Application of electrical analogues for control analysis of simple metabolic pathways

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I have used electrical analogues for calculating the Flux Control Coefficients of metabolic pathways. An analogue circuit consists of resistances that are connected in series (or parallel) with a voltage (or current) source. In constructing the analogues, each of the enzymes in the pathway is associated with a resistance whose magnitude depends on the Elasticity Coefficients of the enzymes. These circuits can be designed in a heuristic fashion directly from the configuration of the pathway, without the necessity of writing down the governing equations with the use of Summation and Connectivity Theorems. The Flux Control Coefficients of the enzymes are represented by voltages across (or currents through) the resistances and are determined by an application of Ohm's Law. Results are given for (a) a simple linear pathway without feedback or feedforward regulation, and (b) a linear pathway with feedback inhibition. The analogue circuits are also convenient for assessing the relative importance of the various enzymes in flux control, and for simplifying the structure of a given pathway.

INTRODUCTION

A quantitative analysis of metabolic regulation is essential for a complete understanding of the overall metabolism in biological and biochemical systems. It is also useful in developing optimal operating strategies for important biotechnological processes such as microbial fermentation. Such an analysis is commonly carried out within the premises of the Metabolic Control Theory, which was developed by Kacser & Burns (1973) and Heinrich & Rapoport (1974) nearly 20 years ago. In Metabolic Control Theory, the response of a flux (or concentration) to a change in enzyme activity is defined in terms of a Flux (or Concentration) Control Coefficient. More precisely, these Control Coefficients describe the fractional change in flux or metabolite concentration with respect to a fractional change in concentration of an enzyme. Two principal theorems, known as Summation and Connectivity Theorems, are devised to relate the Flux Control Coefficients (or Concentration Control Coefficients) to the Elasticity Coefficients. The Elasticity Coefficient of an enzyme towards a particular metabolite measures the fractional change in rate of the reaction catalysed by the enzyme relative to a fractional change in metabolite concentration. These two theorems lead to a system of linear algebraic equations for the Control Coefficients. By solving these equations, the Flux Control Coefficients (or Concentration Control Coefficients) are evaluated in terms of the Elasticity Coefficients. The linear equations can be solved by a variety of methods. It has become customary to cast these equations in a matrix form and calculate the Control Coefficients by inverting the appropriate matrix [see, e.g., Fell & Sauro (1985) or Westerhoff & Kell (1987)]. A diagrammatic procedure has also been developed for control-pattern analysis of metabolic pathways (Hofmeyr, 1989).

In a recent work (Sen, 1990a), I used a graph-theoretic approach for the evaluation of the Control Coefficients. In this approach, the control structure of a metabolic pathway is represented by a weighted directed graph called a signal-flow graph. From an inspection of the topology of the signal-flow graph, the Control Coefficients are determined in a heuristic manner without recourse to matrix inversion or other algebraic procedures.

The purpose of the present paper is to develop an alternative approach, namely application of electrical analogues for calculating the Flux Control Coefficients of metabolic pathways. An analogue circuit consists of resistances that are connected in series (or parallel) with a voltage (or current) source. In constructing these analogues, each of the enzymes in the pathway is associated with a resistance whose magnitude depends on the Elasticity Coefficients of the enzymes. The Flux Control Coefficients are represented by voltages across (or currents through) these resistances and are determined by an application of Ohm's Law. As with the graph-theoretic approach (Sen, 1990a), the analogue circuits can be designed in a heuristic fashion directly from the configuration of the pathway, without the necessity of writing down the governing equations using Summation and Connectivity Theorems. Like the signal-flow graphs, these circuits also provide a visual framework for studying the regulatory behaviour of metabolic pathways.

The presentation is organized as follows. First I describe the methodology of constructing electrical analogue circuits for the analysis of flux-control distribution in an unregulated pathway (i.e. in the absence of feedback or feedforward regulation). This is followed by an investigation of a linear pathway in which the last metabolite acts as an allosteric effector and inhibits the first enzyme. Another feedback pattern, namely inhibition of an intermediate enzyme by an intermediate metabolite, is examined in order to elucidate the general structure of these analogue circuits. Finally, I discuss how the electrical analogues can be utilized for determining the relative importance of the enzymes in flux control and also for simplifying the pathway structure.

A SIMPLE LINEAR PATHWAY

In order to demonstrate that the control structure of a metabolic pathway can be analysed by means of electrical analogues, we first examine the following linear pathway with no feedback or feedforward regulation:

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Here S and P are the initial substrate and the final product respectively; X_i ($i = 1, 2, 3, 4$) represent the internal metabolites, and E_i ($i = 1, 2, 3, 4, 5$) denote the various enzymes. It is assumed that the concentrations of S and P are maintained at constant levels.

According to the Connectivity Theorem of Metabolic Control Theory, the Flux Control Coefficients of any two contiguous enzymes, E_i and E_{i+1} , in pathway (A) are related by the equation:

$$\epsilon_i^t C_i + \epsilon_{i+1}^{t+1} C_{i+1} = 0 \quad (1)$$

The quantities C_i and C_{i+1} are the Flux Control Coefficients of the enzymes E_i and E_{i+1} respectively; ϵ_i^t is the Elasticity Coefficient of enzyme E_i due to inhibition by its product X_i , and ϵ_{i+1}^{t+1} is the Elasticity Coefficient of enzyme E_{i+1} with respect to X_i . Since ϵ_i^t is negative, we shall write $\epsilon_i^t = -\bar{\epsilon}_i^t$, $\bar{\epsilon}_i^t$ being the magnitude of the Elasticity Coefficient. Eqn. (1) can be expressed as:

$$\frac{C_{i+1}}{C_i} = \frac{\bar{\epsilon}_i^t}{\epsilon_{i+1}^{t+1}} \quad (2)$$

from which we may successively write:

$$\frac{C_2}{C_1} = \frac{\bar{\epsilon}_1^1}{\epsilon_2^2} \quad (3a)$$

$$\frac{C_3}{C_1} = \left(\frac{C_3}{C_2}\right)\left(\frac{C_2}{C_1}\right) = \frac{\bar{\epsilon}_1^1 \bar{\epsilon}_2^2}{\epsilon_2^2 \epsilon_3^3} \quad (3b)$$

$$\frac{C_4}{C_1} = \left(\frac{C_4}{C_3}\right)\left(\frac{C_3}{C_1}\right) = \frac{\bar{\epsilon}_1^1 \bar{\epsilon}_2^2 \bar{\epsilon}_3^3}{\epsilon_2^2 \epsilon_3^3 \epsilon_4^4} \quad (3c)$$

$$\frac{C_5}{C_1} = \left(\frac{C_5}{C_4}\right)\left(\frac{C_4}{C_1}\right) = \frac{\bar{\epsilon}_1^1 \bar{\epsilon}_2^2 \bar{\epsilon}_3^3 \bar{\epsilon}_4^4}{\epsilon_2^2 \epsilon_3^3 \epsilon_4^4 \epsilon_5^5} \quad (3d)$$

The Summation Theorem of Metabolic Control Theory states that the Flux Control Coefficients must satisfy the relation:

$$C_1 + C_2 + C_3 + C_4 + C_5 = 1 \quad (4)$$

If we identify the Flux Control Coefficients with electric currents, then in view of the relations (3) and (4) the control structure of pathway (A) can be represented by the electric circuit shown in Fig. 1, which I refer to as a current-analogue circuit. The circuit consists of five resistors corresponding to the five enzymes in the pathway, which are connected in parallel with a current source of magnitude unity. The currents flowing through these resistors characterize the unknown Flux Control Coefficients of the respective enzymes. Clearly, since the voltage across each of the resistors is the same, the currents through any two resistors are inversely proportional to their resistances, consistent with the Connectivity Theorem. Furthermore, by Kirchoff's Law, the sum of the currents through the various resistors is equal to the source current, in keeping with the Summation Theorem.

The above circuit can be constructed directly from the configuration of the metabolic pathway, without referring to the Summation and Connectivity Theorems explicitly. For this purpose, we redraw the pathway displaying the various Elasticity Coefficients, as shown below:

Such a representation has been used earlier (Sen, 1990) in my formulation of the graph-theoretic approach for metabolic control analysis. Here a typical Elasticity Coefficient ϵ_i^t is designated by a broken line with an arrow pointing from the metabolite X_i to the enzyme E_i . The circuit of Fig. 1 is set up by first connecting five resistances in parallel, corresponding to the five enzymes. Next we look at the pathway from the substrate end

Fig. 1. Current-analogue circuit for the unregulated pathway (A), constructed by viewing the pathway from the substrate end

(i.e. the enzyme E_1) and choose the value of R_1 to be unity. The magnitudes of the other resistances are selected as follows. The value of R_2 is taken to be the inverse ratio of the Elasticity Coefficients of the first two enzymes, E_1 and E_2 (with respect to their shared metabolite, X_1), with an appropriate sign. To fix the sign, we adopt the following convention: if the Elasticity Coefficient points in the forward (i.e. downstream) direction of the pathway, then it is taken with its sign unchanged; on the other hand, if the Elasticity Coefficient points in the upstream direction, then it is used with its sign reversed. Note also that the Elasticity Coefficients ϵ_i^t , which are due to product inhibition, are negative. To assign a value for R_3 , we consider the enzyme E_3 and all the enzymes (and metabolites) that are located upstream from E_3 in the representation (A1); we then form the product of the ratios of Elasticity Coefficients of each contiguous pair of these enzymes (with respect to the adjoining metabolites), with their signs decided by the above convention; the reciprocal of this product is used as R_3 . The remaining two resistances, R_4 and R_5 , are chosen in a similar fashion. Finally, a current source of strength unity is connected in parallel with these resistances.

As indicated above, the Flux Control Coefficient (C_i) of an enzyme E_i is equal to the current flowing through the resistance R_i in the circuit of Fig. 1. To calculate these currents, we need to find the voltage (V) across the resistances. The equivalent resistance (R) of the circuit is given by:

$$\frac{1}{R} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} + \frac{1}{R_5} \quad (5)$$

Application of Ohm's Law then gives $V = R$, since the source current is unity. Accordingly, $C_i = V/R_i = R/R_i$, or we may write:

$$C_i = \Gamma_i / \Gamma, \quad i = 1, 2, 3, 4, 5 \quad (6)$$

with

$$\begin{aligned} \Gamma_1 &= \frac{1}{R_1} = 1, \quad \Gamma_2 = \frac{1}{R_2} = \frac{\bar{\epsilon}_1^1}{\epsilon_2^2}, \quad \Gamma_3 = \frac{1}{R_3} = \frac{\bar{\epsilon}_1^1 \bar{\epsilon}_2^2}{\epsilon_2^2 \epsilon_3^3}, \\ \Gamma_4 &= \frac{1}{R_4} = \frac{\bar{\epsilon}_1^1 \bar{\epsilon}_2^2 \bar{\epsilon}_3^3}{\epsilon_2^2 \epsilon_3^3 \epsilon_4^4}, \quad \Gamma_5 = \frac{1}{R_5} = \frac{\bar{\epsilon}_1^1 \bar{\epsilon}_2^2 \bar{\epsilon}_3^3 \bar{\epsilon}_4^4}{\epsilon_2^2 \epsilon_3^3 \epsilon_4^4 \epsilon_5^5} \end{aligned} \quad (7)$$

Fig. 2. Voltage-analogue circuit corresponding to Fig. 1, for the unregulated pathway (A)

so that

$$\Gamma = \Gamma_1 + \Gamma_2 + \Gamma_3 + \Gamma_4 + \Gamma_5 = 1 + \frac{e_1^1}{e_1^2} + \frac{e_1^1 e_2^2}{e_1^2 e_2^3} + \frac{e_1^1 e_2^2 e_3^3}{e_1^2 e_2^3 e_3^4} + \frac{e_1^1 e_2^2 e_3^3 e_4^4}{e_1^2 e_2^3 e_3^4 e_4^5} \quad (8)$$

Here Γ_i is the conductance of the resistor R_i and Γ is the total conductance of the circuit.

An alternative way of representing the control structure of this pathway is to use a resistive network with a voltage source. This is shown in the circuit of Fig. 2, which consists of five resistances connected in series with a voltage source of strength unity. This network is referred to as a voltage-analogue circuit for pathway (A). Note that the resistances in this circuit are reciprocals of the corresponding resistances (i.e. equal to the conductances) in the current-analogue circuit (see Fig. 1). The Flux Control Coefficient C_i of enzyme E_i is now given by the voltage drop (V_i) across the resistor $\bar{R}_i$, $i = 1, 2, 3, 4, 5$. The total resistance of the circuit is $\bar{R} = \bar{R}_1 + \bar{R}_2 + \bar{R}_3 + \bar{R}_4 + \bar{R}_5$, so that the current flowing through these resistors has the value $I = 1/\bar{R}$. Consequently the Flux Control Coefficients are $C_i = \bar{R}_i/\bar{R}$, which have the same expressions as those given in eqns. (6)–(8), since $\Gamma_i = \bar{R}_i$ and $\Gamma = \bar{R}$.

Before leaving this section, it should be pointed out that the control structure of a given pathway can be represented by more than one current-analogue or voltage-analogue circuit. The current-analogue circuit presented above was designed by looking at the pathway from the substrate end and setting the resistance R_1 (corresponding to the enzyme E_1) equal to 1. Another possible current-analogue circuit can be constructed by viewing the pathway from the product end (i.e. enzyme E_5) and taking $R_5 = 1$. This is shown in Fig. 3. The resistances R_1 – R_4 in this circuit are chosen as follows. R_4 , which corresponds to the enzyme E_4 , is taken equal to the ratio of the Elasticity Coefficients of the enzymes E_4 and E_5 towards their shared metabolite X_4 , with an appropriate sign. The sign is determined according to the convention adopted above. To select a value for R_3 , we consider the enzyme E_3 and all the enzymes (and metabolites) downstream from E_3 ; R_3 is the product of the ratios of Elasticity Coefficients of each successive pair of these enzymes (with respect to the adjoining metabolites), with proper signs. An analogous procedure is used for selecting the resistances R_1 and R_2 . It can be shown that this circuit generates expressions for the Flux Control Coefficients that are equivalent to those given in eqns. (6)–(8). The corresponding voltage-analogue circuit is portrayed in Fig. 4, which is constructed in the manner described above with Fig. 2.

A third possibility is to view the pathway from any of the intermediate enzymes, say E_3 , and choose $R_3 = 1$. The resulting current-analogue circuit is shown in Fig. 5. For the sake of brevity, the constructional details are not given here. Analogous circuits can be designed with, for instance, $R_2 = 1$ or $R_4 = 1$.

Fig. 3. Current-analogue circuit for the unregulated pathway (A), constructed by viewing the pathway from the product end

Fig. 4. Voltage-analogue circuit corresponding to Fig. 3, for the unregulated pathway (A)

Fig. 5. Current-analogue circuit for the unregulated pathway (A), constructed by viewing the pathway from enzyme E_3

A LINEAR PATHWAY WITH FEEDBACK INHIBITION

We now consider the scenario in which the last internal metabolite in pathway (A) acts as an allosteric effector and inhibits the activity of the first enzyme in the pathway:

A current-analogue circuit for the control structure of this pathway can be constructed from that of the unregulated pathway (namely Fig. 1) by adding a resistance R'_5 in parallel with R_5 (i.e. in the path of the current C_5), as shown in Fig. 6. The value of this shunt resistance is selected as follows. We redraw the pathway by deleting the feedback loop and all the enzymes and metabolites that are located inside it, thereby treating the enzymes E_1 and E_5 as contiguous enzymes with X_4 as their adjoining metabolite:

In the above representation the relevant Elasticity Coefficients are shown with broken lines, for convenience. The quantity $\epsilon_4^5/\bar{\epsilon}_4^1$, which is the inverse ratio of the magnitudes of Elasticity Coefficients of the enzymes E_1 and E_5 (with respect to X_4) is taken as R'_5 . Note that $\epsilon_4^1 = -\bar{\epsilon}_4^1$, $\bar{\epsilon}_4^1$ being the magnitude of the Elasticity Coefficient due to feedback inhibition. From the circuit shown in Fig. 6 it is easy to see that the Flux Control Coefficients of the first four enzymes are given by:

$$C_i = \Gamma_i / \Gamma^*, \quad i = 1, 2, 3, 4 \quad (9a)$$

where $\Gamma_1, \Gamma_2, \Gamma_3, \Gamma_4$ (and Γ_5) are defined in eqn. (7), and:

$$\Gamma^* = \Gamma_1 + \Gamma_2 + \Gamma_3 + \Gamma_4 + \Gamma_5 + \Gamma'_5 \quad (9b)$$

with

$$\Gamma'_5 = \frac{1}{R'_5} = \frac{\bar{\epsilon}_4^1}{\epsilon_4^5} \quad (9c)$$

The Flux Control Coefficient of the last enzyme, which is equal to the sum of the currents through the resistances R_5 and R'_5 , has the value:

$$C_5 = (\Gamma_5 + \Gamma'_5) / \Gamma^* \quad (9d)$$

For the above pathway, the voltage-analogue circuit that is equivalent to the current-analogue circuit of Fig. 6 is depicted in Fig. 7. As usual, the resistances in this circuit are reciprocals of the corresponding resistances in Fig. 6. Note that the Flux Control Coefficient of the enzyme E_5 is now equal to the total voltage drop across the resistors $\bar{R}_5$ and $\bar{R}'_5$. The current-analogue circuit of Fig. 3 or Fig. 5 can also be modified to incorporate the effect of feedback inhibition in pathway (B). These ramifications are not discussed further in the present paper.

In order to elucidate the general structure of the analogue circuits, we next examine a different pattern of feedback inhibition by considering that the enzyme E_2 in pathway (A) is inhibited by the metabolite X_3 :

A current-analogue circuit for this pathway is presented in Fig. 8. In comparison with the circuit of Fig. 1, this circuit contains two additional resistances R'_4 and R'_5 , corresponding to the enzymes E_4 and E_5 , which are located downstream of the feedback

Fig. 6. Current-analogue circuit for pathway (B), a linear pathway with the first enzyme inhibited by the last metabolite, constructed by viewing the pathway from the substrate end

Fig. 7. Voltage-analogue circuit corresponding to Fig. 6, for pathway (B)

loop in the pathway. To select the magnitudes of these resistances, we redraw the pathway in the manner analogous to the representation (B1) above, by deleting the feedback loop and all its intervening enzymes and metabolites, and treat the enzymes E_2 and E_4 as contiguous enzymes with X_3 as the shared metabolite:

In the representation (C1), we consider the enzyme E_4 (or E_5) and all the enzymes and metabolites located upstream from it (Fig. 8). The value of R'_4 (or R'_5) is the reciprocal of the product of the

Fig. 8. Current-analogue circuit for pathway (C), constructed by viewing the pathway from the substrate end

signed ratios of the Elasticity Coefficients of each consecutive pair of these enzymes with respect to their adjoining metabolites.

From this circuit the Flux Control Coefficients of the enzymes are obtained by an application of Ohm's Law. We have:

$$C_1 = \Gamma_1/\Gamma^{**}, C_2 = \Gamma_2/\Gamma^{**}, C_3 = \Gamma_3/\Gamma^{**} \quad (10a)$$

$$C_4 = (\Gamma_4 + \Gamma_4'')/\Gamma^{**}, C_5 = (\Gamma_5 + \Gamma_5'')/\Gamma^{**} \quad (10b)$$

where

$$\Gamma_4'' = \frac{1}{R_4''} = \frac{\bar{e}_1^2 \bar{e}_3^2}{e_1^2 e_3^4}, \Gamma_5'' = \frac{1}{R_5''} = \frac{\bar{e}_1^2 \bar{e}_3^2 \bar{e}_4^4}{e_1^2 e_3^4 e_4^5} \quad (10c)$$

and

$$\Gamma^{**} = \Gamma_1 + \Gamma_2 + \Gamma_3 + \Gamma_4 + \Gamma_4'' + \Gamma_5 + \Gamma_5'' \quad (10d)$$

The expressions for the conductances Γ_1 – Γ_5 are given in eqn. (7). Note that the resistances R_4'' and R_5'' do not depend on the Elasticity Coefficients of the enzyme E_3 , which is trapped inside the feedback loop. A voltage-analogue circuit corresponding to Fig. 8 can be designed in the usual fashion by connecting seven resistances (whose magnitudes are reciprocals of the magnitudes of the resistances in Fig. 8) in series with a voltage source of strength unity.

In general, if there are, say, n enzymes located downstream from a feedback loop, then in the current-analogue circuit of Fig. 1 we must include a resistance (such as R_4'' or R_5'') in the path of the current corresponding to each of these 'downstream' enzymes. The magnitudes of these resistances are selected by following the same procedure as described in connection with the representation (C1).

RELATIVE PROPORTIONS OF FLUX CONTROL

The relative importance of the various enzymes in controlling the flux through a given pathway can be established by studying the relative magnitudes of their Flux Control Coefficients. To see how this can be done with an electrical analogue, suppose that we want to find the ratio of the Flux Control Coefficients of the enzymes E_5 and E_2 in pathway (B). Consider the current-analogue circuit for this pathway as shown in Fig. 6. Note that the effective resistance ($\bar{R}_5$) through which the current C_5 flows is given by:

$$\frac{1}{\bar{R}_5} = \frac{1}{R_5} + \frac{1}{R_5'} \quad (11)$$

Since the voltages across all the resistances in this circuit are the same, it follows that the ratio of the currents, C_5/C_2 , is equal to $R_2/\bar{R}_5$; accordingly, the ratio of the Flux Control Coefficients of the enzymes E_5 and E_2 has the value:

$$\frac{C_5}{C_2} = R_2 \left(\frac{1}{R_5} + \frac{1}{R_5'} \right) \quad (12)$$

which amounts to:

$$\frac{C_5}{C_2} = \frac{\bar{e}_2^2 \bar{e}_3^2 \bar{e}_4^4}{e_2^2 e_3^4 e_4^5} + \frac{e_1^2 \bar{e}_4^4}{\bar{e}_1^2 e_4^5} \quad (13)$$

This result can also be obtained from the corresponding voltage-analogue circuit depicted in Fig. 7. Recall that the Flux Control Coefficient of the enzyme E_5 is given by the total voltage drop across the resistors $\bar{R}_5$ and $\bar{R}_5'$ in this circuit, whereas the Flux Control Coefficient of the enzyme E_2 equals the voltage drop across the resistor R_2 . Since the same current passes through each of the resistors, the voltage drops across them are directly proportional to their resistances. Thus we have $C_5/C_2 = (\bar{R}_5 + \bar{R}_5')/\bar{R}_2$, which is identical with the result given in eqn. (13).

STRUCTURAL SIMPLIFICATION OF PATHWAYS

Electrical analogues can also be used as an aid to simplify the structure of a metabolic pathway. Suppose, for instance, it is desired to group the enzymes E_2 – E_5 in pathway (B) into a single enzyme E_* , thereby reducing the pathway as shown below:

It would be necessary to determine the Elasticity Coefficient (e_1^*) of this grouped enzyme with respect to the metabolite X_1 . This can be achieved from an electrical-analogue circuit as follows. I will use a current-analogue circuit for this purpose. First set up the current-analogue circuit for the reduced pathway (see Fig. 9), and consider the current-analogue circuit (Fig. 6) of the original

Fig. 9. Current-analogue circuit for the reduced pathway (D)

pathway. In Fig. 6, combine the resistances R_2 – R'_5 , corresponding to the enzymes E_2 – E_5 being grouped together, and equate the total resistance to R_* of Fig. 9. The result is:

$$\frac{1}{R_*} = \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} + \frac{1}{R_5} + \frac{1}{R'_5} \quad (14)$$

from which it follows that:

$$\epsilon_1^* = \epsilon_1^2 \left/ \left(1 + \frac{\bar{\epsilon}_2^2}{\epsilon_2^3} + \frac{\bar{\epsilon}_2^2 \bar{\epsilon}_3^3}{\epsilon_2^3 \epsilon_3^4} + \frac{\bar{\epsilon}_2^2 \bar{\epsilon}_3^3 \bar{\epsilon}_4^4}{\epsilon_2^3 \epsilon_3^4 \epsilon_4^5} + \frac{\bar{\epsilon}_1^2 \bar{\epsilon}_4^4}{\bar{\epsilon}_1^1 \epsilon_4^5} \right) \right. \quad (15)$$

The same result can be deduced from an examination of the corresponding voltage-analogue circuit of Fig. 7.

CONCLUDING REMARKS

Using simple examples, I have demonstrated that the flux-control distribution in metabolic pathways can be analysed with the aid of electrical analogues. An analogue circuit consists of resistances that are connected in series (or parallel) with a voltage (or current) source. The magnitudes of the resistances depend on the Elasticity Coefficients of the enzymes, and can be selected in a heuristic fashion from the configuration of the pathway, without the necessity of writing down the governing equations

with the use of Summation and Connectivity Theorems. The Flux Control Coefficients of the various enzymes are represented by voltages across (or currents through) these resistances and are found by an application of Ohm's Law. The analogue circuits are also useful for assessing the relative importance of the enzymes in flux control, and in simplifying the pathway structure. I have examined the control structure of a linear pathway without feedback or feedforward regulation, and a linear pathway with feedback inhibition. Application of electrical analogues to control analysis of metabolic pathways with multiple feedback loops is described elsewhere (Sen, 1990b).

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REFERENCES

- Fell, D. A. & Sauro, H. M. (1985) *Eur. J. Biochem.* **148**, 555–561
- Heinrich, R. & Rapoport, T. (1974) *Eur. J. Biochem.* **42**, 89–102
- Hofmeyr, J. H. S. (1989) *Eur. J. Biochem.* **186**, 343–354
- Kacser, H. & Burns, J. A. (1973) *Symp. Soc. Exp. Biol.* **27**, 65–104
- Sen, A. K. (1990a) *Biochem. J.* **269**, 141–147
- Sen, A. K. (1990b) *Int. J. Biochem.*, in the press
- Westerhoff, H. V. & Kell, D. B. (1987) *Biotechnol. Bioeng.* **30**, 101–107

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