Training session:
ENGAGING END USERS TO THE OACTIVE WORLD

OActive

Advanced personalised, multi-scale computer models preventing OsteoArthritis

COMBINING BIOMARKERS, BIOMECHANICS, AND ARTIFICIAL INTELLIGENCE FOR PERSONALIZED REHABILITATION AGAINST OSTEOARTHRITIS

29 May 2020

Ioanna Katsavou, AXIA Innovation

AXIA INNOVATION

UNIVERSITY of NICOSIA

Grant agreement 777159

SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

AGENDA

OActive

AXIA INNOVATION

This session is being recorded

INTRODUCTION

09:30 Welcome and opening remarks;
Agenda overview by the Coordinator and short presentation of OActive concept (10')
Kyriacos Felekkis, University of Nicosia
Ioanna Katsavou, Axia Innovation

BIOMARKERS AND BIOMECHANICS

09:40 Biochemical modelling and inflammation biomarkers (20')
Christos Papaneophytou University of Nicosia
& Ramon Messeguer, Leitat Technological Center

10:00 Behaviour modelling and environmental biomarkers (20')
Gianluca de Toma, SMARTEX & Thijs Swinnen, KULeuven
& Sotirios Tasoulis, CERTH

10:20 Biomechanical modelling of the knee (20')
David Britzman, Liverpool John Moores University

10.40 **30 MINUTES BREAK**

AGENDA

OActive

COMPUTATIONAL MODELLING & VALIDATION

11:10 Computational modelling empowered by big data and deep learning (20')
Dimitrios Tsaopoulos, CERTH

11:30 Using artificial tissues as test-bench for rehabilitation against osteoarthritis (20')
Roberto Di Gesù, RIMED

PERSONALISED INTERVENTIONS

11.50 Real time gait monitoring and retraining (20')
Georgios Giarmatzis, University of Patras

CLOSING POINTS

12.10 Training evaluation (5')
Ioanna Katsavou, Axia Innovation

12.15 Closing speech from the coordinator (5')
Kyriacos Felekkis, University of Nicosia

12.20 **END OF DAY**

AXIA INNOVATION

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No. 777159.

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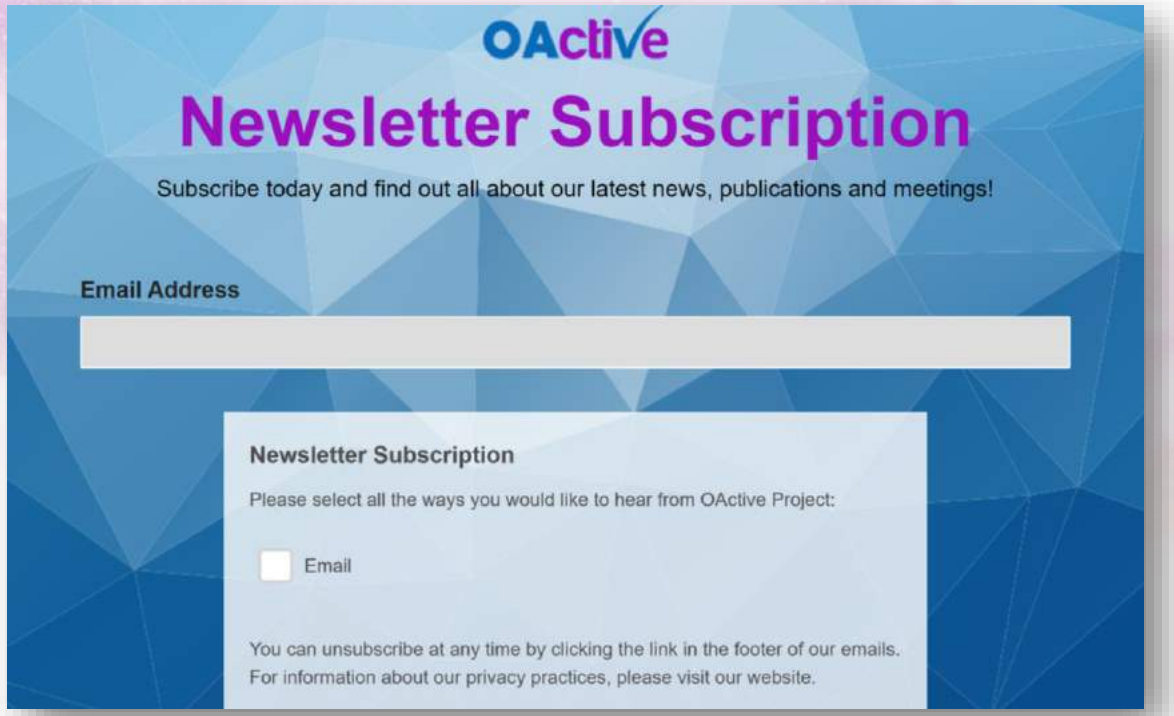
OActive



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Ioanna Katsavou, AXIA Innovation

AXIA INNOVATION

Project full title:

Advanced personalised, multi-scale computer models preventing OsteoArthritis

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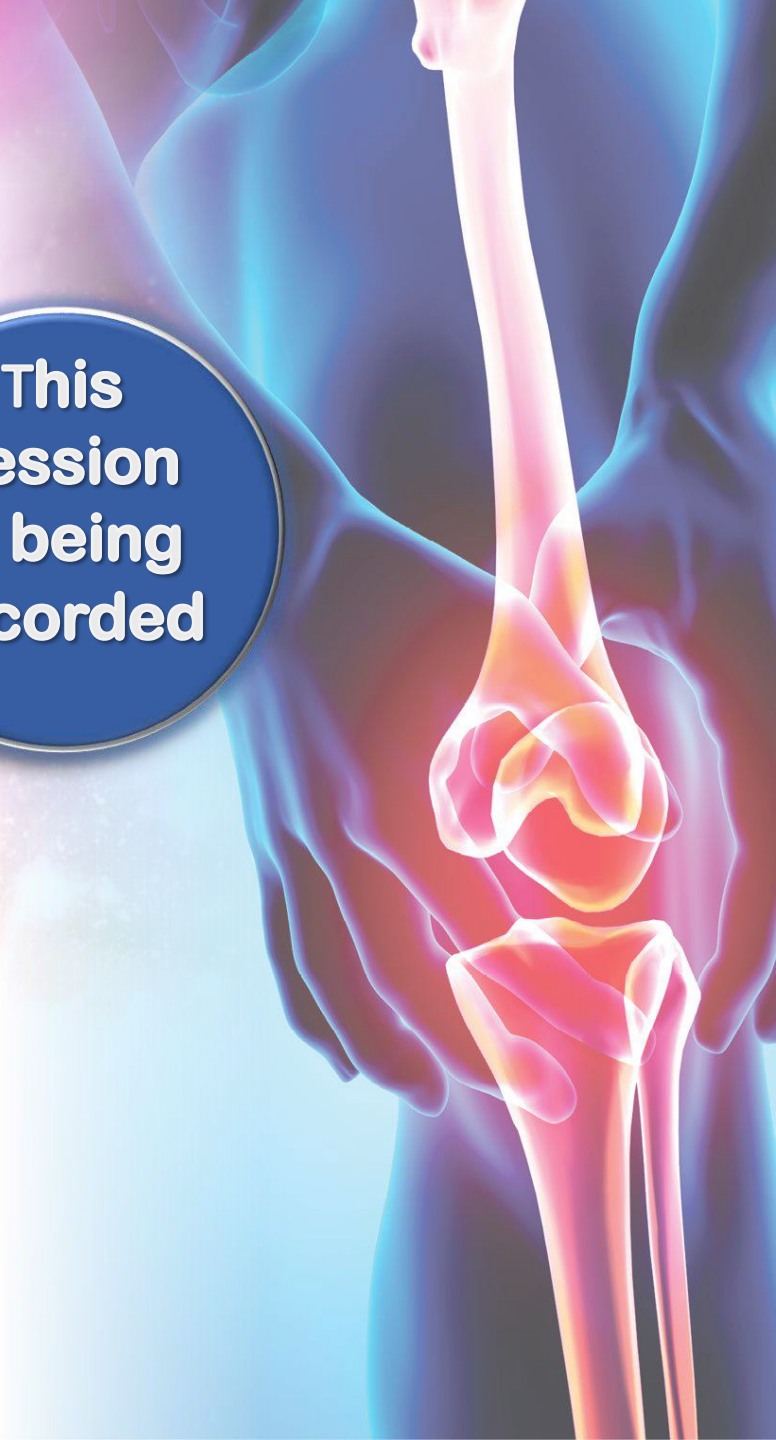

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Training session:

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Agenda overview by the Coordinator and short presentation of OActive concept

Kyriacos Felekkis, University of Nicosia

Grant agreement 777159

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OSTEOARTHRITIS (OA)

- Degenerative disease of the joints and the most common form of arthritis that causes pain and mobility limitations.
- Complex disease- biochemical and biomechanical factors are involved.
- Most important cause of disability in elderly population- ***up 30% of people>65***
- Knee is the most commonly affected joint.

OSTEOARTHRITIS (OA)

- Various risk factors are known: age, gender, hormonal status, BMI, family history, occupation, physical activity, past history of knee injury joint operation and depression.
- OA is not easy to define, predict or treat. Progression is poorly understood and that has resulted in a lack of prevention and treatment interventions.

OACTIVE APPROACH

- Multiscale holistic analysis
- Incorporate patient-specific information from various levels: molecular, cell, tissue and whole body.
- Integrated with information from other sources such as: environmental, behavioral and social risk factors.
- Generate robust predictors for new personalized intervention for delaying progression of the disease.

RESEARCH NETWORK

7 countries

5 SMEs

13 partners

8 RTDs

36 months

5M Euros

Agenda overview by the Coordinator and short presentation of OActive concept

Kyriacos Felekkis, University of Nicosia

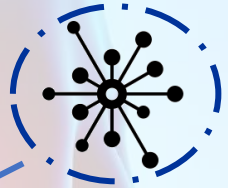
OActive

Biochemical modelling and inflammation biomarkers

Behaviour modelling and environmental biomarkers

Biomechanical modelling of the knee

Computational modelling empowered by big data and deep learning



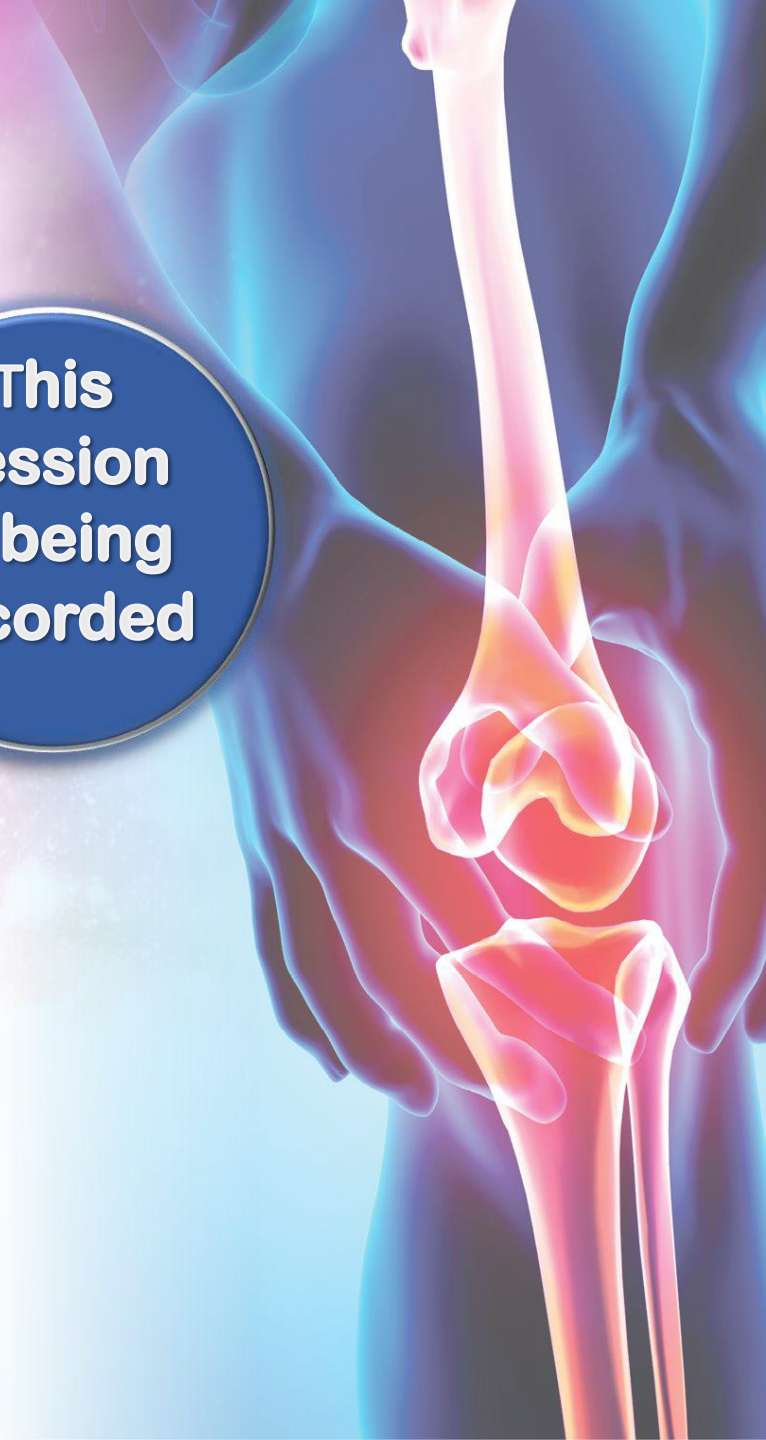
Using artificial tissues as test-bench for rehabilitation against osteoarthritis

Real time gait monitoring and retraining

Project full title:

Advanced personalised, multi-scale computer models preventing OsteoArthritis

OActive



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Training session:

ENGAGING END USERS TO THE OACTIVE WORLD

Biochemical modelling and inflammation biomarkers

Christos Papaneophytou, University of Nicosia &
Ramon Messeguer, Leitat Technological Center

Grant agreement 777159

SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

Biochemical modelling and inflammation biomarkers

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Biochemical modelling and inflammation biomarkers

OActive aims **to explore the potential of OA progress by measuring specific molecular markers (biomarkers) in serum and fluid samples.** The potential biomarkers include anabolic, catabolic as well as inflammatory molecules representing diverse biological pathways. The degree of articular inflammation will be associated with the disease progression and thus inflammation contributing to articular damage. To our knowledge, a comprehensive model correlating the secretion of OA biomarkers in the blood serum and the progress of the disease has not been developed yet.

The objective is to examine the relationship between biochemical markers for OA and clinical diagnosis. These results will be used for the development of advanced computer modelling and simulation tools in order to be used in early diagnosis or prognosis of the disease. Then, we work on:

- Clinical evaluation of patients.
- Determination of concentrations of selected biomarkers levels in serum of patients diagnosed with OA.
- Investigation of exosomal and microbiota biomarkers in terms of their relation with OA development and progression.
- Develop a method to correlate/compare concentrations of biomarkers with clinical diagnosis and OA stage.

1. Objectives of clinical studies

- The OACTIVE **scientific and technological objectives** focus on the development of computer-based **predictive models** and simulation for understanding the onset and progression of OA.
- **The aim of the clinical studies** is to collect data, examine the **relationship** between the **various risk factors** generated by the different information sources and the **clinical diagnosis** (physical examination of clinicians).
- The process involves **data collection in 3 different countries** involving:
  I. Patients that may develop OA (Spain)
  II. Athletes (Greece)
  III. Elderly people with developed OA (Cyprus)
  - These results will be used for the **development of advanced computer modelling** and simulation tools in order to be used in **early diagnosis or prediction of further progression of OA.**
    - Development of **personalized predictive models**
      - AR-based treatments will be proposed and evaluated towards the goal of **personalized medicine** in the cases of athletes and elderly people by modifying the gait pattern and/or proposing carefully selected exercises.

CLINICAL TRIALS

Clinical studies: Methodology

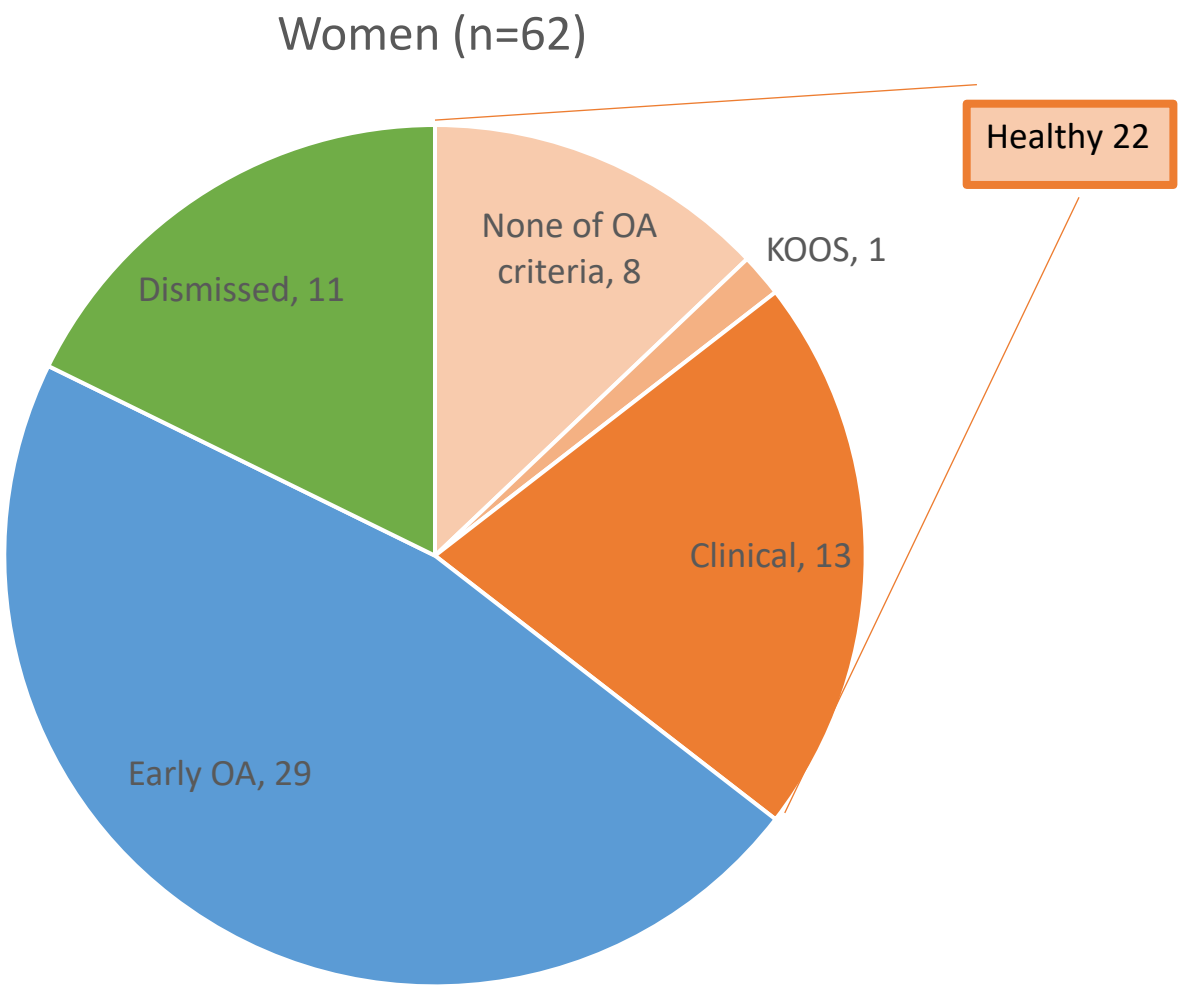
- **Approval** from the **National Bioethics Committees** (UNIC, HULAFE, and ANIMUS)
  - A **questionnaire** has been prepared to collect specific information from each patient during their recruitment.
  - A **consent form** has also been prepared:
    - Patients were asked to participate in this research project with a **voluntary decision** and they should be competent to understand what is involved.
- **Recruitment of patients** by clinicians:
  - Patients have been selected based **on criteria** established by the **American College of Rheumatology** (https://www.rheumatology.org/)
- **Actions to facilitate recruitment** (examples):
  - Leaflet written in simple language (that outlines the benefits for the participation to the study) has been disseminated to OA patients
  - A gait-analysis examination has been offered free of charge to all volunteers
  - Workshop to inform OA patients about the benefits they will have by participating in this study. (UNIC)
  - An email account has been provided for all the potential volunteers to be able to contact the researchers and ask any doubts (HULAFE and ANIMUS)
- **Collection of biological samples** (blood, urine, and fecal):
  - Protocols for samples collection and for handling/storage the samples have been prepared.
    - The anonymity of the patients was maintained.

2. Overview of OACTIVE clinical studies

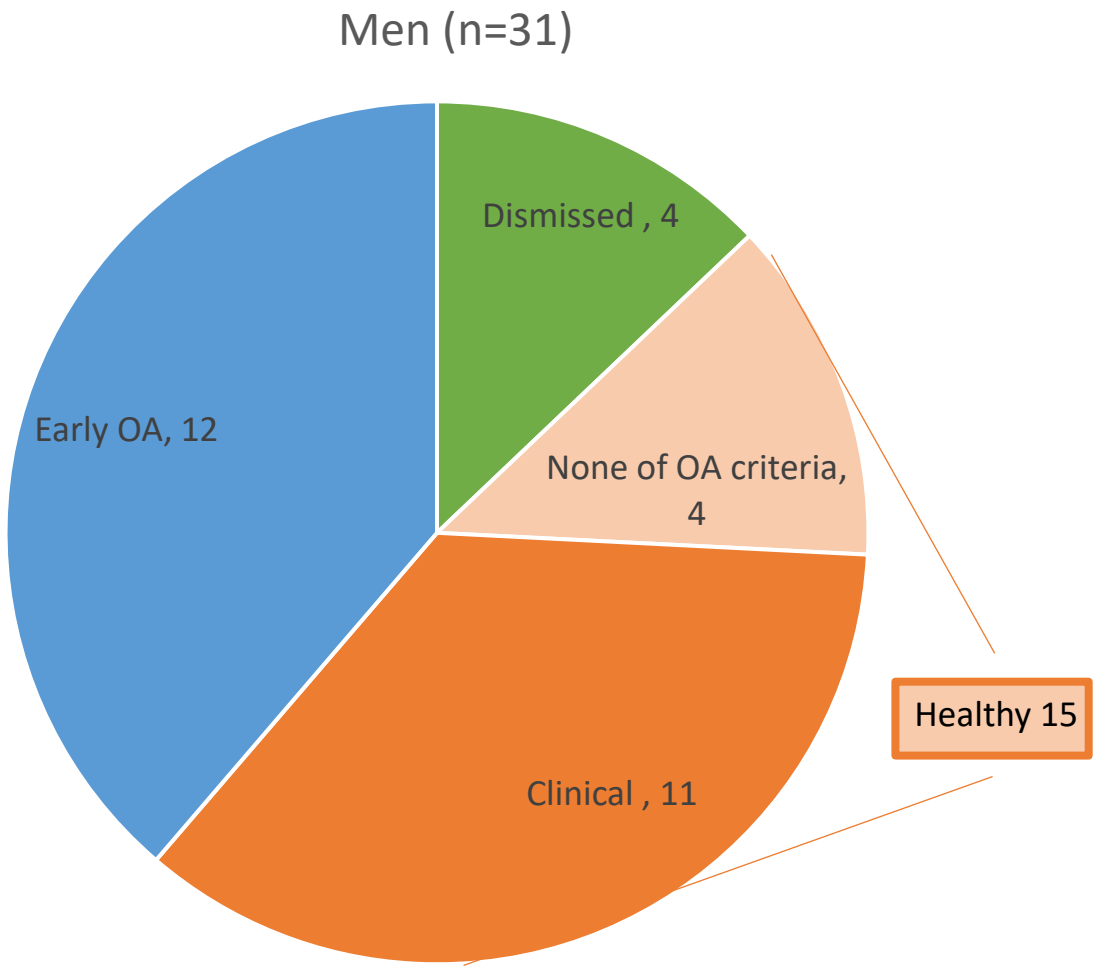
Partner responsible	HULAFE (Spain)	ANIMUS (Greece)	UNIC (Cyprus)
Targeted patients	Healthy ones in high risk of developing OA	Post-traumatic evaluation of athletes	Elderly OA patients (>50 y.o)
Population size	>100 patients	> 90 patients	>130 patients
Information sets	Behavior, imaging, Biochemical, Socio-economic. Target: data collection, examination of the relationship between various collected biomarkers for OA and clinical diagnosis (physical examination of clinicians).		
Outcomes	Development of advanced computer modelling and simulation tools in order to be used in:		
	Early diagnosis or prognosis of OA.	Post-traumatic OA prediction	OA prediction in elderly people
Intervention	-	Testing the efficiency of gait re-training and exercise intervention using (augmented reality) AR.	

CLINICAL TRIALS

Data collection results from HULAFE (Spain)



*Lacking 8 results from KL
*Lacking 9 results from KL



*Lacking 5 results from KL
*Lacking 1 results from KL
*Lacking 2 results from KL

BIOMARKERS

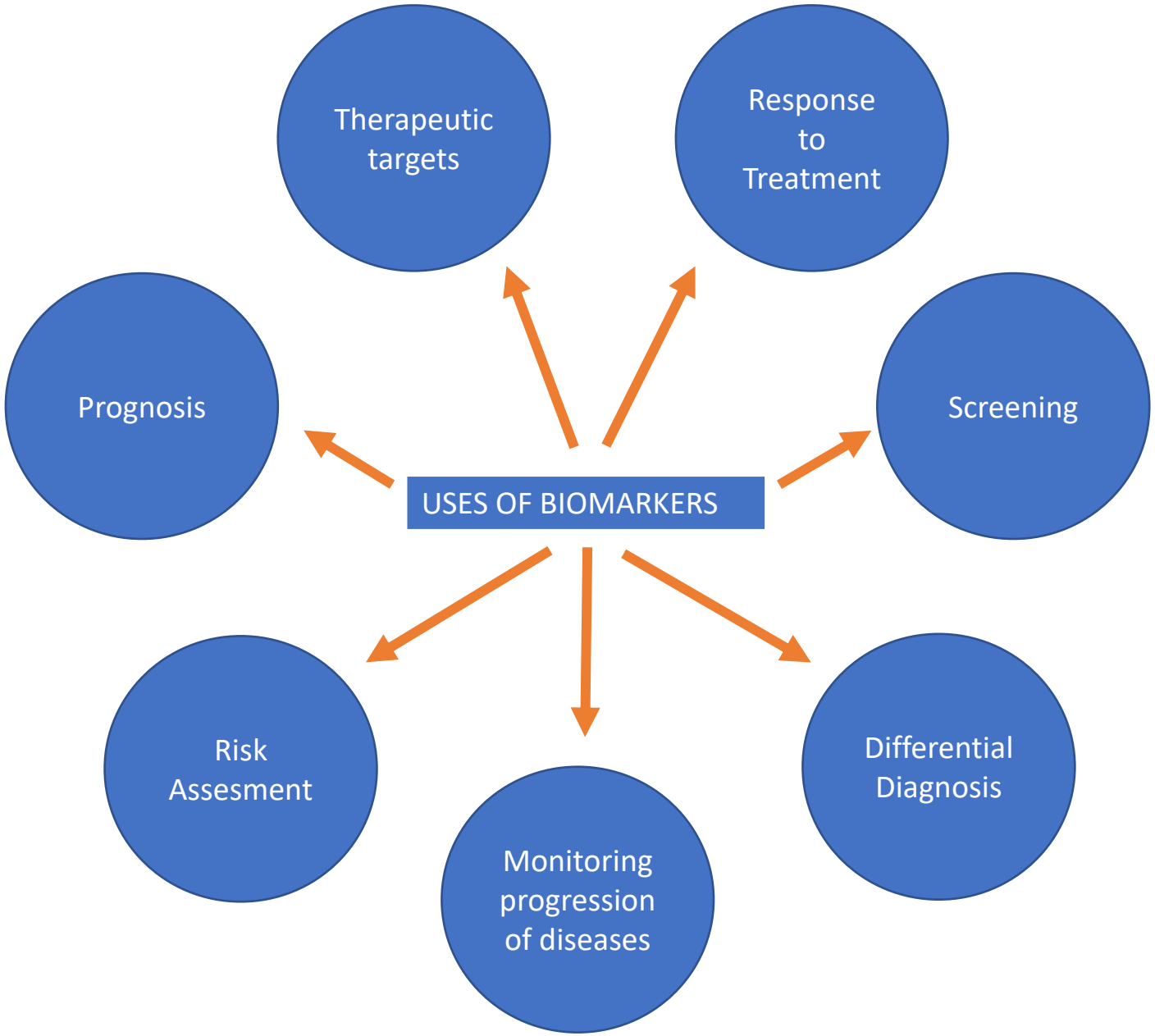
Subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly. Medical signs stand in contrast to medical symptoms, which are limited to those indications of health or illness perceived by patients themselves.

Biomarkers are by definition objective and quantifiable characteristics of biological processes. **They may but do not necessarily correlate with a patient's experience and sense of wellbeing**, and it is easy to imagine measurable biological characteristics that do not correspond to patients' clinical state, or whose variations are undetectable and without effect on health.

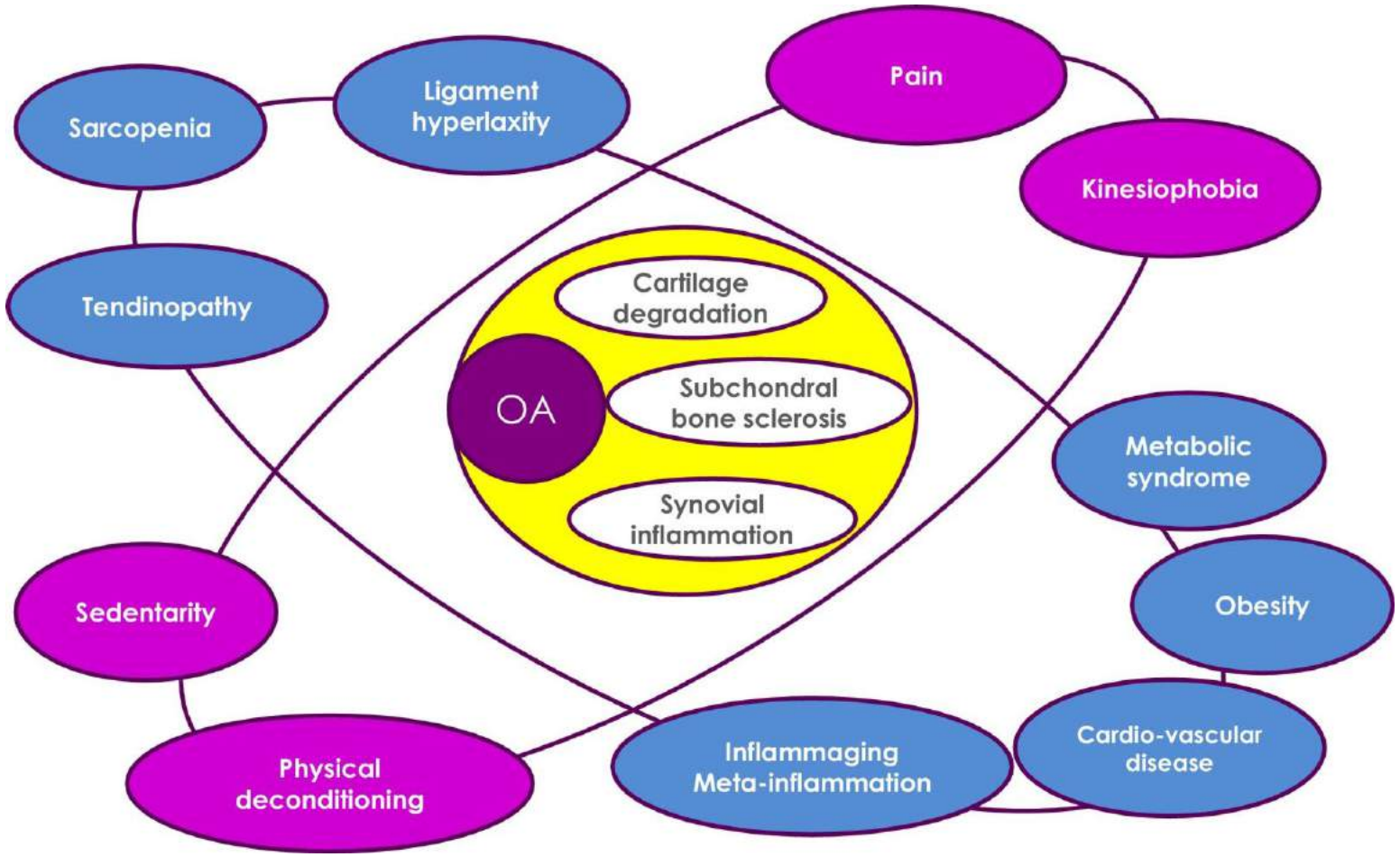
Clinical endpoints are the primary, and to some the only relevant, endpoints of all clinical research, and ultimately of all biomedical research. **Then, when used as outcomes in clinical trials, biomarkers are considered to be surrogate endpoints**. To be considered a surrogate endpoint, **there must be solid scientific evidence** (e.g., epidemiological, therapeutic, and/or pathophysiological) **that a biomarker consistently and accurately predicts a clinical outcome, either a benefit or harm**.

National Institutes of Health Biomarkers Definitions Working Group

BIOMARKERS


Therapeutic targets
Response to Treatment
Prognosis
Screening
USES OF BIOMARKERS
Risk Assesment
Monitoring progression of diseases
Differential Diagnosis

BIOMARKERS OSTEOARTHRITIS



There are many different disease or disorders that may cause the onset of osteoarthritis. This fact makes difficult the study and validation of new biomarkers since multicausality can create confusion and forces to increase the number of cases to be studied in order to verify a signature that can detect the propensity and development of OAR.

Henrotin et al (2016) . Annals of Physical and Rehabilitation Medicine Volume 59, Issue 3, June 2016, Pages 145-148

BIOMARKERS OSTEOARTHRITIS

1. Prognostic biomarkers of synthesis and degradation of bone and cartilage

- **BIPEDS classification scheme of biomarkers for Osteoarthritis** proposed by the National Institutes of Health
  - **Several molecular biomarkers** of bone and cartilage synthesis and degradation have an association with OA
    - Can be detected with commercially available ELISA kits

2. Inflammatory biomarkers

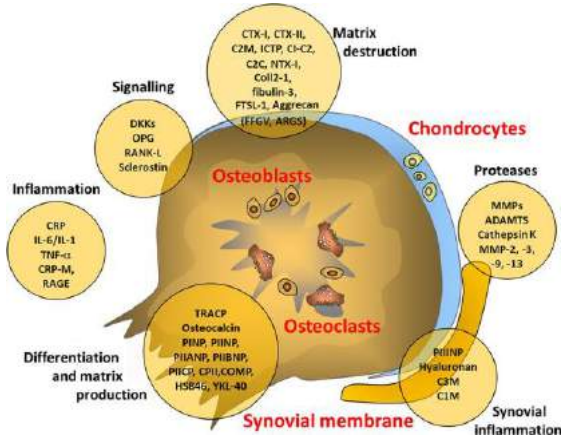
- OA was considered as a non-inflammatory joint disease
- However, specific inflammatory mediators are produced by articular tissues in OA and probably implicated in the pathogenesis and progression of the disease.

BIPED Classification of OA Biomarkers

Burden of Disease	ADAMTS4 ADAMTS5 ARGS Autotaxin C Col 10*	CCL3 CCL4 CD14* CGRP COMP*	**CRPM** **FGF21*** MMP1/3 Sclerostin **TNF-α**
Investigative	C2C*	**CD14***	
Prognosis Predictive	CD163*	hmwAPN*	**Leptin***
Efficacy			
Diagnostic	BDNF*	**Fib3-2***	

Bay-Jensen AC, Reker D, Kjelgaard-Petersen CF, et al. Osteoarth and Cart 2016; 24: 9-20.

I. Prognostic Biomarkers of Bone and Cartilage Degradation and Synthesis			
Biomarker	**Process**	**BIPEDS classification**	**Preliminary findings**
Serum COMP	Cartilage degradation	Knee: BPD	Elevated levels in Knee OA
Serum HA	Osteophyte burden, synovitis	Knee: BPED	
Serum CPII	Type II collagen degradation	Knee: D	
II. Inflammatory Prognostic Biomarkers			
Biomarker	**Presumed source**	**Biomarker subgroup**	**Preliminary findings**
IL-1β	Cartilage, Synovium, Bone	Cytokine/chemokines	Associated with in Knee OA pathogenesis
TNF-α	Cartilage, Synovium, Bone	Cytokine/chemokines	
IL-6	Peripheral blood leukocytes	Transcriptomic biomarkers	



Lotz et al. (2014), PostgradMedJ;90:171–178

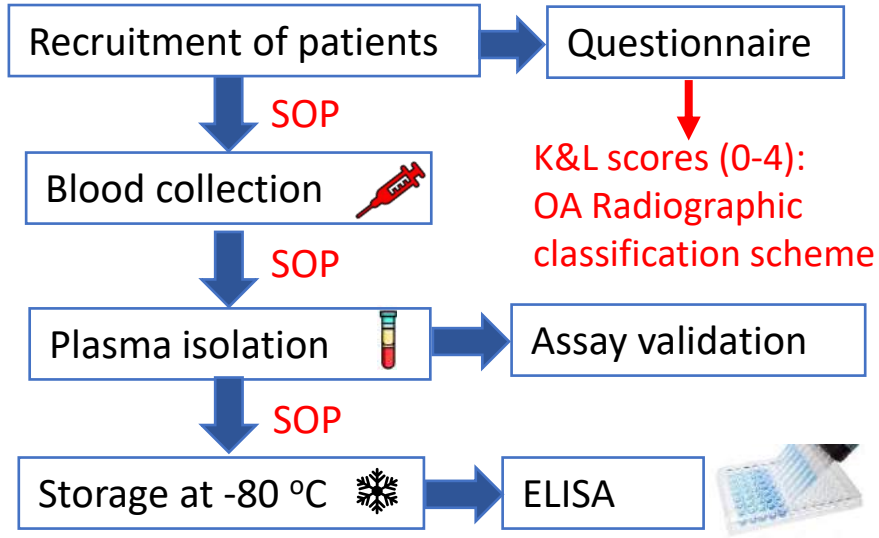
These biomarkers are no really predictive.

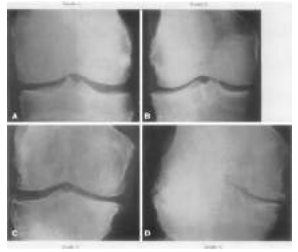
BIOMARKERS OSTEOARTHRITIS

OActive

Quantification of the 6 biomarkers in the plasma samples of OA patients

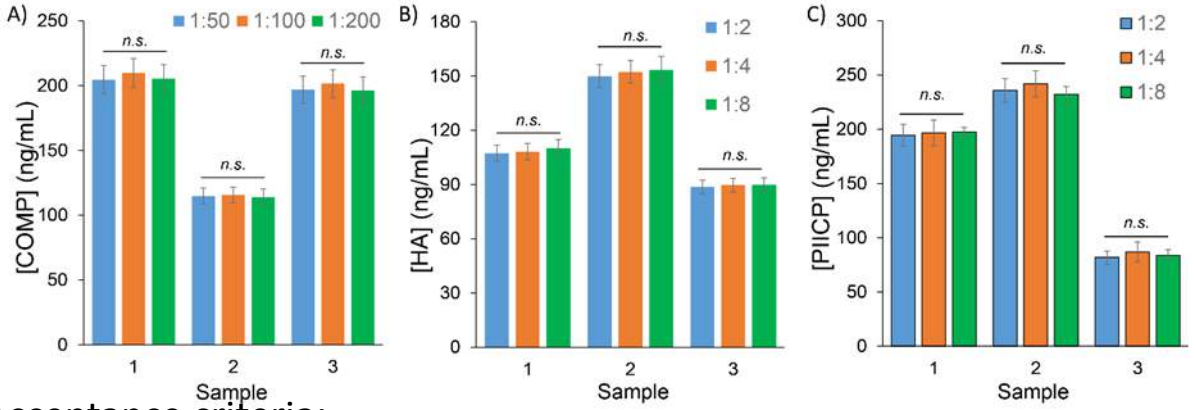
Protocol for blood collection storage, handing, and storage





Clin Orthop Relat Res. 2016, 474: 1886

Determination of the best dilution factor of the plasma samples

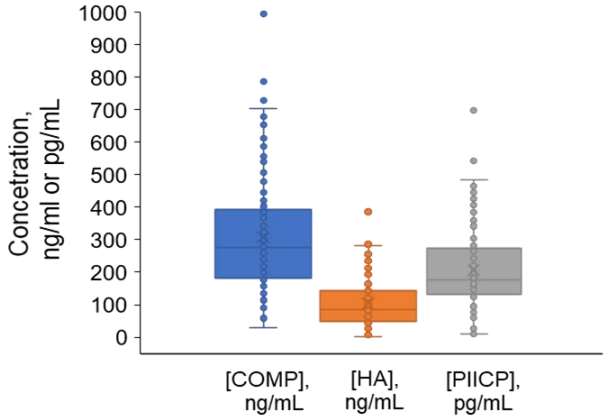


Acceptance criteria:

Inter-assay coefficient of variation (% CV) <15

Difference of among the different dilution factors < 20%

Quantification of the prognostic Biomarkers of Bone and Cartilage Degradation and Synthesis



The levels of the three inflammatory biomarkers (IL1-β, TNF-α, and IL6) in the plasma samples were below their respective Lower Limit of Quantification (LLOQ) of the selected methods

Correlation analysis between the biomarkers of bone and cartilage degradation and synthesis and severity of osteoarthritis (K&L score)

Biomarker	Mean ± SD (range)	K&L score			
		Left knee		Right knee	
		r	p	r	p
COMP (ng/mL)	306.6 ± 170.5 (29.5- 995.5)	0.3446	< 0.0001***	0.2834	0.0011**
HA (ng/mL)	102.2± 72.4 (1.64-385.9)	0.08253	0.3506	0.1940	0.0270*
PIICP (pg/mL)	205.3 ± 130.1 (8.77- 697.4)	0.07242	0.4129	-0.0146	0.8693

Correlation analyses between biomarker levels and severity of knee osteoarthritis (K&L score), was performed using Spearman's rank correlation coefficient (r). p-Values < 0.05 were considered statistically significant and are indicated with asterisks: * p < 0.05; ** p < 0.01, *** p<0.001

BIOMARKERS: Where, Which & How

OActive

CEREBROSPINAL FLUID

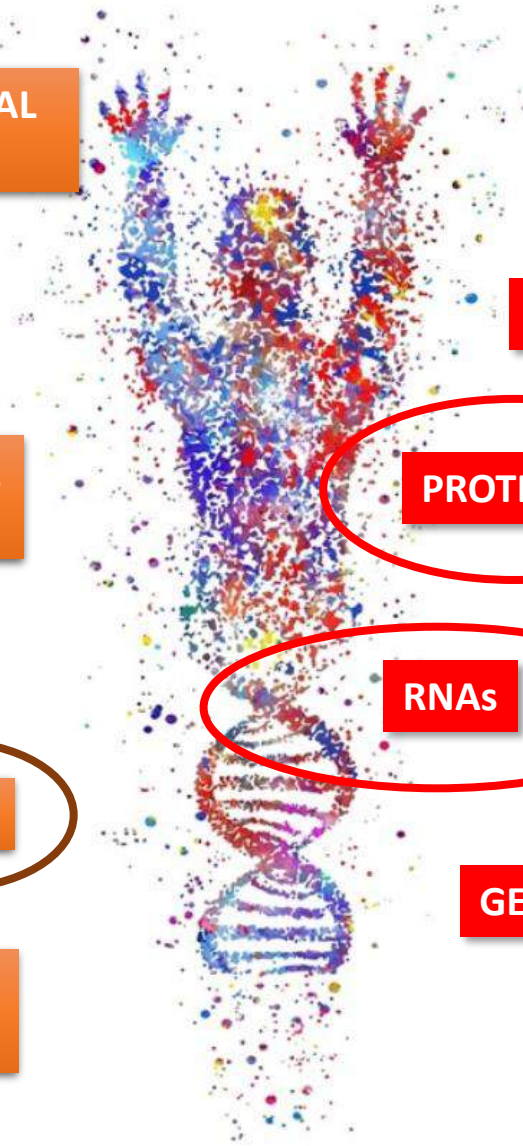
BLOOD

ORGANS & TISSUES

URINE

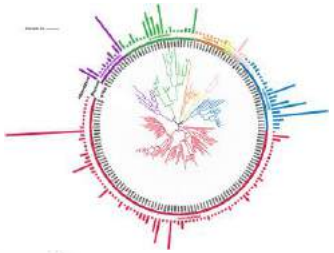
STOOL

SYNOVIAL FLUID



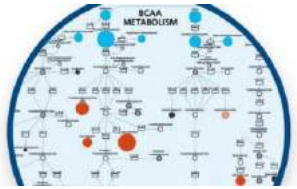
MICROBIOME

METAGENOMICS



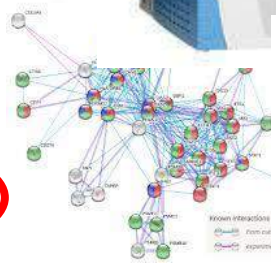
METABOLITES

METABOLOMICS



PROTEINS

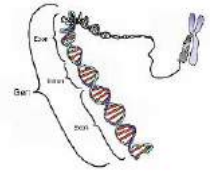
PROTEOMICS



RNAs

TRANSCRIPTOMICS

GENE



GENOMICS

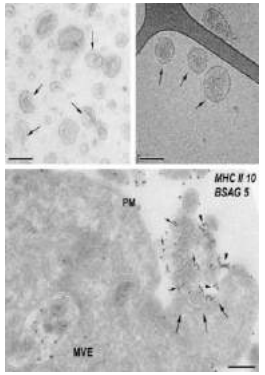
BIOMARKERS: Exosomes

Exosomes are small spherical to cup-shaped nanoparticles/membrane vesicles (30-100 nm in diameter). They are generated in the late endosomal compartment through inward budding of multivesicular bodies (MVBs). Exosomes are actively secreted by almost all cells through exocytosis either constitutively or through induction, under normal or pathological conditions, and in a dynamic, regulated and functionally relevant manner.

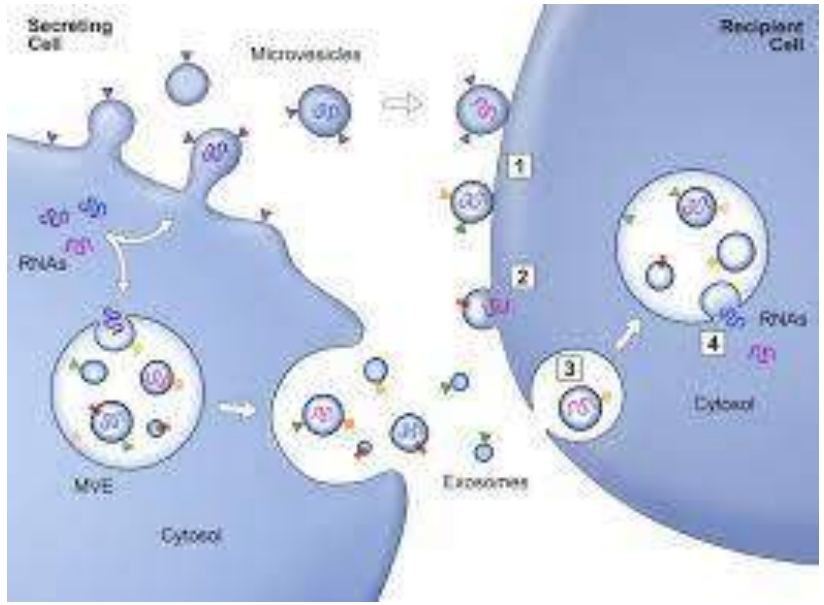
Exosomes have been isolated from a range of cell lines (primary, hematopoietic, cancer, and/or virus infected cell cultures) as well as from biological fluids (serum and plasma) and other body fluids (bronchoalveolar lavage fluid, pleural effusions, synovial fluid, urine, amniotic fluid, semen, saliva, etc).

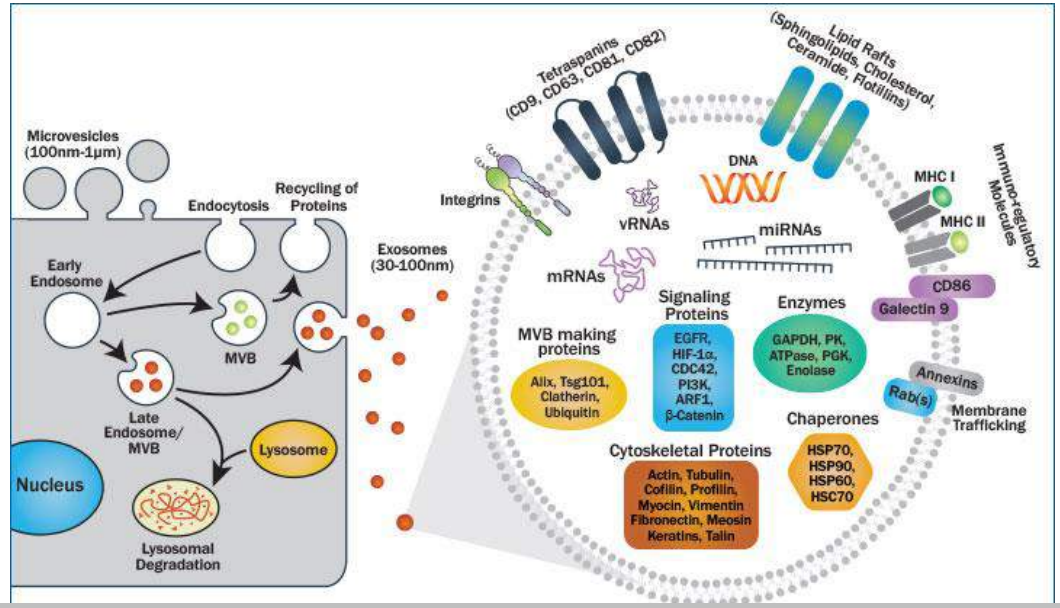
Exosomes have the ability to transfer information in the form of their contents, thus acting as signalosomes, either locally or by travelling to distant tissues wherein they influence various cellular functions. Some of the biological processes which are regulated by exosomes are:

- Cell metabolism and signaling
- Development and regeneration
- Cell adhesion and motility
- Immune response, inflammation
- Exchange of pathogenic proteins/organisms
- Tumor progression and metastasis
- Stemness and reprogramming
- Cardiovascular diseases
- Neural development, homeostasis and neurodiseases (Parkinson's, Alzheimer's and ALS)

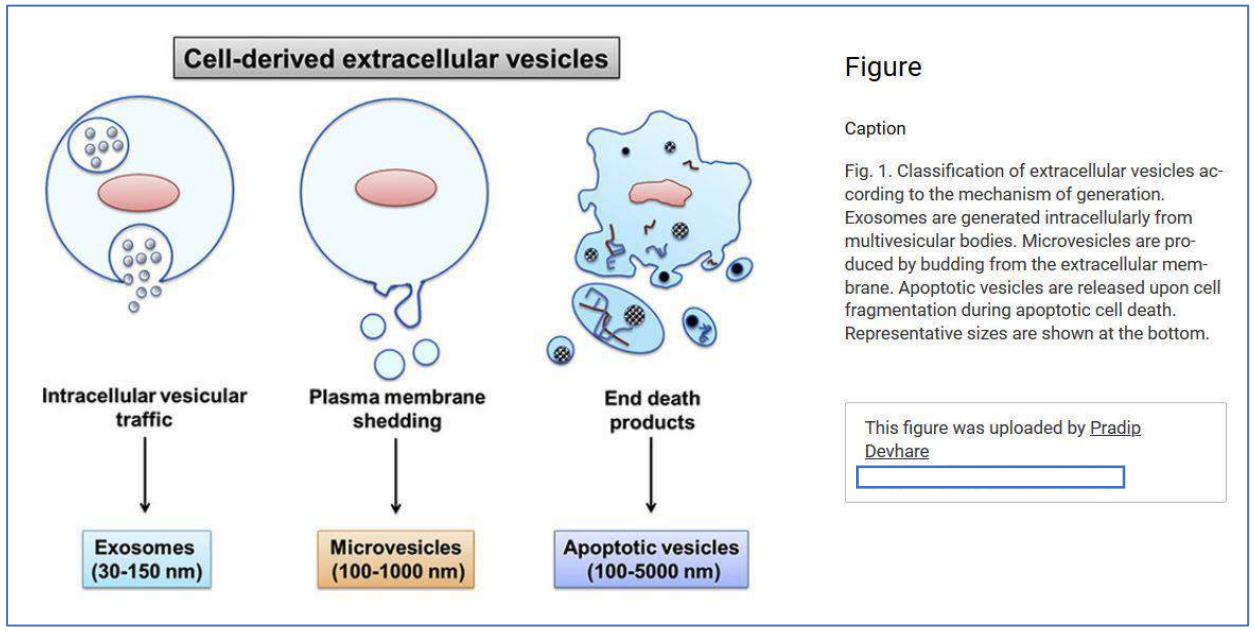


Raposo & Storvogel (2013) J. Cell Biol. Vol. 200 No. 4 373–383





BIOMARKERS: Exosomes



Figure

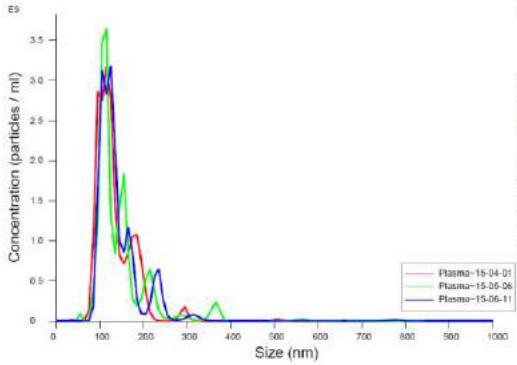
Caption

Fig. 1. Classification of extracellular vesicles according to the mechanism of generation. Exosomes are generated intracellularly from multivesicular bodies. Microvesicles are produced by budding from the extracellular membrane. Apoptotic vesicles are released upon cell fragmentation during apoptotic cell death. Representative sizes are shown at the bottom.

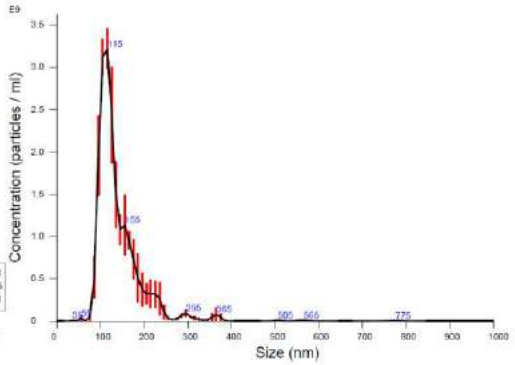
This figure was uploaded by Pradip Devhare

NANOSIGHT

Plasma 2019-11-19 15-03-47



FTLA Concentration / Size graph for Experiment:
Plasma 2019-11-19 15-03-47



Averaged FTLA Concentration / Size for Experiment:
Plasma 2019-11-19 15-03-47
Error bars indicate + / -1 standard error of the mean

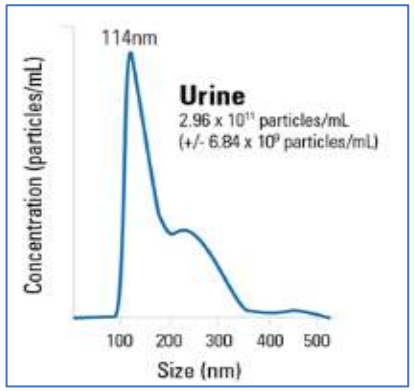
Analysis of the exosomes (Leitat)

Isolation from:

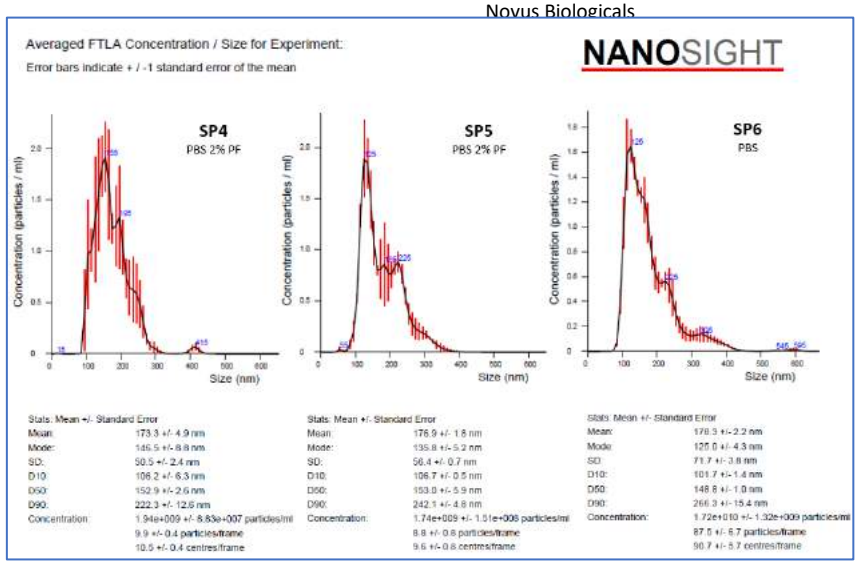
5ml SP4 (male, 8 y/o)

5ml SP5 (male, 3 y/o)

26ml SP6 (female, 32 y/o)



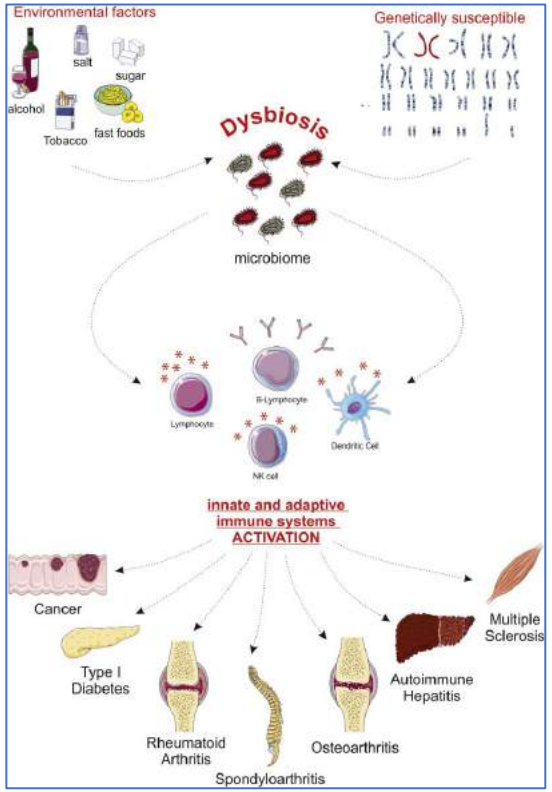
Novus Biologicals



Isolation from plasma samples from the Tissue and Blood Bank

BIOMARKERS: Microbiome

Specific compositions of the microbial community are associated with health and disease and suggest that the detailed characterization, function and variation of the microbiome will reveal important commensal host-microbe as well as microbe-microbe interactions with diagnostic, therapeutic and preventive implications.



Szychlinska (2019), Heliyon. Jan; 5(1): e01134

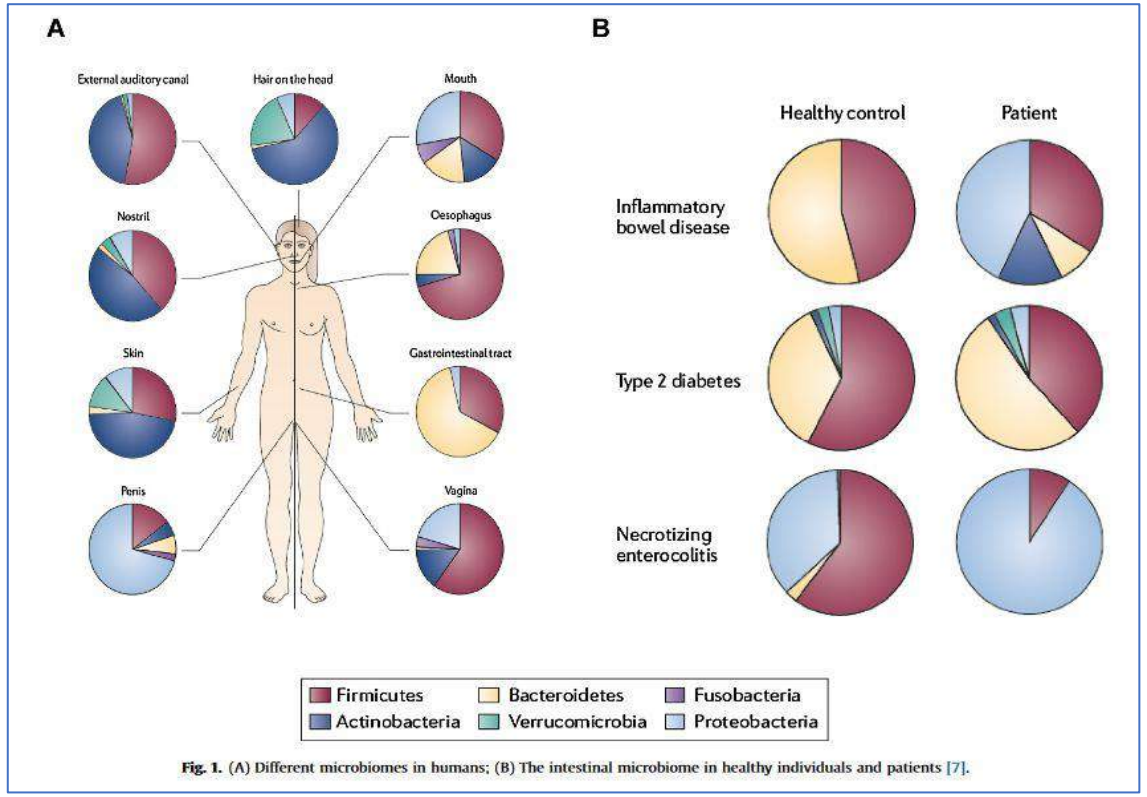


Fig. 1. (A) Different microbiomes in humans; (B) The intestinal microbiome in healthy individuals and patients [7].

H Blum: (2017), Advances in Medical Sciences Vol 62, Pages 414-420

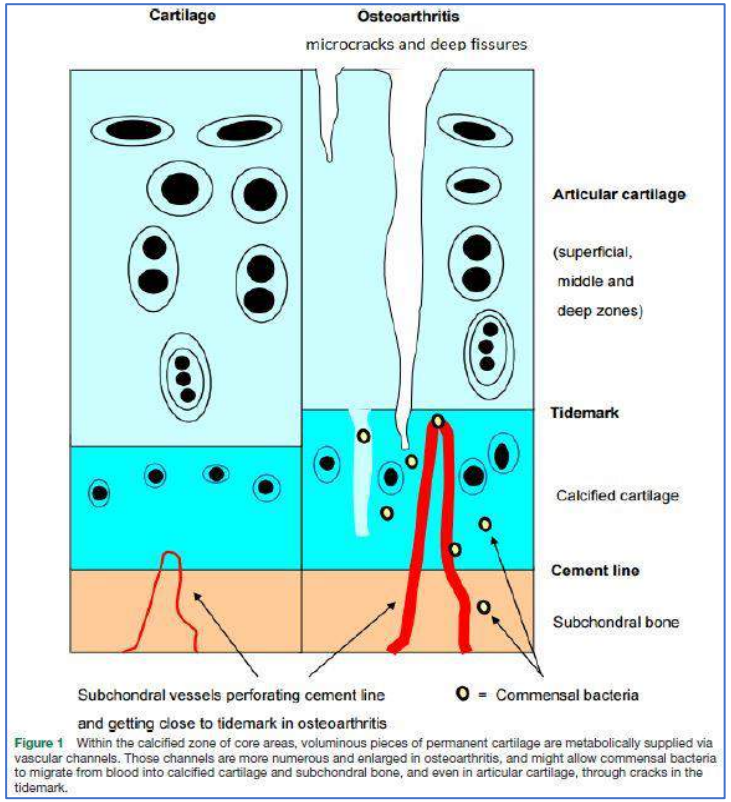


Figure 1 Within the calcified zone of core areas, voluminous pieces of permanent cartilage are metabolically supplied via vascular channels. Those channels are more numerous and enlarged in osteoarthritis, and might allow commensal bacteria to migrate from blood into calcified cartilage and subchondral bone, and even in articular cartilage, through cracks in the tidemark.

Berthelot J-M, *et al*. *RMD Open* 2019;

BIOMARKERS: Microbiome

nature COMMUNICATIONS

Intestinal microbiome composition and its relation to joint pain and inflammation
Cindy G. Boer et al. (2019) 10:4881

Stool microbiome as a Proxy for the gastrointestinal-microbiome composition in relation to knee OA severity, OA-related knee pain, measured by the WOMAC-pain score, and obesity, in a large population-based cohort (1427).

Table 1 General characteristics of the Rotterdam Study Microbiome cohort

Rotterdam Study Microbiome	Females	Males	Total
Cohort participants	821	606	1.427
Age (years)	56.8 (5.9)	56.9 (5.9)	56.9 (5.9)
BMI (kg/m^2)	27.4 (4.9)	27.6 (4.0)	27.5 (4.5)
Alcohol (g/day)	1.3 (2.7)	1.3 (2.3)	1.3 (2.6)
Smoking (y/n)	98 smokers/721 non smokers	97 smokers/507 non smokers	195 current smokers
PPI (y/n)	182 users/638 non-users	114 users/492 non-users	296 current PPI users
NSAIDs (y/n)	127 users/693 non-users	51 users/555 non-users	178 current NSAID users
Knee phenotypes			
Knee OA (y/n)	84 cases/456 controls	40 cases/361 controls	124 cases/817 controls
KLSum score	1.0 (1.4)	0.7 (1.2)	0.8 (1.3)
WOMAC-Pain score	1.2 (2.6)	0.6 (1.9)	0.9 (2.3)
WOMAC-Pain score > 0	206	79	285
α-diversity metrics			
Shannon Index	4.0 (4.1)	4.0 (4.0)	4.0 (0.5)
Inverse Simpson Index	26.0 (12.1)	25.5 (12.2)	25.8 (12.2)

Depicted are the mean and the SD (standard deviation) in parenthesis
PPI oral use of proton pump inhibitors, *NSAIDs* oral use of non-steroidal anti-inflammatory drugs, *OA* osteoarthritis, *WOMAC* Western Ontario and McMaster Osteoarthritis Index

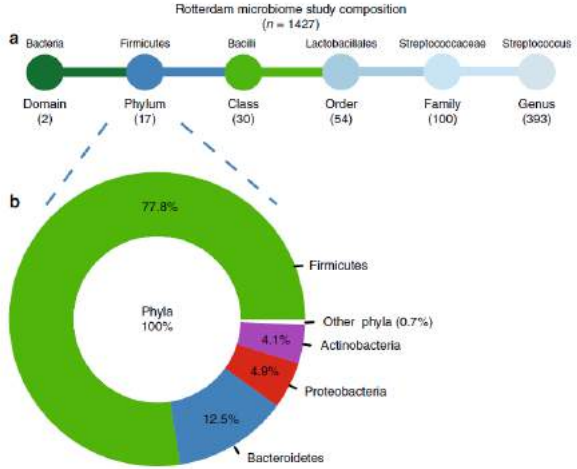


Fig. 1 Schematic representation of the gut-microbiome taxonomic abundance in the Rotterdam Study cohort. **a** overview of the number unique taxonomies detected at each level, unknown and unclassified bacteria were excluded. **a** Above, as an example, the taxonomic classification for *Streptococcus* is shown. **b** Donut plot of the relative abundancy in percentage (%) of the different unique phyla present in the entire dataset ($n = 1427$) unknown and unclassified bacteria were excluded

Table 3 Results of the association analysis of *Streptococcus* and knee joint effusion

Taxonomy	N	Model 1 CoE	Model 1 *P*-value	Model 2 CoE	Model 2 *P*-value
Class *Bacilli*	314	9.4×10^{-03}	3.4×10^{-02}	2.7×10^{-03}	3.5×10^{-01}
Order *Lactobacillales*	314	9.8×10^{-03}	2.7×10^{-02}	2.7×10^{-03}	3.6×10^{-01}
Family *Streptococcaceae*	310	9.6×10^{-03}	1.7×10^{-02}	3.0×10^{-03}	2.6×10^{-01}
Genus *Streptococcus*	308	1.0×10^{-02}	1.3×10^{-02}	3.3×10^{-03}	2.1×10^{-01}

Knee joint inflammation was measured as severity of effusion as measured on knee MRI. Knee MRI's were only available for an all-female obese subgroup of the Rotterdam Study Microbiome dataset ($n = 373$). First model assessed the association of Knee effusion with the microbiome, adjusted for age, sex, DNA isolation batch and TimeInMail (technical covariates). Second model was WOMAC-pain score adjusted for age, sex, technical covariates and, effusion severity. *P*-values were determined by MaAsLin analysis. *N* = number of individuals in cohort where microbial abundancy is not zero for that taxonomy
CoE coefficient

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OActive

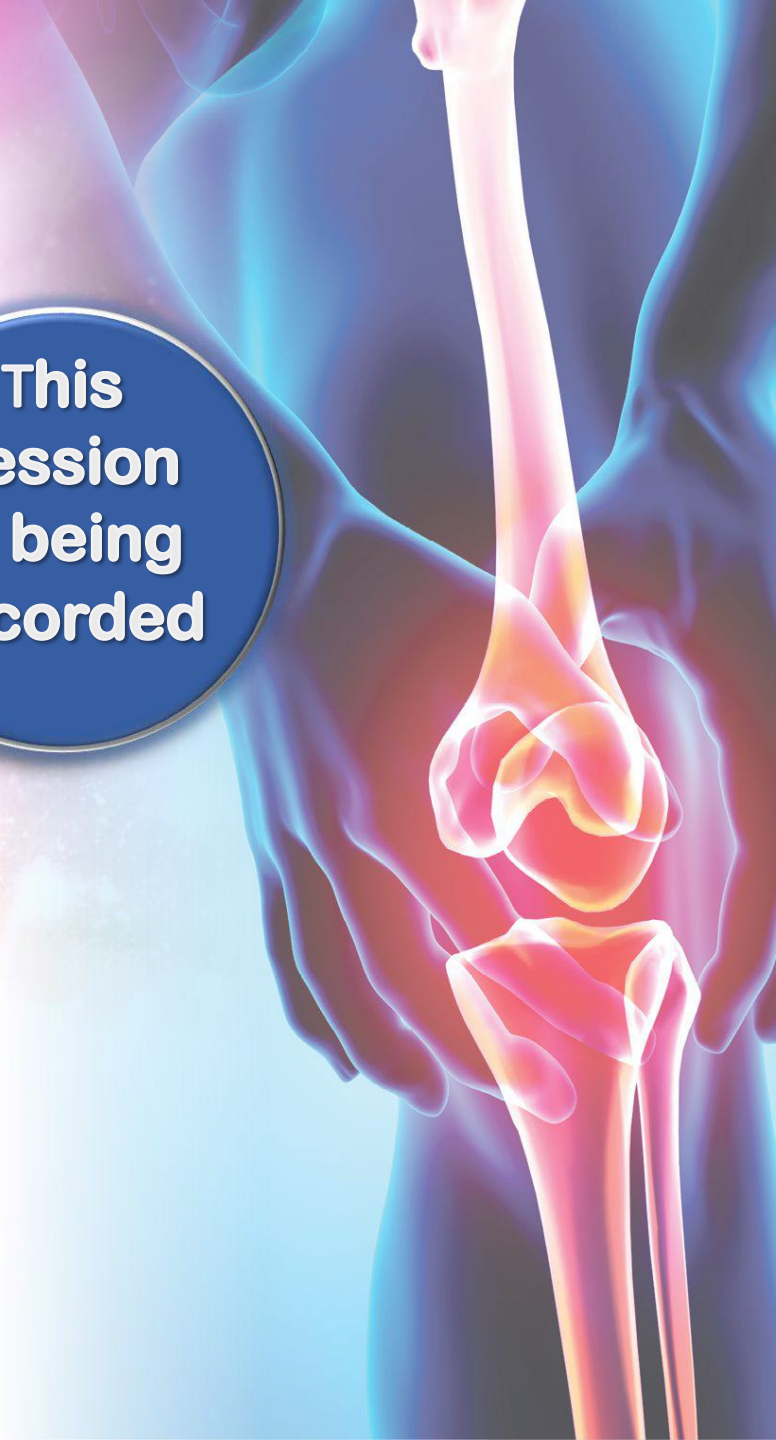
Thank You

Questions

Project full title:

Advanced personalised, multi-scale computer models preventing OsteoArthritis

OActive



This session is being recorded

Training session:

ENGAGING END USERS TO THE OACTIVE WORLD

Behaviour modelling and environmental biomarkers

Gianluca de Toma, SMARTEX
Dimitrios Tsaopoulos, CERTH
Thijs Swinnen, KULeuven

Grant agreement 777159

SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

OActive

Biochemical modelling and inflammation biomarkers

Behaviour modelling and environmental biomarkers

Biomechanical modelling of the knee

Computational modelling empowered by big data and deep learning

Using artificial tissues as test-bench for rehabilitation against osteoarthritis

Real time gait monitoring and retraining

Behaviour modelling and environmental biomarkers

Training session presentation overview

- Activity overview: concept and aims
- Wearable systems development
  - Laboratory setup
  - Home setup
- Behavioural model: approaches and examples
- Social and environmental factors and their relation to knee OA
  - Gathering data methodologies
  - Data analysis

Behaviour modelling and environmental biomarkers

Detect and measure user's physical, mental and social behaviours to develop a mathematical model for OA patient

Objective

- The assessment and modelling of behaviour of OA patients related to physical activity as well as their social interactions and behaviour.

- The development and implementation of models for mental, emotional and social state assessment

- **Further input into the algorithms for assessing risks and providing personalised diagnosis and treatments of OA.**

Concept

Behavioural Model

DATA RECORDING

DATA ANALYSIS

Behavioural attributes interdependencies of physical factors

Model

Social determinants and relation to OA

DATA GATHERING & ANALYSIS

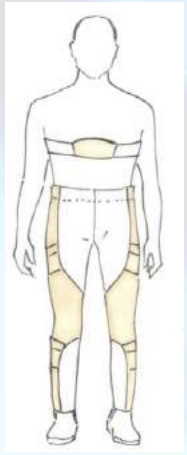
Social attributes, cognitive and social determinants

Personalised interventions through augmented - reality

Hyper-modelling framework empowered by big data and deep learning

Concept: Behavioural Model

WEARABLE SENSORS



Laboratory Monitoring

OA influence on user movements

- Lower limbs movements
- High resolution signals
- Short session

Home Monitoring

OA influence on user habits

- Activity intensity
- Steps
- Posture
- Long period monitoring

DATA ANALYSIS

Behavioural attributes interdependencies of physical factors, features extraction

Model

Design and development of OACTIVE wearable sensors

Controlled condition monitoring
Up to 6 IMUs

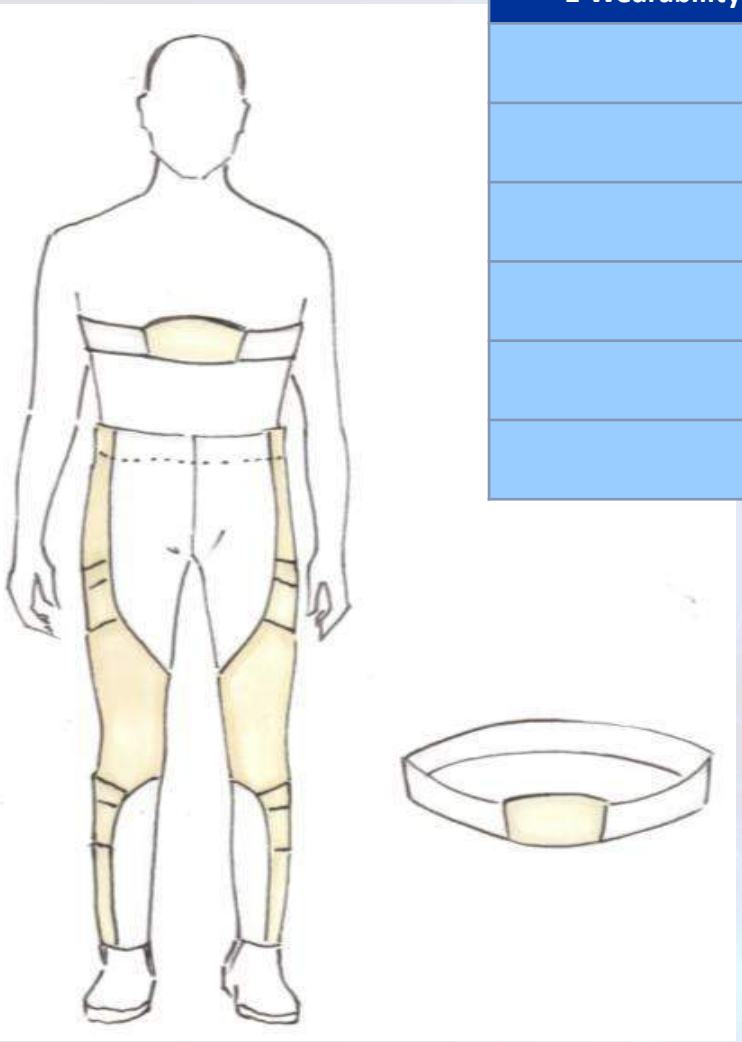
Electronics for multiple devices acquisition

IMU 9250 by Invensense (9 DOF)
Bluetooth 2.1 wireless transmission
Data transmitted: Quaternion, 3 Accelerometer, 3 Gyroscope,3 Magnetometer
Sampling frequency IMU 100Hz
Rechargeable battery 660 mAh
Slaves (MAX 6) paired with a single master
Case and package optimized for handling and comfort when worn

Design and development of OACTIVE wearable sensors

IMUs wearable system: textile, garment & accessories

1 Wearability study	2 Sensors functionality study	3 Integration study	4 Prototype study
Materials selection			
Model and pattern of the prototype			
Cutting of the fabric components of the prototype			
Manufacturing			
Testing: Laboratory evaluation, Usability test			
Changes of the model according users feedback			



Remote monitoring

Electronic for single devices acquisition

IMU 9250 by Invensense (9 DOF)

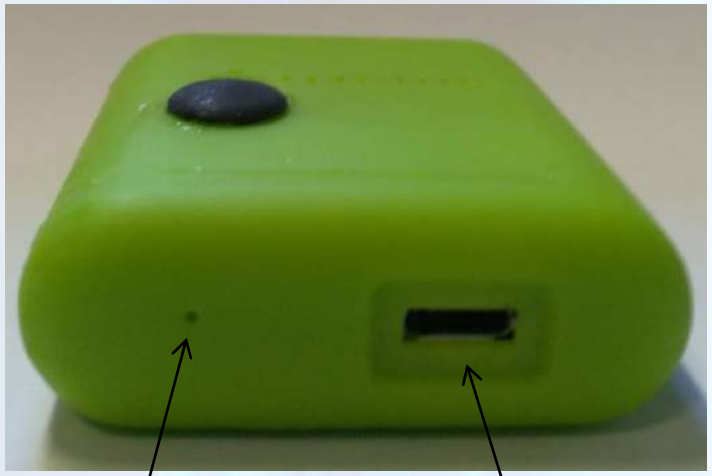
Raw Data acquired and stored on board: Quaternion, 3 Accelerometer, 3 Gyroscope,3 Magnetometer

Data extrapolated on board: Activity Classification (laying/standing, walking, running), Activity Intensity, Pace Counter

Sampling frequency IMU 25Hz

Software for data export in CSV format

A) Mode switch

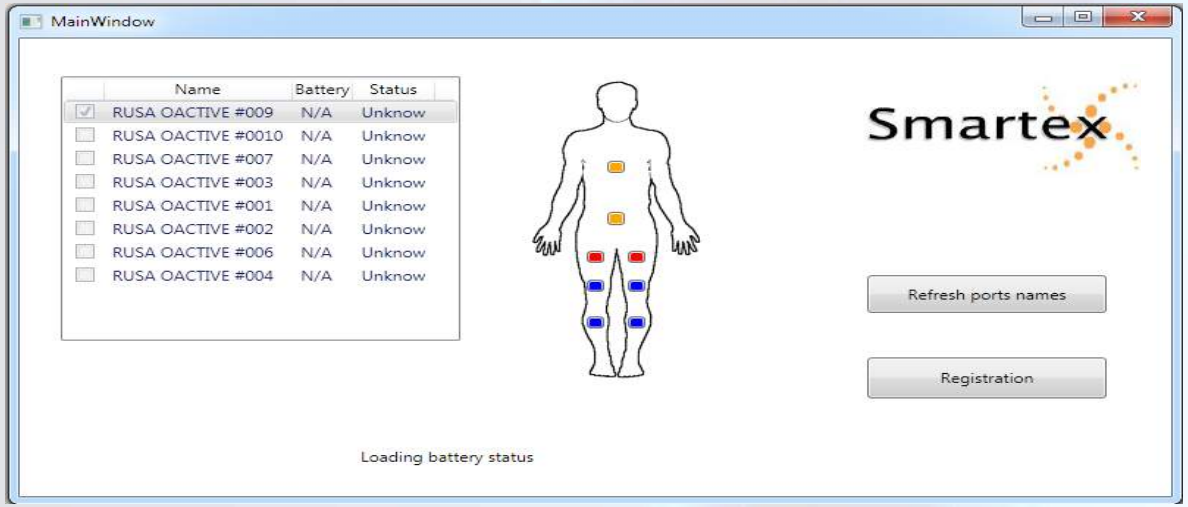


B) Reset hole

C) Micro USB

Design and development of OACTIVE wearable sensors

IMUs wearable system: Windows App



- Pairing of each device
- Assign placement (i.e. IMUxxx->Chest)
- Real time streaming (quaternion)
- Data available: quaternion, 9 DOF row data (100 Hz sampling frequency)
- Simultaneous start/stop recording
- Backup recording on microSD

Design and development of OACTIVE wearable sensors

Activity recognition in Behavioural Modelling

- Task: Study everyday activities in regular environments
  - Using wearable devices
  - Data recorded: accelerometer data / gyroscope data
- **Answer questions such as, how often and how long a person perform an activity.**
- In practice we need Large scale activity tracking
  - Sleeping, Sitting, Low-Intensity Activity/Exercise, Moderate-Intensity Exercise, Houseworks.
  - Data collected in the scale of days, weeks.

Problem: Most activity tracking experiments are limited within a lab! Labelled datasets usually are small and far from realistic.

Need for accurate tracking with wider generalization in large scale data

Activity Recognition 1

We propose: Unsupervised learning for time series segmentations.

To achieve wider generalization!

However:

- Traditional changepoint detection: breakpoints non-trivial to detect
  - rely on a prior parametric model of the time series data
  - often utilize simple features extracted from the input data such as the mean, variance, spectrum, etc

Possible solution: utilize a deep autoencoder model to extract the most representative features in time-series data

Activity Recognition 1- The change detection method

1. First segment the input data into a series of windows
2. Apply deep autoencoder models to extract representative features for the input data.
3. Extracted features can then be utilized to calculate the distance between consecutive windows.
4. The timestamps corresponding to local-maximal distance can be detected as breakpoints.

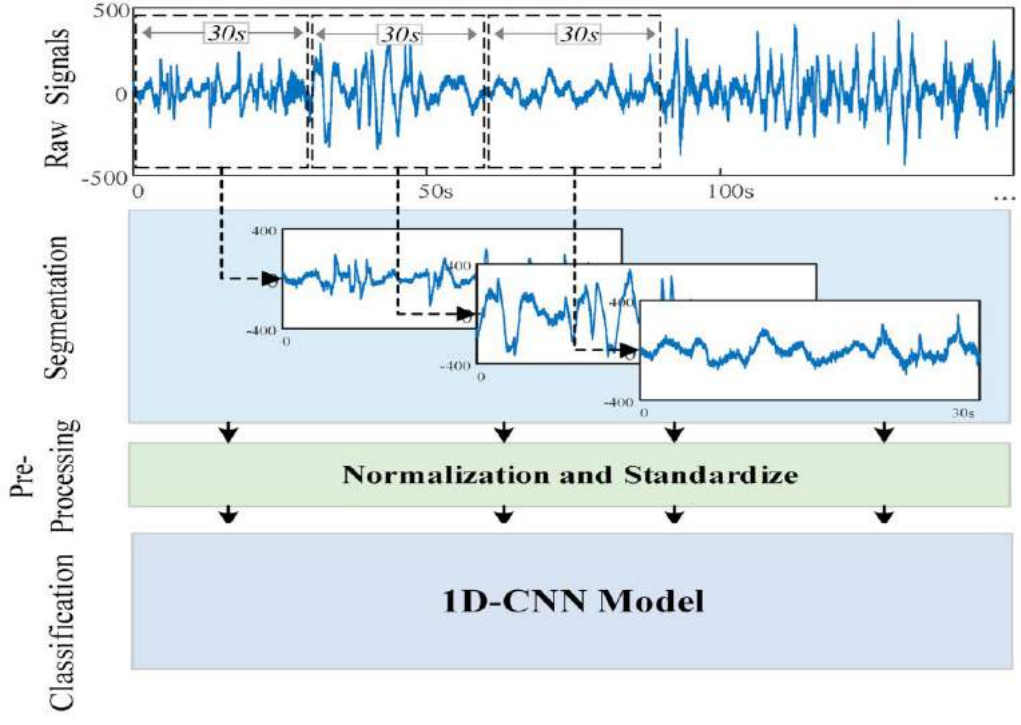
Activity recognition 2 - The characterization method

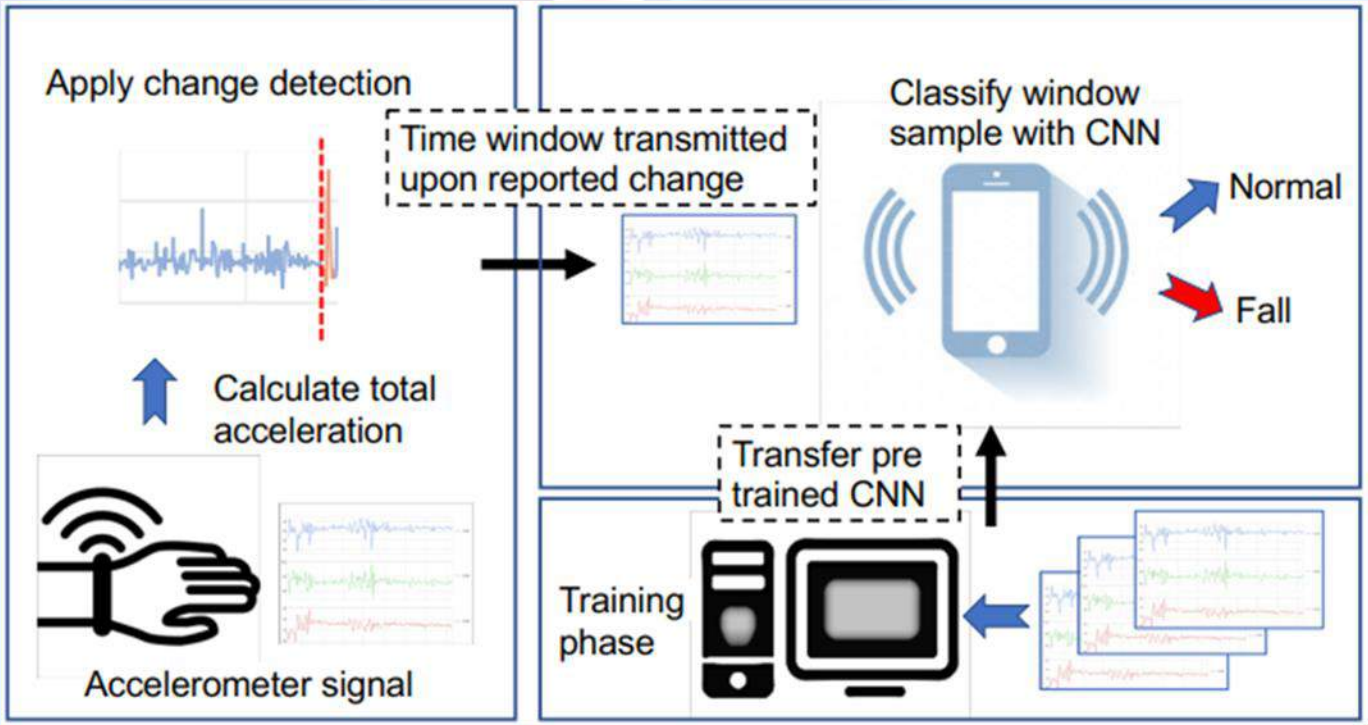
- Classification for activity recognition
  - Window based techniques (CNN-LSTM).
  - Training through a collection of Lab based annotated experiments.
- **Boosted from predefined segments**
  - **A time series segment between two breakpoints can only belong to one class.**
  - **Apply majority voting or ensemble schemes.**
- Achieve higher Accuracy and Robustness

1. S. Georgakopoulos, S. Tasoulis, G. Mallis, A. Vrahatis, V. Plagianakos and I. Magglogiannis, “Change Detection and Convolution Neural Networks for Fall Recognition”, Neural Computing and Applications (NCAA), Springer, 2020, to appear. (IF=4.7)

User behaviour analysis

A complete overview of the proposed methodology based on CNN proposed for **FALL DETECTION SYSTEM**





Risk for progression and poor clinical status?

KNEE OSTEOARTHRITIS

Onset - Progression – End stage (joint replacement)

Risk for progression and poor clinical status?

Intrinsic
Person-related factors

e.g. age,
body composition,
joint health,
biomechanics

KNEE OSTEOARTHRITIS

Onset - Pro … : replacement)

Risk for progression and poor clinical status?

Extrinsic
Environmental factors

e.g. people,
socioeconomic position

Intrinsic
Person-related factors

Onset - Pro : replacement)

Risk for progression and poor clinical status?

Extrinsic
Environmental factors

e.g. people,
socioeconomic position

Intrinsic
Person-related factors

Onset - Pro **: replacement)**

e.g. built enviroment such as parcs

Impact of environmental factors on knee OA

Extrinsic
Environmental factors

Onset - Progression – End stage (joint replacement)

Impact of environmental factors on knee OA

Extrinsic
Environmental factors

Definition contextual factors: "variables that are not outcomes of studies, but need to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers…"
(outcome measures in rheumatology, OMERACT.org)

Onset - Progression – End stage (joint replacement)

Social and environmental factors and their relation to knee OA

OActive

Which method?

CONSULT THE LITERATURE

ASK THE PATIENT

BEST EVIDENCE

ASK THE EXPERTS

How did we use patient and expert opinion?

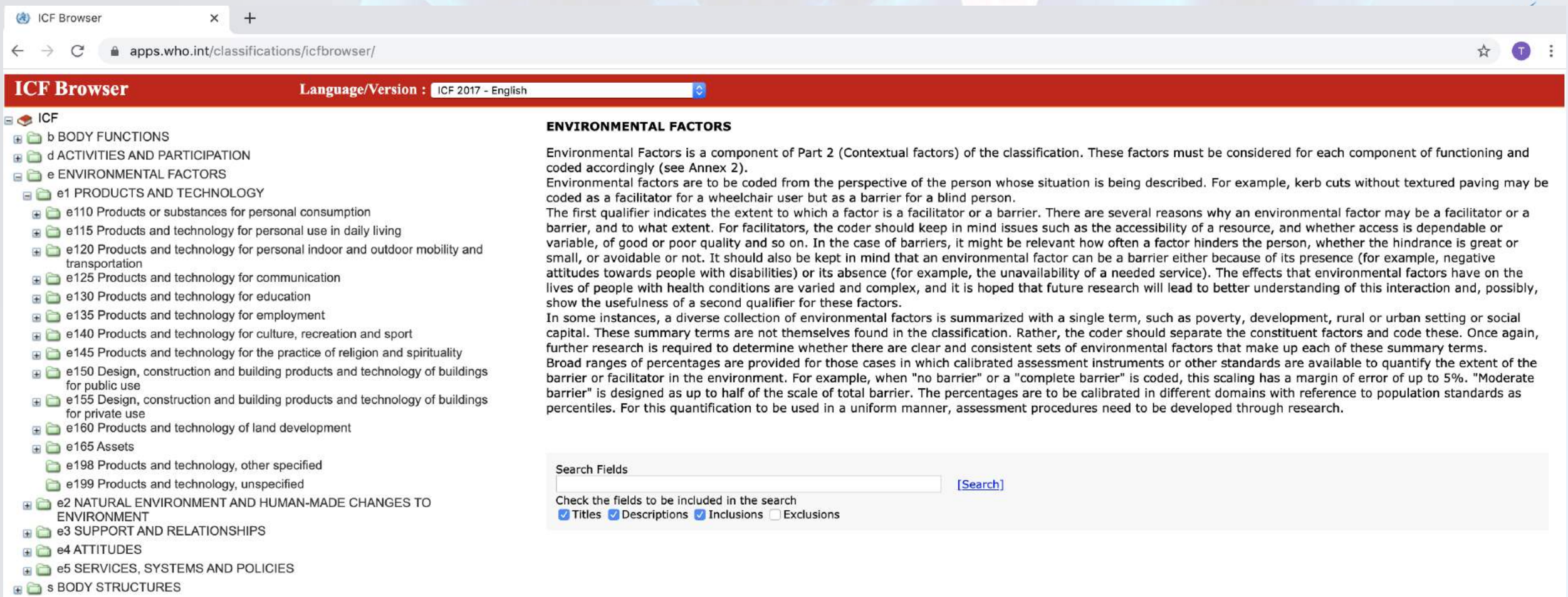
ASK THE PATIENT

ASK THE EXPERTS

Consensus-based approach

- WHO international classification of functioning, disability and health taxonomy
  - ✓ transdisciplinary
  - ✓ International
  - ✓ guiding definitions

https://apps.who.int/classifications/icfbrowser/



Needed tailoring to knee OA research

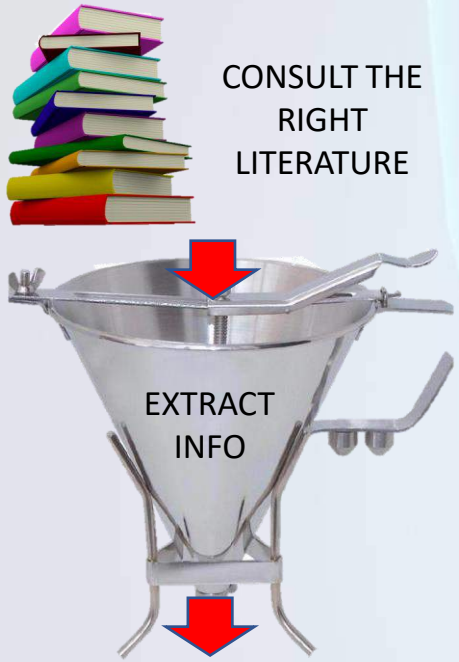
✓ informed by major OA cohorts (OAI, EPOSA, EVOLVE) and expert input

https://apps.who.int/classifications/icfbrowser/

Contextual factors (Oactive / ILAF framework, based on ICF)			EPOSA included?	EPOSA item	LC included?
code	construct	operational definition			
	ENVIRONMENTAL FACTORS				
		Environmental Factors is a component of Part 2 (Contextual factors) of the classification. These factors must be considered for each component of functioning and coded accordingly (see Annex 2). Environmental factors are to be coded from the perspective of the person			
	e1 Products and technology	This chapter is about the natural or human-made products or systems of products, equipment and technology in an individual's immediate environment that are gathered, created, produced or manufactured. The			
	e110 Products or substances for personal consumption	Any natural or human-made object or substance gathered, processed or manufactured for ingestion. Inclusions: food and drugs			
	e1100 Food	Any natural or human-made object or substance gathered, processed or manufactured to be consumed, such as raw, processed and prepared food and liquids of different consistencies (including breast milk), herbs and minerals (vitamin and other supplements).			0
	e1101 Drugs	Any natural or human-made object or substance gathered, processed or manufactured for medicinal purposes, such as allopathic and naturopathic medication.			0
	e1108 Products or substances for personal consumption, other specified				
	e1109 Products or substances for personal consumption, unspecified		1	ies such as rmarket, st office, bank, community centre Categorical 1. a lot 2. some 3. not at all	1
	e115 Products and technology for personal use in daily living	Equipment, products and technologies used by people in daily activities, including those adapted or specially designed, located in, on or near the person using them. Inclusions: general and assistive products and technology for personal use Exclusions: products and technology for personal indoor and outdoor mobility and transportation (e120);products and technology for communication (e125)			

Deliverable: taxonomy with about 300 concepts for consideration, about 50 more relevant based on OA cohorts

How did we use the literature?



Data driven approach

- Step 1: Search for **narrative** reviews
- Step 2: Short **scoping** review
  - ✓ Preliminary searches on topics from OActive environmental factors framework (in PubMed) to conclude:
    - Socioeconomic factors for systematic literature review (this training)
    - Explore other major factors in a pilot cohort study
- Step 3: Final **systematic** literature review (SLR)
- Step 4: **Match** with 'hyper model' parameters (AI-based)

Including the ‘right’ studies: criteria

CONSULT THE **RIGHT** LITERATURE

criteria

- **Patients.** knee osteoarthritis without arthroplasty (without classification criteria needed, self-reported)
- **Interventions.** no restrictions
- **Comparisons.** quantification of the relationship between socioeconomic factors and outcomes
- **Outcome.** pain, imaging, physical function/activity, prevalence/risk
- **Setting.** no restrictions
- **Study design.** RCTs, observational cohort studies and case-control studies aged above 16 years were included. –no year limit, written in English or Dutch

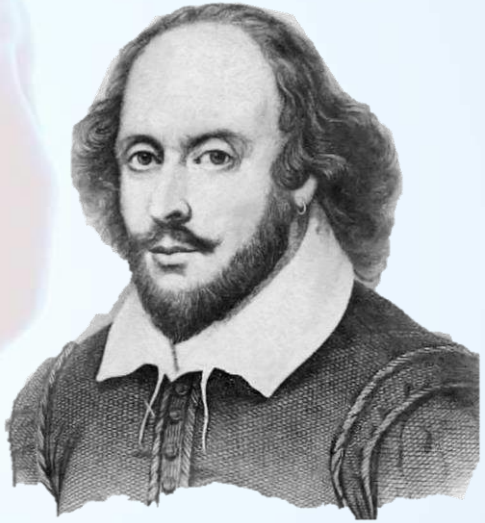
PICOS framework

Finding the right studies (search string)

CONSULT THE **RIGHT** LITERATURE

Criteria / Databases / Search terms

- Conceptually using Oactive framework
- Practically using database thesauri (work with a librarian)
  - ✓Pubmed
  - ✓Embase
  - ✓Web of science
  - ✓CINAHL
- Using synonym list
- From screening most relevant papers



What's in a name?
W. Shakespeare

Translate your string, bit like coding

- **PubMed**

✓ "Osteoarthritis, Knee"[Mesh] OR (("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[Tiab] OR “Osteoarthritides”[Tiab]) AND ("knee"[MeSH Terms] OR "knee*"[Tiab] OR "knee joint"[MeSH Terms]))

- **Embase**

✓ 'knee osteoarthritis'/exp OR (('osteoarthritis'/exp OR ‘osteoarthritis’:ti,ab,kw OR ‘osteoarthritides’:ti,ab,kw) AND ('knee'/exp OR ‘knee*’:ti,ab,kw))

- **Web of Science**

✓ "knee osteoarthritis" OR ((osteoarthritis OR osteoarthritides) AND (knee*))

- **Cinahl**

✓ (MH "Osteoarthritis, Knee" OR (MH "Osteoarthritis" AND (MH "Knee" OR MH "Knee Joint")) OR

✓ AB ("knee osteoarthritis" OR ((osteoarthritis OR osteoarthritides) AND (knee*))) OR

✓ TI ("knee osteoarthritis" OR ((osteoarthritis OR osteoarthritides) AND (knee*)))

- **Cochrane**

✓ [mh "Osteoarthritis, Knee"] OR (([mh "osteoarthritis"] OR "osteoarthritis":ti,ab,kw OR "osteoarthritides":ti,ab,kw) AND ([mh "knee"] OR "knee":ti,ab,kw OR [mh "knee joint"]))

NCBI Resources How To Sign in to NCBI

PubMed Home More Resources Help

PubMed Advanced Search Builder

YouTube Tutorial

("Osteoarthritis, Knee"[Mesh] OR (("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[Tiab] OR “Osteoarthritides”[Tiab]) AND ("knee"[MeSH Terms] OR "knee*"[Tiab] OR "knee joint"[MeSH Terms])))

Edit Clear

Builder

All Fields | hritides”[Tiab]) AND ("knee"[MeSH Terms] OR "knee*"[Tiab] OR "knee joint"[MeSH Terms])) | Show index list

AND | All Fields | Show index list

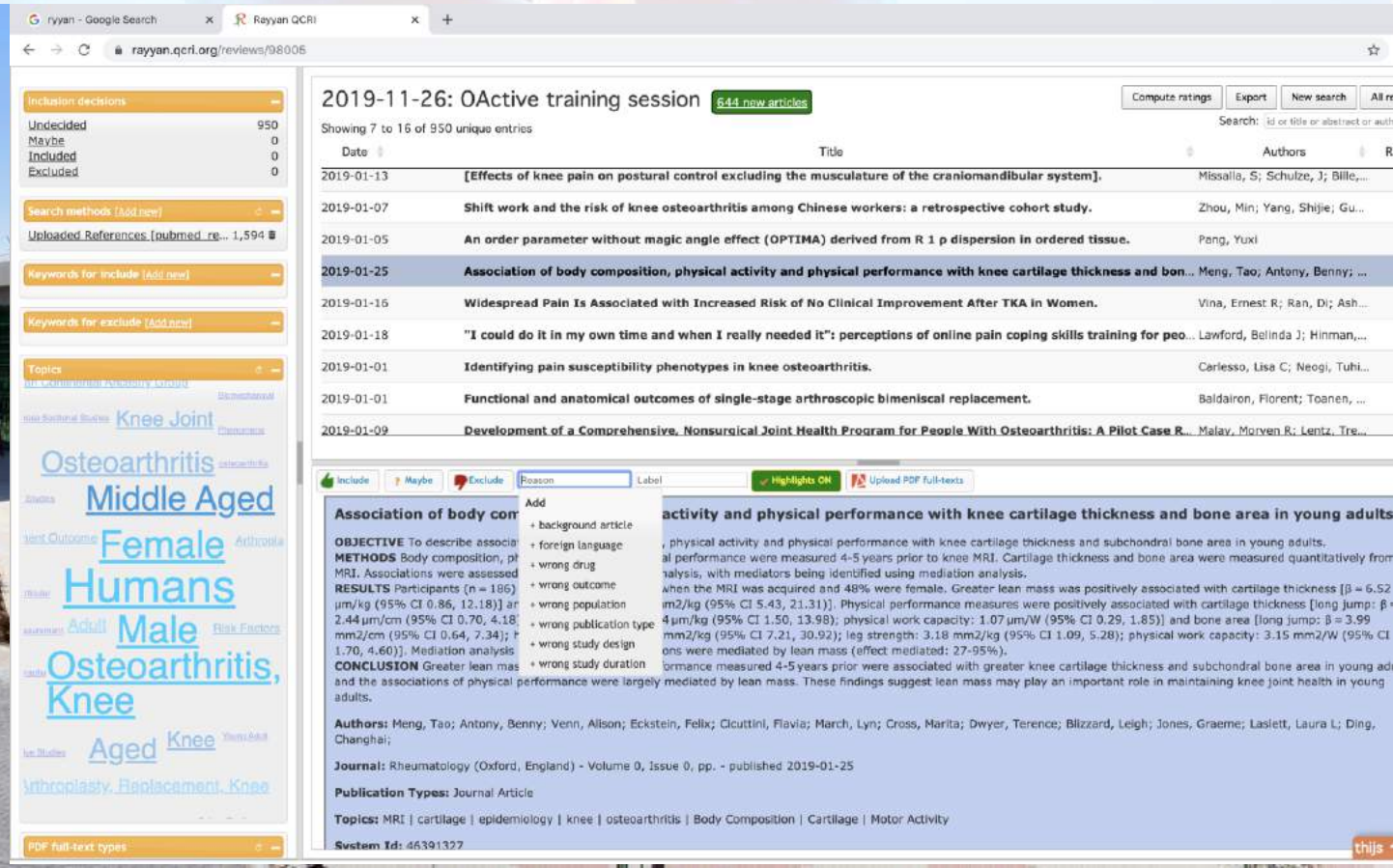
Search or Add to history

History

There is no recent history

Screening the articles using criteria

- Using Ryyan (Qatar Computing Research Institute)



How to extract data

- Coding form

Data-extraction	
Key to symbols / colours	
Not applicable	N/A
Yes, criterium fulfilled	Y
No, criterium not fulfilled	N
Intervention group	IG
Control group	CG

Population	**Article n°**
Description	
Inclusion criteria	
Exclusion criteria	
Participant flow / flowchart of patients included? Reasons for exclusion / non participating?	
Sample size + how determined (power?)	
N° of participants experimental/case group	
N° of participants control group	
Mean age experimental/case group	
Age range experimental/case group	
Surgical technique(s)	

How to assess quality and the decision to perform meta-analysis

- NOS tool / Cochrane ROB tool

	Random sequence generation **(Selection bias)**	Allocation concealment **(Selection bias)**	Baseline variables equal? **(Selection bias)**	Blinding of participants and personnel **(Performance bias)**	Avoidance or similar cointerventions **(Performance bias)**	Acceptable compliance in all groups **(Performance bias)**	Blinding of outcome assessment **(Detection bias)**	Similar timing of outcome assessment **(Detection bias)**	Incomplete outcome data - drop out rate **(Attrition bias)**	Analyses in allocated groups? **(Attrition bias)**	Selective Reporting **(Reporting bias)**
	?	?	1	0	1	?	?	1	?	?	?

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ◘
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ◘
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ◘

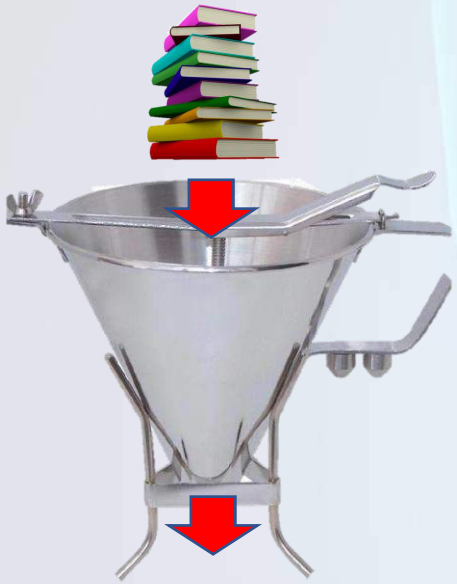
basis of the design or analysis
Select the most important factor.) ◘
◘ (This criteria could be modified to indicate specific

e/control status ◘
tus
e) no description

2) Same method of ascertainment for cases and controls
   a) yes ◘
   b) no

3) Non-Response rate
   a) same rate for both groups ◘
   b) non respondents described
   c) rate different and no designation

Sum things up

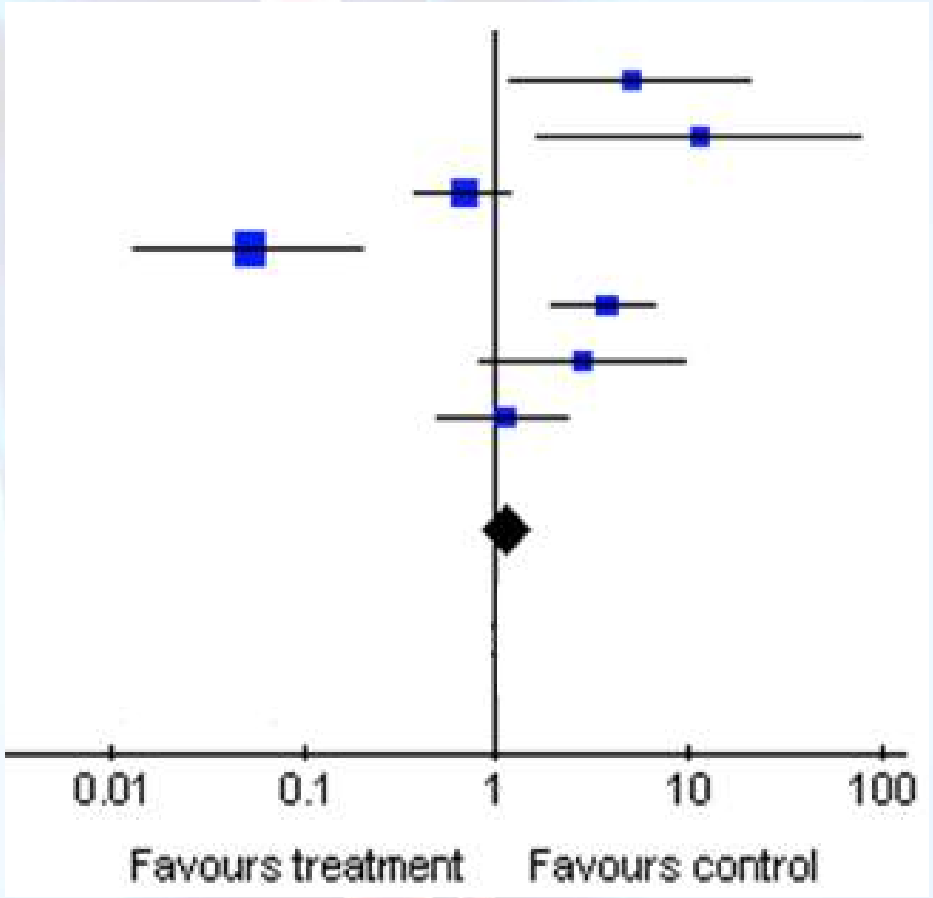


QUALITY CHECK

ANALYSIS

EFFECT CONTEXTUAL FACTORS REPORTING

- Statistics
- Writing process
  - ✓Prisma tool



R= -1.00 ASSOCIATION R= + 1.00

SC1-PM-17-2017

GA 777159

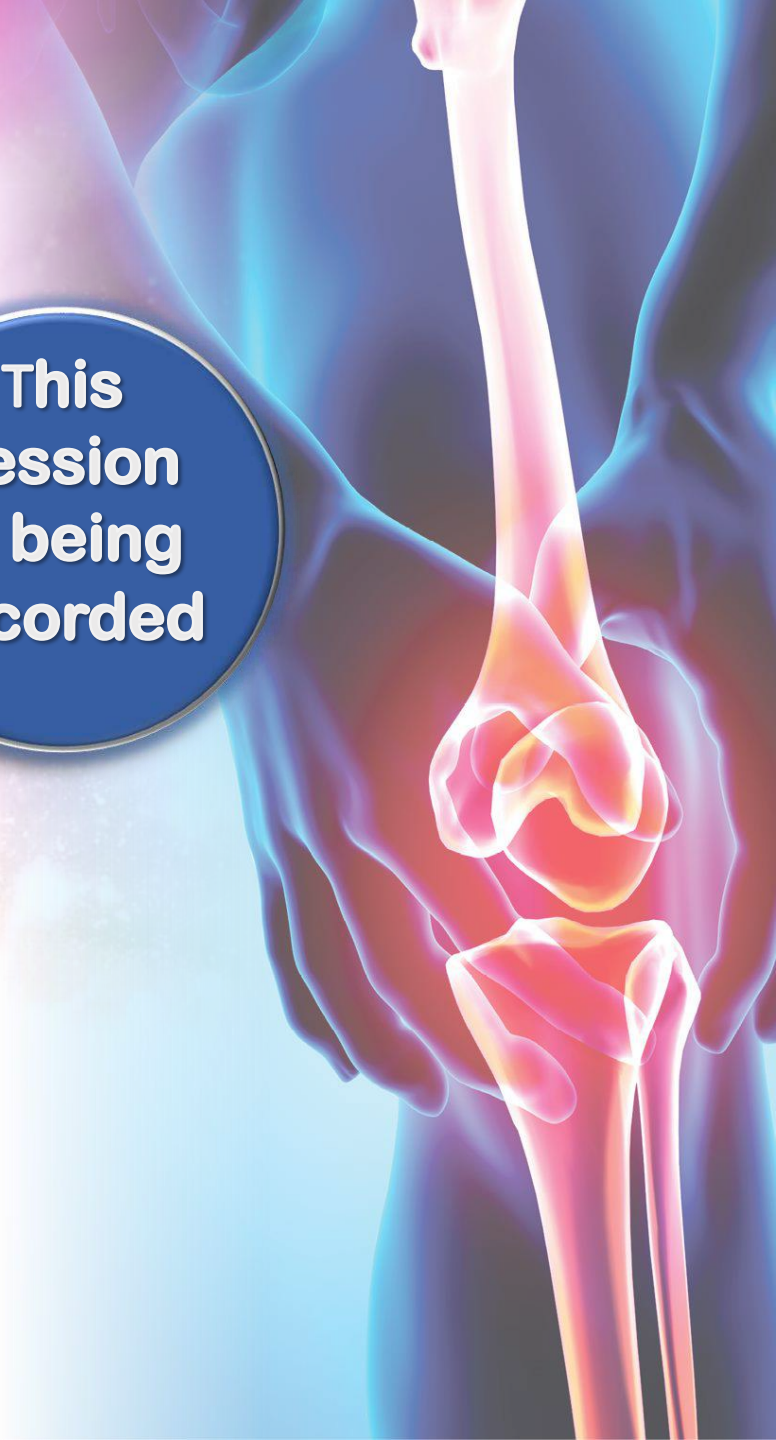
Thank You

Questions

Project full title:

Advanced personalised, multi-scale computer models preventing OsteoArthritis

OActive



This session is being recorded

Training session:

ENGAGING END USERS TO THE OACTIVE WORLD

Biomechanical modelling of the knee

David Britzman, Liverpool John Moores University

Grant agreement 777159

SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

Biomechanical modelling of the knee

David Britzman, Alexander Abel, Bill Baltzopoulos, Costis Maganaris, Liverpool John Moores University

OActive

Biochemical modelling and inflammation biomarkers

Behaviour modelling and environmental biomarkers

Biomechanical modelling of the knee

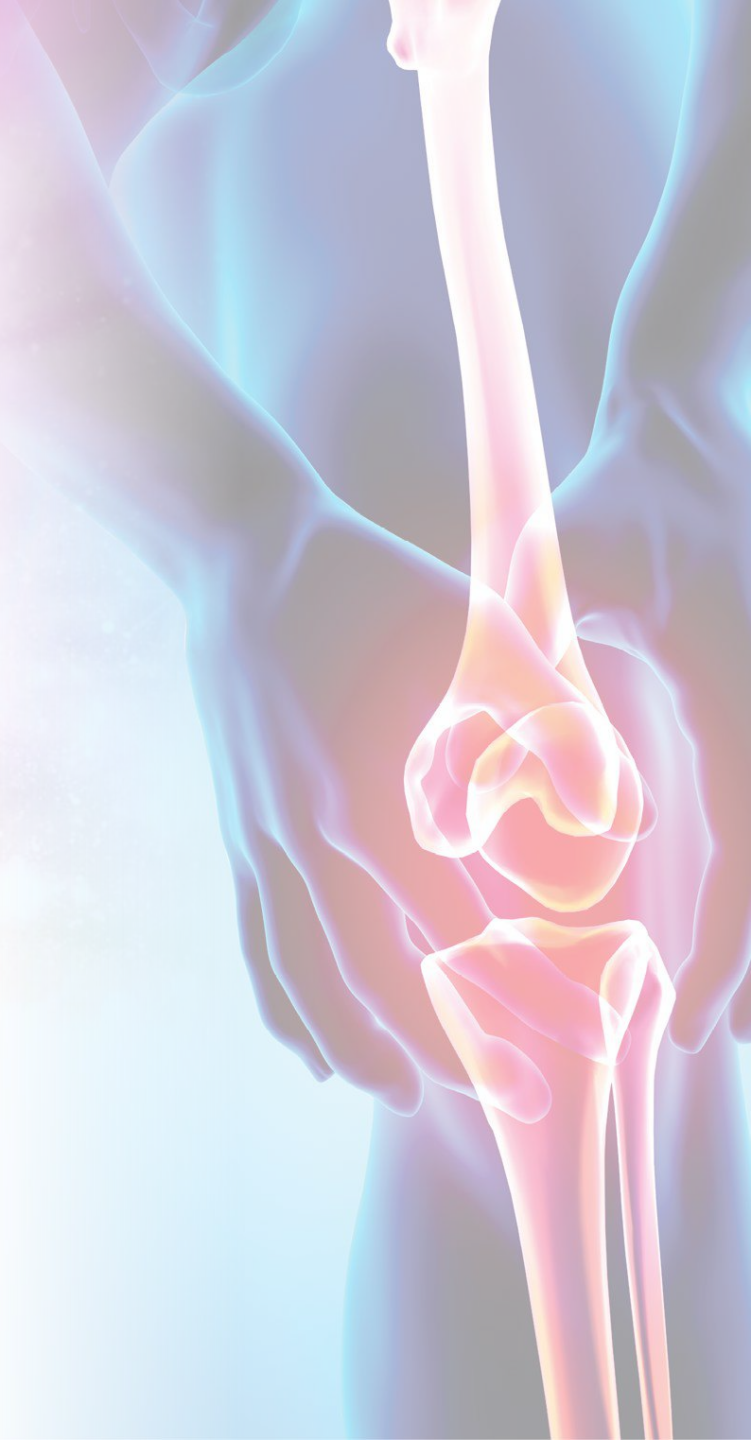
Computational modelling empowered by big data and deep learning

Using artificial tissues as test-bench for rehabilitation against osteoarthritis

Real time gait monitoring and retraining

Outline

- **Introduction and Background**
  - What is Biomechanics?
  - Biomechanics and knee OA
- **OACTIVE biomechanical models**
  - Pipeline Overview
- **Musculoskeletal Models**
  - Creating subject specific lower limb models
  - Inverse Kinematics
  - Muscle and Joint Loading
- **Finite Element Models**
  - Creating subject specific knee geometry
  - Modelling cartilage stresses
- **Conclusion and Closing Remarks**

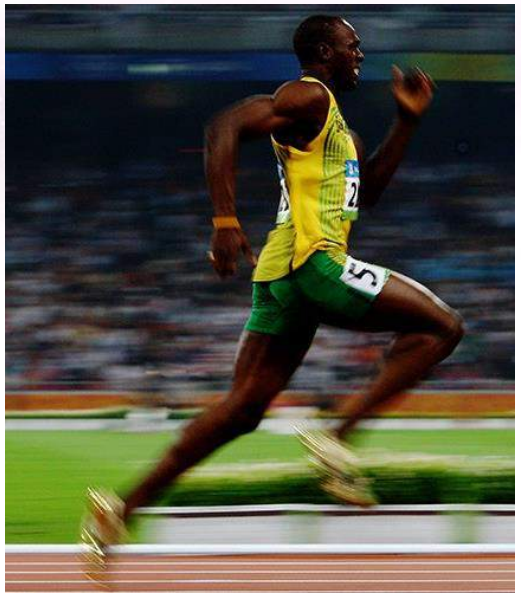


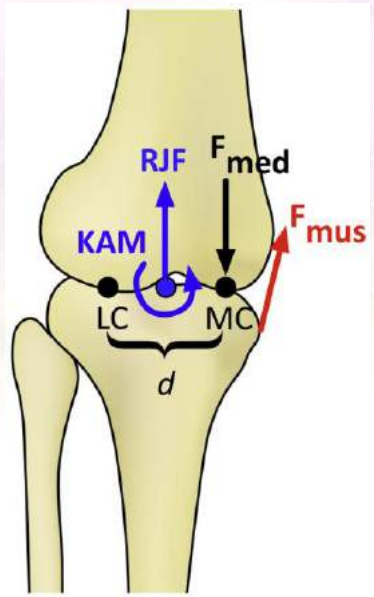
OActive

Introduction

What is Biomechanics?

"The study of the mechanical laws relating to the movement or structure of living organisms"





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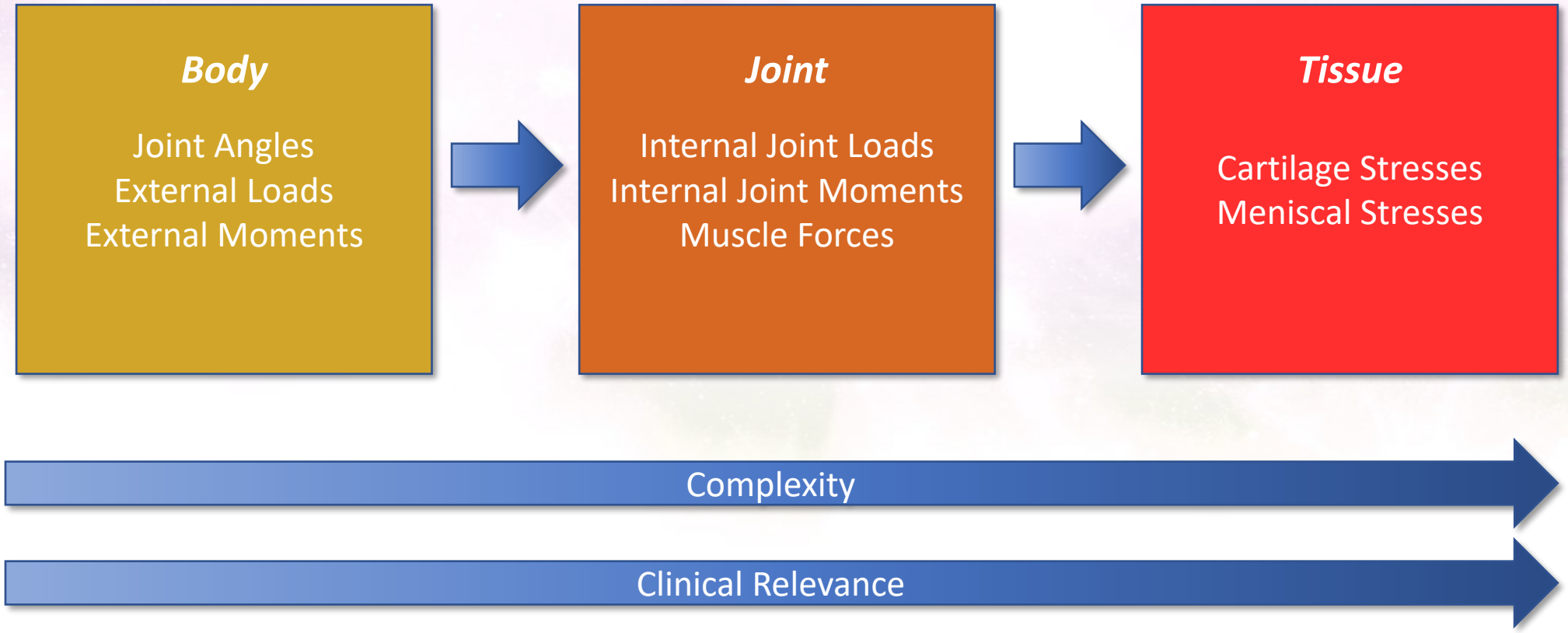
Introduction

Multiscale Biomechanics?



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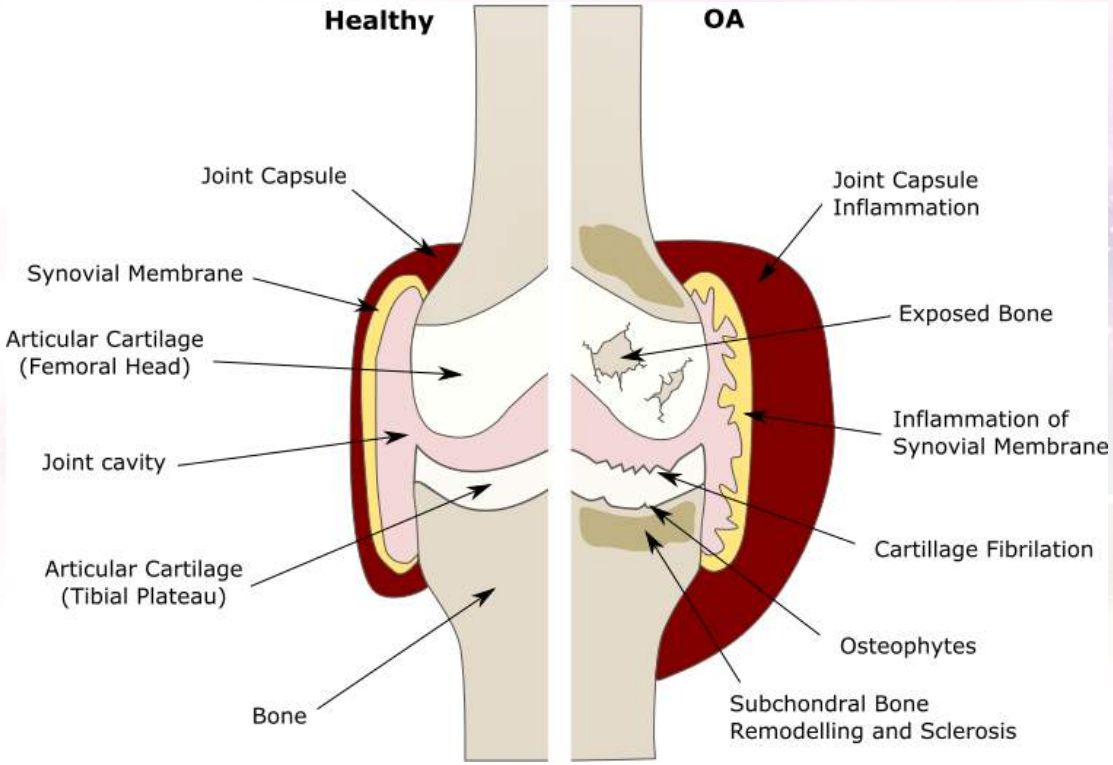
Introduction

Biomechanics and KOA

- Biomechanical knee Instability
- Abnormal mechanics lead to cartilage degradation
- Disrupted Biomechanical Signalling
- Cartilage Matrix Degradation



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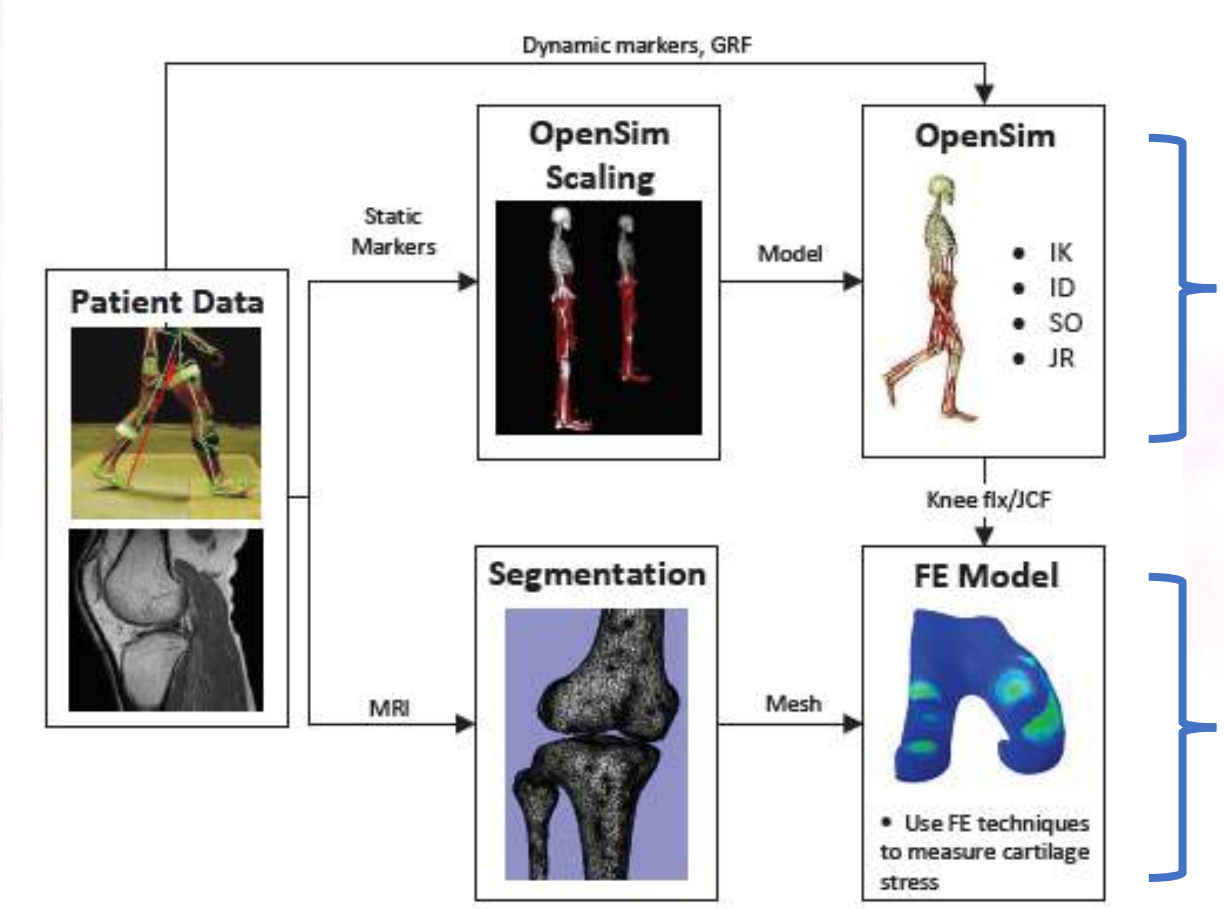
Biomechanics Pipeline



Musculoskeletal Pipeline:
Knee Joint Loading (Joint Level)

Finite Element Pipeline:
Cartilage Stress (Tissue Level)

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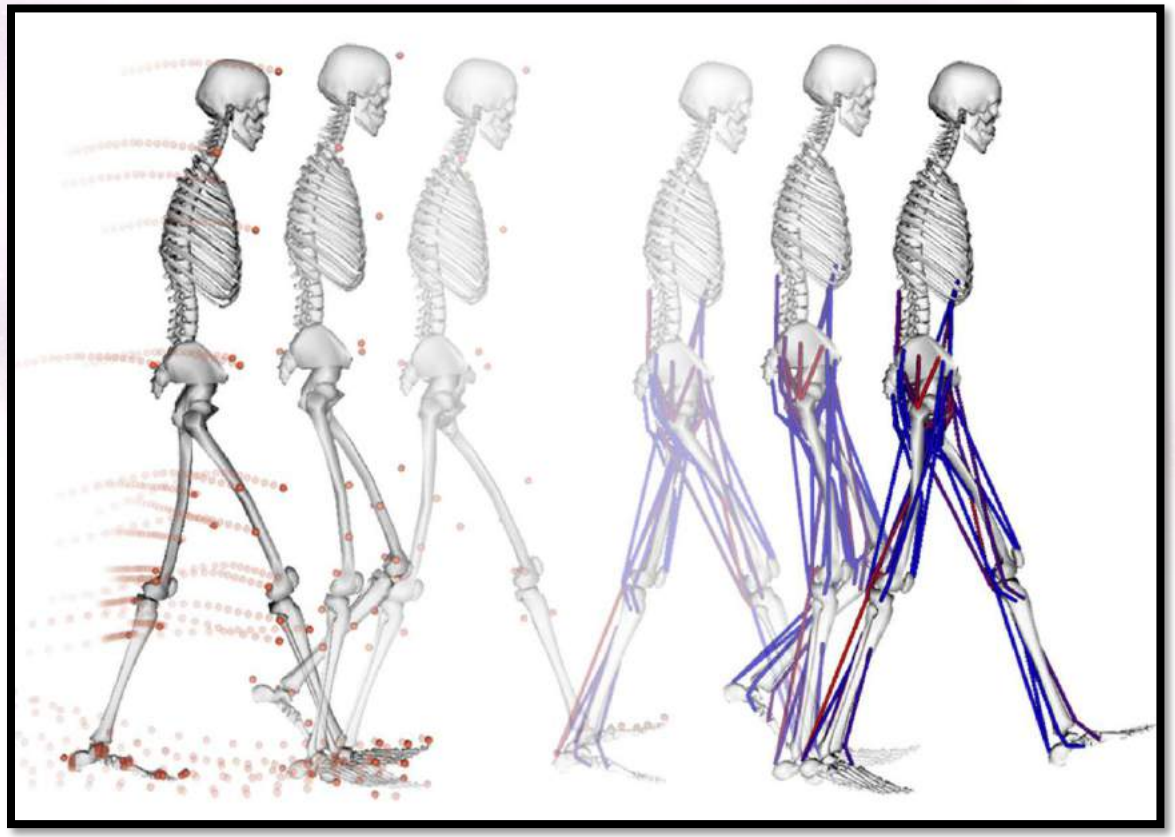
Musculoskeletal Model

OpenSim



Freely available open source software for developing models of the musculoskeletal system

Capable of modelling skeletal structures, joints and soft tissue elements

User extensible for adding new components and functionality

Large community support base

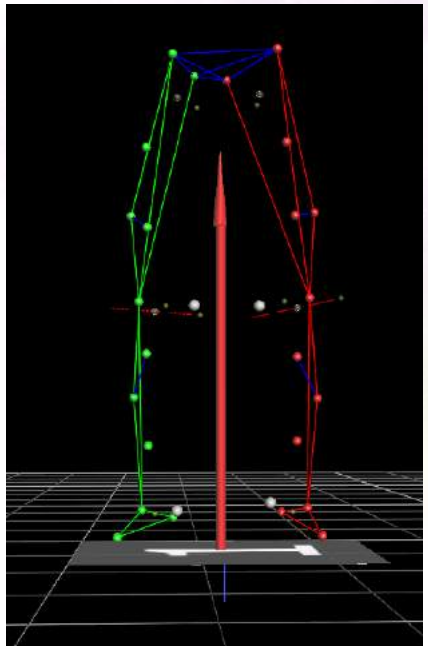
OActive https://simtk.org/projects/opensim

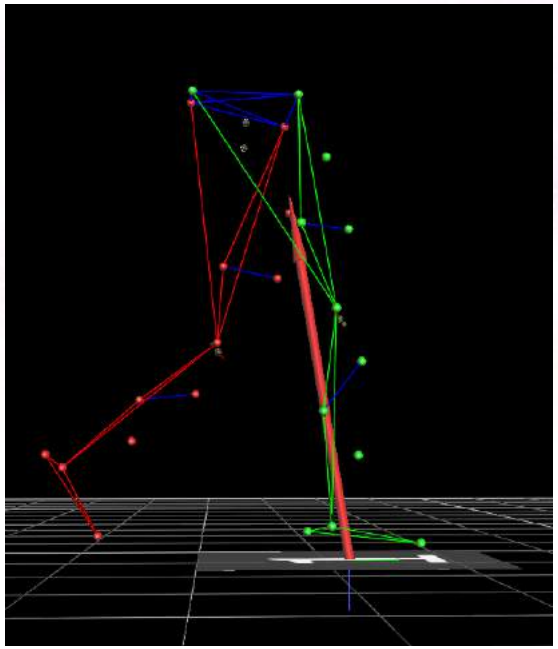
Musculoskeletal Model

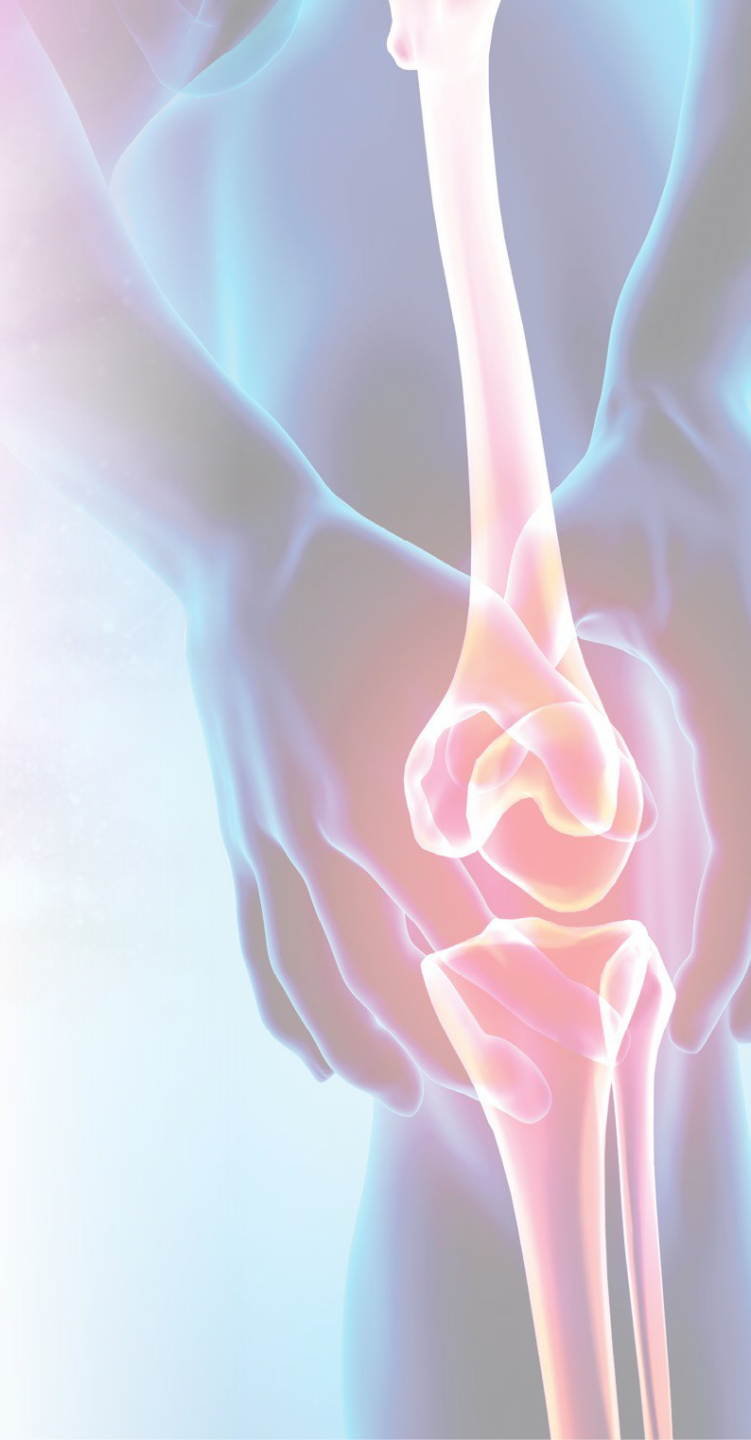
Input Data

Static

Dynamic







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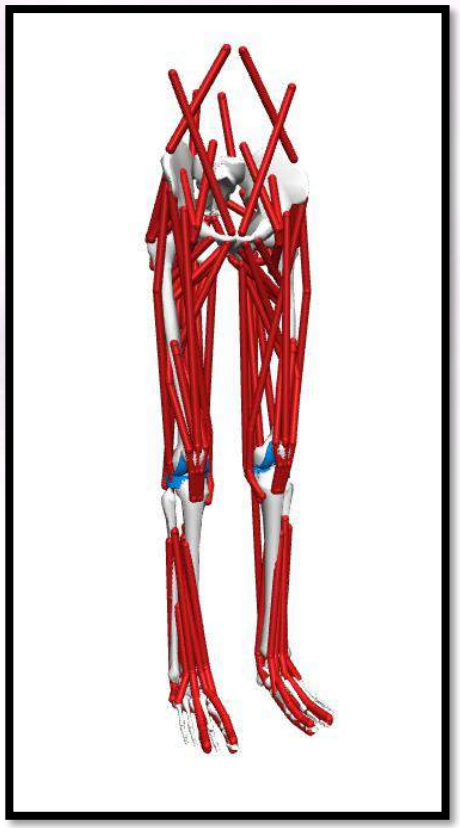
Musculoskeletal Model

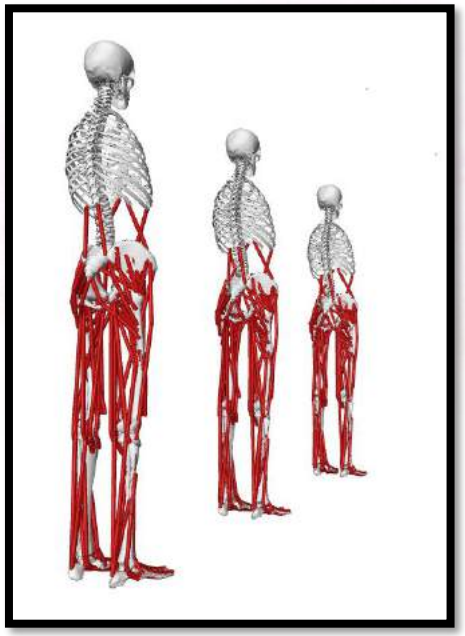
Building the Model

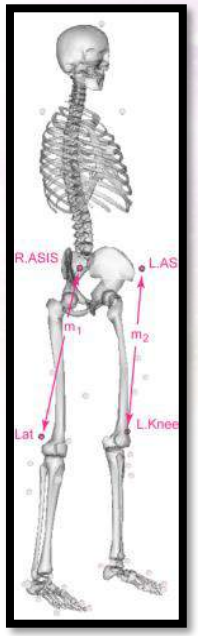


Generic Model

- Generic model of lower limb anatomy
- Often derived from cadaveric studies
- Can contain bodies, muscles, joints and other soft tissue elements

Scaling





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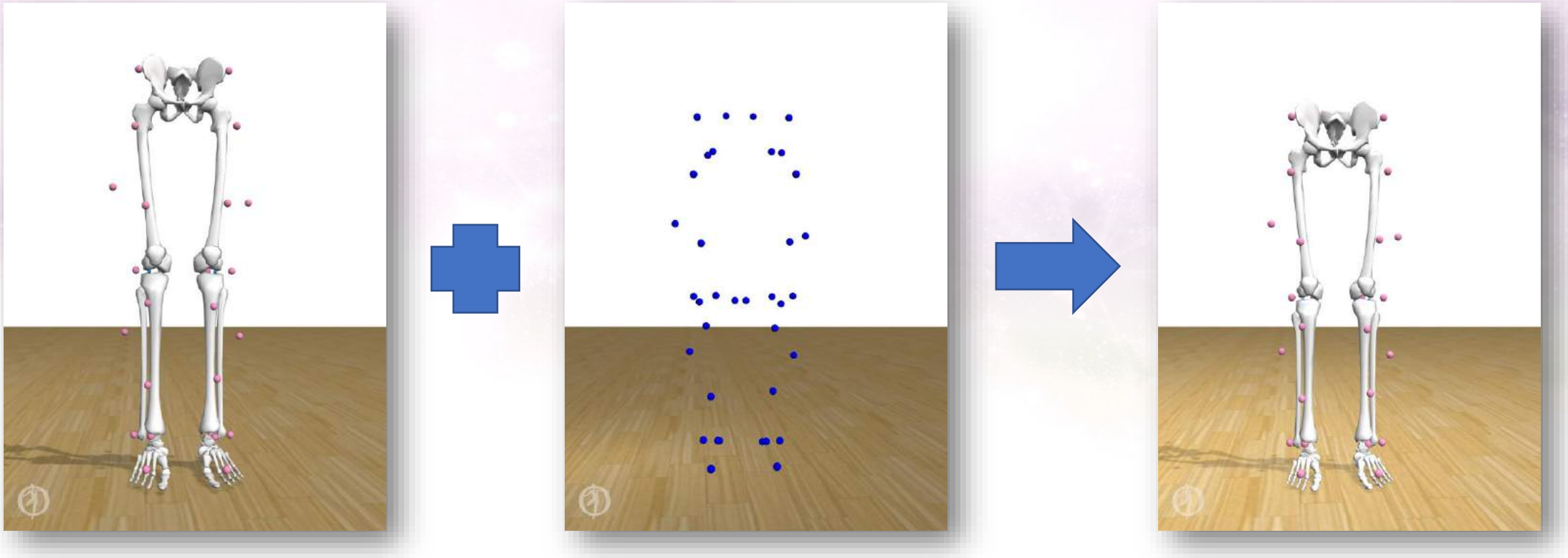
Musculoskeletal Model

Building the Model



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https://simtk-confluence.stanford.edu:8443/display/OpenSim/How+Scaling+Works

Musculoskeletal Model

Inverse Kinematics

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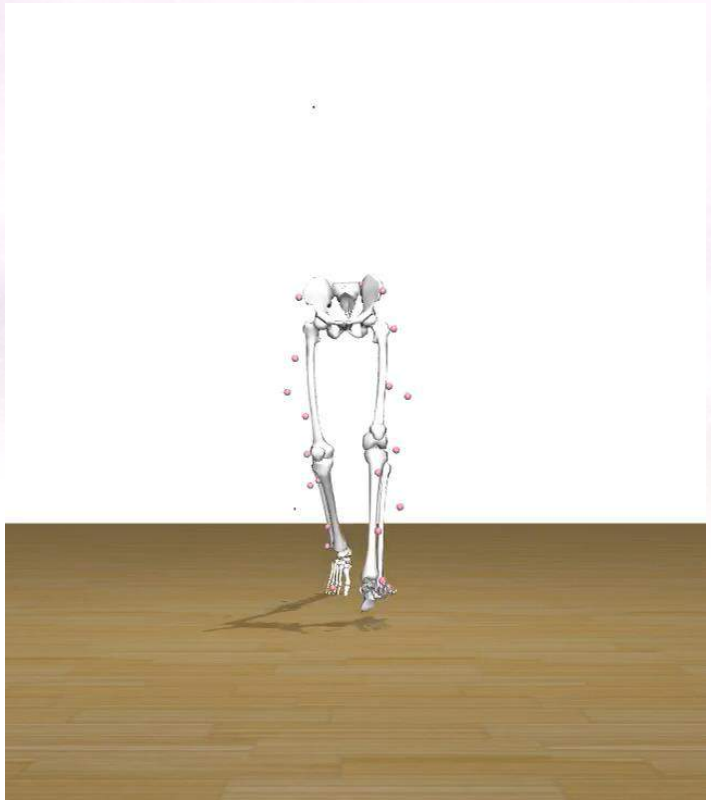
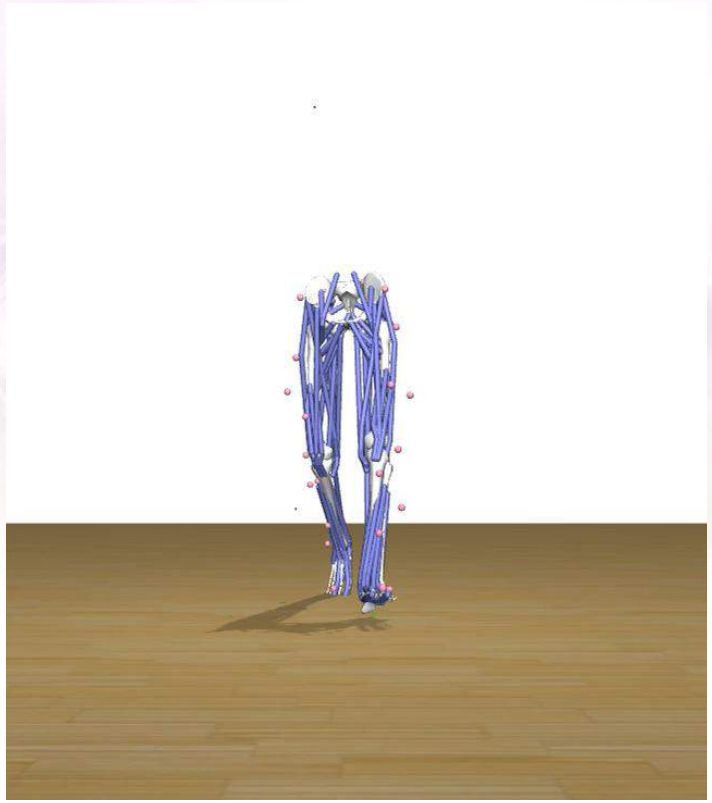
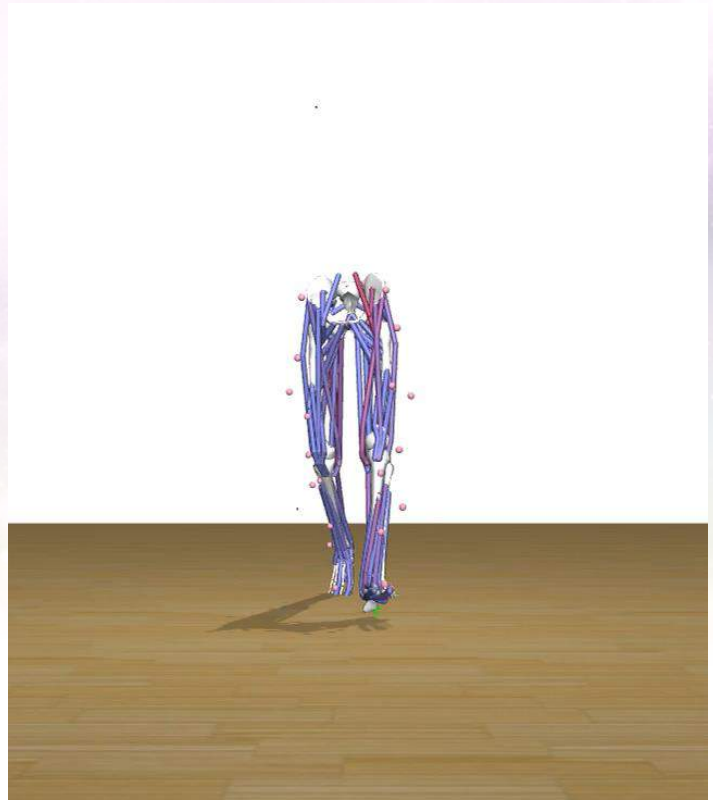
https://simtk-confluence.stanford.edu:8443/display/OpenSim/How+Inverse+Kinematics+Works

Musculoskeletal Model

Muscle and Joint Force Calculations





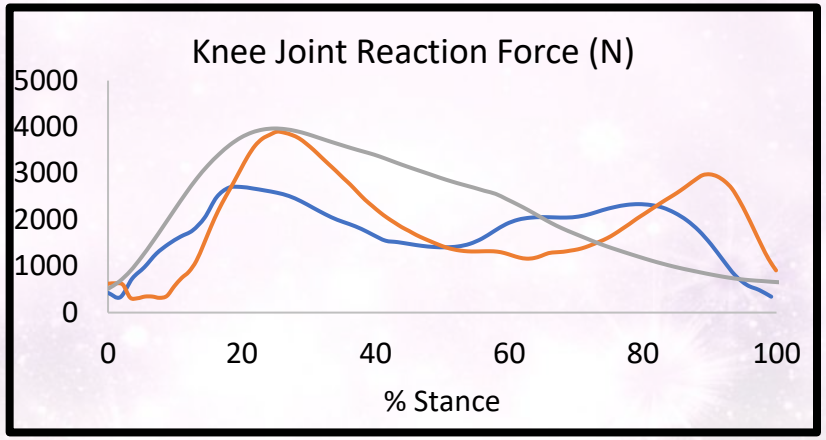


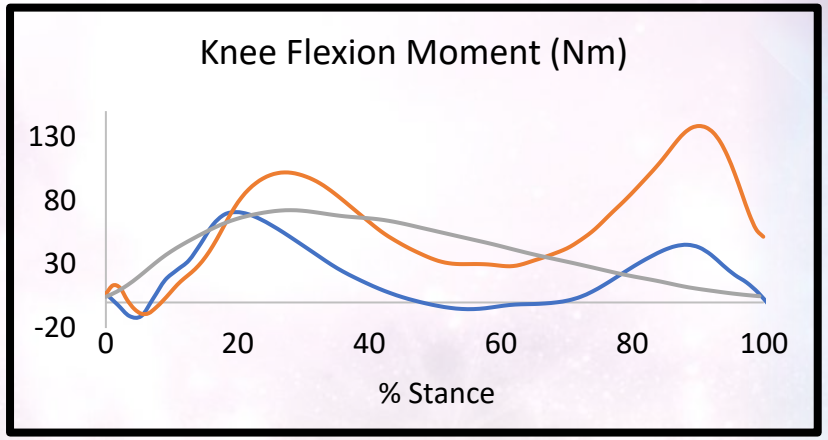
OActive

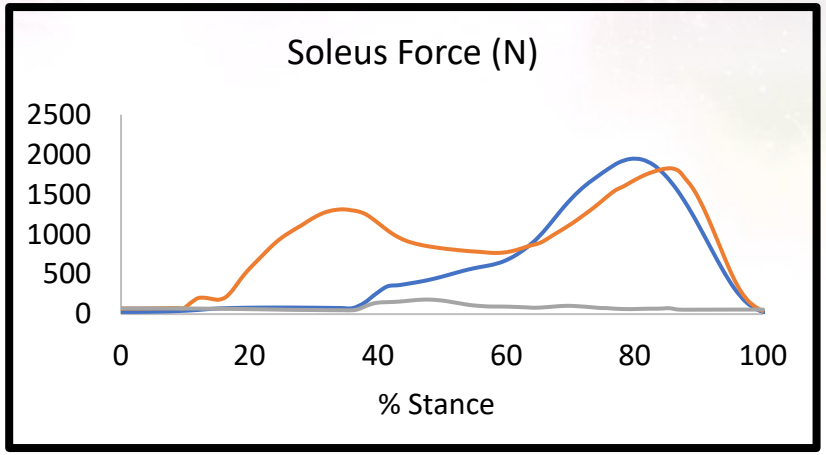
https://simtk-confluence.stanford.edu/display/OpenSim/How+Static+Optimization+Works

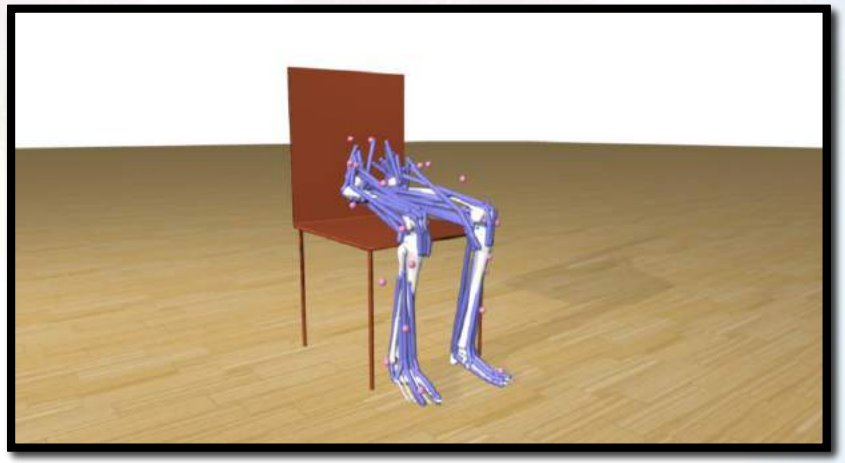
Musculoskeletal Model

Outputs









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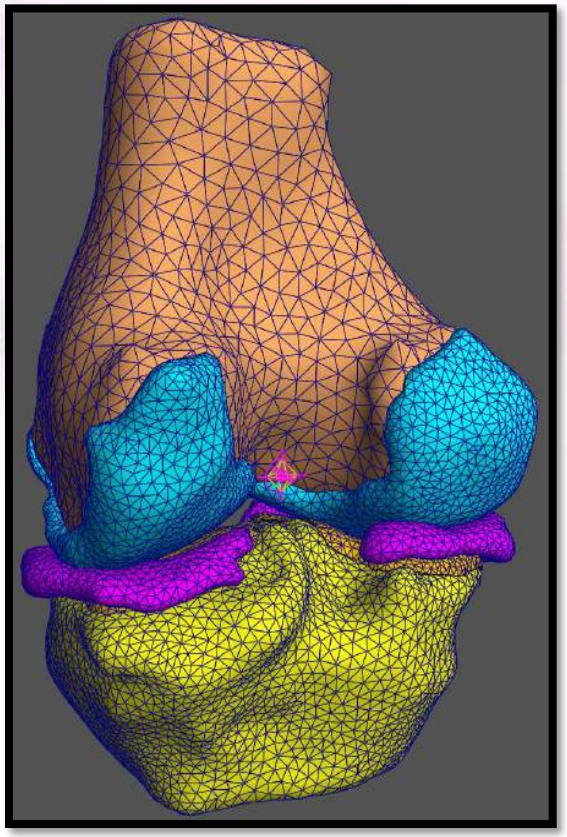
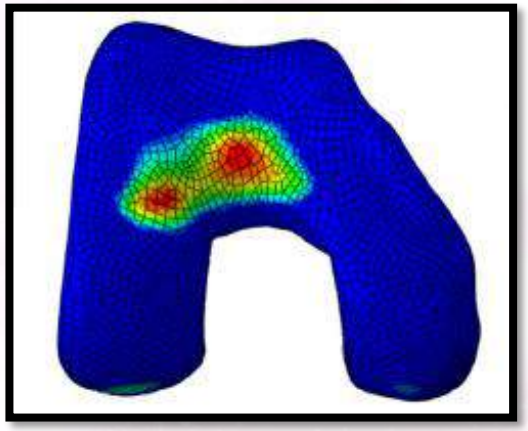
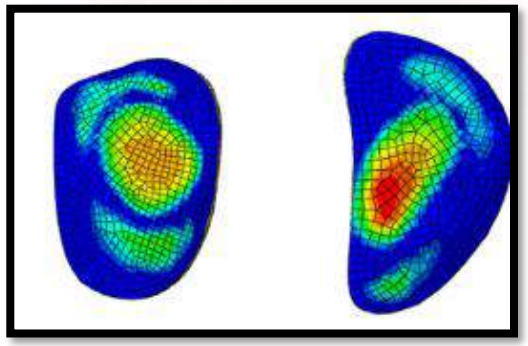
Walking Stepping Standing

Finite Element Model

FEBio





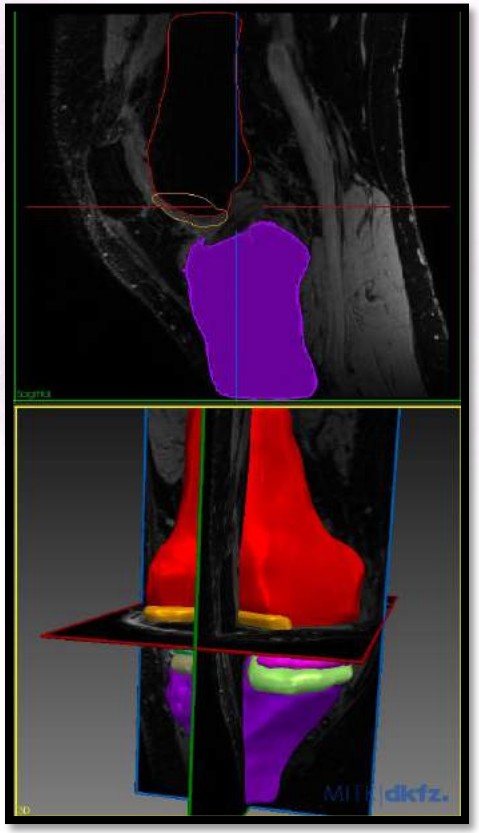


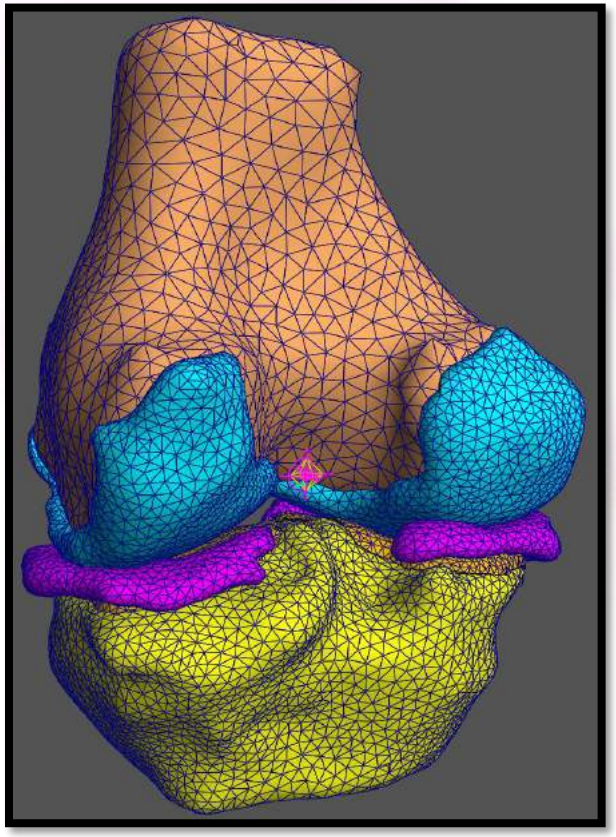
- Open source finite element analysis software
- Capable of calculating stresses on complex structures undergoing motion
- Wide range of material properties can be assigned to model components
- Companion software available for setting up simulations and viewing their output
- Large community support base

OActive https://febio.org/

Finite Element Model

MitK



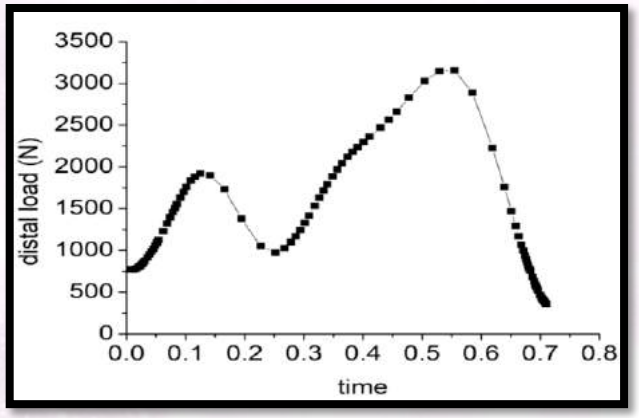


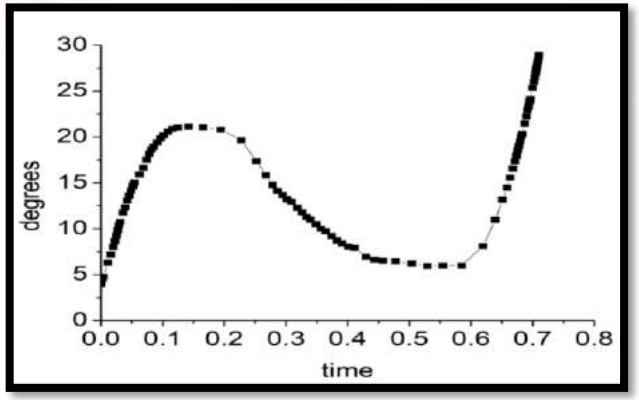
- Open source software
- Capable of interactively creating finite element models from medical images
- Tools for automatic and manual segmentation
- Tetgen tools for creating mesh geometries
- Plugins available to extend functionality and add new features

OActive http://mitk.org/wiki/The_Medical_Imaging_Interaction_Toolkit_(MITK)

Finite Element Model

Inputs





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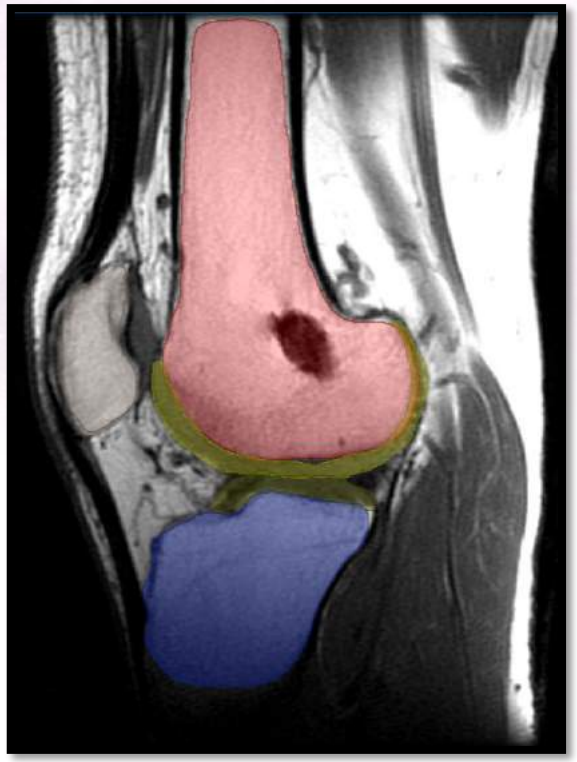
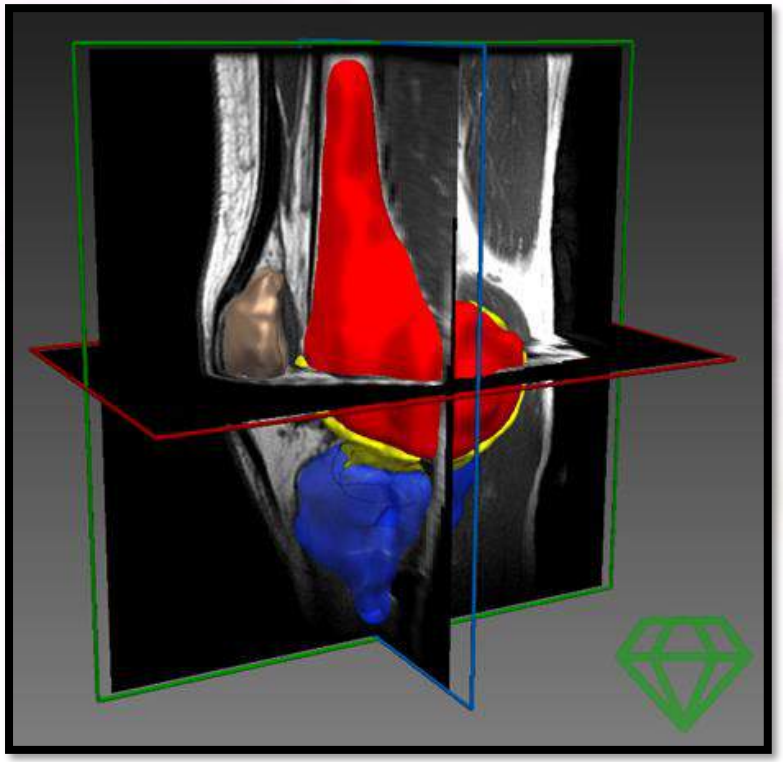
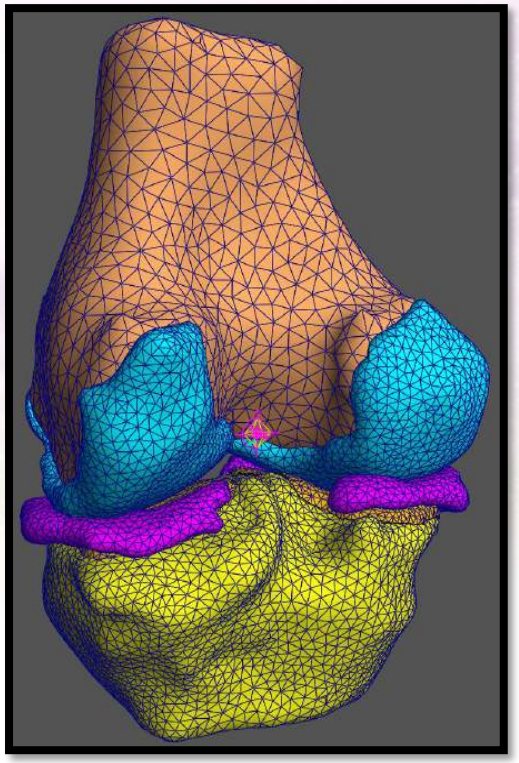
Finite Element Model

Creating a Model of the Knee







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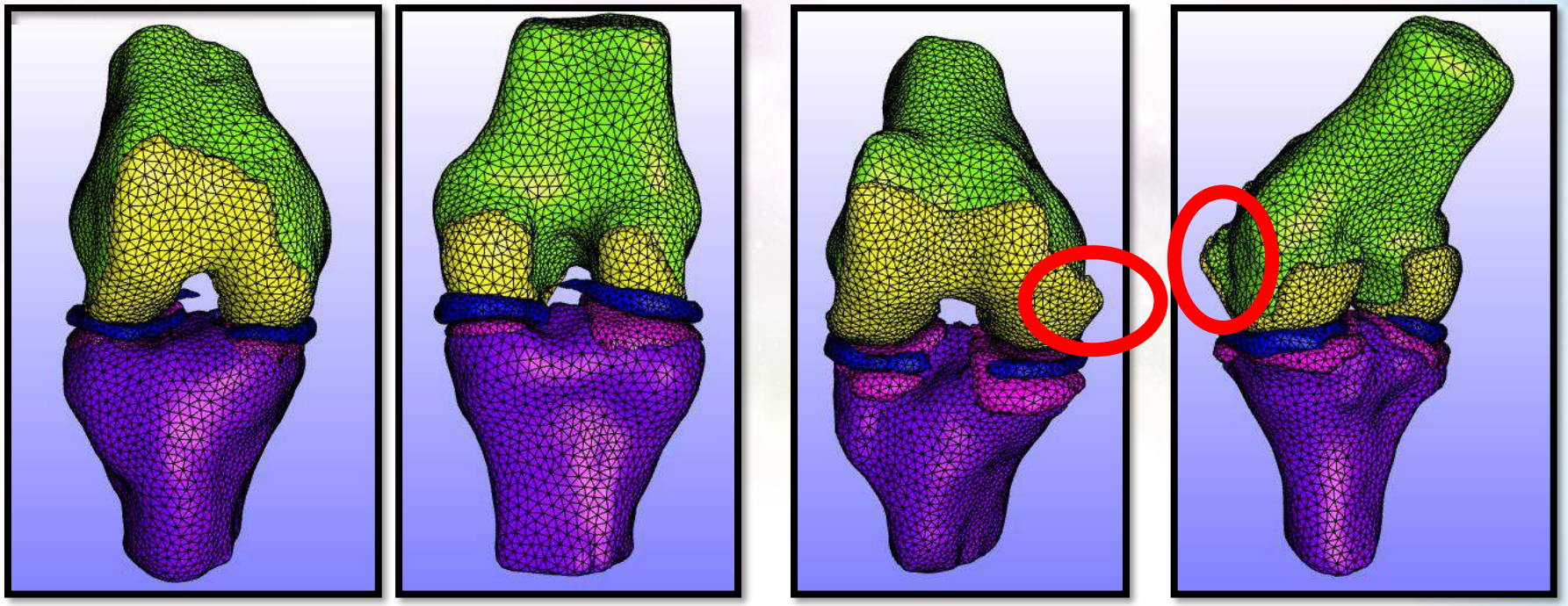
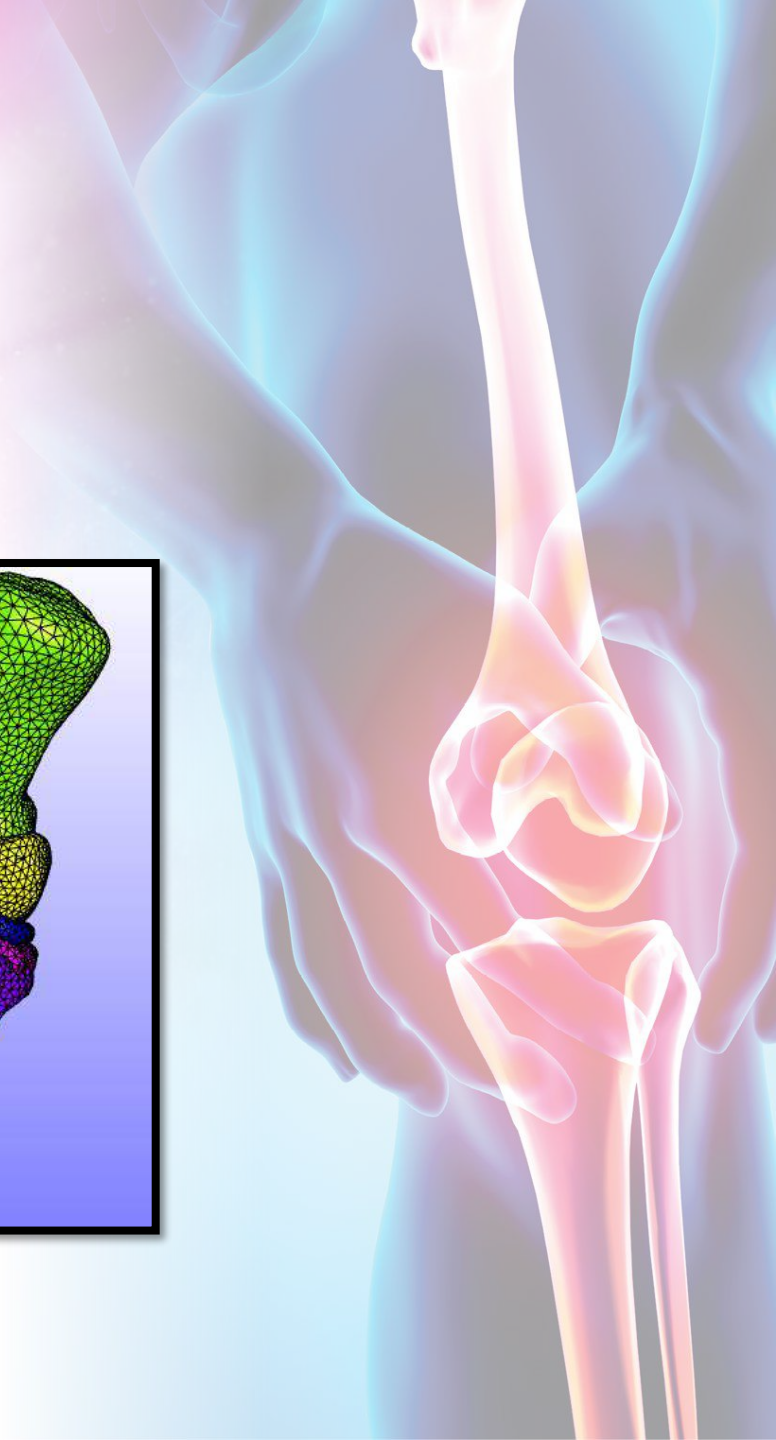
Finite Element Model

KOA Geometry

Healthy (KL=0)

Osteoarthritic (KL=2+)





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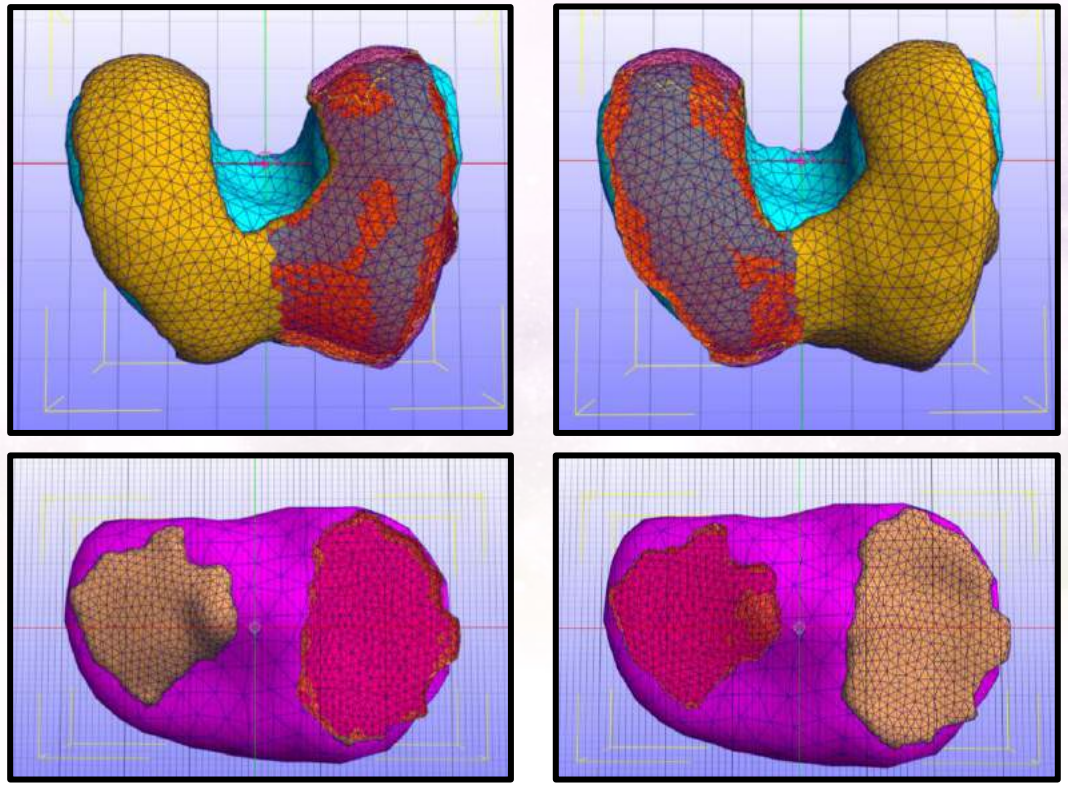
Finite Element Model

Applying Realistic Loading

- Define:
  - Loading parameters (joint contact forces)
  - Kinematic parameters (joint flexion angles)
  - Material properties
  - Contact properties



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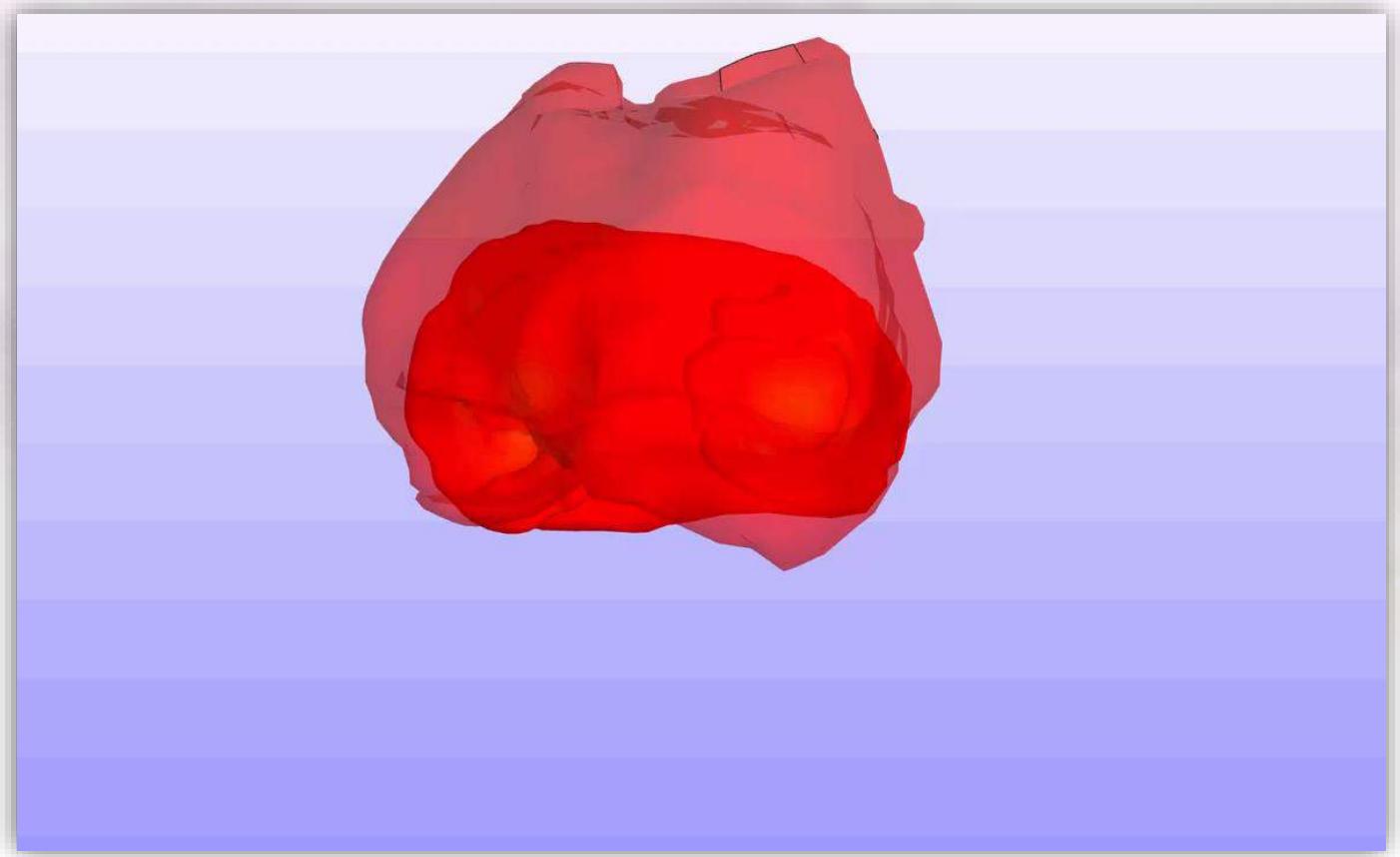
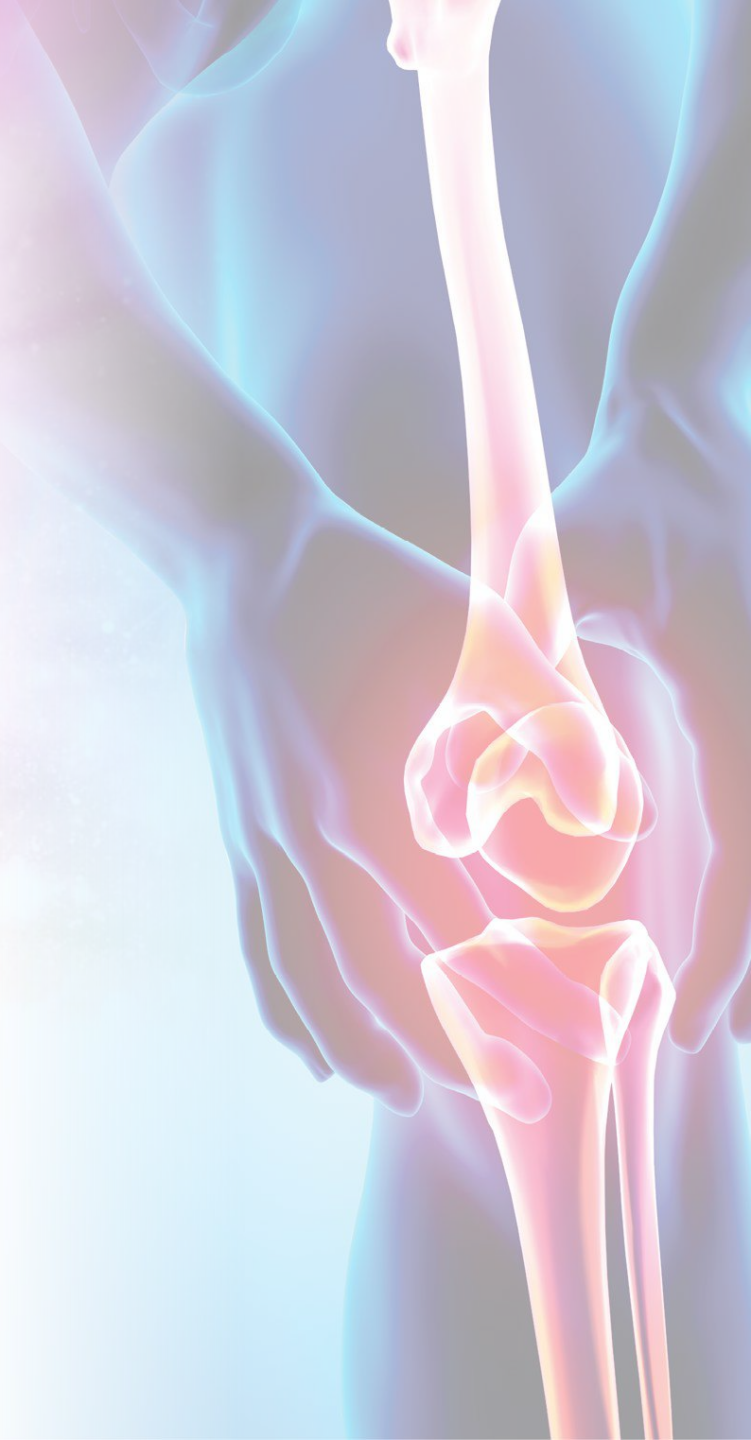
Finite Element Model

Simulation





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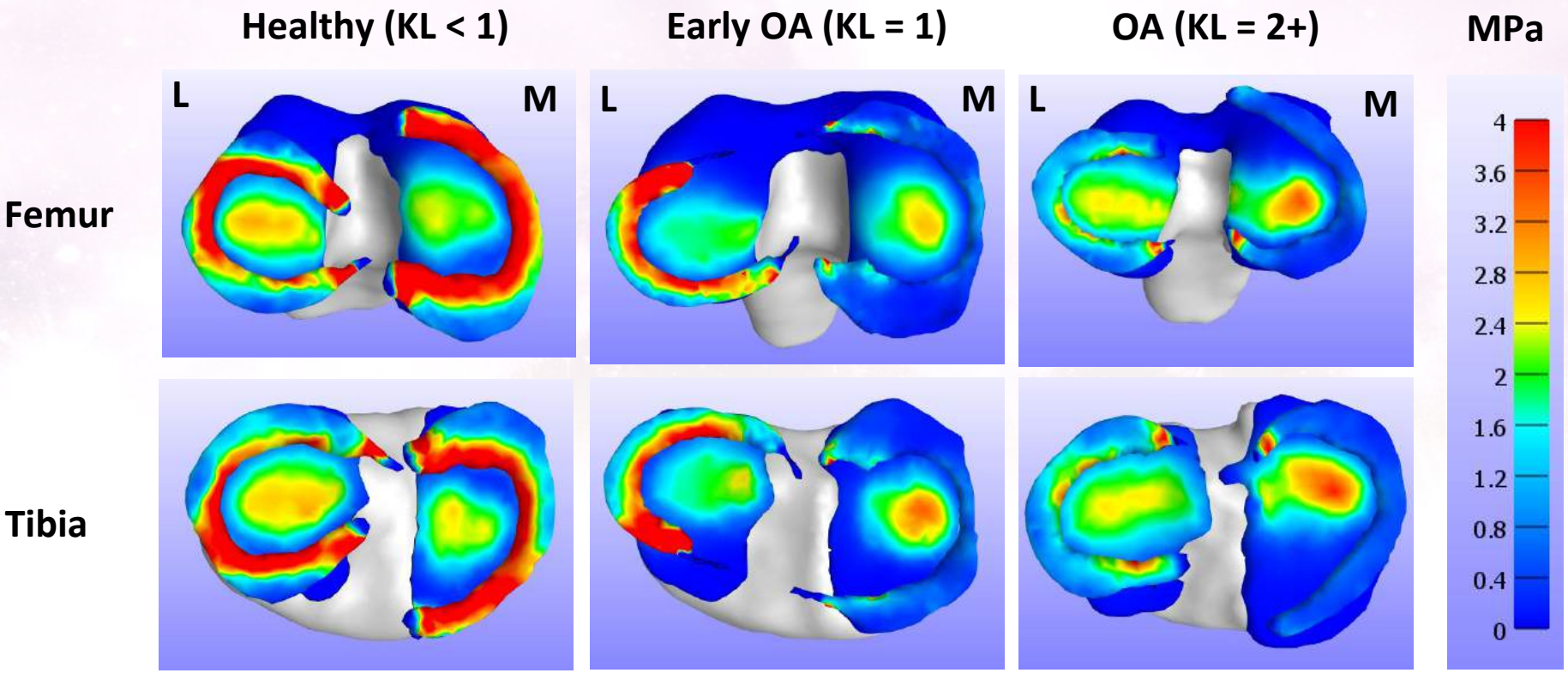
Finite Element Model

Visualizing Cartilage Stress



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Conclusion

Summary:

- Multi-scale models can help us to understand the effect of degenerative disease on joint tissues
- Can be developed using open source software that is freely available
- Play an important role in OACTIVE to provide information about knee joint loading to the neural network

Future Work:

- Validation of models on instrumented datasets
- Full analysis of data collected from complete OACTIVE cohort
- Use the results from the models to inform bioreactor experiments investigating the effect of cartilage stress on gene expression (completing the circle from macro-micro scale)

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Project full title:

Advanced personalised, multi-scale computer models preventing OsteoArthritis

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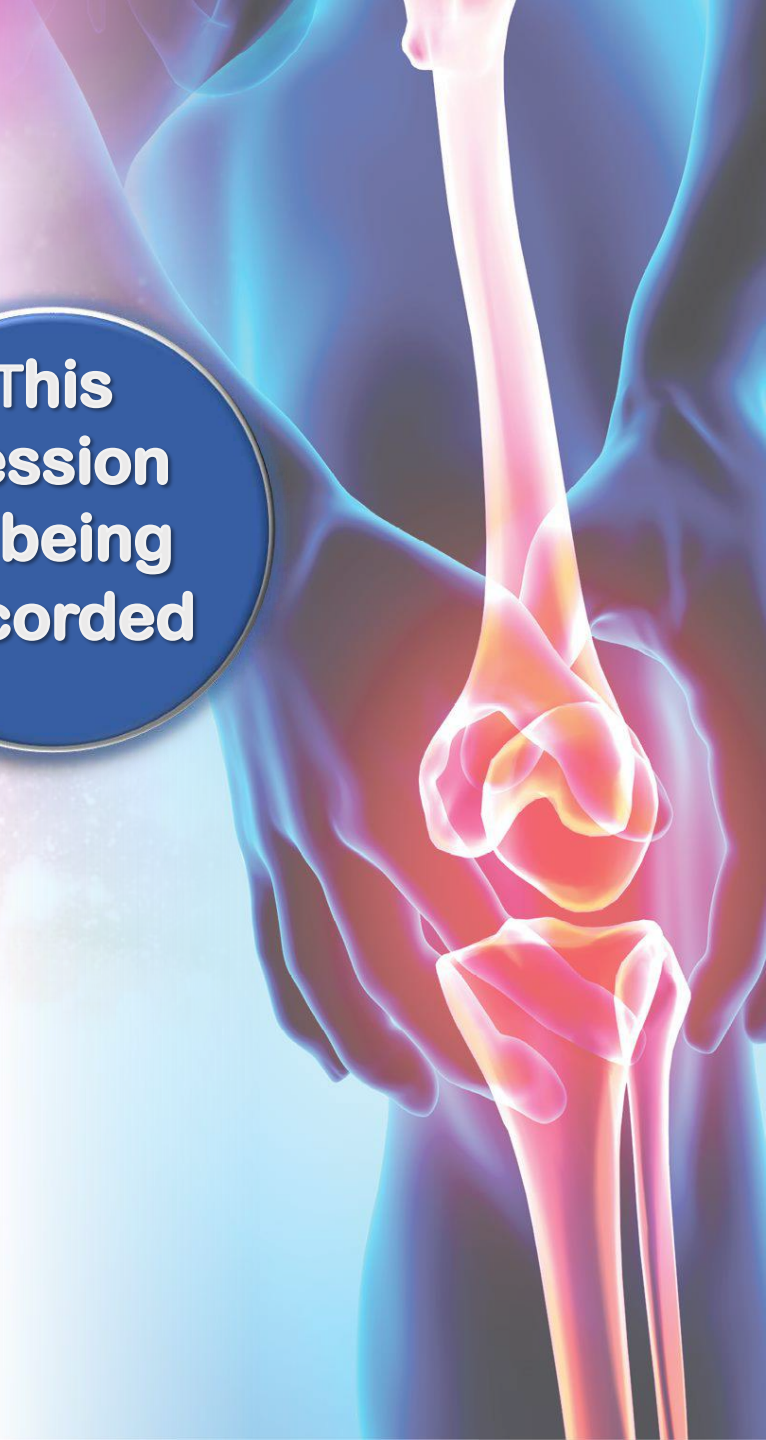


This session is being recorded

Training session:

ENGAGING END USERS TO THE OACTIVE WORLD

Computational modelling empowered by big data and deep learning

Dimitrios Tsaopoulos, CERTH

Grant agreement 777159

SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

OActive

Biochemical modelling and inflammation biomarkers

Behaviour modelling and environmental biomarkers

Biomechanical modelling of the knee

Computational modelling empowered by big data and deep learning

Using artificial tissues as test-bench for rehabilitation against osteoarthritis

Real time gait monitoring and retraining

Training session presentation overview

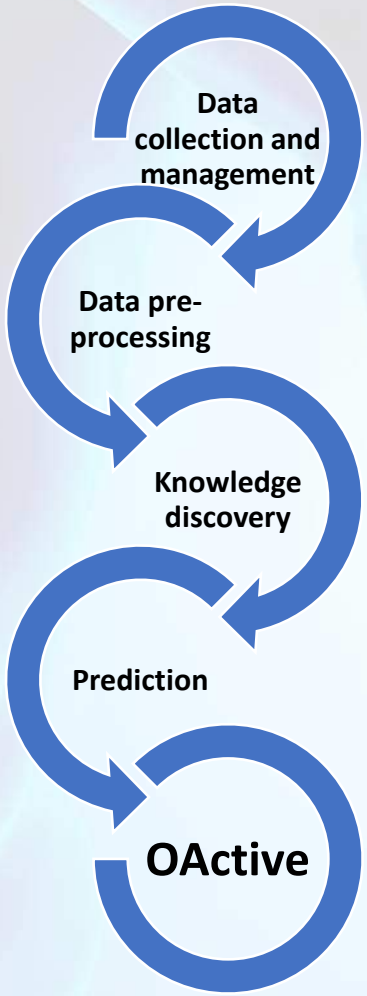
- ✓ Term of Machine Learning
- ✓ Machine learning system
- ✓ Knee Osteoarthritis (KOA) Challenges
- ✓ Advantages of Machine Learning
- ✓ Objectives
- ✓ Concept
- ✓ Data pre-processing
- ✓ Feature selection
- ✓ Machine Learning VS Deep Learning

Knee Osteoarthritis (KOA) Challenges

- KOA is a degenerative disease of the knee joint and the most common form of arthritis.
- There is no known cure for KOA, but there are several medical, biological and environmental risk factors.
- Nowadays biomedical research and clinical practices on KOA are struggling to cope with the growing complexity of interactions with the gained knowledge being fragmented and associated either with molecular/cellular processes or with tissue and organ phenotype changes related to clinical symptoms.
- The aforementioned data characterizing KOA are high-dimensional and heterogeneous.

Objectives

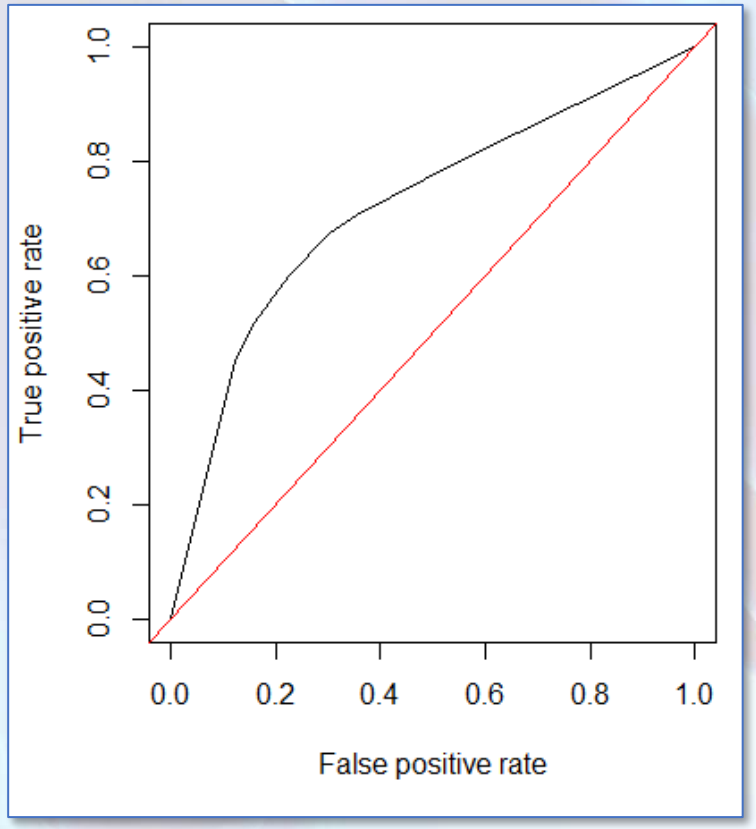
OACTIVE targets to add a new dimension to the diagnosis and treatment of OA by introducing Big Data and Deep Learning technologies



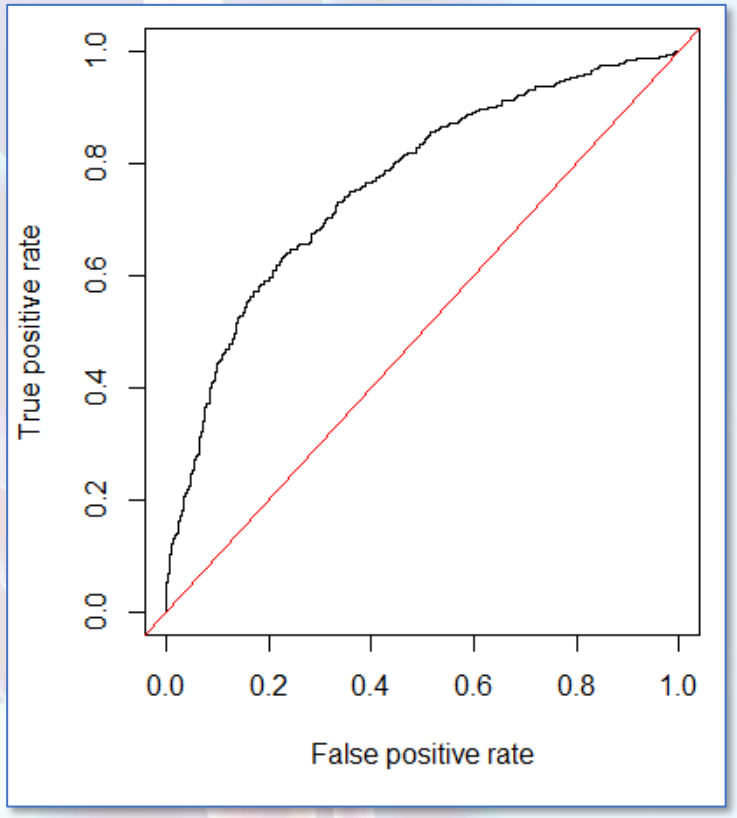
Knowledge discovery

Factors association with KL > 1 at baseline

Data from the OAI



CART: AUC = 0.719

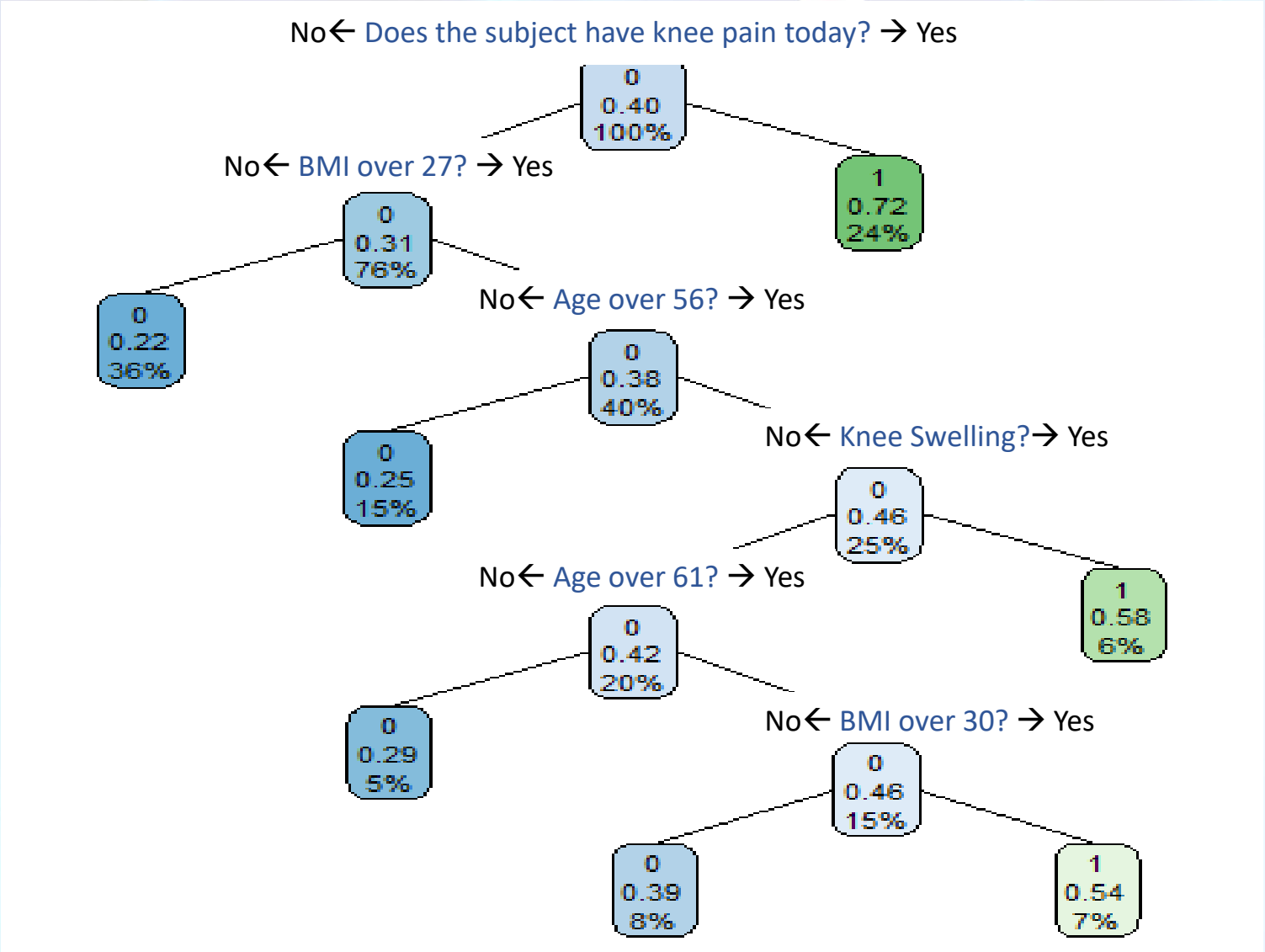


Logistic Regression: AUC = 0.763

Knowledge discovery

Factors association with KL > 1 at baseline

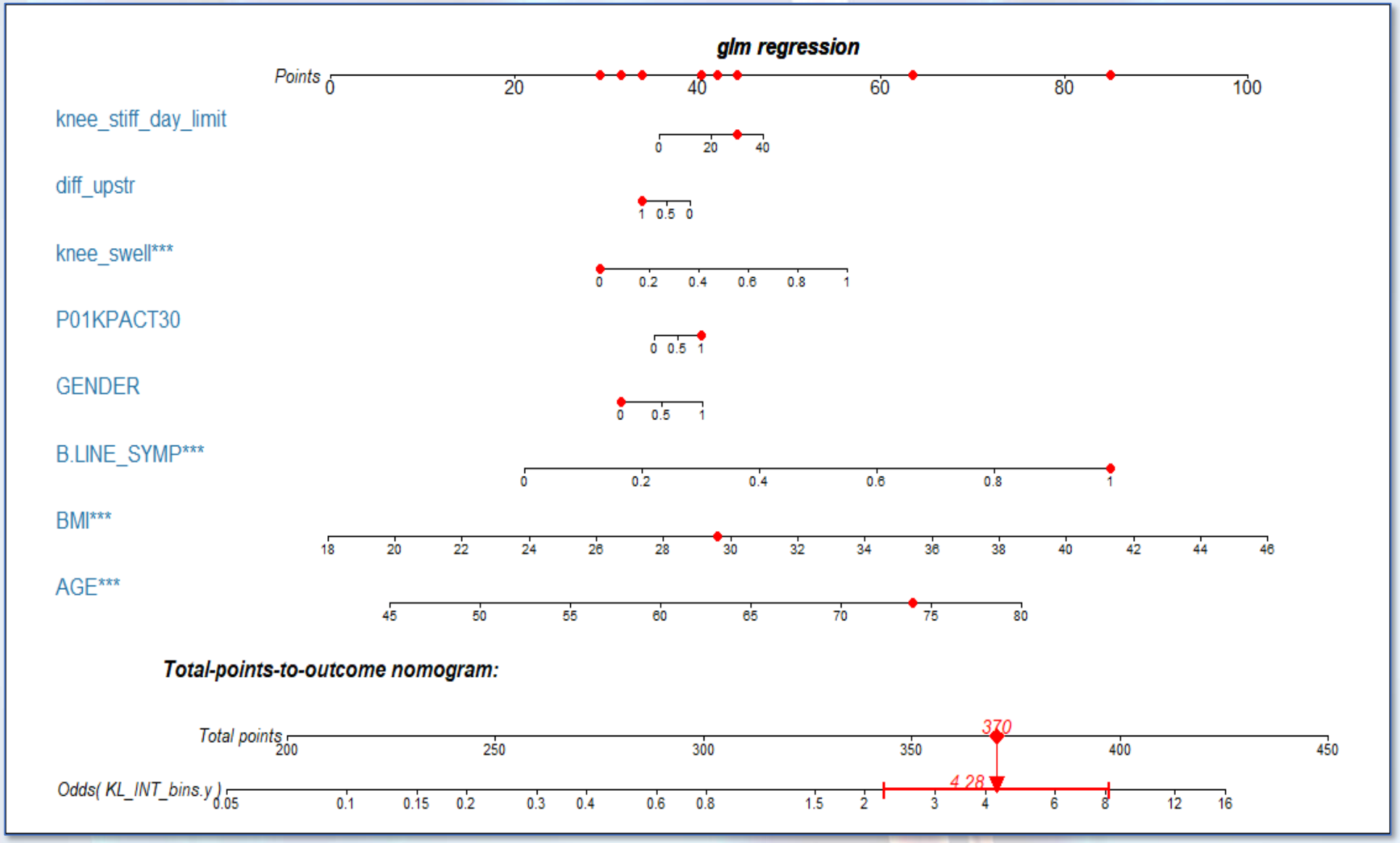
Data from the OAI



Knowledge discovery

Factors association with KL > 1 at baseline

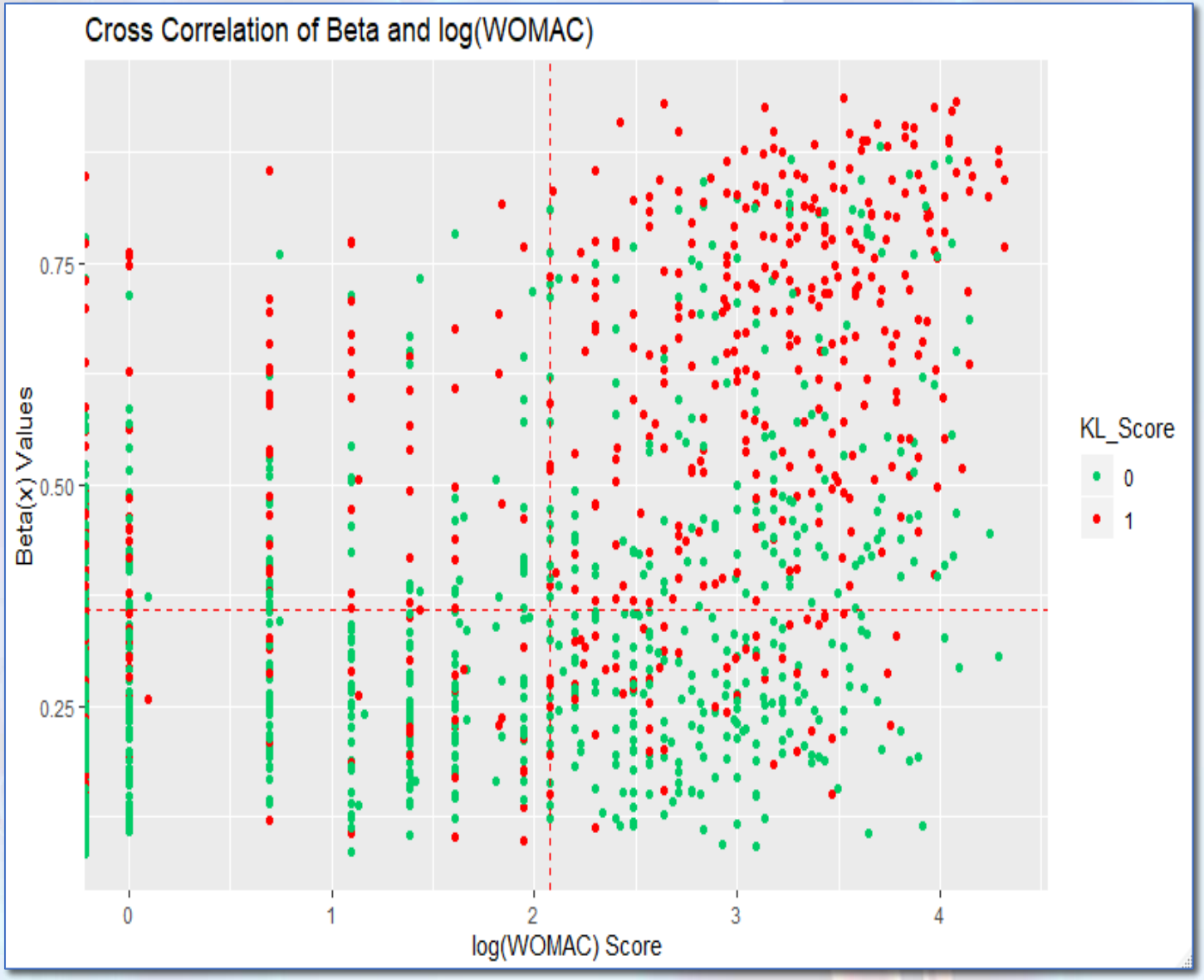
Data from the OAI



Knowledge discovery

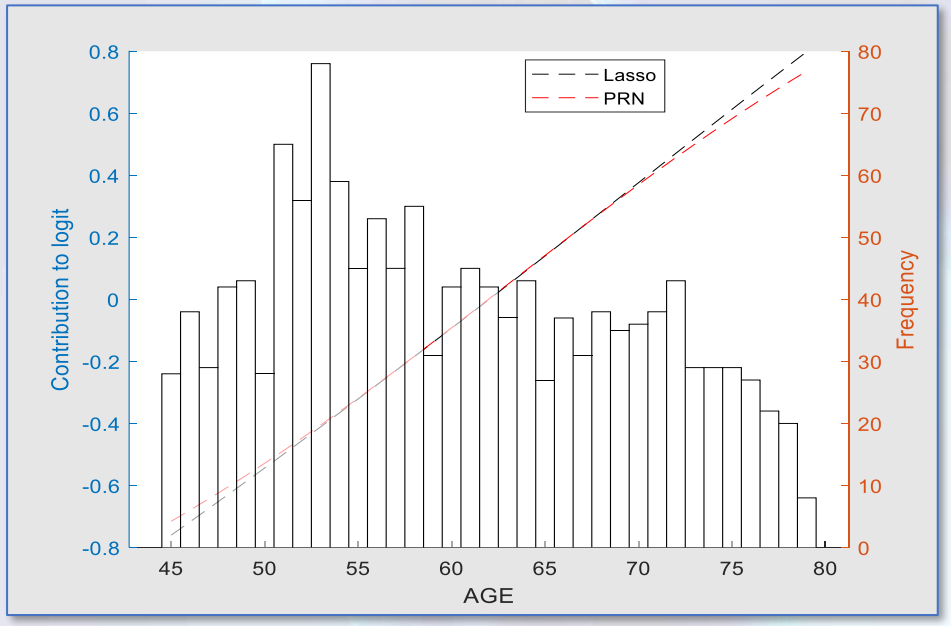
KL *vs.* WOMAC

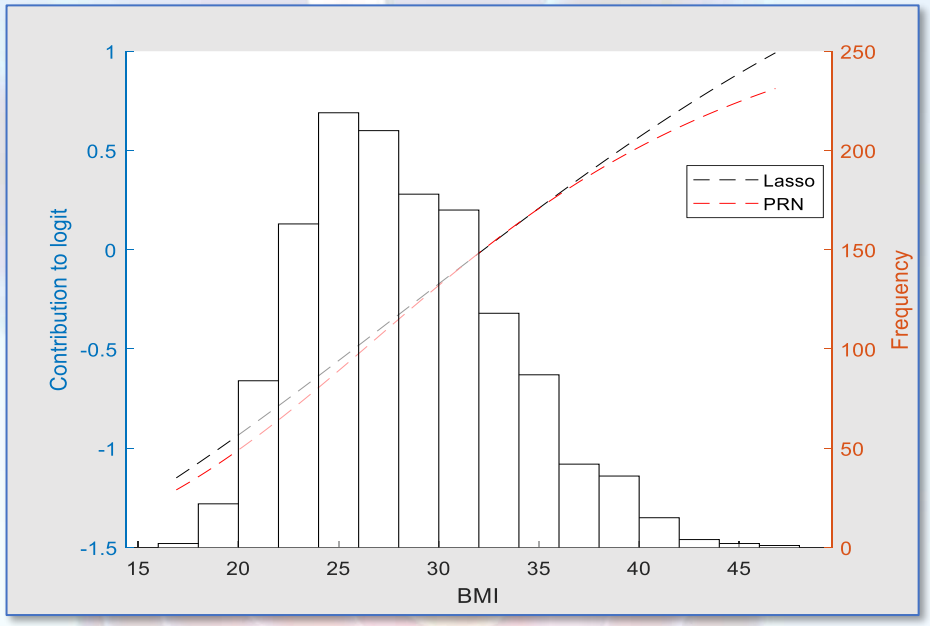
Data from the OAI

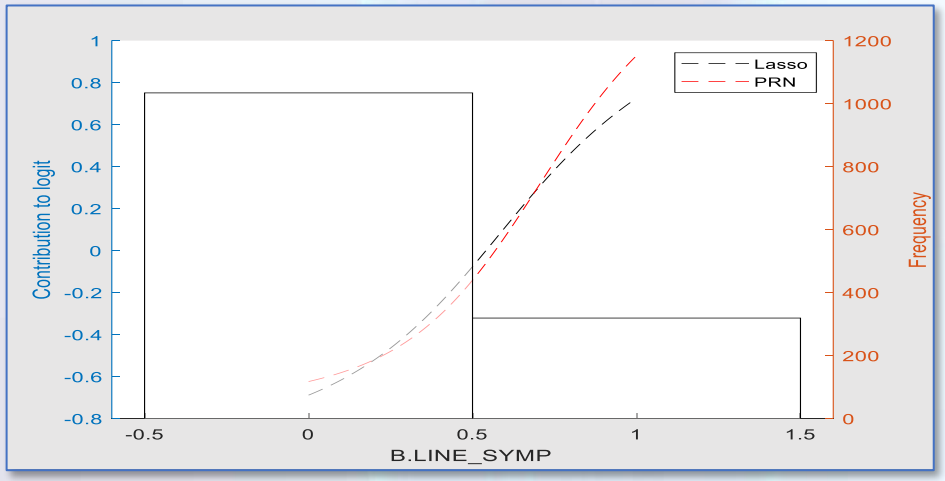


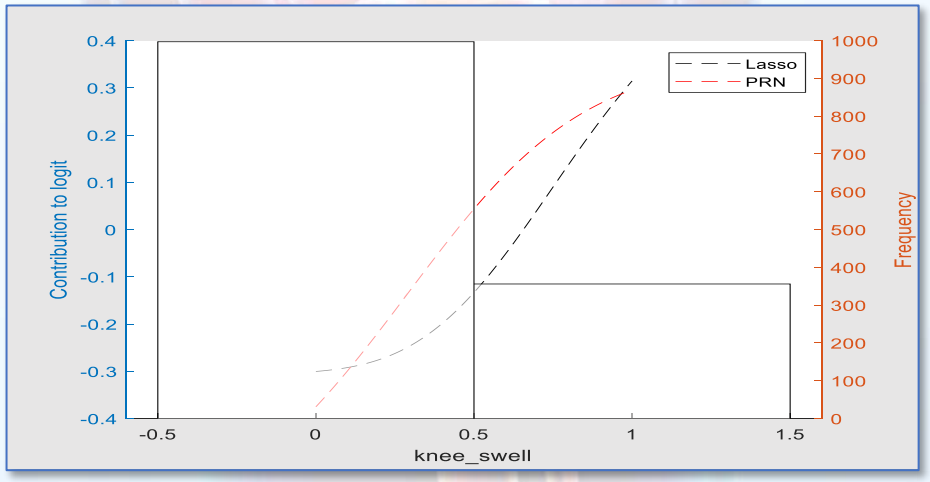
Partial Response Network

Linearity of factors association with KL > 1 at baseline: Data from the OAI









Advantages of Machine Learning

- ✓Machine learning can explore massive design spaces to identify correlations.
- ✓The multiscale modelling can predict system dynamics to identify causality.
- ✓Development of individually tailored treatments leads to maximize the efficacy of treatment.
- ✓Research work at the intersection of machine learning and KOA offers great promise for improving clinical decision-making and accelerating relevant intervention programs.

Computational modelling empowered by big data and deep learning

Step 1: Data pre-processing

A. Data preparation (5 feature sets, Data from the Osteoarthritis Initiative)

- {FS1}: Baseline (*724 features*)
- {FS2}: Progress of visit 12 with respect to baseline(*233 features*)
- {FS3}: Progress of visit 24 with respect to baseline (*275 features*)
- {FS4}: FS1 + FS2(*957 features*)
- {FS5}: FS1 + FS3 (*999 features*)

B. Handling of missing data

- **Deleting Columns (20% of missing values)**
- **Two imputation methods**
  1. K- Nearest Neighbours (KNN)
  2. Most Frequent (mode)

C. Balancing of examples per class & Normalisation

Undersampling to **Class 1**: KL0-1 at BL but no incident KL >=2

Class 2: KL0-1 at BL with incident KL>=2 after visit at M12 (M24)

D. Normalization of data ([0, 1])

Computational modelling empowered by big data and deep learning

Step 2: Feature selection

To avoid bias, features are selected on the basis of 6 FS techniques

Filter Methods:
- ✓ Pearson Correlation
- ✓ Chi-2

Wrapper
- ✓ Recursive Feature Elimination (RFE)

Embedded
- ✓ Logistics Regression L1
- ✓ Random Forest
- ✓ LightGBM

Training: with Baseline (00) + visit M12
Imputation: mode (mode frequent value)

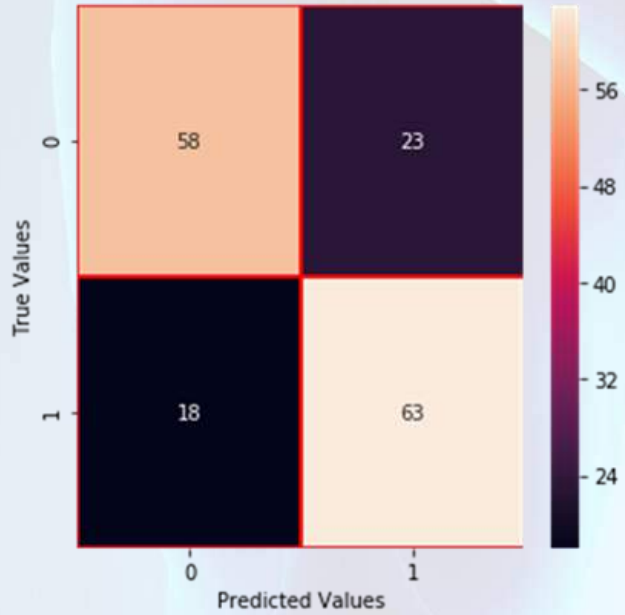
Feature	Description	Category	Criterion
P02WTGA	IEI:Above weight cut-off for age/gender group (calc, used for study eligibility)	Anthropometrics	6/6
V00WPRKN2	EV: Right knee pain: stairs, last 7 days	Symptoms	5/6
V00RXANALG	EV:MIF: Rx Analgesic use indicator (calc)	Medical history	5/6
V00PCTSMAL	SAQ: Block Brief 2000: error flag, percent of foods marked as small portion (calc)	Nutrition	5/6
V00GLUC	EV:Q52b.Used glucosamine for joint pain or arthritis, past 6 months	Medical history	5/6
V00GLCFQCV	EV:Q52bi.Glucosamine frequency of use, past 6 months (calc)	Medical history	5/6
V00CHON	EV:Q52a.Used chondroitin sulfate for joint pain or arthritis, past 6 months	Medical history	5/6
V00CHNFQCV	EV:Q52ai.Chondroitin sulfate frequency of use, past 6 months (calc)	Medical history	5/6
V00BAPCARB	SAQ: Block Brief 2000: daily % of calories from carbohydrate, alcoholic beverages excluded from denominator (kcal) (calc)	Nutrition	5/6
P02KPNRCV	IEI:Q9a.Right knee pain, aching or stiffness: more than half the days of a month, past 12 months (calc, used for study eligibility)	Symptoms	5/6

Computational modelling empowered by big data and deep learning

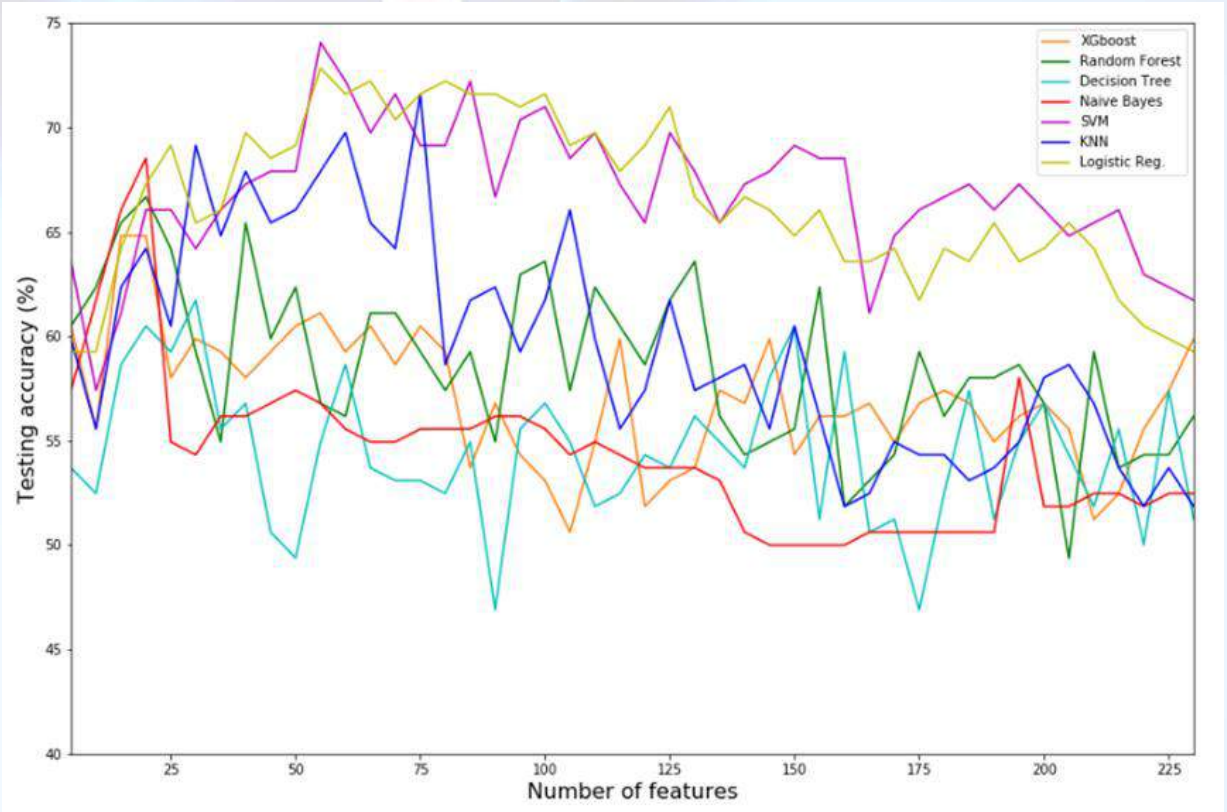
Results of Machine Learning approach

Seven (7) ML models were trained with hyperparameter tuning for each of the approaches:

- Logistic Regression
- KNN
- SVM
- Naïve Bayes
- Decision Tree
- Random Forest
- XGboost



Confusion matrix



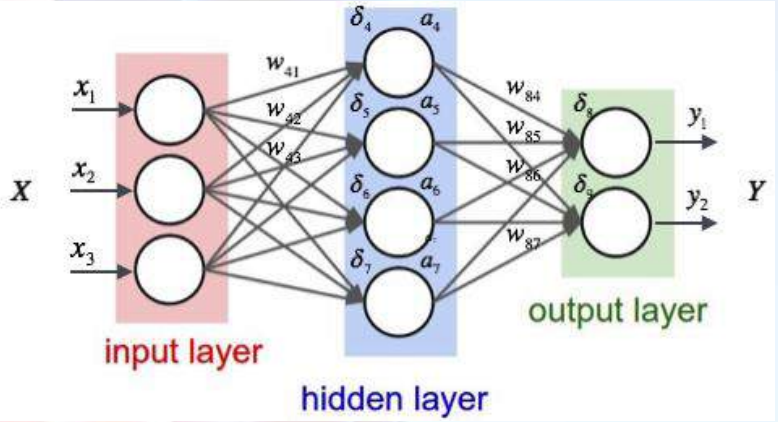
The best accuracy score (74.69%) is achieved by the combination of SVM classifier and 60 Features

Machine Learning VS Deep Learning

1. Data preparation
2. Handling of missing data
3a. Class balancing
3b. Normalisation
4. Feature Selection

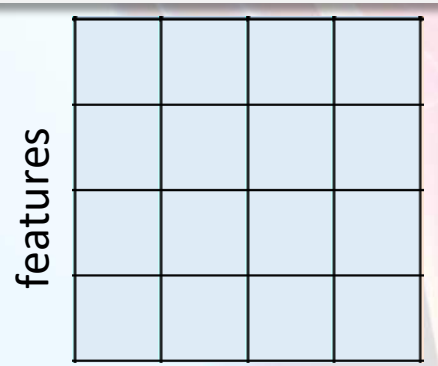
feature vector

5a. Machine Learning

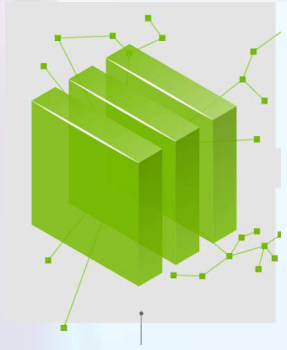


5b. Deep Learning

Feature vector to Image



Transfer learning

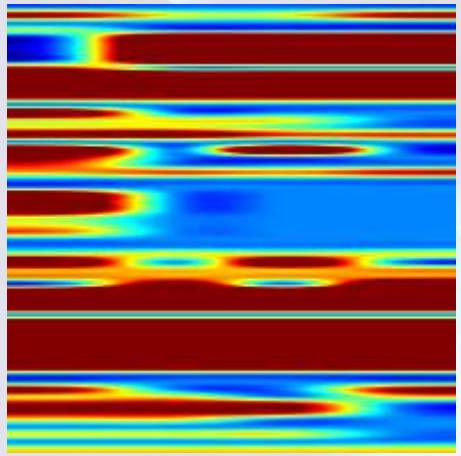


Pre-trained CNN

Deep Learning

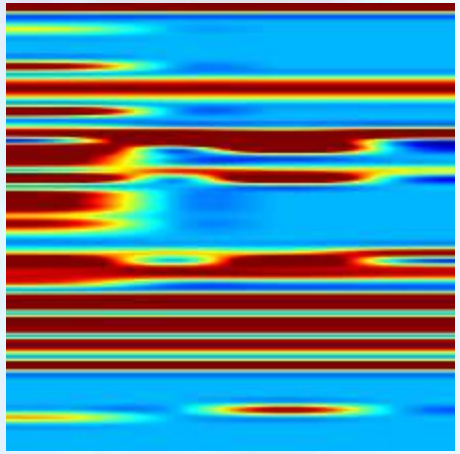
progression

Selected features

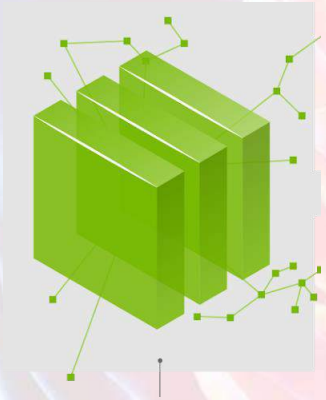


No progression

Selected features



Transfer learning



Pre-trained CNN
(GoogleNet
SqueezeNet)
*with adaptation
of the final layers

Decision
(pending)

Conclusions

- Data pre-processing plays key role.
- To avoid bias, a robust feature selection methodology was employed that combined the outcomes of six FS techniques.
- Artificial intelligence techniques with less complexity are more effective the certain problem.
- To enable appropriate adoption of advanced learning algorithms and stay tuned with the new developments in ML/DL that are embracing research to other medical fields, open data, tools, and discussions must be forceful encouraged within the KOA research community.

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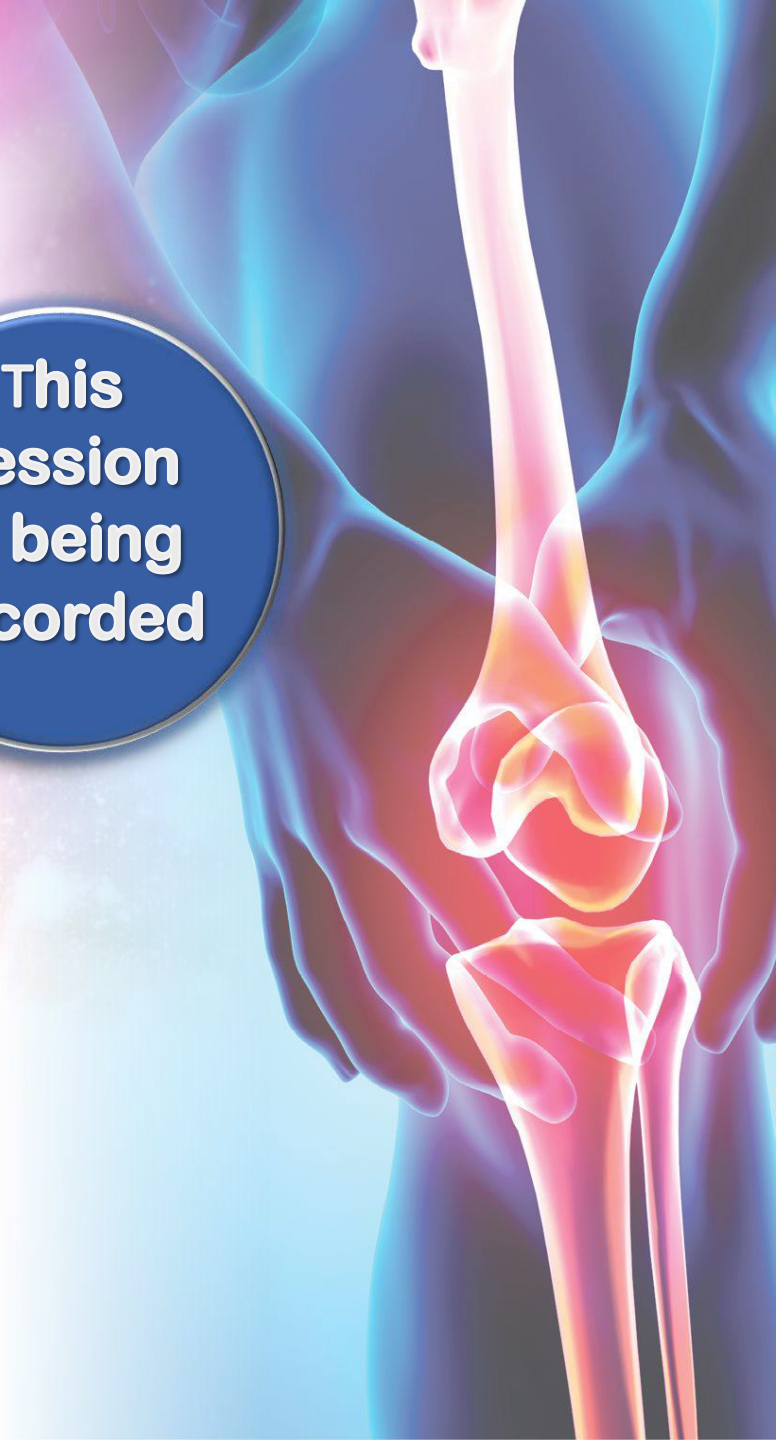
Thank You

Project full title:

Advanced personalised, multi-scale computer models preventing OsteoArthritis

OActive



This session is being recorded

Training session:

ENGAGING END USERS TO THE OACTIVE WORLD

Using artificial tissues as test-bench for rehabilitation against osteoarthritis

Dr. Roberto Di Gesù
Dr. Giovanna Frazziano
Prof. Riccardo Gottardi

Grant agreement 777159

SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

Using artificial tissues as test-bench for rehabilitation against osteoarthritis

Roberto Di Gesù, Ri.MED foundation

OActive

Biochemical modelling and inflammation biomarkers

Behaviour modelling and environmental biomarkers

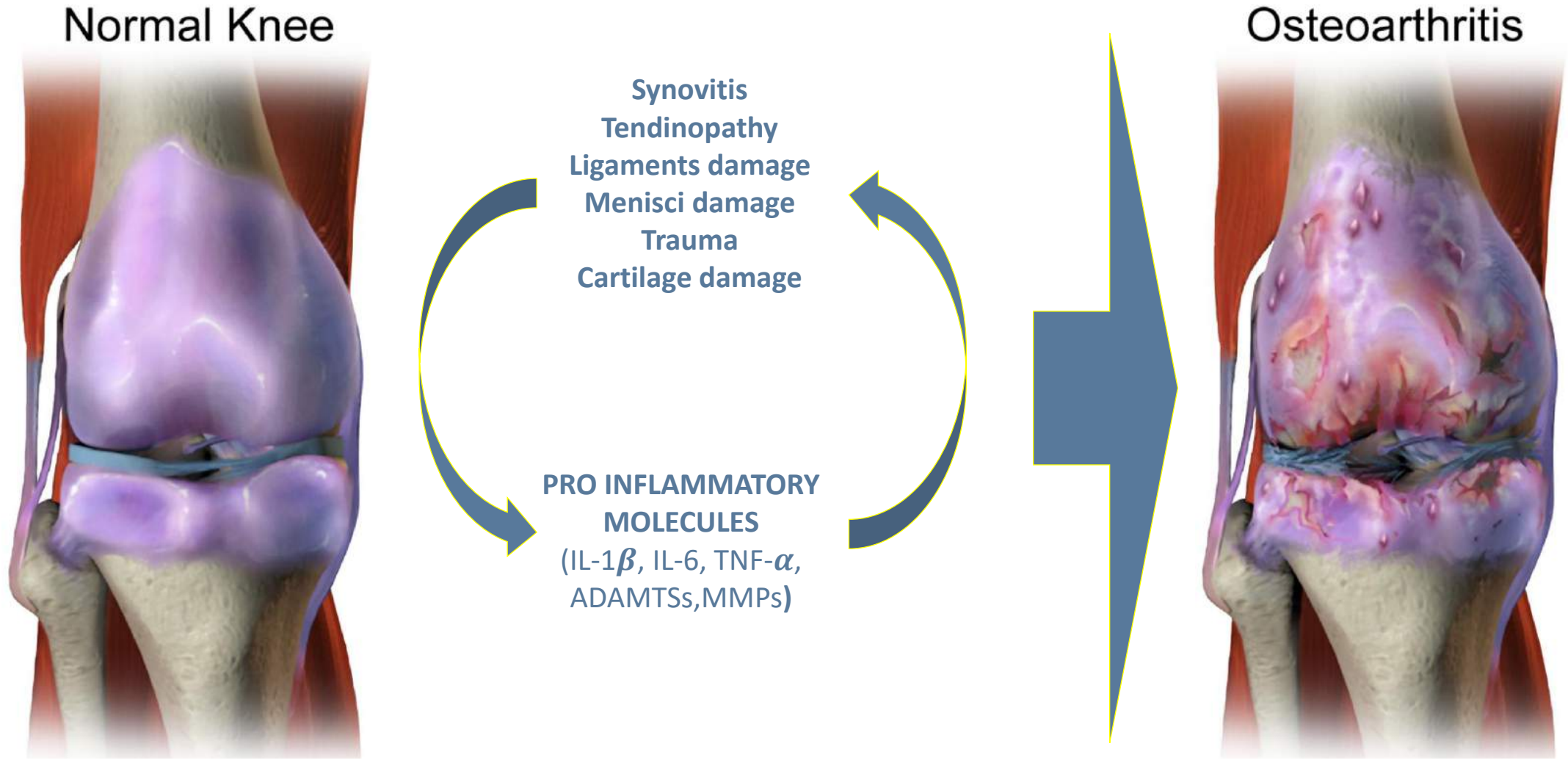
Biomechanical modelling of the knee

Computational modelling empowered by big data and deep learning

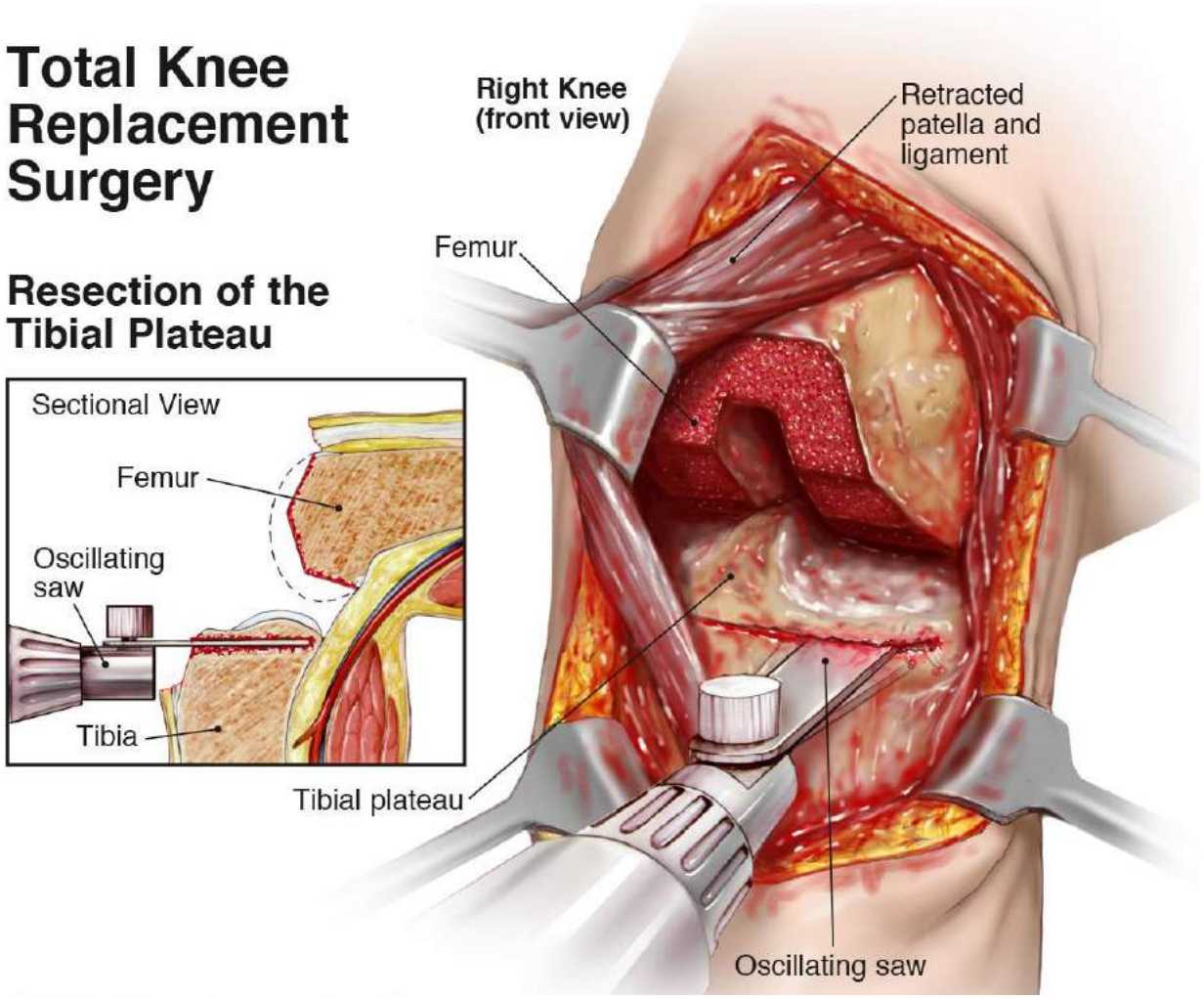
Using artificial tissues as test-bench for rehabilitation against osteoarthritis

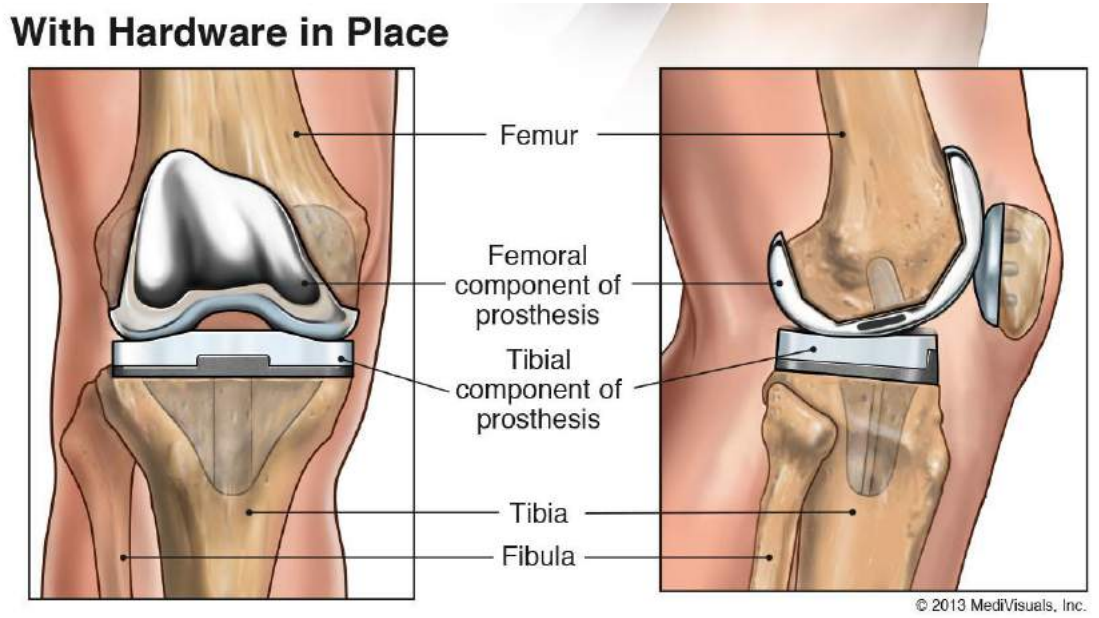
Real time gait monitoring and retraining

OSTEOARTHRITIS



OSTEOARTHRITIS: Available treatments





HOWEVER

- **Prosthesis lifetime = 10 years**
- **Long recovery time**
- **Invasive surgery**

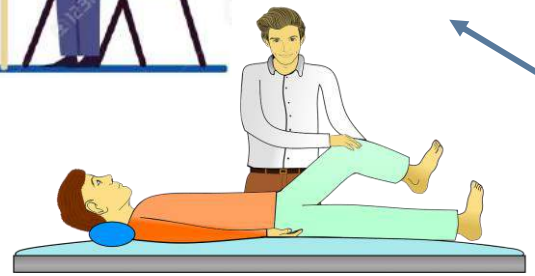
OSTEOARTHRITIS: Available treatments

"Surgery went well, Mr. Moore. I had a lot of fun rebuilding your knee joint."

OSTEOARTHRITIS: What we can do?

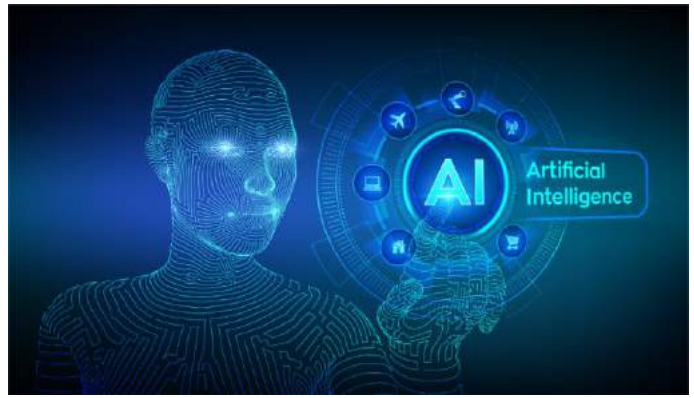
Develop a personalized rehabilitative therapy to prevent osteoarthritis or delay or reeverse its clinical course

OSTEOARTHRITIS: How we do it?

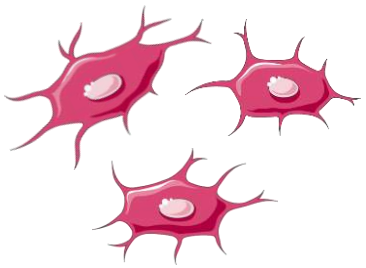


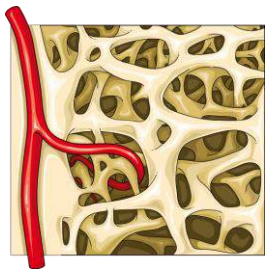
Collecting patients' data

Personalized rehabilitation



Artificial Intelligence (AI)





Fondazione Ri.MED

Effects of rehabilitation on cells and tissue

GOAL

To realize an advanced *in vitro* osteoarthritis (OA) model to test personalized rehabilitation therapies

Ri.MED contribution

1. How does Osteoarthritis look in vitro?

Define the parameters that characterize OA *in vitro* at the tissue and cellular level

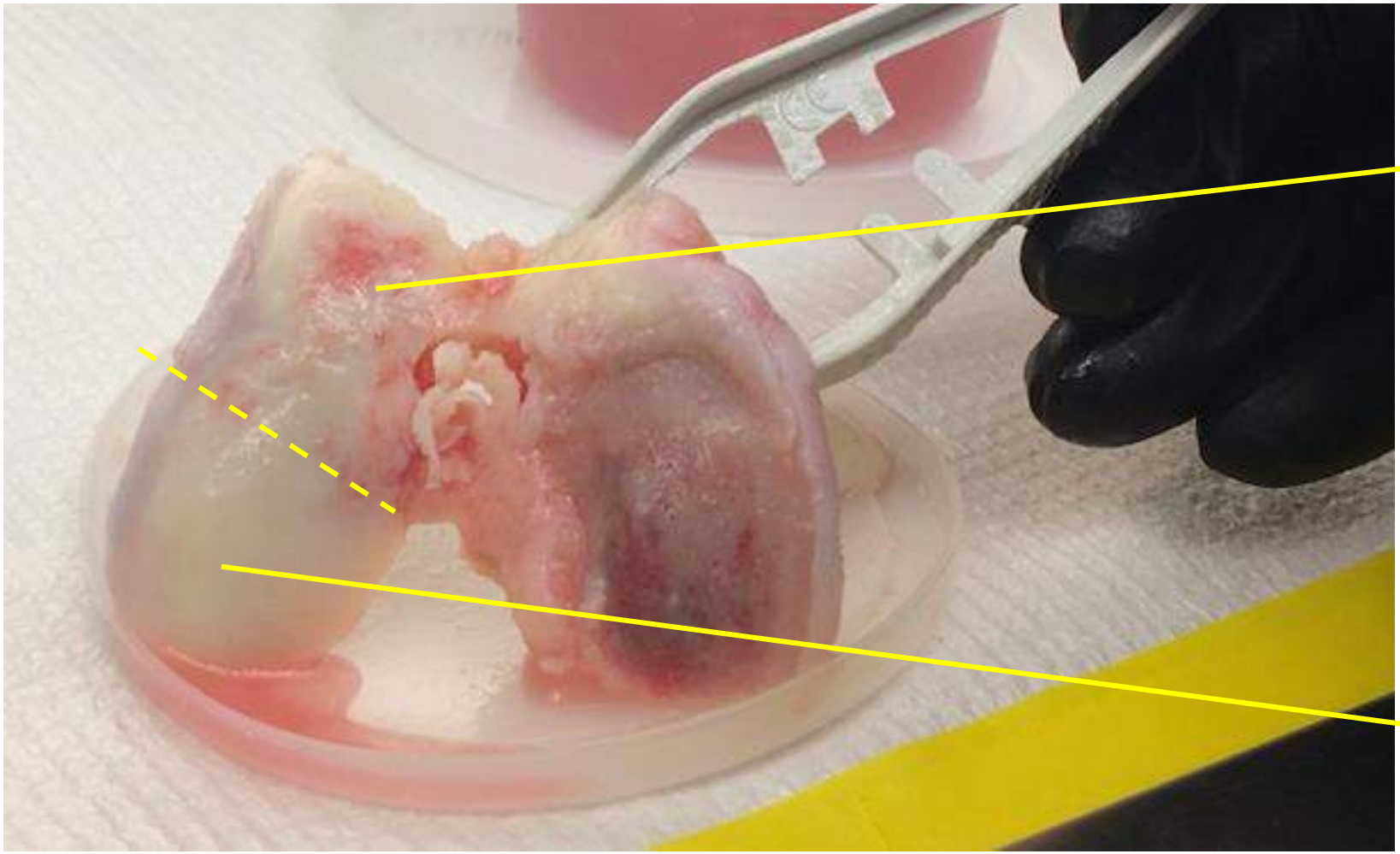
2. What is the best way to model Osteoarthritis in vitro?

Develop an osteochondral model by tissue engineering

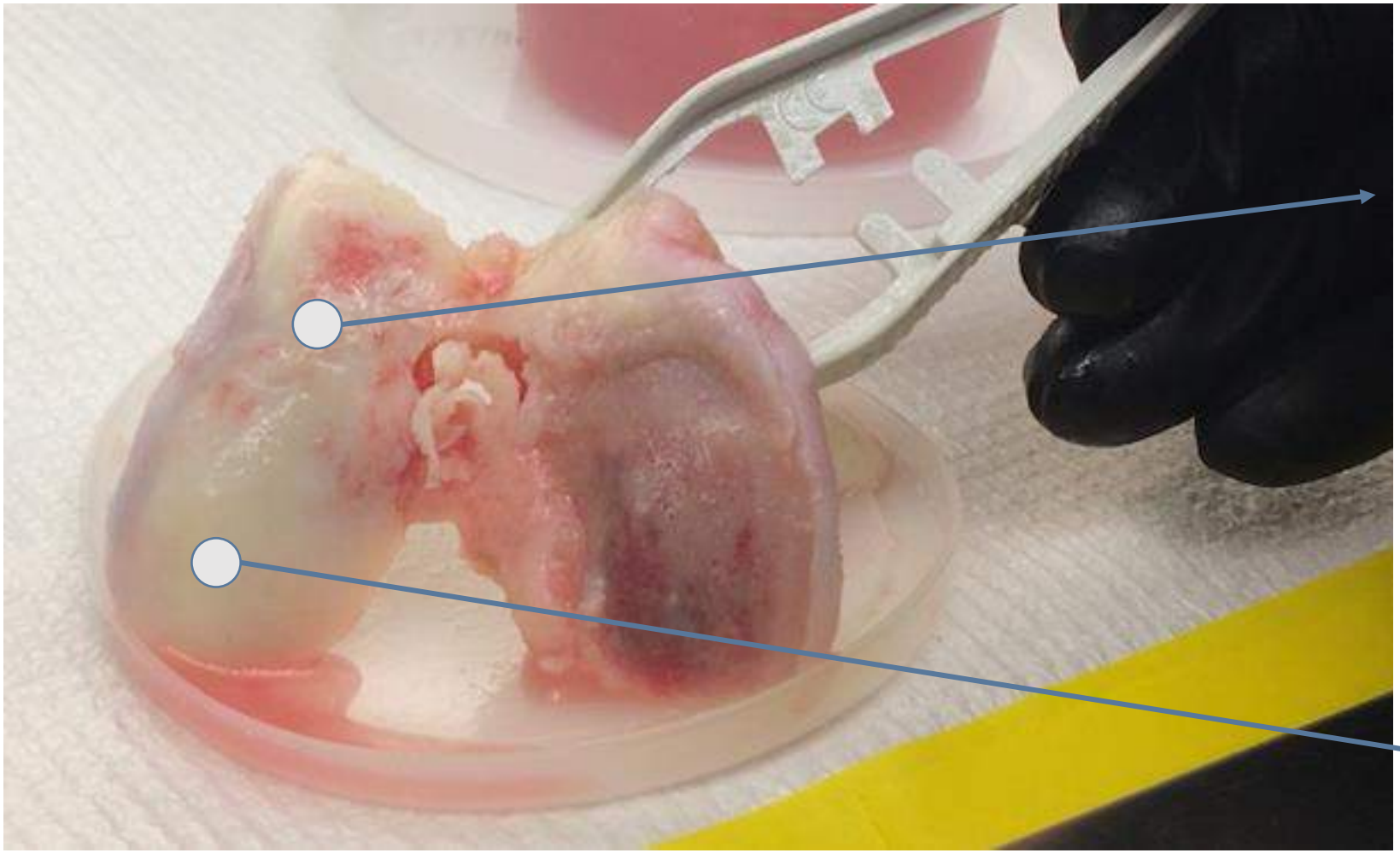
3. What does rehabilitation do to cells and tissues?

Apply controlled mechanical stimuli to Osteoarthritis models

1. How does Osteoarthritis look *in vitro*?



1. How does Osteoarthritis look *in vitro*?

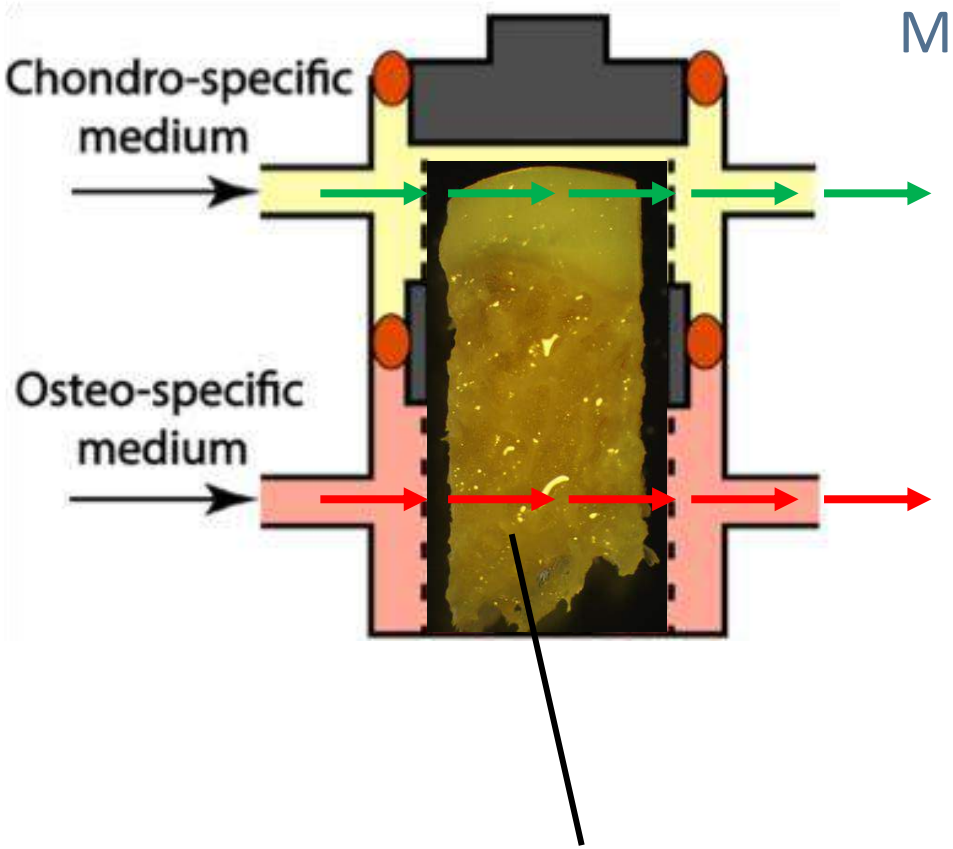


Osteoarthritic osteochondral plug

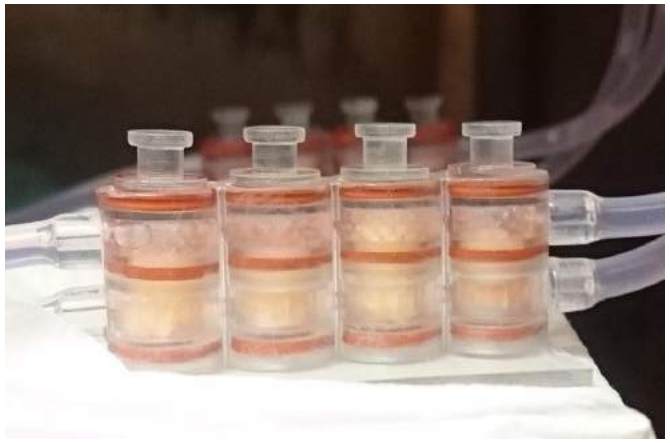
Macroscopically healthy osteochondral plug

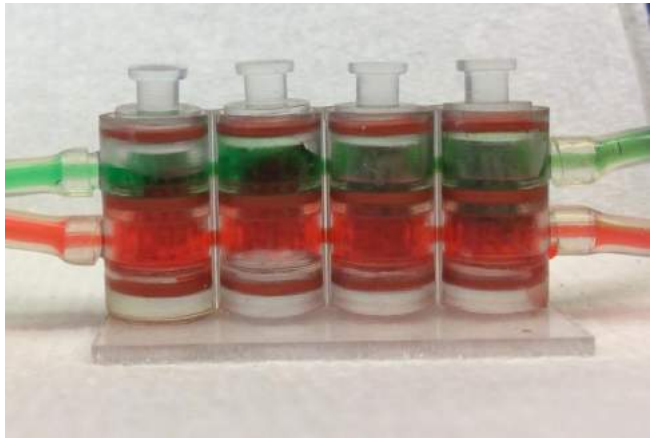
1. How does Osteoarthritis look *in vitro*?

ADVANCED *in vitro* CULTURE SYSTEM



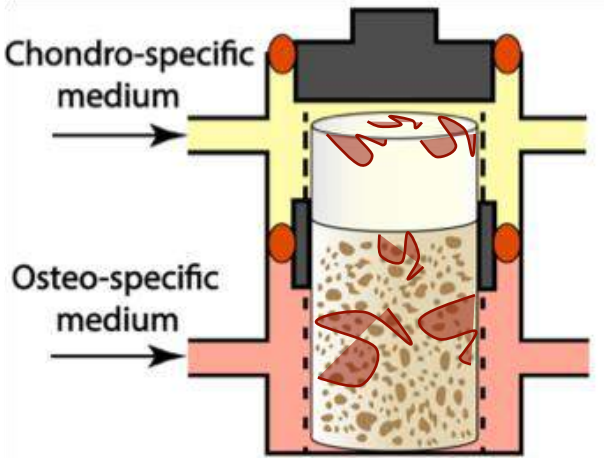
Osteochondral biorector



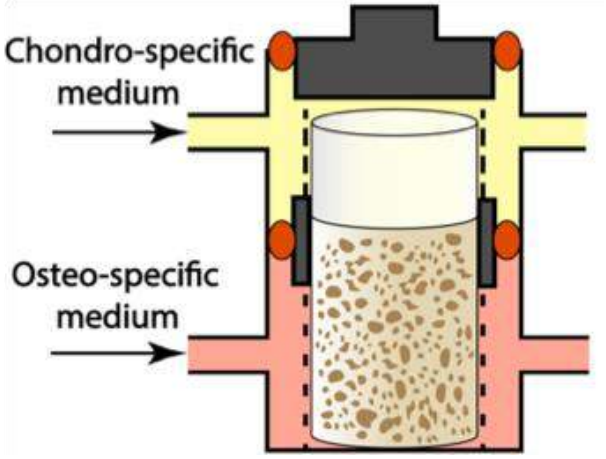


1. How does Osteoarthritis look *in vitro*?

Osteoarthritic



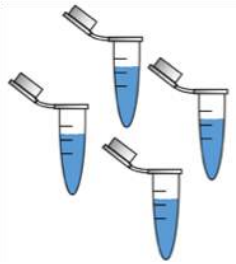
Macroscopically healthy



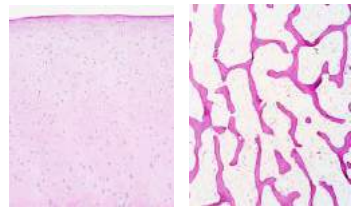
Culturing

Plug

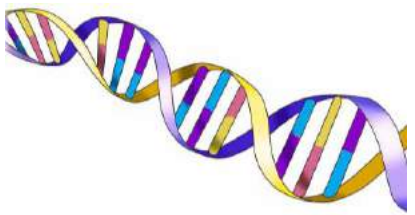
Collected media



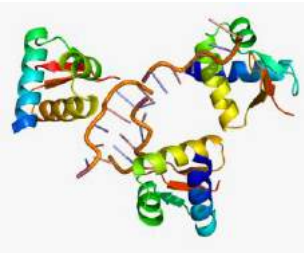
Histochemistry



Gene expression



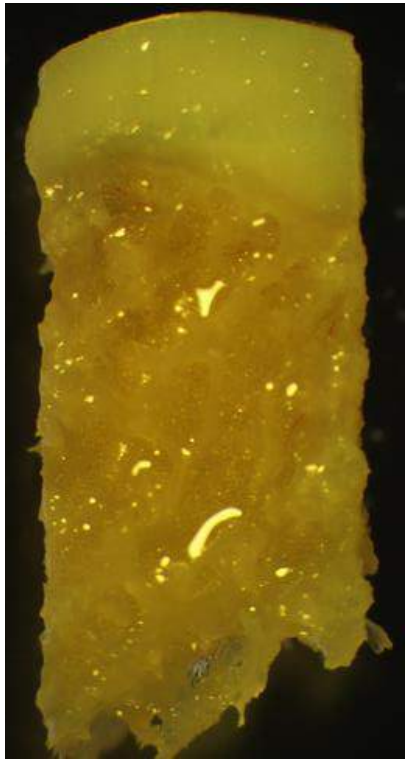
Pro-inflammatory proteins

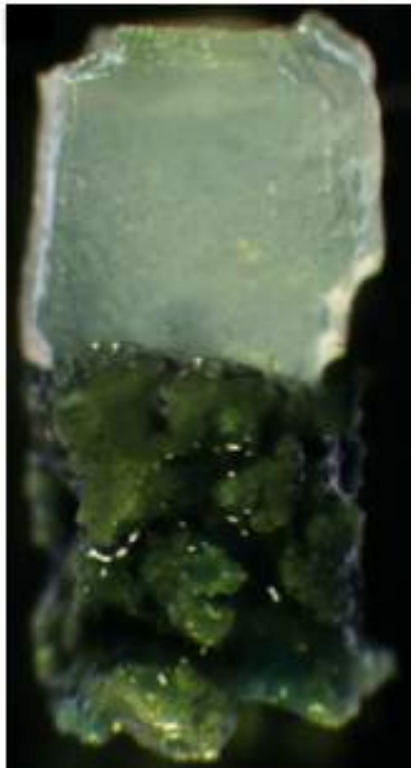


ISSUES

- Shortage of healthy tissues
- Harvesting only from surgical waste

Human plug

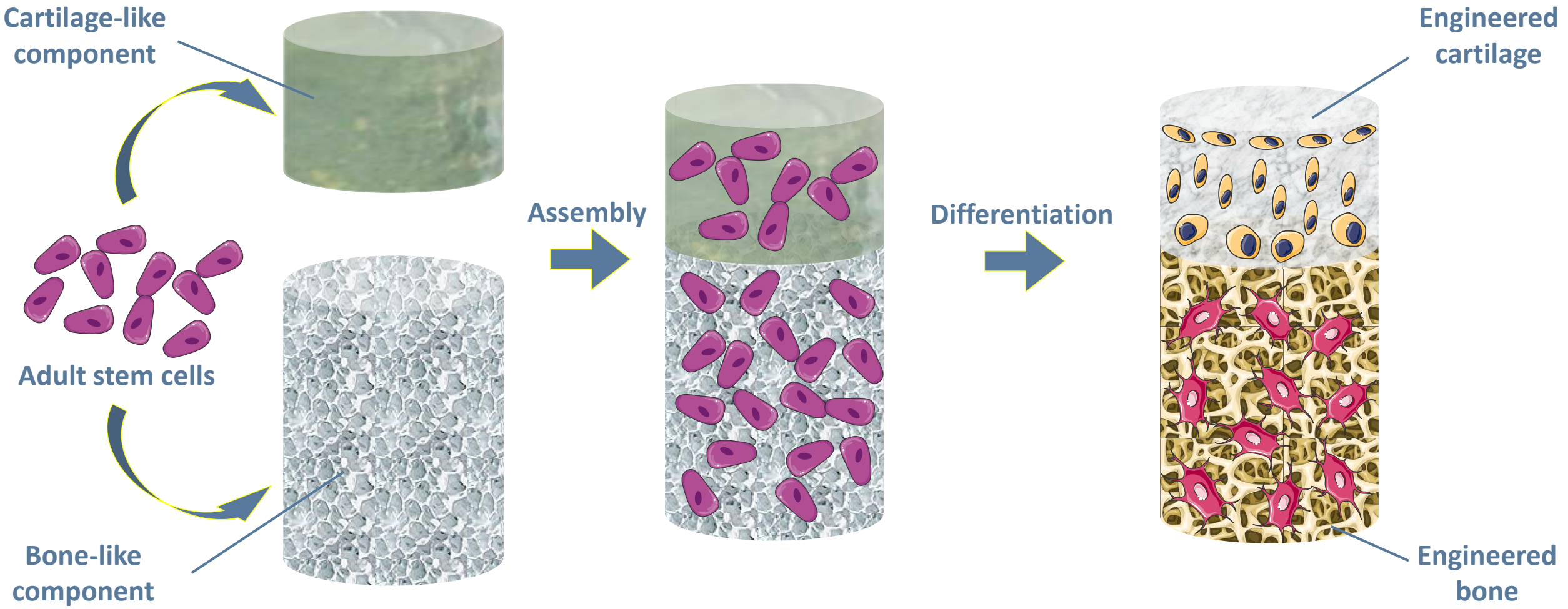




Engineered construct

- High material availability
- High number of replicates
- Possibility to have a healthy control

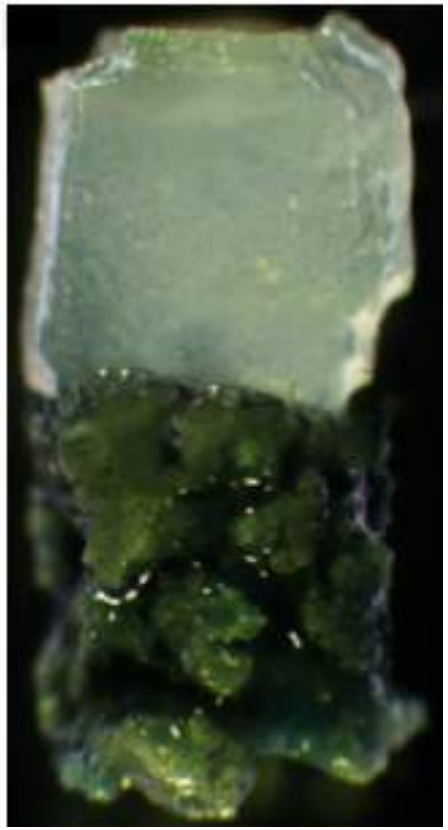
2. What can we use to model Osteoarthritis *in vitro*?



2. What can we use to model Osteoarthritis *in vitro*?

Realization of an *in vitro* OA model

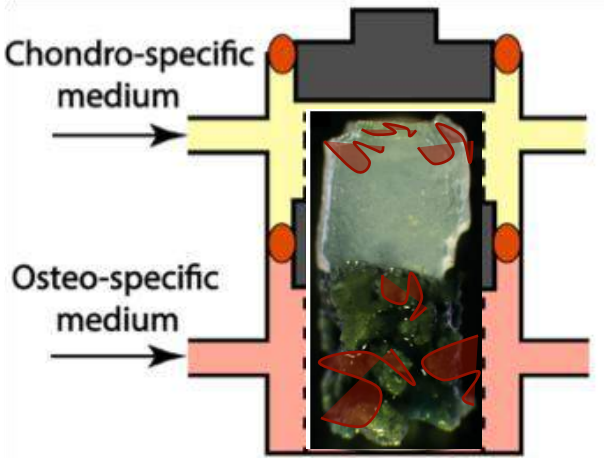
PRO INFLAMMATORY MOLECULES
(IL-1β)



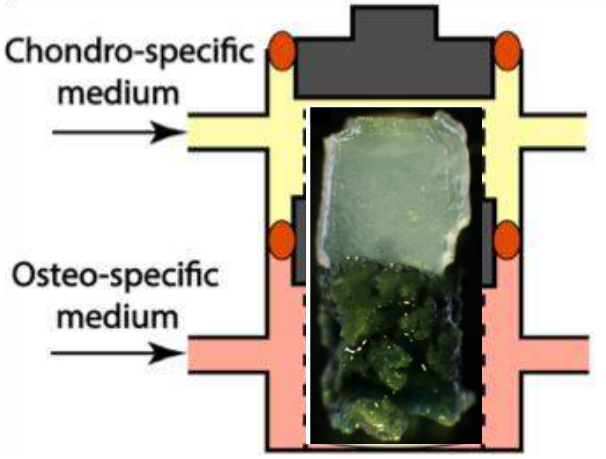
OA model

2. What can we use to model Osteoarthritis *in vitro*?

Osteoarthritic

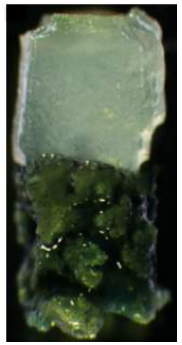


Macroscopically healthy

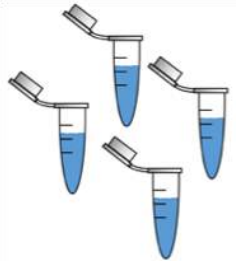


Culturing

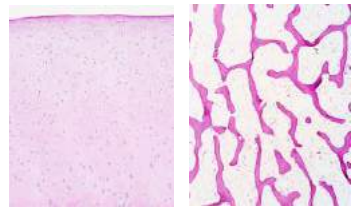
Plug



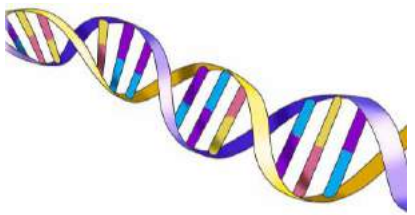
Collected media



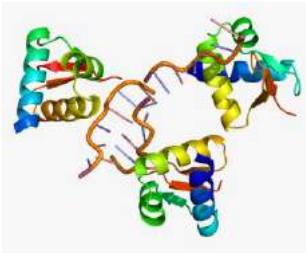
Histochemistry



Gene expression



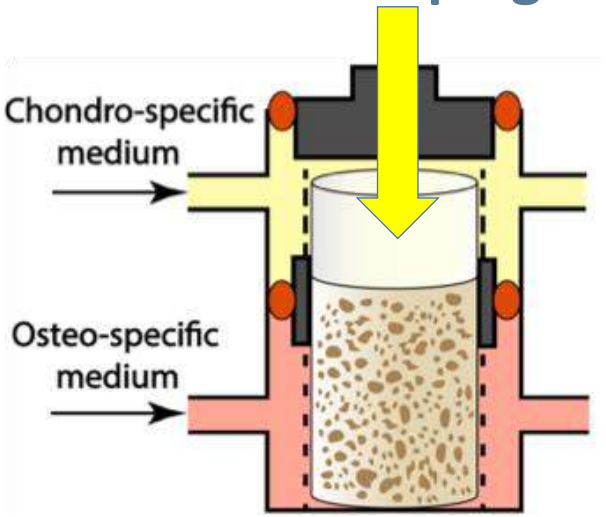
Pro-inflammatory proteins



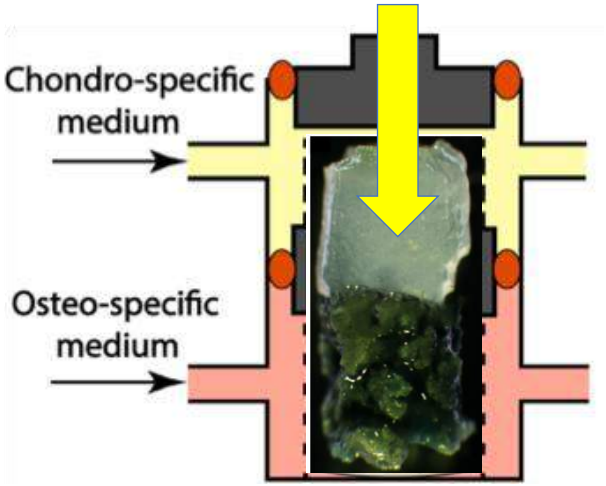
HOW TO SIMULATE REHABILITATIVE MOVEMENTS *in vitro?*

3. What does rehabilitation do to cells and tissues?

Native plug



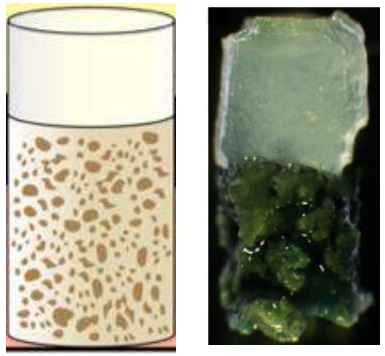
Engineered construct



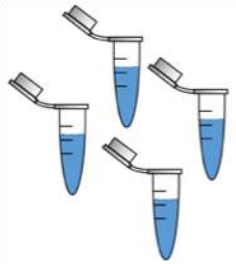
Rehabilitation-like mechanical stimulation

Culturing

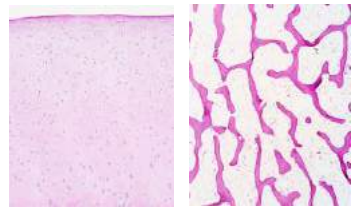
Plugs



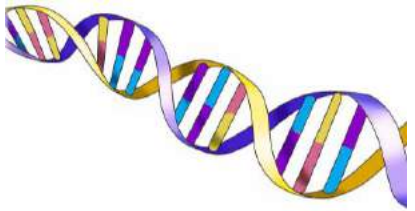
Collected media



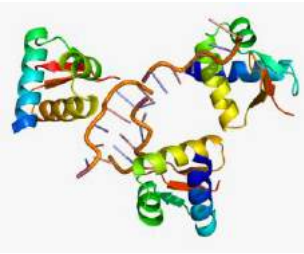
Histochemistry



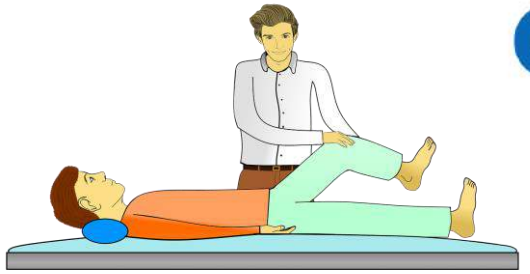
Gene expression



Pro-inflammatory proteins

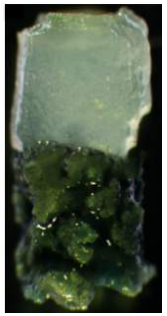


Conclusions



1. Rehabilitation can be used to delay osteoarthritis progression

2. An *in vitro* system based on human tissue is useful to deeply investigate the effect of rehabilitation movements



3. Tissue engineering reduces the need of human tissues and allows to increase the number of samples

4. Our approach allows to design a personalized rehabilitation regimen to reduce or even reverse tissue damage.

SC1-PM-17-2017

GA 777159

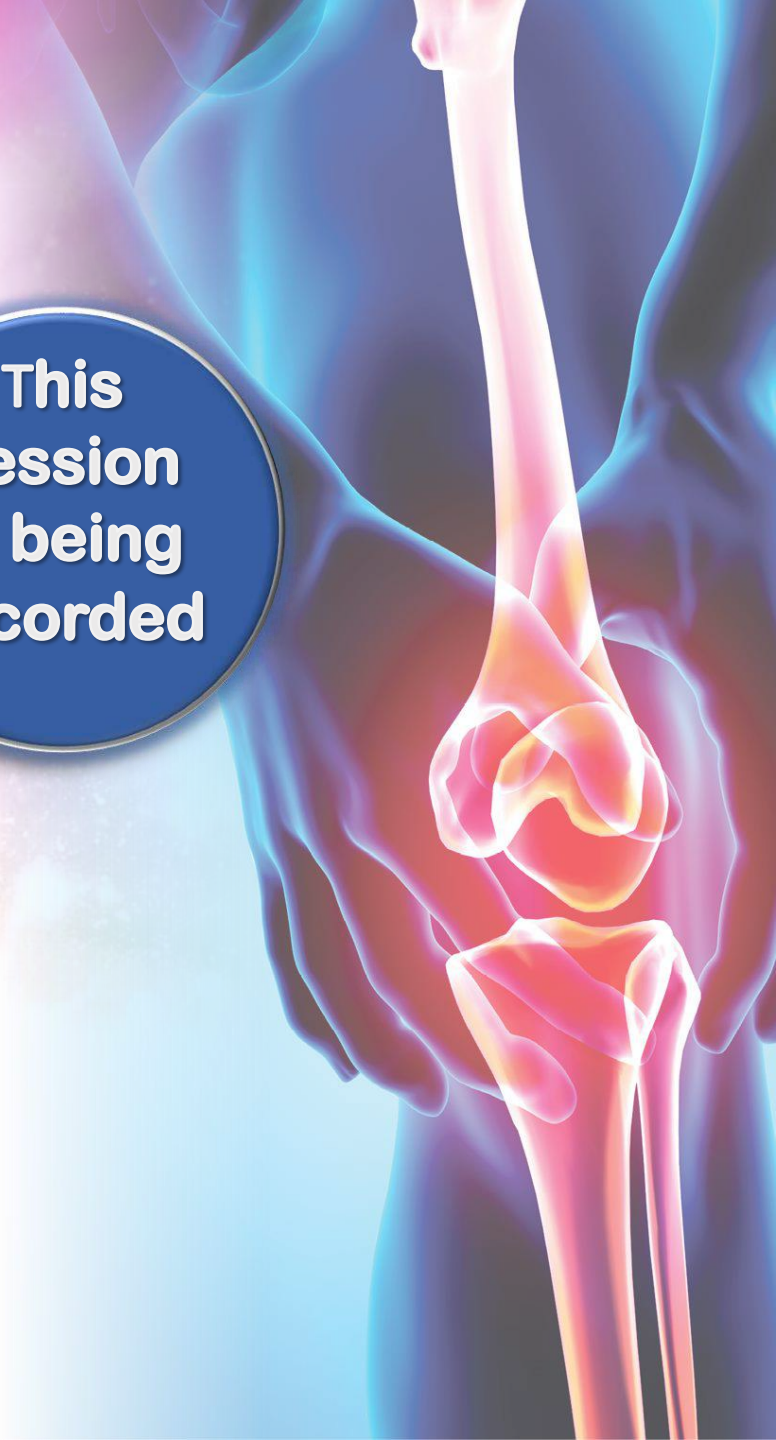
Thank You

Questions

Project full title:

Advanced personalised, multi-scale computer models preventing OsteoArthritis

OActive



This session is being recorded

Training session:

ENGAGING END USERS TO THE OACTIVE WORLD

Real time gait monitoring and retraining

Georgios Giarmatzis, University of Patras

Grant agreement 777159

SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

Real time gait monitoring and retraining

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OActive

Biochemical modelling and inflammation biomarkers

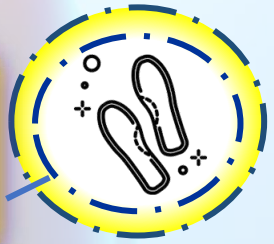
Behaviour modelling and environmental biomarkers

Biomechanical modelling of the knee

Computational modelling empowered by big data and deep learning

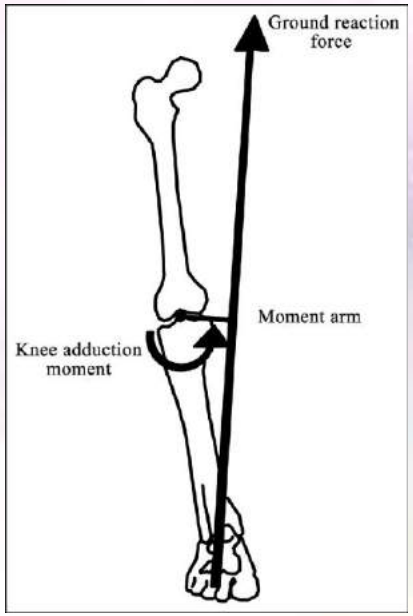
Using artificial tissues as test-bench for rehabilitation against osteoarthritis

Real time gait monitoring and retraining



Background

- Knee OA onset/progression related to mechanical forces
- Cartilage degeneration due to mechanical loading
- Suitable ways to reverse knee OA (pharmacological, surgical, etc)
- Reduction of knee medial torque
  - Braces
  - Gait retraining




Knee OA without bracing


The 3-Point Leverage


Knee OA with bracing

Gait retraining

- How can I reduce knee loading?
  - Increase walking base (keep legs apart)
  - Toe-off (toes outwards)
  - Lean torso sideways
- Uncomfortable – not sustainable
- What is the optimal way?
  - Maybe a combination?

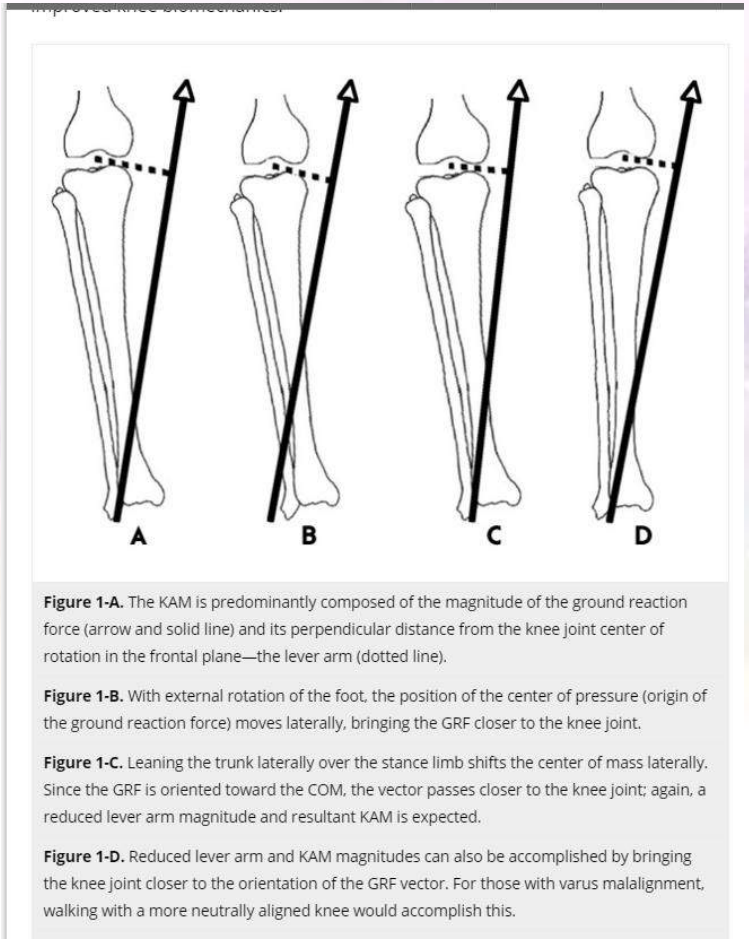


Figure 1-A. The KAM is predominantly composed of the magnitude of the ground reaction force (arrow and solid line) and its perpendicular distance from the knee joint center of rotation in the frontal plane—the lever arm (dotted line).

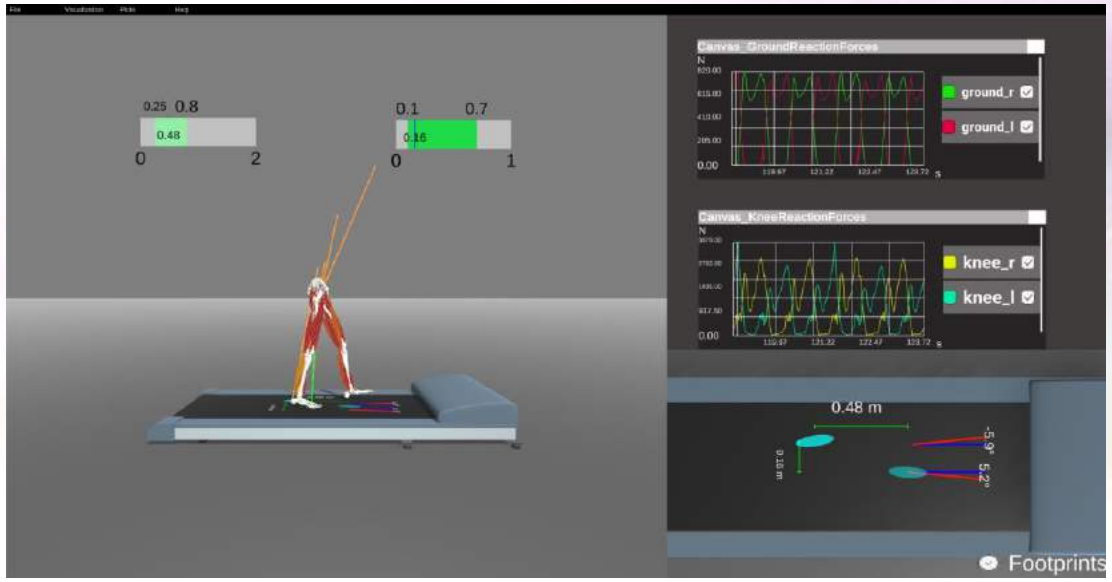
Figure 1-B. With external rotation of the foot, the position of the center of pressure (origin of the ground reaction force) moves laterally, bringing the GRF closer to the knee joint.

Figure 1-C. Leaning the trunk laterally over the stance limb shifts the center of mass laterally. Since the GRF is oriented toward the COM, the vector passes closer to the knee joint; again, a reduced lever arm magnitude and resultant KAM is expected.

Figure 1-D. Reduced lever arm and KAM magnitudes can also be accomplished by bringing the knee joint closer to the orientation of the GRF vector. For those with varus malalignment, walking with a more neutrally aligned knee would accomplish this.

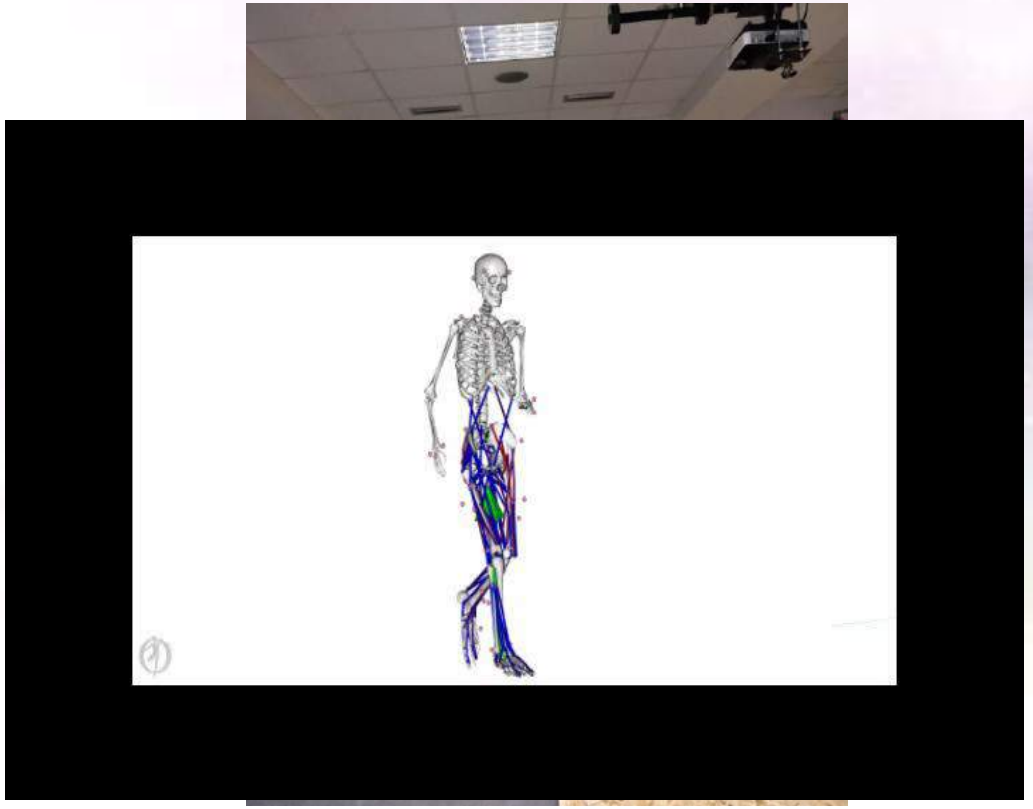
Gait retraining

- Can we make a change in walking strategy maintainable?
- Guidance and feedback
- Real time
- Clinician supervision
- Attractive
- Game-like



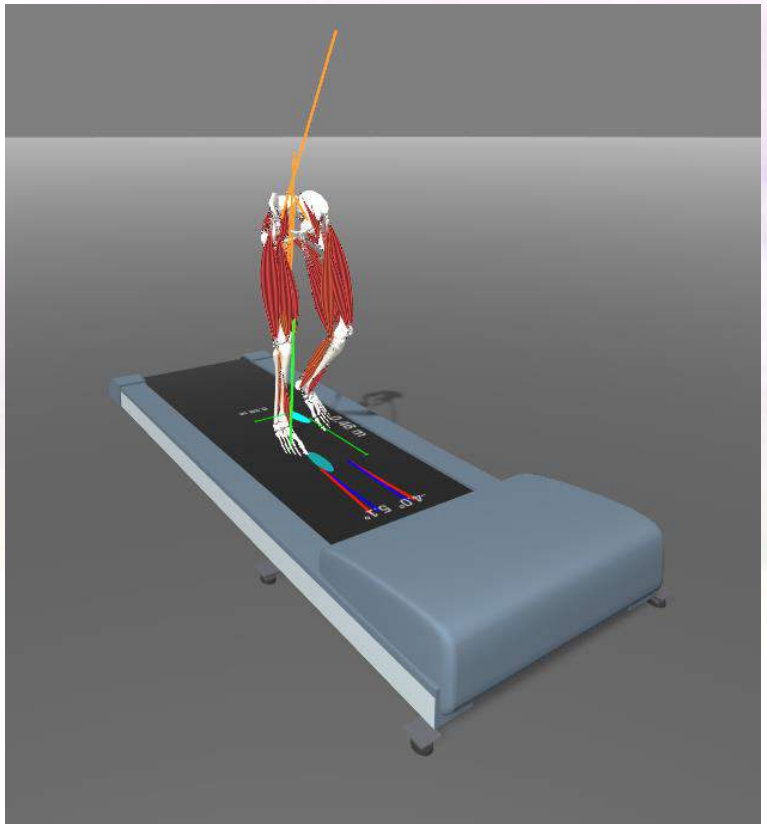
Gait retraining – OActive Approach

- Real time
  - Calculation of knee forces
  - Motion analysis lab
    - Markers
    - Ground reaction forces
  - Modeling of the musculoskeletal modeling
    - Fitting a virtual model to each patient
    - Calculation of joint angles – joint torques
    - Calculation of muscle forces
    - Calculation of joint forces



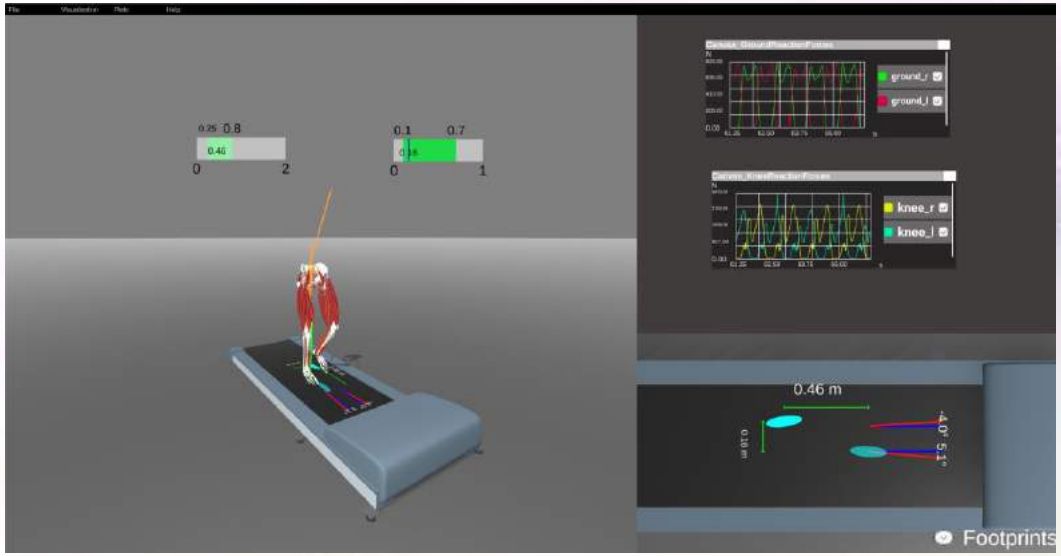
Gait retraining – OActive Approach

- 3D visualization system
  - Skeleton and muscles reproduced for each frame
  - Muscle geometry improved based on muscle points from Opensim
  - Color coding based on activations levels
  - Positions updated every frame

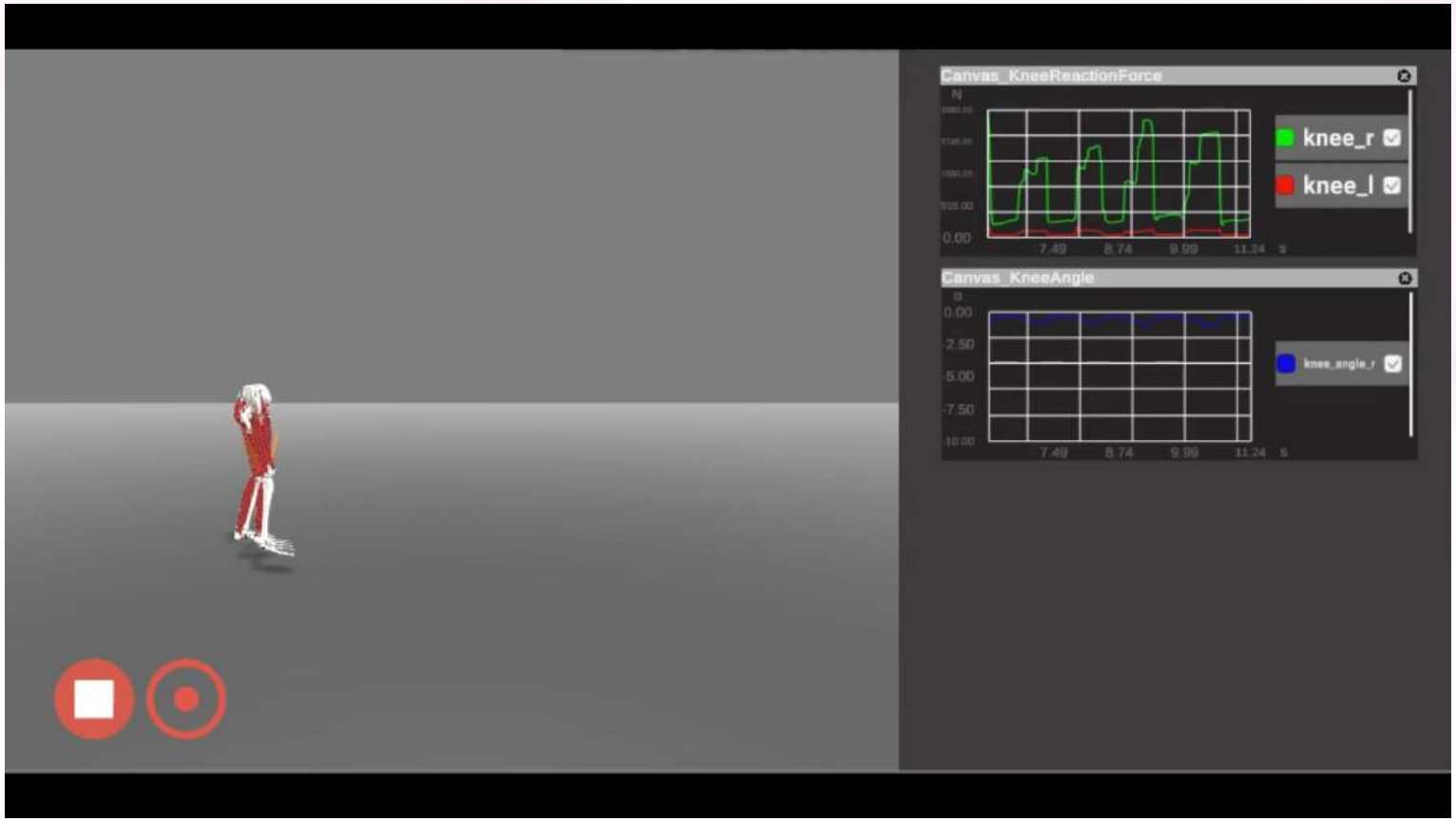


Gait retraining – OActive Approach

- System functionalities
  - Visualization of user-selected metrics and external forces
  - Gamification elements
  - Scores based on performance criteria (on progress)



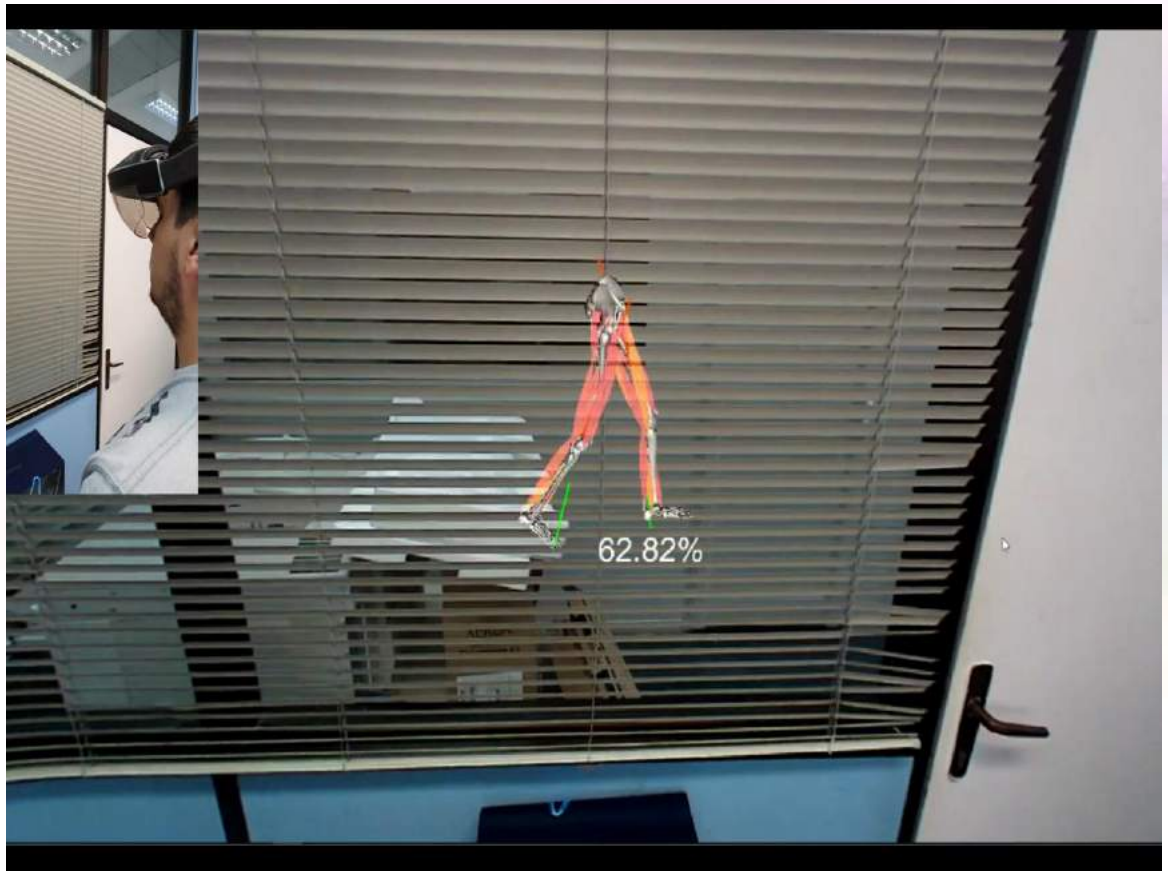
Gait retraining – OActive Approach



Gait retraining – OActive Approach

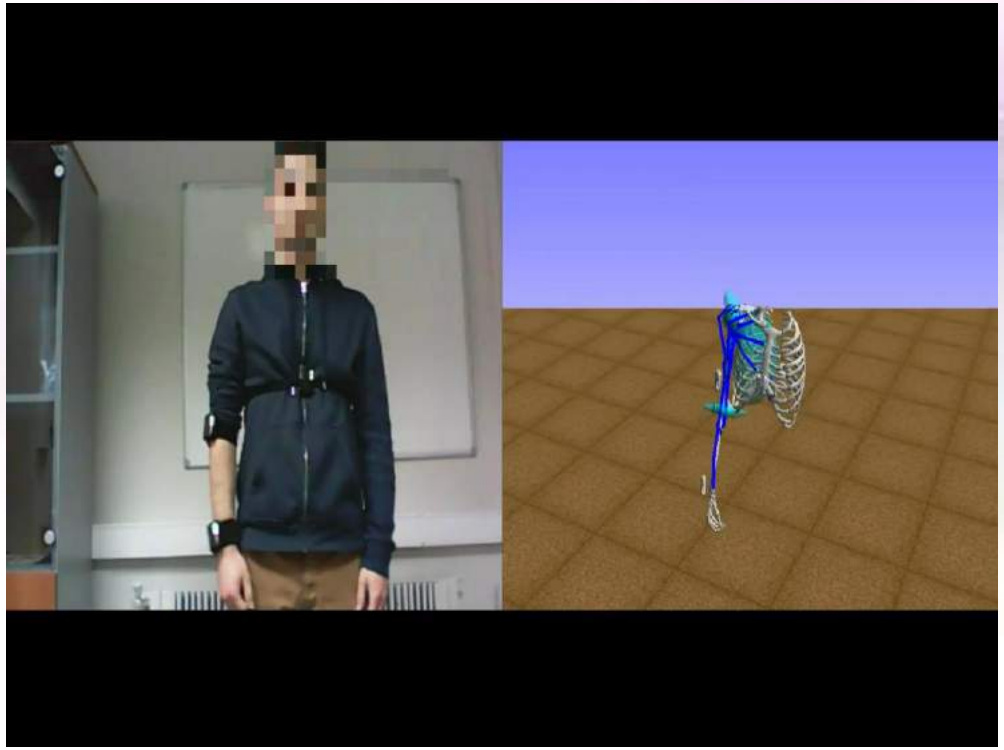
Gait retraining – OActive Approach

- Augmented reality
  - Connection with AR glasses
  - Gamification elements
  - Scores based on performance criteria (on progress)



Gait retraining – OActive Approach

- Next steps
  - Testing of platform in different scenarios
  - Add new gamification elements
  - Scores based on performance criteria (on progress)
  - Explore outdoor solution with Inertial Measurement Units



Gait retraining – OActive Approach

thanks!