Machine Learning for predictive modelling based on small biomedical and clinical data

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  - Challenges with Biomedical and Clinical data
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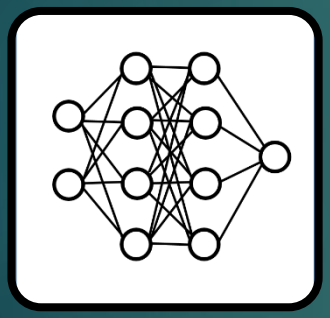
  - Random Forest model
- Summary

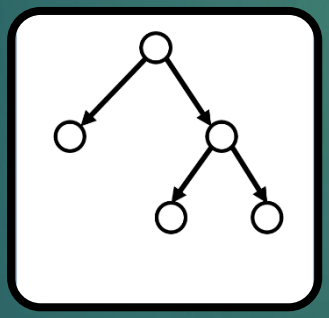
Machine Learning (ML)

- "Field of study that gives computers the ability to learn without being explicitly programmed“ (A. Samuel, 1959)

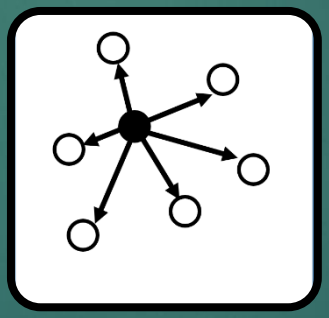
- **Original purpose (1950s)**: creating AI, simulating intelligence
- **Current use**: finding trends in large complex data, recognising patterns (speech, image and semantics)



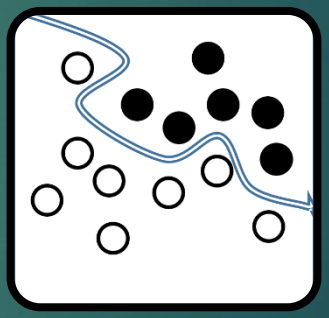
Artificial Neural Networks
- Deep learning



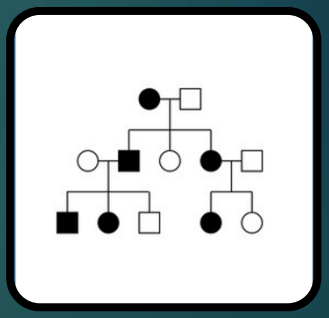
Tree-based methods
- Decision trees
- Random forests



Instance-based learning
- k-Nearest Neighbour



Kernel methods
- Support Vector machines



Genetic algorithms
- Evolutionary theory

ML and Biomedical Engineering

- **Machine Learning (ML) - indispensable tool in Bioinformatics [1,2]**
- **Still a relatively slow take up in biomedical engineering and healthcare**

Why Biomedical/Clinical data are small?

Cost

- Expensive experiments
- Living tissue
- Clinical data

Standards

- Institutional bias
- Ethical approvals
- International data transfer

"Big Data"?

- Too few events
- Exclusion criteria
- Missing data
- Class imbalance

Why is ML rarely viewed in the context of "**Small Data**"?
(<10 observations per predictor variable)

Insufficient training data

Insufficient test data

High volatility

Generalisation issues

ML and Small Data: making it work

Method of multiple runs

- What does it do?

Small data → many ML models

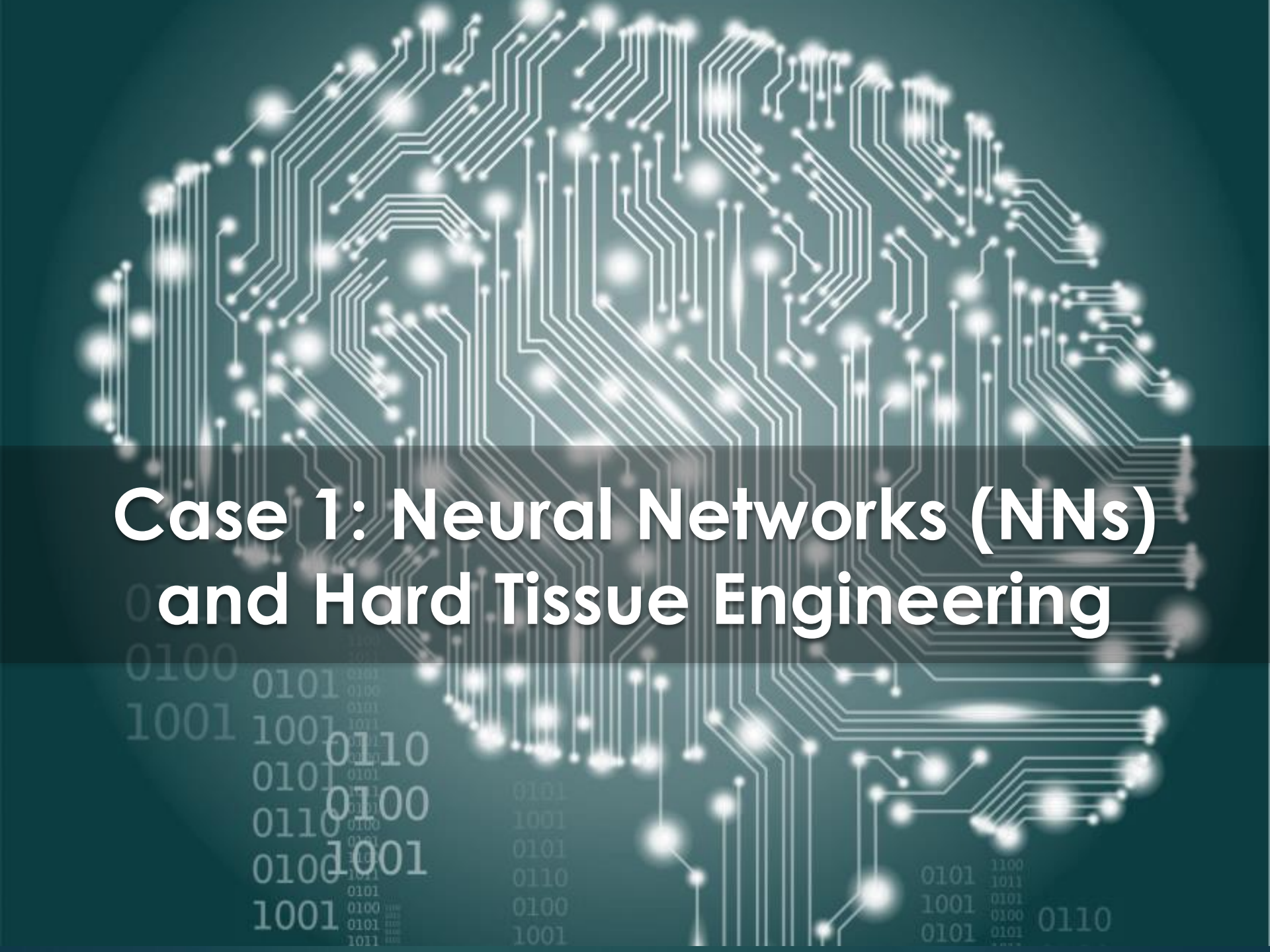
Reduces volatility

Increases consistency

- How does it work?
  - "Run" = thousands of ML models trained in parallel
  - A range of well- and poorly-performing models
  - Allows for iterative design optimisation
  - Performance measured collectively across the run
  - Use output of the best-performing model

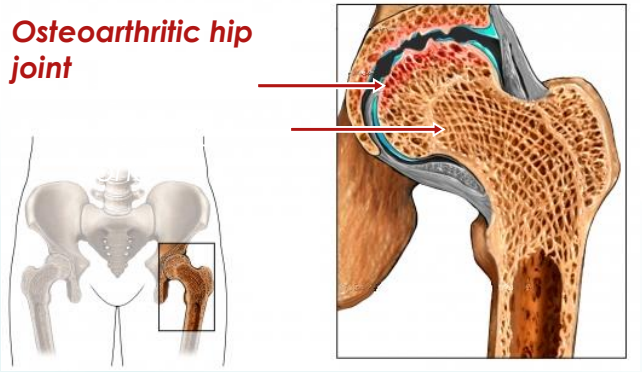
Surrogate data

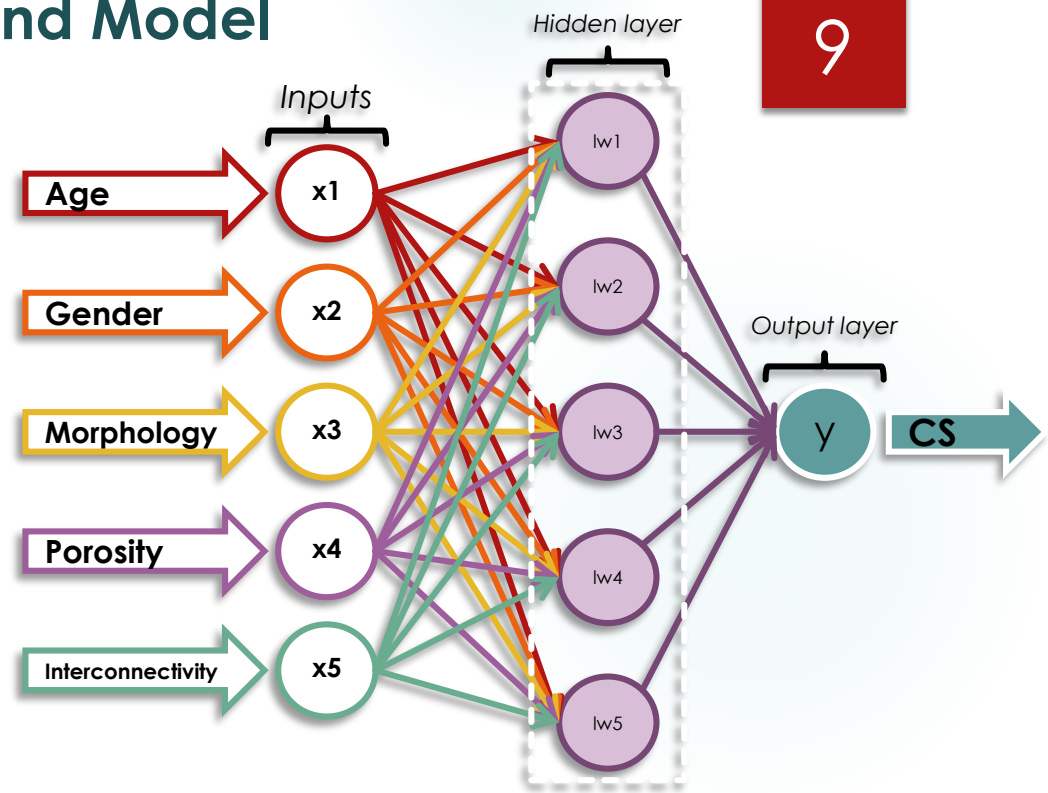
- What does it do?
  - Quantifies random effects due to small data
  - Model validation despite insufficient number of **test** samples
- How does it work?
  - Generate synthetic samples that mimic the real dataset
  - Train and test ML model on surrogate data
  - Highest performing surrogate model = lowest performance threshold for real data models


Case 1: Neural Networks (NNs)
and Hard Tissue Engineering

Case study 1: Background and Model

Regression task: to predict compressive strength (CS) of trabecular bone in severe osteoarthritis



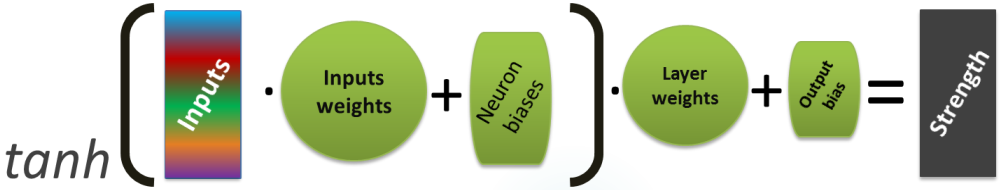


The model

- 35 trabecular bone samples [4]
- 20% reserved for tests
- Feedforward backpropagation NN with 5 input features and 1 output [5]
- Multiple run of 2000 NNs

$$y = \tanh\left[\bar{x} \cdot IW + \overline{b_{(1)}}\right] \cdot \overline{lw'} + b_{(2)}$$

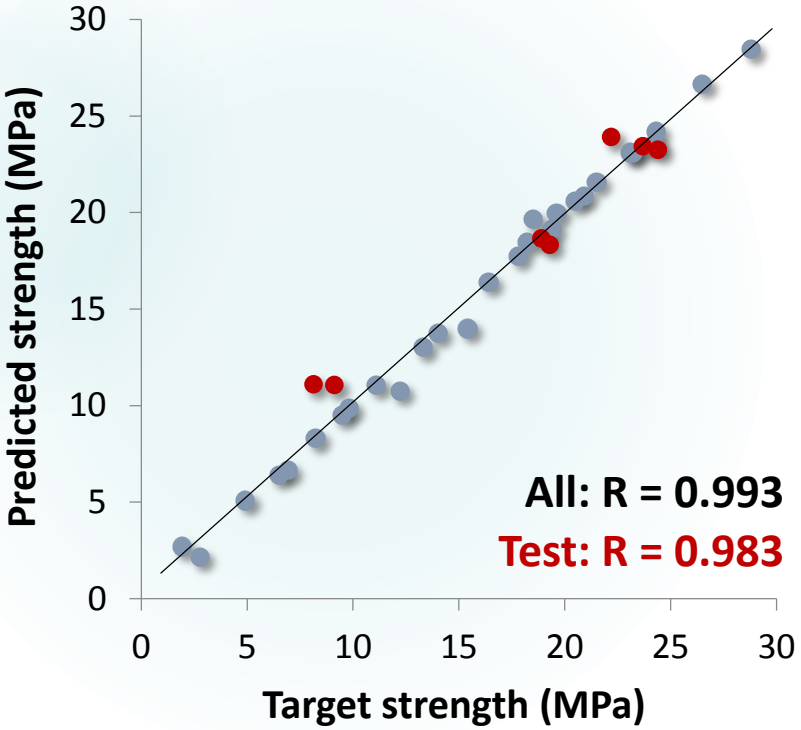
output = tanh(*inputs* × *input weights* + *biases*) × *layer weights* + *output bias*

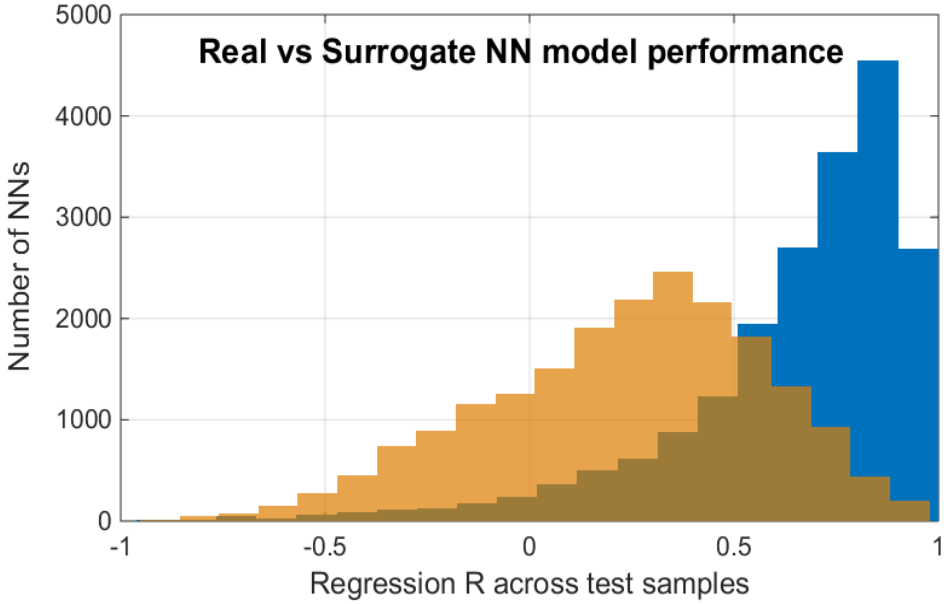


Case study 1: Results

NN performance

- Regression between actual and predicted CS:
  - across all samples, R = 99.3%
  - across 7 test samples, R = 98.3%
- Standard error = 0.85 MPa





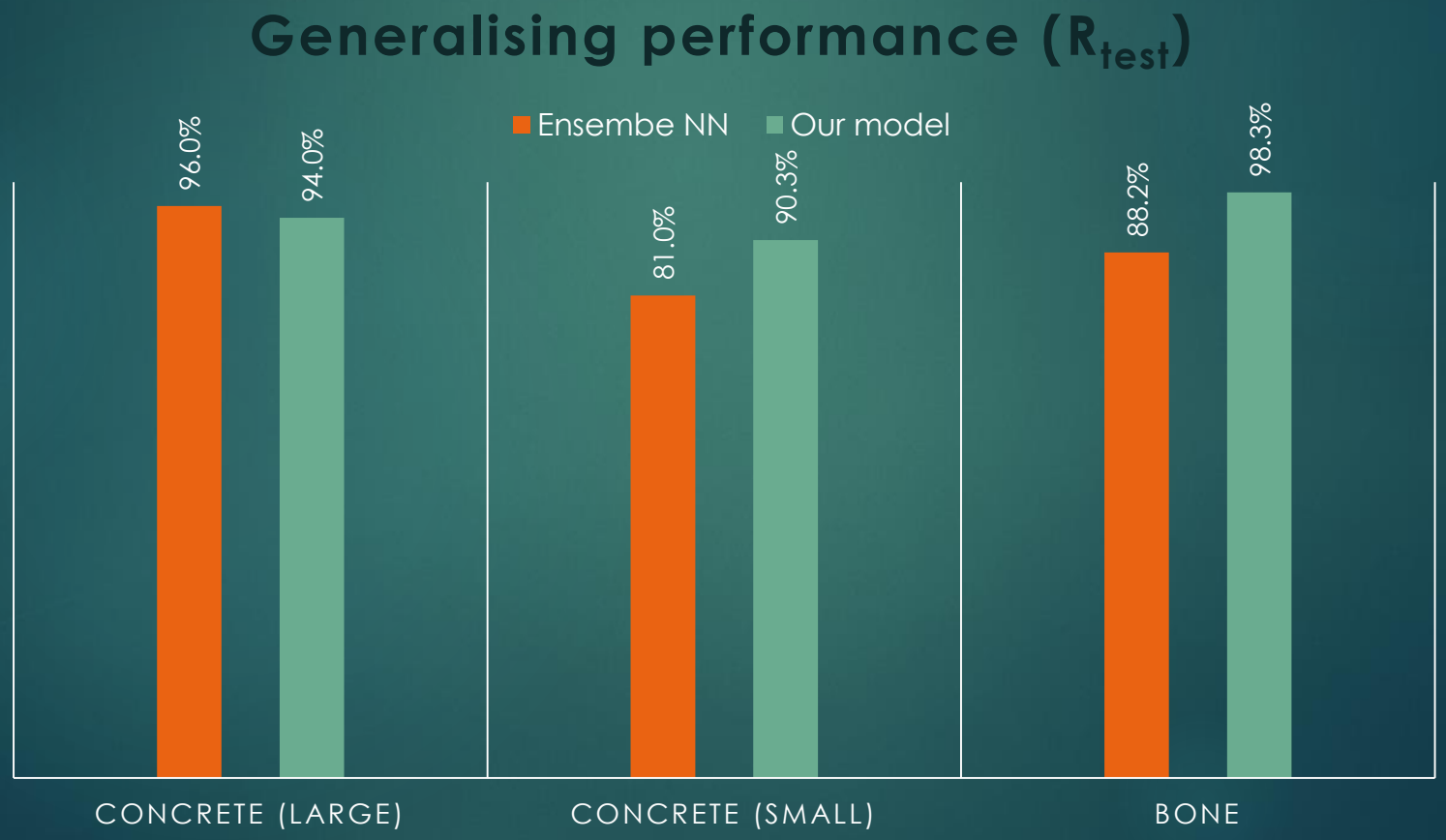
Validation with surrogates

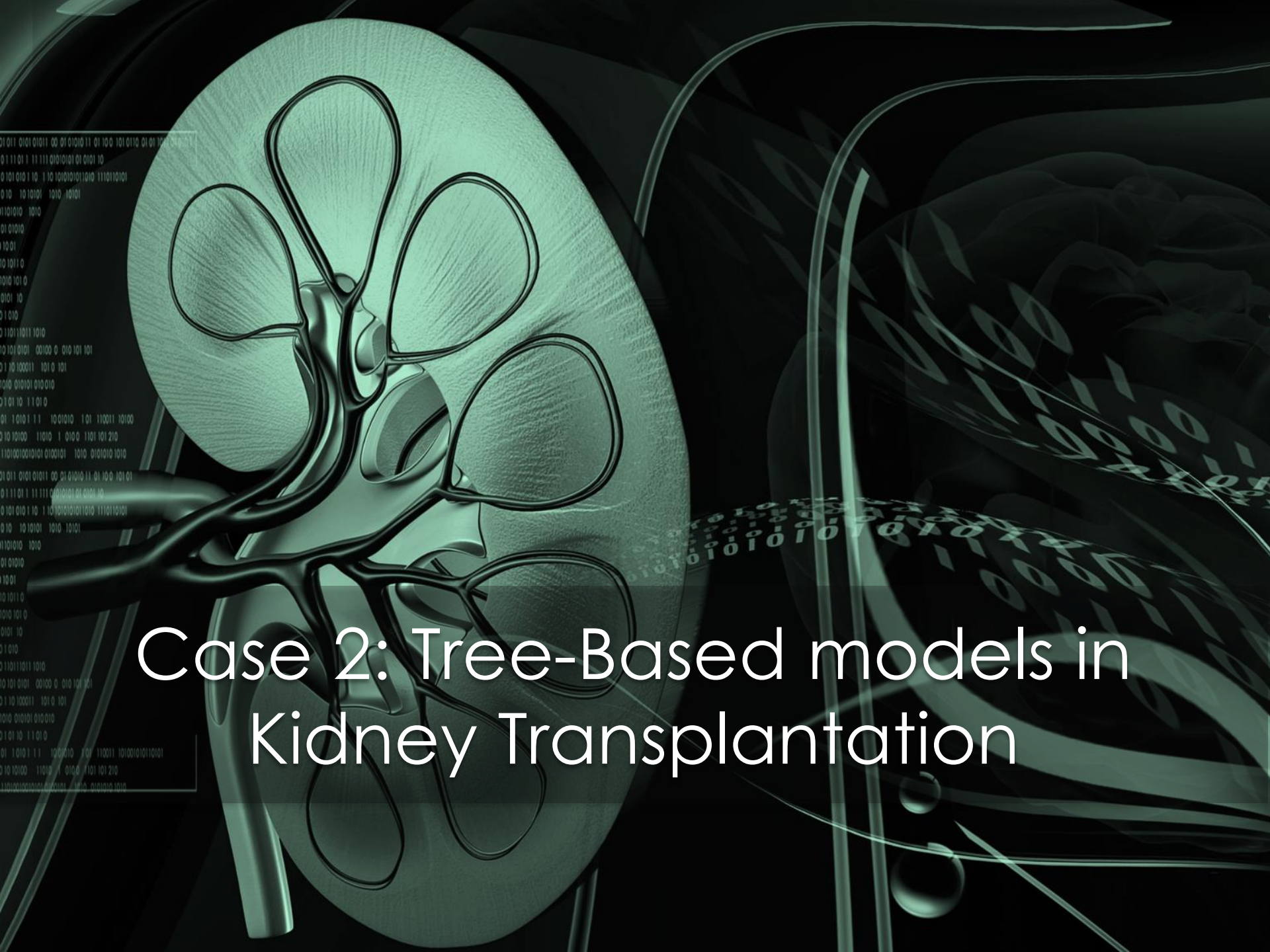
- Wilcoxon rank test (200000 NNs)
  - Hypothesis rejected ($p<0.000001$)
- Mean values
  - Surrogates, R = 0.33
  - Real data, R = 0.68
- Surrogate threshold R = 0.87

Comparison with NN ensembles

NN ensembles – powerful extension to NNs:

- Performed with 96% generalising accuracy on large-data concrete model (2% improvement)
- Underperformed with small-data





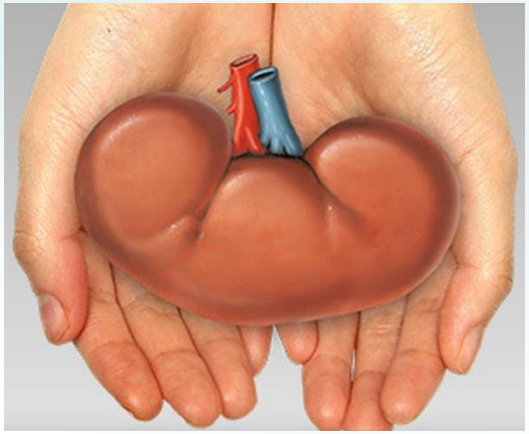
Case 2: Tree-Based models in Kidney Transplantation

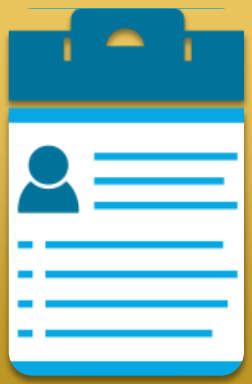
Case study 2: Background of the task

Classification task: to predict rejection (R/NR) of kidney transplants in early (<30 days)post-transplant period

Secondary tasks:

- Identify risk factors
- Dangerous antibody subclasses (IgG1-4)
- Harmful antibody levels





Dataset [6,7] - 80 patients

- **15 predictors**
  - age, gender, tissue mismatches, antibody levels, dialysis, etc.
- **Well balanced** : 46 R and 34 NR
- **Issues:** missing data, heterogeneity
- **Computational intensity**: 60960 splits

Model

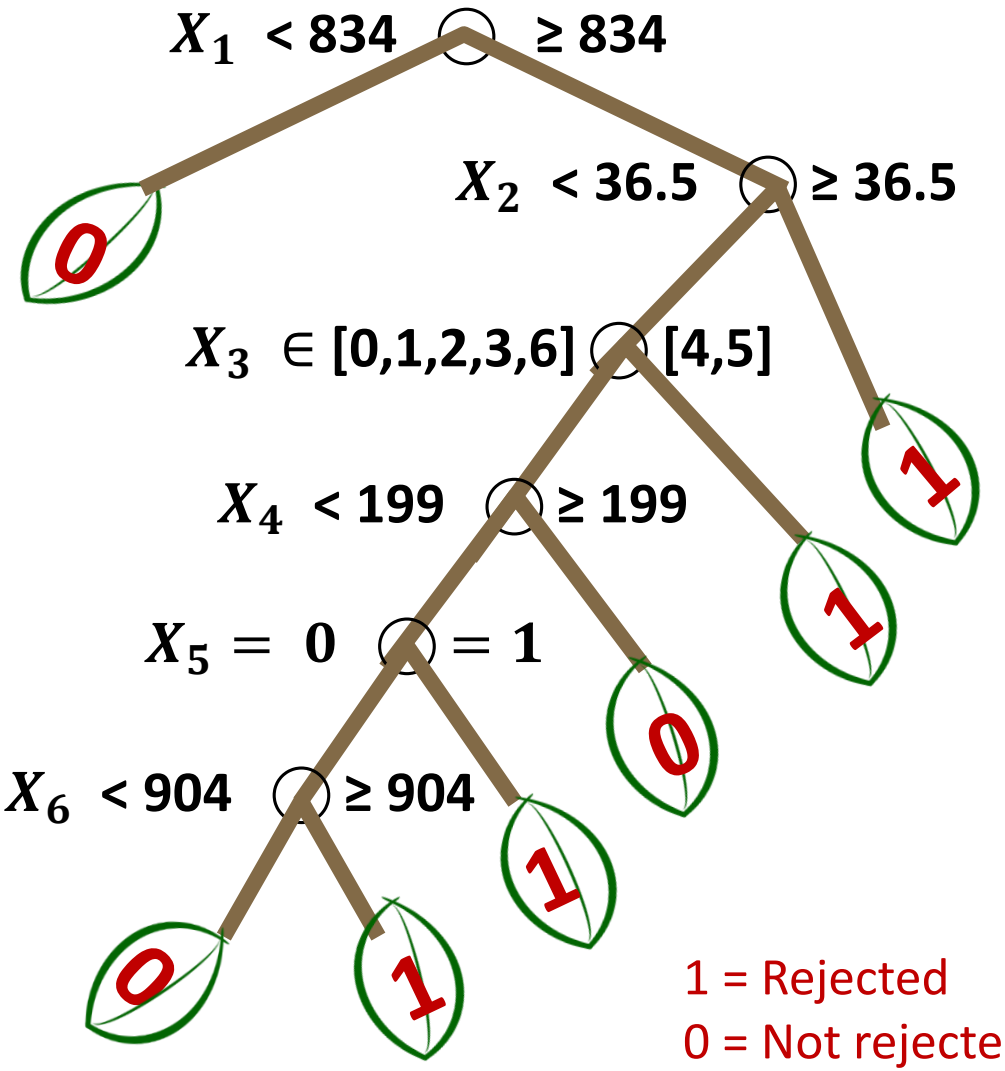
- Standard CART implemented in MATLAB
- Tree pruning: complexity penalised
- Multiple run of 600 DTs
- Random Forest (RF) extension to improve classifier robustness

Case study 2: DT model

- Only 6 (out of 15 possible) predictors were used by the DT:

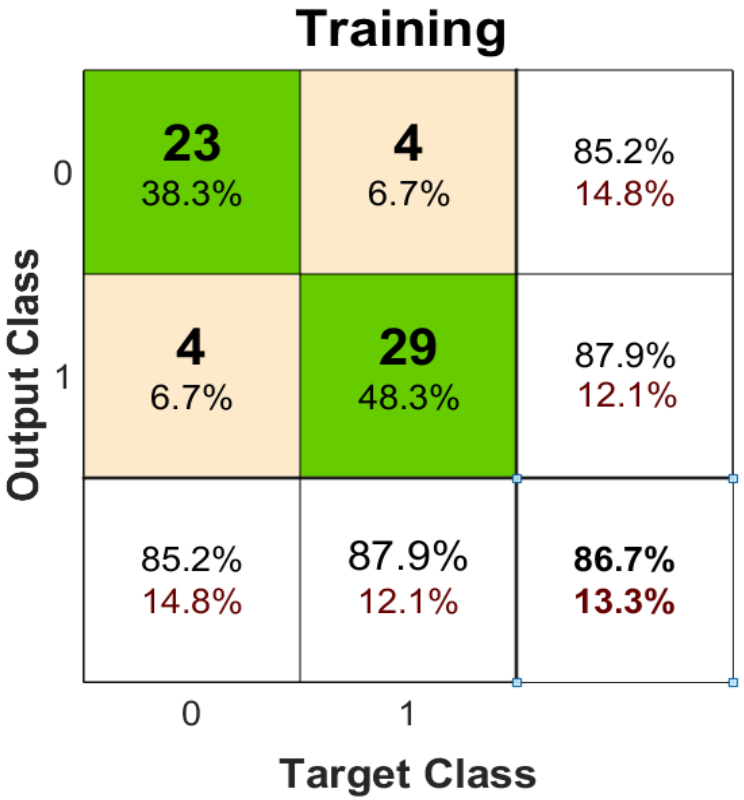
Risk levels:

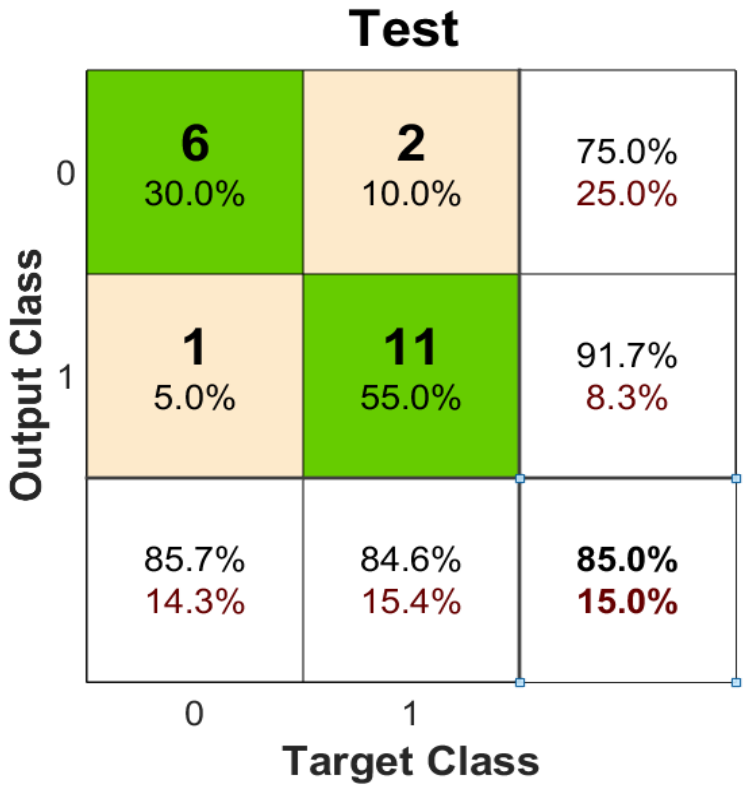
- X_1 highest antibody level
- X_2 total IgG4 ≥ 36.5
- X_3 tissue mismatches
- X_4 total IgG2
- X_5 delayed graft function
- X_6 total IgG1 ≥ 904



Case study 2: DT model results

Confusion matrices





Training accuracy = 86.7%
Sensitivity = 87.9%
Specificity = 85.2%

Generalising accuracy = 85.0%
Sensitivity = 84.6%
Specificity = 85.7%

Summary

- Machine learning is able to learn from small biomedical data:
  - Our framework produces well-generalising predictive models built with limited data, which outperform some state-of-the-art alternative models
  - How much data is enough remains a compromise

- **NN model for strength estimation in trabecular bone**
  - Non-destructive estimation of bone fracture risk
  - Highly-accurate (98.3%)
  - Compressive Strength accurate to 0.85 MPa

- **DT as a predictive tool in Kidney transplantation**:
  - Classified AMR/Non-AMR with 85% accuracy
  - Identified key risk factors
  - Estimated specific levels of antibodies

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Thank you!