Mathematical Models for Extracellular Fluid Measurement to Detect Hydration Level Based on Bioelectrical Impedance Analysis

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***Abstract*—This paper shows mathematical models for extracellular fluid (ECF) measurements for both male and female human being based on bioelectrical impedance analysis along with prediction of hydration level. In this research total 2817 (1397 male and 1420 female) data have been used. Age, height, bioelectrical impedance at 5 kHz frequency, body mass index (BMI) are used for the development of mathematical models and the hydration level has been detected by the ratio of ECF to body weight considering standard limit. The proposed models have been analyzed statistically and the results show that the correlation (Pearson) coefficients are 0.999 (p<0.001) for both male and female individuals which denote excellent matching with actual data. Besides intervals of LOA is only -0.29 L to 0.45 L and -0.64 L to -0.06 L for male and female data respectively and most of the errors follows limit of agreement. The root mean square errors are 0.20 L for male and 0.38 L for female people. The average accuracy of proper detection of hydration level has bound 96.11%. Comparing the results of this research with existing models it is seen that the proposed models can be more suitable for ECF measurement and hydration level detection.**

***Index Terms*—Bioelectrical impedance analysis, extracellular fluid, hydration.**

I. INTRODUCTION

The alteration of the standard limit of the different types of body compositions causes malnutrition. Among the parameters related to body compositions, body fluid is one of the major part from which the information related to hydration level can be predicted. Total body fluid i.e. total body water is classified into two parts and they are extracellular fluid (ECF) and intracellular fluid (ICF) [1]. In general way, total body water with respect to weight is considered to monitor the hydration level of the human body. But, to identify specific level of body hydration, ECF to weight ratio is more suitable parameter as ICF volume may change due to body metabolism in normal condition [2]. The range of ECF to weight ratio for normal hydration level is 23% to 25% for male and 21% to 23% for female people. Beyond this range over hydration and under this range under hydration or dehydration situation occur [3], [4].

Before predicting the hydration level of the human body, measurement of ECF is necessary. There are various methods (both pathological and non-pathological) regarding its estimation. Though sodium bromide ($NaBr$) based pathological method is available for ECF measurement, it is not feasible at all due to its pre-conditions, atmospheric condition for experiment, time length of getting outcomes, cost, not availability to mass people. [5]. Besides pathological method, there is another type of procedure available to measure ECF called bioelectrical impedance based analysis which is a non-invasive way. The term non-invasive refers the procedures which do not involve the physical break or damage of skin, organ, and tissues. Bioelectrical impedance arises in the body tissues while conducting the current through them. It is calculated using the ratio of voltage drop and sending current to the body. Different types of mathematical models are available to measure ECF using bioelectrical impedance considering some physical parameters like age, weight, height, sex. Bioelectrical impedance analysis based method is preferable to implement for measurement purpose due to portability, quickness, cost effectiveness and its simplicity. But, the existing mathematical models cannot be assured for correct prediction. For better accuracy, more accurate mathematical models are required for measurement and detection purposes.

In this paper, new mathematical models for ECF measurement have been developed and implemented into the clinical database of the hydration status to verify the correctness of the prediction. Existing models have also been used and measured the ECF and hydration level to compare the accuracy of the prediction of proposed models. The rest of the paper is organized as follows: In Section II, the effects of the applied frequency on biological tissue is presented. The development of the mathematical models is presented in Section III and results are provided in Section IV. Section V includes discussion and finally, the paper is concluded in Section VI.

II. ELECTRICAL CURRENT CONDUCTION IN TISSUES

The way of current conduction through the biological tissues largely depend on the applied frequency. The more frequency, the more penetration of current into the tissues (cells). At low frequency, usually below 10 kHz, current flows through the ECF and the impedance which is found called as ectracellular impedance or resistance as capacitance is absent in this

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frequency range. To measure ECF, extracellular resistance is required and hence low frequency current is sent to body to measure ECF with the value of extracellular resistance.

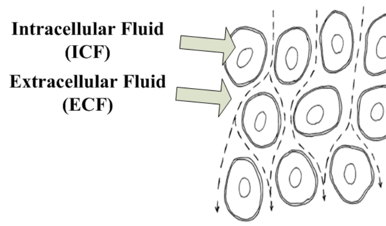

Fig. 1. Current flows through cells at low frequency

III. Materials and Methods

A. Subjects

A group of 2817 (1397 male and 1420 female) participant's database has been used for the model development of ECF and hydration level detection. The mathematical models of ECF measurement for both male and female people have been developed considering 720 male participant's data and 735 female participant's data respectively. The developed models have been implemented into rest of the data (677 male and 685 female) which have clinical remarks on three types of hydration levels (under hydration or dehydration, normal hydration and over hydration) for the verification purpose. The source of the database is National Health and Nutrition Examination Survey (NHANES), 2003-2004 (version 7, updated in July 2016) conducted over US citizen [7]. United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Center of Health Statistics operated various clinical experiments along with physical and bioelectrical measurements in their Mobile Examination Center (MEC) and recorded all the outcomes jointly. HYDRA Bio-Impedance Spectrum Analyzer (Model 4200) manufactured by Xitron Technologies, Inc., San Diego, California was used for bioelectrical impedance data collection. The examinations were performed by trained health technicians maintaining protocol which was written in the Body Composition Procedures Manual on the NHANES website.

B. Bioelctrical Impedance Analysis (BIA)

Four-electrode BIA is an informative, accurate, easy to perform and affordable method of determining whole body impedance [8]. Electrodes were placed in a tetra-polar configuration for whole body impedance measurement using the right foot and hand of each subject. Two electrodes were for sending constant current to human body and another two electrodes were for measuring voltage drop. Using voltage drop and sending current, bioelectrical impedance analyzer computed different types of impedance related values which are available in the databases.

C. BIA based Existing Models of ECF Measurement

There are several regression models for ECF measurements based on bioelectrical impedance analysis. In these models, different types of parameters such as a = age in $years$, w = weight in kg, h = height in cm, s = sex (0 for male and 1 for female) etc. have also been considered along with bioelectrical impedance, resistance, reactance at different frequencies such as Z_1 = impedance at 1 kHz frequency, Z_5 = impedance at 5 kHz frequency, R_{ECF} = Extracellular resistance (not defined frequency), R_{50} = Resistance at 50 kHz frequency and X_{C50} = reactance at 50 kHz frequency. All the impedance, resistance and reactance are in $k\Omega$. Deurenberg $et\ al.$ [9] developed two mathematical models considering 1 kHz and 5 kHz frequency. For development of following equations, 139 patient's data were used and NaBr dilution was used as pathological criterion.

$$ECF(L) = 2.30 + 0.20h^2/Z_1 + 0.07w–0.02a \quad (1)$$

$$ECF(L) = 2.53 + 0.19h^2/Z_5 + 0.07w–0.02a \quad (2)$$

Later Cornish $et\ al.$ [10] tried to make the mathematical model applicable for all persons by developing two separate models considering 60 patients at 0 Hz frequency. The models equations are given below.

$$ECF(L) = 1.2 + 0.194h^2/R_0 + 0.115w \quad (3)$$

$$ECF(L) = -5.3 + 0.480h^2/R_0 + 3.5s \quad (4)$$

Pitchler $et\ al.$ [11] showed two mathematical models for ECF measurement using 116 male and female patients. The model equations are:

$$ECF(Male, L) = 0.11 + 0.11w + 0.24h^2/R_{ECF} \quad (5)$$

$$ECF(Female, L) = 1.24 + 0.09w + 0.28h^2/R_{ECF} \quad (6)$$

T.K. Bera $et\ al.$ [12] proposed a mathematical model to measure ECF both male and female individuals. The equation is giving below:

$$ECF(L) = 3.79 + 0.18h^2/Z_5 + 0.18w \quad (7)$$

Recently Matias $et\ al.$ [13] built a mathematical model for ECW measurement using 139 participant's data. But, this equation was only for athlete which was given below.

$$ECF(L) = 1.58 + 0.06h^2/R_{50} + 0.13w + 0.01h^2/X_{C50} + 0.93s \quad (8)$$

These models mentioned above have been used on the database and compared with the results found by the proposed models.

D. Statistical Analysis

To propose any mathematical model for the prediction of any result, statistical analysis is one of the vital point as the performance evaluation of the proposed models largely depend on the outcomes of the analysis. The correlation coefficient (Pearson coefficient), 95% confidence interval (95% CI), 95% limit of agreement (95% LOA), bias (difference between actual and measured values), p-value (p<0.05 indicate statistical significance) are the key tools of the statistical analysis. Besides root mean square error is also calculated using following formula.

$$RMSE = \sqrt{\frac{\sum(x - x')^2}{n}} \tag{9}$$

Where, x denotes measured or given value and $x^{'}$ denotes predicted value. All types of statistical analysis have been done for this research using IBM SPSS v25.0 and MATLAB 2015b. The 95% LOA is used in Bland-Altman plot which is used to estimate the agreement between the predicted values and measured values in which limits of agreement have been determined by summing and subtracting the average differences from 1.96 times of standard deviation [14].

IV. Results

A. General Characteristics of Data

The general characteristics of different types of data (model and validation data) like age, weight, height, body mass index (BMI), extracellular fluid (ECF) and impedance at 5 kHz frequency for both male and female have been presented in Table I to Table IV in the forms of mean, standard deviation (SD), 95% confidence interval (CI) and p-value.

TABLE I
General Characteristics of Male Model Data

Group	n = 720		
	Mean ± SD	***95% CI***	***p-value***
Age $(years)$	21.23 ± 11.22	20.41 to 22.05	<0.001
Height (cm)	167.58 ± 14.87	166.50 to 168.67	<0.001
Weight (kg)	69.79 ± 22.87	68.11 to 71.46	<0.001
BMI (kg/m^2)	24.24 ± 5.76	23.82 to 24.66	<0.001
ECF (L)	16.38 ± 4.48	16.05 to 16.71.13	<0.001
Z_5 $(k\Omega)$	597.76 ± 93.70	590.91to 604.62	<0.001

TABLE II
General Characteristics of Female Model Data

Group	n = 735		
	Mean ± SD	***95% CI***	***p-value***
Age $(years)$	21.01 ± 11.57	21.17 to 21.85	<0.001
Height (cm)	157.21 ± 10.62	156.44 to 157.97	<0.001
Weight (kg)	63.49 ± 21.84	61.91 to 65.07	<0.001
BMI (kg/m^2)	25.24 ± 7.16	24.72 to 25.76	<0.001
ECF (L)	12.95 ± 3.15	12.73 to 13.18	<0.001
Z_5 $(k\Omega)$	679.09 ± 92.24	672.42 to 685.78	<0.001

B. Proposed Mathematical Models for ECF Measurement

Using the data sets, two equations have been developed for the ECF measurement of male and female people separately by linear regression analysis considering age, body mass index (BMI), bioelectrical impedance at 5 kHz frequency and the ratio of the square of the height to impedance at 5 kHz frequency which have been given below.

$$ECF(male, L) = -8.697 + 0.001a + 0.207b + 0.007Z_5 + 0.321h^2/Z_5 \tag{10}$$

TABLE III
General Characteristics of Male Validation Data

Group	n = 677		
	Mean ± SD	***95% CI***	***p-value***
Age $(years)$	20.37 ± 10.98	20.37 to 19.54	<0.001
Height (cm)	165.47 ± 15.52	164.29to 166.64	<0.001
Weight (kg)	65.92 ± 21.75	64.28 to 67.56	<0.001
BMI (kg/m^2)	23.44 ± 5.33	23.03 to 23.84	<0.001
ECF (L)	15.63 ± 4.46	15.63 to 15.29	<0.001
Z_5 $(k\Omega)$	610.65 ± 94.54	610.65 to 603.52.85	<0.001

TABLE IV
General Characteristics of Female Validation Data

Group	n = 685		
	Mean ± SD	***95% CI***	***p-value***
Age $(years)$	21.60 ± 11.47	20.75 to 22.45	<0.001
Height (cm)	158.85 ± 9.67	158.13 to 159.57	<0.001
Weight (kg)	65.64 ± 18.99	64.23 to 67.05	<0.001
BMI (kg/m^2)	25.64 ± 5.88	25.20 to 26.08	<0.001
ECF (L)	13.34 ± 2.75	13.13 to 13.54	<0.001
Z_5 $(k\Omega)$	669.70 ± 71.14	664.42 to 674.98	<0.001

$$ECF(female, L) = -7.36 + 0.001a + 0.156b + 0.006Z_5 + 0.337h^2/Z_5 \tag{11}$$

Here, a = age in $years$, b = BMI in kg/m^2, h = height in cm, Z_5 = bioelectrical impedance at 5 kHz frequency in $k\Omega$. These two proposed model equations have been applied over the validation data sets to check the hydration level of the subjects.

C. Performance Analysis

According to the results found from the statistical analysis the performance evaluation of the proposed models have been done. The proposed mathematical models show the correlation coefficient 0.999 (p<0.001) for both male and female population and the 95% LOA for male data are -0.29 to 0.45 L and for female data are -0.64 to -0.06 L. The values of different types of errors like bias and RMSE are 0.08 L and 0.02 L for male people and -0.35 L and 0.38 L for female data which indicate little figures of the errors. The linear correlation curves for both male and female have shown in Fig. 2 and Fig. 3 respectively. Bland-Altman plot has been shown in Fig. 4 and Fig. 5. It is

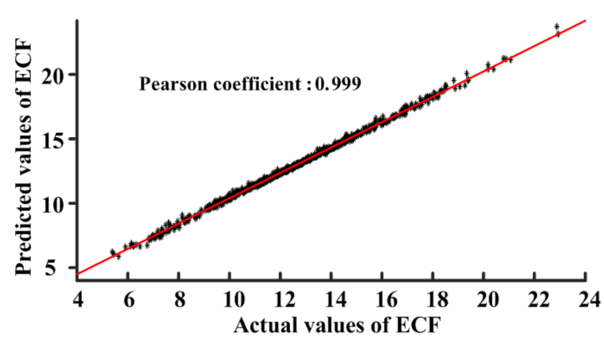

Fig. 2. Correlation curve between actual values and predicted values of ECF (male).

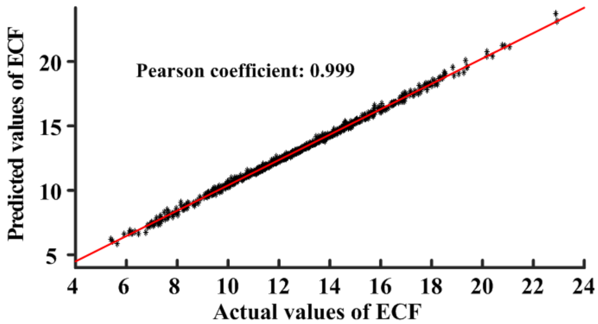

Fig. 3. Correlation curve between actual values and predicted values of ECF (female).

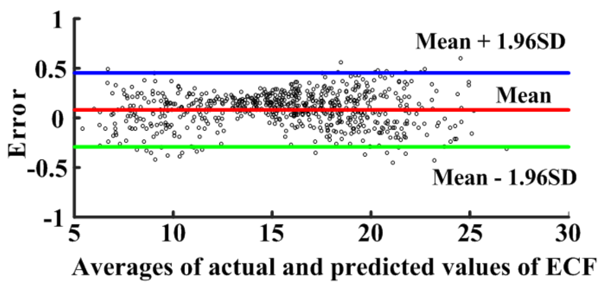

Fig. 4. Bland-Altman plot of ECF (male).

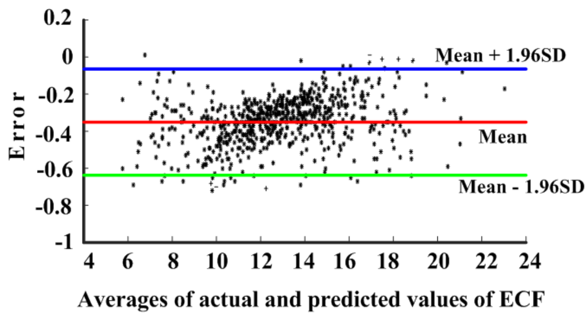

Fig. 5. Bland-Altman plot of ECF (female).

seen from the Bland-Altman plot that almost all the errors are within the 95% limit of agreement with respect to averages of actual and predicted values of ECF which indicate better validation of the proposed models.

D. Detection of Hydration Level using Proposed Models

Three types of hydration levels such as under hydration or dehydration, normal hydration and over hydration were identified in the validation database clinically. By applying the proposed models, the values of ECF to weight ratio have been calculated and certain hydration levels have been marked on every data according to the standard range and the results have been showed in the Table V. The overall accuracy is 96.11% due to the number of the true prediction is 1310 out of 1362 data. The maximum accuracy has been found for under hydration level which will be helpful to identify the degree of dehydration.

TABLE V
PREDICTION SUMMARY OF HYDRATION LEVEL DETECTION USING PROPOSED MODELS

Sex	Prediction Data		
	Hydration Level	***True Prediction***	***Accuracy (%)***
Male	Over Hydration (OH)	207 out of 218	94.95
Male	Normal Hydration (NH)	218 out of 231	94.37
Male	Under Hydration (UH)	224 out of 228	98.25
Female	Over Hydration (OH)	154 out of 162	95.06
Female	Normal Hydration (NH)	269 out of 280	96.07
Female	Under Hydration (UH)	238 out of 243	97.94

V. DISCUSSION

The validation database has also been used to estimate ECF and hydration status using existing bioelectrical impedance analysis based methods and compared with proposed models by performing similar statistical analysis which have been performed on proposed models. The outcomes of the analysis for existing methods have been given in Table VI to VII. From the comparison of statistical analysis the proposed models show high correlation coefficient, lower limit of agreement, lower errors with respect to other existing models for ECF measurement. Mainly body mass index (BMI) and square of the height to bioelectrical impedance ratio have been considered for ECF model development whereas the body height and weight separately considered in the current models and the effect of BMI and height square impedance ratio have more significant influence on body fluids rather height and weight alone and hence the proposed modes show better results than exiting models. Table VIII shows the comparison of the true prediction and accuracy of the hydration level detection. The results found from the comparison exhibit that all the models can detect hydration level, but the rate of accuracy is questionable, because, if any model shows better result in any specific hydration level then fails to predict other hydration level. Through the proposed models, the rate of error of ECF measurement using bioelectrical impedance analysis has been reduced and the prediction of the hydration levels show more accuracy whereas the existing models has showed more errors and as a result the proper prediction of hydration level is tough and the accuracy is not up to the mark.

VI. CONCLUSION

In conclusion, in this paper for the detection of hydration level in human body new mathematical models is proposed which is based on the bioelectric impedance analysis method. The proposed models of ECF showed less error in comparison with the existing methods. It's accuracy in detection of hydration level in human body is about 96.11%. In future, these models can easily be implemented practically and more measurement models related to health condition prediction issue can be developed.

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National Health and Nutrition Survey (NHANES) 2016, United States of America (USA).

TABLE VI
STATISTICAL COMPARISON OF PROPOSED AND CURRENT MODELS (MALE)

Ref.	n = 677				
	Correlation Coefficient	***95% LOA (L)***	***Absolute Error (L)***	***Bias (L)***	***RMSE (L)***
Deurenberg *et al.* [9] (1 kHz frequency)	0.87	-1.29 to 1.57	0.62 ± 0.40	0.14	0.74
Deurenberg *et al.* [9] (5 kHz frequency)	0.86	-1.40 to 1.30	0.57 ± 0.39	-0.05	0.69
Cornish *et al.* [10] (Eq. 4)	0.65	-3.62 to -1.04	1.69 ± 0.43	-1.69	1.74
Cornish *et al.* [10] (Eq. 5)	0.66	-4.23 to -0.63	1.54 ± 1.07	-0.64	1.87
Pitchler *et al.* [11]	0.89	- 4.03 to – 1.00	2.52 ± 0.77	-2.52	2.63
Bera *et al.* [12]	0.87	-12.03 to -4.97	8.50 ± 1.80	-8.50	8.68
Matias *et al.* [13]	0.84	-4.50 to -1.967	3.23 ± 0.65	-3.23	3.29
Proposed	0.999	- 0.29 to 0.45	0.17 ± 0.12	0.08	0.20

TABLE VII
STATISTICAL COMPARISON OF PROPOSED AND CURRENT MODELS (FEMALE)

Ref.	n = 685				
	Correlation Coefficient	***95% LOA (L)***	***Absolute Error (L)***	***Bias (L)***	***RMSE (L)***
Deurenberg *et al.* [9] (1 kHz frequency)	0.87	-1.40 to 0.24	0.61 ± 0.37	-0.587	0.72
Deurenberg *et al.* [9] (5 kHz frequency)	0.86	-1.53 to 0.07	0.74 ± 0.39	-0.73	0.84
Cornish *et al.* [10] (Eq. 4)	0.65	-2.53 to -0.85	2.33 ± 0.66	-2.33	2.42
Cornish *et al.* [10] (Eq. 5)	0.66	-4.09 to 2.80	2.43 ± 0.92	-2.43	2.60
Pitchler *et al.* [11]	0.89	-4.32 to -1.06	2.70 ± 0.83	-2.70	2.82
Bera *et al.* [12]	0.87	-12.62 to -5.06	8.85 ± 1.93	-8.84	9.05
Matias *et al.* [13]	0.84	-4.98 to -1.54	3.26 ± 0.88	-3.26	3.37
Proposed	0.999	-0.64 to -0.06	0.15 ± 0.12	-0.35	0.38

TABLE VIII
ACCURACY COMPARISON

Ref.	Prediction Accuracy (%)						
	OH (M)	***OH (F)***	***NH (M)***	***NH (F)***	***UH (M)***	***UH (F)***	***Overall***
Deurenberg *et al.* [9] (1 kHz frequency)	78.44	80.38	80.08	77.14	88.16	90.53	82.46
Deurenberg *et al.* [9] (5 kHz frequency)	92.20	91.77	84.42	81.43	89.47	93.41	88.78
Cornish *et al.* [10] (Eq. 4)	90.82	89.87	77.06	80.70	80.70	85.60	84.13
Cornish *et al.* [10] (Eq. 5)	87.34	81.65	78.35	79.64	82.45	89.71	83.19
Pitchler *et al.* [11]	88.99	90.51	80.09	84.64	80.26	86.42	85.15
Bera *et al.* [12]	85.78	84.18	82.69	80.35	84.65	83.54	83.53
Matias *et al.* [13]	90.37	89.24	84.92	86.43	87.72	81.89	86.17
Proposed	94.95	95.06	94.37	96.07	98.25	97.94	96.11

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