Details of the Boolean Network Model for Simulation Examples

This material provides detailed descriptions of the Boolean network models used in the simulation examples, which include well-established biological systems. These systems, which have been previously modeled as Boolean control networks (BCNs), include the cortical area development network [1], the ara-operon network [2], the cardiac development network [3], and the T-LGL network [4].

1 Cortical Area Development Network

The cerebral cortex is divided into functionally distinct areas, and the development of these areas during neural growth is influenced by the expression patterns of several key genes. Along the anterior-posterior axis, gradients of genes such as Fgf8, Emx2, Pax6, Coup-tfi, and Sp8 are particularly critical in determining areal identity. The study by [1] employed a computational model to explore the interactions between these genes and identify the specific interactions or combinations of interactions that reproduce the experimentally observed anterior-posterior expression patterns. The model uses Boolean variables to represent gene expression levels, reflecting the qualitative nature of the expression data available.

Overall, this model provides valuable insights into the design principles of the gene network regulating cortical area development and generates novel predictions that can be experimentally tested. Further details of the network model can be accessed at `https://cellcollective.org/#2035/cortical-area-development`.

The Boolean network representation of the model is given by the following equations:

$$\begin{cases} \mathbf{x}_1(t+1) = \neg(\mathbf{x}_4(t) \vee \mathbf{x}_3(t)) \vee \neg(\mathbf{x}_4(t) \vee \mathbf{x}_3(t)) \vee \mathbf{u}_1(t) \vee \xi_1(t) \\ \mathbf{x}_2(t+1) = ((\mathbf{x}_1(t) \wedge \neg\mathbf{x}_3(t)) \wedge \neg\mathbf{x}_5(t)) \wedge \neg\mathbf{x}_4(t) \wedge \mathbf{u}_2(t) \\ \mathbf{x}_3(t+1) = (\mathbf{x}_3(t) \wedge (\mathbf{x}_4(t) \vee \xi_2(t))) \wedge \neg\mathbf{x}_2(t) \\ \mathbf{x}_4(t+1) = (\mathbf{x}_3(t) \wedge \neg\mathbf{x}_2(t)) \vee \mathbf{u}_1(t) \\ \mathbf{x}_5(t+1) = ((\mathbf{x}_4(t) \wedge \neg\mathbf{x}_1(t)) \wedge \neg\mathbf{x}_2(t)) \wedge \xi_1(t) \end{cases} \tag{1}$$

2 Ara-Operon Network

The lactose operon in *Escherichia coli* was the first gene regulatory network to be characterized, and it continues to serve as a prototype for new modeling paradigms. In [2], the authors modeled the well-known arabinose operon in *E. coli* using a Boolean network. The ara-operon model consists of nine Boolean variables, described by the following system of equations:

$$\begin{cases} \mathbf{x}_1(t+1) = \mathbf{u}_1(t) \wedge \mathbf{x}_9(t) \\ \mathbf{x}_2(t+1) = \mathbf{u}_2(t) \wedge \mathbf{x}_9(t) \vee \mathbf{u}_1(t) \\ \mathbf{x}_3(t+1) = \mathbf{x}_2(t) \vee \mathbf{x}_1(t) \wedge \mathbf{u}_3(t) \\ \mathbf{x}_4(t+1) = \neg\mathbf{u}_4(t) \\ \mathbf{x}_5(t+1) = \mathbf{x}_7(t) \\ \mathbf{x}_6(t+1) = \neg\mathbf{x}_3(t) \wedge \mathbf{u}_3(t) \wedge \xi_1(t) \\ \mathbf{x}_7(t+1) = \mathbf{x}_3(t) \wedge \mathbf{x}_4(t) \wedge \neg\mathbf{x}_6(t) \\ \mathbf{x}_8(t+1) = \mathbf{x}_3(t) \wedge \mathbf{x}_4(t) \\ \mathbf{x}_9(t+1) = \mathbf{x}_8(t) \vee \xi_2(t) \end{cases} \tag{2}$$

3 Cardiac Development Network

The cardiac gene regulatory network, as described by Herrmann et al. [3], serves as a biologically inspired example of gene regulation during early heart development. This Boolean model, constructed from both temporal and spatial expression data of genes and their interactions, captures the early signaling events that occur during gastrulation, which lead to cardiac specification and differentiation into the first heart field (FHF) and the second heart field (SHF). As a result, this gene regulatory network provides insights into the early steps of cardiogenic mesoderm determination, which are essential for understanding heart development. Further details of the cardiac development model can be accessed at https://cellcollective.org/#2136/cardiac-development.

The cardiac network comprises 15 genes, denoted as $\mathbf{x}_i(t)$ for $i = 1, 2, \ldots, 15$, where t represents the time steps. In addition, two control inputs, $\mathbf{u}_1$ and $\mathbf{u}_2$, and two disturbances, ξ_1 and ξ_2, are introduced for simulation purposes. The Boolean network model

for the cardiac development network is given by the following set of equations:

$$
\begin{cases}
\mathbf{x}_1(t+1) = \neg\mathbf{x}_2(t) \wedge \mathbf{x}_{13}(t) \vee \mathbf{u}_1(t) \\
\mathbf{x}_2(t+1) = \mathbf{x}_{15}(t) \\
\mathbf{x}_3(t+1) = \mathbf{x}_8(t) \vee (\mathbf{x}_2(t) \wedge \neg\mathbf{x}_{13}(t)) \\
\mathbf{x}_4(t+1) = \neg\mathbf{x}_8(t) \wedge (\mathbf{x}_5(t) \vee \mathbf{x}_{10}(t)) \\
\mathbf{x}_5(t+1) = \mathbf{x}_2(t) \wedge \mathbf{x}_{15}(t) \wedge \xi_2(t) \\
\mathbf{x}_6(t+1) = \mathbf{x}_9(t) \vee \mathbf{x}_8(t) \vee \mathbf{x}_{11}(t) \vee \xi_1(t) \\
\mathbf{x}_7(t+1) = \mathbf{x}_{10}(t) \vee \mathbf{x}_8(t) \vee \mathbf{x}_4(t) \vee (\mathbf{x}_2(t) \vee \mathbf{x}_{15}(t)) \\
\mathbf{x}_8(t+1) = \mathbf{x}_2(t) \wedge \mathbf{x}_{13}(t) \\
\mathbf{x}_9(t+1) = (\mathbf{x}_7(t) \wedge \mathbf{x}_6(t)) \vee \mathbf{x}_{10}(t) \vee (\mathbf{x}_8(t) \wedge \mathbf{x}_3(t)) \\
\qquad\qquad \vee(\mathbf{x}_1(t) \wedge \mathbf{x}_6(t)) \vee \mathbf{x}_{11}(t) \\
\mathbf{x}_{10}(t+1) = \mathbf{x}_5(t) \wedge \xi_1(t) \\
\mathbf{x}_{11}(t+1) = \neg(\mathbf{x}_{10}(t) \vee \mathbf{x}_2(t) \wedge \mathbf{u}_1(t)) \wedge (\mathbf{x}_9(t) \vee \mathbf{x}_{11}(t) \\
\qquad\qquad \vee\mathbf{x}_8(t)) \wedge \neg(\mathbf{x}_3(t) \wedge \neg(\mathbf{x}_8(t) \vee \mathbf{x}_{11}(t))) \vee \mathbf{u}_2(t) \\
\mathbf{x}_{12}(t+1) = 1 \\
\mathbf{x}_{13}(t+1) = \mathbf{x}_{12}(t) \\
\mathbf{x}_{14}(t+1) = \mathbf{x}_{14}(t) \vee \mathbf{u}_2(t) \\
\mathbf{x}_{15}(t+1) = \mathbf{x}_{14}(t)
\end{cases}
\tag{3}
$$

4 T-LGL Network

T-cell large granular lymphocyte (T-LGL) leukemia is a chronic disease characterized by the clonal proliferation of cytotoxic T cells. Since no curative therapy is currently known for this disease, identifying potential therapeutic targets is critical. In the study by Saadatpour et al. [4], a comprehensive dynamical and structural analysis of a Boolean network model of T-LGL leukemia was performed. This model serves to better under-

stand the disease's progression and to inform therapeutic strategies.

The Boolean network model for the T-LGL leukemia consists of multiple genes and their interactions, described by the following system of equations:

$$
\begin{cases}
\mathbf{x}_1(t+1) = \mathbf{x}_2(t) \wedge \neg \mathbf{x}_{16}(t) \wedge \mathbf{u}_1(t) \\
\mathbf{x}_2(t+1) = \neg(\mathbf{x}_5(t) \vee \mathbf{x}_3(t) \vee \mathbf{x}_{16}(t) \vee \xi_1(t)) \\
\mathbf{x}_3(t+1) = (\mathbf{x}_2(t) \vee \mathbf{x}_3(t) \vee \mathbf{u}_2(t)) \wedge \neg \mathbf{x}_{16}(t) \\
\mathbf{x}_4(t+1) = \mathbf{x}_{15} \wedge \neg \mathbf{x}_{16}(t) \\
\mathbf{x}_5(t+1) = \mathbf{x}_4(t) \wedge \neg \mathbf{x}_{16}(t) \vee (\mathbf{u}_3(t) \wedge \xi_2(t)) \\
\mathbf{x}_6(t+1) = \neg(\mathbf{x}_7(t) \vee \mathbf{x}_{16}(t) \\
\mathbf{x}_7(t+1) = \mathbf{x}_{15}(t) \wedge \neg \mathbf{x}_{16}(t) \\
\mathbf{x}_8(t+1) = \mathbf{x}_6(t) \wedge \neg(\mathbf{x}_{15}(t) \vee \mathbf{x}_{16}(t)) \wedge \neg \mathbf{u}_4(t) \\
\mathbf{x}_9(t+1) = (\mathbf{x}_8(t) \vee (\mathbf{x}_6(t) \wedge \neg \mathbf{x}_{11}(t))) \wedge \neg \mathbf{x}_{16}(t) \\
\mathbf{x}_{10}(t+1) = ((\mathbf{x}_{12}(t) \wedge \neg \mathbf{x}_{13}(t)) \vee \mathbf{x}_9(t)) \wedge \neg \mathbf{x}_{16}(t) \\
\mathbf{x}_{11}(t+1) = \neg(\mathbf{x}_9(t) \vee \mathbf{x}_{16}(t)) \\
\mathbf{x}_{12}(t+1) = \neg(\mathbf{x}_{14}(t) \vee \mathbf{x}_{16}(t) \vee \mathbf{u}_2(t)) \\
\mathbf{x}_{13}(t+1) = \neg(\mathbf{x}_{12}(t) \vee \mathbf{x}_{16}(t)) \vee \xi_3(t) \\
\mathbf{x}_{14}(t+1) = \neg(\mathbf{x}_9(t) \vee \mathbf{x}_{16}(t)) \wedge \mathbf{u}_1(t) \\
\mathbf{x}_{15}(t+1) = \neg(\mathbf{x}_8(t) \vee \mathbf{x}_{16}(t)) \\
\mathbf{x}_{16}(t+1) = \mathbf{x}_{10}(t) \vee \mathbf{x}_{16}(t) \vee (\mathbf{u}_2(t) \wedge \mathbf{u}_3(t))
\end{cases}
\tag{4}
$$

References

[1] C. E. Giacomantonio and G. J. Goodhill, "A Boolean model of the gene regulatory network underlying mammalian cortical area development," *Plos Computational Biology*, vol. 6, no. 9, p. e1000936, 2010.

[2] A. Jenkins and M. Macauley, "Bistability and asynchrony in a Boolean model of the

l-arabinose operon in escherichia coli," *Bulletin of Mathematical Biology*, vol. 79, pp. 1778–1795, 2017.

[3] F. Herrmann, A. Groß, D. Zhou, H. A. Kestler, and M. Kühl, "A Boolean model of the cardiac gene regulatory network determining first and second heart field identity," *Plos One*, vol. 7, no. 10, p. e46798, 2012.

[4] A. Saadatpour, R.-S. Wang, A. Liao, X. Liu, T. P. Loughran, I. Albert, and R. Albert, "Dynamical and structural analysis of a t cell survival network identifies novel candidate therapeutic targets for large granular lymphocyte leukemia," *PLoS computational biology*, vol. 7, no. 11, p. e1002267, 2011.