Parasites and Pattern Formation

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Biological information is coded in replicating molecules. To maintain a given amount of information a cooperative interaction between these molecules is essential. The main problem for the stability of a system of prebiotic replicators are emerging parasites. Stabilization against such parasites is possible if space is introduced in the model. Complex patterns like spiral waves and self–replicating spot patterns have been shown to stabilize such systems. Stability of replicating systems, however, occurs only in parameter regions were such complex patterns occur. We show that parasites are able to push such systems into a parameter region were life is possible. To demonstrate this influence of parasites on such systems, we introduce a parasitic species in the Gray-Scott model. The growing concentration of parasites will kill the system, and the cooperative Gray-Scott system will be diluted out in a well mixed flow reactor. While considering space, in the model stabilizing pattern formation in a narrow parameter region is possible. We demonstrate that the concentration of the parasitic species is able to push the system into a region were stabilizing patterns emerge.

Key words: Pattern Formation; Reaction-Diffusion; Molecular Evolution; Parasites; Coevolution; Cooperation.

1. Introduction

The molecular evolution of functional cooperation plays a crucial role in theories concerning the origine of live [1 - 4] and in the development of functional drugs in modern evolutionary biotechnology [5, 6]. Due to the random noise caused by the natural mutation rate the complexity of non-cooperative evolutionary molecular systems is limited [1, 7]. Complex living systems as we can see them in nature can not be developed without any cooperative mechanism involved at a very primitive level of organisation [1, 8, 9]. An accidental and instantaneous formation of complex cooperative systems is very unlikly; life and primitive forms of cooperative systems should have evolved simultaneously via simple cooperative pre-biotic replicator systems [1, 8, 9]. Simple forms of molecular cooperation, however, are unstable against parasites which emerge unavoidably through mutations in the sequence encoding the cooperative function [10, 11]. These parasites compete with the cooperative species from which they evolved. Since their evolution is not restricted to functional sequences, a faster parasitic replicator will occure rapidly. This advantage of the parasites leads to a complete destabilisation of the system, and the cooperative species will die in the homogeneous case. In nature spatial effects may have lead to a stabilisation of functional cooperation. Numerical simulations indeed have shown such a stabilisation against parasitic take over in reaction diffusion systems showing self-replicating spots [12, 13] or spirals [14]. In simple reaction diffusion systems such complex and time–dependend patterns occure only for a special choice of kinetic parameters [15], and it is not obvious how evolution can force and keep a simple system in the narrow parameter region where this pattern formation occurs.

In this work we discuss the related question: Given a simple (cooperative) reaction–diffusion system, for which parameter regime will the system show pattern formation in the case parasites emerge?

2. Interaction of Parasites with a Simple Cooperative System

The simplest system showing a complex pattern is the well-known Gray-Scott model [15 - 17]:

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$$U + V + V \xrightarrow{k_1} 3V, \tag{1}$$

$$V \xrightarrow{\bar{k}} O. \tag{2}$$

Two V species cooperate for their reproduction while a resource species U is consumed. O is an inert product. Let us now introduce a parasitic species P which uses the cooperative function of V for its own reproduction without cooperating for the reproduction of V:

$$U + P + V \xrightarrow{k_2} 2P + V, \tag{3}$$

$$P \xrightarrow{\bar{k}} O. \tag{4}$$

It is obvious that such a (destructive) exploitation of cooperation appears to be unavoidable in nature. An example is the simple cooperative CATCH system, where the cooperation of two DNA strands take place on the molecular level [18 - 20]. A mutation in the sequence of the DNA encoding for the cooperative molecular function produces a non-functional 'parasitic' DNA strand which nevertheless can reproduce and amplify by the cooperative function of the other strands. See [20] for a more detailed description and discussion. Since a cooperative function is connected with some effort (or restrictions for the structure and the sequence on the molecular level) the evolution of a parasitic species wich can amplify faster than the cooperative species is very likely ($k_2 > k_1$). The kinetics of the system is in the sufficiently homogeneous mixed case (Continuous-flow Stirred Tank Reactor: CSTR) described by the system of ordinary differential equations (in dimensionless units)

$$\begin{aligned} \dot{u} &= -uv^2 - \alpha upv + F(1-u), \\ \dot{v} &= uv^2 - (F+k)v, \\ \dot{p} &= \alpha upv - (F+k)p. \end{aligned} \tag{5}$$

F is the dimensionless feed rate, k the dimensionless rate constant for reactions to the inert product O and $\alpha = k_2/k_1$ is the relative advantage of the parasites in its reproduction rate. The ordinary differential equations have a trivial fixed point $u = 1$, $v = p = 0$. In the case of no parasites ($p = 0$) the system has the two additional non-trivial fixed points

$$u^* = \frac{1}{2} \pm \sqrt{\frac{1}{4} - \frac{(F+k)^2}{F}} > 0, \; v^* = \frac{F+k}{u^*}, \tag{6}$$

the stability properties (for $p = 0$) of which are discussed by Pearson [15]. No steady state exists for nonzero concentration of parasites P (for $\alpha \neq 1$). Moreover, the steady states (6) are unstable against growing parasite concentration. This can easily be seen by the condition

$$\dot{p} = \alpha u^* p v^* - (F+k)p = (\alpha - 1)(F+k)p, \tag{7}$$

which for $\alpha < 1$ describes an exponentially decaying concentration $p(t)$ and for $\alpha > 1$ gives an exponential growing parasite concentration. For $\alpha > 1$ the only stable fixed point is the trivial fixed point. Thus an advantageous parasite will kill the system in the homogeneous case. (Remark: A more rigorous stability analysis of the system give the same result.)

Let us assume that $\alpha - 1 > 0$ but very small, and the growth of the parasite concentration is very slow. In this case we may adopt an adiabatic approximation to study the response of the system on a growing parasite. In the adiabatic approximation the system depends only parametrically on the (fixed) parasite concentration ($p = p_{\text{fixed}}$) and the ordinary differential equations reads

$$\begin{aligned} \dot{u} &= -uv^2 - \beta uv + F(1-u), \\ \dot{v} &= uv^2 - (F+k)v \end{aligned} \tag{8}$$

with $\beta = p_{\text{fixed}}\,\alpha$. The nontrivial fixed points (6) change to

$$u^* = \frac{1}{2} - \frac{\beta(F+k)}{2F} \pm \sqrt{\left(\frac{1}{2} - \frac{\beta(F+k)}{2F}\right)^2 - \frac{(F+k)^2}{F}}, \tag{9}$$

$$v^* = \frac{F+k}{u^*}.$$

Two real solutions exist for

$$\left(\frac{1}{2} - \frac{\beta(F+k)}{2F}\right)^2 - \frac{(F+k)^2}{F} \geq 0, \tag{10}$$

leading to the condition

$$k \leq k_{\text{critical}} = \frac{F}{2\sqrt{F} + \beta} - F. \tag{11}$$

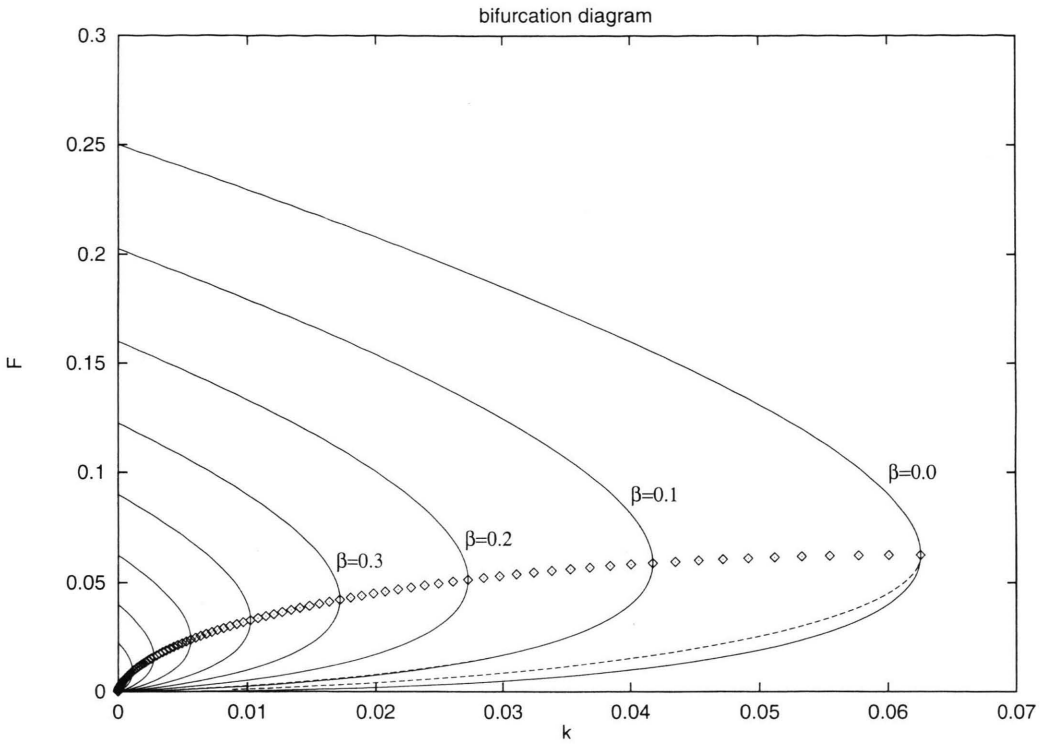

Fig. 1. The region of nontrivial fixed points in the F-k plane for fixed parasite concentration. The regions are shown for various parasite concentrations. For each fixed parasite concentration two nontrivial fixed points exist in the domains bounded by the solid lines. The case $\beta = 0$ corresponds to zero parasite concentration; higher values of β correspond to higher parasite concentration. The domain shrinks with increasing β ($\Delta\beta = 0.1$). The diamonds show the fixed points with maximum k; from right to left with increasing β ($\Delta\beta = 0.01$).

The region $\Omega = \{(k, F) | 0 \geq k \geq \frac{F}{2\sqrt{F}+\beta} - F\}$ in the k, F plane depends parametrically on the (scaled) parasite concentration β, see Fig. 1 for a plot of this regions for various values of β. The diamonds in the plot show the point of the domains $\Omega(\beta)$ with maximal k-value. This point (k_m, F_m) depend (as Ω) parametrically on β:

$$\begin{aligned} k_m &= \frac{F_m}{2\sqrt{F_m}+\beta} - F_m, \\ F_m &= \frac{1}{32}[1 + (1 - 4\beta)\sqrt{1 + 8\beta} + 8\beta^2]. \end{aligned} \tag{12}$$

A linear stability analysis yields the local stability of the fixed points (9). Whereas one fixed point is unstable in the whole region Ω, the other is stable in a subset of Ω bounded by the Hopf bifurcation shown for $\beta = 0$ as a dotted line in Figure 1. For $\beta = 0$, Pearson has shown that spatially inhomogeneous solutions can prevend the collapse of the homogeneous solution near the Hopf bifurcation. Such irregular spatiotemporal patterns, like self-replicating spots, would present preferable conditions for the evolutionary stability of cooperative systems against parasites [5, 12, 14]. Unfortunately these patterns occur only for special choices of the parameters F and k. We now want to study if the scaled parasite concentration β is a Steuerparameter to choose a certain spatiotemporal pattern. In these cases the parasite concentration would increase until a pattern is selected which itself would stop a further growth of the parasites and thus stabilize the system. Such a selforganisized pattern selection and parameter tuning could be an inherent property of evolving systems. The role of the (scaled) parasite concentration as a parameter of the model can be seen by the following simple consideration. Let $(k_0, F_0) \in \Omega_{(\beta=0)}$ be the fixed parameters of the Gray–Scott system without parasites ($\beta = 0$). The plot in Fig. 1 shows that the domain $\Omega_{(\beta)}$ shrinks with increasing β, and for each point $(k_0, F_0) \neq (0, 0)$ we can

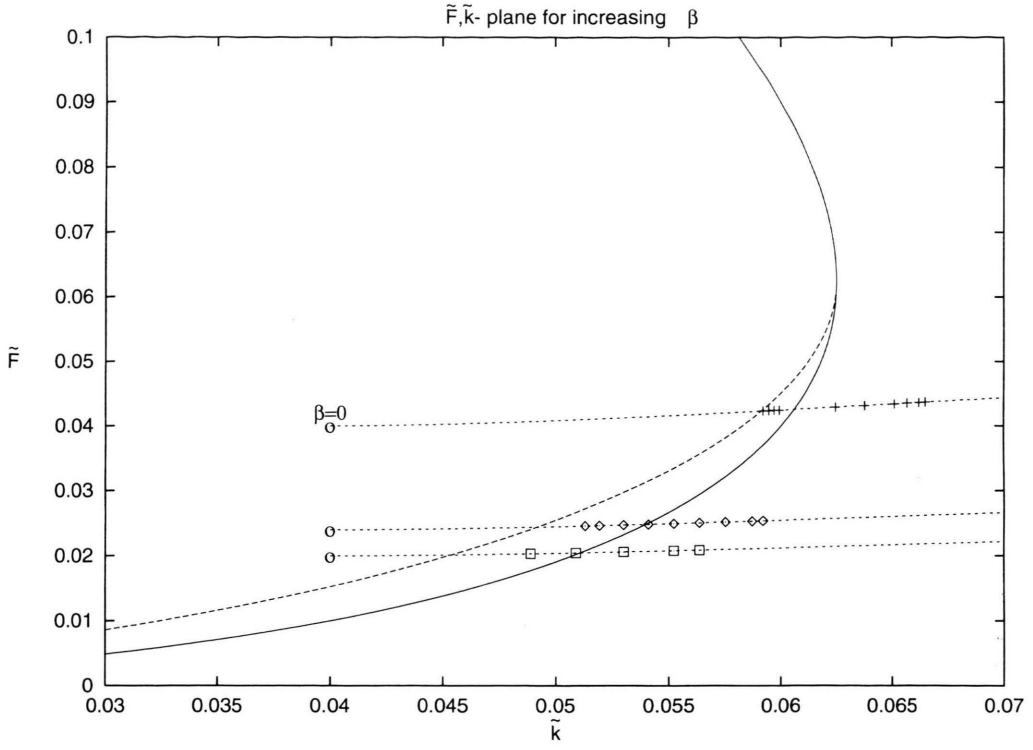

Fig. 2. The postition of the three sets of parameters a) $F = 0.04$, $k = 0.04$; b) $F = 0.024$, $k = 0.04$; c) $F = 0.02$, $k = 0.04$ in the $\tilde{F}, \tilde{k}$ plane for increasing β. The saddle-node bifurcation (solid line) and the Hopf bifurcation (broken line) are plotted for $\beta = 0$. For $\beta = 0$ we have $\tilde{F} = F$ and $\tilde{k} = k$. Increasing β; the position of three parameter sets in the $\tilde{F}, \tilde{k}$ plane go to higher $\tilde{k}$ values, (indicated by dotted lines). The positions for wich pattern formation was found are indicated for $F = 0.04$, $k = 0.04$ by crosses, for $F = 0.024$, $k = 0.04$ by diamonds and for $F = 0.02$, $k = 0.04$ by squares. Some of the patterns are shown in Figures 3 a - c.

find a parameter $\beta_0 > 0$ at which the envelop of $\Omega_{(\beta)}$ crosses the point (k_0, F_0). For all $\beta > \beta_0$ the points (k_0, F_0) lie outside the domain $\Omega_{(\beta)}$. Alternatively one may describe the (major) effect of an increasing β by a linear transformation

$$(k, F) \longmapsto (\tilde{k}, \tilde{F}) \tag{13}$$

with

$$\tilde{k} := \frac{k_m(0)}{k_m(\beta)} k \tag{14}$$

and

$$\tilde{F} := \frac{F_m(0)}{F_m(\beta)} F. \tag{15}$$

In this way the position of maximal $\tilde{k}$ remains unchanged for each $\beta > 0$. Each other point in the F,k plane is shifted to a position which corresponds to its relative position to $(\tilde{k}_m, \tilde{F}_m)$. The set of points

$$I_{k,F}(\beta) = \{(\tilde{k}(\beta), \tilde{F}(\beta)) \mid \beta \geq 0\} \tag{16}$$

describes for each point (F,k) a line in the $\tilde{F}, \tilde{k}$ plane. Examples of such lines are plotted in Fig. 2 together with the lines of the saddle point and the Hopf bifurcation. Pattern formation is likely to occure for each $(F, k) \in \Omega(\beta = 0)$ if the corresponding line (16) crosses the Hopf bifurcation in the $\tilde{F}, \tilde{k}$ plane. This applies to a rather large subset of $\Omega_{(\beta=0)}$. To test this numerically we applied a finite-difference discretization to the diffusion operator and a forward Euler integration to the reaction-diffusion equation

$$\begin{aligned} \dot{u} &= -uv^2 - \beta uv + F(1-u) + D_u \bigtriangledown^2 u, \\ \dot{v} &= uv^2 - (F+k)v + D_v \bigtriangledown^2 v \end{aligned} \tag{17}$$

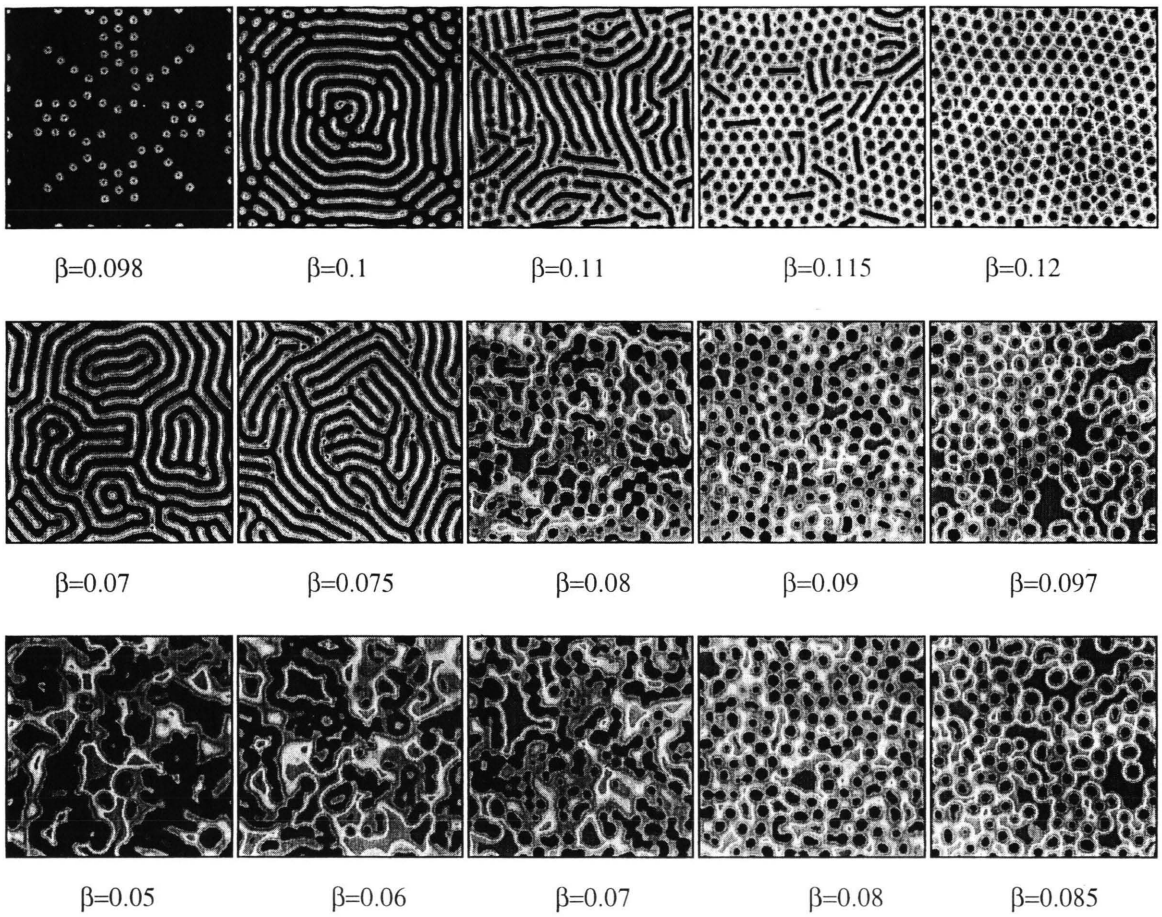

Fig. 3. Numerical simulation in two space dimensions. The simulations are forward Euler integrations of the finite-difference equations resulting from discretization of the diffusion operator. Images are taken after 200,000 time steps. Time step is $dt = 1.0$ and the grid size is 256×256. Diffusion coefficients are $D_u = 2 \times 10^{-5}$ and $D_v = 10^{-5}$. The concentration of the variable U is plotted as a two dimensional image. Lower density means higher concentration of U.
a) The parameters are $F = 0.04$ and $k = 0.04$. The images are calculated with increasing values of β. With $\beta < 0.097$ the calculations result in a nontrivial homogeneous state. $\beta > 0125$ gives the trivial homogeneous steady state.
b) The parameters are $F = 0.024$ and $k = 0.04$. The images are calculated with increasing values of β. With $\beta < 0.06$, the calculations result in a nontrivial homogeneous state. $\beta > 097$ gives the trivial homogeneous steady state.
c) The parameters are $F = 0.02$ and $k = 0.04$. The images are calculated with increasing values of β. With $\beta < 0.05$ the calculations result in a nontrivial homogeneous state. $\beta > 085$ gives the trivial homogeneous steady state.

with periodic boundary conditions. A spatial mesh with 256 × 256 grid points and time steps of one (in dimensionless units) turned out to be sufficiently fine not to influence the results presented here, the distance between two grid points being set to one (in dimensionless units).

Initially, the entire system was placed in the trivial steady state ($u = 1.0$, $v = 0.0$). A 25 × 25 grid points square in the middle of the array is used to start an initial perturbation with $u = 0.5$, $v = 0.25$, and then these initial conditions were perturbed with $\pm 1\%$ random noise.

Simulations were performed for three different values in the F, k plane: ($F = 0.04, k = 0.04$), ($F = 0.024, k = 0.04$) and ($F = 0.02, k = 0.04$). For $\beta = 0$, each of these parameter sets leads to a homogeneous nontrivial steady state solution of the reaction-diffusion equation (17). As the scaled parasite concentration β increased, the transformated values of the parameters in the $\tilde{F}, \tilde{k}$ plane tend to-

ward the line of bifurcation and reach parameter regions where pattern formation can be expected, see Fig. 3. Images are all taken after 200,000 time steps. For ($F = 0.04, k = 0.04$) the solution remains homogeneous for $\beta < 0.097$. For $\beta = 0.098$ a nontrivial pattern of spots emerges which is time stable over the observed time scale. This evolves to a stripe pattern for $\beta \approx 0.1$ and hexagons for $\beta = 0.12$. $\beta > 0.25$ gives the trivial homogeneous solution. For ($F = 0.024, k = 0.04$) and $\beta < 0.06$ the calculations leed to the nontrivial homgeneous solution. For $\beta = 0.065$ and $\beta = 0.07$ stripe like pattern occur with some spots emerging. For a $\beta > 0.075$ and $\beta < 0.097$ we obtained time-dependent spot patterns also with dividing spots. $\beta > 0.097$ pushes the system to the trivial steady state. For ($F = 0.02, k = 0.04$) the system remains homogeneous for $\beta < 0.05$. Further increasing β gives phase turbulence ($\beta = 0.05$), patterns with incomplete spirals and rings ($\beta = 0.06$ and $\beta = 0.07$) and also self-replicating spot patterns ($\beta = 0.08$ and $\beta = 0.085$). $\beta > 0.085$ gives the trivial homogeneous solution.

3. Conclusion

The preferable solution of the parasitic problem of evolving cooperative systems is to consider the role of space. To inhibit a parasitic exploitation and the death of the cooperative systems a spatial pattern formation is required. Regions of high concentration have to be separated by space regions where the growth of parasites is not possible. Several numerical simulations based on spirals or self-replicating spot pattern have shown the applicability of this conceptual idea [5, 12 - 14]. Experimentally this problem is tackled by constructing simple cooperative ecosystems based on replicating DNA strands [18, 21] and by studying these systems in spatially resolved and microstructured flow reactors [22]. Theoretically this system has the ability to form spatial patterns [23, 24]. Similar to the Gray-Scott model, however, the pattern formation behaviour is restricted to a narrow region in the parameter space. To find this parameter region and to keep the system in this region represents an experimental task for an evolving microstructured biochemical flow reactor.

The statement of this work is that the experimentialists do not need to search for the parameter region of pattern formation. Instead it is sufficient to place the system in a parameter region where homogeneous growth is guaranteed. This, of course, is much easier. A growing concentration of parasites will not kill the system but induce a pattern formation which stops a further growth of the parasite concentration. The stabilisation against parasitic invasion will take place by a self-organized selection of a stabilizing pattern. Curiously the parasite concentration is itself the parameter which is responsible for the selection of the pattern and stops a further growth of the parasites. A further growth of the system would kill the whole system (and the parasites).

We used the simple Gray-Scott model to demonstrate the above idea. In view of the experimental systems mentioned above or the prebiotic evolution of cooperation the model is, of course, very simplified. The justification to study this simple system is the demonstration of an inherent property of evolving cooperative systems. Even on the model platform of the Gray-Scott system we neglected importand effects like pattern formation in the parasite concentration itself, the limitation of the mass action kinetics for small concentrations or the diversity of individual molecules in a population of the evolving and replicating molecules. Stochastic models including these effects should show a more complex behaviour but the same inherent property of a self-organized pattern selection and stabilization gainst parastic exploitation as described above.

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