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PRELIMINARY REMARKS TO AN INTEGRATIVE THEORY OF EVOLUTION

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KEYWORDS: RNA-World, Virosphere, Biocommunication, Epigenetics, Modern Synthesis, Integrative Theory of Evolution.

ABSTRACT: *For nearly a century the main focus in biological disciplines such as molecular biology, biochemistry, genetics and evolutionary theory was cellular life as a machine like process in which mechanistic pathways regulate metabolism, genetic reading and translation into proteins and evolution by variations (random error replications) and selection. Modern biochemistry started with the cellular theory of life. Also the modern synthesis focused on cells at the starting event of life. The dominance of this paradigm lasted until ten years ago. Then the comeback of virology offered new empirical data and explanatory models of how viruses determine cellular life through an abundance of parasite host interactions that overrule cellular*

processes. The RNA world hypothesis demonstrated that prior to cellular life RNA group interactions were at the beginning of biological selection before cellular life emerged. Last but not least the central dogma of molecular biology collapsed when epigenetics demonstrated that history and developmental experiences of the past can be epigenetically imprinted and serve as identity markings that in every replication process of any cell in any organism on this planet the timely and locally coordinated replication is regulated and orchestrated by these programmings. In the light of this knowledge a better explanatory model than an extension of the modern synthesis will be more successful in the 21st century.

1. INTRODUCTION

ACCORDING the technical equipment in the first half of the 20th century and the rising sciences of biology it is not surprising that cellular life was in the focus of all investigations, measurements and theoretical models. Evolution of life starts with the first cell and further evolutionary processes occurred by random mutations (error replication) and selection on cellular life. According to the theoretical foundations of the methodology of natural sciences a strict physical chemical description of empirical data was favoured because it was assumed that only mathematical equations can depict material reality in a 1:1 manner. Accordingly biological sciences based their assumption on the definition of life by Nobel Laureate

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Erwin Schrödinger: “Life is physics and chemistry”. Additionally four main assumptions dominated the last half century: (1) one gene-one protein concept, (2) central dogma of molecular biology (DNA-RNA-Protein), and (3) non-coding DNA representing “junk”; (4) genetic variations are the result of error replication events on which selection works.

Meanwhile these core assumptions of the 20th century have been falsified (Shapiro 2009; Mattick 2009a; Witzany 2020a). The gene concept in general is in question, because genes together with their regulatory elements are constantly in a dynamic plasticity that is expressed according to the context dependency of the whole organism involved in real life world interactions and therefore genetic sequences may code for several protein products not only for one. The central dogma proposing the irreversible information flow from RNA to DNA and protein is falsified through knowledge on protein to RNA interactions, e.g., such as all the reverse transcriptase (and RNase H) related processes, the roles of various ribonucleoprotein complexes, the miRNA binding proteins and RNA to DNA information flow (Mattick 2009a; Shapiro 2009; Moelling and Broecker 2015). Also the decades dominating explanatory model, that non-coding DNA is junk and represent useless remnants of former evolutionary stages is falsified through knowledge on the role of non-coding RNAs being relevant in all processes of gene regulation such as transcription, translation, repair, immunity and epigenetic regulation in all steps and substeps. Last but not least the error replication narrative: Yes, error replication is an empirical fact, but error replications do not play important roles in evolutionary processes which are outlined by mobile genetic elements, non-coding RNAs, and persistent viruses that together are the tools for natural genome editing of host genomes (Villarreal 2005; Witzany 2009a; Frias Lassarre 2012). Let's now look at current empirical knowledge on agents that are competent to edit genetic codes of host organisms and generate nucleotide sequence also *de novo*.

2. THE ANCIENT AND THE CURRENT RNA-WORLD

The dramatic change in biology to look not only at cells as the dominant living agents was the rising knowledge about the roles of RNA in all biological processes. Prior to this RNA was noticed as a transitory state in DNA replication with some helper functions. But investigation showed that without RNAs no biological process can function. Additionally it was mentioned that RNAs were abundant before the emergence of cellular life in evolutionary history of this planet (Gilbert 1986; Noller 2012).

One interesting feature of RNA sequences is that if there are few RNA molecules in a line they spontaneously snap back to themselves and form the basic RNA entity, a complementary paired double stranded stem and at the snapback angle a single stranded loop, designated as RNA stem loop or RNA hairpin. Wherever we find ensembles of RNAs or all the conserved RNA structures stored in the DNA storing medium of living organisms we also found ensembles of such RNA stem loops in most cases with different emergence and assembling histories (Harish and Caetano Anolles 2012). Since the 90s of the last century an increasing number of investigations on the interactional motifs of RNAs showed that there is a critical quantity

where RNA interactions constitute biological processes: Whereas single RNA stem loops react according to physical chemical laws exclusively, if multiple RNA stem loops meet biological selection starts (Larson *et al.* 2012; Vaidya *et al.* 2012; Gwiazda *et al.* 2012; Petkovic and Muller 2013; Vaidya 2013).

At the single stranded RNA loops there is a binding prone interaction motif to other single stranded loops of other RNA stemloops which can build larger groups with ribozymatic features. Such group ensembles parasitize and integrate foreign RNA stem loops and outcompete less complex and less functional RNA group ensembles (Eigen 1972; Villarreal and Witzany 2013a; 2018). The early RNA group interactions resemble a kind of social behavior although it is hard to imagine solely RNA molecules to represent living nature (Witzany 2016a; Villarreal and Witzany 2021a). Without a doubt RNA ensembles generate biological information in that they represent agents that interact far from abiotic reaction patterns or as Manfred Eigen stated them as self-instructing species, that “resemble, in many ways, social behavior” (Eigen 1972).

The RNA world hypothesis attained more and more plausibility as it can explain the fundamental roles of RNA ribozymatic and information transporting functions of living cells especially the abundant roles of non-coding RNAs in all gene regulatory processes (Cech and Steitz 2014). Without the ribosome – which in real represents a ribozyme at its core with structure stabilizing proteins on its periphery – no living cell could reproduce life (Root-Bernstein and Root-Bernstein 2015). Ribosomal RNAs, transfer RNAs and messenger RNAs are at the the core of cellular reproduction processes in all organisms in all domains of life since the evolutionary start of cellular life. Most importantly certain highly specialized RNA-groups modulate cellular transcription and translation processes in a context dependent way with RNA-editing, alternative splicing, a variety of tRNA derived fragments, pseudo knotting, ribosomal frameshifting, loop kissing and bypassing translation. (Cech 2012; Witzany 2020a). Various combinations of such modulatory processes ensure plasticity of meaning (function) of genetic information. Such combinatorial results can be epigenetically marked according experienced context in which organisms are embedded (Doudna *et al.* 1989; Blaze and Roth 2012). Additionally all the RNA stem loop modules are prone to exaptation processes, especially the simple structured tRNA fragments (Brosius 1999; Sun and Caetano Anolles 2008; Kim *et al.* 2017; Grigoriev 2021).

3. THE ANCIENT AND THE CURRENT VIROSPHERE

The quasi-species concept of Manfred Eigen is still dominating our view on RNA viruses because they are the older ones and existed prior to the emergence of DNA, which is subsumed being the result of an escape invention out of the highly competitive but interaction rich and volatile RNA world into a stable information storage medium.

With the quasispecies theory the bridge was built from complex RNA group behavior and evolution to the virosphere. Whether viruses are alive or not is still in debate, but without any doubt viruses are the most abundant biological entities on this planet (Villarreal 2005; Nasir and Caetano Anolles 2015). If we would place the

abundance of phage virions on this planet (10^{31}) side-by-side this would reach a distance of more than 42 million light years (Rohwer 2014). For example half of the global bacterial populations are killed every day by the most abundant living entities on this planet: phages. Bacterial survival fitness depends on their high reproductive ability. In 1 ml seawater we can find 1 million bacteria but 10 million viruses. Cell based organisms represent rare islands in a sea of viruses. Viruses and their relatives constantly attack cellular organisms and immune systems are constantly forced to fight back.

Viruses are the only living entities that may exchange genetic sequences as module-like tools between double-stranded DNA, single-stranded DNA, single-stranded RNA, double-stranded RNA, and retroviruses.

Most viruses do not harm their hosts but associate in a symbiotic or even symbiogenetic way. They insert and delete into host genomes and remain as silent (temperate) viruses or in most cases as “defectives”, parts such as SINEs, LINEs, ALUs, long terminal repeats and non-long terminal repeats and various other genetic parasites, such as transposons and retrotransposons, plasmids and group II introns all of them being exapted or co-adapted to cellular needs of their host organisms (Weiner 2006; Witzany 2009a; Koonin and Krupovic 2014, 2018; Vignuzzi and Lopez 2019; Waldern *et al.* 2021). As we know from abundant investigations the roles of infection derived mobile genetic elements in evolutionary adaptive processes for cellular organisms is essential. RNA viruses, non-coding RNA and related quasiespecies share a repetitive sequence syntax, whereas the coding DNA that codes for proteins is missing such repetitive sequences. Wherever we can identify such repetitive nucleic acid sequence syntax, e.g. in intronic regions of the genome, an infection event by genetic parasites can be therefore reconstructed (Edgell *et al.* 2011; Witzany 2017a). If we look at the human genome we can find 1,5% of the DNA coding for proteins of the body whereas 98,5% represents non-coding DNA with repetitive sequence syntax.

Because most sequences of viruses are not found in any organism on this planet it is assumed that viruses predate cellular life. Without doubt, cellular life is a result of virus-cell interactions (Koonin 2009). Especially the eukaryotic nucleus with its genetic integrating and conserving capabilities looks like a large double stranded DNA virus which could assemble former free living prokaryotes into an ensemble with a stably conserved DNA reproduction blue print (Bell 2020; Takemura 2020).

Because of the mass of competing genetic parasites for infection of cellular life, cell based life represents a rare resource for viruses which depend on reproductive capabilities of cellular life. This leads to an abundance of so called addiction modules, in which counter competing genetic parasites are integrated into host genomes together with a host immune system (Villarreal 2012a). We can find them in prokaryotes as Toxin/Antitoxin modules or restriction/modification or other insertion/deletion modules. Such modules protect the prokaryotic host from toxic lysis by its protective antitoxin, but the toxic feature is dangerous for prokaryotic predators or host which do not have the protecting antitoxin (Mruk and Kobayashi 2011). Also the CRISPR/Cas adaptive immune system of prokaryotes represents the way that parts of the attacking genetic parasites are integrated into the host genome and serve as part of the immune function against related genetic parasites (Koonin and

Makarova 2019). Throughout all domains of life we can find the genetic regulation and counterregulation together with start and stop signals being results of such addiction modules. If such regulation gets out of control or gets weak in aging processes or in other stressful situations, disease or death may be the result (FIG. 1).

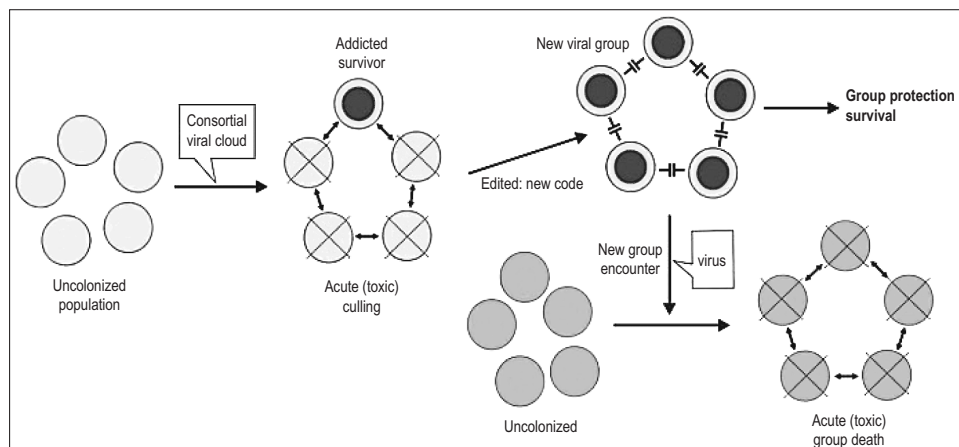


FIG. 1. Basic interactional motif of infection-derived group identities: the addiction module is the result of counterbalanced, infection-derived, and persistent genetic parasites that initiate evolutionary innovations by natural genome editing of host genetic identities. Some we can find as toxin/antitoxin, restriction/modification, insertion/deletion or similar counterregulating modules.

(From Villarreal 2012b. With permission).

Because the virus-host interaction motifs are so intense and in many cases symbiotic to every cell of every organism on this planet and cellular life as well as viruses in a global perspective crucially depend on each other it would be illogical and against all aspects of energy economics for the highly efficient genetic parasites to conserve a redundant genetic self-reproducing module. Therefore it is clear that viruses do not need their own reproductive apparatus because as long as cells are living this is the more efficient way to reproduce than as their own entity. The empirical data suggest viruses being essential agents of life and main drivers in every evolutionary process. Therefore it makes sense to use the term “violution” in evolutionary processes, in which viruses, their relatives or viral derived parts (defectives) play essential roles (Ryan 2009; Witzany 2012a; Villarreal 2015)

4. BIOCOMMUNICATION AS UNIFYING INTERACTION MOTIF

Basically all three levels of living agents, RNA groups (quasispecies), viruses and cell based organisms are intertwined and depend on each other (Villarreal and Witzany 2019, 2021). Would one domain be removed life as we know it would not function. Although the three levels of sign-mediated interactions are quite different in RNA groups, viruses and cell based organisms the unifying motif is the communicative interaction to coordinate and organize common behavior in a species specific way or in an interaction-relation to the host organism.

It is important to note here, that communication within and between living organisms is mediated by signs according three levels of rules: Syntactic rules govern combinations of signs into more complex sign sequences, pragmatic rules govern how living agents use signs according contextual needs and semantic rules govern the correct designation objects (Witzany 2016b). Communication essentially is a social event because it always depends on concrete living agents that together share and use a repertoire of signs and a repertoire of rules, which means one living agent could not invent language or communication (Witzany 2019). It is important to mention here that all kinds of mathematical theories of language and communication which where usual in the 20th century have been falsified in the meanwhile. They cannot explain the typical features of language use in communication processes that with a superficial sign sequence a real life sign user can transport a variety of meanings, because context determines meaning not the syntax. If we take for example the sentence “The Shooting of the Hunters” there is no way to extract concrete meaning out of the syntactic structure (FIG. 2).



FIG. 2. Context determines meaning (e.g. “The shooting of the hunters”) not syntax. Similarly the superficial grammar of DNA does not determine its meaning. The in vivo context which results in epigenetic markings represents a variable deep grammar which determines post-transcriptional modifications such as RNA editing and alternative splicing. Therefore in contrast to the opinions of Manfred Eigen, Sidney Brenner or Craig Venter algorithm-based DNA processing cannot generate both, superficial and deep grammar. (Graphics design: Uta Mackensen, Baluška and Witzany 2012a; With Permission).

A given syntactic sequence structure does not represent an unequivocal meaning (function). Communicating living agents of all domains do not interact mechanistically (Baluška and Witzany 2014). Especially the competence of living agents to generate sign sequences *de novo* and generate new, unexpected and non computable behavioral features that do not fit into the models of mathematical theories of language and communication (Witzany 2017b).

4.1. Cellular Communication

Cells, tissues, organs, and organisms actively coordinate and organize their behavior. This needs signals. Biotic signaling with molecules, serves as a primary tool to coordinate groups of individual living agents such as cells and organisms. Only in plants but most prominently in animals electrical neuronal signalling is dominant. Current knowledge indicates communication as a basic interaction within and between organisms in all domains of life (Witzany 2014a). We can find them in all known phages, akaryotes, protozoa, fungi, animals and plants (Witzany 2011, 2012, 2014b, 2016, 2017c, 2020b, Witzany and Baluška 2012b, Witzany and Nowacki 2016). Communicative interactions are essential within organisms – intraorganismic – to coordinate cell-cell interactions, similar to tissue-tissue and organ-organ coordinations as well as intracellular signaling. Additionally we may identify the interpretation of abiotic environmental indices such as light, temperature, gravity, water, or nutrient availability and sensing, monitoring, and feedback control against stored background memories. We find interorganismic communication in all signal-mediated interactions between same and related species. If species communicate with non-members, we term this transorganismic communication. The symbiotic interactions throughout the living world on this planet demonstrate that. Throughout all kingdoms of life, we do not find any coordination and organization that does not depend on communication (Witzany 2000, 2005).

If we remove communicative interactions based on signals no biological process would occur. Cells coordinate their behavior with other cells by a variety of interaction motifs mediated by various molecules that are generated, sent, received, recycled and adapted. This means cellular organisms with their tissues and organs must coordinate and organize these processes in a rather strict and confident way to secure survival. 38 billion cells are renewed in human body every day and every new cell is the result of a signal, that is sent before living cell is dying or damaged and a new one which is essential to the whole body is produced in a timely and space coherent manner (Sender and Milo 2021). If we investigate the levels of cell cell communication we can identify 4 different levels on which cells communicate throughout their lives (FIG. 3).

Take for example an attractive symbiotic ecosphere of single celled akaryotes that live within host organisms such as bacteria that e.g., settle in the human oral cavity. Here we can find 500 different species with a total of more than 3 billion exemplars that settle within their colonies and share a highly differentiated communicative interaction motif between themselves, between themselves and non-self communities and between themselves and human host. If the communication

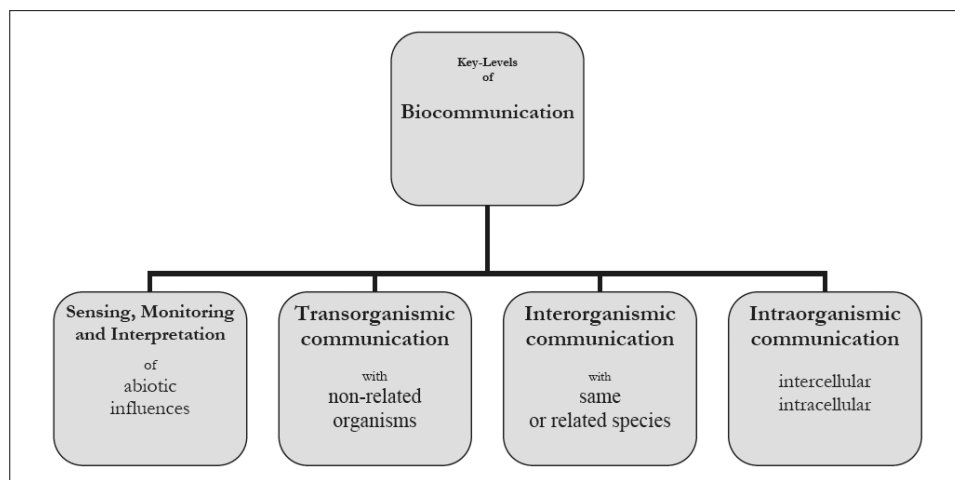


FIG. 3. Key levels of biocommunication in all cell based organisms of all domains of life.

functions to reach an equilibrium the human oral cavity is healthy if the communication is disturbed by overwhelming pathogens disease will be the consequence. (Kolenbrander 2000, *et al.* 2002). Another intriguing example is the complex communication in the plant rhizosphere between plant roots, rhizobacteria, fungi and insects. Plants fundamentally depend on this communicative interactions with several symbiotic partners (Bais *et al.* 2003; Perotto and Baluska 2012)

4.2. Quasispecies Communication

Besides cell-cell communication processes across the whole body with its various highly specialized cell cultures such as tissues and organs, the communication of viruses with themselves and with host organisms, RNA-group communication built different levels of interaction. Together they resemble life as we know it in a complementary way (Root-Bernstein and Dillion 1997). If only one level was missing, life would not function.

RNA stem-loop groups interact with other DNA, RNA, or proteins forming the most important ribo-nucleo-protein complexes (RNP), such as the complementing subgroups of ribosome, spliceosome, and editosome (Mercer and Mattick 2013). Their active site that leads to group behavior are the single-stranded loops or bulges being essential for self/ non-self recognition and group identity.

Ensembles of RNA fragments that self-ligate into self-replicating ribozymes may form cooperative networks unexpectedly (Smit *et al.* 2006; Briones *et al.* 2009; Cheng and Unrau 2010). It has been demonstrated that three-member networks represent cooperative growth dynamics. If such cooperative RNA-networks compete against selfish RNA stem-loop groups, they grow faster which means RNA populations can evolve higher complexity by cooperative interactions. This also demonstrated that cooperation outcompetes selfishness (Hayden and Lehman 2006; Vaidya *et al.* 2012).

Additionally, these single-stranded loops are actively prone to integration or rejection of foreign RNA stem-loops (Higgs and Lehman 2015). Their highly interaction-prone nucleotide “surface” serves as signs (indexical) for competing or cooperating RNA stem-loops, based on complementary base-pairing rules (Schudoma 2011). We can see this also in RNA mimicry as demonstrated recently (Ariza-Mateos and Gómez 2017; Grüll and Massé 2019). Especially the recognition competence of ribozymes will lead to technical exploitation to fight viral diseases because ribozymes are experts in targeting foreign RNA sequences. (Betrand and Rossi 1996, Mishra *et al.* 2016, Berzal-Herranz and Romero-López 2021).

In contrast to cell cell communication RNA groups do not produce chemical signals to transport messages which trigger response behavior. RNA stem loop groups only communicate by signs they are representing themselves, which means they interact by their single stranded loops that fit to non-self loops in a complementary base pairing way (Witzany 2015). They are part of a physical chemical interaction pathway only and the communicative signs we may identify as indices. But as a group stabilized by protein structures they may colonize non-self RNAs and foreign RNA groups, or successfully defend their self status if attacked by others. As part of a group they show biotic interaction motifs that underly selection processes which are completely absent on abiotic planets. The basic RNA group behavior to all living processes led to the suggestion that RNA-networks interact like “Gangs”, in which the only relevant interaction status is the result of contextual needs and additionally may integrate former rejected parts with opposite functions (Villarreal 2015, FIG. 4).

4.3. *Virus Communication*

Virus communication demonstrates that quasispecies populations and subpopulations may cooperate and compete in parallel, dependent on the circumstantial context of host life. Former competing and rejected non-self RNA groups with opposite function may be, later on, integrated if the contextual circumstances better fit such cooperation (Villarreal and Witzany 2019). Social interacting persistent viruses play important roles as host gene regulatory elements – in most cases represented by repetitive sequences – that may react to nearly every unexpected circumstance (Díaz-Muñoz *et al.* 2017; Sanjuán 2018).

Viruses are the only biotic agents that can generate code sequences *de novo*, identify sequence-specific target sites, integrate into pre-existing genetic content, integrate without damage of previous coding regions, recombine according to adaptational purposes, and mark sequence sites to epigenetically fix identity content (Villarreal 2005, 2009b). The whole range of epigenetic marking, which is so essential for cellular-based organisms to coordinate the variety of developmental stages stems from these infectious agents and has been adapted to cellular needs (Wilke and Novella 2003; Witzany 2009a; Murphy *et al.* 2013). Viruses may divide into multipartite genome segments, spread their parts non-randomly throughout host genomes, and reassemble into full functional viral genomes again (Villarreal 2005; Sicard *et al.* 2016, 2019; Lucía-Sanz and Manrubia 2017).

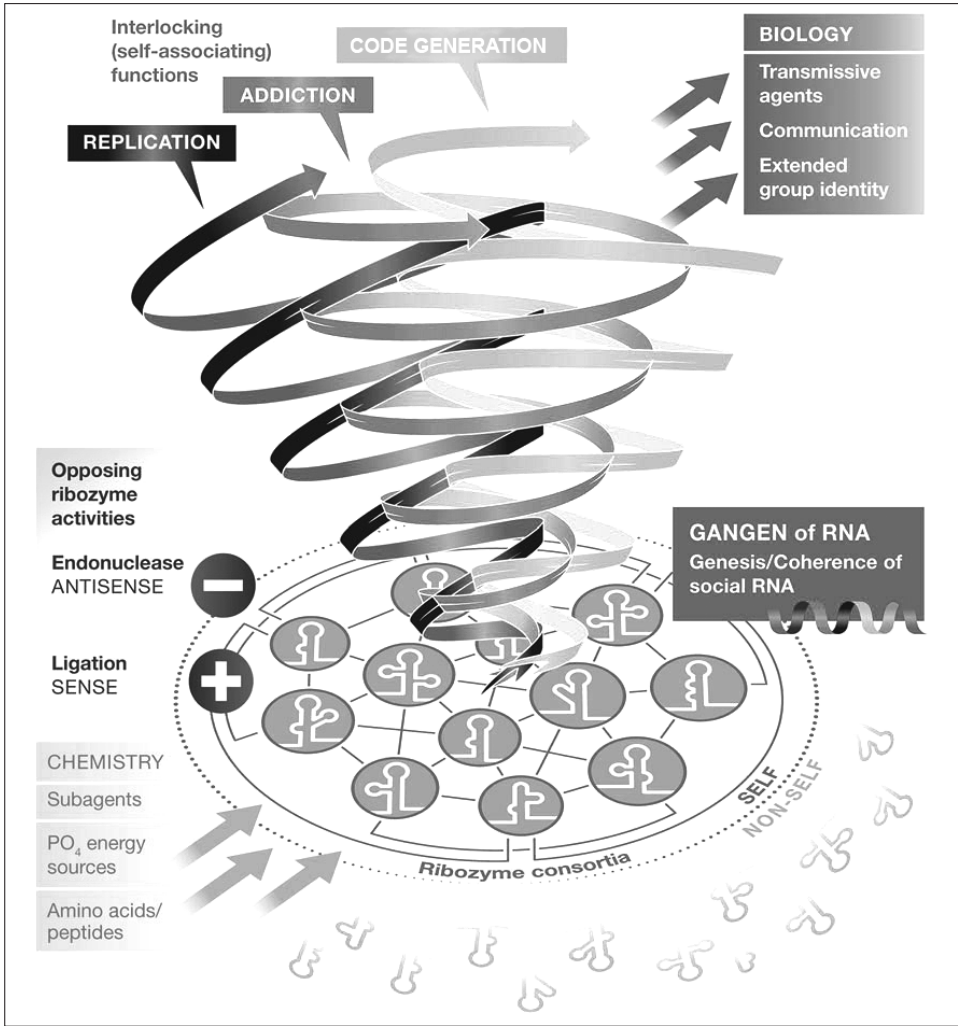


FIG. 4. The RNA gangen hypothesis: group identity and cooperativity of an RNA collective that requires opposite functions for the genesis of life (social behavior of agents). (From: Villarreal 2015. With Permission).

Current research demonstrated that viruses communicate to coordinate their behavior whether it should be lytic or remain in a lysogenic style. The semiochemicals used to communicate at interorganismic levels are peptides (AimP), which reduce the expression of the negative regulator of lysogeny (AimX) by binding to the transcription factor (AimR) promoting lysogeny (Erez *et al.* 2017; Stokar-Avihail *et al.* 2019). Interactional motifs in virus communication range from conflict to cooperation in various forms and mimicry, dependent on situational context (Mei and Zhang 2019; Seligmann 2019).

Viruses are the only living entities that may exchange genetic sequences as module-like tools between double-stranded DNA, single-stranded DNA, single-stranded RNA (+/-), double-stranded RNA, and retroviruses. Most interestingly, as viral clouds they may cooperate and compete in parallel (Koonin *et al.* 2015; Stedman 2015, 2018; Berliner *et al.* 2018).

Virus communication finds itself between quasispecies communication and cellular communication. For e.g. pure RNA viruses that consist of RNA stem loop ensembles only (Flores *et al.* 2012, 2014). They resemble quasispecies communication motifs. As enveloped capsid embedded viruses such viruses also produce peptides as signals for coordinated interactions by common invasion strategies (providing group behavior of self) to attack non-self.

5. EPIGENETICS OR HOW EVOLUTION LEARNED TO LEARN

As we can see on three different levels of communication motifs in the cellular world, the RNA world and the virosphere biotic behavior from the beginning depends on self/non-self differentiation, which means attack and defense of self against non-self agents (Villarreal and Witzany 2019). This means the competence to differentiate between self and non-self is at the beginning of biotic features up until today (Villarreal 2012b). Identity versus non-identity, identity change, identity modulation, identity modification, serving and protecting genetic identities against genetic parasites, the integration of genetic non-self parts into self of host, which then changes (adapt) host genetic identity is a main driver of evolution of immune systems and immune functions (Villarreal 2009a, 2011; Broecker and Moelling 2019). Biocommunication and the success of coordination and organization of cells, tissues, organs and organisms depends on identities which clearly differentiate self from non-self (Witzany 2015). Looking at the interaction profile of genetic parasites and hosts throughout the evolutionary history demonstrates an ongoing never ending and constant interaction and adaptation of immune systems, which means identity systems (Koonin and Krupovic 2014, 2017).

Because every living cell or living organism is the result of a long evolutionary history in which the survived species were successfully protecting self from non-self by their immune functions against genetic parasites, we may look at immune systems as secure identity pools, in that they guarantee the genetic identity of the organisms by rejection of invading and damaging genetic parasites (Villarreal 2009b). Immune systems strongly depend on a very ancient biological interaction motif, which started in the old RNA world. The differentiation competence between self and non-self (Chen *et al.* 2017). Non-self can be deadly, neutral, helpful in a complementary way and these relationships are highly context dependent. Which means in the next moment if environmental situation changes through various reasons the deadly non-self may be helpful or neutral and the helpful genetic parasite may become deadly again. Life moves between high reproductivity to escape the constant immune attack by parasites to identify non-self agents that could harm self and integration of former dangerous non-self agents as useful cooperative parts if circumstances change. This represents real life adaptation.

The genetic parasite predators constantly produce new variants to circumvent the immune function of host organisms. Such innovation pressure lead to the origin of the DNA methyltransferase that later was exapted in eukaryotes for epigenetic markings (Murphy *et al.* 2013). The host organisms integrates new capabilities of parasites to update the immune function against newly emerged genetic parasites (Barrangou *et al.* 2013, Waldern *et al.* 2021). Together this indicates a memory system in which attack and defense are entangled into a coherent interaction motif on which future generations can build up. Such processes look like learning processes, learning to adapt and learning to evolve like the adaptive immunity, which means generating new and innovative variants as relevant players in selection processes (Villarreal 2009a; Boehm and Swann 2014, Lau *et al.* 2018).

The regulatory system that works in development, morphology, cell fate and identity, physiology, genetic instructions, immunity, memory/learning, physical and mental disease depends on epigenetic marks (Jablonka and Lamb 2002; Shapiro 2016; Matt *et al.* 2021). The gene-centrism of the 20th century was misleading to explain the various processes listed above (Shapiro 2005). Genetic sequences of all organisms in all domains of life can be marked according to their environmental and social experiences (Baulcombe and Dean 2002; Braun *et al.* 2020). The communication of cells, persistent viruses and their defectives such as mobile genetic elements and especially non-coding RNA networks ensure both the transport of regulatory instructions and the (re-)programming of these instructions (Slotkin and Martienssen 2007; Maksakova *et al.* 2008; Mattick *et al.* 2009a; Mattick 2018; Frias Las-sarre and Villagra 2018).

With the emergence of epigenetic memory, organisms can fix historical and context- dependent impressive experiences. Evolution from now on learnt to learn (Mattick 2009b). Learning means organisms can avoid reproduction of always the same various genetic and behavioral motifs in living organisms (Watson and Szath-mary 2016). This is key to adaptation.

Epigenetic regulation emerges as a fine-tuned genome-wide network that can rapidly remodel and reprogram genetic content. Epigenetic switching outcompetes genetic mutations (error replications) during adaptation to changing lifeworld (Stajic *et al.* 2021, Gomez-Schiavon and Buchler 2019). Epigenetic markings can have both short-term and long-term functional effects such as soma to germline inheritance (Chen *et al.* 2016; Spadafora 2017; Sciamanna *et al.* 2019). However, inheritance of acquired characteristics is only one of the many examples of the explanatory power of epigenetics (Veigl 2019). Behavioral epigenetics demonstrates the way in which environmental and social experiences produce individual differences in behaviour, cognition, personality, and mental health (Moore 2017; McGowan and Roth 2015).

6. AN EXTENDED MODERN SYNTHESIS CANNOT INTEGRATE THAT

The modern synthesis or the more popular designation of Neo-Darwinism which wanted to update Darwins theory of evolution into the 20th century and adapting molecular biological knowledge as well as modern genetics as key elements to describe evolutionary pathways cannot integrate the above outlined empirical knowl-

edge. Small mutations, which means random-like error replications that accumulate via selection processes together with Mendelian genetics cannot coherently explain the emergence of complexity of innovative tissues, organs and organisms. Also an extended modern synthesis insists on “mutation” because “error replication” should mechanistically explain the generation of variations without which selection processes could not work. The main proponents of Neo-Darwinism did not know about the complex levels of communication outlined above, as they did not know the roles of persistent viruses and their defectives in natural genome editing of host organisms, the roles of non-coding RNAs and RNA group behavior and their roles in genetic regulatory processes which clearly outdates the random mutation narrative (Witzany 2009b, 2011b; Shapiro 2011).

Therefore we may assume the Neo-Darwinistic explanatory model or the Modern Synthesis as insufficiently complex to integrate the above summarized empirical data. It makes less sense to try to integrate somehow this data into the old paradigmatic key terms than to adapt them. The whole theoretical construction cannot integrate the current empirical knowledge also because mechanistic explanations cannot coherently depict non-mechanistic interactions such as communicative interactions. Therefore it is inescapable to develop a new explanatory model of evolution, that can integrate Darwinian theory of evolution, current knowledge on genetics and especially epigenetics, molecular biology, virology, taxonomy and biocommunication research and therefore represents better explanatory power than the modern synthesis. We may term this the integrative theory of evolution.

7. CONCLUSIONS

Explanatory models that cannot integrate the roles of the virosphere and RNA-networks on cellular evolution and development are outdated. The role of viruses and their behavioral main motif, *i.e.*, the persistent status in host organisms as defectives with an abundance of exapted and co-opted regulatory functions, the abundance of non-coding RNAs as key regulators of host genes, the epigenetic programming of each cell of every organism in all domains of life by epigenetic markings and the way how evolution learnt to learn by memorized experienced context to avoid reproduction of always the same has to be integrated into an updated theory of evolution. The modern synthesis and its quasi-dogmatic insistence in old main narratives of the 20th century such as the one gene one protein, the central dogma of molecular biology, non-coding RNA is junk and variations are the result of random-like error replication events are insufficiently complex to integrate the abundance of current knowledge on viruses, non-coding RNAs and their role in natural genome editing. Additionally identity, history and context has to be coherently outlined within an integrative theory of evolution which represents the next step after the mechanistic paradigm of the 20th century.

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