

Combining human intervention and empirical data using interactive elastic network models

André Lanrezac¹, Nicolas Férey^{1,2} and Marc Baaden¹

¹Laboratoire de Biochimie Théorique (LBT - UPR CNRS 9080), Institut de Biologie Physico-Chimique (IBPC), Paris (France)

²Laboratoire Interdisciplinaire des Sciences du Numérique (LISN – UMR 9015), Univ. Paris-Saclay, CNRS, Orsay (France).

Introduction

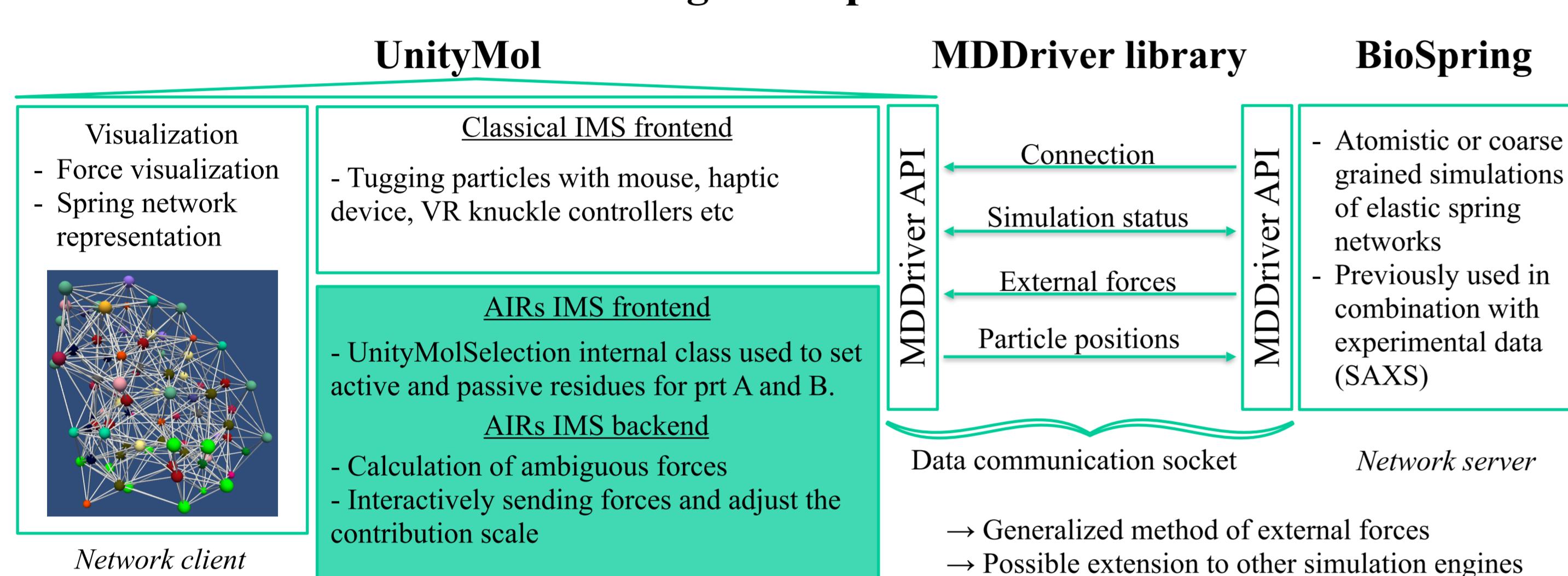
We explore to transpose the use of an equivalent of the HADDOCK Ambiguous Interaction Restraints (AIRs) [1] directly as new feature to UnityMol [2] to guide docking experiments by adding computed forces to satisfy the AIR energy penalties. One can jointly explore, also by adding external forces, other alternative structures while remaining within a framework of constraints whose contribution scale can be chosen. The support for interactive molecular simulations (IMS) is provided by the BioSpring program, whose functioning based on Elastic spring Network Models (ENM) is detailed.

1- An IMS protocol to integrate empirical data?

What is the Interactive Molecular Simulation approach ?

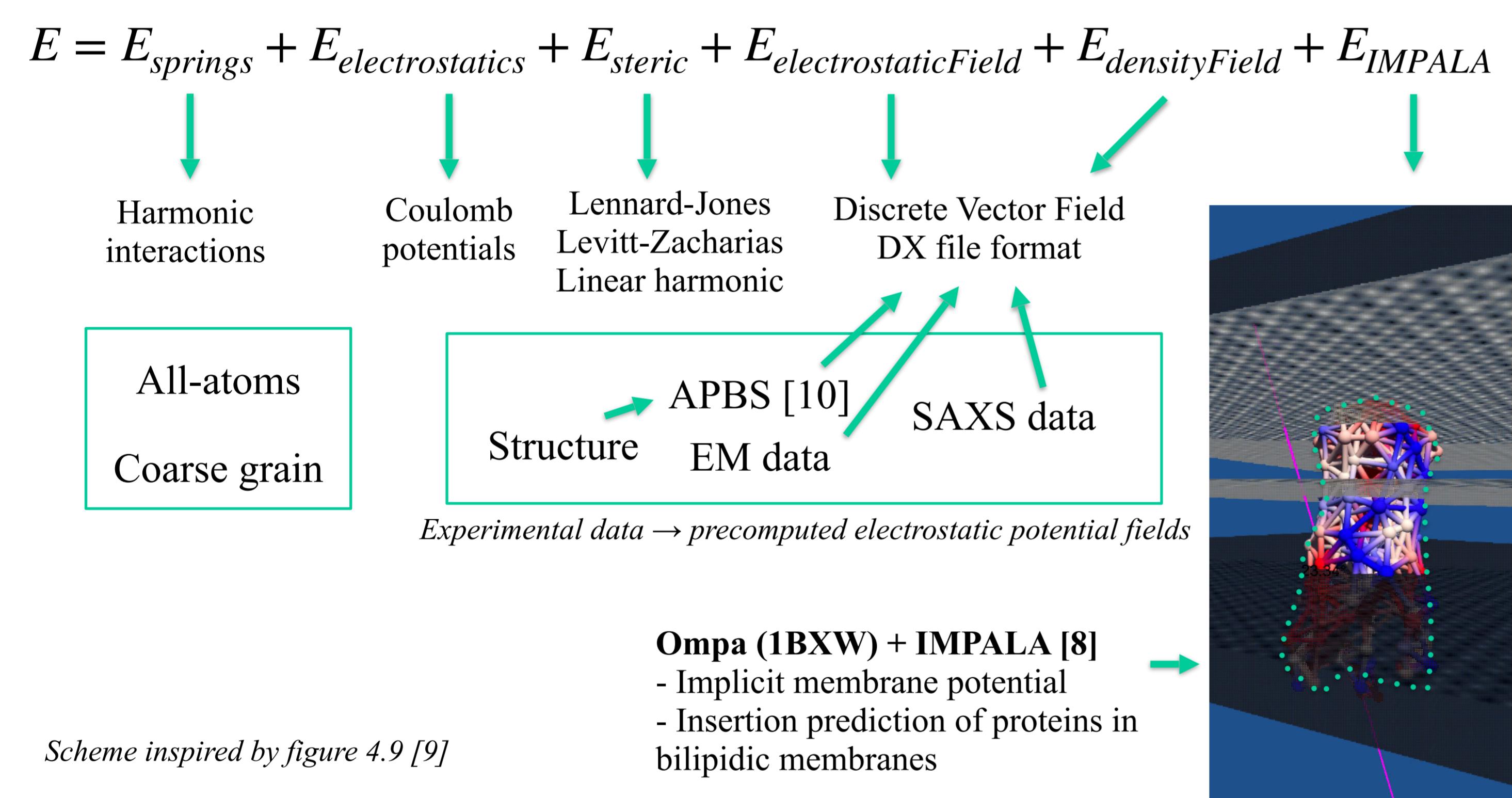
- Visualize the result of an ongoing simulation in line with human perception
- Manipulate the simulation interactively

The general protocol



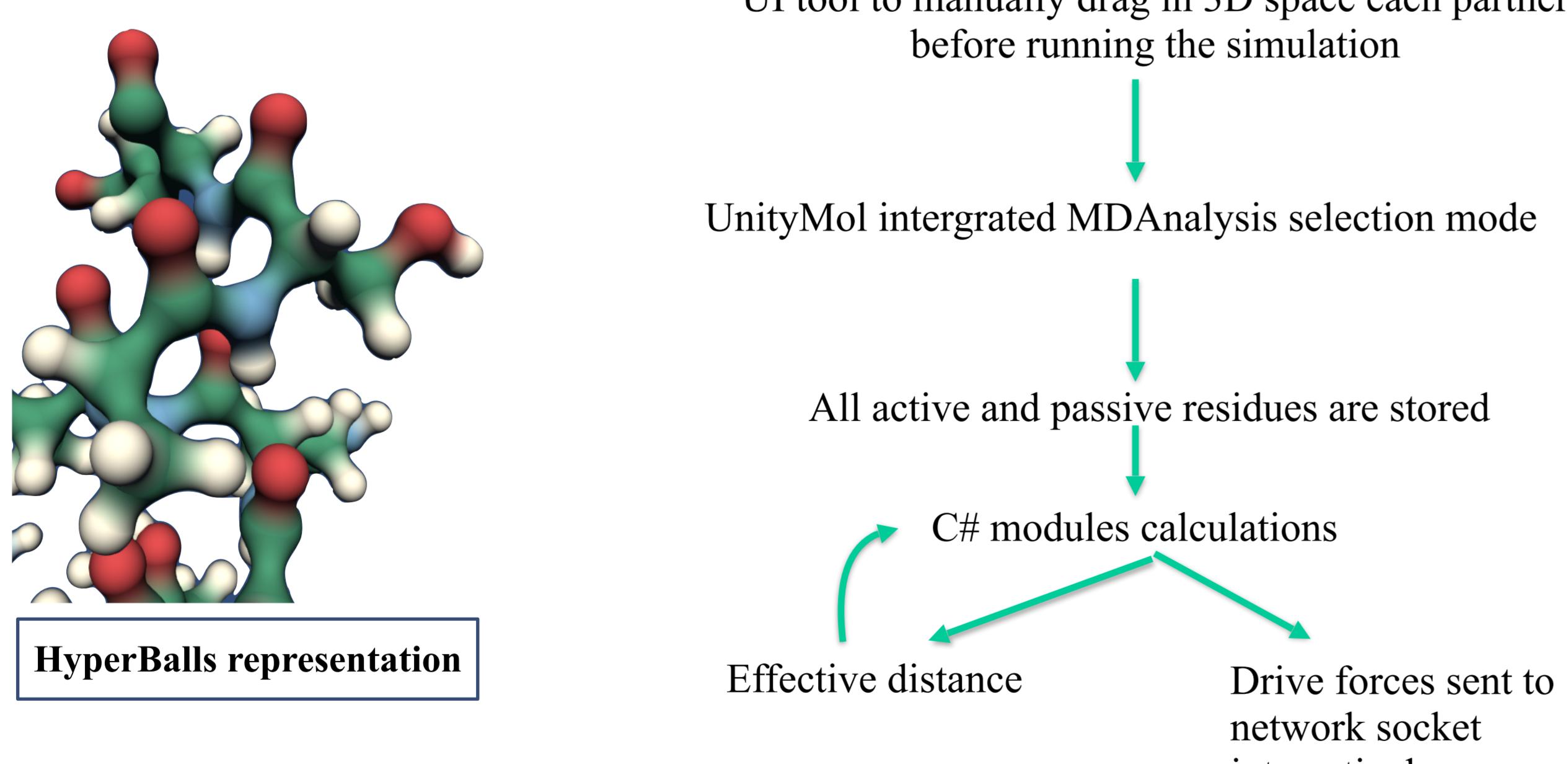
2- BioSpring simulation engine [3][4]

Simulate the overall flexibility of large biomolecular assemblies ...



3- UnityMol visualisation software

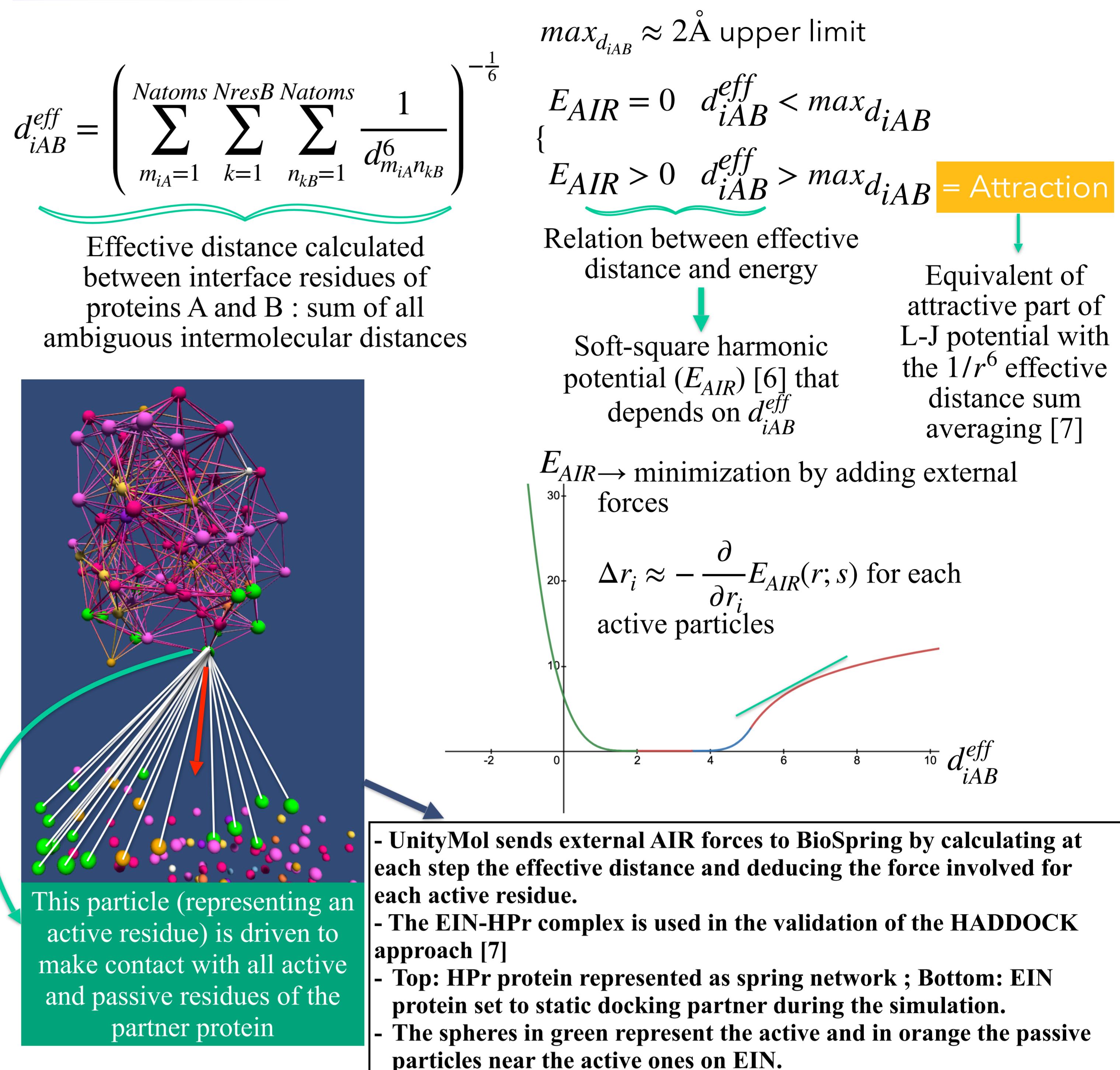
- Use Unity3D game engine with C# programming support/integration
- Augmented with special representation : e.g. HyperBalls [5] and with UI for preparing the system



References

1. De Vries, S. J., Van Dijk, M., & Bonvin, A. M. **2010**, 883-897.
2. Lv, Z., Tek, A., Da Silva, F., Empereur-Mot, C., Chavent, M., & Baaden, M. **2013**, 8(3), e57990.
3. Tek, A., Chavent, M., Baaden, M., Delalande, O., Bourdot, P., Katz, B. F., & Férey, N. **2012**, IntechOpen.
4. Férey, N., Delalande, O., & Baaden, M. **2012**, 433-434.
5. Chavent, M., Vanel, A., Tek, A., Levy, B., Robert, S., Raffin, B., & Baaden, M. **2011**, 2924-2935.
6. Nilges, M., Gronenborn, A.M., Brunger, A.T. & Clore, G.M. **1988**, 27–38
7. Dominguez, C., Boelens, R., & Bonvin, A. M. **2003**, 1731-1737.
8. Ducarme P, Rahman M, Brasseur R. **1998**, 357–371
9. Sébastien Doutreligne thesis: Interactive Molecular Dynamics Software Development
10. Baker NA, Sept D, Joseph S, et al. **2001**, 10037-10041

4- Integration of AIRs into UnityMol-BioSpring



5- Current challenges and outlook

Challenges

- Relevance of energies involved: the energy added to the system by the user inputs should be balanced by a compensating one added by the AIRs ?
- Random deletion of a fraction of restraints at each IMS-AIRs session should be considered
- We still need to consider integrating E_{AIR} directly into BioSpring code instead of sending external forces

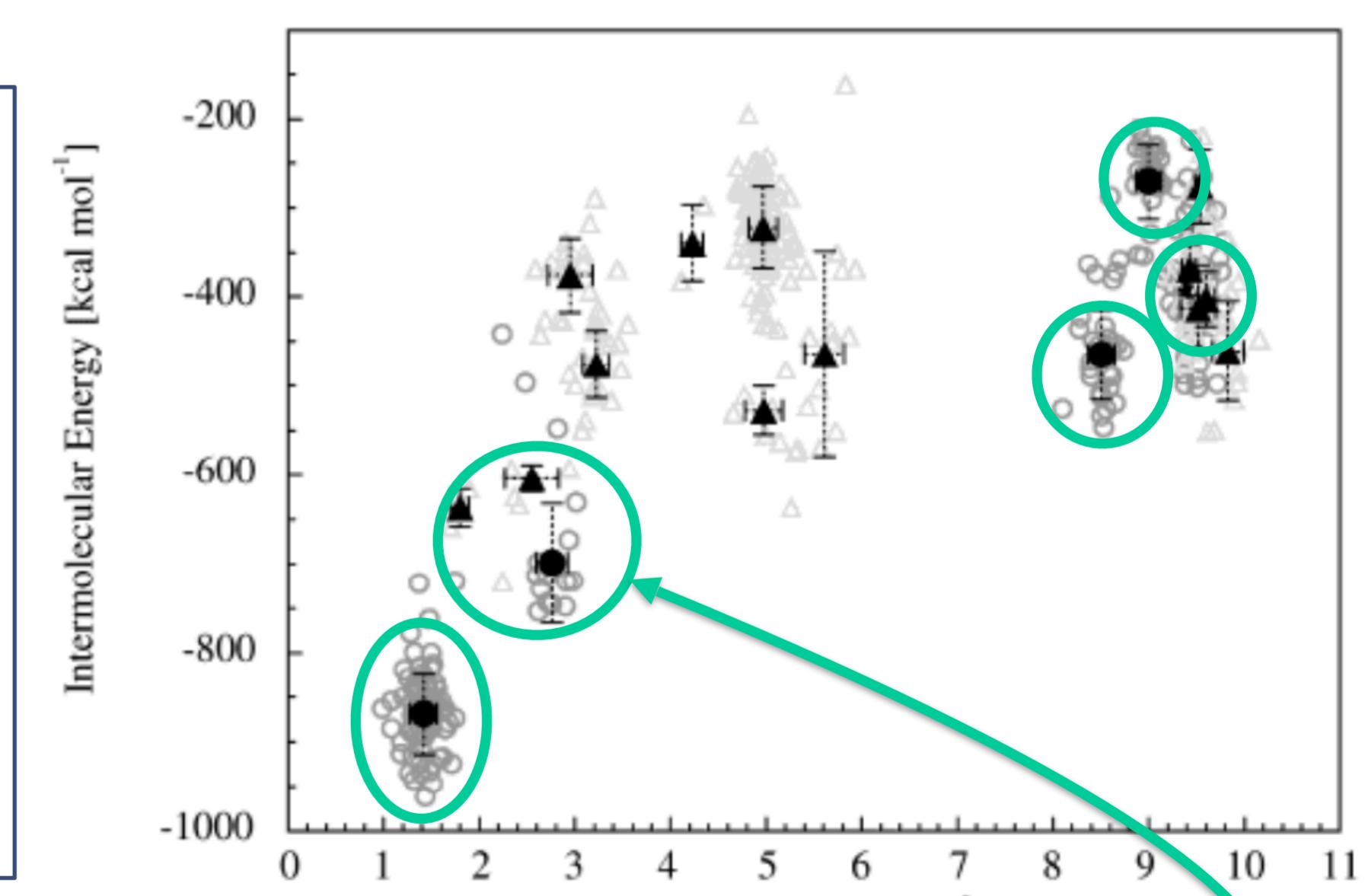
First protocol validation

- Extract intermolecular energy from the BioSpring simulation including the calculated E_{AIR} in UnityMol
- Calculate this energy and the RMSD with respect to the crystallized structure (3EZA).
- Fine-tuning the simulation parameters (e.g. springs parameters, force field, ...) to compare with one of the validation protocol results of the HADDOCK approach [6] presented below

EIN-HPr complex docking

Intermolecular energy vs iRMSD (backbone RMSD at the interface from 3EZA structure).

Docking comparison between **complex conformation** (filled circles) and **free form** (filled triangles) for the starting structures



→ Can these 5 poses clusters (circled in green in the figure) be reobtained with IMS-AIRs simulations?

→ Same for the best cluster / best docking solution ?

Summary

- The protocol is currently being finalized, with significant parts of the validation and comparison research still to be carried out.
- One objective could be to promote the protocol as a pre-simulation tool for preparing more extensive MD simulations.
- Validation and performance testing work is in preparation.
- IMS by human particle tugging intervention allows a quick exploration of all possible configurations at the interface defined by the experimental data, guided by AIRs.

Would you try our framework? Please feel free to contact us: lanrezac@ibpc.fr
We also thank Antonio Iorio for support in preparing this poster.