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Organic memory in embryonic development
Organická paměť v embryonálním vývoji

Ph.D. Thesis

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Praha 2012

I agree that publications which I co-author may be attached to the Ph.D. thesis of Jana Švorcová.

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Jana Švorcová

Prague, August 2012 ….....

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Abstract

The submitted thesis deals with the topic of organic memory, its definition and function, as well as its conceptions from various historical points of view. I use the term "organic memory" in respect to some authors who have previously dealt with this subject (Elsasser 1987, Otis 1994, Barbieri 2003) and also as a term by which to represent a kind of memory distinct from neuronal/cerebral memory.

The general memory metaphors (in the case of neuronal memory) are essentially connected with terms such as storage, matrix, or place. For rather materialistic conception of memory, it is also symptomatic that different states such as emotions or mental faculties can be concretely localized in the brain tissue. On the contrary, some philosophers described memory as a primarily temporal entity without connection to place or matter. The question of organic memory was already vivid in 19th century biology, linked to Lamarckian philosophy (Hering 1870, Haeckel 1876, Butler 1910). The organic memory ideas floundered between vitalistic and rather materialistic conceptions: the first attributed some psychological features to cells or memory particles; the second was based on physics or in Cartesian doctrine, and described memory as essentially localized as a kind of storage of traces or patterns of physical waves.

The most deterministic memory conceptions are rooted in the computer metaphor, influencing the natural sciences to a broad extent. By contrast, the hologram or neuronal networking metaphor offers us the experience dependent memory concept, where experience embraces the facilitation processes that simplify the emergence of certain configurations and information is radically distributed.

My own on language metaphor of life based conception is inspired by the work of Markoš (2002, 2009), Elsasser (1987) and Barbieri (2003), and tries to deconstruct the idea of organic memory as mere DNA storage. Beginning on the level of DNA itself, then on the level of its outputs, my conception further emphasizes that epigenetic memory creates memory engrams in form of diacritics, which are rewritable and radically change the meaning of the primary text. The last conception I mention is that of developmental memory, which is activated after the period of the phylotypic stage and which has a modular character. Although it is fundamentally linked to the *Hox* gene transcription pattern, it embodies memory without storage.

My conclusion forms a language-like conception based on the idea of differences between natural and transcendental worlds, and on differences between reading and program execution. The meaning of a genetic representation is thus a role, way of usage in the language game; it is not formed by the relationships of representation itself, but by praxis, by the implicit rules of language games.

Abstrakt

Předložená dizertační práce se zabývá tématem organické paměti, její definicí a funkcí, a stejně tak i jejími pojetími z různých historických hledisek. Užívám pojem „organické paměti“ ve vztahu k autorům, kteří se tímto tématem již dříve zabývali (Elsasser 1987, Otis 1994, Barbieri 2003) a dále i jako pojem, který představuje paměť jinou než neuronovou/mozkovou.

Obecné metafory paměti (v tomto případě paměti neuronové) jsou zásadně spojeny s pojmy jako úložiště, matice či místo. Pro spíše materialisticky založená pojetí paměti je navíc příznačné, že různé stavy jako emoce či vlastnosti mysli mohou být konkrétně lokalizovány v mozku. Na druhou stranu někteří filosofové popisovali paměť jako primárně časovou entitu bez konkrétní závislosti na hmotě či místě. Otázka organické paměti byla živá již v biologii 19. století, spojena především s filosofií lamarkismu (Hering 1870, Haeckel 1876, Butler 1910). Představy o organické paměti se v té době pohybovaly mezi vitalistickými a spíše materialistickými koncepcemi: v těch prvních byly buňkám či částečkám paměti přisuzovány psychologické atributy; ty druhé byly založeny na fyzikální či karteziánské doktríně a popisovaly paměť jako lokalizovatelné úložiště stop či fyzikálních vln.

Nejdeterminističtější koncepce paměti jsou zakořeněny v metafoře počítače, i tyto metafory zásadně ovlivňují dnešní přírodní vědy. Naopak metafora paměti jako hologramu či neuronové sítě nabízí na zkušenosti závislou paměť, kde zkušenost zahrnuje facilitační procesy, které zjednodušují vznik jistých konfigurací a informace je radikálně distribuovaná.

Má vlastní koncepce založená na jazykové metafoře života je inspirovaná pracemi Markoše (2002, 2009), Elsassera (1987) a Barbieriho (2003) a snaží se zbořit ideu organické paměti jakožto pouhého úložiště v podobě DNA. Začínaje na úrovní DNA samotné a na úrovni jejích výstupů, má koncepce dále zdůrazňuje tvorbu engramů epigenetické paměti ve formě diakritiky, která je přepisovatelná a zcela mění význam původního textu. Poslední zmiňovaná koncepce organické paměti se týká paměti vývojové, která je aktivována po stádiu fylotypu a je modulárního charakteru. Ačkoli je zásadně závislá na přepisu *Hox* genů, představuje paměť bez úložiště.

Závěr mé práce tvoří koncepce založená na jazykové metafoře, která je sama založena na rozdíly mezi přirozeným a transcendentním světem a rozdíly mezi čtením a vykonáváním programu. Význam genetických reprezentací je pak role, způsob užití v jazykové hře; význam není tvořen samotnou reprezentací, ale praxí, implicitními pravidly jazykových her.

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1. Introduction

The term memory has many meanings and connotations (is the footprint left in the sand a memory trace?); there exist various classifications of this term in psychology and cognitive neuroscience (short- and long-term memory, episodic memory etc.), in computer science (volatile and non volatile memory) and in philosophy. In general, what connects all such definitions is that memory represents the ability or process by which a system (human, animal or computer for example) is able to store and later recall its own experience. The definition of memory in respect to systems theory is that the behaviour of systems with memory depends not only on the current combinations of input signals (as in cases of systems lacking memory), but also on combinations of signals which the system had encountered in the past.

In this thesis I shall not deal with the above-mentioned definitions. What interests me is the definition and function of *organic memory*. I use this term in respect to some authors who have previously dealt with this subject (Elsasser 1987, Otis 1994, Barbieri 2003), and also as a defining term for a memory which does not represent cerebral or neuronal memory, but still is essentially bounded with living organisms or living matter (in common sense of the word *organic*, e.g. organic chemistry).

Previously, my diploma thesis (Švorcová 2007) dealt with the interpretation of biological processes from a biosemiotic point of view, and with the discrepancy between "scientific biosemiotics" of Marcello Barbieri (formerly "semantic biology", as he used to call it, Barbieri 2003) and hermeneutic biosemiotics inspired by Anton Markoš (2002, 2009). I need not dwell on such matter here, there are clear differences in the very postulations of our approaches and I think they are also sufficiently discussed in depth elsewhere (Markoš 2010). The concept of organic memory represents another term connecting our interests with those of Marcello Barbieri: he introduced his conception in the book *Organic codes* (2003), after which he did not return to discuss this matter deeper, seeming to prefer to develop his conception of organic codes.

As life continues in time and space, keeps its identity, stays alive in many forms, living strategies and species, there must be some way by which it keeps its continuity and integrity. The question of organic memory was already vivid in 19th century biology

(Hering 1870, Haeckel 1876, Butler 1910); it continues to make appearances in our times (Elsasser 1987, Barbieri 2003).

Is the organic memory a problem even today? Does not DNA suffice as the storage of all information necessary for animal development? What can this concept abandoned from the 19th century offer us?

In my thesis I first introduce some memory metaphors; as memory being such a blurry and hard to define term, it has before all else been described in metaphors. The memory metaphors in the history of philosophy, physiology, biology or psychology are mostly cerebral memory metaphors, as the organic memory of the organismal or developing body was never very popular subject due to its historical vitalistic burden. This work will study organic memory as a biological hypothesis, but it will not study cerebral memory, the memory of the nervous system, or conceptions of some collective memory of a nation or race, which were popular in 19th century (and gained inspiration from Hering and Haeckel as will be shown further in the text). Nevertheless, references to the memory of the brain frequently appear in work of the many authors I mention; therefore cerebral memory occasionally surfaces anyway (in the chapter about the hologram memory metaphor, for example).

Below (in section 6) I will explore organic memory from the perspective of developmental biology and epigenetics, introducing my conception based on three papers that are an integrative part of my thesis. The first paper, *Recorded versus organic memory: Interaction of Two Worlds as Demonstrated by the Chromatin Dynamics* (Markoš & Švorcová 2009), deals with the organic memory idea from the epigenetic perspective of chromatin and DNA modifications. The second, *The phylotypic stage as a boundary of modular memory: non mechanistic perspective* (Švorcová 2012), deals with an idea of modular memory activated after the phylotypic stage, interpreted from the perspective of current evolutionary and developmental biology. The last paper, *Within the skin- and beyond" distributed knowledge in living systems* (Markoš, Švorcová, Lhotský to appear in 2012), discusses the distributive nature of biological information. All three papers take the point of view of the language metaphor of life. Certainly there are other biological topics on which it would be possible to demonstrate the case of organic memory, such as the memory of the immune system (Neuman 2008), but

I choose these examples because they are particularly useful to introduce the language metaphor of life.

In chapter 7 (discussion) my thesis will be completed with the language-like conception of memory, based on the differences between the natural and transcendent world and between the reading of a text and program execution. The whole conception stems from the assumption that even on the level of cellular interactions there are constant games of language.

To study such a phenomenon as organic memory, I have avoided psychological terms, so there is no point in making an extensive introduction to human cerebral memory and its functioning (although all general statements about memory are linked to the human brain). This is because it is probably not possible, in such a short text, to introduce the extensive collection of data available; but most importantly, it is not my aim in this work to make any deeper analogies between neuronal and organic memory.

2. Memory metaphors regarding the cerebral memory

If we start with cerebral, or let us say human, memory, which is not discussed as a separate problem in this thesis but used as mere analogy to organic memory, we can find many representation of its metaphor in history. The metaphors were aimed mainly on how information is stored, rather than processed or retrieved. That is also why the storage term becomes one of the most used terms of this thesis.

In *Theaetetus* Plato draws an analogy between memory and a wax tablet into which all our sensations are imprinted, together with an analogy of a bird cage in which the presence of birds is like the presence of actually existing remembrances (we collect one "bird" after another through our learning ability):

„SOCRATES: I would have you imagine, then, that there exists in the mind of man a block of wax, which is of different sizes in different men; harder, moister, and having more or less of purity in one than another, and in some of an intermediate quality.

THEAETETUS: I see

SOCRATES: Let us say that this tablet is a gift of Memory, the mother of the Muses; and that when we wish to remember anything which we have seen, or heard, or thought in our own minds, we hold the wax to the perceptions and thoughts, and in that material receive the impression of them as from the seal of a ring; and that we remember and know what is imprinted as long as the image lasts; but when the image is effaced, or cannot be taken, then we forget and do not know...

And further:

SOCRATES: Well, may not a man 'possess' and yet not 'have' knowledge in the sense of which I am speaking? As you may suppose a man to have caught wild birds--doves or any other birds--and to be keeping them in an aviary which he has constructed at home; we might say of him in one sense, that he always has them because he possesses them, might we not?" (Plato 2008).

Aristotle introduces a more concrete idea of memory: experiences captured by our senses leave in our memory an image, *eikó*n, similar to one which is left by a seal ring (a metaphor used in *Theaetetus* as well). For Aristotle, memory (*mnémé*) is a special form of imagination or fantasy essentially connected with the consciousness of time. Only

when consciousness of time and consciousness of specific subject work in tandem (the subject does not have to be before our eyes, yet can be vivid thanks to imagination as *fantasma*), the memory function and experience is created. "*For of the present there is sensation, of the future there is expectation, and of the past there is memory. Therefore, all memory happens with time... Exercises preserve the memory by repeated reminding; and this is nothing else than often contemplating the image as a representation and not as something in itself"* (Bloch 2007).

In his definition of memory, Aristotle relies on *pneuma* to distribute all the sensations in the body towards the heart, which is the seat of emotions (Draaisma 2002). A remembrance is a slowly fading motion, which exists as a consequence of how pneuma distributes sensations throughout the body. With Aristotle, there is an attribution of memory capacity to brain structure (although the heart was still superior to the brain), and Galen further developed this idea.

The metaphor of memory as storage is first fully expressed by Augustine in his *Confessions* (although the above mentioned birdcage also stands for a storage), wherein he writes about treasuries and caves of memory (however the treasure analogy was also used by Zeno of Elea). Memory is a storehouse of experience and knowledge, together with sensations and perceptions, imaginations, dreams, emotions and awareness of our self. The identity and continuity of the self is seen as rooted in memory, it imparts unity to the multiplicity of disconnected experiences in the stream of time (Chadwick 2001). Lying deeper than will or knowledge, memory is the "*stomach of the mind*". He writes of what can be "*found in memory"*, assuming that memory is a place-like entity, "*inner place which is yet no place*" (St. Augustine 1998). Robert Fludd, the 16th century physician and cosmologist, describes memory in terms of macro-microcosmos analogy: as a theatre (Draaisma 2002).

The wax tablet analogy also relates to the metaphor of memory as a script, or even as a book. The memory of Thomas Aquinas was itself compared to a book after his death. The particular book metaphor was understandable because in his time books had a more permanent value than buildings such as monasteries. But later, in 17th century, the book metaphor gains a new meaning by losing its rarity (Draaisma 2002), books came to

symbolize vanity and more complex and mechanical memory analogies began to appear[1].

Robert Hooke (1635-1703) interprets memory in the materialistic sense and compares human visual memory to *Lapis Boloniensis*, the mysterious substance which was exceptional because its phosphorescence. According to Hooke the materialistic substance of our visual memory is able to receive and store visual perceptions, as stone is able to store and further emit light in the dark. Substances in the human brain can, similarly, store other perceptions such as sounds or smells. The chemistry of nature shows itself in its perfection. The mechanistic metaphor of memory naturally reflects the Cartesian image of the whole universe wherein all its parts, including the heavens, stars, planets, non-living and organic nature, can be measured and studied within the framework of mechanics, wherein all questions are those of construction and setting. All matter, living or nonliving, is only formed by external conditions and by the laws of nature. Because of its divine origins, the human soul, or *res cogitans* in Cartesian terms, is the singular non-mechanical entity. (Hooke approved of this idea as well; in the contemporary social and intellectual climate he basically did not have any other option.) This metaphor reached its peak with Julien de La Mettrie (1747) who removed the non mechanistic pedestal of the soul, and thereby led this metaphor to absurdity (Draaisma 2002).

After this came a short period of romantic ideas, represented by Carl Gustav Carus (1789-1869) and his metaphor of memory as a labyrinth, or a loom that represents not the transparency and predictability of mechanistic behaviour, but an impenetrability

[1] As Hans Blumenberg shows in *Die Lesbarkeit der Welt* (1989), the book metaphor was a very popular tool in the history of philosophy, mostly representing nature or the universe itself: first, the idea is slightly reflected by Greek atomist who, comparing the atoms to letters, believed that letters of an alphabet (*stoicheion*) are the constituting unit of the world. The book as a metaphor of nature likewise found its place in the philosophy of Plotinus. In scholastic philosophy, the book of nature was second only to the Bible as a book of revelation written by God (e.g. the philosophy of Augustinus or Hugh of St. Victor). The Renaissance philosophy represented by Raimund of Sabunda considered the universe to be a book and every creature in it represented one letter. Not to mention Galileo Galilei, who thought of a nature as a book written in the language of mathematics; this idea led eventually to a search for perfect alphabet, which culminated with the work of Leibniz (Blumenberg 1989).

that draws from the thousands of fibres in the loom (which is quite analogous to neuronal networking). Carus saw a connection between the exterior and interior properties of mind. In this way he interpreted Kant's broad forehead as a reflection of his brilliant analytical skill, but these connections were interpreted as symbolic and harmonic rather than the usual causal manner of direct localization of memory faculties.

The localization of memory function first began with Franz Joseph Gall (1758-1828), an anatomist who compared the human skull to a landscape of some sort. The story of his doctrine (later called phrenology by his student Johann Spurzheim) is quite complex; phrenology was banned in Germany in 1802, but experienced an extensive boom in America. What I find most interesting is the argument about direct localization of mental faculties such as instinct, hope, perception of time or colour, different emotions, talents and including the memory itself. Francois Magendie (1783-1855), a big opponent of phrenology, did not approve of such direct localization. He rather preferred global brain structures, in which we may localize such faculties very broadly; according to Magendie, concrete faculties such as speech, mind, and memory are equally distributed throughout the whole brain (Draaisma 2002).

With the invention of the phonograph, analogies with auditory memory and this machine came to abound (Appleby 1880) (likewise, with the invention of photography the result was very similar). With this, Hermann Ebbinghaus (1850-1909) formulated his famous statistical and experimental principles of how to study remembering and forgetting in a mathematical way (Draaisma 2002). He measured (using himself as subject) the time required to memorize a series of nonsense syllables and stanzas from Byron's *Don Juan*. Using a statistical analysis, he derived general mathematical laws relating the time required for memorization and laid the foundations for new, more experimentally orientated research field. His monograph *Memory* (1885) confirmed Aristotle's theories of memory: more repetition in learning makes better retention; and making associations forms new memories (Otis 1994).

In the list of contributors to the memory concept, we cannot forget Henry Bergson whose 1896 book *Matter and Memory* denied direct localisations of memory to the brain or brain cells. Bergson responded to the book by Théodule Ribot, *The maladies of memory* (1901, in French 1881) in which he claims that memory is stored in the nervous

system and represents a completely materialistic entity. Bergson distinguished two types of memory, the first being habitual (i.e. past actions are repeated for use in present purposes) and automatic, incorporated in the body. The second, pure memory as he called it, represents the remembrances of the past in the form of images that are recognized as past but cannot be completely recreated. The images of memory are not incorporated in the brain or neurons, according to Bergson memory itself is not describable in spatial terms, as it is incapable of residing or being materially represented in anything (this being a criticism of the Cartesian distinction of spirit-body, as memory being matter or *res*).

There was actually another famous figure who denied the memory metaphor as storage five years before Bergson: it was Sigmund Freud who rejected the strict localization model of bodily and linguistic representation in the brain suggested by Theodor Meyert and Carl Wernicke. Meynert had proposed that the cortex contained a representation of the bodily surface created by direct projections and estimated the amount of brain cells to be about 600 million (the current estimation is 10^{12}, Otis 1994).

This quite simplifying and not exhausting enumeration of cerebral memory metaphors was made with one primary goal: to show how the idea of memory was from its beginning deeply associated with notions of a matrix or place, matter, catalogue, or storage. For the mechanistic or materialistic conception of memory, it is also symptomatic that different states of memory can be concretely localized in the brain tissue. On the contrary, some described memory as a primarily temporal entity without connection to a place or matter. However before we get any deeper into psychological connotations of cerebral memory metaphors, let's finally have a look at the origins of the idea of organic memory.

3. Organic memory

The idea of organic, i.e. not cerebral, memory as such appeared in biology with the need to explain how acquired characters are transmitted to the next generation, therefore it is essentially associated with Lamarckian philosophy and theory of heredity; and further with the need to explain how ontogeny recapitulates phylogeny (e.g. Hering 1870, Butler 1877, 1910 see below). The concept further appeared in work of Walter M. Elsasser (1987; Elsasser uses the term "*organic*") and also in the book *Organic Memory: History and the Body in the Late Nineteenth & Early Twentieth Centuries* by Laura Otis (1994) as well as in the biological conception of Marcello Barbieri (2003). This term is used in this thesis not only in respect to these authors, but also as a distinctive term, indicating something other than the neural memory of higher animals.

The meaning of the term has shifted since the 19th century. The most common and contemporary usage of this term now belongs to the area of computer science: so-called organic memory devices (OMD) in computer science, which represent high storage capacity devices with non-volatile memory. These bistable memory devices (organic and inorganic) consist of so called transistors, i.e. a cross-point array of top and bottom electrodes separated by a resistive material. Each place where the top and bottom electrodes cross represents one memory cell. In case of OMD, organic materials such as a monolayer of molecules or an admixture of molecules and/or nanoparticles in an organic polymer matrix are sandwiched between a cross-point array of top and bottom electrodes (Prime & Paul 2009, see Fig. 1).

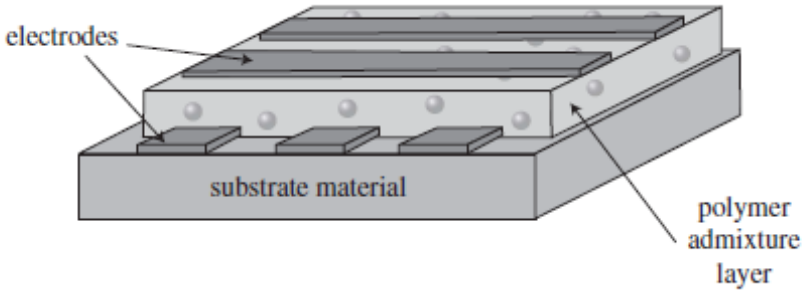

Fig. 1 The structure of an organic memory device, specifically, a polymer memory device. From Prime & Paul (2009).

Some of the OMD may also have an additional metal layer embedded within the organic films or may contain a granular metal (Vuillaume et al. 2004). In contemporary

computer science, the term organic memory naturally represents mere storage, and has a completely opposite meaning from the organic memory of our conception (see further).

3.1. Organic memory concept in the milieu of Lamarckian theory

The mainstream biology of the 19th century was deeply influenced by Haeckel's idea of recapitulation and by Weismann's theory of germ plasm. With the first, Lamarckians were mostly identified: for development to continue - after the organism recapitulated its ancestors - the new traits have to be acquired and become inherited. Also, the fact of recapitulation was in many cases taken as proof that Lamarckism must be the mechanism of evolution (Bowler 1983). With the latter, i.e. Weismann's theory of germ plasm, struggled Lamarckism its whole existence. By definition, germ plasm is completely separated from the somatic line, so characters acquired during the life span of an organism cannot get to the germinal line in any way. As Peter Bowler writes in his *Eclipse of Darwinism* (1983) the main failure of Lamarckian philosophy was its impotence at finding any adequate explanation for how the traits are incorporated into the germ plasm. Later, at the beginning of 20th century after the discovery of Mendelian laws, it failed to come with any alternative and plausible explanation for how the traits are transmitted to progeny.

The first scientist who explicitly attributed the faculty of memory to all organic matter in terms of analogy between heredity and memory was the physiologist Ewald Hering (1834-1918) (he became a professor at Prague University). He believed that all attributes of an organism, hereditary as well as acquired, are stored step-by-step in the organism and further distributed as memory traces available to future generations. Of course this idea was implicitly rooted in Lamarckism, but Hering was the first to work with the term of memory without involving consciousness. He actually says that memory is rather a faculty of unconscious life than a conscious one (Hering 1897). "*It is easily seen that memory is not so much a faculty of conscious as of unconscious life. What was conscious to me yesterday and again becomes conscious to me to-day, where has it been in the interim? It did not exist as a fact of consciousness, and yet it returned. Our concepts appear on the stage of consciousness only transiently; they quickly disappear*

behind the scenes, to make place for others. Only on the stage are they conceptions, as an actor is king only on the stage. As what do they remain behind the scenes? For that they exist somehow we know; a cue only is needed to make them reappear. They do not continue as conceptions, but as certain dispositions of the nervous substance (Stimmung der Nervensubstanz) by virtue of which the same sound that was produced yesterday can again be evoked to-day" (Hering 1897, page 14).

The human, cerebral memory represented only one concrete example of general faculty of organic matter. Comparing such things as growth of muscles after regular exercise, piano player's improvement or chick's ability to get out of its egg shell, Hering concluded that organic matter is able to store and reproduce all kinds of stimuli even on the cellular level (Hering 1897). A new skill, instinct or memory: all these things are related to the ability of living tissue to be altered by sensory impressions (as referred in Otis 1994) and to store these alterations for future generations. Hering was not able to identify the process by which traits are inherited, referring to it only as to a material trace. In this sense every organism is a sum of material traces, accumulated from the beginning of its life span. Nevertheless his organic memory concept was the intellectual background for his research of colour vision and spatial perception.

Auguste Forel (1848-1931), a Swiss clinical psychologist, wondering how an embryo could remember into which adult organism to develop, saw heredity and memory as essentially the same, and aligned heredity as species-specific memory with individual memory (sic!). Both memory and heredity involve the passing on of a hidden script that would later be expressed (Forel's lecture in 1884 *Memory and its Abnormalities,* see Otis 1994). Later in this thesis, it will be shown that Forel was very rightly implying something as a script as a basis of heredity.

Accepting the inheritance of acquired characters as one of the most important processes of evolution (and as a force at least equal to natural selection), Ernst Haeckel (1834-1919) tried to create a theory of heredity that would support Lamarckism (and naturally also his biogenetic law); he therefore also drew an analogy between heredity and memory (Bowler 1983). He tried to explain the similarity of heredity and memory by postulating wavelike motions of "plastidules" as basic units of living matter (Haeckel 1876). As the smallest protoplasmic particles, plastidules possess a capacity for memory

and heredity and their wave pattern is specifically shaped by history and environment (Otis 1994). Haeckel derived the motion of the particles from molecular motion, as every atom disposes of an inherent quantity of energy, so too through the motion of the plastidule particles the cell is able to remember its past and pass it on to the next generation. In this sense, every organism represents a unique pattern of wave motions.

Although today we intuitively (but mistakenly) see Lamarckian and Darwinian theory as contradictory, it was quite symptomatic that many proponents of Haeckel's recapitulation theory (as Haeckel himself) were big admirers of Darwin's work, even when preferring Lamarck's law of heredity of acquired characters to Darwin's law of natural selection. This was not only because of the teleological character of Lamarckian theory of evolution but also because of the emphasis on the individual contribution of the organism to development, thus better suited for the theory that involved development through accumulation of traits (Otis 1994).

Again, as in case of Hering, Haeckel's memory concept of living matter was not based on any driving, creative force of conscious mind. The plastidules have psychic characters like sensation, will and memory, but such traits are all expressed unconsciously (Bowler 1983). Haeckel's theory is rather mechanistic: the response of the organism to its environment is predetermined by this environment and the laws of living matter of the organism, but memory enables it to pass along acquired characters to future generations. Only later, Lamarckism began to support the idea that organisms have the freedom to shape their own evolution.

At the beginning of his interest in evolution, Samuel Butler (1835-1902) was a true admirer of Charles Darwin but later he turned to the Lamarckian philosophy and made the memory analogy the foundation of his near-vitalist interpretation of Lamarckism (Butler 1910). According to him, organisms are capable of remembering their experiences and incorporate them phenotypically, but unconsciously (for modern interpretations see Markoš & Švorcová 2009). This idea of organism remembering its past history perfectly correlates with Haeckel's biogenetic law. Butler and other Lamarckians actually saw this analogy as an idea of how God allowed life to design itself.

In *Life and Habit* (1877) Butler describes phylogeny as a getting used to new

activities which via frequent repetition become automatic and thus unconscious. Butler believed that something becomes a genuine habit (which is a second step of memory organisation), by becoming an unconscious instinct (first step). Therefore every intelligent action eventually becomes instinctive and inherited (due to physical changes in the organism). Analogically also, it is possible to explain embryonic processes as a never-ending repetition of originally conscious activities.

According to Butler, the memory concept explains all the facts of heredity (including acquired characters) as well as the idea of recapitulation. Later in the book *Unconscious memory* (1910), Butler developed the idea of a memory based on vibration patterns of ultimate living particles (similar conception as Haeckel's plastidules); he also interpreted the Hering's memory concept in this sense and translated Hering's paper *Über das Gedächtnis als allgemeine Funktion der organisierten Materie* into English as a constituent part of the above mentioned book[2]. Butler's intellectual journey eventually led to the conclusion that all matter disposes of vivid and divine energy and the universe as a whole is in fact alive.

Emanuel Rádl (2006) also mentions August Pauly, who introduced a very similar doctrine as Butler, describing phylogeny as the habitual process of gradual improvement.

At the same time, the French philosopher and psychologist Théodule Ribot (1839-1916) argued (similarly to Hering) that conscious memory is only one aspect of a more fundamental phenomenon: he proposed thinking about memory in terms of physics, as heredity is only one version of the law of energy conservation (to arrive at this interpretation, he was helped by Helmholz's formulations of energy conservation). Ribot considered the nerve impulses electrical, and suggested that the term of organic memory should be explained only in terms of work, force, energy and particles motion. Ribot believed that memory is based on physiochemical changes and leaves auto reproducible traces in organic matter. He denied the metaphor of the memory as storage, emphasizing

[2] Nevertheless Butler's translation of Hering's paper is biased; he interprets the memory nature in Hering's conception in terms of vibrations pattern, although Hering himself did not understand this phenomenon in such sense. However, vibration theory was revived in the theory of William Bateson, who suggested that repeated (or modular) structures were manifestations of sympathetic vibration or similar interference phenomena. These are the wavelike interference patterns that form when a source of oscillating energy diffuses through a material of some sort (Weis 2002).

the associations or connections that became stable through repetition, i.e. not only the modifications of cells but also the connections among them are the basis for memory conservation (Otis 1994). In his physics-based memory theory, Ribot is symptomatic of the Lamarckian philosophy tradition in France as rather materialistic, inspired and influenced by the Cartesian philosophical heritage (see Bowler 1983).

Being a non-French-Lamarckian in 19th and 20th century thus did not mean that the philosophy of life based on the heredity of acquired characters must necessarily be vitalistic. There were also supporters of Lamarckism whose theories were materialistic such as Spencer or Semon (Semon's idea of a memory was mere informational storage, Semon 1904): in order to explain the puzzle of how newly acquired characters on the somatic level can be inherited via a germ line, Lamarckians began to look for the creation of new hereditary units in germ plasm, rather than continuing their support for the idea of gradual additions to previous developmental stages. By abandoning the recapitulation idea, the whole Lamarckian doctrine quickly became materialistically oriented.

German zoologist Richard Semon (1859-1918) unified the memory and heredity concept in one single term called *mneme* (1904). The *mneme* represented the basic capacity of organic material to maintain an after-effect of stimulation as a stable modification of irritable organic tissue, creating "engrams" in which hereditary information was somehow inscribed (Bowler 1983). Starting from Mendelian laws of heredity, Semon explained dominance and recessiveness as the outcome of competition between engrams inherited from both parents. Due to the lack of explanation concerning the nature of such an engram, Semon was criticized for involving psychical interpretations. But he considered this process to be only physical, reproving especially Butler for his psychical approach.

Butler's friend Francis Darwin, a botanist, also postulated an unconscious memory existing even on the level of plants. He described the germ cell as telegraphically communicating with the whole rest of the plant body. Although he described memory as mechanistic storage, his approach was rather holistic, as the body of every organism was, for him, an interconnected whole (Bowler 1983).

Eugenio Rignano (1870-1930), an Italian philosopher and an admirer of Haeckel's

recapitulation who still tried to remain within the frame of Mendelian laws of heredity, postulated a so called "central zone" in the cell nucleus, where accumulators of energy reside (1911). These accumulators are both senders and receivers, constantly responding to different energy levels; thanks to them, the acquired characters can be remembered and inherited. The cell was a "circuit of life", a network of feedbacks absorbing constantly fluctuating inputs (Bowler 1983, Otis 1994). Rignano was also an ambivalent figure in the vitalistic-mechanistic debate: although denying that organic memory can be explained in terms of physics and chemistry, he still refused the vitalistic point of view as scientifically weak.

3.2. Darwin's and Weismann's memory theory

Darwin was not explicitly talking about the memory problematic, but his work *The Variation of Animals and Plants under Domestication* (1868) discusses the problem of atavism concluding that atavisms were possible due to hidden variability of the germ cells as they contain much more than is manifested in characters of the body. In consonance with his pangenesis theory, the germ cell is an assembly of particles not only from every cell in an organism but also from cells of earlier stages of development and occasionally even from the cells of its ancestors (Otis 1994). Every cell in the body secretes so called "*gemmules*", particles similar to spores of plants or to particles of infectious matter, containing all the necessary information to create a new cell and travelling all over the organismal body. Such particles are attracted to the germ cell from every part of the body, assembling in the germ cell primordia and participating in forming mature germ cells or new organs. They could remain, for many generations, in a dormant state, just to create suddenly a developmental atavism, "*like written on the paper with the invisible ink, lie ready to be evolved whenever the organisation is disturbed by certain known or unknown conditions*" (Darwin 1868).

August Weismann, a big fan of natural selection and the author of the theory of germ plasm, was never a supporter of the Lamarckian organic memory concept. He did not see the point of comparing heredity and memory because he did not approve the

heredity of acquired characters. According to his theory about separated germ and somatic line, the new traits are spontaneous variations that are transmitted in the germ cells from one generation to another, waiting for the right impulses from the environment to express themselves (Otis 1994). Thus the germ cells of the organism are always derived directly from the germ cells of its parents, an immortal continuity from which latent representations of traits are selected.

3.3. The implications of the organic memory idea

The memory idea in the 19th century reflected attempts to explain evolution as a teleological continuum, every organism as a link between past and future, promising an eternal life of some sort; "*instinct, habit and memory representing manifestations of a single underlying process"* (Otis 1994). "*The conscious memory of man dies with his death; but the unconscious memory of nature is faithful and indestructible. Whoever has succeeded in impressing the vestiges of his work upon it, will be remembered forever"* (Hering 1897).

Although some biologists blamed Hering for only replacing the heredity of acquired characters with the term memory and claimed that this replacement brings nothing new into the discussion of evolution (Rádl 2006), the idea of organic memory influenced other disciplines besides biology as well.

For example, Bénédict Morel (1809-73) used it as a basis for his theory of degradation, explaining high incidences of alcoholism, syphilis, epilepsy, criminality or idiocy (Otis 1994) as a consequence of an accumulated hereditary burden of the sins of fathers (this was years before Hering's or Haeckel's theory of organic memory). In a close parallel to the framework of Haeckel's biogenetic law, Cesare Lombroso (1835-1909) described so-called born criminals as atavisms, as at lower stages of development. The theories linking heredity, memory and pathology were also mirrored in literature: in his series of novels from *The fortune of the Rougone* (1870) to *Dr. Pascal* (1893), Emile Zola presents heredity as a force building up and threatening to explode. Zola's novels are stories about accumulating pressure that will eventually produce violent

movement (Otis 1994).

Sigmund Freud (and his disciple, Carl Gustav Jung) was also influenced by the idea of organic memory. Freud believed that the individual unconsciously memorized not only his or her infancy but also the experiences of his/her ancestors (Freud was a fan of Hering's theory as, according to both, most memory is unconscious). Long after most biologists had abandoned Lamarck's and Haeckel's theories, Freud continued to defend them (Otis 1994). Freud believed that every person recapitulates the stages of human development and as the perverts and neurotics represent earlier stages of development, everybody was, at least temporarily, perverted and neurotic.

The organic memory concept was deeply rooted in the intellectual discourse of the 19th century, it had deep social connotations as reflected in literature (Zola, Unamuno and others) and other branches of science: as Laura Otis (1994) brilliantly shows in her book *Organic memory: History and the Body in the Late Nineteenth & Early Twentieth Centuries*, this idea reflected the need to explain the heredity of human culture on individual and collective level as well as the relationship between them because acquired traits are transmitted to following generations on both levels. Rather than a scientific theory, the organic memory idea was a way of thinking motivated by nationalism and the need to explain cultural evolution.

As is apparent from the previous text, organic memory floundered between the vitalistic and rather materialistic conceptions; the first attributed some psychological features to the cells or memory particles; the second was rooted in physics or in Cartesian doctrine and described memory as essentially localized, being storage of traces or pattern of physical waves.

The subject of organic memory appeared later in the work of a physicist Walter M. Elsasser (1987) or in the work of Marcello Barbieri (2003), both conceptions will be discussed below on concrete examples.

4. The origins of computer (machine) metaphor

Memory was compared to the phonograph or the photographic desk soon after these items were invented. The most influential "machine" metaphor, rooted very deeply in contemporary science, is the computer metaphor. This chapter will discuss the computer metaphor only in regard to organic memory, although the history of the computer metaphor regarding cerebral memory is very fruitful and has deeper groundings[3].

With the computer metaphor, the metaphors of the memory as a script or text (which will be mentioned further) and as storage become essentially isomorphic. The influence of computer metaphors on the scientific milieu in general is evident mainly in terms of theoretical notions (encoding, storage, transcription, input, output), and these gained their permanent location in biological, psychological or linguistic dictionaries. It is also quite symptomatic that if you search online for a definition of memory, you will find

[3] Comparing human memory with computer memory was very popular in psychology in 1950s when Information Processing Theory was introduced (Lachman et al. 1979). In this theory, memory processes such as thinking or stimuli analysis were analogized with computational informational processing. Further Estes (1978), an American psychologist and pupil of B.F. Skinner, compared cerebral memory to hardware and software; the hardware is the first level of physical processes that trigger, handle, and store stimuli. These processes are based on the pathways of electrical impulses leading through various chips, and involve magnetizations and demagnetizations of the molecules. The software level is of psychological processes that form the processing, selection and reproduction of offered stimuli, i.e. "loading" or "reading" from memory.

Also, the famous and more recent philosopher of mind, Daniel Dennett (1991), describes the human brain as a parallel and serial processor, and as an implement of "von Neumanesque machine". Information Processing Theory was criticized for not taking into account parallel information processing, however Dennett's theory does.

Apart from the question of who designed such a program as could be followed by a such a computer, whether it be an intelligent designer or divine hacker (the term of Draaisma 2002), the computer metaphor has other conceptual problems: computers are not capable of deception (lying is one of the crucial human capabilities which proves them to be semiotic creatures, Eco 1997), further, they are not capable the deeply rooted heuristics of being in-the-experience, in the case of computers emotions simply cannot be involved, etc.

only connotations to human memory or computer memory such as hard disk or RAM.

The history of this metaphor began with Alan Turing, who designed a thought experiment with a hypothetical machine able to rewrite any program written in binary code. Thus any action that can be written step by step, can be processed by a machine as a row or sequence of symbolic instructions. Hence, a biological Turing machine should be able to transform a finite input string of DNA into output strings of RNA and proteins (Neuman 2008). This analogy between software-hardware and genotype-phenotype that is today a prevailing concept in biology mainly began with Jacques Monod (1970), who extrapolated his *gal* operon model into a paradigm for the whole of life. Developing the Cartesian metaphor further, he was convinced that organisms are chemical, cybernetic machines operated by means of the program written in DNA molecules.

In his book *The Regulatory Genome* (2006), Eric H. Davidson uses the computer metaphor to describe embryonic development of organisms wherein he considers organisms to be cybernetic, chemical machines. He describes the dynamic and complex interactions of cellular environment in terms of regulatory genome architecture (Fig. 2): the genome represents a set of programs and subroutines that can independently regulate their own inputs and outputs in time and space.

Cell control is a hierarchical process and individual levels of regulatory genome (programs and subprograms) reflect the hierarchical activities used in cellular communication. Genes function as communication governing protocols, under which regulatory networks perform their functions.

Such a regulatory network consists of genes coding the *trans*-factors, and its specific combination provides an input at each network node; further, it consists of the *cis*-regulatory modules, which control the particular phases of expression of these genes. The network has also its periphery, which is defined by a series of genes whose products are neither signalling nor transcription factors. The term network architecture refers to the topology of functional link between genes encoding *trans*-factors and their *cis*-regulatory modules in the middle of the network (the *trans*-factors bind these *cis*-sequences). The nodes represent the regulatory network units controlling the informational processing and, thanks to different inputs on these units, diversity in the regulation of ontogenesis is achieved (Švorcová 2007).

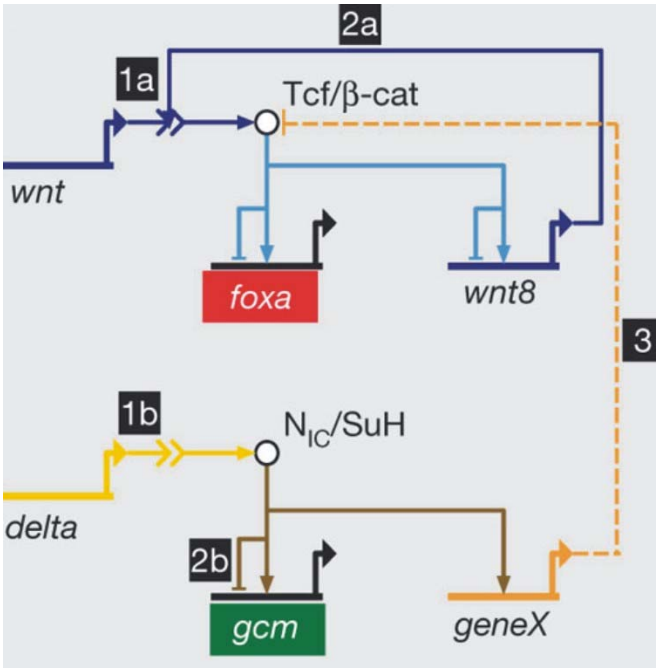

Fig. 2 An example of a genetic regulatory network from Davidson (2011) that determines the separation of mesodermal and endodermal cells (coming from the same endomesodermal precursors of veg2 lineage) in the development of sea urchin. Chronology is indicated by numbers 1–3. Wnt and Delta signals emanate from skeletogenic micromeres (cells on the vegetal pole). Wnt/ β-catenin signalling is necessary for endoderm specification, whereas Delta/Notch signalling for mesoderm specification. The future mesoderm expresses both endoderm and mesoderm regulatory pathways in an inner ring of veg2-derived cells (expression of *foxa* and *gcm* genes), whereas the future endoderm (as peripheral cells) expresses only an endoderm regulatory pathway (expression of the gene *foxa* alone). The *gcm* gene is at the top of mesoderm gene regulatory network and is activated by signalling through the Delta/Notch pathway (via its *cis*-regulatory Suppressor of Hairless (Su(H)) target sites). Further, the partially overlapping expression domains of *foxa* and *gcm* become *exclusive* thanks to the Tcf sites which induce the *foxa* gene repression in presumptive mesoderm- this process depends again on Delta/Notch signalling. GeneX mediates interference with β-catenin activity, leading to Tcf/Groucho mediated repression. For more detailed discussion see Davidson (2011).

In his book, Davidson very systematically explains the paradox of genome similarities, i.e. how it is possible that different morphologies emerge on the same genetic basis. The architecture of regulatory genome has a specific pattern for every organism and in this way variability based on the same genetic script is achieved. Davidson's book is a symptomatic example how deeply the computer metaphor is rooted in today's natural science. I have to mention for clarification: within the extremely complex problem of genetic regulatory networks, the idea of a cellular computer works perfectly and is very much justified as a model. My aim in this section was only to show how deeply computer metaphors have penetrated all different kinds of scientific branches.

5. The hologram metaphor: back to the brain

This section discusses the history of holographic metaphor, but only in relation to cerebral memory, specifically, to visual memory. I decided to add this chapter to my thesis because the idea of holographic memory reflects some of the organic memory features that I would like to highlight in my own conception.

Looking for an analogy between hologram and memory, Dutch Physicist Pieter Van Heerden was inspired by the lectures of J. von Neumann and C. Shannon, and also by the article: *A new microscopic principle* by D. Gabor, published in *Nature* in 1948 (as referred in Draaisma 2002). Van Heerden (1968) focused in his research on two properties of human memory: on immediate associations and large capacity storage. The hologram is an associative memory of some sort, i.e. storage system without the address (while computer memory– like RAM – is locally addressable[4]). This means that information is not identified by position, but by its content. In such case, information can be simultaneously global and local: memory traces are scattered in various parts of the brain as an interference pattern, so the stimulation of the memory fragment can activate the whole idea or image (e.g. in case of stimulation of the hippocampus with electrodes), while conversely the removal of some traces does not interfere with the ability to reconstruct the whole idea/image (e.g. partial injuries to the cortex). This memory interference pattern and also the overlapping of memory traces (i.e. different memory traces can have the same neuronal substrate) help elicit the sizeable plasticity of the brain, because the nature of information storing is distributive, content-addressable. In this way is the brain also less vulnerable.

Karl Pribram further specified the parallel between hologram and memory (Pribram 1966, 1969, 1974 or Goleman 1979). He led analogies between the informational storage processes in the brain and the optical storage of the hologram, the analogy with hologram allows him to demonstrate that permanent change occurs due to input stimuli in the brain: the more a neuron is stimulated, the more sensitive it becomes, i.e. the neural structure is changing as a result of experience. He argues that information is stored everywhere in the brain and that there is no specific location

[4] But there is also special content-addressable computer memory (CAM).

for a specific memory. Information stored in the brain is again both global and local. The whole has knowledge about each part and each part contains knowledge of the whole. If you break a hologram into many pieces, each piece will still contain the entire image, but with limited perspective. Stimulation of memory fragments can then activate the entire image or idea (e.g. hippocampus stimulation with electrodes in Penfields experiments, Draaisma 2002); and on the contrary, the removal of certain memory traces does not prevent the ability to reconstruct the whole image again (e.g. by partial cortical injury of rats brains in Lashley experiments, Draaisma 2002). The degree of injury is decisive, but not its specific loci. Interference memory patterns and overlapping memory traces (i.e. different traces with common neural substrate) explain the large plasticity of the brain: information is stored in a distributive nature and content is not locally addressable.

The hologram metaphor was later abandoned, but the main concepts of neuronal networking came into existence chiefly thanks to this metaphor (distributive and content-addressable properties of memory), although we don't find many references to Karl Pribram in the literature of neuronal networking (Draaisma 2002). The neuronal network actually changes its structure and adapts its configuration based on previous experience. Some nodes are enhanced and then facilitate information processing because neuronal networks adapt to configurations that have been previously processed. Experience embraces facilitation[5] processes that simplify the reproduction of certain configuration and they remember these configurations in a form of predisposition. Not an element of the network itself, but the configuration of connections between elements is decisive.

[5] A connection emerges more easily; more often the associated elements are activated together.

6. Developmental memories

In this chapter, our concept of organic memories based on language metaphor of life will be illustrated (Markoš & Švorcová 2009; Švorcová 2012; Markoš et al. to appear 2012). We deal here with biological processes at various levels of description, such as DNA transcription and translation, putting marks on histone proteins or on DNA or embryonic development in a broader scale. We offer an explanation of how an organic memory works in which it is not considered a mere storage but has a radically distributed nature.

6.1. DNA as memory storage

In Markoš & Švorcová (2009, page 140; see attachment no.1) we defined a "*character (or digit) as a member of some finite alphabet (or table), and its single qualification is its position (its coordinate) in the given alphabet (or table). Characters have no meaning except (i) their membership of the set, and (ii) their position in that set; they are neither signs nor symbols. No additional member may be inserted between two alphabetical places (no position left in between), and no transition characters (e.g. half U, half V) are allowed; the character is absolutely unmistakable from the other digits of a given alphabet. Thanks to this, it can be copied, and distinguished in a string of characters with absolute accuracy*".

In *Mathematical Structures of Language*, Harris (1968) identifies universal and essential properties of language. The first property is that the elements of language are discrete and arbitrary (the sounds of which words are composed do not suggest the meaning of the word), further (2) not all the combinations of these discrete units occur, and (3) the elements have linear order.

In this sense, DNA strands can simply be reduced to an informational store in the form of combinations of four different digital characters A,C,G,T (adenine, cytosine, guanine and thymine). The understanding of DNA as a language of life is not new; the very biological terminology shows the implicit conception of DNA as text (terms

such as transcription, translation, genetic code), and it was acknowledged by Roman Jakobson (Faltýnek 2010) who even claimed that the hierarchy and architecture of language and genetic transcription is based on similar principles (Jakobson made analogies between base/phoneme, codon/word or gene/sentence). According to Jakobson, written language as well as DNA is a medium of memory. DNA can be characterized as hereditary information passed from ancestors to offspring; it is a script/ programme for the reconstruction of the living shape. We can identify language between generations in the changes of the units of first articulation; as with vocabulary, we can find a memory structure that disposes itself on subsequent generations (Jakobson 1971).

Such statements about formal grammar or syntax lying behind the living phenomena had powerful influence on molecular biology in the 1950s and 1960s (Markoš & Faltýnek 2011). Similar views led to opinions that speech itself, or the competence of speaking, is also encoded in the DNA (Ji 1997, 1999). At this point we have to carefully distinguish between the text and the language itself in which the text is written (switching these terms around leads to such confusion as in case of Ji 1997, 1999). We can borrow an example from Searle's Chinese room paradox: to understand a text written in a given language, I have to govern the language itself. A merely perfect manipulation of characters according to given syntactical rules of this language is not the same as an understanding of this language. Or if we say it in a hermeneutical sense: the string of characters becomes a text only when a reader is present. Thus one text can have many interpretations, depending on the history and experience of the reader.

6.1.1. Analogous versus digital information

The idea of how life managed to create a "program" or "recipe" by creating itself in the form of DNA is discussed in *Code-Duality and the Semiotics of Nature* (Emmeche & Hoffmeyer 2005); the authors call this ability self-reference. Self-reference is a necessary condition for a living entity; it includes the ability of self-representation in both digital and analogous world simultaneously. This code duality, duality between the script and flesh, is based on the fact that the memory of the system incorporated in DNA script is simultaneously also the transcription of the system itself. The genome

book can be read only by the analogous information contained in the zygote. In and of itself, nothing in the digital world can make a difference, but also the analogical cannot evolve without digital information (Emmeche, Hoffmeyer 2005).

Information is defined in this thesis in the sense of Bateson (2006) (Shannon's informational theory is not taken into account), as something that is conveyed as a message and provokes a response, i.e. a difference that makes a difference, information in the message that results in meaning. Information is interactive. Information is not the same as a meaning[6], information has some meaning only in a specific context. Context is not a passive background condition. Context is actively set up by agents of interaction (Neuman 2008).

Information is expressed by a sequence of discrete characters (Neubauer 1999). Digital strings as such have no meaning, they "just are". Identical strings can be recognized unequivocally, unlike "bodies" or analogous shapes, two digital strings can only be identical or non-identical (Cvrčková & Markoš 2005). We add to that: information has meaning only in the analogous (natural) world; the digital string of characters has no meaning except when it is confronted with the bodily world. This is a very important step: the digits/characters as we defined them at the beginning of this chapter do not belong to the natural world of shapes and living entities, otherwise they cannot be recognised unequivocally and ideally. Hence, what Hoffmeyer and Emmeche (above) call "digital" is rather *discrete,* i.e. recognizable in the bodily world. In that natural world, digits have to be embodied in a medium such as DNA (Markoš & Švorcová 2009). And when we consider such a medium, the reduction to mere digital information becomes less powerful: the constant movements, rotations and alternative looping of DNA makes of this medium a suddenly very bodily entity, thereby allowing more dynamical interactions between enhancers and *cis*-sequences (Davidson 2006) in distant DNA regions (Fig. 3).

[6] Sensu Barbieri (2003) DNA replication involves information copying (and the new DNA strand can make a difference later), but codons are added according to their complementary relation to each other, there is no meaning involved. But during gene expression, when mRNA is translated into protein, there is conventional genetic code involved and therefore meaning involved.

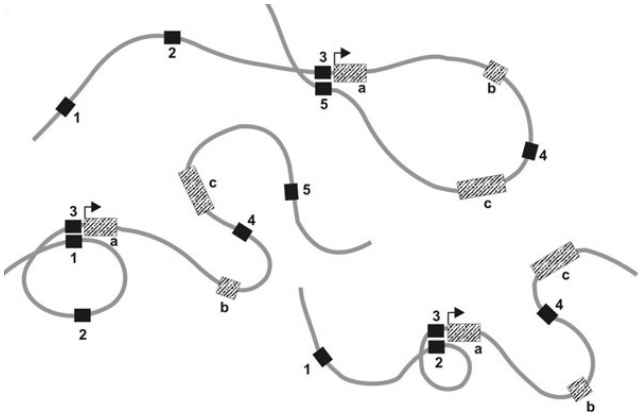

Fig. 3 Alternative looping of DNA strands allowing more dynamical gene regulation (a picture from Švorcová 2012, page 36, see attachment no.2).

Even amino acids embedded into protein chain can be regarded as strings of characters, again belonging to the world of three-dimensional shapes, therefore to the world of analogous information. But such a reduction to mere digital nature forgets the bodily attributes of protein molecules: constant movement at the molecular and submolecular scale, such as rotations around single bonds or a certain degree of molecule flexibility (Cvrčková & Markoš 2005). *"In the cellular context, the shape (and surface characteristics such as electrical charge or hydrophobicity) is decisive for interactions and biochemical activities of the protein…Not only physical factors like temperature, pH, ionic strength etc. (such factors will in some way influence all proteins present) participate in "guiding" a nascent protein molecule towards this shape, but above all targeted (allosteric) regulation of the given protein by a great plethora of regulators that bind to the molecule – be it "messengers" or other proteins present in its surroundings here and now"* (Markoš & Cvrčková 2012). Any such string of amino acids can attain an astronomic number of different shapes: depending on how they are embedded in their cellular environment, only a limited, "meaningful" number of shapes is actually realized.

Already from the 1960s, the genome size paradox was known (this also includes protein coding genes): for example also Davidson (2006) points out that genome size is not crucial in the evolution of organisms: comparison of the genetic reservoirs of various animals (fruit fly, sea urchin, mouse or human) has shown that the amount of genes does not correspond with "higher steps" on the evolutionary scale. The other paradox is that genomes of different classes of organisms are rather similar, especially in case of genes controlling embryonic development (Carroll 2005). Apparently, there is no obvious correlation among the variety of coding DNA on one side and the morphological

variability on the other (see further).

The memory encoded in DNA messaging is the first necessary condition for heredity and is subject to Mendelian laws of heredity (unlike other script-based memory which will be discussed further). Although DNA strands can easily be copied and transferred into progeny or RNA molecules, which represents the digital, mechanistic storage of information fixed in a permanent code, the way in which the script is handled during the translation is not completely determined by the genetic representations themselves.

6.1.2. Code hypothesis

When mRNA is translated into protein, the very string of mRNA and polypeptide are not connected causally (e.g. by chemical correspondence); these correspond only via an established code, which is implemented by a set of adaptor molecules, the aminoacyl—tRNA synthetases[7] and their specific products - tRNAs. Barbieri extrapolates from the existence of the genetic code to all organic processes by postulating that organic codes are the driving force of the evolution and ontogeny. In his book *Organic codes* (2003) he mentions codes of compartmentalization, codes of signalling pathways, hnRNA splicing codes etc. The highest code on the scale of history of life is that which connects written and spoken language (Barbieri 2003, 2010).

According to Barbieri, semiosis comprises the trinity of sign, meaning, and code (and associated operations like coding and decoding, or deriving extraction of meaning).

[7] Barbieri emphasizes the role of tRNAs as adaptors connecting the world of DNA and protein, but the recognition function primarily has an aminoacyl—tRNA synthetases. These enzymes are responsible for translation as well as the "stability" of the genetic code, by recognizing just one of their respective amino acids and the tRNAs which belong to it. In this way, they allow the synthesis of aminoacyl-tRNA active in translation on the ribosome. The accuracy of the synthesis is ensured by the specificity of binding sites and by postsynthetic repair activity of the enzyme aminoacyl-tRNA synthetase. This problem was already discussed in Markoš et al. (2004) or in Švorcová (2007).

The RNA triplets are thus signs[8] and amino acids represent their meaning. Codes had been enacted as historical conventions[9], and therefore they are not deducible from the laws of physics. However, once a code system comes into existence, it behaves deterministically ("according to the code table") and is fully comprehensible by the standard approaches used in (natural) science (Markoš & Švorcová 2009). These codes connect two different worlds (whether worlds of dots and dashes of Morse code and the world of our language; or the DNA/RNA world and the world of proteins), and the relationship between these any two worlds is completely arbitrary.

Later, Barbieri (2007, 2010) came to consider his doctrine an integrative part of biosemiotic studies, and no longer calls his conception a semantic biology as he used to. In the semiotic tradition, a sign (*representamen, synthema*) "*is something standing for something else, in a given frame of contexts. For example, in the frame of naval codes, SOS stays for "help"; in the genetic code AUG means "methionine"; for liver cells,*

[8] Marc Champagne (2009) criticizes Barbieri's identification of sign (DNA/RNA triplet) with its *vehiculum* in organic codes concept. For clarification: John Deely (2008) describes a sign not as a materialistic entity, a so called *vehiculum* or *representamen*, which makes us think about the object for which the entity stands (such as the smoke as a sign for fire or chimney), but he considers the sign to be rather the whole triadic, suprasubjective relationship, invisible, unperceivable, connecting the *vehiculum* with the object itself. Sign is a triadic relationship unifying three members*: representamen*, object (*significans*, the denotated), and the *interpretans.*

[9] It is quite contradictory that Barbieri says this because as a term, convention implies the explicit agreement on something between at least two agents or "speakers". According to Barbieri (2003) it is codes that provide meaning to information structures. The only riddle in this concept is then the origin of the "code table". It was Simon Singh (1999) who introduced the *code table problem* (in terms of cryptography): to communicate via a code, we need a code table. But to be able to agree on such code table, we need to communicate. It seems to me that Barbieri does not see this paradox.

That is why, in order to explain the capability of human language and to crown his theory of organic codes with the coding rules of our natural language, Barbieri admits Chomsky's theory of universal grammar stored in our brains (Barbieri 2010). Universal grammar solves the paradox of the code table, as the table is simply taken for granted: it has been stored in our brains from the moment we are born. Barbieri as well as Chomsky does not explain how is this code table materialized in our brains; he is not interested how such things as code tables can come into existence. Maybe he would agree with John Maynard Smith (2000) that natural selection is the coder of meaning hidden in the string of DNA, and would then believe that both organic codes and universal grammar are contingent events.

insulin means "take up glucose from the bloodstream"; in the highway code an inverted triangle means "yield"; in the world of a hunter a footprint means "game". Words expressed in a given language are signs as well" (Markoš & Švorcová 2009, page 142).

Thus the protein synthesis (in terms of semantic biology) is performed by predetermined machinery that follows the constant, explicit rules "written" in the code table. "*This system of organic codes knows no interpretation: codes themselves are context-free; essentially, their meaning is a question of decoding. Evolution of the system proceeds via adding new organic codes, and/or by building nested hierarchies thereof* "(Markoš & Švorcová 2009, page 131-132).

But "*in processes like cell differentiation or embryonic development (not to speak of language), new meaning come up incessantly: novel rules and novel adaptors appear, and the neat model becomes cumbersome, even unusable. Turner (2007) touched the point in comparing three systems containing signs, adaptors and outputs: (i) The red/green traffic signs will lead in any system acquainted with the traffic code (a driver, a schoolchild, a computer with appropriate sensors) to two possible outputs — stop or go. (ii) In protein synthesis, 64 codons constituting innumerable possible strings will be translated by some 45 adaptors into 21 outputs, also combined into innumerable incidences. (iii) But how to manage, asks Turner, the histone code in chromatin (see below), or processes involved in development, when the number of elementary inputs, outputs, and adaptors may go to hundreds or even millions, and all three sets may change in time? Why should we speak about coding when we can neither write down the table of the code nor quantify the number of components, and the rules of the system? How can any system memorize so many commands and shortcuts, and — even more important — how can it consult them in real time*? *Yet, attempts have been made to prove such a predetermined, synchronous superstructure of nested, overlapping codes in cells (see, e.g. Trifonov 2008; Popov et al. 1996)"* (Markoš & Švorcová 2009, page 133).

This is, in my opinion, why Barbieri (2003) introduces the concept of organic memory. Memory can be ideally distinguished on many levels and I will more or less stick to this distinction in my thesis. The first level is genetic – written in DNA, which we discuss in this chapter. The second type of the memory works on the basis of different epigenetic codes, e.g. histone code. Such codes are created and re-written thanks to quasi-

digital marks, such as histone modification or DNA methylation (Markoš & Švorcová 2009). Epigenetic memory determines the state of every cell in the body and maintains their differentiation. Barbieri's model of organic memory is illustrated on the early embryonic development. "*Development starts with a hardwired (coded) program and proceeds mechanistically up to the stage of the phylotype*." All memory in his conception has the characteristic of a mere storage, *"it takes inputs from the developmental program and from the environment, and ensures coordination of species-specific processes, thus increasing enormously the amount of information and rules, as compared with those available at the moment of fertilization. This "bootstrapping" between the program and the developing memory will — at the phylotype stage — lead to a takeover of the affairs by the memory"* (Markoš & Švorcová 2009, page 133). Barbieri also speaks about neuronal memory and the memory of the immune system at the supracellular level, but I do not deal with these two types here.

6.1.3. How script memory outputs are produced

It is very well known that phenotypic trait can be influenced by one or more groups of genes (so called epistatic interactions) or a single gene can have multiple phenotypic meanings (pleiotropy); the genes sometimes overlap in the same DNA strand (El-Hani et al. 2009); the reading frame can be shifted etc., i.e. the relationship gene – phenotypic trait is not single valued. Because of that (and because of the other facts which will be mentioned further) even the definition of the gene is not clear (see El-Hani et al. 2009). Yet there are many processes how phenotypic diversity based on a rather similar genome in different types of organisms can be produced.

In (Švorcová 2012, page 35) I argued that: *"transcriptional activation requires a cooperative assembly of many upstream transcription factors (*trans-*factors) on the promoter and/or* cis-*regulatory sequences (Davidson 2006). The specific set of* trans-*factor inputs present at a given time will define which downstream genes (outputs) will become regulated at that time, as well as where and how this happens. The modules can gain new functions by new combinations of inputs (1), by mutations affecting the* cis -

sequences (2), and by new relations between outputs (3), generating new regulatory network influencing their downstream genes. It is clear that not only the DNA binding specificity of the trans*-factors but also the interaction among different transcription factors during the gene regulation is crucial. Grenier and Carroll (2000) compared two* trans*-factors, O-Ubx in the grashopper* Acanthocara kaputensis *and D-Ubx1a in the fly* Drosophila melanogaster. *Ubx determines the segment specificity for many cell types, in epidermis, central and peripheral nervous system and mesoderm. Both O-Ubx and D-Ubx1a have a similar homeodomain, but the rest of the protein body differs to a great extent between both species. O-Ubx can repress* surf wings *gene and drive the expression of* decapentaplegic *in the visceral mesoderm as does the D-Ubx1a. On the other hand, O-Ubx cannot repress* distalless *gene as D-Ubx1a can (Wagner 2007). The authors believe that both proteins are engaged in different teams of transcription factors mainly because of differences in their protein domains- which results in diverse regulatory capacities.*

Alternative splicing of the gene transcript provides yet another source of trans*-factor heterogeneity: the differences in products of a single* Ubx *gene, i.e. different proteins are spliced from the same gene. In* D. melanogaster *six different isomorphs of Ubx protein were observed (Alonso 2008). The transcript isomorphs of* Ubx *gene differ in the presence of short additional regions (microexons): isomorphs containing microexons are expressed especially in epidermis, mesoderm and peripheral nervous systems. Isomorphs lacking the microexons are expressed only in central nervous systems. Functional specificity of the selector genes is therefore generated also on the level of RNA splicing*" (Švorcová 2012, page 36).

Also RNAi, i.e. the intervention of small, relatively short strands of RNA, can be involved in immense informational processing in the cell. Short non coding RNA strands are targeting (associated with nuclease-containing regulatory complexes) the complementary strands of coding RNAs, thereby preventing the expression of these mRNAs (Siomi & Siomi 2009). Further RNA editing processes (Lewin 2004) make the relationship between DNA and proteins even more problematic, when individual bases are added to or deleted from existing mRNA molecules (see El-Hani et al. 2009). RNA molecules can be modified also via *trans*-splicing, when RNA molecules encoded in the different loci in the genome are spliced together, "*forming a chimeric molecule"*

(Hastings 2005).

Additionally, as we mentioned earlier, any given protein molecule can have an astronomic number of different shapes and depending on how they are embedded in a cellular environment, only meaningful versions are attained. 'Meaningful' is understood in the context of other cell "inhabitants" (not only chaperon proteins but all pre-existing structures and protein assemblages to which the protein is born). The specific conformation gives to the protein the proper sensitivity to function, i.e. to bind a ligand and by so doing, while changing its conformation, sets off a special operation on the ligand. To give an idea*: "while about one tenth of proteins in the cell are bound to "housekeeping" functions (e.g. respiration, food intake, or special syntheses), the others act as a regulatory, information processing network that make subtle responses to whatever happens to the cell."* (Markoš, Švorcová, Lhotský to appear 2012, page 10).

So not only are digital representations of genes decisive in their translation into proteins, but also contextual processing of information based on variability-generating processes such as specific combinations of *cis*-sequences and *trans*-factors and different types of splicing, RNAi – but also the whole cellular milieu including temperature, nutrition, and "fellow proteins". Not to mention the protein's epimutations, which together with other adaptors decide the accessibly of the concrete gene (see below).

6.2. Epigenetic memory

Above we described DNA as storage in the form of characters or text, and in this chapter we demonstrate two other language-like manipulations within this text. Both processes help cells maintain their spatial and temporal coordinates within the body while they differentiate. The first one is a matter of putting chemical marks similar to diacritics (Markoš, Švorcová, Lhotský to appear 2012; Markoš & Švorcová 2009) on the DNA molecule and the second is a matter of putting diacritics on the proteins of a cell nucleus called nucleosomes.

6.2.1. DNA markings and genomic imprinting

In the case of epigenetic characters written on DNA or on histone proteins (around which the DNA is wrapped in the cell nucleus) we can go even deeper into analogy of memory as script or text storage. Chemical modifications of DNA characters can be compared to various ways of using diacritics. The best known modification is methylation[10] of the character C (or cytosine), provided by a battery of special enzymes. This process creates a fifth character in the string! What is crucial in our communication is that such modifications are reversible: another battery of enzymes (demethylases) can remove such a 'diacritics'.

"Methylation influences the accessibility of concrete region on DNA, i.e. can enhance or hide the particular regions of the string from proteins that would be able to manipulate with it. The reversible process of DNA modification can profoundly influence a cell's internal milieu. This is because it is only by binding proteins to regions of a DNA string that the encoded 'message' can be transmitted to the body-world. Thus, if the functionality of a region is enhanced or hidden, major changes can occur. Such processes therefore function, not only at the level of the cell, but in the organism as a whole. While some epigenetic changes are programmed (as in creating liver cells), others draw on an individual's lived experience. Thus, in identical twins, the pattern of DNA expression is similar early in development. However, across the lifetime, a cascading set of epigenetic effects will draw on processes such as DNA methylation.

In other cases, genetic material remembers its maternal or paternal origin. This leads to manifestations in the overall likeness of an individual and is especially well known in so-called genomic imprinting. In mammals, all females are genetic "chimeras" because, in their cells, only one (of two) X chromosomes functions. In a given cell lineage whether this is maternal or paternal is determined at random. If the active chromosome bears an debilitating mutation, the effect cannot be mended in spite of the second (but inactivated) X chromosome has the right gene. Serious mental diseases may develop when maternal/paternal imprinting gets erased or impaired

[10] Methylation is an addition of a methyl group to a cytosine (sometimes also adenine) residue of DNA converting it to 5-methylcytosine.

(e.g. Prader-Willi or Angelmann syndromes). In some groups (plants, and perhaps also animals), imprinting enables parents to transmit information to their offspring about the environment they are likely to encounter" (e.g., Gilbert and Epel 2009; Allis et al. 2007; as referred in Markoš, Švorcová, Lhotský to appear 2012, page 14).

6.2.2. Nucleosomes

As we show in Markoš & Švorcová (2009) and Markoš et al. (to appear 2012) DNA strings can be taken for a very long linear text, but actually they are part of a multilevel structure containing hundreds of different proteins – chromatin (in eukaryotic nucleus). "*Its lowest level of structuration is a 'rosary' of nucleosomes containing about 147 DNA 'characters' wrapped around 8 proteins (doublets of 4 different histones)* (Markoš, Švorcová, Lhotský to appear 2012, page 14). Each histone complex (2x (H2A, H2B, H3, and H4)) is linked to DNA thanks to zillions of so called weak interactions, and this linking is completely sequence independent (Fig. 4). While functioning to stabilize and fold the strand of DNA, these also enable or deny access by the proteins to particular sections of genetic material. This is dependent on other functions that are irreducible to any form of central control. Actions of specific proteins give rise to modifications like methylation, phosphorylation, acetylation, etc. (e.g. Allis et al. 2007) (and their erasures); the targets of modifications are histone proteins whose end tails stick out from the nucleosome complex. As a result, the modified surface of the nucleosome serves as binding site for other proteins that form a chromatin ecosystem. Such modifications are very conservative across divergent organismal lineages (Bernstein et al. 2006), being used in every eukaryotic cell from fly to human.

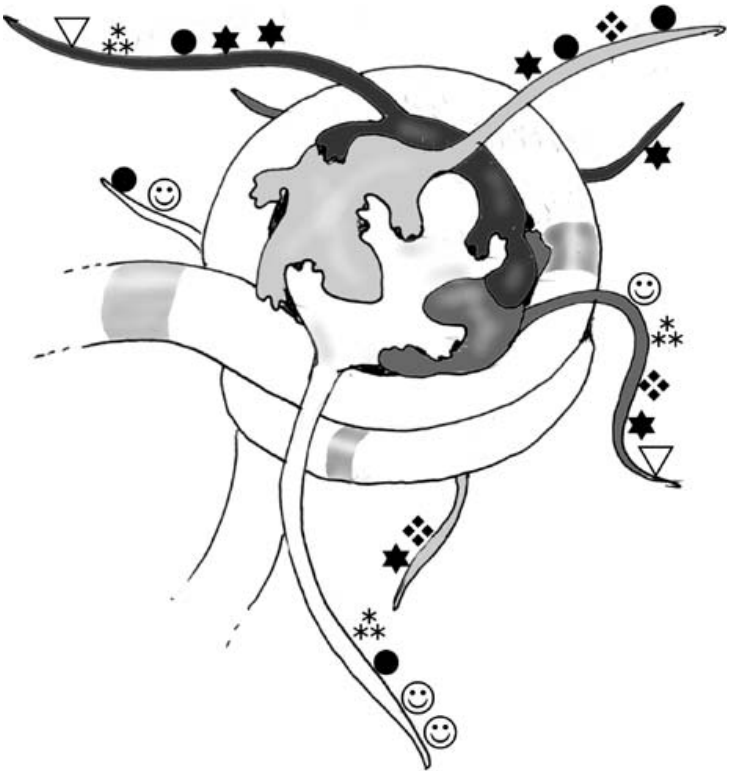

Fig. 4 DNA strands wrapped around the core of 8 histone proteins of four kinds. Histone tails with various marks on them form the individual pattern of the chromatin ecosystem: the marks can be removed and rewritten repeatedly, depending whether the particular area of DNA should be transcribed or not (a picture from Markoš & Švorcová 2009, page 134, see attachment no.1).

Furthermore, this kind of modification can affect **all other proteins** in the cell. Thus many amino acid residues in a protein can be modified (some even in different ways), often each sister copy (product of the same mRNA) being processed differently: "*the uniform population of nascent proteins will soon give rise to a plethora of proteins differing in shape and hence performance. Yet, the instructions to introduce such specific modifications are not stored in any coded string. Epimutations result from the collective action of a protein "ecosystem" in any given compartment, the nucleus in case of histones. Such modification marks may facilitate (or prevent) the binding of various classes of proteins, "readers of the code"; these in turn can recruit whole cascades of proteins bound to such already bound "adaptors", to become yet higher-order adaptors, etc. Their lifetime may be very short (seconds in case of the so called signal particles) or the process leads to the establishment of big irreversible complexes that literally "immure" long sections of DNA, even whole chromosomes"* (Markoš & Švorcová 2009, page 136).

The processes *"result in a network of interactions that maintains cell differentiation (e.g. as liver cells or neurons) while favouring quick and reversible response to external*

or internal cues. For example, some genetic material becomes walled up in a given cell lineage or during A developmental stage. By modifying both the DNA and histones, the system acts as an attractor that silences part of the DNA string – possibly thousands of nucleosomes in a row. In other cases, protein assemblies organize regions to produce a given cell lineage. In most cases, even long-lasting modification may (or should) be reversible in circumstances such as regeneration or, gametogenesis" (Markoš, Švorcová, Lhotský to appear 2012, page 15).

6.2.3. How the epimutations work

"The nascent sequence reads as follows:

ARTQTARKSTGGKAPRKQLTATKAARKSA

Below we give several hypothetical examples how such reversible chemical modifications of the sequence may look like:

AρTκQTARαστGGKAPRKQLATKAARμSA
ARTλQTARKSTGGKAπRKQLATKAARKSA
ARTμQTARλSTGGKAPRKQLAτKAARλSA
ARTKQTARKστGGKAPρKQLATKAARKSA
ARTαQTARηSTGGKAωRKQLATKAARμSA

(α — acetyl lysine, η — hydroxy lysine, κ — monomethyl lysine, λ — dimethyl lysine, μ — trimethyl lysine, ρ — methyl arginine, π — hydroxy proline, ω — proline isomer, τ — phospho threonine, σ — phospho serine)

It is to be noted that:

1. Each such modification requires a specific enzyme, which, in addition, may be site-specific. This means that trimethylation of lysine 4 (K4) is carried out in three steps, by three specific methyl transferases; performing the same task with K27 may require a different battery of transferases. The resulting pattern of modifications thus depends on what enzymes are present in the set of proteins present at the time — it is "agreed"

within such an "ecosystem" of proteins: negotiated, not encoded.

2. To keep modifications reversible, each modifying enzyme must be accompanied by enzymes with a reverse action (e.g., methylases, removing methyl groups).

3. The changes of shape brought to the protein by such modifications give rise to different shapes, hence very specific antibodies can be raised against each modification. This enables researchers to detect such variations across vast expanses of chromatin, and draw conclusion as to the state of chromatin in different parts of the genome, or in different cells.

These *"bar codes", the "diacritics" of modified amino acid "characters", are reversible, i.e. can be erased, edited, or rewritten. Protein epimutations can appear (and disappear) on chromatin within minutes upon arrival of a specific signal. Proof of the biological consequence depending on the individual combination of modification is, however, not always easy to provide and is often based on correlation: proving causality for a modification involves demonstrating that catalytic activity of the enzyme that mediates that modification is necessary for the biological response*" (Markoš & Švorcová 2009, page 137).

6.2.4. Examples of epimutations and their effect

In our paper (Markoš & Švorcová 2009, page 138), we make an overview of the best known examples of chromatin modification: *"probably the best-known histone modification is methylation of lysine #9 on histone 3 (H3K9me); in animals it will initiate a cascade of events resulting in attachment of dozens of proteins of so-called Polycomb group; this leads to tighter condensation and silencing of that region of DNA fibre (Giannis et al. 2005). Modulations like H3K9 and H3K27 are responsible for silencing of the chromosome X in mammalian females. But methylation H3K9 can be found also in transcriptionally active chromatin; in context with H3K4 and H4K20 it helps holding the chromatin active for transcription by binding of the chromatin remodelling complex (Margueron et al. 2005).*

In general, three methylation sites on histones are implicated in activation of transcription: methylation of lysine #4 on histone 3 (H3K4), H3K36 and H3K79.

H3K4me and H3K36me play also role in transcriptional elongation. However in budding yeast another exception can be found: methylation H3K4 is involved in DNA silencing (Bryk et al. 2002). The location of such a modification is also important: H3K36me has a positive effect of activation only when on the coding region, and a negative effect of silencing on the promoter (Vakoc et al. 2005). Existing modifications may promote further labelling: thus phosphorylation of H3S10 facilitates H3K9 and H3K14 acetylation and thereby inhibits H3K9 methylation (Giannis et al. 2005; Kouzarides 2007). H4K20 methylation and H4K16 acetylation were found to preclude each other (Allis et al. 2007). Trimethylation of H3K4 requires ubiquitylation (adding of ubiquitine protein) of H2BK123 and reversely deubiquitylation of H2BK123 leads to trimethylation of H3K27 (Schuettengruber et al. 2007).

Binding of a protein could also be disrupted by a subsequent histone modification: H3K14 acetylation accompanied by H3S10 phosphorylation will dissociate Polycomb group proteins from methylated H3K9 (Fischle et al. 2005). Identical modifications, even in the same region of chromatin, may not necessarily lead to the same output: their context, combination and position are crucial here."

6.2.5. Polycomb and Trithorax Complexes and Cell Memory

"The Polycomb and Trithorax group of proteins belong among key regulators in defining cell identity in eukaryotes. They propose a very good example how the cell memory functions thanks to the chromatin diacritics. Polycomb *genes encode a group of DNA binding proteins, histone modifying enzymes, or chromatine repressive factors with affinity for H3K27me3 (Kingston & Tamkun 2007). H3K27 trimethylation is often distributed over large chromosomal domains, sometimes covering hundreds of kilobases (i.e. thousands of nucleosomes in a row), which might provide the basis for epigenetic inheritance of Polycomb-dependent silencing during cell division (Schuettengruber et al. 2007). These proteins control the silencing of target genes (e.g., chromosome X inactivation, repressing activity of* Hox *genes). One group of Polycomb proteins components has a histone modifying function (methylation of H3K27 and H3K9), whereas the others bind to these modifications and change the chromatin structure.*

In Drosophila*, mouse and human the H3K27me3 is highly correlated with binding of Polycomb group proteins (Schuettengruber et al. 2007). Products of* trithorax *genes exhibit the opposite activity — they involve transcriptional factors or chromatin-remodelling enzymes, which are involved in maintaining the chromatin in an active state (via methylation of H3K4). Polycomb and Trithorax complexes are highly evolutionary conserved; they are supposed to be crucial for the cell differentiation and cell fate plasticity. But they represent only the tip of the iceberg — of massive parallel processing of proteins in chromatin domains, on million of nucleosomes contained in it.*

Histone modifications represent part of the cellular epigenetic memory, i.e., information that must be built up in ontogeny and is heritable through the cell lineages. Many cellular phenotypes are transmitted and maintained in this way, including genomic imprinting, X chromosome inactivation, heterochromatin formation or gene silencing, or the expression state of Hox *genes (see below) involved in specifying cell identity along the axes of segmented animals (Kouzarides 2007; Schuettengruber et al. 2007; Costa 2008).*

The lesson from our histone inquiry is that various kinds of "bar codes" inscribed onto the protein molecule during an individual's life are not inherited in a ready-made state: they come into existence by bootstrapping processes between the hardwired genetic message and the organic memory. Hence, the build-up of organic memory (sensu Barbieri) is accompanied by "taking notes" in the form of a sequence of modifications — epigenetic counterparts of inherited informational molecules (codes). The fact that such quasi-digital texts can be created — written and edited — during the lifespan of an organism, and some of them can even be passed to the next generation, is the central starting point of our investigation" (Markoš & Švorcová 2009, page 139-140).

Modifications as those described are another way how to generate variability on the cellular level without affecting the "master copy" of DNA sequence via mutation. In this sense, we call such changes "epimutations" (including the methylation of DNA, modification of amino acids on histone tails or amino acids of other cellular protein), due to their reversible but hereditary character (some epimutations may be heritable to the next generation of cell and also individuals). We consider these epimutations to be some kind of diacritics of the basic genetic text which, however, radically change the meaning

of the primary text and therefore its shape, function and interaction. In this way and unlike the memory written in DNA characters, epigenetic memory is not subject to Mendelian laws of heredity.

6.3. Developmental memory demonstrated on the phylotypic stage

As previously mentioned, Marcello Barbieri (2003) introduces a concept of organic memory that is quite different from that discussed above. In his concept of the memory activated during embryonic development, the phylotypic stage serves as a boundary between two quantitatively different periods of development. In the first period (up to the phylotype), development is very quick and directed only by the hardwired genetic program. In the second, processes working on the basis of the bodily, i.e. supracellular memory of the body plan, also coordinate development. The supracellular memory is considered "*empty in the beginning (Barbieri 2003); through many rounds of iterative processes, the tight coordination of function at the phylotypic stage allows a gradual ''reconstructing'' of the phenotype from incompletely inherited information"* (as referred in Švorcová 2012, page 38). Before defining developmental memory, we first have to introduce the phylotypic stage and its role in organic memory definition.

6.3.1. The phylotypic stage: history of the concept and its definition

"Inspired by Darwinian teaching, Haeckel (1874) furthered the idea into the so-called basic biogenetic law (phylogenetisches Grundgesetz), asserting that ontogeny recapitulates phylogeny of a given lineage in an abbreviated and rapid way, i.e., embryonic development of an individual organism passes (in an abridged form) along the same path as did its species in history. Thus, a human being starts as a single cell and then proceeds through the stages of coelenterate, planarian, fish, saurian, primitive mammal, and ape, with higher, i.e. phylogenetically later stages, becoming more and more prominent (Haeckel 1874). All species-specific differences appear at later stages of

developmental sequence. The biogenetic law fell later in disfavour, and contemporary models are safely rooted in the insight of Baer (1828) who supposed the early stages of the development to be more similar than the later stages because of their homogeneity, not because of the fact of recapitulation. Baer (1828) was the first to recognize in vertebrate development a stage common to all classes. This led him to the formulation of the ontogenetic law: in embryonic development, general features precede special ones; development proceeds from undifferentiated homogeneity to differentiated heterogeneity (Gould 1977). For a contemporary biologist, the phylotype idea is connected with the hourglass model (Fig. 5) designed independently by Raff (1996) and Duboule (1994), which demonstrates that developmental pathways leading to and from the phylotypic stage are quite different (even among closely related taxa), and the morphological similarity is the highest at the period of the phylotypic stage" (Švorcová 2012, page 31-32).

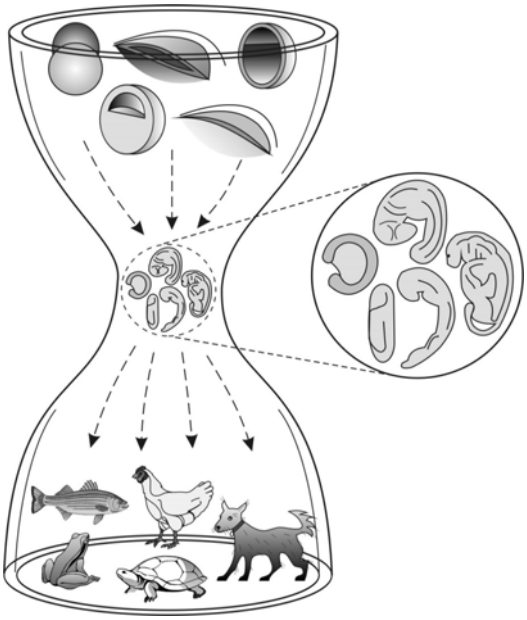

Fig. 5 The hourglass model (a picture from Švorcová 2012, page 32, see attachment no.2).

"The name ''phylotypic stage'' comes from Sander (1983), and such a stage has so far been described for annelids, arthropods and chordates (Bininda-Emons et al. 2003). It has been known by several names, like pharyngula (after the pharyngeal pouches, Ballard 1981) or tailbud stage (Slack et al. 1993) in vertebrates, and the germband stage (Sander 1983) in the development of insects. As was already

emphasized by Sander (1983) in case of arthropods that early developmental pathways leading to the phylotypic stage are highly variable even across closely related taxa" (Švorcová 2012, page 32).

In my article (Švorcová 2012), I also discuss in depth the very existence of the phylotypic stage: I had to adhere to the possibility that the phylotypic stage is a valid concept in developmental biology; although some scientist still consider this concept misleading or even invalid (Richardson 1995, 1997, Bininda-Emons et al. 2003 or Mitteroecker and Huttegger 2009; see Švorcová 2012, page 32). This phylotypic stage is then defined by (1) the **basic morphological structures** (notochord, somites, neural tube, optic anlagen, and pharyngeal pouches), by (2) highly conservative **zootype transcription pattern**, i.e., by the transcription of the orthologous genes shared among vertebrates (e.g. so called *Hox* genes), and by (3) high level of **interactiveness within the phylotypic body.** For (1) see Fig. 6.

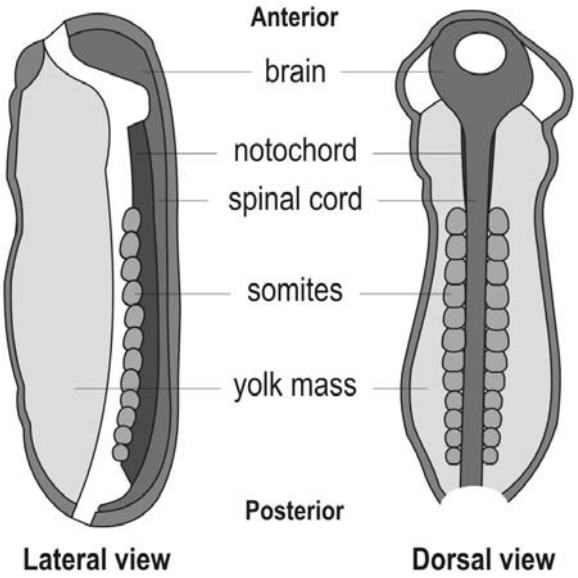

Fig. 6 The vertebrate phylotypic stage with main morphological characteristics (pharyngeal pouches, heart, and optic anlagen are missing) (a picture from Švorcová 2012, page 32, see attachment no.2).

2) The zootype represents a specific anterior-posterior pattern of orthologous gene expression which is activated during the period of the supposed phylotypic stage. This pattern is present in a broad variety of organisms including insects, nematode, amphioxus, and sea urchins; and all their body plans arise from localized expression of such conservative genes. "Hox *genes probably existed in the common ancestor*

of Cnidaria and Bilateria[11] *(Ferrier and Holland 2001). On such a basis, they were able to unite almost the whole animal kingdom under the common concept of zootype. Therefore, the zootype as a genetic pattern is formally superior and evolutionarily older than the morphological structure of phylotype"* (Švorcová 2012, page 33).

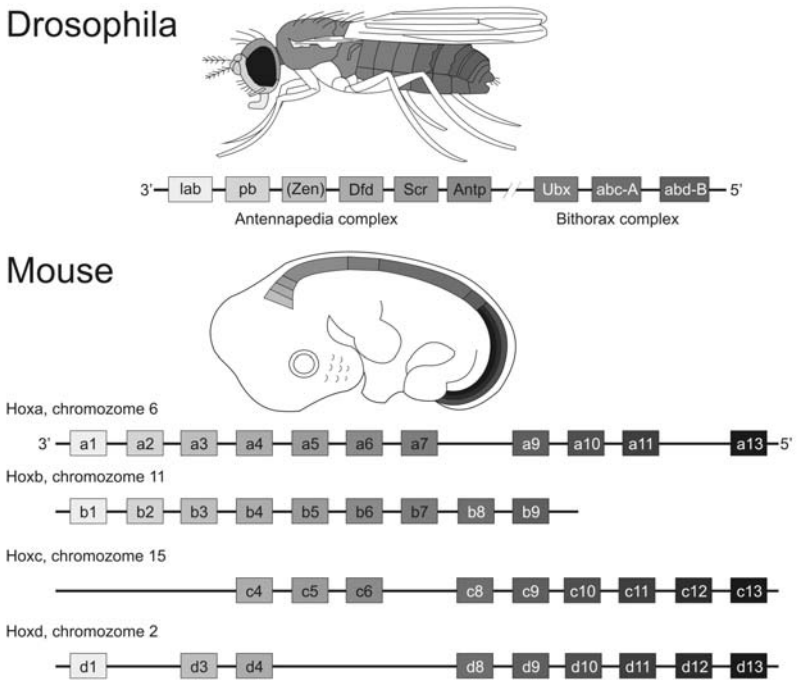

Fig. 7 The zootype transcription pattern In *Drosophila melanogaster* and *Mus musculus*. Note that vertebrates have 4 *Hox* complexes (a picture from Švorcová 2012, page 33, see attachment no.2).

Hox (or homeotic) genes (Fig. 7) "*activate or repress batteries of downstream genes by binding to DNA sequences in* Hox*-response enhancers (Pearson et al. 2005), but they can also control other executive genes. The* Hox *genes are organized in clusters, and their supposed evolution proceeded via duplication of these clusters (vertebrates have four copies of such clusters). Their main function is the determination of the embryonic regions along the anterior–posterior axis and the specifying of the particular identity and relative position of a given structure (Slack et al. 1993). Later in development, the expression, and function of* Hox *genes they also act as region-specific selector genes in diverse structures and tissues (Carroll et al. 2006). In addition, they play a role in cell division, cell death, and cell movement (Pearson et al. 2005).*

[11] The Bilateria have evolved independently for more than 500 My (Ferrier and Holland 2001).

Mutation in homeotic genes may lead to morphological defects or homeotic transformations (Davidson 2006). Note that Hox *genes are best known, but by no means are they singular example of selector genes playing a crucial role in development. Slack et al. (1993) describe the phylotypic stage not only as a defining platform for an individual body plan but also as a link of this body plan to the whole animal phylogeny."* (Švorcová 2012, page 33). The conservative character of *Hox* genes was confirmed by replacing a specific gene of fruit fly with a gene from mouse genome, with the consequence of normal fruit fly eye development (Gehring 1999, Gehring & Ikeo 1999). Although the final protein products coded by these homologous genes differ in many parameters, the function remains the same and the product directs the pathway in the usual way (in respect to the fly embryonic development). Hence the *Hox* genes products work as tools (Carroll 2005) for establishing the developmental pathway itself, not as decisive factors in deciding what an organ should look like.

Finally (3), the high level of interconnectivity within the body is the main reason for the conservative nature of the phylotypic stage according to Raff (1996) or Galis and Metz (2001), thus at this period the whole body functions as one highly connected module, lacking the modular character recognizable later in the development.

6.3.2. Modular character of development

Galis and Metz (2001) experimentally discovered a web of intense interactions among organs of primordia; due to which any small, laboratory-induced mutation (exposure to teratogens) during the period of the supposed phylotypic stage causes pleiotropic (even lethal) effects in the whole embryo. Later in development, after the phylotypic stage, the effects of such mutations are not so damaging for the embryo as a whole. The phylotypic stage is obviously a very conservative period of development, naturally resistant to any mutational change (Galis and Metz 2001), and maximally interconnected (Raff 1996). By contrast, later development operates via discrete semiatonoumous modules and similar exposure to teratogens had lesser impact in the fore-mentioned experiments, as it affected only selected modules of the body.

The module concept is very popular in contemporary biology (for review, see

Švorcová 2012, page 35); the promoters of the modularity role in development were Riedl (1978), Lewontin (1974), Bonner (1988), and Raff (1996) (for review see Nelson 2004 or Wimsatt and Schank 2004). "*The module is a special integrated and relatively autonomous unit (Schlosser 2004) with high degree of internal and a low degree of external interactions (i.e., with other modules of the given structure). The integration of the module means that the input–output relationship of the module depends on the particular connectedness of its components, not only on the additive superposition of these components. An autonomous module is insensitive to perturbation of the context in which they are embedded (Schlosser 2004). Insensitiveness means that the module is able to maintain the same function even in abnormal tissue environments (e.g., ectopically, by transferring the bud, or anlagen, to different location of the embryo).*" As homologous modules share similar genetic and developmental background across different lineages, it seems that modular functions were established very early in evolution. "*...Every change in the genetic network of a single module leads to the pleiotropic effects only within such a module. Developmental and evolutionary function of modules may reside in canalization and environmental perturbation (modularity leads to higher phenotypic stability during development), or in selective buffering against pleiotropic influence of the whole organism, which facilitates adaptation (or escape from adaptive constraints)*" (Wagner et al. 2005; as referred in Švorcová 2012, page 35).

Schlosser (2004) makes distinctions between 5 types of modules activated in different developmental contexts (for more details see Švorcová 2012): (1) gene regulation module (specific combinations of *trans*-factors on the promoter and on *cis*-regulatory sequences); (2) signalling module (intra- and extracellular pathways between communicating cells); (3) positional modules based on the positional-selector genes when "*...the main differences emerge not on the level of genes, but on the level of their regulation by duplication or rearrangements of the* cis-*regulatory sequenc*es, *which is followed by changes in the time and place of the expression of a given gene*" (Švorcová 2012, page 37). An illustrative model based on Carroll (2005) shows the example of *Hox6* expression in vertebrate development (see Fig. 8 below); (4) cell type module that represents the differentiated cell (maintained via epigenetics memory) and (5) organ module like vertebrate limb as functioning relatively independently from other organs.

Most of the module components (*trans*-factor, ligand etc.) are conserved from insect to vertebrates, acting in different tissue environments. For example, in case of signalling module, the Sonic hedgehog pathway is active in wing disk, leg disk or eye disc formation in Drosophila, while in vertebrates it is in dorso-ventral patterning of somites and neural tube and in anterior-posterior and proximo-distal patterning of limbs. In vertebrates, the Sonic hedgehog pathway also participates in gut, pancreas, lung, and tooth formation (Borycki 2004). The universality of the signal transduction module is often hacked by cross talk among pathways.

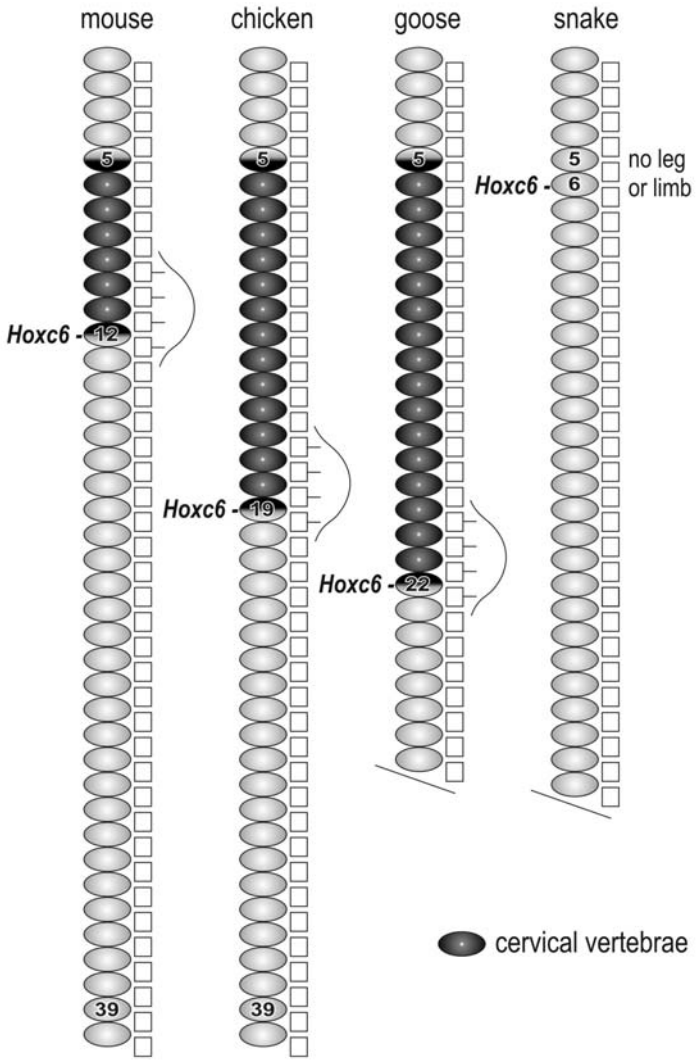

Fig. 8 "*Cervical and thoracic vertebrae. Various vertebrates have different numbers of cervical and thoracic vertebrae and therefore mice have a short neck, geese long one, and snakes none (only one long torso). The boundary between the cervical and thoracic vertebrae corresponds with the expression of gene* Hox6*, which forms the interface between the neck and chest.* Hox6 *gene is activated in every vertebrate species, but its position with regard to the whole body is different. For all four-legged vertebrate, forelimb arises at this boundary. In the case of snakes, there is no obvious boundary between the cervical and thoracic vertebrae, and the expression of* Hox6 *is spreading forward to the head (and no limbs are formed)*" (a picture from Švorcová 2012, page 37, see attachment no.2).

6.3.3. Organic memory- fully represented and stored?

It follows from the fore mentioned that the evolution of animal form is shaped not only by genes but also by the spatiotemporal shifts in gene activation, thanks to contextual, cellular "notes" on DNA or chromatin proteins, thanks to different partners in protein interaction (different combinations of transcriptional factors) and thanks to the context in overall cellular milieu. Other processes such as variable alternative splicing or RNAi are also included. Such new regulatory states are responsible for new interpretations and new usage of the same modules in different tissue environments. *"How, then, is the organism to reconstruct its specific three-dimensional morphologic layout, when the genetic background is very similar across disparate taxonomic groups of fish, bird or mammal (not to mention insect and other evolutionary distanced groups of organisms)? How is the continuity and informational stability of the developmental processes maintained, if most phenotypic characteristics of the whole metazoan are generated not by individual genes acting alone, but by networks of interacting gene products (Salazar-Ciudad and Jernwall 2004)? Why does animal development require a conservative phylotypic stage?"* (Švorcová 2012, page 38).

"On the level of zootype, all the members of the same phylum put the same genetic toolkit in use (Carroll 2005, 2006) to start their embryonic development. Barbieri noticed that it is the very phylotypic stage that launches new, qualitatively different types of development. In the first period (up to the phylotype), development is very quick and directed only by the hardwired genetic program. In the second period, development is also coordinated by processes working on the basis of the bodily, i.e., supracellular memory of the body plan. The supracellular memory is empty in the beginning (Barbieri 2003); through many rounds of iterative processes, the tight coordination of function at the phylotypic stage allows a gradual ''reconstructing'' of the phenotype from incompletely inherited information. Today's knowledge of evolutionary developmental biology coincides with Barbieri's opinion: phylotype itself acts as a single, highly connected module; and immediately after this period, the embryo breaks down into several semi-dependent modules. During this period the spatiotemporal expression of orthologous genes is activated. Such independent spatial and temporal regulations of

gene expression permit individual regulatory genes to have different but specific functions in different contexts (Carroll et al. 2006). The architecture of hierarchical regulatory domains or different level modules can well represent the phenomenon, which Barbieri calls the supracellular memory of the body plan. Barbieri (2003) considers the body plan to be simultaneously a three-dimensional structure and a deposit of information. The information about spatial organization of body plan cannot be transferred without the three -dimensional structure of the conservative phylotype which is typical for the whole phylum. In fact, the structure is four-dimensional: the heterochronic events dependent on the species lineage have to be taken into account as well. The concept of supracellular memory may therefore help us further elaborate the question of conservation of the phylotypic stage" (Švorcová 2012, page 38-39).

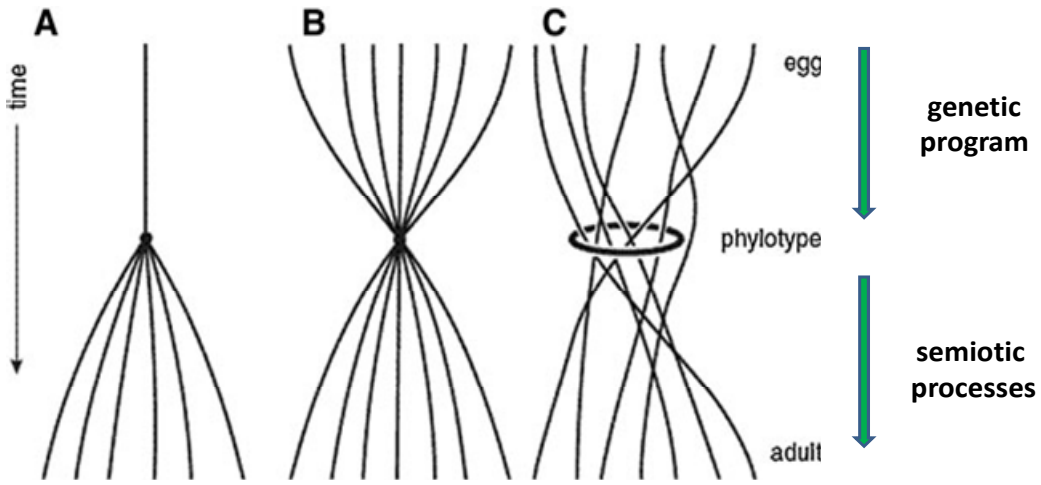

Fig. 9 The sheaf model. Three different models of the development: **a** the broom model represents Haeckel's biogenetic law, **b** the already mentioned hourglass model, and **c** the sheaf model recognizing the conservation of the phylotype but also allowing a loosening of individual straws and circumventing the straw binder (Markoš et al. 2009). The additional darts representing the meeting point of so called Barbieri's platform between genetic program and semiotic processes.

"In Markoš et al. (2009), the term ''Barbieri's platform'' was introduced. It represents the meeting point (Fig. 9) *between the period of development ruled by hardwired genetic information and the period when this information is mollified ''from above'' by semiotic processes. This mechanistic, hardwired, one-module platform is*

a starting point of the species-specific modular development. Phylotype and zootype form together bodily and genetic toolkit of the body plan (Markoš 2002; Markoš et al. 2009). It is also a meeting point for Barbieri's semantic biology and the language or hermeneutic metaphor of life" (Švorcová 2012, page 39).

Barbieri (2003) does not explain the memory concept very exhaustively; "*we shall take the memory for the very realm of semiotic and hermeneutic processes, and from here we shall try landing on the Barbieri's platform "from above": from the realm of historically established "cultural" conventions, which lend the mechanically erected platform a much subtler, ornamented, baroque, species-specific and individuum-specific pattern. It follows that the conventions established should be taken for fuzzy and malleable, language-like: it is here where meaning is generated, and the process cannot be — as in the case of codes — executed by machine-like contraptions, automatons*" (Markoš & Švorcová 2009, page 133).

In contrast to Barbieri, who takes organic memory to be empty at the very beginning, Markoš et al. (2007) "*argue that the organic memory is never empty; it comes with the bodies of the germ cells (and is, at least in part, contributed by the mother) and is really responsible for procuring the individual pattern (body) subject to natural selection". ..."Codes and memories work always in tandem; we never encounter a "read only" code, or an empty memory matrix. Only in this way the massive parallel processing that is taking place in the body can be managed in real time"* (Markoš & Švorcová 2009, page 134).

6.3.4. Organic memory by Walter M. Elsasser

Barbieri was not alone in introducing the organic memory concept; it is traceable back to Walter M. Elsasser (1987), a physicist who came up with the idea of holistic memory as a general principle in the reproduction of cells and organisms. *"The decisive point of our later analysis is that memory must be subjected to the same type of epistemological scrutiny that physicists have for a long time applied to space, time, and causality... we attribute to the organism the ability to pick out of an immense number of patterns available on the basis of purely chemical structure, those that closely resemble*

previous patterns. The organism is able to achieve in this way a transmission of information over an interval of time without there being storage of information in a mechanistic sense" (Elsasser 1987, page 6).

According to Elsasser, memory is based on the process of homogenous[12] replication, i.e. replication based on the molecular stability behaving according to the laws of chemistry and physics and heterogeneous reproduction, i.e. creative selection from immense reservoir of naturally possible atomic-molecular patterns. The replicative memory process is based on the action of storage device (DNA molecules), whereas the reproductive process is based on constant and creative selection. The term ''creative'' means: tied in with the ''laws'' of physics and chemistry – but not only with them. Both processes provide the stability of heritable information and cannot be fully separated from each other (Elsasser 1984), both provide reconstruction from incompletely transmitted information. Elsasser drew his inspiration from the analogy with cerebral memory, stating that *"cerebral memory is a matter of heterogeneous reproduction and only secondarily if at all one of homogenous replication[13]"* (Elsasser 1987, page 87) and criticized the mechanistic approach to the processes of reproduction of living forms (as referred in Švorcová 2012, page 39).

In Elsasser's organic memory concept, memory is not a simple mechanistic storage (here, Elsasser is inspired by Henri Bergson's book *Matter and memory* published in 1896), but a process of heterogeneous reproduction, it is a memory of holistic nature and a primary phenomenon of nature existence which cannot be deduced from any ''law'' (Elsasser 1987).

My main point in the paper on modular memory was a theory that embodies memory without storage[14] (Švorcová 2012*): "memory that is not fixed-inscribed into some permanent code such as DNA. Nowadays, in genocentric neodarwinian biology still dominates the opinion that every phenotypic trait is represented in the form of string(s)—shorter or longer—of DNA molecule (together with some epigenetic modifications).*

[12] Chemist or physicist usually uses homogeneous models, which consist of a number of molecules of similar chemical constitution and predictable behaviour.

[13] This means that cerebral memory cannot be considered as a mere storage device.

[14] The idea of organic memory as storage culminated in the philosophy of biological preformism.

In contrast, supracellular memory of the body plan probably operates in the way of heterogeneous reproduction, choosing specific way in which to use the co-opted regulatory pathway. Developmental processes leading to similar morphological structures can differ even among closely related taxa (Newmann and Müller 2000); the same spatial pattern can be generated by various independent ways acting at roughly the same time (Salazar-Ciudad and Jernwall 2004). What is important is not only the inner representations of orthologous genes or the coding routines, but also various contexts, time, and space in which the products of these representations meet. However, such developmental structure itself (the lineage-specific usage of the toolkit) is not completely stored in any mechanistic sense of mere digital representations; it is stored in the bodily form of the supracellular memory of the species, and in the pattern of the interactive developmental network. Thus, the direct correlation between genotype and phenotype vanishes, and the communicating tissues and cells are the primary level of description, not genes as mere representations. The memory processes the inputs from the developmental program and from the environment and provides the coordination of species specific processes" (Švorcová 2012, page 39).

I believe that *Hox* gene regulation processes show that organic memory cannot be fully described as storage, relying only on information contained in DNA molecules, because very similar script results in various morphological structures. Organic memory has not the mere character of storage (in form of DNA molecule), but also the character of a distributive, experienced based network (let us say of a heterogeneous nature sensu Elsasser), which works via sign-mediated activity. In this thesis, selected processes like DNA-methylation, histone modifications but also spatio-temporal shifts in gene regulation form "engrams", based on the experience and environment of a given species or community. In the following discussion, I would like to show that the level of bodily memory described as a distributive network of engrams or habits is the primary level of organic memory functioning, followed by the secondary level of information stored in DNA .

7. Discussion

7.1. A semiotic perspective on developmental memory

"Barbieri argues that the memory of the body plan follows specific codes, in order to reconstruct the phenotype of a given organism. Such codes are implemented in the phenotype itself. Living beings are able to reinterpret their developmental circuits based on the same genetic toolkit, and these historically created and integrated interactions are able to maintain through the subsequent generations. In the particular study of this topic, it becomes obvious that living beings are primarily historical entities capable of forming habits in the form of regulatory circuits, which are homologous and co-opted in evolution. Barbieri would call this habit a code, but this author and co-worker believe that the path leading to a code or habit is the interpretation, in the hermeneutic sense, where the receiving system is capable of learning, of following its own history and experience (Markoš 2002). In this metaphor, memory represents the deposit of habits, which are unique for every species. This approach should not be considered as a vitalistic point of view, we do not postulate any type of hidden vital principle entering the body from outside, the discussed memory representing the memory of every single species embraces the whole unique recruitment and set-up of the same co-opted evolutionary- developmental modules used in different contexts. Owing to supracellular memory, living beings are able to deal with an enormous amount of informational processing on many levels of embryonic development. The organic memory maintains the convention, continuity, and coherency of the species. Extrapolation from the past evolution of developmental circuits is always difficult, and the semiotic perspective describing the evolution of bodily memory remains an ontological claim that even at the cellular level, there is a semiosis. Yet to assume that the complete memory of the body plan is reconstructed based on representations, such as DNA, or recorded codes of mechanistic nature, would be a larger ontological claim" (Švorcová 2012, page 40).

7.2. The transcendent and natural world

In Markoš & Švorcová (2009), we introduced the idea of transcendent[15] and natural worlds (first introduced in Markoš et al. 2009). This idea explains our point of view on human epistemology, on the way in which we make science and think about nature, but also how we sometimes forget that *the map is not the territory*. The model, which eventually belongs to the transcendent world as well (but don't forget about Russell's paradox),[16] is not very complicated. While it definitely still has many gaps, it helps us quite efficiently highlight the problems of biological codes and their priority in biological processes.

1) **The natural world** represents the world of objects, languages, games and history, all living in its endless extinction and becoming. It is a world of life, experience and events. The important thing is that in this world things may be similar, but never identical; they cannot be copied, only imitated. Attempts at digitalization in the natural world are only approximate, i.e. errors are easy to make. Life, natural language (including its possible analogues in non-human species, cells, etc.), is the product of this natural, or bodily, world (Markoš 2002; Cvrčková and Markoš 2005, Markoš et al 2009).

2) **The transcendent world** is one of our creations, which represents the world of ideas, geometrical objects, mathematics, logic, and all the explicit rules we have made about our activities as well all non-alphabetical scripts and symbols. The string in this world can be trans-coded into different alphabets without mistakes and they can be treated as identical. Characters dwell in the transcendent (virtual) realm; having here a clear-cut definition, and only here can they be lined up into strings that can be copied ideally, i.e. without errors. As to their appearances, i.e., the images that they assume

[15] The term transcendent is not used in the Husserlian sense of an object constituting itself on the level of consciousness or in the epistemological sense of an object exceeding our experience. On the contrary: the transcendent world in our conception is the secondary product of being in the natural world and that is, in our humble opinion, the only way in which it exceeds our experience.

[16] Neuman (2008) considers such paradoxes to be a necessary condition for semiosis. I suppose that it is our language that makes these paradoxes possible. In terms of logic, theories and our idealisations in general, we can always get into such paradoxes, which points to the fact that the realm of logic and quantity belongs to the transcendent world.

in our natural world, these are absolutely arbitrary as soon as their alphabetic coordinates are known (Markoš & Švorcová 2009).

7.2.1. Crossing the barriers between two worlds

We take knowledge invented in transcendent world and use it to our advantage, to influence the natural world. All the objects from the transcendent world, from equations to theories or geometrical objects, are reducible to a common denominator, to strings of digital characters. In this sense, the transcendent world can be decoded only in our natural world; and in reverse, any experience can be written into such strings. The strings constructed from such characters dwell in the transcendent world, but no meaning is attached to them. These strings can gain meaning only by facing the natural world. Digitalization is possible only to a certain degree in the natural world, which is why it is more convenient to talk about DNA nucleotides and modifications, as well as protein modification as quasi-digital.

Only in the transcendent world do meanings come for all the virtual contraptions we encounter, only here are the initial and boundary conditions provided; without such an interaction we would be left with a kind of plain algebra (but even then the rules must be delivered from the natural world). Science gains its calculations and hypotheses here, in the transcendent realm, and takes them across the barrier to the real world to test them (Markoš & Švorcová 2009). Since we are the creators of the transcendent world, it can only exist because of its interactions with the natural world.

But we replace the natural world with our schemes from the transcendent world and we believe that our world is actually ruled by this transcendent realm (if not the laws of God, then we choose laws of nature) forgetting that these are our mere constructs. The natural world sometimes even obeys these rules and that makes the forgetting even easier.

What is most interesting is that the barrier is penetrable, that we can gain inspiration in both worlds, and even state that our virtual constructs — displayed as string of characters — can encode certain properties of the real world (Markoš & Švorcová 2012).

7.3. Differences between program execution (formal language) and reading (natural language)

7.3.1. Program execution and formal language

"As was mentioned earlier the coding/decoding device must dwell in the natural world, and the string must be delivered to it on a suitable medium. For a computer it may have the form of irregularities on a magnetic disk, for its processor it is a succession of electric impulses, for the punched-card reader it is a difference hole/non-hole, for a ribosome the sequence of triplets on mRNA, etc. However, once inscribed into a medium, the characters cease to be absolutely digital: not always can they be distinguished unequivocally.

We call such material embodiment of string sequences discrete or quasi-digital. It follows that they can be neither copied nor trans-coded infallibly: they are prone to mutations — i.e. misreading and mistranscription of their quasi-digits, confusion with a different character of the alphabet, etc. But it is not our task here to discuss the problems of digitalization, i.e., smuggling ideal digits into the quasi-digits of the real world.

What is more important:

(i) A formal language necessary for program execution was derived (created) by entities in command of natural language. Formal language is defined as a set of character strings, and operations upon them (Searls 2002).

(ii) A non-living device, a machine, will suffice for the task of scanning and executing — thoughtlessly, mechanically. As a drastic example take a missile heading towards its target. In other words, formal language is a domain of trans-coding between virtual strings; but the trans-coding program (rules) comes from the natural world, from entities with the command of natural language.

(iii) A virtual string of marks, when embodied into a suitable medium and scanner by a suitable device, can influence the behaviour of the world.

(iv) The question of the maker who constructed the device and wrote the program in a formal language is easy to answer for man-made machines, but enormous problems arise when contemplating self-reproducing automat. Should we consider living beings as

such automata (without adopting the creationist worldview), their coming into being, and evolution, remains an enigma, even though reasonable scenarios had been proposed for the program-first as well as device-first alternative evolutions.

But the most important, and perhaps most controversial, statement of our analysis is this:

(v) Formal languages, as known today, do not know any semiosis — they work on the level of codec. Interpretation is the virtue of natural languages. For the sake of sharpening our vision of the problem we stick to this statement, even if we are fully aware that linguists, philosophers, and scientist are not united over the problem" (Markoš & Švorcová 2009, page 145-146).

7.3.2. Reading (Natural Language)

As we state in Markoš & Švorcová (2009, page 146-148), reading procedure is a semiotic and hermeneutic task, which requires a community of living beings (humans, cells or organisms) whose activity is deeply rooted in language based understanding, in culture and their history transmitted via organic memory. Thus every organism as part of a negotiating community where the habits are transmitted via language-like actions (whether the language of cellular modification or our language).

"Hence, natural language is a phenomenon of the natural world that cannot be transferred into the transcendent realm, and even less can it be reduced to digits. We devote a parallel paper to the language metaphor of life; here we list only a few comparisons that highlight the difference between program execution and reading.

(i) A natural language cannot be produced from scratch, unless we envisage a creator speaking a meta-language (compare with formal languages); a community of speakers, and historical continuity of such a community in time is required.

(ii) Communication in language proceeds in utterances, which — in contrast to language itself — can be parsed, with some reserve, to linear strings of quasidigital units (morphemes); grammatical rules concerning groupings of morphemes can be derived for any given language.

(iii) To produce speech acts (speaking or writing), speakers are required who are

not machines; similarly, to perceive the message, i.e., to accomplish understanding, living interpreters are required who are not machines;

(iv) The quasi-digital nature of strings of morphemes allows, with some reserve and with established rules, to map an utterance in a form of a character string. By this artifact making, the utterance can be saved in the transcendent, atemporal world of characters, and copied infallibly. Artifact-making needs life (Barbieri 2007); life dwells in the real world. As in case of formal languages, strings can be "materialized" by embodying them into a suitable medium (like print on paper, or a file on the hard disk); as in the case of formal languages, the copying of strings and their embodying can be performed by machines.

(v) Reading such strings requires literate speakers in natural language who are able to transform them back into real-world utterances (spoken or not), in order to understand them.

Whereas a coder/decoder will supply a single, deterministic "execution" of a given string, leading every time to identical "interpretative" result, semiotic and hermeneutic abilities of living beings will conjure up, on the same text, a bunch of non-identical interpretations (even if they may be quite similar in some shared contexts). The result of an interpretation cannot be unequivocally foreseen, because every reader approaches the text influenced by her/his/its previous experience ("organic memory"); he/she/it somehow understands the text even before starting reading; if not, reading would be an impossible task. Hence, something deeply interesting occurs during the process of reading. A text written as a string of letters is unequivocal, reproducible, unchanging. Transferred into the real world, however, there pops up — via readers — a great variety of interpretations, very often mutually antagonistic. For writing to have any sense, the community should achieve an agreement on how to read. In case of especially important texts the interpretation is even ordained by an authority — religious, political, judicial, scientific, etc. — and in such cases it resembles the program execution. Even in these cases, however, the consensus often will remain valid only for a limited period of time — no interpretation in natural language is unchangeable and eternal" (Markoš & Švorcová 2009, page 146-148).

7.4. Language games

At this point I would briefly mention the concept of *language games* designed by Ludwig Wittgenstein (1889-1951). In the second period of his philosophical career (after *Tractatus*), he turned away from the concept of logical atomism, where in respect to its usage, language functions on the basis of mere representation or correspondence, i.e. the basic building blocks of language (words, statements) correspond with the basic building blocks of the world (things and relationships among them). Elements of language simply and completely correspond with elements of our world; where there are gaps within this clear mapping, only pseudo-questions and pseudo-problems emerge (Peregrin 1998).

Similarly, in natural sciences there is also a strong precondition of structural isomorphism, particularly present within the neo-Darwinian paradigm concentrating on genetic programs (alleles), which determine the phenotypic traits of organisms. The frequency of particular alleles further determines the characteristics of a given population and its ecological footings ("selfish gene" and "extended phenotype" concepts by Dawkins 1976, 1982).

Later, in the second period of his intellectual journey represented by *Philosophical investigations* (1953), Wittgenstein realised that the relationship of representation or simple correspondence is not a natural makeup of language: it is rather only secondary characteristics of our language, it is a theoretical construct based on the primary level of language games. Thus the meaning of a word is not an object present in the world but rather its use in the language game[17].

In this sense we may say that our language is a code but the code table must have developed – and has been incessantly modified – first within the frame of our language games, our language praxis, in a way of constant bootstrapping (sensu Peregrin 2010 or Markoš & Švorcová 2009). The rules of usage are not primarily written in the code table, the code table is a secondary product describing the relationships of representation.

[17] It seems to me that Deely's suprasubjective relationship mentioned in footnote 9 is isomorphic to Wittgenstein's language game. Nevertheless, in my conception the being in the world of living organisms can be described by both of these philosophical conceptions.

Meaning is a role, way of usage, it is not formed by the relationships of representation itself, but by praxis, by implicit rules of our language games.

Analogically:

1) Living creatures of the natural world also act on implicit rules, constantly reinforcing their roles, strengthening ties by experience (as a metaphor for neural networks). Memory is primarily bodily, stored in an interactive network of rules, which are enhanced by learning, written in language representations that cannot be taken for granted and are rather a secondary, derivative result of lived experience and history. Their meaning is the result of negotiation, representing the explicit rules in the form of grammar rules (such as a code table). In this concept there are no code tables stored in our brains, just regularities, language games in Wittgensteinian sense. This concept considers evolution to be a genuine historical process and its players are not passive segments of chains of living moulded by their environment but individuals sharing mutual understanding, language, memory and experience. “Genetic programs” exist; but they are results of being in the world, not the primary condition of it. The interactions of all inhabitants in semiosphere are not deterministic, but semiotic, contextual and experience dependent.

8. Conclusions

The thesis is an attempt to explain how organic memory works on the level of organic development and how biological information (in sense of Bateson) can be remembered.

1) On the basic memory metaphors coming from different scientific branches, I showed some rather mechanistic and materialistic conceptions of memory which are essentially associated with notions of matrix, place, matter, catalogue or storage. On the other hand, some conceptions deny the concrete localisation of specific states and deny the character of memory being materially represented or stored.
2) By introducing the history of organic memory concept, my aim was to show that the idea of organic memory has its place in the history of natural sciences of the 19th century and that the interpretations of this phenomenon were very different: some biologist were not able to explain this phenomenon more concretely, attributing the faculty of memory to all organic matter (Hering 1897); and even attributing psychological features to the cells or memory particles (Hering 1897, Butler 1910). Others, inspired by physics or Cartesian doctrine, described memory as storage of traces or pattern of physical waves (Semon 1904, Rignano 1911).
3) The mentioned computer metaphor represents a prevalent view in understanding of biological phenomena, on the contrary hologram metaphor reflects some memory features which I highlight in my conception of organic memory: that organic memory is experience dependent, distributed throughout many levels of development (not relying on one specifically placed storage), and can therefore be regarded from more levels of description:
4) One level is genetic memory ("recorded memory" *sensu* Markoš & Švorcová 2009), stored in gene representations and changeable only via mutation; the next level can be distinguished as epigenetic one, rewritable and stored in modifications like methylation (of DNA and histones), acetylation, RNAi etc. Both of these levels form the *quasidigital* nature of memory engrams. The last level discussed is a bodily memory, which is activated after the period of the phylotypic stage and launches a species-specific and modular development. The main point of this work is to argue

that complete organic memory is not a mere mechanistic storage of representation and cannot be described from one level of permanent code; rather, it is bodily, radically distributed, and experience dependent and maintains the continuity of the species. Some experiences can be even forgotten or silenced for some period of time which is very analogical to our own natural language and lived experience.

5) The memory demonstrated in this thesis is primarily bodily, stored in the pattern of the interactive network of rules which are enhanced by every usage and written in cellular language, transmitted via characters and strings but interpreting these specifically, contextually and in a highly interactive way which cannot be reduced to some linear text of DNA. These networks are changing their pattern as a function of experience. Experience matters to intracellular processes; it is involving the facilitation processes stored in the specific memory of a species. Not the gene representation but its usage in different context, modules, or time and space is decisive.
6) As with Wittgenstein's conception of language games, not the object itself but its usage in a game gives a meaning to a word. The primary level of being in the world is the bodily experience, the ad hoc conditions and environment in which the organism lives; only this bodily level mediates its self via sign-mediated activity, via representation of genes, modifications etc., giving meaning to them in the constant game of language. The inscription of this experience into quasi-digital DNA strings or quasi digital modifications of proteins is secondary; it is a resultant level of description and "only" a level derived from the bodily one and not the causal condition of bodily development.
7) If we consider the genetic programs, we should not replace the formal language for the natural one. The natural language is a product of community of speakers, product of the natural world, where every member is already born to the pre-existing semiosphere. Formal language is always a reduction of a natural one; every inscription of the natural world into string of characters (i.e. into formal language) means certain loss of information (replaced by repetition and redundancy of information, Neuman 2008). Grammar is not meaning; it is the result of language negotiating and constant bootstrapping, taking place in the natural world. Similarly,

codes (habits or stabilized ways of *heterogeneous reproduction*) acting in what appears at first sight to be a rather deterministic manner are just such a result of evolved and negotiated heuristics. In my conception, organic memory is linked with sign-mediated activity, characters and strings of character are becoming sings when are manipulated in the natural world, i.e. in systems capable of interpretation, i.e., hermeneutic systems, where meaning involves contexts, history, memory, learning, and experience. Every formal language, programs, code tables are derived by the entities in command of natural language. Formal languages do not know any semiosis; interpretation, dependence on continuity of experience, environment and the community of speakers is the virtue of natural world and natural languages.

8) In contrast to characters, signs may dwell in both transcendental and real worlds, but their interpretation is always coupled to the real world: no interpretation is possible in the transcendent realm only. Signs can be used in both formal and natural languages (Markoš & Švorcová 2009).
9) There are no laws of nature, no code tables stored in our brains, only regularities, games of language (Wittgenstein 1998) and they need a memory continuum to be used again and again in next generations. This memory is not a simple deposit or storage of atomistic representations, its nature is primarily bodily and the information is distributed; it cannot be reduced to formal language of fixed code that depends on executing a program, because such a program is always "only" a derivative of a natural language, i.e. it was created by individuals (proteins, cells or humans) living in the natural world.

"Developing a consensus on how to read these codes is historical and based on the experience of a community of natural speakers… Although rules can be described by formal languages, these do not constitute natural languages. Just as there are no transcendental laws or rules of human language, biological codes are unlikely to depend on by a deeper formal language. Rather, just as in human languaging, biological meaning is extracted by natural 'speakers' who dwell in a historical world of bodily experience" (Markoš, Švorcová, Lhotský to appear in 2012, page 16).

As we pointed out, members of different species (i.e. cultures) treat almost identical scripts in ways that are shared across the group. It follows that the

understanding of a script cannot be reduced to the execution of a program, execution of some mere grammar rules, and most certainly not a passive crystallization of any kind. Every species is a culture (sensu Markoš 2002) and its language is its memory.

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10. Appendix

Publications:

1)Markoš A, Švorcová J (2009) Recorded versus organic memory: Interaction of Two Worlds as Demonstrated by the Chromatin Dynamics. *Biosemiotics* 2:131-149

Contribution:
The authors contributed equally to this communication. The conception of transcendent and natural world and reading versus decoding problematic was primarily introduced by Anton Markoš himself (Markoš et al. 2009).

2)Švorcová Jana (2012) The phylotypic stage as a boundary of modular memory: non mechanistic perspective. *Theory Biosci* 131:31-42

3)Markoš A, Švorcová J, Lhotský J (to appear 2012) Within the skin- and beyond" distributed knowledge in living systems. In: Cowley SJ & Vallée-Tourangeau F (eds) *Cognition beyond the Brain.* Springer

Contribution:
Jana Švorcová wrote some parts of the paper regarding the histone code problematic and ontogeny, but the paper is primarily work of Anton Markoš as a first author.

Confirmation of contribution of Jana Švorcová on mentioned papers:

Anton Markoš, August 2012 ..……

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ORIGINAL PAPER

Recorded Versus Organic Memory: Interaction of Two Worlds as Demonstrated by the Chromatin Dynamics

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Abstract The "histone code" conjecture of gene regulation is our point of departure for analyzing the interplay between the (quasi)digital script in nucleic acids and proteins on the one hand and the body on the other, between the recorded and organic memory. We argue that the cell's ability to encode its states into strings of "characters" dramatically enhances the capacity of encoding its experience (organic memory). Finally, we present our concept of interaction between the natural (bodily) world, and the transcendental realm of the digital codes.

Keywords Chromatin structure and dynamics · Natural and digital worlds · Creation and interpretation of codes

Introduction

Two different modes of semiosis can be distinguished according to Marcello Barbieri (2007):

1. In the frame of a system of "organic codes", semiosis comprises the trinity of sign, meaning, and code (and associated operations like coding and decoding, or deriving meaning). Codes have been enacted in history, and therefore they are *not* deducible from the laws of physics. However, once a code system comes into existence, it behaves deterministically and is fully comprehensible by the standard approaches used in (natural) science. The only enigma that evades scientific understanding, then, is the actual, contingent process, or event, that gave origin to the coding rules. This system of organic codes knows no interpretation: codes themselves are context-free; essentially, their *meaning* is a

Anton Markoš and Jana Švorcová contributed equally to this communication.

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question of decoding. Evolution of the system proceeds via adding new organic codes, and/or by building nested hierarchies thereof.

2. In systems capable of interpretation, i.e., hermeneutic systems, *meaning* involves contexts, history, memory, learning, and experience. Such systems are not directly accessible to scientific scrutiny; their study belongs mainly to the realm of humanities. The prototype here is the natural (vernacular) language, as well as human culture and history.

Heated discussions have debated for decades whether the phenomenon of life is fully comprehensible by scientific objective standards (point 1) — i.e., whether it can be accommodated and handled by biology, or whether life possesses also characteristics which go beyond the reach of science (point 2).

Biosemioticians who work on *scientifically* tangible problems assume, often silently, that the first possibility holds true, and thus that all phenomena of life can ultimately be reduced to semiosis of the first type. However, the second possibility may be no less justified. In Markoš et al. (2007, 2009) we proposed the notion of "Barbieri's platform" for a level of life organization where both approaches may meet. The platform can be climbed "from below", by assembling parts according to established organic codes (or grammars), or touched down from the heights of holistic sciences such as systems biology or hermeneutics. At this level, both tendencies are in equilibrium, or have equal rights, so to speak. The question remains whether such a platform is a realistic model or not. Here we attempt to demonstrate, with the example of chromatin dynamics, that it is indeed justified.

Codes Belonging to the Realm of Science

Two examples of scientifically manageable code systems are given in Barbieri (2003). The first is protein synthesis, where mRNA and polypeptide are not connected causally (e.g. by chemical correspondence); they correspond only via an established code, which is implemented by a set of adaptor molecules, the aminoacyl—tRNAs. Such machinery can be (at least for some proteins) assembled in a test tube; yet this is not a classical chemical reaction, as its components came into existence as a result of long evolutionary tinkering filtered by natural selection.

The second example of a coding system is provided by the rules that connect written and spoken word in any given language. Here, the alleged adaptors reside in the mind of the person who is fluent and literate in that particular language.[1]

The existence of a plethora of analogous coding systems has been proposed in living beings. The above examples introduce however a novel problem. The protein synthesis can be taken — at least at a first approach — as synchronous, i.e., performed by predetermined machinery: the decoding rules borne by adaptors are constant; their whole set is known, and present, from the beginning of the task; and

[1] Today, they can be realized also by computer programs transferring string of letters into sounds and even vice versa; such programs, of course, were created, and mirror what existed in the creators' minds.

the set of rules is manageable. In processes like cell differentiation or development (not to speak of language), however, the complexity grows with time: novel rules and novel adaptors appear, and the neat model becomes cumbersome, even unusable. Turner (2007) touched the point in comparing three systems containing signs, adaptors and outputs: (i) The red/green traffic signs will lead in any system acquainted with the traffic code (a driver, a schoolchild, a computer with appropriate sensors) to two possible outputs — stop or go. (ii) In protein synthesis, 64 codons constituting innumerable possible strings will be translated by some 45 adaptors into 21 outputs, also combined into innumerable incidences. (iii) But how to manage, asks Turner, the histone code in chromatin (see below), or processes involved in development, when the number of elementary inputs, outputs, and adaptors may go to hundreds or even millions, and all three sets may change in time? Why should we speak about coding when we can neither write down the table of the code nor quantify the number of components, and the rules of the system? How can any system memorize so many commands and shortcuts, and — even more important — how can it consult them in real time? Yet, attempts have been made to prove such a predetermined, synchronous superstructure of nested, overlapping codes in cells (see, e.g. Trifonov 2008; Popov et al. 1996).

Codes Enacted *En Passant*

Barbieri gives an answer by introducing the concept of *organic memory*, and illustrates it on the early embryonic development. Development starts with a hardwired (coded) program and proceed mechanistically up to the "platform" — the stage of the *phylotype.* Besides, the developing germ is endowed also with an *organic memory*, which may be taken for empty at the beginning. It takes inputs from the developmental program and from the environment, and ensures coordination of species-specific processes, thus increasing enormously the amount of information and interpretative rules, as compared with those available at the moment of fertilization. This "bootstrapping" between the program and the developing memory will — at the phylotype stage — lead to a takeover of the affairs by the memory.

Barbieri (2003) gives no clues as to the "reification" of the memory (or its parts). For our purpose here, we can identify it with somewhat vague concepts like "fine tuning", "setup" of the "living state". Actually, we shall take the memory for the very realm of semiotic and hermeneutic processes, and from *here* we shall try landing on the Barbieri's platform "from above": from the realm of historically established "cultural" conventions, which lend the mechanically erected platform a much subtler, ornamented, baroque, species-specific and individuum-specific pattern. It follows that the conventions established should be taken for fuzzy and malleable, language-like: it is here where meaning is generated, and the process cannot be — as in the case of codes — executed by machine-like contraptions, automatons. In Markoš et al. (2007) we argue that the organic memory is never empty; it comes with the bodies of the germ cells (and is, at least in part, contributed by the mother) and is really responsible for procuring the individual pattern (body) subject to natural selection.

The model of the "platform" can serve as a good heuristic tool for our understanding of life. In short: codes are hardwired, whereas semiotic processes "from above" mollify and adjust their impact, and extract a meaning (sensu 2) of the whole process. Codes and memories work *always* in tandem; *we never encounter a "read only" code, or an empty memory matrix.* Only in this way the massive parallel processing that is taking place in the body can be managed in real time. Let us now approach, with this concept in mind, the model case of chromatin.

The Structure of Chromatin and the Histone Code

Nucleosome

DNA in the eukaryotic nucleus is folded into a higher-order structure — the nucleosome (Fig. 1); and a major role in this folding is played by proteins known

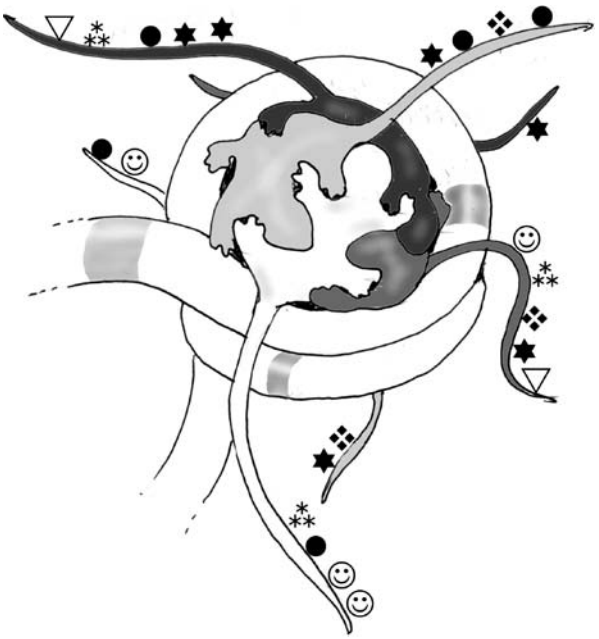

Fig. 1 A cartoon of the nucleosome (approximately in-scale). The "hose" represents DNA, wrapped to create a nest containing a "brood" of 8 histone proteins of four kinds. The pattern of marks on protruded tails of the histones is produced by a "zoo" of hundreds of protein species making up the chromatin ecosystem; other proteins can bite the marks off, or sink their teeth into them and remain stuck. The bodies of all proteins are, or may be, also decorated by similar marks. The result comprises the organic memory at this level of description: a huge, dynamic multiprotein complex around each nest (not shown). Three highlighted segments of DNA represent motifs attractive for yet other proteins; the assembly of such proteins will decide whether that particular area of DNA will be transcribed or not. Such an assembly is a part of, and its composition highly depends upon, the overall meta-assembly of the intracellular "ecosystem" of molecules

as histones. The nucleosome particle consists of 147 base pairs of DNA wrapped around a histone octamer core, comprising pairs of histones H2A, H2B, H3, and H4.

Each histone complex is linked (zipped) to DNA through zillions of so-called weak interactions.[2] The contact of histones with DNA is independent of the DNA sequence, i.e., any part of the long, linear molecule can be wrapped onto the structure. At this level of description, the main task of histone proteins consists in stabilizing the DNA molecule (6 billions of base pairs in a human nucleus) by condensing it into millions more easily manageable packages.

Besides this elementary "zipping" role, nucleosomes play a very important role in short-time and long-time regulation of gene expression, by controlling the recruitment of the protein machinery required for the process. First, the very arrangement of nucleosome units along the DNA strand decides accessibility of particular elements for that machinery; second, the fine tuning of nucleosome shape restricts or enables selective accessibility of the particular DNA segment for higher-order regulatory systems (for a review see Allis et al. 2007). This second function of the nucleosomes is attained by putting bookmarks ("bar codes") on histone tails, which stick out from the octamere core, and are thus available to inspection (or rather palpation) from outside. By their *reversible* chemical modifications, multifarious patterns will be induced in the histone backbone; in turn, the backbone will change its competence as to the shaping of attached DNA, and the docking of regulatory protein(s) present in the nucleus. Hence, selective combinatorics of histone modifications has far-reaching effects resulting in cell differentiation, tissue modifications and organogenesis, and in maintaining such states in a cell (or in a cell lineage) for long periods of time. Such modifications — epimutations — are responsible also for the highly flexible and dynamic responses of chromatin to external cues.

Epimutations

It is well known that a mutation in DNA resulting in a haphazard replacement of a single amino acid may introduce havoc in the resulting protein structure/function. Yet, in a strictly controlled manner, such replacements (like the above-mentioned "bar codes") are widespread at the level of "adult" protein molecules. The difference between both kinds of mutations is as follows:

(i) Nascent proteins are synthesized from a constant set of 20 amino acids according to a sequence code hardwired in DNA. If a mutation occurs at the level of the code, it cannot be detected and repaired, and it will yield misconstrued or truncated proteins forever.

(ii) Epimutations, in contrast, will change amino acid composition by *reversible* chemical modification of amino acid residues already assembled in translation. The effect is fully comparable to that of mutation, as can be seen in the two examples shown in Fig. 2. Thus, phosphoserine is an amino

[2] For non-biologists: "Weak", because they can be broken by mild treatment, like change of acidity, or elevated temperature.

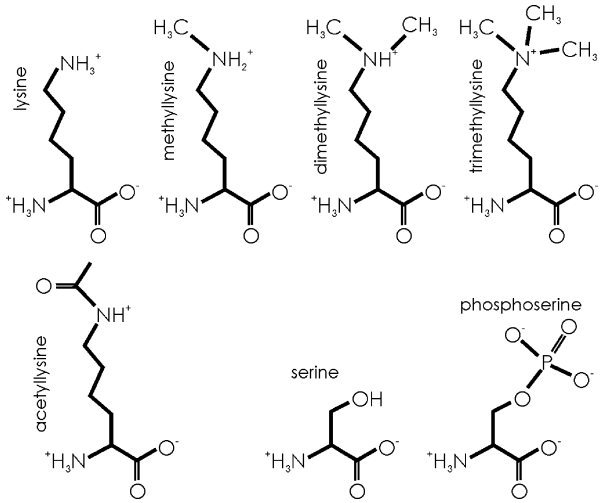

Fig. 2 Modifications (epimutations) of amino acids, as exemplified by lysine and its methylated and acetylated forms, and serine and its phosphorylated form. All such "mutations" of amino acids in a protein are reversible, provided that the cell expresses enzymes responsible for particular transformations

acid with properties drastically different from original serine (S); the same with many derivatives of lysine (K) residue, which can give rise to acetyllysine, mono-, di-, or trimethyllysine, hydroxylysine, or even can be coupled to whole *proteins*.

In a similar manner, almost all amino acid residues in a protein can be derivatized, often each sister copy (product of the same mRNA) differently: the uniform population of nascent proteins will soon give rise to a plethora (even dozens) of proteins differing in shape and hence performance. However, the instructions to introduce such specific modifications are not stored in any coded string. Epimutations result from the collective action of a protein "ecosystem" in any given compartment — the nucleus in case of histones.

Such modification marks may facilitate (or prevent) the binding of various classes of proteins, "readers of the code"; these in turn can recruit whole cascades of proteins bound to such already bound "adaptors", to become yet higher-order adaptors, etc. Their lifetime may be very short (seconds in case of the so called signal particles) or the process leads to the establishment of big irreversible complexes that literally "immure" long sections of DNA, even whole chromosomes.

Examples of Histone Marks

Most histone modifications known today were discovered in budding yeast (Liu et al. 2005), but information available from mouse or human models show that they remain very *conservative across divergent organismal lineages* (Bernstein et al. 2006). Let us illustrate the phenomenon on the protein histone 3, whose "tail" of 29

amino acids (out of about 220) serves as a board accommodating labels. The nascent sequence reads as follows:

```
....5....0....5....0....5....
ARTKQTARKSTGGKAPRKQLATKAARKSA
```

Below we give several hypothetical examples how such reversible chemical modifications of the sequence may look like:

```
AρTκQTARασTGGKAPRKQLATKAARμSA
ARTλQTARKSTGGKAπRKQLATKAARKSA
ARTμQTARλSTGGKAPRKQLAτKAARλSA
ARTKQTARKσTGGKAPρKQLATKAARKSA
ARTαQTARηSTGGKAωRKQLATKAARμSA
```

(α — acetyl lysine, η — hydroxy lysine, κ — monomethyl lysine, λ — dimethyl lysine, μ — trimethyl lysine, ρ — methyl arginine, π — hydroxy proline, ω — proline isomer, τ — phospho threonine, σ — phospho serine)

It is to be noted that:

1. Each such modification requires a specific enzyme, which, in addition, may be site-specific. This means that trimethylation of lysine 4 (K4) is carried out in three steps, by three specific methyl transferases; performing the same task with K27 may require a different battery of transferases. The resulting pattern of modifications thus depends on what enzymes are present in the set of proteins present at the time — it is "agreed" within such an "ecosystem" of proteins: negotiated, not encoded.
2. To keep modifications reversible, each modifying enzyme must be accompanied by enzymes with a reverse action (e.g., methylases, removing methyl groups).
3. The changes of shape brought to the protein by such modifications give rise to different shapes, hence very specific antibodies can be raised against each modification. This enables researchers to detect such variations across vast expanses of chromatin, and draw conclusion as to the state of chromatin in different parts of the genome, or in different cells.

We now approach an extremely important part of our explanation: the "bar codes", the "diacritics" of modified amino acid "characters", are reversible, i.e. they can be erased, edited, or rewritten. Protein epimutations can appear (and disappear) on chromatin *within minutes* upon arrival of a specific signal. Proof of the biological consequence depending on the individual combination of modification is, however, not always easy to provide and is often based on correlation: proving causality for a modification involves demonstrating that catalytic activity of the enzyme that mediates that modification is necessary for the biological response (Kouzarides 2007).

Examples of Epimutations[3]

Probably the best-known histone modification is methylation of lysine #9 on histone 3 (H3K9me);[4] in animals it will initiate a cascade of events resulting in attachment of dozens of proteins of so-called *Polycomb* group; this leads to tighter condensation and silencing of that region of DNA fiber (Giannis et al. 2005). Modulations like H3K9 and H3K27 are responsible for silencing of the chromosome X in mammalian females.

Three lysine methylations are linked with repression of transcription (silencing): H3K9, H3K27 and H4K20. But methylation H3K9 can be found also in transcriptionally active chromatin; in context with H3K4 and H4K20 it helps holding the chromatin active for transcription by binding of the chromatin remodeling complex (Margueron et al. 2005).

In general, three methylation sites on histones are implicated in activation of transcription: methylation of lysine #4 on histone 3 (H3K4), H3K36 and H3K79. H3K4me and H3K36me play also role in transcriptional elongation. However in budding yeast another exception can be found: methylation H3K4 is involved in DNA silencing (Bryk et al. 2002). The location of such a modification is also important: H3K36me has a positive effect only when on the coding region, and a negative one on the promoter (Vakoc et al. 2005).

Existing modifications may promote further labeling: thus phosphorylation of H3S10 facilitates H3K9 and H3K14 acetylation and thereby inhibits H3K9 methylation (Giannis et al. 2005; Kouzarides 2007). H4K20 methylation and H4K16 acetylation were found to preclude each other (Allis et al. 2007). Trimethylation of H3K4 requires ubiquitylation of H2BK123 and reversely deubiquitylation of H2BK123 leads to trimethylation of H3K27 (Schuettengruber et al. 2007).

Binding of a protein could also be disrupted by a subsequent histone modification: H3K14 acetylation accompanied by H3S10 phosphorylation will dissociate *Polycomb* group proteins from methylated H3K9 (Fischle et al. 2005).

Identical modifications, even in the same region of chromatin, may not necessarily lead to the same output: their context and position is crucial here.

Histone modifications represent part of the cellular epigenetic memory, i.e., information that must be built up in ontogeny and is heritable through the cell lineages. Many cellular phenotypes are transmitted and maintained in this way, including genomic imprinting, X chromosome inactivation, heterochromatin formation or gene silencing, or the expression state of Hox genes involved in

[3] Non-interested reader can skip this section and proceed to the next part (Two worlds).

[4] Glossary: H for histone — H3 in our example; K is the abbreviation for amino acid lysine — K9 means lysine residue in position 9 of the histone protein chain (similarly, e.g., R17 is arginine in position 17); "me" is an abbreviation for a methyl group; if more methyl groups are attached, the number will indicate how many, e.g. me2. Examples: H2BK123uq — histone 2B ubiquitylated at lysine in position 123; H3S10p — histone 3 phosphorylated on serine residue in position 10.

specifying cell identity along the axes of segmented animals (Kouzarides 2007; Schuettengruber et al. 2007; Costa 2008).

How Does the Memory Manipulate the Code?

Bernstein et al. (2006) detected the so-called bivalent DNA domains in mouse embryonic stem cells. Such domains (residing mainly in the promoter region of given genes) contain both activating and repressive modifications of histones (for example H3K27me3 is implicated in chromatin silencing, whereas H3K4me3 in its activation). Transcription factors that control certain differentiation processes are in this manner kept in a poised, low-level expression within embryonic stem cells. When cells differentiate, the bivalent domains tend to switch either towards the repressive H3K27 state, or to the activating H3K4 modification.

Also in the case of Hox genes the active state is typically distinguished by continuous stretch of di- or trimethylation of H3K4 in the surrounding chromatin, whereas silent genes are marked by trimethylation of H3K27 (Swigut and Wysocka 2007). Specific demethylases are involved in switch from silencing to activating marks during activating of Hox genes expression (Lan et al. 2007). By contrast, monovalent domains (promoters with mark H3K4me3) are associated with the so called "housekeeping" genes (genes of basic functions-replication, transcription, metabolism) (Mikkelsen et al. 2007).

Polycomb and *Trithorax* Complexes and the Cell Memory

The *Polycomb* and *Trithorax* group of proteins belong among key regulators in defining cell identity in eukaryotes. *Polycomb* genes encode a group DNA-binding proteins, histone modifying enzymes, or chromatine repressive factors with affinity for H3K27me3 (Kingston and Tamkun 2007). H3K27 trimethylation is often distributed over large chromosomal domains, sometimes covering hundreds of kilobases (i.e. thousands of nucleosomes in a row), which might provide the basis for epigenetic inheritance of *Polycomb*-dependent silencing during cell division (Schuettengruber et al. 2007). These proteins control the silencing of target genes (e.g., chromosome X inactivation, repressing the Hox genes activity). One group of *Polycomb* proteins components has a histone-modifying function (methylation of H3K27 and H3K9), whereas the others bind to these modifications and change the chromatin structure. In *Drosophila*, mouse and human the H3K27me3 is highly correlated with binding of *Polycomb* group proteins (Schuettengruber et al. 2007).

Products of *trithorax* genes exhibit the opposite activity — they are transcriptional factors or chromatin-remodeling enzymes, which are involved in maintaining the chromatin in an active state (via methylation of H3K4). *Polycomb* and *trithorax* complexes are highly evolutionary conserved; they are supposed to be crucial for the cell differentiation and cell fate plasticity. But they represent only the tip of the iceberg — of massive parallel processing of proteins in chromatin domains, on million of nucleosomes contained in it.

The lesson from our histone inquiry is that various kinds of "bar codes" inscribed onto the protein molecule during an individual's life are not inherited in a ready-

made state: they come into existence by bootstrapping processes between the hardwired genetic message and the organic memory of the body. Hence, the buildup of organic memory (*sensu* Barbieri) is accompanied by "taking notes" in the form of a sequence of modifications — epigenetic counterparts of inherited informational molecules (codes).

The fact that such quasi-digital texts can be created — written and edited — during the lifespan of an organism, is the central starting point for our further investigation.

Two Worlds

Our model example invites an extremely interesting question concerning the relationship between the natural world and the world of digital coding. A comprehensive study in this area was provided by Emmeche and Hoffmeyer (1991); here we try to develop their views further, by distinguishing between the real and the transcendent world, their roles for living beings, and their "ontological" status.

Before we start our investigation, however, a terminological insertion is necessary, to avoid shaggy interpretations of terms which have been in use, literally, for ages. We need to distinguish clearly between *characters, signs, and symbols*. Our division is not original and we not pretend introducing a new, or correcting some of older systems: we simply need to clarify our usage of terms.

(i) Character (digit, mark, tag) is a member of some finite alphabet (or table), and its *single* qualification is its *position* (its coordinate) in the given alphabet (or table). Characters have no meaning except (i) their *membership* of the set, and (ii) their *position* in that set; they are *neither* signs or symbols. No additional member may be inserted between two alphabetical places (no position left in between), and no transition characters (e.g. half U, half V) are allowed; the character is *absolutely unmistakable* among the other digits of a given alphabet. Thanks to this, it can be copied, and distinguished in a string of characters with absolute accuracy.

Characters dwell in the *transcendent (virtual) realm* (see below and Fig. 3): only here they retain their clear-cut definition, and can be lined up into strings which can be copied, ideally, i. e., without errors. As to their *appearances*, i.e., the images that they assume in *our natural world*, these are absolutely arbitrary as soon as their alphabetic coordinates are known. The string

"This sentence is a string of characters."

remains the same when put in italics:

"This sentence is a string of characters.";

in courier:

"This sentence is a string of characters.";

or in Morse:

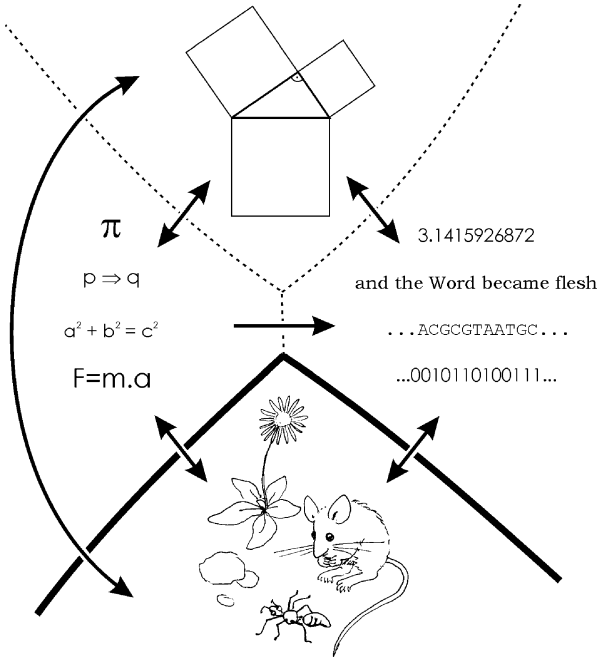

Fig. 3 The two worlds. The domain below the thick line represents the natural world, with its living beings and inanimate objects, languages, games, and history, all in endless becoming and extinction. The domain above is the transcendent world, subdivided to fit our text. The uppermost part represents the world of ideas, geometry, mathematics, logic, and all non-alphabetical scripts and symbols; here also dwells God of those religions which are based on Torah. Its items can be "zipped" into linear strings of *alphabetic* characters, which can be manipulated according to pre-established rules (left). Alphabetical strings, however, may exist also on their own, as singular, nominable entities (right). The items of sub-domains can be interchangeable, but their interpretation is always bound to the world natural

If such a string carries some meaning (in this case for people who speak English), the meaning remains the same upon such transformations, but transformations pay no regard to meaning. To illustrate our point: where Cowley (2008, 321) gives the scheme

adaptor (e.g. Morse) → process → output (e.g. English)

we prefer a reading:

string (English alphabet, Morse font) → click → string (English alphabet, some other font).

The same holds for the Morse-Latin example of coding-decoding provided by Barbieri (e.g. 2003, 93).

The strings of characters may bear no meaning in whatever language, yet *their mutual transformation will proceed correctly*, provided the code is supplied. It should be also stressed that natural language is in no way *produced* by constructing such strings of characters; on the contrary, *some* aspects of language can be mapped on such strings. Only formal languages, i.e., those *created* by humans, can be developed "from below", by starting with strings and a formal grammar.

(ii) A sign (representamen, synthema) will be taken in the ordinary usage: as something standing for something else, in a given frame of contexts. In the frame of naval codes, SOS stays for "help"; in the genetic code AUG means "methionine"; for liver cells, insulin means "take up glucose from the bloodstream"; in the Highway Code an inverted triangle means "yield"; in the world of a hunter a footprint means "game". Words expressed in a given language are signs as well. In contrast to Characters, Signs may dwell in both transcendental and real worlds, but their interpretation is *always* coupled to the real world: *no interpretation is possible in the transcendent realm only.* Signs can be used in both formal and natural languages.

(iii) A symbol (omen) is reserved only for entities loaded with a long cultural, historical, religious, etc., tradition. The meanings of symbol may keep a whole community together, without long deciphering and explanations. Examples: national flags and anthems, the Christian cross, the Red cross, etc. It follows that we can speak about symbols only in connection with natural languages, and we shall not use the term here.[5] In connection with our casuistry, we shall try to stick to the proposed terminology, in order not to use the same term in multiple contexts (like, e.g., in a recent article by Pattee 2007, where "symbol" is used in several meanings, not easily discernible from each other).

Transcendent and Natural

In Fig. 3 we propose an existence of two worlds: the natural world we live in, and the world transcendental, in a Platonic sense, an ideal "otherworld". For the sake of our discussion, we invite the reader to consider the divide between them to be as sharp as possible.

The domain below the line represents the natural, bodily world of cosmos, life, events; the world of our experience where we feel at home. Here, things may be similar, but *never* identical; they cannot be copied, only imitated. Any attempt of digitalization in the natural world is only approximate, hence error-prone. Life, natural language (including its possible analogues in non-human species, cells, etc.) is the product of this natural, or bodily, world (Markoš 2002; Cvrčková and Markoš 2005).

The uppermost domain of our scheme is the ideal world of geometrical objects, ideas, mathematics and logic; entities that behave orderly, much more obediently than those of the natural world. The ideal world does not fill any place in our world; it is a transcendent world, *invented* apparently by the Greeks at the dawn of Western civilization, and cultivated ever since. In the following centuries, people found that

[5] Note: the same appearance may play a role in all three contexts. Hence, Ω is (i) last character of the Greek alphabet, (ii) a sign for the unit of electric resistance (ohm), and (iii) a Christological symbol in theology; similarly "666" is (i) string of three digits, (ii) a sign for a number (with a meaning, in a decimal system, "six hundred and sixty six"), or (iii) a symbol in Kabala and in apocalyptic mysteries. A reverse path is not possible: obviously the Christian cross does not belong to any alphabet, so the character "+" (plus) belonging to the set alphabet of arithmetic digits, has nothing in common with Christian symbolic.

knowledge invented in the transcendental domain is endowed with the power to influence the course of our natural world, and hence can be useful.[6] From such positions, it is easy to adopt a belief that the world is actually *ruled* by this transcendental realm — be it laws of God or, in our days, laws of Nature.

Ideas and philosophical systems were recorded in stone, papyrus, parchment, or paper using alphabetic *characters*, an invention and heritage of Semitic cultures. Apparently alphabetic characters were not invented to record utterances; soon, however, they were adjusted to communicate also language expressions and numerals. Much later, modern science came to the astonishing discovery that the entities of the transcendental realm — ideas, geometry, math, etc., — can all be reduced to a common denominator, i.e., to strings of alphabetic characters. This means that the transcendent world can be communicated to the real world via strings and decoded there, to influence the behavior of the material world. In reverse, experiences gained in the world can be frozen — mapped into such strings.

This brings our attention to the domain in the middle of our scheme (but still safely on the transcendent side of the line). It represents the space of such character strings: virtual, devoid of any sign of bodily existence, digital and accurate. Here they can be copied and trans-coded into different alphabets with an utmost accuracy (never attainable in the real world).

For our purposes, the subspace of strings is subdivided into two parts. We start our examination in the left one, in the realm of mathematics and logics, analytical geometry, ballistic curves etc., the realm of "natural laws"; note that we place *natural* laws *outside* nature, in the transcendental. Analytical geometry, logics, mathematics etc. found their refuge here, neatly expressed in a linear sequence of marks. Here science was born and here she has her seat, here she construes theories, paradigms and hypotheses. This is the space that allows for generalization: the calculation of force from mass and acceleration is universal, the function contains virtually *all* possible combinations of these variables, given initial and boundary conditions; the Pythagoras' theorem is valid for *all* right-angled triangles in a Euclidean space, etc.

An important note: the realm can exist *only* because of its interaction, across the barrier, with the natural world. Only from here, meanings come for all virtual contraptions encountered, only from here the initial and boundary conditions are provided; without such an interaction we would be left with a kind of plain algebra (but even here the *rules* must be delivered from the natural world).

Science gains its calculations and hypotheses here, in the transcendent realm, and takes them across the barrier, to the real world, to test them. To do so, it is necessary to create a kind of interface — an artificial world-in-between — embodied in laboratory models: bodies falling in a vacuum, particle colliders or specially constructed cultures of organisms and cells, or models run on computers. If such models behave according to the expectations of the theory, the scientist leaves the lab and starts to examine the external world, where no vacuum exists, forms of life are "wild", logical theorems do not represent the highest commandment, and

[6] Up to the point that virtual realms are considered better, flawless, and more logical when compared to the world of our everyday lives. Such views resulted in a gradual development of contempt to the bodily world.

digitalization is possible only to a certain degree (quasi-digitalization, see below). If the world does not behave, it means that there is something wrong either with the theory, or with the testing procedure; then the scientist meekly returns to the lab and starts polishing both. Or she postulates additional factors teeming in the world but not taken so far into consideration by the model; after all, *real* falling bodies experience friction; wild organisms are more inventive than tamed laboratory strains, etc. In this way, with the highest carefulness, we scientists cross the barrier between the two worlds many times. If we keep in mind that one of them — the virtual one — is nothing but *our* construct (built on assumptions pronounced, learned, or silently adopted without much contemplation); if we are aware that testing is performed on artificial fragments of the real world stitched to fit our models; if we realize that the path from the model to reality is dangerous and must be taken with utmost carefulness, then the world will cooperate, will yield to our intrusions and will allow constructing artifacts never seen before — say a liner or a microchip. (Remark: An attempt will be made below to subsume under "we" not only scientists, but all living beings.)

Anyway, the astonishing facts is that the barrier is penetrable, that we can gain inspiration in both worlds, and even state that our virtual constructs — displayed as string of characters — can encode certain properties of the real world. Even more, the world will *obey* rules constructed in the virtual realm. There are many, however, who tend to forget about the real world and to enthrone their virtual construct (objective reality) in its place; some even insist that the virtual realm has existed from time immemorial, and the real, bodily world depends on it. In a way, such a stance is comfortable: if something has existed "from the very beginning", it is always the same and obeys identical principles in all places. If so, the history of such a world is not due to fate; it is, instead, governed by *chance and necessity*; either strictly prescribed, or a matter of drawing from the wheel — of ready-made, ever-present scenarios. Many scientists would endorse this last view — of the body turned into a pure code.

Now let us shift our attention to the right part of the digital realm in Fig. 3. Here strings constructed from alphabetical characters are dwelling, but no meaning is attached to them. Let us demonstrate the difference between the two areas of the digital world on an alphabet consisting of five positions: [a], [F], [m], [x], and [=]. The right part allows writing any possible strings, like "==xamaFFx", "FFFFxm=aa", or "aaaaaa"; they may be arbitrarily long, and any combination of characters is allowed, there is no rule or prescription how to compose a string. If we have a string "FFFF...", we cannot guess which digits will come up on the 5th position — we should simply look. No generalization is possible here; strings are nominable transcendental entities (see Barbieri 2007 on such *nominabilia*). It remains to say that the characters of all such alphabets can be reversibly trans-coded into strings of mere two signs of a binary "alphabet" (usually writ as "0" and "1"), i.e., into strings of binary characters.

Meaning and the World of Strings

Our principal thesis is that *strings may acquire meaning only when confronted with the natural world*. If we return to the left part of the digital realm, here we also

encounter strings of alphabetic characters, but *now* we realize that the strings are not arbitrary — this is because here *strings became signs* — they are connected with *meaning*: installed, however, from behind the barrier, from the natural world. To continue with our example, let [a] designate acceleration, [F] force, [m] mass, [x] is the operator "times" in multiplication, and [=] is the sign for equality; moreover, we define the boundary condition and note that we are in the realm of Newtonian mechanics, and use an algebraic notation allowing commutative rules. Suddenly it turns out that only four strings are *allowed* under such conditions, each of a length 5: F=axm, F=mxa, axm=F, mxa=F. Meanings and the framework of boundary conditions drastically reduced the number of possible sequences. This is the reason why, in our scheme, the arrow between both areas of the virtual realm points only in one direction: mathematical and logical formulas, sentences and lemmas *can* be written as a sequence of characters, but strings of digits *cannot* be reduced to mathematical or logical formulas: each such string is unique, and we cannot do more than to *name* it. This can, again, be done only by bestowing the strings with meaning, and meanings (and thus reduction of degrees of freedom in writing) again can enter the digital world only from the natural world: directly, or via the virtual world of ideas. To write them down, we only borrowed the specific marks of some alphabet and put them down into a specific sequence. The nominal realm of strings has also a direct access to the natural world, and the interface, crossing the boundary from *here*, may hold the clue to the mystery of life.

Number, Program, Text: Decoding vs. Reading

The space of sequences (for the sake of simplicity let's suppose that they all come in binary form) may influence the natural world in three extremely interesting ways: strings may come up as *numbers*, *programs*, or *texts*.[7] It is not trivial to distinguish in which way a string should be interpreted in the real world. In principle there can be two categories of entities (i) a coder/decoder (or "codec")[8], and (ii) a reader able to extract meaning from a string when it (she, he) takes it for a text.

It is in the powers of a reader to switch into the codec regime, but a codec can never "decide" to become a reader — it has no clearance for such a decision. The difference is that decoding proceeds in formal language, reading in natural language.

Program Execution (Formal Language)

As mentioned above, the coding/decoding device must dwell in the natural world, and the string must be delivered to it on a suitable *medium*. For a computer it may have the form of irregularities on a magnetic disk, for its processor it is a succession of electric impulses, for the punched-card reader it is a difference hole/non-hole, for a ribosome the sequence of triplets on mRNA, etc. However, by inscription into a

[7] But note that the communication between the transcendent and the real is *not* restricted to digital channels operating with strings of characters.

[8] We prefer "codec" to Barbieri's (2003) "codemaker", which means roughly the same but raises misleading association with some maker, or creator of a code.

medium, the characters cease to be absolutely digital: not always can they be distinguished unequivocally.

We call such material embodiment of string sequences *quasi-digital*. It follows that they can be neither copied nor trans-coded infallibly:[9] they are prone to mutations — i.e. misreading and mistranscription of their quasi-digits, confusion with a different character of the alphabet, etc. But it is not our task here to discuss the problems of digitalization, i.e., smuggling ideal digits into the quasi-digits of the real world. What is more important:

(i) A formal language necessary for program execution was derived (created) by entities in command of natural language. Formal language is defined as a set of character strings, and operations upon them (Searls 2002).

(ii) A non-living device, a machine, will suffice for the task of scanning and executing — thoughtlessly, mechanically. As a drastic example take a missile heading towards its target. In other words, formal language is a domain of trans-coding between virtual strings; *but the trans-coding program (rules) comes from the natural world, from entities with the command of natural language*.

(iii) A virtual string of marks, when embodied into a suitable medium and scanned by a suitable device, can influence the behavior of the world.

(iv) The question of the maker who constructed the device and wrote the program in a formal language is easy to answer for man-made machines, but enormous problems arise when contemplating self-reproducing automata (for a discussion, see Pattee 2008). Should we consider living beings as such automata (without adopting the creationist worldview), their coming into being, and evolution, remains an enigma, even though reasonable scenarios had been proposed for the program-first as well as device-first alternative evolutions (see. e.g. Cairns-Smith 1982, 1985, and Kauffman 2000, for respective possibilities).

But the most important, and perhaps most controversial, statement of our analysis is this:

(v) *Formal languages, as known today, do not know any semiosis — they work on the level of codec. Interpretation is the virtue of natural languages.* For the sake of sharpening our vision of the problem we stick to this statement, even if we are fully aware that linguists, philosophers, and scientist are not united over the problem.

Reading (Natural Language)

To perform reading, a mere device is not sufficient. Reading is a semiotic and hermeneutic task and requires a *community* of living beings (humans or, as we

[9] Actually, copying, i.e. production of identical entities, is *not* possible in a real world: here no two things are identical — only similar; similar *according to* some criteria.

believe, all living beings, or cells, or even protein ecosystems in case of some texts) — anchored in *language*, *culture*, *ecosystem*, *history*. Natural language is a product of a long evolution of such a community of speakers, and can be taken as a field (potential), from which individual speech acts (expressions) unwind, and understanding is negotiated. Hence, *natural language is a phenomenon of the natural world that cannot be transferred into the transcendent realm, and even less can it be reduced to digits.* We devote a parallel paper to the language metaphor of life; here we list only a few comparisons that highlight the difference between program execution and reading.

(i) A natural language cannot be produced from scratch, unless we envisage a creator speaking a meta-language (compare with formal languages); a community of speakers, and historical continuity of such a community in time is required.
(ii) Communication in language proceeds in utterances, which — in contrast to language itself — *can* be parsed, with some reserve, to linear strings of quasi-digital units (morphemes); *grammatical* rules concerning groupings of morphemes can be derived for any given language.
(iii) To produce speech acts (speaking or writing), speakers are required who are *not* machines; similarly, to perceive the message, i.e., to accomplish understanding, living interpreters are required who are *not* machines;
(iv) The quasi-digital nature of strings of morphemes allows, with some reserve and with established rules, to *map an utterance in a form of a character string*. By this *artifact making*, the utterance can be saved in the transcendent, atemporal world of characters, and copied infallibly. Artifact-making needs life (Barbieri 2007); life dwells in the real world. As in case of formal languages, strings can be "materialized" by embodying them into a suitable medium (like print on paper, or a file on the hard disk); as in the case of formal languages, the copying of strings and their embodying can be performed by machines.
(v) Reading such strings requires literate speakers in natural language who are able to transform them back into real-world utterances (spoken or not), in order to understand them.

Whereas a codec will supply a single, deterministic "execution" of a given string, leading every time to identical "interpretative" result, semiotic and hermeneutic abilities of living beings will conjure up, on the same text, a bunch of non-identical interpretations (even if they *may* be quite *similar* in some shared contexts). The result of an interpretation cannot be unequivocally foreseen, because every reader approaches the text influenced by her/his/its previous experience ("organic memory"); he/she/it somehow *understands* the text even before starting reading; if not, reading would be an impossible task. Hence, something deeply interesting occurs during the process of reading. A text written as a string of letters is unequivocal, reproducible, unchanging. Transferred into the real world, however, there pops up — via readers — a great variety of interpretations, very often mutually antagonistic. For writing to have any sense, the community should achieve an agreement on *how* to read. In case of especially important texts the interpretation is even ordained by an authority — religious, political, judicial, scientific, etc. — and in such cases it resembles the program execution. Even in these cases, however, the

consensus often will remain valid only for a limited period of time — no interpretation in natural language is unchangeable and eternal.

Conclusions

If it is true that information flow and inscription/reading constitute the principal distinctions of life, as we believe, we need to suppose that language-like properties exist at various levels of life's organization. Such a conjecture requires the following points:

(i) The presence of a community of speakers, whose historical continuity in time is ensured by "material" (natural) perpetuation (many generations, long periods of time) of individuals, be it cells, community of cells, individuals in a species, ecosystems, cultures, etc. In our example, it is the network of proteins, which is the heir of such an uninterrupted tradition, and has its ways about how to read, as well as to put down, quasi-digital "notes" on media like DNA and histone molecules. In reference to Fig. 3, such "speakers" are limited to the realm of digital string — we do not pretend their inventing mathematics, logic, or even ideas and God.

(ii) As in spoken language, "utterances" can be put into one-dimensional form, and be quasi-digitalized. Such strings of quasi-digital units can be parsed and analyzed by methods developed by linguistics; in this way, science can decipher grammatical rules of processing, which constitute the background in most signal-processing units (second messengers, tags on DNA, on histones, or on other proteins of signaling cascades, etc.).

(iii) All processes of taking notes and bookmarks, as discussed above, can be taken as speech acts (speaking or writing) accomplished by speakers who are *not* machines;

(iv) The quasi-digital nature of linear (in sugars also branched) aperiodic biomolecules is a characteristics which does not need any comment. What *does* need a comment, however, is the question of the order of events; many authors prefer the primacy of spontaneous origin of "written" macromolecular strings; in such a case the whole edifice of this paper would be in serious difficulty.

(v) Reading such strings requires speakers in natural language: such features are best demonstrable in the science of evo-devo: they show that a limited genetic toolkit is sufficient to erect all existing animal body plans (e.g. Carroll 2005; Carroll et al. 2006). In our wording: every species has its own hermeneutic rules of meaning-making.

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ORIGINAL PAPER

The phylotypic stage as a boundary of modular memory: non mechanistic perspective

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Abstract The concept of the phylotypic stage has been strongly integrated into developmental biology, thanks mostly to drawings presented by Haeckel (Anthropogenie oder Entwicklungsgeschichte des Menschen, 1874). They are printed in every textbook as proof of the existence of the phylotypic stage and the fact of its conservation, albeit many times criticized as misleading and simplifying (Richardson in Develop Biol 172:412–421, 1995, Richardson et al. in Anat Embryo 196:91–106, 1997; Bininda-Emons et al. in Proc R Soc Lond 270:341–346, 2003). Although generally accepted by modern biology, doubt still exists concerning the very existence or the usefulness of the concept. What kind of evolutionary and developmental horizons does it open indeed? This article begins with the history of the concept, discusses its validity and draws this into connotation with the idea of a memory activated throughout the development. Barbieri (The organic codes. An introduction to semantic biology, 2003) considers the phylotypic stage to be a crucial boundary when the genetic program ceases to suffice for further development of the embryo, and supracellular memory of the body plan is activated. This moment clearly coincides with the commencing of the modular development of the embryo. In this article the nature of such putative memory will be discussed.

Keywords Phylotypic stage · Zootype · Supracellular memory of the body plan · Modularity · Developmental pathways · Walter M. Elsasser · Semiosis

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Introduction

Inspired by Darwinian teaching, Haeckel (1874) furthered the idea into the so-called basic biogenetic law (*phylogenetisches Grundgesetz*), asserting that ontogeny recapitulates phylogeny of a given lineage in an abbreviated and rapid way, i.e., embryonic development of an individual organism passes (in an abridged form) along the same path as did its species in history. Thus, a human being starts as a single cell and then proceeds through the stages of coelenterate, planarian, fish, saurian, primitive mammal, and ape, with higher, i.e. phylogenetically later stages, becoming more and more prominent (Haeckel 1874). All species-specific differences appear at later stages of developmental sequence. The biogenetic law was later disproved, and contemporary models are safely rooted in the insight of Baer (1828) who supposed the early stages of the development to be more similar than the later stages because of their homogeneity, not because of the fact of recapitulation. Baer (1828) was the first to recognize in vertebrate development a stage common to all classes. This led him to the formulation of his *ontogenetic law*: in embryonic development, general features precede special ones; *development proceeds from undifferentiated homogeneity to differentiated heterogeneity* (Gould 1977).

For a contemporary biologist, the phylotype idea is connected with *the hourglass model* designed independently by Raff (1996) and Duboule (1994) as shown in Fig. 1; the name "phylotypic stage" comes from Sander (1983), and such a stage has so far been described for annelids, arthropods and chordates (Bininda-Emons et al. 2003), and it has been known by several names, like *pharyngula* (after the pharyngeal pouches, Ballard 1981) or *tailbud stage* (Slack et al. 1993) in vertebrates, and the *germband stage* (Sander 1983) in the development of

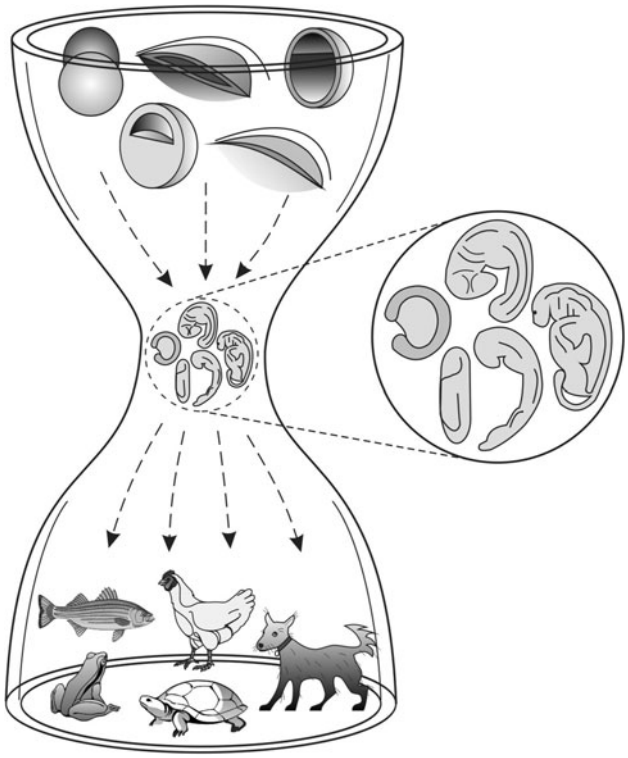

Fig. 1 The hourglass model. The developmental pathways leading to and from the phylotypic stage are quite different (even among closely related taxa), and the morphological similarity is the highest at the period of the phylotypic stage. After Jody F. Sjogren (2000)

insects. It was also already emphasized by Sander (1983) in case of arthropods that early developmental pathways leading to the phylotypic stage are highly variable even across closely related taxa. For simplicity, I focus in this article only on the vertebrates.

Characteristics of the phylotypic stage

The main differences in the early developmental periods of vertebrates generally depend on differences of cleavage, and they may exist between the taxons (meroblastic cleavage in birds, reptiles, and fishes; holoblastic cleavage in amphibians; mammals constructing a blastocyst, chorion, and amnion) or even within the same taxon (holoblastic and meroblastic cleavage in different groups of fishes). They may depend on the amount of yolk, and also on types and timing of the body axe and germ layers setup (Slack et al. 1993; Gilbert 2003; Steinberg 2003). Such differences are most probably caused by adaptation of distinct life forms to various environments—or simply they resulted from historical contingencies. Only later, after gastrulation, all the members of the same *phylum* enter the conservative period in their development during which they most resemble each other: their phenotypic divergence

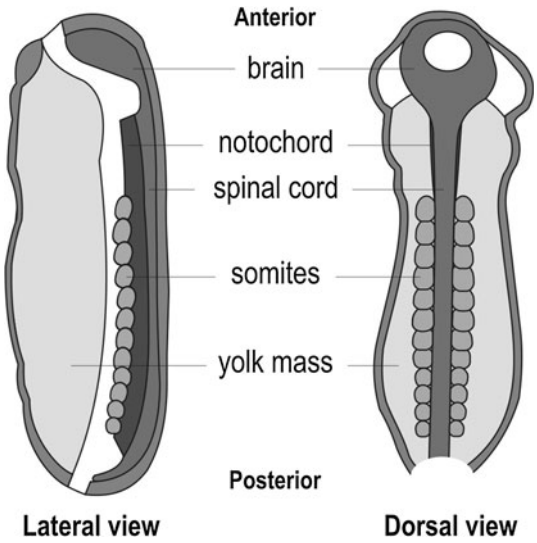

Fig. 2 The vertebrate phylotypic stage. Here, the main morphological characteristics of the vertebrate phylotypic stage are depicted (pharyngeal pouches, heart, and optic anlagen are missing)

is highly reduced, just to the point when they drastically start diverging again in subsequent development. Owing to the low phenotypic divergences in the phylum, this period is supposed to be highly evolutionary constrained (Slack et al. 1993). The hourglass model is nowadays very common, although some scientists consider the metaphor misleading or even invalid[1] (Mitteroecker and Huttegger 2009).

The morphological structure of the vertebrate phylotypic stage (i.e. the *pharyngula* or tailbud stage) is characterized by the presence of the neural tube, notochord and somites, the head with pharyngeal pouches, heart and optic anlagen and, of course, the tailbud (Richardson 1995, 1997) (Fig. 2). The phylotypic stage starts with the process of neurulation and ends when the somites are developed (Galis and Metz 2001). Wolpert (1991) considers as the most conserved period of development the early somite stage just after neurulation. For Duboule it is the period between the head fold and tailbud stage (Duboule 1994).

Slack et al. (1993) went even further: they first recognized a coupling of the phylotypic stage with the anteroposterior expression pattern of a set of specific orthologous genes. The most characteristic genes of this group are represented by the batteries of *Hox* or homeotic genes, very

[1] The authors argue from the perspective of geometric morphometrics with the impossibility to find any quantitative measure how to compare the similarities among organisms passing through the blastula stage and the phylotypic period. The differences among organisms before and after the phylotypic period are supposed to be higher- but the same measures cannot be defined for all compared species: some of the variables are not defined for all species involved; some traits at later stages are too complex to compare between each other, like the human lips or the bird's beak etc.

conservative across the phyla, and present in a broad variety of organisms like insects, nematode, amphioxus, or sea urchins. *Hox* genes probably existed in the common ancestor of *Cnidaria* and *Bilateria* (Ferrier and Holland 2001). On such a basis, they were able to unite almost the whole animal kingdom under the common concept of *zootype*. Therefore, the zootype as a genetic pattern is formally superior and evolutionarily older than the morphological structure of phylotype. (Fig. 3)

Hox genes activate or repress batteries of downstream genes by binding to DNA sequences in *Hox*-response enhancers (Pearson et al. 2005), but they can also control other executive genes. The *Hox* genes are organized in clusters, and their supposed evolution proceeded via duplication of these clusters (vertebrates have four such clusters). Their main function is the determination of the embryonic regions along the anterior–posterior axis and the specifying of the particular *identity* and *relative position* of a given structure (Slack et al. 1993). Later in development, the expression, and function of *Hox* genes they also act as region-specific selector genes in diverse structures and tissues (Caroll et al. 2006). In addition, they play a role in cell division, cell death, and cell movement (Pearson et al. 2005). Mutation in homeotic genes may lead to morphological defects or homeotic transformations (Davidson 2006). Note that *Hox* genes are best known, but by no means they are singular example of selector genes playing a crucial role in development. Slack et al. (1993) describe the phylotypic stage not only as a defining platform for an individual body plan but also as a link of this body plan to the whole animal phylogeny.

Does the phylotypic stage exist?

Richardson (1995) denies the existence of the phylotypic stage, arguing that such a "constant" must have become blurred by the plentitude of evolutionary shifts in developmental timing (heterochrony) and because of extensive variation in somite number among the members of the phylum. Heterochrony mostly concerns the development of nasal and lens placodes, heart tube, and limb buds. Richardson recognizes conservation in the pattern of gene expression at this period, but not conservation on the morphological level; he therefore prefers the term *extended phylotypic period* than phylotypic stage (Richardson 1995). Furthermore, he also describes obvious differences in body size and allometry (changes in the pattern of growth of different fields of embryo; Richardson et al. 1997).

Richardson and his group later provided support for their view by analyzing a great variety of quantitative data (Bininda-Emons et al. 2003) concerning developmental-

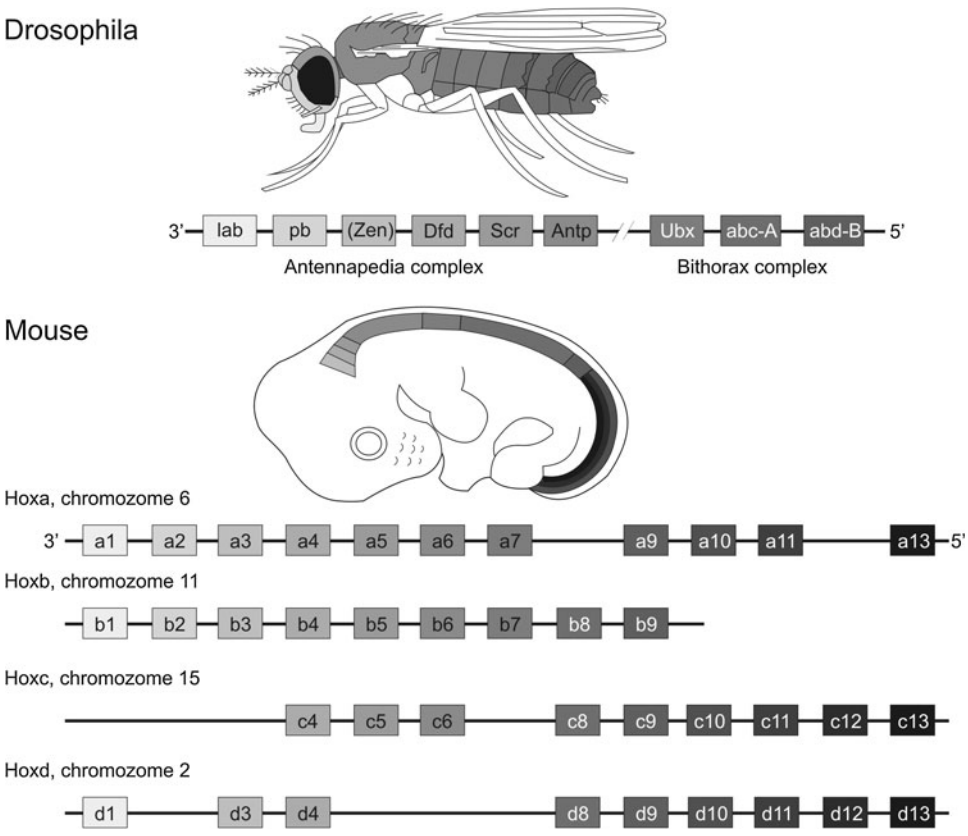

Fig. 3 The zootype transcription pattern in *Drosophila melanogaster* (one Hox complex) and *Mus musculus* (mouse and other vertebrates) have 4 Hox complexes. *Source* www.bio.miami.edu

timing across different vertebrate taxonomic groups, and within the group of mammals.[2] As remarked above, the hourglass model presupposes that phenotypic divergence between lineages should be minimal at the phylotypic period, when compared with earlier or later stages. The authors show, however, that phenotypic variation, i.e. variation in the timing and size of structures appearing at the time of the putative phylotypic stage, was surprisingly high.[3] Mitteroecker and Huttegger (2009) criticize this approach as too simplifying—in their study, the timing of the homologous events was compared, but the morpho-spatial variation of the studied structures were not taken into account.

In contrast, Irie and Sehara-Fujisawa (2007) argue that the expression pattern of the orthologs of vertebrate developmental genes are very similarly right when the supposed phylotypic stage appears (e.g., in mouse development at day 8–8.5). Furthermore, Hazkani-Covo et al. (2005) confirmed the evolutionary conservation at the level of gene expression products, and located the phylotypic stage between the first somite stage and the formation of the posterior neuropore.

Galis and Metz (2001) discovered a web of intense interactions among organs of primordia due to which, any small, laboratory-induced mutation (exposure to teratogens) during the period of the supposed phylotypic stage causes pleiotropic (even lethal) effects in the whole embryo; later on, the effects of such mutations are not as fatal. The phylotypic stage is obviously a very conservative period of development, naturally resistant to any mutational change (Galis and Metz 2001), and maximally interconnected (Raff 1996).

High level of interaction among the traits of the developing embryo was also confirmed during the development of the zebrafish *Danio rerio* (Schmidt and Starck 2004): stages between 15 and 19 h post fertilization are resistant to selection because changing any trait would affect all others that are functionally linked.

Most recently,[4] Domazet-Lošo and Tautz (2010) studied the gene expression in zebrafish genome from the point of

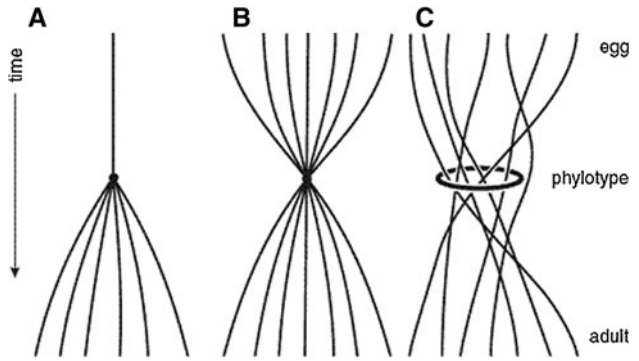

Fig. 4 The sheaf model. Three different models of the development: **a** the broom model represents Haeckel's biogenetic law, **b** the already mentioned hourglass model, and **c** the sheaf model recognizing the conservation of the phylotype but also allowing a loosening of individual straws and circumventing the straw binder (Markoš et al. 2009)

times of origin of various gene sets (i.e., the gene set typical for all living forms, for animal phylum, or for vertebrata). The supposed phylotypic stage is characterized by the expression of the evolutionary oldest sets, whereas during earlier and later stages, evolutionary younger genes are activated. Such results seem to confirm the hourglass model, and the expression of the oldest gene set during this period is explained either by adaptive constraints or by internal constraints which do not allow new gene sets to be involved.

However, shifts in the timing of gene expression and particular protein appearance, of cellular communication patterns and heterochronies in the appearance of homological structures, all obviously take place, although the principal structures are always present at the phylotypic stage. The developmental constraints leading to the phylotypic stage may differ in diverging taxa (Schmidt and Starck 2004); therefore, definition on the morphological level remains more general and broader. Moreover Markoš et al. (2009) came with the "sheaf model" (Fig. 4) reflecting the fact that the phylotypic stage is much looser than that defined by Raff, although the phylotypic constriction is recognized.

Should we set aside the heterochrony and the somite number differences emphasized by Richardson (1995, 1997), we can accept the idea of the phylotypic stage at the mentioned more general level. This phylotypic stage is then defined by the basic morphological structures (notochord, somites, neural tube, optic anlagen, and pharyngeal pouches), by highly conservative zootype transcription pattern, i.e., by the transcription of the orthologous genes

[2] The developmental events being taken into account were transformations (i.e., first appearance of a defined morphology or morphogenetic movement), as they take place during the whole of the mid-embryonic period. Most of these developmental events shared features present in all the species studied: the first dataset consisting of 14 vertebrate species and 41 developmental events and the second 14 mammal, plus two amniote outgroups with 116 developmental events (Bininda-Emons et al. 2003).

[3] For a criticism on the conservation of phylotype, based on interspecific variation in amphibians observed during the development of neural crest, see Collazo (2000).

[4] In the same issue of *Nature*, Kalinka et al. (2010) confirmed the phylotypic status of the germband stage in insects, comparing the expression levels of selected genes and their specific temporal

Footnote 4 continued
relationships among six *Drosophila* species, revealing that the temporal gene expression pattern is the most conservative during the mid-embryonic period.

shared among vertebrates, and by high level of interactiveness within the phylotypic body.

What is the cause of phylotypic conservation?

Duboule (1994) suggested that the conservation of the phylotypic stage is caused by the colinearity of the homeotic genes.[5] Sander (1983) suggested the phylotypic conservation to be caused by pleiotropic nature of interaction among developmental modules. Moreover, Galis and Metz (2001) suppose that interactiveness, rather than the colinear organization of the homeotic genes, causes the fatal effect of any mutation during the phylotypic stage (Galis and Metz 2001). Furthermore, they suggest (2001; see also Raff 1996) that the robust interactiveness observed at the phylotypic stage will later be apparent again between semi-dependent, loosely coupled, developmental modules with different functions and outputs. This is the reason why experimentally induced mutations will exert much lesser impact, by affecting only the selected parts of the developing organism. Hence, the absence of modularity at the phylotypic stage (or phylotypic stage functioning as one interactive module) is one of the key aspects causing its conservative character. Schmidt and Starck (2004) prefer to emphasize high morphologic integration, i.e., high degree of interconnectivity at the period of the phylotypic stage, rather than a lack of modularity, because the different degrees of modularity is hard to test and reconcile. Intuitively, there is a correspondence between both interpretations.

Modularity in the development

Module: general definition

As mentioned above, the phylotypic stage is defined by a high degree of interactiveness within the embryo, while later development operates on the level of discrete semi-autonomous modules. Pioneers emphasizing the role of modularity in development were mainly Riedl, Lewontin, Bonner, and Raff (see Nelson 2004; Wimsatt and Schank 2004). The module is a special integrated and relatively autonomous unit (Schlosser 2004) with high degree of internal and a low degree of external interactions (i.e., with other modules of the given structure). The integration of the module means that the input–output relationship of the module depends on the particular connectedness of its components, not only on the additive superposition of these components. An autonomous module is insensitive to perturbation of the context in which they are embedded (Schlosser 2004). Insensitiveness means that the module is able to maintain the same function in abnormal tissue environments (e.g., ectopically, by transferring the bud, or anlagen, to different location of the embryo).

The functions of each module had to be unified early in evolution, i.e., it has relatively similar genetic and developmental background in different lineages. Every change in the genetic network of a single module leads to the pleiotropic effects *only* within such a module.

Developmental and evolutionary function may reside in canalization and environmental perturbation (modularity leads to higher phenotypic stability during development), or in selective buffering against pleiotropic effects on the whole organism, which facilitates adaptation (or escape from adaptive constraints) (Wagner et al. 2005).

Different types of modules and examples of redeployment

In general, we can observe modularity on many levels of structures emerging during development. Schlosser (2004) makes a distinction between *gene regulation*, *signaling*, *positional*, *cell type*, and *organ modules*.

A *transcriptional activation module* requires a cooperative assembly of many upstream transcription factors (*trans*-factors) on the promoter and/or *cis*-regulatory sequences (Davidson 2006) (Fig. 5a, b). The specific set of *trans*-factor inputs present at a given time will define which downstream genes (outputs) will become regulated at that time, as well as where and how this happens. The modules can gain new functions by new combinations of inputs (new combinatorics of transcriptional factors), by mutations affecting the *cis*-sequences, and by new relations between outputs (generating new regulatory networks influencing their downstream genes). It is clear that not only the DNA binding specificity of the trans-factor but also the interaction among different transcription factors during the gene regulation is crucial. Grenier and Carroll (2000) compared two trans-factors, O-Ubx in *Acanthocara kaputensis* a D-Ubx1a in *Drosophila melanogaster*. Both have a similar homeodomain, but the rest of the protein body differs to a great extent between both species. O-Ubx can repress *surf wings* gene and drive the expression of *decapentaplegic* in the visceral mesoderm as does the D-Ubx1a. On the other hand, O-Ubx cannot repress *distalless* gene as D-Ubx1a can (Wagner 2007). The authors believe that both proteins are engaged in different teams of transcription factors mainly because of differences in their

[5] Colinearity means that the order of the gene cluster on the chromosome corresponds to the order of their expression along the antero-posterior axis of the organism. In vertebrates, colinearity is not only spatial, but also temporal, as genes corresponding to the anterior part of the body are expressed earlier than the genes corresponding to the posterior parts.

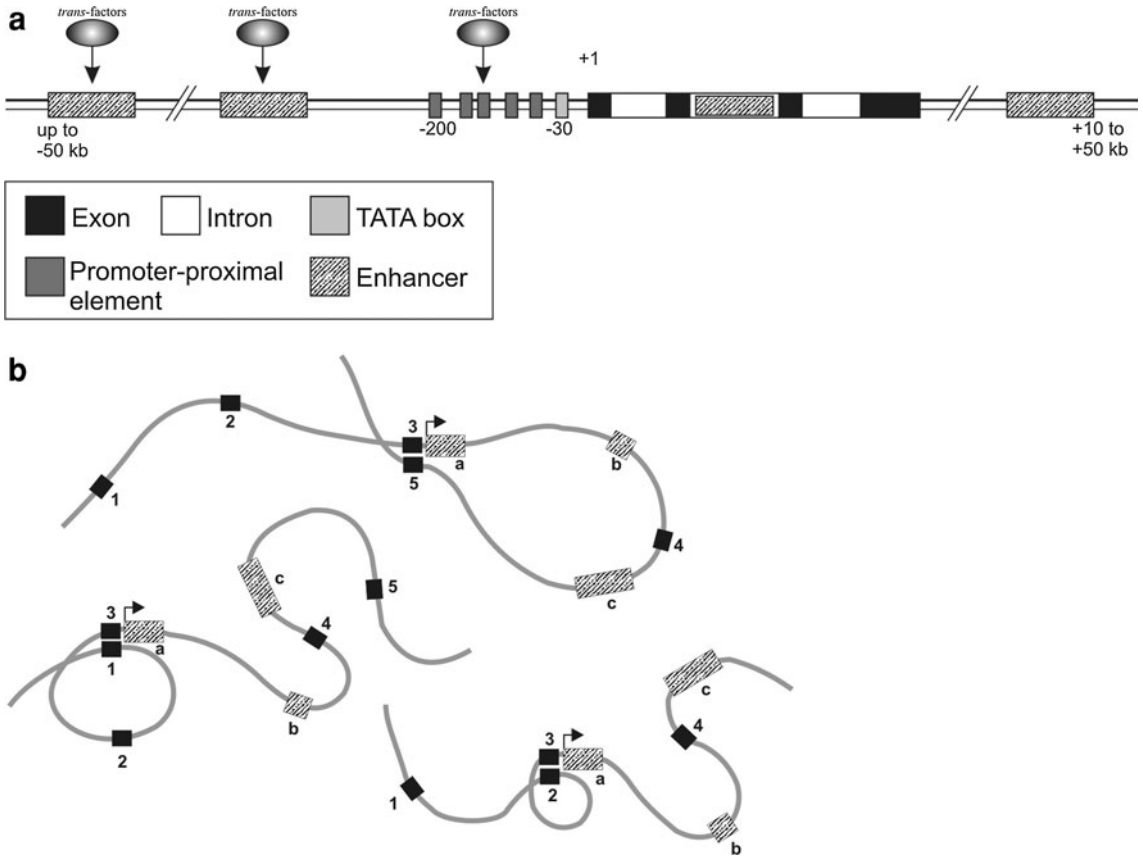

Fig. 5 **a** The *cis–trans* module; **b** DNA looping. **a** The specific assembly of combinations of different transcription factors on the promoter or enhancer/silencer of a given gene is crucial in gene regulation. Promoter (*promoter-proximal element*) with TATA box (starting point of transcription by binding of RNA polymerase) and the enhancer/silencer are the so called *cis*-sequences (draw according to Lodish et al. 2003). The enhancer can lie even within the intron region and the gene can have more than one enhancer. The transcription of the gene is regulated by the binding of transcription factors on *cis*-sequences and their interactions among each other. **b** The dynamic of interactions can be achieved by alternative loopings of DNA (drawing according to Davidson 2006). The orchestration of transcription activation is a lot more complicated than herein described: also the interactions with chromatin structures or other regulating sequences can be included (e.g., *insulators*, which prevent the enhancer to control the neighboring gene, or *global control regions*, which regulate gene transcription over large chromosomal domains, Alonso 2008)

protein domains—which results in diverse regulatory capacities.[6]

S*ignaling modules* between communicating cells represent a plethora of extracellular or intracellular signaling pathways (e.g., the Sonic hedgehog, receptor tyrosine kinase, Wnt, TGFβ, or Notch pathway; e.g., see, Schlosser (2004). These modules are active in different developmental contexts in different tissues. Such pathways are generally initiated by the binding of the ligand on the cell receptor, which activates a transduction pathway resulting in the release of an activator or repressor of some target gene. Most components of such pathways are, again, conserved from insect to vertebrates, acting as independent modules in several tissue environments. For example the Sonic hedgehog pathway is active in wing disk, leg disk or eye disc formation in *Drosophila*, or in vertebrate in dorso-ventral patterning of somites and neural tube and in antero-posterior, and proximo-distal patterning of limbs. In vertebrates, the Sonic hedgehog pathway also participates in gut, pancreas, lung, or tooth formation (Borycki 2004). The universality of signal transduction module is often hacked by cross talk among pathways.

Positional modules are based on the function of positional-specific selector genes. The selector gene is

[6] Alternative splicing of the gene transcript provides yet another source of *trans*-factor heterogeneity: the differences in products of a single *Ubx* gene, i.e. different proteins are spliced from the same gene. In *D. melanogaster* six such different isomorphs were observed (Alonso 2008). *Ubx* determines the segment specificity for many cell types, in epidermis, central and peripheral nervous system and mesoderm. The transcript isomorphs of Ubx gene differ in the presence of short additional regions (microexons): isomorphs containing microexons are expressed especially in epidermis, mesoderm and peripheral nervous systems. Isomorphs lacking the microexons are expressed only in central nervous systems. Functional specificity of the selector genes is therefore generated also on the level of RNA splicing.

expressed in relative space and time, which determines its relationship to other selector genes. This means that the selector genes (García-Bellido 1975; Caroll et al. 2006), such as the *Hox* genes, which control the development of a given module are very conservative across the whole kingdom of organisms, and do not mutate frequently. However the main differences emerge not on the level of genes, but on the level of their regulation by duplication or rearrangements of the *cis*-regulatory sequences, or by changes in the time and place of the expression of a given gene (see Fig. 5). An illustrative model based on Caroll (2005) shows the example of Hox6 expression in vertebrate development (Fig. 6).

Hence, a mutation in a given selector gene similar to a *Hox* gene can have a pleiotropic effect on the functioning of the whole module (i.e., of all genes responsive to it). On the contrary, the rearrangement of inputs (different combinations of TF) and outputs (target *cis*-regulatory sequences) of gene regulatory networks enables the module to gain a completely new development function (Caroll et al. 2006). Complexity in development increases by adding new regulatory states (Davidson 2006), and specificity and diversity in the usage of the same modules arise from the combinatorial control of inputs and outputs of the given module. These modules are therefore quite autonomous: they work in the context of completely unrelated tissues and are able to act ectopically, i.e. in abnormal cellular environments (Schlosser 2004) (Fig. 7).

We shall not discuss the *cell type* and *organ modules* in detail. The first represent the control of determination and differentiation of given cell type, which is usually ruled by a small group of genes that act as cell-specific selector genes. *Organs* (Fig. 8) are modules because their development function relatively independently from other organs (Schlosser 2004), developing in the fashion of morphogenetic field. The best studied example of organ module is vertebrate limb development.

The versatility of different developmental modules of development can be observed on various levels of description: the same gene modules have as outcomes not only different morphologic structures in a variety of species, but also in the different contexts within the same developing body. Developmental processes leading to very similar morphological structures can differ even among closely related species[7] (Swalla and Jeffery 1996).

The evolution of animal form is shaped thanks mainly to the spatiotemporal shifts in gene activation, different partners in protein interaction (different combinations of transcriptional factors), and differences in the activation of downstream targets. Other processes like variable alternative splicing or RNAi are also included. These new regulatory states are responsible for new interpretations and new usage of the same modules in different tissue environment.

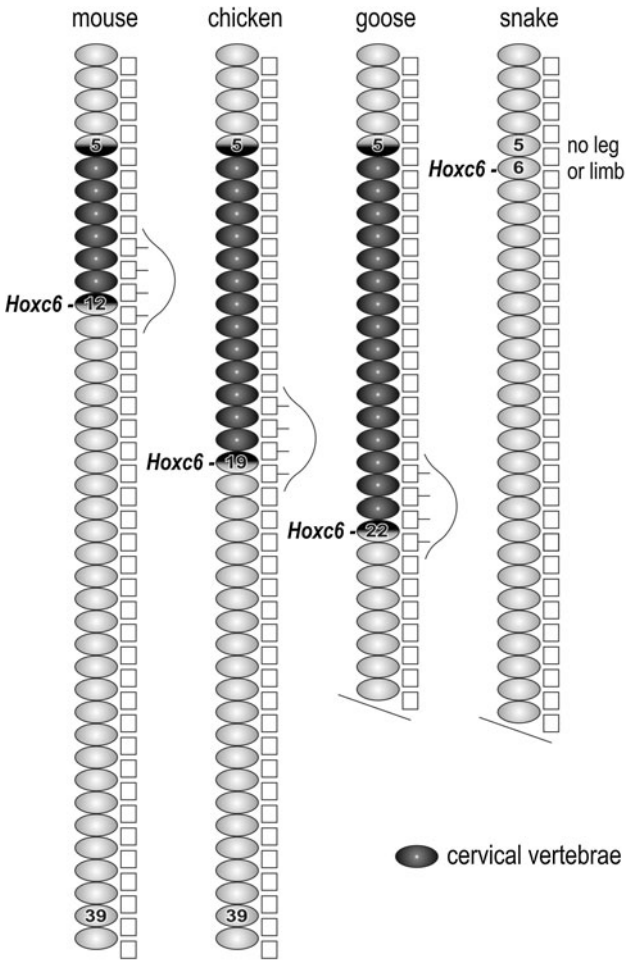

Fig. 6 Cervical and thoracic vertebrae. Various vertebrates have different numbers of cervical and thoracic vertebrae and therefore mice have a short neck, geese long one, and snakes none (only one long torso). The boundary between the cervical and thoracic vertebrae corresponds with the expression of gene Hox6, which forms the interface between the neck and chest. Hox6 gene is activated in every vertebrate species, but its position with regard to the whole body is different. For all four-legged vertebrate, forelimb arises at this boundary. In the case of snakes, there is no obvious boundary between the cervical and thoracic vertebrae, and the expression of Hox6 is spreading forward to the head (and no limbs are formed)—drawing according to Caroll 2005

Why phylotypic stage?

How, then, is the organism to reconstruct its specific three-dimensional morphologic layout, when the genetic background is very similar across disparate taxonomic groups of fish, bird or mammal (not to mention insect and other evolutionary distanced groups of organisms)? How is the

[7] Two related ascidian species undergo different developments: either a conventional tadpole larva, or a tailless larva (Swalla and Jeffery 1996). In addition, changes in sea urchin cytoplasmic determinants can generate sea urchins that develop without larvae, yet accomplishing a normal adult (Gilbert 2003).

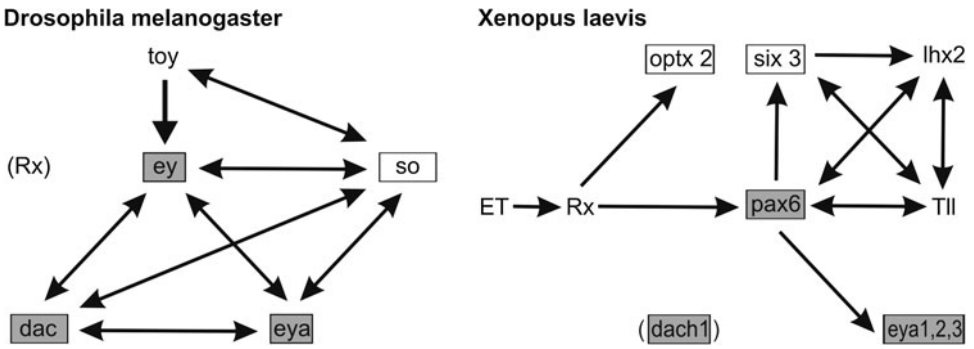

Fig. 7 Pax6 module. Very famous examples of using the same modules in the development of different organs within the same and within different taxa include Pax,-Six,-Eya-Dach gene families which form the regulatory network functioning as a multiply deployed module in vertebrate and also insect development. In *D. melanogaster*, the gene *eyeless* (*ey;* with homology to the Pax gene family in vertebrates) is necessary for eye development. *ey* is part of a small network that includes another transcription factor, *sine oculis* (*so*; with homology to the six gene family in vertebrates), and two transcriptional cofactors, *eyes absent* (*eya*) and *dachshund* (*dac*), and is activated by a paralogue of *ey* called *twin of eyeless* (*toy*) (drawing and text according to Wagner 2007). *Pax6* induce the ectopic eye in *D. melanogaster* as well as in *Xenopus laevis* (Halder et al. 1995; Chow et al. 1999). *so* and its orthologue, *Six1*, play role in *Drosophila* eye development, and in vertebrate myogenesis and ear development (Kardon et al. 2004). The figure depicts two scenarios of *eye* genetic regulatory network *D. melanogaster* and *Xenopus laevis.* In *D. melanogaster*, *toy*, *ey*, *so*, *eya*, and *dac* are necessary for eye development. *Toy*, *ey*, *eya a dac* are sufficient for the induction of eye development and can also mutually induce their own expression. In insects, *ey* is regulated by *toy*, whereas in vertebrates, the transcription factor gene *retinal homeobox* (*Rx* or *Rax*) is upstream of *Pax6*. *Rx* gene is also present in *Drosophila*, but not active during the eye development. *Optx2* a *Six3* are paralogous genes to *so*. Similarly, in vertebrates, *Eya1*, *2*, *3* (homologues of *eya*) do not regulate *Dach1*, the homologue of *D. melanogaster dac*. Orthologous genes are in *gray* boxes, paralogous in *white* boxes

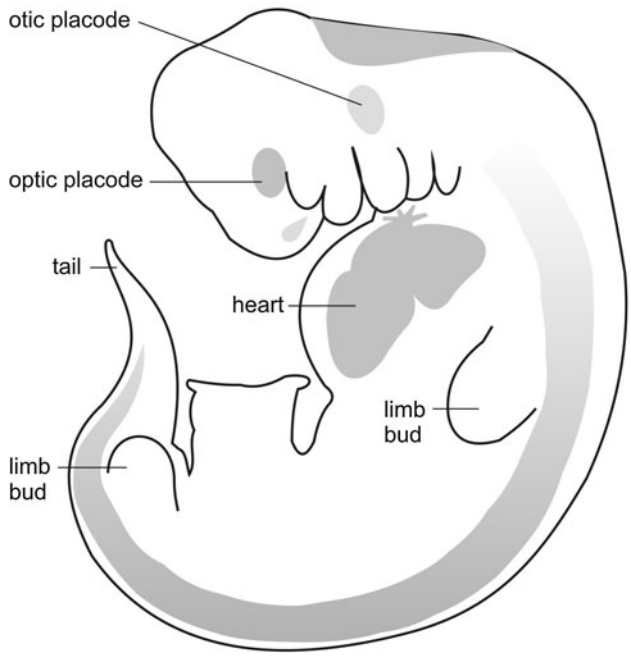

Fig. 8 The vertebrate organ modules. This picture depicts the main morphologic structures acting as modules throughout development

continuity and informational stability of the developmental processes maintained, if most phenotypic characteristics of the whole metazoan are generated not by individual genes acting alone, but by networks of interacting gene products (Salazar-Ciudad and Jernwall 2004)? Why does animal development require a conservative phylotypic stage?

On the level of zootype, all the members of the same phylum put the same genetic toolkit in use (Caroll 2005, 2006) to start their embryonic development. Barbieri[8] noticed that it is the very phylotypic stage that launches new, qualitatively different types of development. In the first period (up to the phylotype), development is very quick and directed only by the hardwired genetic program. In the second period, development is also coordinated by processes working on the basis of the bodily, i.e., supracellular memory of the body plan. The supracellular memory is empty in the beginning (Barbieri 2003); through many rounds of iterative processes, the tight coordination of function at the phylotypic stage allows a gradual "reconstructing" of the phenotype from incompletely inherited information. Today's knowledge of evolutionary developmental biology coincides with Barbieri's opinion: phylotype itself acts as a highly connected module; and immediately after this period, the embryo divides into several semi-dependent modules. This is the time period

[8] In his book *Organic codes*, Barbieri (2003) distinguished several different types of memories. The first level is genetic – in DNA. The second type of the memory works on the basis of different epigenetic codes, e.g. histone code. Such codes are created and re-written thanks to quasi-digital marks, such as histone modification or DNA methylation (Markoš and Švorcová 2009). Epigenetic memory determines the state of every cell in the body and maintains their differentiation. Barbieri also speaks about the neuronal memory and the memory of the immune system at the supracellular level. In his opinion, such memories represent deposits of epigenetic information acquired in ontogeny.

during which the spatiotemporal expression of orthologous genes is activated. This independent spatial and temporal regulations of gene expression permits individual genes to have different but specific functions in different contexts (Caroll et al. 2006). The architecture of hierarchical regulatory domains or different level modules can well represent the phenomenon, which Barbieri calls the supracellular memory of the body plan.

Barbieri (2003) considers the body plan to be simultaneously a three-dimensional structure and a deposit of information. The information about spatial organization of body plan cannot be transferred without *the three-dimensional structure* of the conservative phylotype which is typical for the whole phylum. In this case, we should actually speak about four-dimensional structure: the heterochronic events dependent on the species lineage have to be taken into account as well. The concept of supracellular memory may therefore help us further answer the question of conservation of the phylotypic stage.

In Markoš et al. (2009), the term "Barbieri's platform" was introduced. It represents the meeting point between the period of development ruled by hardwired genetic information and the period when this information is mollified "from above" by semiotic processes. This mechanistic, hardwired, one-module platform is a starting point of the species-specific modular development. Phylotype and zootype form together bodily and genetic toolkit of the body plan. It is also a meeting point for Barbieri's semantic biology and the language or hermeneutic metaphor of life (Markoš 2002; Markoš et al. 2009).

Organic memory of the body plan: is it a mechanistic storage?

The concept of the organic memory in the development is traceable back to Walter M. Elsasser (1987), a physicist, who came up with the concept of holistic memory as a general principle in the reproduction of cells and organisms. This memory is based on the process of *homogenous replication*, i.e., replication based on the molecular stability behaving according to the laws of chemistry and physics and *heterogenous reproduction*, i.e., creative selection from *immense* reservoir of possible patterns in nature. The term "creative" means: tied in with the "laws" of physics and chemistry, but not only with them. Both processes provide the stability of heritable information and cannot be fully separated from each other (Elsasser 1984). Elsasser drew his inspiration from the analogy with cerebral memory, and criticized the mechanistic approach to the processes of reproduction of living forms. In his concept, memory is not a simple mechanistic storage (here, Elsasser is inspired by Henri Bergson's book *Matter and memory* published in 1896), but a process of heterogenous reproduction. Holistic memory is a primary phenomenon of nature existence of which is postulated but cannot be deduced from any "law" (Elsasser 1987).

With regard to the holistic theory we should also mention Russian biologist Ivan Ivanovich Schmalhausen who is known for his holistic approach to the development of organisms. Schmalhausen, strongly influenced by his teacher Alexei N. Sewertzoff, criticized the neo-Darwinian concept of the organism as a mosaic sum of genetically determined characters (Olsson et al. 2010; Levit et al. 2006; Levit 2007). In his conception, the organism was understood as an interconnected whole defined by the relative integrity, i.e., by mutual adaptedness of all parts and functions of the organism to each other, providing the stability of the developing system. According to Schmalhausen, the organism develops as a whole at all developmental stages because of the regulative correlations (genomic, morphogenetic and functional)—in this sense, has Schmalhausen already anticipated the modular character of ontogeny (Schlosser and Wagner 2004).

Here, I do not deal with the conflict between holism and reductionism, yet must attend the theory that embodies memory without storage: memory that is not fixed-inscribed into some permanent code such as DNA.

Nowadays, genocentric neodarwinian biology still dominates, with the opinion that every phenotypic trait is represented in the form of string(s)—shorter or longer—of DNA molecule (together with some epigenetic modifications). In contrast, supracellular memory of the body plan probably operates in the way of *heterogenous reproduction*, choosing specific way in which to use the co-opted regulatory pathway. Developmental processes leading to similar morphological structures can differ even among closely related taxa (Newmann and Müller 2000); the same spatial pattern can be generated by various independent ways acting at roughly the same time (Salazar-Ciudad and Jernwall 2004). What is important is not only the inner representations of orthologous genes, but also various contexts, time, and space in which the products of these representations meet. However, such developmental structure itself (the lineage-specific usage of the *toolkit*) is not completely stored in any mechanistic sense of mere digital representations; it is stored in the *bodily form* of the supracellular memory of the species, and in the pattern of the interactive developmental network. Thus, the direct correlation between genotype and phenotype vanishes, and the communicating tissues and cells are the primary level of description, not genes as mere representations. The memory processes the inputs from the developmental program and from the environment and provides the coordination of species specific processes.

A semiotic perspective

Barbieri argues that the memory of the body plan follows specific codes, in order to reconstruct the phenotype of a given organism. Such codes are implemented in the phenotype itself. This author and coworker have already tried to deal with the ontology of codes (Markoš and Švorcová 2009) and found disagreement with Barbieri's concept.

In their conception (Markoš and Švorcová 2009), there is no semiosis without interpretation; the coding–decoding procedure (the set of character strings, and operations thereupon, Searls 2002) is just a derivative, i.e. the outcome of the semiotic negotiation in terms of natural language. Code does not provide meaning to the informational structures—interpretation does. Code is a well-established interpretation (habit of interaction—in the Peircean sense). Therefore, codes are not simply implemented (stored) in the phenotypes; they are negotiated. Living beings are able to reinterpret their developmental circuits based on the same genetic *toolkit,* and these *historically* created and integrated interactions are able to maintain through the following generations. In the particular study of this topic, it becomes obvious that living beings are primarily historical entities capable of forming habits in the form of regulatory circuits, which are homologous and co-opted in evolution. Barbieri would call this habit a code, but this author and coworker believe that the path leading to a code or habit is the interpretation, in the hermeneutic sense, where the receiving system is capable of learning, of following its own history and experience (Markoš 2002).

In this metaphor, memory represents the deposit of habits, which are unique for every species. This approach should not be considered as a vitalistic point of view, they do not postulate any type of hidden vital principle entering the body from outside, the discussed memory representing the memory of every single species embraces the whole unique recruitment and set-up of the same co-opted evolutionary-developmental modules used in different contexts. Such a memory is never empty at the beginning as Barbieri suggests; it comes with the bodies of the germ cell (Markoš et al. 2007). Owing to supracellular memory, living beings are able to deal with an enormous amount of informational processing on many levels of embryonic development. The organic memory maintains the convention, continuity, and coherency of the species.

Extrapolation from the past evolution of developmental circuits is always difficult, and the semiotic perspective describing the evolution of bodily memory remains an ontological claim that even at the cellular level, there is a semiosis. Yet to assume that the complete memory of the body plan is reconstructed based on representations, such as DNA, or recorded codes of mechanistic nature, would be a larger ontological claim (Markoš and Švorcová 2009).

Conclusion

In this article, I have tried to highlight a significant phenomenon of evolutionary and developmental biology, the concept of phylotype. I focused on the history of discussion on this phenomenon, on its role as a key period in the evolution of the phylum, and also on other characteristics associated with this concept (the zootype transcription pattern, and modularity of development). Although the phylotype is probably not such a strongly conservative period in evolution, as Haeckel and Raff had suggested, at a general level this concept can certainly be accepted. The phylotype is then defined by general morphological structures (as, in chordates, notochord, neural tube, or somites), by the conservative transcription pattern of orthologous genes, and by the high level of interactiveness within the embryo at this time.

This article supports Barbieri's idea of the phylotype as a bodily boundary between two types of development: one strictly based on internal representations in form of DNA, and another having the modular and contextual character of specific usage of the same orthologous *toolkit*, where the bodily form precedes the quasi-digital form of genes.

By attempting to describe the nature of supracellular memory in semiotic terminology, we get to the ontological character of living beings. Davidson (2006) deals with this challenge using the computational metaphor of the embryonic development as a programmed computational network with many hierarchically coordinated nodes. In this approach, genes represent the protocols directing the communication, and the regulatory nodes are the control units of informational processing. These metaphors always imply an external creator or coder (programmer) and consider the animal as a nonautonomous unit.

We therefore propose further another, semiotic, metaphor, wherein the memory of the body plan is represented as a field of semiotic habits, negotiated historically during the life of the species in the sense of "semiotic scaffolding" (Hoffmeyer 2007) or in the sense of species as a cultural entity (Markoš 2002). Such a semiotic perspective, of course, remains an ontological claim to be tested and developed further.

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Living as languaging: distributed knowledge in living beings

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Abstract.

We trace life at different levels of organization and/or description to the cohabitation of individuals within and between historically established lineages. Ways of such cohabitation depend on experience of particular guilds or aggregates; they cannot be easily foretold from any basic level of description, they are distributed across all levels, and across all members of the community. Such phenomena of interactivity constitute a lived world which, we argue, represents a genuine analogy with our domain of human cultures and languages. We draw an analogy with three levels of meaning as defined by Rappaport (2010) and show that life and languaging are virtually analogous.

Introduction

Contributions to this volume show that cognition arises not only 'in the head', but also as the result of living in a network of interactions – in the medium of languaging. These may give rise to particular expectations about a given class of situations and, for example, various kinds of expertise. Following the same logic, language and languages cannot be separated from languaging (Steffensen, this volume); our joint activities make sense because of how we concert our doings in a culture or what Thibault (2011) terms a social meshwork. Outcomes of such doings often depend also on differences that people find as meaningful cues to perform expertly or to construe wordings in a particular way. In other words, much depends on patterns that are extracted by living beings that dwell in a historical world of bodily experience, and of the community into which they are rooted. Indeed, in the context, these ideas will not seem controversial; however, in what follows, we propose taking a further step: we propose that analogical processes help *all* inhabitants of the biosphere / semiosphere to become valuable members of living networks. Our approach may look as yet another contribution to the long list of holistic theories that compete without success with the reigning reductionist paradigm of biology. We, however, do

not deny the explanatory power of contemporary biological theory: by stressing the role of historical bodily experience and of the "cultural" role of communities we strive towards a fuller understanding of life phenomena, much along the line the linguists undertook from the vocabularies through semiotics up to languaging. We invite the reader to take an excursion from the "central dogma" and neodarwinian explanation of evolution, towards what we believe is a more complete view of the living, that extends through 9 orders of magnitudes (or "73 octaves of nature's music", as poetically expressed by M.-W. Ho 1993) and from nanoseconds to 4 billions of years. Our extension to the distributed view is to argue that what goes for cognition and language also applies generally to life.

Levels of meaning

Biologists have much to gain from considering how human cultures exploit what have been termed various 'levels' of meaning. Here, we take inspiration and a leading thread in the book by R. A. Rappaport *Ritual and religion in the making of humanity* (2010); we shall exploit its paraphrase "Ritual in the making of species", still by following Rappaport's argumentation that was intended for human race only.

Rappaport invites us to acknowledge that human cultures as featuring three levels of meaning. Our paper will take the view that the kinds of systems that we find in molecular biology bear remarkable similarities. (1) L*ow-order meaning* is based in differences that can be found in the everyday semantics: thus *rat* differs from both *mouse* and *rate* (in spelling as in pronunciation). Plainly, science is most comfortable with this kind of meaning, and we shall investigate some features of this level in biology. (2) In the *middle-order* of meaning, a person is able to make and construe "similarities hidden beneath the surfaces of apparently distinctive phenomena" (p. 71). While types may still appear, they are now associated with various kinds of metaphors and signs. This is the level of biosemiotics and biohermeneutics, and we took 4 casual examples how an individual construes its body and its *umwelt* at this level of meaning. Finally, (3) *high-order meaning* is "grounded in identity or unity, the radical identification or unification of self with other" (p. 71); in dealing with this, we look beyond models that depend on the regular appearance of discrete types and draw on what we think of as "experience of being" and our sense of belonging in a community. Rappaport concludes (caveat lector, he speaks about human condition!):

"*The distinctions of low order meaning, lodged in language, divide the world into discrete objects; the recognition of similarity constituting middle-order meaning makes connections among those objects; high-order meaning unifies the world into wholeness. Middle-order and high-order meaning may thus prevail, at least from time to time, over the experiences of fragmentation and alienation that are, possibly, concomitants of language's objectifying powers, but it is important to note that the three levels of meaning do not always live easily together. Naive scientism and naive rationalism tend to deny the validity of middle- and high-order meaning, and it is ironically interesting that information may be the enemy of meaningfulness. Conversely, untempered commitment to middle- and high-order meaning may ignore crucial distinctions in the natural and social world."* (Rappaport 2010: 73, our emphasis).

Let us explain the three levels on a Biblical parable: Ezequiel cites the Lord as declaring: *"I have no pleasure in the death of the wicked* (33, 11). While the verse may be new to some readers, it has been cited and interpreted in numerous sermons, moral debates and literary contexts. Yet, we suggest, none of hypothetical readers, naïve or learned, is likely to have considered the sentence in terms of the following syllogism:

p: God has no pleasure in the death of the wicked
q: Mrs. A is wicked
$p \rightarrow q$: Mrs. A is immortal

Yet this what the sentence means in plain English. If language functioned like a unidirectional code, it would evoke Rappoport's low-order level of meaning. Why, then, do we not attribute immortality to Mrs. A? Our case is that the networks or paraphernalia of our civilization leads us to read the verse in relation to higher orders of meaning. This is not based on interpretation of the discrete signs at all: we *feel* that God would not grant such things; our cognitive biases link "death" with "damnation. Readers who are familiar with the Babylonian exile will place the prophet's words yet in another context that derives from our understanding of the original, our acquaintance with Middle Eastern realia, and our own cultural milieu. Still nothing of this will explain, why 2600 years after being written, the verses do still appeal to people in, for example, Central Russia or Arizona.

Middle- and high-level layers of meaning are often seen as bound up with hermeneutics, therefore as part of the humanities, as distinguishing humans from the rest of the biosphere. Biology, it is assumed, can be studied independently of history, cultural contexts, language-like patterns, experience and so on. Yet, in the "*The chaos of everyday life",* Rappaport suggests (2010, xvi), *"stability is bound up with the social facts of a shared collective existence".* Not only do we depend on history, the reiteration of forms and experience but we also draw on, clichés, metaphors, ritualized activities and even strange assumptions. In Umberto Eco's terms:

"*...it is impossible to communicate without putting something into the background frame of mutual agreement and assuming that the other is able to access this presupposed knowledge. Otherwise, each speech event would require a complete restatement, with the result that there would be no time to say, or listen to, anything. This is clearly too great an extension for a presupposition as a sentence phenomenon, since the utterance of even the simplest sentence can presuppose all the world in this sense"* (Eco 1994, 228-9, our emphasis).

In turning to how language and cognition play out 'in the wild', such ways of meaning appear less exotic. Human actions are situated in a normative world where bodies use learning (and other interactional products) to co-ordinate internal and external structure. People, moreover, do this collectively as 'co-acting assemblages' (Cowley & Vallée-Tourangeau 2010: 469). Persons-embedded-in-action and/or-interaction resemble to a "field force", built and rebuilt continuously by inhabitants of a "field" that was inherited from those who long since passed away. Heidegger (1982, 1995) calls this Being-with-others (*Mitsein*) in a Country (*Gegend*). This country is molded by, on the one side, tectonic forces and, on the other, efforts by those who share their being in the here and now. In this way, a countryside or culture is able to evolve across innumerable generations. If this is indeed the basis of cognition, it cannot be traced to simple encodings. This is because, in coming up with thoughts, people draw on distant factors – like the words of an ancient prophet in our example above. Can we, however, generalize from human experience to biosphere, without committing the flaw of anthropomorphization?

In what follows, we show that biological codes such as the DNA script, intracellular and intercellular signal systems and ecological cohabitations; also have a strange duality. While participating in unidirectional processes, they also inhabit

a 'country' of messages and lineages. The "scientific" treatment of "biological syllogisms" applies in artificial, laboratory settings. Like thinking and sense-making, living processes and their evolution depend on interactivity, a process Kirsh (2010) defines as a *back and forth process where a person alters the outside world, the changed world alters the person, and the dynamic continues* (p. 441). Many challenge such a view: in line with the central dogma (see below), many focus on the lowest Rappaportian level. It is hoped that higher levels of meaning are emergent phenomena that can be explained by focusing on such a lowest level of description. It is as if, in studying life, one can ignore the role of living beings. Yet, in Western culture and, thus, the humanities, this view is common; even Rappaport, who should know better, concurs: *"Non-human systems are organic systems constituted largely by genetically encoded information. Human systems are cultural-organism systems constituted by symbolic (linguistic) as well as genetic information"* (2010:10). In challenging this, we aim to rescue the study of life itself from the no man's land that lies between sciences and humanities.

THE LOW ORDER

In biology, by adopting the so called "Central dogma", the focus has fallen exclusively on the low order of meaning (see any modern textbook in molecular or cell biology, e.g., Alberts et al. 2008; the reader who is acquainted with basics of molecular biology can safely skip this section). It claims that information flow in biological systems is unidirectional, from script encoded in DNA to proteins to higher levels of organization. Hence, the basic level of description of any living being is its master copy of DNA containing "data" and "programs" how to build the body. Even instructions how to construct the "hardware" (or better, wetware) of the body must be in its entirety encoded in the genetic script (its "wording" is called *genotype*). In the process of *transcription*, parts of DNA information (about 30.000 "genes", constituting about 2-4 per cent of DNA in human cells) are transferred to much shorter strings of RNA; one class of RNAs (messenger or mRNAs) serves for *translation* of information into a string of a particular *protein* (more about proteins see below). The translation rules – the genetic code – extend the realm of chemistry: the code was established in evolution by *natural conventions* (Barbieri 2008ab). Several thousands of different kinds of proteins constitute the lowest level of cellular agency (higher levels being multiprotein complexes, membranes, organelles, and other

structures) responsible for metabolism, locomotion, cell division, but above all for the extremely reliable *replication,* i.e. copying of DNA master copy, to distribute it to daughter cells, and, of course, also for the transcription and translation processes described above. The assembly of agencies and structures constitute cells, and cells build multicellular bodies; how such an assembly looks like, i.e. what is its *phenotype*, is *primarily* the function of the genetic script implemented in DNA. To repeat again: there is *no reverse flow of information* – no feedback from the world or flesh into the script (see, e.g. the classical treatise *Chance and necessity* by J. Monod 1970). Phenotypes, and other structures of biosphere web, essentially obey, as if verbatim, the genotypic instructions.[1] There are no pterodactyls in contemporary biosphere, because no pterodactyl genotypes operate in contemporary cells, they were lost long ago. Flaws and paradoxes of the theory came to light relatively early (see, e.g. Hofstadter 1979), yet the debates on the topic often end with a mantra "In principle the central dogma holds". The problem, of course, lies in the fact that all living beings have been born of living beings, they do not start from scratch like crystals, flames, neither are they products of assembly lines. Bodies and they genetic scripts are coextensive, neither is "primary" or more basic.

The contemporary neo-Darwinian paradigm, however, draws on the Central dogma. Replication of DNA is highly, but not absolutely reliable (typos, and even more serious disruptions may occur due also to external factors), hence, genes in a population may come out in slightly different "spellings" called *alleles* (likewise, "program" and "programme" represent two alleles of the same word). Alleles (and coalitions of alleles) build phenotypes slightly differing (in this or that respect) from other phenotypes, and such differences may influence the *fitness* of a particular body – in terms of the amount of its descendants. The body (phenotype) is, then, a vehicle to transmit its burden of alleles into the next generation: the fitter the vehicle, the higher the frequency of particular allele(s) in the population in next generation. The fitness is determined by *natural selection* in the external environment: Because of the Central dogma, natural selection acts on the carnal vehicles, whereas the gist of evolution is in transferring pure information as inscribed in DNA. For more succulent version of the story see e.g. Dawkins (1976, 1982).

[1] The analogy with how some Jewish or Christian denominations treat the Scripture is astonishing.

What is important for our further exploration is the fact that the Central dogma and neo-Darwinism model presuppose the concept of a 'basic level' in description of the living. Living beings are viewed as passive machines that are designed to transfer their "software" into their progeny. One way of countering such views is to exploit the language metaphor of life (Markoš & Faltýnek 2011; Markoš et al. 2009; Kleisner & Markoš 2005, 2009). Rather than dwell at the lowest level of meaning, we look beyond models that depend on discrete types and, in so doing, show the relevance of higher levels of meaning to the realm of living. We argue that living systems draw on ecological (or oiko-logical) aspects of meaning. It is our view that recognition of their historical basis is necessary to placing life in a coherent system of knowledge that brings out the continuities that link it with the many human worlds that unfold within a cultural meshwork. As there is no external agency steering the living processes and their evolution, life acts as its own designer (Markoš et al. 2009) – the lowest level of meaning will not satisfy the task.

THE MIDDLE LEVEL

One way of countering such views is to exploit the language metaphor of life (Markoš & Faltýnek 2011; Markoš et al. 2009; Kleisner & Markoš 2005, 2009). Rather than dwell at the lowest level of meaning, we look beyond models that depend on discrete types and, in so doing, show the relevance of higher levels of meaning to the realm of living. In so doing, we face opposition from both the sciences and the humanities (see, e.g. Heidegger 1995). However, we see no need for this: accordingly the paper aims to show that, in contrast to views associated with the kind of logic associated with the central dogma, living systems draw on ecological (or *oiko*-logical) aspects of meaning. It is our view that recognition of their historical basis is necessary to placing life in a coherent system of knowledge that brings out the continuities that link it with the many human worlds that unfold within a cultural meshwork.

We pursue the "language metaphor of life" beyond human beings into communities of living entities. In arguing that it is essential, we show that history and experience matter to intracellular processes, cells living in a body, members of a species and even ecosystems…). Biology depends on cultures or, in Kauffman's (2000) terms *biospheres* made up of populations of cooperating *autonomous agents*. Many of the properties of languaging (Markoš 2002, Markoš et al. 2009, Markoš &

Švorcová 2009, Markoš & Faltýnek 2011) appear in communities or guilds of living entities: the processes that sustain life are *radically distributed in that they depend on 'memory' that is inseparable from their surroundings*. Living beings are not produced or created but, like crystals or tornadoes, merge into being: they are *born* into already present "biospheric fields". Other living things give birth to beings that develop in a domain of rules, values, heuristics and ways of doing things. Hence, besides the genetic script and the body that harbors its patterns, we emphasize the third factor – the community. We now focus our approach around four examples: (1) the intracellular "ecology" of the protein world; (2) epigenetics; (3) symbiosis and symbiogenesis; and (4) the new science of evolution-development, affectionately known as evo-devo.

1. Proteins as agents at the molecular level

In our view it is difficult to understand life without considering properties of the protein community. For readerships who are not biologists, therefore, we pinpoint some of its key features below (see Box 1).

Box: On proteins

Proteins are huge molecules. By comparison, if we treat the "size" of a hydrogen atom as 1 and that of water as 18, a protein averages at about 40.000 (10-100.000). Each of their "building blocks", an amino acid, has a size of around 100. Proteins are always synthesized as linear chains consisting of aperiodic sequences that are constituted by 20 different species of amino acids. In turn, their sequencing is determined by a sequence of DNA building blocks. Parts of the DNA (genes) are copied (transcription) into messenger RNA; is the products are translated in accordance with a sequence of instructions (the genetic code) into the amino acid chain that constitutes the protein. Thus some proteins copy and transfer DNA to their progeny and others copy its content into RNAs. These are relatively easy processes. However, the protein chain or machinery that translates mRNA into complex protein and RNA structures can only arise from translation (not copying). (On copying & coding, see Barbieri 2003.)

The resulting chain shows sensitivity to a particular train of amino acids by wrapping onto itself and creating a 3D molecular protein molecule. Given the view that all necessary information is contained in the DNA (e.g. Monod 1972, Anfinsen,

1973) many thought that a one-dimensional codon sequence unequivocally determined both the chain and the shape of the molecule. On this view, since proteins are the "basic building blocks" of the cell, the shape of cells and multicellular beings is to be traced to the code of a genetic script. In fact, the shape of the protein molecule may be largely determined by its actual environment (see the main text).

Most proteins function to bind a tiny shape (one or more ligands) to different parts of the protein molecule. As a ligand, it may serve a molecule (sugar, hormone), specific parts of other proteins, nucleic acids, or of cell structures). On binding the ligand, the molecule *does* something: it may change the chemical nature of the ligand (enzyme), bind in an antigen (antibiotic), transfer molecules across a membrane (channels, pumps); pass or amplify signals (receptor); etc. etc. These are not coding processes (based on input-output relations) but rather *performances* that change the protein molecule's shape by binding its ligand(s). The set of possible protein shapes is enormous – and never singular. Finally, every protein depends on being able to change its shape.

A mammalian cell contains about 30.000 genes of which, in a given cell, 10.000 are typically 'read'. However, the set of actual protein shapes in the cell is much larger: as explained below, this depends on the protein ecosystem into which new proteins are born. (for more detail and self-explanatory cartoons, see Alberts et al., 2008).

A protein molecule is a string of amino acids that can attain an astronomic number of different shapes. In a given case, however, their embedding in a cellular environment will ensure that only a limited ("meaningful") number are attained, (Fig. 1). Misfoldings are quickly repaired, or removed – by the cell's protein assembly apparatus.

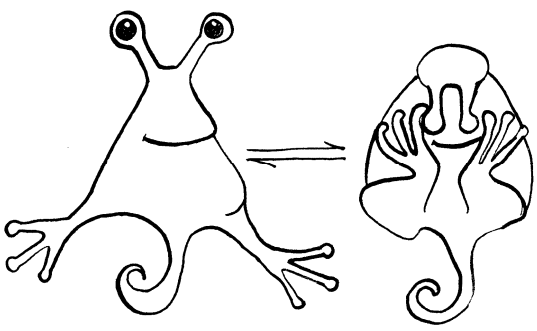

Fig. 1 Two possible conformations of a protein molecule.

In order to attain proper shape a great many nascent proteins depend on "chaperons" (Rutherford & Lindquist 1998; Bergman & Siegal 2003; Taipale et al. 2010; Fig 2). The set of chaperon proteins thus become major regulatory "hubs" that, in different regimes, regulate the cell's crowded protein network by means of fine-tuning (Taipale et al. 2010). In a broader context, not only chaperons but all pre-existing structures and protein assemblages can play formative roles in the environment where a protein molecule is born (e.g., Good et al. 2011). Hence the decision of the context in which the protein is to work is by no means local; it results from the ecosystem of cell "inhabitants". Thus, without any need for central control, proteins function as a meshwork of complex system.

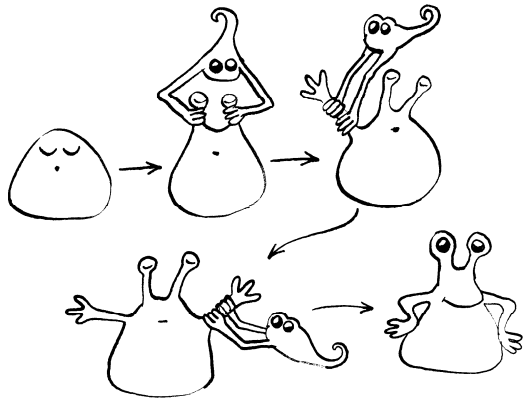

Fig. 2 The action of a chaperone on the nascent protein (in many cases, contact with a chaperone is required across the whole lifetime of a given protein).

Shape transitions are necessary to protein function. To perform a specific action each must take on a conformation that gives exquisite sensitivity in distinguishing and binding its ligand. On binding, the conformation changes and, by so doing, sets off special operations on or with the ligand (see Box 1). It may, for example, be chemically transformed or transported; a change in conformation may switch a signaling pathway or, perhaps, set off protein-protein binding. The changing conformation can prompt a functional complex to perform a task. The effects of such a change are sketched in Figure 3 below. During such functions, the protein's performance (speed, efficiency, etc.) may be fine-tuned by the protein ecosystem. While about one tenth of proteins in the cell are bound to "housekeeping" functions (e.g. respiration, food intake, or special syntheses), the others act as a regulatory, information processing network that make subtle responses to whatever happens to the cell.

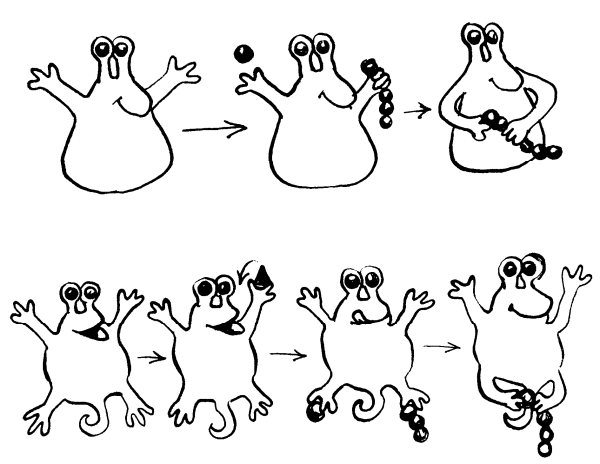

Fig. 3 In the top row a given protein functions by adding a molecular element to a growing chain. The protein has binding sites to both ligands (the monomer and the chain). Thus, when ligands bind onto specific sites, they induce unifying changes in conformation. In the lower row a protein molecule couples with an energy source that enables the inactive conformation to attain the receptive shape required for work (if ligands are available and bound to appropriate sites). In such cases, sites depend on –not codes –but how functions are distributed.

The function of protein is *distributed* in that it does not rely on predetermined features alone; it also draws on historical (evolution, ontogeny) and *ad hoc* contingencies (e.g. temperature, mating season, etc.), or, in short, on the *experience* of the cell and organism. Such a statement somewhat complicates the straightforward model of evolution described above.

Fig. 4-1

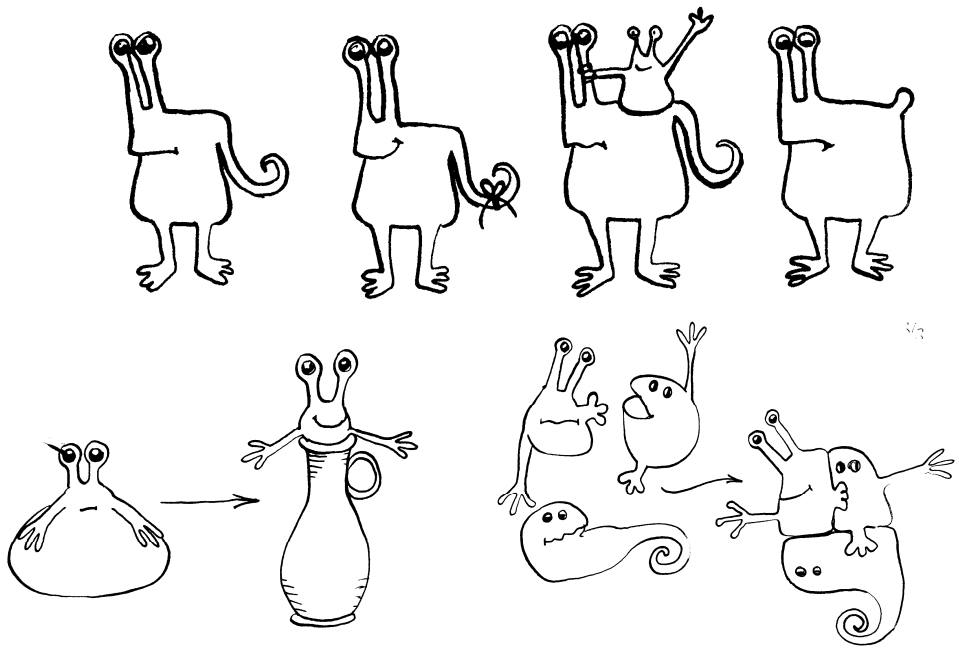

Fig. 4-2

Fig. 4-3

Fig. from 4-1 to 4-3 The performing conformation can be also attained by embedding protein into a structural and/or functional context of a specific environment, or can be delicately (or less delicately) and reversibly modified by specific action from its environment.

Undoubtedly, evolution draws on random change mutation in the genetic script. As described in every textbook, this leads to alterations in the sequence of protein-coding or regulatory areas of DNA. As a result of change in the region of coding, a protein may alter its performance; mutations in the regulatory sequences may also place proteins in new contexts by, for example, altering the timing of ontogenetic gene expression. Changes in the setup of protein network (ecosystem) can have far-reaching consequences for a cell, an individual's likeness and, indeed, for the ecosystem in which it lives. There is, moreover, a second kind of evolutionary change. A whole network of proteins may be induced to change its performance by external agents such as temperature, nutrition, toxins, epidemic, etc. that change the appearance and performance of its bearer. If the whole population is the target of such a change, an unaltered genetic script may nonetheless present a new "attitude towards the world" (see, Matsuda 1987, Hall et al. 2004). Given these two modes of evolution, the network has distributed functions. This is important because, contra the central dogma of biology, this can*not* be traced to inscriptions in genetic code, Indeed, it depends on non-local factors that are co-dependent with biochemistry, molecular configurations, function and evolutionary effects. If epigenetic causation (often reversible from the beginning) takes many generations it may even come to be fixed by genetic algorithms (e. g. Waddington 1975, Rutherforf & Lindquist 1998). Next, therefore, we turn to how cells develop.

2. Epigenetics in the lives of a cell

Not only the protein ecosystem that shapes the "construction of meaning" through cellular epigenesis. Accordingly, we shift our focus from distributed control to consider how a cellular system attunes its current needs by using the 'wording' of genetic texts. We find a sophisticated process that is reminiscent of the subtle use alternations that "accent" an alphabet's basic letters (e.g. 'a') by marking them as (for example) á, ä, à, â, ã ắ å, ặ, ẽ, etc. While from the point of view of the original Latin such modifications look bizarre, they perform many functions. Even if the differences do not matter at one level (e.g. in e-mails), there are substantial differences at others

(e.g. in German, Bar/Bär are different words as are tacher/tâcher in French). In the cell, marks are (reversibly) placed onto DNA or proteins and thus altering the "text" that influences how proteins perform.

Epigenetic use of a diacritic like process is far from simple. They ensure, for example, that cells which inherit the same basic 'text' from the zygote can develop into, say, a liver or a brain. As different sets of proteins contribute to the relevant epigenetic processes, organ formation depends on the highlighting and suppression of different parts of genome and/or proteome. There are two key processes in the cell nucleus that help cells (and cell lineages) to remember their spatial and temporal coordinates.[2] The first of these adds chemical marks (i.e., "diacritics") to DNA molecules. These alter how the script is treated, read and/or understood. The second process uses the organization of the cell's nucleus or scaffolding structures known as nucleosomes. Both processes are tightly interwoven, and deeply influence the cell's orientation and workings.

DNA markings and genomic imprinting

One-dimensional molecules of DNA are often compared to a letter string written in 4 "characters" A, C, G, and T (chemically - nucleotides). On this linear model, the chemical modification of characters resembles human use of diacritics. The commonest of these modifications (methylation) applies to the C character or cytosine In the DNA string. For some mechanisms, nothing has changed (e.g. DNA replication uses the 4 bases); however, for others, the string features a fifth character in the string. Such modifications are reversible in the sense that another battery of enzymes can remove the "diacritics". The method allows methylation to influence the accessibility – and transmissibility – of specific DNA strings. In a reading metaphor, it enhances or hides the text from the performing proteins (Fig. 5). The reversible process of DNA modification can profoundly influence a cell's internal milieu. This is because it is only by binding proteins to regions of a DNA string that the encoded 'message' can be transmitted to the body-world. Thus, if the functionality of a region is enhanced or hidden, major changes can occur. Such processes therefore function, not only at the level of the cell, but in the organism as a whole. While some

[2] Such processes are especially important in the context of multicellular organisms and their ontogeny. It is important that some of them may outlive even to the next generation, thus transferring the experience of parents.

epigenetic changes are programmed (as in creating liver cells), others draw on an individual's lived experience. Thus, in identical twins, the pattern of DNA expression is similar early in development. However, across the lifetime, a cascading set of epigenetic effects will draw on processes such as DNA methylation.

In other cases, genetic material remembers its maternal or paternal origin. This leads to manifestations in the overall likeness of an individual and is especially well known in so-called genomic imprinting. In mammals, all females are genetic "chimeras" because, in their cells, only one (of two) X chromosomes functions. In a given cell lineage whether this is maternal or paternal is determined at random. If the active chromosome bears a debilitating mutation, the effect cannot be mended in spite of the second (but inactivated) X chromosome has the right gene. Serious mental diseases may develop when maternal/paternal imprinting gets erased or impaired (e.g. Prader-Willi or Angelmann syndromes). In some groups (plants, and perhaps also animals), imprinting enables parents to transmit information to their offspring about the environment they are likely to encounter (e.g., Gilbert and Epel 2009; Allis et al. 2007).

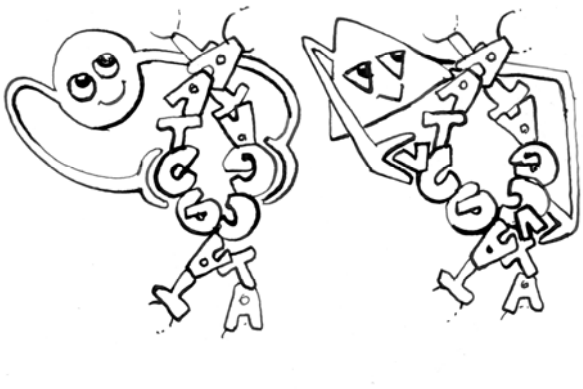

Fig. 5 Epigenetic marking: changing some characters affects the overall shape of a section on DNA. If the section AGCTAA represents a *ligand* for a specific regulatory protein (**a**), a modification (to AGČTAA) turns it into *another ligand*; it becomes the target of a protein (**b**). The complex DNA-protein participates in the cell's protein network by influencing its ability to read other parts of the DNA script: the "reading machinery" behaves differently in cases **a** and **b**.

Nucleosomes

DNA strings (billions of "letters" – in mammals) can be compared to a linear text or a multilevel structure containing hundreds of different proteins. DNA is organized into structures of higher order called *chromatin*: its lowest level of structuration is a "rosary" of *nucleosomes* containing about 147 DNA "characters"

wrapped around 8 proteins (doublets of 4 different *histones*, Fig. 6). While stabilizing the strand of DNA, these also enable or deny proteins access to particular sections of genetic material. This depends on functions that are independent of central control. Rather the actions of specific proteins (e.g. methylation, phosphorylation, acetylation), give rise to modifications (and erasures) of histone proteins whose end tails stick out from the nucleosome (e.g. Allis et al. 2007). The modified surface of the nucleosome can thus serve as binding site for proteins that constitute a chromatin ecosystem. Furthermore, such a modification affects all other proteins. It results in a network of interactions that maintains cell differentiation (e.g. as liver cells or neurons) while favouring quick and reversible response to external or internal cues. For example, some genetic material becomes walled up in a given cell lineage or during A developmental stage. By modifying both the DNA and histones, the system acts as an attractor that silences part of the DNA string – possibly thousands of nucleosomes in a row. In other cases, protein assemblies organize regions to produce a given cell lineage. In most cases, even long-lasting modification may (or should) be reversible in circumstances such as regeneration or, gametogenesis. This view of the cellular ecosystem as akin to reading is shown in the nucleosome pictured in Figure 6 below.

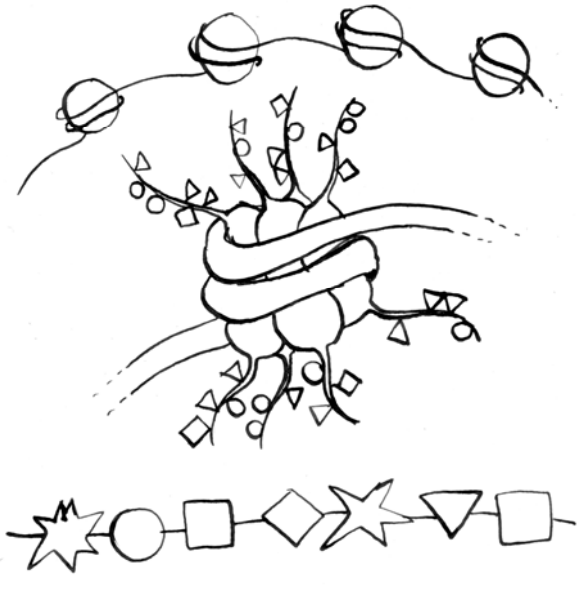

Fig. 6 The nucleosome.
a. DNA is wrapped around 4 kinds of histone proteins. **b.** Histones are prone to binding by regulatory proteins; epigenetic marking (symbols on protruding "tails") can change the set of proteins that bind to a particular part of a histone. Such a change may switch the whole protein network into a different setting. **c.** Each nucleosome (plus proteins attached to it) thus represents a unique, fine-tuned complex that decides how and when the genetic script at that position is to be read. (After Allis et al. 2009)

Elsewhere Markoš and Švorcová (2009) draw an analogy to a natural language that emerges in a natural community of living protein players ("speakers"). This, we argue, cannot be reduced to a fixed code that depends on executing a program. The

parallel is striking: while a histone code can be described in terms of (grammatical) rules, it draws on a dynamical, experience dependent ecosystem or, simply, the total protein milieu. It is argued that any formal language defined as a set of character strings and determinate operations (Searls 2002) is merely derivative of natural language, i.e. it was created by individuals (proteins, cells or humans) who live in the natural world. Developing a consensus on how to read these codes is historical and based on the experience of a community of natural speakers: as Nigel Love (2004) suggests, it consists in second-order constructs. Although rules can be described by formal languages, these do not *constitute* natural languages. Just as there are no transcendental laws or rules of human language, biological codes are unlikely to depend on by a deeper formal language. Rather, just as in human languaging, biological meaning is extracted by natural 'speakers' who dwell in a historical world of bodily experience.

If the correlation between the DNA script and the shape of the protein is contextual, and experience dependent, then emancipation from the genetic script is likely to go further at "higher", supramolecular levels. Accordingly, we now trace parallels between the interactions of biological systems and the metabolic and symbolic aspects of language and, beyond that, what are usually regarded as different language-systems.

3. Symbiotic interactions

In biology, there is often intimate coexistence between two or more lineages of organisms (Sapp 1994, 2003). This *symbiosis* includes endosymbionts that have been long established within the cells (e.g. the mitochondria or chloroplasts that are viewed as integral to eukaryotic cells), ones living inside other bodies (e.g. bacterial communities in bowels) and the more floating interactions that constitute ecosystems. Symbioses are ubiquitous: they serve the biosphere in that, for example, symbiotic bacteria perform activities that their hosts require. They manage photosynthesis, sulphur metabolism, nitrogen fixation, cellulose digestion, and the production of nutrients (e.g. Hoffmeister & Martin 2003). Symbiosis is thus mainly understood as persistent mutualism or, as "associations between different species from which all participating organisms benefit." Symbiotic interactions are not marginal, academic topic but, rather, resemble the distributed cognitive systems that allow humans to use

artifacts and institutions to extend their cognitive powers. In the terms proposed by Douglas (2010):

"Plants and animals live in a microbial world. *Their surfaces are colonized by microorganisms (bacteria and protists) from which they generally derive no substantial harm. Some plants and animals, however, live in specific and coevolved relationships with particular microorganisms, and* these associations have profound impacts on the ecology and evolution *of the taxa involved and, in some instances, also on entire ecosystems. In particular, animal or plants* symbioses *with microorganisms* dominate most terrestrial landscapes, certain coastal environments and the immediate environs of deep–sea hydrothermal vents. […] *Symbioses are important not just because they are widespread and abundant, but also because the acquisition of* symbiosis can dramatically alter the evolutionary history *of some lineages and change the structure of ecological communities."* (Douglas 2010, 19–23, our emphasis).

Although symbiosis can be compared with many aspects of human cognition, we focus on its ecological and evolutionary consequences. As an ecological force, symbiosis ensures that species are bound to cohabit. For example, terrestrial plants typically have an intimate symbiotic connection between their roots and fungi. The most ancient and widespread partnership is *arbuscular mycorrhiza* that dates back ca 460 million years and applies to 250 000 living plant species (Redecker et al. 2000 Fig. 7). Fungi benefit plants by mobilizing nutrients from organic substrates while also delivering water. This is because fungal hyphae are thinner and thus permeate soil better than root hairs. In return, plants subsidize fungi by organic matter.

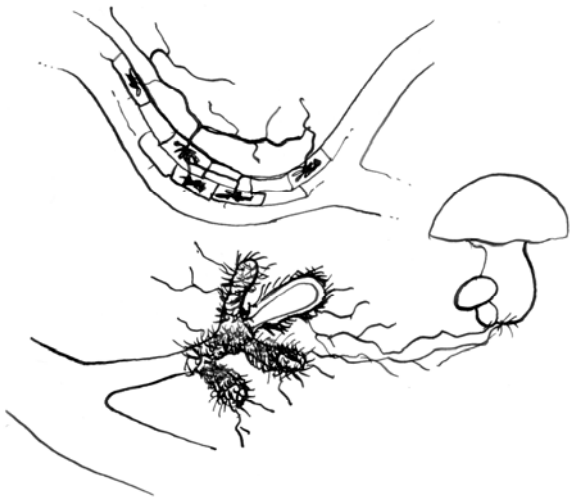

Fig. 7 Mycorrhizal symbiosis – tight cohabitation of fungal mycelium with roots of most plants. Two of many possible configurations are shown: **a.** Endomycorrhiza – fine mycelial protuberances invade the plant-cell cytoplasm and create an elaborated network. **b.** Ectomycorrhiza – while also very intimate, hyphae do not invade the interior of cells. The fungus interconnects trees within its reach, i.e. the whole forest may be networked in this way, the network involving many species of plants, fungi, and other organisms like bacteria.

Symbiosis influences biological evolution profoundly. For example, new lineages of organisms can be engendered by the fusion of previously symbiotically living systems. Symbiogenesis is thought to have given rise to eukaryotic cells that draw on a conglomerate of different bacterial partners (see theory of serial endosymbiosis by Margulis 1993; Margulis & Sagan 2002). Indeed, even those who posit that nature is controlled by something like fixed codes admit that (at least) two kinds of cell organelles – mitochondria and plastids – originated from free-living microbial ancestors. (Douglas 2010,; Margulis & Fester 1991; Overmann 2006; Paracer & Ahmadjian 2000; Sapp 1994, 2003). What is remarkable on symbioses is not the fact that different beings, like Russian dolls, share a composite body. Rather, what matters is that, unlike Russian dolls who are indifferent to each other, symbiosis involves mutual understanding between partners who spent even billions of years as separate lineages.

The moral of the story is becoming clear. In biology, wherever we look, we find interactive communities that "somehow" modify what first seems simple. Once we look "below the skin" of a cell, we find an ecosystem of cellular proteins that bend, prune, decorate and tattoo (but also clear away) other proteins: their existence is dependent on a genetic script but their fate depends on the field beyond. The same pattern appears at other levels: although all genes are present in every cell, their expression is distributed through the workings of structures and processes that will put down epigenetic markings. The unpredictability of the outcomes, i.e. the history of evolution comes to the fore when unrelated lineages enter intimate cohabitations. The same picture applies to ontogenies, i.e. patterning multicellular bodies. Development of a multicellular individual is a fascinating process especially when we trace its historical dimension across lineages and begin to consider what the biosphere has to say about such essentially intimate process.

4. Ontogeny

Many who discuss evolution echo the central dogma in claiming that *the potential of a species to evolve new traits is constrained by its genome or the set of genes it has available. For example, Poe writes: "It might be evolutionary advantageous for your progeny to have wings, but it's simply not possible given the genes H. sapiens has to work with".* (Poe, 2011: 8). Whatever the truth of the claim its

evolutionary basis cannot be what lies in the genome. Indeed, such a view is the biological counterpart of "written language bias" in linguistics (Linell 2005). Just as written letter strings are sometimes seen as basic, even primary, forms of language, DNA strings can be viewed that way. Function is ascribed to static, reproducible, and rational entities that can be seen and known in totality. Written language bias influenced molecular biology in the 1950s and 1960s (see Markoš & Faltýnek 2011) and, even today, some regard "linear biology" as biological common sense. Just as texts can be reduced to sequences (successions) of letters, DNA conforms to sequences of bases in nucleic acids and proteins. On this view, formal syntax lies 'behind' living phenomena – both language and the likenesses of living bodies. Indeed, the "central dogma" takes the extreme view that information is never ambiguous and flows from a script to the body.

The evidence presented above shows why we reject linear models in biology. First, simple proteins do not derive unequivocal shapes from nucleotides sequences. Second, distributed knowledge contextualizes script by assembling cells whose histories contribute to different lineages and organs. Third, members of different lineages use context to construct a world where cohabitation is widespread. Perhaps, then, we should return to our claim that Ezequiel's meaning cannot be extracted *solely* from a sequence of letters. In denying peace to the wicked (if that was his aim), the likeness (of a message, or of a body) is not a function of a sequence, program, or algorithm. Rather, it draws on a context that belongs to a given lineage, group, organism… – and often does so creatively. Members of different species (≡ cultures) treat identical (or very similar) scripts ways that are quite specific: understanding a text is not a passive crystallization or decoding.

Vertebrates, arthropods, earthworms and even echinoderms have lost the two-sided symmetry of their ancestors. In the evolution of these *Bilateria*, all species have the same basic body plan (antero-posterior and dorso-ventral axes, left-right symmetry, etc.; see Švorcová 2012): differences arise from localized expression of ancient, conservative genes. The body plan is set by embryogenesis long before the appearance of body parts. Since bilaterian phyla have evolved independently for more than 500 million years, it is striking that the basis script remains unchanged. While the genes in each lineage underwent changes in "spelling" as some were duplicated, others deleted or otherwise modified, even unrelated lineages have much in common. For example, deletion of a single gene in the genome of fruit fly can be deleterious or

lethal; however, the consequence can be experimentally reversed – by transferring a gene from the genome of a mouse (Gehring 1999). Although proteins coded by such homologous genes differ in many parameters, the message is 'understood': the fly embryo steers the homologue towards a normal developmental pathway. And, of course, "normal" is interpreted as flies (not mice). Thus, if one deletes the gene that initializes eye development in the fly embryo, blind flies will be born. However, a mouse gene restores the development of eyes-those of an insect not a mammal. Thus, a particular protein serves as a tool for establishing a developmental pathway: it does not determine the end product (the eye). Plainly the digital representation of genes (an inscriptional form that may be shared by fruit flies, mice and humans) does not determine how gene works. Rather, this is understood in the "cultural" context of the lineage (species, culture: at the lowest level of description, it depends on an embryo that grows in an ecosystem of interacting proteins (cells and tissues). This complexity allows the same genes to be used in many ways while nonetheless preserving (and transferring) the essentials of the proteins involved. The resulting patterns, ontogenetic outcomes, depend on bodily or lineage memory (see below), not on a linear string that enshrines a memory in a store or depot.

Just as in the Biblical story, the genes are written in an ancient script that is open to non- arbitrary interpretations. Understanding depends on both the individual *and* how the outcome is settled in a given population. The results depend on both situated and non-local factors. To illustrate this matter, one might consider the notorious comparisons between chimp and human genes. While now widely known that their genomes are 98% "similar", there is debate what such a number means (see, e.g., Marks 2002). Our comparison with reading mechanisms of book of life can be further elucidated by examples of inscriptions: thus an ancient philosopher's name is rendered as "Aristotelés" in Czech and "Aristotle" in English.[3] Is his message different for both communities? If it is not, as some will argue, this depends on the history of individuals and populations –not spelling.

Examples such as these may appear trivial. However, we should not assume that, in both life and culture, small changes can have large effects. Changing even

[3] * Versions of written US and UK written English may differ in the spelling in 2 percent of strings. Does this explain the differences between two nations? Remarkably, this line of thinking is pursued by those who seek a genetic Word that is "responsible" for differences in flesh.

a fraction of a percent of genetic material can make a difference – especially if the mutation affects a genomic control center (Davidson 2006; Carroll 2005). In presenting our case, we show only that it is naïve to posit the existence of virtual body plans that are attained (and perhaps even foreseen) by a single "keystroke", or a mutation that creates a "hopeful monster". [4]

THE HIGH LEVEL OF MEANING

We approach the most speculative part of our paper. Rappaport argues (p. 15):

„The survival of any population, animal or human, depends upon social interactions characterized by some minimum degree of orderliness, but orderliness in social systems depends, in turn, upon communication which must meet some minimum standard of reliability if the recipients of the message are to be willing to accept the information they receive as sufficiently reliable to depend upon."

We came to similar conclusions earlier when we compared the coherence of members of a biological species to a culture (Markoš 2002). Yet, Rappaport goes even further: his "standard of reliability" lies in rituals shared (albeit not always necessarily respected) by all living members of the community: it is the tie that defines it. Ritual, for him, is *"The performance of more or less invariant sequences of formal acts and utterances not entirely encoded by the performers"* (p. 24). In other words, it sculpts the "fashion" according to which "we" behave, even if there is no logical necessity to perform exactly in such a way, but it "constructs" the present, as well as the eternity of a given community. *"Societies must establish at least some conventions in a manner which protects them from the erosion with which ordinary usage – daily practice – continuously threatens them."* (p. 323) *"Universal sacred postulates"* in rituals serve as such eternal constant that are not to be questioned, not even interpreted in various ways. Yet, they have their evolution across generations. May it be that biological species also constitute such a community kept together by the ritual inherited from the predecessors? Even if rituals seem eternal, they change in subsequent generations as the *umwelt* or "worldview" of a given lineage shifts in this or that direction. With a very similar "sacred texts", i.e. genome, we have – after 8

[4] In European history, a single "mutation" – insertion of word *filioque* into the Christian creed (and Son) in the 6th century – is often seen as the main "cause" of schism between Orthodox and Western Christianity.

millions years of separation – two cultures of humans and chimps. If the parallel between languaging and life should be fruitful, we should be prepared to think in similar lines. How we look like today is the matter of our genes *and* of the ways how we make use of them in the ever-changing world.

Conclusion

Life cannot be subsumed under physico-chemical principles (even expressible through mathematical notation) because, as Simon (1971) argues, biology and physical science have different objects. Simply said, physical systems lack *meaning*. The fact was first recognized in systems theory and cybernetics (e.g., Bertalanffy 1968); however, no scientific concept of meaning has been developed or needed by the exact and empirical sciences. It is possible, of course, that this is logically impossible or that it just cannot be achieved in quantifiable ways. However, organisms are both ontological and historical: they are products of phylogenetic and evolutionary history. Not only is their multi-scalar nature likely to contribute to the complexity of meaning but this is likely to depend on how relationships use hereditary material to develop over time. As we have seen, this depends on the spatial conformations of DNA molecules and interrelations between them (e.g. DNA-RNA, RNA-protein, protein-protein, etc.) that gives the living world has a character of a network or a web of interactions. To grasp the 'core' properties of biological entities, we always need to know about their exact setting. Conversely, it is *far from enough to rely on knowledge of the structure* of their elements. In developing the language metaphor of life (Markoš & Faltýnek 2011; Markoš et al. 2009; Kleisner & Markoš 2005, 2009), we challenge the view that only the lowest level of meaning is accessible to science. Rather, we examine higher levels, where "meaning" gradually becomes applicable to the realm of living. It is our view that this is the most appropriate basis for explaining life and placing it in a coherent system of knowledge that also gives do weight to the complexity of human worlds that unfold within a cultural meshwork.

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