Applications of the theory of the spatial replicator equations to real-world biological systems

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Evolutionary Principles:

- ► Heredity
- Variability
- Natural selection



 $\begin{array}{c} \text{Charles Darwin,} \\ 1809\text{--}1882 \end{array}$

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RNA World and Eigen's Model:

The RNA world hypothesis proposes that life based on ribonucleic acid (RNA) predates the current world of life based on deoxyribonucleic acid (DNA), RNA and protein.



Manfred Eigen, 1927

- M. Eigen, Naturwisenschaften, 58(10), 1971: 465–523
- M. Eigen, J. McCaskill, P. Schuster, J Phys Chem, 92(24), 1988:181-1891

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 M. Eigen, P. Schuster, The Hypercycle, Springer, 1979

Model for Catalytic Growth of Macromolecules:

Flow reactor



 y_i is the absolute number of the *i*th macromolecule, $i = 1, 2, ..., n, \sum_{i=1}^n y_i = \text{Const.}$

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Particular Cases for the Replicator Equation:

Independent replication:

$$\frac{\dot{y}_i}{y_i} = a_i, \quad i = 1, \dots, n$$

Autocatalytic replication:

$$\frac{\dot{y}_i}{y_i} = b_i y_i, \quad i = 1, \dots, n$$

▶ Hypercyclic replication:

$$\frac{\dot{y}_i}{y_i} = k_i y_{i-1}, \quad i = 1, \dots, n, \ y_0 \equiv y_n$$

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The Replicator Equation:

▶ General case:

$$\frac{\dot{y}_i}{y_i} = \sum_j a_{ij} y_j = (\mathbf{A}\mathbf{y})_i$$

Equations for the flow reactor

$$\frac{\dot{y}_i}{y_i} = c_i - f_1(t)$$
$$\frac{\dot{y}_i}{y_i} = b_i y_i - f_2(t)$$

$$\frac{\dot{y}_i}{y_i} = k_i y_{i-1} - f_3(t)$$

General case

$$\frac{\dot{y}_i}{y_i} = \sum_j a_{ij} y_j - f(t), \quad f(t) = \sum_{i,j=1}^n a_{ij} y_i y_j = \langle \mathbf{A} \mathbf{y}, \mathbf{y} \rangle$$

Principle of Competitive Exclusion:

$$p_i = \frac{y_i}{\sum\limits_{i=1}^n y_i}$$

Independent replication

$$\dot{p}_i = p_i(a_i - \sum_j a_j p_j), \quad \sum p_i = 1$$

Autocatalytic replication

$$\dot{p}_i = p_i(b_i p_i - \sum_j b_j p_j^2), \quad \sum p_i = 1$$



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Hypercyclic Replication:

$$\dot{p}_i = p_i(k_i p_{i-1} - \sum_j k_j p_j p_{j-1}), \quad \sum p_i = 1$$

- ▶ The inner rest point $\hat{\mathbf{p}} \in \text{int } S_n$ is globally stably for the short (n = 2, 3, 4) hypercycles
- The hypercyclic reaction is permanent: for any i $p_i(t) \ge \delta > 0$ starting for some t
- For $n \ge 5$ a globally stable limit cycle appears

 ${\bf Ref:}$ Hofbauer and Sigmund, Evolutionary Games and Population Dynamics, Cambridge, 1998

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Mallet-Paret and Smith, J Dyn Diff Eq, 2, 1990

Variability:



$$\dot{p}_i = p_i(k_i p_{i-1} - \bar{f}), \quad i = 1, \dots, n$$

 $\bar{f} = \sum_{i=1}^4 k_i p_i p_{i-1}, \quad \mathbf{p} \in S_4.$

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Natural Selection:



 $\dot{p}_i = p_i(k_i p_{i-1} - \bar{f}), \ i = 1, 2, 3, \quad \dot{p}_i = p_i(k_i p_{i-1} - \bar{f}), \ i = 4, 5, 6$

$$\bar{f} = \sum_{i=1}^{6} k_i p_i p_{i-1}, \quad \sum p_i = 1$$

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Parasites:



$$\dot{p}_i = p_i(k_i p_{i-1} - \bar{f}), \quad i = 1, \dots, n$$

 $\bar{f} = \sum_{i=1}^4 k_i p_i p_{i-1}, \quad \mathbf{p} \in S_4.$

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Replicator Equation (ODE):

$$\dot{v}_i = v_i \left[(\mathbf{A}\mathbf{v})_i - f^{loc}(t) \right], \qquad i = 1, \dots, n.$$

Here

$$\mathbf{v}(t) = (v_1(t), \dots, v_n(t)), \ \mathbf{v} \in S_n = \{\mathbf{v} \in \mathbb{R}^n_+ \colon \sum_i v_i = 1\},\$$

The mean fitness is given by

$$f^{loc}(t) = \langle \mathbf{A}\mathbf{v}, \, \mathbf{v} \rangle = \sum_{i=1}^{n} (\mathbf{A}\mathbf{v})_{i} v_{i},$$

and the fitness of the i-th molecule is

$$(\mathbf{A}\mathbf{v})_i = \sum_{j=1}^n a_{ij} v_j(t)$$

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Open Replicator System: Stable Inner Rest Point





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Open Replicator System:



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Open Replicator System: Stable Heteroclinic Cycle



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Open Replicator System: The Case of Four Dimensions



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Distributed Replicator Equation with the Global Regulation of the First Type:

$$\partial_t u_i = u_i \left[(\mathbf{A}\mathbf{u})_i - f^{sp}(t) \right] + d_i \Delta u_i, \ i = 1, \dots, n_s$$

Here,

$$\mathbf{u}(\mathbf{x},t) = (u_1(\mathbf{x},t),\ldots,u_n(\mathbf{x},t)), \quad \mathbf{x} \in \Omega \subset \mathbb{R}^m, t > 0.$$

The condition of global regulation:

$$\mathbf{u} \in I_n = \left\{ u_i(\mathbf{x}, t) \ge 0 \colon \sum_{i=1}^n \int_{\Omega} u_i(\mathbf{x}, t) \, d\mathbf{x} = 1 \right\}$$
$$u_i(\mathbf{x}, 0) = \varphi_i(\mathbf{x}), \quad \left. \frac{\partial u_i}{\partial \mathbf{n}} \right|_{\Gamma} = 0, \quad \Gamma = \partial \Omega$$

Mean integral fitness:

$$f^{sp}(t) = \sum_{i=1}^{n} \int_{\Omega} u_i (\mathbf{A}\mathbf{u})_i \, d\mathbf{x} = \int_{\Omega} \langle \mathbf{A}\mathbf{u}, \, \mathbf{u} \rangle \, d\mathbf{x}.$$

Stability of Spatially Homogeneous Solutions in the General Case (Type I):

Theorem

Let $\hat{\mathbf{w}} \in \text{int } S_n$ be an asymptotically stable equilibrium of the ODE replicator equation. Then for this point to be an asymptotically stable stationary solution to the distributed replicator equation (PDE) it is necessary that

$$\sum_{i=1}^{n} d_i > \frac{\beta}{\lambda_1}, \quad \beta = \langle \mathbf{A}\hat{\mathbf{w}}, \, \hat{\mathbf{w}} \rangle,$$

where d_i are diffusion coefficients, and λ_1 is the first nonzero eigenvalue of the following boundary problem:

$$\Delta\psi(\mathbf{x}) + \lambda\psi(\mathbf{x}) = 0, \quad \mathbf{x} \in \Omega, \quad \partial_{\mathbf{n}}\psi|_{\mathbf{x} \in \Gamma} = 0.$$

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The Distributed Hypercyclic System. Numerical Example:





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Distributed Hypercyclic System:

Small perturbation of a hamiltonian system



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Distributed Replicator Equation with the Global Regulation of the Second Type:

$$\partial_t v_i = v_i((\mathbf{A}\mathbf{v})_i - f^{sp}(t) + d_i \Delta v_i), \quad i = 1, \dots, n,$$

where now

$$f^{sp}(t) = \int_{\Omega} (\langle \mathbf{A}\mathbf{v}, \mathbf{v} \rangle - \sum_{i=1}^{n} d_i \|\nabla v_i\|) dx.$$

Stability of Spatially Homogeneous Solutions in the General Case (Type II):

Theorem

Let $\hat{\mathbf{w}} \in \text{int } S_n$ be an isolated equilibrium of the ODE replicator equation. Then the asymptotical stability (instability) of this point implies asymptotical stability (instability) of the same equilibrium for the distributed replicator equation with the global regulation of the second type, if

$$d_{\min} > \frac{\mu}{\lambda_1},$$

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and μ is the maximal real part of the eigenvalues of **A**.

Local Solutions (Type II Global Regulation) :

Consider problem

$$u_{k}(d_{k}u_{k}'' - a_{k}u_{k} + \overline{f}^{sp}) = 0,$$

$$u_{k}'(0) = u_{k}'(1) = 0,$$
where $k = 1, \dots, n.$
One possible solution is
$$u_{1}(x) = \begin{cases} \frac{\overline{f}^{sp}}{a_{1}}(1 + \cos m\pi x) & x \in (0, 1/m], \\ 0, & x \in (1/m, 1) \end{cases}$$

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The Distributed Open Replicator System:



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The Distributed Open Replicator System



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Real Biological Objects:

- T.A. Lincoln, G.F. Joyce.
 Self-Sustained Replication of an RNA Enzyme// Science. 2009. 323. P.1229–1232
- N. Vaidya, M.L. Manapat, I.A. Chen, R. Xulvi-Brunet, E.J. Hayden, N. Lehman.
 Spontaneous network formation among cooperative RNA replicators// Nature. 2012.



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Spontaneous network formation among cooperative RNA replicators

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The origins of life on Earth required the establishment of self-replicating chemical systems capable of maintaining and evolving biological information. In an RNA world, single self-replicating RNAs would have faced the extreme challenge of possessing a mutation rate low enough both to sustain their own information and to compete successfully against molecular parasites with limited evolvability. Thus theoretical analyses suggest that networks of interacting molecules were more likely to develop and sustain life-like behaviour. Here we show that mixtures of RNA fragments that self-assemble into self-replicating ribozymes spontaneously form cooperative catalytic cycles and networks. We find that a specific three-membered network has highly cooperative growth dynamics. When such cooperative networks are competed directly against selfish autocatalytic cycles, the former grow faster, indicating an intrinsic ability of RNA populations to evolve greater complexity through cooperative. We can observe the evolvability of networks through in vitro selection. Our experiments highligh the advantages of cooperative behaviour even at the molecular stages of nascent life.



Figure 2 | Cooperative chemistry out-competes selfish chemistry when directly competed. a, Empirical results using cooperative (I1, I2 and I3, that is, Fig. 1b) and selfish subsystems (S1, S2 and S3, where IGS and IGS targets were changed to be matching in each subsystem). Yields of total W•X•Y•Z RNA tracked the concentrations of cooperative (mismatched) or selfish (matched) W-containing RNAs (0.05 µM initial concentrations) over time either when the cooperative (green) and selfish (red) sets of subsystems were incubated separately (dashed lines) or together in the same reaction mixture (solid lines; upper left inset). Data points are averages of three independent trials. Error bars show the standard error of the mean (s.e.m.), and the yields of the cooperative trials in the mixed experiment are significantly greater than those of the selfish trials at the 10- and 16-h time points ($P \le 0.05$ by t-tests using Sidák's correction for multiple a posteriori comparisons). b, Simulation of growth dynamics using a toy model of the network of cooperation and selfish interactions (see Supplementary Information). Cooperative enzymes fare better in competition than do selfish enzymes, as demonstrated empirically in panel a.



Figure 3 | The randomization experiment. a. Experimental design. The middle nucleotides of the IGS and the tags were randomized to create diverse RNA pools. A reaction of 300 pmol each (0.5 µM) of $\alpha_{\rm M}({\rm Systo-}\alpha_{\rm M}({\rm NY}_{\rm COL}{\rm NY}_{\rm COL}{$

for ease of presentation) of the joint frequencies of all genotypes that can potentially participate in such cycles (ashed line with squares for example, ASA + UxU). The rise of three-membered cycles can be seen from the sum (\$<10000 for ease of presentation 00 joint frequencies of three sets of genotypes; Fg, IJ and its two permutations by junction (solid line; USG + AyA + CAU; UGF + AXA + CAU; UGA + UGA + AXA + CAU; UGA + AYA +

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Numerical Solution for Complex Replicator Matrix:



Figure : A catalytic network of macromolecules. There are six macromolecules. The arrows show the catalytic activity of the molecules. The coefficients are the corresponding rate constants. This network is inspired by the catalytic network of self-replicating RNA molecules, which was shown to be capable of sustained replication

Numerical Solution for Complex Replicator Matrix:

$$\begin{split} \dot{u}_k &= u_k \big((Au)_k - f(u) \big), \quad k = 1, \dots, 6, \\ A &= \begin{pmatrix} 0 & 0 & \alpha & 0 & 0 & \gamma \\ \alpha & 0 & 0 & 0 & \gamma & 0 \\ 0 & \alpha & 0 & \gamma & 0 & 0 \\ \gamma & 0 & 0 & \beta & 0 & 0 \\ 0 & 0 & \gamma & 0 & \beta & 0 \\ 0 & \gamma & 0 & 0 & 0 & \beta \end{pmatrix} \\ f(u) &= \alpha \sum_{1 \le i \le j \le 3} u_i u_j + \gamma \sum_{1 \le i \le j \le 6} u_i u_j + \beta \sum_{4 \le i \le 6} u_i^2 \end{split}$$

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Numerical Solution for Complex Replicator Matrix (Type I):



Figure : Solutions to the replicator equation with the global regulation of the first type on $\Omega = (0,1)$ with with diffusion coefficients $d_1 = (0.4, 0.5, 0.4, 0.5, 0.4, 0.5)$. Left panel: Solutions at the moment t = 60. Right panel: The averages of the solutions $\overline{v}_i(t), i = 1, \ldots, 6$ depending on time t

Numerical Solution for Complex Replicator Matrix (Type II):



Figure : Solutions to the replicator equation with the global regulation of the second type on $\Omega = (0, 1)$ with diffusion coefficients $d_2 = (0.04, 0.05, 0.04, 0.05, 0.04, 0.05)$. Left panel: Solutions at the moment t = 40. Right panel: The averages of the solutions $\overline{v}_i(t), i = 1, \ldots, 6$ depending on time t

Numerical Solution for Complex Replicator Matrix:



Figure : The time dependent behavior of the mean fitness in the model with global regulation of Type I (left) versus the model with global regulation of type II (right) for the same diffusion coefficients $d_2 = (0.04, 0.05, 0.04, 0.05, 0.04, 0.05)$

Numerical Solution for Complex Replicator Matrix (Type II):



Figure : Solutions in the (x, t) space on $\Omega = (0, 1)$

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Thank you for your attention!

Questions?

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