Your Digital Twin: Predicting and Preventing Joint Pain

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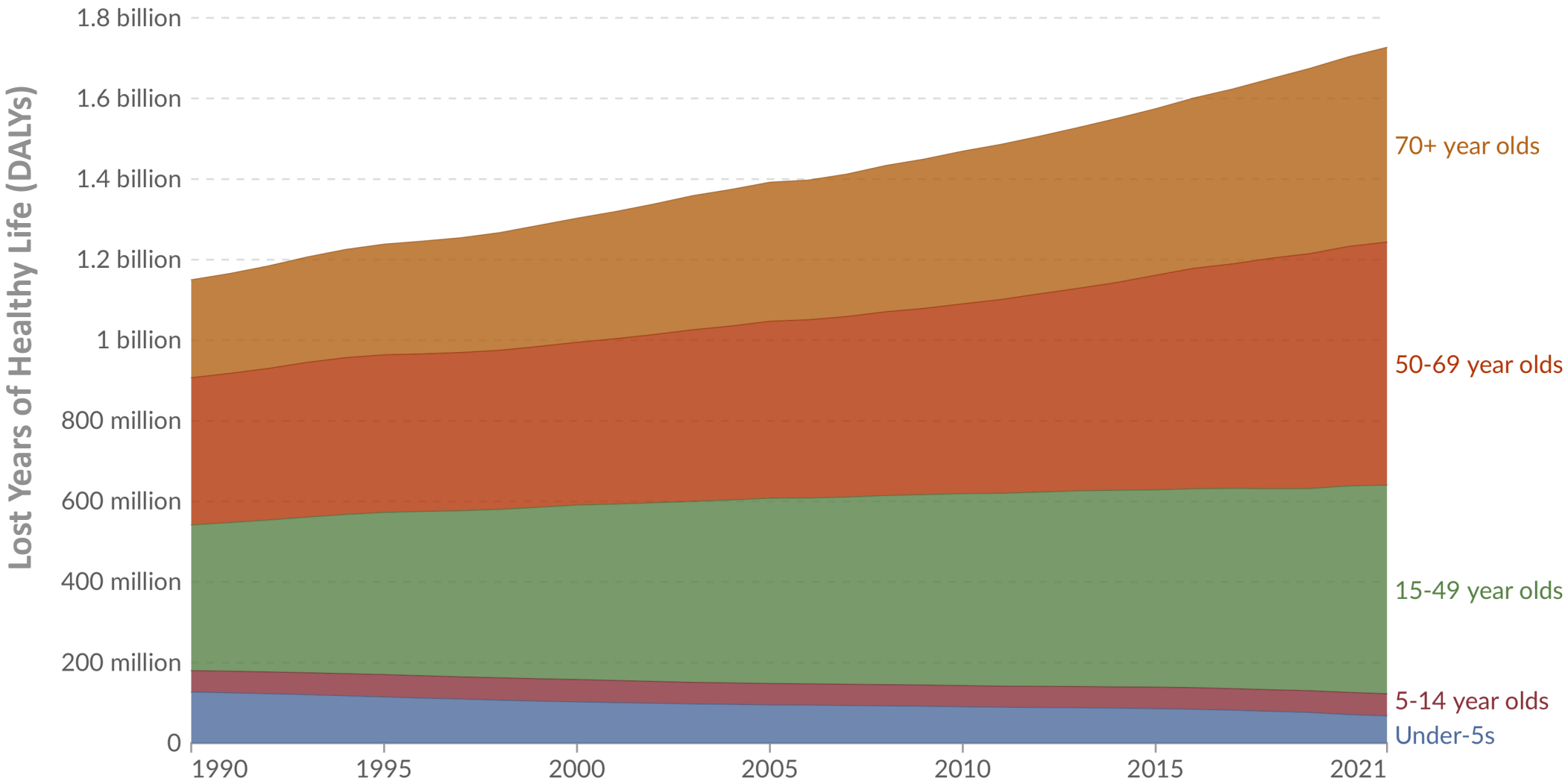
Non-communicable diseases & disorders (NCD)

Disease burden from NCD by age, World, 1990 to 2021



Data source: IHME, Global Burden of Disease (2024)

OurWorldinData.org/burden-of-disease | CC BY

NCD & mechanically loaded organs & tissues

Global Burden of Disease Study 2019

(GBD 2019 Diseases and Injuries Collaborators, Lancet, 396, 2020)

10 most disabling and life threatening disease & disorders (2019)

population 25-49 years of age

Road injuries	#1
HIV/AIDS	#2
Ischaemic heart disease*	**#3**
Low back pain*	**#4**
Headache disorders	#5
Depressive disorders	#6
Gynaecological diseases	#7
Other musculoskeletal disorders*	**#8**
Stroke*	**#9**
Tuberculosis	#10

← NCD

***Non-communicable disease /disorder that affects mechanically loaded organs & tissues**

Coping with Low Back Pain (LBP) with AI: a challenge

npj | Digital Medicine

www.nature.com/npjdigitalmed

REVIEW ARTICLE OPEN

Check for updates

Artificial intelligence to improve back pain outcomes and lessons learnt from clinical classification approaches: three systematic reviews

Scott D. Tagliaferri[1]✉, Maia Angelova[2], Xiaohui Zhao[3], Patrick J. Owen[1], Clint T. Miller[1], Tim Wilkin[2] and Daniel L. Belavy[1]✉

"if AI/ML is to make an impact on LBP management, it will likely need to develop greater reliability and validity compared to current approaches …."

Challenges

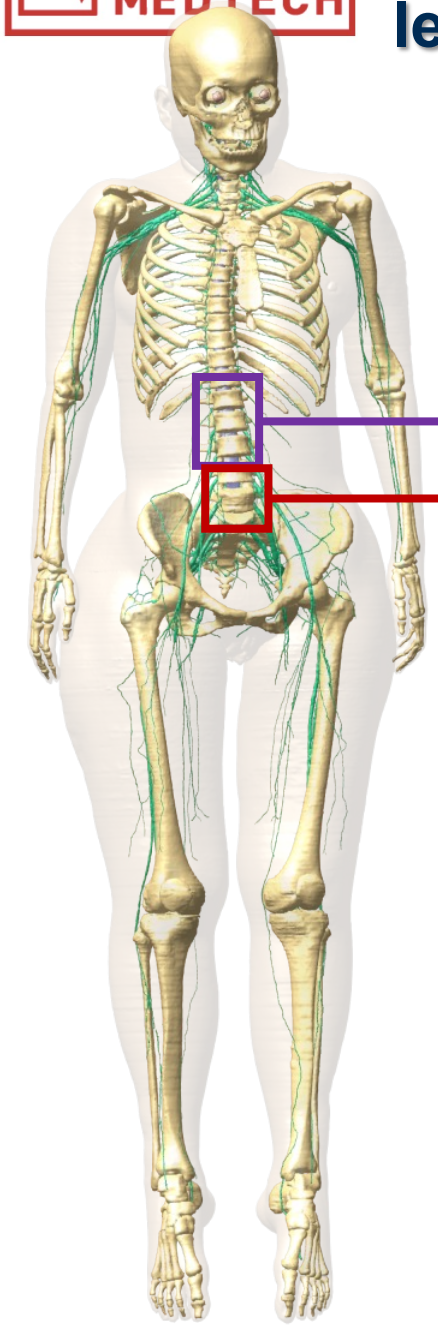
- Small and heterogeneous data
- Classify risk factors

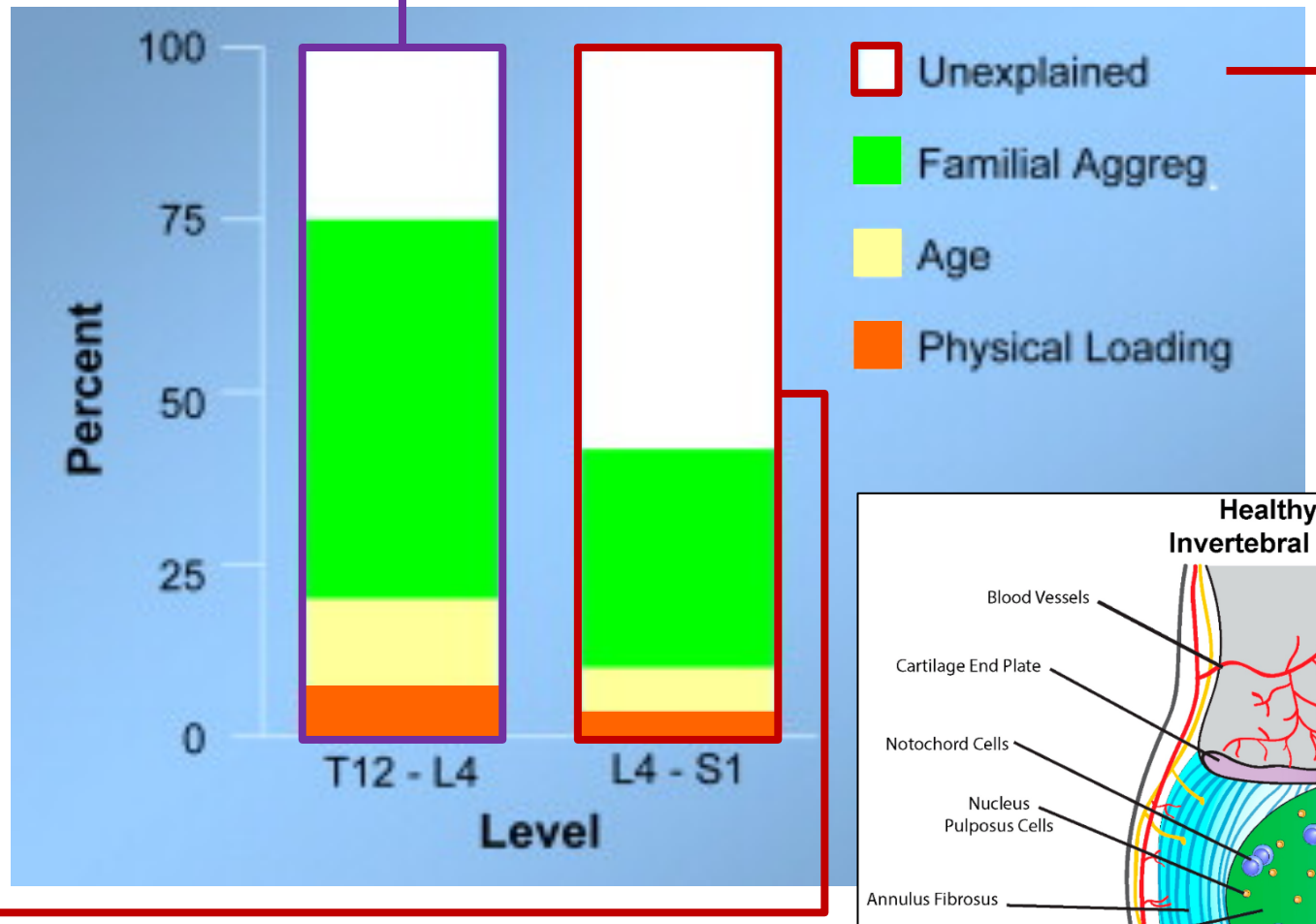
Query, Gemini Pro, Oct 22nd, 2025:

PROMPT by J Noailly: "*Has artificial intelligence been successful in coping with low back pain? Please provide only proven and directly contrastable information.*"

CONCLUSION OF ANALYSIS by Gemini: AI has been "successful" and proven effective in narrow, data-heavy tasks like reading images and calculating prognosis. Its success in direct patient treatment is inconsistent and highly dependent on the specific application and its design.

Determinants of intervertebral disc (IVD) degeneration, a leading unique cause of LBP



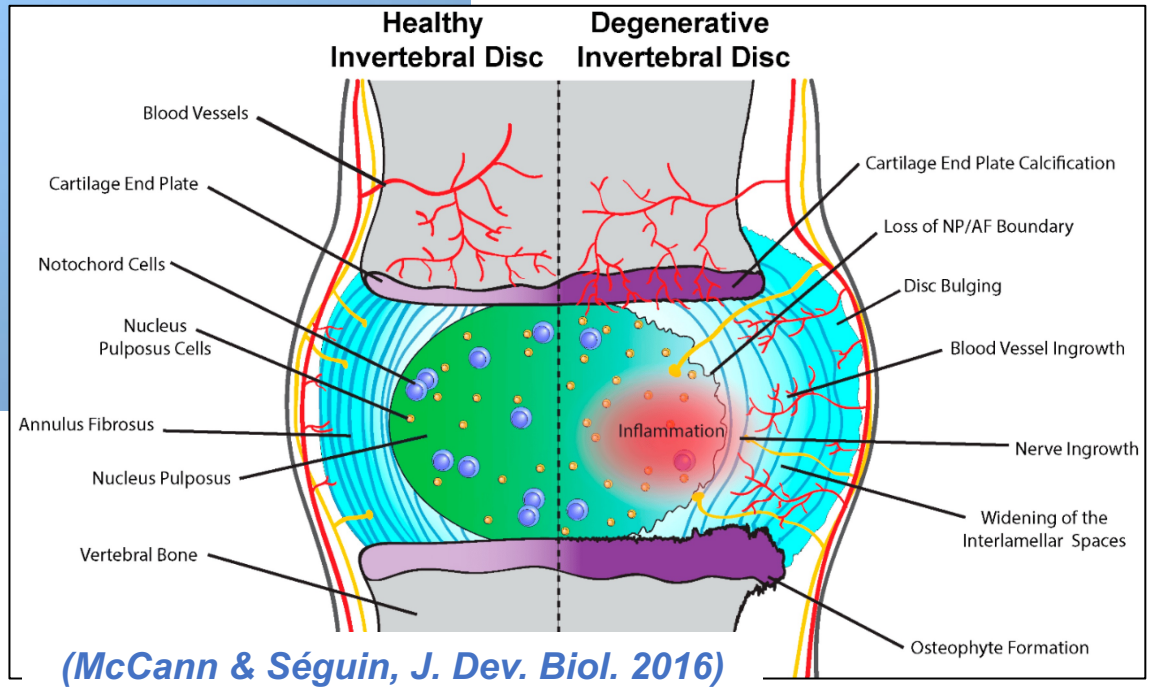


The Twin Spine Study

(Battié et al, The Spine J, 9, 2009)

Interplays among age, biological & mechanical factors

Complex & multifactorial endotypes



(McCann & Séguin, J. Dev. Biol. 2016)

Systems Mechanobiology & intervertebral disc (IVD) degeneration

Reviewed in Baumgartner, et al, Int J Mol Sci, 22, 2021

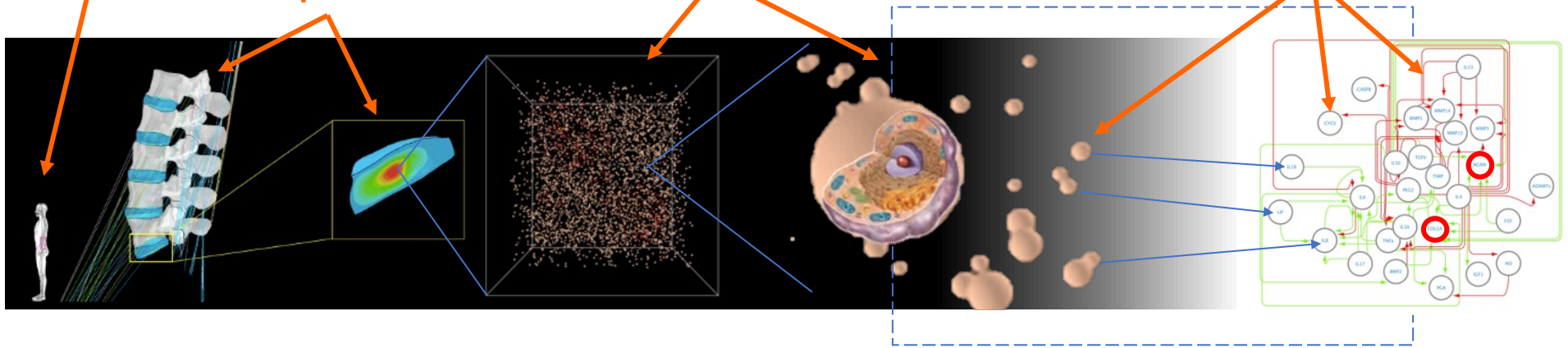
Measurements

Motion capture

Medical images /tissue composition

Cell culture experiments, body fluids analyses

Proteomics, transcriptomics, single cell experiments



PHENOTYPES

ENDOTYPES

Multibody dynamics

Finite element modelling

Agent-based Modelling

Network modelling

Organ forces

3D Tissue deformation, stress & mass transport fields

3D Multicellular (collective) behaviour, protein reaction

Multifactorial cell regulation, individual agent fate

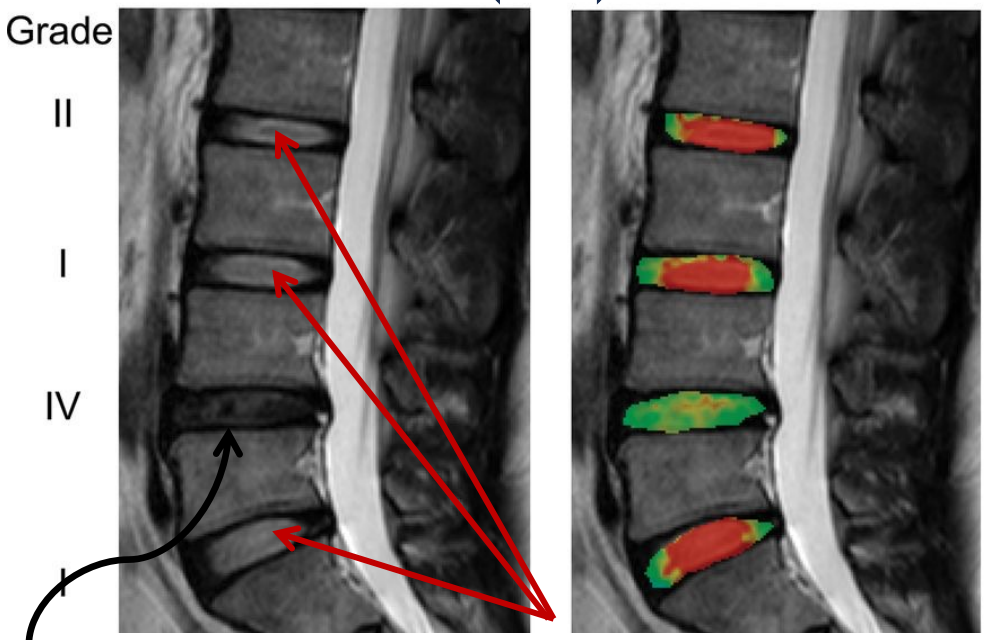
Modelling & Simulation Workflow

SYSTEMS MECHANOBIOLOGY

Composition-based IVD tissue modelling

MRI

T2-weighted ⟷ T1-rho



High contents of water & proteoglycan

↘ with degeneration

Togao et al, Am J Neuroradiol, 39, 2018

TISSUE STRESS: composition-dependent osmo-poroelasticity

$$\underline{\underline{\sigma}} = \underline{\underline{\sigma_{eff}}} - (p + \Delta\pi)\underline{\underline{I}}$$

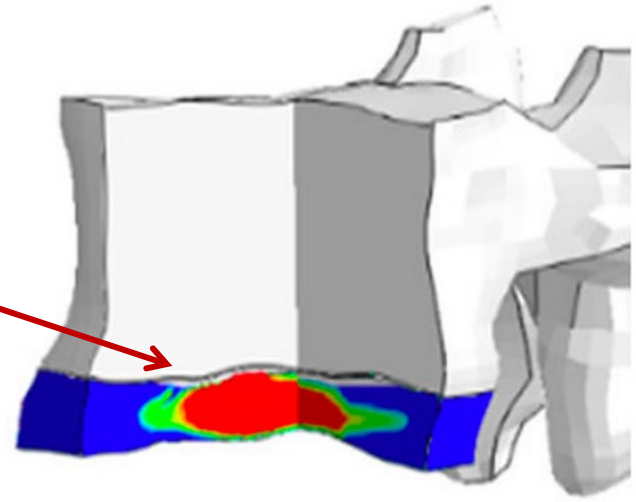
$$\Delta\pi = \phi_{int} RT \left(\sqrt{c_{F,exf}^2 + 4\left(\frac{\gamma_{ext}^{\pm}}{\gamma_{int}^{\pm}}\right)^2 c_{ext}^2} \right) - 2\phi_{ext} RT c_{ext}$$

$$c_{F,exf} = \frac{n_f c_F}{n_{exf}}$$ → Proteoglycan content

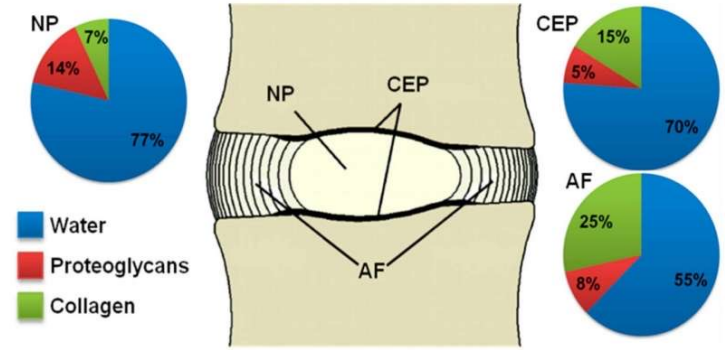
$$n_{exf} = n_f - \varphi_{ci} \times Coll$$

$$\kappa = \alpha(1 - n_{exf})^{-M} \qquad \underline{u_f} = \frac{\kappa}{n_f} \underline{\nabla \mu^f}$$

→ Collagen, water contents



Van Rijsbergen et al, PLoS ONE, 13, 2018



Ruiz Wills et al, J Mech Phys Solids, 90, 2016

Ruiz Wills et al, Front Bioeng Biotechnol, 9, 2018

Carlos Ruiz Wills

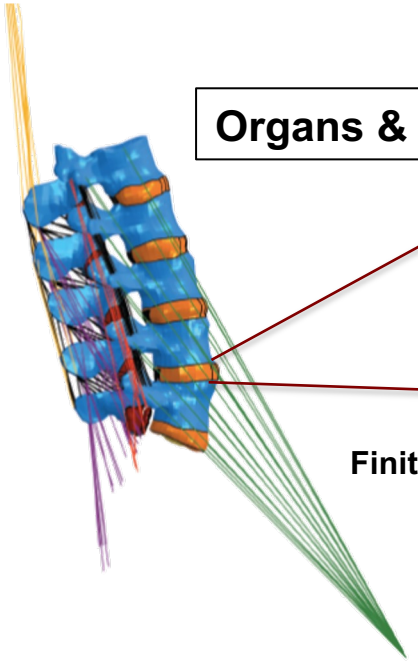
Keita Ito

TU/e EINDHOVEN UNIVERSITY OF TECHNOLOGY

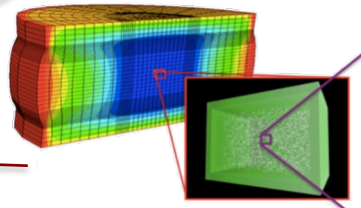
MySpine

Patient-specific spinal treatment simulation

Tissue-level intervertebral disc (IVD) biophysics

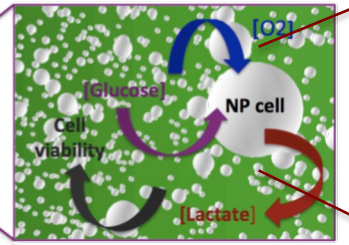


Organs & tissues



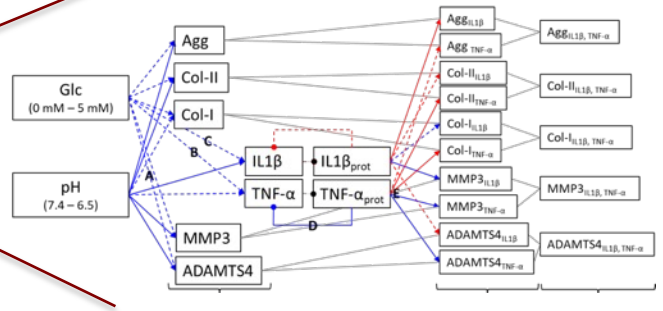
Finite Element Models

Cooperative cell systems



Agent-Based Models

Cell response to multifactorial stimulations



Network Models

Multiphysics modelling: INDIRECT MECHANOTRANSDUCTION

TISSUE STRESS: fibre-reinforced osmo-poroelasticity

$$\Delta\pi = \phi_{int} RT \left(\sqrt{c_{F,exf}^2 + 4\left(\frac{\gamma_{ext}^{\pm}}{\gamma_{int}^{\pm}}\right)^2 c_{ext}^2} \right) - 2\phi_{ext} RT c_{ext}$$

$$c_{F,exf} = \frac{n_f c_F}{n_{exf}}$$ → Proteoglycan content

$$n_{exf} = n_f - \varphi_{ci} \times Coll$$ → Collagen, water contents

$$\kappa = \alpha\left(1 - n_{exf}\right)^{-M} \qquad \underline{u_f} = \frac{\kappa}{n_f} \underline{\nabla \mu^f}$$

METABOLIC TRANSPORT: O2, glucose, lactate

cell nutrition & viability (Indirect mechanotransduction)

$$\frac{\partial C}{\partial t} + \frac{1}{\phi} \underline{u_f} \cdot \underline{\nabla C} - \nabla \cdot \left(\underline{\underline{D}}_{tissue} \underline{\nabla C} \right) = R_{tissue}$$

Accumulation | Convection | Diffusion | Reaction/metabolism

Carlos Ruiz Wills

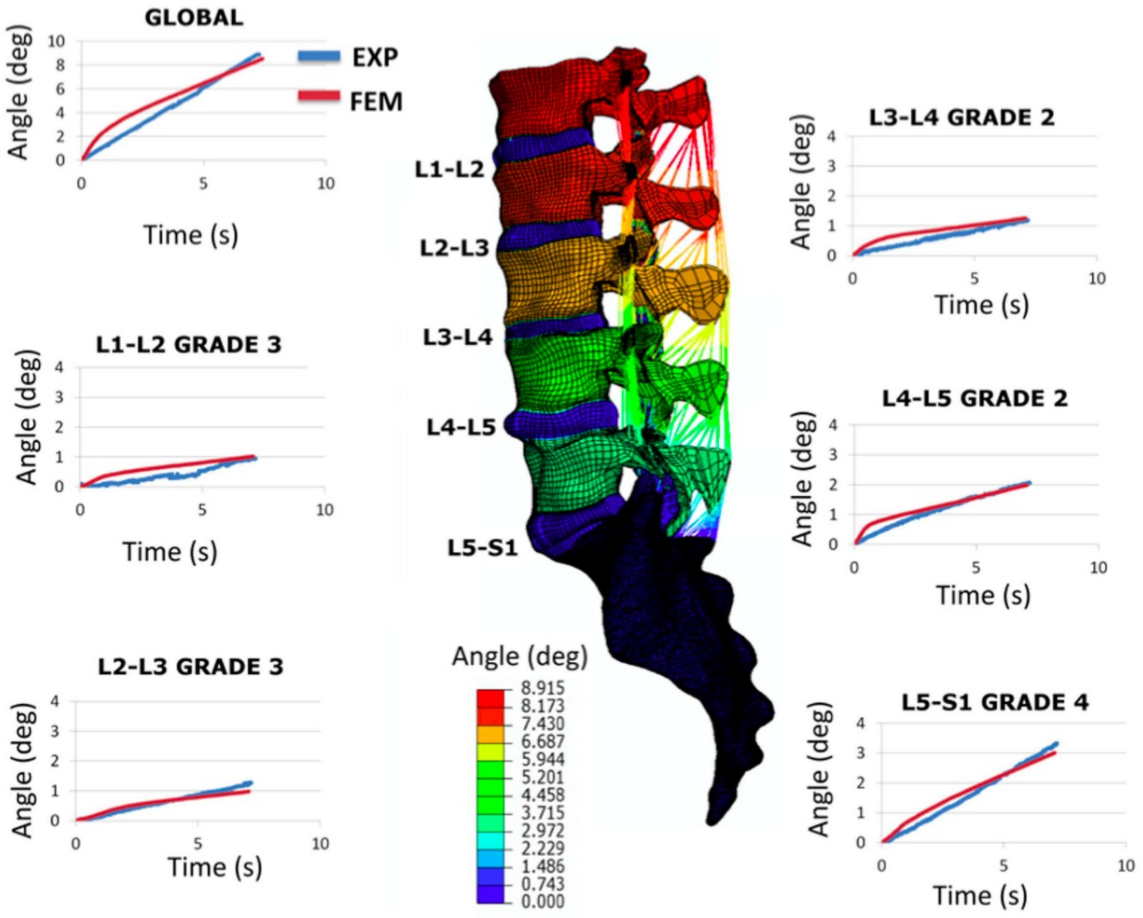
Ruiz Wills et al, J Mech Phys Solids, 90, 2016

Andrea Malandrino

Reviewed in Malandrino et al, MRS Bull, 40, 2015

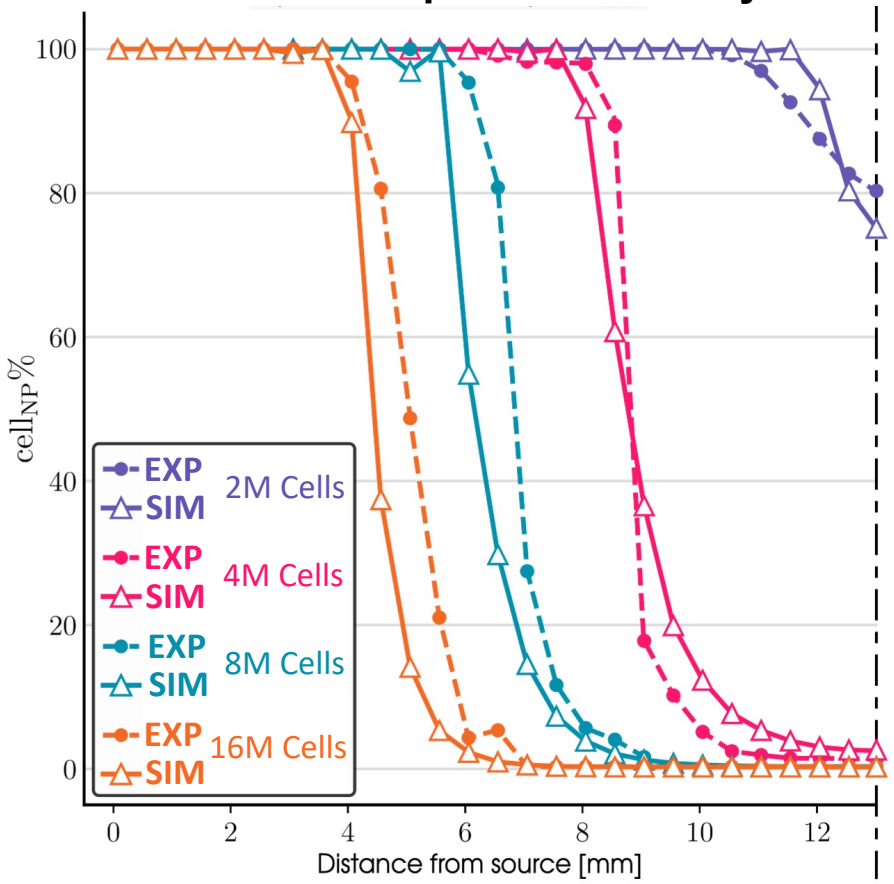
Validation

- **Spine cadaveric specimen testing & modelling**



Hans Joachim Wilke

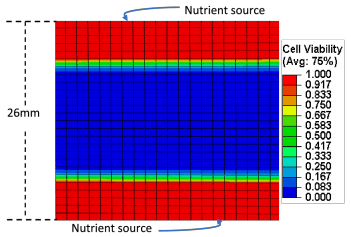
- **Metabolic transport-cell viability in vitro experiments**



Estefano Muñoz-Moya

EXP: *Horner et al, Spine, 26, 2001*

SIM: $\rho_{cell} = \rho_{cell,0} \cdot \exp[-(\alpha_{glucose} + \alpha_{pH})t]$



Andrea Malandrino

Malandrino et al, Front Bioeng Biotechnol, 3, 2015

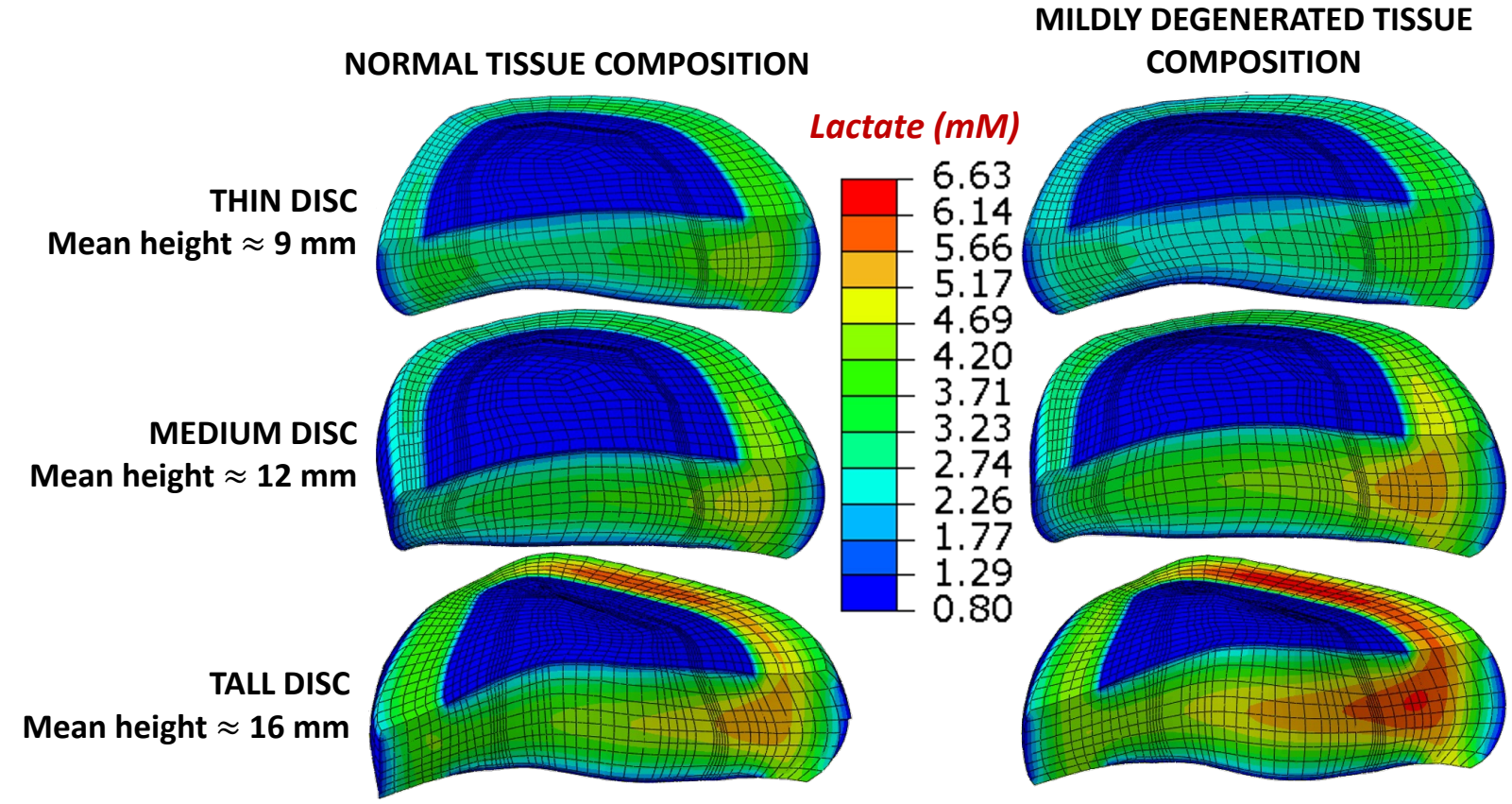
Indirect mechanotransduction findings

Disc patient-specific morphology affects internal mechanics and metabolism, including interactions with tissue properties → IS IT A RISK FACTOR?

Zerihun Workineh

Estefano Muñoz-Moya

(Workineh, Muñoz-Moya et al, Front Bioeng Biotechnol, 13, 2025)



Global Spine Journal
Volume 15, Issue 5, June 2025, Pages 2736-2743

https://doi.org/10.1177/21925682241311515

Sage Journals

Original Article

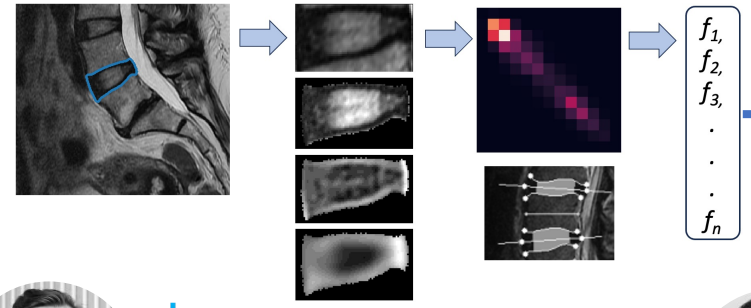
Role of Magnetic Resonance Spectroscopy and T2 Relaxometry as Imaging Biomarker of Early Lumbar Intervertebral Disc Degeneration

Pushpa Bhari Thippeswamy, DNB (Rad), FRCR [1], Shanmuganathan Rajasekaran, PhD [2], Karthik Ramachandran, MS (Ortho), DNB, FNB (spine surgery) [2], Murugesh Easwaran, MSc, PhD [3], Shalini Sivakumar Ramadevi, MSc [1], KS Sri Vijay Anand, MS (Ortho), FISS [2], Ajoy Prasad Shetty, MS (Ortho), DNB [2], and Rishi Mugesh Kanna, MS (Ortho), MRCS, FNB [2]

*"… there were considerable differences in the metabolic molecules between both LBP patients and volunteers in the different age groups, **showing that metabolic alterations precede changes in structural molecules**."*

Relevance of Lactate

Patient-specific /population modelling



Radiomics

Northern Finland Birth Cohort (NFBC), n=1387

UNIVERSITY OF OULU

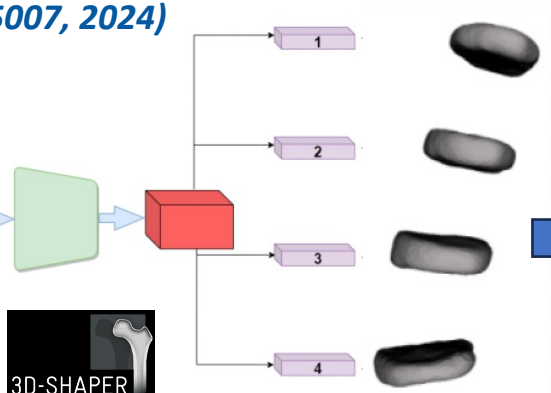
Terence McSweeney

(McSweeney et al, Spine, 10, 2025)

Sai Natarajan

(Natarajan et al, Lect. Notes Comput. Sci., 15007, 2024)

Thick Slice
Sagittal MR volume

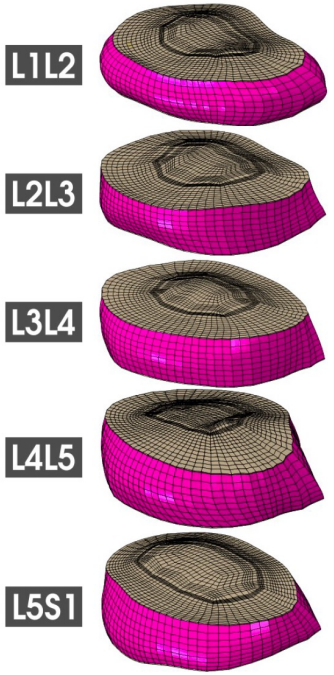


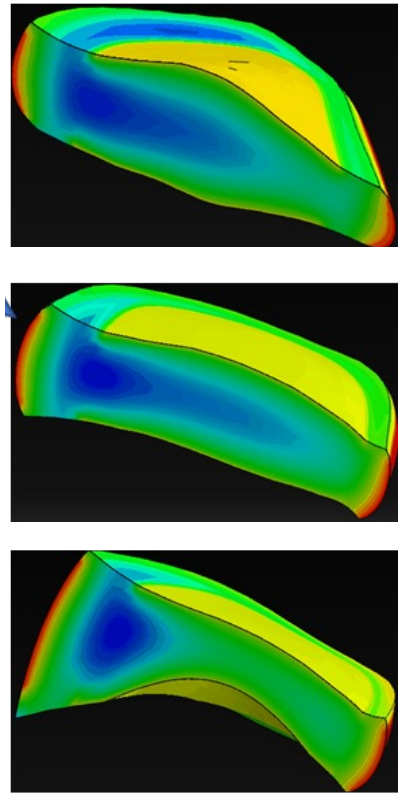
3D-SHAPER MEDICAL

GALGOMEDICAL

2D → 3D

Finite element modelling & simulations

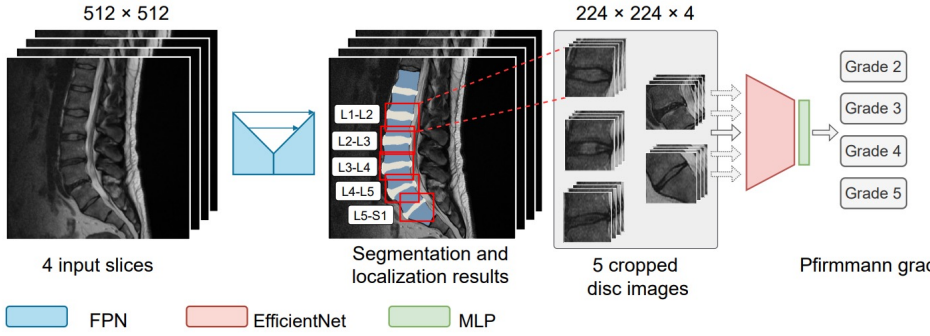




(Kowlagi et al, Spine, 49, 2024)

UNIVERSITY OF OULU

Nash Kowlagi



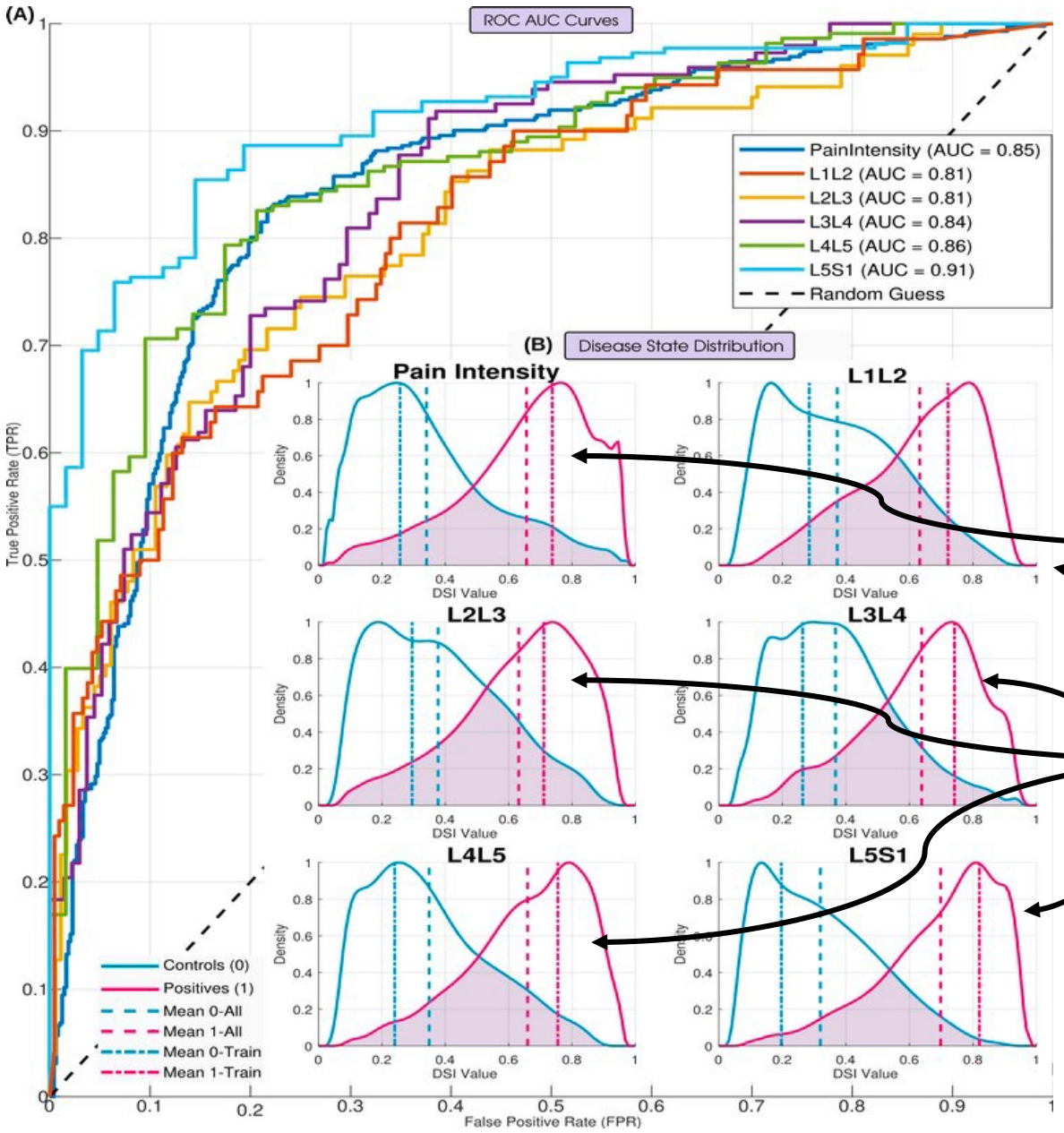
Degeneration grade

(Kowlagi et al, Spine, 10, 2025)

Estefano Muñoz-Moya

(Muñoz-Moya et al, Front Bioeng Biotechnol, 12, 2024)

Stratification: Disease State Index



Mark van Gils

Tampereen yliopisto
Tampere University

Jaro Karppinen

UNIVERSITY OF OULU

Northern Finland Birth Cohort (NFBC)

Age 46 years old

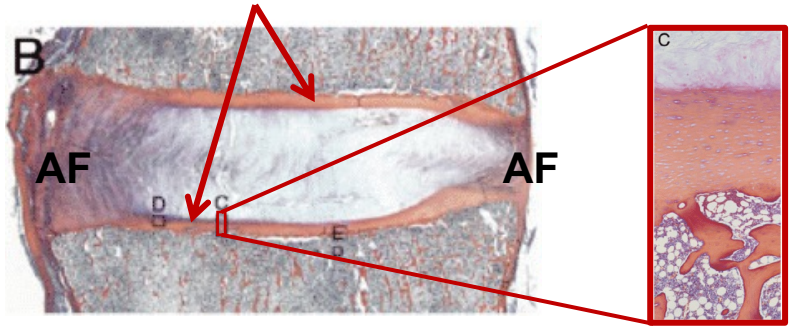
Estefano Muñoz-Moya

Pain: n=4531

Intervertebral disc degeneration + Psychological variables + Cortisol

Intervertebral disc degeneration n=1410

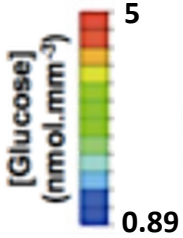
Endplate changes + Radiomics



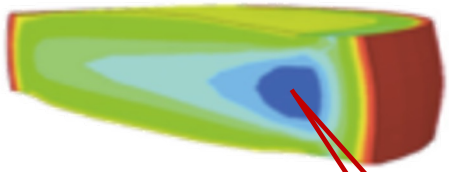
(Lotz et al, Global Spine J, 3, 2013)

Down to the IVD cell: entering the Matrix!

Carlos Ruiz Wills



Endplate changes

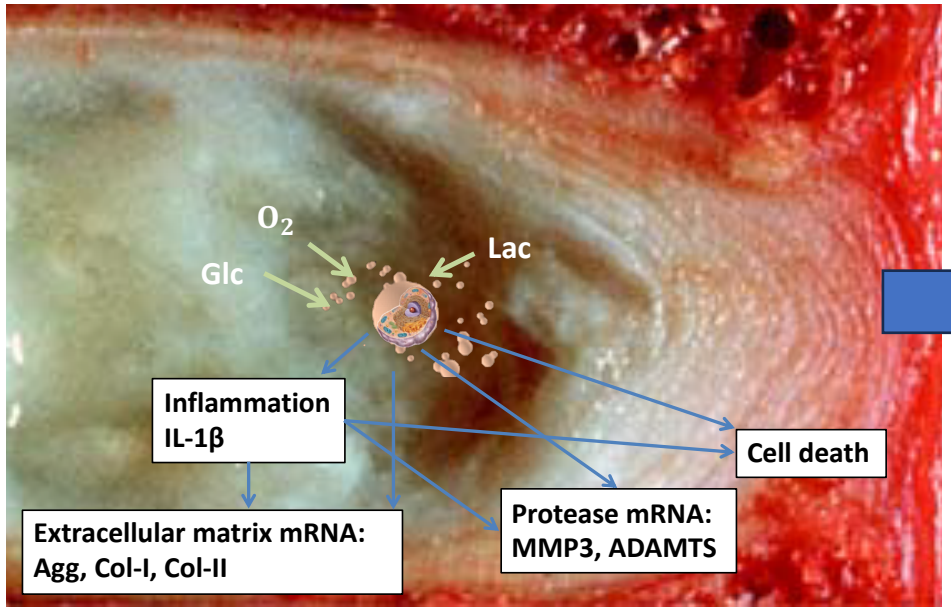


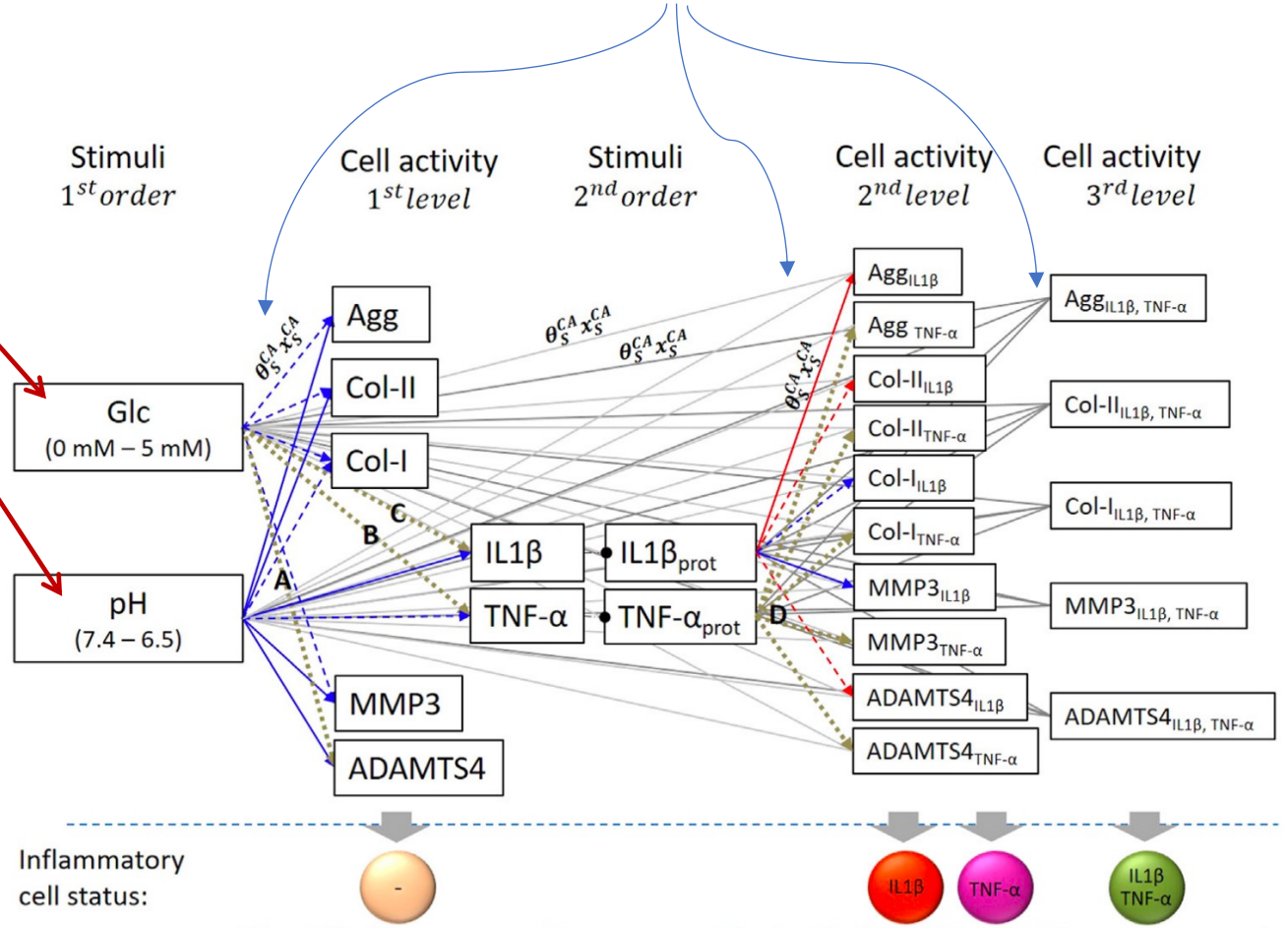
(Ruiz Wills et al, Front Physiol, 9, 2018)

Laura Baumgartner

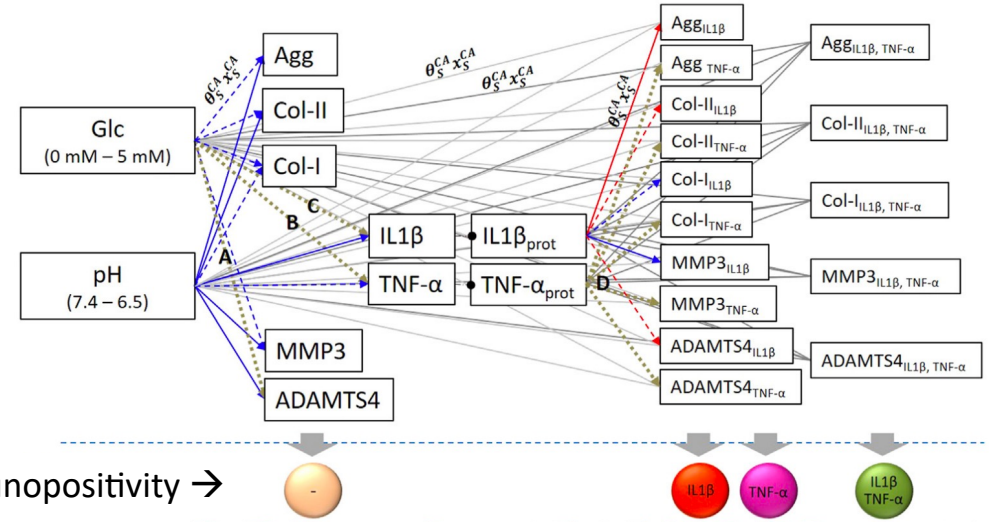
(Baumgartner et al, Bioinformatics, 37, 2021)
(Baumgartner et al, Front Bioeng Biotechnol, 9, 2021)
(Baumgartner et al, JOR Spine, 8, 2025)

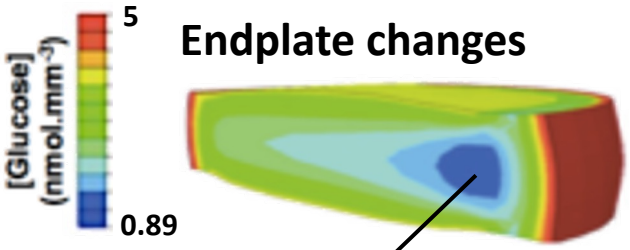
Parallel Network (PN) Modelling → Graph representation integrating *in vitro* nucleus pulposus cell culture measurements





Down to the cell

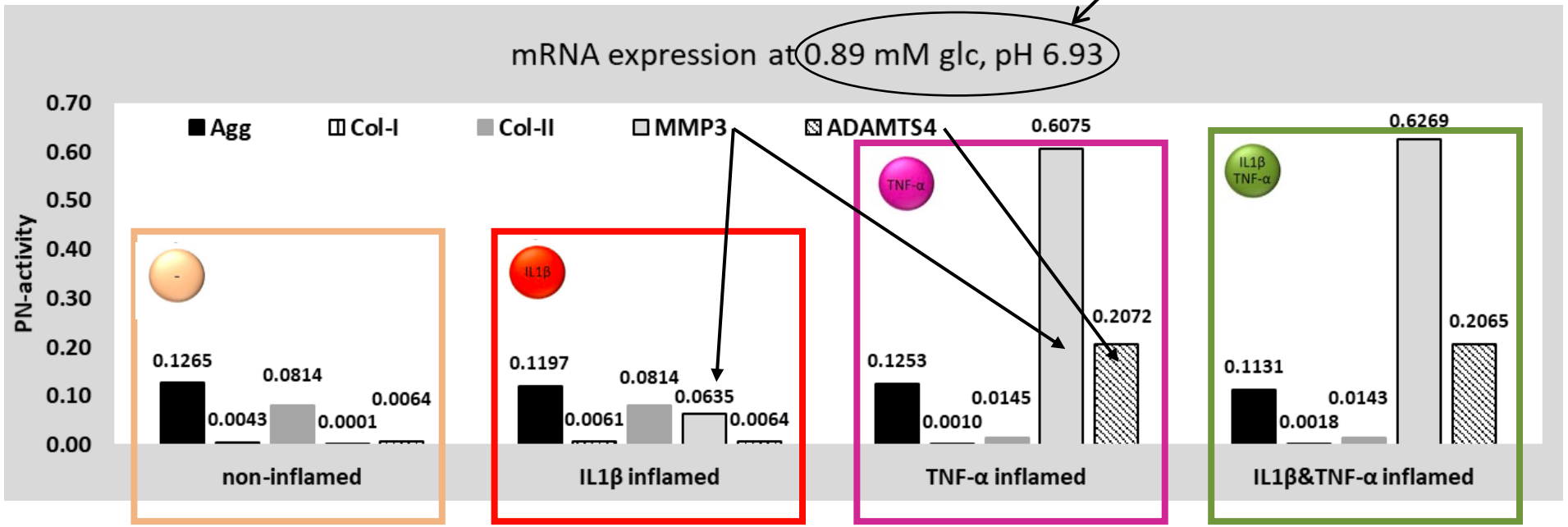




Endplate changes

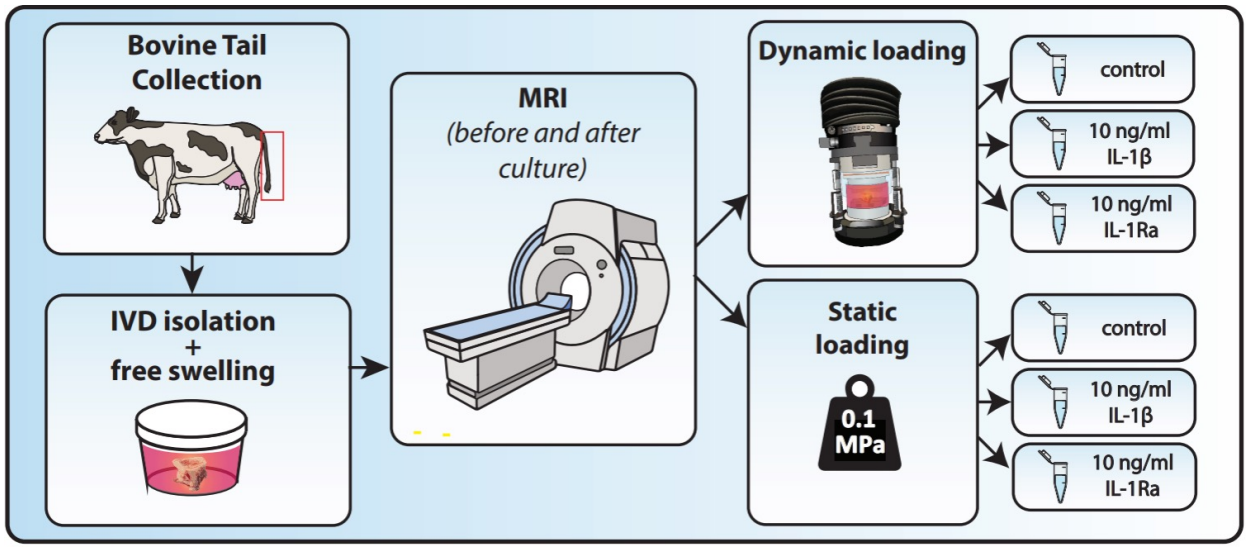
Laura Baumgartner

(Baumgartner et al, Front Bioeng Biotechnol, 9, 2021)



Metabolic stress represents a risk, if intervertebral disc cells are immunopositive for IL1-b and TNF

Organ ⇔ Cell: multiscale validation

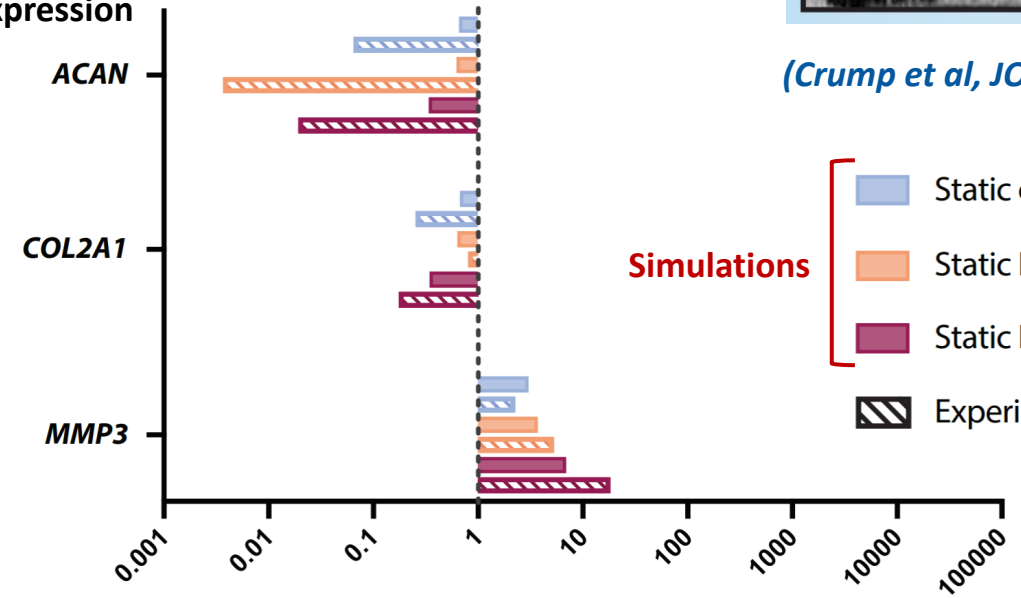


Katherine Crump

Benjamin Gantenbein

b UNIVERSITÄT BERN

Experimental & Simulated fold changes of mRNA expression

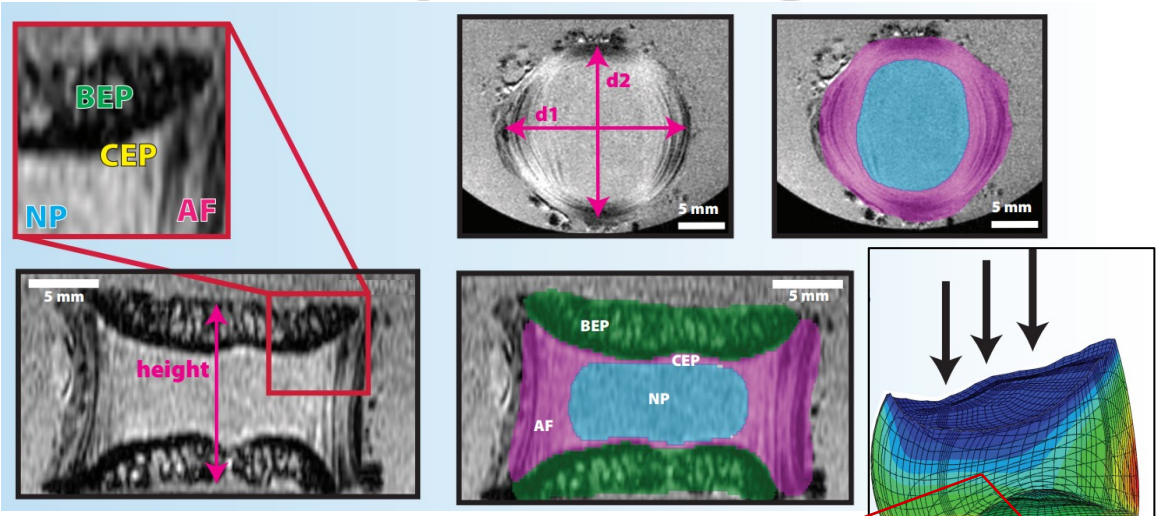


Simulations

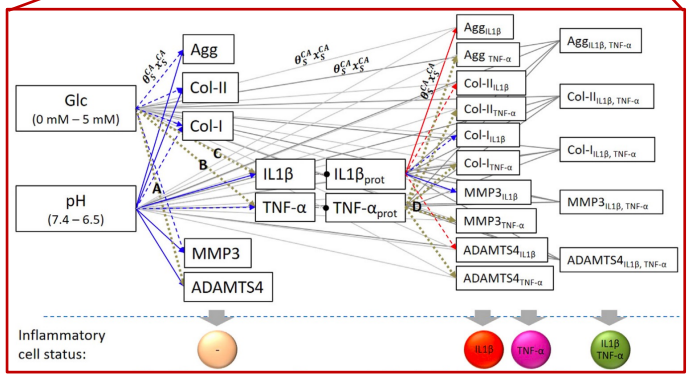
- Static control
- Static IL-1β
- Static IL-1Ra
- Experiment values

Estefano Muñoz-Moya

Laura Baumgartner

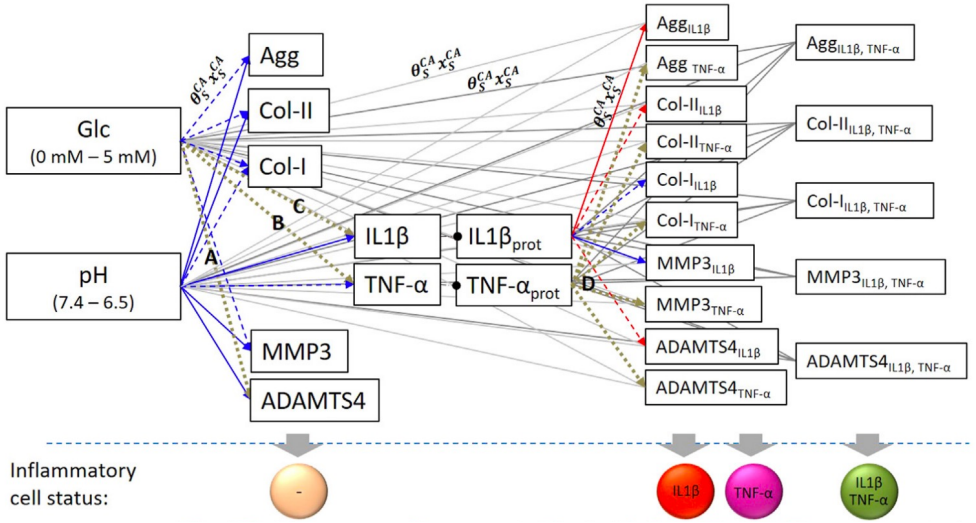


(Crump et al, JOR Spine, Under review)



Knowledge-driven modelling & biological scalability

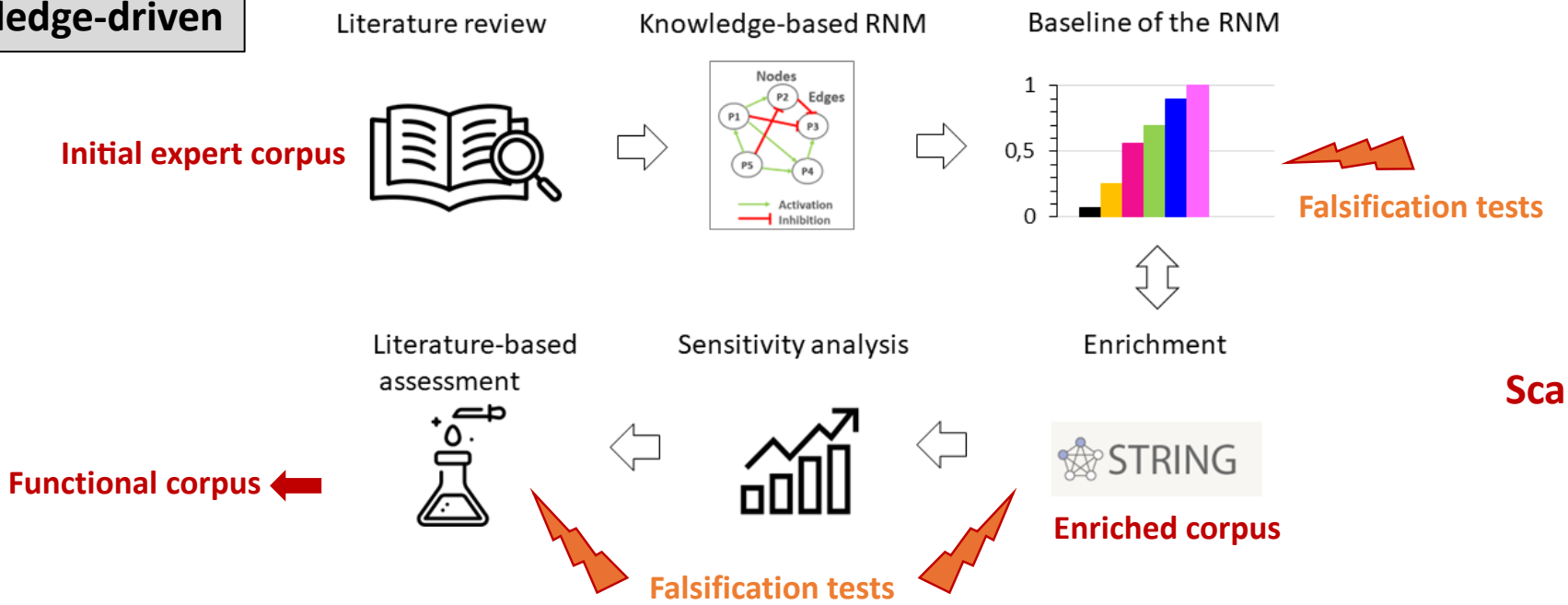
Data-driven



- Forward simulations
- No solver required (only one ODE)

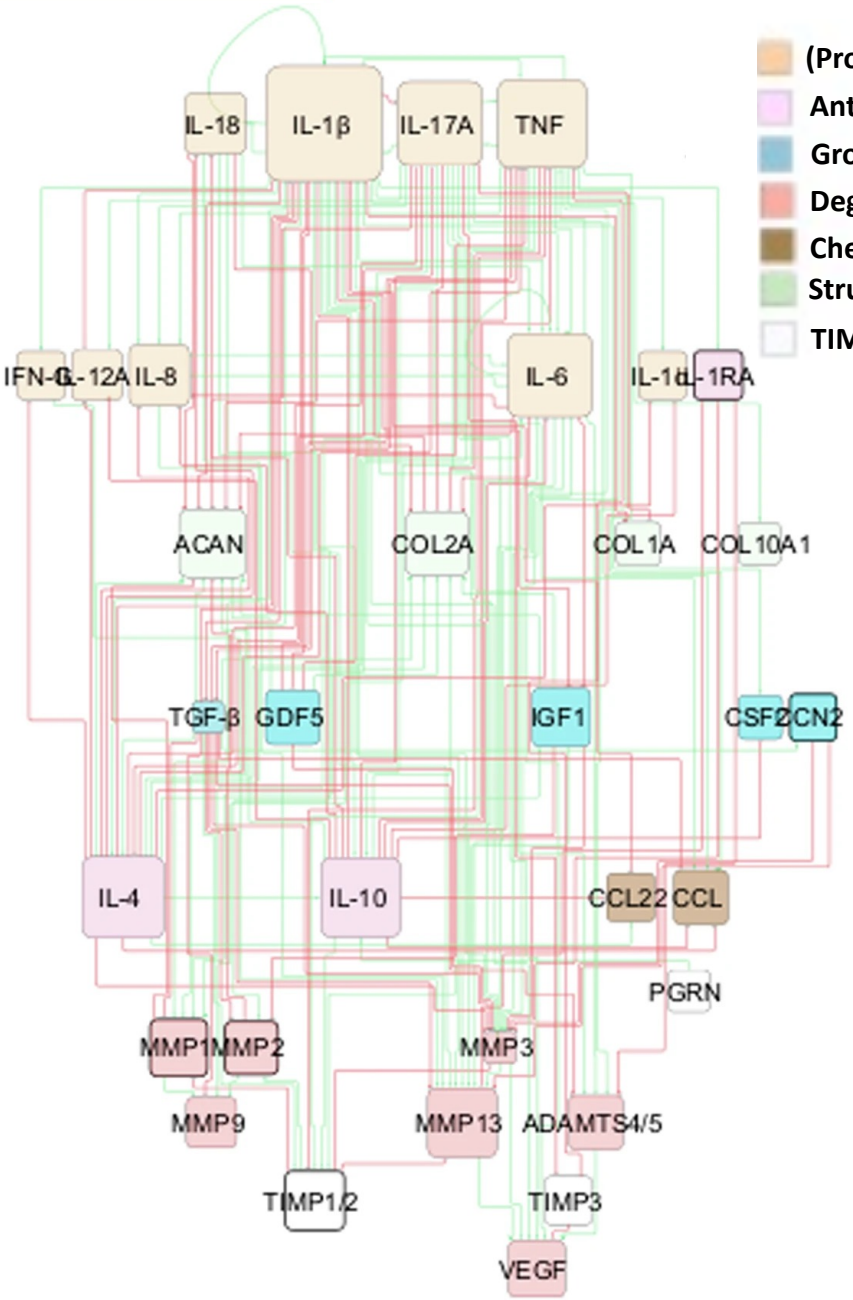
- **BUT:**
  - scalability Depends on *in vitro* experiments
  - Does not explain regulatory mechanisms

Knowledge-driven



Scalable modelling of cell activity

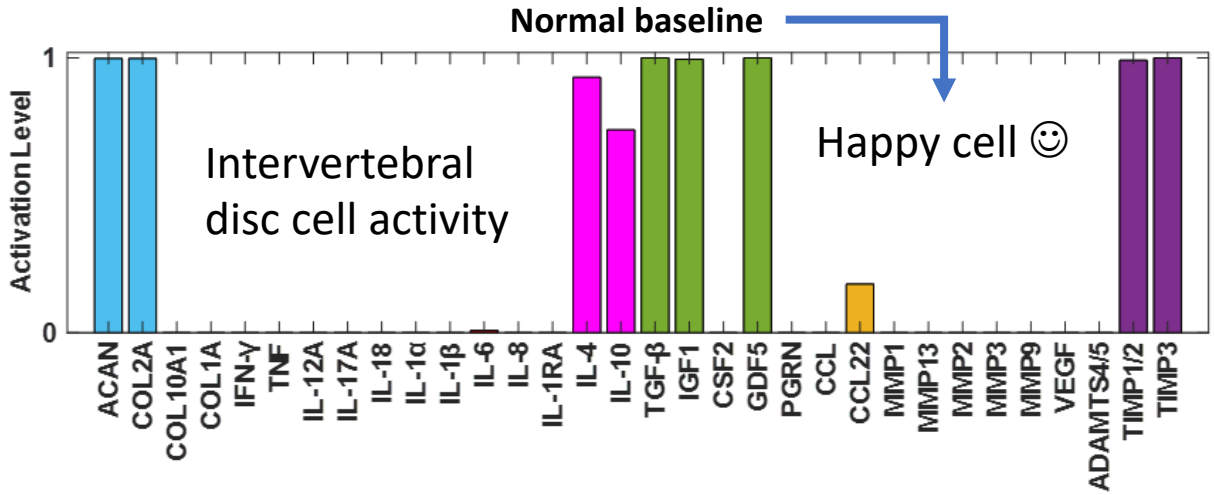
Knowledge-driven modelling



- (Pro-) inflammatory /catabolic cytokines
- Anti-inflammatory /anti-catabolic cytokines
- Growth factors
- Degrading enzymes /Angiogenic factors
- Chemokines
- Structural proteins
- TIMP /Others

(Tseranidou et al, npj Syst Biol Appl, 11, 2025)

Sofia Tseranidou

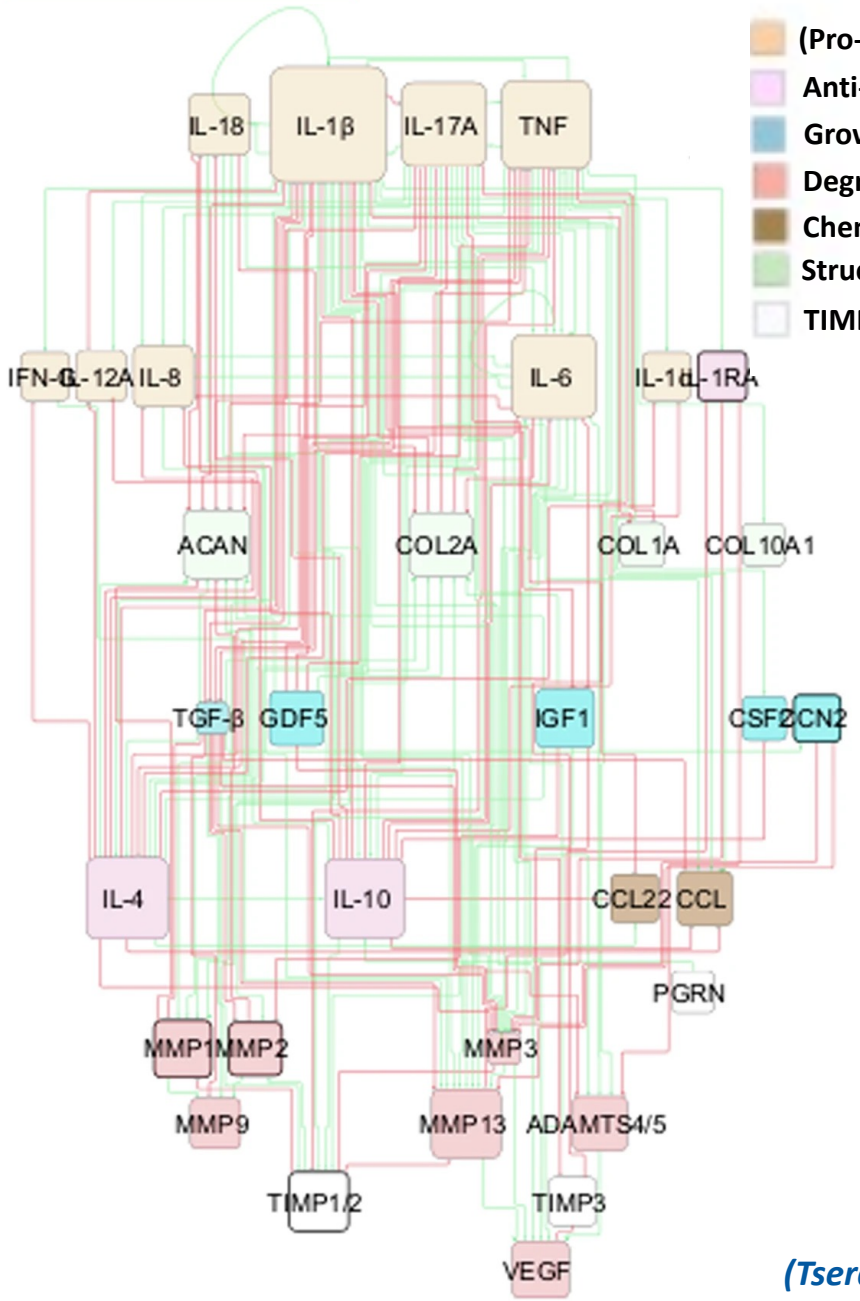


Pro-anabolic basal biological activity of the model ☺

Structural proteins | Pro-inflammatory cytokines | IL-1RA | Anti-inflammatory cytokines | Growth factors | Chemokines

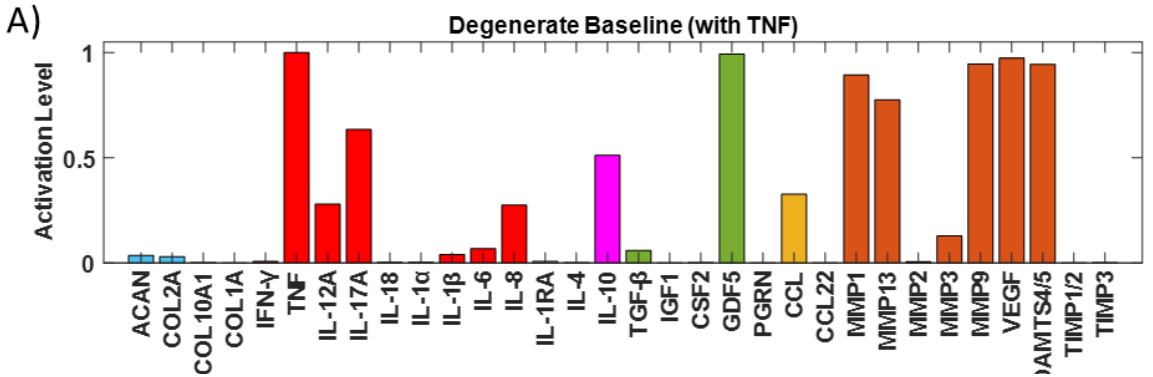
Degrading enzymes/Angiogenic factors | TIMPs

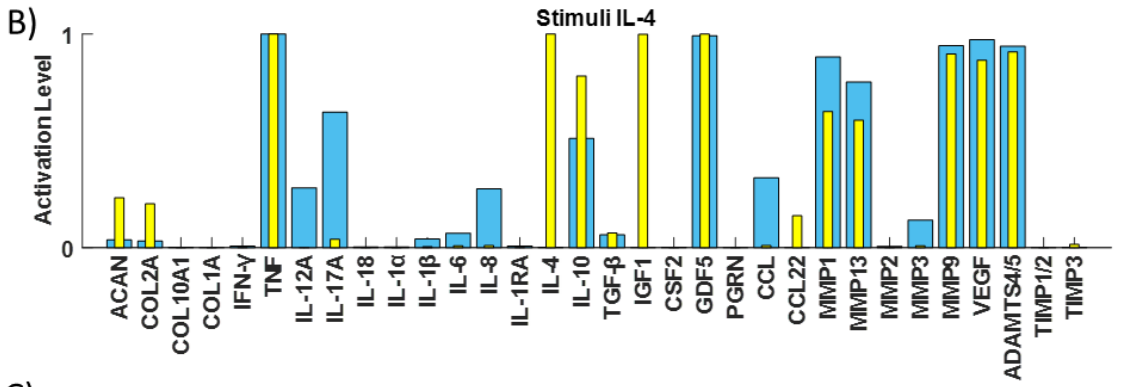
Knowledge-driven modelling

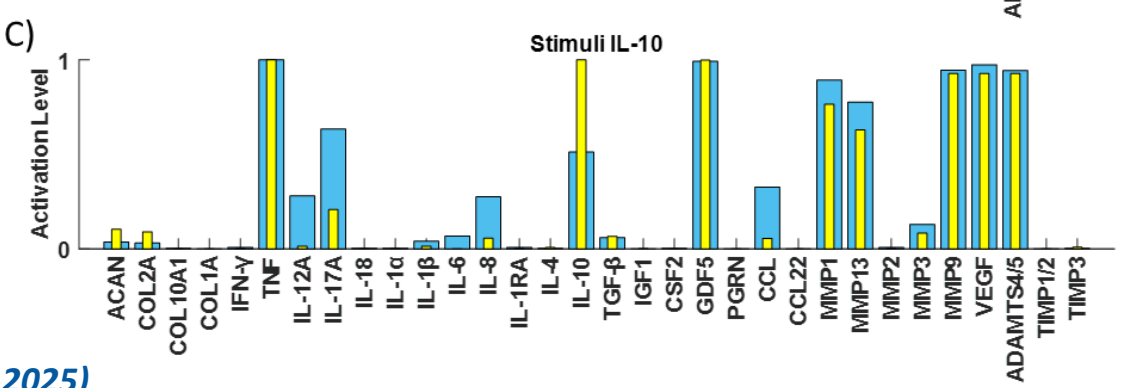


Anti-inflammatory cytokines might rescue cells affected by TNF, but not cells affected by IL1b

Sofia Tseranidou







(Tseranidou et al, npj Syst Biol Appl, 11, 2025)

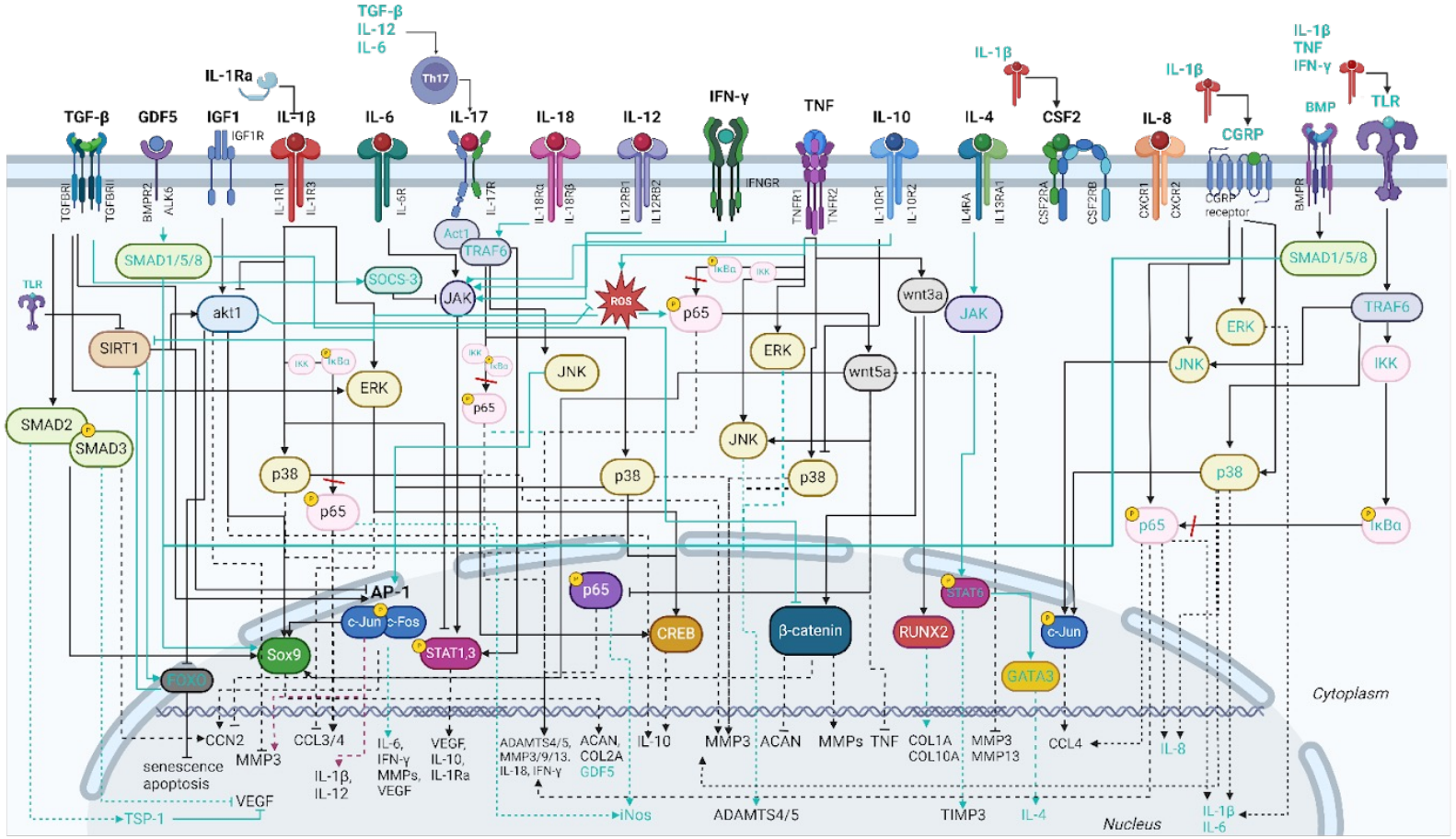
Knowledge-driven modelling

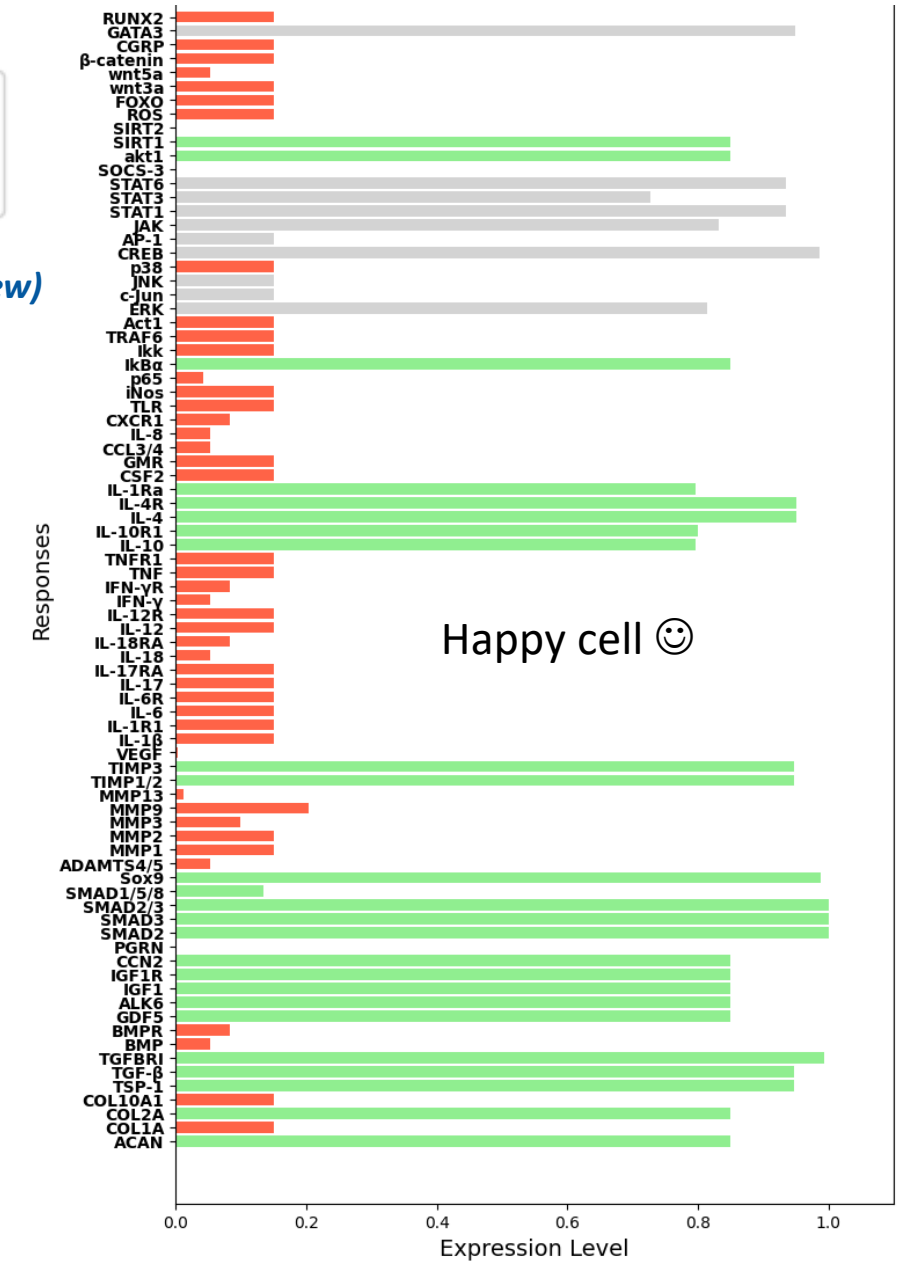
Sofia Tseranidou

Complete signalling pathways with no dead-ends

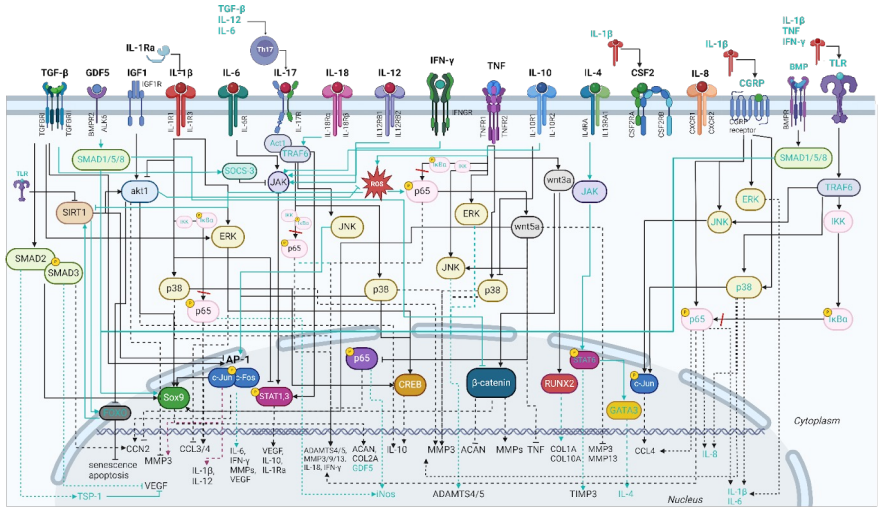
(Pro)-Anabolic Components
(Pro)-Catabolic Components
Dual/Uncertain

(Tseranidou et al, JOR Spine, Under review)





Knowledge-driven modelling: mapping of downstream signalling pathway



Sofia Tseranidou

Validation against phosphoproteomics measurements in stimulated cell culture

(Tseranidou et al, JOR Spine, Under review)

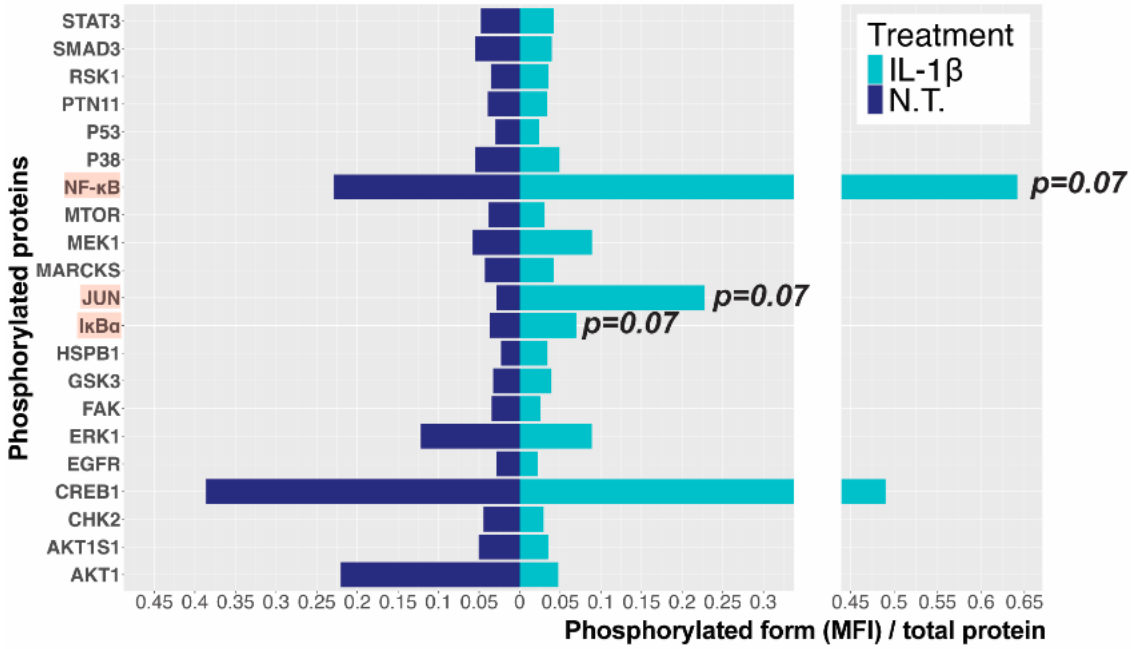
Exarchos Kanelis

Leonidas Alexopoulos

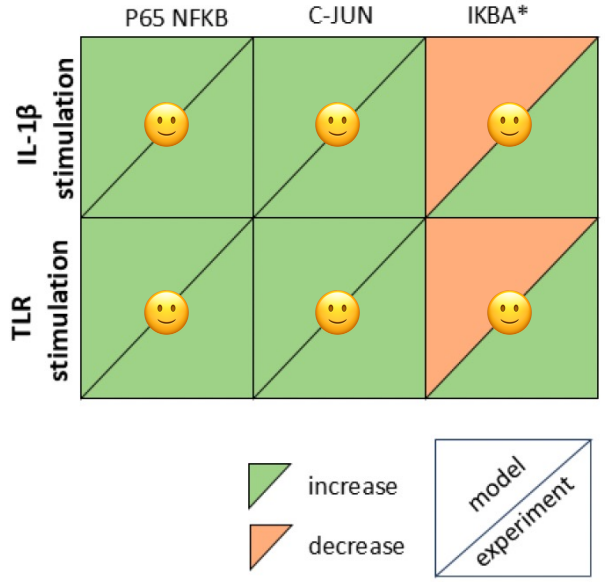
PROTAVIO

THE ART IN MULTIPLEXED ASSAYS

Phosphorylation changes



Relative activation



*Biological agreement implies that if IKBA increases in the experiment, it should decrease in the *in silico* model.

Few take-home messages

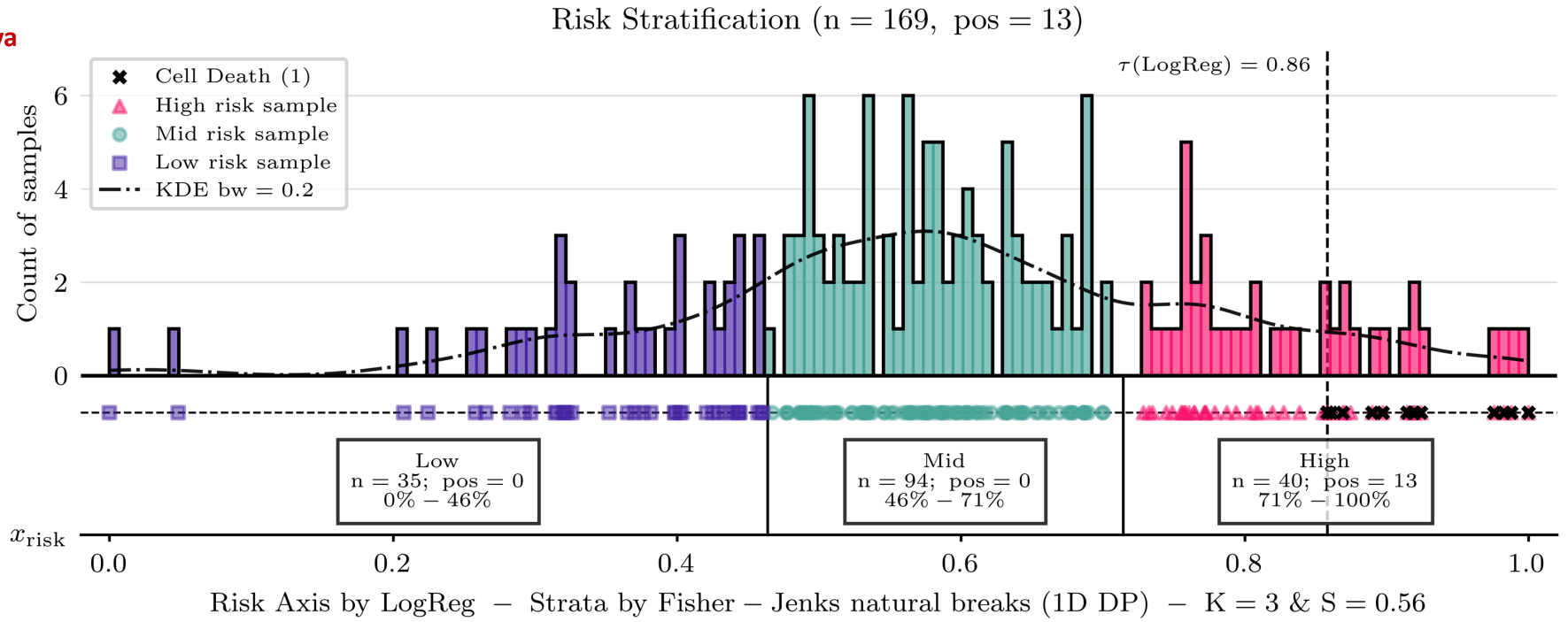
Systems mechanobiology models & simulations in the intervertebral disc have allowed to:

- Identify close relationships among intervertebral disc morphology (**innate phenotype**), mechanics and metabolic stress in the organ (**personalised models**)
- Degenerative phenotypes, such as endplate changes, strongly associated with low back pain (**Northern Finland Birth Cohort**), and with metabolic stress and key biological changes (***in silico***)
- Explore the mechanisms through wich harmful biological changes are controlled, as regulation pathways are described and may indicate local therapeutic targets (**regulatory network models ⇔ experimental models**)

Estefano Muñoz-Moya

Ongoing…

- Morphology-based **stratification of biological risk** defined in patient cohort (MySpine, n=169)
- To be incorporated into DSF and validated in Northern Finland Birth Cohort (n=1410)



Knee Joint Systems Mechanobiology

Measurements

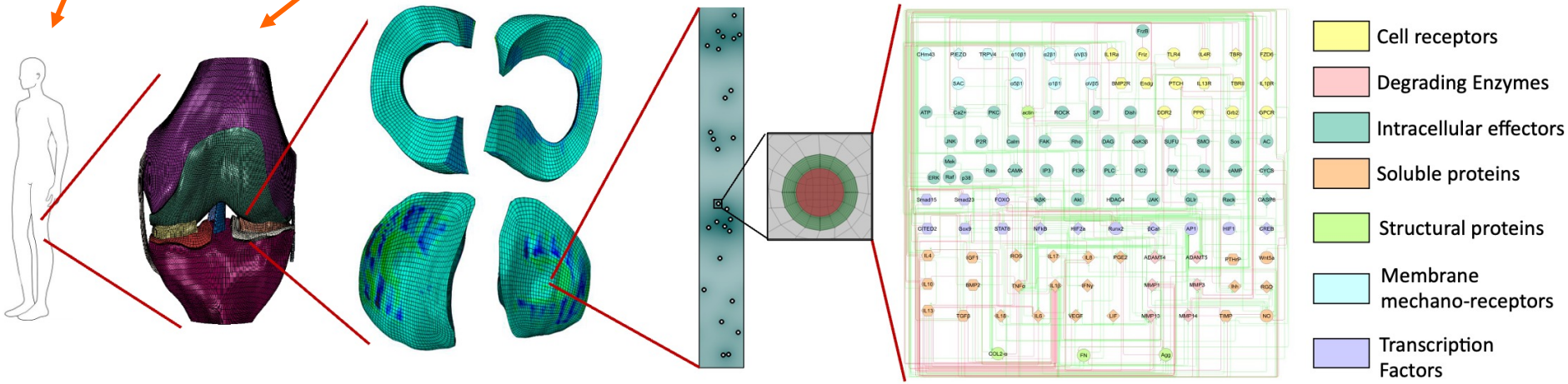
Motion capture

Medical images /tissue composition

Cell/ Tissue culture experiments, body fluids analyses

Proteomics, transcriptomics, single cell experiments

PHENOTYPES



ENDOTYPES

Multibody dynamics

Finite element modelling

Discrete systems Modelling

Network modelling

Organ forces

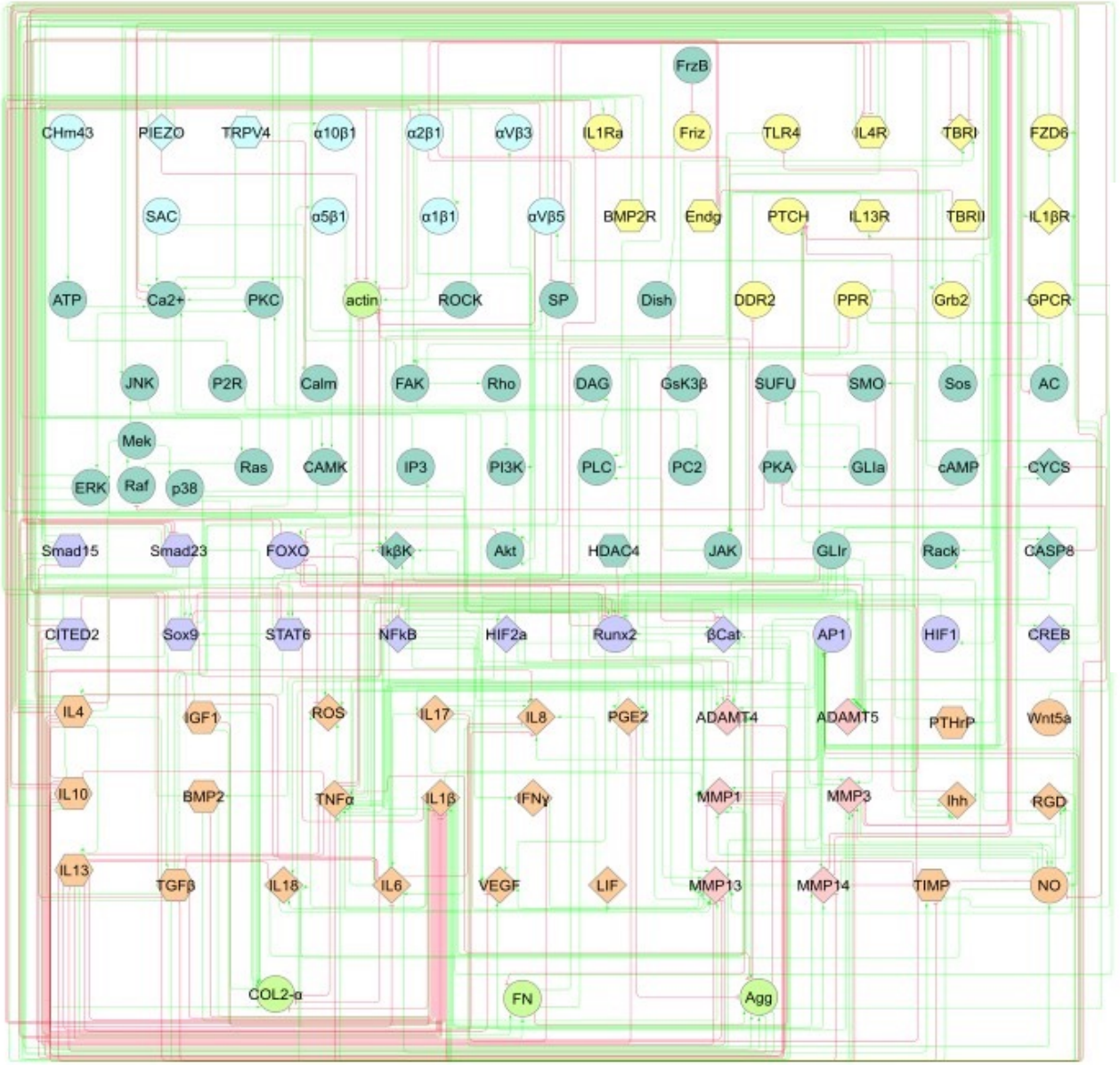
3D Tissue deformation, stress & mass transport fields

3D Multicellular (collective) behaviour, protein reaction

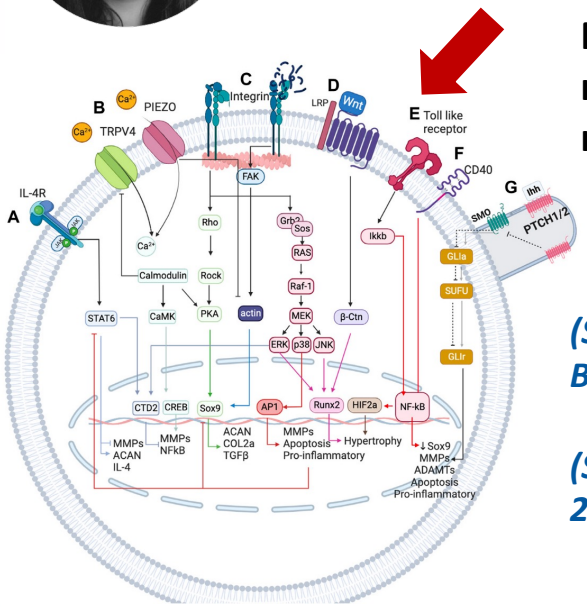
Multifactorial cell regulation, individual agent fate

Modelling & Simulation Workflow

Mechanosensitive knowledge-driven models



Maria Segarra-Queralt



Mapped articular chondrocyte mechanoreceptors and dowstream regulation

(Segarra-Queralt et al, Front Bioeng Biotechnol, 11, 2023)

(Segarra-Queralt et al, Phys Life Rev, 48, 2024)

Cell receptors

Degrading Enzymes

Intracellular effectors

Soluble proteins

Structural proteins

Membrane mechano-receptors

Transcription Factors

Crossing RNM simulations with patient data

Interpret clinical data of a cohort of women (HOLOA /STRATO, n=51, KL 2-3, age 55-70 y.o.) through the mining of clinical, biological and simulation data

Hospital del Mar Research Institute Barcelona

Jordi Monfort Faure

Laura Tio Barrera

input features

1. Clinical Data (CD) (n=51).

Patients that presented effusion with Luminex® technology

2. Synovial fluid (SF) data (subset n=25)

Chondrocyte network model [1]

3. Transcription factor (TF) data (subset n=25)

[1] Segarra-Queralt *et. al.*, **Front**. 2023

classification protocol

Feature selection: Pearson correlation (keep features r < 0.75)

Hyperparameter Tuning of C: 5-fold cross-validation

21 Classification tasks based on SVM [2,3].

× 7 CD as input features

× 7 SF as input features

× 7 TF as input features

Model interpretation

A. Identify importance based on the weight (ω) of the SVM.

B. ROC-AUC analysis

True

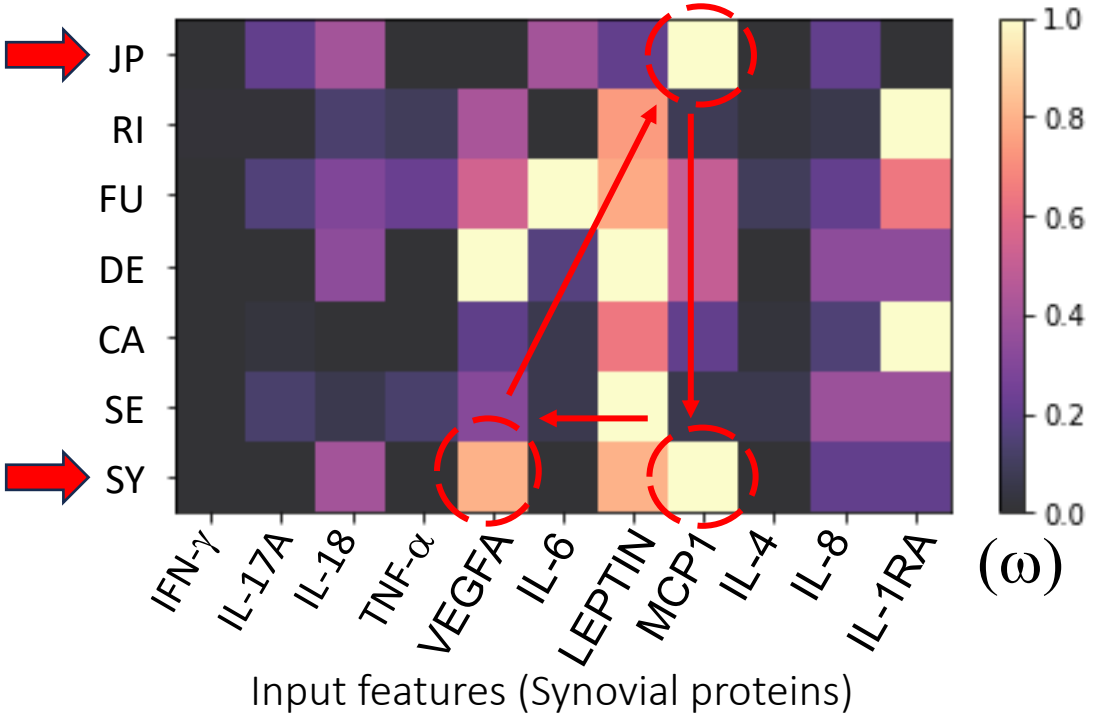
False

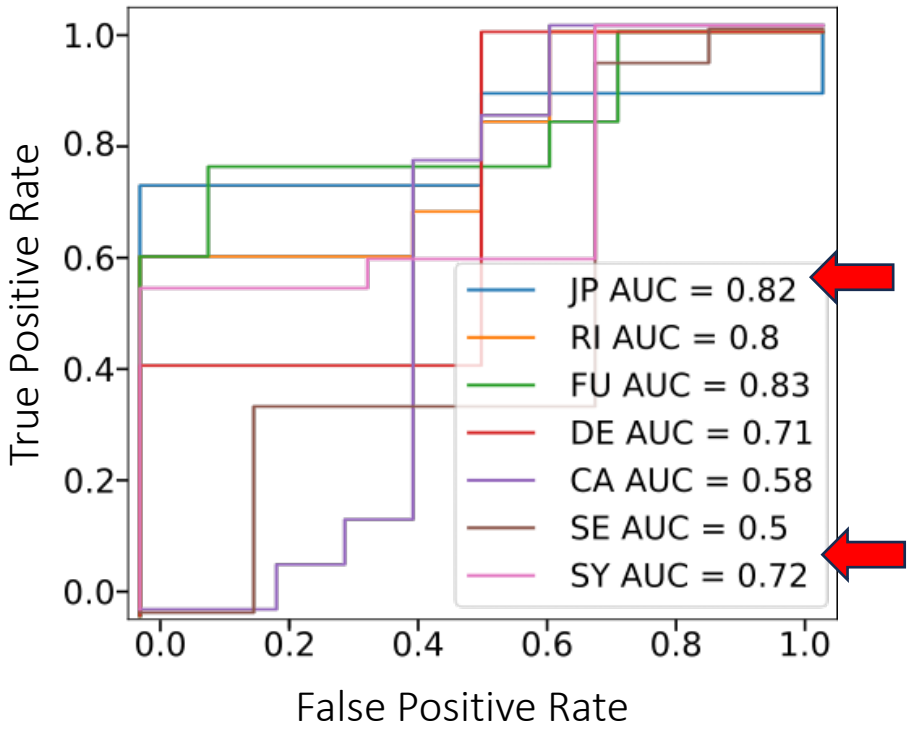
[2] Cortes C. et *al. Machine Learning* (1995), [3] Pedregosa F. et al. *Jou. Mach. Lear. Res.* (2011)

Maria Segarra-Queralt

(Segarra-Queralt et al. Sci Rep, 14, 2024)

Crossing Proteomics with patient data

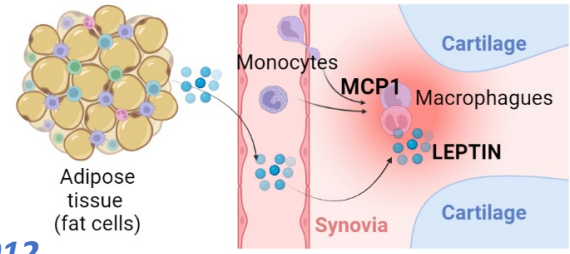




Maria Segarra-Queralt

(Segarra-Queralt et al. Sci Rep, 14, 2024)

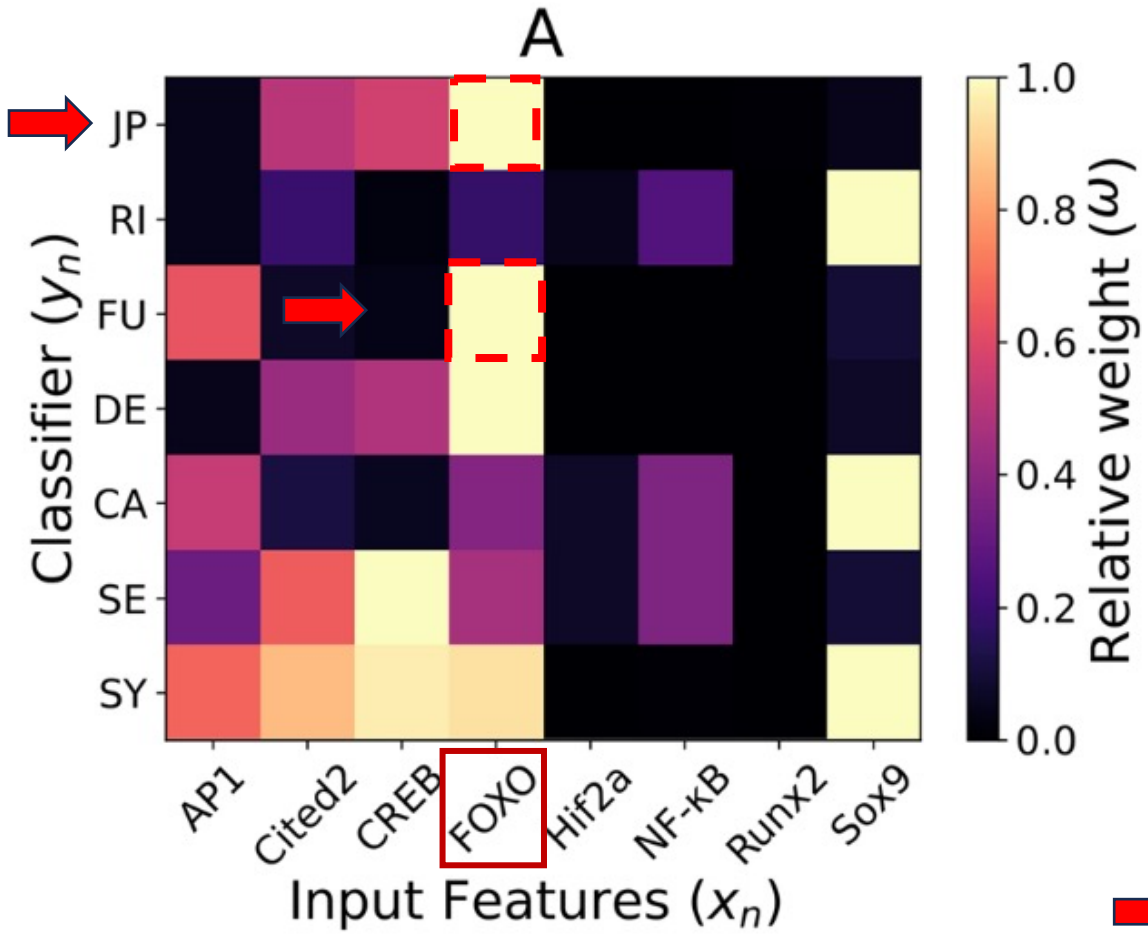
- Important role of Metabolic Syndromes (leptin) [1] & innate immunity (MCP1) [2].
- Macrophage infiltration in joints (+ angiogenesis) → pain + synovitis [3].

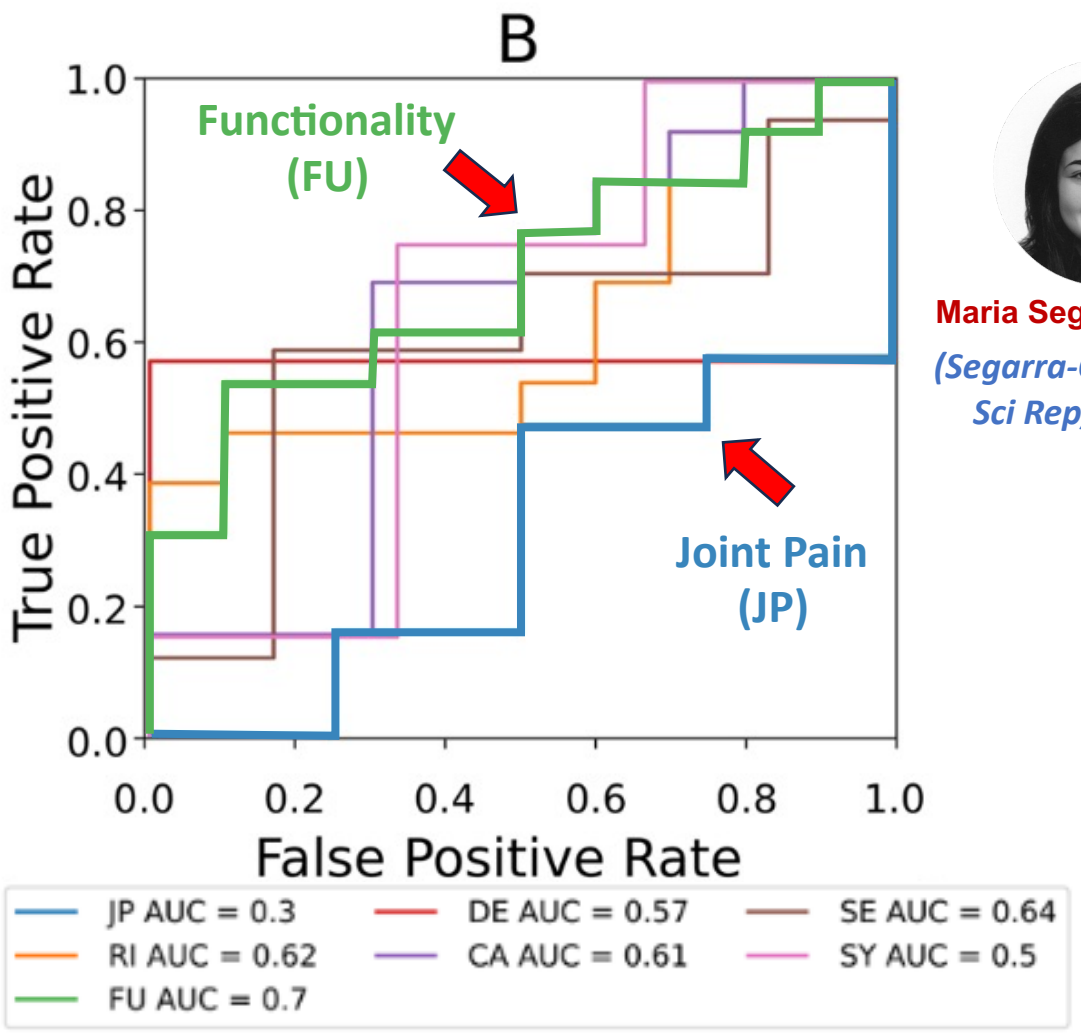


[1] Moilanen et al. Mediators Inflamm, 2009; [2] Daghestani et al. Arthritis & Rheumatology, 2015; [3] Scanzello et al. Bone, 2012

JP: Joint Pain (WOMAC)
RI: Rigidity (WOMAC)
FU: Function (WOMAC)
DE: Depression (HAD)
CA: Catastrophism (HAD)
SE: Sensitization (Pressure tests)
SY: Synovitis (Echography)
EF: Effucion (Echography)

Crossing Network simulations with patient data





Maria Segarra-Queralt

(Segarra-Queralt et al. Sci Rep, 14, 2024)

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BCN MEDTECH

TEAM

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Gemma Piella

BCN MedTech Biomechanics BMMB Mechanobiology Universitat Pompeu Fabra

INSILICOHEALTH

Marie Skłodowska-Curie Actions

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Health erc European Research Council Established by the European Commission

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA E INNOVACIÓN AGENCIA ESTATAL DE INVESTIGACIÓN

STRATO

Bone Strength

EXCELENCIA MARÍA DE MAEZTU

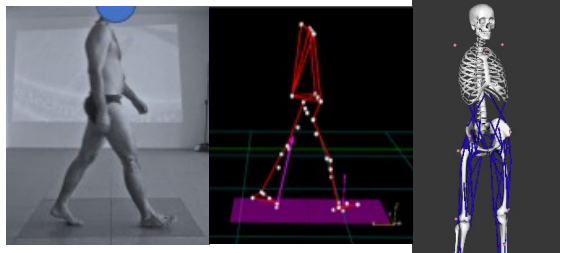
AGAUR Agència de Gestió d'Ajuts Universitaris i de Recerca

OsteoFX

SIMOSPINE

D-RISC

BODY FUNCTION (MOTION CAPTURE & ANALYSIS)



Left in 2025

Voluntary motions

Forces

ORGAN (FINITE ELEMENT MODELS)

Arrived in 2025

Local deformations

TISSUE (PHYSICS /MECHANO-BIOLOGY MODELS)

Cell environment

ZCC

Bone

Arrived in 2025

Tissue composition

CELL / MOLECULE (AGENT-BASED /NETWORK MODELS)

Non-physiological conditions

Physiological conditions

Underloading

Overloading

?

?

Rac-1

Mechanoreceptors (α5β1 integrin)

SP

SP

Left in 2025

MAPK

IKK

NF-κB

eNOS/iNOS

Thrombin

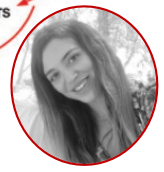
COX-2

PGE_2

HIF-1α

VEGF

MMPs / ADAMTS



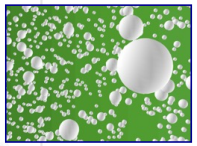
Anti-inflammatory cytokines IL-4, IL-10

MMPs ADAMTS

?

Cartilage destruction

Chondroprotection



DATA | TECH TRANSFER | COMPUTATION