S1 Description & experimental support for the modules of EMT_Mechanosensing.

Table S1a: PhysEnv module

Target Node	Node Gate Node Type Link Type	Node Description Input Node	Link Description
CellDensity_High	**CellDensity_High** = **CellDensity_High**		
	Env		The *CellDensity_High* node in our model represents an extracellular environment with high enough cell density to block cell spreading. This input node is self-sustaining in the absence of *in silico* perturbation.
	← Env	CellDensity_High	*CellDensity_High* is self-sustaining in the absence of *in silico* perturbation.
CellDensity_Low	**CellDensity_Low** = **CellDensity_Low** or **CellDensity_High**		
	Env		The *CellDensity_Low* node represents an environment with cell density comparable to the edge of a monolayer, where cells can maintain strong adhesions with each other but are also able to spread and polarize horizontally.
	← Env	CellDensity_High	*CellDensity_Low* is automatically ON at very high cell density.
	← Env	CellDensity_Low	*CellDensity_Low* is self-sustaining in the absence of *in silico* perturbation.
ECM	**ECM** = **ECM** or **Stiff_ECM**		
	Env		The *ECM* input node represents access to a very soft extracellular matrix that does not support cell spreading or stress fiber formation (< 0.5 kPa), but does support anchorage-dependent survival signaling [1]. This input node is self-sustaining in the absence of a stiff *ECM* (or in silico perturbation), and overridden to an ON state otherwise by *Stiff_ECM*.
	← Env	Stiff_ECM	*ECM* is automatically ON when cells have access to stiff *ECM*.
	← Env	ECM	*ECM* is self-sustaining in the absence of *in silico* perturbation.
Stiff_ECM	**Stiff_ECM** = **Stiff_ECM**		
	Env		The *Sfiff_ECM* input node represents access to a very stiff extracellular matrix that promotes / supports stress fiber formation sufficiently to place no limitation on a cell's capacity to proliferate (> 100 kPa) [1]. This input node is self-sustaining in the absence of *in silico* perturbation.
	← Env	Stiff_ECM	*Sfiff_ECM* is self-sustaining in the absence of *in silico* perturbation.

Table S1b: GrowthFactor_Env module

Target Node	Node Gate Node Type Link Type	Node Description Input Node	Link Description
GF	**GF** = **GF** or **GF_High**		
	Env		The *GF* node represents an extracellular environment with low levels of growth factors capable of sustaining survival signaling. Thus, the *GF* input node is self-sustaining in the absence of in silico perturbation.
	← Env	GF	The *GF* input node is self-sustaining in the absence of in silico perturbation.
	← Env	GF_High	The *GF* node represents an extracellular environment with low levels of growth factors capable of sustaining survival signaling. Thus, this node is ON in high growth factor as well.
GF_High	**GF_High** = **GF_High**		
	Env		The GF_{High} node in our model represents an extracellular environment with saturating levels of growth factors; this input node is self-sustaining in the absence of *in silico* perturbation.
	← Env	GF_High	The GF_{High} input node is self-sustaining in the absence of *in silico* perturbation.

Table S1c: GF_Basal_MAPK module

Target Node	Node Gate Node Type Link Type	Node Description Input Node	Link Description
RTK	**RTK** = (not **CAD**) and (**GF_High** or **GF**)		
	Rec		The ON state of the *RTK* node in our model represents basal growth receptor activation (required to keep a normal cell alive). Thus it requires the absence of *CAD* and at least low growth levels of growth factors in the extracellular environment [2].
	← Ligand	GF	The ON state of the *RTK* node in our model represents basal growth receptor activation by low / medium growth factor availability, encoded by the *GF* node (required to keep a normal cell alive).
	← Ligand	GF_High	Similarly, high growth factor availability also keeps *RTK* on.
	⊢ Per	CAD	Caspase-activated DNase (*CAD*) inhibition of receptor tyrosine kinases ensures that apoptotic cells no longer maintain even basal levels of growth signaling.
Shc	**Shc** = (**RTK** and **GF_High**) and (**FAK** or **Src**)		

Table S1c: GF_Basal_MAPK module

Shc		*Shc* is ON when *RTK*s are activated by high levels of extracellular growth factors (capable of driving proliferation) [3], and its recruitment is aided by active *Src* kinase [4] or focal adhesion kinase (*FAK*) [4]. The two mediators of integrin signaling appears to be able to act independently, forming two parallel links between integrin signaling and full *RTK* activation [4].
Adap		
	← Compl GF_High	The ON state of *Shc* in our model encode the change from basal *Shc* recruitment to weakly stimulated *RTKs* to the level of recruitment seen in high growth factor environments, capable of mediating *Ras* activation.
	← Compl RTK	*Shc* proteins are adaptors that binds to phosphor-tyrosine motifs, facilitating their recruitment to activated receptors such as receptor tyrosine kinases *RTKs* [3].
	← Compl FAK	*FAK* activated at sites of integrin-ECM attachments directly phosphorylates *Shc Tyr-317*, promoting its ability to assemble MAPK-inducing signaling scaffolds, including *Grb2* binding [4].
	← Compl Src	*c-Src* recruited to and activated by integrin-ECM attachments directly phosphorylate *Shc*, promoting its ability to assemble MAPK-inducing signaling scaffolds, including *Grb2* binding [4].
Grb2	**Grb2** = **RTK** and **Shc**	
	Adap	*Grb2* is recruited to *RTKs* receptors upon ligand binding and subsequent recruitment of *Shc* adaptors [5, 6].
	← Compl RTK	The SH2 domain of *Grb2* binds to a phosphotyrosine residue in the activated *RTK*, where it functions as an adaptor protein [5].
	← Compl Shc	*Shc* proteins phosphorylated by tyrosine kinases represent binding sites for *Grb2*, aiding its recruitment to active RTKs [3].
SOS	**SOS** = **Grb2**	
	GEF	*RTK*-bound *Grb2* recruits *SOS*, a guanine nucleotide–exchange protein (GEF) that converts inactive *Ras* to its active GTP-bound form [5].
	← Compl Grb2	*Grb2* recruits *SOS* to activated *RTK*s [5].
Ras	**Ras** = ((**Grb2** and **SOS**) and **Src**) and ((**IQGAP1_LeadingE** or (not **Merlin**)) or **N_bcatenin_H**)	

Table S1c: GF_Basal_MAPK module

	GTPa		*Ras* activation requires the GEF activity of *SOS* and the *RTK*-linked (active) adaptor protein *Grb2* [5] and *Src* [7, 8]. In addition to aiding sustained *Ras/Raf-1* signaling, *Src* may also physically link *IQGAP1* to *RTKs* such as *VEGFR2* [9]. *IQGAP1*, in turn, serves a scaffold for *MAPK* and *PI3K* signaling [10], leading us to link its activation at the leading edge. In contrast, *Merlin* blocks *Ras* activation at sites that link focal adhesions and actin filaments to *MAPK* signaling [11]. Here we assume that concentrated *IQGAP1* at the leading edge can override remaining *Merlin* activity in the rest of the cell. Alternatively, high levels of *β-catenin* can also sustain *Ras* by protecting it from lysosomal degradation [12].
	← Compl	Grb2	*RTK*-bound *Grb2* is required to recruits *SOS*, the GEF responsible for converting inactive *Ras* to its GTP-bound active form [5].
	← GEF	SOS	*SOS* is a GEF that is recruited to activate *Ras* near ligand-bound, active *RTKs* [5].
	← ComplProc	Src	Cellular Src (*c-Src*) is required for mitogenesis initiated by multiple growth factor receptors, including epidermal growth factor (*EGF*), platelet-derived growth factor (*PDGF*), colony stimulating factor-1 (*CSF-1*), and basic fibroblast growth factor (*bFGF*) [7]. In addition to aiding the formation of Shc/Grb2/SOS/Ras/Raf-1 cascade, *Src* may also increase the rate of receptor internalization and aid sustained *MAPK* signaling by internalized *Ras* on endosomes and Golgi [7, 8].
	← ComplProc	Merlin	*Merlin* uncouples *Ras* from growth factor signals by counteracting the ERM (ezrin, radixin, moesin)–dependent activation of *Ras*, which aids *Grb2*, *SOS*, *Ras* complex formation linked to filamentous actin [11].
	← Compl	IQGAP1 _LeadingE	*IQGAP1* acts as a scaffold for the *MAPK* cascade, binding directly to *B-Raf*, *MEK*, and *ERK* and regulating their activation [13]. The *IQGAP1-Leading-E* node in our model specifically links the availability of active *IQGAP1* recruited to lamellipodia and enhanced *MAPK* / *AKT* signaling.
	← Ind	N_bcatenin _H	High levels of *β-catenin* protect *Ras* from lysosomal degradation [12]. Overall, *β-catenin* overexpression / silencing can activate / block *ERK* in a *MEK*-dependent way, like via *Ras/Raf* [14].
RAF	**RAF** = ((not **Casp3**) and **Ras**) and (not **SPRY2**)		
	K		*Raf* is active in response to *Ras* activity in the absence of *Caspase 3*. As active *Raf-1* is continuously dephosphorylated and bound by *14-3-3*, which translocates it to the cytoplasm from the plasma membrane (not modeled explicitly), ongoing *Ras* activity [15] and lack of *SPRY2* inhibition [16, 17] are necessary to keep *Raf* ON.
	← P	Ras	Active *Ras* phosphorylates *Raf*, enhancing its kinase activity [15].
	⊢ IBind	SPRY2	Sprouty2 (*SPRY2*) blocks Raf activity and downstream MAPK signaling [16, 17].

Table S1c: GF_Basal_MAPK module

	⊢ Lysis	Casp3	*Raf-1* is cleaved and inhibited by *Caspase 3* [18].
MEK	**MEK** = **RAF**		
	K		*Raf* phosphorylates and activates the *MEK* kinase [15].
	← P	RAF	*Raf* phosphorylates and activates the *MEK* kinase [15].
ERK	**ERK** = (**MEK** and (not **BIK**)) and (**FocalAdhesions** or **N_bcatenin_H**)		
	K		The *ERK* kinase is active when phoisphotylated by *MEK* [15] and allowed to translocate to the nucleus in the absence of *BIK* [19].
	← P	MEK	*MEK* phosphorylates and activates the *ERK* kinase [15].
	⊢ IBind	BIK	*BIK* binds to active, phosphorylated *ERK1/2* and suppresses its nuclear translocation [19].
	← ComplProc	FocalAdhesions	Focal adhesions recruit the MAPK scaffolding protein GIT1 and locally potentiate *ERK1/2* activation [20].
	← Ind	N_bcatenin_H	*β-catenin* overexpression / silencing can activate / block *ERK* in a *MEK*-dependent way [14].
mTORC2	**mTORC2** = **PIP3** or (not **S6K**)		
	PC		Our model assumes that *mTORC2* is active in quiescent cells with basal levels of *PI3K* activity leading to basal *PIP3* generation. Alternatively, the absence of high growth factor-stimulated *mTORC1* and *S6K1* can also increase *mTORC2* activity.
	← PBind	PIP3	PtdIns(3,4,5)P3 (*PIP3*), interacts with the *mTORC2* component *Sin1* to release its inhibition on the *mTOR* kinase domain. Thus, *PIP3* is necessary for *mTORC2* activation [21].
	⊢ P	S6K	*Rictor*, a component of the *mTORC2 complex*, undergoes *S6K1*-mediated phosphorylation at T1135, dampening *mTORC2*-dependent phosphorylation of *Akt* [22, 23].
PI3K	**PI3K** = (**FAK** or **Src**) and (**Ras** or **RTK**)		
	K		In our model, basal *PI3K* activity can be maintained by active *RTK*s [2], active *Ras* [24, 25]. In addition, survival signalling via *PI3K* requires anchorage-dependent signals via active *FAK* [26] or via *Src*-mediated blocking of basal *PTEN* activity (not modeled explicitly) [27].
	← BLoc	RTK	Active *RTK*s recruit *PI3K* to the signaling complex they nucleate, where *PI3K* catalyzes the production of PtdIns(3,4,5)P3 (PIP3) [2].
	← Compl	Ras	*Ras* binds the catalytic subunit of *PI3K* and *Ras* knockdown / over expression decreases /increases the *PI3K*-dependent generation of PIP3 [24, 25].

Table S1c: GF_Basal_MAPK module

	← PLoc	FAK	Attachment to the ECM activates *FAK* kinase, which promotes anchorage-dependent survival signaling via *PI3K* / *AKT* [26].
	← P	Src	*Src* kinases regulate *PI3K* signaling cascade by altering the function of the *PTEN* tumor suppressor via inhibitory phosphorylation [27].
PIP3	**PIP3** = **PI3K_H** or **PI3K**		
	Met		In our model, PIP3 is ON as a result of basal or high *PI3K* activity.
	← Cat	PI3K	Active *PI3K* recruited to the membrane catalyzes the production of membrane-bound PtdIns(3,4,5)P3 (PIP3) from PtdIns(4,5)P2 (PIP2) [2].
	← Cat	PI3K_H	Active *PI3K* recruited to the membrane catalyzes the production of membrane-bound PtdIns(3,4,5)P3 (PIP3) from PtdIns(4,5)P2 (PIP2) [2].
PDK1	**PDK1** = **PI3K** and **PIP3**		
	K		*PDK1* enzyme activation requires active (at least basal) *PI3K* and *PIP3* [28].
	← BLoc	PI3K	The *PDK1* kinase is recruited to the plasma membrane by *PIP3* at the sites of active *PI3K* activity [28].
	← BLoc	PIP3	The *PDK1* kinase is recruited to the plasma membrane by *PIP3* at the sites of active *PI3K* activity [28].
AKT_B	**AKT_B** = ((not **Casp3**) and **PIP3**) and (**PDK1** or **mTORC2**)		
	K		Basal *AKT1* activity in our model requires the absence of *Caspase 3*, the availability of at least basal levels of *PIP3*, and phosphorylation by *PDK1* or *mTORC2*. In contrast, full mitogen-stimulated *AKT1* activation requires phosphorylation by both (see *AKT_H*) [28].
	← P	mTORC2	Maximal activation of *AKT1* requires phosphorylation of S473 by *mTORC2* [28].
	← BLoc	PIP3	*PIP3* recruits *AKT1* to the plasma membrane and *PIP3* binding changes the conformation of *AKT1* such that it becomes accessible for T308 phosphorylation by *PDK1* [28].
	← P	PDK1	Membrane-recruited *PDK1* phosphorylates *AKT1* at T308, a critical step in its activation [28].
	⊢ Lysis	Casp3	*AKT1* is cleaved and inhibited by *Caspase 3* [18].

Table S1d: GF_PI3K module

Target Node	Node Gate Node Type	Node Description

Table S1d: GF_PI3K module

	Link Type	Input Node	Link Description
p110_H	**p110_H** = **YAP** and ((**FoxO3** and (not **Nedd4L**)) or (**p110_H** and (**FoxO3** or (not **Nedd4L**))))		
	Prot		As *YAP* is a transcriptional inducer of *p110* subunits [29] and their expression is low in high cell density areas where *YAP* activity is suppressed [30], here we assume that high *p110* expression requires active *YAP*. In order to capture the cyclic dynamics of *p110* protein expression, we make the assumption that high *p110* protein levels can be induced by *FoxO3* in the absence of the growth factor-activated *Nedd4L* ubiquitin ligase. Once present, high *p110* can be maintained by *FoxO3* transcription, or the absence of activated *Nedd4L*.
	← Per	p110_H	Our model assumes that maintaining high *p110* levels is easier than driving the re-accumulation of the protein following its rapid destruction.
	← TR	FoxO3	*FoxO3* is a direct inducer *p110α* (*PIK3CA*), the catalytic subunit of *PI3K* [31].
	⊢ Ubiq	Nedd4L	*p110α* (*PIK3CA*) is polyubiquitinated by the E3 ligase *Nedd4L*, leading to its proteasomal degradation. Both free *p110α* and the regulatory subunit-bound protein is subject to ubiquitination by *Nedd4L* [32].
	← TR	YAP	*YAP* is a transcriptional inducer of both catalytic *p110* subunits of *PI3K*, *p110a* and *p110b*; *p110-H* albeit its effect on *p110a* expression requires raising *p110b* levels first. Moreover, *YAP* knockdown leads to downregulation of both subunits [29].
PI3K_H	**PI3K_H** = ((((not **PTEN_c**) and **p110_H**) and **RTK**) and **PI3K**) and **Ras**		
	K		Full, peak-level activation of *PI3K* requires high levels of *p110* protein, basal *PI3K* activation, active *Ras*, and active *RTK*s. As the ON-state of *Ras* in our model represents strong *Ras* activation in the presence of proliferation-inducing (high) growth factors, *PI3K_H* activation can only occur in these conditions. In addition, a reduction of cytoplasmic *PTEN* levels is also required for peak *PI3K* activity.
	← BLoc	RTK	High levels of *PI3K* activation only occur at growth factor-bound *RTK*s, which recruit and activate *PI3K* at the plasma membrane [28].
	← Compl	Ras	*Ras* binds the catalytic subunit of *PI3K* and *Ras* knockdown / over expression decreases /increases the *PI3K*-dependent generation of PIP3 [24, 25].
	← Per	PI3K	In our model, high *PI3K* activation is contingent on the ON-state of the basal *PI3K* node.
	← Per	p110_H	High levels of *PI3K* activity in response to strong growth factor stimulation only occur in cells that express high levels of *p110* protein [30].
	⊢ DP	PTEN_c	Cytoplasmic *PTEN* regulates *PI3K* signaling by dephosphorylating its lipid signaling intermediate *PIP3* [33].

Table S1d: GF_PI3K module

AKT_H	**AKT_H** = (((((**AKT_B** and **p110_H**) and **PI3K_H**) and **PIP3**) and **PDK1**) and **mTORC2**) and (**Ras** or **PAK1**)		
	K		In contact to basal *AKT1*, high *AKT1* activity in our model requires basal *AKT1* (*AKT_B*), the ongoing presence of high *p110* protein levels along with active *PI3K_H* and *PIP3*. In addition this maximal *AKT1* activation requires phosphorylation by both *PDK1* and *mTORC2*, , as well as either active *Ras* [28] or *PAK1* [34].
		← Compl	PIP3	*PIP3* recruits *AKT1* to the plasma membrane and *PIP3* binding changes the conformation of *AKT1* such that it becomes accessible for T308 phosphorylation by *PDK1* [28].
		← P	PDK1	Membrane-recruited *PDK1* phosphorylates *AKT1* at T308, a critical step in its activation [28].
		← Per	AKT_B	In our model, high *AKT1* activation is contingent on the ON-state of basal *AKT1* (*AKT_B*).
		← P	p110_H	Ongoing high *p110* availability and *PI3K_H* activity are required to induce maximal activation of *AKT_H* [28].
		← P	PI3K_H	Ongoing high *p110* availability and *PI3K_H* activity are required to induce maximal activation of *AKT_H* [28].
		← P	mTORC2	Maximal activation of *AKT1* requires phosphorylation of S473 by *mTORC2* [28].
		← Compl	Ras	*Ras* binding to the catalytic subunit of *PI3K* is required for its full potency in *PIP3* generation [24, 25]. Active *Ras* is thus required for inducing peak *AKT_H* activity.
		← P	PAK1	*PAK1* interacts with and directly phosphorylates *AKT1* [35]. In addition, *PAK1* provides a scaffold to facilitate *Akt* stimulation by *PDK1* and to aid *AKT's* membrane recruitment [34].
FoxO3	**FoxO3** = (not((**AKT_B** or **AKT_H**) or **ERK**)) or ((not(**AKT_H** and (((**Plk1** or **Plk1_H**) or **AKT_B**) or **ERK**))) and (not((**Plk1** and **Plk1_H**) and **ERK**)))		
	TF		In order to account for all the influences on *FoxO3* activity, we used the following logic. In the absence of basal or high *AKT1* as well as *ERK*, *FoxO3* remains active. In addition, *FoxO3* can overcame peak (*AKT_H*) activation only if no other inhibitor is present and *AKT_B* is OFF (indicating that *AKT1* levels are falling). Finally, the joint activity of *ERK* and *Plk1* can also block *FoxO3*.
		⊣ P	ERK	ERK downregulates *FoxO3* transcriptional activity by phosphorylating it at three Serines, inducing its *MDM2*-mediated ubiquitination and degradation [36].
		⊣ PLoc	AKT_B	*AKT1* mediates the translocation of the *FoxO3* our of the nucleus through direct phosphorylation of three conserved residues. These events create a recognition site for *14-3-3* family proteins, which export and sequester *FoxO3* in the cytosol [28].

Table S1d: GF_PI3K module

	⊢ PLoc AKT_H	*AKT1* mediates the translocation of the *FoxO3* our of the nucleus through direct phosphorylation of three conserved residues. These events create a recognition site for *14-3-3* family proteins, which export and sequester *FoxO3* in the cytosol [28].
	⊢ PLoc Plk1	*Plk1* binds *FoxO3*, induces its translocation to the cytosol, phosphorylates it and suppresses its activity through most of the the cell cycle, but most significantly during G2 and M [37].
	⊢ PLoc Plk1_H	*Plk1* binds *FoxO3*, induces its translocation to the cytosol, phosphorylates it and suppresses its activity through most of the the cell cycle, but most significantly during G2 and M [37].
PLCgamma	**PLCgamma** = ((((**RTK** and **Grb2**) and **GF_High**) and **p110_H**) and **PI3K_H**) and **PIP3**	
	Enz	Peak activation of *PLCγ* requires active an *RTK* receptor node bound by active *Grb2*, as well as high *PI3K* activity (including high *p110* availability and the presence of PIP3).
	← Compl GF_High	We assume that high levels of *RTK* activity is required for tyrosine phosphorylation of *PLCγ*.
	← P RTK	The SH2 domains of *PLCγ* binds to active *RTK*s at tyrosine autophosphorylation sites, leading to tyrosine phosphorylation of *PLCγ* and stimulation its enzymatic activity [38, 39].
	← BLoc Grb2	*RTK* tyrosine autophosphorylation induces *PLCγ* binding to the *Grb2* adaptor protein and likely aids the translocation of *PLCγ* to the plasma membrane [40].
	← BLoc PIP3	Membrane targeting of *PLCγ* to growth receptor stimulation is mediated by *PIP3* binding of *PLCγ* [41, 42].
	← P p110_H	Membrane targeting of *PLCγ* to growth receptor stimulation requires *PI3K* activity and *PIP3* generation near growth receptors [41]. Thus, peak *PLCγ* activity in our model requires high *p110* protein expression [42].
	← P PI3K_H	In addition to high *p110* protein levels, high *PI3K* activation is also required to fully activate *PLCγ* [41, 42].
IP3	**IP3** = **PLCgamma**	
	Met	Membrane-bound, active *PLCγ* is responsible for converting phosphatidylinositol(4,5)P2 (*PIP2*) to the second messenger inositol(1,4,5)P3 (*IP3*) responsible for triggering a sudden Ca^{2+} influx from the endoplasmic reticulum, along with *DAG* (diacylglycerol, another second messenger) [43].
	← Cat PLCgamma	Membrane-bound, active *PLCγ* is responsible for converting phosphatidylinositol(4,5)P2 (*PIP2*) to the second messenger inositol(1,4,5)P3 (*IP3*) responsible for triggering a sudden Ca^{2+} influx from the endoplasmic reticulum, along with *DAG* (diacylglycerol, another second messenger) [43].

Table S1d: GF_PI3K module

Ca2p	**Ca2p** = **IP3**		
	Met		*IP3* travels from the cell membrane to the endoplasmic reticulum where it opens *IP3*-sensitive Ca^{2+} channels, releasing a sudden Ca^{2+} efflux from the ER into the cytosol [44].
	← Loc	IP3	*IP3* travels from the cell membrane to the endoplasmic reticulum where it opens *IP3*-sensitive Ca^{2+} channels, releasing a sudden Ca^{2+} efflux from the ER into the cytosol [44].
Nedd4L	**Nedd4L** = **Ca2p** and **IP3**		
	UbL		Activation of *Nedd4L* requires both Ca^{2+} and *IP3* binding [45].
	← Compl	IP3	In order to transition to its active form, the E3 ubiquitin ligase *Nedd4L* binds Ca^{2+} and inositol 1,4,5-trisphosphate (*IP3*) [45].
	← Compl	Ca2p	In order to transition to its active form, the E3 ubiquitin ligase *Nedd4L* binds Ca^{2+} and inositol 1,4,5-trisphosphate (*IP3*) [45].

Table S1e: GF_mTOR module

Target Node	Node Gate / Node Type / Link Type	Node Description / Input Node	Link Description
TSC2	**TSC2** = (not **AKT_H**) or (not(**AKT_B** or **ERK**))		
	Prot		Blocking *TSC2* requires ongoing mitogen stimulation through *AKT* and/or *ERK*. In our model, *TSC2* inhibition requires high (peak) *AKT* activity, supported by either *ERK* or basal *AKT* (assuring that complete loss of *AKT* activity is not impending) [46].
	⊣ P	ERK	*ERK* phosphorylates *TSC2* directly, causing dissociation of the complex and inhibition of its activity [47]. In addition, the *ERK* target *p90RSK* can also inactivate *TSC2* [48].
	⊣ P	AKT_B	*TSC2* is phosphorylated by *AKT1*, inhibiting it by dissociating *TSC2* from lysosomal membranes [49], where it stimulates GTP hydrolysis of the small GTPase *Rheb*, this inactivating it [46].
	⊣ P	AKT_H	*TSC2* is phosphorylated by *AKT1*, inhibiting it by dissociating *TSC2* from lysosomal membranes [49], where it stimulates GTP hydrolysis of the small GTPase *Rheb*, this inactivating it [46].
PRAS40	**PRAS40** = (not **AKT_H**) and ((not **mTORC1**) or (not **AKT_B**))		
	Prot		*PRAS40* is inhibited by peak *AKT1* activity aided by either basal *AKT1* (meaning *AKT_H* is on its way down), or ongoing *mTORC1* activation. Both *AKT1* and *mTORC1* phosphorylate *PRAS40*, leading to its dissociation from *mTORC1* [50].

Table S1e: GF_mTOR module

	⊢ P	AKT_B	*PRAS40* is phosphorylated by *AKT*, triggering its dissociation from *mTORC1* [51].
	⊢ P	AKT_H	*PRAS40* is an inhibitory component of the *mTORC1* complex. It is phosphorylated by *AKT*, triggering its dissociation from *mTORC1* and loss of *mTORC1* inhibition [51].
	⊢ P	mTORC1	*PRAS40* is a substrate of the *mTORC1* kinase; its phosphorylation aids its dissociation from *mTORC1* and its sequestration by 14-3-3 proteins [52].
DAG	**DAG = PLCgamma**		
	Met		Membrane-bound, active *PLC*γ is responsible for converting phosphatidylinositol(4,5)P2 (*PIP2*) to the second messenger diacylglycerol (*DAG*), along with *IP3* [43].
	← Cat	PLCgamma	Membrane-bound, active *PLC*γ is responsible for converting phosphatidylinositol(4,5)P2 (*PIP2*) to the second messenger diacylglycerol (*DAG*), along with *IP3* [43].
Rheb	**Rheb** = (not **TSC2**) and **DAG**		
	GTPa		*PKC* (and *DAG*)-dependent activation of *mTORC1* recruits *mTORC1* to the site of *Rheb* activity (to prenuclear lysosomes), while *AKT* and *ERK*-mediated *TSC2* inhibition guarantees that *Rheb* remains potent [53, 54, 55].
	⊢ GAP	TSC2	*TSC2*, a key component of the heterotrimeric *TSC* complex, is a GTPase activating protein (GAP) that induces ATP hydrolysis and deactivation of the small GTPase *Rheb* [53].
	← Ind	DAG	The second messenger *DAG* activates both classical and novel *PKC*s. One of its targets, *PKC*η, is responsible for the translocation and accumulation of *mTORC1* to perinuclear lysosomes, where the majority of *Rheb* is anchored. Thus, *DAG* brings *Rheb* in proximity with its target, *mTORC1* [54].
mTORC1	**mTORC1** = (not **Casp3**) and ((((**Rheb** and (not **PRAS40**)) and (not **Merlin**)) or **E2F1**) or ((**CyclinB** and **Cdk1**) and **GSK3**))		
	PC		*mTORC1* is activated by mitogenic signals via *Rheb* in the absence of *PRAS40*. This, however, also requires inactivation of *Merlin* independently of *RTK*-induced signals. In addition, *E2F1* can promote *mTORC1* activity. Finally, the mitotic *Cyclin B* and its *Cdk1* kinase can also activate *mTORC1*, aided by *GSK3*.
	⊢ IBind	PRAS40	*PRAS40* is an inhibitory component of the *mTORC1* complex, removed by phosphorylation by *AKT* or *mTORC1* itself [46].
	← Compl	Rheb	The *Rheb* small GTPase binds *mTORC1* directly and activates the complex [56].
	← Ind	GSK3	During mitosis, *mTORC1* is activated by the G2/M-specific phosphorylation of *Raptor*, a component of *mTORC1*, by *CyclinB / Cdk1* complexes, aided by *GSK3* [57].

Table S1e: GF_mTOR module

	⊢ ComplProc	Merlin	*Merlin* suppresses *mTORC1* activity via an unknown mechanism that appears to be independent of *PI3K/AKT* or of *TSC2* inhibition [58], and it suppression appears to be critical for integrin-mediated *mTORC1* activation [59].
	← Loc	E2F1	*E2F1* induces *mTORC1* activity by inducing *mTORC1* translocation to late endosomes. This effect does not require *AKT* and is not blocked by high levels of *TSC2* [60].
	← Ind	CyclinB	During mitosis, *mTORC1* is activated by the G2/M-specific phosphorylation of *Raptor*, a component of *mTORC1*, by *CyclinB / Cdk1* complexes, aided by *GSK3* [57].
	← Ind	Cdk1	During mitosis, *mTORC1* is activated by the G2/M-specific phosphorylation of *Raptor*, a component of *mTORC1*, by *CyclinB / Cdk1* complexes, aided by *GSK3* [57].
	⊢ Lysis	Casp3	*Raptor*, a key component of the *mTORC1* complex, is cleaved and inhibited by *Caspase 3* [61].
S6K	**S6K** = (not **Casp3**) and **mTORC1**		
	K	*S6K* is activated by *mTORC1* in the absence of *Caspase 3*.	
	← P	mTORC1	*mTORC1* phosphorylates and activates 40S ribosomal S6 kinases (*S6K*s) [62].
	⊢ Lysis	Casp3	*S6K* is cleaved and inhibited by *Caspase 3* [63].
eIF4E	**eIF4E** = **mTORC1** and (not **Casp3**)		
	Prot	*eIF4E* is activated by *mTORC1*-mediated repression [46]. *eIF4E* is cleaved and deactivated by *Caspase 3* [64].	
	← Ind	mTORC1	*mTORC1* phosphorylates *4EBP*, triggering its dissociation from *eIF4F*, and thus promoting translation initiation [46].
	⊢ Lysis	Casp3	*eIF4E* is cleaved and inhibited by *Caspase 3* [64].

Table S1f: GF_connect module

Target Node	Node Gate Node Type Link Type	 Node Description Input Node	 Link Description
GSK3	**GSK3** = (not **AKT_H**) and (not(**S6K** and **ERK**))		
	K	*GSK3* activity can be completely blocked by peak *AKT* activation (*AKT_H*), or by the joint action of *S6K* and *ERK*.	
	⊢ P	ERK	*ERK* binds and phosphorylates *GSK3β* at Thr-43, which primes it for subsequent phosphorylation by the *ERK* target *p90RSK* at Ser-9, which inactivates *GSK3β* [65].

Table S1f: GF_connect module

	⊢ P	AKT_H	*AKT* blocks *GSK3* kinase activity via an inhibitory phosphorylation on the amino terminus, which blocks the substrate accessibility of *GSK3* [28].
	⊢ P	S6K	*GSK3* is a direct phosphorylation target of *S6K1*, resulting in its inhibition [22].
FoxO1	**FoxO1** = (not **Plk1**) and (not **AKT_H**)		
	TF		*FoxO1* is transcriptionally active in the absence of peak *AKT1* activation and *Plk1* activity.
	⊢ PLoc	AKT_H	*AKT1* mediates the translocation of *FoxO1* our of the nucleus through direct phosphorylation of three conserved residues. These events create a recognition site for *14-3-3* family proteins, which export and sequester *FoxO1* in the cytosol [28].
	⊢ PLoc	Plk1	*Plk1* interacts with and phosphorylates *FoxO1*, mainly at the G2/M phase of the cell cycle. *Plk1*-mediated phosphorylation leads to the impairment of *FoxO1*'s transcriptional activity in an *Akt*-independent manner. *Plk1*-induced *FoxO1* phosphorylation causes its nuclear exclusion [66].
p21 _mRNA	**p21_mRNA** = ((**FoxO1** and **FoxO3**) or ((not **Myc**) and (**FoxO1** or **FoxO3**))) and (not **ZEB1_H**)		
	mRNA		Our model requires both FoxOs to induce $p21^{Cip1}$ if *Myc* is active and one of the two if *Myc* is OFF. This is based on data showing that both *FoxO3* and *FoxO1* bind and induce the $p21^{Cip1}$ promoter and that loss of *Myc* repression alone is not sufficient to induce $p21^{Cip1}$ [67]. Finally, high levels of *ZEB1* repress $p21^{Cip1}$ mRNA expression [68].
	← TR	FoxO3	$p21^{Cip1}$ is a direct transcriptional target of *FoxO3* [67].
	← TR	FoxO1	$p21^{Cip1}$ is a direct transcriptional target of *FoxO1* [67].
	⊢ TR	Myc	*Myc* is a direct transcriptional repressor of the $p21^{Cip1}$ promoter (it is recruited by the DNA-binding *Miz-1*) [69, 70].
	⊢ TR	ZEB1_H	*ZEB1* (old name δEF1) is a direct transcriptional repressor of the p21 promoter [68].
IKKa	**IKKa** = **AKT_H**		
	K		*IKKα* is a subunit of the *IKK* protein complex composed of two catalytic subunits, *IKKα* and *IKKβ*, and the regulatory protein *NEMO*. Activation of the transcription factor *NF-κB* is mediated by the IKK complex, which phosphorylates and degrades the inhibitory *IκB* proteins [71].
	← P	AKT_H	*IKKα* is phosphorylated by *AKT* at T23, and as subsequent *NF-κB* activation is induced when high *AKT* activity is observed, our model requires *AKT_H = ON* for this to occur [72].
NfkB	**NfkB** = **IKKa** or **PAK1**		

Table S1f: GF_connect module

	TF		*NF-κB* is a transcription factor primarily known as a master regulator of inflammatory signaling and the immune system. Its role in cancer is partly due to its ability to aid EMT. It is activated via the destruction of its inhibitory binding partner *IκB*, which is phosphorylated by the *IKK* complex subsequently destroted [71].
		← Ind	IKKa	*IKKα*, part of the *IKK* complex, phosphorylates and degrades the inhibitory *IκB* proteins [71]; an action that can be independent of the *IKKβ* subunit [73].
		← Loc	PAK1	Active *PAK1* binds to with *NF-κB*-inducing kinase *NIK*, which induces degradation of *IκB* and thus activates *NF-κB* [74].
c_Myb	**c_Myb = NfkB** or **E2F1**			
	TF			*c-Myb* is a transcription factor that can induce the epithelial micro-RNA *miR-200* [75]. *c-Myb* is induced by *AKT*-mediated activation of *NF-κB* and/or *E2F1* [76].
		← TR	NfkB	*NF-κB* is a direct transcriptional inducer of *c-Myb* [76].
		← TR	E2F1	*E2F1* is a direct transcriptional inducer of *c-Myb* [76].

Table S1g: Adhesion module

Target Node	Node Gate Node Type Link Type		Node Description Input Node	Link Description
Integrin	**Integrin = ECM**			
	Rec			Integrins are a superfamily of heterodimeric cell adhesion receptors that bind to extracellular matrix ligands, cell-surface ligands, and soluble ligands. Upon ligand binding, integrins transduce biomechanical information to the cell interior [77].
		← Ligand	ECM	*Integrin* activation and signaling requires *integrin-ECM* attachment [78].
FAK	**FAK** = ((not **Casp3**) and (not(**Cdk1** and **CyclinB**))) and **Integrin**			
	K			*FAK* is activated at integrin-ECM attachment sites in the absence of *Caspase 3*-mediated cleavage and *Cyclin B/Cdk1* activity [79, 80, 81].
		← P	Integrin	*Integrin* activation leads to recruitment and phosphorylation of the Focal Adhesion Kinase (*FAK*) [79], one of its key signaling mediators.

Table S1g: Adhesion module

	⊢ Ind	CyclinB	During mitosis, cells detach most of their focal adhesions and round up. This process is *Cdk1/Cyclin B* dependent [82], and it leads to the dissociation of focal adhesion complex components including focal adhesion kinase (*FAK*), *paxillin*, and *CAS*. These proteins all change their phosphorylation status by losing active tyrosine and gaining inhibitory serine/threonine phosphorylation [81].
	⊢ Ind	Cdk1	During mitosis, cells detach most of their focal adhesions and round up. This process is *Cdk1/Cyclin B* dependent [82], and it leads to the dissociation of focal adhesion complex components including focal adhesion kinase (*FAK*), *paxillin*, and *CAS*. These proteins all change their phosphorylation status by losing active tyrosine and gaining inhibitory serine/threonine phosphorylation [81].
	⊢ Lysis	Casp3	Caspase 3 cleaves and deactivates *FAK* during apoptisis by separating its tyrosine kinase from its focal adhesion targeting domain. These fragments further suppress phosphorylation of intact *FAK* [80].
Src	**Src** = (**Integrin** and (**RTK** or **FAK**)) or (**Cdk1** and **CyclinB**)		
	K		*Src* is activated by *FAK* or *RTKs* at sites of integrin-ECM attachments [83, 84]. In addition, *Cyclin B / Cdk1* phosphorylate *Src* during mitosis [85].
	← PLoc	Integrin	*FAK* phosphorylation at Y397 at sites of *integrin-ECM* adhesion creates a high-affinity binding site for *Src*, which leads to the assembly of a *FAK–Src* signaling complex [83].
	← Loc	RTK	*RTKs* cooperate with *integrins* to recruit and activate *Src* kinases, which in turn help potentiate *RTK* signaling. Thus, in our model *Src* may be activated by basal *RTK* activity, and is, in turn, required for peak *RTK* activation [84].
	← PLoc	FAK	*FAK* phosphorylation at Y397 at sites of *integrin-ECM* adhesion creates a high-affinity binding site for *Src*, which leads to the assembly of a *FAK–Src* signaling complex [83].
	← P	CyclinB	Mitotic *Cyclin B/Cdk1* complexes phosphorylate and activate *c-Src* during mitosis [85].
	← P	Cdk1	Mitotic *Cyclin B/Cdk1* complexes phosphorylate and activate *c-Src* during mitosis [85].
Nectin3	**Nectin3** = **CellDensity_Low** or **CellDensity_High**		
	CAM		*Nectins* form weak adhesions between adjacent cells by binding to *Nectins* on other cells and promoting local membrane ruffling that is required for adherens junction formation [86]. As downstream effects of *Nectin3* - *Nectin* binding between two cells do not require tight junction formation and high cell density, *Nectin3* activation in our model only requires the presence of some neighbors.
	← Env	CellDensity _High	Nectins avtivate by forming weak adhesions between adjacent cells [86].

Table S1g: Adhesion module

	← Env	CellDensity _Low	Nectins avtivate by forming weak adhesions between adjacent cells [86].
Necl5	**Necl5** = **FocalAdhesions** or (not(**Nectin3** and **CellDensity _High**))		
	Prot		*Necl-5* activity is controlled by co-localization with focal adhesions where it binds *Spry2* and aids receptor tyrosine kinase signaling [87]. We modeled this by turning the *Necl-5* node ON when the *Focal Adhesions* node is ON (indicating strong attachments that pull on the ECM and can form stress fibers), or in the absence of cell-cell adhesions at all sites of cell ECM-adhesion (i.e, fully surrounded with no free edge).
	⊢ Env	CellDensity _High	At high cell density, adherens junctions that surround the cell suppress integrin-mediated activation and recruitment of *Necl-5* to the cell surface across the entire cell, which releases its block on *Spry2* [87].
	⊢ Unbind	Nectin3	*Necl-5* interacts with *Nectin3* on neighboring cells (*Nectin 3* in our model is a proxy for this, as it is activated by cell-cell contacts), which promotes downstream reorganization of the cytoskeleton to aid adherens junction formation, which, in turn releases *Necl-5* from these adhesions [87].
	← Loc	FocalAdhesions	*Necl-5* is recruited to focal adhesions at the leading edge of cells by direct interactions with integrins [88]. This localization is important for its downstream effects.
SPRY2	**SPRY2** = ((not **Necl5**) and **RTK**) and **Src**		
	Prot		*SPRY2* (*Sprouty 2*) is a negative regulator of growth factor-induced signaling, especially *Ras/MAPK* [89].
	⊢ IBind	Necl5	*Necl-5* localized to integrin clusters binds to and blocks the activity of *SPRY2* [89].
	← Loc	RTK	*Sprouty* proteins are activated by ligand-bound RTKs to modulate / inhibit downstream MAPK signaling [90].
	← P	Src	Growth factor-induced tyrosine phosphorylation of *Spry2* is mediated by a *Src*-like kinase [90].
J _Ecadherin	**J_Ecadherin** = (not **Casp3**) and (**Nectin3** and (**Ecadherin_mRNA_H** or **Ecadherin_mRNA**))		
	CAM		*E-cadherin* proteins are adhesion molecules required for adherens junction formation. The presence of juncitonal *E-cadherin* (J_Ecadherin = ON) in our model requires *E-cadherin* mRNA expression, *Nectin3*-mediated sensing of contact with neighboring cells (binding to nectins) [87] and inactive Caspase 3 [91].
	← TL	Ecadherin _mRNA	*E-cadherin* mRNA expression is required for maintenance of *E-cadherin* protein.
	← TL	Ecadherin _mRNA_H	*E-cadherin* mRNA expression is required for maintenance of *E-cadherin* protein.

Table S1g: Adhesion module

	$\leftarrow$ BLoc	Nectin3	Cadherins are recruited to cell-cell adhesions formed by *Nectin3-nectin* interactions between neighboring cells, where they bind to cadherins on adjacent cells to form AJs [87].
	$\vdash$ Lysis	Casp3	Caspase 3 cleaves junctional E-cadherin, dissociating it from the cell surface and blocking its ability to form adherens junctions [91].
J_bcatenin	**J_bcatenin** = (not **Casp3**) and **J_Ecadherin**		
	Prot		Junctional *E-cadherin* proteins binds to and recruits/sequesters *β-catenin* to adherens junctions. This negatively regulates *β*-catenin mediated transcription, but aids adherens junction formation [92]. Here we assume that *β-catenin* is localized to cell-cell junctions (*J_ bcatenin* = ON) as long as there are *E-cadherin*-mediated attachments to neighboring cells (even if a cell is not fully surrounded) and *Caspase 3* is inactive [93].
	$\leftarrow$ Per	J _Ecadherin	Junctional *E-cadherins* recruits/sequester *β-catenin* to adherens junctions [92].
	$\vdash$ Lysis	Casp3	Active *Caspase 3* cleaves *β-catenin* into several fragments that lose their transcriptional activity and become localized to the cytoplasm [93].
J_acatenin	**J_acatenin** = **J_bcatenin**		
	Adap		Junctional *β-catenin* binds to and recruitcs *α-catenin* to adherens junctions. *α-catenin* links *β-catenin* to the actin cytoskeleton to stabilize adherens junctions [92].
	$\leftarrow$ Compl	J_bcatenin	Junctional *β-catenin* binds to and recruitcs *α-catenin* to adherens junctions [92].

Table S1h: CIP module

Target Node	Node Gate Node Type Link Type	 Node Description Input Node	 Link Description
FocalAdhesions	**FocalAdhesions** = ((**Integrin** and **FAK**) and **ECM**) and (**Stiff_ECM** or ((**YAP** and **Rac1**) and **IQGAP1_LeadingE**))		
	MSt		*Focal adhesions* form at sites of *Integrin-ECM* attachment and clustering [94]. In order to take into account the effect of stiff ECM [95] as well as positive feedback between focal adhesion formation and horizontal cell polarization that creates an active leading edge, here we assume that force-generating Focal Adhesion formation requires ECM-Integrin attachments and *FAK* [96], and either strong traction force generation supported by a stiff ECM, or the existence of a leading edge with active *Rac1* [97] and *IQGAP1* [98, 99, 100] supported by *YAP*-mediated upregulation of adhesion and focal adhesion-associated proteins [101].
	$\leftarrow$ Loc	ECM	*Focal adhesions* form at sites of *Integrin-ECM* attachment and clustering [94].

Table S1h: CIP module

← Loc	Stiff_ECM	Adhesion to stiff ECM engages the *FAK/phosphopaxillin/vinculin* pathway, which generate a fluctuating "tugging" action on the ECM and probe ECM rigidity to aid *focal adhesion* formation and migration towards regions of stiffer ECM (durotaxis) [95].
← Loc	Integrin	*Focal adhesions* form at sites of *Integrin-ECM* attachment and clustering [94].
← Loc	FAK	*FAK* activation at sites of cell-ECM attachments (driven by force generation) can increase paxillin phosphorylation and strengthen cytoskeletal linkage and vinculin recruitment to such adhesions, resulting in *focal adhesion* maturation [96].
← Loc	Rac1	Active *Rac1* promotes the association of nonmuscle myosin II (MIIA) with *focal adhesions* at the leading edge during cell migration, aiding the assembly of mini- filaments in *focal adhesions*. These promote further assembly of *focal adhesions* and modulation of the traction forces cells exert on the ECM [97].
← Compl	IQGAP1 _LeadingE	In migrating cells *IQGAP1* localizes to lamellipodia at the leading edge, recruited by active *RTKs* synergistically activated here by *integrin-RTK* crosstalk. Here, *IQGAP1* supports *Rac1* activation and *focal adhesion* formation; it required for migration in response to growth signals such as *PDGF*, *VEGF*, ect [98, 99, 100].
← TR	YAP	*YAP* is a transcriptional inducer of *f integrins* and *FA* docking proteins, and promotes *focal adhesion* formation by increasing cell spreading and *RhoA GTPase* activity [101].

Stress _Fibers — **Stress_Fibers** = ((not **CellDensity_High**) and **Stiff_ECM**) and **FocalAdhesions**

MSt — In order to model the independent effects of cell density and matrix stiffness on stress fiber formation, we assume that they require both the absence of high cell density, and the presence of focal adhesions attached to a stiff ECM.

⊢ Ind	CellDensity _High	*High cell density* blocks stress fiber formation by forbidding cells access to a large enough area to spread and exert force on the *ECM* [102].
← Ind	Stiff_ECM	In the absence of a sufficiently stiff *ECM*, *Focal Adhesions* are small and stress fibers are less abundant or fail to form, as cells cannot generate sufficient traction [103].
← ComplProc	FocalAdhesions	*Stress Fibers* are anchored to the *ECM* via strong, stable *Focal Adhesions* [103].

YAP — **YAP** = (**FocalAdhesions** and **Stress_Fibers**) and (not((((**ApicalBasal_Pol** and **J_acatenin**) and **AMOT**) and **Merlin**) and **Lats1_2**))

Table S1h: CIP module

YAP	TF		YAP is a mechanosensitive transcriptional regulator of proliferation and migration, and its activation is controlled by both the cell's ability to spread on an ECM (*FocalAdhesions* and *Stress_Fibers*), and the lack of apical-basal polarity with mature adherens junctions that can sequester *YAP* in the cytoplasm by binding and inhibitory phosphorylation. Experimental evidence indicates that in cells that maintain apical-basal polarity, several junctional proteins (*α-catenin*, *AMOT*, *Merlin*) and inhibitory kinases (*Lats1* and *Lats2* work together to sequester and block *YAP* [104, 105].
	← Ind	FocalAdhesions	*YAP* activation is abolished by the absence of *stress fibers* anchored to *focal adhesions*, even in the absence of inhibitory Hippo signaling [102, 106].
	← Ind	Stress_Fibers	*YAP* activation is abolished by the absence of *stress fibers* anchored to *focal adhesions*, even in the absence of inhibitory Hippo signaling [102, 106].
	⊢ Ind	ApicalBasal_Pol	Full inhibition of *YAP* by Hippo signaling linked to adherens and tight junction formation requires the establishment of *apical-basal polarity*, as cells at the edges of monolayers or in decreased cell density areas have active (nuclear) *YAP* in spite of strong remaining attachments to neighboring cells [106, 107].
	⊢ Per	J_acatenin	Junctional *alpha-catenin* binds *YAP* and sequesters it in the cytoplasm [108] [109] [110]. This also concentrates *YAP* close proximity to junction-localized Hippo pathway components such as *Lats1/2*, *Merlin* and *Amot.*
	⊢ Compl	AMOT	*AMOT* localizes to tight junctions, where it suppresses *YAP* activity by direct binding and recruitment of *YAP* inhibitory kinase *LATS2* [104]. By binding both and *YAP/TAZ*, *AMOT* works as a scaffold that connects *LATS1/2* to both its activator *MST1* and its target *YAP/TAZ* [111].
	⊢ BLoc	Merlin	*Merlin* localizes to adherens junctions where it activates the *Hippo pathway* by binding to and recruiting *LATS1/2* kinases and *YAP/TAZ* to *adherens junctions* [112]. In the absence of *Merlin*, Hippo pathway components fail to block *YAP* activity [113]. *Merlin* - *YAP* binding requires active (phosphorylated) *AMOT* [114].
	⊢ IBind	Lats1_2	The *Lats1* and *Lats2* tumor suppressor kinases bind to and phosphorylate *YAP* in vitro and in vivo [115, 105].
TRIO	**TRIO = YAP**		
	GEF		*TRIO* is a *Rac1*-activating GTP-exchange factor induced by *YAP* [107, 116].
	← TR	YAP	*YAP* is a transcriptional inducer of *TRIO* [116].
WT1	**WT1 = YAP**		
	TF		The Wilms Tumor 1 (*WT1*) transcription factor is a repressor of *E-cadherin* expression [107]. Its nuclear localization is controlled by *YAP* binding [116].

Table S1h: CIP module

	$\leftarrow$ BLoc	YAP	*YAP* binds to and controls nuclear localization of the Wilms Tumor 1 (*WT1*) transcription factor [116].
TAZ	**TAZ** = **Stress_Fibers** and (not((((**ApicalBasal_Pol** and **J_acatenin**) and **AMOT**) and **Merlin**) and **Lats1_2**))		
	TF		*TAZ* is a mechanosensitive transcriptional regulator of cell migration, and its activation is controlled by both the cell's ability to spread on stiff ECM (*Stress_Fibers* = ON) and the lack of apical-basal polarity with mature adherens junctions that can sequestered *TAZ* in the cytoplasm by binding and inhibitory phosphorylation [106, 107]. In cells that maintain apical-basal polarity, junctional proteins (α-*catenin*, *AMOT*, *Merlin*) and inhibitory kinases (*Lats1* and *Lats2*) work together to sequester and block *TAZ* [108, 109, 110, 117, 105].
		$\dashv$ BLoc	J_acatenin	Junctional *alpha-catenin* binds *YAP/TAZ* and sequesters them in the cytoplasm [108, 109, 110, 117]. This also concentrates *YAP/TAZ* close proximity to junction-localized Hippo pathway components such as *Lats1/2*, *Merlin* and *Amot*.
		$\leftarrow$ Ind	Stress_Fibers	*TAZ* activation is abolished by the absence of *stress fibers* anchored to *focal adhesions*, even in the absence of inhibitory Hippo signaling [102, 106].
		$\dashv$ Ind	ApicalBasal_Pol	Full inhibition of *TAZ* by Hippo signaling linked to adherens and tight junction formation requires the establishment of apical-basal polarity, as cells at the edges of monolayers or in decreased cell density areas have active (nuclear) *TAZ* in spite of strong remaining attachments to neighboring cells [106, 107].
		$\dashv$ P	Lats1_2	The *Lats1* and *Lats2* tumor suppressor kinases bind to and phosphorylate *YAP/TAZ* in vitro and in vivo [115, 105, 117].
		$\dashv$ IBind	AMOT	*AMOT* localizes to tight junctions, where it suppresses *YAP/TAZ* activity by direct binding and recruitment of *YAP* inhibitory kinase *LATS2* [104, 117]. By binding both and *YAP/TAZ*, *AMOT* works as a scaffold that connects *LATS1/2* to both its activator *MST1* and its target *YAP/TAZ* [111].
		$\dashv$ IBind	Merlin	*Merlin* localizes to adherens junctions where it activates the Hippo pathway by binding to and recruiting *LATS1/2* kinases and *YAP/TAZ* to adherens junctions [112]. In the absence of *Merlin*, Hippo pathway components fail to block *YAP/TAZ* activity [113, 117].
Ecadherin_mRNA_H	**Ecadherin_mRNA_H** = **Ecadherin_mRNA** and (not(**YAP** and **WT1**))		
	mRNA		Experiments show that *YAP* and *WT1* suppress but do not abolish *E-cadherin* protein expression in areas of lowered cell density [107]. To model this, we introduced a *Ecadherin_mRNA_H* node that is blocked by *YAP/WT1* repressor complexes (requiring their joint nuclear localization). *Ecadherin_mRNA_H*, in turn, must be ON to allow cells to establish a ring of adherens junctions sufficient for apical-basal polarity.

Table S1h: CIP module

	⊢ Compl	YAP	Active *YAP* binds *WT1* and localizes it to the nucleus, where they form a complex a the *E-cadherin* promoter and reduce its transcription [107].
	⊢ Compl	WT1	Active *YAP* binds *WT1* and localizes it to the nucleus, where they form a complex a the *E-cadherin* promoter and reduce its transcription [107].
	← Per	Ecadherin _mRNA	High *E-cadherin* mRNA expression requires basal levels of *E-cadherin*. Our previously published epithelial model assumed this to be true [118], whereas in the current model this is only the case when *E-cadherin* expression is not fully inhibited by EMT-promoting repressors (modeled as acting on the *Ecadherin_ mRNA* node).
ApicalBasal _Pol	**ApicalBasal_Pol** = (**ECM** and ((((**CellDensity_High** and **Nectin3**) and **J_Ecadherin**) and **J_bcatenin**) and **J_acatenin**)) and (**Ecadherin_mRNA_H** or (not **Horizontal_Pol**))		
	MSt		In addition to a need for high cell density and cell-cell adhesion proteins that help assemble adherens junctions (*Nectin3*, *J_Ecadherin*, *J_bcatenin*, *J_acatenin*), we assumed that either high (unimpeded) *E-cadherin* mRNA expression or lack of a horizontally polarized cell morphology are required for the establishment of apical-basal polarity.
	← ComplProc	ECM	Establishment of *apical-basal polarity* requires an underlying surface such as *ECM* to define a basal side.
	← Ind	CellDensity _High	Establishment of *apical-basal polarity* requires a ring of adherens and tight junctions that can only form in high cell density [119].
	← Ind	Nectin3	A key driver of *apical-basal polarization*, *Par-3*, is recruited to newly formed cell-cell adhesions by *Nectin-3* binding [119].
	← Ind	J _Ecadherin	Formation of adherens junctions is a prerequisite for tight junction assembly, which is, in turn, required for *apical-basal polarity* [119].
	← Ind	J_bcatenin	Formation of adherens junctions is a prerequisite for tight junction assembly, which is, in turn, required for *apical-basal polarity* [119].
	← Ind	J_acatenin	Formation of adherens junctions is a prerequisite for tight junction assembly, which is, in turn, required for *apical-basal polarity* [119].
	← Ind	Ecadherin _mRNA_H	Formation of adherens junctions in high concentration around the cell is required for *apical-basal polarity* [119], and thus aided by high *E-cadherin* protein expression.
	⊢ Ind	Horizontal _Pol	Horizontal polarization and apical-basal (vertical) polarization are mutually exclusive; cells must first lose the asymmetry between their leading and trailing edge in order to establish a ring of adherens and tight junctions.
N_bcatenin	**N_bcatenin** = (not **Casp3**) and (not(**ApicalBasal_Pol** and **GSK3**))		

Table S1h: CIP module

	TF		When released from cell-cell junctions, *β-catenin* localizes to the nucleus and induces genes that promote proliferation and EMT [120].
	⊢ Loc	ApicalBasal _Pol	Junctional *E-cadherins* recruits/sequesters *β-catenin* to adherens junctions and block *β-catenin* nuclear localization [92]. Here we assume that cells able to form a ring of adherens junctions and establish apical-basal polarity lack nuclear *β-catenin*.
	⊢ Lysis	Casp3	Active Caspase 3 cleaves *β-catenin* into several fragments that lose their transcriptional activity and become localized to the cytoplasm [93].
	⊢ Deg	GSK3	The cytoplasmic pool of *β-catenin* not tied to junctions is highly unstable due to multiple phosphorylations promoting its proteasome-mediated degradation. This phosphorylations is maintained by the "*β-catenin* Destruction Complex" composed of the tumor suppressor *APC*, the scaffolding protein *Axin*, and the serine/threonine kinases *GSK3β* and *CK1* (casein kinase 1, which primes *GSK3*). When *GSK3* is inhibited, unphosphorylated *β-catenin* accumulates, translocates to the nucleus, and promotes transcription [120].
Mst1_2	**Mst1_2 = ApicalBasal_Pol**		
	K		In cells that establish apical-basal cell polarity, *Mst1* and *2* activate the Hippo pathway by phosphorylating *Lats1/2* kinases to promote *YAP/TAZ* inhibition [121, 122, 123].
	← Ind	ApicalBasal _Pol	Activation of the Hippo pathway by *Mst1/2* requires apical-basal cell polarity [123].
Lats1_2	**Lats1_2 = Mst1_2** and **Merlin**		
	K		*Mst1/2* activate *Lats1/2* kinases by phosphorylation, aided by their mutual binding to *Merlin*.
	← P	Mst1_2	*Mst1/2* phosphorylate and activate *Lats 1 / 2* kinases to promote *YAP/TAZ* inhibition [121, 122].
	← BLoc	Merlin	*Merlin* binds to *Lats1/2* and recruits it to the plasma membrane near adherens and tight junctions, where *Mst1/2* can phosphorylate it [112].
AMOT	**AMOT = Lats1_2** and **Merlin**		
	Adap		In our model, *AMOT* = ON represents phosphorylated and tight junction localized *AMOT*, which requires *Merlin* binding and *Lats1/2* mediated phosphorylation [124, 125].
	← P	Lats1_2	*Lats1/2* kinases phosphorylate the N-terminal regions of *Amot*, disrupting its interaction with F-actin [126]. As tight junction localized *AMOT* aids Hippo signaling whereas F-actin bound *AMOT* hinders it [124], *AMOT* = ON in our model represents the phosphorylated, TJ-bound protein.

Table S1h: CIP module

	$\leftarrow$ BLoc	Merlin	*Merlin* binds to *AMOT* proteins and sequesters them to tight junctions [126], shifting its activity from cytoplasmic (where it binds *F-actin* and blocks the *Rac1* inhibitor *Rish1*) to junctional (where it forms a scaffold for Hippo signaling) [125].
miR_29c	**miR_29c = YAP**		
	miR		*YAP* induces the expression of microRNA *miR-29c* to target *PTEN* for degradation [127].
	$\leftarrow$ TR	YAP	*YAP* is a direct inducer of *miR-29c* [127].
PTEN_c	**PTEN_c** = (not **miR_29c**) and ((**S6K** and (not(**ERK** and **GSK3**))) or ((not **ERK**) and (not **GSK3**)))		
	Ph		Cellular *PTEN* is a tumor supressor phosphatase that reverses PIP2 $\rightarrow$ PIP3 conversion carried out by *PI3K*, and thus supresses *PI3K / AKT* signaling [128]. The combinatorial effect of the distinct *PTEN* regulators included below is not well documented. We chose to model cytoplasmic *PTEN* availability as ON in the absence of *miR-29c* [127]. In addition, we combined the positive and negative effects of *S6K*, *ERK* and *GSK3* by assuming that *PTEN* is blocked by the joint action of *ERK* and *GSK3* in the presence of *S6K*, and by either inhibitor in its absence.
	$\dashv$ Ind	miR_29c	*YAP* induces transcription of *miR-29*, which in turn binds to *PTEN mRNA* to block its translation [127].
	$\dashv$ TR	ERK	*ERK* activation suppresses *PTEN mRNA* and protein expression [129, 130].
	$\dashv$ P	GSK3	*GSK3* phosphorylates *PTEN* on Thr366 which leads to destabilization of the *PTEN* protein [131].
	$\leftarrow$ P	S6K	*S6K* phosphorylates *PTEN*, which leads to *PTEN* deubiquitination and export from the nucleus to the cytoplasm [132].

Table S1i: Migration module

Target Node	Node Gate Node Type Link Type	 Node Description Input Node	 Link Description
Merlin	**Merlin** = ((**J_bcatenin** and **J_acatenin**) and (not **PAK1**)) and (not **AKT_H**)		
	Prot		*Merlin* is functionally localized and able to mediate Hippo signaling when recruited by junctional β- and α-*catenin*, and not phosphorylated by high *AKT1*. Since the *AKT_B* node in our model represents basal *AKT* activity which co-occurs with *Merlin*-mediated contact inhibition, we choose the peak *AKT_H* node to mark the level of *AKT* signaling required to block *Merlin*.

Table S1i: Migration module

⊣ P	AKT_H	*Akt* directly binds to and phosphorylates *Merlin* at Thr230 and Ser315, blocking its ability to bind its regular partners and promoting its degradation [133].
← Loc	J_bcatenin	*Merlin* binds to *β-catenin* at adherens junctions, and disruption of *β-catenin* expression recoiples cell density sensing from Hippo signaling downstream *Merlin* [134].
← BLoc	J_acatenin	*Merlin* binds to *α-catenin* to localize to adherens junctions, where it plays a role in their maturation, links AJ formation and the *Par3* polarity complex, and orchestrates Hippo signaling [134, 135].
⊣ P	PAK1	*Pak1* can directly phosphorylate *Merlin* at Ser518 [136]. This phosphorylation prevents it from binding to /textitAMOT and *Lats1/2* [137], and thus carrying out its contact inhibitory function.

IQGAP1_LeadingE

IQGAP1_LeadingE = ((not **CellDensity_High**) and **FocalAdhesions**) and ((**Horizontal_Pol** or **Rac1**) or **Grb2**)

Adap		In our model, *IQGAP1_LeadingE* = ON represents *IQGAP1* localized near the leading edge of a horizontally polarized cell, where it links focal adhesion-mediated and *RTK*-mediated signaling [99]. Its recruitment is sustained by well-established horizontal polarity, or induced by *Rac1* [138] or *RTK-Grb2* binding [13, 139, 140].
⊣ Ind	CellDensity_High	*IQGAP1* localization to the leading edge is blocked by high cell density that leaves no free edge.
← ComplProc	FocalAdhesions	*IQGAP1* interacts with focal adhesion proteins and tyrosine kinase receptors to link focal adhesion and *RTK* signaling. It is thus enriched at the leading edge by increased active FA formation [99].
← ComplProc	Horizontal_Pol	*IQGAP1* localization to the leading edge is reinforced by horizontal polarization and the stabilization of a leading edge [99, 141].
← Compl	Rac1	Active *Rac1* forms a complex with *IQGAP1* and *CLIP-170* and recruits both to the base of the leading edge, where their aid cytoskeletal reorganization, horizontal polarization and directed migration [138].
← BLoc	Grb2	*Grb2* bound to active *RTK* binds and recruits *IQGAP1*, aiding its enrichment at the leading edge where the concentration of active *RTKs* is generally higher [13, 139, 140].

Horizontal_Pol

Horizontal_Pol = (((((not **ApicalBasal_Pol**) and **ECM**) and **IQGAP1_LeadingE**) and **FocalAdhesions**) and **TAZ**) and **FAK**

MSt		For cells to establish and maintain horizontal polarization, our model requires the lack of apical-basal polarization, the presence of an ECM, as well as asymmetric IQGAP1 localization [142], focal adhesions and spreading (FAK [142, 143] and TAZ [101]).

Table S1i: Migration module

⊢ Ind	ApicalBasal _Pol	Apical-basal and horizontal polarization are mutually exclusive; cells must first lose their textitapical-basal polarity before they are able to establish horizontal polarization.
← Ind	ECM	Horizontal polarization requires a leading edge with lamellipodia and a trailing edge linked to stress fibers; both of which require adhesions to an ECM.
← Per	IQGAP1 _LeadingE	Localization of *IQGAP1* to the leading edge is required for the establishment of horizontal polarization. Together with the adenomatous polyposis coli (*APC*) protein that is also recruited to the leading edge by active *Rac1* and *Cdc42*, *IQGAP1* links the actin cytoskeleton to microtubule dynamics to establish cell polarization [142].
← Loc	FocalAdhesions	Horizontal polarization requires a leading edge with lamellipodia and a trailing edge linked to stress fibers, both of which depend on *Focal Adhesions* linked to the actin cytoskeleton.
← Ind	FAK	*FAK* activation at nascent adhesions at the leading edge is required for ongoing cell spreading, which is a prerequisite of ongoing *FA* maturation and maintenance of an active leading edge [142, 143].
← Ind	TAZ	*TAZ*-null cells lose their ability to spread on the ECM, indicating that *TAZ* transcriptional activity is required for the establishment of horizontal polarization [101]. (This is in contrast to *YAP*-null cells, which cannot even form *focal adhesions*.)
Rac1	**Rac1** = (not **Casp3**) and ((((**FocalAdhesions** and **Necl5**) and **Horizontal_Pol**) and **TRIO**) and (((not(**miR_200** and **miR_34**)) and (not((**Merlin** and **Nectin3**) and **J_Ecadherin**))) or **Stiff_ECM**))	
GTPa		Full *Rac1* activation in our model requires the absence of *caspase 3*, as well as horizontal polarization on a stiff ECM, Focal Adhesion formation, *Necl-5* leading edge localization and *TRIO* expression. In addition, on soft ECM *Rac1* activity is inhibited by the presence of *miR-200* [144] and *miR-34* [145], as well as the cooperative action of *Merlin*, *Nectin3* and *E-cadherin* at adherens and tight junctions [146, 125].
← Per	FocalAdhesions	*Rac1* activated at *focal adhesions* by *FAK* is enhanced by force generation supported by stiff ECM, leading to increased intracellular stiffness [147].
⊢ Loc	Necl5	*Necl-5* associates with integrins at the leading edge, where it promotes the activation of *Rac1* and *Cdc42*. *Necl-5* is required for serum-and *PDGF*-induced cell motility cell motility, an effect that does not require Nectin-3 binding on neighboring cells [148].
← Per	Horizontal _Pol	Growth of the microtubule network at leading-edge lamellipodia activates *Rac1* to drive local actin polymerization and further lamellipodial protrusions, thus supporting the maintenance of horizontal polarization [149].

Table S1i: Migration module

	← GEF	TRIO	*TRIO* is a GEF that controls *Rac1* activation during migration [107] as well as proliferation [150].
	← Per	Stiff_ECM	*Rac1* activated at *focal adhesions* by *FAK* is enhanced by force generation supported by stiff ECM, leading to increased intracellular stiffness [147].
	⊢ RNAi	miR_200	*miR-200b/c-3p* represses *Rac1* mRNA by targeting its 3' UTR [144].
	⊢ Ind	miR_34	Though *miR-34* does not appear to directly target *Rac1* mRNA [151], its overexpression blocks GTP-bound (active) *Rac1* [145].
	← Ind	Merlin	A protein complex that includes *Merlin* sequesters *Angiomotin* to tight junctions, releasing it from binding the *Rac1*-inhibitor *Rich1* [125].
	⊢ Compl	Nectin3	During initial cell-cell contact and adherens junciton initiation, cadherins and nectins cooperate to briefly induce, but then rapidly suppress Rac1 [146].
	⊢ Compl	J_Ecadherin	During initial cell-cell contact and adherens junciton initiation, cadherins and nectins cooperate to briefly induce, but then rapidly suppress Rac1 [146].
	⊢ Lysis	Casp3	Caspase 3 cleaves *Rac1* at two sites, resulting in the inactivation of its GTPase activity and *PAK1* binding [152].
PAK1	**PAK1 = Rac1**		
	K		The *p21*-Activated kinase 1 *PAK1*, a serine-threonine kinase interacts with the Rho GTPases *RAC1* and *CDC42* to drive migration, survival, cell cycle, EMT, stress response and inflammation [153]. It is activated by *Rac1*, which binds to *PAK1* and stimulates its kinase activity [154].
	← Compl	Rac1	*Rac1* binds to *PAK1* and stimulates its kinase activity [154].
Fast_Migration	**Fast_Migration** = ((**Horizontal_Pol** and **Stress_Fibers**) and **FocalAdhesions**) and **PAK1**		
	MSt		In our model, the *Fast_Migration* node represents sustained mesenchymal migration of a polarized cell. This requires horizontal polarization, stress fiber maintenance, focal adhesion formation and the activity of *PAK1* kinase [155, 156].
	← Ind	Horizontal_Pol	Directed mesenchymal style migration requires *horizontal cell polarization* with a well defined leading and trailing edge [155].
	← Ind	Stress_Fibers	Mesenchymal style migration requires force generation via stress fibers anchored by *focal adhesions* [155].
	← Ind	FocalAdhesions	Mesenchymal style migration requires force generation via stress fibers anchored by *focal adhesions* [155].

Table S1i: Migration module

← ComplProc	PAK1	Active *PAK1* coordinates a series of cytoskeletal changes at the leading edge that are required for migration and invasion. These include: a) inhibition of myosin light chain kinase in order to decrease contractility if the leading lamellipodium and loss of established actin stress fibers and very strong *focal adhesions* at the leading edge; b) retraction of protrusions and the cell body at the sides and trailing edge with no active *PAK1*; c) suppressing actin filament turnover and promoting leading edge stabilization; d) promote membrane ruffle formation [155, 156].

Table S1j: EMT module

Target Node	Node Gate Node Type Link Type	 Node Description Input Node	 Link Description
SNAI1	**SNAI1** = (((((**ZEB1_H** and **ZEB1**) and (not **miR_34**)) and (not **GSK3**)) or ((**NfkB** and (**ZEB1_H** or **ZEB1**)) and (not(**miR_34** and **GSK3**)))) or (((**NfkB** or **PAK1**) and **ZEB1_H**) and **ZEB1**)) or (**PAK1** and (((not **GSK3**) or **NfkB**) or ((**ZEB1_H** or **ZEB1**) and (not **miR_34**))))		
	TF		
	← TR	ZEB1	*ZEB1* is a direct transcriptional activator of *SNAI1* [157, 158].
	← TR	ZEB1_H	*ZEB1* is a direct transcriptional activator of *SNAI1* [157, 158].
	⊢ RNAi	miR_34	*SNAI1* mRNA is a direct target of *miR-34* suppression [159].
	⊢ Deg	GSK3	*GSK3* both degrades and prevents the transcription of *SNAI1* [160].
	← TR	NfkB	The transcription factor *NF-κB* promotes the expression of *SNAI1* [161], and *NF-κB* inhibition can lower *SNAI1* expression [161].
	← PLoc	PAK1	*PAK1* phosphorylation of *SNAI1* activates and localizes *SNAI1* the nucleus [162].
LEF1	**LEF1** = ((**ZEB1** and (not **miR_200**)) or **ZEB1_H**) or **NfkB**		
	TF		Lymphoid enhancer-binding factor 1, or *LEF1* is a high-mobility group transcription factor and mediator of *Wnt/β-catenin* signaling. In addition to promotong proliferation, *LEF1* helps induce EMT by activating the transcription *SNAI2* and *ZEB1* [163]. It is induced by *NF-κB* [164], its transcriptional potency is boosted by *ZEB1* [165], and it is targeted for degradation by *miR-200*.
	← Compl	ZEB1	*ZEB1* can bind to and significantly boost *LEF1*-mediated transcription [165].

Table S1j: EMT module

	← Compl	ZEB1_H	*ZEB1* can bind to and significantly boost *LEF1*-mediated transcription [165].
	⊢ Ind	miR_200	*miR-200a-3p* is an indirect repressor of *LEF1*, as it limiting basal *Pitx2* and *β-catenin* complexes from inducing *LEF1* transcription [166]. Here we assume that medium *ZEB1* availability can aid *LEF1*-mediated transcription if *miR-200* is repressed, while high levels of *ZEB1* can override *miR-200*.
	← TR	NfkB	*LEF1* is a direct transcriptipnal target of *NF-κB* [164].
Twist	**Twist** = (not **Casp3**) and (**SNAI1** and (**NfkB** or (not **miR_34**)))		
	TF		
	← TR	NfkB	Transcription of *Twist* is induced by *NF-κB* [167].
	← Ind	SNAI1	*SNAI1* is required a rapid inrease in *Twist* protein levels, and aids its subsequent transcription in response to *TGFβ* [168]. In addition, *SNAI1* potentiates *Twist*-mediated enhancer activation [169].
	⊢ RNAi	miR_34	
	⊢ Lysis	Casp3	*Twist* is a direct proteolytic target of *Caspase 3* [170].
SNAI2	**SNAI2** = **Twist** and ((**SNAI2** or **N_bcatenin**) or (**N_bcatenin_H** and **LEF1**))		
	TF		*SNAI2*, also known as *Slug*, is a prototypical EMT transcription factor that regulates tissue development and tumorigenesis [171]. It is induced / maintained in mesenhymal cells by *Twist* [172], *β-catenin* [173, 171], *LEF1* [174] as well as positive auto-regulation [175].
	← TR	Twist	*Twist* is a direct transcriptional inducer of *SNAI2* [172].
	← TR	LEF1	*LEF1* is a direct transcriptional inducer of *SNAI2* [174].
	← TR	N_bcatenin	The *Wnt/β-catenin* pathway promotes *SNAI2* transcription through nuclear *β-catenin* [173, 171].
	← TR	N_bcatenin_H	The *Wnt/β-catenin* pathway promotes *SNAI2* transcription through nuclear *β-catenin* [173, 171].
	← TR	SNAI2	*SNAI2* is able to bind to its own promoter and induce transcription of its own mRNA [175].
ZEB1	**ZEB1** = **SNAI2** or (**b_catenin_TCF4** and (not **miR_200**))		

Table S1j: EMT module

	TF		Zinc finger E-box binding homeobox 1 or *ZEB1* is one of the core regulators of the EMT transcriptional switch [176]. It is induced by *SNAI2* [177] and nuclear *β-catenin/TCF4* [178], while the epithelial microRNA *miR-200* targets its mRNA for destruction [179, 180]. As *ZEB1* has two distinct activation levels in hybrid E/M cells vs fully mesenchynmal ones [181, 182, 183], we modeled *ZEB1* activity with two nodes; this one represents at least medium *ZEB1* activity (characteristic of hybrid E/M cells and compatible with ongoing *miR-200* expression), and the *ZEB1_H* node representing maximal *ZEB1* activation seen in fully mesenchymal cells.
	← TR	SNAI2	*SNAI2* promotes *ZEB1* transcription [177].
	← TR	b_catenin _TCF4	Nuclear *β-catenin/TCF4* are direct transcriptional inducers of the *ZEB1* promoter [178].
	⊢ RNAi	miR_200	*miR_200* mRNA expression of *ZEB1* by targeting its mRNA for destruction [184, 179, 180].
N_bcatenin _H	**N_bcatenin_H** = (((**N_bcatenin** and (not **miR_34**)) and (not **J_acatenin**)) and (not(**miR_200** and **GSK3**))) and (not((**CyclinE** or **CyclinA**) and **GSK3**))		
	TF		The *N_bcatenin_H* node represents maximal nuclear *β-catenin* accumulation. This requires *N_bcatenin* = ON, a lack of *miR-34*, either complete absence of junctions (*J_acatenin* = OFF), and the lack of joint repression *GSK3* and either *miR-200* or *CyclinE/A*-bound *Cdk2*.
	← Per	N_bcatenin	Reaching the *N_bcatenin_H* = ON state requires *N_bcatenin* = ON first.
	⊢ RNAi	miR_34	*β-catenin*'s 3' UTR is a direct *miR-34* target [185].
	⊢ Loc	J_acatenin	Junctional *E-cadherins* recruits/sequesters *β-catenin* to adherens junctions and block *β-catenin* nuclear localization [92]. We assume that cells unable to form any adherens junctions have high nuclear *β-catenin*.
	⊢ Deg	GSK3	When *GSK3* is inhibited, unphosphorylated *β-catenin* accumulates, translocates to the nucleus, and promotes transcription [120].
	⊢ RNAi	miR_200	*β-catenin*'s 3' UTR is a direct *miR-200a* target [186].
	⊢ P	CyclinE	*cyclin E/Cdk2* phosphorylate *β-catenin* on Ser33, Ser37, Thr41, and Ser45, promoting its rapid proteasomal degradation [187].
	⊢ P	CyclinA	*cyclin A/Cdk2* phosphorylate *β-catenin* , promoting its rapid degradation [187].
ZEB1_H	**ZEB1_H** = **ZEB1** and ((**N_bcatenin_H** and **LEF1**) and (**SNAI2** or (not **miR_200**)))		

Table S1j: EMT module

	TF		The *ZEB1_H* node represents maximal *ZEB1* activation seen in fully mesenchymal cells [181, 182, 183]. In our model this requires medium *ZEB1*, as well as high nuclear *β-catenin* [178], *LEF1* [188], and either *SNAI2* [177] or the absence of *miR-200* [179, 180].
		← Per	ZEB1	As the *ZEB1* node represents moderate levels of this trascription factor, *ZEB1_H* = ON requires *ZEB1* = ON.
		← TR	N_bcatenin_H	Nuclear *β-catenin/TCF4* are direct transcriptional inducers of the *ZEB1* promoter [178]. We assume that high levels of nuclear *β-catenin* are required for turning on the *ZEB1_H* node.
		← Ind	LEF1	*LEF1* overexpression lead to a substantial increase in *ZEB1*, indicating that elevated levels of *LEF1* can help push *ZEB1* into its mesenchymal-specific high expression range (*LEF1_H* node) [188].
		← TR	SNAI2	*SNAI2* promotes *ZEB1* transcription [177].
		⊢ RNAi	miR_200	*miR-200* reduces mRNA expression of *ZEB1* by targeting its mRNA for destruction [184, 179, 180].
b_catenin_TCF4	**b_catenin_TCF4** = (**N_bcatenin_H** and **SNAI1**) and **SNAI2**			
	PC		The *b_catenin_TCF4* node represents saturating levels of active nuclear *β-catenin/TCF4* transcriptional activity. In addition to the influences required to accumulate high nuclear *β-catenin*, this node's ON state also requires *SNAI1* and *SNAI2* expression, as both factors promote the formation of active *β-catenin/TCF4* transcriptional complexes [189].
		← Ind	SNAI1	*SNAI1/2* promote the formation of active *β-catenin/TCF4* transcriptional complexes [189].
		← Ind	SNAI2	*SNAI1/2* promote the formation of active *β-catenin/TCF4* transcriptional complexes [189].
		← Compl	N_bcatenin_H	Reaching saturating levels of active nuclear *β-catenin/TCF4* complex formation requires maximal nuclear *β-catenin* accumularion (*N_bcatenin_H* = ON).
miR_34	**miR_34** = (not **SNAI1**) or (not(**ZEB1** or **ZEB1_H**))			
	miR		*miR-34* is an microRNA expressed in epithelial cells and central to blocking the accumulation of EMT-initiating transcription factors such as *SNAI1* and *β-catenin* [190]. *SNAI1*, together with *ZEB1*, feed back to repress *miR-34* expression in mesenhymal and hybrid E/M cells [191].
		⊢ TR	SNAI1	*SNAI1* is a direct inhibitor of *miR-34* transcription [191].
		⊢ TR	ZEB1	*ZEB1* is a direct inhibitor of *miR-34* transcription [191].
		⊢ TR	ZEB1_H	*ZEB1* is a direct inhibitor of *miR-34* transcription [191].

Table S1j: EMT module

miR_200	**miR_200** = **p21** or ((not((**Twist** and **ZEB1_H**) and **SNAI1**)) and (not(((**Twist** and **SNAI1**) and **ZEB1**) and (not(**miR_200** or **c_Myb**)))))		
	miR		The *miR-200* node represents microRNA family expressed in epithelial cells and central to blocking EMT transcription factors [192]. Its levels are increaased by *p21* [193], it is directly induced by *c-Myb* [75] and repressed by *ZEB1* [194, 195]. This repression is indirectly supported by *SNAI1* [196, 197] and *Twist* [198]. Here we assume that in addition to the absence of *p21* and the aid of *SNAI1* and *Twist*, high levels of *ZEB1* (*ZEB_H* = ON) are required to silence the active *miR-200* promoter. In contrast, medium *ZEB1* can maintain repression as long as *miR-200* is silenced and its inducer *c-Myb* is off.
		← Ind	p21	*p21* knockdown downregulates several EMT-blockign miRNAs, including *miR-200a*, *miR-200b*, *miR-200c* and the *miR-183-96-182* cluster. This inhibits EMT, migration and invasion [193]. While it is unclear if *p21* is a direct repressor of the *miR-200* cluster, it was shown to bind *ZEB1* and inhibit its transcriptipnal effets, relieving its ability to repress the *miR-183-96-182* cluster [193]. As this cluster, not explicitly accounted for in our model, further inhibits *ZEB1* expression [193], it is possible that *p21* increases *miR-200* levels indirectly via this cluster, directly by blocking *ZEB1*-mediated repression, or both.
		⊣ TR	ZEB1_H	*ZEB1* is a direct transcriptional repressor of *miR-200* expression [194, 195].
		⊣ TR	ZEB1	*ZEB1* is a direct transcriptional repressor of *miR-200* expression [194, 195].
		⊣ Ind	SNAI1	*SNAI1* induction reduces the expression of *miR-200* [196, 197].
		⊣ Ind	Twist	*Twist* upregulation is required to maintain high levels of *ZEB1* (*Twist* is a direct enhancer of *ZEB1*) [198]. Thus, we assume that *ZEB1* and *SNAI1* cannot fully repress the *miR-200* cluster in the absence of *Twist*. In addition, overexpression of *Twist* resulted in DNA methylation of the *miR-200* locus, though this effect is likely the indirect result of *ZEB1*-mediated repression [199].
		← Epi	miR_200	As the *miR-200* promoter is subject of DNA methylaiton and epigenetic silencing during EMT [199], we assume that it is more difficult to turn off than to maintain its silenced state.
		← TR	c_Myb	The proto-oncogene *c-Myb* induces the expression of the *miR-200* family, unless the locus is silenced by DNA methylation [75].
Ecadherin _mRNA	**Ecadherin_mRNA** = not((((**ZEB1_H** and **ZEB1**) and **SNAI1**) and **SNAI2**) and **Twist**)			

Table S1j: EMT module

	mRNA		The *Ecadherin_mRNA* represents basal *E-cadherin* expression, required to make at least some adherens juncitons with neighbors. This basal expression is only blocked during full EMT by the joint action of *ZEB1* [200], *SNAI1* [201, 184, 191], *SNAI2* [201, 202, 184], and *Twist* [203, 191].
	⊢ TR	ZEB1_H	*ZEB1* is a direct transcriptional inhibitor of *E-cadherin* [200], either in partnership with its co-repressor *CtBP* [204], or by binding to the SWI/SNF chromatin-remodeling protein *BRG1* [205].
	⊢ TR	ZEB1	*ZEB1* is a direct transcriptional inhibitor of *E-cadherin* [200], either in partnership with its co-repressor *CtBP* [204], or by binding to the SWI/SNF chromatin-remodeling protein *BRG1* [205].
	⊢ TR	SNAI1	*SNAI1* is a direct transcriptional inhibitor of *E-cadherin* [201, 184, 191].
	⊢ TR	SNAI2	*SNAI2* is a direct transcriptional inhibitor of *E-cadherin* transcription [201, 202, 184].
	⊢ TR	Twist	*Twist* is a direct transcriptional inhibitor of *E-cadherin* transcription [203, 191].

Table S1k: Restriction_SW module

Target Node	Node Gate Node Type Link Type	Node Description Input Node	Link Description
p21	**p21** = (**p21_mRNA** and (not **Casp3**)) and (not **CyclinE**)		
	Prot		In this model, the *p21* node corresponds to nuclear p21 in cells with relatively high basal *p21* activity. *p21* activity and or localization can be lowered by loss of *FoxO* mediated transcription (see $p21_{mRNA}$ node) and via feedback from *Cyclin E/Cdk2* [206].
	← TL	p21_mRNA	*p21* protein activity requires the presence of *p21* transcription.
	⊢ Deg	CyclinE	*p21* and *Cyclin E/Cdk2* form a positive (double-negative) feedback loop in which *Cyclin E/Cdk2* activates the *SCF/Skp2* complex responsible for the degradation of *Cyclin E/Cdk2*-bound, phosphorylated *p21* [207]. *p21*, in turn, not only blocks *Cyclin E/Cdk2* activity, but it also inhibits *Cyclin D1*. Thus, *p21* interferes with the mitogen signal that turns on *Cyclin E* in the first place. In quiescent cells with high basal *p21* levels, this positive feedback renders cell cycle entry stochastic [206].
	⊢ Lysis	Casp3	*Caspase 3* cleaves and deactivates *p21* [208].
pRB	**pRB** = (((not **Casp3**) and (not **CyclinD1**)) and (not **CyclinA**)) and (**p27Kip1** or (not **CyclinE**))		

Table S1k: Restriction_SW module

TF		*pRB* is active in the absence of *Caspase 3*, *Cyclin D1*, *Cyclin A*, and *Cyclin E*. In addition, *pRB* maintains its activity when active $p27^{Kip1}$ counteracts the effects of *Cyclin E* [209, 210, 211, 212].
	← ComplProc	p27Kip1	Active $p27^{Kip1}$ can counteract the inhibitory effects of active *CyclinE/Cdk2* complexes [209].
	⊢ P	CyclinD1	*Cyclin D1/Cdk4,6* complexes bind and phosphorylate *RB*, inhibiting its activity [213, 214, 211].
	⊢ P	CyclinE	*Cyclin E/Cdk2* complexes bind and phosphorylate *RB*, inhibiting its activity [215, 211].
	⊢ P	CyclinA	*Cyclin A/Cdk1,2* complexes phosphorylate and deactivate *RB* [210].
	⊢ Lysis	Casp3	*Caspase 3* cleaves *RB*, generating fragments that do not associate with *E2F1*, rendering *RB* inactive [216].
p27Kip1		**p27Kip1** = (((not **Casp3**) and (not **CyclinD1**)) and (not(**Cdk1** and **CyclinB**))) and ((((not((**CyclinA** and **Necl5**) and **CyclinE**)) and (**FoxO3** and **FoxO1**)) or (((not **CyclinA**) or (not(**Necl5** or **CyclinE**))) and (**FoxO3** or **FoxO1**))) or ((not **CyclinA**) and (not(**Necl5** and **CyclinE**))))	
		Active $p27^{Kip1}$ is cleaved by *Caspase 3* and inhibited (sequestered) by *Cyclin D1/Cdk4,6* [209] or *Cyclin B/Cdk1* [217]. In addition, maintenance of $p27^{Kip1}$ requires one or both *FoxO* factors when sequestered by *Cyclin E/Cdk2* (one *FoxO* factor) or *Cyclin A/Cdk2* (both *FoxO* factors), but it cannot keep pace with the simultaneous activity of *Cyclin E/Cdk2* and *Cyclin A/Cdk2* [218].
	← TR	FoxO3	*FoxO* factors are direct inducers of $p27^{Kip1}$ expression [219].
	← TR	FoxO1	*FoxO* factors are direct inducers of $p27^{Kip1}$ expression [219].
	⊢ TR	Necl5	*Necl5* downregulates the transcription of *p27Kip1* in response to growth factor stimulation [220].
	⊢ IBind	CyclinD1	Active *Cyclin D/Cdk4,6* complexes competitively bind to *p27Kip1* and progressively inhibit its ability to keep *Cyclin-E/Cdk2* inactive, thereby inducing cdk2 activity and cell-cycle progression [209].
	⊢ Deg	CyclinE	Active *Cyclin-E/Cdk2* phosphorylate *p27Kip1* at threonine 187 (Thr187) [221], which marks it for degradation by the SCF^{SKP2} complex at the onset of S-phase [222]. (*Cyclin-E/Cdk2* complexes remain active in the presence of *p27Kip1* and promote its degradation when *Cyclin-A* is also active.)
	⊢ Deg	CyclinA	*Cyclin A/Cdk2* complexes bind and inactivate $p27^{Kip1}$ by sequestration, phosphorylate it, and promote its degradation [223].
	⊢ PLoc	CyclinB	*Cyclin B/Cdk1* complexes phosphorylate $p27^{Kip1}$ [223], and although they do not promote its degradation, phosphorylated $p27^{Kip1}$ is exported from the nuclear compartment and looses its ability to inhibit *Cdk* activity [217].

Table S1k: Restriction_SW module

⊢ PLoc	Cdk1	*Cyclin B/Cdk1* complexes phosphorylate $p27^{Kip1}$ [223], and although they do not promote its degradation, phosphorylated $p27^{Kip1}$ is exported from the nuclear compartment and looses its ability to inhibit *Cdk* activity [217].
⊢ Lysis	Casp3	*Caspase 3* cleaves *p27Kip1* [224]; the cleaved fragments can no longer associate with *Cdk2 / Cyclin* complexes [225].

Myc

Myc = ((**ERK** and **YAP**) or ((**ERK** or **YAP**) and (**eIF4E** and (not **GSK3**)))) or ((**E2F1** and (not **pRB**)) and ((**eIF4E** or **ERK**) or (not **GSK3**)))

TF

Myc activity is turned on by stabilization of the protein via *ERK* phosphorylation, aided by *YAP*-mediated transcription [226, 227]. To take into account theincrease in translation initiated by *eIF4E* and loss of degradation-promoting phosphorylation when *GSK3β* is off [228], we assumed that they can compensate for the lack of *ERK*, absence of *YAP*. Alternatively, increased transcription by *E2F1* can also promote *Myc* accumulation in the absence of active *pRB* [229], provided that the protein is stabilized by *ERK*, *eIF4E*, or the absence of *GSK3β*.

← P	ERK	Ser-62 phosphorylation by *ERK* increases its half life, leading to *Myc* accumulation [228, 230].
← TR	YAP	*YAP* is a transcriptional inducer of /textitc-Myc [226, 227].
← TR	eIF4E	Increased translational initiation in the presence of activated *eIF4E* leads to an increase in *Myc* protein levels [231].
⊢ P	GSK3	Thr-58 phosphorylation by *GSK-3* promotes *Myc* degradation [228, 232].
⊢ TR	pRB	*E2F1*'s ability to induce *Myc* is blocked by active (hypophosphorylated *pRB*) [233].
← TR	E2F1	*E2F1* binds and activates the *c-Myc* promoter [234, 235].

CyclinD1

CyclinD1 = (not **CHK1**) and (((not **p21**) and ((((not **GSK3**) and **YAP**) and (**Myc** or **E2F1**)) or (((**CyclinD1** and **YAP**) and (**Myc** or **E2F1**)) or (**Myc** and **E2F1**)))) or (((not **pRB**) and **E2F1**) and (((**Myc** and **CyclinD1**) or (**Myc** and (not **GSK3**))) or ((**YAP** and **CyclinD1**) and (not **GSK3**)))))

PC

Ongoing DNA synthesis keeps the *CHK1* kinase active, which inhibits *Cyclin D1*. The precise regulatory logic of *Cyclin D1* as a function of transcriptional control by *Myc* and *E2F1*, combined with the regulation of its protein stability / activity by *GSK3β* / basal *p21* is not known. Here, we assume that in the absence of *p21* (once *p21* levels drop due to growth factor signals and/or *Cdk2* activation), *Cyclin D1* can be activated by *YAP* and either *Myc* or *E2F1* – as long as *GSK3β is OFF*. In the presence of *GSK3β*, we assume that *Cyclin D1* can be induced by the combined action of both *Myc* and *E2F1* [236], but sustained in an ON state by either. In the presence of basal (normal quiescent) levels of *p21*, we assume that *Cyclin D1* transcription requires *E2F1* unencumbered by *pRB*, as well as any two of the following: *Myc*, already active *Cyclin D1*, sustained by *YAP* and not blocked by *GSK3β*.

Table S1k: Restriction_SW module

⊢ P	CHK1	During replication, checkpoint kinases such as *CHK1* (active during normal DNA synthesis) suppress *Cyclin D1* [237], which has a very short half-life ($\sim$ 24 min) [238].
⊢ IBind	p21	$p21^{Cip1}$ is a Cyclin Dependent kinase inhibitor which binds to and blocks the activity of *Cdk2*, *Cdk3*, *Cdk4* and *Cdk6* kinases [239] and thus inhibits *CyclinD1/Cdk4,6* [240].
⊢ P	GSK3	*GSK-3β* phosphorylates *Cyclin D1* on Thr-286, promoting its ubiquitination and degradation [241].
← TR	YAP	*YAP* is a direct transcriptional inducer of *Cyclin D* [242].
← TR	Myc	Extracellular growth signals activate the MAPK pathway, leading to transcriptional activation of *Cyclin D1* by *Myc* [243, 244]. *Myc* overexpression leads to rapid *Cyclin D1* induction and subsequent cell cycle entry [245], while its absence halves *Cyclin D1* levels [246]. In addition, *Myc* induces *Cdk4*, aiding the assembly of active *Cyclin D1 / Cdk4,6* complexes [246, 247].
← TR	E2F1	The *Cyclin D1* promoter is bound by *E2F* factors including *E2F1* [248], and *E2F1* overexpression can increase *Cyclin D1* (though its effects are context-dependent, as *E2F1* overexpression can also lead to apoptosis) [248]. Dominant negative *E2F1* overexpression results in a 2-3 fold decrease in *Cyclin D* expression and *Cyclin D/Cdk4,6* activity [249].
⊢ TR	pRB	*E2F1*'s ability to induce *Cyclin D1* is blocked by active (hypophosphorylated) *RB* protein [250].
← Per	CyclinD1	In order to take into account both production and stability of *Cyclin D1*, we assumed that the presence of active *CyclinD/Cdk2,4* complexes renders transcriptional maintenance of their levels easier.
E2F1	**E2F1** = (not((**CAD** or **CyclinA**) or **pRB**)) and ((**YAP** and (**E2F1** or **Myc**)) or (**E2F1** and **Myc**))	
TF	In the absence of both *CyclinA* and *pRB*, *E2F1* transcription can be induced by *YAP* and *Myc* or maintained by active *E2F1*. *CAD* deactivates *E2F1* as it destroys the cell's DNA.	
← TR	YAP	*YAP* is a direct transcriptional inducer of *E2F1* [251].
⊢ TR	pRB	*RB* binds to *E2F/DP1* complexes and switches their DNA binding activity from activation to repression [250, 252].
← TR	Myc	*Myc* is required for growth-factor mediated induction of *E2F1* [253, 246]. It binds to and remodels the *E2F1* promoter, facilitating *E2F1* transcription [236]. In addition, *Myc* augments protein expression of *E2F1* [254]. Single-cell experiments show that *Myc* is a critical modulator of the amplitude of *E2F* activation [255].

Table S1k: Restriction_SW module

	$\leftarrow$ TR	E2F1	*E2F1* binds to its own promoter and up regulates transcription (as long as *Cyclin D/E* activity blocks *RB-E2F1* binding) [256].
	$\vdash$ P	CyclinA	The phosphorylation of the *E2F1*-binding *DP-1* protein by *Cyclin A*, which binds directly to *E2F-1* (as well as *E2F-2,3*) downregulates *E2F1* transcriptional activity in S phase [257, 258, 259].
	$\vdash$ Deg	CAD	This link from Caspase-activated DNase (*CAD*) to *E2F1* ensures that apoptotic cells settle into an *E2F1*-negative attractor regardless of their initial state. The rationale for this is that *E2F1* cannot maintain its activity if DNA is fragmented.
CyclinE	**CyclinE** = ((**E2F1** and **Cdc6**) and **Pre_RC**) and (not(((**pRB** or **p27Kip1**) or **CHK1**) or **Casp3**))		
	PC		In our model, the ON state of *Cyclin E* represents active *Cyclin E/Cdk2* complexes. Thus, its full activation requires transcription via *E2F1* not blocked by active *pRB*, binding to *Cdc6* and *pre-RC* complexes, and the absence of its inhibitors $p27^{Kip1}$, *CHK1* and *Caspase 3*.
	$\vdash$ TR	pRB	*Cyclin E* transcription by *E2F1* requires the absence of active, un-phosphorylated *RB* [259].
	$\vdash$ IBind	p27Kip1	*p27Kip1* binds to and prevents the activation of *Cyclin E/Cdk2* complexes [209].
	$\leftarrow$ TR	E2F1	*E2F1* is a potent transcriptional activator of *Cyclin E* [260].
	$\leftarrow$ Compl	Cdc6	Chromatin association and full activation of *Cyclin E/Cdk2* requires *Cdc6* [261].
	$\leftarrow$ Compl	Pre_RC	At the G1/S transition, *Cyclin E* is loaded onto chromatin by *pre-RC* complexes (*Cdc6* and *Cdt1* binding), where it is required for *MCM2* loading, origin firing and the start of DNA synthesis [262]. In addition, activation of its partner *Cdk2* by *Cdc6* is contingent on this localization [261].
	$\vdash$ P	CHK1	*Chk1* activation during normal S-phase progression keeps *Cdk2* activity in a physiological range by binding to both *Cdk2* and *Cdc25A*, aiding the loss of *Cyclin E/Cdk1* activity [263].
	$\vdash$ Lysis	Casp3	*Caspase 3* cleaves and deactivates *Cyclin E*, which is then rapidly degraded [264].

Table S1l: Origin_Licensing module

Target Node	Node Gate / Node Type / Link Type	Input Node	Link Description
ORC	**ORC** = **E2F1** or ((**Pre_RC** and **Cdt1**) and **Cdc6**)		

Table S1l: Origin_Licensing module

PC			*ORC* proteins can bind at origins of replication when transcribed by *E2F1* or as part of a fully assembled and licensed *Pre-RC* complex (including active *Cdc6* and *Cdt1*).
	← TR	E2F1	Expression of the *ORC1* gene is regulated by *E2F1* [265].
	← Compl	Cdc6	Availability of stable (unphosphorylated) *Cdc6* in the *Pre-RC* is necessary for the maintenance of licensed origins [266].
	← Compl	Cdt1	Active (unphosphorylated and not geminin-bound) *Cdt1* bound to the *Pre-RC* is necessary for the maintenance of licensed origins [266].
	← Compl	Pre_RC	Licensed but not yet fired replication complexes (*Pre-RC*s containing *ORC*, *Cdc6*, *Cdt1* and inactive *MCM*s) remain stable at sites of replication origin until fired by the activation of the *MCM* helicase [266].
Cdc6			**Cdc6** = ((not **Casp3**) and (not(**f4N_DNA** and **CyclinA**))) and (((**E2F1** and **ORC**) and (not **Plk1**)) or (((**Pre_RC** and **ORC**) and **Cdc6**) and **Cdt1**))
Prot			In our model the *Cdc6* node represents nuclear, chromatin-bound *Cdc6*. Thus, the node is only active during the assembly of pre-replication complexes, or their ongoing presence during DNA replication. *Cdc6* is ON in the absence of *Caspase 3* or *CyclinA / Cdk2* phosphorylation of *Cdc6* in all origins required for the completion of DNA replication (thus, its inhibition by *Cyclin A* also requires 4N DNA). In addition, active *Cdc6* requires either transcription by *E2F1* and recruitment by origin-bound *ORC* proteins in the absence of mitotic *Plk1* or maintenance of *Pre-RCs* by the presence of all of its components.
	← TR	E2F1	Transcription of Cdc6 is directly induced by E2F1 [267].
	← Compl	ORC	*ORC* recruits *Cdc6* to origins of replication [266].
	← Per	Cdc6	Stable (unphosphorylated) *Cdc6* in the *Pre-RC* is necessary for the maintenance of licensed origins [266].
	← Compl	Cdt1	Active (unphosphorylated and not geminin-bound) *Cdt1* bound to the *Pre-RC* is necessary for the maintenance of licensed origins [266].
	← Compl	Pre_RC	Licensed but not yet fired replication complexes (*Pre-RC*s containing *ORC*, *Cdc6*, *Cdt1* and inactive *MCM*s) remain stable and *Cdc6*-bound until fired by the activation of the *MCM* helicase [266].
	⊣ P	Plk1	*Plk1* binds, phosphorylated and strongly recruits Cdc6 to the spindle pole during metaphase, then to the central spindle in anaphase, leading to its exclusion from chromosomes until telophase, when the majority of *Plk1* is degraded by APC/C^{Cdh1} [268].
	⊣ P	CyclinA	Phosphorylation of *CDC6* by *Cyclin A/Cdk2* during DNA replication leads to its re-localization to the cytoplasm [269].

Table S1l: Origin_Licensing module

	⊢ Ind	f4N_DNA	In our model, full deactivation of Cdc6 represents the firing of all ORCs as DNA replication is completed. Thus *Cyclin A*'s inhibitory action takes full effect once the cell reaches 4N DNA content [269].
	⊢ Lysis	Casp3	*Caspase 3* cleaves and deactivates *Cdc6* [270].
Cdt1	**Cdt1** = ((((not **geminin**) and **ORC**) and **Cdc6**) and (not((**CyclinE** and **CyclinA**) and **Cdc25A**))) and ((**Pre_RC** and (**E2F1** or **Myc**)) or (**E2F1** and (**Myc** or (not **pRB**))))		
Prot			Replication-origin bound *Cdt1* requires the absence of *geminin*, the presence of origin-bound *ORC* and *Cdc6*, and the absence of sustained *Cdk2* activity responsible for the firing of all origins during DNA synthesis (modeled as simultaneous *Cyclin E*, *Cyclin A* and *Cdc25A* activity). Bound into a licensed pre-replication complex (*Pre-RC*), *Cdt1* remains stable as long as it is transcribed by *E2F1* [271] or *Myc* [272] (this guarantees that *Pre-RC* complexes cannot persist indefinitely in the absence of de novo transcription). Alternatively, it can be turned on by *E2F1*, aided by *Myc* or the absence of *RB*, and *FoxO3* in cells with 4N DNA.
	⊢ TR	pRB	*E2F1*-mediated transcription of *Cdt1* is blocked by hypophosphorylated (active) *pRB* [271].
	← TR	Myc	*Cdt1* is a direct transcriptional target of the *Myc-Max* complex [272], ensuring its availability for *Pre-RC* formation and maintenance.
	← TR	E2F1	*Cdt1* is a direct transcriptional target of *E2F1* [271], ensuring its availability for *Pre-RC* formation and maintenance.
	⊢ P	CyclinE	Sustained *Cdk2* activity during S-phase (modeled as simultaneous *Cyclin E*, *Cyclin A* and *Cdc25A* activity) is responsible for the firing of all origins required to complete DNA synthesis; it also leads to the phosphorylation and proteasomal degradation of *Cdt1* [266].
	← Compl	ORC	*ORC*-bound origin of replication sites are the point of pre-replication complex assembly, where *Cdt1* is recruited by *ORC*-bound *Cdc6* [266].
	← Compl	Cdc6	*ORC*-bound *Cdc6* recruits *Cdt1* to *pre-RC* complexes [266].
	← Compl	Pre_RC	Licensed but not yet fired replication complexes (*Pre-RC*) remain stable until fired during DNA replication [266].
	⊢ IBind	geminin	*Geminin* binds to *Cdt1* at pre-replication complexes, where it blocks *Cdt1* binding to DNA, sequestering it away from *Pre-RC*s [273].
	⊢ P	Cdc25A	Sustained *Cdk2* activity leads to phosphorylation and degradation of *Cdt1* [266].
	⊢ P	CyclinA	Sustained *Cdk2* activity leads to phosphorylation and degradation of *Cdt1* [266].
Pre_RC	**Pre_RC** = ((**ORC** and **Cdc6**) and **Cdt1**) and (not(**Replication** and **f4N_DNA**))		

Table S1l: Origin_Licensing module

	PC		*Pre-RC* complexes assemble when *ORC*, *Cdc6*, and *Cdt1* are all bound to sites of replication origin along the DNA. The node denoting their licensing turns OFF at the moment of transition from ongoing *Replication* to *f4N_DNA* (it is blocked in the one time-point when both of these nodes are ON).
	← Compl	ORC	*Pre-RC* complexes assemble when *ORC*, *Cdc6*, and *Cdt1* are all bound to sites of replication origin along the DNA [266].
	← Compl	Cdc6	*Pre-RC* complexes assemble when *ORC*, *Cdc6*, and *Cdt1* are all bound to sites of replication origin along the DNA [266].
	← Compl	Cdt1	*Pre-RC* complexes assemble when *ORC*, *Cdc6*, and *Cdt1* are all bound to sites of replication origin along the DNA, leading to the recruitment of the *MCM* helicase [266].
	⊢ Unbind	Replication	*Pre-RC*s fire and fall apart during DNA replication [266].
	⊢ Ind	f4N_DNA	In our model the *Pre-RC* node turns OFF when *Replication* is completed, marked by the time-point when both *Replication* and *f4N_DNA* are ON.
geminin	**geminin** = (**E2F1** and (not **Cdh1**)) and (not(**pAPC** and **Cdc20**))		
	Prot		*Geminin* is present when transcribed by *E2F1* and not targeted for degradation by APC/C^{Cdh1} or APC/C^{Cdc20} [274].
	← TR	E2F1	*Geminin* is a direct transcriptional target of *E2F1* [271].
	⊢ Ubiq	pAPC	*Geminin* is a target of APC/C^{Cdc20} at the metaphase/anaphase transition [274].
	⊢ Ubiq	Cdc20	*Geminin* is a target of APC/C^{Cdc20} at the metaphase/anaphase transition [274].
	⊢ Ubiq	Cdh1	*Geminin* is a target of APC/C^{Cdh1} ubiquitin ligase [275].

Table S1m: Phase_SW module

Target Node	Node Gate / Node Type / Link Type	Node Description / Input Node	Link Description
CyclinA_mRNA	**CyclinA_mRNA** = (not **CAD**) and ((**E2F1** and (not **pRB**)) or **FoxM1**)		
	mRNA		In non-apoptotic cells (no *CAD*), *Cyclin A* is transcribed by *E2F1* in the absence of active *RB* or by *FoxM1*.
	⊢ TR	pRB	Active *RB* blocks *E2F1*'s ability to transcribe *Cyclin A* [276].
	← TR	E2F1	*Cyclin A* is transcriptionally activated by *E2F* factors [259].

Table S1m: Phase_SW module

$\leftarrow$ TR	FoxM1	Depletion of *FoxM1* results in reduced *Cyclin A2* expression (it is not clear whether *FoxM1* is a direct transcriptional inducer of *Cyclin A*) [277, 278, 279, 280].
$\vdash$ Ind	CAD	This link from Caspase-activated DNase (*CAD*) to *Cyclin A* mRNA ensures that apoptotic cells settle into a G0-like attractor regardless of their initial state. The rationale for this is that no mRNA synthesis can be maintained if DNA is fragmented (we only use these links from *CAD* if needed).
Emi1	**Emi1** = ((**E2F1** or (not **pRB**)) or (not **p21**)) and (not(((**Plk1** and **CyclinB**) and **Cdk1**) and (**U_Kinetochores** or **A_Kinetochores**)))	
Prot		Our model allows the sustained presence of *Emi1* protein when it is either actively transcribed by *E2F1* [281, 282] or lacks joint inhibition by *pRB* [282] and *p21* [283]. Degradation of *Emi1* is mediated by *Plk1* and *CyclinB/Cdk1* complexes; initiation of this degradation requires at least temporary co-localization of *Emi1* with *Plk1* at mitotic spindle poles [284].
$\vdash$ Ind	p21	*p21* activation during DNA damage lead to a substantial decrease of *Emi1* levels, not observed in *p21*-null cells [283].
$\vdash$ TR	pRB	Active retinoblastoma protein can block *Emi1* transcription mediated by *E2F1* [282].
$\leftarrow$ TR	E2F1	*Emi1* is a direct transactional target of *E2F1* [281, 282].
$\vdash$ P	Plk1	*Plk1* phosphorylates *Emi1* at mitotic spindle poles, stimulating its β*TrCP* binding and ubiquitination [284].
$\vdash$ Ind	CyclinB	*Cyclin B/Cdk1* enhances the ability of *Plk1* to mediate *Emi1* destruction [284].
$\vdash$ Ind	Cdk1	*Cyclin B/Cdk1* enhances the ability of *Plk1* to mediate *Emi1* destruction [284].
$\vdash$ Ind	U _Kinetochores	As *Plk1*-mediated phosphorylation of *Emi1* occurs at mitotic spindle poles, our model requires ongoing mitosis for this interaction [284].
$\vdash$ Ind	A _Kinetochores	*Plk1* phosphorylates *Emi1* at mitotic spindle poles, stimulating its β*TrCP* binding and ubiquitination [284].
FoxM1	**FoxM1** = (((**Myc** or **YAP**) and **CyclinE**) or ((**CyclinA** and **Cdc25A**) and **Cdc25B**)) or ((**Plk1** and **CyclinB**) and **Cdk1**)	
TF		In our model, *FoxM1* activity requires increased expression by *Myc* [285] or *YAP* [242] and activating phosphorylation by *Cyclin E/Cdk2*. Alternatively, *FoxM1* activity can be sustained by potent *Cdk2 / Cdk1* activity in G2 (supported by *Cdc25A* or *Cdc25B*), or a serial phosphorylation by *Cyclin B/Cdk1* and *Plk1* during mitosis.
$\leftarrow$ TR	YAP	*FoxM1* is a direct transcriptional target of *YAP* [242].
$\leftarrow$ TR	Myc	*FoxM1* is a direct transcriptional target of *c-Myc* [285].

Table S1m: Phase_SW module

← P	CyclinE	*Cyclin E/Cdk2* complexes bind and phosphorylate FoxM1, potently inducing its transcriptional activity, which starts during S-phase [286].
← Compl	Cdc25A	Active *Cdc25A* binds to and enhances the transcriptional activity of *FoxM1*, potentually by bridging FoxM1 and active cyclin-*Cdk2* complexes [287].
← Ind	Cdc25B	*Cdc25B* overexpression can increase *FoxM1*-dependent transcription, likely via aiding *Cdk1* activity [288].
← P	Plk1	*Plk1* binds and phosphorylates *FoxM1*, which activates *FoxM1*-mediated transcription in early mitosis [289].
← P	CyclinA	In addition to *Cyclin E/Cdk2*, *Cyclin A/Cdk2* complexes can also keep *FoxM1* transcriptionally active by phosphorylating its autoinhibitory N-terminal region [290].
← P	CyclinB	*FoxM1* binds *Plk1*, and phosphorylation of two key residues at this binding domain by *Cyclin B/Cdk1* primes it for *Plk1* binding [289].
← P	Cdk1	*FoxM1* binds *Plk1*, and phosphorylation of two key residues at this binding domain by *Cyclin B/Cdk1* primes it for *Plk1* binding [289].
Cdc25A	**Cdc25A** = (((**FoxM1** and **E2F1**) and (not **pRB**)) or ((not **Cdh1**) and (**FoxM1** or (**E2F1** and (not **pRB**))))) and ((((not(**GSK3** or **CHK1**)) or **CyclinE**) or **CyclinA**) or (**CyclinB** and **Cdk1**))	
Ph		As the precise combinatorial regulation of *Cdc25A* throughput the cell cycle is unknown, our model assumes that accumulation of the *Cdc25A* protein requires transcriptional activation by both *E2F1* in the absence of *pRB*, and *FoxM1* to override destruction by APC/C^{Cdh1}. Alternatively, one of the two transcription factors can drive *Cdc25A* accumulation in the absence of APC/C^{Cdh1}. In addition, stabilization of *Cdc25A* either requires the absence of *GSK3β* and *CHK1* (both of which promote its degradation), or stabilization by *Cdk* activity.
⊢ P	GSK3	*GSK3β* phosphorylates *Cdc25A*, promoting its proteolysis [291].
⊢ TR	pRB	Active (hypo-phosphorylated) *pRB* blocks *E2F1*'s ability to drive *Cdc25A* transcription [292, 293].
← TR	E2F1	*E2F1* is a direct transcriptional inducer of *Cdc25A* [292].
← P	CyclinE	*Cdc25A* protein levels are stabilized during S-phase by *CyclinE/Cdk2*-dependent phosphorylation [294].
← TR	FoxM1	*FoxM1* is a direct transcriptional inducer of *Cdc25A* [287].
← P	CyclinA	*Cdc25A* protein levels are stabilized during S and G2 by *Cdk2*-dependent phosphorylation. *Cdk2* first partners with *Cyclin E* [294], then continues to stabilize *Cdc25A* past the point of *Cyclin E* expression by partnering with *Cyclin A* [295].

Table S1m: Phase_SW module

	$\leftarrow$ P	CyclinB	During mitosis, *Cdc25A* is stabilizes by *Cyclin B/Cdk1* phosphorylation, which protects it from the proteasome [296].
	$\leftarrow$ P	Cdk1	During mitosis, *Cdc25A* is stabilizes by *Cyclin B/Cdk1* phosphorylation, which protects it from the proteasome [296].
	$\vdash$ Deg	Cdh1	The APC/C^{Cdh1} complex degrades *Cdc25A* at mitotic exit [297, 298].
	$\vdash$ P	CHK1	*CHK1* phosphorylates *Cdc25A*, promoting its proteolysis and inhibiting its interaction with *Cyclin B/Cdk1* [299].
CyclinA	**CyclinA** = (**CyclinA_mRNA** and (not **pAPC**)) and ((**Cdc25A** and ((not **Cdh1**) or **Emi1**)) or (**CyclinA** and (((not **Cdh1**) and (**Emi1** or (not **UbcH10**))) or (**Emi1** and (not **UbcH10**)))))		
PC	*Cyclin A* activity requires transcription (*Cyclin A* mRNA) and the absence of degradation by phosphorylated (mitotic) *pAPC*. In addition, turning ON inactive *Cyclin A* requires activation of *Cdk2* by *Cdc25A* [300] and the absence / *Emi1*-mediated inhibition of APC/C^{Cdh1}. Once active, *Cyclin A* maintains its activity in the absence of overpowering influences driving its degradation. Namely, *Cyclin A* relies on either *Emi1* or the absence of *UbcH10* for its ability to keep inactive APC/C^{Cdh1} in check. To overpower active APC/C^{Cdh1}, *Cyclin A* requires both *Emi1* and no *UbcH10*. The precise combinatorial regulation of *Cyclin A* is not known; the above logic is consistent with *Cyclin A* activity pattern during cell cycle progression.		
	$\leftarrow$ TL	CyclinA _mRNA	Sustained availability of *Cyclin A* requires ongoing translation from *CyclinA* mRNA.
	$\leftarrow$ Compl	Emi1	*Emi1* binding to *Cdh1* is required to stabilize *Cyclin A* levels at the G1/S transition, allowing *Cyclin A/Cdk2* to block APC/C^{Cdh1} [301, 302, 303].
	$\leftarrow$ DP	Cdc25A	*Cdc25A* promotes active *Cyclin A/Cdk2* complex formation by removing inhibitory phosphorylation of *Cdk2* [300, 304].
	$\leftarrow$ Per	CyclinA	We assume that once activated, *Cyclin A/Cdk2,1* complexes can sustain their activity until *Cyclin A* is degraded.
	$\vdash$ Deg	UbcH10	*Cyclin A* degradation by APC/C^{Cdh1} requires *UbcH10* [305].
	$\vdash$ Deg	pAPC	*Cyclin A* is degraded by the APC/C^{Cdc20} in prometaphase (as soon as the APC/C components are phosphorylated by Cdk1) [306, 307], before the full activation of the complex at SAC passage [308]. In our model, this stage of mitotic APC/C^{Cdc20} activation is represented by *Cdk1*-phosphorylated *APC/C* (*pAPC*).
	$\vdash$ Deg	Cdh1	*Cyclin A* is degraded by APC/C^{Cdh1} in the presence of the *UbcH10* protein [309, 305, 218].
Wee1	**Wee1** = (((not **Casp3**) and (**Replication** or **CHK1**)) and (not(**Cdk1** and **CyclinB**))) and (**CHK1** or (not((**Cdk1** and **CyclinA**) and **Plk1**)))		

Table S1m: Phase_SW module

	K		*Wee1* is active during *Replication*, unless its activity is blocked by *CyclinA/Cdk1* OR *CyclinB/Cdk1* [310].
		⊢ P	Plk1	*Plk1* phosphorylation at S53 promotes *Wee1* degradation [311]. This event is primed by *Cdk1* phosphorylation of *Wee1* at S123 [311]. As the main partner of *Cdk1* in mitosis is *Cyclin B*, we assume that assistance from *Plk1* to block *Wee1* is more relevant when paired with *Cyclin A/Cdk1* complexes.
		⊢ P	CyclinA	*Cyclin A/Cdk1* is a strong inducer of *Wee1* phosphorylation and deactivation [310].
		⊢ P	CyclinB	*Cyclin B/Cdk1* is a strong inducer of *Wee1* phosphorylation and deactivation [310].
		⊢ P	Cdk1	The somatic *Wee1* protein is an order of magnitude more sensitive to *Cdk1* activity than *Cdc25C*. Thus, both *Cyclin A/Cdk1* and *Cyclin B/Cdk1* strongly induce *Wee1* phosphorylation and deactivation [310].
		← ComplProc	Replication	To model the sensitivity of *Wee1* activation to ongoing DNA synthesis even in the absence of damage, our model turns on *Wee1* immediately upon the start of DNA replication and maintains it until both Replication and the checkpoint kinase *Chk1* is OFF [312]. In addition, *Wee1* activity has been implicated in maintaining normal replication fork procession, linking its activity directly to ongoing replication [313].
		← P	CHK1	During DNA replication *Wee1* is activated by the checkpoint kinase *CHK1* [312].
		⊢ Lysis	Casp3	*Caspase 3* cleaves and deactivates *Wee1* [314].
UbcH10	**UbcH10** = (not **Cdh1**) or (**UbcH10** and ((**Cdc20** or **CyclinA**) or **CyclinB**))		
	UbL		The ubiquitin-conjugating enzyme (E2) *UbcH10* is active in the absence of *Cdh1*. Alternatively, active *UbcH10* is maintained in the presence of *Cdh1* when some of its targets are present: *Cdc20* OR *CyclinA* OR *CyclinB* [305].
		← PBind	CyclinA	The presence of APC/C^{Cdh1} substrates, including *Cyclin A*, inhibit the autoubiquitination of *UbcH10* but not its function, thus preserving APC activity [305].
		← PBind	CyclinB	The presence of APC/C^{Cdh1} substrates, including *CyclinB*, inhibit the autoubiquitination of *UbcH10* but not its function, thus preserving APC activity [305].
		← Per	UbcH10	Active *UbcH10* cannot be autoubiquitinated in the presence of APC/C^{Cdh1} substrates and thus remains active [305].
		← PBind	Cdc20	The presence of APC/C^{Cdh1} substrates, including *Cdc20*, inhibit the autoubiquitination of *UbcH10* but not its function, thus preserving APC activity [305].
		⊢ Deg	Cdh1	*UbcH10* is degraded by APC/C^{Cdh1}.
CyclinB	**CyclinB** = (**FoxM1** or (**FoxO3** and **CyclinB**)) and (not(**Cdh1** or (**pAPC** and **Cdc20**)))		

Table S1m: Phase_SW module

	PC		*Cyclin B* node is ON when the concentration of *Cyclin B* proteins is high (does not represent the activity of *CyclinB/Cdk1* complexes). This occurs when *Cyclin B* is transcribed by *FoxM1*, maintained by *FoxO3* transcription, and not undergoing *APC*-mediated degradation by APC/C^{Cdc20} or APC/C^{Cdh1}.
		← TR	FoxO3	*FoxO3* is a direct transcriptional regulator of *Cyclin B*; its activation in G2 helps increase/maintain *Cyclin B* levels [315].
		← TR	FoxM1	*FoxM1* is a direct transcriptional regulator of *Cyclin B1* [280, 316].
		← Per	CyclinB	Here we assume that FoxO3 alone can only maintain, but not independently induce *Cyclin B1* expression.
		⊢ Deg	pAPC	*Cyclin B* is degraded by APC/C^{Cdc20} [309].
		⊢ Deg	Cdc20	*Cyclin B* is degraded by APC/C^{Cdc20} [309].
		⊢ Deg	Cdh1	*Cyclin B* is degraded by APC/C^{Cdh1} [309].
Cdc25B	**Cdc25B** = **FoxM1** and **f4N_DNA**			
	Ph		*Cdc25B* activation requires transcription by *FoxM1*, centrosomal localization, and activation by *Aurora A* kinase on replicated centrosomes.
		← TR	FoxM1	*FoxM1* is an essential inducer or *Cdc25B* [317].
		← Loc	f4N_DNA	*Cdc25B* is localized at centrosomes, where it is activated by *Aurora A* kinase [318]. As *Aurora A* itself is only recruited to duplicated, centrosomes before their separation [319], *Cdc25B* activation requires duplicated centrosomes. As our model does not directly account for centrosome dynamics, we account for this by requiring the completion of S-phase (4N DNA).
Plk1	**Plk1** = ((not **Cdh1**) and (**FoxM1** or **Plk1_H**)) and ((**CyclinB** and **Cdk1**) or ((**CyclinA** and (not **Wee1**)) and **Cdc25A**))			
	K			*Plk1* activity requires the absence of APC/C^{Cdh1}, transcription by *FoxM1*, or high *Plk1* levels transcribed earlier by both *FoxM1* and *FoxO3* (see *Plk1_H* below) [315]. In addition, *Plk1* activation requires phosphorylation by either *CyclinB/Cdk1* during mitosis or *Cyclin A/Cdk2* (aided by lack of *Wee1* and *Cdc25A*) at the G2/M boundary [320].
		← TR	FoxM1	*Plk1* is a direct transcriptional target of *FoxM1* [289].
		← Ind	Cdc25A	As we do not include a separate *Cdk2* node in our model, strong *Cyclin A/Cdk2* activity requires ongoing dephosphorylation of *Cdk2* by *Cdc25A* [321].
		⊢ Ind	Wee1	*Cyclin A*-mediated induction of *Plk1* is blocked by *Wee1* kinase, which specifically inhibits *Cdk2* activity [320].
		← P	CyclinA	*Plk1* activation at the G2/M boundary, before *Cdk1/Cuclin B* complexes are activated, requires active *Cyclin A/Cdk* [320].

Table S1m: Phase_SW module

	← P CyclinB	*Plk1* is activated by *Cyclin B/Cdk1* phosphorylation [322, 323, 324].
	← P Cdk1	*Plk1* is activated by *Cyclin B/Cdk1* phosphorylation [322, 323, 324].
	⊣ Ubiq Cdh1	The majority of *Plk1* is degraded in anaphase by the APC/C^{Cdh1} complex [325].
	← Per Plk1_H	Our model tracks the accumulauton of high-enough levels of *Plk1* to survive APC/C^{Cdh1} mediated destruction into telophase via the *Plk1_H* node. Its ON state represents strong prior *Plk1* activation. Thus, it sustains the *Plk1* node in the absence of *FoxM1*-mediated transcription until *Plk1_H* itself is lost as *Plk1* levels fall.
Cdc25C	**Cdc25C** = (**f4N_DNA** and **Plk1**) and ((**Cdc25B** and (not **CHK1**)) or (**CyclinB** and **Cdk1**))	
	Ph	In our model, *Cdc25C* is active in cells with replicated DNA (see *f4N_DNA* → *Cdc25C* link). Its activation is initiated by a small, initially cytoplasmic pool of *Cyclin B/Cdk1* activated by *Cdc25B* (not directly represented in our model) and further increased by *Cdc25B* itself, which translocates to the nucleus with the aid of *Plk1*. During mitosis, *Plk1* potentiates the ability of *Cyclin B/Cdk1* to maintain *Cdc25C* activity.
	← Ind Cdc25B	*CDC25B* starts the cascade leading to mitotic entry by activating a small centrosomal pool of *Cyclin B/Cdk1*, leading to their nuclear translocation where they trigger the activation of *Cdc25C* and eventually the larger nuclear *Cyclin B/Cdk1* pool [326, 327, 328].
	← P Plk1	In addition, *Plk1* induces nuclear transport of *CDC25B*, where it contributes to the initiation of *Cdk1* activity [329]. During mitosis, *Plk1* helps maintain strong *Cdc25C* activation by phosphorylating it on the same site as *Cyclin B/Cdk1* [330], as indicated by the profound decrease of Cdc25C activity in Plk1-inhibited mitotic cells [323, 331].
	← P CyclinB	*Cyclin B/Cdk1* complexes are potent activators of *Cdc25C*, creating positive feedback that causes switch-like mitotic entry [332, 333].
	← P Cdk1	*Cyclin B/Cdk1* complexes are potent activators of *Cdc25C*, creating positive feedback that causes switch-like mitotic entry [332, 333].
	⊣ P CHK1	*CHK1* phosphorylates *Cdc25C*, leading to its nuclear exclusion, loss of access to its main target, *Cdk1* [334]. In addition, *CHK1* blocks the ability of *Cdc25B* to activate *Cdc25C* at the centrosomes by phosphorylating it and blocking its *Cdk1* activity [335, 336].

Table S1m: Phase_SW module

	← Ind	f4N_DNA	The nature and localization of the signals responsible for the onset and maintenance of *Cdc25C* activity require replicated DNA (*f4N_DNA*) [329, 328]. Namely, *Cdc25C* is initially activated by a small pool of *Cyclin B/Cdk1* (below the ON-threshold of *Cdk1* in our model) which starts our at the replicated centrosome. Moreover, the pool of mitotic *Cdc25C* co-localized with active *Chk1/Cyclin B* is found on condensed chromosomes, again requiring the presence of *f4N_DNA* [334].
Cdk1	**Cdk1** = (**CyclinB** and **Cdc25C**) and ((not **CHK1**) or ((not **Wee1**) and **Cdk1**))		
	K		Full *Cdk1* kinase activation requires its binding partner *Cyclin B* and the *Cdc25C* phosphatase, which maintains *Cdk1* in an active dephosphorylated state. *Cdk1* is inhibited by the checkpoint kinase *CHK1*, unless it is already full active and *Wee1* kinase is inhibited.
	⊣ P	Wee1	*Wee1* is a nuclear protein that ensures the completion of DNA replication prior to mitosis by blocking nuclear *Cdk1* activation [337].
	← DP	Cdc25C	*Cdk1* is subject to inhibitory phosphorylation by *Wee1* or *Myt1*, and its dephosphorylation is carried out by activated *Cdc25C* [332, 338, 333].
	← Compl	CyclinB	Full kinase activation of *Cdk1* in our model requires it to complex with *Cyclin B* [338].
	← Per	Cdk1	We assume that the presence of fully activated, nuclear *Cdk1* is able to overcome the effect of active *Wee1*, given that *Wee1* is very sensitive to *Cdk1*-mediated inhibitory phosphorylation [310].
	⊣ P	CHK1	In the absence of *CHK1* kinase, a small cytosolic (centrosomal) pool of *Cyclin B/Cdk1* can be activated by *Cdc25B*, the nuclear translocation of which can trigger a positive feedback loop that activates the full *Cdk1* pool (assuming nuclear *Wee1* is also inactive). Thus, *CHK1* can maintain the OFF state of inactive *Cdk1* [320].
pAPC	**pAPC** = (((**CyclinB** and **Cdk1**) and **Plk1**) or ((**CyclinB** and **Cdk1**) and **pAPC**)) or (**pAPC** and **Cdc20**)		
	PC		In line with evidence that *Plk1* can aid full activation of *APC/C*, but *Cdk1* appears to be the more potent inducer, our model requires both *Cyclin B/Cdk1* and *Plk1* to activate *APC/C* from an OFF state, but only *Cdk1* activity to maintain it. In addition, ongoing phosphorylation of the functional APC/C^{Cdc20} complex is no longer required.
	← P	Plk1	In addition to *Cyclin B/Cdk1* phosphorylation, full activation of the APC/C^{Cdc20} complex also requires the kinase activity of *Plk1* [339].
	← P	CyclinB	*CyclinB/Cdk1* activation triggers mitotic entry and promotes APC/C^{Cdc20} activity via APC/C subunit phosphorylation [340, 341].

Table S1m: Phase_SW module

	← P	Cdk1	*CyclinB/Cdk1* activation triggers mitotic entry and promotes APC/C^{Cdc20} activity via APC/C subunit phosphorylation [340, 341].
	← Per	pAPC	Activated APC/C^{Cdc20} initiates the Metaphase / Anaphase transition by degrading *Cyclin B* and securin [274]. Once active, APC/C^{Cdc20} no longer requires sustained *CyclinB/Cdk1* or *Plk1* phosphorylation.
	← Compl	Cdc20	Once active, APC/C^{Cdc20} no longer requires sustained *CyclinB/Cdk1* or *Plk1* phosphorylation.
Cdc20	**Cdc20** = ((**pAPC**and(not **Emi1**))and(not **Cdh1**))and((not **Mad2**)or((not **CyclinA**)and (not(**CyclinB** and **Cdk1**))))		
	Prot		In our model, APC/C^{Cdc20} complex formation is represented by the joint activity of *Cdc20* and phosphorylated *APC/C* (*pAPC*). *Cdc20* is thus ON in the presence of *pAPC* when both *Emi1* and *Cdh1* are absent (APC/C^{Cdh1} is represented by the *Cdh1* node, see below). In addition, *Cdc20* activity requires either the absence of *Mad2* at unattached kinetochores, or the absence of *Cdc20* phosphorylation by *Cyclin B/Cdk1* or by *Cyclin A/Cdk2* complexes to potentiate the interaction between *Mad2* and *Cdc20*, and *pAPC* is ON (present and phosphorylated) [342].
	⊣ IBind	Emi1	*Emi1* binds *Cdc20* and inhibits the ubiquitin ligase activity of APC/C^{Cdc20} [302].
	⊣ P	CyclinA	*Cyclin A/Cdk2* complexes phosphorylate *Cdc20* and inactivate the APC/C^{Cdc20} complex during S and G2 [343].
	⊣ P	CyclinB	*Cyclin B* partners with *Cdk1* to keep *Cdc20* phosphorylated, increasing its interaction with *Mad2* rather than *APC/C* [344].
	⊣ P	Cdk1	*Cdk1*-phosphorylated *Cdc20* interacts with *Mad2* rather than *APC/C*, resulting in a block on APC/C^{Cdc20} activation until completion of spindle assembly [342].
	← Compl	pAPC	*Cdc20* becomes active in early mitosis by binding to *APC/C*, an event that requires *Cyclin B/Cdk1*-mediated phosphorylation of several core *APC/C* subunits [298, 345].
	⊣ Deg	Cdh1	APC/C^{Cdh1} complexes degrade *Cdc20*, leading to a complete switch from APC/C^{Cdc20} to APC/C^{Cdh1} during mitotic exit [298, 346].
	⊣ IBind	Mad2	Eukaryotic cells do not separate their replicated genome until they pass the Spindle Assembly Checkpoint (SAC). Namely, all their chromosomes need to be are aligned with respect to the metaphase plane and the two copies of each chromosome need to be attached to opposite poles of the mitotic spindle [341]. This physical alignment is monitored via *Mad2*: kinetochores that remain unattached to microtubules catalyze the sequestration of *Cdc20* and thus inhibit APC/C^{Cdc20} [347, 348].
Cdh1	**Cdh1** = (not(**CyclinB** and **Cdk1**)) and (not(**CyclinA** and (**Emi1** or **Cdc25A**)))		

Table S1m: Phase_SW module

PC			APC/C^{Cdh1} activity requires the absence of Cyclin Dependent kinase phosphorylation by *Cyclin B/Cdk1*, or *Cyclin A/Cdk2* aided by further inhibition of *Cdh1* by *Emi1*, or ongoing *Cdk2* activation by *Cdc25A* in the absence of *Emi1*.
	⊣ IBind	Emi1	*Emi1* blocks APC/C^{Cdh1} binding to its substrates [303], as well as its ability to add ubiquitin chains to them [349].
	⊣ Ind	Cdc25A	As we do not include a separate *Cdk2* node in our model, strong *Cyclin A/Cdk2* activity capable of overriding *Cdh1* activity even in the presence of *Emi1* requires ongoing dephosphorylation of *Cdk2* by *Cdc25A* [332].
	⊣ P	CyclinA	Active *Cyclin A/Cdk1,2* complexes phosphorylate *Cdh1* during S, G2 and early mitosis, impairing its interaction with *APC/C* until late stages of mitosis when *Cdk1/2* activity falls [298, 309].
	⊣ P	CyclinB	*Cyclin B/Cdk1* phosphorylates *Cdh1* during mitosis, impairing its interaction with *APC/C* [298, 309].
	⊣ P	Cdk1	*Cyclin B/Cdk1* phosphorylates *Cdh1* during mitosis, impairing its interaction with *APC/C* [298, 309].

Table S1n: Cell_Cycle_Process module

Target Node	Node Gate Node Type Link Type	Node Description Input Node	Link Description
Replication	**Replication** = ((not **CAD**) and **Pre_RC**) and (((**E2F1** and **CyclinE**) and **Cdc25A**) or (((**Replication** and **CyclinA**) and **Cdc25A**) and (**E2F1** or (not **f4N_DNA**))))		
	Proc		The *Replication* node represents ongoing DNA synthesis. This requires a non-apoptotic cell, licensed pre-replication complexes (*Pre_RC*). The start of DNA synthesis requires *E2F1*-meditated transcription of the genes that help execute it, as well as the firing of the first round of replication origins by *Cyclin E/Cdk2*. Once ongoing, replication is sustained by *Cyclin A/Cdk2* and *Cdc25A*, aided by *E2F1* and terminated by completion of a full round of synthesis (*4N_DNA*).
	← ComplProc	E2F1	In addition to *E2F1* target genes directly included in our model, *E2F1* transcribes an array of critical S-phase genes responsible for carrying out DNA synthesis (e.g, *POLA1*, *POLA2*, *MCM3*, *MCM5*, *MCM6*, *PCNA*, *TOP2A*, *RFC2*, *TK1*) [350, 351].
	← ComplProc	CyclinE	DNA replication is initiated by fully active *Cyclin E/Cdk2* [352].
	← ComplProc	Pre_RC	Ongoing DNA replication requires licensed replication origins, which fire throughout DNA synthesis [353].

Table S1n: Cell_Cycle_Process module

	← ComplProc	Cdc25A	Active *Cdc25A* is required for onset as well as progression through S-phase [354, 355].
	← ComplProc	CyclinA	*Cyclin A/Cdk1* complexes regulate the origin firing program in mammalian cells and are required for the completion of DNA replication [355, 304].
	← Per	Replication	Once ongoing, DNA synthesis continues in the presence of active *Cyclin A/Cdk2*, only ending when DNA content is doubled.
	⊢ ComplProc	f4N_DNA	Complete duplication of a cell's DNA, represented in our model by *f4N_DNA* = ON, marks the end of active *Replication*.
	⊢ ComplProc	CAD	Caspase-activated DNase (*CAD*) destroys DNA, preventing ongoing replication.
ATR	**ATR = Replication**		
	K		*ATR* accumulates at replication forks during unperturbed DNA synthesis [356].
	← Loc	Replication	*ATR* accumulates at replication forks during unperturbed DNA synthesis [356].
CHK1	**CHK1 = ATR**		
	K		*ATR* kinase activates *CHK1* at replication forks, which not only blocks premature mitosis but also regulates the rate of origin firing by keeping *Cdc25* protein levels from increasing above their physiological range [356].
	← P	ATR	*ATR* kinase activates *CHK1* at replication forks (by phosphorylation of serines 317 and 345), which not only blocks premature mitosis but also regulates the rate of origin firing by keeping *Cdc25* protein levels from increasing above their physiological range [356].
f4N_DNA	**f4N_DNA** = (not **CAD**) and ((**Replication** and ((**Pre_RC** and **CyclinA**) or **f4N_DNA**)) or (**f4N_DNA** and (not **Cytokinesis**)))		
	MSt		4N DNA content in our model is reached via the completion of *Replication* (via the firing of the last round of replication origins by *Cyclin A/Cdk* complexes) and maintained in non-apoptotic cells the absence of a contractile ring driving cytokinesis.
	← ComplProc	Pre_RC	*Replication* can only complete DNA synthesis and produce double DNA content if the availability of licensed replication origins is not blocked [353].
	← ComplProc	CyclinA	*Cyclin A/Cdk1* complexes regulate the origin firing program in mammalian cells and are required for the completion of DNA replication [352, 304].
	← ComplProc	Replication	DNA content is doubled by the process of *Replication*.
	⊢ Per	f4N_DNA	Once achieved, a cell's 4N DNA content is sustained up to the point of cytokinesis.

Table S1n: Cell_Cycle_Process module

⊢ ComplProc	Cytokinesis	The process of cytokinesis separates the replicated sister chromatids and resets the DNA content of each daughter cell to a diploid 2N.
⊢ Deg	CAD	Caspase-activated DNase (*CAD*) destroys DNA, preventing maintenance of a double DNA content.
U _Kinetochores	**U_Kinetochores** = ((**f4N_DNA** and (not **Cdh1**)) and (not **A_Kinetochores**)) and ((**CyclinB** and **Cdk1**) or **U_Kinetochores**)	
MSt	The *U_Kinetochores* node in our model is on from the moment the nuclear envelope is dissolved in prometaphase and the mitotic spindle starts to form, until all kinetochores are properly attached. In addition to the presence of unattached kinetochores, *U_Kinetochores* = ON requires attached sister chromatics, the absence of APC/C^{Cdh1} activity. It is turned on my *Cyclin B/Cdk1* and remains on until the spindle is complete (or it is destroyed by APC/C^{Cdh1}).	
← ComplProc	CyclinB	The start of mitotic spindle assembly is initiated by active *Cyclin B/Cdk1* [357].
← ComplProc	Cdk1	The start of mitotic spindle assembly is initiated by active *Cyclin B/Cdk1* [357].
⊢ ComplProc	Cdh1	Premature activation of APC/C^{Cdh1} destroys the incomplete spindle by triggering premature, aberrant anaphase. This occurs due to premature degradation of *APC/C* targets including *Securin* (responsible for keeping sister chromatids attached [358]), *Cyclin B*, *Cdc20*, and Aurora kinase A (*AURKA*) [359].
← ComplProc	f4N_DNA	Metaphase requires replicated sister chromatids (*f4N_DNA*), held together by their kinetochores, face in opposing directions and can be attached to opposite poles of the mitotic spindle.
← Per	U _Kinetochores	Once metaphase starts, the mitotic spindle remains incomplete as long as some of the kinetochores remain unattached.
⊢ ComplProc	A _Kinetochores	In our model, the transition from unattached to all attached kinetochores (*U_Kinetochores* → *A_Kinetochores*) marks the completion of the mitotic spindle and Spindle Assembly Checkpoint (SAC) passage.
Mad2	**Mad2** = **U_Kinetochores** and (not **A_Kinetochores**)	
Prot	Our model represents the SAC via the *Mad2* kinetochore-binding protein. *Mad2* is active as long as the cell has at least one unattached kinetochore and it is responsible for keeping *Cdc20* sequestered from *APC/C*. By keeping *APC* at bay until the spindle is complete, *Mad2* is required for the proper timing of anaphase [348].	
← Compl	U _Kinetochores	The *Mad2* SAC protein is active and potent in the presence of even a single unattached kinetochore [348].
⊢ ComplProc	A _Kinetochores	*Mad2* is inhibited by SAC passage, marked by the completion of the spindle and proper attachment of all kinetochore [348].

Table S1n: Cell_Cycle_Process module

A_Kinetochores	**A_Kinetochores** = ((**f4N_DNA** and (not **Cdh1**)) and (not(**pAPC** and **Cdc20**))) and (**A_Kinetochores** or ((((**U_Kinetochores** and **Src**) and **Plk1**) and **CyclinB**) and **Cdk1**))		
	MSt		The completed spindle, represented by the *A_Kinetochores* node, requires replicated and attached sister chromatids (*f4N_DNA*) and the absence of *APC/C* activity. It turns on when the process of spindle assembly (*U_Kinetochores*) is completed by active *Src*, active *Plk1* localized to unattached kinetochores in the presence of ongoing *Cyclin B/Cdk1* activity, and it remains on until anaphase (*APC/C* activation).
	← ComplProc	Src	*Src* promotes correct spindle orientation [360]. Moreover, absence of *c-Src* leads to severely reduced astral microtubules [361]. Finally, *Src*-mediated phosphorylation of the *Eg5* motor domain is required for the formation of a bipolar spindle and correct chromosome segregation [362].
	← ComplProc	Plk1	*Plk1* activity at unattached kinetochores is required for promoting their attachment [363]. In its absence, kinetochores remain unattached and cells eventually undergo mitotic catastrophe and apoptosis [364].
	← ComplProc	CyclinB	Ongoing *Cyclin B/Cdk1* at unattached kinetochores is necessary to keep *Plk1* active and allow the completion of mitosis [365].
	← ComplProc	Cdk1	Ongoing *Cyclin B/Cdk1* at unattached kinetochores is necessary to keep *Plk1* active and allow the completion of mitosis [365].
	⊢ Deg	pAPC	During normal mitosis, the completed spindle is pulled apart in response to APC/C^{Cdc20}-mediated degradation of *Securin*, which normally blocks *Separate* from severing the *Cohesin* rings keeping sister chromatids attached [358].
	⊢ Deg	Cdc20	During normal mitosis, the completed spindle is pulled apart in response to APC/C^{Cdc20}-mediated degradation of *Securin*, which normally blocks *Separate* from severing the *Cohesin* rings keeping sister chromatids attached [358].
	⊢ Deg	Cdh1	APC/C^{Cdh1} destroys the spindle by triggering anaphase via the degradation of *APC/C* targets, including *Securin* [359].
	← ComplProc	f4N_DNA	Completion of the mitotic spindle requires replicated and attached sister chromatids (*f4N_DNA*).
	← ComplProc	U_Kinetochores	The mitotic spindle is assembled gradually, as the number of unattached kinetochores gradually decreased by the formation of microtubule attachments.
	← Per	A_Kinetochores	Once assembled, separation of the mitotic spindle requires *APC/C* activity to promote the destruction of sister chromatid cohesion [358].
Plk1_H	**Plk1_H** = (**Plk1** and **FoxM1**) and ((**Plk1_H** or **FoxO3**) or **FoxO1**)		

Table S1n: Cell_Cycle_Process module

K			The ON state of *Plk1_H* encodes the short-lived memory of a sufficiently large active *Plk1* pool to temporarily survive *Plk1* destruction by APC/C^{Cdh1} [325], recruit *Ect2* to the central spindle, and thus aid the completion of cytokinesis [366]. Thus, *Plk1_H* requires ongoing *Plk1* activation and transcription by *FoxM1*, and either induction by *FoxO3* or *FoxO1*, or prior accumulation.
	← TR	FoxO3	*Plk1* is a direct transcriptional target of *FoxO3*, but *Plk1* appears to be sufficiently induced in the absence of *FoxO* preteens to aid its G2/M and mitotic functions. In contrast, accumulation if a large enough *Plk1* pool to briefly outlast APC/C^{Cdh1} activation (modeled by the *Plk1_H* node), requires *FoxO* activity in G2 [315].
	← TR	FoxO1	In addition to *FoxO3*, *FoxO1* also binds the *Plk1* promoter, potentially aiding its accumulation during G2 [367].
	← TR	FoxM1	*Plk1* is a direct transcriptional target of *FoxM1*; loss of *FoxM1* severely reduces *Plk1* protein levels [279, 289].
	← Per	Plk1	Active mitotic *Plk1* is a prerequisite for the accumulation of the larger active *Plk1* pool denoted by *Plk1_H*.
	← Per	Plk1_H	Once accumulated, we assume that the *Plk1_H* pool of active *Plk1* remains stable in the absence of *FoxO*-mediated transcription. This is supported by negative feedback regulation of *FoxO* proteins by *Plk1* [37], indicating that ongoing high FoxO activity is likely not required for the maintenance of *Plk1_H*.
Ect2	**Ect2** = (((**f4N_DNA** and **Plk1_H**) and **Cdh1**) and (not **U_Kinetochores**)) and (not **A_Kinetochores**)		
	GEF		*Ect2* activaiton at the spindle midzone represents the step of cytokinesis in our model. Thus, *Ect2* requires *f4N_DNA*, high *Plk1* activity, as well as *Cdh1* for the assembly of a normal spindle midzone. Finally, *Ect2* cannot be recruited to the mid zone before anaphase is completed.
	← Ind	Cdh1	APC/C^{Cdh1}-mediated destruction of Aurora kinase is required for the assembly of a robust spindle midzone at anaphase and for the normal timing of cytokinesis [368].
	← Ind	f4N_DNA	Formation of a spindle midzone, where *Ect2* accumulates in preparation of cytokinesis requires recently separated sister chromatids (4N DNA content).
	⊢ ComplProc	U_Kinetochores	Formation of a spindle midzone requires the separation of sister chromatids; thus it cannot occur before anaphase.
	⊢ ComplProc	A_Kinetochores	Formation of a spindle midzone requires the separation of sister chromatids; thus it cannot occur before anaphase.
	← Ind	Plk1_H	*Plk1* activity in telophase (*Plk1_H*) is required for the recruitment of *Ect2* to the central spindle [325, 369].
Cytokinesis	**Cytokinesis** = (**Ect2** and **FAK**) and **Src**		

Table S1n: Cell_Cycle_Process module

	Proc		In contrast to our previous model in [370] where *Ect2* recruitment to the central spindle marked the start of cytokinesis, in [118] we introduced a separate *Cytokinesis* node to mark cytokinesis and the subsequent resetting of daughter cell DNA content to 2N by a separate node. In addition to *Ect2* recruitment, completion of cytokinesis also requires ECM attachments able to activate *FAK* and *Src* kinases.
	← Loc	Ect2	At the start of cytokinesis, the *Ect2 RhoGEF* is recruited to the central spindle [366]. *Ect2* aids the accumulation of GTP-bound *RhoA* [371, 366] and the formation of the contractile ring.
	← ComplProc	FAK	Integrin-activated *FAK* and *Src* control cytokinetic abscission by decelerating *PLK1* degradation at aiding *CEP55* in recruiting abscission process proteins to the midbody [83, 372].
	← ComplProc	Src	Integrin-activated *FAK* and *Src* control cytokinetic abscission by decelerating *PLK1* degradation at aiding *CEP55* in recruiting abscission process proteins to the midbody [83, 372].

Table S1o: TRAIL module

Target Node	Node Gate Node Type Link Type	Node Description Input Node	Link Description
Trail	**Trail** = **Trail**		
	Env		The *Trail* node represents environmental availability of the *Trail* protein outside the cell.
	← Env	Trail	The *Trail* input node remains on/off if set ON/OFF in the absence of *in silico* perturbation.

Table S1p: Apoptotic_SW module

Target Node	Node Gate Node Type Link Type	Node Description Input Node	Link Description
DR4_5	**DR4_5** = **Trail**		
	Rec		The *DR4* and *DR5* death receptors, represented by the *DR4_5* node, are activated by extracellular *Trail* [373].
	← Ligand	Trail	*DR4* and *DR5* death receptors are activated by extracellular *Trail* [373].
Casp8	**Casp8** = **DR4_5** or **Casp3**		

Table S1p: Apoptotic_SW module

	PTase		*Pro-Caspase 8* may be cleaved independently by *DISC* (not directly reprsented; an adaptor protein for *DR4_5*) or *Caspase 3*.
	← Compl	DR4_5	*Trail*-bound (active) *DR4* and *DR5* receptors trigger the assembly of the pro-apoptotic death-inducing signaling complex (*DISC*), which binds a cluster of *pro-Caspase 8* proteins and initiates their cleavage into active *Caspase 8* [374].
	← Ind	Casp3	*Caspase 3* indirectly activates *Caspase 8* by cleaving *Caspase 6* [375], which, in turn, cleaves *Caspase 8* [376].
Casp2	**Casp2** = **Casp3** or ((**U_Kinetochores** and **Mad2**) and (not(**CyclinB** and **Cdk1**)))		
	PTase		*Pro-caspase 2* is cleaved and activated by *Caspase 3*, or by failed cytokinesis marked by the presence of unattached kinetochores, an active SAC, and the absence of active *Cyclin B/Cdk1* complexes to phosphorylate and inhibit *Caspase 2*.
	⊢ P	CyclinB	*Cyclin B1/Cdk1* phosphorylate *caspase-2* at Ser 340, preventing its activation [377].
	⊢ P	Cdk1	*Cyclin B1/Cdk1* phosphorylate *caspase-2* at Ser 340, preventing its activation [377].
	← Ind	Mad2	A functional spindle assembly checkpoint is required for mitotic cell death upon prolonged mitotic arrest [378] or spindle damage [379].
	← Ind	U _Kinetochores	Although the precise molecular mechanism by which *Caspase 2* is activated during prolonged or stalled mitosis is unclear, its activation platform, the *PIDDosome*, has been localized to unattached kinetochores [380]. Even though a checkpoint protein keeps the *PIDDosome* unresponsive to DNA damage signals, the loss of protective *Cyclin B/Cdk1* phosphorylation only leads to *Caspase 2* activation in the presence of a partially assembled mitotic spindle, and requires active SAC.
	← Lysis	Casp3	*Caspase 2* is a target of *Caspase 3*, as its inhibition severely limits *Caspase 2* cleavage during apoptosis [381, 382].
MCL_1	**MCL_1** = (((not **Casp3**) and (not **Casp2**)) and ((not **GSK3**) or (**AKT_B** and (**ERK** or (not **E2F1**))))) and (not((**Cdk1** and **CyclinB**) and **U_Kinetochores**))		
	Prot		*Caspase 3* or *2*-mediated destruction of *MCL-1* must be absent for *MCL-1* to be ON. Avoiding degradation via textitGSK3 requires the *GSK3*-weakenjng presence of basal *AKT* activity (*AKT_B*) [383] and either *ERK*-mediated stabilization, or the absence of its repressor *E2F1*. Finally, during mitotic arrest (*U_Kinetochores*), *MCL-1* is deactivated by *Cyclin B/Cdk1* phosphorylation, which shields it from the *PPA2*-mediated dephosphorylation of its degradation-targeting sites [384].
	← P	ERK	*ERK* phosphorylates *MCL-1*, promoting its interaction with *Pin1*, which stabilizes it [385, 386].

Table S1p: Apoptotic_SW module

← Ind	AKT_B	In order to account for the loss of *MCL-1* in the complete absence of growth factors versus its presence in low growth factor environments, we required basal *AKT* to modulate the strength of *GSK3* inhibition [383].
⊢ P	GSK3	*MCL-1* is phosphorylated by *GSK3*, leading to ubiquitinylation and degradation of Phosphorylation [383].
⊢ TR	E2F1	*E2F1* is a direct transcriptional repressor of *MCL-1* [387].
⊢ P	CyclinB	In cells arrested in mitosis, phosphorylation by *Cyclin B/Cdk1* on T92 initiates *MCL-1* degradation [388].
⊢ P	Cdk1	Phosphorylation by *Cyclin B/Cdk1* in cells arrested in mitosis initiates *MCL-1* degradation [388].
⊢ Ind	U _Kinetochores	During prolonged mitotic arrest (*U_kinetochores*), *MCL-1* levels drop steadily due to phosphorylation by *JNK*, *p38* and/or *CKII* and its subsequent degradation by the E3 ubiquitin ligase *SCF* (*FBW7*) [384].
⊢ Lysis	Casp2	*Caspase 2* activation destabilizes the *MCL-1* protein [389].
⊢ Lysis	Casp3	*Caspase 3* cleaves and deactivated *MCL-1* [390].
BCLXL	**BCLXL** = ((not **Casp3**) and (**BCL2** and (not **BAD**))) and (((not **U_Kinetochores**) or (**Plk1** and ((not(**CyclinB** and **Cdk1**)) or (**BCL2** and **MCL_1**)))) or ((**BCL2** and **MCL_1**) and (not(**CyclinB** and **Cdk1**))))	
Prot		*Bcl-x_L* activity requires the absence of *Caspase 3*. In addition, *BAD* can block *Bcl-x_L*, as it preferentially binds to it rather than *BCL2* (meaning in the absence of the latter *Bcl-x_L* is more likely to be sequestered by basal levels of *BAD*) [391]. Lastly, mitotic *Bcl-x_L* can be inhibited by *Cdk1* activity if either *BCL2*, *MCL-1*, or *Plk1* are OFF. In the absence of *Plk1*, loss of either *BCL2* or *MCL-1* can result in *Bcl-x_L* inhibition (even without *Cdk1* phosphorylation), as we assume its targets are no longer competitively bound by its family members.
← Ind	Plk1	In addition to other effects of prolonged mitotic arrest on *BCL-2* proteins, *Plk1* inhibition synergistically enhances the inhibitory phosphorylation of *BCL-2* and *BCL-xL*, as well as downregulation of *MCL-1* [392].
⊢ P	CyclinB	During normal mitosis, *Cyclin B/Cdk1* only transiently phosphorylates part of the *BCL-xL* pool. Prolonged mitosis, however, results in high levels of *BCL-xL* (and *Bcl-2*) phosphorylation, priming the system for *Caspase 2*-mediated apoptosis [393, 394].
⊢ P	Cdk1	During normal mitosis, *Cyclin B/Cdk1* only transiently phosphorylates part of the *BCL-xL* pool. Prolonged mitosis, however, results in high levels of *BCL-xL* (and *Bcl-2*) phosphorylation, priming the system for *Caspase 2*-mediated apoptosis [393, 394].

Table S1p: Apoptotic_SW module

⊢ Ind	U _Kinetochores	Prolonged mitosis is required for the accumulation of *BCL-xL* phosphorylation, weakening its interaction with *Bax* [395].
← Ind	MCL_1	*MCL-1* competes with *BCL-xL* for *BAK* binding; the presence of *MCL-1* can keep part of the *BCL-xL* pool active [396].
← Ind	BCL2	*BCL2* competes with *BCL-xL* for *BAD* binding. As *BCL-xL* is a stronger binding partner of *BAD* [391], here we assume that loss of *BCL2* or *BAD* can both result in low *BCL-xL* activity.
⊢ IBind	BAD	*Bad* can bind *BCL-xL* and displace it from *BAX*, thus deactivating it [391].
⊢ Lysis	Casp3	*BCL2* is cleaved and deactivated by *Caspase 3* [397].

BCL2 **BCL2** = (not(((**Casp3** or **BAD**) or **BIM**) or **BIK**)) and (((not **U_Kinetochores**) or (**MCL_1** and **BCLXL**)) or (**Plk1** and ((**BCLXL** or **MCL_1**) or (not(**Cdk1** and **CyclinB**)))))

Prot While the precise combinatorial logic governing *BCL2* activity is not clear from literature, we modeled *BCL2* as ON in the absence of *Caspase 3*, *BAD*, *BIM* or *BIK*. This choice makes *BCL2* the most sensitive of the three family members to activation of its three inhibitors. In addition, mitotic *BCL2* is blocked by *Cdk1* if both *BCL-xL* and *MCL-1* are OFF. In the absence of *Plk1*, loss of either *BCL2* or *MCL-1* can result in *BCL-2* inhibition (even without *Cdk1* phosphorylation), as we assume its targets are no longer competitively bound by its family members.

← Ind	Plk1	In addition to other effects of prolonged mitotic arrest on *BCL2* proteins, *Plk1* inhibition synergistically enhances the inhibitory phosphorylation of *BCL2* and *BCL-xL*, as well as downregulation of *MCL-1* [392].
⊢ P	CyclinB	*Cyclin B/Cdk1* phosphorylates *BCL2* (and *BCL-xL*) during mitosis [393, 394, 397].
⊢ P	Cdk1	Prolonged mitosis results in high levels of *BCL-xL* and *BCL2* phosphorylation, priming the system for *Caspase 2*-mediated apoptosis [393, 394, 397].
⊢ Ind	U _Kinetochores	Prolonged mitosis is required for the accumulation of *BCL2* phosphorylation [393, 394, 397].
← Ind	MCL_1	*MCL-1* competes with *BCL-xL* for binding most of their apoptotic partners, including *BIK*, *BIM*, *BID*, *BAX* and *BAK*.
← Ind	BCLXL	*BCL2* competes with *BCL-xL* for binding most of their apoptotic partners, including *BIK*, *BIM*, *BID*, *BAX* and *BAK*.
⊢ IBind	BAD	*BCL2* competes with *BCL-xL* for *BAD* binding. *BAD* displaces *BCL2* from its inhibitory binding of *Bax/Bak*. Although *BCL-xL* is a stronger binding partner, we assume that *BAD* alone cannot fully block *BCL-xL* in the presence of *BCL2* [391].
⊢ IBind	BIK	*BIK* binds *BCL2* and they mutually inhibit each other's activity [398].

Table S1p: Apoptotic_SW module

	⊢ IBind	BIM	*BIM* binds *BCL2* and they mutually inhibit each other's ability to activate further targets [399].
	⊢ Lysis	Casp3	*BCL2* is cleaved and deactivated by *Caspase 3* [397].
BAD	**BAD** = (**Casp3** or (not(((**AKT_H** or **AKT_B**) or **ERK**) or **S6K**))) or (**Casp8** and ((not((**AKT_B** and **ERK**) and **S6K**)) and (not(**AKT_H** and (**AKT_B** or **ERK**)))))		
	Prot		*BAD* in our model is ON when cleaved by *Caspase 3*, or in the complete absence of survival signals (*AKT*, *ERK* or *S6K*). Alternatively, *BAD* can be cleaved and activated by *Caspase 8* in the absence of strong survival signaling. We modeled this inhibitory survival signal as either the combined activity of *ERK*, *S6K* and (at least) basal *AKT*, or high *AKT* in the joint presence of ERK and basal *AKT* (indicating that *AKT_H* will not drop by the next time-step).
	⊢ P	ERK	*ERK* phosphorylates *BAD* at Ser-112, inducing its sequestration away from the mitochondrial membrane where its BCL-2 family targets are located (e.g., *BCL-2*, *BCL-xL*)[400].
	⊢ P	AKT_B	*Akt* phosphorylates *BAD* at Ser-136, inducing its sequestration away from the mitochondrial membrane where its BCL-2 family targets are located (e.g., *BCL2*, *BCL-xL*) [401].
	⊢ P	AKT_H	*Akt* phosphorylates *BAD* at Ser-136, inducing its sequestration away from the mitochondrial membrane where its BCL-2 family targets are located (e.g., *BCL2*, *BCL-xL*) [401].
	⊢ P	S6K	*S6K1* phosphorylates *BAD* at Ser-155, directly blocking its binding to *BCL-xL* [402].
	← Lysis	Casp8	*Caspase 8* is also able to cleave *BAD*, generating a more potently apoptotic fragment [403]. In addition, *TRAIL*-mediated apoptosis results in *BAD* cleavage by a Caspase upstream of MOMP, creating a potent apoptotic inducer before full *Caspase 3* activation [404].
	← Lysis	Casp3	*Caspase 3* cleaves *BAD*, generating a more potently apoptotic fragment [403].
BIK	**BIK** = not((**MCL_1** or **BCLXL**) or **BCL2**)		
	Prot		*BIK* is free to activate its target, *BAX*, only when it is not sequestered by any of the three *BCL-2* family proteins [396].
	⊢ IBind	MCL_1	*MCL-1* binds *BIK*; they mutually inhibit each other [405].
	⊢ IBind	BCLXL	*BCL-xL* binds *BIK*; they mutually inhibit each other [406].
	⊢ IBind	BCL2	*BCL2* binds *BIK*; they mutually inhibit each other [398].
BIM	**BIM** = **FoxO3** and (**GSK3** and (not(((**ERK** or **MCL_1**) or **BCLXL**) or **BCL2**)))		

Table S1p: Apoptotic_SW module

	Prot		*BIM*'s pro-apoptotic activity requires expression driven by *FoxO3* and aided by *GSK3*, as well as the absence of *ERK* or any of the three inhibitory *BCL2* family proteins.
	⊢ Ind	ERK	The *MEK/ERK* pathway represses *BIM* protein levels, likely via transcriptional repression [407].
	← TR	FoxO3	*FoxO3* is a transcriptional activator of *BIM* [408].
	← Ind	GSK3	*GSK3* kinase is likely required for the *AP1*-dependent expression of *BIM* [409].
	⊢ IBind	MCL_1	*MCL-1* binds *BIM* and inhibits its apoptotic activity [410].
	⊢ IBind	BCLXL	*BCL-xL* binds *BIM* and inhibits its apoptotic activity [399].
	⊢ IBind	BCL2	*BLC2* binds *BIM* and inhibits its apoptotic activity [399].
BID	**BID** = **Casp8** or (**Casp2** and (not((**BCL2** or **BCLXL**) or **MCL_1**)))		
	Prot		*BID* is truncated in response to *Caspase 8* activation. In addition, *Caspase 2* can also promote *BID* activation once all three pro-apoptotic *BCL2* family proteins are blocked.
	← Lysis	Casp8	In response to *TRAIL* (or *FAS* ligand), the initiator *Caspase 8* cleaves *BID* to its active truncated form [411, 412, 413].
	← Lysis	Casp2	*Caspase 2* cleaves *BID* to its active truncated form [414].
	⊢ IBind	MCL_1	All three anti-apoptotic BCL2 proteins (*BCL2*, *BCL-xL* and *MCL-1*) sequesters *BID* into stable complexes, preventing them from activating *BAX* or *BAK* [415].
	⊢ IBind	BCLXL	All three anti-apoptotic BCL2 proteins (*BCL2*, *BCL-xL* and *MCL-1*) sequesters *BID* into stable complexes, preventing them from activating *BAX* or *BAK* [415].
	⊢ IBind	BCL2	All three anti-apoptotic BCL2 proteins (*BCL2*, *BCL-xL* and *MCL-1*) sequesters *BID* into stable complexes, preventing them from activating *BAX* or *BAK* [415].
BAK	**BAK** = (**BID**and((**BIM**or**BIK**)or(not((**BCL2**and**BCLXL**)and**MCL_1**))))or((**BIM**or **BIK**) and (not(**BCLXL** or **MCL_1**)))		
	Prot		Given that *BAK* is preferentially activated by *BID* compared to *BIM* [416] and that it is less responsive to sequestration by *BCL2* than the other two anti-apoptotic *BCL2* family proteins [417, 418], *BAK* in our model turns on when stimulated by *BID* if one or more *BCL2* family proteins are absent, or if *BIM* or *BIK* are also present. In contrast, *BIM* or *BIK* only activate *BAK* if *BCL-xL* and *MCL-1* are absent (*BCL-2* alone cannot block them).
	⊢ IBind	MCL_1	*MCL-1* binds *BAK* and prevent its oligomerization in the mitochondrial membrane [417, 418].

Table S1p: Apoptotic_SW module

	$\vdash$ IBind BCLXL	*BCL-xL* binds *BAK* and prevent its oligomerization in the mitochondrial membrane [419, 417, 418].
	$\vdash$ IBind BCL2	*BCL2* can also bind *BAK* to prevent its oligomerization, but it does so less potently than the other two BCL-2 family members [417, 418, 420].
	$\leftarrow$ Compl BIK	*BIK* can aid the activation of both *BAK* and *BAX* by triggering *BAK* oligomerization on the ER membrane and promoting a Ca^{2+} efflux required for the fragmentation of hyper fused mitochondrial tubules, aiding *BAK* and *BAX* activation [421].
	$\leftarrow$ Compl BIM	*BAK* is preferentially activated by *BID* compared to *BIM*, but *BIM* can also promote BAK oligomerization [416].
	$\leftarrow$ Compl BID	Activated (truncated) *BID* binds to mitochondrial *BAK*, resulting in its activation and oligomerization in the mitochondrial membrane, followed by *cytochrome c* release [422].
BAX	**BAX** = (**BIM**and((**BID**or**BIK**)or(not((**BCL2**and**BCLXL**)and**MCL_1**))))or((**BID**or **BIK**) and (not(**BCL2** or **BCLXL**)))	
	Prot	In contrast to *BAK*, *BAX* is preferentially activated by *BIM* compared to *BID* [416] and it is less responsive to sequestration by *MCL-1* than the other two anti-apoptotic BCL2 family proteins [417, 418]. *BAX* in our model turns on when stimulated by *BIM* if one or more *BCL2* family proteins are absent, or if *BID* or *BIK* are also present. In contrast, *BID* or *BIK* only activate *BAK* if *BCL2* and *BCL-xL* are both absent (*MCL-1* alone cannot block them).
	$\vdash$ IBind MCL_1	*MCL-1* can also bind *BAK* to prevent its oligomerization, but it does so less potently than the other two BCL-2 family members [417, 418, 423].
	$\vdash$ IBind BCLXL	*BCL-xL* binds *BAX* and prevent its oligomerization in the mitochondrial membrane [417, 418].
	$\vdash$ IBind BCL2	*BCL2* binds *BAX* and prevent its oligomerization in the mitochondrial membrane [417, 418].
	$\leftarrow$ Compl BIK	*BIK* can aid the activation of both *BAK* and *BAX* by triggering *BAK* oligomerization on the ER membrane and promoting a Ca^{2+} efflux required for the fragmentation of hyper fused mitochondrial tubules, aiding *BAK* and *BAX* activation [421].
	$\leftarrow$ Compl BIM	Activated *BIM* binds to mitochondrial *BAX*, resulting in its allosteric activation and oligomerization in the mitochondrial membrane, leading to *cytochrome c* release [416].
	$\leftarrow$ Compl BID	*BAX* is preferentially activated by *BIM* compared to *BID*, but *BID* can also promote *BAK* oligomerization [416].
Cyto_C	**Cyto_C** = **BAX** or **BAK**	
	Prot	*Cytochrome C* release from mitochondria requires the oligomerization of either *BAK* or *BAX* [424].

Table S1p: Apoptotic_SW module

	← Loc	BAK	*BAK* oligomerization at the mitochondrial membrane triggers MOMP, which results in the release of *cytochrome C* from mitochondria [424].
	← Loc	BAX	*BAX* oligomerization at the mitochondrial membrane triggers MOMP, which results in the release of *cytochrome C* from mitochondria [425, 426].
SMAC	**SMAC** = **BAX** or **BAK**		
	Prot		*SMAC/Diablo* release from mitochondria requires the oligomerization of either *BAK* or *BAX* [424, 427].
	← Loc	BAK	*BAK* oligomerization at the mitochondrial membrane triggers MOMP, which results in the release of *SMAC/Diablo* from mitochondria [424, 427].
	← Loc	BAX	*BAX* oligomerization at the mitochondrial membrane triggers MOMP, which results in the release of *SMAC/Diablo* from mitochondria [424, 427].
IAPs	**IAPs** = (not **SMAC**) or **AKT_H**		
	Prot		Inhibitor of Apoptosis Proteins (*IAP*s) are active in the absence of *SMAC* inhibition, or following *AKT_H* mediated upregulation (this protection from *SMAC* requires peak or oncogenic *AKT* activity).
	← Ind	AKT_H	*cIAP-2* and *XIAP* are both transcriptionally up-regulated in response to strong *PI3K/AKT1* activation [428].
	⊢ IBind	SMAC	*SMAC/Diablo* binds tightly to *IAP* proteins and blocks their ability to inhibit *Caspase 3* [429].
Casp9	**Casp9** = **Casp3** or ((not **IAPs**) and **Cyto_C**)		
	PTase		*Procaspase 9* is cleaved into active *Caspase 9* by *Caspase 3*, or by the apoptosome (which relies on *cytochrome C* for its assembly) in the absence of *IAP* proteins.
	← Compl	Cyto_C	*Cytochrome c* binds to *APAF-1* proteins, promoting their assembly into the apoptosome, a platform for *procaspase 9* binding and cleavage into its active form [430].
	⊢ IBind	IAPs	*XIAP*, *cIAP1* and *cIAP2* inhibit the *cytochrome c*-induced activation of *procaspase-9* [431].
	← Lysis	Casp3	*Procaspase 9* is a direct cleavage target of *Caspase 3* [382].
Casp3	**Casp3** = ((**Casp9** and **Casp8**) or (**Casp3** and (**Casp9** or **Casp8**))) or ((not **IAPs**) and ((**Casp9** or **Casp8**) or **Casp3**))		
	PTase		Activation of *Caspase 3* requires proteolytic cleavage of *procaspase-3* by initiator caspases such as *Caspase 9* or *Caspase 8*. In our model, cooperation of two of the three caspases (*Casp9*, *Casp8*, *Casp3*) is required in the presence of *IAP*s, which inhibit the proteolytic activity of *Caspase 3* by bind tightly to its active site. In the absence of *IAP*s, either of the three caspases can cleave and activate *Caspase 3*.

Table S1p: Apoptotic_SW module

← Lysis	Casp8	*Caspase 8* can cleave *Caspase 3* [432], but full *Caspase 3* activation also requires MOMP (potentially due to a need for *IAP* inhibition) [433].
⊢ IBind	IAPs	*IAP*s bind tightly to the active site of *Caspase 3*, keeping its activity in check [431, 434].
← Lysis	Casp9	Active *Caspase 9* cleaves *procaspase 3* [435].
← Per	Casp3	Once activated, *Caspase 3* helps sustain its own activation by cleaving *procaspase 8* and *6*. *Caspase 6*, in turn, generates additional active *caspase 8* and *9*. Together they all sustains a continuing active pool of Caspase 3.

Table S1q: DNA_Fragmentation module

Target Node	Node Gate Node Type Link Type	Node Description Input Node	Link Description
CAD	**CAD = Casp3** and **Casp9**		
	DNase		Caspase-activated DNase (*CAD*) is activated when its inhibition is released via the cleavage of *ICAD* (inhibitor of caspase-activated DNase). While *Capsase 3* and *7* (a direct target of *Caspase 9*) can inhibit *ICAD* [436], in our model they are both required, as *CAD* = ON is represents terminal, irreversible apoptotic commitment, which is fully locked in when both *Caspase 3* and *9* are on.
	← Ind	Casp9	In addition of *Caspase 3*, *CAD* inhibition can also be relieved by *ICAD* cleavage by *Caspase 7*, which is a direct target of *Caspase 9* [436].
	← Ind	Casp3	*Caspase 3* relives *CAD* inhibition by cleaving its inhibitor *ICAD* [436].

Table S2a: Key to Node Type Symbols

Symbol	Node Type	Description
Env	Environment	Nodes or modules that represent the extracellular environment of a single cell or cell collective. These are self-sustaining nodes or node groups that maintain their initial states and receive no feedback from the rest of the network (they act as inputs).
Proc	Process	Nodes or modules that stand in for complex cellular processes not modeled in detail (e.g., DNA replication or the process of aligning chromosomes at the metaphase plane during mitosis).

Table S2a: Key to Node Type Symbols

MSt	Macro_Structure	Nodes or modules that represent the state of large, complex cellular structures such as DNA content, cytoskeletal features, junctions or mitochondria.
Met	Metabolite	Regulatory node representing a metabolite (not protein, gene product or complex structure).
mRNA	MRNA	mRNA.
miR	MicroRNA	microRNA.
PC	Protein_Complex	Protein complex represented by a single node or via a key member of the complex.
Rec	Receptor	Cell surface receptor protein or complex.
Adap	Adaptor_Protein	Protein that helps scaffold a signaling complex or other large assembly of proteins.
Secr	Secreted_Protein	Protein secreted into the extracellular environment, such that the state of the node tagged with this type represents the availability fo this protein outside the cell.
TF	TF_Protein	Transcription factor.
K	Kinase	Kinase (enzyme that catalyzes the phosphorylation of its target).
Ph	Phosphatase	Phosphatase (enzyme that catalyzes the removal of phosphorylation from its target).
UbL	Ubiquitin_Ligase	Ubiquitin ligase (protein that recruits an ubiquitin-conjugating enzyme that has been loaded with ubiquitin to a target protein and assists or directly catalyzes the transfer of ubiquitin from the ubiquitin-conjugating enzyme to the target).
PTase	Protease	Protease (enzyme that catalyzes the breakdown of proteins into smaller fragments).
DNase	DNase	Protease ligase.
CAM	CAM	Cell adhesion proteins located on the cell surface.
CDK	CDK	Cyclin-dependent kinase.
CDKI	CDKI	Cyclin-dependent kinase inhibitor.
GEF	GEF	Guanine nucleotide exchange factor.
GAP	GAP	GTPase-activating protein (also called GTPase-accelerating protein).
GTPa	GTPase	GTPase enzymes that hydrolyze ATP to ADP.
Enz	Enzyme	Enzyme that does not fit the more specific enzyme categories listed above.
Prot	Protein	Regulatory protein that does not fit any of the more specific classifications listed above.
LncRNA	LncRNA	Long intervening noncoding RNA
SLig	Cell_Surgace_Ligand	Membrane-bound signaling molecule that serves as a ligand to receptors on neighboring cells.

Table S2b: Key to Link Type Symbols

Symbol	Link Type	Description
Env	Enforced_Env	This link type represents self-loops on Environment nodes, which guarantee that these nodes maintain their initial state throughout a time-course simulation unless they are explicitly altered by the simulation's settings.
Ind	Indirect	Regulatory influence that does not involve direct binding, processing, or enzyme activity.
ComplProc	Complex_Process	Regulatory influence that is not modeled in detail, but involves more than one molecule or a macrostructure. For example, the physical need for kinetochores on replicated sister chromatids for the assembly of certain protein complexes can be represented as a link from the node representing kinetochores to the regulatory proteins, with a Complex_Process link type.
Per	Persistence	This link type represents self-loops that alter the ability of a node to stay in a particular state depending on its own current state. For example, if transcription of a protein is easier to maintain than to induce de novo, this may be encoded by a logic gate that includes the node itself and creates a self-loop. The link type of this loop is "Persistence".
TR	Transcription	Action of a transcription factor to alter the expression of the target node (mRNA or protein). Link type should be used for induction as well as repression (the link effect contains this information).
TL	Translation	Regulatory influence that controls the translation of mRNA into protein; should be used for induction as well as repression of translation.
Ligand	Ligand_Binding	Binding of extracellular ligand to its receptor.
Compl	Complex_Formation	Binding even that leads to a regulatory protein complex.
IBind	Inhibitory_Binding	Binding even that represses the target node's level or activity.
Loc	Localization	Regulatory influence that alters the localization of a molecule.
BLoc	Binding_Localization	Binding even that alters the localization of a molecule.
PBind	Protective_Binding	Binding even that increases / protects the target node's activity.
Unbind	Unbinding	A regulatory influence that causes the target node to be released from a protein complex and change its activity (increase or decrease) as a result.
P	Phosphorylation	Phosphorylation.
DP	Dephosphorylation	Dehosphorylation.
PLoc	Phosphorylation_Localization	Phosphorylation resulting in altered protein localization.
Ubiq	Ubiquitination	Ubiquitination, usually leading to protein degradation.
Deg	Degradation	Regulatory influence leading to the degradation of the target molecule (more general than Ubiquitination; the latter link type should be used when appropriate).
GEF	GEF_Activity	Action of a Guanine nucleotide exchange factor (GEF) leading to GTP loading onto (and usually the activation of) a GTPase.

Table S2b: Key to Link Type Symbols

GAP	GAP_Activity	Actions of a GTPase-activating protein (GAP) leading to the hydrolysis of GTP by (and usually de-activation of) a GTPase.
Lysis	Proteolysis	Protein cleavage.
Cat	Catalysis	Increasing the rate of metabolite production by an enzyme.
Epi	Epigenetic	Process that alters gene expression via modifying chromatin condensation or altering DNA methylation.
Secr	Secretion	Secretion or shedding of a protein or other regulatory molecule to the extracellular environment.
RNAi	RNAi	This process represents inhibitory binding of cytoplasmic mRNAs by RISC-bound microRNAs that block translation and/or enhance mRNA degradation.

Table S2c: Key to Link Effect Symbols

Symbol	Link Effect	Description
$\leftarrow$	Activation	Link in which the input node aids the expression, activity, persistence or localization of the target such that the target is easier to turn/keep in an ON state. It can be used for multi-level nodes as long as these levels represent increasing intervals of activity.
$\vdash$	Repression	Link in which the input node hinders the expression, activity, persistence or localization of the target such that the target is easier to turn/keep in an OFF state. It can be used for multi-level nodes as long as these levels represent increasing intervals of activity.

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