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ON A DYNAMICAL SYSTEM RELEVANT IN GENETICS

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In this paper, we take again the model of dynamical biochemical system (cf. Section 1) which is concerned in genetics (cf. [2]). In particular, we borrow the description of the mathematical model leading to a system of non linear differential equations.

We have drawn the genetic consequences (cf. Section 4) of this study in this previous paper (cf. [2]), whereas in this paper we enter upon mathematical problems involving the stability of the system (cf. Section 2) in the case of one enzyme.

When several enzyme species act competitively on the same substrates, we show that there exists a unique equilibrium point (cf. Section 3).

1. Description of the model (cf. [2]). We consider the biochemical associations involved in enzymatic activity. Let E denote the enzyme and A, B, C, and D its substrates. The stereospecific association between A and E is denoted AE, and AEB stands for the complex of the enzyme with both substrates A and B. A priority rule is assigned to the association AE relatively to the association AEB, so as to neglect such associations as EB. Substrates C and D can be linked with E in the same way and are considered as the output of the reaction. The graph (elementary graph) connected with this enzymatic activity is the following one (Figure 1) where the dotted arrows indicate the high energy activity, of the enzyme.

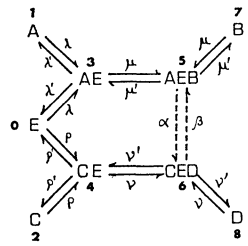

FIG. 1

Let $x_A(t)$ be the concentration of the substrate A at time t. From what happens in the neighborhood of each point of the graph, we derive the kinetics during the time interval $[t, t + h]$. Let λ' be the dissociation constant of complex AE, so that $\lambda' x_{AE}(t)h$ is the increase in the concentration of A during the interval of time $[t, t + h]$; in the same way, if λ stands for the association constant between A and E, $\lambda x_A(t)x_E(t)h$ is the decrease in the concentration of A during the same interval of time. In fact, we can write:

$$x_A(t + h) = x_A(t) + \lambda' x_{AE}(t)h - \lambda x_A(t)x_E(t)h - O(h^2) .$$

The limit of the foregoing equation, for $h \to 0$, gives the following differential equation:

$$\frac{dx_A}{dt} = \lambda' x_{AE}(t) - \lambda x_A(t)x_E(t) .$$

If we denote each chemical species by one index as in the graph, we get the following system of differential equations, which describe the kinetics of the phenomenon as far as the system is closed:

$$\frac{dx_0}{dt} = \lambda' x_3 - \lambda x_0 x_1 + \rho' x_4 - \rho x_0 x_2$$

$$\frac{dx_1}{dt} = \lambda' x_3 - \lambda x_0 x_1$$

$$\frac{dx_2}{dt} = \rho' x_4 - \rho x_0 x_2$$

$$\frac{dx_3}{dt} = -\lambda' x_3 + \lambda x_0 x_1 + \mu' x_5 - \mu x_3 x_7$$

$$\frac{dx_4}{dt} = -\rho' x_4 + \rho x_0 x_2 + \nu' x_6 - \nu x_4 x_8$$

$$\frac{dx_5}{dt} = -\mu' x_5 + \mu x_3 x_7 + \beta x_6 - \alpha x_5$$

$$\frac{dx_6}{dt} = -\nu' x_6 + \nu x_4 x_8 - \beta x_6 + \alpha x_5$$

$$\frac{dx_7}{dt} = \mu' x_5 - \mu x_3 x_7$$

$$\frac{dx_8}{dt} = \nu' x_6 - \nu x_4 x_8 .$$

In these equations, the coefficients ρ', μ', ν' are dissociation constants like λ', and ρ, μ, ν are association constants like λ. The coefficient α

concerns the transition from complex *AEB* to complex *CED*, that is, the high energy activity of enzyme *E* which depends on its association with both substrates *A* and *B*. So does β for the reverse reaction, from *CED* to *AEB*.

We have then the simplest graph (elementary graph) which describes the activity of one enzyme working with an *acceptor substrate A* and a *giver substrate B*. This graph was considered in [3] (pages 241-242) for the study of reactions involving dehydrogenases requiring Nicotinamide Adenine Dinucleotide (NAD) as a coenzyme.

We can generalize this situation in the case where several enzymatic species act competitively on the same substrates. In fact, in the case of a monocatenar enzyme in a diploïd heterozygote, we have to consider two elementary graphs connected in the following way (Figure 2):

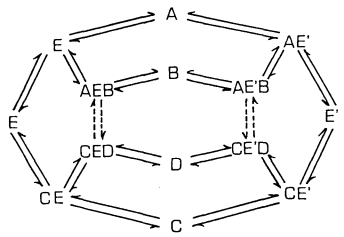

FIG. 2

More generally when several polypeptidic chains build one enzyme, each of them being coded by homologous or non homologous genes, there are in the living cell several enzymatic classes competitive for the same acceptor substrate *A* and the same giver substrate *B*. We assign the index i to a given enzyme species. Then, the equations take the following form, where n is the number of enzyme species:

$$\frac{dx_{0i}}{dt} = \lambda'_i x_{3i} - \lambda_i x_{0i} x_1 + \rho'_i x_{4i} - \rho_i x_{0i} x_2 \quad (i = 1, \cdots, n)$$

$$\frac{dx_1}{dt} = \sum_{i=1}^{n} (\lambda'_i x_{3i} - \lambda_i x_{0i} x_1)$$

$$\frac{dx_2}{dt} = \sum_{i=1}^{n} (\rho'_i x_{4i} - \rho_i x_{0i} x_2)$$

$$\frac{dx_{3i}}{dt} = -\lambda'_i x_{3i} + \lambda_i x_{0i} x_1 + \mu'_i x_{5i} - \mu_i x_{3i} x_7 \quad (i = 1, \cdots, n)$$

$$\frac{dx_{4i}}{dt} = -\rho'_i x_{4i} + \rho_i x_{0i} x_2 + \nu'_i x_{6i} - \nu_i x_{4i} x_8 \quad (i = 1, \cdots, n)$$

$$\frac{dx_{5i}}{dt} = -\mu_i' x_{5i} + \mu_i x_{3i} x_7 + \beta_i x_{6i} - \alpha_i x_{5i} \quad (i = 1, \cdots, n)$$

$$\frac{dx_{6i}}{dt} = -\nu_i' x_{6i} + \nu_i x_{4i} x_8 - \beta_i x_{6i} + \alpha_i x_{5i} \quad (i = 1, \cdots, n)$$

$$\frac{dx_7}{dt} = \sum_{i=1}^{n} (\mu_i' x_{5i} - \mu_i x_{3i} x_7)$$

$$\frac{dx_8}{dt} = \sum_{i=1}^{n} (\nu_i' x_{6i} - \nu_i x_{4i} x_8) .$$

2. Equilibrium and stability conditions. For a closed system, in the case of one enzyme, the equilibrium conditions $dx_i/dt = 0$ $(i = 0, 1, \cdots, 8)$ has a unique meaningful solution. In fact, we have the obvious relations $x_0 + x_3 + x_4 + x_5 + x_6 = b_0$, $x_1 + x_3 - x_7 = b_1$, $x_2 + x_4 - x_8 = b_2$ and $x_0 - x_1 - x_2 = b_3$, where the b_i $(i = 0, 1, 2, 3)$ are real constants and we get the following algebraic equations in x_1 and x_2:

I)
$$(x_1 + x_2 + b_3)\left(ax_1\left(x_1 + \frac{\lambda}{\lambda'}x_1(x_1 + x_2 + b_3) - b_1\right)\right)$$
$$= (x_1 + x_2 + b_3)\left(bx_2\left(x_2 + \frac{\rho}{\rho'}x_2(x_1 + x_2 + b_3) - b_2\right)\right)$$

where $a = \alpha\mu\lambda/\mu'\lambda'$ and $b = \beta\nu\rho/\nu'\rho'$;

II)
$$(x_1 + x_2 + b_3)\left(1 + \frac{\lambda}{\lambda'}x_1 + \frac{\rho}{\rho'}x_2 + \frac{a}{\alpha}x_1\left(x_1 + \frac{\lambda}{\lambda'}x_1(x_1 + x_2 + b_3) - b_1\right)\right.$$
$$\left. + \frac{b}{\beta}x_2\left(x_2 + \frac{\rho}{\rho'}x_2(x_1 + x_2 + b_3) - b_2\right)\right) = b_0 .$$

We have in mind the search for sufficient conditions for the existence of equilibrium points and to do this, we make, first of all, an extensive qualitative study of the equations I and II.

We remark that b_0 is the total quantity of enzyme, hence is much smaller than any sum of concentrations of chemical species among which we have at least one of the species A, B, C or D. In particular, $x_1 + x_2 > b_0 > x_0$ so that we can write $-b_3 = x_1 + x_2 - x_0 > 0$, thus $b_3 < 0$ and $b_0 \ll |b_3|$. In the same way we can show that $b_1 + b_3 \leqq 0$, $b_2 + b_3 \leqq 0$ and $b_1 + b_2 + b_3 \leqq 0$.

The expected solution, if it exists, lies in the convex set $x_1 > 0$, $x_2 > 0$, and $-b_3 \leqq x_1 + x_2 \leqq -b_3 + b_0$, in which we look for the intersection points of curves I and II.

To get a simpler form of equations I and II, we make the following change of coordinates: $y = x_1 + x_2$ and $x = x_1 - x_2$. With these new

coordinates, the preceding convex set is defined by $-b_3 \leqq y \leqq -b_3 + b_0$ and $|x| \leqq y$. Equations I and II become respectively:

I) $$u(y)x^2 - 2v(y)x + w(y) = 0$$

where

$$u(y) = b - a + (y + b_3)\left(b\frac{\rho}{\rho'} - a\frac{\lambda}{\lambda'}\right),$$

$$v(y) = (a + b)y + \left(a\frac{\lambda}{\lambda'} + b\frac{\rho}{\rho'}\right)y(y + b_3) - (ab_1 + bb_2)$$

and

$$w(y) = \left(b\frac{\rho}{\rho'} - a\frac{\lambda}{\lambda'}\right)y^2(y + b_3) + (b - a)y^2 + 2(ab_1 - bb_2)y\,;$$

II) $$p(y)x^2 + 2q(y)x + r(y) = 0\,,$$

where

$$p(y) = \frac{1}{4}(y + b_3)\left(\frac{a}{\alpha}\left(1 + \frac{\lambda}{\lambda'}(y + b_3)\right) + \frac{b}{\beta}\left(1 + \frac{\rho}{\rho'}(y + b_3)\right)\right),$$

$$q(y) = \frac{1}{4}(y + b_3)\left(\left(\frac{a}{\alpha}\left(1 + \frac{\lambda}{\lambda'}(y + b_3)\right) + \frac{b}{\beta}\left(1 + \frac{\rho}{\rho'}(y + b_3)\right)\right)y + \frac{\lambda}{\lambda'} - \frac{\rho}{\rho'} - \left(b_1\frac{a}{\alpha} - b_2\frac{b}{\beta}\right)\right)$$

and

$$r(y) = -b_0 + (y + b_3)\left(1 + \frac{1}{2}\left(\frac{\lambda}{\lambda'} + \frac{\rho}{\rho'} - \left(b_1\frac{a}{\alpha} + b_2\frac{b}{\beta}\right)\right)y + \frac{1}{4}\left(\frac{a}{\alpha}\left(1 + \frac{\lambda}{\lambda'}(y + b_3)\right) + \frac{b}{\beta}\left(1 + \frac{\rho}{\rho'}(y + b_3)\right)\right)y^2\right).$$

There is only one branch of curve I lying in the region defined by $-b_3 \leqq y \leqq -b_3 + b_0$ and $|x| \leqq y$. In fact, the intersection of curve I with the straight line $y = -b_3$ is composed of two points at finite distance (the third one is at infinity), but only one has coordinates $(\xi, -b_3)$ with $|\xi| \leqq |b_3|$. Moreover, it is easy to show that the following inequalities hold: $\sup(b_3, b_3 + 2b_1) \leqq \xi \leqq \inf(-b_3, -b_3 - 2b_2)$.

For the values of $y \geqq -b_3$ and near to $-b_3$, we are sure to find an intersection of the branch of I and those of II. In fact, for $b_0 = 0$ (this is the case without enzyme), the intersection of curves I and II is the point of coordinates $(\xi, -b_3)$. Now we can consider b_0 as a parameter and we have a family of curves II(b_0) depending on the parameter b_0.

By continuity, for small values of b_0 (but this is the case) we have an intersection point of curves I and II in a neighborhood of the point $(\xi, -b_3)$.

In the following, we have to show that the y coordinate for this intersection point lies between $-b_3$ and $-b_3 + b_0$. To do this, we observe that the functions p, q, r of equation II can be written as functions of the variable $h = x_0 = y + b_3$ and $p(h) = hP(h)$, $q(h) = hQ(h)$ and $r(h) = -b_0 + hR(h)$, where P, Q, R are convenient functions of h. The equation II can be written in the following way:

II) $b_0 = h(P(h)x^2 + 2Q(h)x + R(h))$.

The development of P, Q, R by Taylor series in a neighborhood of the orign shows that

$$b_0 = h\Big(1 + \frac{1}{4}(u + v)(x^2 - b_3^2) + \frac{1}{2}\Big(\frac{\lambda}{\lambda'} - u(b_1 + b_3)\Big)(x - b_3) - \frac{1}{2}\Big(\frac{\rho}{\rho'} - v(b_2 + b_3)\Big)(x + b_3) + O(h)\Big)$$

where $u = \mu\lambda/\mu'\lambda'$ and $v = \nu\rho/\nu'\rho'$. Now we have to show that the quadratic function

$$F(x) = \frac{1}{4}(u + v)(x^2 - b_3^2) + \frac{1}{2}(L - ub_3)(x - b_3) - \frac{1}{2}(M - vb_3)(x + b_3)$$

is positive for values of x near to ξ, where

$$L = \frac{\lambda}{\lambda'} - ub_1 \quad \text{and} \quad M = \frac{\rho}{\rho'} - vb_2 .$$

By tedious but trivial calculations and owing to the four inequalities $b_3 < 0$, $b_1 + b_3 \leqq 0$, $b_2 + b_3 \leqq 0$, $b_1 + b_2 + b_3 \leqq 0$ it can be shown that $F(\xi)$ is strictly positive where

$$\xi = \frac{1}{a - b}((a + b)b_3 + ab_1 + bb_2 + s)$$

if $a \neq b$ and

$$\xi = \frac{b_3(b_1 - b_2)}{b_1 + b_2 + 2b_3}$$

if $a = b$, in which $s = \{(ab_1 + bb_2)^2 + 4abb_3(b_1 + b_2 + b_3)\}^{1/2}$. The h coordinate of the intersection point is then positive and smaller than b_0.

Approximate values of the coordinates of this equilibrium point are, for $a \neq b$:

$$\tilde{x}_1 = \frac{1}{2(a - b)}(ab_1 + bb_2 + 2bb_3 + s) = \frac{1}{2}(\xi - b_3) ,$$

$$\tilde{x}_2 = \frac{1}{2(b-a)}(ab_1 + bb_2 + 2ab_3 + s) = -\frac{1}{2}(\xi + b_3) ,$$

$$\tilde{x}_7 = \tilde{x}_1 - b_1 , \quad \tilde{x}_8 = \tilde{x}_2 - b_2 , \quad \tilde{x}_0 = \frac{1}{D}b_0 ,$$

$$\tilde{x}_3 = \frac{1}{D}b_0\frac{\lambda}{\lambda'}\tilde{x}_1 , \quad \tilde{x}_4 = \frac{1}{D}b_0\frac{\rho}{\rho'}\tilde{x}_2 ,$$

$$\tilde{x}_5 = \frac{1}{D}b_0 u\tilde{x}_1\tilde{x}_7 , \quad \tilde{x}_6 = \frac{1}{D}b_0 v\tilde{x}_2\tilde{x}_8 ,$$

where

$$D = 1 + \frac{\lambda}{\lambda'}\tilde{x}_1 + \frac{\rho}{\rho'}\tilde{x}_2 + u\tilde{x}_1\tilde{x}_7 + v\tilde{x}_2\tilde{x}_8$$

can be identified as $D = 1 + F(\xi)$.

If $a = b$ we can obtain the corresponding expressions for the $\tilde{x}_i$ $(i = 0, 1, \cdots, 8)$ by using the corresponding values of ξ (Figure 3).

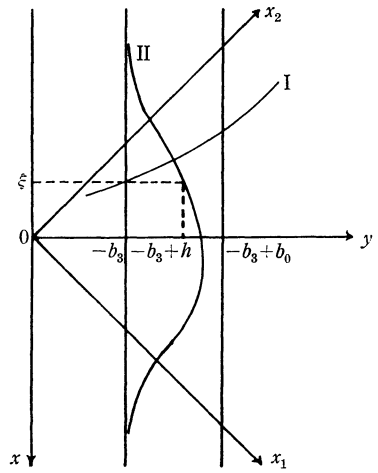

FIG. 3

THEOREM 2.1. *In the domain of biological significance, that is,* $b_3 < 0$, $b_1 + b_3 \leqq 0$, $b_2 + b_3 \leqq 0$, $b_1 + b_2 + b_3 \leqq 0$ *and* $0 < b_0 \ll |b_3|$, *there exists a unique equilibrium point. Moreover, this equilibrium point is an asymptotic stable point.*

The first part of the theorem was proved by the above considerations. For the second one let $(\bar{x}_0, \bar{x}_1, \cdots, \bar{x}_8)$ be the coordinates of the

equilibrium point and consider the new variables $y_1 = x_1 - \bar{x}_1$, $y_2 = x_2 - \bar{x}_2$, $y_3 = x_7 - \bar{x}_7$, $y_4 = x_8 - \bar{x}_8$ and $y_5 = (1/2)((x_5 - \bar{x}_5 + x_7 - \bar{x}_7) - (x_6 - \bar{x}_6 + x_8 - \bar{x}_8))$. We can write:

$$-\frac{dy_1}{dt} = (\lambda' + \lambda(\bar{x}_0 + \bar{x}_1))y_1 + \lambda\bar{x}_1 y_2 - \lambda' y_3 + \lambda y_1(y_1 + y_2)$$

$$-\frac{dy_2}{dt} = \rho\bar{x}_2 y_1 + (\rho' + \rho(\bar{x}_0 + \bar{x}_2))y_2 - \rho' y_4 + \rho y_2(y_1 + y_2)$$

$$-\frac{dy_3}{dt} = -\mu\bar{x}_7 y_1 + (\mu' + \mu(\bar{x}_3 + \bar{x}_7))y_3 - \mu' y_5 + \mu y_3(y_3 - y_1)$$

$$-\frac{dy_4}{dt} = -\nu\bar{x}_8 y_2 + (\nu' + \nu(\bar{x}_4 + \bar{x}_8))y_4 + \nu' y_5 + \nu y_4(y_4 - y_2)$$

$$-\frac{dy_5}{dt} = -\alpha y_3 + \beta y_4 + (\alpha + \beta)y_5 .$$

We look for a Liapunov function of the form $V = \sum_{i=1}^{5} \gamma_i y_i^2$ with $\gamma_i > 0$ $(i = 1, \cdots, 5)$. If we replace in $dV/dt = 2\sum_{i=1}^{5} \gamma_i y_i dy_i/dt$ the values of the derivatives dy_i/dt given above, we have:

$$\begin{aligned}-\frac{1}{2}\frac{dV}{dt} = {} & \gamma_1\lambda(\bar{x}_0 + y_1 + y_2)y_1^2 + \gamma_2\rho(\bar{x}_0 + y_1 + y_2)y_2^2 \\ & + \gamma_3\mu(\bar{x}_3 + y_3 - y_1)y_3^2 + \gamma_4\nu(\bar{x}_4 + y_4 - y_2)y_4^2 \\ & + (y_1 + y_2)(\lambda\bar{x}_1\gamma_1 y_1 + \rho\bar{x}_2\gamma_2 y_2) + (y_1 - y_3)(\gamma_1\lambda' y_1 - \gamma_3\mu\bar{x}_7 y_3) \\ & + (y_2 - y_4)(\gamma_2\rho' y_2 - \gamma_4\nu\bar{x}_8 y_4) + (y_3 - y_5)(\gamma_3\mu' y_3 - \gamma_5\alpha y_5) \\ & + (y_4 + y_5)(\gamma_4\nu' y_4 + \gamma_5\beta y_5) .\end{aligned}$$

But we have $y_1 + y_2 + \bar{x}_0 = x_0 > 0$, $\bar{x}_3 + y_3 - y_1 = x_3 > 0$ and $\bar{x}_4 + y_4 - y_2 = x_4 > 0$ and if we put $\lambda\bar{x}_1\gamma_1 = \rho\bar{x}_2\gamma_2$, $\gamma_1\lambda' = \gamma_3\mu\bar{x}_7$, $\gamma_2\rho' = \gamma_4\nu\bar{x}_8$, $\gamma_3\mu' = \gamma_5\alpha$ and $\gamma_4\nu' = \gamma_5\beta$, this implies that $dV/dt < 0$. It is enough now to take $\gamma_1 = (a/\lambda)\bar{x}_7$, $\gamma_2 = (b/\rho)\bar{x}_8$, $\gamma_3 = \alpha/\mu'$, $\gamma_4 = \beta/\nu'$ and $\gamma_5 = 1$.

The inequalities $V > 0$ and $dV/dt < 0$ are verified in the whole domain of biological significance and V and dV/dt are zero only in the equilibrium point, provided that all association and dissociation constants are different from zero.

3. Equilibrium conditions in the case of several enzymes. In the case of polymeric enzymes or monomeric enzymes in heterozygote cells, different enzymatic species E_i $(i = 1, \cdots, n)$ act competitively on the same substrates A, B, C, and D. The corresponding equations have been given at the end of Section 1. From them, we deduce *trivial relations* which

state the conservation laws of chemical species E_i $(i = 1, \cdots, n)$, A, B, C, and D:

$$b_{0i} = x_{0i} + x_{3i} + x_{4i} + x_{5i} + x_{6i} \quad (i = 1, \cdots, n)$$

$$x_1 + x_2 = \sum_{i=1}^{n} x_{0i} - b_3$$

$$x_1 + \sum_{i=1}^{n} x_{3i} - x_7 = b_1$$

$$x_2 + \sum_{i=1}^{n} x_{4i} - x_8 = b_2$$

where b_{0i} $(i = 1, \cdots, n)$, b_1, b_2, b_3 are real constants submitted to analogous inequalilies as in Section 2.

The conditions $dx_{ij}/dt = 0$ $(i = 0, 3, 4, 5, 6; j = 1, \cdots, n)$ and the conservation of enzymatic species E_j $(j = 1, \cdots, n)$ show that

$$b_{0i} = x_{0i}\left(1 + \frac{\lambda_i}{\lambda_i'}x_1 + \frac{\rho_i}{\rho_i'}x_2 + \frac{\mu_i}{\mu_i'}\frac{\lambda_i}{\lambda_i'}x_1x_7 + \frac{\nu_i}{\nu_i'}\frac{\rho_i}{\rho_i'}x_2x_8\right)$$
$$+ A_i\left(-\frac{1}{\lambda_i'} + \frac{1}{\rho_i'} - \frac{1}{\mu_i'} + \frac{1}{\nu_i'} - \frac{1}{\lambda_i'}\frac{i}{\mu_i'}x_7 + \frac{1}{\rho_i'}\frac{\mu_i}{\nu_i}x_8\right)$$

and

$$x_{0i}\left(\alpha_i\frac{\lambda_i}{\lambda_i'}\frac{\mu_i}{\mu_i'}x_1x_7 - \beta_i\frac{\rho_i}{\rho_i'}\frac{\nu_i}{\nu_i'}x_2x_8\right)$$
$$= A_i\left(1 + \frac{\alpha_i}{\mu_i'} + \frac{\beta_i}{\nu_i'} + \alpha_i\frac{\mu_i}{\mu_i'}\frac{x_7}{\lambda_i'} + \beta_i\frac{\nu_i}{\nu_i'}\frac{x_8}{\rho_i'}\right)$$

where $A_i = \alpha_i x_{5i} - \beta_i x_{6i}$ $(i = 1, \cdots, n)$. If we solve the above system we can express for each i, A_i and x_{0i} as functions of the constants b_{0i}, of biophysical parameters of enzymes E_i and of concentrations x_1, x_2, x_7, x_8 of substrates. If we report such expressions of A_i in the equation $dx_8/dt = \sum_{i=1}^{n} A_i$ we obtain a *generalization of Michaelis equation.*

To obtain the *equilibrium conditions*, we must consider, in addition, the following equations: $dx_i/dt = 0$ $(i = 1, 2, 7, 8)$. These conditions are equivalent to $\sum_{i=1}^{n} A_i = 0$.

By analogy with the case when $n = 1$ (see Section 2), we can obtain an approximate equilibrium point by neglecting $\sum_{i=1}^{n} x_{0i}$, $\sum_{i=1}^{n} x_{3i}$ and $\sum_{i=1}^{n} x_{4i}$ with respect to x_1, x_2, x_7, and x_8 in the last three trivial relations.

We get $x_2 = -x_1 - b_3$, $x_7 = x_1 - b_1$, $x_8 = -x_1 - b_2 - b_3$ so that, the sum $\sum_{i=1}^{n} A_i$ is a function of a single variable x_1 and it is enough to find the zeros of the function $f(x_1) = \sum_{i=1}^{n} A_i$. Denote by $\tilde{x}_{1i}$ the approximate

equilibrium value of x_1 if we suppose that only the enzyme E_i works. Then we can show that $f(x_1)$ has a unique zero $\tilde{x}_1$ in the domain of biological significance (see Theorem 2.1, for the definition of this domain). In fact, we have

$$\inf_{1\leqq i\leqq n} \tilde{x}_{1i} \leqq \tilde{x}_1 \leqq \sup_{1\leqq i\leqq n} \tilde{x}_{1i} .$$

4. **Discussion** (cf. [2]). In the present paper we have worked on a single enzymatic step, which can be seen as an arche type for any metabolic path (Dixon and Webb, 1964). This rather complicated enzymatic model was chosen because it involves several stereospecific associations, and thus embodies the main property of biological systems, and it can be used for polymetric enzymes as well as for monomeric enzymes. The model makes also a clear distinction between purely genetic parameters and environmental conditions. The genetic parameters are coefficients of association and dissociation $\lambda, \lambda', \cdots, \nu, \nu'$, and enzymatic activity coefficients α and β: their hereditary transmission follows the usual rules of population genetics, although their values are temperature dependent. Environmental conditions are expressed by initial values in the medium of substrates concentrations b_1, b_2, b_3 and total enzyme concentration b_0. Although restricted to the simplest case of a closed system with only one class of enzyme, the foregoing results are worth bringing to light:

(i) An equilibrium exists and it is stable, so that the model allows us to give an explicit expression of a quantitative genotype as function of absolute biophysical parameters a and b, and of environmental conditions b_1, b_2, and b_3.

(ii) The hereditary parameters $a = \alpha\lambda\mu/\lambda'\mu'$ and $b = \beta\rho\nu/\rho'\nu'$ involve, on the one hand, the stereospecific capacities of the genetically coded enzyme molecule and, on the other hand, its capabilities of exchange of high energy bounds (α, β) which concern its strictly enzymatic properties. Therefore, we can understand the action of a mutation at the level of the phenotypic expression of a mutated gene, by some handling of the values of these parameters.

The ratio $g = a/b$ takes in consideration not only all the hereditary information of the coefficients $\alpha, \beta, \lambda, \lambda', \cdots$ but also the direction of the removing from the equilibrium $A + B \rightleftharpoons C + D$, and is identical with the coefficient $K = [C][D]/[A][B]$, in kinetics.

(iii) The present approach can be linked with the usual approach of quantitative genetics if we consider a population of cells which are living in the same medium, but carry different allele genes coding for

the enzyme E.

If we suppose that the parameters g of the enzymes are not very different from a standard value g_r, each having the form $g_i = g_r + \omega_i$, then the equilibrium values $x_1(g_i)$ are the sum of two terms: the first one, $x_1(g_r)$, is common to every enzyme of this class, and the second one is specific of an enzyme and is the deviation of a given gene from the standard phenotypic value $x_1(g_r)$.

For instance, if $g_r = 1$, we get:

$$x_1 = -\frac{b_3(b_2 + b_3)}{b_1 + b_2 + b_3} + \frac{b_3(b_1 + b_3)(b_2 + b_3)(b_1 + b_2 + b_3)}{(b_1 + b_2 + 2b_3)^3}\omega + O(x_0) + O(\omega^2|b_3|)$$

$$x_2 = -\frac{b_3(b_1 + b_3)}{b_1 + b_2 + 2b_3} - \frac{b_3(b_1 + b_3)(b_2 + b_3)(b_1 + b_2 + b_3)}{(b_1 + b_2 + 2b_3)^3}\omega + O(x_0) + O(\omega^2|b_3|)\,,$$

where $g = 1 + \omega$. These expressions allow us to put in a concrete form the idea of substitution effect of a gene; for two genes having the hereditary characteristics ω, ω', the effect of the substitution of one by the other is:

$$\frac{b_3(b_1 + b_3)(b_2 + b_3)(b_1 + b_2 + b_3)}{(b_1 + b_2 + 2b_3)^3}(\omega - \omega')$$

for x_1.

Such a quantity involves the action of the gene interacting with the environment. Moreover, it is clear that random fluctuations in the environmental conditions could be taken into account.

(iv) The study of the case with many enzymes indicates that no overdominance might arise for a reaction controlled by one monocatenar enzyme. Overdominance would necessitate that the enzyme is at least dimeric, so that a hybrid cell may carry a new enzymatic species, which cannot be found in the homozygous parental cells, and whose biophysical parameters cannot be related to those of the parental cells.

We have now to prove that the model is also relevant to other situations and can describe such phenomena as allosteric regulation, feedback regulations and strictly genic regulations.

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