Dana Seibert

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Molecular Dynamics: Bcl-XL with BIM BH3 Domain

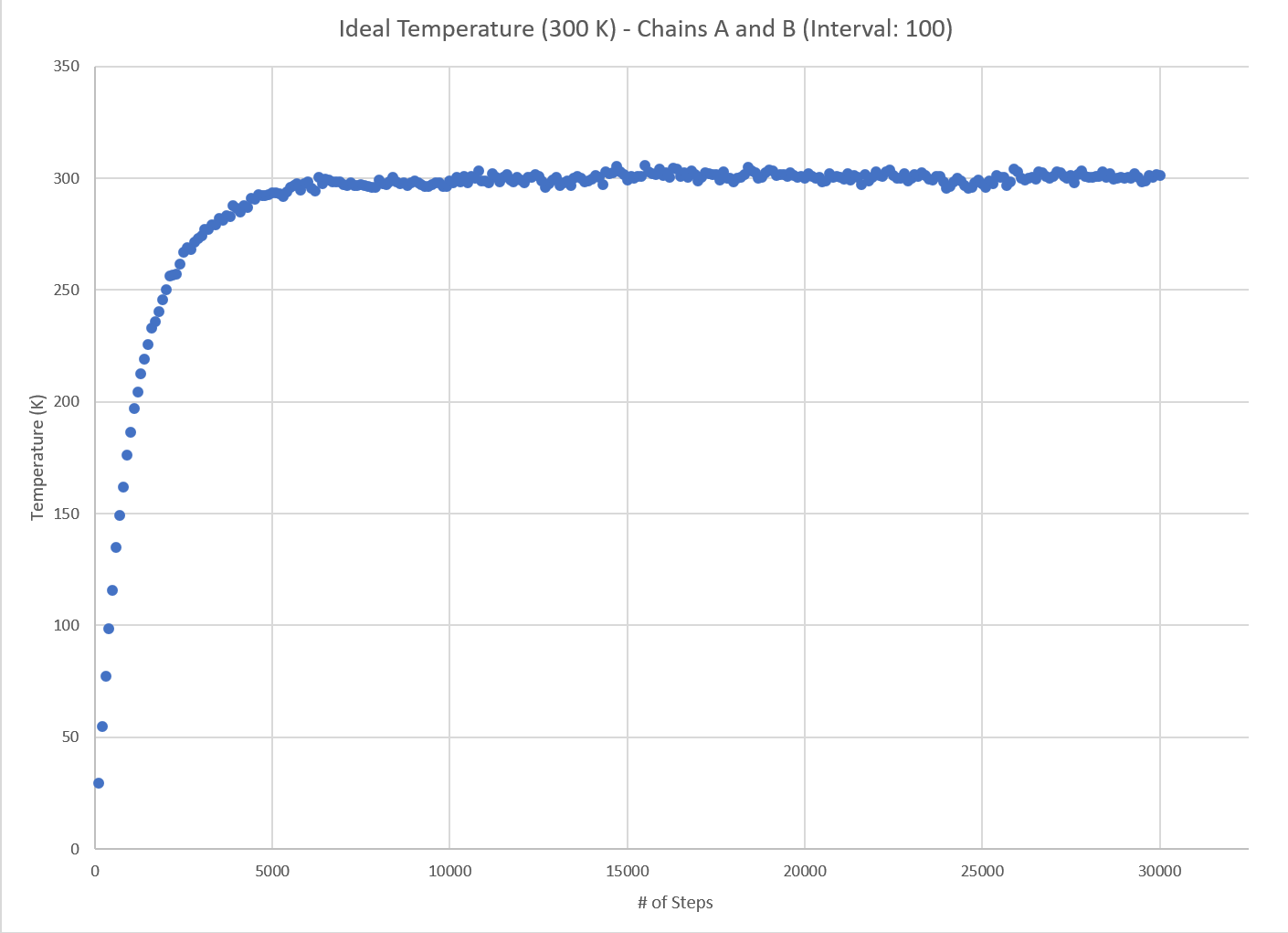
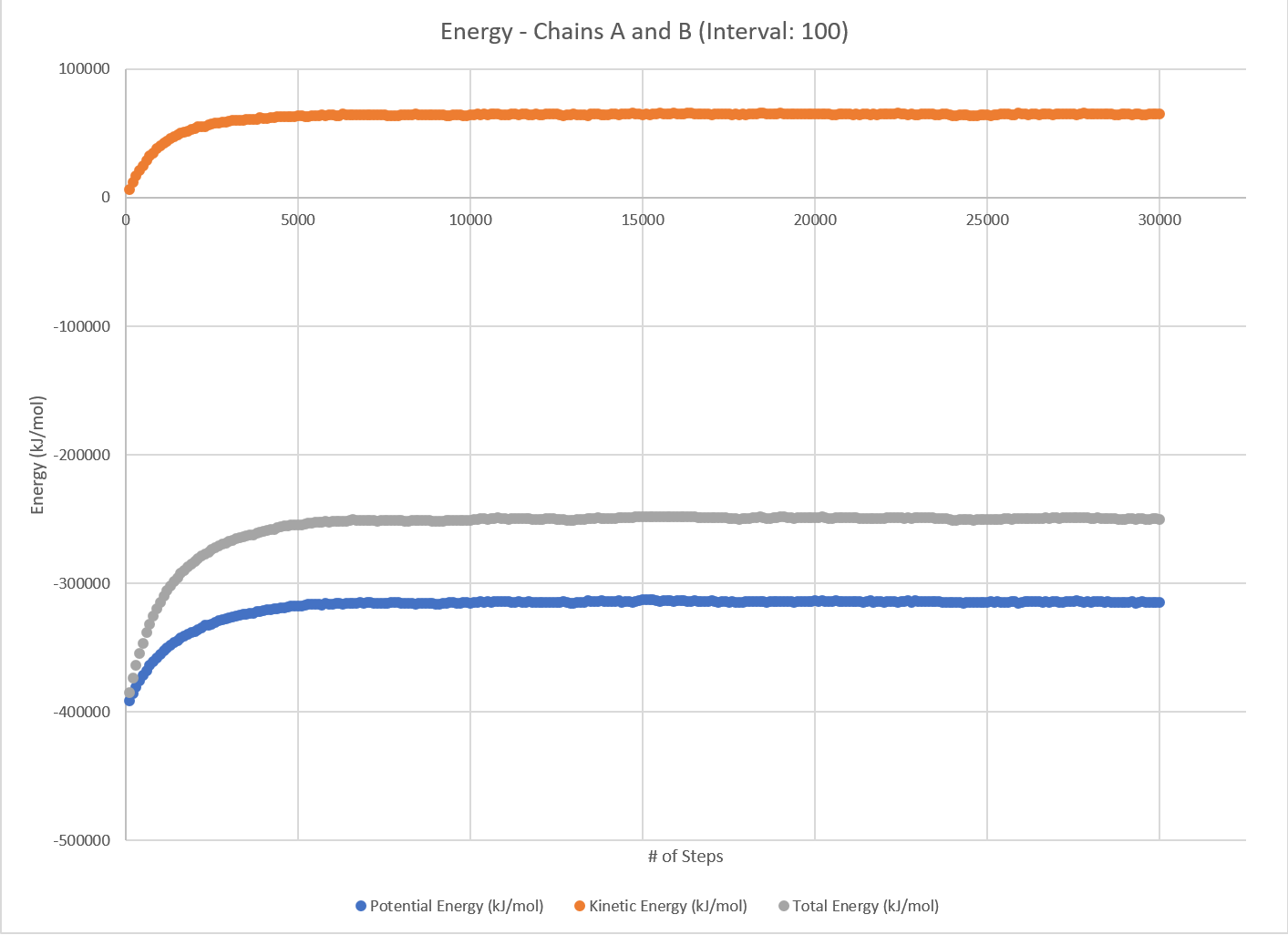
Bcl-XL, a member of the Bcl-2 family, is in charge of regulating apoptosis and maintaining homeostasis during cell death. It does so by targeting mitochondrial outer membranes and preventing the creation of disruptions that release death-promoting proteins into the cells. In order to learn more about this protein, I will visualize this compound in a BIM-BH3 domain using Python, OpenMM, and VBD. By changing certain variables, temperature and measurement increments, I will observe the change in binding energies of the complex’s chains. I hypothesize that changing the temperature, will affect the binding energies and changing increment sizes will increase accuracy of results. It was found that increment size had no noticeable effect on the validity of my measurements. Lowering the temperature of the complex lowered the binding energy, which is most desirable, however the temperature tested is not possible to occur in actual circumstances.

The Bcl-2, B cell leukemia/lymphoma 2, family of proteins are apoptotic regulators and mediate mitochondrial outer membrane permeabilization. This process is the “point of no return” during apoptosis and this family accomplishes the regulation of this process by creating disruptions in the membranes thus releasing death-promoting proteins, such as cytochrome C. The Bcl-2 family is divide into two groups, pro-apoptotic proteins and anti-apoptotic proteins. Bcl-XL is an anti-apoptotic protein. Like most proteins, it contains activation and inhibition sites. The study of its crystalline structure in complex BIM-BH3 can help researchers learn how to better control specialized cell death.

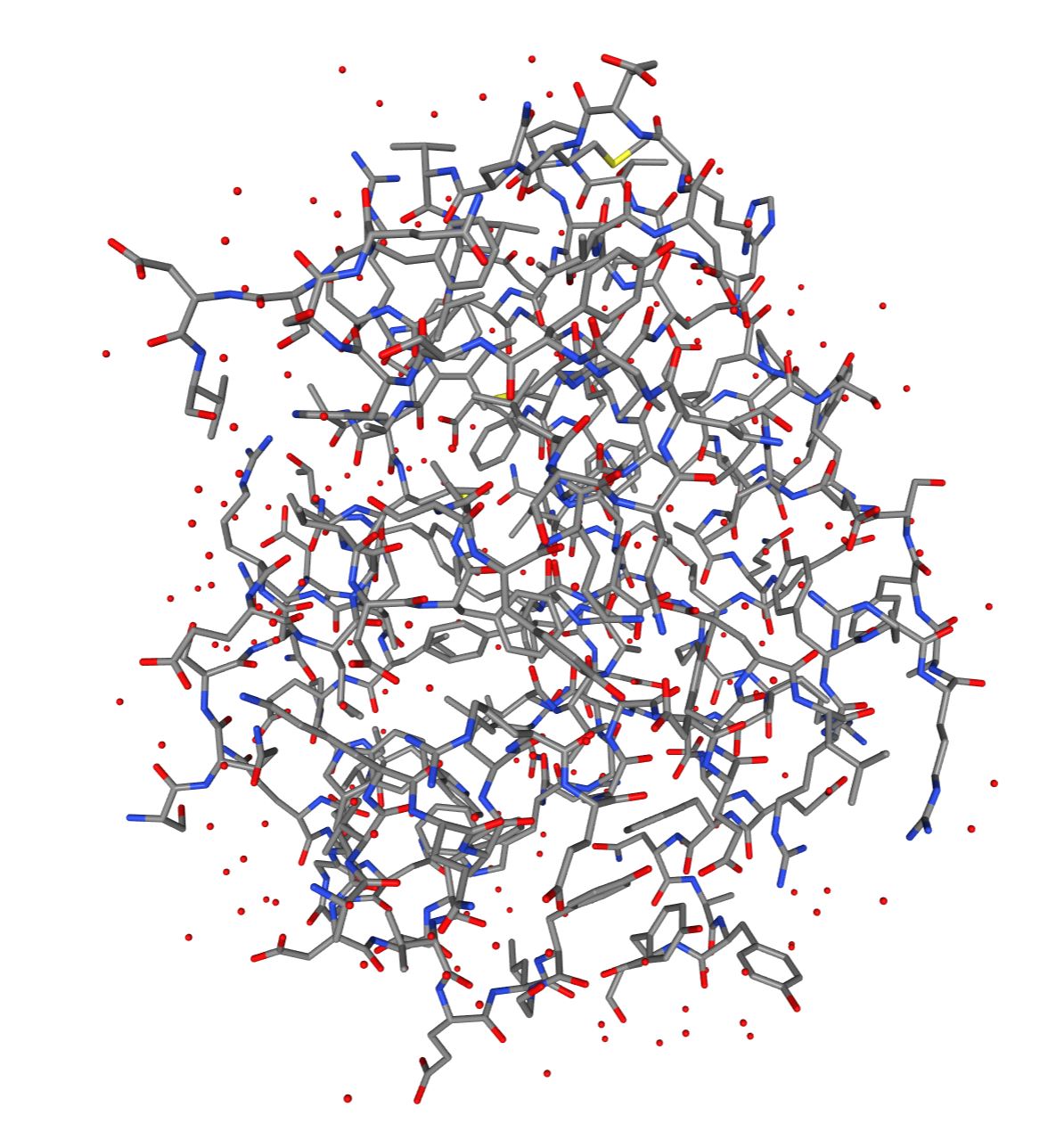
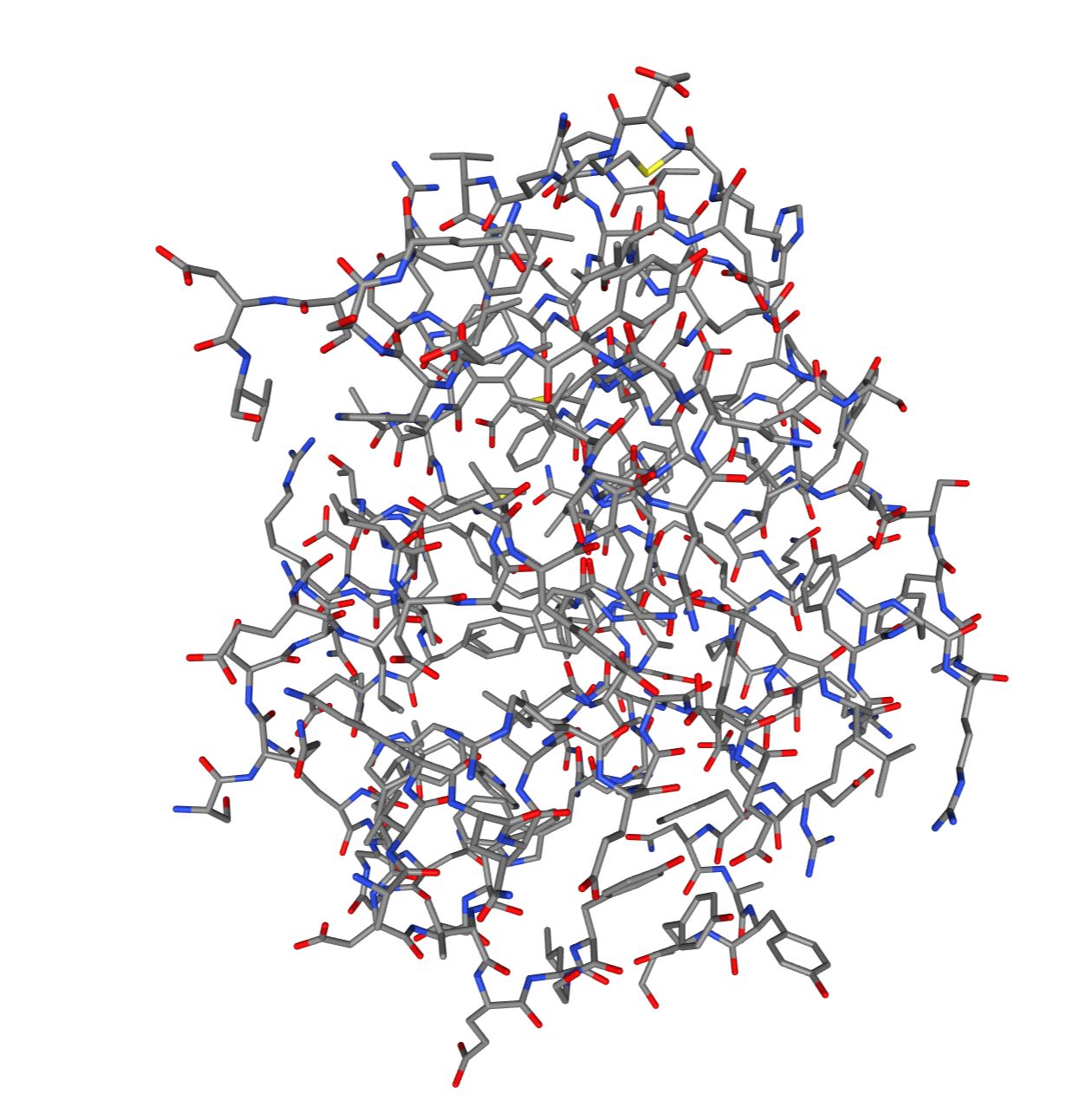
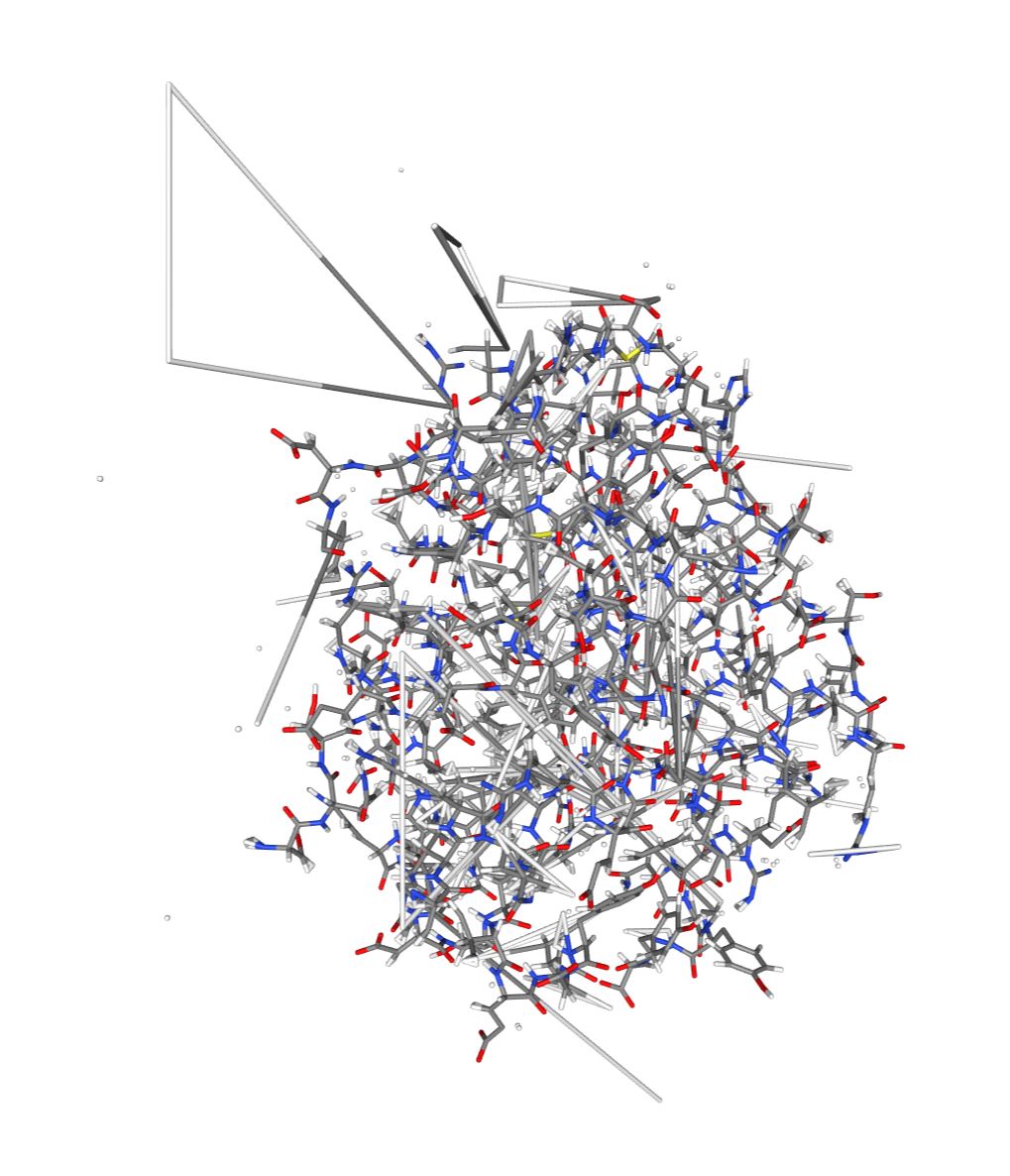
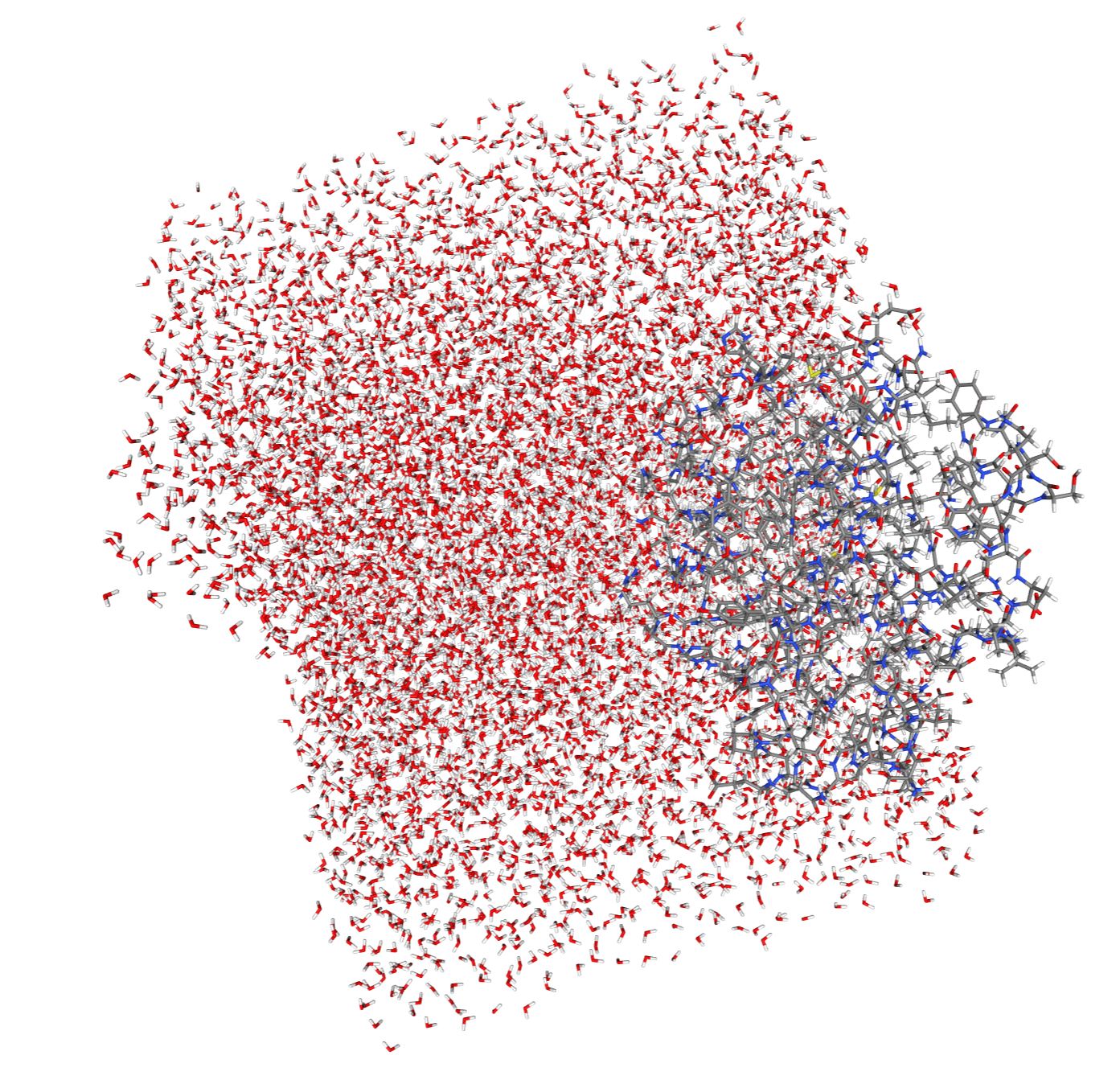
The Bcl-XL complex file can be found through the RCSB database using its specialized code “4QVF”. After downloading the PDB file, it was uploaded to a remote, private server and run using MobaXTerm. The original PDB file has extra information, like author names and experiment instructions, that Python has difficulty reading through. In order to remove this unneeded information, the file was cleaned using the “grep “^ATOM” 4qvf.pdb > 4qvf.clean.pdb” python command. Using example code, a rudimentary program was written to at the needed hydrogen and solvent atoms and visualize the complex. This process did not initially work as the chains appeared to be missing their necessary terminal residues. After extensive research, a solution was found by running this python code to further clean the pdb file: pdbfixer 4qvf.clean.pdb –output=4qvf.clean\_cleaned.pdb. After running this code, the pdb file was able to be altered correctly and visualized. The complex was then split into its two chains and both chains were cleaned and visualized separately. The potential, kinetic, and total energies, as well as temperatures and densities, were measured for all three components. Using this information, the binding energy was found for the whole complex. This process was then repeated as the increment size and temperature were changed to determine their effects on the binding energy.

The original run-through of the entire complex using room-temperature (300 K) and an increment size of 100, resulted in an equilibrium at around 6500 steps, a binding energy of

-161656.16 kJ, and a density of 0.95800248 g/mL.

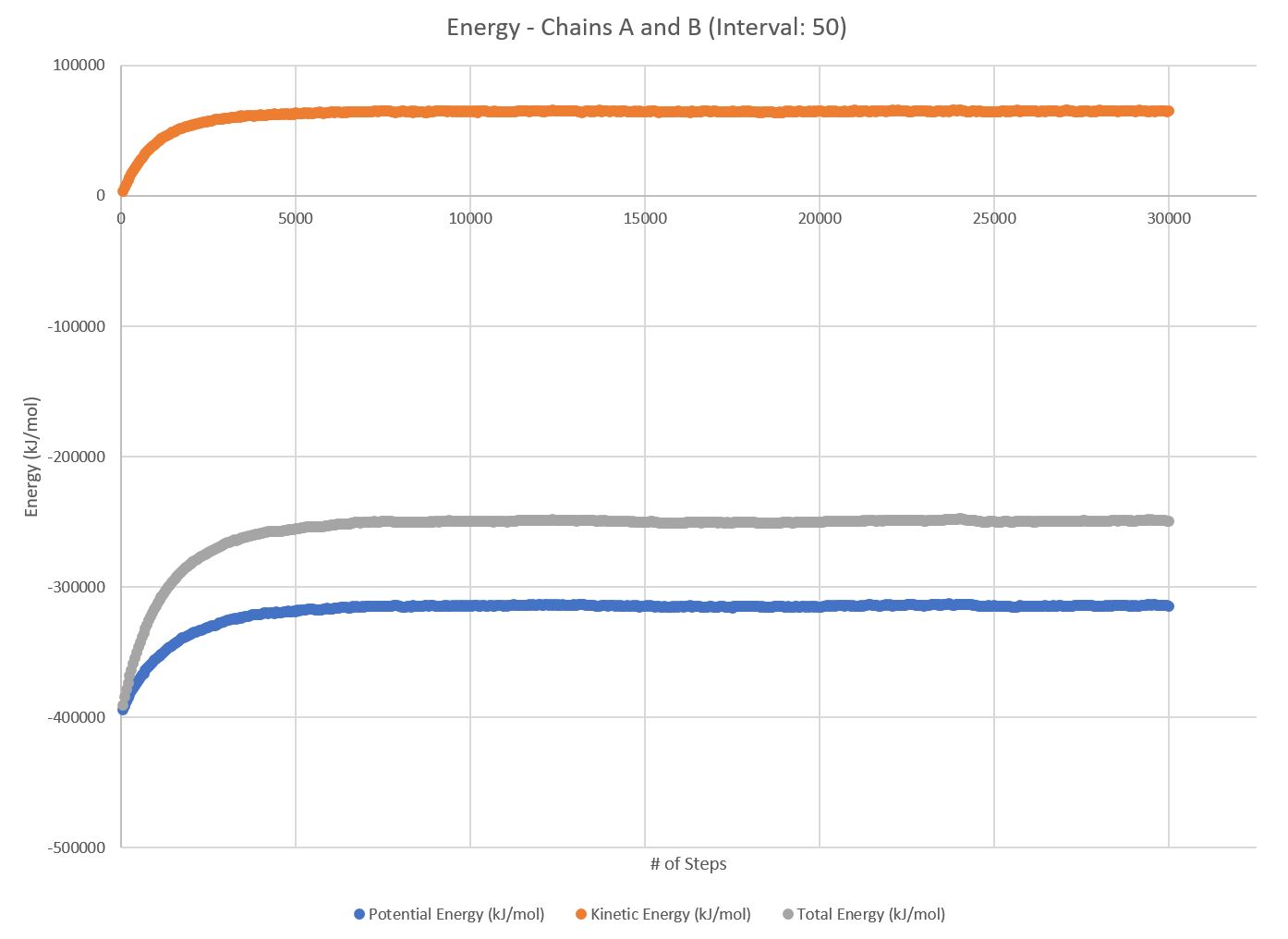
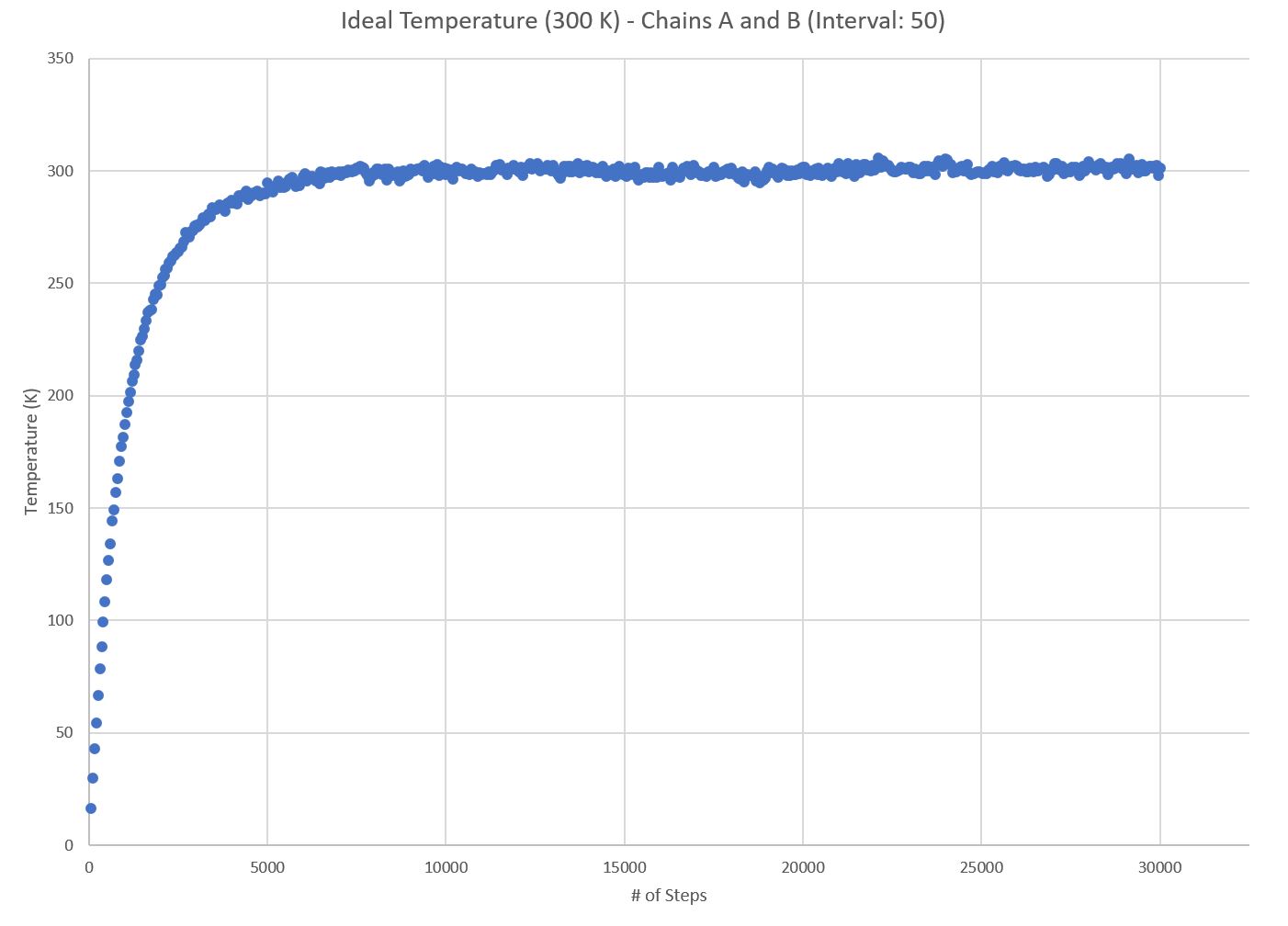


Below: Original PDB file, Cleaned PDB file, File with added terminal groups, and final edited file with added water and solvent molecules

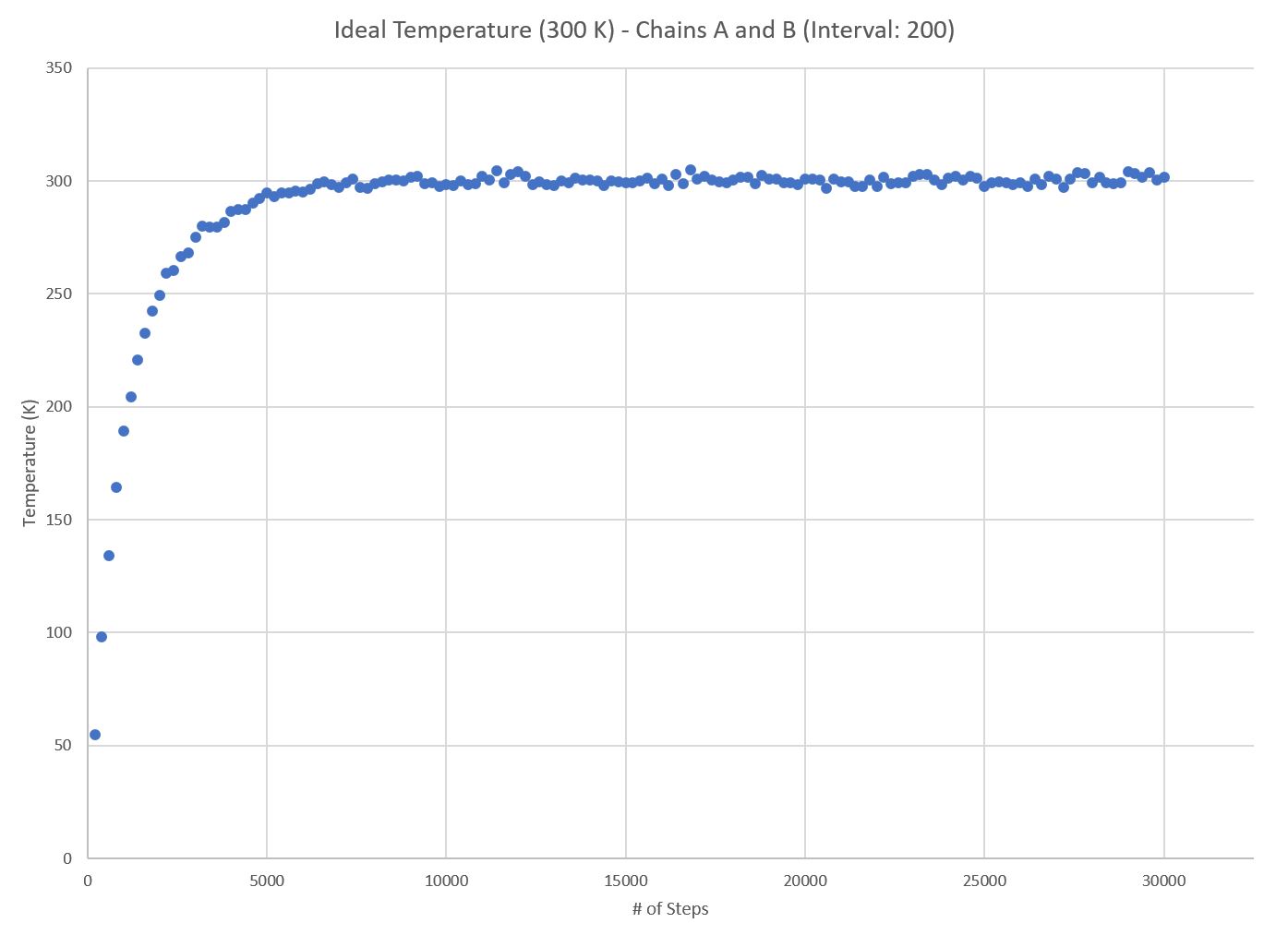
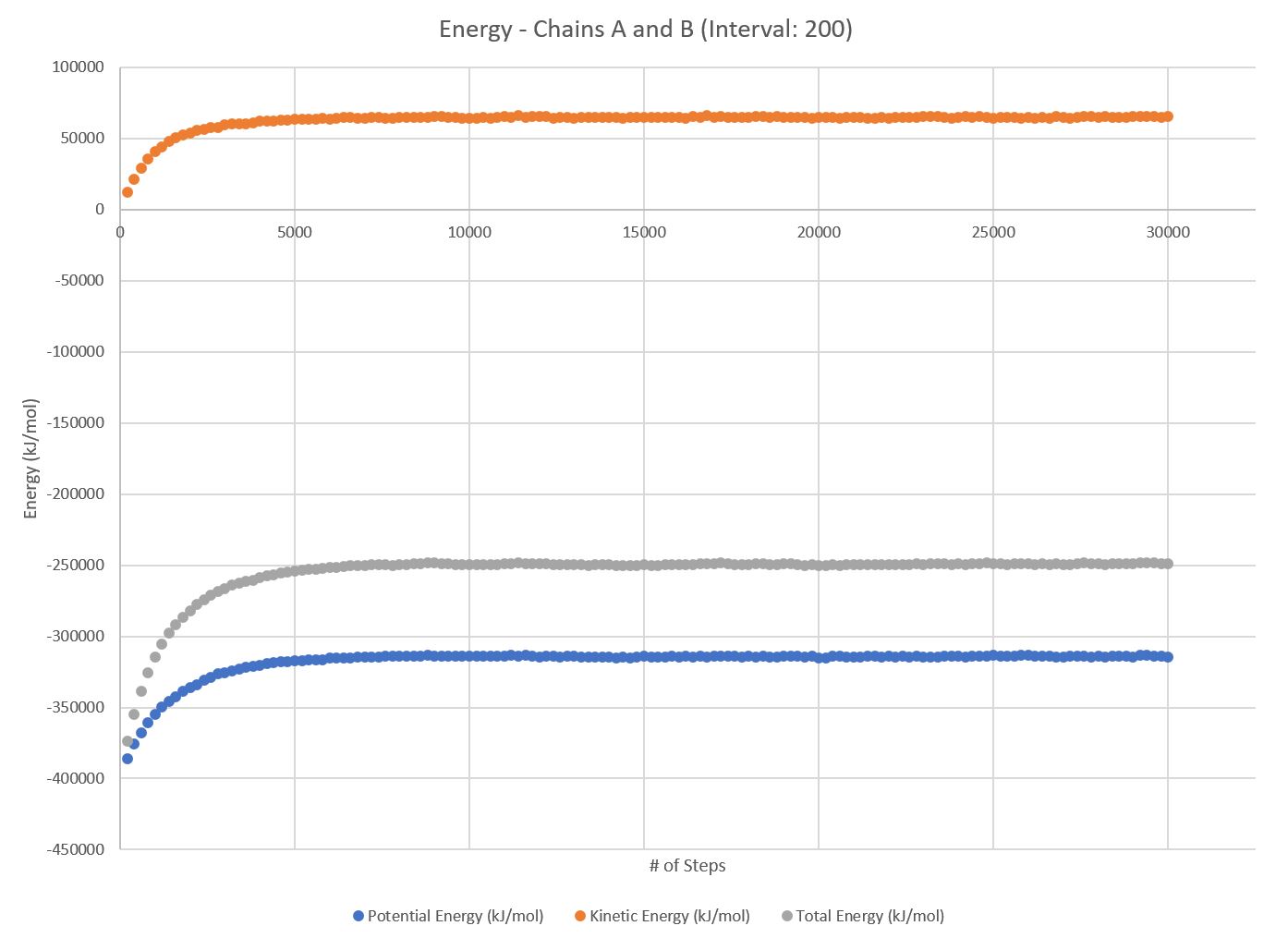
The second run-through of the entire complex using room-temperature (300 K) and an increment size of 50, resulted in an equilibrium at around 7020 steps, a binding energy of

-162075.58 kJ, and a density of 0.95800248 g/mL.

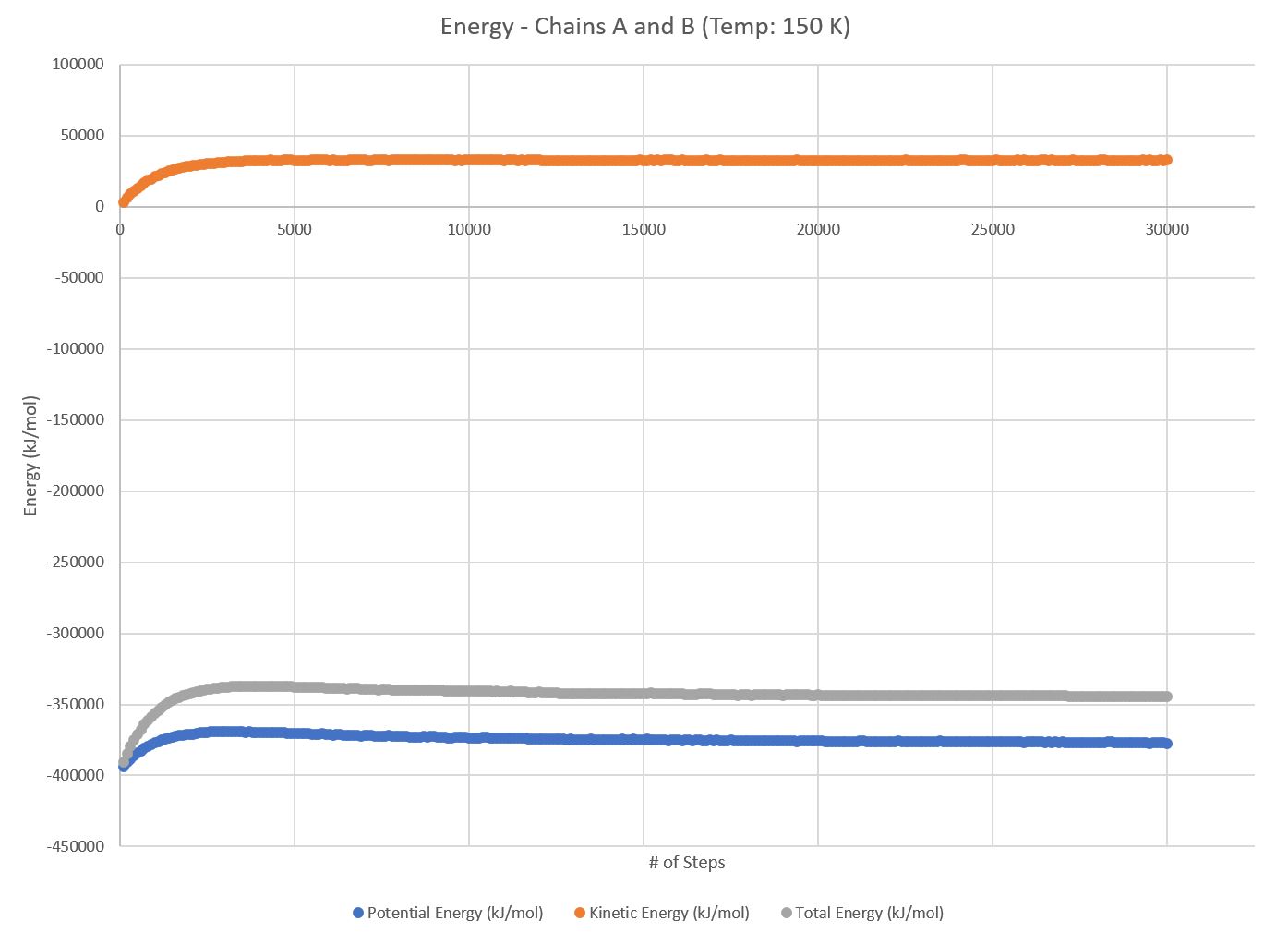
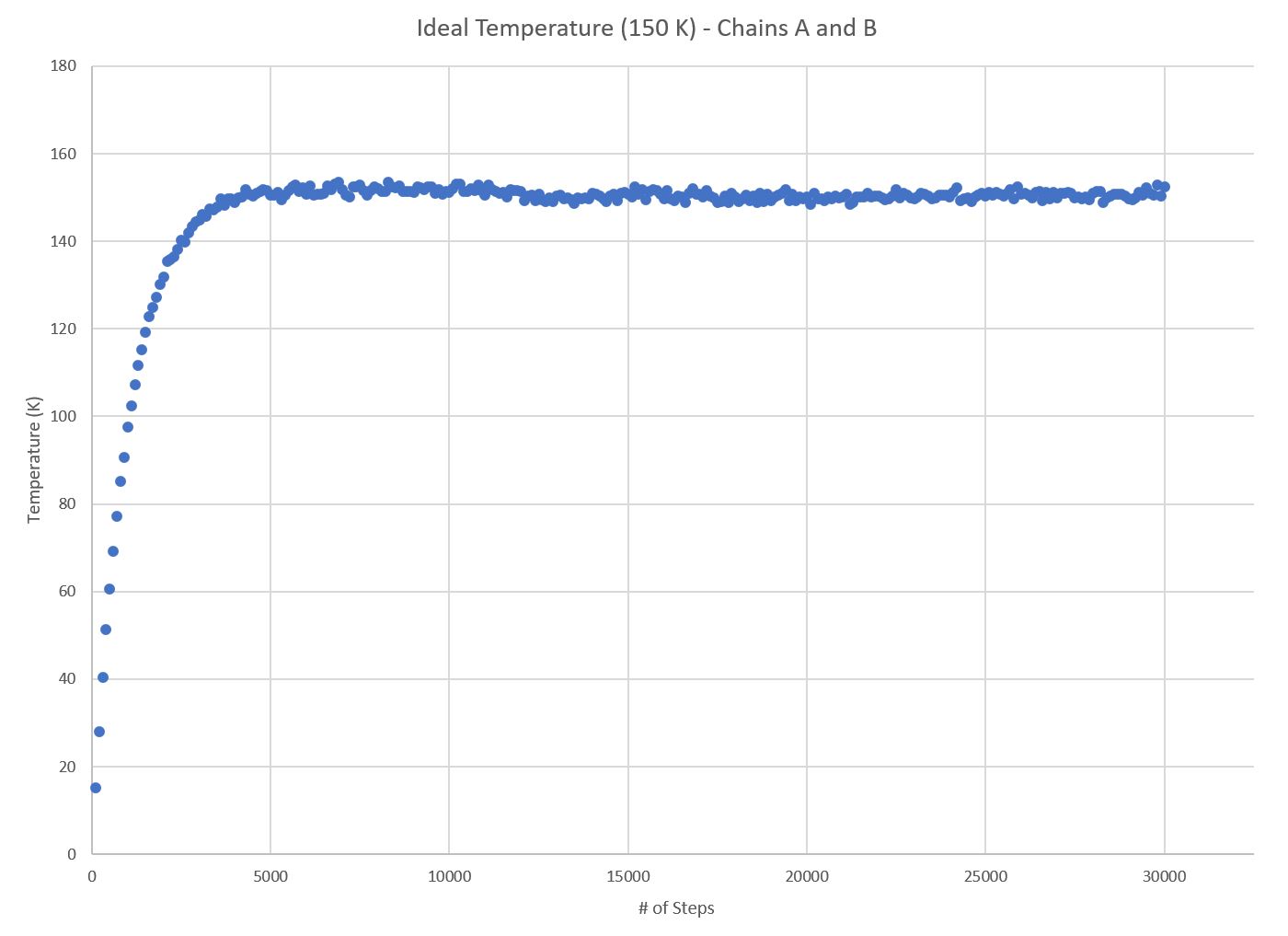
 

The third run-through of the entire complex using room-temperature (300 K) and an increment size of 200, resulted in an equilibrium at around 7200 steps, a binding energy of

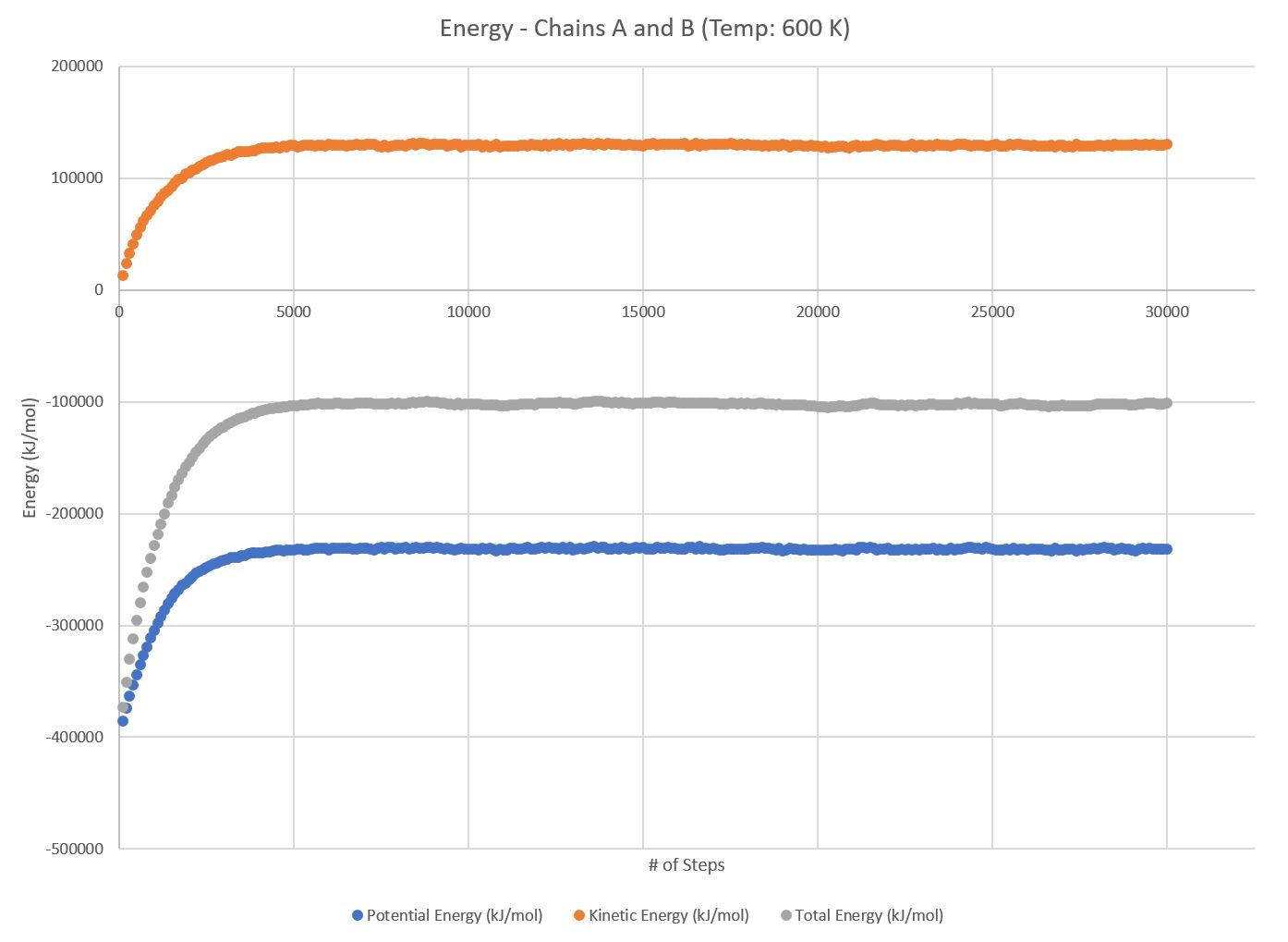
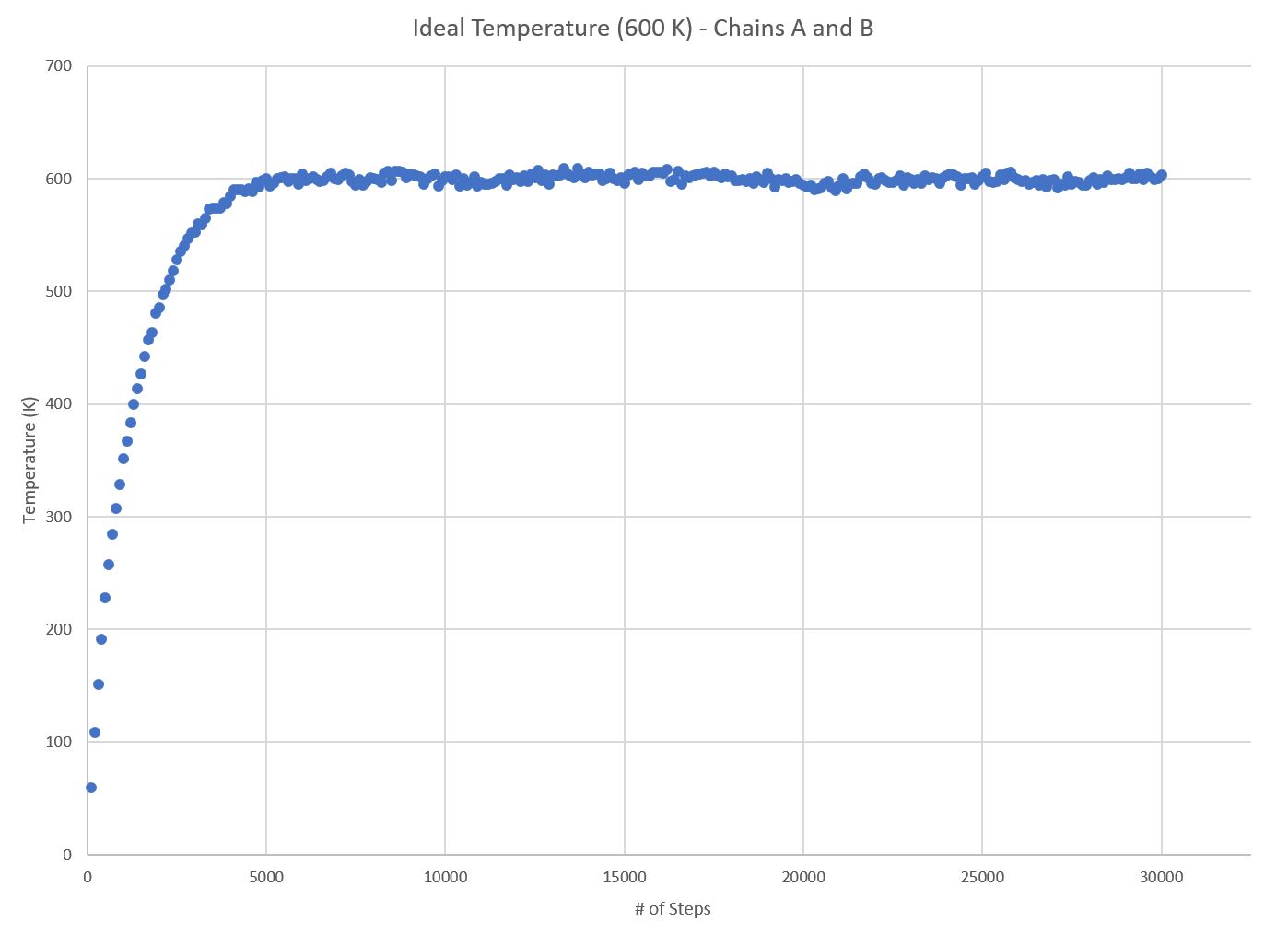
-162701.72 kJ, and a density of 0.95800248 g/mL.



The fourth run-through of the entire complex a temperature of 150 K and an increment size of 100, resulted in an equilibrium at around 12800 steps, a binding energy of -219986.44 kJ, and a density of 0.95800248 g/mL.

The fifth run-through of the entire complex a temperature of 600 K and an increment size of 100, resulted in an equilibrium at around 5500 steps, a binding energy of -75499.41 kJ, and a density of 0.95800248 g/mL.

As seen by the results, the density of the complex never changes through all tests. The size of the increment between measurements did not greatly affect the accuracy of the results. As the temperature decreases, so does the potential energy of the complex. As the potential energy decreases, so does the binding energy. The lower the binding energy, the better. It must be remembered, however, that this protein exists inside the human body thus the protein would never reach as low as 150 K, like what was tested, and would likely deform at that temperature.

Further testing could be done to find the optimal temperature within the human body that these proteins would bind best. The chains’ locations and compositions could be altered to component-by-component to determine the best combinations for binding. A deeper study into this complex could aid researchers in learning more about scheduled cell death and prevent unneeded apoptosis. These findings could be applied to preventing the death of noncancerous, fast-growing cells, like hair follicles, during cancer treatments by targeting only cancer cells or altering the activation and inhibition sites of the Bcl-XL protein.

Works Cited

Chipuk, J E, et al. “Mitochondrial Outer Membrane Permeabilization during Apoptosis: the Innocent Bystander Scenario.” *Nature*, Nature Publishing Group, 19 May 2006, www.nature.com/cdd/journal/v13/n8/full/4401963a.html?foxtrotcallback=true.

Rajan, Sreekanth, et al. “Bh3 Induced Conformational Changes in Bcl‐Xl Revealed by Crystal Structure and Comparative Analysis.” *Wiley Online Library*, Proteins: Structure, Function, and Bioinformatics, 23 May 2015, www.onlinelibrary.wiley.com/doi/10.1002/prot.24816/epdf?referrer\_access\_token=HDqstRRuisjo\_yk2dKNMpE4keas67K9QMdWULTWMo8Mv2et5Yz-Tv2pP76vo2ZmVT3K

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Rajan, Sreekanth, et al. “Bh3 Induced Conformational Changes in Bcl-Xl Revealed by Crystal Structure and Comparative Analysis.” *Proteins*, RCSB, 10 June 2015, www.rcsb.org/pdb/explore.do?structureId=4QVF.