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SOME RECENT DEVELOPMENTS IN THE THEORY AND APPLICATIONS OF REACTION-DIFFUSION WAVES

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Abstract. Some recent developments in the theory and applications of travelling wave solutions of parabolic equations are discussed. These results continue the works by Aizik Volpert on index and solvability conditions of elliptic problems, topological degree, spectral properties and bifurcations, wave existence and stability.

1. Reaction-diffusion waves and elliptic problems

1.1. **The beginning of the theory.** Reaction-diffusion waves, also called in the mathematical literature travelling wave solutions of parabolic equations, were first considered in the works by Michelson in combustion theory [44] and by Luther on chemical waves [40]. More widely known are the works by Fisher [25] and Kolmogorov-Petrovskii-Piskunov (KPP) [38] devoted to the propagation of dominant gene, and by Zeldovich-Frank-Kamenetskii [80], again in combustion, with which the beginning of the theory is often associated. The theory of reaction-diffusion waves had a spectacular development in the 1950s-1980s in relation with the applications in chemical physics, population dynamics, excitable media. More recently, biomedical applications of reaction-diffusion waves, such as tumor growth, blood coagulation, waves in the brain tissue, attracted much attention (see the literature review in [64, 75]).

The mathematical properties of reaction-diffusion waves were first studied in the KPP paper. The authors proved the wave existence, which is quite straightforward in the case of the scalar equation, and convergence of the solution of the Cauchy problem to travelling waves. This result is far from being obvious, and they developed a special method, which can be called comparison of solutions on the phase plane, in order to prove it. This work has initiated numerous studies of the existence and stability of travelling waves described by the scalar equation and by systems of equations (see [64, 75] and the references therein).

1.2. **Mathematical setting.** Consider the reaction-diffusion system of equations

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + F(u), \tag{1.1}$$

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where $u = (u_1, ..., u_n)$, $F = (F_1, ..., F_n)$, D is a diagonal matrix with positive diagonal elements. We consider this system on the whole axis, $x \in \mathbb{R}$, and suppose that the vector-valued function $F(u)$ is sufficiently smooth.

Travelling wave solution of this equation is a solution of the form $u(x,t) = w(x - ct)$, where c is a constant, the wave speed. The function $w(\xi)$ satisfies the equation

$$Dw'' + cw' + F(w) = 0 \tag{1.2}$$

and some limits at infinity

$$w(\pm\infty) = w_\pm, \tag{1.3}$$

where $F(w_\pm) = 0$. Travelling waves oscillating at infinity can also be considered. Since the wave speed c is unknown, the problem of wave existence is formulated as follows: find the value of c for which problem (1.2), (1.3) has a solution.

The existence and the properties of travelling wave solutions depends on the stability of the points $w_\pm$ as stationary solutions of the ODE system

$$\frac{du}{dt} = F(u). \tag{1.4}$$

If all eigenvalues of the matrices $F'(w_\pm)$ lie in the left-half plane of the complex plane, that is, the corresponding solutions of equation (1.4) are stable, then this is the bistable case. If one of the matrices has an eigenvalue with a positive real part and another one is still stable, then this is the monostable case. In this bistable case, the set of solutions of problem (1.2), (1.3) is, in general, discrete, while in the monostable case there can exist continuous families of solutions for which the values of c fill an interval or a half-axis. These different properties of solutions are related to the location of the essential spectrum of the corresponding operator and to its index.

1.3. **Fredholm property for elliptic problems in unbounded domains.** Thus, reaction-diffusion waves are described by the second-order ordinary differential system of equations (1.2) or, in the multidimensional setting, by elliptic problems in unbounded domains. Hence, we need to discuss some properties of the corresponding operators.

Let us recall that a linear operator $L : E_1 \to E_2$, acting in some Banach spaces E_1 and E_2, satisfies the Fredholm property if it is normally solvable, its kernel has a finite dimension and the codimension of its image is also finite. Then the non-homogeneous equation $Lu = f$ is solvable if and only if $\phi_i(f) = 0$ for a finite number of functionals ϕ_i from the dual space E_2^*. In some case, these solvability conditions can be replaced by the orthogonality to the solutions of the homogeneous formally adjoint equations.

Fredholm property, solvability conditions, and the index of linear operators are often used in the methods of linear and nonlinear analysis including the topological degree theory. General elliptic problems in bounded domains with a sufficiently smooth boundary satisfy the Fredholm property if and only if the ellipticity condition, the condition of proper ellipticity and the Lopatinskii conditions are satisfied

[1, 2, 54]. In the case of unbounded domains, these conditions may not be sufficient. One more condition, formulated in terms of limiting operators should be imposed. In order to introduce this condition, let us consider an example of the scalar second-order operator

$$Lu = a(x)u'' + b(x)u' + c(x)u \tag{1.5}$$

acting from the Hölder space $C^{2+\alpha}(\mathbb{R})$ to the space $C^{\alpha}(\mathbb{R})$. Assuming, for simplicity, that the coefficients of the operator have limits at infinity,

$$a_\pm = \lim_{x\to\pm\infty} a(x), \;\; b_\pm = \lim_{x\to\pm\infty} b(x), \;\; c_\pm = \lim_{x\to\pm\infty} c(x),$$

we can introduce the limiting operators

$$\hat{L}_\pm u = a_\pm u'' + b_\pm u' + c_\pm u.$$

Applying the Fourier transform, we find the essential spectrum of the operator L,

$$\lambda(\xi) = -a_\pm \xi^2 + b_\pm i\xi + c_\pm, \quad \xi \in \mathbb{R}, \tag{1.6}$$

that is, the set of complex numbers λ for which the operator $L-\lambda$ does not satisfy the Fredholm property. Hence, this property is satisfied if and only if the curves (1.6) do not cross the origin. In the general case, the definition of limiting operators is more involved [46, 47, 49, 63, 74]. The Fredholm property of general elliptic problems in unbounded domains requires an additional condition that all limiting problems should be invertible.

1.4. **Index.** Elliptic boundary value problems in the plane can be studied by reduction to singular integral equations in one space dimension. This method was developed by I.N. Vekua for certain classes of elliptic problems [51, 52, 53]. It allowed him to prove normal solvability of boundary value problems and to find their index. Further development of these works was due to A.I. Volpert [55, 56, 57]. He used fundamental matrices of elliptic systems of equations constructed by Ya.B. Lopatinskii. In [58] normal solvability was proved and the index was computed for general first-order systems and in [59] for general higher-order systems in the plane. The Dirichlet problem for elliptic systems was studied in [58]. It was shown that the index of this problem can be equal to an arbitrary even number and a formula for the index was given. It was proved that the index is a homotopy invariant and the formula for the index was obtained in terms of this invariant [57].

For the unbounded domains, even the simplest scalar second-order operator (1.5) can have nonzero index [14]. Typically, in the bistable case, where the essential spectrum (1.6) lies in the left-half plane, the index equals 0. In the monostable case, where a part of the spectrum is in the right-half plane, it equals 1. Location of the essential spectrum and the value of the index are used in the construction of the topological degree.

1.5. **Properness and topological degree.** Topological degree for elliptic operators was introduced by Leray and Schauder [39] by the reduction to the operator $I + K$, where I is the identity operator and K is a compact operator. This construction is not applicable to unbounded domains since, contrary to the bounded domains, the inverse to the Laplace operator is not compact. There are various degree constructions in abstract setting [13, 19, 20, 22], [26]-[30] and in the framework of elliptic problems [15, 60, 76, 77]. We will use the degree construction for Fredholm and proper operators with the zero index [78].

An operator $A(u) : E_1 \to E_2$ (possibly nonlinear) is called proper if an inverse image $A^{-1}(G)$ of any compact set $G \subset E_2$ is compact in any bounded closed set $B \subset E_1$. This property implies, in particular, that the set of solution of the operator equation $A(u) = 0$ is compact in any bounded closed set B.

It appears that elliptic problems in unbounded domains may not be proper. We illustrate it with the following example. Consider scalar equation (1.2) with $c = 0$. Assume, further, that $F(0) = F(1) = 0$, $F(w) < 0$ for $0 < w < w_0$, and $F(w) > 0$ for $w_0 < w < 1$. Then this equation has a positive solution with zero limits at infinity if and only $\int_0^1 F(u) > 0$. This solution can be explicitly constructed. If this condition is satisfied, and there exists a solution $w(x)$, then the functions $w(x + h)$ are also solutions for any real h. Therefore, the set of solutions can be bounded in Hölder or Sobolev spaces but it is not compact. The lack of properness does not allow the construction of the topological degree. Moreover, this is not only a technical restriction. There are counterexamples which show that the properties of the degree may not hold.

It appears that general elliptic problems become proper in some appropriate weighted spaces [76, 63] (see also [48]), and the degree construction for Fredholm and proper operators with the zero index becomes applicable in this case [78].

2. Monotone and locally monotone systems

2.1. **Existence of solutions.** The topological degree constructed for Fredholm and proper operators with the zero index can be used to prove the existence of waves in the bistable case for some classes of systems. Let us recall that if the inequalities

$$\frac{\partial F_i}{\partial u_j} > 0, \quad i, j = 1, ..., n, \ \ i \neq j \tag{2.1}$$

hold for all $u \in \mathbb{R}^n$ (or in some domain in $\mathbb{R}^n$ containing the solutions), then systems (1.1) and (1.2) are called monotone systems. If these inequalities are satisfied only at the surfaces $F_i(u) = 0$, then such systems are called locally monotone [60, 75]. Non-strict inequalities in (2.1) can also be considered. Similar to the scalar equation, the monotone systems satisfy the maximum principle and positiveness (comparison) theorems. This is not the case of the locally monotone systems.

2.1.1. *Function spaces and operators.* We consider the Hölder space $C^{k+\alpha}(\mathbb{R})$ consisting of vector-functions of class C^k, which are continuous and bounded on $\mathbb{R}$ together with their derivatives of order k, and such that the derivatives of order k satisfy the Hölder condition with the exponent $\alpha \in (0, 1)$. The norm in this space is the usual Hölder norm. Set $E^1 = C^{2+\alpha}(\mathbb{R})$, $E^2 = C^\alpha(\mathbb{R})$. Next, we introduce the weighted spaces E^1_μ and E^2_μ with $\mu(x) = \sqrt{1+x^2}$. These spaces are equipped with the norms:

$$\|w\|_{E^i_\mu} = \|w\mu\|_{E^i}, \quad i = 1, 2.$$

We introduce the operators which will allow us to study travelling waves, that is, solutions of problem (1.2), (1.3). Consider an infinitely differentiable vector-function $\eta(x)$ such that

$$\eta(x) = \begin{cases} w_- & , \quad x \le -1 \\ w_+ & , \quad x \ge 1 \end{cases} ,$$

where $w_\pm = (v_\pm, c_\pm)$. Set $w = u + \eta$ and consider the operator

$$A_\tau(u) = D(u+\eta)'' + c_\tau(u+\eta)' + F_\tau(u+\eta), \tag{2.2}$$

acting from E^1_μ into E^2_μ. The operator depends on a parameter $\tau \in [0,1]$ providing homotopy in the Leray-Schauder method.

2.1.2. *Leray-Schauder method on subclasses of solutions.* In order to apply the Leray-Schauder method, we need to obtain a priori estimates of solutions. In the case of monotoneand locally monotone systems, they can be obtained for some subset of solutions but not for all solutions. Thus, we will consider two types of solutions, monotone solutions of problem (1.2), (1.3) and non-monotone solutions. By monotone solutions, we understand vector-valued functions $w_m(x)$ all components of which are monotonically decreasing functions of x. Non-monotone solutions $w_n(x)$ do not satisfy this property. Suppose that the following two conditions hold:

1. Separation of monotone solutions. There exists a positive number r such that

$$\|w_m - w_n\|_{E^1_\mu} \ge r \tag{2.3}$$

for any monotone solution w_m and non-monotone solution w_n (possibly for different τ),

2. A priori estimates of monotone solutions. There exists a positive number R such that

$$\|u_m\|_{E^1_\mu} \le R \tag{2.4}$$

for any monotone solution $w_m = u_m + \eta$.

In these conditions are satisfied, then we can apply the Leray-Schauder method only for monotone solutions [60, 75]. Both properties can be proved for monotone and locally monotone systems. Separation of monotone solutions was first used in [33] to prove the existence of waves for a monotone system of two equations by a continuation method.

2.1.3. *Existence of waves.* The wave existence result in the bistable case is given by the following theorem.

Theorem 2.1. *Suppose that system (1.2) is locally monotone, the matrices $F'(w_\pm)$ have all eigenvalues in the left-half plane, and for any other zero w_0 of the function $F(w)$ such that $w_+ \le w_0 \le w_-$ (the inequalities between the vectors are understood component-wise), the matrix $F'(w_0)$ has an eigenvalue with a positive real part. Then problem (1.2), (1.3) has a monotonically decreasing solution for some value of c. If the system is monotone, then this value of c is unique.*

In the monostable case, under the assumption that there are no stable zeros of the function F except for w_+, it is proved that the waves exist for all values of the speed greater than or equal to the minimal speed.

If there are other stable points, then similar to the scalar equation [23, 24, 61, 62], the wave may not exist. In this case, there are systems of waves propagating one after another with different speeds [68].

2.2. **Stability of waves and instability pulses.**

2.2.1. *Spectral properties.* Consider the scalar operator L given by (1.5). Suppose that its essential spectrum (1.6) lies in the left-half plane of the complex plane, and that it has some eigenvalues with non-negative real parts. Then its eigenvalue with the maximal real part (principal eigenvalue) is real, simple, and the corresponding eigenfunction is positive [71]. Moreover, there are no other positive eigenfunctions. These spectral properties generalize the Krein-Rutman theorem for elliptic operators in unbounded domains. They remain valid for more general multi-dimensional operators and for the operators in the case of monotone systems.

2.2.2. *Stability of monotone waves.* Suppose that problem (1.2), (1.3) has a monotonically decreasing (component-wise) solution $w(x)$. Consider the operator linearized about this solution:

$$Lu = Du'' + cu' + F'(w(x))u.$$

It has the zero eigenvalue with the corresponding eigenfunction $w'(x)$. Since $w'(x) < 0$, then, up to multiplication by -1 this eigenfunction is positive.

If the function $F(w)$ satisfies the monotonicity condition (2.1), then in the bistable case the essential spectrum lies in the left-half plane. Therefore, from the spectral properties presented in the previous section it follows that 0 is the principle eigenvalue, and all other spectrum lies in the left-half-plane. Hence, monotone travelling waves of monotone systems are asymptotically stable with shift with respect to small perturbations [69, 71]. It is also proved that they are globally stable. In the monostable case, stability of waves with the speed greater than the minimal speed holds in some weighted norm [70].

2.2.3. *Minimax representation of the wave speed.* Global stability of monotone waves for the monotone systems allows the derivation of the minimax representation of the wave speed in the bistable case:

$$c = \inf_{\rho} \sup_{x,i} \Phi_i(\rho) = \sup_{\rho} \inf_{x,i} \Phi_i(\rho), \tag{2.5}$$

where

$$\Phi_i(\rho) = \frac{\rho'' + F_i(\rho)}{-\rho_i'} \ ,$$

$\rho(x)$ is a monotonically decreasing (component-wise) vector-function continuous together with its second derivative, and having the limits $\rho(\pm\infty) = w_{\pm}$.

This minimax representation is used to obtain the estimates and the asymptotics of the wave speed [75]. In the monostable case, only the first equality in (2.5) holds for the minimal wave speed, since the maximal speed in infinite. Its derivation does not require the stability results. The minimax representation is generalized for the nonlocal models [17].

2.2.4. *Instability of pulses.* If equation (1.1) has a positive stationary solution $w(x)$ with zero limits at infinity, then the eigenfunction $w'(x)$ of the operator L (with $c = 0$) is of a variable sign. Therefore, $\lambda = 0$ is not the principal eigenvalue of this operator. Hence, the principal eigenvalue is positive, and the stationary solution is not stable. Similarly, non-monotone waves of the monotone systems (and of the scalar equation) are unstable.

If we consider the Cauchy problem for equation (1.1) with the initial condition $u(x, 0) = w(x) + \phi(x)$, where $w(x)$ is the pulse solution and $\phi(x)$ is a small perturbation, then the solution $u(x, t)$ uniformly converges to 0 for negative $\phi(x)$, and it locally converges to w_- for positive $\phi(x)$. In the latter case, the solution forms two travelling waves propagating in the opposite directions. In the scalar case, the convergence to such waves is proved, while for the monotone systems of equations it is observed numerically.

Thus, the pulse solution separates two classes of initial conditions with different behavior of solutions of the Cauchy problem. This property is important for various applications in biomedical problems. In the case of blood coagulation, we obtain two conditions of clot growth. The first one is the existence of the pulse solution which is equivalent to the positiveness of the wave speed [31]. The second one is that the initial condition should be sufficiently large (compared to the pulse) in order to provide growth of solution and not its decay. The value of the wave speed can be approximated in this case using the minimax representation [32].

2.2.5. *Stability of pulses in nonlocal equations.* Instead of equation (1.1) consider now the scalar equation

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + au^2(1 - I(u)) - bu, \tag{2.6}$$

where $I(u) = \int_{-\infty}^{\infty} u(x, t)dx$. Such problems arise in population dynamics with global consumption of resources [64]. The existence of two pulses can be easily proved here. Numerical simulations show that one of them is stable [65] (see also the next section).

3. New models and results

3.1. **Existence of pulses.**

3.1.1. *Scalar equation.* Let us recall that positive stationary solutions of equation (1.1) with zero limits at infinity are called pulses. These are solutions of problem (1.2), (1.3) with $c = 0$ and $w_\pm = 0$. Existence of such solutions can be easily studied for the scalar equation. We will use this existence result below for the systems of equations. Suppose that $F(0) = F(1) = 0$,

$$F(w) < 0 \text{ for } 0 < w < w_0; \quad F(w) > 0 \text{ for } w_0 < w < 1 \tag{3.1}$$

for some $w_0 \in (0, 1)$. Then the problem

$$w'' + F(w) = 0, \quad w(\pm\infty) = 0 \tag{3.2}$$

$(D = 1)$ has a positive solution if and only if

$$\int_0^1 F(u)du > 0. \tag{3.3}$$

On the other hand, the wave speed in equation (1.2) is positive if and only if condition (3.3) is satisfied. Indeed, it is sufficient to multiply this equation by w' and integrate from $-\infty$ to ∞. Hence, a pulse solution exists if and only if the wave speed is positive. This formulation is convenient since it does not use condition (3.3). The latter is not applicable for the systems of equations but the result on the existence of pulses formulated in terms of the wave speed remains valid.

3.1.2. *Systems of equations.* Consider now the system of equations

$$w'' + F(w) = 0, \tag{3.4}$$

where $w = (w_1, w_2)$, $F = (F_1, F_2)$,

$$F_1(w) = f_1(w_2) - w_1, \quad F_2(w) = f_2(w_1) - w_2.$$

This is a model problem describing various biomedical applications (e.g., chronic inflammation [18]). Suppose that the functions $f_i(u), i = 1, 2$ are sufficiently smooth, monotonically increasing, $f_i(0) = f_i(1) = 0$. Set $w_+ = (0, 0), w_- = (1, 1)$ and assume that the matrices $F'(w_\pm)$ have negative eigenvalues. Moreover, there exists a unique point $w^0, w_+ < w^0 < w_-$ (the inequalities are understood component-wise) such that $F(w^0) = 0$. We suppose that the matrix $F'(w^0)$ has a positive eigenvalue.

System (3.4) satisfies condition (2.1). Therefore, there exists a unique up to translation solution of problem (1.2), (1.3). We can now formulate the result on the existence of pulses.

Theorem 3.1. *Under the conditions on the function $F(w)$ formulated above, a pulse solution of system (3.4) exists if and only if the wave speed in problem (1.2), (1.3) is positive.*

Contrary to the scalar equation, the proof of this theorem is quite involved [42]. The sufficiency part of the proof uses the Leray-Schauder method with the technique presented in the previous section and adapted to this type of solutions. The necessity is based on the comparison of solutions applicable for the monotone systems. This result was generalized in [43] and applied for the system of competition of species. Existence of pulses for the reaction-diffusion system describing blood coagulation was studied in [31, 45], and for the nonlocal equations in [21, 79].

3.1.3. *One stable point.* Let us return to the scalar equation in order to present another case of pulse existence. Instead of conditions (3.1) we now suppose that $F(w) > 0$ for all $w > w_0$, and $\underline{\lim}_{w\to\infty} F(w) > 0$. Then it can be easily verified that problem (3.2) always has a positive solution. Condition (3.3) is not imposed here. Thus, there are two different cases. In the first one, there are two stable points, and pulse existence is determined by the speed of the wave between them. In the second case, there is only one stable point, the bistable wave does not exist, and the pulse exists without additional conditions.

Consider system (3.4) where

$$F_1(w) = w_1w_2 - k_1w_1\ , \quad F_2(w) = w_1w_2 - k_2w_2, \tag{3.5}$$

k_1 and k_2 are some positive constants. Such problems arise in population dynamics [67]. This is a vector analogue of the situation described above for the scalar equation. There are two zeros of the function $F(w)$, $w_+ = (0, 0)$ and $w^0 = (k_2, k_1)$.

Theorem 3.2. *System (3.4) with functions (3.5) has a pulse solution for any positive constants k_1 and k_2.*

The proof of this theorem uses the Leray-Schauder method with the separation of monotone (on the half-axis) solutions [67]. This result has an interesting application to the integro-differential equation, where the functions $F_i(w)$ are replaced by the expressions

$$F_1(w, I) = w_1w_2(1 - aI_1 - bI_2) - k_1w_1\ , \quad F_2(w, I) = w_1w_2(1 - cI_1 - dI_2) - k_2w_2\ ,$$

where $I = (I_1, I_2)$, $I_i = \int_{-\infty}^{\infty} w_i(x)dx$. In population dynamics such models describe global consumption of resources. The existence of pulses follows from Theorem 3.2. Contrary to the reaction-diffusion system with functions (3.5), in this case, the pulse solution can be stable.

3.2. **Nonlocal and delay equations.**

3.2.1. *Nonlocal equations.* Nonlocal reaction-diffusion equations are studied in relation with various applications in population dynamics. Some of them were presented above. Consider now the scalar equation

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + F(u, J(u)), \tag{3.6}$$

where $J(u) = \int_{-\infty}^{\infty} \phi(x-y)u(y,t)dy$, and $\phi(x)$ is a non-negative kernel function. Specific form of the function $F(u, J(u))$ is given by the following two examples:

$$F_1(u, J(u)) = auJ(u)(1-u) - bu, \quad F_2(u, J(u)) = au^2(1 - J(u)) - bu.$$

If we replace the kernel $\phi(x)$ by the δ-function, then in both cases we obtain the same bistable reaction-diffusion equation. However, if $\phi(x)$ is an integrable function, behavior of solutions in these two cases can be essentially different. Equation (3.6) with the first function satisfies the maximum principle and comparison of solutions. These properties allow us to prove the existence and stability of waves by the methods presented above [3, 5, 16]. In the case of the second function, the maximum principle is not applicable, and there are only few results on the wave existence. On the other hand, this equation manifests interesting nonlinear dynamics with important applications in ecology and evolution [10, 35, 36, 37, 64].

3.2.2. *Delay equation.* Another interesting development of the conventional reaction-diffusion equations is related to the delay equations

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + F(u, u_\tau), \tag{3.7}$$

where $u_\tau(x,t) = u(x, t-\tau)$. We will restrict ourselves here to the function $F(u, u_\tau) = u(1 - u - f(u_\tau))$ arising in a model of immune response [11]. If $f(u)$ is a decreasing function, then the maximum principle is applicable and the existence of waves is proved by conventional methods (in a more general case) [41]. However, if the function $f(u)$ is not decreasing, then this approach is not applicable. The wave existence is proved in this case by the Leray-Schauder method with separation of monotone solutions [50].

3.3. **Other models.**

3.3.1. *Non-monotone systems of equations.* The method to prove the existence of waves presented above is based on a separation of monotone and non-monotone solutions. This property holds for monotone and locally monotone systems. It appears that there are some other systems of equations for which a modification of this approach is applicable. The following reaction-diffusion system of equation was introduced in [12] as a model of immune response:

$$\frac{\partial v}{\partial t} = D_1\frac{\partial^2 v}{\partial x^2} + kv(1-v) - cv, \tag{3.8}$$

$$\frac{\partial c}{\partial t} = D_2\frac{\partial^2 c}{\partial x^2} + \phi(v)c(1-c) - \psi(v)c. \tag{3.9}$$

Here v is the concentration of virus and c is the concentration of immune cells, $\phi(v)$ and $\psi(v)$ are some non-negative functions. The function $f(v) = 1 - \psi(v)/\phi(v)$ determines the zero line of the nonlinearity in the second equation. If $f'(v) < 0$, then system (3.8), (3.9) can be reduced to a locally monotone system. In a more general and biologically realistic case, this function is not monotone but it has a single maximum. If this is the case, then the class of separated solution also changes. These are non-monotone solutions anymore, but the solutions whose c component can have a single maximum. Such solutions are separated from the other solutions in the sense of Section 2, and the existence of travelling waves can be proved by the Leray-Schauder method on subclasses of solutions [66].

3.3.2. *Nonlinear boundary conditions.* In the case of multi-dimensional problems in unbounded cylinders, the method of separation of solutions is applicable for monotone systems [70, 72] (see also [8, 9, 34]) but not for locally monotone systems. Though technically it is more involved than the 1D systems, the main ideas of the existence and stability proofs remain the same. One of the interesting development of the multi-dimensional problems concerns the model with nonlinear boundary condition:

$$\frac{\partial u}{\partial t} = \Delta u + f(u), \tag{3.10}$$

$$y = 0 : \frac{\partial u}{\partial y} = 0, \quad y = 1 : \frac{\partial u}{\partial y} = g(u) \tag{3.11}$$

arising in modelling atherosclerosis. Here f and g are sufficiently smooth functions, $-\infty < x < \infty, 0 < y < 1$. Under appropriate conditions on the functions f and g, the wave existence is proved by the method of separation of monotone solutions [4, 6, 7, 18].

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