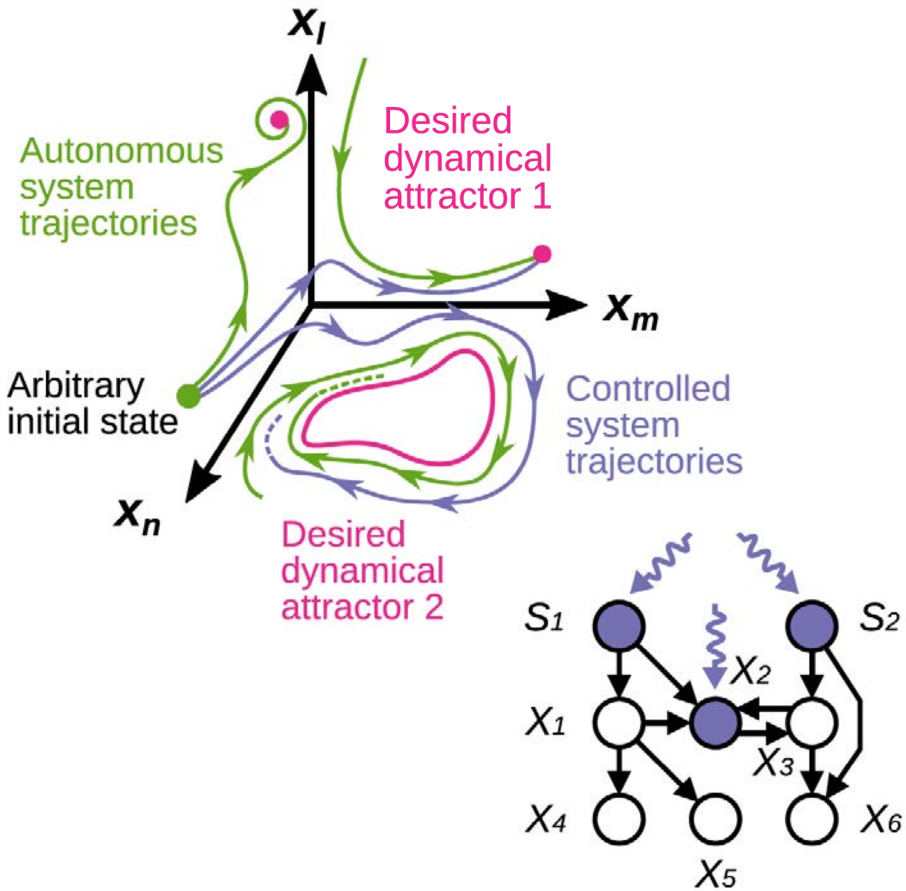
Workshop on Automata Networks 2021
Marseille, France (Remote)
July 15th 2021

Model-dependent and model-independent control of biological network models

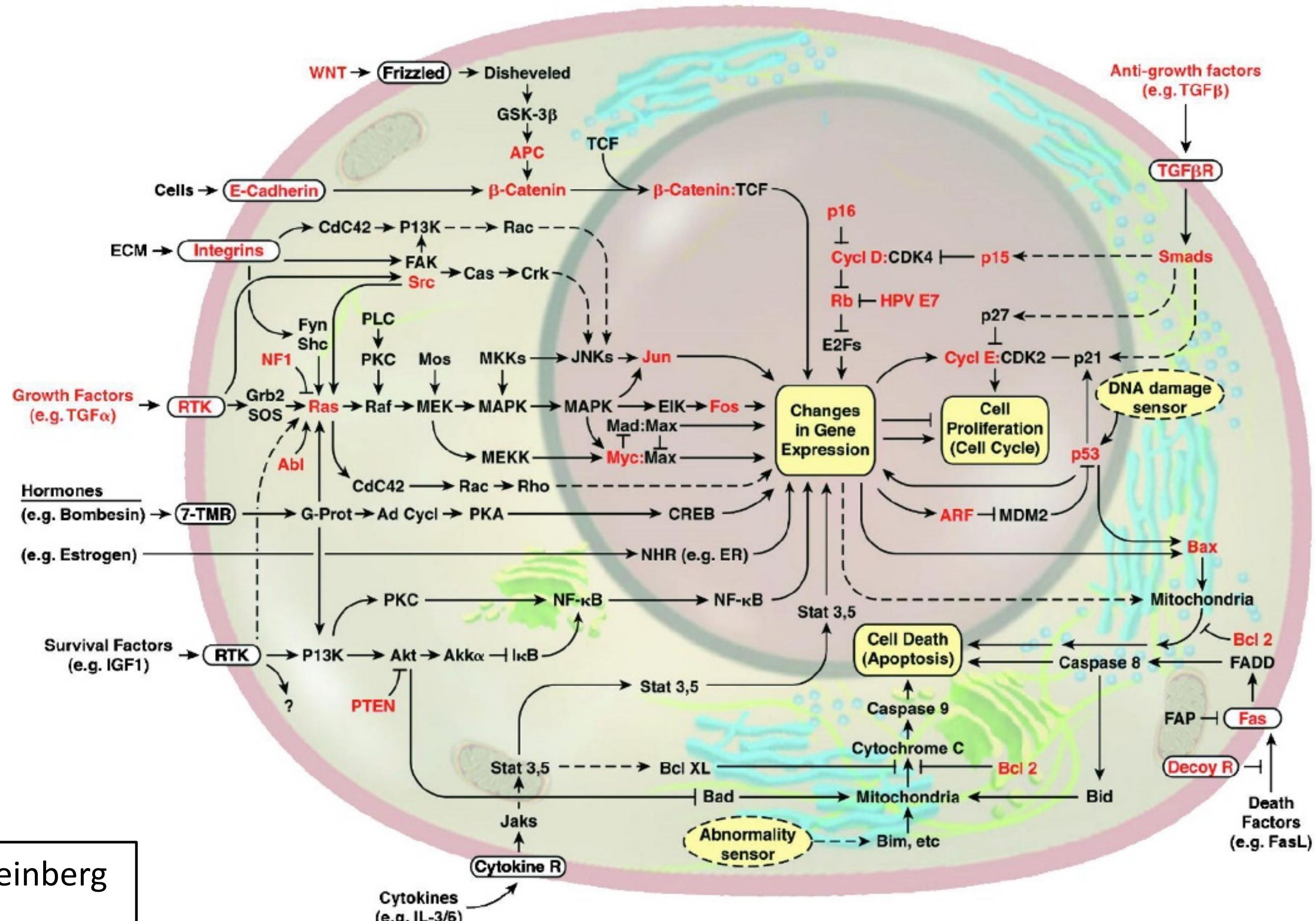


Jorge Gómez Tejeda Zañudo
Postdoctoral researcher
Broad Institute of MIT and Harvard
Dana-Farber Cancer Institute

J.G.T. Zañudo

Cellular phenotypes arise from a complex molecular network

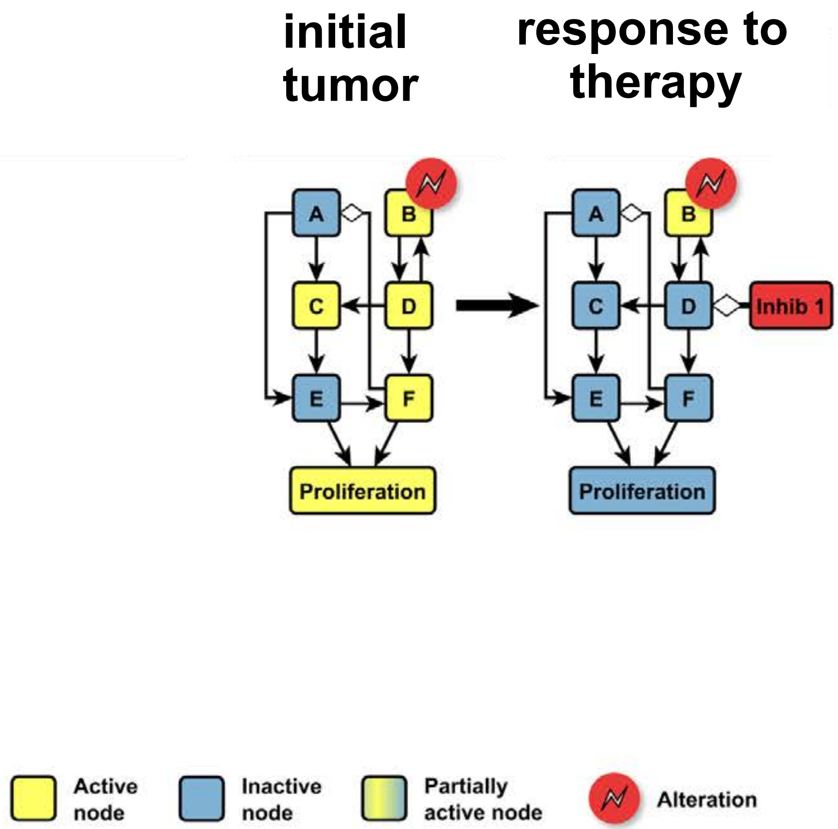
Network model: Dynamics of information propagation through cellular pathways and their connection to cellular behaviors



Hanahan, Weinberg (2000)

Cancer network models

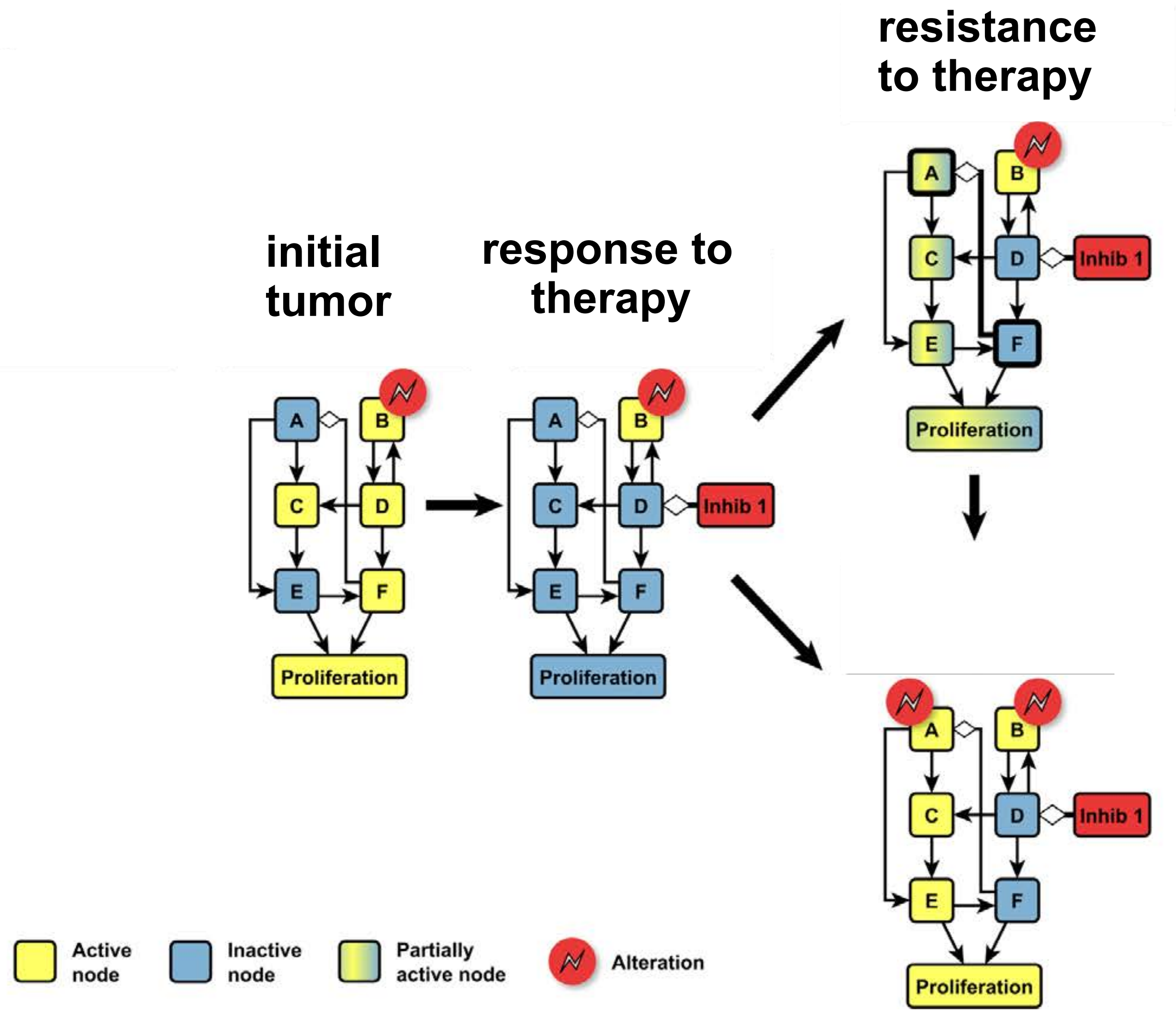
Many current challenges in cancer (drug resistance, combination treatments) can be tackled through mechanistic network modeling



J.G.T. Zañudo, Steinway, & Albert (2018). Curr. Opinion in Syst. Biol.

Cancer network models

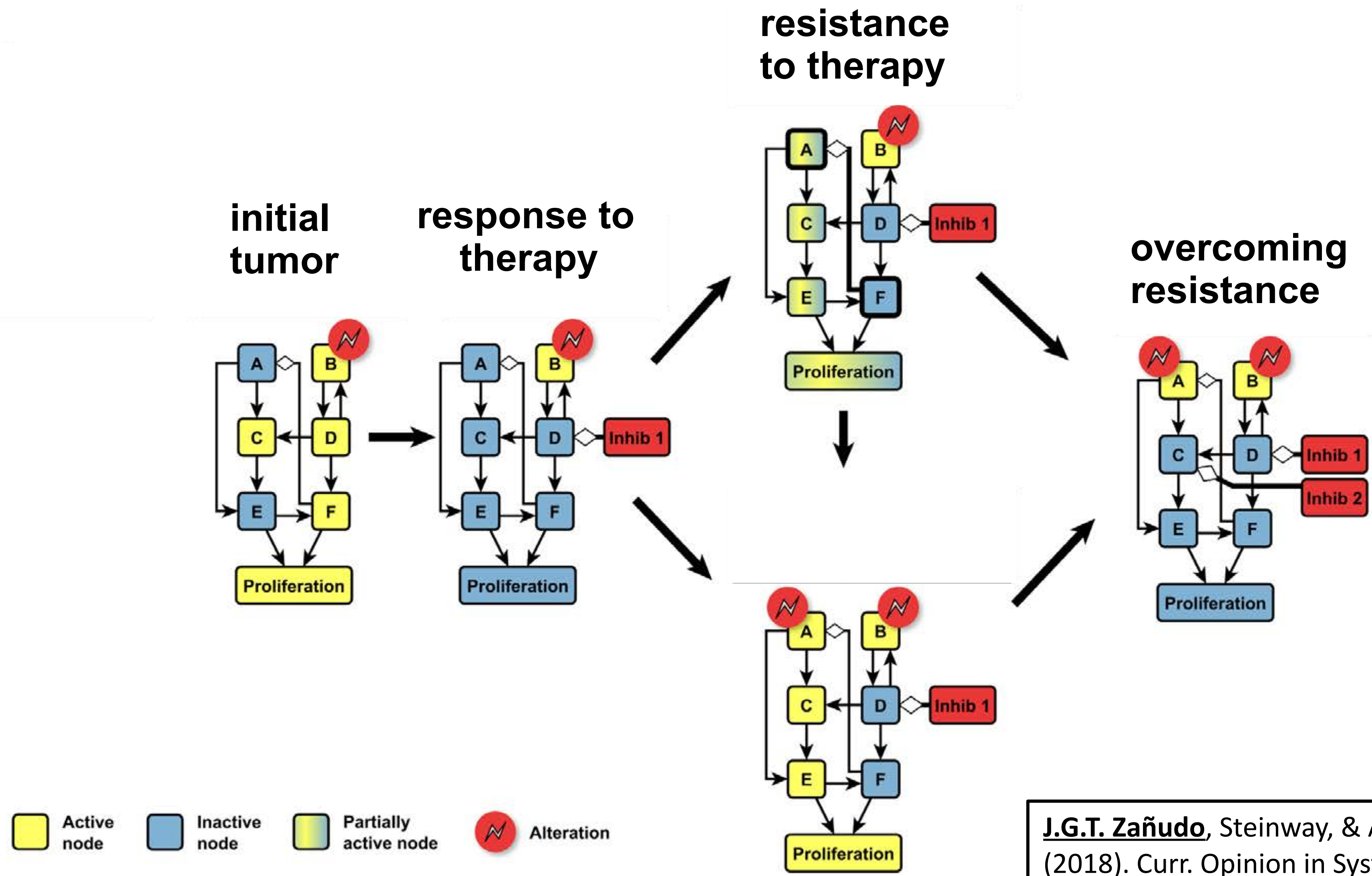
Many current challenges in cancer (drug resistance, combination treatments) can be tackled through mechanistic network modeling



J.G.T. Zañudo, Steinway, & Albert (2018). Curr. Opinion in Syst. Biol.

Cancer network models

Many current challenges in cancer (drug resistance, combination treatments) can be tackled through mechanistic network modeling

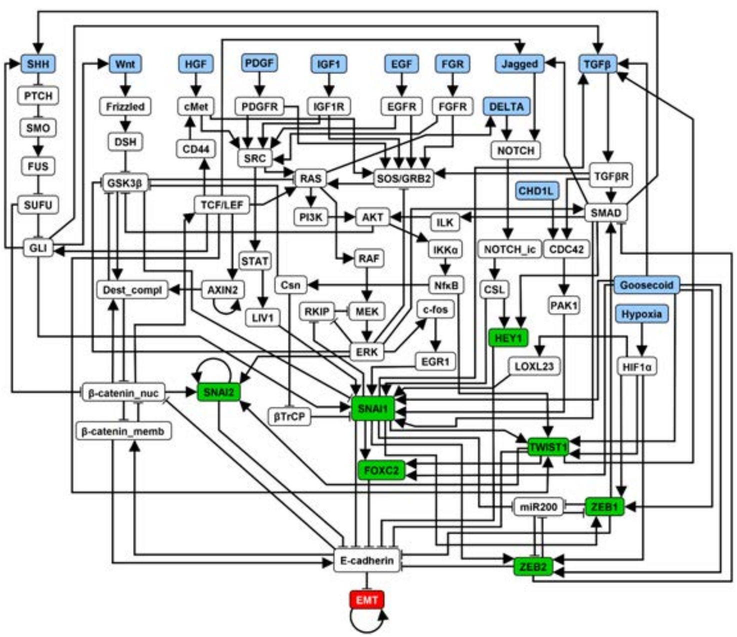


J.G.T. Zañudo, Steinway, & Albert (2018). Curr. Opinion in Syst. Biol.

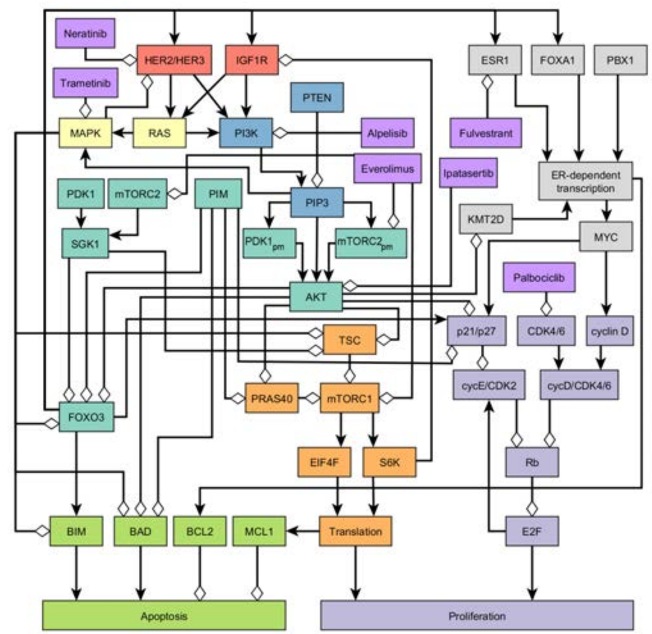
Objective of my research

Use network models and control methods to predict

Nodes that block metastatic reprogramming
(EMT in liver cancer)



Resistance mechanisms and drug combinations
(PI3K inhibition in ER+ MBC)



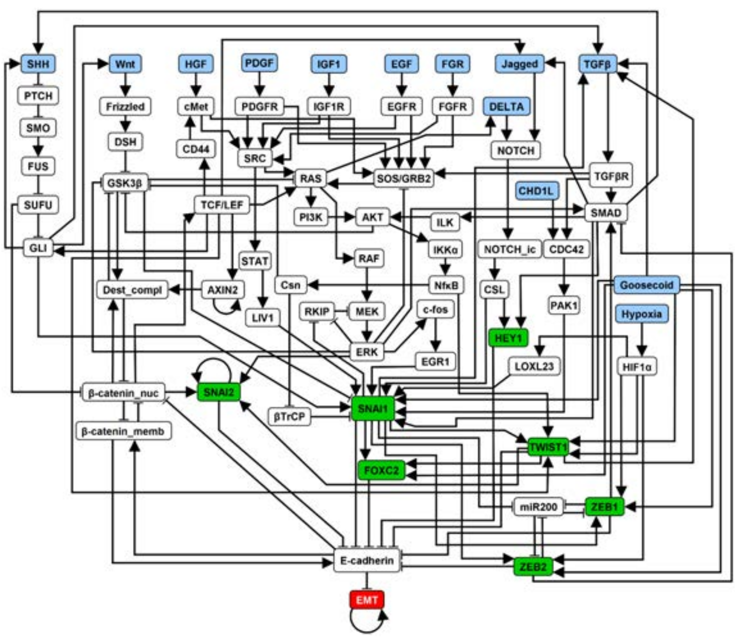
SN Steinway, **JGT Zañudo**, et al. Cancer Res. (2014).
SN Steinway*, **JGT Zañudo***, et al. npj Syst. Biol. & Appl. (2015).

JGT Zañudo, et al. Cancer Convergence. (2017).
JGT Zañudo, et al. bioRxiv. (2020).

Objective of my research

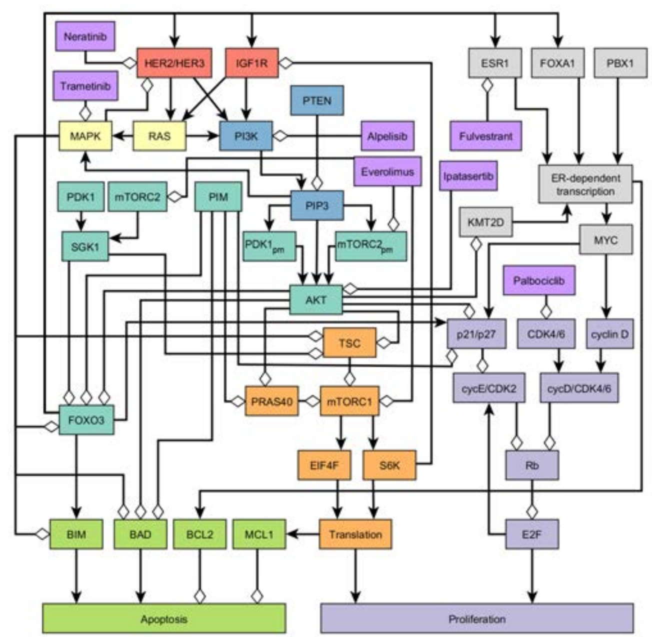
Use network models and control methods to predict

Nodes that block metastatic reprogramming
(EMT in liver cancer)



SN Steinway, **JGT Zañudo**, et al. Cancer Res. (2014).
SN Steinway*, **JGT Zañudo***, et al. npj Syst. Biol. & Appl. (2015).

Resistance mechanisms and drug combinations
(PI3K inhibition in ER+ MBC)

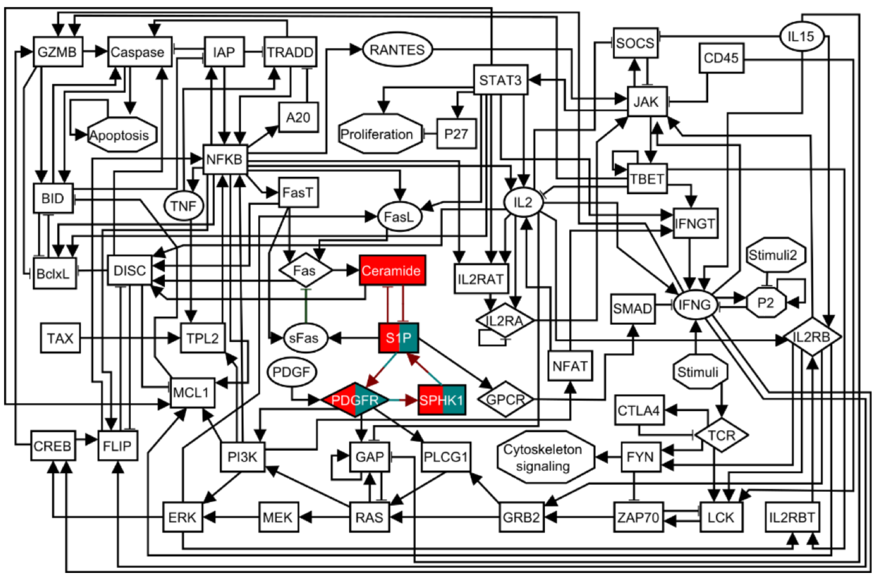


JGT Zañudo, et al. Cancer Convergence. (2017).
JGT Zañudo, et al. bioRxiv. (2020).

Objective of my research

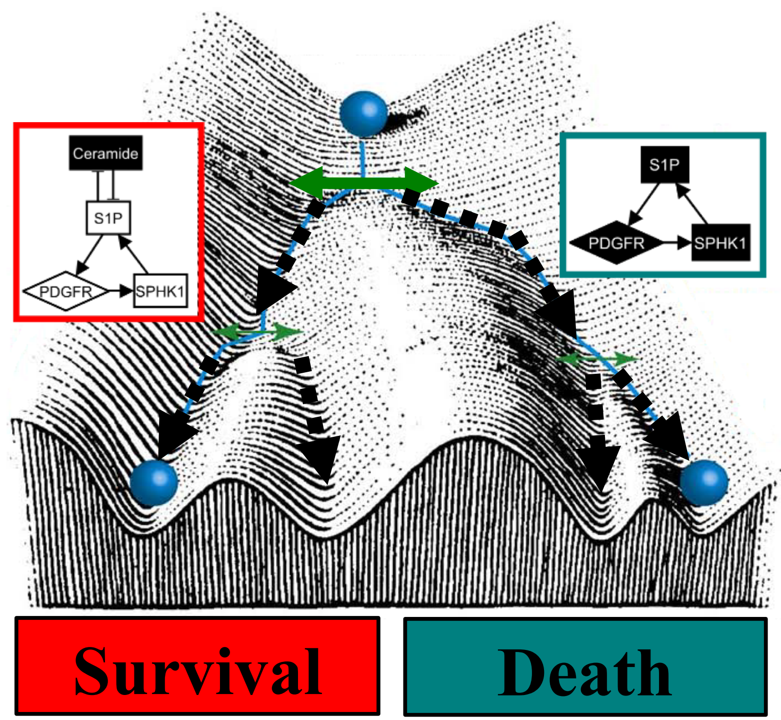
Control methods to connect the network structure to decision-making

Network structure + mathematical model



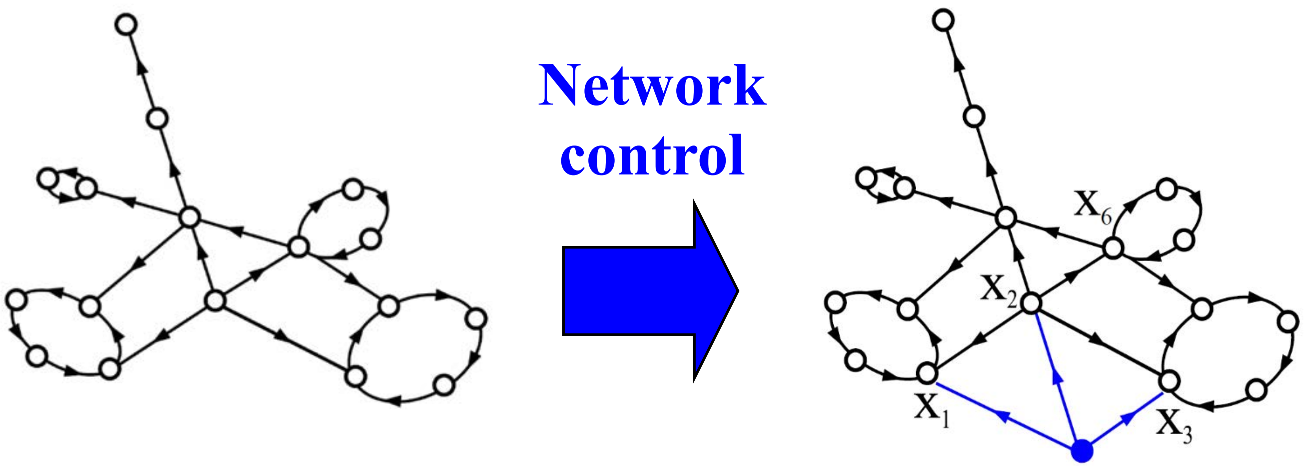
J.G.T. Zañudo et. al. PLoS Comp. Bio. 2015
J.G.T. Zañudo et. al. PNAS 2017
J.G.T. Zañudo et. al. Physical Biology 2019

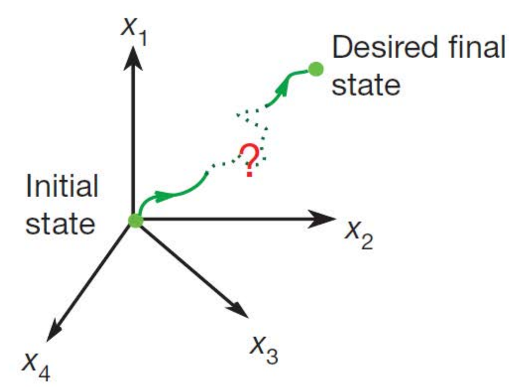
Decision-making dynamics + network-based control methods



Introduction

Network control: Control the internal state of a network and drive it towards a desired state.





YY Liu et al. Nature **473**, 167-173 (2011)

Network control:

- Network + dynamic model
- Intervention + state X → state Y

Network control:

- Network + dynamic model
- Intervention + state X → state Y

	Structure	Structure + Dynamics	Dynamics
Non linear	FVS control (Mochizuki et al., Zañudo et al.)	Stable motif control (Zañudo et al.)	Control & systems theory
Linear	Structural Controllability (Lin, Slotine, Shields, Pearson, Liu et al.)	Kalman controllability (Kalman et al., Luenberger et al)	

Network control:

- Network + dynamic model
- Intervention + state X → state Y

Non linear

FVS control (Mochizuki et al., Zañudo et al.)

Stable motif control (Zañudo et al.)

Control & systems theory

Linear

Structural Controllability (Lin, Slotine, Shields, Pearson, Liu et al.)

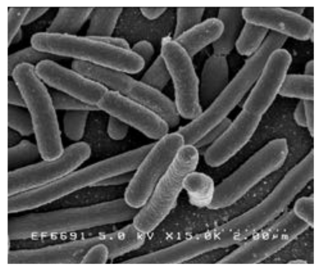
Kalman controllability (Kalman et al., Luenberger et al)

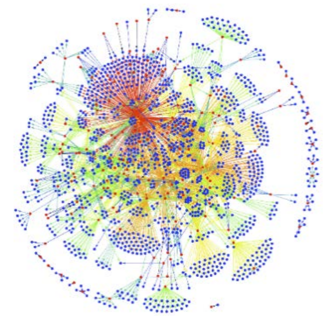
Structure ←→ **Structure + Dynamics** ←→ **Dynamics**

Realistic network dynamics

Realistic dynamics are **nonlinear** and have **dynamical attractors** (e.g. steady states) that correspond to stable patterns of activity:

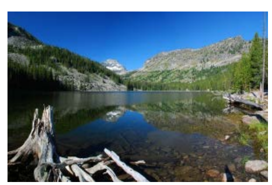
$$\frac{dx_i}{dt} = -Bx_i + \sum_{j=1}^{N} A_{ij} R \frac{x_j^h}{1+x_j^h}$$

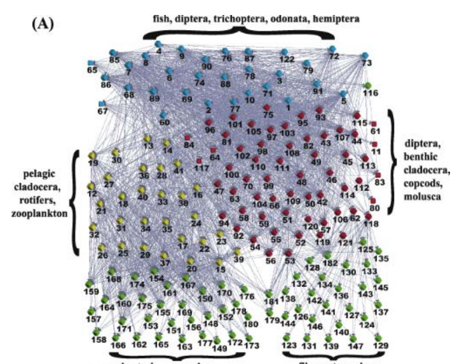




Intracellular dynamics
- cell types or cell states

$$\frac{dx_i}{dt} = -Bx_i^b + \sum_{j=1}^{N} A_{ij} R x_j^a$$





Population dynamics
- stable population sizes

Some definitions and references

Fiedler, B., Mochizuki, A., et al. (2013), *J. Dynamics and Differential Equations.*
Mochizuki, A., Fiedler, B., et al. (2013), *J. Theor. Bio.*
Zanudo J.G.T. & Albert R. et al. (2015), *PLoS Comp. Bio.*
Zanudo J.G.T., Yang G., & Albert R. (2017), *PNAS.*

Dynamics

$x(t)$ is a trajectory in:

- An ODE system: $\dot{x} = F(x)$, $x \in \mathbb{R}^n$, $x_i \geq 0$, F is dissipative,
- A Boolean system: $x(t+1) = B(x(t))$, $x \in \{0,1\}^n, t \in \{0,1,2, \ldots\}$

G is the graph induced by the dynamics.

- ODE system: $i \to j$ if $\partial F_j / \partial x_i \neq 0$, $i \to i$ only if $\partial F_i / \partial x_i > 0$
- Boolean system: $i \to j$ if any prime implicant of B_j depends on x_i

Attractor control

Let $x_{\mathcal{A}}$ be a fixed point (or the trajectory of a limit cycle) of the system

Control approach: we clamp the variables x_I, $I \subseteq \{1,2, \ldots, n\}$ so that $x_k(t) = g_k(t)$ if $k \in I$, otherwise they follow their uncontrolled dynamic equation. The controlled system is denoted $x^*(t)$

Attractor control: $||x^*(t) - x_{\mathcal{A}}|| \to 0$, $\forall x^*(0)$, as $t \to \infty$

What is feedback vertex set control?

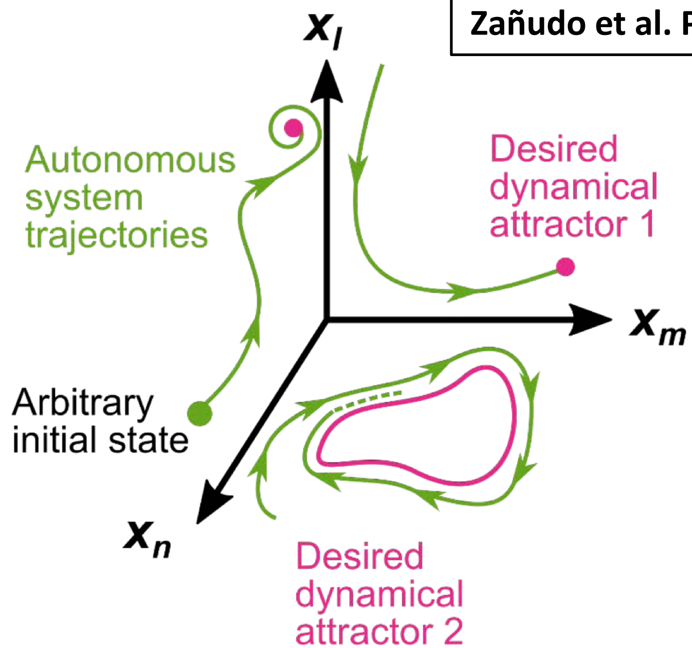
Feedback vertex set control (FC)

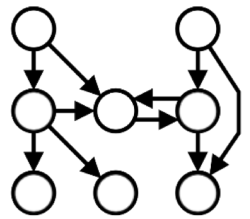
Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

- Dynamics:

$$\frac{dX_i}{dt} = F_i(X_i, X_{I_i}, t),$$

Mass-action kin.
Michaelis-Menten





What is feedback vertex set control?

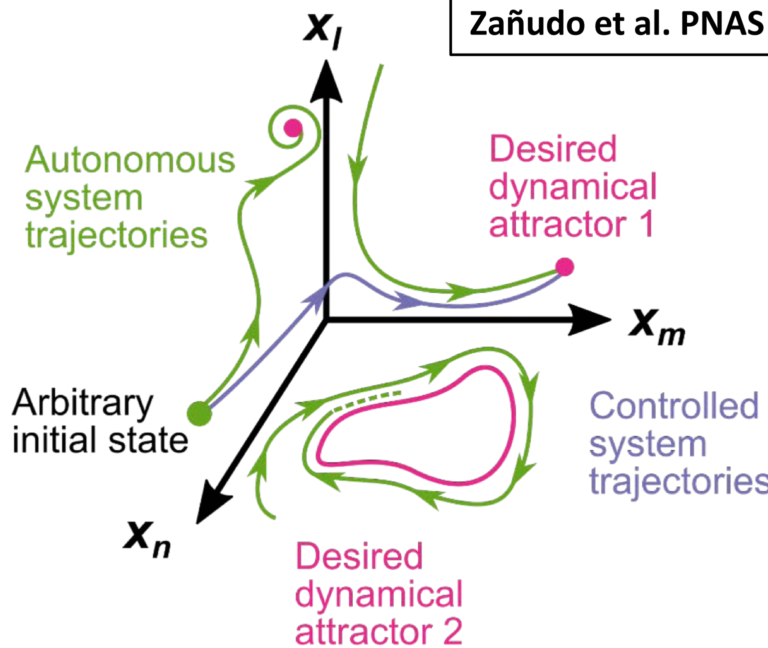
Feedback vertex set control (FC)

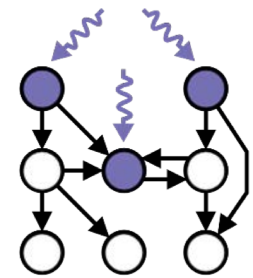
Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

- Dynamics:

$$\frac{dX_i}{dt} = F_i(X_i, X_{I_i}, t),$$

Mass-action kin.
Michaelis-Menten





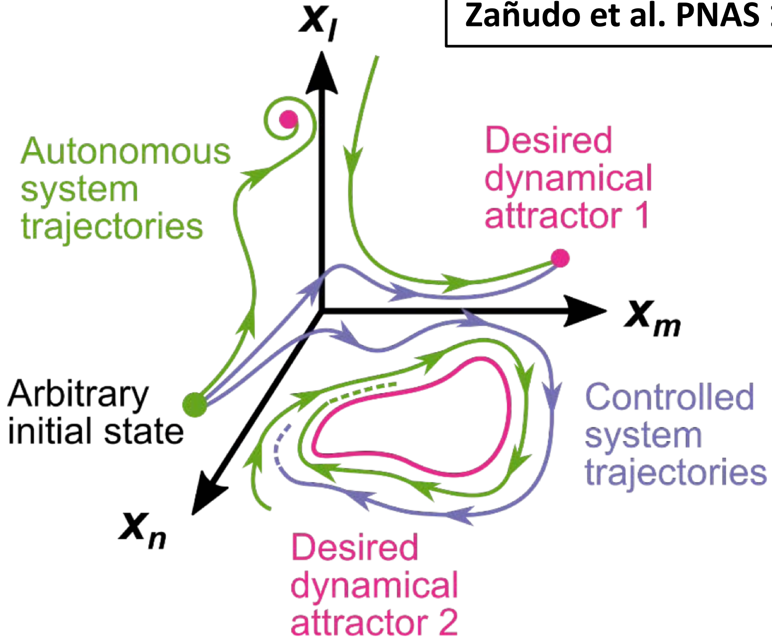
Feedback vertex set control (FC)

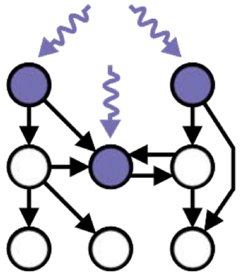
Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

- Dynamics:

$$\frac{dX_i}{dt} = F_i(X_i, X_{I_i}, t),$$

Mass-action kin.
Michaelis-Menten





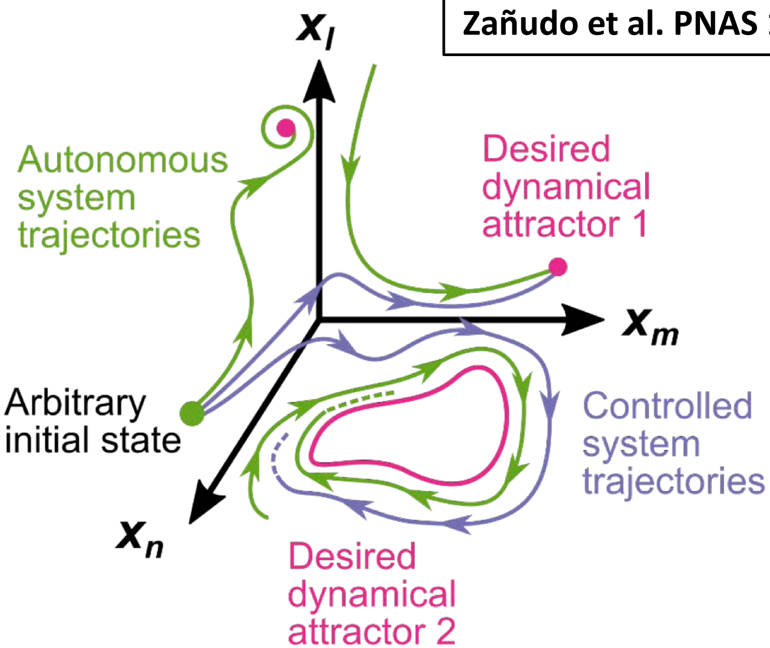
Feedback vertex set control (FC)

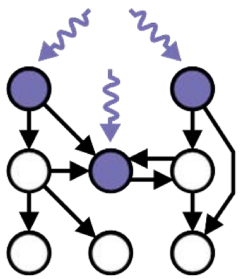
Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

- Dynamics:

$$\frac{dX_i}{dt} = F_i(X_i, X_{I_i}, t),$$

Mass-action kin.
Michaelis-Menten





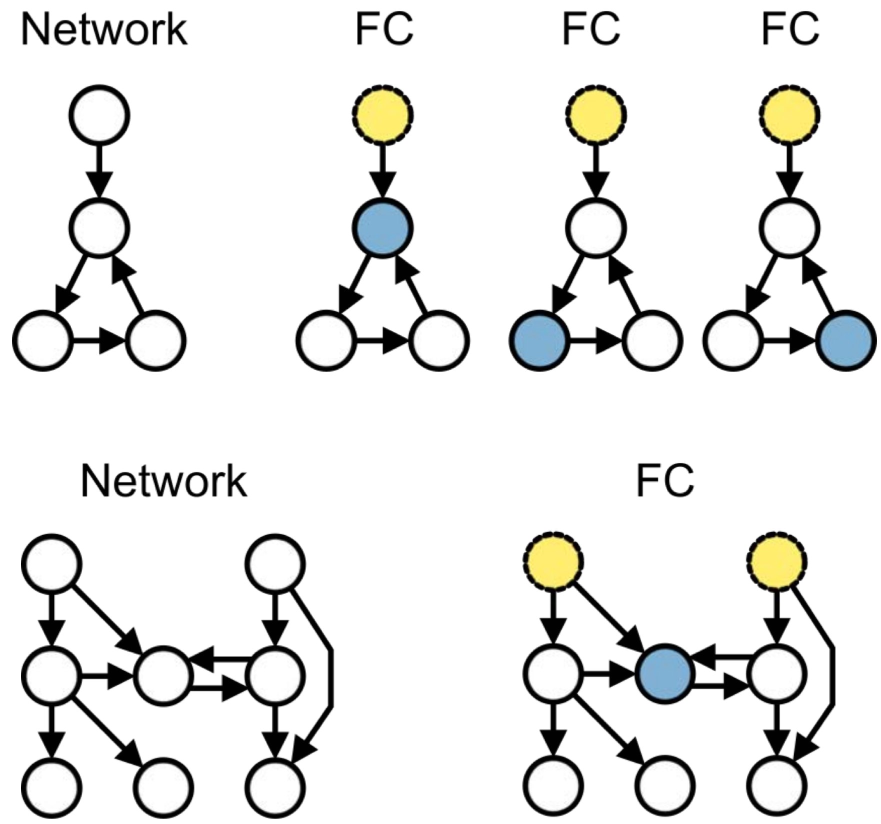
- Feedback Vertex Set Control node set:

- **Given a network, sufficient for control in each model (F_i)**
- **Only control set that works for every model (F_i) on the network**

Feedback vertex set control node set

- What do we need to control?

Source nodes
+
A node in every cycle (FVS)



Mochizuki et al. J. Theor. Biol. 335, 130- 146 (2013)

Zañudo et al. PNAS 114 (28), 7234 - 7239 (2017)

Feedback vertex set control node set

- What do we need to control?

Source nodes
+
A node in every cycle

- Finding exact minimal FVS is NP-hard
- Good heuristics to find near-minimal FVS

Topological ordering + simulated annealing (Galnier et al., J. of Heuristics 19, 2013):
https://github.com/yanggangthu/FVS_python
https://github.com/yanggangthu/FVS_cython

GRASP (Pardalos et al. J. Comb. Optim. 2, 1999)
http://calgo.acm.org/ (Algorithm 815)

Mochizuki et al. J. Theor. Biol. 335, 130- 146 (2013)

Zañudo et al. PNAS 114 (28), 7234 - 7239 (2017)

Feedback vertex set control

- What is the control action?

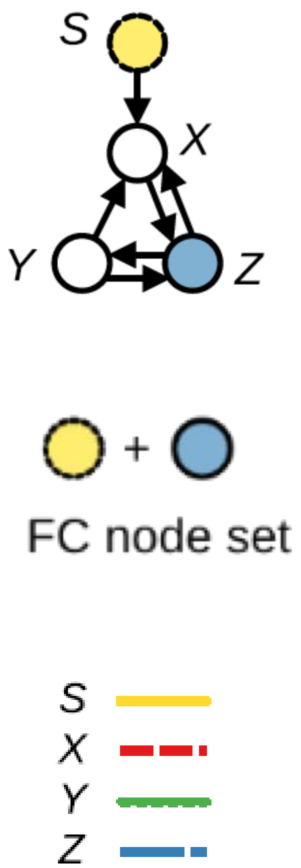
Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

Node state clamping (fix state into attractor trajectory, no “controller”)

- What is the control action?

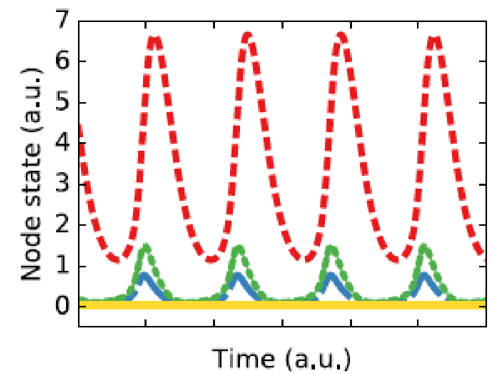
Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

Node state clamping (fix state into attractor trajectory, no "controller")

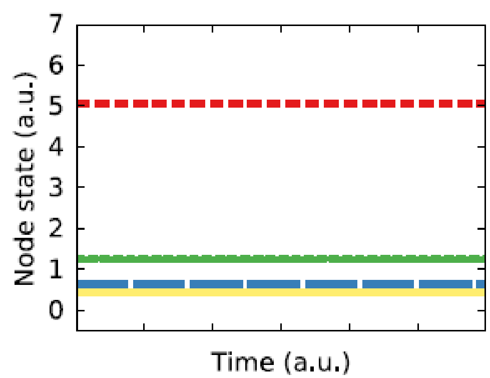


System attractors

Attractor 1



Attractor 2

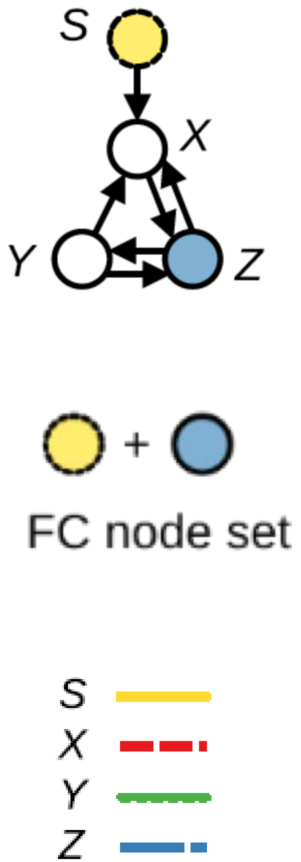


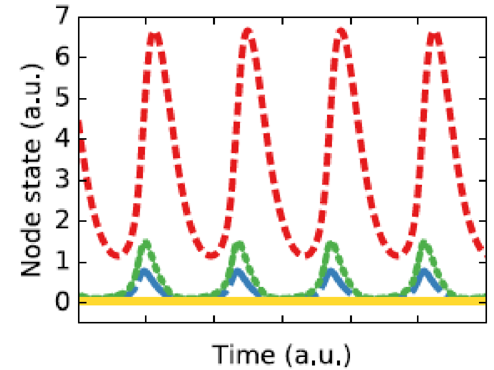
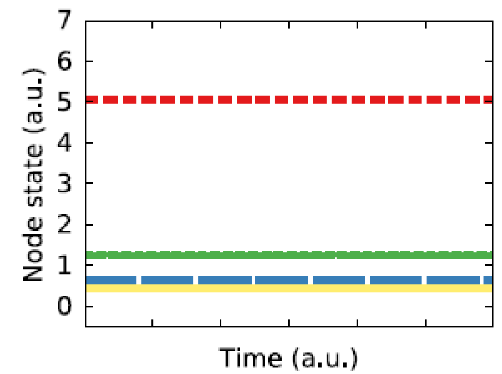
Feedback vertex set control

- What is the control action?

Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

Node state clamping (fix state into attractor trajectory, no "controller")



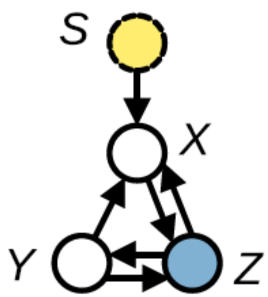
Target attractor	Attractor control
Attractor 1	
Attractor 2	

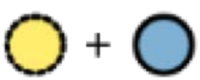
Feedback vertex set control

- What is the control action?

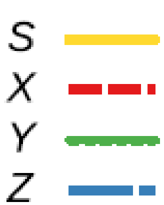
Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

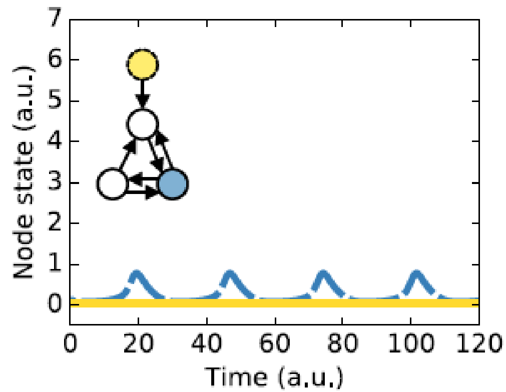
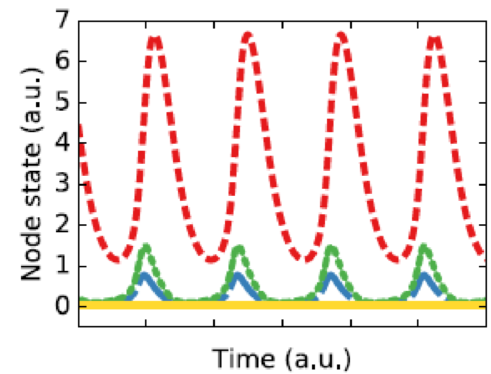
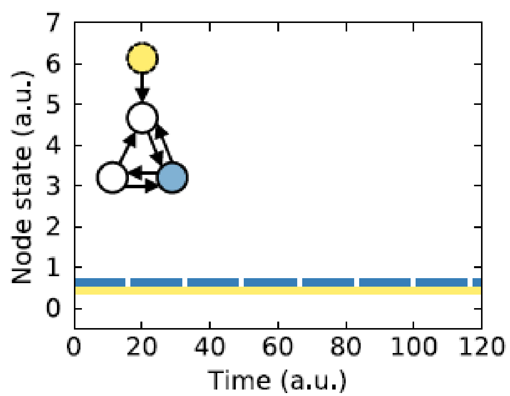
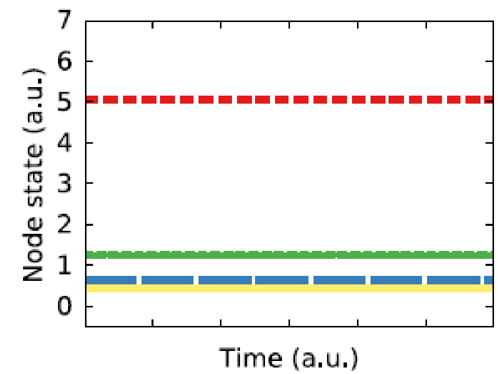
Node state clamping (fix state into attractor trajectory, no "controller")





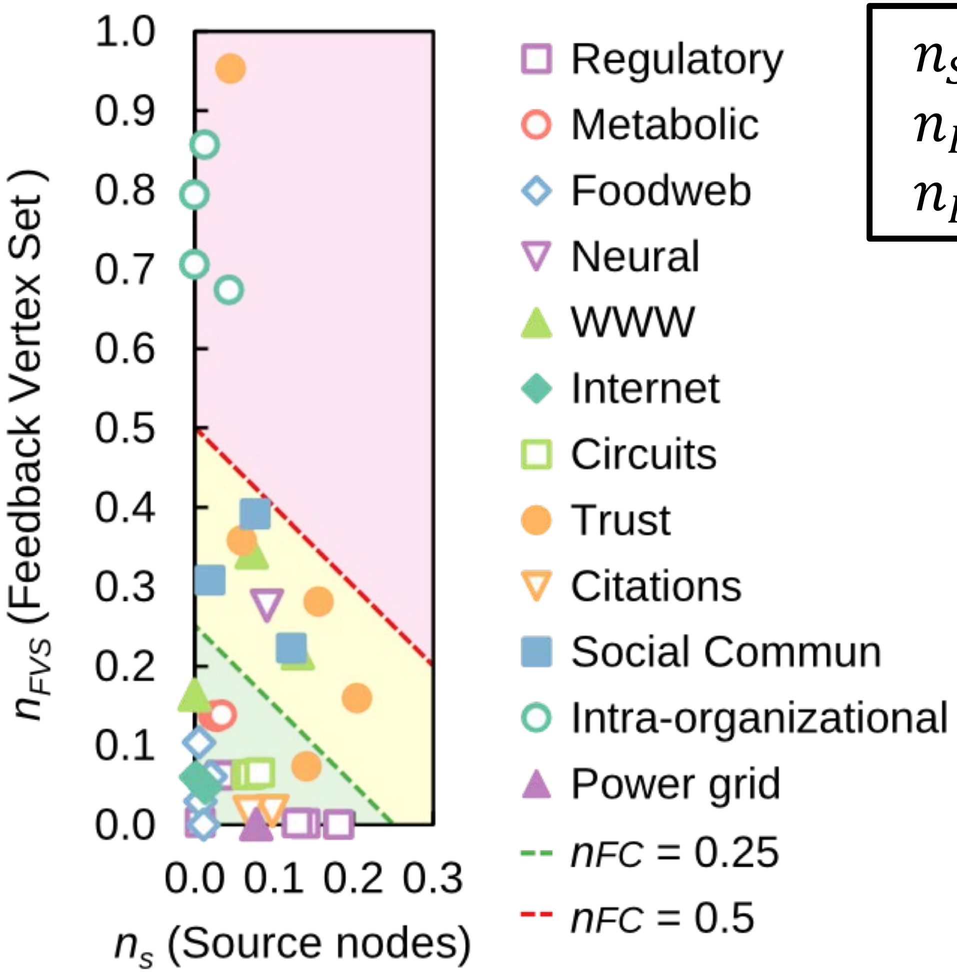
FC node set



Target attractor	Control action (node state override)	→ Attractor control
Attractor 1		
Attractor 2		

BROAD INSTITUTE
DANA-FARBER CANCER INSTITUTE

Real networks require varying fraction of nodes for FVS control

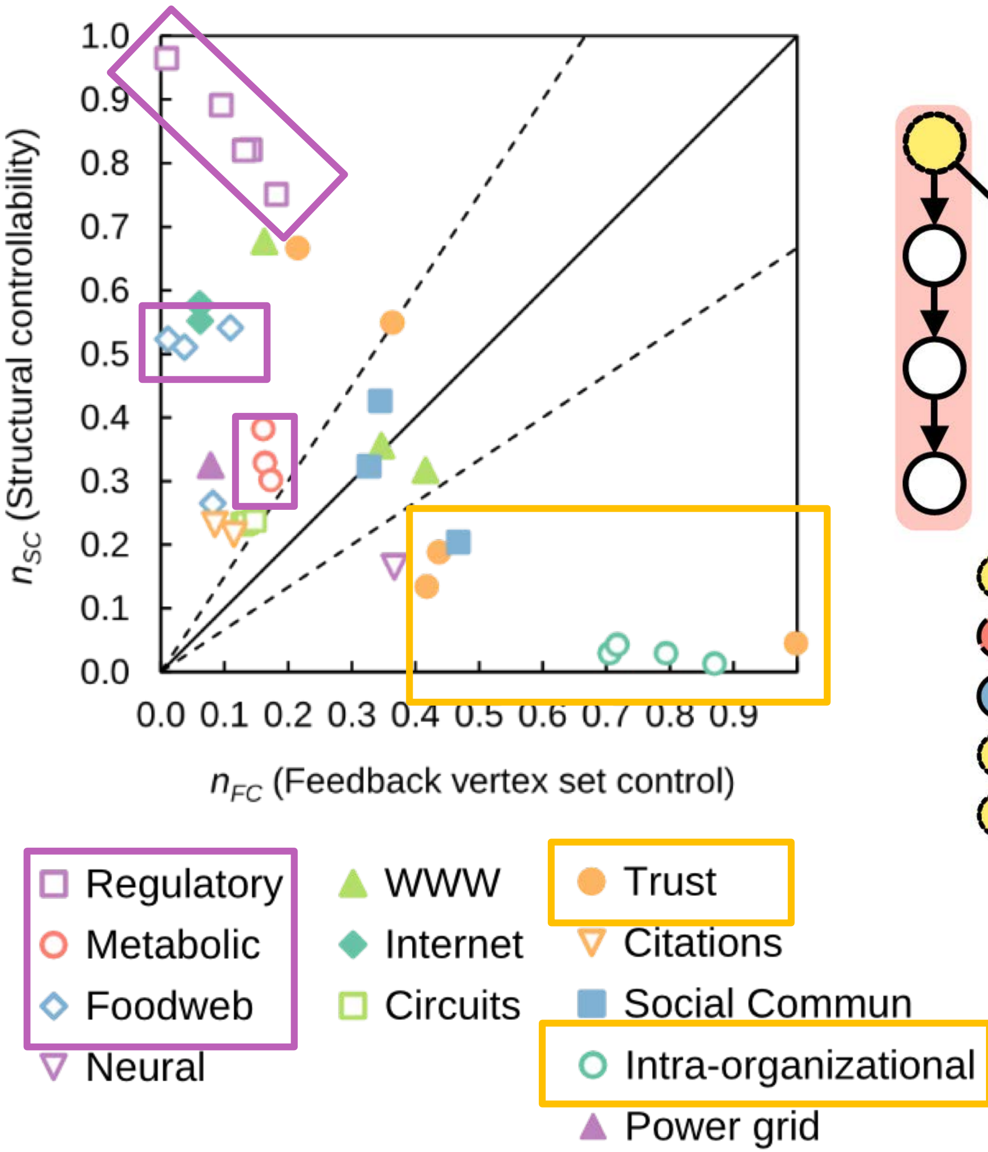


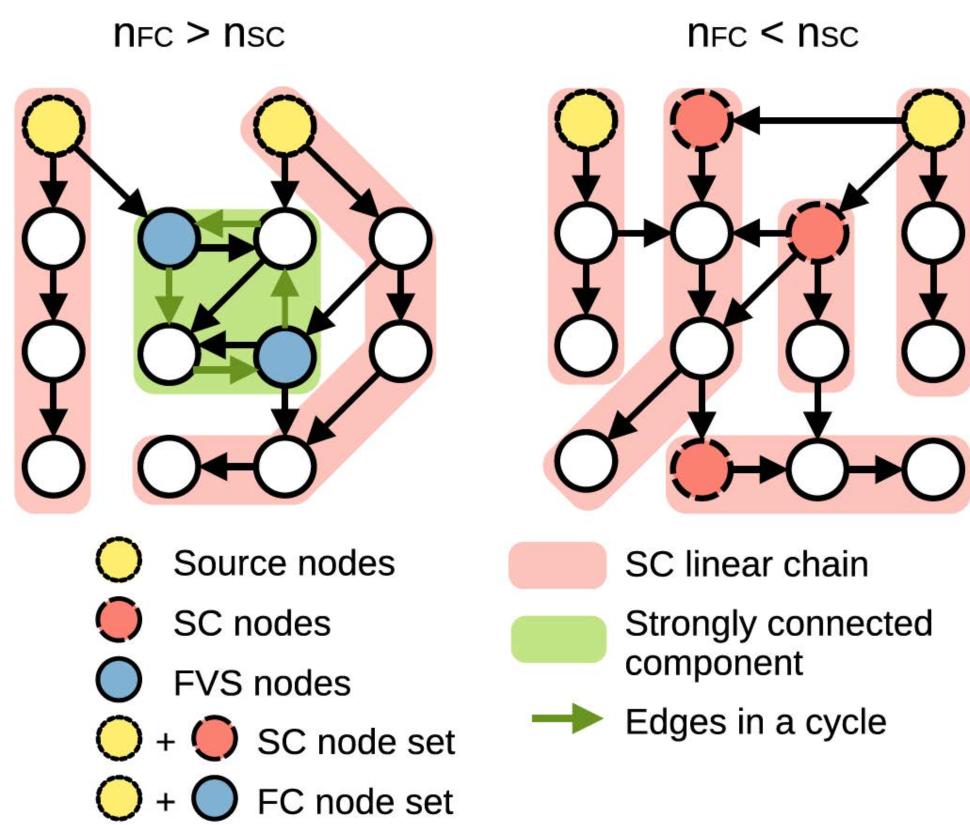
n_S	Sources
n_{FVS}	Feedback vertex set
$n_{FC} = n_S + n_{FVS}$	FVS control

Zañudo et al. PNAS 114 (28), 7234 - 7239 (2017)

Comparing FVS control and SC

Control fractions n_{FC} and n_{SC} are quite different for many networks





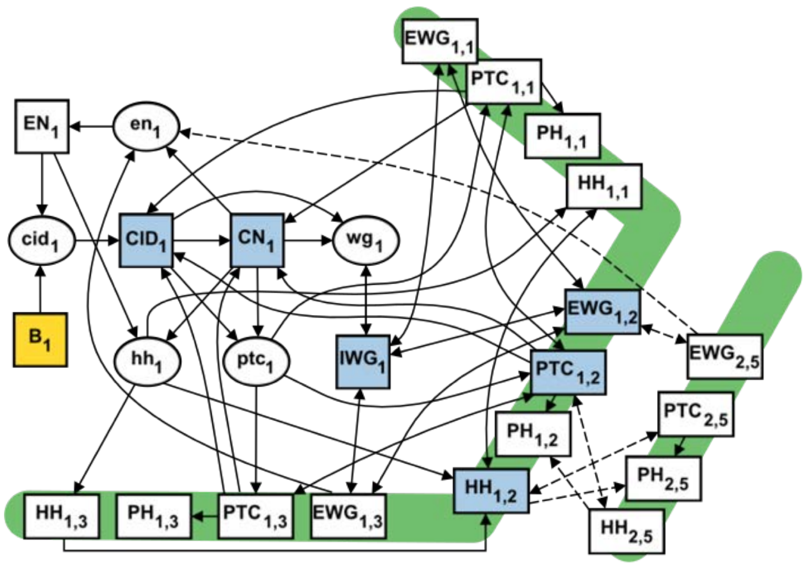
FC: FVS control
SC: Structural controllability

Zañudo et al. PNAS 114 (28), 7234 - 7239 (2017)

What happens when using FVS control on a real biological network model?

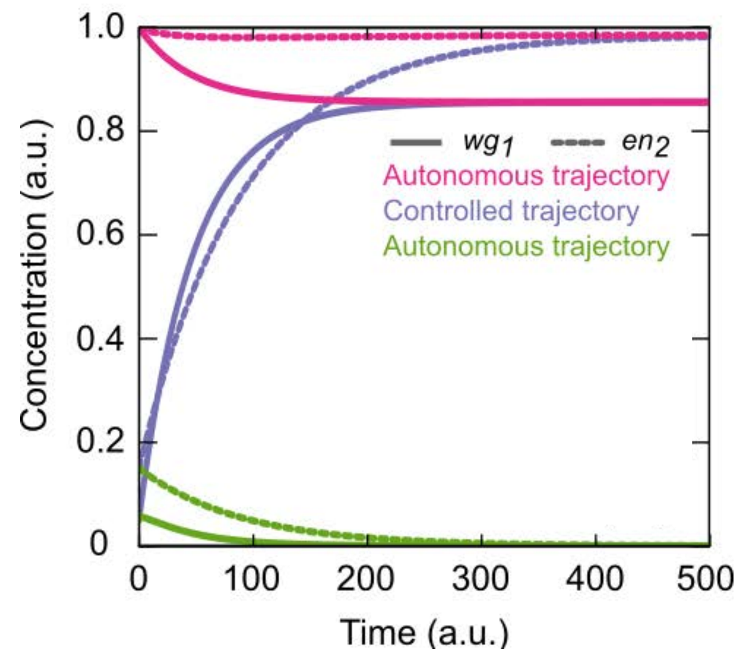
FC makes **model-independent** predictions (valid for all parameters)

Fruit fly segmentation network model



+ FC node set

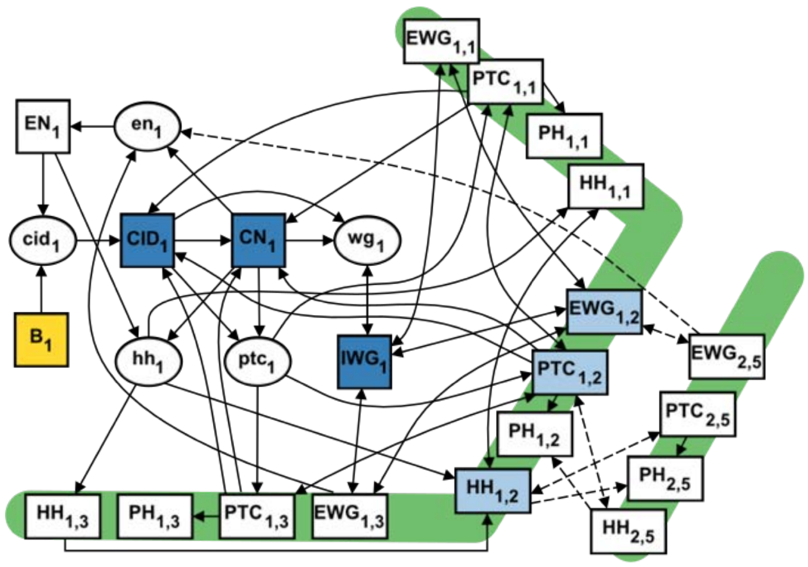
FVS control trajectories



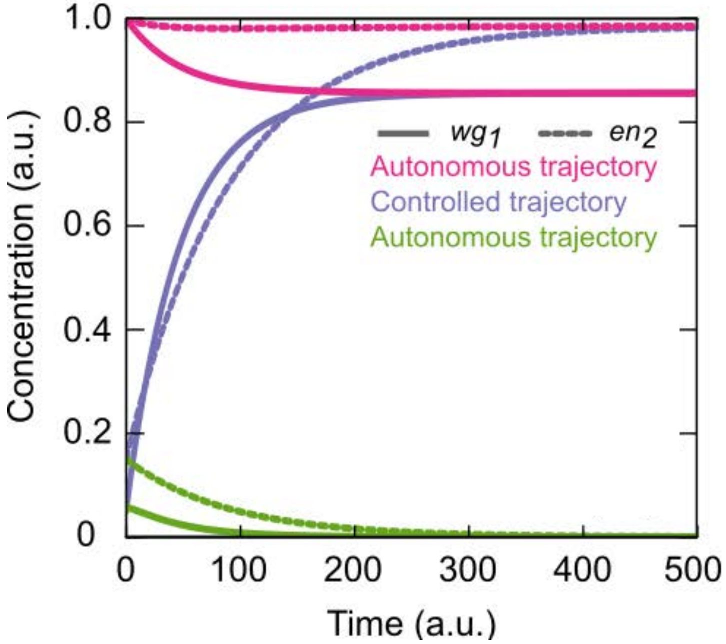
Zañudo et al. PNAS 114 (28), 7234 - 7239 (2017)

FC makes **model-independent** predictions (valid for all parameters)
Starting from FC, we can find **model-dependent** predictions

Fruit fly segmentation network model



FVS control trajectories



\+ \+ FC node set **(model-independent)**

\+ Reduced FC node set **(model-dependent)**

Zañudo et al. PNAS 114 (28), 7234 - 7239 (2017)

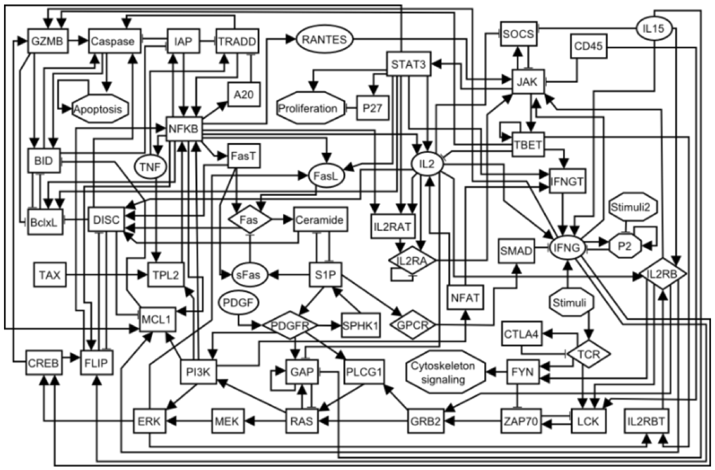
Can we find a more principled way to do model-dependent attractor control?

Can we find a more principled way to do model-dependent attractor control?

Start with simplest nonlinear dynamics: Boolean systems

Note: the method I will describe is very similar to the one described earlier by Jun Pang

Model-dependent attractor control



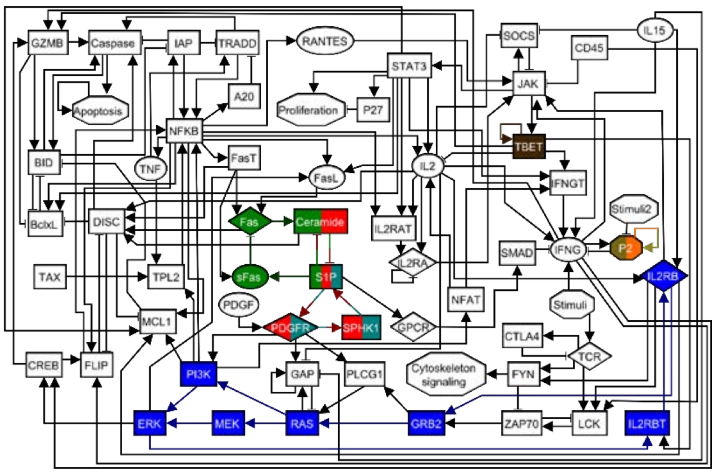
Cell fate A

Cell fate B

Zañudo and Albert PLoS Comp. Biol. 11(4): e1004193 (2015).

Model-dependent attractor control

Attractor control: Find subnetworks that stabilize in a fixed state

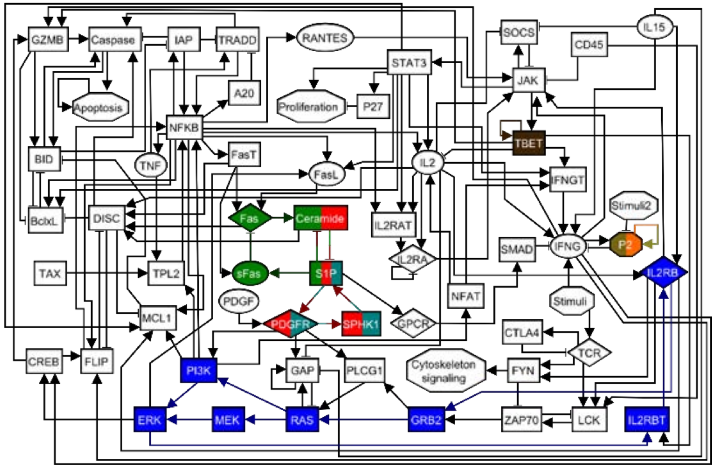


Cell fate A

Cell fate B

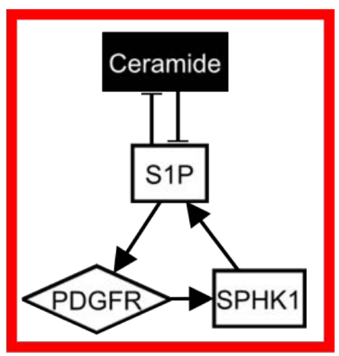
<u>Zañudo</u> and Albert
PLoS Comp. Biol.
11(4): e1004193
(2015).

Attractor control: Find subnetworks that stabilize in a fixed state

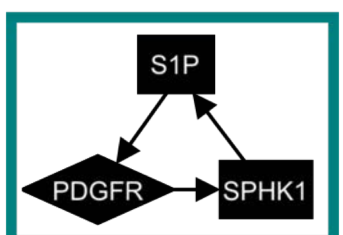


Cell fate A

Cell fate B



Cell fate A



Cell fate B

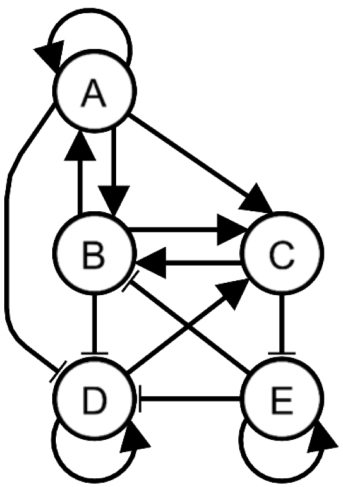
Zañudo and Albert PLoS Comp. Biol. 11(4): e1004193 (2015).

White: ON

Black: OFF

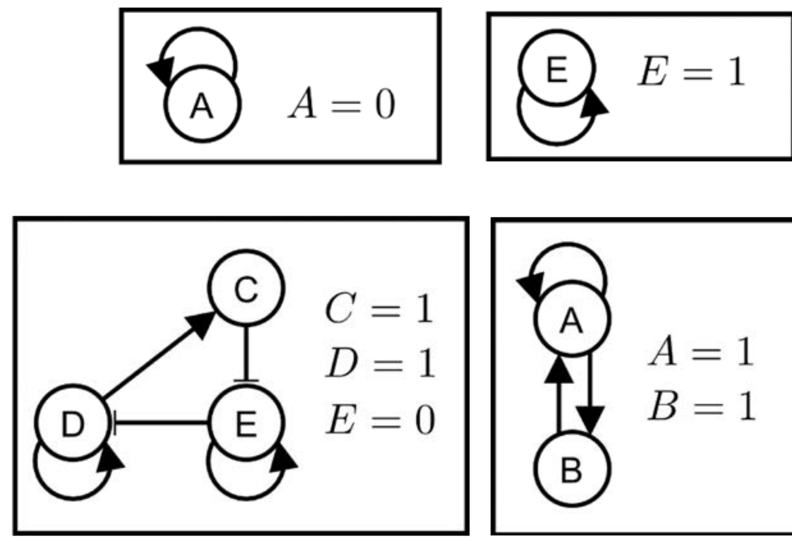
Subnetworks that stabilize in a fixed state: stable motifs

Logical model



$$
\begin{aligned}
f_A &= A \text{ AND } B \\
f_B &= A \text{ OR } C \text{ OR NOT } E \\
f_C &= (A \text{ AND } B) \text{ OR } D \\
f_D &= (\text{NOT } B \text{ AND NOT } A) \\
&\quad \text{OR } (D \text{ AND NOT } A) \\
&\quad \text{OR } (D \text{ AND NOT } B) \\
&\quad \text{OR NOT } E \\
f_E &= E \text{ OR NOT } C
\end{aligned}
$$

Stable motifs



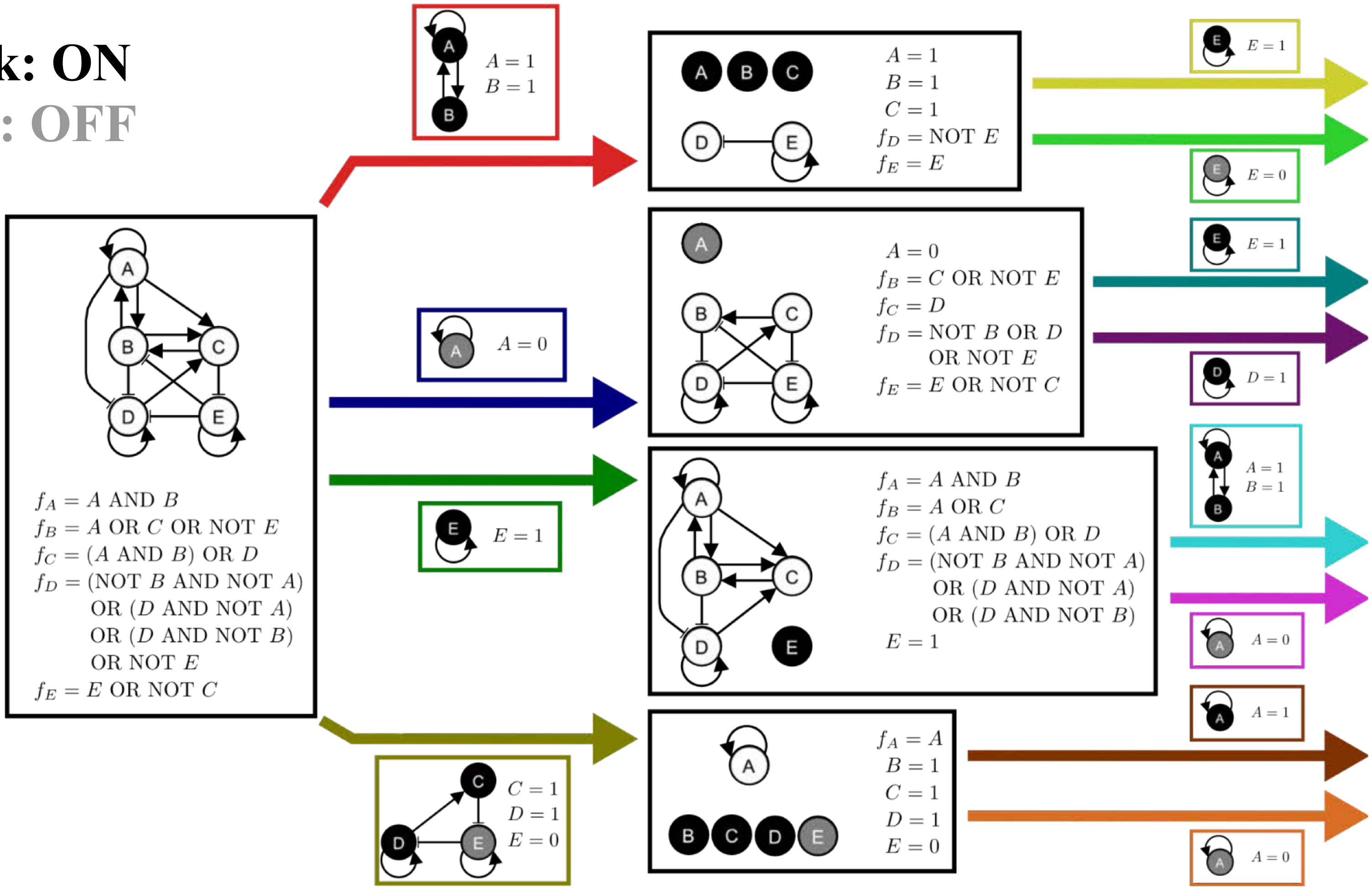
- Stable motifs
  - Identified on a logic-expanded network representation
  - Network property: Intersecting positive feedback loops
  - Dynamical property: Trap subspaces

Zañudo and Albert
Chaos 23 (2)
025111 (2013).

J.G.T. Zañudo

BROAD INSTITUTE
DANA-FARBER CANCER INSTITUTE

Black: ON
Grey: OFF



Original logical network model

Stable motifs of the original network model

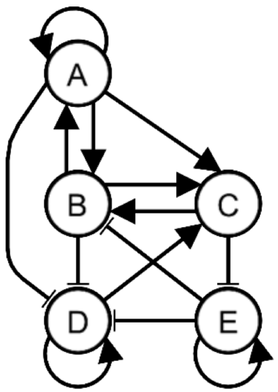
Reduced logical network models

Stable motifs of the reduced network models

Stable motifs and attractor control

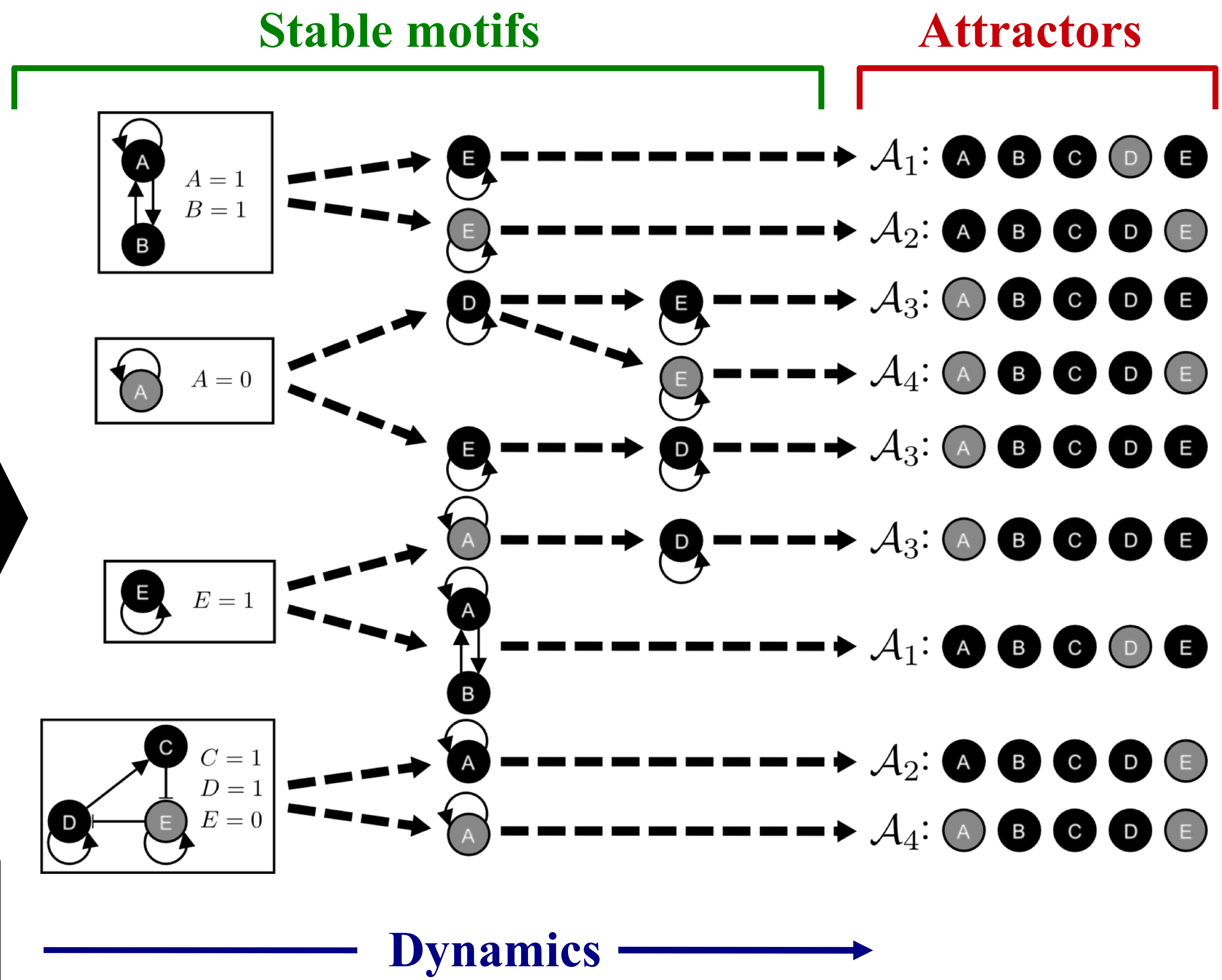
BROAD INSTITUTE
DANA-FARBER CANCER INSTITUTE

Black: ON
Grey: OFF



+

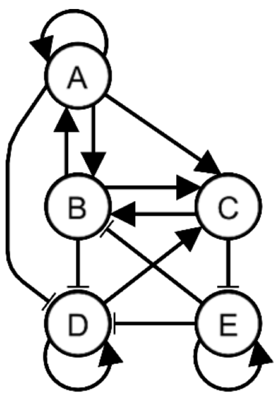
$f_A = A \text{ AND } B$
$f_B = A \text{ OR } C \text{ OR NOT } E$
$f_C = (A \text{ AND } B) \text{ OR } D$
$f_D = (\text{NOT } B \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } B) \text{ OR NOT } E$
$f_E = E \text{ OR NOT } C$



J.G.T. Zañudo and R. Albert. PLoS Comp. Biol. 11(4): e1004193 (2015).

- Attractor control: Sequence of stable motifs → Attractor

Black: ON
Grey: OFF



+

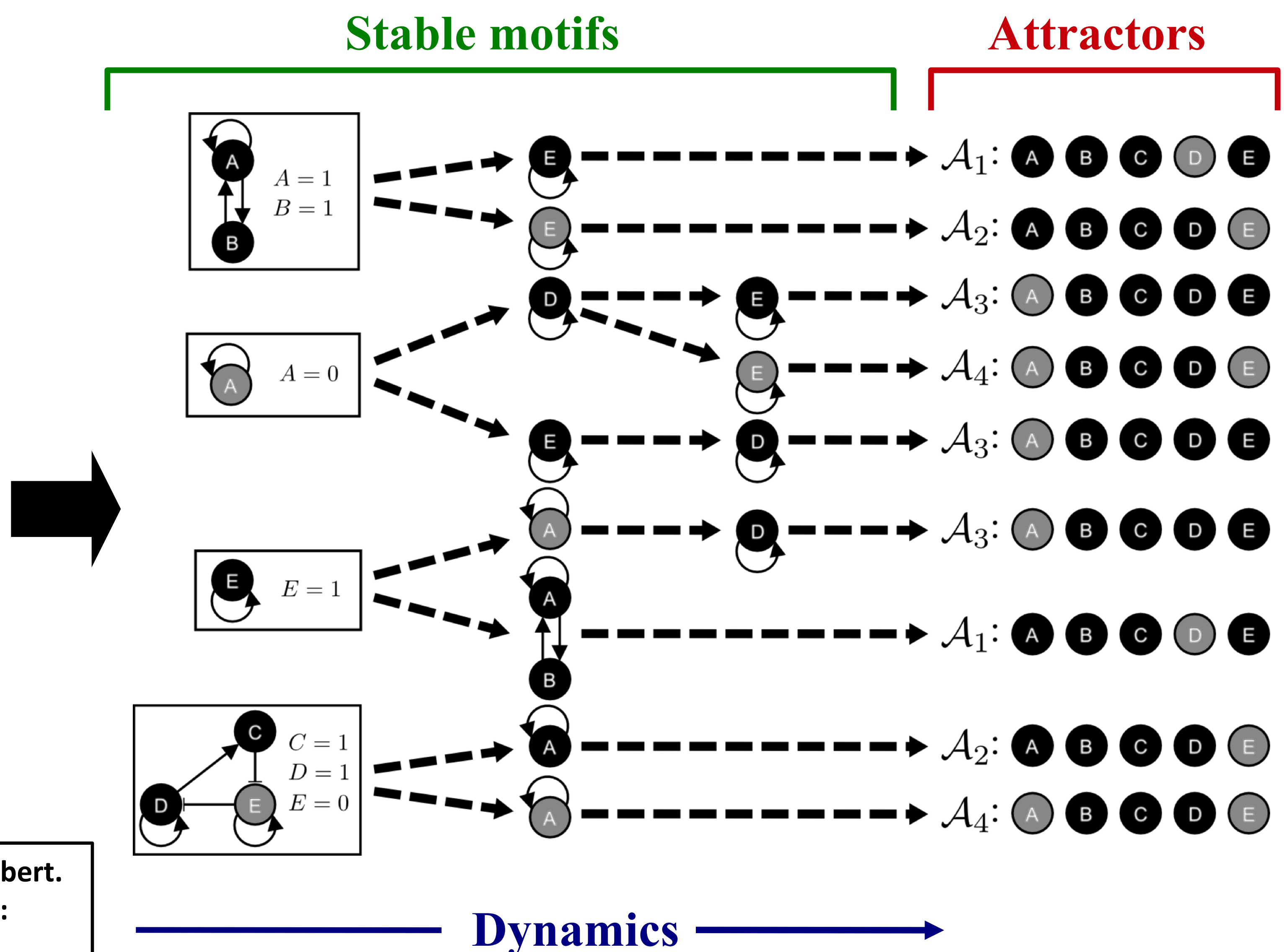
$f_A = A \text{ AND } B$

$f_B = A \text{ OR } C \text{ OR NOT } E$

$f_C = (A \text{ AND } B) \text{ OR } D$

$f_D = (\text{NOT } B \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } B) \text{ OR NOT } E$

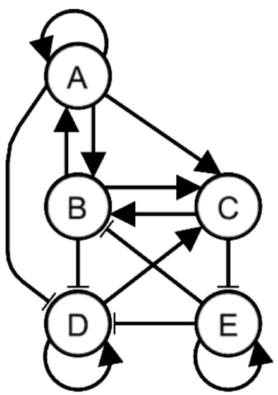
$f_E = E \text{ OR NOT } C$



J.G.T. Zañudo and R. Albert. PLoS Comp. Biol. 11(4): e1004193 (2015).

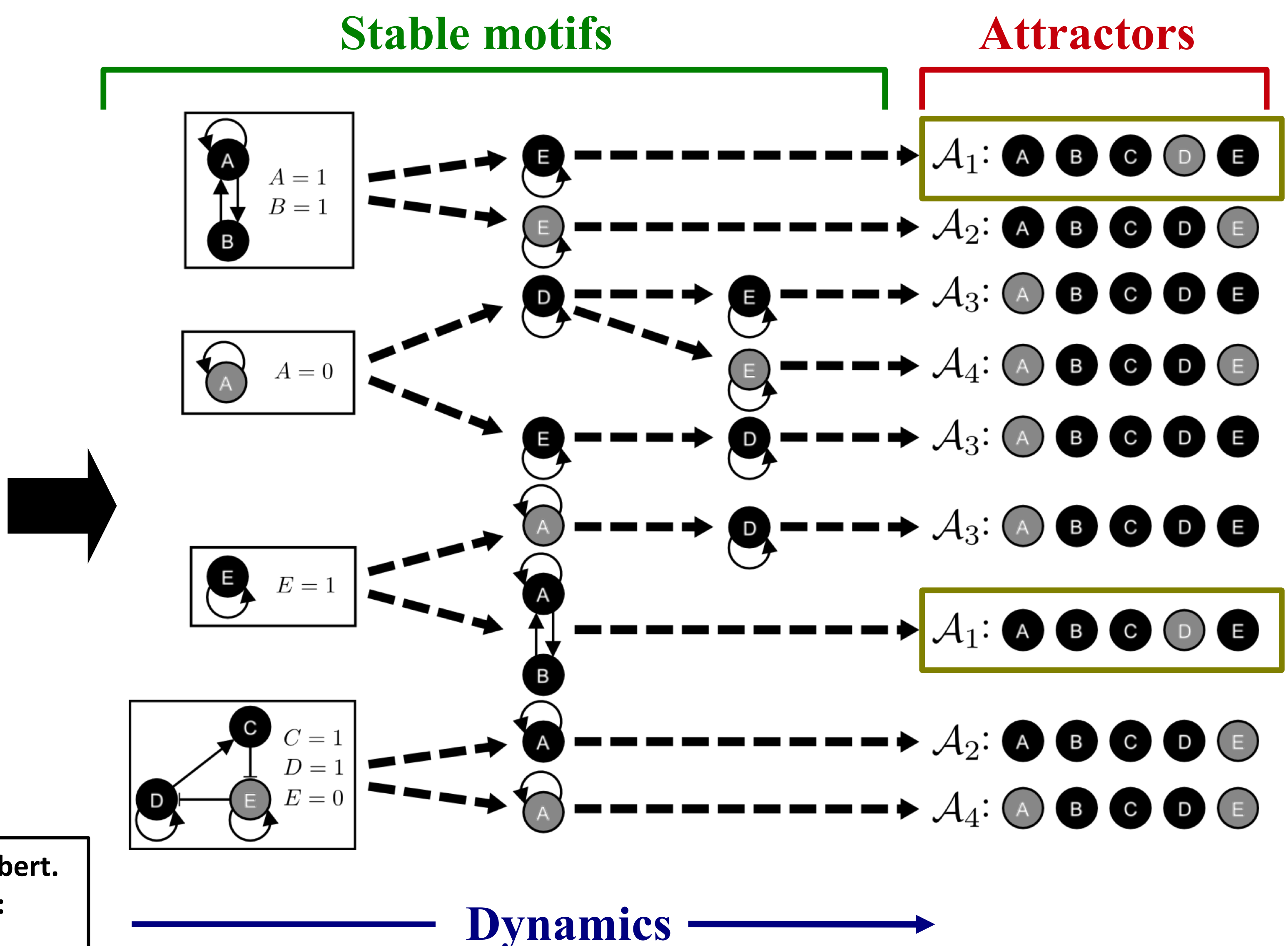
- Attractor control: Sequence of stable motifs → Attractor

Black: ON
Grey: OFF



+

$f_A = A \text{ AND } B$
$f_B = A \text{ OR } C \text{ OR NOT } E$
$f_C = (A \text{ AND } B) \text{ OR } D$
$f_D = (\text{NOT } B \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } B) \text{ OR NOT } E$
$f_E = E \text{ OR NOT } C$

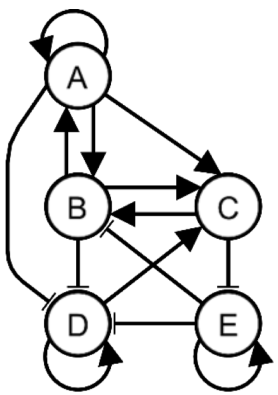


J.G.T. Zañudo and R. Albert. PLoS Comp. Biol. 11(4): e1004193 (2015).

Stable motifs and attractor control

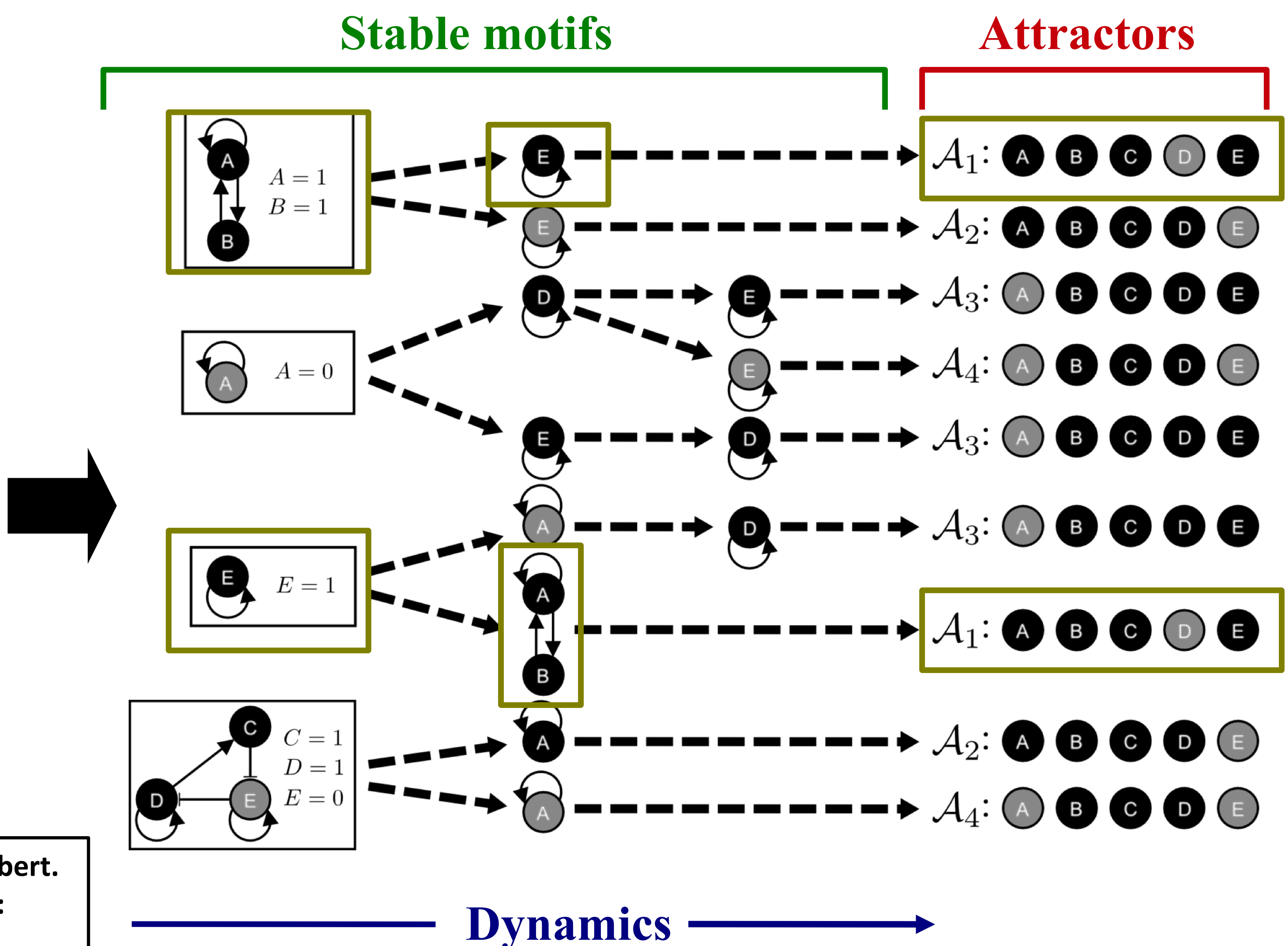
- Attractor control: <u>Sequence of stable motifs → Attractor</u>

Black: ON
Grey: OFF



+

$f_A = A \text{ AND } B$
$f_B = A \text{ OR } C \text{ OR NOT } E$
$f_C = (A \text{ AND } B) \text{ OR } D$
$f_D = (\text{NOT } B \text{ AND NOT } A)$
$\quad \text{OR } (D \text{ AND NOT } A)$
$\quad \text{OR } (D \text{ AND NOT } B)$
$\quad \text{OR NOT } E$
$f_E = E \text{ OR NOT } C$

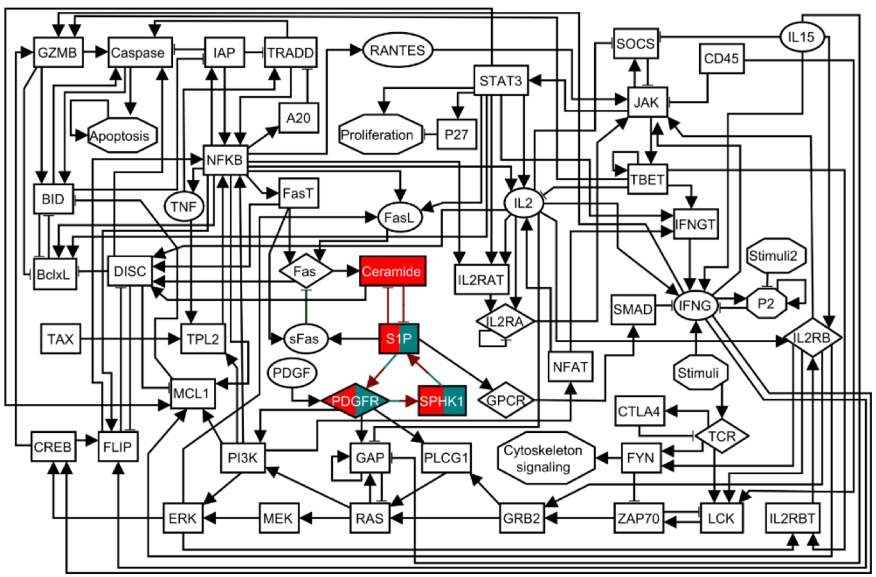


<u>J.G.T. Zañudo</u> and R. Albert. PLoS Comp. Biol. 11(4): e1004193 (2015).

Stable motifs: network + dynamics

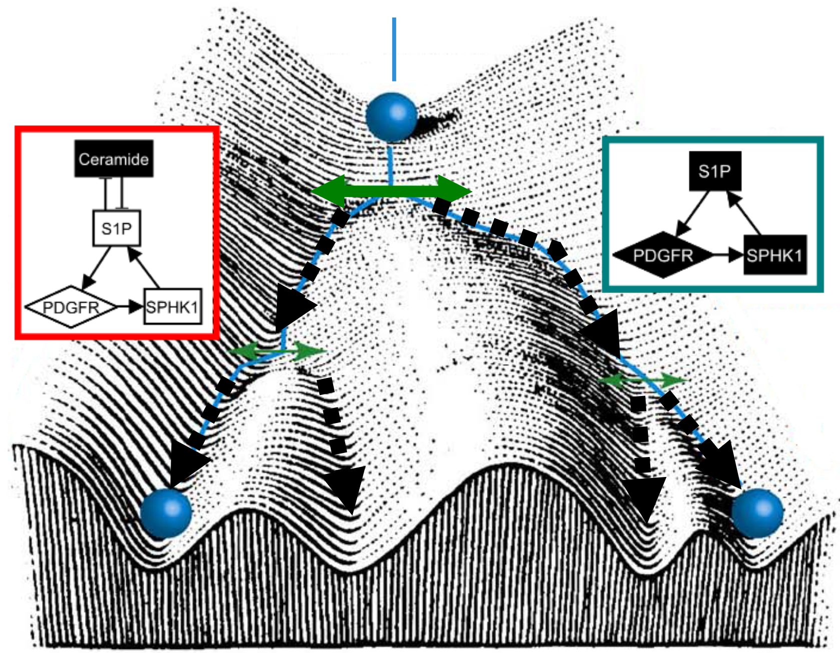
Stable motifs are subnetworks and points of no return in the dynamics

Network and stable motifs



Stable motifs and dynamics

Marble rolling down



Cell fate A

Cell fate B

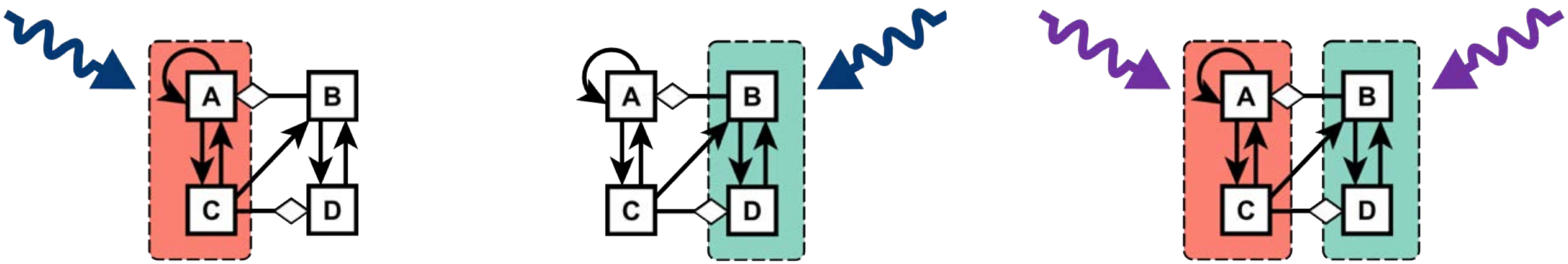
Stable cell states

What is the connection between stable motif control and FVS control?

FVS and stable motif control

Model-dependent (model-specific cycles) vs Model-independent (all cycles)

Control method	Stable motif (SM) control (model-dependent)	Stable motif (SM) control (model-dependent)	Feedback vertex set (FVS) control (model-independent)



Model (parameters)	Model 1 (Parameters = P1)	Model 2 (Parameters = P2)	Model unkown (Parameters = arbitrary)

JGT Zañudo et al. Physical Biology (2019).

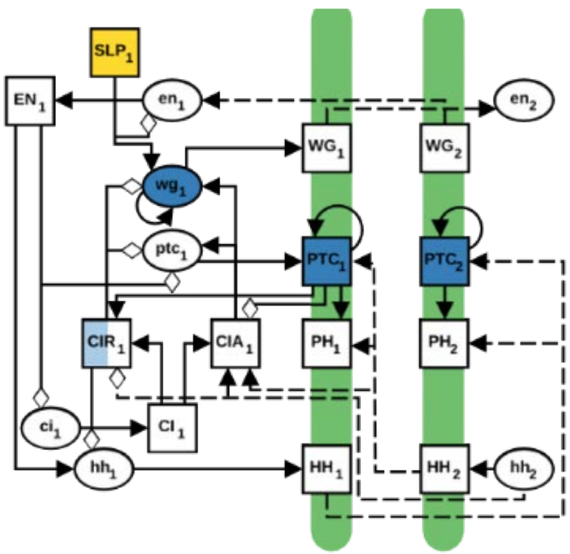
FVS and SM control on Boolean models

J.G.T. Zañudo
Model-dependent and model-independent control of biological network models

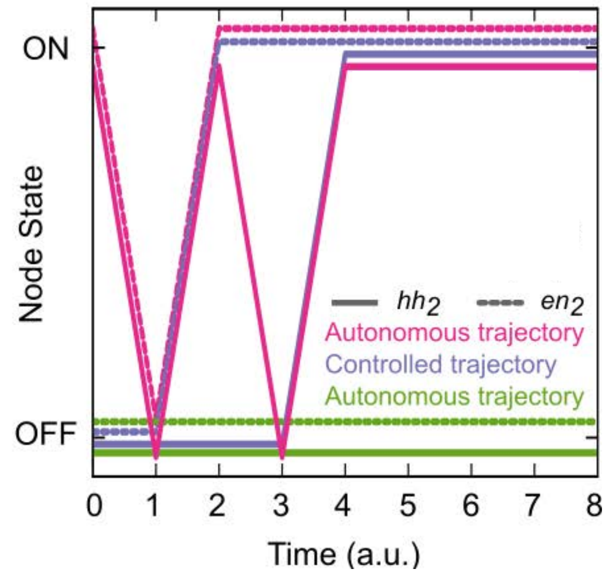
BROAD INSTITUTE
DANA-FARBER CANCER INSTITUTE

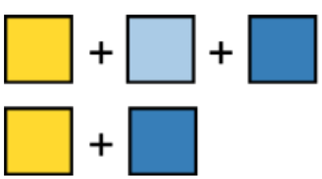
Stable motif control (model-dependent) vs FVS control (model-independent)

Fruit fly Boolean network model



Controlled trajectories





FVS control (model-independent)

Stable motif control (model-dependent)

JGT Zañudo and R Albert. PLoS Comp Biol. 11(4) (2015)	Zañudo et al. PNAS 114 (28), 7234 - 7239 (2017)

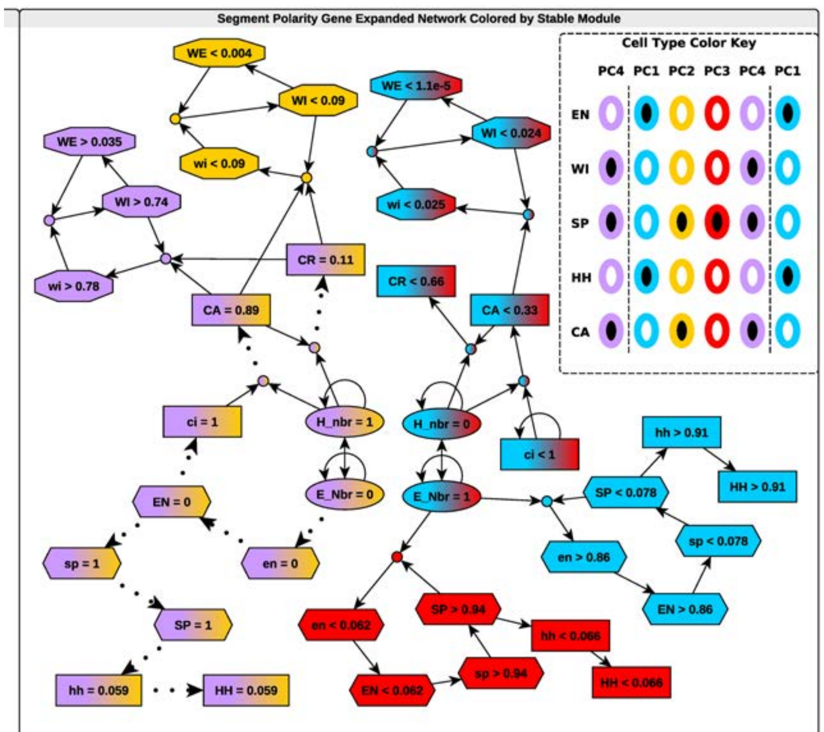
Stable motifs in continuous models might allow model-dependent attractor control predictions for continous systems

PLOS | COMPUTATIONAL BIOLOGY

Identifying (un)controllable dynamical behavior in complex networks

Jordan C. Rozum[1]*, Réka Albert[1,2]

PLoS Comput Biol 14(12): e1006630



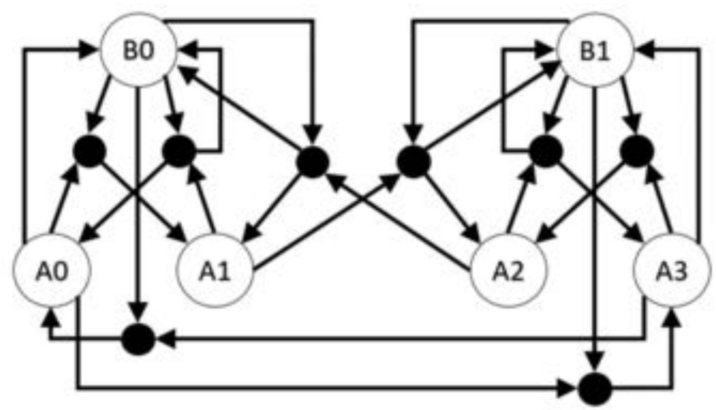
PHYSICAL REVIEW E

covering statistical, nonlinear, biological, and soft matter physics

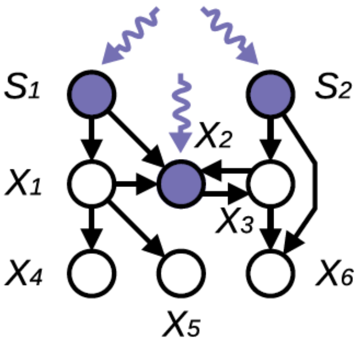
General method to find the attractors of discrete dynamic models of biological systems

Xiao Gan and Réka Albert

Phys. Rev. E **97**, 042308



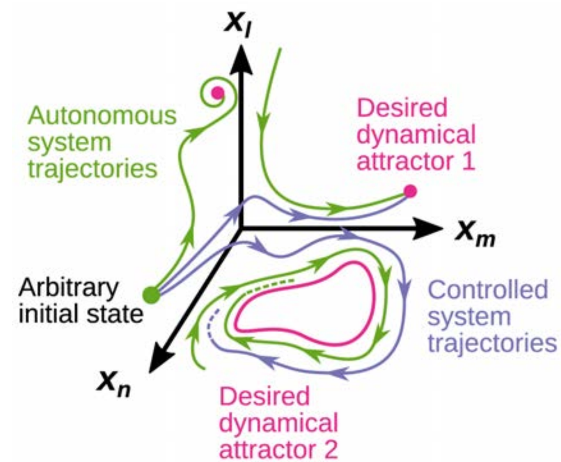
- Structure-based control approach for networks with nonlinear dynamics:



Feedback Vertex Set control

↓

Attractor-based network control



- Stable motif control allows control when the model dynamics are specified

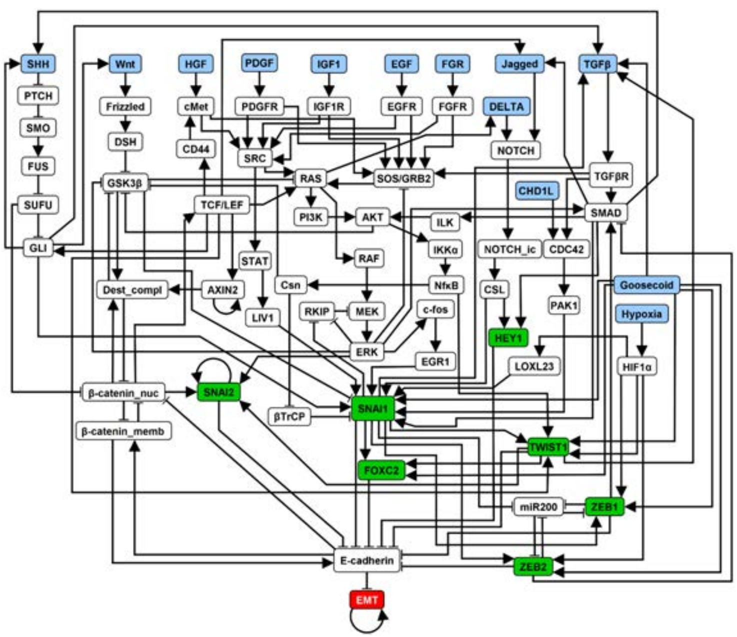
- Cycles in the network are crucial for nonlinear attractor control

- FVS control (model-independent) and stable motif control (model-dependent); complementary control approaches

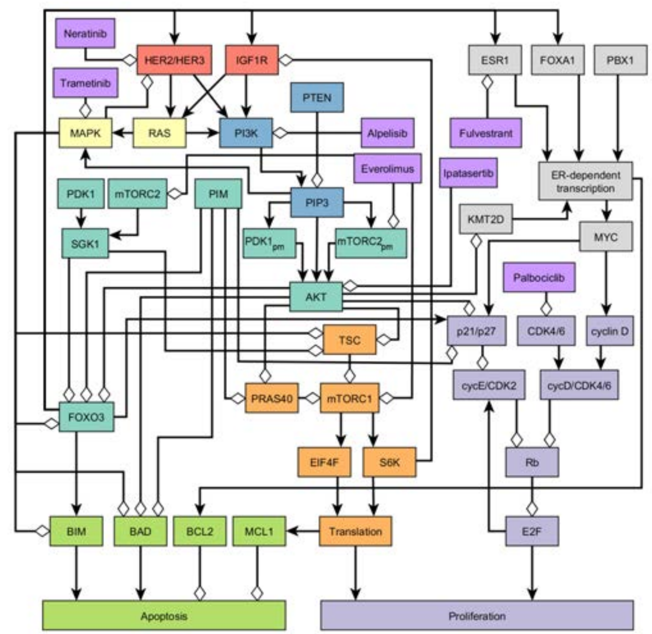
Objective of my research

Use <u>mathematical models</u> and <u>control methods</u> to predict

Nodes that block metastatic reprogramming
(EMT in liver cancer)



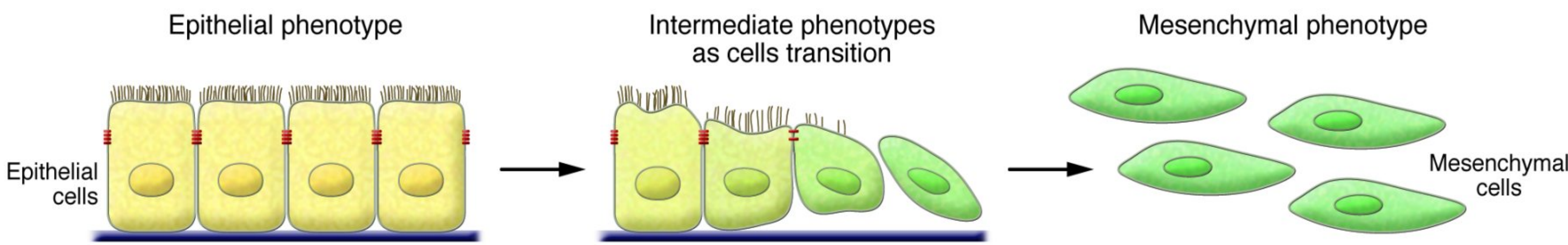
Resistance mechanisms and drug combinations
(PI3K inhibition in ER+ MBC)



SN Steinway, **<u>JGT Zañudo</u>**, et al. Cancer Res. (2014).
SN Steinway*, **<u>JGT Zañudo*,</u>** et al. npj Syst. Biol. & Appl. (2015).

<u>JGT Zañudo</u>, et al. Cancer Convergence. (2017).
<u>JGT Zañudo,</u> et al. bioRxiv. (2020).

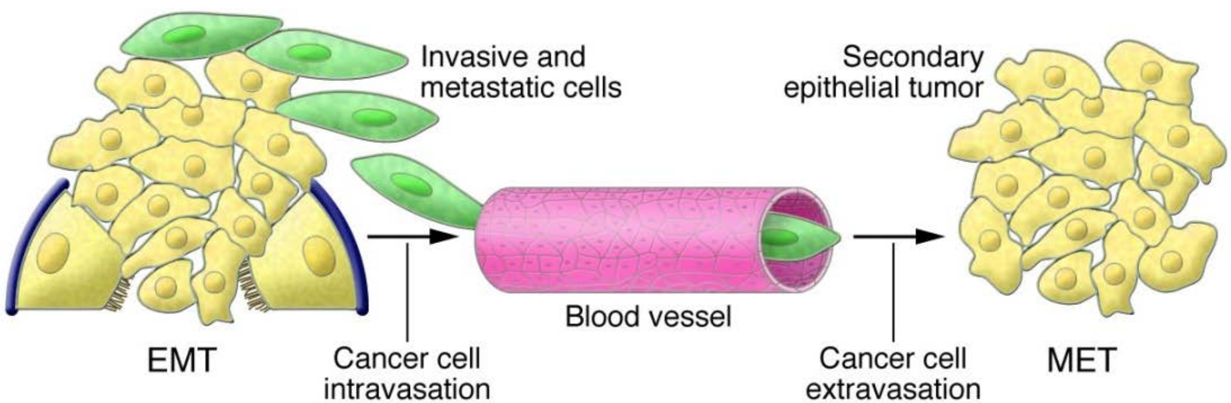
- Epithelial-to-mesenchymal transition (EMT) is a natural developmental and wound-healing cellular process.



High E-cadherin expression
Strong Adhesion

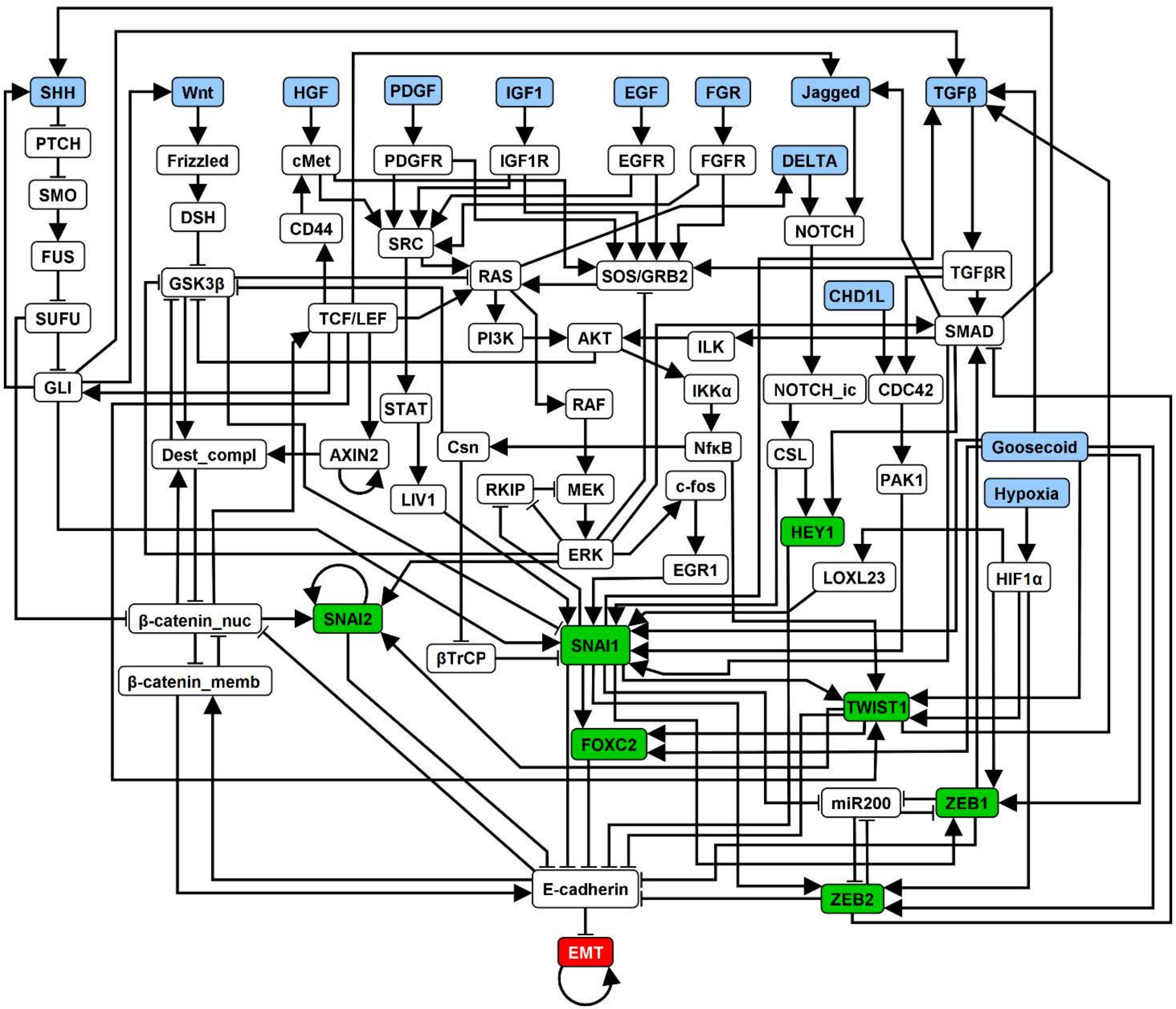
Loss of E-cadherin expression
Weak adhesion

- EMT process is hijacked by cancer cells (initiation of invasion and metastasis).



Kalluri and Weinberg. J Clin Invest **119** (6) (2009).

Network representing the known regulation of EMT was curated from the literature.



69 nodes and
135 interactions

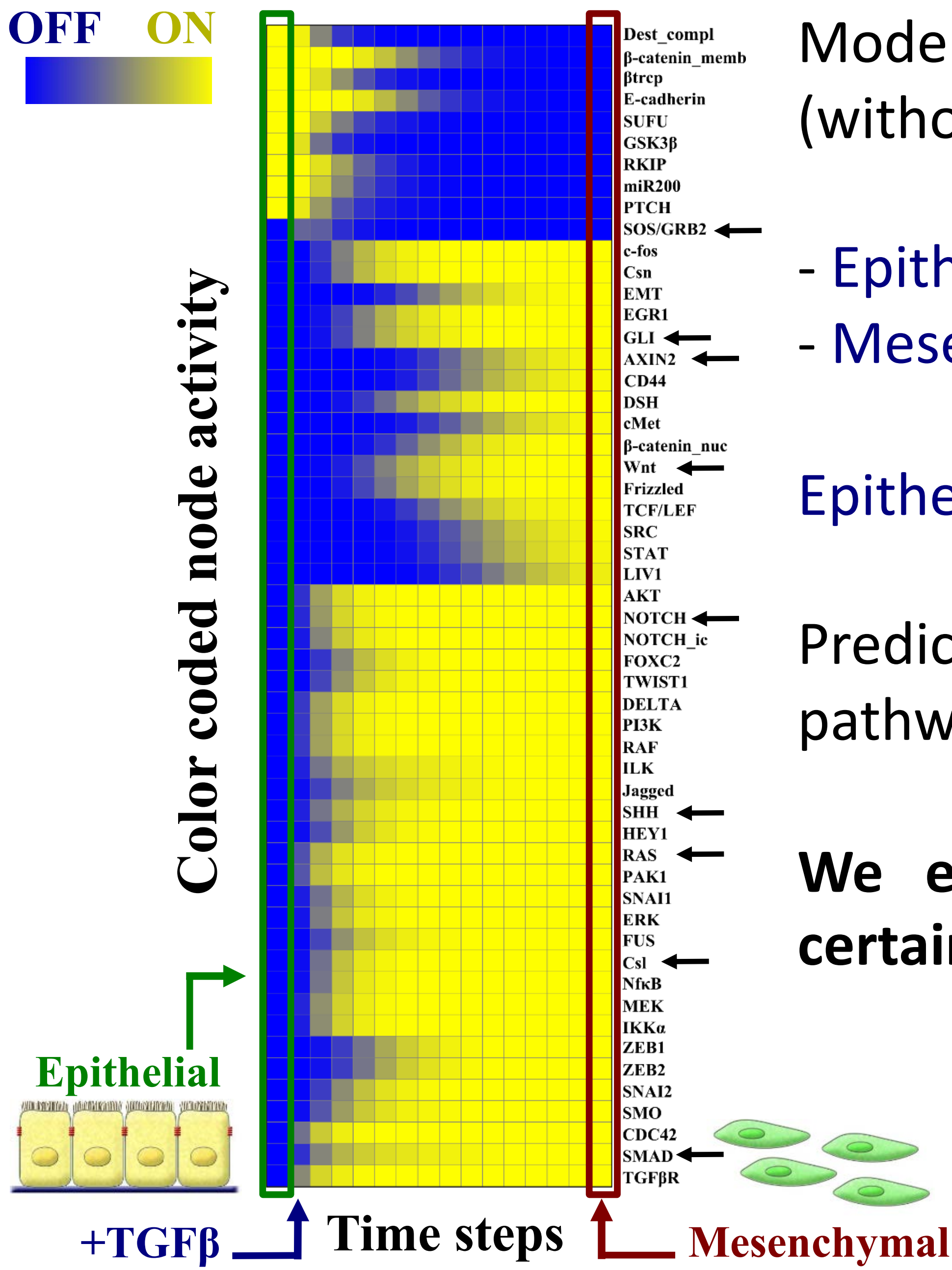
BLUE:
External signals

GREEN:
Transcription factors

RED:
Hallmark node

SN Steinway, JGT Zañudo, W Ding, CB Rountree, D Feith, TP Loughran, R Albert. Cancer Res 74 (21) (2014).

EMT network model



Model we built has two steady states (without external signals):

- Epithelial state (E)
- Mesenchymal state (M)

Epithelial + TGFβ → Mesenchymal

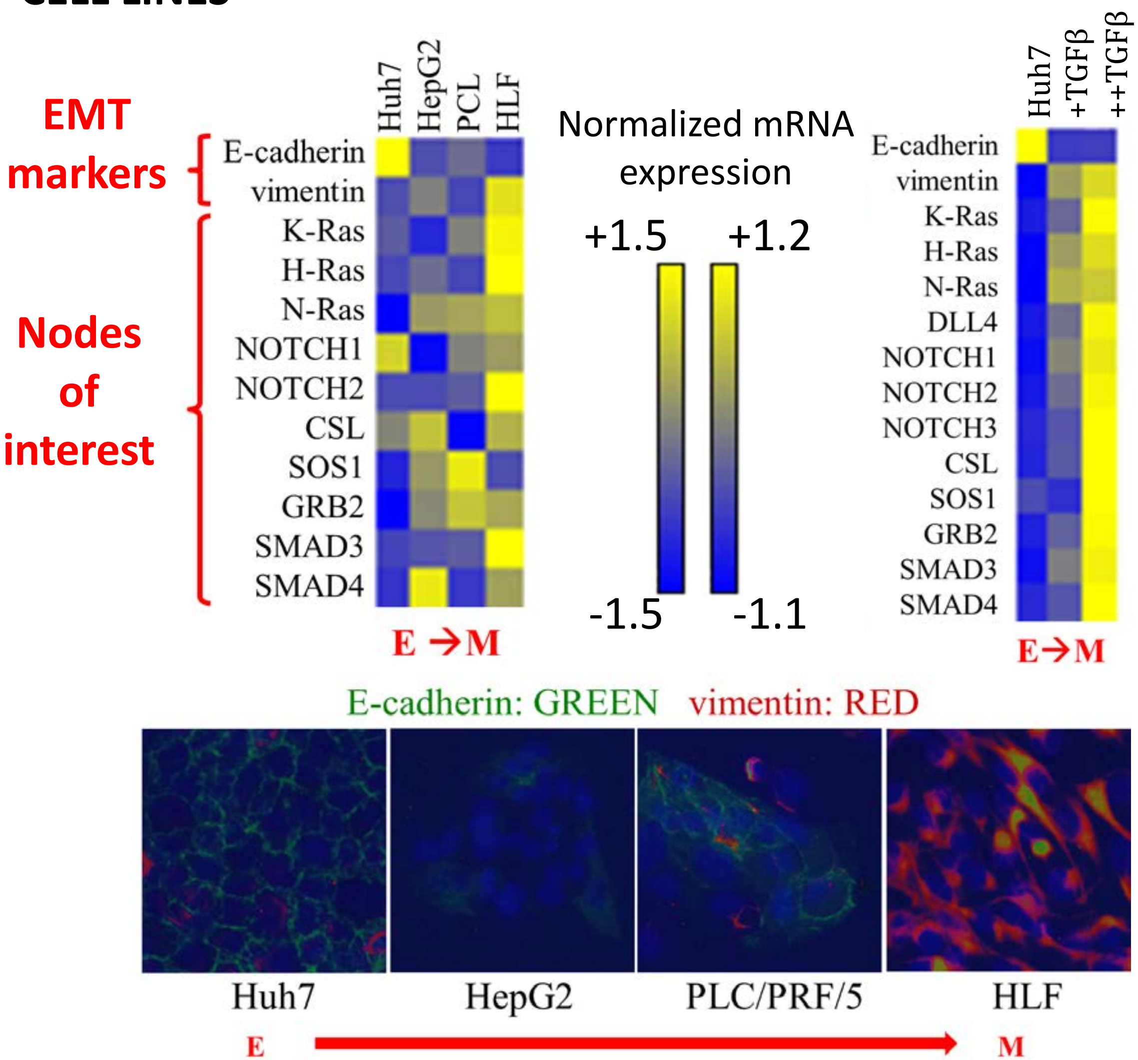
Predicts activation of multiple signaling pathways during TGFβ induction

We experimentally test activation of certain pathways

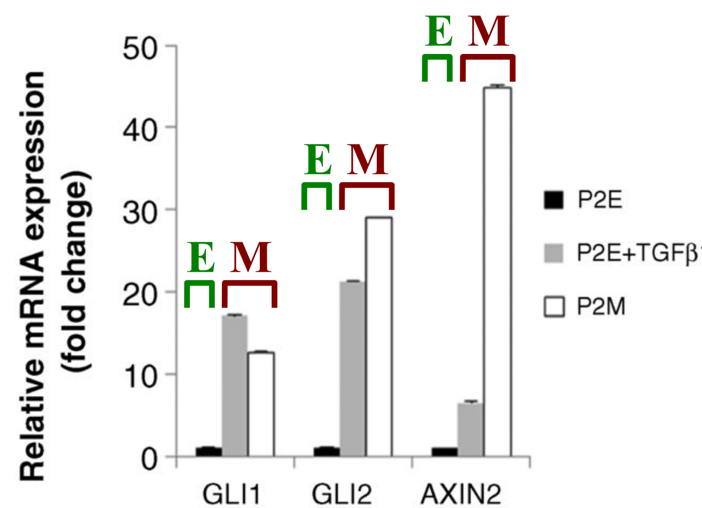
SN Steinway, **<u>JGT Zañudo</u>**, W Ding, CB Rountree, D Feith, TP Loughran, R Albert. Cancer Res 74 (21) (2014).

We validated model-directed activation of several signaling pathways and genes during TGFβ-driven EMT

CELL LINES



MICE

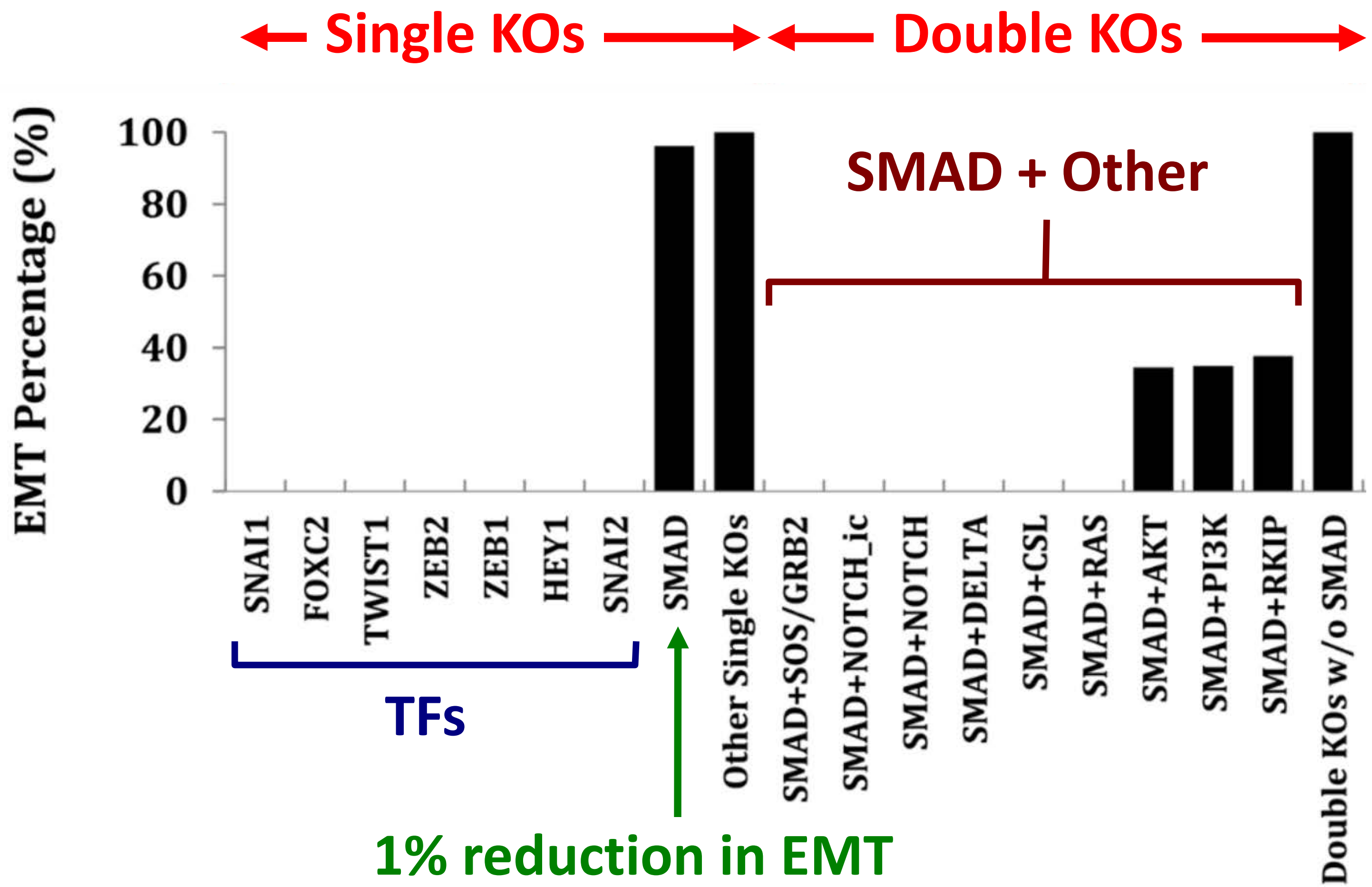


SN Steinway*, **JGT Zañudo***, PJ Michel, D Feith, TP Loughran, R Albert. npj Syst. Biol. and Applic. 15014 (2015).

SN Steinway, **JGT Zañudo**, W Ding, CB Rountree, D Feith, TP Loughran, R Albert. Cancer Res 74 (21) (2014).

How do we disrupt the network to suppress EMT and tumor invasion?

Computational interventions

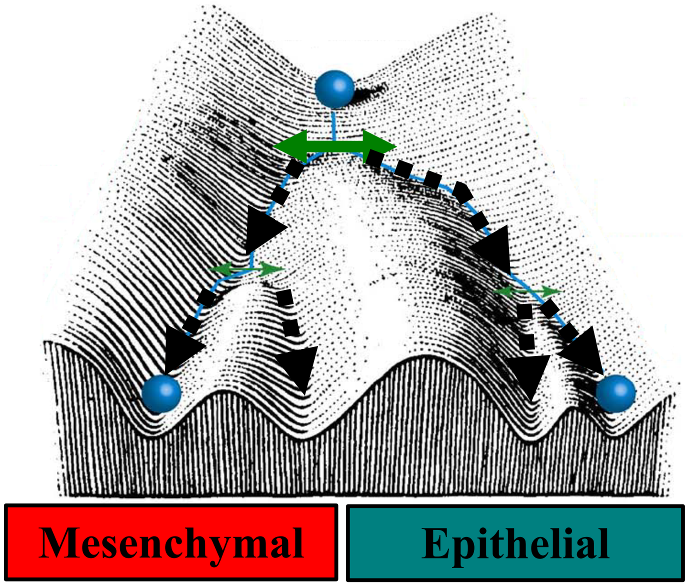


SN Steinway*, **JGT Zañudo***, PJ Michel, D Feith, TP Loughran, R Albert. npj Syst. Biol. and Applic. 15014 (2015).

So what?

Stable motifs help explain the interventions

We used network control theory to identify that TGFβ drives EMT through the activation of intersecting feedback loops (stable motifs)

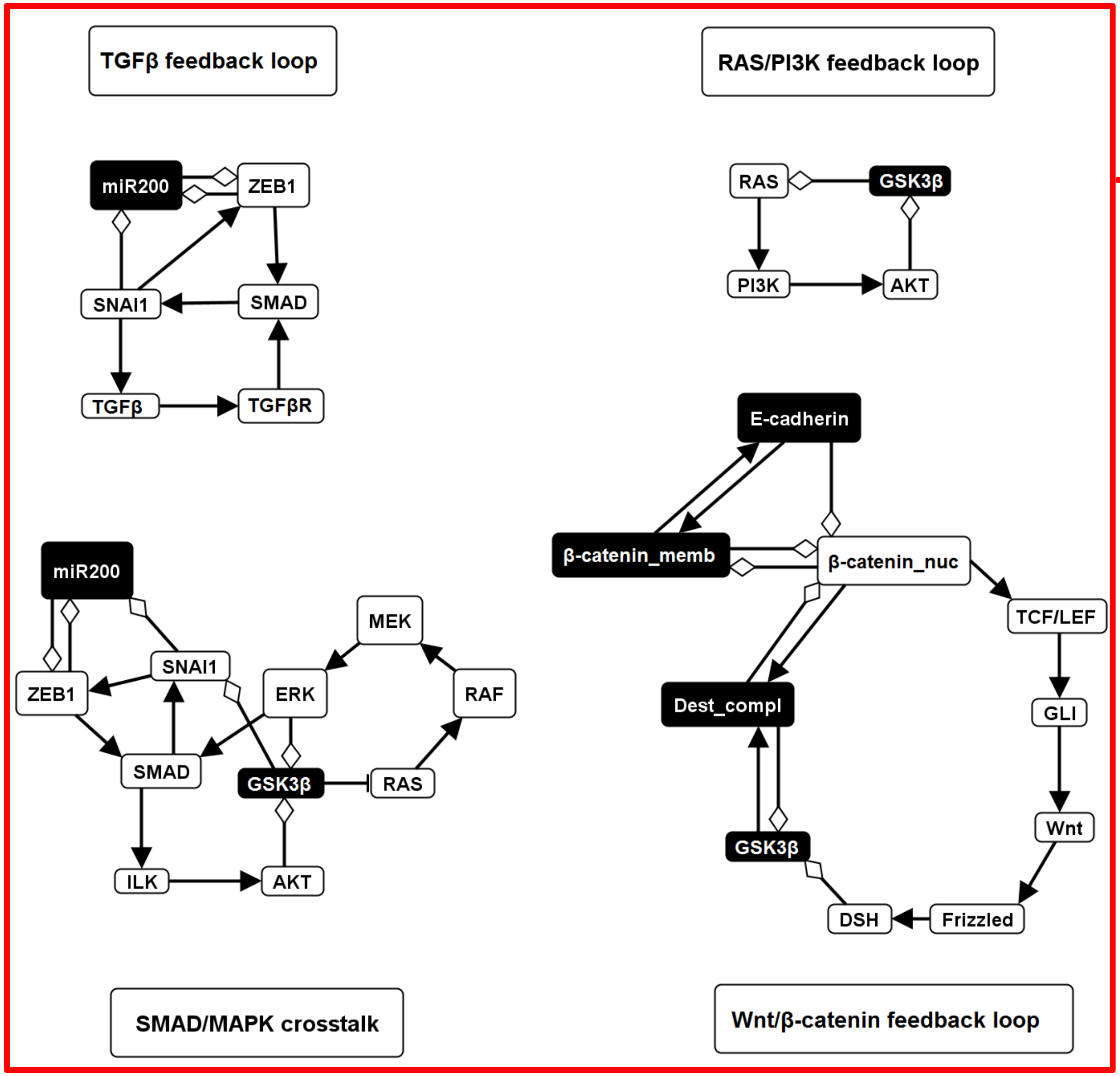


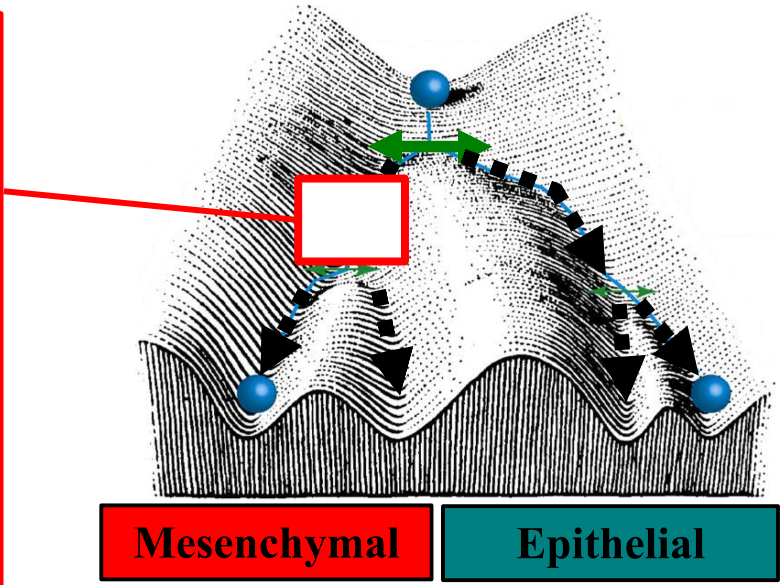
White: ON

Black: OFF

SN Steinway, **JGT Zañudo**, W Ding, CB Rountree, D Feith, TP Loughran, R Albert. Cancer Res 74 (21) (2014).

We used network control theory to identify that TGFβ drives EMT through the activation of intersecting feedback loops (stable motifs)





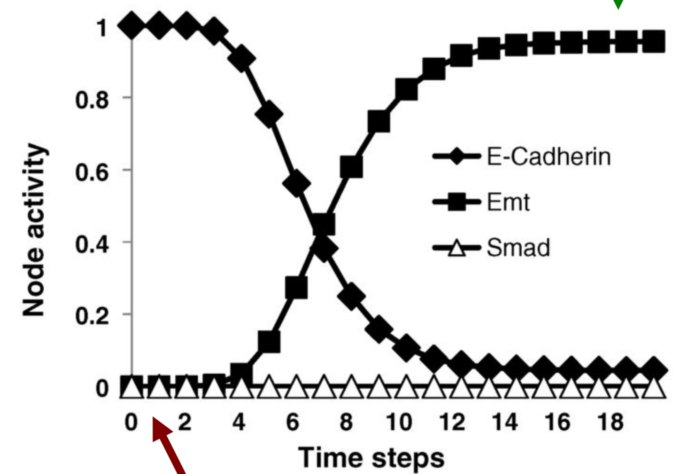
White: ON

Black: OFF

SN Steinway, **JGT Zañudo**, W Ding, CB Rountree, D Feith, TP Loughran, R Albert. Cancer Res 74 (21) (2014).

Stable motifs explain why SMAD KD has minimal effect on EMT induction

1% reduction in EMT



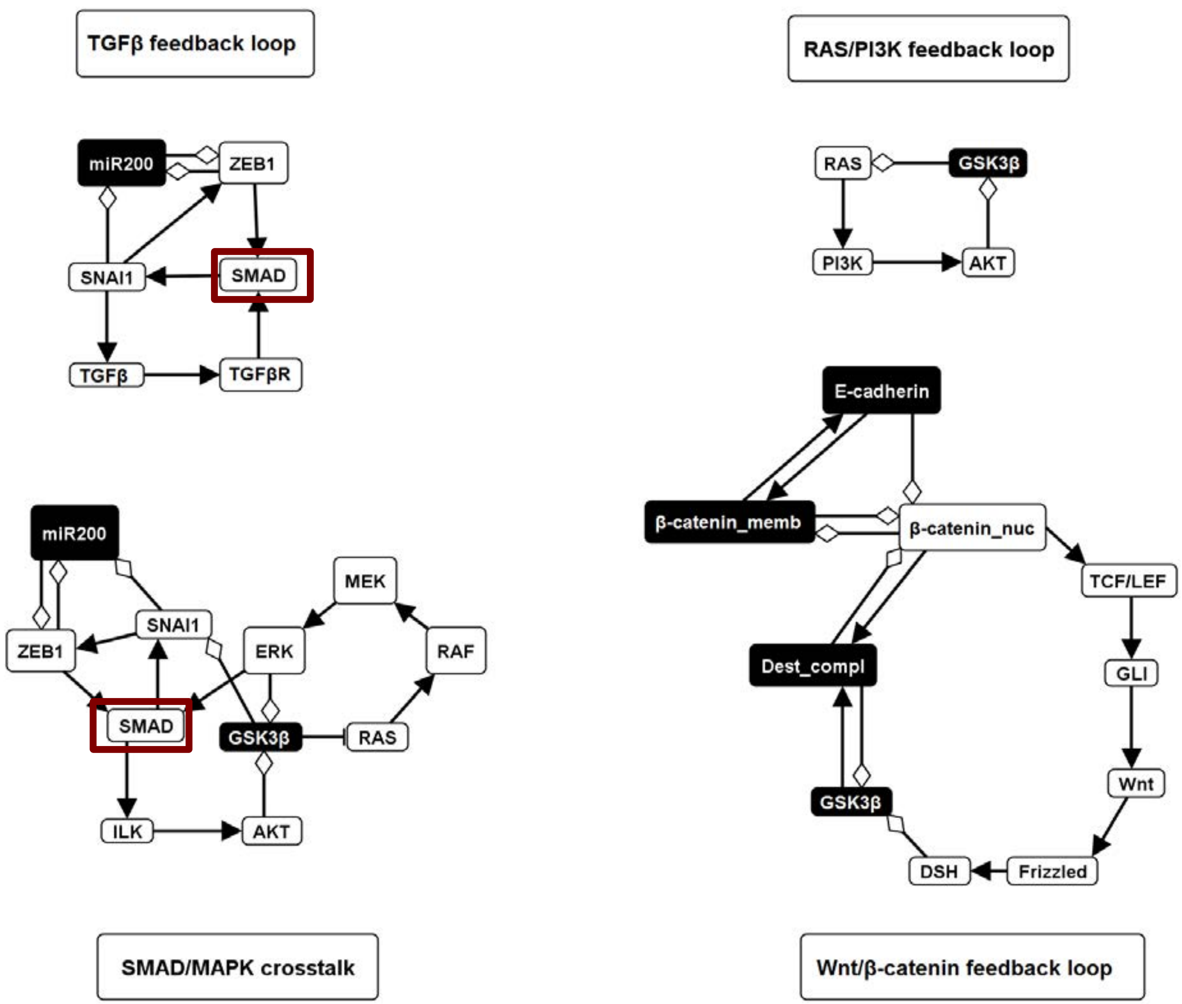
SMAD knock out

White: ON

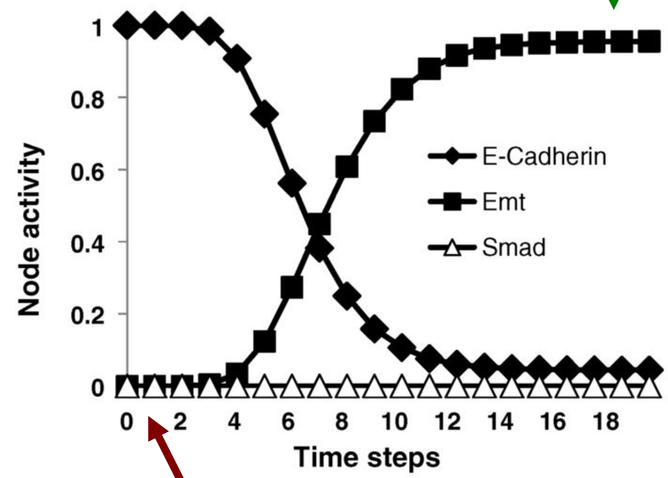
Black: OFF

SN Steinway, **JGT Zañudo**, W Ding, CB Rountree, D Feith, TP Loughran, R Albert. Cancer Res 74 (21) (2014).

Stable motifs explain why SMAD KD has minimal effect on EMT induction



1% reduction in EMT



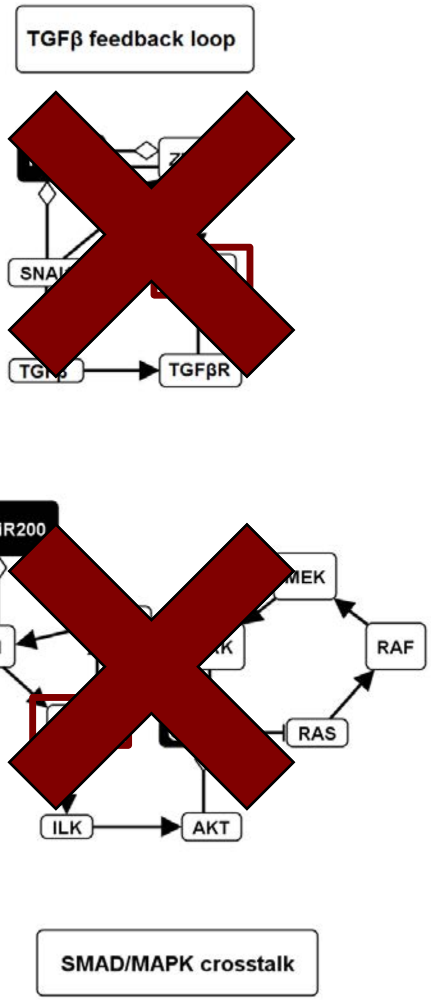
SMAD knock out

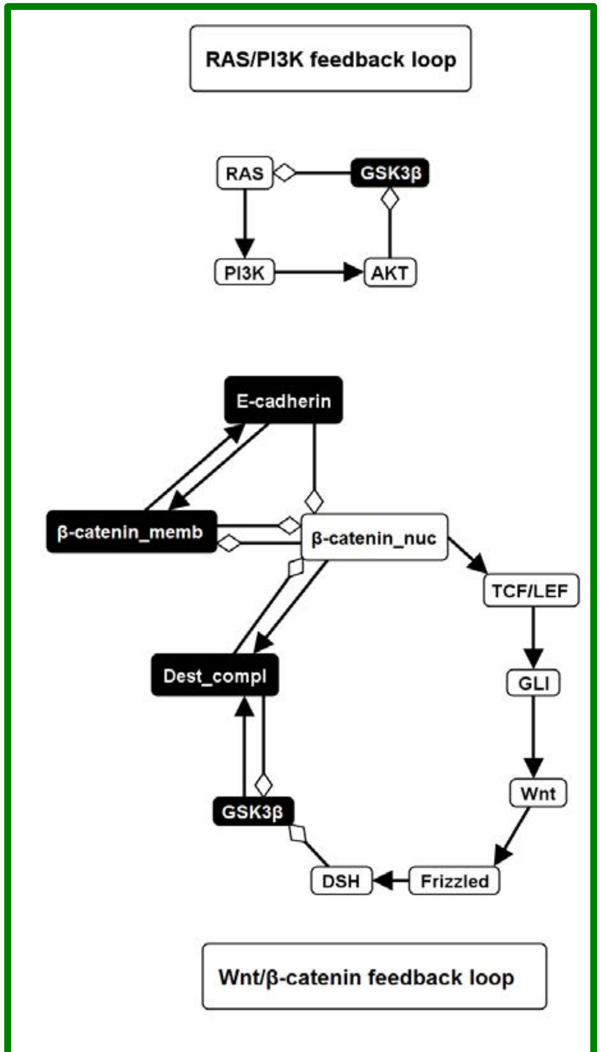
White: ON

Black: OFF

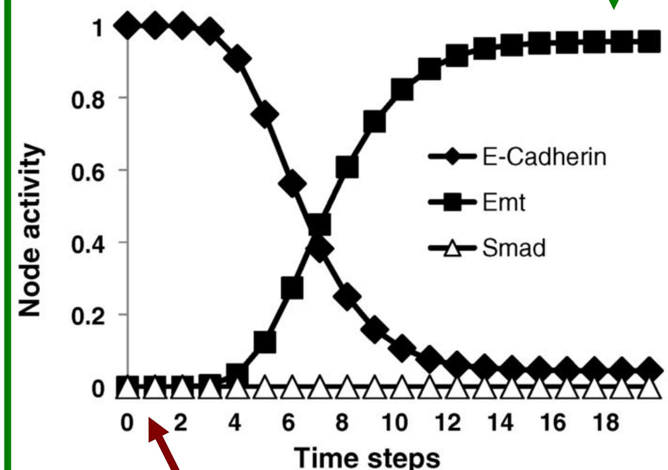
SN Steinway, **JGT Zañudo**, W Ding, CB Rountree, D Feith, TP Loughran, R Albert. Cancer Res 74 (21) (2014).

Stable motifs explain why SMAD KD has minimal effect on EMT induction





1% reduction in EMT



SMAD knock out

White: ON

Black: OFF

SN Steinway, **JGT Zañudo**, W Ding, CB Rountree, D Feith, TP Loughran, R Albert. Cancer Res 74 (21) (2014).

CONCLUSIONS

- Model recapitulates known EMT dynamics and predicts novel pathway cross activation.
- Model predicts KO combinations that suppress TGFβ-driven EMT.
- Wet-lab experiments confirm many combinations suppress EMT.
- Stable motif analysis and control provides the motifs that drive EMT and the mechanism through which the KO combinations act.

Acknowledgements

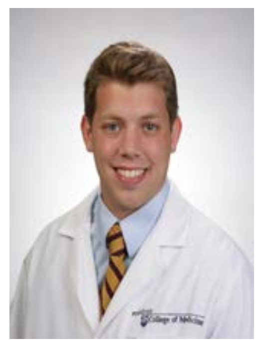
ALBERT GROUP (PSU)

Réka Albert

Gang Yang

WAGLE LAB (DFCI, Broad)

LOUGHRAN LAB



- **Steven N. Steinway**
- Thomas P. Loughran
- David Feith

Discussions and data (FVS)

M. Angulo (UNAM)
YY. Liu (BWH,HMS)
A. Mochizuki (RIKEN)
YC. Lai (ASU)

- Funding from NSF (PHY 1205840 & IIS 1160995)
- Current funding from The V foundation /SU2C Convergence Scholar Award.

Jorge Gómez Tejeda Zañudo
Postdoctoral researcher
Broad Institute of MIT and Harvard
Dana-Farber Cancer Institute

Thank you for your time!

Questions, comments, suggestions?
Complaints???

Contact: jgtz@broadinstitute.org
@jgtzanudo (Twitter)

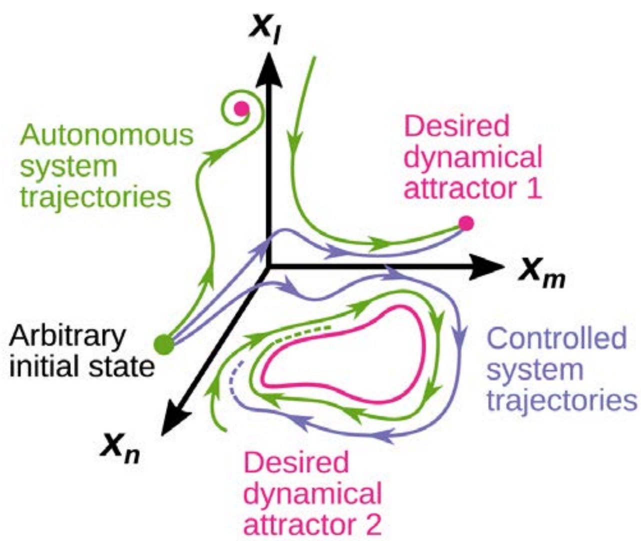
References:

Fiedler, B., Mochizuki, A., et al. (2013), *J. Dynamics and Differential Equations.*
Mochizuki, A., Fiedler, B., et al. (2013), *J. Theor. Bio.*
Zanudo J.G.T. & Albert R. et al. (2015), *PLoS Comp. Bio.*
Zanudo J.G.T., Yang G., & Albert R. (2017), *PNAS.*

Feedback vertex set control (FC)

Mochizuki et al. J. Theor. Biol. 335 (2013)
Zañudo et al. PNAS 114 (2017)

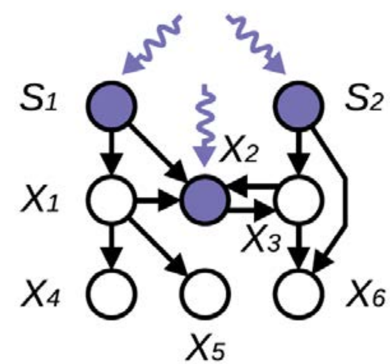
- **Structural:**
  - Control nodes based solely on structure
  - Guarantees control for the ensemble of networks with a given structure



- **Dynamics:**
  - Nonlinear with decay
  - System attractors

$$\frac{dX_i}{dt} = F_i(X_i, X_{I_i}, t),$$

$$\frac{dS_j}{dt} = G_j(t),$$

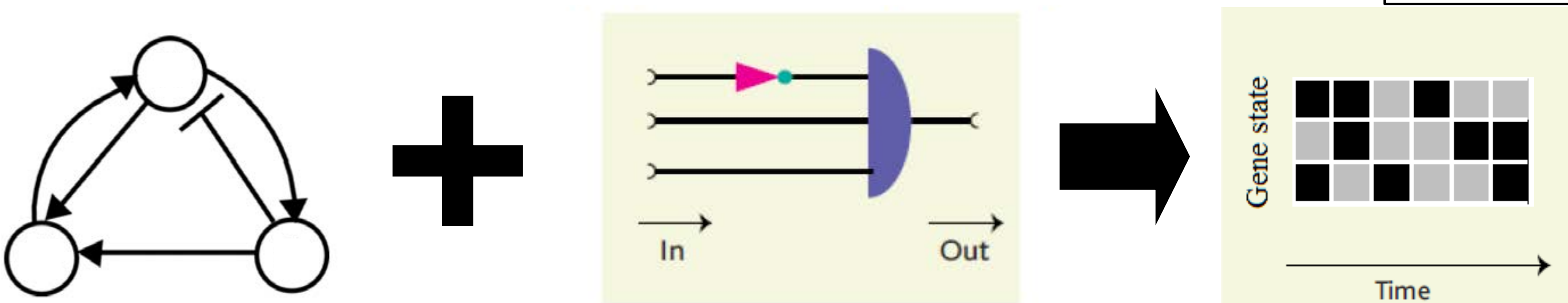


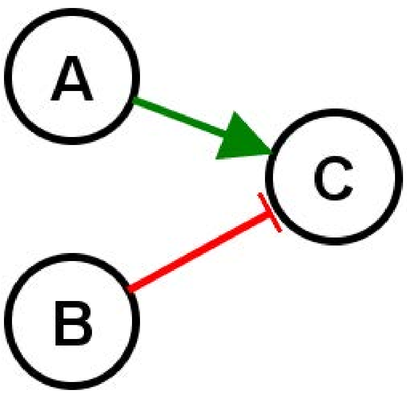
- **Control actions:**
  - Any IC to a target system attractor
  - Fix state variable of FVS & sources into their state in the target attractor

Boolean (logical) modeling scheme

- Boolean models: ON (active) or OFF (inactive)

Bornholdt. Science **310**, 5747 (2005).





Boolean variables

$$C(t+\tau) = A(t) \text{ and } (\text{not } B(t))$$

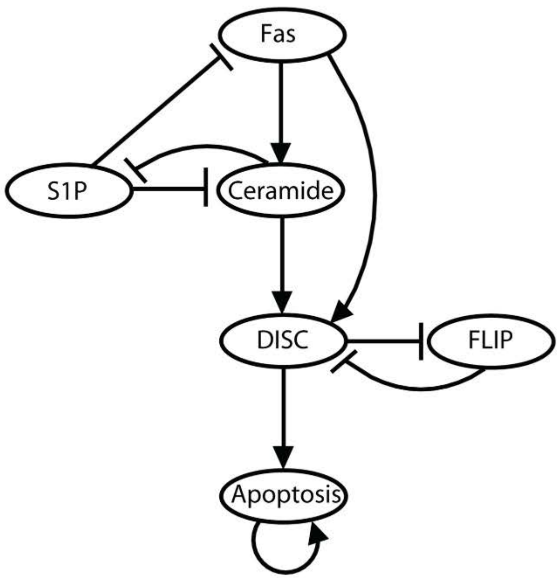
Updating scheme dependent

Logical function

- Updating scheme: stochastic asynchronous (samples all timescales)

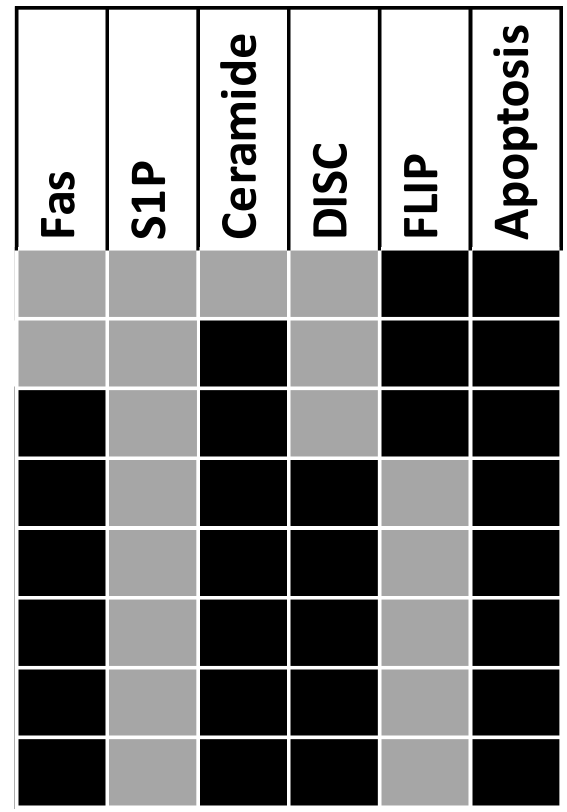
J.G.T. Zañudo
Network-based dynamic modeling and control strategies in complex diseases

Attractors of models of intracellular networks: stable cell states (e.g. healthy state, disease states, etc)



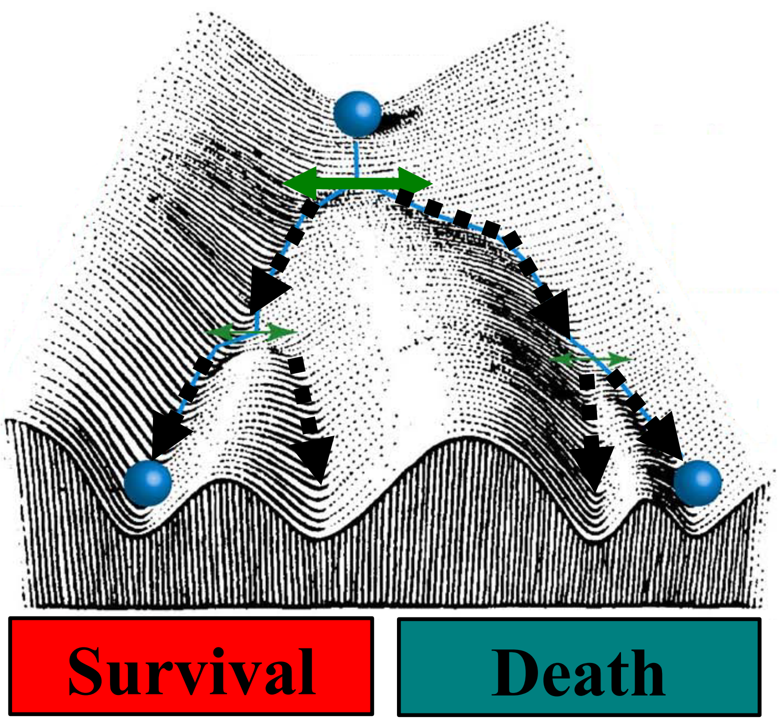
Dynamic model functions

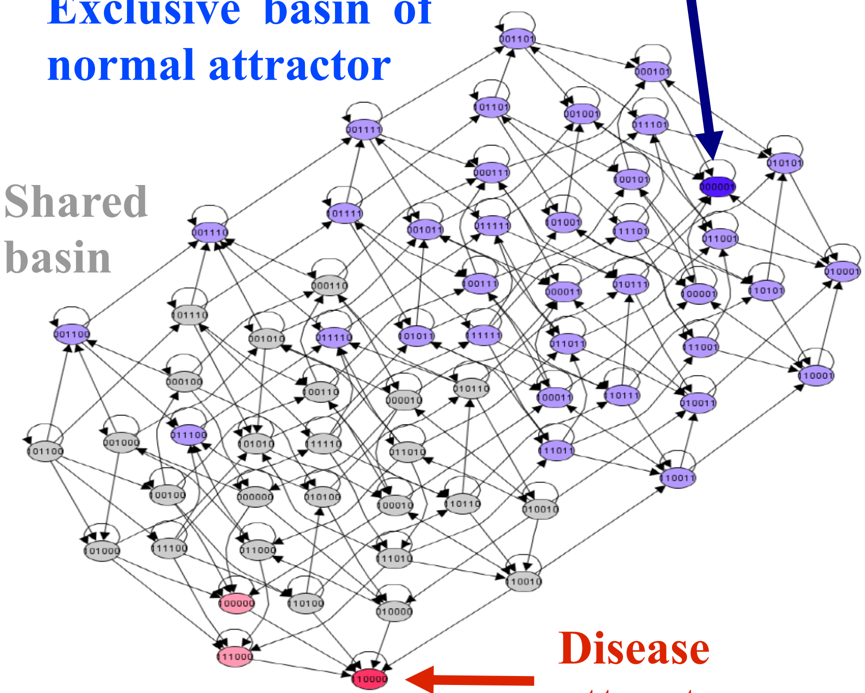
t = 0
t = 1
t = 2
t = 3
t = 4
t = 5
t = 6
t = 7



Saadatpour et. al. PloS Comput. **7** (11) (2011).

Attractors of models of intracellular networks: stable cell states (e.g. healthy state, disease states, etc)

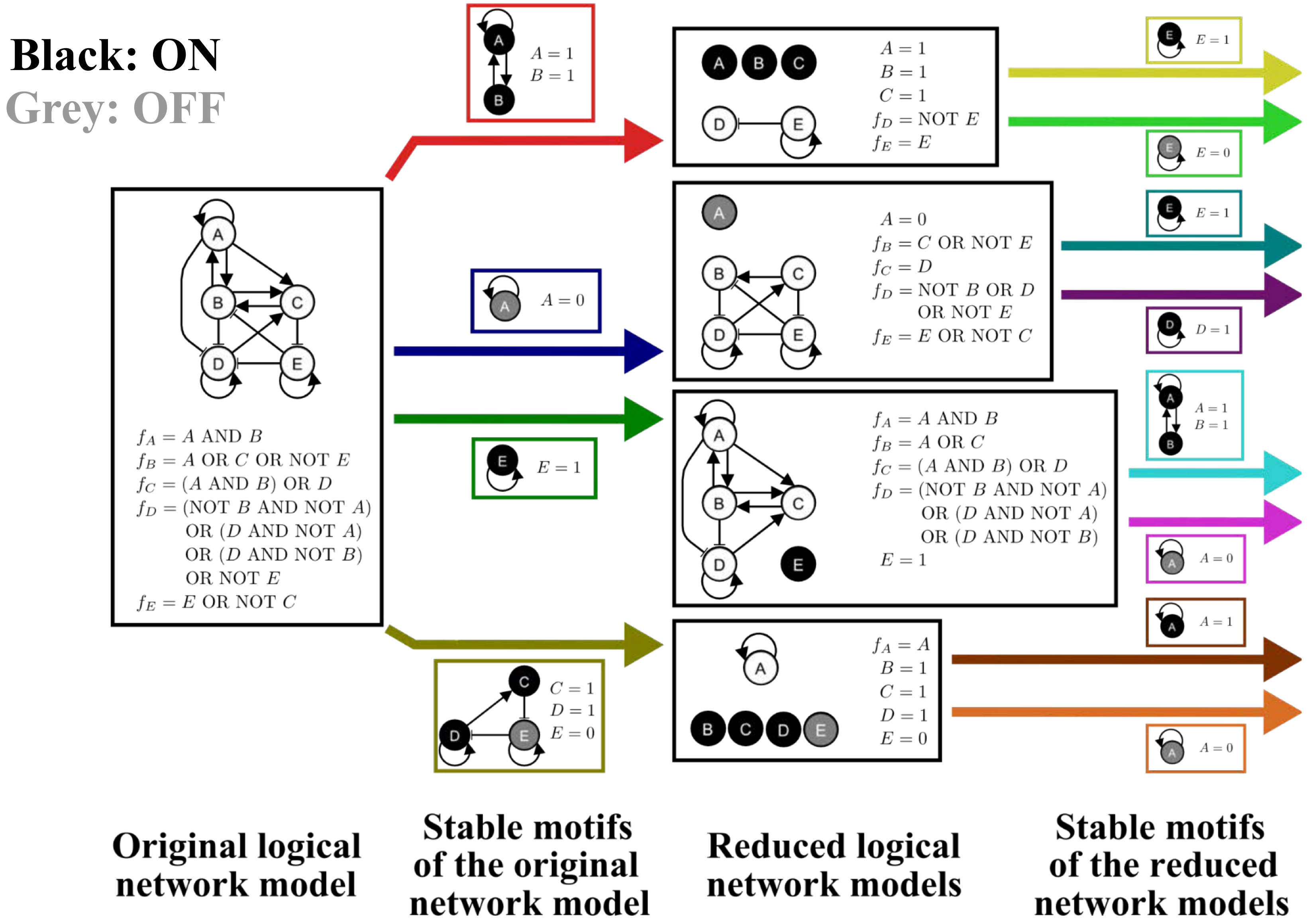




Huang, S. Bioessays, 34(2) (2012)

Saadatpour et. al. PloS Comput. **7** (11) (2011).

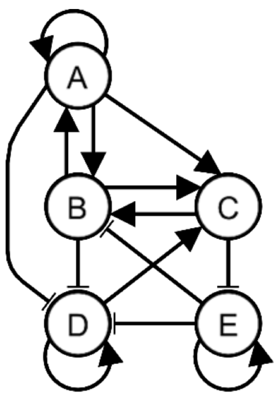
Stable motifs and logical models



Stable motifs and attractor control

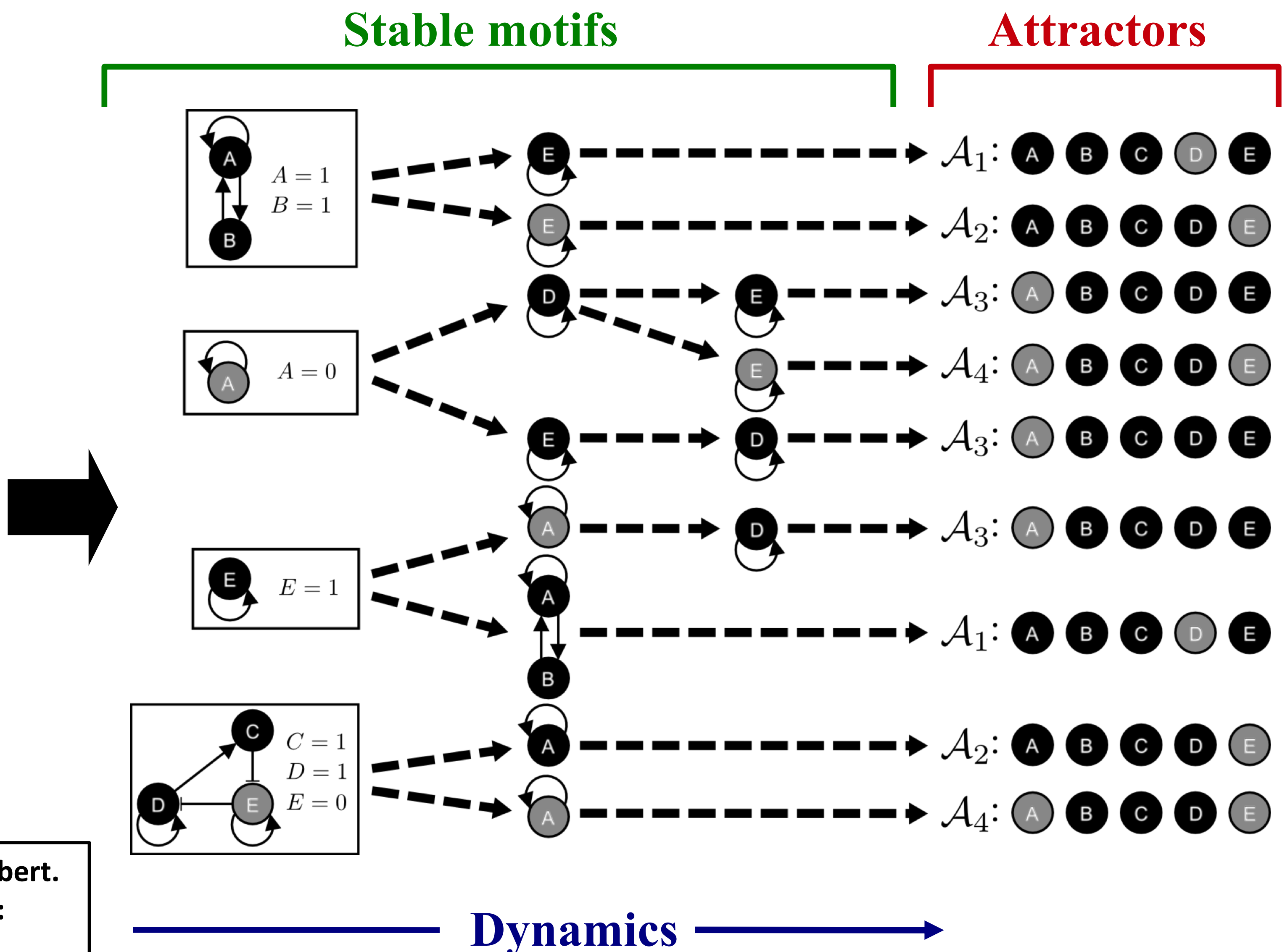
- Attractor control: <u>Sequence of stable motifs → Attractor</u>

Black: ON
Grey: OFF



+

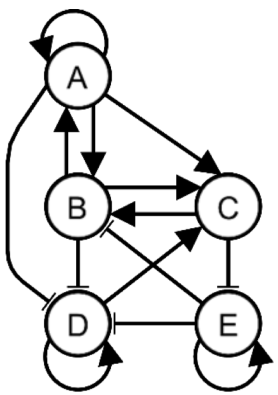
$f_A = A \text{ AND } B$
$f_B = A \text{ OR } C \text{ OR NOT } E$
$f_C = (A \text{ AND } B) \text{ OR } D$
$f_D = (\text{NOT } B \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } B) \text{ OR NOT } E$
$f_E = E \text{ OR NOT } C$



<u>J.G.T. Zañudo</u> and R. Albert. PLoS Comp. Biol. 11(4): e1004193 (2015).

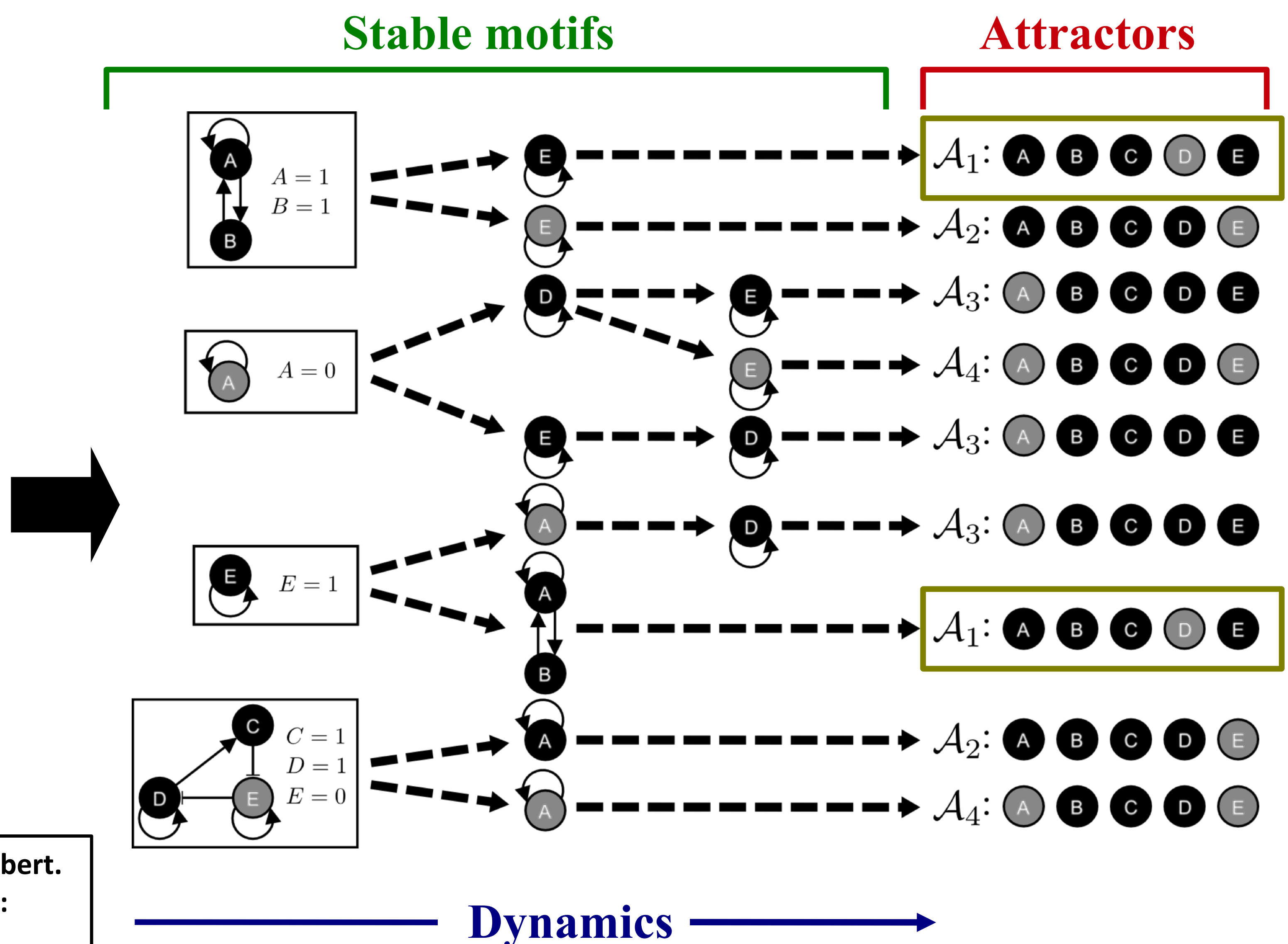
- Attractor control: Sequence of stable motifs → Attractor

Black: ON
Grey: OFF



+

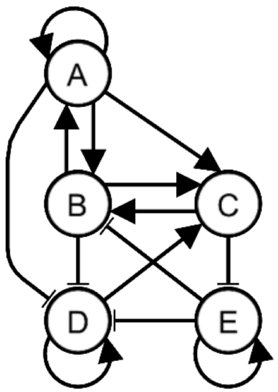
$f_A = A \text{ AND } B$
$f_B = A \text{ OR } C \text{ OR NOT } E$
$f_C = (A \text{ AND } B) \text{ OR } D$
$f_D = (\text{NOT } B \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } B) \text{ OR NOT } E$
$f_E = E \text{ OR NOT } C$



J.G.T. Zañudo and R. Albert. PLoS Comp. Biol. 11(4): e1004193 (2015).

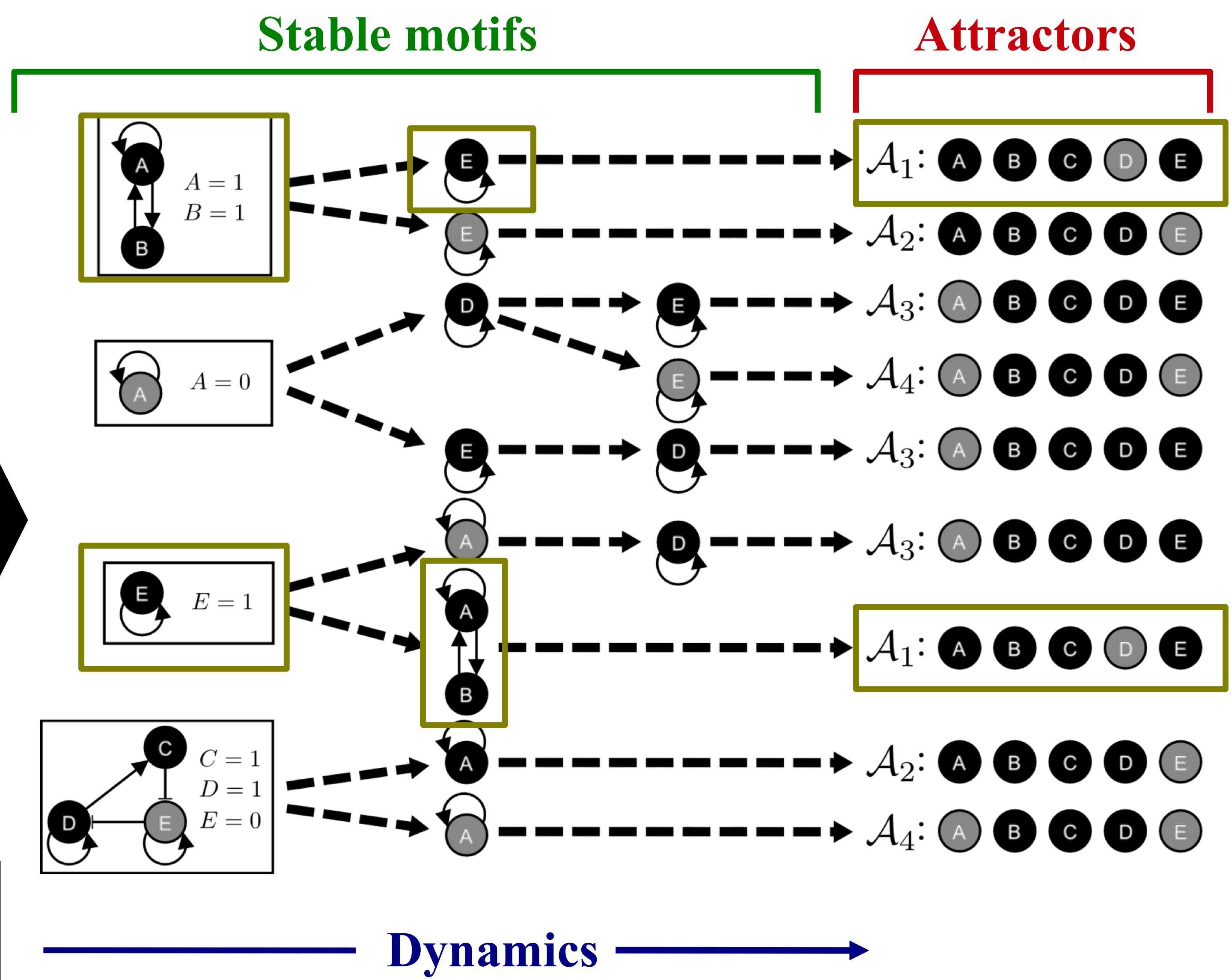
- Attractor control: <u>Sequence of stable motifs → Attractor</u>

Black: ON
Grey: OFF



+

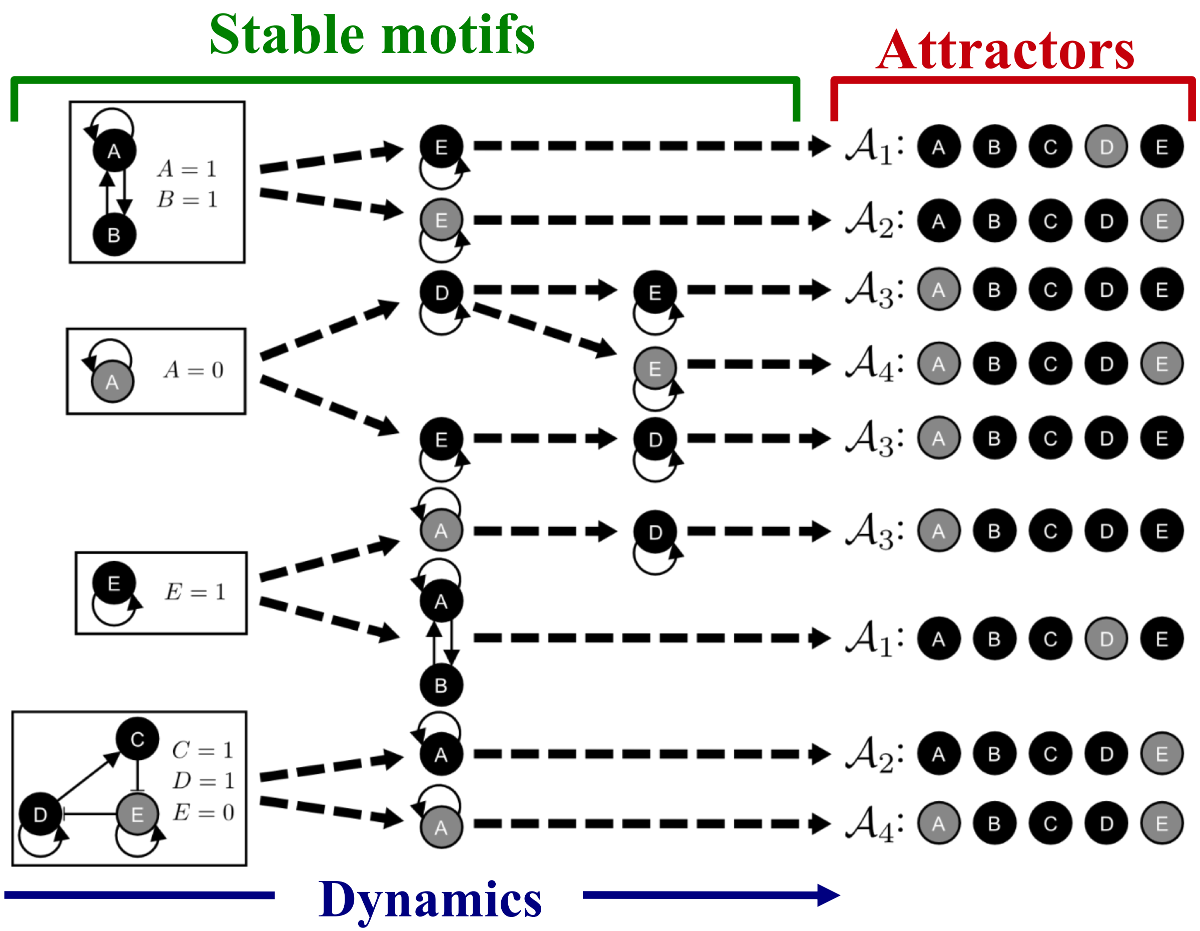
$f_A = A \text{ AND } B$
$f_B = A \text{ OR } C \text{ OR NOT } E$
$f_C = (A \text{ AND } B) \text{ OR } D$
$f_D = (\text{NOT } B \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } B) \text{ OR NOT } E$
$f_E = E \text{ OR NOT } C$



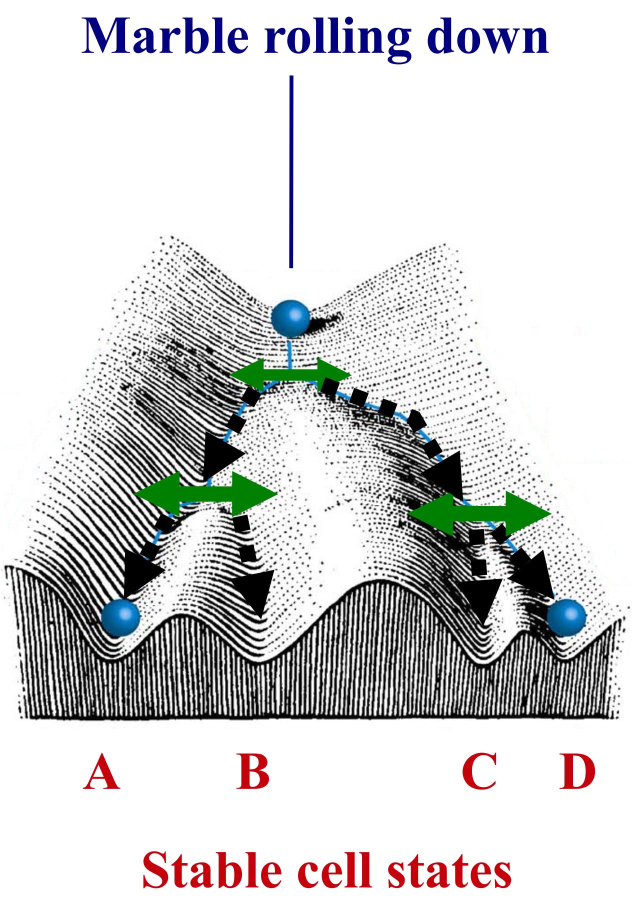
<u>J.G.T. Zañudo</u> and R. Albert. PLoS Comp. Biol. 11(4): e1004193 (2015).

Stable motif succession diagram

Black: ON
Grey: OFF



Waddington's epigenetic landscape



Stable motif control

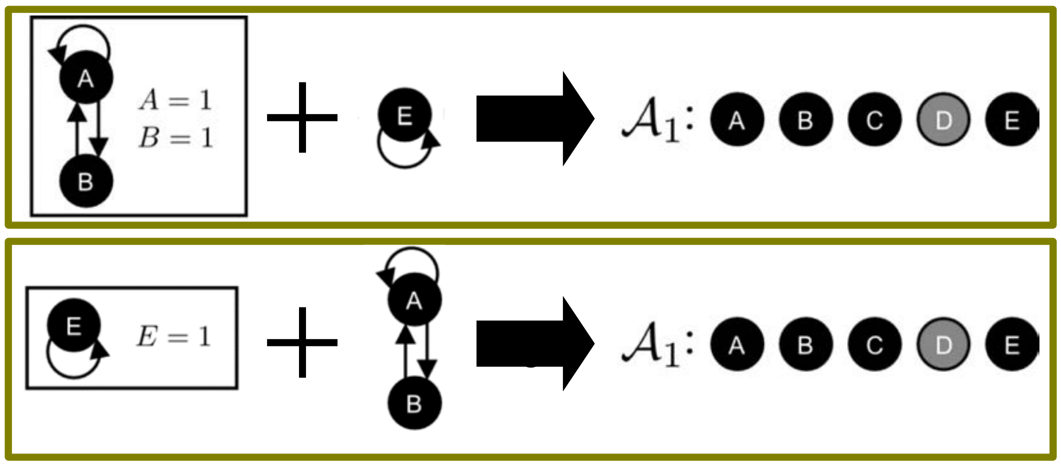
- Stable motif control:

  - Fix stable motif states → all initial conditions go to target attractor
  - Includes steps to reduce number of motifs and states

Black: ON
Grey: OFF

Motif sequence 1

Motif sequence 2



Sequences that lead to A_1

Simplify sequences (remove unnecessary motifs)
Find subset of nodes require to activate motif

Control set for A_1: {A=1, E=1}

J.G.T. Zañudo and R. Albert. PLoS Comp. Biol. 11(4): e1004193 (2015).

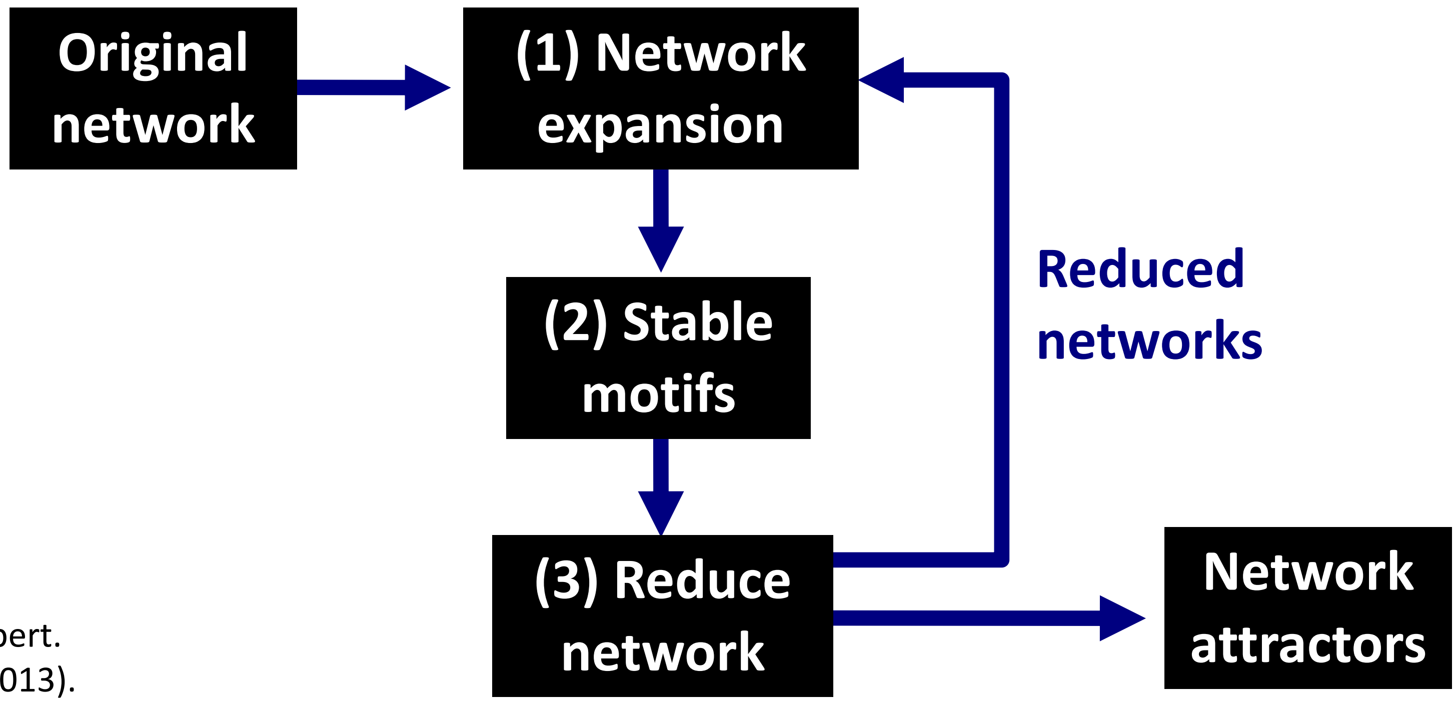
Attractor-finding method

- Our method:

- Network topology + function + network reduction.
- Finds all attractors* (formally, quasi-attractors).
- Tested on small, medium and large networks (~1000 nodes).

- The idea: Find subnetworks or motifs (**stable motifs**) that stabilize in a fixed state (i.e., that are partial fixed points).

<u>Algorithm</u>:

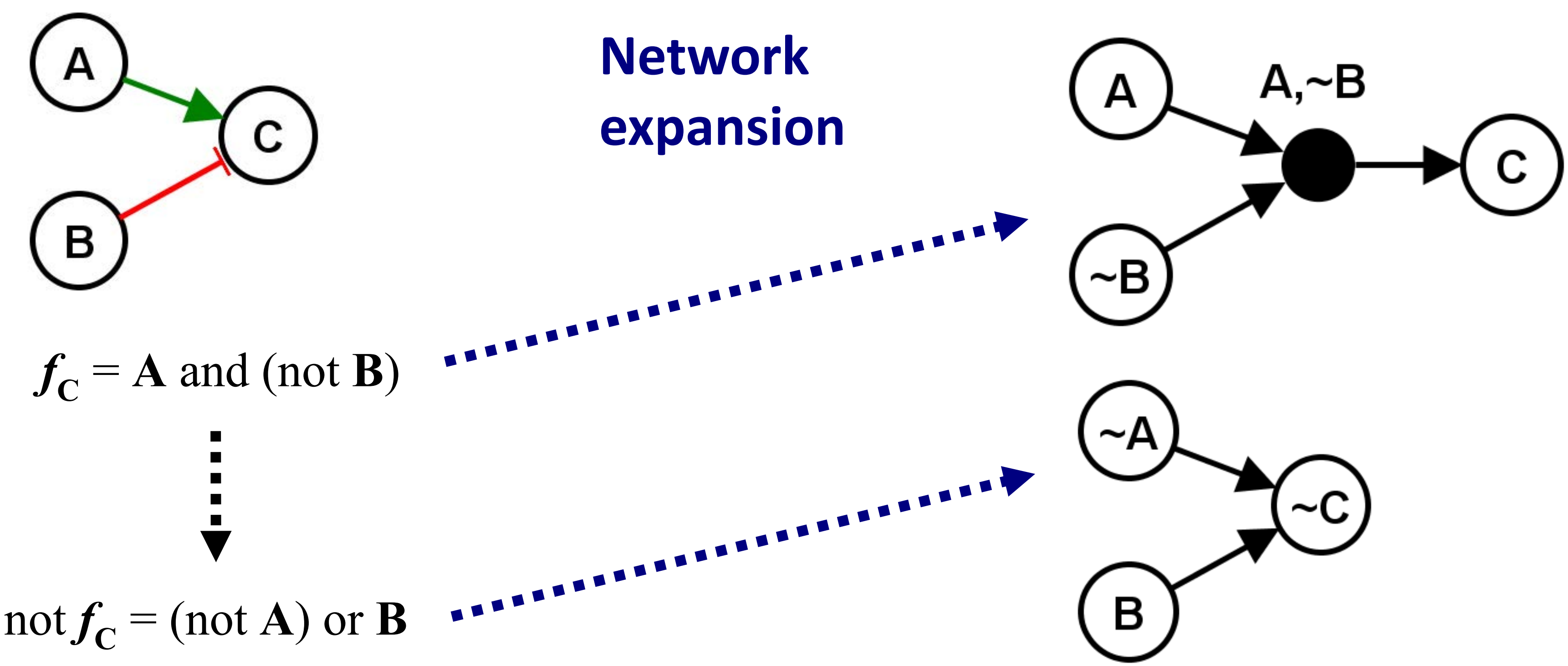


<u>J.G.T. Zañudo</u> and R. Albert. Chaos 23 (2) 025111 (2013).

- <u>Algorithm</u>:

(1) Network expansion: Adds information about combinatorial interactions and their sign through new nodes.

- Composite nodes: AND relationships (● **A, B** = **A** and **B**).
- Complementary nodes: NOT relationships (~A = not **A**).



Attractor-finding method

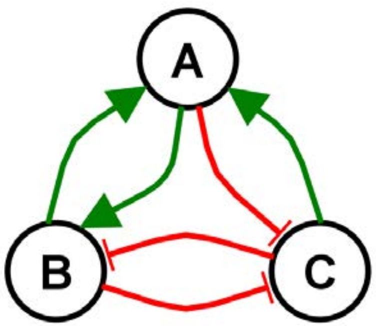
- <u>Algorithm</u>:

(2) Identify stable motifs: Smallest strongly connected components that satisfy two properties.

(i) Contain either a node or its complement.

(ii) Contain all inputs of its composite nodes (if any)

Boolean network

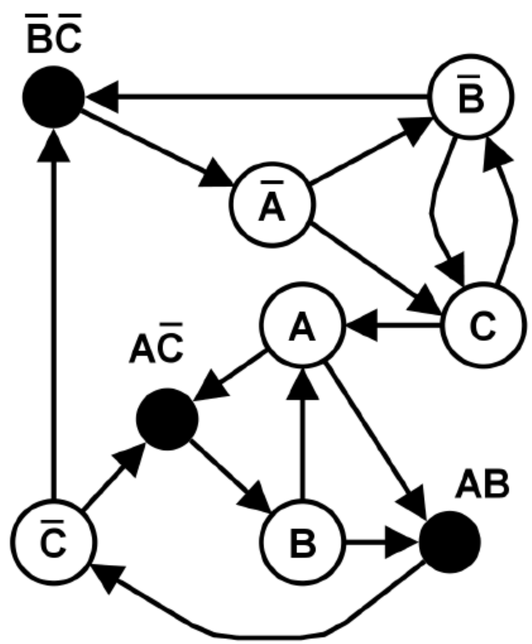


f_A = **B** or **C**

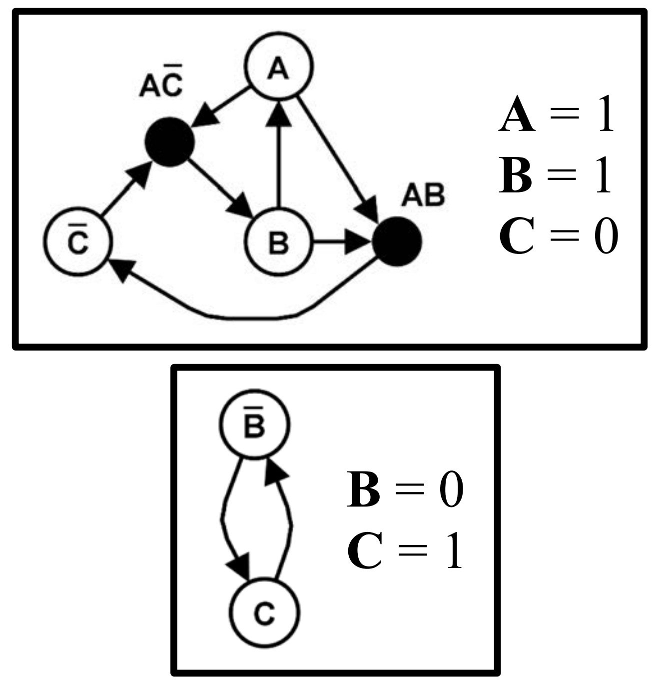
f_B = **A** and (not **C**)

f_C = (not **A**) or (not **B**)

Expanded network

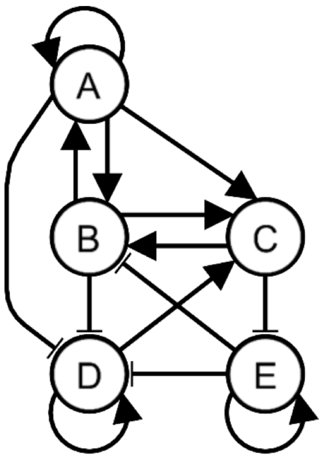


Stable motifs



Attractor-finding method

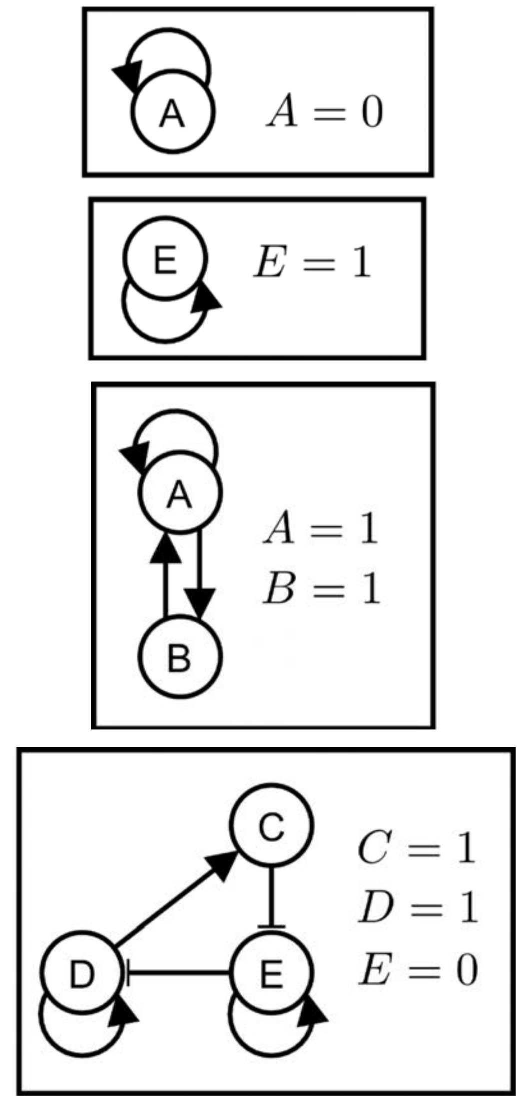
Boolean network



$$
\begin{aligned}
f_A &= A \text{ AND } B \\
f_B &= A \text{ OR } C \text{ OR NOT } E \\
f_C &= (A \text{ AND } B) \text{ OR } D \\
f_D &= (\text{NOT } B \text{ AND NOT } A) \\
&\quad \text{OR } (D \text{ AND NOT } A) \\
&\quad \text{OR } (D \text{ AND NOT } B) \\
&\quad \text{OR NOT } E \\
f_E &= E \text{ OR NOT } C
\end{aligned}
$$

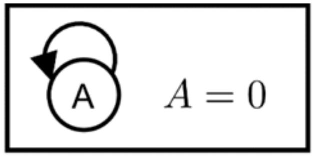
Steps (1) + (2)

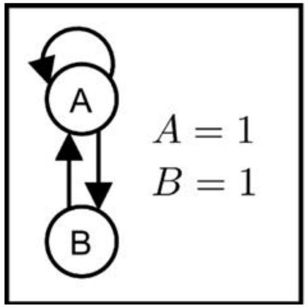
Stable motifs

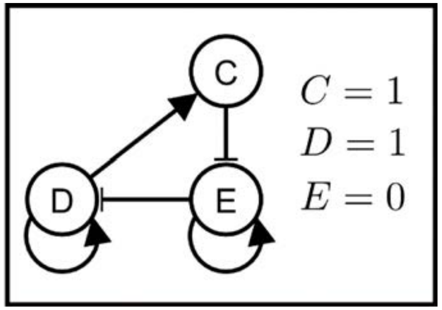


Attractor-finding method

(3) Reduce network using stable motifs.

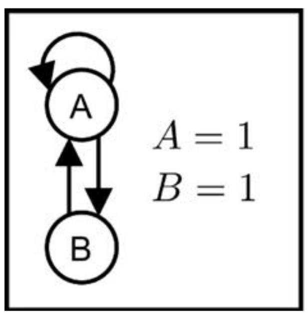




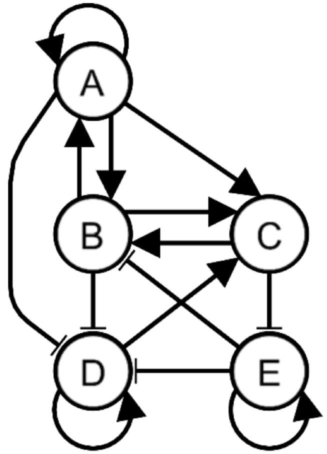


Attractor-finding method

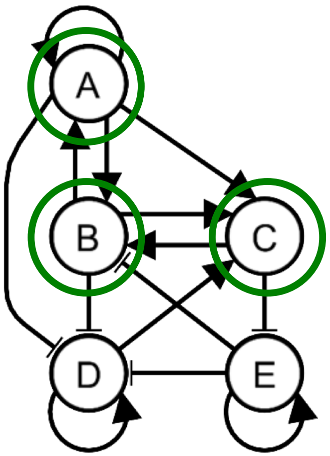
(3) Reduce network using stable motifs.



Plug in



$$f_A = A \text{ AND } B$$
$$f_B = A \text{ OR } C \text{ OR NOT } E$$
$$f_C = (A \text{ AND } B) \text{ OR } D$$
$$f_D = (\text{NOT } B \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } A) \text{ OR } (D \text{ AND NOT } B) \text{ OR NOT } E$$
$$f_E = E \text{ OR NOT } C$$

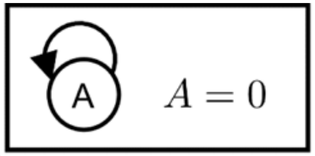


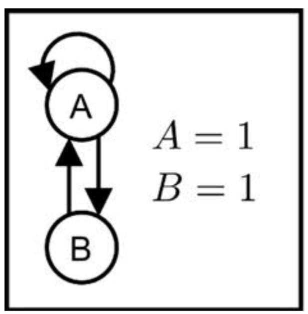
$$f_D = \text{not } \mathbf{E}$$
$$f_E = \mathbf{E}$$

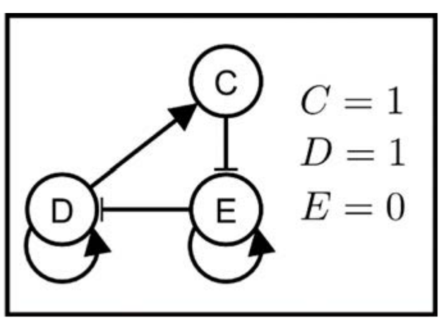
Reduced network

Attractor-finding method

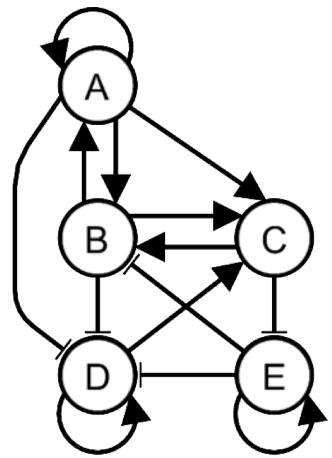
(3) Reduce network using stable motifs.







Plug in



$$
\begin{aligned}
f_A &= A \text{ AND } B \\
f_B &= A \text{ OR } C \text{ OR NOT } E \\
f_C &= (A \text{ AND } B) \text{ OR } D \\
f_D &= (\text{NOT } B \text{ AND NOT } A) \\
&\quad \text{OR } (D \text{ AND NOT } A) \\
&\quad \text{OR } (D \text{ AND NOT } B) \\
&\quad \text{OR NOT } E \\
f_E &= E \text{ OR NOT } C
\end{aligned}
$$

Reduced network 1

Reduced network 2

Reduced network 3

Reduced network 4