Application of CNNs in MHT problems

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Overview

1. Multiple Hypothesis testing (MHT)
2. Convolutional Neural Networks (CNNs)
3. Example 1: Female mice diet
4. Example 2: Normal population
5. Conclusions
6. Appendix

MHT: Introduction

- Testing focused on large-scale data.
- Set of $m > 1$ features. We study each hypothesis test individually.
- Sample units (N): Number of units where the measurements are collected.
- Partition of the m hypotheses into two sets:
  - H_0 is true: m_0.
  - H_0 is false: $m_1 = m - m_0$ (interesting).
  - $p_0 = \frac{m_0}{m}$: proportion true null hypothesis. Assumption: $p_0 \geq 0.9$
- Evidence (against H_0) statistical test: p-value.
- Calibrated p-values: Theoretical sampling null distribution is uniform.
- Focus: Difference between two independent groups. t-test.

MHT: Outcomes when testing m hypothesis

	Declared non-significant	Declared significant	Total
H_0 True	$U = m_0 - V$	V	m_0
H_0 False	$T = m_1 - S$	S	$m_1 = m - m_0$
	$m - R$	R	m

Table: 1. Outcomes of testing m hypothesis under a specified significance level α. (Benjamini and Hochberg, 1995)

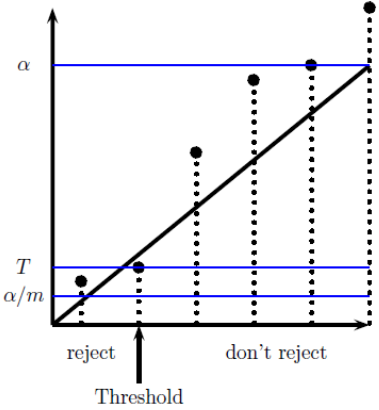
- $R = R_\alpha$: Total number of hypothesis rejected.
- V: Total type-I errors. (FP, False Discovery)
- S: Total TP (True discoveries)
- In practice: m is known, R is an observable RV and V, S are unobservable RVs.

MHT: Classical Procedures

Classical Procedures (CP)

- CP define and control a specific error rate.
- Uncorrected Hypothesis Testing (FPR)
  Rejection (R_{UHT}): $p_i < \alpha$.
- Family Wise Error Rate (FWER)
  Procedure: Bonferroni correction
  Rejection (R_{Bonf}): $p_i < \frac{\alpha}{m}$.
- False Discovery Rate (FDR).
  Procedure: Benjamini-Hochberg (BH)
  Rejection (R_{BH}): $p_{(i)} < \frac{i\alpha}{m}$.

Example: Application of the previous procedures with six ordered p-values.
$R_{UHT} = 4$; $R_{Bonf} = 0$; $R_{BH} = 2$



MHT: Problems

- Dependency of the p-value: Even a tiny cut-off for the p-value can generate many false positives with a high probability.
- Real interest: $\mathcal{P}(H_0|\text{Data})$.
- Low power: Correction procedures reduce the false positive rate but increase the false negatives considerably.
- Null distribution should be known: Classical procedures depend profoundly on the knowledge of the null distribution.

MHT: Alternatives

Collecting evidence

- Based on [Selke et al, 2001].
- Use calibrated p-values for defining a lower bound Bayes Factor.
- Interpretation: Odds of H_0 to H_1

$$LBBF(p) = \begin{cases} -ep\log(p) & \text{if } p \leq e^{-1} \\ 1 & \text{otherwise.} \end{cases}$$

- Example: $LBBF(p = 0.05) = 0.407$, ie $H_0 : 1$ to $H_1 : 2.5$. Not strong evidence against H_0!

Limitations of classical MHT procedures

- Based on [Mary and Roaquin, 2021].
- Proposal: Semi-supervised approach. User does not known null distribution, but has at hand a sample drawn from the null distribution.
- Where the user can obtain this null train sample?
- Previous experiments, expert criteria, part of the data under test, **simulations**, sampling process.

MHT: Proposal: P-value representation

P-value representation

- Set of ordered LBBFs: $\mathcal{B}^m$
  $\{b_{(i)} = LBBF(p_{(i)}) \mid \forall i = 1, ..., m\}$.

- Quotient of the ordered LBBFs:
  Map: $\Psi : \mathcal{B}^m \to \mathcal{M}^{m \times m}$
  For each feature $i = 1, ..., m$:
  $\Psi(b_{(i)}) = \frac{b_{(i)}}{b_{(j)}} = b_{(i)(j)} \; \forall j = 1, ..., m$.

- Scale 0-1
  $b_{\max} = max\{b_{(i)(j)}\}$
  for $i, j = 1, ..., m$.

- Normalized quotient:
  $\bar{b}_{(i)(j)} = \frac{b_{(i)(j)}}{b_{\max}}$.

- **Matrix of relative evidence among test:**

$$\bar{B} = \begin{bmatrix} \bar{b}_{(1)(1)} & \bar{b}_{(1)(2)} & \cdots & \bar{b}_{(1)(m)} \\ \bar{b}_{(2)(1)} & \bar{b}_{(2)(2)} & \cdots & \bar{b}_{(2)(m)} \\ \vdots & \vdots & \ddots & \vdots \\ \bar{b}_{(m)(1)} & \bar{b}_{(m)(2)} & \cdots & \bar{b}_{(m)(m)} \end{bmatrix}$$

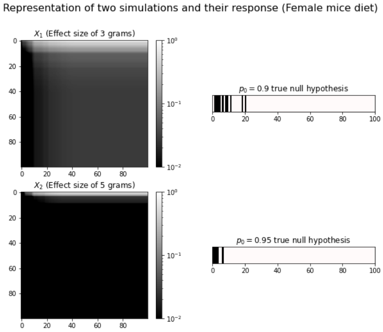
- Input of the supervised algorithm.

MHT: Proposal: Simulation

Supervised Approach

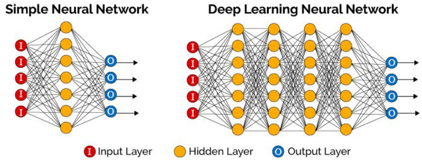
- Multi-label Classification.
- Heavy imbalanced data.
- Performance Metric: Area Under Precision-Recall curve (AUPRC)
- Aggregation: Micro-averaging.
- How to solve the problem? CNNs.
    1. Translation invariance and locality.
    2. Curse of dimensionality.

Example: Matrix representation and response of two independent MHT problems with $m = 100$ features.



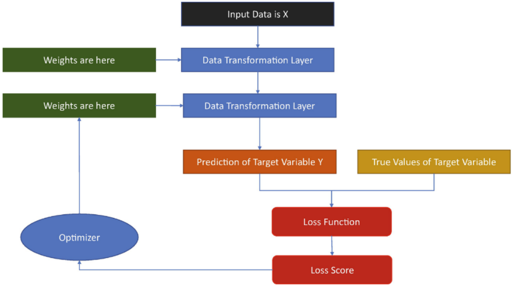
CNNs: Deep Learning

Deep (and breadth)
Number of hidden layers and number of neurons.
Basic architecture: Fully connected neurons



Increase the features $\sim$ increase the complexity of the model

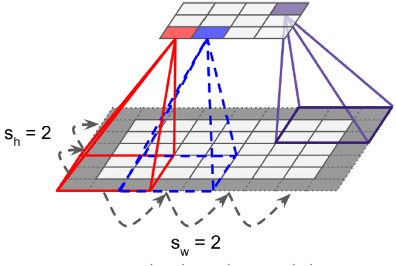
Learning Adjusting the weights via back(for)ward propagation algorithm.



CNNs: Architecture

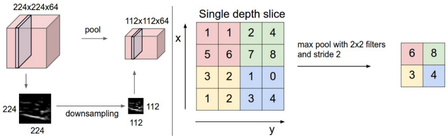
Convolutional Layer

- Spatial convolution over images.
- Parameters:
  1. `kernel_size`
  2. `strides`
  3. `padding`
  4. `filters`



Pooling Layer

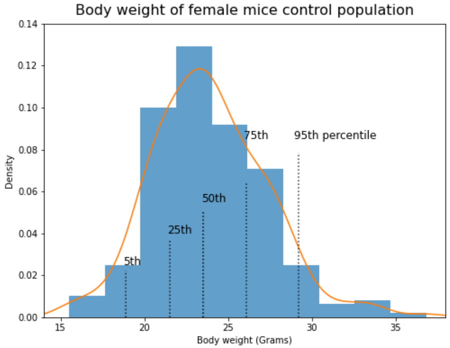
- Downsampling procedure.
- Parameters:
  1. `pool_size`
  2. `strides`
  3. `padding`
  4. Type of aggregation: max, mean.



Simulation 1: Female mice diet

	Value
Population (Individuals)	225
Mean	23.89 (g)
Standard deviation	0.22 (g)
Minimum	15.51 (g)
Maximum	38.84 (g)

Table: 2. Statistical summary female mice body weight.



Simulation 1: Female mice diet $m = 100$.

- Number of features: $m = 100$,
- Sample units: $N = 12$,
- Effect size: 96 distinct values, from 0.5 to 10.0 g, with a difference of 0.1 grams.
- Proportion true H_0, 10 distinct values, from 0.9 to 0.99 (Difference of 0.1 pp)
- MHT problem:
  - H_{0i}: Diet i does not affect weight.
  - H_{1i}: Diet i is effective.

ANN and CNN architectures

(a) *ANN architecture*

Model: "sequential"

Layer (type)	Output Shape	Param #
flatten (Flatten)	(None, 10000)	0
dense (Dense)	(None, 500)	5000500
dense_1 (Dense)	(None, 250)	125250
dropout (Dropout)	(None, 250)	0
dense_2 (Dense)	(None, 100)	25100

Total params: 5,150,850
Trainable params: 5,150,850
Non-trainable params: 0

(b) *CNN architecture*

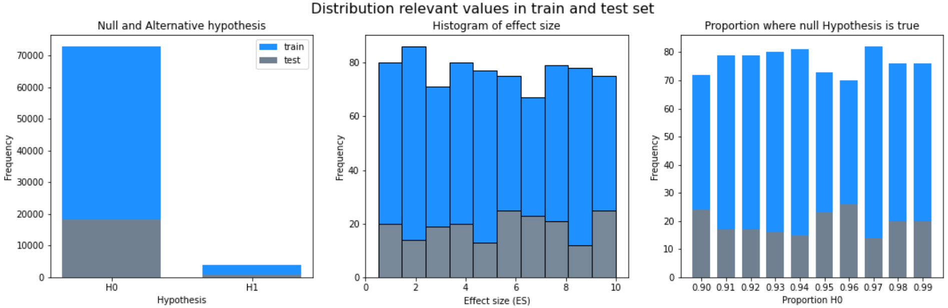
Model: "sequential"

Layer (type)	Output Shape	Param #
conv2d (Conv2D)	(None, 100, 100, 2)	20
max_pooling2d (MaxPooling2D)	(None, 50, 50, 2)	0
flatten (Flatten)	(None, 5000)	0
dense (Dense)	(None, 500)	2500500
dense_1 (Dense)	(None, 250)	125250
dropout (Dropout)	(None, 250)	0
dense_2 (Dense)	(None, 100)	25100

Total params: 2,650,870
Trainable params: 2,650,870
Non-trainable params: 0

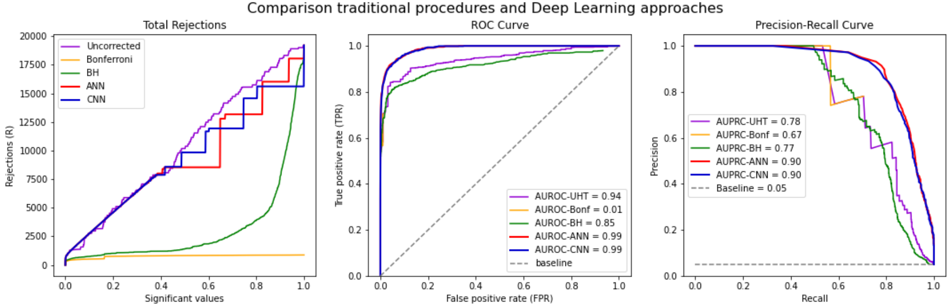
Simulation 1: Split train and test

- Total MHT scenarios: 960 (70% train, 10% validation, 20% test).
- Total features: $960 \cdot 100 = 96\,000$.
  - True H_0: 91 104 diets (72 876 training and 18 228 testing)
  - True H_1: 4 896 diets (3 924 training and 972 testing)



Simulation 1: Performance in test set

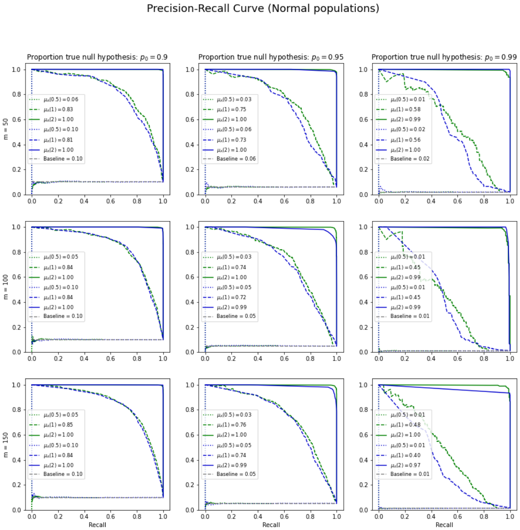
- Total features test set: 19 200 (H_0:18 228, H_1:972)
- AUPRC of CNN (and ANN) 0.9. (Both train and test)
- DL: Precision and recall greater than 80% simultaneously in test set.



Simulation 2: Normal population

- $X_i \sim \mathcal{N}(\mu_i, \sigma_i^2)$, for $i = 1, ..., m$ independent populations and unknown variance σ_i^2.
- MHT problem: $\{H_{0i} : \mu_i = 0 \text{ versus } \mu_i \neq 0 \ \forall \sigma_i^2 > 0\}, i = 1, ..., m$
- Simulation parameters:
  1. Total simulations: $B = 100$
  2. $N = 20$,
  3. $m = 50, 100$ and 150,
  4. $p_0 = 0.9, 0.95$ and 0.99,
  5. $\mu_i = \mu_A$ where $\mu_A = 0.5, 1$ and 2. and $\sigma_i^2 = 1$
  6. Benchmark: BH procedure.

Simulation 2: Normal Population



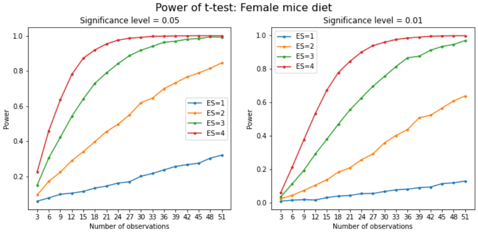
Conclusions

- CNNs offers a competitive alternative of detecting significant features in the context of MHT problems.
- Simulation case 1 (female mice diet) gives satisfactory results for detecting a higher number of cases where the alternative hypothesis is true.
- Simulation 2, shows that we can not potentially generalize a predefined architecture to another datasets or different number of features.
- Future analysis:
    1. Not calibrated p-values: Empirical null distribution of the p-values estimated directly from the data
    2. Curse of dimensionality: Explore sparse representation

Q & A

Appendix 1.1: Hypothesis Testing

- Reliability: Main factors:
  1. Significance level: It is the standard of proof that the phenomenon exists or the risk of mistakenly rejecting the null hypothesis. Implies directly the critical region of rejection.
  2. Power: Probability of rejecting the null when the null is false
  3. Effect size: Degree to which the phenomenon is present in the population.
  4. Sample size: Number of observed samples from the population.



Appendix 1.1: P-values

- Distance between the data and the model prediction is measured using a test statistic.
- P-value is the probability that the chosen test statistic (t-test) would have been at least as large as its observed value if every model assumption were correct.
- p-values are no longer useful quantity to interpret when dealing with high-dimensional data (Many FP with high probability, increasing the features increases the error just by chance)
- Most common MHT methods are based on the evidence provided by test statistics and their corresponding p-values.
- Other ways of collecting evidence? Bayes Factors (BFs).
- BF: likelihood ratio of the alternative against the null hypothesis.
- However, fully defined and interpretable BFs require heavy computational techniques for being adjusted.
- Goal: Interpret the calibrated p-values as lower bounds on Bayes Factors.

Appendix 1.1: Calibration of p-values: LBBF

- Under appropriate test statistic T, larger values would be evidence in favor of H_1.
- Density of p under H_1 should be decreasing in p.
- Consider alternative distributions for the p-values. Selke et al. procedure:

$$H_0 : p \sim \text{Uniform}(0,1) \text{ versus } H_1 : p \sim \text{Beta}(\xi, 1) = \xi p^{\xi-1}$$

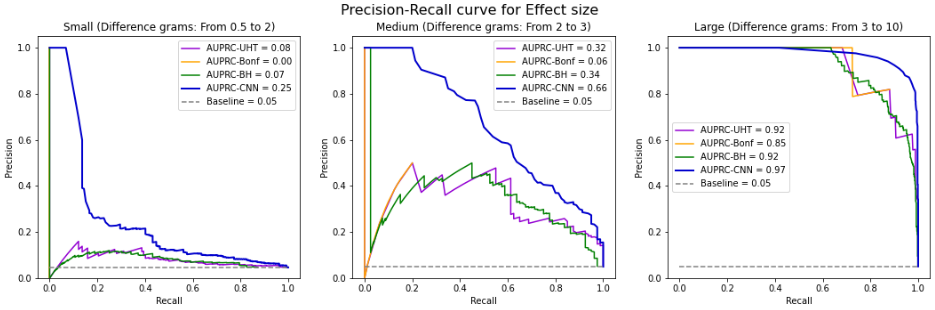
- Why Beta$(\xi, 1)$? Beta is easy to work! With $\xi = 1$, we have H_0.
- Remember: posterior odds $=$ prior odds $\times$ Bayes Factor.
- BF (or odds) of H_0 to H_1 for a given prior density $\pi(\xi)$ is:

$$\text{BF}(p) = B_\pi(p) = \frac{p}{\int_0^1 \xi p^{\xi-1} \pi(\xi)\, d\xi}$$

- $\text{LBBF}(p) = \inf B_\pi(p) = \frac{p}{sup_\xi \xi p^{\xi-1}} = -eplog(p)$ for $p < e^{-1}$.

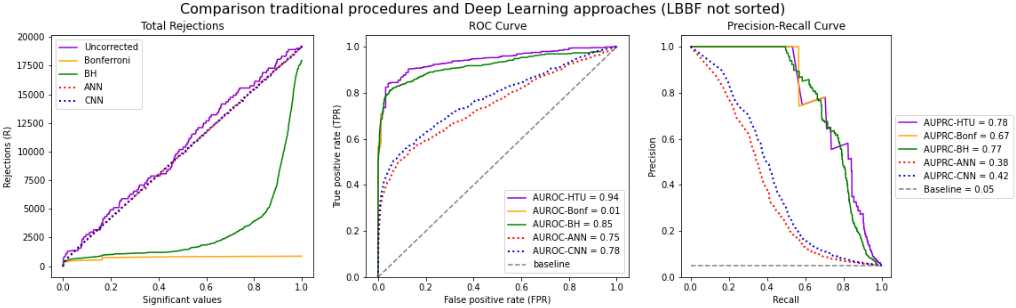
Appendix 2.1: Simulation 1: Performance for effect size

- Effect size depends on the unit of measurement (grams).
- Universal effect size index: Conhen's d. $d = \frac{|m_A - m_B|}{s}$.
- Small ($d = 0.2$), medium ($d = 0.5$), large $d = 0.8$.
- Based on $B = 2000$ simulations, we compute the median ES index for the difference in weight ranging from 0.5 to 10 grams.



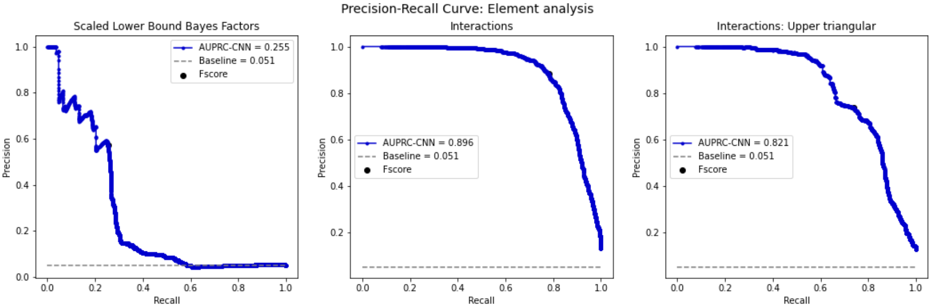
Appendix 2.2: Simulation 1: Order LBBF

- Primary assumption CNN: Compositional data (translation invariance and feature locality)
- In case that we assign randomly position of the LBBF, there is a considerable reduction of the performance in the test set. Overfitting!



Appendix 2.3: Simulation 1: Interaction LBBF and Sparse models

- AUPRC-CNN test set using the complete representation: 0.9
- If we consider only the scaled LBBF, we have AUPRC-CNN = 0.26
- LBBF interaction is crucial in the performance of the models. AUPRC-CNN = 0.89
- If we consider only the upper part matrix of the representation, AUPRC-CNN = 0.82.



Appendix 3.1: Simulation 3: Curse of dimensionality

- ANN and CNN architectures for m = 1000 features
- ANN: 1500 neurons, 300 million parameters
- CNN: Adding several convolutional/max-pooling layers reduces the total parameters around 3 million.

(a) *ANN architecture*

Model: "sequential"

Layer (type)	Output Shape	Param #
flatten (Flatten)	(None, 1000000)	0
dense (Dense)	(None, 300)	300000300
dense_1 (Dense)	(None, 250)	75250
dropout (Dropout)	(None, 250)	0
dense_2 (Dense)	(None, 1000)	251000

Total params: 300,326,550
Trainable params: 300,326,550
Non-trainable params: 0

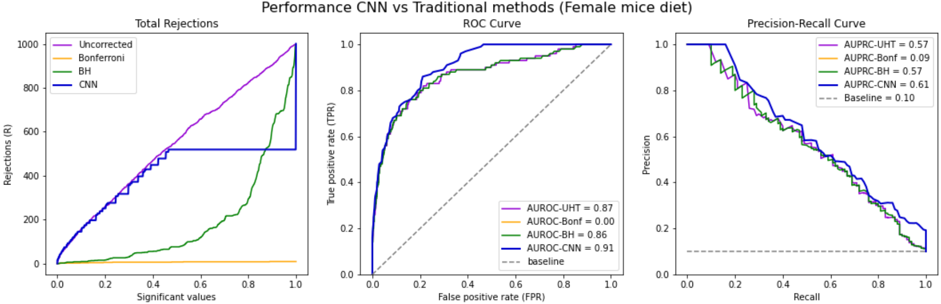
(b) *CNN architecture*

Layer (type)	Output Shape	Param #
conv2d (Conv2D)	(None, 1000, 1000, 2)	20
max_pooling2d (MaxPooling2D)	(None, 500, 500, 2)	0
conv2d_1 (Conv2D)	(None, 500, 500, 4)	76
max_pooling2d_1 (MaxPooling2	(None, 250, 250, 4)	0
conv2d_2 (Conv2D)	(None, 250, 250, 8)	296
max_pooling2d_2 (MaxPooling2	(None, 125, 125, 8)	0
conv2d_3 (Conv2D)	(None, 125, 125, 16)	1168
max_pooling2d_3 (MaxPooling2	(None, 63, 63, 16)	0
conv2d_4 (Conv2D)	(None, 63, 63, 32)	4640
conv2d_5 (Conv2D)	(None, 63, 63, 32)	9248
max_pooling2d_4 (MaxPooling2	(None, 32, 32, 32)	0
conv2d_6 (Conv2D)	(None, 32, 32, 32)	9248
max_pooling2d_5 (MaxPooling2	(None, 16, 16, 32)	0
flatten (Flatten)	(None, 8192)	0
dense (Dense)	(None, 300)	2457900
dense_1 (Dense)	(None, 250)	75250
dropout (Dropout)	(None, 250)	0
dense_2 (Dense)	(None, 1000)	251000

Total params: 2,808,846
Trainable params: 2,808,846
Non-trainable params: 0

Appendix 3.2: Simulation 3: Female mice with m = 1000 features

- $N = 12$, ES ranging from 2 to 15 grams, (0.1 grams distance) and $p_0 = 0.9, 0.95$ and 0.99.
- Total simulations: 390 (281 for training)
- Figure below is used only for a single prediction. Still, we have a competitive model.



Appendix 4.1: Simulation 1: CNN architecture

- First layer: Convolutional.
  1. Number of filters: 2, Kernel size: 3×3, stride: 1.
  2. Padding: **same** (zero-padding)
  3. activation: **ReLu**
  4. Kernel Initializer: **HeUniform**. (Remember, p-values are calibrated).
- Second layer: Max pooling
  1. Pool size: 2×2, stride: 2×2, padding: **same** (Reduction to the dimensions to the half)
- Hidden layers: Fully conneted layers:
  1. Third layer: Fully connected: 500 neurons, activation: **ReLu**, kernel initializer: **HeUniform**
  2. Fourth layer: Fully connected: 250 neurons, activation: **ReLu**, kernel initializer: **HeUniform**
  3. Fifth layer: Dropout: 0.5 probability
  4. Sixth layer: Putput layer: 100 neurons, activation: **sigmoid**
- Loss function: **binary_crossentropy**
- Optimizer: Nadam() (Default settings, high convergence speed and quality)
- Metric: AUPRC

References

David Mary and Etienne Roaquin (2021)
Semi-supervised Multiple Testing
*arXiv*2106.13501.

Selke, T., Bayarri, M., and Berger, J.O. (2001)
Calibration of p values for testing precise null hypothessis
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The End