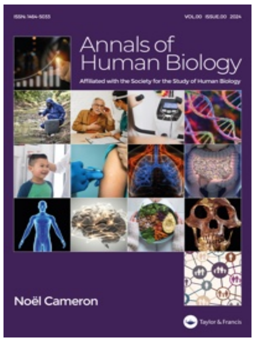

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Commentary to the article: an estimation of the number of cells in the human body

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In 2013, our article "An estimation of the number of cells in the human body" was published in the *Annals of Human Biology* (Bianconi et al. 2013). It was at the coffee machine in April 2007 at the University of Bologna, that one of us (PS) started an unpredicted discussion among people of the research group: "So to speak, how many cells make up a whole human organism?." It readily appeared that although this was a long-standing and basic topic in biology, there was no sound answer to this question. In addition, some consulted colleagues judged it as nonsense, arguing that the answer could greatly vary due to inter-individual variation. However, we reasoned that this variation might not be extreme because several medical tests are based on the consistency of cell counts (e.g. blood cells) or because in some types of variation, the enlargement of the cells may be more important than their increase in number. A search in many classical textbooks and in the biomedical literature revealed that the issue had never been addressed formally and the reported estimations, always without a primary source provided for the number and varying by up to 8 magnitude orders (from 10^{12} to 10^{20}), led to unaffordable conclusions. In the end, in 2011, we decided to start an innovative, collaborative effort to address the theoretical issue of determining the total number of cells in the standard human adult organism.

First, we attempted to use generalisations based on the average volume or weight of a human cell, thus obtaining estimations by taking into account the total volume or weight of a standard human body, respectively. However, it quickly became clear that the high variability in cell size, volume, and weight among different cell types as well as the different relative proportion of each cell type in the organism did not allow for any affordable conclusion. The only way to obtain a realistic conclusion seemed to be a systematic search in the literature for the count of cells in any human organ/system, integrated by various methods of counting for tissues for which no previous estimation was available, with a final summation of all the numbers. The task instilled some fear, but it was undertaken following some meetings where it was proposed that by subdividing the organs among us, with the valuable interdisciplinary contribution of several external colleagues for specific systems, there was a realistic hope to finish the calculation. The main part of the work, coordinated by one of us (SC), was assigned to Eva Bianconi, a PhD student at the time. Regular meetings were held to monitor each task's progress and to discuss the many unexpected issues emerging during the work. Some estimations were revealed to be highly complex due to the necessity of linking the estimations on a small, representative surface/volume to the total extension of the system in the standard reference body (e.g. endothelial cells in the vascular system or Schwann cells in the nerves). The most important part of the work was not only the final estimation for the whole organism (3.72×10^{13} cells, i.e. 37,000 billion cells, $\pm 0.81 \times 10^{13}$, i.e. $\pm 22\%$) but also the table providing the partial estimations systematically obtained for any human structure.

After around a year and a half of work, the manuscript was submitted and eventually accepted after a thorough revision, including a more detailed assessment of inter-individual variation for every single cell system, when available. Indeed, standard deviations of the human cell number were also about 10–30% of the mean value for many distinct organs/tissues. While we were convinced about the possible usefulness and application of the data, the reaction to the article's publication was nevertheless a surprise. We received many reprint requests, comments, and additional data from scientists and students from all over the world, which allowed us to bring several researchers in contact with each other on the topic. We had anticipated in the article several possible uses of the data in many fields of Human Biology and Medicine: modelling of whole organs or systems, baseline for diagnostic and prognostic procedures, biology and kinetics of normal or pathologic cell growth (or cell loss), comparative biology of organism and

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organ complexity to understand inter-species variability at phenotypic level, creation of ontologies of anatomical entities (Bianconi et al. 2013). Regarding developmental biology, the succession of only 45 mitotic cycles is sufficient to produce the estimated total amount of human cells starting from the first cell, the zygote. The most common chromosomal anomaly in humans, trisomy 21, can affect organ mass through a low organ cell number (Landing and Shankle 1995), in the context of a general hypoproliferative attitude likely to also be linked to the remarkable low incidence of solid cancer in Down syndrome. A precise estimate can also help quantify the processes of cellular senescence, apoptosis and regeneration in the context of ageing and understanding how these processes contribute to biological decline over time because the number of cells in the body is directly linked to them (Palmer 2024).

We are amazed to observe that our auspice about the meaning of our article as "a starting point for a common effort to complete the total calculation" has become a reality. In a few years, significant contributions to the estimation of the cell number of the total body as well as that of specific human organs or cell types have been presented, substantially confirming our global figure with some corrections, adjustments or data expansions for specific tissues/organs. Sender et al. (2016) have provided revised estimations for human cells, also pointing out that 90% of them are, in fact, non-nucleated cells (around 85% red blood cells and 5% platelets), so nucleated cells are the remaining 10% (3,300 billion). They also corrected the traditionally proposed quantitative relationship between human and bacterial cells residing in the body, showing that the number of bacteria is actually of the same order as the number of human cells (comment in Abbott 2016). Later, the same group focused on detailed quantitative profiling of human immune cells (Sender et al. 2023). Tomasetti and Vogelstein (2015) have used our results, along with other data (e.g. our estimate for glial cells was revised following Azevedo et al. 2009) to show a relationship in human organs between the estimated number of mitosis and the probability of developing cancer, integrating the estimation of the stem cell number in the organ model. This article has also initiated an intense scientific debate about the relative role of internal and external cancer risk factors. Recently, Ian Hatton et al. (2023) have analysed, in collaboration with Jeff Shander, who was carrying out extensive work on the subject as an independent researcher, the number of 400 cell types in the body across 60 tissues, producing a remarkable online atlas able to display cell number data interactively but also cell mass values for human tissues, organs and systems. They considered not only a representative male body but also female and child models and found unexpected mathematical patterns underlying cell size and quantity. This work outperforms our hope for "an online database resource summarising the complete picture by integrating data from different expert contributors," as we had written ten years before. The field remains active with many other general and specific contributions (e.g. Beraudi et al. 2016 for the number of osteocytes). Future research will likely integrate all available data on cell numbers using artificial intelligence to create increasingly reliable predictive models of cell and organ behaviour that can replicate human organs' cellular diversity and complexity (Kim et al. 2020).

It was really a long, interesting, and unforeseen journey for a job that started at the coffee machine. It shows that there are no trivial questions in research and that there is always a reward for being engaged in pursuing a solution for a problem we come across.

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