Control in perspective

In the discussion forum in *TIBS* (January 1987) Kacser and Porteous and Crabtree and Newsholme discussed their views of the representation and analysis of integrated biochemical networks My own research interests are not directly centered in this area, but I have followed the literature and attended the meetings where these topics were discussed Reading the contributions by the two groups, I was considerably disappointed that they did not mention the pioneering work by Savageau who developed the fundamental concepts of a biochemical systems theory in the late 1960s and who has been continuously extending this theory ever since. Many people with whom I have talked about the analysis of biochemical systems have been confused by the 'independent' developments of control analysis, by its notation and by the unjustified claims of total generality In my opinion, it is of the utmost importance to clarify the relationships between the approaches represented by the different schools as soon and as rigorously as possible in order to give critical researchers in this area a correct view of the current knowledge in this area There is no room in this short note for a detailed analysis of both approaches and their common and different features; however, the chronology in Table I contains specific comparisons of the concepts in the 'biochemical systems theory' (BST) and 'control theory' (CT) and references to the original literature that are necessary for a balanced evaluation

Table I Chronology of key theoretical developments in BST and CA[a]

Developments	Biochemical systems theory (BST)	Control analysis (CA)
Definition of component parameters	Savageau (1969)	Kacser & Burns (1973)
Specification of the underlying formalism	Savageau (1969)	[b]
Ability to characterize branched pathways	Savageau (1969)	Heinrich & Rapoport (1975)
Condition for existence of a steady state	Savageau (1969)	[b]
Explicit steady-state solution	Savageau (1969)	[b]
Introduced standard matrix notation	Savageau (1969)	Heinrich & Rapoport (1974)
Definition of systemic parameters	Savageau (1971)	Kacser & Burns (1973)
Relationship between power-law and conventional kinetic parameters	Savageau (1969, 1971)	Heinrich & Rapoport (1974)
Assessment of accuracy	Savageau (1969, 1971, 1976)	[b]
Computer analysis	Savageau (1970)	[b]
Dynamic properties	Savageau (1970)	Sorribas & Bartrons (1986)
Conditions for stability	Savageau (1970, 1974)	Sorribas & Bartrons (1986)
Explicit relationships between component and systemic parameters	Savageau (1971)	Kacser (1983)
Required measurements	Savageau (1971, 1972)	Kacser & Burns (1973)
Well-controlled comparisons	Savageau (1972, 1976)	[b]
Summation and connectivity relationships	Savageau (1976)	Kacser & Burns (1973)
Aggregate variables	Savageau (1979)	Fell & Sauro (1985)
		Westerhoff & Chen (1984)
Large-scale integration	Savageau (1979)	[b]
Analytical solutions	Voit & Savageau (1984)	[b]
Canonical non-linear form	Savageau (1979)	[b]
	Voit & Savageau (1986)	[b]
Generalization to cellular systems	Voit & Savageau (1982)	[b]
	Irvine & Savageau (1985)	

[a]References to BST are listed below, those to CA can be found in Kacser and Porteous (*TIBS* 12, 5-14, January 1987)
[b]Not available in the current version of CA

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Discovering another view of control analysis

The papers in the *TIBS* discussion forum of January by Kacser and Porteous and Crabtree and Newsholme each claim to have developed a new theoretical approach that is more valid than the other for the analysis of biochemical systems Unfortunately this discussion omitted any reference to other approaches in the field.

I recently became acquainted with this field through the papers of Kacser *et al* and set out to develop a method for analysing the stability of the steady state and relating this fundamental property to the elasticity coefficients, and hence the control properties of the system The possibility of studying the dynamics of the system opened up, for me, a new perspective for this theory

Since this is a fundamental issue, one might ask 'why has it taken so long to be recognized and developed within the theory of control analysis?' The answer is related to the basic character of control analysis In this approach, elasticity coefficients and flux control coefficients are defined in a simplified phenomenological fashion to represent local and global changes in the system, this avoids the complexity of the system by omitting consideration of the fundamental dynamics This simplification is one of

the attractions of control analysis, it also is a major limitation because it masks a number of fundamental issues

Given this limitation, one might ask 'Can control analysis be used to define a general theory for studying biochemical systems?' The common response is, for those who have studied the problem from the point of view of Kacser *et al*, that there is no other way to approach the subject Indeed, Kacser *et al* have systematically repeated that control analysis is an entirely general theory and that without it one cannot really understand biochemical systems

However, after publishing my work on the control analysis of substrate cycles[1] and attempting to extend this analysis to the dynamics of the system, I was surprised to learn that another approach does indeed exist, that it is part of an elaborated theory that was developed some years before the first papers of control analysis

The theory (called biochemical systems theory) was presented originally by M A Savageau[2–7] It has since been developed systematically[8–11] and used in the analysis of many biochemical systems (including gene circuits[9,12] and immune response networks[13,14]) This theory provides a general approach that exhibits rather than masks the fundamental non-linear dynamics of the system being analysed, and provides a systematic way to analyse its dynamic and control properties When biochemical systems theory is applied to the biochemical pathways that fulfil the restrictive assumptions of control analysis, it can be shown that the two approaches provide the same results and thus it can be seen that control analysis is a particular case of biochemical systems theory

Readers must consult the original literature and derive their own conclusion

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Some further comments from the original authors

Replies from Kacser and Porteous: Reply to Savageau

Any model is a mathematical fiction This applies to our treatment as well as that of Savageau All models (including his) have assumptions He describes his own formulations as approximations The real world is much messier than a set of neat equations. One could, for example, construct a very general model where *every* enzyme interacts with *all* metabolites, and *every* metabolite interacts with *all* other metabolites and *every* enzyme interacts with *all* other enzymes There is evidence for *some* instances of *some* interaction in each of the above classes. Such a general model, however, would be quite unmanageable and would have to be reduced severely in laboratory practice The question to ask is whether a particular model is an adequate representation of the particular problem that we choose to study If the assumptions are grossly inadequate, it will come out in the wash Our model contains as few restrictive assumptions as appears necessary, and adds complications only when the evidence warrants it Once set up, however, a rigorous application is called for Control analysis (and especially a brief sketch in *TIBS*) does not attempt to erect a grand theory of all possible systems under all possible circumstances What it has done is to bridge (or narrow) the gap between enzymology and physiology for the common problems which biochemists encounter It has led to new methods of experimentation (of which we quote a number of examples) and to new insights into control in biochemistry and genetics

Savageau cites enzyme–enzyme interactions and cascades as the Achilles heel(s) of our treatment. We comment on enzyme–enzyme elasticities in the reply to Welch and Keleti and similar additions will deal with cascades He does not quote the fact that we acknowledge the possible modifications which may be necessary to particular cases[1,2]. Until we have sufficient quantitative information on specific interactions, a blanket complication of the model is not very useful Such information must come from the experimentalist and not from the mathematician

Similarly, he quite wrongly asserts that we *always* assume enzyme levels to be fixed parameters In one of our early publications[3] we deal explicitly with the problem of variable gene expression He is also wrong in asserting that when enzymes are dependent concentration variables the experimentalist has no direct influence [over them] You can change the gene dose, i e parameters, (as we have done[4,5]) and thus manipulate the enzyme levels

He is wrong again (in referring to the summation and connectivity properties) that our demonstration of these by reference to the small model system in the *TIBS* article 'is a circular argument since derivation of these expressions required (sic) these properties in the first place' These expressions of the control coefficients in terms of elasticities can be and have been obtained by the simple solution of three simultaneous equations (see also Ref 6). They may *also* be obtained by the matrix method involving the above properties[7] He must be aware that the general proofs[1,3] are quite free from circularity Stability problems are important aspects and will crop up in particular systems But as he admits in his comments, '*real* systems might possess these [stable steady states]' Most practising biochemists would be satisfied with a model that assumes this very general state and allows them to work within its framework Much interesting work is being done on oscillations and similar phenomena for which appropriate models are being proposed

The readers of Savageau's letter should also be aware that he is quoting us out of context Thus, in his very first sentence, the quoted passage actually begins with '*In other words*, we should