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Biological evolution cybernetics vs. neutral mutation: Random drift hypothesis

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The neutral mutation-random drift hypothesis cannot explain biological evolution, particularly in the relationship between evolution at the molecular level and phenotype, adaptability, and evolution. Gene random drift cannot be the driving force of biological evolution but exists as polymorphic types in the population and becomes a source of automatic regulation. Biological evolution is neither governed by random variations nor dominated by the environment; rather, it is precisely the manifestation of a biological automatic control process. The role of environmental conditions is neither that of the "creator" nor the "editor" of biological evolution; instead, it serves as a stimulus or inducing factor that promotes biological evolution and is also a target during the automatic control process. Prevalent neutral mutations in nature provide a wide source of selection possibilities for biological evolution during the process of self-regulation and adaptability. A preliminary approach to a mathematical model of biological evolution cybernetics will help us understand the real evolutionary phenomena of organisms more comprehensively.

Key words: Mathematical model of biological evolution cybernetics, autoregulation, polymorphism, conservative, plastic DNAs.

INTRODUCTION

Neutral mutation hypothesis in general

The neutral mutation-random drift hypothesis (hereafter referred to as the neutral mutation hypothesis), proposed by Kimura (1968) and supported by King and Jukes (1969), was further expanded by Ohta (1973, 1992) through the introduction of the nearly neutral theory. This theory emphasizes that the fate of slightly deleterious or advantageous mutations is influenced by population size and selection pressures.

The neutral mutation hypothesis posits that a significant portion of genetic variation occurs in non-protein-coding regions or as synonymous mutations in coding regions, which do not alter protein structure or function. These mutations are random and neutral, and therefore not subject to selection as they do not impact an organism's fitness. Instead, they can be inherited through random genetic drift and accumulate over multiple generations, rather than being driven by positive or adaptive selection. This hypothesis is supported by several key points: 1) changes in some DNA bases in structural genes have no effect on protein structure; 2) some changes in structural genes affect amino acid composition but not protein function, as seen in isozymes; 3) different biological structures and functions evolve at varying rates, but the evolutionary speed at the genetic level remains relatively

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stable; and 4) selective constraint, a form of negative selection, can occur in populations, where negative selection becomes so weak that it is effectively neutral.

Research at the molecular level suggests that biological evolution is driven by the rate of neutral mutations, particularly in small populations, which is determined by the substitution rate of nucleotides and amino acids. This substitution rate is generally constant in each organism. For example, the hemoglobin β chain evolves at a rate of approximately 10^-9 amino acid substitutions per year.

Studies have also shown that different types of molecules have distinct replacement rates and evolutionary rates. However, the evolutionary speed of the same molecule is consistent across different species and is independent of generation length (Kimura, 1991). Furthermore, research on mammalian genes has revealed that while rodent pseudogenes evolve neutrally, primate pseudogenes are subject to purifying selection, with estimates suggesting that 20-40% of genes in primates may be under selective constraint.

Since then, studies analyzing DNA sequence data have largely validated the predictions of the neutral mutation hypothesis. These studies indicate higher rates of evolution in functionally less important sequences and the constancy of molecular evolutionary rates across different lineages. Further research has explored the impact of neutral mutations and genetic drift on genome evolution, including their effects on spatial structures, evolutionary rates among bacterial species, and genetic diversity in honeybees (Gibson et al., 2019; Kuo et al., 2021; Wallberg et al., 2014). Additionally, studies have investigated the interplay between neutral processes and selective forces, as well as the generalizability of mutation effects across different genetic backgrounds (Ribeiro, 2022).

The development of molecular biotechnology, particularly in DNA sequence analysis, has led to increased discussion of positive selection at the protein and nucleotide levels (Lynch and Conery, 2000; Wolf and Swanson, 2002; Nielsen et al., 2005; Voight et al., 2006; Eyre-Walker and Keightley, 2007). Researchers have also examined the impact of mobile genetic elements on genome evolution through the lens of the neutral mutation hypothesis, highlighting the role of random fixation of selectively neutral mutations by genetic drift (Rubin, 1983; Charlesworth and Langley, 1991; Blumenstiel et al., 2014; Arkhipova, 2018; Ho et al., 2021; Giraud et al., 2023).

However, some studies have critically evaluated the neutral mutation hypothesis and challenged its role in biological evolution. Galtier (2024) argues that the neutral model predicts a correlation between genetic diversity within species and effective population size (N_e), but observed polymorphism levels often do not align with species' census population sizes, a discrepancy known as Lewontin's paradox. Other studies have also questioned the hypothesis, citing patterns of variation inconsistent with neutrality and the influence of natural selection (Callier, 2018; Woolfit, 2009).

The neutral mutation hypothesis has sparked ongoing debates between neutralists and selectionists, leading to a deeper exploration of the relative contributions of drift and selection (Rocha, 2018; Callier, 2018; Ahad, 2023). Rather than validating or refuting the neutral mutation theory, research has evolved to understand the complex interplay between neutrality and selection in shaping genomic diversity (Galtier, 2024).

With the advent of modern genome-scale data and the ubiquity of adaptive variation both within and between species, further exploration of evolutionary theory from different aspects will help us understand the real evolutionary phenomenon of organisms more comprehensively and investigate whether the neutral mutation hypothesis can explain the driving force of biological evolution.

Auto-regulation in general

Gene regulation networks are composed of recurring regulatory patterns, known as network motifs. One of the most common network motifs is negative auto-regulation, in which a transcription factor represses its own production. Madar's et al study (2011) demonstrated that negative auto-regulation preserves this function in the context of a natural system, specifically in the native arabinose system of *Escherichia coli*, where it increases the range of arabinose signals to which the system can respond. This suggests that negative auto-regulation may help increase the input dynamic range while maintaining the specificity of cooperative regulatory systems, potentially explaining its common occurrence in biological systems.

The transient response to a stimulus and subsequent recovery to a steady state are fundamental characteristics of living organisms. Research by Jia et al. (2018) showed that positive feedback slows down relaxation kinetics, while negative feedback speeds it up, indicating a possible method to infer the feedback topology of auto-regulatory gene networks using time-series data of gene expression.

Auto-regulation is the direct modulation of gene expression by the product of the corresponding gene. In *E. coli*, as many as 59% of transcription factors regulate the transcription rate of their own genes, suggesting that auto-regulation has important functions. Toxin-antitoxin systems play a crucial role in bacterial response to stress, and studies have shown that auto-regulation of bacterial gene expression affects the heterogeneity of *E. coli* populations at both transcriptional and post-transcriptional levels (Nikolic, 2019).

Auto-regulation can also be combined with additional transcription factors to control gene expression.

Hermsen's et al (2010) used an evolutionary algorithm and a chemical-physical model of transcription regulation to design model cis-regulatory constructs with predefined response functions. The results showed that auto-activation can evolve if it provides a functional benefit, and demonstrated how auto-activation can generate sharp, switch-like activation and repression circuits.

The essence of cybernetics lies in achieving control through automatic adjustment within a wide range of possibilities. Organisms are both strict and flexible automatic control systems, and evolution is the manifestation of this control process. Environmental conditions serve as inducing factors and targets of the control process. As organisms adapt to new environments, they undergo automatic adjustments to narrow the gap with the environment and gain adaptability, exhibiting regular evolution and development. The purpose of biological evolutionary cybernetics is to explore the principles underlying biological evolution.

MATERIALS AND METHODS

The change and development of biological traits are closely related to the living environment. As previously discussed, the reaction of organisms to toxins is an adaptive process regulated by the body in response to environmental stimulation. Over time, as toxicity increases, resistance also increases and becomes heritable. For example, houseflies (*Musca domestica*) developed resistance to the insect growth regulator pyriproxyfen under continuous selection pressure. However, when pyriproxyfen exposure ceased, the resistance gradually reverted toward susceptibility over subsequent generations, indicating that this resistance is reversible and disappears in the absence of toxins.

The evolution of species is invariably closely linked to the surrounding environment. Based on this understanding, an automatic control model of organisms can be proposed to describe the process of biological evolution, as illustrated in Figure 1. This model can serve as a foundation for developing a preliminary mathematical approach to biological evolution cybernetics.

RESULTS AND DISCUSSION

Is the neutral mutation the material basis of biological evolution?

There is no doubt that the changes in DNAs, RNAs, and the proteins or enzymes encoded by them, as well as their mutual relationships and spatial structures, are the material basis for biological evolution. However, according to the neutral mutation theory, most molecular mutations in nature are neutral or nearly neutral, will not affect the survival and adaptability of organisms, and therefore, their changes have no effect on biological evolution and so are not the material basis of biological evolution.

On the other hand, a small number of DNAs and their encoding protein subunits are closely related to the survival of organisms. They are extremely stable, at least in terms of function, have rarely changed over hundreds of millions of years, and are very consistent in the speed or trend of change for the same substance in different species. These can be considered as conservative genetic materials (CGM). For example, fibrin is essential in blood coagulation, forming a mesh that stabilizes clots. Any variation in its amino acid composition will lead to the loss of blood coagulation function and endanger life. The genes encoding fibrinogen's chains—FGA, FGB, and FGG—are highly conserved across terrestrial vertebrates.

However, in the process of fibrinogen turning into fibrin, a part of fibrin peptide will be cut off. The amino acids in this part change very quickly between humans and horses, and their evolution speed is relatively fast, but has little effect on the function of life. This is a completely neutral mutation, and these DNAs encoding replaceable amino acids without affecting protein function can be referred to as plastic genetic materials (PGM).

Another example is cytochrome C, where about 29 among the amino acid residues are irreplaceable, as they are involved in the binding of heme and are necessary for the reaction with cytochrome C oxidase. However, changes in the remaining 74-81 amino acid residues do not affect the function of cytochrome C and are random and neutral mutations. A comparison of cytochrome C in 29 species ranging from Neurospora to humans found that their amino acid sequences are very similar.

Studies on the conservation of hemoglobin and histones have shown similar patterns. Histone IV is a nuclear protein with few amino acid substitutions found in various animals. For instance, only two in 102 amino acids between peas and calf thymus were substituted. These conservative substitutions highlight the extraordinary evolutionary conservation of histone H4, suggesting its critical functional role has remained largely unchanged over approximately 1 billion years since the divergence of plant and animal lineages.

Since these CGM are indistinguishable between species, they are naturally irrelevant to the evolution of organisms and cannot be regarded as the material basis of biological evolution. From this point of view, mutations occurring in CGM regions will immediately affect the physiological functions of species and even endanger life and be eliminated. And mutations occurring in PGM regions are random and neutral, have nothing to do with the survival and adaptation of organisms, and play no role during evolution but can be inherited through random drift and accumulation over years.

It will be very important to understand what role these neutral mutations play in biological evolution and where the accumulated neutral mutations lead to—whether they gradually disappear during the process or finally become an adaptive mutation after its quantitative increase at the same location in uncertain years.

The fixed probability of neutral mutation cannot explain the evolution of organisms

According to the neutral mutation hypothesis (Kimura,

1968), the time to fix a neutral mutation is approximately $4N_e$ generations, where N_e represents the effective population size. Additionally, the probability of fixation is $1/(2N_e)$. Consequently, the larger the population, the less likely it is that a mutant gene will be preserved. Assuming that the current human population is 5 billion and one generation is 20 years, it will take 20 billion generations, or 400 billion years, for a new mutant gene to be fixed in the population. This is just the probability of a new mutant gene being fixed. A trait is often controlled by many genes, and the change of one trait cannot form a new species. If the number of genes determining a trait is 10 and 100 traits change to form a new species, the above number (400 billion years) needs to multiply 1000, or $4x10^{14}$ years to form a new species. Is this possible on our planet? In general, the history of human development is 3.35-3.75 million years. Even when reducing the population to 10000 (N_e=10,000), it still takes about 8 x 10^5 years for a new neutral mutation to be fixed and 8 x 10^8 years to form a new species, which is over 200 times longer than human actual development period.

Human sperm haploid chromosomes contain $4x10^9$ nucleotides. If each nucleotide is replaced by a mutation (neutral), it will be fixed for 4 x 10^{15} ($8x10^5x5x10^9$) years, and it takes 4 x 10^{18} years to form a new species. This is obviously much longer than the actual development time in human beings histroy. Further, if the substitution of a nucleotide pair is considered a mutation, the time required to form a new species will be even longer. Can the history of the earth allow such a long time to form a species?

Continuing with previous example and supposing a pair of alleles (A, a) controls a certain trait, one of which undergoes a neutral mutation, and the parents combine randomly (p=q=0.5). If N_e=10,000 ($2N_e$=20,000 alleles in a diploid population), the neutral mutation does not affect fitness and is subject only to genetic drift.

Then the time to fix the neutral mutation is 40,000 ($4N_e$) generations and the probability of the neutral mutation being fixed in the population is equal to its initial frequency.

$$P_{fix} \approx f_{mutant}(t=0) = 1/2N_e = 1/20000 = 5 \times 10^{-5} \text{ (or 0.005\%)}$$

The likelihood of the mutant allele being fixed is very low because of its neutral nature and the large population size. And the probability that the mutation remains existence in the population (not fixed or lost) after t = 100 generations is 0.995:

$$P_{poly}(t) \approx \exp(-t / 2N_e)$$
$$P_{poly}(t) = \exp[-100 / (2\times10{,}000)] = \exp(-0.005) \approx 0.995$$

Due to their low fixation rate in a short period of time, neutral mutations most likely drift in the population as polymorphic types. The larger the population is, the less possibility will be for the mutant gene to be preserved, which means new traits will be difficult to emerge and biological evolution will rarely happen or even not be able to proceed.

Gene random drift cannot be the driving force of biological evolution

From the study, it can be seen that mutant genes only exist as the form of polymorphism during random drift, and the possibility of completely excluding individuals that have not mutated is extremely small. As the number of individuals in the population increases, the probability of mutant genes taking effect in the population will be smaller and it will be very easy to disappear and hardly to be fixed.

Gene frequencies undergo genetic random drift due to sampling errors, but this will gradually disappear as the number of individuals in the population increases. Assume that the frequency of the original gene and the mutant gene in the population is equal (p=q=0.5) (this is impossible in practice, as q is extremely small). The two populations are N_1=50 and N_2=10000, respectively. Their standard deviations ($\sigma=\sqrt{pq/2N}$) respectively when:

N_1 = 50, $\sigma=\sqrt{\frac{0.5x0.5}{2x50}}$ = 0.05

and

N_2 = 10,000, $\sigma=\sqrt{\frac{0.5x0.5}{2x10000}}$ = 0.00354

The standard deviation of the former is 14 times that of the latter, that is, the probability of the latter retaining a mutant gene in one generation is only 1/14 of the former. Here, 10,000 individuals are not a large group, and the probability of a mutant gene being fixed in one generation by genetic random drift is so small. It can be said that the effect of genetic random drift does not exist in large groups. Then, what is the driving force of biological evolution?

Biological evolution cybernetics

Autoregulation on molecular and cellular level

Like commonly existed self-regulation (Jacob and Monod, 1961;Ptashne and Hogness, 1974; Rutter,1980; Hajheidari et al., 2019; Erber and Herndler-Brandstetter, 2023; Yuan and Duren, 2023), molecular polymorphism, the large potential for changes of genetic materials and the diversity of genes caused by nucleotide substitution are the conditions for biological adaptability and evolution with high environmental influences (Bogan and Yi, 2024; Bennett et al., 2024; Klai et al., 2025). The neutral and random mutations occurred in PGM regions provide

such material basis and flexible potential regulatory ability. The types of mutations that bacteria or other species undergo to adapt to new environments are naturally due to the potential for molecular structure to develop in multiple directions. The existence of this potential space is well supported by the prevalence of convergent evolution, polymorphism of proteins or enzymes and the changes of resistance to toxins. Under the stimulation and induction of the external environment, species' evolution express from physiological homeostasis to the formation of new traits, the time it takes might not be necessarily a very long process.

Example 1: It believes that regulatory enzymes have more polymorphisms than non-regulatory enzymes. Identical resistance-associated mutations are found across divergent taxes, like the mutation enhances the enzyme's resistance ability to metabolize DDT through genetic polymorphisms in regulatory enzymes, and the effective role of enzyme regulation and genetic polymorphisms in developing cross-resistance to multiple insecticide classes (Mitchell et al., 2012, Riveron et al., 2014). It can be inferred that the reason why many adaptive enzymes can be induced under different new environmental conditions is due to the polymorphic characteristics of enzymes from random neutral mutations. The properties of adaptive enzymes and regulatory enzymes are consistent. Insecticides play a central role in controlling major vectors of diseases. In 1955 the WHO Assembly proposed the global eradication of malaria with DDT. However, the shift from malaria eradication to control in 1976 was prompted by the appearance of DDT resistance in many mosquito vectors. When houseflies are exposed to DDT, DDT-Dehydrochlorinase is induced in the epidermis to make DDT lose a hydrogen oxide molecule and become non-toxic DDE. DDT is a man-made drug (Sternburg et al., 1954; Farroqui and Metcalf, 1983; Fonnum, 2009; Low et al., 2010). It is impossible for houseflies to have latent genes for resistance to DDT when DDT does not exist in nature. It is obviously a kind of resistance induced by the stimulation after it is exposed to DDT. It can be seen that at the molecular level of organisms, there are a lot of potential possibilities for responding to a variety of different environmental stimuli (interference), which are the material basis for the occurrence of most neutral mutations.

Example 2: Campbell et al. (1973) cultured a mutant strain of *E. coli* β-galactosidase gene on a lactose-containing medium and regained the ability to hydrolyze β-galactose. DNA mapping analysis showed that the lost gene was re-formed under the stimulation of environmental conditions. The genetic determinant of this new enzyme was named ebg-5 and is localized on the *E. coli* chromosome at 59 min, whereas the original *lac* operon is located at 10 min. This study explores how *E. coli* mutants with deletions in the β-galactosidase gene (*lac*Z) can regain the ability to hydrolyze β-galactosides when subjected to prolonged selection on lactose-containing media. The researchers found that fully hydrolyzing lactose competence was restored through a series of at least five mutations. The enzyme responsible for this regained activity differed from the original *lac*Z β-galactosidase in its immunological, kinetic, and sedimentation properties. This is obviously due to the influence of different environments inducing bacterial mutation types that adapt to new environments, showing the potential for molecular structure to develop in many directions.

Example 3: When organisms are in a toxic environment, their resistance to the poison will gradually change. As time goes by and the toxicity increases, the resistance will continue to increase and become heritable, which is an adaptive process regulated by the body under the stimulation of the environment (Hofsli and Nissen-Meyer, 1989; Haaber et al., 2015; Dunai et al., 2019; Jones et al., 2022; Coleman and annatella, 2022). Researches show that the reaction of organisms to poisons is an adaptive process regulated by the body under the stimulation of the environment. Dan et al. (2021) discussed the mechanisms that enable temporary mutations would be advantageous for organisms forced to adapt in changing environments. Jackson and Koludarov (2020) explored how venom and toxins evolved in organisms, looking at the molecular basis of how toxins recruited and their functional roles in defense. It also delves into the evolutionary processes leading to the "weaponization" of certain molecules, which can increase resistance to toxins in prey species. These articles provide a deeper understanding of how organisms adapt to toxins and the mechanisms that make these traits heritable over generations. However, when toxins no longer exist, this resistance is reversible and disappears as well (Raghavendra et al., 2010; Yang et al., 2014; Bisset et al., 2020). Like, the houseflies (*Musca domestica*) developed resistance to the insect growth regulator pyriproxyfen under continuous selection pressure; but gradually reverted toward susceptibility to the insecticide over subsequent generations when pyriproxyfen exposure ceased, indicating that the resistance can diminish in the absence of the insecticide (Shah et al., 2015). Mutations that confer drug resistance often confer a growth defect in the absence of drug and rapidly reversible mutations are frequently generated by microhomology-mediated tandem duplications (MTDs) in the gene ssp1. It causes rapamycin resistance and a growth defect, and reversal back to wild type restores fitness and drug sensitivity. The studies showed that genomes had evolved to minimize the number of potentially deleterious MTDs and used machine learning to determine the sequence-encoded rules that govern the formation and collapse of MTDs (Dan et al., 2021).

Another significant example is phenotypic degeneration. Kimura (1979) tried to explain phenotypic degeneration using neutral mutation hypothesis. Cave dwellers have lived in a dark environment for many generations, so the nerves that control the sense of smell have become excited, while the nerves that control vision have been inhibited. Over time, the functions of organs related to nerve excitement have developed; while organs closely related to nerve inhibition (such as eyes) have gradually atrophied or even disappeared because they receive less nutrients and energy from the body. Similarly, for humans, apes, guinea pigs and bats etc, they can obtain a large amount of vitamin C from food (such as fresh fruits and vegetables) and gradually loss the ability to synthesize it. However, Kimura believed there was no matter to have eyes or not when it was in the dark, and the ability to synthesize it did not affect organism survival when vitamin C is rich in food, they are all neutral. It is hard to imagine that animals have to consume a lot of energy to synthesize vitamin C when there is already rich vitamin C in their food. This obviously violates the feedback principle.

Example 4: Convergent evolution- Animals have evolved adaptations such as mutations in toxin-binding proteins, changes in receptor sites and sequestration mechanisms neutralized toxins. Studies explores that the phenomenon where toxic species develop resistance to their own venom and how various species have independently evolved resistance mechanisms to counteract toxins, emphasizing the recurring molecular solutions to similar evolutionary pressures. Resistance often comes with fitness costs, such as reduced receptor functionality or increased metabolic demands. The trade-offs influence the evolutionary trajectory of resistance mechanisms. The findings suggest that similar selective pressures have led to the evolution of toxin resistance through parallel genetic changes in distinct species. In the research focusing on mutations in the Na,K-ATPase enzyme, the target site of cardenolides, different insect species exhibit similar amino acid substitutions, showing a pattern of convergent evolution and similar adaptations across diverse insect lineages (Dobler et al., 2012). The pattern of convergent evolution was also found in various animal species (Brodie et al., 2005; Rebecca et al., 2016; Thiel et al., 2022). It indicates that different animal species evolve toxin resistance through similar genetic pathways. This demonstrates the homology of genetic material in different species and similar self-regulatory abilities under similar environmental stimuli.

Auto-regulation on individual and population level

Living organisms must actively maintain themselves in order to continue existing. Autopoiesis is a key concept in the study of living organisms, where the boundaries of the organism is not static by dynamically regulated by the system itself. Adaptive evolution, an important strategy for species survival and persistence, is a process in which variation that confers an evolutionary advantage in a specific environmental context arises and is propagated through a population. Wild animals and plants have developed a variety of adaptive traits driven by adaptive evolution. During the process of species diversification, phenotypic convergence, and inter-species interaction, environmental factors play a very important role in shaping genetic diversity and adaptation (Sosa and Pilot, 2023; Hu et al., 2023).

During organism transition from aquatic to terrestrial life, only a few phyla successfully made the shift to land, while the majority of animal types remain exclusively aquatic. The arthropods and vertebrates that landed on land took different paths to develop. Within arthropods, insects have successfully developed into aerial animals, they use capillaries as respiratory organs and difficult to expand their body size. However, only a few types of vertebrates are capable of flight, they breathe with lungs and can continue to expand their size. Vertebrates transitioned from aquatic to terrestrial life initially through a stage of amphibious existence. Their functions and organs underwent continuous changes; although they could not completely free themselves from aquatic limitations, they were able to live in moist swamps or on land. On land, factors such as temperature, rainfall, sunlight, and atmospheric pressure vary much more than in water. These significant climatic and geographic changes induced or prompted animals that transitioned to land to undergo automatic internal adjustments, which led to corresponding variations in their life functions, organs, tissues and structures, particularly in respiratory and locomotion organs, to adapt to the new terrestrial environment. Just as plants developed new organs such as roots, stems and leaves after moving onto land, along with structures like mechanical tissues that did not exist in aquatic environments, animals' respiratory organs evolved from gills, which absorb oxygen from water, to lungs that absorb oxygen from air. Similarly, locomotion organs evolved from fins to legs capable of walking on land. Through the action of internal automatic regulatory systems, genetic directional variations occurred, allowing plants and animals to gradually develop new organs and features for terrestrial survival and evolve into true land-dwelling types.

The study of Youngolopis fossils has provided substantial evidence for understanding the transition of species from aquatic to terrestrial forms (Chang, 1982, Chang 1996; Zhu et al., 2009). Youngolopis lacked internal nares and is considered a primitive lungfish, closely related to the ancestors of ancient crossopterygians and tetrapods. Tetrapods were the first vertebrates to migrate onto land. The discovery of Youngolopis fossils bridges the gap between fish and tetrapods, elucidating the transformation from aquatic to

terrestrial life, including the changes from fins to limbs, from gill respiration to lung respiration, and the significant structural changes that occurred. It also highlights how early vertebrates adapted to different environments and the challenging evolutionary process that led to the diverse array of land-dwelling animals we see today.

The earliest land-dwelling amphibians still hatched their eggs and went through their juvenile stages in water. Reptiles were originally oviparous (such as the pit viper and snake lizard) and had to develop their babies inside body due to cold and dry weather in high-altitude, which leads a gradually evolution of viviparity and internal constant temperature characters, and reduced their dependence on moisture and temperature. The drastic environmental changes drove terrestrial animals to adapt to cold and arid conditions in several ways: 1) Fertilized eggs produce a significant amount of metabolic water during development to meet the embryo's water needs; 2) The hard-shelled eggs of reptiles and birds are well-suited to prevent water loss; 3) Yolk rich in fats can generate a large amount of water upon decomposition. It is animal's adaptations to low temperature and dry conditions, representing a major leap from variable to constant temperature regulation and from oviparity to viviparity, and set the stage for the extensive development of mammals in the Cenozoic era. However, this evolution also placed a heavy burden on the maternity, leading to reduced reproductive capability and lower offspring numbers.

Additionally, many cells that originally had reproductive functions were repurposed as nutritional sources to support the newly acquired traits. In contrast, amphibians and reptiles' offspring can generally live independently after hatching, while mammalian offspring require a prolonged period of care to survive, with human infants requiring even longer periods of nurturing. These changes are the result of animals adapting to the cold and dry environments of the late Mesozoic through their own regulatory systems.

Organisms have a wide range of potential variation (neutral random mutation) possibilities (space) at the molecular level, which provides them chance to survive under any external conditions. However, organisms will only encounter a certain specific environmental condition at a specific time and place. This condition is the goal chosen by organisms (for example, some reason prompts aquatic animals to develop on land, so terrestrial life becomes the established goal of the organisms). The organisms will continue to transform and develop towards this goal until finally adapt it. The time for a new trait formation will depend on how soon the organisms adapting the environment and forming their own comfortable zoom, which can be in short period or very long time. Therefore, the control process is a procedure for transforming from contingency to necessity (Figure 1). This evolutionary trend has been shown in studies of biological resistance to toxins as described in the work.

Preliminary approach to mathematical model of biological evolution cybernetics

As discussed previously, a living thing is a highly organized, orderly, and complex organism with many different levels of organization. Its components (such as cells and tissues) are closely connected each other and interact with the external environment constantly. Here a simple case was started with, regarding the organism as a whole (not considering the relationship between internal cells or tissues for the time being). Though cybernetics (Wiener,1948) emphasizes feedback and regulation where trait changes explicitly depend on minimizing error in real-time, the biological evolutionary models incorporates genetic drift and variation, both yield similar long-term trends.

Based on biological automatic control model (Figure 1), assuming that environmental variables, like temperature (T) and humidity (H), impose stress on the organisms, and only a fraction of the population survives and reproduces to the next generation through self-regulation (including changes in genetic material), and after many generations of self-regulation the organism gradually adapts to this environment. Our analysis will focus on feedback regulation and control mechanisms in response to environmental changes. The core idea is that the organism and its environment form a self-regulating system**.**

Cybernetic framework: feedback regulation

In a cybernetic system, the organism adapts through a feedback mechanism where: inputs (T, H) represent environmental variables (temperature and humidity), outputs are the adaptive responses of the organism (for example, changes in T_{opt}, H_{opt} and population size N), and control mechanisms regulate the relationship between inputs and outputs to minimize "error."

Error function: Define an error function E that quantifies the deviation between the current environment (T,H) and the organism's optimal state (T_{opt}, H_{opt}):

$$E(T,H) = w_T(T-T_{opt})^2 + w_H(H-H_{opt})^2$$

The goal of the organism is to reduce $E(T,H)$ through self-regulation and adaptation.

Adaptation via feedback control

Organisms "measure" the environmental inputs (T,H) and adjust their internal states (T_{opt}, H_{opt}) to minimize the error $E(T,H)$. This can be represented as a feedback regulation.

Feedback dynamics: Using proportional control (a

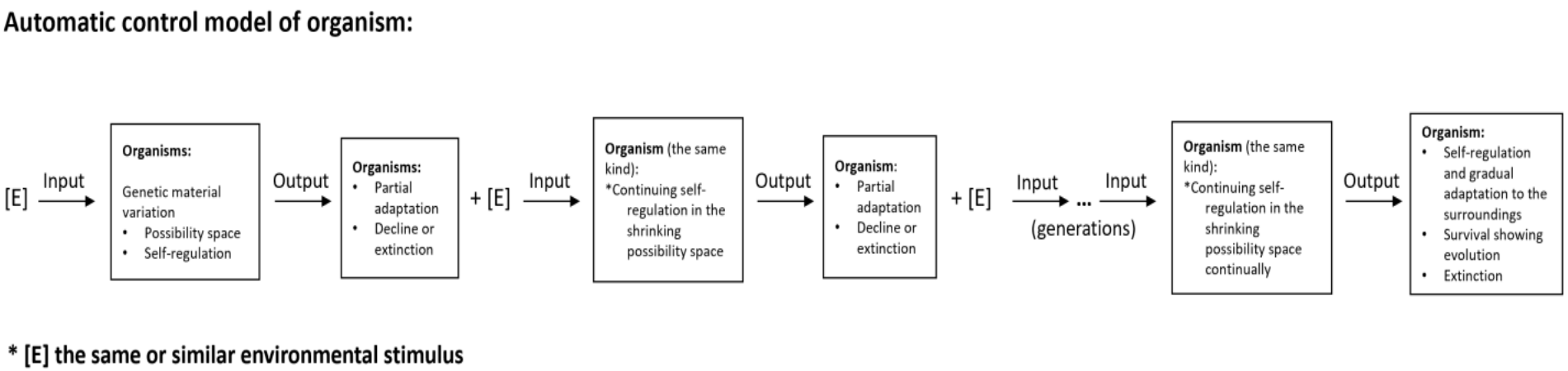

Figure 1. Automatic control model of organism. When exposed to environmental stimuli (input), organisms adjust their internal physiological functions and genetic structures and carry out a series of regulatory processes to respond the environment (output): either survival or expired, each feedback takes the possibility space of the previous output as input and adjusts it in the reduced possibility space, generation after generation, gradually transitioning from temporary adaptation (conditioned reflexes) to permanent adaptation (unconditioned reflexes). Over time, this manifests as formation of new trait or species evolution and produces biological adaptability to the environmental stimuli

common cybernetic principle), the rate of change of an organism's traits is proportional to the gradient of the error:

$dT_{opt}/dt = -k_T(\partial E/\partial T_{opt})$, $dH_{opt}/dt = -k_H(\partial E/\partial H_{opt})$

where k_T and k_H are proportionality constants that govern the speed of adaptation, then:

$dT_{opt}/dt = 2k_Tw_T(T-T_{opt})$,

$dHopt/dt = 2k_Hw_H(H-H_{opt})$

Population dynamics with cybernetics

Population dynamics (N) are regulated by the organism's ability to minimize error and maintain a stable feedback regulation. Cybernetics would model population size as a function of the residual error:

$dN/dt = r\cdot N\cdot[1-\beta E(T,H)]$,

where r is the intrinsic growth rate and β is a scaling factor that translates error into fitness reduction.

Cybernetic adaptation in discrete generations

For discrete steps (generations), the cybernetic system evolves iteratively as of 1) measure Inputs (T,H): assessing the environmental state, 2) calculate Error: evaluating $E(T,H)$, 3) adjust Traits (T_{opt}, H_{opt}): updating internal states to reduce $E(T,H)$, and 4) update population size: computing N_{t+1} based on fitness:

$T_{opt}^{(t+1)} = T_{opt}^{(t)} + \Delta T_{opt}$,

$H_{opt}^{(t+1)} = H_{opt}^{(t)} + \Delta H_{opt}$

where $\Delta T_{opt} = 2k_Tw_T(T-T_{opt}^{(t)})$ and $\Delta H_{opt} = 2k_Hw_H(H-H_{opt}^{(t)})$.

Long-term adaptation

Over many generations, the organism reduces $E(T,H)$, converging to:

$T_{opt} \to T$, $H_{opt} \to H$.

The population stabilizes at:

$N \approx N_{max}/[1+\beta E(T,H)]$

A comparison with evolutionary models reveals that the results align qualitatively but differ in focus. Both approaches predict eventual adaptation to the environment by minimizing a stress or error function. The key differences between the two approaches can be summarized as follows:

1. Cybernetic model: emphasizes real-time feedback and regulation, with trait changes dependent on minimizing error.
2. Evolutionary model: focuses on selection, mutation, and drift, incorporating genetic variation and yielding long-term trends.

The final equation summary (cybernetic model) is as follows:

$E(T,H)=w_T(T-T_{opt})^2 + w_H(H-H_{opt})^2$,

$dT_{opt} / dt = 2k_T w_T(T-T_{opt})$,

$dH_{opt} / dt = 2k_H w_H(H-H_{opt})$,

$dN / dt = r \cdot N \cdot (1-\beta E(T,H))$

***Explain the means of Final Equation Summary (Cybernetic Model*)**

Error function $E(T,H)$:

$E(T,H)=w_T(T-T_{opt})^2 + w_H(H-H_{opt})^2$

It means that the error function measures how far the current environmental conditions (temperature T and humidity H) deviate from the organism's optimal conditions (T_{opt}, H_{opt}). If T and H are close to the organism's optimal values, the error $E(T,H)$ is small. And if T and H differ significantly from the optimal values, $E(T,H)$ becomes larger, indicating more environmental stress. In the model, the error function drives the feedback process by identifying the mismatch between the environment and the organism's current state.

Rate of change of optimal traits:

$dT_{opt} / dt = 2k_T w_T(T-T_{opt})$, $dH_{opt} / dt = 2k_H w_H(H-H_{opt})$

It means that these equations describe how the organism's internal traits (optimal temperature T_{opt} and optimal humidity H_{opt}) adjust over time in response to environmental conditions. Here the constants k_T and k_H determine how quickly the organism can adapt its traits; and the term $(T-T_{opt})$ or $(H-H_{opt})$ represents the direction and magnitude of the error respectively: if T_{opt} is too low compared to T, it will increase over time, and if T_{opt} is too high, it will decrease. These equations implement the feedback mechanism in the model. They show how the organism self-regulates to reduce environmental stress by shifting its internal traits toward the external environment.

Population dynamics:

$dN / dt = r \cdot N \cdot [1-\beta E(T,H)]$

It models how the size of the population (N) changes over time based on environmental conditions. Here, rN represents the natural growth of the population (for example, reproduction) when conditions are ideal, and the factor $[1-\beta E(T,H)]$ reduces the growth rate depending on the error $E(T,H)$. If $E(T,H)$ is small (low stress), the population grows closer to its maximum rate, and if $E(T,H)$ is large (high stress), the population growth slows or becomes negative (population declines). It also links the organism's ability to adapt (via trait adjustment) to the survival and reproduction of the population, showing the populations that fail to reduce $E(T,H)$ will eventually decline or go extinct.

Summary

1. Measure the environmental mismatch: The error function $E(T,H)$ evaluates how stressful the environment is for the organism by comparing the current temperature and humidity to the organism's optimal conditions.
2. Adaptation through feedback: The organism adjusts its internal traits (T_{opt}, H_{opt}) over time, trying to reduce the environmental mismatch. These adjustments are guided by proportional feedback laws.
3. Population survival depends on adaptation: The population size changes based on how well the organism reduces the environmental stress. If the mismatch (error) is too large, the population will decline.

This biological cybernetic model describes a self-regulating system where organisms continuously adapt their traits to align with changing environmental conditions. Successful adaptation leads to survival and reproduction, while failure results in population decline or extinction.

Conclusion

Mutations occurring in CGM regions will immediately affect the physiological functions of species, potentially endangering life, and are likely to be eliminated. In contrast, mutations in PGM areas are random and neutral, with little impact on species' survival and adaptation. These neutral mutations exist as polymorphisms in the population and can be inherited through random drift and accumulation over multiple generations.

The large number of neutral mutations provides organisms with a wide range of automatic adjustment space to adapt to changing surroundings. When exposed to environmental stimuli, organisms adjust their internal physiological functions and genetic structures, carrying out a series of regulatory processes to respond to the environment. Over time, this manifests as evolution, producing biological adaptability to environmental stimuli.

From the perspective of biological evolution cybernetics, organisms accumulate each feedback control and gradually expand their control ability. Each feedback

takes the possibility space of the previous output as input and adjusts it within the reduced possibility space. Through this process, the gap between external stimuli and the body's balance is gradually reduced, achieving dynamic balance within the organism and controllable adaptation to new environments.

Therefore, the self-regulatory mechanism of organisms is the fundamental principle driving species evolution. Biological evolution is neither governed solely by random variations nor dominated by the environment; rather, it is the manifestation of an automatic control process. Environmental conditions serve as a stimulus or inducing factor that promotes biological evolution and is also the target in the automatic control process.

CONFLICT OF INTERESTS

The author has not declared any conflict of interests.

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