Integrating Omics in the Era of AI for Better Patient Specific Outcomes

Presentation Title: Utilizing Multi-Omics Data To Improve the Prediction of Toxicities

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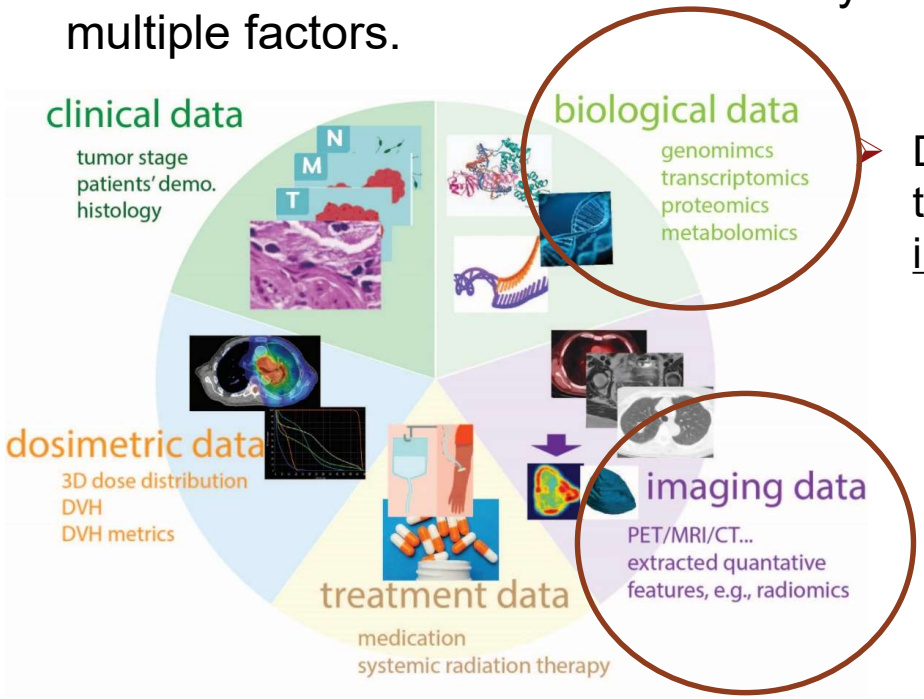
Outlines

- *Motivation:*
  - *what is and why we use multi-omics data?*
- *Method:*
  - *How to build a multi-omics model to predict toxicity*
  - *Validation scheme*
  - *Interpretability of the model*
- *Two case studies: prediction of radiation pneumonitis in non-small cell lung cancer (NSCLC)*

Motivations: Available data

- Conventional radiotherapy outcome models only utilize information about
  - the dose distribution and fractionation.
- Treatment outcomes are mediated by the complex interactions among multiple factors.



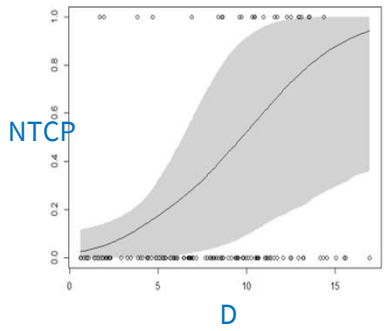
Data driven models are supported by the explosive growth of patient-specific information powered by advances in

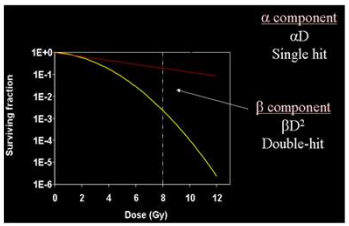
- biotechnology
- imaging
- computational capabilities
- the evolution of electronic health records.

Motivations: Available models

Analytical model → Machine learning model → Incorporate deep learning techniques

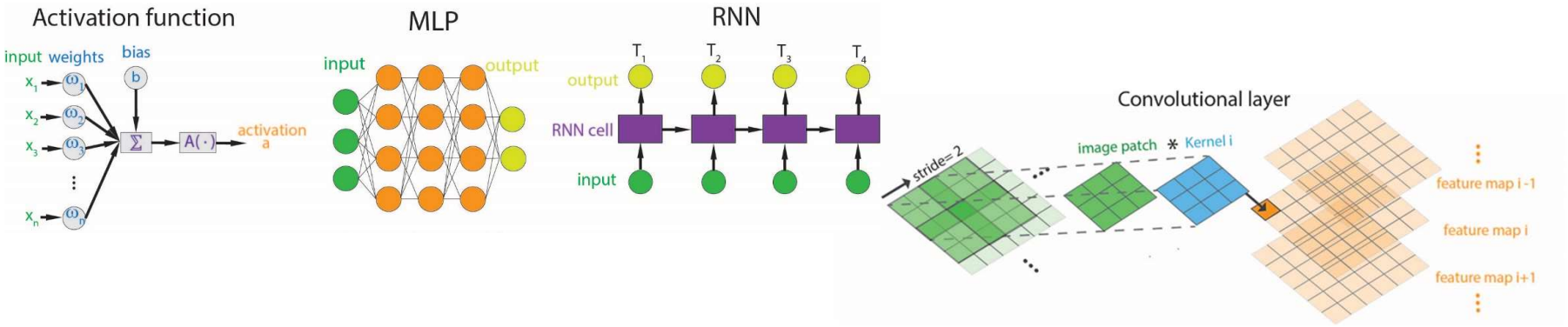
- Analytic models e.g., Linear quadratic (LQ), Lyman models
  - simple understanding of radiobiological effects
  - use dosimetric information only





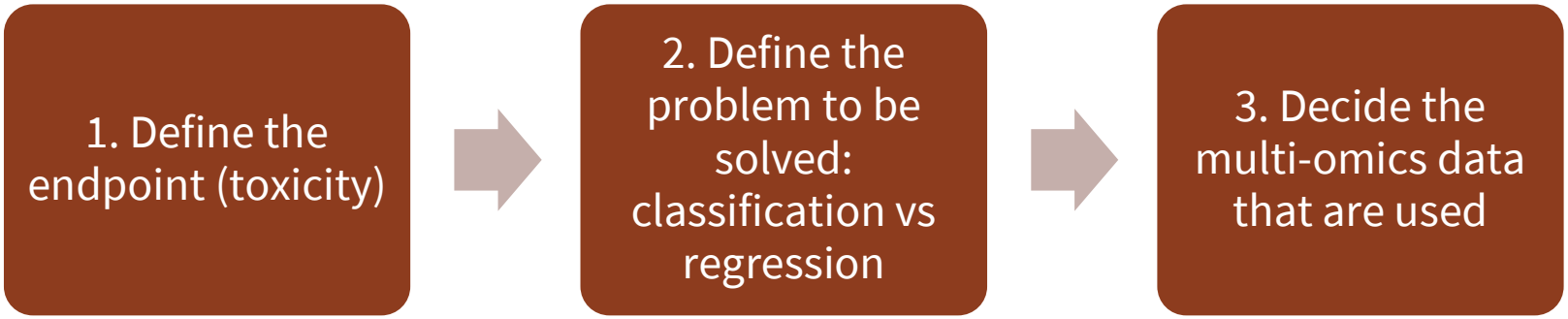
Motivations: Evolutions of outcome models

Analytical model → Machine learning model → Incorporate deep learning techniques



- Machine learning model e.g., Support vector machines (SVM), random forests (RF)
- Deep learning techniques, convolutional neural network (CNN), multi-layer perceptrons (MLPs), recurrent neural networks (RNN)

Method: an outcome model to predict toxicity – define a problem

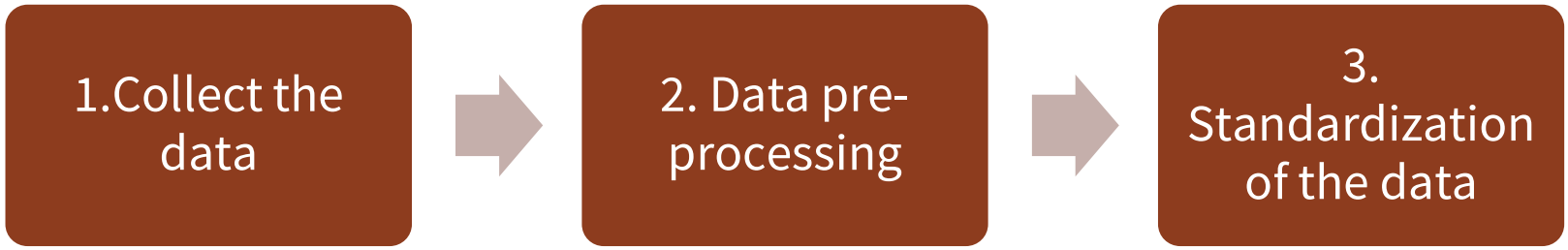


1. NTCP endpoints graded by RTOG or CTCAE criteria, several graded severity scales.

2. Toxicity outcome data are associated with a specific follow-up time, decide whether to use a cutoff time or consider time-to-event in the model.

3. Four major types of data include: clinical data, dosimetric data, imaging data and biological data.

Method: an outcome model to predict toxicity – data pre-processing and preprocessing

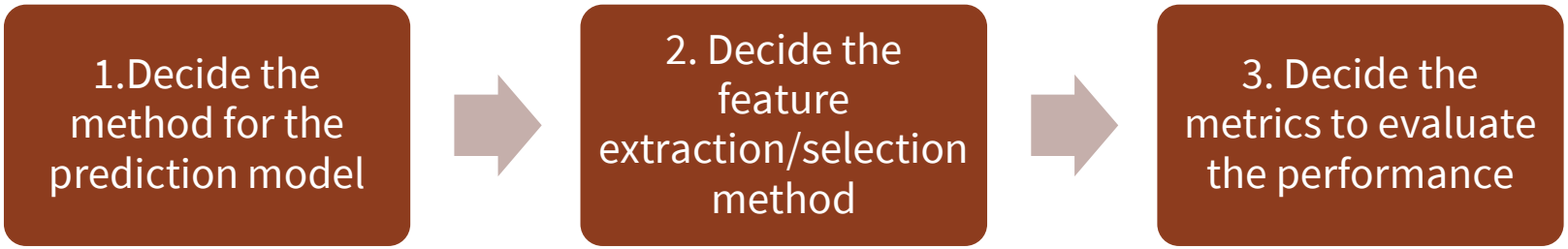


1. Collect clinical data from EHR, dosimetric data from TPS, imaging data from PACS, biological data from lab tests.

2. Decide how to handle missing data; patient include/exclude criteria; check the accuracy and reliability of data

3. Multi-omics data including biological and imaging data may highly vary in the magnitude, data may need to be standardized, e.g., score normalization, min-max scaling

Method: an outcome model to predict toxicity – train the model



1. Common classification/regression models include SVM, RF, Bayesian network, deep neural network;

2. 3 types of feature selection methods: filter methods, wrapper methods, and embedded methods. In deep learning this step is implicit and is realized by the multi-level deep learning architectures

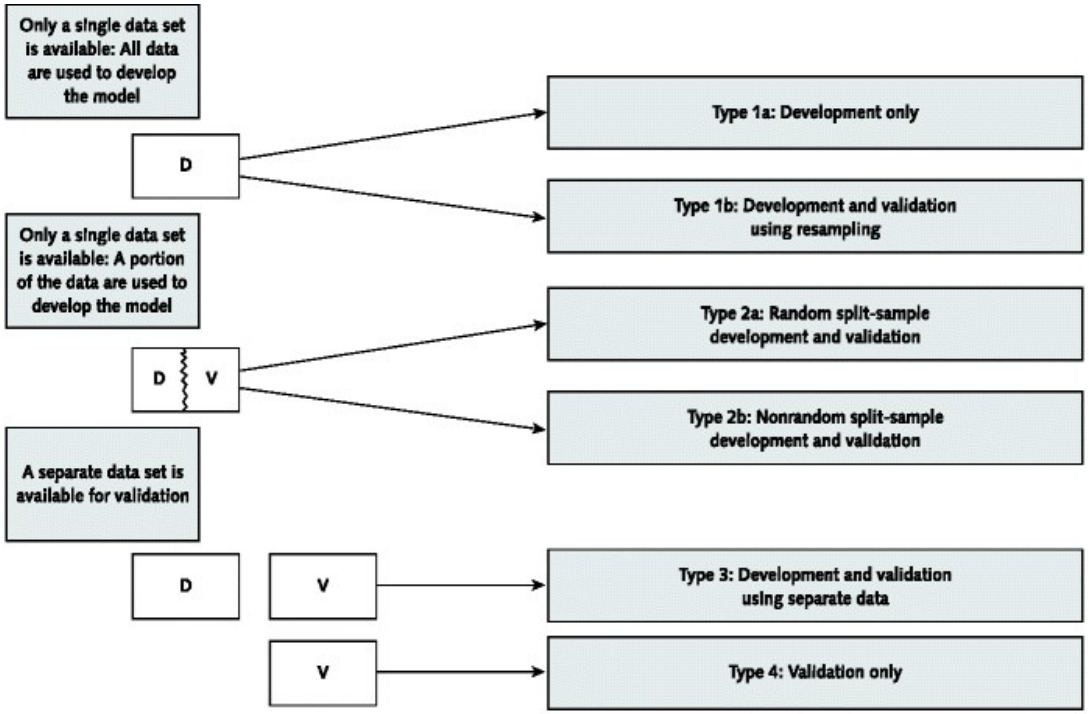
3. Classification: accuracy, confusion matrix, true positive rate (TPR), false positive rate (FPR), operating characteristic curve (ROC). Regression: the concordance index (C-index) can be applied.

Important consideration – validation scheme

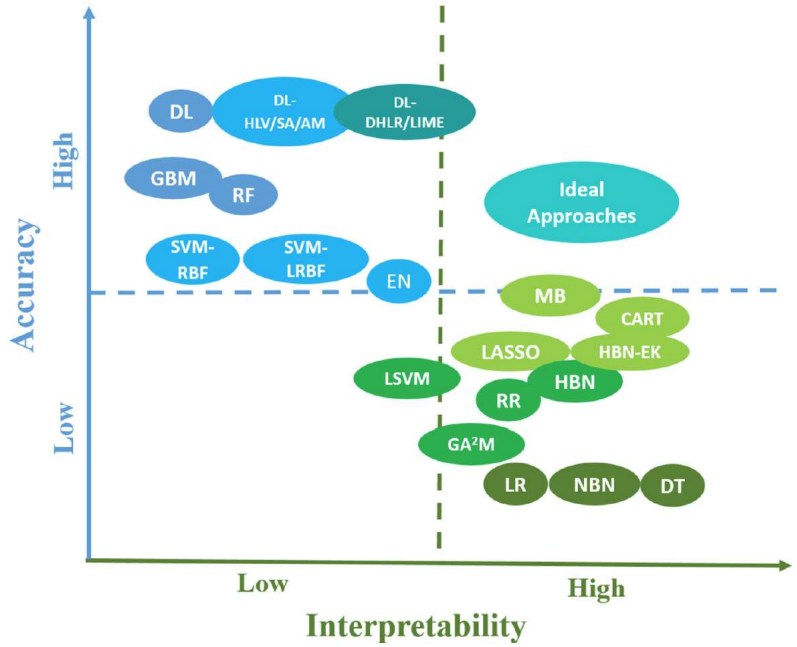
Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD State

Gary S Collins, Johannes B Reit

BMC Medicine **13**, Article numbe



Important consideration – interpretability of the model



- The transition of the outcome model into relies on how the clinician can interpret or understand the specific decision made by the model.
  - Gain trust, increase its credibility
  - Safeguard mechanism
- The interpretability and explainability of models are crucial for clinical implementation.

Adapted from Balancing accuracy and interpretability of machine learning approaches for radiation treatment outcomes modeling,Yi Luo, Huan-Hsin Tseng, Sunan Cui, Lise Wei, Randall K. Ten Haken, and Issam El Naqa BJR|Open 2019 1:1

Two case studies

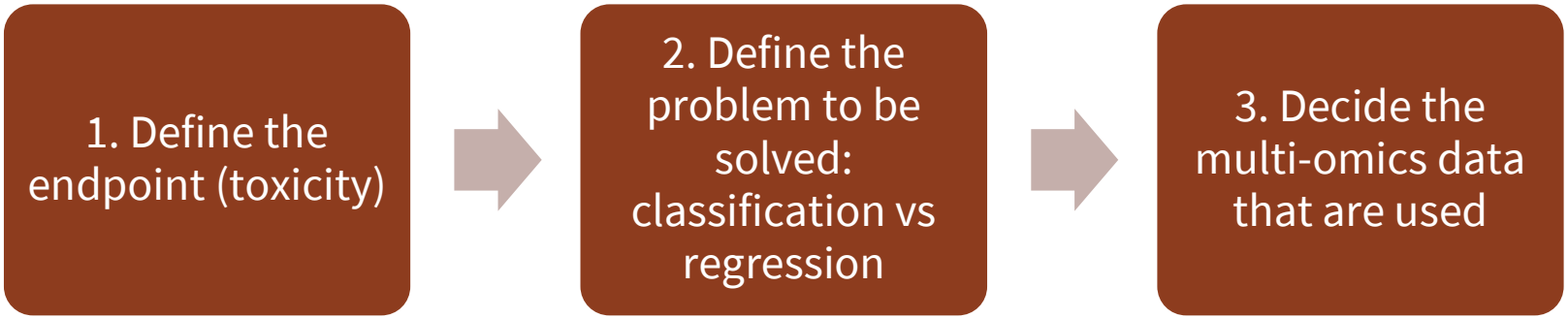
Prediction of radiation pneumonitis in non-small cell lung cancer patients

1. Variation autoencoder (VAE) + multilayer perceptrons (MLP) joint architecture
   - Feature extraction
   - Model selection
2. Deep-learning based composite architecture
   - Validation scheme
   - Interpretability of the model

[1] Combining handcrafted features with latent variables in machine learning for prediction of radiation-induced lung damage. Medical Physics, 2019. 46(5): p. 2497-2511.

[2] Integrating Multiomics Information in Deep Learning Architectures for Joint Actuarial Outcome Prediction in Non-Small Cell Lung Cancer Patients After Radiation Therapy, International Journal of Radiation Oncology*Biology*Physics, 2021 110 (3).

Case 1 Define the problem: prediction of RP2 in NSCLC:

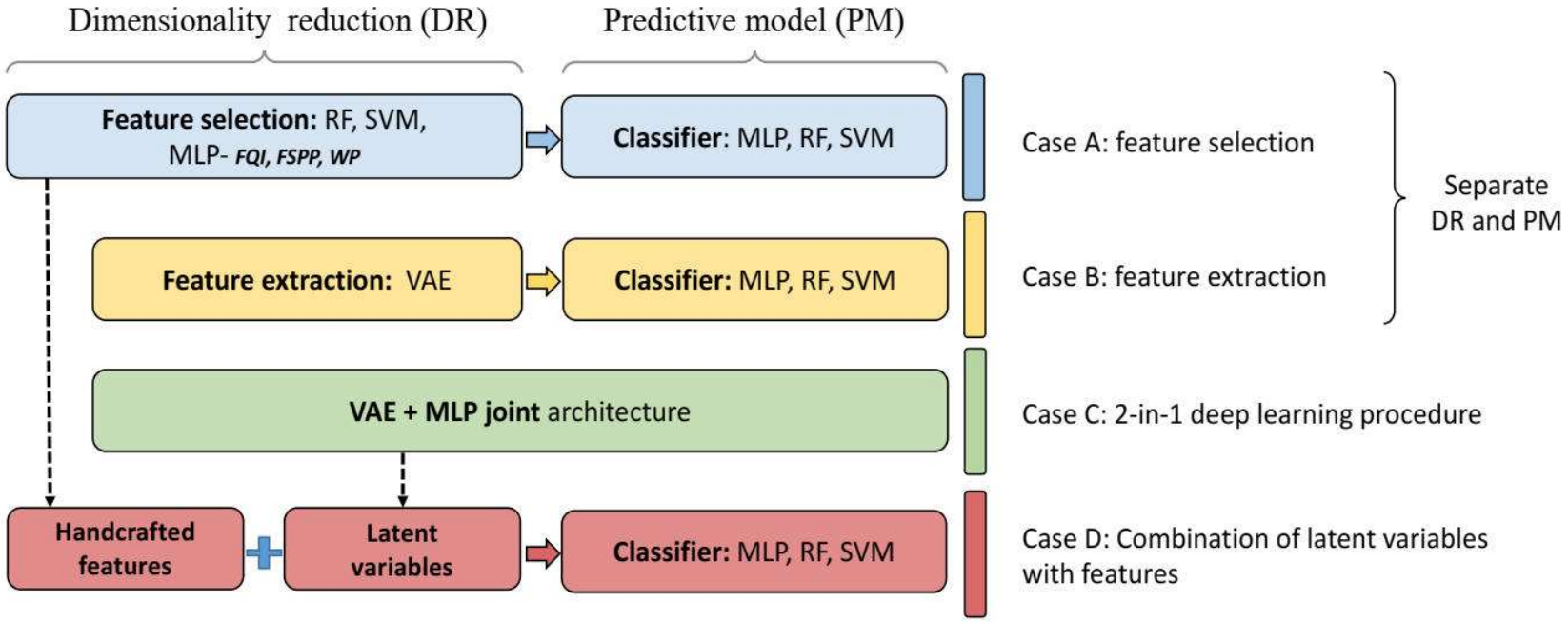


1. Endpoint radiation pneumonitis (RP) CTCAE , graded severity scales 1-5, we predicted grade ≥ 2

2. Classification problem, i.e., binary classification.

3. 13 clinical data including age, stage, smoking, etc, 5 dosimetric data including mean lung dose, V20, V5, etc; 30 cytokines, 62 mi-RNA, 60 SNPs.

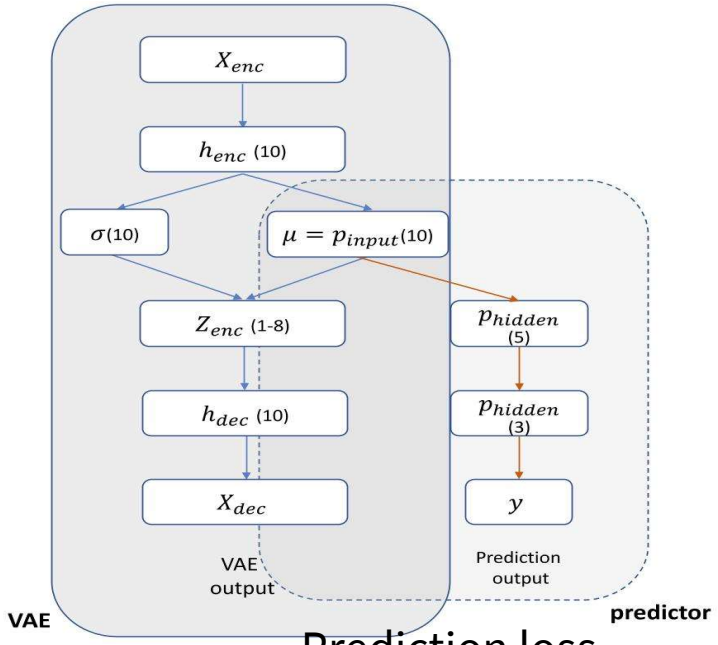
Case 1 Feature extraction: prediction of RP2 in NSCLC



Adapted from Cui, S., et al., Combining handcrafted features with latent variables in machine learning for prediction of radiation-induced lung damage. Medical Physics, 2019. 46(5): p. 2497-2511.

Case 1 Prediction model: prediction of RP2 in NSCLC

- A VAE-MLP joint architecture
  - ➢ enables simultaneous **dimensionality reduction** and **prediction**.
  - ➢ The learning of latent variables guided by **both** reconstruction task and the prediction task.



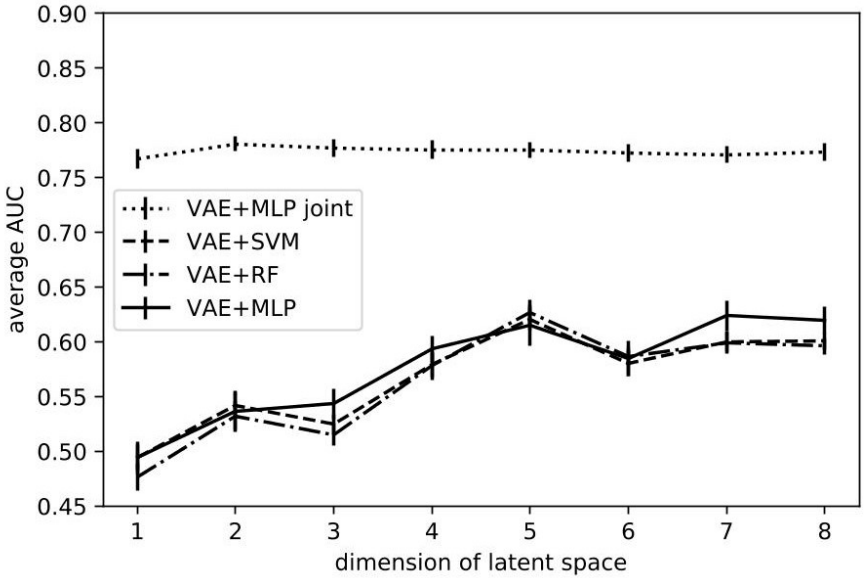
VAE loss

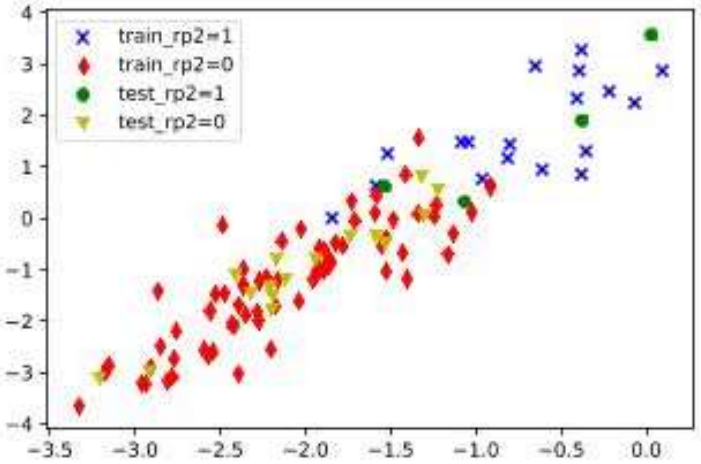
Prediction loss

$$L(x_{enc}, x_{dec}, y) = \| x_{enc} - x_{dec} \|^2 + \frac{1}{2}\sum_{j=1}^{J}\left[1 + \log\left(\sigma_j^2\right) - \sigma_j^2 - \mu_j^2\right] + \lambda\frac{1}{N}\sum_{i=1}^{N} y_i \log(p_1) + (1 - y_i)\log(p_2)$$

Case 1 Model selection: prediction of RP2 in NSCLC

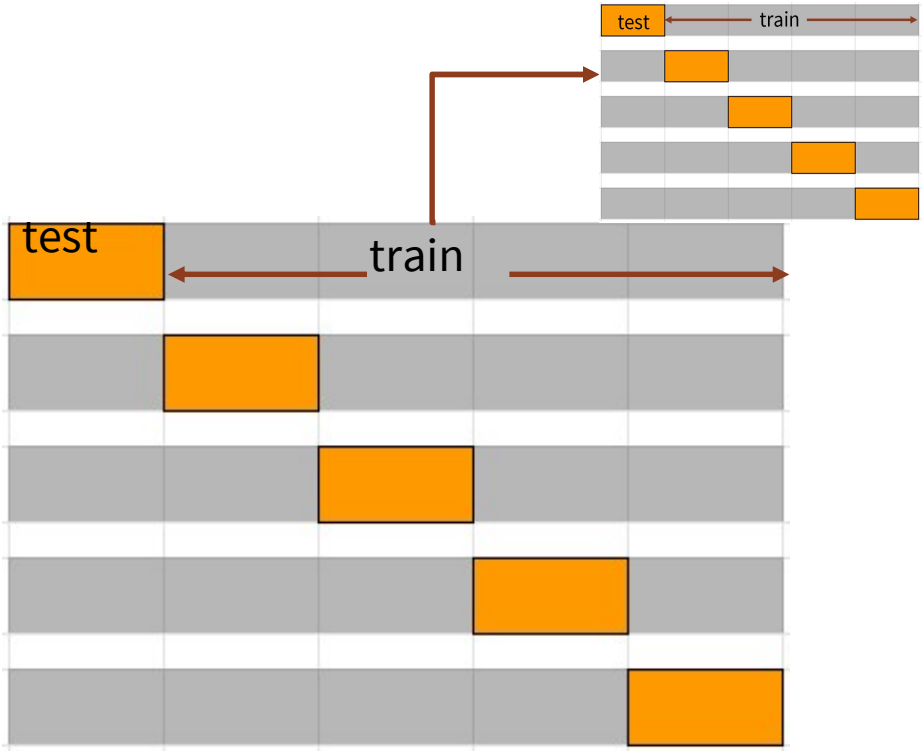
- VAE+MLP joint vs conventional separate VAE and classifier





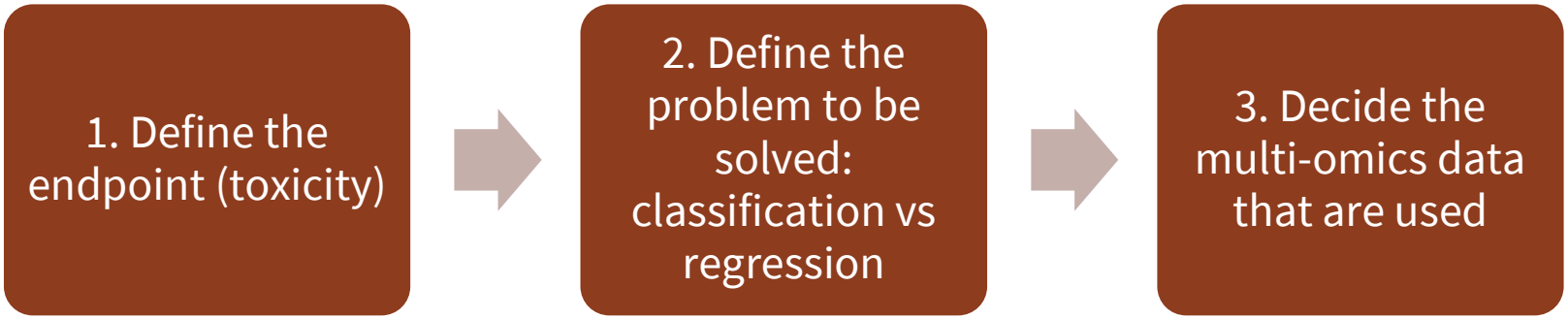
Visualization of latent space

Case 1 Model selection: prediction of RP2 in NSCLC



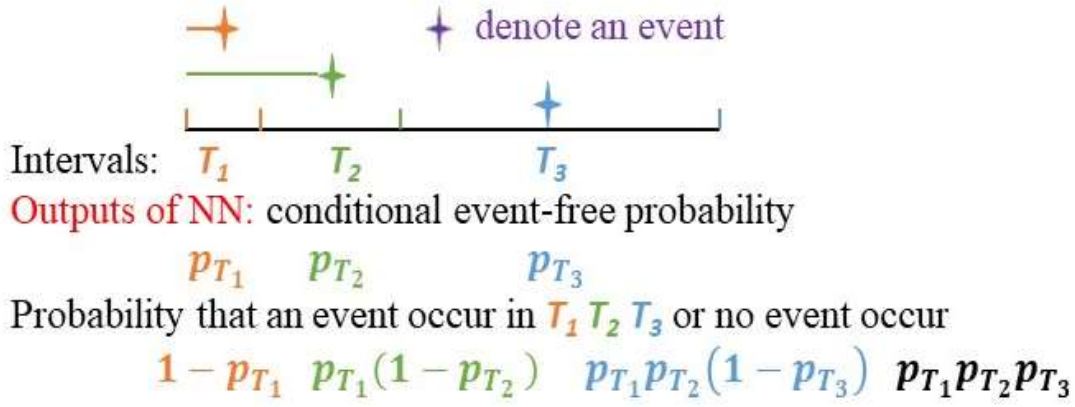
Inner loop cross-validation: used to select the optimal model/features

Case 2 Define the problem: prediction of RP2 in NSCLC:



1. Endpoint radiation pneumonitis (RP) CTCAE , graded severity scales 1-5, we predicted grade ≥ 2
2. Consider both RP2 and time-to-event
3. The whole DVH, 30 cytokines, 62 mi-RNA, 60 SNPs.

Case 2 Predict time-to-event RP2 in NSCLC



Actuarial prediction:

T intervals:

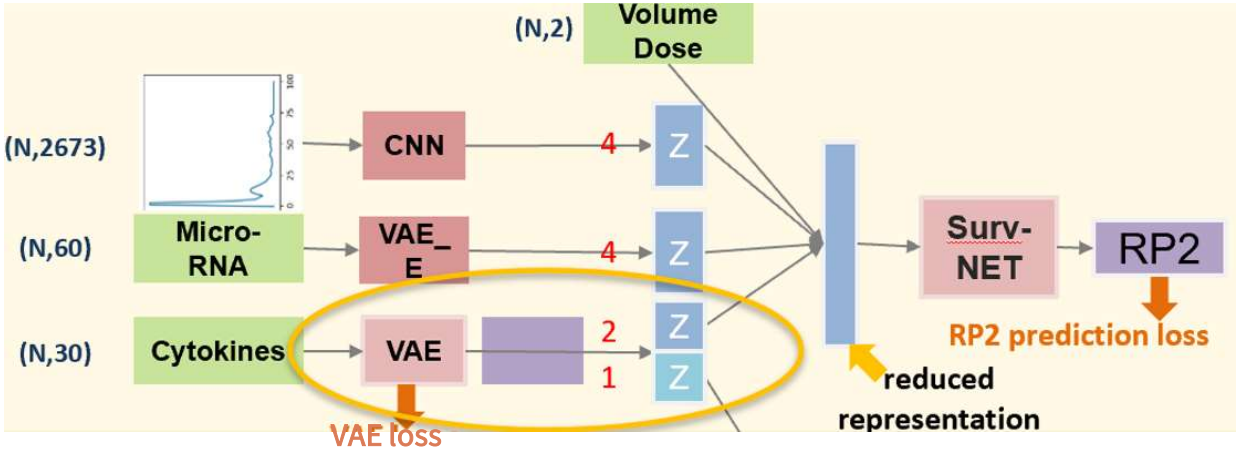
- log-likelihood function for an individual with failure in interval j is defined as,

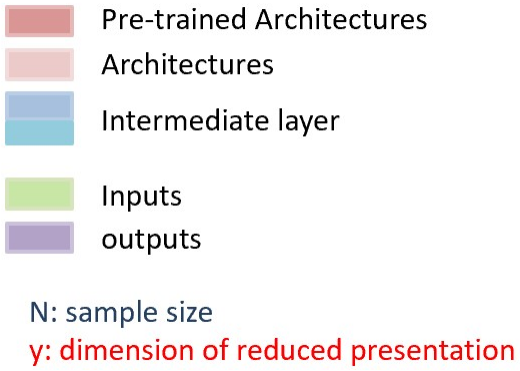
$$l = (1 - P_{T_j}) \prod_{i=1}^{j-1} P_{T_i}$$

- l for an individual without experiencing events through interval j

$$l = \prod_{i=1}^{j} P_{T_i}$$

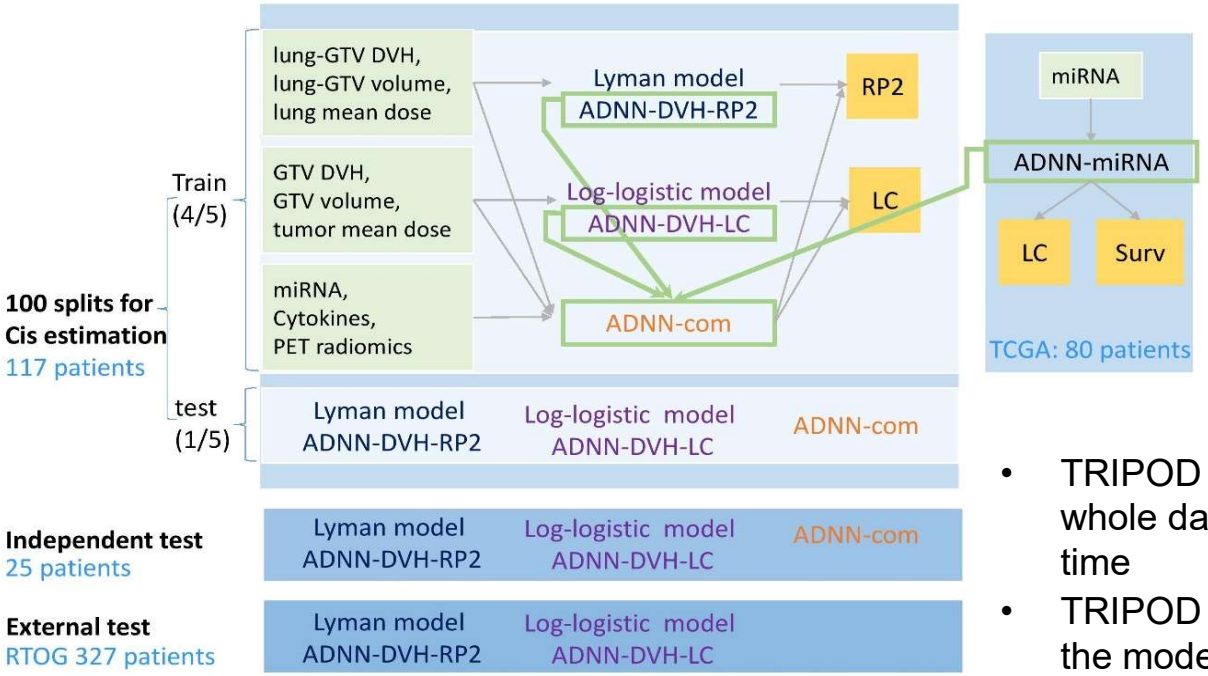
Case 2 Prediction model: prediction of RP2 in NSCLC





$$l_{RP2} = l_{RP2\_prediction} + l_{VAE\_loss}$$

Case 2 Validation scheme: prediction of RP2 in NSCLC

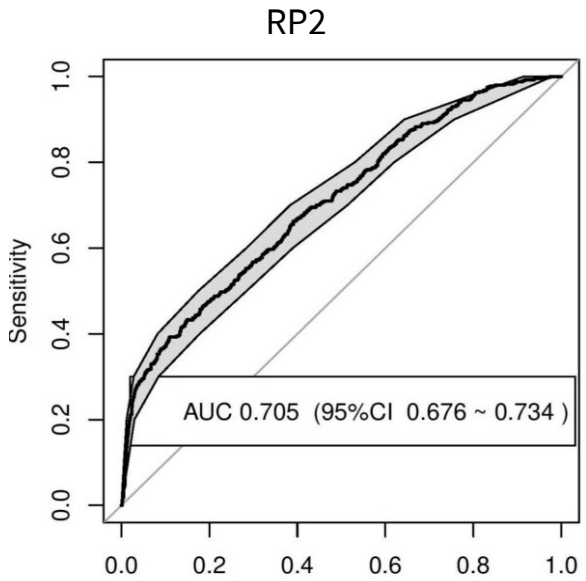


- TRIPOD level 2 type a: dividing the whole dataset into 2 groups: a random split

- TRIPOD level 2 type b dividing the whole dataset into 2 groups based on time
- TRIPOD type 3 validation evaluating the models on an independent external data set

Case 2 Model evaluation: prediction of RP2 in NSCLC

Model evaluation on UM 117 patients	
C-index (95% CI)	RP2
Lyman model	0.613 (0.583-0.643)
ADNN-DVH	0.660 (0.630-0.690)
ADNN-com-joint	**0.705 (0.676-0.734)**
Independent test on 25 newly-treated patients	
Lyman model	0.588
ADNN-DVH	0.667
ADNN-com-joint	0.691
RTOG 0617	
C-index	RP3
Lyman model	0.736
ADNN-DVH	0.762



Case 2: Interpretability of the model –Grad-CAM

- Grad-CAM can highlight (assign higher values to) regions in an activation map that are important for a decision of interest

$$L^c_{Grad-CAM} = ReLU(\sum_k \alpha_k^c A^k)$$

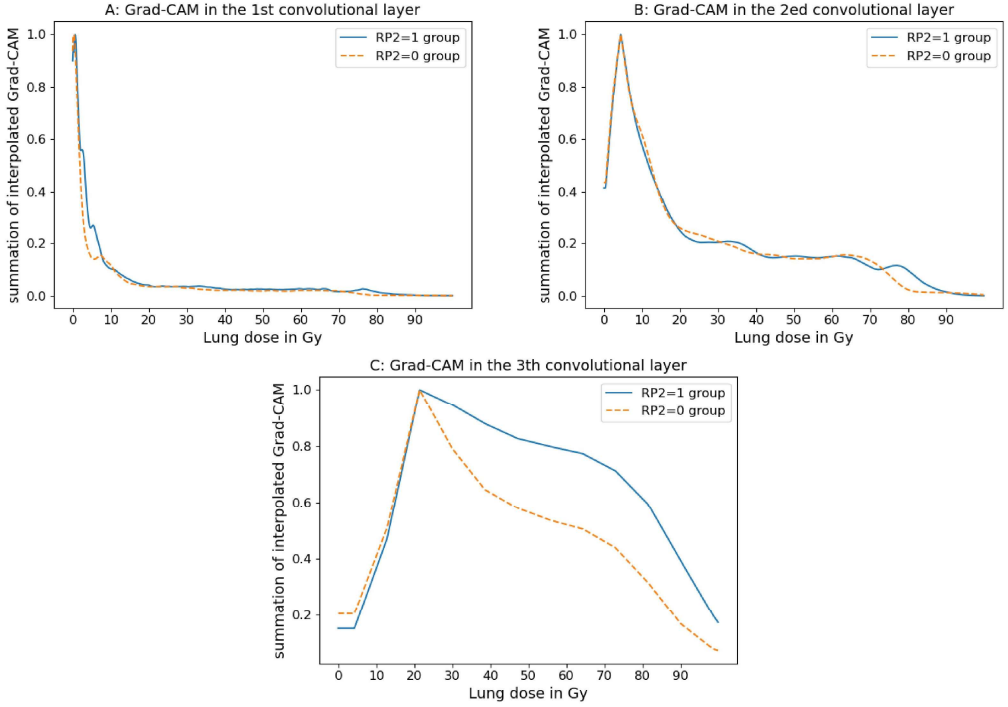
$$\alpha_k^c = \frac{1}{Z}\sum_i \sum_j \frac{\partial y^c}{\partial A_{ij}^k}$$

  - c denotes an arbitrary output; $A_k \in R^{u \times v}$ is the k^{th} feature map with height u and width v; α_k^c is the weight of the k^{th} feature map in discriminating class c.
  - The weight α is defined as gradients of score for class c, y_c with respect to feature maps A_k of a convolutional layer followed by a global average pooling.

Case 2: Interpretability of the model –Grad-CAM

- Grad-CAM shows that deep learning-based outcome models gradually learn that dose regions near 20Gy in DVH are crucial for predicting radiation pneumonitis.

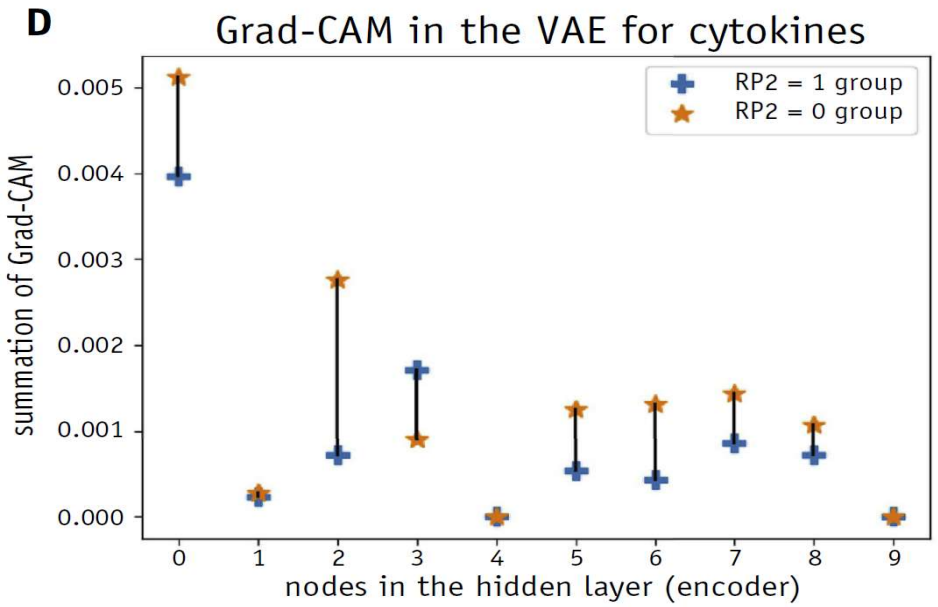
RP2



Case 2: Interpretability of the model –Grad-CAM

- Cytokines were found to contribute more to RP2 prediction.

RP2



Thank you!