Finding Many Stable Molecular Arrangements

Conformational Searching with Genetic Algorithms

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University of Illinois at Urbana-Champaign

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 may need information about one or more low-energy conformations

$\Rightarrow$ Ok, let's find them all!

Possible Solutions

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]
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basin-hopping[24]/ minima hopping[25]	based on moves across the PES combined with local relaxation	**ASE**,[26] **GMIN**,[27] **TINKER SCAN**[28]

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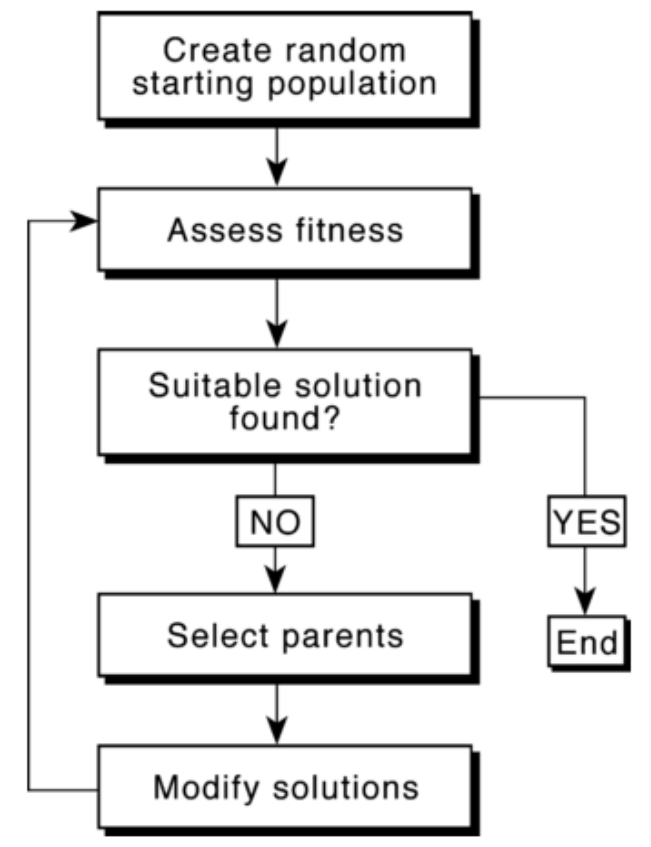
- Parallel-Scalable

The Genetic Algorithm

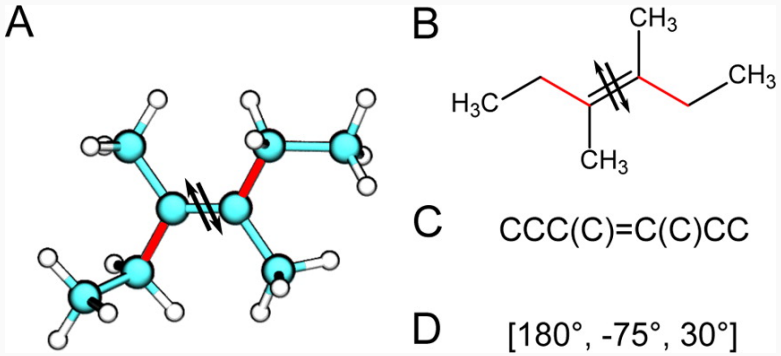
Outline

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



From Structure to Vector

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



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

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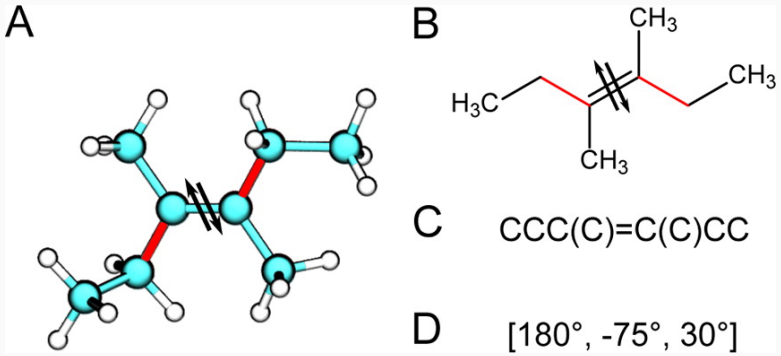

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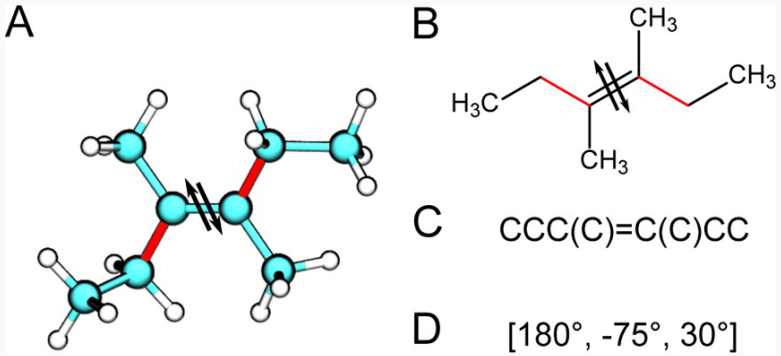

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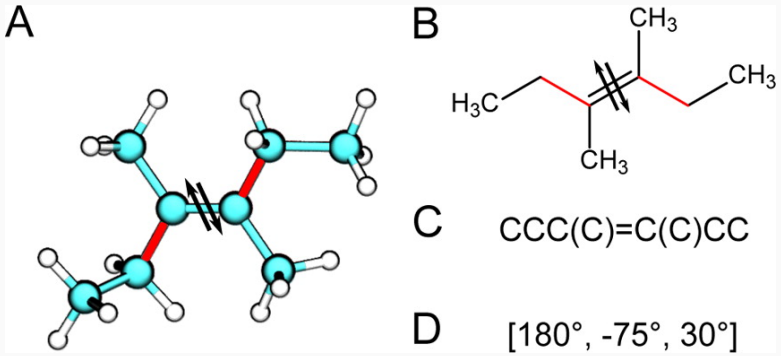

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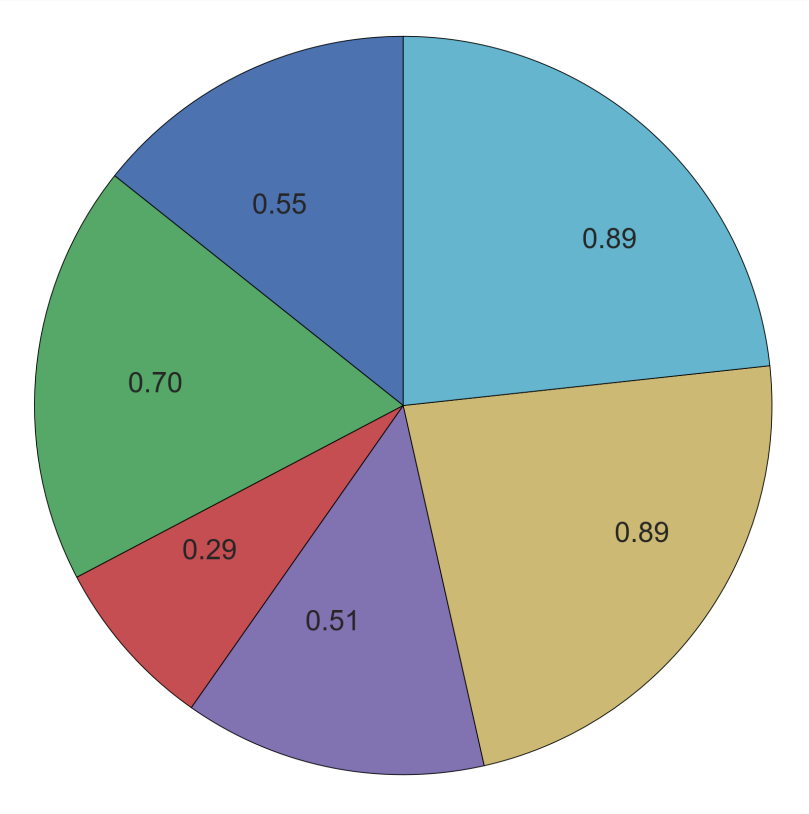

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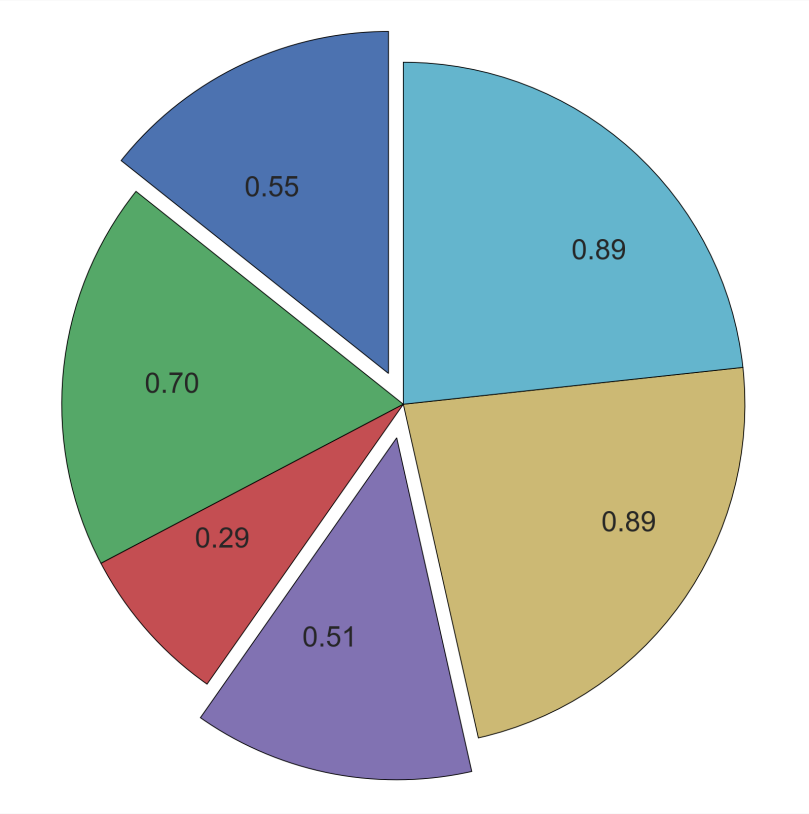
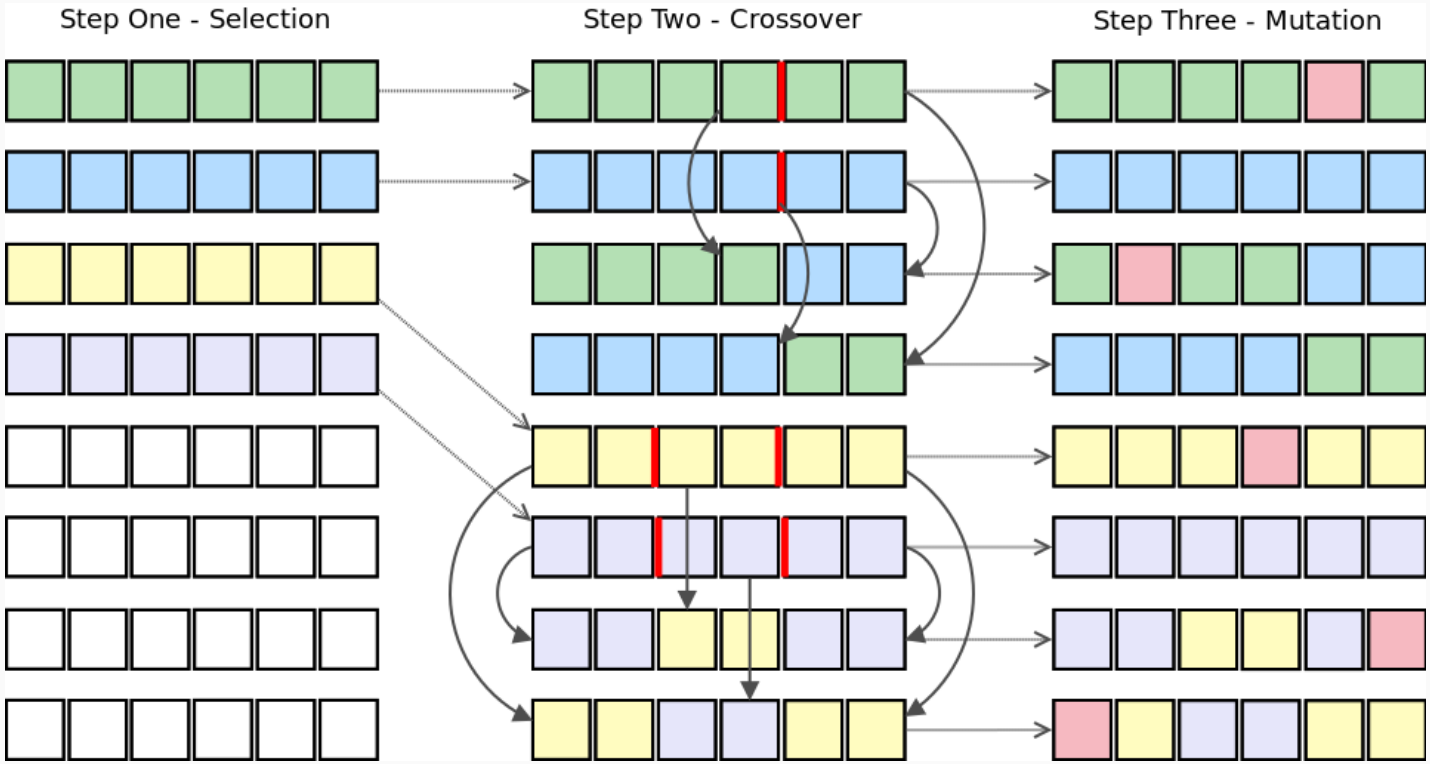


The Next Generation



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

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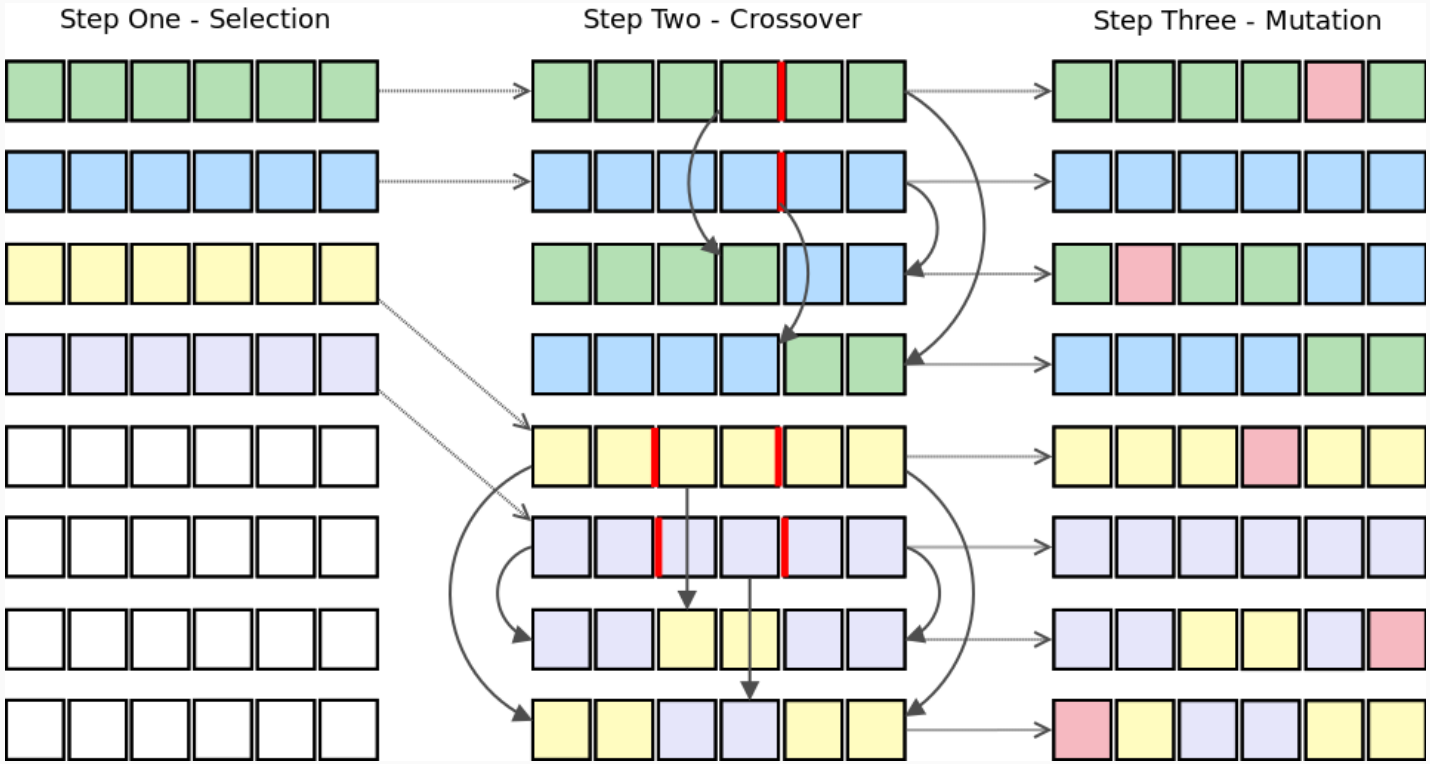

Crossover distinguishes this from Monte Carlo

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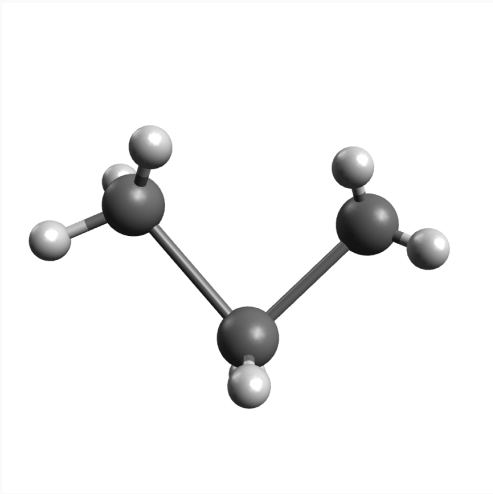
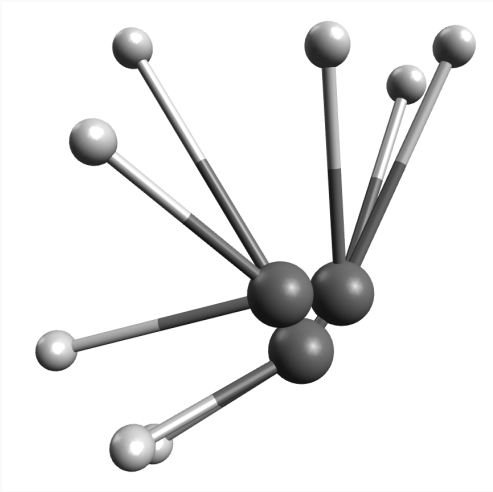


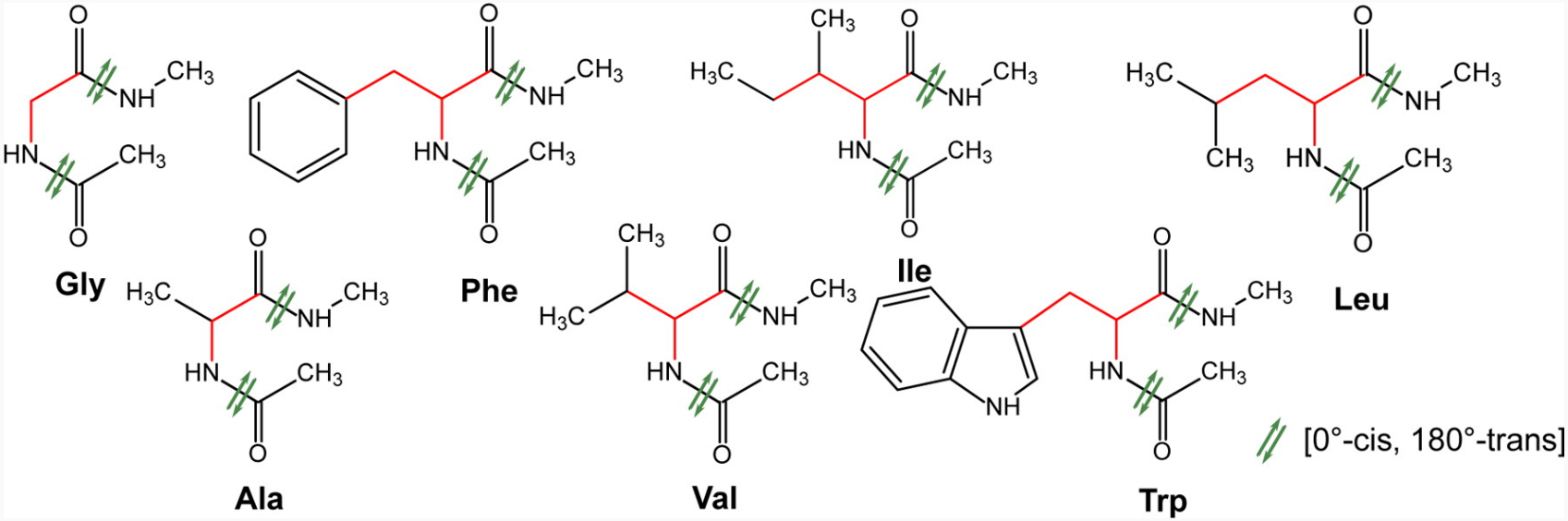
sensible



utter nonsense

Finding Low Energy Conformers of Dipeptides

Dipeptide Structures



Red = Rotatable bonds

⇌ = Cis/Trans Bonds

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)

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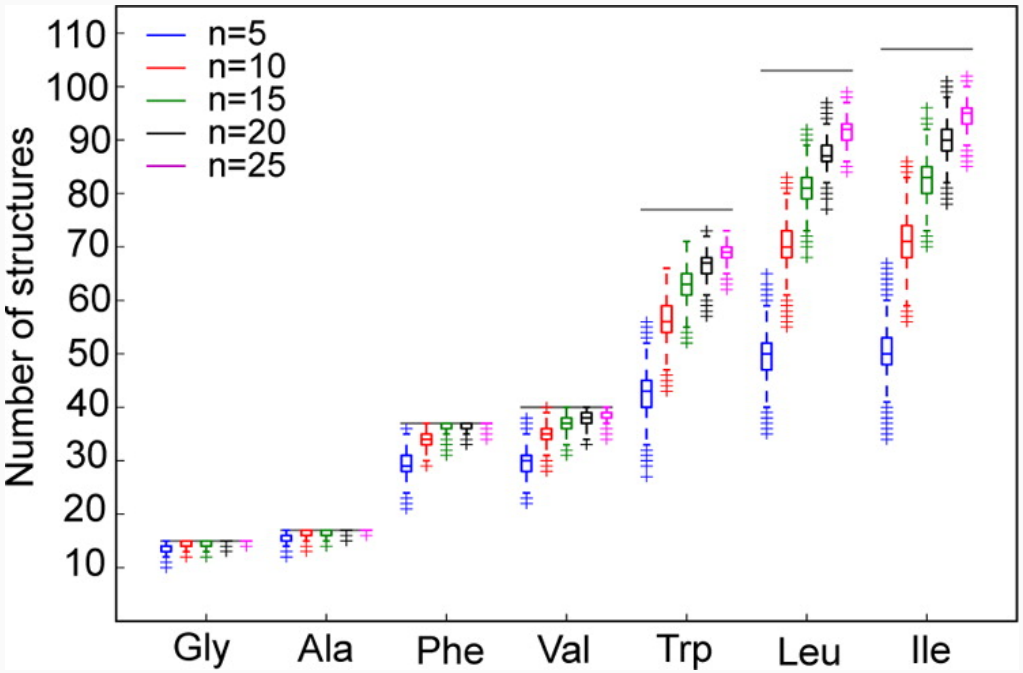
Coverage

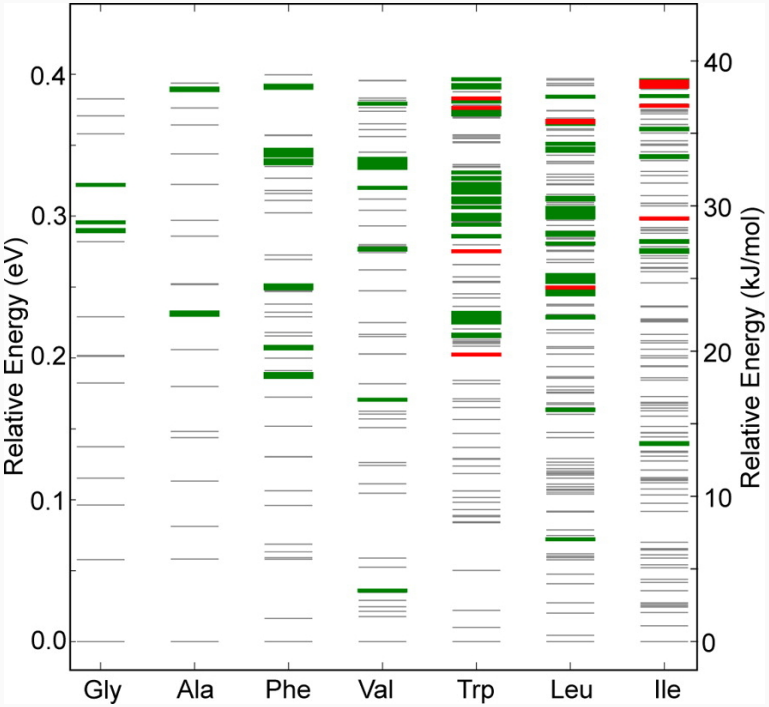
- Smaller systems are reliably sampled
- As # of conformers increases, miss more and more
- Is there a pattern to what is missed?



Proportion of conformers found with incrasing runs of the GA

Coverage

- Most misses are very high energy



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— New Found by GA

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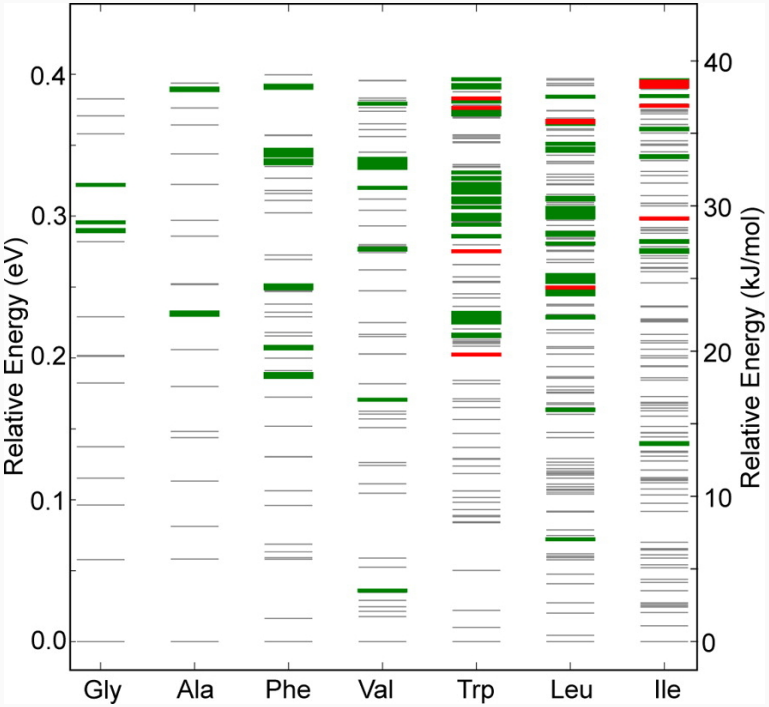
Coverage

- Most misses are very high energy
- Algorithm favors low energy areas of the space



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Coverage

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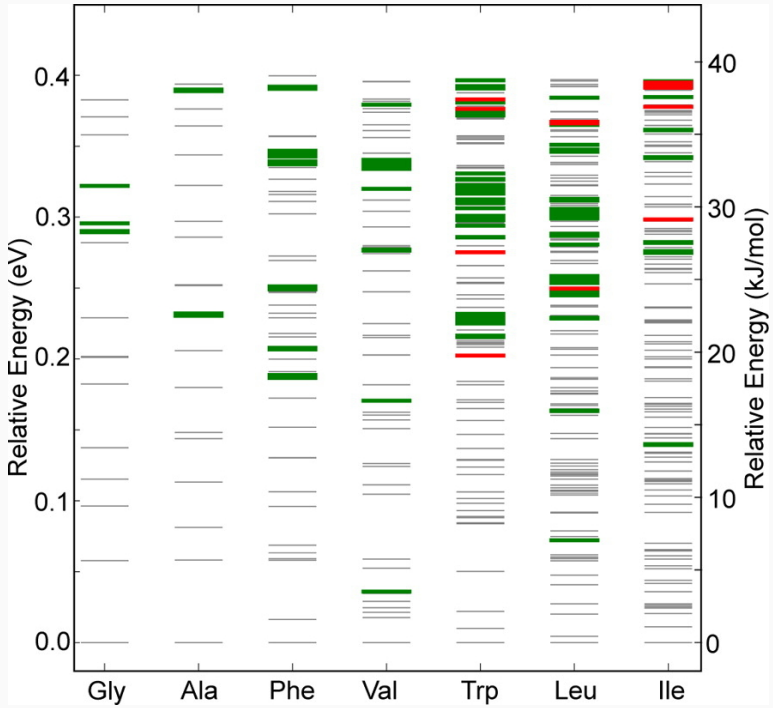
- Algorithm favors low energy areas of the space
- Features low in energy are favored and recombined



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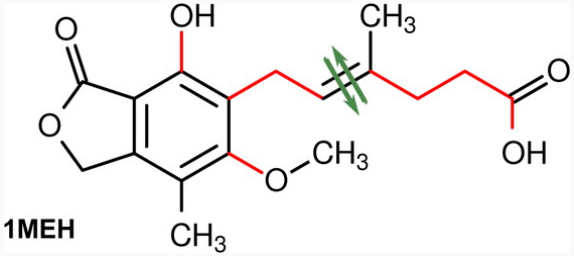
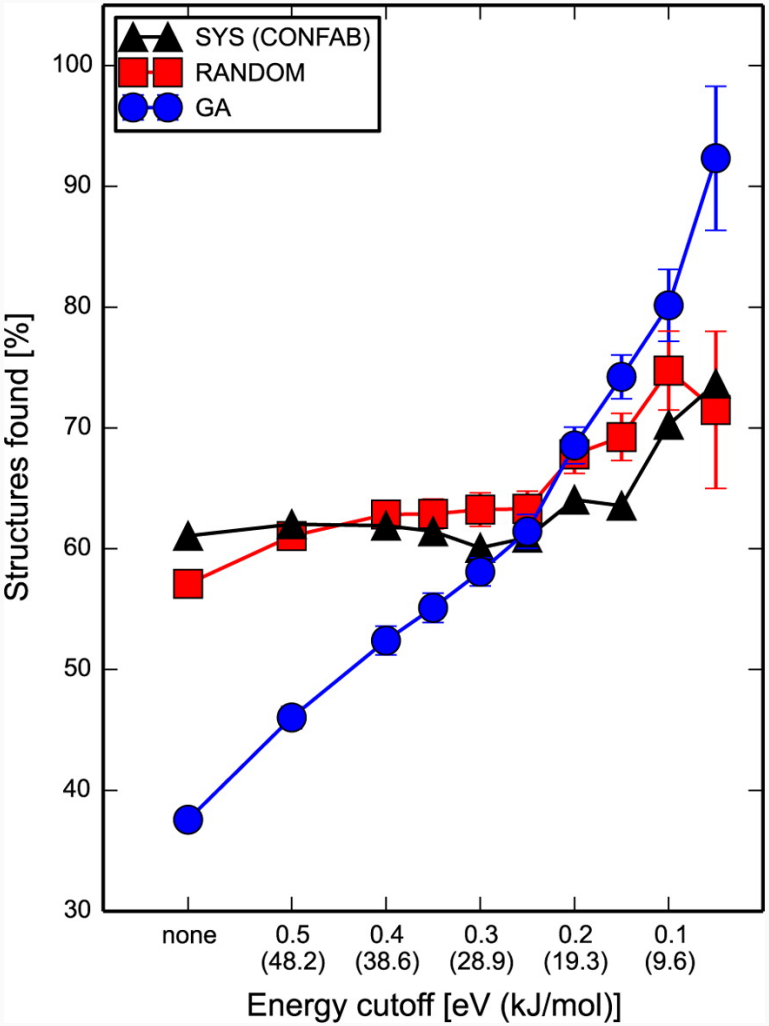


Mycophenolic Acid



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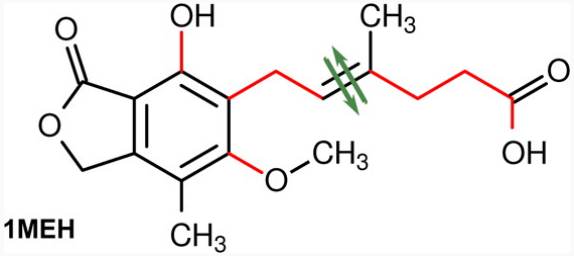

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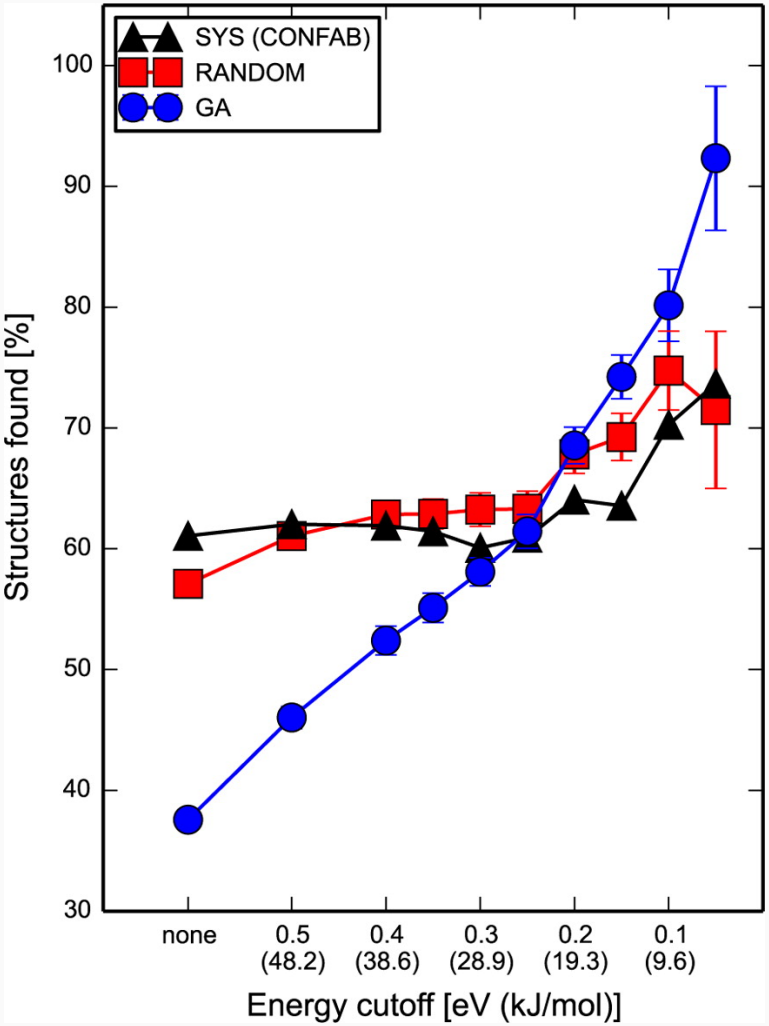

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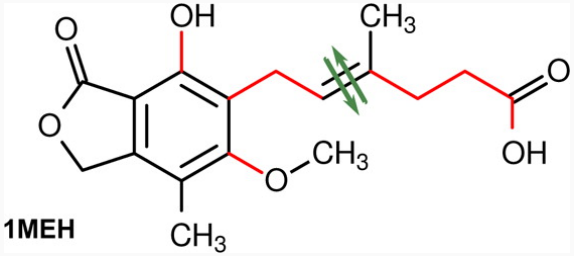

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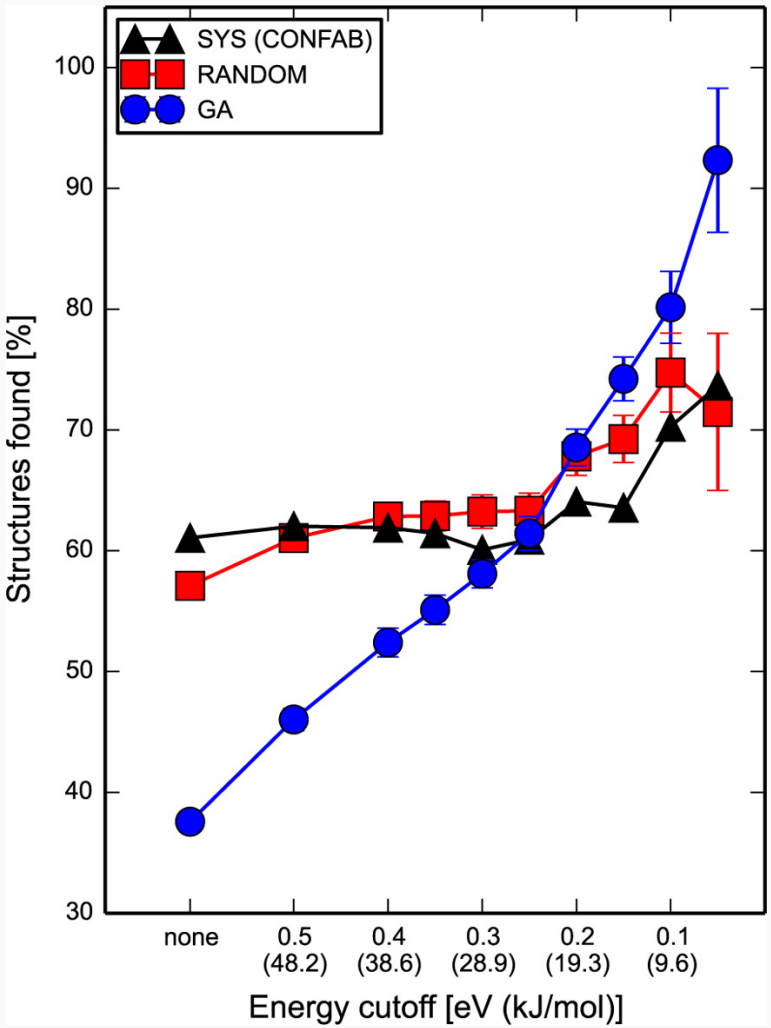
- For finding low energy ensemble, GA outperforms purely stochastic/deterministic method



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- 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?

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.