Putting Structure Based Drug Design on the GRID

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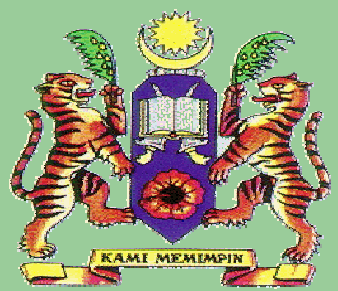
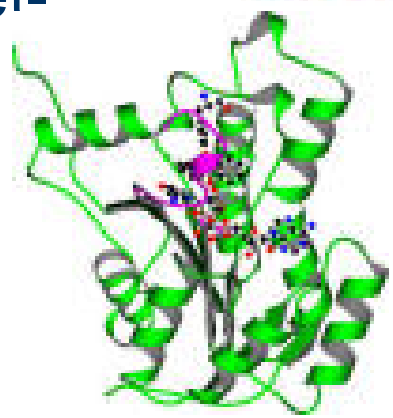


PRAGMA 3, Fukuoka, Japan. 22nd January, 2003

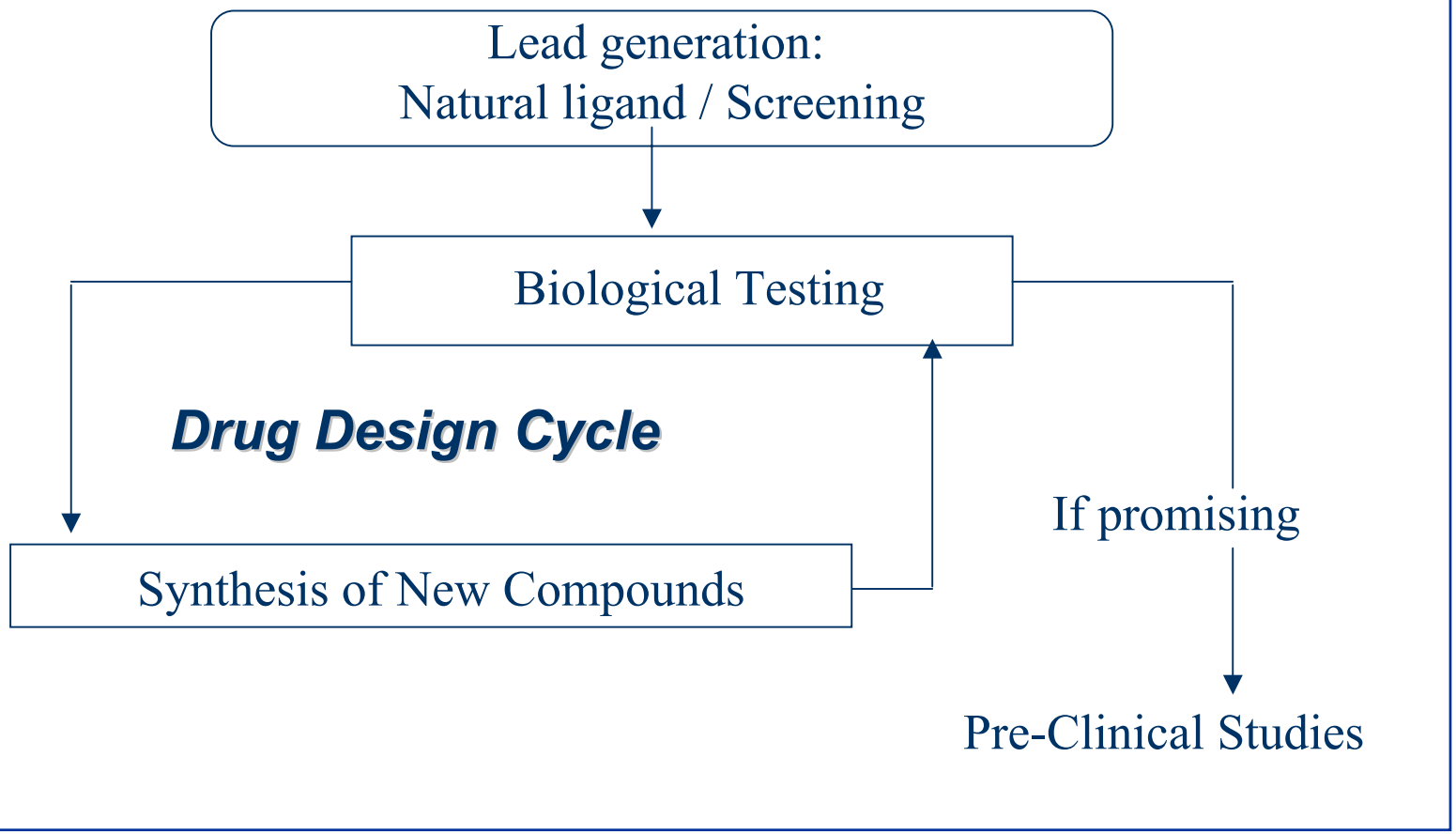
Introduction

- Drug discovery → take years to decade for discovering a new drug and very costly

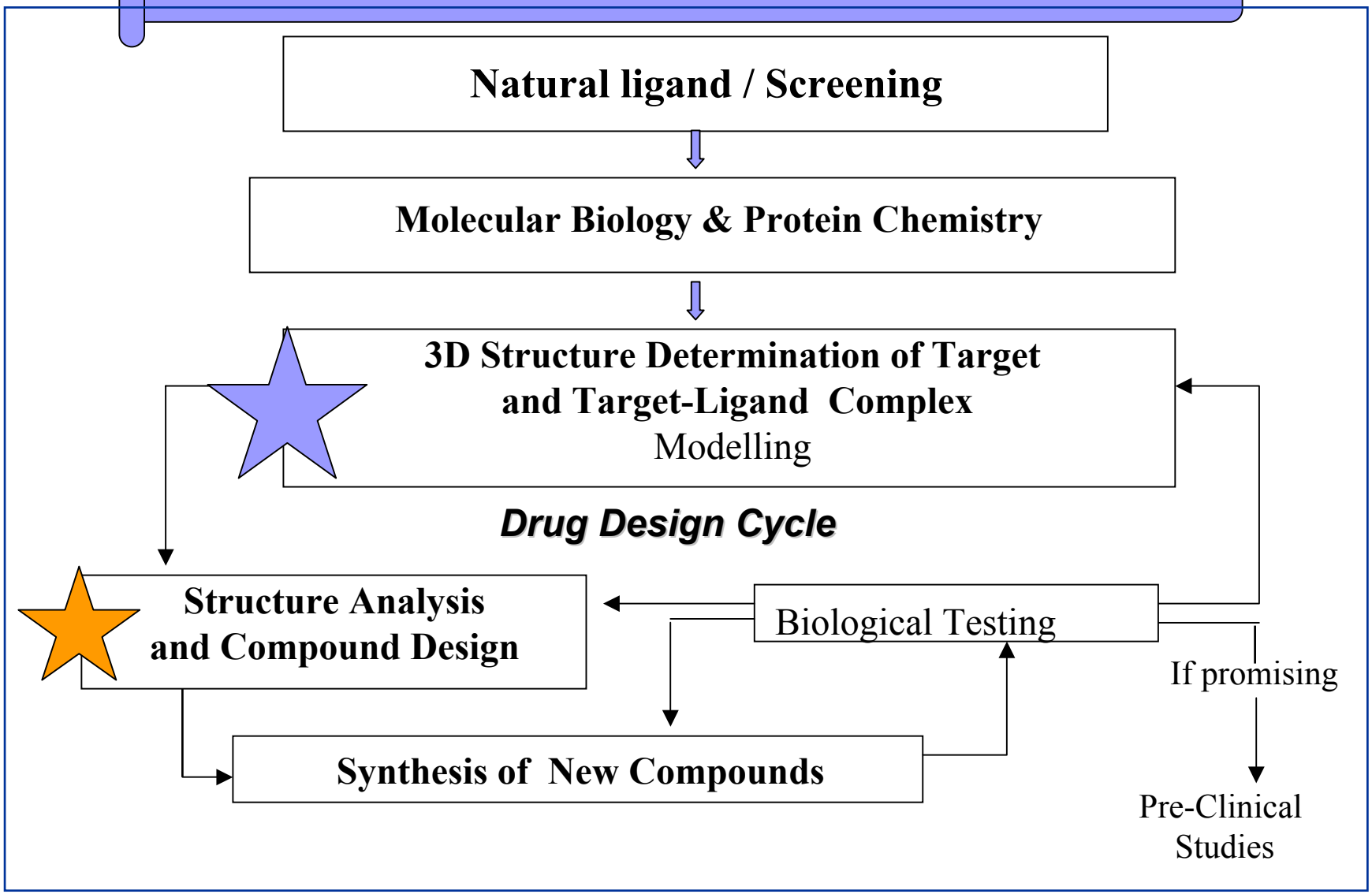
- Effort → to cut down the research timeline and cost by reducing wet-lab experiment → use computer modelling.



TRADITIONAL DRUG DESIGN



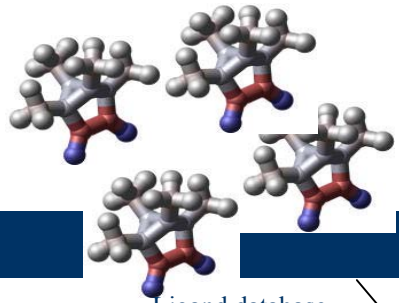
Structure-based Drug Design (SBDD)



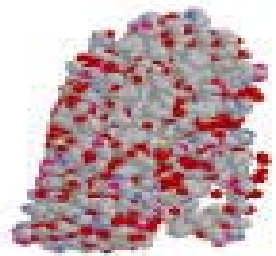
- SBDD:
  - drug targets (usually proteins)
  - binding of ligands to the target (docking)

"rational" drug design

(benefits = saved time and $$$)



Ligand database



Target Protein

Molecular docking

Ligand docked into protein’s active site

Molecular Docking of Isoniazid (INH) and its derivatives on M. Tb. enzymes

- 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
- INH mechanism of action:

  * activated by KatG and binds with NAD to form INADH
  * INADH inhibit InhA (protein involved in mycolic acids synthesis)

TUBERCOLOSIS

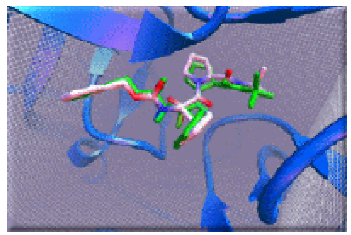
- In SBDD needs to understand binding interaction between antimicrobial and its target at molecular or atomic level
- X-ray crystallography and NMR are expensive and not many protein easily crystallized
- Molecular modeling:

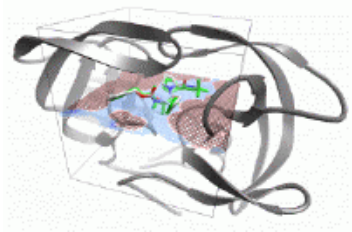
  * the ways to mimic the behavior of molecules and molecular systems

  * understand the mechanism of interaction between protein and ligand at atomic level

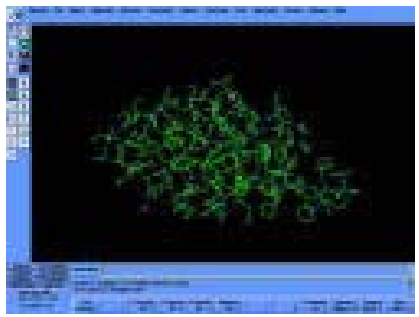
SBDD on the Grid

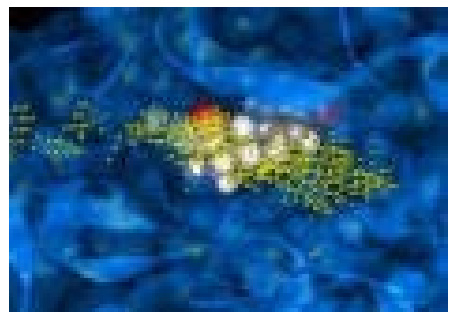
- Molecular Docking
  - Autodock 3.05





- Visualization
  - Rasmol





Grid Computing

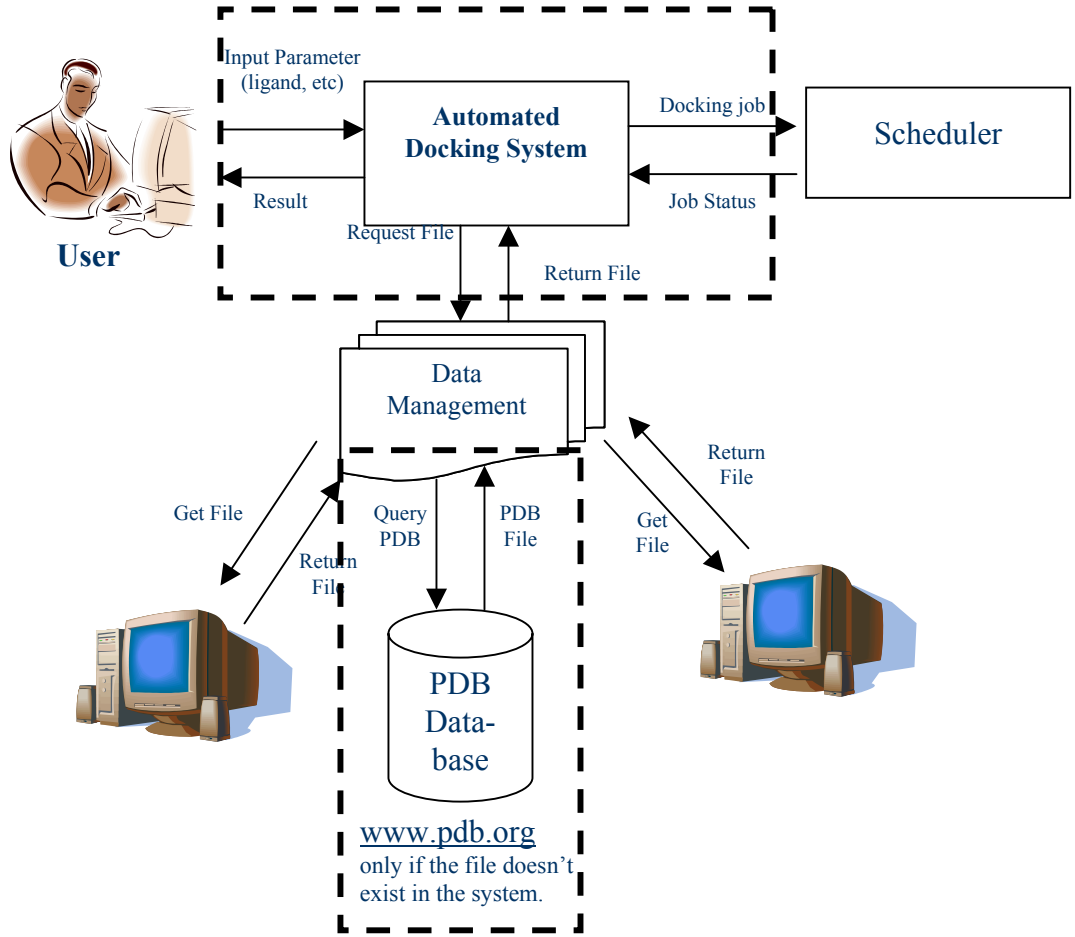
- It is not a new hardware technology – rely on existing networks
- Based on Grid Middleware – for example: Globus
- Grid middleware functions:
  - single sign-on authentication
  - resource discovery
  - resource allocation & process creation
  - automatic data access & transfer
  - transparency

Molecular Docking on e-Science Grid

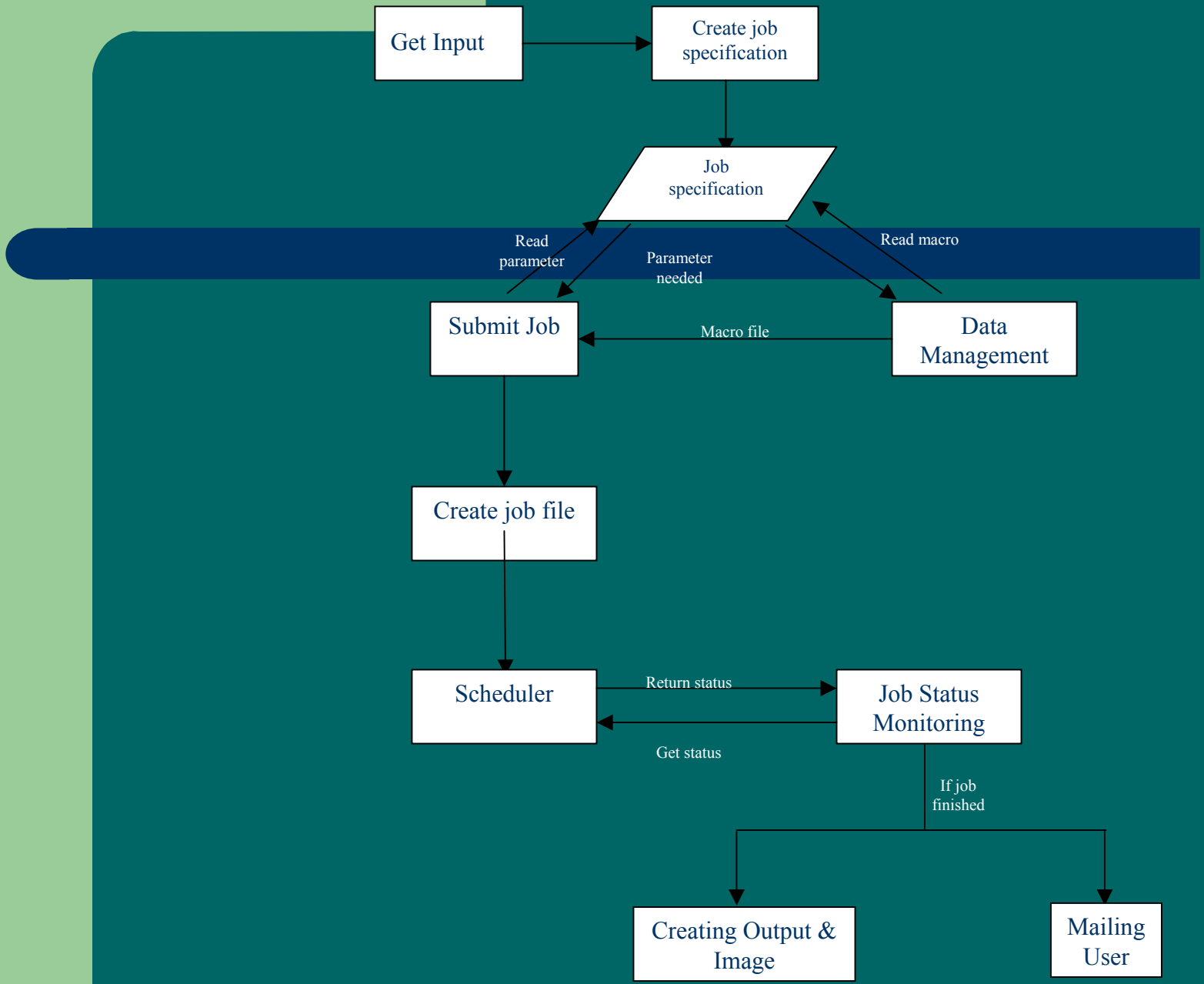
- Current project, we are incorporating the molecular docking application in the grid computing environment.

- Why?
  - Docking is most popular method applied amongst Malaysian biologist.
  - Cheaper?

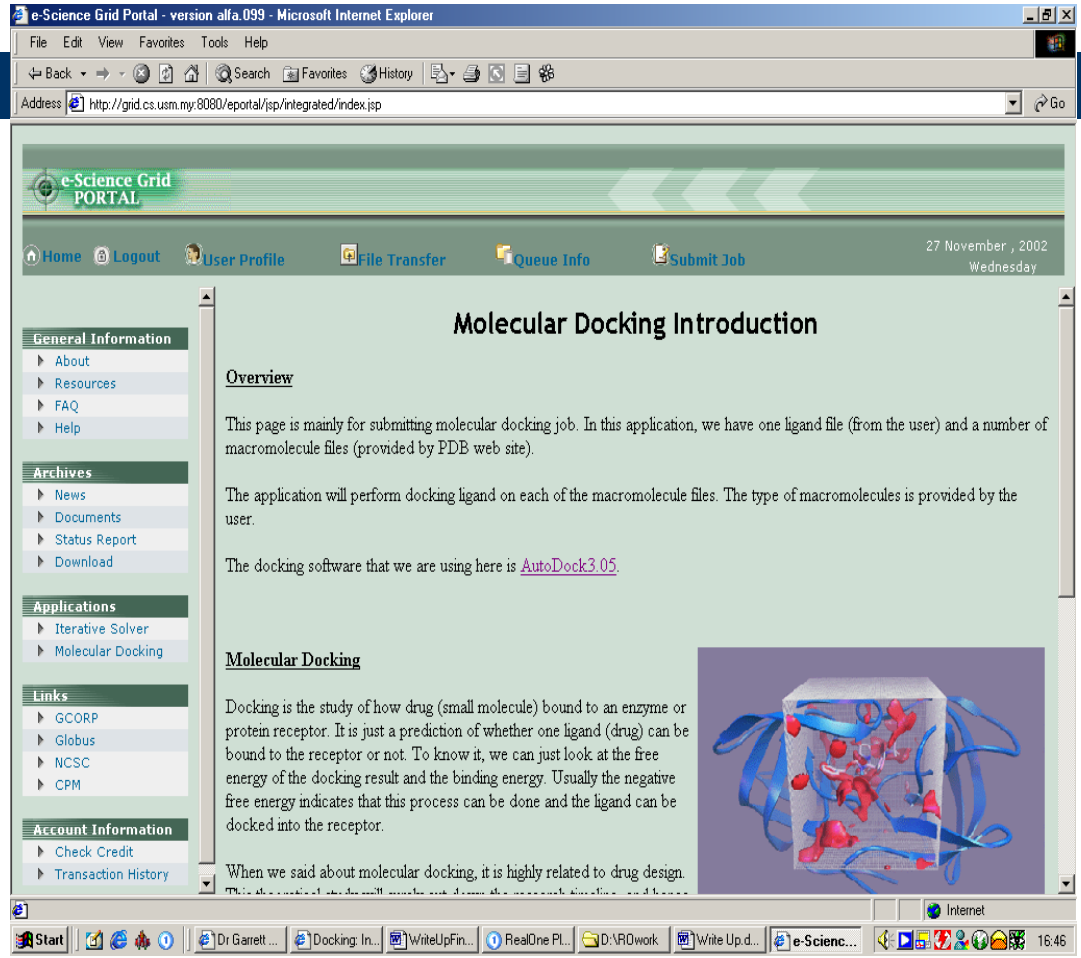
Overall Flow of Automated Docking System



Automated Docking System: The steps in Automated Docking

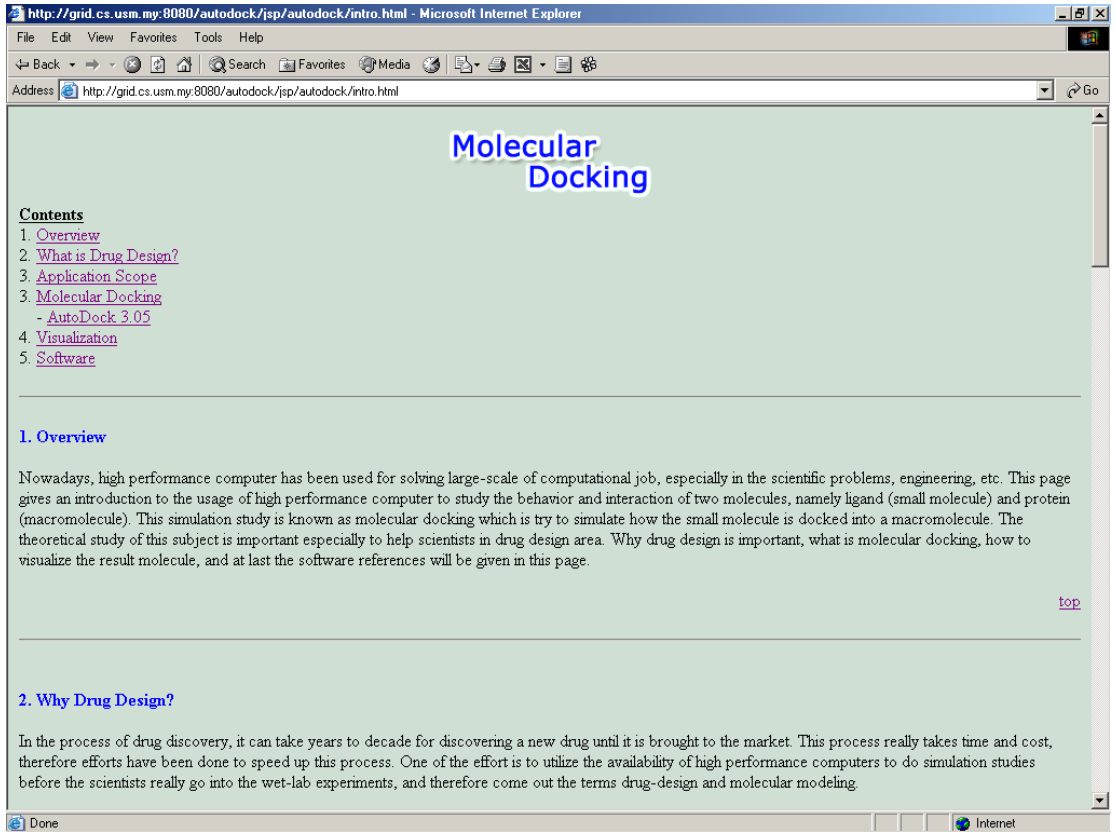


Molecular Docking Introduction Page

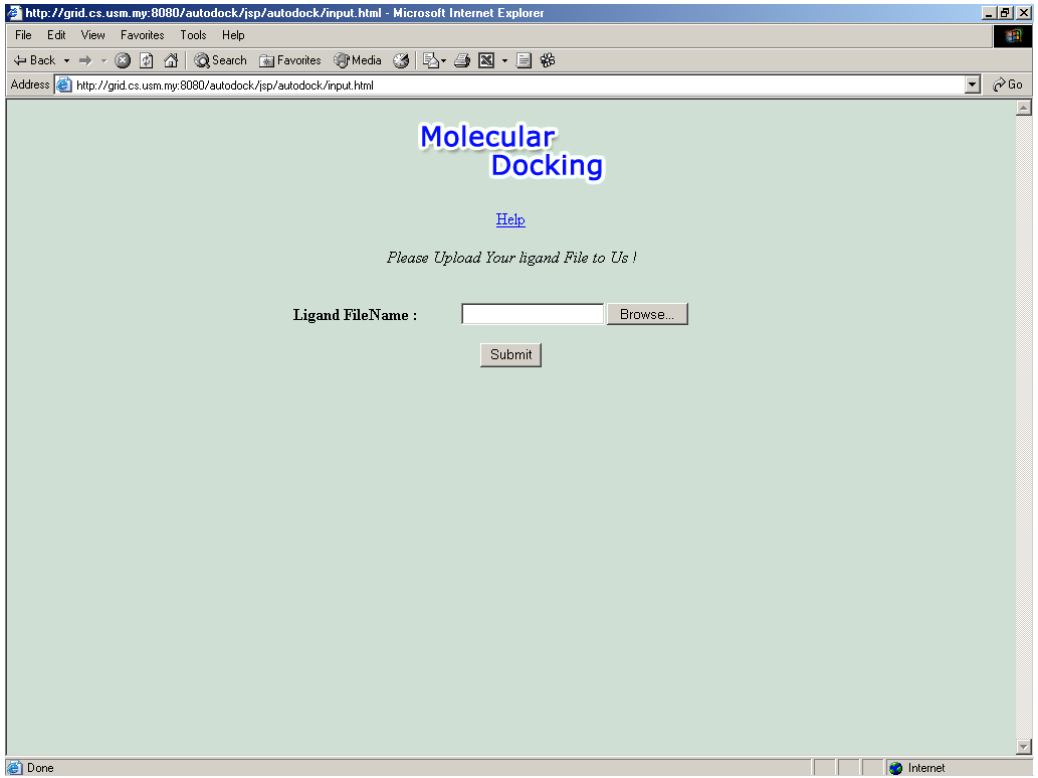


Molecular Docking Page

- Introduction Page



- Input Page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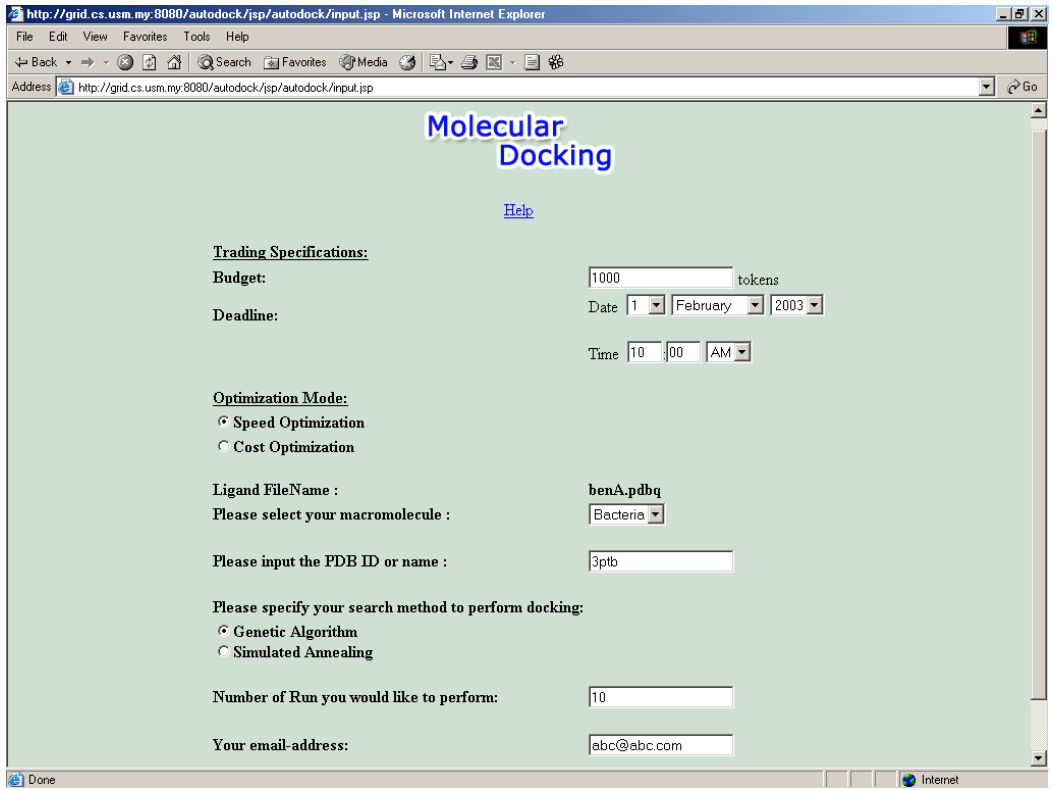
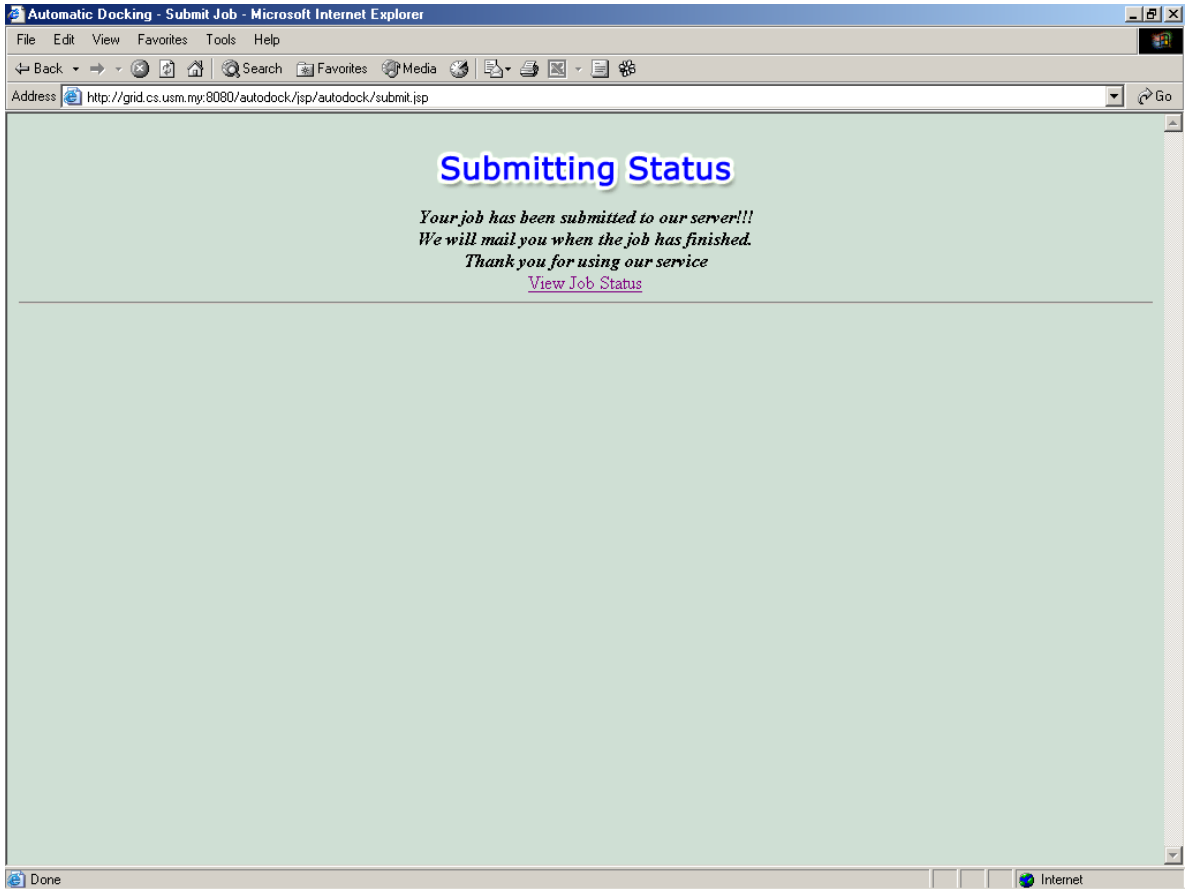
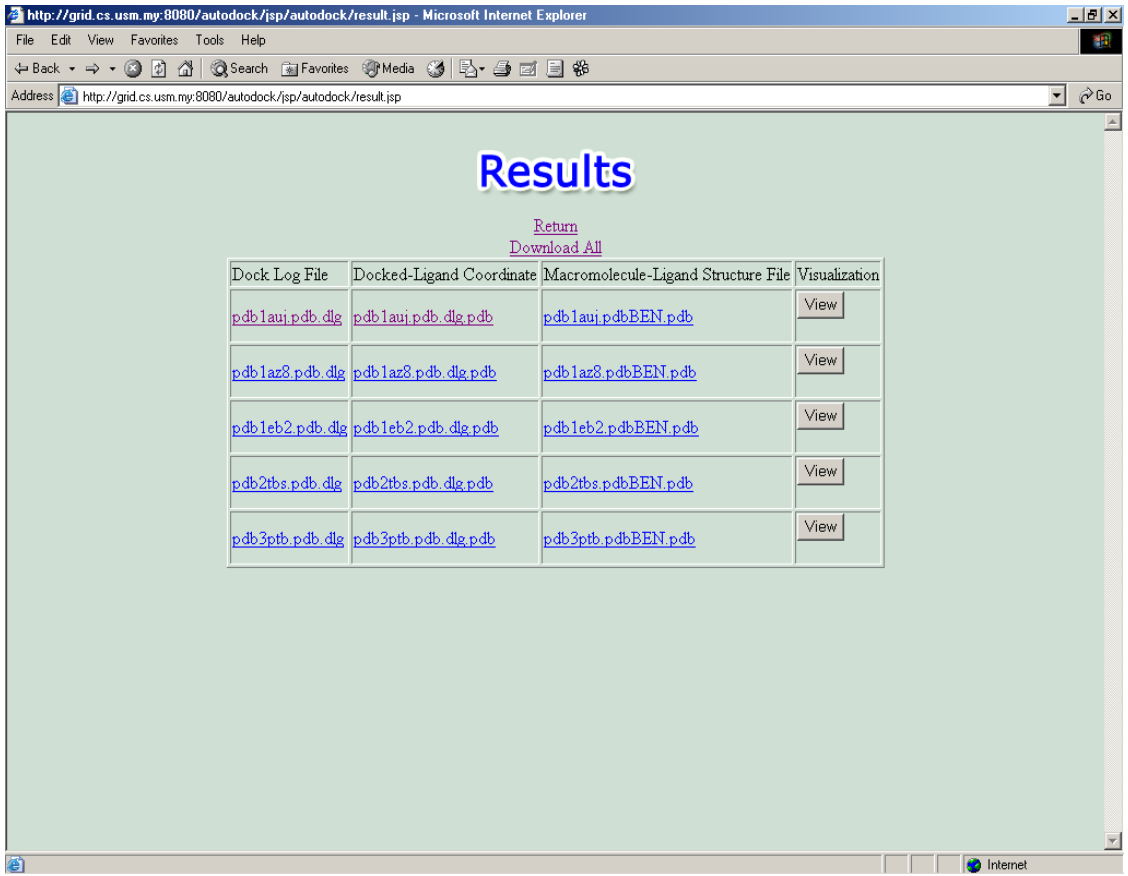
- Input Page (cont..)



- Submitting Job



- Results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Visualization
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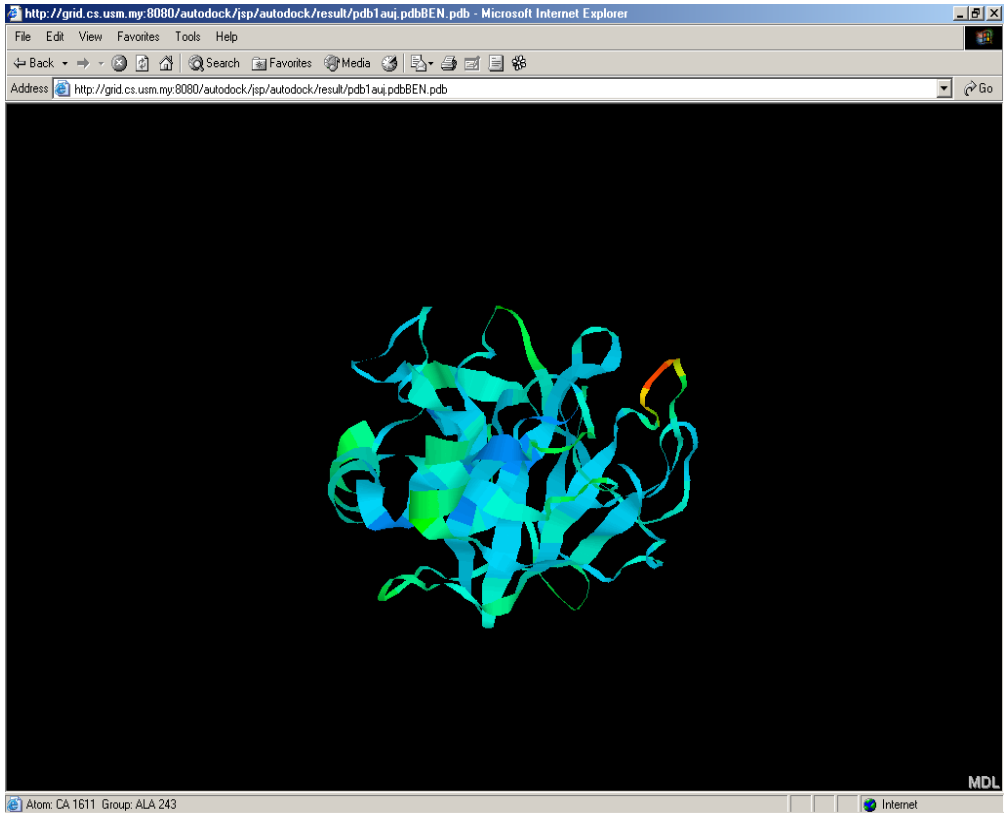
View
Internet

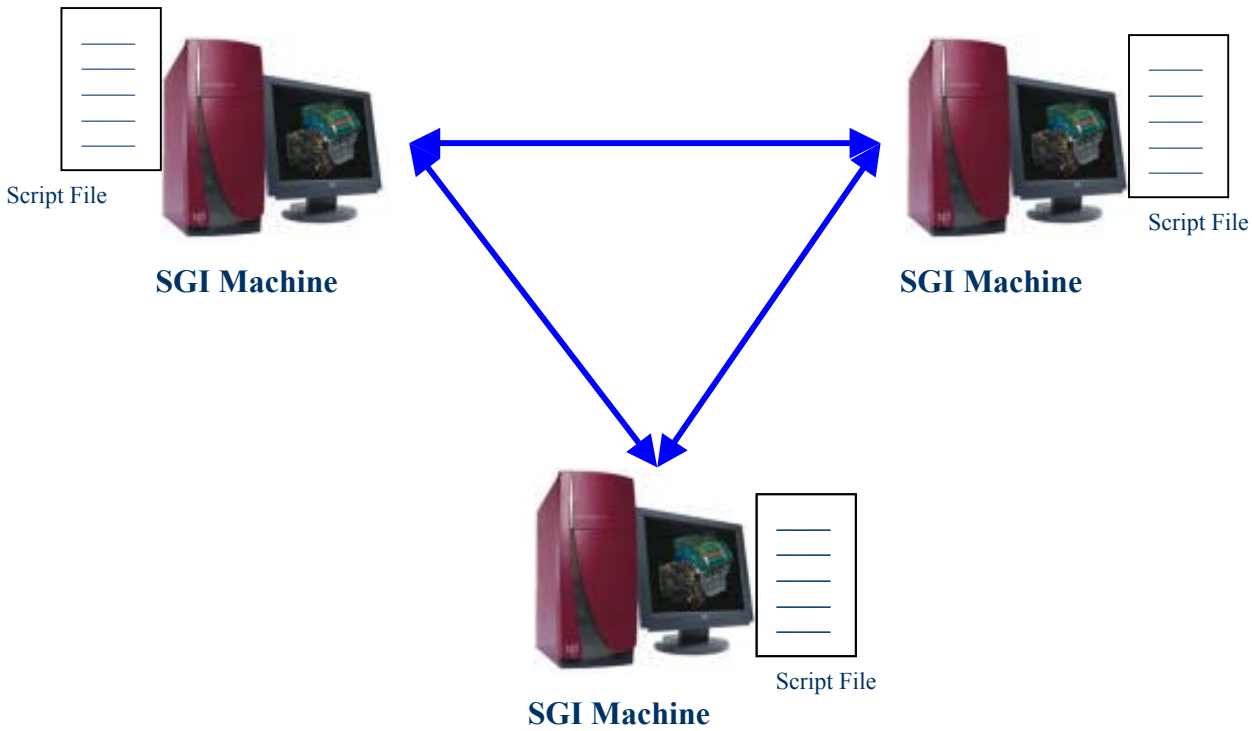
- Results (in visualization form)



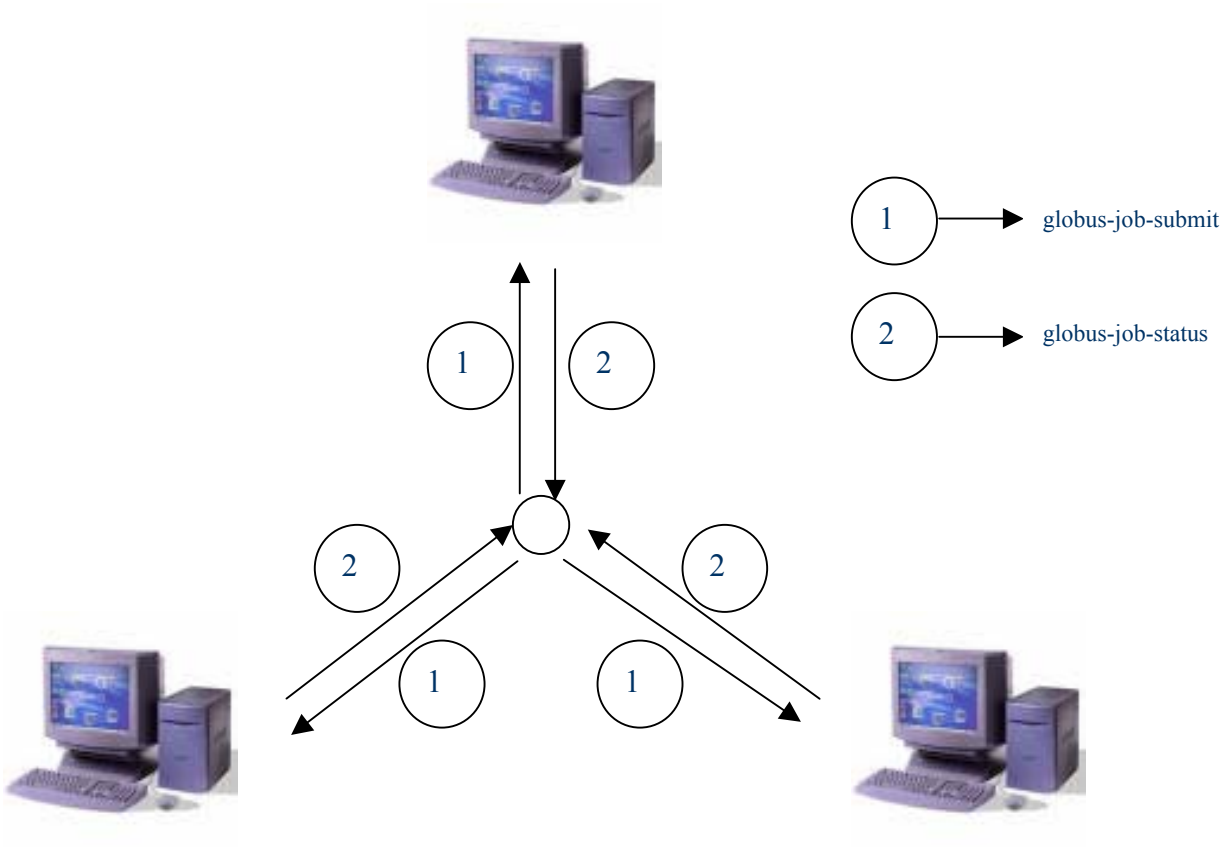
Benchmarking….

- 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

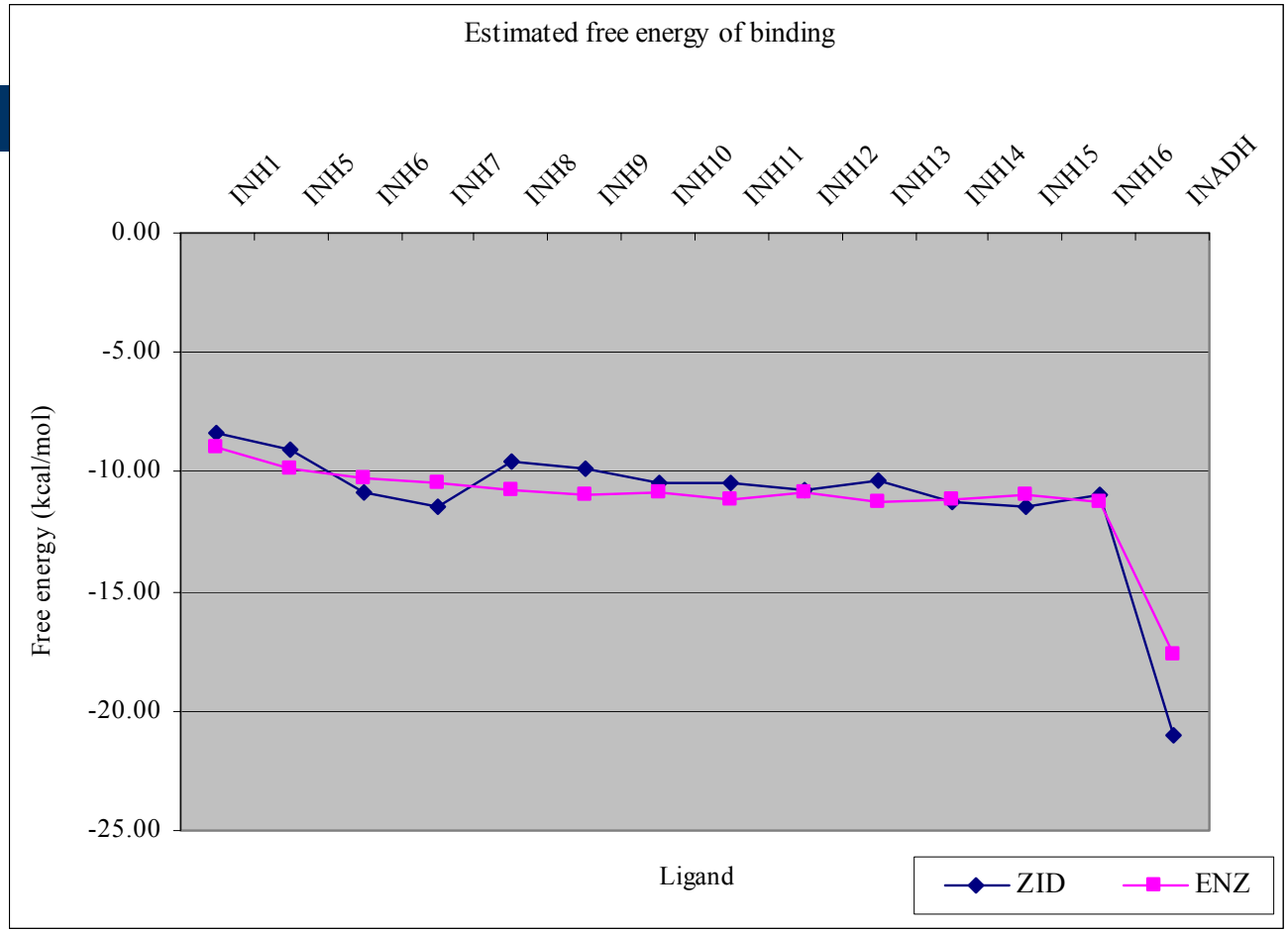
Testing Method (on SGI)



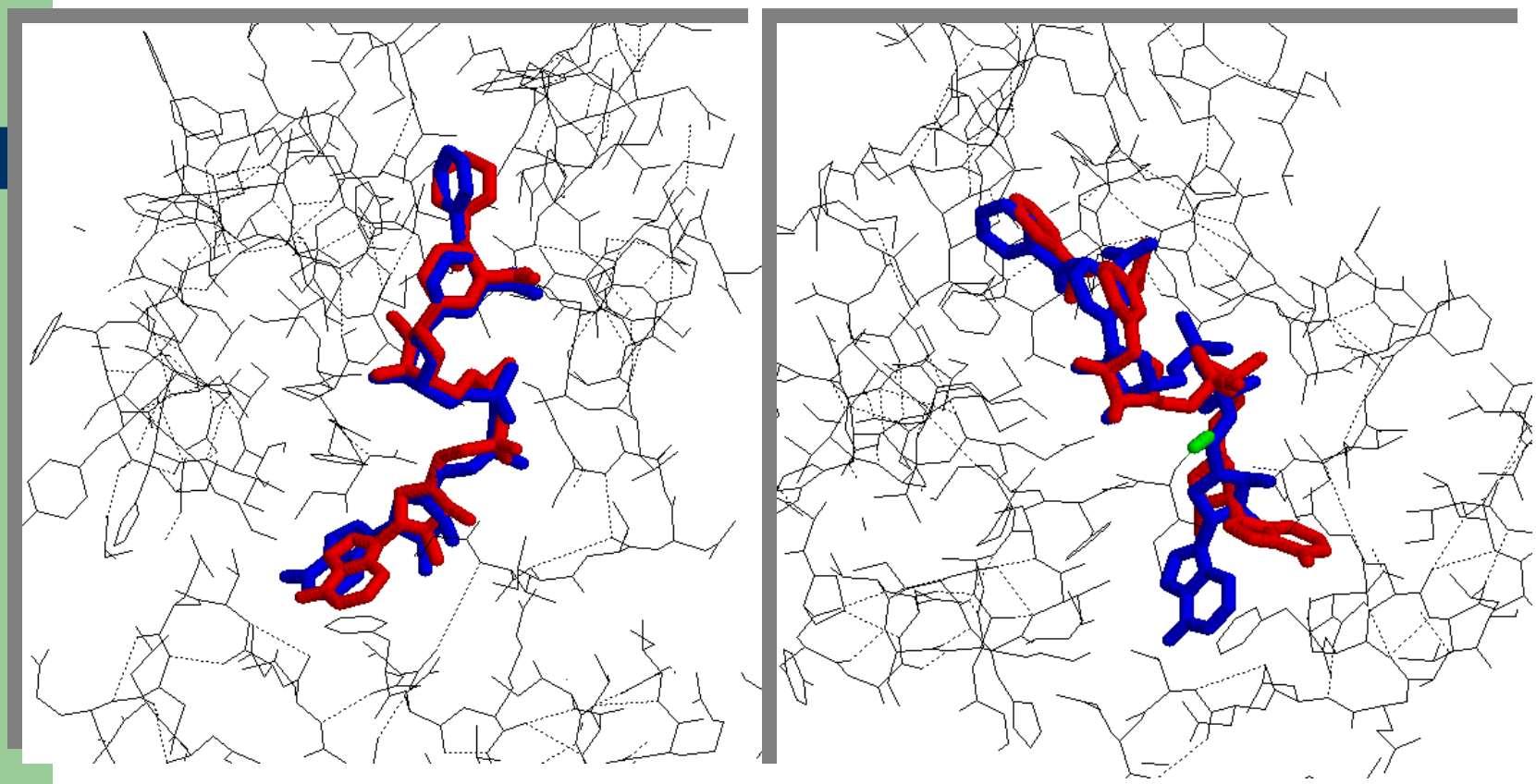
Testing Method (on Linux)



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)

Future Works

- PRAGMA Global Storage?
- 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.
- Create a system that will inform the user once the user's job has been finished (mailing system).
- 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

- Erwin Tontanso
- Choong Yee Siew
- Dr. Fazilah Haron
- Dr. Chan Huah Yong