Scalable Coupling of Deep Learning with Logical Reasoning: from Sudoku to new functional molecules

Thomas Schiex

Joint work with S. Barbe, M. Defresne (PhD student)

Human reasoning and scientific discovery

Inductive and deductive reasoning

- From observations (solutions) we construct a theory ($F = m\gamma$)
- We then use the theory to make predictions and design objects
- Until the theory is proven to be incorrect

Sudoku grid with solution

Protein structure with its sequence

The theory is written as binary Cost Function Network

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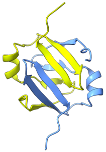
1	2	6	4	3	7	9	5	8
8	9	5	6	2	1	4	7	3
3	7	4	9	8	5	1	2	6
4	5	7	1	9	3	8	6	2
9	8	3	2	4	6	5	1	7
6	1	2	5	7	8	3	9	4
2	6	9	3	1	4	7	8	5
5	4	8	7	6	9	2	3	1
7	3	1	8	5	2	6	4	9

Sudoku grid with solution



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Cost Function Networks

Binary Cost Function Network

- A set X of variables — n variables
- Variable x_i has domain D_i — max. size d
- a set of cost functions — $c_{ij} : D_i \times D_j \to \mathbb{R}^+ \cup \{\infty\}$

Costs and probabilities

- The cost $C(t)$ of an assignment t is the sum of all cost functions on t
- Toulbar2 solves the Weighted Constraint Satisfaction Problem — $\min_t C(t)$
- A CFN defines a probability distribution: $P(t) \propto \exp(-C(t))$ — Markov Random Fields
- Normalizing constant is #P-hard to compute

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Injecting ML / intuition[1]

	2							
			6					3
	7	4		8				
					3			2
	8			4			1	
6			5					
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Φ

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$\Phi \longrightarrow$ Neural net

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							4	

$\Phi \longrightarrow$ Neural net $\longrightarrow$ CFN

$P(X|\Phi)$

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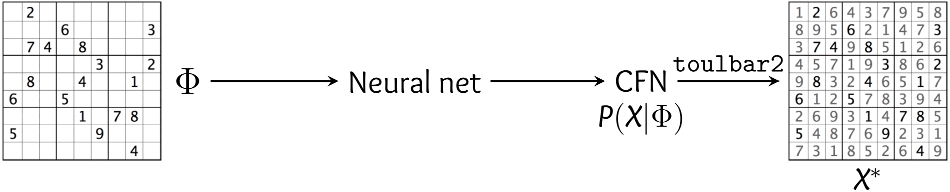

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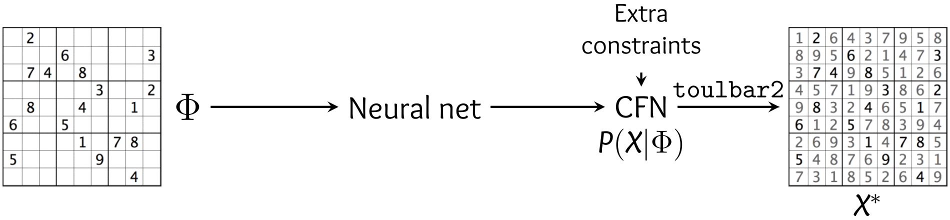

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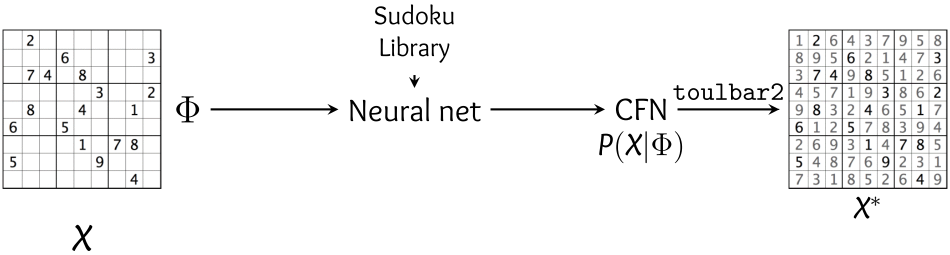

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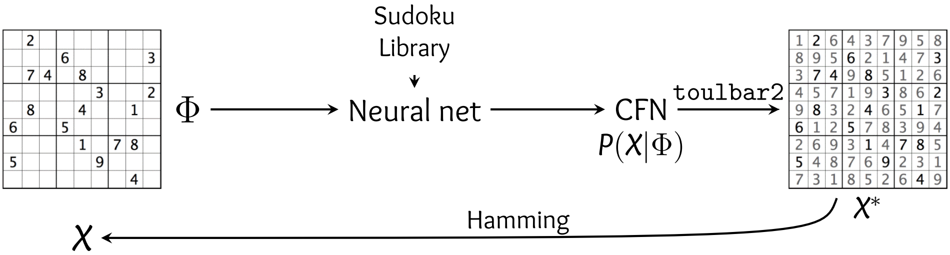

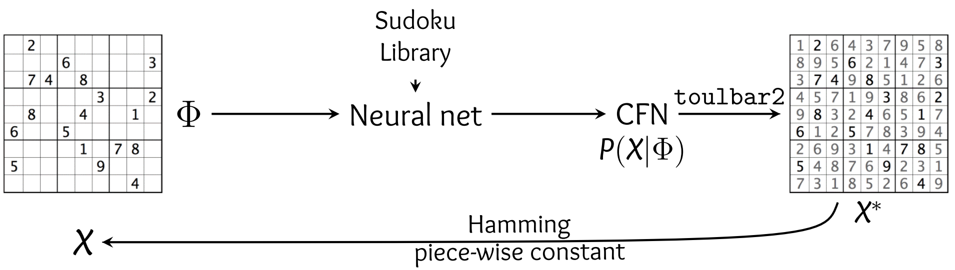

Issues

- Gradients either zero or undefined
- Requires to repeatedly solve random NP-hard instances

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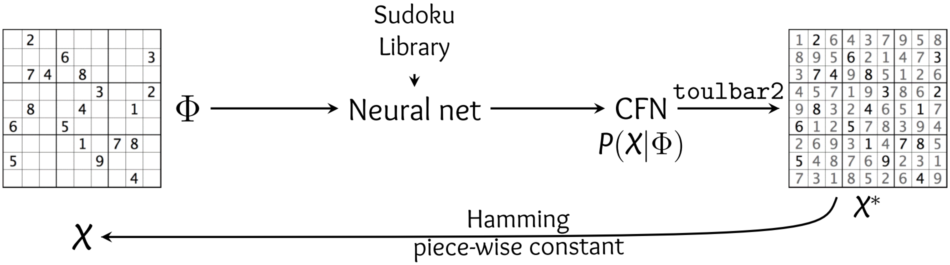

Our solution

IJCAI'2023

- Introduced a dedicated loss: the E-Pseudo Log Likelihood (Defresne et al. 2023)
- Kicked the solver out of the training loop (scalable training)

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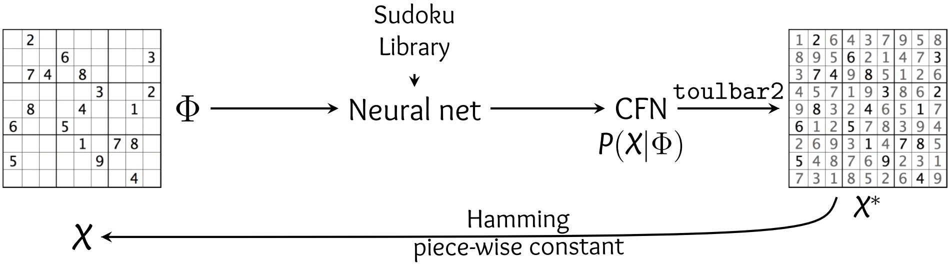


Approach	Architecture	Acc.	Grids	Training set
RRN NeurIPS18	GNN	96.6%	Hard	180,000
SATNet ICML19	Relaxation	99.8%	Easy	9,000
Hybrid IJCAI23	E-PLL	**100%**	Hard	**200**
Symbolic IJCAI23	MaxSAT	**100%**	Hard	**200**

Pseudo-Loglikelihood with holes

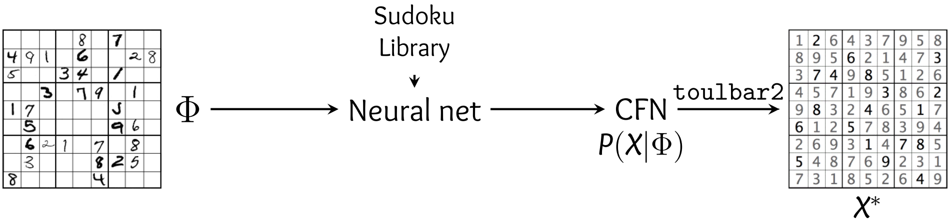
PLL from solution s and current predicted CFN

- $-\log(P(s))$ would be a nice loss — intractable
- For each variable x_i, we mask x_i in the solution
- Compute $P(x_i|X_{-i})$ — easy
- Use $-\sum_{x_i} \log(P(x_i|X_{-i}))$ as the pseudo-loss
- Excellent asymptotic properties — statistically consistent
- Does not work in practice (high costs) — Montanari and Pereira 2009

The Emmental Pseudo-loglikelihood

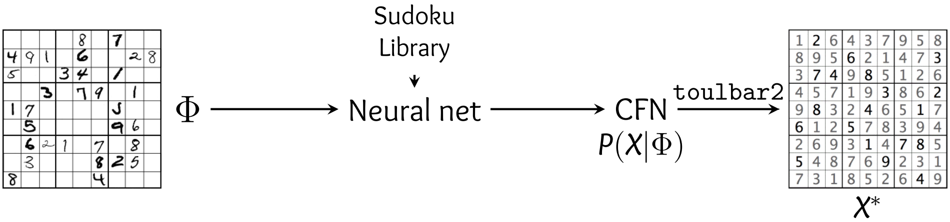
- When we compute $P(x_i|X_{-i})$
- We ignore a random fraction of the neighbors
- Strongly accelerates stochastic gradient optimization

Learning to play Visual Sudoku



Simultaneously learns to recognize digits and to play the Sudoku

SATNet	Theoretical (no corrections)	Hybrid
63.2 %	74.2%	$94.1 \pm 0.8\%$



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Reading numbers without cheating (grounding)

Grounding issue: a nasty form of data leakage (Chang et al. 2020)

- The training set contains images and associated decoded digits (hints).
- Corrected in (Topan et al. 2021) using a complex architecture (GAN+clustering+Distillation)

Easily solvable in our architecture

- In the training set, we replace hints with a new "missing value" (0)
- We connect LeNet output to the CFN generator input
- LeNet learns a permutation of the digits
- The CFN-generator corrects this permutation in its output
- Much longer training (few hours)

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Learning to play Many-Solutions Sudokus

Sudokus have only one solution (single target for DL)

- Existing DL architectures fail on many-solutions Sudokus (Nandwani et al. 2021)
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- Training set with 5 solutions per instance
- Ability to generate additional solutions

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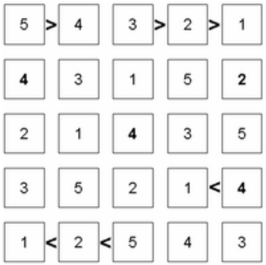
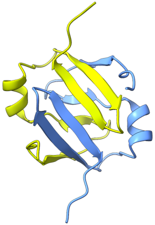
Learning to play Futoshiki

Sudoku is easy, only one type of constraints

- Our architecture directly learns how to play Futoshiki
- Includes both difference and inequality constraints
- Perfect solving, expected constraints learned



Learning to design proteins: Effie



X

PDB
170,000 (Φ, X)
↓
Design constraints
↓

$$\Phi \longrightarrow \text{Neural net} \longrightarrow \underset{P(X|\Phi)}{\text{CFN}} \xrightarrow{\texttt{toulbar2}} X^*$$

Optimizing a complete protein sequence

Full redesign of large proteins in the test set

- Guaranteed `toulbar2` solution expensive
- Using LR-BCD instead (Durante et al. 2022)

Outperforms all-atoms XIXth-century physics

- Metric: **Native Sequence Recovery** rate (NSR)

Approach	Rosetta	Effie
NSR	17.9%	32.8%

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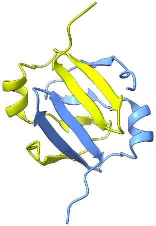
Effie vs. ProteinMPNN (Dauparas et al. 2022)

GPT-style  $\Phi \longrightarrow$ Autoregressive NN $\longrightarrow X_1, X_2, \ldots$

$$\text{PDB} \downarrow$$

$$P(X_i | X_{i-1}, \ldots, X_1, \Phi)$$

Pros and cons

- Heuristic score instead of NP-hard solving
- Capacity to capture higher-order interactions
- Limited control for design constraints

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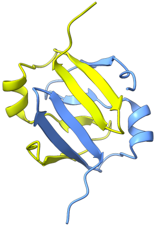
GPT-style 

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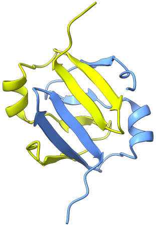

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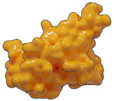
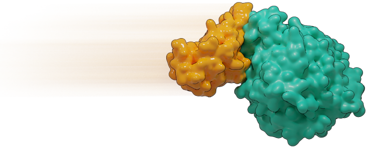
Predicting SARS-CoV2 variants

(Colom et al. 2024)

RBD





ACE2

Enumerate CoViD variants with a bounded number of mutations

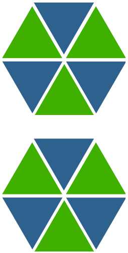
- Uses only the initial March 2020 RBD-ACE2 structure + Effie/toulbar2
- Relies on (Montalbano et al. 2022) global constraint to bound mutations
- Predicts all the first SARS-CoV2 VoCs ($\alpha, \beta, \gamma, \delta, \kappa, \iota, \lambda$ and μ)
- In a few seconds, on one CPU-thread.

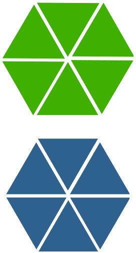
Not achievable by pure autoregressive models (ProteinMPNN)

Design of an enzyme organizing platform

Design of an heteromeric hexamer

- Design and that self-assemble as but not as or
- Physics+logic: requires bi-level optimization (NP^{NP}-complete) (Vucinic et al. 2020)
- Compare Effie+tb2 (NP-complete) with ProteinMPNN, bi-criteria (Buchet et al. 2024)





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How often is better than ?

Scoring →	Effie	PMPNN
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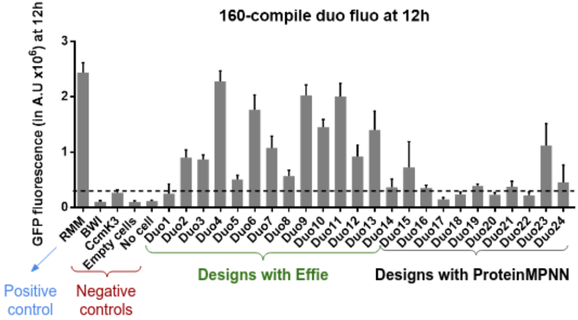

Conclusions

A Neural Net, a CFN and a WCSP solver in a hybrid autoencoder

- A hybrid generic Generative AI that benefits from each component
- Neural Network: ideal to extract a representation of $P(X|\Phi)$ from raw inputs
- Represented as a CFN in a fully explorable and controllable latent layer
- Using decoding by discrete reasoning (toulbar2)
- All this with scalable training

Questions:

What is missing in this architecture to make you happy?

When is Predict-and-optimize useful?

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Acknowledgments

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