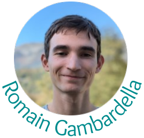
Efficient Neuro-symbolic Learning of Constraints and Criteria from Sudoku to new functional molecules

(Defresne, Gambardella, et al. 2026)

Thomas Schiex



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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 a pairwise Graphical Model (a Cost Function Network)

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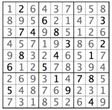

1	**2**	6	4	3	7	9	5	8
8	9	5	**6**	2	1	4	7	**3**
3	**7**	**4**	9	**8**	5	1	2	6
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9	**8**	3	2	**4**	6	5	**1**	7
6	1	2	**5**	7	8	3	9	4
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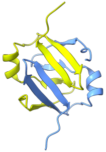
Sudoku grid with solution



Protein structure with its sequence

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Additive discrete graphical model

CFN/WCSP

Reminder

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

Variables and parameters/costs

- The cost $C(t)$ of an assignment t is the sum of all cost functions on t
- The cost is linear in the parameters (costs in CF tables)
- It defines a probability distribution: $P(t) \propto \exp(-C(t))$ Markov Random Fields

Additive discrete graphical model

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Structured output prediction (SOP) with a CFN model

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

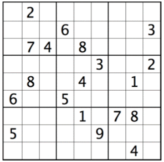
ω

Structured output prediction (SOP) with a CFN model

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

$\omega \longrightarrow$ Neural net

Structured output prediction (SOP) with a CFN model



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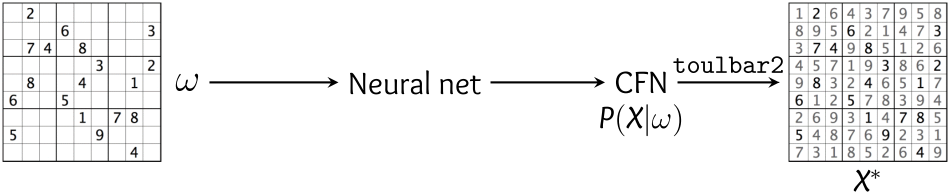
							4	

ω ⟶ Neural net ⟶ CFN

$P(X|\omega)$

Structured output prediction (SOP) with a CFN model



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$$\omega \longrightarrow \text{Neural net} \longrightarrow \text{CFN} \xrightarrow{\texttt{toulbar2}}$$

$P(X|\omega)$

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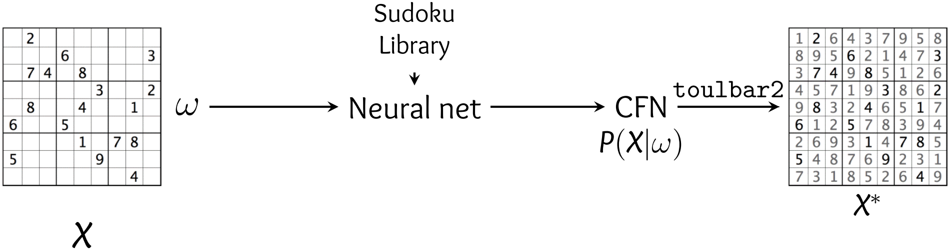

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							4	

X

$\omega \longrightarrow$ Neural net $\longrightarrow$ CFN $\xrightarrow{\texttt{toulbar2}}$

Sudoku Library → Neural net

CFN $P(X|\omega)$

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
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6	1	2	5	7	8	3	9	4
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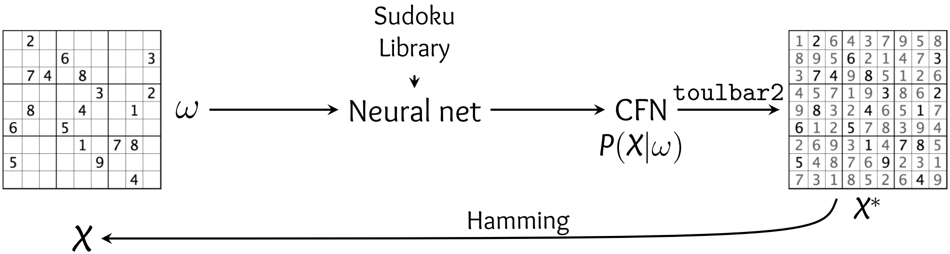

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ω

Sudoku
Library

Neural net

CFN
$P(X|\omega)$

`toulbar2`

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2	6	9	3	1	4	7	8	5
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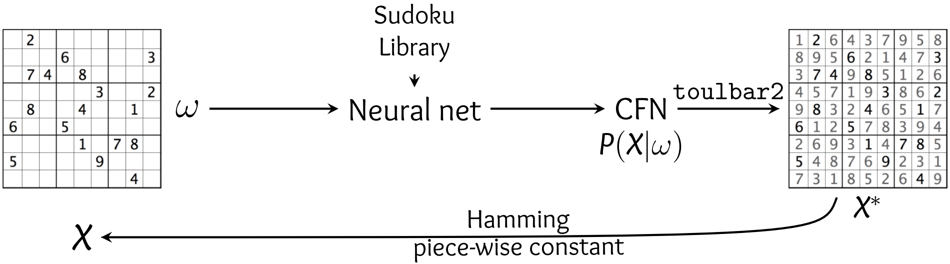
X^*

Hamming

X

Structured output prediction (SOP) with a CFN model



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Sudoku Library

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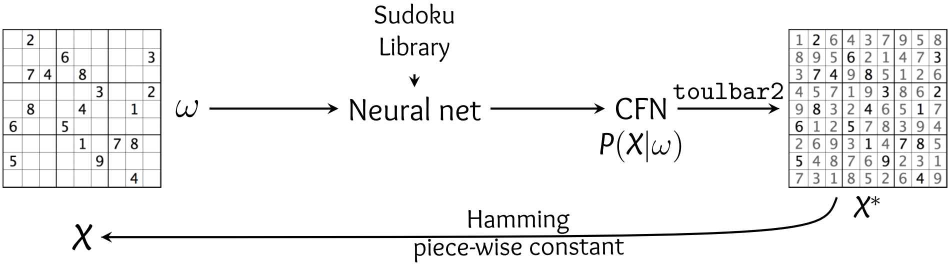
X^*

X ← Hamming piece-wise constant

Issues

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

Structured output prediction (SOP) with a CFN model



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Natural choice: the negative loglikelihood

#P-hard

- Use Besag's pseudo-loglikelihood (1975, efficient)
- Kicks the solver out of the training loop (scalable training)

(Besag 1975)

Besag's Pseudo-Loglikelihood

- The Pseudo-LL masks each variable successively in the solution X (Besag 1975)

$$NLL = -\sum_{x} \log(P(x)) \qquad NPLL = -\sum_{x} \sum_{x_i} \log(P(x_i|x_{-i}))$$

- Nice asymptotic properties statistically consistent
- The NPLL is a “Fenchel-Young” loss (Defresne, Gambardella, et al. 2026; Blondel et al. 2020)
- Does not work in practice (high costs) (Montanari et al. 2009)

Vanishing gradient issue

- If enough constraints have been learned to force the observed value of X_i in the context of x_{-i}, it becomes impossible to learn other constraints.
- Related to the idempotence of logical information

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The Emmental-PLL

Removing vanishing gradients

We ignore a random fraction of the neighbors/functions when computing $P(x_i|x_{-i})$

Easy, hard and extremely hard Sudoku grids

Type	Approach	Acc.	#hints	Train set	Param.	Train time (h)
DL	RRN (Palm et al. 2018)	96.6%	17	180,000	200k	> 50
	Rec. Trans. (Yang et al. 2023)	96.7%	17	180,000	211k	> 50
	Rec. Trans.	76.2–78.2%	17	9,000	-	1.8
	DDPM (Ye et al. 2025)	99.2–100%	33.8	100,000	6M	13.6
	DDPM	0.2%	17	-	-	-
	HRM (G. Wang et al. 2025)	55%	24.8	1,000 × 1,001	27M	>10
Relax+DL	SATNet (P.-W. Wang et al. 2019)	95.1–99.8%	36.2	9,000	600k	2.9
	SATNet	86.1–86.2%	17	-	-	-
CO	(Bessiere et al. 2023)	**100%**	-	200	-	0.01
CO + ML	(Brouard et al. 2020)	**100%**	17	9,000	-	1.5
CO+DL	Hinge (Defresne, Barbe, et al. 2023)	**100%**	17	1,000	180k	>50
	E-PLL (ours)	**100%**	17	**100**	22k	0.05
	E-PLL (HRM dataset)	**100%**	24.8	**10** × 100	22k	0.04

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)
- Corrected using a Reinforcement learning approach
- Training set with 5 solutions per instance
- Ability to generate additional solutions

Our architecture directly learns how to solve many-solutions Sudokus

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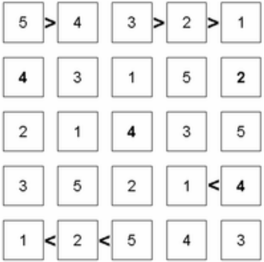
Learning to play Futoshiki

Sudoku is easy, only one type of constraint

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



5 > 4 3 > 2 > 1

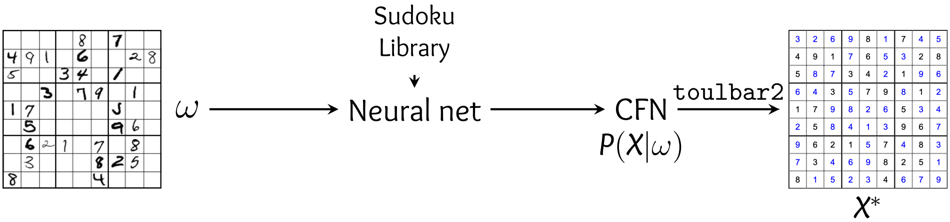
4 3 1 5 2

2 1 4 3 5

3 5 2 1 < 4

1 < 2 < 5 4 3

Learning to play Visual Sudoku



3	2	6	9	8	1	7	4	5
4	9	1	7	6	5	3	2	8
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6	4	3	5	7	9	8	1	2
1	7	9	8	2	6	5	3	4
2	5	8	4	1	3	9	6	7
9	6	2	1	5	7	4	8	3
7	3	4	6	9	8	2	5	1
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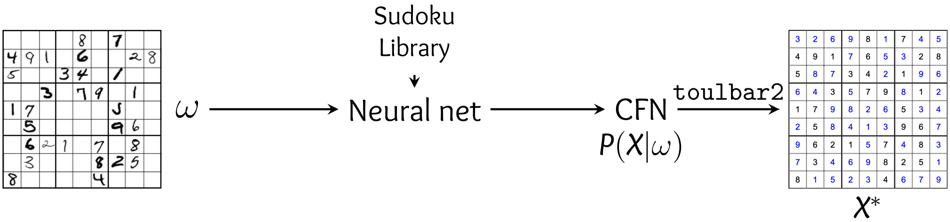
Simultaneously learns to recognize digits and to play the Sudoku

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

Learning to play Visual Sudoku



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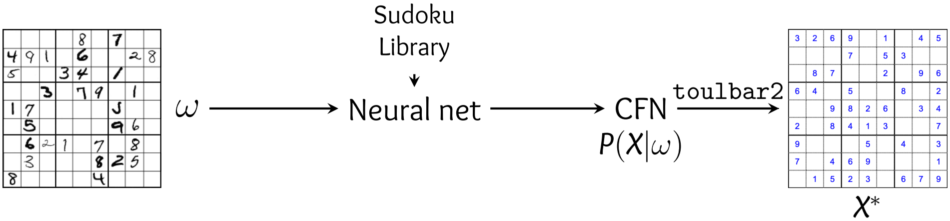
Reading numbers without cheating (grounding)



ω → Neural net → CFN $P(X|\omega)$ $\xrightarrow{\texttt{toulbar2}}$ X^*

Sudoku Library ↓ Neural net

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

X^*

Grounding issue: a nasty form of data leakage

(Chang et al. 2020)

- The training set contains images and associated decoded digits (hints).
- Solved using a complex architecture (InfoGAN+clustering+Distillation) (Topan et al. 2021)
- E-PLL: missing data, imputation by optimisation
- Much longer training (a few hours)

Existing approaches

Approach	MNIST accuracy	Percep.	Solved	Training (h)
SATNet	0.0 %	0.0 %	0.0 %	-
Rec. Trans (Yang et al. 2023)	99.4%	74.8%	75.6%	5.1
NeSy. Prog. (Li et al. 2023)	99.6–99.7%	90.7–93.1%	92.2–94.4%	4.7
E-PLL (Ours)	98.8%	72.9%	93.4%	3.2

Relation with Decision-focused learning

From DFL to Structured Output Prediction

- Data: pairs $\langle \omega, c \rangle$ where c define the criterion parameters
- Assumes constraints are known
- we can compute a SOP data-set (ω, X^*)
- Aim: minimize regret (difference in real cost of the predicted and optimal solution)

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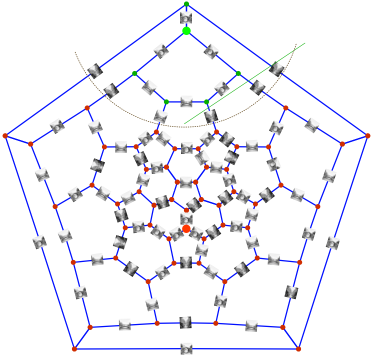
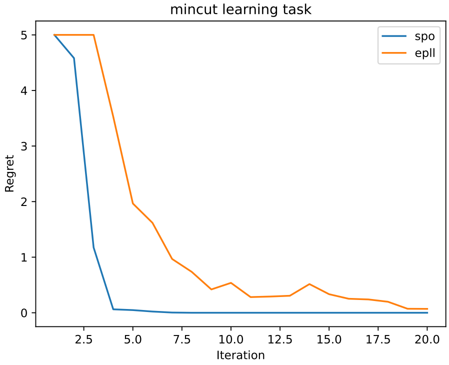
MinCut and MaxCut solving

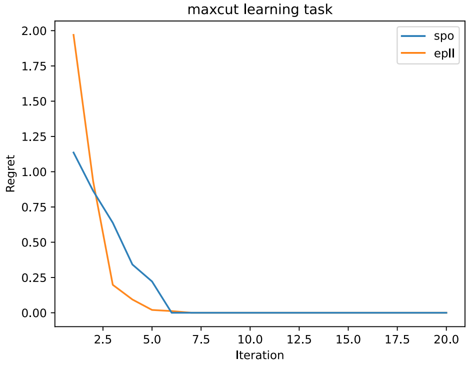
The Min/Max-Cut problems

- one Boolean variable per vertex (cut side)
- per-edge difference (Min-Cut) or equality (Max-Cut) function scaled by a predicted scalar $c(\omega)$
- bridge images with Gaussian noise (std-dev 10)

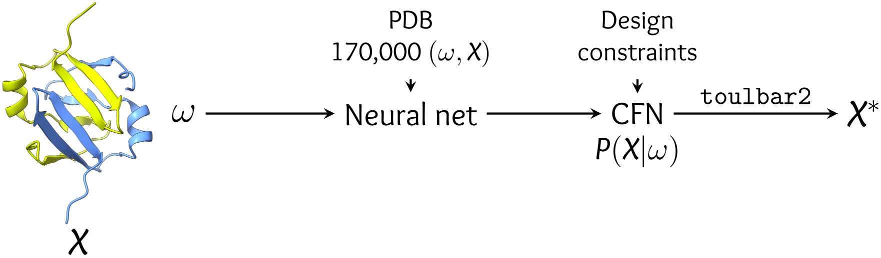


MinCut, MaxCut, Regret and SPO+ (Elmachtoub et al. 2022)





Learning to design proteins: Effie



Neural architecture

- More complex SE(3)-equivariant neural network
- Relies on Gated MLPs (post-transformer architecture)

(Liu et al. 2021)

Optimizing a complete protein sequence

Full redesign of large proteins in the test set

- Guaranteed `toulbar2` solution expensive
- Using LR-BCD SDP solver 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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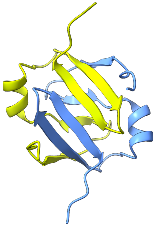
Effie vs. the model-free ProteinMPNN

(Dauparas et al. 2022)

GPT-style



PDB

$\downarrow$

$\omega \longrightarrow$ Autoregressive NN $\longrightarrow X_1, X_2, \ldots$

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

Pros and cons

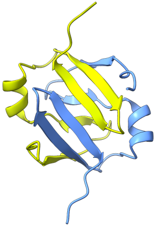
- $P(X_1, \ldots, X_n) = P(X_1)P(X_2|X_1) \cdots P(X_n|X_1, \ldots X_{n-1})$ is a mathematical identity
- But an easily broken one (*e.g.*, low temperature sampling)
- Heuristic score instead of NP-hard solving
- Limited control for design constraints, hard to “reason forward”

	ProteinMPNN	Effie
NSR	45.9%	48.4%

Effie vs. the model-free ProteinMPNN

(Dauparas et al. 2022)

GPT-style



PDB

↓

$\omega \longrightarrow$ Autoregressive NN $\longrightarrow X_1, X_2, \ldots$

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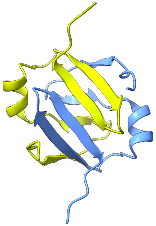

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Predicting SARS-CoV2 variants

Enumerate CoViD variants with a bounded number of mutations

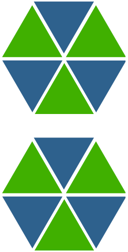
- Uses only the initial March 2020 RBD-ACE2 structure + Effie/toulbar2
- Relies on a global constraint to bound mutations (Ruffini et al. 2021)
- Predicts all the first SARS-CoV2 VoCs ($\alpha, \beta, \gamma, \delta, \kappa, \iota, \lambda$ and μ)
- In a few seconds, on one CPU-thread.

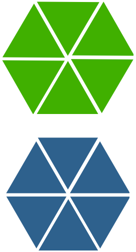
Not achievable by pure autoregressive models (ProteinMPNN).
Previously shown to predict contagious antibody-resistant variants (Colom et al. 2024).

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)





Design of an enzyme organizing platform

Design of an heteromeric hexamer

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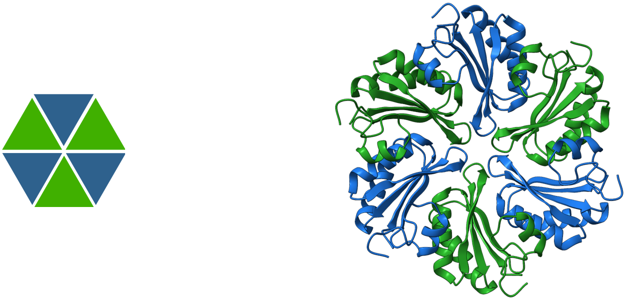

How often is ⬢ better than ⬢?

Scoring →	Effie	PMPNN
Effie	100 %	99.5 %
PMPNN	3.0 %	82.6 %

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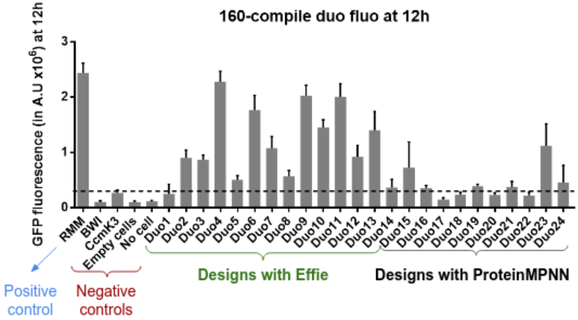

Conclusions

A Neural Net, a GM, and a discrete optimizer in a NeSy autoencoder

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

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