Supplementary Material

1 Proofs of the structural decomposition theorems

This section contains the proofs of the structural decomposition theorems described in the main text. First, we define in full detail the semi-direct product, used to combine two networks in a hierarchical fashion.

Definition 1.1. Consider two Boolean networks,

$$F = (f_1, \dots, f_k) : \{0,1\}^k \to \{0,1\}^k$$

with variables $x = (x_1, \dots, x_k)$ and

$$G = (g_1, \dots, g_m) : \{0,1\}^{\ell+m} \to \{0,1\}^m$$

with external inputs $u = (u_1, \dots, u_\ell)$ and variables $y = (y_1, \dots, y_m)$. Let $\Lambda \subseteq \{1, \dots, k\}$ such that $|\Lambda| = \ell$ and define $x_\Lambda := (x_{\lambda_1}, \dots, x_{\lambda_\ell})$. Then,

$$H = (h_1, \dots, h_{k+m}) : \{0,1\}^{k+m} \to \{0,1\}^{k+m}$$

defines a combined Boolean network by setting

$$h_i(x, y) = \begin{cases} f_i(x) & \text{if } 1 \leq i \leq k, \\ g_{i-k}(x_\Lambda, y) & \text{if } k+1 \leq i \leq k+m. \end{cases}$$

That is, the variables x_Λ act as the external inputs of G. The corresponding coupling scheme is defined to be

$$P = \{x_{\lambda_1} \to u_1, x_{\lambda_2} \to u_2, \dots, x_{\lambda_\ell} \to u_l\}.$$

We denote H as $H := F \rtimes_P G$ and refer to this as the coupling of F and G by (the coupling scheme) P or as the semi-direct product of F and G via P.

Theorem 1.1. If a Boolean network F is not a module, then there exist F_1, F_2, P such that $F = F_1 \rtimes_P F_2$. Furthermore, we can find a decomposition such that F_1 is a module.

Proof. Let $F = (f_1, \ldots, f_n)$ be a Boolean network with variables $X = \{x_1, \ldots, x_n\}$ and assume F is not a module. Then the wiring diagram of F is not strongly connected, implying there exists at least one node y and one node $x_j \neq y$ such that there exists no path from x_j to y in the wiring diagram of F. Let $X_2 = \{x_{j_1}, x_{j_2}, \ldots, x_{j_m}\}$ denote the set of all such nodes, i.e., the nodes for which there exists no paths to y. Further, let $X_1 = X \backslash X_2$ denote the complement set of nodes to X_2. Note that for every $x_i \in X_1$, there exists a path from x_i to y but no paths originating from X_2 to x_i.

Define Λ to be the subset of indices $\Lambda = \{\lambda_1, \ldots, \lambda_\ell\} \subset \{1, \ldots, k\}$ such that for each $\lambda \in \Lambda$ there exists at least one function f_{j_i} with $x_{j_i} \in X_2$ which depends on x_λ.

If $\Lambda = \emptyset$, then the sets X_1 and X_2 represent two groups of nodes, which are disconnected in the wiring diagram. Hence the network F is a Cartesian product of F_1 and F_2. It follows that $F = F_1 \rtimes_P F_2$ with $P = \emptyset$.

If $\Lambda \neq \emptyset$, then for any $x_i \in X_1$, the corresponding update function f_i does not depend on X_2 by construction, as there are no paths from X_2 to x_i, and we set F_1 to be the restriction of F to X_1, $(F_1)_i := (F|_{X_1})_i = f_i$. For any $x_i \in X_2$, if the corresponding update function depends on a node $x_j \in X_1$, then $x_j \in \Lambda$ by the definition of Λ. It follows by construction that any function f_i then can be written as a Boolean function on X_2 with external inputs from x_Λ.

Hence, $F = F_1 \rtimes_P F_2$.

Note that in the above proof we can choose the node y such that it belongs to a SCC that receives no edge from any other SCC. X_1 will contain the nodes of this SCC and hence F_1 will be a module. □

The main structural decomposition theorem follows directly from this:

Theorem 1.2. For any Boolean network F, there exist unique modules $F_1, \ldots, F_m$ such that

$$F = F_1 \rtimes_{P_1} (F_2 \rtimes_{P_2} (\cdots \rtimes_{P_{m-1}} F_m)),$$

where this representation is unique up to a reordering, which respects the partial order of Q (Eq. 1), and the collection of coupling schemes $P_1, \ldots, P_{m-1}$ depends on the particular choice of ordering.

Proof. If F is a module, then $m = 1$ and the result follows.

If F is not a module, we use induction on the downstream subnetwork F_2 in Theorem 1.1 to obtain the result. □

2 Non-autonomous Boolean networks

This section contains the full definition of non-autonomous Boolean networks, as well as two examples.

Definition 2.1. A non-autonomous Boolean network is defined by

$$y(t+1) = H(g(t), y(t)),$$

where $H : \{0,1\}^{k+m} \to \{0,1\}^m$ and $(g(t))_{t=0}^{\infty}$ is a sequence with elements in $\{0,1\}^k$. The network, denoted H^g, is non-autonomous because its dynamics depend on $g(t)$.

A state $c \in \{0,1\}^n$ is a *steady state* of H^g if $H(g(t), c) = c$ for all t. Similarly, an ordered set with r elements, $\mathcal{C} = \{c_1, \ldots, c_r\}$ is an *attractor of length* r of H^g if $c_2 = H(g(1), c_1)$, $c_3 = H(g(2), c_2), \ldots, c_r = H(g(r-1), c_{r-1})$, $c_1 = H(g(r), c_r)$, $c_2 = H(g(r+1), c_1), \ldots$. In general, $g(t)$ is not necessarily of period r and may even not be periodic.

If $H(g(t), y) = G(y)$ for some network G for all t (that is, it does not depend on $g(t)$), then $y(t+1) = H(g(t), y(t)) = G(y(t))$ and this definition of attractors coincides with the classical definition of attractors for (autonomous) Boolean networks.

Example 2.1. Consider the non-autonomous network defined by

$$H(u_1, u_2, y_1, y_2) = (u_2 y_2, y_1)$$

and the two-periodic sequence $(g(t))_{t=0}^{\infty} = (01, 10, 01, 10, \ldots)$, which corresponds to a 2-cycle of the upstream 2-node network. If the initial point is $y(0) = (y_1^*, y_2^*)$, then the dynamics of H^g can be computed as follows:

$$y(1) = H(g(0), y(0)) = H(0, 1, y_1^*, y_2^*) = (y_2^*, y_1^*),$$
$$y(2) = H(g(1), y(1)) = H(1, 0, y_2^*, y_1^*) = (0, y_2^*),$$
$$y(3) = H(g(2), y(2)) = H(0, 1, 0, y_2^*) = (y_2^*, 0).$$

Thus for $t \geq 1$, $y(2t) = (0, y_2^*)$ and $y(2t+1) = (y_2^*, 0)$. It follows that the attractors of H^g are given by 00 (one steady state) and $(01, 10)$ (one cycle of length 2). Note that $(10, 01)$ is not an attractor because $(10, 01, 10, 01, ...)$ is not a trajectory for this non-autonomous network. This is a subtle situation that can be sometimes missed when not considering all trajectories a limit cycle represents.

Example 2.2. Consider the non-autonomous network defined by $H(u_1, u_2, y_1, y_2) = (u_2 y_2, y_1)$, as in the previous example, and the one-periodic sequence $(g(t))_{t=0}^{\infty} = (00, 00, \ldots)$, which corresponds to a steady state of the upstream 2-node network. If the initial point is $y(0) = (y_1^*, y_2^*)$, then the dynamics of H^g can be computed as follows:

$$y(1) = H(g(0), y(0)) = H(0, 0, y_1^*, y_2^*) = (0, y_1^*),$$
$$y(2) = H(g(1), y(1)) = H(0, 0, y_2^*, y_1^*) = (0, 0).$$

Then, $y(t) = (0, 0)$ for $t \geq 2$, and the only attractor of H^g is the steady state 00.

3 Proof of the dynamic decomposition theorem

For a decomposable network $F = F_1 \rtimes_P F_2$, we introduce the following notation for attractors. First, note that F has the form $F(x, y) = (F_1(x), F_2(x, y))$ where F_2 is a non-autonomous network. Let $\mathcal{C}_1 = (r_1, \ldots, r_m) \in \mathcal{A}(F_1)$ and $\mathcal{C}_2 = (s_1, \ldots, s_n) \in \mathcal{A}(F_2^{\mathcal{C}_1})$ be attractors of length m and n, respectively. Then, the sequence $((r_t, s_t))_{t=0}^{\infty}$ has period $l = lcm(m, n)$, so we define the sum (or concatenation) of these attractors to be

$$\mathcal{C}_1 \oplus \mathcal{C}_2 = ((r_1, s_1), (r_2, s_2), \dots, (r_{l-1}, s_{l-1})).$$

Note that the sum of attractors is not a Cartesian product, $\mathcal{C}_1 \times \mathcal{C}_2 = \{(r_i, s_j) | \text{ for all } i, j\}$.

Similarly, for an attractor $\mathcal{C}_1$ and a collection of attractors A we define

$$\mathcal{C}_1 \oplus A = \{\mathcal{C}_1 \oplus \mathcal{C}_2 | \mathcal{C}_2 \in A\}.$$

Our second main theoretical result shows that the dynamics (i.e., the attractor space) of a semi-direct product can be seen as a type of semi-direct product of the dynamics of the decomposable subnetworks. When applied iteratively, this enables a computation of the attractor space from the attractor space of each module.

Theorem 3.1. Let $F = F_1 \rtimes_P F_2$ be a decomposable network. Then

$$\mathcal{A}(F) = \bigsqcup_{\mathcal{C}_1 \in \mathcal{A}(F_1)} \mathcal{C}_1 \oplus \mathcal{A}(F_2^{\mathcal{C}_1}) = \bigsqcup_{\mathcal{C}_1 \in \mathcal{A}(F_1)} \bigsqcup_{\mathcal{C}_2 \in \mathcal{A}(F_2^{\mathcal{C}_1})} \mathcal{C}_1 \oplus \mathcal{C}_2.$$

Proof. Let X_1 and X_2 be the variables of F_1 and F_2, respectively. Further, let $\mathcal{C} = \{c_1, \dots, c_l\} \in \mathcal{A}(F)$ be an arbitrary attractor of F with length l. We can define $\mathcal{C}_1 = \text{pr}_1(\mathcal{C}) = (\text{pr}_1(c_1), \dots, \text{pr}_1(c_l)) =: (c_1^1, \dots, c_l^1)$ as the projection of $\mathcal{C}$ onto X_1, and similarly $\mathcal{C}_2 = \text{pr}_2(\mathcal{C}) =: (c_1^2, \dots, c_l^2)$ as the projection of $\mathcal{C}$ onto X_2. By definition, F_1 does not depend on X_2. Thus, $F_1(\text{pr}_1(x)) = \text{pr}_1(F(x))$, and for any c_j^1,

$$F_1(c_j^1) = F_1(\text{pr}_1(c_j)) = \text{pr}_1(F(c_j)) = \text{pr}_1(c_{j+1}) = c_{j+1}^1.$$

Iterating this, we find that in general $F_1^k(c_j^1) = c_{j+k}^1$, from which it follows that $\mathcal{C}_1 \in \mathcal{A}(F_1)$.

Next, we consider the non-autonomous network $F_2^{\mathcal{C}_1}$ defined as in Definition 2.1 where $y(t+1) = \text{pr}_2 F(g(t), y(t))$, and $g(t) = c_t^1$. If $y(1) = c_1^2$, then

$$y(2) = \text{pr}_2 F(g(1), c_1^2) = \text{pr}_2 F(c_1^1, c_1^2) = \text{pr}_2 F(c_1) = \text{pr}_2(c_2) = c_2^2$$

and in general

$$y(k+1) = \text{pr}_2 F(g(k), c_k^2) = \text{pr}_2 F(c_k^1, c_k^2) = \text{pr}_2 c_{k+1} = c_{k+1}^2$$

Hence $y(l+1) = \text{pr}_2 F(c_l) = \text{pr}_2 c_1 = y(1)$ and thus $\mathcal{C}_2 \in \mathcal{A}(F_2^{\mathcal{C}_1})$. From this we have that $\mathcal{C} = \mathcal{C}_1 \oplus \mathcal{C}_2 \in \mathcal{C}_1 \oplus \mathcal{A}(F_2^{\mathcal{C}_1})$ and thus

$$\mathcal{A}(F) \subset \bigsqcup_{\mathcal{C}_1 \in \mathcal{A}(F)} \mathcal{C}_1 \oplus \mathcal{A}(F_2^{\mathcal{C}_1}).$$

Conversely, let $\mathcal{C}_1 \in \mathcal{A}(F_1)$ and $\mathcal{C}_2 \in \mathcal{A}(F_2^{\mathcal{C}_1})$. We want to show that $\mathcal{C}_1 \oplus \mathcal{C}_2 \in \mathcal{A}(F)$. Let $g(t) = c_t^1$, $y(1) = c_1^2$, and $y(t+1) = \text{pr}_2 F(g(t), y(t))$. Since $\mathcal{C}_2 \in \mathcal{A}(F_2^{\mathcal{C}_1})$, then $y(t+1) = c_{t+1}^2$ by definition. Let $N = |\mathcal{C}_2|$. Then

$$\begin{aligned} F(c_k^1, c_k^2) &= (\text{pr}_1 F(c_k^1, c_k^2), \text{pr}_2 F(g(k), y(k)) \\ &= (F_1(c_k^1), F_2^{\mathcal{C}_1}(c_k^1, y(k+1))) \\ &= (c_{k+1}^1, c_{k+1}^2). \end{aligned}$$

Thus $F^N(c_1^1, c_1^2) = F(c_N^1, c_N^2) = (c_1^1, c_1^2)$ and hence $\mathcal{C}_1 \oplus \mathcal{C}_2 \in \mathcal{A}(F)$. It follows that

$$\bigsqcup_{\mathcal{C}_1 \in \mathcal{A}(F_1)} \mathcal{C}_1 \oplus \mathcal{A}(F_2^{\mathcal{C}_1}) \subset \mathcal{A}(F),$$

from which we can conclude that the sets are equal. □

The following two examples highlight how Theorem 3.1 enables the computation of the dynamics of a decomposable network from the dynamics of its modules. To match attractors from the upstream module with the attractor spaces of the corresponding non-autonomous downstream networks, it is useful to consider the space of attractors in a specified order: we use parentheses (curly brackets) to denote an ordered (unordered) space of attractors. If there is no ambiguity, in practice we can use $\rtimes$ instead of $\rtimes_P$.

Example 3.1. Consider the Boolean network $F(x_1, x_2, y_1, y_2) = (x_2, x_1, x_2y_2, y_1)$. We can decompose $F = F_1 \rtimes F_2$ where $F_1(x_1, x_2) = (x_2, x_1)$ is an upstream module and $F_2(u_2, y_1, y_2) = (u_2y_2, y_1)$ is a downstream module with external parameter x_2. To find all attractors of F by using Theorem 3.1, we find the attractors of F_1 and the attractors of F_2 induced by each of those attractors. It is easy to see that $\mathcal{A}(F_1) = \{00, 11, \{01, 10\}\}$ (where we denote steady states $\mathcal{C} = \{c\}$ simply by c).

- For $\mathcal{C}_1 = 00$, the corresponding non-autonomous network is $y(t+1) = F_2(0, 0, y(t))$. If $y(0) = (y_1^*, y_2^*)$, then

$$y(1) = F_2(0, 0, y_1^*, y_2^*) = (0, y_1^*),$$
$$y(2) = F_2(0, 0, 0, y_1^*) = (0, 0).$$

  Thus, the space of attractors for $F_2^{\mathcal{C}_1}$ is

$$\mathcal{A}(F_2^{\mathcal{C}_1}) = \{00\}.$$

- For $\mathcal{C}_2 = 11$, the corresponding non-autonomous network is $y(t+1) = F_2(1, 1, y(t))$. If $y(0) = (y_1^*, y_2^*)$, then

$$y(1) = F_2(1, 1, y_1^*, y_2^*) = (y_2^*, y_1^*),$$
$$y(2) = F_2(1, 1, y_2^*, y_1^*) = (y_1^*, y_2^*).$$

  Thus, the corresponding space of attractor is

$$\mathcal{A}(F_2^{\mathcal{C}_2}) = \{00, 11, (01, 10)\}.$$

- For $\mathcal{C}_3 = (01, 10)$, we define $g(t) : \mathbb{N} \to \{0,1\}^2$ by $g(0) = (0,1)$, $g(1) = (1,0)$, and $g(t+2) = g(t)$. $F_2^{\mathcal{C}_3}$ is given by $y(t+1) = F_2(g(t), y(t))$. If $y(0) = (y_1^*, y_2^*)$, then

$$\begin{aligned}
y(1) &= F_2(0,1,y_1^*,y_2^*) = (y_2^*, y_1^*),\\
y(2) &= F_2(1,0,y_2^*,y_1^*) = (0, y_2^*),\\
y(3) &= F_2(0,1,0,y_2^*) = (y_2^*, 0),\\
y(4) &= F_2(1,0,y_2^*,0) = (0, y_2^*).
\end{aligned}$$

Then, the corresponding space of attractors is

$$\mathcal{A}(F_2^{\mathcal{C}_3}) = \{00, (01, 10)\}.$$

To reconstruct the entire space of attractors for F, we have

$$\begin{aligned}
\mathcal{A}(F) &= \mathcal{A}(F_1) \rtimes \mathcal{A}(F_2)\\
&= (00, 11, (01, 10)) \rtimes \left(\mathcal{A}(F_2^{\mathcal{C}_1}), \mathcal{A}(F_2^{\mathcal{C}_2}), \mathcal{A}(F_2^{\mathcal{C}_3})\right)\\
&= 00 \oplus \{00\} \cup 11 \oplus \{00, 11, (01, 10)\} \cup (01, 10) \oplus \{00, (01, 10)\}\\
&= \{0000, 1100, 1111, (1101, 1110), (0100, 1000), (0101, 1010)\},
\end{aligned}$$

which agrees with the space of attractors shown in Fig. 4B.

Example 3.2. Consider the linear Boolean network

$$F(x_1, x_2, y_1, y_2) = (x_2, x_1, x_2 + y_2, y_1).$$

We can decompose $F = F_1 \rtimes F_2$ into modules $F_1(x_1, x_2) = (x_2, x_1)$ and $F_2(u_2, y_1, y_2) = (u_2 + y_2, y_1)$. The space of attractors of the upstream module F_1 is

$$\mathcal{A}(F_1) = \{00, 11, (01, 10)\}.$$

Using the dynamic decomposition theorem (Theorem 3.1), we can identify all attractors of F as follows (see Fig. S2 for a graphical description).

- For $\mathcal{C}_1 = 00$, the corresponding non-autonomous network is $y(t+1) = \overline{F}_2(0, 0, y(t))$. If $y(0) = (y_1^*, y_2^*)$, then $y(1) = \overline{F}_2(0, 0, y_1^*, y_2^*) = (y_2^*, y_1^*)$. Thus, the space of attractors for $F_2^{\mathcal{C}_1}$ is

$$\mathcal{A}(F_2^{\mathcal{C}_1}) = \{00, 11, (01, 10)\}.$$

- Similarly, for $\mathcal{C}_2 = 11$, we find that the space of attractors for $F_2^{\mathcal{C}_2}$ is

$$\mathcal{A}(F_2^{\mathcal{C}_2}) = \{(00, 10, 11, 01)\}.$$

- For $\mathcal{C}_3 = (01, 10)$, we define $g(t) : \mathbb{N} \to X_1$ by $g(0) = (0, 1)$, $g(1) = (1, 0)$, and $g(t+2) = g(t)$. $F_2^{\mathcal{C}_3}$ is given by $y(t+1) = F_2(g(t), y(t))$. If $y(0) = (y_1^*, y_2^*)$, then

$$\begin{aligned} y(1) &= (1 + y_2^*, y_1^*), \\ y(2) &= (y_1^*, y_2^* + 1), \\ y(3) &= (y_2^*, y_1^*), \\ y(4) &= (y_1^*, y_2^*) = y(0), \end{aligned}$$

and in general for $t > 0$,

$$\begin{aligned} y(4t) &= (y_1^*, y_2^*), \\ y(4t+1) &= (1 + y_2^*, y_1^*), \\ y(4t+2) &= (y_1^*, y_2^* + 1), \\ y(4t+3) &= (y_2^*, y_1^*). \end{aligned}$$

It follows that there are only 2 periodic trajectories in this case: $(00, 10, 01, 00, 00, 10, 01, 00, \ldots)$ and $(11, 01, 10, 11, 11, 01, 10, 11, \ldots)$, which both have period 4. The corresponding attractor space is

$$\mathcal{A}(F_2^{\mathcal{C}_3}) = \{(00, 10, 01, 00), (11, 01, 10, 11)\}.$$

Note that the repetition of certain states is needed to obtain the correct attractors of the full network F.

To reconstruct the space of all attractors for F, we have

$$\begin{aligned}\mathcal{A}(F) &= (00, 11, (01, 10)) \rtimes \left(\mathcal{A}(F_2^{\mathcal{C}_1}), \mathcal{A}(F_2^{\mathcal{C}_2}), \mathcal{A}(F_2^{\mathcal{C}_3})\right) \\ &= \begin{Bmatrix} 00 \oplus \{00, 11, (01, 10)\} \\ 11 \oplus \{(00, 10, 11, 01)\} \\ (01, 10) \oplus \{(00, 10, 01, 00), (11, 01, 10, 11)\} \end{Bmatrix} \\ &= \begin{Bmatrix} 0000, 0011, (0001, 0010), \\ (1100, 1110, 1111, 1101), \\ (0100, 1010, 0101, 1000), \\ (0111, 1001, 0110, 1011) \end{Bmatrix}.\end{aligned}$$

The linear network F possesses thus two steady states, one 2-cycle and three 4-cycles.

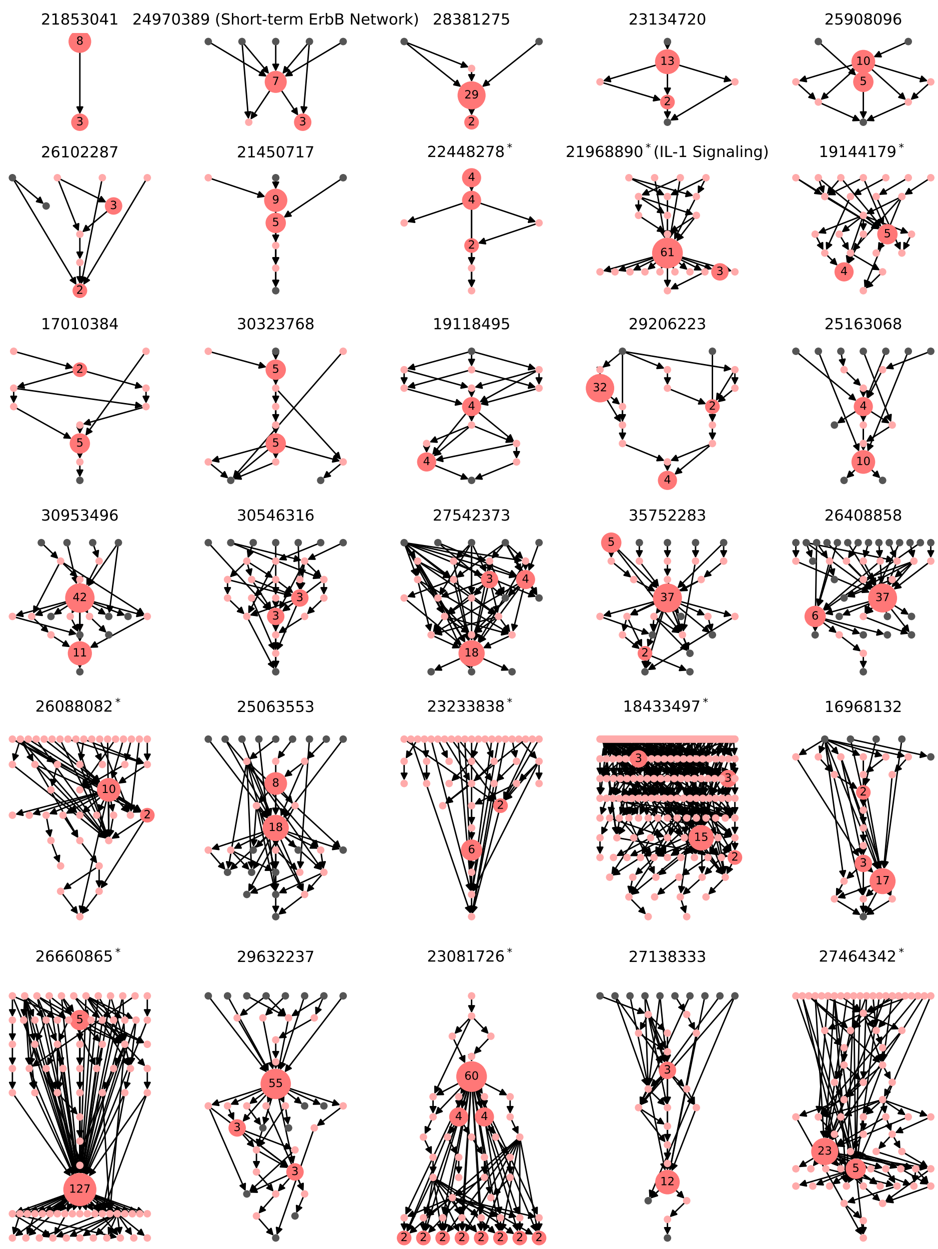

Figure S1: Modular decomposition of all published expert-curated Boolean gene regulatory network models with more than one non-trivial module. Each model is labeled by the Pubmed ID of its source. Each red non-trivial module is labeled by its size, i.e., the number of nodes contained in the module. Trivial modules consist of one node only. They are colored gray if they are input or output nodes, i.e., nodes without incoming or outgoing edges, respectively. Otherwise, they are colored pink. For models with more than 40 modules, input and output modules are omitted for clarity, indicated by * after the Pubmed ID. An arrow from module X to module Y indicates that some node in X regulates some node in Y. The directed acyclic graph of the multicellular pancreatic cancer model, analyzed in Fig. 5, is shown in row 4, column 4 (Pubmed ID 35752283).

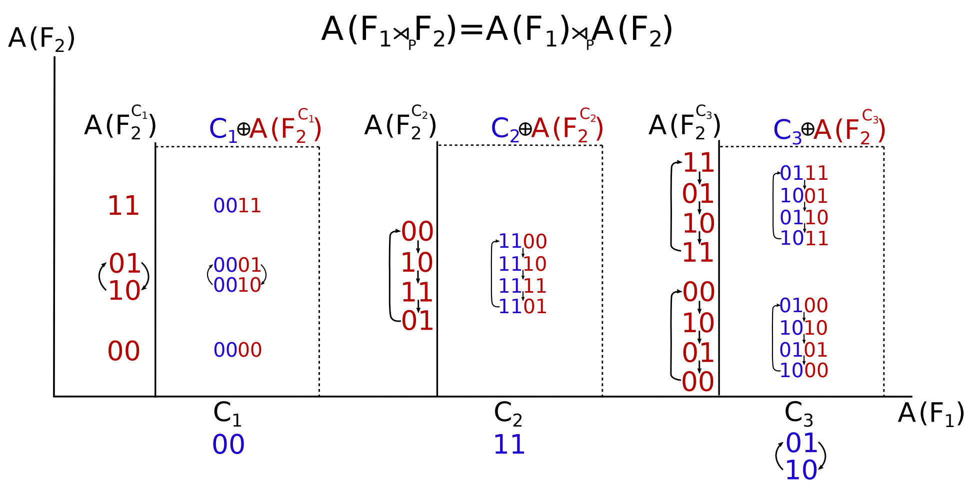

Figure S2: Graphical description of the dynamic decomposition theorem (applied to Example 3.2). The dynamics of $F_1 \rtimes_P F_2$ can be seen as a semi-direct product between the dynamics of F_1 and the dynamics of F_2 induced by F_1 via the coupling scheme P. The dynamics of F_2 induced by attractors of F_1 can vary, and the dynamic decomposition theorem (Theorem 3.1) shows precisely how to combine all of these attractors.