Research Article

Micro- and Macroevolution: A Continuum or Two Distinct Types of Change?

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How microevolution and macroevolution are related is one of the major unanswered questions in evolutionary biology. The most prevalent view is that microevolution and macroevolution are part of a continuum of one type of change and that macroevolution is the cumulative result of microevolution. Mathematics, however, distinguishes two fundamentally different, singular types of change: change of a vector in its parameters versus its dimensions. This mathematical distinction may help to articulate the concept of evolution by distinction of two fundamentally different types of evolution: the change of the state vector of an organism in 1) its parameters (= 'first-order evolution') and 2) its dimensions (= 'second-order evolution'). This distinction can be operationalized by identifying genes and regulatory elements in the nucleotide code of an organism as dimensions of its state vector. This operationalization allows us to substitute the subjective phenotype-based analysis of evolution with a genotype-based analysis and draws attention to the mechanisms that change the parameters or the dimensions of the state vector, respectively. We illustrate the distinction between first- and second-order evolution with a simulation of the adaptive dynamics of a population of digital amoebas. Our mathematical genotype-based approach reveals that micro- and macroevolution are two distinct types of change.

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1. Introduction

In their 150-year anniversary review article of evolutionary biology in *Nature,* Reznick and Ricklefs noted that the relationship between microevolution (adaptation) and macroevolution (speciation and the origin of the divisions of the taxonomic hierarchy above the species level and the development of complex

organs) belongs to "*... some of the major unanswered questions in evolutionary biology*" [1] (p.841). The most prevalent view is that macroevolution is the cumulative result of microevolution, shaped by natural selection and genetic drift, resulting in divergence and radiation pushing lineages apart, where extinction events erase bridges that once joined them [1][2]. According to this concept, microevolution and macroevolution are part of a continuum of one type of change. Mathematics, however, distinguishes two fundamentally-different, singular types of change: change of a vector in its parameters versus change in its dimensions. We propose that such a dichotomy of change also applies to evolutionary biology.

The mathematical distinction between the change of a vector in its parameters and its dimensions is not just a theoretical or philosophical distinction, but also holds for the change of the state vector of every system, including biological systems. We define the change of the state vector of an organism in its parameters as 'first-order evolution' and in its dimensions as 'second-order evolution'. We operationalize the mathematical distinction between first- and second-order evolution by identifying genes and regulatory elements in the nucleotide code of an organism as dimensions of its state vector. This operationalization allows the substitution of the subjective phenotype-based analysis of evolution with a genotype-based analysis, supported by DNA-analysis technology, and draws attention to the mechanisms that change the parameters or the dimensions of the state vector, respectively. We illustrate the distinction between first- and second-order evolution with a simulation of the adaptive dynamics of a population of digital amoebas. Finally, we discuss how the distinction between first- and second-order evolution and their underlying fundamentally different driving mechanisms advances our understanding of evolution and opens new directions for future theoretical and applied research on evolutionary change.

2. Methods-A: first-order versus second-order change

Mathematics distinguishes two fundamentally different types of change:

1. Change of a vector in its **parameters**:

$$\begin{pmatrix} a1 \\ b1 \end{pmatrix} \rightarrow \begin{pmatrix} a2 \\ b2 \end{pmatrix}$$

2. Change of a vector in its **dimensions**:

$$\begin{pmatrix} a1 \\ b1 \end{pmatrix} \rightarrow \begin{pmatrix} a2 \\ b2 \\ c2 \end{pmatrix}$$

The mathematical distinction between the change of a vector in its parameters versus its dimensions is not just a theoretical or philosophical distinction. Indeed, following systems theory [3][4], this distinction holds for the change of every system, including biological systems. To illustrate this, let X be a system in our physical reality, for instance, a sheet of paper, cup of coffee, computer, organization, cell, organ, or organism. The state of X at time '*t*' can be described by the state vector $\boldsymbol{S}(t) = (s_1t, s_2t, ..., s_nt)$. Each dimension s_i (i= 1, 2, ..., n) of the state vector represents one of the characteristic properties of X, whereas the parameter $s_i\alpha$ of the state vector describes the value of dimension s_i at t=α. The set of dimensions $\{s_i\}$ chosen to describe the state of X depends on which properties a researcher considers characteristic for X.

If the time changes from t=α to t=β, the state of X changes from $\boldsymbol{S}(\alpha)$ to $\boldsymbol{S}(\beta)$. This change of the state vector may consist of:

a. a change in its parameters (= '*first-order systems change*'), resulting in a movement of the state vector within its initial system space (= the space limited by the dimensions of the state vector at t=α); or
b. an expansion of its dimensions (= '*second-order systems change*'), resulting in a movement of the state vector beyond its initial system space

When a parameter of a physical system reaches values that can no longer bring the corresponding dimension to expression, the state vector degenerates and its number of functioning dimensions decreases. Because the nonfunctioning dimension is not removed, the number of dimensions of the state vector does not change. Consequently, degeneration of the state vector is a special case of first-order systems change. Therefore, when a physical system changes, its state vector may either keep moving within its initial system space, in a first-order systems change, or may move beyond its initial system space, in a second-order systems change.

As changing the parameters of a state vector can never produce new dimensions, first-order systems change cannot transform into second-order systems change. This can be illustrated by the change of a 2-dimensional system, such as a sheet of paper. According to a researcher who is not interested in its thickness, color, or weight, the state of the sheet of paper can be fully described by its length and width. Using a cutter, the values of both dimensions can be changed. However, this mechanism of change cannot add a third dimension to the sheet and transform it into a paper box, as a box has not only a length and width, but also a height. For this second-order change, a different mechanism is required.

The example of changing a 2-dimensional system by only its parameters versus the change of a 2-dimensional system into a 3-dimensional system by adding a new dimension reveals the necessity to not only distinguish first-order from second-order systems change, but also to distinguish the mechanism(s) driving the change of a system in its parameters from the mechanism(s) driving the addition of new dimensions.

3. Methods-B: Operationalization of first- and second-order evolution of organisms

The distinction between first-order and second-order changes of a system requires the description of its state by a state vector based on the determination of a set of characteristic properties/dimensions, which is a subjective task. The characteristic properties/dimensions of an organism (a biological system) are usually determined by assessing its size and traits. The subjectivity of this approach can be avoided by deriving the characteristic properties/dimensions directly from the nucleotide code of the organism. The well-studied protein-coding genes clearly represent characteristic properties/dimensions of an organism. Since the 90s of the last century, however, evo-devo research has revealed that the nucleotide code not only contains protein-coding genes but also regulatory elements (promoters, operators, enhancers, repressors, silencers, and insulators) that control or regulate the expression of one or more genes [5]. These regulatory elements also represent characteristic properties/dimensions.

The mathematical distinction between first-order change of an organism (= '*first-order evolution*') and second-order change of an organism (= '*second-order evolution*') thus does not need to be grounded in the subjective assessment of its phenotype. Instead, the distinction can be grounded in the assessment of its genotype and operationalized by identifying the genes and regulatory elements in its nucleotide code as its dimensions. In first-order evolution, the nucleotide code of the organism changes only in its parameters, and no new dimensions are added; consequently, the length of the code does not change. In second-order evolution, new dimensions are added to the code, and its length increases. We will explain this in more detail below by specifying the biochemical mechanisms that change the parameters of the state vector of an organism, and by specifying the biochemical mechanisms that add new dimensions.

3.1. First-order evolution and its underlying biochemical driving mechanisms

First-order evolution occurs if the state vector of an organism changes only in its parameters. Gene regulation, epigenetic modification, and recombination of gene variants, followed by selection, are mechanisms that drive first-order evolution, as they do not expand the length of the nucleotide code by adding new dimensions but only vary the impact of the already existing nucleotide code.

Gene regulation. Regulatory elements (promoters, operators, enhancers, repressors, silencers, and insulators) in the nucleotide code control the moment, extent, and duration of the expression of protein-coding genes. Often, one regulatory element controls another, and so on, in a gene regulatory network. An example of gene regulation is the tuning of the production of three enzymes required to metabolize lactose in *Escherichia coli* by a set of regulatory elements called the 'lac-operon' [6].

Epigenetic modification. The DNA molecules of organisms are packed in protein as 'chromatin'. 'Histones' are the primary protein components of chromatin, which bind to the DNA and function as anchors around which the strands are wound, forming a 'nucleosomes' and a 'beads on a string structure'. Nucleosomes can cluster into compact arrays, which, in turn, can form compact fibers. This packaging of the DNA prevents the strands from becoming tangled and plays an important role in reinforcing the DNA during cell division, thereby preventing DNA damage. Modification of histones, by e.g., acetylation and DNA methylation, may alter the expression of genes without changing their nucleotide code [7][8][9]. These 'epigenetic modifications' are dynamic and serve as adaptation mechanisms to a wide variety of environmental and social factors, including diet [10].

Recombination of gene variants and selection. Gene variants – alleles – are present in the gene pool of populations and result from inheritable, unrepaired, non-code-expanding mutations. Random recombination of alleles by crossover during the production of gametes and the selection of advantageous allele combinations provide additional adaptive potential for the parameters of the nucleotide code. This mechanism does not produce new alleles. If, for example, the habitat of a population of Darwin finches changes and almost solely hard seeds are available, finches with a combination of alleles that produce a broad beak will survive, whereas during periods when small insects prevail, finches with a combination of alleles that produce a sharp beak will become more prevalent in the population [11]. By this mechanism, the population of finches can adapt continuously to changing circumstances, whereby the state vector of the individual finches keeps moving within its initial systemspace. Other examples of the efficacy of the mechanism are the observed variation in the form of

dog coats, the rapid development of resistance of bacteria against antibiotics, and convergent evolution in *Anolidae* [11][12][13][14]. In artificial breeding programs, the mechanism can produce a wide variety of dogs, pigeons, tulips, etc. in a short time.

The mechanisms of first-order evolution are not antagonized by mutation repair systems that protect the nucleotide code [15][16][17][18]. Moreover, the mechanism of first-order evolution by the recombination of alleles provides a means of repairing damage to the genome and antagonizing code-expanding mutations, as alleles inherited from the father of an organism are paired with those of the mother. If they differ in length, the crossover fails, the production of gametes is aborted, and the inheritance of code-expanding mutations is stopped [19][20].

In contrast to digital codes, where the dimensions – program modules – can only be switched on or off, the dimensions of nucleotide codes can have many gradations between being silent and fully expressed, resulting in a broad spectrum of effects. Organisms thus possess massive potential to adapt their parameters in first-order evolution to changing circumstances. Consequently, the expression of the nucleotide code of an organism is not deterministic, but rather plastic and self-organizing in a complex manner [21].

3.2. Second-order evolution and its underlying biochemical driving mechanisms

Second-order changes of a biological system are present if new dimensions – protein-coding genes or regulatory elements – are added to its nucleotide code, resulting in the expansion of the length of the nucleotide code. The biochemical driving mechanism of second-order evolution is the accumulation of unrepaired code-expanding mutations of the nucleotide code [22][23][24][25][26]. The mechanism of second-order evolution is antagonized by mutation-repair systems that protect nucleotide codes. Empirical evidence for the mechanism of second-order evolution has been found in radiation- and chemical-induced mutagenesis in organisms that produce new phenotypes [27][28], in polyploidization [29], and in the molecular evolution of *Escherichia coli* in 12 experimental populations [30].

Molecular evolution. Since the 90s of the past century, the rapid increase in digital data processing capabilities and storage capacity has made it possible to develop so-called ‘morphing software’, which transforms step by step any photo, picture, image, or dataset into any other photo, picture, image, or dataset [31]. Morphing software has become a part of custom applications such as Photoshop. Morphing

software appears to be a powerful tool for simulating molecular evolution, such as the transformation of simple molecules into complex molecules, the transformation of a few genes into a family tree of novel genes, or the simulation of how the genome of a species originated from the genome of a bacterium. It is also a powerful tool for analyzing the similarity between base- or amino acid sequences in DNA and proteins, respectively, between taxons [32][33][34][35][36][37][38][39]. Our mathematical definition of first- and second-order evolution identifies the transformations produced by simulated molecular evolution as second-order evolution, because the length of molecular fibers, or strings of nucleotides involved, expands.

Although simulations of molecular evolution illustrate second-order evolution (the accumulation of code-expanding, unrepaired mutations) over deep time, empirical validation of the mechanism whereby this second-order change is realized is necessary. In the past decade, substantial progress has been made in research on self-replicating molecules. It can be shown that in water at approximately 35 °C, basic active substances can produce fibers that grow under mild agitation and compete with one another to obtain the required materials [40][41][42]. Future research at the interface of biology and chemistry is needed to discover the conditions under which self-replication and production of increasingly longer strings of hydrocarbon molecules continues.

3.3. Substitution of a phenotype-based analysis of evolution with a genotype-based analysis

Analogous to the mathematical distinction between the change of a vector in its parameters (= first-order change) and the change in its dimensions (= second-order change), we distinguished first-order evolution (= change of an organism in its parameters) from second-order evolution (= change of an organism in its dimensions). We operationalized this distinction by identifying genes and regulatory elements as dimensions of the state vector of an organism. This operationalization allows the substitution of the research of evolution based on a subjective analysis of the phenotype of organisms by a genotype-based analysis, supported by standard DNA analysis technology that can reveal whether the expansion of the state vector into new dimensions has occurred or only a change in its parameters.

In a phenotype-based analysis of evolution, every change of phenotype (for instance, the prevalence in a population of finches of a broad beak instead of a small one) is explained as caused by a mutation. In a genotype-based analysis of evolution, a distinction can be made in a change of a state vector in its parameters (first-order) or its dimensions (second-order), where a first-order change is driven by gene regulation, epigenetic modification, and/or recombination of gene variants and selection. These changes

are not antagonized by the mutation repair mechanisms of the DNA and can be denoted more accurately as variations, where the state vector continues to move within the initial system space (for instance, the initial system space of a population of finches). Second-order changes are driven by the accumulation of unrepaired code-expanding mutations of the DNA. Using standard DNA analysis technology, it can be assessed whether code expansion has occurred or not. This allows us to determine whether the change of phenotype has been driven by gene regulation, epigenetic modification, and/or recombination of gene variants and selection, or by the accumulation of unrepaired, code-expanding mutations of the DNA. Table 1 summarizes the distinguishing characteristics of first- and second-order evolution.

	First-order evolution	Second-order evolution
Definition	Change of the state vector of an organism in its parameters	Expansion of the state vector of an organism in its dimensions
Illustration	$\begin{pmatrix} a1 \\ b1 \end{pmatrix} \rightarrow \begin{pmatrix} a2 \\ b2 \end{pmatrix}$	$\begin{pmatrix} a1 \\ b1 \end{pmatrix} \rightarrow \begin{pmatrix} a2 \\ b2 \\ c2 \end{pmatrix}$
Biochemical driving mechanisms	Gene regulation, epigenetic modification and recombination of gene variants, followed by selection	Accumulation of unrepaired, code-expanding mutations
Expansion of the nucleotide code	No	Yes
Production of new genes and regulatory elements	No	Yes
Antagonized by mutation repair	No	Yes
Evidence	Abundant empirical evidence, e.g., the variation in the shape and size of the beaks of Darwin's finches	Radiation and chemical mutagenesis experiments on organisms that produce new protein-coding genes or regulatory elements, and accurate computerized reconstruction of molecular evolution over deep time

Table 1. First- and second-order evolution, and their distinguishing empirical characteristics

4. Results: First- and second-order evolution of a population of digital amoebae

To illustrate the distinction between change of the state vector of an organism in its parameters (= first-order evolution) and expansion of the state vector of an organism in its dimensions (= second-order

evolution), we use a population of digital amoebae.

A digital amoeba – a 'Damoeb' – consists of a small (3.3 Kbytes) C++ program that imports two numbers from an input file, processes them into another number, and exports it to an output file [25]. The processing of the input depends on the value of a control parameter in the Damoeb program code, which can have values of 1, 2, 3, or 4, regulating the activation of the operators for summation, subtraction, division, or multiplication, respectively. A replication and random variation (RRV) program is used to make a copy of a Damoeb and to assign, with differing probabilities, a value of 1, 2, 3, or 4 to the control parameter of the copy Damoeb, resulting in an α-type Damoeb, a β-type Damoeb, a γ-type Damoeb, or a δ-type Damoeb, respectively. The copy Damoeb receives the control parameter value of the original Damoeb with a 94% chance or one of the three alternative values of the control parameter with a 2% chance each. The RRV program simulates the exchange of alleles that is present in the gene pool of an amoeba population [13]. It can also be viewed as simulating gene regulation and the inheritance of gene expression to posterity [43][44]. During a replication time interval τ, a Damoeb enters the RRV program once, and after an existence of 5 τ, a Damoeb is deleted. The simulation starts with one α-, one β-, one γ-, and one δ-type Damoeb. They are fed with the number pair (20,5) and replicate freely until the population consists of approximately 1000 Damoebas equally distributed over each type. Subsequently, selection rule S1 is imposed on the population, which allows only Damoebas that produce an output number between 0 and 20 to replicate. Hereafter, the share of β- and γ-type Damoebas in the population grows strongly at the expense of the α- and δ-types, which produce an output number of 25 and 100, respectively. However, the α- and δ-types do not become extinct because the RRV program allows them to arise sporadically (2% chance each) from the replication of β- and γ-type Damoebas. After approximately six replication cycles of random variation and selection, the distribution of Damoeb types reaches a new dynamic equilibrium. Next, selection rule S1 is replaced by rule S2, allowing only Damoebas that have an output greater than 50 to reproduce. Now, the population moves towards a distribution with mainly δ-type Damoebas and a very small share of α-, β-, and γ-type Damoebas. When S2 is replaced by selection rule S3, demanding that the output be between 0 and 10 or between 20 and 50, the α- and γ-type Damoebas start to dominate the population. The population of Damoebas (Figure 1) shows the same evolutionary dynamics as those observed in, for instance, a population of bacteria or finches [11].

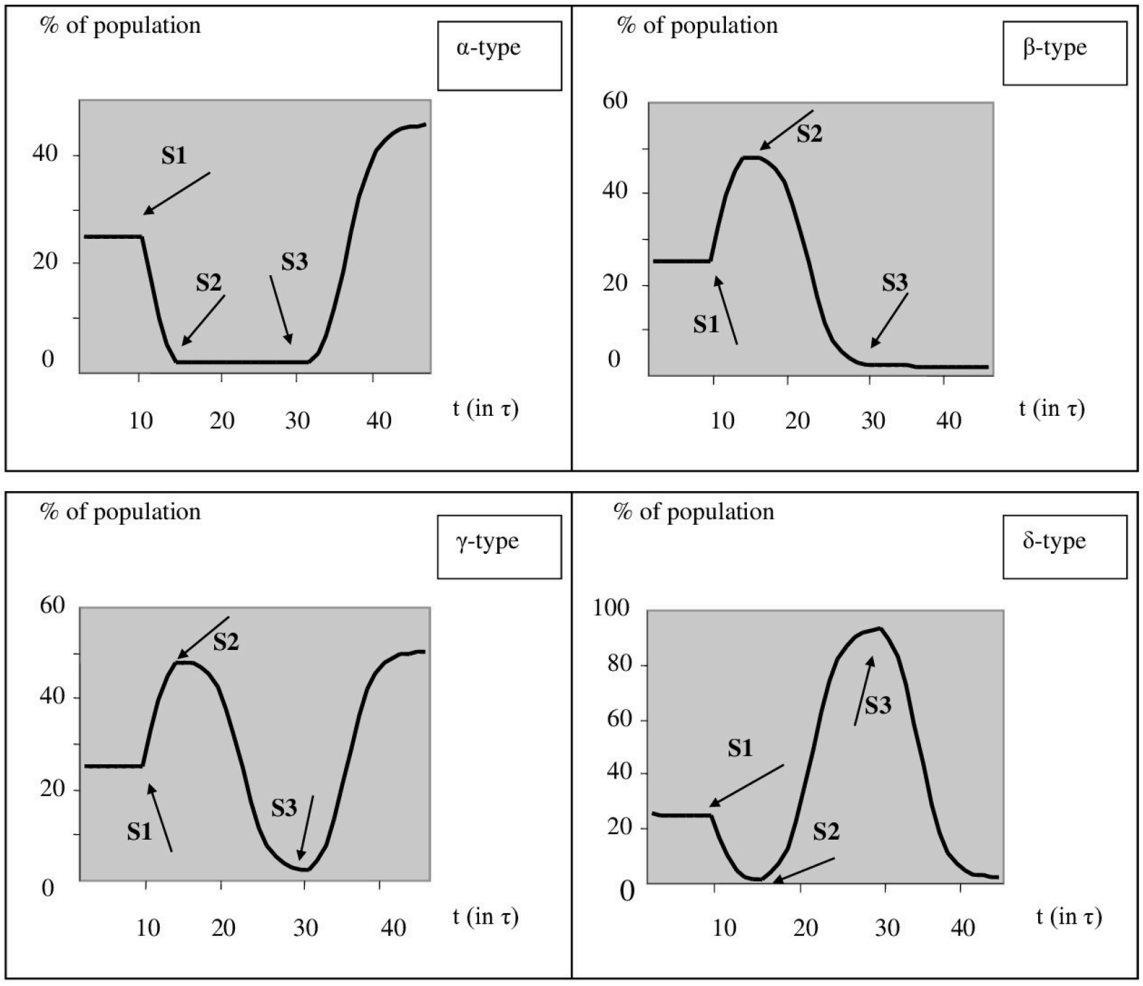

Figure 1. Evolutionary dynamics of a Damoeb population as a response to selection rules S1, S2 and S3 imposed respectively at 9 τ , 15 τ, and 29 τ, where τ is the replication time of a Damoeb. For explanation of selection rules, see text. Source: [25]

Damoebs possess one characteristic property or dimension: 'the ability to transform the number pair (20,5) into a single number', depending on the value of a control parameter, which

can have a value of 1, 2, 3, or 4, regulating the activation of the operator for summation, subtraction, division, or multiplication. The state of a population of Damoebs at time *t* can be described by a state vector with one dimension, where its entry represents the parameter value of the Damoeb-type that has the highest frequency in the population at time *t*. In response to the changing selective pressures mentioned above, the state vector of the population of Damoebs moves within its initial one-dimensional system space from coordinate (1) at $t_0 = 0\tau$ to coordinate (2) at $t_1 = 9\tau$, to (4) at $t_2 = 19\tau$, and to (3) at $t_3 = 34\tau$.

We visualize this movement of the state vector from coordinate to coordinate in its one-dimensional system space using a sequential set of columns of one entry $\{S1t_i \mid i= 0, 1, 2, 3\}$, as shown in Fig. 2.

After t=t_3, the number pair (20,5) slowly disappears, threatening the population with extinction. To survive this severe selective pressure, the Damoebs need to develop a new characteristic property/dimension by the mechanism of second-order evolution: the accumulation of code-expanding, unrepaired mutations. DeJong and Degens [25] attempted to simulate this mechanism by expanding the RRV module with a submodule that randomly changes bits of the digital code of a Damoeb and inserts copies of random parts elsewhere in the code, resulting in second-order change of the program code of a Damoeb. However, when the expanded RRV module was used, the mutated Damoebs generated error messages at the bit level or spelling and syntax errors at higher levels of the program code, produced by the standard mutation protection of digital codes and the standard error protection of systems software. Therefore, we apply an alternative approach and simulate second-order evolution by a form of operator-based programming [45], combining standard Excel operators with 'scripted manually-executed operators', which may be substituted with 'dedicated-designed Excel operators' in the next phases of computerization of the simulation.

To survive the decreasing availability of number pair (20,5), the Damoebs need to develop the ability to digest alternative food. Therefore, we imagined: (1) a set of alternative foods $\{AF_i\}$, consisting of the integer numbers between 1 and 15; (2) an additional digestive process that transforms a single number AF into a duplet number (X, Y) = (CP1*AF, CP2*AF); (3) a set of possible parameters CP1 and CP2 to control the digestive process, consisting of the integer numbers between 1 and 10 plus each number divided by 10. Subsequently, the alternative digestive process was fed at random with alternative food and regulated by a random choice of the control parameters. Hereafter, the fitness of the alternative digestive process to survive the absence of the number pair (20,5) was tested. This random procedure finally resulted in the development of a new characteristic property/dimension of a Damoeb, consisting of the ability to read the number 10 and transform it by the alternative digestive process controlled by CP1=2 and CP2=0.5 into the disappearing food (20,5). The Excel sheet in Fig. 2 visualizes this and shows how the sequential set of state vectors of one entry $\{S1t_i \mid i= 0, 1, 2, 3\}$ is followed at t=t_4 by a state vector with two entries $S2t_4$, describing the expansion of the state vector with one dimension, revealing the occurrence of second-order evolution.

After development by one Damoeb of a new dimension ('the ability to digest the number 10'), the Damoeb population is able to survive and grow again. Hereafter, the population responds in first-order evolution

to fluctuations in the availability of the number 10 at t=t_5, t=t_6, and t=t_7, which can be described by a sequential set of state vectors of two entries {S2t_i | i= 5, 6, 7}.

After t=t_7 the survival of the Damoeb population is threatened again because other organisms start to eat the number 10. In response to this threat, one Damoeb develops at t=t_8, by the approach described above, the ability to transform a triplet of numbers (5,11,20) into the number 10. In addition, the Damoeb develops a new dimension to fight its competitors by producing the number 30, which is lethal to them. Consequently, the state vector moves in second-order evolution beyond its 2-dimensional system space into a 4-dimensional system space. After this expansion of its dimensions, the population can survive and starts to respond in first-order evolution to fluctuations in the presence of its competitors and the availability of the triplet (5,11,20). The resulting movement of the state vector of the population within a 4-dimensional systemspace can be described by adding a sequential set of state vectors of four cells {S4t_i | i= 9, 10}. At t=t_{11}, t=t_{15} and t=t_{19} second-order evolution occurs again, followed by a period of first-order evolution, as shown in Fig. 2.

The entire Excel table, with its growing number of columns and expanding number of rows, visualizes the alternation between first- and second-order evolution with time. The dimensionality of the state vector can be reduced by making assumptions on the relevance of certain rows in the Excel table [46][47], but the fundamental difference between first- and second-order evolution remains visible. This fundamental difference can also be noticed in evolutionary gaming, for instance when the computer program for simulating a ‘tit for tat strategy’ is expanded into a new dimension by addition of a program module that simulates the impact of ‘forgiveness’ or ‘reputation’ [48][49][50].

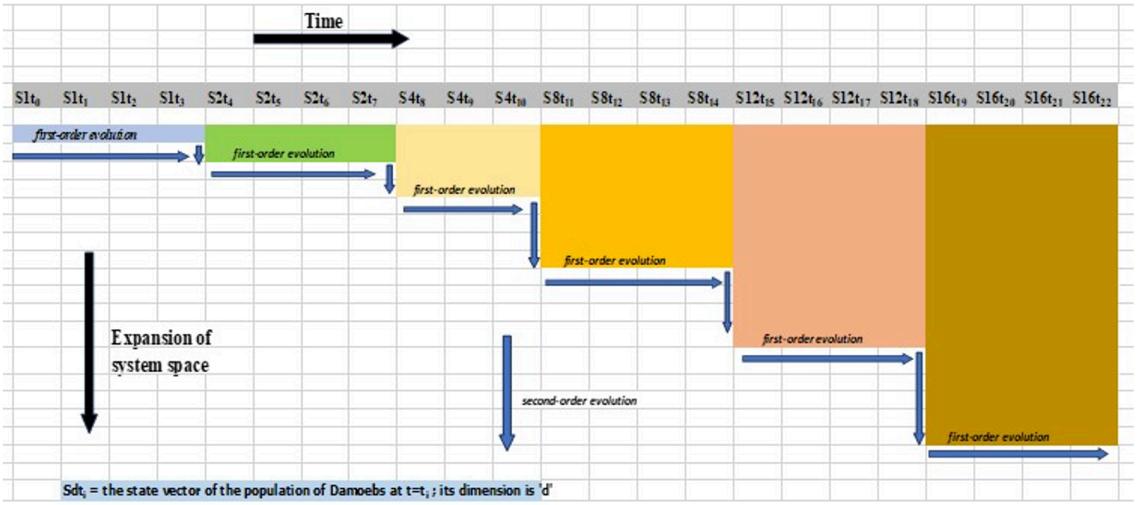

Figure 2. The adaptive dynamics of a population of digital amoebae ('*Damoebs*') mathematically represented by a sequential set of state vectors $\{Sdt_i \mid i = 0, 1, 2, ...21, 22\}$ and visualized in an Excel spreadsheet, where 'd' is the number of dimensions of state vector Sdt_i . Periods of time when the dimension of the state vector does not change (= *first-order evolution*) alternate with periods of time when the dimension of the state vector increases (= *second-order evolution*).

5. Discussion

5.1. Micro- and macroevolution

The relationship between microevolution (adaptation) and macroevolution (speciation and the origin of the divisions of the taxonomic hierarchy above the species level, and the development of complex organs) remains a major controversy in evolutionary biology [1] (p.841). In general, macroevolution is considered a lot of microevolution, shaped by natural selection and genetic drift, resulting in divergence and radiation pushing lineages apart, where extinction events erase bridges that once joined them. In this concept, microevolution and macroevolution are part of a continuum of one type of change, called evolution.

Following from the mathematical distinction between the change of a vector in its parameters versus the change in its dimensions, we have defined two distinct types of evolution: 'first-order evolution' (= change of the state vector of an organism in its parameters) and 'second-order evolution' (= expansion of the state vector of an organism in its dimensions). Both types of change differ fundamentally in their empirical characteristics: (a) the underlying driving mechanisms; (b) the expansion of the nucleotide

code, or not; (c) the production of new genes and regulatory elements, or not; (d) the antagonization by mutation repair, or not (see Table 1).

In first-order evolution, an organism adapts to a changing environment by changing only the parameters of its state vector, not its dimensions. This adaptation is analogous to microevolution. Therefore, first-order evolution is identical with microevolution. In second-order evolution, an organism adapts to a changing environment by developing new characteristic properties, such as complex organs, resulting in the expansion of the dimensions of its state vector. This is analogous to macroevolution. Therefore, second-order evolution is identical with macroevolution.

Our simulation of the adaptive dynamics of a population of digital amoebae, represented by a sequential set of state vectors (see Fig. 2), illustrates both types of evolution. During first-order evolution of the population of Damoebs, only the parameters of the program code of the Damoebs change, resulting in continuous adaptation to a changing environment, which is analogous to microevolution. During second-order evolution of the population of Damoebs, new program code is developed, resulting in new complex organs, which is analogous to macroevolution.

5.2. Evolutionary novelty and innovation

Explaining the evolutionary origins of morphological novelty and behavioral innovation is a central endeavor in contemporary evolutionary biology. The explanation of evolutionary novelty appears to be a 'problem of ever-increasing depth' [51] (p.301), without consensus [22][23][52][53][54][55][56][57]. A key source of controversy is the definition of evolutionary novelty, where a 'novel' trait, feature, function, or character according to one definition is not novel according to another. In other branches of science, such as economics, organization science, technology, and (creative) industry, the definitions of novelty and innovation are similarly problematic [58][59][60][61]. Nevertheless, a dichotomy is usually observed between 'ordinary change' on the one hand and 'novelty', 'innovation', 'invention', 'second-order change', 'transformation', 'metamorphosis', 'quantum jump', or 'out-of-the-box change' on the other hand.

In the discourse on evolutionary novelty, Erwin [62] applies the mathematical concept of 'space' to clarify its essence. He draws attention to "*... the difference between adaptive searches within an existing space and the construction of new spaces*"(p.4), and argues that "*... the generation of new operators as well as the generation of new evolutionary spaces reflects macroevolutionary change*" (p.6). Following this line of thought, Erwin [63] (p.736) notes: "*The ideal goal would be to identify a formal (i.e., mathematical) model of novelty and innovation...*". Our mathematical definition of first- and second-order evolution provides such

a formal model. It defines second-order evolution as the expansion of the state vector of an organism into one or more new dimensions, resulting in the generation of new spaces. Therefore, evolutionary novelty is equivalent to second-order evolution and differs from first-order evolution, which is a process of searching for combinations of attributes that increase fitness (by gene regulation, epigenetic modification, and recombination of alleles and selection) within an already existing space (as defined by the nucleotide code of an organism).

5.3. Computer simulation of first- and second-order evolution

We have illustrated the dichotomy between first-order and second-order evolution with a computer simulation of the evolution of a population of digital amoebes (see Fig.2). Below, we add four more examples to this illustration, taken from the extensive literature on computer simulations of evolution, and discuss the presence of first- and second-order evolution.

AVIDA is a computerized environment in which a fixed set of predefined low-level computer instructions is combined at random, resulting in independent programs ('digital organisms') that replicate and compete with one another for runtime [64]. For example, when a string of 80 predefined computer instructions is required to move a computer processor from a predefined initial state to a predefined end state, random recombination of these instructions and giving a competitive advantage to strings of instructions that consume little processor time can produce alternative routes to the end state that take approximately 30 instructions only [65]. During the optimization process, the predefined set of processor instructions remains unchanged. Consequently, the state vector of each digital organism keeps moving within its initial system space (= first-order evolution) along a path determined by its calculated fitness at a certain moment. Second-order evolution can be achieved by upgrading the computer processor using a processor that can perform one or more additional instructions. With these new instructions, the digital organisms may become fit for survival under conditions that otherwise would have caused their extinction, for instance, the condition that the end state should be produced within 25 instructions.

REvoSim produces computerized organism-level evolution simulations [66]. A digital organism in REvoSim possesses a 'coding genome' of 32 bits, which determines its fitness in an environment, plus a 'non-coding genome' of 32 bits, which provides additional genetic differences with other digital organisms present in REvoSim. The state of a digital organism in REvoSim can be described by a state vector with 64 dimensions, each of which may vary in the corresponding parameter (0 or 1). The number of dimensions does not change during the simulation. As a result, the state vector of each digital

organism continues to move within its initial system space (= first-order evolution) along a path determined by its calculated fitness at a certain moment. If a random expansion module is added to the genome of a digital organism, its state vector can expand beyond its initial system space, resulting in second-order evolution. By selection, expansions that make the organisms fit for survival under circumstances that they would not have survived otherwise can be obtained.

Lotka-Volterra simulations of evolution. An alternative approach to modeling the evolution of a biological system applies a set of differential equations called the Lotka-Volterra model [67]. The equations capture, for instance, the adaptive dynamics of a prey population interacting with a predator population, where the changes in the size of both populations can be represented by the stable movement – despite small disturbances – of a two-dimensional vector around an attractor. In this phenotype-based approach to evolution, the phenotype of a population is represented by a scalar. This population may be invaded by a mutant. If the mutant shows positive invasion fitness, the attractor defining the stable dynamics of the phenotype of the population starts to move. As a result of an ongoing random process of the death or invasion of mutants, a path emerges showing singular points where branching of the phenotype occurs, followed by further growth or truncation, resulting in an 'evolutionary tree of life' [68][69][70]. The branching of this tree of life models the rise and extinction of populations through random processes. Each branch can be denoted as a new dimension in which evolution proceeds. However, these dimensions have no relationship with the dimensions of the state vector of an organism, as defined in our genotype-based approach to evolution.

In the Lotka-Volterra simulations, evolution is modeled as a sequence of monomorphic or polymorphic population states, where the transition from one state to the next occurs when an advantageous mutant comes around and spreads [69] (p.48). This approach can be refined by incorporating the influence of continuous small perturbations [71][72]. For populations where the relative dynamics are slow compared to and decoupled from their aggregated dynamics, the Lotka-Volterra model produces a diverse life without the need to relegate speciation to extraneous mechanisms [73]. The adaptive dynamics of a population in the produced evolutionary tree of life are illustrated by shorter or longer lines connecting the end and nodal points of the tree. The paths are driven by random processes, but the tree does not leave the initial (2-dimensional) system space, thus representing first-order evolution. The simulation of second-order evolution requires a transition beyond the initial system space. This can be achieved by expanding the set of differential equations into a new dimension driven by selective pressures that would lead to the extinction of the population within the initial dimensions of the model.

MABE produces computerized organism-level evolution simulations [74]. A digital organism in MABE possesses a code called 'genome', which defines a data processor called 'brain' that converts inputs into outputs. The genome may change through biologically inspired crossover and recombination processes. The state of a digital organism in MABE can be described by a state vector of N dimensions, each of which may vary in its corresponding parameters. During a simulation, N does not change. As a result, the state vector of each digital organism continues to move within its initial system space (= first-order evolution), along a path determined by the calculated fitness at a certain moment. Driven by severe selective pressure that threatens the survival of the digital organisms, their genomes may be expanded by a random process during a simulation. The selection of expansions that make the brains of some organisms fit for surviving circumstances they would not have survived otherwise allows the population to overcome the threat of extinction by second-order evolution.

5.4. Covid-19

In late 2019, a novel human coronavirus named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2, or Covid-19), emerged in Wuhan, China, and caused a pandemic. The virus is common in armadillos [75]. Its nucleotide code of 29,903 bases [76] describes its characteristic inheritable properties (dimensions), such as how to connect to a specific host cell, how to enter it, and how to make the host cell reproduce, multiply, and spread the virus. Inheritable, unrepaired, non-code-expanding mutations allow the virus to continuously adapt its parameters to changing selection pressures, resulting in, for instance, altering the 3-dimensional shape of its 'spikes' that allow the virus to bind with one of the receptors of a host cell for the Angiotensin-Converting Enzyme 2 (ACE2), which is most abundant in the type II alveolar cells of the lungs [77].

Covid-19 differs in its dimensions from the population of viruses that the human immune system normally encounters, since the virus traversed the boundary that prevents viruses in bats or armadillos from entering human cells. Consequently, the human immune system has no experience with these new dimensions and needs to adapt with a second-order change, which is especially challenging for older or weak immune systems.

The ordinary human influenza virus differs from the influenza virus in the past year only in terms of its parameters. After the assessment of the parameters that have changed, the parameters of the vaccine in the past year can be adapted to obtain a vaccine for the current year. Since Covid-19 traversed the boundary that prevents viruses of bats or armadillos from entering human cells, current vaccines could

not be adapted by changing their parameters to counteract Covid-19; instead, a second-order change was needed in the production of vaccines, demanding substantial effort, time, and money. In the past few years, these vaccines have been adapted already several times in their parameters to counteract new variants of Covid-19, produced by amino acid substitutions [78]. In the future, the adaptation of vaccines in their parameters to emerging new variants of Covid-19 must continue.

The distinction between changes of a biological system in its parameters (= first-order evolution) versus change in its dimensions (= second-order evolution) thus helps to clarify: (a) the fundamental differences between Covid-19 and the human influenza virus; (b) the impact of Covid-19: more than 242 million confirmed infections worldwide, with nearly 5 million deaths; (c) the necessity to avoid zoonosis and thus second-order change in the domain of human viruses, for instance, by the removal of bio-industrial complexes from highly populated areas; and (d) the necessity to keep adapting the vaccines to new variants of Covid-19.

5.5. Directions for future research

A first direction for future research is further development of the operator-based simulation of second-order evolution presented here. The scripted manually executed operators can be substituted step-by-step with 'dedicated Excel operators' to represent the occurrence and spread of second-order evolution more accurately.

A second direction for future research is longitudinal genotype-based research into the response of organisms, populations, and ecosystems to man-made rapid environmental changes, which leave them, in evolutionary terms, a short time to adapt in first- or second-order evolution. Interesting research questions are: "Does the response to rapid environmental changes come from first- or second-order evolution, or from both?" "Does the rate of first- and second-order evolution change?" and "What differences can be observed between species?" Standard DNA analysis technology can reveal whether or not new genes or regulatory elements emerge. This will enhance our understanding of how biological systems respond to man-made changes in the environment and may inform actions to react more effectively to these changes, for instance, by preventing the loss of dimensions of a population of organisms instead of preventing the loss of a specific set of parameters.

A third direction of future research is the discovery of new dimensions within nucleotide codes. Research by the ENCODE consortium has revealed that at least 80% of the human nucleotide code participates in at least one biochemical RNA- and/or chromatin-associated event in at least one cell type, and that the

fraction of nucleotides involved in direct gene regulation is significantly higher than that ascribed to the well-researched protein-coding exons [79]. The same applies most likely to the nucleotide codes of other organisms, which leaves ample room for the discovery of new dimensions, such as the inheritance of characteristic color patterns. Many organisms show color patterns on their exterior, which often differ between adults and their young, and between males and females. These patterns are produced by pigments encoded by the protein-coding genes. The geometry of the inheritable color patterns, however, is not incorporated in these protein-coding genes, but must be coded elsewhere in the nucleotide code of the organism by a set of 'topographic color pattern dimensions'. In addition, regulatory elements must be present to switch from the characteristic patterns belonging to the young to the characteristic pattern of an adult male or female. Future research may be directed toward discovering which non-protein-coding nucleotides are involved in producing the characteristic color patterns of an organism. These non-protein-coding nucleotides represent additional dimensions of the nucleotide code. Interesting research questions are: "Which regions of the nucleotide code of an organism are involved in the inheritance of its characteristic color patterns?", "What are the biochemical mechanisms that bring these dimensions to expression, how, where, and when?" "How do other code systems of the cell, such as the coactivator code, the bioelectric code, and the sugar code [80][81][82] interact with these dimensions?" The discovery of the topographic color pattern dimensions of nucleotide codes and the related mechanisms to bring them to expression may open new directions for innovative treatment of cancer or aging by targeting a specific locus or region at the outside of an organism with a virus-like nano-robot that releases or produces a medicine or substance only at this specific locus. This may seem far-fetched, but bioengineering that seemed far-fetched 30 or 40 years ago is common today.

A fourth direction of future research is the application of the distinction between first- and second-order evolution in applied systems analysis, in combination with distinguishing the underlying driving mechanisms. These distinctions may advance our understanding of the adaptive dynamics of physical, technical, and social systems. In general, the representation, simulation, and visualization of the evolution of a (biological) system by a sequential set of state vectors, which may change either in their parameters or in their dimensions, opens new avenues for studying the adaptive dynamics of changing (biological) systems more accurately.

6. Conclusions

Every system may change in two fundamentally different ways: in its parameters or in its dimensions. We defined the change of the state vector of an organism in its parameters as first-order evolution and the expansion of its dimensions as second-order evolution. We operationalized this distinction based on the genotype of an organism, which allows the substitution of a subjective phenotype-based approach of evolution with a genotype-based approach supported by DNA analysis technology.

The articulation of the concept of evolution by distinguishing first-order and second-order evolution, as well as their specific underlying driving processes, makes it possible to answer one of the major unanswered questions in evolutionary biology: the relationship between micro- and macroevolution. We identified microevolution as first-order evolution and macroevolution as second-order evolution. We illustrated their fundamental differences with a computer simulation of the alternation of first-order and second-order evolution of a population of digital amoebae.

In all branches of science, a concept is articulated more precisely if it comprises two fundamentally different subconcepts [83]. The integrity of science does not permit exclusion of the concept of evolution from this scholarly principle. The articulation of the concept of evolution as a combination of first-order and second-order evolution advances science and opens new avenues for theoretical and applied research in biology and bioengineering.

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Data accessibility: The simulation of first- and second-order evolution of a population of digital amoebae (doi:10.5061/dryad.00000008s) is accessible at https://datadryad.org/stash/share/50XAsHvc9GJONgGLgTwTZdlhgV1wZudBjpZ2btrMCaA

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Declarations

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