

Second Part Of The Project
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1. Repository of Logically Consistent Real-World Boolean Network Models

The paper titled "Repository of Logically Consistent Real-World Boolean Network Models" presents the development and description of the Biodivine Boolean Models (BBM) dataset, a comprehensive and open-source collection of Boolean network models used in systems biology. Boolean networks are a fundamental framework for modeling biological systems, often utilized to represent gene regulatory networks and other complex biological processes.

The BBM dataset consists of over 210 Boolean network models compiled from various sources, including databases like CellCollective, GINsim, Biomodels, and the COVID-19 Disease Map, as well as independent publications. The dataset is unique in its emphasis on quality control and logical consistency. Each model in the BBM dataset has undergone extensive validation to ensure that its logical structure, including its update rules and influence graphs, aligns correctly. The paper highlights the identification and repair of over 400 potential issues in widely used models, enhancing their reliability for further research and tool development.

The validation pipeline employed by BBM checks for various logical inconsistencies, such as mismatches in monotonicity between regulatory edges and update functions, missing or redundant regulations, and the presence of disconnected components in the network. This rigorous validation ensures that the models in the BBM dataset are not only logically consistent but also usable for automated analysis and benchmarking of Boolean network tools.

In addition to model validation, BBM offers tools for customization, allowing users to export models in different formats (bnet, aeon, sbml) and with different representations of input nodes. The dataset is version-controlled, ensuring reproducibility and easy integration into various research workflows. BBM also includes a metadata repository that tracks the origin, modifications, and key characteristics of each model, facilitating transparency and reproducibility in systems biology research.

The paper also discusses the broader impact of BBM, emphasizing its role in simplifying the validation and benchmarking of Boolean network tools. It highlights the dataset's compatibility with existing analytical tools within the CoLoMoTo (Consortium for Logical Models and Tools) environment, making it a valuable resource for the systems biology community. The authors aim to continuously update the dataset, addressing any limitations and incorporating new models as they become available.

In summary, the BBM dataset represents a significant advancement in the field of systems biology, providing a large, validated, and accessible collection of Boolean network models. This resource supports more reliable and reproducible research, facilitating the development of new computational tools and the exploration of complex biological systems.

2. Boolean Network Model Predicts Cell Cycle Sequence of Fission Yeast

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0001672>

<https://github.com/sybila/biodivine-boolean-models/tree/main/models/%5Bid-095%5D%5Bvar-9%5D%5Bin-1%5D%5BFISSION-YEAST-2008%5D>

3.

Boolean Network Model Predicts Cell Cycle Sequence of Fission Yeast

Authors: Maria I. Davidich, Stefan Bornholdt

i. An Overview of the Article's Main Contributions

The paper by Maria I. Davidich and Stefan Bornholdt presents a Boolean network model for the cell-cycle regulatory network of fission yeast (*Schizosaccharomyces pombe*).

The main contributions of the article include:

1. Boolean Network Model Construction:

- The authors developed a simplified Boolean network model based solely on the known biochemical interaction topology of the fission yeast cell cycle. The model successfully replicates the sequence of regulatory protein activities throughout the cell cycle without requiring detailed kinetic parameters.

2. Robustness of the Biological Network:

- The model demonstrates the inherent robustness of the fission yeast cell cycle regulatory network. The G1 phase, a crucial stationary state, is identified as the dominant attractor in the network's state space, indicating that the biological system is structured to reliably return to this state even when perturbed.

3. Comparison with Budding Yeast:

- The article compares the cell cycle regulatory network of fission yeast with that of budding yeast (*Saccharomyces cerevisiae*), highlighting significant differences in their circuitry and dynamics. Despite these differences, both networks ensure proper cell cycle progression, illustrating the diverse mechanisms that can achieve similar biological outcomes.

4. Simplified Modeling Approach:

- The study illustrates that even a highly simplified model, such as a Boolean network, can effectively capture the essential dynamics of complex biological systems. This finding challenges the necessity of detailed kinetic data and emphasizes the importance of network connectivity and logic in determining biological behavior.

ii. Identify a Shortcoming in the Article (or How It Can Be Improved)

One notable shortcoming of the article is its reliance on a simplified Boolean network model that excludes the timing and quantitative aspects of protein interactions. While the model reproduces the sequence of events in the fission yeast cell cycle, it overlooks the precise kinetic parameters and time scales of these interactions. This simplification, although beneficial for reducing complexity, may limit the model's applicability in scenarios where timing precision is critical, such as in mutant strains or under stress conditions.

Improvement Suggestion: To enhance the model's accuracy and broader applicability, future work could integrate hybrid approaches that combine Boolean logic with

time-delay elements or fuzzy logic. These enhancements would allow the model to capture both the qualitative sequence and the quantitative timing of regulatory events, providing a more comprehensive understanding of cell cycle dynamics.

iii. Describe Your Impressions of the Article

Overall Impressions: The article is a compelling exploration of how simplified models can effectively capture complex biological processes. The use of a Boolean network to model the fission yeast cell cycle is particularly impressive due to its ability to reproduce the sequence of regulatory events without relying on detailed kinetic parameters. This approach is innovative and valuable, as it challenges the traditional reliance on more complex models.

Positive Aspects:

- The paper successfully demonstrates the robustness of the fission yeast cell cycle network, highlighting the importance of network structure in maintaining biological stability.
- The comparison between fission yeast and budding yeast models offers valuable insights into the diversity of regulatory mechanisms across different organisms.

Criticisms:

- The lack of experimental validation under varied conditions is a potential weakness, as it limits the confidence in the model's predictive power in real-world scenarios.
- The model's exclusion of biological noise and stochasticity could be seen as an oversimplification, potentially missing critical aspects of cellular behavior.

Conclusion: Overall, my impression of the article is positive, with some reservations about the model's generalizability and the absence of experimental validation. The study is thought-provoking and demonstrates the power of Boolean networks in modeling biological systems, but it also highlights the need for careful consideration of the contexts in which such models are applied.

iv. Definitions and Results Explained

Boolean Network Model:

- A Boolean network represents complex systems using binary variables (on/off states) for each component, such as proteins or genes. The interactions between these components are defined by Boolean functions that dictate how the state of one component influences others.

Cell Cycle Phases:

- The cell cycle includes four main phases: G1 (cell growth), S (DNA synthesis), G2 (preparation for mitosis), and M (mitosis). The model accurately represents these phases by simulating the regulatory proteins involved in controlling the cycle.

Attractors in the Network:

- Attractors are stable states towards which the system naturally converges. In the Boolean network model, the G1 phase is the dominant attractor, meaning the system tends to settle into this state, reflecting the biological tendency of cells to remain in G1 when not dividing.

Robustness of the Network:

- The study finds that the fission yeast cell cycle regulatory network is robust, meaning it can return to the correct sequence of states even after small disturbances. This robustness is a key feature of biological systems, ensuring reliable cell cycle progression.

Comparison with Budding Yeast:

- The fission yeast network operates as an auto-excited system with feedback loops, while the budding yeast network relies more on external signals. Despite these differences, both networks successfully manage the cell cycle, illustrating the flexibility of biological regulation.

Simplicity vs. Detail:

- The study shows that a simplified Boolean model can still accurately capture the dynamics of the cell cycle. By focusing on the network's structure and logical interactions, the model reveals fundamental principles governing the cell cycle, even without detailed kinetic data.

Disclosure Statement

In accordance with university guidelines, I hereby disclose that this project is entirely my own work. Generative AI (GENAI) tools were used solely to assist with summarizing certain sections and improving the English vocabulary. The ideas, content, and analysis presented are my own, and the use of these tools was limited to ensuring clarity and

conciseness. All efforts have been made to adhere to the university's academic integrity policies.