

Building a Virtual Twin of the Rheumatic Joint

Digital Twins for human immune-mediated complex diseases

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Twinsanté: Les jumeaux numériques pour la santé et la recherche médicale

Webinaire INSERM en partenariat avec l'Alliance internationale des
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26 September 2025

The concept of a Digital Twin



ipopba / Getty Images

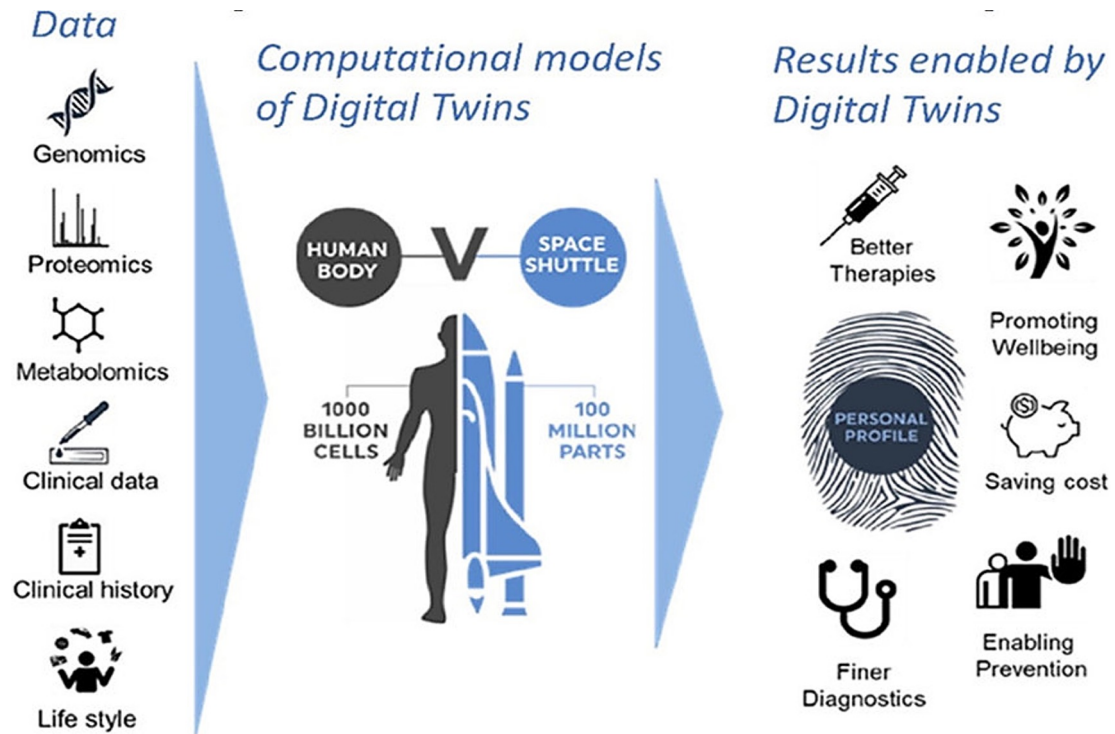
Digital Twins are virtual equivalents, or twins, of physical objects.

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

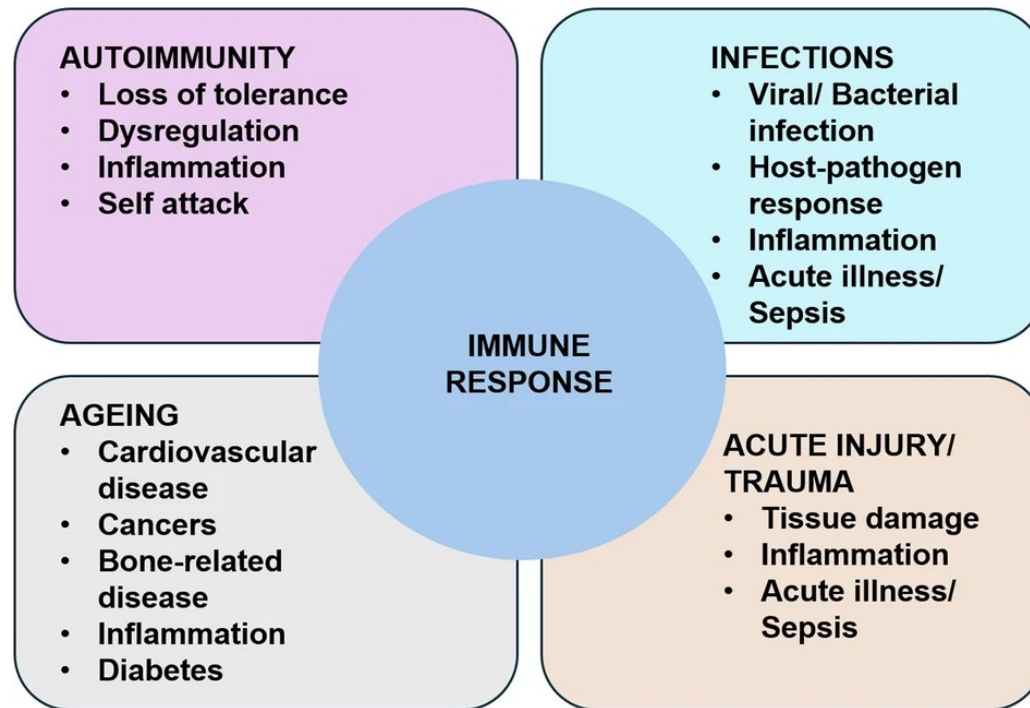


BBC/ Getty Images

The concept of a Digital Twin for complex human pathologies



Human immune response in various pathologies



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News Research & Innovation News

Using digital twins to improve care for inflammatory diseases

1st March 2023

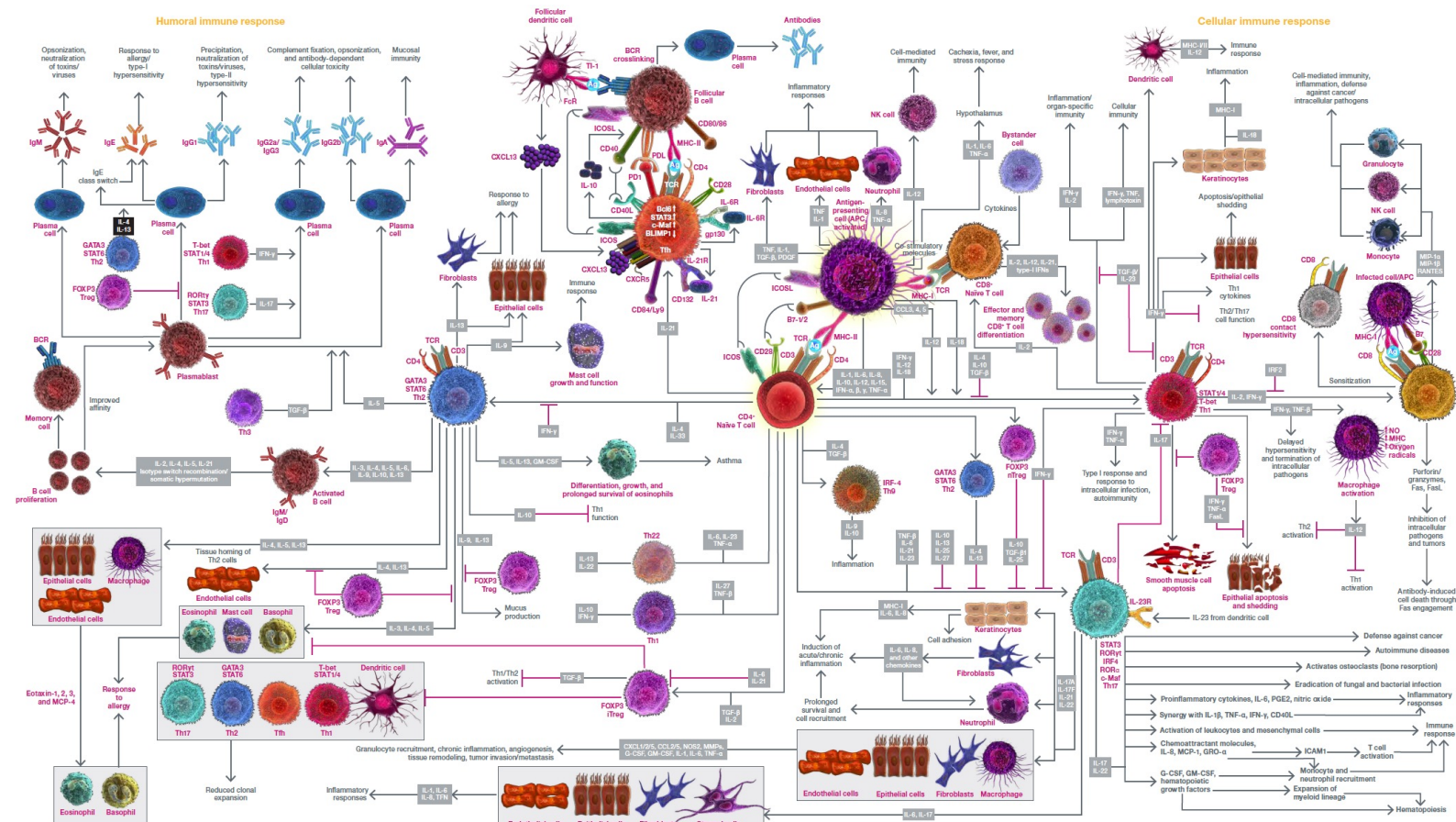


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Niarakis, A., Laubenbacher, R., An, G. *et al.* Immune digital twins for complex human pathologies: applications, limitations, and challenges. *npj Syst Biol Appl* **10**, 141 (2024).

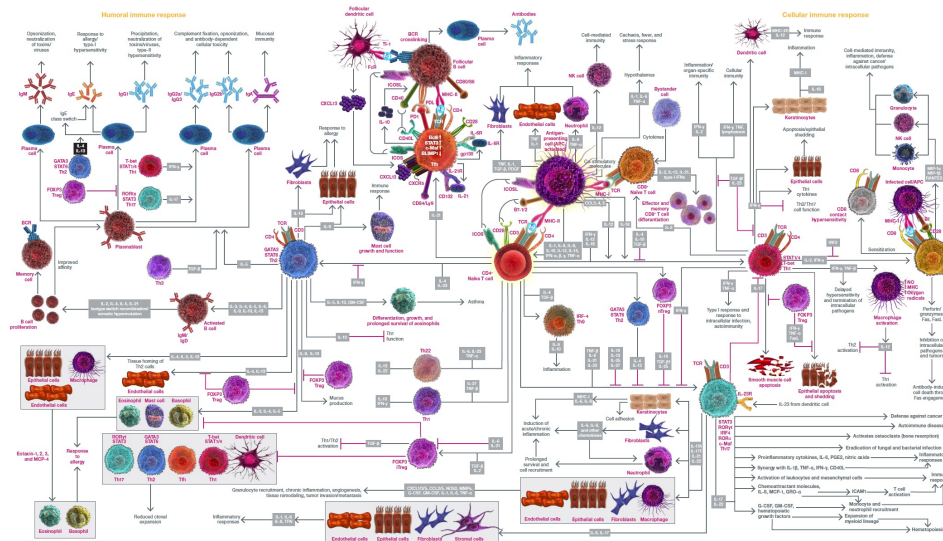
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Immune response is complex!

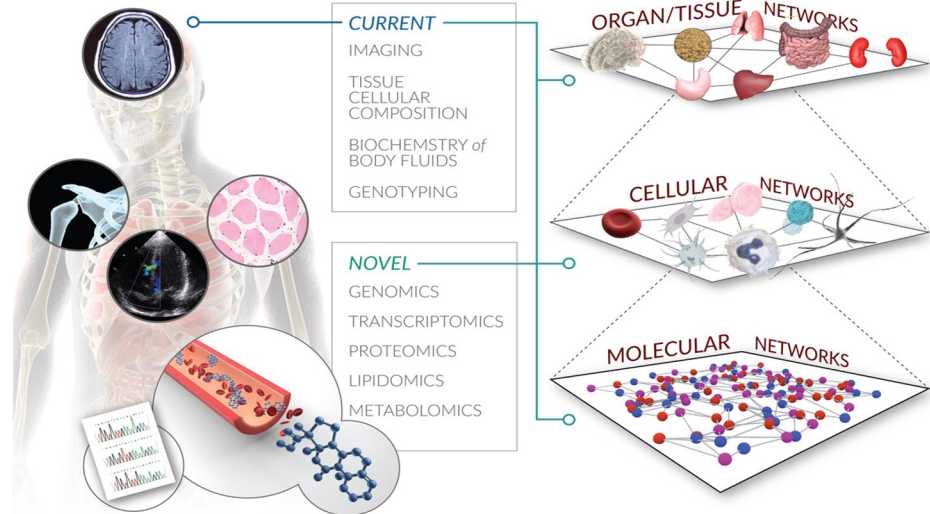


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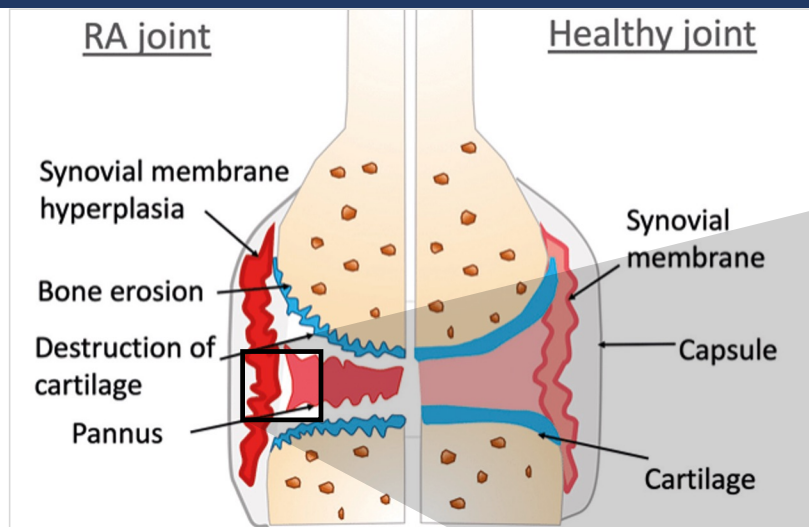
Networks as model back-bones



DIAGNOSTIC APPROACHES



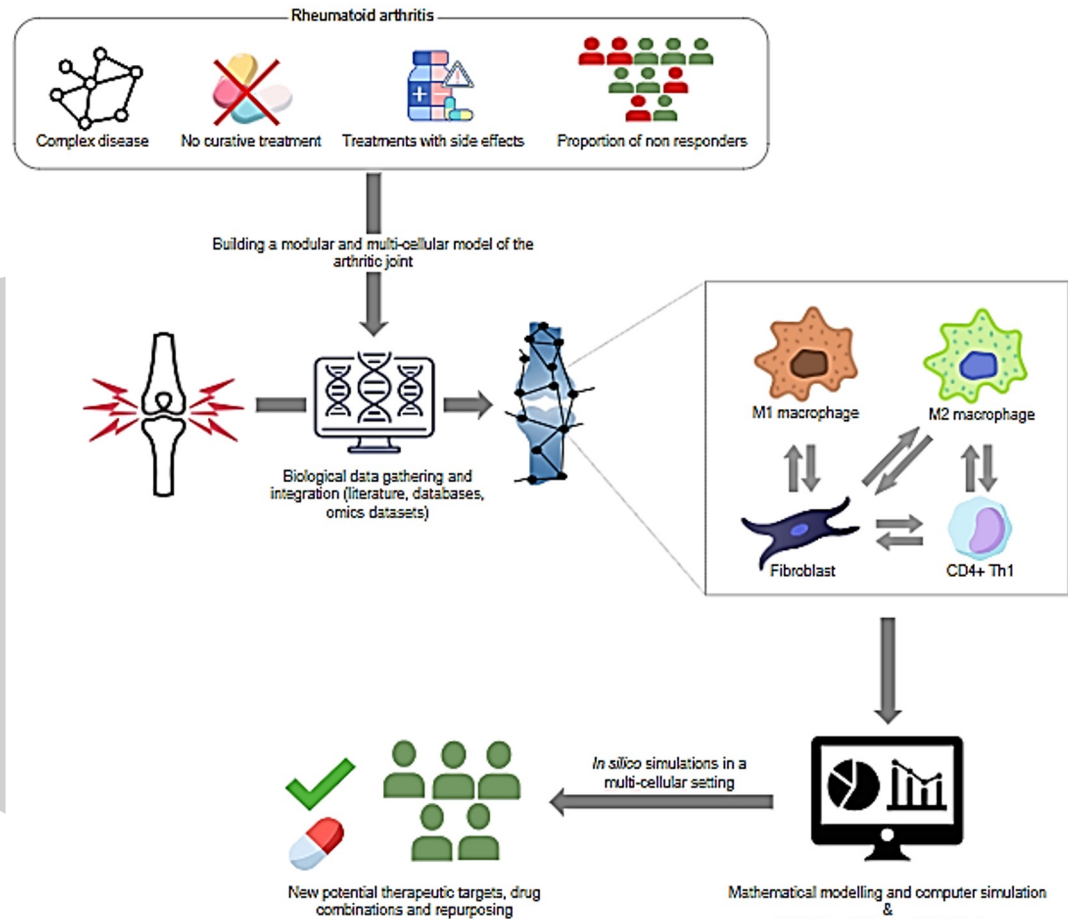
Rheumatoid arthritis



- Autoantibodies production
- Crosstalk between resident and immune cells
- Chronic inflammation and synovial hyperplasia
- Excessive angiogenesis and osteoclastogenesis
- Cartilage destruction and bone erosion

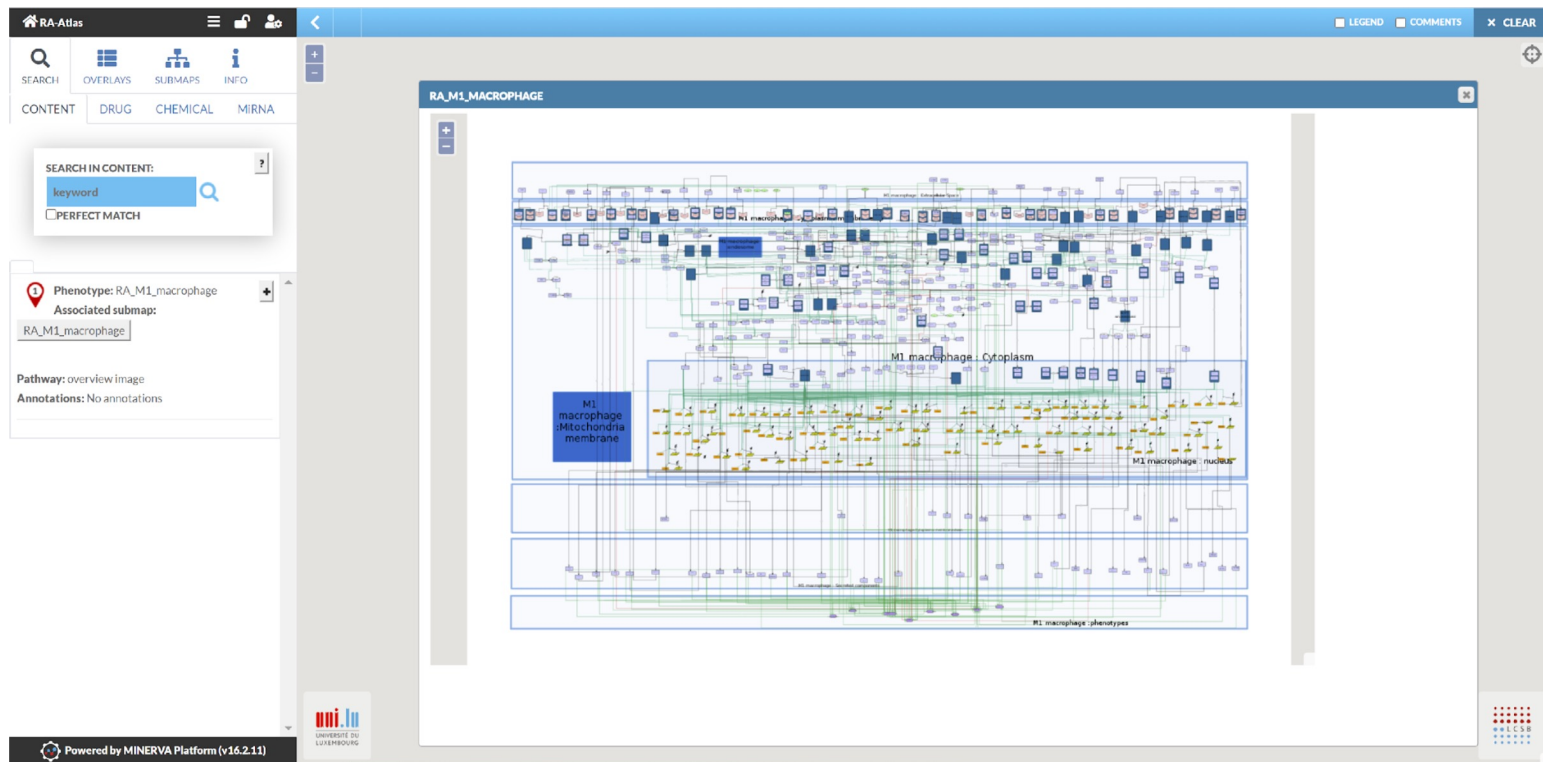
(Walsh and Choi, 2014)

(Isabel Lopez-Oliva et al., 2019)



The RA-Atlas

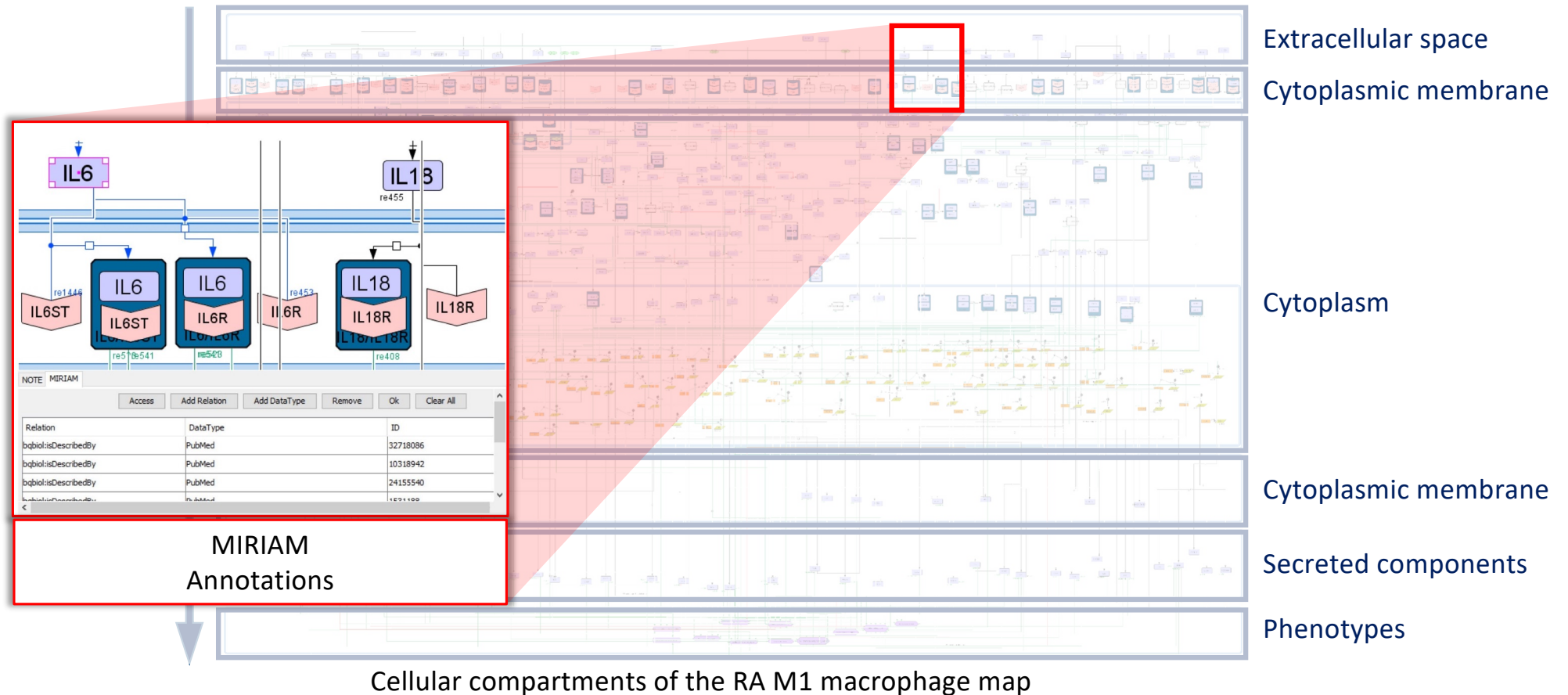
- All cell-specific maps are available as online interactive maps on the standalone web server MINERVA at <https://ramap.uni.lu/minerva/>



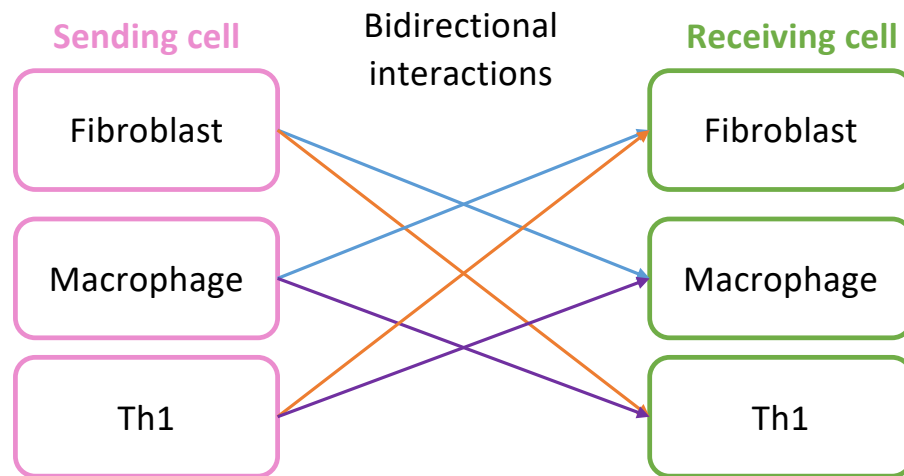
(Zerrouk et al., 2022)

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Construction, annotation and curation of the maps



Datasets selection & filtering criterias for the identification of cell-cell communication



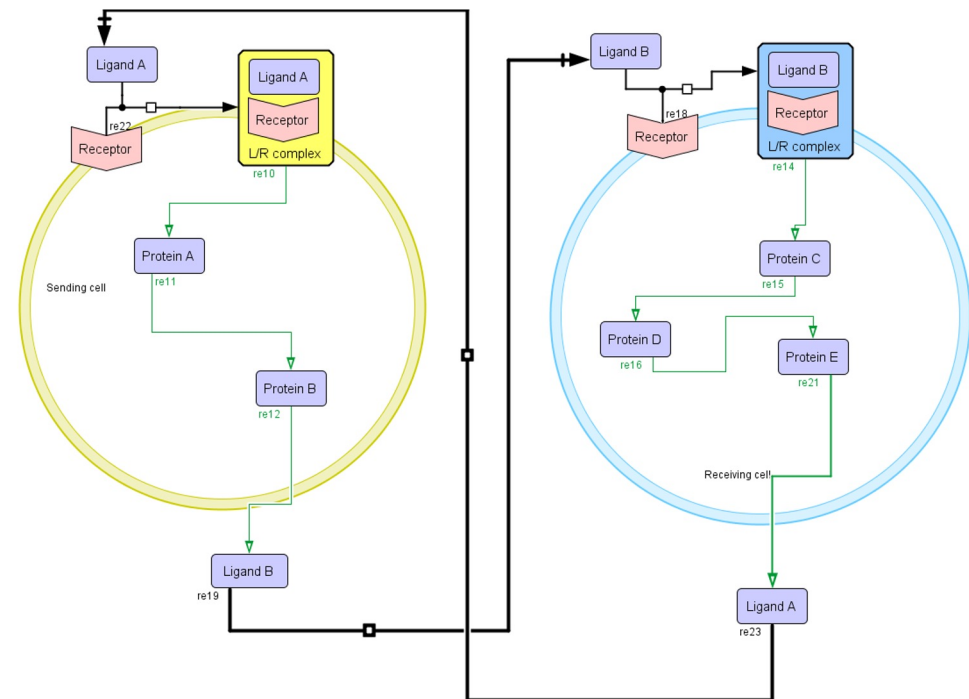
- Three different scRNA datasets (only 1 dataset containing the three synovial cell types)
- Cross validation via the combination of datasets coming from different experimental studies
- ComBat method to correct the batch effect (Zhanh et al. 2020, NAR)

Filtering criterias

- Statistically significant adjusted p-values
- Both in ICELLNET and DiSiR
- Associated with at least two different pairs of datasets, or two different approaches
- Associated with at least two different sources of information

Construction of the RA multicellular map

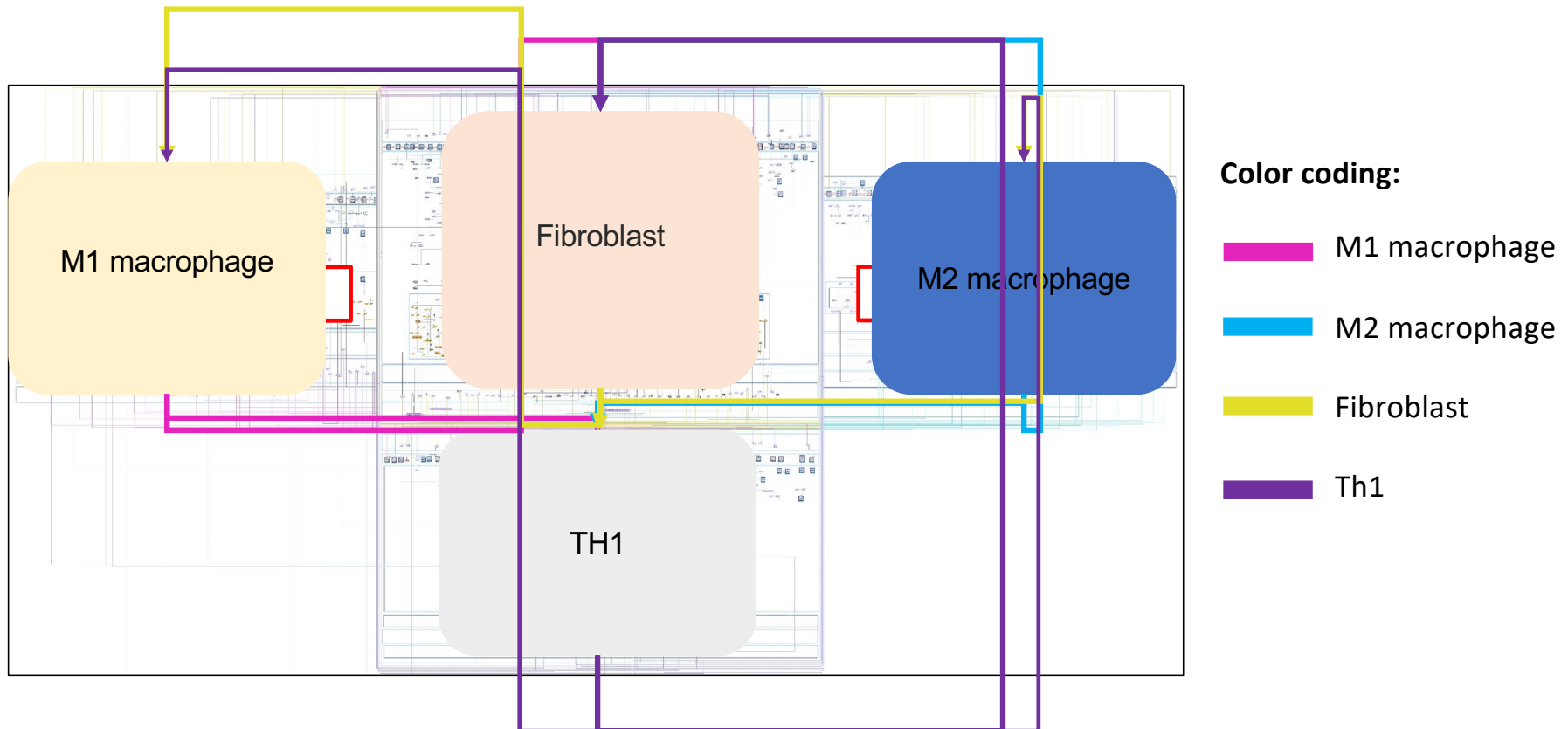
- **The black arrow:** transport of the secreted ligand
- **Yellow cell :** Sending and Receiving cell
- **Blue cell :** Sending and Receiving cell



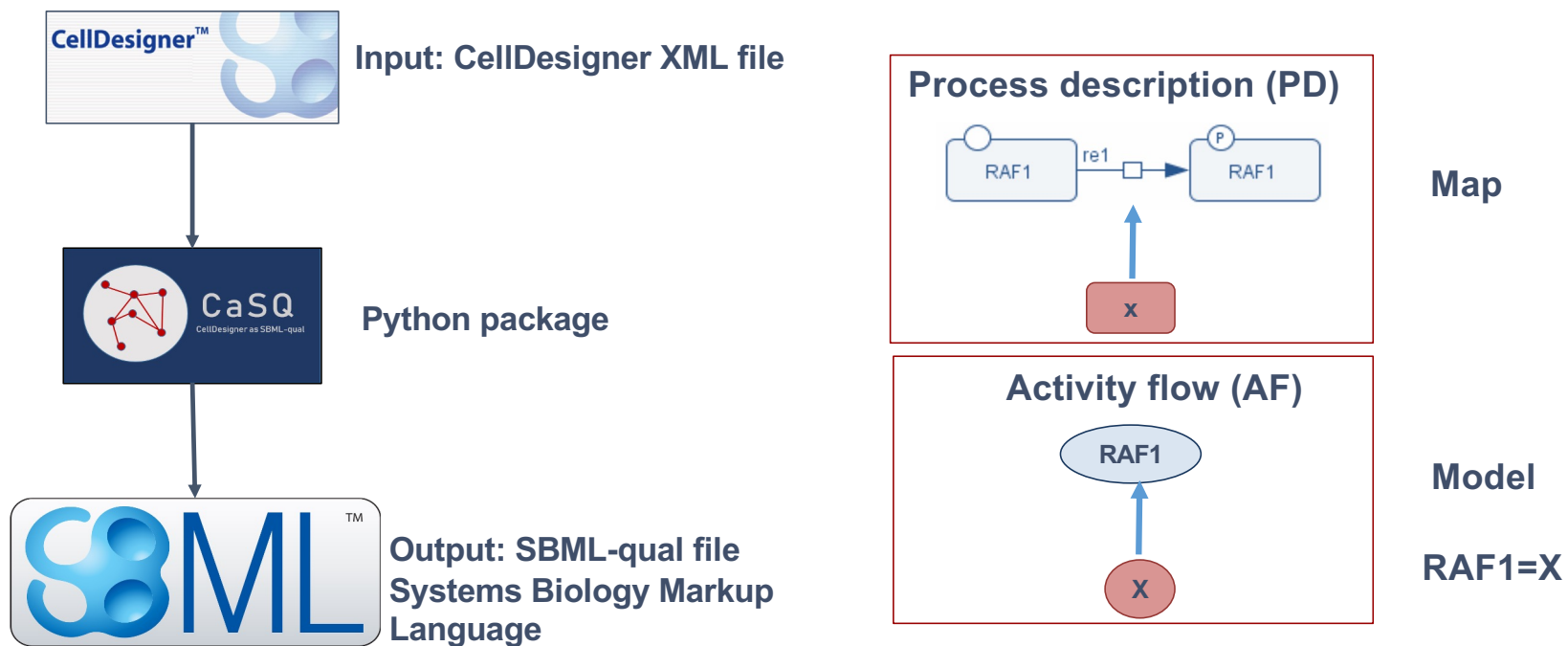
Schematic representation of the intercellular interactions

The RA multicellular map

- **2232** components that interact with one another via **1461** reactions including **118** intercellular interactions



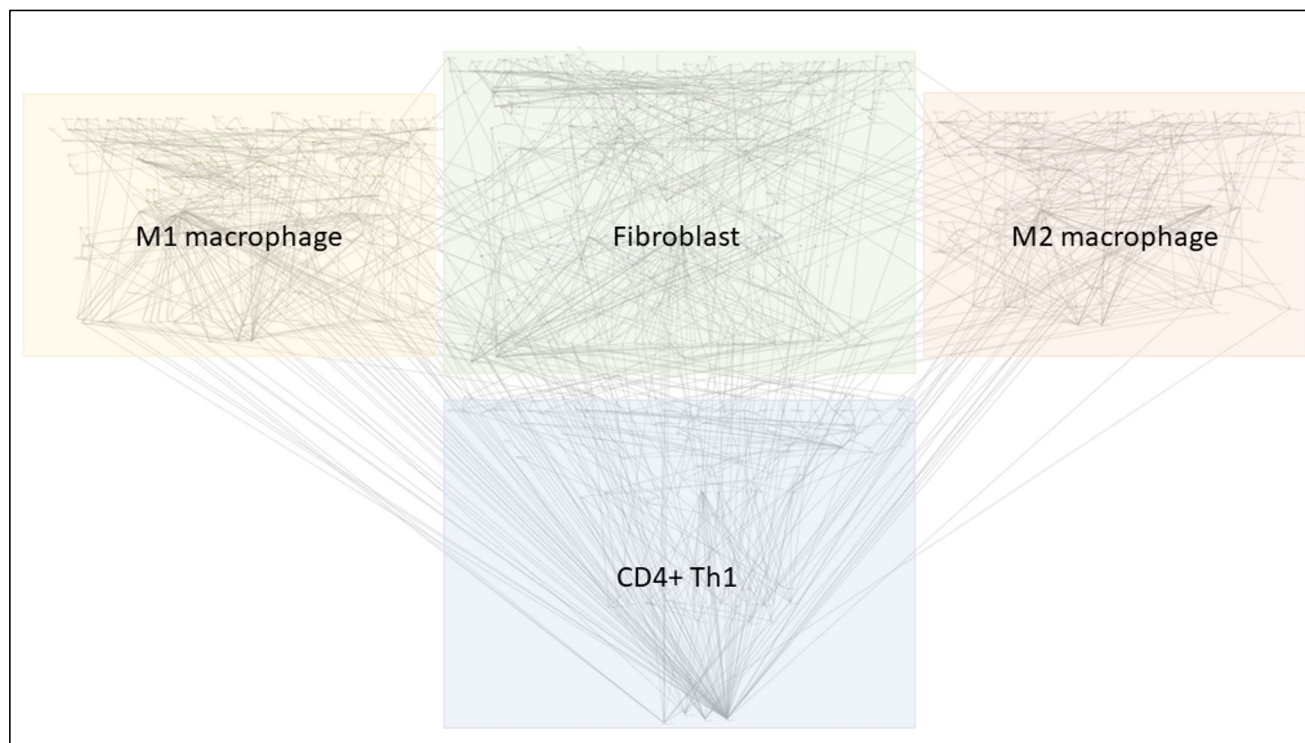
Executable Boolean models from molecular interaction maps



From the RA multicellular map to a multicellular executable model

1104 nodes, including 240 inputs, and 1845 interactions

Size of published Boolean models since 2020



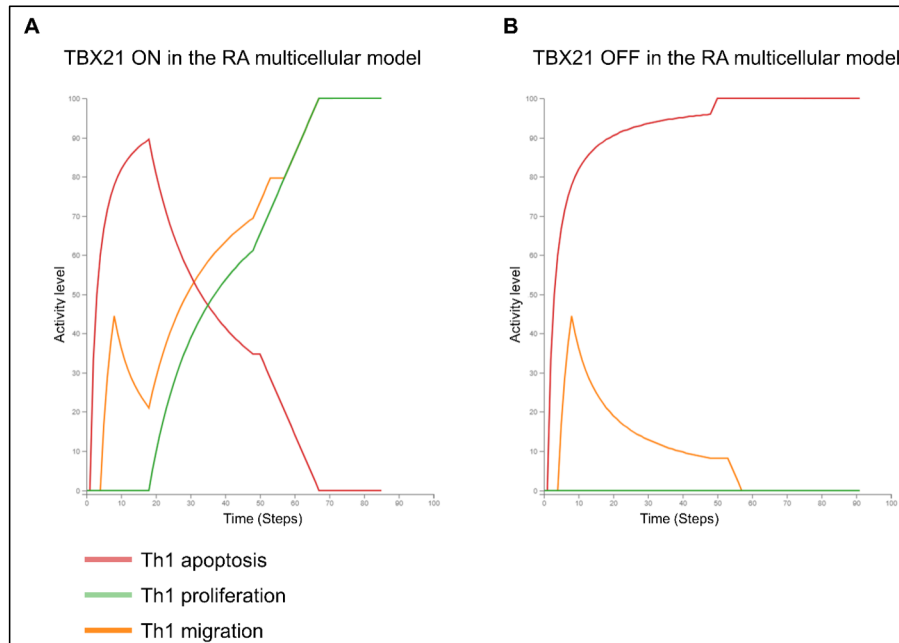
(Zerrouk et al., npj Digital Medicine, 2024)

Publication	Number of nodes
Zerrouk et al, 2024	254
Zerrouk et al, 2024	309
Aghakhani et al., 2023	463
Aghakhani et al., 2022	359
Singh et al., 2022	321
Dnyane et al., 2021	265
Howell et al., 2022	175
Montagud et al., 2022	133
Corral-jara et al, 2021	82
Park et al., 2021	77
Bolouri et al., 2020	64
Cacace et al., 2020	56
Howell et al., 2023	38
de León et al., 2021	29
Ordaz-Arias et al., 2022	29
Gupta et al., 2023	26
Chapman et al.,2023	26

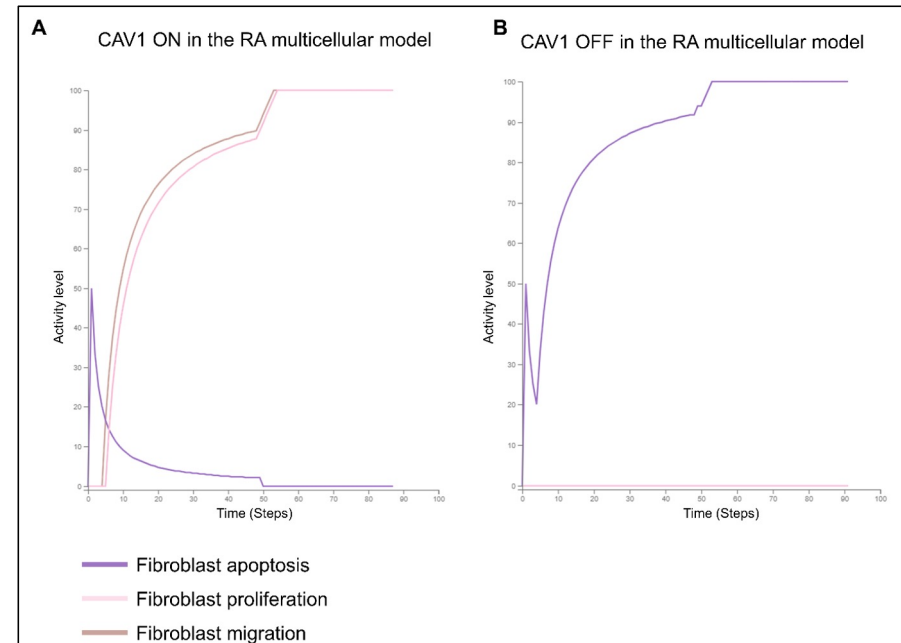
In silico simulations



In silico simulations using the RA multicellular model

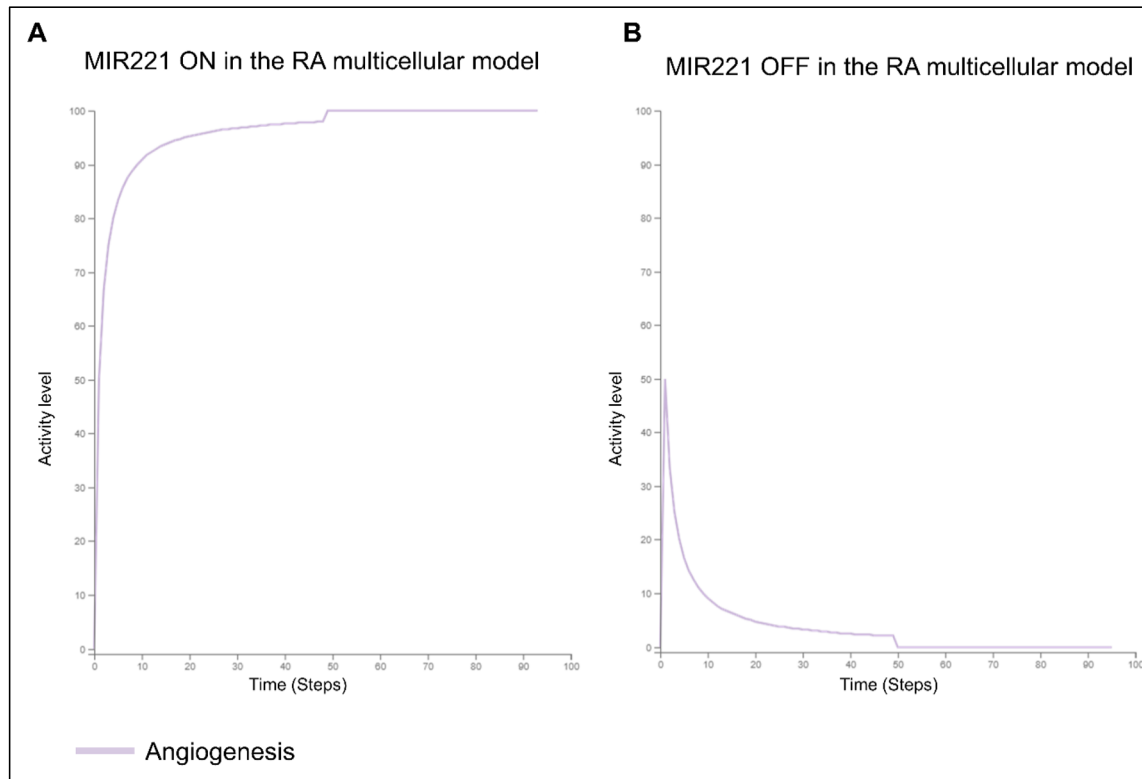


Published experimental evidence support **TBX21** inhibition for **downregulating hyperactive RA Th1** (Xue et al., 2014, Bruyn et al., 2007)



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

In silico simulations using the RA multicellular model

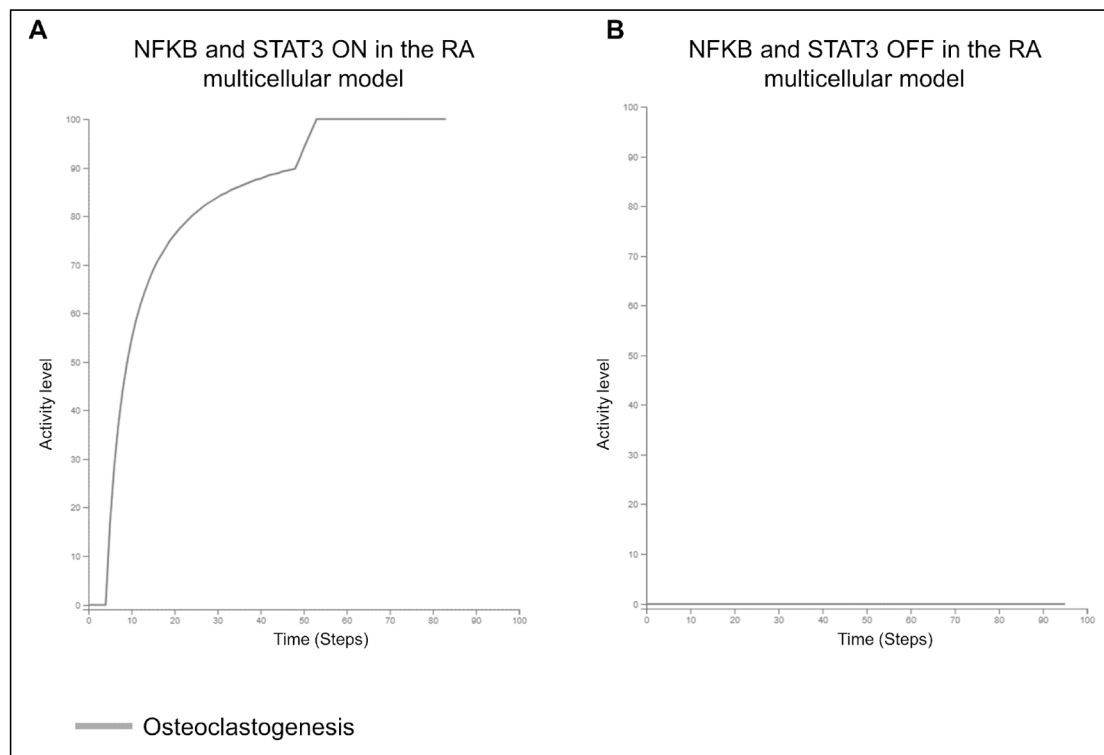


Experiments show that **MIR221** inhibition could reduce the **angiogenesis** in the arthritic joint (Mcmorrow et al., 2013)



MIR221 inhibition → Subsequent activation of THBS1

New potentially therapeutic combinations



NF-κB and STAT3 double KO inhibited the differentiation of osteoclast precursor cells in the RA multicellular model

NF-κB and STAT3 is not associated with literature supporting its potential value as therapeutic target

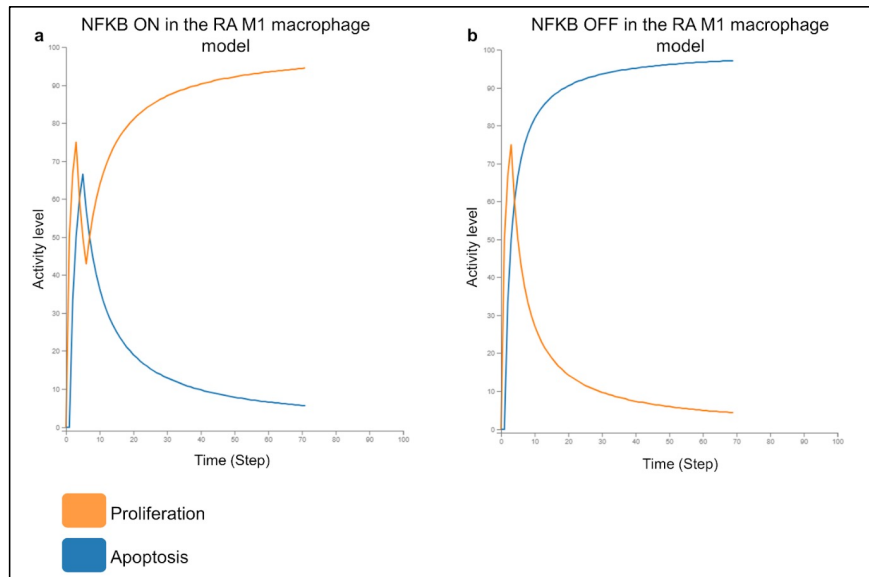
Targets and repurposed drugs

Successful targets	RA multi-cellular model's phenotypes														
	M1		M2			Fibroblast			Th1			Joint			
	macrophage		macrophage												
	A p o p t o s i s	P r o l i f e r a t i o n	C s t o c l a s s i c	A p o p t o s i s	P r o l i f e r a t i o n	A p o p t o s i s	P r o l i f e r a t i o n	M i g r a t i o n	A p o p t o s i s	P r o l i f e r a t i o n	M i g r a t i o n	I n f l a m m a t i o n	A n g i o g e n e s i s	M a t r i x d e g r a d a t i o n	O s t e o c l a s t o g e n e s i s
AKT2						↘	↘								
CAV1						↗	↘	↘							
CREB1							↘								
GSK3β				↘	↗										
ERK1		↘	↘												
MIR221													↘		
mTOR									↗	↘	↘				
NF-κB	↗	↘	↘					↘		↘	↘			↘	
TBX21									↗	↘	↘				

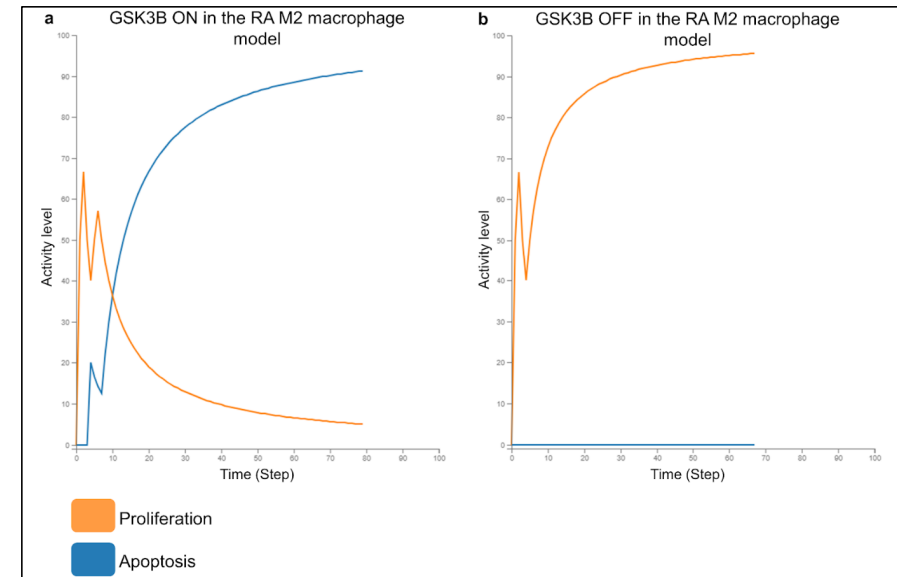
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Successful targets	Target type	Associated disease(s)	Drugs with the highest status
CAV1	Literature-reported target	/	/
AKT2	Literature-reported target	/	Akt inhibitor VIII (Investigative)
CREB1	Literature-reported target	/	/
NF-kappaB	Successful target	Irritable bowel syndrome, Rheumatoid arthritis, Choreaiform 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	/	/

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

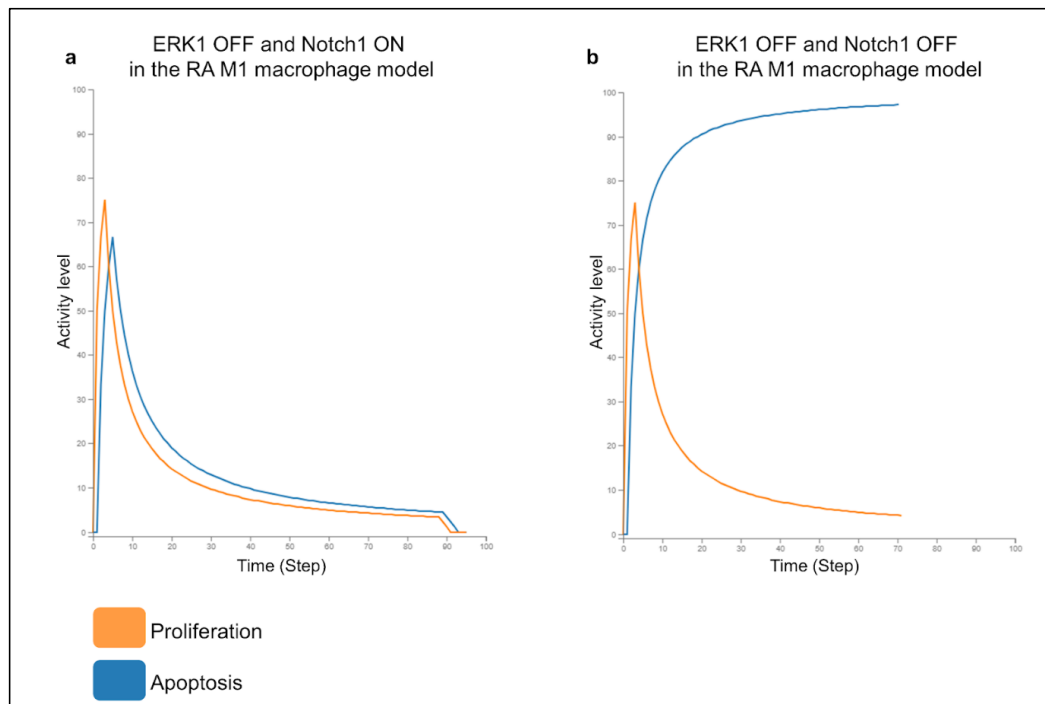


NF- κ B inhibition for therapeutic interventions in **RA** & for downregulating the **M1 markers** (Xia et al., 2018, Cutolo et al., 2022)



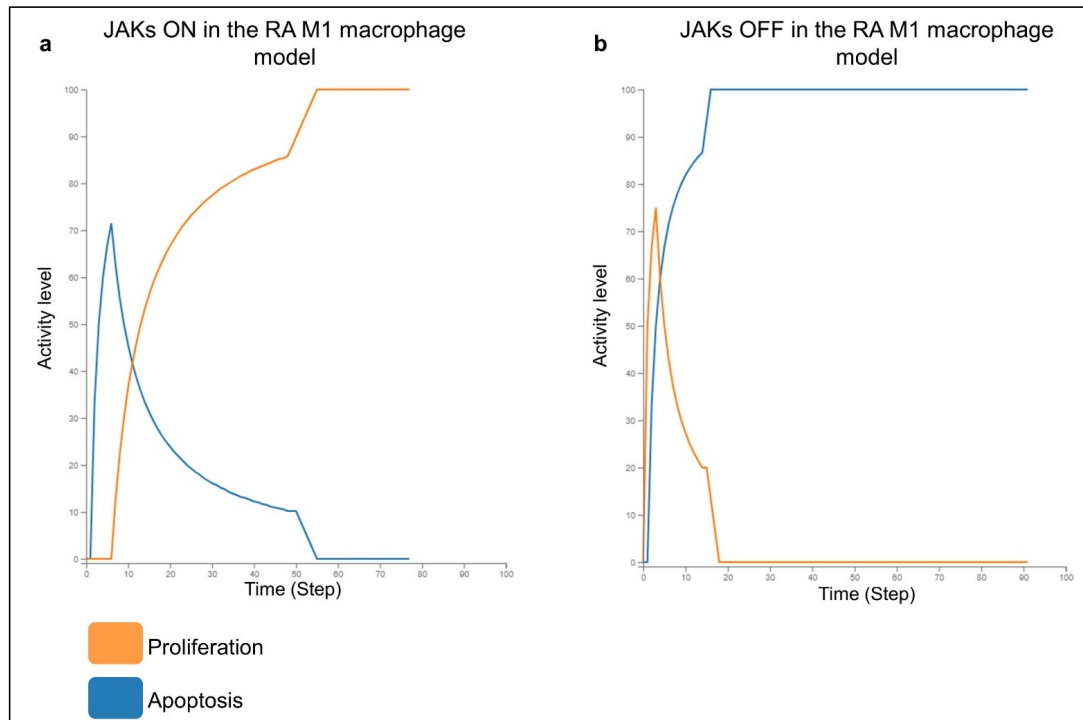
GSK3B inhibition for therapeutic interventions in **RA** & for increasing the expression of the **M2 markers** (Kwon et al., 2014, Peng et al., 2022)

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



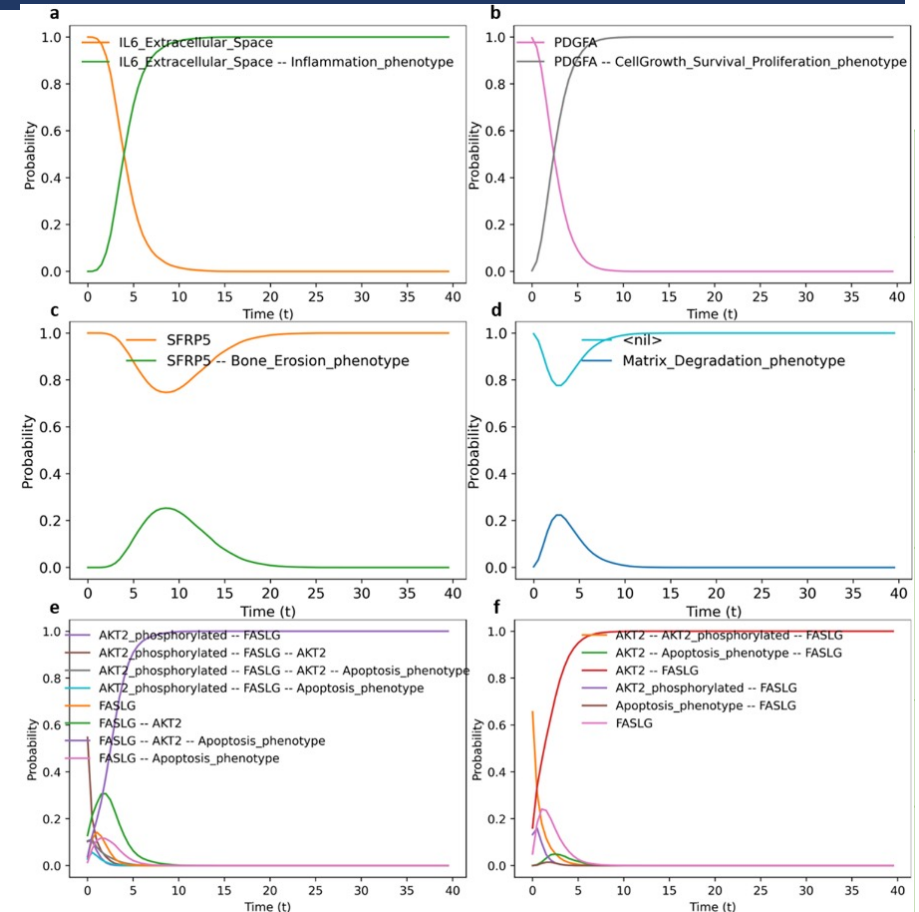
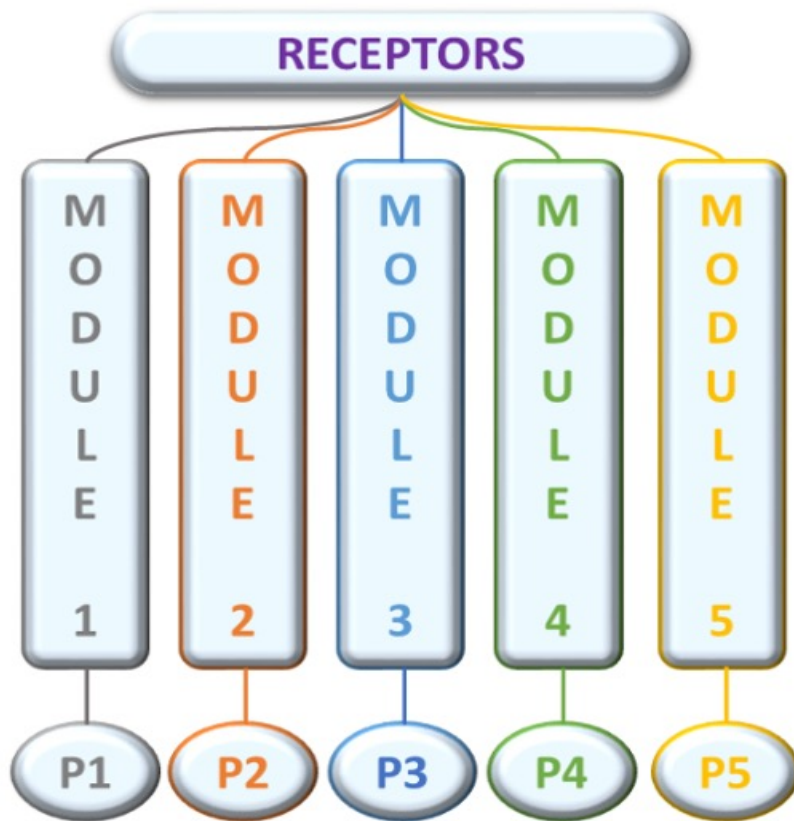
The potential therapeutic value of co-targeting **ERK1** and **Notch1** has already been demonstrated in cancer but **not in RA** (Krepler et al., 2016)

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



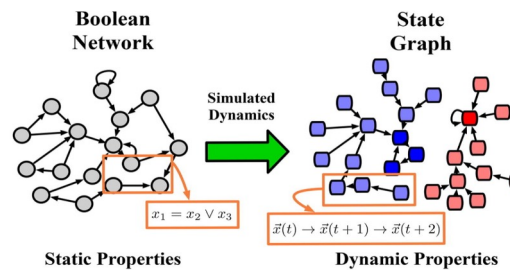
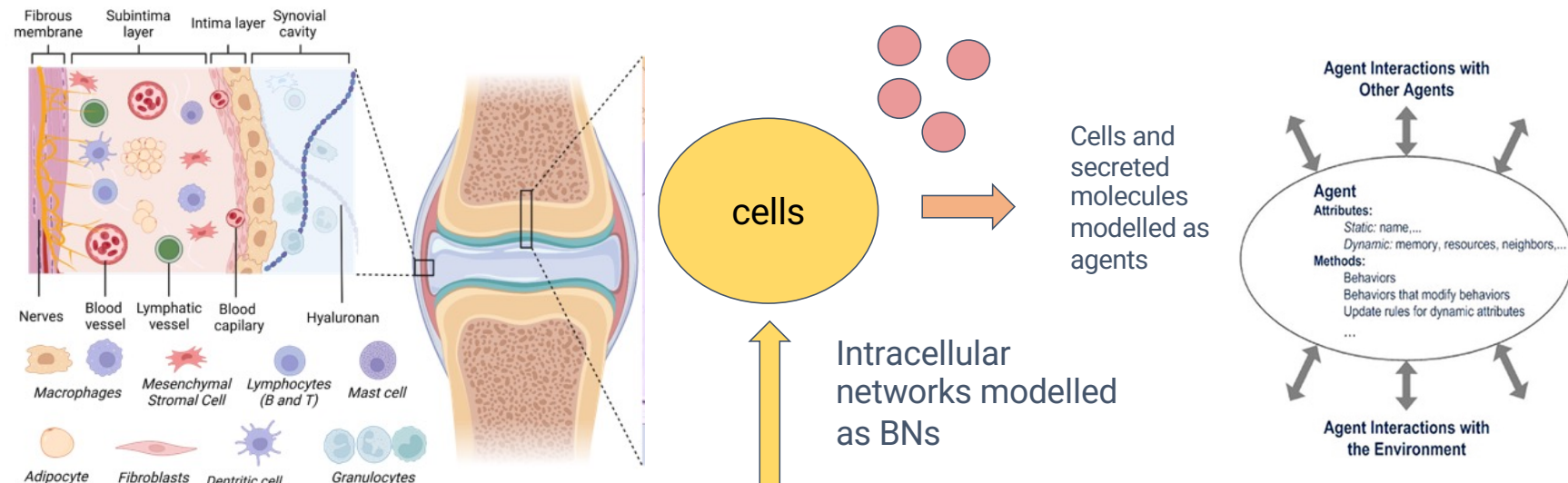
Baricitinib is an FDA approved drug for treating RA → Its **effect on the macrophage's phenotypes is not understood** (Magnon et al., 2019, Palasiewicz et al., 2021)

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

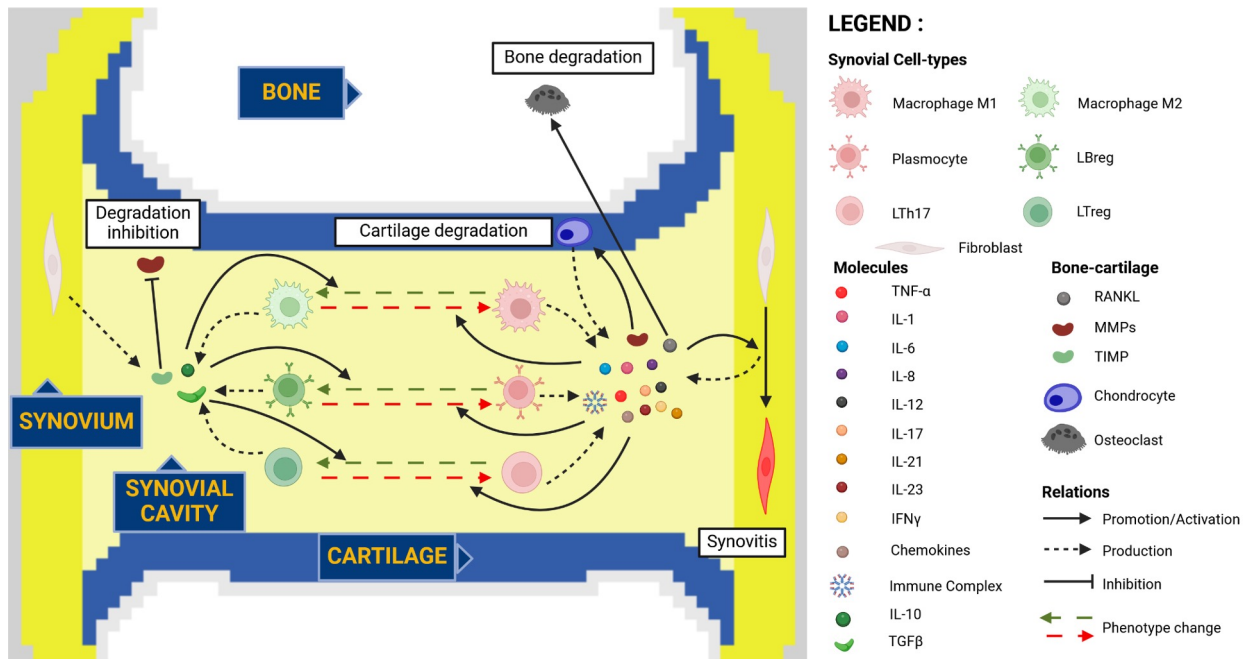
Nested ABMs – The Babushka effect



Decision-making systems for the agents



Agent-Based Modelling



Main actors

Pro-inflammatory

Contributes to the inflammatory cycle and activates reactive components

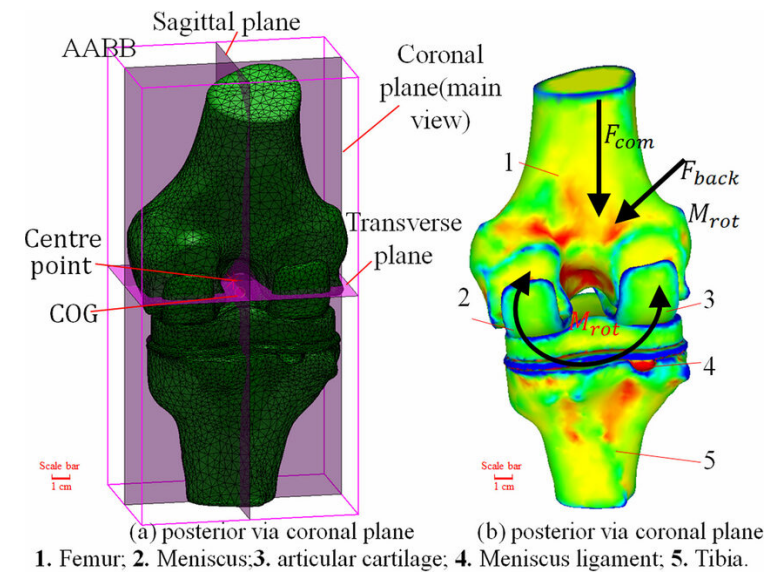
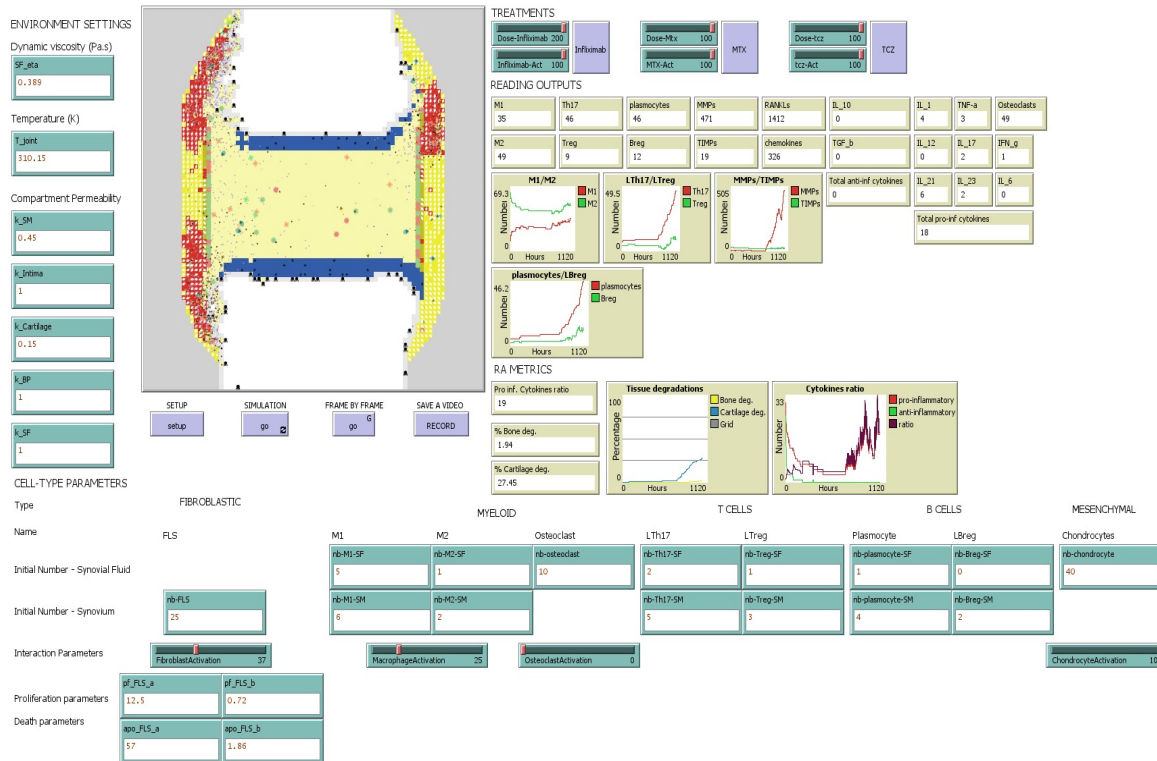
Reactive

Depends on the signals of other components, can better or worsen the inflammation and degradation

Anti-inflammatory

Helps alleviating the immune response and tends to help keeping the system's integrity

Reconcile micro & macro scales



ABM of RA knee joint (scRNAseq-guided prototype)

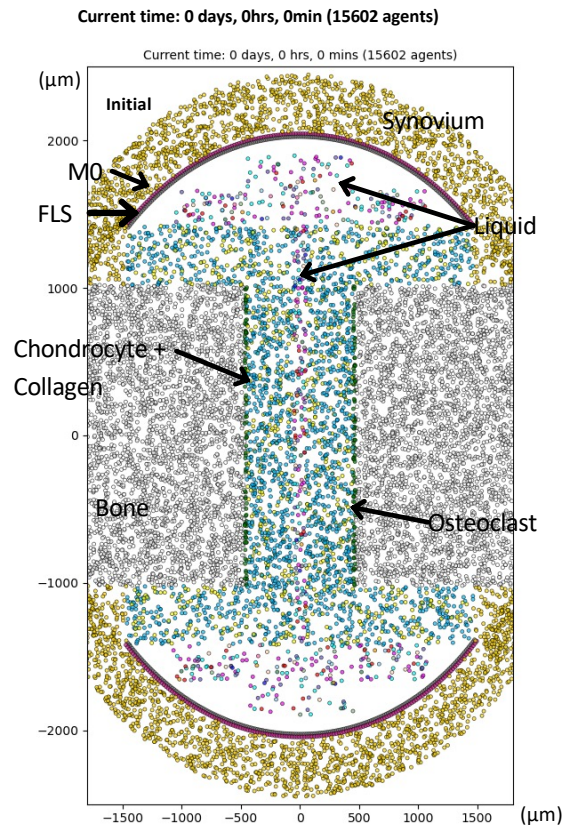


Figure 1 : Initial conditions for the agent-based model (ABM) of a rheumatoid arthritis knee joint, based on the conceptual model. To simplify the simulation, cell infiltration via blood vessels is not modeled. The system is initialized after infiltration, with a pre-swollen synovial fluid.

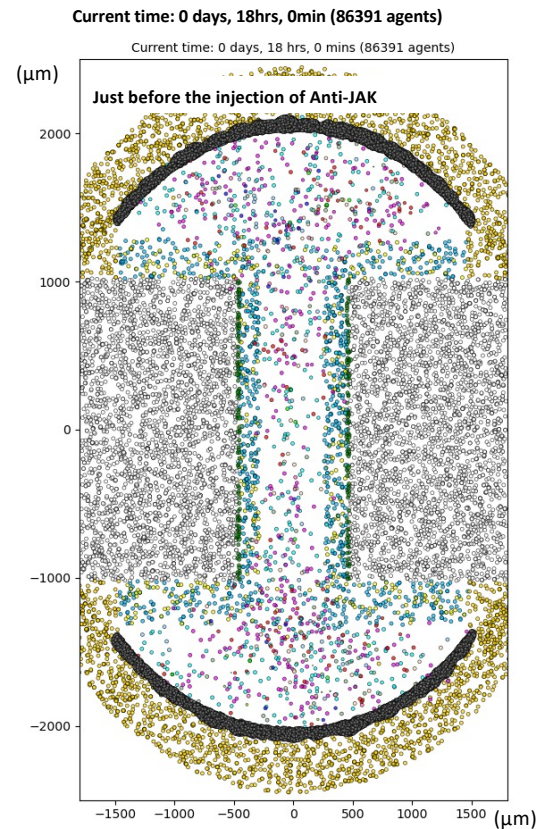


Figure 2 : Evolution of the joint subject to RA, 18 hours after the beginning of the simulation. The cartilage die, the fibroblasts increase, cells of the liquid are multiplied. 5 mg are injected

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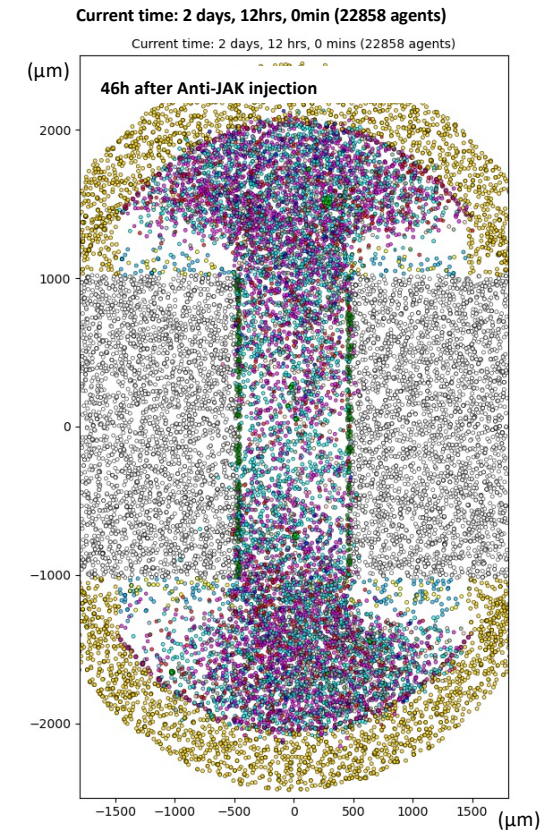


Figure 3 : Evolution of the joint subject to RA, 46 hours after the injection of the Anti-JAK, Tofacitinib. The quantity of fibroblast decrease, however cartilage continue to die and cell liquid to multiply.

Results on the evolution of the model

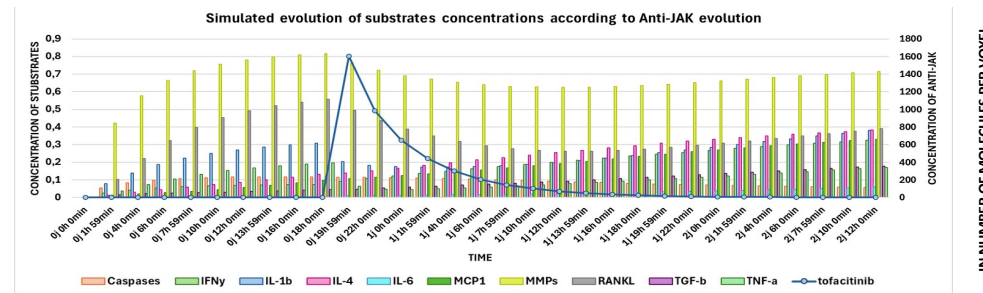


Figure 1 : Evolution of the concentration of the substrates present in a rheumatoid arthritis joint according to the evolution of Tofacitinib concentration. Once the model is calibrated this result will allow to adjust the quantity and rate of injection of Tofacitinib according to the patient need to reduce inflammatory substrates.

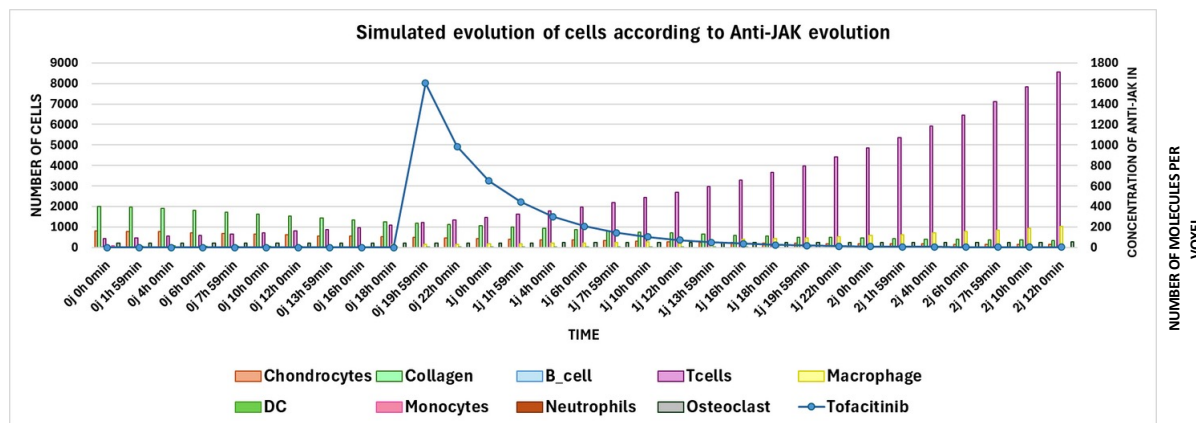


Figure 2 : Evolution of the number of cells present in a rheumatoid arthritis joint according to the evolution of Tofacitinib concentration.

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Rheumatoid Arthritis

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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](#)

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Abstract

Rheumatoid arthritis is a complex disease marked by joint pain, stiffness, swelling, and chronic synovitis, arising from the dysregulated interaction between synoviocytes and immune cells. Its 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 the arthritic joint by building a large, modular biochemical reaction map of intra- and intercellular interactions. This network, featuring over 1000 biomolecules, is then converted to one of the largest executable Boolean models for biological systems to date. Validated through existing knowledge and gene expression data, our model is used to explore current treatments and identify new therapeutic targets for rheumatoid arthritis.

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

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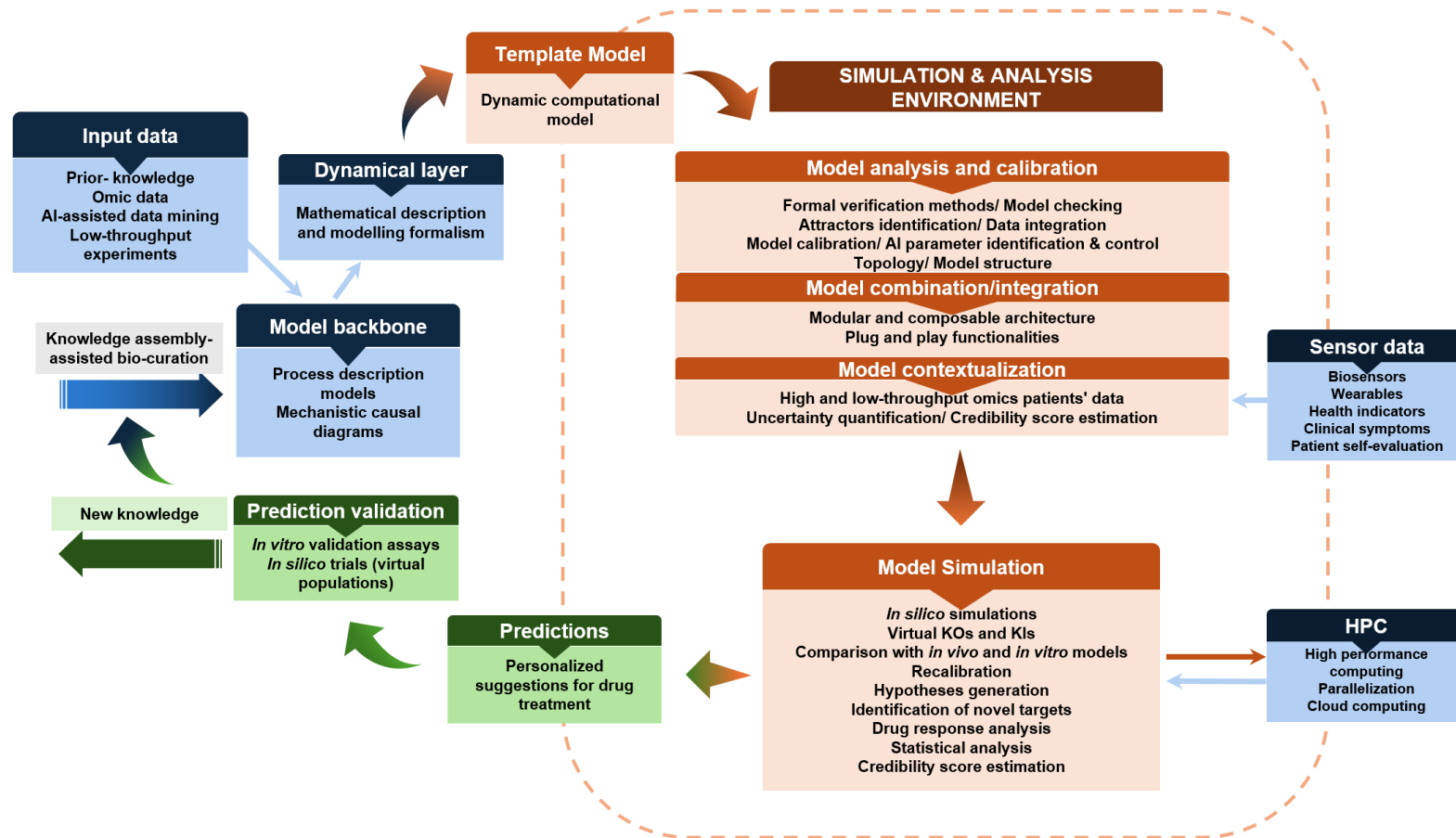
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Abstract

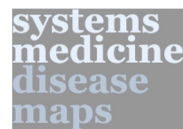
nistic mapping of the molecular pathways and cellular crosstalks is essential to ological processes and different disease manifestations. In this regard, we preser aridized, interactive, manually curated representation of existing knowledge rel of RA. This state-of-the-art RA-Atlas includes an updated version of the globa

Abstract

Digital Twins: more than a model



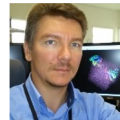
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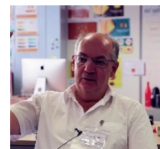
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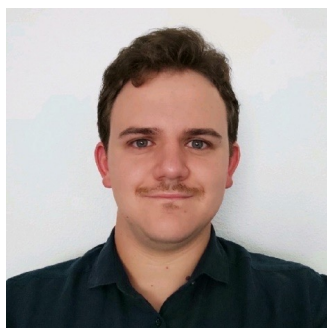


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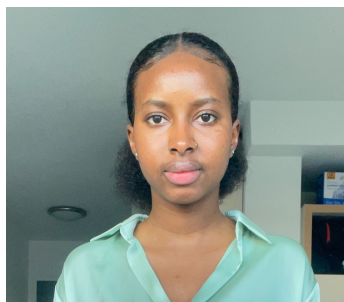
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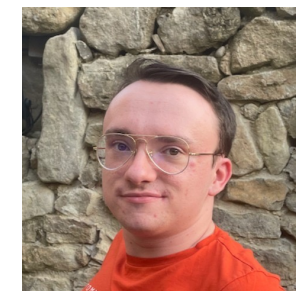
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