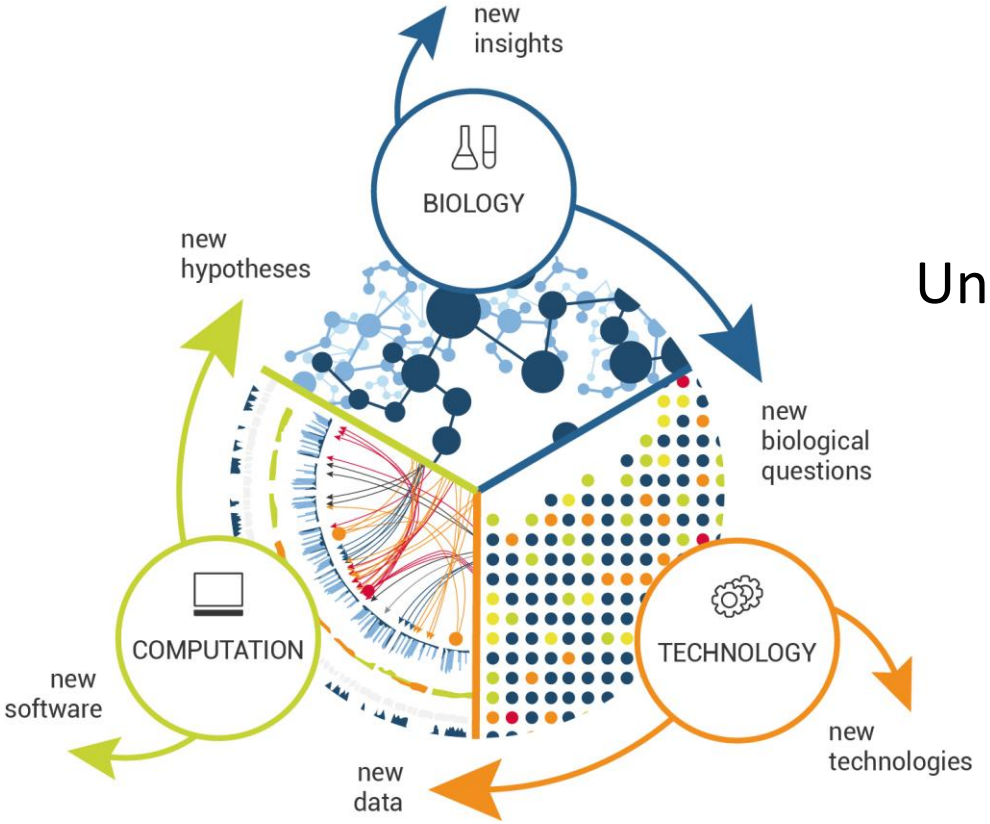
Digital Twins for Human Immune-Mediated Complex Diseases



Professor Anna Niarakis,

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The concept of a Digital Twin

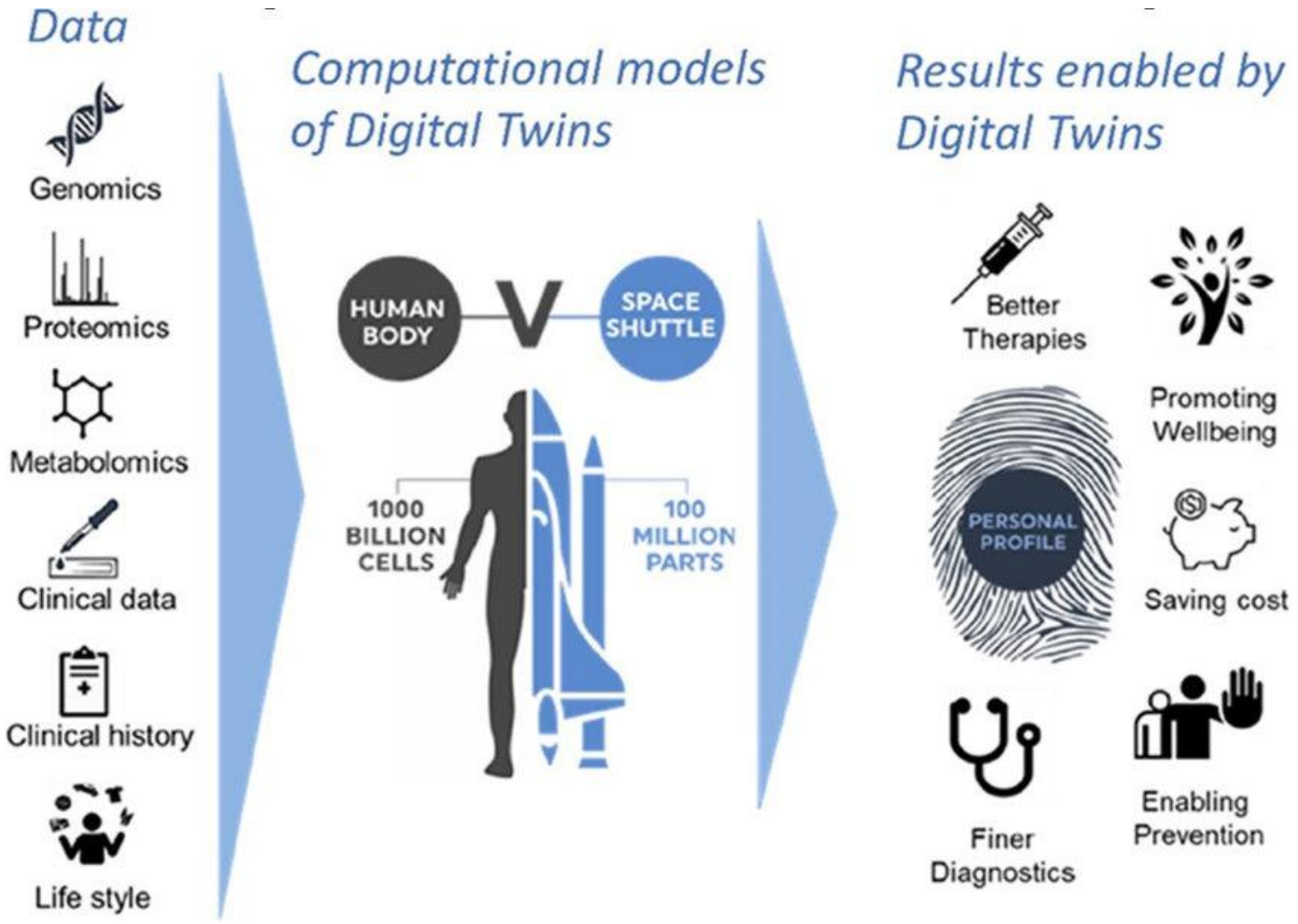
ipopba / Getty Images

Digital Twins are virtual equivalents, or twins, of physical objects.

These digital copies are increasingly popular because they can be used to drive important simulations that haven't been possible until now.

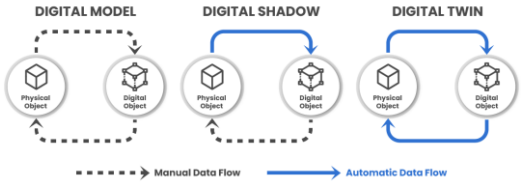
BBC/ Getty Images

The concept of a Digital Twin for complex human pathologies



Lee et al., 2020

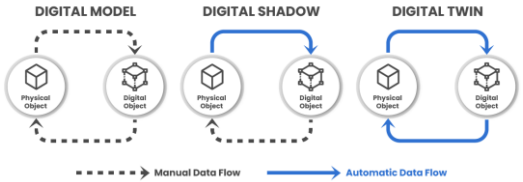
Is everything digital a “Digital Twin” ?



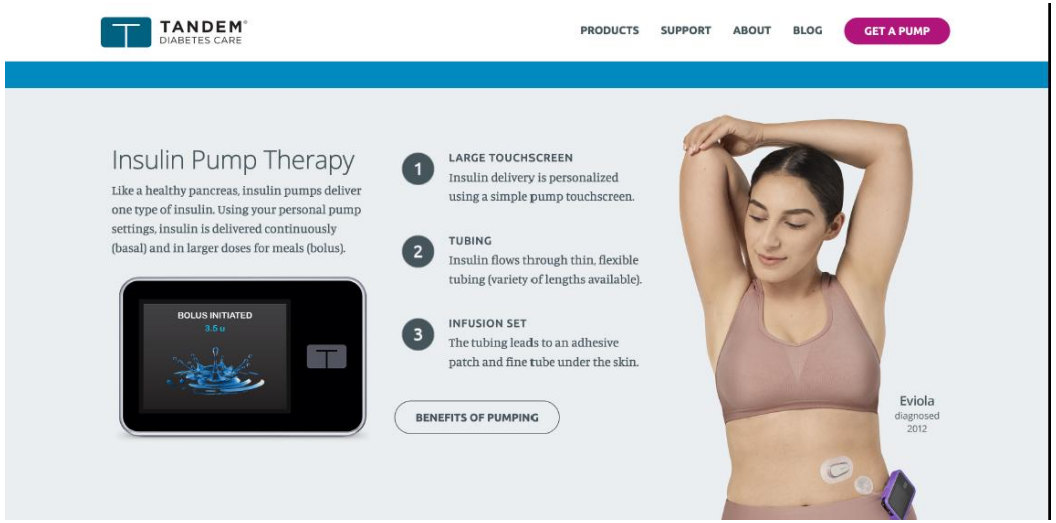
- **Digital Model:**
- **a virtual representation of a physical object, system, or process** (algorithm, mathematical model, 3D representation etc).
- Visualization, analysis, and manipulation of objects or systems in a digital environment, aiding in design, optimisation, and testing.
- Used for *in silico* simulations and hypothesis testing (predictions) of how a physical object, system, or process might operate in the future or in a particular environment.

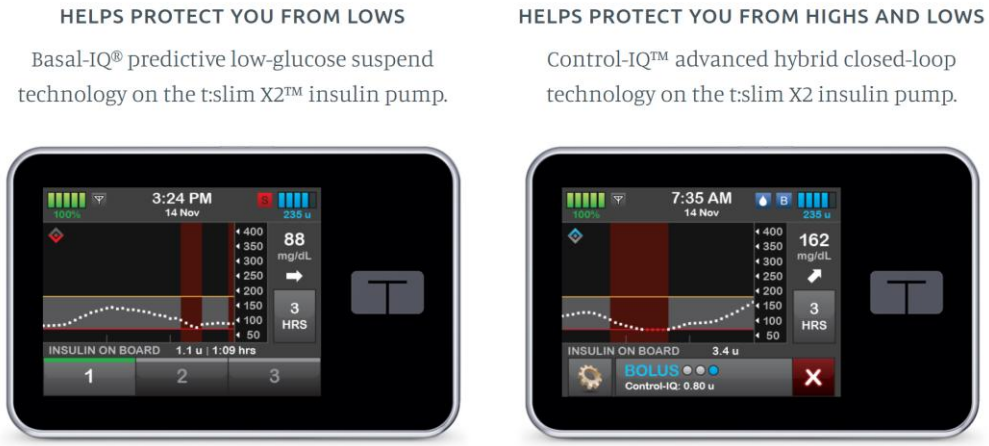
- **Digital Shadow:**
- A digital shadow is an **evolving digital representation** that mirrors the current state and behaviour of a physical entity or system.
- It collects data through sensors, Internet of Things (IoT) devices, or other sources and provides a feed of information that is fed into the model.
- Typically, digital shadows are mathematical models, but they could also be 3D representations.
- They enable monitoring, predictive analysis, and decision-making.

Real “Digital Twin”



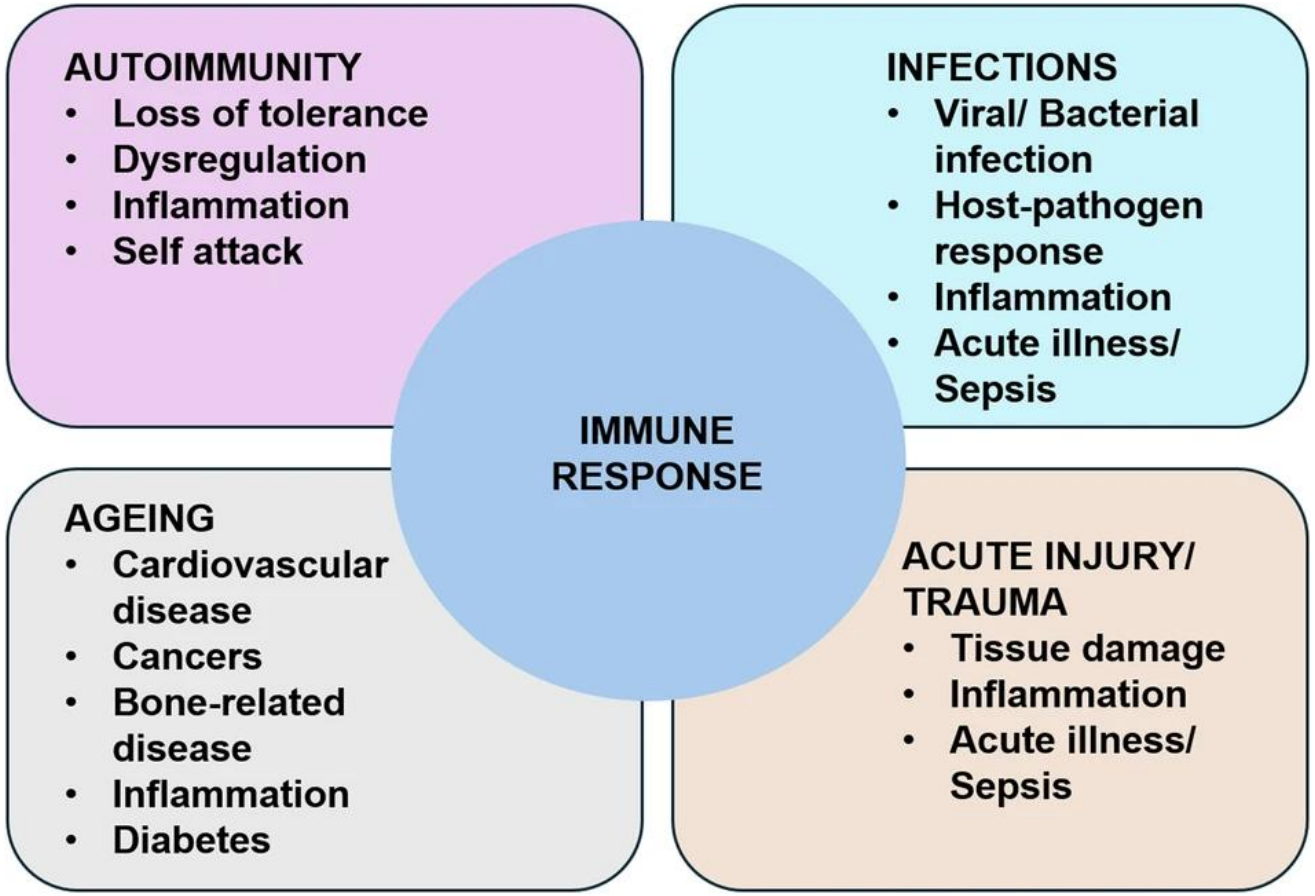
- Real-time connection between the physical entity and its digital counterpart, where the physical object gives information to the digital replica and vice versa.
- Digital twins simulate, monitor, and **control** physical objects or systems, facilitating analysis, optimisation, and predictive maintenance.
- They enable **live feedback loops and foster insights for improving performance, efficiency, and reliability.**
- To put it differently, there is a two-way interaction between the physical and the digital environments, where the digital replica is able to change how the physical entity operates.





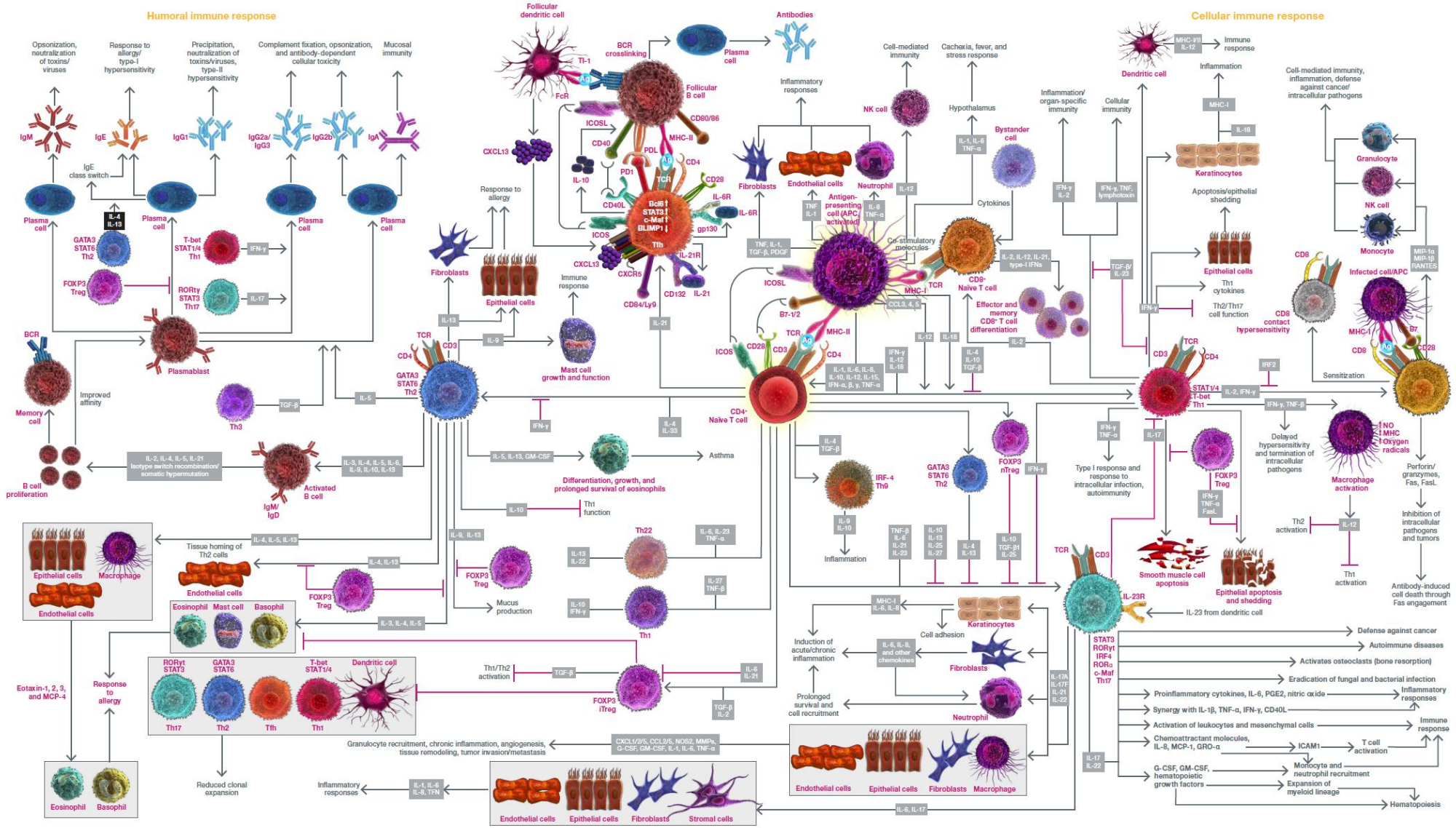
https://www.tandemdiabetes.com/

Human immune response in various pathologies

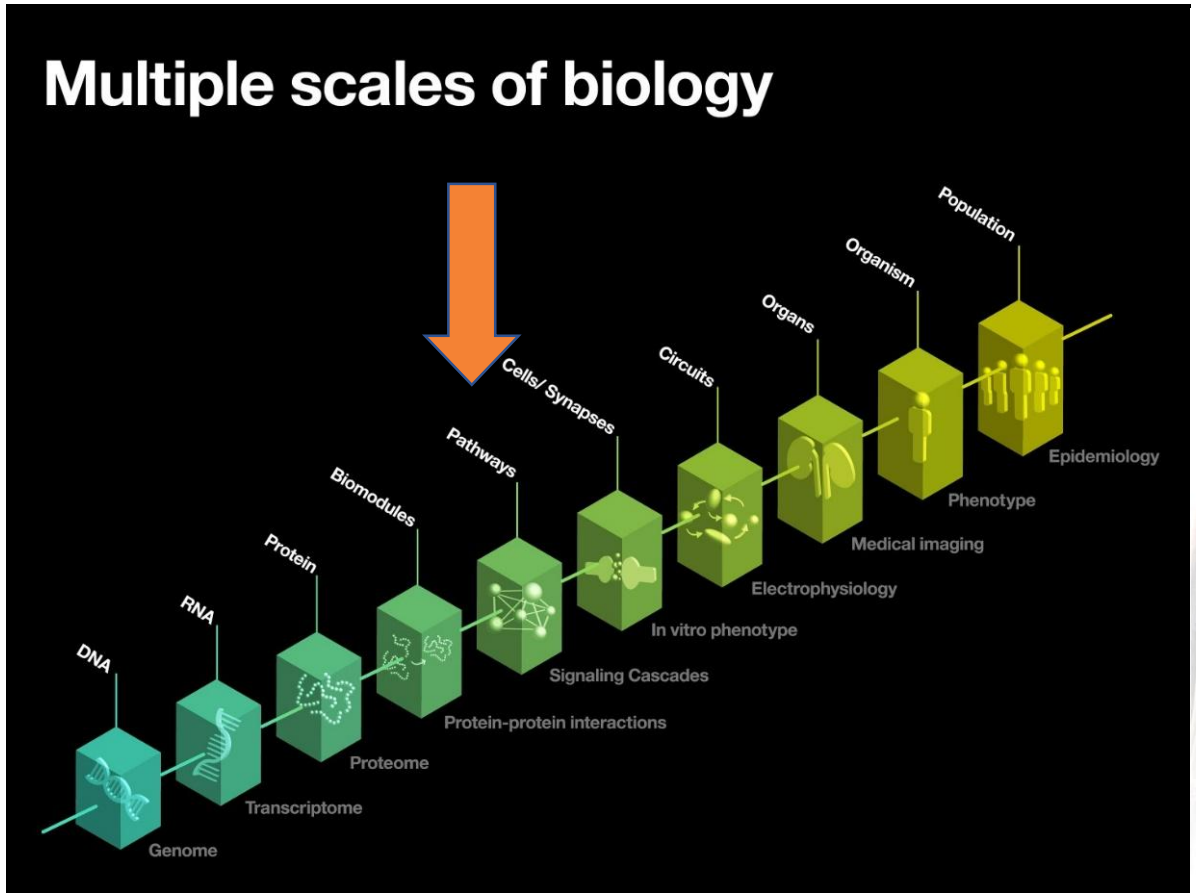


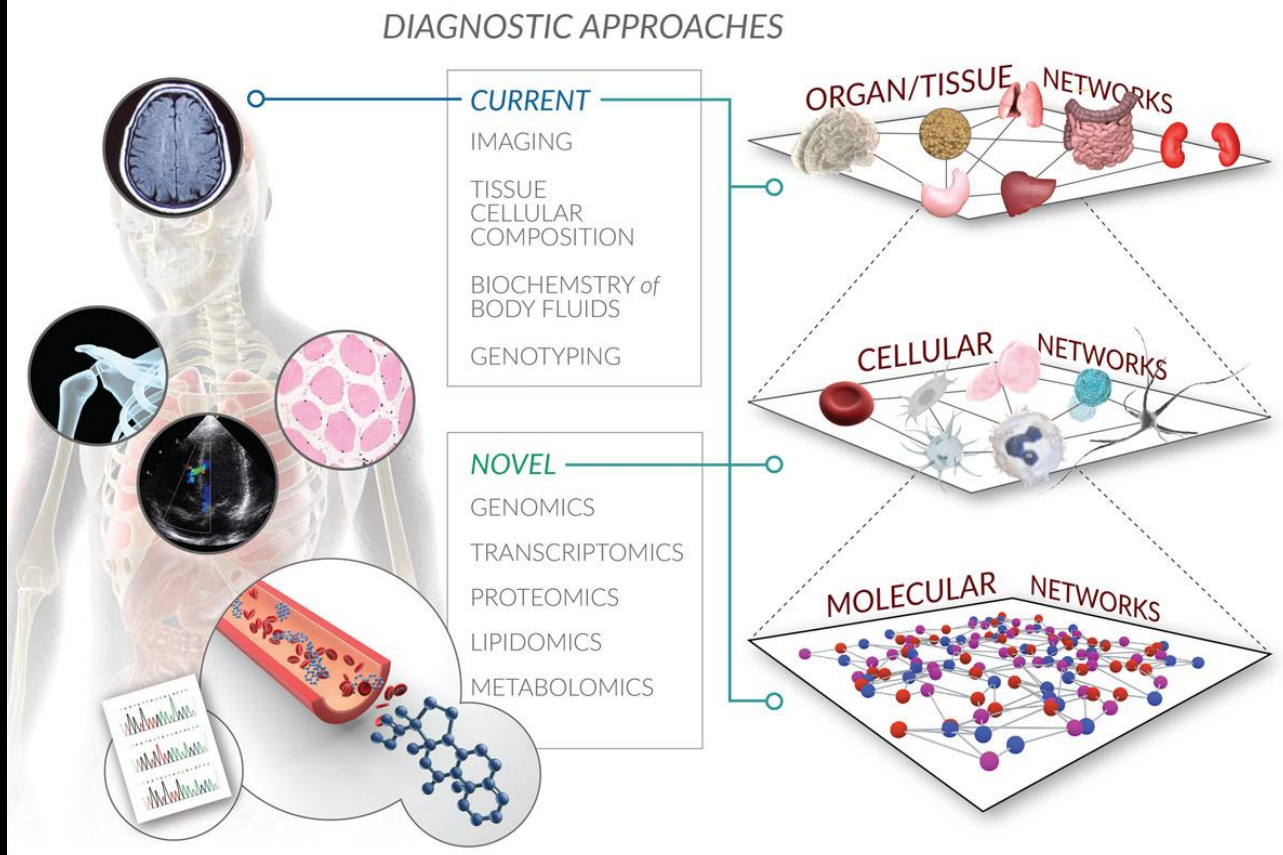
Niarakis, A., Laubenbacher, R., An, G. *et al.* Immune digital twins for complex human pathologies: applications, limitations, and challenges. *npj Syst Biol Appl* **10**, 141 (2024).

Immune digital twins



Where to start?





https://www.bioregulatory-systems-medicine.com/en/brsm-model/autoregulation-of-biological-networks

What is the plan?

- Mapping of cell(s) and pathways involved in the pathogenesis / mechanism of interest
- Construction of causal networks using low and high throughput experimental evidence, AI assisted literature mining, reverse engineering algorithms and human curation

Build causal mechanistic networks

- Automatic inference of executable, computational large-scale models based on the causal mechanistic networks
- Model validation, and enrichment using experimental observations and omics data

Infer dynamical models

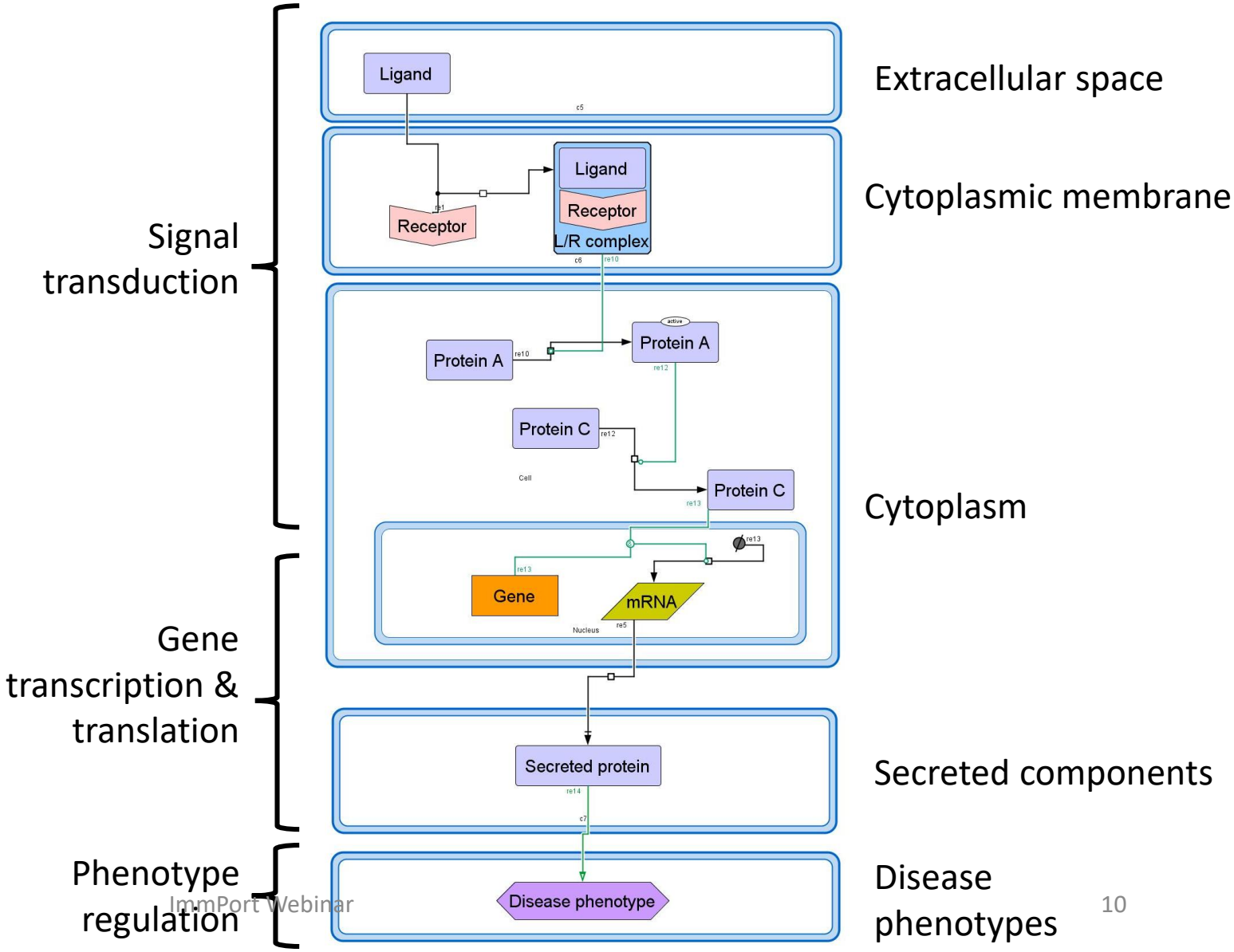
- 1. Predictions and hypotheses testing
- 2. Identification of novel druggable targets (combinations)
- 3. Drug-repurposing analysis

Perform *in silico* simulations and perturbation analyses

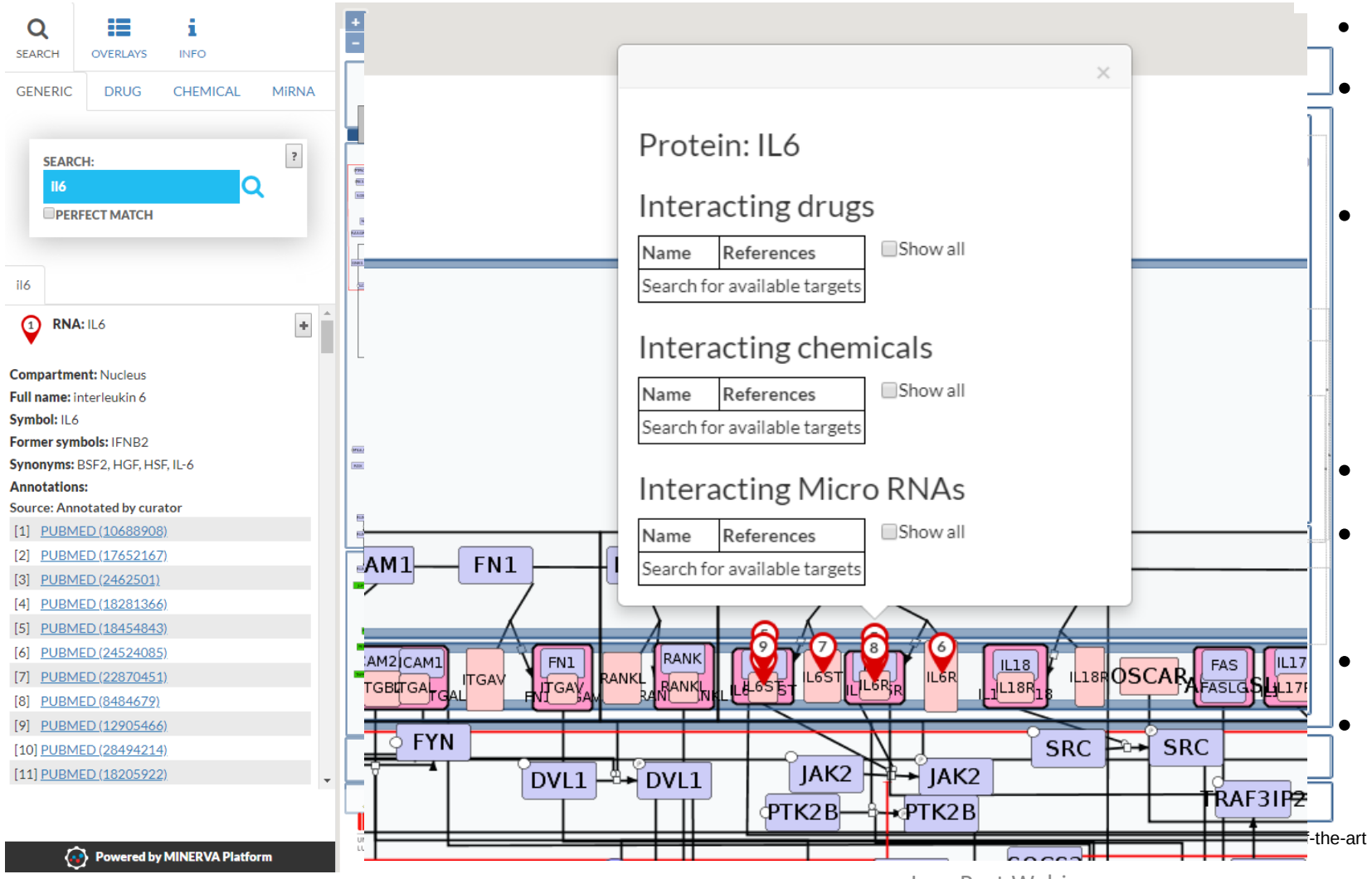
Systems biology to better understand complex diseases

- Assemble the available and fragmented knowledge in **disease maps**
- Manually curated and extensively annotated
- Both human and machine-readable
- Standardized : SBGN PD, MIRIAM, stable identifiers and HGNC symbols

(Mazein et al., 2018)
(Le Novère et al., 2009)
(Juty et al., 2012)



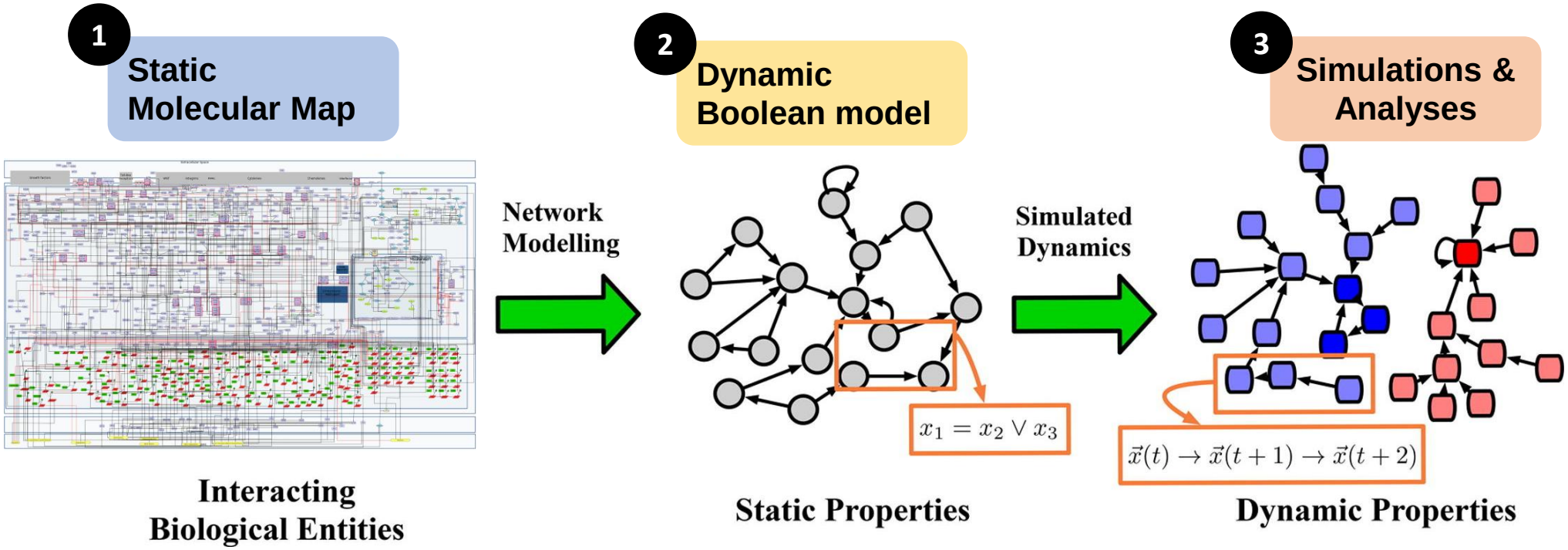
Rheumatoid Arthritis Map (RA-Map V2)



- Addition of the missing interaction:
- **SBGN PD** compliant;
- **720 species** (329 proteins, 135 genes, 136 RNAs, 54 simple molecules, 1 ion, 65 molecular complex)
- **9 phenotypes**
- **602 reactions**
- **575 PMIDs**
- **MIRIAM** standards for annotations.

-the-art

Static and dynamic representations of causal networks



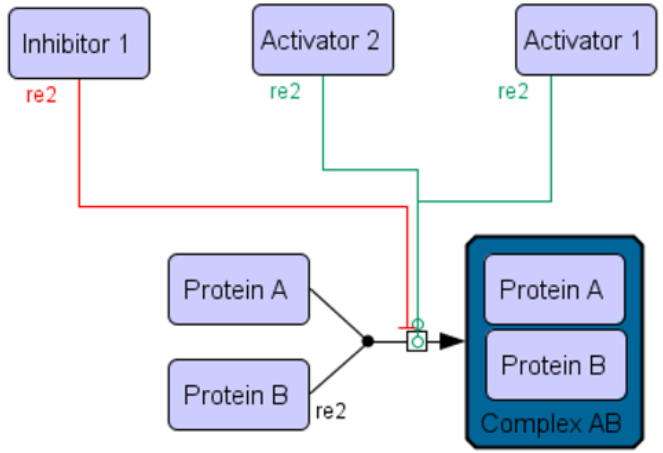
- Node: 0 or 1 → biological entity absent/inactive or present/active
- Edges: activators or inhibitors
- Activation of one or multiple nodes → Model behavior

Adapted from Schwab et al., 2020

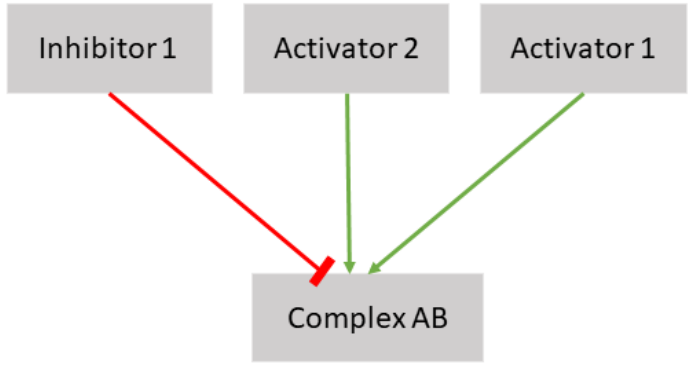
CaSQ to automatically infer Boolean models from MIMs

Three steps : 1) Map reduction 2) PD to AF form conversion 3) Computation of the logical rules

A AB complex formation in Celldesigner



B The corresponding model

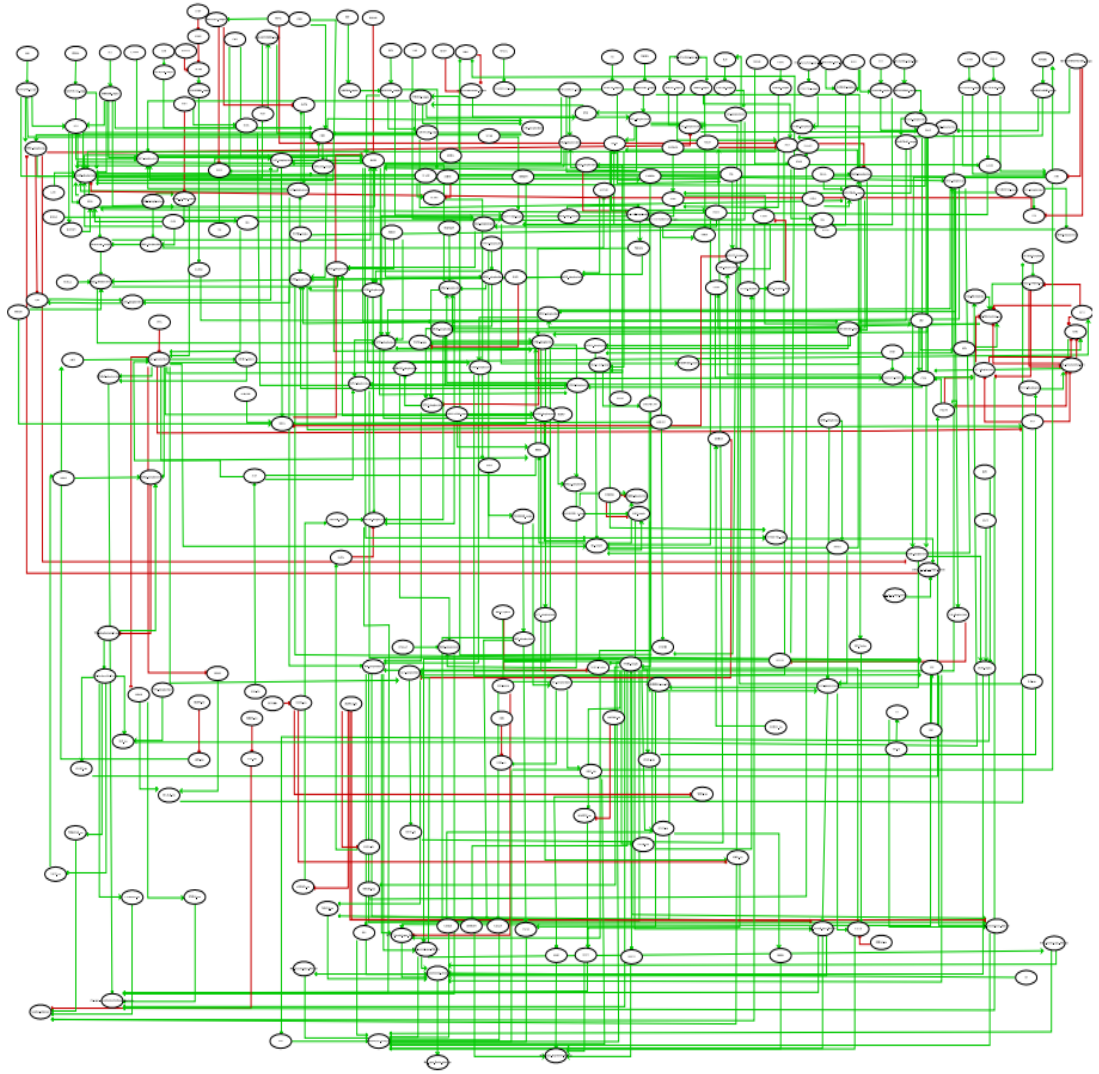


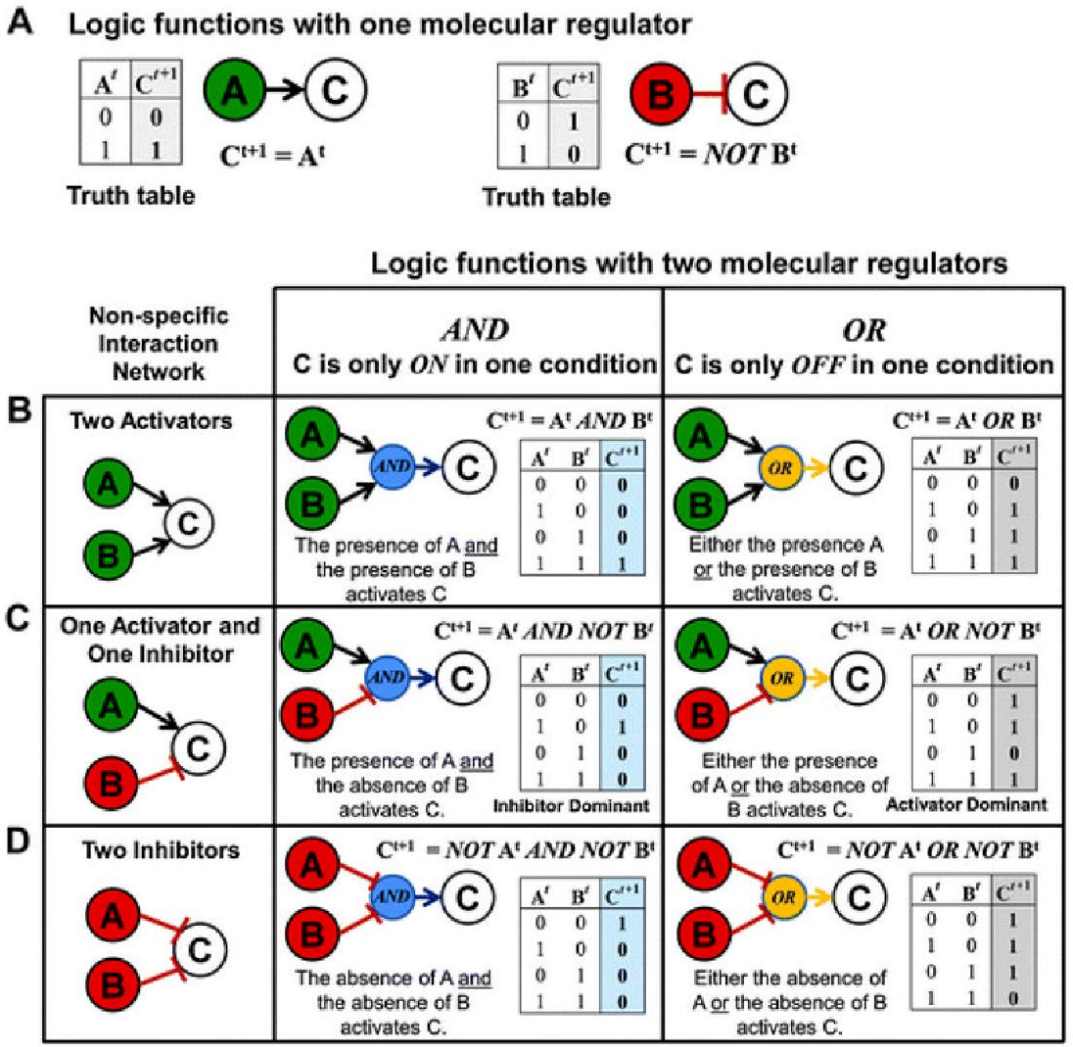
C The logical rules associated with each node of the model

Nodes	Logical rules
Complex AB_complex	(Activator 2 | Activator 1) & ! Inhibitor 1
Activator 1	Activator 1
Activator 2	Activator 2
Inhibitor 1	Inhibitor 1

(Aghamiri et al., 2020)

A large-scale Boolean model for RA

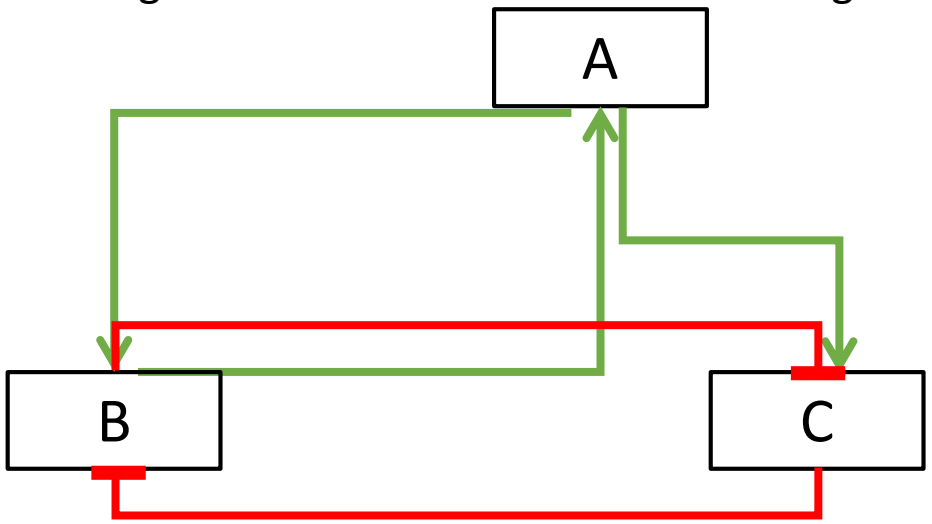




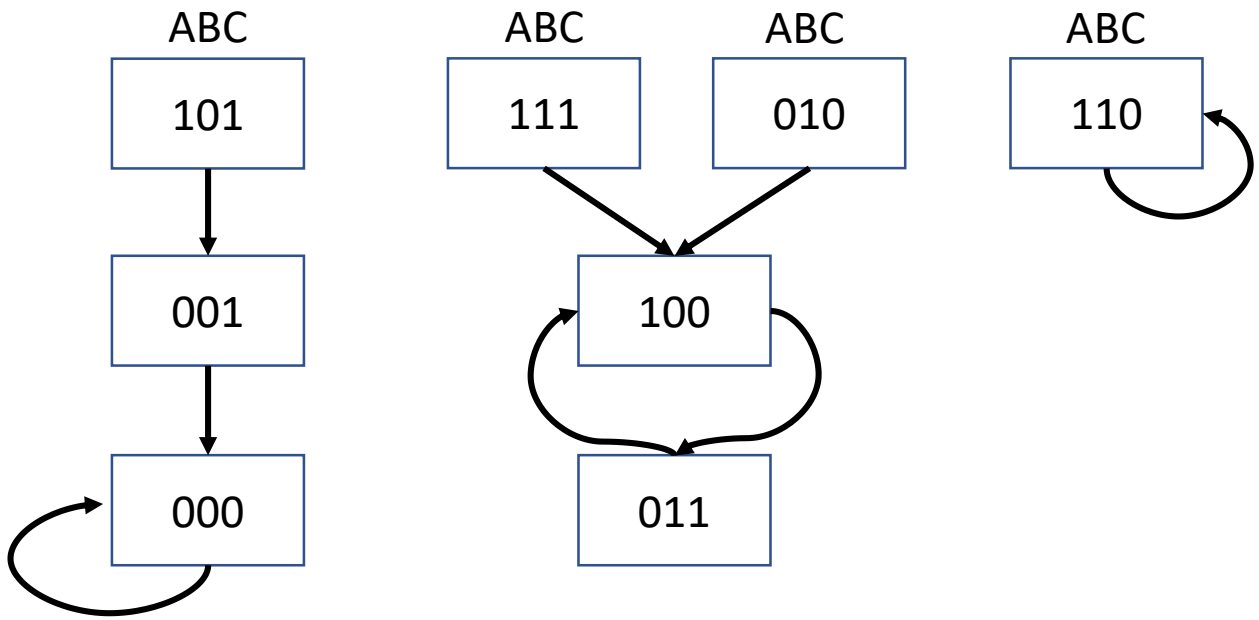
V. Singh, M. Ostaszewski, G.D Kalliolias, G. Chiocchia, R. Olaso, E. Petit-Teixeira, T. Helikar, A. Niarakis Computational Systems Biology Approach for the Study of Rheumatoid Arthritis: From a Molecular Map to a Dynamical Model. Genomics and Computational Biology Vol 4 No 1 (2018)

Systems biology to better understand complex diseases

- State graph : the transition of one variable from one point in time to the next
- Synchronous and asynchronous updating schemes
- **In synchronous models all Boolean functions are applied at the same time while in asynchronous models only one randomly chosen function is updated per step.**
- Long-term behavior = attractors = biological phenotypes



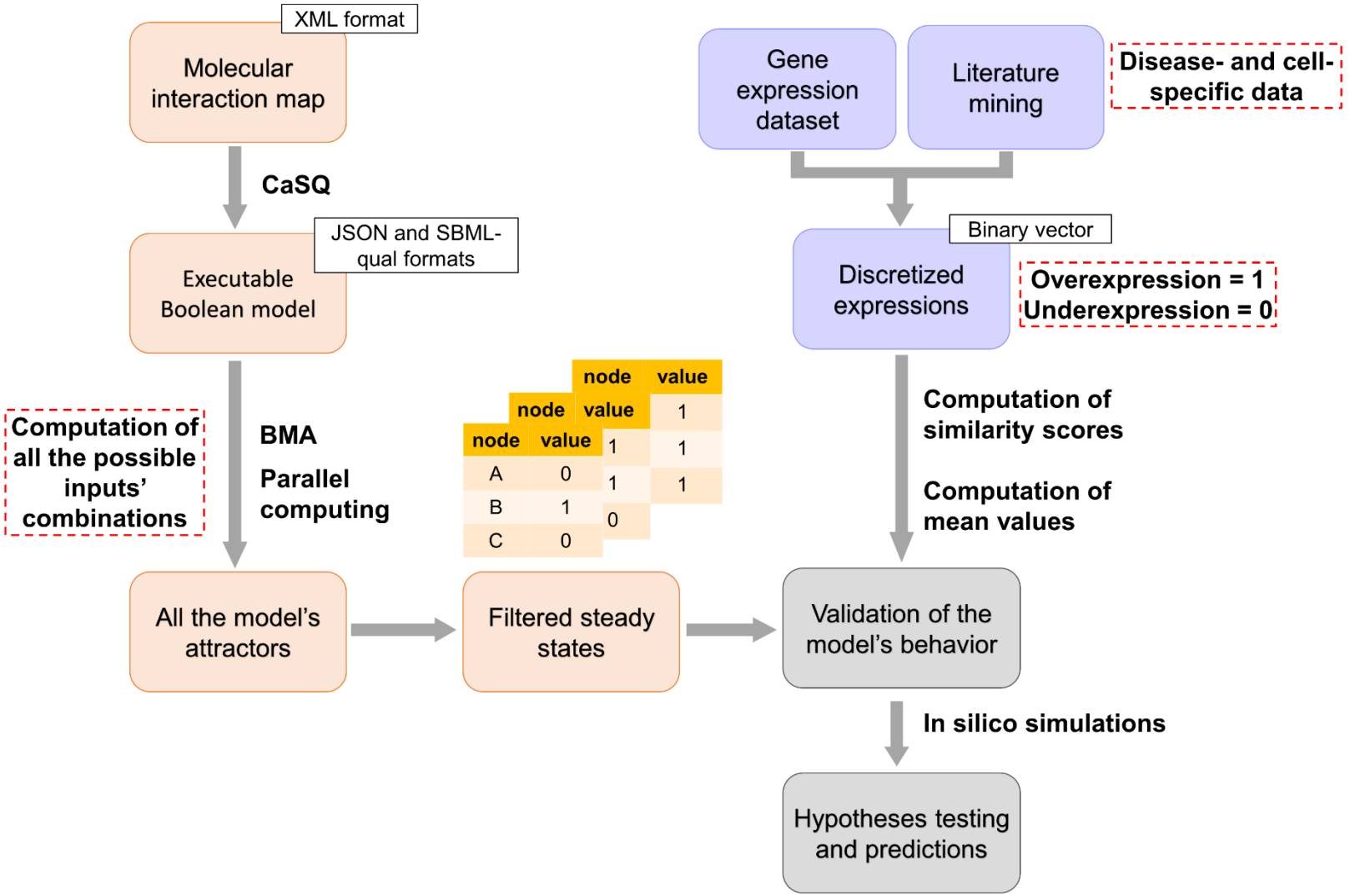
A = B
B = A AND NOT C
C = A AND NOT B



State transition graph and attractors of the toy model

(Schwab et al., 2020)

The proposed computational framework



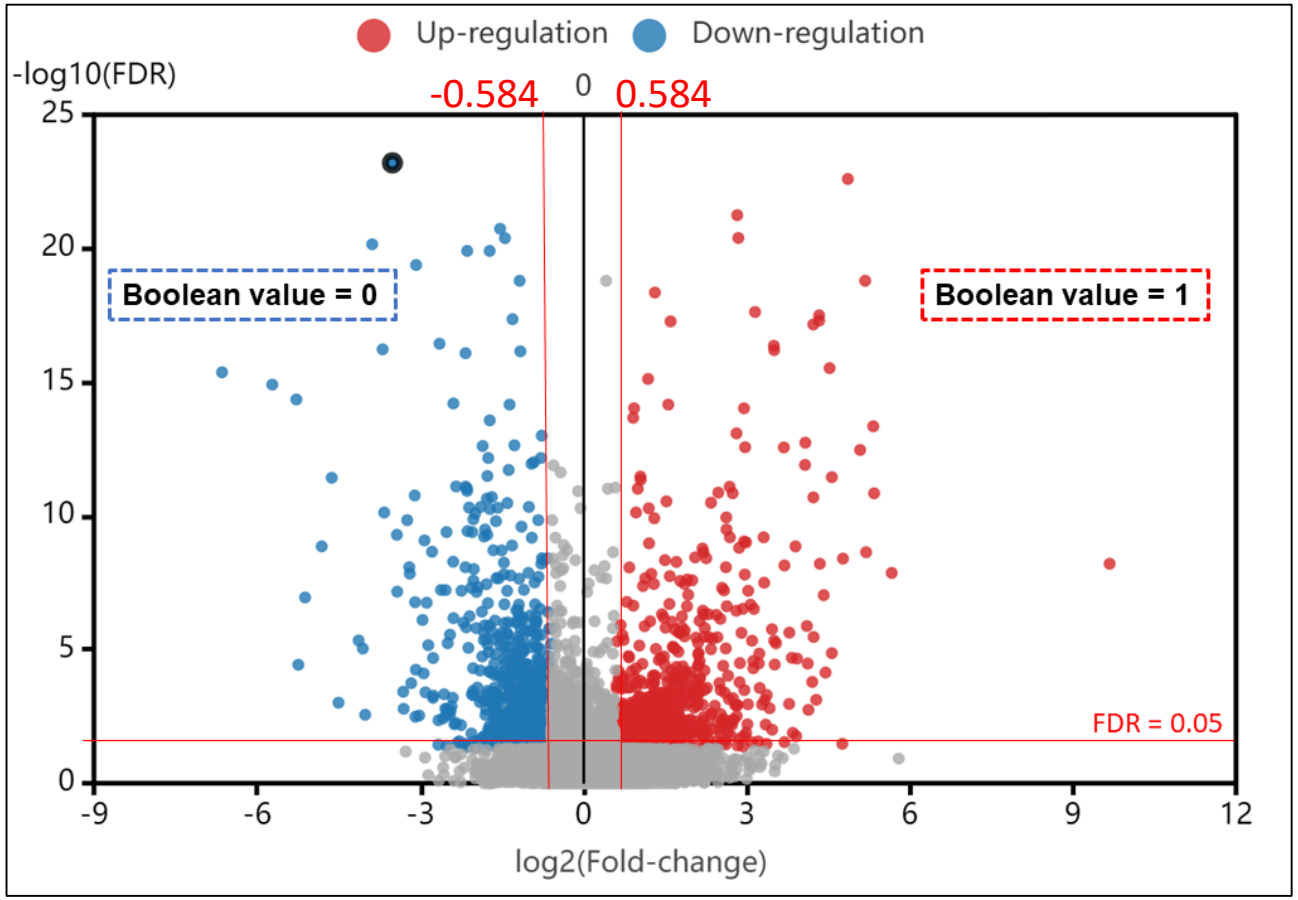
(**Zerrouk** et al., npj systems biology & applications, 2024)

Validation of the model's behavior

- Similarity score S = ($N00$ + $N11$)/($N00$ + $N11$ + $N10$ +$N01$)

N00 and N11 = number of nodes **with the same state** in both the steady state and the discretized vector of experimentally observed expressions

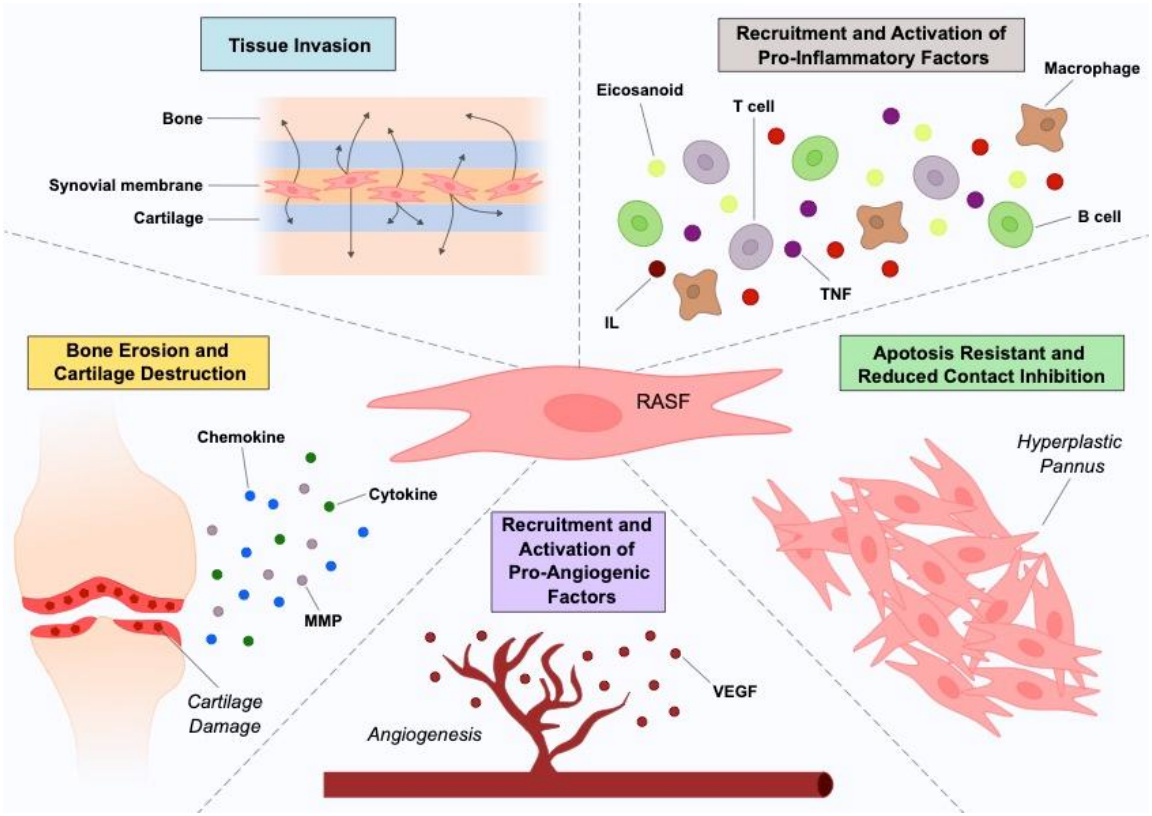
N01 and N10 = number of nodes with **different states** in the steady state and the discretized vector of experimentally observed expressions



Gene expression discretization on a volcano plot showing the DEGs between RA and osteoarthritis synovial fibroblasts. DEGs were filtered using an FDR equal to 0.05 and a logFC equal to 0.584.

(**Zerrouk** et al., npj systems biology & applications, 2024)

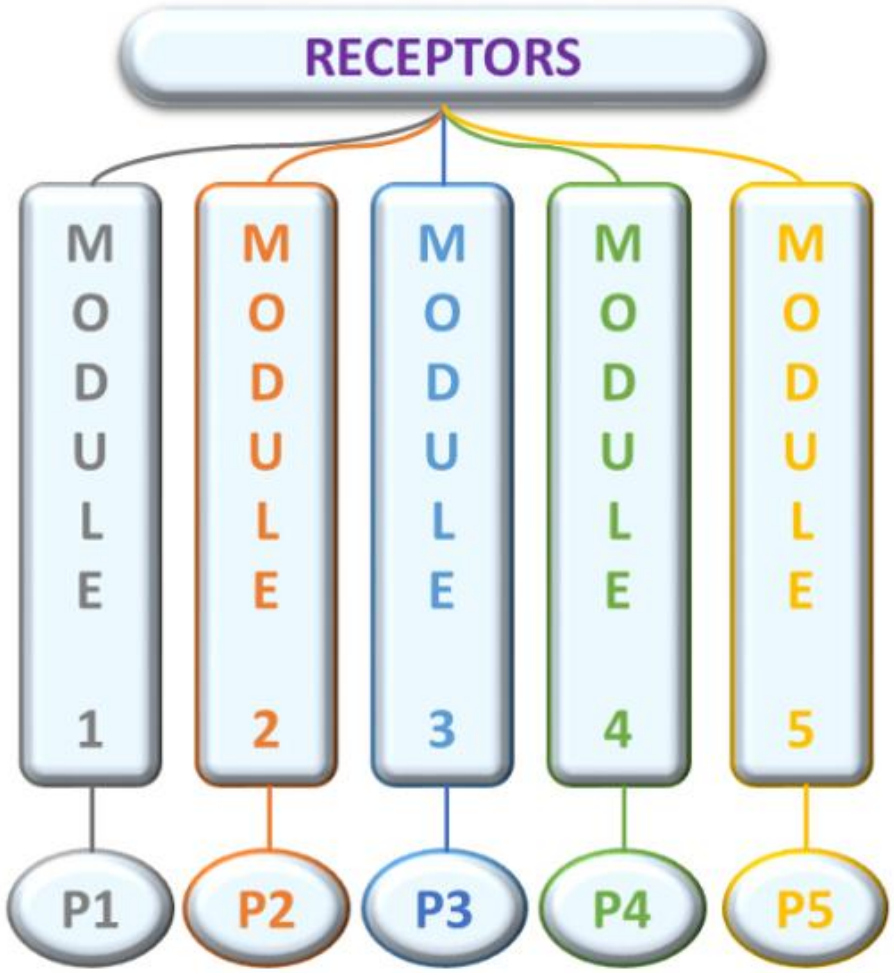
Building a joint one cell at a time?

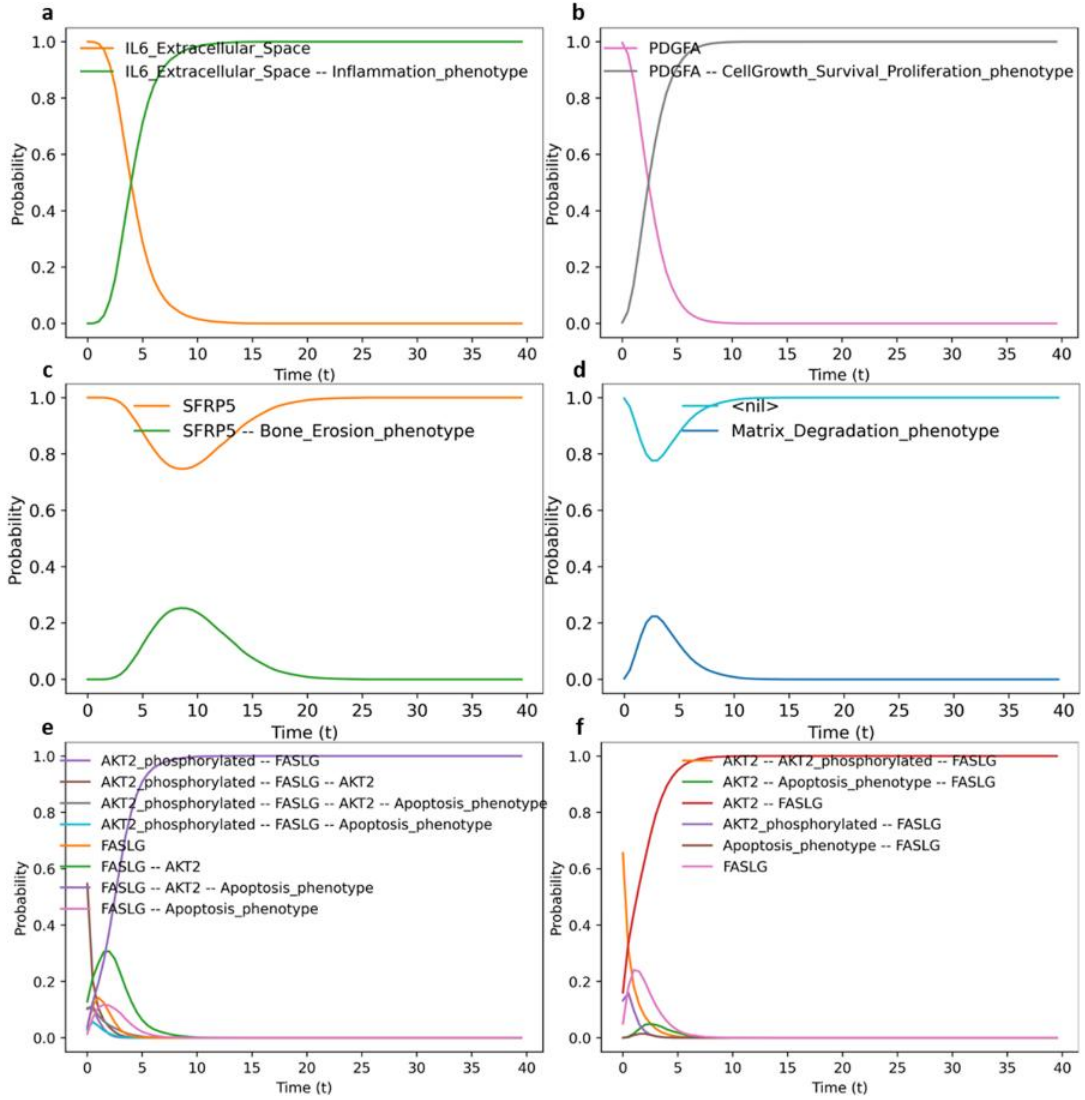


Adapted from **Aghakhani, S**.; Zerrouk, N.; Niarakis, A. *Cancers* (2021)

Models	Number of nodes	Number of edges
Cell proliferation/ cell growth/survival	235	364
Apoptosis	233	352
Inflammation	230	368
Osteoclastogenesis and bone erosion	217	341
Matrix Degradation	195	280
Model with five phenotypes	309	504

A large-scale Boolean model for RA-FLS





Vidisha Singh, Aurelien Naldi, Sylvain Soliman, Anna Niarakis, A modular, large-scale Boolean model of the Rheumatoid Arthritis fibroblast-like synoviocytes, *npj Systems Biology & Applications, 2023*

Modelling the effect of mono/ combined treatment

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A large-scale Boolean model of the rheumatoid arthritis fibroblast-like synoviocytes predicts drug synergies in the arthritic joint

Vidisha Singh, Aurelien Naldi, Sylvain Soliman & Anna Niarakis

npj Systems Biology and Applications **9**, Article number: 33 (2023) | Cite this article

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Abstract

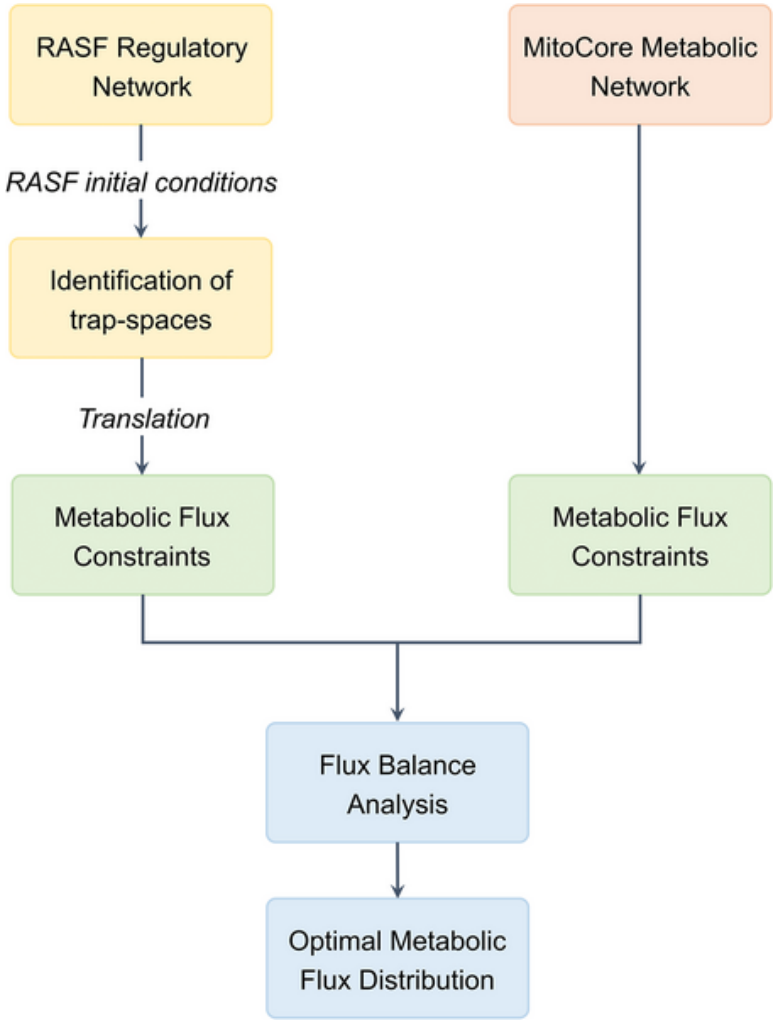
Rheumatoid arthritis (RA) is a complex autoimmune disease with an unknown aetiology. However, rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) play a significant role in initiating and perpetuating destructive joint inflammation by expressing immuno-modulating cytokines, adhesion molecules, and matrix remodelling enzymes. In addition, RA-FLS are primary drivers of inflammation, displaying high proliferative rates and an apoptosis-resistant phenotype. Thus, RA-FLS-directed therapies could become a complementary approach to

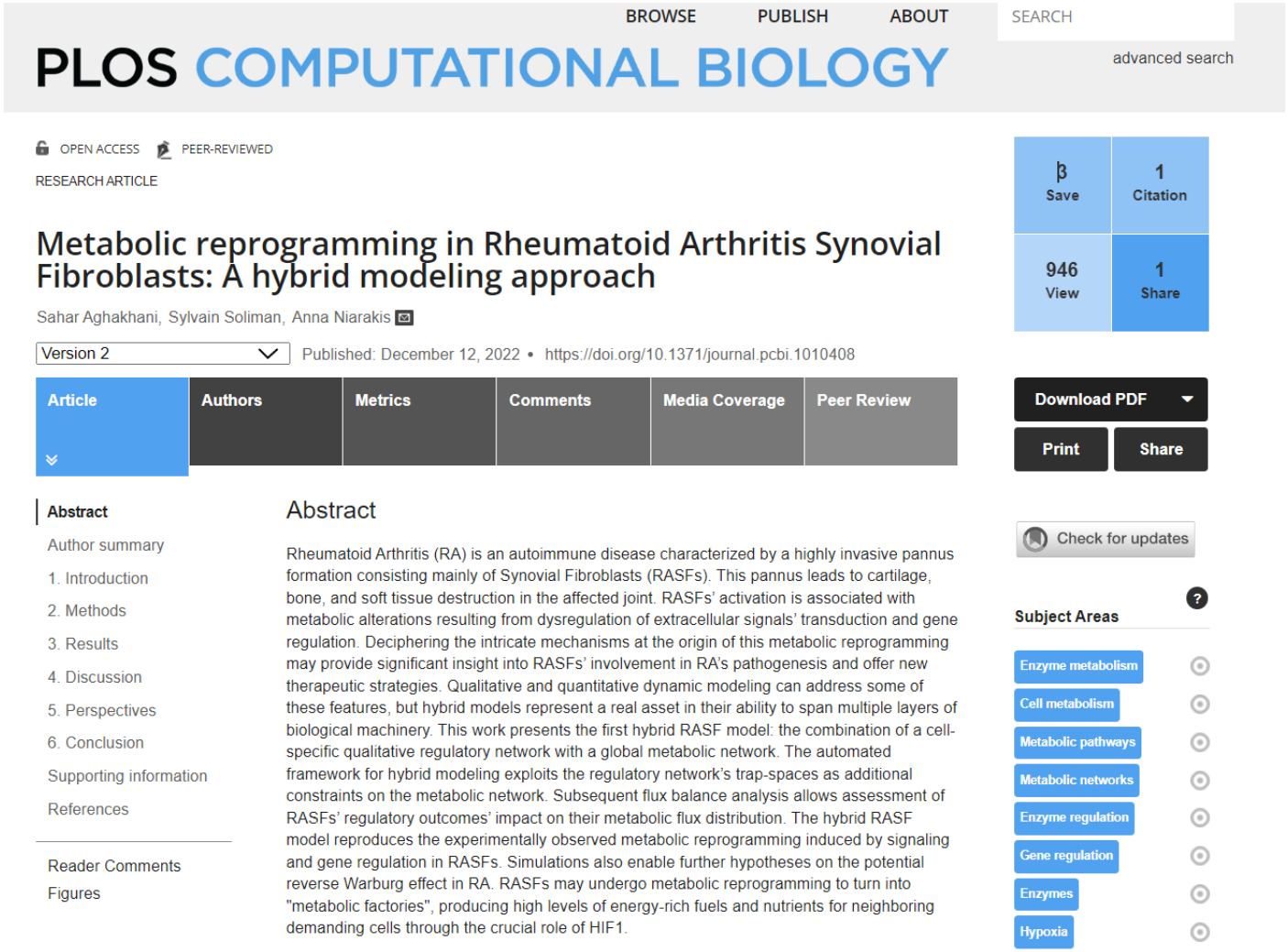
Mono drug therapy	Targets
Tocilizumab, Sarilumab	IL-6[98]
Etanercept, Infliximab, Adalimumab, Golimumab, and Certolizumab Pegol	TNF[65,98]
Tofacitinib (RA-FLS), Baricitinib, Itacitinib	JAK[98,99]
Secukinumab	IL-17[98]
Andecaliximab, Celastrol (RA-FLS)	MMP9[98,100,101]
Imatinib	PDGF[16,102]
Methotrexate	IL1B, PDGF, NFKB[103,104]
Anakinra	IL1B[105]

Combined drug therapy	Targets
Methotrexate + Sarilumab (or Tocilizumab)	NFKB, PDGFA, IL1B targeted by Methotrexate + IL-6 targeted by Sarilumab[106,107]
Methotrexate + Cyclosporine	NFKB, PDGFA, IL1B targeted by Methotrexate + Calcineurin targeted by Cyclosporine[108,109]
Methotrexate + Azathioprine	NFKB, PDGFA, IL1B targeted by Methotrexate + RAC1 by Azathioprine[110,111]
Methotrexate + Hydroxychloroquine	NFKB, PDGFA, IL1B targeted by Methotrexate + TLRs targeted by hydroxychloroquine[112,113]

Identified drugs	Target components	Target phenotypes and expected effect
Pamidronate, Incadronate, and Zoledronic Acid	CAV1	Apoptosis ↑
Sarilumab, Tocilizumab	IL-6	Inflammation ↓
GSK2618960, and T-5224, Acitretin	IL7 AP-1	Bone erosion ↓
Batimastat	MMP3	Matrix degradation ↓
666-15 and AS1842856	CREB1 YWHAQ (FOXO1)	Cell proliferation ↓

General architecture of the hybrid modeling framework.





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RESEARCH ARTICLE

Metabolic reprogramming in Rheumatoid Arthritis Synovial Fibroblasts: A hybrid modeling approach

Sahar Aghakhani, Sylvain Soliman, Anna Niarakis

Version 2 Published: December 12, 2022 • https://doi.org/10.1371/journal.pcbi.1010408

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Abstract
Author summary
1. Introduction
2. Methods
3. Results
4. Discussion
5. Perspectives
6. Conclusion
Supporting information
References
Reader Comments
Figures

Abstract

Rheumatoid Arthritis (RA) is an autoimmune disease characterized by a highly invasive pannus formation consisting mainly of Synovial Fibroblasts (RASFs). This pannus leads to cartilage, bone, and soft tissue destruction in the affected joint. RASFs' activation is associated with metabolic alterations resulting from dysregulation of extracellular signals' transduction and gene regulation. Deciphering the intricate mechanisms at the origin of this metabolic reprogramming may provide significant insight into RASFs' involvement in RA's pathogenesis and offer new therapeutic strategies. Qualitative and quantitative dynamic modeling can address some of these features, but hybrid models represent a real asset in their ability to span multiple layers of biological machinery. This work presents the first hybrid RASF model: the combination of a cell-specific qualitative regulatory network with a global metabolic network. The automated framework for hybrid modeling exploits the regulatory network's trap-spaces as additional constraints on the metabolic network. Subsequent flux balance analysis allows assessment of RASFs' regulatory outcomes' impact on their metabolic flux distribution. The hybrid RASF model reproduces the experimentally observed metabolic reprogramming induced by signaling and gene regulation in RASFs. Simulations also enable further hypotheses on the potential reverse Warburg effect in RA. RASFs may undergo metabolic reprogramming to turn into "metabolic factories", producing high levels of energy-rich fuels and nutrients for neighboring demanding cells through the crucial role of HIF1.

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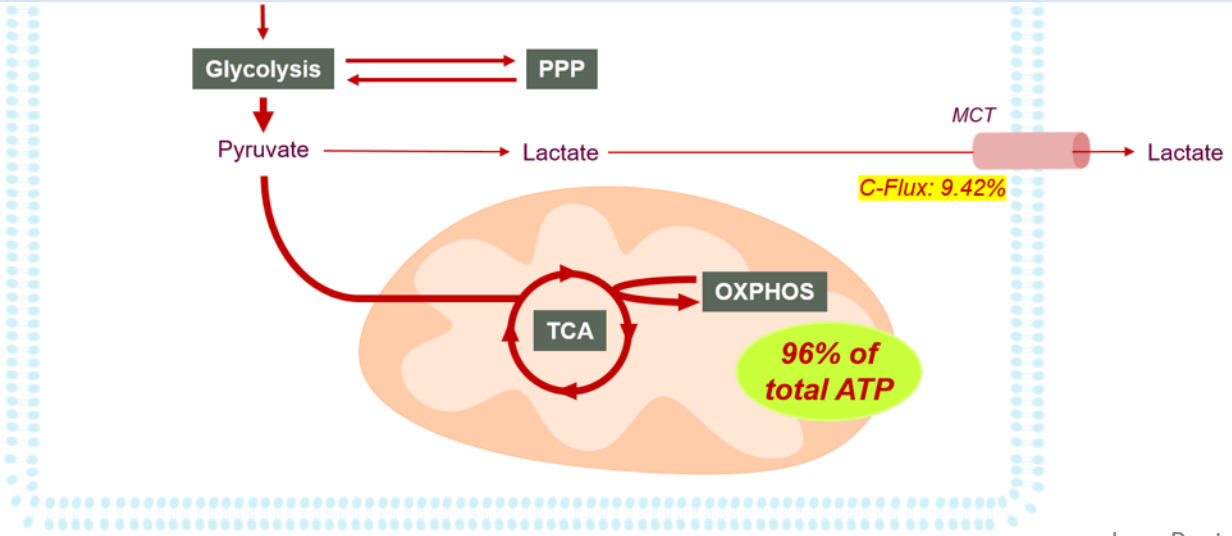
Aghakhani S, Soliman S, Niarakis A (2022) Metabolic reprogramming in Rheumatoid Arthritis Synovial Fibroblasts: A hybrid modeling approach. PLOS Computational Biology 18(12): e1010408. https://doi.org/10.1371/journal.pcbi.1010408
https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1010408

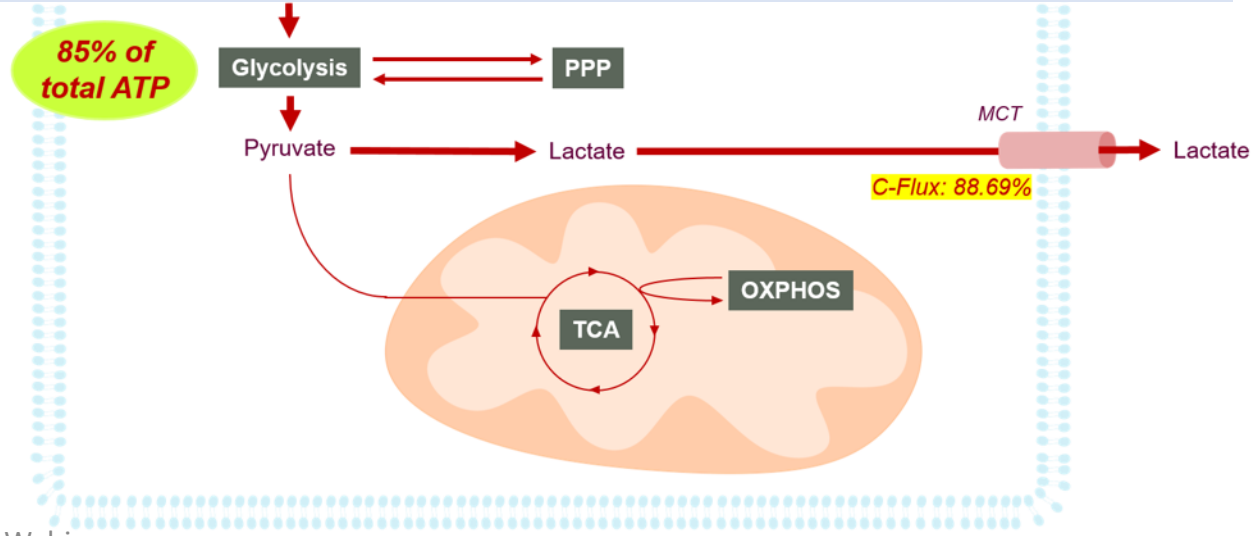
A hybrid model for RASF

Constraining FBA with Stable States Constraints

- **8 trap-spaces** identified;
- **12 metabolite's stable states = 0** (out of 29 common metabolites between RASF-Model and MitoCore);
- **7 metabolic enzyme's stable states = 0** (out of 19 common enzymes between RASF-Model and MitoCore);

⇒ **50 metabolic reactions' flux constrained to 0** from the regulatory network.





Knockout simulations and FBA results reveal an important role of HIF1 as a metabolic switch

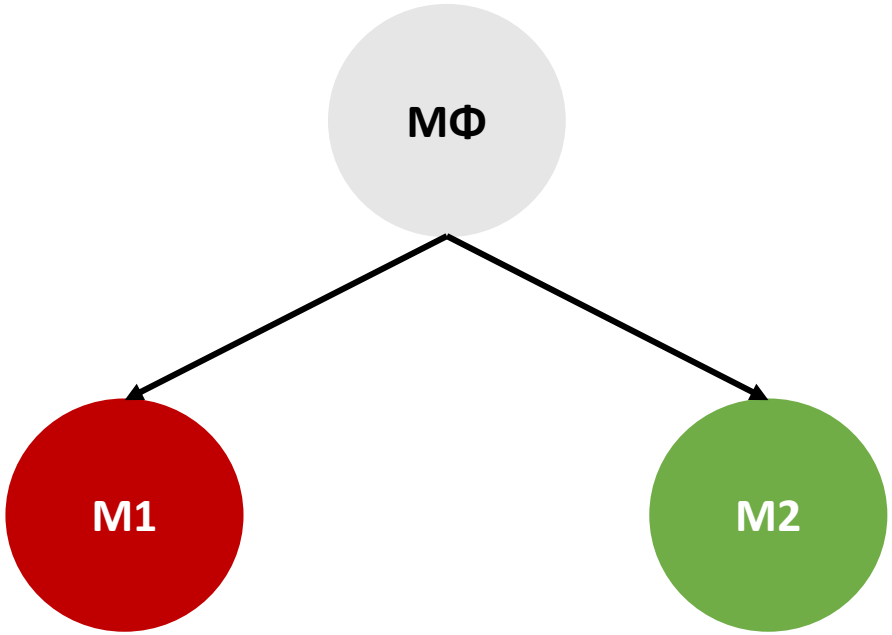
Component	Set of Initial Conditions													
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14
FASLG	0	1	1	1	1	1	1	1	1	1	1	1	1	1
FGF1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
HIF1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
IKBA/NFKB1/RELA	1	1	1	0	1	1	1	1	1	1	1	1	1	1
IL17A	1	1	1	1	0	1	1	1	1	1	1	1	1	1
IL18	1	1	1	1	1	0	1	1	1	1	1	1	1	1
IL6	1	1	1	1	1	1	0	1	1	1	1	1	1	1
MIR192	0	0	0	0	0	0	0	1	0	0	0	0	0	0
PDGFA	1	1	1	1	1	1	1	1	0	1	1	1	1	1
RANKL	1	1	1	1	1	1	1	1	1	0	1	1	1	1
SFRP5	0	0	0	0	0	0	0	0	0	0	1	0	0	0
TGFB1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
TNF	1	1	1	1	1	1	1	1	1	1	1	1	0	1
WNT5A	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Glycolysis	85.1	85.1	0	85.1	85.1	85.1	85.1	85.1	85.1	85.1	85.1	85.1	85.1	85.1
OXPHOS	14.9	14.9	100	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9

https://doi.org/10.1371/journal.pcbi.1010408.t004

This finding suggests that targeting HIF1 could participate in the restoration of a healthy metabolic profile in RASFs.

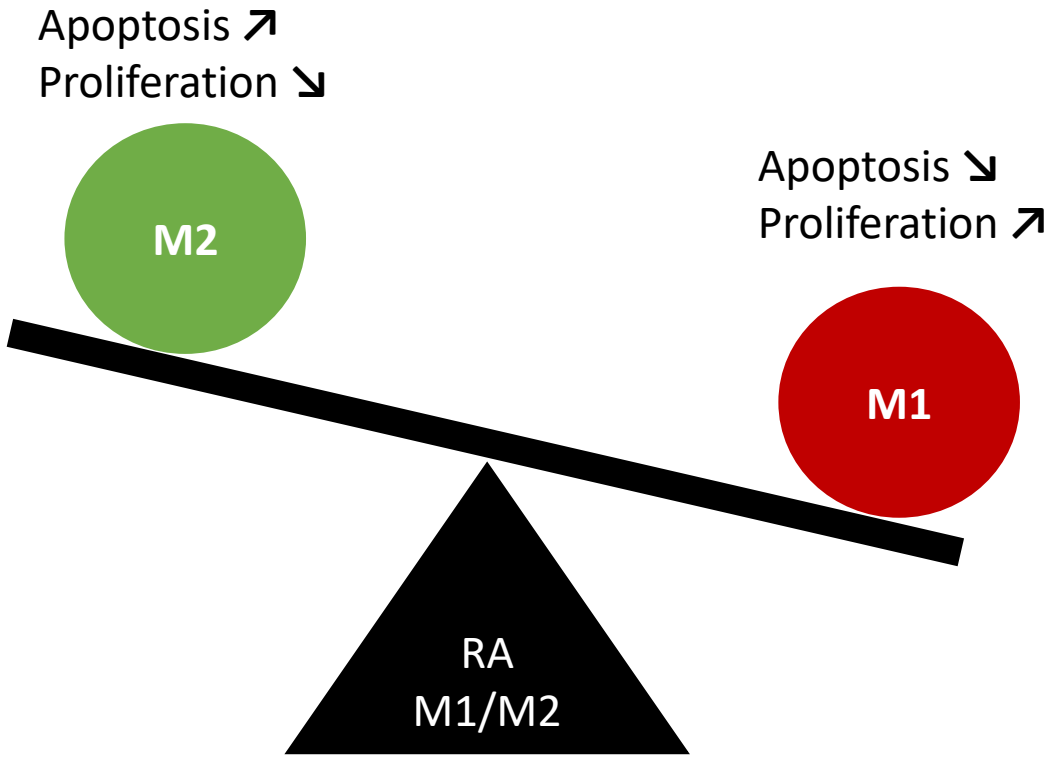
Furthermore, this is consistent with recent experimental studies demonstrating that HIF1 knockdown reduces glycolytic metabolism in human synovial fibroblasts.

Targeting macrophages in RA



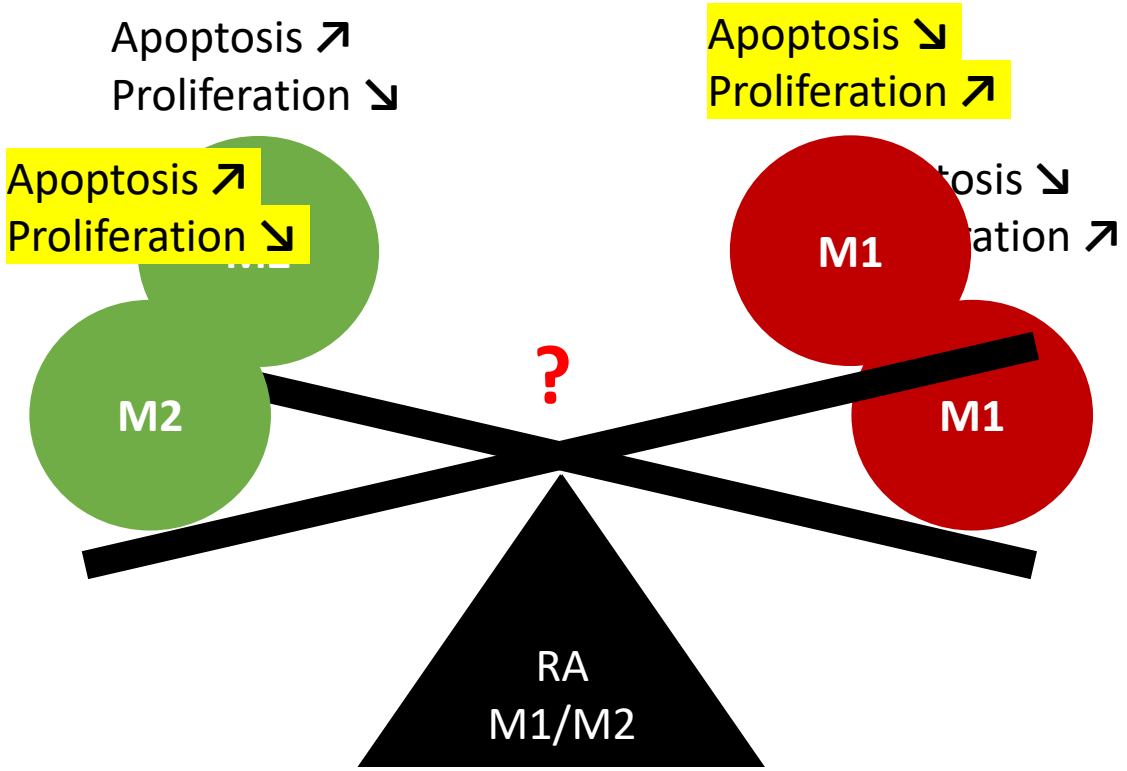
Inflammatory cytokines
Matrix degradation enzymes
Proinflammatory T activation

Anti-inflammatory cytokines
Tissue homeostasis and repair
Regulatory T cells activation

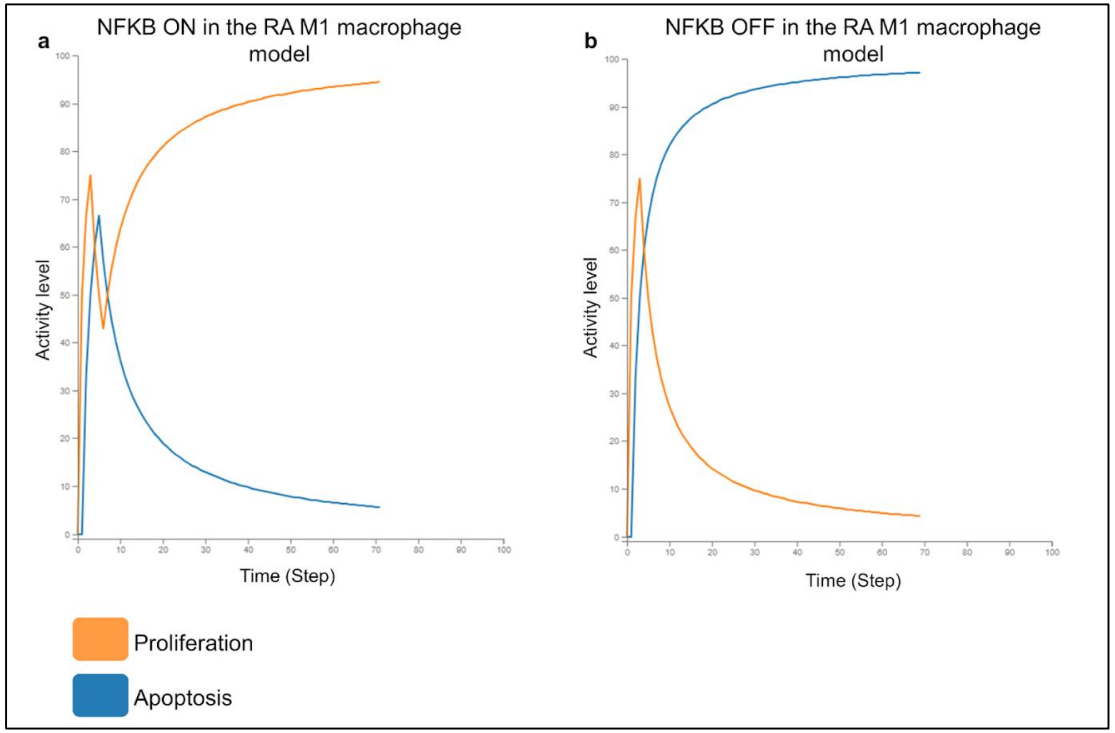


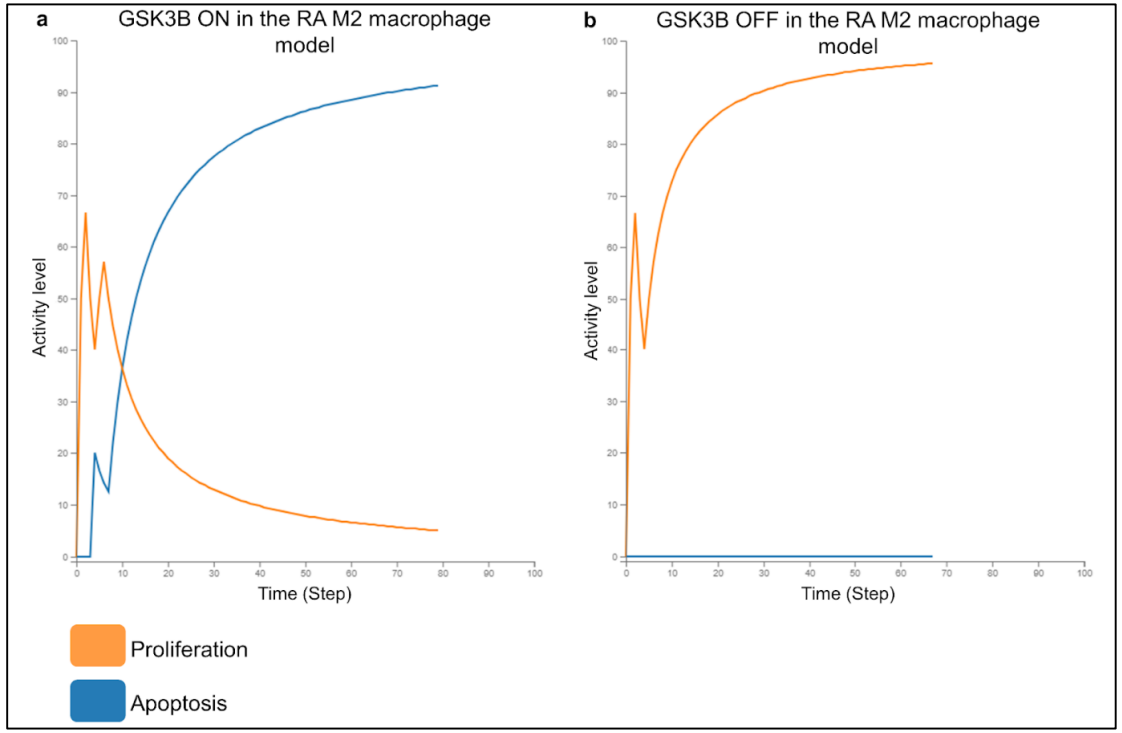
(Yang et al., 2020)
(Cutolo et al., 2022)

Selective M1 macrophage depletion and M2 macrophage promotion in the RA synovium



Selective M1 macrophage depletion and M2 macrophage promotion in the RA synovium



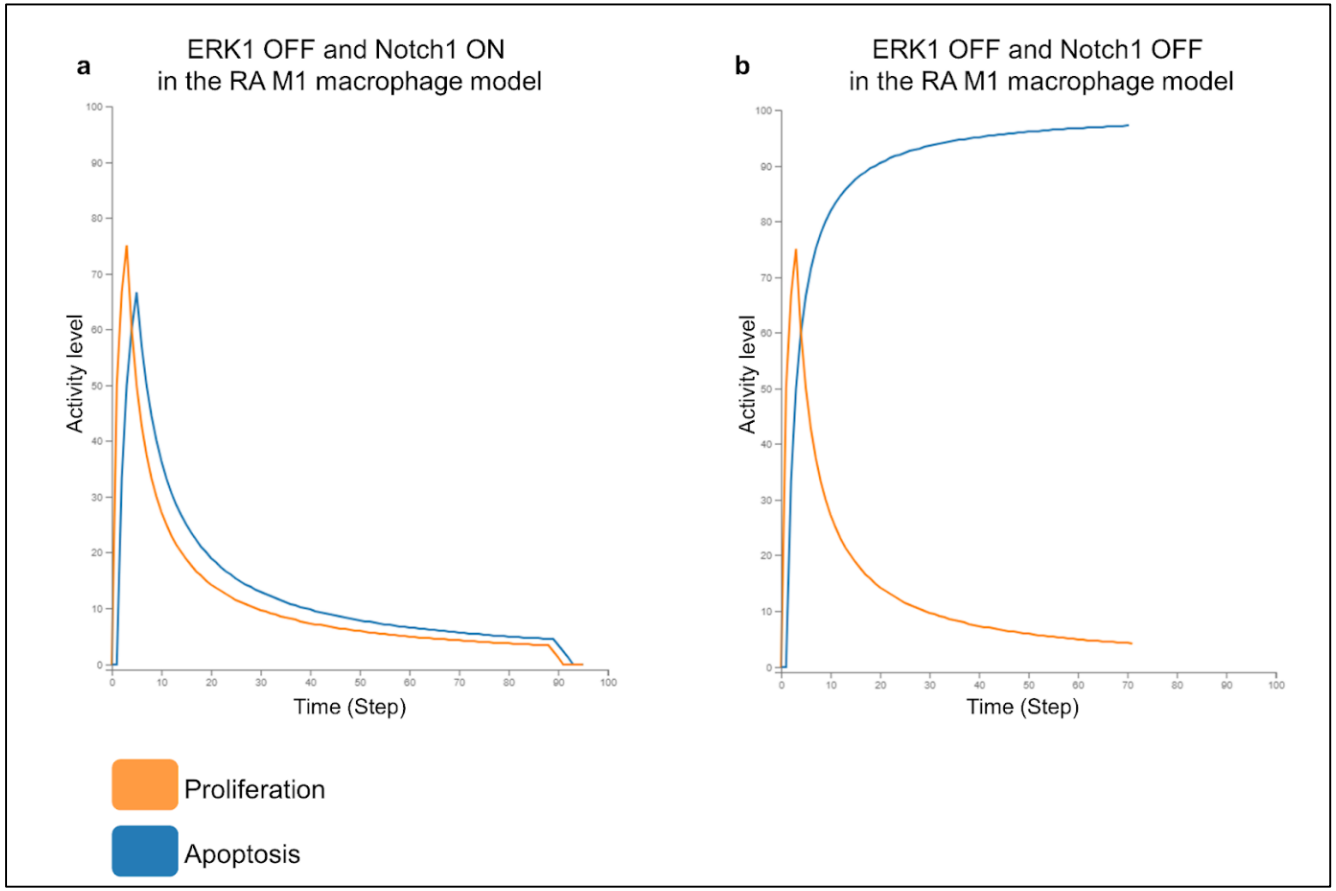


NF-κB inhibition for therapeutic interventions in **RA** & for downregulating the **M1 markers**
(Xia et al., 2018, Cutolo et al., 2022)

GSK3B inhibition for therapeutic interventions in **RA** & for increasing the expression of the **M2 markers** (Kwon et al., 2014, Peng et al., 2022)

(**Zerrouk** et al., npj SBA, 2024)

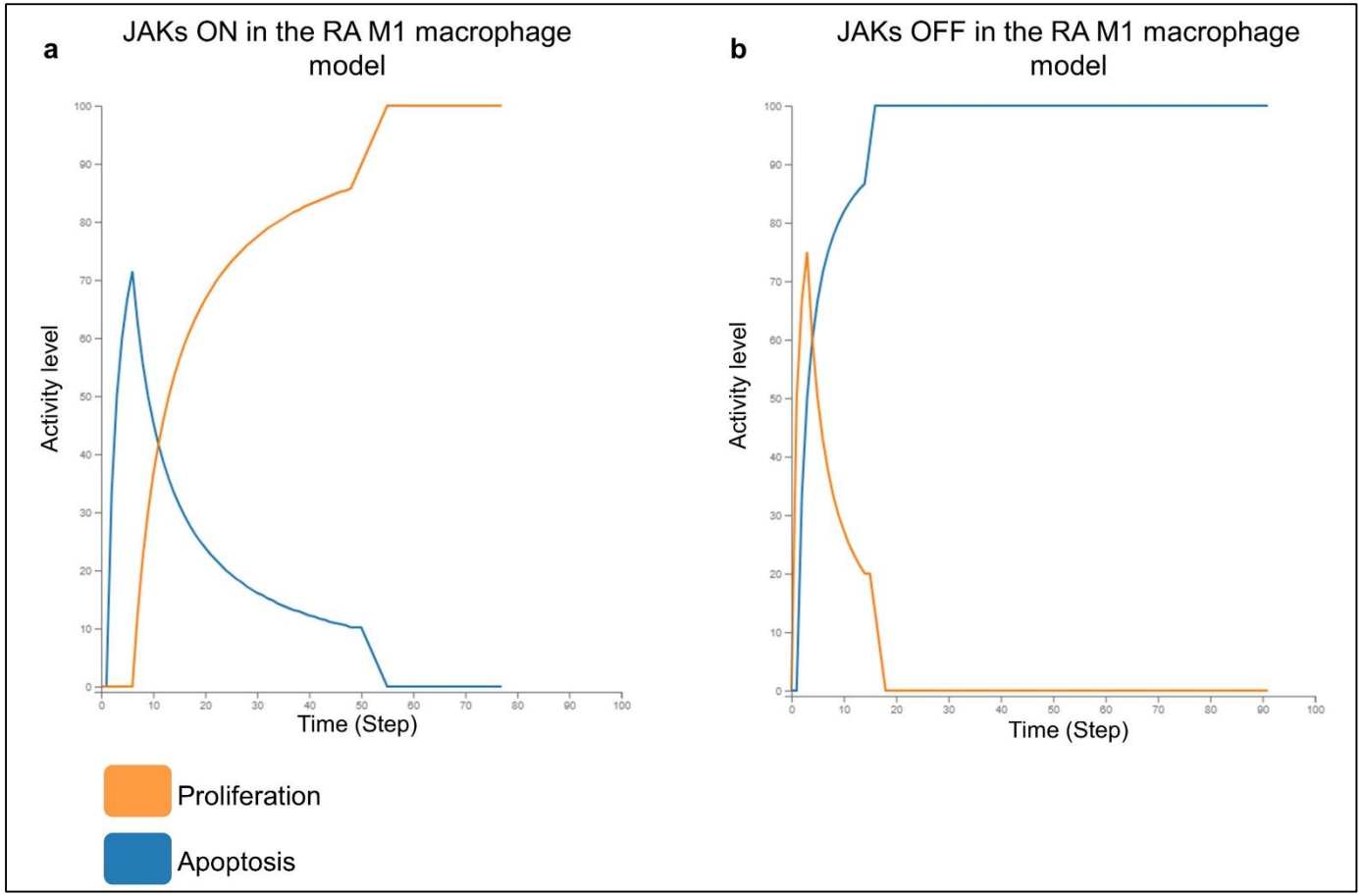
Selective M1 macrophage depletion and M2 macrophage promotion in the RA synovium



The potential therapeutic value of co-targeting **ERK1 and Notch1** has already been demonstrated in cancer but **not in RA** (Krepler et al., 2016)

(**Zerrouk** et al., npj SBA, 2024)

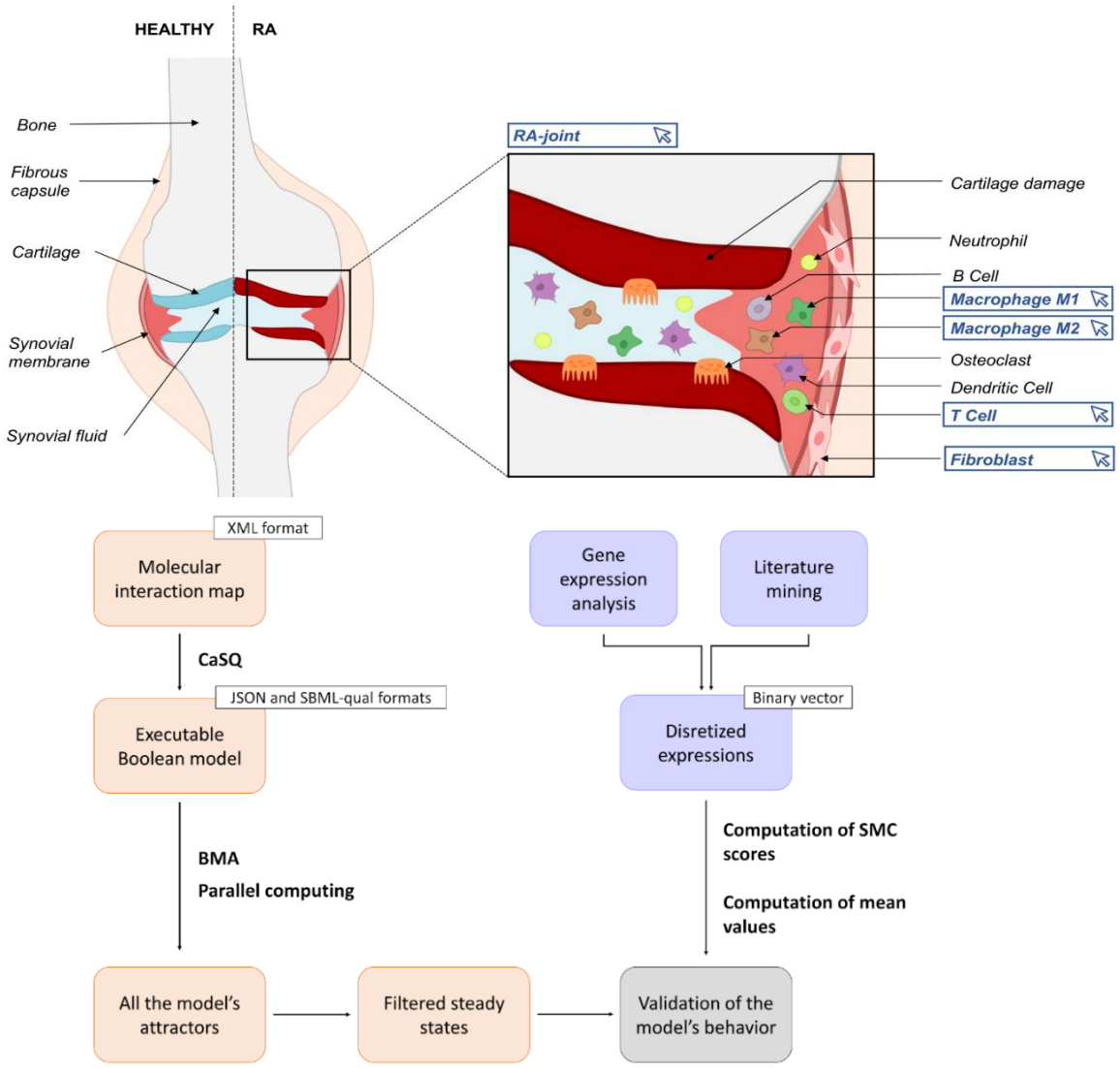
Selective M1 macrophage depletion and M2 macrophage promotion in the RA synovium

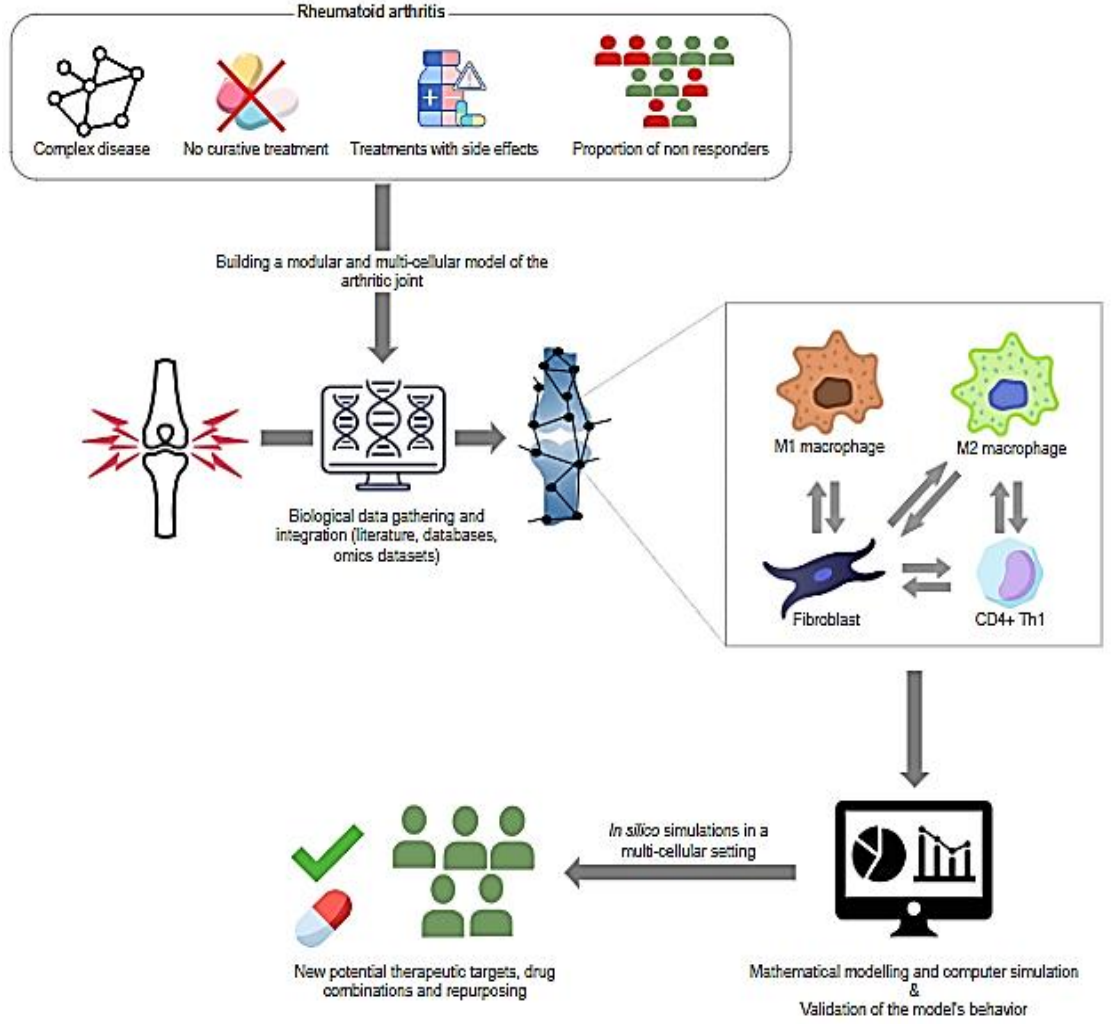


(**Zerrouk** et al., npj SBA, 2024)

Baricitinib is an FDA approved drug for treating RA → Its **effect on the macrophage's phenotypes is not understood** (Magnon et al., 2019, Palasiewicz et al., 2021)

Building a multicellular model for RA – SANOFI R&D

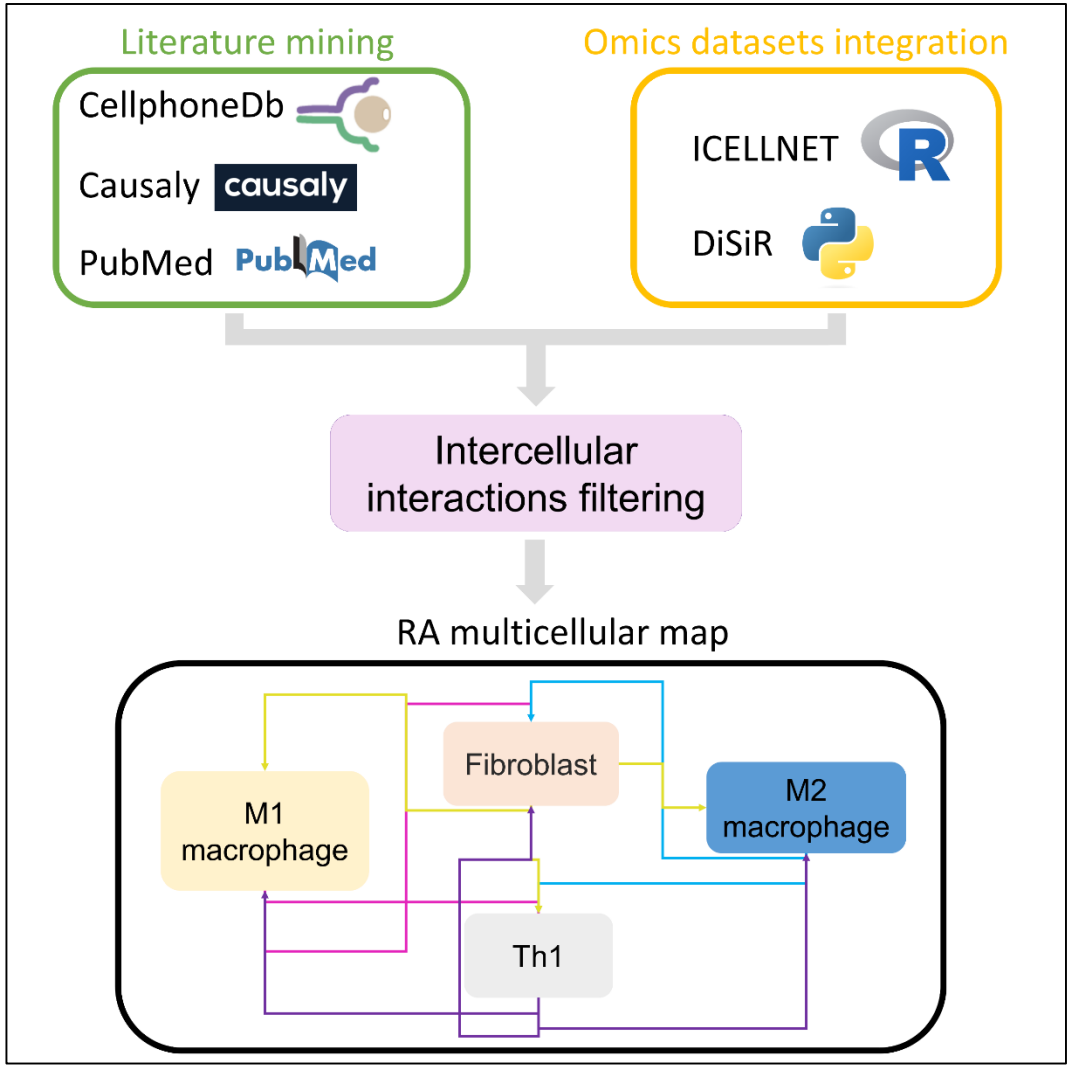




A Mechanistic Multicellular Atlas of the Rheumatic Joint , Naouel Zerrouk, Sahar Aghakhani, Vidisha Singh, Franck Augé and Anna Niarakis, Frontiers in Systems Biology, 2022

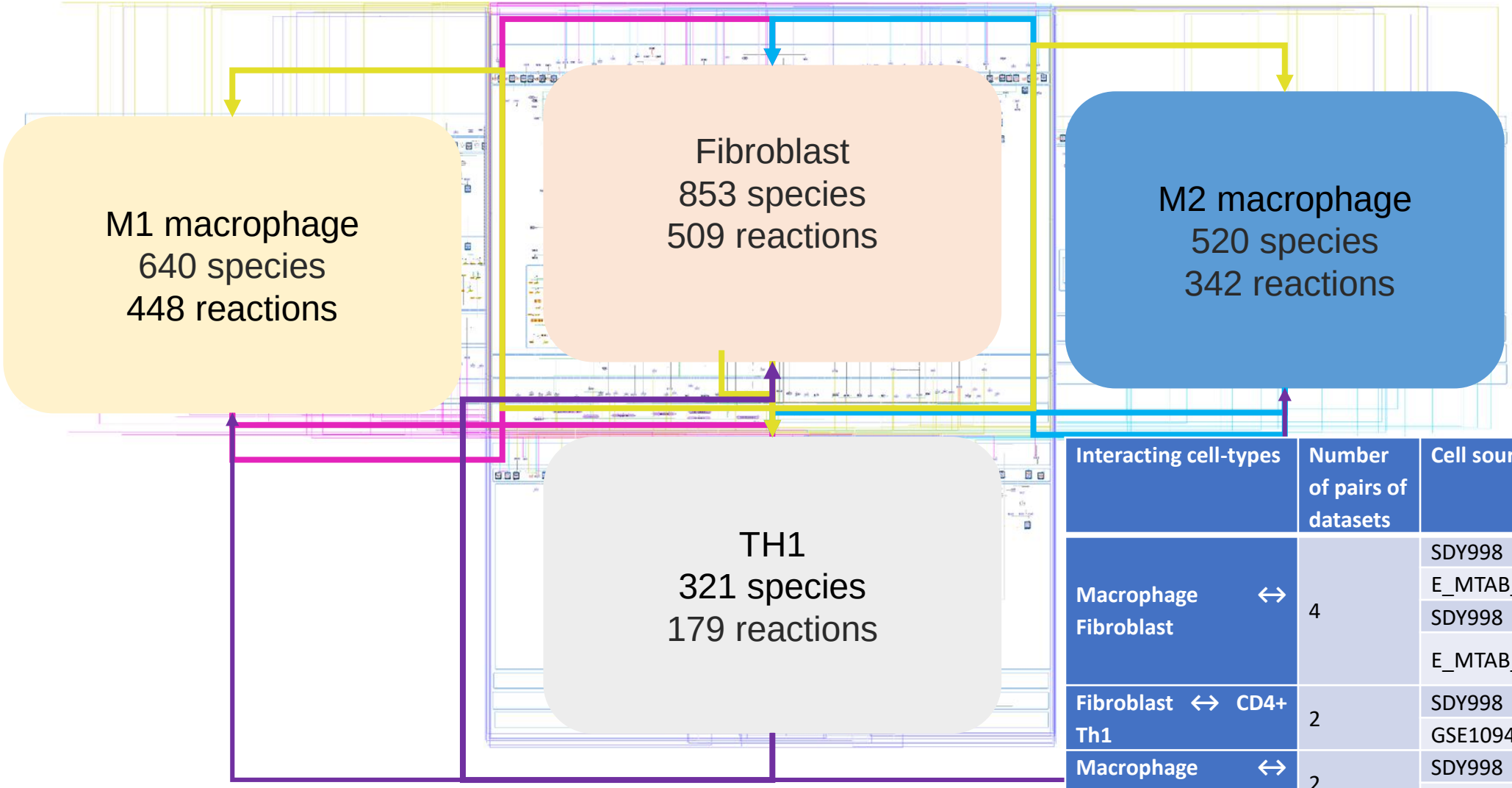
RA multicellular map construction

- Literature and databases mining, Causaly and CellphoneDB, search in PubMed
- Integration of omics datasets via ICELLNET and DiSiR to identify statistically significant interactions
- Filtering of the retrieved interactions to cross validate the results
- Connection of the RA cell-specific maps and generation of the first RA multicellular map.



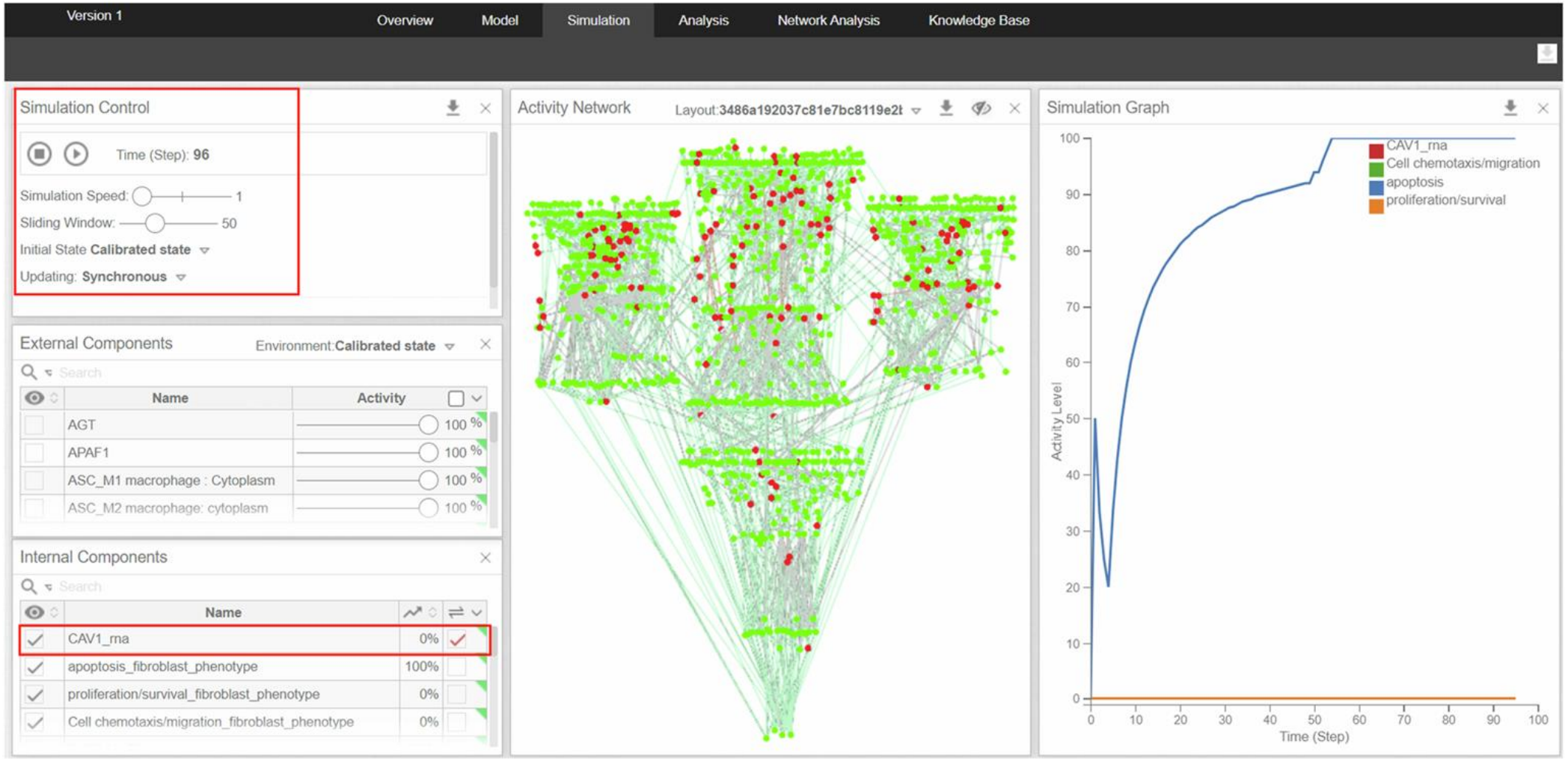
(https://www.causaly.com/our-company)
(Efremova et al., 2020)
(Noel et al., 2021)
(Vahid et al., 2023)

Integrating detailled cellular crosstalk between cell specific maps (source of multiple challenges)

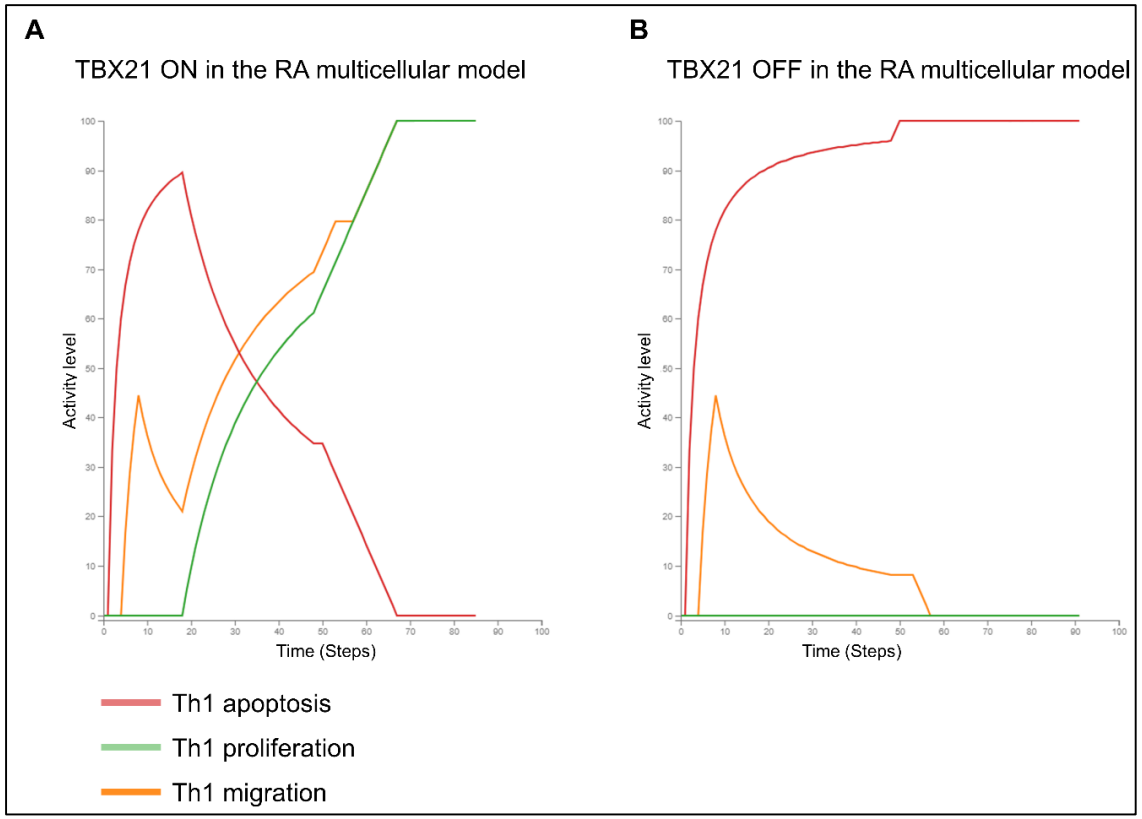


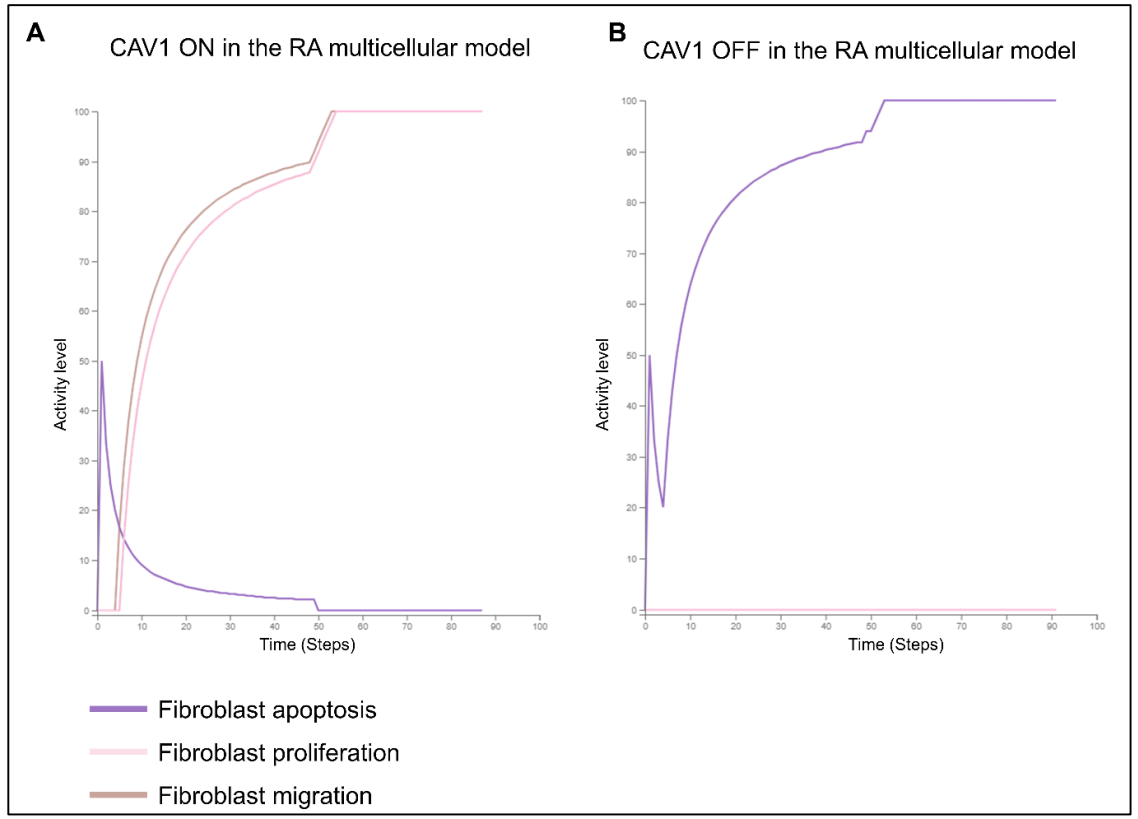
Interacting cell-types	Number of pairs of datasets	Cell source 1	Cell source 2
Macrophage ↔ Fibroblast	4	SDY998	SDY998
		E_MTAB_8322	SDY998
		SDY998	GSE109449
		E_MTAB_8322	GSE109449
Fibroblast ↔ CD4+ Th1	2	SDY998	SDY998
		GSE109449	SDY998
Macrophage ↔ CD4+ Th1	2	SDY998	SDY998
		E_MTAB_8322	SDY998

In silico simulations



Investigation of new therapeutic options using the RA multicellular model

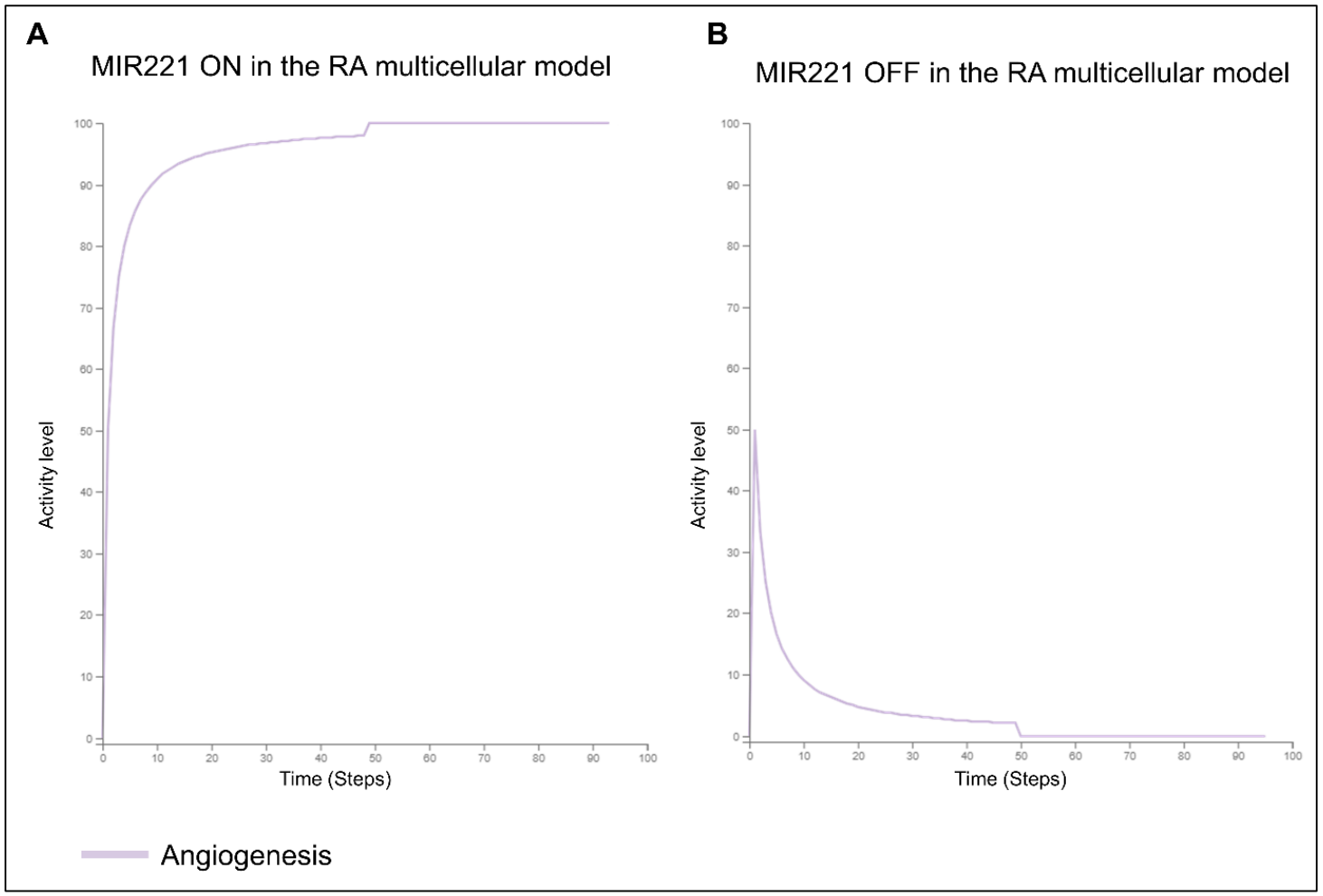




Published experimental evidence support **TBX21** inhibition for **downregulating hyperactive RA Th1** (Xue et al., 2014, Bruyn et al., 2007)

Published literature support **CAV1** inhibition for **downregulating hyperactive RA fibroblasts** (Xing et al., 2016, Li et al., 2017, Takeba et al., 2000)

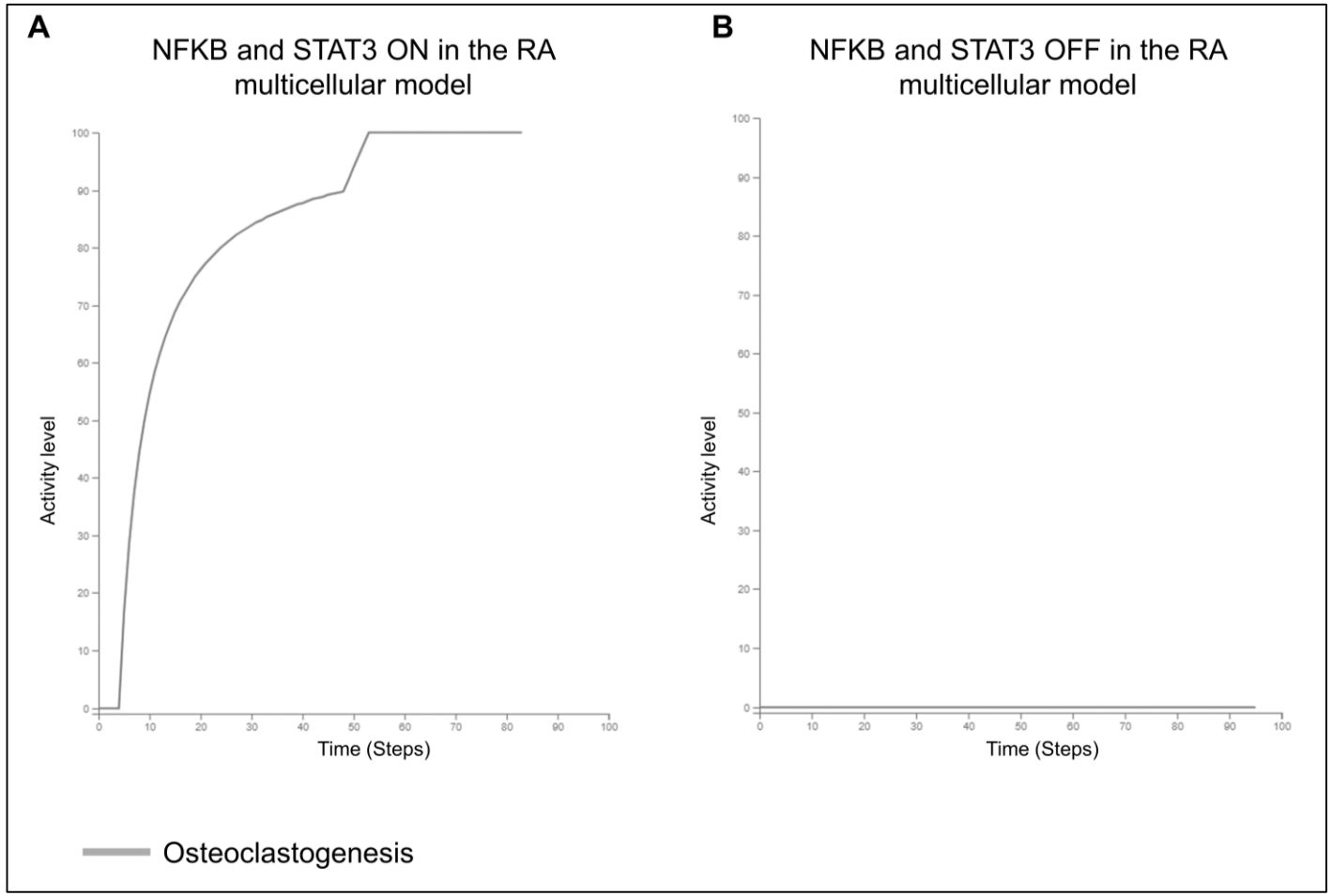
Investigation of new therapeutic options using the RA multicellular model



Experiments show that **MIR221** inhibition could reduce the **angiogenesis** in the arthritic joint (Mcmorrow et al., 2013)

MIR221 inhibition → Subsequent activation of THBS1

Investigation of new therapeutic options using the RA multicellular model



Therapeutic targets that perturb RA phenotypes in the RA multi-cellular model

Successful targets	RA multi-cellular model's phenotypes														
	M1 Macrophage			M2 macrophage		Fibroblast			Th1			Joint			
	Apoptosis	Proliferation	Osteoclastogenesis	Apoptosis	Proliferation	Apoptosis	Proliferation	Migration	Apoptosis	Proliferation	Migration	Inflammation	Angiogenesis	Matrix degradation	Osteoclastogenesis
AKT2							↘	↘							
CAV1						↗	↘	↘							
CREB1							↘								
GSK3β				↘	↗										
ERK1		↘	↘												
MIR221													↘		
mTOR									↗	↘	↘				
NF-κB	↗	↘	↘					↘		↘	↘			↘	
TBX21									↗	↘	↘				

Successful targets	Target type	Associated disease(s)	Drugs with the highest status
CAV1	Literature-reported target	/	/
AKT2	Literature-reported target	/	Akt inhibitor VIII (Investigative)
CREB1	Literature-reported target	/	/
NF-kappaB	Successful target	Irritable bowel syndrome, Rheumatoid arthritis, Choreiform disorder, Lupus erythematosus, Multiple sclerosis...	Sulfasalazine (Approved)
TBX21	Literature-reported target	/	/
MTOR	Successful target	Arteries/arterioles disorder, Chronic myelomonocytic leukaemia, Hydrocephalus, Multiple myeloma, Renal cell carcinoma	Everolimus (Approved)
ERK1	Clinical trial target	Melanoma, Pancreatic cancer, Cancer, Arteries/arterioles disorder, Mature T-cell lymphoma	BVD-523 (Phase 2)
GSK3β	Clinical trial target	Myotonic disorder, Acute myeloid leukaemia, Osteosarcoma, Fragile X chromosome, Myeloproliferative neoplasm	Tideglusib (Phase 2/3)
MIR221	Literature-reported target	/	/

npj | digital medicine

Article | Open access | Published: 24 December 2024

Building a modular and multi-cellular virtual twin of the synovial joint in Rheumatoid Arthritis

Naouel Zerrouk, Franck Augé & Anna Niarakis

npj Digital Medicine **7**, Article number: 379 (2024) | Cite this article

Abstract

Rheumatoid arthritis is a complex disease marked by joint pain, stiffness, swelling, and chrc synovitis, arising from the dysregulated interaction between synoviocytes and immune cells unclear etiology makes finding a cure challenging. The concept of digital twins, used in engineering, can be applied to healthcare to improve diagnosis and treatment for complex diseases like rheumatoid arthritis. In this work, we pave the path towards a digital twin of th arthritic joint by building a large, modular biochemical reaction map of intra- and intercellu interactions. This network, featuring over 1000 biomolecules, is then converted to one of th largest executable Boolean models for biological systems to date. Validated through existir knowledge and gene expression data, our model is used to explore current treatments and identify new therapeutic targets for rheumatoid arthritis.

npj | systems biology and applications

Perspective | Open access | Published: 30 November 2024

Immune digital twins for complex human pathologies: applications, limitations, and challenges

Anna Niarakis, Reinhard Laubenbacher, Gary An, Yaron Ilan, Jasmin Fisher, Åsmund Flobak, Kristin Reiche, María Rodríguez Martínez, Liesbet Geris, Luiz Ladeira, Lorenzo Veschini, Michael L. Blinov, Francesco Messina, Luis L. Fonseca, Sandra Ferreira, Arnau Montagud, Vincent Noël, Malvina Marku, Eirini Tsirvouli, Marcella M. Torres, Leonard A. Harris, T. J. Sego, Chase Cockrell, Amanda E. Shick, Hasan Balci, Albin Salazar, Kinza Rian, Ahmed Abdelmonem Hemedan, Marina Esteban-Medina, Bernard Staumont, Esteban Hernandez-Vargas, Shiny Martis B, Alejandro Madrid-Valiente, Panagiotis Karampelesis, Luis Sordo Vieira, Pradyumna Harlapur, Alexander Kulesza, Niloofar Nikaein, Winston Garira, Rahuman S. Malik Sheriff, Juilee Thakar, Van Du T. Tran, Jose Carbonell-Caballero, Soroush Safaei, Alfonso Valencia, Andrei Zinovyev & James A. Glazier — Show fewer authors

npj Systems Biology and Applications **10**, Article number: 141 (2024) | Cite this article

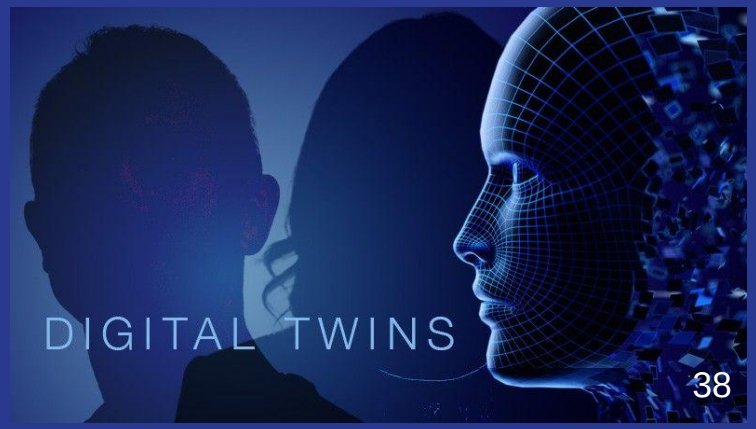
Abstract

Digital twins represent a key technology for precision health. Medical digital twins consist of computational models that represent the health state of individual patients over time, enabling optimal therapeutics and forecasting patient prognosis. Many health conditions involve the immune system, so it is crucial to include its key features when designing medical digital twins. The immune response is complex and varies across diseases and patients, and its modelling requires the collective expertise of the clinical, immunology, and computational modelling communities. This review outlines the initial progress on immune digital twins and the various initiatives to facilitate communication between interdisciplinary communities. We

DigiTREAT

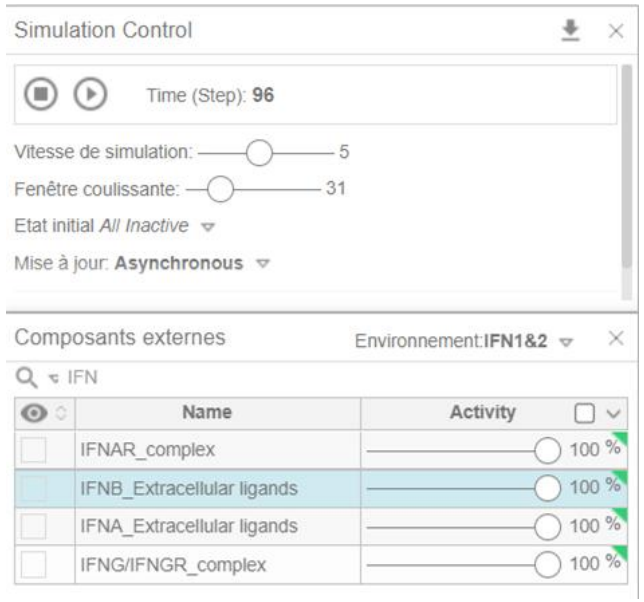
Building a Digital Twin
for the personalised treatment of
RhEumatoid ArthriTis

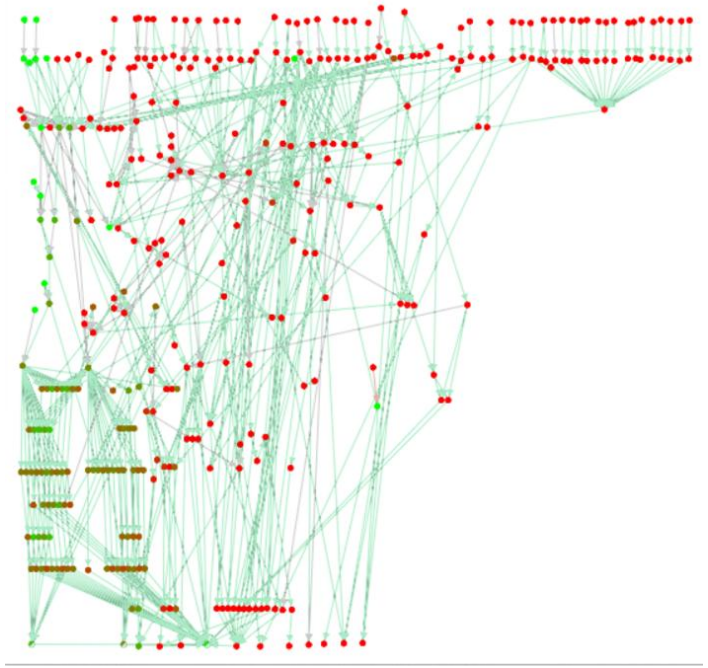
PEPR DIGITAL HEALTH

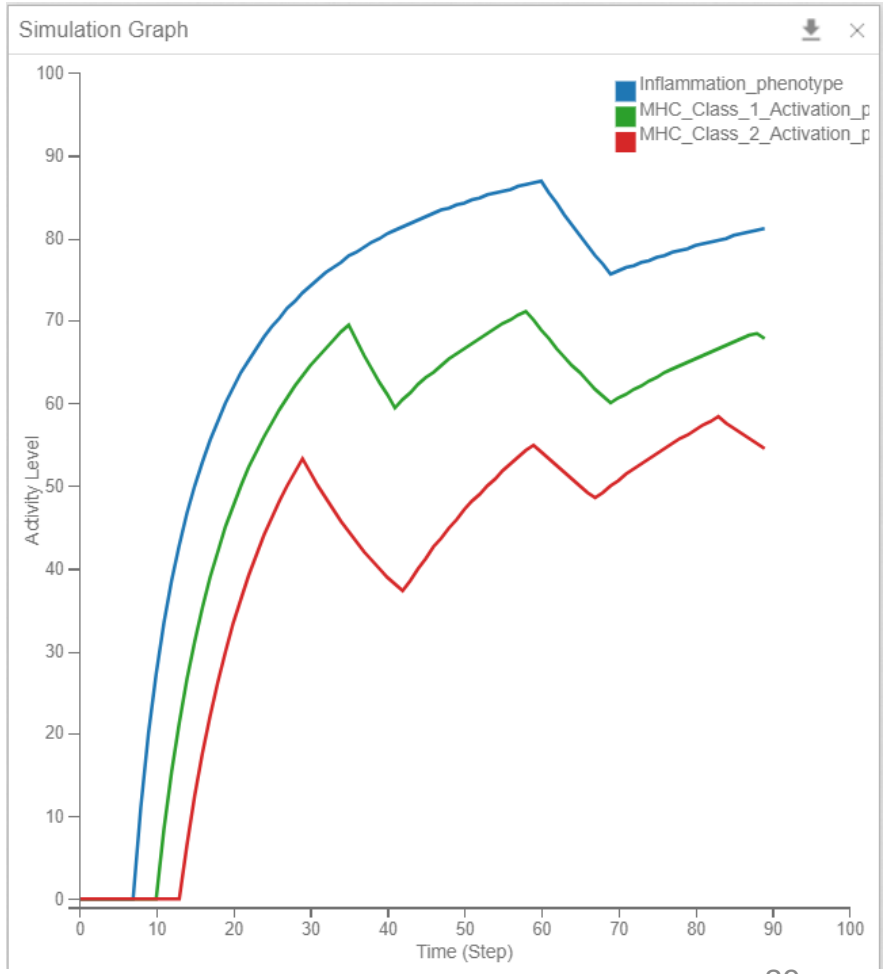


In silico simulations: reproducing experimental evidence

Simulation of **IFN type 1 and 2**



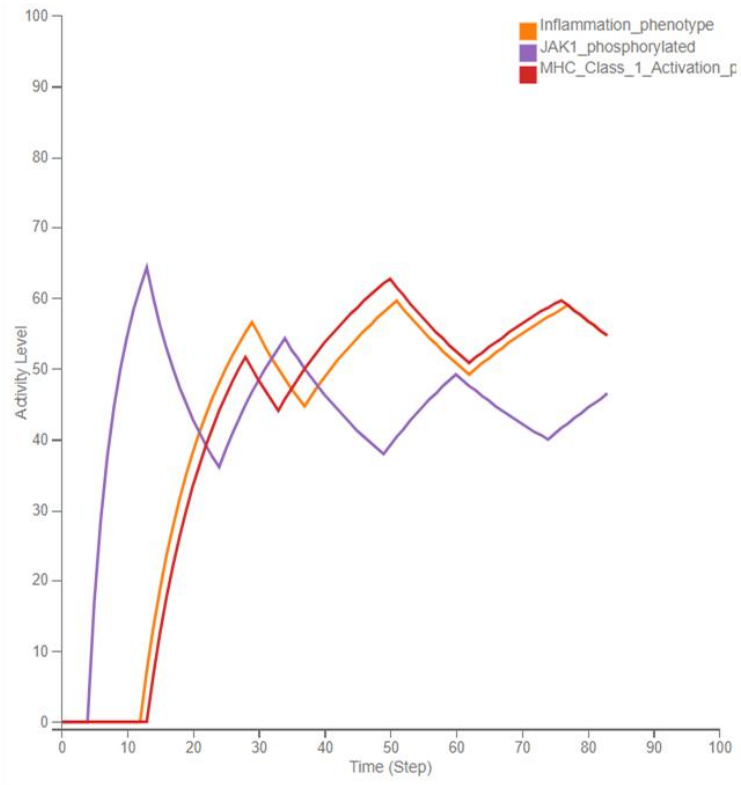




→ Unstable phenotypes such as **Inflammation**, **MHC class 1 Activation** and **MHC Class 2 Activation** (Associated PMIDs: 2444171 & 25102056)

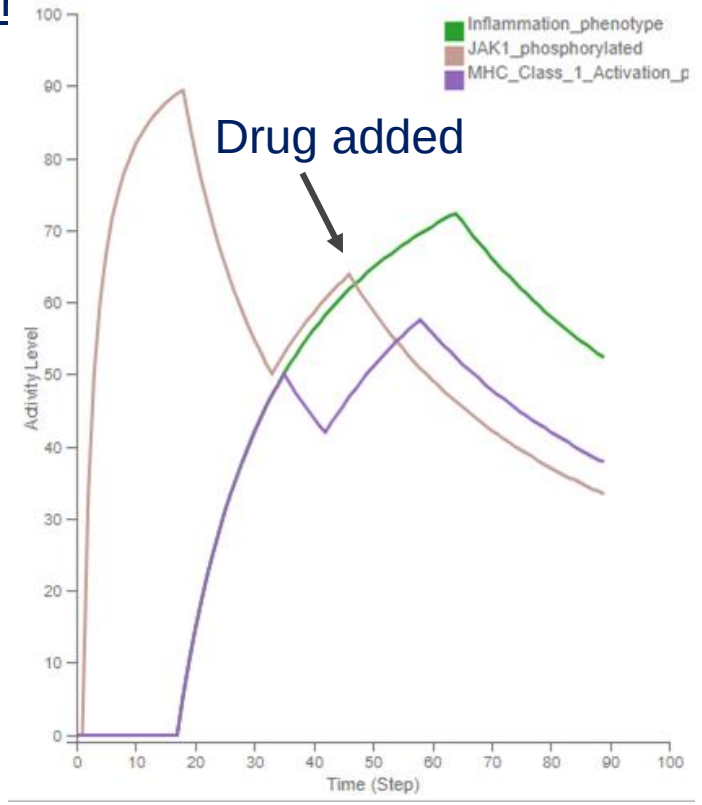
In silico simulations: simulating drug effects

Simulation of **IFN Type 1**



→ Inflammation **oscillating**
→ **Negative feedback loop** By SOCS3 (JAK1 inhibition) (Associated PMID: 26995659)

Simulation of **IFN Type 1** after adding Tofacitinib (JAKi)



→ **Decrease** of inflammation and MHC Class 1 Activation

DigiDermA

- MODELLING THE CROSSTALK BETWEEN MAST CELLS AND SENSORY NEURONS IN ATOPIC DERMATITIS

Bibliometric analysis

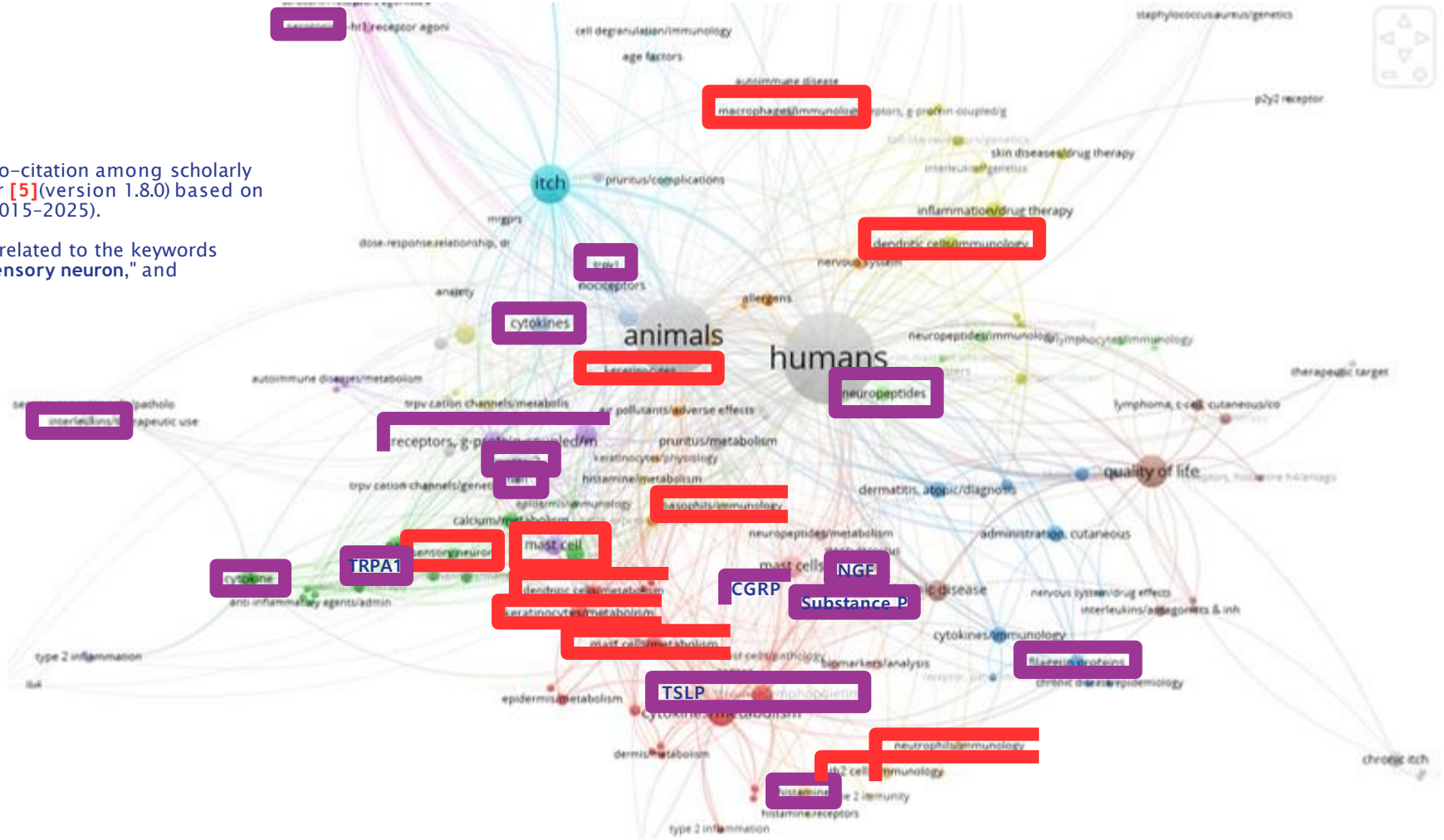
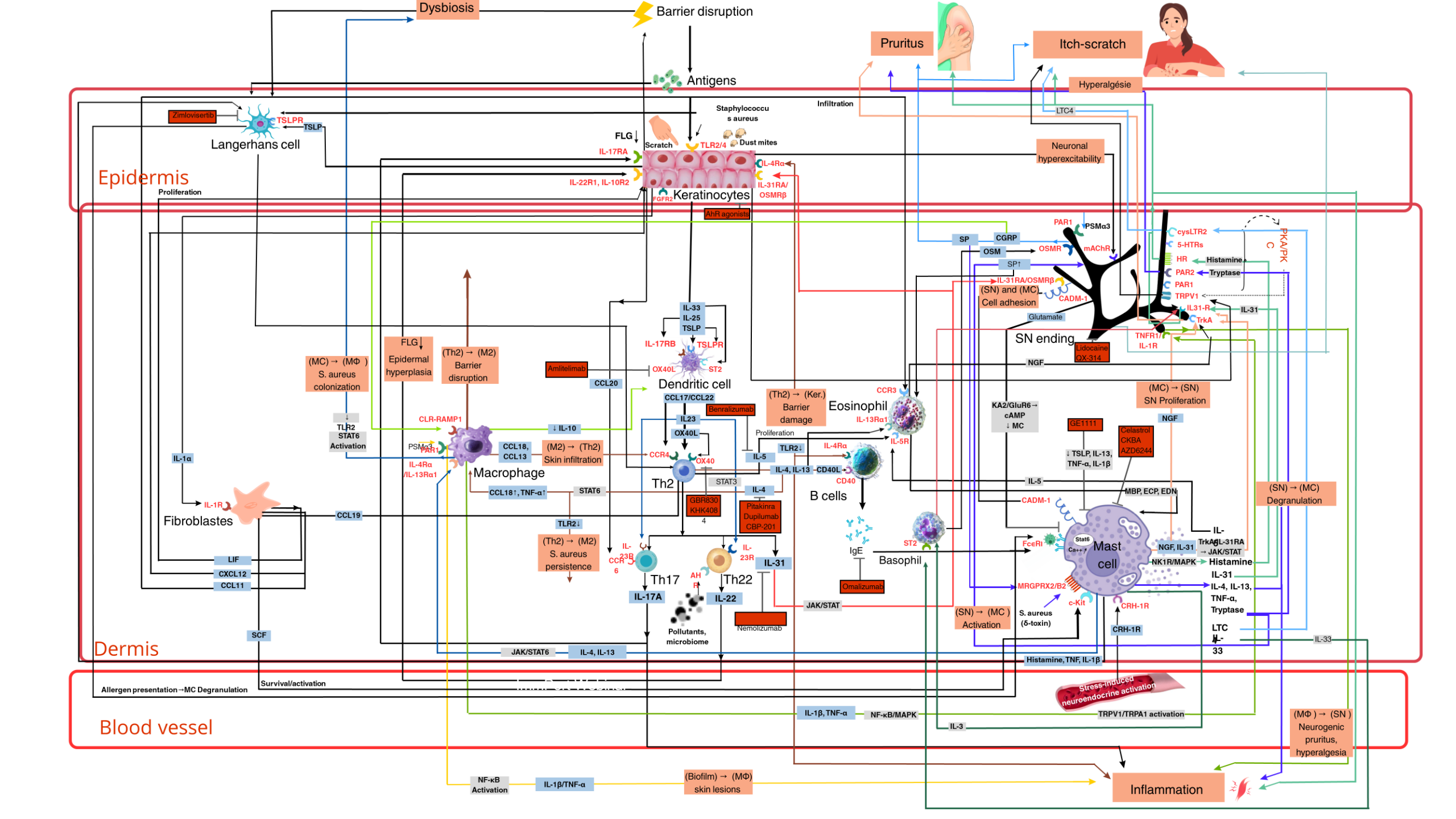


Figure 1: Network visualization of co-citation among scholarly sources, generated with VOSviewer [5](version 1.8.0) based on materials indexed in Lens.org [6](2015–2025).

The dataset includes publications related to the keywords "**atopic dermatitis**," "**mast cell**," "**sensory neuron**," and "**cytokines**."


Dysbiosis
Barrier disruption
Antigens
Pruritus
Itch-scratch
Hyperalgésie
Infiltration
Epidermis
Zimlovisertib
TSLPR
TSLP
Langerhans cell
Staphylococcus aureus
Scratch
TLR2/4
Dust mites
FLG
IL-17RA
IL-22R1, IL-10R2
IL-4Rα
IL-31RA/ OSMRβ
FGFR2
Keratinocytes
Proliferation
AhR agonists
LTC4
Neuronal hyperexcitability
PAR1
PSMα3
mAChR
SP
CGRP
OSM
OSMR
SP↑
IL-31RA/OSMRβ
(SN) and (MC) Cell adhesion
CADM-1
Glutamate
cysLTR2
5-HTRs
HR
Histamine
PAR2
Tryptase
PAR1
TRPV1
IL31-R
TrkA
IL-31
PKA/PKC
SN ending
TNFR1/ IL-1R
Lidocaine QX-314
NGF
(MC) → (SN) SN Proliferation
KA2/GluR6→ cAMP ↓ MC
GE1111
Celastrol CKBA AZD6244
↓ TSLP, IL-13, TNF-α, IL-1β
IL-33
IL-25
TSLP
IL-17RB
TSLPR
OX40L
ST2
Dendritic cell
Amlitelimab
CCL20
(MC) → (MΦ) S. aureus colonization
↓ TLR2 STAT6 Activation
FLG↓ Epidermal hyperplasia
(Th2) → (M2) Barrier disruption
CCL17/CCL22
Benralizumab
IL23
OX40L
↓ IL-10
CLR-RAMP1
PSMα3
PAR1
IL-4Rα /IL-13Rα1
CCL18, CCL13
(M2) → (Th2) Skin infiltration
Macrophage
CCR4
OX40
Th2
IL-4, IL-13
CD40L
CD40
B cells
IL-5
STAT3
IL-4
GBR830 KHK408 4
Pitakinra Dupilumab CBP-201
CCL18↑, TNF-α↑
STAT6
TLR2↓
(Th2) → (M2) S. aureus persistence
IL-1α
IL-1R
Fibroblastes
CCL19
LIF
CXCL12
CCL11
SCF
IL-23R
CCR6
Th17
IL-17A
AHR
Th22
IL-22
IL-31
Pollutants, microbiome
Nemolizumab
JAK/STAT6
IL-4, IL-13
(Th2) → (Ker.) Barrier damage
Proliferation
TLR2↓
IL-4Rα
IL-5
Eosinophil
CCR3
IL-13Rα1
IL-5R
IgE
Omalizumab
Basophil
ST2
JAK/STAT
IL-5
MBP, ECP, EDN
CADM-1
FcεRI
Stat6
Ca++
Mast cell
NGF, IL-31
NK1R/MAPK
MRGPRX2/B2
c-Kit
CRH-1R
CRH-1R
S. aureus (δ-toxin)
(SN) → (MC) Activation
Histamine, TNF, IL-1β
IL-31RA → JAK/STAT
Histamine
IL-31
IL-4, IL-13, TNF-α, Tryptase
LTC4
IL-33
(SN) → (MC) Degranulation
Dermis
Allergen presentation→MC Degranulation
Survival/activation
Stress-induced neuroendocrine activation
TRPV1/TRPA1 activation
IL-1β, TNF-α
NF-κB/MAPK
IL-3
Blood vessel
NF-κB Activation
IL-1β/TNF-α
(Biofilm) → (MΦ) skin lesions
Inflammation
(MΦ) → (SN) Neurogenic pruritus, hyperalgesia

Single-cell transcriptome analysis

Dataset Overview:

Organism: Homo sapiens → **Skin biopsies** → **Healthy or Atopic Dermatitis ?** → **Single-cell RNA sequencing** → **Method:** 10x Genomics platform, and libraries were sequenced with Illumina HiSeq 2500.

Healthy or Atopic Dermatitis ? →
- Healthy humans **(8 samples)**
- Atopic Dermatitis Patients **(09 samples)**

Healthy humans **(8 samples)** →

Healthy humans (08 samples)

- GSM4430462 (S4_H)
- GSM4430464 (S6_H)
- GSM4430466 (S8_H)
- GSM4430467 (S9_H)
- GSM4430468 (S10_H)
- GSM4430470 (S12_H)
- GSM4430471 (S13_H)
- GSM4430475 (S17_H)

Atopic Dermatitis Patients **(09 samples)** →

4 lesional LS.

- GSM4430459 (S1_LS)
- GSM4430460 (S2_LS)
- GSM4430463 (S5_LS)
- GSM4430465 (S7_LS)

5 non-lesional samples

- GSM4430461 (S3_NL)
- GSM4430469 (S11_NL)
- GSM4430472 (S14_NL)
- GSM4430473 (S15_NL)
- GSM4430474 (S16_NL)

https://www.ncbi.nlm.nih.gov/geo/query /acc.cgi?acc=GSE147424

Single-cell transcriptome analysis

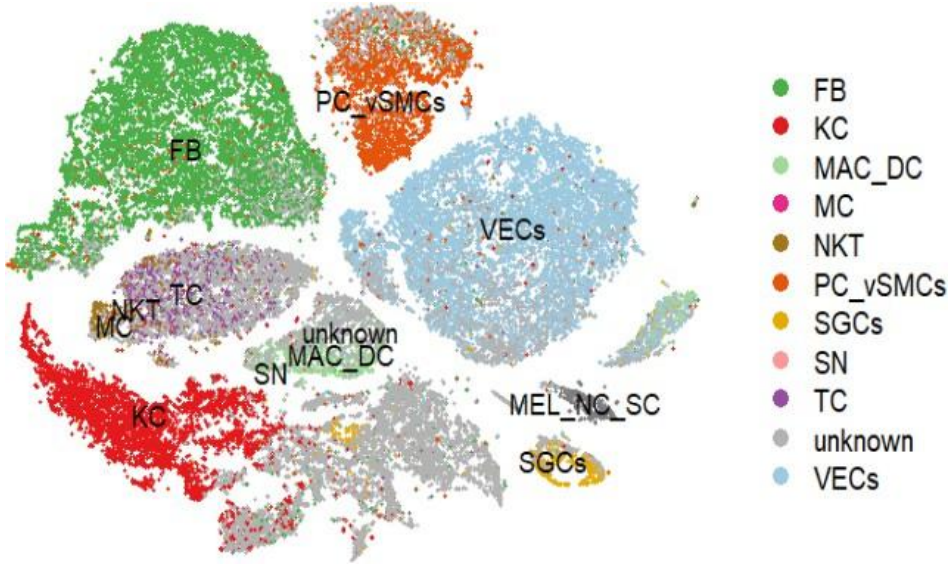


Figure 2:
t-SNE plot for 39,042 skin cells from AD patients (lesional/nonlesional) and healthy controls. Cell identities were annotated using the SCINA.

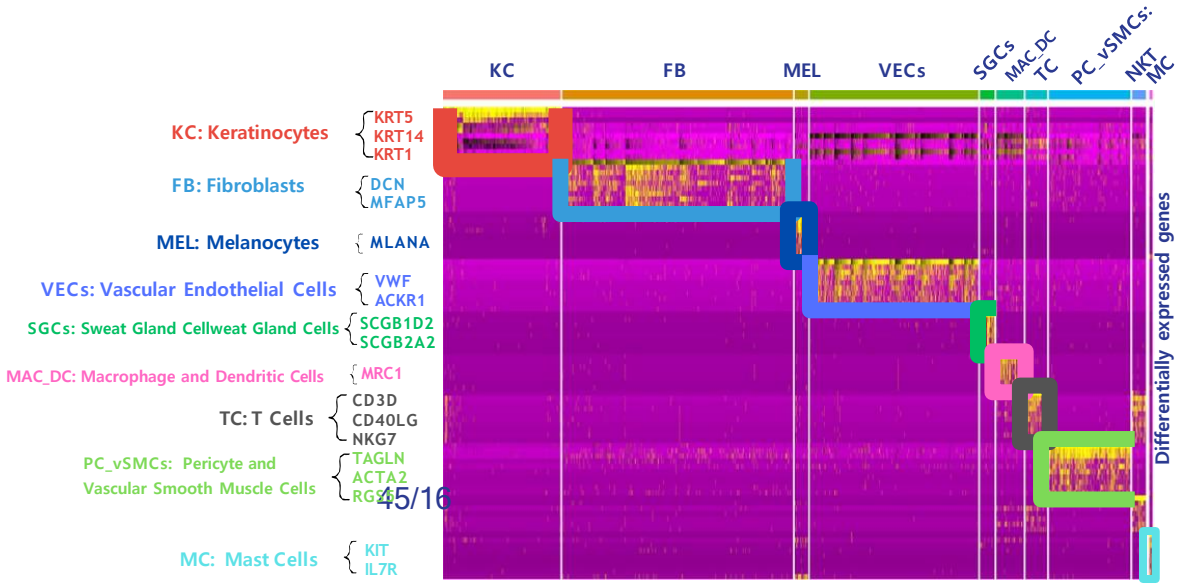
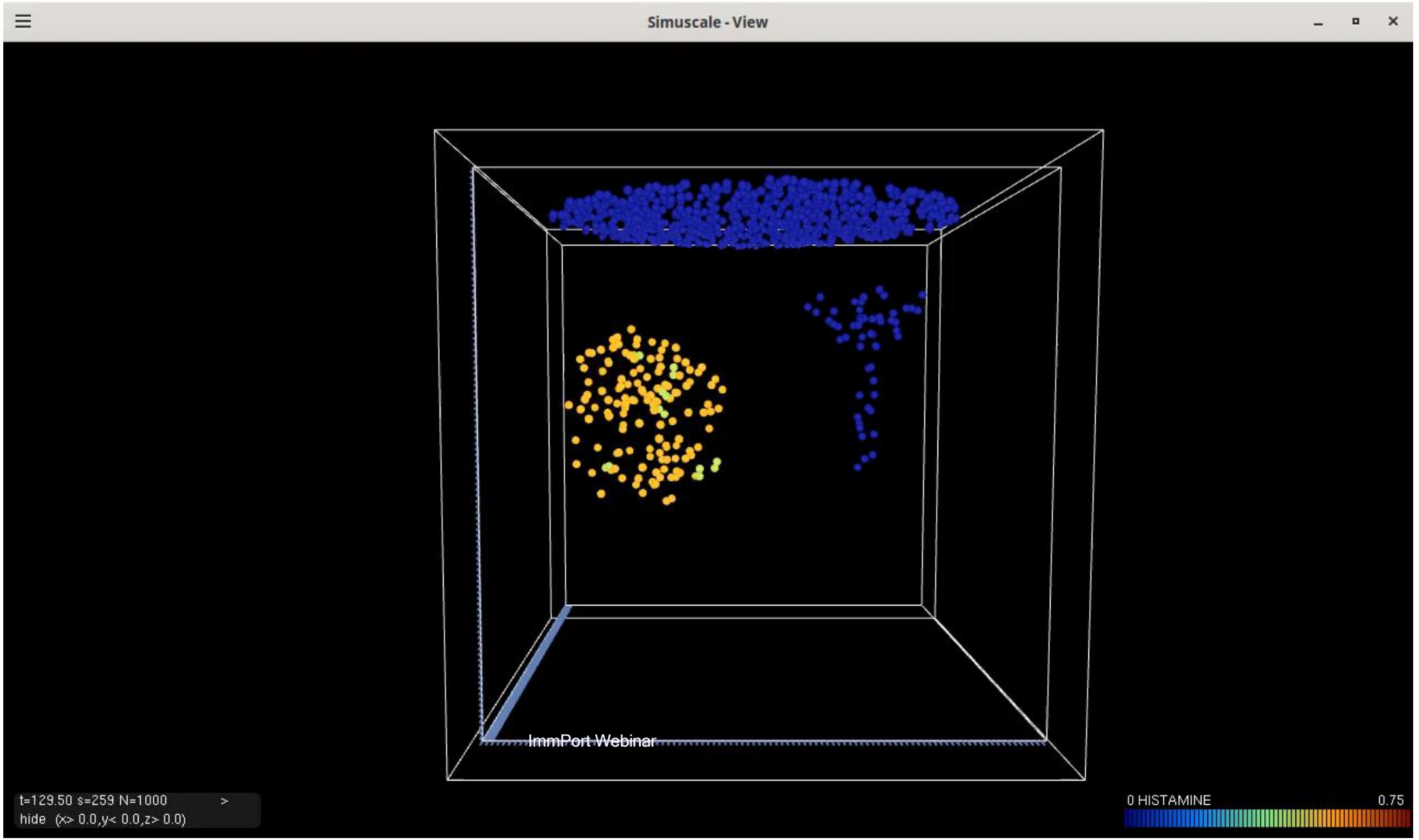


Figure 3: : Distinct gene signatures (top 10 differentially expressed genes; Wilcoxon rank sum test) of skin cell populations identified in single-cell RNA sequencing data.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ImmPort Webinar
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0 HISTAMINE
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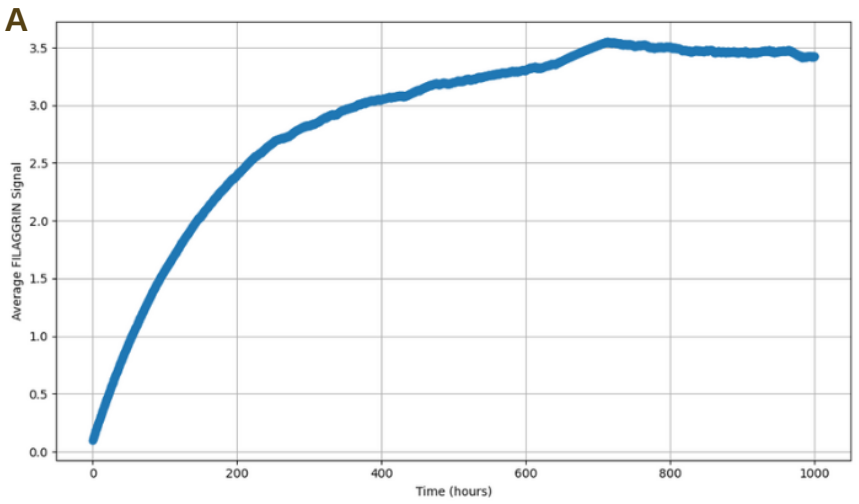
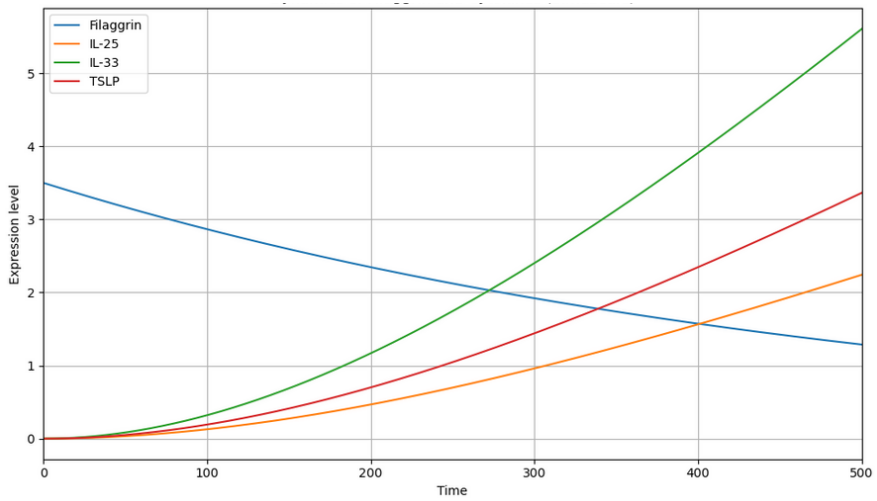
Simuscale Implementation and simulation

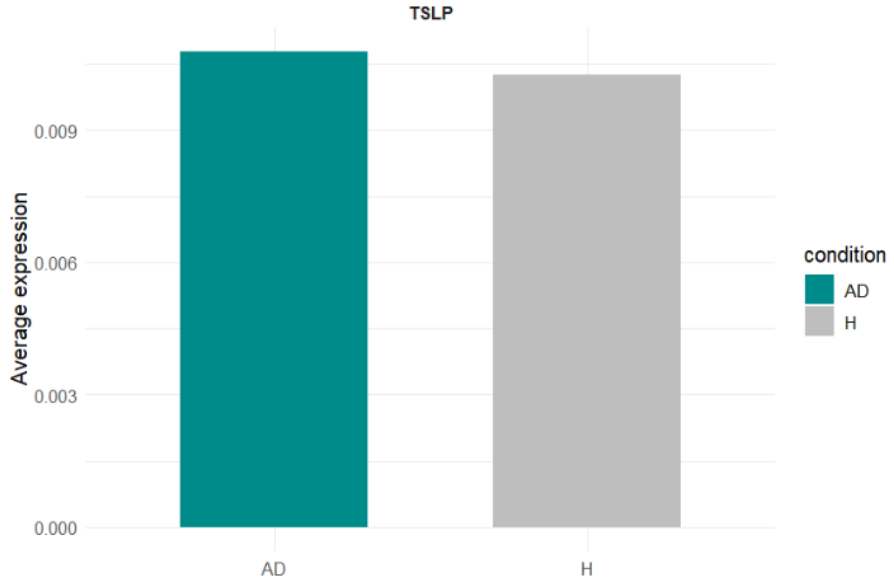


A) Temporal dynamics of filaggrin expression in keratinocytes (Healthy condition).



B) Reduced filaggrin and upregulation of IL-25, IL-33, and TSLP in keratinocytes (Atopic dermatitis condition).

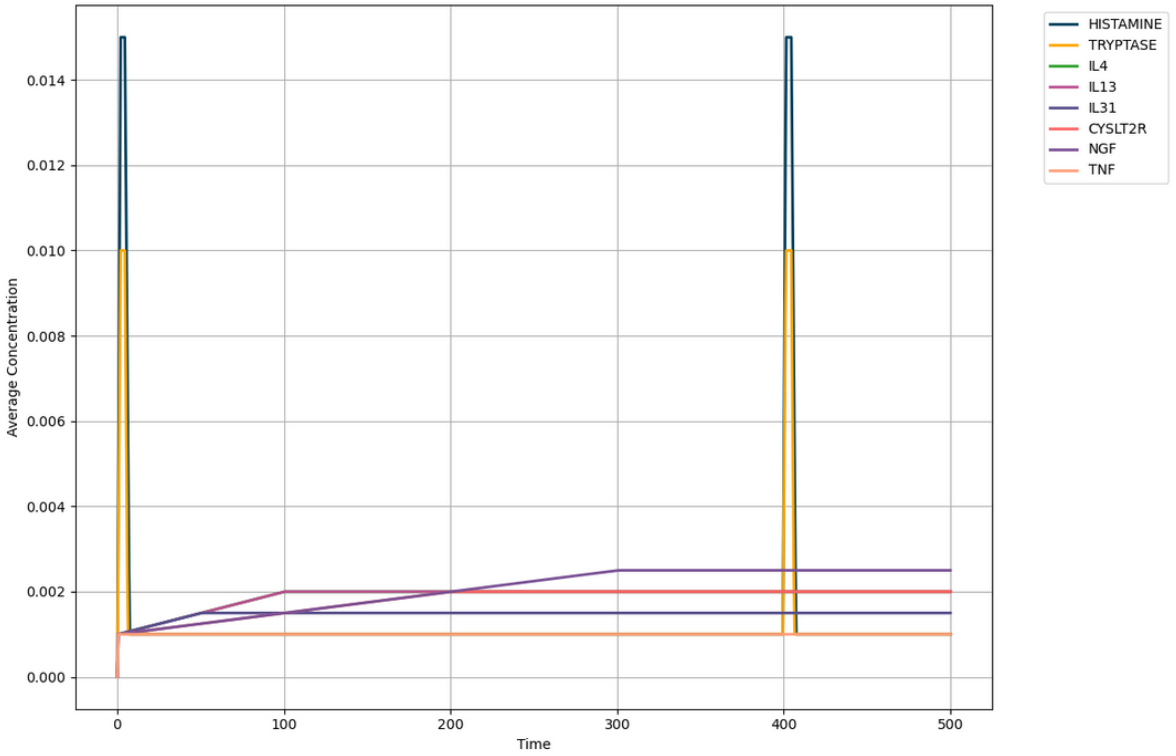
Loss of filaggrin → barrier disruption → allergen penetration → activation of mast cells and stimulation of sensory neurons via increased cytokine production (IL-25, IL-33, TSLP) by keratinocytes → chronic inflammation (atopic dermatitis).



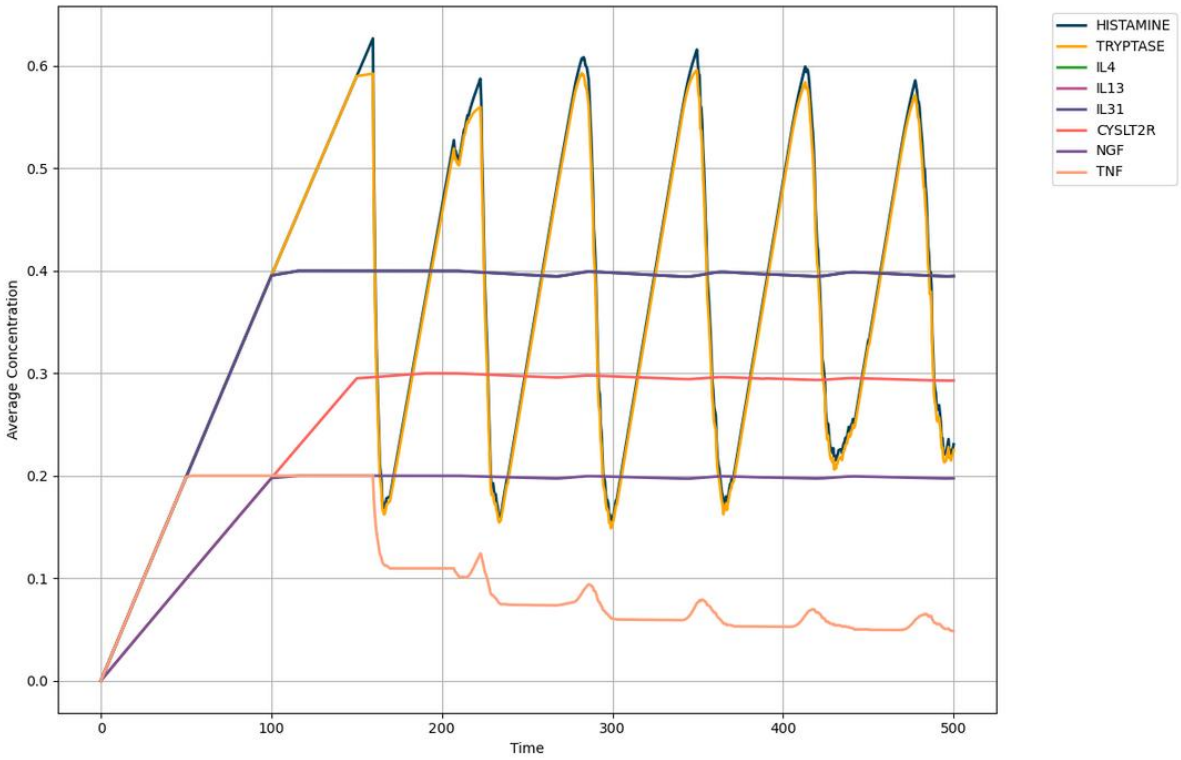
Barplot showing the average expression of TSLP in each condition.

Data source: GEO Series GSE147424 [9].

Simuscale Implementation and simulation

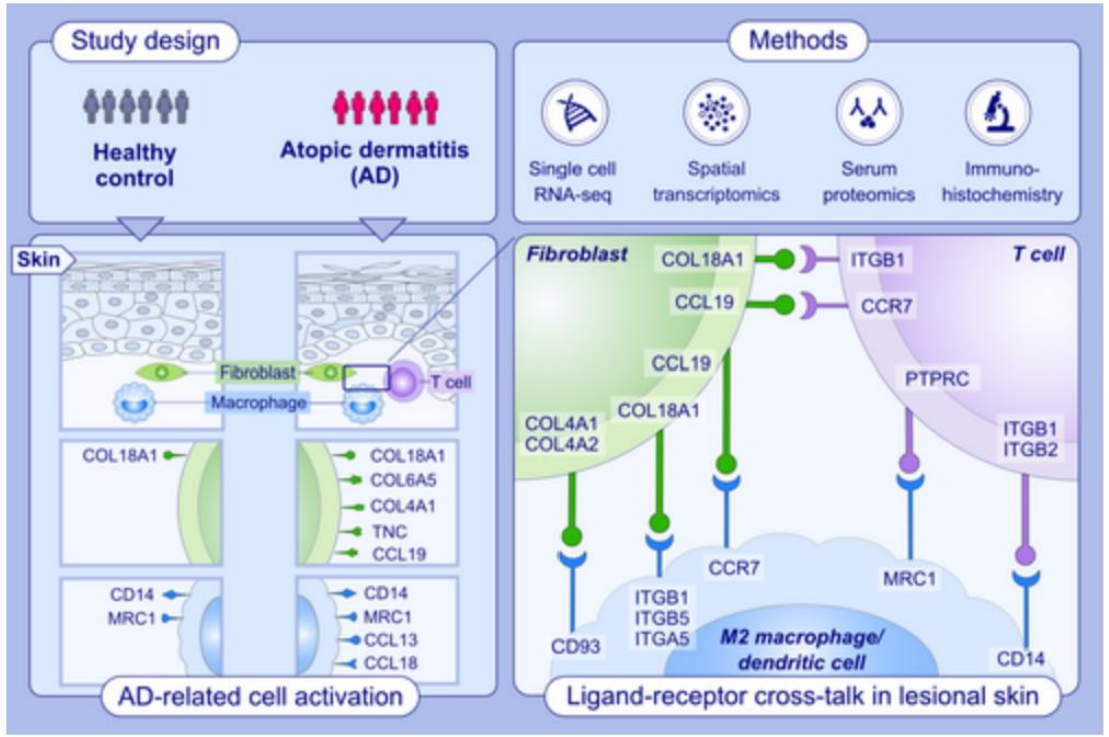


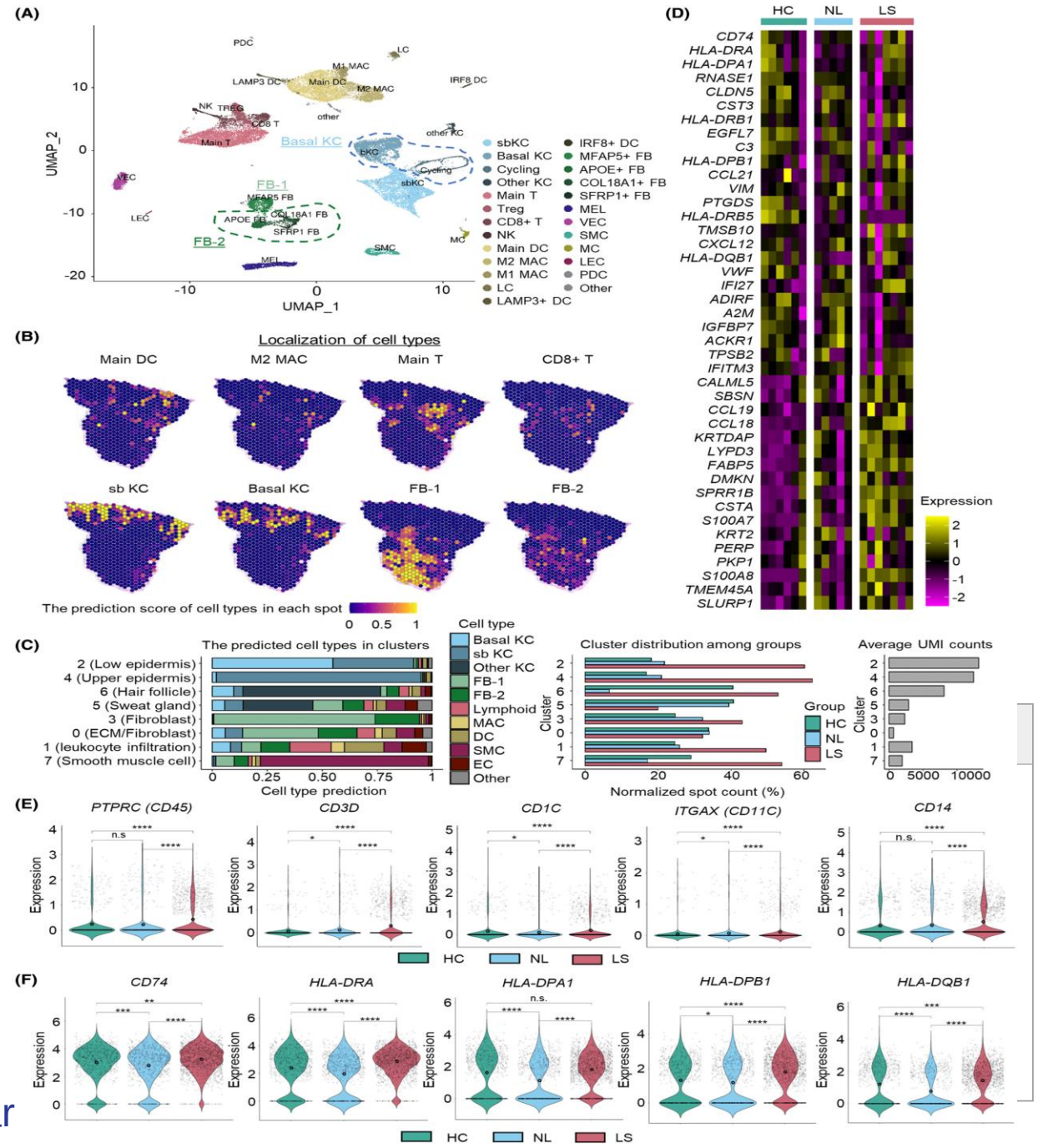
Temporal dynamics of HISTAMINE, TRYPTASE, IL4, IL13, IL31, CYSLT2R, NGF, TNF (Healthy condition).



Temporal dynamics of HISTAMINE, TRYPTASE, IL4, IL13, IL31, CYSLT2R, NGF, TNF (AD condition).

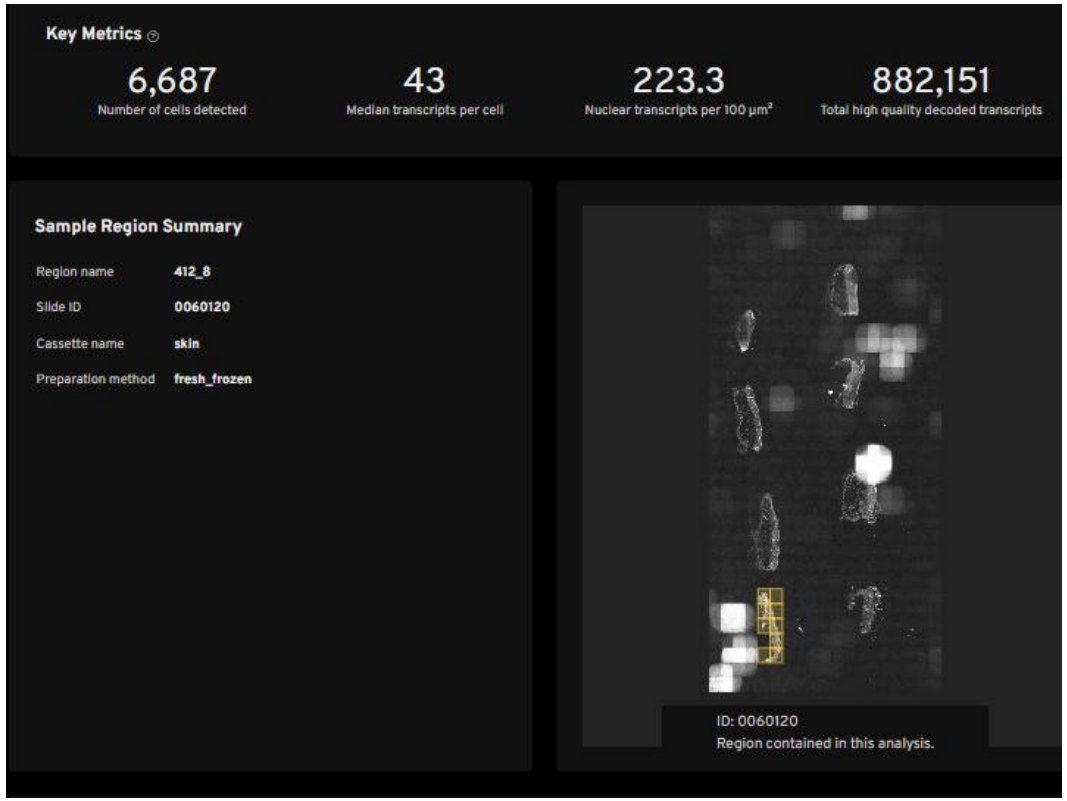
Analysing spatial transcriptomics

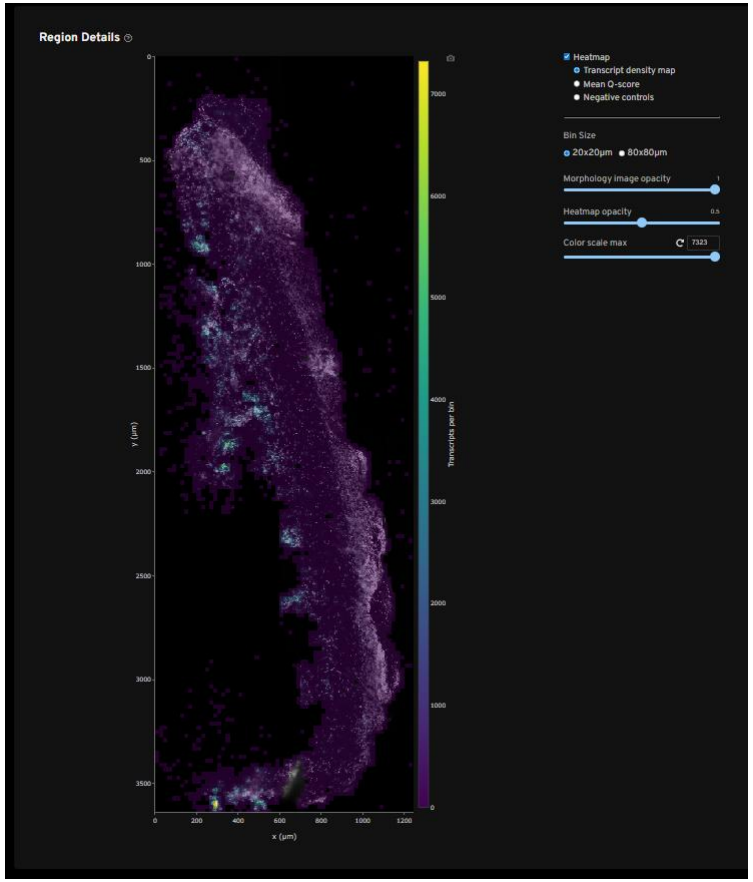




ImmPort Webinar

Mice studies using Xenium 10x Genomics





First batch of 4 mice of contact dermatitis

Second batch of 4 mice of the oxazolone model

Added value of the in silico part

- Dynamic aspect→ predictions, hypothesis testing
- Accelerating research by prioritizing targets/ combinations
- Complementary approaches that help understand better the mechanistic aspect of different biological processes
- Adapted for signaling/ GRN/ metabolism
- Methods usually disease –agnostic: contextualization/ personalization of the models with data
- Advances in scaling and computational cost handling
- **Challenge of the "one question one model" dogma: building of models that can be re-used and expanded to serve multiple purposes**

- Limitations:
- Usually **data available are wide but not deep**
- Depending on the approach –quantitative/ qualitative (smaller scale/ loss of information)
- Interoperability and standardization issues for tissue level models
- Still time consuming to build

Digital Twins in healthcare - how far are we?

- Some successful examples: (diabetes, cardiovascular diseases)
- AI is developing fast
- Causal AI will play a major role in automatic model reconstruction
- Access to real patient data / medical records is becoming a necessity
- Scaling up can be tricky: HPC infrastructure
- Formal approaches and methodologies that can robustly handle complexity

- Ethical aspects: human in the loop
- Clinician involvement from the start of the project design (real versus virtual patient)
- Policies for medical devices
- Implementation

Acknowledgements

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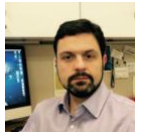

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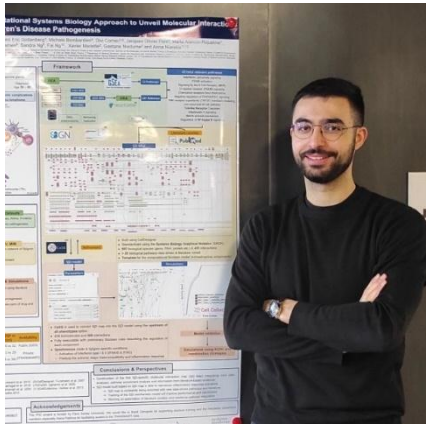

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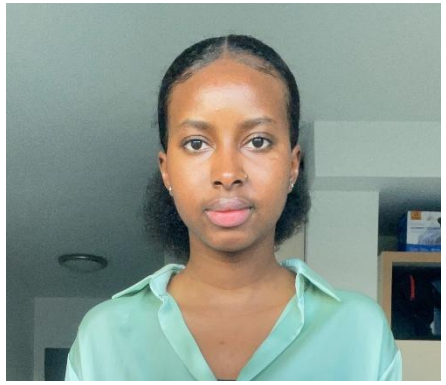

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Bringing stakeholders together!

Building Immune Digital Twins

Building Immune Digital Twins

15 mai 2023 à 2 juin 2023
Institut Pascal
Fuseau horaire Europe/Paris

Entrer le

- Accueil
- Scientific colloquia
- Objectives of the workshop
- Action items/Deliverables
- Target audience
- Inscription
- Scientific committee
- Enquêtes
- Orateurs/Speakers
- Program

Bamissa SANGARE
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Orateurs/Speakers

Keynotes
Jasmin Fisher, UCL
Mustafa Kammash, ETH Zurich
Julio Saez Rodriguez, University of Heidelberg
Emmanuel Barillot, Institut Curie, France
Maria Rodriguez Martinez, IBM Zurich
Yaron Ilan University of Jerousalem

Advanced talks
Reinhard Laubenbacher, University of Florida
François Fages, INRIA Saclay
Irene Vignon Clementel, INRIA Saclay
Dagmar Waltemath, University of Greifswald
Gary An, University of Vermont
James Glazier, University of Indiana Bloomington
Gaetane Nocturne, Hopitaux Universitaires Paris-Sud
Tomas Helikar, University of Nebraska Lincoln
Benjamin Hall, UCL
Anna Niarakis, University of Evry, Paris-Saclay and INRIA Saclay
Anabelle Balesta, INSERM and Institut Curie
Asmund Flobak, NTNU

Advanced tutorials
Laurence Calzone, Institut Curie, Paris
Gaultier Stoll, INSERM U1138, Université Paris Descartes, Gustave Roussy
Vincent Noel, Institut Curie, Paris
Pedro Monteiro, Technical University of Lisbon
Sylvain Soliman, INRIA Saclay
Anna Niarakis, University of Evry, Paris Saclay & INRIA Saclay
Arnau Montagud, Barcelona Supercomputing Centre
Tomas Helikar, University of Nebraska Lincoln
TJ Tiego, University of Florida

Platforms and private sector presentations/ panel discussion participation
Christophe Lanneau, Genopole
Franck Augé, SANOFI
Markus Rehberg, SANOFI
Nicola Gaudenzio, Genoskin
Vassili Soumelis, Owkin
Alexander Kulesza/ Shiny Martis, Novadiscovery
Rachel Clipp, Brian Helba, KITWARE
Serkawt Khola - EvoPlexus Medics
Andrei Zinovyev - Evotec

immunedt.github.io

Building Immune Digital Twins
A community effort to make IDTs a reality!

Projects Models Webinars Team Publications Events RDA BIDT

Building Immune Digital Twins

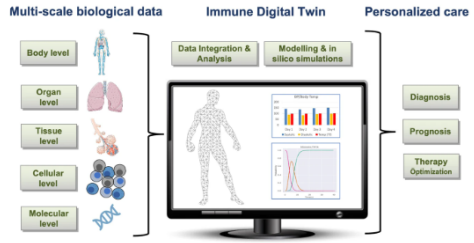
Welcome to the Building Immune Digital Twins (BIDT) initiative — a global, community-driven effort to develop computational replicas of the human immune system. Our goal is to advance our understanding and treatment of diseases by simulating immune responses tailored to individuals.

Whether you're a researcher, clinician, or data scientist, join us in shaping the future of personalized medicine.

🔍 What are immune digital twins?

Immune digital twins are dynamic computational models designed to simulate how an individual's immune system responds to infections, therapies, and vaccines. By integrating biological knowledge, clinical data, and modeling techniques, we aim to support:

- Personalized diagnostics
- Predictive medicine
- Targeted therapeutic development
- Systems-level understanding of immunity



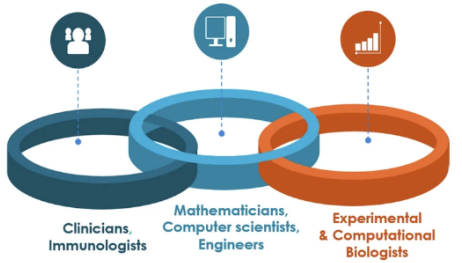
Source: 10.1038/s41746-022-00610-z

🚀 Our mission

We are building an open, collaborative ecosystem for:

- Curation of high-quality immunology data
- Development of reusable and interoperable models
- Best practices for constructing and validating digital twins
- Integration with platforms like the Virtual Human Twin

Learn more in our RDA Working Group Case Statement ›



Source: 10.1038/s41540-024-00450-5

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Thank you for your attention!