Biosemiotics (2016) 9:331–343
DOI 10.1007/s12304-016-9276-1

Distributed Heredity and Development: a Heterarchical Perspective

Jana Švorcová [1]

Received: 15 January 2016 / Accepted: 14 September 2016 / Published online: 20 September 2016

Abstract This review paper discusses the perspective of complex biological systems as applied to inheritance and ontogeny, focusing on the continuity of genetic, epigenetic (transgenerational) and microbiotic inheritance. The informational processuality within this continuity can be used as to exemplify the insufficiency of hierarchical concepts in grasping the complex and integrated nature of biological processes. The argument follows Bruni and Giorgi (*Progress in Biophysics and Molecular Biology* 119, 481–92, 2015) in emphasizing that while structures and substrates are organized hierarchically, communicational processes are organized heterarchically. The essay also argues the insufficiency of a single, basic, i.e. genetic level of description, which is the prevalent idea of twentieth century biology, to explain all phenotypic variation. I argue that inheritance and development cannot be fully explained by some sub- or super-ordination and that such descriptions are merely heuristic tools that do not reflect the nature of such processes.

Keywords Transgenerational epigenetic inheritance · Microbiota · Heterarchy

Introduction

Heredity in biological systems is usually interpreted as a transmission of genetic information from one generation to another, parent to offspring. Such information is stored in gene representation of four different - let us say *quasi digital* (Markoš and Švorcová 2009) - characters A, C, G and T (adenine, cytosine, guanine and thymine) and their sequence is changeable only via random mutation. Since the era of the modern synthesis, such mutation and subsequent selection are considered the major

✉ Jana Švorcová
jana.svorcova@natur.cuni.cz

[1] Department of Philosophy and History of Sciences, Charles University, Viničná 7, 12843 Praha 2, Czech Republic

force in evolution. The level of genetic information is supposed to be a basic cause of an organism's appearance and behavior. According to the modern synthesis, everything should be explained from this level as genes constitute the only genuine inheritance system. The mutual influence of environment and organism, an organism's experience, and its own contribution to development and evolution are not taken into account or are considered mere background condition. Such ideas are usually mocked for being Lamarckian or vitalistic.

In the history of biology, there have been many attempts to describe the nature of genetic information; it is compared to texts, languages or even programs (Jakobson 1971; Faltýnek 2010), and the correlative idea of linearity remains a strong premise in biological thinking about heredity related phenomena. Such statements about formal grammar or a syntax lying behind the living processes had a powerful influence on molecular biology in the 1950s and 1960s (Markoš and Faltýnek 2011) and similar opinions also led to the conclusion that the competence of speech itself is encoded in DNA molecules (Ji 1997, 1999).

Every metaphor must eventually meet its own epistemological and explanatory boundaries; in this case, these are found in the importance of bodily structures - the cellular environment that interprets the genetic information. The relationships between genes and proteins are not straightforward, any string of amino acids can attain an astronomic number of different shapes, and the structure of any given protein eventually depends on the cellular environment, i.e., on its fellow proteins, pH etc. Alternative splicing and further RNA editing processes make the relationship between DNA and proteins even more problematic. Even the DNA molecule itself relies significantly on its bodily structure, as when very distant DNA regions, sometimes hundreds of kilobases distant from each other, interact via transcriptional regulators. Thus the mere reduction to linear strings of characters will never be a complete description (for further readings see Davidson 2006, Cvrčková and Markoš 2005).

Similarly, the program metaphor always assumes some creator of such formal language; it is an understandable analogy in case of man-made machines, but problematic in case of self-reproducing entities such as cells or living beings in general (see Markoš and Švorcová 2009).

The genetic information stored in DNA strings is the first and necessary condition for heredity and it is subjected to Mendelian laws of heredity, representing the storage of information fixed in a code: however the way in which the script is handled during translation is not completely determined by the genes themselves. Additionally, differences between species often result from different interpretations of very similar genetic information. E.g., there is only about a 2 % difference in genetic sequences between the genomes of humans and chimpanzees (Marks 2002), however a more significant degree of speciation is found in differing interpretations of genetic sequences as represented in cellular differentiation via differential patterns of epigenetic modifications, or through differences in spatiotemporal gene activation (see below).

Several levels of inheritance will be described in this paper, but my aim is not to cover this agenda completely. Starting from genetic inheritance above, I will also discuss the case of epigenetic inheritance and some examples of transgenerational epigenetic inheritance, from plants to mammals. Further, a quite young branch of biological studies, studies done on mouse and human microbiota and its heredity and

influence on our physical and psychical nature and development, will be discussed. After a short list of other examples of inheritance, I will discuss the reasons for a heterarchical perspective in order to model such processes.

The Role of Epigenetic Processes in Development

Since 1980, epigenetic processes have revealed that the development of organisms does not rely merely on genetic information stored in DNA molecule, but also on a significant amount of parallel information processed in terms of DNA methylation, histone and many other protein modifications, RNA mediated processing, structural templating, etc. (Jablonka and Raz 2009). This information is hereditary but not part of the DNA script, i.e. it is not caused by random changes in DNA (mutations), but induced by environmental as well as internal conditions (e.g., DNA methylation is also thought to be induced stochastically).

DNA methylation is an addition of a methyl group to a cytosine (or adenine residue), converting it to 5-methylcytosine. This modification, written either on a gene or a promoter region, usually enhances or blocks the transcription of a concrete gene. It can often be found on repetitive regions and plays a role in X-chromosome inactivation and genomic imprinting.

DNA methylation works together with histone modifications, i.e. methylation of lysines and arginines, phosphorylation of serines, acetylation of lysines, ubiquitination or biotinylation of lysines (attachment of protein ubiquitin or biotin to the amino acid) etc.

Such histone proteins serve as a substrate in the eukaryotic cell in order to stabilize, condensate and regulate the DNA strands. Specific group of proteins can write, read, or delete a plethora of modifications on histone amino acid tails. This is a very important point: unlike some mutations of DNA script, epimutations of histone proteins are reversible, appearing and disappearing within minutes after a specific signal as histone modifying enzymes are often regulated by various metabolites present in the intra- or extracellular environment (Turner 2009). Such regulation of the DNA script enables cellular differentiation in the body: every cell has more or less the same genetic information, but the pattern of activated and deactivated genes differs in every cell type.

These modifications are very conservative and form another kind of code which, as I mentioned earlier, leads to the activation of specific genes or on the contrary, to gene silencing. For example, the methylation of lysine 9 on histone 3 (H3K9me) usually leads to tighter condensation and thus silencing of a specific DNA region; together with H3K27 (plus Xist RNA and other proteins and molecules), this modification silences the X chromosome in mammalian females. On the other hand, H3K4, H3K36 and H3K79 are modifications usually found in transcriptionally active chromatin (for a more detailed review see also Markoš & Švorcová 2009). About 100 different modifications of histone amino acids with various outputs are now known. Some of their outputs are not easily predictable: the combination and position of modifying marks (if close to a promoter or gene region) are crucial. For example, as in case of transcriptional activation there is a typical combination of di/trimethylation of H3K4 together with acetylation of H3K9. Such interdependence has been also demonstrated by the

treatment of the cells by the histone deacetylase inhibitors which led not only to hyperacetylation of the histones, but also to hypermethylation of H3K4 (while the other lysines remained unaffected, Nightingale et al. 2007). The interdependence of histone modifications was also shown in yeast, where the phosphorylation of H3S10 (modification important for chromosome condensation, cell cycle but also for gene activation during interphase) facilitates the acetylation of H3K14; on the contrary the phosphorylation H3K9 prevents the H3K9 methylation (Biel et al. 2005). Methylation of H3K9, typically found in silenced chromatin, can also act together with methylation of H3K4 and H4K20 helping to maintain the chromatin active (also by binding the BRAHMA chromatin remodeling complex, de la Cruz et al. 2005). Such examples show that histone code can be interpreted contextually, depending on the combination of modifications.

In the listing of epigenetic processes, we cannot omit different noncoding RNA molecules (microRNA; long non-coding RNA or piwiRNA) that are able to interfere with complementary RNA molecules in the cell cytoplasm and silence them via degradation. piwiRNAs, for example, are very effective in the silencing of retrotransposons, RNA's product in germ cells.

Long non-coding RNAs (longer than 200 bp) and many small RNAs can also regulate epigenetic processes: they can guide chromatin-modifying enzymes to their target sites or act as a scaffold for chromosomal organization. RNAs bind to polycomb chromatine repressive complexes, trithorax chromatine activating complexes, to histone proteins or to DNA methyltransferases directing them to the different loci in the cells (for more detailed review see Morris and Mattick 2014). RNA can also regulate transcription or recruit regulatory or effector proteins, small RNAs (as well as piwiRNA in germ cells) interact with heterochromatin protein 1 and histone methyltransferases inducing heterochromatin formation in *Drosophila* and DNA methylation in mammalian germ cells (Mattick et al. 2009). Such examples mentioned here, are only a very small segment of knowledge gathered about RNA epigenetic regulation.

Additionally the ENCODE project published in *Nature* and other biological journals in September 2012 (36 seminal paper altogether) revealed that more than 80 % of the human genome has a biological function, which denies the fact that most of our genome is formed by so called *junk* DNA. The authors of ENCODE project further revealed that the part of the genome which is formed by the protein coding sequences (exome) is much smaller than anticipated and especially comparing to the regulome, i.e. such parts which have a protein binding or regulatory RNA molecule coding function (60 % of the above mentioned 80 %). RNA processing in the cells is enormous and many of their functions remain unknown. They also revealed a great variability of epigenetic marking of chromatin systems: 3 millions of nucleosome types were found (each of them with differential histone modification pattern), but only 3700 of them are in all 147 studied human cell types.

Examples of Transgenerational Epigenetic Inheritance

Epigenetic inheritance is, in the broad sense, the inheritance of developmental variations that are not related to the differences in the DNA script. It can include anything from cell to cell transmission to symbolic communication. Today the term *epigenetic*

inheritance is used in a narrower sense referring to the informational transmission in sexual or asexual cell lineages which is not a result of differences in DNA sequences (for a complete review see Jablonka and Raz 2009).

Heritability of epigenetic modifications (even induced from the environment) through mitosis is a well known fact (Ng and Gurdon 2008). Nowadays, what is strongly discussed in terms of epigenetics is the inheritance of such modifications through the germline (i.e., the inheritance of DNA methylation as well as RNA molecules, but also of some histone modification). The inheritance of RNA molecules via spermatozoa or eggs is not so surprising: one of the defining faculties of such molecules is the capability to cross the plasma membrane and to interfere with the cell's RNA. What is more surprising is the inheritance of DNA methylation marks and also histone modification. Apparently some of the methylated marks survive the reprogramming during the germ cell maturation and development. Also, in case of histones not all of these proteins are replaced in sperm by protamines, and some of histone marks can be thus inherited in future generation (Siklenka et al. 2015).

Jablonka and Raz documented cases of epigenetic inheritance in 42 species already in 2009: 12 cases in bacteria, 8 cases in protists, 17 in fungi, 36 in plants, and 28 in animals. And since the publication of Jablonka's article, cases of transgenerational epigenetic inheritance (TEI) are accumulating. TEI is more to be expected in the case of plants, the most plastic group of organisms, than in mammals, because plants lack the Weismann barrier.

Some cases of TEI have already found their way into textbooks (Gilbert and Epel 2009). TEI was reported in *Arabidopsis thaliana* (Schmitz et al. 2011) and in *Taraxacumofficinale* (dandelion) (Verhoeven et al. 2010). In the case of apomictic dandelion plants, Verhoeven et al. (2010) showed that not only stress (such as biotrophic pathogens, herbivorous insects or low nutrition) induces *DNA methylation* changes within one generation, but that these changes are also transmitted to future generations. Schmitz et al. (2011) showed that the methylation pattern of epialleles was meiotically stable and heritable across many generations in the studied population of *Arabidopsis thaliana.*

In *Drosophila melanogaster*, Seong et al. (2011) reported heat stress induced TEI of *chromatin structure*; similarly, Siklenka et al. (2015) showed that environmentally induced (under laboratory conditions) alteration in chromatin modifications were heritable in the absence of any further exposure to the alteration in the next generations. Also, various *RNAs* can often be transmitted in mice via sperm (Rassoulzadegan 2011).

Epigenetic inheritance in mice is a well-known phenomenon, described primarily on two frequently cited examples: one refers to the A^{vy} locus (a dominant mutation of the *agouti* locus) resulting in an obese yellow fur phenotype. A sufficient methyl donor diet (supplemented with folic acid, methionine etc.) can change the epigenetic state of the A^{vy} allele promotor in the germline via *DNA methylation* and these modifications can be retained through the epigenetic reprogramming that occurs during early embryogenesis (Morgan and Whitelaw 2008). Such changes on the epigenetic level lead to a normal mouse (non Agouti) phenotype (Waterland and Jirtle 2003; Cropley et al. 2006). The second example (Weaver et al. 2004, 2005; Meaney 2001; Meaney and Szyf 2005) shows that the behaviour of the mother can influence the pattern of *DNA methylation* marks and therefore the phenotype of mice. When the new-born mice do not obtain sufficient maternal care (i.e., grooming), the enhancer of glucocorticoid

receptor remains methylated, therefore silenced, and the mouse suffers from an insufficient number of receptors in the hippocampus and is not able to deal with stress as efficiently as mice that experienced intensive grooming. Of course, the depressive behavior of the mother is furthered by depressive behavior of the adult offspring: if the pups get a nurturing mother, the effect vanishes.

Dias and Ressler (2014) showed that, when combined with traumatic exposure even an olfactory experience can influence the behavior and neuroanatomy of two subsequent generations. Male mice exposed to the smell of acetophenone while subjected to electric shocks learned to fear the smell. But surprisingly, their offspring in two subsequent generations feared it as well, although they had never been exposed to the same conditioning as their ancestors or to the smell of acetophenone at all. Compared with control groups and their progeny, the brains of all three generations of mice also developed a higher number of neurons with acetophenone specific receptors. These fearful memories are supposed to be transferred via DNA methylation in germ cells; in this case, fewer DNA methylation marks of acetophenone-sensing gene leading to its greater expression in the brain tissue. (The experiments were first conducted on males in order to show that the modifications were really transferred via sperm, not via in utero exposure; and later on females with the same results.) Epigenome studies have also been conducted in the case of humans (Rakyan et al. 2011), and TEI has been reported in terms of *metastable epialles* (Waterland et al. 2010) and heritable *histone marks* transmissible via sperm (Ooi and Henikoff 2007; Hammoud et al. 2009; Brykczynska et al. 2010; Siklenka et al. 2015).

Environmental cues such as light, temperature, nutrition, pressure, gravity, stress, the presence of predators or symbionts, and even the mannerisms of maternal care and the presence of other members of the same species can have a great influence on the phenotype. These differential influences are thus mirrored in what is termed phenotypic plasticity. Not all such differences are reflected in the genome, but are the results of differences of memory traces captured on chromatin or in small regulating RNA molecules, *transmitted to future generations* via germ cells (meiotically). These traces reflect the individual history of an organism; they form a population-specific memory and change their pattern as a function of experience. The character of epigenetic memory is, from its very definition, rather unstable; the traces are constantly written and rewritten, their origin is often hard to unfold as they are induced both randomly and environmentally. Experiments similar to those establishing the heredity of fearful memories in mice could even lead to a change of how we think about such thing as instinctive animal behavior, because it shows how something primarily conditioned becomes unconditioned (and instinctive). Discussions of the importance of TEI continue (Grossniklaus et al. 2013), despite the high number of molecular studies in this area, evolutionary biology still faces a long haul in reevaluating its relevancy.

Epigenetic Inheritance of Microbiota

The facts that different organisms live in various relationships of mutual symbiosis and that eukaryotic organelles are a result of endosymbiosis are rather trivial nowadays (for further interest see Lhotský et al. to appear in 2016). Even the heredity of symbionts in arthropods is a well known fact. What I find more appealing are the rising data about

the importance of human, or in broader sense mammalian (most experiments are done on mice), microbiota and the ways in which these microbiota are inherited.

Human bodies contain up to 1000 of different bacterial species, which makes about 10^{14} non human cells in every human body (up to 90 % of the cells in whole human body). It is a known fact that these bacteria help us digest food, metabolize polysaccharides and/or provide us with essential vitamins of fatty acids, and prevent possible inflammation caused by "bad" bacteria (Nyholm and McFall-Ngai 2014). According to microbiome studies, abnormal changes in our microflora (due to the presence of pathogens or excessive antibiotics use) can change the ontogeny and health of the host organism. A link between people with autism and abnormal microflora in their intestine has been found; autistic people usually have a so called "leaky gut" or other digestive tract problems. Experiments on mice have shown that mice manifesting autism-like behavior lacked *Bacteroides fragilis*, and when the bacteria was supplied them in their food, their behavior changed to a normal mice behavioral pattern (Hsiao et al. 2013).

Human dysbiosis, i.e. abnormal microbial spectrum, probably causes a variety of autoimmune diseases such as inflammatory bowel disease, type I diabetes or multiple sclerosis (Lee and Mazmanian 2010). Symbiotic bacteria also produce all sorts of signaling molecules involved in brain development, influencing it via *nervus vagus* and having a major influence on human psychical condition and our subsequent behavior. Dysbiosis is often connected with depressive and anxious behavior (Hsiao et al. 2013).

In one of his essays, the developmental biologist Scott Gilbert (2014) discusses a new narrative of human birth in terms of tight connection with bacterial symbionts. He stresses that the birth of a new human being is not the birth of an individual but the origin of a new community. Not only are the genes from the mitochondria and the nucleus transferred, but also the genomes of symbionts. Up to 90 % of maternal cells are microbial, almost a third of mammalian metabolites in blood have a bacterial origin. Unlike insects, which inherit bacteria via germline, mammals get their bacterial symbionts at birth from their mother (her skin, vagina and breast milk) and their environment, therefore horizontally. Some bacteria are even able to pass through the amniotic barrier and colonize the developing fetus (Funkhouser and Bordenstein 2013); surprisingly, the first colonizers come from the oral cavity of the mother (see Human Microbiome Project Consortium 2012). So the idea of a fetus developing in a sterile environment is no longer considered true.

Remarkably, the microbiome composition is almost unique from the beginning of a holobiont's[1] life (Raveh-Sadka et al. 2015); during the first three years of life a human child has a very changeable ecosystem (Koenig et al. 2011). Chiu and Gilbert (2015) therefore describe holobiont as a "*fluctuating chimera of different species and populations*". Monozygotic twins have a much more similar sample of microbiota than dizygotic twins, which also points to the suggestion that some microbiota are heritable (Goodrich et al. 2014). The microbial variation stays diverse among individuals as well, depending on the way of life (diet, environment, early life exposure etc.)

Human interdependence with microbiota is thus far more important than we had thought, and they represent a very important part of the inherited biological

[1] Holobiont was first defined by Lynn Margulis and Fester (1991) and is usually understood as a community of different species forming various relationships of symbiosis.

information. Without microbiota, human brain, immune and digestive system cannot fully function and develop. Selection acts not only on the level of genes, individuals or groups, but obviously also on the level of microbiotic and host communities, because evolutionary, developmental, physiological and even psychological nature of many organisms is indeed holobiotic.

Other Types of Inheritance

Previously (Švorcová 2012), I discussed the case of a *memory of the body plan* acting during development, after the supposed phylotypic stage, when very conservative genes shared among such organism like fly, mouse or human, are used in different spatiotemporal and tissue contexts, which eventually lead to very different phenotypes as we know them. I interpreted such developmental networks, in which the same gene can be used to build eyes, kidneys or other organs, as a network of habitual interaction (sensu Peirce). Such a network is experience dependent when, for example, a gene is used in some completely new tissue context (genes are coopted for a novel context by the bodily experience). In my conception, the memory of a developmental body represents a deposit of habitual interpretations, which are heritable and unique for every species. Such memory maintains the convention, continuity and coherency of the species and has to be transmitted through the bodily medium (the egg); the body plan is thus not reconstructed only by reliance on DNA representations, but has to be reconstructed from a primary bodily setup stored in the egg structure (this view is very similar to the concept of *embryonic signalome* introduced by Bruni 2007). In my view, bodily memory represents another case of inheritance.

To fill out the list of other types of inheritance that are not particularly tied to the DNA script, we must briefly mention other systems such as *structural inheritance*, i.e. inheritance of 3-D structures. Jablonka and Raz (2009) give examples of the inheritance of *Paramecium* cilia: this being a case of the heredity of whole cellular components (e.g. the heredity of plasma membrane during the cell division) – which also happens in the heredity of prions in yeast. In *Evolution in four dimensions* (Jablonka and Lamb 2005), Jablonka and Lamb distinguish 4 different levels of heredity from genetic to symbolic (genetic, epigenetic, behavioral and symbolic). Another heavily discussed topic these days is niche construction or *ecological inheritance*, which emphasizes reciprocal causation among organisms and their environments (Laland et al. 2015). Chiu and Gilbert (2015) argue in their paper that the very example of interactions between human and microbiota and the holobiotic birth are actually very convenient instances of mutual construction of developmental, ecological and evolutionary niches (and also instance of reciprocal scaffolding of development). Basically, if we use Weismannian terminology, inheritance can occur from germ line to germ line (genetic, epigenetic), from soma to germ line (epigenetic), from soma to soma (symbiotic, behavioral, cultural or symbolic), or from soma to soma via the external environment (niche inheritance; Laland et al. 2015).

Hierarchies or Heterarchies?

During the last century the main source of variation and therefore the basic level of description was considered to be genetic information (and its mutation). It was the

grounding which the rest of the possible hierarchical levels across development and inheritance was explained from, usually in deterministic terms of bottom-up chain of causality. But let us now take the example of gene regulation via epigenetic information. In such a case, what is prior to what? The chromatin modifying enzymes and RNA molecules are of course encoded in the genome, but epigenetic regulation can act upon it from one generation to another, influence its manifestation or even enhance mutational changes in the genetic script. For example methylated cytosines can influence DNA sequence through spontaneous hydrolityc deamination of cytosine into uracil which can, in few steps and with the help of repair enzymes, lead to A = T base pair in place of the original G = C (Turner 2009). Or even the simple fact that the silenced DNA is being manipulated, unwrapped and exposed, can more probably lead to possible mutational events.

Levels of genetic and epigenetic processing in eukaryotic organisms are so interdependent and include complex downward and upward loops of communication, that our distinction within different developmental and inheritance levels can be only a matter of our attempt to categorize these processes within hierarchical schemes and mechanism (which often reflect the progress of our knowledge about these phenomena). But in reality it is not possible to depict strict relationships of sub- and super-ordination, the main difference is the permanence and emergence of such codes in evolution, the epigenetic being more plastic, reversible and evolutionary younger.

Hierarchical schemes are not sufficient enough if we want to grasp the workings of all signaling and coding processes existing within and through bodily structures and do not reflect the complexity of reality of these processes. If you consider genetic expression in eukaryotic cell, there are several components in play: possible external stimulus from the environment, signal transduction pathway with all its possible cross-talks, chromatin remodeling complexes, RNA molecules targeting these complexes, histone modifications in their specific combination, RNA polymerase, intron splicing and post-translational modification and we are not even taking the cellular environment and fellow proteins into account. Such signal from the environment can relate different structural domains as we can distinguish them hierarchically for the purpose of scientific description (for example somatic and germ cells at once, see Turner 2009), but the communicational processes (mediated for example by RNA molecules) within and among these levels have rather heterarchical nature.

That is why I find to some extent the heterarchical approach much more suitable for description of phenomena such as development or manifold types of inheritance, than merely a hierarchical one. The concept of heterarchy (unlike that of hierarchy where there are usually defined strict relations of sub- or super-ordination) defines relations of complementarity and subordination between categories of different levels of description such that the description resembles a more network-like interaction where horizontal interactions are as important as vertical (see Bruni and Giorgi 2015). More importantly Bruni and Giorgi (2015) also argue that heterarchical organization is inherent to communication processes, while physical structures and substrates are by definition organized in hierarchies. It does not mean that heterarchies and hierarchies are necessarily exclusive to each other; I believe that in terms of inheritance and ontogeny we can always define hierarchically organized structures (nucleus, cell, cellular mass, tissue, organ, body, symbiotic organism, parasite etc.), but as also Bruni and Giorgi (2015) emphasize, such structures scaffold heterarchically organized

processes, especially when communicational processuality in terms of codes or signals is involved.

Or take the example of inheritance of microbiota, which is quite hard to grasp from a single level of description. Microbiota communicate with human cells on neuronal, gut or even immune levels; they cohabit with human on skin surface as well as in the bodies and within the organs; their metabolites are actively used by different tissues in human bodies – and even by the tissues of babies. One very charming example of the tight co-evolution with bacteria is the motherly production of complex sugars which the baby is not able to digest, but which serve as food for infant's Bifidobacteria, which help the baby gut to develop and prevent the colonization of pathogens (Sela et al. 2011). This particular *Bifidobacterium, B. longum subspecies infantis*, has a specific set of genes that its relatives lack which are connected to the digestion of complex sugars. Such DNA regions are a direct proof of the beneficial co-evolution of human and bacterial genomes (for more detailed review of such relationships and impact on infant's health, see Chiu and Gilbert 2015). Obviously, as we try to grasp the inheritance and influence of microbiota on the human well being, our description necessarily transcends and ties together many levels on scales both micro and macro, going beyond perceived beings themselves (as when, in the mother-child relationship, mother's milk feeds the infant's bacteria). Communicational processes among human microbiota do not respect the order of hierarchical structures, signals can relate different levels of hierarchies in heterarchical manner. Workings of microbiota can influence the gut milieu, which can influence the brain, which can further influence the behavior, behavior can impinge on epigenetics, i. e. as Bruni and Girgi emphasize, such processes relate different domains of structural hierarchy, working in non-transitive manners.

Conclusions

I believe that the given examples show that organisms are highly integrated units whose being is interconnected with their environment and with fellow organisms, all of which influences each other on multifarious levels. Our former (twentieth century) schemes feather away and we can no longer grant primacy to genes or argue the impossibility of heredity of acquired characters.[2] We cannot say that selection works on only the single level of genetic heredity and that this level is prior to the other levels; rather, variation results of multiple aspects, not only random mutation. Organic memory is distributed, it stores its traces of experience on many levels and is restored in every generation by various members of a vastly entangled interspecific community.

As described in this article, inheritance and developmental systems should not be thought of only in terms of hierarchical organization of informational processing, rather, as emphasized in Bruni and Giorgi (2015), such processes are embedded heterarchically within hierarchically organized physical structures. Heterarchical

[2] Shift in the interpretation of the possibility of Lamarckian dimensions in heredity are apparent from the number of emerging publication in this area (e.g. Gissis and Jablonka 2011; Pigliucci and Müller 2010; Gilbert and Epel 2009). In addition, *The 23 Annual International Workshop on the History and Philosophy of Science* held in Jerusalem in 2009 to celebrate 200th anniversary of Lamarck's *Philosophie zoologique* attracted all the principal personalities in philosophy of biology as well as those of research agendas such as evolutionary developmental biology or ecological evolutionary biology.

approaches should be integrated into scientific and philosophical interpretations of life, because they stress the contextual nature of biological processes, as in case of specific combinatorics of biological codes; they can also grasp the historical character of evolution (when unique agents meet in the developmental network for example) and interpret better the holobiotic interrelations.

Acknowledgments This paper was supported by the project Linguistic and lexicostatic analysis in collaboration of linguistics, mathematics, biology and psychology no. CZ.1.07/2.3.00/20.0161, the Grant Agency of The Czech Republic 13-24275S and also by Charles University in Prague within the UNCE project 204004.

References

Biel, M., Wascholowski, V., & Giannis, A. (2005). Epigenetics-an epicenter of gene regulation: histones and histone-modifying enzymes. *Angewandte Chemie (International Ed. in English), 44*, 3186–3216.

Bruni, L. E. (2007). Cellular Semiotics and Signal Transduction. In M. Barbieri (Ed.), *Introduction to Biosemiotics. The New Biological Synthesis*. Berlin: Heidelberg: Springer.

Bruni, L. E., & Giorgi, F. (2015). Towards a heterarchical approach to biology and cognition. *Progress in Biophysics and Molecular Biology, 119*, 481–492.

Brykczynska, U., Hisano, M., Erkek, S., Ramos, L., Oakeley, E. J., Roloff, T. C., Beisel, C., Schübeler, D., Stadler, M. B., & Peters, A. H. F. M. (2010). Repressive and active histone methylation mark distinct promoters in human and mouse spermatozoa. *Nature Structural & Molecular Biology, 17*, 679–687.

Chiu, L., & Gilbert, S. F. (2015). The Birth of the Holobiont: Multi-species Birthing Through Mutual Scaffolding and Niche Construction. *Biosemiotics, 8*, 191–210.

Consortium, H. M. P. (2012). *Nature, 486*, 207–214.

Cropley, J. E., Suter, C. M., Beckman, K. B., & Martin, D. I. K. (2006). Germ-line epigenetic modification of the murine A^{vy} allele by nutritional supplementation. *PNAS, 103*, 17308–17312.

Cvrčková, F., & Markoš, A. (2005). Beyond bioinformatics: Can similarity be measured in the digital world? *Journal of Biosemiotics, 1*, 93–112.

Davidson, E. H. (2006). *The regulatory genome. Gene regulatory networks in development and evolution*. Amsterdam: Academic Press.

de la Cruz, X., Lois, S., & Molina, S. S. (2005). Do protein motifs read the histone code? *BioEssays, 27*, 164–175.

Dias, B. G., & Ressler, K. J. (2014). Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nature Neuroscience, 17*, 89–96.

Faltýnek, D. (2010). Evolvování Romana Jakobsona. In A. Markoš (Ed.), *Jazyková metafora živého* .Pavel Mervart

Funkhouser, L. J., & Bordenstein, S. R. (2013). Mom knows best: the universality of maternal microbial transmission. *PLoS Biology, 11*, e1001631.

Gilbert, S. F. (2014). A holobiont birth narrative: the epigenetic transmission of the human microbiome. *Frontiers in Genetics, 5*, 282.

Gilbert, S. F., & Epel, D. (2009). *Ecological developmental biology. Integrating epigenetics, medicine, and evolution*. Sunderland: Sinauer Associates.

Gissis, S. B., & Jablonka, E. (2011). Transformations of *Lamarckism*. In *From Subtle Fluids to Molecular Biology*, *Vienna Series in Theoretical Biology*. Cambridge: MIT Press.

Goodrich, J. K., Waters, J. L., Poole, A. C., Sutter, J. L., Koren, O., Blekhman, R., Beaumontm, M., Van Treuren, W., Knight, R., Bell, J. T., Spector, T. D., Clark, A. G., & Ley, R. E. (2014). Human genetics shape the gut microbiome. *Cell, 159*, 789–799.

Grossniklaus, U., Kelly, W. G., Ferguson-Smith, A. C., Pembrey, M., & Lindquist, S. (2013). Transgenerational epigenetic inheritance: how important is it? *Nature Reviews Genetics, 14*, 228–235.

Hammoud, S. S., Nix, D. A., Zhang, H., Purwar, J., Carrell, D. T., & Cairns, B. R. (2009). Distinctive chromatin in human sperm packages genes for embryo development. *Nature, 460*, 473–478.

Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., et al. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell, 155*, 1451–1463.

Jablonka, E., & Lamb, M. J. (2005). *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symbolic Variation in the History of Life*. MIT Press.

Jablonka, E., & Raz, G. (2009). Transgenerational epigenetic inheritance: Prevalence, mechanisms, and implications for the study of heredity and evolution. *The Quarterly Review of Biology, 84*, 131–176 Also available at http://ts-si.org/files/JablonkaQtrRevBio2009.pdf.

Jakobson, R. (1971). *Selected Writings II*. The Hague, Mounton: *Word and language*.

Ji, S. (1997). Isomorphism between cell and human languages: molecular biological, bioinformatic and linguistic implications. *Biosystems, 44*, 17–39.

Ji, S. (1999). The linguistics of DNA: Words, Sentences, Grammar, Phonetics, and Semantics. In: Molecular Strategies in Biological Evolution. *Annals of the New York Academy of Sciences, 870*, 411–417.

Koenig, J. E., Spor, A., Scalfone, N., Fricker, A. D., Stombaugh, J., Knight, R., Angenent, L. T., & Ley, R. E. (2011). Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences of the United States of America, 1*, 4578–4585.

Laland, K. N., Uller, T., Feldman, M. W., Sterelny, K., Müller, G. B., Moczek, A., Jablonka, E., & Odling-Smee, J. (2015). The extended evolutionary synthesis: its structure, assumptions and predictions. *Proceeedings of The Royal Society Publishing B, 282*, 20151019.

Lee, Y. K., & Mazmanian, S. K. (2010). Has the microbiota played a critical role in the evolution of the adaptive immune system? *Science, 330*, 1768–1773.

Lhotský, J., Pranab, D., Švorcová, J., & Markoš, A. (2016 to appear). Expanding the concept of umwelt. Submitted to Theory in Biosciences 31.7.2015

Margulis, L., & Fester, R. (1991). *Symbiosis as a Source of Evolutionary Innovation*. Cambridge: MIT Press.

Markoš, A., & Faltýnek, D. (2011). Language metaphors of the living. *Biosemiotics, 4*, 171–200.

Markoš, A., & Švorcová, J. (2009). Recorded versus organic memory: interaction of two worlds as demonstrated by the chromatin dynamics. *Biosemiotics, 2*, 131–149.

Marks, J. (2002). *What it means to be 98 % chimpanzee: apes, people, and their genes*. University of California Press.

Mattick, J. S., Amaral, P. P., Dinger, M. E., Mercer, T. R., & Mehler, M. F. (2009). RNA regulation of epigenetic processes. *BioEssays, 31*, 51–59.

Meaney, M. J. (2001). Maternal care gene expression and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience, 24*, 161–192.

Meaney, M. J., & Szyf, M. (2005). Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues in Clinical Neuroscience, 7*, 103–123.

Morgan, D. K., & Whitelaw, E. (2008). The case for transgenerational epigenetic inheritance in humans. *Mammalian Genome, 19*, 394–397.

Morris, K. V., & Mattick, J. S. (2014). The rise of regulatory RNA. *Nature Reviews Genetics, 15*, 423–437.

Ng, R. K., & Gurdon, J. B. (2008). Epigenetic memory of an active state depends on H3.3 incorporation into chromatin in the absence of transcription. *Nature Cell Biology, 10*, 102–109.

Nightingale, K. P., Gendreizig, S., White, D. A., Bradbury, C., Hollfelder, F., & Turner, B. M. (2007). Cross-talk between histone modifications in response to histone deacetylase inhibitors: MLL4 links histone H3 acetylation and histone H3K4 methylation. *The Journal of Biological Chemistry, 282*, 4408–4416.

Nyholm, S. V., & McFall-Ngai, M. J. (2014). Animal development in a microbial world. In A. Minelli & T. Pradeu (Eds.), *Towards a theory of development* (pp. 260–273). Oxford University Press.

Ooi, S. L., & Henikoff, S. (2007). Germline histone dynamics and epigenetics. *Current Opinion in Cell Biology, 19*, 257–265.

Pigliucci, M., & Müller, G. B. (2010). *Evolution: The Extended Synthesis*. Cambridge: MIT Press.

Rakyan, V. K., Down, T. A., Balding, D. J., & Beck, S. (2011). Epigenome-wide association studies for common human diseases. *Nature Reviews Genetics, 12*, 529–541.

Rassoulzadegan, M. (2011). An evolutionary role for RNA-mediated epigenetic variation? In S. B. Gissis & E. Jablonka (Eds.), *Transformations of Lamarckism. From Subtle Fluids to Molecular Biology*, *Vienna Series in Theoretical Biology* (pp. 227–236). Cambridge: MIT Press.

Raveh-Sadka, T., Thomas, B. C., Singh, A., Firek, B., Brooks, B., Castelle, C. J., et al. (2015). Gut bacteria are rarely shared by co-hospitalized premature infants, regardless of necrotizing enterocolitis development. *Elife, 4*, e05477.

Schmitz, R. J., Schultz, M. D., Lewsey, M. G., O'Malley, R. C., Urich, M. A., Libiger, O., Schork, N. J., & Ecker, J. R. (2011). Transgenerational Epigenetic Instability Is a Source of Novel Methylation Variants. *Science, 334*, 369–373.

Sela, D. A., Li, Y., Lerno, L., et al. (2011). An infant-associated bacterial commensal utilizes breast milk sialyloligosaccharides. *The Journal of Biological Chemistry, 286*, 11909–11918.

Seong, K.-H., Li, D., Shimizu, H., Nakamura, R., & Ishii, S. (2011). Inheritance of Stress-Induced, ATF-2-Dependent Epigenetic Change. *Cell, 145*, 1049–1061.

Siklenka, K., Erkek, S., Godmann, M., Lambrot, R., McGraw, S., Lafleur, C., et al. (2015). Disruption of histone methylation in developing sperm impairs offspring health transgenerationally. *Science, 350*, aab2006–1–aab2006-12.

Švorcová, J. (2012). The phylotypic stage as a boundary of modular memory: non mechanistic perspective. *Theory in Biosciences, 131*, 31–42.

Turner, B. M. (2009). Epigenetic responses to environmental change and their evolutionary implications. *Philosophical Transactions of the Royal Society B, 364*, 3403–3418.

Verhoeven, K. J. F., Jansen, J. J., van Dijk, P. J., & Biere, A. (2010). Stress-induced DNA methylation changes and their heritability in asexual dandelions. *The New Phytologist, 185*, 1108–1118.

Waterland, R. A., & Jirtle, R. L. (2003). Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Molecular Cell. Biology, 23*, 5293–5300.

Waterland, R. A., Kellermayer, R., Laritsky, E., Rayco-Solon, P., Harris, R. A., Travisano, M., Zhang, W., Torskaya, M. S., Zhang, J., Shen, L., Manary, M. J., & Prentice, A. M. (2010). Season of conception in rural Gambia affects DNA methylation at putative human metastable epialleles. *PLoS Genetics, 6*, e1001252.

Weaver, I. C. G., Cervoni, N., Champagne, F. A., D'Allessio, A. C., Sharma, S., Seckl, J. R., Dymov, S., Szyf, M., & Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*, 847–854.

Weaver, I. C. G., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., & Szyf, M. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. *Journal of Neuroscience, 25*, 11045–11054.