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ORIGINAL ARTICLE

An estimation of the number of cells in the human body

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Abstract

Background: All living organisms are made of individual and identifiable cells, whose number, together with their size and type, ultimately defines the structure and functions of an organism. While the total cell number of lower organisms is often known, it has not yet been defined in higher organisms. In particular, the reported total cell number of a human being ranges between 10^{12} and 10^{16} and it is widely mentioned without a proper reference.
Aim: To study and discuss the theoretical issue of the total number of cells that compose the standard human adult organism.
Subjects and methods: A systematic calculation of the total cell number of the whole human body and of the single organs was carried out using bibliographical and/or mathematical approaches.
Results: A current estimation of human total cell number calculated for a variety of organs and cell types is presented. These partial data correspond to a total number of 3.72×10^{13}.
Conclusions: Knowing the total cell number of the human body as well as of individual organs is important from a cultural, biological, medical and comparative modelling point of view. The presented cell count could be a starting point for a common effort to complete the total calculation.

Keywords

Cell size, human cell number, organ, total cell count, theoretical issue

History

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Introduction

Since Schleiden's and Schwann's first formulations of cell theory (Mazzarello, 1999), it has been known that all living organisms are made of individual and identifiable cells, whose size, number and type ultimately define the structure, functions and size of an organism.

Cell size appears to be regulated by the amount of DNA (ploidy): for example, the diploid yeast is larger than the haploid one (Su & O'Farrell, 1998); cells in a tetraploid salamander are twice the size of those in a diploid salamander, although the corresponding organs in the two animals have the same size, because the organisms of the tetraploid salamander contain half as many cells as those of the diploid (Conlon & Raff, 1999). Nevertheless, the issue of what kind of relationship or signalling there is between cell size and DNA content is still unresolved. It has been hypothesized that there is a maximal protein-production rate from a genome because there is an upper limit to gene transcription and translation rates. Since proteins have a limited lifetime, there is a maximal amount of protein-associated cell mass that can be supported by a genome (Gomer, 2001). In size-control mechanisms, even cell communication has a role in defining specific organs, as reported by Depaepe et al. (2005).

Cell number, on the other hand, appears to be under strict genetic and developmental control in lower organisms: for example, *bacteria* and yeasts are composed of single cells, while the adult *Caenorhabditis elegans* worm consists of exactly 959 (male) or 1031 (ermaphrodite) somatic cells (Alberts et al., 2002). In contrast, how cell number is determined in higher organisms is not understood, although it is presumably regulated by wider mechanisms of homeostasis such as proliferation, differentiation and cell death. According to this, Notch signalling can prolong precursor cell division and can maintain stem cells in a self-renewing pattern of division, thereby indirectly increasing the number of differentiated cells that are ultimately produced (Conlon & Raff, 1999). There are currently several examples of secreted factors that regulate tissue size, by both increasing and limiting proliferation. Examples are myostatin, which regulates skeletal muscle mass; leptin, which regulates the amount of adipose tissue; growth hormone and insulin-like growth

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factors, which regulate total body mass (Roisin-Bouffay & Gomer, 2004), and Hh-Gli signalling factors, which play a central role in controlling precursor cell numbers in the brain and other organs (Stecca & Ruiz i Altaba, 2009).

Some factors, such as insulin-signalling pathway, are central in controlling cell number and size from worms to humans, supporting the idea that key functions of the pathway have been powerfully conserved through evolution (Moore, 2003). However, it has also been suggested that there may be fundamental differences in the mechanisms by which mammals and insects control their body size. This is the case of *c-myc*, indicated as a crucial signal mediator: in mice its reduction resulted in multi-organ hypoplasia, while *Drosophila c-myc* mutants were found to be smaller because of hypotrophy (Trumpp et al., 2001).

In complex organisms, composed of many billions of cells, it is expected that control of cell number does not reach precision at the level of single cells. However, at least a defined order of magnitude in body cell number should be conserved among humans, on the basis of several considerations. First, although there are obvious differences in body height and mass among adult individuals, these variations are not greater than one order of magnitude and they may be due to an increase in cell size along with or in absence of an increase in cell number, such as in obesity (Avram et al., 2007; Salans et al., 1973). In addition, analysis of cell number at single organ or tissue level shows a considerable degree of conservation among human organisms, i.e. blood cells count. Biological experimental data point to an ‘‘organ-size checkpoint’’ that generates organs of reproducible shape and size in metazoans by regulating cell division, cell growth and apoptosis, involving genes regulating patterning or controlling cell adhesion and cell polarity (Leevers & McNeill, 2005). Finally, consistency of basic molecular and cellular mechanisms for the development of an initial single cell (zygote) into a complete organism with a reproducible anatomy and physiology and conservation of these mechanisms through evolution, suggest that a fine control of cell number is exerted at genetic level in a similar manner for all individuals of a certain species. In fact, there are clear physical constraints on upper and lower limits of organism and organ size, such as bone or heart mechanics and surface-to-volume ratio, and biological mechanisms aimed at controlling body and tissue cell number (Gomer, 2001; Hafen & Stocker, 2003).

The aim of this work is to discuss the theoretical issue of the total number of cells that compose the standard human adult organism.

First, we noticed that these data were typically mentioned in the literature without citing a reference; second, we observed wide ranges among data reported by different sources, ranging from 10^{12}–10^{20}.

We followed different lines of research in order to: undertake a systematic survey of available information about the number of cells of a human organism known to date; assess this number using rough estimations for the body as a whole; provide a framework and accurate count of specific organs or cell types. In addition, we discuss the relevance of this topic with regard to its applications in biology and medicine, the complexity of deriving the total cell number and, finally, we launch an international open debate aimed at a final and documented solution of the problem.

Materials and methods

Different approaches were used to retrieve all data available to date on the total human cell number for a human being or for a specific system/organ or cell type. Moreover, we obtained useful data from the literature in order to calculate the total cell number of specific system/organ or cell types not yet known. Since the cell number and cell size of various organs or systems, as well as the size of the organ or system itself, may vary according to several parameters such as age, sex, weight, pathology or evolutionary adaptations, we searched for a single reference for the ‘‘average man’’ or ‘‘standard human being’’. Since this does not exist, for the purposes of this work we chose a 30-year old young adult, weighing 70 kg, 1.72 m tall and with a body area of 1.85 m^2 (Irving, 2007). When retrieved data were different from this ‘‘average man’’ this was indicated in the specific section.

Bibliographical search

In order to find primary literature articles with information about the cell number of a human organism, we systematically searched the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/). Searching for the MeSH term ‘‘Cell Count’’, corresponding to ‘‘cell number’’, led to non-specific results (more than 168 000 items found). The PubMed search was therefore adjusted by using MeSH sub-headings and by restricting results to *Homo sapiens*. The search was performed using the expression: (‘‘Cell Count’’[Mesh] OR ‘‘cell number’’) AND (‘‘Body Weights and Measures’’[Mesh] OR ‘‘Body Size’’[Mesh] OR ‘‘Body Constitution’’[Mesh] OR ‘‘Body Composition’’[Mesh]) AND ‘‘Humans’’[Mesh] AND (1809[PDAT]: 2012/01/31[PDAT]). In addition, a search including the explicit expression ‘‘cell number’’ along with the terms ‘‘body’’ or ‘‘organism’’, limited to humans but not including the MeSH sub-headings used above, was performed in the title/abstract fields of PubMed. In this case the PubMed query was: (Human[Title/Abstract] OR ‘‘Humans’’[Mesh]) AND (body[Title/Abstract] OR organism[Title/Abstract]) AND ‘‘cell number’’[Title/Abstract] AND (1809[PDAT]: 2012/01/31[PDAT]). Finally, a further search, not including restriction to the presence of ‘‘body’’ or ‘‘organism’’ terms and directed to the presence of the expression ‘‘cell number’’ in the item title was performed by the query: ‘‘Cell number’’[TI] AND human AND (1809[PDAT]: 2012/01/31[PDAT]).

At the same time, we performed a specific search of the PubMed database with the purpose of finding primary literature articles with information on how to calculate the total cell number of a specific system/organ or cell type not yet known.

The publication date of the articles searched ranged from 1809 to January 2012. Moreover, we reviewed printed versions of available texts covering Biology, Genetics, Histology, Anatomy, Physiology and other potentially useful available printed sources. In addition, we searched for this information in the main repositories of electronic versions of books, NCBI Books (http://www.ncbi.nlm.nih.gov/sites/entrez?db = books) as well as of Google Books (http://books.google.com/books), in their versions available up to January 2012.

The NCBI Books collection includes many reference textbooks widely used in the biomedical field. It was queried using a general expression formulated according to the NCBI Entrez query language: (''Human body'' OR ''Human organism'') AND (Cells OR ''Cell number'') or a specific request.

The Google Books collection includes books on any subject whose text has been freely made totally or partially available. It was searched by using the expression: (''Human body'' OR ''Human organism'') (Cells OR ''Cell number'') or a specific request.

The internet search engine Google was searched using the expression: (''Human body'' OR ''Human organism'') AND (Cells OR ''Cell number'') or a specific request.

Morphological estimation

It was possible to calculate cell volumes using an ultramicroscopic cell or an organ picture by the ''solid revolution method''. First, we filtered the pictures in which the scale bar was reported, the cell/organ was well magnified and its edge was cleaned.

We plotted the Cartesian axes on the cell/organ picture so that the axes origin was on the cell edge, the cell lay on the positive abscissa and this axis split the cell into two identical parts. We then traced bars with equal base size and intersecting cell/organ edge in the middle of their top side (Figure 1); the bars were built so that the sum of their areas was, as much as possible, equal to the area of the cell/organ contained in the first quadrant of the Cartesian axes.

An approximation of the cell/organ volume was obtained by the following formula:

$$V_{\text{approx}} = \sum_{i=1}^{n} \pi \cdot f(x_i)^2 \cdot \Delta x$$

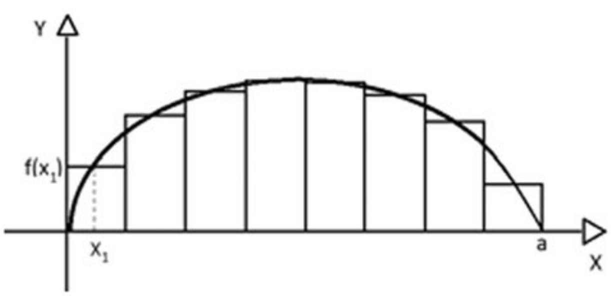

Figure 1. Schematic representation of the cell image position in the Cartesian axes. It was possible to calculate the cell volume by the ''solid revolution method'' approximated by the summation formula, using an ultramicroscope cell picture. In particular, Cartesian axes have to be drawn on the cell image so that the *x*-axis is a symmetrical axis of the cell, the upper half of the cell (represented by the curve line in the figure) lies in the first quadrant and the cell edge intersects the origin of the axes. Bars of identical width have to be drawn in the cell area included between the cell edge and the *x*-axis, intersecting the cell edge in the middle of their top side. In this manner the sum of the areas of all the bars will approximate the area of this cell portion, while the cell volume is obtained by measuring each bar height and inserting it in the summation formula (see details in the ''Morphological estimation'' section).

In order to attain a better approximation of the cell/organ volume, we chose to sample the function $f(x)$, that represents the cell/organ edge, in the middle of each interval Δx. Moreover we sub-divided the abscissa axis (the ''a'' segment in Figure 1) laid upon the shape into n equal parts, each with length . Finally, we re-scaled the cell/organ volume in cubic micrometres.

Mathematical calculations

Most of the time, data obtained by previous described methods required mathematical elaborations to find the total cell number of a human being or the specific system/organ or a cell type searched. Every time more than one *datum* was given, the mean value and the corresponding errors (standard deviation, SD) were reported alongside the value together with the corresponding reference that reports them. Furthermore, when cell size was necessary to perform the calculation, we declared it in the organ-specific results section.

Moreover, a gross estimation of the total human cell number was obtained by dividing the mass or volume of a reference adult human body by the mass or volume, respectively, of an average human cell.

Results

Estimation of the human total cell number in the literature

We optimized the PubMed search in order to obtain useful information about the composition of the human body in terms of cell number.

The search strategies in PubMed database described in the ''Bibliographical search'' section led us to retrieve 3407 articles. However, only two articles addressing the specific issue of the global cell number in the human body were found (see ''Original article'' in Appendix A, Table A1).

Searches in printed books, in online NCBI and Google Books gave useful estimations of total cell number in the human body (see ''Printed book'' and ''Online book'' in Appendix A, Table A1).

None of these values were justified by primary literature data and no citation source was available. Many websites retrieved via Google search reported estimations for the human whole body cell number. Due to criteria used by the Google search engine, we consulted the first 100 results, which led to estimations ranging from 5×10^{12} to 7×10^{16}, with a single site reporting 2×10^{20}.

Excluding the results without an available primary source, the estimation of the total human cell number, supported by a bibliographical reference, ranges from 10^{12}–10^{16}, with a modal value of 10^{13} (see Figure 2 and Table A1 in Appendix A).

Gross estimation of the human total cell number by mass and by volume

Although high variability in the size and weight of cells from different normal tissues makes it difficult to choose a reference for human cell weight and volume average values, we assumed that a global compensation among body regions exists.

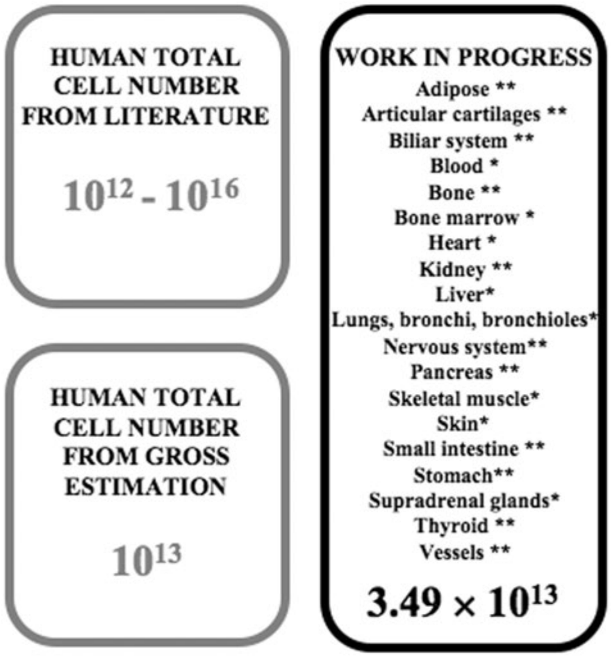

Figure 2. Human total cell number comparison. *Total cell number calculated for the whole organ; **total cell number calculated only for some cell types of the organ.

Therefore, since the mean weight of a mammalian cell has been estimated to be 1 ng (Makarieva et al., 2008), for a standard body weight of 70 kg (Irving, 2007), there would be 7×10^{13} cells.

The mean volume of a mammalian cell has been estimated to be $4 \times 10^{-9}\,cm^3$ (Alberts et al., 2002) (i.e. 4 pL). The human body mean volume has been calculated by Nagao et al. (1995) by two different physical methods: the obtained values were 63.83 and 66.61 L. Considering the average value, the resulting cell number is 1.63×10^{13} cells. Moreover, considering the body volume indicated by Irving (2007), equal to $60 \times 10^3\,cm^3$, the total human cell number resulted to be 1.50×10^{13} (Figure 2). However, if a single, 90 fL volume, blood red cell were to be considered (Tønnesen et al., 1986), this would translate into a larger number of total cells, 7.24×10^{14}.

On the other hand, the estimation of a mean volume of 6 pL for each endothelial cell and of a total number of 35×10^{12} human endothelial cells (Genest et al., 1983) would result in an over-estimated body volume of 210 L.

Estimation of total cell number of specific systems, organs or cell types

We present here results on the cell number of specific systems, organs or cell types obtained to date with our research.

Some of the values regarding the cell number of whole human organs or cell type were obtained directly from an in-depth bibliographical search. Other data on total cell number of whole human organs or cell type needed integration of some or all methods described above. We report below these methods and results together for each of them (see Appendix B, Table B1).

Articular cartilages: Femoral condylar, humeral head and trochlear surface of talus cartilage total cell number

Articular cartilage cell number was calculated for some main joints: the femoral condylar cartilage, the shoulder (humeral head) and the ankle (trochlear surface of talus). Femoral, humeral head and talus cartilage volumes have been reported at $2503 \pm 568\,mm^3$ (lateral femur cartilage), $2770 \pm 536\,mm^3$ (medial femur cartilage) (Baysal et al., 2004), $4200\,mm^3 \pm 1120$ (Vanwanseele et al., 2004) and $3320 \pm 550\,mm^3$ (Millington et al., 2007), respectively. Femoral, humeral head and talus cartilage cell densities have been reported at $14\,100 \pm 3200$ cells/mm^3, 14 600 cells/mm^3 and 12 150 cells/mm^3 (Stockwell, 1971), respectively.

Based on these data, the calculated cell numbers of two femoral condyles, two humeral heads and two talus cartilages were $1.49 \pm 0.46 \times 10^8$, $1.23 \pm 0.35 \times 10^8$, $8.06 \pm 1.56 \times 10^7$, respectively.

Biliary system: Gallbladder and biliary ducts epithelium total cell number

The biliary system is composed of the gallbladder and biliary ducts (Borley, 2005a).

We calculated the gallbladder internal surface (47.03 cm^2), by gallbladder internal volume (Irving, 2007) and size (Borley, 2005a) assuming that it has a prolate spheroidal shape. By dividing the estimated surface by the single cell basal surface ($29.20 \pm 4.21\,\mu m^2$), attained by morphological estimation (as described in the Methods section) from an epithelium microimage (Wolf & Scarbrough, 2012), we obtained the total number of gallbladder epithelium cells to be $1.61 \pm 0.23 \times 10^8$. Besides the columnar epithelium, gallbladder width is composed of a sub-epithelial stroma and complex smooth fibromuscolar layers. Sub-epithelial stroma and smooth fibromuscolar layers volumes were calculated by morphological estimation (Bergman et al., 2004). We calculated the interstitial Cajal-like cells ($4.94 \pm 0.04 \times 10^5$) and other stromal gallbladder cells ($8.48 \pm 0.09 \times 10^6$) starting from data reported by Hinescu et al. (2007). We then calculated the total myocytes cell number (considering the maximum length and the minimum diameter of each cell (Portincasa et al., 2004)) by dividing the smooth fibromuscolar layer volume ($2.80 \pm 0.46 \times 10^{12}\,\mu m^3$) by the single myocyte cell volume ($1770 \pm 350\,\mu m^3$), obtaining $1.58 \pm 0.40 \times 10^9$ cells.

As for to the biliary ducts, we were able to estimate the total epithelial cell number of the extra hepatic ducts ($7.03 \pm 5.30 \times 10^7$) by dividing the total surface of the ducts (Castelain et al., 1993; Khalil et al., 2005) by the cylindrical epithelial cell basal surface.

Bones: Osteocytes total number

Since the total volume of bone tissue (BV) was not directly measurable, it was necessary to compute it starting from total skeleton weight (TW), extrapolated from the literature (Trotter, 1954; Seale, 1959). The amount of cortical and trabecular tissue was also investigated (77% and 23%, respectively) (Malluche & Faugere, 1986). Based on micro-CT analysis, it was possible to obtain the average porosity (bone volume over total volume fraction, BV/TV) of both types of tissue and the correlation between bone porosity and ash density (Tassani et al., 2011), defined as the ratio between the bone weight and total geometrical volume of the specimen, including empty spaces of porosity.

BV was computed as follows:

$$\text{Ash Density} = \text{m} \times \text{BV/TV} + b;$$
$$\text{T}_\text{s}\text{V} = \text{TW} \times \text{Ash Density; and}$$
$$\text{B}_\text{s}\text{V} = \text{BV/TV} \times \text{T}_\text{s}\text{V}$$

where m is the slope of the linear regression (trabecular 1.04 g/cm^3, cortical 1.15 g/cm^3) and b is the intercept (0.03 g/cm^3 for both trabecular and cortical bone), $R^2 = 0.97$ for trabecular bone and $R^2 = 0.91$ for cortical bone (Tassani et al., 2011). BV/TV is measured as the average value for the trabecular (13 ± 5%) and cortical (89 ± 11%) bone. Knowing the average ash density (trabecular 0.16 ± 0.05 g/cm^3, cortical 1.06 ± 0.14 g/cm^3) of the two types of tissue and their dry TW which is 3939 ± 471 g (906 ± 108 g trabecular and 3033 ± 363 g cortical) average from literature (Seale, 1959; Trotter, 1954), it is possible to compute total skeletal volume (T_sV, trabecular 5618.04 ± 1931.49 cm^3, cortical 2916.85 ± 513.27 cm^3) and total bone skeletal volume (B_sV, trabecular 722.56 ± 377.99 cm^3, cortical 2602.17 ± 553.50 cm^3).

The osteocyte (OCY) number estimated in a man less than 50 years old was expressed as a number for mm^2 of bone surface (trabecular 98.97 ± 1.24 cells/mm^2 cortical 56.34 ± 1.69 cells/mm^2) (Torres-Lagares et al., 2010). In order to compute a volumetric analysis assuming bi-dimensional cells distribution, a uniform distribution was hypothesized. Therefore, linear density was first obtained (trabecular 9.95 ± 0.09 cells/mm, cortical 7.51 ± 0.16 cells/mm) and finally the number of OCY for mm^3 was computed (trabecular 984.59 ± 21.37 cells/mm^3, cortical 422.89 ± 21.97 cells/mm^3). Consequently the OCY total numbers for whole bone tissue is $7.11 \pm 3.72 \times 10^8$, trabecular and $1.10 \pm 0.24 \times 10^9$, cortical.

Bone marrow total cell number

The number of bone marrow nucleated cells was 1.11×10^{10} (mean of 10 subjects, SD = 5.25, count in rib sections) or 1.04×10^{10} (mean of the same 10 subjects, SD = 3.36, count in crest aspirates) per body kilograms (Harrison, 1962). Using the average of the two values, we have an estimate of $7.53 \pm 2.18 \times 10^{11}$ cells for the reference weight of 70 kg (Irving, 2007).

Liver total cell number

Since hepatic volume is 1470 cm^3 (Irving, 2007), hepatocyte volume is 4900 μm^3 (Prothero, 1982) and the parenchimal cell percentage of the total liver is 80% (Borley, 2005b), we estimated the total hepatocyte cell number at 2.41×10^{11}. Total stellate cells (2.41×10^{10}) were calculated as 1/10 of hepatocyte cells (Geerts, 2001), while total Kupffer cells (9.63×10^{10}) were obtained as 4-times the total stellate cells (Dong et al., 2007). Therefore, the total cell number of the liver is 3.61×10^{11}.

Nervous system: Glial cells total number

Since the total glial cells in the nervous system are 10–50 times the neurons (Kandel et al., 2000; Standring et al., 2005) (for details, see Table B1 in Appendix B), their number is estimated as $3.00 \pm 0.66 \times 10^{12}$.

Pancreas: Islet total cell number

The total number of islet cells ($2.95 \pm 0.78 \times 10^9$) was calculated by multiplying the cell number per islet $1.56 \pm 0.02 \times 10^3$ (Pisania et al., 2010) and the mean number of islets in the human pancreas equal to $1.89 \pm 0.5 \times 10^6$ (Meier et al., 2008).

Skin: Epidermal and dermal total cell number

We found the density of corneocytes, epidermal nucleate cells, Langerhans cells and melanocytes in Hoath and Leahy (2003). We obtained the relative total cell number by dividing the standard human body surface (1.85 m^2) (Irving, 2007) by the specific density, to obtain an overall number of $1.76 \pm 0.44 \times 10^{11}$ cells. Epidermal Merkel cells resulted 3.62×10^9 as 0.20–5.00% compared to the total epidermal cells (Boulais & Misery, 2007). By dividing the human body surface by the specific densities of fibroblasts (Randolph & Simon, 1998) and mast cells (Grimbaldeston et al., 2000) we obtained an overall of $1.85 \pm 0.26 \times 10^{12}$ dermal cells. Therefore, the total dermal and epidermal cell number were found to be $2.03 \pm 0.30 \times 10^{12}$ (for details, see Appendix B, Table B1).

Small intestine: Jejunum and ileum enterocytes total number

To calculate the surface of the jejunum and the ileum of the small intestine (0.35 m^2), we considered them as two cylinders. Their lengths and diameters are 2.00 m and 2.50 cm (jejunum) and 3.00 m and 2.00 cm (ileum) (Borley, 2005c). Then, considering the *valvulae conniventes*, the total surface (1.04 m^2) increases 3-fold (Teodori 1987). By an exact graphyc reproduction (Cattaneo & Baratta, 1989), we estimated 1000 ± 3.40 cells *per villus*. Knowing that there are 13 ± 1 *villi*/mm^2, the total number of cells covering them is estimated at 1.35×10^{10}. The total number of cells covering the *cryptae* is $3.24 \pm 0.14 \times 10^9$ if we consider that they represent 12/50 of the *cryptae* covering each villus (Weiss & Greep, 1981; Cattaneo & Baratta, 1989) and that the estimated number of *cryptae* and *villi* is roughly the same (Cattaneo & Baratta, 1989). Therefore, the total enterocyte cell number was calculated to be $1.67 \pm 0.71 \times 10^{10}$.

Supradrenal gland total cell number

Normal mean adrenal gland volumes have been reported to be 5.70 (SD = 4.90 and 1.90 for the right and left gland, respectively) in a study that considered a group of 52 men with an average age of 48.4 years (Geraghty et al., 2004).

Cortex and medulla zones represent 90% and 10%, respectively, of the total gland volume. Reticularis, fasciculata and glomerularis zones represent 7%, 78% and 15%, respectively, of the cortex total volume (Martini 1994). Based on these data, we calculated the volumes of the reticularis

($0.36\,cm^3$), fasciculata ($4.00\,cm^3$), glomerularis ($0.77\,cm^3$) and medulla ($0.57\,cm^3$) zones. Cell volumes of the fasciculata, glomerularis and medulla zones were 1200, 870 and 970 μm^3, respectively (Bocian-Sobkowska et al., 1997). These data referred to new-born humans, but cell size does not change in this organ during lifetime (Staton et al., 2004). We calculated the radius (6.25 μm) of the reticularis zone cells, described as round shaped (Borley, 2005d), by a morphological analysis of a microimage (Hui et al., 2009) and then the volume ($1023\,\mu m^3$). Finally, by dividing the single zone into the specific cell type volumes, we obtained the mean of the total cell number of the single zones, reported in Table B1. The total cells of the two supradrenal glands are $1.03 \pm 0.16 \times 10^{10}$ (for details, see Appendix B, Table B1).

Vessels: Total endothelial cell number

The endothelium is composed of roughly 50–70 μm long and 10–30 μm wide cells, which cover the internal layer of the vessel (Félétou, 2011). To calculate the total endothelial cell number, we used two different approaches to estimate the vessel's internal surface and we then divided it for a single cell area. For systemic capillaries, superior and inferior *vena cava*, we considered their length as 8.00×10^9 cm (Loe & Edwards, 2004), 7.00 cm (Testut & Latarjet, 1959; Johnson et al., 2005), and 23.50 cm (Testut & Latarjet, 1959), respectively, and their average diameter as 7.50×10^{-4} (Loe & Edwards, 2004), 3.00 cm (Ganong, 2006; Germann & Stanfield, 2006), respectively. For the other vessels, we estimated their length by using the blood volume occupying the vessels, their diameter and assuming vessels were cylindrical (Ganong, 2006; Germann & Stanfield, 2006; Guyton & Hall, 2002; Mountcastle, 1980; Rhoodes & Planzer, 2004; Testut & Latarjet, 1959). The calculations led to a total number of $2.03 \pm 1.05 \times 10^{12}$ endothelial cells.

Current estimation of human total cell number

Our current estimation of human total cell number was calculated only on a variety of organs and cell types, as listed in Appendix B, Table B1. These partial data correspond to a total number of $3.72 \pm 0.81 \times 10^{13}$ (Figure 2). This number invalidates previous references, at least those indicating 10^{12} as the human total cell number and creates the starting point for a complete work that considers all the components of the human body.

Discussion

The estimation of a reference cell count for the human whole body was revealed to be not a trivial task. The results of our bibliographical research show considerable variation in terms of order of magnitude, which is not justifiable by inter-individual differences (see Appendix A, Table A1). Furthermore, we noted a consistent lack of citations of the original literature providing the pertinent data in printed books, online available books and websites. This is not totally unexpected, following our difficulties in retrieving articles discussing this specific issue by systematic searches in the PubMed database. General estimations based on mean cell volume or weight have not proved to be reliable, due to the high variability in cell size, volume and weight among different cell types and, in turn, due to high variability in cellularity for each cell type in the human organism.

The most reliable way to determine the human number of cells seems to be to sum the cell counts for individual organs. This also presents the advantage of providing valuable reference data for the study of each part of the human organism. Data about static, kinetic and pathological cell counts for organs and systems have been produced in the context of a wide variety of fields in biology and medicine. We have shown here that in many cases a precise count may be obtained from the literature. However, several problems have emerged while conducting this analysis. First, a major difficulty was estimation of the number of stromal and accessory cells in tissues and organs for which, instead, an accurate count of parenchymal cells has been performed. Secondly, it was difficult to obtain data for diffuse systems, e.g. vessels or nerves, both in their different section and in their global dimensions. In fact, a systematic survey of the whole biomedical literature is not a trivial exercise, because the pertinent data may have often have been disclosed in the context of a particular study.

Finally, different sources of variability in cell number may hamper estimation of a general reference number. Some organ or tissue cellularity varies in function of sex, age or evolutionary adaptation, not only because of a pathological condition. For instance, erythrocyte cell count differs in males and females as well as during pregnancy and in populations adapted to high-altitudes. However, this appears to be a minor problem because it is expected that these variations do not reach an order of magnitude and a mean estimation remains a reasonable end-point for this research. As reported in our current partial estimation of total cell number of the ''average man'' (Irving, 2007) we have an SD equal to 0.81×10^{13}, which is less than one order of magnitude.

We believe that knowledge of the cellularity of organs and total body would be not only be culturally important but it may also have biological and medical relevance, as demonstrated by some key applications described below.

A quantitative model of development should explain how it is possible to sustain a proliferation rate able to lead to a whole human organism starting from a single cell. The wide fields of cell growth and stem cell proliferation are potentially included in this problem. Modelling of whole organs or systems needs cell number data in order to produce affordable physiological views from the cells to the whole body. For example, a recent report of ion transport by pulmonary epithelia (Hollenhorst et al., 2011) cited quantitative available data about the alveolar surface and cell number (Crapo et al., 1982).

The determination of an organ or a tissue cell number is relevant in medicine for diagnostic and prognostic procedures. In fact, cellularity of biopsies leads to assessment of specific pathologic states due to cell number deregulation. For example, estimation of total number of hepatocytes in cirrhotic patients gave a mean value of 1.72×10^{11} (Imamura et al., 1991) in comparison with the mean value of 2.40×10^{11} reported by us for a healthy organ. In the case of blood cell counts, accessibility of tissue and standardization of methodology has led to quantitative and qualitative characterization of cell types and sub-types. In the same way, it would be important to know the cell number of other tissues and organs, along with the mechanisms regulating it, which could be crucial in understanding the biology and kinetics of cancer (Albanes & Winick, 1988), as well as the development of many other human diseases. For instance, dysregulation of organ size control has been implicated in diabetes and hypertrophy (Yang & Xu, 2011) and trisomy 21, where the relatively greater volume of the cell population of heart, skeletal muscle, liver and brain is only a partial compensation for the smaller cell number and not strong enough to produce normal organ mass (Landing & Shankle, 1995). Moreover, estimation of cellularity, organ and cell size of diseased organs would benefit modern strategies of human biological and disease research. In fact, the size of some organs can decrease as a result of malnutrition and disease during gestation or critical growth periods. For example, it has been proposed that the number of adult nephrons may be determined during renal development *in utero* and may be related to foetal malnutrition (Barker, 1995; Lackland, 2005). Finally, from an evolutionary point of view, data about cell number in different species could allow a measure of organism and organ complexity valuable in order to classify and understand inter-species variability at phenotypic level (Herculano-Houzel, 2011; Kothari et al., 1978). The formal description of cell types and number of different organisms could be valuable, in conjunction with other measures of complexity such as gene number and function (Szathmary et al., 2001), in order to develop better indices quantitatively related to the ''complexity'' of an organism (Grizzi & Chiriva-Internati, 2005).

Since we believe that the total human cell number may be obtained by summing all data related to the single organs and that the systematic work on each human section is complex and requires a meticulous work, we believe that this issue is an ideal candidate for a collaborative effort.

The problems outlined here could stimulate attainment and publication of useful data worldwide, in order to provide a systematic organ-by-organ view of human organism cellularity and a final detailed estimation of the total cell number in a standard human adult. Ideally, the last step could be preparation of a forum paper and an on-line database resource summarizing the complete picture by integrating data from different expert contributors. With this aim, we release our current estimations (Figure 2) so that they are available for correction, integration and completion from any interested researcher. These final results could be, in future developments, integrated into or related to formal description of anatomical entities provided by ongoing attempts to formalize anatomical data through the creation of ontologies (Baldock & Burger, 2005; Hayamizu et al., 2005).

Conclusions

We have shown the importance and the usefulness of searching for a reference number of the cells present in a human body, providing hypotheses for a solution of the problem. Our current estimation of 3.72×10^{13} cells for a variety of organs and cell types is higher than some estimations found in the literature. We believe that our initial reference table for cell number in the human body, when completed, possibly with a common effort, will have many useful applications in all biomedical fields needing quantitative measurement in order to build structural, functional, pathological and comparative models of human organs and of the whole body.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Appendix A

In order to find primary literature articles with information about the total cell number of a human organism, we systematically searched the PubMed database and the available printed and on line NCBI and Google books. Only data supported by a primary source are presented here.

Table A1. Estimations of human total cell number from bibliographical search.

Cell number	Reference	Source
10^{12}	Hanslmeier (2009)	Online book
10^{13}	Conlon & Raff (1999)	Original article (Baserga, 1985)*
	Boncinelli (2007)	Printed book
	Asimov (1963)	Printed book
	New Encyclopaedia Britannica (1976)	Printed book
	Van Amerongen et al. (1979)	Printed book
	Freitas (1999)	Printed book
	Baserga (1985)	Printed book
	Alberts et al. (2002)	Online book
	Cooper (2000)	Online book
	Griffiths et al. (2000)	Online book
	Baron (1996)	Online book
	Brown (2002)	Online book
	Griffiths et al. (1999)	Online book
	Goodsell (2010)	Online book
	Ratner & Bankman (2009)	Online book
	E-Notes Study Matter (2011)	Website (Asimov, 1963; New Encyclopaedia Britannica, 1976; Van Amerongen et al., 1979)†
	Bry et al. (1995)	Website (Freitas, 1999)†
10^{14}	Hood and Galas (2003)	Original article
	Strachan and Read (1999)	Printed book
	National Institutes of Health (2007)	Online book
	Lodish et al. (2000)	Online book
	Pittman (2011)	Online book
	Claybourne (2006)	Online book
	Samaras et al. (2007)	Online book
	The Carnegie Library of Pittsburgh (2011)	Online book
	Swenson (2000)	Online book
	Ehrenfeucht et al. (2004)	Online book
10^{16}	Zweiger (2002)	Printed book
	Frank (2007)	Online book

*References are cited by the specific ''Original article''.
†References are cited by the specific ''Website''.

Appendix B

We present here the results on the cell number of specific systems, organs or cell types obtained to date with our research. Some of the values were obtained directly from an in-depth bibliographical search, other data needed an integration of some or all methods described in the manuscript. In the ''SD'' column we indicate the standard deviation of the cell type calculations as obtained from available bibliographical data; we use ''NA'' to indicate that no data were available to calculate an error estimate. In the ''References'' column we indicate the bibliographical sources used for our estimations.

Table B1. Total cell number of organs or cell types.

Organ/system	Cell type	Mean total cell number	SD	References
Adipose tissue	Adipocytes	5.00×10^{10}	2.30×10^{10}	Spalding et al. (2008)*
Articular cartilages	Femoral cartilage cells	1.49×10^{8}	0.46×10^{8}	Baysal et al. (2004); Stockwell (1971)†
	Humeral head cartilage cells	1.23×10^{8}	0.35×10^{8}	Stockwell (1971); Vanwanseele et al. (2004)†
	Talus cartilage cells	8.06×10^{7}	1.56×10^{7}	Stockwell (1971); Millington et al. (2007)†
Biliary system	Biliary ducts epithelial cells	7.03×10^{7}	5.30×10^{7}	Bergman et al. (2004); Borley (2005a); Castelain er al. (1993); Khalil et al. (2005); Wolf & Scarbrough (2012)†
	Gallbladder epithelial cells	1.61×10^{8}	0.23×10^{8}	Bergman et al. (2004); Borley (2005a); Irving (2007); Wolf & Scarbrough (2012)†
	Gallbladder Interstitial Cajal-like cells	4.94×10^{5}	0.05×10^{5}	Hinescu et al. (2007); Irving (2007)†
	Gallbladder smooth myocytes	1.58×10^{9}	0.40×10^{9}	Irving (2007); Portincasa et al. (2004)†

(*continued*)

Table B1. Continued

Organ/system	Cell type	Mean total cell number	SD	References
	Gallbladder other stromal cells	8.48×10^{6}	0.09×10^{6}	Hinescu et al. (2007)†
Blood	Erythrocytes	2.63×10^{13}	0.51×10^{13}	Alberts et al. (2002); Loe & Edwards (2004); Young & Heath (2001)*
	Leucocytes	5.17×10^{10}	2.43×10^{10}	Alberts et al. (2002); Young & Heath (2001); Stock & Hoffman (2000)*
	Platelets	1.45×10^{12}	0.57×10^{12}	Alberts et al. (2002); Young & Heath (2001)*
Bone	Cortical osteocytes	1.10×10^{9}	0.24×10^{9}	Malluche & Faugere (1986); Seale (1959); Tassani et al. (2011); Trotter (1954); Torres-Lagares et al. (2010)†
	Trabecular osteocytes	7.11×10^{8}	3.72×10^{8}	Malluche & Faugere (1986); Seale (1959); Tassani et al. (2011); Trotter (1954); Torres-Lagares et al. (2010)†
Bone marrow	Nucleate cells	7.53×10^{11}	2.18×10^{11}	Harrison (1962)†
Heart	Connective tissue cells	4.00×10^{9}	NA	Adler & Costabel (1975)*
	Heart muscle cells	2.00×10^{9}	NA	Adler & Costabel (1975)*
Kidney	Glomerulus total cells	1.03×10^{10}	0.36×10^{10}	Steffes et al. (2001)*
Liver	Hepatocytes	2.41×10^{11}	NA	Borley (2005b); Irving (2007); Prothero (1982)†
	Kupffer cells	9.63×10^{10}	NA	Dong et al. (2007)†
	Stellate cells	2.41×10^{10}	NA	Geerts (2001)†
Lungs, bronchi, bronchioles	Alveolar cells (type I)	3.86×10^{10}	0.95×10^{10}	Crapo et al. (1982); Stone et al. (1992)*
	Alveolar cells (type II)	6.99×10^{10}	1.45×10^{10}	Crapo et al. (1982); Stone et al. (1992)*
	Alveolar macrophages	2.90×10^{10}	0.73×10^{10}	Crapo et al. (1982); Stone et al. (1992)*
	Basal cells	4.32×10^{9}	0.95×10^{9}	Mercer at al. (1994)*
	Ciliated cells	7.68×10^{9}	1.62×10^{9}	Mercer at al. (1994)*
	Endothelial cells	1.41×10^{11}	0.30×10^{11}	Crapo et al. (1982); Stone et al. (1992)*
	Goblet cells	1.74×10^{9}	0.51×10^{9}	Mercer at al. (1994)*
	Indeterminate bronchial/bronchiolar cells	3.30×10^{9}	1.00×10^{9}	Mercer at al. (1994)*
	Interstitial cells	1.37×10^{11}	0.16×10^{11}	Crapo et al. (1982); Stone et al. (1992)*
	Other bronchial/bronchiolar secretory cells	4.49×10^{8}	1.97×10^{8}	Mercer at al. (1994)*
	Preciliated cells	1.03×10^{9}	0.34×10^{9}	Mercer at al. (1994)*
Nervous system	Glial cells	3.00×10^{12}	0.66×10^{12}	Kandel et al. (2000); Standring et al. (2005)†
	Neurons	1.00×10^{11}	NA	Purves et al. (2001); Williams & Herrup (1988)*
Pancreas	Islet cells	2.95×10^{9}	0.78×10^{9}	Meier et al. (2008); Pisania et al. (2010)†
Skeletal muscle	Muscle fibers	2.50×10^{8}	NA	Howell & Fulton (1949)*
	Satellite cells	1.50×10^{10}	0.17×10^{10}	Morgan & Partridge (2003)*
Skin	Dermal fibroblasts	1.85×10^{12}	0.26×10^{12}	Irving (2007); Randolph & Simon (1998)†
	Dermal mast cells	4.81×10^{7}	2.82×10^{7}	Grimbaldeston et al. (2000); Irving (2007)†
	Epidermal corneocytes	3.29×10^{10}	0.47×10^{10}	Hoath & Leahy (2003); Irving (2007)†
	Epidermal nucleate cells	1.37×10^{11}	0.39×10^{11}	Hoath & Leahy (2003); Irving (2007)†
	Epidermal Langerhans cells	2.58×10^{9}	0.65×10^{9}	Hoath and Leahy (2003); Irving (2007)†
	Epidermal melanocytes	3.80×10^{9}	NA	Hoath & Leahy (2003); Irving (2007)†
	Epidermal Merkel cells	3.62×10^{9}	NA	Boulais & Misery (2007)†
Small intestine	Enterocytes	1.67×10^{10}	0.71×10^{10}	Borley (2005c); Cattaneo & Baratta (1989); Teodori (1987); Weiss & Greep (1981)†
Stomach	G-cells	1.04×10^{7}	0.30×10^{7}	Royston et al. (1978)*
	Parietal cells	1.09×10^{9}	0.08×10^{9}	Cox (1952); Naik et al. (1971)*
Supradrenal gland	Medullary cells	1.18×10^{9}	0.18×10^{9}	Bocian-Sobkowska et al. (1997); Geraghty et al. (2004); Martini (1994)†
	Zona fasciculata cells	6.67×10^{9}	1.02×10^{9}	Bocian-Sobkowska et al. (1997); Geraghty et al. (2004); Martini (1994)†
	Zona glomerularis cells	1.77×10^{9}	0.27×10^{9}	Bocian-Sobkowska et al. (1997); Geraghty et al. (2004); Martini (1994)†
	Zona reticularis cells	7.02×10^{9}	0.11×10^{9}	Bocian-Sobkowska et al. (1997); Geraghty et al. (2004); Hui et al. (2009); Martini (1994)†
Thyroid	Clear cells	8.70×10^{5}	NA	Gibson et al. (1982)*
	Follicular cells	1.00×10^{10}	NA	Gibson et al. (1982)*
Vessels	Endothelial cells	2.54×10^{12}	1.05×10^{12}	Félétou (2011); Ganong (2006); Germann & Stanfield (2006); Guyton & Hall (2002); Johnson et al. (2005); Loe & Edwards (2004); Mountcastle (1980); Rhoodes & Planzer (2004); Testut & Latarjet (1959)†

Bibliographical method is highlighted with *, while an integration of methods with †.