Variable Neighborhood Search with Cost Function Networks to Solve Large Computational Protein Design Problems

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download : http://github.com/toulbar2

Summary

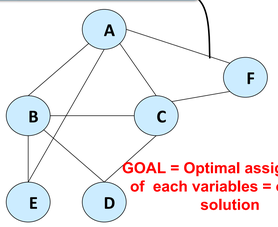
Graphical models factorize a global probability distribution/energy function as the product/sum of local functions. A major inference task, known as MAP in Markov Random Fields and MPE in Bayesian Networks, is to find a global assignment of all the variables with maximum a posteriori probability/minimum energy. A usual distinction on MAP solving methods is complete/incomplete, i.e. the ability to prove optimality or not. Most complete methods rely on tree search, while incomplete methods rely on local search. Among them, we study Variable Neighborhood Search for graphical models. **In this work, first we explored various mutator for improving VNS robustness for the protein design . But the method is generic and can be used very likely in various context of molecular modelling if energy table can be precomputed.**

Cost Function Networks ⇔ Markov Random Field

(Shapiro, Haralick, IEEE PAMI 81)

- *n* variables $X = \{X_1,...,X_n\}$
  - finite domains $X_i \in D_i, |D_i| \le d$
- *e* local/global functions $F = \{f_1,...,f_e\}$
  - scope, function with costs
- Costs ∈ {0,...,+∞} finite or infinite integer

Minimize $\sum_F f_i(X)$ arity **r** — NP-hard



GOAL = Optimal assignement of each variables = optimal solution

Random variables X with discrete domains joint non normalized probability distribution p(X) defined as a product of positive real-valued functions:

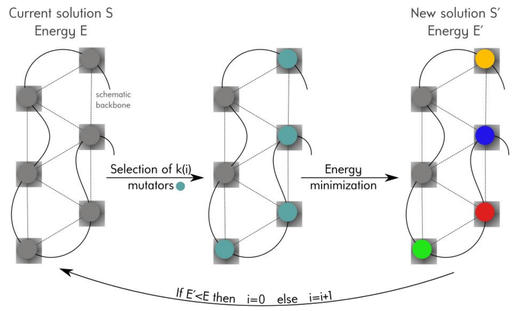
$$\mathbb{P}(x) = \frac{1}{Z}\prod_{f_S \in \mathcal{F}} f_S(x_S)$$

$$Z = \sum_{x \in \Delta}\prod_{f_S \in \mathcal{F}}$$

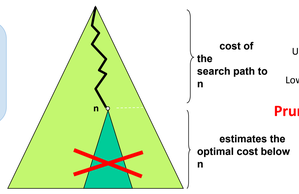
For optimization (**MAP = Maximum a posteriori**), MRF and CFN are essentially equivalent after a **− log transform.**

GMEC = MAP = Global OPTIMAL solution = solution with minimal Energy

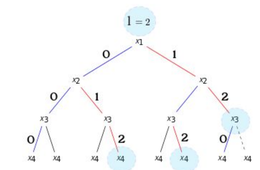
Variable Neighbourhood Search



Branch-and-Bound Search



Limited discrepancy search



LUBY Mutator (growing slow down)

Optimal speedup of Las Vegas algorithms = **Luby serie**

(luby, M.; Sinclair, A.; Zuckerman, D.. Proc. Of TCS. **1993**; pp 128–13)

Luby strategy (supposed to be optimal when not particular knowlege about a given random algorithm)

Let i the current iteration of the algorithme
(i.e search on y current neighborhood)

Let a = ln(i + 1) and b = 2^{a-1};

luby(i) = { b, if i==b ; luby(b-1) }

S_{univ} = (1,1,2,1,1,2,4,1,1,2,1,1,2,4,8,...)

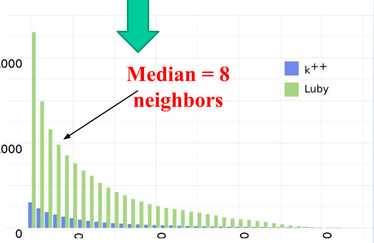
$$\text{If } luby(i) = 2^m, \quad k(i) = k(i-1)+1$$
$$\text{Otherwise,} \quad k(i) = k(i-1)$$

if (m= 0) sequence of increments becomes

{1,1,0,1,1,0,0,1,1,0,1,1,0,0,0,1,...}

with a larger m ,
the mutator number increases even more slowly

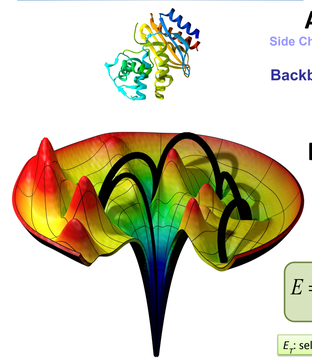
With m=3 □ 2^3 =8

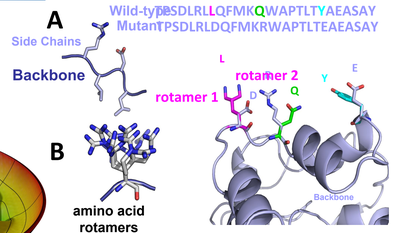


Histograms of the mutator numbers explored during , the FULL design
Using the k++ (blue) and Luby (green) growing sequences

CPD FORMULATION

Mutation landscape



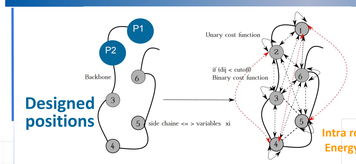


$E_{i,j}$: backbone-rotamer energy

$$E = E_T + \sum_i E(i_r) + \sum_{i,j>i} E(i_r, j_s)$$

E_T: self backbone energy — $E_{i,j}$: rotamer-rotamer energy

COMPUTATIONAL PROTEIN DESIGN



Precomputation and storage of all position

Energy Table

Intra rotamer Energy

P1	A1	V1	V2	V3	S1	S2	S3
A1	0.1	8.2	-4.9	-2.1	5.4	-3.2	9.1

P2	A1	V1	V2	V3	S1	S2	S3
A1	0.3	-0.1	-1.2	-1.1	-0.9	4.1	2.3	0.7
V1	-2.7	-0.3	2.3	4.7	8.1	1.9	8.5	3.2
V2	5.6	-0.2	3.1	5.2	6.3	1.3	4.5	2.9
V3	8.2	-0.6	2.9	6.4	5.8	0.9	3.2	4.7
S1	-1.9	1.7	4.3	8.2	4.4	-0.9	-2.6	8.6
S2	7.9	2.1	5.7	6.4	8.1	-0.8	-4.9	7.5
S3	-0.4	3.7	6.4	2.9	7.7	-0.4	-5.5	-0.1

Pairwise interaction

COST Function Network

Allowed rotamers

P1	P2
A1	A1
V1	V1
V2	V2
V3	V3
S1	S1
S2	S2
S3	S3

Designed positions

Benchmarking

Problem set □ (mignon & al jcc 2015)

	PDB	# MUT
SH3	1ABO	48
SH3	1CKA	49
PDZ	1R6J	72
PDZ	1G9O	76
PDZ	2BYG	82
SH2	1BM2	88
SH2	1M61	88
SH2	1A81	92
SH2	1O4C	96

- ***Search space size*** $(248^{\#mut})$:
  - **N20** : □ [**2*10^{61}** ,... **9*10^{123}**]
  - **N30** : □ [**1*10^{82}** ,... **2*10^{137}**]
  - **FULL**:□ [**8*10^{114}** ,.., **7*10^{229}**]

99 problems

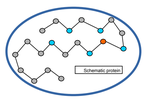
- **AMBER Force field**
- **CASA implicit solvent Model**
- **Tuffery rotamer library (248 rotamers)**

Non mutated positions remains flexible
(except GLY , PRO position)

	Full		N30		N20	
VNS	+	0	+	0	+	0
Luby/d-prob	98%	0%	65%	31%	31%	68%
Luby/random	99%	0%	63%	31%	31%	69%
Luby/nearest	94%	0%	60%	31%	28%	66%
k^{++}/d-prob	80%	0%	56%	27%	27%	66%
k^{++}/nearest	80%	0%	54%	21%	21%	62%

Table 2: Frequency of energy improvement with VNS: each row represents a VNS heuristic and reports the percentage of runs in which the energy improved (+) or was unchanged (0) compared to SDH+MC+REMC.

d prob selection



$$p_{i,j} = \frac{1}{d_{i,j} * \sum_{k=1,k\neq i}^{n} \frac{1}{d_{i,k}}}, i \neq$$

$$p_{i,i} = 0$$

Table 3: Averages $\langle\overline{\Delta E}\rangle_C$ of the mean energy improvement, compared to MC+REMC+SDH, over the test category C, and average $\langle\sigma(\Delta E)\rangle_C$ of its standard deviation.

	Full		N30		N20	
VNS	$\langle\overline{\Delta E}\rangle_C$	$\langle\sigma(\Delta E)\rangle_C$	$\langle\overline{\Delta E}\rangle_C$	$\langle\sigma(\Delta E)\rangle_C$	$\langle\overline{\Delta E}\rangle_C$	$\langle\sigma(\Delta E)\rangle_C$
Luby/d-prob	3.17	1.03	0.77	0.35	0.15	0.01
Luby/random	2.95	1.06	0.76	0.32	0.15	0.01
Luby/nearest	2.78	1.36	0.69	0.33	0.13	0.07
k^{++}/d-prob	0.77	2.40	0.59	0.47	0.13	0.11
k^{++}/nearest	1.03	2.21	0.43	0.59	0.10	0.20
k^{++}/random	0.55	2.47	0.58	0.48	0.14	0.05

FULL DESIGN Energy Gap Box plot

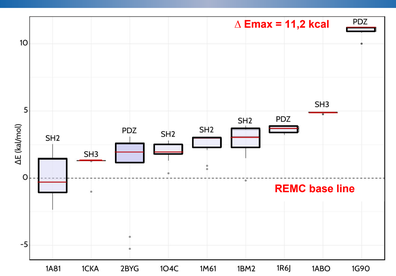


Figure 5: Box plot of ΔE values with VNS Luby/d-prob from ten runs on each Full test.

Optimal solution recovery rate

heuristic	Full (90)	%	N30 (450)	%	N20 (450)	%
k^{++}/d-prob	10	0.111	320	0.711	425	0.944
k^{++}/k-nearest	10	0.111	258	0.573	405	0.90
k^{++}/random	15	0.167	319	0.709	440	0.978
Luby/d-prob	40	0.444	407	0.904	447	0.993
Luby/k-nearest	33	0.367	356	0.791	438	0.973
Luby/random	37	0.411	401	0.891	449	0.998

For each Heuristic (line) and type of instance (columns) the table give the number and the recovery rate of the optimal Solution over the 90 , 450 runs respectively for the FULL , N20 and N30 set of problems.

COMPUTATION TIME LESS THAN 2H on 1CPU
Parallel release available

IMPORTANT MESSAGES

- **VNS converge faster than the other global search methods .**
- **Luby + probabilistic selection based on variable distance improves VNS robustness**
- **VNS allows to explore large search space**
- **VNS + cost function is compliant with n-body energetic terms .**
- **polarisable force field or fragment based method with QM description could be used for improving the model.**

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