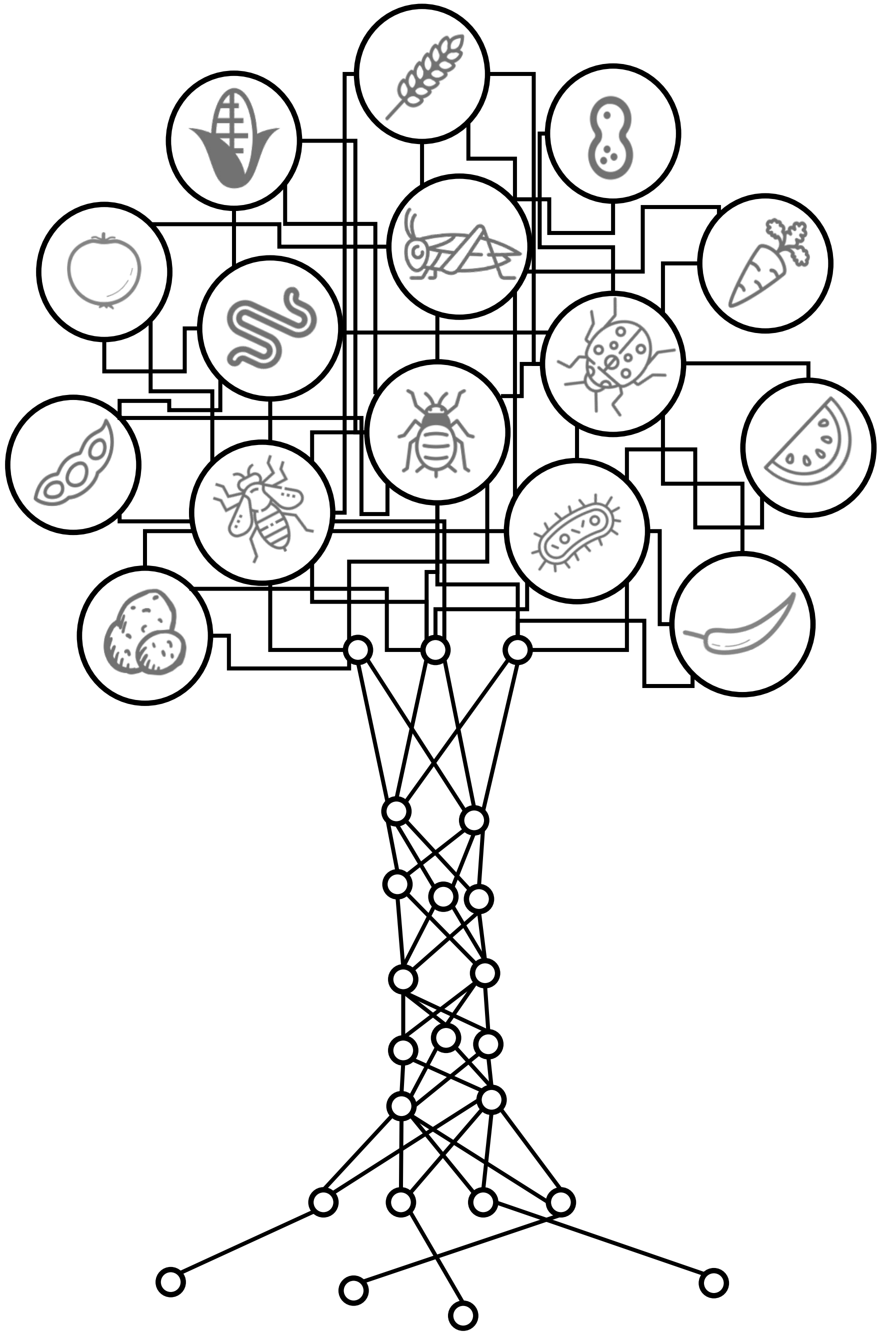


UNIVERSITÉ CÔTE D'AZUR
MAISON DE LA MODÉLISATION, DE LA SIMULATION ET DES INTERACTIONS

INRAE
la science pour la vie, l'humain, la terre

NERD (Nematode EffectoR Discovery)

a tool to predict proteins involved in nematodes' plant parasitism.

Djampa KOZLOWSKI, PhD (MSI/UCA/INRAe)

Silvia BOTTINI, PhD.
Medical Data Laboratory

Etienne DANCHIN, PhD.

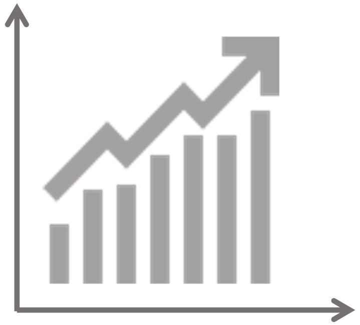
UNIVERSITÉ CÔTE D'AZUR
Centre de calculs

Plant Parasitic Nematodes (PPNs), a threat to global food safety

Population

9.7 bil.
(2064)

8 bil.
(2022) (1)



Food needs + 25-70% in 2050 (2)

(1) Vollset et al; The Lancet, 2020
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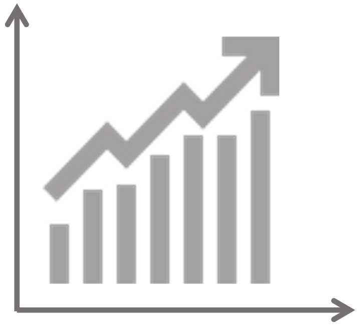

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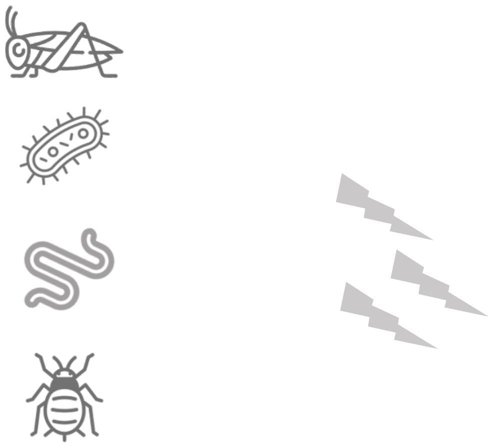

Crop pest are one of the major threat to food sustainability (20-30 % Mondial Loss) (3)

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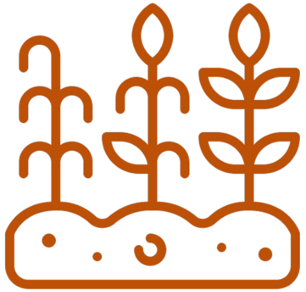

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Plant Parasitic Nematodes (PPNs) (12% Mondial loss) (3)

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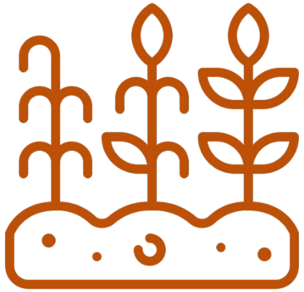

Crop pest are one of the major threat to food sustainability (20-30 % Mondial Loss) (3)

Plant Parasitic Nematodes (PPNs) (12% Mondial loss) (3)

Better understand the biology of those species and how they interact with their environment / host is necessary to develop new control methods.

(1) Vollset et al; The Lancet, 2020
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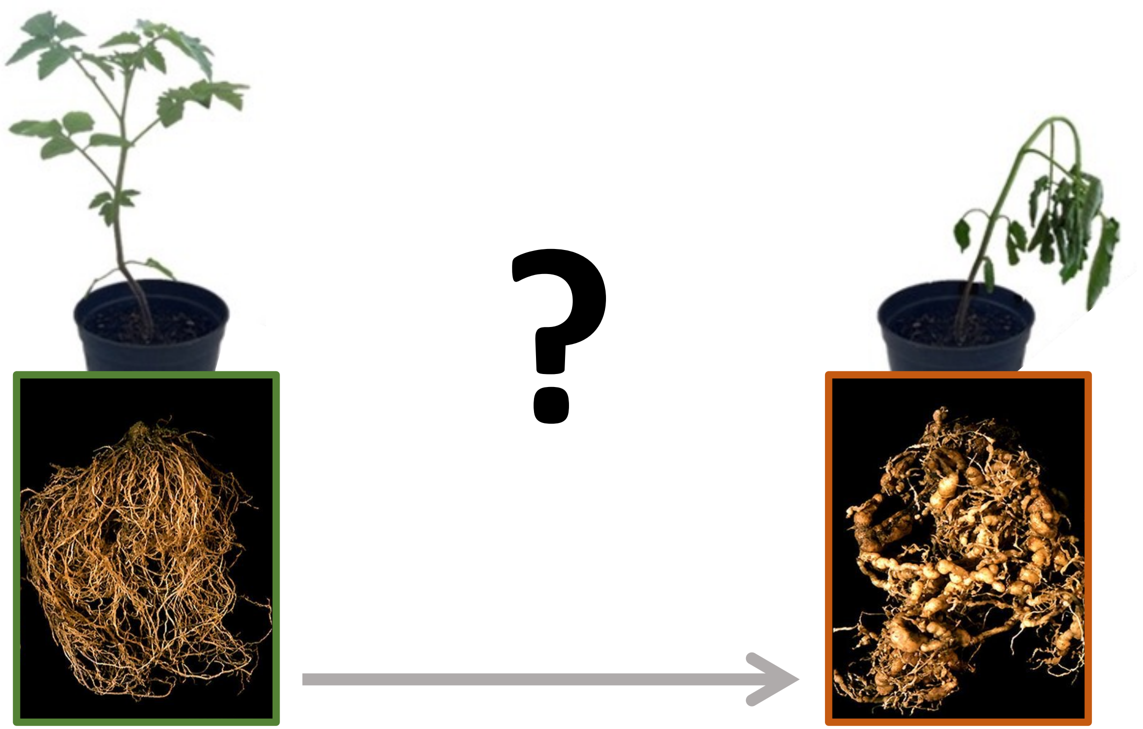
The Plant Parasitic Nematode (PPNs) infectious toolbox : the effector proteins



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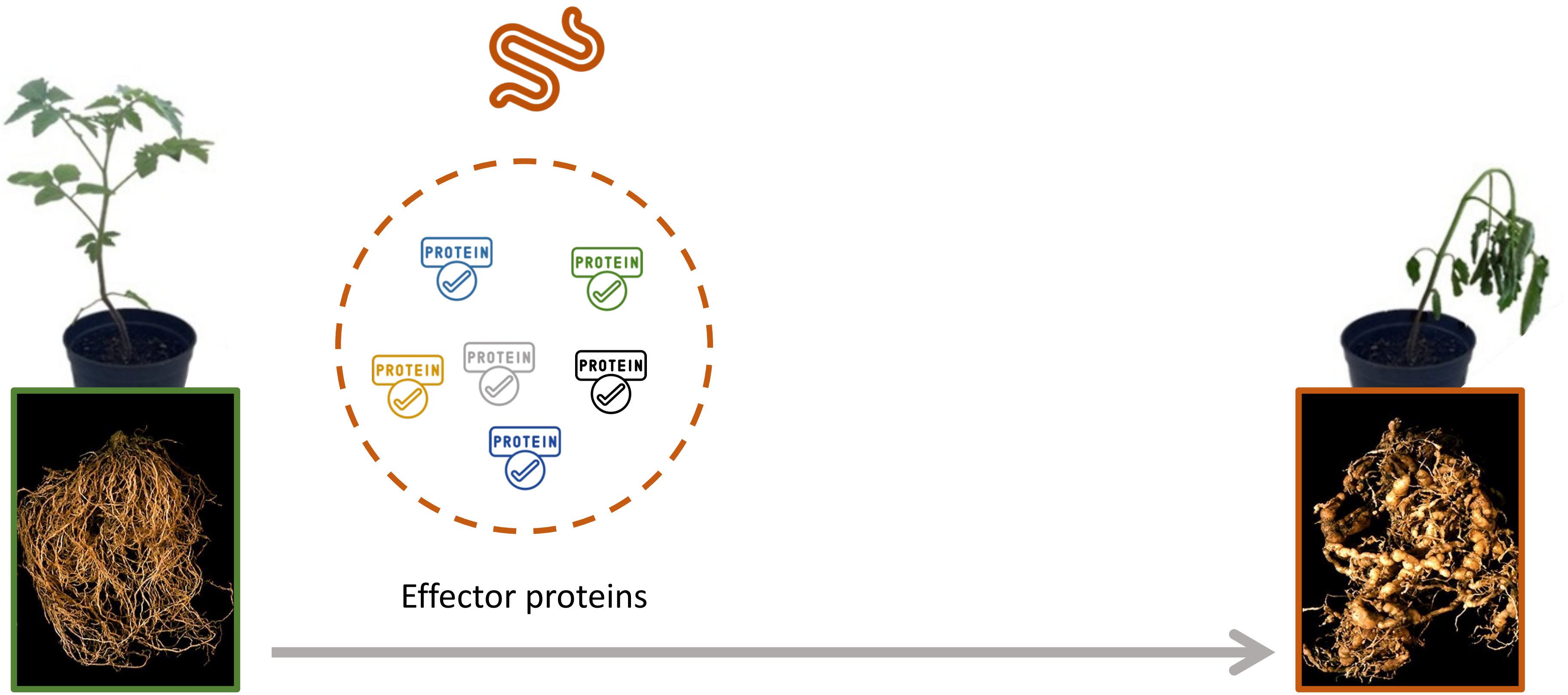

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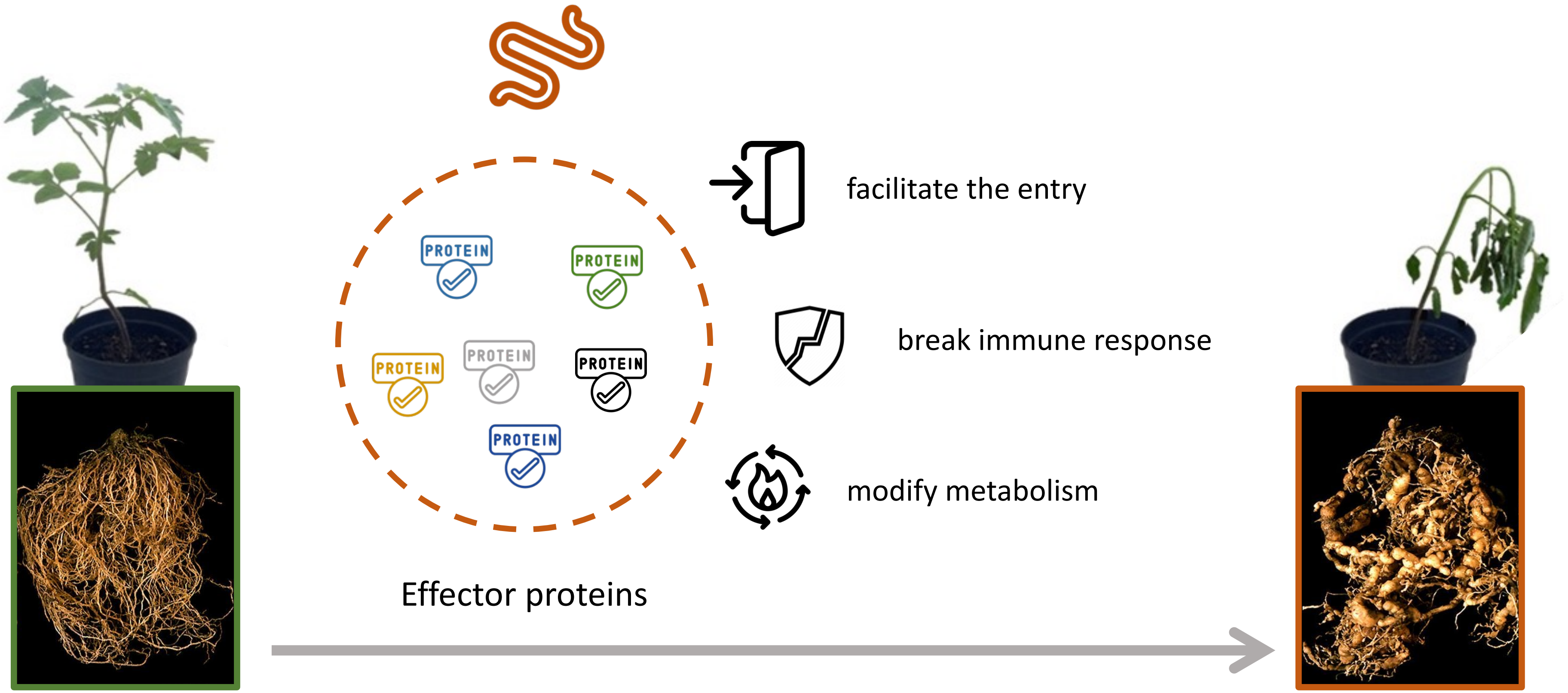

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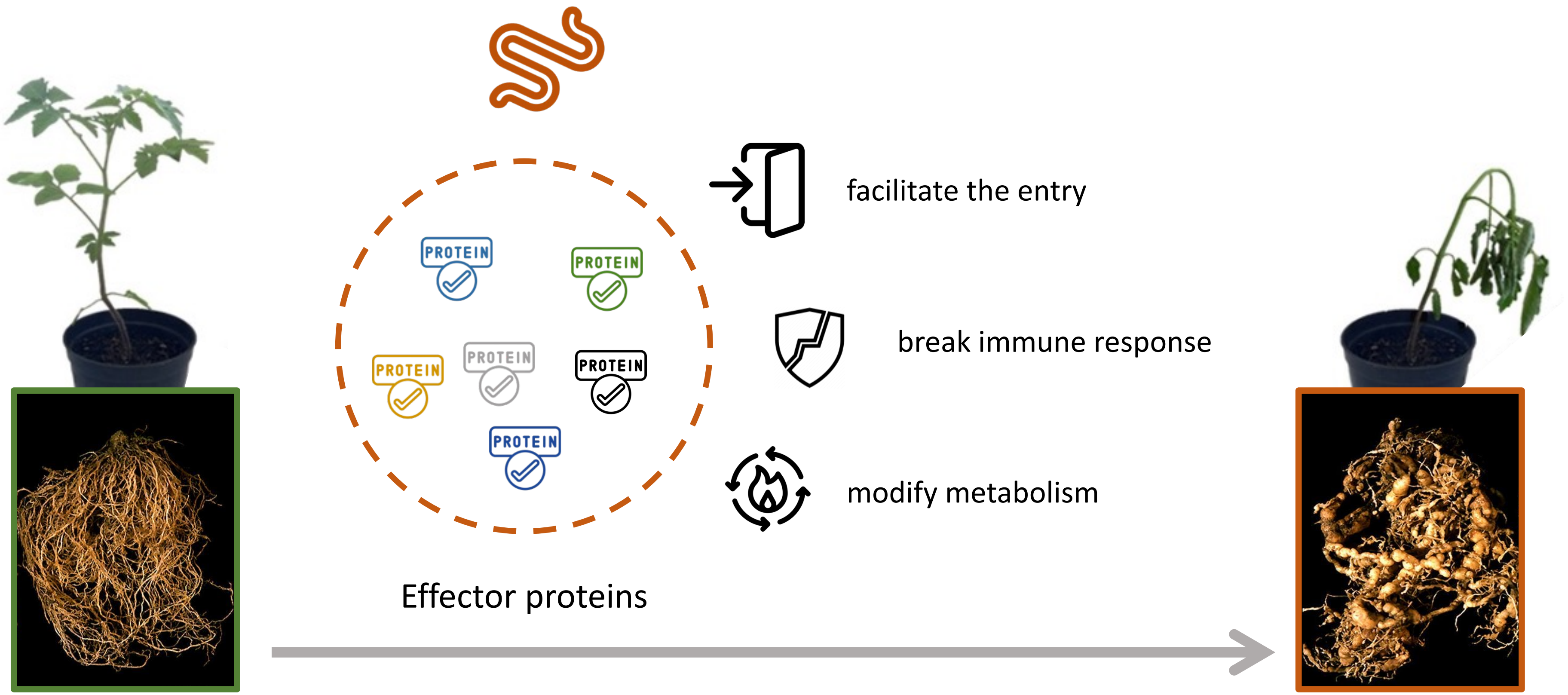
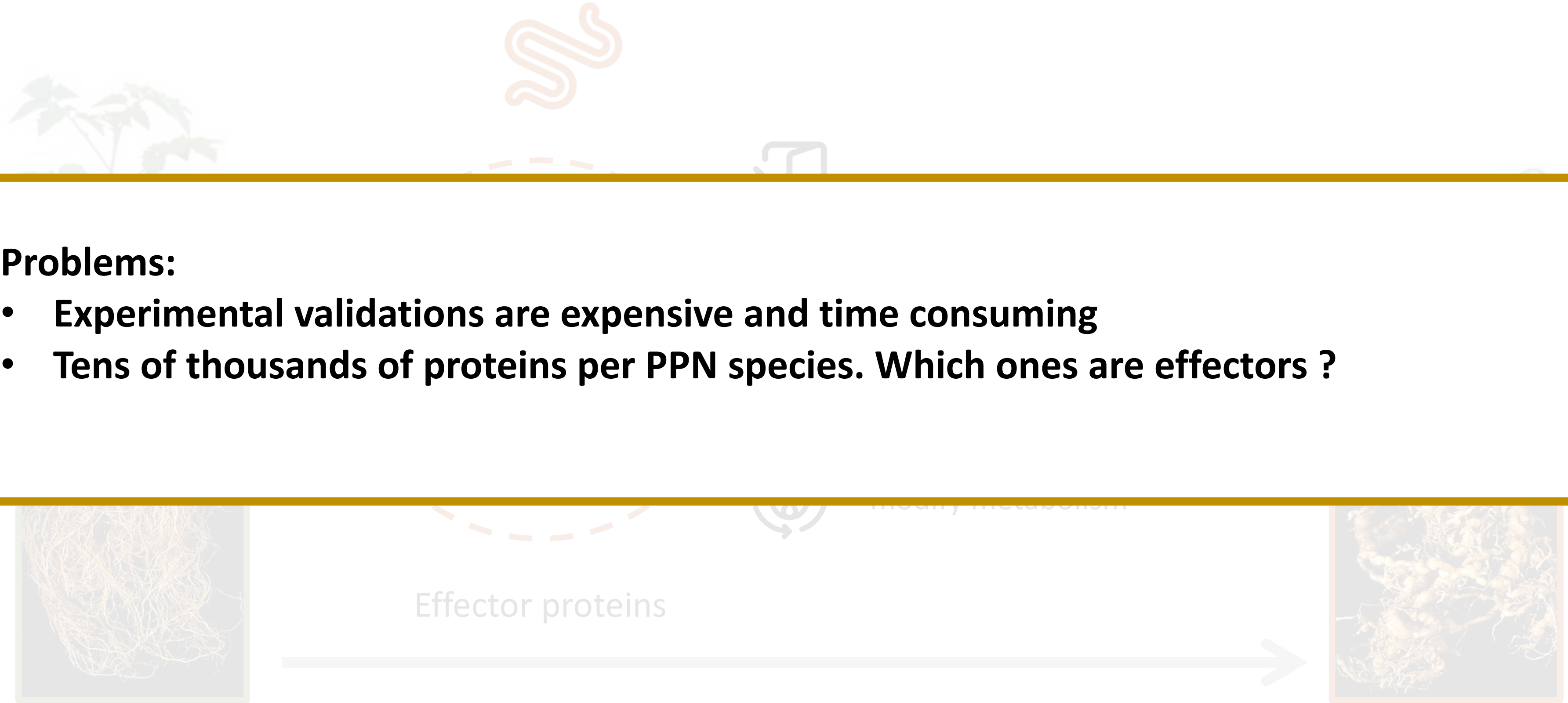


Effectors proteins are a major key of the host-pathogen interaction and must be studied

The Plant Parasitic Nematode (PPNs) infectious toolbox : the effector proteins



Problems:

- **Experimental validations are expensive and time consuming**
- **Tens of thousands of proteins per PPN species. Which ones are effectors ?**

Effectors proteins are a major key of the host-pathogen interaction and must be studied

The Plant Parasitic Nematode (PPNs) infectious toolbox : the effector proteins

Problems:

- **Experimental validations are expensive and time consuming**
- **Tens of thousands of proteins per PPN species. Which ones are effectors ?**

In-silico approach is necessary to identify effector proteins candidates for experimental validation

Effectors proteins are a major key of the host-pathogen interaction and must be studied

Methodology : datasets creation

11 **Plant Parasitic Nematode(PPN)** species
(5 genera)

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Experimentally validated effector proteins from the literature

- Amplification (orthologous sequences from proteomes)
- Redundancy reduction

546 protein sequences

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Proteins universally conserved among nematodes (64 species, PPN and not-PPN)

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3849 protein sequences

Methodology : datasets creation

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(5 genera)

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\+ 546 protein sequences

Proteins universally conserved among nematodes (64 species, PPN and not-PPN)

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\- 3849 protein sequences

Data splitting
(same proportion of positive and negative sequences in each dataset)

\+ 382 seqs.
\- 2694 seqs.

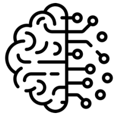
Training set (70%)

\+ 164 seqs.
\- 1155 seqs.

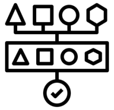
Test set (30%)

Methodology : Predict effector proteins, a challenging task

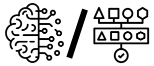
Existing tools



MERCI-1.0 **(1)**
EffectorP-3.0 **(2)**
Deepredeff-0.1.1 **(3)**



EffHunter-1.0 **(4)**



Predector-1.2.7 **(5)**

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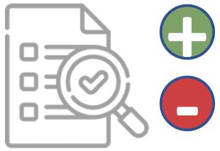
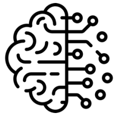
Methodology : Predict effector proteins, a challenging task

Test set



164 seqs.
1155 seqs.

Existing tools



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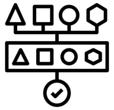

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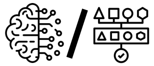

Predector-1.2.7 **(5)**

Performances evaluation

	0 (pred.)	1 (pred.)
0 (obs.)	**TN**	**FP**
1 (obs.)	**FN**	**TP**

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Methodology : Predict effector proteins, a challenging task

Test set

+ 164 seqs.
- 1155 seqs.

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Performances evaluation

	0 (pred.)	1 (pred.)
0 (obs.)	TN	FP
1 (obs.)	FN	TP

$$\textbf{Precision} = \frac{TP}{TP + FP}$$

$$\textbf{Recal} = \frac{TP}{TP + FN}$$

"Ability of the classifier not to label as an effector a protein that is not an effector"

"Ability of the classifier to find all the effector proteins"

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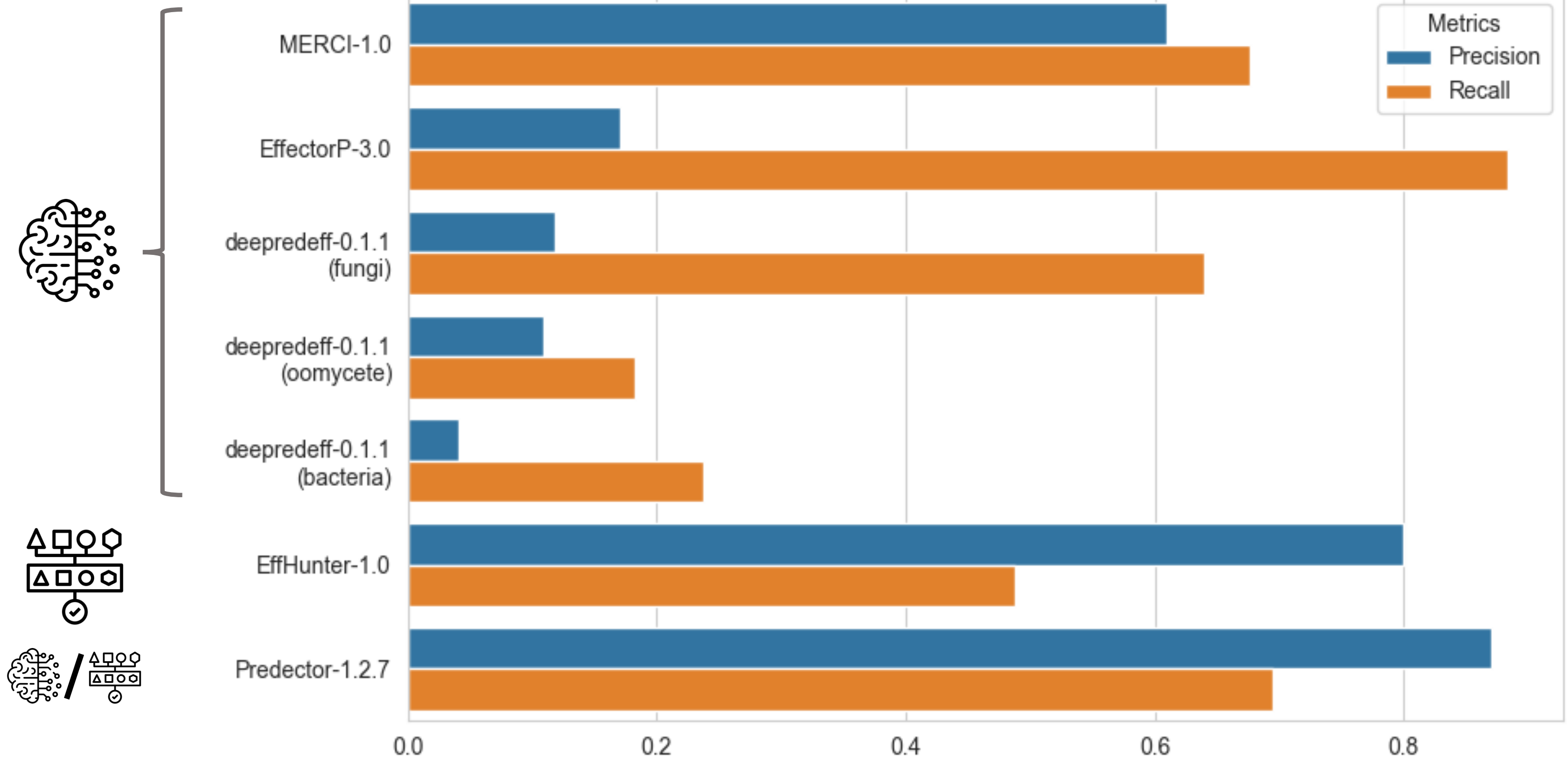
Methodology : Predict effector proteins, a challenging task

Performances on PPN test set

(164 effectors, 1155 non-effectors; detailed after)



P. = 0.87

R. = 0.69

$$\text{Precision} = \frac{TP}{TP + FP}$$

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Methodology : Predict effector proteins, a challenging task

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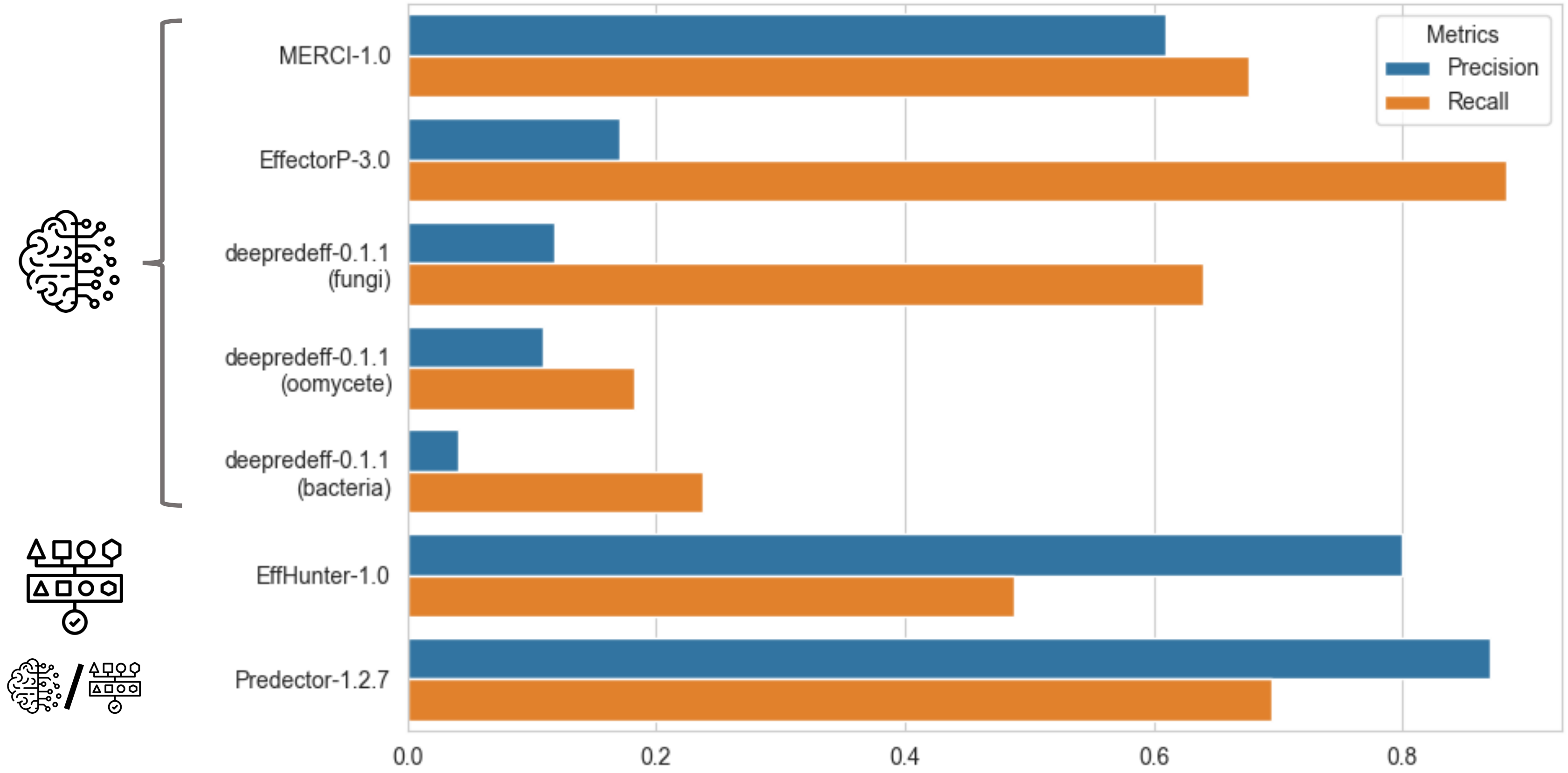

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Drawbacks:

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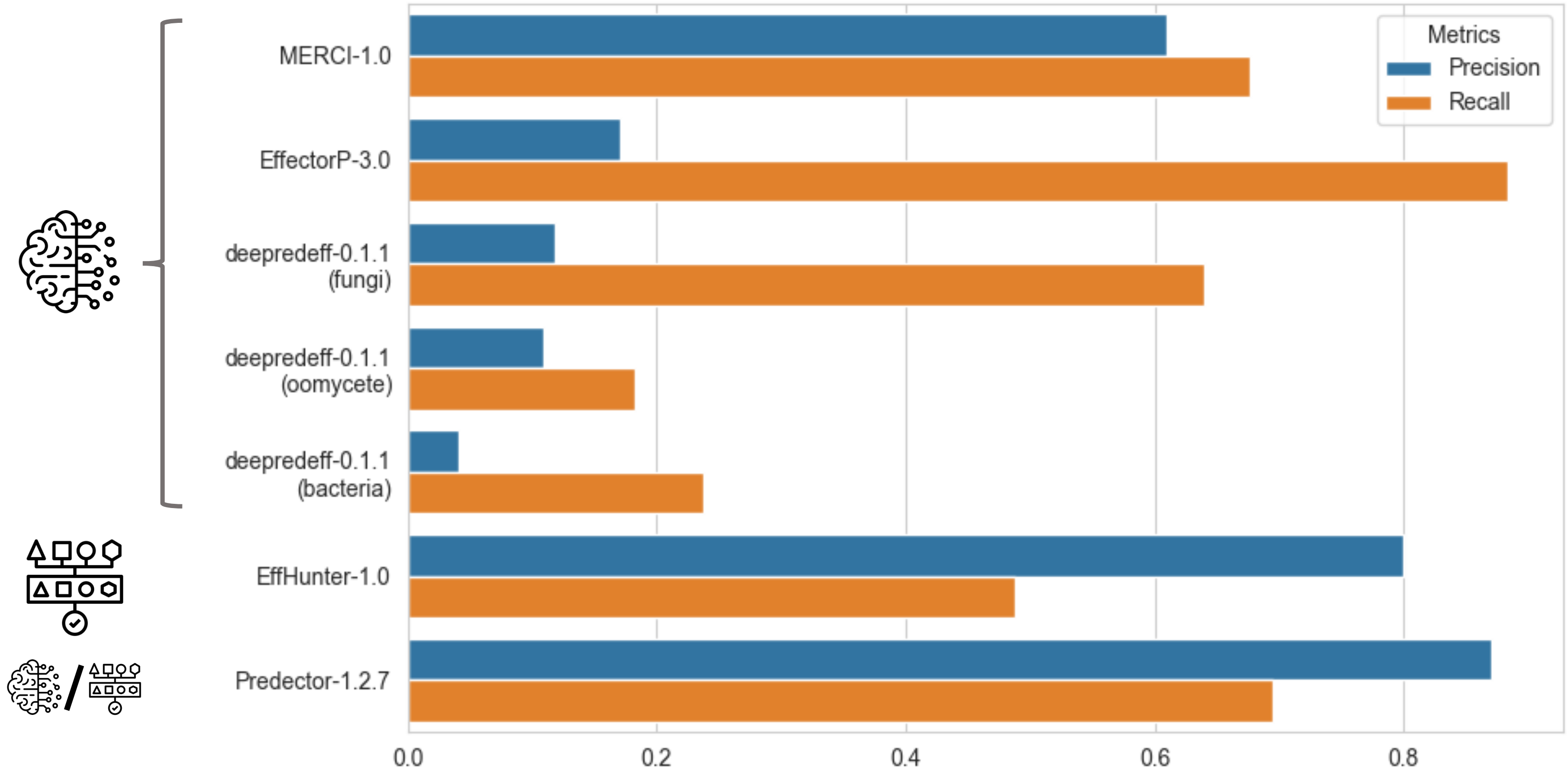

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- effectors proteins are poorly conserved. Hence, no simple discriminative characteristics.
- Tools were not trained on PPNs ( ).

Methodology : Predict effector proteins, a challenging task

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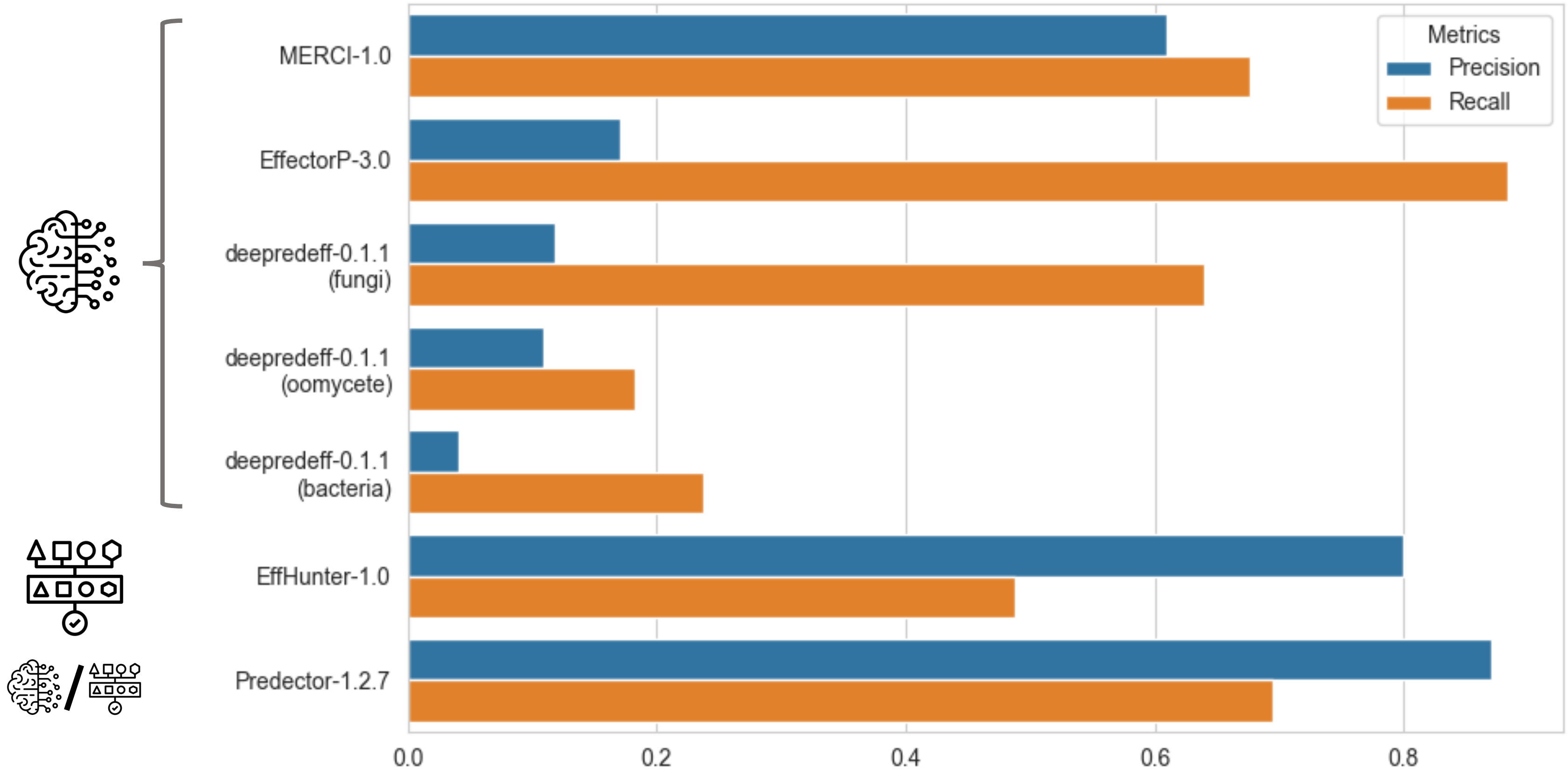

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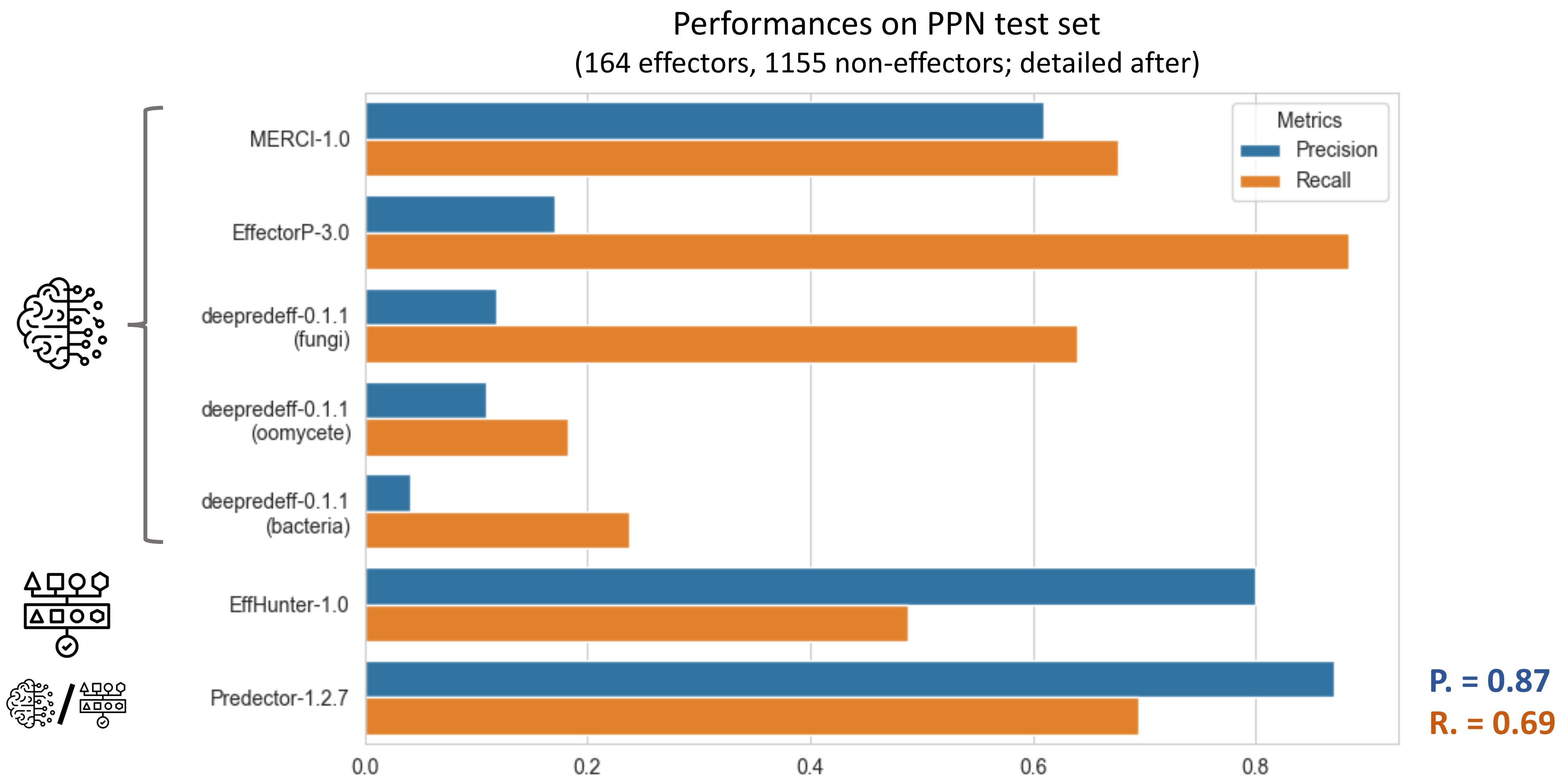

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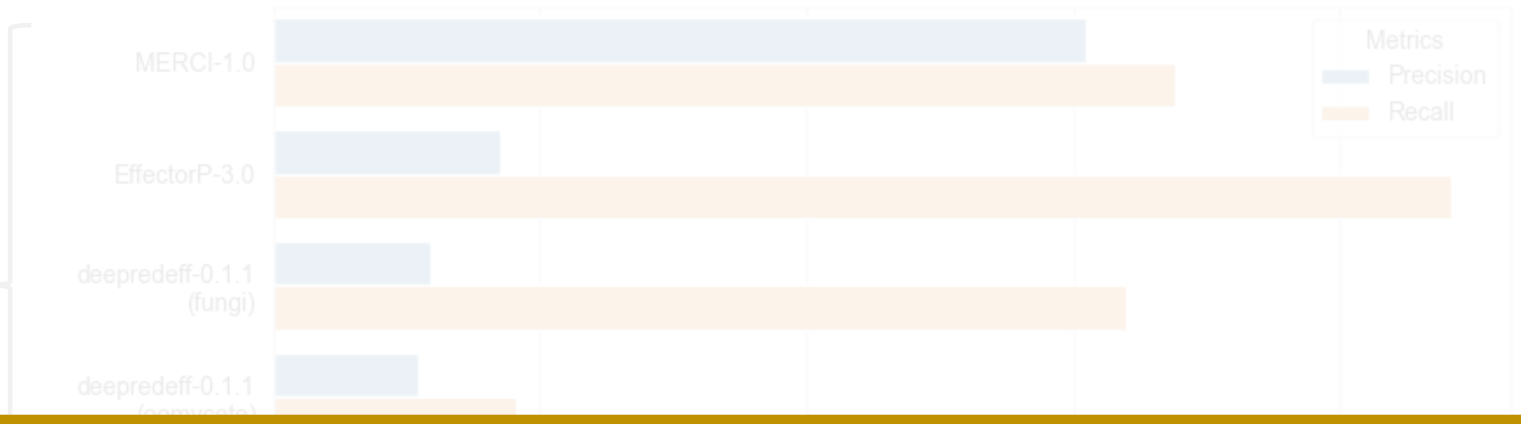

$$\text{Precision} = \frac{TP}{TP + FP}$$

Existing tools are not suited for PPNs.

It is necessary to develop a new tool to efficiently predict and rank protein effector candidates for experimental validation

Drawbacks:

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- No availa... ...stics.
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Methodology : NERD, a NLP approach to effector prediction (FRAMEWORK)

NERD

NLP based encoder (pre-trained)
Elnaggar *et al.*, IEEE, 2021

Binary classifier (NN)

Methodology : NERD, a NLP approach to effector prediction (FRAMEWORK)

NERD

>seq
MKSKLVAILMALMAFY

Pre-trained ProtT5-XL-UniRef50 (encoder only) [1]

Language model (auto-encoder T5)
trained on Uniref50
(45 million proteins, whole tree of life)

words

M K S K L V A I L M A L M A F Y

sentence

Embedded sequences

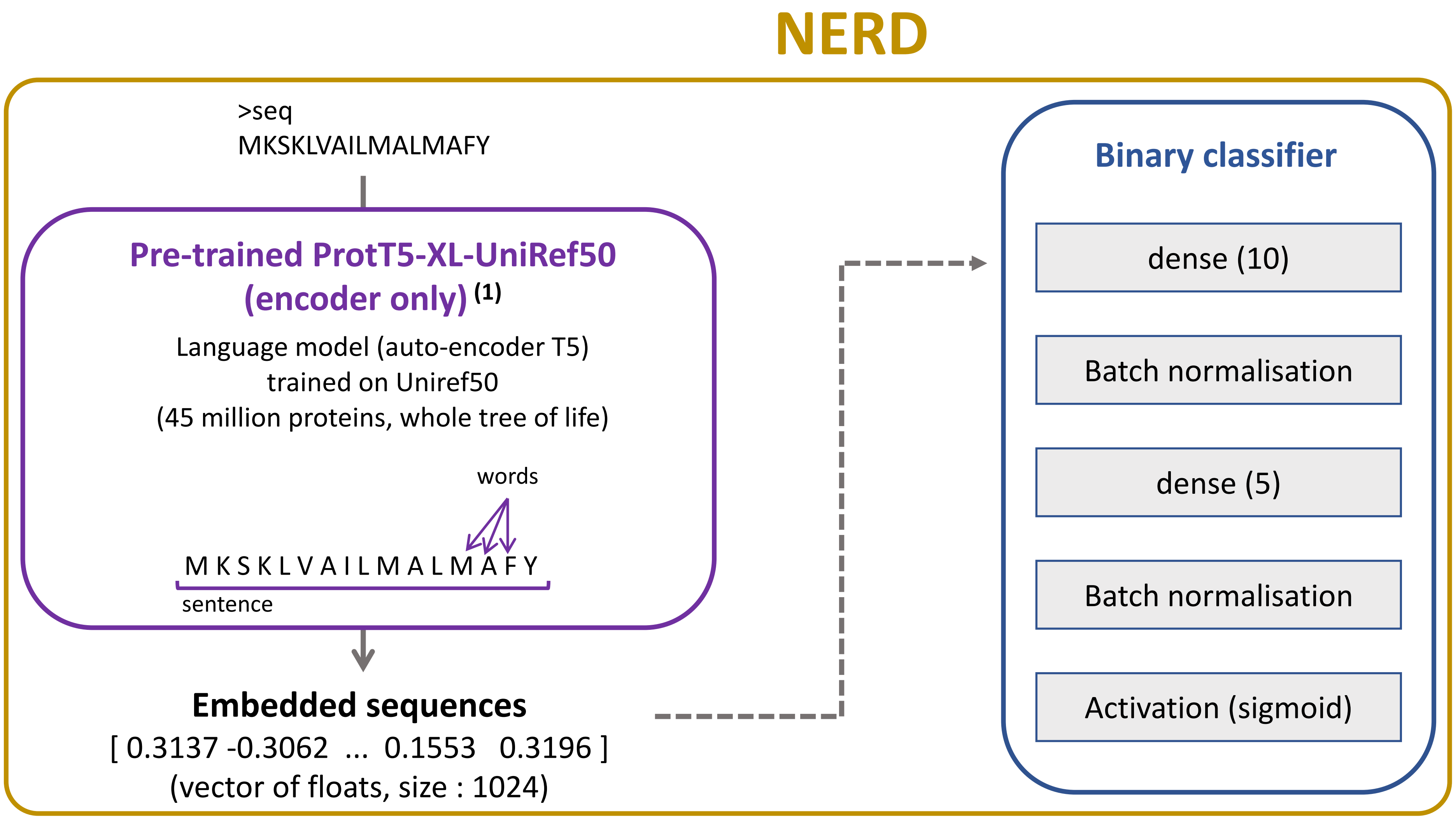
[0.3137 -0.3062 ... 0.1553 0.3196]

(vector of floats, size : 1024)

Binary classifier (NN)

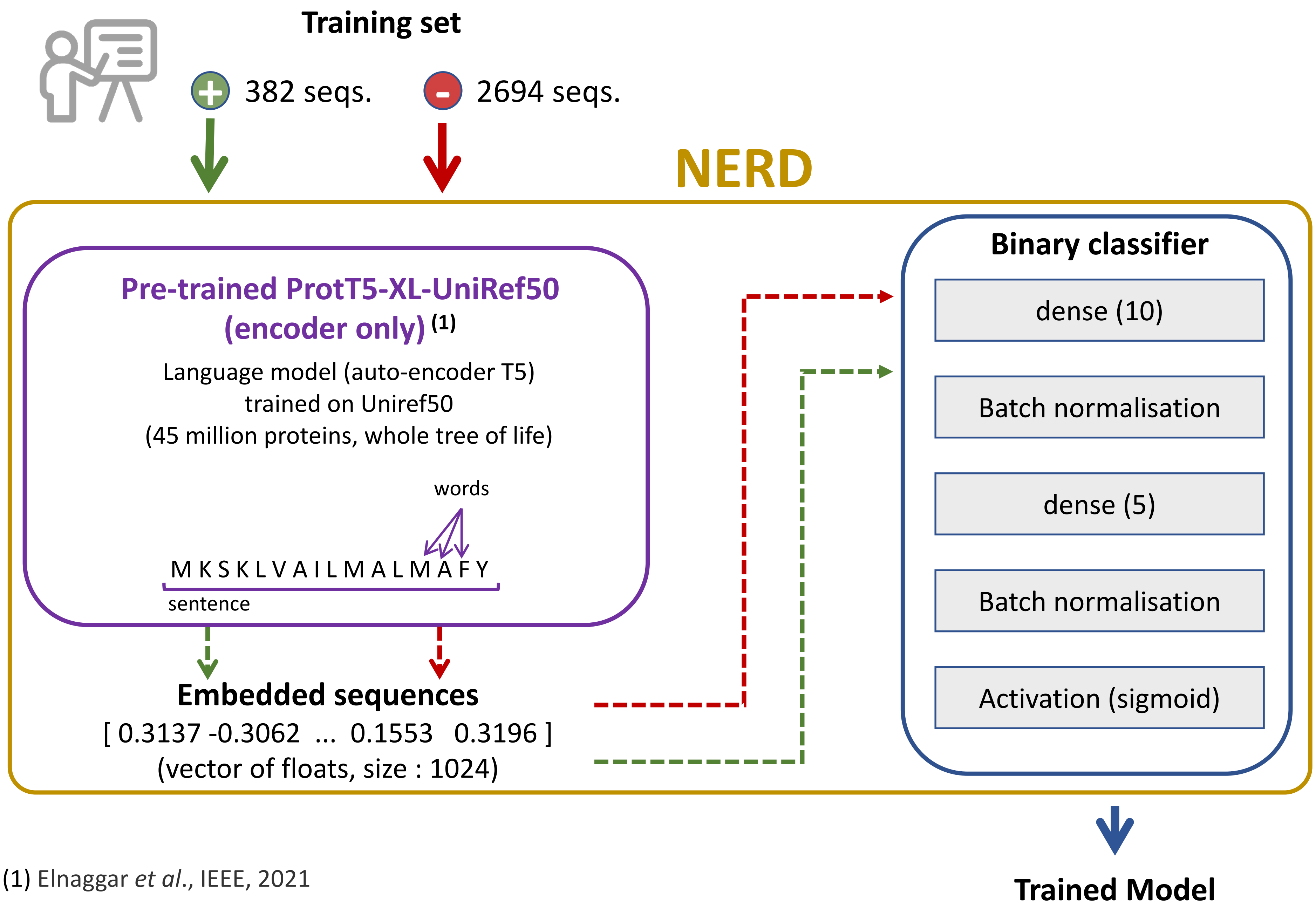
(1) Elnaggar *et al*., IEEE, 2021

Methodology : NERD, a NLP approach to effector prediction (FRAMEWORK)



(1) Elnaggar *et al.*, IEEE, 2021

Methodology : NERD, a NLP approach to effector prediction (TRAINING)



Training parameters:
Loss : Binary cross-entropy
Optimizer : Adam
Max epochs : 500
Batch size : 32
Early stopping criterion : best weights
Patience (5)

Ressources (AZZURA) :
1 GPU (Testla V4)
8 CPU
32 Go ram

(1) Elnaggar *et al.*, IEEE, 2021

Methodology : NERD, a NLP approach to effector prediction (PREDICTION)

Protein sequences

> seq_1
MKSKLVAILMALMAFYA
> seq_2
MTETMLDCSDKVTESKE

NERD

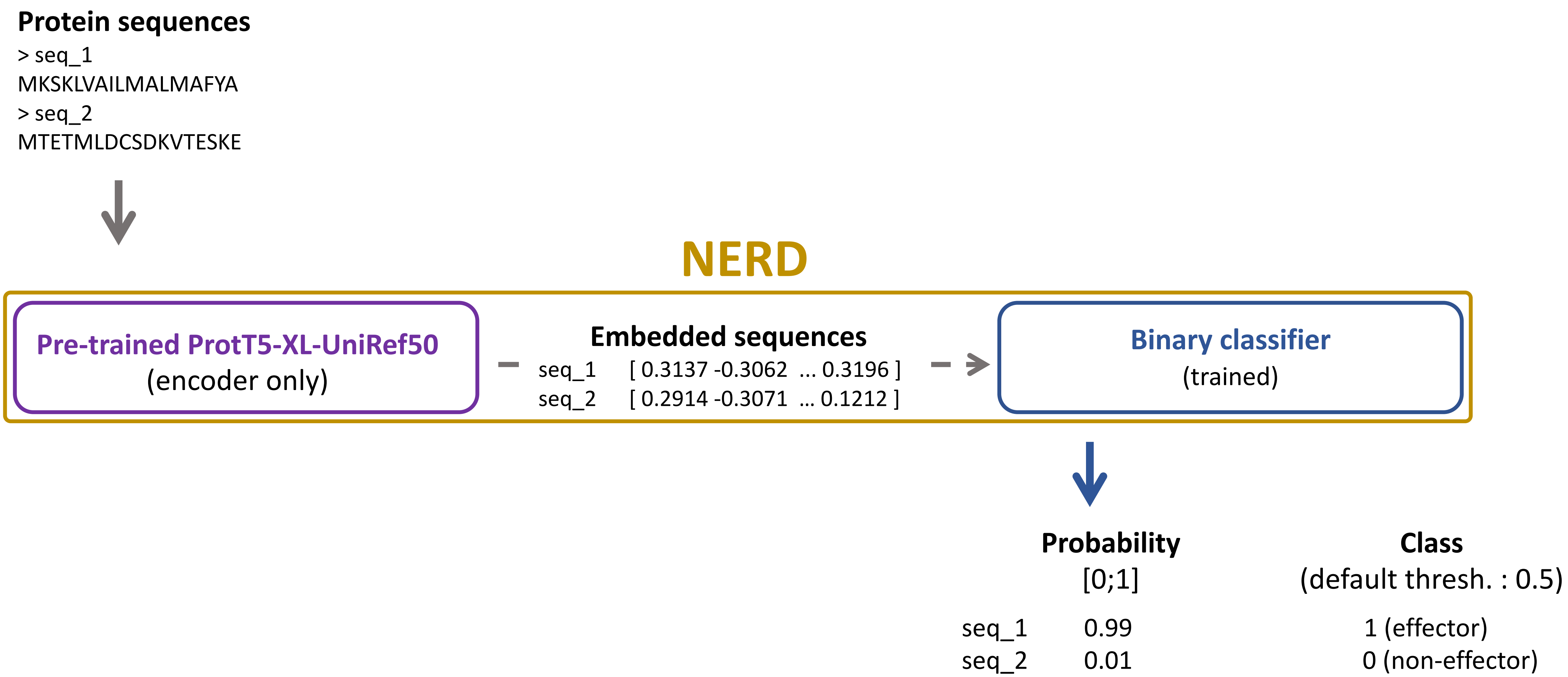
Pre-trained ProtT5-XL-UniRef50
(encoder only)

Embedded sequences

seq_1 [0.3137 -0.3062 ... 0.3196]
seq_2 [0.2914 -0.3071 ... 0.1212]

Binary classifier
(trained)

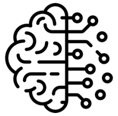
Methodology : NERD, a NLP approach to effector prediction (PREDICTION)



NERD performances evaluation and comparison with existing methods (test set)

Tools

NERD (trained)



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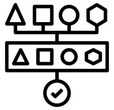
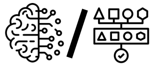


[(4)] EffHunter-1.0



[(5)] Predector-1.2.7

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NERD performances evaluation and comparison with existing methods (test set)

Test set

164 seqs.

1155 seqs.

Tools

NERD (trained)

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Performances evaluation

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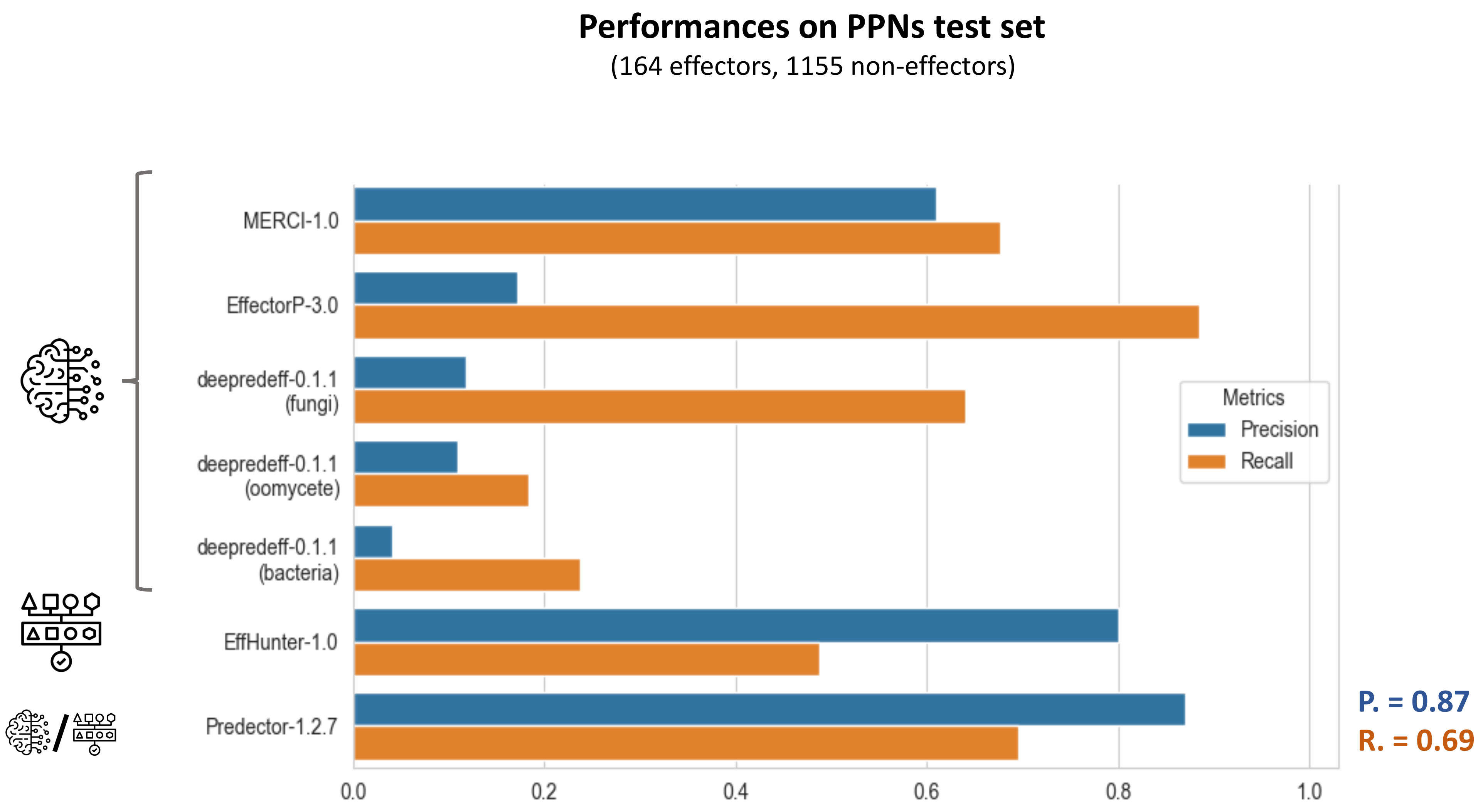

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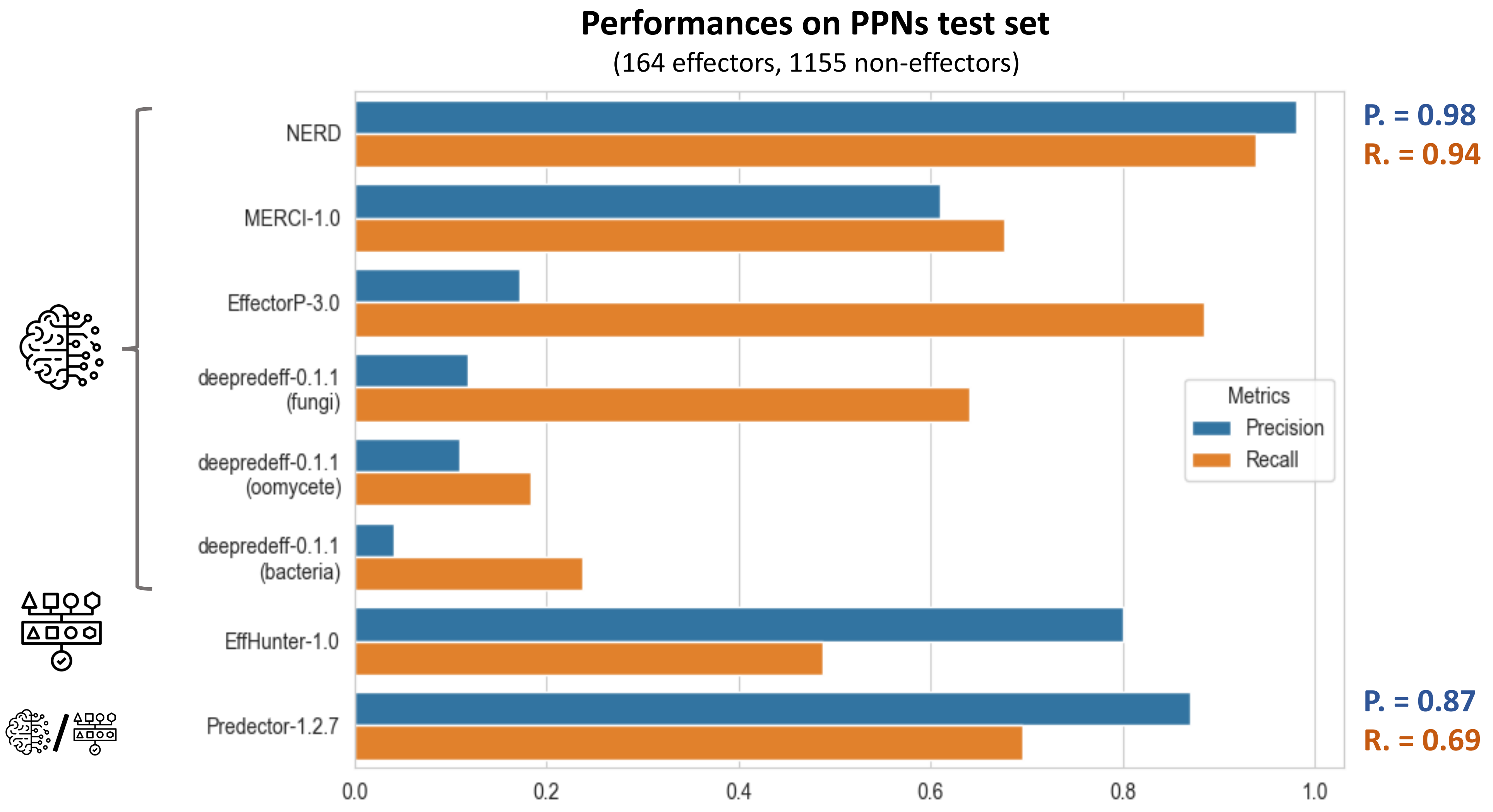
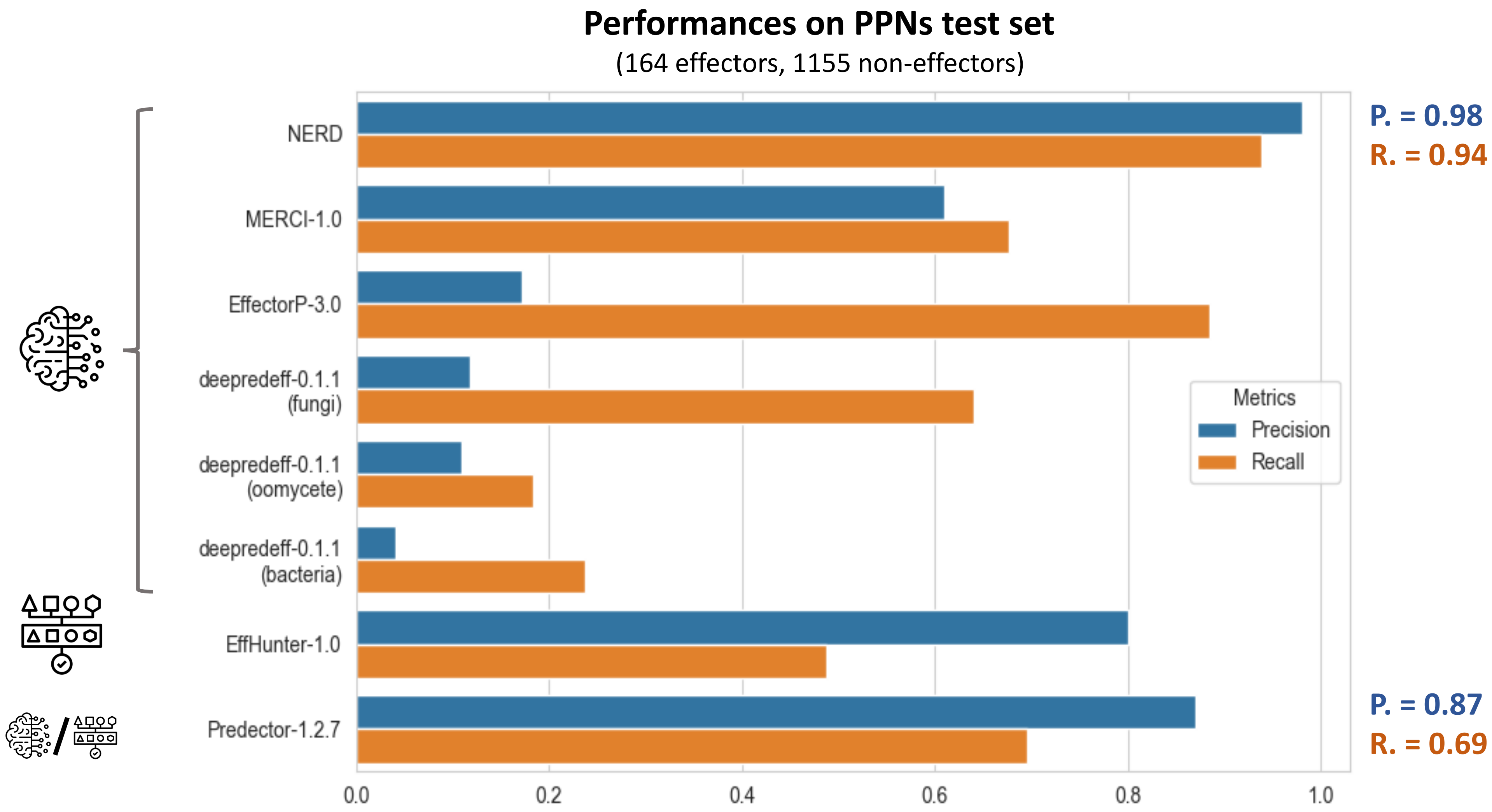


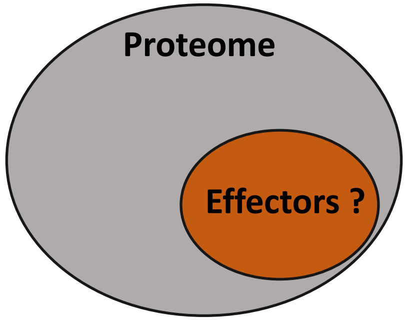
- NERD outperforms all the existing methods on the test set.

NERD performances evaluation and comparison with existing methods (test set)



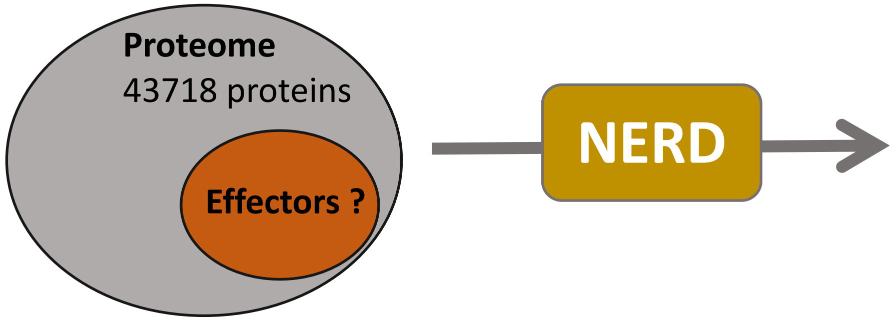
- NERD outperforms all the existing methods on the test set.
- NERD associates a probability to each sequence. Useful to rank the candidates for potential experimentation.

Real world predictions



Real world predictions

Meloidogyne incognita
Plant-parasitic Nematode



6985 candidates (15.9 %)

Real world predictions

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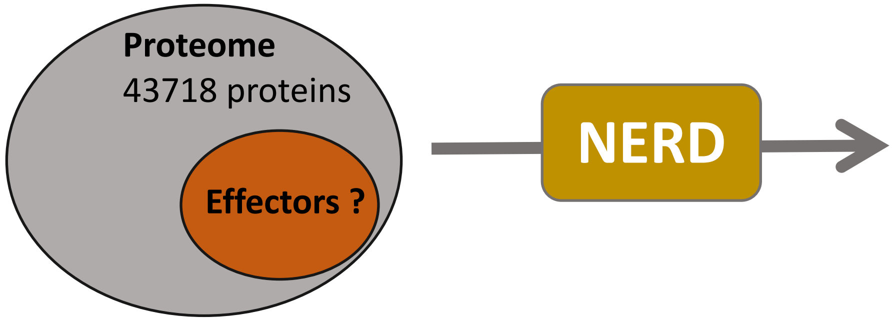

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- High number of candidates but consistent with organism life style (multiple protein needed to parasitise).

Real world predictions

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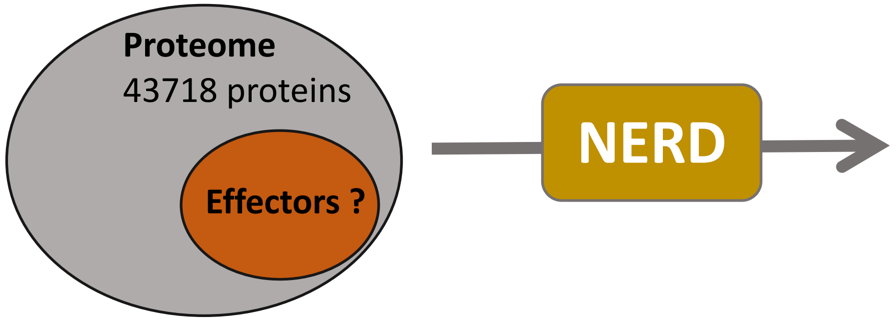
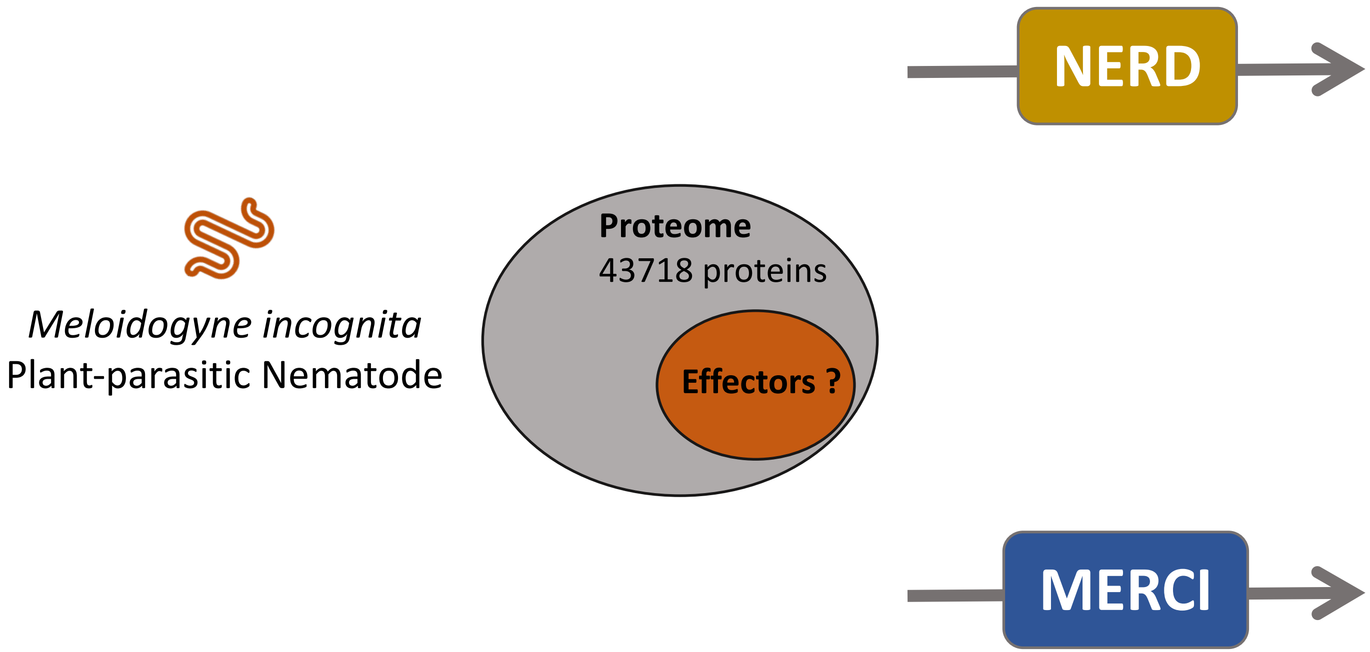


6985 candidates (15.9 %)

- High number of candidates but consistent with organism life style (multiple protein needed to parasitise).
- Finds 100% of *M. incognita* known effectors from positive test set (33 seqs.) with a prob. >= 0.999199

Real world predictions



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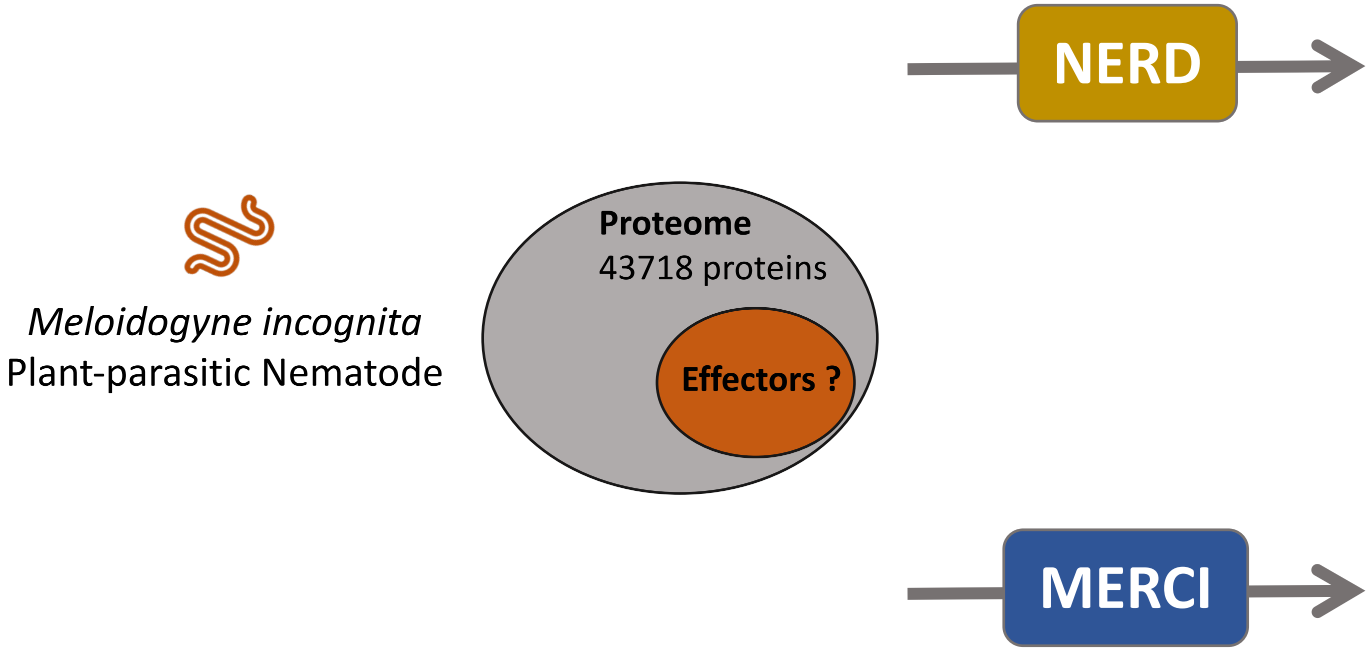

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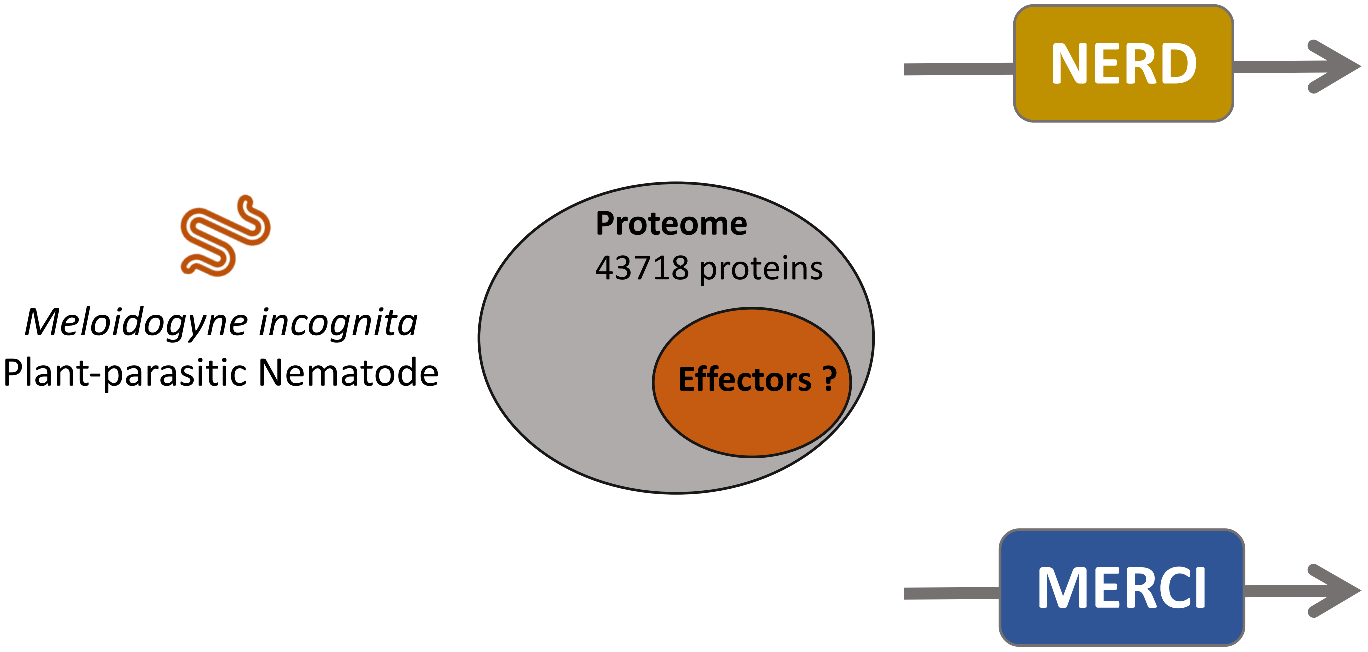

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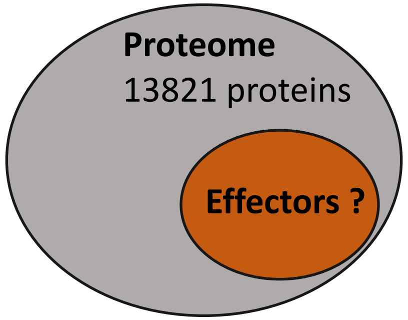
Limitations

Drosophila melanogaster

Not a nematode, not a plant parasite



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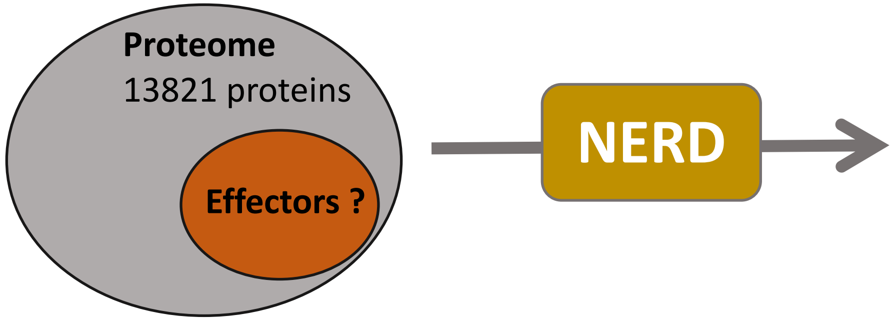

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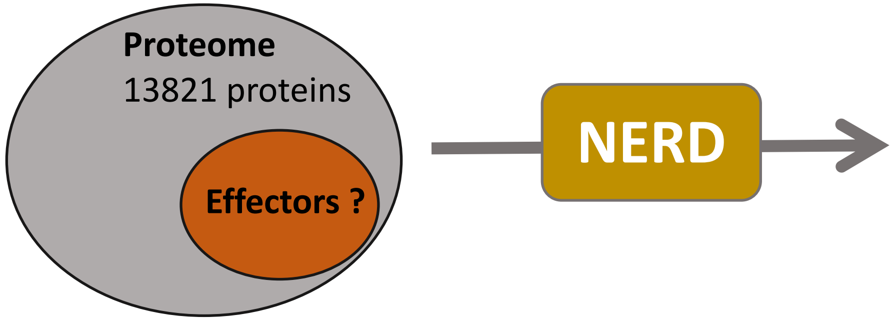

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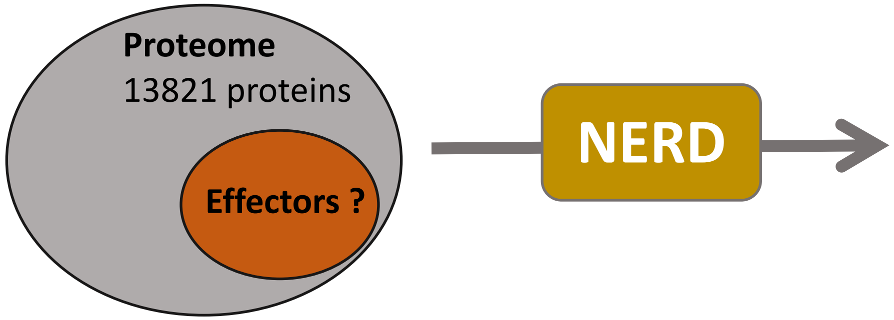

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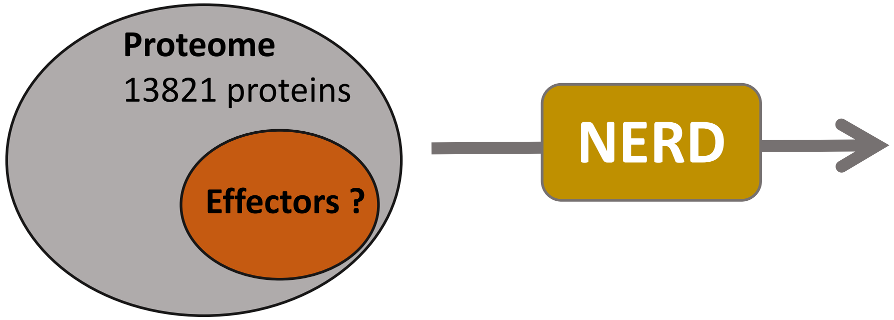

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BUT:

Molecular Plant Pathology

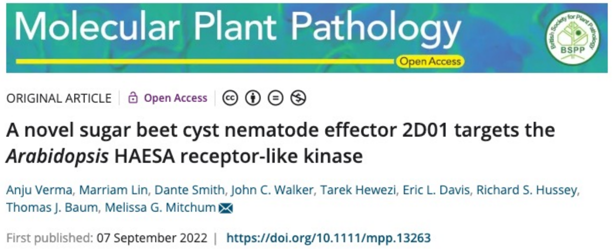
ORIGINAL ARTICLE | Open Access

A novel pine wood nematode effector, BxSCD1, suppresses plant immunity and interacts with an ethylene-forming enzyme in pine

Tong-Yue Wen, Xiao-Qin Wu, Long-Jiao Hu, Yi-Jun Qiu, Lin Rui, Yan Zhang, Xiao-Lei Ding, Jian-Ren Ye

First published: 16 August 2021 | https://doi.org/10.1111/mpp.13121 | Citations: 1

Predicted proba. : 0.9999



Molecular Plant Pathology

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A novel sugar beet cyst nematode effector 2D01 targets the *Arabidopsis* HAESA receptor-like kinase

Anju Verma, Marriam Lin, Dante Smith, John C. Walker, Tarek Hewezi, Eric L. Davis, Richard S. Hussey, Thomas J. Baum, Melissa G. Mitchum

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Proteome
13821 proteins

Effectors ?

NERD

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TAKE HOME MESSAGES

NERD:

- outperforms existing tools on PPNs data.

- is useful to efficiently predict effectors in PPNs and will help experimental biologist in their candidate choice.

- gives good results despite small amount of positive sequences, a considerable plus for biology where sample can be scarce.

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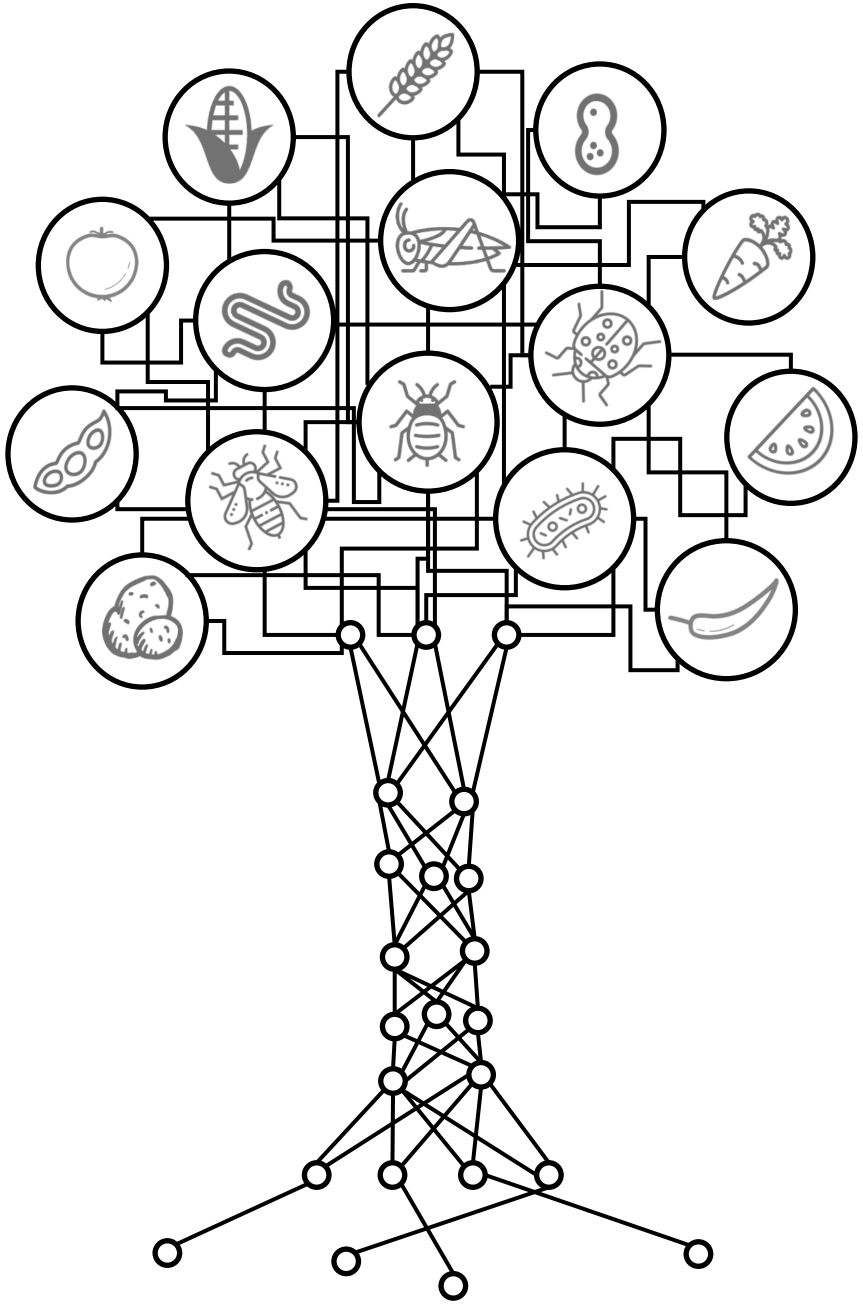
Future improvements:

- NERD is still a work in progress : we noticed generalisation issues outside the PPNs which need to be further investigated.
- Extend NERD (new models) to other plant parasites which produce effectors proteins (mycetes, oomycetes)
- Study NERD predictions to identify underlying protein characteristics related to parasitism (Explanatory Learning)
- Other suggestions ?



NERD (Nematode EffectoR Discovery) : a tool to predict proteins involved in nematodes' plant parasitism.

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Thank you for your attention !