Manipulation of Self-Aggregation Patterns and Waves in a Reaction-Diffusion System by Optimal Boundary Control Strategies

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Reaction-diffusion systems are of considerable importance in many areas of physical sciences. For many reasons, an external manipulation of the dynamics of these processes is desirable. Here we show numerically how spatiotemporal behavior like pattern formation and wave propagation in a two component nonlinear reaction-diffusion model of bacterial chemotaxis can be externally controlled. We formulate the control goal as an objective functional and apply numerical optimization for the solution of the resulting control problem.

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Nonequilibrium processes in open physicochemical systems are the basis for many aspects of the high degree of structure and organization that is observed throughout nature [1]. Nonlinear chemical and biochemical reaction processes far from equilibrium coupled with diffusion underlie most mechanisms for spatiotemporal pattern formation and self-organization [2,3].

As experimental techniques become more and more accurate and provide detailed quantitative data for modeling complex dynamical systems, especially from the applicational point of view there is increasing interest in controlling these systems. External control in this context means to influence the system by interference from its surroundings in order to achieve specific desired behavior. Control of self-organization in spatially distributed and highly nonlinear dynamical systems is an ambitious goal, and modeling is inevitably required in that context because there is no intuitive way of specific control.

Heterogeneous catalysis is an example of a complex process which is central for many technical processes for production of chemicals, and aspects of production efficiency and selectivity are important issues. Experimental observations using modern surface spectroscopy have shown that pattern formation dynamics are involved here which influence the whole process considerably [4]. Recently, Ertl and co-workers showed numerically and experimentally that turbulent surface patterns in CO oxidation on platinum can be controlled using global delayed feedback [5]. Chaos control ideas [6] have been used to design wave propagation patterns in excitable media [7], propagating wave segments could be stabilized [8], and oscillatory cluster patterns were induced in the photosensitive Belousov-Zhabotinsky reaction [9]. These studies are based on the introduction of a feedback function for either local gradient control [7] or global control [5,8,9] fed back into the system. Specific targeting of spatiotemporal patterns has been investigated in [10,11]. Here, one point observation and related feedback control was shown to drive a spatially extended system to particular structures. In [12], control of spiral wave movement in excitable media and its suppression have been studied numerically by introducing spatial inhomogeneities into the medium, and turbulence control and synchronization based on the Ginzburg-Landau equation model have been investigated in [13]. Pertsov *et al.* [14] analyze spiral wave control in cardiac tissue by small parameter gradients. Also, in nonlinear optics feedback control of pattern formation has been discussed [15]. None of these studies allow for a systematic way of influencing the systems with respect to general control aims.

Here we show numerically for a two component reaction-diffusion model describing bacterial chemotaxis that it is possible to systematically control spatiotemporal dynamical behavior. Our strategy does not interfere with the system itself but operates as a boundary flux control connecting the system and its surroundings. The control aim is incorporated into an objective functional to be minimized as a function of the control variables. The objective represents in a mathematically suitable formulation the deviation of the desired behavior from the real controlled system dynamics.

The model equations are based on continuity equations for both components and represent a system of parabolic partial differential equations of reaction-diffusion type. The 1D model equations, which have been proposed by Tyson *et al.* [16,17], are

$$\frac{\partial z}{\partial t} = D\frac{\partial^2 z}{\partial x^2} - \alpha\frac{\partial}{\partial x}\left(\frac{z}{(1+c)^2}\frac{\partial c}{\partial x}\right),$$
$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} + \frac{z^2}{1+z^2}. \qquad (1)$$

The variable $z(x, t)$ describes the cell density of *E. coli* bacteria in a liquid medium cell culture; $c(x, t)$ describes the concentration of a chemical species called chemoattractant. The closed long thin (quasi-1D, $x \in [0, L]$) tube containing the medium is modeled by assuming no flux von Neumann boundary conditions $z_x(0, t) = z_x(L, t) = c_x(0, t) = c_x(L, t)$. Bacteria move in liquid

medium without chemoattractant stochastically with alternating periods of flagella driven movement along straight lines and periods of chaotic tumbling without moving forward [18]. This corresponds to a random walk and can be modeled by Ficks diffusion law in the many particle limit [19]. The second term in the first model equation describes the influence of chemoattractant, which is produced by the cells themselves, on the movement of bacteria. Experimental observations confirm that they move in an uphill direction of the chemoattractant gradient.

Coupling of the nonlinear production kinetics, the chemoattractant induced uphill movement of cells, and the diffusion of both cells and chemoattractant in the model (1) leads to complex spatiotemporal dynamics. In experiments, patterns such as island formation and wave propagation have been observed both in a quasi-1D glass capillary system [20] and in the quasi-2D cell chamber [21,22].

We reproduce the 1D patterns in numerical simulations and get very similar results to those described in [16,17], but we use completely different numerical methods which are suited to treat the differential equations as constraints in an algorithm for optimal control problems. Figures 1 and 2 show the results for two pattern scenarios depending on initial conditions for the system (1); the first is island formation (bacterial clumps) induced by a random perturbation of homogeneous cell density, and the second is wave propagation due to a singular perturbation of uniform cell density.

In order to control the spatiotemporal behavior of the cell density, we introduced a nonzero chemoattractant flux at the right-hand side boundary $x = L$ of the 1D system which could be realized experimentally by imposing a semipermeable membrane with small pore size. The boundary flux of chemoattractant is controlled by adjusting the concentration of the chemoattractant in an external reservoir. This external concentration is represented by a control function $u_0(t)$ assumed to be piecewise constant on small time intervals. The boundary flux $c_x(L, t)$ of chemoattractant is modeled by $c_x(L, t) = c(L, t) - u_0(t)$. On the basis of this control scenario, we show that the system can be forced to specific spatial cell distributions.

The problem is solved by numerical solution of the optimal control problem of minimizing the root mean square deviation of a predetermined fixed cell distribution $z_T(x)$ at time T from the real cell distribution $z(x, T)$ arising from the controlled system dynamics. The deviation can be formulated in terms of L^2 norm and the resulting optimal control problem has the form

$$\min F(u) := \tfrac{1}{2}\|z(x, T) - z_T(x)\|^2_{L^2([0,L])} + \lambda T,$$

subject to

$$\frac{\partial z}{\partial t} = D\frac{\partial^2 z}{\partial x^2} - \alpha\frac{\partial}{\partial x}\left(\frac{z}{(1+c)^2}\frac{\partial c}{\partial x}\right), \quad \frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} + \frac{z^2}{1+z^2}, \quad \frac{\partial z(0,t)}{\partial x} = \frac{\partial z(L,t)}{\partial x} = \frac{\partial c(0,t)}{\partial x} = 0, \quad \frac{\partial c(L,t)}{\partial x} = u_0(t) - c(L,t),$$
$$z(x,0) = z_0(x), \quad c(x,0) = c_0(x), \quad 0 \le u_0(t) \le 1, \quad 0 \le x \le L, \quad 0 \le t \le T \in [0, T_{\max}]. \tag{2}$$

Optionally, the optimal control problem can have free end time T, which in that case can be subject to optimization as well. This means that, with respect to a weighting factor λ, also time optimal controls can be computed. The control function is assumed to be bounded to values in [0,1]. The lower bound is due to the physical meaning of $u_0(t)$ representing a concentration of chemoattractant.

After semidiscretization with respect to the spatial variable x using second-order accurate finite difference approximation of the right-hand sides in equation system (1), we obtain a high dimensional system of ordinary differential equations. The L^2-norm integral in the objective functional is discretized using trapezoidal rule, and the resulting high dimensional optimal control problem is solved with the advanced numerical methods implemented in the optimal control package MUSCOD-II [23]. The MUSCOD-II algorithm is based on a multiple shooting

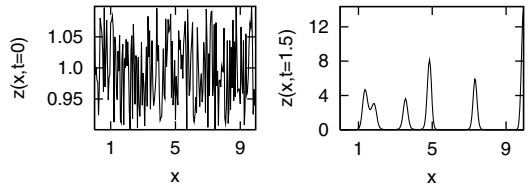

FIG. 1. Simulation of island patterns in 1D chemotaxis system (1), starting from a perturbed initial steady state $z(x, 0) = z_0(x) = 1.0 \pm 0.1 \times \text{rand}$, $c(x, 0) = c_0(x) \equiv 0$ with computer generated random number $\text{rand} \in (0, 1)$, $L = 10$, $D = 0.33$, $\alpha = 80$, and von Neumann boundary conditions $z_x(0, t) = z_x(L, t) = c_x(0, t) = c_x(L, t) = 0$.

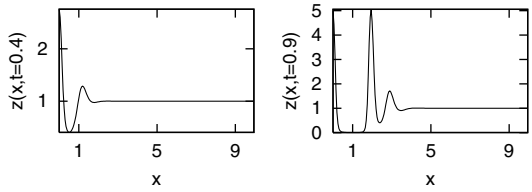

FIG. 2. Simulation of wave propagation in 1D chemotaxis system (1), starting from a singular perturbation $z(0, 0) = z_0(0) = 1.2$, $z(x, 0) = z_0(x) = 1.0$ for $x \neq 0$, $c(x, 0) = c_0(x) \equiv 0$ of the initial steady state $z(x, 0) = z_0(x) \equiv 1.0$, $c(x, 0) \equiv 0$, $L = 10$, $D = 0.33$, $\alpha = 80$, and von Neumann boundary conditions $z_x(0, t) = z_x(L, t) = c_x(0, t) = c_x(L, t) = 0$.

approach [23,24], where time discretization is carried out implicitly on a rather coarse grid by specifying some multiple shooting points. On each multiple shooting interval, the large scale ordinary differential equation (ODE) system is integrated separately and control functions are parametrized (for example, by piecewise constant representation). The resulting nonlinear programming problem is solved by a specially tailored sequential quadratic programming algorithm [23].

Figure 3 shows the numerical results for two different control scenarios where specific cell distributions at a fixed time T could be achieved by optimal boundary control with piecewise constant control functions on multiple shooting intervals $[(n-1)T/20, (nT)/20]$, $n = 1, \ldots, 20$. Obviously, it is possible to force the system to even symmetric cell distributions by applying nonsymmetric control and without interfering the system itself, but only controlling a flux through the systems boundary. Consequently, the intrinsic dynamical behavior of the system seems to play a crucial role for its controllability. Therefore, in general, unstable nonlinear dynamical systems may offer a great potential for external control because of the immense spatiotemporal effects that can be produced by selective perturbations induced from outside into the system.

From an applicational point of view, dynamical effects such as pattern formation and exponentially growing modes due to system instabilities are often undesired. Figure 4 shows how pattern formation and wave propagation in the chemotaxis system can be inhibited by a boundary control. Here the objective functional of the corresponding optimal control problem (2) is the deviation from the (unstable) homogeneous cell distribution. The induced perturbations for initial conditions are the same as those shown in Figs. 1 and 2 for the simulation results. In order to take the issue into account that inhibition of wave propagation might be desired to be achieved as fast as possible, we set up a time optimal control scenario of type (2) with a small factor λ. This factor accounts for the relative weight of time optimality compared to a specific control aim. Of course, the latter is assumed to be predominant here. As can be concluded from Fig. 4, the pattern formation can be inhibited and the wave propagation can be reduced very efficiently in optimal time.

The control functions for all scenarios described above are nontrivial, and an interesting result is that the optimal controls for the parabolic cell distribution (Fig. 3, bottom) and the inhibition of pattern formation (Fig. 4, top) are very similar. Obviously, here the same control strategy is

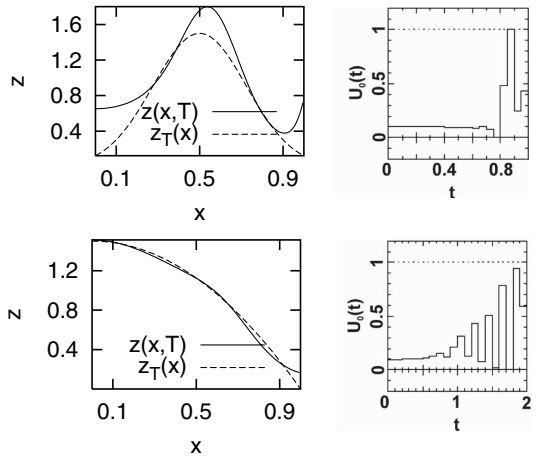

FIG. 3. Enforcement of specific cell distributions according to (2), starting from a randomly perturbed steady state as in Fig. 1, $L = 1$, T fixed, $D = 0.33$, $\alpha = 80$, von Neumann boundary conditions $z_x(0, t) = z_x(L, t) = c_x(0, t) = 0$. A linear model $c_x(L, t) = c(L, t) - u_0(t)$ is used for the boundary flux control at $x = L$, $u_0(t)$ is the controlled external chemoattractant concentration. Left: Real distribution $z(x, T)$ at fixed time $T = 1$ (top) and $T = 2$ (bottom) arising from controlled system dynamics and desired cell distributions $z_T(x) = 1.5 \times \exp[-10(x - 0.5)^2]$ (top) and $z_T(x) = 1.5(1 - x^2)$ (bottom). Right: Corresponding optimal control functions $u_0(t)$ according to problem (2) with $\lambda = 0$ computed with the optimal control package MUSCOD-II.

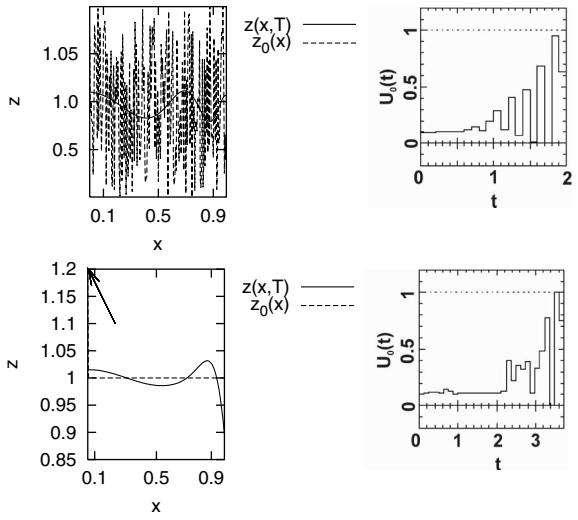

FIG. 4. Top: Inhibition of pattern formation according to (2), starting from a randomly perturbed steady state as in Fig. 1, $L = 1$, $T = 2$ fixed, $D = 0.33$, $\alpha = 80$, $\lambda = 0$, von Neumann boundary conditions $z_x(0, t) = z_x(L, t) = c_x(0, t) = 0$. A linear model $c_x(L, t) = c(L, t) - u_0(t)$ is used for the boundary flux control at $x = L$, $u_0(t)$ is the controlled external chemoattractant concentration. Bottom: Inhibition of wave propagation, starting from a singularly perturbed initial steady state (arrow indicates the perturbation at $x = 0$) as in Fig. 2, $L = 1$, T free and subject to minimization. Left: Real distributions $z(x, T)$ at fixed time $T = 2$ (top) and optimal time $T = 3.7$ (bottom) arising from controlled system dynamics and desired homogeneous cell distributions $z_T(x) \equiv 1.0$. Right: Corresponding optimal control functions $u_0(t)$ according to control problem (2) with $\lambda = 0$ (top) and $\lambda = 0.001$ (bottom) computed with the optimal control package MUSCOD-II.

used which resembles to some extent a periodic regular oscillation of the boundary flux with increasing amplitude. There is only a very small quantitative difference between the optimal control functions for both scenarios.

We have shown here that it is possible to externally control spatially distributed nonlinear dynamical systems with respect to specific control aims concerning spatiotemporal behavior of these systems. The key idea was to formulate the control aim as an optimization problem and to minimize the deviation from specific desired dynamical behavior. In order to realize such control scenarios, it is inevitable to model the systems under consideration and make use of further mathematical ideas from optimal control theory. The advanced optimal control tool MUSCOD-II allows numerical computation of optimal controls for systems of nonlinear parabolic partial differential equations describing spatiotemporal dynamics. In general, the software MUSCOD-II is suitable for solving optimal control problems for very large ODE systems, differential-algebraic equations, and after spatial discretization also parabolic partial differential equations. In principle, our boundary control scenario used for the chemotaxis model can be applied for arbitrary chemical reaction-diffusion systems if the influx of at least one component can be externally adjusted and an accurate model is available.

Specific control is believed to have great influence on technical processes and, in particular, biological systems. In biology, self-organizing systems play a dominant role as the fundamental physical basis for the phenomenon "life" [25]. Any form of functionality in living cells is strictly related to spatiotemporal biological structure and dynamics of biochemical systems far from equilibrium. Because of elaborate experimental techniques from molecular and cell biology, many biosystems become accessible to modeling [26,27], and detailed understanding of cellular processes and finally their external control may play a crucial role in future medicine and drug development [28].

There is ongoing research to extend the basic control ideas described here to 2D systems and to make use of optimization based nonlinear model predictive control (NMPC) strategies [29,30] in order to control also transient dynamics of spatially distributed systems on moving time horizons. Thus far, we referred only to a fixed time horizon; NMPC would allow specific trajectory tracking.

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