Published in final edited form as:

Biosemiotics. 2017 July ; 10(2): 157–178. doi:10.1007/s12304-017-9301-z.

Composite Agency: Semiotics of Modularity and Guiding Interactions

Alexei A. Sharov

National Institute on Aging, Laboratory of Genetics, 251 Bayview Blvd., Baltimore, MD 21224, USA

Abstract

Principles of constructivism are used here to explore how organisms develop tools, subagents, scaffolds, signs, and adaptations. Here I discuss reasons why organisms have composite nature and include diverse subagents that interact in partially cooperating and partially conflicting ways. Such modularity is necessary for efficient and robust functionality, including mutual construction and adaptability at various time scales. Subagents interact via material and semiotic relations, some of which force or prescribe actions of partners. Other interactions, which I call “guiding”, do not have immediate effects and do not disrupt the evolution and learning capacity of partner agents. However, they modify the extent of learning and evolutionary possibilities of partners via establishment of scaffolds and constraints. As a result, subagents construct reciprocal scaffolding for each other to rebalance their communal evolution and learning. As an example, I discuss guiding interactions between the body and mind of animals, where the pain system adjusts mind-based learning to the physical and physiological constraints of the body. Reciprocal effects of mind and behaviors on the development and evolution of the body includes the effects of Lamarck and Baldwin.

Keywords

constructivism; modularity; evolvability; scaffolding; constraints on learning

1. Introduction

One of the hard problems in science and philosophy is the nature of agency (Yolles 2006; Weiss 2013). In philosophy, agents are mostly associated with humans (Bandura 2001), and thus the discussion is anthropocentric. In contrast, cybernetics is mostly focused on human artifacts (e.g., robots) and thus the discussion of agency is biased towards mechanistic explanations. In biology, whole living organisms or groups of interacting organisms are viewed as agents (Burge 2009). The universal features of agents include goal-directedness (or normativity) and self-governed activity (autonomy), which implies the use of internal energy and signs/information for a choice and execution of actions (Tønnessen 2015) (see section 2).

Science cannot fully explain how agential features emerge from non-agential physical world both in time (the origin of life) and in space (non-agential atoms and molecules make a living organism). I address this challenge by assuming that (i) agency is a scalable phenomenon, i.e., agents can be roughly sorted by the degree of their agential capacities (both quantitatively and qualitatively) from very simple (molecular-level agents) to highly organized agents (humans); and (ii) most agents are composed of subagents (or dependent agents) with lower agential capacity. Thus, the gap between the physical world and agency (both in time and space) becomes filled with agents of progressively higher agential capacities. This approach, on one hand, eliminates binary dualism between agents and physical world, and on the other hand, does not allow reduction of agential capacities to the function of subagents (because subagents have lower agential capacities). The scale of agential capacity includes qualitative steps of semiotic competence (Hoffmeyer and Stjernfelt 2016). The importance of subagents was emphasized by Hoffmeyer, who wrote about “swarm semiotic organization of the bodies” (Hoffmeyer 2006). Finally, I assume that (iii) all agents are linked with mutual production relationships. They cannot get assembled from non-agential components by chance (except the emergence of very simple molecular agents at the origin of life; this case requires special consideration, see section 2). Instead each agent is produced by one or many parental agents with similar or higher level of agential capacity (Sharov 2010).

Production of agents requires manufacturing of components and assembling them into functional complexes and networks according to a plan. In this respect, it resembles the construction of houses and machines by humans, and thus, the term *construction* can be extrapolated to any creative activity of agents in general. Without construction/production capacity agency would never exist; thus, *constructivism* is often advocated as a methodology for studying agency (Piaget 1964). According to constructivism, the knowledge of the world is a social construction driven by human goals and practices (Kincheloe 2005). It offers a simpler path towards attaining useful knowledge than the traditional methodology of objectivism which sees the goal of science in knowing the true state of the world. Although ‘constructivism’ is mostly an epistemological concept, I consider it in a broader sense, including ontological construction of body parts and subagents by living organisms (Sharov 2016c). The reasons for such generalization, which was inspired by the theory of autopoiesis (Maturana and Varela 1980), are that (i) the construction of body parts and subagents is regulated according to a heritable program - an early predecessor of mental knowledge; and (ii) the emergence of mental constructs (e.g., representations or models) is assumed to be supported by physical construction and remodeling at the level of molecular subagents, synapses, and neurons.

Theoretical studies on agent construction started from the theory of self-reproducing automata, which is based on the idea of a universal constructor machine (von Neumann 1966). Although this theory has been highly influential in the integration of biology with cybernetics, it offers a poor representation of the evolution of living organisms. Living organisms continuously enhance their construction capacities and thus the idea of a constant universal constructor machine is an oversimplification. Akoff and Emery (2005 [1972]) explored the nature of purposeful systems and considered the analysis of purposes as a complementary approach to the mechanistic description of systems. The most fundamental

concept of this theory is that purposeful systems are always involved in production/construction of other systems. The concept of a living cell as a *hypercycle* assumes that multiple genes assist each other in self-replication (i.e., construction) activities (Eigen and Schuster 1979). Cooperation between self-reproducing molecules has been implicated as a possible pathway towards the origin of life (Conrad 1982; Kauffman 1986). Kauffman assumed that life started from an autocatalytic set of molecules (e.g., peptides), where each component is produced via chemical reactions catalyzed by other molecules. Mathematical models confirmed that under certain conditions, such cross-catalysis is more likely to appear spontaneously than autocatalysis of a single kind of molecules. The theory of metabolic-repair (M,R) systems integrated self-repair of agents with their self-reproduction (Rosen 1972). In brief, a set of inputs A is mapped to a set of outputs B by function f . Inputs and outputs include cell components, and thus, the (M,R) system resembles an autocatalytic set. In addition, the (M,R) system includes a repair function (ϕ) that modifies the input-output relation depending on the output, B . Self-reproduction then appears as a natural extension of self-repair. If the repair function is heritable, then the (M,R) system can be further expanded into the evolutionary model where repair is optimized to support self-reproduction (Rosen 1991). The notion of self-construction closure was further developed within the theory of *autopoiesis* (Maturana and Varela 1980). An important novelty of this theory is that the notion of self-construction is expanded from mere making components to *establishment of relations and capacities*. Following this idea, Bickhard (2005) wrote about *recursive construction*: “procedures for construction are themselves recursively constructable” (p. 169). Another novel idea was that autopoiesis is a primitive form of knowledge or cognition, which involves the knowledge of internal organization (as construction recipes) and the knowledge of the environment (as adaptive responses).

Existing applications of constructivism thinking to theoretical biology are however not sufficient because they lack the notion of signification and meaning. In other words, they fail to incorporate semiotics as a core component. In their theory of purposeful systems, Akoff and Emery (2005 [1972]) followed the method of “objective teleology”, which is essentially equal to behaviorism. They assumed that purposes are “derived from observed behaviors under varied but specified conditions” (p. 6). They further defined production as a possible (i.e., necessary but not sufficient) cause-effect relationship (p. 22). In contrast, semiotic relations are not reducible to efficient causation because they involve agents with goal-directed behaviors (see next section). Meanings are products of agential evolution or learning, and they can be equally well represented by a wide variety of sign vehicles with entirely different physical properties. Theories of (M,R) systems and autopoiesis incorporate evolution, and recognize non-reducibility of living organisms to physics, however the authors did not use semiotic terms as far as I know. Links with semiotics were likely avoided since semiotics remains mostly anthropocentric and mind-centric, and thus it is perceived not suitable for integration with biology. One of the founders of semiotics, Charles Peirce defined signs in relation to mind. He considered sign as a relation between sign vehicle (representamen), inferred object, and resulting change of the state of mind, which he called *interpretant* (Peirce 1998). This definition of sign is difficult to apply to organisms without mind, such as bacterial cells¹.

Integration of biology with semiotics emerged only within the methodology of *biosemiotics* (Anderson et al. 1984; Sebeok and Umiker-Sebeok 1992; Hoffmeyer 1996, 2008; Kull et al. 2009). Jacob von Uexküll was one of the founders of biosemiotic ideas (although he did not use the term). He claimed that species of organisms develop their own models of environment, called *Umwelten* (von Uexküll 1982). Living organisms view outside objects as meaningful components of their behavior patterns: food sources, building materials, shelters, or navigation landmarks. Such models of the environment may be even individual-specific because each animal has its unique experience and habits such as navigation and activity within the territory adjacent to its nest (von Uexküll 1957). Uexküll's theory is consistent with the methodology of constructivism because animals construct their models of the world and then use these models in their behaviors. Obviously, the subjectivity of an *Umwelt* does not imply that the world does not exist (as in solipsism). The multiplicity of *Umwelten* only means that there are many alternative models of the world that can equally well support the life of organisms with unique needs. Despite of being subjective, *Umwelten* are not combinations of randomly selected components. Instead, they are strongly constrained by the *pragmatic requirement*: each *Umwelt* must support the survival and self-reproduction of organisms to keep them competitive in natural ecosystems (Sharov 2001), because otherwise the population would get extinct. Organisms develop their models of the environment together with the development of the body, and body parts (e.g., sense organs and effectors) integrated by internal communication system (e.g., nerves and brain) serve as a scaffold for *Umwelt*-building supporting its heritable components (see section 5). In addition, *Umwelt* formation is shaped by the environment via sensorial inputs, degree of success in various behaviors, including interactions with other agents.

Biosemiotics was initially influenced by its predecessor – zoosemiotics, which is focused on animal behavior (Sebeok 1972). Because most animals have brains and, in this respect, are like humans, it was easy to adopt the semiotic terminology of Peirce, where signs are associated with objects and interpreted by mind, and apply it to animals. The discovery of complex epigenetic and signaling processes in living cells supported the idea that cells may carry out mind-like processes, and associate signs with objects and generate interpretations of signs, completing the Peirce's triadic sign relation at the level of single cells. Thus, living cell was considered as a minimal agency capable of supporting semiosis (Bruni 2008; Arnellos et al. 2012). There were attempts to adjust Peirce's triadic sign relations to agents without minds, such as replacing interpretant with action (Collier 2014) or including agent into the sign relation (Hoffmeyer and Emmeche 1991; Hoffmeyer 1996).

Some biosemioticians however explored sign processes below the level of whole cells. Molecular signaling and information processes that initiate or regulate cell functions were called “protopsemiosis” (Prodi 1988; Sharov and Vehkavaara 2015) or “microsemiosis” (von Uexküll et al. 1993). Barbieri (2003, 2009) developed a theory of organic codes, where code is a mapping between a set of signs (e.g., nucleotide triplets) and a set of meanings (e.g., potential actions of a ribosome, that include start and stop of polypeptide synthesis and appending of specific aminoacids to the constructed polypeptide). Barbieri called it

¹Although Hoffmeyer (1996), Collier (2014), and many others followed this approach.

manufacturing semiosis because signs are used by cells to make proteins (Barbieri 2009). Construction processes in organisms include material interactions (e.g., catalysis, cell division, embryogenesis), which often carry semiotic functions, but they also include higher-level ideal changes such as development of novel sign relations and assembling an Umwelt. Organisms can learn to detect new differences (e.g., visual images or sensory-motor couplings) that make a difference in the sense of Gregory Bateson's definition of information (Bateson 1972). Finally, niche construction (Odling-Smee 2003) integrates ideal changes in behaviors with material changes in the environment. Thus, biosemiotic can be integrated with the constructivism-related theories such as autopoiesis, enactivism, and viable systems theory (Rodríguez 2016; Yolles 2006; Rubin 2017).

Integration of biosemiotics and constructivism may help both approaches to move into the domain of biological evolution. So far, the autopoiesis theory was mostly focused on evolutionary stability (i.e., self-replacement). However, more recent studies included adaptability and anticipation (Yolles 2006). Studying of evolution is impossible without understanding the interactions of construction processes at multiple scales from functional molecules to organisms, colonies, and consortia (Sharov 2016c). In this paper, I focus on the problem that requires all three components: biosemiotics, constructivism, and evolutionary theory. I explore the composite nature of living agents, and discuss why it is important for organisms to carry various kinds of subagents. The short answer is that internal multiplicity is necessary for robust self-construction and adaptability at various time scales. Subagents interact via material and semiotic relations, some of which cause forced or prescribed actions of partners. Other interactions, which I call “guiding”, do not have immediate effects and do not disrupt the evolution and learning capacity of partner agents. However, they modify the range of learning and evolutionary possibilities of partners via establishment of scaffolds and constraints.

2. Agents

I start the discussion with the notion of agency² and its relation to physics, biology, and philosophy. As noted above, the universal features of agents are goal-directedness and self-governed activity (autonomy). Non-disputable examples of agents include living organisms, interacting groups of organisms (colonies, populations, and consortia), and living cells. In addition, for reasons explained below, I recognize certain agential capacity in automated human-made devices, cellular subagents (e.g., organelles, molecular complexes, and genes), and viruses as non-cellular life forms. These agents have partial autonomy and can function only in the network with other agents. Some of them cannot reproduce, but they are all products of self-reproducing parental agents. Because agents have a vast range of complexity, the types of goal-directedness and self-regulation vary dramatically. The goals of humans are diverse, highly dynamic, and contextual, whereas ‘goals’ of simple evolving living systems are merely represented by *natural self-interest* in the sense that some heritable (or reproducible) traits contribute to the maintenance of the living state and therefore beneficial for the system (Bickhard 2001; Vehkavaara 2003: 564). Because agents are recursively constructed (see Introduction), they carry encoded meanings and goals of their

²Agency here is a short name for *semiotic agency*; it does not include “chemical agents”.

parental agents. Thus, agents keep their semiotic identity over long times covering potentially millions of generations, and in this respect, they are *ontologically of different type* than physical objects.

Here I argue against a common idea that agency and life starts at a relatively high level of organization, such as living cell, whereas organelles and molecules within a cell lack agential features (Bruni 2008; Arnellos et al. 2012). The first argument is that life could not have originated together with cellular organization, because cells are too complex to self-assemble by chance. Even the simplest protocell with a bilayer lipid membrane and self-copying polynucleotide (Szostak 2011) is far too complex to emerge spontaneously. It seems more plausible that life started with functional molecular agents capable of self-construction and heritable variations, which are all necessary conditions for Darwinian selection (Sharov 2016a). Mathematical model (GARD) clearly shows that primitive form of heredity can exist in self-reproducing compositional assemblies of molecules, such as lipids in the lipid-world scenario of the origin of life (Segre et al. 2001; Shenhav et al. 2007). A coenzyme-world model of the origin of life similarly assumes compositional heredity without nucleic acids (Sharov 2016a). These hypotheses are further supported by the idea that molecular complexes within cells are relics of simpler ancestral primordial proto-organisms. In particular, ribosome structure indicates that it may have been a self-replicating system at some stage of early evolution (Root-Bernstein and Root-Bernstein 2015). Thus, it makes sense to recognize simple agency in ribosomes and other molecular complexes, because their predecessors evolved autonomously long ago.

Molecular-level agency should not be confused with simple autocatalytic or self-supporting systems such as crystals, fire, or tornadoes. For example, it was proposed that functions appeared before agency via self-organization (Keller 2010; Arnellos and Moreno 2012). Keller wrote “I use the term function in the sense of a simple feedback mechanism. Like a thermostat.” (p. 24). These authors further argued that selection for stability/persistence preceded natural selection. Arnellos and Moreno used candle as an example of a self-supporting system. I agree that thermostat and candle have functions but not for the reason of having feedback regulation. The real reason is that both thermostat and candle are produced by humans for specific human purposes that are imprinted in their design during production. In contrast, natural non-living systems with negative or positive feedbacks (crystals, fires, tornadoes) are not produced by agents. They have no purposes, and thus, they do not perform functions. The theory of meaning generation via satisfaction of constraints (Menant 2011) has a similar problem: constraints can be defined for crystals, fires, and tornadoes, but these constraints did not appear via evolution or learning. Functions, meaning, and agency exist only in evolving or learning systems that are *recurrently produced* either phylogenetically, or ontogenetically, or collectively (Rodríguez 2016). Thus, the second argument in favor of molecular-level agency is that these agents are constructed recurrently for performing specific cellular functions such as making proteins or regulating metabolism. These molecules are programmed for purposeful activity by their parental agents in a comparable way as thermostat or candle is used by humans. The ‘goals’ of such dependent agents are derived from parental goals and become hard-wired in their structure.

Molecular-level agents have a much narrower repertoire of potential actions than living cells, but they have real choices in their activities, and can select specific options in a sign-dependent way, which is the third argument. For example, a ribosome can select between types of aminoacyl-tRNA to use for peptide synthesis as guided by a triplet of nucleotides in the attached mRNA.

When errors are found, then the protein synthesis is aborted, and molecules may be targeted for degradation. Another example is the habituation effect in bacterial chemoreceptors: repeated activation of these receptors causes methylation of their glutamic acid residues, which in turn reduces the sensitivity of receptors (Porter et al. 2011). Thus, molecules and molecular complexes within cells have information-processing capacities such as sensing, signaling, and memory operation. Molecular agents show habituation but they are not capable of adaptive learning. However, self-reproducing lineages of molecular agents can evolve adaptively if modifications of molecule structure or relations with other molecules appear heritable (Segre et al. 2001; Sharov 2016a).

The notion of molecular agency does not imply the methodology of physicalism. Although the behavior of agents does not contradict to physical laws and models, it cannot be explained by physics alone³. The notion of agency is essentially non-physical; it refers to the capacity of agents to perform various functions in a set of possible environments in order to achieve such goals as eating, digesting, moving, sensing, hiding, smelling, and reproducing. Obviously, *functions* and *goals* do not belong to the vocabulary of physics. Physics is interested mostly in changes restricted by natural laws that are best seen in either closed systems or systems with steady boundary conditions. In contrast, the main component of agent behavior is in the overcoming of physical constraints by exploiting variations in boundary conditions: agents selectively interact with external components and use them to achieve their goals. Thus, molecules isolated in a glass tube are not agents because their functions are disrupted; in a cell, however, they are produced for certain purposes, which makes them functional.

There is no consensus on the agential status on artificial systems with automated behavior, such as computers and robots. Proponents of Artificial Life usually treat computers or even computer programs as agents, whereas biosemioticians tend to disagree: “A computer contains codes but is not a semiotic system” (Barbieri 2008: 594); “Not all sign processes need to be biological, although all signs seem to involve at some point in their semiosis interpreters who typically would be biological organisms” (Emmeche 2011: 96). In this respect, I think, the distinction of agents and non-agents is not the same as the dichotomy between fully autonomous and dependent agents that are partially autonomous. Computers and programs are certainly not fully autonomous, but so are many parasitic organisms, whose life depends on their host species. Computers are artificial, but all organisms are also artificial in some sense because they are constructed⁴. Computer programs can self-

³Agent can be viewed as a physical body, and some functions can be described as physical processes. However, such biophysical approach does not explain why these specific functions are present, how did they emerge in evolution or learning, and why they are useful for the organism.

⁴Traditionally, the notion of ‘artificial’ is used solely for human-made non-living objects. However, Barbieri (2008) used this term in a broad sense: “proteins can truly be referred to as artificial molecules, as artifacts made by molecular machines” (p. 579).

reproduce and spread over the Internet like viruses in living cells. Actions of computers and robots are automated, but so is the bulk of activities in living organisms and their subsystems. Automation is the hallmark of agency because it allows organisms to repeat and improve their functions. Thus, there seem to be no reason to deny agential properties of artificial automated systems.

All agents are produced by other agents (see Introduction), but the modes of construction vary. Clonal organisms, such as bacteria, have recursive self-reproduction resulting in infinitely branching lineages that do not merge (Fig. 1A). Biparental self-reproduction, which is most common among organisms, makes intersecting lineages (Fig. 1B). However, lineages are relatively homogeneous because the differences between sexes are usually small. In contrast, intra-cellular molecular agents are constructed by many parental agents of various kinds, which can be described as communal construction (Fig. 1C). Proteins are made via cooperative actions of specific genes and RNA polymerase proteins in the nucleus, and ribosomes in the cytoplasm. Then newly-constructed proteins contribute to the production of new ribosomes in two pathways: ribosomal proteins serve as building blocks of ribosomes; and RNA polymerase proteins make ribosomal RNA (rRNA) molecules, which then become assembled into ribosomes together with ribosomal proteins. Replication of DNA also requires multiple components: DNA polymerase proteins and parental genomic DNA that is used as a template. In the communal mode of construction, some parental agent may impose a dominant (i.e., information-rich) effect on the functional identity of a newly constructed agent, and in this case, agential lineages can be drawn based solely on these dominant effects. For example, the DNA sequence of a gene depends mostly on the parental gene sequence, whereas other parental agents may be responsible for minor effects such as mutation rates or DNA methylation marks. Thus, genes have their own lineages that are partially independent from the species lineages (Puigbo et al. 2013).

Genes as self-reproducing agents have several phases in their “life cycle”: DNA, RNA, and protein, which can be compared to stages in a life cycle of insects: an egg, larvae, pupae, and adult. The protein state is usually the most active in the life cycle of a gene, but some genes are active at the RNA state (e.g., non-coding RNA). Considering genes as agents helps to accept the notion that viruses are agents with host-independent phylogeny (Villarreal and Witzany 2010). Also, it explains the phenomenon of junk DNA, when some segments of DNA (e.g., transposons) manage to evade control mechanisms of cells and start reproducing faster than the rest of the genome.

The communal mode of agency construction is more common than people think. The notion of *self-reproduction* refers only to the dominant contribution of a parent to the genotype and phenotype of the offspring. Most agents are not fully autonomous, and their production and development is affected by symbionts and nearby organisms. Thus, there is no reason to deny self-reproduction in viruses based on their dependency on the host cells. This view is supported by some biologists (Raoult and Forterre 2008; Villarreal and Witzany 2010; Dupré and O'Malley 2009). The common notion that viruses are not alive contradicts to the fact that millions of other living species are parasites that cannot survive and reproduce without exploiting their host organisms. Many intracellular parasites lack certain genes and compensate their functions by taking advantage of the host genes. Thus, there is nothing

special in the lack of ribosomal genes in viruses. Also, from a theoretical point of view, the reproduction of viruses matches the definition of potential self-reproducing system formulated with Petri nets (Sharov 1991).

3. Why agents are composite?

All living organisms include a multitude of subagents. Human body has ~30 trillion cells (Sender et al. 2016), and the brain has 86 billion neurons (Herculano-Houzel 2009). Each cell includes ~21,000 of protein-coding genes and >18,000 non-coding genes (Consortium 2012). The human genome includes ~5 million transposable repeats, out of which ~0.7 million are retro-virus fragments (Treangen and Salzberg 2011). In addition, human body appears to be a consortium of many species linked via symbiotic, commensalistic, and parasitism relationships. In other words, the human body is a *holobiont* (Gilbert et al. 2012). Each liver cell has 1000-2000 mitochondria which are descendants of ancient symbiotic prokaryotes that were probably close to rickettsia (Emelyanov 2003). Composite agents also include multi-organism agents such as colonies or symbiotic consortia.

Naturally, there is a question: why agents are composite? Theoretically, an agent can exist without subagents if all functions are coordinated from a single center based on all incoming sensorial inputs. And yet, living agents develop composite modular organization without exclusively centralized control. Size matters for agents (e.g., to capture a resource or win a competition), and the simplest evolutionary path towards larger size seems to be via uniting a number of smaller agents (see Section 4). Then the question arises why “big” organisms remain modular and do not integrate their components further? Among the advantages of modular organization is that it tends to make functions more efficient and robust and supports the adaptability of organisms at various time scales.

Functions of living systems are diverse and generally cannot be all performed by a single agent, and therefore, organisms require subagents. Cooperation of subagents can be compared to outsourcing of certain tasks by human enterprises. Thus, figuratively speaking, cells outsource the task of protein synthesis to ribosomes. Each kind of function needs specific tools and regulatory networks, and requires dedicated subagents. For example, a single-cell ciliate *Paramecium* develops numerous organelles for specific functions (Fig. 2). The gullet is needed for feeding and making food vacuoles, and these vacuoles are responsible for digestion.

Undigested particles are removed from the cell at the anal pore. Osmosis is regulated by contractile vacuoles. Cilia on the surface are used for locomotion, whereas trichocysts are weapons for self-defense. Micronucleus is the main storage of genetic information (chromosomes), whereas macronucleus carries multiplied copies of actively transcribed chromosome fragments. Organelles function autonomously or semi-autonomously and employ self-regulating signaling networks; thus, they qualify to be called subagents. For example, the discharge of trichocysts in *Paramecium* is mediated by local calcium-dependent mechanisms (Plattner 2015), whereas food vacuoles regulate all stages of digestion (Ramoino et al. 1996).

Autonomy of subagents (or modules) has several advantages: it supports a faster response to incoming signals, hides internal complexity of subagent regulation which makes it easier to control subagents from the higher level of cell regulation, and protects subagents from unwanted external and internal changes at physiological and evolutionary time scales. Modularity has been recognized as a leading principle in the organization of embryo development (Schlosser and Wagner 2004; Arnellos and Moreno 2012). Modules are individual subagents or networks of communicating subagents that perform specific functions in organisms (e.g., construction) in robust and self-regulating ways. They control inputs and outputs, counteract external disturbances, and thus, combine responsiveness to external signals with enhanced persistence and stable function. Besides supporting freedom and flexibility in semiotic networks, modules are reusable; they can be recruited by different subagents or duplicated and modified for slightly different jobs. For example, the set of genes that regulate limb patterning and growth in vertebrates is reused for each limb with slight modifications (Schlosser and Wagner 2004). Moreover, this set of genes can be adjusted to produce a variety of limb shapes that are needed for such specialized functions as swimming, soil digging, or jumping.

Now let us discuss the advantages of composite agency in developing adaptations via evolution and learning. Adaptation requires development of novel components and/or novel relations between components in order to solve a particular living problem (e.g., increased temperature or toxic chemical released by a competing species). Most living organisms, rely on trial-and-error strategy in developing new adaptations. These trials are tested and selected either by learning within an organism's life span or by differential reproduction within multiple generations of organisms in evolving lineages (these are hereditary "trials"). Natural selection is thus quite similar to some kind of learning (Campbell 1974; Hoffmeyer 2011). Adaptive changes have to emerge relatively fast to support the survival of organisms and lineages in unfavorable conditions. Thus, the success of adaptations largely depends on the frequency and diversity of memorized (or heritable) changes of body parts and functions. A single agent has only a few options for modifying its actions, whereas composite agents have many subagents available for modification (Sharov 2014). Thus, the role of subagents is not limited to their everyday tasks; it also includes potential life-saving tasks that can be activated in emergency situations. For example, bacteria have a variety of detoxifying metabolic pathways (e.g., esterases, hydrolases, dehydrochlorinases, amidases, oxireductases) that can be utilized for degrading foreign chemicals, including those that have not been ever encountered (e.g., synthetic antibiotics and pesticides) (Russell et al. 2011). Another example is that some insects benefit from detoxifying capacity of symbiotic bacteria when exposed to pesticides (Kikuchi et al. 2012). Because symbiotic bacteria reproduce much faster than their eukaryotic host organisms, they can adapt to detoxify novel chemicals faster than their hosts. Thus, by carrying subagents organisms gain protection against environmental change and enhance their adaptability.

The scope of possible modifications is not limited to the changes of individual subagents. The most profound increase of possible modifications comes from the manifold of possible relations between sub-agents and their products. By relations I mean transient or weak interactions that do not cause irreversible change in the structure of subagents. Some relations are indirect and can be mediated by changes of local environments such as surface

properties of molecular complexes or modification of a cytoskeleton. There are many potential kinds of relations even between simple subagents, which can turn and approach each other from different sides. Indirect interactions are even more diverse than direct interactions due to the variety of other cell components that may serve as signals or resources. Relations between subagents may become heritable signs if they reinforce each other, or appear self-reinforced.

4. Interaction of Subagents in Composite Agents

Here I discuss the strategies of interactions between agents and their subagents, which help to explain the origin of composite agency and the balance of subagent interests. Interaction strategies can be roughly divided into two groups: top-down strategies are applied from the whole system to individual subagents, and bottom-up strategies are used by subagents to survive and succeed in a larger system. The process of agent integration into a super-agency was first analyzed by Valentin Turchin (1977), who called it *metasystem transition*. This transition may take long evolutionary times spanning possibly millions of generations, but it can be recapitulated fast during embryo development. In brief, it includes the reproduction of lower-level agents without separation (phase I), followed by their functional specialization (phase II) accompanied or followed by the establishment of new-level controlling networks that integrate and coordinate the functions of the emerging composite agent (phase III) (Fig 3A). The latter phase is often associated with the loss of self-reproduction of certain subagents. This type of meta-system transition I call “metagenesis” to distinguish it from symbiogenesis, which is discussed below.

Turchin did not foresee that composite agency can become established via symbiosis of entirely different kinds of previously free-living agents (Fig. 3B). Now symbiogenesis is accepted in biology as a possible evolutionary path towards systems of higher-complexity (Seckbach 2006) and can be viewed as an alternative mechanism of metasystem transition (Sharov 1999). Examples of symbiogenesis include the origin of eukaryotic cells via symbiosis of ancestral protoeukariote cells with bacteria that eventually transformed into mitochondria (or plastids), and the origin of lichen via symbiosis of fungus, algae, and possibly yeast. Symbiosis often originates from commensalism or parasitism because these relationships require close contacts between distinct species of organisms, which is a precondition for development of mutually beneficial interactions. Thus, symbiogenesis usually involves one large organism (host) and multiple smaller symbionts (Fig. 3B). Latent viral infection is an example of a transition from parasitism to symbiosis: viruses often protect their hosts from other infections (Barton et al. 2007; Lederberg 1951). Many symbionts are transmitted vertically to the offspring of host organisms: intra-genomically (latent viruses), intra-cellularly (mitochondria, plastids, and rickettsia), via contamination of egg shell (insect gut microbiota) or shared habitat (fungi on bark beetles). If symbionts are not transmitted vertically, then they have to be recruited from the environment. For example, lichen-forming fungi recruit algae, and micorrhyzae-forming plants or orchids recruit fungus. Evolution of symbiotic organisms (i.e., holobionts) includes further differentiation of subagent functions (phase II) and establishment of regulatory networks (phase III) (Fig. 3B). Regulation may include digestion or destruction of subagents for regulatory purposes (e.g., gut microbiota) or control of their reproduction (see below).

No matter how they are formed, composite agents implement top-down and bottom-up strategies via repeated interactions of subagents. The initial top-down strategy in a metasystem transition (phase I) is targeted at supporting self-reproduction of subagents, which is normally achieved by sharing resources and various products. First multicellular organisms possibly shared their extracellular matrix, mineral deposits, and possibly energy and nutrients. Composite agents often require scaffolds to prevent the dispersal of common resources. For example, cell-like systems need a strong membrane. Also, composite agents need top-down strategies to preserve the composition of subagents in the long term. Organisms mostly rely on self-reproduction of subagents to replenish their numbers. Thus, the loss of all subagents of a certain kind may appear irreversible, except for those organisms that can either remodel other kinds of subagents into the missing type, or recruit subagents (e.g., symbionts) directly from the environment. The loss of subagents may appear lethal for the whole system/agent if these subagents are irreplaceable and their functions cannot be compensated by other subagents. This kind of mortality should support natural selection targeted at development of regulatory mechanisms to maintain the minimum required copy numbers of all irreplaceable types of subagents. For example, eukaryotic cells likely die if they lose all their mitochondria or all copies of some important metabolism-related gene (e.g., RNA polymerase).

Although top-down strategies are attributed to a higher-level system, they are implemented by lower-level subagents that perform higher-level functions. The capacity of system components to perform functions of different levels is known as *heterarchy* (Crumley 1995). Heterarchy is common in human society where individuals play certain social roles in addition to their individual functions. The same is true for other composite agents: cells, multicellular organisms, brains, colonies, and consortia. Heterarchy was recognized as a crucial factor in the organization of multilevel agency (Bruni and Giorgi 2016). The level of functions depends on their evolutionary and/or social origin. Individual functions are assumed to result from individual selection and/or learning, whereas group functions apparently come from some kind of group selection and/or group learning. However, criteria for distinguishing these levels are not fully clear (see Nowak 2006; Catania et al. 2016), and require special analysis that is outside of the scope of this paper.

The benefits of these top-down strategies can be offset by selfish bottom-up strategies of individual subagents if they exploit the system either by excessive self-reproduction, exhausting of communal resources, or by stopping the expected production services (e.g., via leaving the system). Examples of such selfish activities are well known at various levels of biological organization. Self-production of misfolded prion proteins results in various kinds of neural degeneration in animals. Uncontrolled self-reproduction of cells causes cancer. Cancer cells, often use deception (e.g., stimulate growth of blood vessels to the tumor) or avoid detection by immune system (Vinay et al. 2015). Replication of transposable genetic elements (mostly of viral origin) populates the genome with nonfunctional junk DNA. The capacity to leave a higher-level agent is a real possibility for many subagents. For example, cancer cells can turn into evolutionary independent parasitic species if they become transmitted between animals (Murchison et al. 2014). There is also evidence that some symbionts can switch to alternative host species, showing certain freedom in their evolutionary paths (Bright and Bulgheresi 2010). These internal conflicts are inevitable in

composite agents because they stem from the semiotic freedom of subagents, which cannot be fully suppressed without the loss of functional and evolutionary advantages of modularity. Thus, composite agents maintain a balance of interests between partially cooperating and partially conflicting subagents.

If selfish behaviors become frequent, they trigger the emergence of tighter top-down control mechanisms (at phase III) that restrict or even disrupt self-reproduction of certain subagents. Full disruption of reproduction can be applied only to replaceable subagents (e.g., to differentiated cells in multicellular organisms), because otherwise the entire system may stop growing and die. Examples of self-reproducing irreplaceable subagents within cells include genes (with their DNA-, RNA-, and protein stages), mitochondria, plastids, plasma membrane, and centrioles. However, reproduction of all these components is under strict top-down control. For example, the main function of mitosis is to keep a fixed copy number of each gene (e.g., $n = 2$ for diploid organisms) in the genome. Control of self-reproduction of cell components is achieved via replacing of autonomous self-construction (e.g., as in Fig. 1A) with communal construction (as in Fig. 1C). Reproduction of mitochondria and plastids is also strictly controlled by host cells.

Animals and plants have complex mechanisms to restrict unlimited reproduction of somatic cells. Telomere length progressively decreases with each cell cycle of somatic cells which eventually stops proliferation of these cells (Lodish et al. 2000). Only germ cells can reproduce indefinitely. Mammalian germ cells protect their status via simultaneous expression of multiple synergistically acting genes that support the expression of each other (Chen et al. 2008). An accidental activation of any single gene from this set of germ-line specific genes has no consequences because the gene cannot function alone. However, cancer cells can overcome this security protection by shutting down certain repressive components of the gene regulatory network (e.g., p53 signaling). To prevent the uncontrolled reproduction of pathogens, symbionts, or cancer cells, organisms require advanced policy-maintenance subagents collectively known as the immune system. Restriction of reproduction exists also at the super-organism level. For example, the majority of bees, ants, and termites cannot reproduce; only the queen and a small number of males can reproduce. Reproduction of these social insects is controlled by complex chemical and behavioral communication between individuals. Group-living mammals (e.g., some rodents, ungulates, and primates) also developed complex behavioral control of reproduction.

Interactions between subagents combine both material and semiotic components in various proportions. Material aspects predominate in such interaction of agents as construction of resources, tools, and scaffolds, or assembly of subagents. Examples of semiotic interactions between subagents are: regulatory signaling (signal transduction in cells), providing informational resources (copying DNA or making mRNA), control and programming of subagents (transfer of hereditary information from parents to offspring). The enormous complexity of communication pathways between cells and organs in multicellular organisms was described as “endosemiosis” (von Uexküll et al. 1993).

Semiotic interactions are mediated by signs; thus, the nature of signs must be addressed. Most definitions of signs (Saussure) originate from linguistics, where language is primarily

seen as a synchronic structure (langue) that can be studied on its own without considering users/agents. This kind of “segregational model of signification”, as characterized by Harris (1996), is not helpful in biosemiotics which is focused on the “agential meaning grounding” (Rodríguez 2016). Peirce's approach is more dynamic; he viewed signs as a medium of cognition (Vehkavaara 2007). However, Peirce's approach is not universal; it is applicable only to agents with advanced interpretation capacities (e.g., capacity to identify, characterize, and track objects) (Sharov and Vehkavaara 2015). Thus, I use a generic definition: “sign is something that repeatedly and consistently regulates or guides the actions of organisms or their subagents (e.g., cells or molecular complexes) in a useful way” (Sharov 2016c). Signs are always represented by material carriers, often called as ‘sign vehicles’, whereas the capacity of agents to interact meaningfully via sign exchange represents the ideal component of signs. Sign vehicles either degrade naturally or become actively destroyed, whereas ideal components of signs are potentially immortal and persist in lineages of self-reproducing agents. The meaning of signs is grounded in the interactions of agents, such as in the case of moths that find mating partners with the help of pheromones. In contrast, traditional semiotics views signs as if they exist on their own. Both production and interpretation of signs is goal-driven. Producers of signs anticipate specific changes in the behavior of receiver agents that are expected to be beneficial for producers. In cooperative semiotic interactions, the goals of producers and receivers of signs mainly coincide. For example, memory signs are produced and then received by the same agent in the future. Because future goals are generally consistent with current goals, memory appears helpful in the future. Another example is cooperative communication between the whole animal and its mitochondria in the muscles. In dangerous situations animals produce adrenaline to activate energy production necessary for the fight-or-flight response. Adrenaline induce calcium release, which is a signal for mitochondria to activate oxidative phosphorylation and generate a large amount of energy in the form of ATP (Luongo et al. 2015). Mitochondria survive and reproduce only within host organisms; thus, it is ‘beneficial’ for them to provide host cells with ATP when the energy is demanded. In antagonistic interactions, goals of sign producers and sign receivers are often different. For example, most animals generate smell (from sweat or urine) that is used mostly for intraspecific communication such as marking territorial borders or determining dominance. However, the same smell can be used by predators for finding prey. Semiotic interactions often support antagonistic relations between species. For example, single-cell parasites *Toxoplasma gondii* change the behavior of infected mice so that they become attracted to cat's urine (Ingram et al. 2013). This response is apparently beneficial for parasites because infected mice become more likely to be eaten by cats, and parasites can reproduce sexually only within cats. Similarly, parasitic fly *Apocephalus borealis* can change the behavior of infected honeybees. Larvae of this parasite reprogram the brain of bees to distal dispersal, which facilitates the dispersal of the parasite (Core et al. 2012).

5. Guiding Interactions of Subagents

There is a wide spectrum of semiotic interactions between subagents ranging from nearly deterministic coding (e.g., protein synthesis) to context-mediated changes that allow considerable freedom in responses of partner subagents. Intracellular interactions of

molecules or organelles are often based on codes that are either context-free or allow only a few context-dependent switches. However, interactions at the level of cells, organs, and whole organisms allow considerable freedom in the response of sign receivers. In this section, I discuss a specific type of interactions, called here *guiding interactions*, where dominant agents manipulate their semiotic partners without diminishing their learning and/or evolutionary capacities.

Examples of guiding interactions can be found even in prokaryotes. For example, viruses that integrate into the genome of bacteria often use a toxin-antidote system to prevent their bacterial hosts from developing antiviral defense mechanisms (Villarreal 2009). Both the toxin and the antidote are encoded by genes located in the viral genome, and corresponding proteins are synthesized by the ribosomes of the host bacteria. If a bacterial cell manages to inactivate the virus, then both the toxin and antidote will no longer be synthesized. The unstable antidote protein quickly disappears but the stable toxin persists and kills the bacterial cell. By far analogy, it can be said that infected bacteria become addicted to the presence of virus and experience “withdrawal syndrome” after attempts to get rid of the virus (Villarreal 2009: 37). This addiction-like mechanism blocks a certain evolutionary pathway in bacterial cells.

A human being has been traditionally viewed as a unity of body and mind⁵. However, the studies of the body and meaningful neural processes that roughly correspond to “mind” are poorly connected. Development of the body is studied by embryology, whereas the dynamics of mind is a subject of cognitive science, and these two approaches are mostly independent from each other. Biosemiotics with its emphasis on studying agency and specifically composite agency offers a new way of bridging this gap: let us consider body and mind as two subagents connected via reciprocal guiding interactions and explore how internal senses, such as pain, serve as a guiding scaffold for the developing mind, and how mental functions affect the development and evolution of the body.

We all have experienced pain; but why do we have it? Why the pain system has emerged and persisted in evolution? Here I argue that the role of pain may be in providing an interface between the body and mind and facilitating learning. Examples of pain-mediated learning include avoiding falls, hits, and other damaging movements. Pain easily becomes associated with additional signals such as heat, images of wasps, or rapidly moving objects, and these associations turn into conditioning behaviors that are aimed at avoiding pain. One of the advantages of the pain sensorial system is that it preserves the information about the location in the body. Thus, in addition to general discomfort we perceive pain as a well-localized disturbance. Information about the source of pain helps us to develop more precise behaviors for avoiding pain. If we accidentally touch a hot surface we move away our hand rather than a foot. This kind of response is facilitated by the structure of the brain itself, known as sensory-motor coupling. It appears that human body is mapped onto the brain cortex along

⁵Aristotle considered it a unity of matter (body) and form (soul). Although mind is closely related to soul, these notions are not equivalent. Mind is mostly associated with rational thinking whereas emotions and faith are often considered as properties of the soul. Here I consider mind is a broad sense including all meaningful neural processes, including emotions, and even subconscious experience. For simplicity, I do not discuss “minimal mind” that does not require brains and may exist even in individual cells (Sharov 2013).

the central groove, where motor cortex areas are located near sensorial cortex areas for the same body part (Schott 1993). Information on the source of pain is also used for attracting attention to wounds and other injuries. Animals use wound licking as first aid for cleaning, and possibly, disinfection because saliva has antibacterial properties (lysozymes, peroxidase, defensins, and antibodies). Higher animals utilize the pain system for interaction within families and larger groups. Fighting and punishment are used to support the dominance relations between organisms and to protect resources (food, mating partners). Playful biting is a common element of interaction between animals that may indicate warning or affection. There are even more complex behavioral patterns based on pain, such as “feeling” pain of others, or grief.

Sense of pain is just one of the scaffolds provided by the body to facilitate neural-based learning. Another important sensorial scaffold is *proprioception* which yields information on the state of muscle contraction and relative position of body parts. Besides striated fibers that generate the power of contraction, muscles include so called intrafusal fibers that are connected with the endings of sensory neurons. Proprioception is a precondition for learning of all basic movements (walking, standing, crawling, swimming, etc.) of animals. Other scaffolds for learning movements include five conventional senses (sight, hearing, smell, taste, and touch), effector organs (muscles, bones, glands), and innervation of both sensory organs and effector organs. The control of voluntary movements by mind is guided by the morphology of the body, sense organs, and innate neural circuits.

Considering the significant role of body scaffolds in learning, it is necessary to reevaluate the notion of heritability of learned habits. The common view in behavioral sciences is that only innate behaviors/reflexes are heritable, whereas learned behaviors are not heritable. The distinction between innate and learned behaviors is indeed fundamental because innate behaviors are executed from the first attempt and do not change, whereas learning requires relatively long periods of trials and errors, and behaviors gradually improve with experience. But this difference should not be confused with a dichotomy of heritable versus non-heritable behaviors. Because learning is guided by a set of body scaffolds, which are largely heritable traits, the resulting learned habits also appear heritable. If learned behaviors were not heritable, it would be difficult to explain why most of them are nearly identical in animals within a population and why these behaviors persist in lineages over millions of years.

The neo-Darwinism theory assumes a deterministic view of heritability as if the heritable component of the phenotype is determined by the genotype. Thus, it was a revolutionary turn in biological thinking when Waddington (1968) proposed a new model of heritability based on the convergence of developmental trajectories in the so called *epigenetic landscape*. In his model, genes do not determine the phenotype but instead regulate embryo development in a context of changing internal and external conditions (Sharov 2014; Rubin 2017) This model marked the birth of the evo-devo concept and facilitated the development of Extended Evolutionary Synthesis (Pigliucci and Müller 2010). This model can be further expanded to learning traits and learning trajectories. It is natural to expect that learning trajectories can converge due to common sensorial information, effector organs, sensory-motor coupling, and other networks and scaffolds, which together can be viewed as a

behavioral analog of the Waddington's developmental epigenetic landscape. Being supported by fast neural signaling, the behavioral epigenetic landscape is apparently more dynamic than the developmental one, and possibly can be remodeled by learning. One of the examples of such approach is the analysis of the behavioral epigenetic landscape of alcoholism (Krishnan et al. 2014).

Convergence of behavioral trajectories does not contradict to the fact that many learned behaviors vary among individuals. These variations can be caused by differences in body scaffolds, development history, social rank, environment, or other contextual factors. Besides that, the variability of behaviors may result from the presence of multiple adaptive peaks in the space of possible actions. For example, predators may benefit either from catching their prey on the run or from hiding and waiting for approaching prey. These two strategies may be equally successful but they require entirely different behaviors. Such kind of multiplicity of adaptive peaks can presumably support rapid changes in behaviors within a life span of an individual. It also may result in a mixed strategy where both behaviors are used depending on the situation. Thus, learned behaviors evolve by two complementary processes: (a) by natural selection mediated by heritable changes in bodily scaffolds and (b) by individual switch of alternative adaptive peaks in the space of possible actions. The former mechanism is slow and gradual, whereas the second one may generate rapid changes.

Now we consider the reciprocal effects of mind and behaviors on the development and evolution of the body. Lamarck apparently was the first to notice the effect of behavioral change on strengthening of corresponding organs via exercise. Animal body has enormous plasticity and can adapt to various kinds of behavioral change. The mechanisms of these effects are not fully clear, but it is conceivable that the body “learns” how to deal with new mind-driven behaviors. For example, it is possible that individual cells try different modes of functioning and then select the mode that results in receiving specific feedbacks from the network of their partner cells. In addition, adaptive changes in the body may be caused by selective reproduction of cells with certain heritable variations. Both processes are likely based on epigenetic changes (e.g., chromatin modifications), which represent relatively short-term cellular memory. Simple models of epigenetic regulation support the idea that cell-level learning may result from selective activation or repression of genomic regulatory regions called *enhancers* based on molecular signaling (Sharov 2010).

Another effect of mind on the body is associated with the reshaping of the fitness landscape of organisms caused by a changed behavior, which may result in the emergence of novel body structures in evolution; this effect was named after James Mark Baldwin (Baldwin 1896). Although Baldwin effect is difficult to validate, it has been supported as a viable hypothesis by several evolutionary biologists (Dennett 2003; Depew and Weber 1995). Dennett (1995) argued that learned behaviors can become stable in lineages by either genetic automation or selection for increased “intelligence”. It is conceivable that Baldwin effect facilitated the emergence of flight in insects as follows. Insect ancestors presumably started using protrusions of their thorax chitin cover (tergum) for gliding (e.g., when falling from vegetation or during jumps). New behavior then changed the fitness landscape and redirected evolution towards development of wider and longer protrusions of the tergum. As these appendages became longer, another change in behavior followed: insects started

bending these proto-wings to control gliding direction and height. This may have prompted a new direction in evolution towards stronger muscles that moved proto-wings. Finally, insects started using muscles for powering their flight, and this caused further strengthening of wing muscles. The Baldwin effect is an attractive hypothesis because it may explain high rates of evolution in birds and mammals, which are two most “intelligent” lineages of animals (Hoffmeyer and Kull 2003). Indeed, behaviors can change very rapidly, even within one generation. Thus, they can boost the evolutionary rates by controlling the direction of evolutionary change (Sharov 2016b).

6. Conclusions

Agents are construction-dependent systems: they are constructed by parental agents and many agents have construction capacity. Agents require resources, tools, subagents, scaffolds, and signs, most of which are constructed either internally (i.e., by self-construction) or by other agents. The notion of construction can be further expanded into the evolutionary/learning domain, so that we can talk about the ideal aspect of construction which is the production of new kinds of components and new sign relations. These novelties are potentially immortal as they persist through self-constructing processes. Thus, the theory of agency requires the methodology of constructivism.

Evolving agents include subagents that tend to specialize in certain tasks. The evolutionary advantage of composite agents is in their capacity to support robust recursive self-construction and increased adaptability during catastrophic environmental changes. Subagents interact via material and semiotic relations, some of which cause forced or prescribed actions of partners, whereas “guiding” interactions modify the range of learning and evolutionary possibilities of partners via establishment of scaffolds and constraints. In particular, the body of animals uses the pain sensory system to guide mind-based learning and provide an interface for mind-body interaction. Reciprocal effects of mind and behaviors on the development and evolution of the body includes the effects of Lamarck and Baldwin.

Acknowledgments

This paper was supported entirely by the Intramural Research Program of the National Institute on Aging (NIA/NIH), project Z01 AG000656-13.

References

- Ackoff, RL., Emery, FE. On purposeful systems: An interdisciplinary analysis of individual and social behavior as a system of purposeful events. New Brunswick, NJ; London: Aldine Transaction, Transaction Publishers; 2005 [1972].
- Anderson M, Deely J, Krampen M, Ransdell J, Sebeok TA, von Uexküll T. A semiotic perspective on the sciences: Steps toward a new paradigm. *Semiotica*. 1984; 52(1/2):7–47.
- Arnellos A, Bruni E, El-Hani CN, Collier J. Anticipatory functions, digital-analog forms and biosemiotics: integrating the tools to model information and normativity in autonomous biological agents. *Biosemiotics*. 2012; 5(1):331–367.
- Arnellos A, Moreno A. How functional differentiation originated in prebiotic evolution. *Ludus Vitalis*. 2012; 20(37):1–23.
- Baldwin MJ. A new factor in evolution. *American Naturalist*. 1896; 30:441–451.

- Bandura A. Social cognitive theory: An agentic perspective. *Annual Review of Psychology*. 2001; 52(1):1–26.
- Barbieri, M. *The organic codes: An introduction to semantic biology*. Cambridge, New York: Cambridge University Press; 2003.
- Barbieri M. Biosemiotics: a new understanding of life. *Die Naturwissenschaften*. 2008; 95(7):577–599. [PubMed: 18365164]
- Barbieri M. Three types of semiosis. *Biosemiotics*. 2009; 2(1):19–30.
- Barton ES, White DW, Cathelyn JS, Brett-McClellan KA, Engle M, Diamond MS, et al. Herpesvirus latency confers symbiotic protection from bacterial infection. *Nature*. 2007; 447(7142):326–329. [PubMed: 17507983]
- Bateson, G. *Collected essays in anthropology, psychiatry, evolution, and epistemology*. San Francisco: Chandler Pub. Co.; 1972. Steps to an ecology of mind.
- Bickhard, MH. Function, anticipation, representation. In: Dubois, D., editor. *Computing Anticipatory Systems CASYS 2000 - Fourth International Conference*. Melville, NY: American Institute of Physics; 2001. p. 459–469.
- Bickhard MH. Functional scaffolding and self-scaffolding. *New Ideas in Psychology*. 2005; 23:166–173.
- Bright M, Bulgheresi S. A complex journey: transmission of microbial symbionts. *Nat Rev Microbiol*. 2010; 8(3):218–230. [PubMed: 20157340]
- Bruni, LE. Cellular semiotics and signal transduction. In: Barbieri, M., editor. *Introduction to biosemiotics The new biological synthesis*. Dordrecht: Springer; 2008. p. 365–407.
- Bruni LE, Giorgi F. Multi-level semiosis: a paradigm of emergent innovation. *Biosemiotics*. 2016; 9(3):307–318.
- Burge T. Primitive agency and natural norms. *Philosophy and Phenomenological Research*. 2009; 79(2):251–278.
- Campbell, DT. Evolutionary epistemology. In: Schilpp, PA., editor. *The philosophy of Karl R Popper*. LaSalle, IL: Open Court; 1974. p. 412–463.
- Catania F, Krohs U, Chitto M, Ferro D, Ferro K, Lepennetier G, et al. The hologenome concept: we need to incorporate function. *Theory Biosci*. 2016
- Chen X, Xu H, Yuan P, Fang F, Huss M, Vega VB, et al. Integration of external signaling pathways with the core transcriptional network in embryonic stem cells. *Cell*. 2008; 133(6):1106–1117. [PubMed: 18555785]
- Collier, J. Signs without minds. In: Fernández, VRaE, editor. *Peirce and biosemiotics: A guess at the riddle of life*. Dordrecht, New York, London: Springer; 2014. p. 183–197.
- Conrad M. Bootstrapping model of the origin of life. *Biosystems*. 1982; 15(3):209–219. [PubMed: 7139085]
- Consortium E. An integrated encyclopedia of DNA elements in the human genome. *Nature*. 2012; 489(7414):57–74. [PubMed: 22955616]
- Core A, Runckel C, Ivers J, Quock C, Siapno T, Denault S, et al. A new threat to honey bees, the parasitic phorid fly *Apocephalus borealis*. *PLoS One*. 2012; 7(1):e29639. [PubMed: 22235317]
- Crumley CL. Heterarchy and the analysis of complex societies. *Archeological Papers of the American Anthropological Association*. 1995; 6(1):1–5.
- Dennett, DC. *Darwin's dangerous Idea: Evolution and the meanings of life*. New York: Simon & Schuster; 1995.
- Dennett, DC. The Baldwin effect, a crane, not a skyhook. In: Weber, BH., Depew, DJ., editors. *Evolution and learning: The Baldwin effect reconsidered*. Cambridge, MA: MIT Press; 2003. p. 69–106.
- Depew, DJ., Weber, BH. *Darwinism evolving: Systems dynamics and the genealogy of natural selection*. Cambridge, Mass: MIT Press; 1995.
- Dupré J, O'Malley MA. Varieties of living things: Life at the intersection of lineage and metabolism. *Philos Theor Biol*. 2009; 1:e003.
- Eigen, M., Schuster, P. *The hypercycle, a principle of natural self-organization*. Berlin, New York: Springer-Verlag; 1979.

- Emelyanov VV. Mitochondrial connection to the origin of the eukaryotic cell. *Eur J Biochem.* 2003; 270(8):1599–1618. [PubMed: 12694174]
- Emmeche, C. Organism and body: The semiotics of emergent levels of life. In: Emmeche, KKC., editor. *Towards a semiotic biology: Life is the action of signs.* London: Imperial College Press; 2011. p. 91-111.
- Gilbert SF, Sapp J, Tauber AI. A symbiotic view of life: we have never been individuals. *Q Rev Biol.* 2012; 87(4):325–341. [PubMed: 23397797]
- Harris, R. Signs, language, and communication: Integrational and segregational approaches. London, New York: Routledge; 1996.
- Herculano-Houzel S. The human brain in numbers: a linearly scaled-up primate brain. *Front Hum Neurosci.* 2009; 3:31. [PubMed: 19915731]
- Hoffmeyer, J. Signs of meaning in the universe. Bloomington, IN: Indiana University Press; 1996.
- Hoffmeyer, J. Genes, development and semiosis. In: Rehmann-Sutter, ENHaC, editor. *Genes in Development Re-reading the Molecular Paradigm.* Durham and London: Duke University Press; 2006. p. 152-174.
- Hoffmeyer, J. Biosemiotics: An examination into the signs of life and the life of signs. Scranton, PA: University of Scranton Press; 2008.
- Hoffmeyer, J. Biology is immature biosemiotics. In: Emmeche, C., Kull, K., editors. *Towards a semiotic biology Life is the action of signs.* London: Imperial College Press; 2011. p. 43-65.
- Hoffmeyer, J., Emmeche, C. Code-duality and the semiotics of nature. In: Anderson, M., Merrell, F., editors. *On semiotic modeling.* Berlin, New York: Mouton de Gruyter; 1991. p. 117-166.
- Hoffmeyer, J., Kull, K. Baldwin and biosemiotics: What intelligence is for. In: Depew, BHWaDJ., editor. *Evolution and learning: The Baldwin effect reconsidered.* Cambridge MA, London: MIT Press; 2003. p. 253-272.
- Hoffmeyer J, Stjernfelt F. The great chain of semiosis. Investigating the steps in the evolution of semiotic competence. *Biosemiotics.* 2016; 9(1):7–29.
- Ingram WM, Goodrich LM, Robey EA, Eisen MB. Mice infected with low-virulence strains of *Toxoplasma gondii* lose their innate aversion to cat urine, even after extensive parasite clearance. *PLoS One.* 2013; 8(9):e75246. [PubMed: 24058668]
- Kauffman SA. Autocatalytic sets of proteins. *J Theor Biol.* 1986; 119(1):1–24. [PubMed: 3713221]
- Keller, EF. It is possible to reduce biological explanations to explanations in chemistry and/or physics. In: Arp, FJAaR, editor. *Contemporary debates in philosophy of biology.* Oxford, Chichester, UK: Willy-Blackwell; 2010. p. 19-31.
- Kikuchi Y, Hayatsu M, Hosokawa T, Nagayama A, Tago K, Fukatsu T. Symbiont-mediated insecticide resistance. *Proc Natl Acad Sci U S A.* 2012; 109(22):8618–8622. [PubMed: 22529384]
- Kincheloe, JL. *Critical Constructivism Primer.* New York: Peter Lang; 2005.
- Krishnan HR, Sakharkar AJ, Teppen TL, Berkel TD, Pandey SC. The epigenetic landscape of alcoholism. *Int Rev Neurobiol.* 2014; 115:75–116. [PubMed: 25131543]
- Kull K, Deacon T, Emmeche C, Hoffmeyer J, Stjernfelt F. Theses on biosemiotics: Prolegomena to a Theoretical Biology. *Biological Theory.* 2009; 4(2):167–173.
- Lederberg, J. Inheritance, variation, and adaptation. Werkman, PWWCH., editor. New York: Academic Press; 1951. p. 67-100.
- Lodish, H., Berk, A., Zipursky, SL., Matsudaira, P., Darnell, J. *Molecular cell biology.* 4th. New York: W. H. Freeman and Co; 2000.
- Luongo TS, Lambert JP, Yuan A, Zhang X, Gross P, Song J, et al. The mitochondrial calcium uniporter matches energetic supply with cardiac workload during stress and modulates permeability transition. *Cell Rep.* 2015; 12(1):23–34. [PubMed: 26119731]
- Maturana, H., Varela, F. *Autopoiesis and cognition: The realization of the living.* Vol. 42. Dordrecht: D. Reidel Publishing Co; 1980. Boston Studies in the Philosophy of Science
- Menant, C. Computation on information, meaning and representations. An evolutionary approach. In: Burgin, GDCaM, editor. *Information and computation Essays on scientific and philosophical understanding of foundations of information and computation.* Vol. 2. New Jersey, London: World Scientific; 2011. World Scientific Series in Information Studies

- Murchison EP, Wedge DC, Alexandrov LB, Fu B, Martincorena I, Ning Z, et al. Transmissible dog cancer genome reveals the origin and history of an ancient cell lineage. *Science*. 2014; 343(6169): 437–440. [PubMed: 24458646]
- Nowak, MA. *Evolutionary dynamics*. Cambridge MA: Harvard University Press; 2006.
- Odling-Smee, JF. *Niche construction The neglected process in evolution*. Princeton, NJ: Princeton University Press; 2003.
- Peirce, CS. *The essential Peirce: Selected philosophical writings*. Vol. 2. Indiana: Indiana University Press; 1998.
- Piaget, J. Developing and learning. In: Rockcastle, RERaVN., editor. *Peaget rediscovered: A report of a Conference on Cognitive Studies and Curriculum Development*. Ithaca NY: Cornell Univ. Press; 1964. p. 7-19.
- Pigliucci, M., Müller, GB. Elements of an extended evolutionary synthesis. In: Pigliucci, M., Müller, GB., editors. *Evolution - the extended synthesis*. Cambridge MA, London: MIT Press; 2010.
- Plattner H. Molecular aspects of calcium signalling at the crossroads of unikont and bikont eukaryote evolution--the ciliated protozoan *Paramecium* in focus. *Cell Calcium*. 2015; 57(3):174–185. [PubMed: 25601027]
- Porter SL, Wadhams GH, Armitage JP. Signal processing in complex chemotaxis pathways. *Nat Rev Microbiol*. 2011; 9(3):153–165. [PubMed: 21283116]
- Prodi G. Material bases of signification. *Semiotica*. 1988; 69(3/4):191–241.
- Puigbo P, Wolf YI, Koonin EV. Seeing the Tree of Life behind the phylogenetic forest. *BMC Biol*. 2013; 11:46. [PubMed: 23587361]
- Ramoino P, Beltrame F, Diaspro A, Fato M. Time-variant analysis of organelle and vesicle movement during phagocytosis in *Paramecium primaurelia* by means of fluorescence confocal laser scanning microscopy. *Microsc Res Tech*. 1996; 35(5):377–384. [PubMed: 8989767]
- Raoult D, Forterre P. Redefining viruses: lessons from Mimivirus. *Nat Rev Microbiol*. 2008; 6(4):315–319. [PubMed: 18311164]
- Rodríguez S. Recurrences and human agential meaning grounding: Laying a path in walking. *Biosemiotics*. 2016; 9(2):169–184.
- Root-Bernstein M, Root-Bernstein R. The ribosome as a missing link in the evolution of life. *J Theor Biol*. 2015; 367:130–158. [PubMed: 25500179]
- Rosen, R. Some relational cell models: The metabolism-repair systems. In: Rosen, R., editor. *Foundations of mathematical biology*. Vol. 2. New York: Academic Press; 1972. p. 217-253.
- Rosen, R. *Life itself: a comprehensive inquiry into the nature, origin, and fabrication of life*. New York: Columbia University Press; 1991.
- Rubin SS. From the cellular standpoint: Structural meaning of exogenetic material. *Biosemiotics*. 2017; 10(2) this issue.
- Russell RJ, Scott C, Jackson CJ, Pandey R, Pandey G, Taylor MC, et al. The evolution of new enzyme function: lessons from xenobiotic metabolizing bacteria versus insecticide-resistant insects. *Evol Appl*. 2011; 4(2):225–248. [PubMed: 25567970]
- Schlosser, G., Wagner, GP. Introduction: The modularity concept in developmental and evolutionary biology. In: Schlosser, G., Wagner, GP., editors. *Modularity in development and evolution*. Chicago, London: University of Chicago Press; 2004. p. 1-11.
- Schott GD. Penfield's homunculus: a note on cerebral cartography. *J Neurol Neurosurg Psychiatry*. 1993; 56(4):329–333. [PubMed: 8482950]
- Sebeok, TA. *Perspectives in zoosemiotics*. Vol. 122. The Hague: Mouton; 1972. *Janua linguarum*. Series minor
- Sebeok, TA., Umiker-Sebeok, JE., editors. *Biosemiotics*. New York: Mouton de Gruyter; 1992.
- Seckbach, J., editor. *Symbiosis: Mechanisms and model systems*. New York, Boston: Kluwer Academic Publishers; 2006.
- Segre D, Shenhav B, Kafri R, Lancet D. The molecular roots of compositional inheritance. *J Theor Biol*. 2001; 213(3):481–491. [PubMed: 11735293]
- Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol*. 2016; 14(8):e1002533. [PubMed: 27541692]

- Sharov AA. Self-reproducing systems: structure, niche relations and evolution. *Biosystems*. 1991; 25(4):237–249. [PubMed: 1742472]
- Sharov AA. The origin and evolution of signs. *Semiotica*. 1999; 127:521–535.
- Sharov AA. Umwelt theory and pragmatism. *Semiotica*. 2001; 134:211–228.
- Sharov AA. Functional information: Towards synthesis of biosemiotics and cybernetics. *Entropy*. 2010; 12(5):1050–1070. [PubMed: 22368439]
- Sharov AA. Evolutionary constraints or opportunities? *Biosystems*. 2014; 123:9–18. [PubMed: 25047708]
- Sharov AA. Coenzyme world model of the origin of life. *Biosystems*. 2016a; 144:8–17. [PubMed: 26968100]
- Sharov AA. Evolution of natural agents: preservation, advance, and emergence of functional information. *Biosemiotics*. 2016b; 9(1):103–120. [PubMed: 27525048]
- Sharov AA. Evolutionary biosemiotics and multilevel construction networks. *Biosemiotics*. 2016c; 9(3)
- Sharov AA, Vehkavaara T. Protosemiosis: agency with reduced representation capacity. *Biosemiotics*. 2015; 8(1):103–123. [PubMed: 25937852]
- Shenhav B, Oz A, Lancet D. Coevolution of compositional protocells and their environment. *Philos Trans R Soc Lond B Biol Sci*. 2007; 362(1486):1813–1819. [PubMed: 17510019]
- Szostak JW. An optimal degree of physical and chemical heterogeneity for the origin of life? *Philos Trans R Soc Lond B Biol Sci*. 2011; 366(1580):2894–2901. [PubMed: 21930580]
- Tønnessen M. The Biosemiotic Glossary Project: Agent, agency. *Biosemiotics*. 2015; 8(1):125–143.
- Treangen TJ, Salzberg SL. Repetitive DNA and next-generation sequencing: computational challenges and solutions. *Nat Rev Genet*. 2011; 13(1):36–46. [PubMed: 22124482]
- Turchin, VF. The phenomenon of science. New York: Columbia University Press; 1977.
- Vehkavaara T. Natural self-interest, interactive representation, and the emergence of objects and Umwelt. *Sign Systems Studies*. 2003; 31(2):547–587.
- Vehkavaara, T. From the logic of science to the logic of the living. The relevance of Charles Peirce to biosemiotics. In: Barbieri, M., editor. *Introduction to Biosemiotics: the New Biological Synthesis*. Dordrecht: Springer; 2007. p. 260–262.
- Villarreal, LP. Origin of group identity Viruses, addiction and cooperation. New York: Springer; 2009.
- Villarreal LP, Witzany G. Viruses are essential agents within the roots and stem of the tree of life. *J Theor Biol*. 2010; 262(4):698–710. [PubMed: 19833132]
- Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol*. 2015; 35(Suppl):S185–198. [PubMed: 25818339]
- von Neumann, J. *Theory of self-reproducing automata*. Urbana: University of Illinois Press; 1966.
- von Uexküll, J. A stroll through the worlds of animals and men: A picture book of invisible worlds. In: Schiller, CH., editor. *Instinctive Behaviour: The development of a modern concept*. New York: International Universities Press Inc; 1957. p. 5–80.
- von Uexküll J. The theory of meaning. *Semiotica*. 1982; 42(1):25–82.
- von Uexküll T, Geigges W, Herrmann JM. Endosemiosis. *Semiotica*. 1993; 96(1-2):771–817.
- Waddington CH. Towards a theoretical biology. *Nature*. 1968; 218(5141):525–527. [PubMed: 5650959]
- Weiss, G. *Multiagent systems*. Cambridge MA: MIT Press; 2013.
- Yolles, M. L Swan (Ed), *Origins of mind*. 2006. Minimal mind; p. 343–360.
- Sharov, AA. *Organizations as complex systems: an introduction to knowledge cybernetics*. Vol. 2. Greenwich CT: Information Age Publishing; 2013. Managing the complex

Figure 1.

Lineages of agent construction: (A) clonal self-reproduction, (B) biparental self-reproduction, (C) communal construction of cellular subagents. Ovals show interaction of parental agents; thick arrows show dominant information effects.

Figure 2. Organelles of a *Paramecium* single-cell organism. Modified from Wikipedia Commons, file:Paramecium_sp.jpg.

Figure 3.

Two types of meta-system transitions: (A) metagenesis – reproduction without separation (phase I) followed by specialization (phase II) and mutual regulation (phase III); (B) sybiogenesis – cooperation of non-related organisms (phase I) followed by diversification of symbionts (phase II) and mutual regulation (phase III).