YASARA – Energy Minimization

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The energy minimization feature of the YASARA module predicts the lowest energy state of your target structure or ligand complex. Several force field including AMBER and YASARA's own in-house portfolio are available for the 3D refinement of your models.

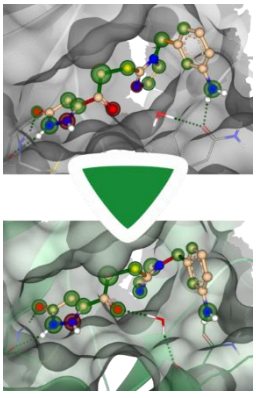
How does YASARA's energy minimization work?

The lowest-energy state of a structure is the most favorable conformation, which can also be associated with the native form of the structure. In other words, the lower the calculated energy of the structure, the more likely it is to provide a good starting point for modeling experiments.

YASARA (**Y**et **A**nother **S**cientific **A**rtificial **R**eality **A**pplication) does exactly that: it takes a structure (protein, DNA, RNA, etc.) or a complex and calculates the energetically most favorable conformation based on a variety of possible force fields, which can then be used as input for computational approaches.
In this process, a sound conformation is sought whose energy level represents a minimum around the input structure, taking into account co-crystallized factors such as water, metals, and other ligands.

Structure refinement

The applications of energy minimization are highly versatile. They can be used to improve the quality of starting points for docking or SAR analysis.
Through energy minimization, the complex can be further refined to adjust the ligand's scoring and identify additional potential interactions. This can also include water molecules to provide insights into the strength of hydrogen bonds with the target structure and the ligand.



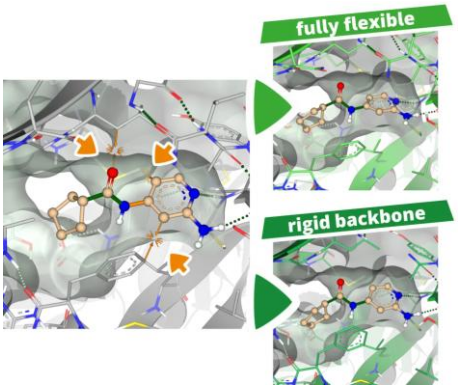
Particularly in the context of fragment-based drug design (FBDD), it is of utmost importance to work with refined poses, as many of the subsequent steps rely on the fragment's initial state as the basis for their calculations.

Versatile applications in drug discovery

The applications of energy minimization also include exploring potential binding sites. If a potential ligand exhibits clashes in the binding site, energy minimization can simulate an induced fit, where the ligand and binding site adapt to each other. This process involves sampling rotamers and modifying the topology to accommodate the ligand.
It is also possible to specify whether the protein's backbone should be treated as flexible or rigid during the process.

Additionally, the core task of any energy minimization is to improve starting structures, particularly models. Homology or AlphaFold models can be prepared for docking studies or virtual screening campaigns with SeeSAR and YASARA to enhance the quality of the results.

The methodology is also ideal for generating energetically favorable conformations of the ligand within the binding pocket after it has been docked. For example, it can help reduce molecular torsions as well as inter- and intra-molecular clashes.



Which force fields are available?

YASARA supports various well-known AMBER forcefields (03, 10, 11, 12, 14, 14IPQ, 15FB, 15IPQ, 94, 96, 99), as well as YASARA's own force fields: NOVA, YAMBER and YASARA.
NOVA resembles common molecular dynamic force fields and has been optimized for two particular aspects, namely to improve models based on a H-bonding network optimizer and to provide results with at least the same level of quality than high-resolution X-ray structures.
YAMBER is a second generation, self-parametrizing force field derived from AMBER and improved with the NOVA optimization procedure.
YASARA is the third generation force field, applying knowledge-based potentials for structure prediction and refinement. It performed the best in the CASP8 challenge and is the recommended go-to option of YASARA's in-house force fields.

Literature

Krieger, E.; Joo, K.; Lee, J.; Lee, J.; Raman, S.; Thompson, J.; Tyka, M.; Baker, D.; Karplus, K. Improving Physical Realism, Stereochemistry, and Side-chain Accuracy in Homology Modeling: Four Approaches That Performed Well in CASP8. *Proteins Struct. Funct. Bioinforma.* **2009**, *77* (S9), 114–122. https://doi.org/10.1002/prot.22570.

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