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The pangenome concept: a unifying view of genetic information

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Summary

A way of viewing the genetic information in all organisms on Earth as constituents of the Pangenome is proposed. According to this concept, the Pangenome is the common (collective) genetic system of all living organisms, the organic molecules and their complexes (DNA- and RNA-containing viruses, plasmids, transposons, insertion sequences) involved in the storage and transmission processes of genetic information. Pangenomic stability and variability are discussed. This concept alerts to the inherent fluidity and transmissibility of DNA among organisms of all types, including horizontal gene transfer between closely related and formally unrelated macro- and microorganisms. The roles of death and of all known food chains as universal ways of gene distribution among different organisms are discussed. The contribution of bacteria and viruses in maintaining the circulation of genes within the Pangenome is presented. This concept implies that newly emerging genes are not bound to disappear together with the death of an organism or the extinction of a species and microorganisms are the main pool of genes. Some negative aspects of the intervention of molecular genetics, biotechnology, and ecology, including the spread of transgenic plants and animals, are summarized. It is shown that this concept may be used in medicine for the prognosis of an epidemic situation, particularly newly spreading pathogens, and for the development of new methods for the prophylaxis and early diagnosis of oncologic diseases. This concept can also help to find promising approaches to the discovery of drugs with novel principles of action.

key words: **genome • variability • evolution • Pangenome**

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Background

The genomes of some organisms have been sequenced in recent years, including those of about 100 unicellular organisms such as bacteria, archaea, fungi, and the human. Intensive development of gene engineering and biotechnology has led to the appearance of new opportunities to change the genetic information of individual cells and organisms. Plants that contain genes, which are not inherent to them, are created in some countries for use in the animal or human food supply. First attempts to change the human genome have already been carried out.

Approaches to the study of the genetic system and proteins have changed as well, and have resulted in the emergence of new disciplines of science: genomics and proteomics. In spite of all these achievements, the main part of the research has no general theoretical basis containing a model of total gene interactions in all live beings. There is no concept that describes the general system that could show possible ways to solve different biological problems and enable us to estimate the real consequences of some genetic manipulations. As a result, it is practically impossible to search for new direct methods for safe intervention in the structure of a genetic system. At present, many investigations have low efficiency and can sometimes even have dangerous consequences without a general theory. At the same time, the data from biology and medicine compiled and summarized today allow us to construct some models and formulate theories on the organization of life at the genetic level. We offer here a concept based on the idea of the association of the genetic information of all living things living on Earth.

The prerequisite for the existence of the *Homo sapiens* genome, including human genes and the genes of his microflora, was announced by Joshua Lederberg. As a designation of such a summary genome [1], he offered the term "Microbiome". According to our concept there is one common (collective) genetic system, the "Pangenome", of all living organisms, the organic molecules and their complexes (DNA- and RNA-containing viruses, plasmids, transposons, insertion sequences) involved in processes of genetic information storage and transmission. According to this model, the maintenance and development of the Pangenome is the goal or "main expediency" of what we call life. The proposed concept is presented here as separate items, provided with short comments for more convenient interpretation. The following useful term is included – Pangenome – the sum of the genes of all live organisms, viruses, and different mobile genetic elements (the term was first introduced in the journal "Tsitologia") [2];

Structure

The Pangenome possesses a module structure: it includes the genetic material of all living creatures (Figure 1). Every large module includes small ones. Multicellular organisms consist of numerous cells that contain chromosome(s) and gene elements (the genomes of single cells of eu- and prokaryotes include not only the chromosome itself, but proviruses, plasmids, and other genetic elements). The distinguishing feature of these smallest modules is a partial dependence on chromosomes, the capacity to make new copies of themselves (often in great amount), and a mobility that reveals itself in moving within and between modules. The main part of the Pangenome is represented by the sum of the genes of various unicellular organisms, i.e. bacteria, fungi, algae, and protozoa, and non-cellular forms, such as viruses and other gene elements.

Unicellular organisms, viruses and gene elements meet the requirements to be the main part of the Pangenome. More than 10^9 bacterial species are believed to inhabit the biosphere [3,4]. The total mass of all bacteria in the world is approximately 7.5×10^9 tons, much larger than the total mass of all other live creatures: plants with 5.5×10^9 tons and animals with 0.5×10^9 tones. Cells and gene elements are the most widespread creatures on Earth and occupy different ecological niches. Microbes are characterized by high rates of growth and multiplication (reproduction of genetic information), they are found everywhere in soil and water, they are adapted to live at various temperatures (from –20°C to +250°C) and different pH levels (from 2 to 9), under high radiation, etc. Microbes can be found inside and on the surface of practically all multicellular organisms and, moreover, animals and plants cannot live without them. Bacteria that represent normal microflora exceed the number of all host cells. It is considered that the human body consists of 10^{13} cells and at the same time the number of microorganisms that form human normal microflora is 10^{14} cells [5,6]. It is practically impossible to estimate even approximately the number of gene elements on the planet. It is considered that viruses are the most common biological agents in seawater, their number typically running to ten billion per liter [7]. The population of dsDNA tailed phages alone amounts to $>10^{30}$ in the biosphere and outnumbers prokaryotic cells by about 10-fold in environmental samples [8]. This fantastic number belongs to only one variant of virus widespread in the biosphere. At the same time we know that every cell possesses different gene elements, the number of which changes from a few to up to thousands. So the number of gene elements in multicellular organisms is more than the number of host cells and microbes by factors of tens and thousands. One more important property of microorganisms is their capacity to maintain viability (for viruses this concept, of course, is conditional) for a very long time. Spores of bacteria are long-livers; according to some data, exposed now to continual verification, they keep their viability tens and even hundreds of millions of years [9,10]. Obviously, fungal spores can maintain viability for a long time as well. Nobody now has estimated the "real life time" of viruses, that formally belong to living nature.

We can imagine the Pangenome as an "ocean" that is formed by microbes (cells) and gene elements in which the genomes of multicellular organisms (humans, plants, animals, fungi) are shipped. The Pangenome, as well as its separate modules, has to realize two closely connected processes for its maintenance: conservation of the structure and its modification. Its "stability" and "variability" are conventional terms because they are factually provided by the same processes.

Stability

Pangenomic structure stability is connected with supporting the species' existence. It is realized at the molecular level by the correct functioning of enzymes that control DNA and RNA synthesis and the repair of various DNA damage.

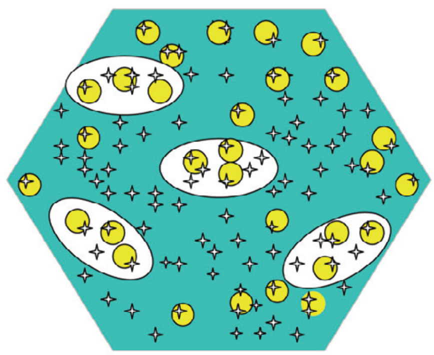

Figure 1. Pangenome structure.

At the same time it is possible to suppose that the strategy of Pangenomic stability differs from that used in respect to organisms or species. For the Pangenome, most important is the presence of genes of different types. The existence of different types of structural and regulatory genes and their functionally active complexes is the main "value" of the Pangenome. Different uni- and multicellular organisms and gene elements within the Pangenome are only a result of the work of a separate, functionally active set of genes. The biomotivation ("logic") of such a system is supreme in comparison with the safety of a species, population, or biocenosis. All organisms play only a temporary role that is connected with the maintenance and reproduction of a concrete set of genes and the formation of new variants of them. For Pangenomic conservation it is important that the death of an organism or the disappearance of a species does not lead to the loss of their genes and their functionally active complexes. According to the current theory, such a conservation of genes can be achieved in the Pangenome not only by the evolution of organisms, during which new-forming species conserve the genes of their ancestors, but also thanks to the constant spread of new genes between cells and their inclusion in different gene elements.

The conservation of genes during evolution undoubtedly plays an important role. It is known that many more complicated organisms store the genetic information of their ancestors (embryogenesis repeats phylogenesis). At the same time, such a means of genetic information storage has its defects, connected with the comparatively low speed of reproduction among most multicellular organisms, the loss of some genes due to the disappearance of species that have no genetic descendants, the limited variance of ecological niches, and so on. Storage of genes due to their spreading in the Pangenome is much more rapid. Such movements of genes take place constantly, and the donors of genes are both live and dead organisms. The constant movement of genes plays a key role in the maintenance of the Pangenome's existence. The distribution of unchanged genes and changed variants allows saving them in case of the extinction of species and is a basis for Pangenomic variability. According to the concept offered, the total genetic network is continuous, and the transfer of genes between various modules occurs constantly. Efficiency of transmission depends on the evolutionary distance between the donor and the recipient and the distance that the DNA must overcome on the way from one module to the other.

Until now the transfer of genes between closely related microbes has been the most investigated, but more and more data have been collected on the transfer of DNA between formally unrelated macro- and cells. Thus the existence of gene transfer between different bacteria and between bacteria and archeae, including with the help of various gene elements, was shown [11–16]. It is necessary to remark that DNA transfer between bacteria can be realized with the help of special "gene transfer agents" [17–19]. Morphologically, these elements resemble viruses, but they contain genes of bacterial chromosome and their release from cells is not accompanied by destruction of the latter. Gene transfer in multicellular organisms is also realized constantly, and viruses and free extracellular DNA that circulate in the blood serum of various animals and humans play an essential role in this process [20]. Gene transfer between evolutionarily unrelated objects with different levels of organization is also an established fact and occurs in variants, as when the donor is a multicellular organism and the recipient is a cell or a gene element, and in the opposite direction. The moving of Ti plasmid from bacteria to plant cells [21] can be an example of gene transfer between simple (bacteria) and complex (plants) organisms.

It seems quite possible that gene transfer occurs not only from bacteria to plants, but also from bacteria to animals and humans. The transfer of DNA from bacteria to human cells in culture was recently demonstrated [20]. The source for such DNA can be microorganisms that colonize the surface of the skin or mucous membranes and form normal microflora. Viral and plasmid DNA fed to mice has been found to resist digestion in the gut. Large fragments passed into the bloodstream and into white blood cells and spleen and liver cells. In some instances the viral DNA was found attached to mouse DNA and *E. coli* DNA, suggesting that it had integrated into the mouse and bacterial cell genome, respectively. When fed to pregnant mice, large fragments of the DNA were found in the nuclei of cells of the fetus and the newborn [22,23]. Foreign DNA (DNAfrom viruses) uptake by animal spermatozoa, which then becomes a component of the genome of the future organism, was recently reported [24–26]. Genes of plants are found in bacterial chromosomes, and bacterial genes were found in the chromosome of an insect [27]. One of the possible ways of gene distribution between organisms is their transfer by viruses capable of infecting unrelated animals or plants [28]. The existence of gene transfer between evolutionary unrelated organisms is also confirmed by the fact that large numbers of bacterial genes were found in human chromosomes [29]. Current data on gene redistribution suggest that there may be "relict gene elements" that appeared during early stages of evolution and have been able to move between unrelated organisms until now.

It is obvious that all biomodules can, depending on conditions, act both as donors and as recipients of genes. Donors of eu- and prokaryotes secrete DNA during life [30], transfer DNA (genes) when they form apoptotic bodies [31], and include their genes in gene elements [32]. In this last case, amplification of concrete genes can take place, as demonstrated, for example, during specific transduction [33]. Recipients that receive new genetic information can use it to change their properties or can just conserve and replicate it (insertion into "not working" areas). It seems possible to identify in the Pangenome special modules which are the main gene recipients. It is obvious that recipients should be quite accessible to the reception of genes from any module. Only microbes (all unicellular organisms and viruses) meet the basic requirements of such acceptors. They are widespread and have the opportunity to receive genes from all organisms, including multicellular ones on which they represent normal microflora. Only microbes can provide the accumulation of genes and their conservation, amplification with alteration, and future redistribution. There are some bacterial species that can store genetic information received from unrelated organisms. It is thought that in the bacteria forming human residential flora that function is, presumably, carried out by Gram-negative anaerobes *(Bacteroides spp.)*. These bacteria are cosmopolites and can receive and transmit genes from representatives of their own species as well as from unrelated Gram-negative and Gram-positive bacteria. Gene elements can play an essential role in the process of gene storage. Viruses can carry and amplify not only their own genes, but also the genes of the cells they were reproduced in. It is necessary to take into consideration that during the reproduction cycle of viruses, some defective particles carrying genes of the host cell are formed. It is known that viruses carrying alien genes partially lose their own genes. Genes brought by defective viruses can start "working" in new cells or can stay there without activation for a long time.

An overview of gene distribution as one of the most important components of Pangenomic stability allows us to suppose the existence of one more explanation for the biological meaning of „death". The death of any organism leads to its entering some food chain, which occurs with the help of microorganisms if decomposition takes place in the environment or inside unicellular organisms or the digestion tracts of multicellular ones. The dead or dying cells are likely to release naked DNA that may survive for many hours. An experiment showed that DNA adhering to clay soil particles survived an average of about 28 hours, as DNA is protected from enzyme attack when adsorbed to solid particles. Naked DNA may survive on the ocean surface for 45-83 hours and for up to 235 hours in the bottom sediment. According to this we can view death as a universal way of giving a new portion of genes to the Pangenome that are intended for redistribution among biomodules. In any case, microbes take part in this process every time. Thus death and all known food chains can also serve as universal ways of gene distribution in different organisms (the genes of cells and gene elements of „food" can be included in the microflora cells of the eating organism or of the environment, i.e. the water and soil). Gene spread in food chains provides gene movement between organisms (genera) that do not communicate directly in „real time", for example from deep-sea micro- and macro-organisms to representatives of ground flora and fauna. Such a movement of genes effects their spread in the Pangenome to great distances and allows them to „try on" the functions of various organisms. It is possible to suppose that microorganisms check the applicability of new variants of genes for perfection of the Pangenome, help to overcome distances in space (for example from the bottom of the ocean to humans), and save themselves in time (the species can become extinct, but the new variant of genes will be maintained).

VARIABILITY

Pangenomic change is a warranty for its existence in the variable environmental conditions of our planet. Mutagenesis constantly leads to the appearance of new variants of genes that are tested for viability in this cell or organism in present conditions. The frequency of appearance of spontaneous mutations varies from 10^5–10^n genes/cell generation. Though the frequency of spontaneous mutation is high itself, there are "centers" with increased variability in the Pangenome. To such centers belong mutator strains of microbes and transformed eukaryotic cells. The frequency of the spontaneous mutations in such modules is 10,000 to 100,000 times higher than in their unchanged predecessors [11,34]. Another source of new genes is RNA-containing viruses, which are characterized by a high frequency of mutation (300 times higher than in DNA-containing viruses). This is connected with the particularity of action of RNAd-RNA polymerases and RNAd-DNA polymerases [34–37]. The reproduction of some RNA-containing viruses is accompanied by the synthesis of DNA copies that are integrated into the cell chromosome, so the way from RNA viruses to the DNA genomes of multicellular organisms is very short.

An additional source of variable genes is induced mutations. Many microorganisms in the environment, including animals and humans, possess mutagenes, which raise the variability of their population and that of many adjacent, unrelated cells [11]. Recombination also takes place constantly, and its speed depends on the module's type. The high variability depends on DNA recombination, and for some microorganisms it has even resulted in the occurrence of the conception of "quasi species" [38,39].

The conservation of new genes and their combinations are controlled by numerous factors, including natural selection. A very important condition for the variability of the Pangenome is a wide circulation of new variants of genes within it. This process is the basis for further selection, conservation, and the use of new genes by Pangenomic modules. To fix a new variant of a gene or gene block in the Pangenome, they should possess the ability to amplify and spread it more dynamically than the initial variant. Multiplication can occur due to an increase in the number of copies of a gene within a given cell (amplification) as a result of an increase in cell amplification speed or in the speed of multiplication (fruitfulness) of the multicellular organism. The spread of information in the Pangenome occurs at different levels. The shortest way is the insertion of a gene into a new place within a chromosome of the same cell. Then gene transmission between modules of related and unrelated organisms takes place. New genes, distributed (spread) in the same ways their precursors used for the stability of the Pangenome.

A common example of how the necessity of the Pangenome to amplify and distribute new variants of genes is realized is the malignant growth inherent to practically all multicel-lular organisms. Malignant cells containing changed genes possess the necessary attribute of "novelty" and are characterized by high growth rates, are metastasis prone, and have enhanced synthesis of DNA. This DNA can be released from the cells and can be detected in blood serum [20]. As a result, malignant cells promote amplification and spread of the changed genes both by increasing their secretion during their life cycle and by their release of genes after death into the general circulation, which is connected with food chains. The necessity to actively amplify any changed genes, the number of which is on the order of a hundred times greater than that of the oncogenes, indicates that the latter only play the role of a helper in the process of malignancy. Thus it is possible that some oncogenes can be the "executors" of signals of other changed genes, having undergone "favorable" changes, and provide their further amplification and distribution. The presence of different types of malignant transformation indicates that most likely there are several auxiliary genetic "complexes of malignancy". Activation of this or that complex can be connected to the localization of genes, features of their properties, or character of changes. It is possible to suppose that altered genes or their complexes possess special markers that are still unknown and which are interpreted by oncogenes (or intermediate acceptors) as signals for their activation. Revealing such markers assumes a new approach to the diagnostics, treatment, and prophylaxis of tumor diseases.

Pangenomic modifications affect living things, the inhabitants of our planet. Changes can occur in different ways, gradually or very rapidly, and can have different significance to nature. Each type of variability should possess specific signs that are typical of it, so that its appearance could be prognosticated. Pangenomic changes can be divided into "favorable", "neutral", and "unfavorable", according to their results. Favorable changes should accelerate the Pangenome's improvement and development, provide conditions for the redistribution and conservation of new variants, and improve accordance with the environment. Unfavorable changes effect the opposite. Neutral changes form a special group, because their existence can be connected with the appearance and accumulation of mutations that do not change the properties of living creatures under the present conditions. Such changes accumulate and persist for a long time in non-working genes, in gene elements which are not getting into live cells, in spores, and by other means. Later, these changes, with conservation and spread, can lead to explosion-like changes in the Pangenome. This concept assumes the presence of special "programs" in the Pangenome that interfere with the conservation and spread of unfavorable genes, their combinations, or the biomodules containing them. Thus in the Pangenome, special modules capable of destroying subunits "harmful" to it, are formed and distributed. The Pangenome's elimination of its uni- and multicellular organisms that become the carriers and distributors of unfavorable genetic information can be one of the causes of the disappearance of some species during evolutionary history.

The formation and appearance of epidemic strains of different microorganisms and the formation of new pathogens may be one of the manifestations of such activity of the Pangenome. It is known that the self-regulation of an epidemic process is the result of the activity of many factors that determine changes in the pathogen and the sensitivities of possible targets (in the case of human infection spread, the population) [11,40]. Recently we can see the formation and spread of new variants of pathogens which cause nosocomial infections. All these bacteria have a large number of "additional" genes that control antibiotic resistance and the formation of various virulence factors. The appreciable formation of these strains is caused by the accumulation of genes that carry information which is "negative" for us in the normal (residential) microflora of the human body. During persistence of such strains in the normal microbial flora of hospital staff, two processes take place that are dangerous to us: amplification of these genes during microorganism multiplication and their spread among people and in the environment. As a result it is quite probable that the transfer of such dangerous genes, including pathogens to other species, can cause an epidemic. It is possible that the spread of cells having genes dangerous to other uni- and multicellular organisms in the environment can lead to the formation of absolutely new pathogens that will cause an epidemic, already not limited by hospitals walls. There are reasons to believe that drug-resistant strains of *Mycobacterium tuberculosis, Streptococcus pneumoniae,* the new *Vibrio cholerae* serotype O139, enterohemorrhagic *Escherichia coli* of serotype O157, and the *Haemophihis influenzaebiotype aegypticus* have all emerged through macroevolutionary events mediated through horizontal gene transfer. [41,42].

Another way of epidemic strain formation is connected with the involvement of new microorganisms that have not been causative agents of a pathological process in this concrete group of multicellular organisms (or human, or animals, or plants, or fungi). The appearance and spread of yersiniosis, viruses of human immunodeficiency, and some hemorrhagic fevers in the last century and SARS in this one can be sad examples of such pathogen transfer from one species to others. In view of this, human activity should obviously be analyzed from a new perspective. Overcrowding, environmental change, technogenic influences and the like can have negative consequences for the Pangenome. Special attention should be paid to such human activities as biotechnology, one of the fastest growing industries, including artificial reproduction and the spread of different modules (microorganisms in agriculture) in human and veterinary medicine as probiotics used to normalize resident microfloral functions, applications in the food-processing industry, pharmacy, and for other industrial goals, cross-breeding at the genetic level, the creation of new biotypes and species, and the transplantation of cells and organs to unrelated recipients. Practically all transgenic plants have one viral promoter which is from the cauliflower mosaic virus, which is closely related to the human hepatitis B virus and, less so, to retroviruses such as the AIDS virus. The promoter can drive the synthesis of these other viruses [43–47]. As all genomes contain dormant viruses, there is a potential for the cauliflower mosaic virus promoter to reactivate them. Its strong promoter activity causes the introduced genes to be overexpressed, and may also have effects on host genes far from the site of the foreign gene insertion. All that can lead to the formation, selection, and spread of cells and gene elements that are directed against the creator of these violations, i.e. humans.

CONCLUSIONS

The proposed concept allows viewing the search for perspective directions in scientific research in biology and practical medicine in a new fashion. It allows developing methods for forecasting and estimating possible negative after-effects of interventions of molecular genetics, biotechnology, and ecology. According to this concept, all genetic information in all living organisms and organic molecules and their complexes (DNA and RNA containing viruses, plasmids, and gene elements) can be presented as constituents of a common system: the Pangenome. This concept implies that newly emerging genes are not bound to disappear together with the death of an organism or the extinction of a species and microorganisms are the main pool of genes. Using this concept it is possible to find new ways to diagnosis various diseases, primarily those caused by microbes and connected with cell transformation. This concept can also help to discover a new ideology for the creation of drugs with novel principles of action.

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Effective search tool for collaborators worldwide. Provides easy global networking for scientists. C.V.'s and dossiers on selected scientists available. Increase your professional visibility.

IC Virtual Research Groups [VRG]

Web-based complete research environment which enables researchers to work on one project from distant locations. VRG provides:

- customizable and individually self-tailored electronic research protocols and data capture tools,
- statistical analysis and report creation tools,
- profiled information on literature, publications, grants and patents related to the research project,
- administration tools.

IC Journal Master List

Scientific literature database, including abstracts, full text, and journal ranking. Instructions for authors available from selected journals.

IC Patents

Provides information on patent registration process, patent offices and other legal issues. Provides links to companies that may want to license or purchase a patent.

IC Conferences

Effective search tool for worldwide medical conferences and local meetings.

IC Grant Awareness

Need grant assistance? Step-by-step information on how to apply for a grant. Provides a list of grant institutions and their requirements.

IC Lab & Clinical Trial Register

Provides list of on-going laboratory or clinical trials, including research summaries and calls for co-investigators.