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Henrik Kacser (1918–1995): metabolism of control

Obituary

Henrik Kacser has been referred to as the 'pope' of Metabolic Control Analysis (MCA), with perhaps a 'patriarch' in Berlin (Sam Rapoport), Jim Burns, Tom Rapoport and Reinhart Heinrich as 'apostles' and, after a lag phase of nine years, Bert Groen, Ron Wanders and many others as 'preachers'. In hindsight, a better picture is that of a 'converter' battling the reluctance of a congregation to substitute useful concepts for unsuccessful dogmas.

The dogma that every metabolic pathway has a single rate-limiting step ('master reaction'¹), usually at the beginning, and far from equilibrium ('irreversible'), was not falsifiable; i.e. the rate-limiting step had not been defined unequivocally. Henrik and others defined the extent to which an enzyme limits the flux (now called the flux-control coefficient), as (essentially) the percentage change in flux resulting from a 1% experimental modulation of that enzyme^{1,2}. Inspired by computer simulations, Jim Burns and Henrik discovered a number of 'control properties', such as that the sum of the flux-control coefficients (with respect to any flux, summed over all steps) must equal one. The implication was that, if there is more than one rate-limiting step, then the flux-control coefficients must lie in between zero and one (I forgo the occasional complication). Consequently, the quantitative definition of the flux-control coefficient, which makes answers between zero and one possible, was essential for testing the dogma of the single rate-limiting step.

When applying MCA to experimental situations, Henrik compared heterokaryons of *Neurospora* in order to determine the dependence of metabolic flux on gene dosage. Ornithine-carbamoyl transferase, at the beginning of the pathway, was certainly not rate limiting; in fact, Henrik found no rate-limiting step at all^{1,3}. The same was true when he looked at alcohol-dehydrogenase alleles in *Drosophila* (Ref. 4). However, because the sum of the control coefficients was far below one, Henrik could have

missed the rate-limiting step. He much appreciated the work of Bert Groen and colleagues who followed the MCA methodology to identify at least 80% of the total control of mitochondrial oxidative phosphorylation, and found that it is distributed among the enzymes: there was no single rate-limiting step⁵.

Those who had the privilege of seeing Henrik cook a meal and tasting the result know that he had various ways of making metabolism a dynamic object of study and experimentation. His talks at meetings were exciting and entertaining and, like his proofs of the control properties, 'metabolized' control: a simultaneous increase of all enzyme activities by a fraction f yields a new steady state in which all fluxes are increased by the fraction f , and the concentration of all components remains unchanged. Consequently, the sum of the control of all enzymes on a flux must be $f/f=1$ and on any concentration $0/f=0$ (the summation theorems). To prove the connectivity property between flux-control coefficients and elasticity coefficients, Jim and Henrik considered simultaneous balanced changes in the concentration of a metabolite and the enzymes immediately involved in its metabolism, such that the rate of every reaction remained constant². This interest in what actually happens around the enzymes was characteristic of Henrik.

Henrik used to provoke 'control-niks', by saying that the theory of MCA was complete, but he stressed that more experimental work was essential. Of course, Henrik had long taught students of the theory of MCA to be as stubborn as he had been, and they continued to remove limitations related to metabolite channelling, oligomeric enzymes, large modulations and flux maximization. After his formal retirement from the Department of Genetics of Edinburgh University, Henrik himself addressed and solved many of these same problems in conjunction with a group of enthusiastic young scientists^{6–8}. For a long time, the UK research-

funding agency had allowed much of the development of MCA to escape to places such as Amsterdam, Berlin, Bordeaux, Moscow, and Stellenbosch, but they appeared to wake up to the importance of MCA just as it was approaching adulthood.

MCA has made life more rational, though also more difficult, for biotechnology. In order to increase flux or concentration, it may not be sufficient to amplify the rate-limiting enzyme, for there may not be one; one should consider all enzymes with significant control coefficients, and/or alter elasticities rather than concentrations. The effects of large changes can be predicted fairly accurately⁷, and genetic modulations can be engineered such that flux control is not transferred to elsewhere in the metabolic network, leading to a substantial increase in flux^{8,9}. In a change to their previous standpoint on the validity of MCA, industry has changed its attitude from critical to silent, or even enthusiastic... (see accompanying meeting report).

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