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Metabolic Control Theory and Biochemical Systems Theory: Different Objectives, Different Assumptions, Different Results

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The claim by Savageau *et al.* (1987*a*, *b*, *Math. Biosci.* **86,** 127-145, 147-167) that the theory of metabolic control associated with Kacser & Burns (1973, *Symp. Soc. Exp. Biol.* **27,** 65-104) and with Heinrich & Rapoport (1974, *Eur. J. Biochem.* **42,** 89-102) is no more than a special case of the biochemical systems theory of Savageau and colleagues is examined. It is shown to be based on a misconception of the objectives and assumptions of metabolic control theory. In particular, the control and elasticity coefficients that play a central role in metabolic control theory are not constants and cannot be treated as constants. Consequently they cannot in general be equated with the kinetic orders that appear in biochemical systems theory, though they do correspond at the point where the two theories are tangential to one another.

1. Introduction

Recent years have seen a rapid increase in the attention paid to the theory of biochemical control developed from the landmark papers of Kacser & Burns (1973) and Heinrich & Rapoport (1974). Theoretical advances have dealt, for example, with the matrix representation of control properties (Fell & Sauro, 1985), novel summation properties (Westerhoff & Chen, 1984), the biochemical explanation of the genetic phenomenon of dominance and recessivity (Kacser & Burns, 1981; Cornish-Bowden, 1987; Keightley & Kacser, 1987), the treatment of pathways containing conserved cycles (Hofmeyr *et al.*, 1986), and of systems in which enzyme-enzyme interactions are not negligible (Welch *et al.*, 1988), etc. There has also been a rapid increase in the number of experimental systems to which these ideas are being applied (e.g. Stuart *et al.*, 1986; Woodrow, 1986; Salter *et al.*, 1986; Dykhuizen *et al.*, 1987).

Although it is usual to discuss this theory as if it originated around 1973-1974, in reality much of the theory developed rigorously in Kacser & Burns (1973) was foreshadowed in an earlier paper by them (Kacser & Burns, 1968), and anyway both groups made it clear that they were building on ideas developed by Higgins (1963, 1965). Kacser & Burns (1973) wrote that:

> "Higgins (1963) has presented a kinetic treatment of sequential reactions and has analysed system responses in terms of 'reflection coefficients'. Our treatment is based on essentially the same approach."

Likewise, Heinrich & Rapoport (1974) compared their definition of the "control strength" [equivalent, at constant enzyme concentrations, to the quantity for which

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the name "flux control coefficient" has now been agreed by several groups (Burns *et al.*, 1985)] with that of Higgins (1965). Higgins (1965) himself wrote that "most of the results brought out in the preceding analysis have been intuitively and in some cases quantitatively realized by many others".

Metabolic control theory did not therefore emerge in a complete and final form at one moment but grew from the ideas of others. The work of Kacser & Burns (1973) and Heinrich & Rapoport (1974) cannot be regarded as a "re-discovery" of a special case of a general theory that was published some years after the work of Higgins (1963, 1965) and that of pioneers such as Garfinkel & Hess (1964) in the use of computers for analysing metabolic systems. Nonetheless, Savageau (1987), Voit (1987) and Sorribas (1987) have maintained that metabolic control theory is nothing but a special case of the biochemical systems theory of Savageau (1969*a*,*b*; 1970, 1976). Subsequently the arguments were set out in a more substantial form (Savageau *et al.*, 1987*a*,*b*; Voit & Savageau, 1987), supported by an additional paper dealing with other aspects of their theory (Savageau & Voit, 1987).

Priority arguments have little importance for science as a whole, even if, as in this instance, they may debase in the minds of uninformed readers the value of some of the major intellectual achievements in biochemistry of the past 15 years. However, if it is accepted that the opinions expressed by Savageau (1987), Voit (1987), Sorribas (1987), Savageau *et al.* (1987*a*,*b*) and Voit & Savageau (1987) represent a genuine belief that much work in metabolic control theory has been nothing more than an exercise in rediscovery, then it is pertinent to ask what kind of philosophical point of view can have led to such a belief. Important questions about the nature of scientific discovery are implicit in these papers, and they need to be answered.

I believe that these papers misunderstand the objectives of metabolic control theory, assuming, despite evidence to the contrary, that they are identical with their own objectives. They do not, therefore, perceive the value of the summation relationships, which are essential if one is to *understand* metabolic control even if they have little direct application to modelling of metabolism. Second, they misunderstand the assumptions of metabolic control theory, treating as constants quantities whose variation plays an essential and well emphasized role in the theory. Most important from the philosophical point of view, they assume that examination of a special case of a general theory is of little value: I shall discuss in Section 5 why I disagree with this assumption.

2. Terminology: What is Metabolic Control Theory?

I shall use the agreed terminology (Burns *et al.*, 1985) for referring to the ideas that have developed from the work of Kacser & Burns (1973) and Heinrich & Rapoport (1974). As a convenient shorthand I shall also use the term "metabolic control theory" to refer to the body of ideas as a whole, but will refrain from giving it capital initial letters or abbreviating it to MCT, as is done by Savageau *et al.* (1987*a*,*b*), to avoid any suggestion of a monolithic exclusive theory. Universal agreement on all points does not exist among the workers in metabolic control

theory, and one ought not to exclude from the general term use ideas that are certainly concerned with the theory of metabolic control even if one disagrees with them, such as some of the ideas expressed by Newsholme & Crabtree (1987). For the purposes of the present paper only, where I shall not discuss the ideas of Newsholme & Crabtree (1987), I shall use the term "biochemical system theory" to refer to the ideas of Savageau and his school, and the term "metabolic control theory" to refer to those of Kacser & Burns, Heinrich & Rapoport and their schools.

3. Objectives of Metabolic Control Theory

The primary objective in metabolic control theory has been to assign clear meanings to some of the concepts used vaguely and inconsistently in earlier discussions of metabolic control, to analyse the theoretical properties of the quantities thus defined, and to use the analysis to understand why real systems behave in the way they do. Any assessment of the success of metabolic control theory must consider the extent to which these objectives have been realized. There is no necessary implication here that metabolic control theory should also provide an effective basis for modelling metabolic processes in the computer.

The objectives of biochemical systems theory, to develop mathematically tractable models of metabolic systems that mimic the behaviour of real systems and allow one to predict howithey will behave in new circumstances, appear to be quite different. Adding to one's understanding of the underlying mechanisms of control is no longer a primary objective. It is hardly surprising, therefore, that metabolic control theory has, in my view, been more effective than biochemical systems theory in promoting understanding of control, whereas it has contributed less to modelling.

One could loosely categorize metabolic control theory as belonging to the domain of science, whereas biochemical systems theory belongs to the domain of engineering. To say this is not to deny the value of either or the difficulties in either. One can easily think of examples of large projects in which the solutions to the scientific problems were largely known at the outset, but in which great intellectual effort was needed to make them work in practice, i.e. to solve the engineering problems.

In protein chemistry the contrast between the scientific and the engineering points of view may be illustrated by comparing the Hill equation (Hill, 1910):

$$y = x^h/(K + x^h), \tag{1}$$

in which y is the fractional saturation of a protein at a ligand concentration of x, and K and h are parameters, with the equation of Monod *et al.* (1965):

$$y = \frac{[Lc(1 + cx/K_R)^3 + (1 + x/K_R)^3]x/K_R}{L(1 + cx/K_R)^4 + (1 + x/K_R)^4} \tag{2}$$

in which y and x have the same meanings as in eqn (1) and L, c and K_R are parameters. Both equations address the same experimental problem, but whereas eqn (1) is a simple equation of two adjustable parameters, eqn (2) has a much more complex appearance and contains three. It is easy to estimate the parameters of eqn (1) and it often gives an excellent fit to experimental data over the whole range

of interest; it is much more difficult to estimate the parameters of eqn (2) and, despite its extra parameter, it may provide a poor fit to data that are accurately described by eqn (1). Nonetheless, one cannot conclude that eqn (1) is preferable to eqn (2): whatever its practical convenience, eqn (1) is not derived from a mechanism (the mechanism sometimes written for it is physically impossible unless h is integral, as experimentally it usually is not, and has only limited validity even then except in the trivial case of $h = 1$), and tells us almost nothing about the mechanisms that make y dependent on x. On the other hand, eqn (2) is derived from a mechanism, and even when it fails to fit well this failure can itself add to understanding of the protein.

From the engineering point of view, however, an equation that is easy to use and gives accurate predictions is clearly preferable to one that is more difficult to use and has less predictive power. Whatever its theoretical objections, therefore, the Hill equation remains in widespread use as a valuable way of summarizing the co-operative behaviour of a protein; in computer simulations of metabolic behaviour it is likely to be more useful than mechanistically explicit equations.

The contrast between points of view is also seen in the criteria one uses to judge whether an equation gives a good fit to data. If one is primarily concerned with understanding the physical basis of a phenomenon one will prefer a statistical interpretation of goodness of fit and will wish to minimize some *average* measure of deviation. If one is concerned with making predictions, however, one will not tolerate an equation that gives a good fit on average if one thereby risks a very bad fit in the worse case: instead, one will prefer a *minimax* fit in which one uses the methods of numerical analysis to minimize the worst deviation. (Surprisingly, in discussing which of different approximations give a better fit to kinetic equations, Voit & Savageau (1987) assert that the average difference between a model and reality gives a measure of its superiority, despite the fact that they are clearly dealing with a problem of numerical analysis, not statistics.) Even in a statistical context, however, a minimax fit may be very useful as a way of avoiding reading tables or storing them in the computer. For example, the following equation:

$$F(0{\cdot}95, 1, n) = 3{\cdot}836 + 1/[(0{\cdot}08889502/n) - 0{\cdot}18868 + 0{\cdot}010613n] \qquad (3)$$

provides values of the 5% percentage point for an F test with 1 and n degrees of freedom. Although the numbers used as coefficients do not provide a best average fit to the true function they provide a minimax fit, which is much more useful in practice, as it allows one to be confident that even in the worst case the calculated value of F will be correct to within 0·15%.

4. Control and Elasticity Coefficients

The dominant theme in metabolic control theory is the study of *control coefficients.* For example, the flux control coefficient for an enzyme E_i [known in earlier work as its "reflection coefficient" (Higgins, 1963, 1965), its "sensitivity" (Kacser & Burns, 1973) or its "control strength" (Heinrich & Rapoport, 1974)] may be defined as

follows:

$$C_i^J = \frac{\partial \ln J}{\partial \ln [E_i]} \tag{4}$$

and is a measure of the influence of the particular enzyme on a flux J (which may be, but does not have to be, the flux through the reaction catalysed by E_i). A major objective in control theory has been to explore the relationships between control coefficients and the corresponding *elasticity coefficients*, which express in a similar way the dependence of the properties of the individual enzymes, isolated from their pathways, on the concentrations of substrates, products, inhibitors, etc. For example, the elasticity coefficient of the rate v_i of the reaction catalysed by E_i, with respect to a metabolite concentration x_j, may be defined as follows:

$$\varepsilon_{x_j}^i = \frac{\partial \ln v_i}{\partial \ln x_j}. \tag{5}$$

Elasticity coefficients are, of course, closely related to the kinetic parameters such as the Michaelis constant, limiting rate etc. that are measured in conventional steady state investigations of enzymes, but they differ from them in referring to conditions that exist in the cell, and in being derivatives that express the sensitivity of the rate to infinitesimal changes in conditions; they make no claim to define behaviour over a finite range.

There is no implication in eqns (4–5) that either control coefficients or elasticity coefficients are constant, and from the earliest papers in metabolic control theory the importance of recognizing their lack of constancy for understanding control has been emphasized. One may refer, for example, to Section 3 of Higgins (1965), to p. 21 of Kacser & Burns (1968), or to figs 4 and 5 of Kacser & Burns (1973). It is incorrect, therefore, to discuss metabolic control theory as if it required the control and elasticity coefficients to be constant; it is only if one does this, however, that one can arrive at the idea that metabolic control theory is a special case of biochemical systems theory.†

Thus Savageau *et al.* (1987*a*) state that a power-law approximation to the dependence of a rate v_i on a set of concentrations $x_1 \ldots x_n$ may be written in the notation

† I am grateful to a referee for pointing out that Savageau and colleagues nowhere in their recent papers state explicitly that they consider their kinetic orders to be constants, questioning whether they intend them to be taken as constants. This is an important point, but I remain convinced that there is a clear implication that kinetic orders are constants. First of all, use of the term "kinetic order" entitles the reader to assume that it has a close connection with the use of the term "order of reaction" in chemical kinetics, where it is defined clearly in IUPAC recommendations as "independent of concentration and of time" (IUPAC, 1981). Second, the term "power law" occurs with great frequency in the writing of Savageau and colleagues: if the quantities in which a law is expressed are not constant over the range of application of the law, in what sense is it a law? Third, Voit & Savageau (1987) examine in detail "the range of concentrations over which each power-law representation and the 'actual' rate law differ by at most a given tolerance": I find it impossible to attach a meaning to this description, or to the analysis that follows in the paper, that does not involve interpreting the kinetic orders as constants. Thus, despite the referee's reservations, I remain unapologetic about the statement made here and elsewhere in this paper that Savageau and colleagues treat their kinetic orders as constants. It is certainly possible that I have misunderstood their intentions on this point, but if so others may have done so also, and the misunderstanding may be the key to the apparent inability of each school to see merit in the work of the other.

of metabolic control theory as follows [their eqn (5)]:

$$v_i(x_1, \ldots, x_n) = [\mathrm{E}_i] \prod_{j=1}^{n} x_j^{\varepsilon^i_{xj}}. \qquad (6)$$

Their argument that metabolic control theory is a special case of biochemical systems theory rests on their supposition that an equation of this kind embodies the essential ideas of metabolic control theory. Moreover, they find (Voit & Savageau, 1987) that equations of this kind lead, in many situations, to poorer approximations to the true kinetic equations than a different version of the power-law approximation that they prefer. This leads them to conclude that metabolic control theory is not merely a special case of biochemical systems theory, but an inferior special case.

It is certainly true that one can express some of the ideas of biochemical systems theory in the symbolism of metabolic control theory by means of equations like eqn (6). Moreover, partial differentiation of eqn (6) with respect to x_j readily generates eqn (5). Thus *if* eqn (6) is true one can derive eqn (5) from it; moreover, if eqn (6) proved to be true in practice one might feel that it provided a more natural way of thinking about an elasticity coefficient than eqn (5). However, although Voit & Savageau (1987) demonstrate that eqn (6) is not a particularly good approximation in practice, they do not draw the natural conclusion that it is not a very helpful way to look at eqn (5). It forms no part of metabolic control theory to treat elasticity coefficients or control coefficients as constants; consequently a demonstration that they are not constants is irrelevant to the question of whether metabolic control theory is a valid theory.

It is misleading, therefore, to state that "the elasticities (or effector strengths) proved to be identical to the kinetic orders in biochemical systems theory" (Savageau *et al.*, 1987*a*). The most that can be said is that the two theories are tangential at the particular operating point where biochemical systems theory is exact. At this point only, they lead to identical results, and it is true that the central theorems of metabolic control theory can be demonstrated in the context of biochemical systems theory, and that in principle this could have been done before 1973 (Savageau *et al.*, 1987*a*). In fact, however, it was not.

5. The Usefulness of Special Cases

As indicated in the previous section, I believe the claim that metabolic control theory is a special case of biochemical systems theory to be incorrect. I also, as discussed in the Introduction, consider that one can only argue that biochemical systems theory is older than metabolic control theory if one ignores the work of Higgins (1963, 1965) and the clearly stated links between it and the papers of Kacser & Burns (1973) and Heinrich & Rapoport (1974). Nonetheless, in this section I shall suspend my disbelief and examine the following question: suppose that "biochemical system theory was largely complete for the steady state domain and published before the first papers on metabolic control theory appeared" (Savageau *et al.*, 1987*a*), and suppose, moreover, that "biochemical systems theory and metabolic control theory are identical over the domain of metabolic control theory";

does it then follow that metabolic control theory has no claims on the attentions of serious students of control, no claim to originality, and no right to a separate existence?

Such a conclusion may have a superficial plausibility, but it is based on a philosophical view of the nature of scientific discovery with which I disagree profoundly. That it is a misconception may be seen by examining the nature of research in mathematics. A small part of this involves the propounding of new axioms, and this is clearly original by any definition. However, most work in mathematics does not involve new axioms, but instead searches for novel and interesting consequences of existing axioms. However, as these consequences are in general wholly contained within the known axioms, an argument along the lines of that of Savageau *et al.* (1987*a*,*b*) would lead inevitably to the conclusion that nearly all mathematical research is unoriginal. Nonetheless, one might perhaps feel that mathematics provides an inappropriate illustration of the the nature of scientific discovery, and so I shall examine whether the same is true of biochemistry.

The history of our understanding of the nature of co-operative interactions in proteins provides an alternative illustration. The equation for binding of a ligand at equilibrium to a tetrameric protein was given more than 60 years ago by Adair (1925*a*,*b*): it represents this binding in terms of four association constants and assumes no relationships between them. It is a general equation that must include any valid model for binding to a tetramer as a special case. It includes, therefore, the "classic" models of co-operativity advanced in the 1960s (Monod *et al.*, 1965; Koshland *et al.*, 1966) as special cases (this point is developed more fully elsewhere: see Ricard & Cornish-Bowden, 1987). One could adapt the argument of Savageau *et al.* (1987*a*) to say that:

> "at this fundamental level, and thus with regard to actual results of applications, Adair's equation and the model of Monod *et al.* are identical over the domain of the latter. In this fundamental sense the model of Monod *et al.* represents a rediscovery of the earlier Adair equation".

No one familiar with the development of ideas about co-operativity would readily accept such an argument. A more conventional view would be to say that Adair's equation has been useful for setting limits on what is possible, but that it contributes almost nothing to understanding how co-operativity actually arises, and that this understanding has developed from the work of Monod *et al.* (1965), Koshland *et al.* (1966), and others in identifying particular special cases of Adair's model that are worthy of closer examination. These two papers stimulated a flood of experimental research to answer questions that were not and could not have been raised by Adair's papers, published more than 40 years before. Subsequently, there have been various attempts to combine the models of Monod *et al.* (1965) and Koshland *et al.* (1966) into a general model that includes them both as special cases: does anyone remember these attempts or, if they do, do they think that co-operativity has been il'uminated by them?

The reality is that the study of special cases has nearly always been more useful in promoting understanding than the erection of all encompassing general equations. Clearly this is related to the idea of falsifiability as a criterion of whether a theory

is scientific (Popper, 1978): a theory that can explain anything explains nothing. Moreover, identifying informative special cases is neither easier nor more derivative than devising a general model. To take a different biochemical example, anyone can, if they take the trouble, derive the equations that describe the simultaneous rates of enzyme-catalysed transfer of label from a doubly labelled reactant to two different products, but few have the originality to recognize that within the almost hopeless confusion of the resulting equations there lies a simple and practical method for investigating the orders of product release in enzyme mechanisms (Britton, 1966, discussed more fully in Cornish-Bowden, in press).

6. The Summation and Connectivity Relationships

Savageau *et al.* (1987*a*) recognize, with most others who have studied metabolic control theory, that the summation and connectivity relationships constitute its major achievements. These relationships are most compactly and elegantly expressed in a single matrix equation, as Sauro *et al.* (1987) have pointed out:

$$\mathbf{C\varepsilon} = \mathbf{I} \tag{7}$$

which states that the product of **C**, the matrix of control coefficients, and $\boldsymbol{\varepsilon}$, the matrix of elasticity coefficients, is the identity matrix **I** of order equal to the number of enzymes. Each column of **C** refers to a particular enzyme and, in the simplest case of an unbranched pathway, its first row consists of the flux control coefficients and the others consist of concentration control coefficients, with one row per intermediate. The first column of $\boldsymbol{\varepsilon}$ is a unit vector and the rest of $\boldsymbol{\varepsilon}$ contains the reversed-sign elasticity coefficients for all of the intermediates (one column per intermediate) with all of the enzymes (one row per enzyme). The products of selected rows of **C** with selected columns of $\boldsymbol{\varepsilon}$ contain all of the relationships reported by Kacser & Burns (1973) and Westerhoff & Chen (1984). These are the summation theorem for flux control:

$$\sum C_i^J = 1, \tag{8}$$

the summation theorem for concentration control:

$$\sum C_i^{x_j} = 0, \tag{9}$$

the connectivity theorem for flux control:

$$\sum \varepsilon_{x_j}^i C_i^J = 0, \tag{10}$$

and two connectivity theorems for concentration control:

$$\sum \varepsilon_{x_j}^i C_i^{x_j} = -1, \tag{11}$$

$$\sum \varepsilon_{x_{k\neq j}}^i C_i^{x_j} = 0. \tag{12}$$

In all cases the summation is over all enzymes, i.e. all i values, not j or k. Equation

(7) is more general than these examples: it remains true if **C** and ε are defined more generally, e.g., to take account of multiple fluxes (in different branches) in a branched pathway.

As mentioned, Savageau *et al.* (1987*a*) described the summation and connectivity relationships as the major achievements of metabolic control theory, adding that they are not apparent in biochemical systems theory . . . "what is most visible and central in one approach appears invisible and peripheral in the other". In their second paper (Savageau *et al.*, 1987*b*) they examine the relationships in more detail and show that all of the relationships implied by eqn (7) can be demonstrated within the terms of reference of biochemical systems theory. This part of their paper presents no logical difficulties for the reader wishing to form a fair judgement of the central issue. Problems arise, however, when Savageau *et al.* (1987*b*) set out to explain why the relationships were initially overlooked in biochemical systems theory, and why they still regard them as having little role to play.

These are, of course, different aspects of the same question: provided that one recognizes that the analysis is within the domain of linear algebra and that one is aware of the established results of linear algebra, the truth of eqn (7) and its special cases becomes so natural as to be hardly in need of proof. The problem is not so much to explain why the summation and connectivity relationships were not first proved in biochemical systems theory, but to explain why it did not seem worth while to point them out, and why even now they are considered of little interest in biochemical systems theory. This is most easily explained by the different objectives of metabolic control theory and biochemical systems theory, discussed in Section 3—given that the latter is not interested in re-expressing the traditional ideas of biochemical control in precise terms and examining the properties of the resulting coefficients, one cannot be surprised that it sees little value in relationships that are not needed and are of little help when one is attempting to model metabolic systems.

However, although modelling metabolic systems is a valuable activity that has been advanced in important respects by Savageau and his colleagues, it is not the activity in which most experimental biochemists are normally engaged. They are more concerned with understanding the roles of individual enzymes within systems, and with establishing whether particular enzymes are "important" (however one defines the term) in regulation. To put this concern on a more secure foundation they require precise definitions, and they need the summation and connectivity relationships to perceive the contradictions in such traditional ideas as "key enzymes", "metabolic bottlenecks", etc.

Given that Savageau *et al.* (1987*b*) consider that the summation and connectivity relationships have no significant role to play, and that they never thought it important to highlight them apart from noting that they could readily verify them within their own terms of reference (Savageau, 1976), it may be that ultimately the priority issue will be seen as trivial. If future biochemists interested in control come to regard the summation and connectivity relationships as central to their understanding of control (something that has not happened yet!), they will regard the importance of metabolic control theory as established regardless of whether they think that it is a sub-set of biochemical systems theory. Even if they do regard it as such a sub-set they will

recognize the importance of isolating and proving the simple control properties of enzymes.

7. Negative Flux Control Coefficients: Do they Invalidate Metabolic Control Theory?

Savageau *et al.* (1987*b*) make a fair criticism of metabolic control theory in commenting that the summation relationship for flux control, eqn (8), is commonly interpreted in a way conditioned by the fact that it was introduced and first discussed by reference to an unbranched pathway (Kacser & Burns, 1973). Such a pathway simplifies discussion because only one flux needs to be considered, but it has the less desirable characteristic (from the point of view of illustrating general principles) that in an unbranched pathway all flux control coefficients are positive; it cannot therefore provide any guide to the effects of negative flux control coefficients.

The importance of this is that as long as all flux control coefficients are positive it is evident from eqn (8) that their average magnitude must be small even in a short pathway, and very small in a long one. Moreover, as long as there is only one flux to be considered this average is a useful measure of the control properties of individual enzymes. As soon as one considers branched pathways, however, two difficulties arise: first, one must consider the effects of negative flux control coefficients; and second, one must recognize that one is usually interested in the degree of control exercised by an enzyme on the flux through its own reaction rather than on a flux in some other part of the system.

Once negative flux control coefficients are admitted, it is possible in principle for many coefficients to be large in magnitude (some positive, some negative) without violating eqn (8). As all real metabolic systems are branched, this might appear to negate the main conceptual ideas introduced by metabolic control theory. This is the substance of the point made by Savageau *et al.* (1987*b*), and it is probably a fair one to the extent that this aspect of metabolic control theory has been somewhat "over-sold". Nonetheless, the criticism is also a little exaggerated: one can no longer assert that the average magnitude (without regard to sign) of the flux control coefficients will be equal to the reciprocal of the number of enzymes, and hence extremely small in a large system. As long as large negative flux controls are very rare one can still express the same sort of simple ideas in a somewhat weaker form (see Kacser, 1983).

It is intuitively likely that the largest flux control coefficients for a given flux in a branched system will tend to be found for the enzymes in the branch concerned. Although direct experimental evidence of this is lacking, computer simulations by the approach described by Hofmeyr (1986) suggest that it is reasonable. Given this, it follows that although the average magnitude of flux control coefficients over all of the enzymes in a system may have little relevance to the flux control coefficient of a particular enzyme for the flux in its own branch, the average of those in its own branch is relevant. This will tend to be small unless the branch is very short. Thus although some of the more extreme concepts of metabolic control theory may need revision, they remain true (and useful for understanding metabolic control), if expressed in a weaker form. Although one cannot say that a "typical" enzyme will have a flux control coefficient for its own flux equal to the reciprocal of the

number of enzymes in the system, one can say that it will be approximately equal to the reciprocal of the number of enzymes in the same branch.

Savageau *et al.* (1987*b*) make a further important point in commenting that the predictions of metabolic control theory cannot be tested by calculating the sums of control coefficients calculated from the model, because these will obey the summation relationships regardless of whether the model is valid or not. Only experimentallly determined control coefficients are of diagnostic value. They are right to point out that this distinction has not always been made.

8. Discussion

The theory of metabolic control originated by Higgins (1963, 1965), Kacser & Burns (1973) and Heinrich & Rapoport (1974) has been developed by them and others during the past 15 years; it is becoming more and more widely accepted as the basis on which any attempt to understand control processes in living systems must be built. For this it is not vitally important, except to the people concerned, whether it truly originated with these workers or whether it should be regarded as a special case of the theory of biochemical systems developed by Savageau (1969*a*,*b*, 1970, 1976). Nonetheless, the criticism has been made (Savageau *et al.*, 1987*a*,*b*) that metabolic control theory is derivative, and I have tried to answer it in this paper. The clearest point against the criticism is that the earliest papers on metabolic control theory (Higgins, 1963, 1965) pre-date those of Savageau that have been proposed as the originators of the ideas.

This point of simple chronology would seem to be unanswerable (unless still earlier papers come to light), but for understanding the controversy it is perhaps less important than the question of whether metabolic control theory is truly a special case of biochemical systems theory. I have argued in Section 4 that this categorization is only possible if one treats the control and elasticity coefficients of metabolic control theory as constants, in which case they can indeed be equated with certain kinetic orders that are treated as constants in biochemical systems theory. However, as the lack of constancy in control and elasticity coefficients has been emphasized in metabolic control theory for more than 20 years, this equation would seem to be improper.

The controversy has philosophical implications that go beyond the particular case of biological control, and underlie all scientific research. Much of the criticism of metabolic control theory by Savageau *et al.* (1987*a*,*b*) appears to take it as axiomatic that a special case of an existing theory can never be worthy of study for its own sake, and results found for such a special case can never be regarded as original contributions to knowledge. I have argued in Section 5 that, far from being unoriginal, the identification of special cases that are of particular interest, either because of the simplification in treatment that they permit or because of the insight into the underlying behaviour that they give, is often characteristic of the most original and important research.

In Section 6 I have argued that the lack of importance given to the summation and connectivity relationships in biochemical systems theory reflects my view that

this theory is primarily a theory of modelling or engineering (Section 3), and that it therefore has little need of relationships that do not contribute to the modelling of metabolic processes. For developing a genuine understanding of metabolic control, an essential objective in metabolic control theory, such relationships become crucial.

Finally, in Section 7 I have discussed the arguments of Savageau *et al.* (1987*b*) that the proponents of metabolic control theory have been guilty of improper extrapolation, making general statements about metabolism on the basis of results rigorously worked out only for linear pathways in which certain characteristics of general systems (notably the possibility of negative flux control coefficients) are not admitted. To a limited extent this last criticism appears valid. Nonetheless, it falls far short of establishing the claim that metabolic control theory is derivative and without interest or importance.

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