The Usage of Synthetic Biology in Designing Neuromodulatory Treatments for Hippocampal Deterioration Caused by Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are characterized by the deterioration of neurons, specifically in the hippocampus (the brain's center for memory and cognition). Current therapies are slowing symptoms but are failing to repair/reverse the damage. Synthetic biology offers a solution by enabling the precise engineering of biological systems. This is explored using genome editing tools (e.g., CRISPR/Cas9), synthetic gene circuits, and modified stem cells. This paper examines how synthetic biology can be used to modulate and regenerate neural pathways, especially in hippocampal regions affected by neurodegeneration. The Python-developed models identified the most significant factors in re-stabilizing brain health. They examined their leveraging to positively impact the formation and growth of new brain cells, long-term memory, and the reduction of inflammation. Through Random Forest Regression, the model was trained on a simulated dataset created by referencing literature studies reviewed using PRISMA methodology. The resulting graphs suggest that the most important factors in activating the mechanisms for hippocampal repair were the precision of the gene editing and delivery across the blood-brain barrier. Due to the lack of available clinical data, our model was constrained to be based on a simulated dataset. However, this study overall supports conclusions in current literature and further supports proof of this concept, as a basis for future biological basic science studies.

Key Words: brain repair, CRISPR/Cas9, delivery efficiency, hippocampus, memory loss, neurodegeneration, neurodegenerative diseases, synthetic biology

Introduction

Synthetic biology uses engineering principles to redesign biological systems for specific purposes, such as replicating natural biological structures and behaviors. There is a focus on creating artificial life using synthetic molecules or modifying components derived from natural biology to design systems that function in unnatural ways (Karataş & Ayaz, 2025). Synthetic biology is a key tool for combating neurodegenerative diseases due to its ability to precisely target specific biological areas and adjust these processes, directly addressing the underlying mechanisms of these diseases rather than simply alleviating symptoms.

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, or Huntington's disease, are often linked due to their severe impacts on the hippocampus—the part of the brain in charge of memory creation and cognition (Cleveland Clinic, 2024). Thus, protein aggregation disrupts synaptic communication between neurons. Additionally, neuroinflammation and stress damage neurons, impairing the production of new neurons in the hippocampus. This causes hippocampal deterioration, resulting in side effects such as memory loss and cognitive decline.

Currently, the treatments in use mostly slow down the progression of effects. However, with newer advancements in biology, specifically synthetic biology, science is working to eliminate these effects. Through the use of synthetic tools, such as CRISPR/Cas9 and base editing, scientists can correct mutations and regulate gene expression linked to neurodegeneration. For instance, gene circuits and engineered proteins can modulate neuron production and factors of activity. Stem cell engineering, when combined with synthetic circuits, can repair hippocampal circuits, memory, and cognitive processes. This paper will focus on the specific conditions necessary to establish treatments for hippocampal

deterioration through synthetic biology and recent biomedical advancements.

Methods

This study combined a literature-based approach with a computational simulation to explore the use of synthetic biology in addressing the hippocampal deterioration caused by neurodegenerative diseases. The research identified key biological mechanisms that contributed to hippocampal damage caused by diseases such as Alzheimer's or Parkinson's. Key biological mechanisms include, but are not limited to, synaptic loss, protein aggregation, inflammation, and impaired neurogenesis. Various synthetic biological strategies, such as CRISPR/CAS-9–mediated gene editing, synthetic gene circuits, and stem cell therapies, were reviewed to assess their therapeutic potential.

To explore and predict the combined effects of these inventions, a machine-learning model was developed using a Random Forest Regression; the Python model was trained on a simulated dataset. Input features included the degree of CRISPR gene editing, the complexity of engineered gene circuits, the efficiency of the blood-brain barrier delivery system, and stem cell survival rates after modification. The outputs modeled included the activation levels of four key brain repair pathways: BDNF (neuroplasticity), CREB (learning/memory), anti-inflammatory pathways (e.g., IL-10), and neurogenesis markers.

Although no direct clinical data were available, the simulated dataset was constructed based on relationships observed in existing studies. Model performance was evaluated using R^2 scores (assessing how well the model's predictions match the real values) and mean squared error (MSE) metrics (showing deviation of the predictions on average), and feature importance was computed to determine which interventions had the largest predicted influence on pathway activation.

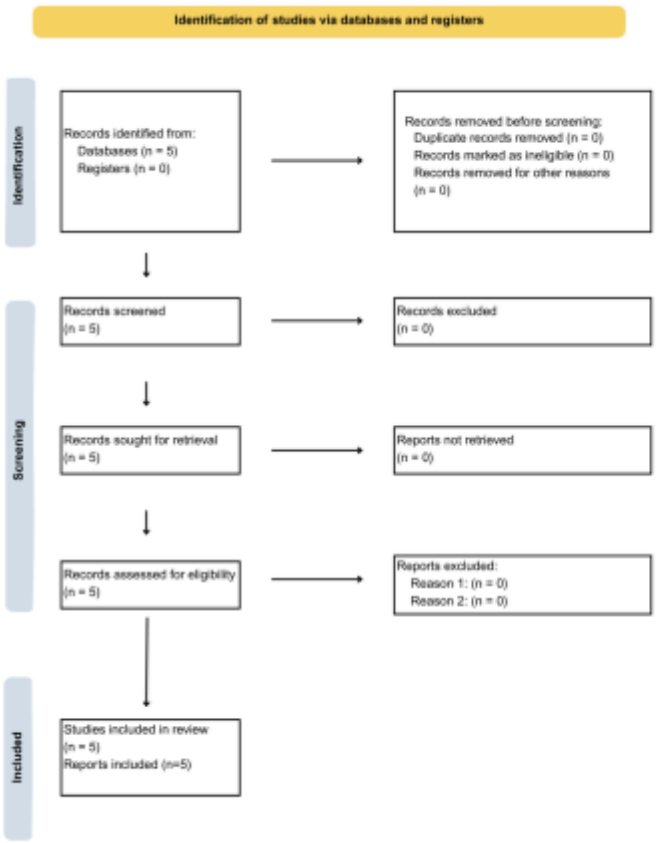

Figure 1: PRISMA Diagram. The literature review was conducted with searches from BioMedCentral and PubMed. This review utilizes Boolean search terms that combine "Synthetic Biology Treatments" with various neurodegenerative diseases. In total, 5 records were found using searching and reference training. After all the reports were fully reviewed, all were kept and used for the study.

Results

The machine learning model demonstrated high predictive performance in forecasting the activation levels of brain repair pathways in response to synthetic biology interventions. The Random Forest Regressor produced an R^2 score of approximately 0.91, indicating strong alignment between the model's predictions and the simulated output values.

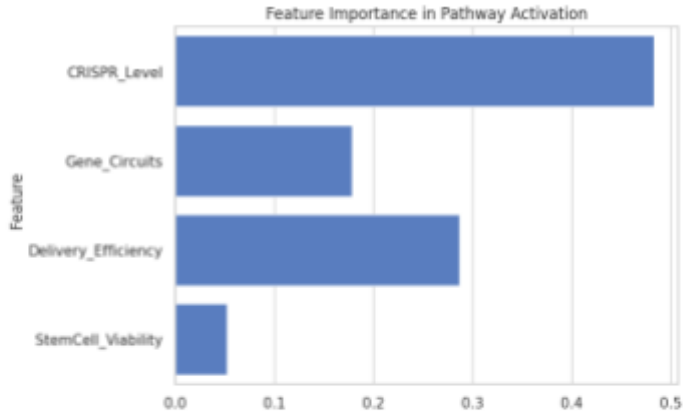

Figure 2: Pathway Activation Importance Based on Feature. This bar chart displays which changes matter the most. It shows which factors are the most important for improving brain repair. CRISPR_Level represents how much gene editing is done. Gene_Circuits represents how complex the synthetic biology circuits are. Delivery_Efficiency represents how well the treatment gets across the blood-brain barrier. StemCell_Viability represents how well the stem cells survive after being modified. In this diagram, the bar length represents how big the impact of each feature is. Since the CRISPR level bar is the longest, this means that gene editing makes the biggest difference in activating brain-repair pathways. This is super important and helpful in supporting the hypothesis that synthetic biology has the ability to repair hippocampal degeneration.

The feature importance analysis revealed that CRISPR Level and Delivery Efficiency were the most significant contributors across all outputs, followed by Stem Cell Viability and Gene Circuit Complexity. This suggests that the precision of gene editing and the success of delivery across the blood-brain barrier are critical for activating brain repair mechanisms.

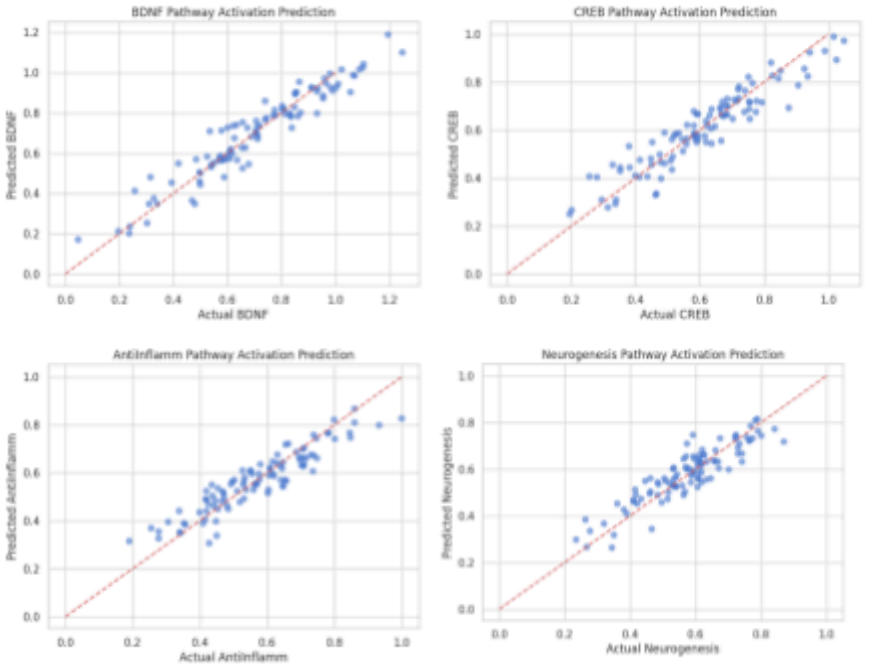

Figure 3: Predictions and Accuracy for Seperate Brain Repair Pathways. In this diagram, each graph represents one of four brain repair pathways. BNDF helps brain cells grow and form new connections (key for memory). CREB supports learning and long-term memory. AntiInflamm reduces brain inflammation (which worsens memory loss). Neurogenesis helps make new brain cells. Each dot on the graphs represents one of the simulated experiments conducted (one combination of CRISPR, gene circuits, delivery, etc.). The X-axis represents the actual pathway response and the Y-axis represents what the model predicted. The red, dashed line signifies a perfect prediction. The closer the dots are to the line, the more accurate the model's predictions are. If they're far from the line, it's not as accurate.

Four separate scatter plots were generated to evaluate predicted vs. actual values for each pathway (BDNF, CREB, Anti-inflammatory, and Neurogenesis). The plots showed a tight clustering around the diagonal reference line, indicating a strong model accuracy and minimal error.

Conclusion

This study demonstrates possible applications of synthetic biology when combined with computational modeling to design targeted neuromodulatory strategies for repairing hippocampal deterioration in neurodegenerative diseases. Through literature-based insights and a machine learning framework, CRISPR-mediated gene editing and efficient delivery systems were identified as the most impactful factors for activating brain repair pathways.

These results suggest that synthetic biology interventions, particularly those enhancing genetic targeting and delivery, can be systematically modeled and optimized to promote hippocampal repair in neurodegenerative disease contexts. While the results are based on simulated data, they align with findings in the current literature, which is useful for future biologically validated studies.

One limitation of this study is the reliance on synthetic data; while grounded in biological plausibility, they may not fully reflect the complexity of in vivo environments. Future research should include real-world biological validation of these predictions to assess their translational potential.

Ultimately, this work contributes to a growing understanding of evidence suggesting that synthetic biology can be systematically utilized to address the underlying mechanisms of neurodegeneration, moving beyond symptom management/assessment and toward functional outcomes.

References

Agustín-Pavón, C., & Isalan, M. (2014). Synthetic biology and therapeutic strategies for the degenerating brain. *Bioessays*, *36*(10), 979–990. https://doi.org/10.1002/bies.201400094

Ciurea, A. V., Mohan, A. G., Covache-Busuioc, R.-A., Costin, H.-P., Glavan, L.-A., Corlatescu, A.-D., & Saceleanu, V. M. (2023). Unraveling Molecular and Genetic Insights into Neurodegenerative Diseases: Advances in Understanding Alzheimer's, Parkinson's, and Huntington's Diseases and Amyotrophic Lateral Sclerosis. *International Journal of Molecular Sciences*, *24*(13), 10809. https://doi.org/10.3390/ijms241310809

Darehbagh, R. R., Seyedoshohadaei, S. A., Ramezani, R., & Rezaei, N. (2024). Stem cell therapies for neurological disorders: current progress, challenges, and future perspectives. *European Journal of Medical Research*, *29*(1). https://doi.org/10.1186/s40001-024-01987-1

Kolli, N., Lu, M., Maiti, P., Rossignol, J., & Dunbar, G. L. (2018). Application of the gene editing tool, CRISPR-Cas9, for treating neurodegenerative diseases. *Neurochemistry International*, *112*, 187–196. https://doi.org/10.1016/j.neuint.2017.07.007

Terstappen, G. C., Meyer, A. H., Bell, R. D., & Zhang, W. (2021). Strategies for delivering therapeutics across the blood–brain barrier. *Nature Reviews Drug Discovery*, *20*(5), 362–383. https://doi.org/10.1038/s41573-021-00139-y