Rooms and Doors

RNA virus opens the door from fittest type to RNA collectives:
a personal account by Luis Villarreal

Center for Virus Research, University of California Irvine

Competition- old room

(individual fittest type, lytic virus, selfish, mathematical, game theory, population genetics)

vs

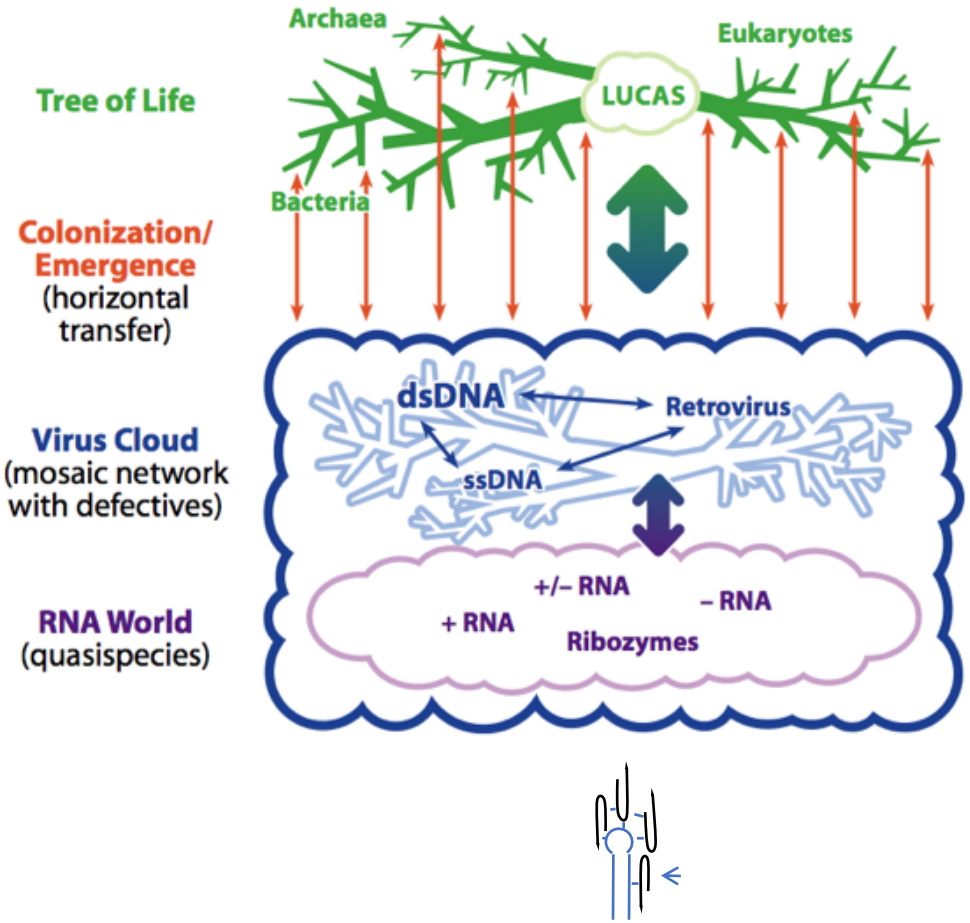
Cooperation- new room

(symbiosis, diffuse group selection, persistent cryptic-virus, synergistic social genomes, context dependent, regulatory networks)

Lytic vs persistent virus as a necessary set?!

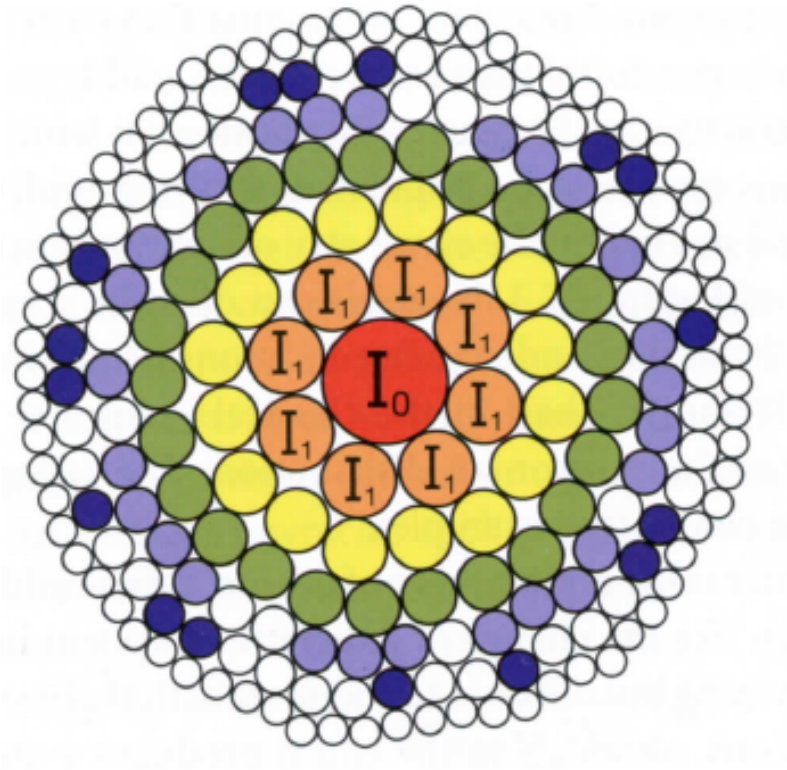
Silence is golden (and small RNA usually involved)

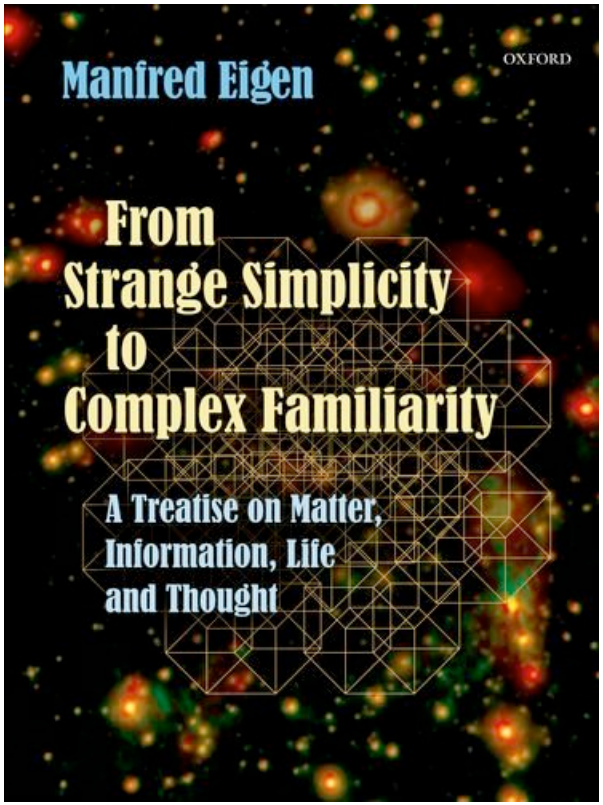
The virosphere is both!



Collective of RNA sub-agents

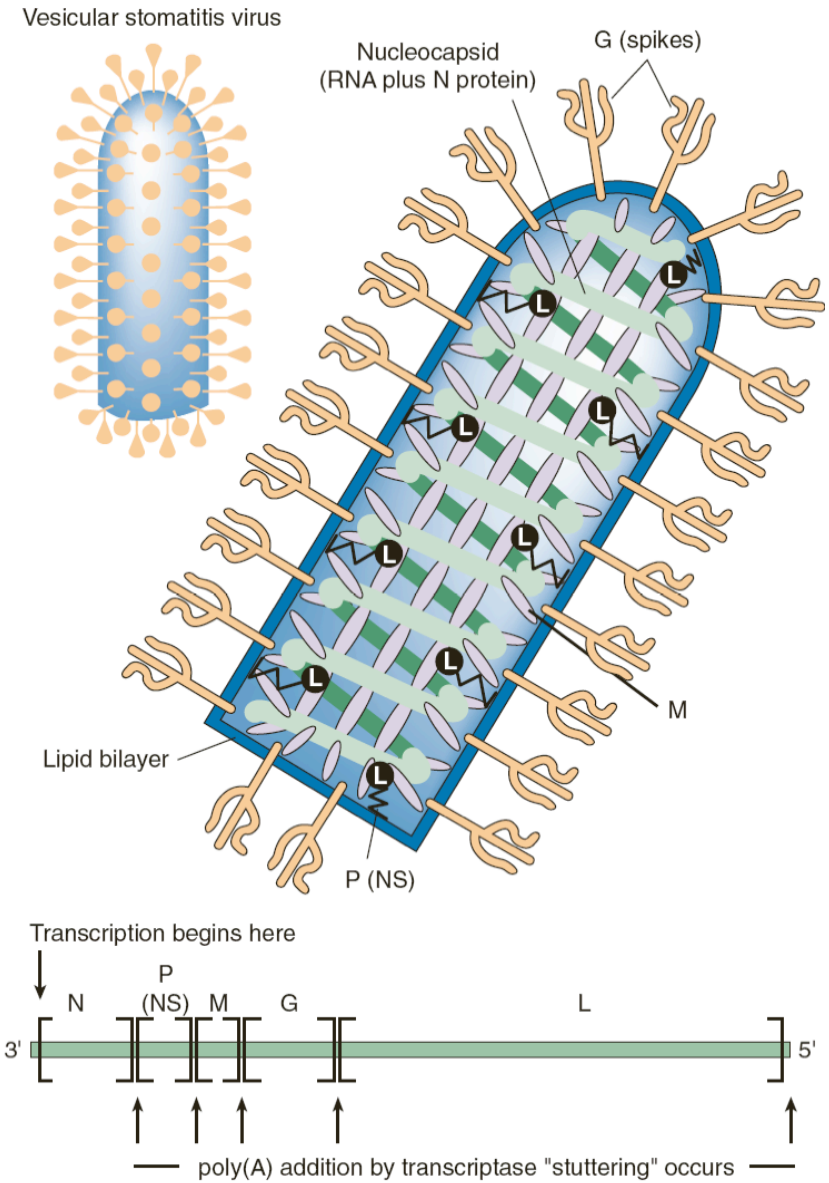
No life is fit unless it is in the context of its current virosphere





Eigen's QS: mutant halo around master fittest type (no interactions)

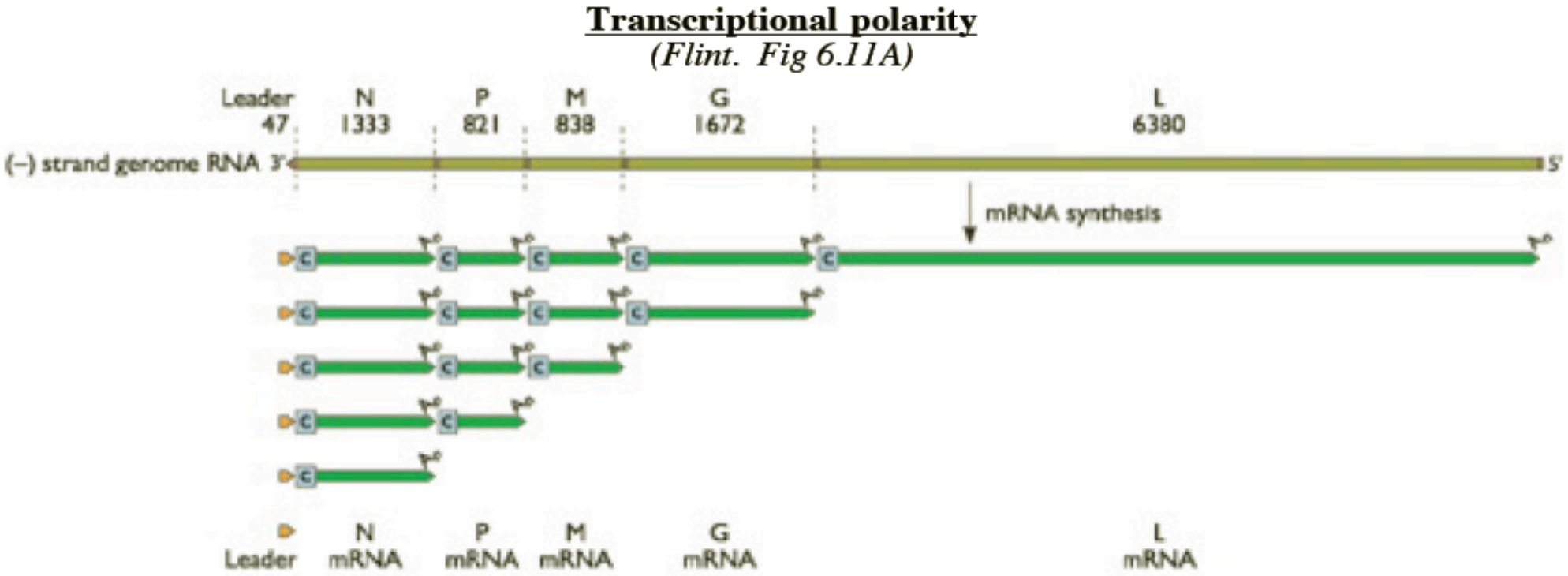
A theoretical construct – little experimental reference



VSV Virion and Genome

- Bullet shaped virus
- 5 proteins present in different amounts (N, G, M, P and L)
- ~ 11,000 bases, genes in opposite order of how you see mRNA
- L and P function together to cap mRNA, generate mRNA, polyA +-sense viral mRNA and replicate viral genome (RNA synthesis enzymes in virion)

Transcriptional Polarity



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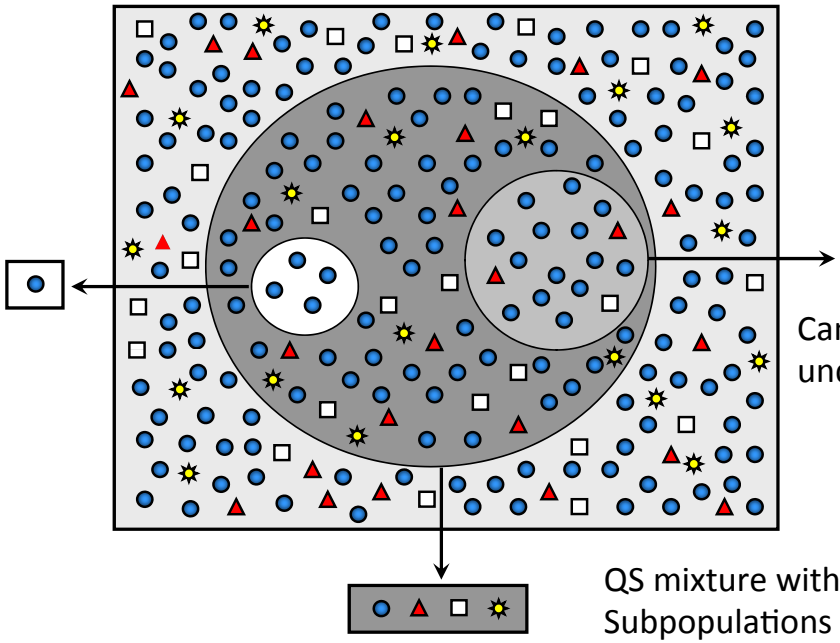
Defective product; small (stem-loop) RNAs: strong interference with 'master fittest type' – can promote persistence

Fig. 7

Esteban Domingo, J. Sheldon and C. Perales. 2012.
"Viral Quasispecies Evolution." *Microbiology and Molecular Biology Reviews* 76 (2): 159–216:



Can be distinct regions
under distinct pressure

QS mixture with subpopulations
Subpopulations work together
and against each other
Not needing consensus change
Can suppress 'Master fittest type"

QS-C (cooperative)
Polio/YFV vaccine: HCV transplants

Perales, Mateo, Matue, Domingo. 2007 JMB

many remarkable insights. The most basic, far-reaching, awesomely predictive tenet of quasispecies theory will never be overshadowed; numerous variant genomes are bound together through extreme mutation rates, forming obligatorily co-selected partnerships in a vast, error-prone mutant spectrum from which they cannot escape, and from which they inevitably and coordinately may exert myriad, changing, ultimately unforseeable effects on all life forms. This tenet has been unquestionably and elegantly confirmed recently by the U. C. San Francisco, Stanford and Penn State groups (as reviewed above and elsewhere in this volume).

Established characteristics of quasispecies evolution

- Not fittest type; a consortia that needs errors (group selection with consensus type)
- Participation of defectives and mutants important (the lethal/unfit)
- Complementation, cooperation, interference preclusion, competition all occur
- Diversity per se provides fitness
- Preclusion of prior consensus type: dynamic

The HCV examplar: QS based identity/exclusion

Dynamic persistence via ongoing RNA synthesis

Quasispecies determined biology

Group (clade) preclusion (identity)

The role of stem-loop RNA interactions - consortia

Laskus T, Wang L-F, Radkowski M, Vargas H, Nowicki M, et al. 2001. Exposure of hepatitis c virus (hcv) rna-positive recipients to hcv rna-positive blood donors results in rapid predominance of a single donor strain and exclusion and/or suppression of the recipient strain. *J. Virol.* 75(5):2059–66

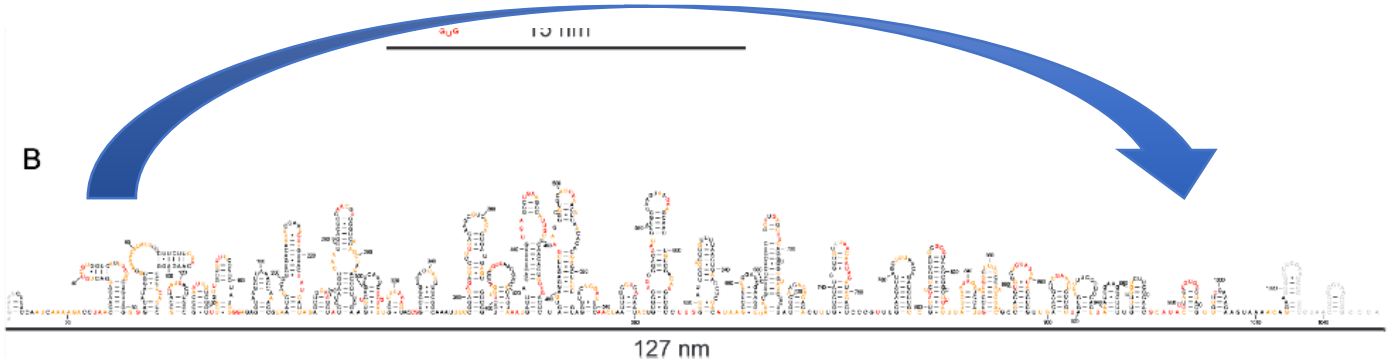


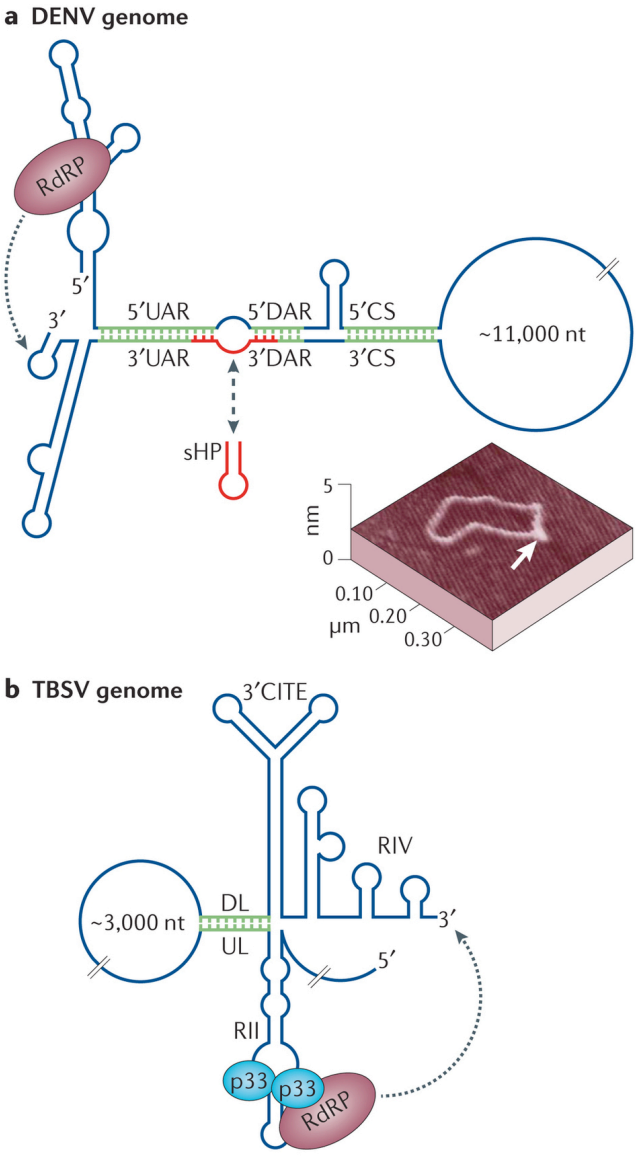
Figure 3. Secondary structure models for the STMV RNA *ex virio*. (A) SHAPE-directed model. Maximum allowed base pairing distance was 600 nucleotides.[22] The start and stop codons for the capsid protein are boxed. (B) Linked stem-loop model, created using SHAPE data and parameters designed to force formation of short stem-loop motifs by restricting the maximum base pairing distance to ≤50 nucleotides. Nucleotides are colored by SHAPE reactivity (see legend); gray indicates no data were obtained. Calculated lengths of major structural features in each structure are shown (in nanometers).

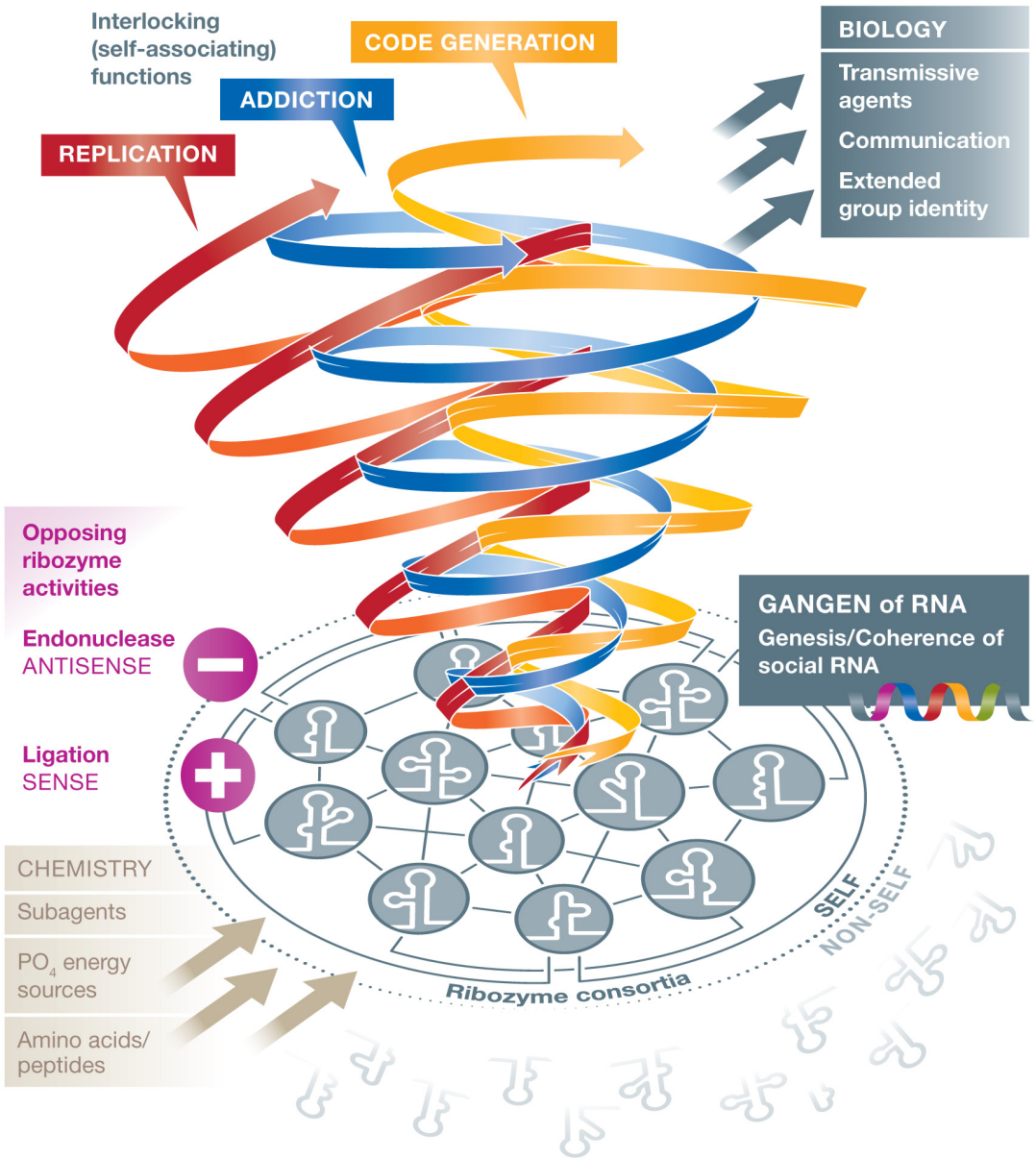
Archer, Eva J., et al. "Long-Range Architecture in a Viral RNA Genome." *Biochemistry* (2013).

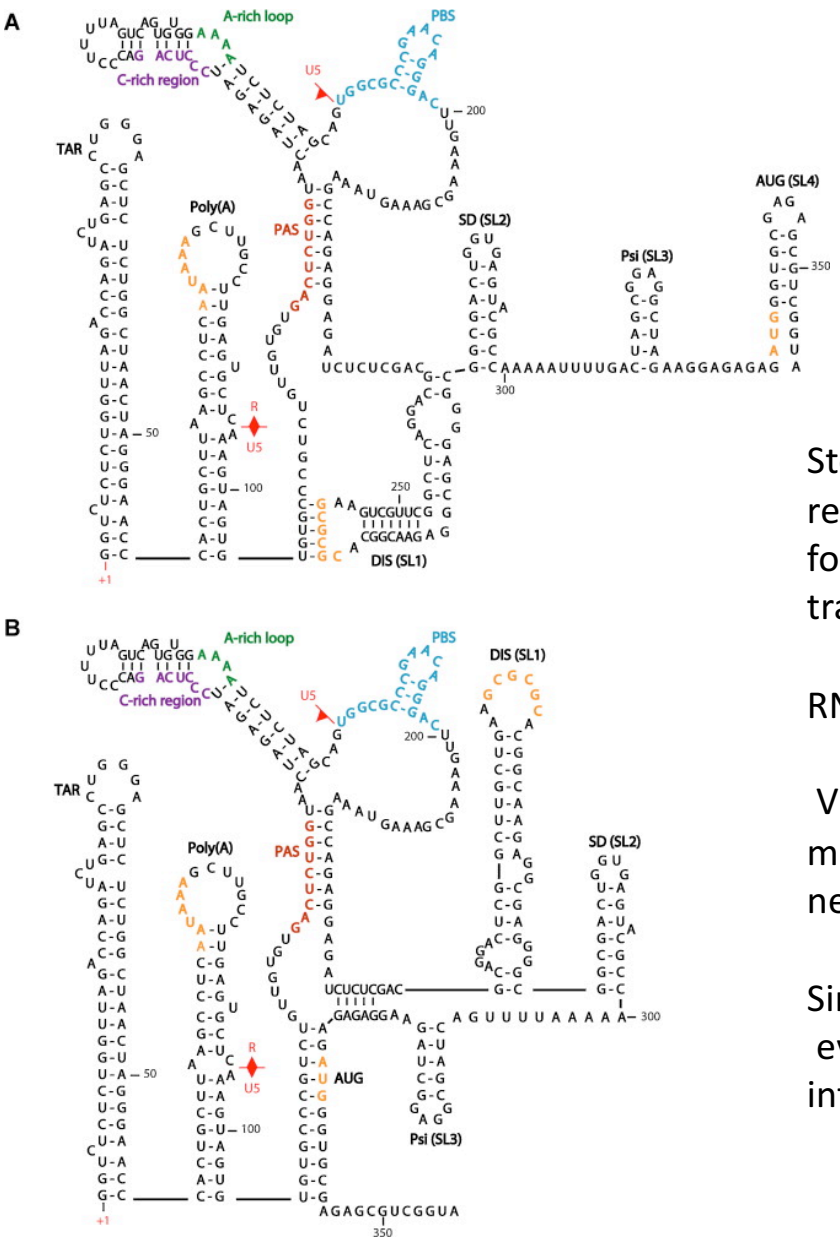
Satellite tobacco mosaic virus (STMV) as the 'hydrogen' of + RNA viruses (McPherson): core role for stem-loop RNA interactions (**1058 nucs)**

Strong evidence that 'cooperative' long distance RNA-RNA interactions (kissing loops) are needed for gene expression and replication. (FMDV, HCV - IRES)

RNA stem-loops as predecessors (viroids/hammer heads)– **a way to create interacting networks**


a DENV genome
RdRP
5′
3′
5′UAR
5′DAR
5′CS
3′UAR
3′DAR
3′CS
~11,000 nt
sHP
5
nm
0
0.10
μm
0.20
0.30
b TBSV genome
3′CITE
RIV
~3,000 nt
DL
UL
3′
5′
RII
p33
p33
RdRP


Interlocking
(self-associating)
functions
CODE GENERATION
ADDICTION
REPLICATION
BIOLOGY
Transmissive agents
Communication
Extended group identity
Opposing ribozyme activities
Endonuclease
ANTISENSE
Ligation
SENSE
GANGEN of RNA
Genesis/Coherence of social RNA
CHEMISTRY
Subagents
PO4 energy sources
Amino acids/ peptides
Ribozyme consortia
SELF
NON-SELF



Secondary structure of the 5’-UTR
of the HIV-1 genomic RNA (Deforges et al 2011)

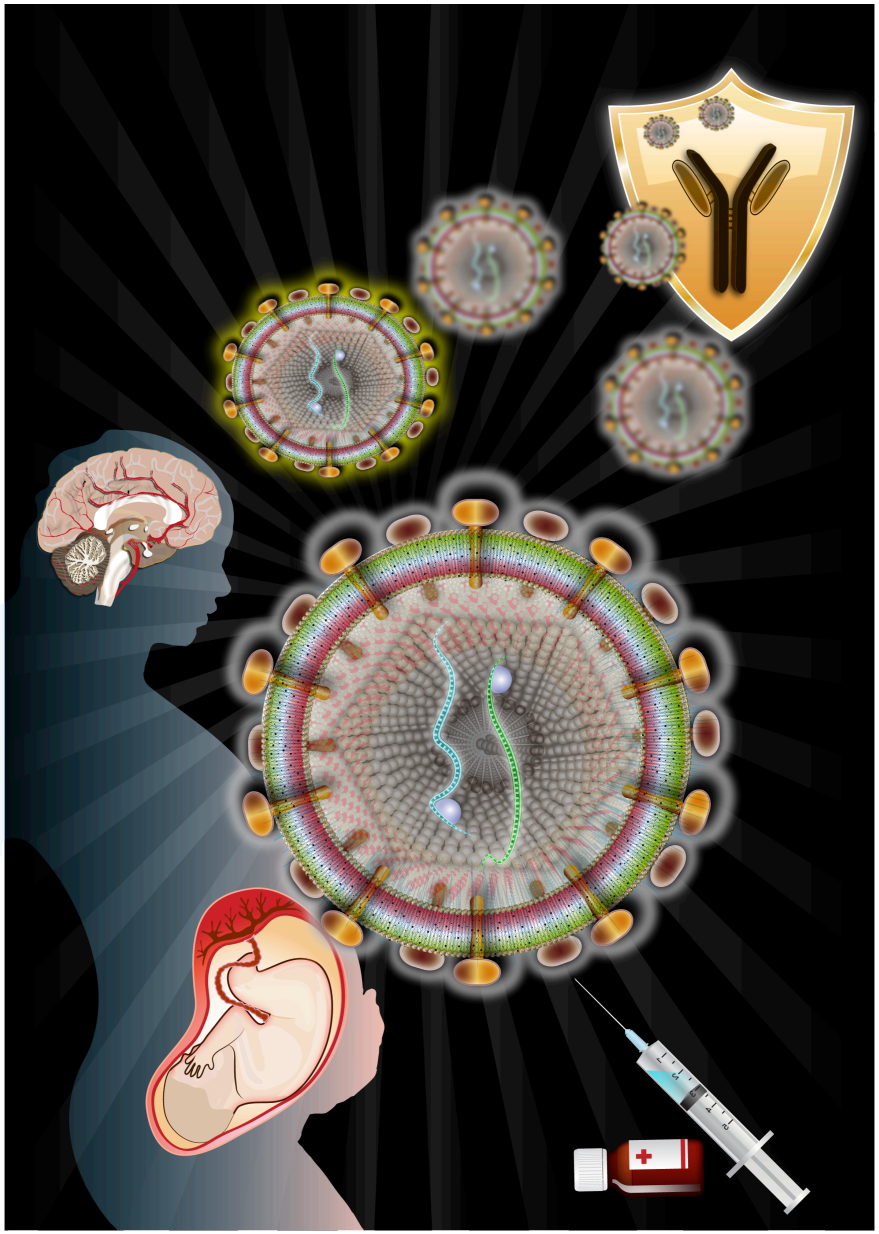
Sleiman, Dona, et al. "Initiation of HIV-1 reverse transcription and functional role of nucleocapsid-mediated tRNA/viral genome interactions." *Virus research* (2012)

Stem loop interactions crucial for RNA virus replication, RNA dimerization, provirus formation, regulation, packaging (Identity), bind transcription factors, GAG translation

RNA is interacting as a QS-C, DNA is stable

Virus can provides LTRs (via defectives) en mass to host DNA:. New QS-C based RNA network acquisition?

Similarly, defective viral DNA colonization events (i.e. Maverick) can also provide diffuse interacting stem-loop RNAs (polyadenylation)



Virus role in origin of the placenta: Immunity/gamete development/behavior

Darwinian view – exapted viral *env* genes
convenient serial source of genes for membrane fusion & immune regulation.
Error generated network (serial)

Problems: 10 independent events
diversity of roles/biology
ongoing ERV/*env* displacement
transports immunity/not barrier
affect the first cell to differentiate
failure to explain network origins
does not account for coherent complexity

A virus-first view – Persistence as key via defectives
virus persistence modifies
immunity via ERV/QS and addiction modules,
allows group survival and creates identity networks
Behavior - motherhood

Distinct viral role also in parasitoid wasp reproduction

EX VIRUS OMNIA!