Guenther Witzany
Telos-Philosophische Praxis

Natural Genome Editing

Why Editing Needs Editors

The **biocommunicative** approach investigates:

both

- communication processes within and among cells, tissues, organs and organisms as sign-mediated interactions, and

- nucleotide sequences as code, i.e. language-like text, which follows in parallel three (3) kinds of rules:

  combinatorial (syntactic),

  context-sensitive (pragmatic) and

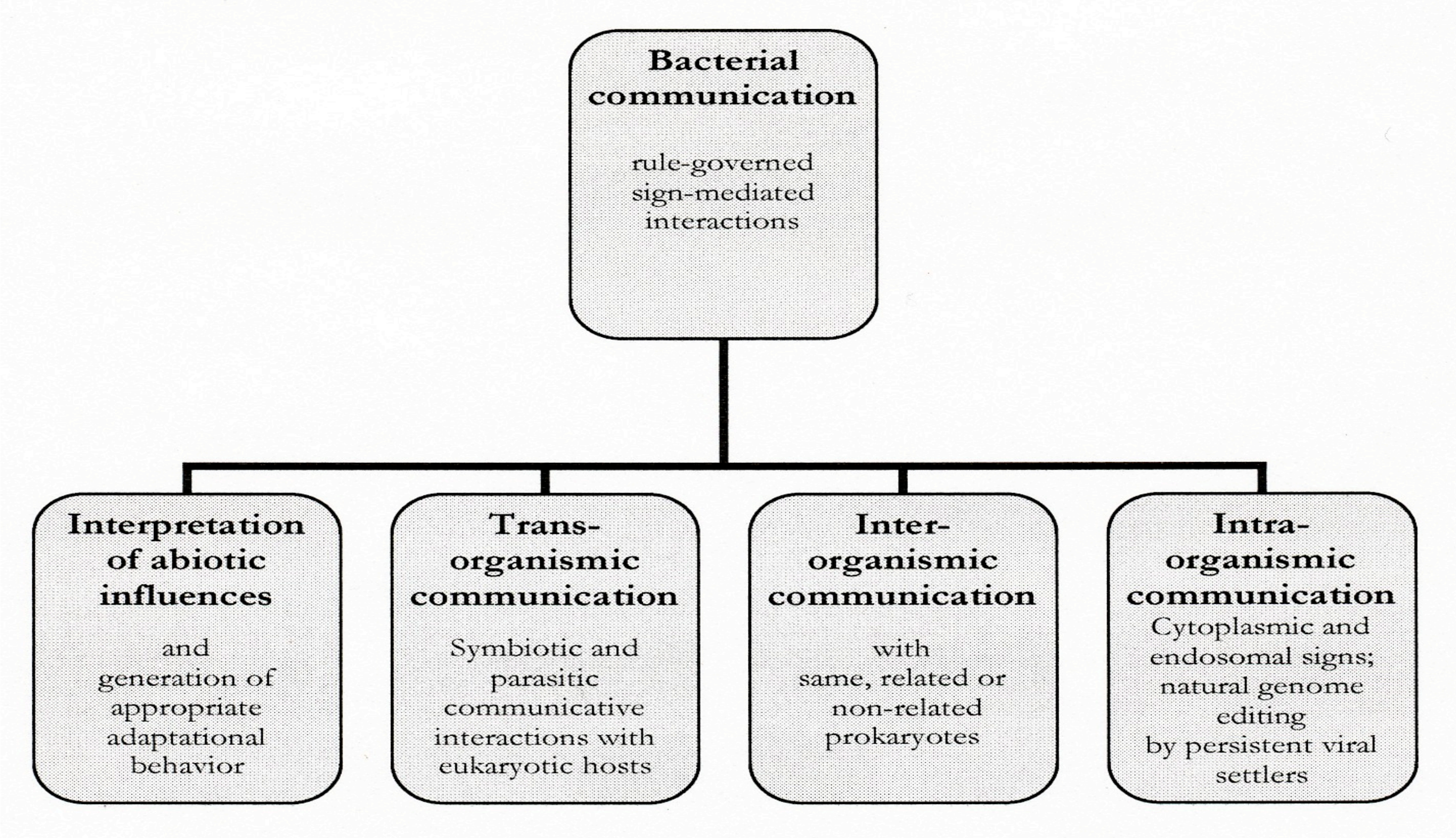
  content-specific (semantic).

In this respect over the last 20 years I have investigated:

- **The scientific discourse on „language“ and „communication“** between 1920 and 1980.
  (logical empirism, critical rationalism, systems theory, information theory, mathematical theory, hermeneutics, action theory)

- Language and communication of **honey bees** of the northern hemisphere

- **Plant** communication
- **Fungal** communication
- **Coral** communication (together with Pierre Madl)
- **Bacterial** communication
- Natural genome editing competences of **viruses**


Bacterial communication
rule-governed sign-mediated interactions
Interpretation of abiotic influences
and generation of appropriate adaptational behavior
Trans-organismic communication
Symbiotic and parasitic communicative interactions with eukaryotic hosts
Inter-organismic communication
with same, related or non-related prokaryotes
Intra-organismic communication
Cytoplasmic and endosomal signs; natural genome editing by persistent viral settlers

Genetics and Genomics

If we look at the genetic and genomic level we can identify a remarkable process of change from a mechanistic view to a perspective of genetic information processing which is more coherent with most recent empirical data

Examples of natural genetic engineering according to James Shapiro:

- **The format of the genome is constructed by signals for compaction, attachment, transcription, replication, transmission and repair**
- **Large scale genetic rearrangements together with small size changes enable fine tuning**
- **Targeting increases functional integration and reduces content damage**
- **Every genetic component works as part of the whole informational content**
- **Genetic novelty arises by invention or rearrangement of modular components**
- **Genetic novelties can arise suddenly and involve multiple DNA changes**
- **Transposases, Recombinases and Nucleases all have sequence recognition features**

Examples of viral genome editing by invention and integration of new genes as shown by Luis Villarreal

- RNA, DNA
- replicase, polymerase, integrase
- DNA repair
- restriction / modification
- methylation
- bilayer nuclear envelope
- eukaryotic nucleus
- division of transcription and translation
- nuclear pores
- tubulin based chromosome duplication
- chitin, calcification
- linear chromosomes
- innate immune system (MHC-Komplex, RNAi)
- adaptive immune system
- cartilage, bones
- skin, dermal glands for poison, mucus and milk
- larvae, egg, placenta, flowering plants
- viviparous mammals

Natural Genome Editing

from a biocommunicative perspective is

competent agent-driven *generation* and *integration* of meaningful nucleotide sequences into pre-existing genomic content arrangements

and

the ability to (re-)combine and (re-)regulate them according to context-dependent (i.e. adaptational) purposes of the host organism.

- Natural genome editing integrates the hierarchical order of *all* temporal and spatial steps to create a functionally and highly integrated complex organismal genome

- "Eukaryotic genomes consist of genes "floating in a sea" of retroposons with retroviral descent."

AGENTS?

Persistent exogenous or endogenous settlement of host genomes

If we postulate agent driven genetic editing then we have to look at their *in vivo* life-strategies to understand their habits and the situational contexts which determine their content arrangements

More and more indicators seem to prove that every cellular life is colonized by exogenous or endogenous viruses in an non-lytic but persistent lifestyle.

Persistent lifestyle in cellular life-forms most often seem to derive through an equilibrium status reached by three factors: at least two competing genetic settlers and the immune function of the host which keeps them in balance.

Signs, Rules, Agents

If genetic sequences within a genomic order have real language-like features it must have all the elements of any biotic language:

- a limited number of elements that can be used as *signs*
- a limited number of *rules* that determine their combination, context, content
- competent sign-generating and -using *agents*

Genetic text sequences are NOT a random mixture

- Genetic sequences that function as code are not a statistically random-like mixture of nucleotides but informational content in a syntactic order coherent with the whole sequence space

- As in every language each character, each word and each sentence together with start, stops, comas and spaces in- between has a function and is generated by competent agents.

***de novo* generation**

- Biotic agents that are competent to use a language share a unique feature not found in non-biotic entities :

  under certain circumstances they are able to generate syntactically correct sequences ***de novo***, i.e. there is no algorithm available to which this production can be reduced.

Linguistic competences are communal

- Linguistically competent agents are not *solus ipse* agents but are competent as swarms, “clouds”, i.e. communities that share these competences.

- Their competence is communal, each of them being capable of self /non-self identification.

Communal Interacting Agents I

- If we look at interacting communities such as ribosomes and spliceosomes (each containing subunits without which they cannot function) we see their communal competence.
- If we look at the hierarchical processes of gene expression, transcription, RNA processing, mRNA and tRNA transport for translation we see communally acting agents.
- They are now mutually interacting but may derive from formerly competing agents. mRNA and tRNA maturation in eukaryotes in particular seem to reflect communal processing.

Communal Interacting Agents II

- Formerly competing agents have reached an equilibrium status with the immune response of the infected host to achieve a persistent life-style in the host genome such as e.g., toxin/antitoxin-modules

- The number of communal acting agents represented by e.g. ribosomes, spliceosomes or even in the adaptive immune system ranges from a few to hundreds and thousands.

  In the latter case communal agents interact in DNA rearrangements with enormous consequences for many protein based products that play important roles in immune functions.

Some questions concerning natural genome editing

from the bio-communicative perspective:

1. Does the pattern of movement of retroposons, transposons and other mobile genetic agents represent endogenised (single) steps of former exogenous viral infection pathways?

How do communal interacting agents coordinate with each other?

2. If many of the key tools of genetic content processing are regulated by former free living agents the question is:

   What are the sign-mediated interactions that connect them and what happens if regulation is not correct?

Communal Interacting Agents III

3. Small nuclear RNAs (snRNA) base-pair with short sequences in pre-mRNAs to mark sequences to be spliced out. A total of 200 small nucleolar RNAs are known to act as guides. They are encoded in introns and transcribed by RNA polymerase II. In some organisms these introns are more conserved than the exons.

- Could this indicate that intron encoded RNA agents with regulatory functions are more important than ensembles of protein-encoding exons?

Communal Interacting Agents IV

4. As small nuclear RNAs and small nucleolar RNAs co-regulate themselves in essential processing:

   is it possible that they represent formerly competing RNA agents that have reached a persistent endogenous host-genome status?

Subviral RNA agents

5. Might these small non-coding RNAs indicate that natural genome editing is not limited to endogenised viral agents? Will we have to look at a deeper level:

   Do subviral RNAs (short hairpin structures) also share common natural genome editing competences ? Do they act as modular tools of bigger networks?

   The subviral database opens interesting aspects in this respect:

   http://subviral.med.uottawa.ca/cgi-bin/home.cgi

Telomere and centromere repeats

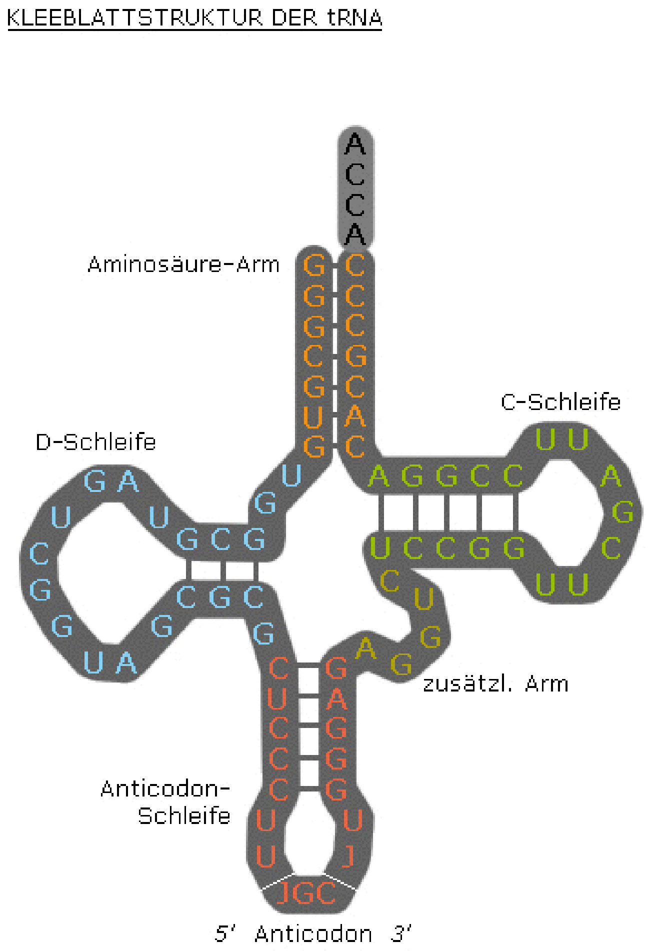
7. Since telomere repeats at the ends of linear chromosomes seem to have ward-off functions against genetic parasites (similar to centromere repeats) the question arises whether repeat sequences in general share a kind of special immune function?

- Is it the special syntax of these repeat-sequences that are involved in such immune functions or maybe other factors such as nearby regulatory networks ?

Pseudouridylation pockets with identity function?

8. Pseudouridylation pockets are essential characteristics of ribozymes, self splicing RNAs, snoRNAs, snRNAs and other secondary structure RNAs,e.g. tRNA.

- Are they characteristic features of identity?
- What are the main functions for these non-pairing within pairing structures?



<u>Summary:</u> characteristics of biocommunication

- Without sign-mediated interactions there is no biotic coordination or organisation

- Non reducible levels of rules that govern sign-use:
  combination (syntax),
  context (pragmatics) and
  content (semantics)

- Without biotic agents there are no signs or sign-use

- Without communal evolution there are no competent individual agents

- Without rule-sharing communality there is neither
  communicative (interactive) nor
  linguistic (nucleotide sequence editing) competence

- Without competent genomic editors there is no natural genome editing

„The meaning of a word is its **use** within a language“

„To understand a sentence means to understand a language. To understand a language means to be a master of a technique“

Ludwig Wittgenstein, Philosophical Investigations