Variational Approach to Self-Adjointness and Some Applications to Biomathematics

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In this paper using variational approach, we obtain necessary and sufficient conditions for a nonlinear boundary value problem to be self-adjoint. Analytic representations of Lagrangian and Hamiltonian are given. Several interesting applications to biological models are also discussed. © 1988 Academic Press, Inc.

1. Introduction

The study of models of biological systems in mathematical biology takes the form of first-order differential equations:

$$Q_i' = Q_i(t, Q, Q') \qquad (i = 1, 2, 3, ..., n), \qquad (1.1)$$

where the functions Q_i depend upon the model in question but are in general non-linear in nature.

In 1964, Kerner [3] considered such models when he introduced Lagrangian into the study of biological systems. The main thrust for such a development was to find a Hamiltonian by making use of Lagrangian through a Legendre transformation. According to Kerner [3] the resulting Hamiltonian is an integral of the motion with respect to the system of differential equations (1.1). Earlier works in the area of Mathematical biology making use of Lagrangian representation have failed to explain two fundamental questions:

(i) What is the criteria that a system of ordinary differential equations must satisfy in order to ensure the existence of a Lagrangian?

(ii) Does there exist an algorithm that enables one to construct the Lagrangian from the dynamical equations?

134

The second question was proposed by Lumsden and Trainer [4]. For the first time Helmholtz [2] formulated such conditions for the existence of a Lagrangian and indicated that a necessary and sufficient condition for the existence of a Lagrangian for a system of ordinary differential equations, is that the system

$$F_i(t, Q, Q', Q'') = 0 \qquad (i = 1, 2, 3, ..., n),$$

be variationally self-adjoint. Later various authors have studied the so-called inverse problem of mechanics. In 1978, Santelli [7], comprehensively studied and wrote on the problem of classical mechanics. On the other hand, modern analysis of the inverse problem of classical mechanics makes use of a variety of sophisticated mathematical tools.

In 1982 Gregory H. Paine [5] obtained the self-adjoint conditions for a system of n-first-order ordinary differential equations by variational approach. One of the theorems of [5] also gives criteria under which a Lagrangian representation for a system of ordinary differential equations is possible.

In this paper we mainly concentrate on nth-order nonlinear differential systems and by using variational approach, we obtain the adjoint equations for nth-order systems. Using this we give necessary and sufficient conditions for an nth-order system to be variationally self-adjoint. We observe that the conditions for self-adjointness to first-order systems obtained by Gregory H. Paine [5] become a particular case here. The results obtained here are validated by certain biological systems.

2. VARIATIONAL APPROACH TO SELF-ADJOINTNESS

Let us consider a system of $n - n$th-order nonlinear differential equations

$$F_i = F_i(t, Q, Q', ..., Q^{(n)}) = Q_i^{(n)} - Q_i(t, Q, Q', ..., Q^{(n)}) = 0, \qquad (2.1)$$

where $Q \in R^n$ $(i = 1, 2, 3, ..., n)$.

We assume that system (2.1) satisfies certain global existence theorems.

The main aim of this paper is to give answers to the questions posed in regard to the system (2.1) and give a criterion for a system (2.1) to be variationally self-adjoint.

Consider only the functions F_i rather than the equations $F_i = 0$, we can characterize by one-parameter functions $\{Q_i(t, \alpha)\}$, $t \in (t_1, t_2)$, where α is infinitesimal $(i = 1, 2, 3, ..., n)$. As from the definition the variation of admissible paths are

$$y_i(t) = \frac{\partial Q_i}{\partial \alpha}\bigg|_{\alpha = 0} \qquad (i = 1, 2, 3, ..., n) \qquad (2.2)$$

are the finite parts of the contemporaneous first-order variations of Q_i, that is, $\delta Q_i = y_i(t)\,\alpha$, where α is infinitesimal. The system of variational forms of (2.2) are obtained by

$$M_i = \left.\frac{dF_i}{d\alpha}\right|_{\alpha = 0}$$

$$= \left.\frac{\partial F_i}{\partial Q_i}\right|_{\alpha = 0} y + \left.\frac{\partial F_i}{\partial Q_i'}\right|_{\alpha = 0} y' + \left.\frac{\partial F_i}{\partial Q_i''}\right|_{\alpha = 0} y'' + \cdots + \left.\frac{\partial F_i}{\partial Q_i^{(n)}}\right|_{\alpha = 0} y^{(n)},$$

where

$$y = \left.\frac{\partial Q_i}{\partial \alpha}\right|_{\alpha = 0}, \qquad y' = \left.\frac{\partial Q_i'}{\partial \alpha}\right|_{\alpha = 0}, \, ..., \, y^{(n)} = \left.\frac{\partial Q_i^{(n)}}{\partial \alpha}\right|_{\alpha = 0}.$$

Denoting

$$\frac{\partial F_i}{\partial Q_i} = P_0, \qquad \frac{\partial F_i}{\partial Q_i'} = P_1, \qquad \frac{\partial F_i}{\partial Q_i''} = P_2, \, ..., \, \frac{\partial F_i}{\partial Q_i^{(n)}} = P_n,$$

$$(i = 1, 2, 3, ..., n).$$

We get

$$M = [P_0\, y + P_1\, y' + P_2\, y'' + \cdots + P_n\, y^{(n)}].$$

or

$$M = \sum_{r=0}^{n} P_r\, y^{(r)}. \tag{2.3}$$

Here the variation of y_i is not unique. In fact, there exists a family of admissible variations which we shall denote by $\{M_i\}$. By considering more admissible paths $Q_i(t, \alpha)$, $\tilde{Q}_i(t, \alpha)$, we can construct more elements of this family. Then the variations yield

$$y_i = \left.\frac{\partial Q_i}{\partial \alpha}\right|_{\alpha = 0}, \quad \tilde{y}_i = \left.\frac{\partial \tilde{Q}_i}{\partial \alpha}\right|_{\alpha = 0}, \, ... \tag{2.4}$$

For each system of variational forms $M_i(y)$, we can define an adjoint system $\tilde{M}_i(y)$ that is related uniquely to $M_i(y)$. Now we define an adjoint system of variational forms of M_i.

DEFINITION 2.1. A system of variational forms $\tilde{M}_i(y)$ is called the adjoint system of forms $M_i(y)$ when there exists a function $J(y, \tilde{y})$ such that

$$\tilde{y}_i M_i(y) - y_i \tilde{M}_i(y) = \frac{d}{dt} J(y, \tilde{y}). \tag{2.5}$$

Equation (2.5) is called the Lagrangian identity. From (2.4) we can write

$$yM(y) = [yP_0 y + yP_1 y' + yP_2 y'' + \cdots + yP_n y^{(n)}]$$

$$= y[yP_0 - (yP_1)^{(1)} + (yP_2)^{(2)} - (yP_3)^{(3)} + \cdots + (-1)^r (yP_r)^{(r)}]$$

$$+ \frac{d}{dt}\left[\sum_{r=1}^{n} (-1)^{r-1} (yP_r)^{(r-1)}\right] y + \left[\sum_{r=2}^{n} (-1)^r (yP_r)^{(r-2)}\right] y'$$

$$+ \left[\sum_{r=3}^{n} (-1)^{r+1} (yP_r)^{(r-3)}\right] y'' + \cdots.$$

Defining

$$M(y) = \sum_{r=0}^{n} (-1)^r (yP_r)^{(r)} \tag{2.6}$$

We get

$$J(y, \tilde{y}) = \left[\sum_{r=1}^{n} (-1)^{(r-1)} (yP_r)^{(r-1)}\right] y + \left[\sum_{r=2}^{n} (-1)^r (yP_r)^{(r-2)}\right] y'$$

$$+ \left[\sum_{r=3}^{n} (-1)^{r+1} (yP_r)^{(r-3)}\right] y'' + \cdots. \tag{2.7}$$

Thus we obtain unique definitions for $J(y, \tilde{y})$ and the adjoint $M(y)$. Now we define self-adjointness for a system of variational forms of $M_i(y)$.

DEFINITION 2.2. A system of variational forms $M_i(y)$ is said to be self-adjoint if it is identical with its adjoint form $\tilde{M}_i(y)$ for all y, that is, $M_i(y) = \tilde{M}_i(y)$, $(i = 1, 2, 3, ..., n)$. Therefore, we must have

$$\sum_{r=0}^{n} P_r y^{(r)} = \sum_{r=0}^{n} (-1)^r (yP_r)^{(r)}. \tag{2.8}$$

From (2.8) we write the conditions for self-adjointness for a system of variational forms. First we write, the conditions for n-first-order ordinary differential equations:

$$F_i(t, Q, Q') = Q_i' - Q_i(t, Q, Q') = 0, \qquad (i = 1, 2, 3, ..., n).$$

Utilizing (2.8), we get

$$\tilde{P}_0 - P_0 = P_1^{(1)} \tag{2.9}$$

$$P_1 + \tilde{P}_1 = 0. \tag{2.10}$$

Thus for n-nth-order ordinary differential equations the self-adjoint conditions are

$$P_0 = \sum_{r=0}^{n} (-1)^r (P_r)^{(r)}$$

$$P_1 = \sum_{r=1}^{n} (-1)^r r(P_r)^{(r-1)}$$

$$P_2 = P_2 - 3P_3^{(1)} + 6P_2^{(2)} + 10P_5^{(3)} + \cdots \qquad (2.11)$$

$$\vdots \qquad \qquad \vdots \quad \vdots \quad \vdots$$

$$P_n = (-1)^r P_n.$$

The Lagrangian representation is given by

$$L(t, Q, Q', ..., Q^{(n)}) = -\sum_{i=1}^{n} Q_i \int_0^1 F_i(t, Q, Q', ..., Q^{(n)}) \, dt. \qquad (2.12)$$

The theory developed in this section will now be applied to certain biological models.

3. Representation of Lagrangians for Biological Models

(a) *A Mathematical Model of Glucose and Insulin Interaction*

Let $G(t)$ denote the level of blood glucose at time t_0 and $H(t)$ represent the net hormone level on the blood at the same tie t, the weighted average of all endocrine secretions which tend to alter blood glucose is assumed to be included in $H(t)$. Assume that G_0, H_0 are the constants, fasting values of glucose, and net hormone level, respectively. Define $x_1(t)$ and $x_2(t)$ by the equations

$$x_1(t) = G(t) - G_0$$

$$x_2(t) = H(t) - H_0.$$

When it is assumed that G and H are not too different from G_0 and H_0, then we get

$$\begin{aligned} x_1'(t) &= -m_1 x_1 - m_2 x_2 \\ x_2'(t) &= -m_3 x_2 + m_4 x_1 + u(t) \end{aligned} \qquad (3.1)$$

with $m_1, m_2, m_3 > 0$, $m_4 \geqslant 0$.

In the absence of $u(t)$, that is, the rate of infusion exogeneous hormone, (3.1) becomes

$$x_1'(t) = -m_1 x_1 - m_2 x_2$$
$$x_2'(t) = -m_3 x_2 + m_4 x_1. \tag{3.2}$$

Obviously, this system of equations does not satisfy the self-adjoint conditions. However, by multiplying the system (3.2) by a nonsingular skew-symmetric matrix function $G(t, x)$, we obtain

$$F(t, x, x') = \begin{bmatrix} 0 & g \\ -g & 0 \end{bmatrix} \begin{bmatrix} x_1' + m_1 x_1 + m_2 x_2 \\ x_2' - m_4 x_1 + m_3 x_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

From (2.13) and considering a purely time-dependent g, we get a partial differential equation of the form

$$\frac{\partial g}{\partial t} = g(m_1 + m_3) + \frac{\partial g}{\partial x_1}(m_1 x_1 + m_2 x_2) + \frac{\partial g}{\partial x_2}(m_3 x_2 - m_4 x_1). \tag{3.3}$$

Solving for time-dependent g, we get

$$g(t) = C \exp(m_1 + m_3) t, \tag{3.4}$$

where C is an arbitrary constant. Using (2.12) (for $n = 1$) we get the corresponding Lagrangian as

$$L(t, x, x') = \tfrac{1}{2} e^{(m_1 + m_3)t} [x_2 x_1' - x_1 x_2' + m_4 x_1^2 + m_2 x_2^2 + (m_1 - m_3) x_1 x_2]. \tag{3.5}$$

Now an integral of motion H for the system of the ordinary differential (3.2) is

$$H(t, x_1, x_2) = \tfrac{1}{2} e^{(m_1 + m_3)t} [(m_3 - m_1) x_1 x_2 - m_2 x_2^2 - m_4 x_1^2]. \tag{3.6}$$

For individuals with diabetes there is an impaired ability to produce endogeneous insulin and eventually, in this case, the system (3.2) is

$$L(t, x, x') = \tfrac{1}{2} C e^{(m_1 + m_3)t} [(m_3 - m_1) x_1 x_2 - m_2 x_2^2] \tag{3.7}$$

and an integral of motion H is

$$H(t, x_1, x_2) = \tfrac{1}{2} C e^{(m_1 + m_3)t} [(m_3 - m_1) x_1 x_2 - m_2 x_2^2]. \tag{3.8}$$

In 1964, Kerner [3] found the Lagrangian corresponding to the time-independent case by taking the diagonal elements (here $m_2 = m_4 = 0$) to be

zero for a linear system of type $x' = Ax$ in which A has been diagonalized from the beginning $A_{ij} = \lambda_i \delta_{ij}$. Now analyzing the above system with diagonal A for a time-independent G, the function g must satisfy the partial differential equation

$$\lambda_1 x_1 \frac{\partial g}{\partial x_1} + \lambda_2 x_2 \frac{\partial g}{\partial x_2} = -(\lambda_1 + \lambda_2) \, g. \tag{3.9}$$

A solution is of the form

$$g(x_1, x_2) = x_1^{-\lambda_2/\lambda_1} x_2^{-\lambda_1/\lambda_2} \qquad (\lambda_1 \neq \lambda_2).$$

The time-independent Lagrangian can be obtained from (2.12) and is given by

$$L(x, x') = \frac{\lambda_1 \lambda_2}{(\lambda_1 + \lambda_2)^2} \, x_1^{-\lambda_2/\lambda_1} x_2^{-\lambda_1/\lambda_2} [x_1 x_2' - x_2 x_1' + (\lambda_1 - \lambda_2) \, x_1 x_2) \tag{3.10}$$

and, correspondingly, an integral of motion is

$$H(x_1, x_2) = \frac{\lambda_1 \lambda_2}{(\lambda_1 + \lambda_2)^2} \, [(\lambda_2 - \lambda_1) \, x_1 x_2].$$

If $\lambda_1 = \lambda_2$ the expression $g(x_1, x_2)$ is also a valid solution of (3.9). However, when applying (2.12), the matrix function $G(x)$ gives an undefined integral. Hence we have to search for another $G(x)$ and also note that the Lagrangian obtained here (3.10) is not same as obtained by Kerner [3] for the time-independent Lagrangian which tells the fact that the representation of the Lagrangian need not be unique.

(b) *Malaria Model*

The probability per unit time that an uninfected human becomes infected is called the innoculation rate. This probability depends on the infectiousness of mosquitoes. Nevertheless it seems possible to avoid modelling disease dynamics in the mosquito population.

The DMT (Dietz, Molineaux, and Thomas) Method is the innoculation rate without any dynamical equations for mosquitoes by means of an epidemiological index called the vectorial capacity [1]. Although Ross [6] predated the formal definition of that index, one of his models used the same device. The other model included a differential equation for infected mosquitoes.

In both of Ross Models [6] the human population size and the density m of mosquitoes are assumed constant. Let $y(t)$ be the proportion of infected people and $x(t)$ the density of infected mosquitoes. Then the model is

$$y' = b \times a(1 - y) - \gamma y$$
$$x' = c(m - x) \, ay - \mu x. \tag{3.11}$$

The parameters a, b, c, γ, μ are: a is the human biting rate of mosquitoes, b is the proportion of bites of mosquitoes infections on susceptible humans which result in infection, c is the proportion of bites by susceptible mosquitoes on infections huans which result infection, γ is the recovery rate from parasitemia, and μ is the death rate of mosquitoes and $(b \times a)$ is the innoculation rate.

System (3.11) can be written as

$$x_1' = x_1 + x_2 + 2x_1 x_2$$
$$x_2' = -x_1 - x_2 + 2x_1 x_2.$$

As the system cannot satisfy directly the self-adjoint condition, however, we multiply the system by nonsingular skew-symmetric matrix function $G(t, x)$, we obtain

$$F(t, x, x') = \begin{bmatrix} 0 & g \\ -g & 0 \end{bmatrix} \begin{bmatrix} x_1' - x_1 x_2 - 2x_1 x_2 \\ x_2' + x_1 + x_2 - 2x_1 x_2 \end{bmatrix}.$$

Considering purely time-independent g, we get partial differential equation

$$\frac{\partial g}{\partial x_1}(x_1 + x_2 + 2x_1 x_2) - \frac{\partial g}{\partial x_2}(x_1 + x_2 - 2x_1 x_2) = g(2x_1 + 2x_2).$$

Time-independent solution of the above partial differential equation is

$$g(x_1, x_2) = K e^{(x_2 - x_1)},$$

where K is an arbitrary constant. The Lagrangian, correspondingly, for time-independent g, from (2.12), is

$$L(x, x') = \frac{e^{(x_2 - x_1)}}{(x_1 + x_2)^2} [x_2 x_1' - x_1 x_2' - 2x_1 x_2 - (x_1^2 + x_2^2) + 2(x_1^2 x_2 - x_1 x_2^2)].$$

We get, correspondingly, an integral of motion H,

$$H(x, x') = \frac{e^{(x_2 - x_1)}}{(x_1 + x_2)^2} [2(x_1 x_2 - x_1^2 x_2 + x_1 x_2^2) + (x_1^2 + x_2^2)].$$

(c) *Model of Immuno-Competent Cells*

Immuno-competent B cells arise by difference of stem cells and are especially sensitive to induction of tolerance at an immature stage. Therefore we consider two populations of B cells which can react specifically with antigen mature immuno competent cells (x cells) and immature cells (I cells). This enables us to use the same model to
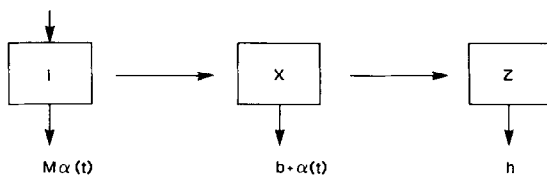
FIGURE 1

investigate experimental situations in which both I and x cells are irreversibly inactivated and also situations in which only I cells are assumed to be irreversibly inactivated.

Populations of immature (I) and mature (x) immuno competent cells and rates of cell transfer. Also the inclusion of an I cell population in the model introduces an implicit time delay in the onset of reactivity after the induction of tolerance such a time delay is observed in experiments. Let s, a, and b be the rates of differences of precursors of I cells, of maturation of I cells into x cells (cells which die before reaching the mature state are not considered) and of natural death of x cells, respectively, and let $\alpha(t)$ and $M\alpha(t)$ be the rates of elimination of x cells and I cells by antigen (M is dimensionless constant >1) reflecting the fact that I cells are more sensitive to tolerance induction than x cells). Then the development $I[i(t)]$ and $X[x(t)]$ cell populations with time can be described as

$$\frac{di(t)}{dt} = \delta - [a + M\alpha(t)]\, i(t)$$

$$\frac{dx(t)}{dt} = ai(t) - [b + \alpha(t)]\, x(t); \tag{3.15}$$

thus in the absence of δ, this system (3.15) can be written as

$$x_1' = -a_1 x_1$$

$$x_2' = -a_2 x_2 + a_3 x_1.$$

As in the earlier sections we obtain the Lagrangian for time-dependent g, from (2.12)

$$L(t, x, x') = \frac{e^{(a_1 + a_2)t}}{2}\, [x_2 x_1' - x_1 x_2' + (a_1 - a_2)\, x_1 x_2 + a_3 x_1^2].$$

Now an integral of motion H is

$$H(t, x, x') = \frac{e^{(a_1 + a_2)t}}{2}\, [(a_2 - a_1)\, x_1 x_2 - a_3 x_1^2].$$

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