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Evolutionary Hybrids for Flexible Ligand Docking (Electronic Notes)

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Overview

1. Evolutionary algorithms (EAs)

2. EA Hybrids
   - Design
   - Motivation
   - Dynamics
   - Applications

3. Drug Docking with AutoDock
   - Problem formulation
   - Empirical evaluation of EA hybrids

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Evolutionary Algorithms — Overview

Idea: a multi-point search strategy inspired from natural evolutionary processes

Motivation:

- Selection of better individuals (Darwin)
- Generation of variants from selected individuals (Mendel)

Analogous Search Mechanisms:

- Stochastic competitive selection
- Selective recombination (a.k.a. crossover)

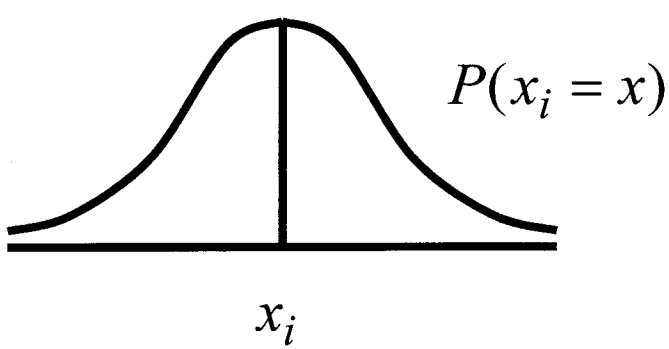
Evolutionary Algorithms: genetic algorithms, genetic programming, evolutionary programming, evolutionary strategies

Methods for generating variants

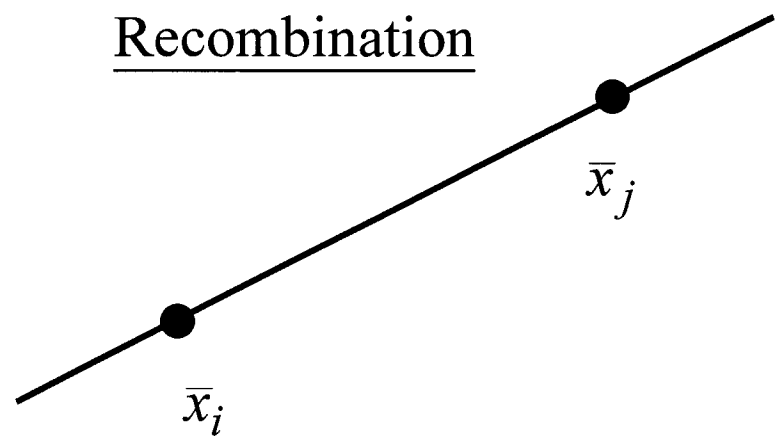
- Mutation - generate a simple change
- Recombination - combine two or more search points (a.k.a. parents)

Example: searching R^n

Mutation



Recombination



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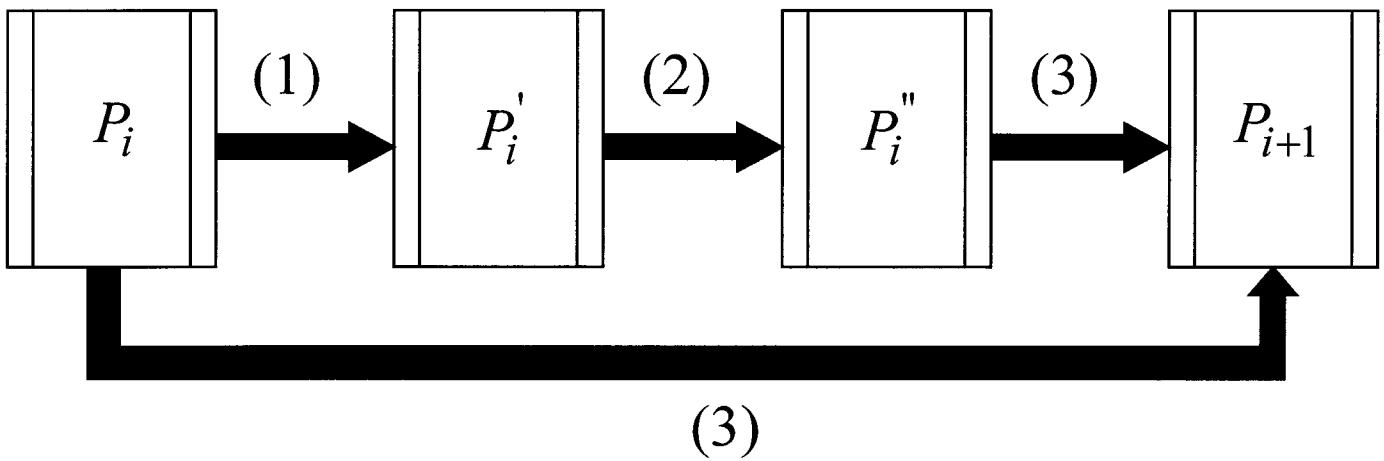
Evolutionary Algorithms

Main Loop



(1) Stochastic competition

(2) Generate new variants

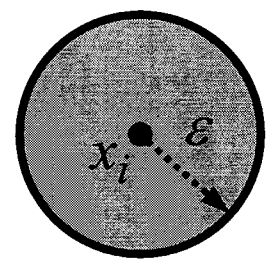
(3) Replacement competition

Local Search

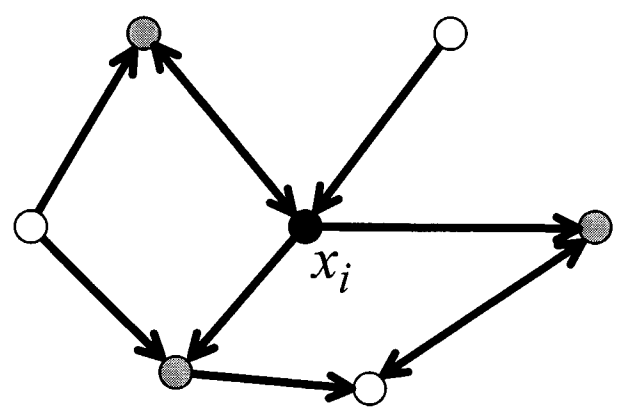
Idea: iterative examine solutions in a local neighborhood and select one that has a lower value.

Examples of local neighborhoods:

- An ε-close ball (in R^n)



- Adjacent nodes in a graph



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EA Hybrids with Local Search

Motivation

Idea: utilize local search to refine solutions in each iteration of the EA.

Biological Motivation

- Organisms utilize phenotypic adaptations (e.g. learning) to adapt to their environment
- Evolution modifies an individual's genotype across generations
- Phenotypic adaptations smooth the evolutionary landscape

Mathematical Motivation

- Local search quickly refines solutions
- Global search ensures that all areas of the search domain are adequately explored
- Most effective global search methods combine global and local search

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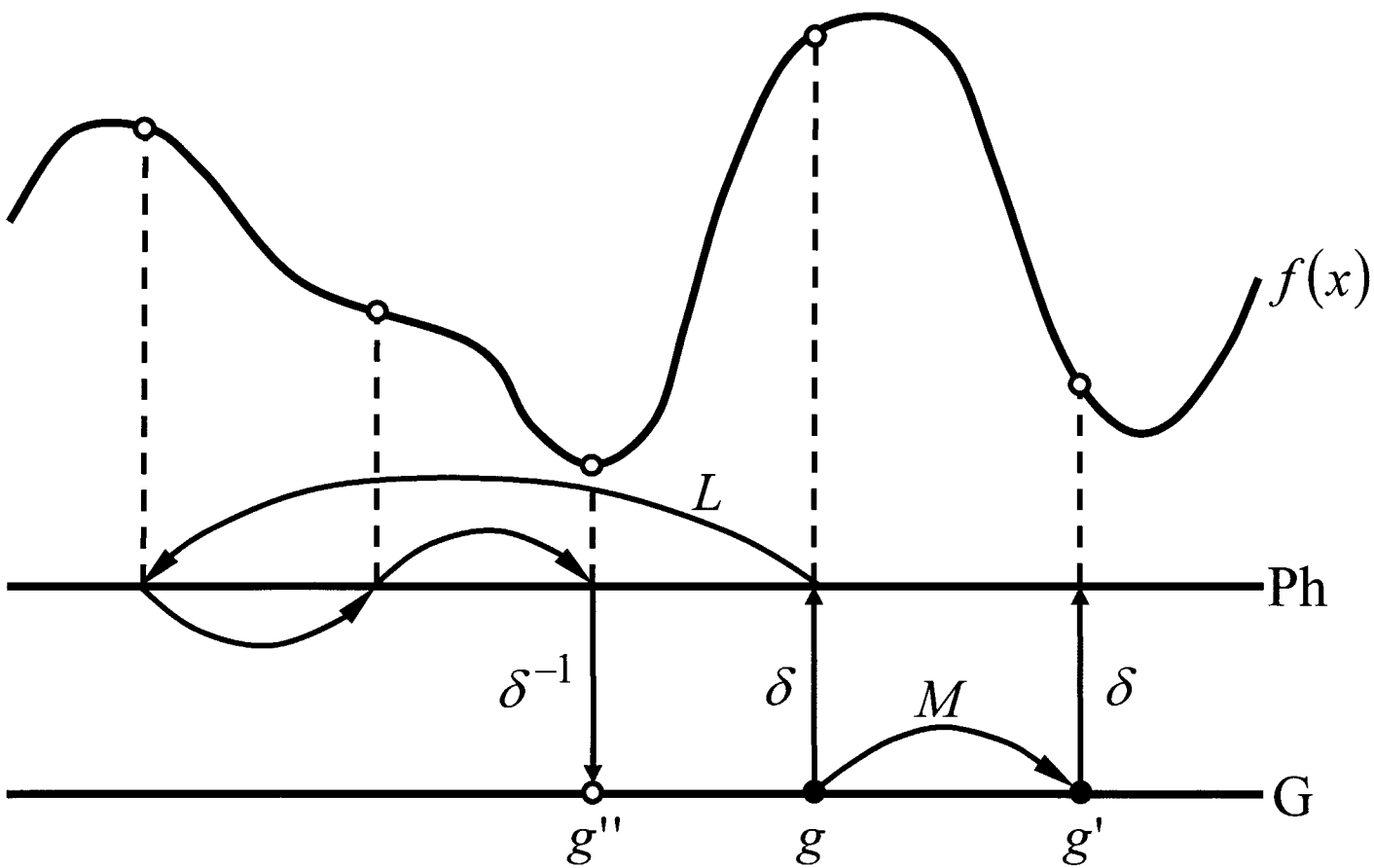
Model

Local search can distinguish between a genotypic and phenotypic search space through a developmental map $\delta : G \rightarrow Ph$.



Model (cont'd)

Lamarckian Local Search

- modifies the fitness value and solution parameters
- is typical used for optimization

NonLamarckian Local Search

- modifies only the fitness value
- can be useful when the EA's selection pressure is "too strong"
- can be viewed as a "repair mechanism for constrained problems

EA Hybrids

Design

Pseudo Code

Initialize a population of points $\{x_0^0, \ldots, x_0^N\}$
Perform local search?
Repeat
    Perform competitive selection to select $\{\hat{x}_t^0, \ldots, \hat{x}_t^N\}$
    Apply evolutionary operators (mutation, recombination)
    Apply local search (A)
    Replace previous population of points
    Apply local search (B)
Until stopping rule satisfied

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EA Hybrids

Design (cont'd)

Design Issues

- Duration of local search
- Type of local search (robustness!)
- How local search is initialized
- What points are refined with local search
- Lamarckian or nonLamarckian local search

Hybrid designs:

memetic algorithms

parallel genetic algorithms

Lamarckian genetic algorithms

genetic local search

genetic hillclimbing

EA-LS hybrids

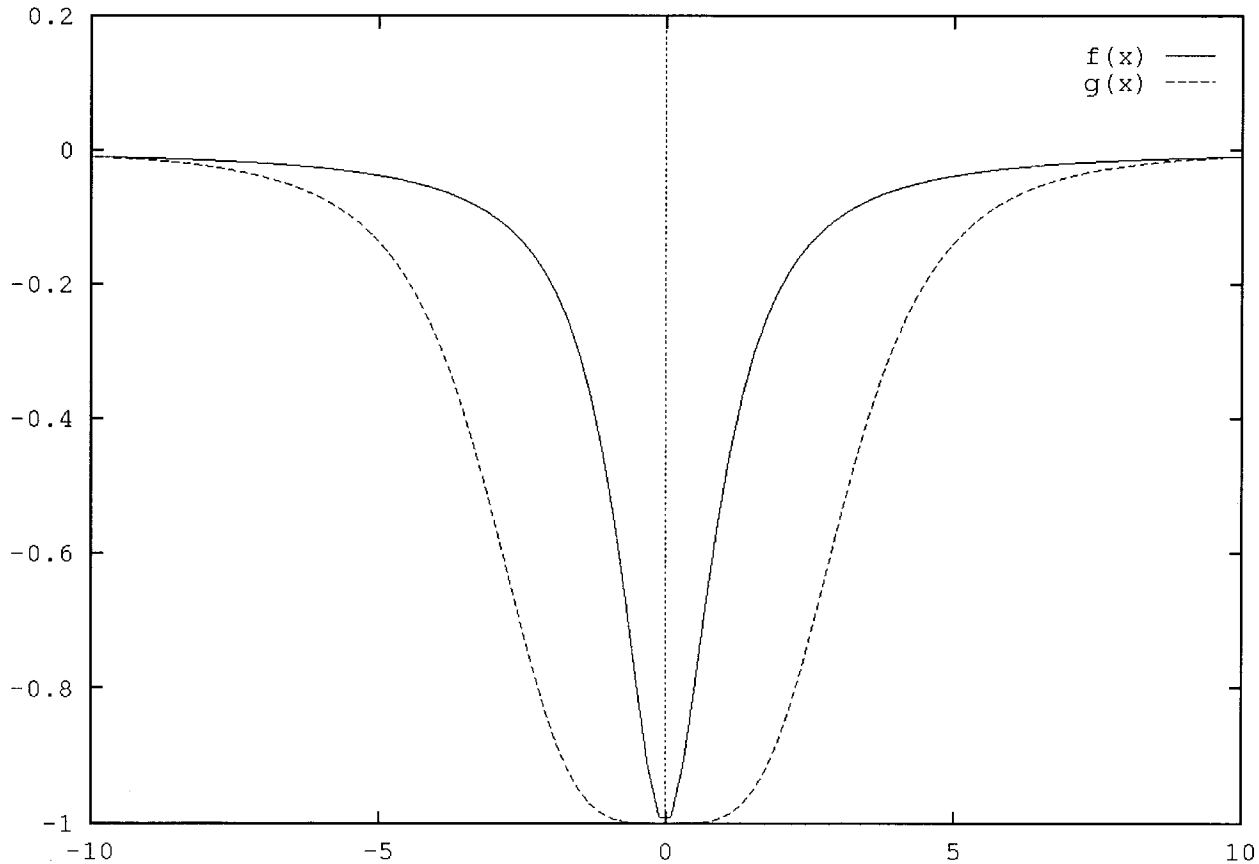
Fitness Transformation

Local search can play a variety of roles in EAs (Hart et al, 94)

I. Fitness transformation: nonLamarckian EA hybrids

f(x) Func

g(x) Transformed func



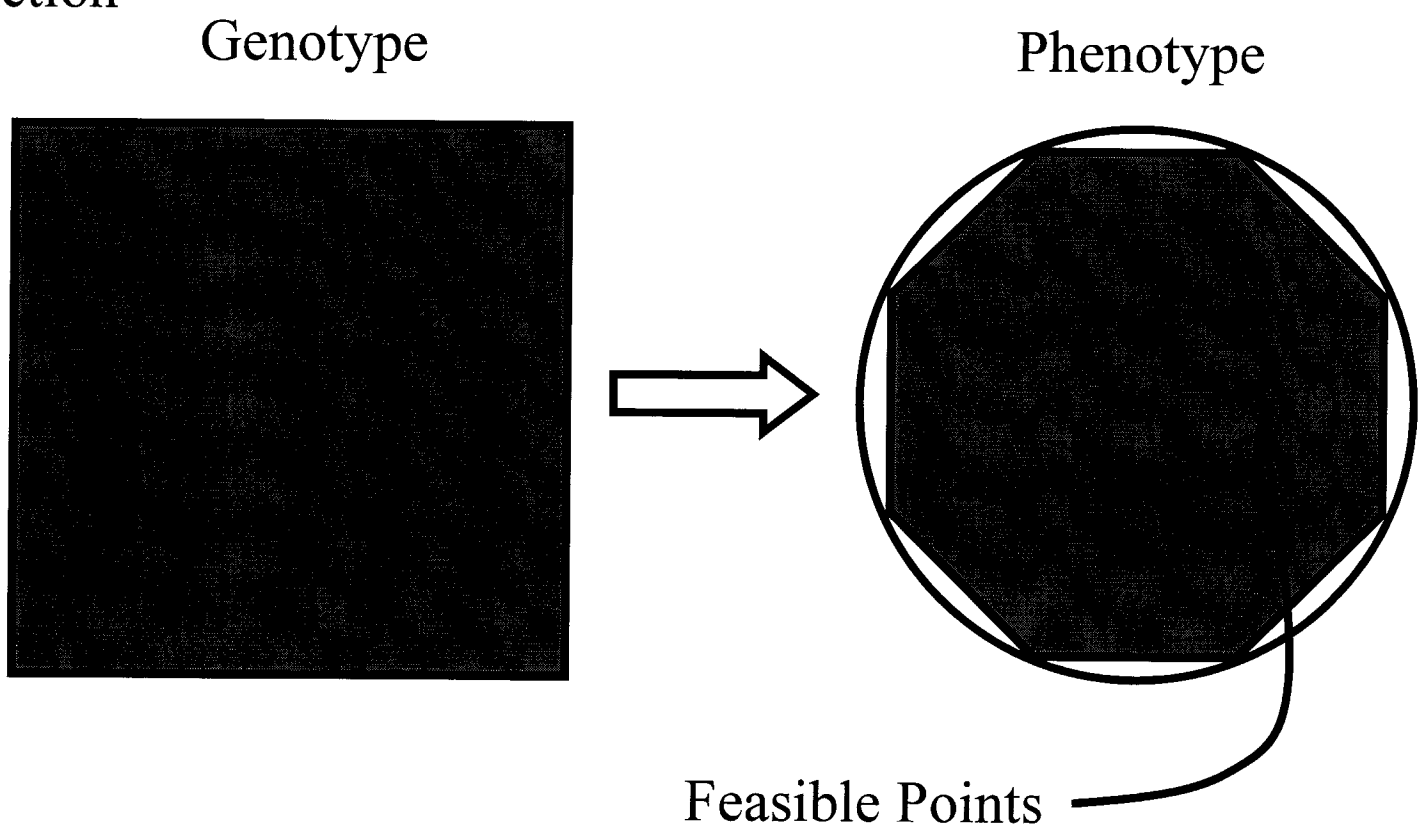
II. Refinement operator: Lamarckian EA hybrids

Extreme Case

- all solutions are mapped to their respective local minima
- recombination and mutation define transition between local minima
- Example: genetic local search

Repair Operator

III. Repair operator: nonLamarckian EAs with a genotype-phenotype distinction



Example: evolving grammars (Kammeyer and Belew, 97)

Applications of EA Hybrids

Thin Film Metrology (Land et al, 97)

Flowshop Scheduling (Ishibuchi et al, 97)

Drug Docking (Rosin et al, 97; Morris et al, 98; Hart et al, 99)

Reliable Communication Networks (Dengiz et al, 97)

QAP (Mühlenbein, 91)

Neural Network (Belew et al, 91; Keesing and Stork, 91; Gruau and Whitley, 93)

[See also www.ing.unlp.edu.ar/cetad/mos/memetic_home.html]

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Motivation

Goal: develop docking tools for structure-based drug discovery

AutoDock Method

- Flexible ligand
- Rigid receptor
- Conformational search used to find good docking configurations

The AutoDock Potential Energy Model

Energy Potential:

- Long-range electrostatic forces
- Short-range weak van der Waals attractive forces
- Hydrogen bonds (12-10 LJ potential)
- Unfavorable conformational entropy
- Desolvation measure (Stouten et al '93)

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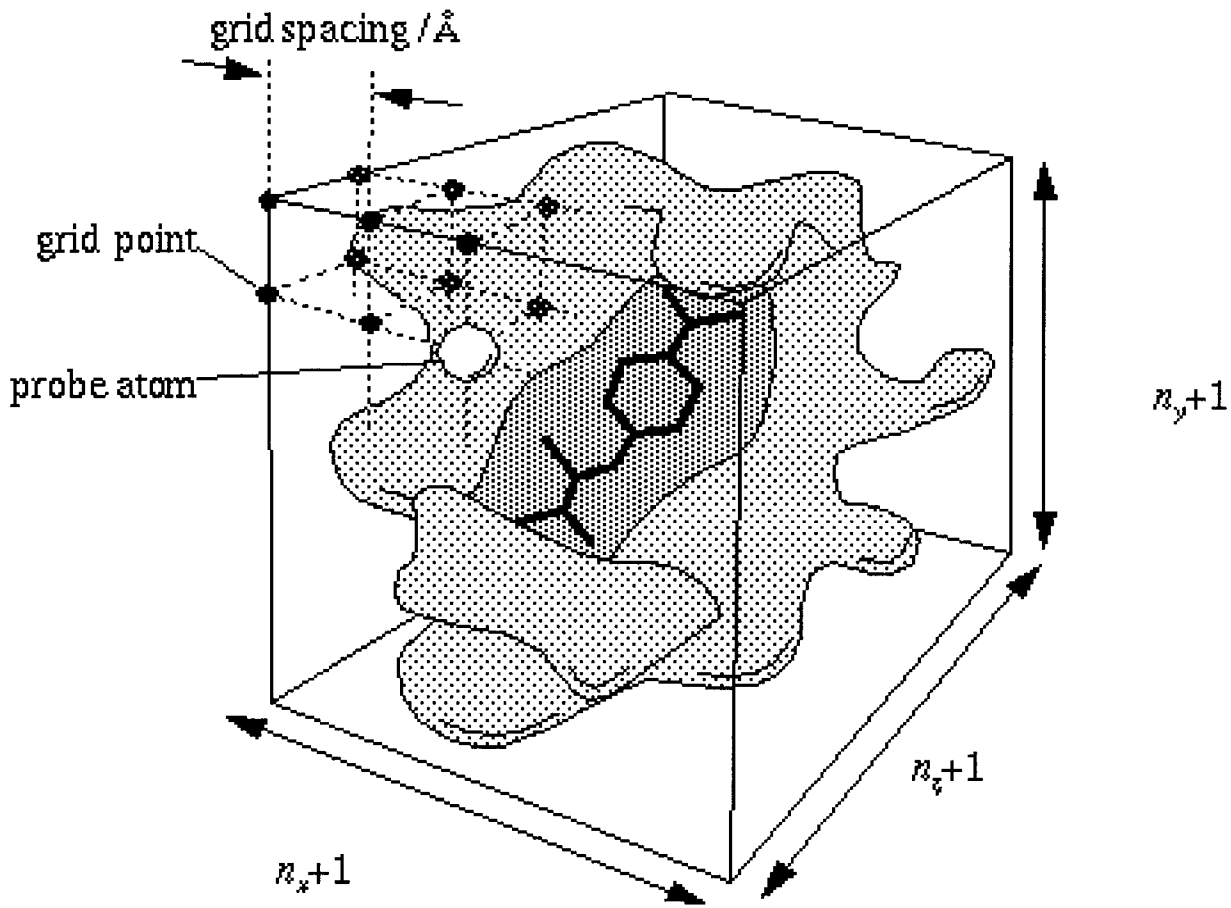
Computing Potential Energies

Ligand-protein pairwise interaction energies are precalculated



Grid-based method rapidly computes interpolated energies

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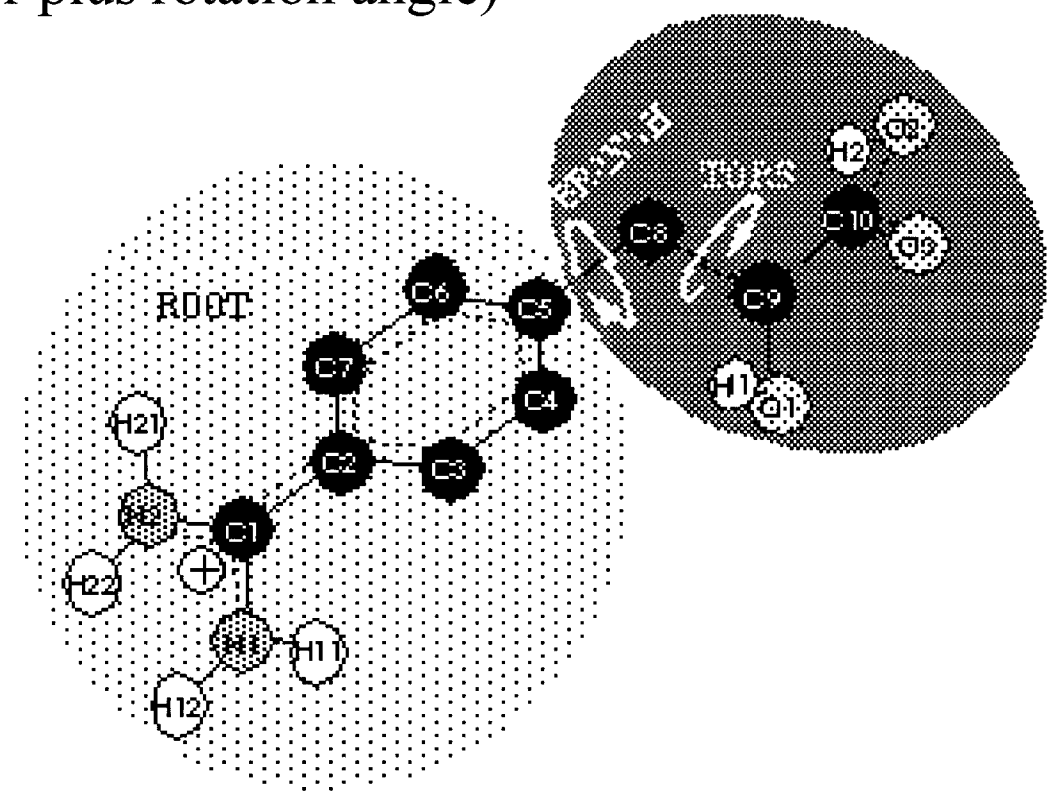
Docking Formulation

Search Dimensions

- Cartesian Coordinates (3 dimensions)
- Quarternion (unit vector plus rotation angle)
- Torsion angles



Docking Formulation (cont'd)

Optimization Formulation

- Unconstrained variables
- Quadratic penalty for coordinate bound constraints
- Quarternion vector renormalized

Note: this objective is nondifferentiable

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Optimization Methods

Simulated annealing

- Steepest descent that accepts inferior points with probability

$$e^{-\Delta E / T},$$

  where ΔE is the difference in energy and T is a "temperature" constant
- Good for "walking through" shallow local minima

Evolutionary algorithms

- Evolutionary programs
- Evolutionary pattern search
- EA hybrids

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Evolutionary Programming

Evolutionary operator: mutation

- Idea: add a scaled random variable to each dimension
  - Normal: $\mathrm{N}(0,\sigma_i)$
  - Cauchy: $\mathrm{C}(0,\sigma_i)$

Self-adaptation

- Mutation scale adapted (co-evolved) with the search parameters
- Idea: multiply scale by a random variable
  - Gaussian: $+\alpha\,\mathrm{N}(0,1)$
  - Lognormal: $\exp(\tau'\mathrm{N}(0,1)+\tau\,\mathrm{N}_i(0,1))$

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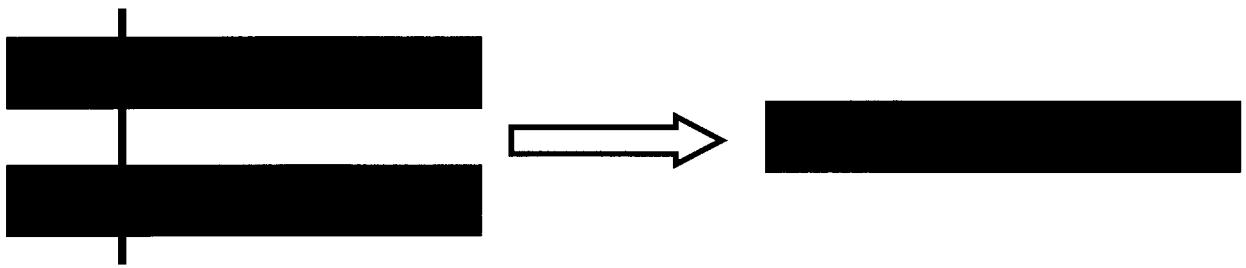
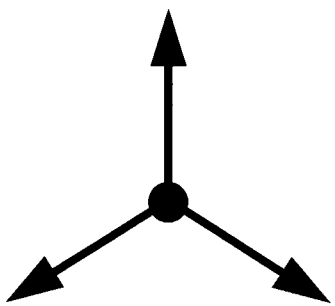
Evolutionary Pattern Search

An adaptive EA

- Evolutionary operators: coordinate-wise crossover and mutation



- Uses a global mutation step scale parameter Δ_t
  - For all individuals
  - For all dimensions
- Uses a fixed pattern of mutation offsets



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EA Hybrids for Docking

Experimental options

- Cauchy mutation and coordinate-wise crossover
- Infrequent local search
- Local search
  - Solis-Wets
  - Pattern Search
- Fixed local search duration
  - 300 function evaluations
  - 3000 function evaluations
- Step-length initialization
  - Fixed
  - Adaptive

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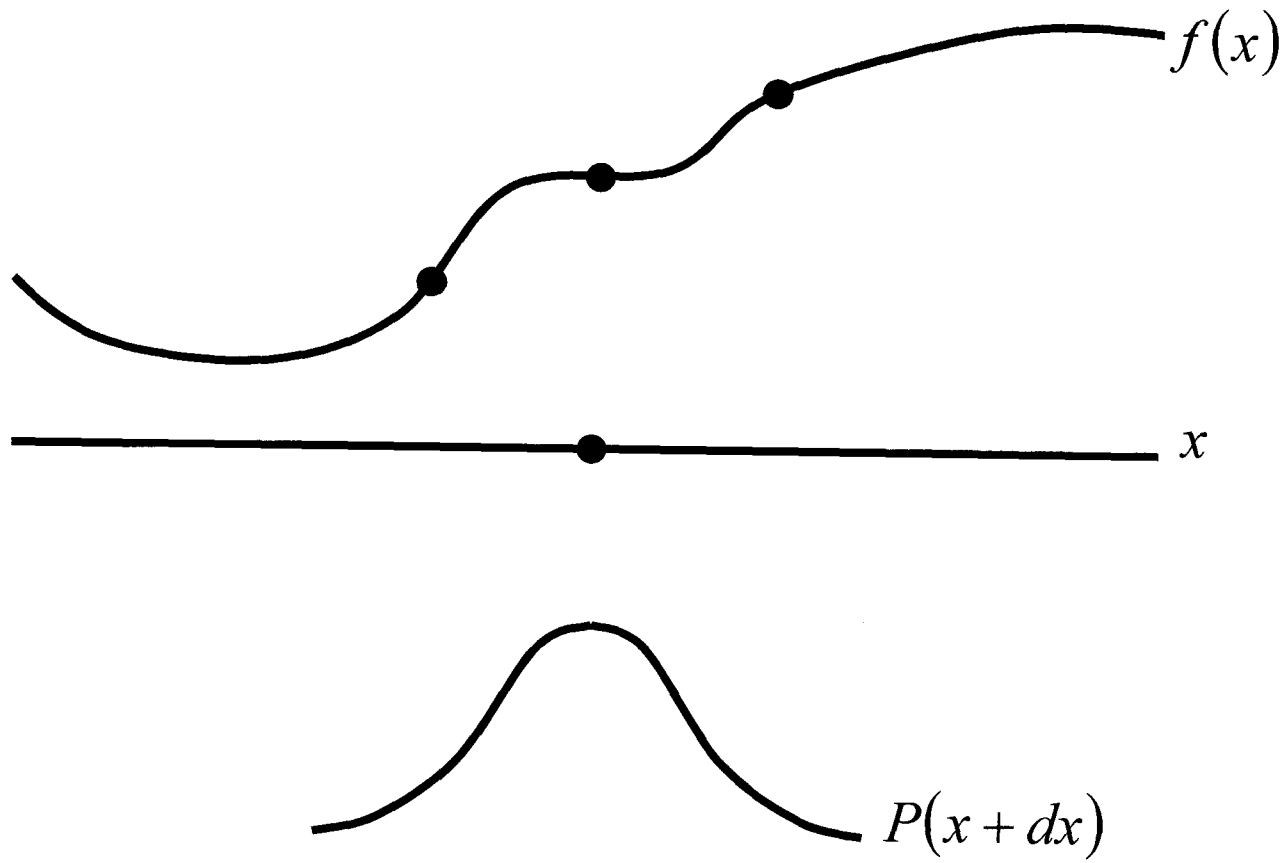
Solis-Wets Local Search



Solis-Wets Local Search (cont'd)

Properties

- Cheap local search (especially in high dimensions)
- Can rapidly adjust the step length parameter
- Convergence properties unclear
- Does not have robust stopping rules

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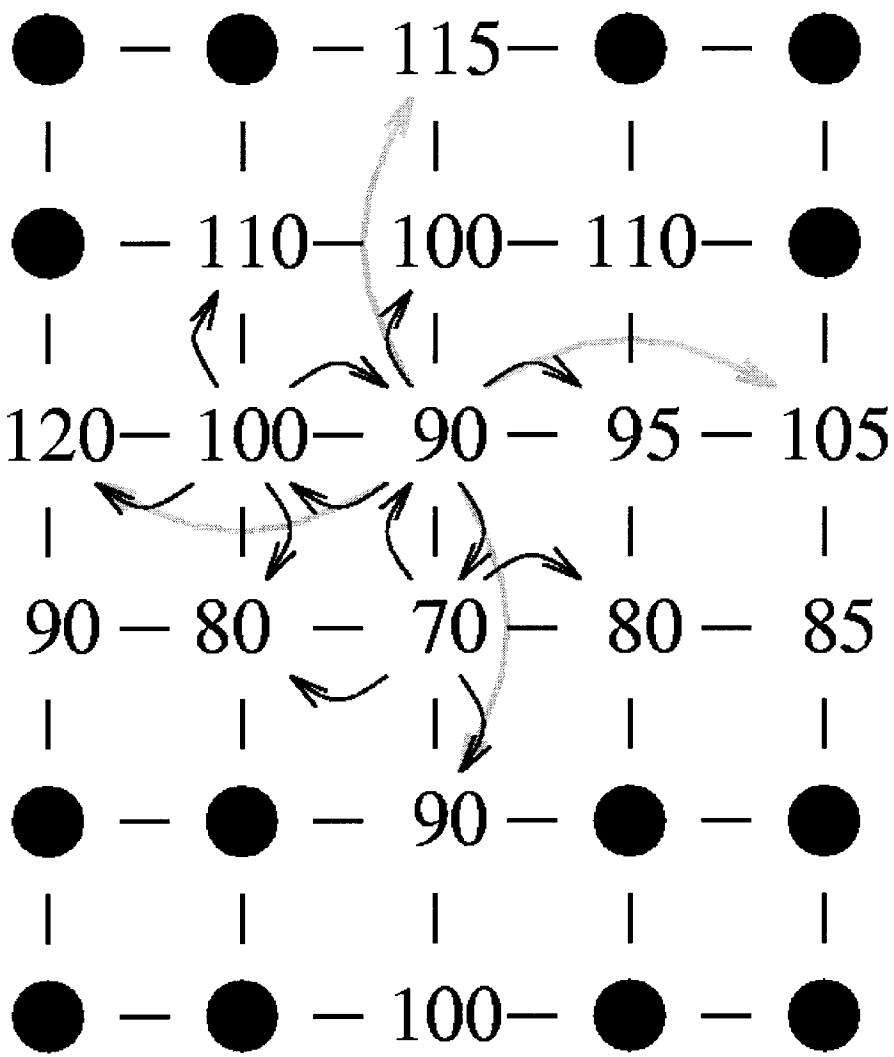
Pattern Search Local Search



Deterministic NESW Search

Step 1

Step 2

Step 3

Step 4

Pattern Search Local Search (cont'd)

Properties:

- More expensive search (especially in high dimensions)
- Slowly adjust the step length parameter
- Can guarantee that $P\left(\liminf_{k\to\infty}\left|\nabla f\left(x_k\right)\right|=0\right)=1$ on c.d.f.'s
- Reasonable stopping rules exist

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Experiments

Six Docking Test Problems

Ligand/Protein Complex	PDB Code	Number of Torsions	Number of Dimensions
β-Trypsin/Benzamidine	3ptb	0	7
Cytochrome P-450cam/Camphor	2cpp	0	7
McPC-603/Phosphocholine	2mcp	4	11
Streptavidin/Biotin	1stp	5	12
HIV-1 protease/XK263	1hvr	10	17
Influenza Hemagglutinin/sialic acid	4hmg	11	18

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Relative Performance

	Hybrid EA		EPSA 0.0		EPSA 0.5		EP	
	Min	Mean	Min	Mean	Min	Mean	Min	Mean
1hvr	-21.42	-21.40	-21.39	-6.33	-21.23	-10.55	-21.09	3.77
1stp	-10.17	-10.15	-8.89	-5.65	-10.06	-6.09	-9.74	-5.17
2cpp	-7.36	-7.36	-7.35	-7.19	-7.36	-7.22	-7.36	-7.26
2mcp	-5.55	-5.52	-5.34	-3.41	-5.32	-3.43	-5.00	-2.64
3ptb	-8.19	-8.16	-8.19	-7.93	-8.19	-8.08	-8.17	-7.09
4hmg	-7.91	-7.85	-7.00	-3.54	-6.97	-4.55	-7.00	-2.66

Note:

- All EAs were terminated after 1.5M function evaluations
- The EPSAs were also terminated with a step-size criterion

Hart, 99; Hart, Rosin, Belew and Morris, 99

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Relative Performance (cont'd)

EA hybrids

- Better mean energy than previous methods
- New best energies for 5 of the 6 test problems
- Lower mean rmsd than previous methods (less than one!)

Local search evaluation

- Pattern search more consistent than Solis-Wets
- Long searches particularly important for pattern search
- Initial step length of local search not a significant factor

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Length of Optimization

Question: Are 1.5M function evaluations really needed?

Stall Statistic: The last iteration where an improvement of more than 0.0001 was found

Results

- 2cpp,3ptb: Terminate within 400,000 function evaluations
- 1hvr,1stp,2mcp,4hmg: Require at least 1M function evaluations

Note: preliminary experiments suggest that a multistart method could be more efficient

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Future Work

Reconsider problem formulation

- Used constrained optimizers
- Periodic boundary constraints
- Work around singularities in problem representation (Quarternions)
- Rescale search w.r.t. torsion angles (scalability of method?)

Exploit local smoothness

- More rapid convergence
- Guarantee convergence to a local optimum

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Acknowledgements

Evolutionary Programming

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