Automated pipeline for the inference of Boolean models from molecular interaction maps.

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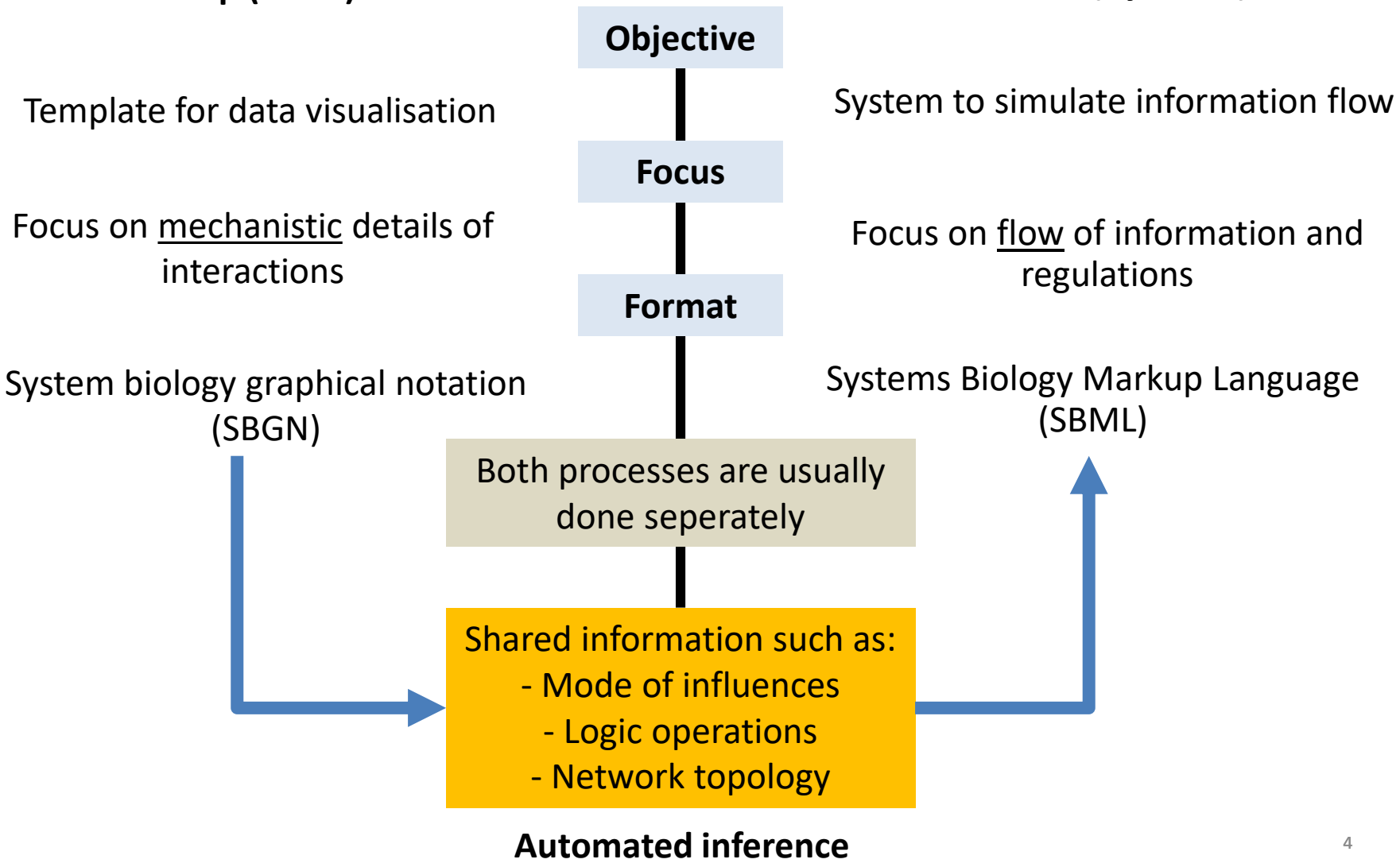
Describing mechanisms in an systematic fashion

- **Molecular Interaction Maps:**
- **High quality source of knowledge** –template for data visualization (*i.e* control versus treatment).
- Can be seen and analyzed as **a complex network** (topology/structure).
- Can serve as a scaffold for a **mathematical model.**

Molecular Interaction Maps:

- **Increasing popularity**
- **Many systematic efforts** (DiseaseMap Project, The Curie Atlas of Cancer Signalling Network, Cancer Cell Map Initiative etc..)
- **Interdisciplinary teams** (biologists, curators, clinicians, bioinformaticians etc)
- **Standardization** (SBGN, mEPN)

From static to dynamic:



The Molecular Interaction Map needs to be:

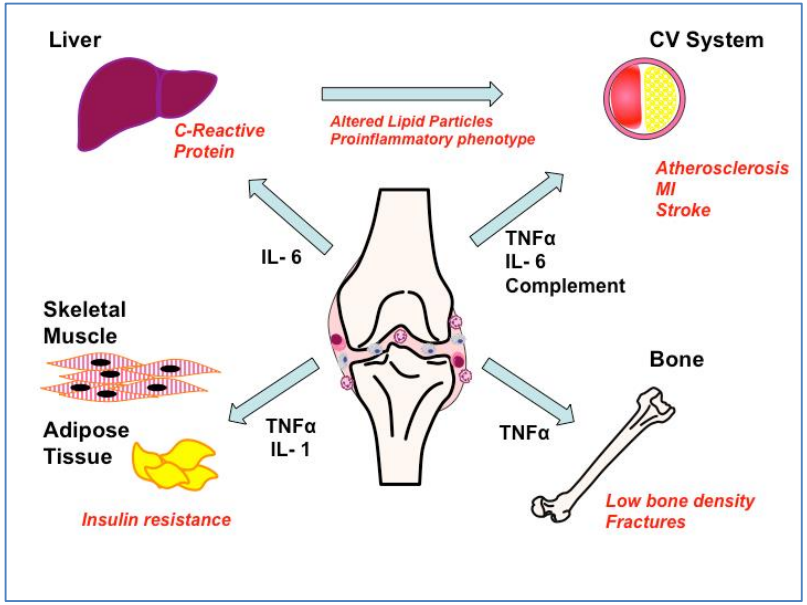
- **Accurate** – correctly represents our empirical knowledge.
- **Reusable** – well annotated and referenced.
- **Comprehensive** – accounts for all known reactions within the selected scope.
- **Machine readable** – can be processed and analyzed using computers.
- **Executable** – corresponds to a computational model that can be simulated.
- **Functional** – can explain the known system-level behavior of the biological network.

(Inspired by Systems Biology, ed. Nielsen and Hofmann, Chapter 8, Wiley -VCH, 2016 and Community-driven roadmap for integrated disease maps, Ostaszewski et al., 2018)

CONSTRUCTION OF THE RA DISEASE MAP

Rheumatoid Arthritis (RA):

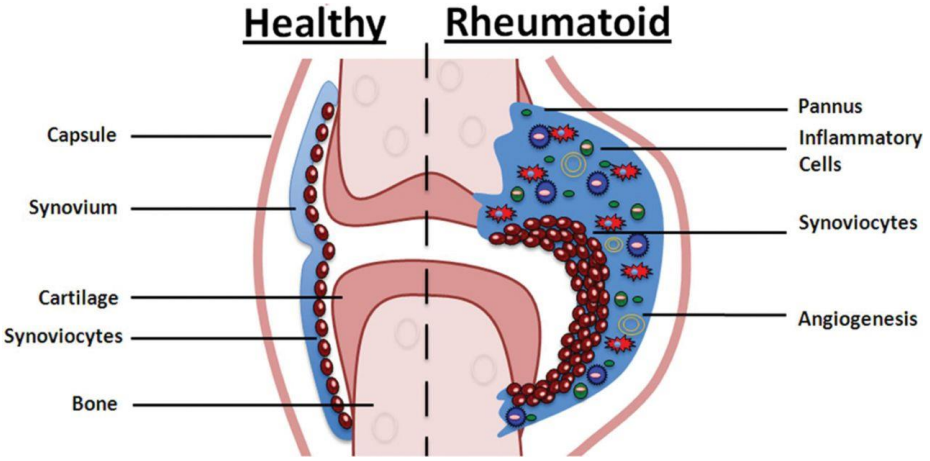
- Multifaceted autoimmune disease that causes chronic inflammation of the joints.
- **Etiology** of the disease remains **unclear**.
- Can also cause inflammation and injury in other organs in the body therefore considered as a **systemic disease**.



(Figure from McInnes & Schett, 2011)

Rheumatoid Arthritis (RA):

- RA greatly affects the synovial joints in the body:
- **The immune system mistakenly attacks the synovial lining surrounding the joints leading to an inflammatory response.**
- **This response thickens the synovium by laying down fibroblasts and causes destruction of the cartilage and bone.**
- The result of this process is severe deformation.



(Figure from Hawtree S, et al, 2013)

Molecular Interaction map of RA (Wu et al.2010):

- **28 studies high throughput**, including drug treatment experiments (2003-2009)
- Large **heterogeneity** of source studies (PBMC, SF, PMN, cartilage)
- **False positives** possible (due to RNA expression data)
- Lack of **experts validation**
- Not very sophisticated layout
- **Connectivity problems** (several nodes with very low degree)
- **Very basic annotation of the** CellDesigner file
- **No standards** (SBGN, MIRIAM annotations)

Current state of the RA map:

- **80 new mediators**, derived from literature published after 2010, using public databases and exhaustive manual curation (at least 2 articles for each molecule added, small scale experiments).

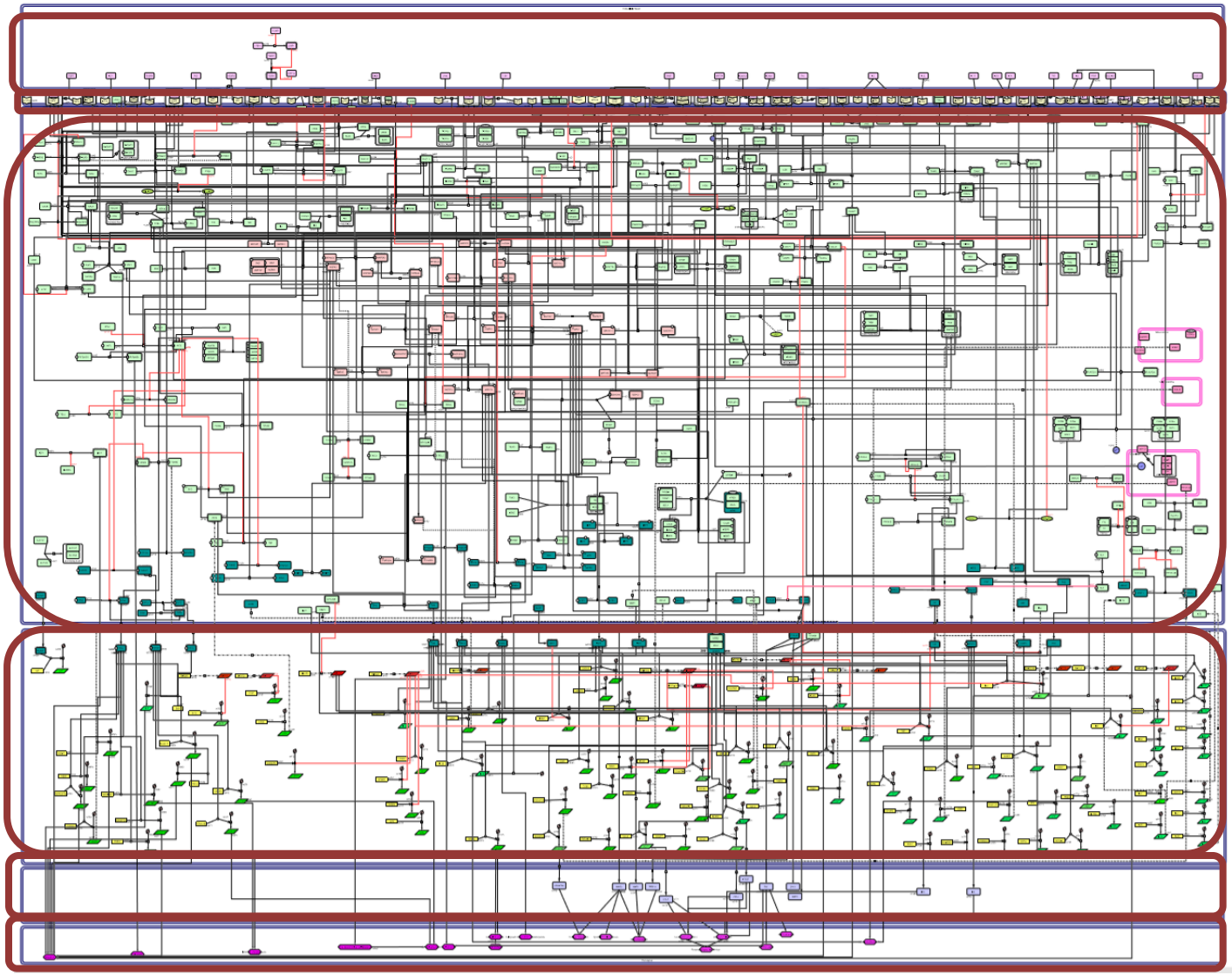
- All interactions and mediators are being reassessed using strict curation criteria **(20 mediators removed)**.

- Detailed annotations including **PubMed identifiers, HUGO names and Cell/fluid types, fully detailed MIRIAM annotation section**.

- **Fully SBGN compliant**.

- **Quality control** of the integrated information and its representation is carried out by a collective effort of our collaborators (**clinicians, experts in RA and inflammation) (restructure of the initial map), use of Ingenuity pathway analysis (IPA)**.

Updated RA map (CellDesigner file):



ECM

PLASMA MEMBRANE

CYTOPLASM

>400 components
>150 scientific papers
Fully SBGN
Experts' validation
Detailed annotations
Strict curation criteria

NUCLEUS

SECRETED MOLECULES

PHENOTYPES

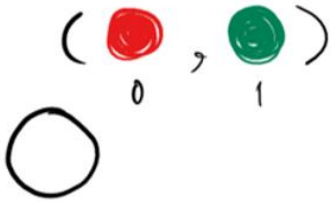
FROM A DISEASE NETWORK TO A BOOLEAN MODEL

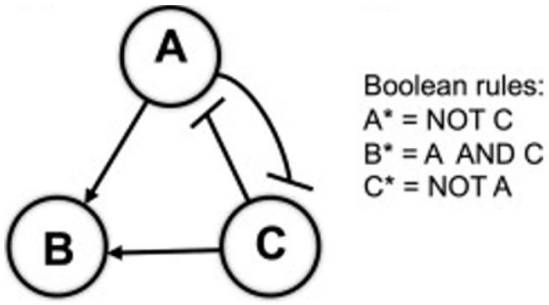
Biological questions of more dynamic nature concerning RASFs

- Can we **induce apoptosis**? (either by forcing apoptosis pathway or by blocking cell survival pathways)
- Can we **block structural damage** by blocking intermediate components?
- Are they subjected to **negative feedback** control like macrophages?
- Do they **differentiate** depending on the initial stimuli?

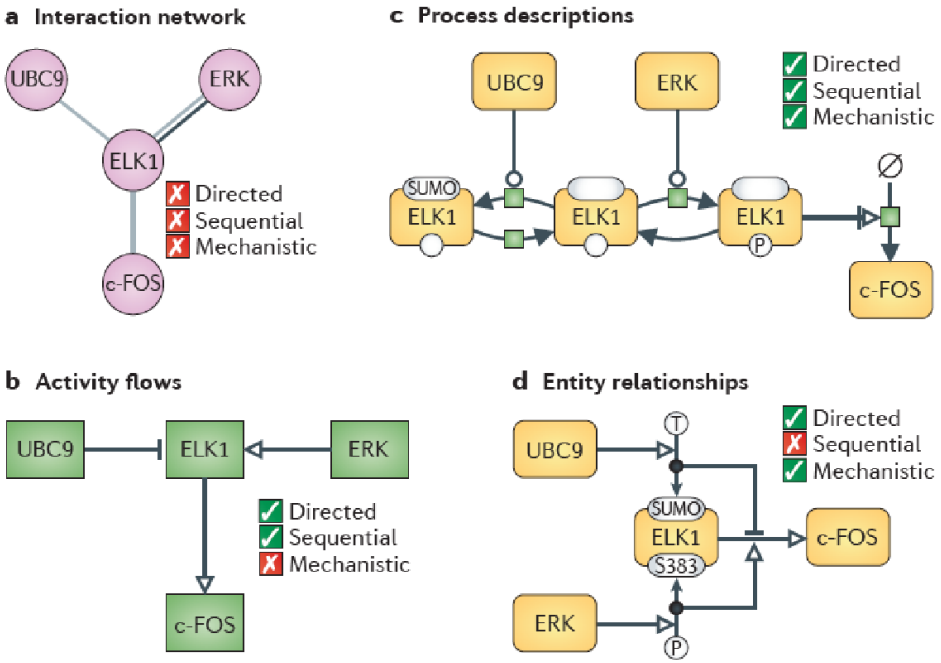
Capture dynamic properties: Boolean model

- Simplest form of mathematical model governed by logic operators (AND, OR, NOT).
- Parameter free.
- Scalable, can range from 3 components up to more than 200 components.
- Suitable for modeling large signaling networks.
- *In silico* simulations, qualitative predictions





Different network representations:

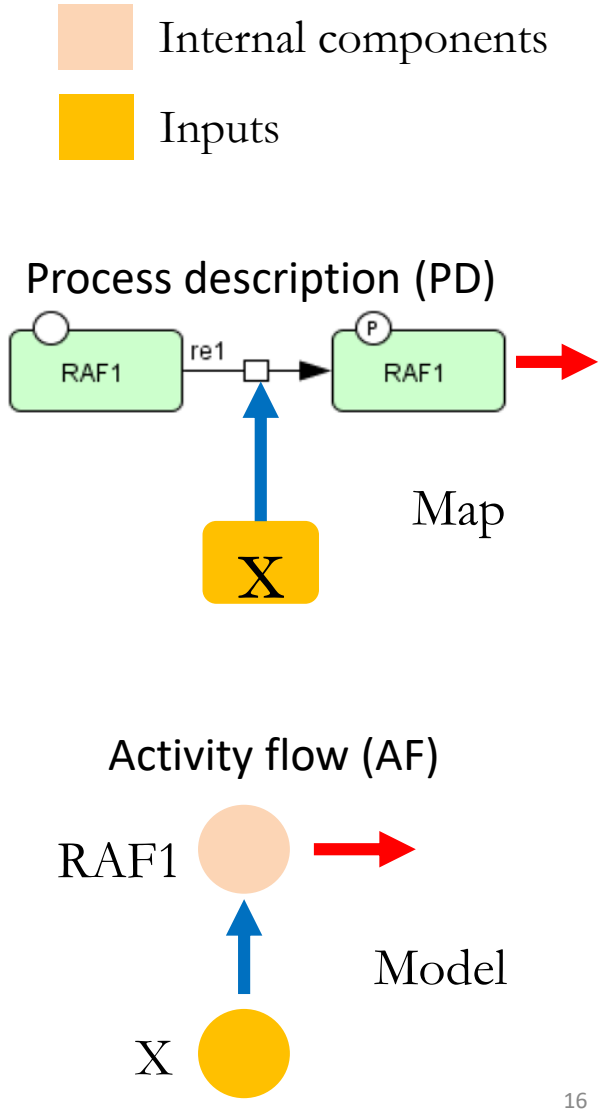


(Figure from Le Novere, 2015)

CaSQ (CellDesigner as SBML-qual)

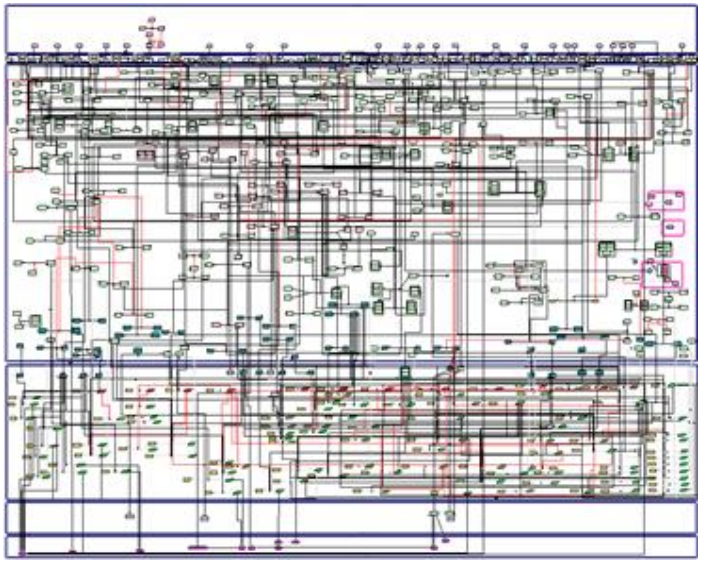
How does it work exactly?

- **Process description** compressed to resemble more to an **activity flow** diagram.
- Unregulated components = **inputs**.
- **Logical operators** assigned based on the network's topology and the semantics already present in the map (activation/inhibition, complex formation etc).
- **Annotated references** and **layout** retained in the output file.



Executable Disease Map

CellDesigner



CaSQ

Cell Collective modelling platform

Disease Network:

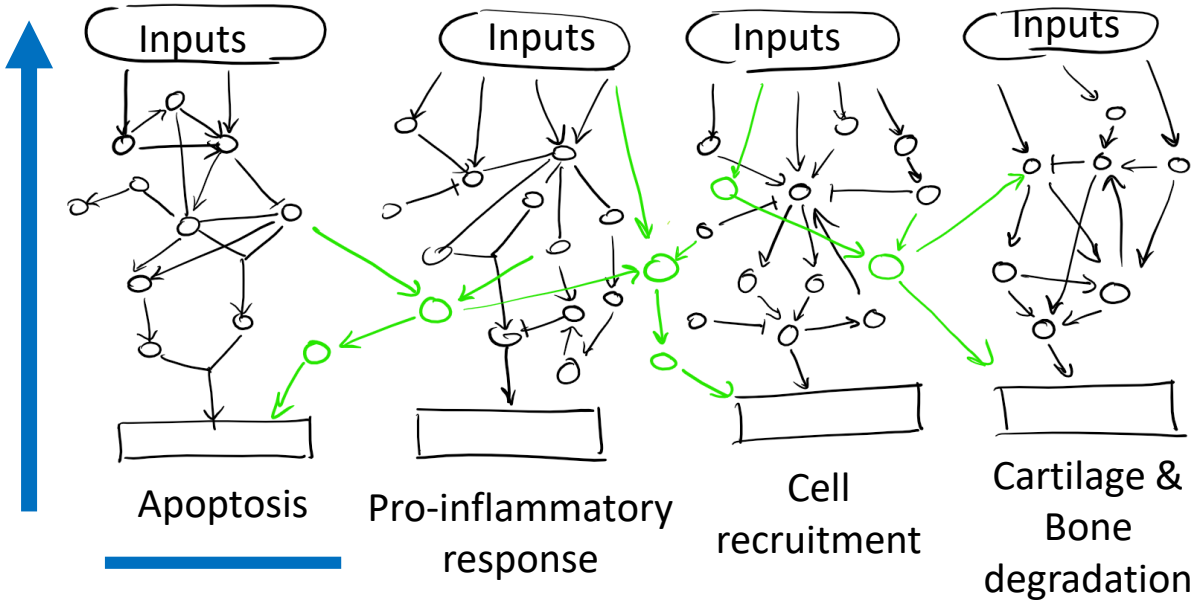
- Global
- Heterogeneous
- Too big and complex to tune and execute

View of the boolean network generated from the Disease Map, in Cell Collective

Construction of RASF specific model:

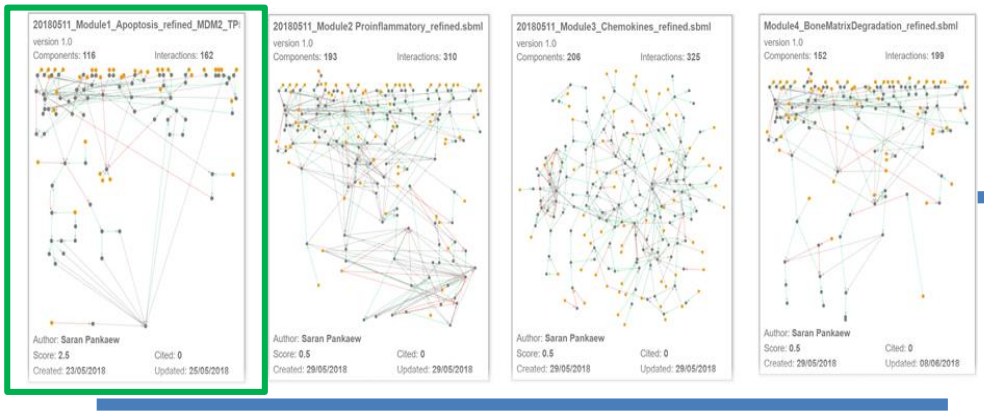
- Focusing on 4 functional outcome of RASFs.

- "Module" is defined by - pathway(s) that lead(s) to certain expression.



Simulation : understanding dynamic properties

Boolean modules



Easy to observe input-output relation and tune systems

Smaller size, less complexity, easier to check input output relationships (one output per module)

Merged RASF model

To observe global response

252 components
390 interactions (high overlap between modules)

Easier fine-tuning

Simulations on the AKT pathway:

- Results show that both the module and the whole model were able to **recapitulate known regulation of AKT**.

Function	Components	Biological function	Module simulation	Model simulation
Apoptosis	BAX	inactive	inactive	inactive
	MDM2	active	active	active
	FOXO1	inactive	inactive	inactive
	BCL2L11	inactive	inactive	inactive
Proinflammatory response	NF-kB	active	N/A	active
	IL-6	active	N/A	active
	TNF	active	N/A	active
Chemokine secretion	IL-8	active	N/A	active
	CXCL 1-3	active	N/A	active
Bone & matrix degradation	MMP3	active	N/A	active
	RANKL	active	N/A	active
Cell cycle control	CDKN1B	inactive	N/A	N/A
Glycolysis	GSK3	inactive	N/A	N/A

Difficulties:

- Issues of interoperability between different tools (CellDesigner, Cell Collective, GINsim).
- Hard to calculate attractors.
- 4 modules still large and complex.
- Computationally costly.

Conclusions:

- **Successful translation** of a molecular map to an executable model.
- Pipeline **applicable to other maps** available.
- **Flexibility:** direct translation for cell specific maps, modular approach for network subtraction.
- The resulting model **retains annotations, references and hierarchical layout** of the original map, facilitating reusability and simulations.

To do list:

- **Further simulations and testing is needed**, both on the sub-modules and the merged RASF model in order to have a fully functional model.

- **Model reductions will be required** to solve the computational explosion for in depth analysis of dynamical properties (finding attractors).

- **Tool development is needed** in order to bypass technical issues and computational cost.

- Application of **control theory to Boolean networks** (currently not adapted to large scale) based on topological features (like betweenness centrality).

Dream team:

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