Finding Many Stable Molecular Arrangements

Conformational Searching with Genetic Algorithms

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University of Illinois at Urbana-Champaign

Outline

Primary Resource

First-Principles Molecular Structure Search with a Genetic Algorithm
Supady, A.*P*[1]; Blum, V.[1]; Baldauf, C. J.[1,2] Chem. Inf. Model. 2015, 55 (11), 23382348.

1. Fritz-Haber-Institut der Max-Planck-Gesellschaft, Berlin
2. Department of Mechanical Engineering & Materials Science, Duke University

Background Information

The Problem

Computational methods require knowledge of molecular structure

We need to find the lowest energy structure

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The potential energy surface (PES) is high dimensional and has many minima

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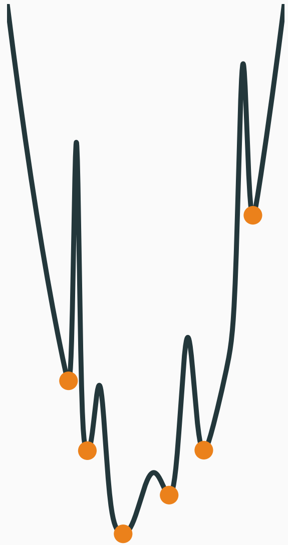
We may need information about one or more low-energy conformations

- Ok, let's find them all!



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- Under a cutoff

Possible Solutions

- Many techniques are well established

Method	Implented in
grid-based	CEASAR, **Open Babel, Confab,** MacroModel, MOE
rule-based	**ALFA, CONFECT,** CORINA, ROTATE, **COSMOS**, OMEGA
population-based	**Balloon, Cyndi**
basin-hopping	**ASE, GMIN, TINKER SCAN**

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- None are perfect

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Desirables

What Algorithmic Properties do we want for conformer search?

1. Accurate energies & Structures

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4. Minimize human bias

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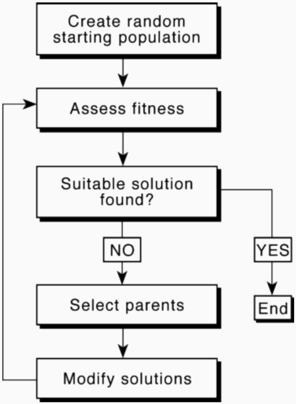
What Algorithmic Properties do we want for conformer search?

1. Accurate energies & Structures
2. Minimize # of geometry optimizations
3. Find many low energy conformations
4. Minimize human bias
5. Parallel

The Genetic Algorithm

Outline

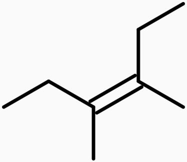
- Inspired by biological evolution
- Evolve a population over generations
- Survival of the fittest
- Requirements:
    - Represent individuals as vector
    - Fitness function
- $v = \begin{pmatrix} x_1 & y_1 & z_1 & x_2 & y_2 & z_2 & \cdots & x_N & y_N & z_N \end{pmatrix}$
- $F = \frac{E_{\text{max}} - E}{E_{\text{max}} - E_{\text{min}}}$



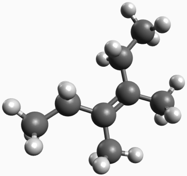
Carwright, H. Reviews in Computational Chemistry 2007 (25), pp 349389.

The Many Representations of a Molecule

2D Image



3D Image



Name

(3Z)-3,4-Dimethyl-3-hexene

SMILES

CCC(C)=C(C)CC

InChI

1S/C8H16/c1-5-7(3)8(4)6-2/h5-6H2,1-4H3/b8-7-

Cartesian Coords

	x	y	z
C	0.90	-0.25	0.02
C	2.35	0.15	-0.17
C	2.91	1.30	-0.67

Internal Coords

		r		θ
C				
C	1	1.51		
C	2	1.38	1	131

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The Many Representations of a Molecule

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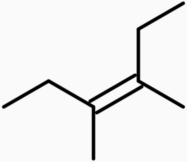

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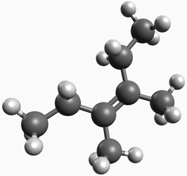

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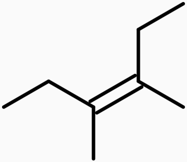

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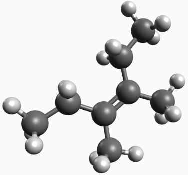

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Selecting Parents

Roulette Wheel Method

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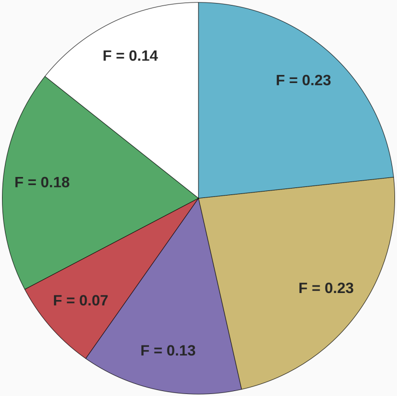

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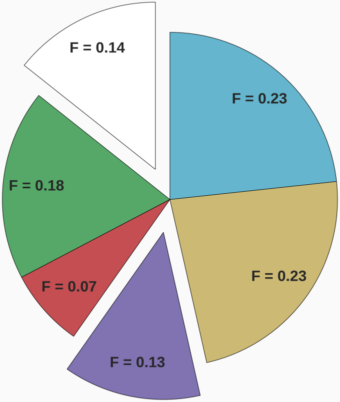

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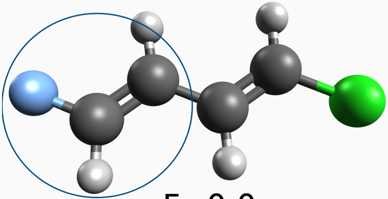
The Next Generation



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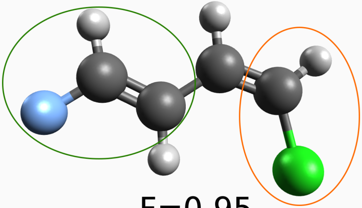

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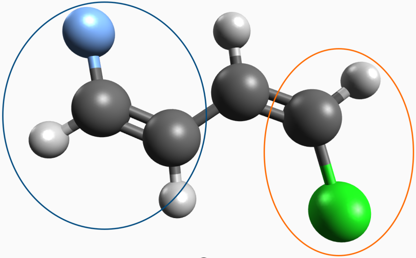

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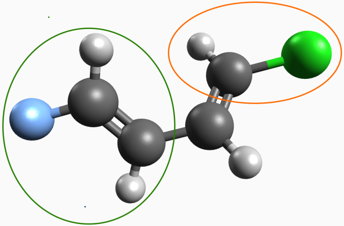

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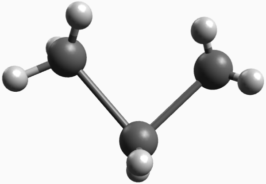
The Whole Algorithm

1. Generate N random, sensible geometries



sensible

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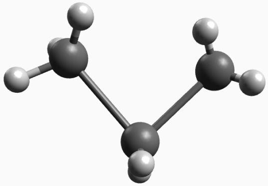

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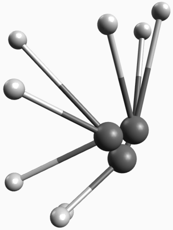

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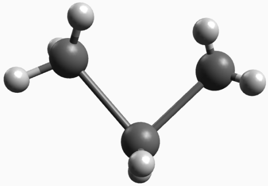
The Whole Algorithm

1. Generate N random, sensible geometries
2. Optimize



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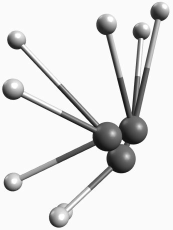

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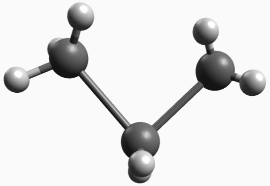
The Whole Algorithm

1. Generate N random, sensible geometries
2. Optimize
3. Select Parents



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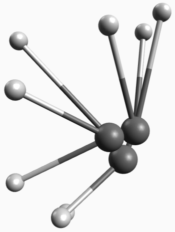

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The Whole Algorithm

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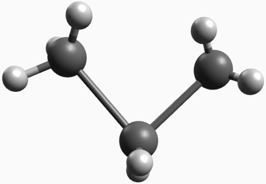
3. Select Parents
4. Crossover & Mutate



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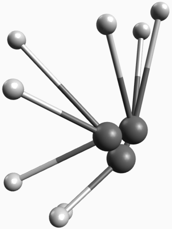

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The Whole Algorithm

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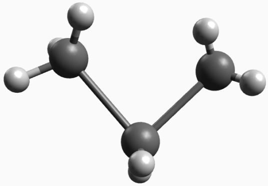
2. Optimize
3. Select Parents
4. Crossover & Mutate
5. Add Children to population



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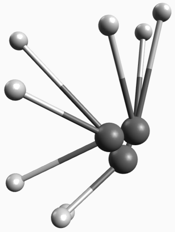

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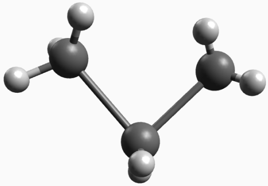
6. Remove the unfit



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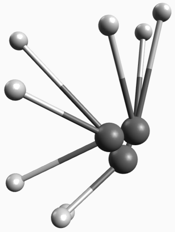

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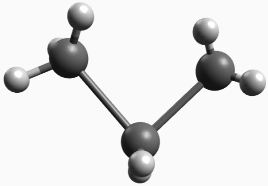
7. If converged:
   - Done!



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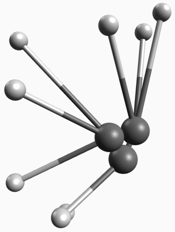

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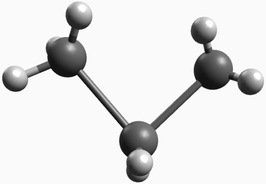
   Otherwise:
   - Go to 2



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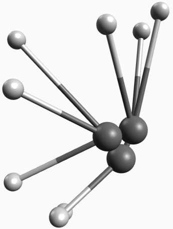

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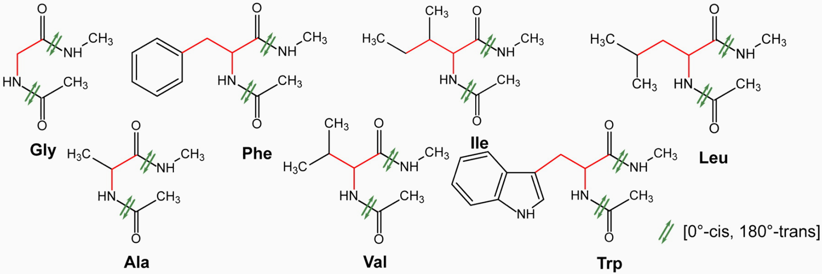
Finding Low Energy Conformers of Dipeptides

"Dipeptide" Structures



Red = Rotatable bonds

= Cis/Trans Bonds

"We use the term dipeptide for amino acids with an acetylated N terminus and an amino-methylated C terminus"

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Combinatorics

- GA beats other methods if space is large
- Space gets large **fast**

Molecule	N	# Rotatable + # Cis/Trans Bonds	# Conformers
Gly	19	2 + 2	15
Ala	22	2 + 2	28
Phe	32	4 + 2	64
Val	28	3 + 2	60
Trp	36	4 + 2	141
Leu	31	4 + 2	183
Ile	31	4 + 2	176

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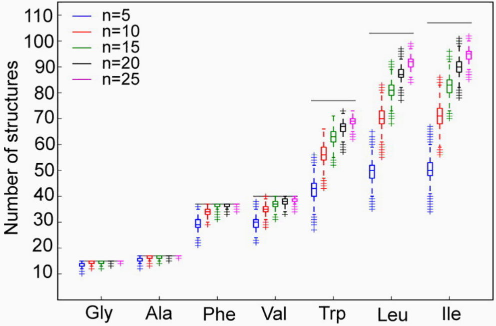
- Smaller systems are reliably sampled
- As # of conformers increases, miss more and more
- Is there a pattern to what is missed?



Proportion of conformers found with incrasing runs of the GA

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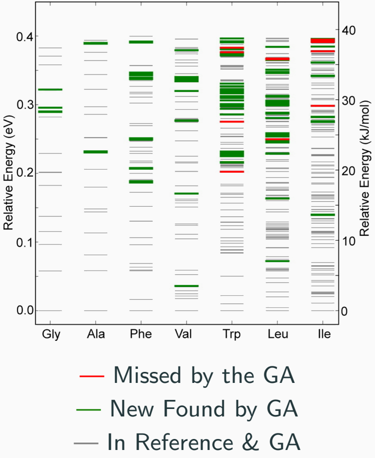
Coverage

- Most misses are very high energy



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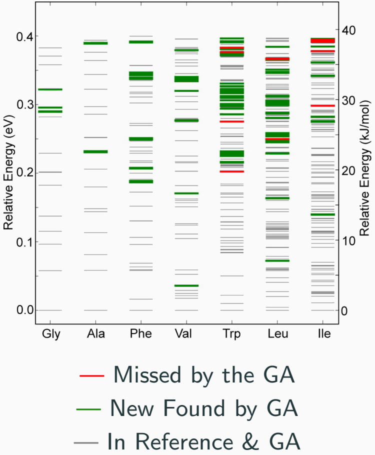
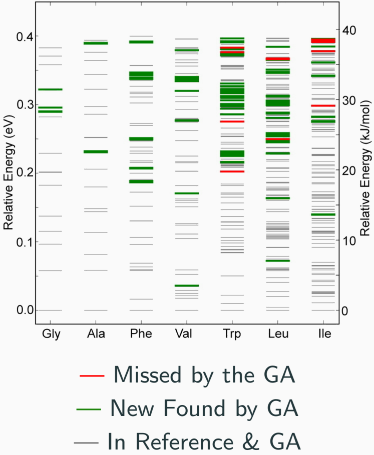


Coverage

- Most misses are very high energy
- Algorithm favors low energy areas of the space
- Features low in energy are favored and recombined



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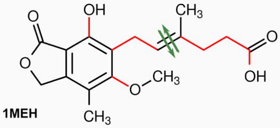
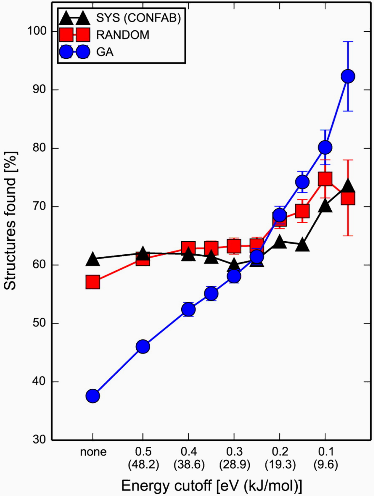
Energy Cutoff



Mycophenolic Acid



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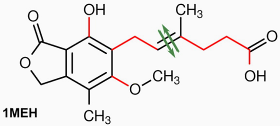
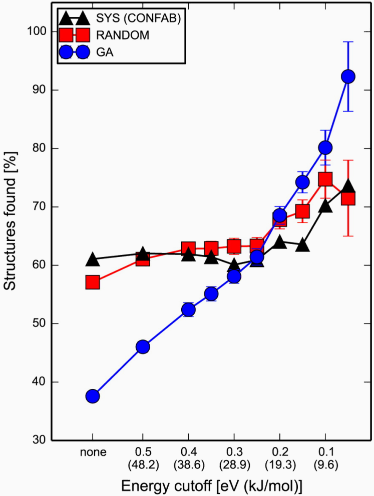


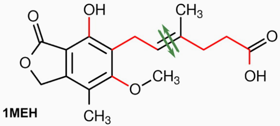
Mycophenolic Acid

- GA is more sensitive to energy cutoff



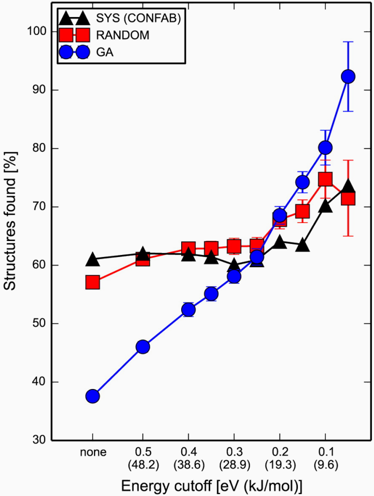
Supady, A.; Blum, V.; Baldauf, C. J. Chem. Inf. Model. 2015, 55 (11), 23382348.

Energy Cutoff



Mycophenolic Acid

- GA is more sensitive to energy cutoff
- For finding low energy ensemble, GA outperforms purely stochastic/deterministic method



Concluding Remarks

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Review

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Review

- Conformational searching is expensive
- The Genetic Algorithm is a guided global search
- It shines when asked to find many low energy solutions
- GA can be used with any electronic structure package
- This one is available under the GNU Lesser General Public License: `https://github.com/adrianasupady/fafoom`

Supady, A.; Blum, V.; Baldauf, C. J. Chem. Inf. Model. 2015, 55 (11), 23382348.

Questions?

Backup slide

- Geometry optimization step makes the algorithm more Lamarckian (Jean Baptiste Larmarck, [1744-1829])

1. Supady, A.; Blum, V.; Baldauf, C. J. Chem. Inf. Model. 2015, 55 (11), 23382348.
2. http://www.chemspider.com/Chemical-Structure.2298795.html

Genetic Algorithm Parameters

Geometry Optimization: DFT PBE + VdW, *tier1* basis in FHI-aims[1]. Convergence at 0.005 eV /Å

	parameter	value
molecule	SMILES	CC(=O)N[C@H](C(=O)NC)[C@H](CC)C
	distance_cutoff_1	1.2 Å
	distance_cutoff_2	2.0 Å
	rmsd_cutoff_uniq	0.2 Å
	chiral	true
run settings	max_iter	10
	iter_limit_conv	10
	energy_diff_conv	0.001 eV
GA settings	popsize	5
	energy_var	0.001 eV
	selection	roulette wheel
	fitness_sum_limit	1.2
	prob_for_crossing	0.95
	cross_trial	20
	prob_for_mut_cistrans	0.5
	prob_for_mut_rot	0.5
	max_mutations_cistrans	1
	max_mutations_torsions	2
	mut_trial	100

GA Parameters for Isoleucine Dipeptide[2]

(1) Blum, V. et.'ál., M. Comput. Phys. Commun. 2009, 180 (11), 21752196.
(2) Supady, A.; Blum, V.; Baldauf, C. J. Chem. Inf. Model. 2015, 55 (11), 23382348.