3 The Secrets of Life

The Vital Roles of RNA Networks and Viruses

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Viruses and related infectious genetic parasites are the most abundant biological agents on this planet. They invade all cellular organisms, are key agents in the generation of adaptive and innate immune systems, and drive nearly all regulatory processes within living cells.

The lives of humans and other large animals might seem distantly connected to bits of subcellular agents such as viruses and similar genetic parasites. Their fates, however, are intimately entwined. A typical human body contains more microbes than human cells, and incorporation of retroviruses and related genetic parasites into DNA accounts for at least half of the human genome. Understanding human life requires understanding life – and, specifically, communication and cooperation – on the tiniest of scales.

The modern philosophy of communication makes clear that natural languages or codes emerge through population-based interactions. Any natural language or code is the result of social interaction in which biotic populations can communicate, to coordinate and organize common goals. No natural language speaks itself, and no natural code codes itself. Therefore, there must be competent agents to generate language signs or codes (including the genetic code), combine signs to sequences based on grammar rules, designate something by content-coherent rules (*semantics*), and use signs in communicative interactions in real-life circumstances in a context-dependent way (*pragmatics*).

The study of ribonucleic acid (RNA) and viruses (*virology*) has illuminated how and why a genetic code emerged, evolved, and plays essential roles in all living agents on this planet. Examining the genetic code together with current RNA biology and virology reveals that RNA and viruses *cooperate*. In addition, scholarly cooperation between virology and philosophy of communication creates a new perspective to better understand life, its complexity, and its

evolution. Cooperation – not selfishness – provides the key to understanding the secret of life. In this essay, we describe some of the most important themes of this cooperation.

Falsified Key Assumptions of the 20th Century

Several key assumptions of the last century serve as a basis for a picture of life, a picture which underlies most research projects and convictions on emergence of disease, and therefore underlies investments in the development of new drugs. Those assumptions no longer hold up against scientific knowledge:

- The *one gene-one protein hypothesis* has been falsified through *epigenetics,* which demonstrates that *varieties* of different proteins can be translated out of *identical* genetic information.
- The idea that *noncoding deoxyribonucleic acid (DNA) is junk* has been falsified by demonstrating that noncoding regions assemble noncoding RNAs that *play essential roles* in transcription, translation, and an abundance of gene regulations.
- The *central dogma of molecular biology* (DNA →RNA → Protein) has been falsified by demonstrating that RNAs that *regulate gene expression* may be coded into DNA or, together with proteins, change genetic identities.
- The idea that *evolution results entirely from random genetic variations and biological selection* has been falsified. Genetic variations have been assumed to be caused mainly by replication errors. Today's genomic analysis reveals that besides error-based mutations that may cause disease, *most beneficial genetic variations are the result of persistent viruses and their defective relatives* such as transposons and retrotransposons.

A New Picture of Life

Exposing the deep flaws in those key assumptions has set the stage for a new picture of life, a view grounded in radically new understandings of the roles DNA, RNA, and viruses.

DNA Serves Only as Habitat (the "House"), RNAs Act as Inhabitants

For decades, DNA has been the central focus of efforts to understand the determinants of evolution and development of all organisms (except RNA viruses). DNA sequencing promised knowledge

about which genes are responsible for features, capabilities, and disease in all life forms, including humans. Genetic manipulation as well as genetic engineering in breeding and gene therapy mainly looked at DNA as a toolbox of molecular bricks. This focus persists today. But DNA is only a relatively stable storage medium. DNA is inhabited by RNA parasites with a variety of group-behavioral motifs and goals. Given the more active and dynamic role for RNA in living organisms, we should consider RNAs as the living agents and DNA as their habitat. From this perspective, RNAs can be seen as open space invaders.

Evolution of Genetic Novelty by RNA Groups

How do RNA parasites exceed their physio-chemical boundaries to transform life? Even at this subcellular level, a key principle operates: Group membership is crucial for living networks to emerge. Beyond DNA and RNA base *pairs* (e.g., the bases guanine and cytosine forming a G–C base pair), RNA has *multi-base* sequences at the end of the molecule (*stem loops*). Single RNA stem loops interact with other molecules in a physico-chemical way without features that are *biotic* (i.e. characteristic of life forms). But any interaction involving one RNA molecule can involve many other, different RNA molecules. These interactions are building blocks of life.

When the density of RNA stem loops reaches a critical mass, *biological selection* emerges. Crucially, within biological selection of RNA stem loops, a core of historic *behavioral motifs* is ever present. These motifs include *parasitism*, splicing (*ligation*), splitting (*cleavage*), and group building. The motifs reflect and shape genetic and group identities, a process of *dynamic self-directed learning*. Initial learning requires learning *self-identity*.

How does self-identity emerge in RNA group building? Single RNA stem loops join groups, and group membership is the prerequisite for self/non-self-differentiation. To survive, RNA stem loop replicators must assemble in groups that dynamically generate group identity. RNA stem loops are ligated to other stem loops that fit into the group identity and cleave those that do not fit. Self-ligation of RNA stem loops forms a module-pool that participates in many cooperative interactions, leading to ribozymes and the capacity for RNA cleavage. Interestingly, the genetic identity of RNA stem loops groups may change quickly in response to environmental necessities, and formerly rejected stem loops may later fit well into the group (or vice versa).

The ongoing, dynamic nature of group identity and selection also is expressed in how infectious RNA stem loops operate via RNA groups. These extended groups are called *quasi-species consortia*. Quasi-species consortia produce and depend on diversity; diversity is not an "error" but rather a fundamental property of the groups. RNA stem loop variations play a crucial role in building quasi-species consortia: Especially the binding-prone single-stranded loops and bulges interact and build new groups with distinct identities. An RNA group with a specific identity may cooperate with other RNA groups in building networks. Importantly, RNA groups retain memory of past events via minorities, so their survival does not depend on selection of a "Fittest Type" but rather on an ongoing process of selection for heterogeneity.

The evolution of early RNA-based life, then, was *communal*: Cooperation is key, and RNA group behavior generated the origin of the genetic code, a real natural language.

Viruses Are Masters in the Editing of Genetic Codes

Viruses and related infectious genetic parasites are the most abundant biological agents on this planet. They vastly outnumber cellular life forms, invade all cellular organisms, and serve as key agents in the generation of adaptive and innate immune systems. The invasion strategy that results in persistence within host genomes (*genomic parasitism*) provides novel evolutionary genetic identities that were not present prior to the invasion. The remnants of persistent viral infection events include transposable elements (transposons and retrotransposons) in the host genome which all share a repetitive sequence syntax. Even highly fragmented parasitic genetic elements can create new RNA networks that are directly involved in gene regulation found in all organisms. When viruses cooperate with hosts, they are the *only* living entities that share all variants of genetic sequence syntax from RNA to DNA, from single-stranded to double-stranded, and from repetitive to nonrepetitive sequences.

One cooperative motif that is successful for invading DNA habitats is the *addiction module*. It is the main behavioral motif that interconnects communication of RNA groups, viruses, and cell-based organisms and accounts for the persistence of viral elements. Competing genetic parasites, together with a host immune system, build counterbalancing modules and genetic counterregulation (e.g., toxin/antitoxin, restriction/modification, insertion/deletion, etc.). In such a counterbalanced module, viruses do not harm the host.

Host organisms depend on such counterbalancing agents and are in that sense "addicted" to them: If the counterbalance is disturbed, then one part of the addiction module (e.g., a toxin) may become dominant and harm the host. Most disease results from addiction modules being out of counterbalanced control.

Thus, like stem-loop RNA consortia, viruses are a force for ancient, recent, and contemporary life. They are natural genome editors with core competences including innovation, integration, regulation, and setting the stage for further selection (*exaptation*). Wherever viruses exist and interact with hosts (the *virosphere*), persistent viral life strategies are beneficial for their hosts. The strategies result from special group behavioral motifs ever present in the virosphere such as cooperation (in addiction modules, to reach persistent balance) and collective actions of dispersed defective viruses in infection and integration processes.

RNA Networks, Viruses, and Cells Constitute Life

Cellular life means metabolizing entities with membranes that ensure genetic identity and rejection of parasites via immune systems. Cellular life characterizes organisms from bacteria, amoeba, and fungi to animals and plants. Before cellular life emerged, RNA networks replicated. Although cellular life is a result of RNA consortia interactions, genetic parasites such as viruses shaped cellular life through constant infection, innovation, immune function, and selection via reproduction. Capsid-encoding viruses and cellular life may have originated in a complementary way, but viruses undoubtedly had their roots in the depth of the RNA world and represent many genes and sequences never found in the cellular world, which indicates a pre-cellular origin.

A Social Science Perspective on RNA Networks, Viruses, and Cells

The new concept of *quasi-species consortia* primarily focuses on RNA interactions together with viruses that represent groups with identity, which means they differ from groups that do not share that identity. This social science perspective looks at RNA societies which share a self/nonself-identification competence. Group behavior of RNA networks including viruses (i.e., their infection competence) has several motifs to integrate foreign stem loop groups that fit into present group identity or to expand group identity for novel context-relevant functions.

The main objective remains group identity, which is constituted not by uniform members, clones, or similar low-level variations but mainly of very different members such as former competing agents and rejected minorities. The quasi-species consortia are characterized by different agents that compete, are rejected, or remain as defectives. Such consortia also present a selection profile: A consortium regulates gene expression, creates epigenetic marks, and generates new, evolutionarily relevant nucleotide sequences, all of which is subject to selection. Each member serves a counterbalancing function and can react to specific circumstances in ways that other members cannot; therefore, a consortium integrates competing RNA stem loop groups in context-relevant ways. The two subunits which form a *ribosome* (RNA with associated proteins), for instance, have a group identity very different from the identities of other large RNA stem loop groups; each has its own evolutionary history and original function, and each may integrate or reject other foreign RNA stem loops. A group identity arises with this integration/rejection (self/nonself) behavioral motif. They are integrated via addiction module function into a DNA-stored essential tool, for all cellular life.

The social science perspective on RNA biology and virology has more explanatory power than previous theories because it can integrate diverse motifs of RNA stem loop groups into a consortial biotic behavior that formerly was described only in a physio-chemical realm of individual Fittest Types. Further, what has been explained in the past by replication errors – namely variations – is now an essential feature of RNA stem loop group behavior to generate unforeseeable, newly created forms, functions, and structures of RNA groups. To call this productivity "error" now looks like an outdated error of the last century.

Conclusion

Virology and philosophy of communication together present a new perspective to look at life as a whole and on life in all its details based on the most recent empirical and philosophical knowledge. If we look at key features of life as we know it on our planet, including immune systems, replication, transcription, translation, and repair in all its steps and substeps, we can justify the conclusion that all these features and properties are the result of evolutionary innovations caused, generated, and introduced by viruses, RNA consortia, and other genetic parasites. These infectious agents are the innovators of

RNA stem loop group interactions of all life. They insert and delete, adapt, modify, and, most importantly, counterbalance competing genetic identities. They cooperate, edit genetic codes, and are at the basis of the secrets of life – including human life.

For Sources and Further Reading

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