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

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Abstract

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 and the level of expression as parameters of its state vector. This operationalization allows us to substitute the phenotype-based analysis of evolution with a genotype-based analysis and draws attention to the molecular 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 amoebae. Our genotype-based systems approach reveals that micro- and macroevolution are largely similar to first- and second-order evolution respectively, and are not a continuum 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.

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** (= the values noted in the components/entries/elements/cells of the vector):

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

2. Change of a vector in its **dimensions** (= the spaces of values associated with the components/entries/elements/cells of the vector):

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

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 also holds for the state vector of every system (e.g., a cup of coffee, a computer, a network of companies, a society), including biological systems (e.g., a cell, an organ, an organism, a population, an ecosystem, a network of ecosystems).

The construction of the state vector of a system X at time *t* starts in the physical domain by identifying its characteristic properties: $\{cp_i \mid i = 1, 2, \ldots, n\}$. The value of each characteristic property at time *t* can be noted qualitatively or quantitatively as a parameter $cp_i(t)$ of the state vector $\boldsymbol{S}(t)$ of X. Consequently, each characteristic property of X in the physical domain is associated with a dimension of the state vector in the mathematical domain.

$$\boldsymbol{S}(t) = \begin{pmatrix} cp_1(t) \\ cp_2(t) \\ cp_3(t) \\ \cdots \\ \cdots \\ \cdots \\ cp_n(t) \end{pmatrix}$$

The identification of the characteristic properties of a system is a subjective task. Different researchers will produce different sets of characteristic properties. These differences are often rooted in differences in view of the boundaries of the system, and in differences in telling the change story of the system [5]. Discussion between researchers helps to develop a shared view and to gain more insight into the differences that may persist.

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

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

Degeneration of the state vector

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 first-order systems change, or may move beyond its initial system space, in second-order systems change.

Changing the parameters of a (state) vector cannot change its dimensions. Therefore, 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 a state vector with two dimensions: '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 change of organisms

The approach described in section 2 to distinguish first-order and second-order systems change, can also be applied to organisms, which are biological systems. Firstly, a set of characteristic properties must be determined. The characteristic properties of an organism are usually determined by assessing its size and traits. The subjectivity of this approach can be reduced by deriving the set of characteristic properties of an organism directly from its nucleotide code. The well-studied protein-coding genes clearly represent characteristic properties 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 [6]. These regulatory elements also represent characteristic properties. Using the protein-coding genes and regulatory elements as dimensions, the state vector of the organism can be constructed. The parameters in the state vector have a qualitative or quantitative value, and describe the activity of the corresponding genetic element at a moment of time '*t*' in relationship with its genetic variance and the interaction with its environment.

In first-order change of an organism – which we denote as *first-order evolution'* – the state vector of the organism changes only in its parameters, in contrast to second-order change of an organism – which we denote as *'second-order evolution'* – where one or more new dimensions are added to the state vector. Standard DNA analysis technology can reveal whether

or not new genetic elements emerge. A first test is measuring the length of the DNA of the organism (its total number of nucleotides). Increase of the length of the DNA is a necessary condition for the addition of a new genetic element to the DNA. If an increase is found, subsequent research can reveal where this increase has occurred and what the functionalities are of the new genetic element. The distinction between first- and second-order evolution thus can be made by only measuring the length of the DNA, and does not require to identify every genetic element in the DNA and its function.

We will now specify the molecular mechanisms that underly first- and second-order evolution, and summarize their genotype-based characteristics in Table 1.

3.1. *First-order evolution and its underlying molecular driving mechanisms*

First-order evolution occurs if the state vector of an organism changes only in its parameters. Production of gene variants, recombination of gene variants, gene regulation and epigenetic modification, are mechanisms that drive first-order evolution, as they do not add new dimensions to the state vector, but only vary the activity of the already existing genetic elements. The variation of parameters is not limited to the lifetime of an organism but can be transferred to the next generation.

In contrast to digital codes, where the characteristic properties – program modules – can only be switched on or off, the genetic elements of nucleotide codes can have many gradations between being silent and fully expressed, resulting in a broad spectrum of effects. As a result, organisms possess massive potential to adapt their nucleotide code 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 [7].

Production 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. They allow populations to adapt to changing circumstances, by selection of advantageous variants, resulting in a change of the parameters of their state vector [8].

Recombination of gene variants and selection. 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. 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 [9]. 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 system space. 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* [9][10][11][12]. In artificial breeding programs, the mechanism can produce a wide variety of dogs, pigeons, tulips, etc. in a short time.

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' [13]. The regulatory elements provide organisms with additional capacity to adapt their nucleotide code in first-order evolution to changing circumstances [14].

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 [15][16][17]. Epigenetic modifications can also result from the different expression levels of non-coding RNAs such a miRNA [18]. These 'epigenetic modifications' are dynamic and serve as adaptation mechanisms to a wide variety of environmental and social factors, including diet [19][20][21][22].

The mechanisms of recombination of alleles and selection, gene regulation, and epigenetic modification are not antagonized by the mutation repair systems that protect the nucleotide code [23][24][25][26]. The mechanism of recombination of alleles and selection not only produces first-order evolution, but also 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 [27][28]. The mechanism of production of alleles and selection produces first-order evolution, but is antagonized by mutation repair systems. Moreover, recent research suggests that gene regions for the most biologically essential genes are wrapped around histones with particular chemical marks, which detect mutations and release chemical signals to bring in DNA repair proteins [29]. Non-code expanding mutations in the most biologically essential genes seem most likely to be repaired.

3.2. *Second-order evolution and its underlying molecular driving mechanisms*

Second-order evolution of a biological system is present if new characteristic properties – protein-coding genes or regulatory elements – are added to its nucleotide code, resulting in the expansion of the state vector of the biological system with one or more new dimensions. The molecular driving mechanism of second-order evolution is the accumulation of unrepaired code-expanding mutations of the nucleotide code [30][31][32][33][34]. 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 [35][36], in polyploidization [37], and in the molecular evolution of *Escherichia coli* in 12 experimental populations [38].

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 [39]. 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 might have 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 [40][41][42][43][44][45][46][47]. Over deep time, the simulations of molecular evolution produce new genes, and thus second-order evolution. However, empirical validation of the underlying mechanism (the accumulation of code-expanding, unrepaired mutations) 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 [48][49][50]. Future research at the interface of biology and chemistry is needed to discover the circumstances under which self-replication and production of increasingly longer strings of hydrocarbon molecules continues, as a necessary condition to produce new genes.

In a phenotype-based approach of evolution, genetic drift, divergence, radiation, erasure of bridges, species sorting, extinction, branching, and development of new patterns, are identified as mechanisms that produce macroevolution [1][51]. How these mechanisms are related to the genotype-based molecular mechanisms that underly first- and second-order evolution requires further research, as outlined in the discussion section.

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

	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	$\begin{pmatrix} a1 \\ b1 \end{pmatrix} \rightarrow \begin{pmatrix} a2 \\ b2 \end{pmatrix}$	$\begin{pmatrix} a1 \\ b1 \end{pmatrix} \rightarrow \begin{pmatrix} a2 \\ b2 \\ c2 \end{pmatrix}$
Molecular driving mechanisms	Production, recombination and selection of gene variants; gene regulation; epigenetic modification	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, except the production of gene variants	Yes
Evidence	Abundant empirical evidence, e.g., the appearance of Covid-19 variants, the variation in the shape and size of the beaks of Darwin's finches, the change of phenotype between young and adults, or the change of phenotype over the seasons.	Radiation and chemical mutagenesis experiments on organisms that produce new protein-coding genes or regulatory elements, and computerized reconstruction of molecular evolution over deep time

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

To illustrate the distinction between first and second-order evolution, we use a computer simulation of the evolution of a population of digital amoebae (‘Damoebs’). The simulation, which is accessible at Dryad [52], builds on an earlier organism-based simulation of the evolutionary dynamics of a population of Damoebs [33]. Each Damoeb consists of a small C++ program and possess one characteristic property: ‘the ability to transform the number pair (20,5) into a single number’. The transformation depends 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, resulting in an α-type Damoeb, a β-type Damoeb, a γ-type Damoeb, or a δ-type Damoeb, respectively. Dependent on the selective pressure in the environment, the share of the Damoeb-variants in the population changes, allowing the population to adapt and survive. Changing the selection rules at t=t_1, t=t_2 and t=t_3 results in the same evolutionary dynamics as those observed in, for instance, a population of bacteria or finches [9] (see Fig. 1).

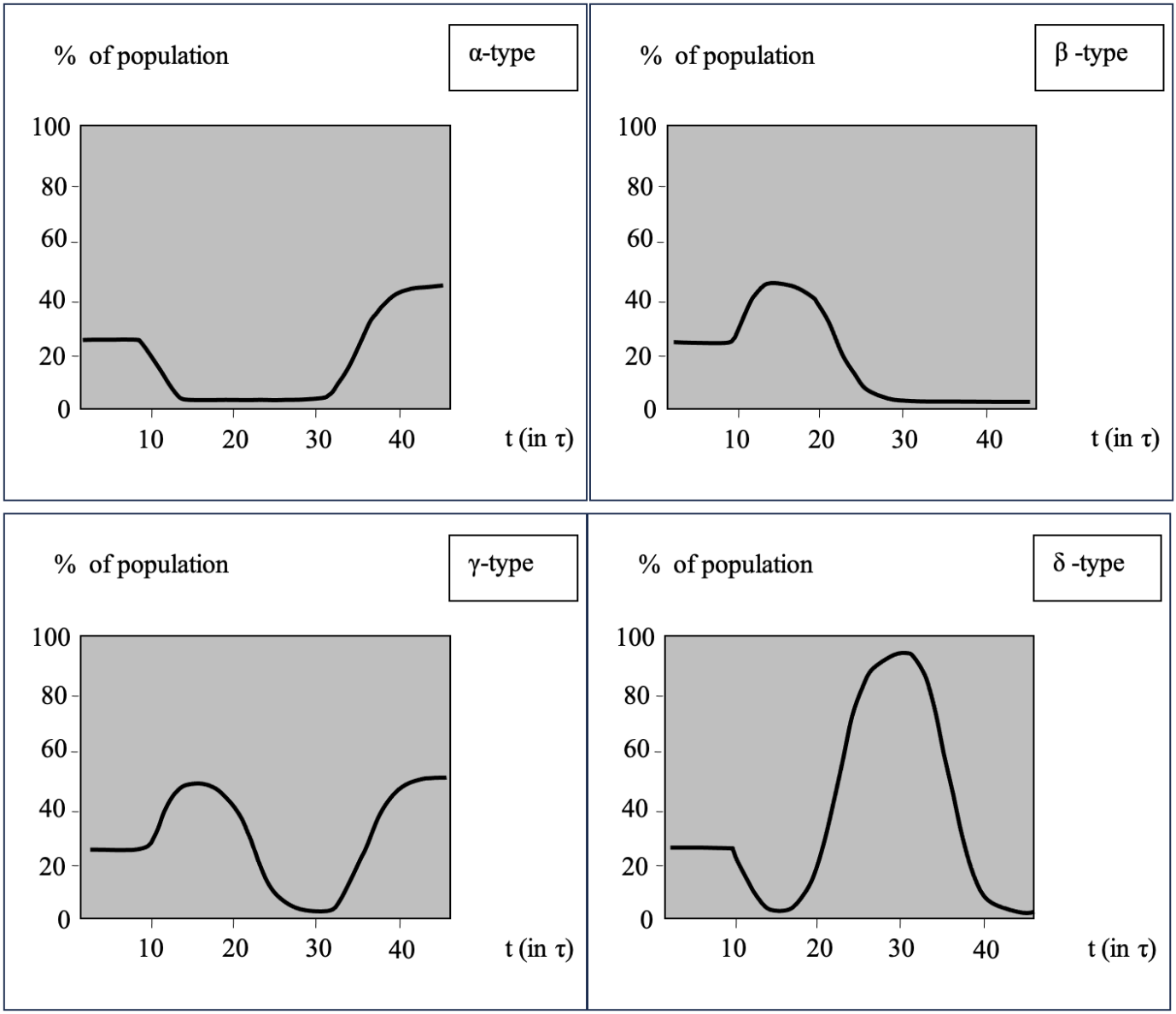

Figure 1. Evolutionary dynamics of a Damoeb population in response to changing selection rules imposed respectively at t_1=9 τ , t_2=15 τ, and t_3=29 τ, where τ is the replication time of a Damoeb. Source: [33]

The state of the population 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= 0τ to coordinate (2) at t_1=9τ, to (4) at t_2=19τ, and to (3) at t_3=34τ. 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 by the mechanism of second-order evolution: the accumulation of code-expanding, unrepaired mutations. DeJong and Degens [33] attempted to simulate this mechanism by randomly changing bits of the digital code of a Damoeb and inserting copies of random parts elsewhere in

the code, resulting in second-order change of the program code of a Damoeb. However, 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 the systems software. Therefore, we now apply an alternative approach and simulate second-order evolution by a form of operator-based programming [53], 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 a set of alternative foods and an additional digestive process that transforms a single number into a duplet number according to an imagined digestive process, controlled by two parameters that can be chosen at random. Hereafter, the fitness of the alternative digestive process to survive in the absence of the number pair (20,5) was tested. This random procedure finally resulted in the development of a new characteristic property of a Damoeb, consisting of the ability to eat the number 10 and transform it by the alternative digestive process 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 characteristic property ('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 $\{S2t_i \mid i= 5, 6, 7\}$.

After $t=t_7$ the survival of the Damoeb population is threatenedagain 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 characteristic property 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 entries $\{S4t_i \mid i= 9, 10\}$. 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 vectors in the Excel table can be reduced by making assumptions on the relevance of certain rows [54][55], 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' [56][57][58]. The matrix in Fig. 2, visualizing the

evolution of the population of Damoebs, shows ‘punctuated growth’ and has a remarkable resemblance with the growth quakes and stasis in iterations of inflating complex random matrices [59][60]. This resemblance requires further research.

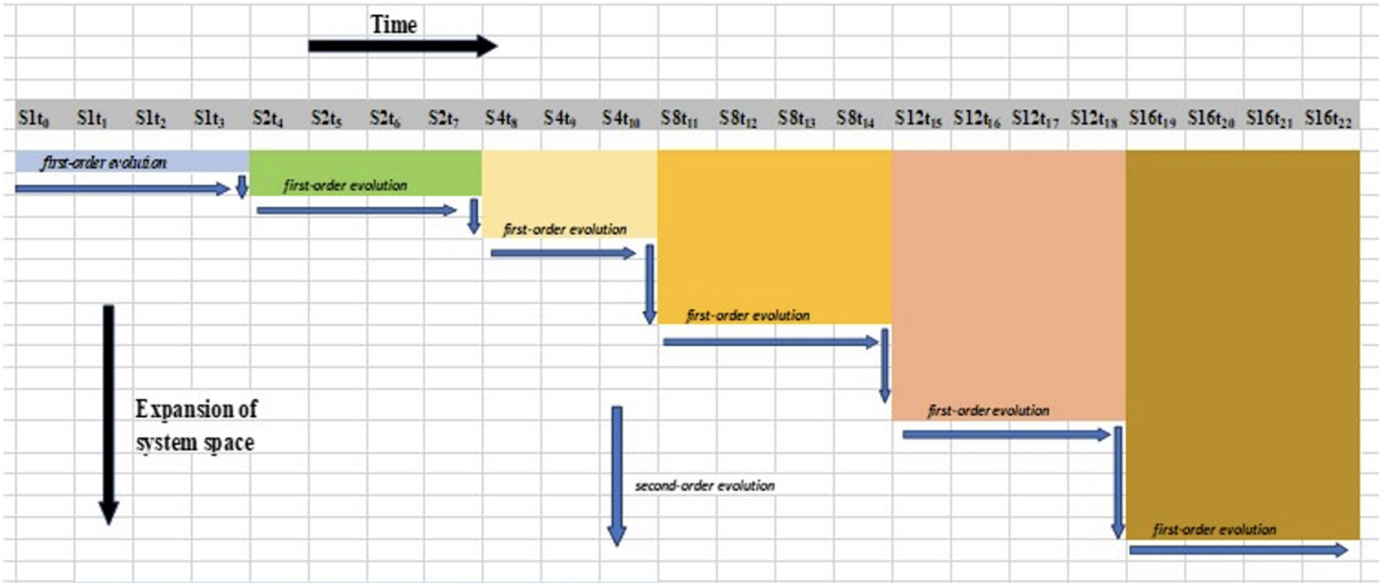

Figure 2. The adaptive dynamics of a population of digital amoebae (‘ *Damoebs*’) mathematically represented by a sequential set of state vectors $\{Sdt_i \mid i = 0, 1, 2, \ldots 21, 22\}$ and visualized in an Excel spreadsheet, where ‘d’ is the number of dimensions of state vector Sdt_i. Periods of time when the number of dimensions of the state vector does not change (= *first-order evolution*) alternate with periods of time when the number of dimensions 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 genotype-based characteristics (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 by first-order evolution is largely similar to the adaptation of organisms, called

microevolution. In second-order evolution, an organism adapts to a changing environment by developing new characteristic properties, resulting in the expansion of the dimensions of its state vector. This development of new characteristic properties is largely similar to the development of complex organs, called macroevolution. Micro- and macroevolution thus are largely similar to first- and second-order evolution respectively. In addition, it can be proven – by a '*reductio ad absurdum*' – that micro- and macro-evolution are not a continuum of change: (1) Let micro- and macroevolution be a continuum of change. (2) Because microevolution is largely similar to first-order evolution and macroevolution is largely similar to second-order evolution, first-order and second-order evolution would be at least partly positioned in the same continuum of change. (3) This, however, contradicts the definition of first- and second-order evolution as two distinct types of change. Distinct types of change cannot be at least partly positioned in the same continuum of change. (4) Therefore, micro- and macroevolution are not part of the same continuum of change. In other words: They are not a continuum of change.

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' [61] (p.301), without consensus [30][31][62][63][64][65][66][67]. 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 [68][69][70][71]. 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[72] 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[73] (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 production and recombination of alleles and selection, gene regulation, and epigenetic modification) within an already existing space (as defined by the genetic elements in the nucleotide code of an organism).

Our genotype-based systems approach to evolution makes a distinction between movement of the state vector of a biological system within its initial systems space and expansion of the state vector beyond the initial system space. This seems similar with the approach of Longo and Montévil using the concept of 'phase space' to describe evolution more accurately [74]. Further research is required to assess the relationship between both approaches.

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 amoebae (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 [75]. 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 [76]. 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 [77]. 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.

The Lotka-Volterra model is a set of differential equations that can be used to simulate the evolution of biological systems [78]. The equations capture, for instance, the adaptive dynamics of a prey population interacting with a predator population, where the phenotype of each population is represented by a scalar. The model produces a stable movement – despite small disturbances – of a two-dimensional vector around an attractor, representing the changes in phenotype of both populations. In terms of our systems approach, the model describes the movement of a two-dimensional state vector through its initial system space, where the parameters of this state vector represent the phenotype of two sub-populations within a population of organisms at a certain moment of time.

When a sub-population is invaded by a mutant that 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 phenotypes occurs, followed by further growth or truncation, resulting in an 'evolutionary tree of life' [79][80][81]. The branching of this tree of life models the rise and extinction of populations. By incorporating the influence of continuous small perturbations, the drawing of the tree of life can be refined [82][83]. 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 [84] The tree of life and the underlying state vector, however, do not leave their initial (2-dimensional) system space. Therefore, the model produces 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 [85]. 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 [86]. Its genetic code of 29,903 bases [87] 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 the parameters of its state vector 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 [88].

Covid-19 differs in its characteristic properties/dimensions from the 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 [8].

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 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.

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 rapid environmental changes, which result in high selective pressure to adapt. Interesting research questions are: "Does the response to environmental changes come from first- or second-order evolution, or from both?" "Does the rate of first- and second-order evolution change?", "What differences can be observed between species?", and "Do phenotype-based mechanisms as genetic drift, divergence, radiation, erasure of bridges, species sorting, extinction, branching, and development of new patterns result in first- or second-order evolution?" Standard DNA analysis technology can reveal an increase in the length of the DNA of organisms, as a necessary condition for the appearance of new genetic elements. If the length of the DNA does not differ between life-forms, the DNA has not been expanded with new genetic elements, and thus first-order evolution is present. If the length has expanded, new genetic elements may have emerged. In a next stage of research, the DNA-analysis can be focused on finding the new genetic element(s), and subsequently be focused on the investigation of its function and its effects on the phenotype. This will enhance our understanding of how biological systems respond to rapid 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 [89]. 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 molecular 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 [90][91][92] 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 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 found that microevolution and macroevolution are largely similar to first-order and second-order evolution, respectively. In addition, we found that micro- and macroevolution are not

part of the same continuum of change. These findings may contribute to the ongoing debate on micro- and macroevolution.

In all branches of science, a concept is articulated more precisely if it comprises two fundamentally different subconcepts [93]. 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.

Additional note of the authors specifying the improvements made in this version 2

In our comment to each review, we have specified in detail the improvements to be made in version 2. These intended improvements have been implemented.

Summarizing, we have:

- Clarified the concept of 'dimensions' in the context of the state vector, as there is confusion whether it refers to genetic elements or the physical length of DNA. (Mentioned by: Casali M.)
- Provided a more detailed explanation of how the model of a vector changing in parameters or dimensions applies to the Lotka-Volterra simulations presented. (Mentioned by: Gimenez M.)
- Addressed the feasibility of completely identifying an organism's genome and tracking real changes over time, and whether there are studies supporting this or if it remains hypothetical. (Mentioned by: Gimenez M.)
- Clarified the relationship between 'dimensions' and 'properties' within the context of the paper, and whether they are synonymous or distinct concepts. (Mentioned by: Casali M.)
- Discussed the heterogeneity of mechanisms specified for 'first-order evolution' and whether they refer to physiological processes or evolutionary time. (Mentioned by: Casali M.)
- Explained the role of unrepaired code-expanding mutations of DNA in second-order changes and how they relate to macroevolution. (Mentioned by: Casali M.)
- Considered making the section on the 'digital amoeba' more accessible and less reliant on the conventions from the initial paper. (Mentioned by: Benisty H.)
- Strengthened the argument on how the concept of discrete levels of evolution can apply to complex interaction networks and the relevance of degrees of freedom. (Mentioned by: Benisty H.)
- Addressed the topic of 'matrix inflation' in models of micro-evolution and macro-evolution, and consider including references that focus on this concept. (Mentioned by: Benisty H.)
- Revised the use of terminology and symbology for clarity and consistency throughout the paper, especially when discussing changes in vectors between parameters and dimensions. (Mentioned by: Casali M.)
- Provided justification for the claim that genotype-based analysis is objective and free from subjective influences, as opposed to phenotype-based analysis. (Mentioned by: Casali M.)
- Considered the implications of rapid environmental changes on first-order and second-order evolution, and clarify the

timescales involved in macroevolution. (Mentioned by: Casali M.)

- Moderated the strong claims made about the paper's ability to answer major unanswered questions in evolutionary biology, and presented it as a contribution to ongoing debate instead. (Mentioned by: Casali M.)
- Eliminated repetitions. (Mentioned by: George M.)

Statements and Declarations

Author contribution statement: Both authors contributed equally to the work.

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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