Grid computing simulations to model protein complexes involved in Fragile X Syndrome

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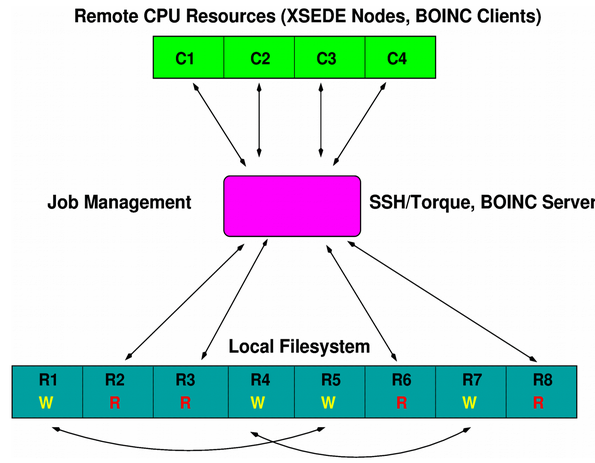
Background

Fragile X Syndrome, a genetic disorder caused by a change in the FMR1 gene, is the most common form of inherited mental retardation and can cause autism in carriers. Biologists know that Fragile X Syndrome is caused by the absence of the FMRP protein in neuronal cells. Computer models of biological macromolecules are used to gain insights not easily obtainable by experimental means. However, these models require large computation resources. Grid computing, a type of distributed computing in which an organization uses idle machines to run large computations, is a promising platform to provide computational power for research studies of this kind.

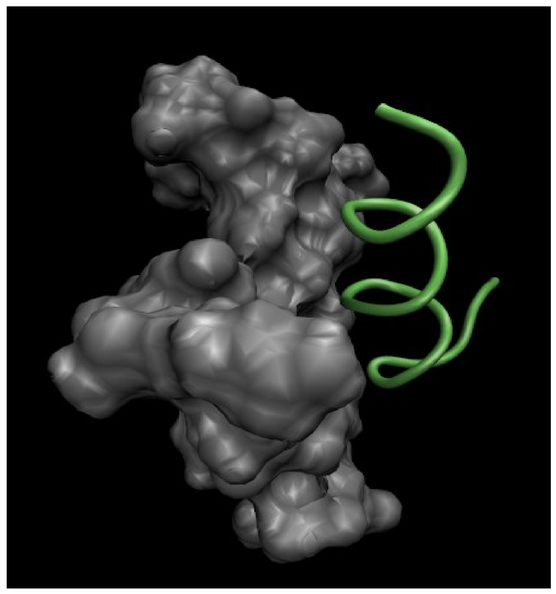
Materials and methods

- The BOINC software framework was used to build a computational grid utilizing over 250 desktops from Brooklyn College's student PC lab during off-hours.
- Thousands of molecular dynamics threads running on our computational grid were coupled together to compute the strength of binding between two proteins: eIF4E and CYFIP1, which are known to be involved in the development of neural synapses.
- Asynchronous Replica Exchange (AsyncRE) software was used to obtain binding data for wild type CYFIP1 and three mutants.
- Protein trajectory analysis code for CYFIP1 and its mutants was written in Python.

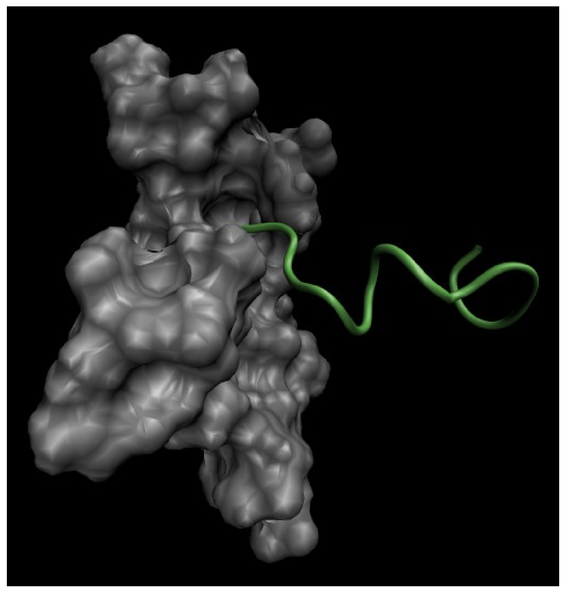


Schematic diagram of AsyncRE software on a BOINC-based grid computing system.

Results



Wild type CYFIP1 binding to eIF4E.



Mutant CYFIP1 binding to eIF4E.

- CYFIP1 mutants bind more weakly and in an unconventional manner compared to wild type CYFIP1.

- Our computational models provide the structure of the eIF4e-CYFIP protein complex, which can be used to inform the development of peptidomimetics inhibitor drugs against eIF4E to treat cancer. (For an example: HIV-protease inhibitors.)

Conclusions

Computer models and large grid computing resources have successfully been deployed and have provided invaluable data to understand the molecular causes of Fragile X Syndrome.

The structures generated by the computational models, which are not available experimentally, rationalize the biochemical data and serve as a guide for future drug design studies to find therapies for Fragile X Syndrome.

Without the computing power provided by our grid computing infrastructure, it would be impossible to gather enough data to perform a meaningful analysis of the interaction between eIF4E and CYFIP1, and their role in the expression of Fragile X Syndrome.

Acknowledgments

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Further information

- **AsyncRE software:** https://github.com/ComputationalBiophysicsCollaborative/AsyncRE
- **Lab website:** http://sites.google.com/site/emiliogallicchiolab
- Daniele Di Marino, Silvia De Rubeis, Tilmann Achsel, Giovanni Chillemi, Anna Tramontano, and Claudia Bagni. MD and docking studies reveal that the functional switch of CYFIP1 is mediated by a butterfly-like motion. J. Chem. Theory Comput., 2015. In press.