Machine learning approach to address sarcopenia on skeletal muscle tissue

1st Dr. Dreder Abdouladeem
Genetic Engineering Department
Biotechnology Research Center
Tripoli, Libya
adeem_sasi@yahoo.com

2nd Dr. Chambo Elferjani
Computer Science Department
Libyan University for Humanities and Applied Science
Tripoli, Libya
elferjanichambo@gmail.com

3rd Dr. Hmadi Mohamed
Computer Science Department
Faculty of Science Azzaytuna University
Tarhuna, Libya
hmadi2595@gmail.com

***Abstract*— Body weight loss (BWL) or skeletal muscle atrophy (SMA) are normal and common in elderly individuals. The satellite cells are located in the space between the basal lamina and the sarcolemma; often these cells are quiescent. There have been several attempts conducted using machine learning methods to uncover the significant age-related genes. However, these investigations have not described the impact of age on skeletal muscle mass in human. Microarray datasets involve tens of thousands of genes, but just a few genes could lead to uncover the relationship between age and muscle atrophy. The main goal of this paper is to identify age-related genes with high accuracy, the final subset of selected genes was based on Multi-filter single wrapper system (MFSWS). Microarray expression profiles, downloaded from GEO database: GSE1428 was chosen to screen the differentially expressed genes of arm tissue and to compare three age groups of both males and females. Results revealed that our approach is able to identify a subset of genes with high performance of accuracy compared to the existed system (Liu et al, 2013) [27] and MFS (2016) [28].**

Keywords—body weight loss (BWL), machine learning methods, multi-filter single wrapper system (MFSWS)

I. INTRODUCTION

Body weight loss (BWL) or skeletal muscle atrophy (SMA) are normal and common in elderly individuals. A measure of weight in kilograms divided by height in metres squared is called the body mass index (BMI). If the BMI is less than 22, this associated with a higher mortality in both males and females above the age 65. Skeletal muscle mass is harbinger of poor outcome (Thomas et al, 2007) [1]. There is a relationship between mortality and BMI (Calle et al, 1999) [2], where for example losing more than ten percent after the fifth decade of age, people with stable weight is associated with sixty percent increase in mortality (Thomas, 2005) [3]. The Loss of about one or two percent per year among people after the fifth decade is normal because this decline muscle weight happens in both sedentary and active ageng adults (Tzankoff and Norris, 1978) [4]. The side effects of muscle loss are not limited to increasing a mortality, it contributes towards a decline in functional status. For example, for women 60–74 years old who lose more than 5% of body mass, and this leads a doubled risk of disability (Thomas, 2003) [5]. Skeletal muscle mass loss is accompanied by muscle fibre loss, and this reduction appears in the type IIa fibre. (Doherty et al, 1993; Brown and Hasser,1996) [6][7]. DNA methylation has also been observed in a few human tissues and other species have been documented and decreases in methylation in numerous groups of aged mouse tissues (Calvanese et al., 2009; Wilson et al, 1987)[8][9]; Zykovich et al, 2014[10]. The three main categories of skeletal muscle loss involve sarcopenia, cachexia and starvation. Sarcopenia was first presented in 1988 by Irwin [11] Rosenberg31as an age-associated with decrease in muscle mass. The acute loss of both fat-free and fat mass is called cachexia which usually is accompanies disease, for example immunodeficiency or cancer. Sarcopenia prevalence rates range from 6% to 24% depending on the definition and measure of muscle mass used (Newman et al, 2006; Park et al, 2006)[12].

The loss of muscle size and weight is called skeletal muscle atrophy; it is often accompanied with a decrease in muscle fibre. In humans there are several factors that can lead to skeletal muscle atrophy, including tumours, laziness and extreme training.

The skeletal muscle represents more than 45% of the human body, it helps during movement, and the cell organization of this organism is highly structured. Mitochondria are cellular organelles and the main function is to convert metabolic fuels, such as glucose and fatty acids, into energy (Sandri, 2010) [13]. The latest data reported that autophagy could lead to sarcopenia and the excessive damage of skeletal muscle mass which occurs in ageing (Wohlgemuth et al, 2010) [14]. With advancing age there is a progressive disorder of mitochondrial function with activation of autophagy.

In hypertrophy, the main processes, protein synthesis and satellite cell recruitment have an active role in the increase of muscle mass size. Disorder of these processes is observed in Chronic Obstructive Pulmonary Disease (COPD) muscle atrophy.

Hawke and Garry (2001) [15] reported that satellite cells are located in the space between the basal lamina and the sarcolemma; often these cells are quiescent. Satellite cells bail up to the damaged fibre in order to repair the muscle.

Despite these cells having an active role in fibre growth, their contribution towards hypertrophy in muscles is still unclear (O'Connor and Pavlath, 2007[16]; McCarthy and Esser, 2011[17]). However, in 2012[18], Kudryashova et al. reported that the deterioration of satellite cell function may cause muscle atrophy. Several studies, such as Goldspink et al. (1983) [19]and Bolster et al. (2004) [20], have suggested

Received-August 2020, Accepted-October 2020, and Published-December 2020

that protein synthesis has an active role in muscle growth and hypertrophy. In addition, it may lead to an increase in protein degradation.

In the human body, changes in muscle mass can be the result of many physiological effects on muscle degeneration and synthesis. Normally these influences may appear over decades of life, such as through progress to adulthood or in the elderly. The period of muscle mass changes continues and is considered a part of normal growth in adults until the third decade of life. Janssen (2011) declared that the loss of muscle mass and strength starts after the fourth decade, with about six percent loss per decade in humans [21]. There have been several studies conducted to address the loss of muscle size.

D'Antona et al. (2003) documented that Vmax in ageing skeletal muscle is slower in type Iia [22]. There is also evidence to suggest that the size of type II fibres decreases with advanced age (Larsson et al., 1978) [23]. Recent findings of D'Antona et al. (2003) [24] established that young and ageing fibres differ and these can be distinguished. Moreover, it has been recently discovered that Vmax might be a disorder among old people due to inherent alterations.

In 2013, Day et al. provided more evidence that skeletal muscle tissue is more reliable than other tissues for identifying age related genes based on differently expressed genes. They compared between different types of tissues including human blood, brain, kidneys, and skeletal muscles. The main aim was to identify tissue-specific age effects, followed by statistical analyses. The results indicated that skeletal muscle only showed age-dependent methylation associated with tissue-specific expressed genes. Liu et al [27] used three cases of studies (old female versus old males, old males versus young males, old females versus young females), and they used simple statistical analysis that included a intensity-based Bayesian moderated t-test and logistic regression in order to find a subset of genes that could interpret the difference between males and females in each set of age using a microarray. that contained gene expression profiles from skeletal muscle arm tissue

Raue et al. (2007) analysed microarray data in order to identify the impact of age on muscles. Different tests were carried out covering [25]. 14 females (8 young and 6 old). In conclusion, the results showed that the older females' genes were expressed at a higher level compared to the young adults, which means that they are more susceptible to muscle atrophy than young adults. Ding et al. (2005) presented a new feature selection system called minimum redundancy — maximum relevance (MRMR)[26]. This system idea was based on Naıve Bayes (NB), linear discriminant analysis (LDA), logistic regression (LR) and SVM class prediction methods, leave-one-out cross validation (LOOCV) was applied and its accuracy was computed. The main goal was to identify subset genes associated with age for young and old males that could be used to discriminate the two groups (older and young). 14 young (19–25 yr. old) and 14 older (70–80 yr. old) healthy men participated in this study

II. PROPOSED METHOD

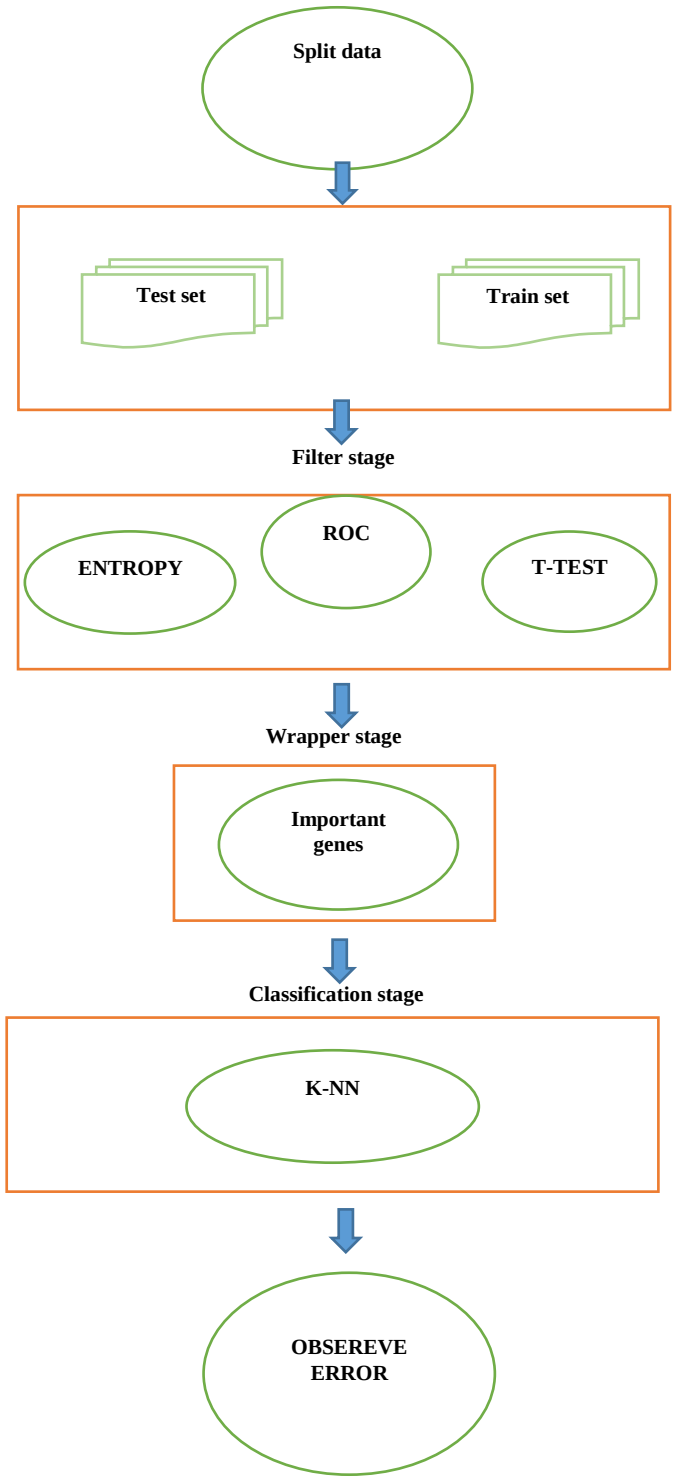

Figure 1: Multi filter single wrapper system (MFSWS)

Received-August 2020, Accepted-October 2020, and Published-December 2020

III. METHOD OF APPLIED STUDY

A. Data Source

The microarray expression profiles of spinal cord injury were extracted from the GEO (Gene Expression Omnibus, http:// www.ncbi.nlm.nih.gov/geo/) database Liu et al [27], with 22 healthy men and women of various ages, in which 7 men and 7 women were young (20-29 years old), and 4 men and 4 women were old (61-81 years old).

To address this problem, it is important to select a small subset of related features subset to reduce processing time and avoid over-fitting problem [6]. In our most recent study, filter based approaches are explored to identify a subset of genes [21]. MFS is able to significantly reduce the number of genes. However, there still are lot of irrelevant genes that need to be identified and excluded. In this study. random subset feature selection I RSFS is used to exclude these irrelevant genes. Figure 1 shows the proposed system based on wrapper feature selection method

B. Classification

Selected subset of genes are tested for its generalization power using supervised classification. knearestneighbor (KNN) classifier (k=1,3) is used to evaluate the system performance. The leaveone-out cross validation (LOOCV) technique is used for evaluation.

C. This Study is Based on Three Age Groups as Following

- Young Men versus Old Men.
- Old Men versus Old Women.
- Young Women versus Old Women.

IV. RESULTS AND DISCUSSION

In this section, the performance of the multi-filter single system (MFSWS) will be evaluated. The results of our system are also compared with the system presented in [27] for Dataset, in which genes are identified for three categories (young male versus old male, young female versus old female and old male versus old female) out of 54623 in total genes. In order to have a fair comparison, the same number of genes are selected from MFSWS and compared with the genes identified in [27] and [28]. The evaluation metrics used in this investigation are: Classification accuracy, Sensitivity and Specificity.

A. Case Study 1: Young Men versus Old Men

A total number of individuals are 11 male samples (7 young and 4 old). The performance of first 20 genes identified by MFSWS have been compared with Liu et al [27] and MFS [28] genes as shown in table 1. The best performance was obtained by MFSWS using K-NN classifier which is 100%. The MFS and Liu et al, (2013) [27] are only able to achieve 90%.

In study A all tables are follows (1=MFS, 2= Liu et al and 3=MFSWS)

TABLE I. YOUNG MEN VERSUS OLD MEN

TABLE II.

classifier	Correct Rate			Sensitivity			Specificity		
	MFS	Liu et al, (2013)	Proposed MFSWS	MFS	Liu et al, (2013)	Proposed MFSWS	MFS	Liu et al, (2013)	Proposed MFSWS
1NN	100%	81%	**100%**	100%	75%	100%	100%	100%	100%
3NN	0.72	0.72	**100%**	85%	85%	100%	50%	50%	100%

B. Case Study 2: Young Females versus Old Females

This case study involved 7 Young Female versus 4 Old Females. It is observed that the highest classification performance has been achieved by MFSWS compared to other systems and the classification accuracy is approximately 100% using` both K-NN with high Sensitivity and Specificity as shown in table 2.

TABLE III. YOUNG FEMALE VERSUS OLD FEMALE

TABLE IV.

Classifier	Correct Rate			Sensitivity			Specificity		
	MFS	*Liu et al, (2013)*	*Proposed MFSWS*	*MFS*	*Liu et al, (2013)*	*Proposed MFSWS*	*MFS*	*Liu et al, (2013)*	*Proposed MFSWS*
1NN	81%	81%	**100%**	71%	75%	100%	100%	100%	100%
3NN	90%	90%	**100%**	85%	85%	100%	100%	100%	100%

C. Case Study 3: Old Men versus Old Women

This case study involves eight individuals (4 old men versus 4 old women). The aim of this study was to examine a basal level gene expression among Old (male and female). Based on table3. MFSWS and MFS achieved the best performance, but MFSWS had the higher performance starting from the first feature compared to MFS which start after the fourth feature as shown in figure 3. It is observed that genes selected using MFSWS had the classification accuracy of 100% using both 1NN and 3NN with high Sensitivity and Specificity.

Received-August 2020, Accepted-October 2020, and Published-December 2020

TABLE V. OLD MEN VERSUS OLD WOMEN

TABLE VI.

Classifier	Correct Rate			Sensitivity			Specificity		
	MFS	*(2013)*	*MFSWS*	*MFS*	*(2013)*	*MFSWS*	*MFS*	*(2013)*	*MFSWS*
1NN	100%	0.75%	**100%**	100%	50%	100%	100%	100%	100%
3NN	100%	0.75%	**100%**	100%	50%	100%	100%	100%	100%

V. CONCLUSON

In this investigation, a multi-filter single wrapper system (MFSWS) has been proposed to select a significant subset of genes for Males and Females using skeletal muscles. Evaluation methods (t-Test, Entropy. ROC) have been used to sort the important age-related genes, and then wrapper feature selection has been used to select the subset of genes in order to improve the generalization of the system. MFSWS has been evaluated on publicly available microarray datasets of gene expression of skeletal muscle tissue.

Results have showed that the MFSWS classification performance yields the best performance compared to previous studies MFS and Liu et al 2013[27].

Future work aims to extend ore work by applying an ore system on two datasets instead of one. Furthermore, other analyses will be conducted on the selected subset of genes. In addition should be statistical tests such as P-value and fold change (FC) are considered

REFERENCES

[1] Thomas, D. R. (2007). "Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia." Clinical nutrition 26(4): 389-399.

[2] Calle, E. E., M. J. Thun, J. M. Petrelli, C. Rodriguez and C. W. Heath Jr (1999). "Body-mass index and mortality in a prospective cohort of US adults." New England Journal of Medicine 341(15): 1097-1105.

[3] Thomas, D. R. (2005). "Weight loss in older adults." Reviews in Endocrine and Metabolic Disorders 6(2): 129-136.

[4] Tzankoff, S. P. and A. H. Norris (1978). "Longitudinal changes in basal metabolism in man." Journal of Applied Physiology 45(4): 536-539.

[5] Thomas, D. R. (2003). "The relationship between functional status and inflammatory disease in older adults." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 58(11): M995-M998.

[6] Doherty, T. J., A. A. Vandervoort, A. W. Taylor and W. F. Brown (1993). "Effects of motor unit losses on strength in older men and women." Journal of Applied Physiology 74(2): 868-874.

[7] Brown, M. and E. M. Hasser (1996). "Complexity of age-related change in skeletal muscle." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 51(2): B117-B123.

[8] Calvanese, V., E. Lara, A. Kahn and M. F. Fraga (2009). "The role of epigenetics in aging and age-related diseases." Ageing research reviews 8(4): 268-276.

[9] Wilson, V. L., R. Smith, S. Ma and R. Cutler (1987). "Genomic 5-methyldeoxycytidine decreases with age." Journal of Biological Chemistry 262(21): 9948-9951.

[10] A Zykovich, A Hubbard, JM Flynn, M Tarnopolsky (2014)- Aging cell, - Wiley Online Library 3(02): 360-366

[11] Irwin H. Rosenberg, 1989. " Sarcopenia: Origins and Clinical Relevance " The Journal of Nutrition, Volume 127, Issue 5, May 1997, Pages 990S–991S

[12] Park, S. W., B. H. Goodpaster, E. S. Strotmeyer, N. de Rekeneire, T. B. Harris, A. V. Schwartz, F. A. Tylavsky and A. B. Newman (2006). "Decreased muscle strength and quality in older adults with type 2 diabetes The Health, Aging, and Body Composition Study." Diabetes 55(6): 1813-1818.

[13] Sandri, M. (2010). "Autophagy in skeletal muscle." FEBS letters 584(7): 1411-1416.

[14] Wohlgemuth, S. E., A. Y. Seo, E. Marzetti, H. A. Lees and C. Leeuwenburgh (2010). "Skeletal muscle autophagy and apoptosis during aging: effects of calorie restriction and life-long exercise." Experimental gerontology 45(2): 138-148.

[15] TJ Hawke, DJ Garry (2001) – "Journal of applied physiology"-://doi.org/10.1152/jappl.2001.91.2.534

[16] Roddy S. O'Connor, and Grace K. Pavlath 2007.''Satellite cell addition is/is not obligatory for skeletal muscle hypertrophy". https://doi.org/10.1152/japplphysiol.00101.

[17] Drummond, M. J., J. J. McCarthy, M. Sinha, H. M. Spratt, E. Volpi, K. A. Esser and B. B. Rasmussen (2011). "Aging and microRNA expression in human skeletal muscle: a microarray and bioinformatics analysis." Physiological genomics 43(10): 595-603.

[18] Kudryashova 2012. "Satellite cell senescence underlies myopathy in a mouse model of limb-girdle muscular dystrophy 2H". J Clin Invest. 2012;122(5):1764–1776.

[19] D F Goldspink; P J Garlick; M A McNurlan (1983). " Protein turnover measured in vivo and in vitro in muscles undergoing compensatory growth and subsequent denervation atroph". Biochem Journal 210 (1): 89–98.

[20] Douglas R. Bolster (a1), Leonard S. Jefferson (a1) and Scot R. Kimball (2004). "Regulation of protein synthesis associated with skeletal muscle hypertrophy by insulin-, amino acid- and exercise-induced signalling". Published online by Cambridge University Press. Volume 63, Issue 2 May 2004, pp. 351-356

[21] Janssen, I. (2011). "The epidemiology of sarcopenia." Clinics in geriatric medicine 27(3): 355-363.

[22] D'Antona, G., M. A. Pellegrino, R. Adami, R. Rossi, C. N. Carlizzi, M. Canepari, B. Saltin and R. Bottinelli (2003). "The effect of ageing and immobilization on structure and function of human skeletal muscle fibres." The Journal of physiology 552(2): 499-511.

[23] Lars Larsson, Bertil Sjödin, Jan Karlsson (1978). " Histochemical and biochemical changes in human skeletal muscle with age in sedentary males, age 22–65 years ". Acta Physiologica Scandinavica. Volume103, Issue1 May 1978 Pages 31-39.

[24] Giuseppe D'Antona (2003). "The effect of ageing and immobilization on structure and function of human skeletal muscle fibres". The Journal of Physiology.Volume552, Issue2 Pages 499-511

Received-August 2020, Accepted-October 2020, and Published-December 2020

[25] Raue, U., D. Slivka, B. Jemiolo, C. Hollon and S. Trappe (2007). "Proteolytic gene expression differs at rest and after resistance exercise between young and old women." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 62(12): 1407-1412.

[26] Ding, C. and H. Peng (2005). "Minimum redundancy feature selection from microarray gene expression data." Journal of bioinformatics and computational biology 3(02): 185-205.

[27] D. Liu, M. A. Sartor, G. A. Nader, E. E. Pistilli, L. Tanton, C. Lilly, L. Gutmann, H. B. IglayReger, P. S. Visich, E. P. Hoffman et al., "Microarray analysis reveals novel features of the muscle aging process in men and women," The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, p. glt015, 2013

[28] A. Dreder, M. A. Tahir, H. Seker, and M. N. Anwar, "Majority voting approach for the identification of differentially expressed genes to understand gender-related skeletal muscle aging," International Journal on Bioinformatics and Biosciences (IJBB), vol. 6, no. 2, 2016

Received-August 2020, Accepted-October 2020, and Published-December 2020