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NONLINEAR DIFFERENTIAL EQUATIONS FROM BIOLOGY

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In this lecture some results on nonlinear differential equations are presented, ordinary differential equations, first order partial differential equations, elliptic equations. In each case the study has been motivated by a problem from biology or a biological model.

1. An Epidemic Model

We consider a population infected by parasites, where the number of parasites per host is an important feature, and where the life expectancy of hosts is influenced by the number of parasites. The nucleus of the model is the classical model for an age structured population [1].

Let $n(t,a,r)$ be the number of individuals of age a carrying r parasites at time t. Let $\varphi(t)$ be the rate of acquiring parasites at time t. It is assumed that φ depends only on the average number of parasites per host

$$\varphi(t) = \beta f(\bar{u}(t)), \tag{1.1}$$

$$\bar{u}(t) = \int_0^\infty \sum_{r=0}^\infty r n(t,a,r)da \Big/ \int_0^\infty \sum_{r=0}^\infty n(t,a,r)da . \tag{1.2}$$

Here $f : [0,\infty) \to [0,\infty)$ is a continuously differentiable function, such that $f(0) = 0$, $f'(0) = 1$, $f(u) > 0$ for $u > 0$, and $\beta > 0$ is a constant which will be used as a bifurcation parameter.

We assume that individual hosts die according to the death rate $\mu(a) + \alpha r$, where $\mu(a)$ is the age-dependent death rate of individual hosts and α is the differential death rate due to the presence of one parasite. The death rate of parasites is σ.

Thus the functions n(t,a,r) satisfy an infinite system of ordinary differential equations

$$\frac{\partial n(t,a,r)}{\partial t} + \frac{\partial n(t,a,r)}{\partial a}$$

$$= - [\varphi(t) + \mu(a) + \alpha r + \sigma r] n(t,a,r)$$

$$+ \varphi(t) n(t,a,r-1) + \sigma(r+1) n(t,a,r+1) \qquad (1.3)$$

for $r \geq 1$, and for $r = 0$

$$\frac{\partial n(t,a,0)}{\partial t} + \frac{\partial n(t,a,0)}{\partial a} = - [\varphi(t) + \mu(a)] n(t,a,0) + \sigma n(a,t,1).$$

With assistance of the generating function

$$u(t,a,z) = \sum_{r=0}^{\infty} n(t,a,r) z^r \qquad (1.4)$$

these equations can be condensed into one partial differential equation

$$u_t + u_a + [\alpha z + \sigma(z-1)] u_z - [\beta(z-1) f(\bar{u}) - \mu(a)] u = 0 \qquad (1.5)$$

where

$$\bar{u} = \int_0^\infty u_z(t,a,1)\,da \Big/ \int_0^\infty u(t,a,1)\,da. \qquad (1.6)$$

This equation is accompagnied by initial and boundary conditions

$$u(0,a,z) = u_0(a,z) \quad \text{at} \quad t = 0, \qquad (1.8)$$

$$u(t,0,z) = N(t,z) \quad \text{at} \quad a = 0. \qquad (1.9)$$

This model has been discussed in a joint paper with K. Dietz [2]. In a first approach the boundary datum N is assumed as a given function. In a more realistic model N should depend on the actual state of population, e. g.

$$N(t,z) = \int_0^\infty B_0(t,a,z)u(t,a,z)da \qquad (1.10)$$

where B_0 is a kernel describing fertility depending on time, age, and parasite load.

If u does not depend on z, then $u_z \equiv 0$, $\bar{u} \equiv 0$, and the equations reduce to the well-known model for age structure

$$u_t + u_a + \mu(a)u = 0.$$

Our approach to the equation is the following: assume $\varphi(t)$ were known, then the equation becomes linear,

$$u_t + u_a + [\varkappa z-\sigma]u_z - [(z-1)\varphi(t) - \mu(a)]u = 0 \qquad (1.11)$$

where $\varkappa = \alpha + \sigma$.

This equation can be solved by the method of characteristics in a straightforward manner. One has to take care of the discontinuity at $t = a$.

The solution for $a > t$ is

$$u(t,a,z) = u_0(a-t,L(z,t)) \exp K(t,a,z) \qquad (1.11a)$$

where

$$K(t,a,z) = \int_0^t (L(z,t-s)-1)\varphi(s)ds - \int_{a-t}^a \mu(s)ds$$

and the solution for $t > a$ reads

$$u(t,a,z) = N(t-a,\ L(z,a))\ \exp K_1(t,a,z) \tag{1.11b}$$

$$K_1(t,a,z) = \int_0^a (L(z,a-s) - 1)\varphi(t-a-s)\,ds - \int_0^a \mu(s)\,ds$$

where

$$L(z,t) = 1-(1-z)e^{-\varkappa t} - \frac{\alpha}{\varkappa}\,(1-e^{-\varkappa t}). \tag{1.12}$$

From this explicit representation one easily obtains expressions for $\int u_z(t,a,1)\,da$, $\int u(t,a,1)\,da$ which can be inserted into equation (1.1), (1.6). The result is an integral equation for the function φ,

$$\varphi(t) = (\mathfrak{F}\,\varphi)(t) \tag{1.13}$$

$$(\mathfrak{F}\,\varphi)(t) = \beta f\left(\frac{\int_0^t e^{A\varphi}\{\bar{N}_z+\bar{N}B\varphi\}\,da + e^{C\varphi}\{F_z + FD\varphi\}}{\int_0^t e^{A\varphi}\bar{N}\,da + e^{C\varphi}F}\right). \tag{1.14}$$

Here, with $L_1(t) = L(1,t) - 1$,

$$(A\varphi)(t,a) = \int_{t-a}^{t} L_1(t-s)\varphi(s)\,ds,$$

$$(B\varphi)(t,a) = \int_{t-a}^{t} e^{-\varkappa(t-s)}\varphi(s)\,ds,$$

$$(C\varphi)(t) = \int_0^t L_1(t-s)\varphi(s)\,ds,$$

$$(D\varphi)(t) = \int_0^t e^{-\varkappa(t-s)}\varphi(s)\,ds.$$

$$\bar{N} = e^{-M(a)}N(t-a,L(1,a))$$

$$\bar{N}_z = e^{-M(a)-\varkappa a}N_z(t-a,L(1,a))$$

$$F = \int_t^\infty e^{-M(a)+M(a-t)}u_0(a-t,L(1,t))da$$

$$F_z = \int_t^\infty e^{-M(a)+M(a-t)}u_{0z}(a-t),L(1,t))da$$

So far we have obtained local and global existence under reasonable assumptions on the functions f, u, u_0 and N [1]. The main difficulties in the proofs are the complexity of the whole equation and the fact that the denominator may approach zero. We assume that u_0 and u_{0z} are exponentially decaying functions of a.

Next try to find stationary solutions. Suppose that N is constant in t. For simplicity we assume that $N > 0$ is also constant in z: This assumption is quite natural: newborns are not infected.

For stationary solutions φ becomes a constant which satisfies a certain scalar equation. Let

$$q(a) = \frac{1}{\varkappa}(a-e^{-\varkappa a}) \tag{1.15}$$

$$Q(a) = \int_0^a q(s)ds = \frac{1}{\varkappa}(a-q(a)) \tag{1.16}$$

$$I_0(\varphi) = \int_0^\infty e^{-\alpha Q(a)\varphi-M(a)}da \tag{1.17}$$

$$I_1(\varphi) = \int_0^\infty e^{-\alpha Q(a)\varphi-M(a)}q(a)da \tag{1.18}$$

$$W(\varphi) = I_1(\varphi)/I_0(\varphi) \tag{1.19}$$

Then the constant φ is obtained from the equation

$$\varphi = \beta f(W(\varphi)\varphi), \tag{1.20}$$

and the corresponding solution of the full problem is

$$u(a,z) = N \exp[-((1-z)q(a)-\alpha Q(a))\varphi-M(a)] \ . \tag{1.21}$$

The branch of nontrivial solutions can be represented explicitly as

$$\beta = \varphi/f(W(\varphi)\varphi). \tag{1.22}$$

It starts at $(\beta_0,0)$ where

$$\beta_0 = \int_0^\infty e^{-M(a)}da/ \int_0^\infty e^{-M(a)}q(a)da \ . \tag{1.23}$$

If f does not grow too fast, i.e. if

$$u^{-2}f(u) \to 0 \qquad \text{for } u \to \infty \ , \tag{1.24}$$

then the branch exists for all $\beta > \beta_0$. If f satisfies certain monotonicity and concavity conditions

$$\frac{df(u)}{du} \geq 0, \qquad \frac{d}{du}\left(\frac{f(u)}{u}\right) \leq 0, \tag{1.25}$$

then for each $\beta > \beta_0$ there is exactly one positive φ .

The conditions (1.25) are met for acquisition functions which have some tradition in epidemiology such as $f(u) = u$, $f(u) = u/(1+u)$, $f(u) = 1-e^{-u}$.

A direct stability analysis of equation (1.5) appears difficult. On the other hand, if one uses the integral equation (1.14) and the derivative $\partial \mathcal{F}/\partial\varphi$ which is used in the existence proof anyway, one can reduce the stability problem to the study of a linear integral equation: If S(t) contains the influence of the perturbation of the initial data and ψ the deviation in φ from the stationary constant then ψ satisfies an integral equation

$$\psi(t) = \mathcal{L}_t \psi(t) + S(t) . \tag{1.26}$$

One can show that the stationary solution corresponding to $\varphi = 0$ (no parasites, natural age distribution) is linearly stable for $\beta < \beta_0$ with respect to exponentially decaying (as functions of a) perturbations.

2. Reaction-diffusion equations and invariant sets

Many phenomena in biology can be described as the result of the interaction of diffusion and reactions between species: Let the interaction of species be described by an ordinary differential equation

$$\mathring{u} = f(u) \tag{2.1}$$

where $u \in R^m$ and $f: R^m \to R^m$. Let $u = \bar{u}$ be a stationary solution. It is exponentially stable if all eigenvalues of $f'(\bar{u})$ are located in the left half-plane.

The ordinary differential equation describes the chemical reaction under well-stired conditions. If the reactands diffuse, possibly with distinct rates, the reaction can be described by an equation

$$u_t = D\Delta u + f(u) \tag{2.2}$$

where Δ is the Laplacian, acting componentwise on the vector u, and $D = (D_j \delta_{jk})$ is the matrix of diffusion rates. In typical situations equation (2.2) is studied in some bounded spatial domain Ω with smooth boundary, together with homogeneous Neumann conditions

$$\frac{\partial u(t,x)}{\partial \nu} = 0 \text{ on } \partial\Omega \tag{2.3}$$

(ν = outer normal) or nonhomogeneous Dirichlet conditions

$$u(t,x) = \psi(x) \qquad \text{for } x \in \partial\Omega. \tag{2.4}$$

It is well-known that the spatially homogeneous solution $u = \bar{u}$ of (2.2), (2.3) may become unstable, if the diffusion rates are sufficiently wide apart and the domain is large. A necessary condition is that the matrix $f'(\bar{u})$ is excitable. For $m = 2$ the matrix

$$f'(\bar{u}) = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

is stable, but excitable, if the determinant $ad - bc$ is positive, the trace $a + d$ is negative, but either $a > 0$ or $d > 0$. If $a > 0$, and $d < 0$, the reactand u_1 acts "autocatalytic", the rectand u_2 "inhibitory".

If the homogeneous state looses its stability, non-homogeneous stationary solutions may arise. In the neighborhood of the bifurcation point their shape will be determined by the linearized equation, farther away they may change their behavior, undergo secondary bifurcations a. s. o. Similar complicated behavior can be expected in the Dirichlet problem. A first step in the analysis is the proof of existence for stationary solutions.

Suppose $M \subset R^m$ is a positively invariant set for the ordinary differential equation, i. e. for any $u \in \partial M$ and any outer normal p to ∂M at u holds

$$p \cdot f(u) \leq 0. \tag{2.5}$$

One could conjecture that the cylinder $G \subset C^m(\bar{\Omega})$,

$$G = \{ u \in C^m(\bar{\Omega}) : u(\bar{\Omega}) \subset M \}$$

is a positively invariant set for the equation (2.2) with boundary conditions (2.4), provided the boundary data satisfy $\psi(\partial\Omega) \subset M$. However, this claim is invalid.

If the diffusion rates D_j are equal, then, according to an invariance theorem of Weinberger [3], the conjecture can be shown for M compact, convex, with interior points, with some regularity conditions on ∂M.

If the diffusion rates are distinct, then, in general, only sets of the form

$$M = \{ u: \ a_j \leq u_j \leq b_j, \quad j = 1, \ldots, m \} \tag{2.6}$$

can be allowed. However, in many applications the diffusion rates are essentially distinct and the vector field f does not admit positively invariant sets of the form (2.6).

Nevertheless one can exploit the fact, that many well-known examples f allow convex invariant sets, and that in many cases the vector fields f and g, where

$$g(u) = D^{-1}f(u), \tag{2.7}$$

have a similar structure. Then the Dirichlet problem

$$-\Delta u = g(u) \text{ in } \Omega, \; u = \psi \text{ on } \partial\Omega \tag{2.8}$$

can be approached via Weinberger's invariance principle for vectorvalued elliptic equations and a degree argument [4], [5] vector q valued.

This approach can be carried through [4] for the Lotka-Volterra model

$$\begin{aligned} u_t &= au(1-u/K)-buv+D_1\Delta u \,, \\ v_t &= cuv - dv + D_2\Delta v \,, \end{aligned} \tag{2.9}$$

the Brusselator

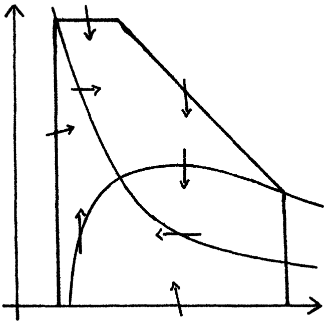
$$\begin{aligned} u_t &= u^2v - (C+1)u + A + D_1\Delta u \,, \\ v_t &= -u^2v + Cu + D_2\Delta v \,, \end{aligned} \tag{2.10}$$

and the Gierer-Meinhardt model

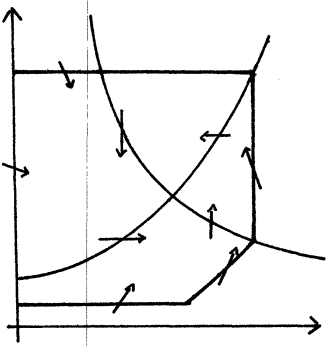
$$\begin{aligned} u_t &= cu^2 v - u u + D_1\Delta u \,, \\ v_t &= bu^2 - \gamma v + d + D_2\Delta v \,. \end{aligned} \tag{2.11}$$

In each of these cases a family of convex compact sets can be constructed, which are positively invariant and exhaust the quarterplane $u > 0$, $v > 0$, i. e. every compact subset of $u > 0$, $v > 0$ is contained in one of these sets [4] .

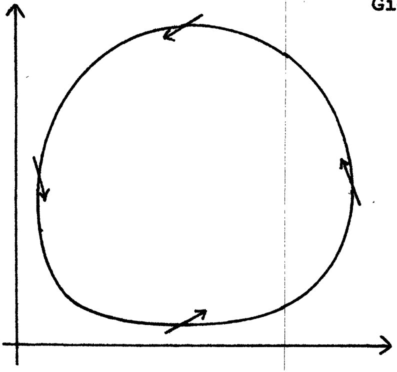
In the Lotka-Volterra case the sets are related to the well-known Lyapunov function, in the case of the Brusselator there is a family of convex pentagons, and for the Gierer-Meinhardt model there is a family of sets bounded by straight lines and exponential arcs.



Brusselator



Gierer-
Meinhardt



Lotka-Volterra

3. The classical model of population genetics

The Fisher-Wright-Haldane model of population genetics describes the development of a population under selection and Mendelian segregation. It is assumed that the population is genetically homogeneous with the exception of a single locus with $n \geq 2$ alleles $a_1, \ldots, a_n$. Then there are n^2 genotypes $a_j a_k$, $j, k=1, \ldots, n$. We shall not identify $a_j a_k$ and $a_k a_j$ but always assume that these types occur with the same frequency.

To each genotype $a_j a_k$ we attribute a fitness parameter, which measures the proportion of the descendants of this type among the offspring. Other interpretations derive the fitness parameter from a notion of viability.

The state of the population is described by the genotype frequencies

$$\alpha_{jk} = \alpha_{kj} \geq 0, \qquad \sum_{j,k=1}^{n} \alpha_{jk} = 1 \; . \tag{3.1}$$

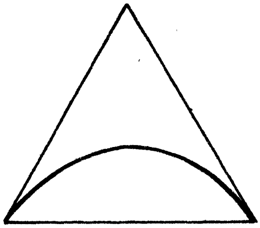
From these the gene frequencies

$$p_j = \sum_{k=1}^{n} \alpha_{jk} = 0, \qquad \sum_{j=1}^{n} p_j = 1 \, , \tag{3.2}$$

can be computed. Of course, in general one cannot obtain the genotype frequencies from the gene frequencies. However, if the total population is formed by random mating then these frequencies are related by the Hardy-Weinberg law

$$\alpha_{jk} = p_j p_k . \tag{3.3}$$

The state space of the population can always be interpreted as a simplex in some space of appropriate dimension. For $n = 2$ the state space of gene frequencies is a segment, the state space of genotype frequencies is the de Finetti diagram, (now a_1a_2 and a_2a_1 identified), and the set of all populations satisfying (3.3) is the Hardy-Weinberg parabola.



In general the development of the population should be described by a difference equation (discrete time) or a differential equation (continuous time) for the α_{jk},

$$\alpha_{jk}^{t+1} = \mathfrak{G}(\alpha_{jk}^{t}), \tag{3.4}$$

or

$$\dot{\alpha}_{jk} = \mathfrak{F}(\alpha_{jk}). \tag{3.5}$$

In the discrete time case (separated generations), always observing the population at birth, the equation (3.4) is equivalent with an equation for the gene frequencies

$$p_j^{t+1} = \sum_{k=1}^{n} f_{jk}p_j^t p_k^t \Big/ \sum_{r,s=1}^{n} f_{rs}p_r^t p_s^t \quad . \tag{3.6}$$

In the continuous time case, the equation for the gene frequencies

$$\dot{p}_j = \sum_{k=1}^{n} f_{jk} p_j p_k - \sum_{r,s=1}^{n} f_{rs} p_r p_s p_j \qquad (3.7)$$

can be interpreted as approximation for equations (3.5), for finite time, in the neighborhood of the Hardy-Weinberg set.

Let $p = (p_j)$ be the vector of gene frequencies, and $P = (p_j \delta_{jk})$ be the corresponding diagonal matrix. Let $F = (f_{jk})$ be the symmetric matrix of fitness coefficients. Then the equations (3.6) and (3.7) assume the form

$$p^{t+1} = P^t F p^t / p^{t*} F p^t \quad , \qquad (3.8)$$

$$\dot{p} = PFp - p^* Fp \cdot p \quad . \qquad (3.9)$$

Then the state space for both equations is the simplex of probability vectors

$$S = \{ p \geqq 0,\ e^* p = 1 \} \ ,\ e^* = (1, \ldots, 1) \quad . \qquad (3.10)$$

The mean fitness of the population in state p is the quantity

$$W(p) = \Sigma\, \alpha_{jk} f_{jk} = \Sigma\, f_{jk} p_j p_k = p^* F p \quad . \qquad (3.11)$$

In each of the two models the function $W: S \rightarrow R$ is a Lyapunov function [6][7][8] . Thus every solution approximates a continuum of stationary states.

The stationary states are the solutions of the equation

$$PFp = p^* Fp \cdot p \quad . \qquad (3.12)$$

Each solution of this equation is located in the relative interior of some subsimplex, i.e.

$$p = \begin{bmatrix} q \\ 0 \end{bmatrix} \qquad (3.13)$$

with $q > 0$. There is a corresponding partition of the matrix F,

$$F = \begin{bmatrix} F_{11} & F_{12} \\ F_{21} & F_{22} \end{bmatrix} . \qquad (3.14)$$

If p is stationary and in the interior of S then $Fp = p^*Fp \cdot e$. On the other hand, if x is a positive solution of the equation $Fx = e$, then $p = x/e^*x$ is a stationary point in the interior of S. Similarly, stationary points in some face $\tilde{S}$ of S of the form (3.13) (after appropriate reordering of components) correspond to solutions of the equation $F_{11}x = e$.

Let $F_{11}x = e$ have a positive solution x and assume $\dim \ker F_{11} = \nu \geq 1$. Let $\tilde{S}$ be the face of S which contains the corresponding stationary state. Then the set of stationary points in S is a manifold of dimension ν. It is the intersection of a linear manifold with $\tilde{S}$.

Corresponding to the faces of S there are at most 2^n-1 continua of stationary points.

4. The convergence problem

In the case of non-isolated stationary points the asymptotic behavior of trajectories is not obvious. The Jacobian at a stationary point is

$$J = PF + [Fp] - 2pp^*F - p^*Fp \cdot I, \qquad (4.1)$$

where $[Fp] = ((Fp)_i \delta_{ij})$. Equivalently, with (3.13) and $Q = (q_j \delta_{jk})$,

$$J = \begin{pmatrix} QF_{11} - 2q^*F_{11}q \cdot qe^* & (Q-2qq^*)F_{12} \\ 0 & [F_{21}q] - q^*F_{11}q \cdot I \end{pmatrix}. \qquad (4.2)$$

If there is a manifold of stationary points of dimension ν then dim ker $J = \nu$. But from above dim ker $(QF_{11}-2q^*F_{12}q \cdot ge^*)$ = dim ker $F_{11} = \nu$.
The hyperbolicity requirement that dim ker J should not exceed the dimension of the manifold leads to the hypothesis

$$(F_{21}q)_i \neq q^*F_{11}q, \qquad i = 1,\ldots,n-m \qquad . \qquad (4.3)$$

A stationary point with the property (4.3) is called regular. Regularity has an obvious biological meaning:
At the stationary point p the genes $a_1,\ldots,a_m$ are maintained, whereas $a_{m+1},\ldots, a_n$ are absent. Condition (4.3) says that the fitness of any of the absent alleles is different from the mean fitness of the population.
In [9] a partial solution to the convergence problem is given: If for a given trajectory the ω-limit set contains a regular stationary point, then the trajectory converges to that point.
From the explicit representation of the Jacobian (4.1) one can easily derive a stability criterion for a polymorphism, i.e. a positive stationary solution: Suppose F has eigenvalues $\lambda_1 \geq \lambda_2 \geq \ldots \geq \lambda_k \geq 0 > \lambda_{k+1} \geq \ldots \geq \lambda_n$. By Sylvester's inertia theorem PF has eigenvalues $\mu_1 \geq \mu_2 \geq \ldots \geq \mu_k \geq 0 > \mu_{k+1} \geq \ldots \geq \mu_n$. By Perron's theorem $\mu_1 > -\mu_n$.

Of course $\mu_1 = p^*Fp$. Thus J has the eigenvalues $\mu_2 \geqq \ldots \geqq \mu_k \geqq 0 > \mu_{k+1} \geqq \ldots \geqq \mu_n > -\mu_1$. Since $-\mu_1$ is the eigenvalue corresponding to the eigenvector e^*, the polymorphism is exponentially stable iff F has n-1 negative eigenvalues. We return to this property in Section 5.

The classical model does not include mutation. Let $\Gamma = (\gamma_{jk})$ be a column stochastic matrix of mutation rates: γ_{jk} is the probability that the allele a_k mutates into a_j. Then Fisher's equation assumes the form

$$\dot{p} = \Gamma PFp - W(p)p \qquad (4.4)$$

where

$$\Gamma \geqq 0, \; e^*\Gamma = e^* . \qquad (4.5)$$

From the implicit function theorem follows that non-degenerate stationary points are only slightly perturbed if $\Gamma - I$ is small. However, stationary points on the boundary of S can move outside S. Consider a situation where for $\Gamma = I$ there is an exponentially stable polymorphism p. Then p is a global attractor in the interior of S, and W(p) is strictly convex over S. From the biological interpretation one can conjecture that for $\Gamma > 0$ there is only one stationary point. In fact, at a stationary point near the boundary selection and mutation act in the same direction, the stationary point could not be maintained. In [10] this conjecture has been proved for the special case of equal mutation rates, i.e. for

$$\Gamma = (1-\gamma)I + \gamma\frac{ee^*}{n} \quad . \qquad (4.6)$$

The problem of asymptotic behavior of arbitrary solutions of equation (4.4) remains open.

5. A related problem for positive matrices

In reactor physics the following problem occurs [11] : Find an optimal distribution of fuel such that a minimal total amount of fuel leads to criticality. This problem can be formulated in terms of integral operators with positive kernels of which the following is a finite-dimensional version.

Let $A = (a_{jk})$ be a symmetric matrix with positive elements. Consider the following

Problem I: Find a positive (nonnegative, but $\neq 0$) diagonal matrix $U = (u_j \delta_{jk})$ such that the positive (non-negative) matrix UA has spectral radius 1 and such that $e^* Ue$ is minimal.

This problem is equivalent with the following

Problem II: Maximize the spectral radius $\varrho(UA)$ under the side condition $e^*Ue = 1$.

Indeed, if $\bar{U}$ is a solution to Problem II, and $\bar{\varrho} = \varrho(\bar{U}A)$, then $\bar{U}/\bar{\varrho}$ is a solution to Problem I.

Of course Problem II has a solution, because the set $U \geq 0$, $e^*Ue = 1$ is compact.
If we put $W = U^{1/2}$, $w = We$, we have

$$UA = W(WAW)W^{-1},$$

$$e^*Ue = w^*w \; .$$

Thus we can compute the optimum via the Rayleigh quotient

$$R^* = \sup_{v,w \neq 0} R(v,w), \tag{5.1}$$

where

$$R(v,w) = \frac{v^*WAWv}{v^*v\cdot w^*w} = R(w,v) \tag{5.2}$$

in view of $Wv = Vw$.

Using this symmetry, we find from

$$\frac{\partial R(v,w)}{\partial v} = \frac{2}{w^*w}\cdot\frac{1}{v^*v}\cdot[(v^*v)\,v^*WAW - (v^*WAWv)\cdot v^*]$$

the Euler equations

$$\begin{aligned} WAWv &= \frac{v^*WAWv}{v^*v}\cdot v \\ VAVw &= \frac{w^*VAVw}{w^*w}\cdot w\ . \end{aligned} \tag{5.3}$$

We can assume $v^*v = w^*w = 1$ and put

$$\lambda = v^*WAWv \quad . \tag{5.4}$$

Then the necessary conditions read

$$WAWv = \lambda v \quad , \qquad VAVw = \lambda w . \tag{5.5}$$

From these relations it follows immediately that w and v have the same pattern of zeros.

Case 1: $v > 0$, $w > 0$. Put $Wv = u$. Then $AWv = \lambda e$, thus

$$Au = \lambda e,\ u > 0,\ \lambda = u^*Au \quad .$$

Conversely, if $Ax = e$ has a solution $x > 0$ then put $u = x/e^*x$, $\lambda = u^*Au$, $v = w = U^{1/2}e$.

Case 2: $v = \binom{\bar{v}}{0}$, $w = \binom{\bar{w}}{0}$, where $\bar{v} > 0$, $\bar{w} > 0$ have the same dimension. Then one obtains a similar problem for a submatrix of A.

Thus the global maximum has to be sought among the solutions of the equation

$$Au = U^*Au \cdot u \ . \tag{5.6}$$

This equation is identical with the condition (3.12) for stationary points in the population genetic model. It is clear from Section 4 that if equation (5.6) has a positive solution then it is the unique global maximum iff the matrix A has n-1 negative eigenvalues.

6. Fertility depending on mating

In contrast to Fisher's model one can assume that fitness or fertility is not a property of a single genotype but rather depends on the mating pair.

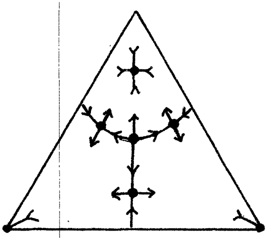
Such models have been constructed by W. Bodmer and others (see [12]). The simplest situation arises for two alleles. Then there are three genotypes $x_1 = a_1a_1$, $x_2 = a_1a_2$, and $x_3 = a_3a_3$. To the mating x_ix_j we attribute the fertility $f_{jk} = f_{kj} > 0$. If x_j describes the fertility of the corresponding genotype, then, under the random mating hypothesis, the functions x_j satisfy the following set of differential equations ([12]).

$$\begin{aligned}
\dot{x}_1 &= f_{11}x_1^2 + f_{12}x_1x_2 + \tfrac{1}{4}f_{22}x_2^2 - \Phi x_1 \\
\dot{x}_2 &= f_{21}x_1x_2 + 2f_{13}x_1x_3 + \tfrac{1}{2}f_{22}x_2^2 + f_{23}x_2x_3 - \Phi x_2 \\
\dot{x}_3 &= \tfrac{1}{4}f_{22}x_2^2 + f_{32}x_3x_2 + f_{33}x_3^2 - \Phi x_3
\end{aligned} \tag{6.1}$$

where

$$\Phi(x) = \sum_{j,k=1}^{3} f_{jk}x_jx_k \ . \tag{6.2}$$

These equations represent just another normalized quadratic system. It bears much similarity to Fisher's model for <u>three</u> alleles. In fact, for some degenerate cases the two models coincide. On the other hand, the system (6.1) seems more difficult, in general the function Φ is not a Lyapunov function; a Lyapunov function is not known. The Fisher model for three alleles has in general seven stationary points: one in the interior and six on the boundary. In the present model only $x_1 = 1$ and $x_3 = 1$ can occur as stationary states on the boundary. In any other state a missing type is immediately replaced by Mendelean segregation. Hence in general we expect five stationary points in the interior of the state simplex and a rather complicated dynamics. In [12] the stationary states and their stability have been investigated for some restricted part of the parameter space. A typical example is given in the figure



We see that there are three basins, which are the domains of attraction of the two pure (homozygotic) states $x_1 = 1$ and $x_2 = 1$ and of a polymorphism with $0 < x_1 = x_3 < 1/2$. The question of convergence to equilibrium has been left open.

In [13] Butler, Freedman and Waltman have approached the convergence problem via Dulac's criterion. Their results cover a large portion of the parameter set, but they are not exhausting.

In the following we review several approaches to the convergence problem and to the problem of periodic orbits.

7. Exclusion of periodic orbits, copositive matrices

1) Consider a vector field $f: R^n \to R^n$ and the corresponding autonomous differential equation

$$\dot{x} = f(x). \tag{7.1}$$

Are there any periodic orbits? A useful approach to that problem is computing the divergence

$$\operatorname{div} f = \operatorname{tr} f'(x), \tag{7.2}$$

where f' denotes the Frechet derivative. Suppose a nontrivial periodic solution $\bar{x}$ with period $\omega > 0$ exists. Then we can integrate

$$\dot{X}(t) = f'(\bar{x}(t))X(t) \ , \quad X(0) = I \tag{7.3}$$

from 0 to ω to find the linearized Poincaré map. The eigenvalues of the corresponding matrix $X(\omega)$ are the characteristic multipliers. The Wronskian $w(t)$ satisfies the differential equation

$$\dot{w}(t) = \operatorname{tr} f'(\bar{x}(t))w(t) \tag{7.4}$$

thus

$$w(\omega) = \exp \int_0^\omega \operatorname{tr} f'(\bar{x}(t))dt. \tag{7.5}$$

If the periodic orbit is completely contained in some domain $\Omega \subset R^n$ such that

$$\operatorname{div} f(x) > 0 \text{ in } \Omega \tag{7.6}$$

then it follows $w(\omega) > 1$. Hence there is at least one characteristic multiplier which exceeds 1 in modulus: The periodic orbit is unstable. Equivalently: A domain Ω with the property (7.6) cannot contain a stable periodic orbit.

For dimension $n = 2$ the negative criterion of Bendixson leads to a sharper result: Suppose for $n = 2$ there is any nontrivial periodic solution. Suppose the trajectory is contained in some simply connected domain Ω, where condition (7.6) holds. Then from Gauss' theorem follows immediately a contradiction.

Similarly, if $\Omega \subset R^2$ is simply connected, and

$$\operatorname{div} f(x) < 0 \text{ in } \Omega \tag{7.7}$$

then Ω does not contain a periodic orbit.

This Bendixson criterion can be extended in several ways

1. For any n one can multiply the vector field f by a nonvanishing scalar field g, which amounts to a time scaling along trajectories. Since in general $\operatorname{div}(gf) = \operatorname{grad} g \cdot f + g \cdot \operatorname{div} f \neq \operatorname{div} f$ one obtains a whole family of criteria (Dulac's criterion).
2. It can be allowed that div f vanishes in isolated points.
3. For $n = 2$ the criterion can be extended to k-fold connected domains [14].

The application of Dulac's criterion to "quadratic" differential equations of the type (6.1) can be somewhat systematized. Let the differential equations

$$\dot{y} = f(y) \quad , \qquad y \geq 0$$

$$f_i(y) = \sum b_{ijk} y_j y_k$$

describe the interaction of some species, and let

$$x = y/e^* y$$

represent the relative frequencies. Then x satisfies the equation

$$\dot{x} = g(x) - e^T g(x) x.$$

One can easily check that the function

$$D(x) = e^* x \cdot \mathrm{tr}\, g'(x) - e^* g'(x) - (n-1) e^* g(x)$$

coincides with the divergence of the vector field on the state space S. D(x) is a quadratic form with the explicit representation

$$D(x) = \sum_{j,k} a_{jk} x_j x_k \tag{7.8}$$

$$a_{jk} = \sum_{i=1}^{n} (b_{iji} + b_{iik} - (n+1) b_{ijk}) \ .$$

Thus the divergence of f is positive on S if the quadratic form D is positive on the cone of nonnegative vectors in R^n, i. e. if the matrix $A = (a_{jk})$ is a so-called copositive matrix.

A matrix A is copositive if the quadratic form x^*Ax is nonnegative on the cone of nonnegative vectors $x \geqq 0$. The notion of copositivity has been introduced by Motzkin 1952. In the space of real symmetric matrices of dimension n the copositive matrices form a closed convex cone C. This cone contains the cone S of positively semidefinite matrices and the cone P of matrices with nonnegative elements. For $n \geqq 5$ $C \neq P + S$. Several criteria for copositiveness are known [18], usually expressed in terms of eigenvalues / eigenvectors or minors. In particular a matrix A of order 2 is copositive if

1. $a_{11} \geqq 0$, $a_{22} \geqq 0$
2. $a_{12} \geqq 0$ or $\det A \geqq 0$, (7.9)

and a matrix of order 3 is copositive if for i,j = 1,2,3

1. $a_{ii} \geqq 0$
2. $a_{ij} \geqq -\sqrt{a_{ii}a_{jj}}$ (7.10)
3. $a_{12}\sqrt{a_{33}} + a_{23}\sqrt{a_{11}} + a_{31}\sqrt{a_{22}} \geqq 0$
   or $\det A \geqq 0$.

Observe that the case n = 3 applies to the case where S is a planar triangle.

8. Quasimonotone systems

Application of Dulac's criterion to the example (6.1) does not lead to a complete result.
We introduce the transformation of coordinates

$$u = \frac{x_1}{x_2} \quad , \quad v = \frac{x_3}{x_2} \quad , \quad t = \int_o^{\tilde{t}} x_2(s)ds$$

which carries the system into

$$\begin{aligned} \dot{u} &= f_{11}u^2+f_{12}u+\tfrac{1}{2}f_{22}-f_{21}u^2-2f_{13}u^2v-\tfrac{1}{2}f_{22}u-f_{23}uv \\ \dot{v} &= f_{33}v^2+f_{32}v+\tfrac{1}{2}f_{22}-f_{12}uv-2f_{31}v^2u-\tfrac{1}{2}f_{22}v-f_{23}v^2 \ . \end{aligned} \qquad (8.1)$$

We observe that (8.1) with $t \to -t$ is a quasimonotone system of differential equations. A system

$$\dot{x} = f(x)$$

is called quasimonotone if at each point x the Jacobian $A(x) = f'(x) = (a_{jk}(x))$ has non-negative off-diagonal entries. This condition is equivalent to the property that $\exp(tA) \geq 0$ for all $t \geq 0$. Quasimonotone systems have been introduced by M. Müller [16] and Kamke [17] and since then have found widespread applications to estimates.

From a rather simple argument follows [15] that a quasimonotone system in R^n, $n \geq 2$ cannot have any exponentially stable limit cycles. In R^2 there cannot be any limit cycles at all. Furthermore, in R^2 every trajectory for $t \to \pm\infty$ converges to a point or goes to infinity. This result has also applications to so called competition models in ecology. More detailed results for $n \geqslant 3$ have been obtained in [19].

9. Selection in periodic environments

For n = 2 in the models (3.6) and (3.7) the frequency p_2 can be eliminated by putting $p_1 = p$, $p_2 = 1-p$. Then the equations assume the form

$$u_{t+1} = g(u_t) \tag{9.1}$$

$$\dot{u} = f(u) \quad , \tag{9.2}$$

where, with $f_{11} = \sigma$, $f_{12} = \varrho$, $f_{22} = \tau$, $\varrho - \tau = a$, $\varrho - \sigma = b$,

$$g(u) = \frac{\sigma u^2 + \varrho u(1-u)}{\sigma u^2 + 2\varrho u(1-u) + \tau(1-u)^2} \tag{9.3}$$

$$f(u) = u(1-u)(a-(a+b)u) \quad . \tag{9.4}$$

There are essentially four cases: For $\varrho > \sigma, \tau$ (heterozygotes superior) there is a stable polymorphism, and the pure states are instable. If $\varrho < \sigma, \tau$ (heterozygotes inferior) the polymorphism is unstable, every solution except the polymorphism converges to one of the pure states. For $\sigma > \varrho > \tau$ (or $\sigma < \varrho < \tau$, heterozygotes intermediate) there is no polymorphism, every solution except p = 0 converges to p = 1 (or conversely).

Both models have been studied in deterministically or stochastically changing environments. In the following we consider some simple deterministic cases. Suppose in the discrete case there are two alternating environments $(\sigma_1, \varrho_1, \tau_1)$ and $(\sigma_2, \varrho_2, \tau_2)$ defining functions g_1 and g_2, respectively. Then the variable p satisfies

$$\begin{aligned} u_{2k+1} &= g_1(u_{2k}) \\ u_{2k+2} &= g_2(u_{2k+1}) \;. \end{aligned} \tag{9.5}$$

Essentially the behavior of the population is governed by the function $g = g_2 \circ g_1$.
One would conjecture that a stable polymorphism is maintained also in a periodic environment: However, one can show [20]: For any given σ_1, ρ_1, τ_1 with $\sigma_1 < \sigma_1 < \rho_1$ there is a parameter set σ_2, ρ_2, τ_2 with $\sigma_2 < \tau_2 < \rho_2$ such that the function $g_2 \circ g_1$ has three fixed points in $(0,1)$. Of course these fixed points correspond to two attractors separated by a repeller. Thus in a discrete time model with periodic environment it is quite natural that a polymorphism bifurcates.
In the case of continuous time a seasonally changing environment corresponds to periodic coefficients $a(t+1)=a(t)$, $b(t+1)=b(t)$. One can easily prove ([20]): If $\int_0^1 a(t)dt > 0$, $\int_0^1 b(t)dt > 0$ then there is a nonconstant periodic solution with values in $(0,1)$. If $a(t) + b(t) > 0$ for all t then there is at most one such solution. Of course this problem is a special case of the question how many periodic solutions a differential equation

$$\dot{u}(t) = \sum_{j=0}^{n} c_j(t) u^j, \qquad c_j(t+1) = c_j(t)$$

can have (see [21]).

10. Travelling fronts

The equation (9.2) (9.3)

$$\dot{u} = u(1-u)(a-(a+b)u) \tag{10.1}$$

with constant a,b in the cases of intermediate or of inferior homozygotes is a special case of an equation

$$\dot{u} = f(u) \tag{10.2}$$

where $f \in C^1\,[0,1]$, $f(0) = f(1) = 0$, and either

I) $f(u) > 0$ for $0 < u < 1$, $f'(0) > 0$, $f'(1) < 0$

or, for some $\alpha \in (0,1)$,

II) $f(u) < 0$ for $0 < u < \alpha$, $f(u) > 0$ for $\alpha < u < 1$,
$f'(0) < 0$, $f'(1) < 0$.

Of course one can realize more general equations than (10.1) as population genetic models if one introduces density-dependent selection coefficients.
Now we consider equation in a one-dimensional habitat with density dependent capacity and diffusion rate,

$$u_t = \frac{1}{m(u)}(k(u)u_x)_x + f(u) \; . \tag{10.3}$$

Here the subscripts x and t stand for partial derivatives with respect to space and time.

Suppose equation (10.3) has a solution in the form of a travelling front

$$u(x,t) = \Phi(x-ct) \tag{10.4}$$

where

$$\begin{gathered} 0 \leq \Phi(x) \leq 1 \\ \Phi(-\infty) = 1, \; \Phi(+\infty) = 0 \; . \end{gathered} \tag{10.5}$$

Then the function of one variable Φ satisfies the ordinary differential equation

$$\frac{1}{m(\Phi)}\,(k(\Phi)\Phi')' + c\Phi' + f(\Phi) = 0 \qquad (10.6)$$

or, equivalently, the first order system

$$\begin{aligned} u' &= v \\ v' &= -\frac{k'(u)}{k(u)}\,v^2 - c\,\frac{m(u)}{k(u)}v - \frac{m(u)}{k(u)}f(u) \quad . \end{aligned} \qquad (10.7)$$

With the function

$$h(u) = \frac{1}{\varkappa}\int_0^u m(s)ds, \qquad \varkappa = \int_0^1 m(s)ds \qquad (10.8)$$

one can substitute

$$\tilde{u} = h(u), \quad \tilde{v} = \frac{1}{\varkappa}k(u)v \qquad (10.9)$$

$$\tilde{f}(\tilde{u}) = \frac{1}{\varkappa}f(h^{-1}(\tilde{u}))k(h^{-1}(\tilde{u})) \qquad (10.10)$$

$$\tau = \int_0^t \frac{m(u(s))}{k(u(s))}\,ds \qquad (10.11)$$

and obtain

$$\begin{aligned} \frac{d\tilde{u}}{d\tau} &= \tilde{v} \\ \frac{d\tilde{v}}{d\tau} &= -\,c\tilde{v} - \tilde{f}(\tilde{u}) \end{aligned} \qquad (10.12)$$

i.e. one can reduce the general case to the case $m(u) = 1$, $k(u) = 1$. Of course such a reduction is not possible for the partial differential equation. The type of the equation (I or II above) is not changed by the transformation.

In Case I there is a half-line $[c_0,\infty)$ of possible speeds with $c_0 = 2\sqrt{\tilde{f}'(0)}$. The minimal speed can be characterized by two variational principles

$$c_0 = \inf_g \sup_u \left\{ g'(u) + \frac{\tilde{f}(u)}{g(u)} \right\}$$

where $g \in C^1[0,1]$, $g(u) > 0$ in $(0,1)$, $g(0) = 0$, $g'(0) > 0$.

$$c_0 = \sup_g \inf_u \; \inf \left\{ g'(u) + \frac{\tilde{f}(u)}{g(u)} \quad , \; 2g'(0) \right\}$$

where $g \in C^1[0,1]$, $g(u) > 0$ in $(0,1)$, $g(0) = g(1) = 0$, $g'(0)g'(1) < 0$.

In case II there is a single speed c_0,

$$c_0 = \left\{ \begin{matrix} \inf\limits_g \sup\limits_u \\ \\ \sup\limits_g \inf\limits_u \end{matrix} \right\} \left\{ g'(u) + \frac{\tilde{f}(u)}{g(u)} \right\}$$

where $g \in C^1[0,1]$, $g(u) > 0$ in $(0,1)$, $g(0) = g(1) = 0$, $g'(0)g'(1) < 0$.

It follows a continuity result [22]: The minimal speed c_0 depends continuously on the function $\tilde{f}$ with respect to the norm

$$\|f\| = \sup_{0<u<1} \frac{|f(u)|}{u(1-u)} .$$

References

1. F. Hoppensteadt, Mathematical Theories of Populations: Demographics, Genetics and Epidemics. SIAM Reg. Conf. Series, Philadelphia 1975.

2. K.P. Hadeler, K. Dietz, Nonlinear hyperbolic partial differential equations for the dynamics of parasite populations. In: M. Witten (ed.) Computers and Applied Mathematics, Special issue, Academic Press.

3. H.F. Weinberger, Invariant sets for weakly coupled parabolic and elliptic systems, Rendiconti di Matematica 8, Serie 6, 295-310 (1975).

4. K.P. Hadeler, F. Rothe, H. Vogt, Stationary solutions of reaction diffusion equations. Math. Methods in the Applied Sciences 1, 418-431 (1979).

5. F. Rothe, Solutions for systems of non-linear elliptic equations with non-linar boundary conditions, Math. Methods in the Applied Sciences 1, 545-553 (1979).

6. J.F.C. Kingman, On an inequality in partial averages, Quart. J. of Math. 12, 78-80 (1961).

7. K.P. Hadeler, Selektionsmodelle in der Populationsgenetik, Methoden und Verfahren der Mathematischen Physik 9,136-160 BI-Verlag 1973.

8. K.P. Hadeler, Mathematik für Biologen, Springer-Verlag, Berlin 1974.

9. B. Aulbach, K.P. Hadeler, Convergence to equilibrium in the classical model of population genetics, preprint 83, Math. Inst. Universität Würzburg 1982.

10. K.P. Hadeler, Stable polymorphisms in a selection model with mutation, SIAM J. Appl. Math. 41, 1-7 (1981).

11. G. Goertzel, Minimum critical mass and flat flux. J. of Reactor Science and Technology 2, 19-25 (1952).
I. Marek, Report of the Nuclear Science Institute of the Czechoslovac Academy of Science.

12. K.P. Hadeler, U. Liberman, Selection models with fertility differences, J. Math. Biol. 2, 19-32 (1975).

13. G.J. Butler, H.I. Freedman, P. Waltman, Global dynamics of a selection model for the growth of a population with genotypic fertility differences, J. Math. Biol., to appear.

14. N.G. Lloyd, A note on the number of limit cycles in certain two-dimensional systems, J. London Math. Soc. (2), 20, 277-286 (1979).

15. K.P. Hadeler, D. Glas, Quasimonotone systems and convergence to equilibrium in a population genetic model, J. Math. Anal. Appl., to appear.

16. M.Müller, Über das Fundamentaltheorem in der Theorie der gewöhnlichen Differentialgleichungen. Math.Zeitschr. 26, 619-645 (1926).

17. E.Kamke, Zur Theorie der Systeme gewöhnlicher Differentialgleichungen II, Acta Math. 58, 57-85 (1932).

18. K.P.Hadeler, On copositive matrices, Lin.Algebra and Appl., to appear.

19. M.W.Hirsch, Systems of differential equations which are competitive or cooperative I,II. Preprints Center for Pure and Applied Mathematics, University of California , Berkeley.

20. K.P.Hadeler, Selection in cyclically changing environment, Theor.Pop.Biol., in revision.

21. N.G.Lloyd, The number of periodic solutions of the equation $\dot{z} = z^N + p_1(t)z^{N-1} + \ldots + p_N(t)$, Proc.London Math.Soc. 27, 667-700(1973).

22. K.P.Hadeler, Travelling fronts and free boundary value problems, Proc.Oberwolfach Conference on Free Boundaries 1980 (J.Albrecht, L.Collatz, K.H.Hoffmann ed.) Birkhäuser Verlag 1981.

23. K.P.Hadeler,Free boundary value problems in biological models, Proc.Conference on Free Boundary Value Problems, (A.Fasano, M.Primicerio ed.), Montecatini 1981, Pitman Publisher.