Neural networks-based prediction of insulin resistance by means the homeostatic model assessment without the insulin concentration test

Gerardo Chacón, PhD[1], Valmore Bermúdez, PhD[2], Johel E. Rodríguez, PhD[2], Juan Diego Hernández, MSc[2], Aldo Pardo, PhD[1], Richard Mendoza, MSc[3], Diana Martínez, PhD[3], Delia Madriz, PhD[4], Antonio Bravo, PhD[4]

[1]Grupo de Automatización y Control, Universidad de Pamplona, Cúcuta 540004 Colombia

[2]Universidad Simón Bolívar, Facultad de Ingenierías, Cúcuta 540004, Colombia

[3]Grupo de Investigación de Inteligencia de Datos y Computación, Universidad de Pamplona, Cúcuta 540004 Colombia

[4]Programa Calidad y Productividad Organizacional, Decanato de Investigación, Universidad Nacional Experimental del Táchira, San Cristóbal, 5001, Táchira, Venezuela, dmadriz@unet.edu.ve, abravo@unet.edu.ve

Abstract*– Tissues insulin sensitivity has been estimated using the homeostasis model assessment. The insulin resistance is thus calculated from the plasma insulin and glucose concentrations. However, the insulin testing is an expensive test. Here, a computational approach based on neural networks for predicting the insulin resistance index through the homeostasis model assessment without considering the insulin testing results is proposed. A dataset of the prevalence study of metabolic syndrome (MS) is used to develop our approach. A total of 1919 subjects is used. The dataset if randomly split into a training set, a testing set, and a validating set for prediction approach performance assessment. Two of the neural networks commonly used in medical application are selected as functional predictors. The indexes obtained using the predictors are compared with the homeostasis model assessment-based index reported on the used dataset. From the comparison, one of neural networks-based approaches is considered the best predictor.

Keywords*—Insulin resistance, homeostatic model assessment, neural networks, multi-layer perception, radial basis function.

I. INTRODUCTION

Insulin resistance (IR) is a condition characterized by impaired sensitivity to insulin mediated glucose disposal in the tissues [1]. Insulin resistance plays an important role in the pathophysiology of obesity and type-2 diabetes development, metabolic and polycystic ovary syndromes, and cardiovascular diseases, some neurodegenerative diseases, moreover, the condition has been associated with aging and physical inactivity [2,3,4,5]. IR quantification before or during the disease would be useful in order to establish the appropriate pathophysiology stratification and the proper management of the associated disease [6].

The glycemic/hyperinsulinemic clamp is considered the gold standard method for IR measurement, however, it requires the frequent blood sampling, is burdensome for participants, is costly, and require a research setting [7]. IR has been also estimated by means two simple metabolic variables, such as basal plasma glucose and insulin concentrations throughout of the Homeostasis Model Assessment (HOMA) [8]. HOMA-IR method is a practical, easy and cost-effective way in the clinical and research settings; however, the high cost of plasma insulin test limits its use in the low-income population.

Currently, the clinical research community is making efforts to provide non-invasive and accurate methods to estimate routine clinical parameters useful for characterizing pathophysiology certain diseases from routine laboratory data. In this sense, the iron deficiency anemia and iron serum level have been predicted using artificial neural network-based models [9].

Neural networks (NN) have also been used to predict the cirrhosis in patients with chronic hepatitis using the routine clinical host and viral parameters [10,11]. The packed red blood cell transfusion has been managed by the successful prediction of the degree of postoperative anemia using neural networks [12]. Additionally, some anemia types have been accurately predicted by means pattern classification algorithms [13,14].

The aim of this paper is to propound a smart approach for predicting the value of the HOMA-IR index. The idea is developed a predictor capable of exploiting the rich structure information existing in a clinical large dataset by means a powerful non-linear feature mapping of the routine laboratory data, the anthropometric measurements and physical assessment, with the HOMA-IR index reported in the clinical dataset. The proposed predictor is based on artificial NN models trained without considering the insulin testing results.

II. METODOLOGY

A. Data description

The dataset used in this research corresponds with the data recollected in the Maracaibo parishes, Venezuela from January 2007 through April 2009. These data were initially recollected for performing a cross-sectional study based on MS prevalence [15].

Digital Object Identifier: (to be inserted by LACCEI).
ISSN, ISBN: (to be inserted by LACCEI).

For this research, 58 variables of the original dataset are only considered. These variables correspond with the data recollecting components associated to anamnesis, routine laboratory, and physical examination, specifically vital signs and basic anthropometry. For example, gender, education, marital status, race and categories of race, socioeconomic status, smoking habit, physical activity (general pattern, in work, in transportation, in home, in leisure, total), alcohol consumption, about the study participants is included as variables with respect to the general information component.

Regarding the laboratory tests, total cholesterol, HDL (mean and low), cLDL, VLDL, triacylglycerides (high and mean), fasting glycemia (high and mean), high glycaemia according to ATP III, are considered, the plasma insulin concentration according to the proposed hypothesis is excluded. Among the vital signs included in the set of variables are: blood pressure systolic, diastolic, high, and mean.

As for the basic anthropometric measures, body mass index, weight, height (m and cm), abdominal circumference, waist circumference, are included. Additionally, waist/height ratio, logarithmic waist/height ratio, visceral adiposity index, logarithmic visceral adiposity index, dichotomous visceral adiposity index, obesity classification according to WHO, are used.

Non-HDL cholesterol, MS diagnosis (IDF 2005, ATP III 2003, ATP III 2005, 2009 definition), combinations of MS criteria, high waist circumference (dichotomous, ATP III 2003, ATP III 2005, IDF 2005), waist circumference cut-off Point [16], triglycerides/glucose index (normal and dichotomous), alterations of lipid groups, TAG/HDL index, blood pressure levels according to the JNC 7 classification, multiple risk factors aggregation [17], HOMA-IR [18], are also considered.

B. Data preprocessing

The IR estimation dataset is composed of 58 variables, 57 forecast variables and the single dependent variable to predict, the HOMA-IR, in 1919 subjects. All qualitative variables are described as categorical variables which take on discrete numerical values. In order to apply the smart operator neural network-based, the dataset is normalized between zero and one [19]. In this work, 30% of the data is taken to train the smart operators, 20% to test the functioning and 50% to validate. This selection is performed pseudorandomly [20,21,22].

C. Neural networks-based prediction approach

As insulin concentration test is expensive and as there is available a large dataset of MS, it is very important to select a model to forecast the value of IR by means the HOMA without the insulin concentration test reasonably accurately. Two artificial NN approximation models [23], the well-known multi-layer perception (MLP) or backpropagation network, and the radial basis function (RBF) network, are evaluated and compared for their ability to predict the HOMA-IR index value from a dataset of the prevalence study of MS.

1) Model 1: RBF-based predictor: The structure of the proposed RBF neural network includes a 57 dimension input layer, one for each forecast variable; a fairly smaller dimension hidden layer of 25 neurons, this number of neurons are those self-generated by means the training algorithm; and the output layer [24]. The Gaussian typical radial basis functions are used in the hidden layer [25,26,27], and the log-sigmoid transfer function is used as activation function of output layer [28].

2) Model 2: MLP-based predictor: A MLP neural network is also proposed with an input layer of the 57 neurons, one for each forecast variable, an intermediate layer constitutes by 8 neurons assigned a priori [29]. Each neuron in the network is modeled by a nonlinear activation function of the output [30], the sigmoidal activation function is considered in this case [31]. The backpropagation algorithm can also be interpreted as an optimization problem in which the synaptic connections are systematically modified so that the response of the network approximates the desired response [32].

III. Results and Discussion

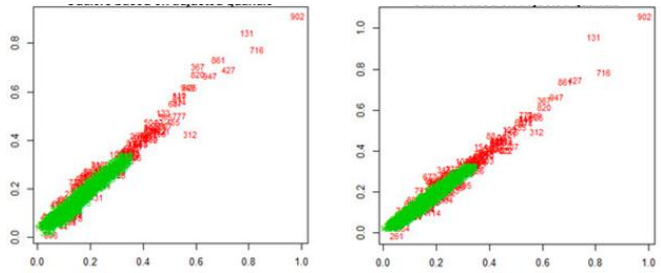
The aim of this section is to compare the HOMA-IR predicted values with the HOMA-IR index reported in the dataset considered in this work.

A. Correlation between the HOMA-IR index reported in the dataset and the predicted values

The results obtained using the NN-based predictors about the HOMA-IR, are correlated with the values reported in the dataset. The Pearson correlation coefficient [33] is initially proposed. A bivariate exploratory analysis is performed in order to identify the potential outliers [34]. The outlier identification criterion is based on robust Mahalanobis distance [35]. A bivariate normality analysis is also performed using Mardia [36], Henze-Zirkler [37], and Royston [38] tests. Linearity is confirmed by scatter plots [39].

Figure 1 shown the potential outliers based on Mahalanobis distance. This Figure reveals the presence of leverage points, but not of outliers, for both predictors. The entire normality tests are negative; because in all cases, the P values are sufficiently small to reject this conjecture. Moreover, it is further considered that, when a large sample size is considered the P values go quickly to zero [40].

In this sense, the use of the Spearman-Brown correlation coefficient is proposed in order to evaluate the affinity between the HOMA index reported in the dataset and those predicted by the NN-based predictors. This coefficient does not require that data be adjusted to any particular distribution [41]. The findings in this section, shown in Table I, reflect a strong, positive and statistically significant correlation between such the HOMA-IR predicted values and the HOMA-IR reported in the dataset.



(a) (b)

Fig. 1. Bivariate exploratory analysis for identifying the potential outliers. (a) Radial basis function (b) Multi layer perceptron.

TABLE I
SPEARMAN-BROWN CORRELATION BETWEEN DATASET REPORTED AND PREDICTED HOMA-IR INDEXES.

Variables to correlate	Rho (p-value)
HOMA reported in the dataset - HOMA RBF-based predictor	0.982 (<.001)
HOMA reported in the dataset - HOMA MLP-based predictor	0.972 (<.001)

B. Comparison between the HOMA-IR index reported in the dataset and the predicted values

The problem associated to analyze the data with large sample size by means the use of statistical significance tests [42,43,44] can be addressed through the use of confidence intervals, descriptive statistics, graphical tools, exact p-values, statistical power and the effect size [45,46,47,48,49].

Table II shows some descriptive statistics associated with the dataset reported and predicted HOMA-IR indexes. Moreover, the mean absolute error (MAE), the mean absolute percentage error (MAPE), the mean error (ME) and the mean percentage error (MPE) are also considered. From the Table II, HOMA RBF-based predictor estimates more exactly than the MLP-based predictor (0.1684 vs. 0.1706 | $\mu = 0.1691$), though it is slightly less precise (64.73% vs. 62.18%). The RBF predictor generates estimates that slightly underestimate the dataset reported HOMA value (0.65%), whereas MLP predictor generates assessments that overestimate it to a greater degree (2.68%). MAPE also suggests that the RBF predictor is slightly superior to the MLP predictor when approximating HOMA-IR index without the insulin concentration test.

As to the hypothesis test and confidence intervals, normality and independence of the differences must be initially verified. In this sense, the Kolmogorov-Smirnov-Lilliefors test50 is used. Table III shows normality should be rejected; however, in terms of independence, the data behavior does not suggest autocorrelation among the observations.

From the findings shown in the Table III, the comparison by means the nonparametric Wilcoxon signed-rank test [51] is performed, and also the confidence intervals are constructed based on the approximation proposed by Hodges-Lehmann [52]. Table IV shows the comparison results. Although, the differences are declared statistically significant, they are almost irrelevant. In fact, the confidence intervals include by approximation the zero. In consequence, if a slightly wide posture is assumed, the values generated by the predictors can be considered identical to those of the HOMA reported in the dataset.

TABLE II
COMPARISON OF THE DATASET REPORTED AND PREDICTED HOMA-IR INDEXES THROUGH DESCRIPTIVE STATISTICS.

Statistic	HOMA reported in the dataset	HOMA RBF-based predictor	HOMA MLP-based predictor
N	1016	1016	1016
Mean	0.1691	0.1684	0.1706
Median	0.1462	0.1409	0.1409
Variance	0.0112	0.0119	0.0113
Standard Deviation	0.1058	0.1090	0.1061
Coefficient of variation	62.54%	64.73%	62.18%
Minimum	0.0231	0.0110	0.0119
Maximum	0.9846	1.0593	0.9135
Range	0.9615	1.0483	0.9016
MAE	NA	0.0108	0.0127
MAPE	NA	7.24%	9.80%
ME	NA	0.0007	-0.0015
MPE	NA	0.61%	-2.68%

TABLE III
NORMALITY AND INDEPENDENCE OF THE DIFFERENCES VERIFICATION.

Variables	Normality		Independence	
	Statistic (p-value)	Conclusion	Statistic (p-value)	Conclusion
Difference between reported & RBF-based predictor	0.120 (1.11×10^{-39})	Reject	0.126 (.900)	Do not reject
Difference between reported & MLP-based predictor	0.088 (1.97×10^{-20})	Reject	0.753 (.451)	Do not reject

TABLE IV
WILCOXON SIGNED-RANK TEST AND CONFIDENCE INTERVALS APPROXIMATION BETWEEN THE HOMA REPORTED IN THE DATASET AND HOMA INDEXES PREDICTED.

Variables	Z	P-value	Lower limit.	Upper limit.	Conclusion
Reported & RBF-based predictor	-2.817	.005	-0.002	-0.000	Significant dif.
Reported & MLP-based predictor	-2.142	.032	0.000	0.002	Significant dif.

In order to calculate the effect size, the Z statistic obtained from the Wilcoxon signed-rank test is divided by the square root of the sample size [47]. The differences magnitude

is classified [48,49] at the low (between 0.10 and 0.29, inclusive), medium (between 0.30 and 0.49, inclusive) or high (from 0.50 upwards). The information shown in Table V supports the previous reasoning results because the effect, if that indeed exists, is practically negligible, as is also the size of the differences between the HOMA-IR index reported in the dataset and the predicted values.

TABLE V
EFFECT SIZE OF THE WILCOXON SIGNED-RANK TEST.

Variables	Z	N1/2	Effect	Conclusion
Reported & RBF-based predictor	-2.817	31.87	0.09	Minimum dif. Null effect
Reported & MLP-based predictor	-2.142	31.87	0.07	Minimum dif. Null effect

The box plots are used to graphically analyze the prediction results. As can be observed in Figure 2, both predictors approximate considerably the HOMA reported in the dataset: the medians are almost in the same ordinate, and the amplitude of the graphs is considerably similar. For both predictors, there are univariate outliers that correspond with data not included between the whiskers, specifically exceeding the maximum. These outliers are also shown in the box plot of the HOMA reported in the dataset.

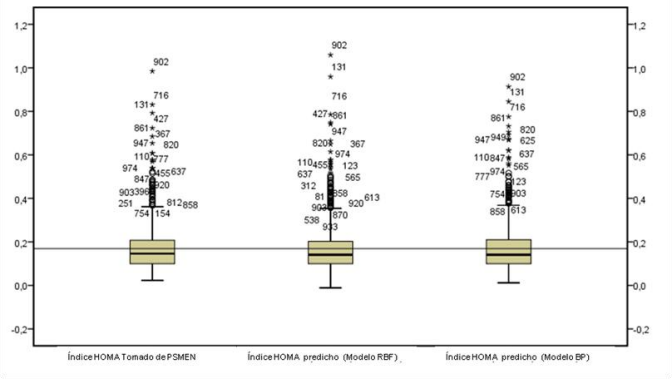


Fig. 2. Box plots for the HOMA-IR index reported in the dataset and the predicted values.

IV. CONCLUSIONS

Two neural networks-based computational approaches are developed in order to predict the insulin resistance by means the homeostatic model assessment without the insulin concentration test. The RBF and MLP neural network schemes are considered in the approaches developed. The descriptive results obtained from the statistical analysis contribute to conclude that both the RBF-based predictor and the MLP-based predictor generate estimates of the HOMA index whose difference with respect to the reference value is significant but irrelevant. The effect size is so small that from a practical approach is inconsiderable; this fact allows concluding that the neural network technique is suitable as functional predictors. The comparison of the results obtained using the neural network-based predictors do not tip the balance in favor of any. Perhaps an overly thorough analysis would indicate that the RBF-based approach is a better predictor.

As future work, a predictor of insulin resistance could be developed by means of the homeostatic model assessment without the fasting glucose concentration test. It could also be predicted the IR by means of HOMA-IR without the fasting glucose and insulin concentration tests. Finally, an analysis aimed at discriminating which predictive variables taken from the dataset of MS prevalence study activate the neurons of the proposed networks can be proposed.

ACKNOWLEDGEMENTS

Authors would like to thank the Universidad de Pamplonam Clombia, the Universidad Simón Bolívar, Colombia, and the Investigation Dean's Office of Universidad Nacional Experimental del Táchira, Venezuela for their support to this research.

REFERENCES

[1] Reaven, G., The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinol Metab Clin North Am, 33(2): 283-303, 2004.

[2] DeFronzo, RA., & Ferrannini, E., Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 14(3):173-194, 1991.

[3] Schubert, M., et al., Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci U S A, 101(9), 3100–3105, 2004

[4] Rojas, J. et al., Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. Int J Reprod Med, 2014: 719050, 2014

[5] Frier, B., Yang, P. & Taylor, A.W. Diabetes, aging and physical activity. Eur. Rev. Aging. Phys. Act., 3(2): 63-73,2006

[6] Muniyappa, R., Lee, S., Chen, H., Quon, MJ., Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 294(1):E15-26, 2008

[7] Tam, C. S., Xie, W., Johnson, W. D., Cefalu, W. T., Redman, L. M., & Ravussin, E. Defining Insulin Resistance From Hyperinsulinemic-Euglycemic Clamps. Diabetes Care, 35(7): 1605–1610, 2012

[8] Turner, R.C. et al., Insulin deficiency and insulin resistance interaction in diabetes: Estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. Metabolism, 28(11):1086-1096, 1979

[9] Azarkhish, I., Raoufy, MR., Gharibzadeh, S., Artificial intelligence models for predicting iron deficiency anemia and iron serum level based on accessible laboratory data. J Med Syst. 36(3): 2057-2061, 2012

[10] Raoufy, M.R., Vahdani, P., Alavian, S.M. et al. A novel method for diagnosing cirrhosis in patients with chronic hepatitis b: artificial neural network approach. J Med Syst, 35(1): 121-126, 2011

[11] Haydon, G. H., Jalan, R. , Ala-Korpela, M. , Hiltunen, Y. , Hanley, J. , Jarvis, L. M., Ludlum, C. A. and Hayes, P. C., Prediction of cirrhosis in patients with chronic hepatitis C infection by artificial neural network analysis of virus and clinical factors. J Viral Hepat., 5: 255-264, 2002

[12] Yu, C-H. et al., Anemic Status Prediction using Multilayer Perceptron Neural Network Model, 3rd Global Conference on Artificial Intelligence, Miami, USA, 213-220, 2017
[13] Sanap, S., Nagori, M., & Kshirsagar, V., Classification of Anemia Using Data Mining Techniques, Proceedings of the Second International Conference on Swarm, Evolutionary, and Memetic Computing, Volume Part II, 113-121, 2011
[14] Abdullah, M., & Al-Asmari, S., Anemia types prediction based on data mining classification algorithms, International Conference on Communication, Management and Information Technology, Cosenza, Italy, 615-621, 2016
[15] Bermúdez, V., et al., The Maracaibo city metabolic syndrome prevalence study: design and scope. Am J Ther., 17(3): 288-94, 2010
[16] Bermúdez, V., et al., Optimal Waist Circumference Cut-Off Point for Multiple Risk Factor Aggregation: Results from the Maracaibo City Metabolic Syndrome Prevalence Study, Epidemiology Research International, 2014, 9 pages, 2014
[17] Bermúdez, V., Rojas, J., Salazar, J., Añez R., et al. Anthropometric Predictors for Multiple Risk Factor Aggregation in Adults from Maracaibo City. J Obes Overweig. 2(1): 101, 2016
[18] Wallace, TM., Levy, JC., & Matthews, DR., Use and abuse of HOMA modeling, Diabetes Care, 27(6):1487-1495, 2004
[19] Mitchell, T. M,. Machine Learning. New York: McGraw-Hill, 1997
[20] Bishop, C. Neural networks for pattern recognition. Oxford University Press, USA, 1995
[21] DasGupta, A., Probability for statistics and machine learning: fundamentals and advanced topics. Springer New York, 2011
[22] Epp, SS., Discrete mathematics with applications. Boston, MA: Brooks/Cole: Cengage Learning, 2011
[23] Poggio, T., & Girosi, F., Networks for approximation and learning, Proc of the IEEE, 78(9): 1481-1497, 1990
[24] Park, J., & Sandberg, IW., Universal approximation using radial-basis-function networks, Neural Computation, 3(2):246-257, 1991.
[25] Haykin, S.S., Neural networks and learning machines. Upper Saddle River, NJ: Pearson Education, 2009
[26] Graupe, D., Principles of artificial neural networks. World Scientific, NJ, USA, 2007
[27] Karayiannis, N. & Venetsanopoulos, AN., Artificial neural networks: learning algorithms, performance evaluation, and Applications, Springer US, 2013
[28] Langari, R. , Liang Wang & Yen, J., Radial basis function networks, regression weights, and the expectation-maximization algorithm, IEEE Trans. Syst., Man, Cybern. A, Syst., Humans, 27(5):613-623, 1997
[29] Cybenko, G., Approximation by superpositions of a sigmoidal function, Math. Control Signal Systems, 2(4): 303-313, 1989
[30] Gurney, k., An introduction to neural networks, UK, CRC Press, 1987
[31] Beale, R, & Jackson, T., Neural computing - An Introduction, UK, CRC Press, 1990
[32] Callan, R., The essence of neural networks, Prentice Hall, 1998
[33] Puth, M., Neuhauser, M. & Ruxton, G., Effective use of Pearson's product-moment correlation coefficient. Animal Behaviour. 93(2):183-189, 2014
[34] Barnett, V. & Lewis, T., Outliers in statistical data, John Wiley & Sons, New York, 1994
[35] Leys, C., Klein, O., Dominicy, Y., Ley, C., Detecting multivariate outliers: Use a robust variant of the Mahalanobis distance, Journal of Experimental Social Psychology, 74:150-156, 2018
[36] Mardia, KV., Tests of univariate and multivariate normality. In Krishnaiah, PR. editor, Handbook of Statistics, 1:279–320. North Holland, 1980
[37] Henze, N. & Zirkler, B., A class of invariant consistent tests for multivariate normality. Comm. Statist. Theory Methods. 19:3595–3617, 1990
[38] Royston, P., Estimating departure from normality, Stat Med, 10(8):1283-1293, 1991
[39] Chatterjee, S. & Hadi, AS., Regression analysis by example, John Wiley & Sons, 2013
[40] Lin, M., Lucas, H., & Shmueli, G., Too big to fail: Large sample and the p-value problem. Information System Research. 24(4):906-917, 2013
[41] Lord, FM. & Novick, MR. Statistical theories of mental test scores. Reading, MA:Addison-Wesley, 1968
[42] Silva, G., & Guarnieri, F. Comments on when is statistical significance not significant?. Bras Political Sci Rev, 8(2):133-136, 2014
[43] Dahiru, T. P – value, a true test of statistical significance? a cautionary note. Ann Ib Postgrad Med, 6(1):21-26, 2008
[44] Vacha-Haase, T., & Thompson, B. Further comments on statistical significance tests. MECD, 31(1):63-67, 1998
[45] APA Publications and Communications Board Working Group on Journal Article Reporting Standards. Reporting Standards for Research in Psychology: Why Do We Need Them? What Might They Be? Am Psycho, 63(9):839-851, 2008
[46] American Psychological Association. Publication manual of the American Psychological Association. 5. Washington, DC: Author; 2001
[47] Rosenthal, R.. Parametric measures of effect size. The handbook of research synthesis. New York, EE. UU.: Russell Sage Foundation, 1994
[48] Cohen, J., Statistical power analysis for the behavioral sciences. New Jersey: Lawrence Erlbaum Associates, 1988
[49] Cohen, J. Things I have learned (so far). Amer Psychologist. 45(12):1304-1312, 1990
[50] Lilliefors, HW., On the Kolmogorov–Smirnov test for normality with mean and variance unknown. J. Amer. Stat. Assoc., 62(318):399-402, 1967
[51] Whitley, E., & Ball, J. Statistics review 6: Nonparametric methods. Crit Care, 6(6):509-513, 2002
[52] Hershberger, S.L., Hodges-Lehmann Estimators. In: Lovric M. (eds) International Encyclopedia of Statistical Science. Springer, Berlin, Heidelberg, 2011