Read: Chapter 6 of Robeva: *Steady state analysis of Boolean models: a dimension reduction approach.* By D. Murrugarra and A. Veliz-Cuba, pages 121–139.

1. Consider the following Boolean network:

$$f_{x_1} = x_1 \lor x_2, \qquad f_{x_2} = x_2 \land x_3, \qquad f_3 = \overline{x_1}.$$

   Reduce this network by eliminating one of the variables, and draw the resulting state space and wiring diagram. Find the fixed points of the reduced network, and use this to reconstruct the fixed points of the original network.

2. Draw the wiring diagram of the Boolean network

$$f = (f_1, f_2, f_3, f_4, f_5, f_6) = (x_6, \ x_1, \ x_2, \ \overline{x_3}, \ x_4, \ \overline{x_5})$$

   and then reduce it by eliminating the variables in the order $x_6, x_5, \ldots$. At each step along the way, write out the functions and draw the wiring diagram.

3. Suppose we want to reduce a Boolean network by removing a vertex x_i with no self-loop (equivalently, f_{x_i} doesn't depend on x_i). First, for every vertex y such that $x_i \longrightarrow y$, substitute f_{x_i} into x_i:

$$f_y(x_1 \ldots, \underbrace{\cdots x_i \cdots}_{\text{pos. } y}, \ldots, x_n) \qquad \text{becomes} \qquad f_y((x_1 \ldots, \underbrace{\cdots f_{x_i} \cdots}_{\text{pos. } y}, \ldots, x_n) \, .$$

   Next, each pair of edges $v \longrightarrow x_i \longrightarrow y$ in the wiring diagram must be replaced with the single edge $v \longrightarrow y$. The situation is similar for the other three possibilities:

   (a) $v \longrightarrow x_i \longmapsto y$

   (b) $v \longmapsto x_i \longrightarrow y$

   (c) $v \longmapsto x_i \longmapsto y$

   For each of these pairs of edges, determine what to replace them with in the wiring diagram of the new network. This would allow one to characterize algorthmically how to construct the wiring diagram of a reduced Boolean network.

4. Consider the following Boolean network model of the *lac* operon:

$x_1 = lac$ mRNA (M)	$f_1 = x_4 \land \overline{x_5}$
$x_2 = lac$ permease (P)	$f_2 = x_1$
$x_3 = \beta$-galactosidase (B)	$f_3 = x_1$
$x_4 = $ catabolite activator protein (C)	$f_4 = \overline{x_{11}}$
$x_5 = $ repressor protein (R)	$f_5 = \overline{x_6} \land \overline{x_7}$
$x_6 = $ high allolactose (A)	$f_6 = x_3 \land x_8$
$x_7 = $ medium allolactose (A_m)	$f_7 = x_6 \lor x_8 \lor x_9$
$x_8 = $ high intracellular lactose (L)	$f_8 = x_2 \land x_{10} \land \overline{x_{11}}$
$x_9 = $ medium intracellular lactose (L_m)	$f_9 = (x_8 \lor x_{10}) \land \overline{x_{11}}$
$x_{10} = $ extracellular lactose (L_e)	$f_{10} = x_{10}$
$x_{11} = $ extracellular glucose (G_e)	$f_{11} = x_{11}$

(a) Reduce this Boolean network starting from the last variable. It is strongly recommended that you use Macaulay2 in Sage or at `web.macaulay2.com`.

(b) Draw the wiring diagram of the reduced network. Find its fixed points and use these to determine the fixed points of the original network.

(c) Repeat Part (a) but using a completely different variable order.

Summary of relevant literature.

The reduction algorithm described in the lecture was from [VC11]. It was later improved in the special case of AND-NOT network models [VCAL15]. Another version that encorporated computational algebra was given in [VCAHL14].

A reduction algorithm for logical networks (essentially *asynchronous* local models) that preserves the fixed points was published in [NRTC11]. A version that also preversed the complex attractors was published in [ZA13].

References

[NRTC11]   A. Naldi, E. Remy, D. Thieffry, and C. Chaouiya. Dynamically consistent reduction of logical regulatory graphs. *Theor. Comput. Sci.*, 412(21):2207–2218, 2011.

[VC11]   A. Veliz-Cuba. Reduction of Boolean network models. *J. Theor. Biol.*, 289:167–172, 2011.

[VCAHL14]   A. Veliz-Cuba, B. Aguilar, F. Hinkelmann, and R. Laubenbacher. Steady state analysis of Boolean molecular network models via model reduction and computational algebra. *BMC Bioinformatics*, 15(1):221, 2014.

[VCAL15]   A. Veliz-Cuba, B. Aguilar, and R. Laubenbacher. Dimension reduction of large sparse AND-NOT network models. *Electron. Notes Theor. Comput. Sci.*, 316:83–95, 2015.

[ZA13]   J.G.T. Zañudo and R. Albert. An effective network reduction approach to find the dynamical repertoire of discrete dynamic networks. *Chaos*, 23(2):025111, 2013.