Revista de la
Unión Matemática Argentina
Volumen 37, 1991.

VARIATIONAL PRINCIPLES IN BIOLOGY

CALIXTO P. CALDERON and TOR A. KWEMBE

"Conclusiones non solum ad medicinam, verum ad sacram theologian applicari valent mutando illum terminum moveri vel motus in aliquem istorum terminorum, scilicet, febris vel meritum vel mereri.

-These conclusions can be applied not only to medicine, but also to divine Theology; all we have to do is to change the terms to move to become feverish or to merit..."

Juan de Celaya (1490-1558), Tertius Liber Physicorum fol.88.

"Expositio in octo libros physicorum Aristotelis cum questions eiusdem"

-Celaya thought that mathematics should be applied to, medicine, theology, etc.

Afred J. Lotka in his landmark book "Elements of Physical Biology – 1924" conceived the changes in Biology in terms of redistribution in time of the biomass. He introduced a descriptive quantitative modality in the form of a system of differential equations; known today as Lotka – Vol terra system of differential equations. A careful analysis of inter group and intra–group evolution was described in chapters IV and V. Lotka's equations can be written as

$$\frac{dx_i}{dt} = F_i(x_1,\ldots,x_n,P_1,\ldots,P_n,Q_1,\ldots,Q_n)$$

$x_i(t)$ are the biomass at time t, the P's are constants describing the inter group action, and the Q's describe the intra–group actions. The x_i could be thought of being the biomass of species interacting with one another. If x_i stands for the population of species S_i, $\frac{dx_i}{dt}$ stands for the rate at which x_i is changing.

Constraints:

Suppose that species $S_1,...,S_n$ evolve within an habitat imposing the over all constraint

$$x_1 + x_2 + ... + x_n = \text{Constant}$$

or more generally

$$\phi(x_1,...,x_n) = \kappa$$

If ϕ is a C^1 function within the domain of variation of the $(x_1,...,x_n)$, then, ϕ must necessarily be a first integral of the system

$$\frac{dx_i}{dt} = F_i(x_1,...,x_n,P,Q) \qquad (1.1)$$

or equivalently ϕ satisfies

$$\sum_1^n F_i \frac{\partial\phi}{\partial x_i} = 0$$

The above equation imposes a quantitative modality to ϕ.

Equilibria:

As it is very well known, the permanency of the system (1.1) can be discussed in terms of its equilibrium points. In other words, in terms of the mathematical stability of (1.1). This analysis is formalized by looking at the points $x_i = C_i$; $i = 1,...,n$ for which

$$F_1 = F_2 = ... = F_n = 0$$

If the F_i's are continuously differentiable within a neighborhood of $(C_1,...,C_n)$, then the system (1.1) can be linearized and the point $(C_1,...,C_n)$ can be classified according to the nature of the eigenvalues of the matrix

$$\begin{bmatrix} \frac{\partial F_1}{\partial x_1},...,\frac{\partial F_1}{\partial x_n} \\ \frac{\partial F_2}{\partial x_1},...,\frac{\partial F_2}{\partial x_n} \\ \cdots\cdots\cdots \\ \frac{\partial F_n}{\partial x_1},...,\frac{\partial F_n}{\partial x_n} \end{bmatrix} = \left\{ \frac{\partial F}{\partial X} \right\}$$

evaluated at $x_i = C_i$ (The steady states)

For instance, if the real parts of the eigenvalues of $\{ \frac{\partial F}{\partial X} \}$ are all negative, then the point $(C_1,...,C_n)$ will be called asymptotically stable. For details see (David Sanchez [7]).

Departure from equilibrium:

Many laws of nature are conveniently expressed in terms of a maximum (or minimum) of a certain functional. For example minimum energy, minimum path, minimum time etc.The steady states $(C_1,\dots,C_n)$ can be expressed in terms of a minimum (see Lotka [5, page 158–159], which in turn goes back to Pièrre Duhem [2, page 460] and following ones). Consider the function

$$G(x_1,\dots,x_n) = \varphi(t)$$

Its critical points are to be found by solving

$$\sum_{1}^{n} \frac{\partial G}{\partial x_i} \cdot \frac{dx_i}{dt} = 0$$

or equivalently from (1.1)

$$\sum_{1}^{n} \frac{\partial G}{\partial x_i} \cdot F_i = 0$$

which is obviously satisfied when $x_i = C_i$.

If $G(x_1,\dots,x_n) = \sum_{i,j} C_{i,j}\, x_i\, x_j = Q(x,x)$

is a quadratic form, then depending on whether it is positive or negative definite we will have a maximum or a minimum at $x_i = C_i$.

On the other hand, it is very important to be able to describe the restoration of equilibrium in variational terms. To our recollection the first attempt to do so can be found in Perelson et al [6].

The restoration of equilibrium:

For the sake of simplicity we are going to assume that the parameters P,Q are one. That is $P = Q = u$. Furthermore we may assume that u is a function of the time t. That is $u = u(t)$. From now on, u is going to be called a control. Then equation (1.1) becomes "state equations"(using control theory terminology).

$$\dot{x}_i = F_i(x_1,\ldots,x_n,u(t)) \tag{1.2}$$

The action that restores the equilibrium is represented by an additional equation, namely

$$\dot{A} = G(x_1,\ldots,x_n) \tag{1.3}$$

The restoration of the equilibrium will be reached if A reaches a value A^* and u becomes P and the variables $x_i(t)$ becomes C_i, a steady state.

We shall assume that

$$G(x_1,\ldots,x_n) > \delta > 0$$

in a certain domain D.

A change of variable reduces our system to a new system

$$\frac{dx_i}{dA} = \frac{F_i(x_1,\ldots,x_n,u)}{G(x_1,\ldots,x_n)}$$

and we want to select $u = u(t)$ such that $(x_1(t),\ldots,x_n(t)) \to (C_1,\ldots,C_n)$ as $A \to A^*$ in minimum time. Using the brachistochrone formulation, we have to find:

$$T = \int_0^{A^*} \frac{\left(1 + \sum_1^n \left(\frac{dx_i}{dA}\right)^2\right)^{1/2} dA}{\sqrt{F_1^2 + F_2^2 + \ldots + F_n^2 + G^2}} = \text{minimum}$$

If we look for solutions that are perpendicular to the hyperplane $A = A^*$, then

$$\frac{dx_i}{dA} = 0 \quad \text{at} \quad x_i(A^*) = C_i$$

This in particular implies

$$\frac{dx_i}{dA} = 0 \Leftrightarrow \frac{dx_i}{dt} = 0$$

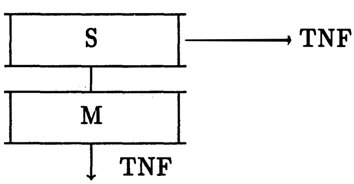
given the assumption made on G.

The minimum time principle is a form of interpreting natural selection as an optimization. In fact this approach has been introduced in Perelson et al [6, page 343]. " starting from the assumption that natural selection is an optimization process .."

An example from Immunology – Tumor Necrosis Factor (TNF)

The tumor necrosis factor (TNF) is serum factor produced by the leukocytes that have a tumoricidal effect on certain neoplasms. The TNF produced by the Macrophages is called (TNF,α) and the one by the cytolytic lymphocytes is called (TNF,β). Chemically these factors are not identical, but have the same effect and furthermore, they act synergistically. For all practical purposes we shall lump them together and just call them TNF.

For the sake of simplicity call S the population of pluripotent stem cells.



Since (TNF,β) is only a small proportion of the total (TNF), we may assume for simplicity that it is produced directly by the stem cells. (here we have simplified the intermediate step, "the Lymphocytes")

The equations look like:

$$\frac{dA}{dt} = \kappa(S + \gamma M) \tag{1}$$

where A is the level of TNF.

$$\frac{dS}{dt} = bu(t)S - d[1 - u(t)]S - \mu_s S$$

$$\frac{dM}{dt} = d[1 - u(t)]S - \mu_m M$$

In the above system, the first equation represents the extra condition that should restore the equilibrium in a large setting – There $\gamma >> 1$.
We want the process to reach the plane $A = A^*$ in minimum time. Instead of using the brachistochrone approach, we shall use Pointryagin minimum principle.

$$\min \int_0^T dt$$

$$A(T) = A^*$$

this leads to the Hamiltonian

$$H = \lambda_0 + \lambda_1 \kappa(S + \gamma M) + \lambda_2[bu - (1 - u)d - \mu_s]S + \lambda_3[d(1 - u) - \mu_m M\}$$

The adjoint equations are

$$\lambda_1 = -\frac{\partial H}{\partial A} \quad ; \quad \lambda_2 = -\frac{\partial H}{\partial S} \quad ; \quad \lambda_3 = -\frac{\partial H}{\partial M}$$

Satisfying the boundary conditions

$$(\lambda_1, \lambda_2, \lambda_3) \perp \{A = A^*\}$$

$$\lambda_1(T) = c_1, \qquad \lambda_2(T) = 0, \qquad \lambda_3(T) = 0.$$

The solution of this problem leads to a bang – bang type of result, with the optimal control being

$$u^* = \begin{cases} 1 \text{ if } \sigma(t) = (b+d)\lambda_1 - d\lambda_2 > 0 \\ 0 \text{ if } \sigma(t) < 0 \end{cases}$$

See Leitmann and Stalford [4].

It should be emphasized here, that many problems in Medicine and Biology lead to the application of optimality principles, in particular Pontryagin's principle.

See for example [3 , page 246] and following ones.

If one wants to go back to the brachistochrone formulation (see above), we may cite Theorem 5.4.3 in [3 ,page 249] that gives as $n-1$ the number of switching for the optimal time control of

$$\dot{X} = A X + B u$$

where A has n distinct real eigenvalues. This suggests that for u the natural space would be $\{ u; \overset{T}{\underset{0}{V}} u(t) \leq (n-1)\mu \}$, where V denotes the variation.

Finally, it should be pointed out that the formulation of the problem in terms of a classical variational one is simpler, however the right space for u is suggested by the Pointryagin principle. A combination of the two approaches seems to be the natural method to employ for these particular problems.

REFERENCES

1. B. Beutler : The Tumor Necrosis Factors : Cachectin and Lymphotoxin; Hospital Practice; 25; No. 2 : 45 – 56 (Feb. 15, 1990).
2. P. Duhem : Traité d'Énergétique; 1 : 460 et seq (1911).
3. D. E. Kirk : Optimal control Theory, An Introduction, Prentice – Hall, Inc., Englewood Cliffs, New Jersey, 1970.
4. G. Leitmann and H. Stalford : A sufficiency theorem for optimal control; J. Optimization Techniques and Applic.; 8 : 169 – 174 (1971).

5. A. J. Lotka : Elements of Mathematical Biology, Dover Publications, Inc., New York, 1956.

6. A. S. Perelson et al : Optimal strategies in Immunology, J. Math. Bio.; 3 : 325 – 367 (1976).

7. D. A. Sanchéz : Ordinary differential equations and stability theory, An Introduction, Dover Publications, Inc., New York, 1979.

Calixto P. Calderón

Department of Mathematics, Statistics, and Computer Science,M/C 249,

The University of Illinois at Chicago, Chicago, Illinois 60680.

Tor A. Kwembe

Department of Mathematics and Computer Science,

Chicago State University, 95 th at King Drive, Chicago, Illinois 60628.