Biodivne Boolean Models: A Comprehensive Logical Modelling Benchmark

Samuel Pastva

Abstract

The space of powerful tools for computational analysis of logical models (represented as Boolean networks) has been growing considerably. However, comparing the validity, efficiency, and scalability of such tools necessitates a comprehensive benchmark set of realistic Boolean networks.

At the moment, this need is largely served by databases of biological models such as CellCollective, GINsim, or Biomodels. However, these databases are more focused on human curated, biologically relevant networks, and are therefore limited in scope. Furthermore, the models in such databases may not always be available as a single dataset or in the desired format. This requires additional time for preprocessing and data collection, which the tool authors are often unwilling or unable to spend.

In this technical report, we describe a comprehensive, open-source benchmark dataset that has been created by surveying the aforementioned databases, as well as a large body of other literature to obtain as many realistic Boolean networks as possible. To make the dataset useful to a wide range of tool maintainers, we provide the models in different machine-readable formats and ensure all models are valid and logically consistent using an automated static-analysis workflow. At the moment of writing, the dataset comprises more than 210 networks.

1 Introduction

Logical models provide a very useful and simple framework for describing complex biological phenomena. The most common mechanism for formalising executable logical models are Boolean networks [129]. In recent years, we have seen a rapid development of new tools and algorithms for analysis of large Boolean networks. However, in many instances, it is hard to assess usefulness and scalability of such tools due to a lack of commonly recognised "benchmark dataset" of networks on which the tools can be compared.

This purpose is often served by models obtained from databases maintained by the authors of some of the larger modelling tools, such as CellCollective [55], GINsim [96], or Biomodels [78]. However, these models are often hard to obtain in bulk or may require additional processing (e.g. to convert into an appropriate format). Additionally, tool authors often modify the models in minor ways (e.g.

by tweaking valuations of network inputs), which prevents meaningful comparisons between publications. Finally, these databases are far from comprehensive, so a wide range of models is often omitted.

As a result, most papers develop an ad hoc benchmark set that is often partially proprietary and hard or impossible to replicate and compare to. In this technical report, we describe a comprehensive, open-source benchmark dataset that can be used for this purpose instead.

Disclaimer: The model dataset as well as this report will be gradually updated as new models and data become available. If possible, please refer to the latest version of this report on arXiv and the latest revision of the dataset in the github repository.

2 Goals and scope

Eligible models To cover the widest possible assortment of realistic models, we currently allow submission of any logical model which can be reliably retrieved from a known database, repository, or an associated publication. The only requirement is that the model must be based on real biological information. That is, we do not accept randomly generated models. However, we do not require any specific level of curation either—the model can be hand made, automatically synthesised, or anything in between. Similarly, we accept many different model formats and we are willing to assist with translation if a machine-friendly format is not available. We also accept multi-valued models, however, for now the dataset only contains their Booleanized versions.

Editions The goal is to gradually evolve the dataset by adding new models (or by removing problematic/redundant models). Consequently, we plan to regularly release *editions* of the dataset, such that the users can refer to the whole history of editions as necessary. Preliminary plan is to release editions in roughly yearly intervals. Initially, editions will be available as Github releases, with a possible future addition of Zenodo artefacts. In each edition, the user can then filter models with specific properties (size, keywords, source, etc.).

Model metadata While we do not perform any biological curation of models, we collect basic meta-data about each model to make filtering and search easier. In particular, each model has:

- A numeric identifier that is unique within a specific dataset edition.
- A human-readable name. For simplicity, the name is limited to numbers, capital letters and the dash symbol (e.g. MODEL-NAME-5). To improve legibility, we may use spaces instead of dashes in text that is not meant to be machine readable (i.e. MODEL NAME 5).

- The DOI of the associated publication and its bibliographic entry (in Bibtex). Note that a single publication can contain multiple models—some DOIs thus appear in relation to multiple models.
- The URL where the model data was downloaded. This can be a list of URLs if the model is available from multiple sources. This can also be the publication DOI if the model is based directly on the published supplementary data.
- Basic structural metadata, such as the number of model *variables*, *inputs*, and *regulations*. The plan is to also incorporate additional structural measures of the regulatory graph later (e.g. feedback-vertex-set, SCC sizes, etc.), once additional static analysis steps are added.
- A set of curated *keywords*. Generally, these represent additional technical metadata, such as listing the databases where the model is available, or whether the model is based on multi-valued logic. At the moment, the dataset does not contain any biological keywords (e.g. cancer, differentiation, etc.). However, we are open to incorporating any community suggestions for additional keywords.
- A markdown document with any additional notes or relevant information about the model.

For each model, the metadata is summarised in a human-readable markdown README.md file, as well as a machine-readable .json document.

Contributions The dataset is managed using a versioned Github repository. Submitting a new model into the collection can be thus performed by anyone using the pull-request functionality (project readme has more detailed instructions about preparing such pull requests). Alternatively, we also accept submissions using issues: Simply create an issue with the bibliographic entry of the model you wish to include and we will try to incorporate it as soon as possible.

3 Technical information

The dataset is organized as follows:

- /models contains the whole dataset with all model and metadata files.
- /sources directory contains the machine-readable source files that are used to generate the models directory.
- /report directory contains the LaTeX source files for this report.
- /sync.py is the Python script for model processing and static analysis.

 $^{^{1} \}verb|https://github.com/sybila/biodivine-boolean-models/$

Keywords The metadata for each model can contain a set of keywords. In theory, any keyword can be added to identify specific classes of models. However, at the moment, we specifically recognise the following keywords:

- curated: A curated model is not only based on biological information, but is also (partially) validated by a human. That is, a model resulting from a purely automatic translation or inference can be included in the dataset, but is not automatically considered curated.
- repaired: A model where one or more logical inconsistencies have been resolved (a complete list of possible repairs is given later in this report). The modifications should be listed in model notes.
- multi-valued: A model whose original version is multi-valued, but which is presented in a Booleanized form (the original multi-valued model should be included in the sources directory).
- cell-collective/ginsim/biomodels/covid-disease-map: Indicates that the model is available in the corresponding database (or multiple databases).
- casq: Indicates that the model has been translated from a CellDesigner pathway using the CaSQ tool [3].

Formats and representation At the moment, we support three major model formats for BN representation:

- .bnet; a simple plaintext file with the logical update functions [67].
- .aeon; also a plaintext format, but one that also incorporates the regulatory network of the model (with monotonicity and essentiality) [10].
- .sbml; XML-based format with support for additional meta-data (model layout, entity references and comments, etc.) [14].

Each model is available in all three formats. Any of the three formats can be also used as a model source (however, only limited static analysis is available for .bnet models due to the missing regulatory network). To ensure compatibility across all tools, we also perform model variable renaming when necessary. For example, .sbml supports (almost) arbitrary strings as variable names, while other formats follow a more typical C-like naming requirements. As such, regardless of the source format, variable names are normalized such that they are valid in any format.

Model inputs We also normalize the representation of model *inputs* and *constants*. Formally, an input or a constant is an entity with no incoming regulations, and either an identity (input) or true/false (constant) update function. The update function for inputs can be also missing entirely to indicate that the value is unknown/undetermined.

The specific representation of such variables is typically at the discretion of the model authors and differs from model to model. For example, some authors use constant update functions for inputs with a "typical" or "assumed" value, while other authors use the identity function, and other authors omit the functions entirely, only describing the expected values in text.

To make the resulting models as canonical as possible, we opted to *omit the* update function for every constant or input variable. If you wish to use the original setting as published by the authors, this information is still available in the sources directory, or as part of the associated publication.

For benchmarking and tool comparison, we generally recommend sampling a non-trivial subspace of input valuations, as the behaviour of the model can often differ substantially based on the values of inputs. The model with all input values erased is therefore a good starting point for such sampling.

Multi-valued networks Some logical models are not Boolean, but multi-valued. Our dataset also includes models of this type. However, every such model is only given in the Booleanized format where the multi-valued entities are expanded into multiple Boolean variables. At the moment, the Booleanization is performed manually using the GINsim [96] software. In the future, we may include this as an automated step in the analysis workflow. Every Booleanized multi-valued model is marked with the multi-valued keyword. The original multi-valued model is also available in the corresponding sources sub-directory.

Duplicates Some models are available from multiple sources (typically multiple model databases). To eliminate duplicates, we typically only include a single version of the same model, but list multiple model URLs as possible sources (note that different databases can sometimes have slightly different versions of the same model). The information about duplicates and model-database mapping is also tracked in a shared spreadsheet. Note that some publications can still contain multiple models, in which case we include all such models (each model is linked to the single shared publication). Similarly, multiple publications can describe variations or derivatives of a single model. We then typically include the variations as separate models, as long as there is a non-trivial difference from the original model (e.g. new/removed variables or regulations).

Model repair Many published models contain logical *inconsistencies* that we are able to detect as part of our static analysis workflow. Such issues have to be resolved before the model can be included in the dataset. For every model where such "repair" operation was performed, we use the repaired keyword and describe the repair process in the model notes. Furthermore, the original (unaltered) model file should be available in the sources directory. In general, we recognise the following types of problems:

 $^{^2} https://docs.google.com/spreadsheets/d/1YFMaT3SKOwsReW3r6umv7Atqjoe1AZJmeMQ3HBPnIUI/edit?usp=sharing$

- Monotonicity: When a model declares a regulation as (positively or negatively) monotonous, but the actual update function does not adhere to this assumption, we remove the monotonicity requirement from the regulation.
- Essentiality: When a model declares a regulation but the regulator has no impact on the output of the update function, we mark the regulation as non-essential. This problem has two variants: Either the regulator is completely unused (in which case this is likely the intention of the model author), or the regulator appears in the update function, but has no actual impact on its output (in which case it is likely that the model author was not aware of this problem).
- Redundant variables: We expect the dependency graph of each model to be weakly connected, or at least to not contain completely disconnected variables. If such variables are found, they are removed.
- Typos and other issues: Sometimes, the logical inconsistency is due to an obvious typo in the model specification (e.g. substitution of two similar variable names), in which case we fix the typo to the best of our ability.

The goal of each repair is to retain the original update functions of the model (as these are typically crucial for reproducibility). We thus typically adjust the regulatory network to match the actual update functions.

4 Models

In the rest of the report, we give a complete enumeration of all models included in the dataset with basic metadata and associated bibliographic entries. A machine readable (.csv) version of this summary is available as part of each dataset editions.

ID	Name	Vars.	Inps.	Regs.	Source
001	SIGNALING IN MACROPHAGE ACTIVATION	302	19	533	[110]
002	SIGNAL TRANSDUCTION IN FIBROBLASTS	130	9	557	[54]
003	MAMMALIAN CELL CYCLE	19	1	51	[120]
004	ERBB RECEPTOR SIGNALING	225	22	1100	[53]
005	FA/BRCA PATHWAY	28	0	123	[114]
006	HGF SIGNALING IN KERATINOCYTES	62	6	103	[134]
007	CORTICAL AREA DEVELOPMENT	5	0	14	[38]
008	DEATH RECEPTOR SIGNALING	25	3	45	[13]
009	YEAST APOPTOSIS	60	13	114	[63]
010	CARDIAC-DEVELOPMENT	13	2	37	[58]
011	GUARD CELL ABSCISIC ACID SIGNALING	40	4	78	[70]
012	T-CELL RECEPTOR SIGNALING	94	7	158	[119]
013	CHOLESTEROL REGULATORY PATHWAY	32	2	41	[64]
014	T-LGL SURVIVAL NETWORK 2008	54	7	193	[151]
015	NEUROTRANSMITTER SIGNALING PATHWAY	14	2	20	[50]
016	IL-1 SIGNALING	104	14	218	[117]
017	DIFFERENTIATION OF T-LYMPHOCYTES	41	9	97	[82]
018	EGFR-ERBB SIGNALING	76	28	226	[121]
019	IL-6 SIGNALING	71	15	149	[117]
020	APOPTOSIS NETWORK	39	2	73	[77]
021	BODY SEGMENTATION IN DROSOPHILA 2013	14	3	29	[80]
022	B-CELL DIFFERENTIATION	17	5	39	[85]
023	MAMMALIAN CELL CYCLE 2006	9	1	34	[30]
024	BUDDING YEAST CELL CYCLE	16	4	42	[142]
025	T-LGL SURVIVAL NETWORK 2011	54	6	195	[118]
026	BUDDING YEAST CELL CYCLE 2009	18	0	59	[59]
027	WG PATHWAY OF DROSOPHILA	12	14	29	[84]
028	VEGF PATHWAY OF DROSOPHILA	10	8	18	[84]
029	TOLL PATHWAY OF DROSOPHILA	9	2	11	[84]
030	SPZ NETWORK OF DROSOPHILA	18	6	28	[84]

ID	Name	Vars.	Inps.	Regs.	Source
031	CELL CYCLE TRANSCRIPTION	9	0	19	[102]
032	T-CELL SIGNALLING 2006	37	3	53	[66]
033	BT474 BREAST CELL LINE LONG TERM	19	5	68	[27]
034	HCC1954 BREAST CELL LINE LONG TERM	19	4	68	[27]
035	BT474 BREAST CELL LINE SHORT TERM	11	5	46	[27]
036	HCC1954 BREAST CELL LINE SHORT TERM	11	5	46	[27]
037	SKBR3 BREAST CELL LINE SHORT TERM	11	5	41	[27]
038	SKBR3 BREAST CELL LINE LONG TERM	21	4	81	[27]
039	HIV-1 INTERACTIONS WITH T-CELL SIGNALING	124	14	368	[105]
040	T-CELL DIFFERENTIATION	19	4	34	[89]
041	INFLUENZA VIRUS REPLICATION CYCLE	120	11	302	[74]
042	TOL REGULATORY NETWORK	14	10	48	[132]
043	BORDETELLA BRONCHISEPTICA	33	0	79	[140]
044	TRICHOSTRONGYLUS RETORTAEFORMIS	25	1	58	[140]
045	HH PATHWAY OF DROSOPHILA	11	13	32	[84]
046	B BRONCHISEPTICA AND T RETORTAEFORMIS	52	1	135	[140]
047	FGF PATHWAY OF DROSOPHILA	14	9	24	[84]
048	GLUCOSE REPRESSION SIGNALING 2009	55	18	97	[17]
049	OXIDATIVE STRESS PATHWAY	18	1	32	[136]
050	CD4 T-CELL SIGNALING	154	34	351	[21]
051	COLITIS ASSOCIATED COLON CANCER	69	1	153	[71]
052	SEPTATION INITIATION NETWORK	23	8	50	[15]
053	PREDICTING VARIABILITIES IN CARDIAC GENE	13	2	37	[43]
054	PC12 CELL DIFFERENTIATION	61	1	108	[100]
055	HUMAN GONADAL SEX DETERMINATION	19	0	79	[113]
056	IGVH MUTATIONS IN LYMPHOCYTIC LEUKEMIA	66	25	125	[5]

ID	Name	Vars.	Inps.	Regs.	Source
057	FANCONI ANEMIA AND CHECKPOINT RECOVERY	15	0	66	[115]
058	ARABIDOPSIS THALIANA CELL CYCLE	14	0	66	[103]
059	BORTEZOMIB RESPONSES IN MYELOMA CELLS	62	5	131	[18]
060	STOMATAL OPENING	44	5	167	[36]
061	TUMOR MICROENVIRONMENT IN LYMPHOBLASTIC LEUKAEMIA	24	2	79	[29]
062	CD4 T-CELL DIFFERENTIATION AND PLASTICITY	12	6	78	[81]
063	LAC OPERON	10	3	22	[146]
064	METABOLIC INTERACTIONS IN GUT MICROBIOME	8	4	27	[137]
065	TUMOUR CELL INVASION AND MIGRATION	30	2	156	[19]
066	CD4 T-CELL DIFFERENTIATION	29	9	96	[55]
067	REGULATION OF L-ARABINOSE OPERON	9	4	18	[61]
068	AURORA KINASE-A IN NEUROBLASTOMA	19	4	43	[24]
069	IRON ACQUISITION AND STRESS RESPONSE	20	2	38	[11]
070	MAPK CANCER CELL FATE	49	4	104	[44]
071	CASTRATION RESISTANT PROSTATE CANCER	28	14	51	[6]
072	LYMPHOPOIESIS REGULATORY NETWORK	67	14	160	[88]
073	LYMPHOID AND MYELOID CELL SPECIFICATION	31	2	94	[20]
074	T-LGL SURVIVAL NETWORK 2011 REDUCED	18	0	43	[118]
075	INFLAMMATORY BOWEL DISEASE	47	0	287	[8]
076	SENESCENCE ASSOCIATED SECRETORY PHENOTYPE	49	2	96	[90]
077	SIGNALLING PATHWAY FOR BUTANOL PRODUCTION	53	13	139	[94]
078	IMMUNE SYSTEM	151	13	506	[55]
079	COLORECTAL TUMORIGENESIS	184	13	747	[16]
080	TCR SIGNALING 2018	95	15	212	[116]
081	TLR5 SIGNALING 2018	40	2	68	[116]
082	TCR-TLR5 SIGNALING 2018	112	16	257	[116]
083	SIGNALING IN PROSTATE CANCER	122	11	420	[93]

ID	Name	Vars.	Inps.	Regs.	Source
084	ABA INDUCED STOMATAL CLOSURE	58	23	155	[4]
085	REPROGRAMMING TESTES DERIVED STEM CELLS	23	4	49	[51]
086	TUMOUR CELL INVASION AND MIGRATION REDUCED	18	2	88	[19]
087	INFLAMMATORY GENE EXPRESSION IN MACROPHAGES	99	34	190	[112]
088	MIR-9 NEUROGENESIS	6	0	11	[22]
089	MAPK REDUCED 1	13	4	78	[44]
090	MAPK REDUCED 2	14	4	60	[44]
091	MAPK REDUCED 3	12	4	58	[44]
092	HEPATOCELLULAR CARCINOMA	61	8	139	[138]
093	IMMUNE CHECKPOINT INHIBITORS	51	15	128	[68]
094	MACROPHAGE POLARIZATION STATES	23	8	52	[107]
095	FISSION YEAST 2008	9	1	27	[25]
096	ERBB REGULATED G1-S TRANSITION	19	1	48	[60]
097	DROSOPHILA WINGS AP	8	2	14	[41]
098	MACROPHAGE POLARIZATION EXTENDED	30	12	72	[79]
099	YEAST HYPHAL TRANSITION	16	3	36	[149]
100	ACUTE MYELOID LEUKEMIA	18	3	30	[106]
101	GUARD CELL CO2 SIGNALLING	61	24	155	[62]
102	PANCREATIC CANCER MICROENVIRONMENT REDUCED	17	5	52	[109]
103	PANCREATIC CANCER MICROENVIRONMENT	65	4	110	[109]
104	DROSOPHILA CELL CYCLE	11	3	42	[32]
105	PLANT GUARD CELL SIGNALLING	46	3	113	[76]
106	STOMATAL RESTING STATE	58	22	151	[75]
107	DNA DAMAGE INDUCED AUTOPHAGY	32	1	99	[49]
108	GEROCONVERSION	23	2	67	[147]
109	ASYMMETRIC CELL DIVISION A	5	0	15	[127]
110	ASYMMETRIC CELL DIVISION B	9	0	12	[127]
111	APOPTOSIS	18	15	40	[104]
112	COAGULATION PATHWAY	85	27	195	[104]
113	ER STRESS	107	75	266	[104]
114	ETC	46	38	154	[104]
115	E PROTEIN	17	18	40	[104]
116	HMOX1 PATHWAY	89	55	228	[104]
117	IFN LAMBDA	28	19	52	[104]
118	INTERFERON 1	66	55	190	[104]

ID	Name	Vars.	Inps.	Regs.	Source
119	JNK PATHWAY	13	6	21	[104]
120	KYNURENINE PATHWAY	78	72	304	[104]
121	NLRP3 ACTIVATION	39	18	91	[104]
122	NSP14	74	94	558	[104]
123	NSP4 NSP6	43	17	62	[104]
124	NSP9 PROTEIN	119	133	257	[104]
125	ORF10 CUL2 PATHWAY	34	17	92	[104]
126	ORF3A	24	18	56	[104]
127	PAMP SIGNALING	44	35	109	[104]
128	PYRIMIDINE DEPRIVATION	56	34	131	[104]
129	RTC AND TRANSCRIPTION	33	1	40	[104]
130	RENIN ANGIOTENSIN	43	34	130	[104]
131	TGFB PATHWAY	7	14	24	[104]
132	VIRUS REPLICATION CYCLE	129	19	268	[104]
133	ROOT STEM CELL 2010	8	2	16	[7]
134	RHEUMATOID ARTHRITIS	35	3	59	[91]
135	SIGNAL TRANSDUCTION	28	2	33	[73]
136	EGF TNF ALPHA SIGNALLING PATHWAY	26	2	31	[14]
137	SIGNALLING IN LIVER CANCER	71	11	118	[139]
138	APOPTOSIS-UPDATED	17	14	37	[37]
139	ACUTE RESPONSES DURING	10	9	64	[101]
\vdash	HYPERINSULINEMIA				. ,
140	BREAST CANCER DRUG RESISTANCE	62	18	211	[40]
141	HIGH OSMOLARITY AND MATING PATHWAYS	43	2	94	[145]
142	BLOOD STEM CELL	27	2	126	[52]
143	BREAST CANCER INHIBITORS	71	26	223	[39]
144	SNF1-AMPK-PATHWAY	146	56	482	[72]
145	MELANOGENESIS	61	1	113	[69]
146	BUDDING YEAST FAURE 2009	40	10	271	[31]
147	BUDDING YEAST EXIT MODULE	11	5	44	[31]
148	AGS CELL FATE DECISION	83	0	185	[34]
149	AGS CELL FATE DECISION REDUCED	12	2	62	[34]
150	CELL FATE DECISION MULTISCALE	31	2	52	[13]
151	TCR REDOX METABOLISM	130	3	417	[128]
152	TCR REDOX METABOLISM REDUCED	50	3	288	[128]
153	CONTROL OF PROLIFERATION	17	1	34	[150]
154	CONTROL OF TH1 TH2 DIFFERENTIATION	18	3	50	[87]

ID	Name	Vars.	Inps.	Regs.	Source
155	CONTROL OF TH1 TH2 TH17 TREG DIFFERENTATION	45	26	164	[95]
156	CONTROL OF TH1 TH2 TH17 TREG DIFFERENTATION REDUCED	23	13	108	[95]
157	CONTROL OF TH DIFFERENTATION	62	41	234	[1]
158	LAMBDA PHAGE LYSOGENY	7	0	30	[141]
159	BUDDING YEAST CORE	31	8	158	[31]
160	IL17 DIFFERENTIAL EXPRESSION	76	16	246	[23]
161	DIFFERENTIATION OF MONOCYTES	94	2	244	[99]
162	DROSOPHILA DPP PATHWAY	10	8	40	[84]
163	DROSOPHILA EGF PATHWAY	24	10	84	[84]
164	EGGSHELL PATTERNING MECHANISTIC	17	7	62	[33]
165	EGGSHELL PATTERNING PHENOMOENOLOGICAL	4	4	16	[33]
166	DROSOPHILA JAK STAT PATHWAY	7	12	36	[84]
167	MESODERM SPECIFICATION IN DROSOPHILA	41	16	130	[83]
168	DROSOPHILA NOTCH PATHWAY	7	6	26	[84]
169	DROSOPHILA GAP A	5	2	17	[125]
170	DROSOPHILA GAP B	4	3	15	[125]
171	DROSOPHILA GAP C	5	2	20	[125]
172	DROSOPHILA GAP D	5	2	12	[125]
173	GLUCOSE REPRESSION SIGNALLING	62	14	116	[17]
174	HEPATOCELLULAR CARCINOMA REDUCED	19	0	71	[138]
175	SEA URCHIN	32	9	95	[35]
176	MYELOFIBROTIC MICROENVIRONMENT	47	2	148	[28]
177	LYMPHOID CELL SPECIFICATION	31	3	96	[20]
178	MAST CELL ACTIVATION	45	3	72	[97]
179	MICROENVIRONMENT CONTROL	46	10	149	[130]
180	MORPHOGENETIC CHECKPOINT	11	1	36	[31]
181	MULTILEVEL CELL CYCLE	12	1	59	[143]
182	BOOLEAN CELL CYCLE	12	2	59	[143]
183	ALTERATIONS IN BLADDER	31	4	111	[111]
184	P53 MDM2 NETWORK	5	1	15	[2]
185	CHICKEN SEX DETERMINATION	12	3	34	[123]

ID	Name	Vars.	Inps.	Regs.	Source
186	CHICKEN SEX DETERMINATION REDUCED	7	3	25	[123]
187	MAMMAL SEX DETERMINATION 1 CELL	13	6	55	[122]
188	MAMMAL SEX DETERMINATION 2 CELL	30	7	132	[122]
189	TRP BIOSYNTHESIS	5	1	13	[133]
190	BRAF TREATMENT RESPONSE	32	5	74	[9]
191	SEGMENT POLARITY 1 CELL	17	2	55	[124]
192	SEGMENT POLARITY 6 CELL	102	0	352	[124]
193	SENESCENCE G1S CHECKPOINT	28	2	100	[92]
194	VULVAR PRECURSOR CELLS	78	28	236	[148]
195	CTLA4 PD1 CHECKPOINT INHIBITORS	161	55	439	[57]
196	T-LYMPHOCYTE SPECIFICATION	58	3	237	[12]
197	ANTERIOR POSTERIOR BOUNDARY	48	8	253	[42]
198	PAIR RULE MODULE	11	0	48	[126]
199	HEPATOCELLULAR CARCINOMA COMPARTMENTALIZED	30	0	97	[86]
200	LUNG-CANCER-CELL-CYCLE	25	1	71	[48]
201	ONKOGENE ROLE OF INCRNA ANRIL	31	2	94	[45]
202	ONKOGENE ROLE OF INCRNA XIST	30	1	107	[47]
203	DDR SIGNALLING PATHWAYS	39	1	143	[46]
204	HUMAN BRAIN ORGANOIDS	76	1	205	[108]
205	EPITHELIAL-MESENCHYMAL TRANSITION IN BLADDER	41	4	118	[65]
206	EPITHELIAL-MESENCHYMAL TRANSITION IN BREAST	36	5	97	[65]
207	BREAST CANCER TUMOUR	85	18	441	[131]
208	HEMATOPOIESIS AGING	15	0	36	[56]
209	ABERRANT CELL CYCLE PROGRESSION	85	2	372	[135]
210	DRUG SYNERGY PREDICTION	144	0	367	[98]
211	EPITHELIAL-DERIVED CANCER CELLS	183	0	602	[144]
212	ESCHERICHIA COLI TRYPTOPHAN	13	3	27	[26]

References

[1] Wassim Abou-Jaoudé, Pedro T Monteiro, Aurélien Naldi, Maximilien Grandclaudon, Vassili Soumelis, Claudine Chaouiya, and Denis Thieffry.

- Model checking to assess t-helper cell plasticity. Frontiers in bioengineering and biotechnology, 2:86, 2015.
- [2] Wassim Abou-Jaoudé, Djomangan A Ouattara, and Marcelle Kaufman. From structure to dynamics: frequency tuning in the p53–mdm2 network: I. logical approach. *Journal of theoretical biology*, 258(4):561–577, 2009.
- [3] Sara Sadat Aghamiri, Vidisha Singh, Aurélien Naldi, Tomáš Helikar, Sylvain Soliman, and Anna Niarakis. Automated inference of boolean models from molecular interaction maps using casq. *Bioinformatics*, 36(16):4473–4482, 2020.
- [4] Réka Albert, Biswa R Acharya, Byeong Wook Jeon, Jorge GT Zañudo, Mengmeng Zhu, Karim Osman, and Sarah M Assmann. A new discrete dynamic model of aba-induced stomatal closure predicts key feedback loops. *PLoS biology*, 15(9):e2003451, 2017.
- [5] María Camila Álvarez-Silva, Sally Yepes, Maria Mercedes Torres, and Andres Fernando Gonzalez Barrios. Proteins interaction network and modeling of igvh mutational status in chronic lymphocytic leukemia. *Theoretical Biology and Medical Modelling*, 12(1):1–15, 2015.
- [6] Osama Ali Arshad and Aniruddha Datta. Towards targeted combinatorial therapy design for the treatment of castration-resistant prostate cancer. *BMC bioinformatics*, 18(4):5–15, 2017.
- [7] Eugenio Azpeitia, Mariana Benítez, Iliusi Vega, Carlos Villarreal, and Elena R Alvarez-Buylla. Single-cell and coupled grn models of cell patterning in the arabidopsis thaliana root stem cell niche. *BMC systems biology*, 4(1):1–19, 2010.
- [8] Violeta Balbas-Martinez, Leire Ruiz-Cerdá, Itziar Irurzun-Arana, Ignacio González-García, An Vermeulen, José David Gómez-Mantilla, and Iñaki F Trocóniz. A systems pharmacology model for inflammatory bowel disease. PloS one, 13(3):e0192949, 2018.
- [9] Jonas Béal, Lorenzo Pantolini, Vincent Noël, Emmanuel Barillot, and Laurence Calzone. Personalized logical models to investigate cancer response to braf treatments in melanomas and colorectal cancers. PLOS Computational Biology, 17(1):e1007900, 2021.
- [10] Nikola Beneš, Luboš Brim, Jakub Kadlecaj, Samuel Pastva, and David Šafránek. AEON: attractor bifurcation analysis of parametrised boolean networks. In *International Conference on Computer Aided Verification*, pages 569–581. Springer, 2020.
- [11] Madison Brandon, Brad Howard, Christopher Lawrence, and Reinhard Laubenbacher. Iron acquisition and oxidative stress response in aspergillus fumigatus. *BMC systems biology*, 9(1):1–18, 2015.

- [12] Elisabetta Cacace, Samuel Collombet, and Denis Thieffry. Logical modeling of cell fate specification—application to t cell commitment. *Current Topics in Developmental Biology*, 139:205–238, 2020.
- [13] Laurence Calzone, Laurent Tournier, Simon Fourquet, Denis Thieffry, Boris Zhivotovsky, Emmanuel Barillot, and Andrei Zinovyev. Mathematical modelling of cell-fate decision in response to death receptor engagement. PLoS Comput Biol, 6(3):e1000702, 2010.
- [14] Claudine Chaouiya, Duncan Bérenguier, Sarah M Keating, Aurélien Naldi, Martijn P Van Iersel, Nicolas Rodriguez, Andreas Dräger, Finja Büchel, Thomas Cokelaer, Bryan Kowal, et al. Sbml qualitative models: a model representation format and infrastructure to foster interactions between qualitative modelling formalisms and tools. BMC systems biology, 7(1):1–15, 2013.
- [15] Anastasia Chasapi, Paulina Wachowicz, Anne Niknejad, Philippe Collin, Andrea Krapp, Elena Cano, Viesturs Simanis, and Ioannis Xenarios. An extended, boolean model of the septation initiation network in s. pombe provides insights into its regulation. *PloS one*, 10(8):e0134214, 2015.
- [16] Sung-Hwan Cho, Sang-Min Park, Ho-Sung Lee, Hwang-Yeol Lee, and Kwang-Hyun Cho. Attractor landscape analysis of colorectal tumorigenesis and its reversion. *BMC systems biology*, 10(1):1–13, 2016.
- [17] Tobias S Christensen, Ana Paula Oliveira, and Jens Nielsen. Reconstruction and logical modeling of glucose repression signaling pathways in saccharomyces cerevisiae. *BMC systems biology*, 3(1):1–15, 2009.
- [18] Vaishali L Chudasama, Meric A Ovacik, Darrell R Abernethy, and Donald E Mager. Logic-based and cellular pharmacodynamic modeling of bortezomib responses in u266 human myeloma cells. *Journal of Pharmacology and Experimental Therapeutics*, 354(3):448–458, 2015.
- [19] David PA Cohen, Loredana Martignetti, Sylvie Robine, Emmanuel Barillot, Andrei Zinovyev, and Laurence Calzone. Mathematical modelling of molecular pathways enabling tumour cell invasion and migration. *PLoS computational biology*, 11(11):e1004571, 2015.
- [20] Samuel Collombet, Chris van Oevelen, Jose Luis Sardina Ortega, Wassim Abou-Jaoudé, Bruno Di Stefano, Morgane Thomas-Chollier, Thomas Graf, and Denis Thieffry. Logical modeling of lymphoid and myeloid cell specification and transdifferentiation. *Proceedings of the National Academy of Sciences*, 114(23):5792–5799, 2017.
- [21] Brittany D Conroy, Tyler A Herek, Timothy D Shew, Matthew Latner, Joshua J Larson, Laura Allen, Paul H Davis, Tomáš Helikar, and Christine E Cutucache. Design, assessment, and in vivo evaluation of a computational model illustrating the role of cav1 in cd4+ t-lymphocytes. Frontiers in immunology, 5:599, 2014.

- [22] Marion Coolen, Denis Thieffry, Øyvind Drivenes, Thomas S Becker, and Laure Bally-Cuif. mir-9 controls the timing of neurogenesis through the direct inhibition of antagonistic factors. *Developmental cell*, 22(5):1052–1064, 2012.
- [23] Karla Fabiola Corral-Jara, Camille Chauvin, Wassim Abou-Jaoudé, Maximilien Grandclaudon, Aurélien Naldi, Vassili Soumelis, and Denis Thieffry. Interplay between smad2 and stat5a is a critical determinant of il-17a/il-17f differential expression. Molecular Biomedicine, 2(1):1–16, 2021.
- [24] Meike Dahlhaus, Andre Burkovski, Falk Hertwig, Christoph Mussel, Ruth Volland, Matthias Fischer, Klaus-Michael Debatin, Hans A Kestler, and Christian Beltinger. Boolean modeling identifies greatwall/mastl as an important regulator in the aurka network of neuroblastoma. *Cancer letters*, 371(1):79–89, 2016.
- [25] Maria I Davidich and Stefan Bornholdt. Boolean network model predicts cell cycle sequence of fission yeast. *PloS one*, 3(2):e1672, 2008.
- [26] Isadora Deal, Matthew Macauley, and Robin Davies. Boolean models of the transport, synthesis, and metabolism of tryptophan in escherichia coli. arXiv preprint arXiv:2202.11182, 2022.
- [27] Silvia Von der Heyde, Christian Bender, Frauke Henjes, Johanna Sonntag, Ulrike Korf, and Tim Beissbarth. Boolean ErbB network reconstructions and perturbation simulations reveal individual drug response in different breast cancer cell lines. BMC systems biology, 8(1):1–22, 2014.
- [28] Christophe Desterke, Christophe Martinaud, Nadira Ruzehaji, Le Bousse-Kerdilès, et al. Inflammation as a keystone of bone marrow stroma alterations in primary myelofibrosis. *Mediators of inflammation*, 2015, 2015.
- [29] Jennifer Enciso, Hector Mayani, Luis Mendoza, and Rosana Pelayo. Modeling the pro-inflammatory tumor microenvironment in acute lymphoblastic leukemia predicts a breakdown of hematopoietic-mesenchymal communication networks. Frontiers in physiology, 7:349, 2016.
- [30] Adrien Fauré, Aurélien Naldi, Claudine Chaouiya, and Denis Thieffry. Dynamical analysis of a generic Boolean model for the control of the mammalian cell cycle. *Bioinformatics*, 22(14):e124–e131, 2006.
- [31] Adrien Fauré, Aurélien Naldi, Fabrice Lopez, Claudine Chaouiya, Andrea Ciliberto, and Denis Thieffry. Modular logical modelling of the budding yeast cell cycle. *Molecular BioSystems*, 5(12):1787–1796, 2009.
- [32] Adrien Fauré and Denis Thieffry. Logical modelling of cell cycle control in eukaryotes: a comparative study. *Molecular BioSystems*, 5(12):1569–1581, 2009.

- [33] Adrien Fauré, Barbara MI Vreede, Élio Sucena, and Claudine Chaouiya. A discrete model of drosophila eggshell patterning reveals cell-autonomous and juxtacrine effects. PLoS computational biology, 10(3):e1003527, 2014.
- [34] Åsmund Flobak, Anaïs Baudot, Elisabeth Remy, Liv Thommesen, Denis Thieffry, Martin Kuiper, and Astrid Lægreid. Discovery of drug synergies in gastric cancer cells predicted by logical modeling. *PLoS computational* biology, 11(8):e1004426, 2015.
- [35] Swann Floc'Hlay, Maria Dolores Molina, Céline Hernandez, Emmanuel Haillot, Morgane Thomas-Chollier, Thierry Lepage, and Denis Thieffry. Deciphering and modelling the $\operatorname{tgf-}\beta$ signalling interplays specifying the dorsal-ventral axis of the sea urchin embryo. *Development*, 148(2):dev189944, 2021.
- [36] Xiao Gan and Réka Albert. Analysis of a dynamic model of guard cell signaling reveals the stability of signal propagation. *BMC systems biology*, 10(1):1–14, 2016.
- [37] Michael Getz, Yafei Wang, Gary An, Andrew Becker, Chase Cockrell, Nicholson Collier, Morgan Craig, Courtney L Davis, James Faeder, Ashlee N Ford Versypt, et al. Rapid community-driven development of a sarscov-2 tissue simulator. *BioRxiv*, 2020.
- [38] Clare E Giacomantonio and Geoffrey J Goodhill. A boolean model of the gene regulatory network underlying mammalian cortical area development. *PLoS Comput Biol*, 6(9):e1000936, 2010.
- [39] Jorge Gómez Tejeda Zañudo, Pingping Mao, Clara Alcon, Kailey Kowalski, Gabriela N Johnson, Guotai Xu, Jose Baselga, Maurizio Scaltriti, Anthony Letai, Joan Montero, et al. Cell line–specific network models of er+ breast cancer identify potential pi3kα inhibitor resistance mechanisms and drug combinations. Cancer research, 81(17):4603–4617, 2021.
- [40] Jorge Gómez Tejeda Zañudo, Maurizio Scaltriti, and Réka Albert. A network modeling approach to elucidate drug resistance mechanisms and predict combinatorial drug treatments in breast cancer. Cancer convergence, 1(1):1–25, 2017.
- [41] Aitor González, Claudine Chaouiya, and Denis Thieffry. Dynamical analysis of the regulatory network defining the dorsal–ventral boundary of the drosophila wing imaginal disc. *Genetics*, 174(3):1625–1634, 2006.
- [42] Aitor González, Claudine Chaouiya, and Denis Thieffry. Logical modelling of the role of the hh pathway in the patterning of the drosophila wing disc. *Bioinformatics*, 24(16):i234–i240, 2008.
- [43] Melanie Grieb, Andre Burkovski, J Eric Sträng, Johann M Kraus, Alexander Groß, Günther Palm, Michael Kühl, and Hans A Kestler. Predicting

- variabilities in cardiac gene expression with a boolean network incorporating uncertainty. *PLoS One*, 10(7):e0131832, 2015.
- [44] Luca Grieco, Laurence Calzone, Isabelle Bernard-Pierrot, François Radvanyi, Brigitte Kahn-Perles, and Denis Thieffry. Integrative modelling of the influence of mapk network on cancer cell fate decision. *PLoS compu*tational biology, 9(10):e1003286, 2013.
- [45] Shantanu Gupta and Ronaldo F Hashimoto. Dynamical analysis of a boolean network model of the oncogene role of lncrna anril and lncrna ufc1 in non-small cell lung cancer. *Biomolecules*, 12(3):420, 2022.
- [46] Shantanu Gupta, Pritam Kumar Panda, Ronaldo F Hashimoto, Shailesh Kumar Samal, Suman Mishra, Suresh Kr Verma, Yogendra Kumar Mishra, and Rajeev Ahuja. Dynamical modeling of mir-34a, mir-449a, and mir-16 reveals numerous ddr signaling pathways regulating senescence, autophagy, and apoptosis in hela cells. Scientific reports, 12(1):1– 13, 2022.
- [47] Shantanu Gupta, Daner A Silveira, Ronaldo F Hashimoto, and Jose Carlos M Mombach. A boolean model of the proliferative role of the lncrna xist in non-small cell lung cancer cells. *Biology*, 11(4):480, 2022.
- [48] Shantanu Gupta, Daner A Silveira, and José Carlos M Mombach. Atm/mir-34a-5p axis regulates a p21-dependent senescence-apoptosis switch in non-small cell lung cancer: a boolean model of g1/s checkpoint regulation. FEBS letters, 594(2):227–239, 2020.
- [49] Shantanu Gupta, Daner A Silveira, and José Carlos M Mombach. Towards dna-damage induced autophagy: A boolean model of p53-induced cell fate mechanisms. DNA repair, 96:102971, 2020.
- [50] Simone Gupta, Siddharth S Bisht, Ritushree Kukreti, Sanjeev Jain, and Samir K Brahmachari. Boolean network analysis of a neurotransmitter signaling pathway. *Journal of theoretical biology*, 244(3):463–469, 2007.
- [51] Praveen Kumar Guttula, Pedro T Monteiro, and Mukesh Kumar Gupta. A boolean logical model for reprogramming of testes-derived male germline stem cells into germline pluripotent stem cells. Computer Methods and Programs in Biomedicine, 192:105473, 2020.
- [52] Fiona K Hamey, Sonia Nestorowa, Sarah J Kinston, David G Kent, Nicola K Wilson, and Berthold Göttgens. Reconstructing blood stem cell regulatory network models from single-cell molecular profiles. *Proceedings* of the National Academy of Sciences, 114(23):5822–5829, 2017.
- [53] Tomáš Helikar, Naomi Kochi, Bryan Kowal, Manjari Dimri, Mayumi Naramura, Srikumar M Raja, Vimla Band, Hamid Band, and Jim A

- Rogers. A comprehensive, multi-scale dynamical model of erbb receptor signal transduction in human mammary epithelial cells. *PloS one*, 8(4):e61757, 2013.
- [54] Tomáš Helikar, John Konvalina, Jack Heidel, and Jim A Rogers. Emergent decision-making in biological signal transduction networks. *Proceedings of* the National Academy of Sciences, 105(6):1913–1918, 2008.
- [55] Tomáš Helikar, Bryan Kowal, Sean McClenathan, Mitchell Bruckner, Thaine Rowley, Alex Madrahimov, Ben Wicks, Manish Shrestha, Kahani Limbu, and Jim A Rogers. The cell collective: toward an open and collaborative approach to systems biology. BMC systems biology, 6(1):1–14, 2012.
- [56] Léonard Hérault, Mathilde Poplineau, Estelle Duprez, and Élisabeth Remy. A novel boolean network inference strategy to model early hematopoiesis aging. bioRxiv, 2022.
- [57] Céline Hernandez, Morgane Thomas-Chollier, Aurélien Naldi, and Denis Thieffry. Computational verification of large logical models—application to the prediction of t cell response to checkpoint inhibitors. Frontiers in physiology, 11:558606, 2020.
- [58] Franziska Herrmann, Alexander Groß, Dao Zhou, Hans A Kestler, and Michael Kühl. A boolean model of the cardiac gene regulatory network determining first and second heart field identity. *PloS one*, 7(10):e46798, 2012.
- [59] David J Irons. Logical analysis of the budding yeast cell cycle. *Journal of theoretical biology*, 257(4):543–559, 2009.
- [60] Nobuhisa Ito, Go Kuwahara, Yuta Sukehiro, and Hiromitsu Teratani. Segmental arterial mediolysis accompanied by renal infarction and pancreatic enlargement: a case report. *Journal of Medical Case Reports*, 6(1):1–5, 2012.
- [61] Andy Jenkins and Matthew Macauley. Bistability and asynchrony in a boolean model of the l-arabinose operon in escherichia coli. *Bulletin of mathematical biology*, 79(8):1778–1795, 2017.
- [62] Aravind Karanam, David He, Po-Kai Hsu, Sebastian Schulze, Guillaume Dubeaux, Richa Karmakar, Julian I Schroeder, and Wouter-Jan Rappel. Boolink: a graphical interface for open access boolean network simulations and use in guard cell co2 signaling. *Plant Physiology*, 187(4):2311–2322, 2021.
- [63] Laleh Kazemzadeh, Marija Cvijovic, and Dina Petranovic. Boolean model of yeast apoptosis as a tool to study yeast and human apoptotic regulations. *Frontiers in physiology*, 3:446, 2012.

- [64] Gwenael Kervizic and Laurent Corcos. Dynamical modeling of the cholesterol regulatory pathway with boolean networks. *BMC systems biology*, 2(1):1–14, 2008.
- [65] Faiz M Khan, Stephan Marquardt, Shailendra K Gupta, Susanne Knoll, Ulf Schmitz, Alf Spitschak, David Engelmann, Julio Vera, Olaf Wolkenhauer, and Brigitte M Pützer. Unraveling a tumor type-specific regulatory core underlying e2f1-mediated epithelial-mesenchymal transition to predict receptor protein signatures. *Nature communications*, 8(1):1–15, 2017.
- [66] Steffen Klamt, Julio Saez-Rodriguez, Jonathan A Lindquist, Luca Simeoni, and Ernst D Gilles. A methodology for the structural and functional analysis of signaling and regulatory networks. BMC bioinformatics, 7(1):1–26, 2006.
- [67] Hannes Klarner, Adam Streck, and Heike Siebert. PyBoolNet: a python package for the generation, analysis and visualization of boolean networks. *Bioinformatics*, 33(5):770–772, 2017.
- [68] Maria Kondratova, Emmanuel Barillot, Andrei Zinovyev, and Laurence Calzone. Modelling of immune checkpoint network explains synergistic effects of combined immune checkpoint inhibitor therapy and the impact of cytokines in patient response. *Cancers*, 12(12):3600, 2020.
- [69] Ho-Sung Lee, Myeong-Jin Goh, Junil Kim, Tae-Jun Choi, Hae Kwang Lee, Yong Joo Na, and Kwang-Hyun Cho. A systems-biological study on the identification of safe and effective molecular targets for the reduction of ultraviolet b-induced skin pigmentation. *Scientific reports*, 5(1):1–11, 2015.
- [70] Song Li, Sarah M Assmann, and Réka Albert. Predicting essential components of signal transduction networks: a dynamic model of guard cell abscisic acid signaling. *PLoS Biol*, 4(10):e312, 2006.
- [71] Junyan Lu, Hanlin Zeng, Zhongjie Liang, Limin Chen, Liyi Zhang, Hao Zhang, Hong Liu, Hualiang Jiang, Bairong Shen, Ming Huang, et al. Network modelling reveals the mechanism underlying colitis-associated colon cancer and identifies novel combinatorial anti-cancer targets. Scientific reports, 5(1):1–15, 2015.
- [72] Timo Lubitz, Niek Welkenhuysen, Sviatlana Shashkova, Loubna Bendrioua, Stefan Hohmann, Edda Klipp, and Marcus Krantz. Network reconstruction and validation of the snf1/ampk pathway in baker's yeast based on a comprehensive literature review. NPJ systems biology and applications, 1(1):1–10, 2015.
- [73] Aidan MacNamara, Camille Terfve, David Henriques, Beatriz Peñalver Bernabé, and Julio Saez-Rodriguez. State—time spectrum of signal transduction logic models. *Physical biology*, 9(4):045003, 2012.

- [74] Alex Madrahimov, Tomáš Helikar, Bryan Kowal, Guoqing Lu, and Jim Rogers. Dynamics of influenza virus and human host interactions during infection and replication cycle. *Bulletin of mathematical biology*, 75(6):988–1011, 2013.
- [75] Parul Maheshwari, Sarah M Assmann, and Reka Albert. A guard cell abscisic acid (aba) network model that captures the stomatal resting state. Frontiers in physiology, 11:927, 2020.
- [76] Parul Maheshwari, Hao Du, Jen Sheen, Sarah M Assmann, and Reka Albert. Model-driven discovery of calcium-related protein-phosphatase inhibition in plant guard cell signaling. *PLoS computational biology*, 15(10):e1007429, 2019.
- [77] Zhongxing Mai and Haiyan Liu. Boolean network-based analysis of the apoptosis network: irreversible apoptosis and stable surviving. *Journal of theoretical biology*, 259(4):760–769, 2009.
- [78] Rahuman S Malik-Sheriff, Mihai Glont, Tung VN Nguyen, Krishna Tiwari, Matthew G Roberts, Ashley Xavier, Manh T Vu, Jinghao Men, Matthieu Maire, Sarubini Kananathan, et al. Biomodels—15 years of sharing computational models in life science. *Nucleic acids research*, 48(D1):D407–D415, 2020.
- [79] Malvina Marku, Nina Verstraete, Flavien Raynal, Miguel Madrid-Mencía, Marcin Domagala, Jean-Jacques Fournié, Loïc Ysebaert, Mary Poupot, and Vera Pancaldi. Insights on tam formation from a boolean model of macrophage polarization based on in vitro studies. *Cancers*, 12(12):3664, 2020.
- [80] Manuel Marques-Pita and Luis M Rocha. Canalization and control in automata networks: body segmentation in drosophila melanogaster. *PloS one*, 8(3):e55946, 2013.
- [81] Mariana Esther Martinez-Sanchez, Luis Mendoza, Carlos Villarreal, and Elena R Alvarez-Buylla. A minimal regulatory network of extrinsic and intrinsic factors recovers observed patterns of cd4+ t cell differentiation and plasticity. *PLoS computational biology*, 11(6):e1004324, 2015.
- [82] Pablo Martínez-Sosa and Luis Mendoza. The regulatory network that controls the differentiation of T lymphocytes. *Biosystems*, 113(2):96–103, 2013.
- [83] Abibatou Mbodj, E Hilary Gustafson, Lucia Ciglar, Guillaume Junion, Aitor Gonzalez, Charles Girardot, Laurent Perrin, Eileen EM Furlong, and Denis Thieffry. Qualitative dynamical modelling can formally explain mesoderm specification and predict novel developmental phenotypes. *PLoS computational biology*, 12(9):e1005073, 2016.

- [84] Abibatou Mbodj, Guillaume Junion, Christine Brun, Eileen EM Furlong, and Denis Thieffry. Logical modelling of drosophila signalling pathways. *Molecular BioSystems*, 9(9):2248–2258, 2013.
- [85] Akram Méndez and Luis Mendoza. A network model to describe the terminal differentiation of b cells. *PLoS computational biology*, 12(1):e1004696, 2016.
- [86] Péter Mendik, Márk Kerestély, Sebestyén Kamp, Dávid Deritei, Nina Kunšič, Zsolt Vassy, Péter Csermely, and Daniel V Veres. Translocating proteins compartment-specifically alter the fate of epithelial-mesenchymal transition in a compartmentalized boolean network model. npj Systems Biology and Applications, 8(1):1–11, 2022.
- [87] Luis Mendoza. A network model for the control of the differentiation process in th cells. *Biosystems*, 84(2):101–114, 2006.
- [88] Luis Mendoza and Akram Méndez. A dynamical model of the regulatory network controlling lymphopoiesis. *Biosystems*, 137:26–33, 2015.
- [89] Luis Mendoza and Ioannis Xenarios. A method for the generation of standardized qualitative dynamical systems of regulatory networks. *Theoretical Biology and Medical Modelling*, 3(1):1–18, 2006.
- [90] Patrick Meyer, Pallab Maity, Andre Burkovski, Julian Schwab, Christoph Müssel, Karmveer Singh, Filipa F Ferreira, Linda Krug, Harald J Maier, Meinhard Wlaschek, et al. A model of the onset of the senescence associated secretory phenotype after dna damage induced senescence. PLoS computational biology, 13(12):e1005741, 2017.
- [91] Quentin Miagoux, Vidisha Singh, Dereck de Mézquita, Valerie Chaudru, Mohamed Elati, Elisabeth Petit-Teixeira, and Anna Niarakis. Inference of an integrative, executable network for rheumatoid arthritis combining data-driven machine learning approaches and a state-of-the-art mechanistic disease map. *Journal of personalized medicine*, 11(8):785, 2021.
- [92] José Mombach, Cristhian A Bugs, and Claudine Chaouiya. Modelling the onset of senescence at the g1/s cell cycle checkpoint. *BMC genomics*, 15(7):1–11, 2014.
- [93] Arnau Montagud, Jonas Béal, Luis Tobalina, Pauline Traynard, Vigneshwari Subramanian, Bence Szalai, Róbert Alföldi, László Puskás, Alfonso Valencia, Emmanuel Barillot, et al. Patient-specific boolean models of signalling networks guide personalised treatments. *Elife*, 11:e72626, 2022.
- [94] Jana Musilová. Signaling pathway for butanol production in solventogenic clostridium bacteria. Master's thesis, Brno University of Technology, 2019.

- [95] Aurélien Naldi, Jorge Carneiro, Claudine Chaouiya, and Denis Thieffry. Diversity and plasticity of th cell types predicted from regulatory network modelling. *PLoS computational biology*, 6(9):e1000912, 2010.
- [96] Aurélien Naldi, Céline Hernandez, Wassim Abou-Jaoudé, Pedro T Monteiro, Claudine Chaouiya, and Denis Thieffry. Logical modeling and analysis of cellular regulatory networks with ginsim 3.0. Frontiers in physiology, 9:646, 2018.
- [97] Anna Niarakis, Yacine Bounab, Luca Grieco, Romain Roncagalli, Anne-Marie Hesse, Jérôme Garin, Bernard Malissen, Marc Daëron, and Denis Thieffry. Computational modeling of the main signaling pathways involved in mast cell activation. Fc Receptors, pages 69–93, 2014.
- [98] Barbara Niederdorfer, Vasundra Touré, Miguel Vazquez, Liv Thommesen, Martin Kuiper, Astrid Lægreid, and Åsmund Flobak. Strategies to enhance logic modeling-based cell line-specific drug synergy prediction. Frontiers in Physiology, page 862, 2020.
- [99] Karen J Nuñez-Reza, Aurélien Naldi, Arantza Sánchez-Jiménez, Ana V Leon-Apodaca, M Angélica Santana, Morgane Thomas-Chollier, Denis Thieffry, and Alejandra Medina-Rivera. Logical modelling of in vitro differentiation of human monocytes into dendritic cells unravels novel transcriptional regulatory interactions. *Interface Focus*, 11(4):20200061, 2021.
- [100] Barbara Offermann, Steffen Knauer, Amit Singh, María L Fernández-Cachón, Martin Klose, Silke Kowar, Hauke Busch, and Melanie Boerries. Boolean modeling reveals the necessity of transcriptional regulation for bistability in pc12 cell differentiation. Frontiers in genetics, page 44, 2016.
- [101] Cihan Oguz, Layne T Watson, William T Baumann, and John J Tyson. Predicting network modules of cell cycle regulators using relative protein abundance statistics. *BMC systems biology*, 11(1):1–24, 2017.
- [102] David A Orlando, Charles Y Lin, Allister Bernard, Jean Y Wang, Joshua ES Socolar, Edwin S Iversen, Alexander J Hartemink, and Steven B Haase. Global control of cell-cycle transcription by coupled cdk and network oscillators. *Nature*, 453(7197):944–947, 2008.
- [103] Elizabeth Ortiz-Gutiérrez, Karla García-Cruz, Eugenio Azpeitia, Aaron Castillo, María de la Paz Sánchez, and Elena R Álvarez-Buylla. A dynamic gene regulatory network model that recovers the cyclic behavior of arabidopsis thaliana cell cycle. PLoS computational biology, 11(9):e1004486, 2015.
- [104] Marek Ostaszewski, Alexander Mazein, Marc E Gillespie, Inna Kuperstein, Anna Niarakis, Henning Hermjakob, Alexander R Pico, Egon L Willighagen, Chris T Evelo, Jan Hasenauer, et al. Covid-19 disease map, building a computational repository of sars-cov-2 virus-host interaction mechanisms. *Scientific data*, 7(1):1–4, 2020.

- [105] Oyebode J Oyeyemi, Oluwafemi Davies, David L Robertson, and Jean-Marc Schwartz. A logical model of hiv-1 interactions with the t-cell activation signalling pathway. *Bioinformatics*, 31(7):1075–1083, 2015.
- [106] Alessandro Palma, Marta Iannuccelli, Ilaria Rozzo, Luana Licata, Livia Perfetto, Giorgia Massacci, Luisa Castagnoli, Gianni Cesareni, and Francesca Sacco. Integrating patient-specific information into logic models of complex diseases: application to acute myeloid leukemia. *Journal* of Personalized Medicine, 11(2):117, 2021.
- [107] Alessandro Palma, Abdul Salam Jarrah, Paolo Tieri, Gianni Cesareni, and Filippo Castiglione. Gene regulatory network modeling of macrophage differentiation corroborates the continuum hypothesis of polarization states. Frontiers in physiology, 9:1659, 2018.
- [108] Jong-Chan Park, So-Yeong Jang, Dongjoon Lee, Jeongha Lee, Uiryong Kang, Hongjun Chang, Haeng Jun Kim, Sun-Ho Han, Jinsoo Seo, Murim Choi, et al. A logical network-based drug-screening platform for alzheimer's disease representing pathological features of human brain organoids. *Nature communications*, 12(1):1–13, 2021.
- [109] Daniel Plaugher and David Murrugarra. Modeling the pancreatic cancer microenvironment in search of control targets. *Bulletin of Mathematical Biology*, 83(11):1–26, 2021.
- [110] Sobia Raza, Kevin A Robertson, Paul A Lacaze, David Page, Anton J Enright, Peter Ghazal, and Tom C Freeman. A logic-based diagram of signalling pathways central to macrophage activation. *BMC systems biology*, 2(1):1–15, 2008.
- [111] Elisabeth Remy, Sandra Rebouissou, Claudine Chaouiya, Andrei Zinovyev, François Radvanyi, and Laurence Calzone. A modeling approach to explain mutually exclusive and co-occurring genetic alterations in bladder tumorigenesismathematical model of bladder tumorigenesis. *Cancer research*, 75(19):4042–4052, 2015.
- [112] Julia Rex, Ute Albrecht, Christian Ehlting, Maria Thomas, Ulrich M Zanger, Oliver Sawodny, Dieter Häussinger, Michael Ederer, Ronny Feuer, and Johannes G Bode. Model-based characterization of inflammatory gene expression patterns of activated macrophages. *PLoS computational biol*ogy, 12(7):e1005018, 2016.
- [113] Osiris Ríos, Sara Frias, Alfredo Rodríguez, Susana Kofman, Horacio Merchant, Leda Torres, and Luis Mendoza. A boolean network model of human gonadal sex determination. *Theoretical Biology and Medical Modelling*, 12(1):1–18, 2015.
- [114] Alfredo Rodriguez, David Sosa, Leda Torres, Bertha Molina, Sara Frias, and Luis Mendoza. A boolean network model of the fa/brca pathway. *Bioinformatics*, 28(6):858–866, 2012.

- [115] Alfredo Rodríguez, Leda Torres, Ulises Juárez, David Sosa, Eugenio Azpeitia, Benilde García-de Teresa, Edith Cortés, Rocío Ortíz, Ana M Salazar, Patricia Ostrosky-Wegman, et al. Fanconi anemia cells with unrepaired dna damage activate components of the checkpoint recovery process. Theoretical Biology and Medical Modelling, 12(1):1–22, 2015.
- [116] Otoniel Rodríguez-Jorge, Linda A Kempis-Calanis, Wassim Abou-Jaoudé, Darely Y Gutiérrez-Reyna, Céline Hernandez, Oscar Ramirez-Pliego, Morgane Thomas-Chollier, Salvatore Spicuglia, Maria A Santana, and Denis Thieffry. Cooperation between t cell receptor and toll-like receptor 5 signaling for cd4+ t cell activation. *Science signaling*, 12(577):eaar3641, 2019.
- [117] Anke Ryll, Regina Samaga, Fred Schaper, Leonidas G Alexopoulos, and Steffen Klamt. Large-scale network models of IL-1 and IL-6 signalling and their hepatocellular specification. *Molecular Biosystems*, 7(12):3253–3270, 2011.
- [118] Assieh Saadatpour, Rui-Sheng Wang, Aijun Liao, Xin Liu, Thomas P Loughran, István Albert, and Réka Albert. Dynamical and structural analysis of a t cell survival network identifies novel candidate therapeutic targets for large granular lymphocyte leukemia. *PLoS computational* biology, 7(11):e1002267, 2011.
- [119] Julio Saez-Rodriguez, Luca Simeoni, Jonathan A Lindquist, Rebecca Hemenway, Ursula Bommhardt, Boerge Arndt, Utz-Uwe Haus, Robert Weismantel, Ernst D Gilles, Steffen Klamt, et al. A logical model provides insights into T cell receptor signaling. *PLoS computational biology*, 3(8):e163, 2007.
- [120] Özgür Sahin, Holger Fröhlich, Christian Löbke, Ulrike Korf, Sara Burmester, Meher Majety, Jens Mattern, Ingo Schupp, Claudine Chaouiya, Denis Thieffry, et al. Modeling erbb receptor-regulated g1/s transition to find novel targets for de novo trastuzumab resistance. BMC systems biology, 3(1):1–20, 2009.
- [121] Regina Samaga, Julio Saez-Rodriguez, Leonidas G Alexopoulos, Peter K Sorger, and Steffen Klamt. The logic of EGFR/ErbB signaling: theoretical properties and analysis of high-throughput data. *PLoS computational biology*, 5(8):e1000438, 2009.
- [122] Lucas Sánchez and Claudine Chaouiya. Primary sex determination of placental mammals: a modelling study uncovers dynamical developmental constraints in the formation of sertoli and granulosa cells. *BMC systems biology*, 10(1):1–11, 2016.
- [123] Lucas Sánchez and Claudine Chaouiya. Logical modelling uncovers developmental constraints for primary sex determination of chicken gonads. Journal of The Royal Society Interface, 15(142):20180165, 2018.

- [124] Lucas Sánchez, Claudine Chaouiya, and Denis Thieffry. Segmenting the fly embryo: logical analysis of the role of the segment polarity cross-regulatory module. *International journal of developmental biology*, 52(8):1059–1075, 2002.
- [125] Lucas Sánchez and Denis Thieffry. A logical analysis of the drosophila gap-gene system. *Journal of theoretical Biology*, 211(2):115–141, 2001.
- [126] Lucas Sanchez and Denis Thieffry. Segmenting the fly embryo:: a logical analysis of the pair-rule cross-regulatory module. *Journal of theoretical Biology*, 224(4):517–537, 2003.
- [127] Ismael Sánchez-Osorio, Carlos A Hernández-Martínez, and Agustino Martínez-Antonio. Modeling asymmetric cell division in caulobacter crescentus using a boolean logic approach. In *Asymmetric Cell Division in Development, Differentiation and Cancer*, pages 1–21. Springer, 2017.
- [128] José Antonio Sánchez-Villanueva, Otoniel Rodríguez-Jorge, Oscar Ramírez-Pliego, Gabriela Rosas Salgado, Wassim Abou-Jaoudé, Céline Hernandez, Aurélien Naldi, Denis Thieffry, and María Angélica Santana. Contribution of ros and metabolic status to neonatal and adult cd8+ t cell activation. *PLoS One*, 14(12):e0226388, 2019.
- [129] Julian D Schwab, Silke D Kühlwein, Nensi Ikonomi, Michael Kühl, and Hans A Kestler. Concepts in boolean network modeling: What do they all mean? *Computational and structural biotechnology journal*, 18:571–582, 2020.
- [130] Gianluca Selvaggio, Sara Canato, Archana Pawar, Pedro T Monteiro, Patrícia S Guerreiro, M Manuela Brás, Florence Janody, and Claudine Chaouiya. Hybrid epithelial–mesenchymal phenotypes are controlled by microenvironmental factorsmicroenvironment driving emt plasticity. Cancer research, 80(11):2407–2420, 2020.
- [131] Domenico Sgariglia, Alessandra Jordano Conforte, Carlos Eduardo Pedreira, Luis Alfredo Vidal de Carvalho, Flavia Raquel Gonçalves Carneiro, Nicolas Carels, and Fabricio Alves Barbosa da Silva. Data-driven modeling of breast cancer tumors using boolean networks. Frontiers in big Data, 4, 2021.
- [132] Rafael Silva-Rocha and Víctor de Lorenzo. The tol network of p seudomonas putida mt-2 processes multiple environmental inputs into a narrow response space. *Environmental microbiology*, 15(1):271–286, 2013.
- [133] E Simao, Elisabeth Remy, Denis Thieffry, and Claudine Chaouiya. Qualitative modelling of regulated metabolic pathways: application to the tryptophan biosynthesis in e. coli. *Bioinformatics*, 21(suppl_2):ii190–ii196, 2005.

- [134] Amit Singh, Juliana M Nascimento, Silke Kowar, Hauke Busch, and Melanie Boerries. Boolean approach to signalling pathway modelling in hgf-induced keratinocyte migration. *Bioinformatics*, 28(18):i495–i501, 2012.
- [135] Herbert Sizek, Andrew Hamel, Dávid Deritei, Sarah Campbell, and Erzsébet Ravasz Regan. Boolean model of growth signaling, cell cycle and apoptosis predicts the molecular mechanism of aberrant cell cycle progression driven by hyperactive pi3k. *PLoS computational biology*, 15(3):e1006402, 2019.
- [136] Sriram Sridharan, Ritwik Layek, Aniruddha Datta, and Jijayanagaram Venkatraj. Boolean modeling and fault diagnosis in oxidative stress response. *BMC genomics*, 13(6):1–16, 2012.
- [137] Steven N Steinway, Matthew B Biggs, Thomas P Loughran Jr, Jason A Papin, and Reka Albert. Inference of network dynamics and metabolic interactions in the gut microbiome. *PLoS computational biology*, 11(6):e1004338, 2015.
- [138] Steven Nathaniel Steinway, Jorge GT Zañudo, Wei Ding, Carl Bart Rountree, David J Feith, Thomas P Loughran, and Reka Albert. Network modeling of $\operatorname{tgf}\beta$ signaling in hepatocellular carcinoma epithelial-to-mesenchymal transition reveals joint sonic hedgehog and wnt pathway activationnetwork modeling of epithelial-to-mesenchymal transition. Cancer research, 74(21):5963–5977, 2014.
- [139] Camille Terfve, Thomas Cokelaer, David Henriques, Aidan MacNamara, Emanuel Goncalves, Melody K Morris, Martijn van Iersel, Douglas A Lauffenburger, and Julio Saez-Rodriguez. Cellnoptr: a flexible toolkit to train protein signaling networks to data using multiple logic formalisms. BMC systems biology, 6(1):1–14, 2012.
- [140] Juilee Thakar, Ashutosh K Pathak, Lisa Murphy, Réka Albert, and Isabella M Cattadori. Network model of immune responses reveals key effectors to single and co-infection dynamics by a respiratory bacterium and a gastrointestinal helminth. PLoS computational biology, 8(1):e1002345, 2012.
- [141] Denis Thieffry and René Thomas. Dynamical behaviour of biological regulatory networks—ii. immunity control in bacteriophage lambda. *Bulletin of mathematical biology*, 57(2):277–297, 1995.
- [142] Robert G Todd and Tomáš Helikar. Ergodic sets as cell phenotype of budding yeast cell cycle. 2012.
- [143] Pauline Traynard, Adrien Fauré, François Fages, and Denis Thieffry. Logical model specification aided by model-checking techniques: application to the mammalian cell cycle regulation. *Bioinformatics*, 32(17):i772–i780, 2016.

- [144] Eirini Tsirvouli, Vasundra Touré, Barbara Niederdorfer, Miguel Vázquez, Åsmund Flobak, and Martin Kuiper. A middle-out modeling strategy to extend a colon cancer logical model improves drug synergy predictions in epithelial-derived cancer cell lines. Frontiers in molecular biosciences, 7:502573, 2020.
- [145] Stefania Vaga, Marti Bernardo-Faura, Thomas Cokelaer, Alessio Maiolica, Christopher A Barnes, Ludovic C Gillet, Björn Hegemann, Frank van Drogen, Hoda Sharifian, Edda Klipp, et al. Phosphoproteomic analyses reveal novel cross-modulation mechanisms between two signaling pathways in yeast. *Molecular systems biology*, 10(12):767, 2014.
- [146] Alan Veliz-Cuba and Brandilyn Stigler. Boolean models can explain bistability in the lac operon. *Journal of computational biology*, 18(6):783–794, 2011.
- [147] Loic Verlingue, Aurélien Dugourd, Gautier Stoll, Emmanuel Barillot, Laurence Calzone, and Arturo Londoño-Vallejo. A comprehensive approach to the molecular determinants of lifespan using a boolean model of geroconversion. *Aging cell*, 15(6):1018–1026, 2016.
- [148] Nathan Weinstein and Luis Mendoza. A network model for the specification of vulval precursor cells and cell fusion control in caenorhabditis elegans. *Frontiers in Genetics*, 4:112, 2013.
- [149] David J Wooten, Jorge Gómez Tejeda Zañudo, David Murrugarra, Austin M Perry, Anna Dongari-Bagtzoglou, Reinhard Laubenbacher, Clarissa J Nobile, and Réka Albert. Mathematical modeling of the candida albicans yeast to hyphal transition reveals novel control strategies. PLoS computational biology, 17(3):e1008690, 2021.
- [150] Jorge GT Zañudo, Steven N Steinway, and Réka Albert. Discrete dynamic network modeling of oncogenic signaling: Mechanistic insights for personalized treatment of cancer. *Current Opinion in Systems Biology*, 9:1–10, 2018.
- [151] Ranran Zhang, Mithun Vinod Shah, Jun Yang, Susan B Nyland, Xin Liu, Jong K Yun, Réka Albert, and Thomas P Loughran. Network model of survival signaling in large granular lymphocyte leukemia. *Proceedings of the National Academy of Sciences*, 105(42):16308–16313, 2008.