

# Finding Many Stable Molecular Arrangements

Conformational Searching with Genetic Algorithms

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Evan Curtin

December 2, 2016

University of Illinois at Urbana-Champaign

# Outline

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

*First-Principles Molecular Structure Search with a Genetic Algorithm*

Supady, A.<sup>P1</sup>; Blum, V.<sup>1</sup>; Baldauf, C. J.<sup>1,2</sup> Chem. Inf. Model. 2015, 55 (11), 23382348.

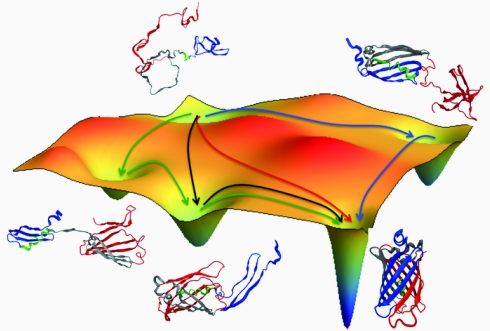
1. Fritz-Haber-Institut der Max-Planck-Gesellschaft, Berlin
2. Department of Mechanical Engineering & Materials Science, Duke University

## Background Information

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# The Problem

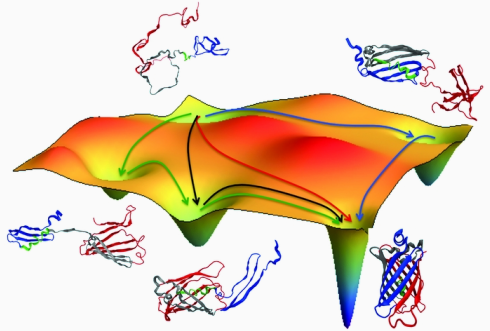
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Reddy, G.; Liu, Z.; Thirumalai, D. Proc. Natl. Acad. Sci. 2012, 109 (44), 1783217838.

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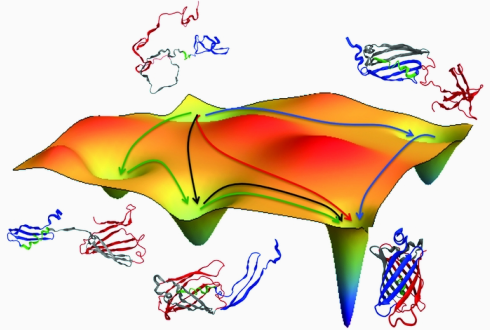
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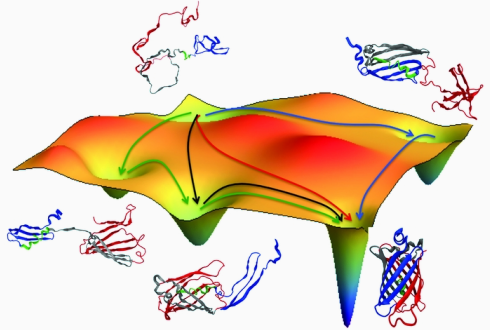
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# The Problem

- Protein folding is important
- Peptides are building blocks of protein
- Peptide conformations → protein folding
- How do we understand peptide conformations?



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**Computational methods require knowledge of molecular structure**

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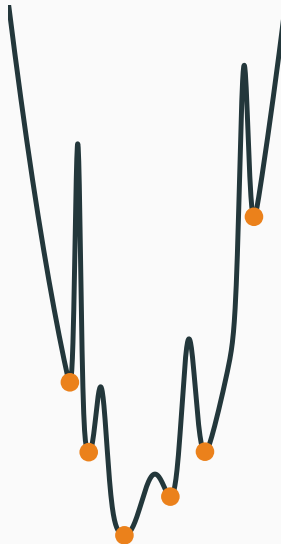
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We can't tell for sure if we've found the **global** minimum

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- Ok, let's find them all!
- Under a cutoff



# Possible Solutions

- Many techniques are well established

Method	Implented in
grid-based	CEASAR, <b>Open Babel</b> , <b>Confab</b> , MacroModel, MOE
rule-based	<b>ALFA</b> , <b>CONFECT</b> , CORINA, ROTATE, <b>COSMOS</b> , OMEGA
population-based	<b>Balloon</b> , <b>Cyndi</b>
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- None are perfect

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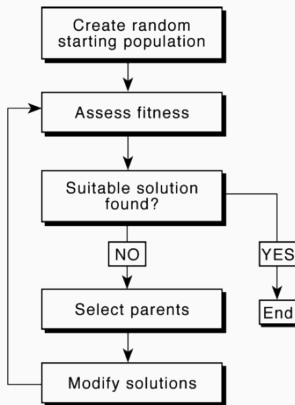
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4. Minimize human bias
5. Parallel

# The Genetic Algorithm

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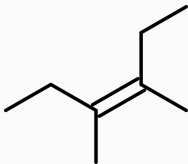
# Outline

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

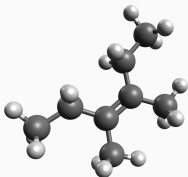


# The Many Representations of a Molecule

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

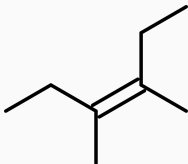
Internal Coords

		r		$\theta$
C				
C	1	1.51		
C	2	1.38	1	131

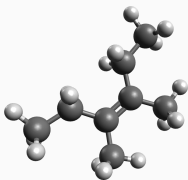
1. Supady, A.; Blum, V.; Baldauf, C. J. Chem. Inf. Model. 2015, 55 (11), 23382348.
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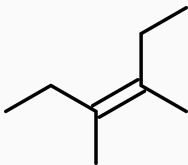
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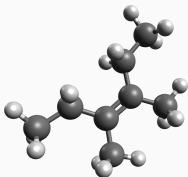
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## Roulette Wheel Method

1. Reinforce good characteristics

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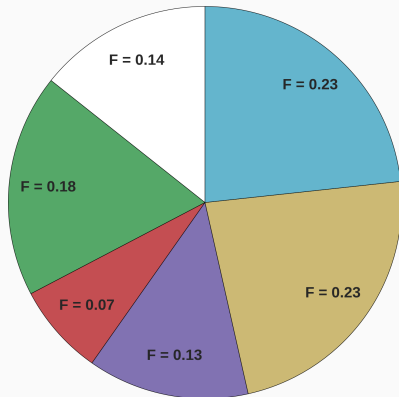


**Sum of Fitness Scores = 1.0**

# Selecting Parents

## Roulette Wheel Method

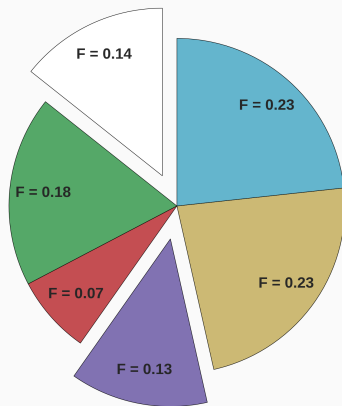
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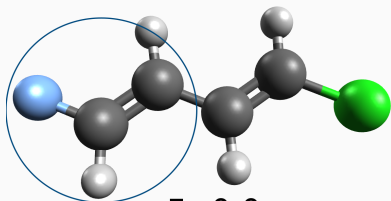
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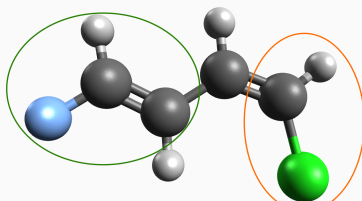
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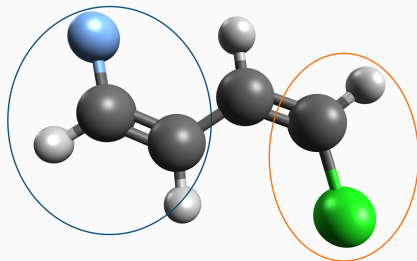
# The Next Generation



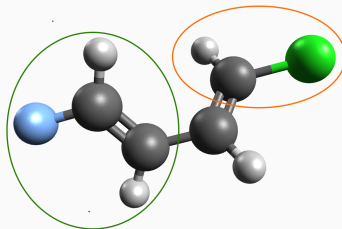
$F=0.0$



$F=0.95$



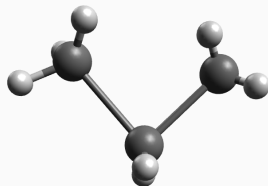
$F=1.0$



$F=0.86$

# The Whole Algorithm

1. Generate N random, sensible geometries

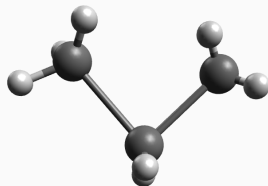


sensible

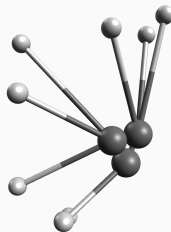


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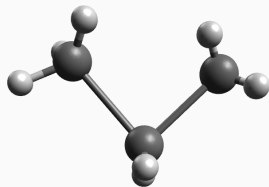
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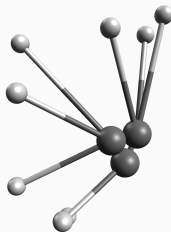
utter nonsense

# The Whole Algorithm

1. Generate N random, sensible geometries
2. Optimize



sensible



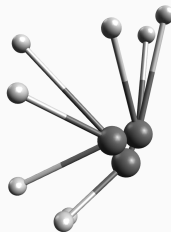
utter nonsense

# The Whole Algorithm

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



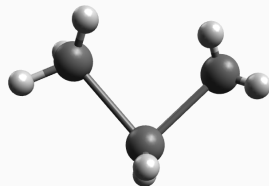
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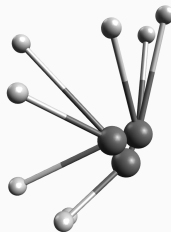
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# The Whole Algorithm

1. Generate N random, sensible geometries
2. Optimize
3. Select Parents
4. Crossover & Mutate



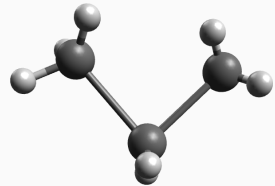
sensible



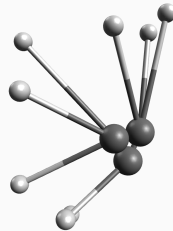
utter nonsense

# The Whole Algorithm

1. Generate N random, sensible geometries
2. Optimize
3. Select Parents
4. Crossover & Mutate
5. Add Children to population



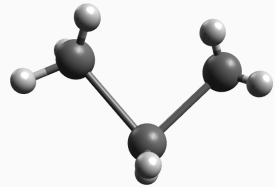
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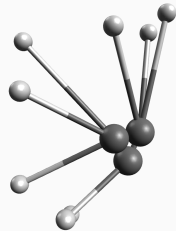
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6. Remove the unfit



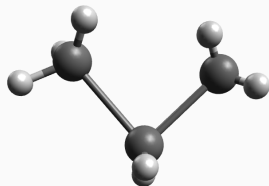
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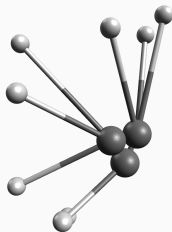
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7. If converged:
  - Done!



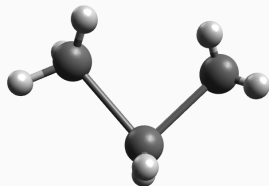
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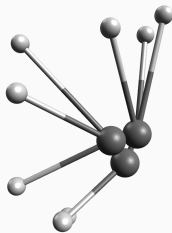
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7. If converged:
  - Done!Otherwise:
  - Go to 2



sensible



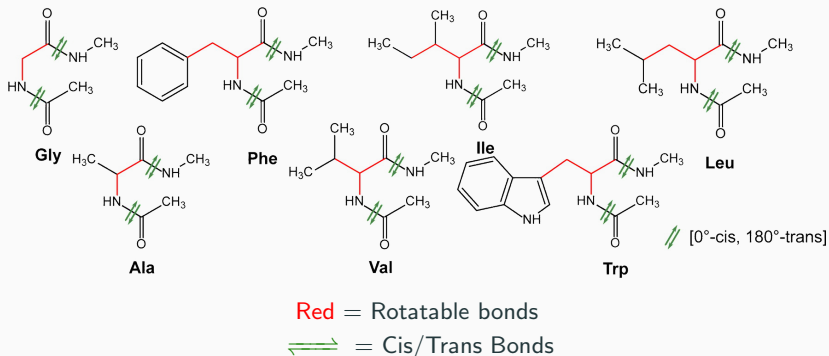
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# Finding Low Energy Conformers of Dipeptides

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# "Dipeptide" Structures

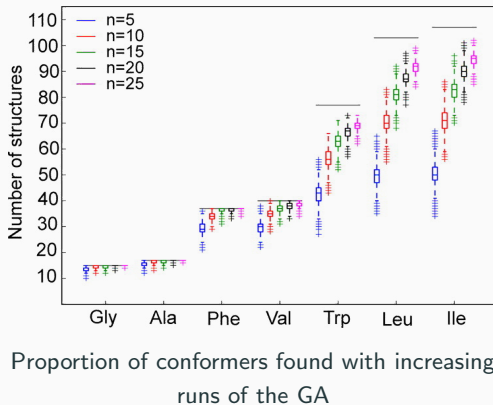


*"We use the term dipeptide for amino acids with an acetylated N terminus and an amino-methylated C terminus"*

	Molecule	N	# Rotatable +	# Conformers
			# Cis/Trans Bonds	
• GA beats other methods if space is large	Gly	19	2 + 2	15
	Ala	22	2 + 2	28
	Phe	32	4 + 2	64
• Space gets large <b>fast</b>	Val	28	3 + 2	60
	Trp	36	4 + 2	141
	Leu	31	4 + 2	183
	Ile	31	4 + 2	176

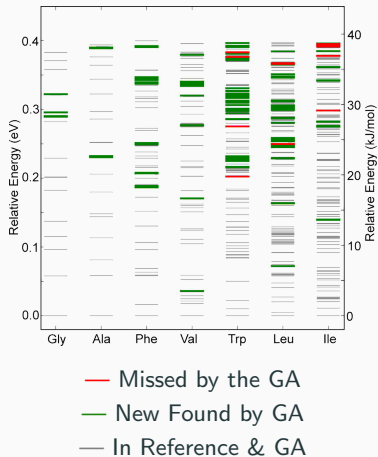
# Coverage

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



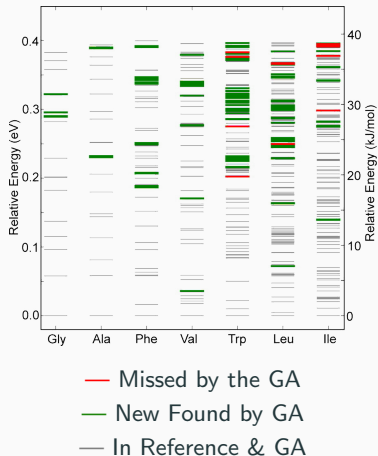
# Coverage

- Most misses are very high energy



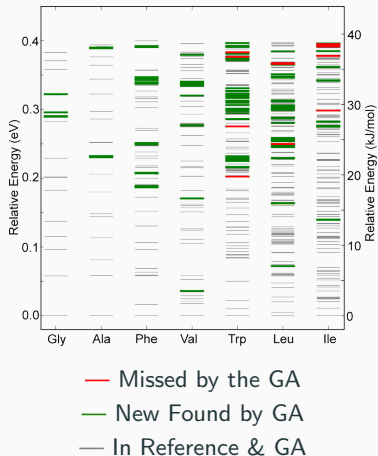
# Coverage

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

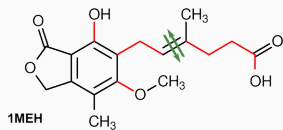


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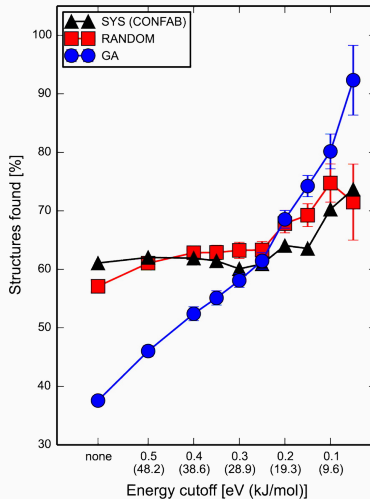
- Most misses are very high energy
- Algorithm favors low energy areas of the space
- Features low in energy are favored and recombined



# Energy Cutoff

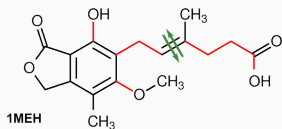


Mycophenolic Acid



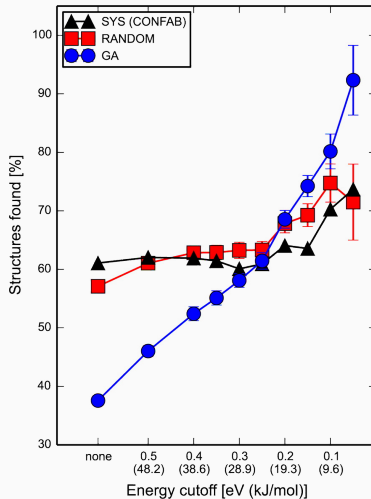


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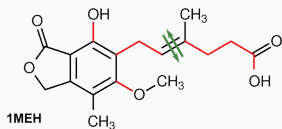


Mycophenolic Acid

- GA is more sensitive to energy cutoff

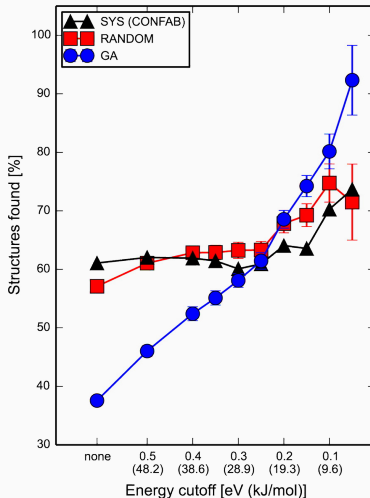


# Energy Cutoff



Mycophenolic Acid

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



## Concluding Remarks

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## Review

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- 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>



**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-aims<sup>1</sup>.  
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 Dipeptide<sup>2</sup>

(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.