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Body composition analysis: Cellular level modeling of body component ratios

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Abstract

During the past two decades, a major outgrowth of efforts by our research group at St. Luke's-Roosevelt Hospital is the development of body composition models that include cellular level models, models based on body component ratios, total body potassium models, multi-component models, and resting energy expenditure-body composition models. This review summarizes these models with emphasis on component ratios that we believe are fundamental to understanding human body composition during growth and development and in response to disease and treatments. In-vivo measurements reveal that in healthy adults some component ratios show minimal variability and are relatively 'stable', for example total body water/fat-free mass and fatfree mass density. These ratios can be effectively applied for developing body composition methods. In contrast, other ratios, such as total body potassium/fat-free mass, are highly variable in vivo and therefore are less useful for developing body composition models. In order to understand the mechanisms governing the variability of these component ratios, we have developed eight cellular level ratio models and from them we derived simplified models that share as a major determining factor the ratio of extracellular to intracellular water ratio (*E/I*). The *E/I* value varies widely among adults. Model analysis reveals that the magnitude and variability of each body component ratio can be predicted by correlating the cellular level model with the *E/I value. Our approach thus provides new insights into and* improved understanding of body composition ratios in adults.

Keywords

Body cell mass; density of fat-free mass; lean-soft tissue; soft-tissue minerals; total body potassium; total body protein; total body water

Introduction

Body composition research includes three interconnecting areas: body composition rules or models; influences of biological factors on body composition; and in-vivo methods for measuring various body components [1].

To explore the quantitative relationships between body components, two fundamental approaches are possible. The first, based on experimental data, is a data-driven (ie, empirical) approach. The second, modeling, is based on the relationships between body

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components that give rise to the resulting experimental data. In this review we shall concentrate our discussion on body composition modeling.

Body composition modeling presents an abstraction of reality regarding quantitative connections between body components and their properties. In other words, body composition modeling can provide a logical and quantitative association between body components and their properties. Through modeling analysis, we can gain a constructive and instructive understanding of human body composition, and both the clinical and the research benefits of applying quantitative metrics to their analysis.

Required for body composition models is the hypothesis that the fundamental physiologies of human body composition are fixed across all subjects and time. Whenever measured observations differ from those predicted, the first reason may be that the model is incorrect. Second, there is a lack of sufficient body components/properties in the model.

A major outgrowth of the efforts of our group has been the development of new concepts for body composition modeling. Specifically, we suggested definitions for body components and described a five level model: atomic, molecular, cellular, tissue-organ, and whole-body [1]. Human body composition can be studied at the five levels of increasing complexity. In the relevant research, we developed a systematic approach to describing each body composition level quantitatively, and showed that simultaneous models can be written for each body composition level [2,3]. These studies provided a foundation for body composition modeling, a creating framework to organize body composition models. The five-level model is now widely accepted as a cornerstone for body composition studies.

During the past two decades, our St. Luke's research team has made great efforts on body composition modeling, including potassium-related models, resting energy expenditure modeling, and cellular level modeling of body component ratios. In a previous review, we summarized potassium-related models [4]. In this review, we shall summarize our progress on multi-component and resting energy expenditure modeling, and then summarize with an emphasis on the cellular level modeling of ratios between body components.

Multi-component models

Prior to 1990, body composition methodology relied on two-component (2-C) model methods that were based on thirty-year-old models with known limitations. In the 2-C model, body mass is divided into fat and fat-free body mass. Three measurements: total body water, total body potassium, and body density were solved for these two components. These 2-C models are based on the assumed constants observed in young Caucasian men. These assumptions had not been validated in women, non-white ethnic groups, or in children and the elderly. In order to overcome inherent limitations of the 2-C model methods, a new three-component (3-C) model was proposed by Siri [5], and new measurements were applied across a wider range of gender, race, age and weight. We therefore derived new 3-C model coefficients in vivo and compared these estimates to those derived by Siri [6].

By adding bone mineral mass measured by dual-energy X-ray absorptiometry (DXA), many investigators accomplished the goal of a four-component (4-C) model, dividing body mass into fat, water, mineral, and protein. Our research extended these findings to develop a sixcomponent (6-C) model: fat, water, bone mineral, protein, soft-tissue minerals and glycogen [7]. The 4-C model method compares very favorably to the 6-C model method by *in vivo* neutron activation analysis. Additionally, the 4-C model method allows computation of density and hydration of FFM, and, like the more complex 6-C neutron activation model method, is presumed valid across all adults. This is because no assumptions are made in either the 4-C or 6-C models that are influenced by gender, ethnicity, age or disease [8].

Today, following these pathways in our laboratories, and by many other groups around the world, powerful multi-component model methods are available that can reliably estimate total body fat and other major components at the molecular level of body composition.

Resting energy expenditure – body composition modeling

Resting energy expenditure (REE) is a major part (-60%) of total energy expenditure in adults. During the past two decades our St. Luke's research group has studied modelling REE in steady-state healthy adults. REE can be summarized by a general formula:

$$
REE = f(C) \tag{1}
$$

where C represents mass of body components. REE-body composition prediction methods are distinguished according to the mathematical function (*f*) (descriptive or mechanistic), and the body composition level (whole-body, tissue-organ, cellular, or molecular) [9].

Organ-tissue level REE model

Our group proposed a mechanistic model: REE equals the sum of resting energy requirements by all organs and tissues [10]. On the organ-tissue level, the human body can be divided into liver, brain, heart, kidneys, skeletal muscle, adipose tissue and other organs/ tissues. All organs and tissues are metabolically active. Therefore, REE can be represented by the sum of products of individual organ/tissue masses and their resting metabolic rates,

$$
REE = \Sigma (k \times Mi) \tag{2}
$$

where M is the individual organ/tissue mass, i the organ/tissue number $(i = 1, 2, ..., n)$, and *k* the assumed constant resting metabolic rate for each of the individual organs and tissues, as suggested by Elia [11]. An accurate prediction of whole-body REE is dependent on complete body composition measurements at the organ-tissue level. By using multiscan magnetic resonance imaging (MRI), with its exquisite capacity to quantize individual organs, even when they are variably distributed, as with adipose tissue depots, we have extended our body composition analyses to seven components including liver, brain, heart, kidneys, skeletal muscle, adipose tissue, and 'miscellaneous tissues' (ie, body mass minus the sum of 6 measured organs and tissues). Our group [10] used MRI to measure the volumes of the seven organ-tissue level components in 13 young adults. A strong correlation (r=0.94, *P*=0.001) was found between predicted REE and measured REE by indirect calorimetry and there was no significant difference between the measured and predicted REE.

Modified organ-tissue level REE model

Although the organ-tissue model predicted REE well in young adults, it over-predicted REE by ~11% in elderly adults [12]. We pointed out that this over-prediction occurs because of a decline in the fraction of organ and tissue masses as cell mass with aging. Our group thus developed a modified organ-tissue level REE model as

$$
REE=[(BCM/FFM)/0.58] \times \Sigma(ki \times Mi)
$$
 [3]

where BCM/FFM is the fraction of fat-free mass as body cell mass, the metabolically-active component; and 0.58 is the BCM/FFM ratio in the Reference Man [13]. Fifty-four healthy subjects 23 to 88 yrs had organ and tissue masses measured by MRI, body cell mass

calculated from total body potassium measured by whole-body 40 K counting, and FFM by DXA. According to the modified organ-tissue level REE model, predicted REE was highly correlated with measured REE $(r=0.91; P<0.001)$; there were no significant differences between measured REE and predicted REE for the whole group, and these differences were not associated with age (*P*>0.05) [14]. The combination of two aging-related factors (i.e., decline in both organ/tissue masses, and the cellular fraction of organs and tissues) account for the lower REE observed with age in elderly adults [12].

Cellular level REE model

Of the five body composition levels from atomic to whole-body, the cellular level is the first at which the energy metabolism of living organisms appears. The human body is composed of three components at the cellular level: cells, extracellular fluids, and extracellular solids. Whole-body REE represents the sum of energy consumed by all individual metabolically active cells at the resting conditions. A comprehensive cellular level REE model can be written as [9,14]

$$
REE = \Sigma (Ji \times Ci)
$$
 [4]

where C is cell mass by individual cell category, i is the cell category number $(i = 1, 2, ...,$ n), and *J* is the assumed constant resting metabolic rate of the individual cell category. This REE prediction model demonstrates that whole-body REE is determined by two factors, cell mass as individual cell category, and the resting metabolic rate of that cell category.

As individual cells are the energy-consuming units of the human body, the cellular level REE model can provide a mechanistic expression for the fundamental linkage between REE and body composition. A basic assumption of this model is that the resting metabolic rate of individual cell categories is constant within and between individuals. This assumption should be reasonable since the same-category cells in the basal state likely consume equivalent amounts of oxygen and produce equivalent amounts of heat. However, variation in body temperature and sympathetic nervous system activity might influence energy expended by specific cell groups.

Although equation 4 provides a comprehensive model for REE prediction, at present it is not possible to measure the cell mass as individual categories of cells in vivo. Therefore, the cellular level REE prediction model can only be applied theoretically at present. In the future it may be possible to measure tissue/organ cell mass in vivo using methods such as nuclear magnetic resonance spectroscopy.

Cellular level models of body component rations

One of the primary aims of body composition modeling research is to find quantitative relationships between body components. Several relatively stable body component ratios are recognized in healthy adults, such as the ratio of total body water to fat-free mass (TBW/ FFM=0.73) and FFM density (1.10 kg/l). In contrast, other body component ratios have large variations, such as the ratio of total body potassium to fat-free mass (TBK/FFM) and ratio of body cell mass to fat-free mass (BCM/FFM). Both FFM hydration and FFM density are applied in two-component model methods for total body fat estimation. The importance of the fat estimation led us to explore the inter-subject variability of various body component ratios.

Although the literature on this area has expanded extensively, ratios between body components have never been systematically compared, and fundamental questions remain

unanswered: Why do some body component ratios vary within a small range, but others vary within a large range? Are FFM hydration of 0.73 and FFM density of 1.10 biologically stable in adults, reflecting underlying physiological regulation? Alternatively, are the hydration and density of FFM reported at 0.73 and 1.10, respectively, across healthy adults the coalescence of several independent factors that generally result in a TBW/FFM of 0.73 and FFM density of 1.10, with minimal variability?

The only suggested means of studying body component ratios is by experimental measurements. Both in-vitro and in-vivo experimental approaches in general have two primary limitations. First, a large subject sample is necessary to explore the full range of various body component ratios. Second, even small errors in measurements may have a significant effect on the magnitude of calculated body component ratios.

During the past two decades, our group has studied eight body component ratios (Table 2), including the ratios of TBW to FFM, total body potassium to FFM, total body protein to FFM, body cell mass to FFM, FFM density, total body potassium to body cell mass, softtissue mineral to total body water [15–21] and total body water to lean-soft tissue [22]. Corresponding models of body component ratios have been developed at the cellular level. Based on these models, the mean magnitudes and variations of each body component ratio can be understood and predicted in healthy adults.

Cellular-level fat-free mass model

At the cellular body composition level, the body mass consists of cells, extracellular fluids (ECF), and extracellular solids (ECS). The cellular component can be further divided into fat and body cell mass (BCM), defined as a 'component of body composition containing the oxygen-exchanging, potassium-rich, glucose-oxidizing, work-performing tissue' [23]. Body mass can thus be expressed as

Body mass = cells + ECF + ECS

\n
$$
= fat + BCM + ECF + ECS
$$

\n[5]

Fat-free mass (FFM) is a complex body component at the molecular level. According to the definition, FFM can be expressed as the sum of three cellular level components,

$$
FFM=BCM+ECF+ECS
$$
 [6]

Both BCM and ECF consist of aqueous and solid compartments. Body cell mass can be expressed as $BCM = ICW/a$, where ICW is intracellular water, and *a* is the fraction of BCM as ICW. Extracellular fluid can be expressed as ECF = ECW/*b*, where ECW is extracellular water, and *b* is the fraction of ECF as ECW. In addition, ECS can be expressed as a function of total body water (TBW), $\text{ECS} = c \times \text{TBW} = c \times (\text{ICW} + \text{ECW})$, where *c* is the ratio of ECS to TBW. Equation 6 can thus be converted into

$$
FFM=ICW/a+ECW/b+c \times (ICW+ECW)
$$
\n^[7]

Intracellular water and ECW are interrelated compartments of body water; ECW can be expressed as a function of intracellular water: $ECW = (E/T) \times ICW$, where E/T is the ratio of ECW to ICW. Equation 7 can thus be further converted to

$$
FFM=[1/a+(1/b)\times (E/I)+c+c\times (E/I)]\times ICW
$$
 [8]

Equation 8 expresses FFM as a combination of a series of ratios. This approach allows us to develop and compare the variability among various body component ratios.

Our modeling studies reveal that each ratio between body components is determined by several factors. For modeling purposes, most of these determinant factors can be assumed relatively stable (Table 1). These assumptions should be reasonable for healthy adults. For example, both the fractions of body cell mass as water and the potassium concentration in cells are relatively constant at 0.70 and 152 mmol/kg H_2O , respectively.

Water distribution (ie, the ratio of extracellular water to intracellular water, ECW/ICW or *E/ I*) is the major determinant of the variability of body component ratios. Water distribution is highly variable between subjects and within subjects over time. In a previous study [15], we estimated the mean E/I value of 0.95 for healthy adults, although there is a significant between-gender *E/I* ratio difference (i.e., 0.82±0.16 for adult men *vs* 1.07±0.22 for adult women, $P<0.001$). In order to compare the variability among various body component ratios, we make an assumption that the *E/I* varies in a range from 0.8 to 1.1 in healthy adults with a mean magnitude of 0.95.

We now apply the cellular level FFM model (equation 8) to summarize and compare the variability of various body component ratios.

Total body water to fat-free mass ratio

The TBW/FFM ratio was originally derived from empirical observations in adult mammals. Many adult mammals, including human, share a similar ratio of total body water to fat-free mass (TBW/FFM=0.73) [24–26]. The importance of TBW/FFM is that estimation of TBW by the dilution approach allows prediction of total body fat mass based on a two-component model. In a previous study, a cellular level model was developed that can explain the mean magnitude and variation of the TBW/FFM ratio [15].

Full model

Water exists within two components, BCM and ECF, so that TBW is the sum of ICW (ie, BCM water) and ECW (ie, ECF water). A primary TBW/FFM model can be derived as

$$
TBW/FFM = \frac{ICW + ECW}{BCM + ECF + ECS}
$$
 [9]

From equations 8 and 9, a full TBW/FFM model (Table 2) was developed as

$$
TBW/FFM = \frac{1+E/I}{1/a+1/b \times (E/I) + c + c \times (E/I)}
$$
\n[10]

Simplified model

Assuming that determinants *a* (i.e., 0.70), *b* (i.e., 0.98), and *c* (i.e., 0.14) are stable in young adults (Table 1), equation 10 can be simplified as

$$
TBW/FFM = \frac{1+E/I}{1.569 + 1.16 \times (E/I)}
$$
 [11]

According to the simplified model, the mean magnitude and variation of the TBW/FFM ratio is mainly determined by the range of *E/I*. When *E/I* is equal to 0.95, TBW/FFM=0.730. This mean magnitude is similar to that from in-vivo studies on human adult cadavers and other adult mammals. When *E/I* value varies from 0.8 to 1.1, TBW/FFM increases from 0.721 to 0.738 (Table 3). The relative variability is equal to 2.3%, calculated as: [(TBW/ FFM at *E/I* 1.1) – (TBW/FFM at *E/I* 0.8)] / (TBW/FFM at *E/I* 0.95). This mathematical feature indicates that changes in water distribution have only a small effect on TBW/FFM [15]. FFM and total body fat mass can thus be predicted from measuring total body water, $fat = body mass - TBW/0.73$.

Total body potassium to fat-free mass ratio

The TBK/FFM ratio was a widely applied in body composition research [27]. From whole body chemical analysis data of a limited number of cadavers, Forbes and Lewis [28] derived a mean (\pm SD) TBK/FFM ratio of 68.1 \pm 3.1 mmol/kg and then introduced an in-vivo method for estimating total body fat mass. Although the TBK/FFM ratio is assumed stable, large individual and group deviations are recognized [29]. In order to probe the observed variability, TBK/FFM modeling was developed on the cellular body composition level [16].

Full model

Potassium exists within two components, BCM and ECF, so that TBK is the sum of intracellular K (ie, BCM potassium) and extracellular K (ie, ECF potassium). A primary TBK/FFM model can be derived as

$$
TBK/FFM = \frac{\text{intracellular K} + \text{extracellular K}}{\text{BCM} + \text{ECF} + \text{ECS}} \tag{12}
$$

From equations 8 and 12, a full TBK/FFM model (Table 2) was developed as

$$
TBK/FFM = \frac{[K]_{\text{rcw}} + [K]_{\text{rcw}} \times (E/I)}{1/a + 1/b \times (E/I) + c + c \times (E/I)}
$$
\n[13]

Simplified model

Assuming that the determinants $[K]_{ICW}$ (ie, the potassium concentration in intracellular fluid, 152 mmol/kg), $[K]_{ECW}$ (ie, the potassium concentration in extracellular fluid, 4 mmol/ kg), a (ie, 0.70), b (i.e., 0.98), and c (ie, 0.14) are stable in young adults (Table 1), equation 13 can be simplified as

$$
TBK/FFM = \frac{152 + 4 \times (E/I)}{1.569 + 1.16 \times (E/I)}
$$
 [14]

According to the simplified model, the mean magnitude and variation of TBK/FFM ratio is mainly determined by the range of the *E/I*. When *E/I* is equal to 0.95, TBK/FFM = 58.3 mmol/kg. When *E/I* value varies from 0.8 to 1.1, TBK/FFM decreases from 62.2 to 55.0 mmol/kg (Table 3). Thus the relative variability is as high as 12.3%, calculated as [(TBK/ FFM at *E/I* 0.8) – (TBK/FFM at *E/I* 1.1)] / (TBK/FFM at *E/I* 0.95). This mathematical feature indicates that changes in water distribution have a large effect on TBK/FFM [16]. Therefore, FFM and total body fat mass cannot be accurately calculated from total body potassium content alone.

Total body protein to fat-free mass ratio

Protein is a major component at the molecular level of body composition, and plays a central role in biochemical and physiological processes. The Reference Man of 70 kg body mass (or 56.7 kg FFM) contains 10.6 kg protein or 18.7% of FFM [13]. With chronic diseases there are inordinate losses of protein, particularly of skeletal muscle protein. In order to explore its magnitude and variation, a modeling of ratio between total body protein and fat-free mass (TBPro/FFM) was developed at the cellular level of body composition [17].

Full model

Protein exists in all three FFM components, so that total body protein is the sum of BCM protein, ECF protein, and ECS protein. A primary TBPro/FFM modeling can be derived as

$$
TBPro/FFM = \frac{BCM\ protein + ECF\ protein + ECS\ protein}{BCM + ECF + ECS}
$$
 [15]

From equations 8 and 15, a full TBPro/FFM modeling (Table 2) was developed as

$$
\text{TBPro/FFM} = \frac{\left[\text{Pro}\right]_{\text{BCM}}/a + \left[\text{Pro}\right]_{\text{ECF}} \times (E/I)/b + \left[\text{Pro}\right]_{\text{ECS}} \times c \times \left[1 + (E/I)\right]}{1/a + 1/b \times (E/I) + c + c \times (E/I)}
$$
\n[16]

Simplified model

Assuming that the determinants $[Pro]_{BCM}$ (i.e., protein concentration in the body cell mass, 0.27), [Pro]_{ECF} (i.e., protein concentration in extracellular fluid, 0.01), [Pro]_{ECS} (ie, protein concentration in extracellular solids, (0.423) , a (ie, (0.70) , b (ie, (0.98) , and c (ie, (0.14)) are stable in young adults (Table 1), equation 16 can be simplified as

$$
TBPro/FFM = \frac{0.445 + 0.069 \times (E/I)}{1.569 + 1.16 \times (E/I)}
$$
 [17]

As the simplified model indicates, the TBPro/FFM function is a decreasing concave curve. The magnitude and variation of TBPro/FFM ratio in adults is mainly determined by the range of *E/I* value. When *E/I* is equal to 0.95, TBPro/FFM = 0.191. This mean magnitude is similar to that in the Reference Man (protein is 18.7% of FFM). When *E/I* values vary from 0.8 to 1.1, TBPro/FFM decreases from 0.200 to 0.183 (Table 3). The relative variability is equal to 8.9%, calculated as [(TBPro/FFM at *E/I* 0.8) – (TBPro/FFM at *E/I* 1.1)] / (TBPro/ FFM at *E/I* 0.95). This mathematical feature indicates that changes in water distribution have a large effect on TBPro/FFM. Therefore, total body protein mass cannot be accurately estimated from FFM [17].

Body cell mass to fat-free mass ratio

Both body cell mass and fat-free mass are considered 'metabolically-active' components, and are often applied interchangeably to explain between-individual differences in resting energy expenditure. However, knowledge of body composition reveals that only the BCM, rather than the whole FFM, is the metabolically active component. Forbes was one of the first investigators to explore the BCM/FFM ratio [30]. According to Forbes, FFM has 68.1 mmol K/kg, and BCM has 120 mmol K/kg, and thus BCM is 57% of FFM (ie, 68.1/120).

Is the BCM/FFM ratio constant among adults? In order to answer this question, BCM/FFM ratio modeling was developed on the cellular level [21].

Full model

The primary BCM/FFM model can be written as

$$
BCM/FFM = \frac{BCM}{BCM + ECF + ECS}
$$
 [18]

From equations 8 and 18, a full BCM/FFM modeling (Table 2) can be derived as

$$
BCM/FFM = \frac{1/a}{1/a + (E/I)/b + c + c \times (E/I)}
$$
\n[19]

Simplified model

Of the four determinants, $a = 0.70$, $b = 0.98$, and $c = 0.14$ can be assumed for modeling purpose to be stable in healthy adults (Table 1). In contrast, *E/I* is highly variable within subjects over time and between subjects. Equation 19 can thus be converted as a simplified modeling,

$$
BCM/FFM = \frac{1.429}{1.569 + 1.16 \times (E/I)}
$$
\n[20]

This simplified model reveals that the BCM/FFM ratio is a decreasing concave curve and is not stable. The magnitude and variation of the BCM/FFM ratio is determined by the value of *E/I*. When *E/I* is equal to 0.95, BCM/FFM = 0.535. When *E/I* varies from 0.8 to 1.1, BCM/ FFM decreases from 0.572 to 0.502 (Table 3). The relative variability is as high as 13.1%, calculated as [(BCM/FFM at *E/I* 0.8) – (BCM/FFM at *E/I* 1.1)] / (BCM/FFM at *E/I* 0.95). This mathematical feature indicates that changes in water distribution have a large effect on BCM/FFM. Therefore, body cell mass cannot be accurately calculated from FFM [21].

Density of the fat-free mass

A classic body fat estimation method relies on an assumed stable density for FFM. The original means of exploring FFM density in humans is by cadaver analysis or by *in vivo* experimental studies. On the basis of the analysis of cadavers, Siri proposed an FFM density value of 1.100 kg/L [5]. In order to understand the magnitude and stability of FFM density, a cellular level body composition model was developed [20].

Full model

The density of fat-free mass is equal to FFM divided by FFM volume. The volume of the FFM can be expressed as the sum of the volumes of the three cellular level components:

[21]

where D_{BCM} , D_{ECF} , and D_{FCS} are the densities of BCM, ECF, and ECS, respectively.

A primary FFM density model can be derived

$$
D_{FFM} = \frac{BCM + ECF + ECS}{BCM/D_{BCM} + ECF/D_{ECF} + ECS/D_{ECS}}
$$
\n[22]

From equations 8 and 22, a full FFM density model (Table 2) was developed as

$$
D_{FFM} = \frac{1/a + (E/I)/b + c + c \times (E/I)}{1/(a \times D_{BCM}) + (E/I)/(b \times D_{ECF}) + c/D_{ECS} + c \times (E/I)/D_{ECS}}
$$
\n[23]

Simplified model

Among the seven model determinants, $D_{\rm BCM}$ (i.e., density of body cell mass, 1.078 kg/L), D_{ECF} (ie, density of extracellular fluid, 1.010 kg/L), D_{ECS} (i.e., density of extracellular solids, 1.96 kg/L), *a* (ie, 0.70), *b* (i.e., 0.98), and *c* (ie, 0.14) are assumed for modeling purpose to be stable in healthy adults (Table 1). Equation 23 can be simplified to

$$
D_{\text{FFM}} = \frac{1.569 + 1.16 \times (E/I)}{1.396 + 1.081 \times (E/I)}
$$
 [24]

The simplified FFM density model indicates that the FFM density function is a decreasing concave curve, and the ratio of ECW to ICW is the major determinant of individual variation in adult FFM density. When E/I is equal to 0.95, FFM density = 1.103. This mean magnitude is close to that measured in in-vitro studies of human adult cadavers (1.100). When *E/I* varies from 0.8 to 1.1, FFM density decreases from 1.105 to 1.101 (Table 3). The relative variability is equal to 0.36% that is calculated as $[(D_{FFM} \text{ at } E/I 0.8) - (D_{FFM} \text{ at } E/I$ 1.1)]/(D_{FFM} at E/I 0.95). This mathematical feature indicates that changes in water distribution have a very small effect on FFM density [20]. Therefore, the relative stable FFM density can be applied to predict total body fat mass.

Total body potassium to body cell mass ratio

The concept of the body cell mass was proposed four decades ago, reflecting the cellular component that is involved in biochemical processes and energy metabolism [23]. Nutritional status, physical activity level, and disease states alter BCM, which in turn serves as a biomarker of these processes. Assuming that all body potassium is within cells and the average cell potassium content is stable (ie, 120 mmol/kg), Moore et al. [23] developed a BCM estimation formula from total body potassium: BCM (kg) = $0.00833 \times \text{TBK}$ (mmol). Based on a TBK-independent study, however, Cohn et al [31] suggested that the TBK/BCM ratio is 108.7 mmol/kg, suggesting that Moore's equation may underestimate BCM. In order to explore the magnitude and variation of the ratio of TBK to BCM, we developed a TBK/ BCM models on the cellular level [19].

Full model

Potassium exists within two components, BCM and ECF, so that TBK is the sum of intracellular K (ie, BCM potassium) and extracellular K (ie, ECF potassium). A primary TBK/FFM model can be derived as

$$
TBK/BCM = \frac{intracellular K + extracellular K}{BCM}
$$

[25]

From equation 25, a full TBK/FFM model (Table 2) was developed as

$$
TBK/BCM = a \times \{ [K]_{\text{ICW}} + [K]_{\text{ECW}} \times (E/I) \}
$$

Simplified model

Assuming that the determinants $[K]_{ICW}$ (ie, potassium concentration in intracellular fluid, 152 mmol/kg), $[K]_{ECW}$ (ie, potassium concentration in extracellular fluid, 4 mmol/kg) and a (i.e., 0.70) are stable in young adults (Table 1), equation 26 can be simplified as

$$
TBK/BCM = 106.4 + 2.8 \times (E/I)
$$
\n^[27]

According to the simplified model, the mean magnitude and variation of TBK/FFM ratio is mainly determined by the range of *E/I* value. When *E/I* is equal to 0.95, the mean magnitude of TBK/BCM = 109.1 mmol/kg. When *E/I* varies from 0.8 to 1.1, the TBK/BCM ratio slightly increases from 108.6 to 109.5 mmol/kg (Table 3). The relative variability is equal to 0.81%, calculated as [(TBK/BCM at *E/I* 0.8) – (TBK/BCM at *E/I* 1.1)] / (TBK/BCM at *E/I* 0.95). This mathematical feature indicates that changes in water distribution have only a very small effect on the TBK/BCM ratio. The BCM can thus be accurately calculated from measured total body potassium, BCM (in kg) = TBK/109.1 = $0.00917 \times$ TBK (in mmol) [19].

Soft-tissue mineral to total body water ratio

Soft-tissue minerals (Ms) consist of soluble minerals in body fluid. Although the Ms content is relatively small $(-0.4 \text{ kg in adults})$, its contribution to body density and X-ray attenuation occurs because the Ms collectively have higher density and mass attenuation than other molecular-level components such as fat, water and protein. In order to develop a reliable prediction for Ms, a ration model between Ms and total body water was developed on the cellular level of body composition [18].

Full model

Soft-tissue mineral distributes within both BCM and ECF components, so that Ms can be expressed as the sum of intracellular Ms and extracellular Ms. A primary Ms/TBW model can be written as

$$
Ms/TBW = \frac{\text{intracellular Ms} + \text{extracellular Ms}}{\text{ICW} + \text{ECW}} \tag{28}
$$

A full Ms/TBW model (Table 2) was developed as

$$
Ms/TBW = \frac{[Ms]_{icw} + [Ms]_{icw} \times (E/I)}{1 + E/I}
$$
\n[29]

Simplified model

Among the three determinants of the full model of the Ms/TBW ratio, $[Ms]_{ICW}$ (ie, 0.0162) kg/kg) and $[Ms]_{ECW}$ (ie, 0.0095 kg/kg) are relatively stable in young adults (Table 1). Equation 29 can be simplified as,

 $\text{Ms}/\text{TBW} = \frac{0.0162 + 0.0095 \times E/I}{1 + E/I}$ [30]

As indicated in our previous study, the Ms/TBW function is a decreasing concave curve, and the magnitude and variation range of the Ms/TBW ratio is largely determined by the range of E/I (18). When E/I is equal to 0.95, the mean magnitude of Ms/TBW = 0.0129. When the *E/I* value varies from 0.8 to 1.1, Ms/TBW decreases from 0.0132 to 0.0127 (Table 3). This variability is equal to 3.9%, calculated as [(Ms/TBW at *E/I* 0.8) – (Ms/TBW at *E/I* 1.1)] / (Ms/TBW at *E/I* 0.95). This mathematical feature indicates that changes in water distribution have a modest effect on Ms/TBW. Whole-body Ms can thus be calculated from total body water mass, $Ms = 0.0129 \times TBW$.

Total body water to lean-soft tissue ratio

An important advance in body composition research is the availability of dual-energy X-ray absorptiometry (DXA) which partitions body mass into three components: fat, lean-soft tissue (LST), and bone mineral (Mo). Water is present exclusively within the LST compartment, and one assumption of DXA measurements is that the water content of LST is relatively stable across subjects [32]. In our previous study, a cellular level model was developed which explained the mean magnitude and variation of the TBW/LST ratio [22].

Full model

The fat-free mass can be divided into three components: BCM, ECF, and extracellular solids (ECS). The ECS consist of organic ECS (ie, ECS protein) and inorganic ECS (ie, bone mineral, Mo). The lean-soft tissue measured by DXA can be expressed as the sum of three cellular level components:

[31]

Water exists within two components, BCM and ECF, so that TBW is the sum of ICW (ie, BCM water) and ECW (ie, ECF water). A primary TBW/LST model can be stated as

$$
TBW/LST = \frac{ICW + ECW}{BCM + ECF + ECS protein}
$$
\n[32]

The ratio of ECS protein to Mo is assumed relatively constant at 0.73 (17. Wang et al, 2003). ECS protein can be expressed as a function of total body water: ECS protein = 0.423 $\times c \times$ TBW. A full TBW/LST model (Table 2) was developed as

$$
TBW/LST = \frac{1+E/I}{1/a+1/b \times (E/I)+0.423 \times c+0.423 \times c \times (E/I)}
$$
\n[33]

Simplified model

Assuming that the determinants *a* (0.70), *b* (0.98), and *c* (0.14) are stable in young adults (Table 1), equation 33 can be simplified as

[34]

$$
TBW/LST = \frac{1 + E/I}{1.488 + 1.080 \times (E/I)}
$$

According to the simplified model, the mean magnitude and variation of the TBW/LST ratio is largely determined by the physiologic range of *E/I*. When *E/I* is equal to 0.95, TBW/LST $= 0.776$. When *E/I* value varies from 0.8 to 1.1, TBW/LST increases from 0.765 to 0.785 (Table 3). The relative variability is equal to 2.6%, calculated as [(TBW/LST at *E/I* 1.1) – (TBW/LST at *E/I* 0.8)] / (TBW/LST at *E/I* 0.95). This mathematical feature indicates that changes in water distribution have only a small effect on TBW/LST. The TBW/LST modeling reveals that the hydration of the DXA-derived LST component is relatively stable in healthy adults. This modeling has implications for the accuracy of body fat measurements by DXA, and the use of TBW as a means of checking DXA system calibration [22].

Summary and conclusion

Body component ratios have been measured based on previous experimental studies, showing that some ratios are relatively stable under most circumstances, forming the basis of 'normal' body composition methodology. The cell is the basic structural unit of the human body, so that the cellular level is central to the five levels model of human body composition. Eight body component ratios were expressed as mathematical models at the cellular level. The key features of these modeling approaches can be summarized as follows:

- **•** The modeling approach for body component ratios reveals quantitative associations between body components, allowing expression of the features of body component ratios, including their magnitude, variation, and the influences of age and gender. It is only through the modeling approach, and especially by inferences of cause and effect, that we gain a mechanistic and analytic understanding of human body composition in terms suitable to serial measurement, and to metric analysis (Table 2).
- **•** Body component ratios are determined by several influencing factors, such as intracellular hydration (*a*) and extracellular fluid hydration (*b*). These factors are maintained relatively stable by physiologic homeostatic mechanisms in healthy adults. (Table 1).
- **•** In contrast, the extracellular water to intracellular water ratio (*E/I*) varies over a much larger range, and may have substantial influence on the variations of body component ratios. In healthy adults, the mean *E/I* value is smaller in men than in women. Some body component ratios thus differ remarkably by gender.
- The simplified models can be applied to compare the variability between body component ratios (Table 3). With the same *E/I* range, some ratios such the densities of FFM, TBK/BCM, TBW/FFM and TBW/LST, have small relative variability (<3%). Other ratios, such as TBK/FFM, TBPro/FFM and BCM/FFM, have greater relative variability (>8%), and may not be used for tight predictions of model components.

In conclusion, the modeling approach to body component ratios has allowed new insight into basic biological processes, and may enhance understanding of body composition kinetics, and foster application of body composition methodologies.

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Table 1

Assumed constant parameters in young adults.

Table 2

Full and simplified cellular level models of body component ratios.

Body component ratios: BCM/FFM, ratio of body cell mass to fat-free mass; FFM density; fat-free mass density; Ms/TBW, ratio of soft-tissue minerals to total body water; TBK/BCM, ratio of total body potassium to body cell mass; TBK/FFM, ratio of total body potassium to fat-free mass; TBPro/FFM, ratio of total body protein to fat-free mass; TBW/FFM, ratio of total body water to fat-free mass; TBW/LST, ratio of total body water to lean-soft tissue.

Abbreviations: *a*, fraction of body cell mass as water; *b*, fraction of extracellular fluid as water; *c*, ratio of extracellular solids to total body water; DBCM, density of body cell mass; DECF, density of extracellular fluid; DECS, density of extracellular solids; FFM, fat-free mass; *E/I*, ratio of extracellular water to intracellular water; [K]ECW, potassium concentration in extracellular fluid; [K]ECW, potassium concentration in intracellular fluid; [Ms]ECW, concentration of soft-tissue minerals in extracellular fluid; [Ms]_{ICW}, concentration of soft-tissue minerals in intracellular fluid; [Pro]BCM, protein concentration in body cell mass; [Pro]ECF, protein concentration in extracellular fluid; [Pro]Ecs, protein concentration in extracellular solids.

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Body component ratios: BCM/FFM, ratio of body cell mass to fat-free mass (in kg/kg); FFM density, fat-free mass density (in kg/L); Ms/TBW, ratio of soft-tissue minerals to total body water (in kg/kg);
TBK/BCM, ratio of t TBK/BCM, ratio of total body potassium to body cell mass (in mmol/kg); TBK/FFM, ratio of total body potassium to fat-free mass (in mmol/kg); TBPro/FFM, ratio of total body protein to fat-free mass (in **Body component ratios:** BCM/FFM, ratio of body cell mass to fat-free mass (in kg/kg); FFM density, fat-free mass density (in kg/L); Ms/TBW, ratio of soft-tissue minerals to total body water (in kg/kg); kg/kg); TBW/FFM, ratio of total body water to fat-free mass (in kg/kg); TBW/LST, ratio of total body water to lean-soft tissue (in kg/kg). kg/kg); TBW/FFM, ratio of total body water to fat-free mass (in kg/kg); TBW/LST, ratio of total body water to lean-soft tissue (in kg/kg).

Abbreviation: E/I, ratio of extracellular water to intracellular water (in kg/kg). **Abbreviation:** *E/I*, ratio of extracellular water to intracellular water (in kg/kg). Variability of body component ratio: For instance, the relative variability of TBW/FFM ratio can be calculated as [(TBW/FFM at E/11.1) - (TBW/FFM at E/10.8)/(TBW/FFM at E/10.95) = (0.738 -**Variability of body component ratio:** For instance, the relative variability of TBW/FFM ratio can be calculated as [(TBW/FFM at E/I 1.1) – (TBW/FFM at E/I 0.8)]/(TBW/FFM at E/I 0.955) = (0.738 –
0.721)/0.730 = 2.3%. 0.721)/ $0.730 = 2.3%$.