Learning how to design biomolecules using a neuro-symbolic architecture

Thomas Schiex

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

Human reasoning and scientific discovery

Inductive and deductive reasoning

- From observations 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 pairwise Cost Function Network

Human reasoning and scientific discovery

Inductive and deductive reasoning

- From observations 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 pairwise Cost Function Network

Human reasoning and scientific discovery

Inductive and deductive reasoning

- From observations 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 pairwise Cost Function Network

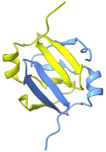
Human reasoning and scientific discovery

Inductive and deductive reasoning

- From observations 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

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



Protein structure with its sequence

The theory is written as pairwise Cost Function Network

Cost Function Networks

Pairwise Cost Function Network (Ising/Potts/Graphical model)

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

Costs and probabilities

- The cost $E(t)$ of an assignment t is the sum of all cost functions on t
- Toulbar2 finds $\operatorname{argmin}_t E(t)$ and proves optimality.
- A CFN defines a probability distribution: $P(t) \propto \exp(-E(t))$ — Markov Random Fields
- Normalizing constant is #P-hard to compute

Cost Function Networks

Pairwise Cost Function Network

(Ising/Potts/Graphical model)

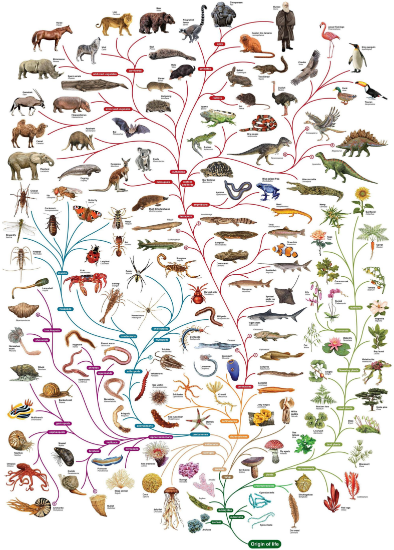
- A set X of variables — n variables
- Variable x_i has domain D_i — max. size d
- a set of cost/energy functions — $e_{ij} : D_i \times D_j \to \mathbb{R} \cup \{\infty\}$

Costs and probabilities

- The cost $E(t)$ of an assignment t is the sum of all cost functions on t
- Toulbar2 finds $\mathrm{argmin}_t\, E(t)$ and proves optimality.
- A CFN defines a probability distribution: $P(t) \propto \exp(-E(t))$ — Markov Random Fields
- Normalizing constant is #P-hard to compute

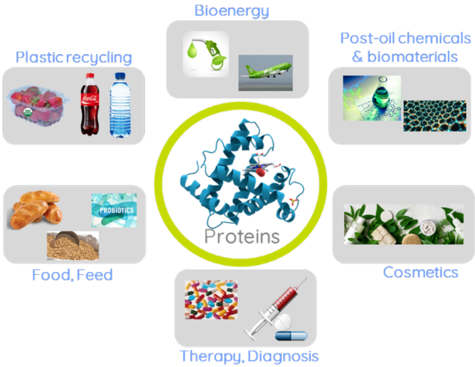
The engines of Life

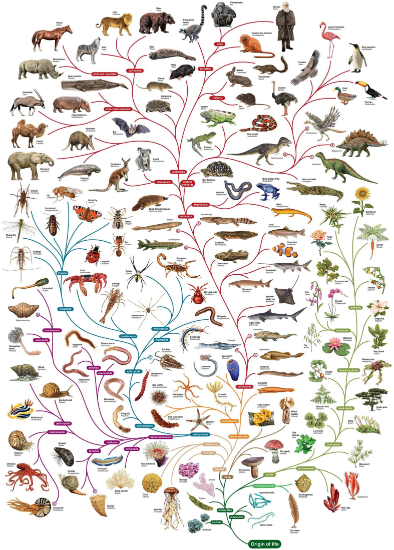
- Most active molecules of life (virus to humans)
- Useful in health to green chemistry



The engines of Life

- Most active molecules of life (virus to humans)
- Useful in health to green chemistry





Protein folding

DVVGKVVDGKDD· · · GVKVGDKVKVKKV

Organizes different types of atoms in 3D

Sequence $\rightsquigarrow$ Structure $\rightsquigarrow$ Function

Protein folding

DVVGKVVDGKDD· · · GVKVGDKVKVKKV

$\rightsquigarrow$

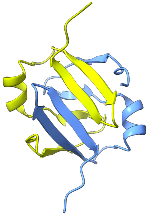
Organizes different types of atoms in 3D

Sequence $\rightsquigarrow$ Structure $\rightsquigarrow$ Function

Protein folding

DVVGKVVDGKDD· · · GVKVGDKVKVKKV

$\rightsquigarrow$



Organizes different types of atoms in 3D

Sequence $\rightsquigarrow$ Structure $\rightsquigarrow$ Function

Protein folding

$\mathcal{X}$

Amino acid sequence
(20 letters alphabet)

$\rightsquigarrow$

Φ

Continuous SE(3)-invariant
3D structure

Organizes different types of atoms in 3D

Sequence $\rightsquigarrow$ Structure $\rightsquigarrow$ Function

Protein folding

χ

Amino acid sequence
(20 letters alphabet)

$\rightsquigarrow$

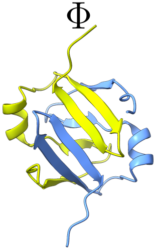
Φ

Continuous SE(3)-invariant
3D structure

Organizes different types of atoms in 3D

Sequence $\rightsquigarrow$ Structure $\rightsquigarrow$ Function

Designing Proteins with physics

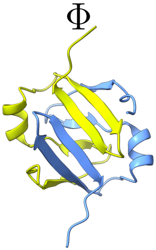


A quite successful all physics+logic generative process

The Toulbar package […] significantly improved the state-of-the-art efficiency for protein design

Com. ACM-20, B. Donald et al.

Designing Proteins with physics



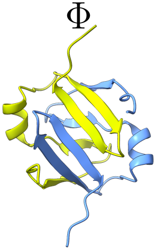
$$\xrightarrow[\substack{\text{Rosetta} \\ \texttt{beta\_nov16}}]{\text{Physics}} \begin{array}{c}\text{Binary CFN} \\ P(X|\Phi)\end{array}$$

A quite successful all physics+logic generative process

The Toulbar package […] significantly improved the state-of-the-art efficiency for protein design

Com. ACM-20, B. Donald et al.

Designing Proteins with physics

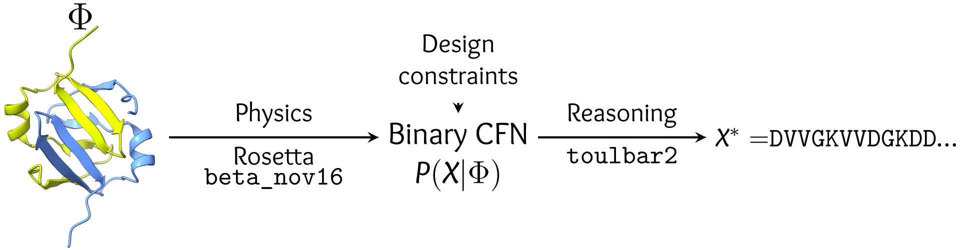


$$\Phi \xrightarrow[\text{Rosetta } \texttt{beta\_nov16}]{\text{Physics}} \text{Binary CFN } P(X|\Phi) \xrightarrow[\texttt{toulbar2}]{\text{Reasoning}} X^* = \texttt{DVVGKVVDGKDD}\ldots$$

A quite successful all physics+logic generative process

The Toulbar package […] significantly improved the state-of-the-art efficiency for protein design
Com. ACM-20, B. Donald et al.

Designing Proteins with physics



Φ

Physics

Rosetta
`beta_nov16`

Design constraints

Binary CFN

$P(X|\Phi)$

Reasoning

`toulbar2`

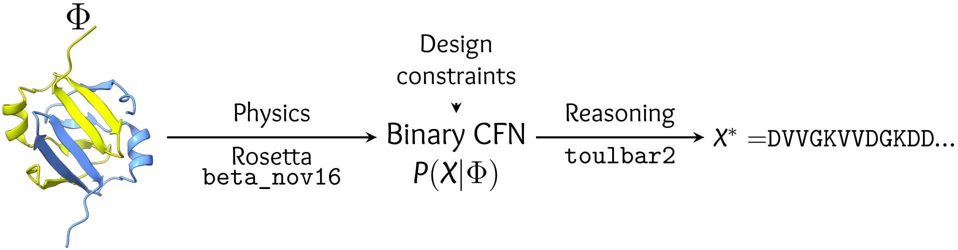
X^* =DVVGKVVDGKDD...

A quite successful all physics+logic generative process

The Toulbar package […] significantly improved the state-of-the-art efficiency for protein design

Com. ACM-20, B. Donald et al.

Designing Proteins with physics



Φ

Physics

Rosetta
`beta_nov16`

Design
constraints

Binary CFN
$P(X|\Phi)$

Reasoning

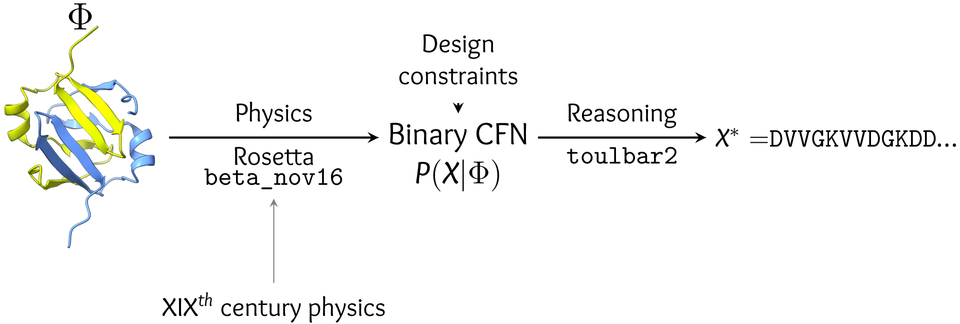
`toulbar2`

$X^* =$DVVGKVVDGKDD...

A quite successful all physics+logic generative process

The Toulbar package [...] significantly improved the state-of-the-art efficiency for protein design
Com. ACM-20, B. Donald et al.

Designing Proteins with physics



Φ

Physics

Rosetta beta_nov16

XIXth century physics

Design constraints

Binary CFN $P(X|\Phi)$

Reasoning

toulbar2

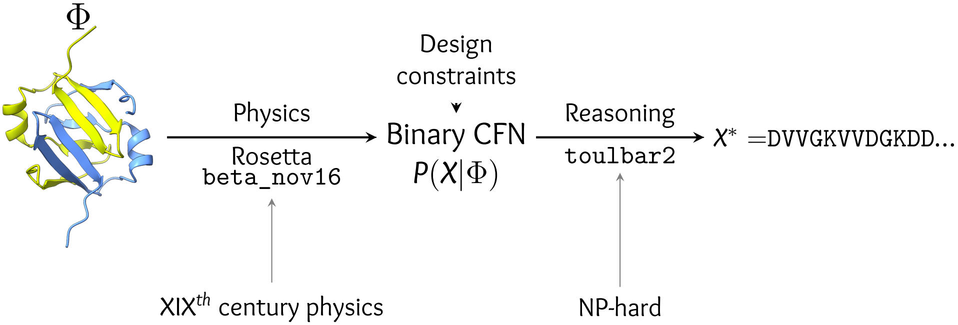
X^* =DVVGKVVDGKDD...

A quite successful all physics+logic generative process

The Toulbar package [...] significantly improved the state-of-the-art efficiency for protein design

Com. ACM-20, B. Donald et al.

Designing Proteins with physics



Φ

Physics

Rosetta `beta_nov16`

Design constraints

Binary CFN

$P(X|\Phi)$

Reasoning

`toulbar2`

$X^* =$ `DVVGKVVDGKDD...`

XIXth century physics

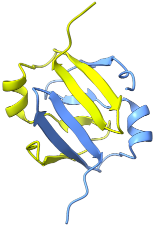
NP-hard

A quite successful all physics+logic generative process

The Toulbar package [...] significantly improved the state-of-the-art efficiency for protein design

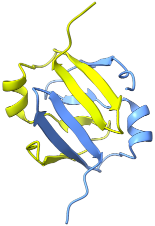
Com. ACM-20, B. Donald et al.

Injecting ML / intuition[1]



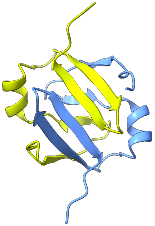
Φ

Injecting ML / intuition[1]



$\Phi \longrightarrow$ Neural net

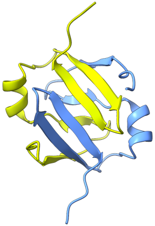
Injecting ML / intuition[1]



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

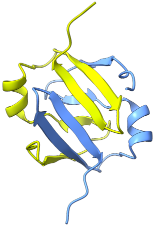
$P(X|\Phi)$

Injecting ML / intuition[1]



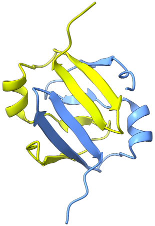
$$\begin{tikzcd}\Phi \arrow[r] & \text{Neural net} \arrow[r] & \text{CFN} \arrow[r, "\texttt{toulbar2}"] & X^* \\ & & P(X|\Phi) & \end{tikzcd}$$

Injecting ML / intuition[1]



$$\begin{tikzcd} & & \text{Design constraints} \arrow[d] & \\ \Phi \arrow[r] & \text{Neural net} \arrow[r] & \underset{P(X|\Phi)}{\text{CFN}} \arrow[r, "\texttt{toulbar2}"] & X^* \end{tikzcd}$$

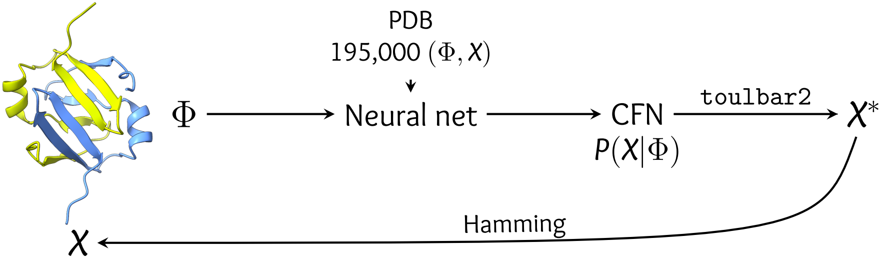
Injecting ML / intuition[1]



X

$$\begin{tikzcd} & \text{PDB} \\ & 195{,}000\ (\Phi, X) \arrow[d] \\ \Phi \arrow[r] & \text{Neural net} \arrow[r] & \underset{P(X|\Phi)}{\text{CFN}} \arrow[r, "\texttt{toulbar2}"] & X^* \end{tikzcd}$$

Injecting ML / intuition[1]



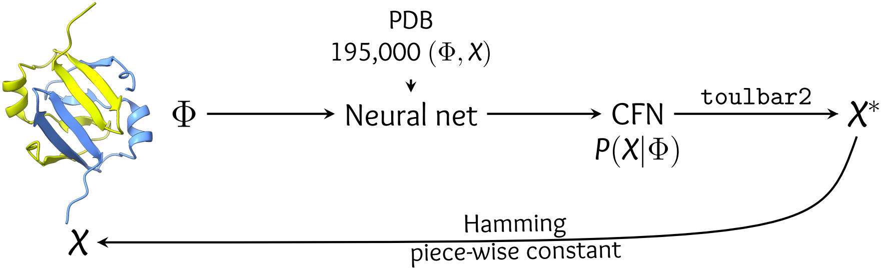
PDB

195,000 (Φ, X)

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

X^* $\xrightarrow{\text{Hamming}}$ X

Injecting ML / intuition[1]



PDB

$195{,}000\ (\Phi, X)$

Φ

Neural net

CFN

$P(X|\Phi)$

toulbar2

X^*

Hamming

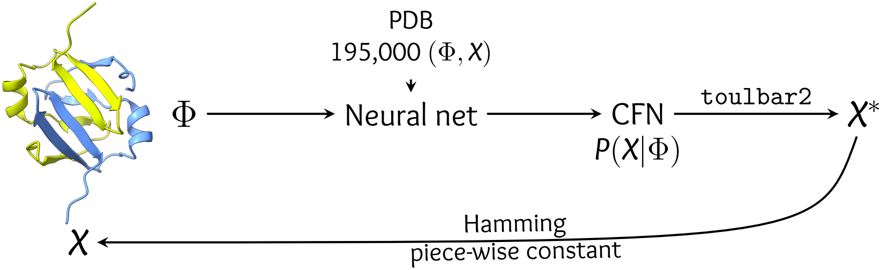
piece-wise constant

X

Issues

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

Injecting ML / intuition[1]



PDB

195,000 (Φ, X)

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

Hamming

piece-wise constant

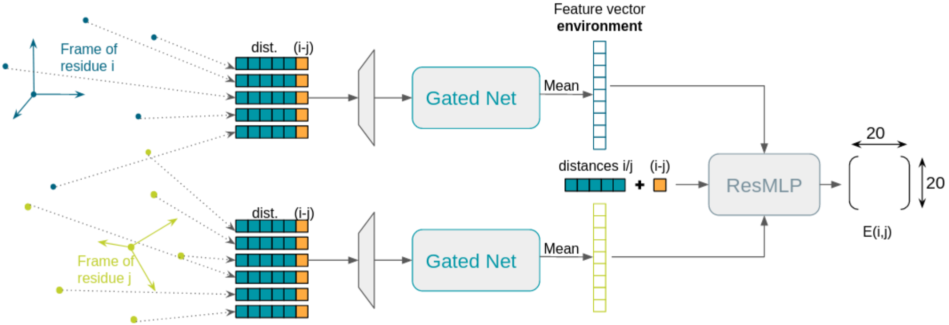
X

Our solution

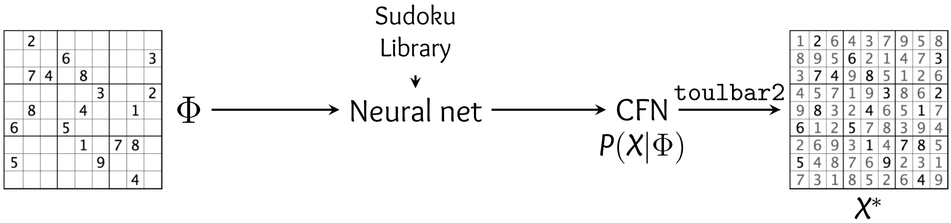
IJCAI'2023

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

Protein Design architecture



Learning to play Sudoku



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

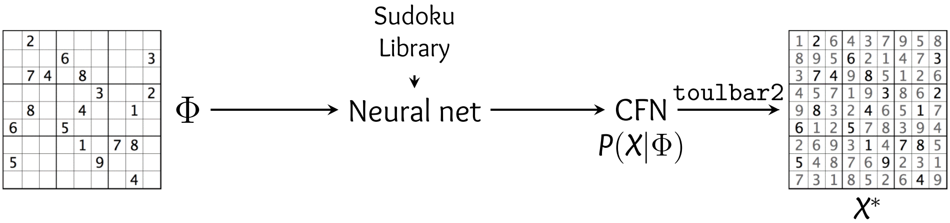
Φ → Neural net → CFN $P(X|\Phi)$ $\xrightarrow{\texttt{toulbar2}}$ X^*

Sudoku Library ↓ Neural net

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

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

Learning to play Sudoku



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

Φ → Neural net → CFN $\xrightarrow{\texttt{toulbar2}}$ X^*

Sudoku Library ↓ Neural net

CFN

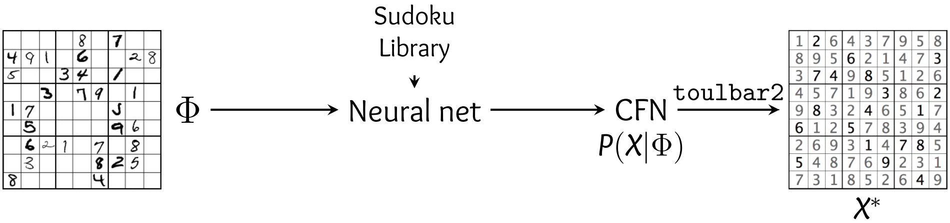
$P(X|\Phi)$

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

X^*

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**

Learning to play Visual Sudoku

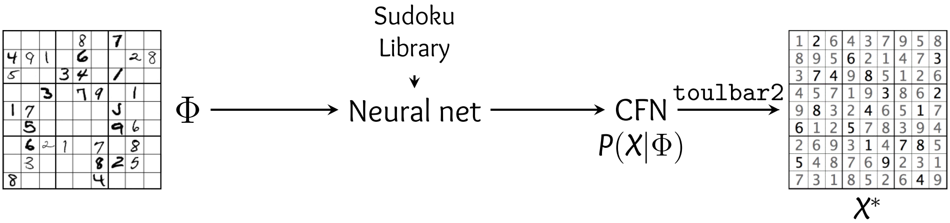


1	2	6	4	3	7	9	5	8
8	9	5	6	2	1	4	7	3
3	7	4	9	8	5	1	2	6
4	5	7	1	9	3	8	6	2
9	8	3	2	4	6	5	1	7
6	1	2	5	7	8	3	9	4
2	6	9	3	1	4	7	8	5
5	4	8	7	6	9	2	3	1
7	3	1	8	5	2	6	4	9

Simultaneously learns to recognize digits and to play the Sudoku

SATNet	Theoretical (no corrections)	Hybrid
63.2 %	74.2%	94.1 ± 0.8%

Learning to play Visual Sudoku



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

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

Simultaneously learns to recognize digits and to play the Sudoku

SATNet	Theoretical (no corrections)	Hybrid
63.2 %	74.2%	**94.1** ± 0.8%

Learning to play Futoshiki

Sudoku is easy, only one type of constraints

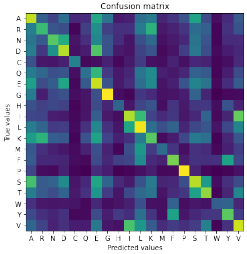
- Our architecture directly learns how to play Futoshiki
- Includes both difference and inequality constraints
- Perfect solving, expected constraints learned

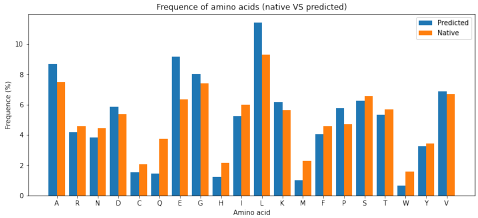
5	>	4		3	>	2	>	1
4		3		1		5		2
2		1		4		3		5
3		5		2		1	<	4
1	<	2	<	5		4		3

Learning to design proteins: Effie

Recovering amino acid properties

- Correctly predicts 51% of amino acids from their environment





Zero-shot prediction of the effect of single mutations

- 79% accuracy on ATOM3D benchmark
- 0.4 correlation stability score/predicted energy (Rocklin et al. 2017)

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%

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)

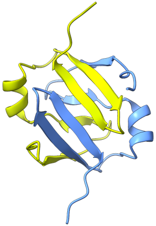
Outperforms all-atoms XIXth-century physics

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

Approach	Rosetta	Effie
NSR	17.9%	32.8%

Effie vs. ProteinMPNN (Dauparas et al. 2022)

GPT-style



$$\begin{tikzcd} & \text{PDB} \arrow[d] & \\ \Phi \arrow[r] & \text{Autoregressive NN} \arrow[r] & X_1, X_2, \ldots \end{tikzcd}$$

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

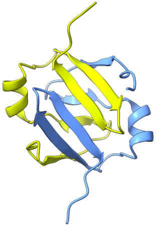
Pros and cons

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

	ProteinMPNN	Effie
NSR	45.9%	48.4%

Effie vs. ProteinMPNN (Dauparas et al. 2022)

GPT-style



$$\Phi \longrightarrow \overset{\text{PDB}}{\overset{\downarrow}{\text{Autoregressive NN}}} \longrightarrow X_1, X_2, \ldots$$

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

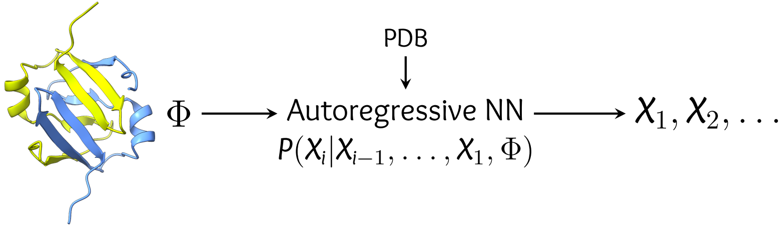
Pros and cons

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

	ProteinMPNN	Effie
NSR	45.9%	48.4%

Effie vs. ProteinMPNN (Dauparas et al. 2022)

GPT-style



PDB

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

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

Pros and cons

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

	ProteinMPNN	Effie
NSR	45.9%	**48.4%**

Predicting SARS-CoV2 variants

(Colom et al. 2024)

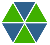
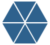
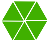
Enumerate CoViD variants with a bounded number of mutations

- 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

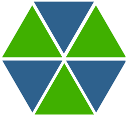
Design of an heteromeric hexamer

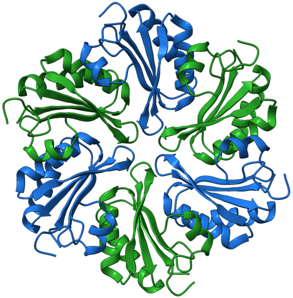
- Design and that self-assemble as  but not as  or 
- Physics+logic: requires bi-level optimization (NP^{NP}-complete) (Vucinic et al. 2020)
- Compare Effie+tb2 (NP-complete) with ProteinMPNN, bi-criteria (Buchet et al. 2024)

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)



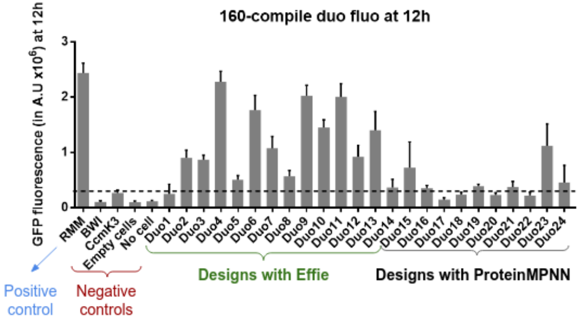


How often is ⬢ better than ⬢?

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

How often is ⬢ better than ⬢?

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



Conclusions

A Neural Net, a CFN and a CFN prover 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

Conclusions

A Neural Net, a CFN and a CFN prover 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

Conclusions

A Neural Net, a CFN and a CFN prover 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

Conclusions

A Neural Net, a CFN and a CFN prover 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

Conclusions

A Neural Net, a CFN and a CFN prover 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

Acknowledgments

AI/toulbar2

S. de Givry (INRA)
G. Katsirelos (INRA)
M. Zytnicki (PhD, INRA)
D. Allouche (INRA)
M. Ruffini (INRA)
V. Durante (ANITI, PhD)
H. Nguyen (PhD, INRA)
C. Brouard (ML, INRA)
S. Buchet (INRAE/ANITI)
P. Montalbano (ANITI, PhD)
M. Cooper (IRIT, Toulouse)
J. Larrosa (UPC, Spain)
F. Heras (UPC, Spain)
M. Sanchez (Spain)
E. Rollon (UPC, Spain)
P. Meseguer (CSIC, Spain)
G. Verfaillie (ONERA, ret.)
JH. Lee (CU. Hong Kong)
C. Bessiere (LIMM, Montpellier)
JP. Métivier (GREYC, Caen)
S. Loudni (GREYC, Caen)
M. Fontaine (GREYC, Caen),...

DL/Protein Design

A. Voet (KU Leuven)
A. Olichon (INSERM)
D. Simoncini (UFT, Toulouse)
S. Barbe (INSA, Toulouse)
M. Defresne (INRAE, PhD)
Y. Bouchiba (INSA, PhD)
C. Dumont (INSA, Toulouse)
J. Vucinic (INRA/INSA)
S. Traoré (PhD, CEA)
C. Viricel (PhD)
K. Zhang (Riken, CBDR)
S. Yagi (Riken, CBDR)
S. Tagami (Riken, CBDR)
RosettaCommons (U. Washington)
W. Sheffler (U. Washington)
V. Mulligan (Flatiron Institute, NY)
C. Bahl (IPI, Boston)
PyRosetta (U. John Hopkins)
B. Donald (U. North Carolina)
K. Roberts (U. North Carolina)
T. Simonson (Polytechnique)
J. Cortes (LAAS/CNRS),...

MIA TOULOUSE

BioEco Graduate School Biotechnology Building Bio-Based Economy

tbi Toulouse Biotechnology Institute Bio & Chemical Engineering

INRAE

UNIVERSITÉ TOULOUSE 1 CAPITOLE

INSA TOULOUSE

My apologies to those missing in these lists. Even imperfect lists seem better than no list

References

Bessiere, Christian et al. (Aug. 2023). “Learning Constraint Networks over Unknown Constraint Languages”. In: Proceedings of the Thirty-Second International Joint Conference on Artificial Intelligence, IJCAI-23. Ed. by Edith Elkind. Main Track. International Joint Conferences on Artificial Intelligence Organization, pp. 1876–1883. DOI: 10.24963/ijcai.2023/208. URL: https://doi.org/10.24963/ijcai.2023/208.

Buchet, Samuel et al. (2024). “Bi-objective Discrete Graphical Model Optimization”. In: International Conference on the Integration of Constraint Programming, Artificial Intelligence, and Operations Research. Springer, pp. 136–152.

Colom, Mireia Solà et al. (Aug. 2024). “Complete combinatorial mutational enumeration of a protein functional site enables sequence-landscape mapping and identifies highly-mutated variants that retain activity”. In: Protein Science 33.8, e5109. DOI: 10.1002/pro.5109. URL: https://hal.science/hal-04646616.

Dauparas, J. et al. (2022). “Robust deep learning-based protein sequence design using ProteinMPNN”. In: Science 378.6615, pp. 49–56. DOI: 10.1126/science.add2187.

Defresne, Marianne et al. (2023). “Scalable Coupling of Deep Learning with Logical Reasoning”. In: 32nd International Joint Conference on Artificial Intelligence, IJCAI 2023. Macao, SAR, China: ijcai.org, pp. 3615–3623. DOI: 10.24963/IJCAI.2023/402.

Durante, Valentin et al. (July 2022). “Efficient low rank convex bounds for pairwise discrete Graphical Models”. In: Thirty-ninth International Conference on Machine Learning.

References II

Montalbano, Pierre et al. (2022). "Multiple-Choice Knapsack Constraint in Graphical Models". In: Proc. of CPAIOR'22.

Rocklin, Gabriel J et al. (2017). "Global analysis of protein folding using massively parallel design, synthesis, and testing". In: Science 357.6347, pp. 168–175.

Vucinic, Jelena et al. (2020). "Positive multistate protein design". In: Bioinformatics 36.1, pp. 122–130.