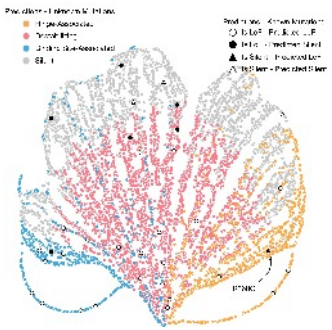
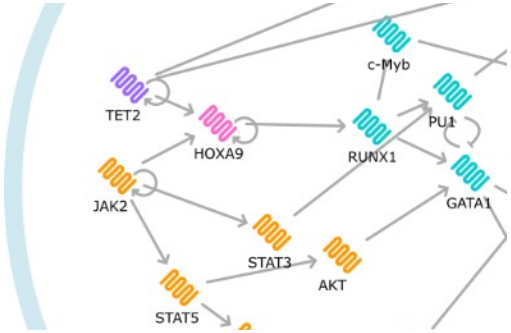
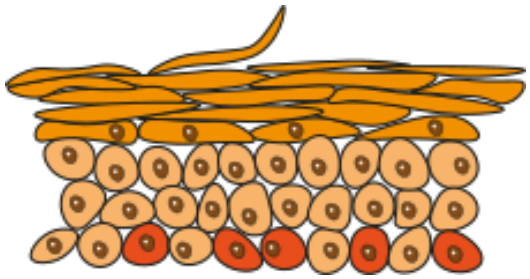
UCL
MEDICAL PHYSICS & BIOMEDICAL ENGINEERING





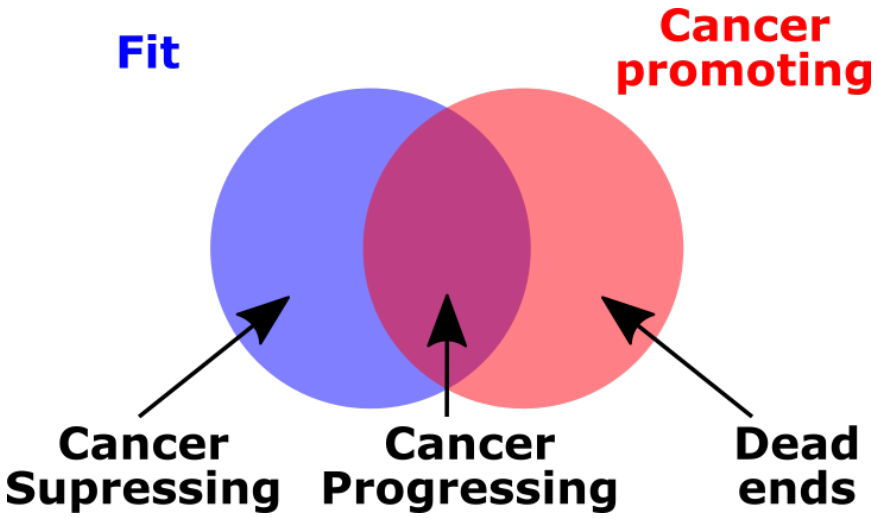


BioModelAnalyzer: Using formal verification to understand cancer development

Ben Hall

19/05/2021

- For cancer to develop in its earliest stages, cells in aging tissues must gain mutations that
  - Promote cancer enabling behaviours
  - Are fitter than their neighbours to persist and expand in the tissue



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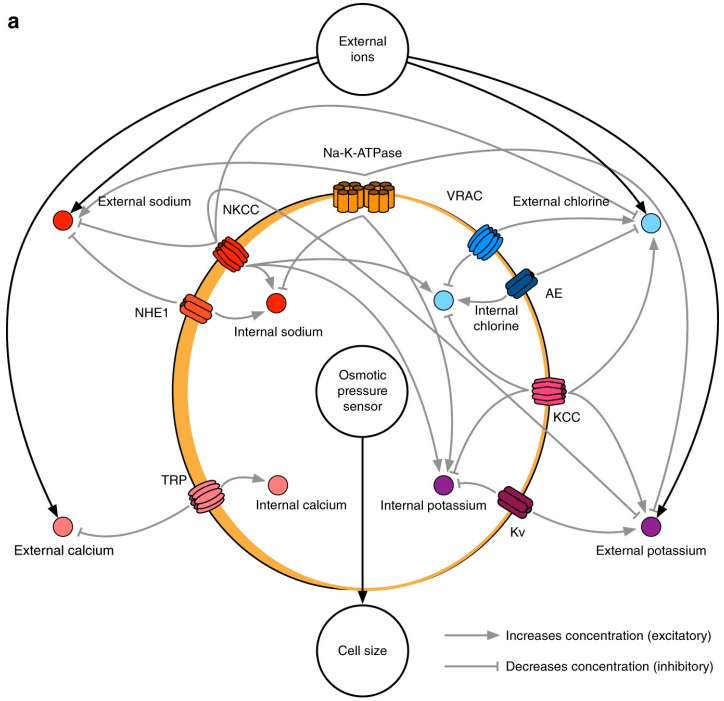
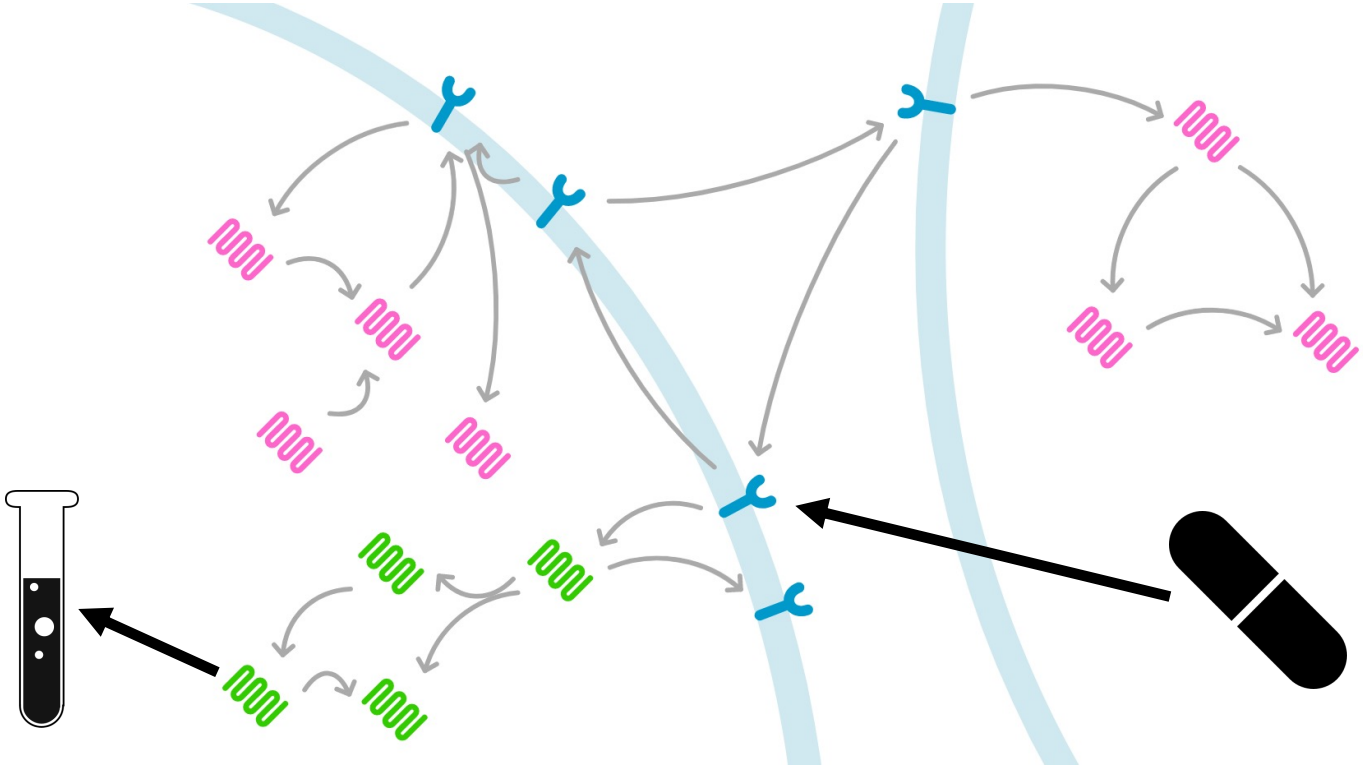


Competition
Space

Control
Networks

- Mechanistic understanding of early events
- Opportunities: markers, drugs



Introduction

- Modelling the networks that underlie cellular oncogenesis and fitness
- Executable models and BioModelAnalyzer
  - Algorithms and technologies behind BMA
- Recent development
  - Visualising and working with large networks
- Future directions

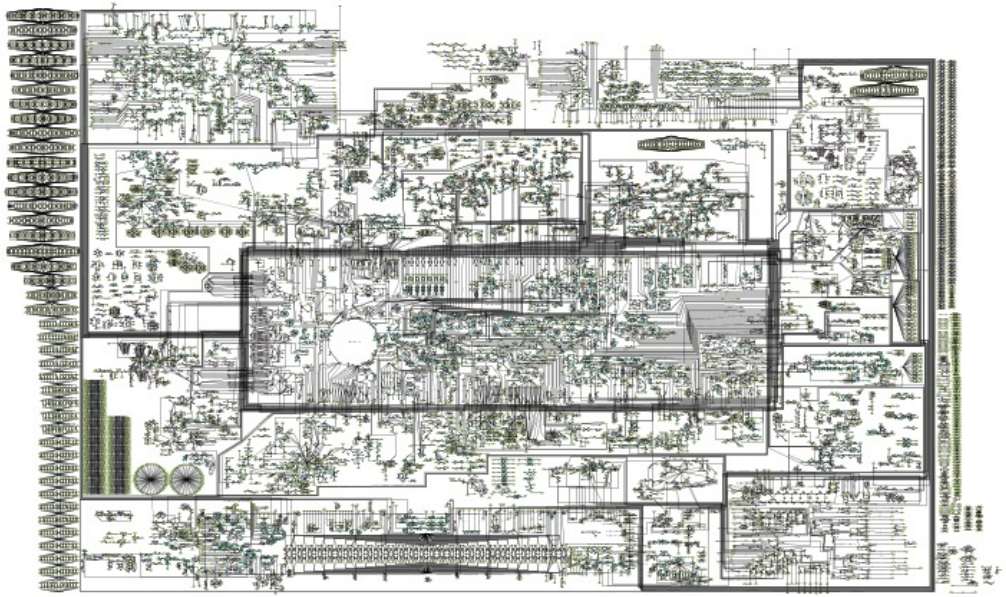
Robustness and rare events

- Biological systems are frequently characterised by robustness
  - Homeostasis and equilibrium dominate cellular and biochemical systems
- Robustness underlines cellular function

- Diseases are often associated with rare events
- Cancer is an exemplar of rare failure
  - The wrong mutations occurring in exactly the wrong order
  - 1 in 70 trillion cells develop into cancer, over a lifetime

- How to capture rare events? How to guarantee they don’t exist?

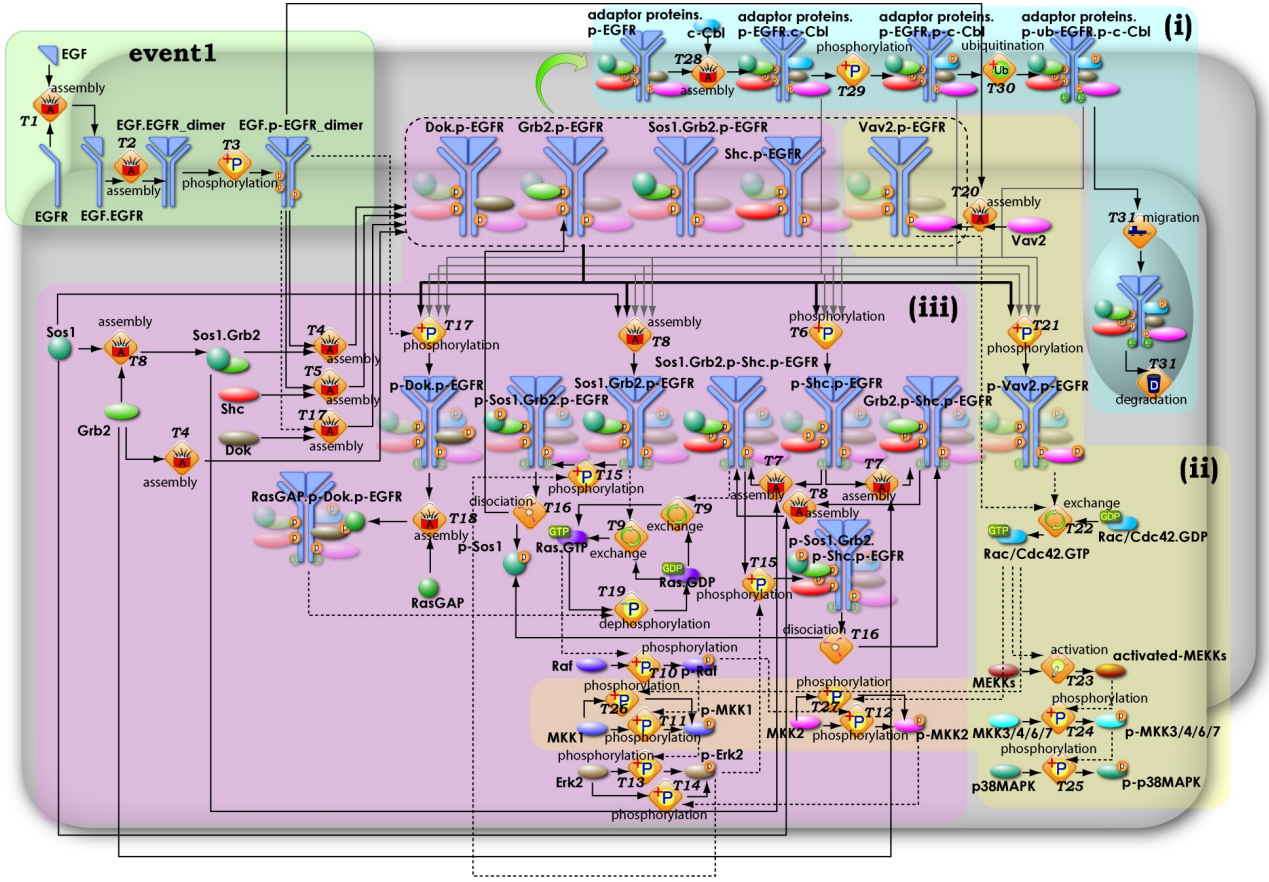
Cellular metabolism



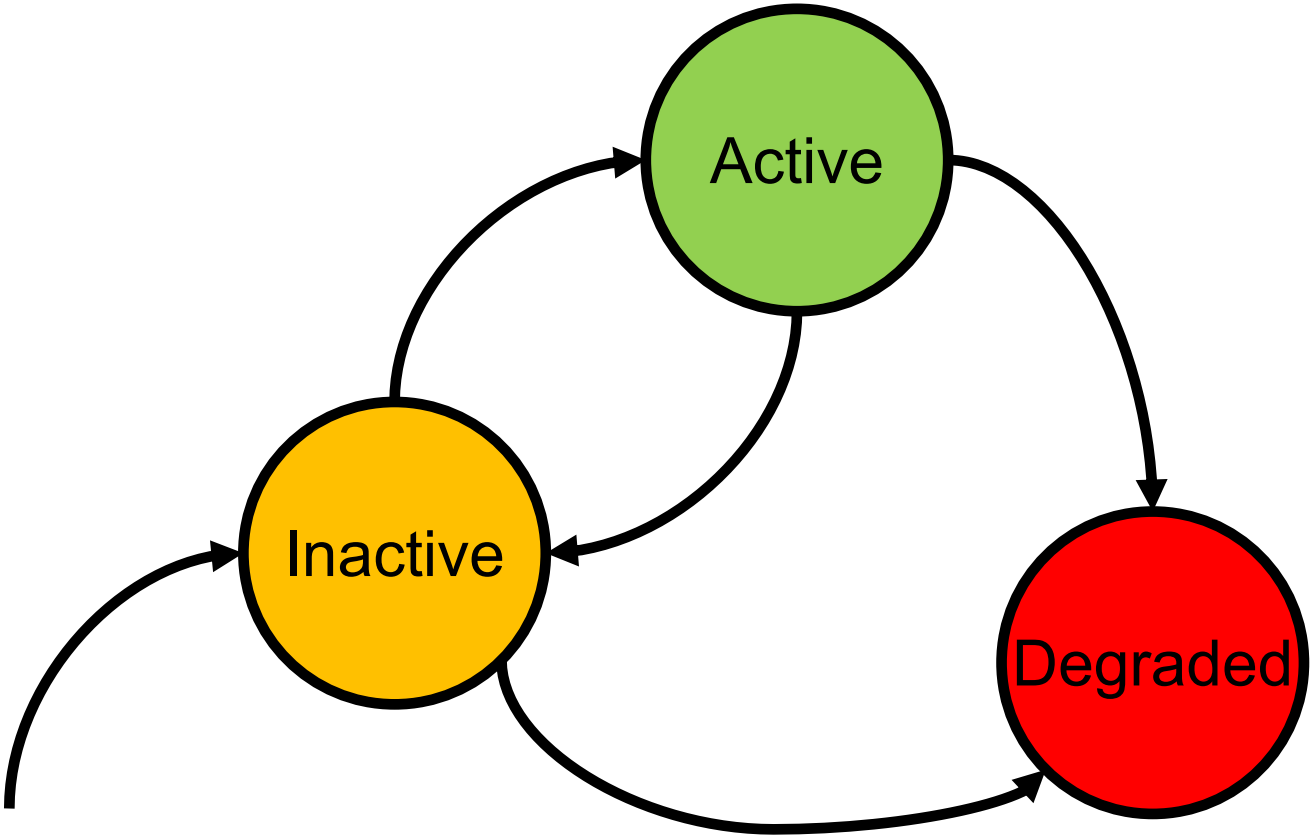
Biocomplexity

- As systems become more complex, the space for rare events increases
- The implications of uncertainties are magnified in large systems
- Models become larger → increased potential for error
- Models become larger → harder to explore

EGFR signalling pathway



Executable biology

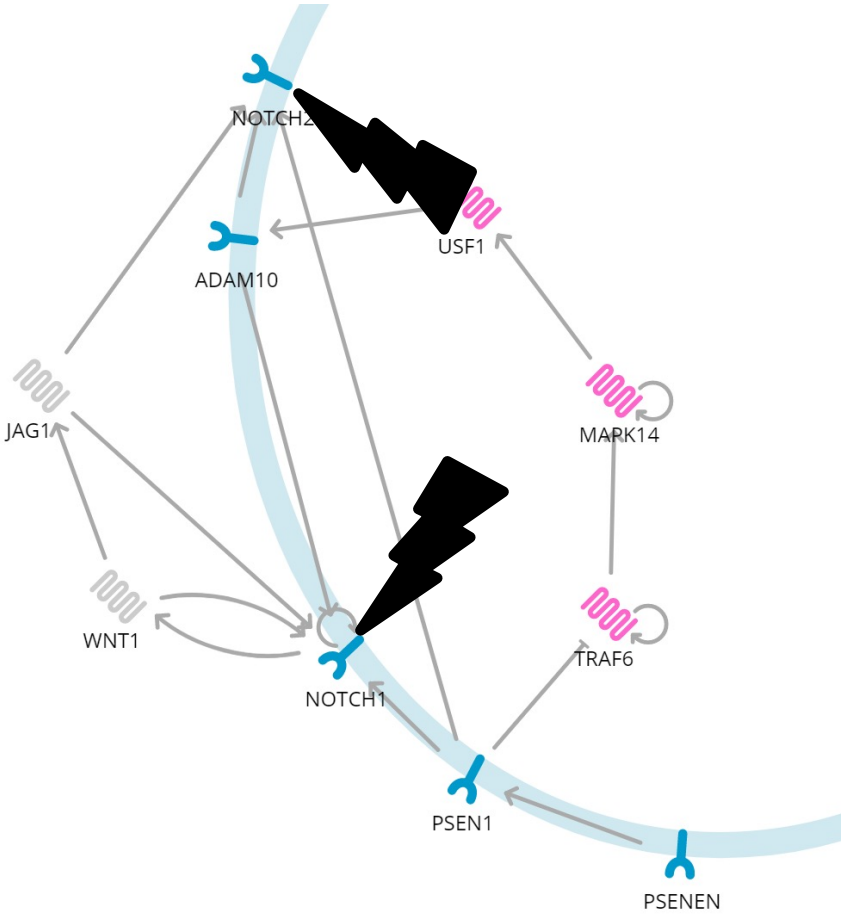


Model checking = guarantees

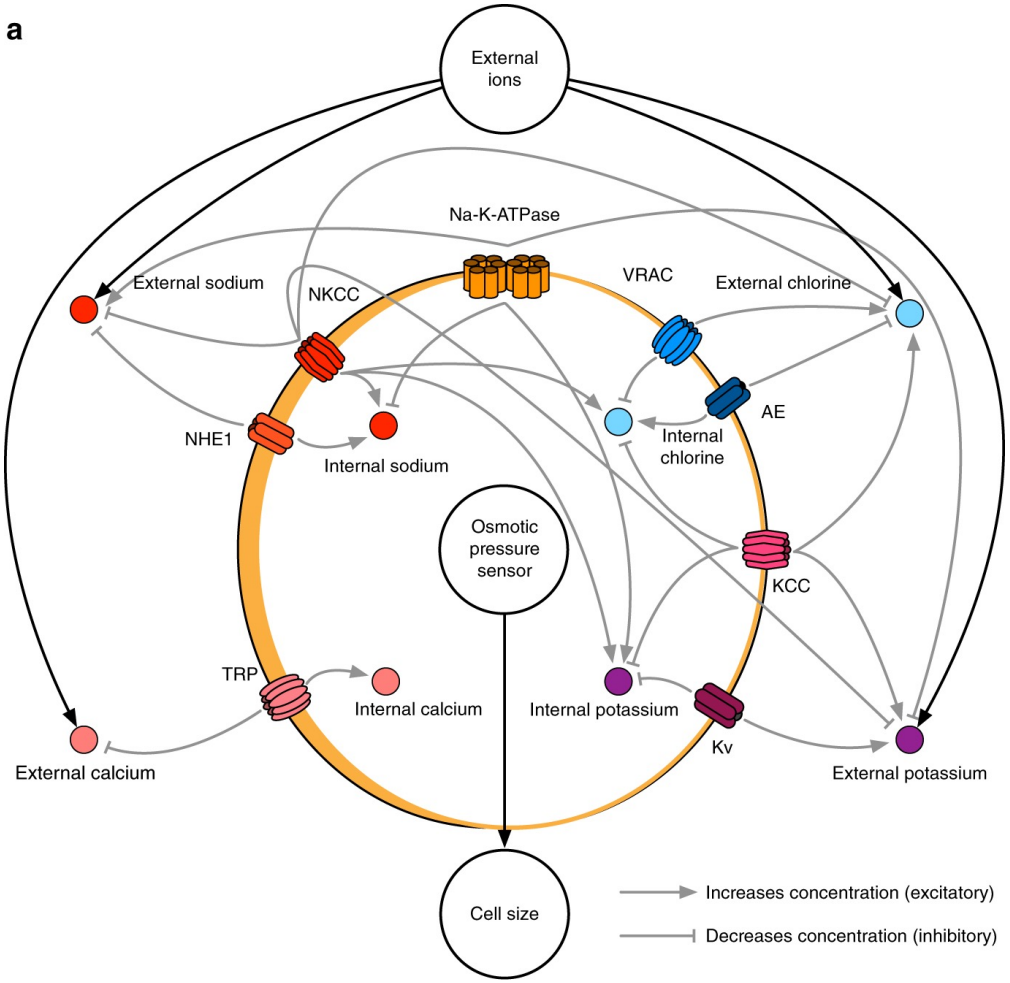
- Model checking addresses all of state space through mathematical proofs
- This give us guarantees
  - This can happen (rare events)
  - This never happens (robustness)
- *Model checking can solve problems for both the issues, and problems that exist at their intersection*

Networks determine cellular behaviour

- Molecular mechanisms of transformation



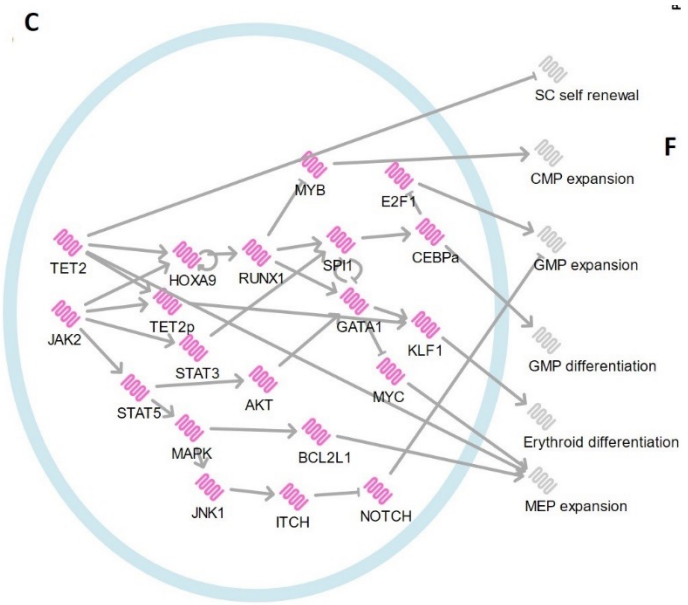
Networks models of ion channels



Riedel,… Hall and Shields, Nature Immunology 2016
Shorthouse,…, Shields and Hall Nature Communications 2018
Shorthouse et al, biorxiv preprint available 2020

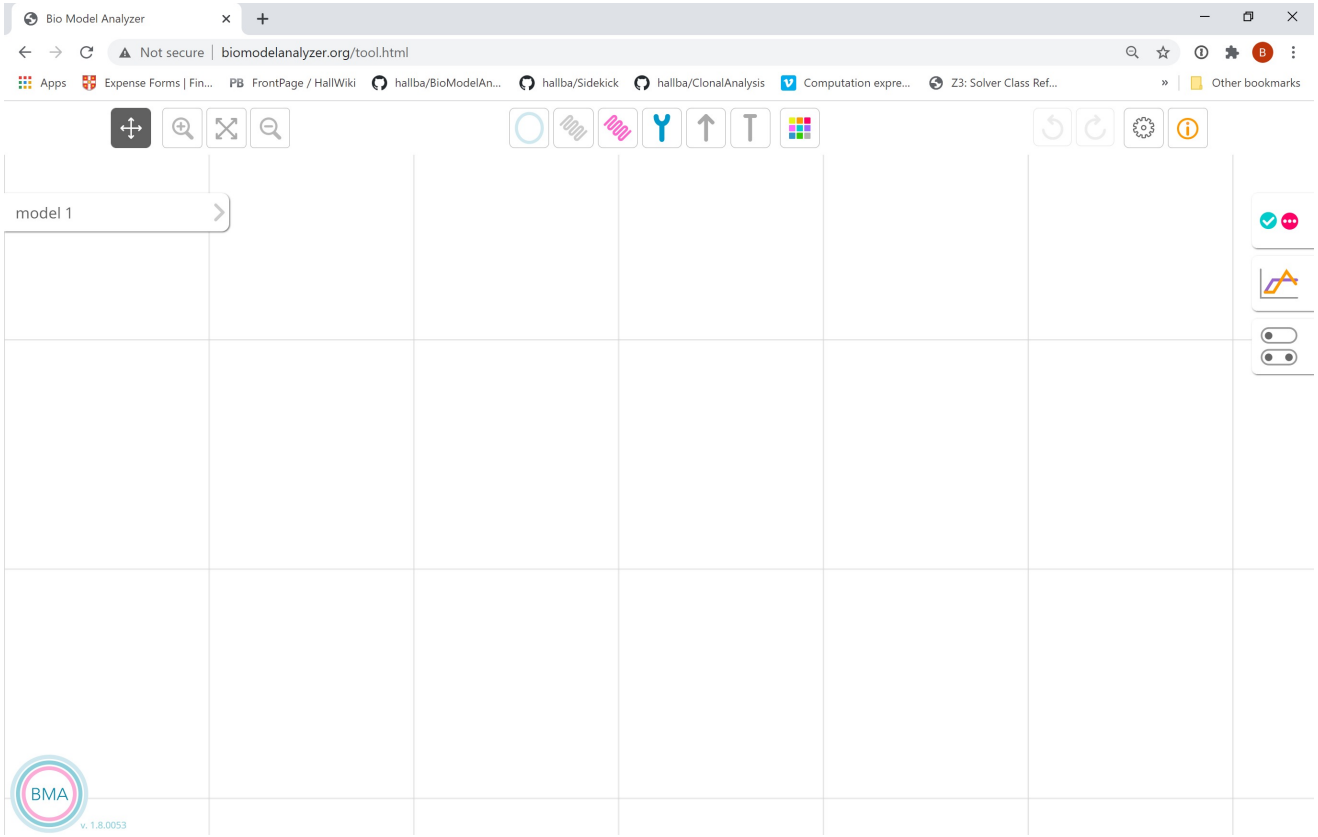
Switches controlling evolutionary progression

- Different orders of mutation give different clinical outcomes in MPN
- Network model proposes underlying network controlling phenotype



Talarmain et al, biorxiv preprint available 2021

BioModelAnalyzer (BMA)

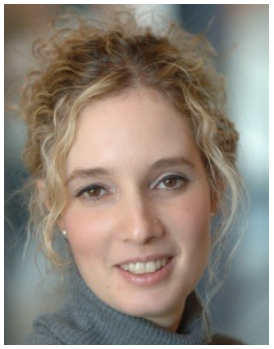


BMA

- Open source (MIT)
  https://github.com/hallba/BioModelAnalyzer
- Web tool
  http://biomodelanalyzer.org/
- Standalone binaries
  - Local webserver
  - Console
- A-level worksheets developed with OCR

Team

Ben Hall
UCL



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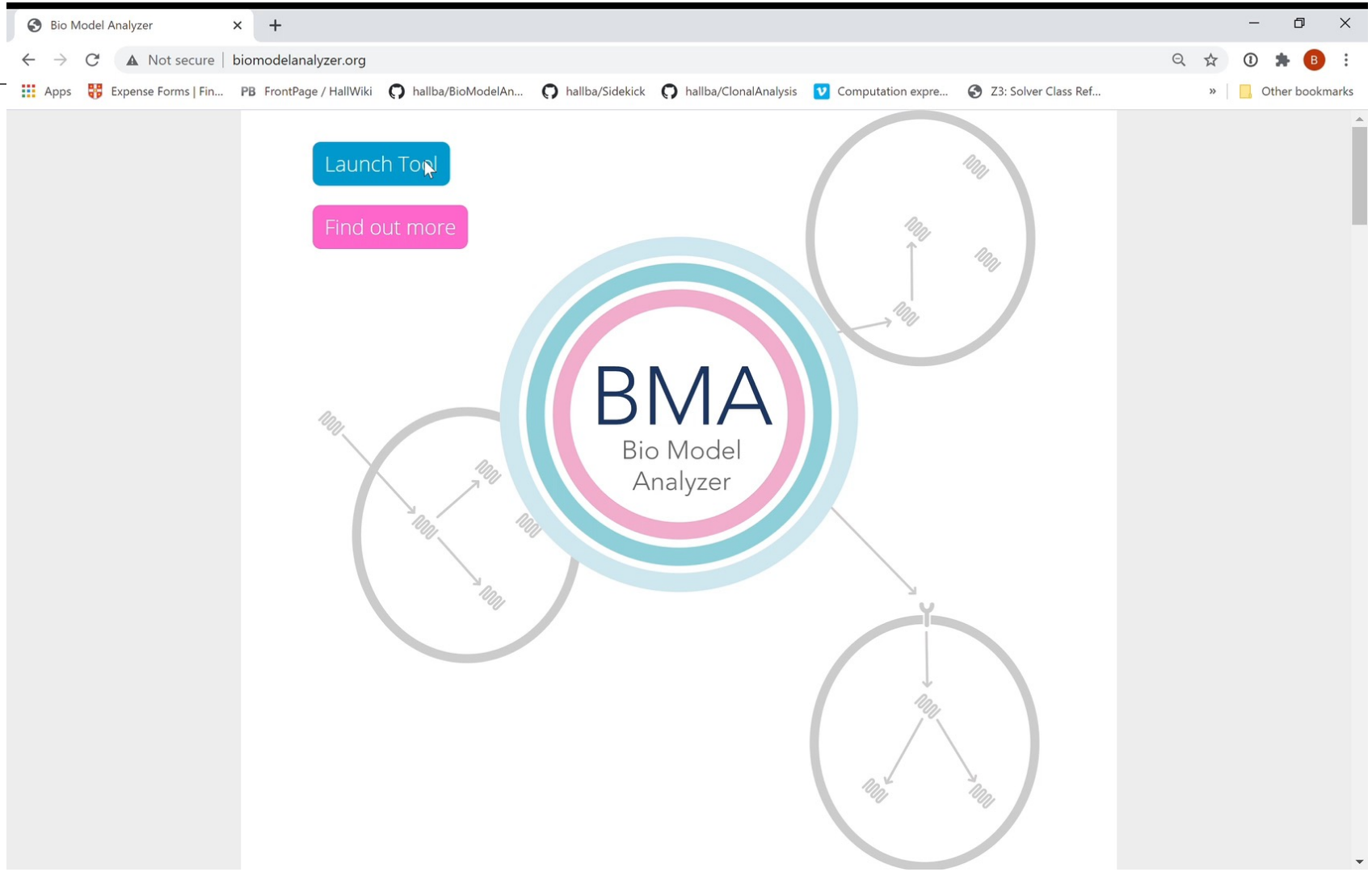
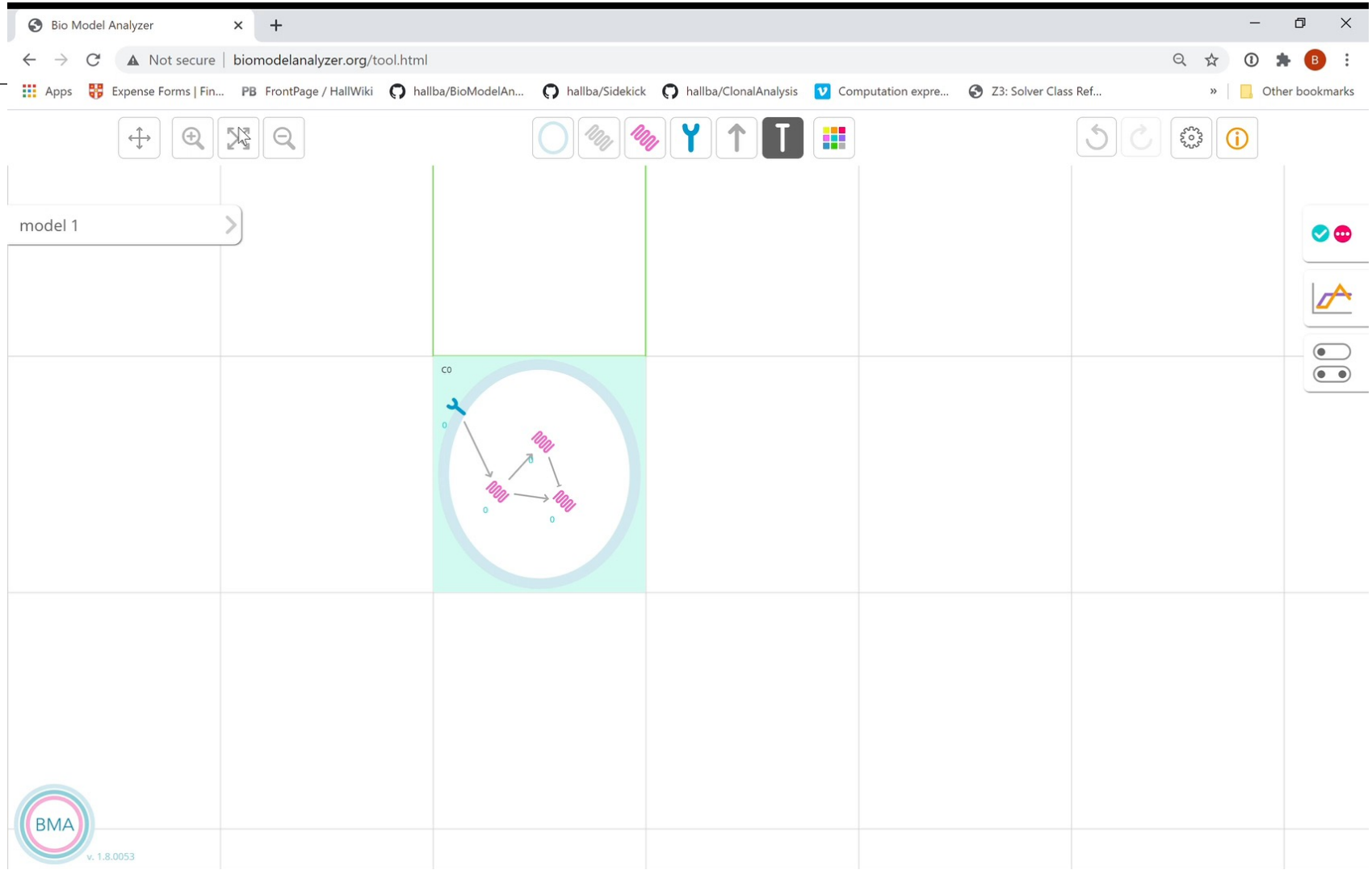

Bio Model Analyzer
Not secure
biomodelanalyzer.org
Apps
Expense Forms | Fin...
FrontPage / HallWiki
hallba/BioModelAn...
hallba/Sidekick
hallba/ClonalAnalysis
Computation expre...
Z3: Solver Class Ref...
Other bookmarks
Launch Tool
Find out more
BMA
Bio Model
Analyzer


Bio Model Analyzer
Not secure | biomodelanalyzer.org/tool.html
Apps
Expense Forms | Fin...
PB FrontPage / HallWiki
hallba/BioModelAn...
hallba/Sidekick
hallba/ClonalAnalysis
Computation expre...
Z3: Solver Class Ref...
Other bookmarks
model 1
c0
BMA
v. 1.8.0053

Architecture

- Console tool and underlying libraries in F#, using SMT solver Z3
- Web interface running on Azure, proofs run using Azure functions

Algorithms

- Highly scalable algorithms for testing model features
- Stability proof
  - Homeostasis or equilibrium
  - Bifurcations, oscillations
- Linear temporal logic queries
  - “Simulation search”

QN fundamentals

- Models are synchronous qualitative networks
- Each variable has a granularity and target function, describing how the variable updates

$$d'_v = \begin{cases} d_v + 1 & d_v < T_v(s) \text{ and } d_v < N, \\ d_v - 1 & d_v > T_v(s) \text{ and } d_v > 0, \\ d_v & \text{otherwise.} \end{cases}$$

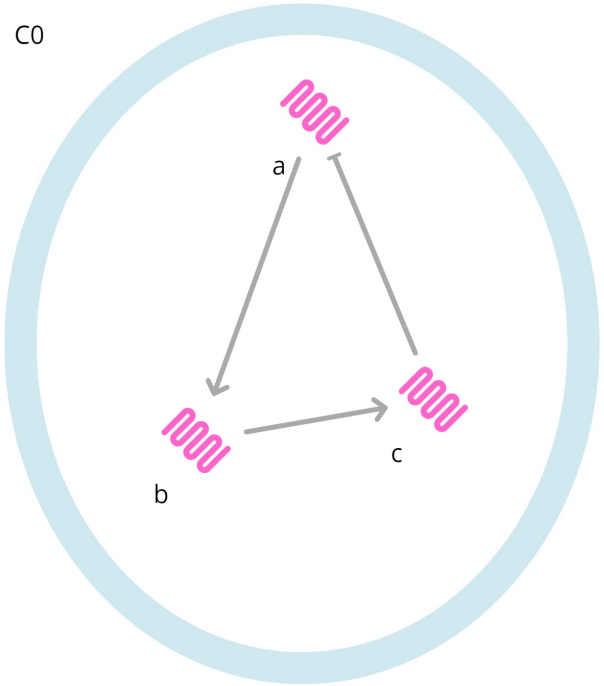
Stability proof

- "Does the model have a single fix point attractor"
  - Alternatives- multiple fix points or a cycle
- Common method- compute state transition graph

- BMA approach; prove the stability of the system by iteratively proving the stability of individual variables, by reducing their range

Cook et al, VMCAI 2011

Example (ToyModelStable)

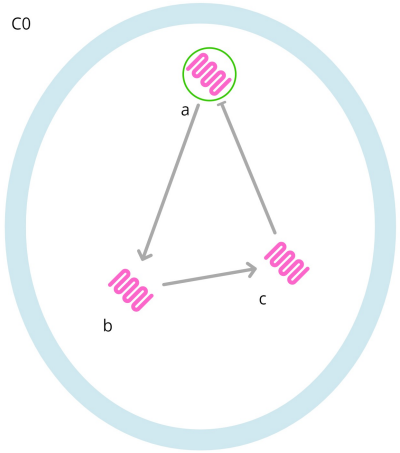


- Variables have default target function
- All range from zero to four

Process

- At each step
  - Pick a variable
  - From the ranges of its dependents, attempt to reduce the range
- Iterate until either all ranges are a singleton, or ranges cannot be reduced further

a



a ranges from 0-4

$T(a) = 0 - c$

c ranges from 0-4

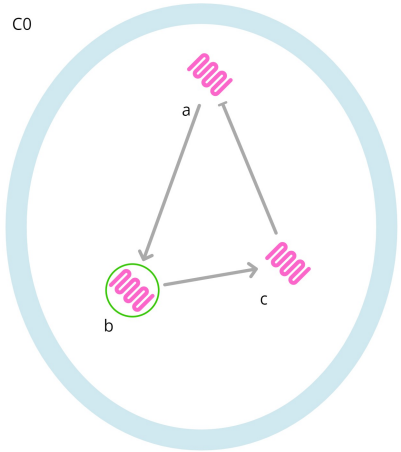
So

a can only be equal to 0

Proof Progression

Name
a
b
c

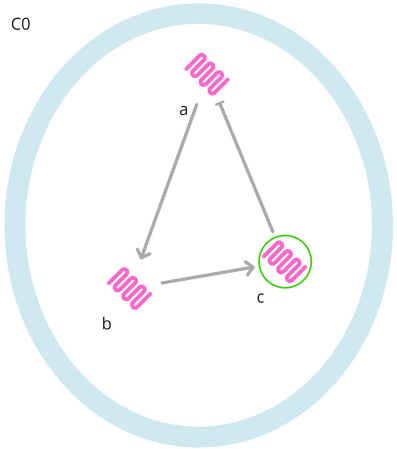
b



b ranges from 0-4
T(b) = a
a = 0 *(previous step)*
So
b can only be equal to 0

Proof Progression

Name	T = 0
a	0
b	0 - 4
c	0 - 4



c ranges from 0-4

T(c) = b

b = 0

So

c can only be equal to 0

Proof Progression

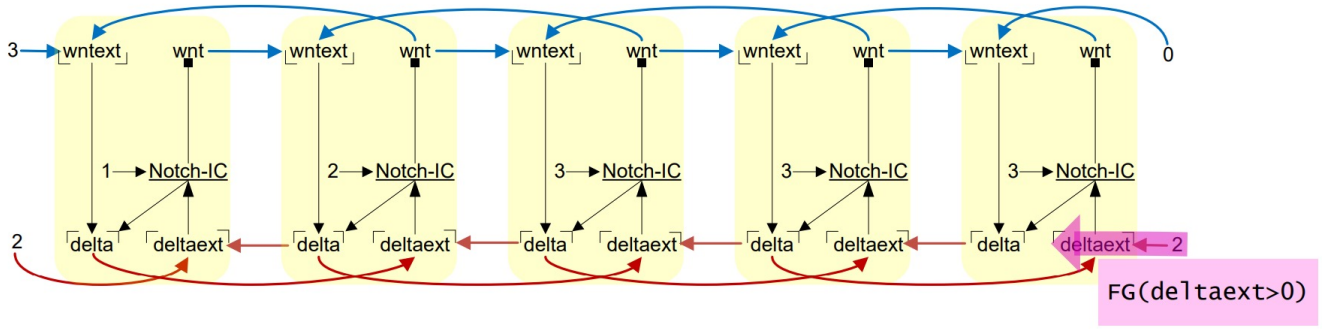
Name	T = 0	T = 1
a	0	0
b	0 - 4	0
c	0 - 4	0 - 4

What if its not proved stable?

- Does not imply instability
- In the tool, “further testing” runs a second test to determine what the endpoints are

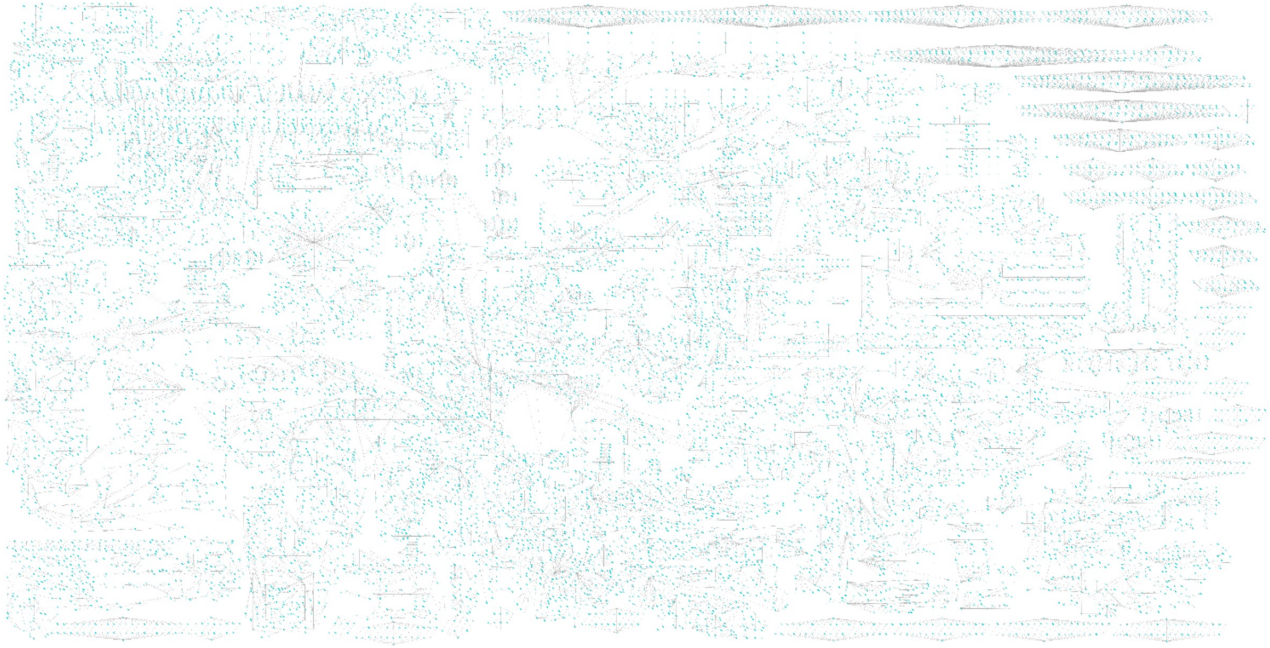
- This is assessed by using the reduced ranges from the first step and a Z3 query to search for fixpoints and cycles

Scalability



~5^5000

Scalability



~2^17000

Linear Temporal Logic

- LTL allows users to “search” for simulations
  - “Does this gene ever transiently become active?”
  - “If this mutation is present, do cells ever become senescent?”
- Query and simulation length as inputs
- Returns example simulations

- In BMA; three responses are generated from a single query
  - This is true for all simulations (always)
  - This is true for some simulations (sometimes)
  - This is false for all simulations (never)

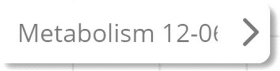
Claessen et al, CAV 2013

Ongoing challenges- scaling

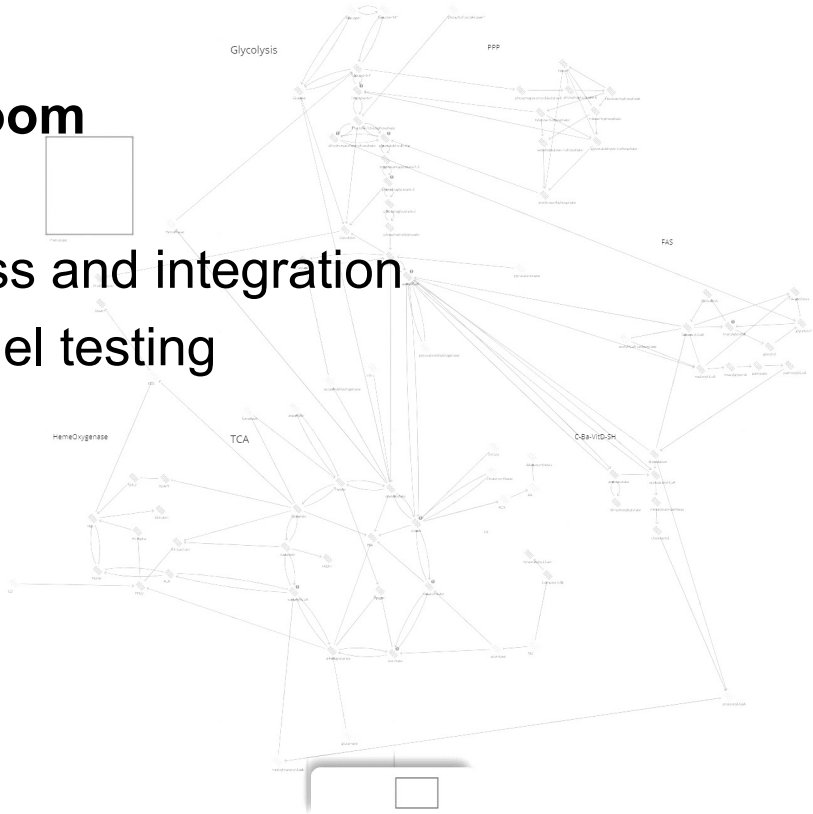
- We can analyse large models, but model building and refinement requires a way to interact and visualize them
- Data deluge from high throughput experiments
  - CRISPR screens
  - Protein interaction screens
- Maps and databases of small scale experiments
  - Omnipath
  - https://disease-maps.org/
- How to use and integrate?

Software features





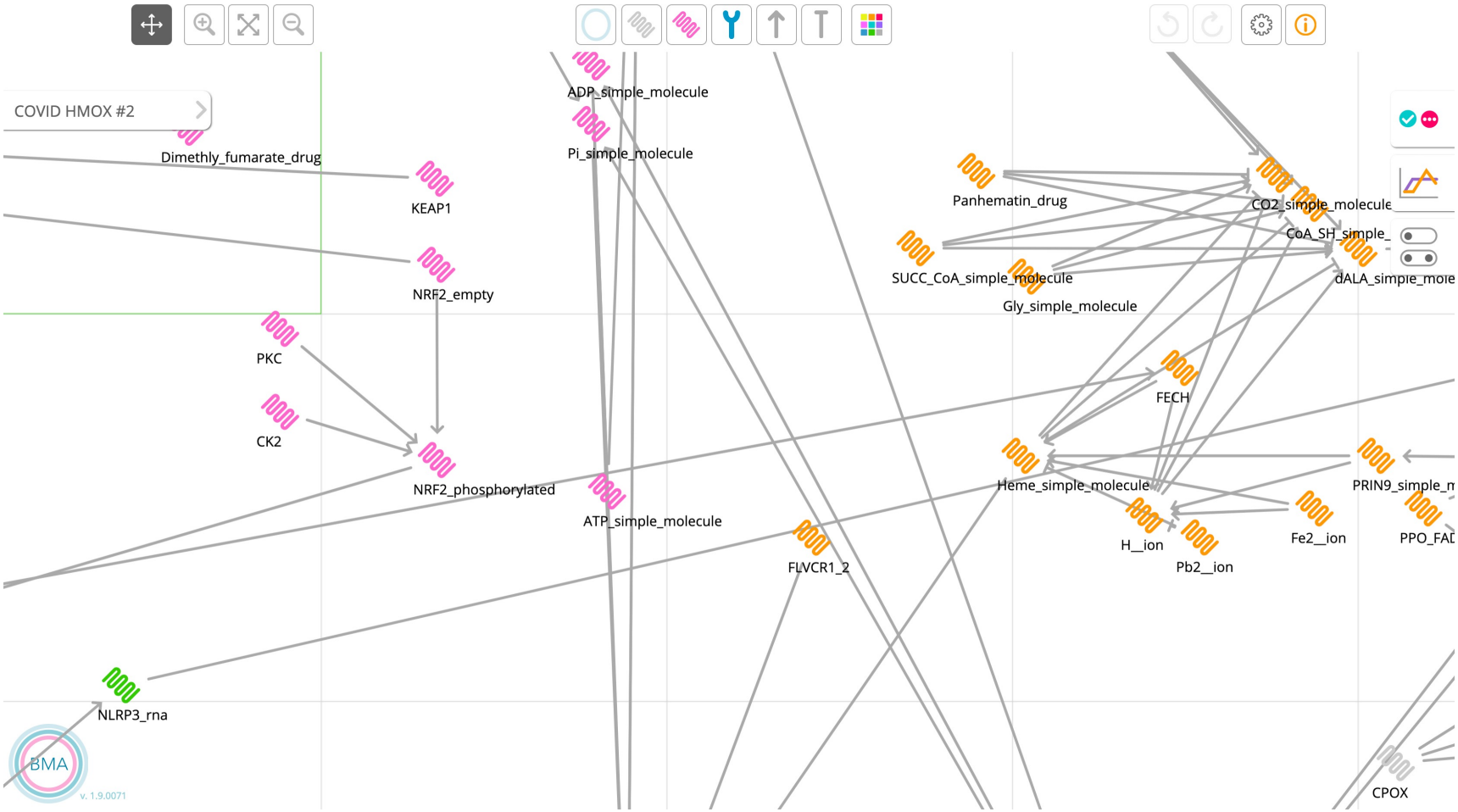
- **“Intelligent” zoom**



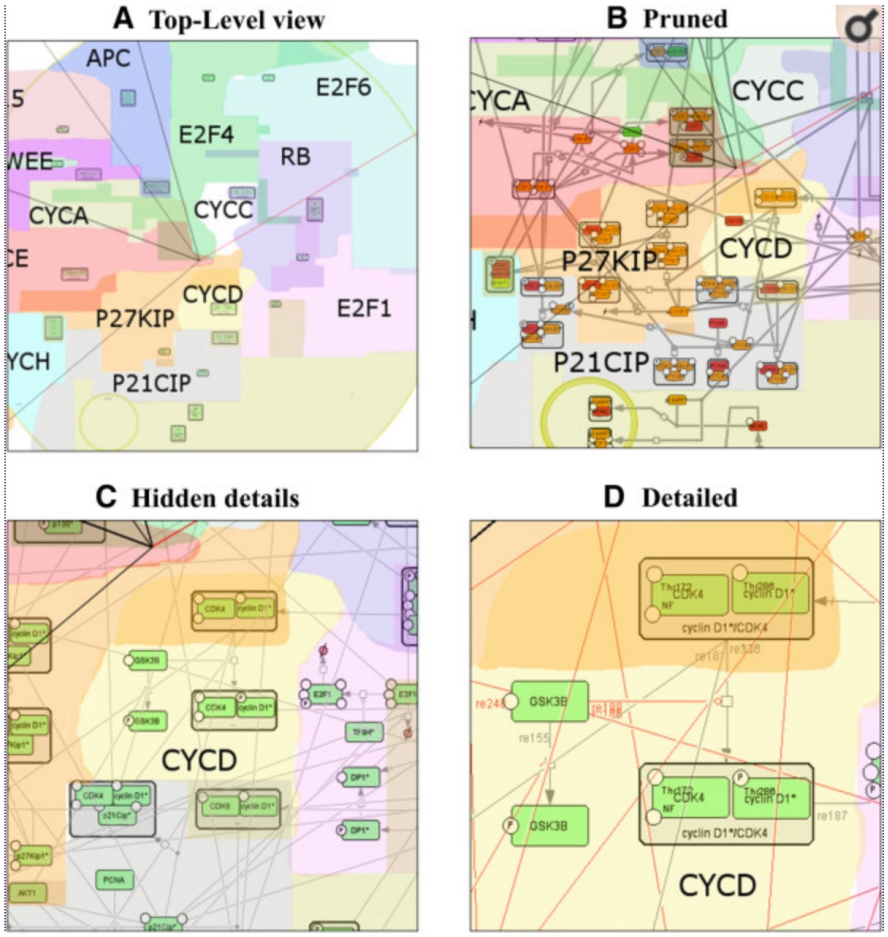
- Database access and integration
- Automated model testing
- ‘Omics import

v. 1.7.0019

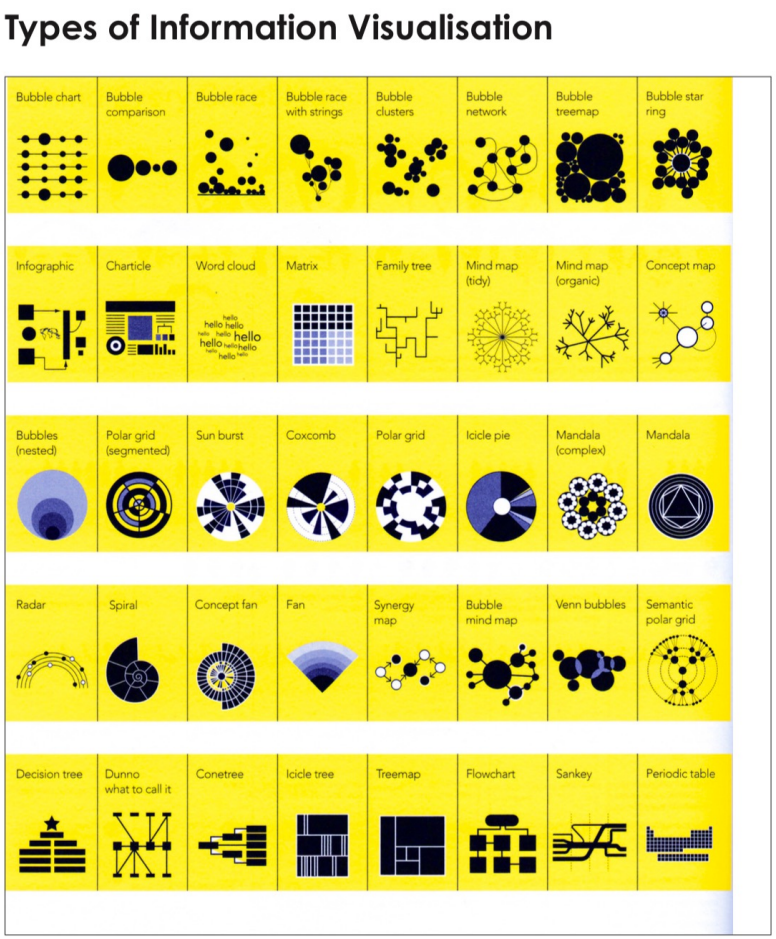
Visualising large models

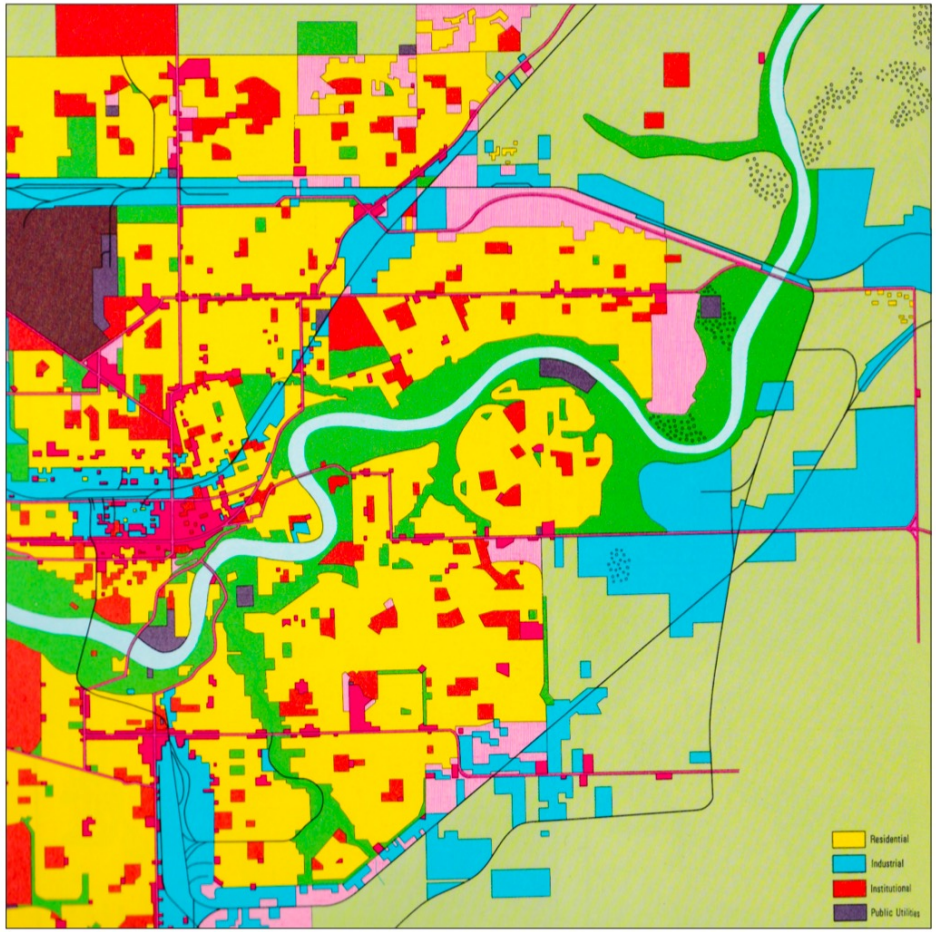


“Google maps” → NaviCell

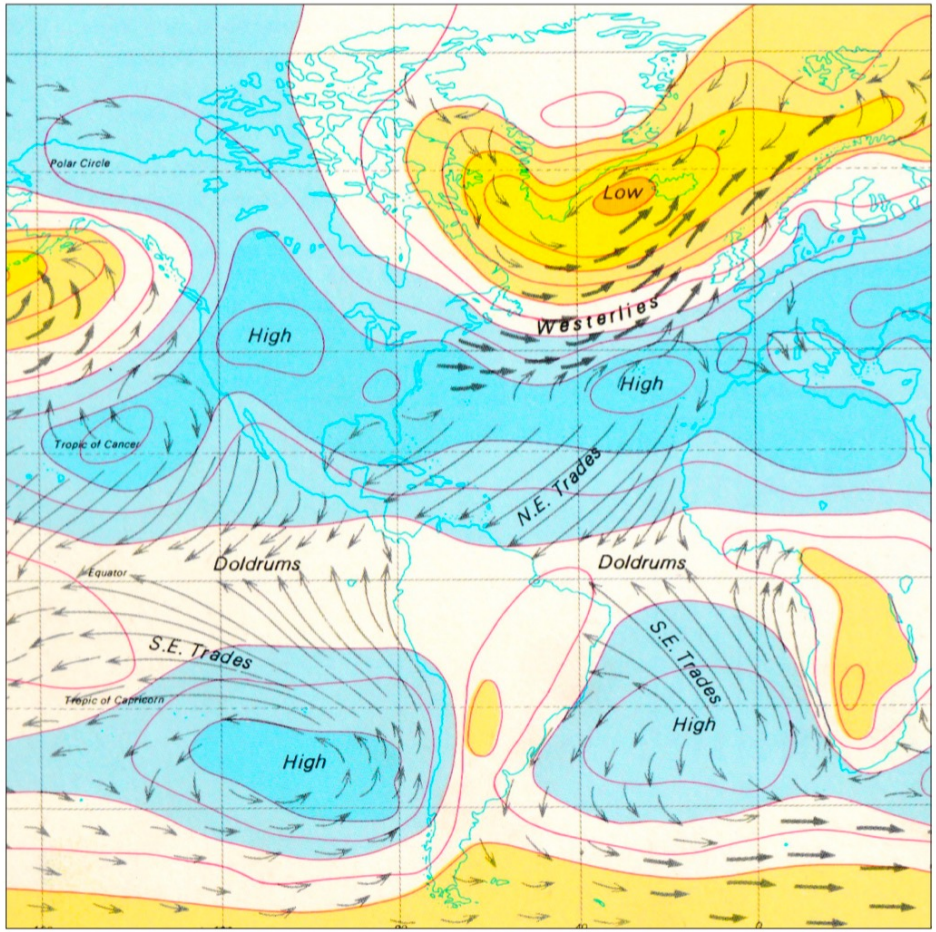


Abstracting the UI

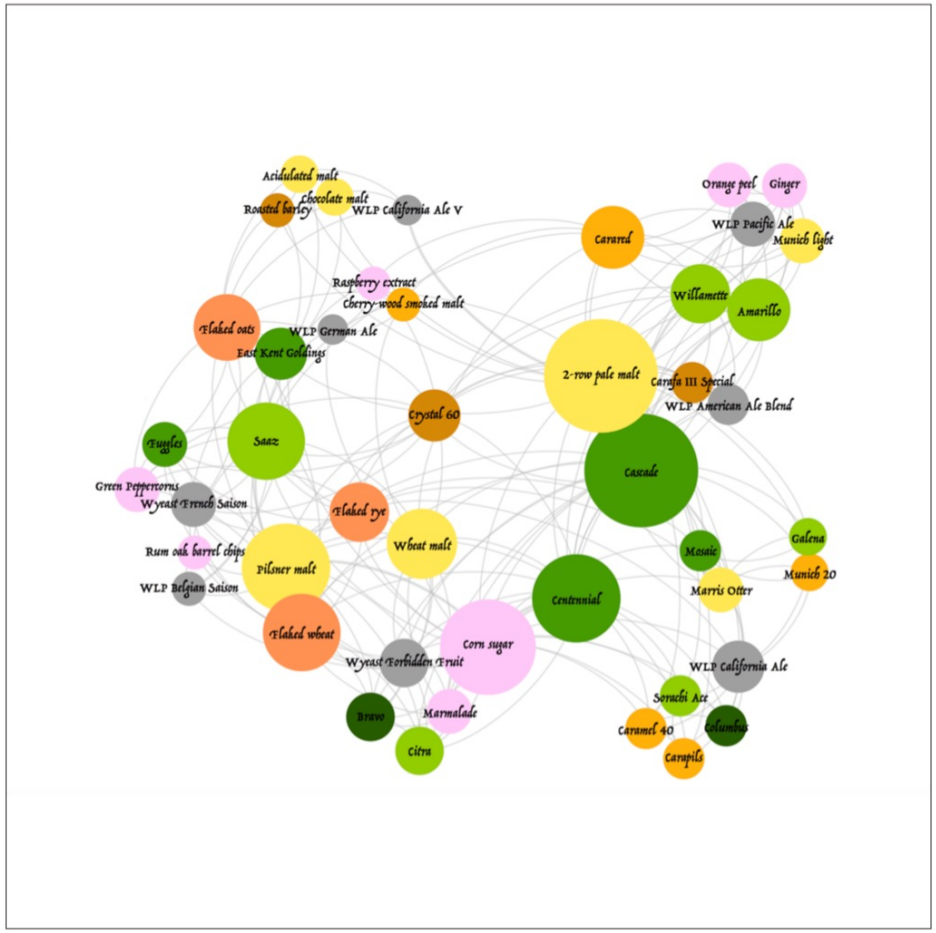




The Blond World Atlas

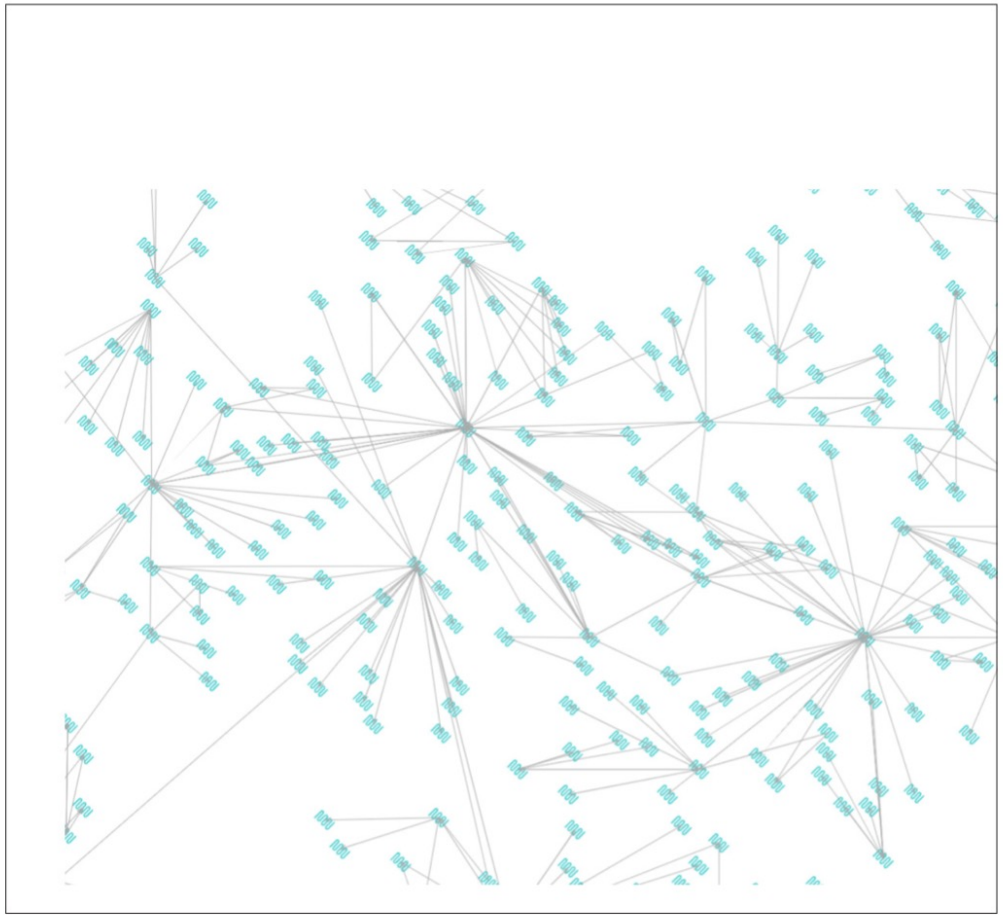


The Blond World Atlas

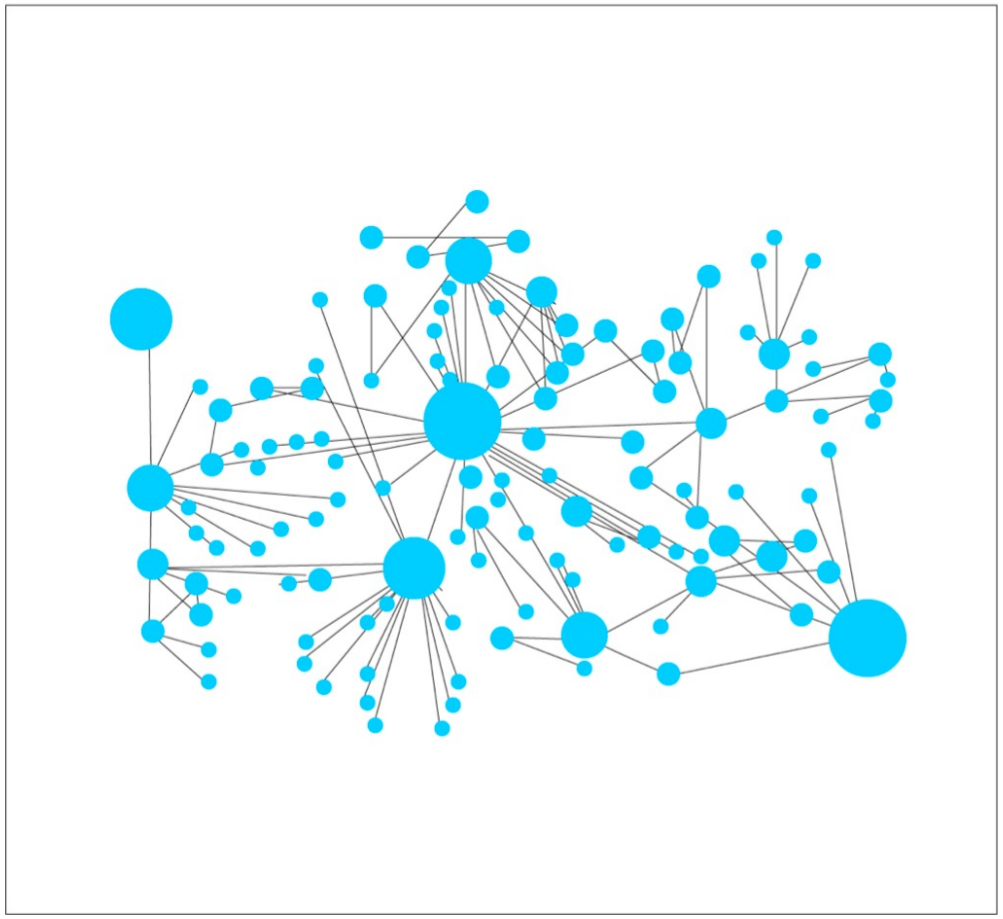


"Network visualization of my homebrew recipes"
revDaydreamr, Imgur

Variables



Bubbles

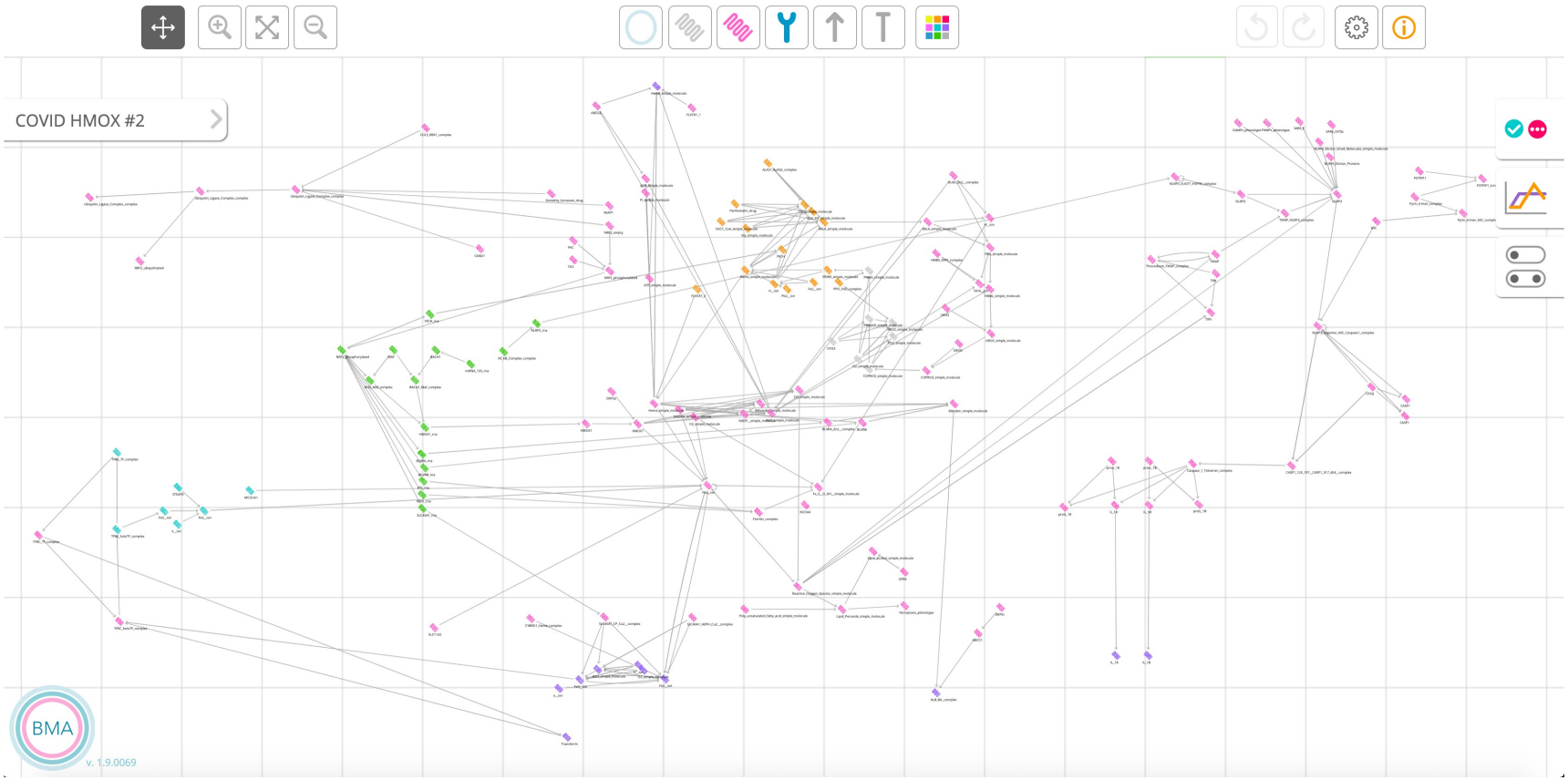


How?

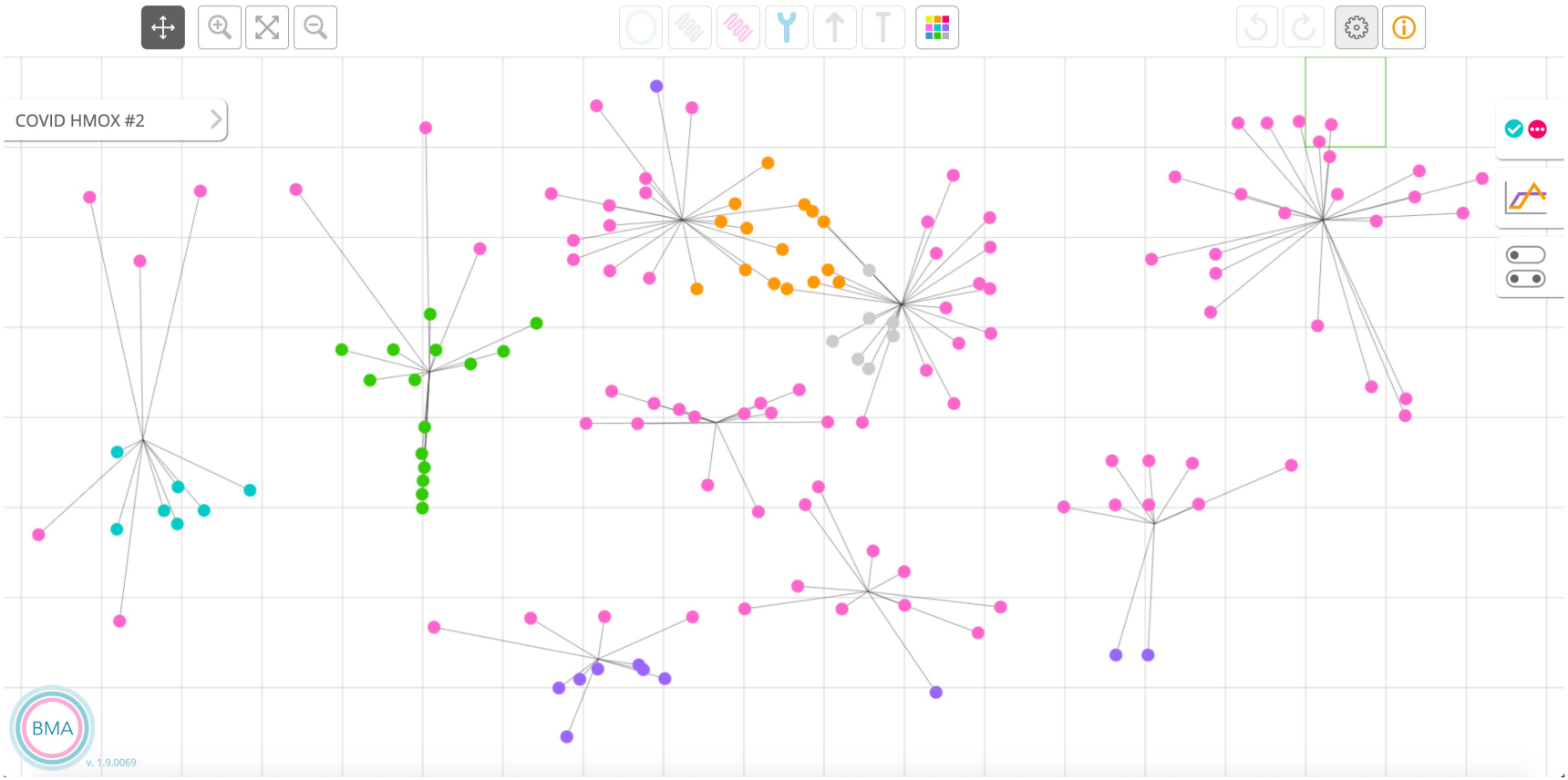
- KMeans clustering to generate “bubbles”
  - √N bubbles for N variables
- Bubble membership indicated by intermediate “constellations” visualization

- Switch rendering from vector based to raster based to improve performance

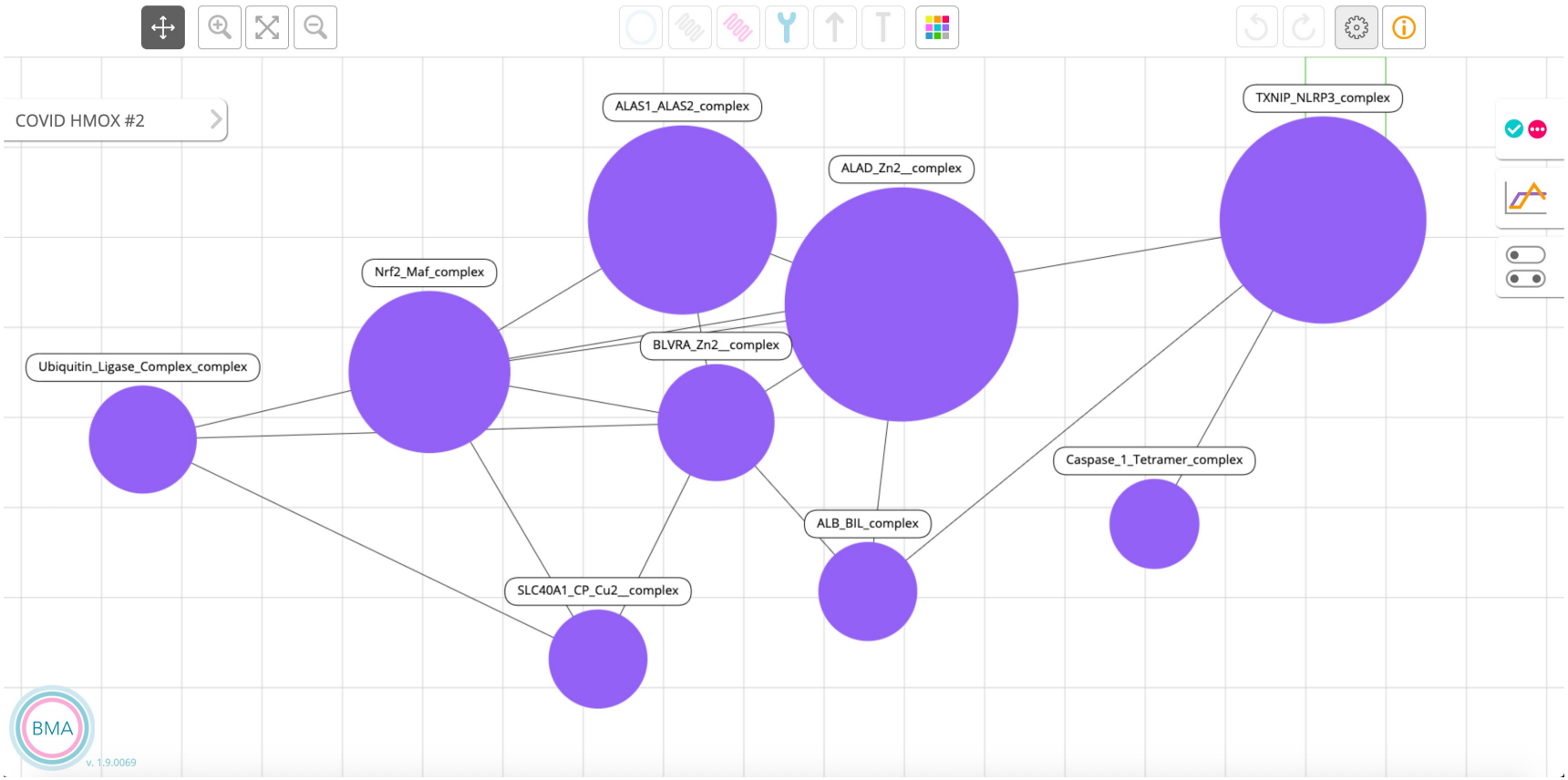
Variables



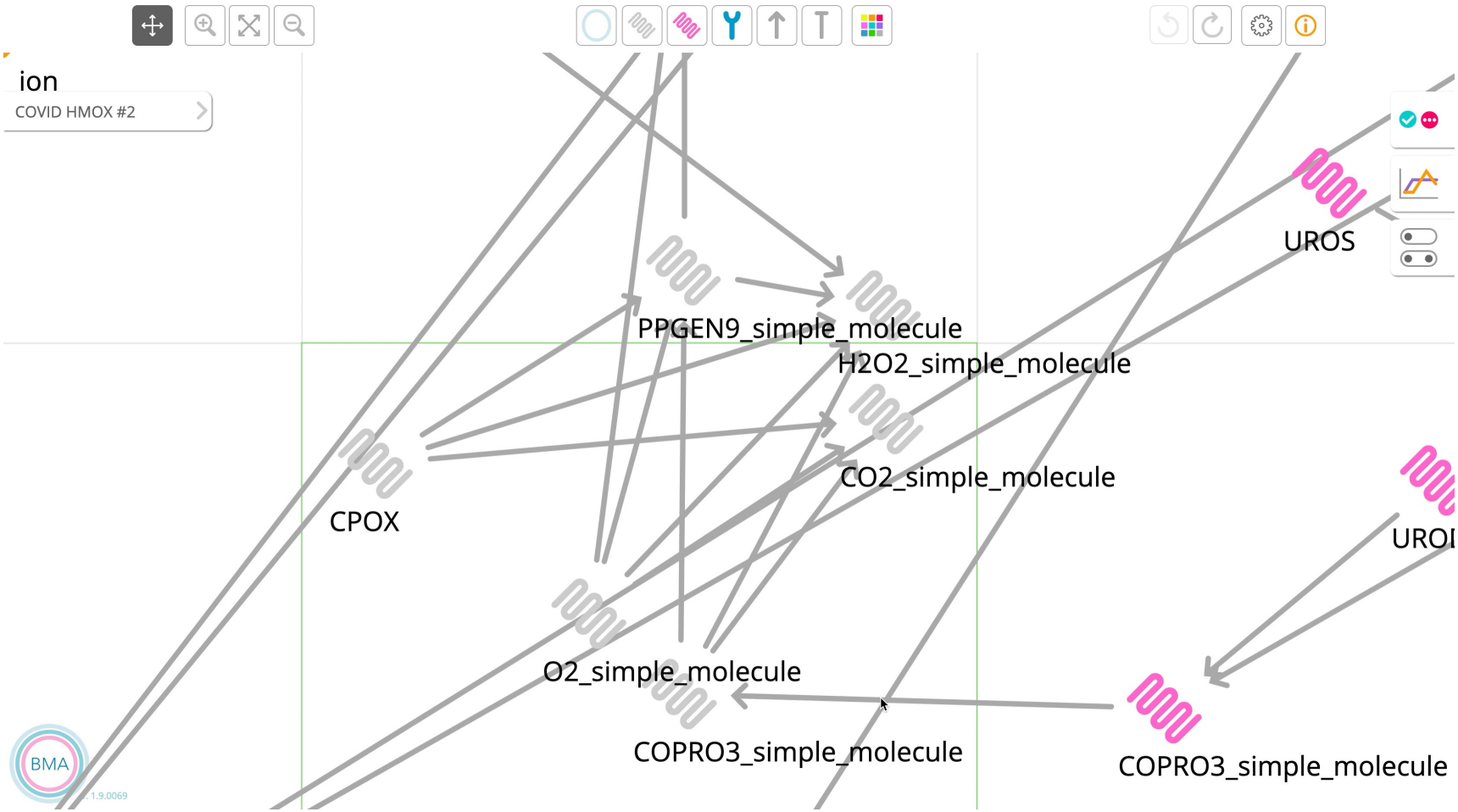
Constellations

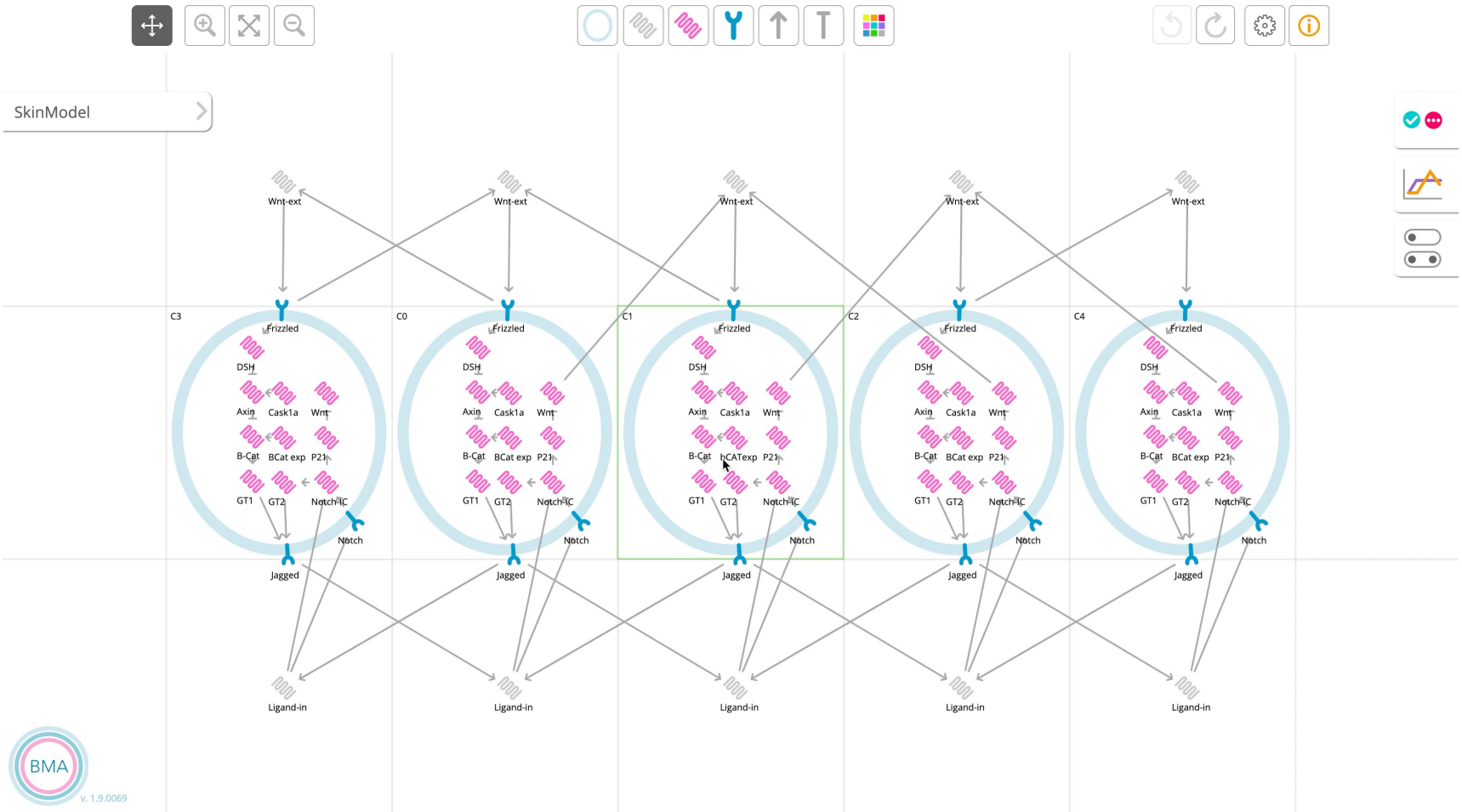


Bubbles


COVID HMOX #2
ALAS1_ALAS2_complex
ALAD_Zn2__complex
TXNIP_NLRP3_complex
Nrf2_Maf_complex
BLVRA_Zn2__complex
Ubiquitin_Ligase_Complex_complex
Caspase_1_Tetramer_complex
ALB_BIL_complex
SLC40A1_CP_Cu2__complex
BMA
v. 1.9.0069

Dynamic visualisation switching




SkinModel
Wnt-ext
C3
C0
C1
C2
C4
Frizzled
DSH
Axin
Cask1a
Wnt
B-Cat
BCat exp
hCATexp
P21
GT1
GT2
Notch IC
Notch
Jagged
Ligand-in
BMA
v. 1.9.0069

User testing

- 5 users, mix of experienced and novice
- 30 mins, task orientated
- Positive feedback on UI

- Mixed feelings about constellation visualisations
  - Confused some as it introduced links where none existed
  - Others valued their support to explain how clusters were made

- Model organization varies across individuals
  - Some organize their models spatially according to subsystems- fits well with bubbles
  - If this doesn’t happen the bubble membership can be confusing
  - Alternative, switchable algorithm for clustering?

Future plans

- Integrate with knowledge databases
- Automated testing
- Omics import

Acknowledgements

- Hall group

- BMA development team
- Fisher group, Nir Piterman

- Work funded by Royal Society, Medical Research Council

Questions