DAT350

Summary.

Survival analysis

$$d = (0,1) = \begin{cases} 1 & \text{if failure} \\ 0 & \text{censored (event not observed)} \end{cases}$$

Hazard function h(t)

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}$$

The hazard is therefore the probability of failing within the time Δt, given that you have survived up until t.

$$P(t \leq T < t + \Delta t | T \geq t) = P(\text{individual fails in the interval } [t, t + \Delta t] | \text{survival up to time } t)$$

The hazard function has **no upper bound**.

Kaplan-Meier curves

The probability of surviving past time t based on observed data.

$$\hat{S}(t_{(f)}) = \prod_{i=1}^{f} (1 - \frac{m_{(i)}}{n_{(i)}}) = \prod_{i=1}^{f} \hat{P}[T > t_{(i)} | T \geq t_{(i)}]$$

$$= \hat{S}(t_{(f-1)}) \times \hat{P}(T > t_{(i)} | T \geq t_{(i)})$$

Log-rank test

Tests whether the Kaplan-Meier curves differ. For instance to check whether survival rate for men vs. women are significantly different. "Evaluate whether or not KM curves for two or more groups are statistically equivalent." Where the null-hypothesis H_0 is that there is no difference between the survival curves.

Log-rank test for two groups

Chi-square test for the overall comparison of KM curves.

$$e_{1f} = \underbrace{\left(\frac{n_{1f}}{n_{1f}+n_{2f}}\right)}_{\text{proportion in risk set}} \times \underbrace{(m_{1f}+m_2 f)}_{\text{n failures in both groups}}$$

$$e_{2f} = \left(\frac{n_{2f}}{n_{1f}+n_{2f}}\right) \times (m_{1f}+m_2 f)$$

Where m is the number of failures per time point, and n the total number of patients. The 1 and 2 signify which group they belong to.
The log-ranc statistic is calculated as

$$\chi^2 = \frac{(O_2 - E_2)^2}{\mathrm{Var}(O_2 - E_2)}$$

where

$$O_i - E_i = \sum_{f=1}^{\substack{\text{n failure}\\ \text{times}}} (m_{if} - e_{if})$$

If the test statistic χ^2 is below the critical value (from chi-squared table) there is not enough evidence to reject the null-hypothesis H_0.

Alternatives to the log-rank test

Weighting the test statistic.

Cox proportional hazard

The proportional hazard is given by

$$h(t, \vec{X}) = h_0(t) e^{\sum_{i=1}^{p} \beta_i X_i}$$

where $h_0(t)$ is the baseline hazard (independent of $\vec{X}$), and the exponential is time-independent.
$h_0(t)$ is unspecified and can therefore adapt itself to different situations.
When in doubt, the Cox model is a "safe" choice.
The Cox PH model is "robust" and will closely approximate correct parametric model.
If the correct model is:

- Weibull ⇒ Cox will approximate Weibull
- Exponential ⇒ Cox will approximate exponential

Machine learning estimates the parameters β done by maximising the likelihood function (to best describe the data).

$$\frac{\delta \ln(L)}{\delta \beta_i} = 0$$

where ln(L) is the log-likelihood function.

$$L = \prod_{j=1}^{k} L_j$$

where k is the number of failure times, and L_j;

$$L_j = \frac{h_0(t)e^{\beta_j}}{\sum_{i=j}^{k} h_0(t)e^{\beta_i}}$$

NOTE: only the sum from the current j and the "next", not the previous.

Assumptions

- The baseline hazard does not change once measured ($\vec{X}$-independent).
- $h_0(t)$ is unspecified $\rightarrow$ can take any form.
- $h_0(t)$ may be concidered as the hazard for an individual where all features $X = 0$.
- $e^{\sum_{i=1}^{p} \beta_i X_i}$ is a factor that increases/decreases the hazard.
- $e^{\sum_{i=1}^{p} \beta_i X_i}$ is the relative risk for feature vector x_i relative to 0.
- A one-unit increase in x_{ij} corresponds to an increase in $h(t, x)$ by a factor e^{β_j}.

General rule: if the hazards cross, then a Cox PH model is NOT appropriate (not constant hazard ratio).

Performance metrics

C-index (Harrel's concordance index)

For each observation, the estimated risk score $\hat{\eta}_i$ is calculated. For instance by using the estimated Cox model coefficients

$$\hat{\eta}_i = \hat{\beta}_1 x_{i1} + \ldots + \hat{\beta}_p x_{ip}$$

Under the assumption theat higher t_i lead to a lower $\hat{\eta}_i$, the C-index is given by

$$C = \frac{\sum_{i,i':t_i>t_{i'}} I(\hat{\eta}_{i'} > \hat{\eta}_i) d_{i'}}{\sum_{i,i':t_i>t_{i'}} d_{i'}}$$

where

$$I(\hat{\eta}_{i'} > \hat{\eta}_i) = \begin{cases} 1 & \text{if } \hat{\eta}_{i'} > \hat{\eta}_i \\ 0 & \text{otherwise} \end{cases} \qquad d_i \in \{0, 1\}$$

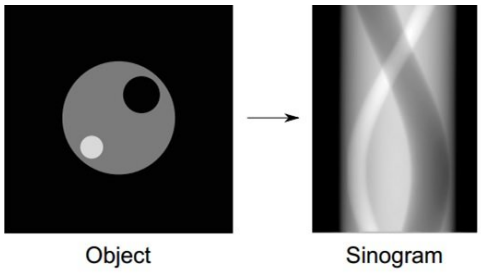
The C-index tells us something about the accuracy of the model. A C-index of 0.9 tells us that the model can predict with 90% accuracy which sample will get the event first.

CT (Computed Tomography)

Sends x-ray beams (ionizing radiation) through the body which are captured on the other side by detectors. Different tissues absorb x-rays to different extents, which lets us transform an image from the **sinogram**.

Sinogram

A sinogram is the measurements at different angles. The sinogram is then used to reconstruct an image through an iterative process.



The use of CT scans has become a fundamental tool in medical diagnostics. It is particularly valuable for its high spatial resolution and ability to quickly provide detailed images of bones, organs, and other internal structures. Despite its benefits, CT scans do come with drawbacks, such as a relatively high dose of radiation compared to other imaging techniques and reduced contrast resolution when compared to MRI.

PET (Positron Emission Tomography)

A radioactive substance is injected into the body. When this substance decays, it emits positrons which then collide with electrons and annihilate thereby producing gamma rays. These gamma rays are then captured in a detector. The radioactive substance used plays a big role in the interpretability. It is common to use substances which acts as glucose – which gives insight into metabolic activity because cells (like cancer cells) will consume more of this radioactive glucose.

PET scans also produce **sinograms**, which are a type of graphical representation of the raw data obtained from the detectors. This data is then reconstructed to form an image that shows the distribution of the radiotracer in the body. This imaging technique is especially useful for identifying regions of high metabolic activity, typically associated with rapidly dividing cells, as in tumors.

The resulting images can be used not only to detect cancer but also to evaluate the progress of treatment, to assess brain function in neurological disorders, and to study cardiac tissue viability. PET imaging is a powerful tool in both clinical and research settings, as it provides functional information about tissues, rather than structural details that are typically obtained from CT or MRI.

However, PET scanning has its limitations. The spatial resolution is lower than that of CT or MRI, meaning smaller lesions may not be resolved well. Additionally, PET requires the use of radioactive substances, which can only be used in limited quantities for safety reasons. The production of these radiotracers requires a nearby cyclotron, which can be costly and limits the availability of PET scans to well-equipped medical centers.

MRI (Magnetic Resonance Imaging)

MRI uses a strong magnetic field to align the spin of hydrogen atoms. When subjected to a radiofrequency pulse, these atoms get excited. Once the pulse is turned off, these atoms return to their original state, emitting signals in the process. The time it takes and the way these signals decay form the basis of the MRI image contrast.

TR (Time to Relaxation)

> TR is the time between successive pulse sequences applied to the same slice. It's the interval from the application of one RF pulse to the application of the next RF pulse.
>
> TR is crucial in determining the T1 weighting of an image. A short TR allows less time for longitudinal relaxation and tends to produce images with strong T1 weighting. A long TR gives tissues more time to relax between pulses, which reduces T1 weighting effects.

TE (Time to Echo)

> TE is the time between the application of the RF pulse and the peak of the signal induced in the coil, known as the echo.
>
> TE is mainly used to determine the T2 weighting of an image. A short TE captures the signal before much transverse relaxation has occurred, minimizing T2 weighting. A longer TE allows more transverse relaxation to occur, enhancing T2 weighting effects.

T1

> T1-weighted images are generated by choosing specific timing parameters in the MRI sequence (short **Time to Repetition (TR)** and short **Time to Echo (TE)**) that highlight the differences in the T1 relaxation times of tissues. Tissues with short T1 relaxation times (like fat) appear brighter, and those with longer T1 times (like fluid) appear darker.
>
> T1 relaxation is the time it takes for protons to realign with the magnetic field after the radiofrequency pulse is turned off. The alignment occurs as the protons release energy to their surroundings (lattice). Different tissues release this energy at different rates, which is why they can be distinguished on T1-weighted images.

T2

> T2-weighted images rely on longer TR and TE times. This makes tissues with longer T2 relaxation times (like fluid) appear brighter, while those with shorter T2 times (like fat or fibrous tissue) appear darker.
>
> T2 relaxation measures the time it takes for protons to lose phase coherence among the transverse plane following the RF pulse. This decay of signal is due to interactions between spinning protons. The rate of this decay differs among various types of tissue, which is reflected in the T2-weighted images.

Flair

> FLAIR images are a type of T2-weighted image with an inversion pulse added to null the signal from fluids like cerebrospinal fluid (CSF). The resulting images suppress the fluid signal, providing a clearer view of the periventricular regions and lesions that might be obscured by CSF in standard T2-weighted images.
>
> The FLAIR technique involves applying an inversion pulse to selectively null the signal from fluids with a particular T1 value. By carefully selecting the inversion time (TI), the signals from fluids can be nulled, while the signals from other tissues are not affected. This makes it especially useful for detecting lesions like multiple sclerosis plaques, which can be masked by CSF in other types of scans.

Radiotherapy

Radiotherapy is an essential component of cancer treatment. By utilizing ionizing radiation, it aims to destroy cancerous cells while minimizing damage to surrounding healthy tissues.

Principles of Radiation Therapy

> Radiation therapy exploits the interaction of radiation with matter, particularly focusing on the differential absorption in cancerous vs. normal tissues. This interaction is a physical phenomenon where radiation energy is transferred to atoms and molecules in the tissue, often leading to ionization and damage to DNA, thereby inhibiting cell replication.

Advances in Treatment Planning

> Computer science has revolutionized treatment planning through sophisticated software that can simulate radiation dose distributions. Monte Carlo simulations and algorithmic optimizations are examples where physics and computer science converge to improve the precision and efficacy of radiotherapy.

Technological Examples

> Linear accelerators (LINACs) are the most common devices used, which are capable of delivering high-energy x-rays or electrons to the region of the patient's tumor. Techniques such as Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) are examples of advanced radiotherapy that allow for more precise dose delivery with the aid of computer-controlled systems.

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Image Segmentation

Image segmentation plays a pivotal role in extracting meaningful information from medical images, which is a prerequisite for many computer-aided diagnosis systems.

Segmentation Techniques

> Classical image segmentation techniques include thresholding, region growing, and contour models. Recently, deep learning approaches like Convolutional Neural Networks (CNNs), particularly U-Net architecture, have become popular due to their high accuracy in segmenting complex structures.

Application Example

> In radiotherapy planning, image segmentation helps delineate the target (tumor) and organs at risk. For instance, MRI images can be segmented to identify brain tumors accurately, assisting in devising targeted treatment plans.

Physics in Imaging

> Understanding the physical properties of the imaging modality, such as the magnetic properties in MRI or the attenuation of X-rays in CT scans, is crucial in optimizing segmentation algorithms.

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Radiomics and Image Standardisation

Radiomics is a field that utilizes advanced computational methods to extract large amounts of quantitative features from medical images that can be correlated with diagnostic, prognostic, and predictive information.

Feature Extraction

> Features can include shape, intensity, texture, and wavelet features. For example, texture analysis can help differentiate between benign and malignant tumors by analyzing the patterns of pixel intensity in a region of interest.

Standardisation Techniques

> To facilitate consistent analysis, image standardisation is critical. This can involve spatial normalization, intensity normalization, and use of phantoms to calibrate imaging devices across different institutions.

Challenges in Radiomics

> Challenges include the standardisation of image acquisition parameters and the need for large annotated datasets to train robust models. Moreover, integrating radiomic data with other clinical data requires careful data fusion techniques to handle the heterogeneity in the data.

RENT

The Radiation Exposure Normalization Technique (RENT) is a notional concept proposed here to describe techniques that aim to standardize radiation doses in therapeutic contexts.

Dose Calculation Algorithms

> Algorithms are used to personalize radiation dose distribution based on patient anatomy and tumor geometry. Physics-based dose calculation algorithms, such as the Analytical Anisotropic Algorithm (AAA), are used to predict dose distribution accurately.

Adaptive Radiotherapy

> This refers to the modification of treatment plans based on patient-specific changes during therapy. Techniques like cone-beam CT allow for on-the-fly imaging and dose adjustments, a direct application of RENT principles.

Computational Considerations

> The development of RENT-related methods requires extensive computational modeling and simulation, integrating principles of radiation physics with sophisticated algorithmic strategies.

Multiblock analysis

Multiblock analysis addresses the challenge of integrating multiple heterogeneous data sources for comprehensive analysis in medical research and treatment planning.

Data Integration Strategies

> Strategies include concatenation of datasets, model-based integration, and joint modeling approaches. An example is the integration of imaging, genomic, and electronic health records for comprehensive patient profiling.

Multimodal Imaging

> In the context of physics, this refers to the use of various imaging modalities like CT, PET, and MRI, each providing different but complementary data about the patient's anatomy and physiology.

Analytical Challenges

> Analytical challenges include handling missing data, high dimensionality, and ensuring the interpretability of the integrated models. Machine learning techniques such as random forests and neural networks are often employed to tackle these challenges.