Error Threshold and Compartmentalization:

*limited diffusibility and small population size counteract group selection*

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Maintenance of information in life

- 1 locus, 2 alleles.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Fitness</th>
</tr>
</thead>
<tbody>
<tr>
<td>wild</td>
<td>$s(&gt;1)$</td>
</tr>
<tr>
<td>mutant</td>
<td>1</td>
</tr>
</tbody>
</table>

Mutation rate $= u$ (no back mutation)

Question: what are the conditions for the survival of wild types?
Equations of the model

- The fraction of genotypes
  \[ p_1: \text{wild} \quad p_0: \text{mutant} \]
  \[ p_1 + p_0 = 1 \]

- \( p_1' \) represents the fraction of the wild type at the next generation. The same for \( p_0' \)

\[
\begin{align*}
p_1' &= \frac{1}{\bar{f}} (1 - u) sp_1 \\
p_0' &= \frac{1}{\bar{f}} (p_0 + usp_1) \\
(\bar{f} &= \text{average fitness})
\end{align*}
\]
Conditions for the survival of wild types

- The equation

\[
\begin{bmatrix}
p'_1 \\
p'_0
\end{bmatrix} = \frac{1}{f} \begin{bmatrix}
(1 - u)s & 0 \\
us & 1
\end{bmatrix} \begin{bmatrix}
p_1 \\
p_0
\end{bmatrix}
\]

- The condition for \(p_1 > 0\)

\[(1 - u)s > 1\]

\[1 - u > s^{-1}\]
A closer look at a locus

Making a model of a replicative string
(M. Eigen 1971)

\[ \text{length} = N; \quad \frac{\text{correct replication}}{\text{one base}} = q; \quad \text{superiority} = s \]

\[ Q = q^N \quad (\text{Prob. correct replication}) \]
Put $q^n$ into the survival condition of wild type

- Our previous result is that $1 - u > s^{-1}$
- This is the same as $Q > s^{-1}$
- Since $Q = q^N$

\[ q^N > s^{-1} \]

Therefore, getting the following (Eigen 1971).

\[ N < \frac{\ln(s)}{1-q} \]
What does a graph of $N < \frac{\ln(s)}{1-q}$ look like?

Error Threshold: limiting error rate

No survival

Survival
In the very beginning of life

- There is a gap in the length of genome between the first replicators (RNA based without protein) and the first reproducible translation mechanism (with protein). (Eigen Schuster 1979)
  → Evolutionary barrier.

- Neutral evolution may takes too long time (as the age of Earth)

- How to overcome error threshold?
What people have thought

- Hypercycle (Eigen & Schuster 1977)

![Diagram of the hypercycle model]

- Compartmentalization (Eigen et al. 1981)

- Survival of altruistic molecules is possible do not need Hypercycle
- Mutations (and thus length) are missing in the Stochastic Corrector Model.
What people have thought

- Hypercycle (Eigen & Schuster 1977)
  - Problem in ecological stability (oscillation)
  - Problem in evolutionary stability (parasite, evolvability)
What people have thought

What people have thought:

- Hypercycle (Eigen & Schuster 1977)
- Compartmentalization (Eigen et al. 1981)
- Stochastic Corrector Model (selection between cell like compartments without Hypercycle) (Szathmáry et al. 1987 1995 2002)
  - Survival of altruistic molecules is possible
  - Do not need Hypercycle

Mutations (and thus length) are missing in the Stochastic Corrector Model.
What people have thought

- Hypercycle (Eigen & Schuster 1977)
  → Compartmentalization! (Eigen et al. 1981)

- Stochastic Corrector Model (selection between cell like compartments without Hypercycle)
  (Szathmáry et al. 1987 1995 2002)

Mutations (and thus length) are missing in the Stochastic Corrector Model.
The objective of our study

- Finite populations & compartments have a decreasing effect on error thresholds.
  - Finite population causes a decrease of error thresholds due to stochasticity (Nowak Schuster 1989)
  - Limited diffusion causes a decrease of error thresholds due to small effective population size (Altmeyer McCaskill 2001)

- However, inter-group selection has an increasing effect on error thresholds.

- Do compartments decrease/increase error thresholds?
Modeling direction and language

- To begin simpler
  → Non-interacting molecules

- Individuals in space
  → Two layer Cellular Automata
Our model

- Replicator: Cellular Automata
  - A grid can take a master sequence (wild type) or a mutant or can be empty.
  - Copying prob. Master=0.8; mutant=0.5. Death rate=0.1
  - Asynchronous update
  - Diffusion within a compartment
  - 150 by 150 grids.
Our model

- Replicator: Cellular Automata
- Vesicle (compartment): Cellular Potts Model (Glazer Graner 1992)

Vesicles comprise of several CA cells.
One vesicle CA cell is the same scale as one replicator CA cell.
Energy minimization. Contribution from volume and boundary.
Our model

- Replicator: Cellular Automata
- Vesicle (compartment): Cellular Potts Model (Glazer Graner 1992)
How to connect vesicle dyn. and replicator dyn.

- **Birth**: vesicles divide when the # of replicators reaches a threshold value (DIVPOP).
- **Death**: vesicles are taken out by chance (death rate).
- **We compare 3 models**, changing the functions of replicators on vesicle level:
  - **white** = master (wild); **red** = mutants; **black** = vesicle boundary.

![Diagram of vesicle distribution with white, red, and black vesicles]
How to connect vesicle dyn. and replicator dyn.

- Birth: vesicles divide when the # of replicators reaches a threshold value (DIVPOP).
- Death: vesicles are taken out by chance (death rate).
- We compare 3 models, changing the functions of replicators on vesicle level:
  - Neutral: no functional difference in replicators except for replicator growth rate.
  - Step mortality: master sequences = 0, vesicles die with \( \text{prob} > 0 \); master sequences > 0, vesicles do not die.
  - Step division: vesicles divide when # of master sequences exceeds a threshold.
Results: error threshold VS vesicle death rate

Neutral

Step Mortality

Differential Division

DIVPOP: Green 80; Red 40; Black 10
Results: error threshold VS vesicle death rate

Neutral

Step Mortality

Differential Division

DIVPOP: Green 80; Red 40; Black 10

\[
\frac{dX}{dt} = G(1 - M)X(1 - X - Y) - \mu X - DX
\]

\[
\frac{dY}{dt} = gY(1 - Y - X) + \mu X + GMX(1 - X - Y) - DY
\]
Results: error threshold VS vesicle death rate

Neutral

Step Mortality

Differential Division

DIVPOP: Green 80; Red 40; Black 10
Results 2: Bifurcation diagram

- Does error threshold increase or decrease?

Neutral

Step Mortality

Differential Division

Error Threshold: - decrease; + increase; * system collapses
Relative to the reference error threshold
(0.33 without vesicles)
Results 2: Bifurcation diagram

- Does error threshold increase or decrease?

Neutral

Error Threshold: - decrease; + increase; * system collapses
Relative to the reference error threshold
(0.33 without vesicles)

DIVPOP:
Green 80;
Red 40;
Black 10

Error Threshold and Compartmentalization: – p.14/17
Conclusions

- Relative speed of vesicle dynamics and replicator dynamics is important
  Group selection VS Individual selection
- Error threshold decreases if master sequence and mutants are different only in their growth rate, not with respect to vesicle dynamics.

Thus, the negative effect of compartmentalization is stronger than the positive effect if no extra function is added to master sequences “for free”.
Closer look, Stochastic Corrector Model

- Compartment dynamics
  A quasispecies equation of compartments with internal competition
  \[ \frac{d}{dt} \bar{X} = (MA - E) \bar{X} \]  
  (1)

- Replicator dynamics
  \[ \frac{dx}{dt} = ax(xy)^{1/4} - dx - x(x + y)/K \]
  \[ \frac{dy}{dt} = bx(xy)^{1/4} - dx - y(x + y)/K \]
  \[ \frac{ds}{dt} = s((c_1 x + c_2 y)(xy)^{1/2})^{1/2}/(M + s + (x + y)^2/\mu) - \delta s \]

- How to integrate two level of selection?
  - Make M-equation of Replicator dynamics
  - Calculate M, A in (1) from M-equation
The result of Stochastic Corrector Model

- Does the model really make sense?

"nonviable compartment types are not counted with”
(Szathmáry Demeter 1987)

Where are empty vesicles?
The result of Stochastic Corrector Model

- Does the model really make sense?
- Doesn’t compartment decrease the error threshold?
  - Finite population causes a decrease of the error threshold due to stochasticity (Nowak Schuster 1989)
  - Limited diffusion causes a decrease of the error threshold due to small effective population size (Altmeyer McCaskill 2001)