



Can AI Predict Pain Progression in Knee Osteoarthritis Subjects From Structural MRI?

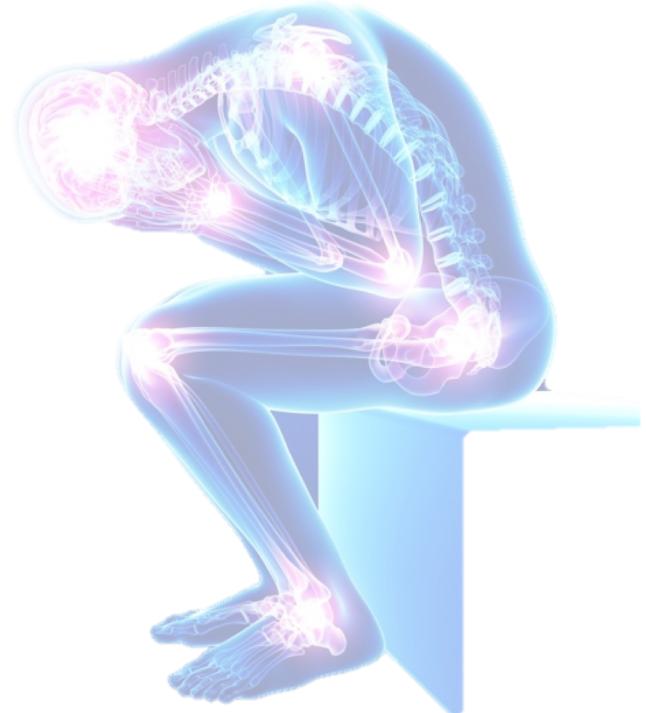
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Motivation

- Despite the widely perceived association between structural change and pain in knee osteoarthritis, direct relationship has not been well established
- Understanding the symptomatic OA and predicting the future pain progression can be very useful



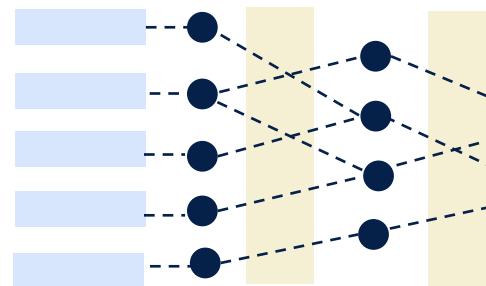
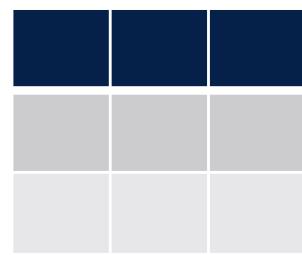
Losina E, Collins JE. Forecasting the future pain in hip OA: can we rely on pain trajectories? *Osteoarthritis Cartilage*, doi:10.1016/j.joca.2016.01.989

Aims

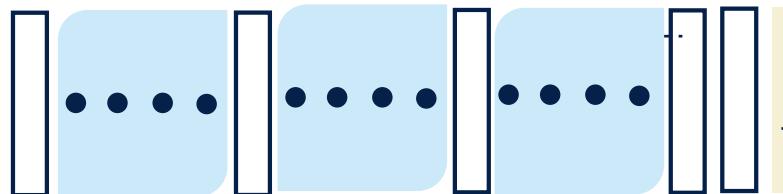
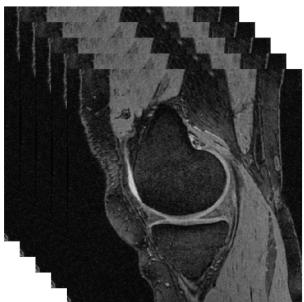
- **Aim 1: To model patient-specific pain trajectory (progression of pain over time)**
- **Aim 2: To build a multi-modal deep learning model fusing MRI and clinical data to predict pain trajectory of subjects with no pain at baseline**

Overview

AIM 2: Pain trajectory prediction



Model 1:
Non-image
feature only



Model 3: Multi-modal data fusion

$\{c_i, \emptyset_i\}_{i=1}^K$



Model 2:
MR Image input only

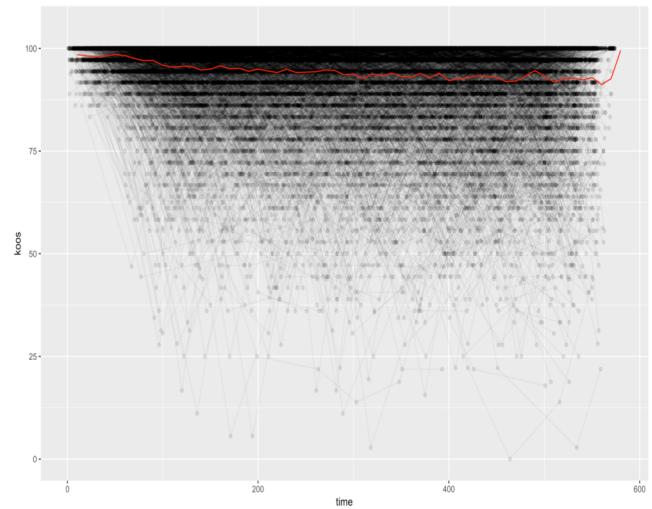


Department of Radiology
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6/14/19

Dataset – Study population

- Completed, multicenter, 10-year longitudinal observation study conducted by **Osteoarthritis Initiative**
- Repeated measure of **KOOS pain score (0-100, 0: worst)** for each knee for up to 12 timepoints
- Focused on 2,799 participants (4,077 exams) who reported **no pain** (KOOS knee pain score: 100 or WOMAC score: 0) at baseline
- Split dataset into train/validation/test (65/15/20) based on subject and the same split was used for the all models



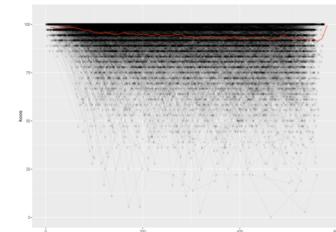
Roos EM, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 2003;1:64a

Dataset – Descriptive statistics of population

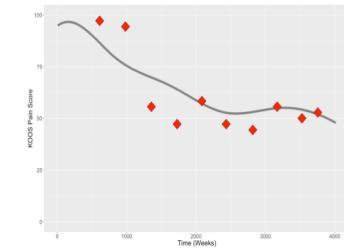
- N = 4,077 exams (2,799 unique participants)
- Age: 61.40 ± 9.20
- Male/Female: 1,819 / 2,258
- KL grade (0/1/2/3/4): 1396 / 724 / 842 / 242 / 22
- Mean KOOS pain score at baseline: 98.38

Methods

- Longitudinal observation of temporal KOOS pain progression
 - High dimensional
 - Inherent noise
 - Missing data (~30%)
- Pain trajectory modeling
 - Functional data analysis, statistical analysis of samples of curves, can be used in this setting
 - **Functional Principal Component Analysis**
 - Decomposition of pain trajectory into weighted linear combination of basis function
 - Basis functions are shared by all subjects, with coefficients only we can reconstruct the pain trajectory



$$\{c_i, \phi_i\}_{i=1}^K$$



Dataset –Osteoarthritis Initiative

▪ Non-Image data from baseline survey (p = 365)

- Demographic, Subject characteristics
- Medical history, medication, physical exam, health survey, nutrition
- Physical activity, strength measures, performance measures, accelerometry exam results
- Knee symptoms, knee function, knee exam results
- Other joint pain in hip, back, hand, foot, etc.
- Side specific on hip, knee, ankle, legs were further specified to ipsilateral vs contralateral

▪ MR Image data

- Bilateral sagittal knee images
- 3D Double Echo Steady State (DESS)
- Image size were center cropped to 350 * 350 * 120

ID	Age	BMI	KL	Pain medicine	...
900001_LEFT	67	21.25	0	1	
900005_RIGHT	61	31.96	1	0	
999999_LEFT	70	24.50	0	1	

Demographic/Health survey data



3D Sagittal DESS

Methods – FPCA score prediction

- Regression problem – Predict K PC scores , $\{c_i\}_{i=1}^K$
- Loss function – Weighted mean squared error
 - Weighted MSE = $\frac{1}{K} \sum_{k=1}^K w_k * (c_{nk} - \widehat{c_{nk}})^2$ where $w_k = 1/k$
- Evaluation on the model
 - Sampling of predicted FPCA scores from DL model with dropout bootstrapping principle
 - Construct 95% confidence interval of pain progression trajectory
 - Summarize over all study population by measuring the ratio of overlapping of observed KOOS \pm MDD

Methods

- Data preprocessing

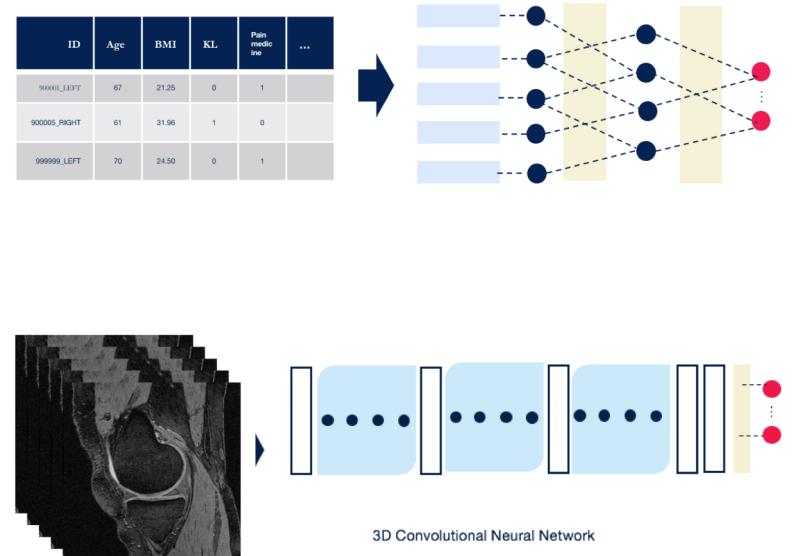
- Standardization, median imputation for NAs for continuous variable
 - **Entity embeddings** for categorical variables

- Image registration and preprocessing

- Knee MRI scan as acquired (no localization or segmentation)
 - Data augmentation: Random crop, Random rotation

- Model architecture

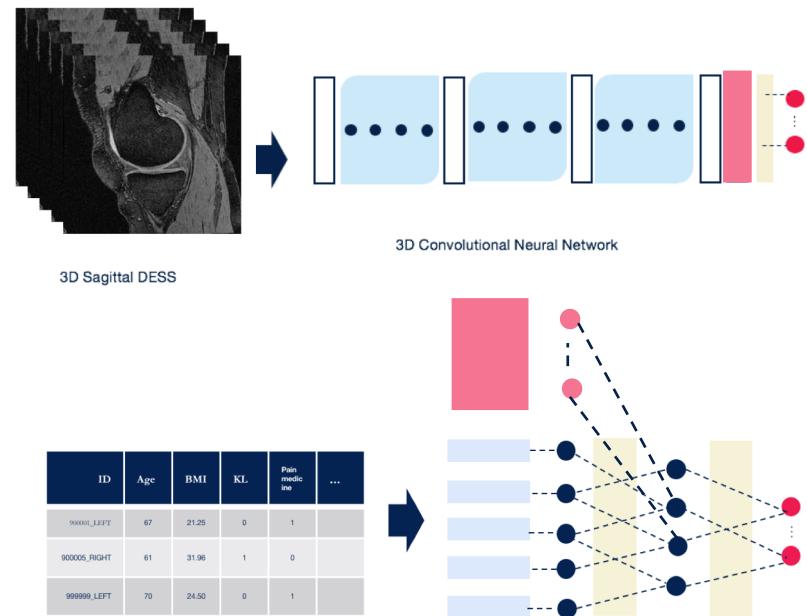
- Two fully connected (FC) layers of size [512, 256]
 - Leaky ReLU, BatchNorm (1D), and Drop out layers
 - 3D extension of DenseNet121



Huang G, et al., Densely connected convolutional networks, arXiv preprint arXiv:1608.06993, 2016a

Combining health survey data and MR

- Image features from the last fully connected layer of size 256 were extracted from Model 2
- Then concatenated with preprocessed non-image data from Model 1
- Architecture
 - Two fully connected(FC) layers of size [512, 256]
 - Leaky ReLU, BatchNorm(1D), and Drop out layers



Results – Pain trajectory modeling

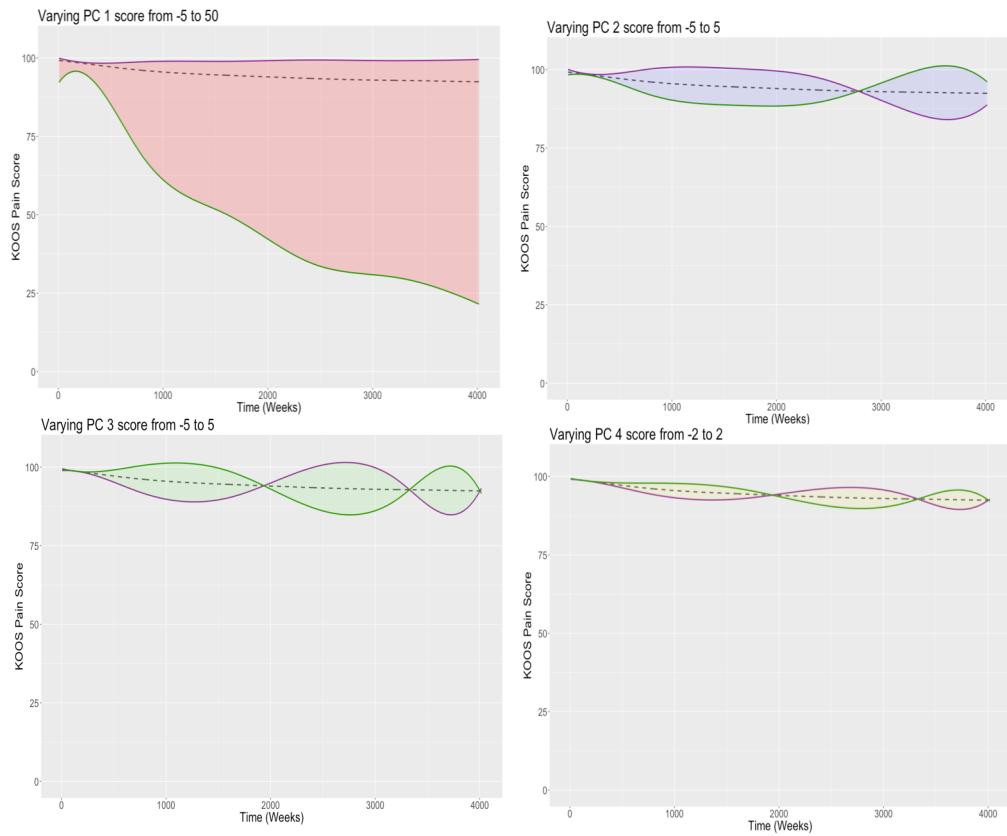
Selected model

- Dimension of the process = 8
- Number of process (K) = 4

	PC1	PC2	PC3	PC4
eigenvalue	50.62	5.91	2.96	1.55
Cumulative explained variance (%)	82.93	92.61	97.46	100.00

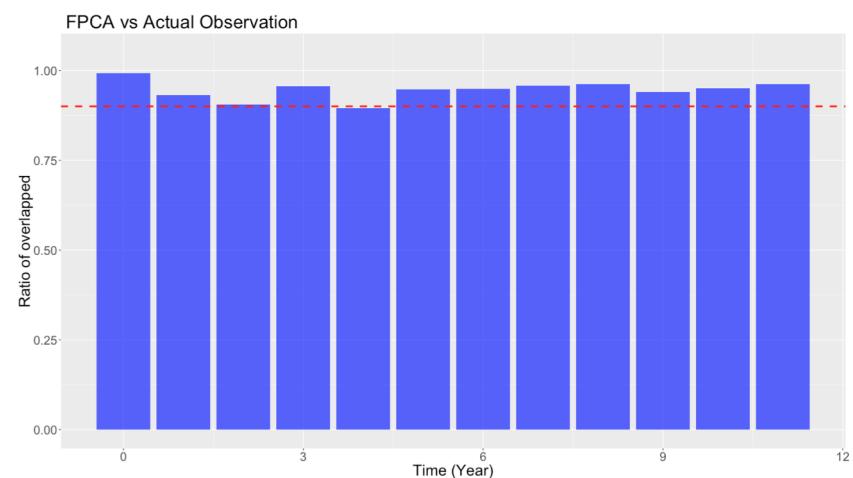
FPCA scores

- Patient-specific functional scores are estimated based on the selected model



Results - FPCA vs Actual observation

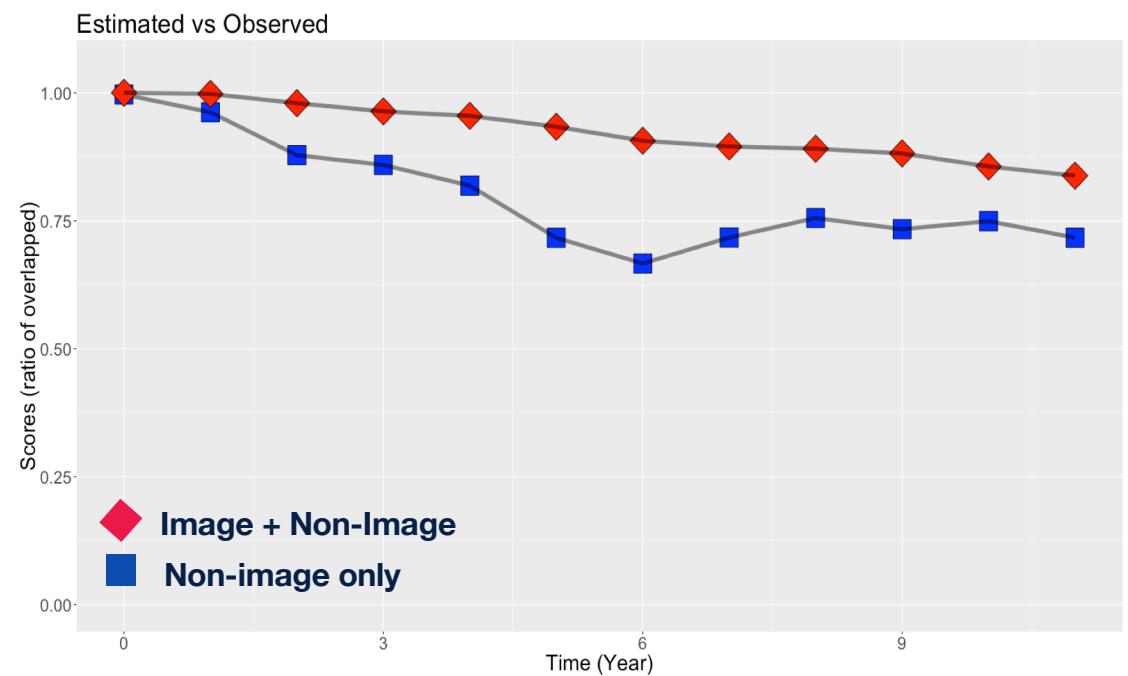
- FPCA closely approximates the actual observation using hold out test set
- By measuring the overlapping interval of FPCA \pm MDD and actual KOOS \pm MDD
- During study period, FPCA scores were within MDD over 90%



Results

Loss metrics evaluated on
Hold-out test set

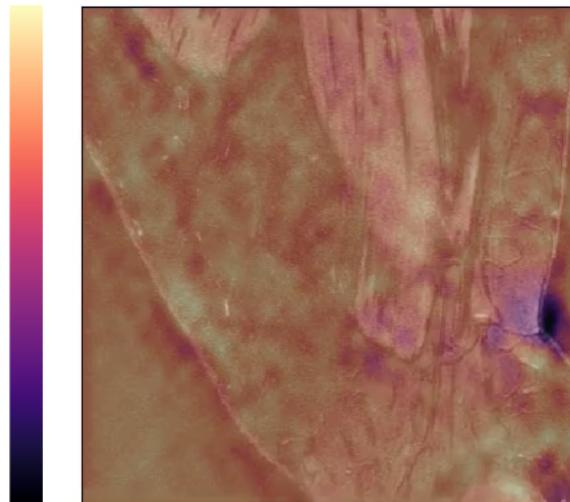
	Weighted MSE	MAE
Model 1 (Non-Image only)	11.09	1.70
Model 2 (MR Image only)	9.54	1.67
Model 3 (Image + Non- Image)	7.36	1.46



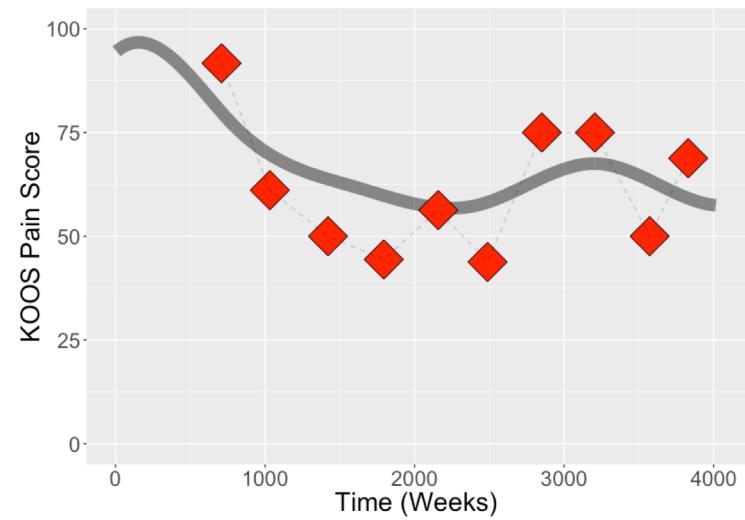
Discussion and future direction

- Study cohorts can be biased
 - US-based
 - Older population
 - Categorized at high risk of developing OA at enrolment
- Follow up window (11 years) is shorter than the average OA development
- Subcategorization based on symptoms (clinical subtypes) don't necessarily agree with the one based on molecular subtypes
 - Extend the multi-modality by including
 - Genetics, Biomechanics, Neuro imaging

Activation map from CNN



52yo Female
BMI = 42.4
KLG: 0
KOOS: 91.7
Estimated PC1: 27.53



Summary

- We proposed FPCA to build a patient-specific pain trajectory model
- We showed Multi-modal data fusion combined with deep learning models can predict the future pain trajectory of subjects with no pain at baseline

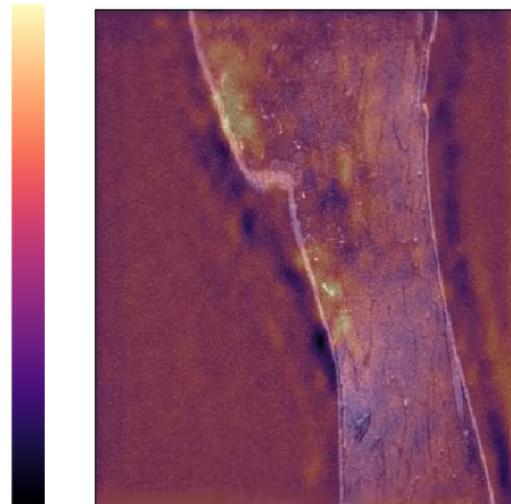
Acknowledgement

- This study was funded by the National Institutes of Health - National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH-NIAMS). Grant numbers: R00AR070902 (VP), R61AR073552 (SM/VP)
- The OAI is a public-private partnership comprised of five contracts (N01- AR-2-2258; N01-AR-2-2259; N01-AR-2- 2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health.

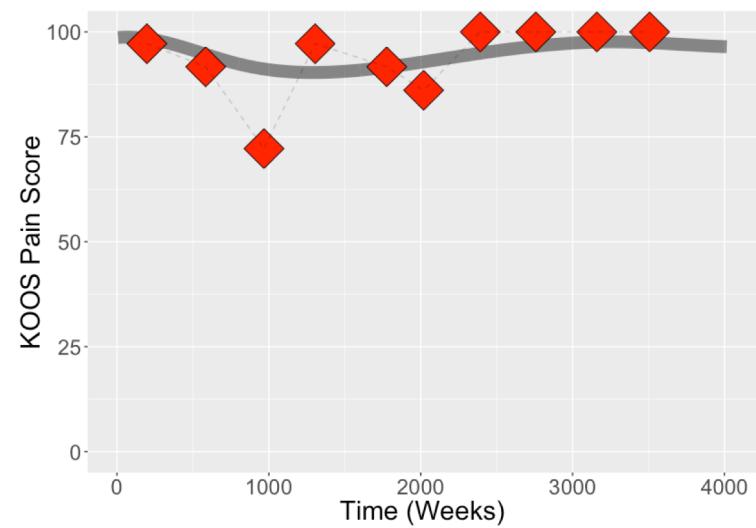


Results – Activation map from CNN

- Model 2: Weighted MSE = 9.5402, MAE = 1.6726

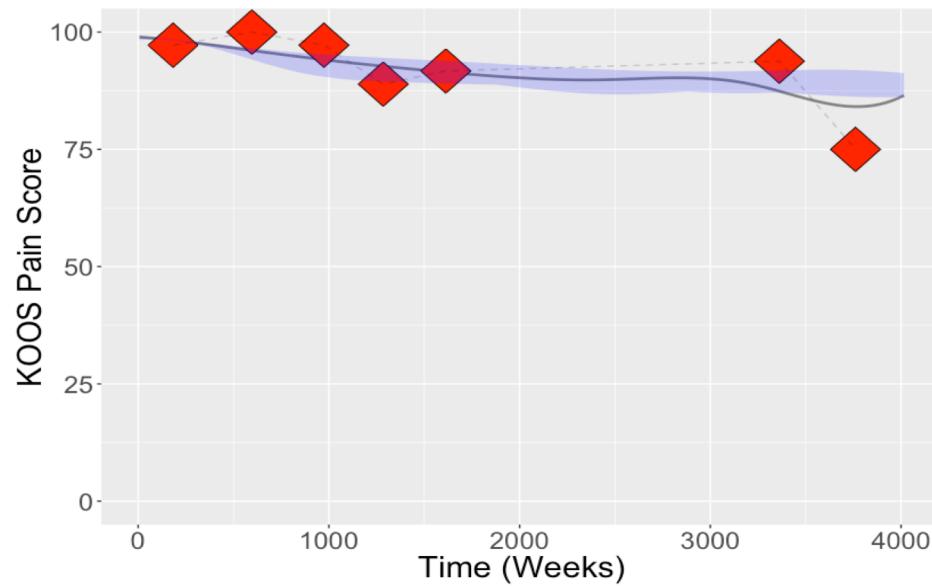


51yo Female
BMI = 16.5
KLG: 0
KOOS: 97.2
Estimated PC1: -1.15



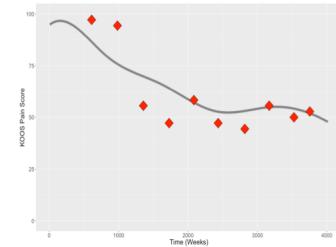
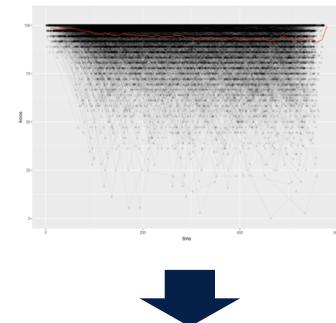
Results

- Example of predicted pain curve

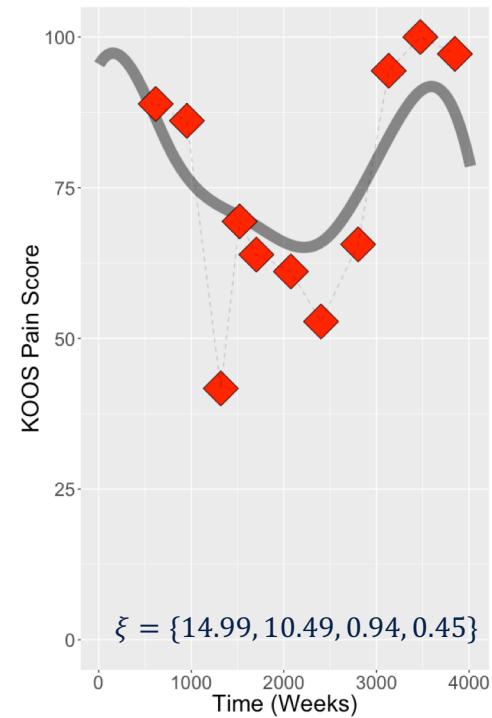
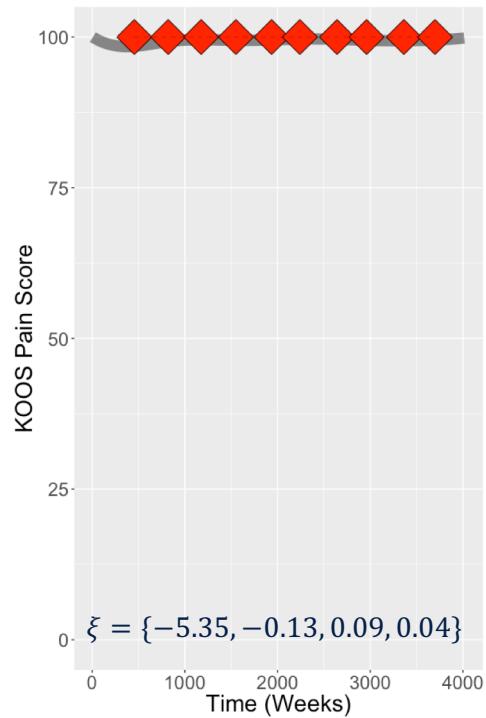


Methods – Pain trajectory modeling

- Longitudinal observation of temporal KOOS pain progression
 - High dimensional
 - Inherent noise
 - Missingness in data (~30%)
- Functional principal components analysis (FPCA)
 - Assume underlying continuous functions
 - Data-driven base functions to summarize the properties of the curves
 - Can identify latent pattern of pain trajectory and reduce the dimension
 - Allows evaluation at any time points, rates of change
 - $Y_{ij} = \mu(t_{ij}) + \sum_{k=1}^K c_{ik} \phi_k(s_{ij}), K < \infty$
- FPCA for sparse sampling
 - Actual timepoint (week) of pain scores were reported was used for the grid
 - Restricted Maximum likelihood estimator by Newton-Raphson algorithm
 - Model selection based on leave-one-out cross-validation
 - Number of basis function
 - Dimension of the process

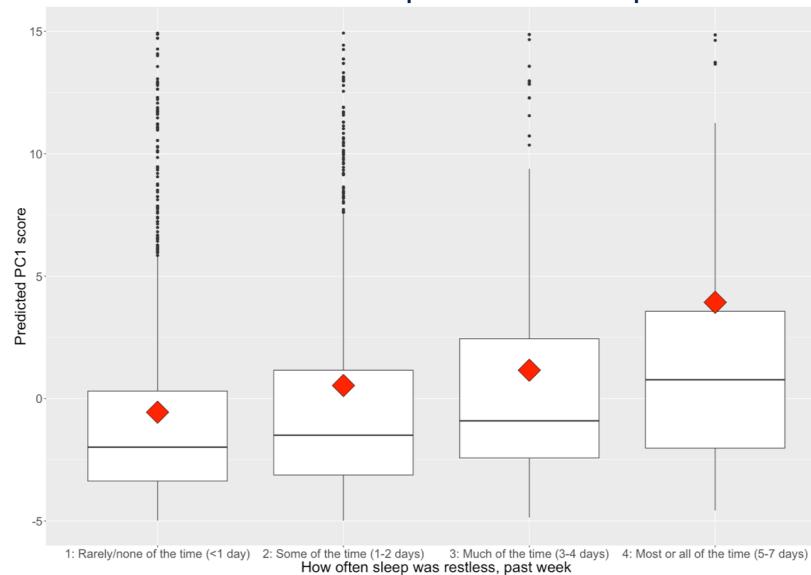


Results – Pain trajectory modeling

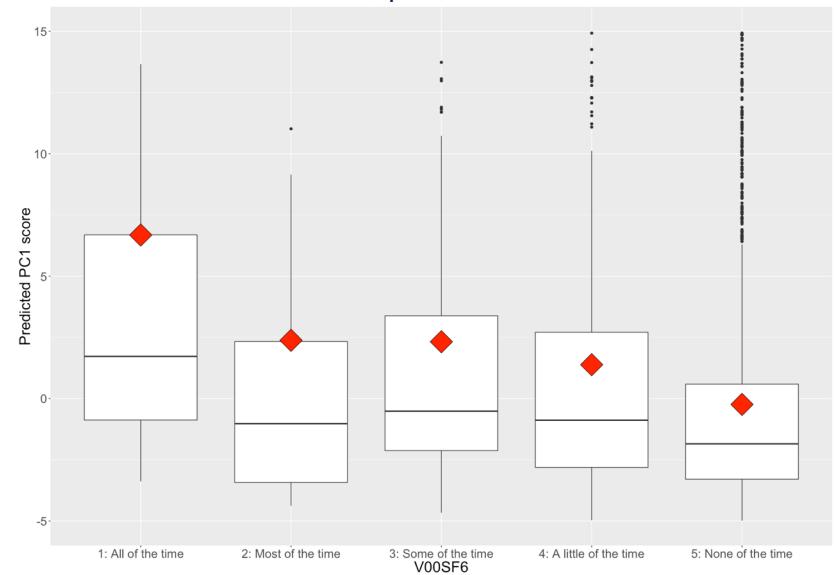


NN – Model interpretation / Prediction

PC1 vs How often sleep was restless past week?



How often emotional problems result in accomplishing less than would like with work or other activities, past 4 weeks?



NN – Conditional effects plot

