How Low Can You Go? The Numbers of Cells That Make Up Bodies: Large Numbers and Small Numbers

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This book deals with all sorts of numbers. Most of them have to do with the number of molecules in cells, with small numbers taking center stage. However, it may be difficult to understand how small these numbers are. To get a better sense of these numbers, we will try to think about the numbers of cells that make up the bodies of various creatures, great and small. Even if you know that the human body is made up of an incredibly large number of cells, you would have to be quite well informed to imagine what a large number it is. Even if you know that organisms much more primitive than humans are made up of very small numbers of cells, there is no way you would know the exact number. Here, through a conversation between parents and their child at the dinner table, we will think about how many or how few cells are in various organisms by comparing their numbers to grains of rice in a bowl.

(At the dinner table)
Son: More rice please.
Mom: How much?
Son: A regular amount.
Mom: Okay, is this enough?
Son: Is that it? That's not much.
Mom: You don't look happy. If you're not happy, then tell me exactly how much you want!
Dad: Don't get into a fight over portions of rice. Everyone has different ideas of how much is a lot or a little.
Son: Okay, then how should I say it?
Dad: How about by weight?
Son: Come on, I have no idea how much a bowl of rice weighs.
Mom: And I am pretty sure I don't want to bother with a scale just to serve rice.

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Dad: Then how about saying how many grains of rice you want?

Mom/Son: That's an even bigger pain!

Dad: Hey now, numbers are really important. You know human bodies are made up of cells, right?

Son: Duh, everyone knows that. Muscles and nerves and stuff, it's all cells, isn't it?

Dad: Then, do you know how many cells make up the human body?

Son: I've heard the number before. It's 60 trillion, isn't it?

Dad: We thought for a long time that it was 60 trillion, but that number is out of date. A study done in 2013 showed it's only a little more than half that—about 37 trillion [1].

Son: Huh. A trillion is such a big number that I can't even imagine it, but when scientists actually sat down and figured it out, it turned out to be only about half of what they said before? They really messed up. But how did they count such a big number?

Dad: If you counted them one by one like grains of rice, at a rate of one per second, it would take 1.1 million years to count out. Even if you counted the cells at a pace of 580 per second, it would still take 2,000 years. That gives you an idea of what a ridiculously big number 37 trillion is.

Son: So, you're saying they didn't count 37 trillion cells one by one?

Dad: That's right. Basically, they figured out the densities of cells in the heart, the brain, and every other organ, and then did some multiplications to arrive at about that number. By the way, they got the former number of 60 trillion with a rough calculation in which they considered the standard weight of a cell as 1 ng and divided 60 kg, the standard weight of a person, by 1 ng. When they redid detailed calculations for each organ, they arrived at 37 trillion.

Son: So you're saying that 37 trillion is still vague, and that they might get a different number if they counted more accurately? There are lots of numbers in the world, and some of them may be arbitrary. I feel like I can't believe anything.

Dad: You're totally right. But if lots of different studies independently estimate the total number of cells in the human body in the tens of trillions, at least the order of magnitude shouldn't change. It's really hard to count anything accurately. It's a challenging issue for science. I'm interested to see what the estimate for the number of cells in a human will be in 10 years. By the way, speaking of numbers, do you know how many types of cells there are in the human body?

Son: By "types of cells", do you mean muscles and nerves and stuff?

Dad: Right, right. Even with broad classifications, the human body has about 300 different types of cells. That's a tiny number compared to 37 trillion, but you can probably only think of maybe 10 types of cells, such as nerve, muscle, and blood cells. So you realize that there are so very many different kinds of cells. If you look at the 37 trillion cells in the body by type, the most common type of cell is red blood cells. There are a huge number of them — 26 trillion.

Son: So 2/3 of the human body is red blood cells? What's the least common type of cell?

Dad: The least common are cells that are the precursors of eggs. In women past puberty, it's said there are about 200,000 egg cells.

Son: 200,000, huh? That's way smaller than a trillion, but it's still a pretty big number. It seems that lots of cells are needed to make up the human body, but what's the smallest number of cell types the body needs, and how many cells for each type?

Dad: It sounds like you're more interested in small numbers. In that case, a roundworm might be a good example.

Son: Roundworm? Is that some kind of bug?

Dad: It's not a bug. It's a type of animal called a nematode that lives in soil and eats bacteria. It's shaped like a thin tube. There's a species of nematode called *Caenorhabditis elegans* that's about 1 mm long and has a transparent body. It's been studied thoroughly, so we know exactly how many cells make up its body. A male has 1,031 cells and a hermaphrodite, 959 cells.

Son: Huh? You had been saying "about" until just now, but you're suddenly totally confident about these numbers.

Dad: Like humans and other animals, *C. elegans* starts as a single fertilized egg that divides and divides to form all the cells that make up its body, but *C. elegans* is surprisingly precise in when, where, and how many times its cells divide. Every individual organism has the exact same number of cells.

Son: It's more like a robot than a living thing.

Dad: Yeah, it really is like a robot the way its cells divide with almost no errors. All of its 1,000 or so cells have names are classified into 17 types. The most common type of cell is nerve cells, with 302 of them. It has 56 glial cells, which are related to nerve cells, and 95 muscle cells. On the other end of the spectrum, the least common type of cell is reproductive cells—it has only 2 of them. By the way, research on *C. elegans* led to the discovery of the mechanism by which its cells commit suicide. It was such a big discovery that it was awarded the Nobel Prize.

Son: I guess even organisms I've never heard of can be useful. So, if you were going to try to make a roundworm by collecting one of every cell type, you'd need at least 17 cells, then.

Dad: There's no way it could live with only one nerve cell and one muscle cell, but how many would you need? That's a good question. How many nerve cells do you need for intelligence to form? How far can you reduce the number of red blood cells without causing anemia? How many of which types of cells have to be assembled for the functions of an organism to emerge? They're all important questions.

Son: Then, just how many cells does an organism need to live?

Dad: The minimum is 1, of course. I'm sure you've heard of unicellular organisms. You know that *Escherichia coli* and yeast and similar organisms can live as a single cell, right?

Son: But bacteria and humans are completely different, aren't they?

Dad: Indeed they are. The opposite of unicellular is multicellular. Let's think about the multicellular organism with the fewest cells. For starters, a multicellular system involves multiple cells with different roles assembling and then working

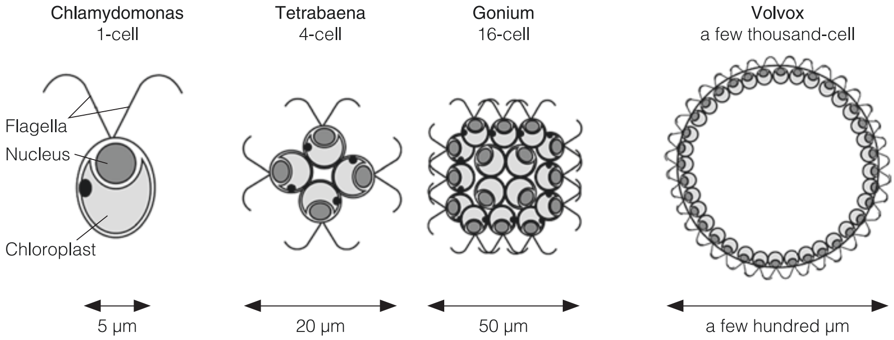

Fig. 1 The cell number variation of green algae

together to maintain life. In other words, a multicellular organism can't live if you break up its cells into individual units. Unlike a unicellular organism, you can't just assemble a bunch of the same type of cells and call it a multicellular organism. As for the organism with a multicellular system that's made of the smallest number of cells, have you ever heard of *Volvox*?

Son: I think it was in my high school biology textbook.

Dad: *Volvox* is a ball-shaped green algae that's about 1/10 of a millimeter in size, lives in places such as rice paddies, and is made up of thousands of small cells with two hairs called flagella (Fig. 1). Each individual cell closely resembles a unicellular organism called *Chlamydomonas*, but *Volvox* can't live if its cells are broken up, so it's classified as a multicellular organism.

Son: Thousands of cells? That's more than a roundworm has, so what's so interesting about that?

Dad: I'm just getting to the interesting part. There are relatives of *Volvox* that are made up of cells that resemble *Chlamydomonas*, just like *Volvox* is. There's *Pleodorina*, which is made of 128 or 64 cells; *Eudorina*, which has 32 cells; and *Gonium*, which has 16 cells (Fig. 1).

Son: The number of cells always doubles. It's like they're showing evolution in the way the number of cells changes.

Dad: Exactly. All of these relatives of *Volvox* are thought to have evolved from unicellular *Chlamydomonas*. If the number of cells that makes up the body doubles, then it seems that there should be a multicellular organism made up of as few as 2 cells, right? But no such organism has been discovered. *Tetrabaena socialis* is considered to be the multicellular organism made up of the smallest number of cells, with 4 cells (Fig. 1).

Son: Only 4 cells? That's a really small number. It can't live if the 4 cells are broken up, but it can if they work together. It really does seem like life.

Dad: If you're trying to understand what exactly life is like, focusing on the number of cells is a good place to start. Actually, lots of scientists have studied how many cells it takes for new functions to emerge.

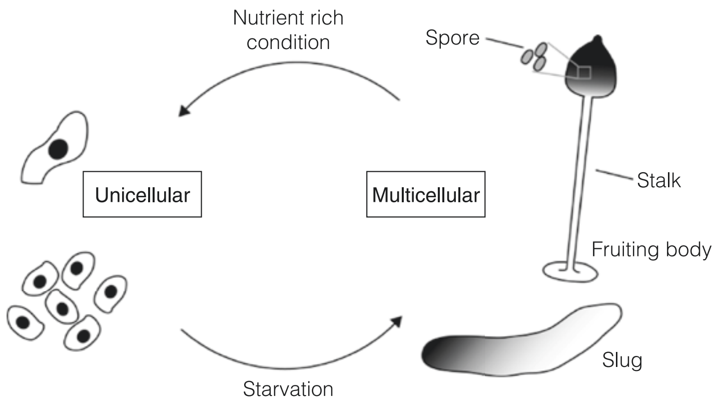

Fig. 2 Life cycle of *D. discoideum D. discoideum* cells switch the life style from unicellular to multicellular mode. Cells actively proliferate under the nutrient rich condition. Upon starvation, cells aggregate and develop into the multicellular slug and fruiting body

Son: So it's not just about counting cells, it's about finding out the minimum number of cells it takes for coordination to emerge, huh? Then if you could manipulate cell numbers at will, it seems that you could learn all sorts of things.

Dad: Unfortunately, for roundworms and almost all other animals, the number of cells that makes up the body is set in stone, so it's hard to manipulate cell numbers. But if you think in terms of an organism that can freely change its number of cells, you should look at a cellular slime mold, which can live as a unicellular and a multicellular organism. Cellular slime molds are very accessible organisms that can be found under piles of dead leaves. When they eat things like bacteria and grow, they act as unicellular organisms; but when they run out of sustenance, lots of cells congregate and form multicellular structures called fruiting bodies, which are shaped like mushrooms (Fig. 2).

Son: No kidding. It's like they evolve from unicellular to multicellular organisms as they live.

Dad: Right. As a survival strategy, it joins with others of its kind to become multicellular, and it produces spores that can withstand desiccation and starvation. When it does, the stalk cells die and leave only a husk, lifting the spores off of the ground to help them be scattered in a new environment. Basically, even though a cellular slime mold is essentially a group of identical cells, some of the cells become spores in order to leave offspring, while the rest of the cells sacrifice themselves for the sake of the spores, their children. Because of this social nature, cellular slime molds are also called social amoebae.

Son: So, there's a spirit of cooperation even in cellular society.

Dad: By the way, these social amoebae have a unique trait: they can form multicellular structures of any size. But the size of a newborn animal is pretty much set. Human babies all weigh about 3,000 g when they're born; a baby is never born with 10 times the normal weight or height, right? But social amoebae can produce

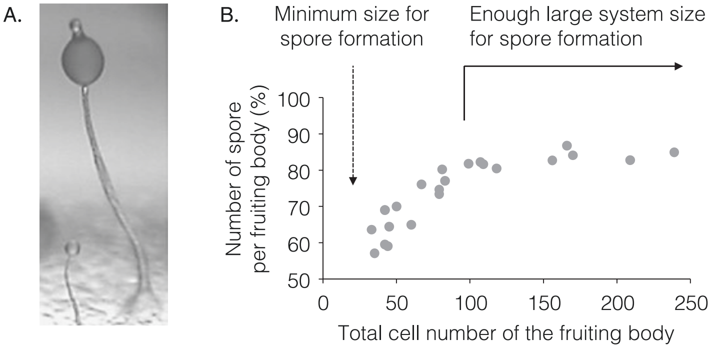

Fig. 3 Spore formation depends on the size of fruiting body. (**a**) Variation in the size of fruiting body. Large and small ones consist of ~10,000 and ~100 cells, respectively. (**b**) Spore forming ability of the fruiting body with different size. While 80% of cells differentiated into the spore in a large fruiting body (>100 cells), the percentage of spore cells decreased in the small fruiting body. Spore-less stalk consisting of as few as 18 cells suggested that 19 cells would be essential for the spore differentiation

spores from a massive size of 10,000 cells to a small size of hundreds of cells. And when they produce spores, the ratio of spores to stalks stays constant at 4:1. Science pretty much understands the mechanism behind accurately reproducing bodies of the same size but knows almost nothing about how cellular slime molds freely produce bodies 100 times their own size with the same pattern.

Son: It's normal for adults and children to be of different sizes, but I guess it's not normal for body sizes to be different at birth.

Dad: Social amoebae aren't born from eggs, but for now, it's okay to imagine they are. If you use these social amoebae, you can examine how few cells can make up a proper multicellular body. I'll tell you the answer first. If the social amoeba has at least 100 cells, it can produce spores with a 4:1 ratio of spores to stalks, but the fewer cells there are, the smaller the spore ratio gets; eventually, you would end up with an incredibly small fruiting body of 3 spores supported by 16 stalk cells. This means that a social amoeba needs to have at least 19 cells to divide into two types of cells (Fig. 3).

Son: What happens if it has fewer than 19 cells?

Dad: Then, it would end up forming just a stalk with no spores. Basically, all the cells would end up sacrificing themselves, and the social amoeba wouldn't be able to produce spores. So, in effect, the society would die out.

Son: So I guess that means that 19 cells is the borderline between self-interest and self-sacrifice.

Dad: Human society is like that too. There are plenty of instances in which something that would be hard for one person to accomplish alone can be done if lots of people get together. In the same way, we should be able to learn much more about the mechanism of cooperation among cells and the proteins that make them up by counting them accurately and manipulating their numbers at will.

Son: I'm really psyched about numbers now! I'm going to go count those grains of rice.

(The next morning)

Son: There were a total of 2,876 grains of rice in the bowl. It took me 3 hours to count them. It was hard, but now I feel like I have a more tangible grasp of numbers. But now, I don't want to look at rice again for a while, so I'll have bread for breakfast.

Dad: Okay, so do you know how many grains of wheat there are in a slice of bread?

Son: I get it! Numbers are important. Enough already… (sob)

Reference

1. Bianconi, E., Piovesan, A., et al. (2013). An estimation of the number of cells in the human body. *Annals of Human Biology, 40*(6), 463–471.