Computational Protein Design as an Optimization Problem

T. Schiex

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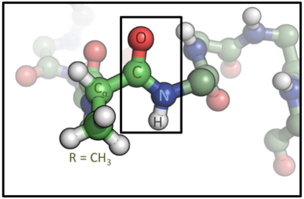
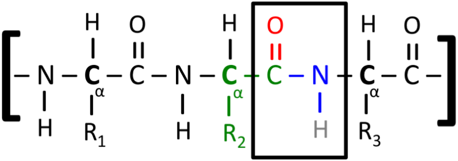
What is a protein ?

(Kudos to wikipedia)

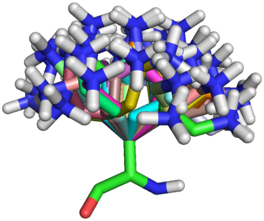
Amino acids, proteins

- Proteins are linear chains of amino-acids (20 natural AAs).
- All AAs share a common “core” and have a variable side-chain.





Side-chains are flexible (ARG)



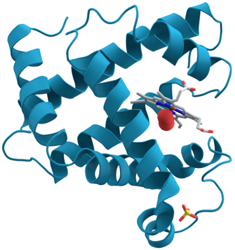
Why ?

- Proteins have various functions in the cell: catalysis, signaling, recognition, regulation...
- Efficient, biodegradable, 10^6 to 10^{20} speedups
- Some reactions / ligands miss enzymes / partners.
- Medecine, cosmetics, food, bio-energies...
- Nano-technologies (shape more than function).

Protein function linked to its 3D shape through its amino acid composition.

Protein design's aim

Identify sequences that have a suitable function (shape).



Protein Design

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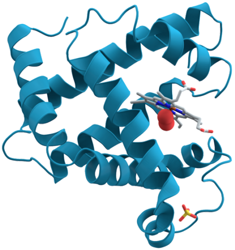
Issue

There are 20^n proteins of length n.
Impossible to synthesize and test all of them.



The CPD problem - stability variant

Preparation

- A backbone is chosen/built from a known protein/structure (or *de novo*).
- Positions are set as mutable, flexible or rigid
- The aim is to find an AA sequence that folds, stably, in the backbone.

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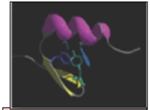
Issues

- CPD is a sort of inverse of folding.
- But folding is far from being a solved problem

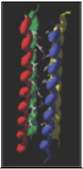
Successes of Protein Design

INRA SCIENCE & IMPACT

1997



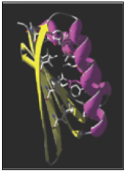
- Zinc-finger
  Dahiyat et al
  (Science 1997)

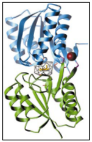


- Coiled-coils
  Harbury et al
  (Science 1998)

2003

- A novel topology (Top7) *Khulman et al (Science 2003)*

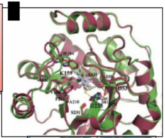




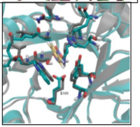
- Sensors & receptors toward non native ligands *Hellinga et al (Nature, 2003)*

2008

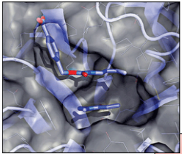
- New catalyst for a multi-step-reaction (retro-aldolase) *Jiang et al (Science 2008)*



- De novo design of new functional enzyme (Kemp elimination) *Rothlisberger et al (Nature 2008)*



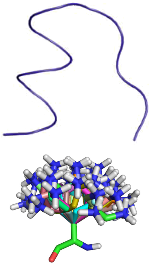
2010



Design of Biocatalyst for a stereoselective & bimolecular reaction (Diels-alder)
Siegel et al (Science 2010)

Rigid backbone variant

1. Assume a rigid protein backbone.
2. Choose 1 AA among possible ones at each mutable position.
3. Spatial conformation discretized in rotamers.
4. Statistically frequent orientations.
5. Several 100's rotamers per position.



The (basic) CPD problem: search space

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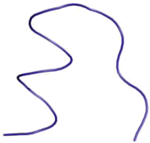

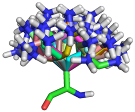

Search Space

1. Fully discrete description, defined by a choice of rotamer (AA $\times$ conformation) for each position.
2. Search space can be $\approx 250^n$

Stable = minimum energy (GMEC, NP-hard [PW02])

Energy: interactions between atoms.

- Electrostatic, van der Waals (Amber)
- Dihedral torsion angles, Implicit Solvation (EEF1)
- "Statistical terms" (Talaris)
- Cutoff functions

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Pairwise decomposable energy

- backbone/backbone (constant)
- backbone/rotamer (depends on rotamer)
- rotamer/rotamer (depends on pairs of rotamers)

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$$E(c) = E_{\varnothing} + \sum_{i=1}^{n} E(i_r) + \sum_{i<j} E(i_r, j_s)$$

Dedicated CPD Methods

Dominance / Sustitutability / Dead End Elimination [Des+92]

$$E(i_a) + \sum_{j \neq i}^{n} \min_{c} E(i_a, j_c) > E(i_b) + \sum_{j \neq i}^{n} E \max_{b} E(i_b, j_c)$$

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Strenghtened by [Gol94]

$$E(i_a) - E(i_b) + \sum_{j \neq i}^{n} \min_c \left[E(i_a, j_c) - E(i_b, j_c)\right] > 0$$

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Many further enhancements (splitting, pairs...). Polynomial time pre-processing.

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"(Soft) substitutability" [Coo97; LRD12]
Dominating 1-clause rule in MaxSAT [NR00].

polytime DEE, GMEC NP-hard

- DEE cannot reduce all domains to singletons
- Followed by A^* best-first search using the following lower bound (admissible heuristics) [GLD08]:

$$\underbrace{\sum_{i=1}^{d} E(i_r) + \sum_{j=i+1}^{d} E(i_r, j_s)}_{\text{Assigned}} + \sum_{j=d+1}^{n} \Big[\underbrace{\min_s (E(j_s) + \sum_{i=1}^{d} E(i_r, j_s)}_{\text{Forward checking}} + \underbrace{\sum_{k=j+1}^{n} \min_u E(j_s, k_u))}_{\text{DAC counts}} \Big]$$

DEE + A^*

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Lower bound

- Same as a lower bound introduced in AI (WCSP) in 1994 [Wal95].
- Obsoleted by local consistencies.

T. Schiex. "Arc consistency for soft constraints". In: *Principles and Practice of Constraint Programming - CP 2000*. Vol. 1894. LNCS. Singapore, Sept. 2000, pp. 411–424

Solving the Fixed Backbone CPD problem

Our targets [All+14]

- Identify a most efficient model/solving technique for the rigid backbone/rotamer based/pairwise energy CPD problem.
- Do one of the first large spectrum comparison of NP-complete optimization techniques (AI: CFN, CP, SAT, MRF and OR: ILP, QP, QPBO) on one well defined, important optimization problem.
- Learn from it.

Cost Function Networks (aka WCSP or MRF)

Cost Function Network (X, D, E)

1. $X = (1, \ldots, n)$, n variables (indices).
2. $D = (D^1, \ldots, D^n)$, n domains
3. C set of non negative integer cost functions c_S.
4. $c_S : D^S = \prod_{D^i, i \in S} \to \{0, \ldots, k\}$

$$\min_{t \in D^X} E(t) = \sum_{c_S \in C} c_S(t[S])$$

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- k is an intolerable cost. May be finite or not.
- Cost functions defined as tables, analytic formulas or predicates (global cost functions).
- Bounded addition, subtraction. $c_\varnothing$ is a lower bound.

Solving techniques (CFN solver: toulbar2)

Inspired by Constraint Satisfaction

1. Backtrack becomes Branch and Bound (Depth First)
2. Local consistency reformulates the problem in a more explicit equivalent problem (Equivalence Preserving Transformation).
3. Provides non naive $c_\varnothing$ (lb), incremental.

Pause pub

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mulcyber.toulouse.inra.fr/projects/toulbar2

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13. Parallel VNS search [Oua+14]

Past successes...

1. First/second in approximate graphical model MRF/MAP challenges (2010, 2012, 2014).
2. Bioinformatics: pedigree debugging [SGS08], Haplotyping (QTLMap), structured RNA gene finding [ZGS08], Computational Protein Design [Tra+13] (now in OSPREY)
3. RLFAP: closed all CELAR min-interference RLFAP instances fap.zib.de/problems/CALMA
4. Inductive Logic Programming [AR07], Natural Langage Processing (in hltdi-l3), Multi-agent and cost-based planning [KZ10; CRR11], Model Abstraction [SFN11], diagnostic [MJS11b], Music processing and Markov Logic [PT12; PT13], Data mining [MLC13], Partially observable Markov Decision Processes [Dib+13], Probabilistic counting [Erm+13] and inference [MJS11a], ...

Arc EPT

- A cost function c_S, here c_{ij}.
- EPT $\texttt{Project}$ $(\{ij\},\{i\},a,\alpha)$ shifts cost α between $c_i(i_a)$ and the cost function c_{ij}.
- projection $(\alpha \geq 0)$, extension $(\alpha < 0)$.

Precondition: $-c_i(i_a) \leq \alpha \leq \min_{t' \in D^{ij}, t'[i]=i_a} c_{ij}(t')$;

Procedure $\texttt{Project}(\{i,j\},\{i\},a,\alpha)$

  $c_i(i_a) \leftarrow c_i(i_a) \oplus \alpha$;

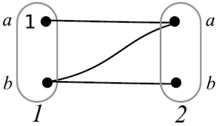
  foreach *($t' \in D^{ij}$ such that $t'[i] = i_a$)* **do**

    $c_{ij}(t') \leftarrow c_{ij}(t') \ominus \alpha$;

  end

$\oplus$ is $m-$bounded addition. Pseudo-inverse $\ominus$ (you can take whatever you want from k).

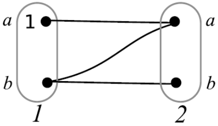
Example

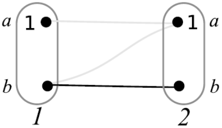


Example

$\texttt{Project}(\{1,2\},\{2\},a,1)$

$\rightarrow$





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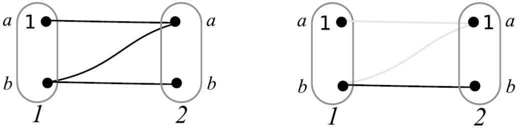

$\leftarrow$

$\texttt{Project}(\{1,2\},\{2\},a,-1)$

Example

$\texttt{Project}(\{1,2\},\{1\},b,1)$

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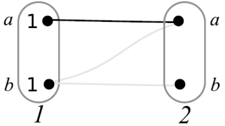

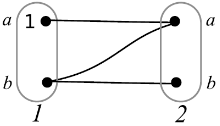

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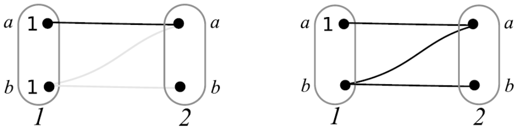

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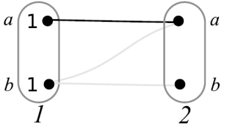

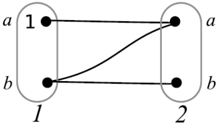

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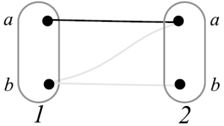

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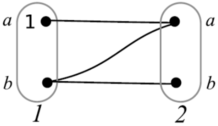

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$c_{\varnothing} = 1$

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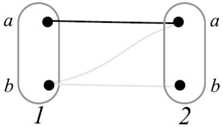
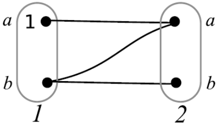
$\leftarrow$





$\Downarrow \qquad \texttt{Project}\ (\{1\},\varnothing,[],1)$

$c_\varnothing = 1$

Non confluent (multi fix-point). Not all as good in term of lb.
With integer costs, finding the best fix-point is NP-hard [CS04].

Local consistencies

Polynomial time filtering

- Node consistency: at the variable level. Moves cost to $c_\varnothing$, upper bounding ($c_i(a) + c_\varnothing = k$).
- Arc consistency, directional AC, Full directional AC, EDAC, VAC, OSAC (Optimal Soft Arc Consistency).
- VAC and OSAC solve submodular subproblems.

T. Schiex. "Arc consistency for soft constraints". In: *Principles and Practice of Constraint Programming - CP 2000*. Vol. 1894. LNCS. Singapore, Sept. 2000, pp. 411–424

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Optimal Soft Arc Consistency

OSAC

An LP that identifies a set of EPTs (rational costs) that maximizes the lower bound. After propagation of hard (k) costs using Arc Consistency.

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maximize $\sum_i u_i$ where

- u_i: amount of cost projected from c_i to $c_\varnothing$
- $p^S_{i_a}$: amount of cost projected from c_S to i_a

$$\forall i \in X, \forall a \in d_i, \quad c_i(a) - u_i + \sum_{(c_S \in C), (i \in S)} p^S_{i,a} \geq 0$$

$$\forall c_S \in C, |S| > 1, \forall t \in \ell(S) \quad c_S(t) - \sum_{i \in S} p^S_{i, t[\{i\}]} \geq 0$$

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ILP models

ILP for WCSP/CPD/MRF

1. Koster's ILP model for WCSP [KHK99]. Used for CPD in [KCS05]. Is the "local polytope" of MRF [Wer07]
2. One 0/1 variable per value and per pair (relaxable for pairs).

$$
\begin{array}{rll}
\text{min} & \sum_{i,r} E(i_r).d_{i,r} + \sum_{i,r,j,s} E(i_r, j_s).p_{i,r,j,s} & \\
\text{s.t.} & \sum_r d_{i,r} = 1 & (\forall i) \\
 & \sum_s p_{i,r,j,s} = d_{i,r} & (\forall i, r, j)
\end{array}
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Relaxation = dual of OSAC LP

1. Arc consistencies: limited Block Coordinate Descent algorithms for the dual of this specific LP.

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2. Not so specific: any LP can be reduced to it in linear time [PW15].

As quadratic 0/1 programs

QP - Cplex

$$\begin{aligned}
\min \sum_{i,r} E(i_r).d_{ir} + \sum_{\substack{i,r,j,s \\ j>i}} E(i_r, j_s).d_{ir}.d_{js} \\
\text{s.t.} \quad \sum_{r} d_{ir} = 1 \quad (\forall i) \\
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QPBO - MaxCut (BiqMac/SDP bound): Big M

$$\min \sum_{i,r} (E(i_r) - N).d_{ir} + \sum_{\substack{i,r,j,s \\ j>i}} (E(i_r, j_s) - N).d_{ir}.d_{js} + \sum_{\substack{i,r,s \\ s>r}} M.d_{ir}.d_{is}$$

MRF methods

daoopt [OD12]

1. won the UAI (PIC) approximate inference challenge in 2012.
2. lower bound based on "Mini-buckets" (dynamic programming with bounded width).
3. tree-decomposition used in AND/OR search

MPLP [Son+12]

1. Dual relaxed solution (lower bound) provided by BCD optimization.
2. Strengthens the Dual by including empty ternary cost functions.
3. Heuristics for Primal.
4. Iterative, no search.

Partial Weighted maxSAT

PW MaxSAT

- Boolean variables, litteral: variable or its negation
- Weighted clauses: disjunction of litterals.
- criteria: sum of weight of violated clauses.
- B&B - Core solvers: MiniMaxSat [HLO08],akMaxSat [Kue10] - bincd [HMM11],wpm1/2 [ABL09; ABL10],MaxHS [DB13]

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Direct encoding

- d_{i_a}: use i_a
- $\forall i_r, i_s, i_r \neq i_s, (\neg d_{i_r} \vee \neg d_{i_s})$ (AMO)
- $\forall i, (\bigvee_r d_{i_r})$ (ALO)
- $(\neg d_{i_r}, E(i_r)$ and $(\neg d_{i_r} \vee \neg d_{j_s}, E(i_r, j_s))$

Property [Bac07]

In CSP, Unit Propagation on this encoding enforces AC on the CSP. Close to the ILP model.

Tuple encoding

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Direct encoding

- d_{i_a} + AMO + ALO.
- $p_{i_r j_s}$: pair i_a, j_s is used.
- $\forall i_r, j_s : (d_{i_r} \vee \neg p_{i_r j_s})$ and $(d_{j_s} \vee \neg p_{i_r j_s})$.
- $\forall i_r, j(\neg d_{i_r} \vee \bigvee_s p_{i_r j_s})$
- idem for $E(i_r)$, $\forall i_r, j_s(\neg p_{i_r j_s}, E(i_r, j_s))$

Pure CP - Soft as Hard model [PRB00]

General idea

1. add one "cost" variable to every cost function to make a ternary constraint.
2. use a global "Sum" constraint on these new cost variables.

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Can be expressed in MiniZinc [Mar+08]

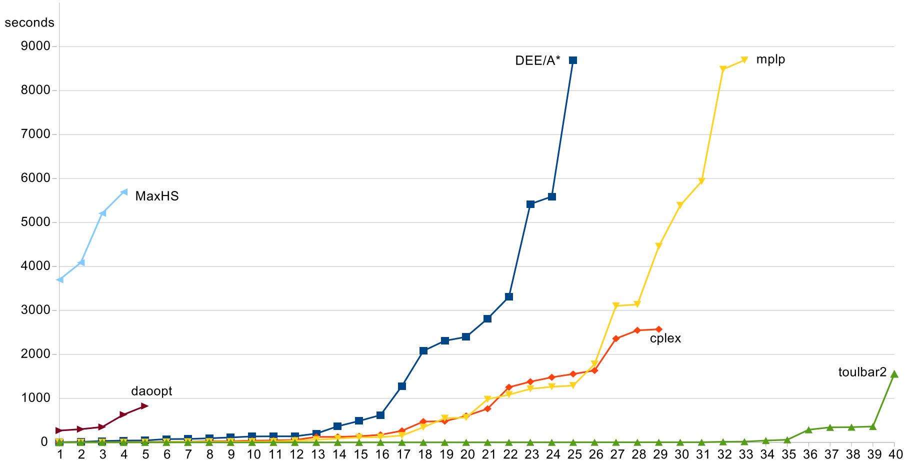
1. GeCode (`http://www.gecode.org/`),
2. Mistral (Python `numberjack` interface, `http://numberjack.ucc.ie/`),
3. Opturion/CPX `http://www.opturion.com/cpx.html`

A realistic benchmark: 35+12 designs tested

The designs

1. Extracted from the litterature,
2. Good resolution of the PDB structures,
3. Structure preparation,
4. Domains assigned based on accessibility,
5. Amber + EEF1 + No cutoff (almost complete graphs)
6. Variable search space size, from 10^{26} to 10^{249}
7. Largest solved has size 10^{98}

Results - 9000 seconds



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4. **MaxSAT, tuple**: b&b,strong lower bound (should be similar to VAC for core based solvers). Still weaker than tb2 and very slow (2 nodes before timeout at best for akmaxsat). No incumbent. Core based better (maxHS, good lb).

Analysis

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… to Successes

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A Lesson for (AI) Optimization

The lower bounding/search efforts compromise is not, AFAiK, understood, nor exploited. But may be crucial.

Enumerating all suboptimal solutions on 35 designs

All within 2 kcal/mol of GMEC, 100 h, tb2 and DEE/A*

- Enumeration feasible for 1 design only (DEE/A*)
- Enumeration finished for all solved designs (CFN).
- More than 1 billion sequence-conformations for one design.

May be useful for partition function estimation [Vir+15].
Additional progresses since.

Final note and Acknowledgments

This is all for a rigid backbone. Modern CPD increasingly uses "flexible" representations (eg. with a backbone ensemble).

Thanks to...

- Bruce Donald and Kyle Roberts (Duke Univ.) for the open source software Osprey and helping us with it.
- Hugo Bazille (ENS/INRIA): for testing ASP on the CP2012 instances.

Questions ?

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