Biological Computation – Final Project

Selected Model (link):

MIR-9-NEUROGENESIS

Paper (link):

miR-9 Controls the Timing of Neurogenesis through the Direct Inhibition of Antagonistic Factors

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Repository of logically consistent real-world Boolean network models

Overview

This paper introduces a repository of over 210 Boolean network models, compiled from various databases and literature, designed to support systems biology research. The repository ensures logical consistency and provides tools for thorough validation and analysis.

Background

Boolean networks are essential for modeling gene regulatory networks in systems biology. However, inconsistencies and errors in models can hinder their effectiveness. The repository addresses these issues by standardizing and validating models from diverse sources like CellCollective, GINsim, and BioModels.

Methods

1. **Model Collection and Standardization**: Aggregating models from multiple sources and standardizing them for uniformity.
2. **Validation Pipeline**: Automated checks for input monotonicity, essentiality, disconnected variables, and missing regulations using tools like aeon.py and biolqm.
3. **Analysis Tools**: Integration of tools for various analyses:
    - **aeon.py**: Symbolic analysis and bifurcation analysis.
    - **biolqm and GINsim**: Multi-valued model analysis and format translation.
    - **cabean**: Network control and reprogramming.
    - **maboss**: Stochastic update semantics.
    - **pyboolnet**: Random network generation and synchronous simulation.
    - **pystablemotifs**: Attractor computation and network reprogramming.
    - **trappist**: Trap space and fixed point computation.

Results

The repository and its tools significantly enhance the quality and usability of Boolean network models, ensuring robust and reproducible research. Researchers can submit new models, promoting ongoing updates and improvements.

Conclusion

The repository and validation tools provide a critical resource for systems biology, facilitating reliable and reproducible studies by ensuring model accuracy and consistency. The repository is accessible on GitHub, encouraging community contributions and continuous development

miR-9 Controls the Timing of Neurogenesis through the Direct Inhibition of Antagonistic Factors

Overview of the Article's Main Contributions

The paper primarily explores the role of microRNA-9 (miR-9) in regulating the timing of neurogenesis in the zebrafish hindbrain.
The study reveals several key findings:

- Role of miR-9 in Neurogenesis: The research shows that miR-9 is essential for controlling the timing of cell-cycle exit in neural progenitor cells by inhibiting specific antagonistic genes.

- Direct Targets of miR-9**:** Target protection analyses identify her6, zic5 (promoting progenitor maintenance), and elavl3/HuC (promoting cell-cycle exit) as direct targets of miR-9, allowing it to balance progenitor maintenance and neuronal differentiation.

- Impact of miR-9 Knockdown: miR-9 knockdown delays cell-cycle exit, increasing the production of late-born neurons, suggesting miR-9 ensures timely neuron production by promoting progenitor transition to differentiated states.

- Progenitor State Amplification: miR-9 activity creates an ambivalent progenitor state that responds to both maintenance and differentiation cues, adjusting neuronal production to local signals during late embryogenesis.

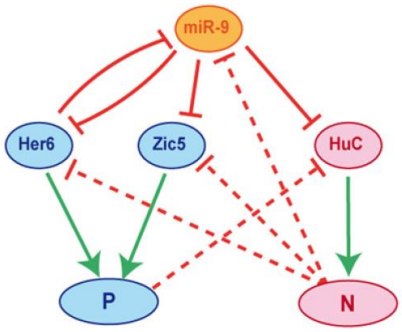
Boolean Network Analysis

The Boolean network model illustrated in the article provides a framework for understanding the regulation of neurogenesis through miR-9 and its target genes. The Boolean network consists of the following components:

- **miR-9**: A microRNA that regulates the expression of its target genes.
- **Her6 and Zic5**: Genes promoting progenitor cell proliferation.
- **elavl3 (HuC)**: A gene promoting neuronal differentiation.
- **Progenitor State (P)**: A state characterized by cell proliferation.
- **Neuronal Precursor State (N)**: A state characterized by cell cycle exit and differentiation.
- **Ambivalent State (A)**: A transitional state responsive to both proliferative and differentiation signals.

Network Diagram

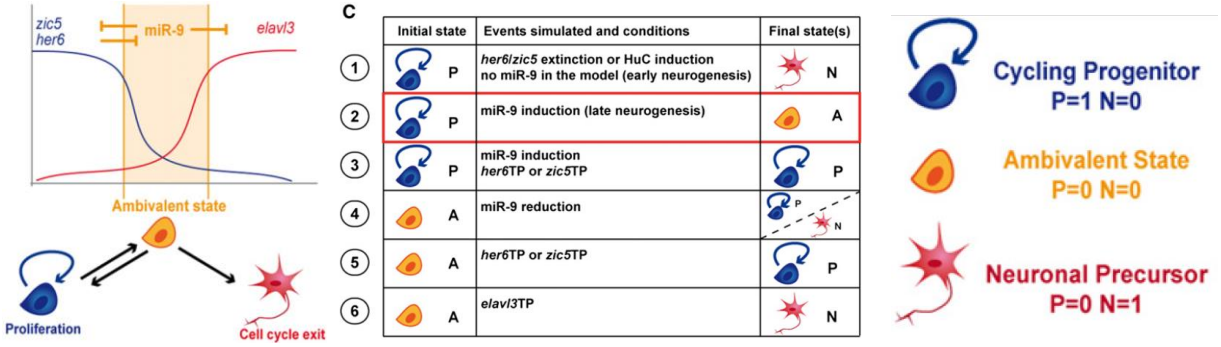
shows the regulatory interactions among these components:



- miR-9 inhibits Her6 and Zic5, reducing progenitor cell proliferation.
- miR-9 also inhibits elavl3, modulating the timing of differentiation.
- Her6 and Zic5 promote the progenitor state, while elavl3 promotes the neuronal precursor state.

State Transitions

The Boolean network describes several state transitions based on the levels of miR-9 and its target genes:



Progenitor State to Neuronal Precursor State:

Without miR-9, the extinction of Her6/Zic5 or the induction of elavl3 leads to the transition from the progenitor state (P) to the neuronal precursor state (N).

Progenitor State to Ambivalent State:

Inducing miR-9 during late neurogenesis transitions the progenitor state (P) to the ambivalent state (A).

Ambivalent State Maintenance:

- Reduction of miR-9 from the ambivalent state can lead to either the progenitor state (P) or the neuronal precursor state (N) depending on the context.
- The induction of Her6 or Zic5 maintains the progenitor state (P) from the ambivalent state.
- Induction of elavl3 leads to the neuronal precursor state (N) from the ambivalent state.

Shortcoming in the Article and Potential Improvements

One shortcoming of the article is the lack of exploration into the long-term effects of miR-9 knockdown on the overall development and function of the nervous system in zebrafish. While the study focuses on the immediate impact of miR-9 inhibition on neurogenesis timing, it does not address whether these changes lead to functional deficits or compensatory mechanisms in the mature nervous system. Future studies could benefit from a longitudinal analysis to understand the full spectrum of miR-9's role in development and its potential implications for neurological health.

Personal Impressions of the Article

The article presents an investigation into the role of miR-9 in neurogenesis, contributing valuable insights to the field of developmental biology. The use of zebrafish as a model organism is appropriate given its transparent embryos and well-characterized genetic background, which facilitate studies of neurodevelopment.

While the focus on zebrafish is scientifically valid, the article would benefit from additional data on other vertebrate models to enhance the relevance of the findings to broader neurodevelopmental contexts.

Explanation of Definitions
(We have mentioned the main results on the first page under 'key findings')

Since this is a theoretical article rather than a tool-focused one.

1. **MicroRNA (miR-9)**: miR-9 is a small non-coding RNA molecule that regulates gene expression by binding to complementary sequences on target mRNAs, usually resulting in gene silencing.
2. **Neurogenesis**: The process by which neural progenitor cells proliferate and differentiate into mature neurons. Timing of neurogenesis is crucial for proper brain development.
3. **Progenitor-Promoting Genes (her6, zic5)**: Genes that maintain the proliferative state of neural progenitor cells, preventing them from differentiating prematurely.
4. **Cell-Cycle Exit-Promoting Gene (elavl3/HuC)**: A gene that promotes the transition of progenitor cells from proliferation to differentiation into neurons.

Overall, the paper contributes significantly to our understanding of how miR-9 regulates the balance between progenitor maintenance and neuronal differentiation, a critical aspect of brain development.