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Unlocking the Pathobiome Evolution Clock (PEC) by Devo-omics

Mehrdad Alizadeh*and Mahyar Mobasseri

Department of Plant Pathology, Tarbiat Modares University, Tehran, Iran

Abstract

The phylogeny and its tools generally applicate for different aims in bioscience. In recent years, phylogeny broadly utilizes in interpreting microbiome data. The microbiome occupied the body of plants, humans, and animals and play essential roles in functional patterns for organisms. The healthbiome (microbiome) can convert to pathobiome with present happens in hosts, environments, and climate changes. The best tools for showing and drawing in changes are phylogenetic analyses in various aspects. This pathobiome has expressed a position for considered organisms in which they when will disease or weak or die. Pathobiome and its effects influence total parts of the environment and hosts. Associated microbes in pathobiome probably or certainly exposure in divergent, convergent, and parallel. Pathobiome evolution clock (PEC) is a new perspective for predictions and investigation about pathobiome effects in organisms and environments. So, pathobiome is a frontier between life and death, or it is a transition stage from health-biome to death-biome. Additionally, we introduce Devo-omic as a new concept and term for the description of the microbiome from born to death (or microbiome changes from birth to death). PEC can be accurately evaluated under devo-omics investigations.

Keywords: Phylogeny • Microbiome • Pathobiome • Evolution

Introduction

Microbial communities

In the description of microbe's physiology, we must culture these microorganisms in experimental conditions with media cultures. Microbe's metabolism, environmental duties, and growth features are unknown in most cases, also the most of phylogenetically new groups of these microorganisms have at all been cultured [1]. The dynamics and function of microbial communities (MCs) are not clear and understandable which so it is out of reach for achieving to predict and manage MCs behaviors in soils, plants, atmospheres, animals, and humans [2]. In 2019, simple animal models were chosen for microbiome research that was Drosophila (dipteran fly), C. elegans (nematode worm), Zebrafish (cyprinid fish), Honeybee (social hymenopteran insect), Hydra (hydrozoan coelenterate), and Squid (cephalopod mollusc). These models can be utilized for the bilateral targets to scrutiny molecular and cellular mechanisms in related interactions among host and microbiome [3]. To control and predict MCs, integrated approaches can progress predictive understands of MCs that involves creating mathematical methods and promoting the experimental method and data gathering [2]. The transition period of next-generation sequencing (NGS) technologies that culture-based methods promoted to genome-based methods are defined as metagenomics [4].

For metagenomics, application of direct sequencing for extracted host-associated [5] or environmental DNA (eDNA) has indicated that the linages of many microorganisms are not isolated in pure culture media [6,7]. The amplicon sequencing mostly used 16S ribosomal RNA gene in bacteria and archaea, 18S in eukaryotic-specific, and ITS in fungi-specific. Nevertheless, this method is confronted with problems including restricted taxonomic resolution and hardness in diagnosing closely related species [5]. Whole metagenome sequencing data is progressively used in microbiome researches, as these data are utilized to accumulate new genomes, and disclose the presence and absence of genes and pathways [8]. Despite the existence of transcriptomics, metabolomics, and proteomics in omics studies, we referred to metagenomics and their results that directly shown microbial change results in different organisms.

Research challenges in devo-omics and PEC

All considered organisms that their bodies internally or externally occupied by microorganisms by passing through birth to death will change themselves microbiome. The pathobiome is an intermediate stage from health-biome to death-biome stage and it has overlapped microbiomes between these two stages. Devo-omics describe microbiome changes from birth to death. Each period in the development of organisms has a specific microbiome and different conditions can negatively or positively modify the present microbiome. Finally, changes in microbiome may lead to pathobiome creation. Different aspects play essential roles in determining pathobiome that how long will it be and how long will it take?. Pathobiome decrease devo-omics time and scale. The investigations of pathobiome will predict the time of improvement or death. In fact, Pathobiome evolution clock (Path-Evo Clock= PEC) is a new perspective with all related approaches in prevention, control, and eradication or replacement of pathobiome with health-biome in spatio-temporal scales in bodies of organisms. PEC will contribute to more accurate answers in microbiome changes in host favor. Additionally, PEC, as one new tool in microbiome or pathobiome investigations, will show that how and why health-biome converts to pathobiome and how we can manage this pthobiome with present scientific works or tools to achieve the desired goals.

Phylogeny and related concepts for research challenges

Phylogenetic is a branch of biology that examines the evolutionary relationship between different groups of species, such as species or populations, derived from molecular sequencing data and morphological data matrices [9]. The branching pattern of the tree that represents evolutionary divergence is called phylogeny. Prior to molecular evolution, data such as morphology, behavior, geographical distribution were used to infer the phylogeny of the data. In fact, phylogeny can be studied in various ways [10]. Surveys are usually conducted using fossils that contain morphological information of current species ancestors and divergence intervals. But fossils have many limitations, they may be available only to certain species. Available fossil data

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***Address for Correspondence:** Mehrdad Alizadeh, Department of Plant Pathology, Tarbiat Modares University, Tehran, Iran; E-mail: Mehrdad.alizadeh@modares.ac.ir*

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can be incomplete and their collection is usually limited by frequency, location, geographical range, and other factors. Interpretations of their morphological features are limited to the role of various genetic factors is often ambiguous [11]. Therefore, the use of fossils to determine phylogenetic relationships can be misleading or misleading. On the other hand, there are no fossil microbes for microorganisms and thus their phylogeny cannot be studied in this way.

A phylogenetic tree is also a branching diagram called a tree (graph), showing evolutionary relationships among different biological species or even individuals based on phylogenetic similarities and physical differences or genetic characteristics. Units connected in a tree are separated from a common ancestor [12]. Evolution can be described as a process of division, a process whereby populations of living things change over time and, as a result of variation, diverge into separate branches, merge, or die by extinction. This process can be visualized by a phylogenetic tree. The basic problem in phylogenetics is that genetic information is only useful for present-day arrays, and fossil records contain little information and more vague morphological features. A phylogenetic tree represents a hypothesis about the process by which evolutionary events are assumed to have taken place.

If several species from a group of living organisms are phylogenetically related and derived from a common ancestor, it is thought that the best way to discover this phylogenetic relationship is to measure the total similarity between the species studied. But it really isn't. The total similarity may lead to misleading conclusions, because there are two reasons for the similarity between two living things, one of which is due to the phylogenetic and reflective relationship. In other words, one of the reasons that resemble a particular trait between two arrays is that the trait is inherited through common ancestry, and this type of homology resembles, for example, a pair of paws, pigs, camels, even paws. And the tiger is a homologous trait because it is inherited from the common ancestor of these animals. Another reason for the similarity between two or more arrays is that these species have found adaptations in their life cycles and this has led to a convergence in evolution and similarity. And when two living creatures are similar in convergence, they are called that property (analogue or homoplasy), for example, the presence of parrots and elongated bodies in marine animals is an example of homoplasy [13].

Only homologous similarities are due to the evolutionary relationship between living things. But the question is if the two beings had the most homologous similarity, would they have the most phylogenetic relevance?. Surprisingly, the answer is no. A homologous trait may have been recently inherited from species derivation or may have been inherited from related ancestors as a result of early ancestry. Thus, only homologous traits that have recently been inherited in a series of arrays are evidence of the phylogenetic relevance of most species. These traits are also said to be apomorphic, such as the first living vertebrates living on the land with five fingers, hence many onshore vertebrates such as turtles, crocodiles, and chimpanzees. And the frog has five fingers because it is inherited from common ancestry. This trait is homologous to all species. In comparison horse, zebra and donkey are simple fingers with trait venom from which the ancestral trait was later developed and inherited in the common ancestor of zebra, horse, and donkey.

Coevolution

The change in the genetic makeup of one species (or group) is in response to a genetic change in another species. At a glance, it may be thought that, along with evolution, it encompasses everything. This assumption may be due to the fact that all living things interact with each other, likely influencing their evolution in some way. The coevolutionary term is used to describe cases where two or more species mutually affect each other's evolution. For example, an evolutionary change in the morphology of a plant may affect the vegetarian morphology from which the plant feeds. As a result of the evolution of the two affected by each other. Evolution probably occurs when different species interact closely with each other. These ecological relationships include:

- Hunter/prey and parasites/host
- Competitive species
- Mutualistic

In some cases, it is completely proprietary. For example, between the two cellular activities - chloroplast and mitochondria once lived in a single cell and free, then entered the cytoplasm of other cells. An example of an endosymbiosis phenomenon another method involves the competitive interaction between two specific species. A good example - a study on salamander (Plethodon). Two of these salamanders compete fiercely in the Great Smoky Mountains, a mountain range along the Tennessee-North Carolina border in the southeastern United States. (If the population size of each species decreases, the other species will increase) There is also a bilateral interaction between the two species. Plants and insects represent classic evolutionary examples. Many plants and their pollinators are completely interdependent and have very unique relationships, and biologists see this as a result of the evolutionary process (Coevolution).

The microbiome can influence by evolutionary, immunological, and ecological processes [14], host genotype, and habitat [15]. Also, Astrangia poculata microbiome composition meaningfully varied rather than surrounding seawater within each of seasons with changes in host physiology with excess photosynthate [16]. Even in sexual behaviors was validated that the gut microbiome can change and these changes influenced the immune system and HIV acquisition at Men who have sex with men (MSM) [17].

Based on McLoughlin K, et al. [18] theory, adhesive molecules that produces by hosts can manage microbial compositions. This mucus flow changes and acts in selection and against microbes. Most parts of the literature confirmed that the host and some gut symbionts co-evolved and these microbiomes have effects on immune system ontogeny with relations of host-species specific [19]. Fecal samples from human and living mammals in zoos can clarify the fact about gut microbiome evolution that derived from evolutionary driving factors. These findings must answer questions about functional features of microbes and acquired and reacquired during vertebrate evolution which is related to coevolution [20]. As well, beneficial symbionts in corals may cause evolving pathways for disordering or block of the immune response in their hosts [21]. The microbiome of plants contributes to the microevolution of their hosts in pairwise symbioses through manipulation in plant physiology to enhance host fitness and direct response to the environment in favor of the plant [22]. Douglas AE [4] used the evolutionary developmental (evo-devo) approach for attaining evolutionary origins and diversification with the application of a development in symbiotic organs (harbored structures by microbial symbionts).

Convergent

The consistent evolution of apparently similar structures, such as the wings of birds and insects, in unrelated species, exposed to the same environment (convergent evolution). Systematic scientists are trying to develop evolutionary relationships by examining the similarities between living things. But unfortunately, not all similarities are inherited from a common ancestor. If the species have the same ecological and natural selection roles, which have evolved into similar and comparable adaptations, although they may be from different evolutionary branches, they may look alike. This is called convergent evolution, and analogy as a result of convergence is called analogy. In the natural sciences, convergent evolution is concerned with living creatures that are not closely related, each independently acquiring similar traits, while in separate or sometimes different ecosystems. About convergent adaptation to myrmecophagy at 15 species of mammalian, as a model system, i.e. Armadillos, anteaters, aardvarks, pangolins, and aardwolves, this subject determined that the evolution of gut microbiota-derived by diet and phylogeny with cases of convergence in global composition. Their results have been shown the important role of diet adaptation as a main driving factor in convergence that plays an essential role in the composition of the gut microbiome over the timescales of evolution [23].

Parallel

The independent evolution of similar traits starts from a similar ancestral point, resulting from identical environments or other evolutionary pressures. Often this is the case in ancestors that are closely related, where several species respond similarly to environmental stresses. Evolution of groups that are not geographically separated and have physical similarities. A prominent example is a similarity between Australian mammal mammals and mammalian mammals elsewhere, although they have separate evolutionary pathways but have remarkably similar forms.

Divergent

The process by which a species comes in two or more progeny or different shapes, as well as the process of tracking two or more species back to a common ancestor. The multitude of differences between groups, which can lead to the formation of a new species, is usually due to the distribution of the same species adapted to different environments. That is, in this new species, mutations have been created that have led to their natural selection. It is a kind of evolutionary change that results in an increase in morphological differences between early ancestors that resembled each other. The process by which the two species move away from traits that they share from a common ancestor to further adapt to their environment. For example, if we consider the diversity of bird species, ducks, hummingbirds, ostriches, and penguins all come from an ancestral bird species, and until now, all of them were adapted to the environment Their own particulars have found certain traits that have ultimately led to their distancing from one another. Divergent evolution can be used to identify traits in molecular biology, for example, divergent evolution can be used for genes and proteins, such as nucleotide and protein sequences derived from two or more homologous genes. Land. Both orthologous genes (which are the result of the species differentiation process) and paralog genes (which are the result of gene replication within a population) show divergent evolution. Divergent evolution may occur due to the latter (paralog genes) between two genes in a species. Divergence in allele frequencies genome-wide in natural populations of Drosophila melanogaster clarified that divergence is the result of differences in microbiome composition, and these microbiome compositions might be a doer of natural selection for driving rapid evolution and polygenic adaptation over short timescales (Rudman et al.,). With assessments on the gut microbiota of eight Glires species (four lagomorph species and four rodent species), the studies have been revealed that the differences of microbiome were positively correlated with host divergence time. Their results proposed the composition of the gut microbiome is correlated with the phylogeny of the host, thus the differences of the gut microbiome in animals might foretell the time of host divergence [17]. Rogers GB, et al. [24] revealed that genetic divergence affects microbiome differences and the divergence of the gut microbiome can be affected by a strong diet. Even the host genes are modified by neutral evolutionary processes.

Cophylogenetic

In fact, cophylogenetics seeks to explain and describe the interactions that are simultaneously evolving and affecting each other's evolution, such as the relationship between hosts and their parasites. Charles Darwin observed the evolutionary interactions between flowering plants and insects in 1859. The foundations of coevolution theory are already well developed and the findings suggest that they can play important roles in fundamental evolutionary changes such as sexual evolution or change in ploidy and on the structure and function of ecological communities as well as disease dynamics. They have an impact. Coevolution encompasses many forms of metabolism, host parasitism, and predator-species relationships, and in many cases, it is the selective pressure that gives one species superiority over another. But this "evolutionary co-evolution" is not always particularly close, precisely between the two species, and is also seen in the family or higher distribution populations, as between flowering plants and pollinating insects such as bees, flies, and beetles happened.

The term "cell evolution" is largely a biological concept, but researchers use it with various sciences, such as computer science, sociology, and so on. Nothing in biology has been as well-known and refined as the concept of evolution [25]. However, nowadays another term is added to the concept that “nothing evolves in isolation”, in some cases, it points to the importance of the role of epigenetics alongside genetics. In any biological system, there are many interactions between individuals, between species, and between sexes and the environment, these roles being the inevitable result of biological life.

Tree thinking

Lineage patterns can also be influenced by ecological relationships between species, such as parasitism or symbiosis. When a species depends on distant species for its survival, the performance of these host species is almost like a geographical area where symbiosis and parasitism are limited [26]. The geographical theme of the distribution is similar to the topic of hosting changes. It is expected that a generation of parasites will rarely obtain a new host [27]. Similar to dispersal events over long distances, host change events rarely occur because they are in dire need of founding beings to create a new segment or environment (for example, a new host) and sufficiently. Be lucky to be able to survive and reproduce in the new environment. Evolution also has some similarities to Vicariance (the geographical separation of a jetty, which is mainly caused by a physical barrier from a previous mountain or river slope). Just as geographical vicissitudes cause gaps within a species' domain, host specificity also restricts gene flow between host-compatible strains of the partner species. This means that the separation of generational lines within a host can lead to similarity and adaptation of the genera in their parasitism or symbiosis. As a result, a pair of phylogenetic trees is created for the two interacting groups that share many nodes. This is similar to matching trees found at a time when the evolution of multiple groups is shaped by a set of events similar to Vicariance. The study of groups with similar phylogenies is commonly called the science of cophylogenetics. In many cases, it does not appear that phylogeny of parasites and hosts or phylogeny of specific biomes (such as plants and pollinators) is greater than that without co-speciation the actual is expected to match. In some cases, there have been several hosting change events, which their analysis shows a significant differentiation from what is expected by chance. These results clearly indicate that species interacting can influence each other's evolution. Host-parasite interaction and their spatial and spatial adaptation in heterogeneous environments is one of the important aspects studied in biological science. In fact, the effect of parasitism may vary widely depending on the time or between different populations of the host. Identification of geographical patterns of evolution has led to many empirical studies and studies of species interaction. In spatially heterogeneous environments, evolution may lead to the adaptation of populations to that location from environmental conditions. Local adaptation occurs when the average population adaptation is greater than their own habitat relative to remote habitat. When averaging the quality of habitats of different populations over time, the mean of local populations in a metapopulation (the mean of different local adaptations in each population) can be used [28]. Changes such as evolution, gene duplication, and other genetic and phenotypic changes that occur in microorganisms appear to affect higher organisms such as plants and animals due to their close relationships with each other. Evolution in the micro-world also applies to the macro world [26]. Coevolution means a series of two-way evolutionary adaptations in two different species. Coevolution occurs when a change in one species acts as a new selective force on the other species and the adaptations of the second species influence the selection of the first species [29]. In turn, a successful pathogen invasion can disrupt the plant microbiota and drive higher community heterogeneity [30]. This increase in heterogeneity among infected microbiotas is termed the Anna Karenina principle, based on the first sentence of Leo Tolstoy’s book: “Happy families are all alike; every unhappy family is unhappy in its own way”. This can be transposed to microbiology as: “All healthy microbiomes are similar; each dysbiotic microbiome is dysbiotic in its own way” [30].

Example: Evolution in the nectar bird with ornithophilus flowers

Hummingbirds belong to a family of about 340 species. Flies are the only birds that can fly backward. Some members of this family (Mellisuga helenae) are the smallest known birds on the planet, measuring 5 cm in length and 1.8 g in weight. In some species, the heart rate reaches 1260 times a minute and some of them can fly up to 80 times per second, so their metabolism rate is very high and with a lot of energy need. These birds feed on the nectar of ornithophilus flowers (meaning bird-friendly flowers) but also hunt small insects and spiders to provide amino acids, vitamins, and minerals. The nectar bird and the ornithophily flowers each have adaptations that help attract the other. As mentioned, these birds require a great deal of energy and nectar as they eat up to 5 times their daily weight, so they do not reach for flowers with a sugar content of less than 15% and flowers. Prefer those whose nectar is about 25 percent sugar. This factor, as a selective force, increases the chances of pollination and propagation of nectar flowers. On the other hand, the nectar bird is not very strong in terms of smell. In contrast to the flowers that are pollinated by these birds, they do not produce much odor, instead of producing great nectar. The production of nectar has many problems, such as attracting insects such as flies, a fly can often enter a flower and use its nectar without assisting in flower pollination.

These flowers have made some interesting adjustments to prevent this problem: the colors of these flowers are red or orange. The insects for these colors are colorless and see these colors as gray or black, so less so. They are attracted to these flowers, but the same colors of red and orange attract the flies as they produce pollen from insects that produce the most abundant sugar. It contains glucose and fructose, but the flowers that are pollinated by these birds produce a nectar with a high sucrose concentration, sucrose is the favorite sugar of this bird. On the other hand, these flowers are in the form of a tuber or deep cylinder that the insects have difficulty reaching the end of, but the long-legged chicken can easily reach the end of the flower. In addition, the edges of these flowers are almost flat, so there is sometimes no support for the insect that feeds on the nectar of the flower [31]. Gut microbiota generally affected by ecological and evolutionary forces, but evolutionary dynamics less studied for considered changes over time. These evolutionary dynamics for the microbial populations are mostly surmounted by fast adaption. Garud NR, et al. [32] was confirmed that the gut bacteria at some sweeps might evolve on human-relevant timescales, and the short-term and longer-term evolutionary dynamics may highpoint the connections between these periods.

Human microbiome

Among the coexistence relationships between organisms, probably due to the importance of the subject, the most studied is the relationship between humans and their microbial coexistence, so that a thorough understanding of the effect of microorganisms on the human body has led to the suggestion of a human secondary gene project. The purpose of this project is to determine the microbial genome of the human body [33]. If we accept that symbiotic microorganisms play an important role in the life of their eukaryotic hosts, it can be concluded that they are even more effective in the evolution of higher organisms [34]. With the help of the theory of hologenome evolution, we will examine this issue. The hologenome is a host of genetic information sets and microorganisms that co-exist with it. In other words, several holobionts make one hologenome. These two terms are the structural and dynamic units of theory of evolution [35]. Despite the extensive research on symbiosis, few model systems have been developed in which only one symbiotic is examined. In addition to the main symbionts, the hologenome hypothesis addresses other microorganisms, especially those that have been discovered in recent years using new methods. The broad empirical information that underpins the theory of hologenesis is grouped into four groups:

- All animals and plants form symbiotic relationships with a variety of microorganisms.
- Coexisting microorganisms can be passed on from generation to generation.
- The relationships between host organisms and the microbial community influence the presence of environmental organisms.
- Genetic variation in holobionts may be altered by changing populations of different symbionts, environmental requirements and different gene processes.

Factors causing high diversity of symbiotic microorganisms

one of the important factors of this diversity is the specificity of many microorganisms. In addition, the hosts are exposed to a variety of cannabis, which causes the microorganisms to change as the host evolves. Diet and other environmental factors require a diverse community of microorganisms [36]. Another factor contributing to the diversity of microorganisms is bacteriophages; given that plants and animals have a high concentration of bacteriophages, if any bacterial species is overgrown, the kill the winner's theory would be that mathematical models of bacterial dynamics would be supported, it can be destroyed by bacteriophages [37]. So reducing the number and adding to species diversity increases the chance of survival. This microbial diversity makes holobiont more selective and adapts quickly to environmental conditions. It can be concluded that microbial diversity can play a vital role in environmental oscillatory conditions as an insurance policy [38]. On the other hand, factors such as the innate immune system that are adaptable also act to reduce the number of strains of microorganisms. The innate or nonspecific immune system is the first line of defense and includes physical barriers, antimicrobial molecules, enzymes, and specific binding proteins. The variety of raw material is evolution. In other words, evolution depends on the presence of gene diversity in the population. According to hologenome theory, genetic variation can be due to genome changes during sexual reproduction or chromosome rearrangement or mutation. These processes can also occur despite significant differences in microorganisms. Replication occurs in haploid microorganisms. In some species, there is some sort of DNA transfer and transfer. In addition, changes in the genome of microorganisms can occur in three other ways rapidly and under environmental requirements, which may be an important element in the evolution of plants and animals. On the other hand, it has been proven that the diversity of microorganisms occurs randomly or is the result of factors such as nutritional changes, phage infections, temperature changes and other environmental factors (Figure 1).

Devo-omics investigations

The conceptual image of devo-omics shown at (Figure 2). For description of devo-omics, several examples selected based on microbiome changes during development at different organisms. The flexibility, functional and taxonomic differences of gut microbiota significantly exhibited in children than those the adult in during the first decade of life. Additionally, different aspects showed the changes in evolution, variation, and response to dietary challenges. The microbiota changes may slowly happen in some children [39]. Also, these differences were confirmed in the diversity, compositional, and functional of gut microbiota [40]. The life cycle of insects initiates eggs and it finally reaches adult. These microbes have vital functions in their hosts, such as nutrition, physiology, and behavior. In the herbivore insect (*Spodoptera littoralis*), the analysis of microbial community-verified that microbial diversity reduced from egg to pupa, but the adults sheltered high richness of bacteria [41]. Microbial analysis from egg stage to adult stage in lepidoptera (*Brithys crini*) determined that the developmental stage of lepidoptera play essential role in composition and potential functions of gut microbial [42]. In pathogen vector, *Haemaphysalis longicornis*, the assessments of the bacterial community in the developmental stages were proved that the early stage had less bacterial community than bloodmeals and molting stages [43]. Also, bacterial density investigations from egg to adult in leaf-cutting ants have been shown that remained similar at *Acromyrmex echinatior* than *Atta cephalotes* [44].

In another research on gut microbiome at embryos, chicks, and maternal hens, the results have been showing that microbiome inherited from maternal hens and the microbial diversity and abundance was affected by environmental and host genetic factors during development [45]. Additionally, dynamic shifts of gut microbiota have been observed in the 3 stages of the development of chicken embryos [46].

The microbiome of seeds seems to be inherited between plant generations and these microbiomes can influence plant development and activities. Even these microbiomes can engineer and progress plant traits [47]. Notable in a holistic view, the endophytes of seed that vertically transmitted can generate numerous phytohormones, enzymes, antimicrobial compounds, secondary metabolites, and progress biomass and yield in plants with the presence of biotic and abiotic stresses [48].

The findings in the Nile tilapia larvae (*Oreochromis niloticus*, Linnaeus) were specified that gut bacterial were affected by water bacterial communities during larval development and water microbial management can apply as strategies for changes in gut microbial communities [49]. Also, the studies about corals exhibited a high frequency of microbiome taxa at larvae and early recruits than later life stages [21].

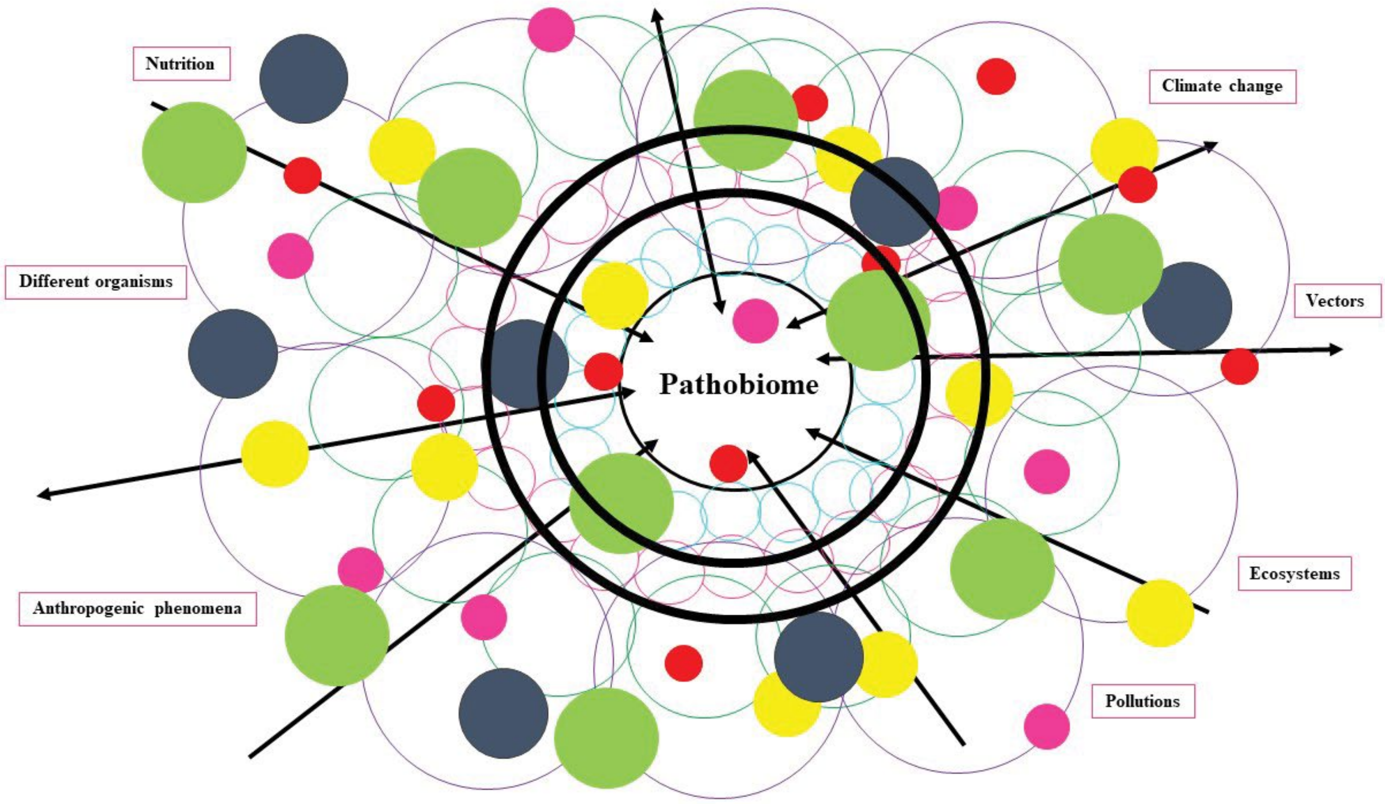

Figure 1. Different aspects can affect microbiome or pathobiome in different organisms. These agent included foreign and inner agents.

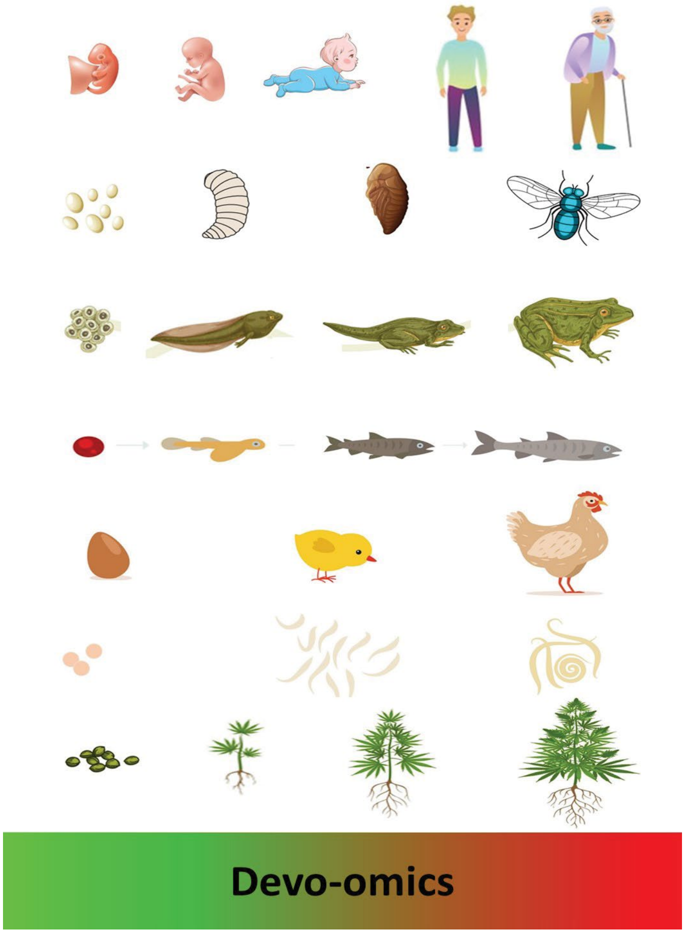

Figure 2. Devo-omics defined as meta-omics investigations from genesis (birth) to death. The life of organisms initiate from embryo or egg and then reaching to adult will die. All stages can assess during development in different organisms, including mammals, birds, reptiles, amphibians, and fish.

In the holistic view with considering the above studies about the microbiome, devo-omics play as an interesting tool for replying to different questions and unknown phenomenon and effects.

Pathobiome investigations in different organisms

The microbes can directly or indirectly play essential roles in our life, these microbes can affect development and various functions in humans [50,51], plants [52], domesticated terrestrial animals [53,54], fish [55,56], etc (Figure 3).

The microbiome definition re-visited by Berg G, et al. [57] that it include the microbiota (community of microorganisms such as fungi, bacteria, archaea, protists, algae) and their “theatre of activity” (nucleic acids (RNA and DNA), structural elements, metabolites, signaling molecules, toxins, (an) organic molecules, and the surrounding environmental conditions).

The pathobiome concept was firstly introduced by Vayssier-Taussat M, et al. [58]. In fact, the pathobiome defines interactions or interactive effects between pathogenic and healthy microbes for propelling the health-biome to the unhealthy-biome that the disease process initiates. After introducing this concept, researchers and scientists have initiated using this new concept in their studies and this concept had found valuable data and information in different fields for considered works. Pitlik SD and Koren O [59] have been hypothesized that all diseases may determine by a turmoil of the health-microbiome (health-biome) into a pathobiome.

The pathobiome can specify the possible pathogenic agents and other players of the pathosystem. The pathobiome in rice sheath blight (RSB) disclose *Pseudomonas fuscovaginae* and *Sarocladium oryzae* as independent agents associated with this disease [60]. In olive knot (OK) disease, the results indicated that the pathobiome derived from complicated interactions between the pathogen, the plant, and resident bacteria [15]. In another disease, Acute oak decline (AOD), it was referred that this disease originated from an interactive bacterial pathobiome or polymicrobial complexes [61]. Also in *Meloidogyne*-based disease complex, the microbiome was displayed a role as pathobiome in coffee and tomato plant [62]. In entomopathogenic nematode-associated microbiota were determined the effect of pathobime for functioning in the infectious process [63].

High compositional homogeneity was observed in pathobiome of diseased corals rather than health-biome (microbiome). The results were an insight into the movement from one-pathogen-one-disease paradigm to multiple pathogenic agents in diseases [64]. In *Acropora millepora*, as a coral, the created lesions were resulted from the pathobiome changes (multiple bacterial species associated with coral disease) and declining of health after the biotic trouble and direct effect of any specific pathogen cannot be true for creating disease [65]. There is a clear need for precious studies on the genetic and environmental sources of microbiome community at different animals, plants, and humans to elucidate only when, why, and how we should expect healthbiome convert to pathobiome. These endeavors must pursue a system-level approach to illuminate the timing and mode of healthbiome shifts to pathobiome in light of ecological, morphological, physiological, and phylogenetic (divergence, convergence, parallel, and cophylogenetic) aspects. In between, the evolution with microbiome science can interestingly help to find new approaches for unsolved questions (Figure 4).

Questions about PEC

1. What can agents influence the microbiome or pathobiome?
2. Has the core-microbiome changed in organisms over time?
3. Is pathobiome involved in extinction or speciation?
4. Is pathobiome the result of incompatibility?

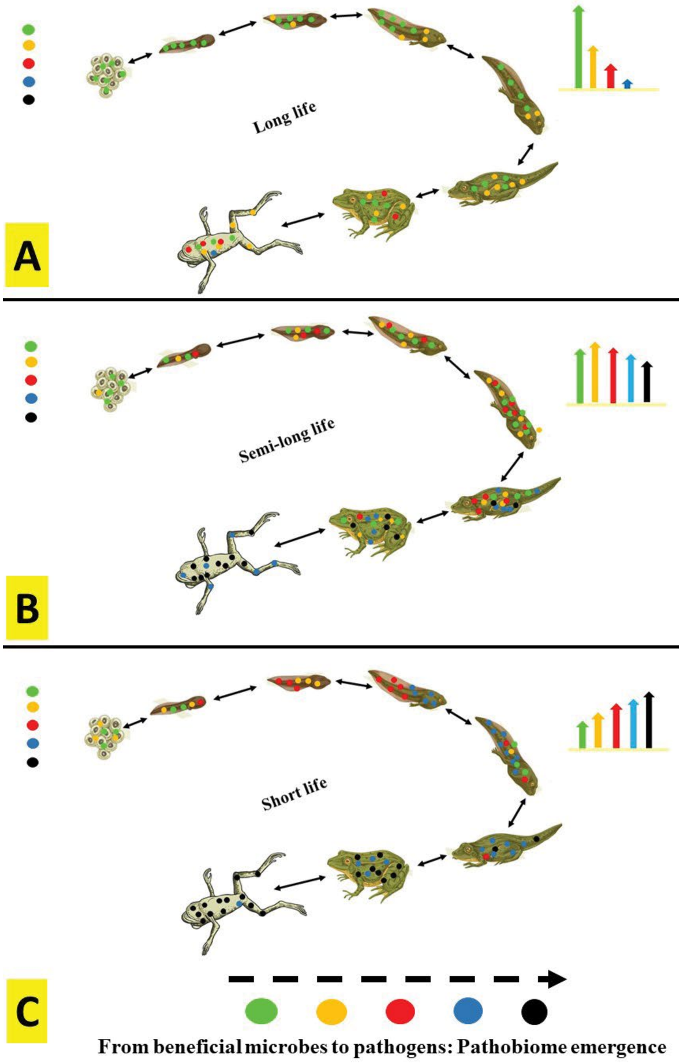

Figure 3. Microbiome change during development of organisms. These changes may be fast or slow, so the emergence of pathobiome will be fast or slow. Fast emergence of pathobiome will decrease the life of organisms and decrease the beneficial microbes in the body of these organisms.

Figure 4. All the organisms directly or indirectly have relations with each other. In other words, the microbiome or pathobiome can be exchanged between different groups of organisms. Change in microbiome or microbial populations may consider as pathobiome formation or fluctuations in pathobiome for getting better or worse. With devo-omics assessments, we will capable for determine a precious clock in the evolution of healthbiome to pathobiome.

5. Can the exchange of microbiome in mating lead to the formation of pathobiome or the removal of pathobiome?

Conclusion

Evidently, the path-evo clock can be a conceptual and framework for determining pre-pathogenicity periods, pathogenicity time, changes in pathogenicity, changes in investigated hosts, post-pathogenicity periods, and changes in associated microbes in pathobiome in different periods of pre-pathogenicity, in-pathogenicity, and post pathogenicity. This clock will be a golden time for prediction and utilization in the management or prevention of diseases. The gold time will say to our that what is the best time for using drugs or pesticides or other considered components for prevention, decreasing or stopping diseases in hosts. Thereby, the pathobiome engineering will design for more studies in diseased hosts in humans, animals, and plants. Additionally, our suggestions emphasize the need to sample different organisms or specified organism across the globe with a variety of diets, lifestyles, environments, etc. to provide new insights and database within a host species and their microbes, in coevolving with their bodies or their environments, have helped shaped our answers for unknown questions and assumptions about all aspects of evolution and pathobiome in different periods and various organisms.

Conflict of Interest

The authors have no conflict of interest.

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