Dynamical systems of population dynamics

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Abstract. After a short review of the the role of population dynamics in the formation of the theory of dynamical systems some recent developments are described, centered around work within the DANSE project: Reaction transport equations which are refinements of reaction diffusion equations, showing travelling front solutions and pattern formation, with applications to chemotaxis and the formation of polarized groups of animals or cells. Populations structured by age are modeled by conservation laws and by delay equations, the thorough investigation of the close connection between these two classes of systems leads to a solid justification of the latter as population models. Particular attention is given to models for the spread of infectious diseases: Models describing outbreaks in closed populations, optimal vaccination and control policies, the conditions for backward bifurcations and (unwanted) hysteresis phenomena in public health. Epidemic spread in space (travelling front problems), simplification of complex models to modulation equations. Modeling the behavior of single individuals connects dynamical systems to stochastic processes: Synchronous and asynchronous cellular automata, interacting particle systems, concrete applications are ring vaccination (in animal husbandry) and contact tracing (in human populations).

1 Introduction

Population dynamics, as a part of biology, is concerned with the numbers of plants and animals, with changes in population density resulting from interactions with the environment and between individuals of the same species and between species. These changes are expressed in terms of reproduction, mortality, and migration. Population dynamics is closely connected to ecology, population genetics, human demography, the theory of infectious diseases (epidemiology), parasitology, and other fields like bioeconomics. The goal of population dynamics is to describe these changes, based on field observations and experimental data, and to understand or even predict the evolution of biological systems. In population dynamics the use of mathematical models is essential.

Among all fields of biology, especially population dynamics has provided mathematical research with interesting problems in the form of dynamical systems. These are quite different from those supplied by physics and engineering where concepts like "energy" and "symmetry" play a dominant role whereas "mass action kinetics" is the underlying mechanism of most biological interactions. We recall some dynamical systems approaches to population dynamics. The dynamical systems of population genetics were introduced around 1924/30 (the Fisher-Wright-Haldane model and the "fundamental law of population genetics" [9]), evolutionary game dynamics by Maynard Smith and others 1972 ff. [31], followed by adaptive dynamics in evolutionary landscapes, reaction diffusion equations for the advance of traits and population fronts were invented around 1937 (Fisher and Kolmogorov-Petrovskij-Piscunov), oscillations in interacting populations (Volterra 1926, Kolmogorov 1936), nonlinear delay equations (Hutchinson's model 1948), hyperbolic systems and renewal equations for structured populations (Sharpe-Lotka 1911, Feller 1941, McKendrick 1936); cooperative and competitive systems emerged in mathematics (M.Müller 1926, Kamke 1932), gained recognition in population biology and were systematically explored by M.Hirsch and others 1982 ff.). Modelling infectious diseases started before 1900, the first dynamical system appeared around 1927 (Kermack and McKendrick [33]). Population dynamics modeling by deterministic dynamical systems has been paralleled by stochastic approaches, e.g. in the form of birth and death processes, branching processes, stochastic epidemic models. An intermediate class of models are (deterministic and stochastic) cellular automata models and interacting particle systems [7] [5].

In the following we shall describe recent developments in the field with some bias towards problems that have been studied within the DANSE project. We hope that we nevertheless put the results in right proportions.

All topics that we have just mentioned play a major role in present day research. Here we shall report on research on spatial spread, in particular on detailed description of individual motion by reaction transport equations, on the mathematical description of aggregations of microorganisms (chemotaxis) and of schools, flocks, and herds of animals. We show how structured population models in the form of hyperbolic partial differential equations can be reduced to differential delay equations. A major topic is the study of dynamical systems modelling infectious diseases, the spread of diseases in populations and in geographical regions, vaccination and public health policies, and containment strategies based on studying individual contact patterns. Finally we report on totally discrete dynamical systems such as cellular automata, edge processes and interacting particle systems. We mention in passing results that the Tübingen DANSE group has obtained results on dynamical systems not related to population dynamics, e.g. [13] [23].

2 Spread in space and reactions

2.1 Reaction transport equations

The classical model for reaction and spatial spread is the reaction diffusion equation

$$u_t = D\Delta u + f(u). \tag{1}$$

Here $u(t,x)$ is the density of the population at the point x at time t. The ordinary differential equation $\dot{u} = f(u)$ describes the underlying reaction, and spatial spread is modeled by the diffusion equation $u_t = D\Delta u$. Reaction diffusion equations are one of the most widely used classes of dynamical systems in biology. Vector-valued reaction diffusion equations govern interactions of ecological or chemical species, propagation of nerve excitation, epidemic spread, etc. [51] [58] [49]. However, in the diffusion equation all characteristic features of moving particles are lumped into a single parameter, the diffusion coefficient D. Furthermore, the diffusion equation (and Brownian motion) show the unrealistic effect of infinitely fast transport, and the reaction diffusion equation shows the same effect. A more detailed description, where individual particles are characterized by their position in space and their individual velocity, leads to reaction transport equations. Let $u(t,x,s)$ be the density of particles at position $x \in \mathbb{R}^n$ and time t, with velocity $s \in V \subset \mathbb{R}^n$. Here V is some bounded domain, typically a ball or a sphere (in the case of constant speed). Then the linear transport equation reads

$$u_t + s \cdot \nabla_x u + \mu u = \mu \int_V K(s,\tilde{s}) u(t,x,\tilde{s}) d\tilde{s}. \tag{2}$$

Here μ is the rate at which turning events occur (changes of velocity) and $K(s,\tilde{s}) \geq 0$, with $\int_V K(s,\tilde{s}) ds = 1$, is the probability distribution for the new velocity. For $\mu = 0$ equation (2) is mere book-keeping: Each particle moves on a straight line with its own velocity. For $\mu > 0$ particles move on straight lines, stop, and choose a new direction. There are various ways in which birth and death processes can be incorporated into this system. We split the nonlinearity in the equation $\dot{u} = f(u)$ into a birth term $m(u)u$ and a death term $g(u)u$ [15] [16] [17]. Then $f(u) = m(u)u - g(u)u$. With this splitting the corresponding reaction transport equation reads

$$u_t + s \cdot \nabla_x u + \mu u = \mu \int_V K(s,\tilde{s}) u(t,x,\tilde{s}) d\tilde{s} + \frac{1}{|V|} m(\bar{u})\bar{u} - g(\bar{u}) u \tag{3}$$

where

$$\bar{u}(t,x) = \int_V u(t,x,s) ds \tag{4}$$

is the population density at position x at time t and $|V|$ is the volume of V.

We consider equation (3) as the standard system for reaction and transport. The simplified system where birth and death are incorporated in one function $f(\bar{u})$ we call the “isotropic” system,

$$u_t + s \cdot \nabla_x u + \mu u = \mu \int_V K(s,\tilde{s}) u(t,x,\tilde{s}) d\tilde{s} + \frac{1}{|V|} f(\bar{u}). \tag{5}$$

A linear hyperbolic system has been introduced by Cattaneo 1948 as another system which lacks the deficiencies of the heat equation. Nonlinear Cattaneo systems can be seen as intermediates between reaction diffusion systems and “full” reaction transport equations. A nonlinear Cattaneo system has the form of a conservation law with source terms together with an equation coupling the flow to the gradient

$$\begin{aligned} u_t + \operatorname{div} v &= f(u) \\ \tau v_t + D \operatorname{grad} v + h(u)v &= 0. \end{aligned} \tag{6}$$

In the limiting case $\tau = 0$ we can solve for v in the second equation and replace v in the first equation to obtain a diffusion equation.

If the space dimension is $n = 1$ and there are only two velocities $s = \pm\gamma$ then we can write $u^{\pm}(t,x)$ instead of $u(t,x,\pm\gamma)$,

$$\begin{aligned} u_t^+ + \gamma u_x^+ &= \tfrac{1}{2}\mu(u^- - u^+) + m(u)u - g(u)u^+ \\ u_t^- - \gamma u_x^- &= \tfrac{1}{2}\mu(u^+ - u^-) + m(u)u - g(u)u^-. \end{aligned} \tag{7}$$

Equation (7), for $m = g = 0$, describes a correlated random walk. We introduce the total particle density $u = u^+ + u^-$ and the flow $v = \gamma(u^+ - u^-)$ to obtain a system of the form (6) with $\tau = 1/\mu$ and $D = \gamma^2/\mu$,

$$\begin{aligned} u_t + v_x &= f(u) \\ \tau v_t + D u_x &= -(\mu + g(u))v. \end{aligned} \tag{8}$$

Hence, in the special case of dimension 1 and constant speed, the transport equation, the correlated random walk, and the Cattaneo system are equivalent. There is no such result in dimension $n \geq 2$.

If $h(u) \equiv 1$ then we can eliminate the flow v in system (6) (the "Kac trick") and arrive at a damped wave equation or telegraph equation for the function u

$$\tau u_{tt} + (1 - \tau f'(u))u_t = D\Delta u + f(u). \tag{9}$$

For $\tau = 0$ one gets the diffusion approximation (1). Similar systems can be derived in the case of several dependent variables.

The main results obtained so far concern convergence to equilibrium (in bounded domains) [28] [55] [57], existence and stability of travelling fronts [17] [56], and Turing patterns (see below). Furthermore, approximation and scaling properties have been investigated. If time and space or, equivalently, turning rate and velocity, are appropriately scaled, then the random walk equation approximates a parabolic equation. Approximation properties have been shown for single trajectories as well as for the attractor [46] [55] [30].

2.2 Travelling front and waves, emerging patterns

Reaction diffusion equations, reaction transport equations and related integral equation models show typical bifurcation phenomena and asymptotic behavior. One of the basic phenomena is the travelling front which has been discovered as a model for a genetic trait advancing in a population by Fisher

1936. Some authors suggest that most phenomena in reaction diffusion systems can be explained in terms of interacting travelling fronts [10]. Consider a scalar reaction diffusion equation (1) in the plane with $f(u) = u(1-u)$ (often called the "Fisher equation") in the plane, with an initial datum that is positive on some compact domain and zero outside. Near the boundary of the support matter will spread outward and then increase due to the reaction term. Hence the solution will converge to 1 uniformly on compact sets. But globally the solution behaves like a circular wave. There is a critical number c_0 such that, for any unit vector e and $t \to \infty$, $u(t, x + cet) \to 0$ for $c > c_0$ and $u(t, x + cet) \to 1$ for $c < c_0$. Asymptotically the solution behaves, in a given direction, like a planar front, i.e., like a solution $u(t, x) = u(x - c_0 t)$ to $u_t = Du_{xx} + u(1-u)$ with $u(t, -\infty) = 1$, $u(t, +\infty) = 0$. Travelling front solutions have been found in many population dynamic problems. Scalar fronts describe the propagation of a single species, vector-valued fronts may describe, e.g. the joint propagation of a prey and a predator [6] [39]. In the present context the existence of traveling fronts has been shown for the correlated random walk models (7) in [17] and for the general reaction transport equation in [56].

The typical behavior of scalar reaction diffusion equations or transport equations (coefficients and source term not depending on space or time, no drift terms) in bounded domains is convergence to equilibrium. Vector-valued problems show much richer behavior. The classical example is the Turing instability. In Turing's original work the phenomenon is exhibited as a possible mechanism for morphogenesis, and it has been used to explain all kinds of coat patterns in mammals and reptiles, wing patterns in butterflies and patterns on sea shells. While some of these explanations are still lacking sufficient connection to the underlying biochemistry and genetics, it is without doubt that Turing patterns occur in chemical experiments like the Belousov-Zhabotinsky reaction and the oxygen-carbon monoxid reaction on platinum surfaces. It can be assumed that many regular patterns into which plants and animals (e.g. corals) arrange themselves are based on the Turing mechanism.

In the simplest form of the Turing model there is a system of the form (1) with two reactants, the activator u_1 and the inhibitor u_2 which coexist at a stable equilibrium under well-stirred conditions (or, which amounts to the same, in very small domains). In large domains where differential diffusion plays a role, the homogeneous state may lose its stability. Indeed, let $\bar{u}$ be the stationary state, $A = f'(\bar{u}) = (a_{jk})$ the Jacobian (a matrix of order 2), and let $a_{11} > 0$ (activator enhancement), $a_{22} < 0$ (inhibitor decay), $a_{12} < 0$ (inhibitor inhibits activator), $a_{21} > 0$ (activator enhances inhibitor), $\operatorname{tr} A = a_{11} + a_{22} < 0$, $\det A = a_{11}a_{22} - a_{12}a_{21} > 0$ (stability). With these assumptions it is true that for sufficiently distinct diffusion rates $D_2/D_1 >> 1$ and suitably large domains some modes become unstable. For the reaction diffusion case the exact conditions for this instability are well known [49] [15]. In [27] the conditions for the corresponding random walk and Cattaneo problems have been determined.

2.3 Hyperbolic models for chemotaxis

One common feature of all living systems is, that they sense their environment and that they respond to it. Especially moving species (most animals, many microorganisms) have strategies to find food, to avoid harmful substances or enemies, and to find mates. In many cases (bacteria, amoebae, algae, insects, mammals) chemical signals are sent out to attract or repel other individuals, a well-known example is the slime mold *Dictyostelium discoideum.* Insects release pheromones to attract potential sexual partners. The mathematical description of these processes leads to interesting problems, like the interplay of diffusion and drift terms and questions of global existence or finite time blow-up. The classical parabolic model for chemotaxis is the Patlak-Keller-Segel model. We give a brief derivation here.

We assume that in absence of any external signal the spread of the population is governed by the diffusion equation that says that the net flux j is proportional to the negative gradient, $j = -D\nabla u$. It is assumed that an external signal produces a *chemotactic velocity* β resulting in a total flux $j = -D\nabla u + u\beta$ (D has the dimension sec/cm^2). As observed in many experiments, the chemotactic velocity is proportional to the gradient ∇S of some external signal $S(t,x)$, hence $\beta = \chi(S)\nabla S$ with some *chemotactic sensitivity* $\chi(S)$. With this modified flux we arrive at the parabolic chemotaxis equation

$$u_t = \nabla(D\nabla u - \chi(S)\nabla S u). \tag{10}$$

The case $\chi(S) > 0$ is called *positive taxis*, whereas $\chi < 0$ indicates *negative taxis.* Depending on the concrete species the external signal is produced and also perceived by the individuals themselves. We assume that the spatial spread of the external signal is driven by diffusion with constant $B > 0$. Then the full system for u and S reads

$$\begin{aligned} u_t &= \nabla(D\nabla u - \chi(S)\nabla S u) \\ \tau S_t &= B\Delta S + f(S,u), \end{aligned} \tag{11}$$

where $f(S,u)$ describes production and decay of the signal and $\tau \geq 0$ indicates that the spatial spread of the organisms u and of the signal S occur on different time scales. The model (11) has first been derived by Patlak [50] and Keller, Segel [34] hence Patlak-Keller-Segel (PKS) model.

This and related models have been discussed in detail in the mathematical literature (see [30]). Lyapunov functions are known for some examples but also scenarios with blow up in finite time. However, the criticism on parabolic systems mentioned earlier applies to (PKS) as well. In [30] [29] an alternative hyperbolic model has been derived and discussed. It is based on the correlated random walk (7) in one dimension and has the form

$$\begin{aligned} u_t^+ + (\gamma(S)u^+)_x &= -\mu^+(S,S_x)u^+ + \mu^-(S,S_x)u^- \\ u_t^- - (\gamma(S)u^-)_x &= \mu^+(S,S_x)u^+ - \mu^-(S,S_x)u^- \\ \tau S_t &= BS_{xx} + f(S, u^+ + u^-). \end{aligned} \tag{12}$$

The velocity $\gamma(S)$ and the turning rates $\mu^{\pm}(S, S_x)$ depend on S and its gradient. The qualitative behavior of (12) depends crucially on these functions. We have assumed linearity for S, i.e., $f(S,u) = -\beta S + \alpha u$ for some positive constants α, β.

In [30] we considered the case of constant speed γ. Under quite general assumptions we were able to prove local and global existence. It turned out that the control of the $W^{1,\infty}$-norm of the signal S is crucial for global existence. In numerical simulations we also found scenarios which show blow-up (at least numerically), see Fig.1.

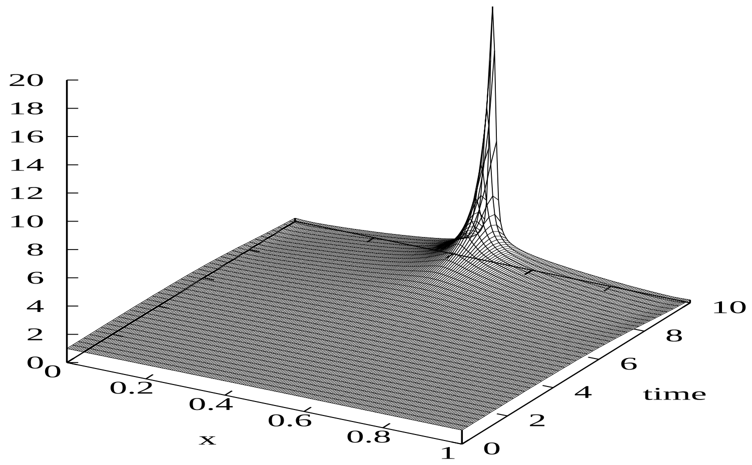

Fig.1: Finite time blow-up for a hyperbolic chemotaxis model

In [29] the effect of non-constant velocity, $\gamma = \gamma(S)$, was investigated. For the limiting case $\tau = 0$ of (12) solutions in L^1_{loc} could be found using a vanishing viscosity method. In numerical simulations aggregation behavior and also formation of steep gradients (shocks) could be observed.

Moreover in [30] the formal relation of the general hyperbolic model (12) to the classical PKS-model has been discussed. This comparison gives an explicit relation of the microscopic parameters like turning rate μ and velocity γ to macroscopic parameters like motility D and chemotactic sensitivity χ. The microscopic parameters can be determined from experiments.

2.4 Alignment

Aggregation is a common phenomenon in many animal species. Group size and structure differ between the species and according to the situation. A striking example of individuals moving in groups are schools of fish or flocks of birds where all individuals move in the same direction. The process by which an individual adapts its direction of motion (body axis) to the one of its neighbor(s) is called alignment. It can also be observed on a microscopic level, e.g. in actin filaments.

Most detailed models for alignment in the form of discrete particle systems have been studied by simulation methods [8] [5]. In analytical models it is usually assumed that particles align but do not move, i.e., that spatial movement is slow compared to the alignment process (an exception is [40]). These models assume the form of partial integro-differential equations [8] [40] [12].

The basic ideas are as follows [12] (see also [32] for a more detailed exposition). Let $v \in V = [0, 2\pi]$ denote the angular direction and $u(t,v)$ the density of particles in direction v at time t. Particles interact with a certain rate $\eta = \eta(v_1, v_2) = \eta(v_1 - v_2)$ (interaction frequency) which depends on the (relative) orientation of the particles. Upon an interaction a particle chooses a new direction according to a function $\omega(v_0 - v_1, v_2 - v_1)$ which describes the probability that a particle in direction v_1 turns into direction v_0 after interacting with another particle with direction v_2. The master equation is a gain-loss equation for the different directions

$$\begin{aligned} \frac{\partial}{\partial t}u(t,v) = &-u(t,v)\int_V \eta(v-v_1)u(t,v_1)dv_1 \\ &+\int_V\int_V \omega(v-v_1, v_2-v_1)\eta(v_2-v_1)u(t,v_2)u(t,v_1)dv_2dv_1 \end{aligned} \tag{13}$$

where η, ω satisfy certain symmetry conditions. The situation where all directions are equally distributed is stationary and its stability depends on the choice of the interaction frequency and the turning probability. A detailed bifurcation analysis of a more general model is carried out in [11]. For special choices of η and ω a linear stability analysis is given in [12]. If turns to the new direction are precise enough and if the angular difference is thereby decreased then the homogeneous situation becomes unstable. Several computer simulations show a rich variety of emerging patterns. The situation of total alignment (i.e., u is a delta distribution in V) is shown to be stable.

Here a simplistic model for alignment and spatial movement has been chosen in the form of a reaction transport equation [36]. The reaction (orientation process) is modeled by comparing the velocity of a particle to the average velocity (at the point considered). We assume constant speed γ. Let $u(t,x,v)$ be the density of particles with $v \in V = \gamma S^1$ (orientation). The full transport equation reads

$$u_t(t,x,v) + v \cdot \nabla_x u(t,x,v) = \rho(\bar{u})[\bar{v} \cdot v - |\bar{v}|^2]u(t,x,v), \tag{14}$$

where $\bar{v}$ is the normalized first moment of u with respect to V, i.e. $\bar{v} = \int_V vudv/(2\pi\gamma)$, ρ is a positive function describing the "force of alignment" depending on the total mass $\bar{u} = \int_V udv$ and $\cdot$ is the scalar product (the turning parameter μ is chosen as zero to ease the presentation). One can generalize the model (13) slightly by allowing the turning probability ω to depend on the density [8]. Then for a special choice of η and ω model (14) is obtained. This derivation allows the following interpretation of the "macroscopic" equation (14) on the individual level: Particles interact most strongly if they meet in opposite directions and hardly ever if they are already aligned. If they turn then they choose the direction in which there are most other particles. This interpretation makes sense biologically and provides a mechanism for avoiding collisions.

In one space dimension with constant speed the model reads in its simplest form

$$\begin{aligned} u_t^+ + \gamma u_x^+ &= \frac{r}{u^3} u^+ u^- (u^+ - u^-) \\ u_t^- - \gamma u_x^- &= \frac{r}{u^3} u^+ u^- (u^- - u^+). \end{aligned} \tag{15}$$

Comparison with (7) (m=g=0) shows that the turning rates μ are now nonlinear and they change sign. For the general model in several space dimensions global existence of solutions has been shown and the limit sets have been characterized in one space dimension. The process of alignment can be studied in connection with simple birth and death processes. There are indeed situations where an aligning population survives and its non-aligning counterpart goes extinct [36].

3 Age structure and delays

The classical model for a population structured by age has been formulated by A.G. McKendrick in the form of a hyperbolic partial differential equation describing aging and mortality and a distributed boundary condition describing birth

$$u_t + u_a + \mu(a)u = 0, \quad u(t,0) = \int_0^\infty b(a)u(t,a)da \tag{16}$$

based on earlier work by Sharpe and Lotka. The operator $\partial/\partial a + \mu(a)$, with the given boundary condition, can be seen as the generator of a positive semigroup in $L_1(0,\infty)$. The important feature is the existence of an exponential or "persistent" solution $u(t,a) = \bar{u}(a)e^{\hat{\lambda}t}$ (under mild conditions on the coefficients μ and b). The number $\hat{\lambda}$ is the exponent of growth which is the unique solution of the characteristic equation $\int_0^\infty p(a)b(a)e^{-\lambda a}da = 1$ where $p(a) = \exp\{-\int_0^a \mu(s)ds\}$ is the survival function. Feller's renewal theorem says that most solutions approach the exponential solution for large times.

If the coefficients b and μ depend not only on age but also on population density, typically on a weighted mean $W(t) = \int_0^\infty w(a)u(t,a)da$, then we arrive at models of the Gurtin-MacCamy type

$$u_t + u_a + \mu(a,W)u = 0, \quad u(t,0) = \int_0^\infty b(a,W)uda. \tag{17}$$

With appropriate assumptions on the functions $\mu(a,W)$ and $b(a,W)$ (μ strictly increasing to ∞ as a function of W, and b strictly decreasing to 0; and a condition which ensures that the population grows at low densities such as $\int_0^\infty b(a,0)\exp\{-\int_0^a \mu(s,0)ds\}da > 1$) it follows that there is a unique nontrivial stationary state. In many situations this state describes a stable population equilibrium. However, in general, this state is not stable, and it is rather difficult to establish criteria for stability (Hopf bifurcations can occur).

On the other hand, population dynamics has been modeled by equations with retarded arguments (differential delay equations, delay equations), e.g. by Hutchinson's equation (delayed logistic equation)

$$\dot{u}(t) = au(t)(1 - u(t-\tau)/K). \tag{18}$$

This equation is equivalent with Wright's equation $\dot{v}(t) = -\alpha v(t-1)(1+v(t))$ and hence equivalent (via elementary transformations) to a special case of the equation

$$\dot{v}(t) = -\nu v(t) - \alpha f(v(t-\tau)) \tag{19}$$

which has been studied in great detail by many authors [24] [37] [38]. Hutchinson's model (18) is usually motivated by saying that somehow the population grows towards its carrying capacity K but reacts to exploited resources only with some delay due to hatching or maturation periods. In [4] a maturation period has been introduced in the McKendrick model (16). It is assumed that the mortality is a step function with a step at the age $a = \tau$ separating a juvenile from an adult age group, and that the birth rate has a delta peak at $a = \tau$ and is constant thereafter. This choice of the coefficients defines a system which is a reasonably realistic caricature of many natural populations where there is a clear division between juveniles and adults and where young adults have a relative high reproduction rate. With these assumptions the densities of the total juvenile and adult populations $U(t) = \int_0^\tau u(t,a)da$, $V(t) = \int_\tau^\infty u(t,a)da$ satisfy a set of differential delay equations. This system has the following structure. For $0 \le t \le \tau$ the variables U, V satisfy a non-autonomous system of ordinary differential equations (taking account of the history), but for $t > \tau$ they satisfy a system of neutral delay differential equations. This system separates (if juveniles do not reproduce, as we have assumed here), and the equation for adults reads

$$\dot{V}(t) = ((b_1 + b_2\mu_1)V(t-\tau) + b_2\dot{V}(t-\tau))e^{-\mu_0\tau} - \mu_1 V(t). \tag{20}$$

Here μ_i, b_i are the coefficients in $\mu(a) = \mu_0 + (\mu_1 - \mu_0)H_\tau(a)$, $b(a) = b_1 H_\tau(a) + b_2\delta_\tau(a)$ (H, δ are the Heaviside and delta function, respectively). This seems to be the first rigorous justification of a neutral differential delay equation as a population model [4].

If one applies similar considerations to the Gurtin-MacCamy model, one arrives at a nonlinear delay equation for the total adult population

$$\dot{V}(t) = g(V(t-\tau))V(t-\tau) + h(V(t-\tau))\dot{V}(t-\tau) - \mu(V(t))V(t). \quad (21)$$

In particular, for $h = 0$ the function $g(V)$ is the density-dependent birth rate and $\mu(V)$ is the death rate. The resulting equation is better motivated than equation (18).

4 Modeling infectious diseases

4.1 Vaccination policies

The nucleus of most, if not all, deterministic epidemic models is the Kermack-McKendrick system

$$\dot{u} = -\beta uv/P, \quad \dot{v} = \beta uv/P - \alpha v, \quad \dot{w} = \alpha v \quad (22)$$

which describes the transition from susceptible u to infected v and to recovered (immune) w. The parameter β is the transmission rate and α is the recovery rate. The basic reproduction number R_0 is, in general, the average number of newly infecteds which are produced by one infected individual in a totally susceptible population. In the present case it is simply $R_0 = \beta/\alpha$. The basic reproduction number can be seen as a normalized bifurcation parameter. The system (22) has the distinguished stationary point $(u, v, w) = (P, 0, 0)$ describing a totally susceptible population. If $R_0 < 1$ then this point is globally stable. If $R_0 > 1$ then a trajectory is emanating from this point which describes an infected population. Along this trajectory the number of infecteds increases first and then decreases to zero, leaving a positive number of remaining susceptibles. In this case it is obvious or easy to show that all relevant quantities such as the basic reproduction number, maximal number of infecteds (maximal prevalence), total size (number of all individuals ever infected) depend in a monotone fashion on the parameters, here β and α. In more complex models for the transmission of disease, in particular in models for sexually transmitted diseases in two-sex populations with infectivity depending on time since infection, it is not obvious (and in general not true) that the basic reproduction number depends on the transmission rate. Such problems have been studied in some detail in [44] using linear complementary problems and, with simpler proofs based on coupling methods in [45].

There are various strategies to fight the spread of infectious diseases such as vaccination, quarantine, education by public health authorities. If such policies are incorporated into disease transmission models, then new groups such as vaccinated or educated individuals must be distinguished. For these more complex models the simple scenario of a transcritical bifurcation at $R_0 = 1$ need not hold any more. In fact, it seems typical for multi-group models that there are regions in the parameter space where the bifurcation is backward (i.e., subcritical). The backward bifurcation may lead to hysteresis phenomena. This mathematical observation has important consequences in public health. It can be shown that inefficient vaccination or education policies (leading to partial immunity or slightly changed behavior) may have detrimental effects [18] [25].

In a sense, vaccination is nothing else then moving individuals from the susceptible to the vaccinated class. In the formulation of a model for a population structured by age and infection, vaccination enters just as a transition term. Let u, w, v be the susceptibles, vaccinated, and infecteds,

$$\begin{aligned} u_t + u_a + \mu(a)u &= -\psi(a)u - \beta(a)uV/N \\ w_t + w_a + \mu(a)u &= \psi(a)u - \tilde{\beta}(a)uV/N \\ v_t + v_a + \tilde{\mu}(a)v &= -\alpha v + (\beta(a)u + \tilde{\beta}(a)w)V/N \end{aligned} \tag{23}$$

with boundary condition

$$u(t,0) = \int_0^\infty [b(a)(u(t,a) + w(t,a)) + \tilde{b}(a)v(t,a)]da, \ w(t,0) = 0, \ v(t,0) = 0$$

where $V = \int_0^\infty k(a)v(t,a)da$ is the total infectivity and $N = \int_0^\infty (u+w+w)da$ is the total population size. Here $\psi(a)$ is the rate at which susceptibles of age a are moved into the vaccinated class. The reproduction number $R(\psi)$ of the disease in the presence of the vaccination policy ψ can be represented in the form $R(\psi) = R_0 - F(\psi)$ where $F(\psi) \geq 0$ is some functional of the policy ψ. Then one can formulate several optimization problems, e.g. to achieve a reduction of the reproduction number $R(\psi) \leq R^* < 1$ at minimal expenses [20]. Several of these optimization problems have been discussed and solved in [20] [41] [42]. The results are somewhat astonishing (at first glance): In most of these problems, optimal policies vaccinate the population at one or two ages. There is a rather close relation to optimal harvesting or culling problems in bioeconomics. If a population structured by age or size is harvested at equilibrium and the net gain is to be maximized then optimal harvesting strategies use two age or size groups only [21].

4.2 Epidemic spread in space

There are basically two different ways in which the spread of an infectious disease in a spatially distributed population can be imagined. We can think of the individuals fixed at certain positions and being in contact according to some contact distribution. With this view the position of the individual is given by its residence and the contact distribution describes all contacts with individuals at different locations. In the second view the individuals move according to some stochastic process and may contact individuals which they meet at the actual position. Of course we can join both views and consider individuals which move and have contacts elsewhere. In the first view the SIR model assumes the form

$$\begin{aligned} u_t &= -\beta u \int k(x-y)v(t,y)dy \\ v_t &= \beta u \int k(x-y)v(t,y)dy - \alpha v. \end{aligned} \tag{24}$$

Here the kernel k describes the infectivity which an infected individual at position y exerts upon a susceptible at position x. In the second view we have models of the form

$$\begin{aligned} u_t &= -\beta uv + D(\int K(x-y)u(t,y)dy - u(t,x)) \\ v_t &= \beta uv - \alpha v + \tilde{D}(\int \tilde{K}(x-y)v(t,y)dy - v(t,x)). \end{aligned} \tag{25}$$

In models of the form (25) we can replace the diffusion operator by a transport operator to get a possibly more realistic model for the migration process. In [19] the following system has been studied

$$\begin{aligned} u_t(t,x,s) + su_x(t,x,s) &= \int_V K(s,\tilde{s})u(t,x,\tilde{s})d\tilde{s} - \mu u(t,x,s) \\ &\quad -\beta u(t,x,s) \int_V L(s,\tilde{s})v(t,x,\tilde{s})d\tilde{s} \qquad (26) \\ v_t(t,x,s) + sv_x(t,x,s) &= \int_V \tilde{K}(s,\tilde{s})v(t,x,\tilde{s})d\tilde{s} - \tilde{\mu} v(t,x,s) \\ &\quad +\beta u(t,x,s) \int_V L(s,\tilde{s})v(t,x,\tilde{s})d\tilde{s} - \alpha v(t,x,s). \end{aligned}$$

Existence of mild solutions has been shown using a Kaniel-Shinbrot iteration and the asymptotic behavior has been explored [19].

Epidemic models of the form (24) or (25) and the corresponding diffusion approximations have typically travelling front solutions that describe the propagation of disease into a susceptible population. Existence of travelling fronts and the minimal speed have been studied in [14].

4.3 Modulation equations

Models in mathematical biology are often very complex and not suited for analytical treatment. Numerical simulations lead to some insight, but may be not completely satisfying. However, the most interesting phenomena are connected to bifurcations. Near a bifurcation a complex system may be reduced using, for example, center manifold theory. Center manifold theory requires discrete spectra and hence its application is restricted to bounded space domains. Its analogue for unbounded domains is the theory of modulation equations or amplitude equations. This theory started with the Ginzburg-Landau equation developed in solid state physics. Only quite recently [26] [52] the underlying mathematical structure has been clarified: Modulation equations describe the evolution of the amplitude of the solution over the unstable modes, rescaled in an appropriate way, up to higher orders of a small parameter (in general the bifurcation parameter). The equation takes into account the mode-interaction (again, up to higher order terms of the small parameter). The Ginzburg–Landau equation

$$A_t = \Delta A + c_1 A + c_2 |A|^2 A \tag{27}$$

describes the generic situation, where the first unstable mode is a nonzero Fourier mode.

In epidemiology, the primary bifurcations are transcritical: A susceptible population loses its stability and the infective agent invades. A typical model for spatial spread of an epidemic has the form of equation (1) where $u(t, x)$ denotes the vector of densities for susceptibles, infecteds a.s.o. If the scalar equation $\dot{u} = f(u)$ undergoes a transcritical bifurcation, then the first unstable Fourier mode of the full system is zero. Hence the corresponding modulation equation is the classical KPP or Fisher equation

$$A_t = \Delta A + A - A^2.$$

However, most epidemic models have an additional symmetry: The vector field is homogeneous of degree one, $f(\alpha u) = \alpha f(u)$ for $\alpha > 0$. This symmetry gives additional structure, similar to the phase equation (see [35]), and the modulation equation becomes a system

$$A_t = \Delta A + 2(\nabla B)^T \nabla A + A - A^2, \quad B_t = \Delta B + |\nabla B|^2 + cA \tag{28}$$

for variables A, B governing the prevalence of infection and the total population size at the point (x, t), respectively. In many cases the solutions of these equations approach traveling fronts for large times [43]. It is an interesting point that the velocity of the spread depends only on the reproduction number and the exponent of growth of the susceptible population; whether or not the population breaks down in endemic regions has no influence on this velocity. Only if in endemic regions the population starts to *grow* much faster than in infection–free zones (a situation only of theoretical interest), then the infection may be pushed forward and spreads even faster if the growth rate of the infected population increases.

5 Models describing single individuals

In the previous sections, always the density of a structured population has been considered. This density describes the behavior of an average individual;

it is not possible to gain insight in the fate of a single individual. For many cases, this simplified approach gives enough information about interesting phenomena. Moreover, it leads to dynamical systems which can be analysed using a wide range of elaborated analytical tools. However, in some situations it is necessary to focus on single individuals (examples are given below). The formulation of these individual based models is often simpler than that of deterministic models: The only thing one has to do is to formulate the different behavioral patterns of single individuals and let these individuals interact. The great success of these models in recent years can partly be explained by the fact that these ideas can easily be communicated to non-mathematicians. Unfortunately, only very few tools are available to analyse individual based models. Some models and methods are presented in the following sections.

5.1 Cellular automata and particle systems

A cellular automaton consists of a grid G of cells, in most cases a subset (grid domain) of the square lattice $\mathbb{Z}^2$ (or $\mathbb{Z}^1$), a neighborhood U, typically the Moore neighborhood of nine cells or the von Neumann neighborhood of five cells, a set E of elementary states, typically $E = \{0, 1\}$ (empty/occupied or white/black) and finally a local function f_0. The cellular automaton (G, U, E, f_0) defines a discrete dynamical system $z^{(t+1)} = f(z^{(t)})$ on states $z : G \to E$ where the global function f is obtained from the local function as

$$f(z)(x) = f_0(z|_{U(x)}). \tag{29}$$

Cellular automata can be evaluated synchronously or asynchronously. In the asynchronous case each cell is called according to a Poisson process (with the same rate for every cell). For the same local function, trajectories of the synchronous or the asynchronous automaton look quite different. Whether synchronous or asynchronous, the "flip", i.e., the exchange of the states of two neighboring cells, cannot be realized in a standard cellular automaton. Therefore the new concept of a dimer automaton has been introduced [54]. A dimer automaton is a system (G, U, E, f_0) with a grid, a neighborhood and elementary states as before. However, the local function is a mapping $f_0 : E \times E \to E$. Hence a dimer automaton works as follows. A first cell is called according to a Poisson process, then a second cell y is called from the neighborhood $U(x) \setminus \{x\}$, then the local function is applied to the pair $(z(x), z(y))$. For a given grid domain and neighborhood, there are 256 different dimer automata. This set can be partitioned into 51 equivalence classes, and for each of these the dynamical behavior can be described qualitatively by stochastic properties such as ergodicity (see [2]) and quantitatively by mean field approximations [54]. Extensions of dimer automata can be constructed as follows. A grid domain together with a neighborhood defines a graph. The cells correspond to the vertices, an edge is running from cell x

to cell y if $y \in U(x)$. Since the Moore neighborhood is symmetric, each two connected cells are connected by a pair of edges. Hence one can extend the concept to arbitrary directed graphs. Then one can consider convex combinations of dimer automata on directed graphs as follows. Define a priori a distribution on the set of all dimer automata. The graph and this distribution define an "edge process": Call an edge, inspect the states of the vertices, select a dimer automaton according to the given distribution, apply the local rule. In [3] it has been shown that, up to some rescaling of the underlying stochastic processes which amounts to monotone transformations of the time variable along realizations, edge processes can be essentially interpreted as convex combinations of seven basic processes. The travelling fronts of certain cellular automata have been studied in [53], and recently asynchronous automata have been studied which can be seen as ultimate discretizations of the Cahn-Hilliard equation [22].

5.2 Individual based models and epidemiology

Infectious diseases can be seen as a problem of public health and as events in individual life. These different views are most obvious with respect to vaccination, where public health wants to prevent outbreaks and endemics whereas the individual wants protection. If the disease is not fatal and vaccination bears some risk to the vaccinated individual, then the goals of the individual and public health may diverge [42]. Deterministic models are essentially public health models; detailed information on individual fates would even be misleading. The situation is somewhat different with respect to stochastic models. There is a well developed theory of stochastic epidemics which, at least for simple transmission laws, yields explicit expressions for critical parameters, prevalence, total size of an epidemic a.s.o. If one compares the outcomes of deterministic models to the expectations in stochastic models then one finds characteristic differences that can be attributed to the variance in stochastic models.

However, there are various situations where a control policy addresses the contact structure of a single individual. In such cases models and methods based on the description of individuals are necessary. A typical example is ring vaccination, where all individuals in a neighborhood of a discovered infectious individual (the index case) are treated. In human populations the family, friends and colleagues of an infected person become protected by vaccination. In an agricultural setting, the spatial structure of contacts becomes important: A standard example is foot- and mouth disease (FMD) in cattle. Once a farm with infected animals is discovered, all farms within a certain distance (typically three to twenty kilometers) are treated. This procedure creates a ring of vaccinated farms around the index case.

Contact tracing, as opposed to mass screening, is another example of an individual based control policy. Once an infected individual is discovered (the index case), this person is interviewed about recent possibly infectious contacts. Especially for sexually transmitted diseases, these contacts are simple to characterize and at least theoretically easy to be followed up and notified. The notified persons are then examined. In this way more infected persons are discovered and again interviewed. In case these persons are asymptomatic, contact tracing is the only way to discover them.

While ring vaccination for FMD is based on spatial structure, contact tracing may be modeled in a homogeneously mixing population. Because of this difference, also the models and the methods used are slightly different.

5.3 Particle systems and branching processes modeling ring vaccination

The spread of FMD can be modeled as a particle system [48]. One characteristic feature of FMD is the existence of two different contact rates: short range contacts occur at a high rate, leading to many infected cases close to a primary case. Long range contacts occur at a lower rate and cause infections at farms far away from primary infected farms. In a first modeling step, one considers only local contacts by means of a cellular automaton (on a finite square grid with the Moore neighborhood U) where the state $z(x)$ at the site x can assume three values S, I and R representing a farm with animals all susceptible, some infected or all immune, respectively. The transitions $I \to R$ and $R \to S$ occur according to a Poisson process at prescribed rates. The transition $S \to I$ describes the infection process and is slightly more complex. We assume that the infection rate is a nondecreasing function of the number of infected neighbors, a cell x changes its state from S to I in a time interval of length Δt according to

$$S \to I \;\text{ with probability }\; \beta_s \#\{y \in U(x) \,|\, z(y) = I\} \Delta t + o(\Delta t).$$

The second step is modeling global contacts: At a low rate β_l, each infected particle (farm) may infect any other particle in the grid. With these global interactions, the system is not a cellular automaton any more but an interacting particle system. The total resulting probability for infection of a cell x in the state S during a small time interval Δt is

$$\begin{aligned} S \to I \quad &\text{with probability} \\ &\beta_s \#\{y \in U(x) \,|\, z(y) = I\} \Delta t + \beta_l \#\{y \in \Gamma \,|\, z(y) = I\} \Delta t + o(\Delta t). \end{aligned}$$

In the last modeling step one introduces ring vaccination: First of all, there is a discovery rate at which index cases are observed. Once an infected site is found, all neighbors of this site are screened. If a site is susceptible, then it becomes vaccinated and hence immune. If the site is infected, it is treated (all animals at this farm are slaughtered) and recursively also around this site ring vaccination is performed.

Simulations show that local outbreaks occur in the form of several infected sites close together that are created by local contacts. These local outbreaks cause, by global contacts, other local outbreaks. Since the infected sites within local outbreaks are close together, mostly the local outbreak is completely eradicated by ring vaccination after the first index case has been discovered. This structure fits well with observed patterns of FMD.

For certain parameter ranges it is possible to approximate the dynamics of this complex nonlinear interacting particle system by a linear stochastic birth and death process on two levels. The first level, describing the dynamics of local outbreaks, is a branching process with catastrophes (at the discovery of the first member of a local outbreak the whole infectious population is locally eradicated). These local outbreaks behave like individuals which give birth to other individuals (local outbreaks) and die (due to ring vaccination or due to spontaneous recovery of all members of a local outbreak). Using the theory of branching processes on two levels [1], it is possible to derive expressions for characteristic quantities for the dynamics, e.g. for the reproduction number or the time to extinction.

Furthermore, it is possible to introduce mass vaccination, and in this way to compare mass vaccination to ring vaccination. This comparison is especially interesting, since the European Community (EU) changed its FMD policy recently: Before mass vaccination has been the rule, while now the EU relies on ring vaccination only. Since with ring vaccination herd immunity is lost, it is interesting to know how powerful certain aspects of ring- and mass vaccination are.

5.4 Nonlinear branching processes modeling contact tracing

In contrast to ring vaccination for FMD, contact tracing can be modeled in a homogeneously mixing population [47]. Assume N individuals, S susceptibles and I infecteds. In the absence of contact tracing the infection process is given by

$$(S, I) \mapsto (S-1, I+1) \quad \text{with} \quad \text{probability} \quad \beta S I \varDelta t + o(\varDelta t)$$

and recovery by

$$(S, I) \mapsto (S+1, I-1) \quad \text{with} \quad \text{probability} \quad \alpha I \varDelta t + o(\varDelta t)$$

Now one introduces contact tracing. Like in ring vaccination, an index case has to be discovered first. Index cases are detected according to a Poisson process. Once an index case has been discovered, one starts to investigate the contacts of this person: The infected persons form a directed graph $\varGamma$. A node represents an infected person, a directed edge runs from an infector to the person infected. The graph of infected persons is not necessarily connected because recovered individuals leave the graph. Each connected component of $\varGamma$ is a tree, i.e., $\varGamma$ itself is a forest. If one discovers one index case in a connected component of this forest, then all neighbors of this index case can be also discovered. In general, not every neighbor will be found for sure (since people are not likely to notify e.g. all sexual partners), but for each neighbor there is a certain probability of detection, the tracing probability. In a given realization of this stochastic process, the neighbors which are actually discovered are converted into new index cases. In this way, the tracing process is running over one connected component of Γ, starting at the first index case. The size and the structure of these connected components change over time; at the onset of an outbreak, there are only very few infected individuals and the connected components are small. The components grow with time until they reach an equilibrium distribution with respect to size and structure.

The key point of the analysis is to derive the mean infectious period, since the effective reproduction number is the product of the infection rate β and the mean infectious period. Since the mean infectious period depends on the state of the infectious population as a whole, the dynamics of the forest Γ must be described.

In order to investigate the dynamics at the onset of the disease, one assumes that there are no nonlinear effects due to the infectious process, i.e., that every contact of an infected person reaches a susceptible person. The embedded Galton-Watson process, where one considers generations of infected individuals instead of time, is not stationary but asymptotically stationary. It is possible to derive recursive integro-differential equations for the probability to be infectious after time of infection a for a particle of generation i of infected persons. These functions converge with $i \to \infty$, and in this way the mean infectious period can be computed.

Heuristic time scale arguments allow for a deterministic approximation of the density of susceptible and infected individuals of the full, nonlinear process with contact tracing and infection in form of ordinary differential equations. Interesting questions that can be approached via the stochastic process are, for example: Should one look for "infectors" (i.e., the one that has infected the index case) rather than "infectees" (the persons, who are infected by the index case)? Is it sufficient to inspect the the direct neighbors of the index case or does it pay to follow the full recursivity of the dynamical process? These questions have practical implications for the design of contact tracing.

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