Electronic Supplementary Material (ESI) for Integrative Biology
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Supplementary Figures for

Logic-based models in systems biology: a predictive and parameter-free network analysis method

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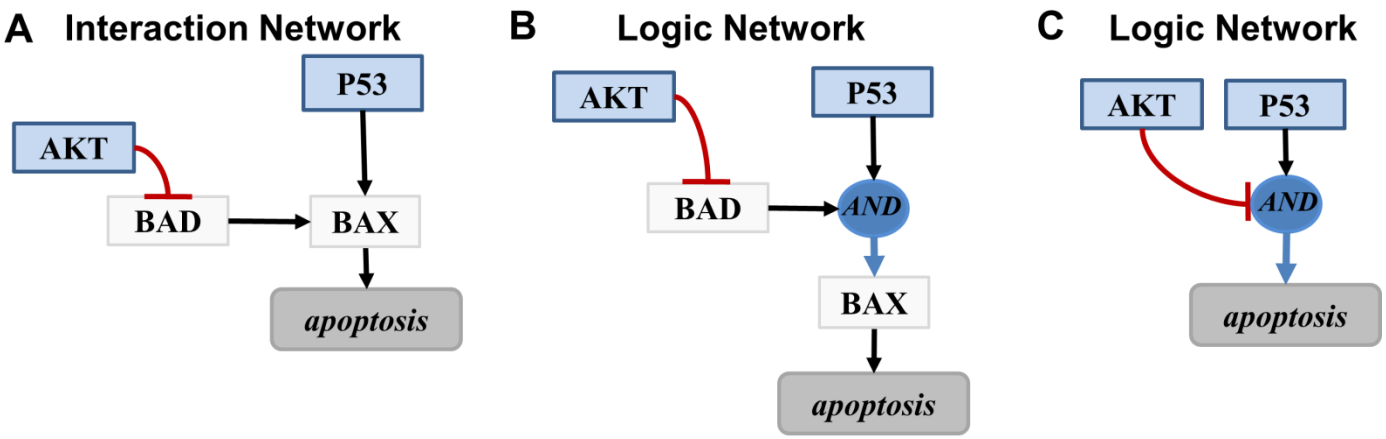

Supplemental Figure 1. Network reduction example with linear regulations. (**A**) Interaction network with **AKT** inhibiting **BAD**. Both **BAD** and **P53** are positive regulators of **BAX**, which is a direct regulator of **apoptosis** in this network. (**B**) It is assumed in this logic network that both the activation of **BAX** and the activation of **P53** are required to induce **apoptosis**: the activation of only one or the other will not induce **apoptosis**. (**C**) Given the logic network in (**B**) and the linear relationship between **AKT** and **BAX**, the logic network can be simplified by removing **BAX** and making **AKT** a direct inhibitor of **apoptosis**.

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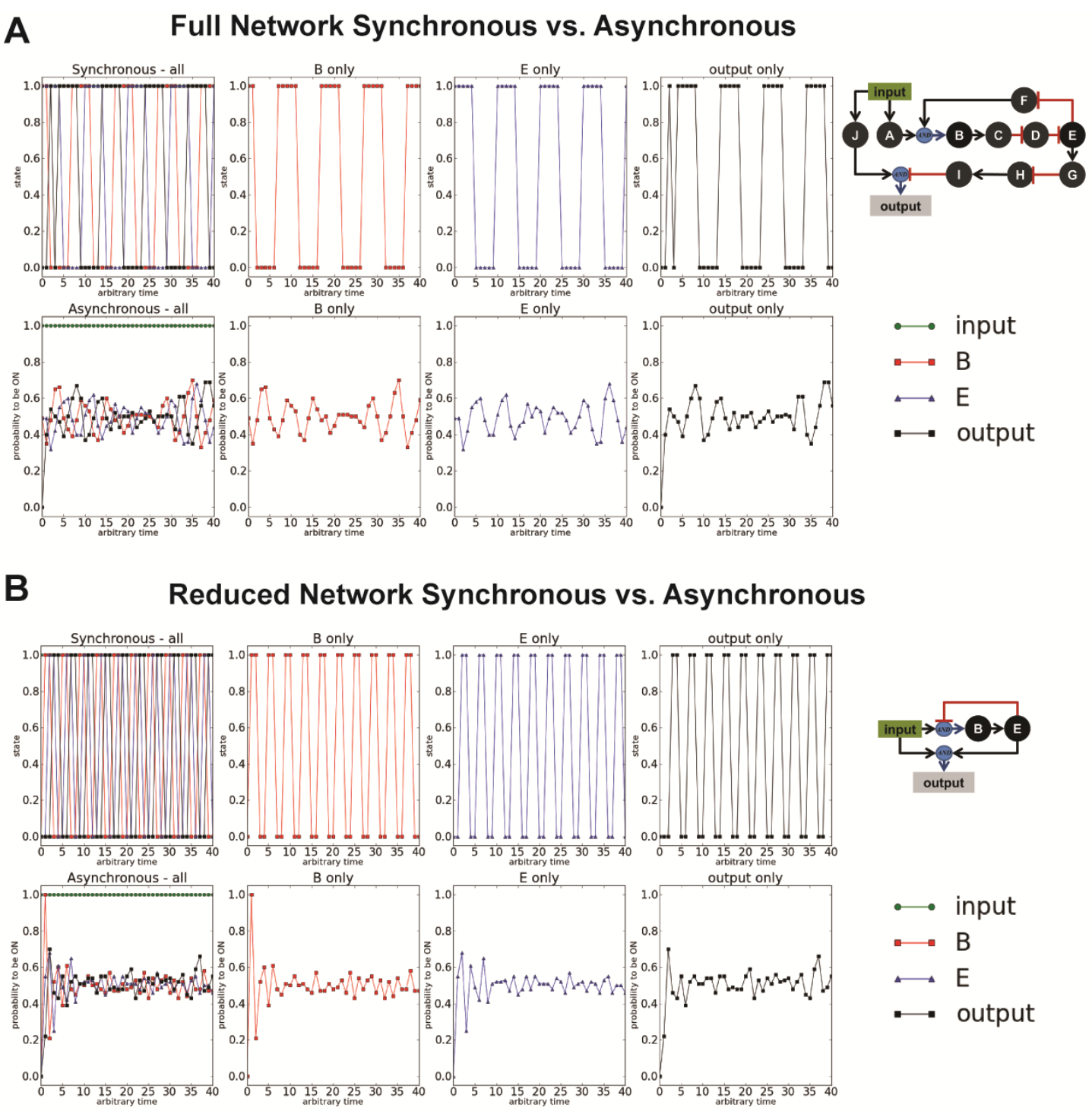

Supplemental Figure 2. Qualitative comparison of output from the full and reduced hypothetical network examples with 12 nodes and 4 nodes, respectively. (**A**) Synchronous (top) and asynchronous (bottom) simulations for the full 12 node network presented in Figure 2 of the main text. (**B**) Synchronous (top) and asynchronous (bottom) simulations for the reduced 4 node network presented in Figure 3 in the main text. The reduced logic network was derived by lumping linear regulations into a single regulation, as described in the main text. Input conditions used for the simulations: **input** node ***ON*** in all cases; all other node values randomly selected. Asynchronous simulations included 100 repeated simulations to get a probability that a node was ***ON*** in the attractor. As can be seen in the synchronous plots at the top of (**A**) and (**B**), the same qualitative output is produced in both forms of the model. The most striking difference in this example is the length of the oscillations produced by the two models. Depending on the initial conditions chosen (ours were randomized), the length of the oscillations may be shorter than that observed in (**A**) (data not shown).

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Supplementary File - Excel spreadsheet for Figure 5's Model I Network

Each row in a truth table represents a unique input condition. The output for each row's input, is presented in the far right shaded column.
The number of rows in a truth table is dependent on the number of regulating nodes (r) each node has.
In these examples, there are only 2 possible values for each node, so there are 2^r rows in a truth table

Logic Function:

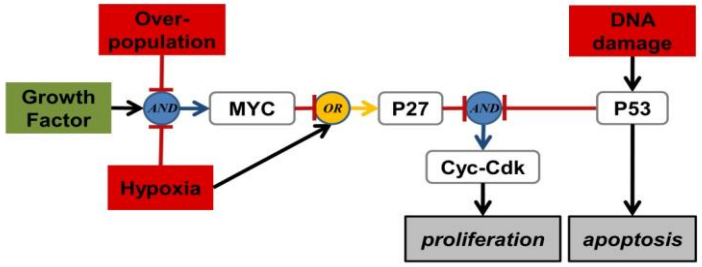
MYC^{t+1} = $GrowthFactor^t$ ***AND NOT*** $OverPop^t$ ***AND NOT*** $Hypoxia^t$

GrowthF	OverPop	Hypox	MYC^{t+1}
0	0	0	**0**
0	1	0	**0**
0	0	1	**0**
0	1	1	**0**
1	0	0	**1**
1	1	0	**0**
1	0	1	**0**
1	1	1	**0**

Biological Meaning of Logic Function:

MYC is only ON (in 1/8 conditions) when Growth Factor is active
AND the negative proliferative signals (Overpopulation and Hypoxia) are absent.

FIGURE 5, MODEL I



Logic Function:

$P27^{t+1}$ = $Hypoxia^t$ ***OR NOT*** MYC^t

Hypox	MYC	$P27^{t+1}$
0	0	**1**
1	0	**1**
0	1	**0**
1	1	**1**

Biological Meaning of Logic Function:

P27 is only OFF when MYC is present but Hypox (and SMAD) is not.
All other conditions, including the absence of both regulators turns P27 on

Logic Function:

$Cyc\text{-}Cdk^{t+1}$ = ***NOT*** $P27^t$ ***AND NOT*** $P53^t$

P27	P53	$Cyc\text{-}Cdk^{t+1}$
0	0	**1**
1	0	**0**
0	1	**0**
1	1	**0**

Biological Meaning of Logic Function:

Cyc-Cdk is only activated when both P27 activation and P53 activation are absent.
The activation of just one of the two inhibitors is enough to turn off Cyc-Cdk activation.

Logic Function:

$P53^{t+1}$ = $DNA\ Damage^t$

DNA Dam	$P53^{t+1}$
0	**0**
1	**1**

Biological Meaning of Logic Function:

P53 is only activated in the model when DNA Damage is present.

Logic Function:

$Prolif^{t+1}$ = $Cyc\text{-}Cdk^t$

Cyc-Cdk	$Prolif^{t+1}$
0	**0**
1	**1**

Biological Meaning of Logic Function:

Proliferation only occurs in this model when functional levels of Cyc-Cdk are present to regulate cell cycle progression.

Logic Function:

$Apop^{t+1}$ = $P53^t$

P53	$Apop^{t+1}$
0	**0**
1	**1**

Biological Meaning of Logic Function:

Apoptosis only occurs in this model when functional levels of P53 are present to mediate programmed cell death response.

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Supplementary File - Excel spreadsheet for Figure 7's Network

Each row in a truth table represents a unique input condition. The output for each row's input, is presented in the far right shaded column.
The number of rows in a truth table is dependent on the number of regulating nodes (r) each node has.
In these examples, there are only 2 possible values for each node, so there are 2^r rows in a truth table

Logic Function:

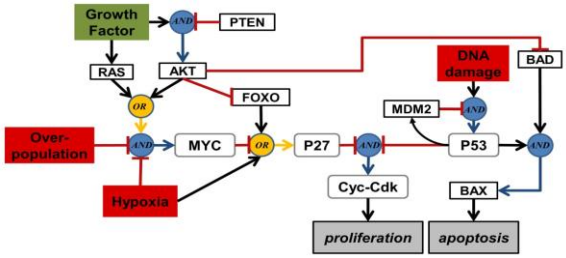
MYC^{t+1} = (AKT^t ***OR*** RAS^t) ***AND NOT*** $OverPop^t$ ***AND NOT*** $Hypoxia^t$

AKT	RAS	OverPop	Hypox	**MYC^{t+1}**
0	0	0	0	**0**
0	0	1	0	**0**
0	0	0	1	**0**
0	0	1	1	**0**
0	1	0	0	**1**
0	1	1	0	**0**
0	1	0	1	**0**
0	1	1	1	**0**
1	0	0	0	**1**
1	0	1	0	**0**
1	0	0	1	**0**
1	0	1	1	**0**
1	1	0	0	**1**
1	1	1	0	**0**
1	1	0	1	**0**
1	1	1	1	**0**

Biological Meaning of Logic Function:

MYC is only ON (in 2/16 conditions) when proliferative signaling through RAS or AKT is present AND the negative proliferative signals (Overpopulation and Hypoxia) are absent.

FIGURE 7



Logic Function:

RAS^{t+1} = $GrowthFactor^t$

Growth F	**RAS^{t+1}**
0	**0**
1	**1**

Biological Meaning of Logic Function:

RAS can only be activated by Growth Factor signaling in this model

Logic Function:

$FOXO^{t+1}$ = ***NOT*** AKT^t

AKT	**$FOXO^{t+1}$**
0	**1**
1	**0**

Biological Meaning of Logic Function:

FOXO is active in the model unles AKT is activated, which allows for direct inhibition

Logic Function:

AKT^{t+1} = $Growth\ Factor^t$ ***AND NOT*** $PTEN^t$

Growth F	PTEN	**AKT^{t+1}**
0	0	**0**
1	0	**1**
0	1	**0**
1	1	**0**

Biological Meaning of Logic Function:

AKT is only activated by Growth Factor signaling but PTEN inhibition of AKT is stronger than Growth Factor activation.

Logic Function:

$P27^{t+1}$ = $FOXO^t$ ***OR*** $Hypoxia^t$ ***OR NOT*** MYC^t

FOXO	Hypox	MYC	**$P27^{t+1}$**
0	0	0	**1**
0	1	0	**1**
0	0	1	**0**
0	1	1	**1**
1	0	0	**1**
1	1	0	**1**
1	0	1	**1**
1	1	1	**1**

Biological Meaning of Logic Function:

P27 is only OFF when MYC is present but Hypox (via SMAD) and FOXO are not. All other conditions, including the absence of all three regulators, turn P27 on.

Logic Function:

$Cyc\text{-}Cdk^{t+1}$ = ***NOT*** $P27^t$ ***AND NOT*** $P53^t$

P27	P53	**$Cyc\text{-}Cdk^{t+1}$**
0	0	**1**
1	0	**0**
0	1	**0**
1	1	**0**

Biological Meaning of Logic Function:

Cyc-Cdk is only activated when both P27 activation and P53 activation are absent. The activation of just one of the two inhibitors is enough to turn off Cyc-Cdk activation.

Logic Function:

$P53^{t+1}$ = $DNA\ Damage^t$ ***AND NOT*** $MDM2^t$

DNA Dam	MDM2	**$P53^{t+1}$**
0	0	**0**
1	0	**1**
0	1	**0**
1	1	**0**

Biological Meaning of Logic Function:

P53 is only activated in the model when DNA Damage is present and MDM2 is not.

Logic Function:

$Prolif^{t+1}$ =$Cyc\text{-}Cdk^t$

Cyc-Cdk	**$Prolif^{t+1}$**
0	**0**
1	**1**

Biological Meaning of Logic Function:

Proliferation only occurs in this model when functional levels of Cyc-Cdk are present to regulate cell cycle progression.

Logic Function:

BAD^{t+1} = ***NOT*** AKT^t

AKT	**BAD^{t+1}**
0	**1**
1	**0**

Biological Meaning of Logic Function:

BAD is active in the model unles AKT is activated, which is a direct inhibitor of BAD.

Logic Function:

$MDM2^{t+1}$ = $P53^t$

P53	**$MDM2^{t+1}$**
0	**0**
1	**1**

Biological Meaning of Logic Function:

MDM2 can only be activated by P53 activation in this model.

Logic Function:

$Apop^{t+1}$ = BAX^t

BAX	**$Apop^{t+1}$**
0	**0**
1	**1**

Biological Meaning of Logic Function:

Apoptosis only occurs in this model when functional levels of BAX are present.

Logic Function:

BAX^{t+1} = $P53^t$ ***AND*** BAD^t

P53	BAD	**$P53^{t+1}$**
0	0	**0**
1	0	**0**
0	1	**0**
1	1	**1**

Biological Meaning of Logic Function:

BAX is only activated in the model when P53 and BAD are present. The assumption is that P53 must bind to BAD to induce activation of BAX.