Explorations of Machine Learning Methodologies to Enhance the Design of RNA-based Dopamine Biosensors

James Craven and Matthew Lindsey

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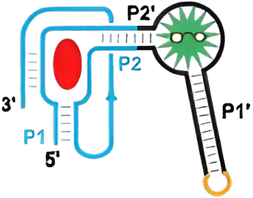
Benefits of a Dopamine Sensor

Dopamine is a neurotransmitter and plays a role in a variety of functions such as memory, learning, and reward systems. Detecting dopamine levels could help with diagnosing:

- addiction
- mental illness
- neurodegenerative disorders

Building a Synthetic Ribosensor

Research Question: How can we leverage machine learning to inform the necessary nucleotide sequence for the designed ribosensor in order for the ribosensor to emit a strong fluorescence in the presence of dopamine?



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While this seems like a healthy amount of experimental data, many machine learning models need 10-100x that amount to discover relationships between the features and target of a dataset.

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- the MLP outperforms other regression-based models in predicting fluorescence
- all models tested performed better when trained on nucleotide sequences instead of derived thermodynamic parameters

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1. Using both the toehold switch dataset and the Fernandez lab data, do models perform better when trained on nucleotide sequences than thermodynamic parameters? Additionally, does the MLP outperform other regression-based models for both datasets?
2. Can we leverage the 90,000+ labeled toehold switch dataset to train a ML model and make accurate predictions on the Fernandez ribosensor data?

Handling Sequences

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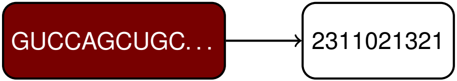

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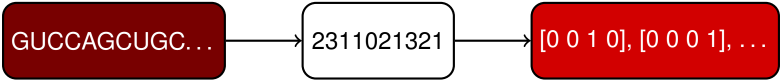

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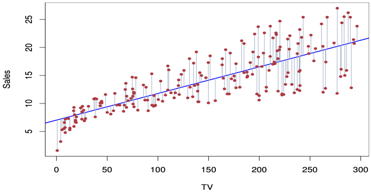
- To properly compare the results of the data sets, these two values were normalized using range-based normalization.
- With the data preprocessed, we trained and cross-validated seven regression-based models on the nucleotide sequence and thermodynamic parameters separately for both datasets.

Constructing Regression Models



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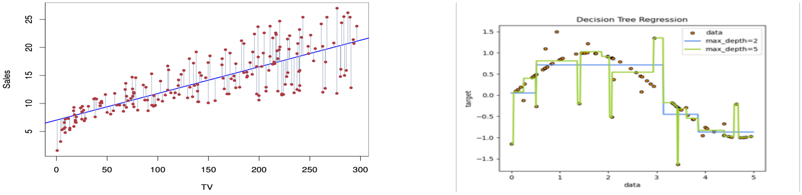

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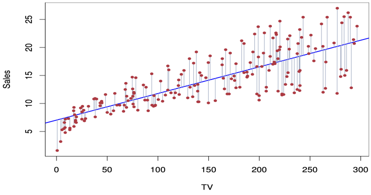

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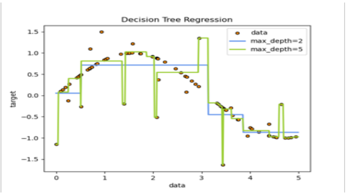

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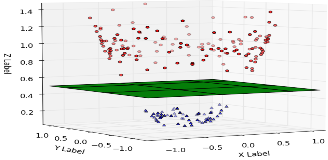

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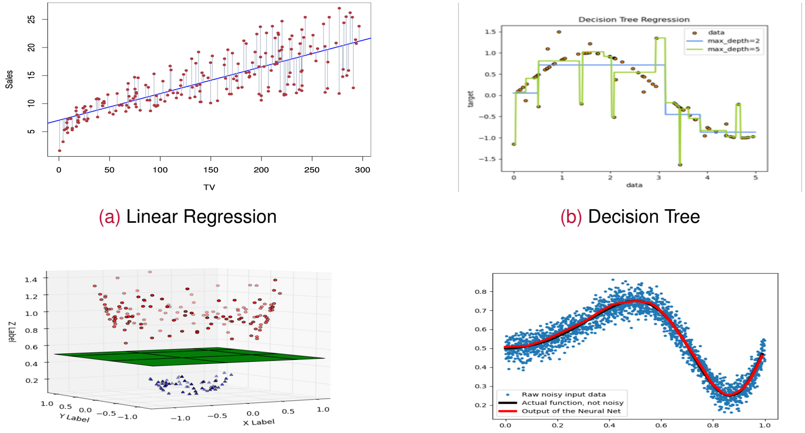

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A Metric for Comparing Regression Models

We utilize scikit-learn's implementation of the coefficient of determination:

$$R^2(y, \hat{y}) = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2}$$

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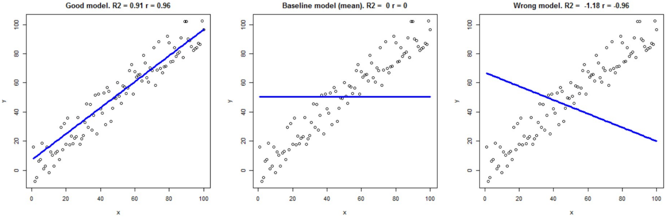

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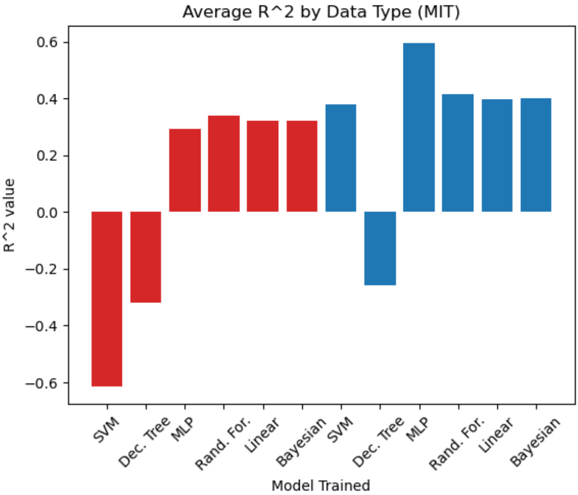
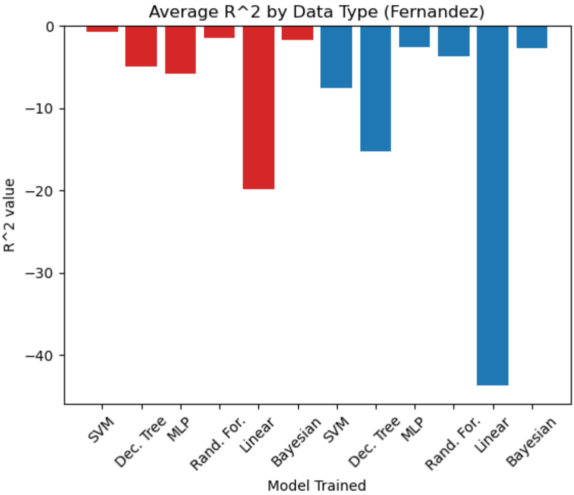


Results for Ribosensor Data



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Results: We trained a MLP on the full 90,000+ toehold switch dataset and tested on the ribosensor data. In doing so, we obtained an R^2 score of -0.458.

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Summary of Results:

- Sequence data appears to be better for model training due to potential information loss in calculating thermodynamic parameters
- Neural Networks are effective models for this type of problem
- There is either not enough similarity between the datasets or there is not enough data, in general, to do cross-training between the two

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- Semi-supervised learning by generating millions of sensor sequences and using Large Language Models (LLM) to learn general RNA patterns that can be applied to the smaller labeled dataset
- Revisiting the literature to see if other data sources are closer in design to our dopamine sensors

References

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Acknowledgements

Thanks! Any questions?

GitHub

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