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Deep Mendelian Randomization: Identifying and Verifying Genomic Deep Learning Models' Causal Knowledge

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1. Introduction

- **Motivation**: interrogating causal relationships learned by multi-task sequence-to-function machine learning models.
- **Method summary**: Our method estimates causal effects for user-provided cause and effect feature pairs based on synthetic data generated by a sequence-to-function model. It requires:
  - A trained multi-task (classification or regression) model.
  - Method for getting the model to output predictive means and standard errors or a full predictive distribution.
  - Sample sequence inputs.
- **Experiments summary**: To test our method, we conducted 3 experiments:
  1. Simulation experiment
  2. TF binding model (Avsec et al. (2020)) experiment
  3. TF + other feature (TODO) (Zhou and Troyanskaya (2015)) experiment
- **Results summary**: The simulation experiment validated that our method can partially recover causal relationships. In the TF binding experiment, our model recovered the expected order of causal effects between the 4 TFs included. In the TF + other feature experiment, ...
- **Related work**:
  1. Builds on genomic DL literature
  2. Leverage probabilistic DL model papers - MC dropout & deep ensembles
  3. Complements interpretability work

2. Methods

2.1 Algorithm

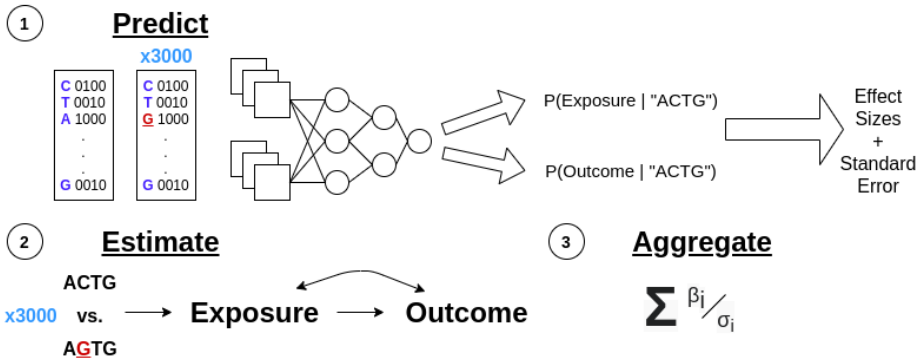


Figure 1: Graphical representation of Deep MR's high-level steps combining *in silico* mutagenesis and MR (see Section 2.1.1). Predict corresponds to steps 1 through 4. Estimate corresponds to step 5. Aggregate corresponds to step 6

Inputs Deep MR takes a calibrated, trained model and a set of one-hot encoded sequences as input. In our case, the one-hot encoded sequence represents a sequence of nucleotides for the model to make predictions on.

Outputs Deep MR outputs local, sequence-specific causal effects and global, exposure-specific causal effects.

2.1.1 Overview

Deep MR accomplishes its goal via the following procedure:

1. Randomly sample sequences to predict exposure and outcome values for "reference sequences".

2. Perform *saturation in-silico mutagenesis* for each reference sequence to generate (sequence length $\times$ alphabet size $-$ 1) mutated sequences per reference sequence.

3. For each reference and set of mutated sequences, use MC-dropout Gal and Ghahramani (2016) to generate predictive means and standard errors of binding probabilities for the reference and mutated sequences.

4. Generate (sequence length $\times$ alphabet size $-$ 1) *effect sizes* by subtracting each reference sequence's predictive mean from the corresponding mutated sequences' predictive means. Also, compute the standard errors of these differences.

5. Estimate a per-exposure, per-sequence region causal effect by running MR on the effect sizes and their standard errors.

6. Estimate overall per-exposure causal effects using a random effects meta-analysis.

2.1.2 Key Assumptions

Devote a paragraph(s) to discussing the assumptions Deep MR relies on and maybe 1 sentence just mentioning why we think the assumption is satisfied for each. These assumptions are:

- Local linearity
- MR DAG faithfulness
- Model performance
  - Accuracy upper bound and variant effect prediction warning
  - Inherited biases
  - Calibration (reference later section on dealing with this)

2.1.3 Components

Mendelian Randomization

- Introduce MR assumptions
- Discuss method we choose and its additional assumptions / features (what assumptions it allows us to weaken)

Calibrated probabilistic model

- We use deep learning models in all of our experiments
- Discuss two methods we use for making DL models probabilistic
- Reference how we calibrate them (Kuleshov et al. (2018))

3. Experiments

In which we describe the three experiments we conducted and their results.

3.1 Simulation

3.1.1 Setup

- Describe generative process (here or in appendix?)
- Three sub-experiments: no confounding, sequence-based confounding, and non-sequence-based confounding
- Questions we were trying to answer:

  Can Deep MR identify the "true" local and global causal effects?

3.1.2 Results

Simulation Estimated Effects			
Confounding	Global CE (True)	Global CE (Estimated)	Calibration
None			
Sequence-based			
Random			

What we found: good estimation of global CE in non-confounded and random confounding case, OK calibration of sequence region level CEs, . . . in sequence-based confounding case

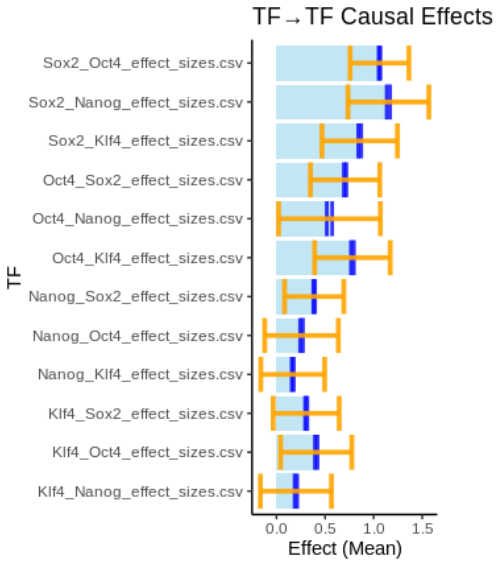
3.2 BPNet

3.2.1 Setup

- Introduce BPNet, mention ensemble and calibration method, and dataset / features

- Question we were trying to answer: can we correctly identify the key features of the TF-to-TF relationships discussed in the paper? Principally, Oct4/Sox2 strong effects on others vs. weak effect of others on others

3.2.2 Results



(a) Global CEs for all pairs of TFs predicted by BPNet. TODO: Annotate with predictions from BPNet paper.

(b) Example MR plots for 5 sequences and Oct4 → Sox2 and Klf4 → Nanog respectively.

3.3 DeepSEA

3.3.1 Setup

- Introduce DeepSEA, mention ensemble and calibration method, and dataset / features
- Question we were trying to answer: depends on which features we choose to use

4. Discussion

TODO: More separate discussion of local vs. global CE quality?

4.0.1 Strengths

- Deep MR recovers known patterns in both real model experiments
- Deep MR can generate new hypothesized relationships for experimental work to investigate
- Deep MR's global effect patterns can help validate and improve confidence in models
- Deep MR is compatible with existing, already trained models

4.0.2 Limitations

- Strong assumptions inherited from MR
- Quality of estimates depends on model quality
- Calibration of CE intervals
- Inability to determine correct direction from data

4.0.3 Future Work

- Network analysis
- Bi-directionality & weakening need for other assumptions
- Diagnostics for whether Deep MR can be safely applied

5. Conclusion

- Summarize most important results
- Repeat or emphasize framing of deep MR as exciting proof-of-concept for determining what causal relationships multi-task genomic deep learning models learn
- (Maybe) connect to larger context/project of trying to make multi-task genomic models more trustworthy

References

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