BEmuse: A Tool for Drug Design on the Grid

Stefano Cozzini
National Simulation Center DEMOCRITOS (IT),
EU-IndiaGrid Technical Director

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Outline

- The scientific problem and the method
- The grid implementation: Bemuse
- The opportunities for non academic research

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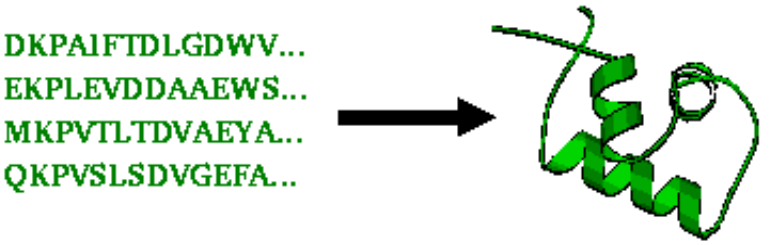
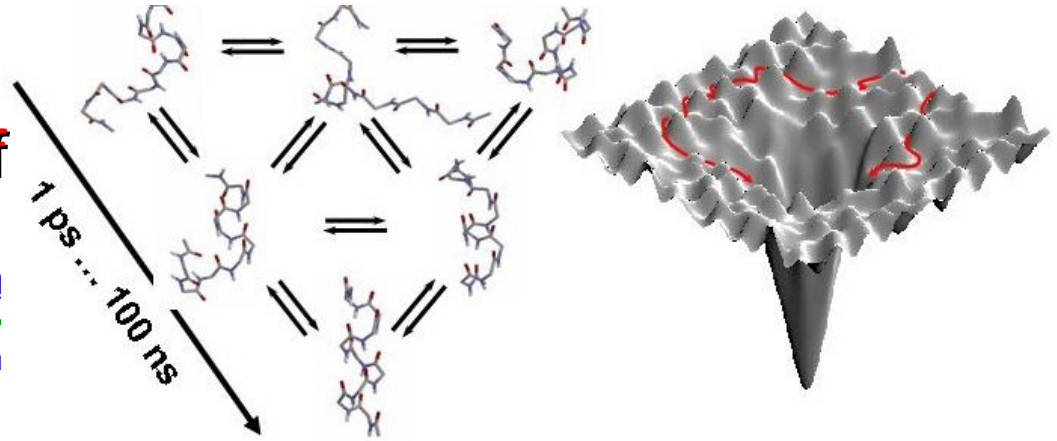
Scientific problem: protein folding

- obtain 3D structure from linear sequence of amino acids



- thermodynamic stability of folded state and intermediates
- kinetic pathways of folding

CHALLENGE: explore/ reconstruct the free enery multidimensional landscape of complex system



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Simulation Method: the simplest one

- Molecular Dynamics: Time Evolution of the system wait till it reaches the folding state
  - 1 day of CPU time -> 1 ns of simulation time
  - small proteins fold in 10^4 – 10^6 ns
  - so we need 100-10,000 years of CPU time !!!
- Folding@Home approach:
  - distributed computing on 10^4 home PCs
  - connected through internet (equilibrium MD)
  - individual folding trajectories are obtained
  - the folded state must be known in advance (!)
  - stability of intermediates?
  - impressive computational cost
  - V. S. Pande et al., Biopolymers 68, 91 (2003)

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Simulation method: advanced solutions

- Metadynamics approach:
  - modify the plain MD using one collective variables (reaction coordinate) to speed up the sampling process
    [A. Laio and M. Parrinello, PNAS, 99,12562 (2002)]
- Biased Exchange Metadynamic
  - Run several metadynamics at the same T,
    - each biasing different collective variables
    - Try to exchange the bias potential at fixed time intervals (Metropolis)
  - S. Piana and A. Laio, J. Phys. Chem. B 111, 4553 (2007)

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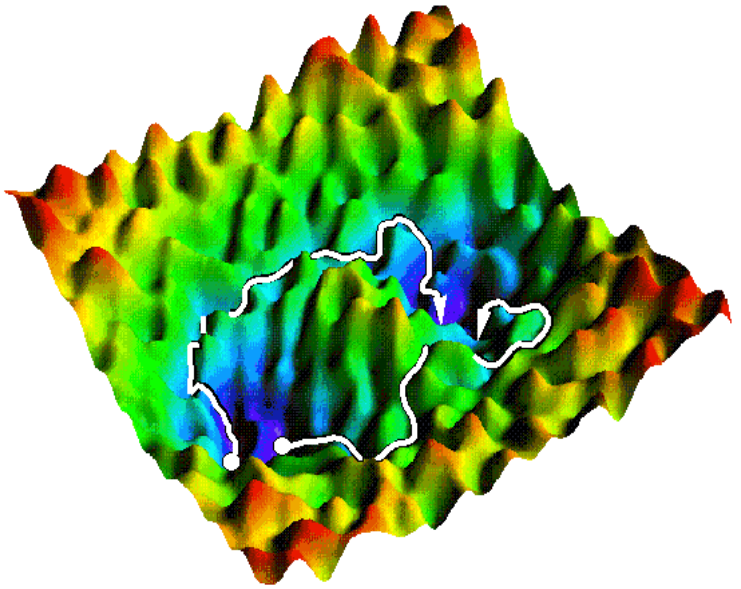
BES in a nutshell

- An enhanced sampling technique
- developed less than two years ago by researchers at Sissa/Trieste and in Perth.
- It is capable of predicting rare events in biological systems with an unforeseen accuracy.



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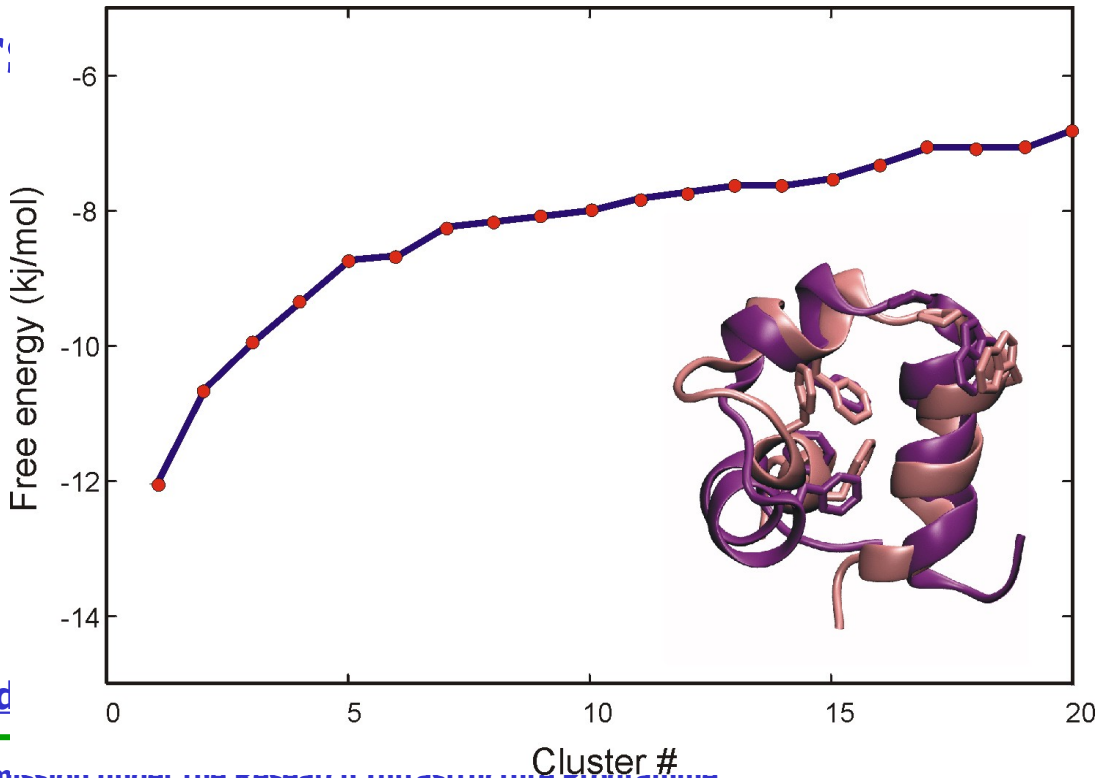
BES first result: folding of Advillin

- 36 AA three helix bundle.
  - Folding rate: 5-14 micros
  - Amber force field, PME, NPT,
  - T = 323 K, 3633 water

COMPUTATIONAL COST:
MPI on HPC platform:

8 cpu for 40 nanosecond
less than 1 year CPU



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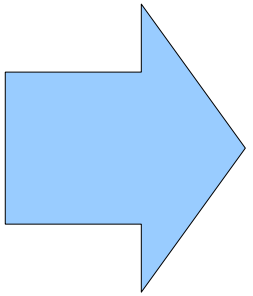
BES & the GRID

- BES algorithm:
  - loosely coupled
  - CPU intensive
  - not I/O bounded



FITS PERFECTLY the GRID COMPUTING ENVIRONMENT ala EGEE/gLITE

FULLY DEVELOPED AND IMPLEMENTED WITHIN EU-INDIAGRID INFRASTRUCTURE

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BEMUSE

- Biased Exchange Metadynamics Submission Environment
  - developed by EU-IndiaGrid Team at ICTP in strict collaboration with A.Laio and F.Pietrucci
- Based on client/server architecture: CPU are recruited dynamically and simulation can run in an asynchronous way.
- It allows to easily manage complex BES computational experiments on EU-Indiagrid infrastructure
- It allows to recruit computational resource among different environment as well (interoperability at application level)

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Bemuse&Interoperability

- Bemuse core is decoupled by the computational environment
  - any computational resource can be recruited
  - only requirement: outbound connectivity to allow the cpu to contact the server.
- Current experiment:
  - a server collecting resources from EU-Indiagrid infrastructure and HPC local resources at SISSA

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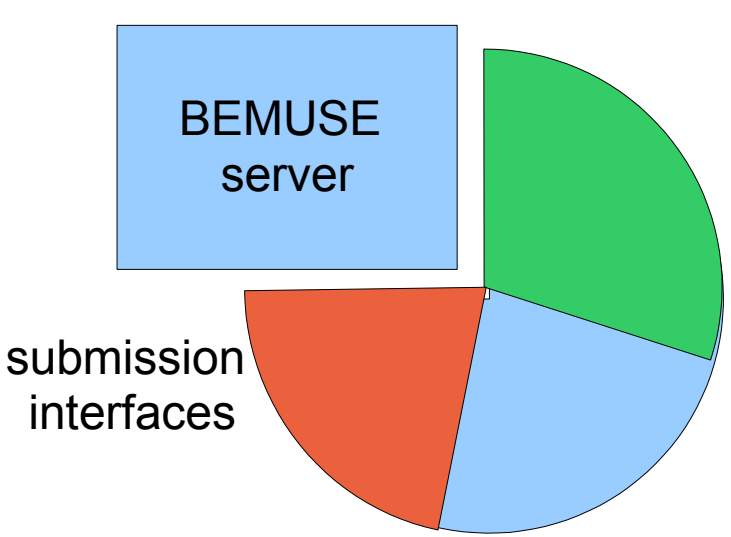
Interoperability



GRID INFRASTRUCTURE

HPC facility

Generic
Computational platform

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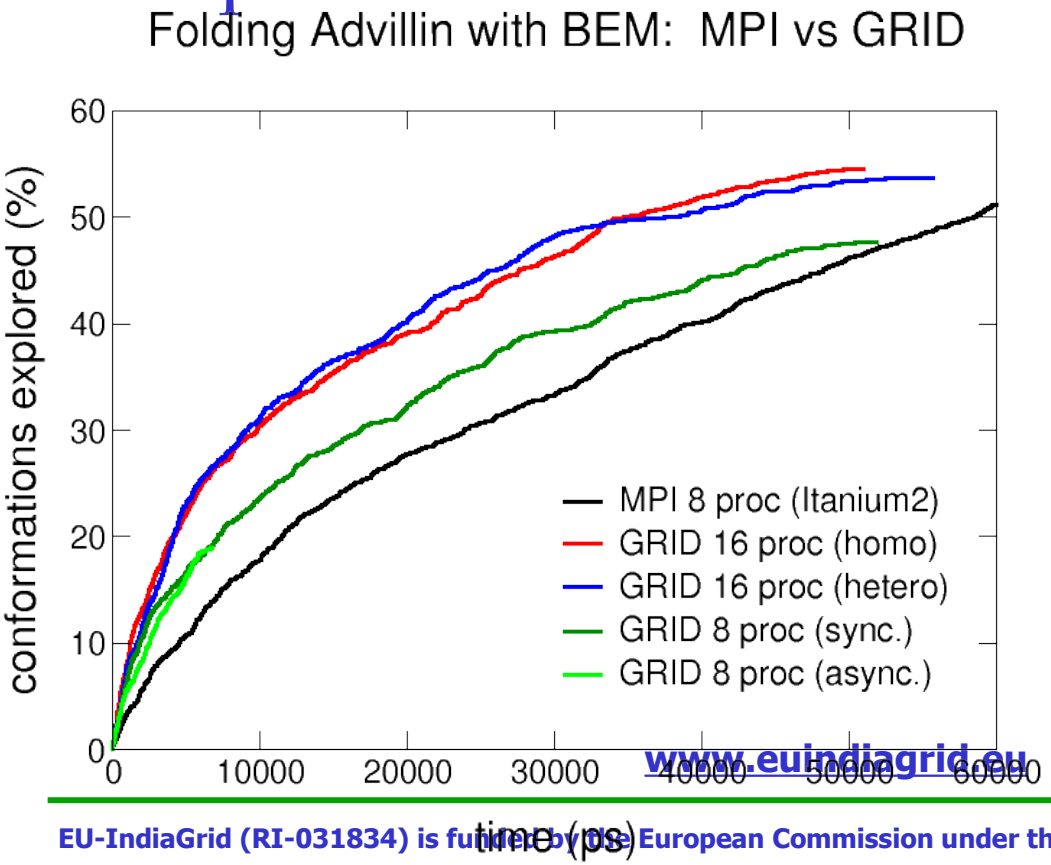
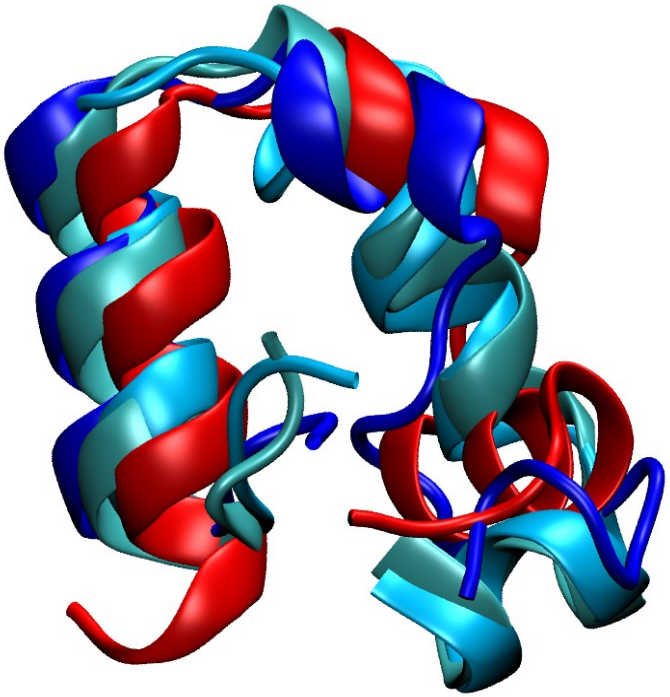
BEMUSE results:

- Our simulations were able to explore the conformations of the protein at a speed comparable to MPI !!!





RMSD < 4 A from exp.

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BEMUSE facts:

- It is able to use the grid resources with the same efficiency as HPC resources
- It is able to solve the problem of folding a 36aa protein at a cost (< 1 year of CPU time) far lower than other GRIDbased techniques (Folding@Home required 1000 years of CPU time)
- It is able to couple the advantages of GRID with the advantages of the BiasExchange Metadynamics algorithm

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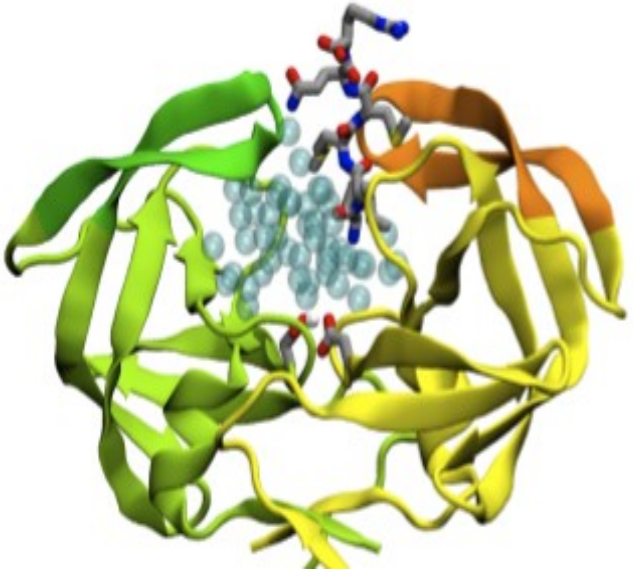
Bemuse is right now in production for:

- Bonding between drugs and HIV-1 protease (>200 amino acids, all atom explicit solvent, ∽100 procs)
- Folding of a 56amino acids protein in water (src-SH3)



Binding mechanism of HIV-1 protease

enzyme necessary for replication of HIV virus, it cuts long proteins. Target for anti-AIDS therapy

CA cavity+ligand

BeMuse for non academic users

- Bemuse offers a leading-edge computational tool for prediction of rare events in biological system
- It hides all the complexity to identify / recruiting the right computational resources
- It is ready to run across several computational environments

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What Bemuse can do ?

- Docking in explicit solvent taking into account the flexibility of the ligand and of the target.
- Accurate prediction of the binding affinity
- Protein-protein interaction.
- Folding of peptides of up to 40 residues

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Conclusions

- BEMuSE is coupling the power of the GRID with the power of smart sampling algorithms
- This tool allows the prediction of rare events in biological system with great accuracy.
- Many different applications can be thought for such a tool in drug design activities.

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Credits&Contacts

- Riccardo di Meo
- Alessandro Laio
- Fabio Pietrucci
- Xavier Barnies

- for contacts:
  - cozzini@democritos.it
  - laio@sissa.it

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