

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

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⇒ We can't tell for sure if we've found the **global** minimum

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

⇒ Ok, let's find them all!

Many techniques are well established

method	description	implemented, e.g., in
grid-based	based on grids of selected Cartesian or internal coordinates (e.g., grids of different torsional angle values of a molecule)	CAESAR, ⁹ Open Babel , ¹⁰ Confab , ¹¹ MacroModel, ¹² MOE ¹³
rule/knowledge-based	use known (e.g., from experiments) structural preferences of compounds	ALFA , ¹⁴ CONFECT , ¹⁵ CORINA and ROTATE, ^{16,17} COSMOS , ^{18,19} OMEGA ²⁰
population-based metaheuristic	improve candidate solutions in a guided search	Balloon , ²¹ Cyndi ²²
distance geometry	based on a matrix with permitted distances between pairs of atoms	RDKit ²³
basin-hopping ²⁴ / minima hopping ²⁵	based on moves across the PES combined with local relaxation	ASE , ²⁶ GMIN , ²⁷ TINKER SCAN ²⁸

^aNames of freely available programs are highlighted in boldface.

Possible Solutions

Many techniques are well established

None are perfect

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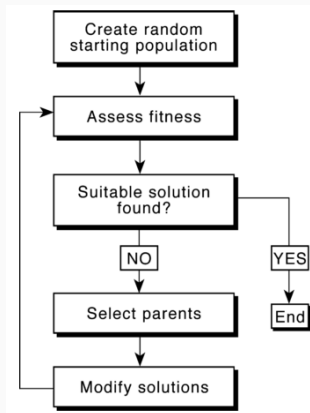
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- Parallel-Scalable

The Genetic Algorithm

Outline

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



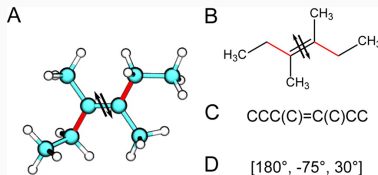
From Structure to Vector

- Several Ways to Define Structure

Cartesian

Internal Coordinates (bond length, angle ...)

SMILES, InChI



Representations of
(3Z)-3,4-Dimethyl-3-hexene¹

1. Supady, A.; Blum, V.; Baldauf, C. J. Chem. Inf. Model. 2015, 55 (11), 23382348.
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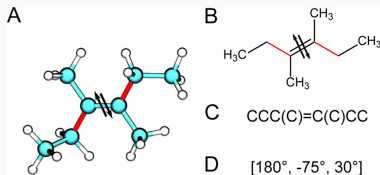
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1S/C8H16/c1-5-7(3)8(4)6-
2/h5-6H2,1-4H3/b8-7-



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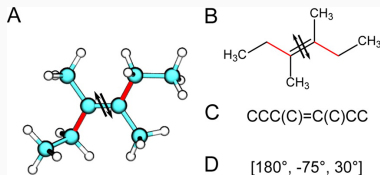
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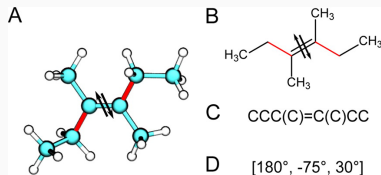
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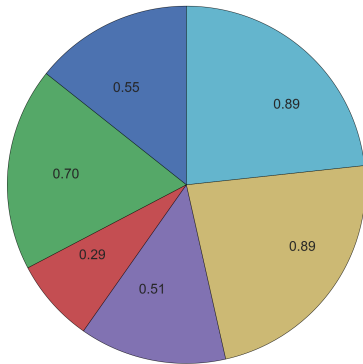
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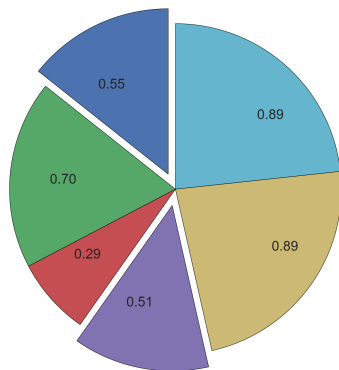
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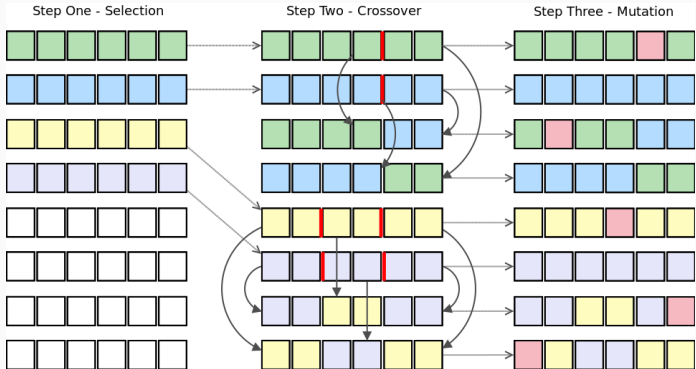


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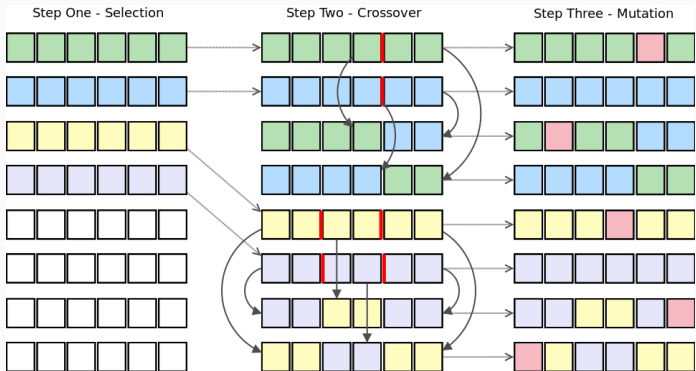
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The Next Generation



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Crossover distinguishes this from Monte Carlo

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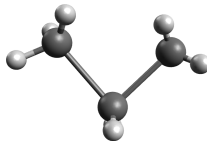
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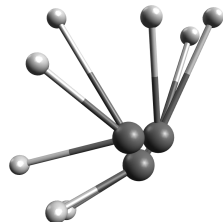
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 - Go to 2



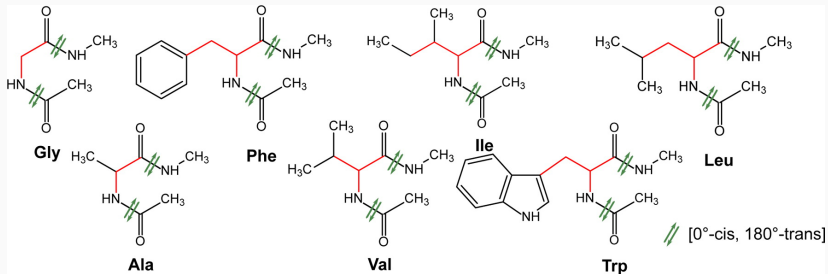
sensible



utter nonsense

Finding Low Energy Conformers of Dipeptides

Dipeptide Structures

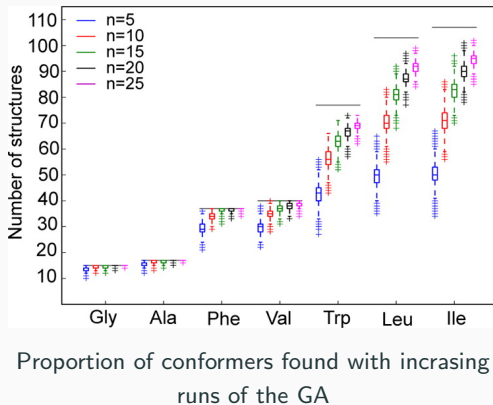


- GA beats other methods if space is large
- Space gets large **fast**

amino acid dipeptide	abbr	no. of atoms	no. of rotatable bonds + no. of cis/trans bonds	no. of conformers (below 0.4 eV \approx 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)

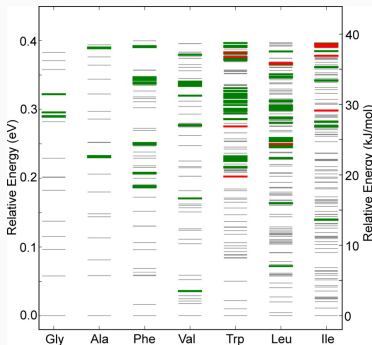
Coverage

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



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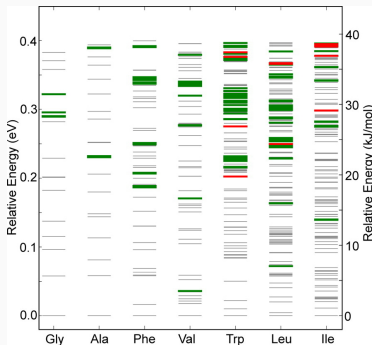
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— Missed by the GA
— New Found by GA
— In Reference & GA

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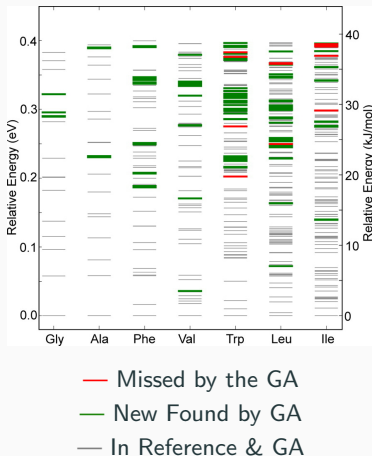
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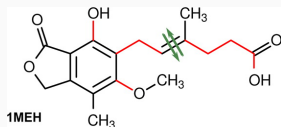
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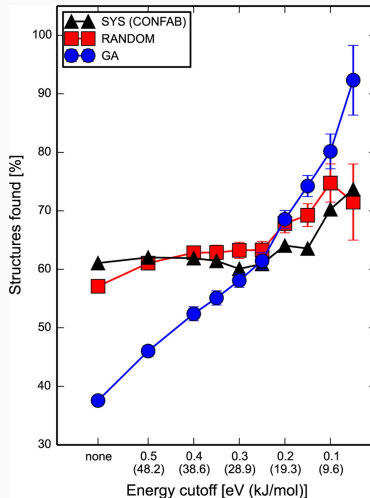
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- Features low in energy are favored and recombined



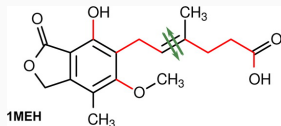
Energy Cutoff



Mycophenolic Acid

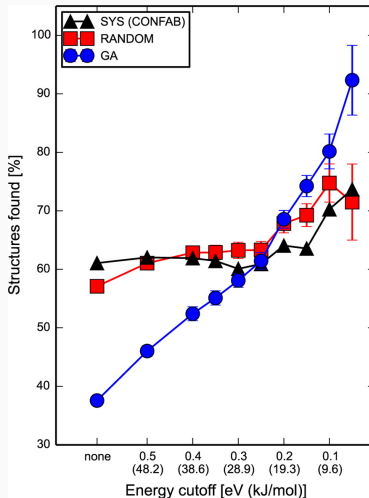


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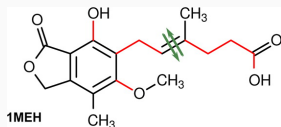


Mycophenolic Acid

- GA is more sensitive to energy cutoff

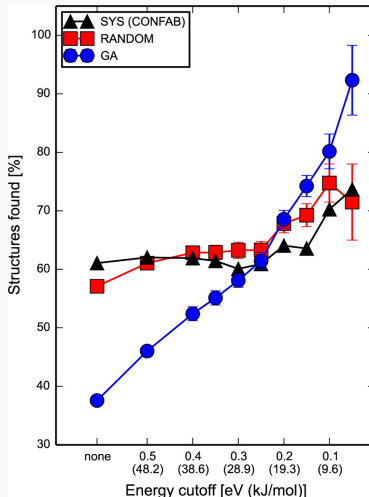


Energy Cutoff



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>

Questions?

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

Genetic Algorithm Parameters

Geometry Optimization: DFT PBE + VdW, *tier1* basis in FHI-aims¹.
Convergence at 0.005 eV / Å

	parameter	value
molecule	SMILES	<chem>CC(=O)N[C@H](C(=O)NC)[C@H](CC)C</chem>
	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 Dipeptide²

(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.