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Development of Multivariate Regression Models for Estimation of Extracellular Fluid of Human Body from Bioelectrical Impedance Analysis

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Abstract:

This work proposes new multivariate regression models for the estimation of Extracellular Fluid (ECF) measurements for both male and female people. The proposed models have been developed based on bioelectrical impedance analysis. In this research total 466 (231 male and 235 female) data have been considered. Different types of data like height, weight, age, bioelectrical impedance and body mass index (BMI) have been chosen for the development of estimation models. The statistical analysis show that the correlation coefficients are 0.98 for both male and female people. This results show good similarity with actual data. The limits of agreement (LOA) are -1.3350 L to 2.4090 L and -1.42557 L to 1.844373 L for male and female data respectively. The absolute errors (mean ± Standard Deviation) are (0.5370 ± 0.9551) L and (0.2094 ± 0.83417) L for male and female data respectively. The validation results of this research have been compared with the current models and it is seen that proposed mathematical models show far better results with reduced intervals of LOA and absolute error rate. So, the proposed mathematical models can be more suitable for ECF measurements.

Keywords **—Multivariate regression, xbioelectrical impedance analysis, extracellular fluid, extracellular impedance**

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I. INTRODUCTION

Extracellular fluid (ECF) means all body fluid outside the cells. About 45 to 75% of total body weight is total body water and approximately two thirds of this is intracellular fluid within cells, and one third is the extracellular fluid [1]. The major part of the extracellular fluid is the interstitial fluid that consists of cells. Extracellular fluid is the internal fluid condition of all multicellular animals, and in those animals with a blood circulatory system a proportion of this fluid is blood plasma [2]. At least 97% of ECF are covered by two compartments which are plasma and interstitial fluid. Lymph consists of a small percentage of the interstitial fluid [3]. The remaining small portion of the ECF includes the trans-cellular fluid (about 2.5%). The ECF can also be considered as having two components – plasma and lymph as a delivery system, and interstitial fluid for water and solute exchange within the cells [4]. Different types of diseases have impact on ECF. Patients of kidney failure and dengue fever have immense impact ECF. During kidney dialysis, the rate of change of ECF is necessary to measure how much fluid filters. It has already been established that bioelectrical impedance is the most important parameter for non-invasive technology. The term non-invasive refers the procedures which do not involve the physical break or damage of skin, organ, and tissues. Equivalent impedance of human body which is called bioelectrical impedance is the most prominent factor for finding different types of information. ECF can be measured from bioelectrical impedance analysis and from that different types of diseases can be detected. Measurement of this impedance is quite easy to do within low cost and has no adverse effect on human body. So mathematical modelling for measurement of ECF and detection of diseases can easily be done using bioelectrical impedance concept.

II. MATERIALS AND METHODS

A. *Subjects*

For developing mathematical models for extracellular fluid of human body based on bioelectrical impedance databases from 'National Health and Nutrition Survey' (NHANES) of United States of America (USA) updated in 2016 have been collected [5]. From NHANES we have taken separate databases for both male and female patients in which age, weight, height, actual values of extracellular fluid, extracellular impedance and body mass index (BMI) .We have selected total 466 patients (150 male patient's data and 150 female patient's data) for model development and (81 male patient's data and 85 female patient's data) for model validation. The general characteristics data are summarized in the following tables.

TABLE I
GENERAL CHARACTERISTICS OF DATA USED IN MODEL DEVELOPMENT

Parameters	**Male (n = 150)**	**Female (n = 150)**
	Mean ± SD	***Mean ± SD***
Age (years)	38.50 ± 21.04	56.41 ± 15.76
Weight (kg)	83.32 ± 22.14	79.29 ± 22.76
Height (cm)	176.68 ± 9.79	165.49 ± 6.71
Height (m)	1.67 ± 0.0671	1.72 ± 0.0671
BMI (kg/m^2)	29.65 ± 9.40	29.65 ± 8.30
Z_5 (Ω)	670.07 ± 101.42	680.58 ± 109.94
ECF (L)	14.92 ± 5.63	14.75 ± 4.57

TABLE III
GENERAL CHARACTERISTICS OF DATA USED IN MODEL VALIDATION

Parameters	**Male (n = 81)**	**Female (n = 85)**
	Mean ± SD	***Mean ± SD***
Age (years)	35.50 ± 21.04	54.41 ± 15.76
Weight (kg)	80.32 ± 22.14	78.29 ± 22.76
Height (cm)	174.68 ± 9.79	162.42 ± 6.71
Height (m)	1.6242 ± 0.0671	1.6242 ± 0.0671
BMI (kg/m^2)	29.65 ± 8.30	29.65 ± 8.30
Z_5 (Ω)	663.07 ± 101.42	678.58 ± 109.94
ECF (L)	14.52 ± 4.63	14.42 ± 4.43

B. *Pathological Method for ECF Measurement*

In pathological tests, ECF can be measured in dilution method. The common method is based on sodium bromide (*NaBr*) solution with water [1]. In *NaBr* based method, at first two blood samples are taken to measure Br level before giving dose to blood. Then a dose of 30 mmol of *Br* (10 mL of a 3 mmol/mL solution of *NaBr*) followed by 150 mL of deionized water is given to the blood. After 3 hours additional two blood samples are taken to measure *Br* level again. Then ECF can be calculated by following formula.

$$ECF(L) = 0.873 \times \frac{(NaBr\ dose)}{A - B} \tag{1}$$

where, A = Br level before dose [mEq/L], B = Br level after dose [mEq/L].

C. *Bioelectrical Impedance Analysis (BIA)*

Bioelectrical impedance is found in biological tissues while sending current through them from the ratio of the voltage drop to sending current. Two pairs of electrodes are required, one pair for sending current and another pair for measurement of voltage drop. A pair of electrodes (one is current electrode and another is voltage electrode) is set up on the right hand. Another pair of electrodes comprising similar configuration is set up on the right feet. After dividing the voltage drop to the sending current, bioelectrical impedance is measured [10].

D. *Current Models of ECF Based on BIA*

There are several linear regression models for ECF measurements based on bioelectrical impedance analysis but the accuracy levels are not satisfactory. Hannan*et al.* [6] proposed two mathematical models for ECF measurement and compared with pathological test using *NaBr* solution. These models were only applicable for 43 surgical patients which is a major limitation. The equations of the models are given below.

$$ECF\ (L) = 5.75 + 0.01h^2/X_{C50} + 0.165h^2/R_{50} \tag{2}$$

$$ECF\ (L) = 6.15 + 0.019h^2/X_{C50} + 0.123h^2/R_{50} \tag{3}$$

where, h = height of the patient in cm, X_{C50} = reactance in Ω at 50 kHz frequency, R_{50} = resistance in Ω at 50 kHz frequency in Ω. Equation 2 is for male and 3 is for female. Cornish *et al.* [7] developed two mathematical models suitable for general people from 60 patients. The models equations are given below.

$$ECF\ (L) = 1.2 + 0.194h^2/R_0 + 0.115w \quad (4)$$

$$ECF\ (L) = -5.3 + 0.480h^2/R_0 + 3.5s \quad (5)$$

Here, h = height of the patient in cm, R_0 = resistance in Ω at 0 Hz frequency, w = weight in kg, s = sex (0 for male and 1 for female). Sergi*et al.* [8] also developed two mathematical models for ECF measurement considering 40 individuals. The model equations are stated below

$$ECF\ (L) = -7.24 + 0.34h^2/R_1 + 0.06w + 2.63hc + 2.57s \quad (6)$$

$$ECF\ (L) = -5.22 + 0.20h^2/R_{50} + 0.005h^2/X_{C50} + 0.08w + 1.90hc + 1.86s \quad (7)$$

where, h = height in cm, R_1 = resistance at 1 kHz frequency in Ω, R_{50} = resistance at 50 kHz frequency in Ω, w = weight in kg, X_{C50} = reactance at 50 kHz frequency in Ω, hc = health condition (for healthy = 1, ill = 2), s = sex (for male =0, female = 1). Recently Pitchler*et al.* [9] proposed following two mathematical models for ECF measurement considering 116 male and female patients. The model equations are:

$$ECF\ (Male,\ L) = 0.11 + 0.11w + 0.24\ h^2/R_{ECF} \quad (8)$$

$$ECF\ (Female,\ L) = 1.24 + 0.09w + 0.28\ h^2/R_{ECF} \quad (9)$$

where, w = weight in kg, h = height in cm, R_{ECF} = extracellular resistance in Ω.

E. Statistical Analysis

To validate any proposed model, different types statistical evaluations are required. The correlation coefficient, 95% limit of agreement with Bland Altman Plot, bias and absolute error have been considered in this research to validate proposed models.

III. RESULTS

A. Proposed Multivariate Regression Models for ECF Estimation

The For the development of mathematical model for ECF measurement, age weight, height, body mass index (BMI), extracellular impedance at 5 kHz frequency have been considered. Using the data sets, following equations have been proposed for ECF measurement.

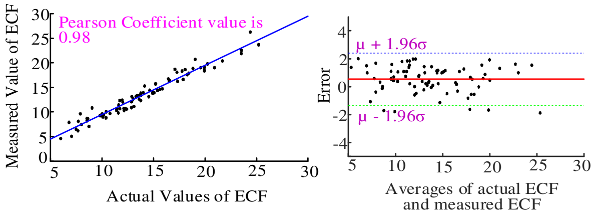
$$ECF\ (Male,\ L) = 0.406 + 0.077w - 0.001a - 0.007b + 0.001Z_5 + 0.221\ h^2/Z_5 \quad (10)$$

$$ECF\ (Female,\ L) = -0.574 + 0.001a + 0.060w + 0.009b + 0.001Z_5 + 0.244\ h^2/Z_5 \quad (11)$$

where, a = age in years, b = BMI in kg/m^2, h = height in cm,w= weight in kg,Z_5= bioelectrical impedance at 5 kHz frequency in Ω.

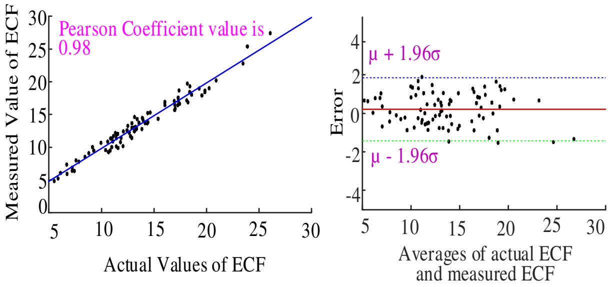
B. Statistical Evaluation of Proposed Models

Considering the developed mathematical model, it is seen that, measured ECF is almost close to the actual results. The rate of the absolute error is little comparing to other models. It has been already stated that the correlation (Pearson) coefficient is 0.98 for both male and female datasets and maximum of the data are in the range of interval of limit of agreement (LOA) which is [μ - 1.96σ to μ + 1.96σ] where μ is mean of the averages of the differences between actual ECF and measured ECF that is error and σ is the corresponding standard deviation. The values of mean, μ are found to be 0.5370 L and 0.2094 L for male and female participant's data respectively. The values of standard deviation, σ are found to be 0.9551 L and 0.83417 L for male and female participant's data respectively. So, the LOA for male is found to be -1.3350 L to 2.4090 L and LOA for female is found to be -1.42557 L to 1.844373 L.



(a) (b)

Fig. 1. (a) Pearson correlation between the actual values and measured values of ECF for male datasets. (b) Bland-Atman plot of averages of actual ECF and measured ECF for male datasets.



(a) (b)

Fig. 2. Pearson correlation between the actual values and measured values of ECF for female datasets. (b) Bland-Atman plot of averages of actual ECF and measured ECF for female datasets.

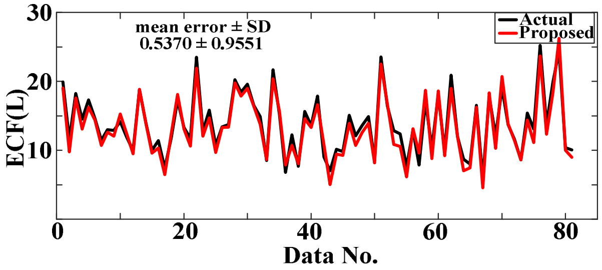


Fig. 3. Performance Evaluation Curve of Proposed Model Outputs with Actual Data (Male)

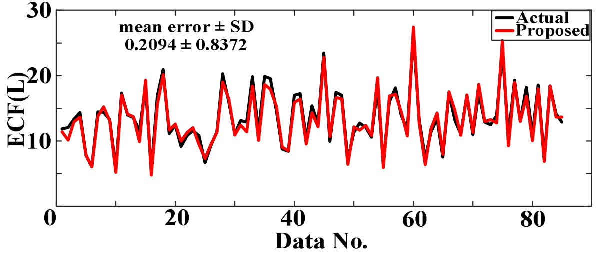


Fig. 4. Performance Evaluation Curve of Proposed Model Outputs with Actual Data (Female)

Fig. 1 and 2 clearly show that correlation (Pearson) coefficients are 0.98 for both figures and the differences between upper limit and lower limit of the limit of agreement (LOA) are only 1.074 L for male and 0.418803 L for female which are very low and all the measured data are in the range of LOA. It is seen from fig. 3 & 4, which indicate that the measured values of ECF closely match with the actual ECF i.e. the error rate very low which manifests major improvement of the ECF models.

IV. DISCUSSIONS

For the verification of the robustness of the proposed models we have considered all data which have been used during model development in different existing models and found improved correlation (Pearson) coefficients, intervals of LOA and the absolute error rate in the proposed models. From the above results and figures, it is clear that proposed mathematical models of ECF are quite better than previous models described in [6-9]. The correlation coefficients of different models [6-9] are from 0.65 to 0.89 stated in the research articles whereas the proposed models exhibit 0.98, almost close to unity which have already been shown in fig. 2 and 3. But evaluating the current models by the data used in this research, the correlation coefficients are found ranging from 0.46 to 0.91 which are less than stated values in [6-9] which are shown in the following tables. The intervals LOA are also improved in the proposed models. The intervals of LOA of different models are given in the following tables.

TABLE III

STATISTICAL COMPARISON OF PROPOSED AND CURRENT MODELS (MALE)

Model	**Correlation (Pearson) coefficients**	**Bias (L)**	**Absolute errors (mean ± SD) (L)**	**Interval of LOA (L)**
Hannan*etal.* [6]	0.81	-3.69	6.35 ± 3.92	[-1.34 to 14.03]
Cornish *etal.* [7]	0.51	-1.69	7.48 ± 4.80	[-1.92 to 16.89]
	0.85	-0.64	8.26 ± 6.13	[-3.75 to 20.27]
Sergi*etal.* [8]	0.77	-6.45	6.22 ± 4.73	[-3.04 to 15.48]
	0.57	0.42	8.96 ± 4.83	[-0.51 to 18.44]
Pitchler*etal.* [9]	0.46	-2.52	6.58 ± 4.35	[-1.95 to 15.13]
Proposed	0.98	0.08	0.54 ± 0.96	[-1.34 to 2.41]

TABLE IV

STATISTICAL COMPARISON OF PROPOSED AND CURRENT MODELS (FEMALE)

Model	**Correlation (Pearson) coefficients**	**Bias (L)**	**Absolute errors (mean ± SD) (L)**	**Interval of LOA (L)**
Hannan*etal.* [6]	0.83	-5.85	4.29 ± 3.29	[-2.15 to 10.74]
Cornish *etal.* [7]	0.57	-2.33	5.90 ± 4.63	[-3.17 to 14.97]
	0.91	-2.43	7.72 ± 5.50	[-3.07 to 18.50]
Sergi*etal.* [8]	0.84	-6.12	5.76 ± 4.58	[-2.15 to 10.74]
	0.70	-1.11	4.39 ± 3.55	[-2.56 to 11.36]
Pitchler*etal.* [9]	0.62	-2.69	5.80 ± 4.44	[-2.80 to 14.50]
Proposed	0.98	-0.35	0.21 ± 0.83	[-1.44 to 1.84]

From the Table III and IV it is clearly seen that the range of intervals is greatly reduced in the proposed models whereas existing models show wide range of LOA and the results are not in the limit. Besides the absolute error rates in the proposed models have also been reduced. The mean and standard deviation of the errors of the different models are summarized in the following tables. The absolute rate of errors and the standard deviation of the results of proposed models are less than 1 in which other models exhibit more errors and the standard deviations. The following figures will demonstrate the error rates of different models and compare improvement of proposed models more specifically.

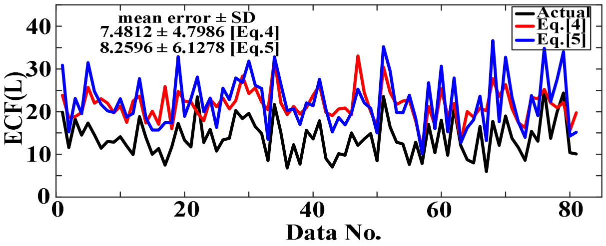


Fig. 5. Performance Comparison Curves of Cornish *et al.* [7] (both models) Outputs with Actual Data (Male)

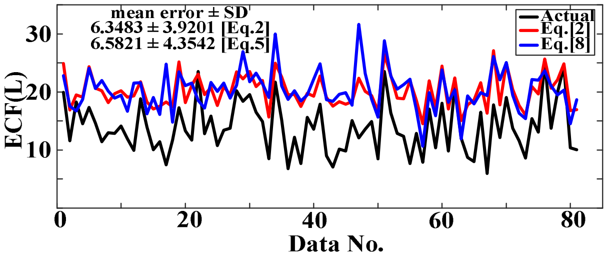


Fig. 6. Performance Comparison Curve of Hannan *et al.* [6] and Pitchler *et al.* [9] Outputs with Actual Data (Male)

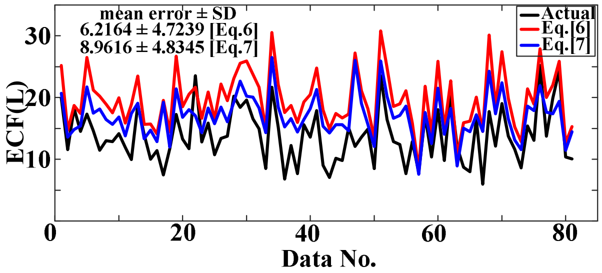


Fig. 7. Performance Comparison Curves of Sergi *et al.* [8] (both models) Outputs with Actual Data (Male)

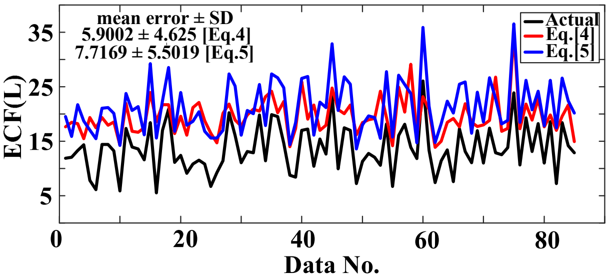


Fig. 8. Performance Comparison Curves of Cornish *et al.* [7] (both models) Outputs with Actual Data (Female)

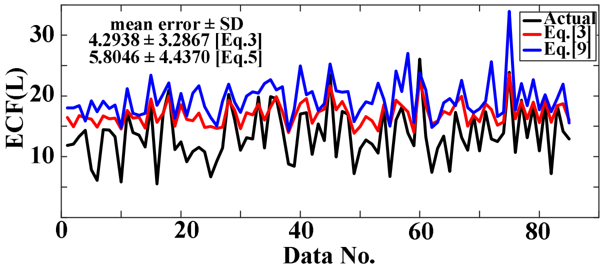


Fig. 9. Performance Comparison Curve of Hannan *et al.* [6] and Pitchler *et al.* [9] Outputs with Actual Data (Female)

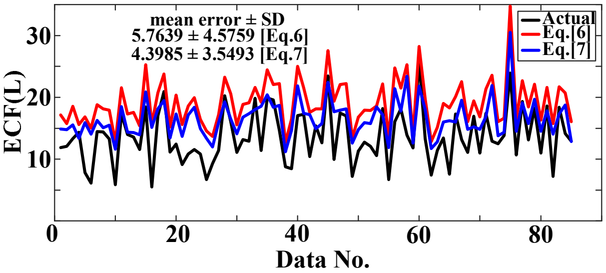


Fig. 10. Performance Comparison Curves of Sergi *et al.* [8] (both models) Outputs with Actual Data (Female)

However, the analysis which have been done above clearly indicate that the proposed models for ECF measurement based on bioelectrical impedance analysis will give more accurate measurements than current mathematical models.

V. CONCLUSION

The developed mathematical models for ECF measurement will make easier to develop more advanced algorithms for disease detections like dengue fever detection, kidney failure, congestive heart failure etc. As bioelectrical impedance analysis is very effective tool for analysis of human body by non-invasive way, the ECF measurement based on it has reduced time for getting outputs whereas pathological methods need couple of hours to give outputs. If diseases information from ECF can be predicted using non-invasive ways, the mass people all over the world will be benefited and get latest health care technology with very low cost. So these developed models will be an enigmatic tool in the field of medical sciences.

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