BUJNICKI LAB

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Modeling of large macromolecular complexes using hybrid approach

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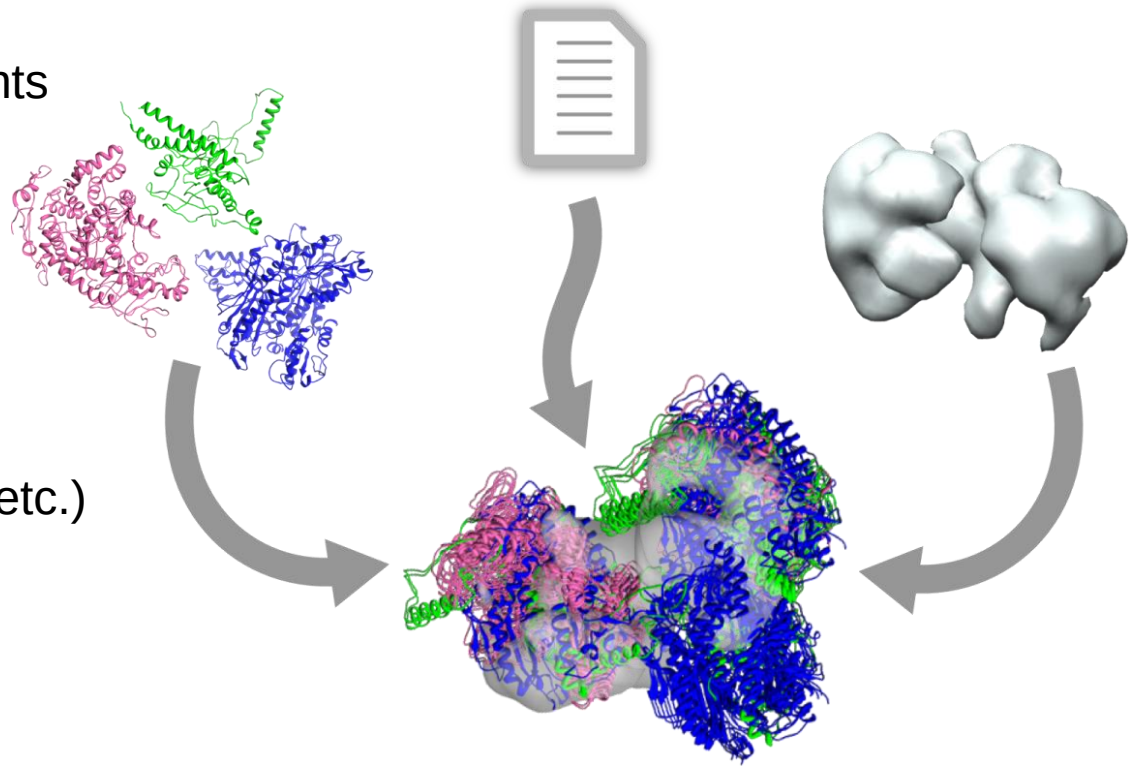
Hybrid modeling motivation

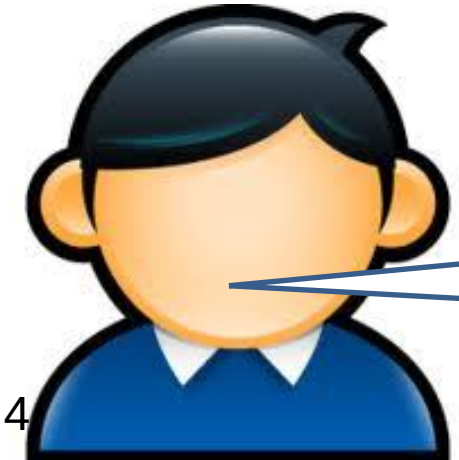
A problem to solve:

- Large macromolecular complexes play key roles in the cell (ribosomes, spliceosomes, various multisubunit molecular machines)
- Experimental determination of their structures is difficult
- They are often dynamic and contain a lot of intrinsic disorder
- Typically, we have only heterogeneous biochemical data, and structures or models of individual components (proteins, RNAs)

Making sense out of the available data

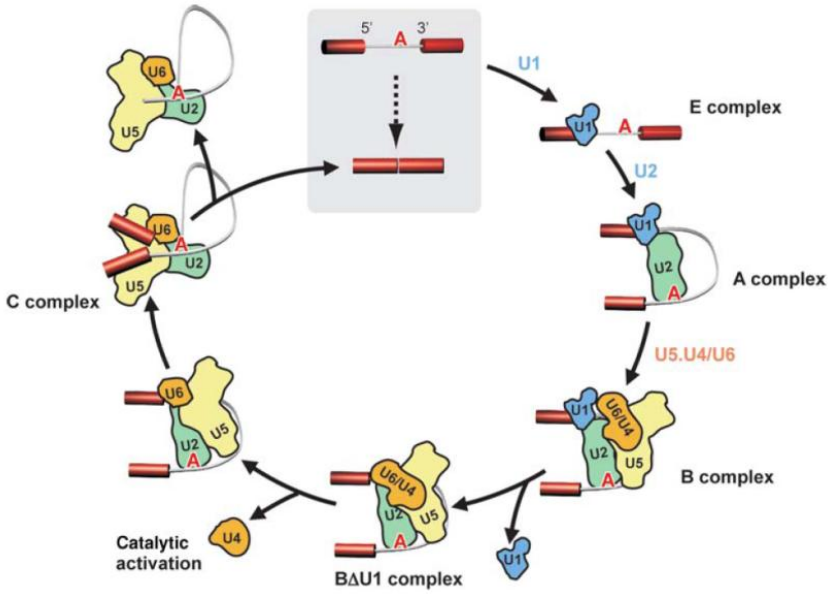
- sequences of all components
- structures of some components
- models of some components
- disorder / flexibility
- shapes of the molecules
  (**cryoEM, SAXS/SANS**)
- distance restraints
  (**FRET, EPR, cross-linking**, etc.)
- accessibility
  (**exposed active sites,** etc.)

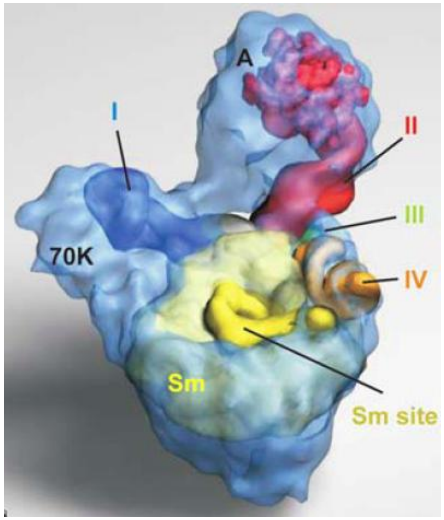


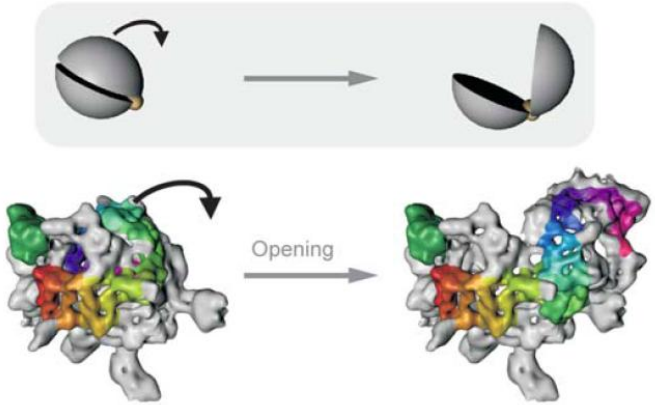


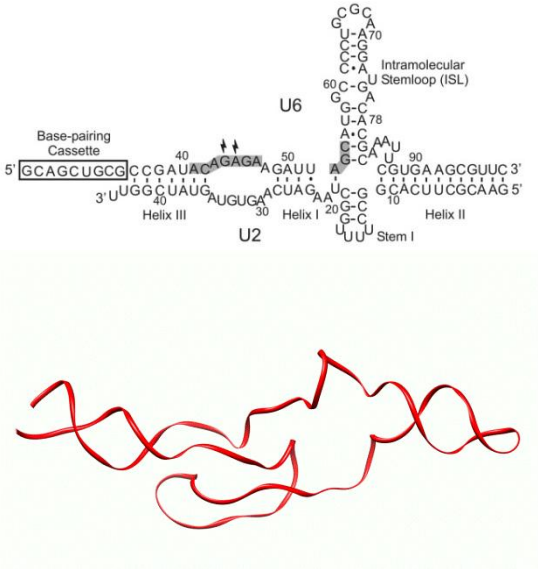
Is it possible to build a 3D model consistent with these data?

Example: mRNA splicing



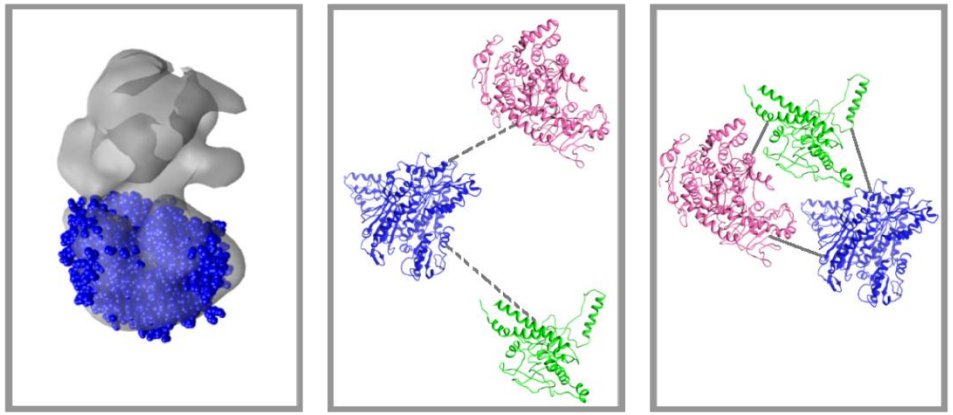




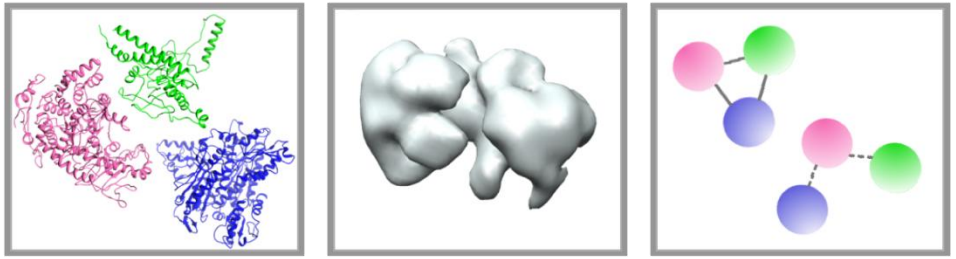


How to use it all in the modeling?

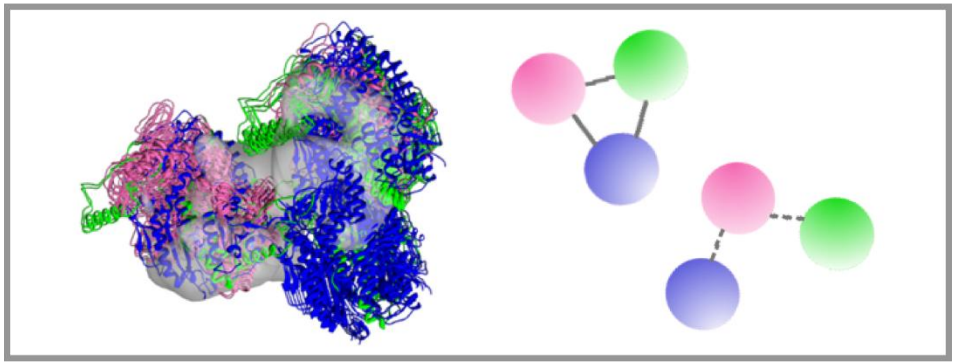
EXPERIMENTAL DATA



ENCODING EXPERIMENTAL DATA AS SPATIAL RESTRAINTS

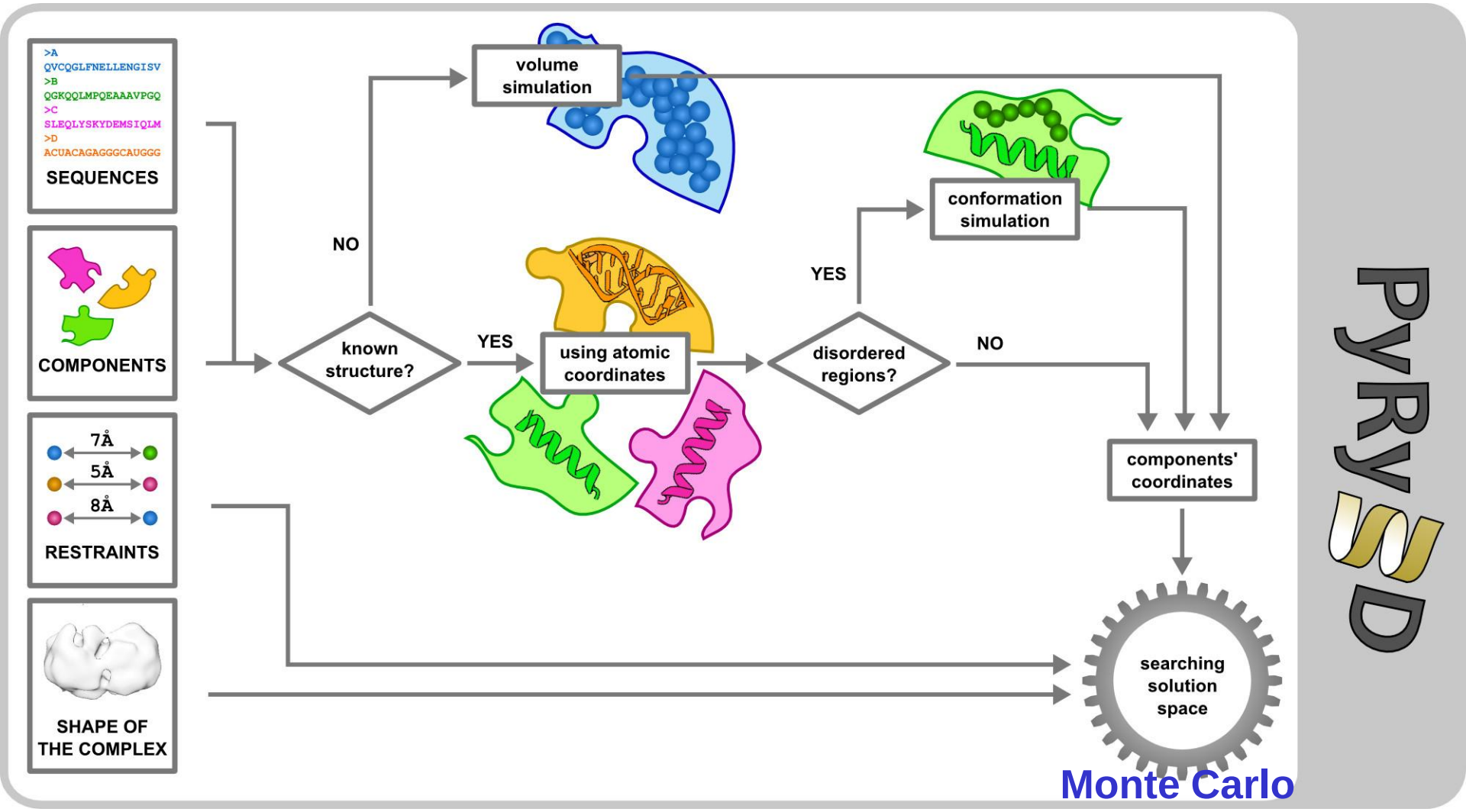


OPTIMIZATION



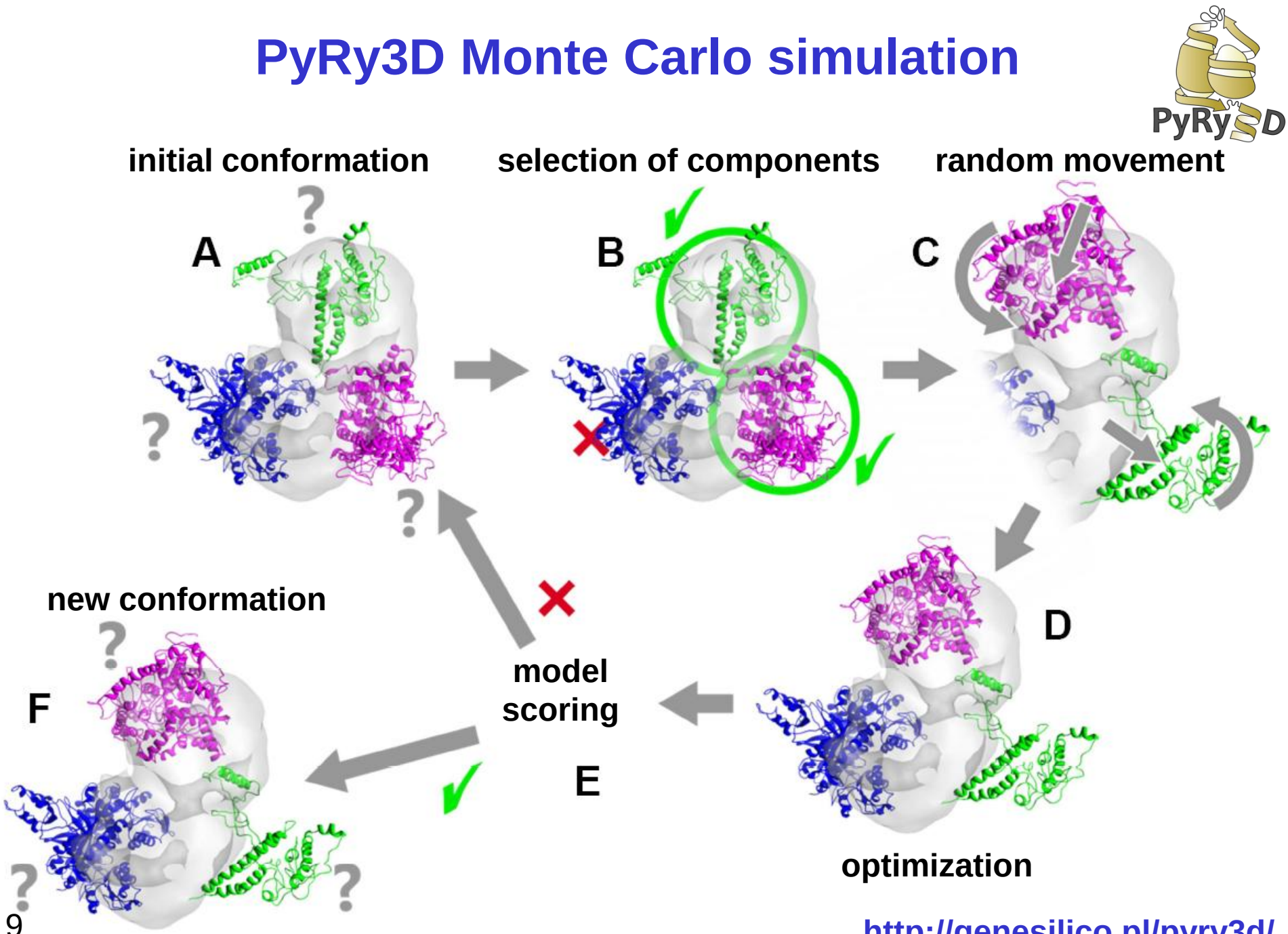
*pyry – regional name for potatoes in Poznań

PyRy3D workflow



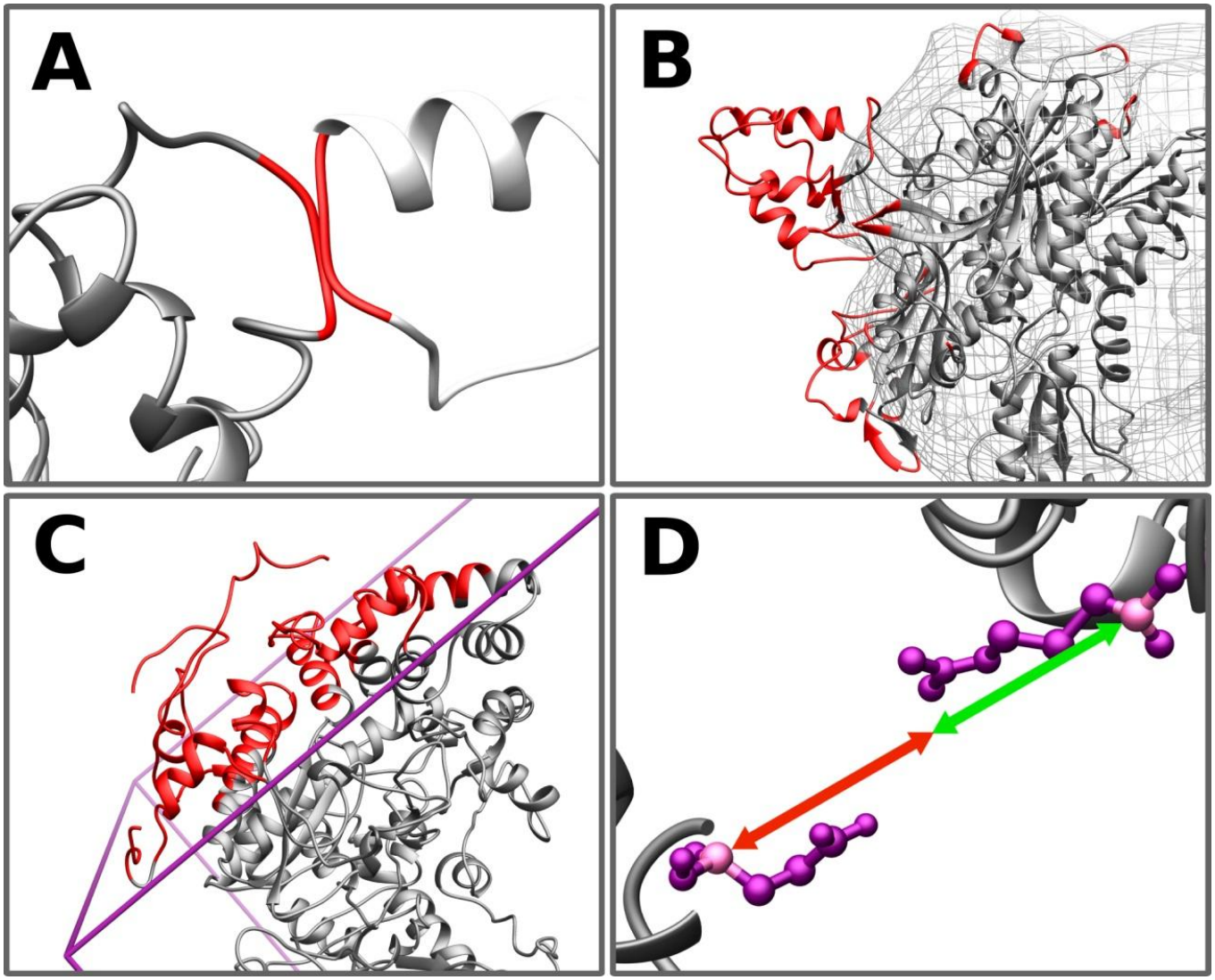
Monte Carlo simulation

PyRy3D Monte Carlo simulation



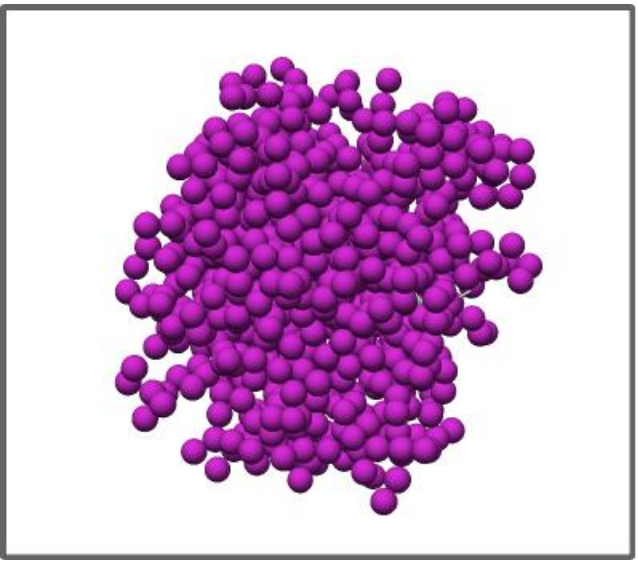
http://genesilico.pl/pyry3d/

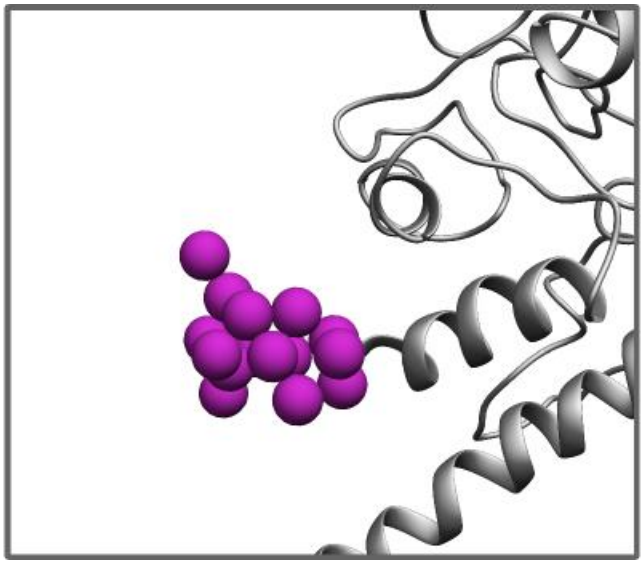
Scoring function

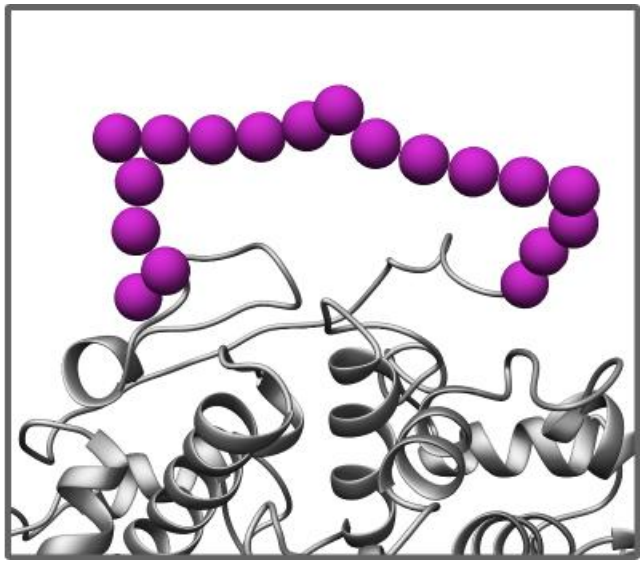


http://genesilico.pl/pyry3d/

Including information about disorder and flexibility







Pseudoatoms are used to build components with:

- **no structural data**
- **missing terminal fragments**
- **missing internal fragments**

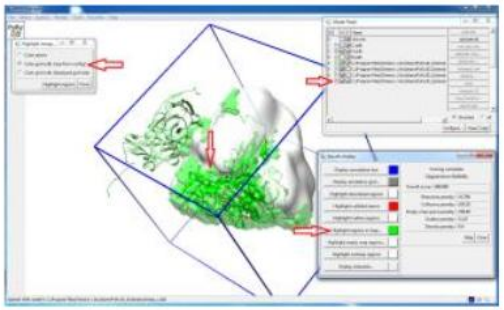
and their conformation is randomly changed during simulation

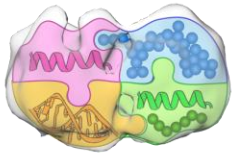
PyRy3D usage

PyRy3D command-line (engine)

```
E:\pyrky\PyRy3D_v4.2>python pyry3d.py --help

   PyRy3D
   program for macromolecular docking into cryoEM maps

   (c) 2010 by Joanna M. Kasprzak

   usage: python pyry3d.py --help

Usage: pyry3d.py [options]

Options:
  -h, --help            show this help message and exit
  -s FILE, --seq_file=FILE
                        input file with sequences in FASTA format
  -d FILE, --dirfile=FILE
                        input file with structure
  -r FILE, --restr_file=FILE
                        input file with restraints in Filtrest3D format
  -m FILE, --map_file=FILE
                        input file with complex map
  -x FILE, --saxs_file=FILE
                        input file with complex map shape
  -c CONFIG, --config=CONFIG
                        config file with simulation parameters
  -o OUTPUT, --output=OUTPUT
                        write output to file
  -t TRAFLFILE, --traflfile=TRAFLFILE
                        write output to trajectory file
  -f FULLATOM, --to full atom model=FULLATOM
                        write best model in fullaton representation
  -v MOVEHISTORY, --save history of moves=MOVEHISTORY
                        save all moves into a file
  -s SCORE_PLOT, --save plot with complexes scores=SCORE_PLOT
                        save plot with complexes scores
```

PyRy3D Extension (GUI)





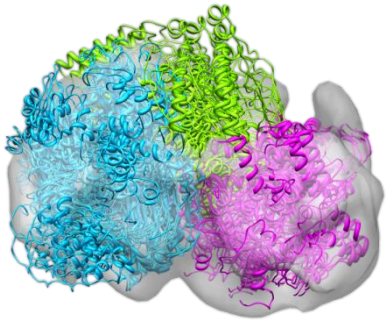
web server

http://pyry3d.icm.edu.pl

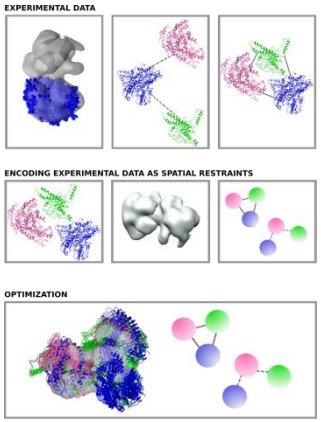
http://genesilico.pl/pyry3d/

Summary

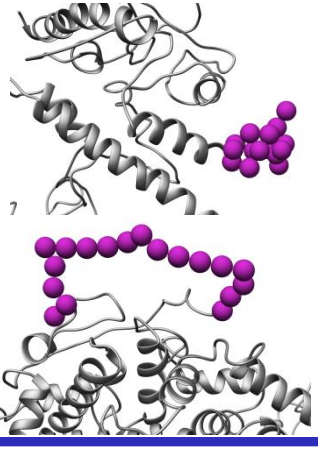
BUILDS LOW-RESOLUTION MODELS



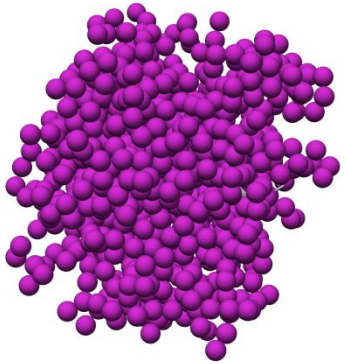
WORKS WITH RESTRAINTS



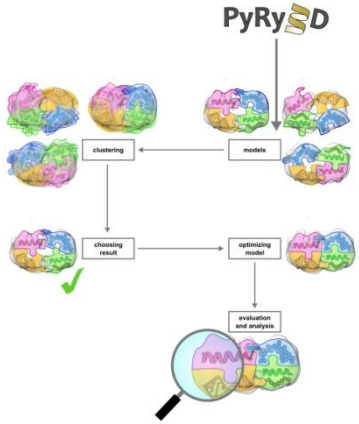
ADDS MISSING FRAGMENTS



SIMULATES VOLUMES



PROVIDES ENTIRE MODELING PIPELINE

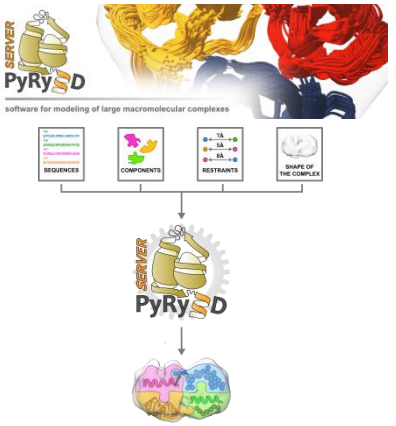


FULLY SCRIPTABLE

http://genesilico.pl/pyry3d

GRAPHICAL INTERFACE

ONLINE SERVER



http://pyry3d.icm.edu.pl

Highlights of PyRy3D

Easy to use for non-experts

Fully scriptable, expert users can write Python scripts for complicated operations

Enables the use of electron density maps and SAXS/SANS data to describe shapes

Enables the use of many different restraints from experiments and predictions

Can use crystal structures, NMR ensembles, theoretical models, arbitrary shapes

Can model disordered segments and sequences without known structure

http://genesilico.pl/pyry3d/

PyRy3D team

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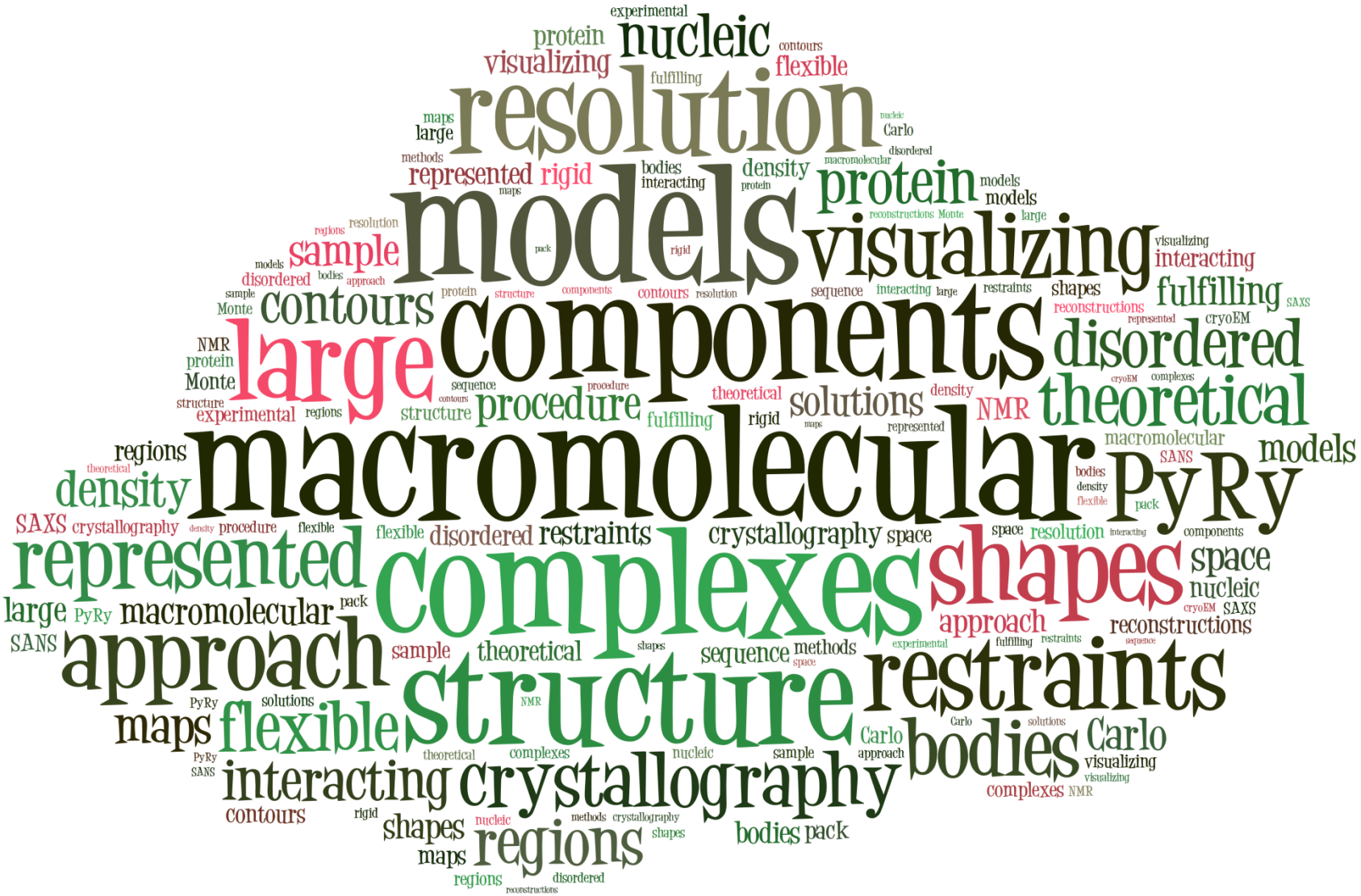
Wojciech Potrzebowski

Witold Rudnicki
Mateusz Susik
Laura Pogorzelska
Rafał Niemiec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