

# Dynamically consistent mergers of Boolean models within the PSBN framework

**Samuel Pastva**, Ondřej Huvar, Nikola Beneš, David Šafránek



# Motivation

Work in progress!

Key benefit of logic-based models is **interpretability**:

- *Variable activity* represents realistic *concentration levels*;
- *Regulations* represent real-world mechanistic *processes*;
- *Update functions* constrain the effect of *interactions between regulators*.

*Interpretability* intuitively suggests some notion of *composability*: If the models are **compatible in their assumptions**, "merging" multiple models should also produce an interpretable model that is **dynamically consistent with its smaller constituents**.



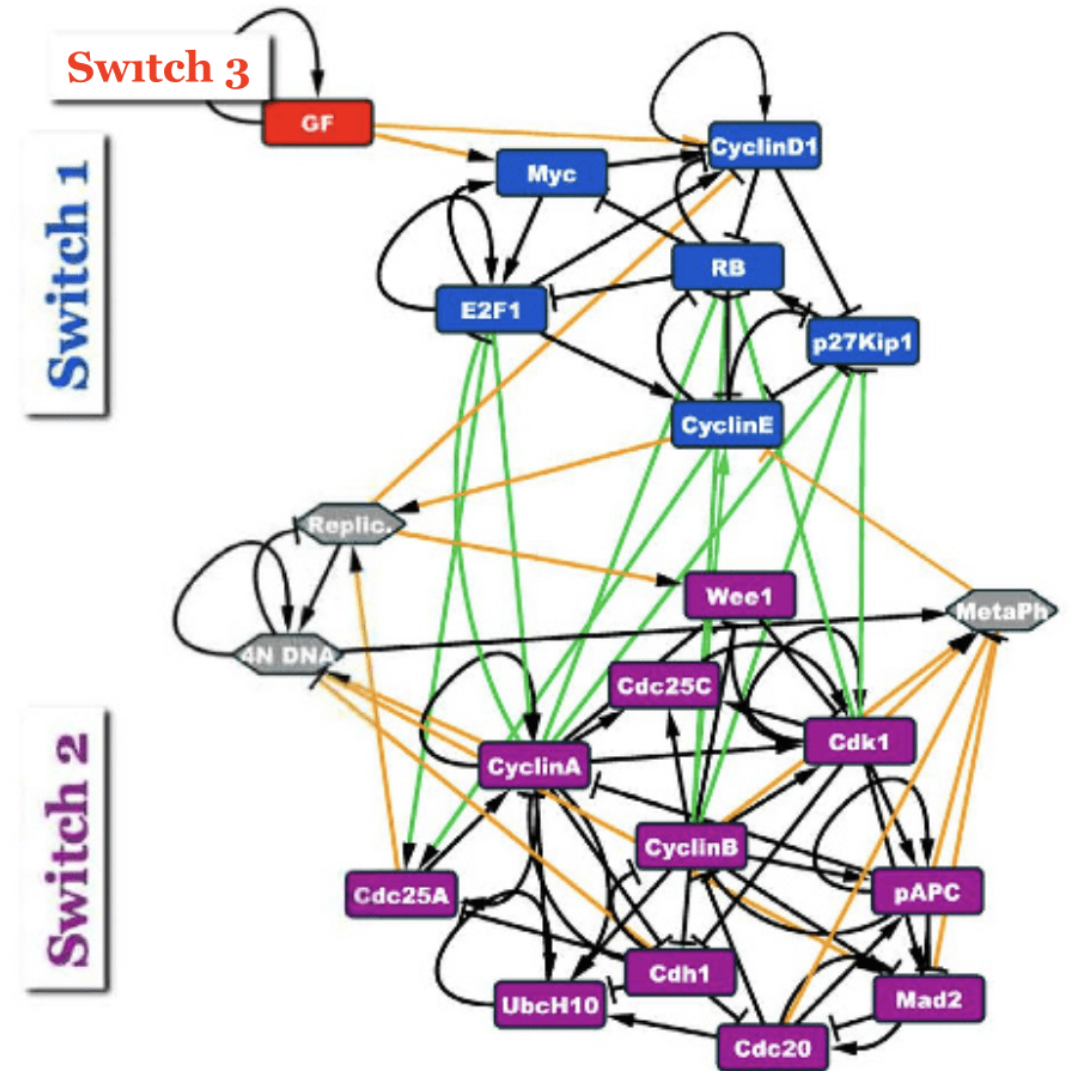
# Model mergers in practice

Informal mergers, extensions, or compositions of logic-based models are *relatively common*.

Merged models consist of all variables and regulations in the constituent models, possibly with some additional connecting "glue".

Often **manual** process: Unclear how update functions of the larger model incorporate the dynamics of the smaller models, or how to automate their construction.

Existing automation and theory often only operate at the level of influence graph SCCs.



Deritei, D., Aird, W. C., Ercsey-Ravasz, M., & Regan, E. R. (2016). Principles of dynamical modularity in biological regulatory networks. *Scientific reports*, 6(1), 21957.

# Compatibility of mechanistic assumptions

Merging two models may not make sense if they model the same things in different ways! (duh)

- **Compatibility of shared state:** If a variable appears in both models, its discretization criteria must be compatible ("x=1" must "mean the same thing").
- **Compatibility of shared influence:** If a regulation appears in both models, its biological interpretation should be the same.
- **Absence of non-essential model elements:** A model silently assumes that *any element not included in it is irrelevant* to the studied process (e.g., constant variable, unused regulation, ...). Models sometimes contain non-essential elements that are not supported by biological evidence. Merging such elements can cause arbitrary but unnecessary conflicts.

# Dynamical consistency

**Definition:** Let  $M_{big}$  and  $M_{small}$  be two models, such that  $M_{big}$  includes all variables of  $M_{small}$ , i.e.,  $Vars(M_{small}) \subseteq Vars(M_{big})$ . Let  $Ctx$  be a subspace of  $M_{big}$ .

We say that  $M_{small}$  is ***embedded within  $M_{big}$  via context  $Ctx$*** , if for every model state  $x \in Ctx$  and every variable  $A \in Vars(M_{small})$ , we have:

$$f_A^{(M_{big})}(x) = f_A^{(M_{small})}(x|_{Vars(M_{small})}).$$

**Intuition:** Within  $Ctx$ , if  $M_{small}$  prescribes some dynamics,  $M_{big}$  copies it exactly. Variables not described by  $M_{small}$  can evolve arbitrarily. Outside of  $Ctx$ ,  $M_{big}$  is also free to evolve arbitrarily, including all variables of  $M_{small}$ .

# Dynamical consistency

## Definition (cont.):

- Model  $M_{small}$  is **completely embedded** within  $M_{big}$ , if for every  $A \in \text{Vars}(M_{small})$ , we have  $Ctx_A = \star$ .
- The embedding of  $M_{small}$  in  $M_{big}$  is **stable** if  $Ctx$  is a *trap space*.

**Intuition:** When the embedding is complete,  $M_{big}$  within some context  $Ctx$  performs every asynchronous state transition admissible in  $M_{small}$ .

When the embedding is stable, relevant attractor states of  $M_{small}$  can be extended to attractor states of  $M_{big}$  (but the attractor itself can be larger due to additional variables in  $M_{big}$  unconstrained by  $Ctx$ ).

# Dynamical (in)consistency

Stability and completeness are not always required (or desired!) properties:

- **Ex. 1:** If  $M_{small}$  is only validated for a specific combination of input values, requiring full completeness propagates possibly non-biological behavior into  $M_{big}$  (recall absence of non-essential model elements). *Completeness requirement implicitly asserts that the whole  $M_{small}$  model is a correct representation of biological reality.*
- **Ex. 2:** Assume  $M_{small}$  describes a transient phenotype, such as a specific cell cycle phase switch. If  $M_{big}$  is to reproduce the behavior of  $M_{small}$  within the full cell cycle, the  $M_{small}$  embedding cannot be stable (shifting to the next cell cycle phase is eventually possible). *Stability requirement implicitly asserts that other variables or modules not covered by  $M_{small}$  are also stable, which may not be true in the long-term.*

# Example time (finally!)

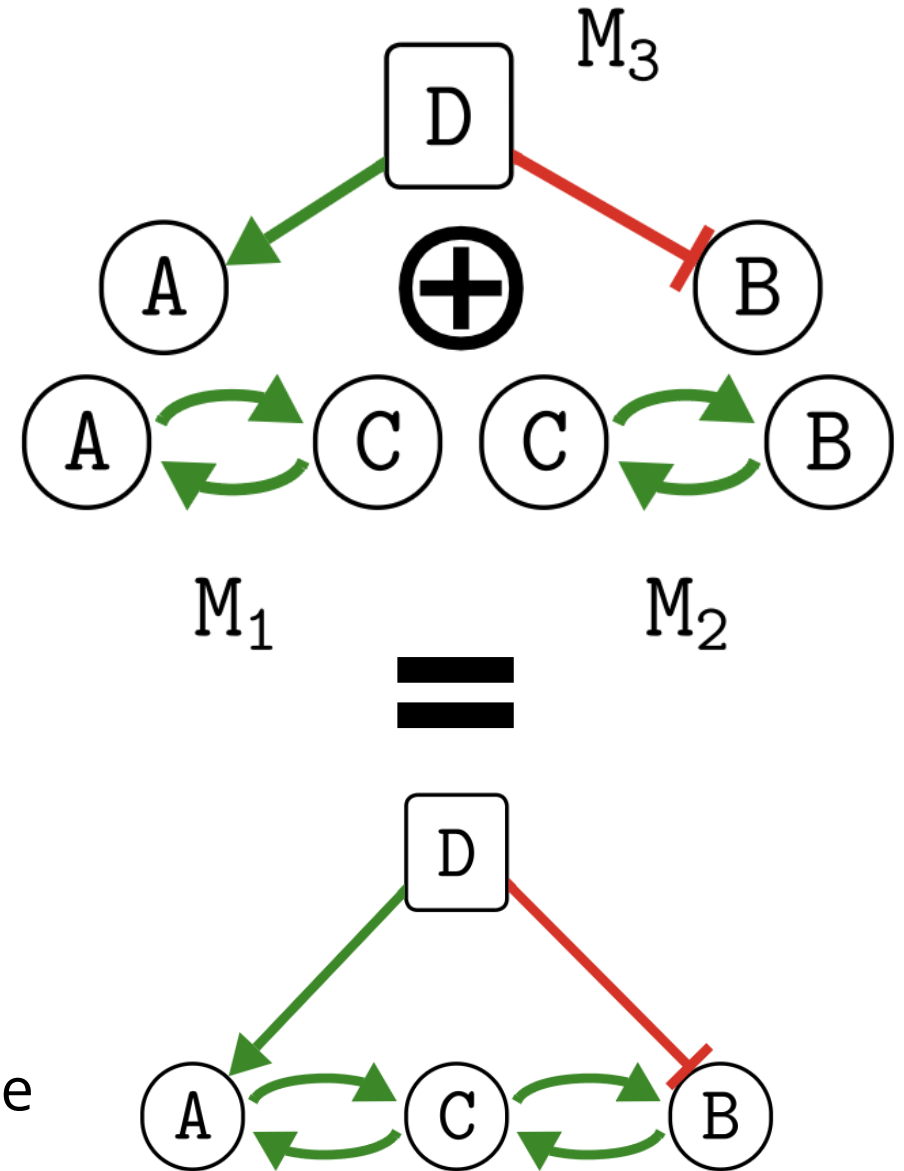
Models  $M_1$  and  $M_2$  are just bistable switches.

Model  $M_3$  propagates input  $D$  downstream.

| Model | Update rules                                                        |
|-------|---------------------------------------------------------------------|
| $M_1$ | $f_A = C; f_C = A$                                                  |
| $M_2$ | $f_B = C; f_C = B$                                                  |
| $M_3$ | $f_A = D; f_B = !D; f_D = D$                                        |
| $M$   | $f_A = C \ \& \ D; f_B = C \ \& \ !D;$<br>$f_C = A \mid B; f_D = D$ |

Models  $M_1$  and  $M_2$  have **complete and stable embeddings** in  $M$  (consider subspaces  $\{D \mapsto 1, B \mapsto 0\}$  and  $\{D \mapsto 0, A \mapsto 0\}$ ).

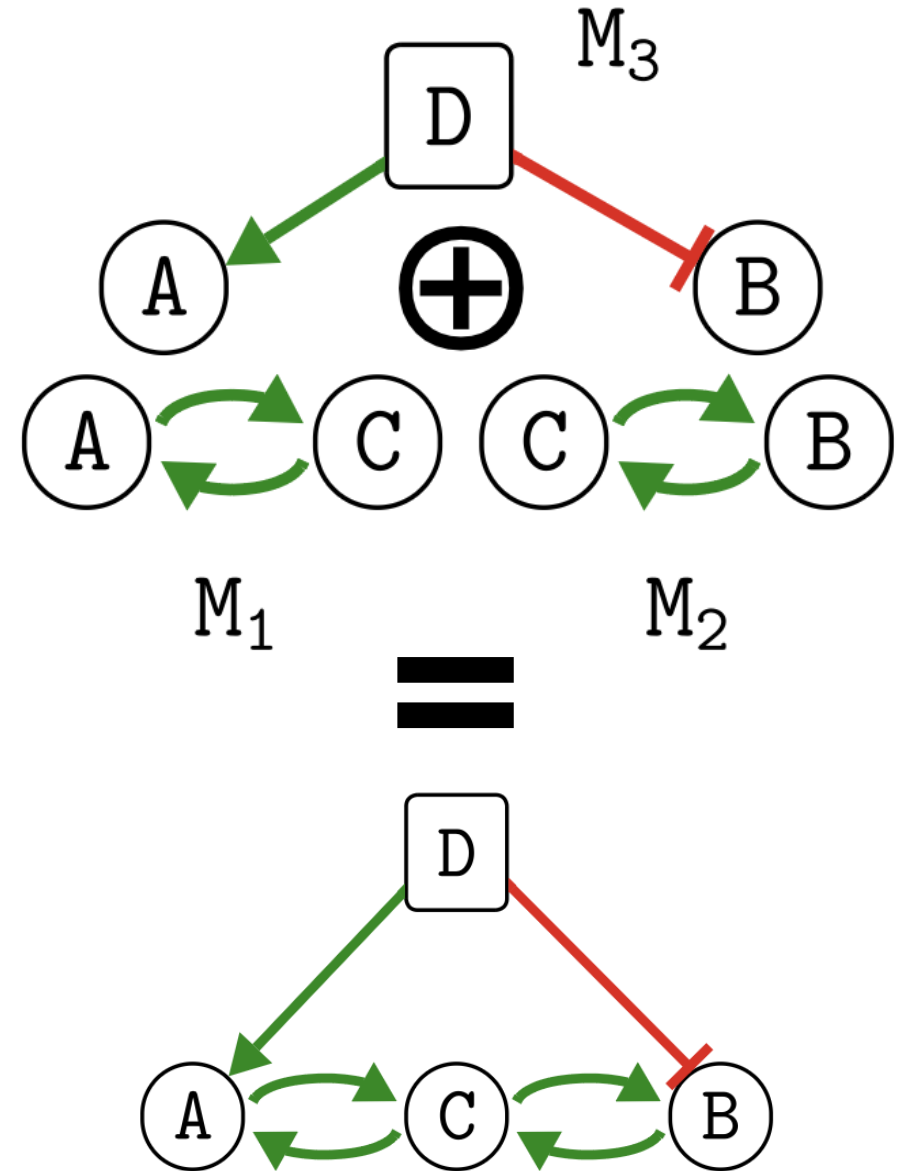
Model  $M_3$  has a **complete embedding** (subspace  $\{C \mapsto 1\}$ ), but **no stable embedding**.



# Example time (finally!)

## Conclusion:

- $M_1$  and  $M_2$  are smaller models valid in mutually exclusive contexts.
- The choice between  $M_1$  and  $M_2$  behavior is modulated by  $D$  and signaled via  $M_3$ .
- $M_3$  does not have a stable embedding, because it is not a terminal decision; it ignores that either  $A$  or  $B$  can still change due to the  $M_1$  or  $M_2$  switch.



# Deciding dynamical consistency

**Question 1 (verification):** Given  $M_{small}$ ,  $M_{big}$ , and  $Ctx$ , does  $M_{small}$  have an embedding within  $M_{big}$  via  $Ctx$ ?  $\Rightarrow$  *Test of function equivalence ( $\Pi_1$ ). Feasible for Boolean models represented via, e.g., prime implicants or BDDs.*

**Question 2 (detection):** Given  $M_{small}$  and  $M_{big}$ , find  $Ctx$  through which  $M_{small}$  has the desired (e.g., complete or stable) embedding within  $M_{big}$ . What is the inclusion maximal/minimal  $Ctx$  with this property?  $\Rightarrow$  *Existence of a  $Ctx$  satisfying Question 1 ( $\Sigma_2$ ). Can be encoded as ASP or QBF problem.*

**Question 3 (inference):** Given  $M_{small}$  and a larger influence graph  $IG_{big}$ , is there some model  $M_{big}$  (based on  $IG_{big}$ ) in which  $M_{small}$  has the desired embedding?  $\Rightarrow$  *Requires encoding of the unknown functions of  $M_{big}$ ; feasible (at least) for small arity or incomplete DNF encoding (alla Bonesis).*

# Dynamical consistency in PSBNs

**Motivation:** The embedding inference problem can be expressed through static properties of Partially Specified Boolean Networks (PSBNs).

Ex.: 
$$f_A(x) = x_B \vee \mathbf{F}(x_C, x_D, x_E)$$

A PSBN encodes an ensemble of concrete BNs (interpretations) by admitting *uninterpreted update functions* (e.g.,  $\mathbf{F}$ ) in BN dynamics. Static properties reason about these functions in first-order logic w. quantifiers.

Ex.: 
$$\forall x. \mathbf{F}(x_C, 0, x_E) \leq \mathbf{F}(x_C, 1, x_E) \quad (\text{monotonicity})$$

Valid interpretations can be enumerated and studied via automated reasoning: binary decision diagrams (BDDs), satisfiability modulo theories (SMT), etc. But high function arity and complex quantifiers make this challenging (some problems may not need them though\*).

\*Huvar, Ondřej, Martin Jonáš, and Samuel Pastva. "SMT with Uninterpreted Functions and Monotonicity Constraints in Systems Biology." *arXiv preprint arXiv:2604.07496* (2026).

# Dynamical consistency in PSBNs

Returning to our running example...

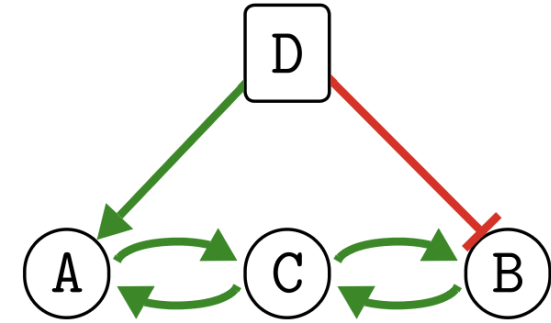
A subspace can be encoded as a pair of its most "extreme" states  $\Rightarrow$  static properties can quantify over subspaces.

$$f_A(x) = \mathbf{F}_A(x_C, x_D)$$

$$f_B(x) = \mathbf{F}_B(x_C, x_D)$$

$$f_C(x) = \mathbf{F}_C(x_A, x_B)$$

$$f_D(x) = x_D$$



$$\exists Ctx_{M_1}. \forall x. (x \in Ctx_{M_1}) \Rightarrow ((\mathbf{F}_A(x_C, x_D) = x_C) \wedge (\mathbf{F}_C(x_A, x_B) = x_A))$$

$$\exists Ctx_{M_2}. \forall x. (x \in Ctx_{M_2}) \Rightarrow ((\mathbf{F}_B(x_C, x_D) = x_C) \wedge (\mathbf{F}_C(x_A, x_B) = x_B))$$

$$\exists Ctx_{M_3}. \forall x. (x \in Ctx_{M_3}) \Rightarrow ((\mathbf{F}_A(x_C, x_D) = x_D) \wedge (\mathbf{F}_B(x_C, x_D) = \neg x_D))$$

+ Assert completeness  
and/or stability of  $Ctx_{M_i}$ .

Concrete update functions of  $M_1$ ,  $M_2$  and  $M_3$ .

# Wrapping up

- "Merging" multiple Boolean models is a natural operation that we often perform even without formal guarantees.
  - Modularity simplifies model construction and inference.
- We can formally understand mergers as *embeddings* of "smaller" model dynamics within the "larger" model.
- Be careful what you wish for: *Complete* and *stable* embeddings are not always desirable! (They require additional assumptions on the smaller model)
  - *Model authors still need to understand what their model is for, but can focus on high level architecture instead of individual model functions.*
- Model embeddings can be studied and encoded within existing automated reasoning and inference frameworks for BNs; but many encoding and optimization challenges remain.
- Not all models can be merged safely. *What structural/dynamical properties cause models to be incompatible?*