Finding Many Stable Molecular Arrangements

Conformational Searching with Genetic Algorithms

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Outline

1. Background Information
2. The Genetic Algorithm
3. Finding Low Energy Conformers of Dipeptides
4. Concluding Remarks

Background Information

The Problem

Computational methods require knowledge of molecular structure

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⇒ We need to find the lowest energy structure

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

⇒ Ok, let's find them all!

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**

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

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- Many techniques are well established
- None are perfect

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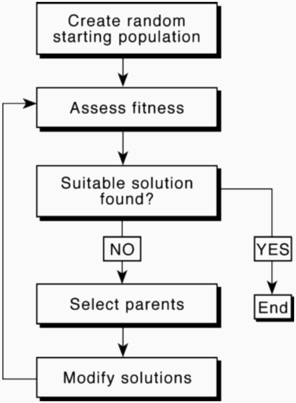
3. Find the entire low energy population of conformations
4. Minimal human input
5. Parallel-Scalable

The Genetic Algorithm

Outline

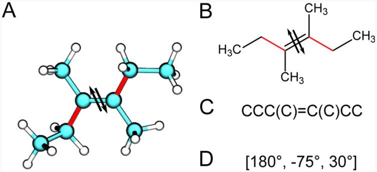
- Inspired by biological evolution
- Evolve a population over generations
- Survival of the fittest
- Requirements:
    - Represent individuals as vector
    - Fitness function
- $v = \begin{pmatrix} x_1 & y_1 & z_1 & x_2 & y_2 & z_2 & \cdots & x_N & y_N & z_N \end{pmatrix}$
- $F = \frac{E_{max} - E}{E_{max}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



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

From Structure to Vector

- Several Ways to Define Structure
  - Cartesian
  - Internal Coordinates (bond length, angle ...)
  - SMILES, InChI



Representations of (3Z)-3,4-Dimethyl-3-hexene[1]

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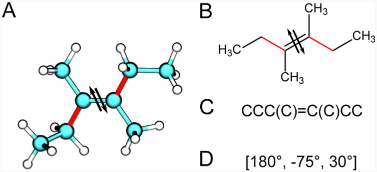

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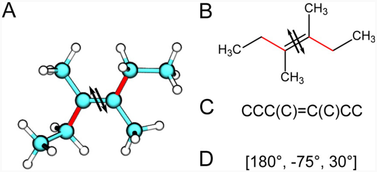

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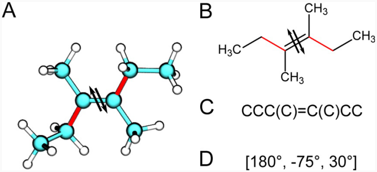

CCC(C)=C(C)CC

[180°, -75°, 30°]

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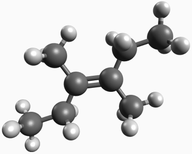
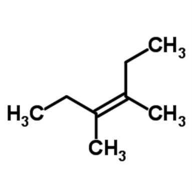
From Structure to Vector 2

2D



3D



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(3Z)-3,4-Dimethyl-3-hexene	CCC(C)=C(C)CC	1S/C8H16/c1-5-7(3)8(

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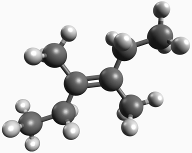

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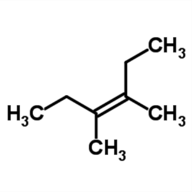

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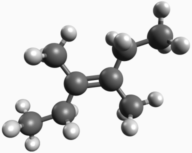

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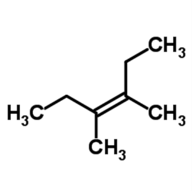

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Sum of Fitness Scores = 1.0

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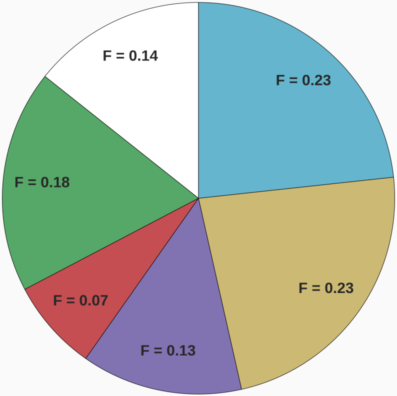

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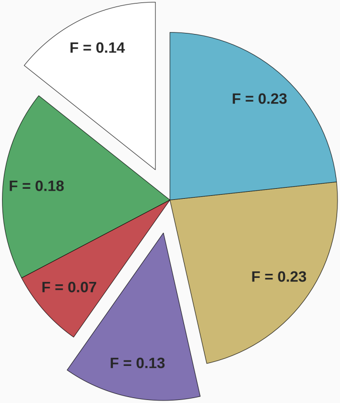
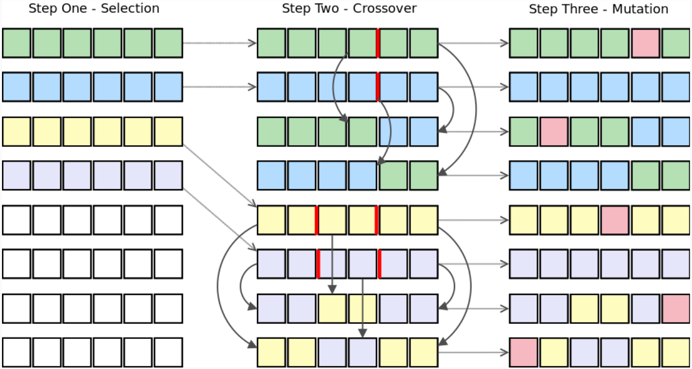


The Next Generation



http://www.turingfinance.com/computational-finance-updates-ieee-world-congress-computational-intelligence

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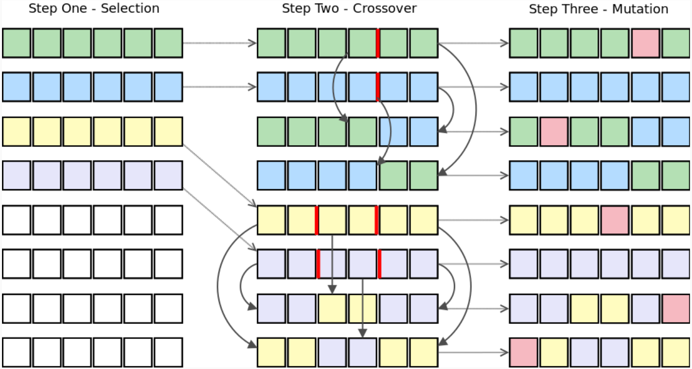

Crossover distinguishes this from Monte Carlo

http://www.turingfinance.com/computational-finance
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5. Crossover & Mutate into sensible geometry

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4. Select Parents
5. Crossover & Mutate into sensible geometry
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6. Add Children to population
7. Remove High energy individuals

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8. If converged:

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    - Done!

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   Otherwise:

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8. If converged:
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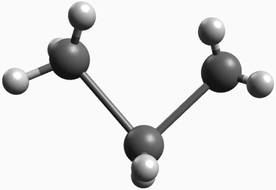
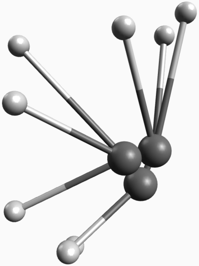
    Otherwise:
    - Go to 2



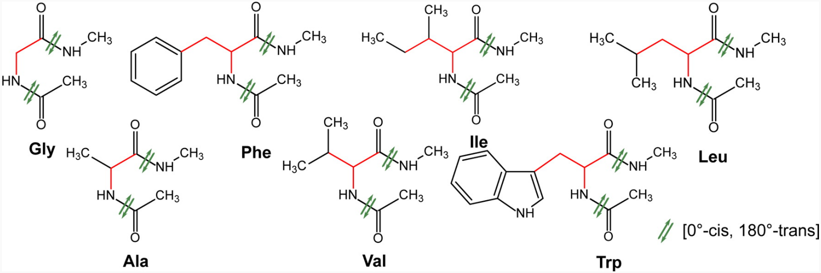
sensible



utter nonsense

Finding Low Energy Conformers of Dipeptides

Dipeptide Structures



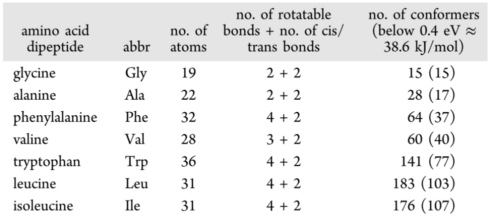
Red = Rotatable bonds

$\rightleftharpoons$ = Cis/Trans Bonds

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

Combinatorics

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

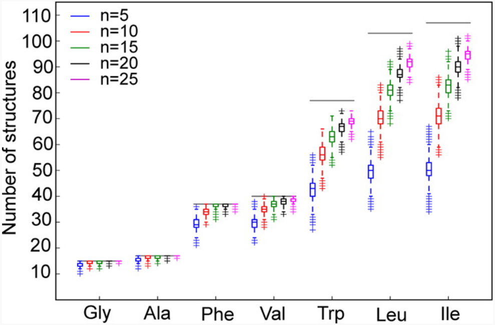


amino acid dipeptide	abbr	no. of atoms	no. of rotatable bonds + no. of cis/trans bonds	no. of conformers (below 0.4 eV ≈ 38.6 kJ/mol)
glycine	Gly	19	2 + 2	15 (15)
alanine	Ala	22	2 + 2	28 (17)
phenylalanine	Phe	32	4 + 2	64 (37)
valine	Val	28	3 + 2	60 (40)
tryptophan	Trp	36	4 + 2	141 (77)
leucine	Leu	31	4 + 2	183 (103)
isoleucine	Ile	31	4 + 2	176 (107)

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

Coverage

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

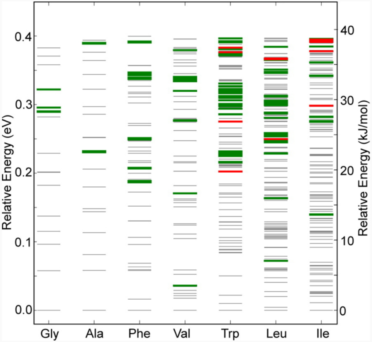


Proportion of conformers found with incrasing runs of the GA

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

Coverage

- Most misses are very high energy



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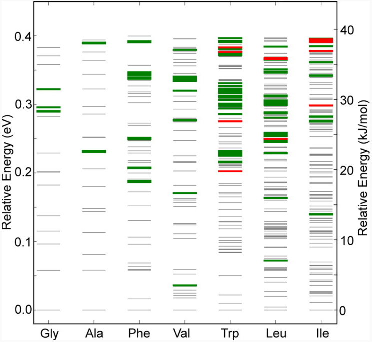

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Coverage

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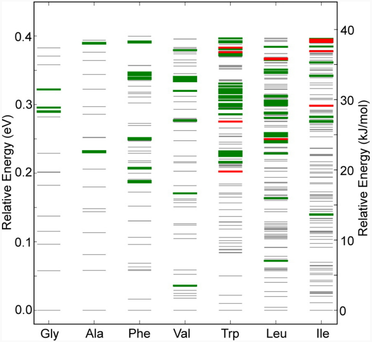
- Features low in energy are favored and recombined



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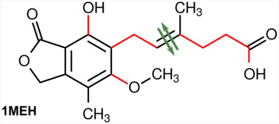
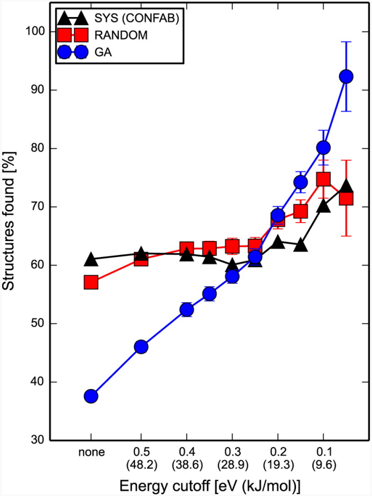
Energy Cutoff



Mycophenolic Acid



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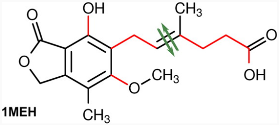
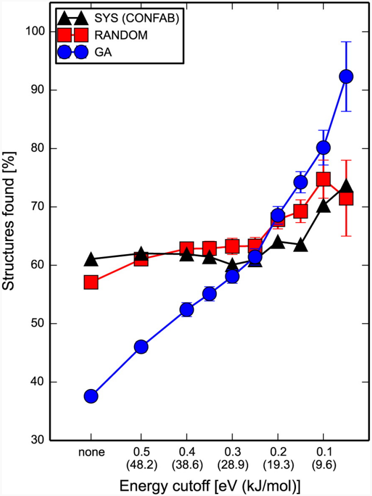


Mycophenolic Acid

- GA is more sensitive to energy cutoff



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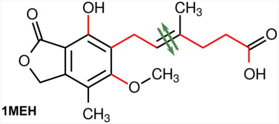
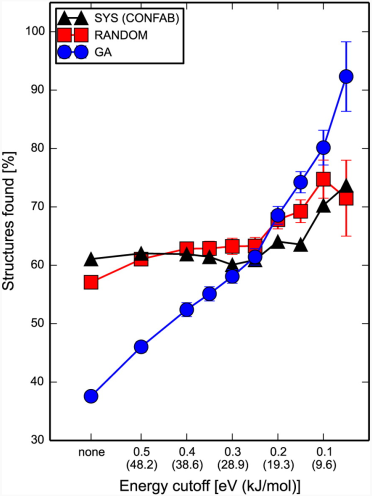


Mycophenolic Acid

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



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- It shines when asked to find a host of low energy solutions
- GA wrapper can be interfaced with a variety of electronic structure packages(NWChem, ORCA) and is available under the GNU Lesser General Public License at `https://github.com/adrianasupady/fafoom`

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

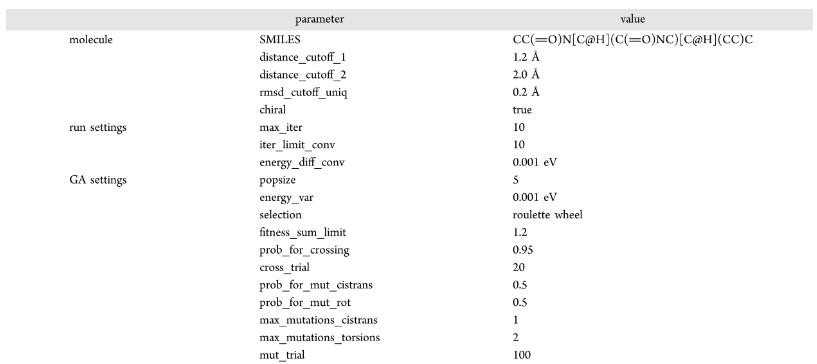
Questions?

Backup slide

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

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