Long-lived sets: The missing oscillatory phenotypes of Boolean networks

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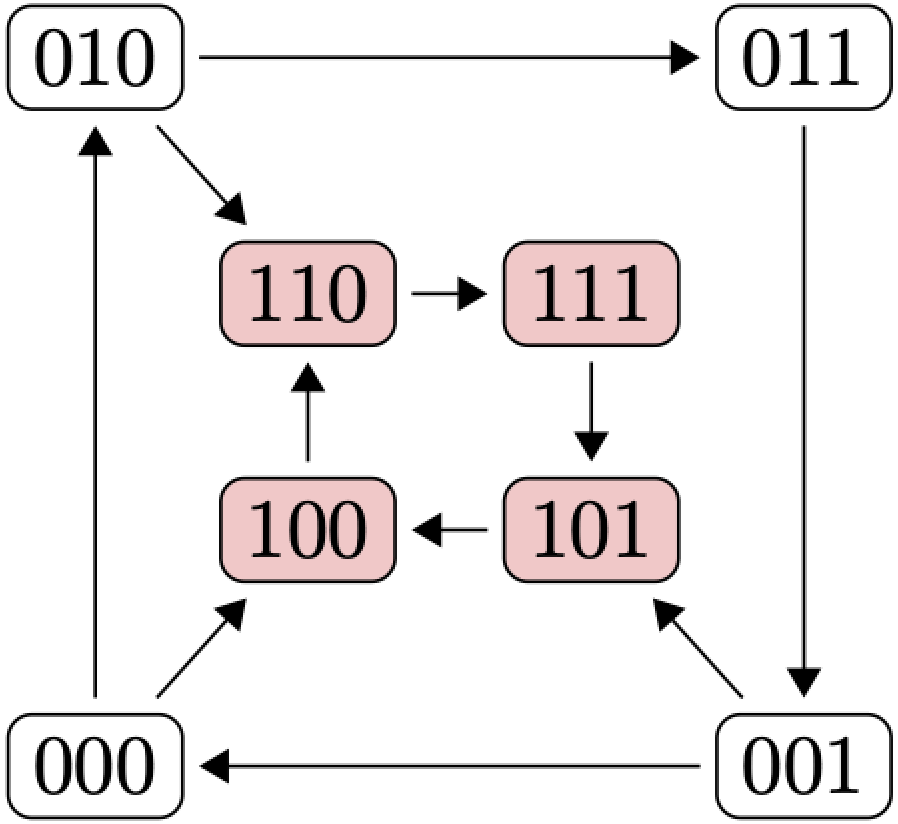
Attractors...

Central dogma of logic-based models:
Model dynamics inevitably converges towards an attractor.

Alternative fairness formulation:
If a transition is enabled infinitely often, it must eventually be taken.

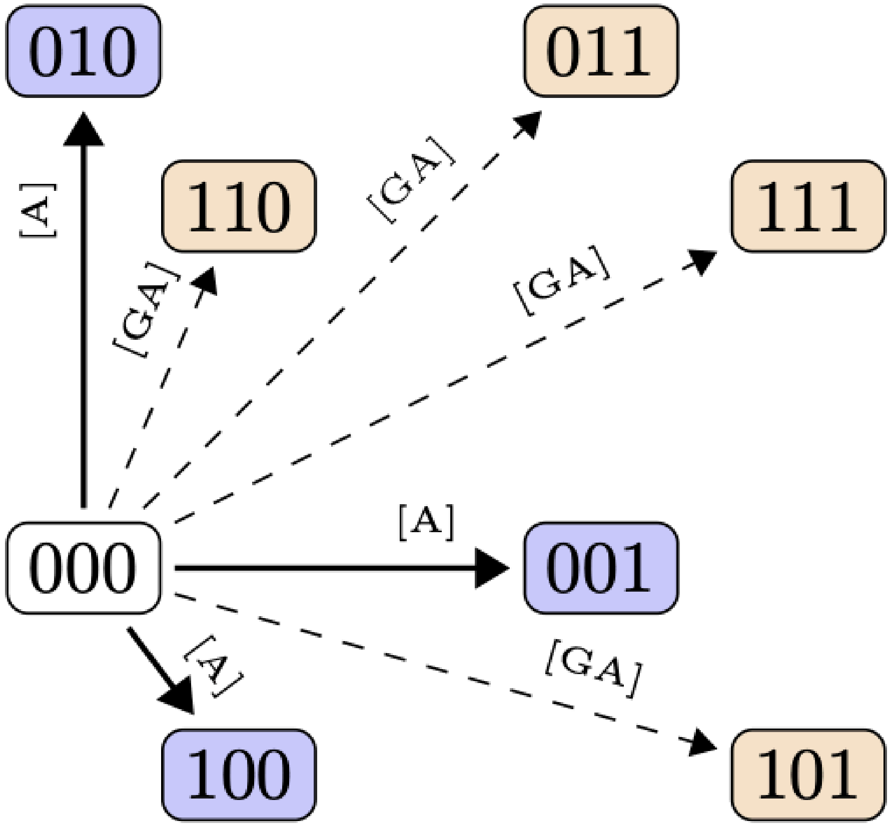


… are not good enough?

(Most) Boolean models are meant to be over-approximations of biology:

We don't know the exact kinetic parameters, concentrations, etc.

⇒ We take the conservative approach: if a state transition it is not impossible, it is allowed.

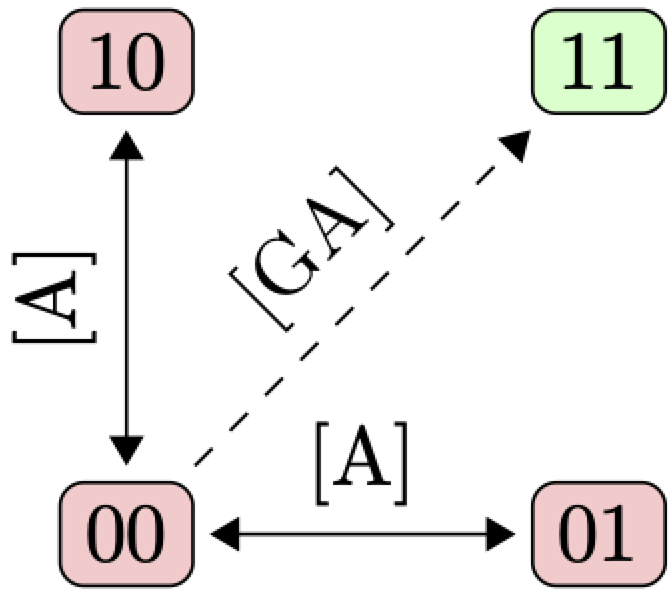


Asynchronous [A] ≤ Generalized asynch. [GA] ≤ Most permissive [MP]

Attractors do not over-approximate long-term behavior

Adding more state transitions (*increasing over-approximation*) can only ever eliminate attractors (*pruning the "long-term behavior"*).

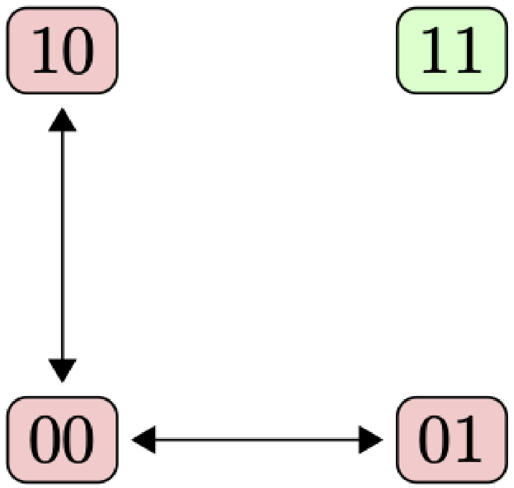
Why is this a problem? Some of those transitions are "wrong"; but we don't know which ones! ⇒ We may be throwing away viable phenotypes.

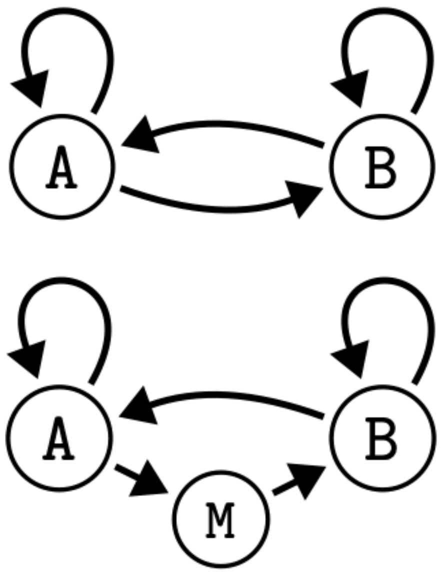


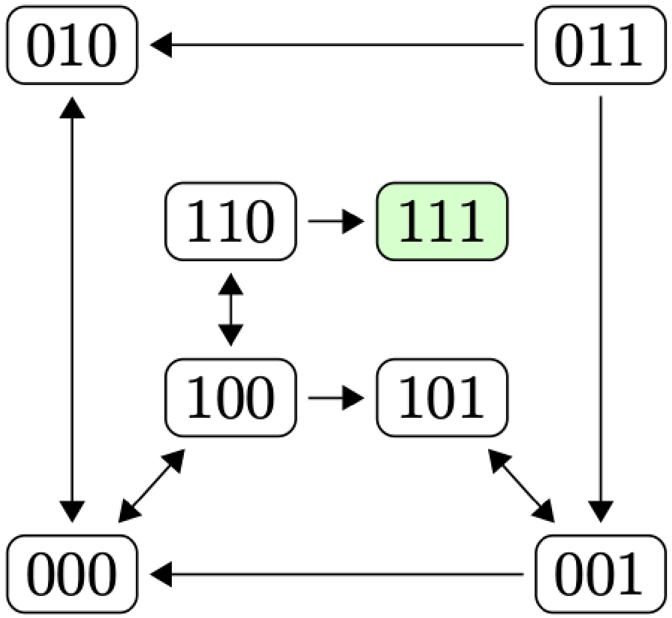
Its not just the update schemes...

Network reduction creates attractors, refinement destroys attractors.

⇒ "Less granular" models can have additional long-term behavior compared to "more granular" models.





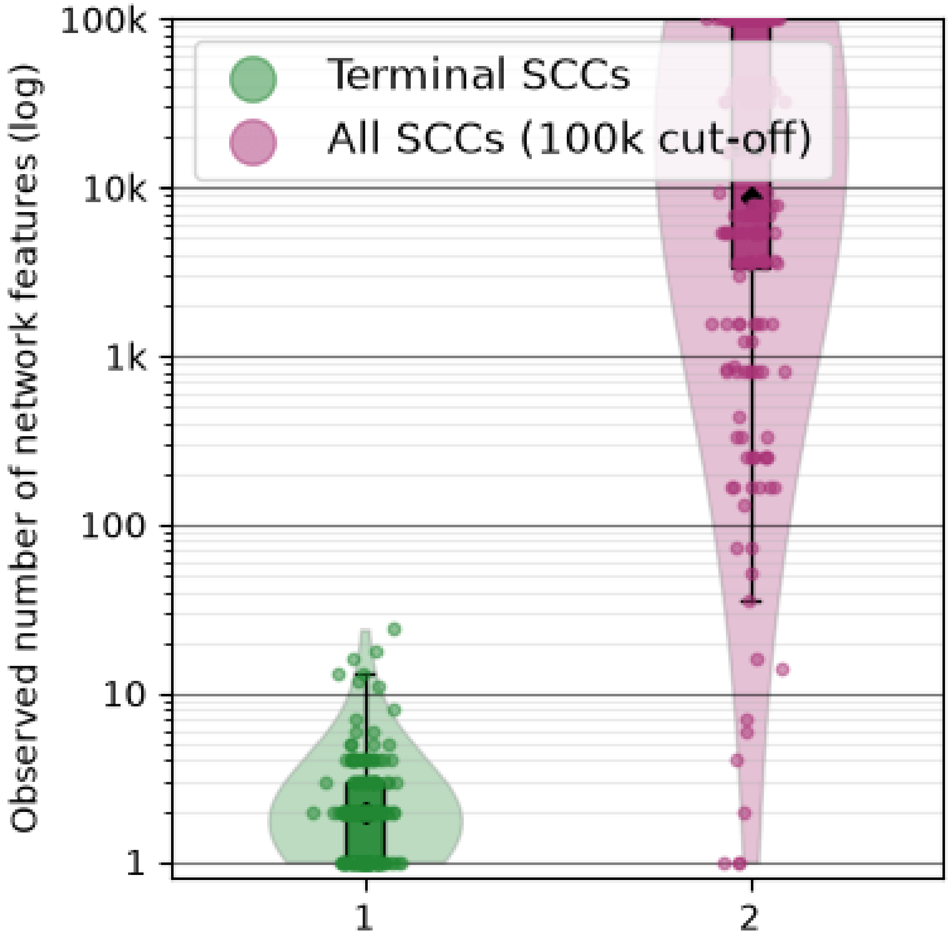


Similar "granularity problems" arise when trying to use BNs as over-approximations of (even simple) continuous dynamics.

How do we fix this?

Good news: Considering all cycles (or SCCs) has all the properties we wanted from attractors. ⇒ *Cycles provably over-approximate every "expected" long-term behavior.*

Bad news: There are too many cycles in most Boolean networks. ⇒ *This is a valid over-approximation, but not a useful one.*

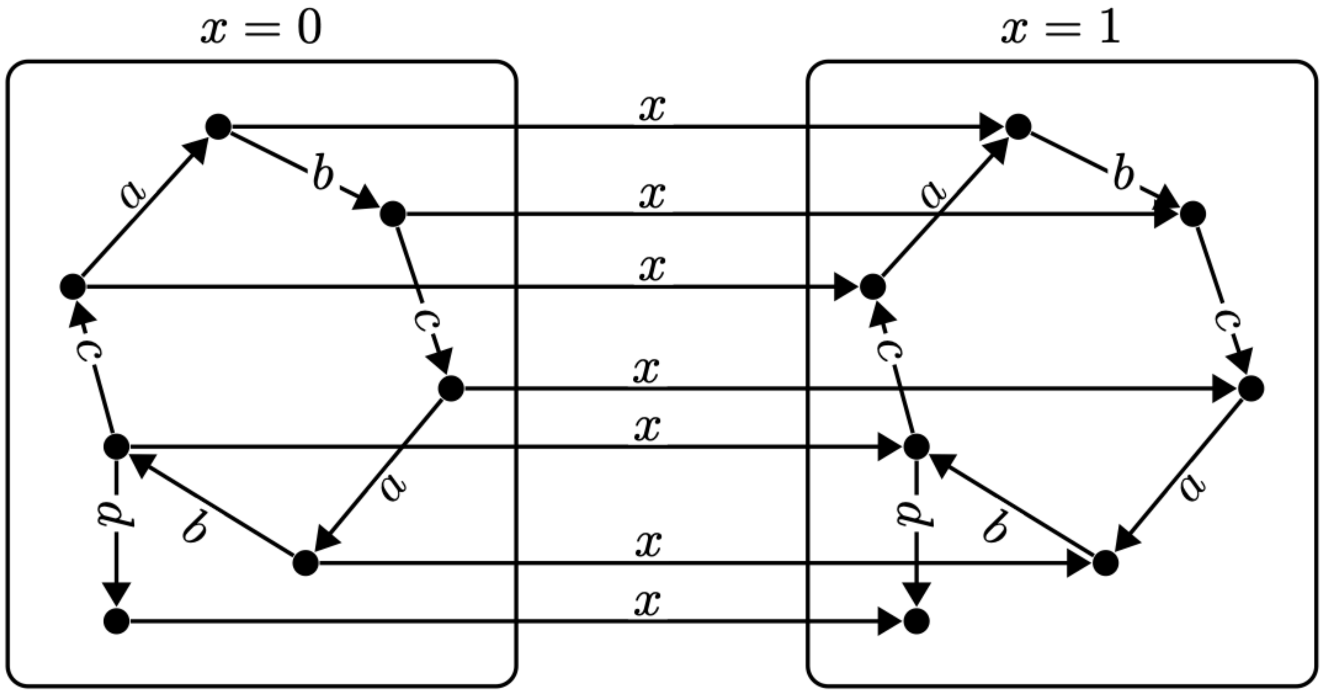


Biodivine Boolean models; Input nodes fixed;
Removed completely acyclic networks.

How do we *actually* fix this?

A set of states is "long-lived" if it cannot be escaped by value percolation (in any variable). $\Rightarrow$ The value of variable x percolates to 1 in set C if $f_x(state) = 1$ for every $state \in C$ (analogously for 0).

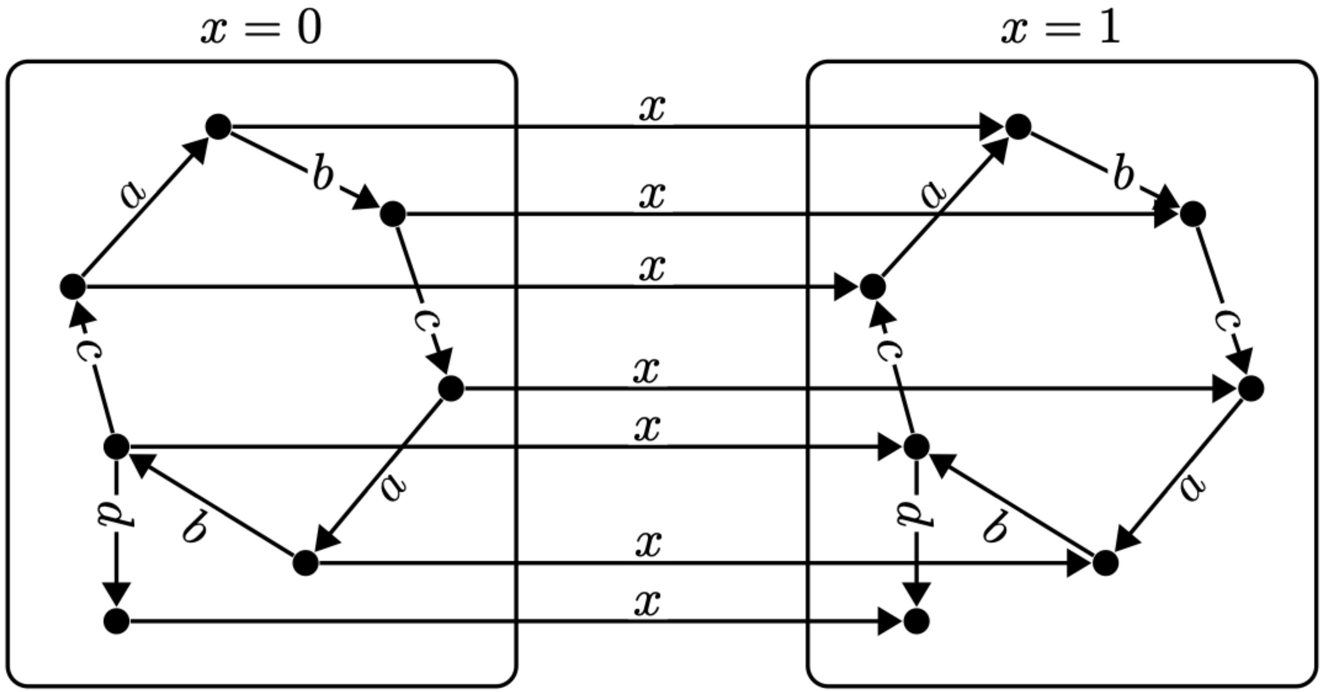
Example: Neither cycle is terminal, but the one with $x = 1$ (right) is long-lived.



Interpretability

If we understand $f_x(state) = 1$ as "x is growing", we can interpret value percolation as "if x only grows, it must eventually become 1". Meanwhile, when $f_x(state) = 1$ for some states and $f_x(state) = 0$ for others, x could stay 0 indefinitely.

Fairness formulation:
If a transition is enabled *uninterrupted*, it must eventually be taken. Intermittently active transitions are not guaranteed to be taken.

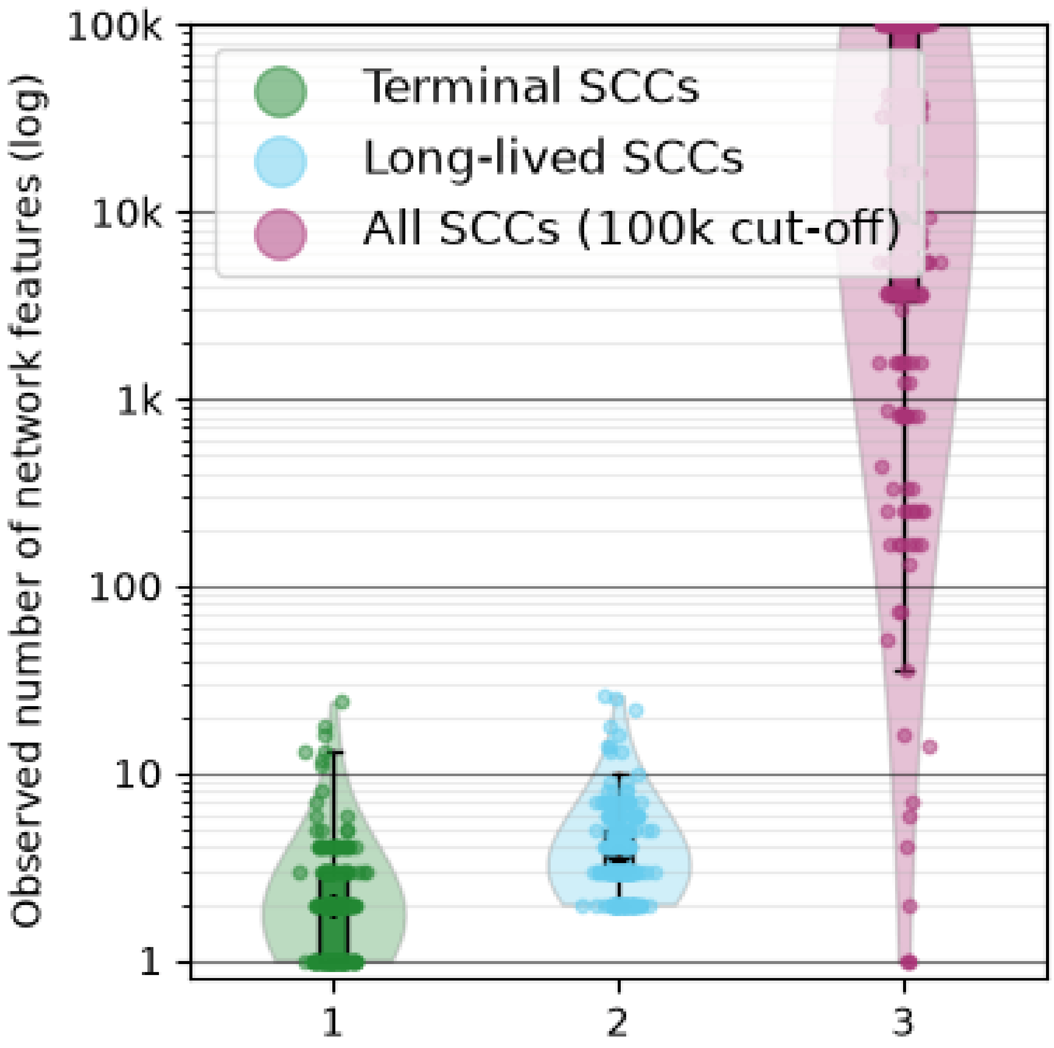


Did it work?

Due to prevalence of canalyzing functions in BNs, value percolation is actually very common!

⇒ Long-lived cycles (or SCCs) are therefore quite rare. Almost as rare as attractors.

⇒ Long-lived cycles still have the nice theoretical properties that we wanted. ("More granular" models contain all phenotypes of "simpler" models)

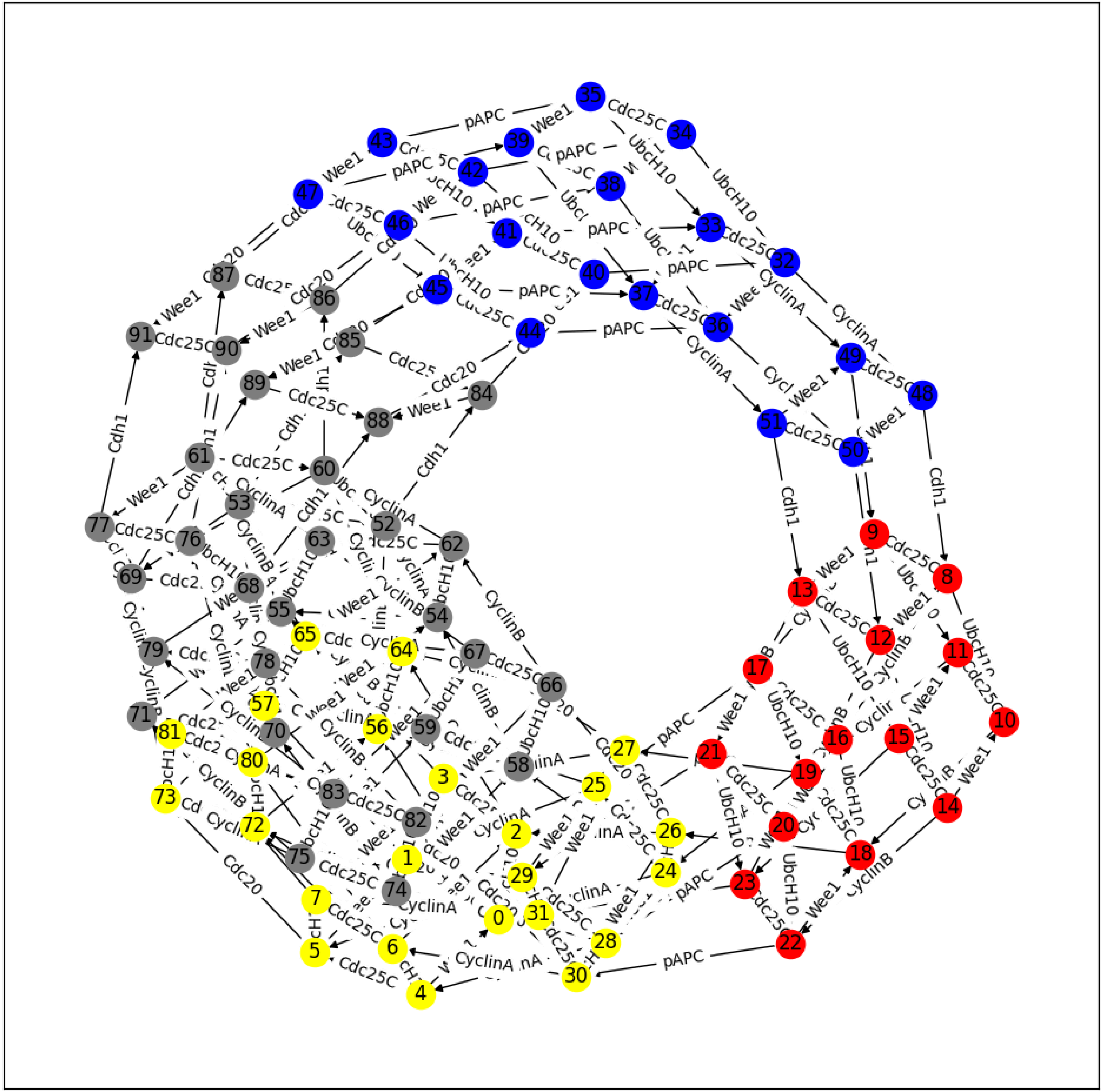


Biodivine Boolean models; Input nodes fixed;
Removed completely acyclic networks.

Does it recover oscillatory phenotypes?

There is no "cell cycle attractor" in the asynchronous update, but the expected behavior is present as a long-lived SCCs (including correct phase transitions).

Deritei, D., Rozum, J., Ravasz Regan, E., & Albert, R. (2019). A feedback loop of conditionally stable circuits drives the cell cycle from checkpoint to checkpoint. Scientific reports, 9(1), 16430.



What if we don't care about oscillation?

Several hypothesized T cell hybrid phenotypes only appear as asynchronous long-lived SCCs; not as attractors.

⇒ Many similar examples of "exclusively long-lived" phenotypes in other models.

	Tbet	GATA3	Foxp3	RORgt
Th0	0	0	0	0
Th1	1	0	0	0
Th2	0	1	0	0
iTreg	0	0	1	0
Th17	0	0	0	1
Th1-Th2	1	1	0	0
Th1-iTreg	1	0	1	0
iTreg-Th17	0	0	1	1
Th1-iTreg-Th17	1	0	1	1
Th1-Th2-iTreg	1	1	1	0

Puniya, B. L., Todd, R. G., Mohammed, A., Brown, D. M., Barberis, M., & Helikar, T. (2018). A mechanistic computational model reveals that plasticity of CD4+ T cell differentiation is a function of cytokine composition and dosage. Frontiers in physiology, 9, 878.

Wrapping up

- Attractors are useful, but they work *against* the over-approximation property assumed by most Boolean networks.
  - Counter-intuitive behavior when transitioning between update schemes, changing the influence graph, etc.
- Generic cycles (or SCCs) are better suited, but too numerous.
- *Inevitability of value percolation* as an additional modeling assumption.
  - Leads to the notion of "long-lived oscillation" $\Rightarrow$ Retains nice formal properties of generic cycles, but much more realistic.
- Long-lived oscillations:
  - Are almost as rare as attractors;
  - Recover expected oscillatory phenotypes;
  - Often recover phenotypes that cannot be realized via attractors.