Selection Dynamics in Transient Compartmentalization

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1. Introduction

2. The Model

3. Results

4. Mutations

5. Conclusion
Motivation

The RNA World hypothesis

How could self-replicating molecules maintain their activity, in spite of inevitable replication errors?

How could functional molecules overcome their disadvantages wrt non-functional (but faster-replicating) mutants?

COMPARTMENTALIZATION
The Questions

• Can *transient* compartmentalization be sufficient to maintain active ribozymes in the presence of fast-replicating parasites?
• Which quantities determine success or failure of the process?
ORIGIN OF LIFE

Transient compartmentalization of RNA replicators prevents extinction due to parasites.

Shigeyoshi Matsumura, Eörs Szathmáry, András Szilágyi, Ádám Kun, Alejandra Gómez, Faith Coldren, Andrew D. Griffiths

Shigeyoshi Matsumura et al., 2016

RESEARCH REPORTS

on December 8, 2016

http://science.sciencemag.org/

Allowed life to take hold.

Opportunistic functionality. Thus, TC in nature takes over by parasitic mutants. TC tends to select a critical step in the origin of life. However, parasitic replicators would take over and would propagation and allowing group selection at the level of parasites.

The appearance of molecular replicators (molecules that can be copied) was probably a key step in the origin of life. However, parasites would take over and would.

Compartmentalization of reproducing protocells (model) in local groups, similar to Wilson's trait group hypothesis.

Here, we demonstrate that repeated cycles of mixing and transient compartmentalization (TC) in an inert carrier oil, replicate in the microfluidic system, RNA molecules are recombinant, replication domain and ribozyme activity contributes to the exclusion of parasites (iv). (iii)

In vitro using the viral replicase, 83% of the RNA molecules recover fluorescent product.

Drop breaking and RNA pooling

Compartmentalization of RNA in drops

Drop selection (fluorescence-activated sorting)

RNA replication and catalysis

Molecular replicators

Poisson distribution with a mean,

Drop breaking and RNA pooling

Compartmentalization of RNA in drops

Drop selection (fluorescence-activated sorting)

RNA replication and catalysis

Molecular replicators

MATSUMURA ET AL., 2016
Experiment Results

Bulk

- Round 1: $\mu = 3 \cdot 10^{-9}$
- Round 2: $\mu = 2 \cdot 10^{-9}$

Selected, Compartmentalized

- Round 1: $\mu = 8 \cdot 10^{-5}$
- Round 2: $\mu = 1 \cdot 10^{-5}$
The process

i) Inoculation
ii) Maturation
iii) Selection
iv) Pooling
Inoculation

- Droplets are initialized with a large number \( (N_e) \) of \( Q\beta \) enzymes, and activated nucleotides
- Droplets are seeded with \( n \) RNA templates: \( n \) is Poisson-distributed with average \( \lambda \)
- RNA templates come in two kinds: ribozymes and parasites
- In a given droplet there are initially \( m \) ribozymes and \( y = (n - m) \) parasites (\( m \) is random, of average \( \lambda x \))
- \( x \): fraction \#ribozymes/\#RNAs in the solution (at the end of the previous round)
- We begin by neglecting mutations producing new parasites (mutation rate is very small)
- The role of mutations will be discussed later
Maturation

- RNAs initially replicate autocatalytically: \( n(t) \sim \exp(t) \) (exponential phase)
- Parasites replicate faster than ribozymes: \( m(t) \sim m e^{\alpha t} \), \( y(t) \sim y e^{\gamma t} \), \( \gamma > \alpha \)
- When \( n(t) \approx N_e \), \( Q_\beta \) is the growth-limiting factor: further growth is linear with time (linear phase)
- In the linear phase, the ratio \( y(t)/m(t) = \# \text{parasites}/\# \text{ribozymes} \) remains constant
- At the end of the maturation phase, we have \( m(t) = \bar{m} \), \( y(t) = \bar{y} \), with
  \[
  \frac{\bar{y}}{y} = \Lambda \frac{\bar{m}}{m} \quad \Lambda > 1
  \]
- Thus given \( (x, m, n) \), one has
  \[
  \bar{m} = \frac{N \cdot m}{n\Lambda - (\Lambda - 1)m} = N \bar{x}
  \]
  \[
  \bar{y} = N - \bar{m}
  \]
Selection

- Droplets are selected according to the number $\bar{m}$ of ribozymes contained
- $N$: number of RNAs at the end of the maturation phase
- $\bar{x} = \bar{m}/N$: fraction of ribozymes
- Selection function:

\[
f(\bar{x}) = \frac{1}{2} \left(1 + \tanh \left(\frac{\bar{x} - x_{th}}{x_w}\right)\right)
\]
Pooling

- Each round \( k \) yields \( x \rightarrow x' \):

\[
x' = \frac{\sum_{m,n} \bar{x}(m,n) f(\bar{x}(m,n)) P(x|m,n; \lambda, \Lambda)}{\sum_{m,n} f(\bar{x}(m,n)) P(x|m,n; \lambda, \Lambda)}
\]

- Does \( x \) reach a fixed point as \( k \to \infty \)?
- Evaluate \( \Delta x = x' - x \) vs. \( (\lambda, x) \) for fixed \( \Lambda \)
$\Delta x \text{ vs. } (\lambda, x)$
Dynamics

\[ \Delta x \text{ vs. } (\lambda, x) \quad \Lambda = 4 \]
Phase diagram
Asymptotes

\[ \Lambda \gg 1: \text{ R-B line at } \lambda_0: \lambda_0 f(1) = (e^{\lambda_0} - 1) f(0) \quad (\lambda_0 \simeq 6.95) \]
\[ \text{ B-P line at } \lambda_1: \lambda_1 f(0) = (e^{\lambda_1} - 1) f(1) \quad (\lambda_1 \simeq 1.49 \cdot 10^2) \]

\[ \Lambda \gg 1: \text{ R-C line at } \Lambda = 1 + (f'(1)/(f(1)\lambda)) + O(\lambda^{-2}) \]
\[ \text{ C-P line at } \Lambda = 1 + (f'(0)/(f(0)\lambda)) + O(\lambda^{-2}) \]

The exact shape of \( f(x) \) is not important
Population dynamics

$\lambda = 5, \Lambda = 10$ (C)

(i) No compartments

(ii) Compartments, no selection

(iii) Compartments with selection
Population dynamics

\[ \lambda = 10, \Lambda = 5 \ (P) \]
Linear Selection Function
Mutations

- Mutation rate: $\mu$
- Growth equations:

$$\frac{d}{dt} \begin{pmatrix} m \\ y \end{pmatrix} = \begin{pmatrix} \alpha - \mu, & 0 \\ \mu, & \gamma \end{pmatrix} \begin{pmatrix} m \\ y \end{pmatrix}$$

- Modified iteration:

$$\bar{x} = \frac{m}{(1 + \delta)m + (y - m\delta)\bar{\Lambda}}$$

$$\delta = \frac{\mu}{(\alpha - \mu - \gamma)}$$

$$\bar{\Lambda} = e^{\mu T} \lambda$$

$T$: time at the end of the exponential phase
Mutations

- The pure ribozyme phase ($R: x = 0$) disappears
- There can be either pure parasite ($P$) or coexistence ($C$)
- Phase diagram: stability of the $x = 0$ fixed point

\[
\bar{\Lambda} = 1 + \frac{f(0) - f(\bar{x})}{f(0)\delta}, \quad \frac{\bar{x}f(\bar{x})}{f(0)} = 1
\]
Error threshold

- In the case $\Lambda < 1$ the ribozymes grow faster than the parasites.
- The P phase is reached at high mutation rates: Error Threshold.
Error threshold

- In this case the external selection \((f)\) is not necessary
- Phase diagram without external selection:

\[
\lambda \approx \frac{2\delta}{1 + \delta} \text{ for } \delta \ll 1
\]
N.B.: The parasite phase is on the left of the coexistence phase:

- For $\lambda \ll 1$: non-empty compartments contain either a single ribozyme or a single parasite
- The first ones will end up with only parasites
- The second ones will end up with ribozymes AND parasites, due to mutations
- This entails enrichment of parasites
Summary

- Transient compartmentalization with selection may succeed in purging parasites, provided $\lambda$ is small enough (and selection is strong enough).
- Here selection is extrinsic but the same scenario applies to intrinsic selection (due, e.g., to cooperativity).
- Transient compartments may bridge the gap between metabolism-based (Oparin, Dyson) and information-based (Eigen, Schuster) scenarios for the origin of life.
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