

# METAGUI – A VMD EXTENSION TO ANALYZE AND VISUALIZE METADYNAMICS SIMULATIONS

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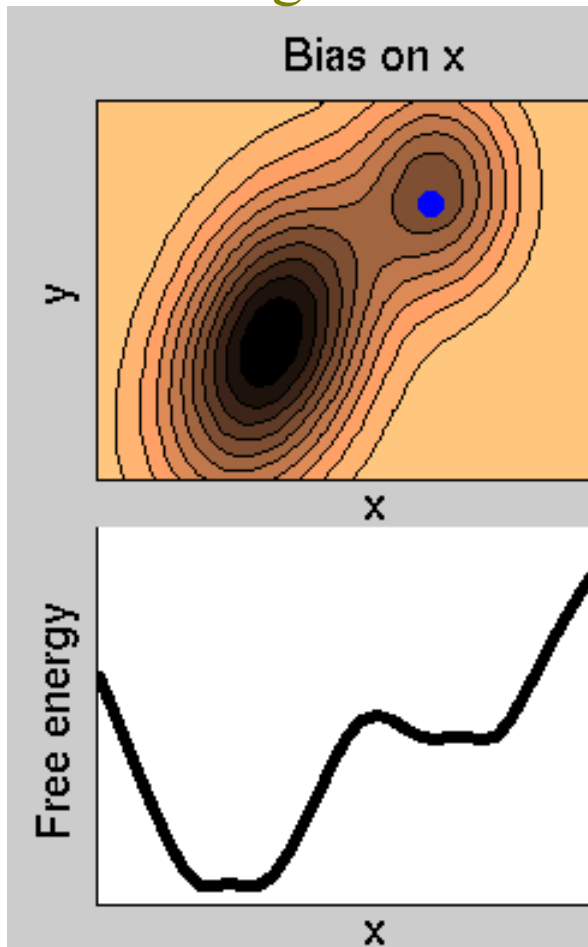


DEMOCRITOS  
DEmocritos MOdeling Center for  
Research In aTOMistic Simulation INFM

Coworkers: Xevi Biarnes  
Fabio Pietrucci  
Fabrizio Marinelli

# Metadynamics (Laio A. and Parrinello M., 2002).

Filling the free energy wells with “computational sand”



- choose a collective variable  $s(x)$  (in the example  $s(x)=x$ )
- Bias the dynamics with a potential of the form

$$V_G(s(x), t) = w \int_0^t dt' \exp\left(-\frac{\|s(x) - s(x(t'))\|^2}{2\delta s^2}\right)$$

- $V_G(s, t)$  for large  $t$  is an approximation of  $-F(s)$

Other methods based on similar ideas:

Taboo search: Cvijovic, D.; Klinowski, J.

Local elevation: T. Huber, A.E. Torda and W.F. van Gunsteren

Adaptive force bias: E. Darve and A. Pohorille

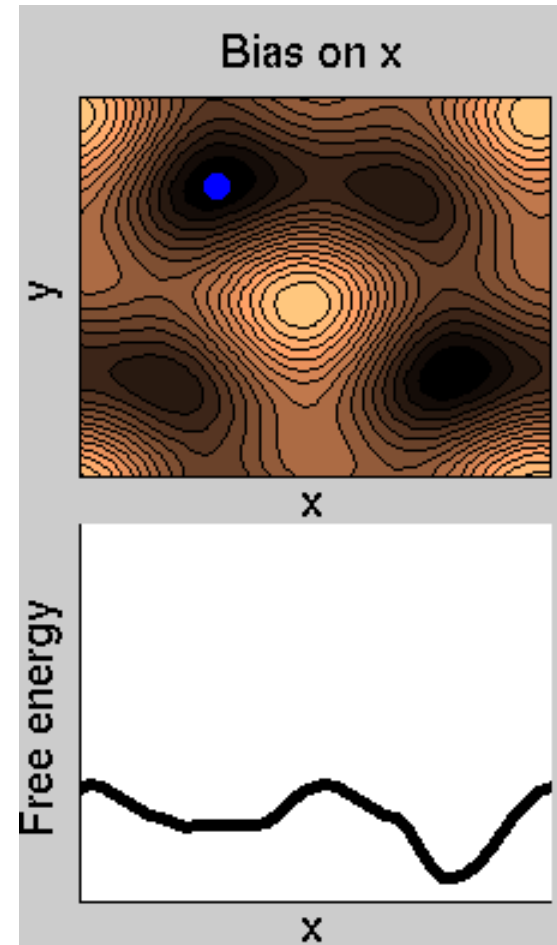
Wang and Landau

# Limitations

It is difficult to “know” in advance all the relevant variables

If one is forgotten → **hysteresis!!!**

Even if you know all: the filling speed **decreases exponentially** with the dimensionality of the free energy.



# Bias-exchange metadynamics

- Run several metadynamics each biasing a **different collective variable**:

Replica 1: collective variable “a”, bias potential  $V^a(x,t)$

Replica 2: collective variable “b”, bias potential  $V^b(x,t)$

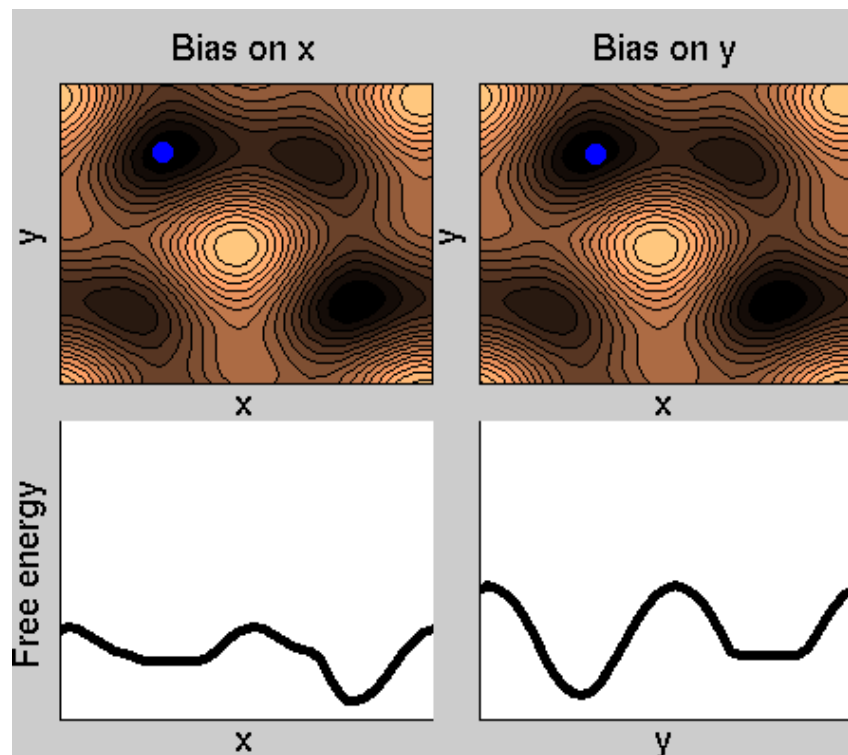
Replica 3: ....

- Attempt swapping the coordinates between the two replicas.

- Accept the move with a probability

$$P = \min[1, \exp(-\beta(V^a(x^b,t) + V^b(x^a,t) - V^a(x^a,t) + V^b(x^b,t)))]$$

- Parallel reconstruction of  $F(s)$  in a virtually unlimited number of CVs
- The accuracy of each  $F(s)$  is greatly enhanced by the jumps in CV space due to the exchanges.



S. Piana and AL, JPCB, 111, 4553 (2007)

Related works:

Replica exchange on proteins: Sugita, Y.; Okamoto, Y. *Chem. Phys. Lett.* 314, 141-151 (1999).

Replica exchange+ metadynamics: G. Bussi, F.L. Gervasio, AL and M. Parrinello, JACS 128, 13435 (2006)

# Bias Exchange Metadynamics



HALKER 1



HALKER 2



HALKER 3



HALKER 4

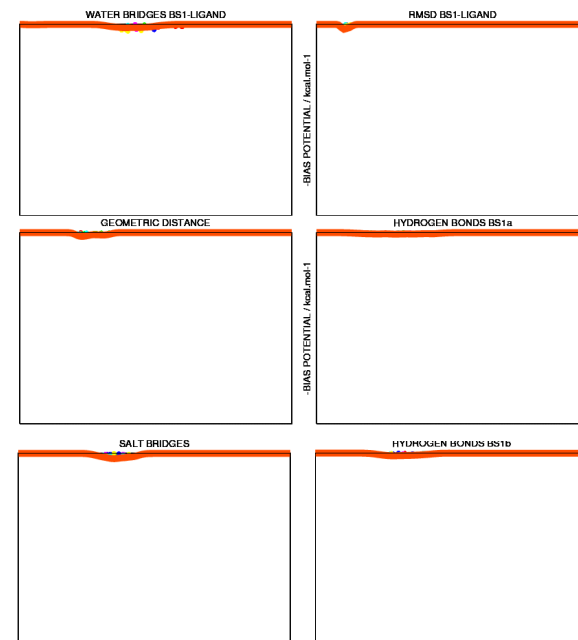


HALKER 5



HALKER 6

**Bias Exchange Metadyn.**  
**6 replicas**  
**6 Collective Variable**  
**6 Bias Potential (1D)**



**6 XYZ**  
**6 COLVAR**  
**6 HILLS**

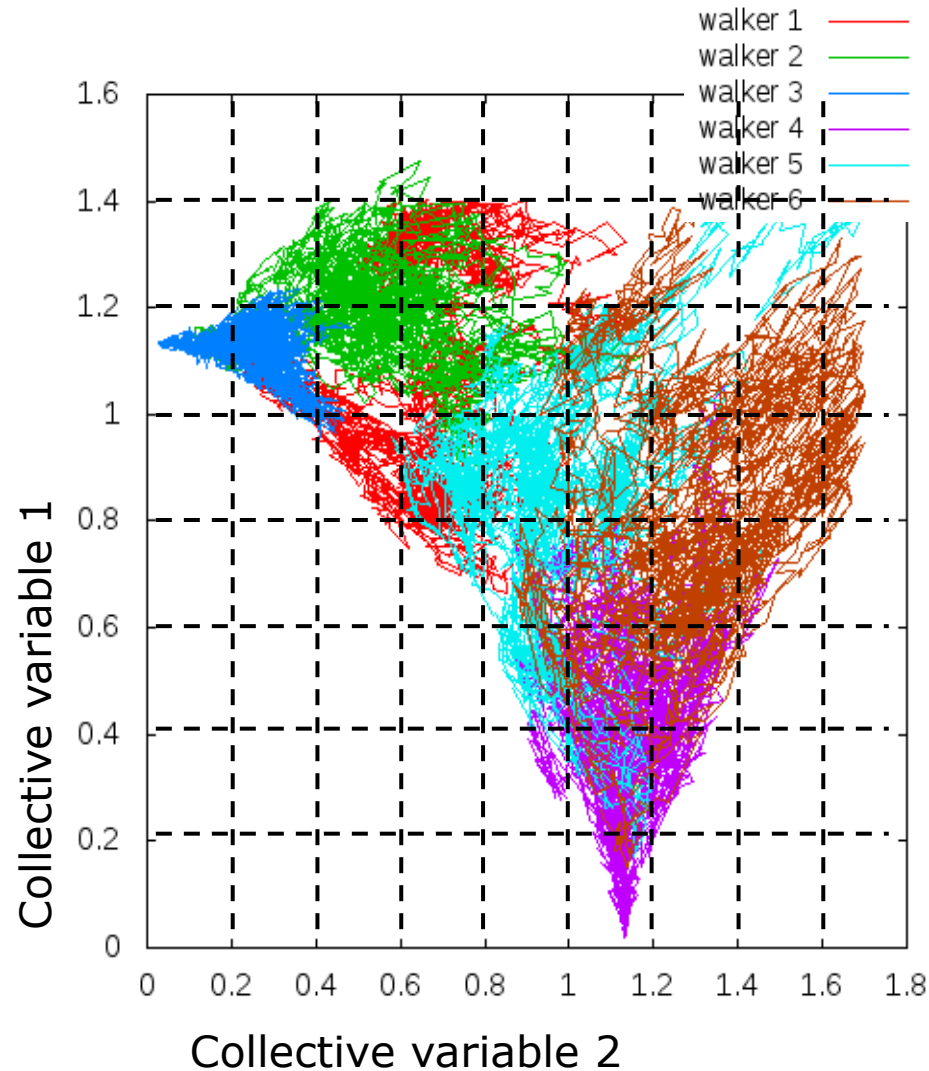
*Piana and Laio, J Phys Chem B 2007*  
*Marinelli et al, PLoS Comp Biol 2010*

**From NR one-dimensional free energies**

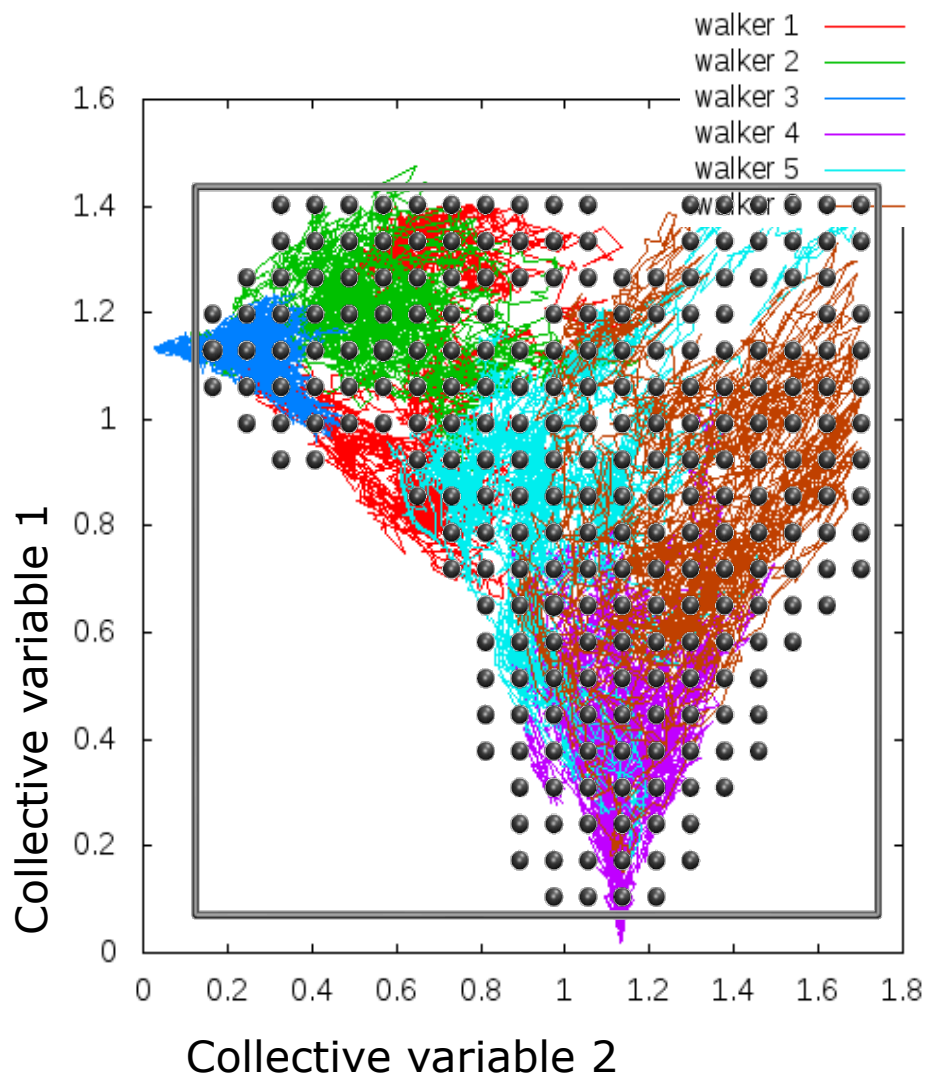
**To an NR-dimensional free energy hypersurface**

Select a subset of the biased CVs for the analysis

Divide the CV space in hypercubes



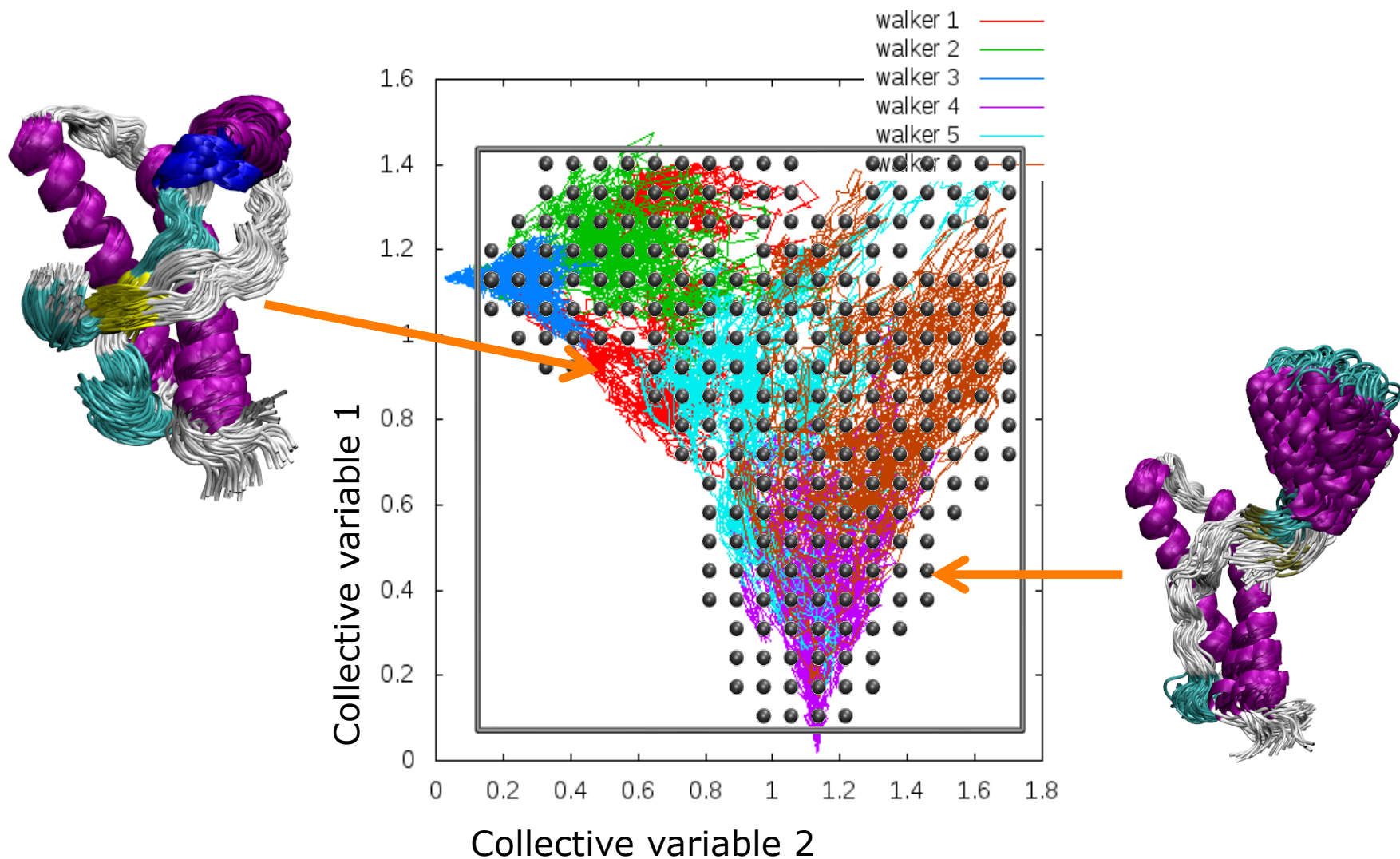
# The structures belonging to each hypercube define a microstate





The structures belonging to each hypercube define a microstate

Structures belonging to a microstate **MUST** be similar



## BIASED POPULATIONS ( $n_\alpha$ )

to be corrected by the metadynamics bias ( $V_\alpha$ )

$$p_\alpha^i = n_\alpha^i e^{\beta(V_\alpha^i - f^i)}$$

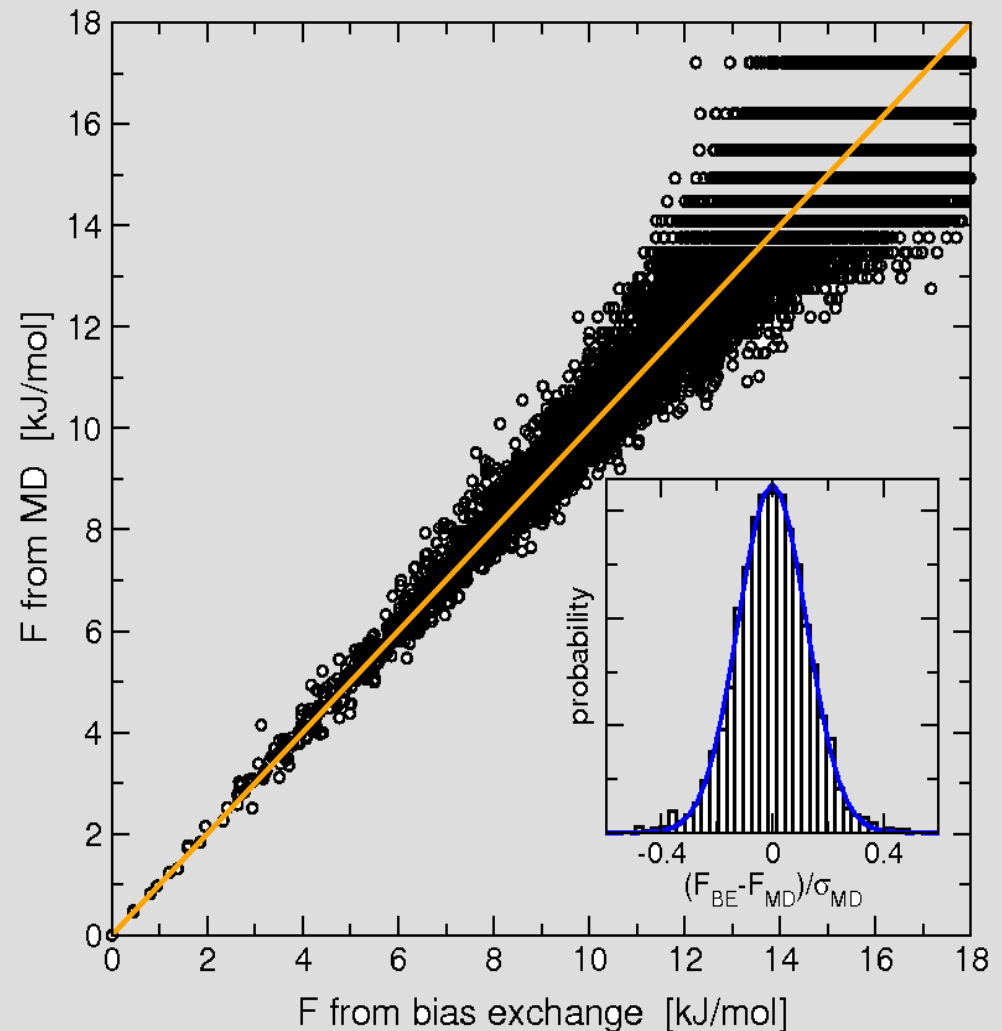
**Combine different estimates of  $p_\alpha$  by WHAM:**

$$p_\alpha = C \frac{\sum_i \frac{1}{\sigma^2(p_\alpha^i)} p_\alpha^i}{\sum_i \frac{1}{\sigma^2(p_\alpha^i)}}$$

$$F_\alpha = -k_B T \log p_\alpha$$

# Free energy of the microstates: test on 3ALA

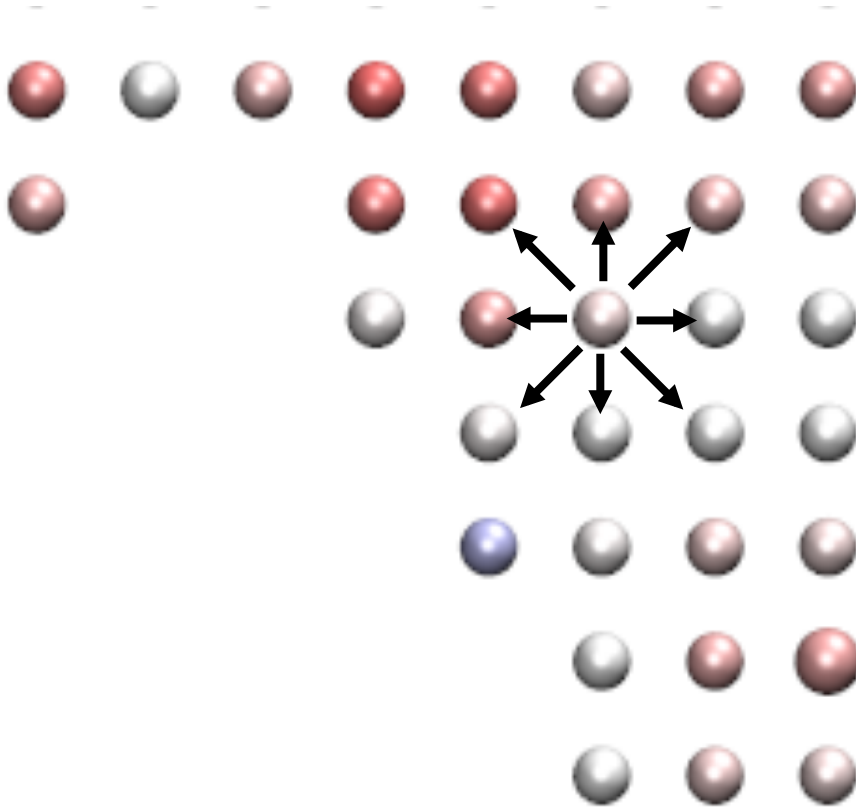
- Cluster analysis in the 6-dimensional CV space: ~ 10000 clusters.
- For each cluster we compute the free energy from the 1800 ns of **normal MD** and by the WHAM procedure on the **bias-exchange** results



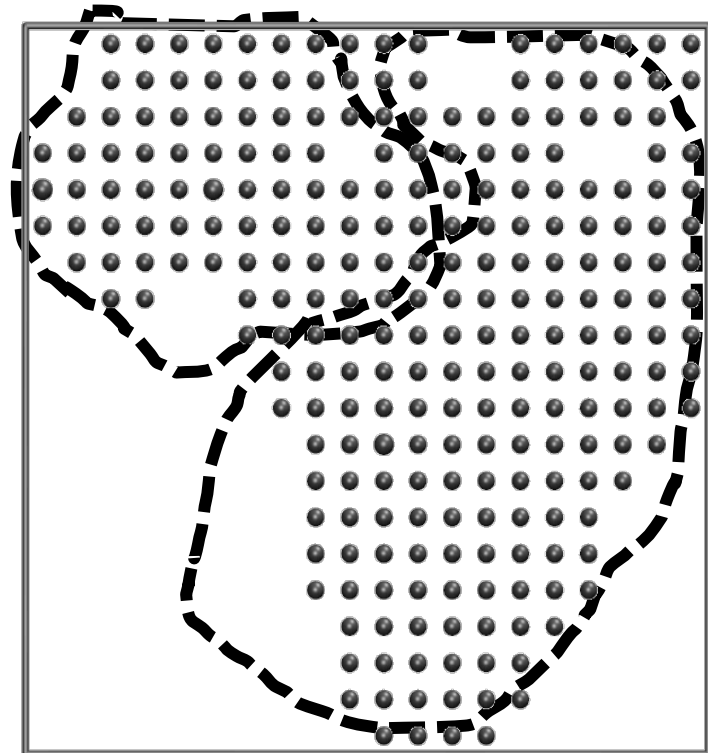
# From MICROSTATES to kinetic basins

## Transition Rate Matrix

$$k_{\alpha\beta} = \chi_{\alpha\beta} k_{\alpha\beta}^0 e^{-\frac{1}{2}(F_{\beta} - F_{\alpha})/k_B T}$$



- **Eigenvalues**  
How many relevant basins?
- **Eigenvectors**  
Which microstates belong to a basin?

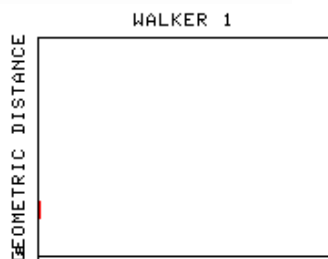


# Analyzing Metadynamics Results

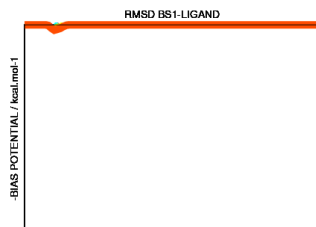
- Metadynamics output files
  - Coordinates Trajectories (XYZ)



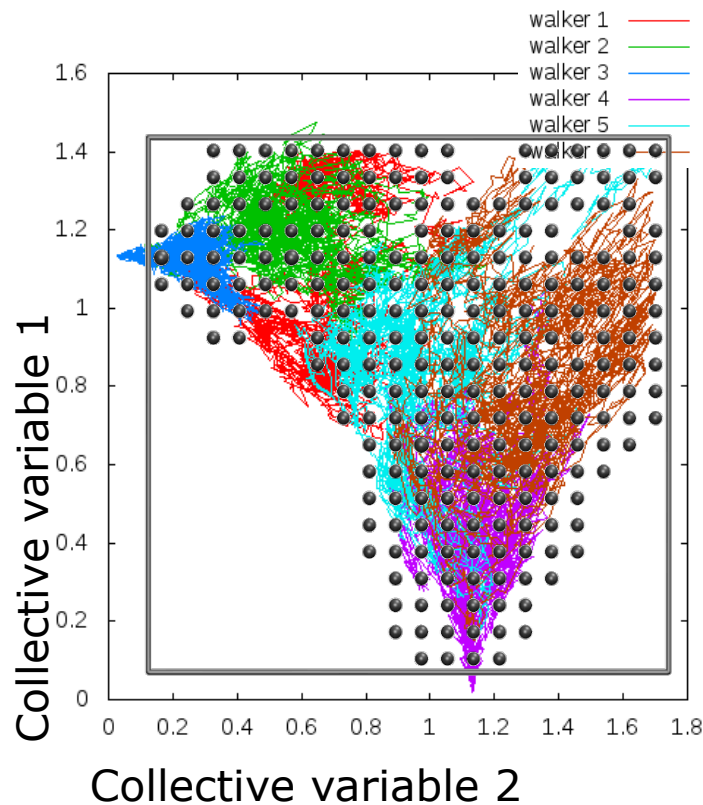
- Collective Variables Trajectories



- Time dependent Bias Potentials



## 1) Find the microstates

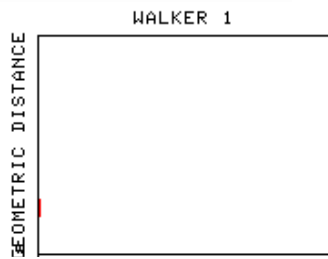


# Analyzing Metadynamics Results

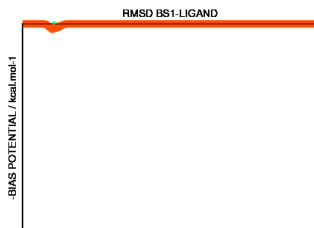
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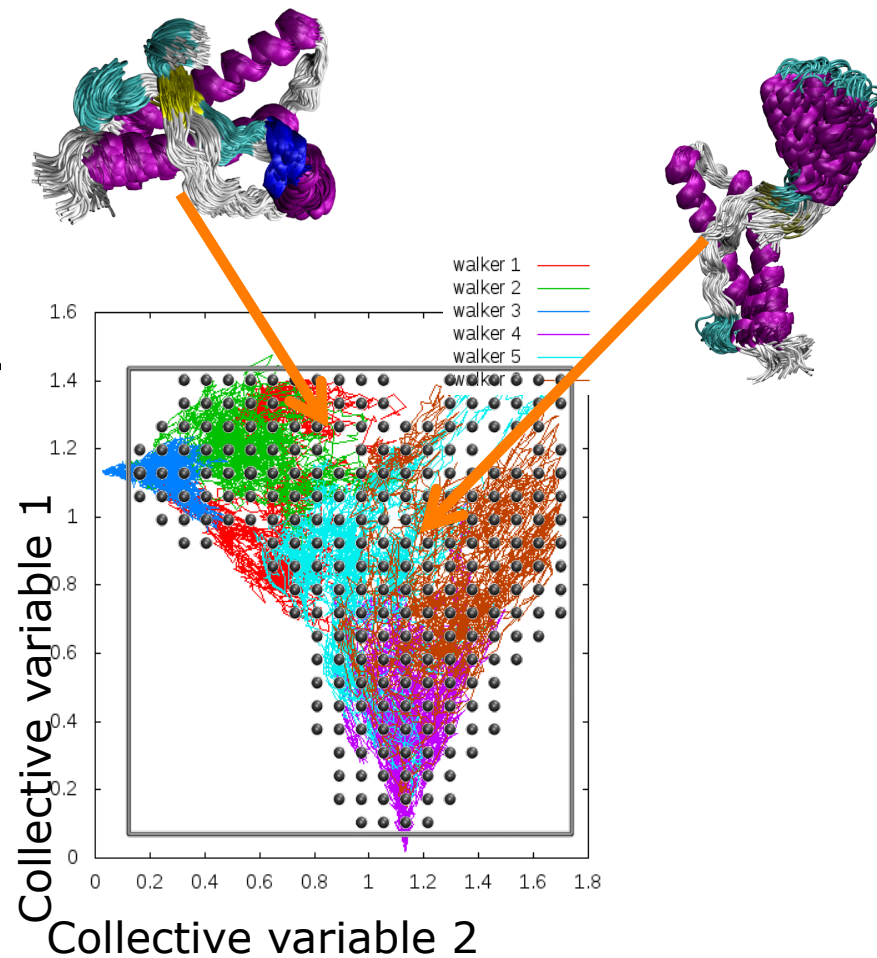
- Collective Variables Trajectories



- Time dependent Bias Potentials



**2) Check their structural consistency**

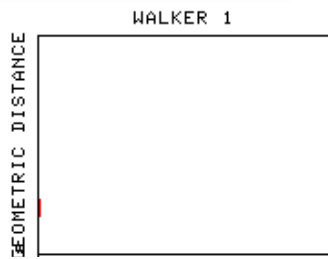


# Analyzing Metadynamics Results

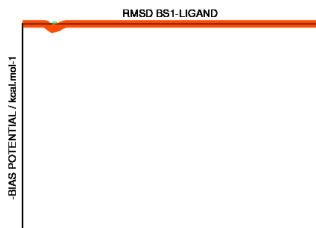
- Metadynamics output files
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- Collective Variables Trajectories

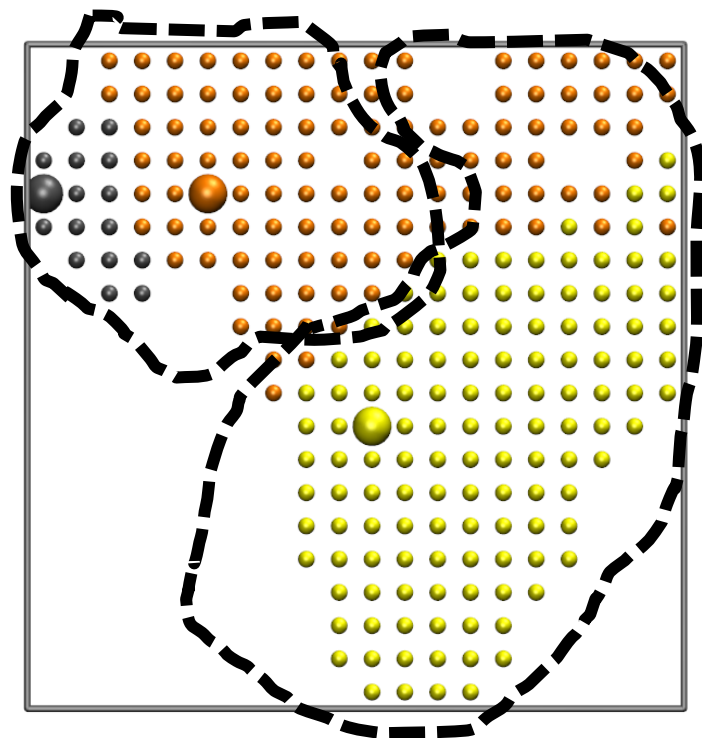


- Time dependent Bias Potentials



**3) Compute their free energy by WHAM**

**4) Find the kinetic basins**



# METAGUI – Unified Analysis Tool for Metadynamics



**1) Structural clustering  
of the trajectories**



**2) Compute the free  
energy hypersurface**



**3) Identify the main  
basins**



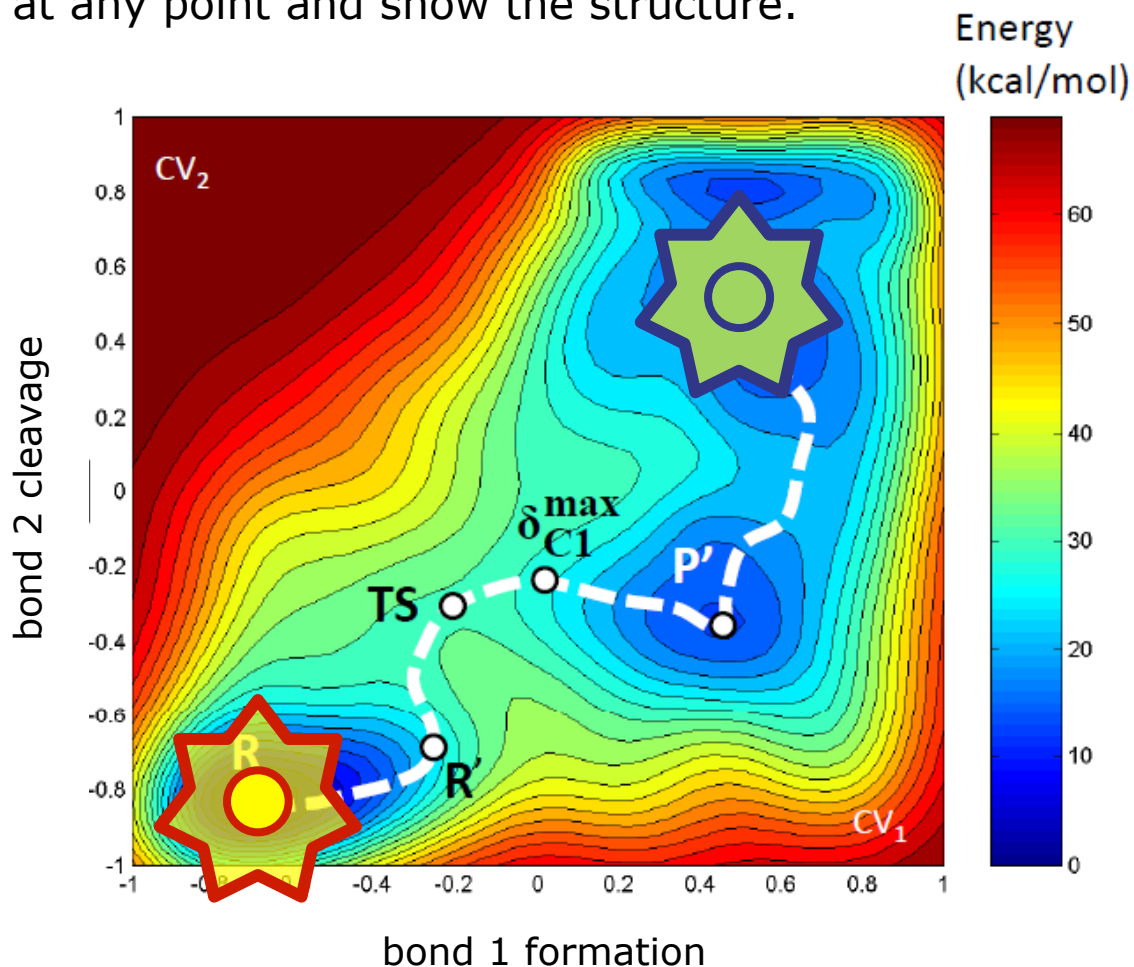
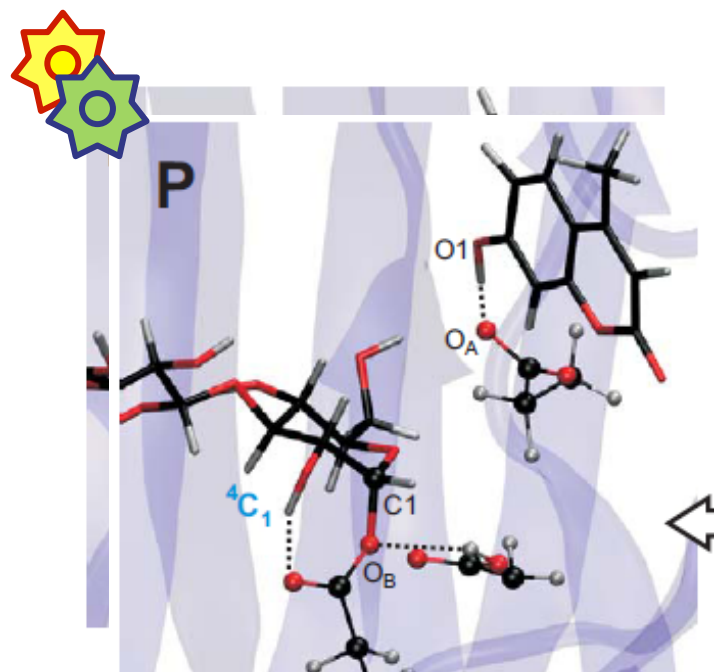
**4) Interactively explore the  
structures of the system**

**VMD (TCL/TK)  
+  
FORTRAN90**



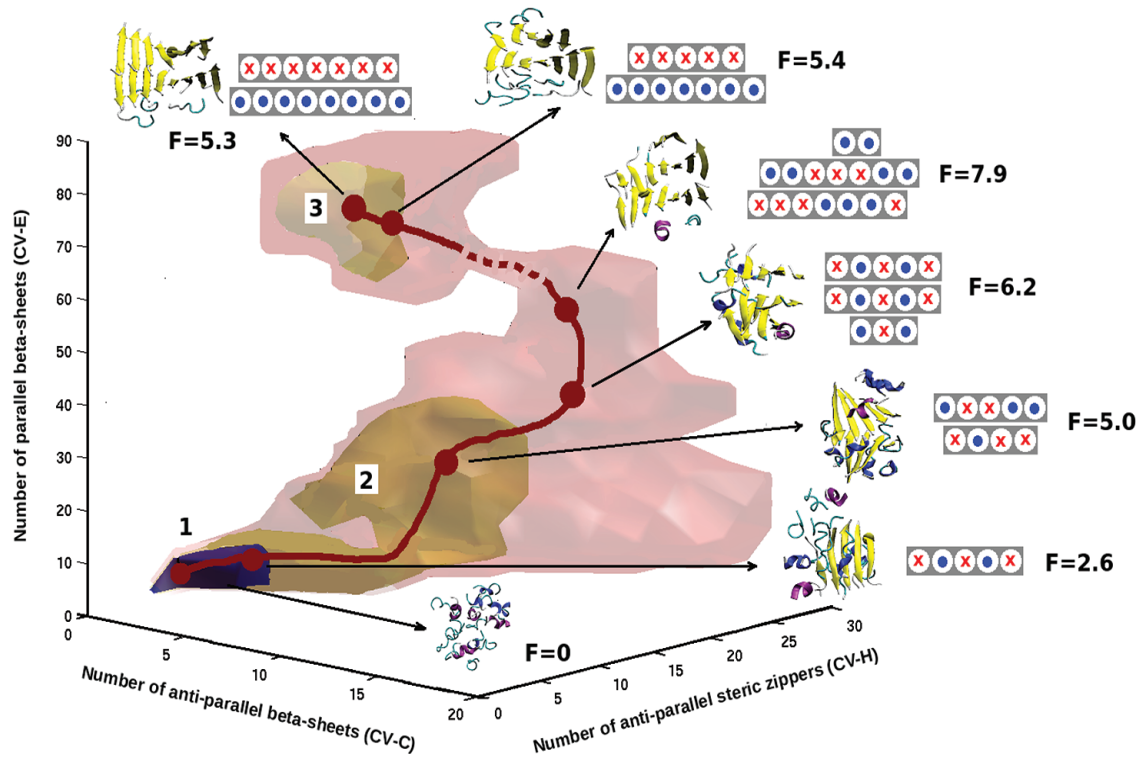
# the main scope of METAGUI

- METAGUI simplifies the analysis of metadynamics simulations, and directly connects CV based results onto 3D structures.
- ex. 2D Free Energy Surface of an enzymatic reaction
  - > click at any point and show the structure.



# Multidimensional View of Amyloid Fibril Nucleation in Atomistic Detail

Fahimeh Baftizadeh,<sup>†</sup> Xevi Biarnes,<sup>‡</sup> Fabio Pietrucci,<sup>¶</sup> Fabio Affinito,<sup>§</sup> and Alessandro Laio<sup>\*,†</sup>

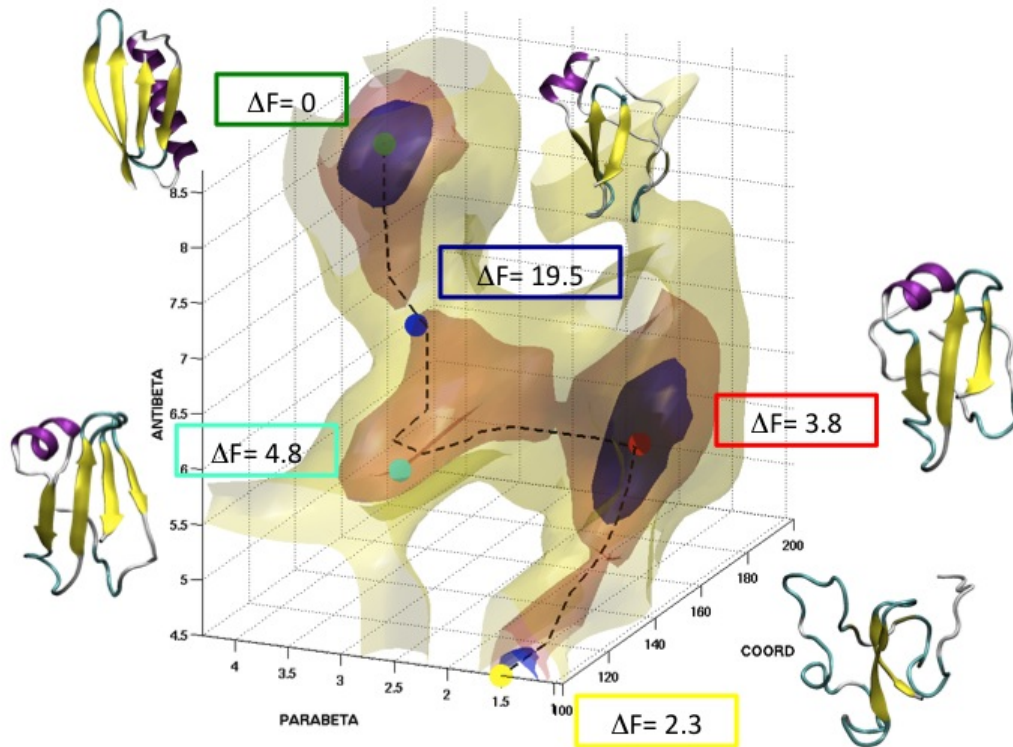


**8 collective variables describing parallel and antiparallel packing, etc.**

**500 ns on 8 replicas**

# Folding free energy landscape of the GB3 protein

Daniele Granata, Carlo Camilloni, Michele Vendruscolo



**6 collective variables describing hydrophobic packing, alpha and beta fraction, etc. One CV describing the consistency with experimental chemical shifts.**

**400 ns on 7 replicas**

**Thanks:** Xevi Biarnes  
Fabio Pietrucci  
Fabrizio Marinelli

**Available at:**



[www.plumed-code.org](http://www.plumed-code.org)