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.

Genotype	Fitness
wild	$s(>1)$
mutant	1

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: wild p_0: mutant

  $$p_1 + p_0 = 1$$

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

$$\begin{aligned} p_1' &= \frac{1}{\bar{f}}(1-u)sp_1 \\ p_0' &= \frac{1}{\bar{f}}(p_0 + usp_1) \\ (\bar{f} &= \text{average fitness}) \end{aligned}$$

Conditions for the survival of wild types

- The equation

$$\begin{bmatrix} p_1' \\ p_0' \end{bmatrix} = 1/f \begin{bmatrix} (1-u)s & 0 \\ us & 1 \end{bmatrix} \begin{bmatrix} p_1 \\ p_0 \end{bmatrix}$$

- The condition for $p_1 > 0$

$$(1-u)s > 1$$

$$\boxed{1-u > s^{-1}}$$

A closer look at a locus

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

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

$$Q = q^N \quad \text{(Prob. correct replication)}$$

Put q^n into the survival condition of wild type

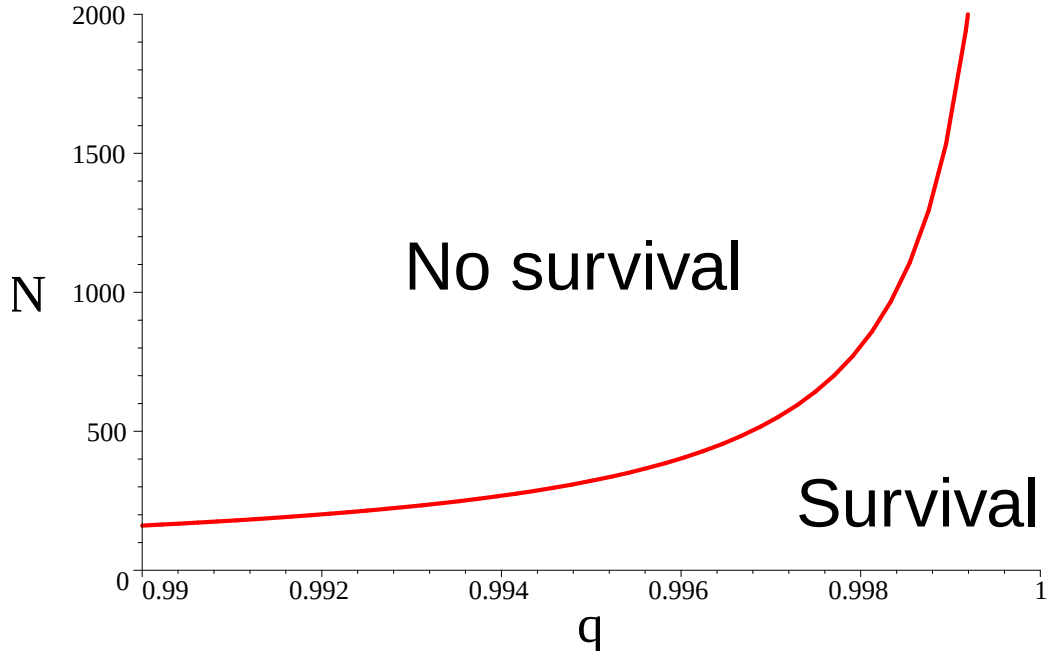
- Our previous result is that $1 - u > s^{-1}$
- This is the same as $Q > s^{-1}$
- Since $Q = q^N$

$$q^N > s^{-1}$$

Therefore, getting the following (Eigen 1971).

$$\boxed{N < \frac{\ln(s)}{1-q}}$$

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



Error Threshold: limiting error rate

In the very beginning of life

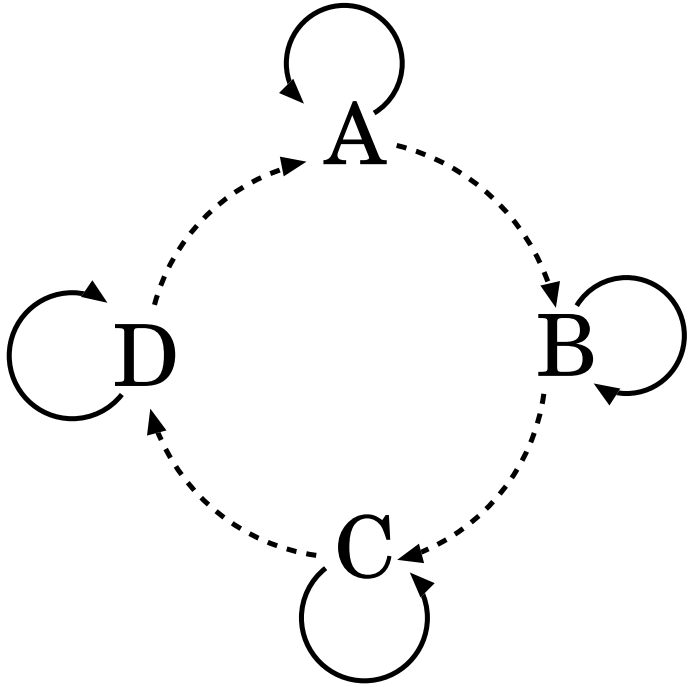
- There is a gap in the length of genome between the first replicators (RNA based without protein) and the first reproducible translation mechanism (with protein). (Eigen Schuster 1979)
  $\rightarrow$ Evolutionary barrier.

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

- How to overcome error threshold?

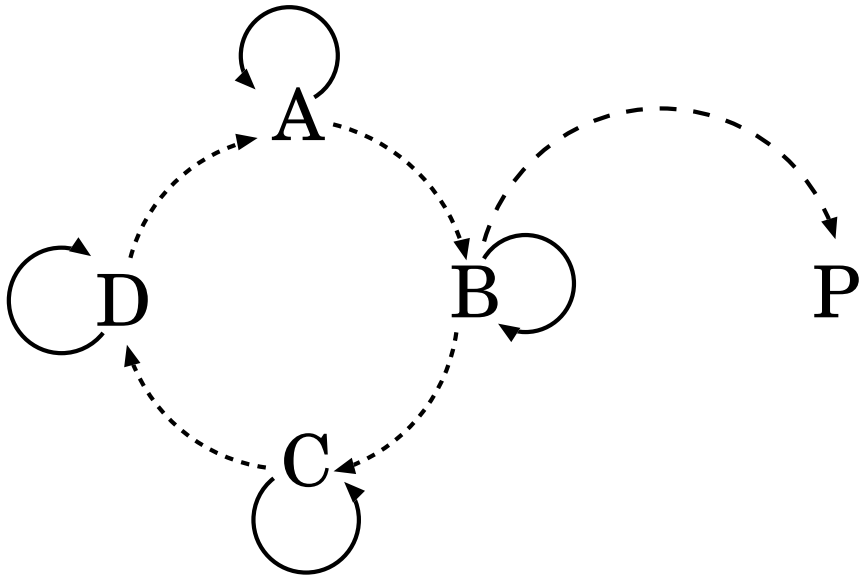
What people have thought

- Hypercycle (Eigen & Schuster 1977)



What people have thought

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



What people have thought

- Hypercycle (Eigen & Schuster 1977)
  $\rightarrow$ Compartmentalization! (Eigen *et al.* 1981)

What people have thought

- Hyper 7)
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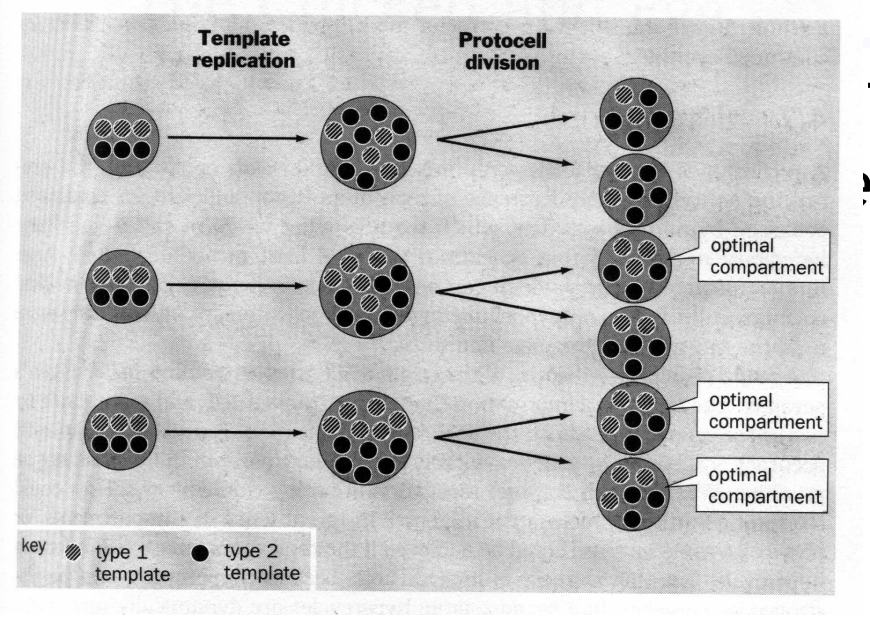


- Stochastic Corrector Model (selection between cell like compartments without Hypercycle) (Szathmáry *et al.* 1987 1995 2002)
  → Survival of altruistic molecules is possible
  → Do not need Hypercycle

What people have thought

- Hypercycle (Eigen & Schuster 1977)
  $\rightarrow$ 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?

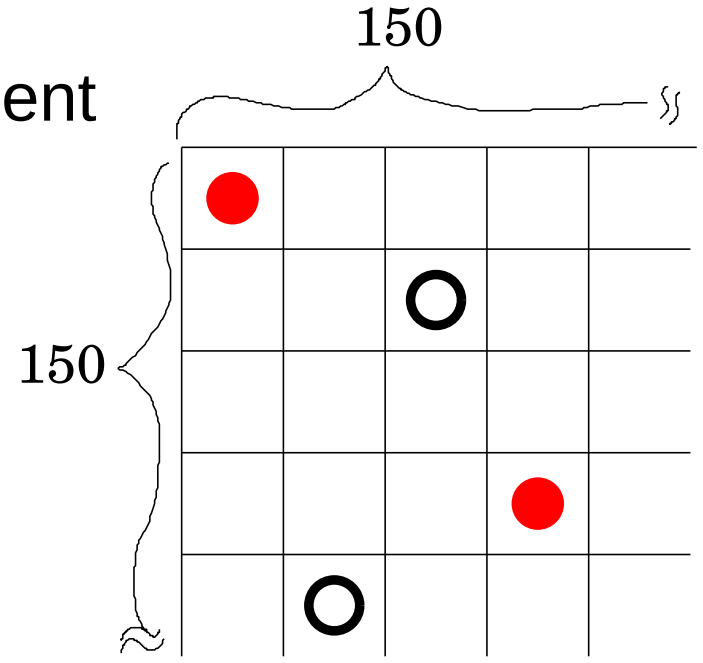
Modeling direction and language

- To begin simpler
  $\rightarrow$ Non-interacting molecules

- Individuals in space
  $\rightarrow$ Two layer Cellular Automata

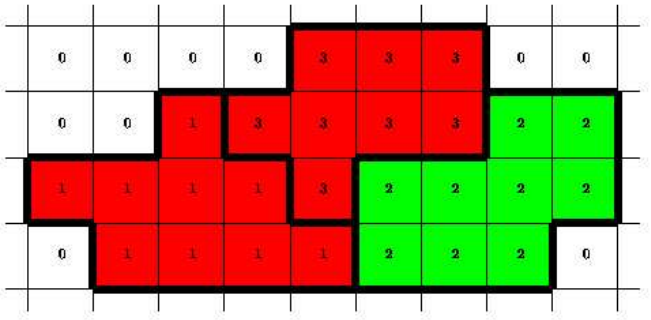
Our model

- 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)



$$\mathcal{H} = \sum J + \lambda(v - V_{\text{target}})^2$$

- 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

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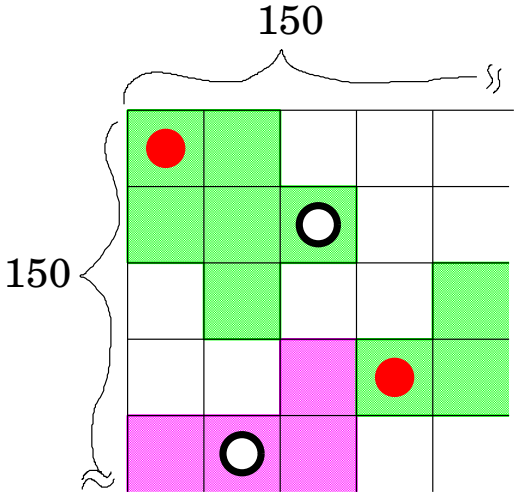
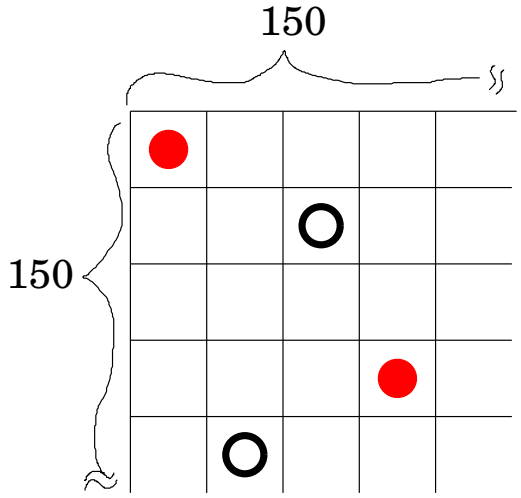
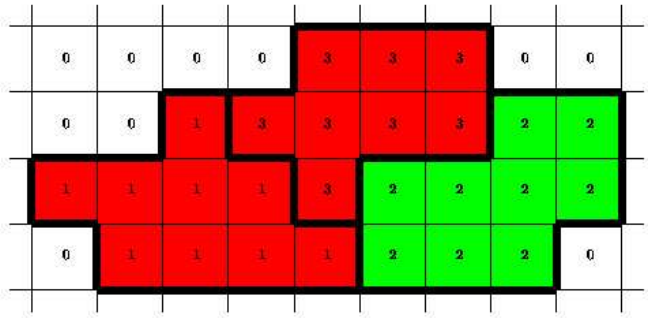


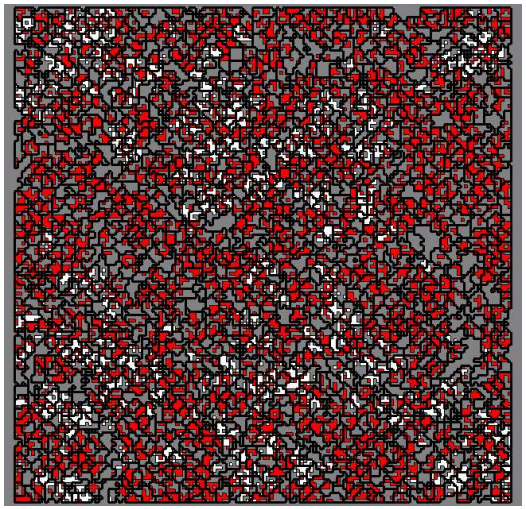


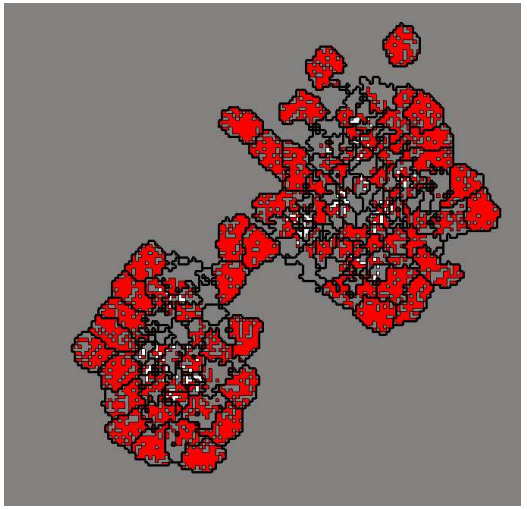


How to connect vesicle dyn. and replicator dyn.

- 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.



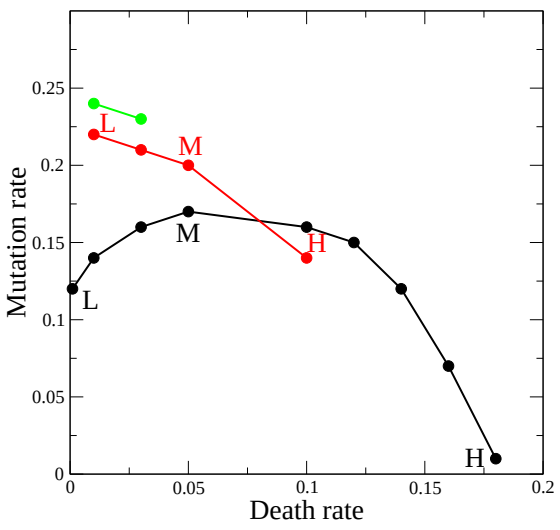


How to connect vesicle dyn. and replicator dyn.

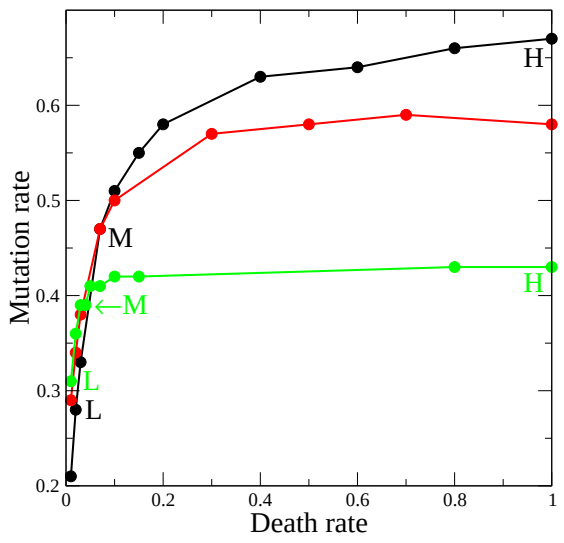
- Birth: vesicles divide when the # of replicators reaches a threshold value (DIVPOP).
- Death: vesicles are taken out by chance (death rate).
- We compare 3 models, changing the functions of replicators on vesicle level:
  - Neutral: no functional difference in replicators except for replicator growth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

Results: error threshold VS vesicle death rate

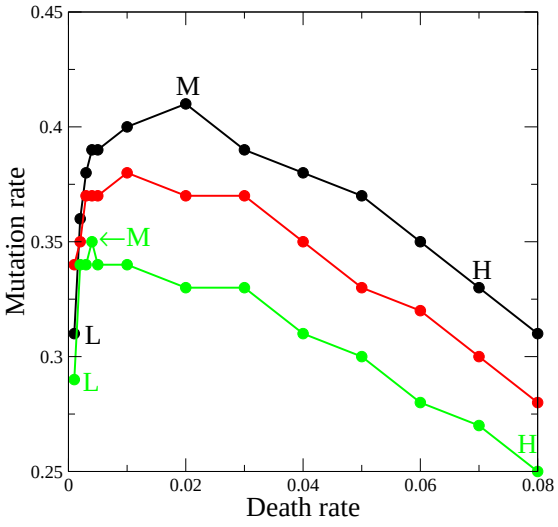
Neutral



Step Mortality



Differential Division

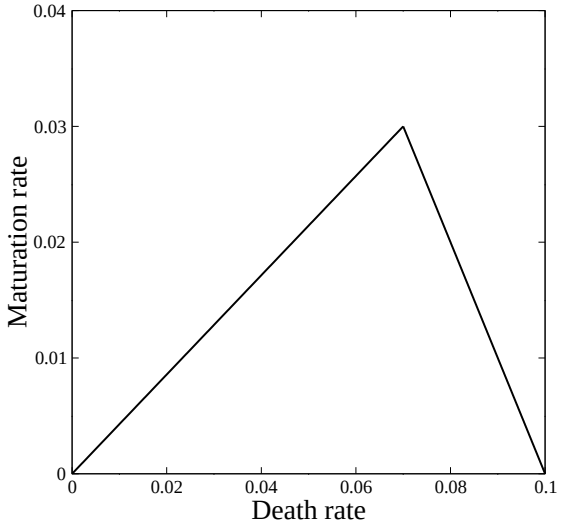


DIVPOP: Green 80; Red 40; Black 10

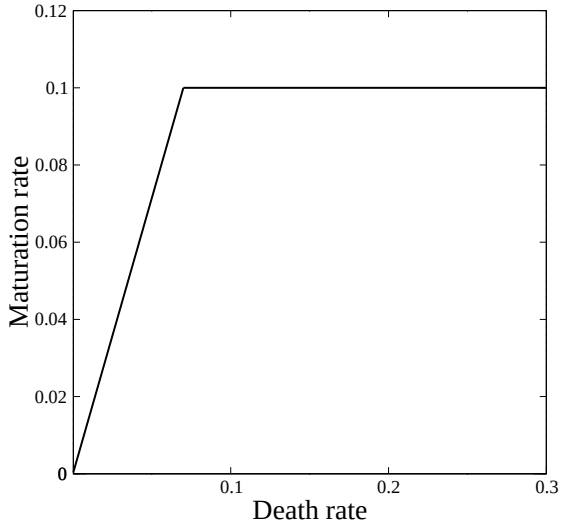
Results: error threshold VS vesicle death rate

ODE predictions

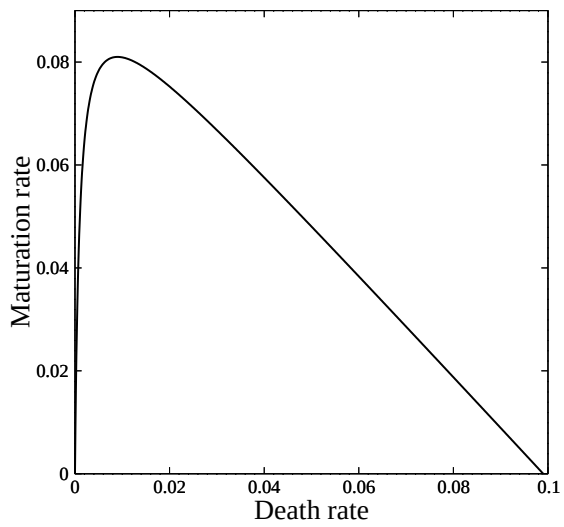
Neutral



Step Mortality



Differential Division



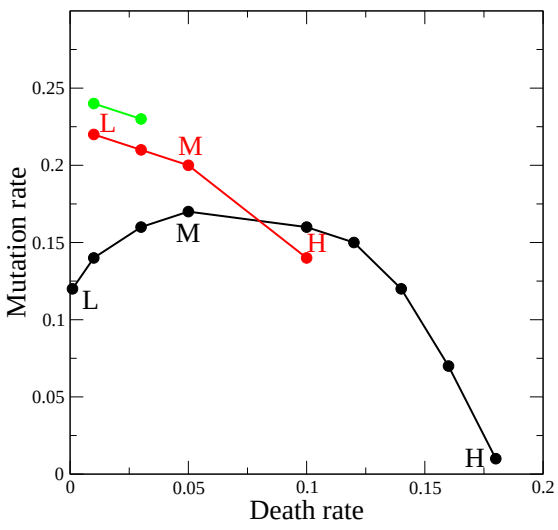
DIVPOP: Green 80; Red 40; Black 10

$$\frac{\mathrm{d}X}{\mathrm{d}t} = G(1-M)X(1-X-Y) - \mu X - DX$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = gY(1-Y-X) + \mu X + GMX(1-X-Y) - DY$$

Results: error threshold VS vesicle death rate

Neutral



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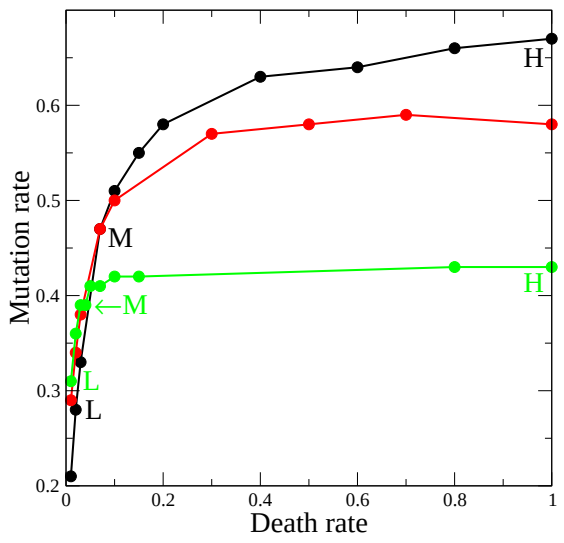

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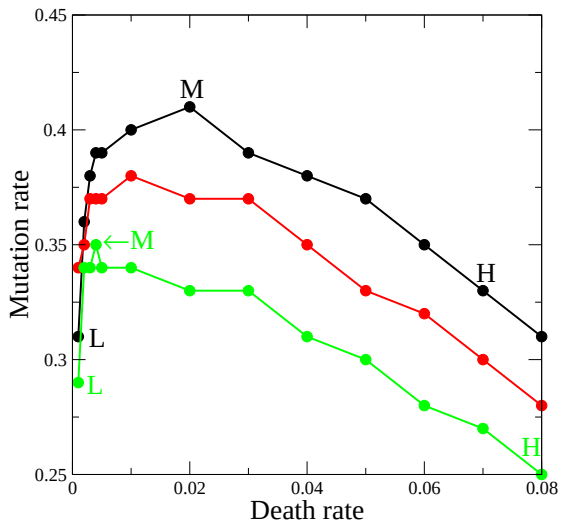
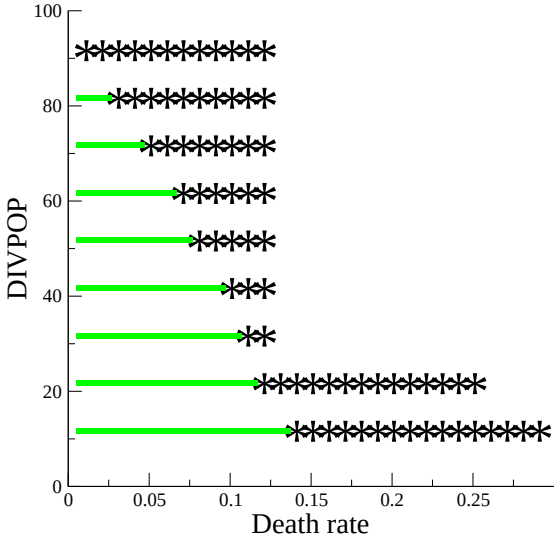


DIVPOP: Green 80; Red 40; Black 10

Results 2: Bifurcation diagram

- Does error threshold increase or decrease ?

Neutral



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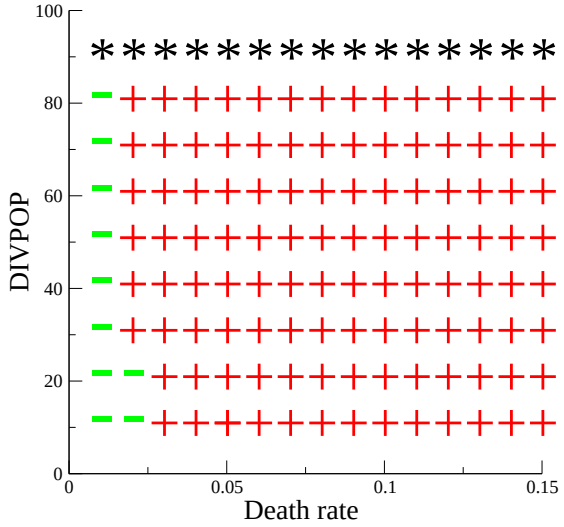

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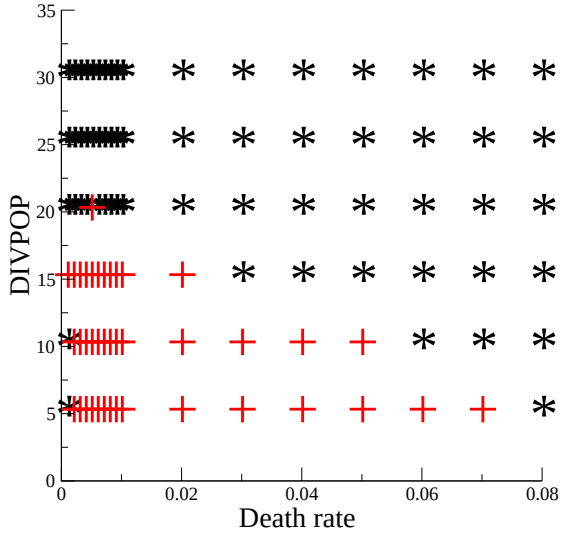


Error Threshold: - decrease; + increase; * system collapses

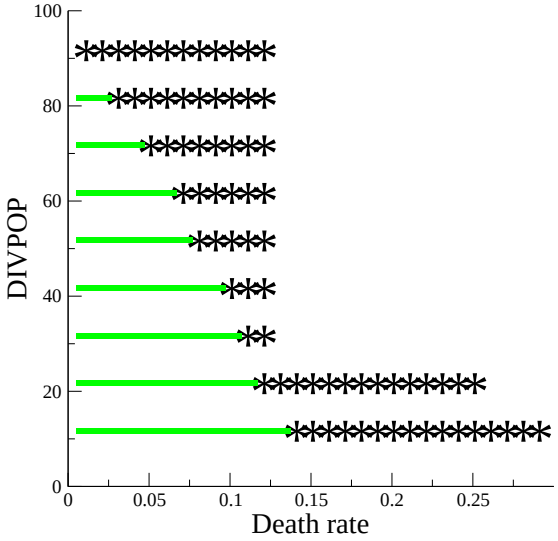
Relative to the reference error threshold

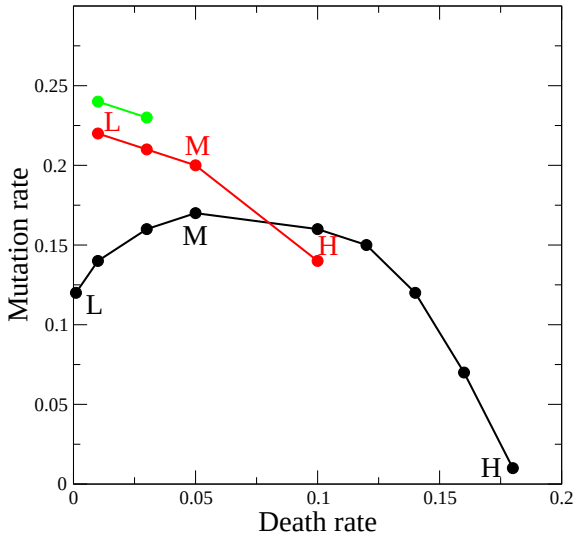
(0.33 without vesicles)

Results 2: Bifurcation diagram

- Does error threshold increase or decrease ?

Neutral





DIVPOP:
Green 80;
Red 40;
Black 10

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

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 quasispesies equation of compartments with internal competition
  $\frac{\mathrm{d}}{\mathrm{d}t}\vec{X} = (\mathbf{MA} - \mathbf{E})\vec{X}$ (1)
- Replicator dynamics
  $\frac{\mathrm{d}x}{\mathrm{d}t} = ax(xy)^{1/4} - dx - x(x+y)/K$
  $\frac{\mathrm{d}y}{\mathrm{d}t} = bx(xy)^{1/4} - dx - y(x+y)/K$
  $\frac{\mathrm{d}s}{\mathrm{d}t} = s((c_1x + c_2y)(xy)^{1/2})^{1/2}/(M + s + (x+y)^2/\mu) - \delta s$
- How to integrate two level of selection?
  - Make M-equation of Replicator dynamics
  - Calculate $\mathbf{M}$, $\mathbf{A}$ in (1) from M-equation

The result of Stochastic Corrector Model

- Does the model really make sense?

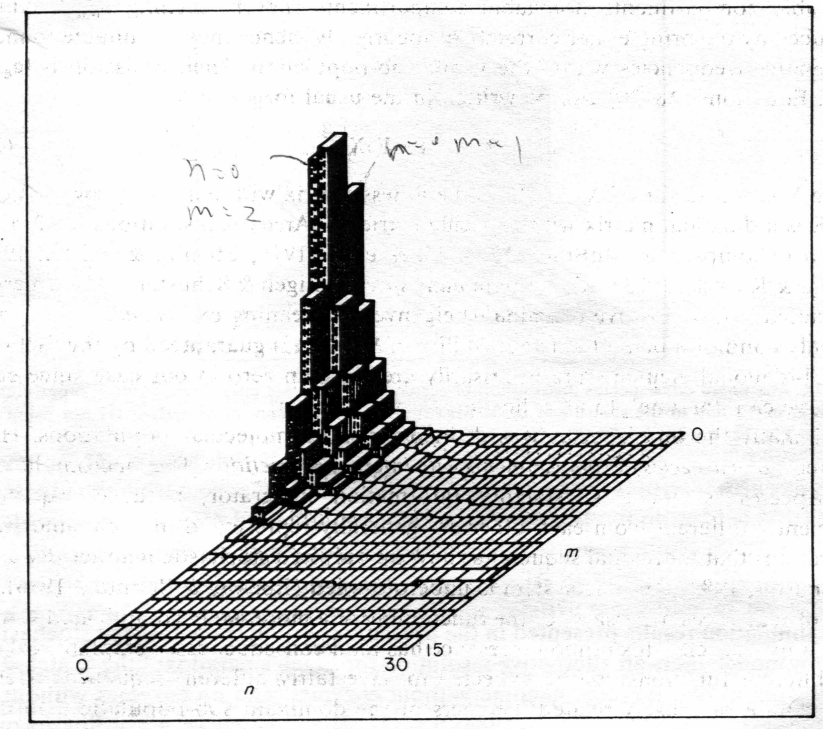


FIG. 7. Simulation result of the master equation (11) just before fission for compartment with $P(1, 2) = 1$ at $t = 0$ (system I, $b = 45$). Because of the short generation time the distribution is still narrow. Maximum = 0·19.

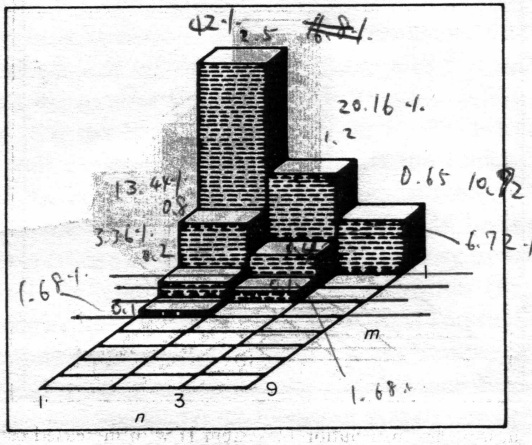


FIG. 9. Dominant quasispecies distribution (system I) as the stationary numerical solution to eqn (21). Maximum = 0·42.

"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)