Automating the Fragmentation of Proteins

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Background

- Many-body expansion
  - Problems
  - Optimization
- Computational complexity of energy calculations
  - Polynomial vs. Exponential
- ML approaches
  - Need for training data
- Breaking proteins up by amino acid

$$E_{\text{tot}} \approx E^{(n)}_{\text{eb-MBE}} = \sum_{I} E^{(1)}_{I} + \sum_{I<J} \Delta E^{(2)}_{IJ} + \sum_{I<J<K} \Delta E^{(3)}_{IJK} + \cdots + \sum \Delta E^{(n)}_{IJK\ldots}.$$

Figure: Energy-based many-body expansion [2]

Methodology

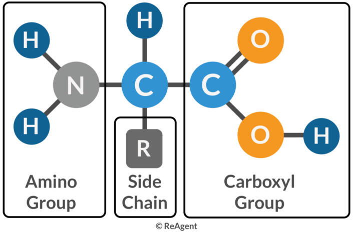
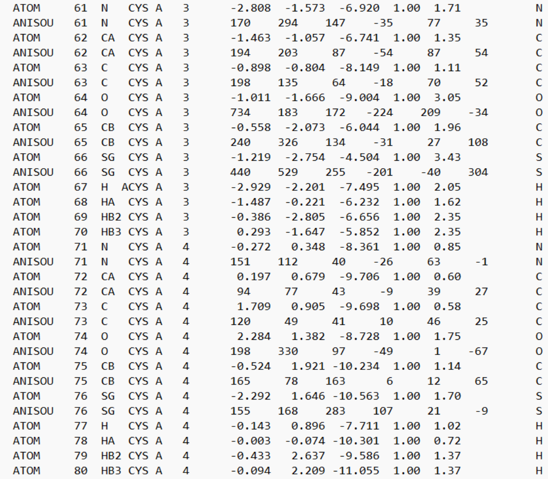


Figure: General amino acid structure [1]

- Segment by amino acid
- Write as .xyz file
- Establish bonds
- Test correctness of created molecule
- Cap atoms where bonds are missing
- Submit to testing

Example PDB File Layout

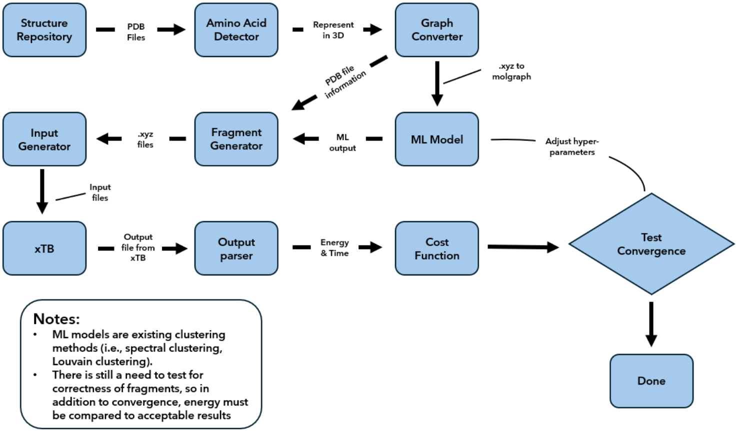


```
ATOM     61  N   CYS A   3      -2.808  -1.573  -6.920  1.00  1.71           N
ANISOU   61  N   CYS A   3      170    294    147    -35     77     35       N
ATOM     62  CA  CYS A   3      -1.463  -1.057  -6.741  1.00  1.35           C
ANISOU   62  CA  CYS A   3      194    203     87    -54     87     54       C
ATOM     63  C   CYS A   3      -0.898  -0.804  -8.149  1.00  1.11           C
ANISOU   63  C   CYS A   3      198    135     64    -18     70     52       C
ATOM     64  O   CYS A   3      -1.011  -1.666  -9.004  1.00  3.05           O
ANISOU   64  O   CYS A   3      734    183    172   -224    209    -34       O
ATOM     65  CB  CYS A   3      -0.558  -2.073  -6.044  1.00  1.96           C
ANISOU   65  CB  CYS A   3      240    326    134    -31     27    108       C
ATOM     66  SG  CYS A   3      -1.219  -2.754  -4.504  1.00  3.43           S
ANISOU   66  SG  CYS A   3      440    529    255   -201    -40    304       S
ATOM     67  H  ACYS A   3      -2.929  -2.201  -7.495  1.00  2.05           H
ATOM     68  HA  CYS A   3      -1.487  -0.221  -6.232  1.00  1.62           H
ATOM     69  HB2 CYS A   3      -0.386  -2.805  -6.656  1.00  2.35           H
ATOM     70  HB3 CYS A   3       0.293  -1.647  -5.852  1.00  2.35           H
ATOM     71  N   CYS A   4      -0.272   0.348  -8.361  1.00  0.85           N
ANISOU   71  N   CYS A   4      151    112     40    -26     63     -1       N
ATOM     72  CA  CYS A   4       0.197   0.679  -9.706  1.00  0.60           C
ANISOU   72  CA  CYS A   4       94     77     43     -9     39     27       C
ATOM     73  C   CYS A   4       1.709   0.905  -9.698  1.00  0.58           C
ANISOU   73  C   CYS A   4      120     49     41     10     46     25       C
ATOM     74  O   CYS A   4       2.284   1.382  -8.728  1.00  1.75           O
ANISOU   74  O   CYS A   4      198    330     97    -49      1    -67       O
ATOM     75  CB  CYS A   4      -0.524   1.921 -10.234  1.00  1.14           C
ANISOU   75  CB  CYS A   4      165     78    163      6     12     65       C
ATOM     76  SG  CYS A   4      -2.292   1.646 -10.563  1.00  1.70           S
ANISOU   76  SG  CYS A   4      155    168    283    107     21     -9       S
ATOM     77  H   CYS A   4      -0.143   0.896  -7.711  1.00  1.02           H
ATOM     78  HA  CYS A   4      -0.003  -0.074 -10.301  1.00  0.72           H
ATOM     79  HB2 CYS A   4      -0.433   2.637  -9.586  1.00  1.37           H
ATOM     80  HB3 CYS A   4      -0.094   2.209 -11.055  1.00  1.37           H
```

Applications and Additional Functionality

- Removing the need for user input
- Testing for correctness in generated .xyz files
- Identifies double and triple bonds within a molecule
- Allows for the generation of large quantities of files

Pipeline



Notes:

- ML models are existing clustering methods (i.e., spectral clustering, Louvain clustering).
- There is still a need to test for correctness of fragments, so in addition to convergence, energy must be compared to acceptable results

Figure: ML Pipeline for Automating Fragmentation of Proteins

SIMCODES Commentary

- Professional development
  - Application of CS, DS, and MA practices
  - Collaboration with a team
- Structure
- Encountering complexities
  - Chemistry's resistance to algorithms
  - Using unfamiliar software like Jupyter notebooks
  - Designing code with modularity in mind

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References

[1] Jessica Clifton. *What Are Amino Acids*. 2021. URL: https://www.reagent.co.uk/blog/what-are-amino-acids/.

[2] Stefanie Schürmann et al. “Accurate quantum-chemical fragmentation calculations for ion–water clusters with the density-based many-body expansion”. In: *Phys. Chem. Chem. Phys.* 25 (1 2023), pp. 736–748. DOI: 10.1039/D2CP04539G. URL: http://dx.doi.org/10.1039/D2CP04539G.

Resources

PDB converter repository:

- https://github.com/SIMCODES-ISU/Campbell_Repo

xTB gitHub:

- https://github.com/grimme-lab/xtb

xyz2graph gitHub:

- https://github.com/zotko/xyz2graph/tree/main