Neural Pairwise Regression

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Agenda

Regressing Hard Targets

Reformulating Regression

Initial Investigation

Subsequent Steps

Supplementary Material

Regressing Hard Targets

Canonical Regression Problem

- Many fields seek **surrogate models** for arbitrary quantities of interest
  - solubility as a function of a molecular embedding instead of experiment
  - band gap as a function of formula instead of expensive simulation
- When target y is continuous this is a regression problem $y = f(x; \theta)$
  - x is some static or learned *embedding*
  - $f(\ldots; \theta)$ is an arbitrary model with parameters

Regression Methods

- Terminology is loose[1] but broadly we use:
  - Statistical Modeling (SM): (regularized) linear methods
  - Machine Learning (ML): Decision Trees, Neighbors-Based, and *Ensembles*
  - Artificial Intelligence (AI): Neural Networks (NNs)
- Broadly speaking, moving down that list:
  - requires more data to fit an accurate model because f has more parameters θ
  - offers a higher accuracy 'ceiling' and can fit 'harder' datasets
  - reduces interpretability

[1] Some use these interchangeably i.e. linear regression = AI

Canonical Neural Network

- NNs are especially popular
  - easy to train with high-level languages
  - trivial hardware acceleration
  - interpretability drawbacks secondary to improved performance
- Generality reduces the ‘time-to-model’

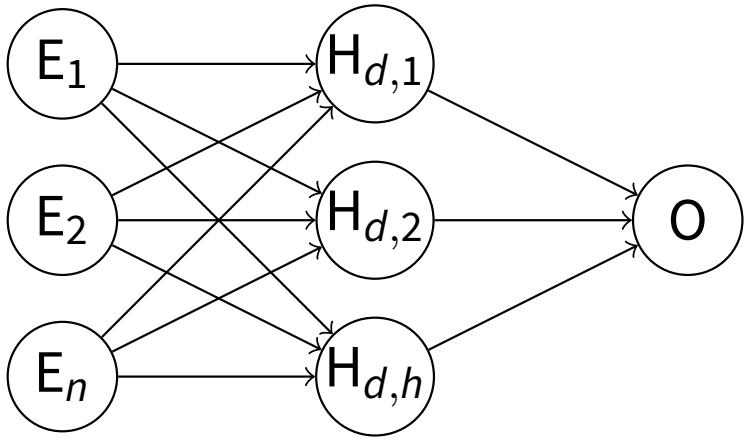


Figure 1: Schematic of typical Feedforward Neural Network with input encoding E of dimension n, Hidden Layers H of height h and depth d, and Output O. Arbitrary activation functions (i.e. ReLU) at output of each node not shown.

Data Limitations

- Large, high-quality datasets are rare
  - *especially* in science domains where experiments are expensive
  - negative ramifications for coverage of feature space
- Mapping structure $\rightarrow$ target is *hard*
  - static and learned representations are *very* high-dimensional, $O(100)$+ features
  - relationships are often unpredictably non-linear (i.e. Activity Cliffs, some examples in (Stumpfe et al., 2019))

The Wicked Problem

Neural networks are well-suited for our problems but we lack sufficient data to fit them accurately.

Reformulating Regression

Pairwise Regression

- We can address The Wicked Problem by recasting our regression problem to difference prediction:
  - instead of predicting the output directly: $y = f(x; \theta)$
  - we predict the *difference* in target for two inputs at a time: $y_1 - y_2 = \Delta_{1,2} = f(x_1, x_2; \theta)$
- This addresses our key constraint
  - quadratic increase in the amount of training data
- Offers additional benefits
  - ensemble of predictions during inference provides well-calibrated uncertainty estimates (Wetzel et al., 2020)
  - theoretical evidence that inference is easier (OOS vs OOD) (Netanyahu et al., 2023)

Pairwise Architecture

- Choose the most *basic* approach to achieve this mapping
  - inputs are directly concatenated
  - keeps SHAP-ability (Lundberg & Lee, 2017)
  - leans on NN Universal Approximation Theorem [a]

[a] Closed-form width and depth requirements for ReLU networks known (Shen et al., 2022)

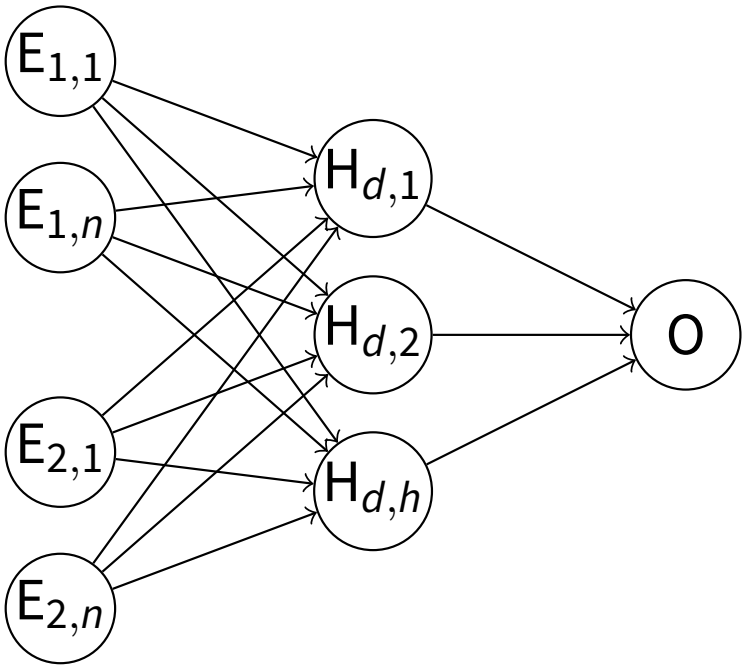


Figure 2: Schematic of a Neural Pairwise Regressor with concatenated input encodings $E_{i,n}$

Need for Naivete

Empirical exploration suggests avoiding **inductive bias** in NN architecture

- Literature has explored alternative design in the general case (see next slide)
- My previous work with collaborators explored it specifically for solubility (Attia et al., 2024)

Existing Alternatives

There are many ways to inject bias into the model:

- (Tynes et al., 2021): input $x_1 \oplus x_2 \oplus (x_1 - x_2)$ and use ML
  - inductive bias in input distance (i.e. unreduced manhattan) is probably unhelpful
- (Netanyahu et al., 2023): include an operation in later layers (i.e. subtraction) to enforce self 'loop'
  - do we really want to enforce this property?
- (Wetzel et al., 2020): additional latent layers for each input
  - makes it *possible* for network to learn a different embedding for each input 'branch' (bad!)
  - (Wetzel et al., 2021) moved away from this and has no embedding layers
  - a *shared* learnable embedding would be OK (foreshadowing)

The Bitter Lesson

Rich Sutton famously pointed out in a blog post [2] that in the Computer Vision world:

- architectures based on human intuition for how to process images failed
- Convolutional NNs (which have almost *no* inductive bias) dominate the space

The Bitter Lesson

The most general, scalable approach is the most effective.

One criticism of this argument is that hardware is no longer following Moore's law … but we (and 99.9% of people) aren't looking at a scale where that matters.

[2] Representative publication: (Yousefi & Collins, 2024)

‘Physics’ Constraints

There are a number of cases of the ‘cycle closure’ rule that we *might* want to enforce:

- Arbitrary loop: $\Delta_{1,2} + \Delta_{2,n} + \ldots + \Delta_{n,1} = 0$
  - Get this ‘for free’ with an accurate model
- Pairwise ‘loop’: $\Delta_{1,2} + \Delta_{2,1} = 0$
  - Requires positional invariance of inputs in f
- Self ‘loop’: $\Delta_{1,1} = 0$
  - Inductive bias in model architecture (i.e. subtract the latent representations) can explicitly enforce this

Visualizing Training Augmentation

We can take our inputs representations and x:

$$\mathbf{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix}, \quad \mathbf{x}^T = \begin{bmatrix} x_1 & x_2 & \cdots & x_n \end{bmatrix}$$

And generate all of the pairs with this matrix:

$$\begin{bmatrix} x_1 \oplus x_1 & x_1 \oplus x_2 & \cdots & x_1 \oplus x_n \\ x_2 \oplus x_1 & x_2 \oplus x_2 & \cdots & x_2 \oplus x_n \\ \vdots & \vdots & \ddots & \vdots \\ x_n \oplus x_1 & x_n \oplus x_2 & \cdots & x_n \oplus x_n \end{bmatrix}$$

Augmentation Impacts

Each part of the matrix enforces a different property by being present during training:

- Diagonal: Self loop [a]
- SUT *or* SLT [b]: general loop consistency
- SUT *and* SLT: Pairwise 'loop'

$$\begin{bmatrix} x_1 \oplus x_1 & x_1 \oplus x_2 & \cdots & x_1 \oplus x_n \\ x_2 \oplus x_1 & x_2 \oplus x_2 & \cdots & x_2 \oplus x_n \\ \vdots & \vdots & \ddots & \vdots \\ x_n \oplus x_1 & x_n \oplus x_2 & \cdots & x_n \oplus x_n \end{bmatrix}$$

[a] *Very* underrepresented (~1:n)

[b] Strictly Upper/Lower Triangular

Inference Augmentation

Given a vector of known y values corresponding to the training data, i.e. anchors y^a

$$\mathbf{y^a} = \begin{bmatrix} y_1^a & y_2^a & \cdots & y_n^a \end{bmatrix}^T, \quad \mathbf{y} = \begin{bmatrix} y_1 & y_2 & \cdots & y_m \end{bmatrix}^T$$

We can run inference against all of the anchors using this 'vector product':

$$\mathbf{y^a y}^T = \begin{bmatrix} y_1^a \\ y_2^a \\ \vdots \\ y_n^a \end{bmatrix} \begin{bmatrix} y_1 & y_2 & \cdots & y_m \end{bmatrix} = \begin{bmatrix} y_1^a - y_1 & y_1^a - y_2 & \cdots & y_1^a - y_m \\ y_2^a - y_1 & y_2^a - y_2 & \cdots & y_2^a - y_m \\ \vdots & \vdots & \ddots & \vdots \\ y_n^a - y_1 & y_n^a - y_2 & \cdots & y_n^a - y_m \end{bmatrix}$$

But you can also augmented in the *other* direction *if* you have enforced pairwise loop consistency during training, i.e.

$$\mathbf{y^a}^T\mathbf{y} = \begin{bmatrix} y_1^a & y_2^a & \vdots & y_n^a \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \\ \dots \\ y_m \end{bmatrix} = \begin{bmatrix} y_1 - y_1^a & y_1 - y_2^a & \cdots & y_1 - y_m^a \\ y_2 - y_1^a & y_2 - y_2^a & \cdots & y_2 - y_m^a \\ \vdots & \vdots & \ddots & \vdots \\ y_n - y_1^a & y_n - y_2^a & \cdots & y_n - y_m^a \end{bmatrix}$$

Mapping back to absolute predictions can be done with averaging.

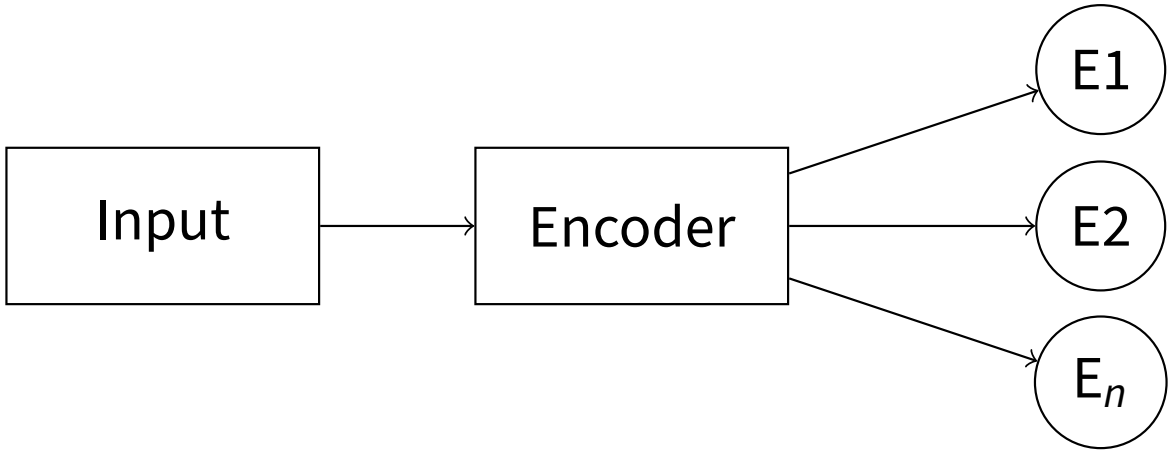
Augmentation Alternatives

Running inference with this approach is an open research area:

- ML theorists suggest:
  - ‘full’ augmentation and averaging (Wetzel et al., 2020)
  - various post-training weighting schemes to identify ‘best’ anchors (Belaid et al., 2024)
  - use K-nearest anchors in embedding space (Netanyahu et al., 2023)
- Chemistry practitioners seem to ignore it:
  - train and infer with one direction (Tynes et al., 2021)
  - check self loop consistency after-the-fact (Fralish et al., 2023)

Encoder

Up to this point I have been quietly assuming that some function like this exists:



We may want to *learn* this embedding rather than keep it static

- Fully differentiable architecture, can readily plug in modules like ChemProp's message passing
- DeepDelta has done an incorrect version of this in which they had two separate MP blocks (Fralish et al., 2023)

Initial Investigation

Implementation

```
from py2opsin import py2opsin

smiles_string = py2opsin(
  chemical_name = "ethane",
  output_format = "SMILES",
)
```

Fitting Arbitrary Surfaces

demo notebook

Aqueous Solubility Prediction

Here we use `mordred(-community)` as the encoder.

Subsequent Steps

Learned Embeddings

Show a diagram where the encoder outputs both representations

Supplementary Material

Miscellaneous Thoughts

Cited Works I

Attia, L., Burns, J. W., Doyle, P. S., & Green, W. H. (2024). Organic solubility prediction at the limit of aleatoric uncertainty. *ChemRxiv*. https://doi.org/10.26434/chemrxiv-2024-93qp3

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Wetzel, S. J., Ryczko, K., Melko, R. G., & Tamblyn, I. (2020). Twin neural network regression. *CoRR*, *abs/2012.14873*. https://arxiv.org/abs/2012.14873

Yousefi, M., & Collins, J. (2024). *Learning the bitter lesson: Empirical evidence from 20 years of CVPR proceedings*. https://arxiv.org/abs/2410.09649