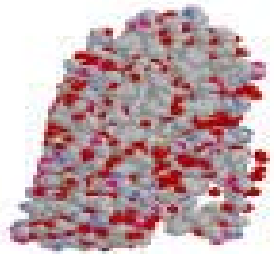
- **Brief introduction to the application (area)**
- Reasons for using Grids?
- Problems of:
  - building a testbed/production grid
  - writing/running your applications

Area of application:

- Computational Biology
  - Specifically structure-based drug design involving protein-drug binding
  - One of the methods in rational drug design
  - Can be applied in molecular biology
  - Enzyme-substrate/inhibitor complex
  - Protein function, mutation and resistence.

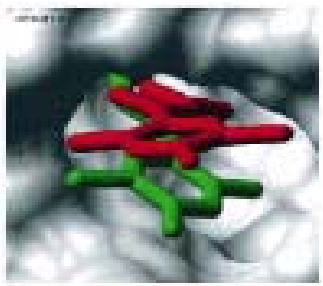


Ligand database



Target Protein

Protein-Ligand docking



Ligand docked into protein's active site

Outline:

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  - writing/running your applications

Reasons for using Grid

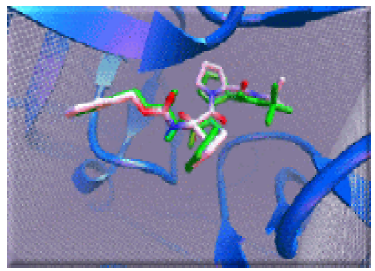
- In usual virtual drug discovery, thousands of compounds screened onto its target.
- Each compound-target interaction requires extensive computation, typically about a day calculation on a workstation.
- Protein-ligand studies – very popular in Malaysia.
- Promote computational modelling in these studies.
- Make the Computation looks effortless for biologist – i.e. they just send the input files to the program and the program will do the rest.

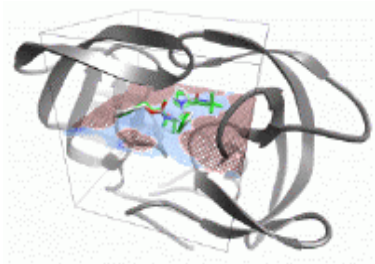
Reasons for using Grid

- Workstation is very expensive in Malaysia
- Computation on the grid environment provide opportunities for:
  - **Harnessing CPU cycle**
  - **Accessing remote databases**
  - **User friendly – instructions are clear**
  - **Effortless computation**
  - **Easy obtaining the output**

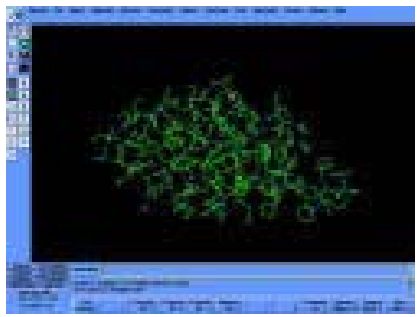
Searching for a drug on the Grid

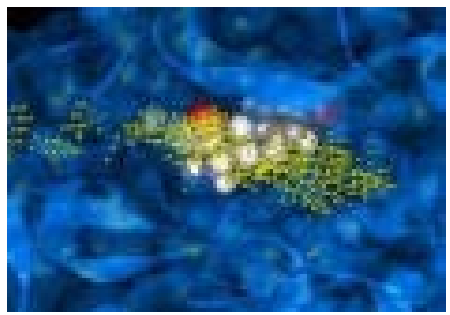
- Molecular Docking
  - Autodock 3.05



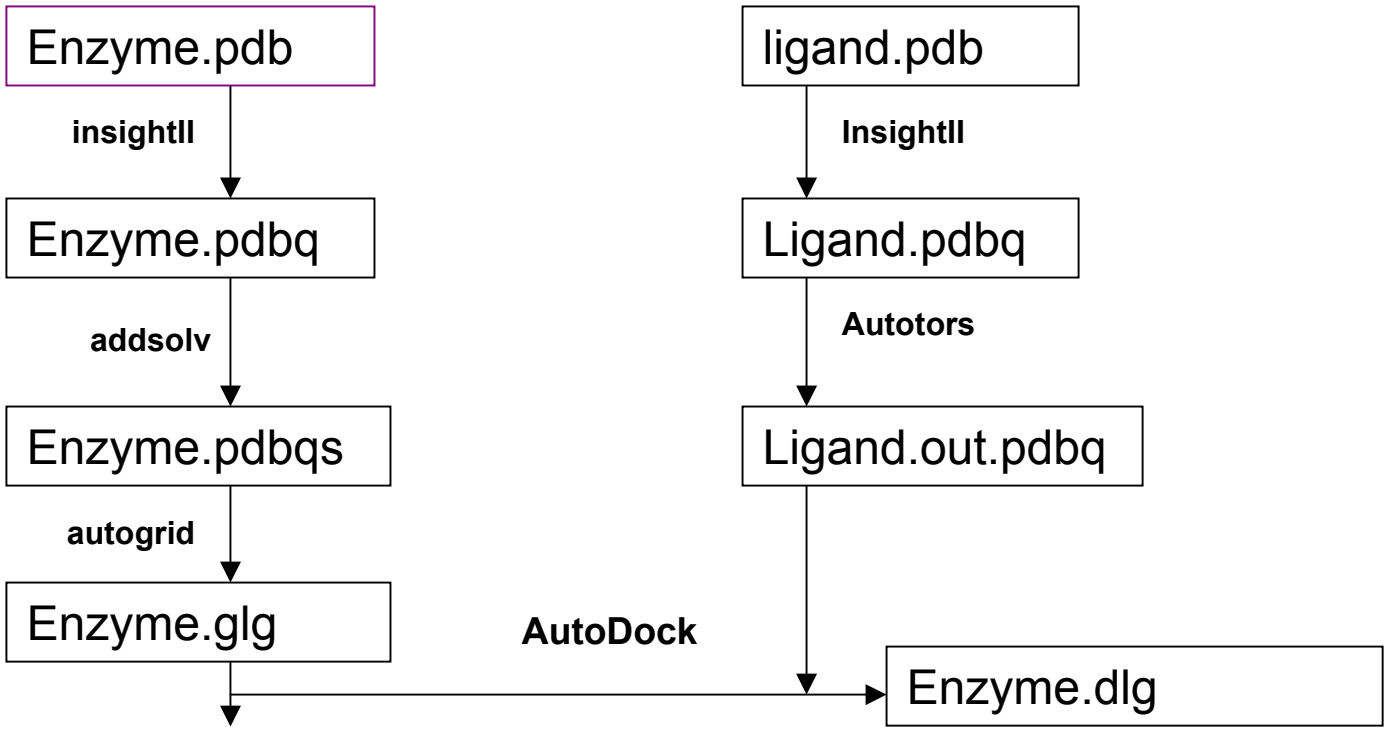


- Visualization
  - Rasmol
  - Chimes

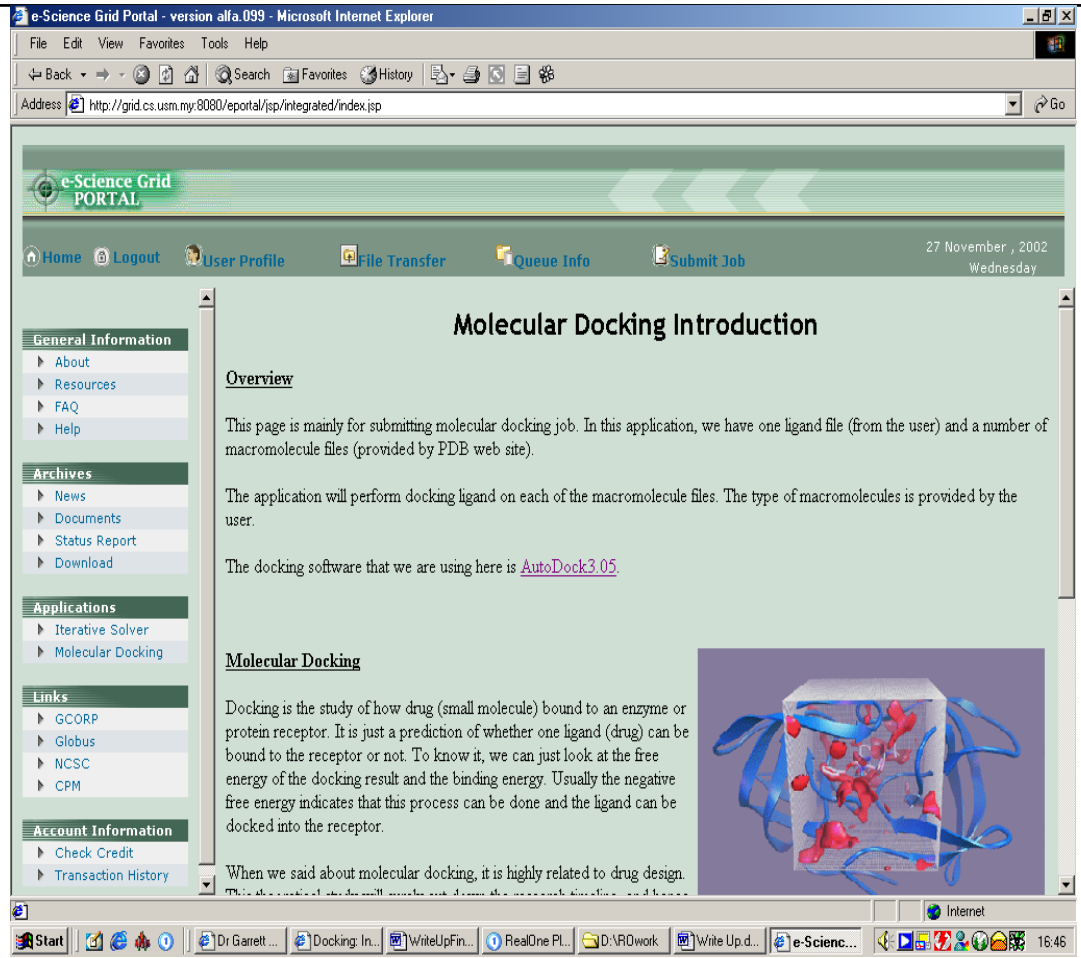




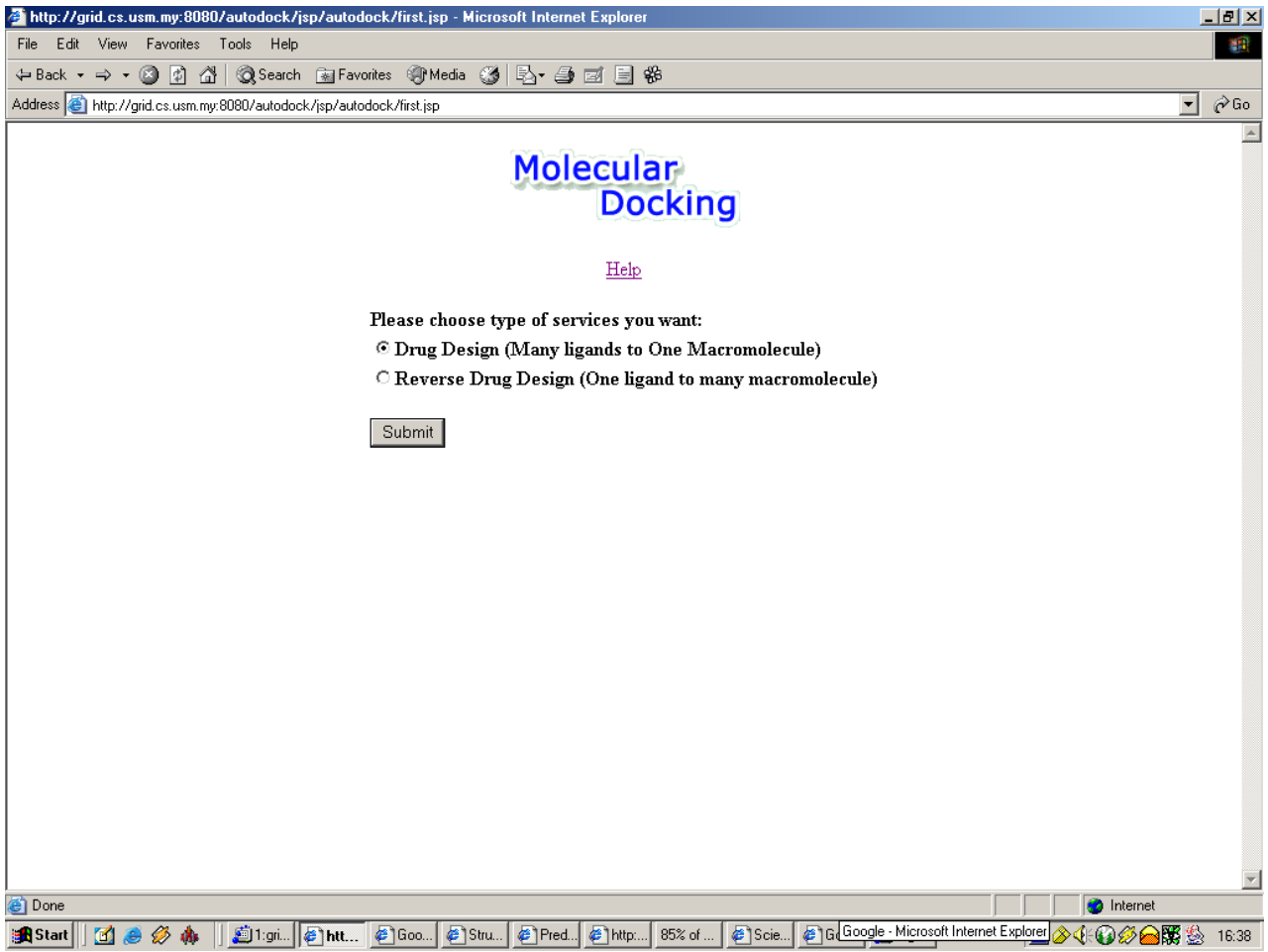
Setting-Up AutoDock



Molecular Docking Introduction Page



Input Page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Please choose type of services you want:
Drug Design (Many ligands to One Macromolecule)
Reverse Drug Design (One ligand to many macromolecule)
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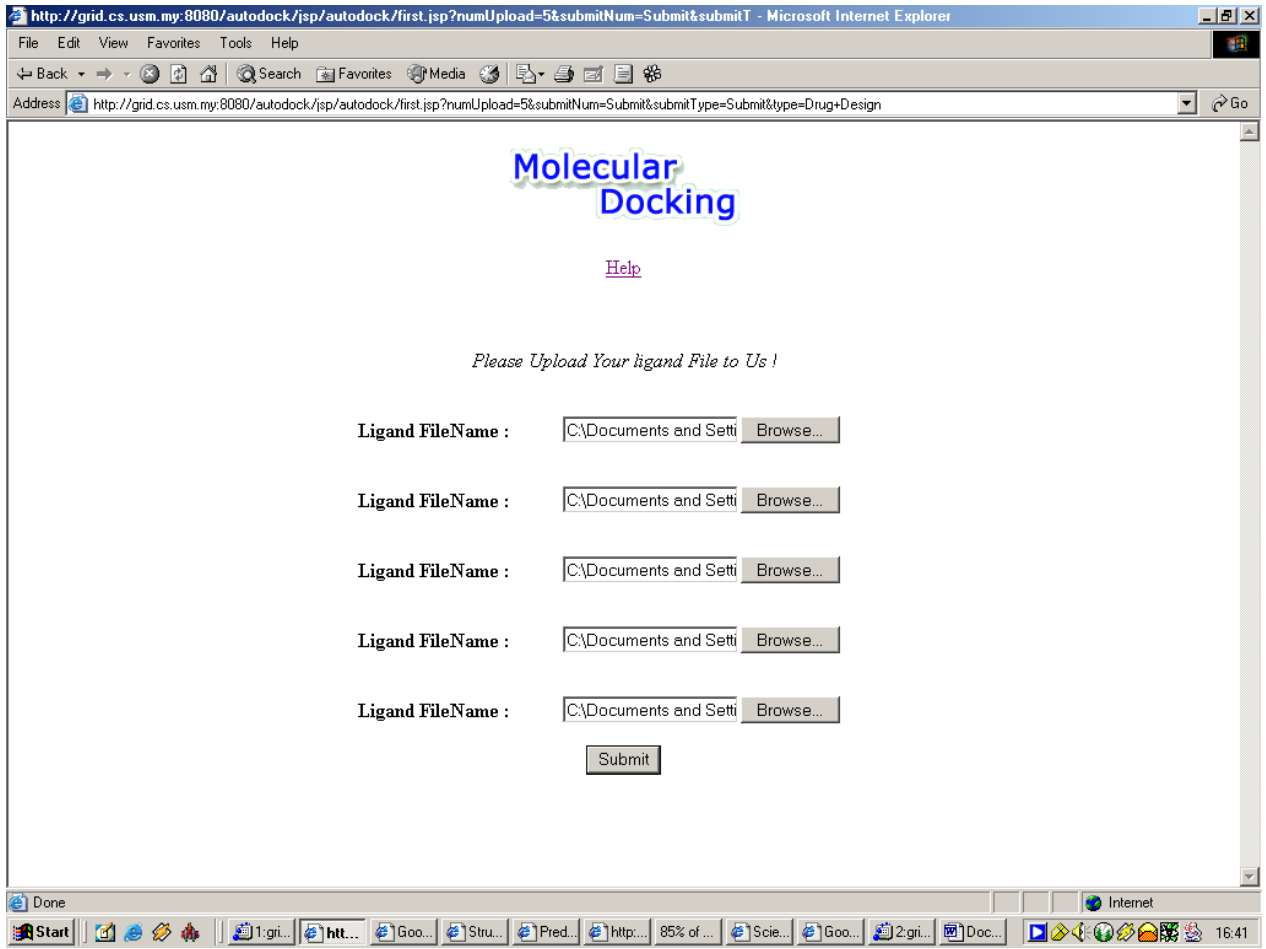
Input Page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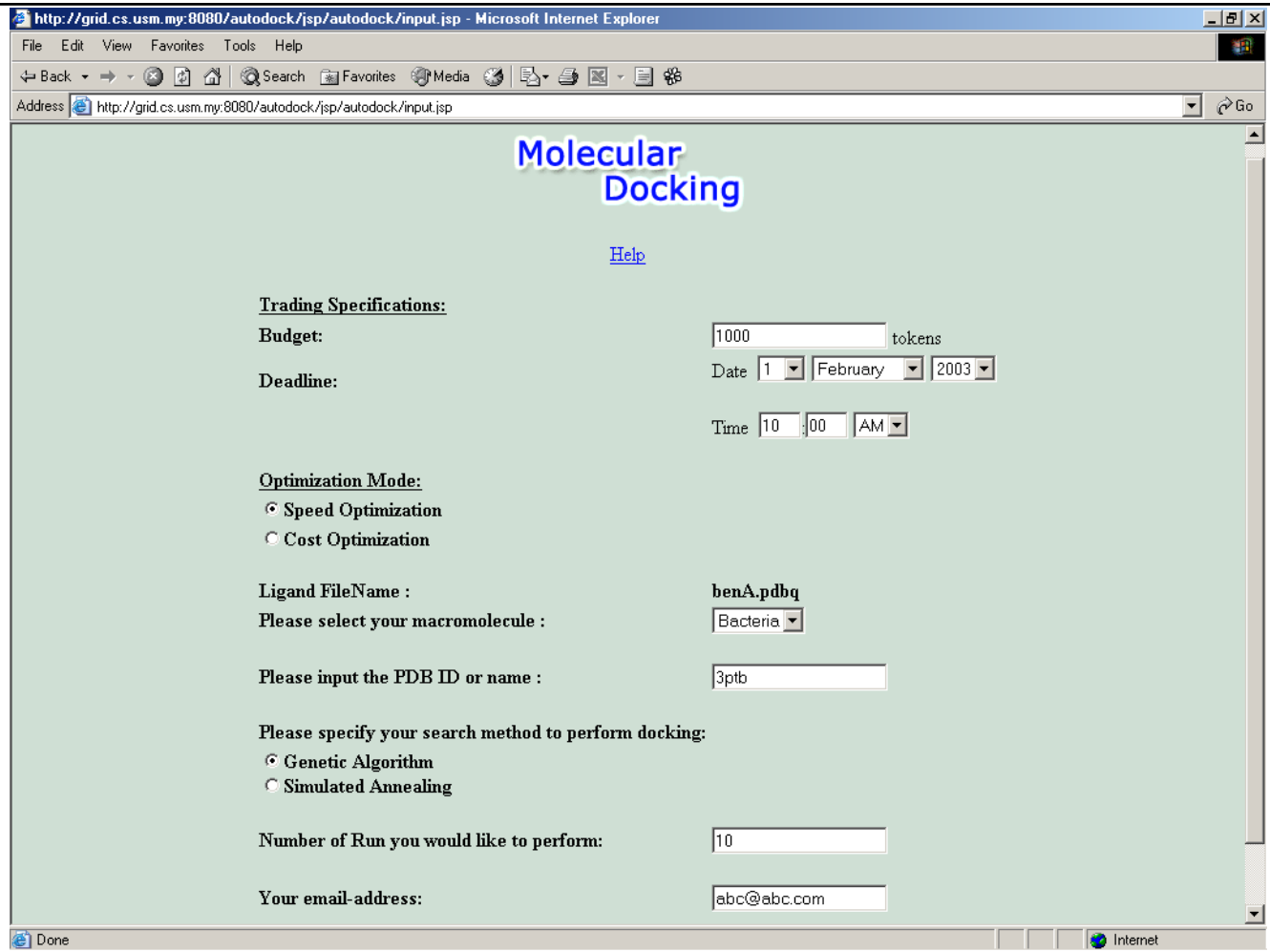
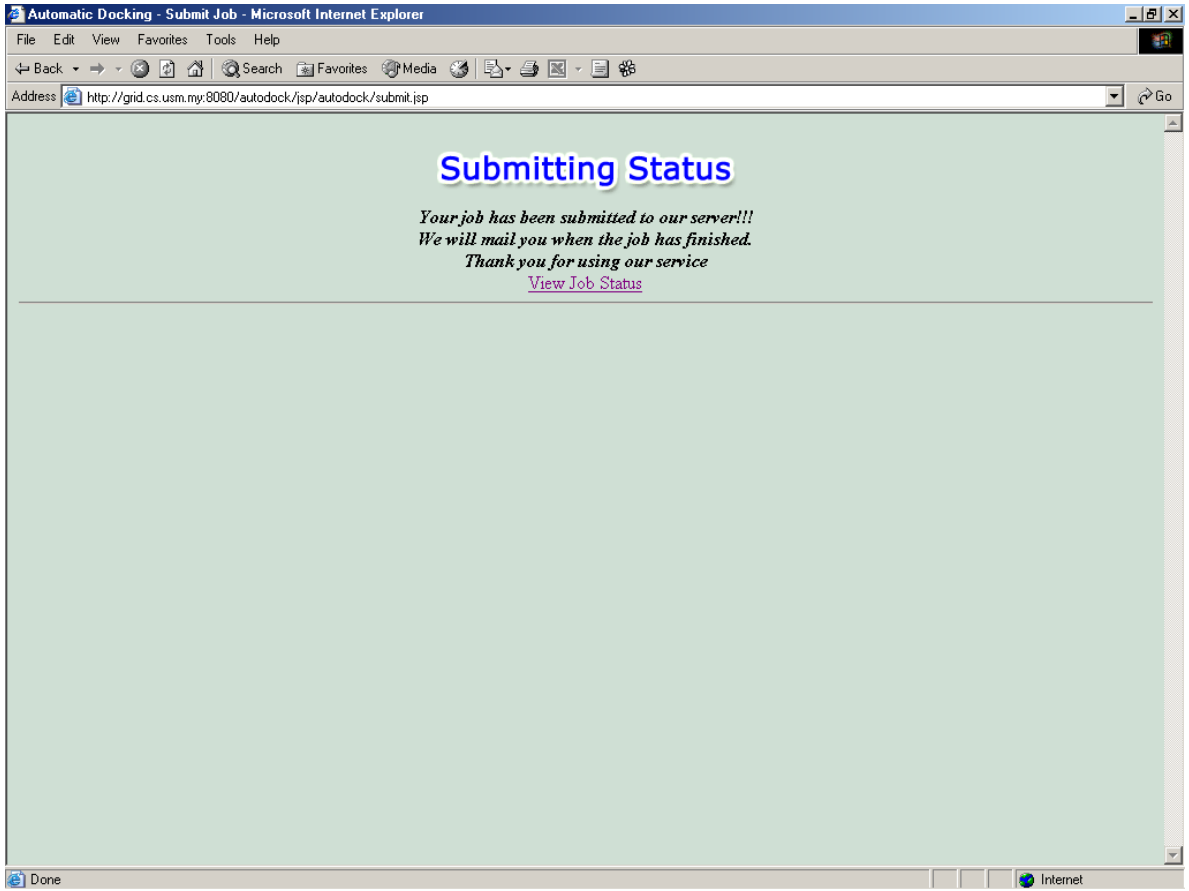
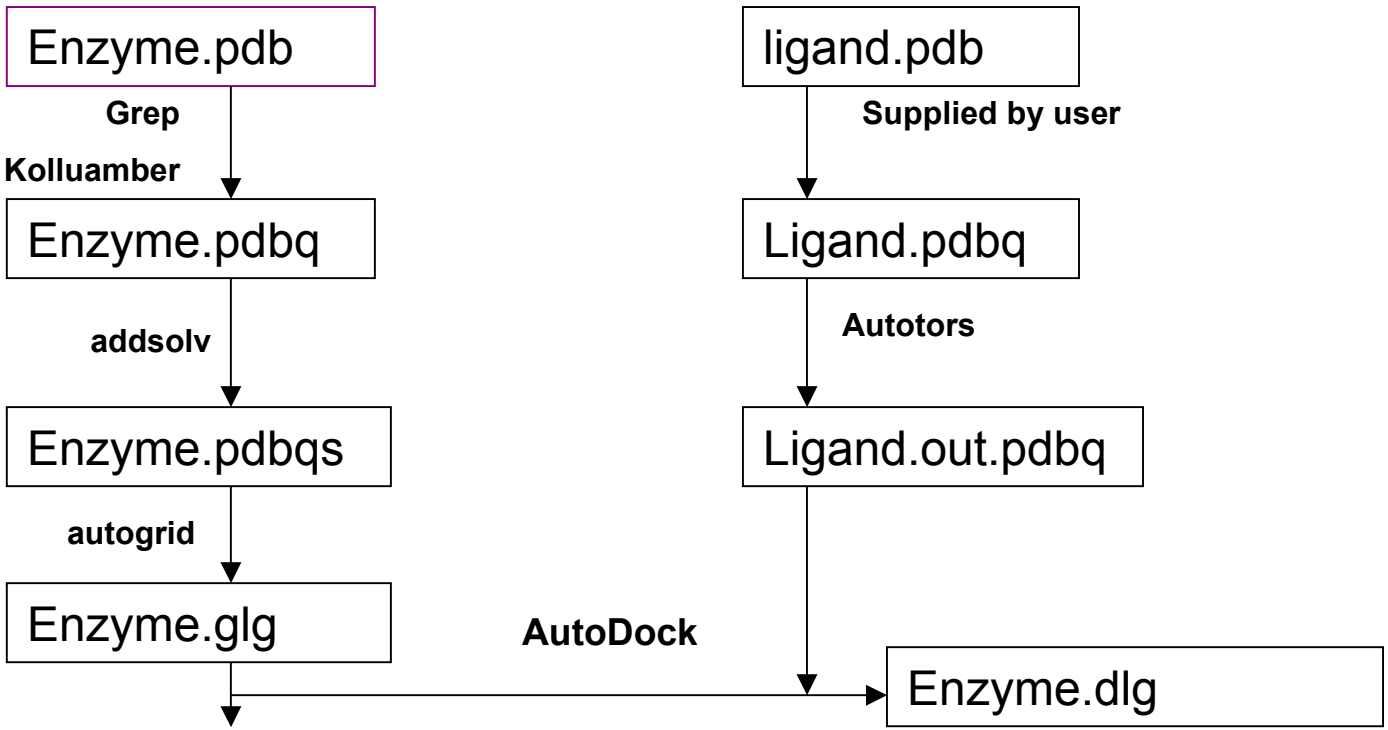


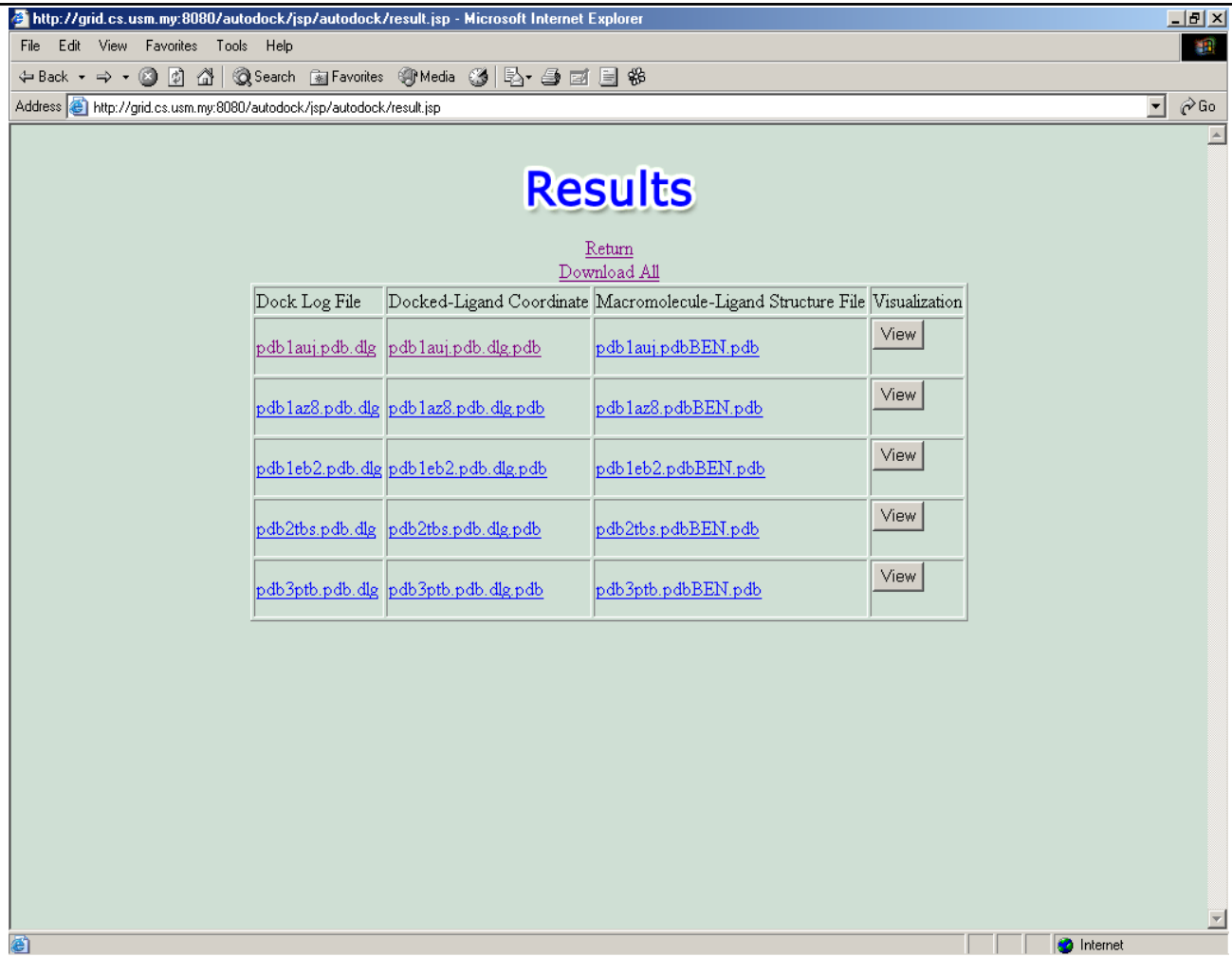
Submitting Job



AutoDock on the grid



Results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Macromolecule-Ligand Structure File
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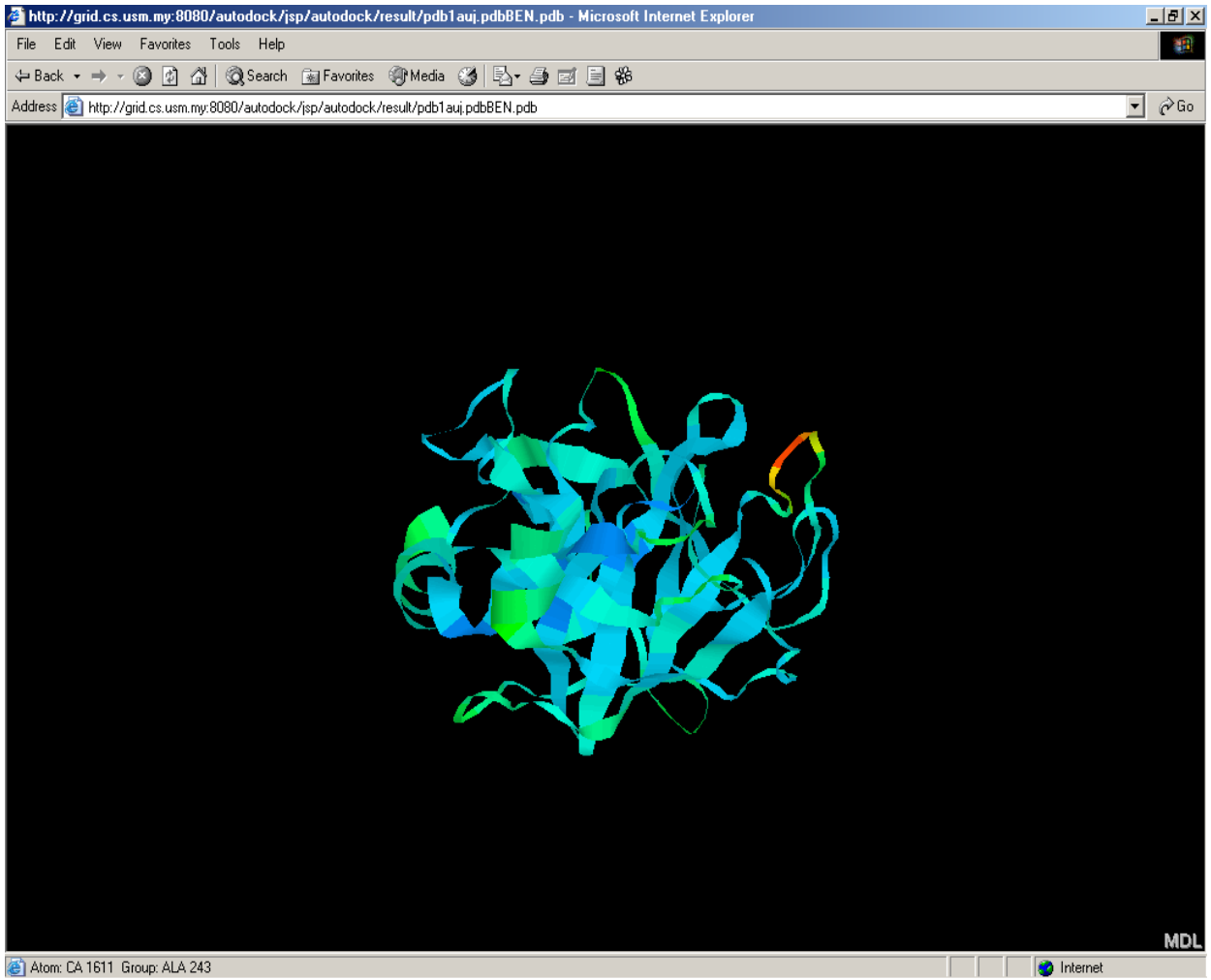
- Results (in visualization form)



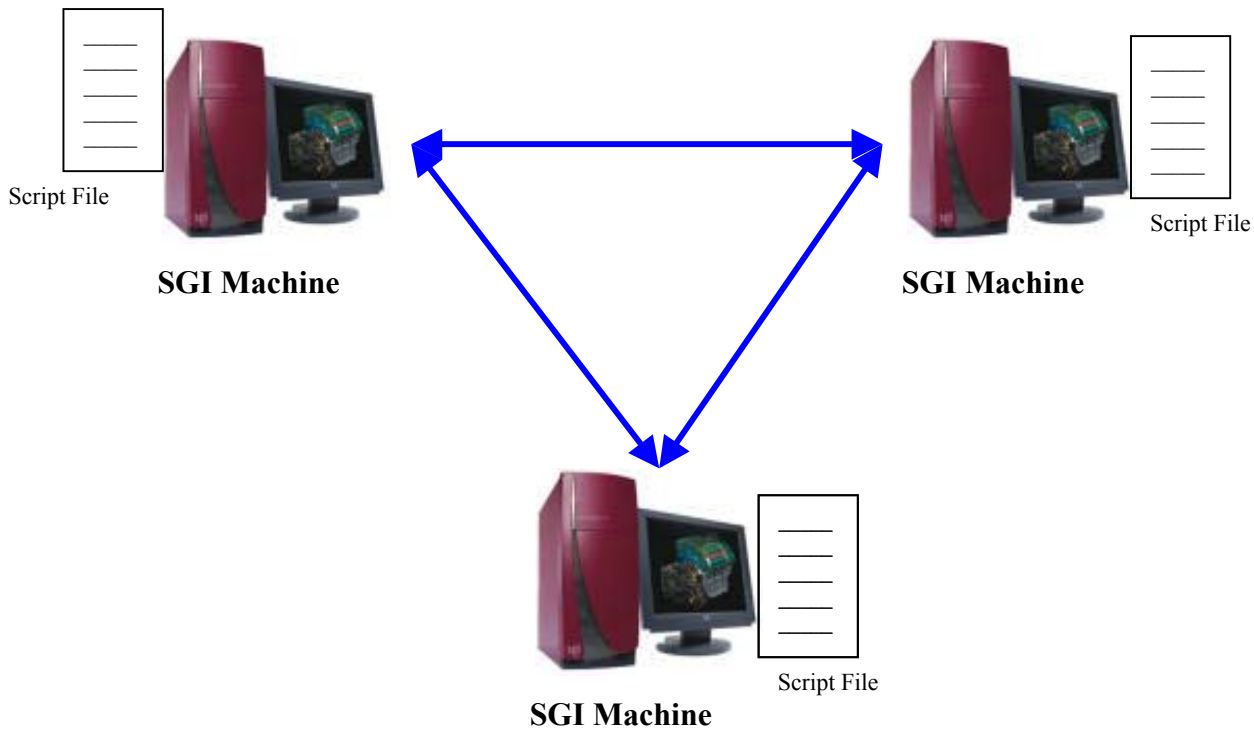
Benchmarking….

- Testing on 3 SGI machines
- Testing on 3 Linux Machines
  - Pentium IV 1.70 GHz , 256 MB Memory
  - Pentium III 1000 MHz , 512 MB Memory
- Data / Molecules:
  - Macromolecule of wild and mutant type
  - 14 types of ligands
  - Total number of docking = 14 x 2 = 28

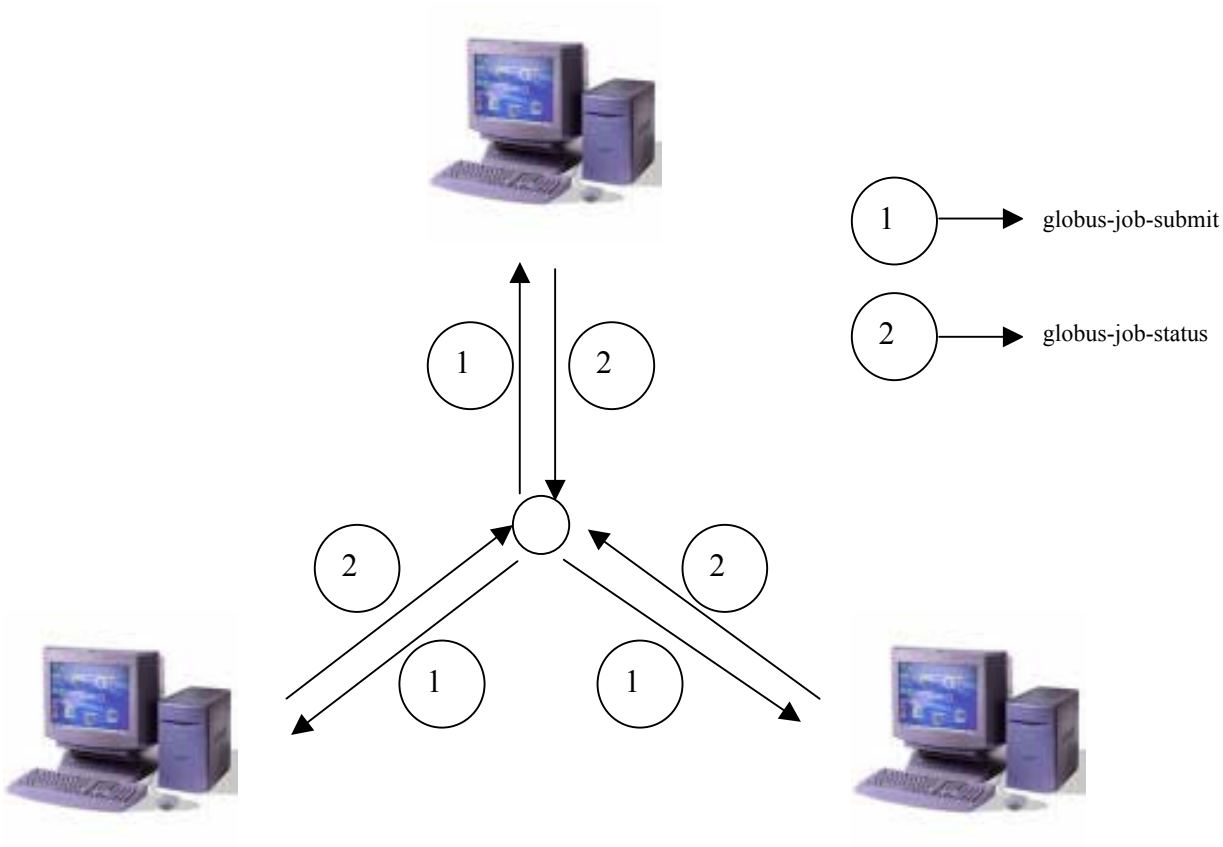
Searching For A New Anti-tuberculosis Drug on the GRID

- One third of the world population is infected.
- Multi-drug resistant especially in HIV/AIDS patients
- As much as 30% on INH (front-line drug) resistant strain
- Use AutoDock3.1 to understand drug(s) interaction with its MTB protein target.
- 16 INH derivatives synthesised in USM subjected Molecular Docking experiment on the grid to choose which of the derivatives would be a good alternative to INH

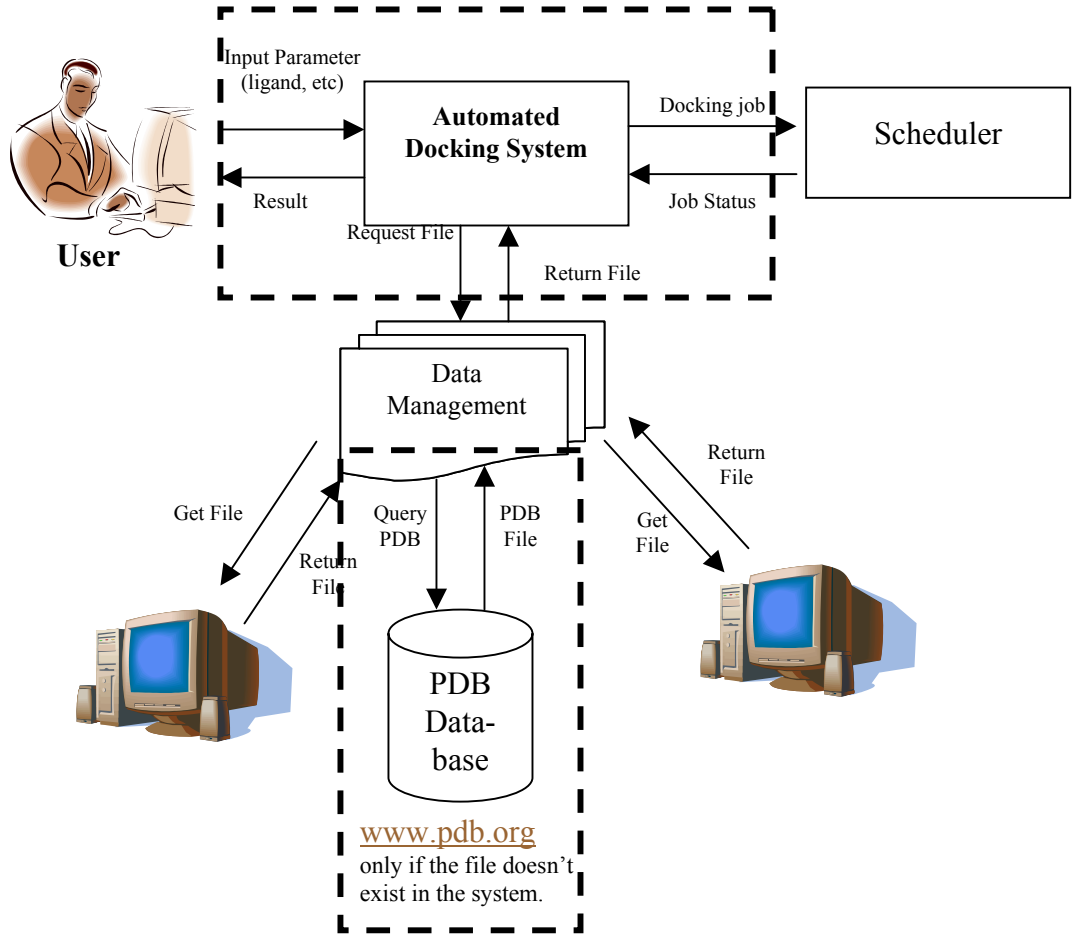
Testing Method (on SGI)



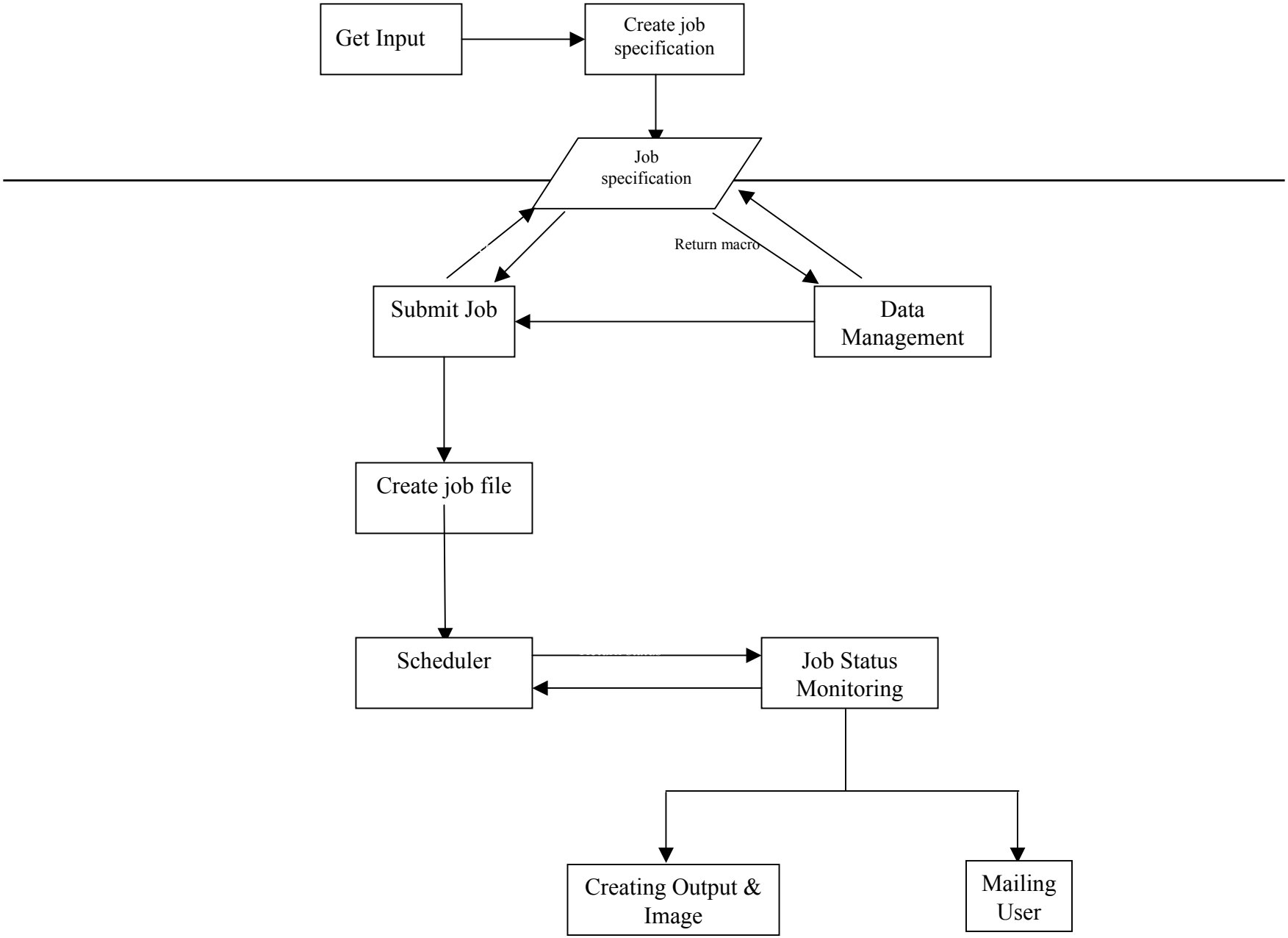
Testing Method (on Linux)



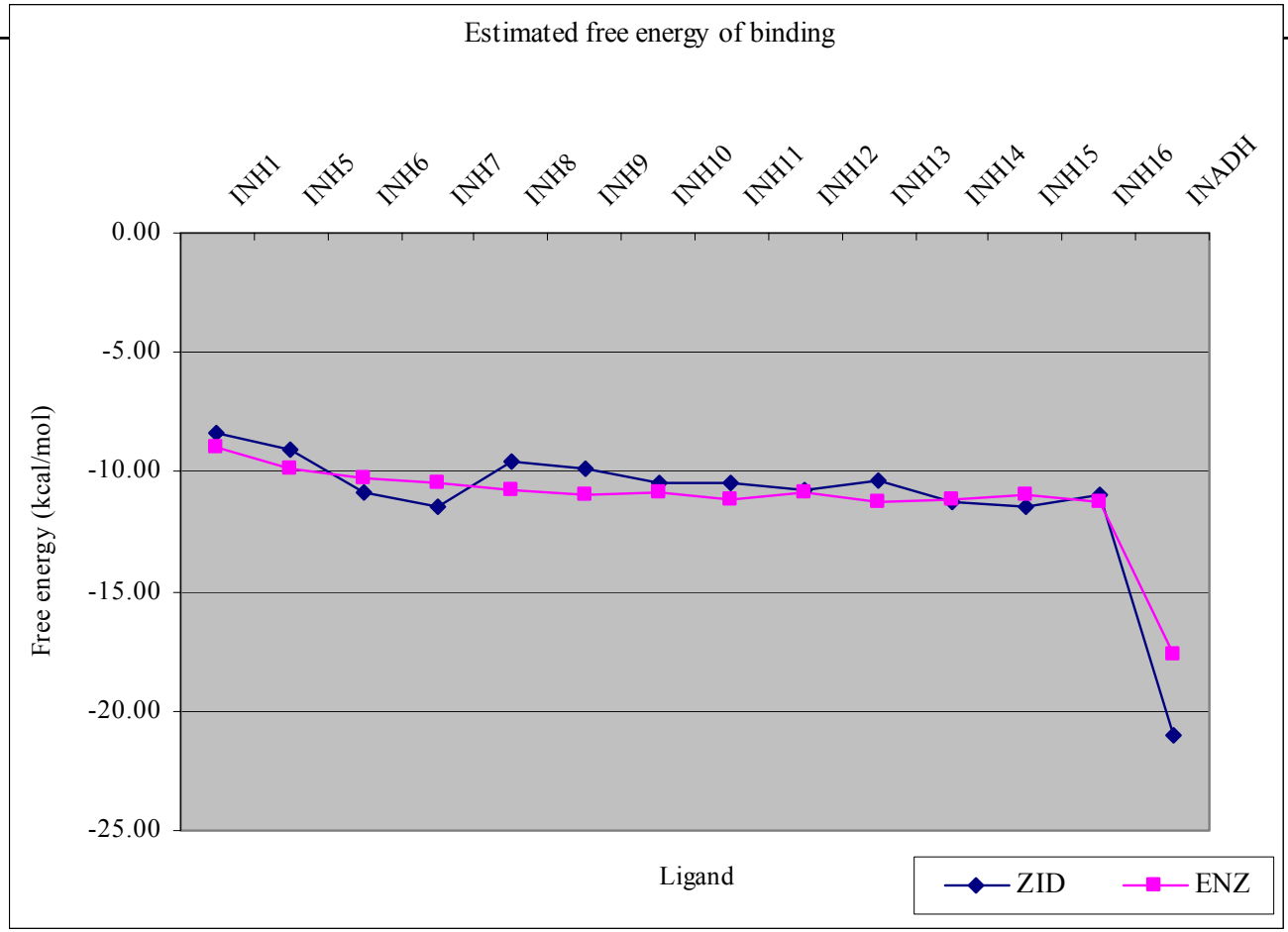
Overall Flow of Automated Docking System



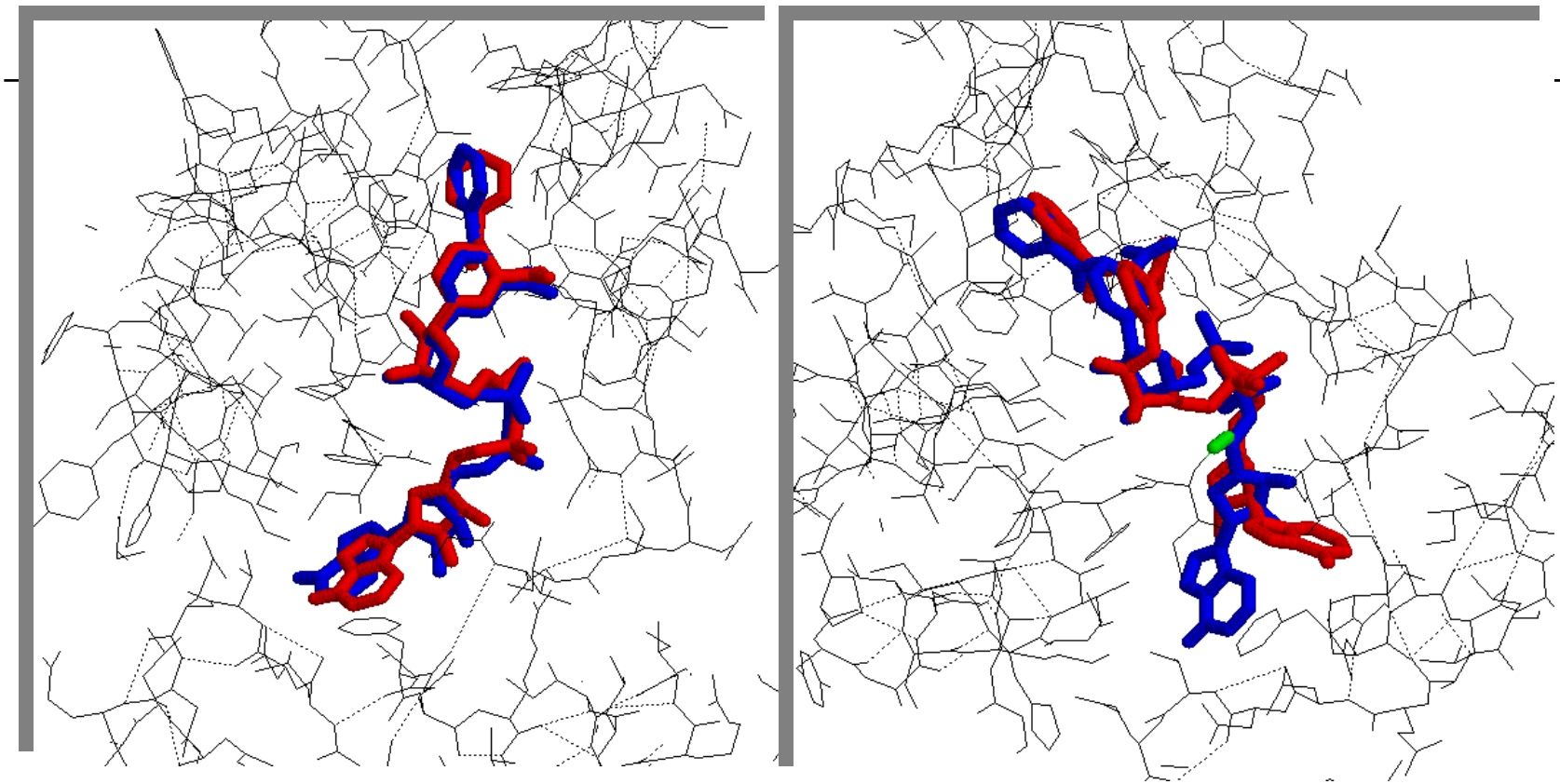
Automated Docking System: The steps in Automated Docking



Result


Estimated free energy of binding
INH1
INH5
INH6
INH7
INH8
INH9
INH10
INH11
INH12
INH13
INH14
INH15
INH16
INADH
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
Free energy (kcal/mol)
Ligand
ZID
ENZ

Result



Result (total time)

On SGI	On Linux PC
220h 24min 59.34s (1 machine= 73h 8min 21.11s)	333 hrs 1 min 22 s (1 machine= 111h 0min 27s)

Result ($/time)

On SGI	On Linux PC
$1.85/min (1 machine= ~USD25K)	$0.075/min (1 machine= ~USD 1.5K)

Outline:

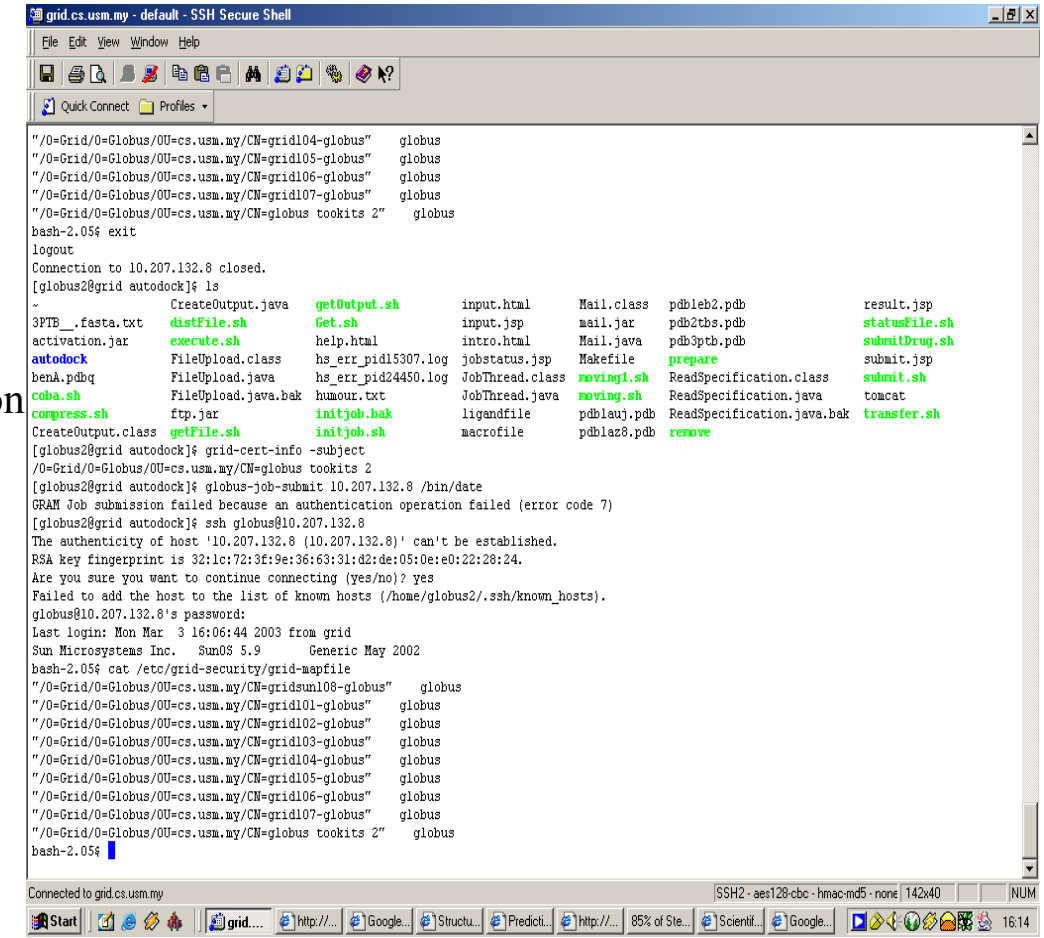
- Brief introduction to the application (area)
- Reasons for using Grids?
- **Problems of:**
  - **- building a testbed/production grid**
  - **- writing/running applications**

Problems:

- Testbeds:
  - This is a our pleminary work in integrating an application on the grid environment.
  - Our test-beds are very minute, only local PC – homogenous platform (only 3 to be precise!).
  - Globus was installed in each PC and job submission is through local server.
  - Still working on building testbed – 2*16 nodes clusters are still in tender process.
  - Looking to tap ApGrid and PRAGMA testbeds.

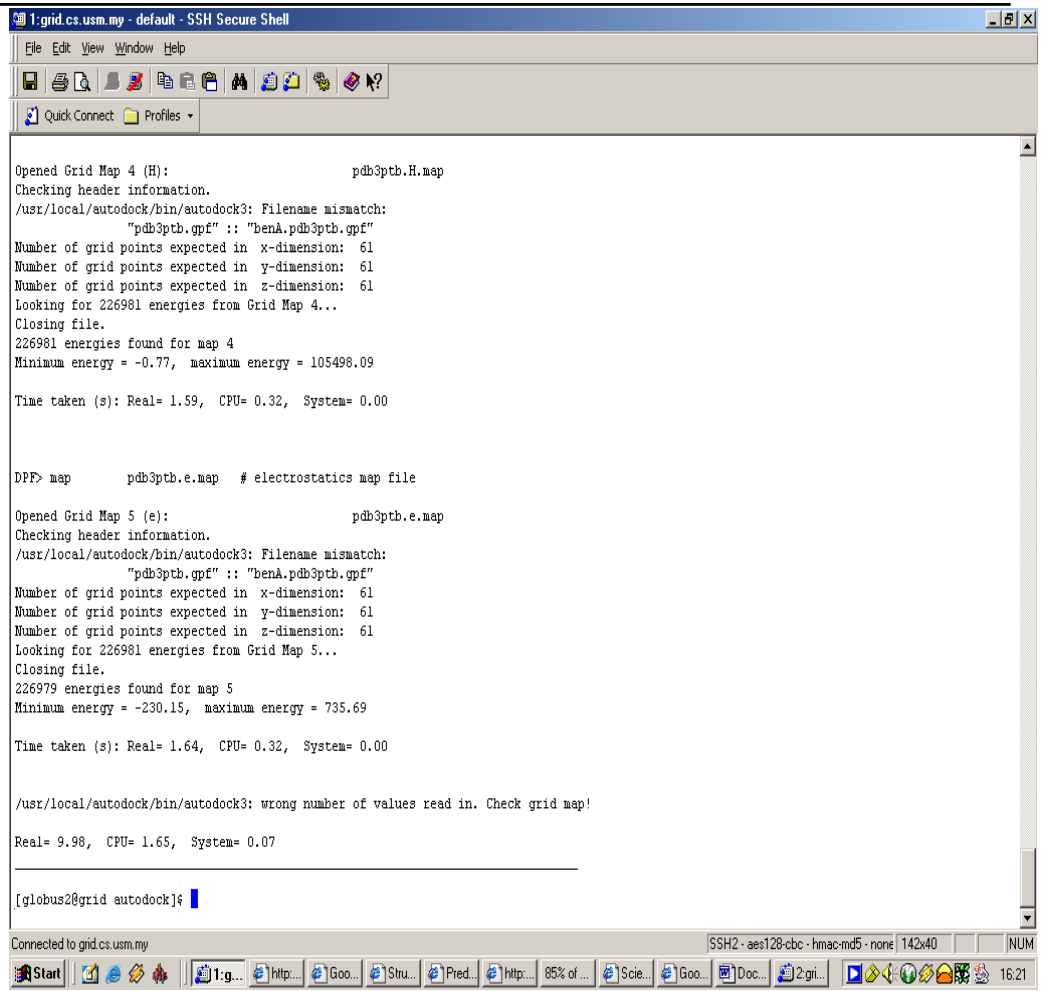
Running the Application

- Job scheduler not working properly
- Problem in submission:
  - Problem with Globus:
    - Unability to submit job due to authentication problem. (Authentication operation failed: Error Code 7)
    - Even after checking the grid-map file, job still failed to be submitted.
    - Proxy must be started otherwise job fails.



Running the Application

- Other problems:
  - Job did not finish properly. The output file is not as what is supposed to be.
  - Job was not submitted at all.
  - output overwritten if the same user submit the job.



Future Works

- Improvement of the submitting the same job. Meaning that user can still submit the same job anytime and the system will be able to execute it.
- Improve the visualization of the result given once the docking job has finished.
- Performance Evaluation, by doing comparison between sequential and distributed version in the grid environment.

Acknowledgement

- Dr. Yoshio Tanaka & AAPS WG
- Prof. Shinji Shimojo
- Tomomi Takao
- Osaka University
- PRAGMA
- Choong Yee Siew
- TB Research Group
- Grid Computing Research Group

THANK YOU