KTH
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AI for Research in Biology

EQ2461 seminar course — Feb 5th, 2025

Antoine Honoré (Postdoc)

Advisor: Prof. Ming Xiao

Outline

Introduction

Research in Biology

Cell Functions

Variant effect prediction

Proteins

Evolutionary constrain assumption

Data

Predictors

More predictors, based on Transformers

Future perspectives

Conclusions

Introduction: Research in Biology

- Study of living organisms and their interactions with the environment
- Aim: understanding of the principles and processes that govern life at different levels, e.g. molecular, or generally at organism level:
  - (Molecular biology) What is the molecular basis for cell function ?
  - (Physiology) How did specific chemical/physical functions emerge in a biological system ?
- Research in biology can be either
  - Basic: Discovering the determinants of functions in living organisms
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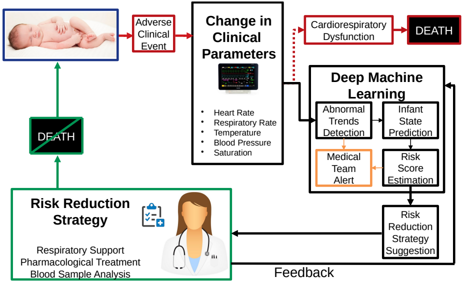
Human physiology

- Basic research: How do infections affect the internal stability of the body ? [1]
- Applied research: Is it possible to leverage the observation of physiological patterns to predict the onset of an infection ? [2]



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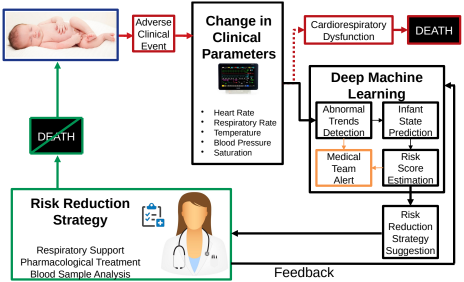

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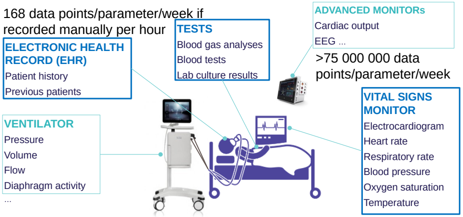
- Research: conclusions are limited in part by the ability to collect sufficiently large datasets to account for all sources of variance in the problem
- Recent techniques allow to collect (and store) large databases, e.g. :
  - Human physiology : observed with a multitude of high-throughput sensors
  - Cell biology : variant-cell function maps are sampled abundantly & efficiently with deep mutational scanning experiments



168 data points/parameter/week if recorded manually per hour

ELECTRONIC HEALTH RECORD (EHR)
Patient history
Previous patients

TESTS
Blood gas analyses
Blood tests
Lab culture results

ADVANCED MONITORs
Cardiac output
EEG ...

>75 000 000 data points/parameter/week

VENTILATOR
Pressure
Volume
Flow
Diaphragm activity
...

VITAL SIGNS MONITOR
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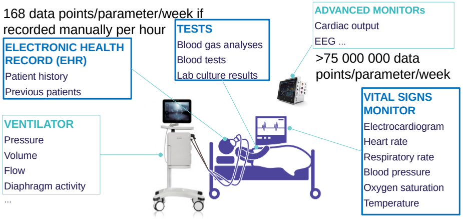

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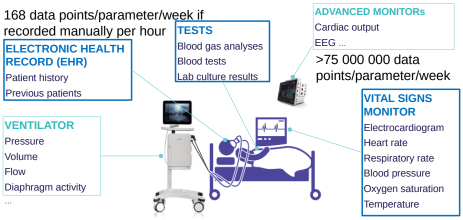

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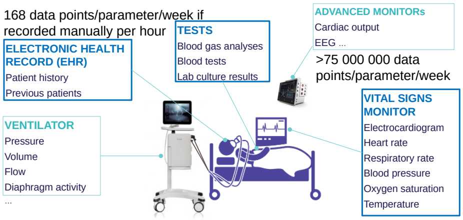

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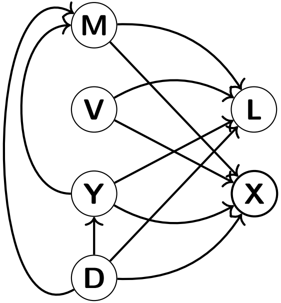
- This allows to make inference in networks such as:



Legend

- **M**: Medication
- **L**: Laboratory values (Blood gas analysis)
- **D**: Demographics (including age)
- **V**: Mechanical Ventilation
- **Y**: Clinical condition
- **X**: Vital signs
- **G**: Genetic background

- Instead of being limited to simpler networks such as : **Y** → **X**.

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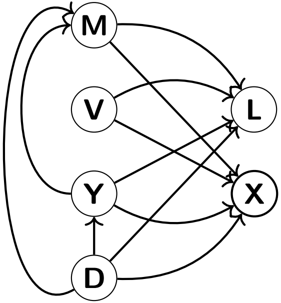

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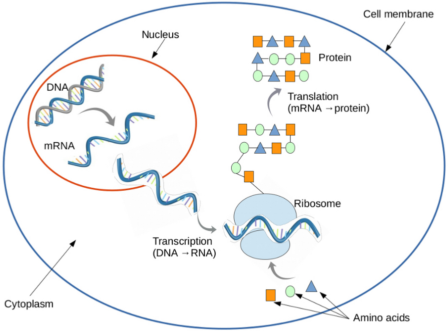
- Basic research: How do variations (mutations) in the genome affect the function of certain proteins in cells ? [3]
- Applied research: From a variant → cell function prediction tool, can we predict the effect of a chemotherapy drug on a cancer patient ? [4]



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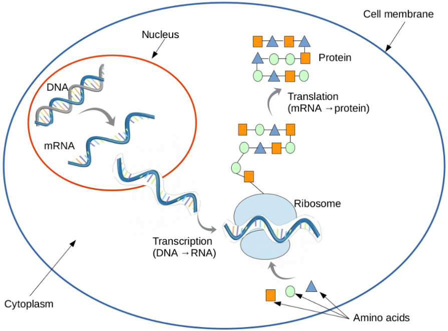

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- The functions in cells are determined by proteins:

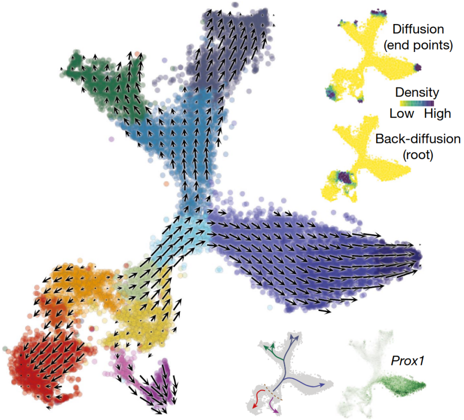

Figure: Each point is related to the 2d-projection of the proteome of a cell for an organism. Each color represents a group of cells with similar function.

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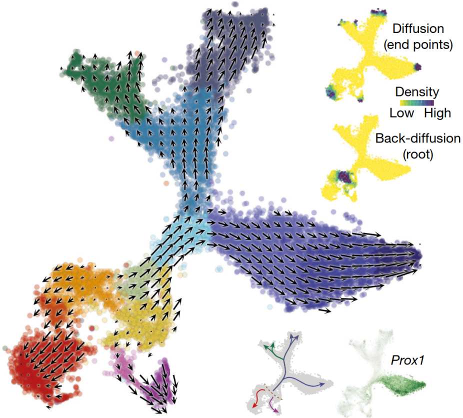

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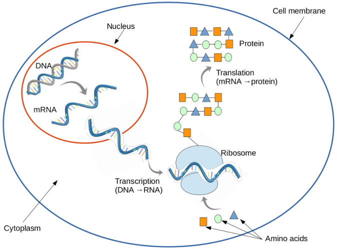

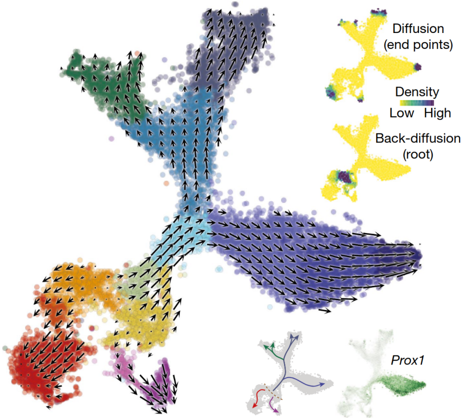

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Variant effect prediction: Proteins

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In cells

- Sequences of elementary molecules: amino-acids (AA)
  - There are $d = 20$ amino-acids (in humans), each with p specific bio-physical properties, e.g. mass, volume.
  - The length of a protein is typically $L = 300$ AAs (can vary: 10-2000)
- Determined by their sequence of amino-acid:

  `PPGPTPLPVIGNILQIGIK...`
- Fold into different 3D-structures because of the bio-physical properties of AAs.

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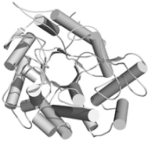
avGFP

Bgl3



GB1

Variant effect prediction: Proteins

Encoding

Proteins can be encoded as

① sequences of one-hot vectors in $\{0,1\}^d$, i.e. $\underline{\mathbf{x}} \in \{0,1\}^{L\times d}$, (using the alphabet of AAs).

② sequences of vectors in $\mathbb{R}^p$, i.e. $\underline{\mathbf{x}} \in \mathbb{R}^{L\times p}$, (using p bio-physical properties).

③ graph signals: $(\underline{\mathbf{x}}, \mathcal{E})$, where there is an edge (collected in the set $\mathcal{E}$) between two amino-acids (the nodes) if the amino-acids are close in 3D space.

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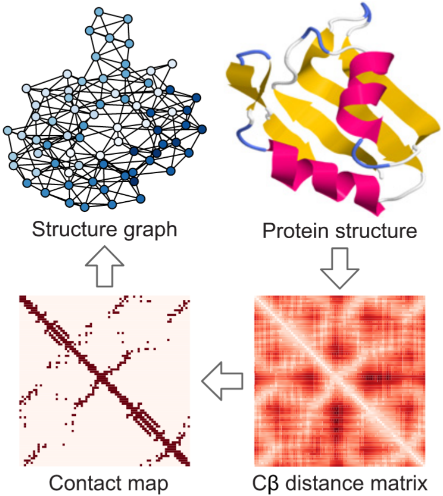

Variant effect prediction: Proteins

Why predicting protein variant effects ?

- In our project we focus on drug transporter proteins:
  - Membrane proteins involved in drug absorption, distribution, metabolism and excretion (ADME) [5].
- Loss-of-function variants are directly related to an individual's ability to respond to a drug treatment, e.g. chemotherapy.
- Being able to predict the effect of variants on these proteins can help select personalized patient treatments.

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Formulated in terms of positional information content

- Given N observations of a certain protein, e.g. across species:
  - Positions where many observations have the same amino-acids are functionally important
    - Why? because preserved by evolution.
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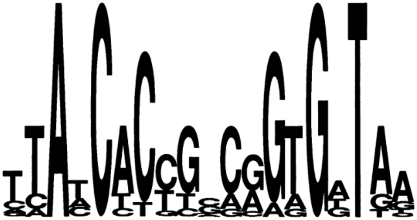

A sequence logo. From [7].
x-axis: Position in a sequence of AA

y-axis:

- At each position i, $f_{i,j}$ the frequency of letter j
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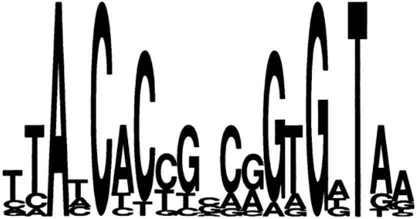

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- Another way to phrase it, found in [8]:
  1. The distribution of protein sequences observed in nature is the result of billions of evolutionary experiments
  2. Unfit variants were selected out
  3. By learning a distribution over these sequences we implicitly capture the biochemical constraints that characterize fit variants

The degree of fitness of a variant can be quantified as a log-likelihood ratio:

$$\ln \frac{p(\underline{\mathbf{x}}^{(v)}|\theta)}{p(\underline{\mathbf{x}}^{(wt)}|\theta)}, \qquad (1)$$

- $\underline{\mathbf{x}}^{(v)}$ (resp. $\underline{\mathbf{x}}^{(wt)}$): the encoded sequence with (resp. without) the variant.
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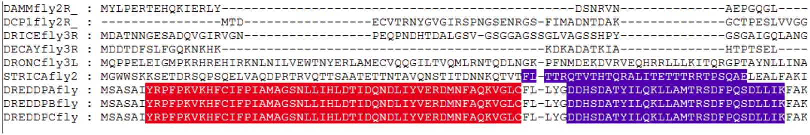
Variant effect prediction: Data

Multiple Sequence Alignment (MSA)

Observations of a protein in different organisms

- Aligned sequencing outputs for different observations of a protein:



```
DAMMfly2R_ : MYLPERTEHQKIERLY----------------------------------------------DSNRVN---------------AEPGQGL----
DCP1fly2R_ : ----------------MTD-----------------ECVTRNYGVGIRSPNGSENRGS-FIMADNTDAK--------------GCTPESLVVGG
DRICEfly3R : MDATNNGESADQVGIRVGN-----------------PEQPNDHTDALGSV-GSGGAGSSGLVAGSSHPY--------------GSGAIGQLANG
DECAYfly3R : MDDTDFSLFGQKNKHK-------------------------------------------KDKADATKIA--------------HTPTSEL----
DRONCfly3L : MQPPELEIGMPKRHREHIRKNLNILVEWTNYERLAMECVQQGILTVQMLRNTQDLNGK-PFNMDEKDVRVEQHRRLLLKITQRGPTAYNLLINA
STRICAfly2 : MGWWSKKSETDRSQPSQELVAQDPRTRVQTTSAATETTNTAVQNSTITDNNKQTVTFL-TTRQTVTHTQRALITETTTRRTPSQAELEALFAKI
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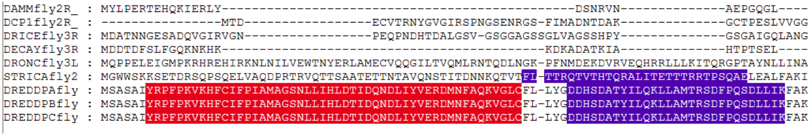
Variant effect prediction: Data

Multiple Sequence Alignment (MSA)

Observations of a protein in different organisms

- Aligned sequencing outputs for different observations of a protein:



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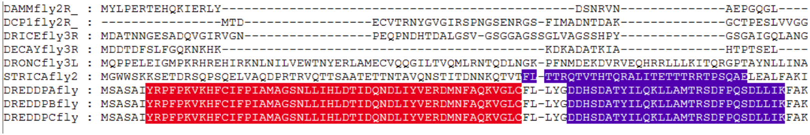

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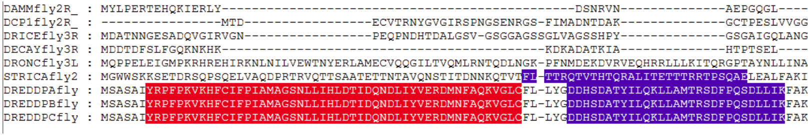

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Deep Mutational Scanning

Hard-coding mutations in cells

① Create a collection of cells with many single variants

- Sequence the collection of cells to get a count of the initial variants (✤)

② Expose the cells to an environment

- Sequence again and count the remaining variants (✦)

③ Compare ✦ and ✤ to get a cell variant ”survival score”

Output

$\{(X, y)\}$: X a varied sequence and $y \in \mathbb{R}$ a regression target !

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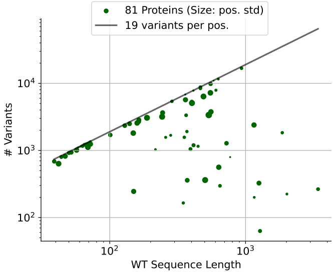

Figure: Position coverage of many experiments

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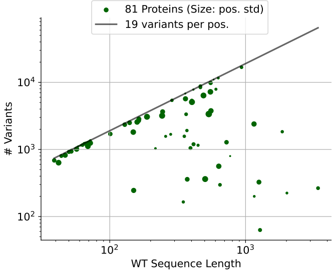

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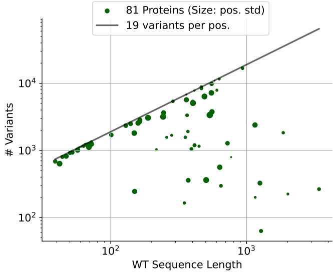

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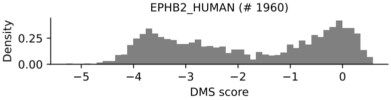

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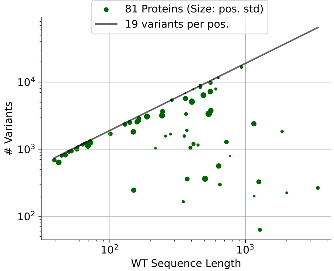

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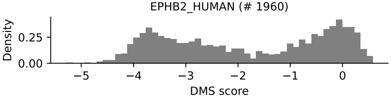

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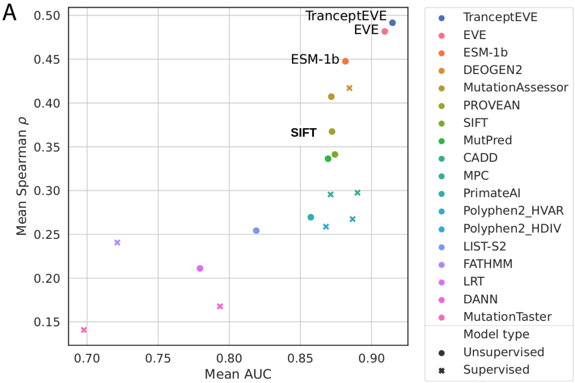
Variant effect prediction: Predictors

Benchmarking

Models are evaluated on variants used in a DMS experiment, and referenced in a clinical database.

1. x-axis: AUC (Area under the receiver-operating curve)
   - Computed against clinical observation
2. y-axis: Correlation between the rank predicted and the rank in the DMS experiment.



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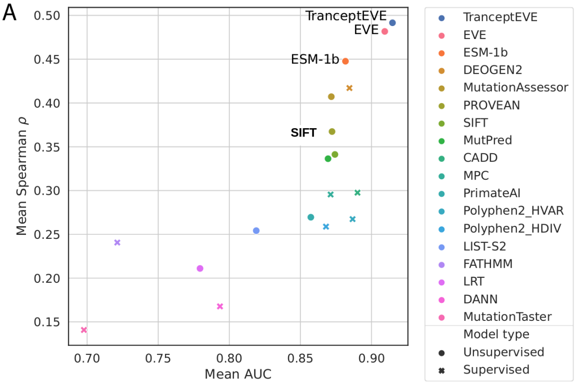

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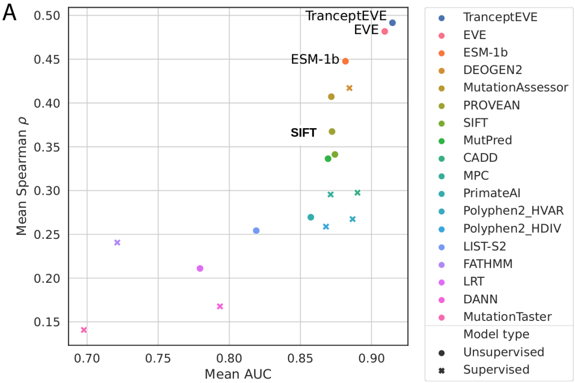

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Predictors: SIFT

SIFT: Sorting Intolerant From Tolerant

① Given an input WT sequence and a variant

② Query databases to find similar aligned sequences

③ Computes Shannon entropy at each position [10]

④ Sum to high entropy $\implies$ likely benign variant.

Limitations

① The prediction depends upon the similar sequences that were queried

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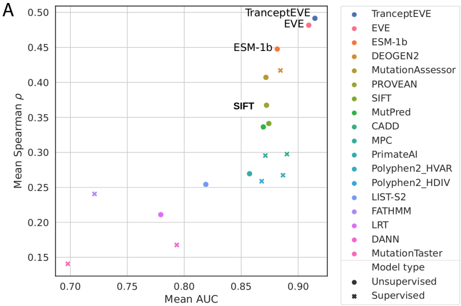

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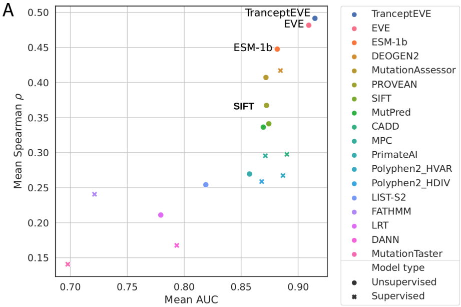

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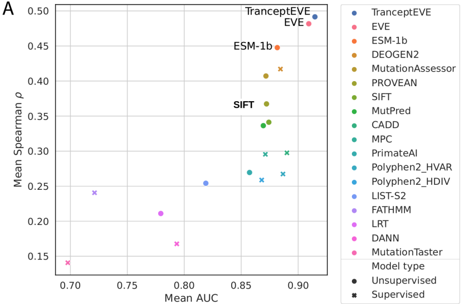

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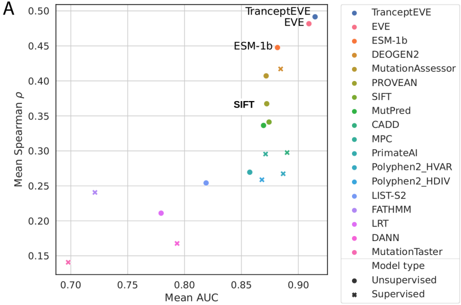

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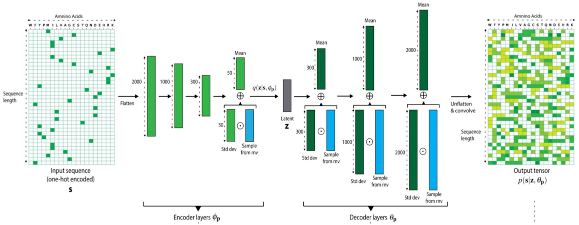
Predictors: Deep Sequence

Deep Sequence

A variational auto-encoder (VAE) [3]

- Learn the parameters of the log-likelihood by maximizing a lower bound



Limitations

① Vectorized input !

- Needs retraining on new proteins

② Unimodal distribution in the latent space

- Limit expressivity of latent vectors

③ For inference, the ratio of likelihoods is replaced with a ratio of lower bounds:

$$\ln \frac{p(\underline{\mathbf{x}}^{v}|\theta)}{p(\underline{\mathbf{x}}^{wt}|\theta)} \approx \ln \frac{\mathcal{L}_{VLB}(\underline{\mathbf{x}}^{v}|\theta)}{\mathcal{L}_{VLB}(\underline{\mathbf{x}}^{wt}|\theta)} \qquad (2)$$

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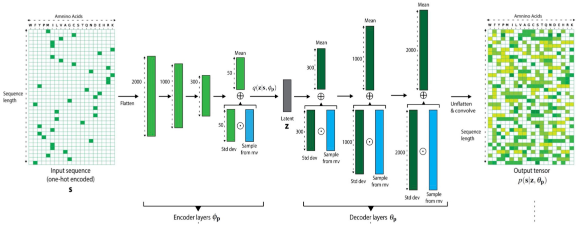

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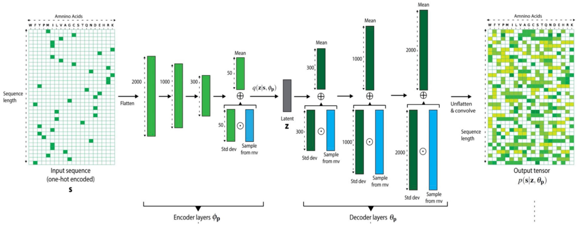

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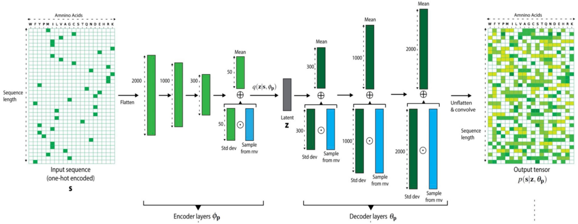

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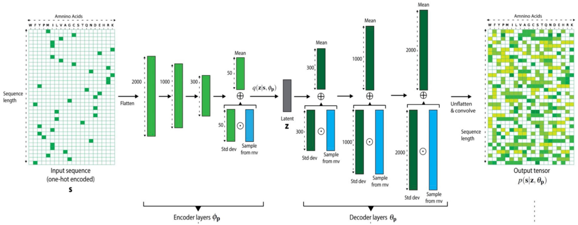

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Predictors: Deep Sequence

My current work: addressing the limitations of DeepSequence

- Allow multimodality in the latent space:
  - Mixture of Gaussian, instead of Gaussian ?
  - Did not work, the mixture was not used by the model.
- Better idea:
  - Latent space = probability simplex
  - Replace D_{KL} with entropy of latent vector in the lower bound

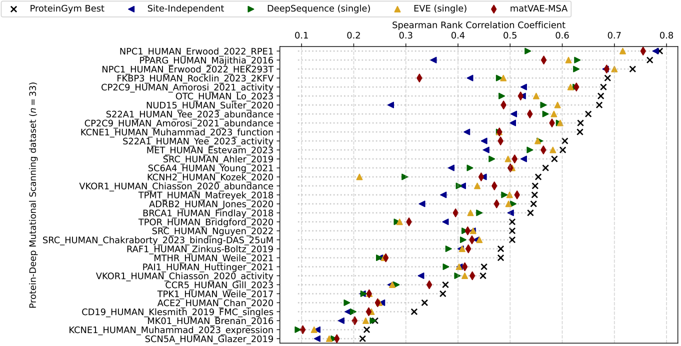
Recall: $\ln p(\mathbf{x}) = D_{KL}\left(q_\phi(\mathbf{z}|\mathbf{x})||p(\mathbf{z}|\mathbf{x})\right) - D_{KL}\left(q_\phi(\mathbf{z}|\mathbf{x})||p(\mathbf{z})\right) + \mathbb{E}_{q_\phi(\mathbf{z}|\mathbf{x})}\left[\ln p_\theta(\mathbf{x}|\mathbf{z})\right]$

Predictors: Deep Sequence

My current work: addressing the limitations of DeepSequence

- Less parameters (8-9M) (no need for Bayesian decoder)
- More interpretability,
- Better/similar results!

Model name	Spearmanr
Best Benchmark	0.529 ± 0.151
EVE (single)	0.432 ± 0.161
matVAE-MSA	0.428 ± 0.15
DeepSequence (single)	0.412 ± 0.149
Site-Independent	0.39 ± 0.145



More predictors, based on Transformers: ESM

ESM: Evolutionary Scale Modeling

A protein model with $650M$ parameters [11]

① Given an input varied sequence $\underline{\mathbf{x}}^v = (\mathbf{x}_1, \ldots, \mathbf{x}_L)^T$, the statistical model is similar to a large language model :

$$p(\underline{\mathbf{x}}^v|\theta) = \prod_{i=1}^{L} p(\mathbf{x}_i|\mathbf{x}_{N(i)}, \theta), \qquad (3)$$

with $N(i)$ a randomly masked neighborhood for i.

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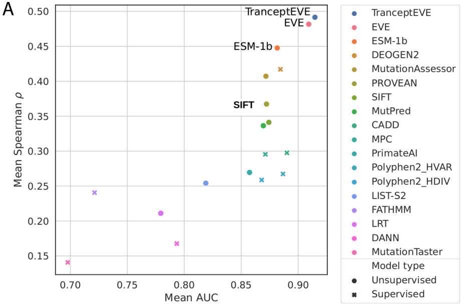

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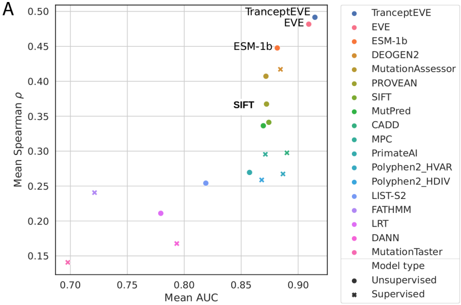

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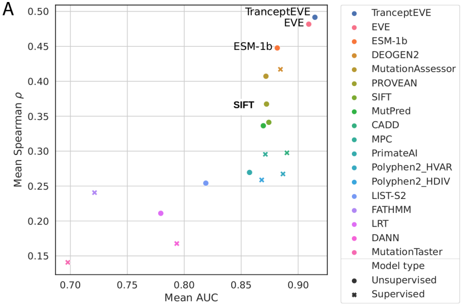

More predictors, based on Transformers: TranceptEVE

TranceptEVE: Tranception + EVE

An auto-regressive protein language model combined with other models [3]

- Tranception [12]: auto-regressive model, i.e. similar to ESM but the neighborhood is all the previous AAs.

$$p_T(\mathbf{x}_1, \dots, \mathbf{x}_L | \theta) = \prod_{i=1}^{L} p_T(\mathbf{x}_i | \mathbf{x}_{i-1}, \dots, \mathbf{x}_1, \theta). \tag{5}$$

- The final log-likelihood is computed as a convex combination of log-likelihood from other models:

$$\log p(\underline{\mathbf{x}} | \theta) \propto \sum_{i=1}^{L} (1-\beta)[(1-\alpha)\log p_T(\mathbf{x}_i | \mathbf{x}_{<i}) + \alpha \log p_R(\mathbf{x}_i)] + \beta \log p_E(\mathbf{x}_i), \tag{6}$$

- p_R is the empirical distribution from the MSA, p_E is the output of EVE, (α, β) are hyper-parameters which favor p_T when the MSA is shallow, i.e. unreliable.

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Future perspectives

1. Existing prediction models remain reliant on evolutionary constrain assumption:
   - Either through the informational or probabilistic formulation, or both.
   - Problem: Drug transporter proteins were not constrained by evolution (similar to nutriment transport in and out of cells)
2. Many models do not take into account the 3d structure of proteins:
   - A few works used graph neural networks, did not show very big improvements over e.g. CNN
3. Deep mutational scanning data are promising
   - Problem:
     - lack of standardization of experimental methods, i.e. output are not always numerically comparable.
   - Advantages:
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Conclusions

① We have seen what research in biology focuses on: understanding the processes that govern life

② We have seen how AI systems can be used to help research in biology

- i.e. have the potential to provide conclusive answers to difficult questions by integrating the large amount of data generated by technological advances

③ Certain models are at the forefront of research: graph neural networks, transformers, VAEs

④ Engineering efficient analysis pipelines remains important to harness powerful models and large datasets

Thank you !

SciLifeLab

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WASP
WALLENBERG AI,
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