Modular control of Boolean networks

David Murrugarra

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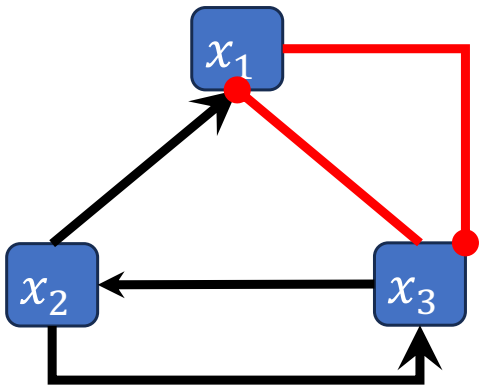
Modularity Seminar,
Feb 18, 2025.

Boolean Networks (BN)

a



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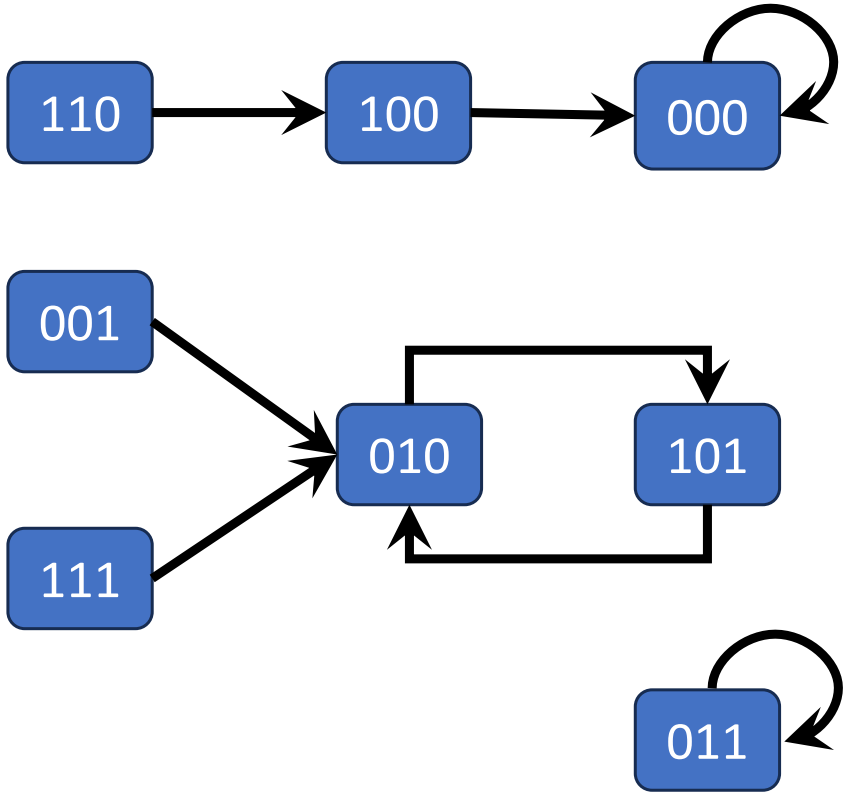


Rules: $F(x_1, x_2, x_3) = (x_2 \wedge \neg x_3, x_3, \neg x_1 \wedge x_2)$

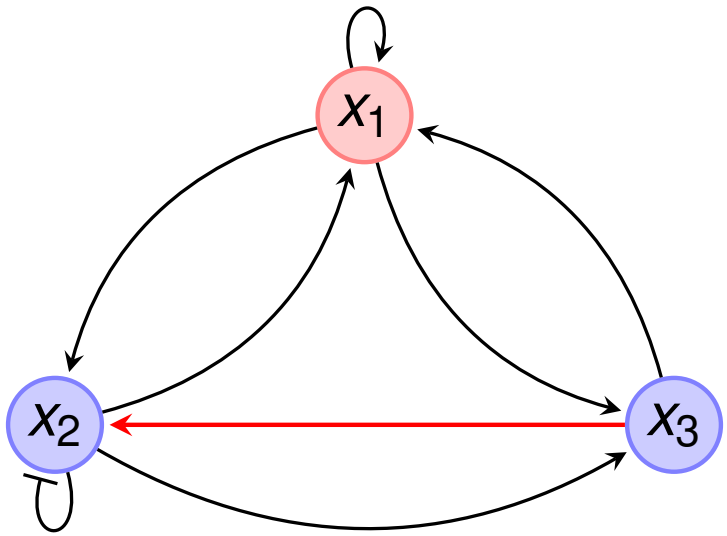
(a) The wiring diagram encodes the dependency between variables.

(b) The state transition graph or state space. This graph encodes all possible trajectories.

Control Targets on Boolean Networks

We consider two types of control actions:

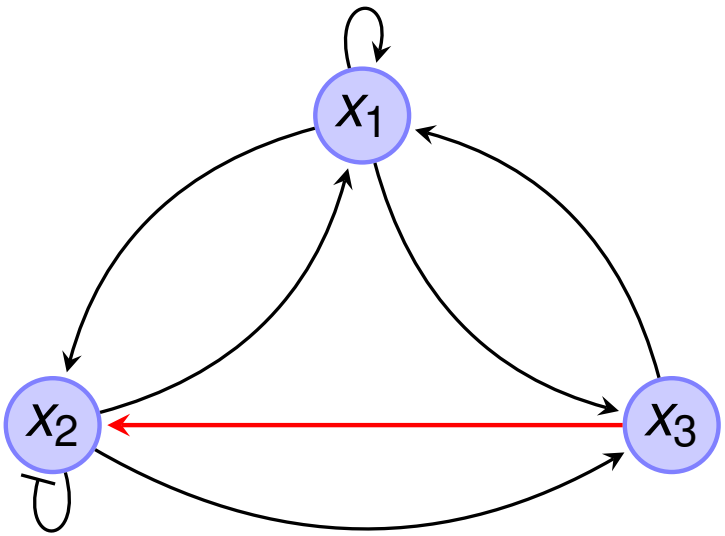
1. Deletion or constant expression of edges
2. Deletion or constant expression of nodes.



Identification of control targets in Boolean molecular network models via computational algebra.
David Murrugarra, Alan Veliz-Cuba, Boris Aguilar, and Reinhard Laubenbacher.
BMC Systems Biology, 10:94, 2016.

Edge Deletion

Network



Controlled System

$$\mathcal{F}_2(\mathbf{x}, u_{3,2}) = f_2(x_1, x_2, (u_{3,2}+1)x_3)$$

- For $u_{3,2} = 0$, $\mathcal{F}_2(\mathbf{x}, 0) = f_2(x_1, x_2, x_3)$.
  The control is not active.
- For $u_{3,2} = 1$, $\mathcal{F}_2(\mathbf{x}, 1) = f_2(x_1, x_2, 0)$.
  The control is active and the action represents the deletion of the edge $x_3 \to x_2$.

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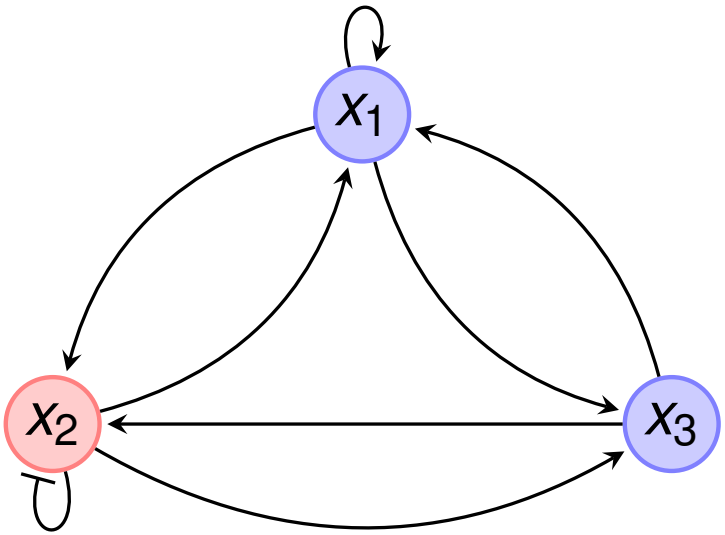
Node Deletion

Network



Regulatory rule

$$\mathcal{F}_j(\mathbf{x}, u_i^-, u_i^+) := (u_i^- + u_i^+ + 1)f_j(\mathbf{x}) + u_i^+$$

- For $u_i^- = 0, u_i^+ = 0$, $\mathcal{F}_j(x, 0, 0) = f_j(x)$. The control is not active.
- For $u_i^- = 1, u_i^+ = 0$, $\mathcal{F}_j(x, 1, 0) = 0$. This action represents the knock out of the node x_j.
- For $u_i^- = 0, u_i^+ = 1$, $\mathcal{F}_j(x, 0, 1) = 1$. This action represents the constant expression of the node x_j.
- For $u_i^- = 1, u_i^+ = 1$, $\mathcal{F}_j(x, 1, 1) = f_j(x_{t_1}, \ldots, x_{t_m}) + 1$.

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Identifying control targets

Let $\mathbf{F} = (f_1, \ldots, f_n) : \mathbb{F}^n \to \mathbb{F}^n$ where $\mathbb{F} = \{0, 1\}$.

- Suppose that $\mathbf{y}_0 = (y_{01}, \ldots, y_{0n}) \in \mathbb{F}^n$ is a desirable cell state (for instance, it could represent the state of cell senescence).
- It might be the case that $\mathbf{y}_0$ is not a fixed point, i.e., $\mathbf{F}(\mathbf{y}_0) \neq \mathbf{y}_0$.

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Goal: stabilizing or Generating new steady states

Find a set of controllers $\mu = \{\mu_1, \ldots, \mu_n\}$ so that $\mathcal{F}(\mathbf{y}_0, \mu) = \mathbf{y}_0$.

To solve this problem we consider the system of polynomial equations in the u parameters:

$$\mathcal{F}_j(\mathbf{y}_0, u) - y_{0j} = 0, j = 1, \ldots, m. \tag{1}$$

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Given $\mathbf{F} = (f_1, \ldots, f_n) : \mathbb{F}^n \to \mathbb{F}^n$ with $\mathbf{F}(\mathbf{x}_0) = \mathbf{x}_0$, for $\mathbf{x}_0 \in \mathbb{F}^n$.

Suppose that $\mathbf{x}_0$ is an undesirable attractor (it could represent a tumor proliferative cell state that needs to be avoided).

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Given $\mathbf{F} = (f_1, \ldots, f_n) : \mathbb{F}^n \to \mathbb{F}^n$ with $\mathbf{F}(\mathbf{x}_0) = \mathbf{x}_0$, for $\mathbf{x}_0 \in \mathbb{F}^n$.

Suppose that $\mathbf{x}_0$ is an undesirable attractor (it could represent a tumor proliferative cell state that needs to be avoided).

Goal: blocking transitions or removing fixed points

Find a set of control edges such that $\mathcal{F}(\mathbf{x}_0, \mu) \neq \mathbf{x}_0$.

To solve this problem consider the following equation,

$$[\mathcal{F}_1(\mathbf{x}, u_{j,1}) - x_{01} + 1] \cdots [\mathcal{F}_n(\mathbf{x}, u_{j,n}) - x_{0m} + 1] = 0 \tag{2}$$

In general, for blocking a transition, consider

$$[\mathcal{F}_1(\mathbf{x}, u_{j,1}) - z_{01} + 1] \cdots [\mathcal{F}_n(\mathbf{x}, u_{j,n}) - z_{0n} + 1] = 0 \tag{3}$$

Blocking transitions or removing fixed points

Let $\mathbf{F} = (f_1, \ldots, f_n) : \mathbb{F}^n \to \mathbb{F}^n$ where $\mathbb{F} = \{0, 1\}$.

Suppose a particular value of a variable, $x_k = a \in \mathbb{F}_2$, triggers an undesirable pathway, or is the signature of an abnormal cell, then we want all steady states of the system to satisfy $x_k \neq a$.

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Goal: blocking regions in the state space

In this case, we consider the systems of equations

$$\begin{aligned} \mathcal{F}_j(x, u) - x_j = 0, j = 1, \ldots, m, \\ x_k - a = 0. \end{aligned} \tag{4}$$

Since the steady states with $x_k = a$ are to be avoided, we want to find controls u for which Equation 4 has no solution.

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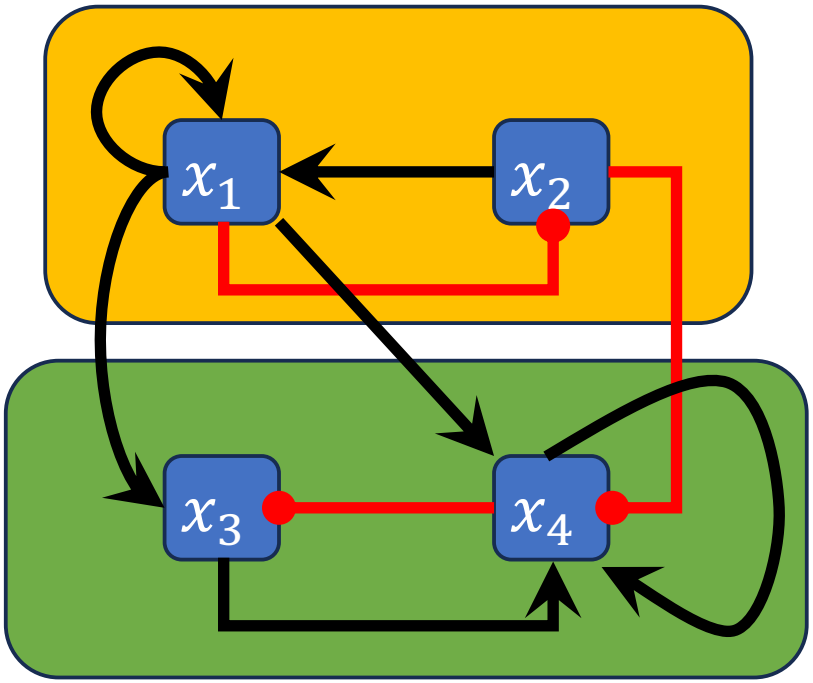
Modules

a



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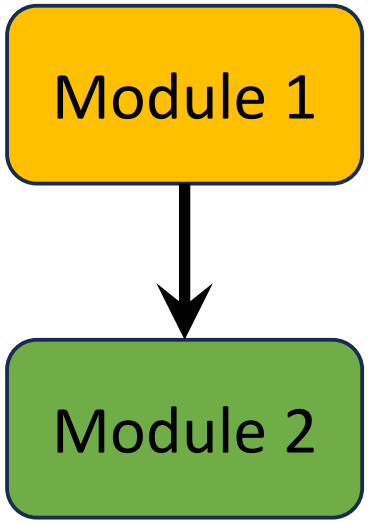


Rules: $F(x) = (x_2 \wedge x_1, \neg x_1, x_1 \vee \neg x_4, (x_1 \wedge \neg x_2) \vee (x_3 \wedge x_4))$

(a) Wiring diagram of a Boolean network where the non-trivial modules are highlighted by amber and green boxes.

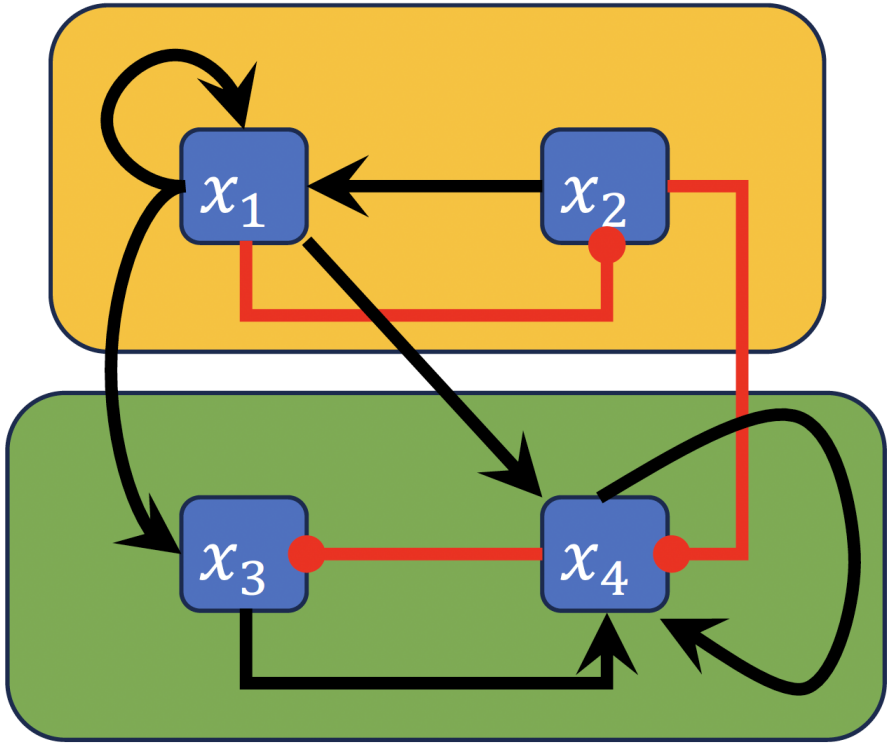
(b) Directed acyclic graph describing the corresponding connections between the nontrivial modules.

Restriction of a BN to a subsets of its variables

Consider the Boolean network
$F(x) = (x_2 \wedge x_1, \neg x_1, x_1 \vee \neg x_4, (x_1 \wedge \neg x_2) \vee (x_3 \wedge x_4))$

with wiring diagram in the left.

The **first module** (indicated by the amber box) is the restriction of F to $S_1 = \{x_1, x_2\}$ which is the 2-variable network
$F|_{S_1}(x_1, x_2) = (x_2 \wedge x_1, \neg x_1)$.



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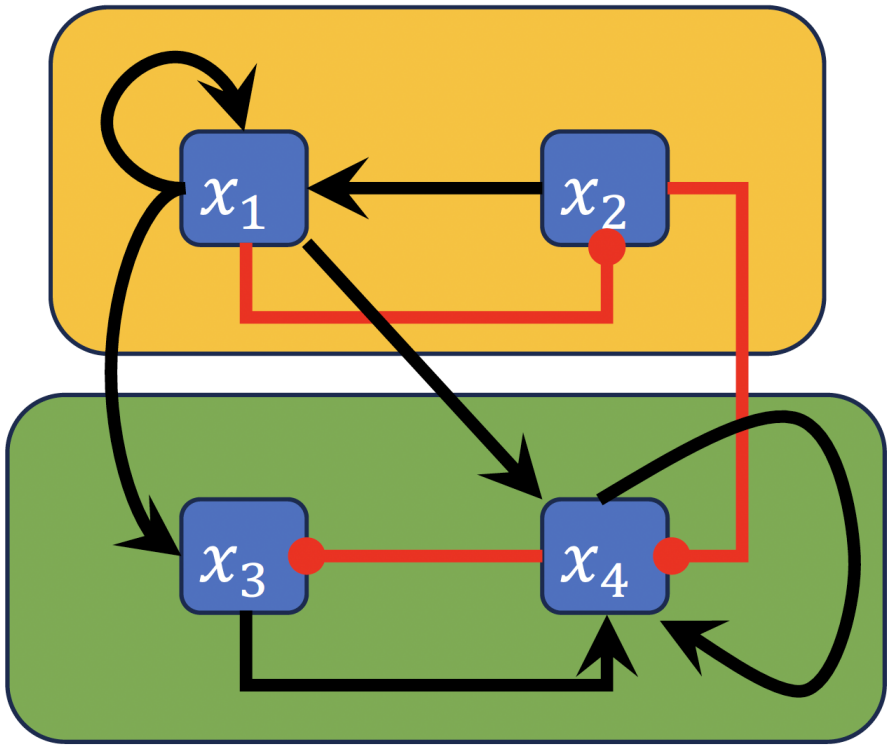
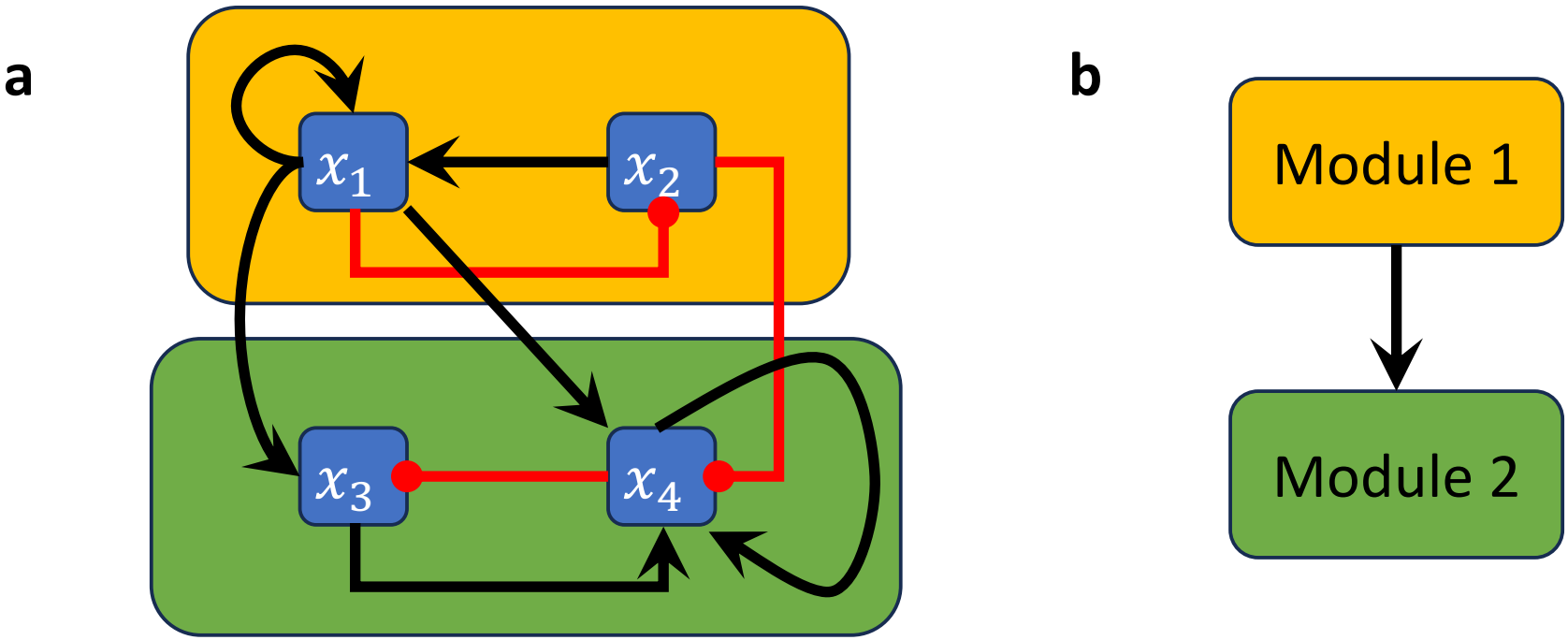


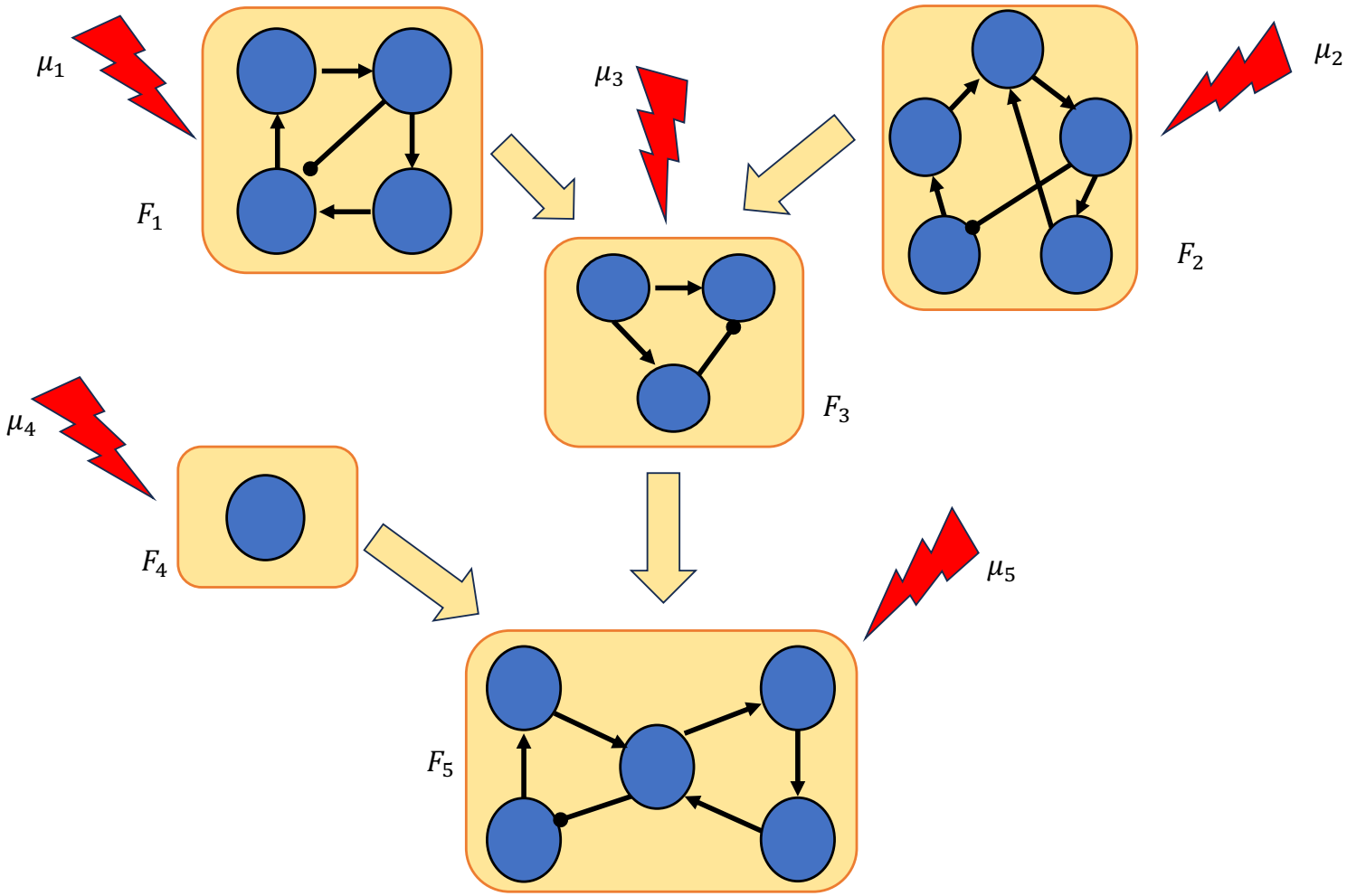
The **second module** (indicated by the green module) is the restriction of F to $S_2 = \{x_3, x_4\}$ which is the 2-variable network with external parameters e_1 and e_2 $F|_{S_2}(x_3, x_4) = (e_1 \vee \neg x_4, (e_1 \wedge \neg e_2) \vee (x_3 \wedge x_4)))$.

Modules

Given a F with wiring diagram W. Let $W_1, \ldots, W_m$ be the SCCs of W with pairwise disjoint sets of variables S_i. The *modules* of F are then the restrictions to these sets of variables, $F|_{S_i}$. Further, the modular structure of F can be described by a directed acyclic graph $Q = \{(i,j) \mid W_i \longrightarrow W_j\}$ by setting $W_i \longrightarrow W_j$ whenever there exists a node from W_i to W_j.



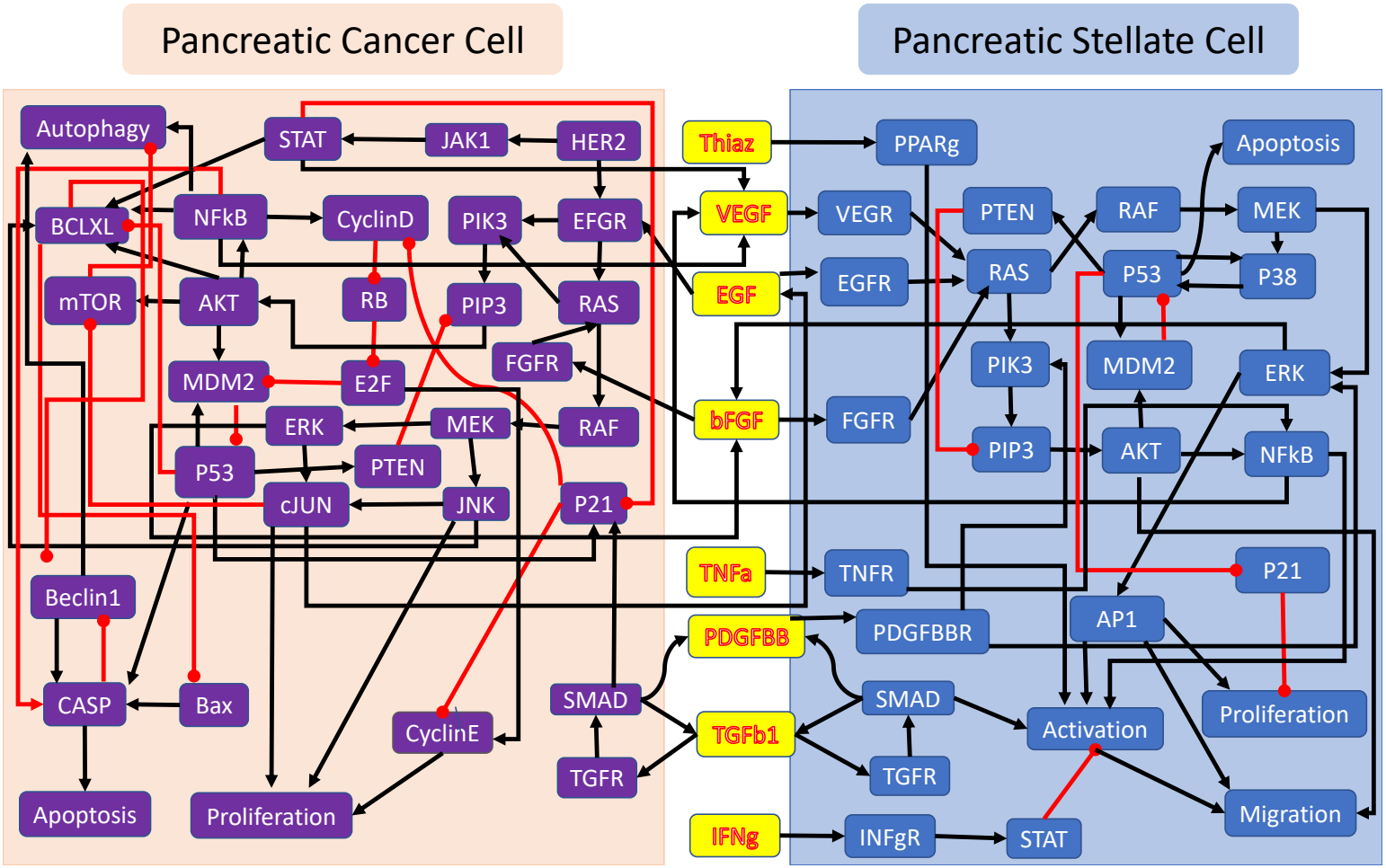
Control via modularity



The network is decomposed into its constituent modules: $F_1, \ldots, F_n$. Then, controls are identified for each module: $\mu_1, \ldots, \mu_n$. Combining the controls of the modules $\mu = (\mu_1, \ldots, \mu_n)$ we obtain a control for the entire network.

Modular control of Boolean network models. David Murrugarra, Alan Veliz-Cuba, Elena Dimitrova, Claus Kadelka, Matthew Wheeler, Reinhard Laubenbacher. Under review, 2025. `https://arxiv.org/abs/2401.12477`.

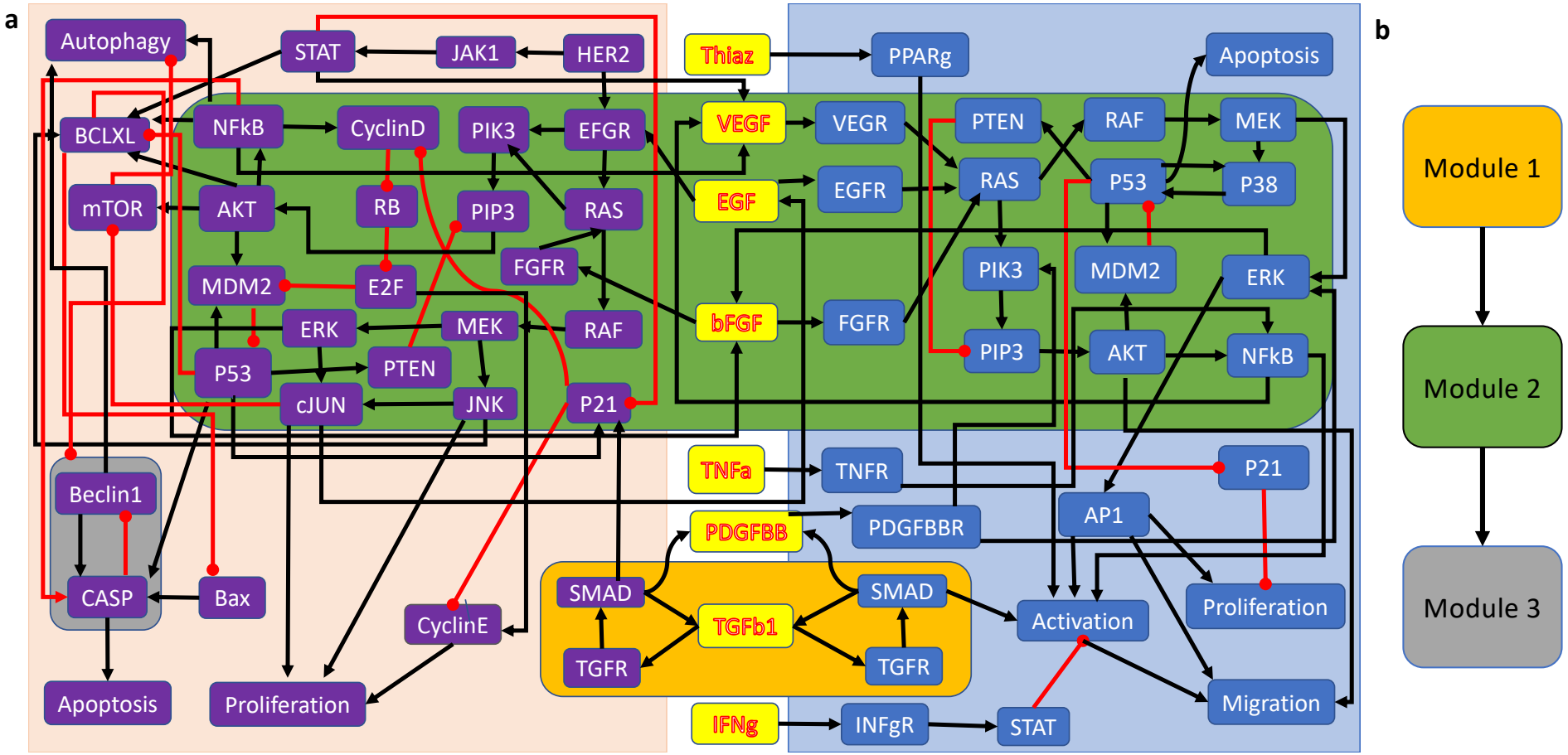
Larger models



The colors of nodes indicate the cell type. Black arrows indicate signal activation, while red arrows indicate suppression.

Modeling the Pancreatic Cancer Microenvironment in Search of Control Targets. Daniel Plaugher and David Murrugarra. *Bulletin of Mathematical Biology*, 83, (11):115, 2021.

Modules in larger models



(a) Wiring diagram of a Boolean multicellular pancreatic cancer model, which describes the interactions of pancreatic cancer cells (purple nodes), pancreatic stellate cells (blue nodes), and their connecting cytokines (yellow nodes). The non-trivial modules are highlighted by amber, green, and gray boxes. (b) Directed acyclic graph describing the connections between the non-trivial modules.

Aggression Scores

Uncontrolled Attractor Aggression Scores																
Weight	N.I.	KRAS	TP53	CycD	SMAD	T-K	C-K	S-K	T-C	T-S	C-S	T-C-K	T-S-K	C-S-K	T-C-S	T-C-S-K
Same	2.00	2.00	3.09	2.00	2.00	3.16	2.00	2.00	2.00	4.00	2.00	2.00	4.00	2.00	2.00	2.00
High/Low	5.78	5.71	15.44	9.99	2.00	15.78	10.00	2.00	10.00	19.98	10.00	10.00	20.00	10.00	10.00	10.00
Low/High	6.22	6.29	11.79	2.00	10.00	12.40	2.00	10.00	2.00	19.98	2.00	2.00	20.00	2.00	2.00	2.00
Average	4.67	4.67	10.11	4.66	4.67	10.45	4.67	4.67	4.67	14.65	4.67	4.67	14.67	4.67	4.67	4.67

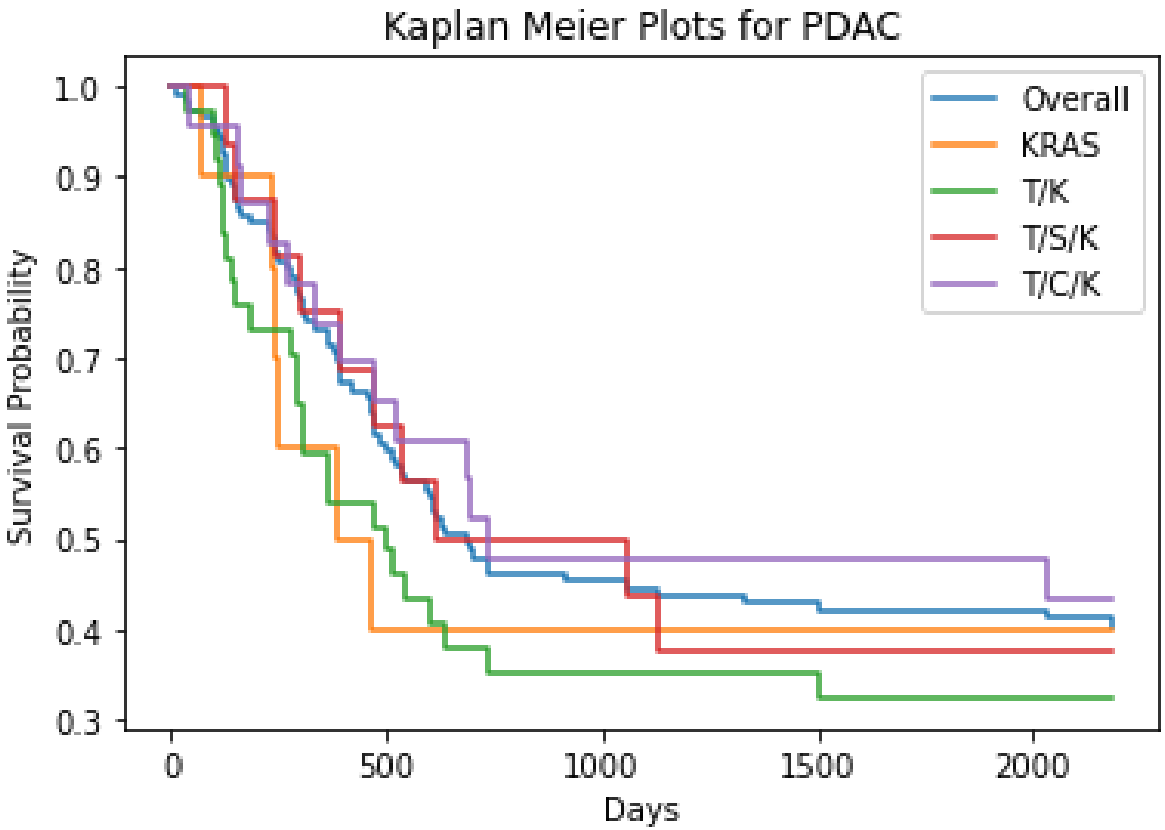
Uncontrolled Trajectory Aggression Scores																
Weight	N.I.	KRAS	TP53	CycD	SMAD	T-K	C-K	S-K	T-C	T-S	C-S	T-C-K	T-S-K	C-S-K	T-C-S	T-C-S-K
Same	1.09	1.12	3.03	1.56	1.14	3.05	1.56	0.71	1.92	3.72	1.55	1.95	3.81	1.58	1.92	1.93
High/Low	5.16	5.37	10.74	8.11	5.36	10.84	8.18	3.56	9.54	11.36	8.09	9.71	11.55	8.14	9.61	9.62
Low/High	2.79	2.80	7.51	1.70	2.82	7.49	1.67	2.63	2.06	11.08	1.65	2.07	11.36	1.72	2.00	2.05
Average	3.01	3.10	7.09	3.79	3.11	7.12	3.80	2.30	4.51	8.72	3.76	4.58	8.91	3.81	4.51	4.53

Control Set 1 Trajectory Aggression Scores																
Weight	N.I.	KRAS	TP53	CycD	SMAD	T-K	C-K	S-K	T-C	T-S	C-S	T-C-K	T-S-K	C-S-K	T-C-S	T-C-S-K
Same	-0.896	-0.848	-0.913	-0.894	-0.891	-0.89	-0.893	-0.863	-0.9	-0.882	-0.905	-0.885	-0.883	-0.915	-0.911	-0.887
High/Low	-0.768	-0.624	-0.817	-0.726	-0.779	-0.738	-0.725	-0.687	-0.74	-0.754	-0.753	-0.701	-0.771	-0.771	-0.751	-0.711
Low/High	-0.696	-0.616	-0.745	-0.766	-0.675	-0.722	-0.773	-0.639	-0.78	-0.674	-0.761	-0.733	-0.603	-0.819	-0.815	-0.735
Average	-0.78667	-0.696	-0.825	-0.79533	-0.78167	-0.78333	-0.797	-0.72967	-0.80667	-0.77	-0.80633	-0.773	-0.75233	-0.835	-0.82567	-0.777667

Control Set 2 Trajectory Aggression Scores																
Weight	N.I.	KRAS	TP53	CycD	SMAD	T-K	C-K	S-K	T-C	T-S	C-S	T-C-K	T-S-K	C-S-K	T-C-S	T-C-S-K
Same	-0.91	-0.856	-0.445	-0.872	-0.876	-0.399	-0.892	-0.856	-0.463	-0.409	-0.873	-0.427	-0.428	-0.843	-0.406	-0.427
High/Low	-0.846	-0.704	-0.317	-0.72	-0.756	-0.247	-0.844	-0.744	-0.359	-0.257	-0.737	-0.323	-0.308	-0.635	-0.246	-0.347
Low/High	-0.83	-0.696	-0.341	-0.744	-0.772	-0.207	-0.772	-0.688	-0.351	-0.209	-0.769	-0.339	-0.276	-0.723	-0.23	-0.315
Average	-0.862	-0.752	-0.36767	-0.77867	-0.80133	-0.28433	-0.836	-0.76267	-0.391	-0.29167	-0.793	-0.363	-0.33733	-0.73367	-0.294	-0.363

Uncovering potential interventions for pancreatic cancer patients via mathematical modeling. Daniel Plaugher, Boris Aguilar, David Murrugarra. *Journal of Theoretical Biology*, 548, 111197, 2022.

Aggression Scores: validation



Survival Estimates. This graph shows the Kaplan-Meier survival plots for the key mutation combinations used previously. The time-to-death variable is recorded in days, and each curve represents the probability of survival for patients in each cohort.

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Acknowledgments: Thank You!

Manuscript: Modular control of Boolean network models. David Murrugarra, Alan Veliz-Cuba, Elena Dimitrova, Claus Kadelka, Matthew Wheeler, Reinhard Laubenbacher. Under review, 2025. `https://arxiv.org/abs/2401.12477`.

Additional references:

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- Phenotype control techniques for Boolean gene regulatory networks. Daniel Plaugher and David Murrugarra. *Bulletin of Mathematical Biology*, 85:89, 2023.
- Cancer mutationscape: revealing the link between modular restructuring and intervention efficacy among mutations. Daniel Plaugher, and David Murrugarra. npj Systems Biology and Applications, 2024-10-74.

Part of my research is supported by a Collaboration grant (850896) from the Simons Foundation.

And thanks to funding from the NSF to continue this research.