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REGULATION OF AN ENDOCRINAL SYSTEM

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Résumé. On modélise l'évolution de deux hormones intervenant dans un système biologique endocrinien par un couple d'équations différentielles. On présente tout d'abord une méthode d'identification des paramètres. Puis on exhibe des feedbacks qui permettent de réguler le système, grace à une méthode de programmation dynamique discrétisée.

Abstract The evolution of two hormones related to a biological endocrinal system is modelized by a couple of differential equations. A method of identification of parameters is first presented. And a discretized dynamic programing is used to exhibit feedback controls which enable to regulate the system

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1. INTRODUCTION

A model for the regulation of ago-antagonistic couples was built which describes some physio-pathological and therapeutical problems related to a special type of endocrinal disorders. It seeks to correct the imbalance that may occur with in the dynamics between the Adreno-cortico-harmone (ACH) and the Antidiuretic-harmone (ADH) secreted by neuro-post-pituitary gland. In normal state a feedback cycle exists governing the process. These harmones have agonistic action as far as volemia, response to the stress are concerned; and antagonistic action as far as water diuresis, water shifts in interstitial and cell body compartments, cell growth and multiplication, extra cellular osmolarity are concerned.

2. MODEL:

Let x denote the ADH action and y denote the ACH action. In a physiological state there is antagonistic balance described by $x = y$ and agonistic balance described by $x + y = m$, m being a parameter. The control variables are $p = u - v$ and $q = u + v$, where u is the ADH therapy and v is ACH therapy, which are of same nature as the state variables. With these notations the system can be written down as :

$$(S)\quad \begin{cases} \dfrac{dx}{dt} = k_1(x-y+u-v)+c_1(x+y-m+u+v)+k_2(x-y+u-v)^2+c_2(x+y-m+u+v)^2 \\[2ex] \dfrac{dy}{dt} = k_3(x-y+u-v)+c_3(x+y-m+u+v)+k_4(x-y+u-v)^2+c_4(x+y-m+u+v)^2 \end{cases}$$

since the period of treatment can not be predetermined, the cost function is evaluated over infinite horizon. In fact it is taken to be a quadratic function over infinite horizon.

$$J_{x,y} = \int_0^\infty e^{-\alpha t}\,(x^2 + y^2)\,dt \qquad \text{where } \alpha > o.$$

The problem is to determine u and v minimizing $J_{x,y}$.
Further the physical considerations demand a closed form solution to the optimal control problem valid for any initial condition.

A detailed exposition on Biomedical aspects of this problem can

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be found in Bernard-Weil (1). An analogic study of this model was carried out in Bernard-Weil et al. (2); a theoretical study comprising existence, stability... was performed by Sellam (8). Later work also reports investigations on the system identification encluding determination of best initial values of the given observations and optimal control with specific initial condition and cost with finite horizon. Bernard-Weil in his Thesis and other (3) (4) (5) developed another type of optimal control that was formed by two control equations of the same type of the state equations and used their conclusions of this study for medical applications in the neurosurgical field. He showed how the same model in its cubic form improved considerably the stability. As far as identification was concerned, Santi et al. (7) gave some interesting results with a multilinear regression followed by a minimization, and Bernard-Weil brought some results decreasing the residual error by the choice of a convenient initial field followed by Hooke-Jeeves or Davidon-Fletcher-Powell method (5).

3. IDENTIFICATION

3.1 Theoritical considerations :

Let $Z = \begin{bmatrix} z_1 \\ z_2 \end{bmatrix}$ be a two dimensional vector ($z_1 = y-x$; $z_2 = x+y$).

Let $(z^i)_{i=0}^{m}$ be a set of given observed values. We deal with the system (S) with control variables suppressed. With obvious transformations we can rewrite the system as

$$(S') \qquad \frac{dz}{dt} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} Z + \begin{bmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{bmatrix} \begin{bmatrix} z_1^2 \\ z_2^2 \end{bmatrix} \qquad \text{with } z(o) = Z_o.$$

Where :

$$a_{11} = k_3 - k_1 \quad a_{12} = c_3 - c_1 \quad b_{11} = k_4 - k_2 \quad b_{12} = c_4 - c_2$$

$$a_{21} = k_1 + k_3 \quad a_{22} = c_1 + c_3 \quad b_{21} = k_2 + k_4 \quad b_{22} = c_2 + c_4$$

.../...

Let us denote $A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$ and $B = \begin{bmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{bmatrix}$

The theoritical basis for this study is the Implicit function theorem.

Let $I = [o,\tau]$. Consider the function spaces $L^2(I,\mathbb{R}^2)=L^2$ and $H^1 = H^1(I,\mathbb{R}^2)$. Let $A_c = \{a\epsilon R^8 : a = (a_{11}, a_{12}, a_{21}, a_{22}, b_{21}, b_{11}, b_{12}, b_{22})\}$

Define $\psi: A_c \times H^1 \to L^2$ by

$$\psi(a,z) = -\frac{dz}{dt} + Az + B\begin{bmatrix} z_1^2 \\ z_2^2 \end{bmatrix}; \text{for all } z \in H^1,\ a = (A,B) \in A_c.$$

Clearly the partial derivative $\frac{\partial\psi}{\partial z}$ exists. In fact

$$\frac{\partial\psi}{\partial z}(a,z) = -D + A + 2BC \text{ where } D = \frac{d}{dt} \text{ and } C = \begin{bmatrix} z_1 & 0 \\ 0 & z_2 \end{bmatrix}.$$ Thus $\frac{\partial\psi}{\partial z}$

is continuous. The invertibility of the operator is equivalent to find solutions to differential equation

$$\frac{dx}{dt} = Ax + 2BC\,x - g\ ;\quad g \in L^2$$

satisfying $x(o) = 0$. The Peano's theorem assures the existence of solutions sought. Hence $\frac{\partial\psi}{\partial z}$ is invertible and has a continuous inverse. Now due to implicit function theorem there exists a continuous function

$$\emptyset : A_c \dashrightarrow H^1 \text{ such that } \psi(a,\emptyset(a)) = 0.$$

Further $z_a = \emptyset(a)$ is differentiable. Define the square error function J by :

$$J(a) = \sum_{i=1}^{m} \| z_a - z_i \|^2 = \sum_{i=1}^{m} \| \emptyset(a) - z_i \|^2.$$

Evidently J(a) is continuous and convex.

So J(a) has a local minimum.

i.e. $\exists a^* \epsilon A_c ; J(a^*) \leq J(a)$ for all $a \in A_c$ with $\| a - a^* \| < \delta$.

.../...

3.2 Computational considerations.

The system (S') has no analytical solution. This is demontrated by particular choice of parameters :

Let $A = \begin{bmatrix} 0 & \propto \\ -\propto & 0 \end{bmatrix}$ $B = \begin{bmatrix} 0 & \beta \\ -\beta & 0 \end{bmatrix}$

Then $z_1 = \propto z_2 + \beta z_2^2$

$z_2 = \propto z_1 - \beta z_1^2$

Which has no analytical solution except when $\beta = 0$ so we seek numerical solutions.

It may be noted that the solutions are unbounded for certain parameters :

$$A = \begin{bmatrix} a_1 & 0 \\ 0 & a_2 \end{bmatrix} \qquad B = \begin{bmatrix} b_1 & 0 \\ 0 & b_2 \end{bmatrix}$$

Then $z_1 = a_1 z_1 + b_1\ z_1^2$

$z_2 = a_2 z_2 + b_2\ z_2^2$

the solution of which are $z_i = \dfrac{a_i}{K_i\ e^{-a_i t}\ -b_i}$ $i = 1,2$

The unconstrained optimization for J(a) was carried out by a variable metric method.

Since analytical gradients are not available, numerical gradients with help of finite differences, were used. This some times leads to instability for certain parameters, which can be avoided by changing the initial guess.

The choice of initial vector was done either by

(i) considering the uncoupled system with appropriate parameters, or by

(ii) considering linear approxmation by setting B = 0.

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Algorithm FMFP of IBM library of subroutines based upon the variable metric method of Fletcher and Powell [6] was used for the unconstrained optimization. (see the results at the end of the paper)

4. FEEDBACKS :

4.1 Theoretical considerations :

We now consider the system (S) along with the following constraints on the control variables :

$$|u| \le \frac{1}{2} \text{ and } |v| \le \frac{1}{2}$$

With $p = u - v$ and $q = u + v$ the system can be written down as

$$z = A \begin{bmatrix} z_1 + p \\ z_2 + q \end{bmatrix} + B \begin{bmatrix} (z_1 + p)^2 \\ (z_2 + q)^2 \end{bmatrix}$$

Where A and B are 2 x 2 matrices.

Set
$$f_1 = a_{11}(z_1+p)+a_{12}(z_2+q)+b_{11}(z_1+p)^2+b_{12}(z_2+q)^2$$

$$f_2 = a_{21}(z_1+p)+a_{22}(z_2+q)+b_{21}(z_1+p)^2+b_{22}(z_2+q)^2$$

Let Br be the closed ball of radius 'r' and cc(Br) be the set of all compact convex subsets of B.

Define $F : \mathbb{R}^2 \dashrightarrow cc(Br)$ by

$$F(z) = \left\{ \begin{bmatrix} f_1 \\ f_2 \end{bmatrix} \quad |p| \le 1 \; ; \; |q| \le 1 \right\}$$

Then the system (S) is equivalent to the differential relation

(S'') $\quad \dot{z} \in F(z) \qquad$ satisfying $z(o) = z_o \quad \mathbb{R}^2$.

We use the following result of Sentis [9] as a basis for computation.

<u>Theorem:</u> (Sentis) <u>Let F</u> : $[o,\infty) \times \mathbb{R}^k \dashrightarrow cc(Br)$. <u>For each</u>

.../...

$z \in \mathbb{R}^k$ let U_z be the set of the functions u of $L^\infty([o,\infty),\mathbb{R}^k)$ such that there exists y_u in $C([o,\infty),\mathbb{R}^k)$ satisfying :

$$\begin{cases} \dot{y}_u(s) = u(s) \text{ and } u(s) \in F(y_u(s)) \text{ for } s \in [o,\infty) \text{ a.e} \\ y_u(o)=z \end{cases}$$

Let $\quad f : \mathbb{R}^k \times \mathbb{R}^k \dashrightarrow \mathbb{R}$ and $\alpha > 0$.

Consider the cost

$$J_z(u) = \int_o^\infty e^{-\alpha t} f(y_u,u)dt \qquad \forall \in U_z$$

Suppose following conditions are satisfied :

(i) $F(z)$ is a compact convex subset of Br and $z \dashrightarrow F(z)$ satisfies Lipschitzian condition w.r.to Hausdorff metric.

(ii) $f(z,.)$ is convex and f is Lipschitzian in both variables

(iii) there exists $w \in \mathbb{R}^k$ such that

$$w \in F(z) \text{ for all } z \in \mathbb{R}^k$$

Then

(a) there exist multimappings (discretized feedbacks)

$$G_n : \mathbb{R}^k \dashrightarrow cc(\mathbb{R}^k) \text{ such that } G_n(z) \subseteq F(z) \quad z \in \mathbb{R}^k.$$

(b) if a sequence sequence $(z_n^k)_{k=o}^n$ is constructed as follows (whith $h_n > o, h_n \to o$)

$$z_n^o = z_o \text{ and } z_n^{k+1} = z_n^k + h_n u_n^k \text{ where } u_n^k \in G_n(z_n^k)$$

for $k = 1, 2, \ldots, n$. and if $u_n : [o,\infty) \dashrightarrow \mathbb{R}^k$ is defined by

$$u_n(s) = u_n^k \text{ for } s \in [t_n^k, t_n^{k+1})$$

then any point of accumulation of the sequence (u_n) in the weak*topology of L^∞ is optimal and

.../...

$$J_n(u_n) \dashrightarrow \operatorname*{Min}_{u \varepsilon u_z} J_z(u) .$$

Clearly the conditions (i) and (ii) are satisfied for the present problem and since F takes values in a closed ball of radius 'r', it is possible to choose the controls such that

$$0 \varepsilon F(z) \text{ for all } z \varepsilon \mathbb{R}^2.$$

Hence according to above theorem there exist discretized feedbacks for (s'') which approach the optimum and the sequential procedure gives feedbacks near grid points which are optimal for smaller discretization step.

4.2 Computational Considerations

Solutions of system (S) were computed using following implicit scheme. Let h_n be the discretization step

$$t_n^k = kh_n, \; k = 0, \ldots, n \text{ and } z_n^k = z(t_n^k).$$

$$\frac{z_n^{k+1} - z_n^k}{h_n} = A\, z_n^{k+1} + B \begin{bmatrix} (z_{n,1}^k)^2 \\ \\ (z_{n,2}^k)^2 \end{bmatrix}$$

i.e.

$$z_n^{k+1} = (I - h_n A)^{-1} \; z_n^k + h_n B \begin{bmatrix} (z_{n,1}^k)^2 \\ \\ (z_{n,2}^k)^2 \end{bmatrix}$$

To compute the feedbacks we select the convergence parmeter α depending on the matrices A and B in such a way that the discritized return functions $V_{n,k}$ given by the recurrence relation :

$$V_{n,0}(z) = 1/\alpha(1 - \exp(\alpha h_n)) \sum_{k=0}^{\infty} \exp(-\alpha k h_n) \;\; f(z + kh_n, q)$$

and

.../...

$$V_{n,k+1}(z) = \min_{q \in F(z)} \left(\frac{1-e^{-\alpha h n}}{\alpha} \right) f(z,q) + e^{-\alpha h_n} \; V_{n,k}(z+qh_n)$$

form monotonically decreasing sequence in k., i.e.,

$$V_{n,k+1}(z) \leq V_{n,k}(z) \text{ for all } z \in \mathbb{R}^2 \text{ and } V_n(z) = k \quad V_{n,k}(z)$$

Smaller values of difference of two successive values of functions $V_{n,k}$ indicate the convergence and corresponding controls are optimal feedback controls.

To compute feedbacks at the nongrid points a bilinear interpolation in two variables was employed. Using the feedback controls, optimal response trajectory was computed with specific initial values.

4.5 Results and discussion :

Among the several data sets given three of them are chosen for the presentation. Data in the form of response curves is presented in Fig.5.1, 5.2 and 5.3. Obviously all the three exhibit certain asymptotic properties. The graphs of Fig.5.1, 5.2 exhibit asymptotic stability while the one in 5.3 exhibits orbital stability.

Corresponding results on system identification are presented in tables 5.7, 5.8. These tables contain numerical values of data curves and that of computed curves along with the identified parameters. Smaller valuesfor gradients indicate convergence. To ensure the global nature of the optimum the scheme was initialized from different points. The final criterion for acceptance of parameters was the asymptotic agreement of the computed curves and the data curves.

The results on feedback controls is represented by the solutions to problem of Fig.5.3. From presentation point of view, only one sample was selected due to space limitations. Table 5.10, 5.11 represent initial and final return functions. Parameters included at the foot of the table are related to convergence. These tables form a subset of much larger tables with a mesh of 15 x 15 size. While $V_{n,o}(x,y)$ of table 5.10 exhibits well behaved strictly convex function, the $V_n(x,y)$ of table 5.11 exhibits a convex function but not necessarily strictly convex.

The algorithm employed is aimed at computing nonsmooth feedbacks (even discontinuous) through piecewise constant approximations. Table 5.12 shows

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optimal feedbacks for this problem.

Using the feedbacks so computed the response trajectories from some given initial values are sketched in Fig. 5.4, 5.5 and 5.6. The figure 5.4 exhibits jump discontinuity of feedback w.r.t state variables. The optimality of these curves is visually evident since when the state decreases monotonically to equilibrium position the feed-back is set to zero. Further when state remains steady, the feedback also remains steady. All these figures 5.4-5.6 exhibit following asymptotic equilibrium property :

$$\lim_{t\to\infty} (x + u) = \lim_{t\to\infty} (y + v) = m/2.$$

The computations with FMFP were carried out in IBM-360 at the M. S. University, Baroda. The preliminary computations were carried out on IBM-370 at CIRCE, Paris.

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INITIAL TRAJECTORIES

DATA I

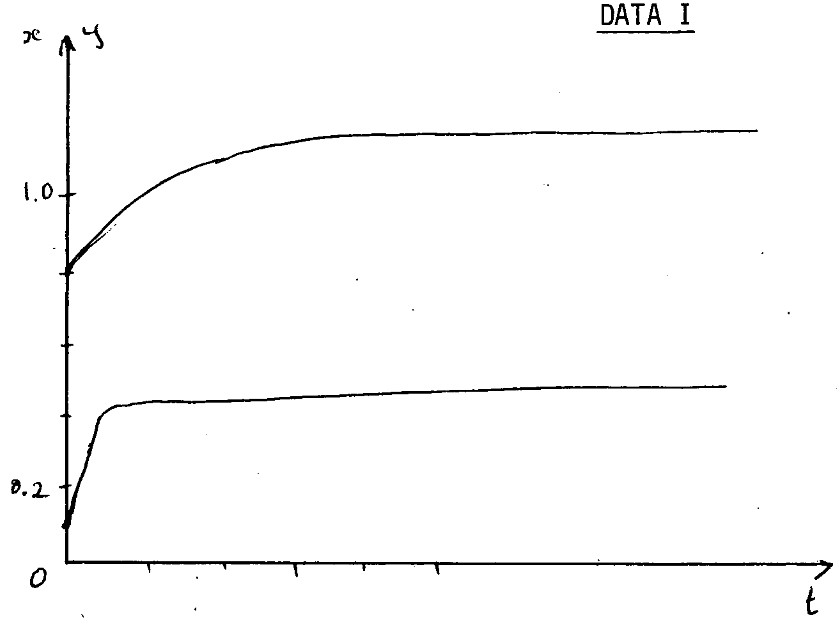

Fig 5.1

DATA II

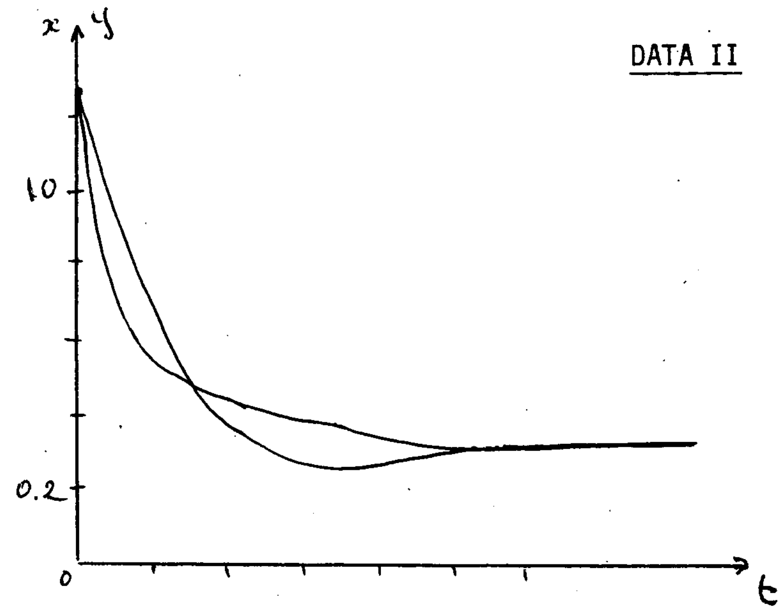

Fig 5.2

DATA III

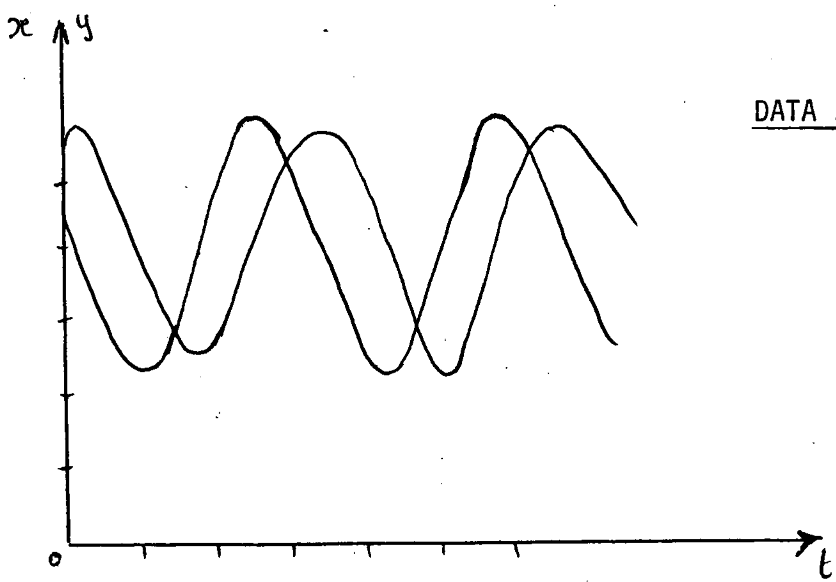

Fig 5.3

FEEDBACK TRAJECTORIES

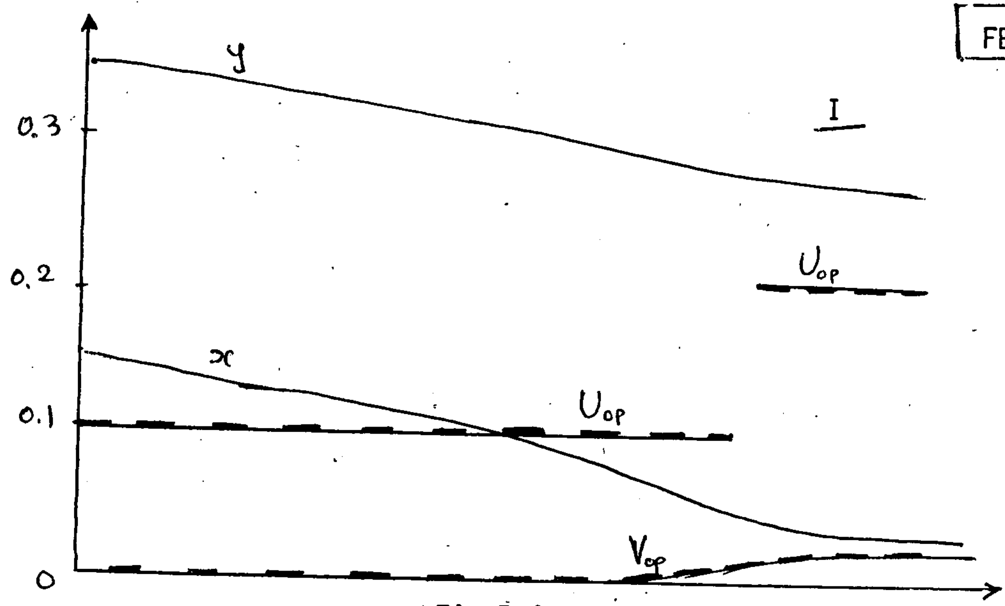

Fig 5.4

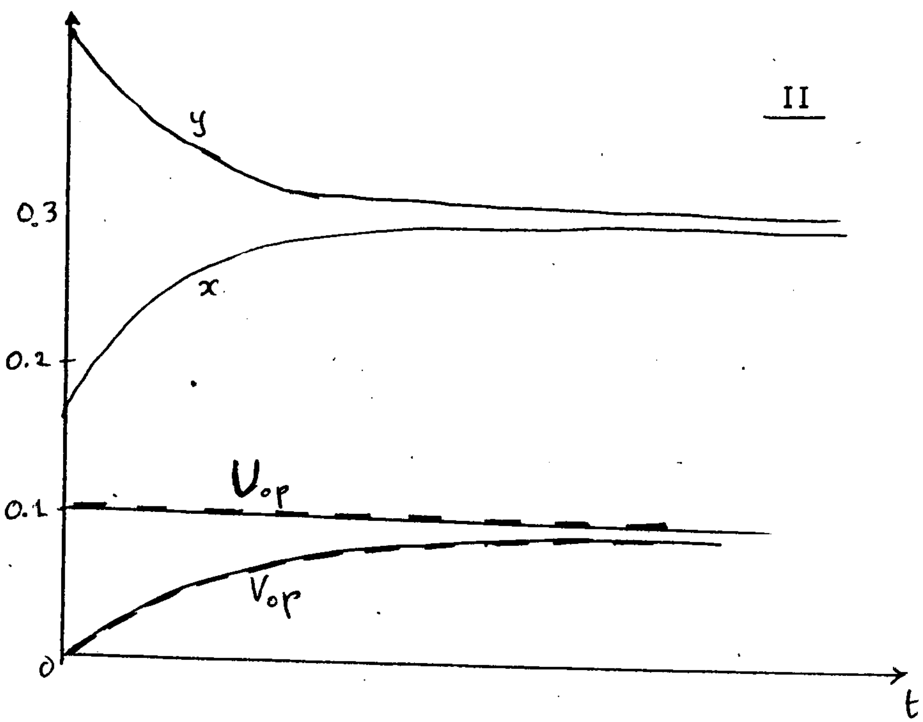

Fig 5.5

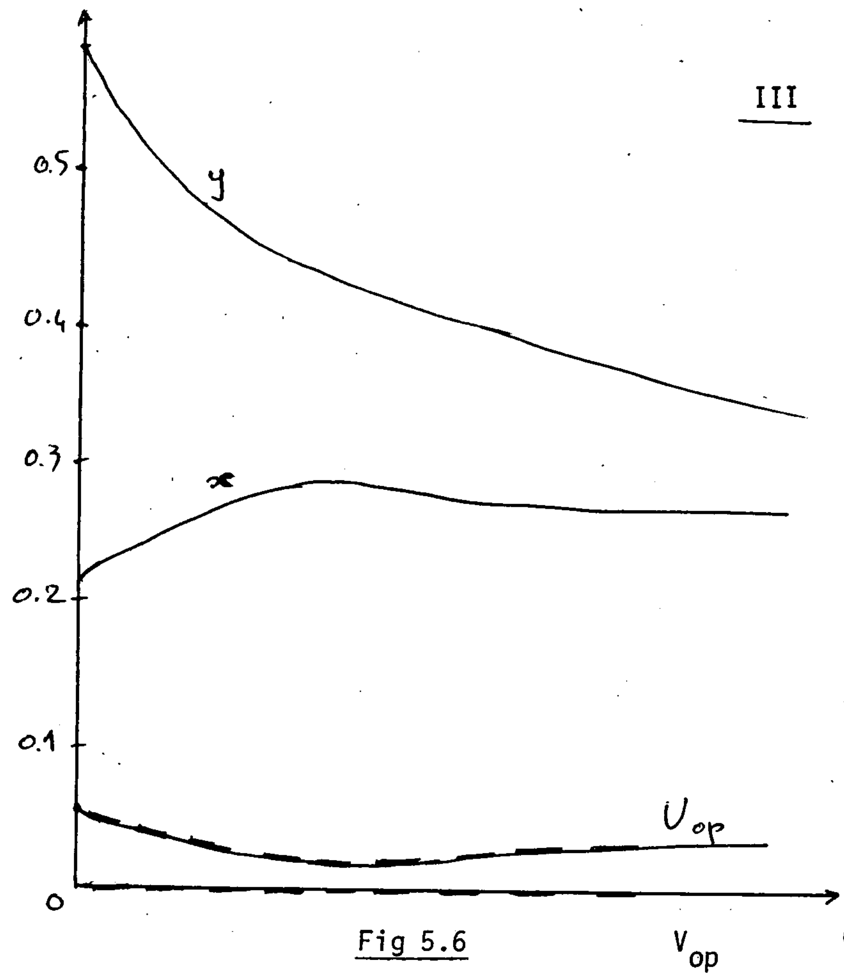

Fig 5.6

Table 5.7

(DATA I)

Data curves (transformed)	ZDX	0.70	0.58	0.525	0.5825	0.605	0.6125	0.62	0.6325	0.635	0.642	0.65
		0.645	0.65	0.647	0.65	0.69	0.69	0.695	0.7	0.7	0.7	
	ZDY	0.30	0.64	0.725	0.8175	0.85	0.8675	0.88	0.9075	0.915	0.9375	0.95
		0.965	0.97	0.977	0.998	1.03	1.04	1.045	1.05	1.05	1.05	
Solution curves	ZX	0.7000	0.5955	0.5652	0.5639	0.5727	0.585	0.5964	0.6077	0.6181	0.6276	0.6362
		0.6543	0.6681	0.6784	0.6859	0.6915	0.6955	0.6984	0.7006	0.7021	0.7032	
	ZY	0.3000	0.6074	0.7406	0.8159	0.8516	0.8752	0.8935	0.909	0.9228	0.9352	0.9462
		0.9701	0.9877	1.0007	1.0103	1.0178	1.0224	1.0261	1.0287	1.0307	1.0321	

Table 5.8

(DATA III)

Data curves (trans formed)	ZDX	-0.12	-0.24	-0.16	0.03	0.23	0.16	-0.035	-0.17
		-0.24	-0.14	0.15	0.24	0.09	-0.09	-0.22	-0.23
	ZDY	0.18	0.02	-0.16	-0.21	-0.01	0.20	0.235	0.13
		-0.04	-0.18	-0.17	0.10	0.27	0.230	0.06	-0.07
Solution curves	ZX	-0.1200	-0.2286	-0.1836	0.0459	0.2283	0.1539	-0.186	-0.1793
		-0.2428	-0.1203	00.1448	0.2322	0.0966	-0.0837	-0.2245	-0.2322
	ZY	0.1800	0.0261	-0.1365	-0.2038	-0.0174	0.2158	0.2479	0.1312
		-0.0376	-0.1875	-0.1705	0.0899	0.2617	0.2250	0.0768	-0.0977

Initial Return Function : $V_{n,e}(x,y)$ (for Data III) $\times 10^{-2}$

Table 5.10

y \ x	0.3	0.4	0.5	0.6	0.7	0.8	0.9
0.3	0.549	0.254	0.254	0.800	0.604	0.519	0.931
0.4	0.723	0.254	0.254	0.534	0.980	1.046	0.702
0.5	0.254	0.254	0.254	0.960	0.467	0.668	0.532
0.6	0.254	0.254	0.254	0.000	0.574	1.226	1.134
0.7	0.254	0.254	0.254	0.254	0.638	0.716	0.802
0.8	0.254	0.254	0.254	0.254	0.734	1.117	0.596
0.9	0.254	0.254	0.254	0.254	1.110	0.717	1.042

Final Return Function : $V_n(x,y)$ (for Data III) $\times 10^{-3}$

Table 5.11

y \ x	0.3	0.4	0.5	0.6	0.7	0.8	0.9
0.3	0.212	0.104	0.104	0.106	0.220	0.957	1.117
0.4	0.111	0.000	0.000	0.000	0.113	0.443	0.994
0.5	0.109	0.000	0.000	0.000	0.112	0.441	0.991
0.6	0.111	0.000	0.000	0.0	0.112	0.441	0.991
0.7	0.214	0.104	0.104	0.104	0.212	0.536	1.079
0.8	0.522	0.413	0.413	0.413	0.518	0.837	1.372
0.9	1.036	0.927	0.927	0.927	0.103	0.134	1.874

FEEDBACKS (DATA III)

y \ x	0.3	0.4	0.5	0.6	0.7	0.8	0.9
0.3	0.5	0.1	0.1	0.0	0.0	0.0	0.0
0.4	0.5	0.1	0.1	0.0	0.0	0.0	0.0
0.5	0.5	0.1	0.1	0.0	0.0	0.0	0.0
0.6	0.5	0.1	0.1	0.0	0.0	0.0	0.0
0.7	0.5	0.1	0.1	0.0	0.0	0.0	0.0
0.8	0.5	0.1	0.1	0.0	0.0	0.0	0.0
0.9	0.1	0.1	0.0	0.0	0.0	0.0	0.0

$U^{op}(x,y)$

y \ x	0.3	0.4	0.5	0.6	0.7	0.8	0.9
0.3	0.1	0.1	0.1	0.1	0.5	0.5	0.5
0.4	0.1	0.1	0.1	0.1	0.5	0.5	0.5
0.5	0.1	0.1	0.1	0.5	0.5	0.5	0.5
0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.9							

$V^{op}(x,y)$

Table 5.12