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


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**download : http://github.com/toulbar2**

## Summary

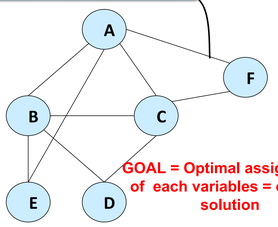

Graphical models factorize a global probability distribution/energy function as the product/sum of local functions. A major inference task, known as MAP in Markov Random Fields and MPE in Bayesian Networks, is to find a global assignment of all the variables with maximum a posteriori probability/minimum 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:

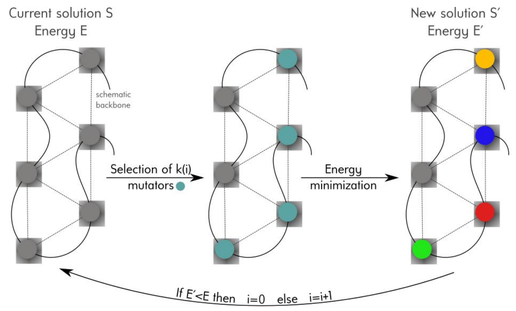
$$\mathbb{P}(x) = \frac{1}{Z}\prod_{f_S \in \mathcal{F}} f_S(x_S)$$

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

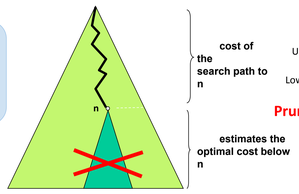
For optimization (**MAP = Maximum a posteriori**), MRF and CFN are essentially equivalent after a **− log transform.**

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

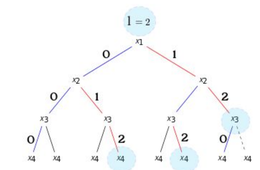
## Variable Neighbourhood Search




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,...)

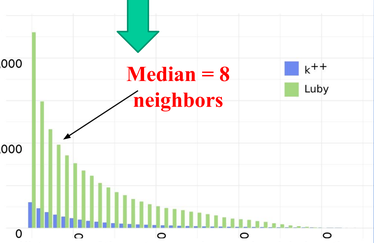
$$\text{If } luby(i) = 2^m, \quad k(i) = k(i-1)+1$$
$$\text{Otherwise,} \quad k(i) = k(i-1)$$

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

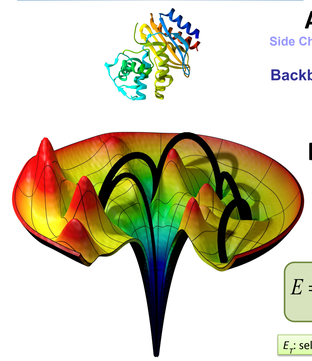
With m=3 □ $2^3$ =8

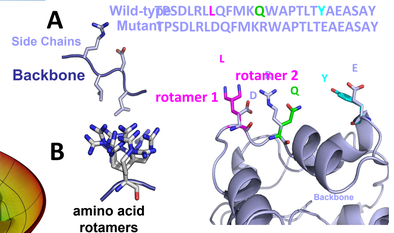



**Histograms of the mutator numbers explored during , the FULL design**
**Using the k++ (blue ) and Luby (green) growing sequences**

## CPD FORMULATION

### Mutation landscape



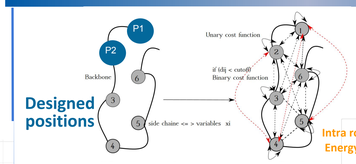



$E_{i,j}$: backbone-rotamer energy

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

$E_T$: 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**

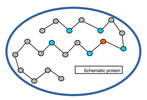
- **AMBER Force field**
- **CASA implicit solvent Model**
- **Tuffery rotamer library ( 248 rotamers )**

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

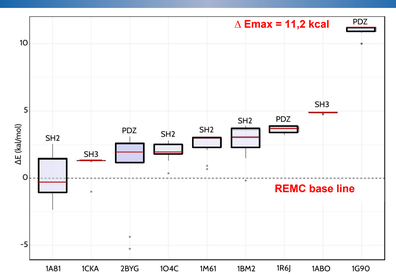



Figure 5: Box plot of $\Delta E$ values with VNS Luby/d-prob from ten runs on each Full test.

## 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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