The role of transient compartmentalization for origin of life scenarios

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Origin of life

One puzzle in the field :

What is the origin of order in biological macromolecules ?

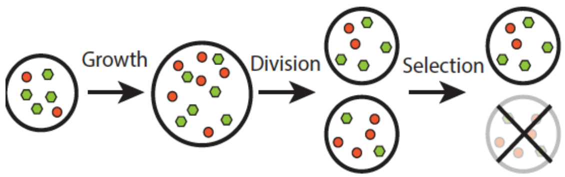
A related puzzle : once created, how to maintain order in macromolecules ?

To be a functional replicator, a molecule must be long enough

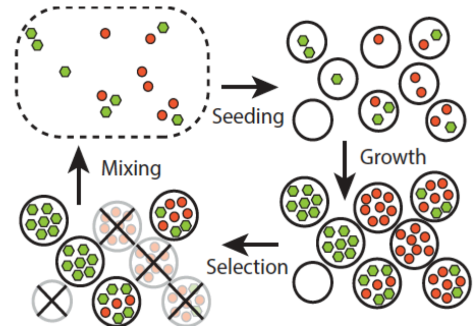
but if it is too long, it can not be replicated accurately **-> error threshold**

Eigen, 1971

Stochastic corrector model vs. transient compartmentalization



E. Szathmary, 1987



A. Blokhuis et al., PRL (2018)

Cell division is not needed and typically requires complex machinery

Transient compartmentalization is simpler and could be induced by fluctuations in the environment (eg. day-night cycles)

Transient compartmentalization of RNA replicators prevents extinction due to parasites

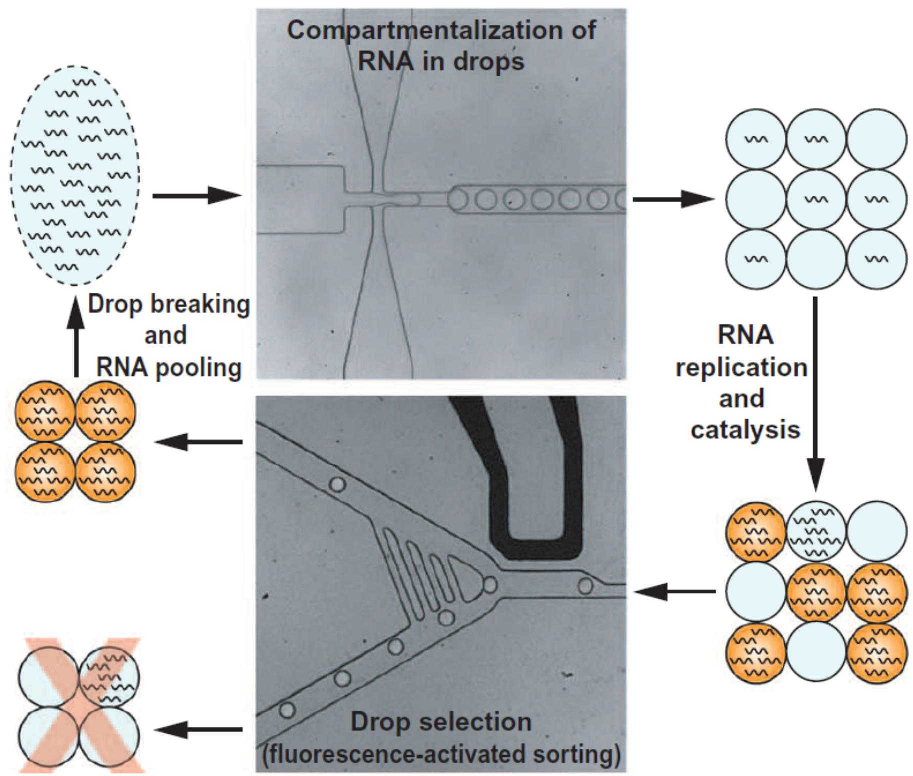
S. Matsumura et al., Science, 2016

1. **Inoculation**
   of droplets with RNA molecules

2. **Maturation:**
   replication of RNA by Qβ molecules
   parasites grow faster

2. **Selection**
   based on catalytic activity
   parasites have no activity

4. **Pooling**
   of selected compartments



Compartment dynamics with pooling

A. Blokhuis, D. L., P. Nghe, L. Peliti, Phys. Rev. Lett., 2018

1. **Each compartment is seeded with a total of n molecules of which m are ribozymes**

Distribution of the initial condition : $$P_\lambda(n,x,m) = \mathrm{Poisson}(\lambda,n)\mathrm{B}_m(n,x)$$

2. **Exponentially growing phase (maturation)**

Ratio of # daughter molecules of parasite / # daughter molecules of ribozymes :

Exponential phase ends when

Fraction of ribozyme at the end of growth phase

Compartment dynamics with pooling

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1. **Each compartment is seeded with a total of molecules of which are ribozymes**

   Distribution of the initial condition :

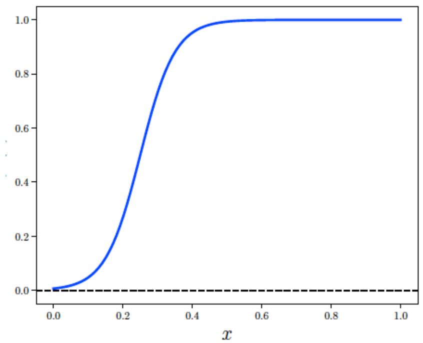
2. **Exponentially growing phase (maturation)** $\bar{m} = me^{\alpha T}, \quad \bar{y} = (n-m)e^{\gamma T}$

   # daughter molecules of parasite / # daughter molecules of ribozymes : $\Lambda = e^{(\gamma-\alpha)T} > 1$

   Exponential phase ends when $N = \bar{n} + \bar{m} = n_{Q\beta}$

   Fraction of ribozyme at the end of growth phase $\bar{x}(n,m) = \dfrac{\bar{m}}{N} = \dfrac{m}{n\Lambda - (\Lambda - 1)m}$

3. Selection of compartments



Selection function :

$$f(\bar{x}) = 0.5\left(1 + \tanh\left(\frac{\bar{x} - x_{th}}{x_w}\right)\right)$$

Fraction of false positives $f(0) \simeq 0.0067$

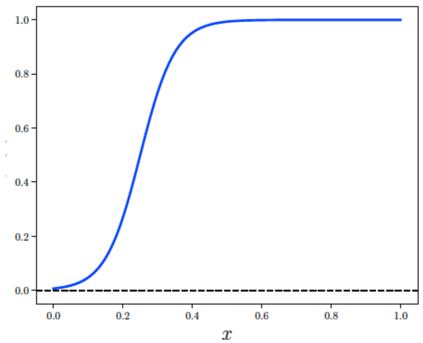
4. Pooling

leads to a recursion equation for the fraction of ribozymes

- **Contour plots of**

Fixed point analysis and linear stability analysis

3. Selection of compartments



Selection function :

Fraction of false positives

4. Pooling

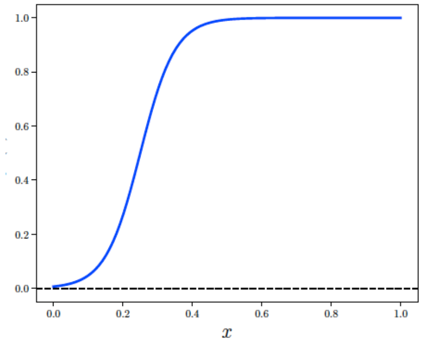
leads to a recursion equation for the fraction of ribozymes

$$x'(\lambda, x) = \frac{\sum_{n,m} \bar{x}(n,m) f(\bar{x}(n,m)) P_\lambda(n,x,m)}{\sum_{n,m} f(\bar{x}(n,m)) P_\lambda(n,x,m)}.$$

- Contour plots of

Fixed point analysis and linear stability analysis

3. Selection of compartments



Selection function :

Fraction of false positives

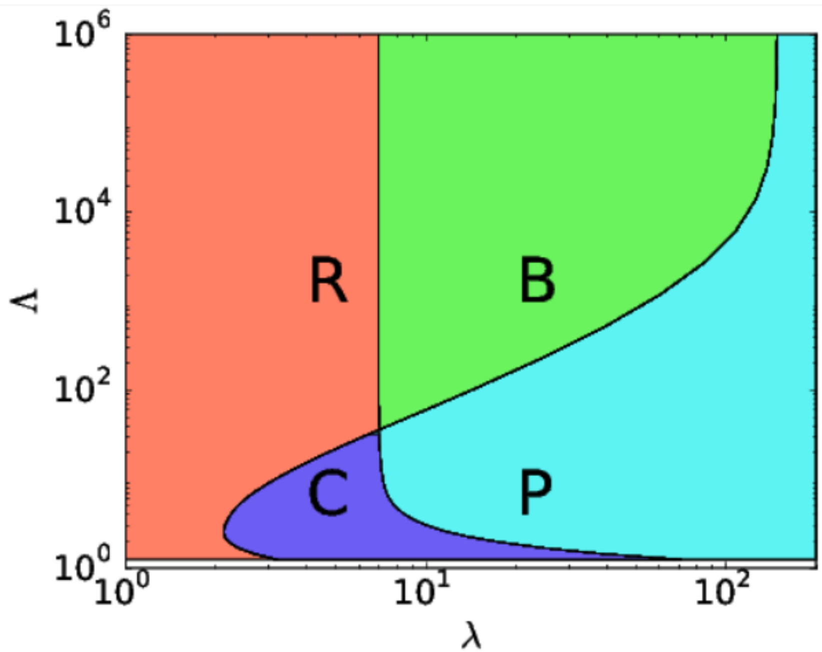
4. Pooling

leads to a recursion equation for the fraction of ribozymes

- **Contour plots of** $\Delta x = x'(\lambda, x) - x$

Fixed point analysis and linear stability analysis

Phase Diagram



Compartment Size (λ)

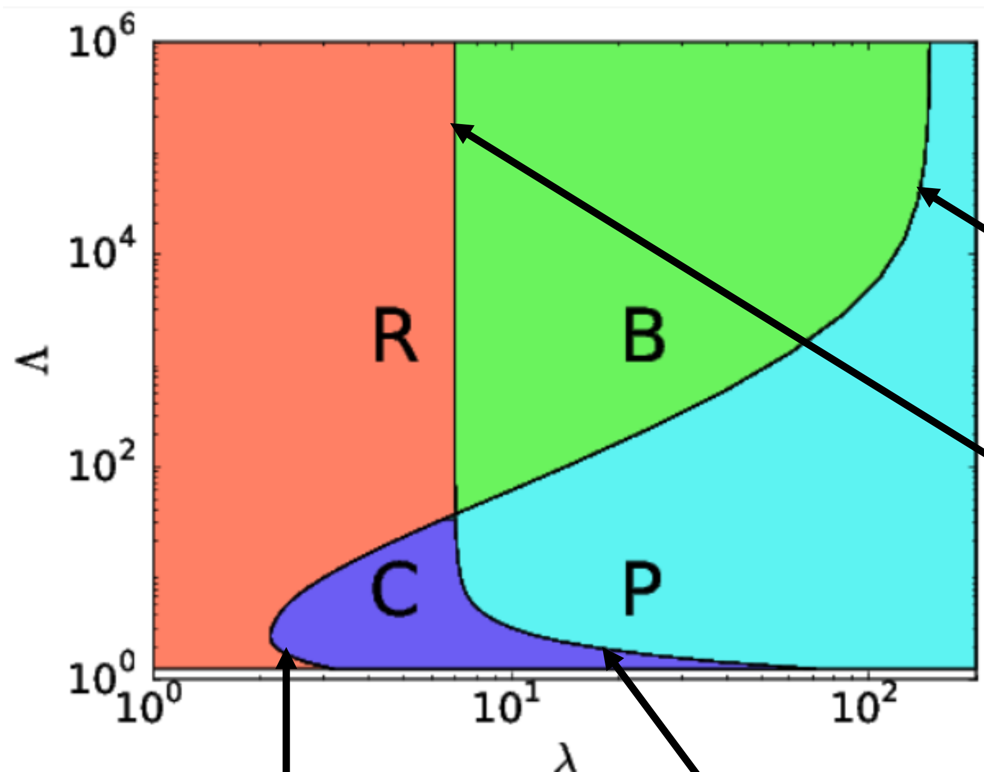
Ribozyme phase (R)
Stable fixed point at $x=1$

Parasite phase (P)
Stable fixed point at $x=0$

Coexistence region (C)
Stable fixed point at $0<x<1$

Bistable phase (B)
Two stable fixed points at $x=0$ and $x=1$

Asymptotes



Hard parasites $\Lambda \gg 1$

$$\lambda = G(f(0), f(1))$$

$$\Lambda \simeq 1 + \frac{f'(1)}{f(1)\lambda}$$

$$\Lambda \simeq 1 + \frac{f'(0)}{f(0)\lambda}$$

Large compartments (bulk)

$$\lambda \gg 1$$

Modified error thresholds due to mutations and noise

A. Blokhuis et al., ArXiv: 1901.04753 (2019)

(under review for JTB)

Mutations

- Mutation rate : μ

- Growth equations
$$\dot{m} = (\alpha - \mu)m,$$
$$\dot{y} = \gamma y + \mu m.$$

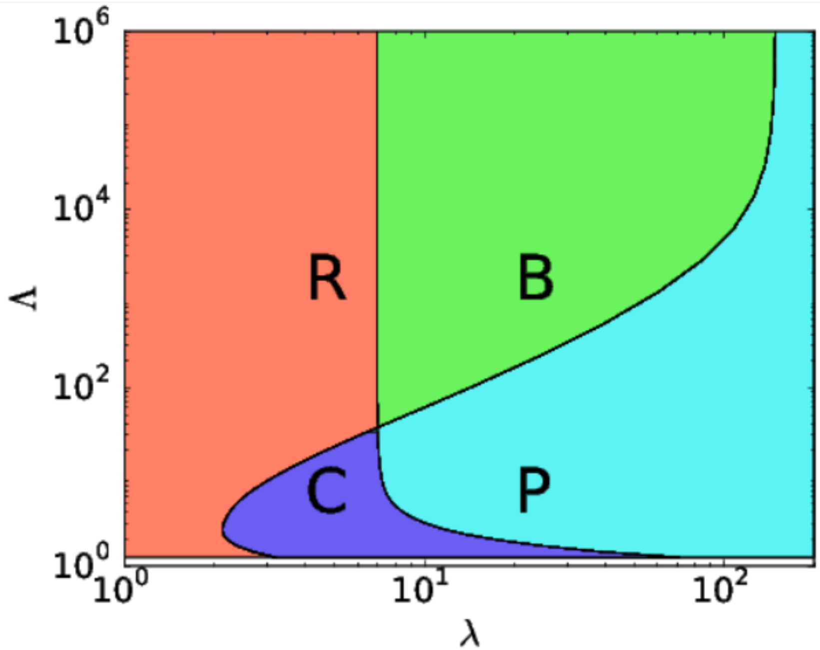
- Modified iteration :

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

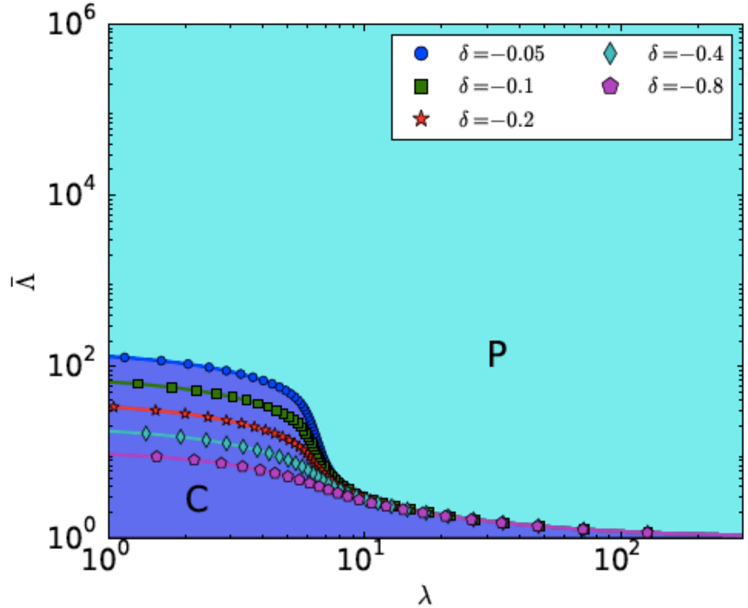
$$\delta = \frac{\mu}{\alpha - \mu - \gamma}, \qquad \bar{\Lambda} = e^{\mu T}\Lambda$$

Time at the end of the exponential phase : T

- Regime $\delta < 0, \quad \text{and} \quad \bar{\Lambda} \geq 1$
- Only two phases left : pure parasite (blue) or coexistence (violet)
- Phase diagram : stability of the x=0 fixed point

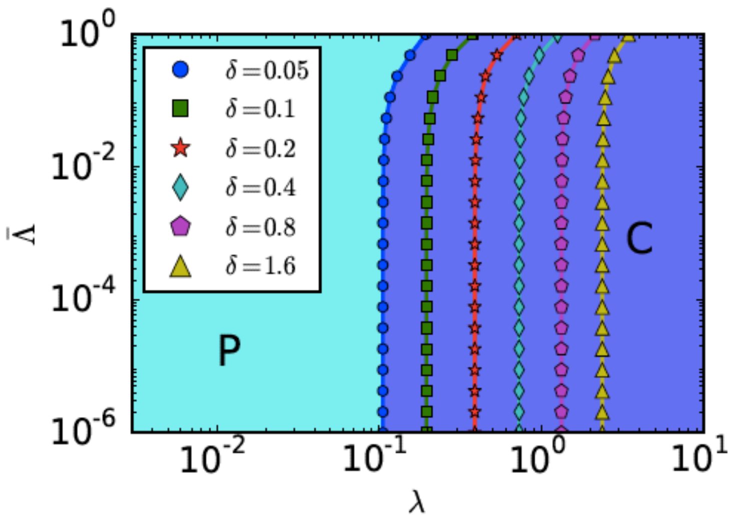


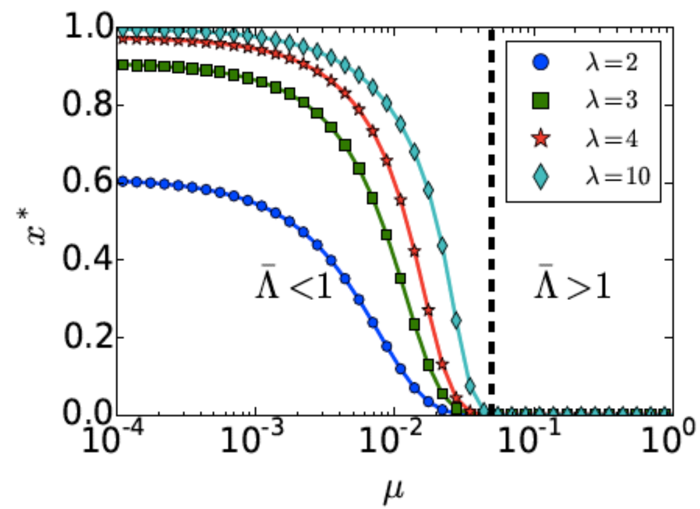
without mutations



with mutations

- Regime $\delta > 0, \quad \text{and} \quad \bar{\Lambda} \leq 1$ ribozymes grow faster than parasites
- P phase reached at high mutation rates: error threshold





- Original error threshold Eigen, 1971

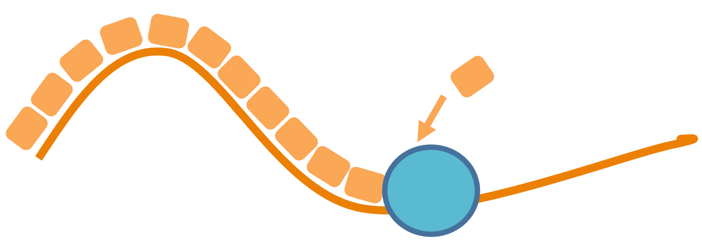
Modified error threshold

$$L \leq \frac{\ln(s')}{\epsilon} \longrightarrow L \leq \frac{\ln(s)}{\epsilon \alpha T} \quad \text{with} \quad s = f(\bar{x})/f(0)$$

Minimal model for the replication of a single molecule

A. Diffusion of replicase to polymer

Diffusion time to target : t_D



B. Incorporation of a fixed number of monomers sequentially

Replication time $t_L = \sum_{i=1}^{L} t_i$ is Gamma distributed

Total time : $t = t_D + t_L$

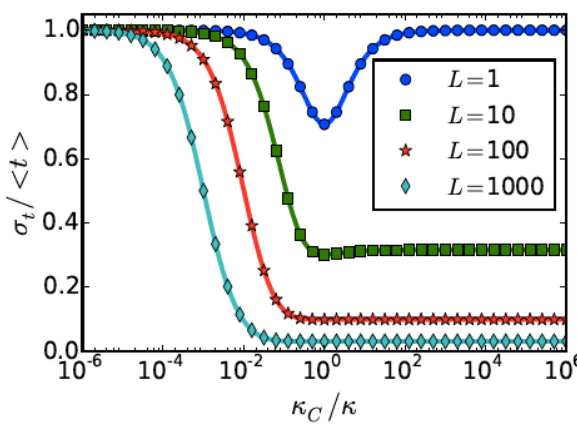
1. **Diffusion limited regime** $t_L \ll t_D$

- The time for the formation of the complex with the replicase is limiting
- Large variability $\sigma_t \simeq \langle t \rangle$

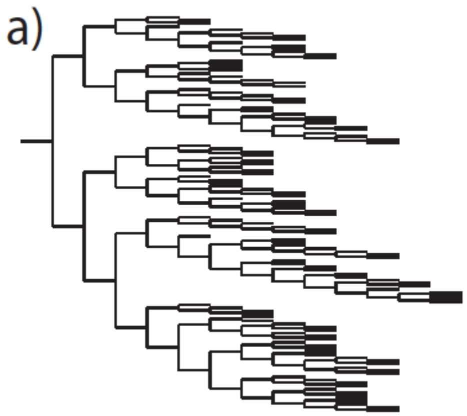
2. **Replication limited regime** $t_D \ll t_L$

- The time to incorporate the L nucleotides is limiting
- Small variability for large polymers $\dfrac{\sigma_t}{\langle t \rangle} \simeq \dfrac{1}{\sqrt{L}}$

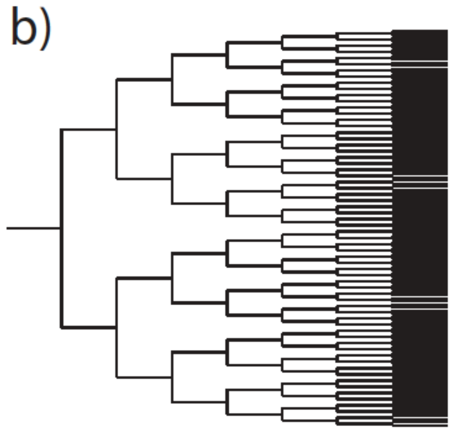
Cross-over between the two regimes :



In a generations representation : (branching process with i.i.d. generation times)

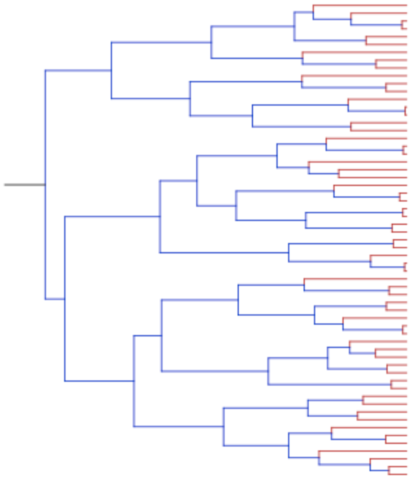


Diffusion limited



Replication limited

In continuous time representation



Noise in growing populations

- Exponential growth of the population $N(t) \simeq N(0)e^{\alpha t}$
- In the replication limited regime, the noise on N is

$$\frac{\sigma_N}{\langle N \rangle} \simeq \frac{\sqrt{2}\ln 2}{\sqrt{L}\sqrt{N(0)}} \longrightarrow \sigma_{\bar{x}} \simeq \frac{1}{n}\sqrt{\frac{my}{n}}$$

population noise compositional noise

- Due to a fixed and large number of rate limiting steps (L>>1), compositional noise is reduced

Template polymerization allows to reduce compositional noise, which permits heredity

Summary

- Transient compartmentalization is a central feature in Origin of life scenarios
- Smallness of λ essential to generate diversity on which selection can act
- This mechanism does not require a proper cell division mechanism