Physical Paradigm of Life as a Generalization of Biochemical Conception. A Physical Law Governing Life Origin and Development

Yuri K. Shestopaloff

Abstract

The present view of biological phenomena is based on a biomolecular paradigm that development of living organisms is entirely defined by information stored in a molecular form as some genetic code. However, new facts and discoveries indicate that biological phenomena cannot be reduced to a biomolecular realm alone, but are also governed by mechanisms of other nature. These mechanisms, acting in tight cooperation with biochemical mechanisms, define life cycles of individual organisms, and, through this, the origin and evolution of the living world. Here, we present such a physical mechanism (General growth law), which represents a new physical law of nature. It acts at cellular, organ, system and whole organism scale levels, directing growth and reproduction together with biomolecular mechanisms by imposing uniquely defined constraints on distribution of nutrients between biomass production and maintenance, thus defining the composition of biochemical reactions, their change and irreversibility during the organismal life cycle. Mathematically, this law is represented by the growth equation. Using this equation, we introduce growth models and explain division mechanisms for unicellular organisms. High adequacy of obtained results to experiments proves validity of the General growth law and of the new physical paradigm of Life based on this law.

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PHYSICAL PARADIGM OF LIFE AS A GENERALIZATION OF BIOCHEMICAL CONCEPTION. A PHYSICAL LAW GOVERNING LIFE ORIGIN AND DEVELOPMENT

YURI K. SHESTOPALOFF

Preamble: Background and general context of the study

This is by far my *the most significant* scientific contribution (among over 120 articles and 14 books I published). It presents a genuine *fundamental physical law of Nature*, the General growth law, which I discovered, and published the first paper about in 2008. Since then, I accumulated lots of proofs of validity of this discovery. The problem with the notion of a law in the present science is that many people do not see the difference between the *real law* of Nature, like the Second law of Mechanics, and some *regularity*, often found through ad hoc technical means, such as regression analysis. An example of such a "law" can be the so called Kleiber's law, which, in fact, is the result of a regression analysis of experimental data, claiming a particular value of a metabolic allometric scaling exponent. Unlike the Second law of Mechanics, it gives no explanation of the observed phenomenon, nor it names parameters this exponent depends upon (in fact, even the declared value (of 3/4) is not constant but varies a lot depending on many circumstances). The real law of Nature produces the required quantitative descriptions from its mathematical formulation, given input parameters (like finding a mathematical description of a trajectory of a thrown stone using mathematical formulation of the Second law of Mechanics).

Another extreme approach, to a certain degree the opposite one, is when every quantitative description of natural phenomenon is considered only as a *model*. This view effectively eliminates the notion of a physical law as such. Therefore, we have no more Ohm's law, Newton's laws of Mechanics (which, no doubt, are real fundamental laws of Nature), but only Ohm's model and Newton's model, but that is ridiculous.

In accordance with the philosophical principles of validation of scientific knowledge, one of the most important confirmations of validity of a more general theory (or a law) is that in particular cases it should converge to the earlier discovered results, which were proved to be true. In case of the General growth law, when its mathematical formulation, the growth equation, is applied to particular growth scenarios, such as growth of certain cells, it produces less general known results, like logistic curves. This class of curves, defined by logistic equation, is presently used on ad hoc basis for modeling growth phenomena. However, the growth equation produces such curves *naturally*, given input parameters, without the need to use arbitrary coefficients having no clear physical meaning. There is an ultimately beautiful harmony in observing how the general growth equation easily, elegantly and naturally produces the whole class of results, each of which, if obtained separately, would be considered as a miraculous revelation of Nature's secrets.

Besides these proofs, there are many other results of different level of generality, which also confirm validity of the General growth law. Of course, as usually this happens in science, I cannot publish this article *for years*. There are several reasons for this very much expected situation, of which one is that many people can understand *incremental* novelty, while the discovery of the General growth law is a *heuristic* one. Understanding heuristic discoveries requires a quite different mindset than the conventional one. Heuristic discovery introduces an entirely new area, unknown *terra incognita*. Heuristic knowledge cannot be *derived*; because, by and large, there is nothing it could be derived from. The gap between the prior knowledge and the new heuristic one is too wide to just step it over, but requires a really long jump in conclusions, coherently incorporating many diverse inputs. With regard to the General growth law, the situation is even much worse than that, since it contradicts the main modern biological paradigm that the story of life is created by biomolecular mechanisms. This view is true, but only in part. The other part is composed of mechanisms, acting (in inherent cooperation with biomolecular mechanisms) at higher than molecular scale levels, and the General growth law is one of the major players in this Life game. Understanding the General growth law is moderately difficult. Accepting it is the biggest challenge.

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Annotation. The present view of biological phenomena is based on a biomolecular paradigm that development of living organisms is *entirely* defined by *information* stored in a molecular form as some genetic *code*. However, new facts and discoveries indicate that biological phenomena cannot be reduced to a biomolecular realm alone, but are also governed by mechanisms of other nature. These mechanisms, acting in tight cooperation with biochemical mechanisms, define life cycles of individual organisms, and, through this, the origin and evolution of the living world. Here, we present such a *physical* mechanism (General growth law), which represents a new *physical* law of nature. It acts at cellular, organ, system and whole organism scale levels, directing growth and reproduction together with biomolecular mechanisms by imposing uniquely defined constraints on distribution of nutrients between biomass production and maintenance, thus defining the composition of biochemical reactions, their change and irreversibility during the organismal life cycle. Mathematically, this law is represented by the growth equation. Using this equation, we introduce growth models and explain division mechanisms for unicellular organisms. High adequacy of obtained results to experiments proves validity of the General growth law and of the new *physical* paradigm of Life based on this law.

Keywords: General growth law; biological paradigm; physical paradigm of Life, division mechanisms; cellular cycle control.

Table of contents

1. Introduction

1.1. *Biomolecular paradigm of life origin and development. Alternative concepts*

The founding of a biomolecular paradigm in biology is often attributed to famous Physicist E. Schrödinger[1] and his public lectures delivered in 1943. He was probably the first who pronounced the words '*information*' and '*code*' relative to organismal atomic structures, although not exactly in such determinate meaning, which was later canonized in textbooks, such as in Ref.2. What he actually said, was "In calling the structure of the chromosome fibres a code script we mean that the all penetrating mind, once conceived by Laplace, to which every causal connection lay immediately open, could tell from their structure whether the egg would develop, under suitable conditions, into a black cock or into a speckled hen, into a fly or a maize plant, a rhododendron, a beetle, a mouse or a woman. To which we may add, that the appearances of the egg cells are very often remarkably similar; and even when they are not, as in the case of the comparatively gigantic eggs of birds and reptiles, the difference is not been so much the relevant structures". Compare the meaning of this quote to its transformed version in Ref. 2: "The cell-cycle control system is based on a connected series of biochemical switches, each of which initiates a specific cell-cycle event. This system of switches possesses many important engineering features that increase the accuracy and reliability of cell-cycle progression. First, the switches are generally *binary* (on/off) and launch events in a complete irreversible fashion". Even though the concept of a cell-cycle control presented in the second quote follows from the Schrödinger's thought, the distance is noticeable. However, what is important to understand, both are mere *hypotheses*, and both are not invincible from the known facts and consistent logic - for instance, they do not provide an answer to the first question coming to mind - *which* mechanism triggered *the very first* switch (or the very first switches?), not to say about myriads of other principal questions immediately arising in the inquisitive mind.

The Schrödinger's problem was that he interpreted his *assumption* as a proven theory, while it was not. He says: "For it is simply *a fact of observation* that the guiding principle in every cell is embodied in a single atomic association existing only one copy (or sometimes two) - and a fact of observation that it may results in producing events which are a paragon of orderliness. Whether we find it astonishing or whether we find it quite plausible that a small but highly organized group of atoms be capable of acting in this manner, *the situation is unprecedented, it is unknown anywhere else except in living matter*. The physicist and the chemist, investigating inanimate matter, *have never witnessed phenomena which they had to interpret in this way*." (Italics is mine.)

In fact, the aforementioned observed order could be well guided by other mechanisms, why not? The fact that we observe the visible implementation of some effect does not mean that this implementation is the primary cause; it very well could be an intermediate instrument in the hands of the real, primary cause, of which we just are not aware. Unfortunately, Schrödinger disregards such a possibility, without reasons. He declares the living matter a special case, ignoring the previous scientific human experience, and in particular the one acquired in physics and chemistry. One of the main pillars of this experience is that matter is governed by hierarchical structure of different laws of nature cooperatively acting *at different scale levels*.

Cutting ties with a macro world and descending into a molecular realm, Schrödinger still adheres to physical principles: "We must be prepared to find a new type of physical law prevailing in it. Or are we to term it a non-physical, not to say a super-physical, law? No. I do not think that. For the new principle that is involved is a genuinely physical one: it is, in my opinion, nothing else than the principle of quantum theory over again." Here, he contradicts himself: if the principle is on par in generality with quantum theory, then it should be applied to *all* matter, but he already detached the living matter from the rest.

On the other hand, Schrödinger does not exclude entirely that Life is governed by some more conventional law: "We seem to arrive at the ridiculous conclusion that the clue to the understanding of life is that it is based on a pure mechanism, a 'clock-work' in the sense of Planck's paper, The conclusion is not ridiculous and is, in my opinion, not entirely wrong, but it has to be taken 'with a very big grain of salt." He does not explain, why "a very big grain of salt" has to be taken, but it is clear from his paper that the only "rationale" behind this statement is that he separated living matter from the rest of matter, drawing the borderline even for the fundamental properties inherent to both living and "inanimate" matter. In any case, even such a strong proponent of a biomolecular paradigm of life origin and development - and, to some extent, its founder - could not entirely dismiss the possibility that Life is governed by some 'ordinary' *physical* law. In fact, such a physical law was discovered and will be presented in this article. This law de facto introduces a new more coherent and realistic paradigm of life development as a phenomenon, universally governed by cooperative workings of a physical law and biochemical mechanisms, with a leading role of the physical law imposing constraints biochemical mechanisms have to comply with. This cooperative working is not on the surface, its implementation is often complex, with feedback loops and lots of evolutionary adaptations affected by numerous and ever changing factors, but it's there, at the core of everything what is happening with living matter. One can use the same elevator for years without ever thinking what mechanism produces its motion, just accepting the elevator's function as a matter of fact. In the same way, one can see dynamics of biochemical reactions in a living organism without ever thinking *why* composition of biochemical reaction changes, what "engine" propels such ordered changes? The current answer in biology is 'genetic code', which nobody really knows, what does it mean - successive chains of biochemical reactions, epigenetic mechanisms and its changes, certain sequences in DNA, or all these things together, or maybe something else?

In this paper, we present a physical law, governing growth and reproduction at a cellular, organ, system and whole organism levels, and consider its application to modeling growth of unicellular organisms, and understanding their division mechanisms. Knowledge of why and how cells grow and reproduce, what kind of fundamental mechanisms so universally and persistently govern cellular processes, is of great importance both for the practical needs (medical, crop production, growth and productivity of domesticated animals, biotechnological, etc.) and scientific studies opening new areas for practical applications and explorations. However, in our case, the chore is even more grandeur - we have to introduce a more general new *biological paradigm* - a *physical* paradigm of Life, which, at the same time, includes all previously discovered and yet unknown biochemical mechanisms as its inherent part. This new paradigm will change one day the ways biology and all related disciplines develop. However, will the discovery remain known till those remote days, or will it disappear in vain and somebody rediscover it again, nobody knows.

1.2. *Studies of cellular growth and division mechanisms*

Most studies on the subject of cell growth and division explore biochemical mechanisms, representing chains of biochemical reactions, implementing transitions through successive growth and division phases. Examples can be Refs. 3-8.

Another direction of research was inspired by ideas to find systemic level mechanisms responsible for the cell growth and division. In his review[9], Mitchison says with regret: "It would be satisfying if the main parameters of cell cycle growth had been established in the earlier work. Not surprisingly, however, there were still major uncertainties left when people moved from this field to the reductionist approaches of molecular biology." Review Ref. 7 also accentuates specific properties of cellular growth and reproduction, which are unlikely to be resolved exclusively at a biomolecular level.

Many concepts with regard to general growth and division mechanisms were proposed. Such are the "sizing" and "timing" hypotheses, claiming accordingly the priority of a cell size and of a certain time as primary factors defining the cell cycle progression. P. Fantes[10] found experimentally that actually both "sizing" and "timing" homeostasis takes place. Note, in most instances, it is implicitly assumed that some biochemical mechanisms are at the core of such hypothetical systemic mechanisms, sensing the cell size, or time, or other cellular macro-characteristics.

"Sizing" concept is represented by different, often conflicting, views. For instance, in Refs. 11, 12, the authors use an absolute size. Ref. 13 suggests that the cell cycle is driven by the "constant size extension". For the bacteria *Escherichia coli* and *Caulobacter crescentus* they infer that these bacteria "achieve cell size homeostasis by growing on average the same amount between divisions, irrespective of cell length at birth". The "constant size extension", in fact, is not constant, but noticeably varies. The authors acknowledge: "The constant extension mechanism does not need to be precise, with experimental CVΔL of 19–26%.", where 'CV' means standard deviation/mean.

Ref. 14 proposed complex relationship between the size and cell cycle in the form of a "noisy map". They say: "noisy linear map implements a negative feedback on cell-size control: a cell with a larger initial size tends to divide earlier, whereas one with a smaller initial size tends to divide later." However, their inference does not agree with the "constant size extension" suggestion; for instance, such are the results shown in Extended Data Figures 2 and 10 in Ref. 13.

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In Ref. 15, the authors came to a conclusion that "The size of the cell at division is proportional to the initial size of the cell", studying *Caulobacter crescentus* cells. This result contradicts both the "noise map" and the "constant size extension" hypotheses.

Authors of Ref. 16 agree with none of the above propositions, but think that, at least for *E. coli*, "size control is effected by changes in the doubling time, rather than in the single-cell elongation rate" and "the current size is not the only variable controlling cell division, but the time spent in the cell cycle appears to play a role".

In other words, neither the "sizing" hypotheses, nor the "timing" ones could provide convincing proofs of universality of found relationships and explain all known observational facts related to a cell cycle control. However, the cited and many other works agree that there should be such controlling mechanisms, of which the experimentally obtained stable cell size distributions (including the ones in the aforementioned works) could be considered as indirect evidence. On the other hand, the implicit underlying assumption remains the same - at the core, these "laws" are defined by some biomolecular mechanisms.

1.2.1. *Studies of growth mechanisms acting at higher than molecular level*

Note that the general growth law, which is considered in this article, explains results of *all* models and "laws" reviewed in this section, which present only certain aspects of the growth and division phenomena, at certain conditions for particular organisms. From the perspective of scientific methodology, the laws of Nature do not work in such a simple way as the "sizing" or "timing" hypotheses assume. Fundamental laws of Nature, at the least, are:

(1) Universal;

(2) Optimal; in the sense that from all possibilities their description requires the least possible number, and of the most fundamental, values, which all have to interrelate; if this is a mathematical description, then all these fundamental parameters have about equally weighed and indispensable and irreplaceable roles;

(3) Provide the most possible stability of described phenomena without jeopardizing the scope of applicability, which has to include all such phenomena;

(4) Include parameters, which are both necessary and sufficient for the description of any phenomenon belonging to the problem domain;

(5) In the limits, they have to convert to more particular, earlier confirmed and cross validated knowledge, mechanisms and laws.

The most known and illustrative examples of such laws of Nature, exhibiting these characteristics, are the laws of classical mechanics, electricity, thermodynamics.

Prominent scholar D'Arcy W. Thompson, in his prolific book "On Growth and Form"[17] presents considerations why there should be mechanisms, acting at higher than molecular levels, responsible for the growth of living organisms. A book "Life's other secret"[18] presents similar ideas and supporting proofs that the true "Secret of Life" is not in biomolecular mechanisms, and DNA in particular (it also narrates that Crick, the discoverer of the double helix structure of DNA, allegedly once said in a pub, that "DNA is not the secret of Life!").

In fact, such a *physical* mechanism was discovered ten years ago and comprehensively verified by experiments and predictions, made on its basis, which later found experimental proofs. This mechanism, called the General growth law, indeed, works at higher than molecular levels, and, based on supporting experimental data, appears to be an influential player in the growth and reproduction of cells[19-21], tissues, organs[22,23] and whole multicellular organisms. The General growth law (a) *without a single exception* reconciles *all* known facts about cellular growth and division; (b) predicts certain growth and reproduction effects, which found experimental confirmations; (c) is seamlessly integrated with a cellular biochemical machinery; in fact, both work in tight cooperation, with the leading role of the General growth law imposing macro constraints the biomolecular machinery has to comply with.

2. Forces Shaping Biological Phenomena

The earlier discussed biochemical paradigm of Life assumes that life cycle of living organisms is coded in genes in the sense of successive binary switches (recall a quote from Ref. 2 in the Introduction). The known workings of biochemical mechanisms, on the other hand, by no means exclude mechanisms of other nature, which could act at other scale levels, but rather appeal for some "external" management from higher scale levels. Such an arrangement is inherent to a physical world, when a multitude of different mechanisms, acting at different scale levels, shapes the same phenomenon. In this regard, living organisms rather represent an uninterrupted continuation of an inorganic world (such, Tobacco virus self-assembles in the presence of certain inorganic substances[18]). The book by Lane[24] presents hypotheses how inorganic matter could eventually produce living organisms in hydrothermal vents. By and large, there are no fundamental reasons that such a multifaceted phenomenon as Life, including the origin, life cycle and evolution of living species, should be defined entirely and exclusively by biomolecular mechanisms alone. It is intuitively clear that the *objective* causes which led to appearance of living organisms existed *before* the biochemical mechanisms, and DNA in particular, were created. These "founding" mechanisms belong to an inorganic world. It is much due to *their* action that living organisms originated and progressed through their evolutionary paths. Then, why the action of all these forces belonging to inorganic world had to stop after the Life origin? For instance, DNA of an evolutionarily developed single cell could not contain everything needed for a multicellular structure, like a balanced growth of organs and systems in multicellular organisms. There should be other forces of nature, which took care of such tasks at appropriate scale levels - besides the workings of biomolecular machinery.

The well defined set of cell shapes, how did it happen? Was it only a random play of chemical reactions? Very unlikely, given that the optimal functionality of microbes and other microorganisms is supported, besides other macro-characteristics, also by certain geometrical shapes, like rods, spheres. What about the level of tissues, organs, systems, whole multicellular organisms? Should we still assume that these multi-scale constructions are managed from a molecular level? Maybe the shape of living organisms is also defined by some unknown mechanisms at higher than molecular level, in the same way as motion of planets, composed of innumerable number of molecules, is defined by Newtonian mechanics? Why not? This is how the physical world we know is arranged, and the living creatures present an inherent part of the *physical* world. It is just the *belief* in ultimate power of biomolecular mechanisms alone, which separates us from such a step to a more multidimensional and comprehensive understanding of life phenomenon.

3. Physical Growth Mechanism - the General Growth Law

3.1. *Introduction of the General growth law. The growth equation*

Here, we use the General growth law for modeling growth and explaining division mechanisms. First, it was introduced in Refs. 25, 26, with the following advancements and applications in Refs. 19-23, 27-31 and other publications. The principal role of this mechanism is that it uniquely distributes nutrients, acquired by an organism, between the biomass synthesis and maintenance needs. In other words, using the mathematical representation of this General growth law, the growth equation, we can find how much nutrients are used for biomass synthesis, and how much for organism's maintenance needs, *at each moment of organism's life cycle*. The implications such knowledge provides are of fundamental value for biology and related disciplines. For instance, one of such important consequences is that this way one can directly tie the composition of biochemical reactions in both the entire organism and its constituents to the amount of produced biomass.

Understanding this mechanism is rather difficult, for several reasons, such as its generality and non-obvious omnipresence in nature - for instance, in plants, because of their complex nutrients supply and waste removal structure. However, the greatest challenge, in the author's view, stems from the need to accept a *new paradigm* for the biological community that Life, besides biochemical mechanisms, is governed by fundamental *physical* and other laws, acting at different scale levels, thus merging physical, biochemical, biological and other possible mechanisms into a single coherent concept of organic life, which the community is not ready to do.

One of the main physical phenomenon, underlying the General growth law, is a conflict between the slower increasing abilities of the *surface* to supply nutrients and the nutritional needs of faster growing *volume*. However, in nature, this conflict is resolved not in *absolute*, but *in relative* dimensionless transformed form, and the actual arrangement is more complicated and more elegant, providing much greater flexibility, adaptability, stability and optimality than the surface-to-volume conflict in absolute values would allow. This is why all previous explanations involving size of organisms, or growth time did not succeed.

Simplifying the matter for explanation, we can think of a spherical cell growing in three dimensions. Its surface increases proportionally to *square* of a radius (by four times

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for the radius's increase by two times), while volume increases proportionally to the *cube* of the radius (in our data, by eight times). If the nutrient supply per unit surface remains the same, that would mean that the unit volume of a grown cell will obtain twice as less nutrients (8/4=2). Organisms normally compensate for that increasing nutrient influx through the surface during growth. However, since the cubic function increases faster than the quadratic one, and the nutrient supply through the surface is *principally* restricted (by the environment and/or by the cell's membrane capacity), at some point, the surface inevitably won't be able supplying the same amount of nutrient per unit volume, and so the unit volume won't be able to function as before; then, the organism needs to do something, either "inventing" new mechanisms and moving to the next developmental phase, or to stop growth. In a nutshell, this is what limits the size of a cell for the given evolutionary formed metabolic mechanisms[*] and available nutrient supply. Of course, other factors of lesser influence could modulate the process too. Transportation expenditures also take a toll; the longer the communication routes, the more nutrients are required for transportation, and the less remains for other activities[34]. Similarly, the same conflict between volume and surface takes place for one- and two-dimensional growth. Even if nutrients are supplied through a stem (like in an apple), they are still distributed through the surface (internal surface, in this case), so that the surface-volume conflict is still there. The central location of a seed-bag in fruits, especially in the ones with short vegetation periods, besides other functions also creates an initial surface from which nutrient start distributing towards periphery.

One of the important consequences of such a resolution of the surface-volume conflict is that the fraction of nutrients used for biomass production is a value, which is uniquely defined by input growth parameters, first of all by geometrical characteristics. The rest of nutrients is used for maintenance needs.

The General growth law explains why cells of the same species can grow large and small, depending on different factors. That's because the growth and division mechanisms, which act in large and small cells, are the same, and trigger successive growth phases and division at *the same* values of certain parameters regardless of the size and growth time (cells trapped in stones during volcano eruptions may have cell cycle measured in years, because of few nutrients).

The growth equation for a simple growth scenario, when nutrients are acquired through the cell surface, is as follows.

$$p_c(X)dV(X,t) = k(t) \times S \times \left(\frac{R_S}{R_V} - 1 \right) dt \qquad (1)$$

where X represents a spatial coordinate, p_c is the density of the cell (units of measure $kg \cdot m^{-3}$), t is time in *sec*, k is a specific nutrient influx (amount of nutrient per unit

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[*] Refs. 32, 33 explore factors shaping metabolic properties of organisms from the perspective of a food chain creation.

surface per unit time) measured in $kg \cdot m^{-2} \cdot \sec^{-1}$, *S* is the total surface (in m^2) nutrients are acquired through; *V* is volume (in m^3).

The left part of Eq. (1) is the mass increment. The right part is the product of the total influx through the surface (the term $k(t) \times S$), by a dimensionless parameter $\left(R_S / R_V - 1\right)$, called the *growth ratio* (*G*); it defines which *fraction* of the total nutrient influx is used for biomass production. Thus, the right part represents the *amount* of nutrients used for biomass synthesis in a time period *dt*.

The most important parameter in Eq. (1) is the growth ratio *G*. Why the nutrient distribution between the biomass synthesis and maintenance in nature has to be so definitive? The answer is this. The primary evolutionary goal of any living organism is its successful reproduction. No reproduction - no organism. For that purpose, the organism must use acquired resources *optimally*. If the biomass synthesis is non-optimal - for instance, too slow, then the reproduction process is in jeopardy. If non-optimal insufficient amount of nutrients is directed to maintenance, then the organism won't be able to produce biomass fast enough, and then the reproduction will be delayed too. Thus, nature, as is the case with its other fundamental laws, goes *on an optimal path*, securing the fastest reproduction time for the given conditions.

What is also extremely important, this optimal path provides *the greatest stability possible* for a given phenomenon[35]. (The fundamental stability of the world we know is the *consequence* of such optimality of laws of nature.) This optimality is tied to a certain *geometrical* form. *All* organisms do have some geometrical form, which is the base of why such a nutrient distribution is *universal* for all species and their constituents, from the cellular level to organs to whole multicellular organisms. The growth ratio is a mathematical representation of this optimal distribution of nutrients, implemented in Nature.

In physics, the *same* principle of maximum stability due to optimality is behind the facts that acceleration of a body in mechanics is directly proportional to applied force and inversely proportional to mass, or electric current in a circuit is directly proportional to applied voltage and inversely proportional to resistance. It was shown in Ref. 35 that when relationships between fundamental parameters deviate from such an optimum, the world which we know would be unlikely to exist, because of the inherent *instability* brought by these apparently minor changes. The growth ratio and the General growth law are from the *same* category of fundamental parameters and relationships between them, although they are more difficult to understand.

Note that the growth ratio and the growth equation were discovered *heuristically*, which is *the only way* for discovering fundamental parameters and relationships between them[19], since there is nothing yet to derive them from. (Recall famous "Eureka!" by Archimedes.) It is defined as follows. Suppose that a cell can grow to a maximum volume $V_{\max}$, which has a maximum surface $S_{\max} = S(V_{\max})$. Then, the dimensionless parameters - a relative surface R_S and a relative volume R_V, are as follows:

$$R_S = S(V) / S(V_{\max}) \qquad (2)$$

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$$R_V = V / V_{\max} \qquad (3)$$

While the dimensionless growth ratio is:

$$G = \frac{R_S}{R_V} - 1 \qquad (4)$$

As a function of volume, the growth ratio monotonically decreases when the organism's volume increases. According to Eq. (1), it means that the more the organism grows, the less nutrients are available for biomass synthesis, and more nutrients are used for maintenance. This is understandable, since the growing biomass requires more and more nutrients for maintenance. Eventually, this conflict stops the growth.

The maximum size can change during growth depending on nutrients availability and other parameters. Such, a cell that begins to grow in an environment with low nutrient content, is destined to have a smaller final size. However, if, at some phase of growth, the environment is enriched in nutrients, then the cell grows bigger, which experimental observations confirm[13,36]. In many instances, the maximum size can be known upfront, if all growth conditions are defined at the beginning and do not change unpredictably later. Otherwise, the maximum size can change. This mathematical specific of the growth equation does not mean that it has some defects or it is of approximate nature. This is just an adequate mathematical description of the growth phenomena in nature, when the change of parameters during the growth alters the final size of a grown organism. Similarly, we can compute a trajectory of a thrown stone. However, if the stone accidentally hits the tree branch, then its trajectory will change, and we will have to recalculate the new one.

The possible variability of the maximum possible volume can be addressed by adding the dependence of its value from other parameters; for instance, from nutrient influx, temperature. Below we will discover that in certain types of growth scenarios knowing the maximum volume is not required.

3.2. *Finding nutrient influx*

The next important parameter in Eq. (1) is nutrient influx *k*, the amount of nutrients per unit surface per unit time. Note that the product $k \times S$ represents the *total* nutrient influx *K*. This fact reflects the property of the growth equation that it does not matter which way the nutrient influx was acquired. Such, in a growing budding yeast part of nutrients comes from the mother cell; in an apple nutrients come through the fruit's stem.

In Ref. 34, the amount of nutrients required for cellular transportation depending on the shape of cells was found, while in Ref. 21 the overall amount of nutrients required for the growth of *S. pombe* and *amoeba* was obtained. It was discovered in Refs. 37, 38 that in some elongated cells, like *E. coli*, *S. cerevisiae*, the rate of RNA synthesis is twice the rate of protein synthesis. Taking into account this double rate of nutrient consumption for RNA synthesis, we can write for the nutrient influx $K_{\min}$ required for biomass synthesis and maintenance (without transportation costs) the following.

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$$K_{\min}(v) = N\left(C_p^s v + C_r^s v^2\right) \qquad (5)$$

Here, C_r^s and C_p^s are fractions of nutrient influx required for RNA and protein synthesis; v is the relative increase of organism's volume (the ratio of the current volume to the volume at the beginning of growth, so that $v \geq 1$); N is a constant.

For an elongating cylinder-like cell, whose diameter remains constant, volume is proportional to the relative increase of length L. Using the same consideration as in Refs. 21, 34 about proportionality of transportation costs to the traveled distance, and substituting $K_{\min}$ from Eq. (5), we obtain an equation for the total nutrient influx.

$$dK(L) = C_t K_{\min}(L) dL \qquad (6)$$

where C_t is a constant.
Solving (6), we find

$$K(L) = N_1 C_t\left((1/2)C_p^s L^2 + (1/3)C_r^s L^3\right) = A\left(C_p L^2 + C_r L^3\right) \qquad (7)$$

where N_1 is a constant; $A = N_1 C_t / 2$; $C_p = C_p^s$; $C_r = (2/3)C_r^s$.

Similarly, we can find the total required nutrient influx for a disk and a sphere. We assume that a disk grows in two dimensions (height remains constant); a sphere increases proportionally in three dimensions.

$$K(v)_{disk} = \left(C_p v^{3/2} + C_r v^{5/2}\right) \qquad (8)$$

$$K(v)_{sph} = \left(C_p v^{4/3} + C_r v^{7/3}\right) \qquad (9)$$

Obtaining analytical solutions as (7) - (9) is not always possible. Such, there is no analytical solution for an elongating ellipsoid. In this case, the following growth equation should be solved numerically[19, 31].

$$p_c dV(r) = k_{\min}(V(r)) \times (r / r_0) \times S(r) \times \left(\frac{R_S}{R_V} - 1\right) dt \qquad (10)$$

Here, r_0 is the beginning radius in the same direction of growth, which is defined by a radius-vector $\boldsymbol{r}$.

4. Growth Model of *Amoeba* and its Division Mechanism

4.1. *Amoeba's growth model developed on the basis of the General growth law*

We will start from a simpler and, apparently, evolutionarily the earliest growth scenario, which is implemented in *amoeba*. A*moeba* might be not the oldest organism, but there are no reasons why it cannot use a primordial growth and division mechanism, if it serves the purpose; in the same way, we still use an ancient tool, a hammer, because it is adequate to our tasks. (As a side note, interesting consideration is presented in Ref. 24 that the ancestor's root of eukaryotes, including protists, could be much older than it is presently assumed. If this is so, then the basic growth and reproduction mechanisms could be the only option for amoeba's ancestor, and more sophisticated mechanisms were built later *on top* of these basic mechanisms.)

Let us define parameters of the growth equation.

Density and mass calculation. For all considered microorganisms, we assume the density to be constant during the growth and equal to 1 $g \cdot cm^{-3}$. This assumption is a reasonable approximation[39]. The mass of a grown *amoeba* used in calculations corresponds to the last experimental measurement.

Maximum possible volume. A parameter "spare growth capacity" (SGC) was introduced for the characterization of the maximum possible volume in Refs. 19, 30. It is defined as $SGC = 1 - V_d / V_f$. Here, V_d is the volume when cell divides; V_f is the maximum possible volume, which the growth curve asymptotically approaches. For available experimental data, SGC value was in the range 1.0 - 2.8%. Two *amoebas* did not divide and, indeed, increased their mass by about 2% after missing division, so that SGC is a *real* value. In calculations, we used the maximum possible volume, which exceeded the last measurement by 2%.

Geometrical form. *Amoeba* is modeled by a disk whose height *H* is equal to the initial disk radius R_b . The maximum possible disk radius is R_0 . Such a model was chosen based on analysis of *amoeba's* images from different sources, which indicate rather two-dimensional increase of this species. (A more sophisticated pinion-like form, accounting for *amoeba's* pseudopods, produced close results.) Substituting the above parameters into (2) - (4), we obtain:

$$R_{Sd} = \frac{R(R+H)}{R_0(R_0+H)}\,;\; R_{Vd} = \frac{R^2}{R_0^2}\,;\; G_d = \frac{R_{Sd}}{R_{Vd}} - 1 = \frac{R_0(R+H)}{R(R_0+H)} - 1 \qquad (11)$$

where index *'d'* denotes 'disk'.

Nutrient influx. The rate of nutrient consumption for RNA and protein synthesis are assumed to be the same for *amoeba*[19, 21, 30], which transforms Eq. (8) into

$$K(v)_{disk} = v^{3/2}\left(C_p + C_r\right) \qquad (12)$$

Model verification. Using the above parameters, we *first* computed the growth curves, and only *then* compared them with experimental dependencies. So, this comparison *is not* a data fitting procedure in the usual sense, but actually a *principally* much more rigorous verification of the model's adequacy. (Note that the same verification was used for *all other models*, presented in this article, for which experimental data were available.)

Solution of the growth equation. Substituting the above parameters into Eq. (1), we obtain the following differential equation.

$$4p\pi dR = \frac{k(R_0 - R)R}{(R_0 + H)R_b^3}dt \qquad (13)$$

Solution of this equation is as follows.

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$$t = \frac{2p\pi(R_0 + H)R_b^3}{kR_0} \ln\left(\frac{R(R_0 - R_b)}{R_b(R_0 - R)}\right) \qquad (14)$$

Certainly, we can use (14) to draw the growth curve. However, it would be better to find a direct analytical solution for the radius R as a function of time t. The solution, indeed, is a remarkable one.

$$R = \frac{R_0 \exp(t/c_0)}{(R_0/R_b - 1) + \exp(t/c_0)} \qquad (15)$$

where $c_0 = \dfrac{2p\pi(R_0 + H)R_b^3}{kR_0}$.

The remarkable thing about Eq. (15) is that this is a *generalization* of a solution $P(t) = \left(1 + \exp(-t)\right)^{-1}$ of the well known logistic equation $\dfrac{dP}{dt} = (1 - P(t))P(t)$, where P is the population quantity. However, our solution Eq. (15) has been obtained *independently*, on very different grounds. Unlike the classic solution, which requires adding constant coefficients using ad hoc considerations, Eq. (15) produces all coefficients *naturally*, as functions of the model's input parameters, which is a significant and *qualitative* advancement. The fact that the heuristically introduced growth equation produced a generalized solution of the known logistic equation (which is also used for modeling growth phenomena, both for populations and individual growth), should be considered as a remarkable result, a strong argument in favor of validity of the growth equation, according to criteria for validation of scientific truths. (Note that the growth equation Eq. (1) represents a *new type of equation of mathematical physics*, so that obtaining such an interesting and significant result is a good start for its mathematical explorations too.)

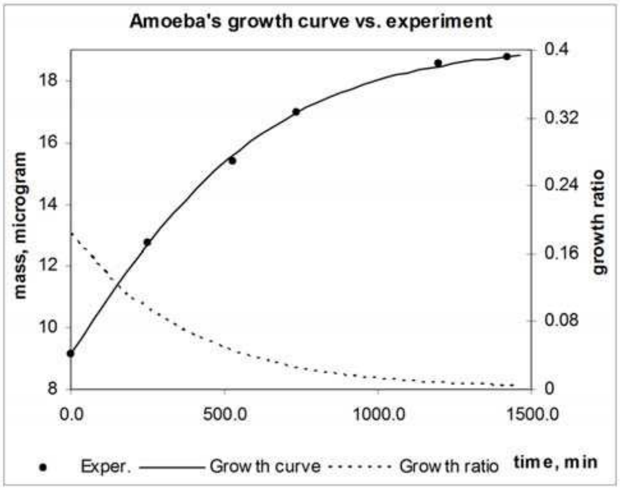

Fig. 1. Computed amoeba's growth curve versus experiment, and the growth ratio, depending on time. Experimental data are from Ref. 39.

Fig. 1 shows the computed growth curve for *amoeba* versus experimental data from Ref. 39, and the corresponding growth ratio. We can see that the computed growth curve corresponds to experimental measurements very well. Comparison with other experiments shows slightly more dispersion of experimental points relative to the computed growth curves. However, the experiment in Fig. 1 was chosen not for the least deviation from the computed growth curve, but for the *stability* of growth conditions compared to other experiments, in which nutrient influx was not so stable. If we could know the actual nutrient influx, we would compute the growth curves for other experiments more accurately too.

4.2. *Amoeba's division mechanism*

A continuous redistribution of nutrient influx between maintenance needs and biomass production, defined and enforced by the general growth law, explains deceleration of the growth rate and subsequent stopping of growth. Indeed, growing biomass requires more nutrients for maintenance to support it, and so fewer nutrients are available for biomass synthesis. The decrease of the growth ratio during growth is a quantitative expression of this fact in a mathematical form. This arrangement of the growth phenomena has far reaching implications. Here is why. Organismal biochemical machinery represents a *single unity*. There are no separate biochemical machineries for maintenance and for biomass production, but all biochemical reactions *interrelate*; they are arranged in such a way that output substances of previous reactions become inputs for the next. Success of methods of metabolic flux analysis is based entirely on this arrangement, when through such interdependencies, described by a system of stoichiometric equations, it is possible to *unambiguously* find how much of each substance participates in the biochemical interchange[31, 40].

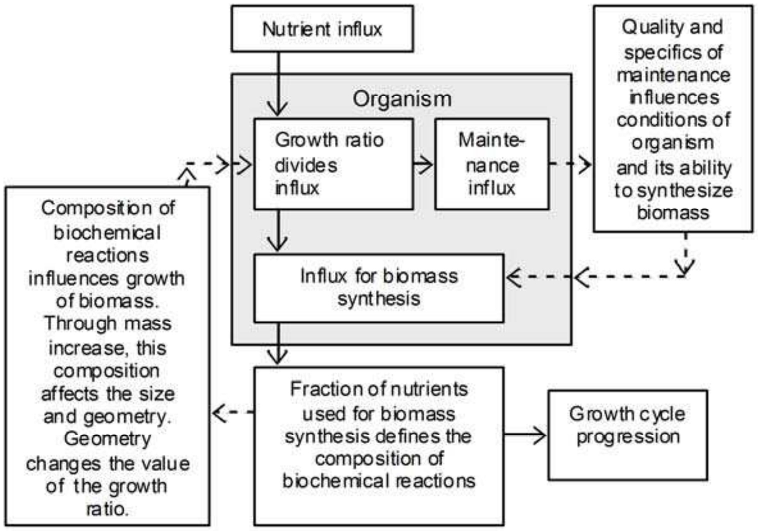

Fig. 2. Growth cycle regulation and progression defined by the General growth law.

According to works on metabolic flux analysis, the solution of a system of stoichiometric equations produces the *most adequate* results when this solution is optimized for a *maximum amount of produced biomass*. Indeed, evolutionary development shaped the composition of biochemical reactions in the direction prioritizing fast reproduction; in other words, making the amount of produced biomass a *leading* parameter, which the composition of biochemical reactions is tied to. So, if the amount of synthesized biomass changes, the composition of biochemical reactions changes too. In which direction though? The answer is: In the direction securing successive transitions through the entire growth period, optimized for the fastest reproduction.

Before proceeding further, we should make the following side note. Nutrients are transformed to biomass by chemical reactions, for which the law of conservation of matter is fulfilled, so that the *mass of nutrients*, which are used for biomass synthesis, is equal to the mass of *synthesized biomass*. Therefore, in the following, it is legitimate using interchangeably these two notions.

Let us reiterate how the growth and reproduction is regulated from the standpoint of the General growth law using Fig. 2 (it shares most elements with my Fig. I-1 in Ref. 19, used here by permission). In nature, a conflict between supplying abilities of the surface and the faster increasing demands of volume is resolved through optimization of nutrient distribution between biomass synthesis and maintenance. Quantitatively, this optimum is expressed as the value of the growth ratio, which is defined by geometry (that is logical, since the surface and volume are primary geometric characteristics inherent to all living organisms). This way, through the growth ratio, the General growth law imposes constraints on the fraction of nutrients that go to biomass production at each moment of growth and reproduction. Biochemical mechanisms comply with this constraint. The increasing biomass requires more nutrients for maintenance, and so lesser fraction of nutrients is available for biomass synthesis. This continuous nutrient redistribution is reflected in the value of the growth ratio, which monotonically decreases during the life cycle. Composition of biochemical reactions is tied to the relative amount of produced biomass (relative to the total amount of acquired nutrients, meaning all substances used by biochemical machinery). Thus, the changes in the relative amount of produced biomass, forced by changing geometry, are realized by changes in the composition of biochemical reactions, so that the newer composition corresponds to the new relative amount of produced biomass. (In particular, such change of composition of biochemical reactions forced by the changed amount of produced biomass could be one of the main factors triggering cell specialization. However, this hypothesis requires further studies.)

We know that growth processes and organisms' life cycles are generally *irreversible*, including such phenomenon as aging of multicellular organisms. The described arrangement explains irreversibility during growth and reproduction. The decreasing relative amount of nutrients diverted to biomass production acts as a ratchet, preventing the current composition of biochemical reactions to revert to the previous state, when a greater relative amount of biomass was produced. For such a reversion to happen, the fraction of nutrients used for biomass production has to increase. However, the grown biomass already took for maintenance the part of nutrient influx, which was earlier used for biomass synthesis; and the entire biochemical machinery was adjusted accordingly. In order to increase the fraction of nutrients for the biomass production, the growth ratio has to be increased. It can happen through the size reduction or by substantial change of geometrical form, which is not impossible, but would cause certain energetic, functional and developmental complications. If the said is true, then at least some simpler organisms might be able to "rejuvenate" through the decrease of biomass. Indeed, in Refs. 41, 42, the authors acknowledged that by periodically resecting part of *amoeba's* cytoplasm *it is possible* to indefinitely prevent it from entering division; in other words, making it practically immortal. By reducing *amoeba's* size, the experimenter, in fact, increased the growth ratio, which apparently led to adjustment of composition of biochemical reactions to a greater value of the growth ratio (in other words, to a new fraction of nutrients that could be used for biomass synthesis), or - at the least - led to freezing for some time the composition of biochemical reactions existing at the moment of resection. (Attention experimenters: Both propositions could be relatively easy to verify experimentally.)

However, in general, the growth cycle is difficult to reverse for the reason explained above, and this is the price for the smooth and persistent proceeding through the entire growth and reproduction cycle. (The objection to the said above can be that there are cells that divide without growth. However, these cells reside within multicellular organisms, whose other parts increase their biomass and can send appropriate signals to other cells, forcing them to divide.) The described division process is rather a backbone mechanism, which, as usual, can be modulated by nature-virtuoso in many ways, but these modifications, still, are built on top of this core mechanism.

Quantitatively, the leading role of the growth ratio (or, which is the same, of nutrient distribution between biomass production and maintenance) in the rate of change of the amount of synthesized biomass can be confirmed as follows. Let us rewrite Eq. (1) to explicitly show the amount of produced biomass m_b.

$$dm_b = k(X,t) \times S(X) \times \left(\frac{R_S}{R_V} - 1 \right) dt \qquad (16)$$

As we will see later, the specific nutrient influx *k* for amoeba at the end of growth changes little, as well as its volume and consequently the surface area. From the three terms in (16), the growth ratio $G = \left(R_S / R_V - 1 \right)$ changes by far the quickest, so that the changes in the amount of produced biomass are defined mostly by changes of the growth ratio. It is important to understand that it is not the absolute, but the *relative* changes in the amount of produced biomass (relative to the total amount of consumed nutrients), which alter the composition of biochemical reactions. 50% decrease of small amount of produced biomass affects composition of biochemical reactions *more* than 25% decrease of a bigger amount of synthesized biomass.

This is common sense that the division mechanism has to satisfy the following requirements:

(1) to be tied to the most important organismal characteristics;

(2) rate of change of these characteristics has to be substantial when approaching the division phase;

(3) for the same species (or maybe even for a class of species, having similar, at the core, growth and reproduction mechanisms) the values of these characteristics (or a characteristic) have to be *invariant* to all possible growth and reproduction scenarios (at least to be invariant with high accuracy).

The growth ratio satisfies all these criteria, while none of the other competing parameters. For instance, the other candidate for the role of such a division trigger is often assumed to be the size of an organism. Fig. 3 presents graphs of a relative change of the growth ratio and volume during the whole growth period for equal time intervals τ, that is the values $(V(t+\tau) - V(t)) / V(t)$ and $(G(t+\tau) - G(t)) / G(t)$. We can see that relative changes of volume before the division are *substantially smaller,* about sixty times, than the relative changes of the growth ratio. Moreover, volume's relative change *decreases*, while in case of the growth ratio the relative change remains constant. Apparently, a triggering mechanism, which reacts to a *greater* and (even better) *increasing* parameter (which is the case for *S. pombe*, as we will see later), will work more reliably than a trigger reacting on a small and decreasing value.

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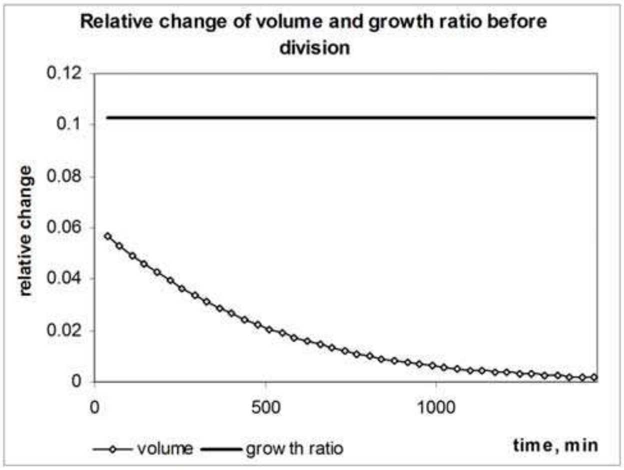

Fig. 3. Relative change of volume and growth ratio for *amoeba* during the growth period.

The other important factor supporting our hypothesis about the role of the growth ratio as a major division trigger is this. Size of the same species varies a lot. Such, the length of a grown *S. pombe* can differ as much as four times; other cells also show wide range of grown sizes, at least tens of percent, depending on many factors, like nutrients availability, temperature, etc. In individual growth, cells also demonstrate wide variations of ratios between the ending and the initial sizes. Small *S. pombe* or *E. coli* can grow into a big cell, on par with the cells, which started growing being much bigger already. How some hypothetical size sensitive division mechanism could determine, at which size it has to start the division, given such *principal* variability of sizes relative to initial sizes, and also high variability of the initial sizes too, for the same species? Such a division mechanism just has no reference points to be tied too. On the other hand, the growth ratio is a well defined value for *any* growth scenario. For the same species with similar geometrical forms, it does not matter, a big cell or a small one, increases it by two or four times, the growth ratio will be changing similarly during the entire growth period, *always* reaching a certain value, *which is invariant to size*, corresponding to a division point. In other words, this division point corresponds to the same fraction of nutrients directed towards biomass production. In turn, it is *namely this* fraction, which defines and forces changes in the composition of biochemical reactions throughout the life cycle, and, in particular, it triggers a division phase. With the growth ratio as a division trigger, *all* known facts are explained, and *all* affecting factors are tied together. In case of size as a possible trigger of a division mechanism, on the contrary, we have conflicting considerations; it just has no reference points such a mechanism can be tied too.

The invariance of value of the growth ratio, corresponding to division, is indirectly confirmed by results from Ref. 14: "… a cell with a larger initial size tends to divide earlier, whereas one with a smaller initial size tends to divide later." Indeed, according to the General growth law, large cells of the same species reach the threshold division value

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of the growth ratio earlier, since they start with a smaller growth ratio already and so it will decrease faster, while smaller cells generally start with a greater value of the growth ratio and need to grow - in relative terms - more in order to reach the same small value of the growth ratio corresponding to division. Of course, this is only a qualitative reasoning, since the growth ratio is defined by *geometry* at the first place, not by the size alone.

So, the growth ratio in this competition for the cellular cycle control by far supersedes the organism's volume (and consequently other related to size absolute parameters). Thus, this is not the size of an organism, which eventually triggers the division and enforces ordered changes of compositions of biochemical reactions through the growth cycle, but the *change* in the amount of produced biomass relative to the total nutrient influx, tied to a *relative* size and geometrical form. This arrangement is certainly outside the mainstream biomolecular biological paradigm, but unlike other hypotheses, it by far supersedes all other hypotheses; it explains *all* known facts about growth and reproduction phenomenon, *without a single exception*.

The General growth law also allowed predicting new effects. Such were explanations why organisms have certain forms, like a cylindrical or spherical ones, a theoretical discovery of a growth suppression mechanism based on change of a geometrical form[19, 21, 30]. The last one later found experimental confirmation in cellularization of the syncytial blastoderm in Drosophila[43] and pigs' blastocysts[44] (more on that in subsection 5.3). These effects were discovered based on calculating growth time for different geometrical forms using the growth equation, and later found experimental confirmation.

Unlike the other hypotheses, the introduced growth and division model is supported by a mathematical apparatus, which produces results very accurately corresponding to experiments. None of the other hypotheses about growth and reproduction mechanisms has such an adequate and universal mathematical apparatus, and passed such a robust verification based on strict scientific methodology. So, although the discovered answer to Life development problem resides in the area nobody was expecting it to be at - indeed, we discovered that this is rather a classical *physical* law, acting at higher than molecular levels - the discovery should not be discarded on that ground. Important scientific breakthroughs, like the military ones, originate in unexpected directions.

A note about the constant value of the relative change of the growth ratio in Fig. 3. This is a surprising result. Its mathematical proof is as follows. Let us substitute the value of R as a function of t from (15) into the expression for the growth ratio G in (11).

$$G(t) = \frac{(R_0/R_b - 1)H}{(R_0 + H)\exp(t/c_0)} = \frac{(R_0/R_b - 1)H}{(R_0 + H)}\exp(-t/c_0) \qquad (17)$$

Therefore, the growth ratio as a function of growth time is an *exponential function*. Recall that the growth ratio is the ratio of the relative surface to relative volume (Eqs. (2) and (3)) minus one, and *none* of them, of course, contains even a hint to exponents. Obtaining such an unexpected result in the given circumstances rather means that we found some important new geometrical property of the *real world* (which is, in the first place, a geometrical one).

The first derivative of an exponential function is also an exponential function, so that the relative change of the growth ratio (its first derivative) is an exponent. However, for illustrative purposes, let us consider equal discrete time intervals τ . Then, we can find the relative change of the growth ratio as follows.

$$\frac{G(t+\tau)-G(t)}{G(t)}=\exp(-\tau/c_0)-1 \qquad (18)$$

So, for the equal time intervals the relative change of the growth ratio, indeed, remains constant. What is the meaning of this relationship in the real world? It is an interesting and a very *natural* one. It means that at equal time intervals the amount of nutrients that is diverted to biomass production is reduced *by the same fraction* from the ending amount of the previous time interval (recall compounding interest on mortgage or annuity, or decrease of atmospheric pressure with height, or decrease of current in electrical circuits[35]; mathematically, this is are phenomena of the same class). There are many such natural processes defined by fundamental laws of Nature. So, we can say with certainty that the *heuristic* growth equation Eq. (1) and its main parameter, the growth ratio, are definitely associated with the realm of *natural* processes. According to scientific methodological criteria of validation of scientific theories, finding such relationships should be considered as a one more strong argument in a favor of validity of the growth equation and of the General growth law.

4.3. *Amoeba's metabolic properties*

Once we know the total nutrient influx $K(t)$ and the growth ratio $G(t)$, we can find separately nutrient influxes for growth - $K_g(t)$, and maintenance - $K_m(t)$.

$$K_g(t)=K(t)G(t) \qquad (19)$$

$$K_m(t)=K(t)(1-G(t)) \qquad (20)$$

Also, we can find nutrient influxes per unit surface $k_s(t)=K(t)/S(t)$ and per unit of volume $k_v(t)=K(t)/V(t)$; accumulated amount of nutrients used for biomass synthesis M_g, maintenance M_m, and the total amount of consumed nutrients M_{tot} during the time period (t_1,t). We will use units of measure for the influx $pg\cdot\min^{-1}$ ($1pg=10^{-12}g$), except for *amoeba*, for which the unit of measure is $\mu g\cdot\min^{-1}$. Influx $k_s(t)$ is measured in $pg\cdot\min^{-1}\cdot\mu m^{-2}$; $k_v(t)$ in $pg\cdot\min^{-1}\cdot\mu m^{-3}$ (for *amoeba*, accordingly $\mu g\cdot\min^{-1}\cdot\mu m^{-2}$ and $\mu g\cdot\min^{-1}\cdot\mu m^{-3}$).

$$M_g(t)=\int_{t_1}^{t}K_g(\tau)G(\tau)d\tau \qquad (21)$$

$$M_m(t)=\int_{t_1}^{t}K_m(\tau)G(\tau)d\tau \qquad (22)$$

$$M_{tot}(t) = \int_{t_1}^{t} K(\tau)G(\tau)d\tau \qquad (23)$$

Application of Eqs. (19) - (23) to the growth curve in Fig. 1 produces metabolic characteristics presented in Fig. 4.

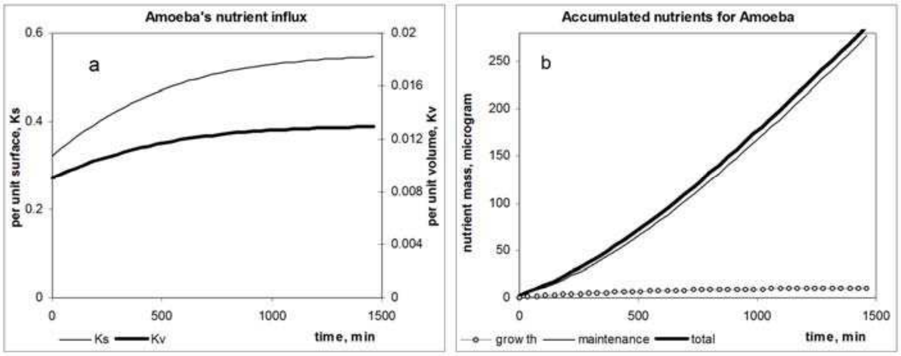

Fig. 4. Nutrient influx and accumulated amount of nutrients for *amoeba*, depending on time. a - Specific nutrient influx $k(t)$ per unit of surface ($\mu g \cdot \min^{-1} \cdot \mu m^{-2}$) and per unit of volume $k_v(t)$ ($\mu g \cdot \min^{-1} \cdot \mu m^{-3}$). b - Accumulated amount of nutrients used for growth and maintenance, and the total amount, in μg.

Metabolic properties of studied organisms will be compared in Table 1. For now, note that (a) *amoeba* consumes about 28 times more nutrients for maintenance than for growth; (b) we can find amount of synthesized biomass *directly*, while finding this critical for biotechnological applications parameter, in particular by methods of metabolic flux analysis, is a big problem today.

4.4. *Amoeba's growth and division mechanism from the evolutionary perspective*

Geometrical form is an inherent property of *any* living organism and its constituents, down to a molecular level. Since the growth ratio is inherently tied to the geometrical form, the growth and division mechanisms based on direct changes of growth ratio are probably the most ancient ones. (We will call them as the growth and division mechanism of the *first type*.) Its characteristic features are as follows:

(1) The growth proceeds almost through the *entire* possible growth period (corresponding to the growth curve described by the growth equation);
(2) The rates of protein and RNAs synthesis are the same;
(3) The value of the spare growth capacity is small, about 2%.

5. Fission yeast *S. pombe*. Growth and Division

5.1. *Modeling growth of S. pombe using the growth equation*

This model organism represents the *second type* of the growth and division scenario. Such organisms do not go through the whole possible growth cycle, but use only the fastest part of the whole growth curve, switching to division much earlier, at the inflection point of the growth curve. This evolutionary enhancement secures the fastest possible growth time. Evolutionarily, such mechanism was very likely developed on top of more basic mechanisms, like the ones studied in *amoeba*, since it requires a set of advanced features, which unlikely appeared simultaneously.

For illustration, we used experimental data, courtesy of Baumgartner and Tolic-Norrelykke[45]. Earlier, in Ref. 21, similar results were obtained for 85 experiments from the same study, for the temperatures of $32\,^0\mathrm{C}$, $28\,^0\mathrm{C}$ and $25\,^0\mathrm{C}$, and also for experimental graphs from Ref. 46. Therefore, the presented results can be considered as statistically meaningful.

We use the same geometrical model of *S. pombe* as in Refs. 19, 21. The organism is modeled by a cylinder with a length *l*, radius *r*, with hemispheres at the ends; beginning length is l_b, ending length is l_e. In these notations, using Eqs. (2) - (4), the relative surface, relative volume and the growth ratio can be found as follows.

$$R_{Sc} = \frac{(2r+l)}{(2r+l_e)}\,;\; R_{Vc} = \frac{((4/3)r+l)}{((4/3)r+l_e)}\,; \tag{24}$$

$$G_c = \frac{R_{Sc}}{R_{Vc}} - 1 = \frac{((4/3)r+l_e)(2r+l)}{((4/3)r+l)(2r+l_e)} - 1 \tag{25}$$

where index '*c*' denotes 'cylinder'.

We will also need the relative lengths' increases $L = l/l_b$ and $E = l_e/l_b$, and a relative radius's increase $R = r/l_b$. Then, the growth ratio from Eq. (25) can be rewritten as follows.

$$G_c = \frac{(2/3)R(E-L)}{((4/3)R+L)(2R+E)} \tag{26}$$

Volume V of a cylinder with hemispheres is $V = (4/3)\pi r^3 + \pi r^2 l$. The differential is $dV = \pi r^2 dl$. The nutrient influx is defined by Eq. (7).

Note that Eq. (26) uses the *relative* length's increase for the cylindrical part of the organism, not for the *whole* length. The rationale is that the cell's volume increases through the elongation of the *cylindrical* part. (This consideration is not critical - using the whole length produces close results.)

Substituting these parameters into Eq. (1), we obtain the following differential equation.

$$p\pi r^2 l_b dL = A(C_p L^2 + C_r L^3)\frac{(2/3)R(E-L)}{((4/3)R+L)(2R+E)}dt \tag{27}$$

The analytical solution of Eq. (27) was considered in Refs. 19, 21, which is as follows.

$$t = \frac{B}{A}\left(f\left(\frac{1}{L_b} - \frac{1}{L} \right) + d\ln\left(\frac{L}{L_b} \right) + \frac{g}{C}\ln\left(\frac{1+CL}{1+CL_b} \right) + h\ln\left(\frac{E-L_b}{E-L} \right) \right)$$

(28)

where

$$B = 3p\pi\pi R_b^3(2R+E)/(2C_p)\,;\ f = \frac{4R}{3E}\,;\ d = \frac{1+f-fCE}{E}\,;\ h = \frac{d+fC}{CE+1}\,;$$

$$g = C(h-d) \qquad (29)$$

Unlike in *amoeba*, the rate of RNA synthesis in *S. pombe* is about double of the rate of protein production[19, 21]. This is why we obtained the cube of length in (26). It is often assumed[45] that the double rate of RNA synthesis triggers after completing S phase, while before that the rates of protein and RNA synthesis are the same. In this case, $K(L) = AL^2(C_p + C_r)$, and the solution of the growth equation is as follows[21].

$$t = \frac{B_S}{A_S}\left(f_S\left(\frac{1}{L_b} - \frac{1}{L} \right) + d_S\ln\left(\frac{L}{L_b} \right) + g_S\ln\left(\frac{E-L_b}{E-L} \right) \right) \qquad (30)$$

where $B_S = 3p\pi\pi R_b^3(2R+E)/(2(C_p+C_r))$; $f_S = 4R/(3E)$; $g_S = d_S = (1+f)/E$.

Model's input parameters are listed in Table 1. A diameter and a fraction of nutrients used for RNA synthesis were estimated based on the fact of fast growth and analogy with other microorganisms, like in Ref. 36, and large initial size of the considered species. Unfortunately, these parameters were not measured.

As we can see from Fig. 5a, *S. pombe*, unlike *amoeba*, does not proceed through the whole possible growth cycle, defined by the full growth curve, but switches to the division phase *at inflection point*, which secures the minimum growth time at a maximal possible rate of biomass production (this can be proved mathematically). This significant evolutionary enhancement secures much faster growth.

The value of the spare growth capacity (SGC) for *S. pombe* is much greater than *amoeba*'s 2%, and resides in the range of 30-40%. However, knowledge of SGC for computing growth curves in case of *S. pombe* and similarly growing organisms (including *B. subtilis, E. coli*) is not required, since comparison with experimental data is based on the beginning of division, which coincides with the inflection point.

As it was the case with *amoeba*, the relative (to the total nutrient influx) amount of produced biomass, defined by the growth ratio, remains the leading parameter, which defines composition of biochemical reactions through the growth cycle. However, in *S. pombe*, it triggers the beginning of division phase at the inflection point of the growth curve.

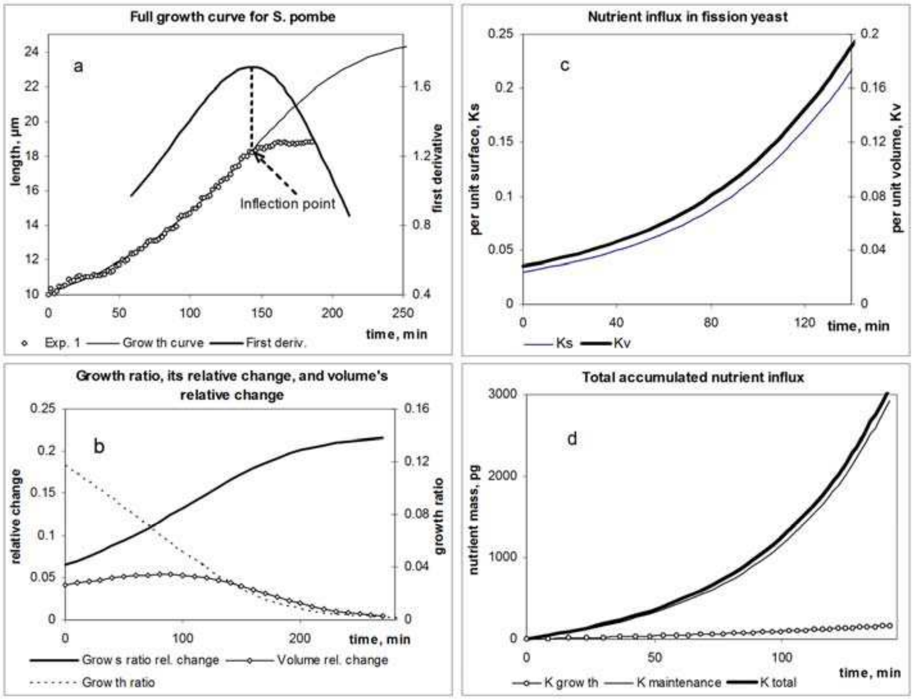

Fig. 5. *S. pombe's* growth and metabolic characteristics. a - Full growth curve for *S. pombe* versus experiment 1 from $32\,^0\mathrm{C}$ dataset from Ref. 45. Maximum of the first derivative of the growth curve corresponds to the beginning of division phase and inflection point of the growth curve. b - Change of the growth ratio, and the relative changes of the growth ratio versus the relative change of volume, for equal time intervals. c - Nutrient influx per unit surface k_s (measured in $pg\cdot\mu m^{-2}\cdot\min^{-1}$) and per unit of volume k_V (measured in $pg\cdot\mu m^{-3}\cdot\min^{-1}$). d - Accumulated nutrients for maintenance, growth and the total amount, in pg.

High value of SGC (and accordingly the possibility of continuing to grow beyond the inflection point) for *S. pombe* is not a mathematical ad hoc. Many cells can grow substantially bigger than their normal size, when the division is suppressed[7]. For *S. pombe*, it was confirmed experimentally in Ref. 45. Computations in Ref. 21, on the basis of Eq. (30), confirmed this too, and produced a growth curve similar to experimental data.

Metabolic properties of *S. pombe* were studied using Eqs. (19) - (23). Fig. 5b is presenting further evidence that the amount of produced biomass is that leading parameter which drives growth and division process of *S. pombe*, forcing changes in the composition of biochemical reactions in such a way that the organism proceeds through its life cycle. Indeed, we can see that the relative change of the growth ratio computed at equal time intervals is *substantially greater* than the relative change of volume (by 3.8 times at the division point). Also, the rate of change of the growth ratio quickly *increases* at the beginning of the division phase, while the relative change of volume *decreases*. So, it is very unlikely that changes in volume (or of any absolute dimensional parameter) could be a factor triggering *S. pombe's* division, besides the fact that changes in volume do not explain, why the same species, which could differ in size at the division point as much as four times, divide; or why such organisms continue to grow once the division is suppressed, and so on. The General growth law, in this regard, explains *all* known properties and facts about growth and division of such organisms, as well as explains why they have certain shapes, allows finding their metabolic properties, etc.

Fig. 5c shows change of specific nutrient influxes $k_s(t)$ and $k_v(t)$. Unlike in *amoeba* (see Fig. 4a), the increase of these influxes accelerates all the time. This is also a factor contributing to fast reproduction. Fig. 5d shows amount of accumulated nutrients for growth and maintenance, and the total amount of consumed nutrients. Note that maintenance requires about 18.2 times more nutrients than biomass production, while in *amoeba* this ratio was equal to 28.

The obtained results also address a long debated issue, is *S. pombe's* growth curve exponential or piecewise linear. Eqs. (28) and (30) answer the question - neither one in a pure form. However, given the presence of logarithmic functions, the reverse dependences (producing the growth curves in question) are rather closer to exponential functions than to piecewise linear dependencies. Ref. 21 presents statistical evidence in this regard.

5.2. *Growth and division mechanism of the second type*

The considered second type of growth and the division mechanisms very much differ from the same mechanisms of the first type, used by *amoeba*. (Note that both types of growth also have very different characteristics of population growth[47].)

The following features are characteristic for the second type of growth:

(1) Species do not go through the entire possible growth cycle, but switch to division much earlier, at the inflection point of the growth curve;

(2) The growth curve has a well expressed inflection point;

(3) Such species are elongated (the inflection point is better expressed for the elongated forms);

(4) The rate of RNA synthesis is double the rate of protein synthesis (which is also a factor contributing to better expression of an inflection point and faster growth);

(5) If the division is suppressed, such cells continue to grow further (because of the high value of SGC, which represents a qualitative measure of unrealized growth potential for such organisms).

5.3. *Dependence of growth rate on geometrical form*

Note that according to the General growth law, among all elongated forms a cylinder has the fastest growth time due to a higher value of the growth ratio[19, 21]. Fig. 6 shows such a dependence graphically for a double frustum whose base changes from zero to a base's diameter, that is from a double cone to a cylinder. The shortest growth time corresponds to a cylinder. The second fastest growing form is a double cone. On the other hand, a certain shape of a double frustum has the slowest growth time; in other words, it

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suppresses the growth. This effect of growth suppression by elongating the form was first discovered theoretically, and then experimental confirmations were found[43, 44], as it was earlier mentioned.

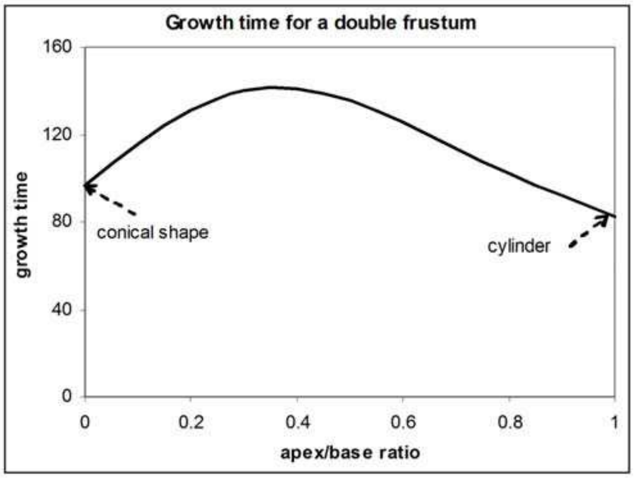

Fig. 6. Growth time for a double frustum depending on the relative upper apex's diameter. Change of apex diameter provides transition from a double cone shape to a cylinder.

Maximizing the growth ratio (in other words, maximizing the amount of produced biomass) is one of the reasons why so many elongated microorganisms have a cylinder shape. The argument that such a shape is due to the need for a lesser resistance during motion does not sustain - many immobile or low motility organisms also have a cylinder form, like *B. subtilis*. Also, the cylinder form is less restrictive with regard to the maximum length, since the value of the growth ratio changes slowly towards the end of growth for elongated forms. (This effect and the earlier triggering of division, in turn, explain large variations in the relative length's increase of *S. pombe* and other elongated organisms.)

Overall, all known facts about growth of *S. pombe*, overgrowth and its cylindrical form, as well as about similar characteristics of other elongated organisms and cells, are well explained by the General growth law.

A side note. Fig. 6 shows that the second fastest growing form is a double cone. Shape of a carrot is very likely a consequence of this effect. Even though the nutrient and water supply go through a network of interacting xylem and phloem flows, in case of a carrot, and plants in general, deposition of sugars into sink cells is done through the *surface*, although this is an *internal* surface this time (unpublished study).

A sphere is also a fast growing form. Although its growth curve does not have a well expressed inflection point, and such organisms should not enter division prematurely, as *S. pombe* does, the sphere's growth ratio at the beginning is more than two times greater

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than that of a cylinder with the ratio of length to a diameter of 2 : 1. This is why many unicellular organisms have a spherical shape, as well as many fruits and vegetables, especially when the vegetation period is short, which is the case for Northern berries, apples. Overall, geometry and interaction of relative surface and relative volume, reflected in the value of the growth ratio, governs the growth of plants too, although in a more complicated, transformed form, influenced by other factors and adaptation mechanisms to specific environments.

6. Growth and division of *B. subtilis*, *E. coli*

S. pombe, B. subtilis and *E. coli* exercise the growth and division mechanisms of the second type, although the first one is eukaryote, the other two are bacteria. Nutrient influx for them is defined by Eq. (7), since, as it was previously discussed, *E. coli* has a double rate of RNA synthesis compared to protein synthesis. There are no such data for *B. subtilis*, but it can be assumed the same, with very high probability, given the similarity of geometrical forms of *E. coli* and *B. subtilis* and their fast growth. Both factors, according to the results for *S. pombe*, strongly correlate with a double rate of RNA synthesis.

Fig. 7a,b show computed growth curves for *E. coli* (by Eqs. (28) and (30)) versus the two experimental data sets from Ref. 48. Fig. 7c shows a similar growth curve for *B. subtilis* versus the exponential data fit from Ref. 49. In all instances, we see a very good correspondence between the computed growth curves and experiments. Model's input parameters are listed in Table 1. The fraction of nutrients for RNA synthesis was estimated based on the rate of growth (the higher the rate of growth is, the greater this fraction) and the possible range of this value (0.035 to 0.246 for *E. coli*, according to Ref. 36.) The diameter was estimated based on geometrical proportions of organisms.

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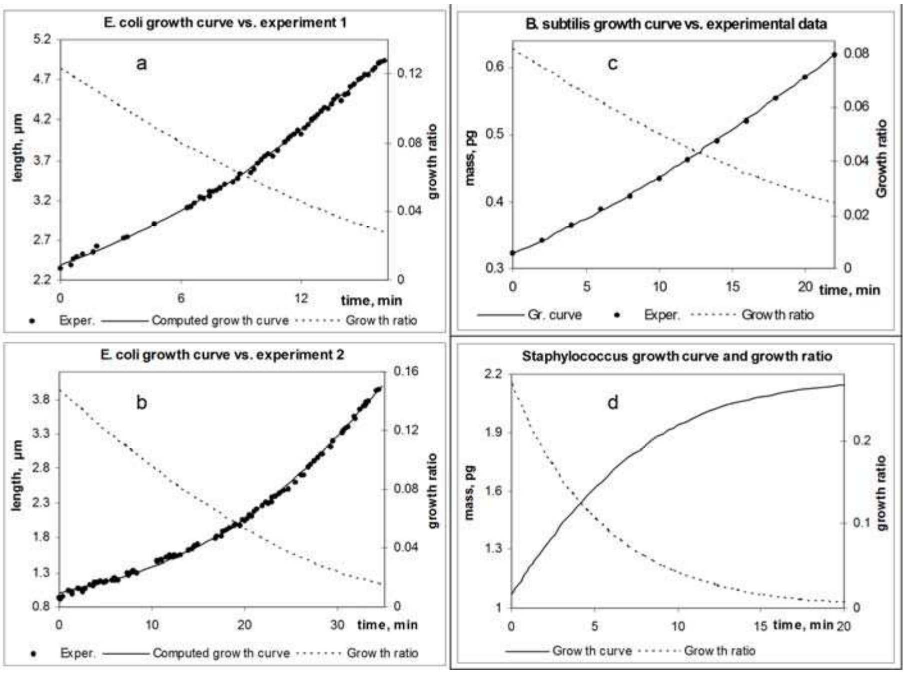

Fig. 7. Computed growth curves for *E. coli* and *B. subtilis* versus experimental data, and the computed growth curve for *Staphylococcus*. Experimental data for *E. coli* are from Ref. 48. For *B. subtilis* - from Ref. 49. a - The growth curve for *E. coli* vs. the data the authors suggested to model by a bilinear curve. b - The same for the data the authors suggested to model by a tri-linear curve. c - a computed growth curve for *B. subtilis* versus the experimental data. d - a computed growth curve and the growth ratio for *Staphylococcus*.

It was suggested in Ref. 48 approximating *E. coli's* growth curve as a bilinear or tri-linear function. If we take into account rounding of the tip of a divided microbe in the first minutes of growth, which is the cause of faster length's increase at the very beginning, then, the computed growth curves actually correspond to experiments noticeably better than the authors' bi- and tri-linear approximations. The length's increase due to the tip rounding at the beginning of growth was proved in Ref. 45, and later was confirmed in Ref. 21.

For *E. coli* and *B. subtilis*, metabolic properties (the graphs for nutrient influx and accumulated nutrients for growth and maintenance) are similar to ones for *S. pombe*, that is they are quickly increasing convex curves. For *Staphylococcus*, the appropriate metabolic curves resemble the concave curves for *amoeba*.

7. Growth and division model of *Staphylococcus*

Staphylococcus's growth was modeled by an increasing sphere. It turned out to be an interesting model. The rate of RNA and protein synthesis was assumed the same.

(Although, there is a possibility that the rate of RNA synthesis can be greater, similar, for instance, to *S. cerevisiae*[37].) Then, Eq. (9) transforms into

$$K(v)_s = (C_p + C_r)v^{4/3} \tag{31}$$

(index '*s*' denotes 'sphere').

The growth ratio can be found as follows.

$$R_{Ss} = \frac{R^2}{R_0^2};\ R_{Vs} = \frac{R^3}{R_0^3};\ G_s = \frac{R_S}{R_V} - 1 = \frac{R_0}{R} - 1 \tag{32}$$

where R_0 is the maximum possible (asymptotic) radius; R is the current radius.

Substituting G_s from (32), and nutrient influx from (31) into Eq. (1), we obtain the following differential equation.

$$4p\pi dR = \frac{kR(R_0 - R)}{R_b^4} dt \tag{33}$$

where R_b is the beginning radius of the sphere.
Solution of (33) is as follows.

$$t = \frac{4p\pi R_b^4}{kR_0} \ln\left(\frac{R(R_0 - R_b)}{R_b(R_0 - R)}\right) \tag{34}$$

It is very similar to (14) for *amoeba*. Denoting $c_{0s} = 4p\pi R_b^4/(kR_0)$, and solving (34) for radius R, we obtain a generalized solution, similar to solution of logistic equation, which is *exactly* the same as Eq. (15) for *amoeba*, save for the constant term c_{0s}. Certainly, thus obtained equation has the same interesting properties - close relationship with a logistic equation, and the exponential dependence of the growth ratio on time. So, for now, we found two geometrical forms, a disk and a sphere, possessing these two interesting properties. Both from the mathematical and physical perspectives, these results are of great interest, representing some fundamental properties of the real world, including its geometry, which so far were unknown. These and previous results allow to conclude that the growth equation represents a *new type of equation of mathematical physics*, whose study will undoubtedly provide new important insights to the properties of our world.

Division mechanism of *Staphylococcus* is very likely of the first type, as in *amoeba*. The reasons for such a suggestion is that the growth curve of a sphere does not have a well expressed inflection point, or other specific features, which could serve as the checkmarks for starting an earlier division without going through the whole possible growth curve. We can see from Fig. 7d that the growth ratio is much higher in *Staphylococcus* at the beginning of growth (a value of 0.27 versus 0.117 for *S. pombe*). This accordingly means a 2.3 times greater fraction of nutrients going to biomass production at the beginning, which apparently compensates for the slower growth at the end. Thus, we made a set of predictions regarding growth and division mechanisms of

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Staphylococcus and other organisms having a spherical shape, based on the General growth law, which can and should be tested experimentally.

8. Metabolic properties of cells. Allometric scaling

Table 1 presents the summary of metabolic properties of considered organisms and input parameters for their models, which can serve as an additional verification of obtained results and of the General growth law and growth equation. If they are correct, then (a) we should obtain the allometric scaling coefficient within the experimentally found range; (b) the dependence of metabolic rates on volume, presented in logarithmic coordinates, should be close to a linear one.

In addition to the earlier introduced characteristics, the following metabolic parameters were calculated: average and maximal metabolic rates per unit surface k_{Sav} and $k_{S\max}$; average and maximal metabolic rates per unit volume k_{Vav} and $k_{V\max}$; the total maximal, average and minimal nutrient influxes, accordingly $K_{\max}$, K_{av}, $K_{\min}$.

Table 1 considers nutrient influxes, but not the actual metabolic rates. We assume that the amount of produced energy is proportional to consumed nutrients[33]. On one hand, using nutrients has an advantage over the conventional methods, which may not account for all metabolic mechanisms. In particular: (a) it becomes possible to compare the consumed amount of food with the measured metabolic output; (b) knowing metabolic mechanisms of particular organisms, it is possible to translate the amount of consumed nutrients into the metabolic output. On the other hand, metabolic output for the same amount of nutrients can differ in different organisms. Besides, different types of nutrients could provide different metabolic outputs.

Note the large variations of nutrient influxes *per unit volume* (up to 80 times) between different organisms in Table 1, while the nutrient influx *per unit surface* differs little (of about 4 times). If we think for a moment, this is understandable, since nutrients are acquired by considered cells through the *surface*, from the common nutritional environment, and so the differences, indeed, should not be as great, being much dependent on the concentration of nutrients in the surrounding environment. It is interesting that from this observation a well founded theory of interspecific metabolic allometric scaling in unicellular organisms was developed, which exposed fundamental causes of this phenomenon and led to far reaching conclusions[34]. This can serve as a one more example of usefulness of the General growth law for diverse biological studies.

We can verify the validity of obtained in Table 1 metabolic parameters using a metabolic allometric scaling effect[33]. Fig. 8a presents such a dependence[33]. The found values of metabolic rate, indeed, are located on a straight line, and the value of allometric exponent of 0.758 complies with results from Ref. 50, according to which allometric exponents for unicellular organisms are in the range from 2/3 to more than one.

Table 1. Summary of metabolic properties of considered organisms and input parameters for their growth models.

	B. subtilis	Staphylo coccus	E. coli, 3-Linear	E. coli, 2-Linear	S. pombe	Amoeba
k_{Sav}, $pg \cdot \mu m^{-2} \cdot min^{-1}$	0.083	0.135	0.1053	0.2194	0.0957	0.493
$k_{S\,Max}$, $pg \cdot \mu m^{-2} \cdot min^{-1}$	0.134	0.147	0.284	0.433	0.222	0.545
k_{Vav}, $pg \cdot \mu m^{-3} \cdot min^{-1}$	0.672	0.5336	1.0073	0.8933	0.0866	0.01215
k_{Vmax}, $pg \cdot \mu m^{-3} \cdot min^{-1}$	1.066	0.552	2.65	1.71	0.195	0.013
V_{max}, μm^{-3}	0.617	2.145	3.999	16.975	325.4	1.88E+7
Diameter, μm	0.536		0.446	1.09	5	
Diameter beg. μm		1.27				285.7
Diameter end, μm		1.6				409.5
Beginning length, μm	1.608		1.003	2.39	10.1	
Ending length, μm	2.915		3.999	4.957	18.24	
Asymptotic length, μm	4.7		6.563	7.641	24.9	
k_{av} , $pg \cdot min^{-1}$	0.3538	0.98	0.26	2.86	4.984	1.96E+5
K_{max}, $pg \cdot min^{-1}$	0.658	1.184	1.59	7.34	63.59	2.44E+5
K_{min}, $pg \cdot min^{-1}$	0.116	0.47	0.025	0.688	4.723	8.28E+4
M_g (nutr. growth), *pg*	0.295	1.106	0.472	2.41	160.74	9.95E+6
M_m (nutr. maint.), *pg*	6.82	18.49	13.33	43.64	2930	2.77E+8
M_t (nutr. total), *pg*	7.12	19.6	13.8	46.05	3091	2.87E+8
M_m / M_g	23.1	16.72	28.2	18.12	18.23	27.83
Fraction of nutrients for RNA synthesis, %	12		6	10	60	
Logarithm k_{Vav}	-0.397	-0.628	0.0073	-0.113	-2.447	-4.41
Logarithm k_{Vmax}	0.064	-0.59	0.97	0.538	-1.64	-4.35
Logarithm V_{max}	-0.48	0.76	1.386	2.832	5.785	16.75
Logarithm K_{max}	-0.42	0.169	0.465	1.994	4.152	12.405

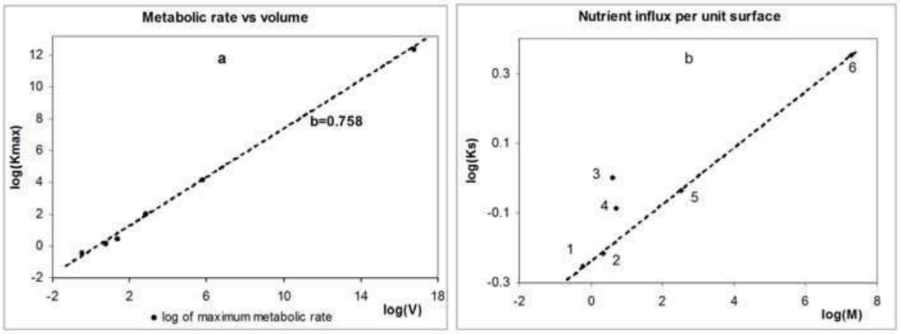

Fig. 8. Change of metabolic rate and nutrient influx depending on volume, in logarithmic scale. Numbered data points from left to right correspond to *B. subtilis* (1), *Staphylococcus* (2), *E. coli 1* (3), *E. coli 2* (4), *S. pombe* (5), a*moeba* (6). a - Maximal total metabolic rate. b - metabolic influx per unit volume. (Graphs are from Ref. 33).

The obtained in Table 1 results are also very important from another perspective. Using this result, it was shown in Ref. 33 that the entire food chain is organized in such a way

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that it preserves its continuity, on one hand, and a dynamic balance between different species composing the food chain, so that none of them could have an overwhelming advantage, on the other hand. This important result is due to the General growth law as well. Thus, we obtained an additional solid proof of validity of the General growth law and its high value for studying diverse problems in biology and related disciplines.

However, the results in Table 1 are even more revealing. Fig. 8b presents dependence of nutrient influx per unit surface for different unicellular organisms depending on mass, in logarithmic scale. We can see that except for *E. coli*, which is a *highly motile* organism, the values of nutrient influx for other microorganisms, which are all *sedentary*, very well fit a straight line. This fact has very important implications, resulted in discovery of an evolutionary mechanism of food chain creation, as well as obtaining other important results and explaining prior known but not understood facts and effects[33]. Together, these new findings also provide additional proofs of validity of the General growth law and the growth equation.

9. The New Physical Paradigm of Life as a Comprehensive and Transparent Cognitive Framework

Every new development brings new questions. Scientific ideas, by definition, are prohibited to be carved in stone. Given its generality and omnipresence, the discovery of the General growth law brings lots of questions, which have to be answered in order to move forward. The main idea behind such questioning is to have a clear and entirely transparent understanding of fundamental mechanisms defining Life, and clear vision of fundamental concepts underlying such both known and yet undiscovered mechanisms. There should not be blank spots filled with "obvious" assumptions (which in most instances actually turned out to be *beliefs*), similar to an idea about the all-managerial role of some genetic code responsible for everything. The new physical paradigm of Life provides directions for such studies and all sorts of opportunities to make them meaningful, efficient and successful.

For that, Life should be understood as an *entirely automated autonomous process and mechanism* at the same time, in which all details fit together and each one is fully exposed to the observer in its principles, appearance and action. One should be able to understand *why*, not only to see *how* (as it often happens now) this mechanism takes raw materials in certain conditions as an input, and, passing them through the process, delivers a living organism at the output. The analogy could be a flight of a thrown ball: we know that before the flight it was accelerated with certain force acting at a certain distance, and so the launching speed is described by such and such equation of classical mechanics. Then, the ball starts slowing its motion. Yes, that's right, says one - that because of the force of gravity, which acts on it, pulling it approximately to the center of the Earth, which is for this latitude defined by such and such formulas. Then, yes, friction of the air has to be taken into an account, which is defined by such and such equations, whose parameters we can find using such and such measurements. And so on. At every moment of flight, we know what laws of nature act, why and how they work, and what quantitative apparatuses describe them, leaving no gaps for unfounded assumptions.

One may not know some things, but there should be the right conceptual framework to move to such understanding. Does the present biochemical paradigm allow doing so? The answer is 'No', since it apriori excludes possible mechanisms, which might act at higher than molecular levels, while such mechanisms, indeed, could exist, given the known physical arrangement of the world. Thus, there is definitely a need in a new, more comprehensive and more transparent cognitive and methodological paradigm, based on right fundamental principles, and this is exactly what the proposed physical paradigm of Life provides.

10. Conclusion

The article began with a discussion of a fundamental question - What is Life? Different - often opposing - views of different level of generality on possible mechanisms governing Life origin and development were considered. We followed arguments of E. Schrödinger in his famous lectures and found, what led him to make the assumptions, which presumably influenced so much on the following course of the entire discipline. The truth is that Schrödinger did not exclude an idea that Life is governed by an 'ordinary' physical law, although gave such a possibility low priority, while giving higher preference to the idea that living matter is special from the rest, and, accordingly, is governed by some very special - although still physical - law. His reflections, as it was shown, had some principal flaws, which were the reasons of his inaccurate judgments.

There is nothing wrong with that when it comes to solving so complicated fundamental level problems. The scientific progress is by definition an iterative and incremental endeavor. It's just important to continue moving *forward*, whatever the state of affairs is, regardless of how final, perfect and satisfying it might look at a first glance. Motion is an inherent property of matter as such; it never stops. No paradigm, no concept can be final, representing the end of story. When such a situation happens, it just means that the paradigm or idea became a *dogma*, which from that moment becomes an obstacle in the following development. That's it. It does not mean that such a paradigm has to be necessarily rejected, by no means. Normally, the right things become foundations for the following progress. In case of theories or paradigms, such prior developments, whole or in part, are included into the newer more general theories and paradigms, thus securing the succession and continuity of knowledge. If this does not happen, than the discipline is in trouble, as it happens with philosophy, once the classic German philosophy, the jewel of human intelligence and reasoning, was rejected as the basis for the following development, and numerous opportunists began proposing their new "philosophies" from scratch. In case of the physical paradigm of Life, all known biochemical mechanisms are included into it, presenting its inherent, inseparable part. It's just that they play a somewhat different role.

From all possibilities that Schrödinger considered, eventually the idea of fundamentally special properties of living matter was accepted, and then it was amplified and modified to the status of an exclusively biochemical paradigm of Life origin and development. (The essence of this paradigm, as we discussed, is that all properties of living matter, at all scale levels, are entirely defined at a molecular level by *information* stored in a molecular form as some genetic *code*, which is implemented by biochemical mechanisms, successively triggering one after another according to this code, thus defining the life cycle progression.) The idea, apparently, appealed to the way of human thinking many people adhere to, which is extracting one aspect from a multifactor phenomenon, and stick with it, ignoring the rest of factors and evidences. Despite some opposition, de facto, the biochemical paradigm of Life quickly became the main biological idea, favored by grants, high ranking publications, prestige awards, etc.

The opponents, accordingly, were suppressed through the same means. It was easier to do so, since they could not present real mechanism, which could support their ideas. Now, the situation is different in this regard: Such a fundamental *physical* law of nature, the General growth law, was discovered, studied and validated from different perspectives. However, the biochemical paradigm is now so solidly established - organizationally, educationally, businesswise and in people's mentality, including the general public, that it is very difficult to change it.

This new *physical* biological paradigm was comprehensively verified using both high level philosophical considerations and discovered concrete growth and division mechanisms for particular unicellular organisms, while previous works[22, 23] proved the validity of this approach for organs. It is important to note that this physical paradigm by no means rejects, but seamlessly incorporates all biochemical mechanisms discovered within the biochemical paradigm of Life. In this regard, one should not consider the new paradigm as an alternative. In fact, this new physical paradigm is a *more general*, of the *next qualitative* level, concept of Life origin and development, which includes *all* previous knowledge. It accommodates and reconciles all previous studies, while opening new horizons and providing *conceptual* and *methodological* frameworks for the following studies, as well as perspectives and guidance.

The core of this new physical paradigm is a general growth mechanism, the General growth law, which is a fundamental law of nature; on par - in generality - with laws of classical mechanics. In the same way as laws of classical mechanics are valid in the entire Universe, the General growth law is also an inseparable attribute of the Universe. It works at a cellular scale level and above, up to the whole organisms, in tight cooperation with biochemical mechanisms, by imposing uniquely defined constraints on the distribution of nutrients between the maintenance needs and biomass production (as well as performing some other tasks we did not discuss here). The physical foundation for this law is a geometrical conflict between the slower growing surface and the (principally!) faster growing volume.

Using this *real* physical law and its mathematical representation the growth equation, we developed and validated by experimental data and other means growth and division models for unicellular organisms. In addition, we briefly considered metabolic characteristics of the studied organisms, using the General growth law, and found that (a) obtained values, indeed, are located on a straight line in logarithmic coordinates, as it should be if the General growth law and the growth equation are valid, (b) the value of the allometric exponent complies with experimental observations. Besides, we discovered that the nutrient influx through the surface also scales as a straight line in logarithmic coordinates for sedentary microorganisms, which entirely agrees with findings and properties of food chains considered in Refs. 32, 33. These results, on one hand, one more time confirm the validity of the General growth law and its mathematical representation, the growth equation. On the other hand, they effectively demonstrate the role of the General growth law as an efficient scientific tool, which allows solving difficult problems and explaining known puzzling facts. (The problem of metabolic allometric scaling is still considered as unsolved, although the actual mechanisms were discovered and presented in Refs. 32-34. The reason is the recent fixation in this area, the so called phylogenetic correction. However, such a correction should not be applied to organismal metabolic properties, which are much defined by the environment, and on a much shorter time scales than the phylogenetic trees consider. Fortunately, this dogmatic view meets more conflicting facts and growing distrust[51].)

Another important problem, the General growth law certainly will be very useful for, and actually without which the problem cannot be completely solved *in principal*, is a much debated topic of safety and consequences of consuming genetically modified food by people and domesticated animals. We won't discuss the issue here, but even at the present stage the General growth law can provide principal insights for this problem, indicate the optimal directions and methods for its study and - to some extent - foresee the results of such studies.

Next area of application, for which the new physical paradigm of Life would be extremely useful, is the terrestrial Life, like evaluating probabilities of its origin in different environments, on different time scales, possible development scenarios, etc, not mentioning the answering the main question - is terrestrial Life possible? - which is still unknown. The General growth law already can give a definitive answer - absolutely 'Yes'.

It might seem embarrassing finding so many important characteristics and explanations from a single growth equation. However, this is how fundamental laws of nature *always* work. What is needed to compute the trajectories of a thrown stone or a planet? By and large, only the Newton's Second law of mechanics - represented by a simple equation with three linear terms, $a = F/m$ (acceleration, force and mass). The general growth law is also a law of nature from the same category of fundamental laws, so that such "fertility" should not come as a surprise. The only difference is that the General growth law is somewhat more complicated and more difficult for understanding (otherwise, it probably would be discovered already).

One more argument in favor of the General growth law and other similar possible physical mechanisms is that there are many biological phenomena, which originate at a higher than biomolecular level. Ref. 32 gives an example of how the cell size matters for the metabolic properties of multicellular organisms - the result, which cannot be derived from biomolecular mechanisms. The results on livers and liver transplants' growth in dogs and humans, obtained by the General growth law, *principally* cannot be obtained on a biomolecular basis.

Besides the presented proofs and considerations, there are lots of other intricate interconnections, facts and effects, common sense and philosophical considerations, which add to the validity of the General growth law, but which were impossible to discuss here. Ten years of work, done in spare time, preceded this article; about seven hundred thousand words, only in *final* versions of books and articles, were written; several hundred of *final* graphs and diagrams were calculated and plotted, all to describe the essence and numerous subtleties of the General growth law and its applications. It's difficult to convey such knowledge in a relatively short article. So, the emphasis was made on concrete results, on correspondence of obtained growth curves and metabolic properties to experimental data. Some critics said that such conformity is the result of fitting and manipulations by equation's parameters. Indeed, some models include approximate parameters - for instance, a diameter of fission yeast, for which only average values were estimated. However, such estimations are realistic. Previous works show that variations of such parameters within the estimated ranges of errors affect the shape of growth curves little[21].

Apart from the experimental data, the second stream of proofs relates to mathematics and rather philosophical criteria used for verification of scientific theories. One of the most powerful criteria of validity of general theories is that they should provide convergence to prior obtained more particular results and less general theories. Indeed, we obtained the generalized solution of the growth equation for a particular growth scenario, which includes a known logistic formula as a particular case of the growth equation Eq. (1), when it was applied to two geometric forms - a disk and a sphere. According to the theory of verification of scientific knowledge, this is a very strong evidence of validity of the General growth law. Furthermore, we found that the growth ratio for these forms is an *exponential* function of time, which is also the result important from the validation perspective - many natural processes, indeed, are described by exponential functions, like the attenuation of waves in absorbing media, transitional electric processes, etc. In this, of especial importance is the fact that the input data - the relative volume and the relative surface of a disk and a sphere - contain no exponential functions. The fact that this result is not an abstract mathematical interplay, but the property of *real* physical and biological processes, the property of a *real world*, makes the results even more valuable. Their fundamental meaning is yet to be understood, but it is already clear that some important feature of the real world was discovered, related to its *fundamental* geometrical properties.

It takes time and efforts to understand the value of the General growth law, which proves that biological phenomena, indeed, are driven by *physical* laws guiding *biomolecular* machinery in a feedback manner. The idea of the General growth law is against only the *unilateral* understanding of life origin and development as an entirely biomolecular affair, as the only possible cause. However, it does not dismiss biochemical mechanisms, but includes them into a new *physical* paradigm of Life as an inherent component. In this regards, the physical paradigm of Life is a qualitatively more general concept, or theory, which includes the previous biochemical paradigm. According to the theory of verification of scientific knowledge, this fact, the inclusion of the older theory into a new one, is of great importance that provides strong support in favor of validity of the General growth law and of the new theory - the physical paradigm of Life.

The General growth law, in fact, makes understanding of life mechanisms much simpler; it removes the aura of mystery surrounding the notion of preprogrammed genetic codes - never discovered, thus reducing the entire phenomena to transparent workings of physical laws. On phenomena of such scales as Life, Nature works on simpler, more elegant, and much more reliable and optimal principles than relying on particular molecular events. By and large, biochemical mechanisms are *executors* - very active, persistent, sending feedbacks, with lots of possibilities and workarounds, tireless and absolutely indispensable foundation of life. But not the only and, by and large, not the leading ones, however heretically this statement could sound now.

At some point, the presently fragmented biochemical mechanisms have to be united on a more general basis (or bases). The General growth law and the new physical paradigm of Life, proposed here, include and unify these mechanisms, as well as all other known facts and knowledge, at *all* scale levels. In short, this physical paradigm states: *Life is governed by physical laws of nature acting at different scale levels, from molecules to cells to organs and systems to whole organisms. The physical law - the General growth law, acting at cellular level and above, imposes macro-constraints, tied to geometry of organisms, defining the relative amount of produced biomass (relative to the total nutrient influx). Biomolecular mechanisms comply with the imposed constraints at each moment of growth and reproduction. The major constrain, the relative amount of produced biomass, defines composition of biochemical reactions, while the biomass increase, in a feedback manner, causes the change of the constraint. This change, in turn, alters the composition of biochemical reactions and secures their irreversibility. This way, organisms are forced to autonomously and automatically proceed through different phases of their life cycles.*

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