consumption in the cytoplasm were considered. The results showed that diffusion of adenine nucleotides (ADP) between the two mitochondrial membranes does not limit the free-energy flux. Indeed, competition for ADP between the creatine kinase reaction and diffusion occurred only when the diffusion coefficients of the involved species decreased significantly. The magnitudes of these coefficients had to be decreased by at least a factor of 100 000 for an appreciable fraction of the Gibbs energy flux to be directed via creatine kinase. Consequently, the intermembrane space is not considered as a significant diffusion barrier for ADP flow. Modeling ADP diffusion through the pores of the outer mitochondrial membrane, we found rate dependent concentration gradients for ADP between the intermembrane space and the extramitochondrial space, in line with experimental results [1]. Two experimental systems (hexokinase or creatine kinase added as ATP-consuming processes [1]) were simulated. The results agreed well with the experimental data. In either system the rate of oxidative phosphorylation decreased with increasing pyruvate kinase concentration. However, in the hexokinase system this rate decreased to zero, while in the creatine kinase system it decreased only to about 15% of the maximal value. The results suggest that at very low ADP concentrations in the cytoplasm diffusion of creatine and phosphocreatine through the outer mitochondrial membrane accounts for an appreciable fraction of the free-energy flux.

The experiments used for these calculations were performed with isolated rat heart mitochondria in the absence of macromolecules. Under these conditions the mitochondrial intermembrane space is enlarged [2]. In the presence of macromolecules the permeability of the outer mitochondrial compartment for adenine nucleotides is reduced [3,4].

1 Gellerich FN, Wagner M, Kapischke M, Brdiczka D (1993) in *Modern Trends in BioThermo-Kinetics* (Schuster S, Rigoulet M, Ouhabei R, Mazat J-P, eds) Plenum Press, New York: 313-318
2 Bakeeva LE, Chentsov YS, Jasaitis AA, Skulachev VP (1972) *Biochim Biophys Acta* **275**: 319-332
3 Gellerich FN, Kapischke M, Kunz W, Neumann W, Kuznetsov A, Brdiczka D, Nicolay K (1994) *Mol Cell Biochem* **133-134**: 85-104
4 Gellerich FN et al (1994) in *What is Controlling Life?* (Gnaiger E, Gellerich FN, Wyss M, eds) *Modern Trends in BioThermoKinetics* 3: 181-185

How to Vary the Proportion of Dynamic Channelling Flux at Constant Total Flux (and Decrease the Intermediate Pool Size...)

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Cornish-Bowden and Cárdenas [1] have claimed to prove that 'channelling of an intermediate cannot affect its free concentration at constant net flux'. Whilst these authors prove their algebraic derivation for a special case, we show that its result cannot be generalized as in [1], where the sentence quoted implies that

the intermediate's free concentration (C in Fig. 1) cannot be affected by *any* parameter change that increases the channel flux (J_7) while keeping the total flux (J_6) constant.

We show *several* ways in which the above generalisation [1] can be refuted, *i.e.* ways of increasing the channel flux with a *simultaneous* decrease of the intermediate's free concentration *at constant total flux*. One simple way in which

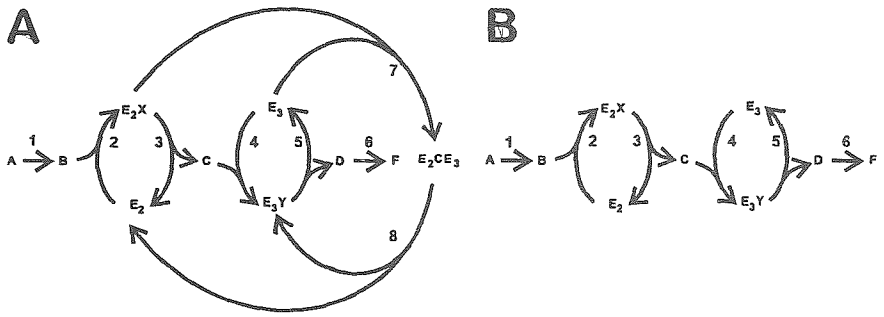

Fig. 1. Model of dynamic channelling in a four-enzyme pathway. (**A**) the full schematic model; (**B**) the same pathway without channelling, in which the interactions between E_2 and E_3 that allow for the channelling of C are absent. Arrow heads refer to the positive direction of fluxes; all steps except 6 are treated as kinetically reversible.

this can be achieved is by making asymmetrical changes in the rate constants around the complex E_2CE_3 (with similarly asymmetric changes in the parameters around C to conform with thermodynamic constraints).

1 Cornish-Bowden A, Cárdenas ML (1993) Channelling can affect concentrations of metabolic intermediates at constant net flux: artefact or reality? *Eur J Biochem* **213**: 87-92

A New Approach to Knowledge-Based Potentials of Mean-Force in Polypeptides and Proteins

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Tertiary structure prediction of polypeptides and proteins can be subdivided into two problems, *(1)* a suitable algorithm for the global energy minimization is needed which is able to escape from local minima in the complicated energy surface; *(2)* the potential of mean-force itself. Since the real potentials are not physically accessible, one uses semi-empirical or rough quantum-mechanical approaches. We focus on the latter problem and want to take the reverse way to obtain the potentials of mean-force from known structures. Different approach-