Metabolic efficiency: Is it a useful concept?

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The idea of metabolic efficiency is widely known in biochemistry, and appears in some form or other in many textbooks (e.g. Lehninger, 1975; Segel, 1976; Metzler, 1977). Rather less common is any discussion of what the calculation of a metabolic efficiency actually means [though an excellent one may be found in Atkinson (1977)], presumably because it is regarded as intuitively obvious.

The simplest, and most clearly objectionable, kind of efficiency is one calculated from the ratio of standard Gibbs energies of two reactions. Consider, for example, the reaction catalysed by hexokinase:

$$\text{Glucose} + \text{ATP} \rightleftharpoons \text{glucose 6-phosphate} + \text{ADP} \qquad \Delta G^{0\prime} = -16.7\,\text{kJ/mol}$$

For purposes of thermodynamic calculation this may be regarded as the difference between two hydrolytic reactions:

$$\text{Glucose 6-phosphate} + H_2O \rightleftharpoons \text{glucose} + P_i \qquad \Delta G^{0\prime} = -13.8\,\text{kJ/mol}$$

$$\text{ATP} + H_2O \rightleftharpoons \text{ADP} + P_i \qquad \Delta G^{0\prime} = -30.5\,\text{kJ/mol}$$

Not only may the stoicheiometry of the hexokinase reaction be obtained by subtracting the hydrolysis of glucose 6-phosphate from that of ATP, but also its standard Gibbs energy of -16.7 kJ/mol can be obtained by subtracting -13.8 kJ/mol from -30.5 kJ/mol. So far the analysis is quite legitimate: there is no objection to adding and subtracting reactions and their standard Gibbs energies in this way; indeed, it is precisely because this can be done that standard Gibbs energies provide such a useful way for biochemists to think about equilibria and equilibrium constants. But it is by no means as legitimate to claim that in the hexokinase reaction 30.5 kJ/mol of Gibbs energy is 'consumed' but only 13.8 kJ/mol is 'stored' in glucose 6-phosphate, so that the efficiency of the reaction is 13.8/30.5, or 45%. As Atkinson (1977) has remarked, such a statement is false in every part.

There are several reasons why this sort of efficiency is meaningless. Any one of them ought to be sufficient for the concept to be discarded, but I shall consider them in turn in the belief that different arguments appeal to different people. Perhaps the first point to note is that efficiencies in the range 40–60% seem to be psychologically satisfying, because efficiencies outside this range are rarely reported, though they are not difficult to find. Consider, for example, the reaction catalysed by fatty acyl-CoA synthetase:

$$RCO_2^- + \text{ATP} + \text{CoASH} \rightleftharpoons \text{RCO–SCoA} + \text{AMP} + PP_i \qquad \Delta G^{0\prime} = -10.4\,\text{kJ/mol}$$

This reaction may also be regarded as the difference between two hydrolytic reactions:

$$\text{RCO–SCoA} + H_2O \rightleftharpoons \text{CoASH} + RCO_2^- \qquad \Delta G^{0\prime} = -31.4\,\text{kJ/mol}$$

$$\text{ATP} + H_2O \rightleftharpoons \text{AMP} + PP_i \qquad \Delta G^{0\prime} = -41.8\,\text{kJ/mol}$$

so that it proceeds with an efficiency of 31.4/41.8, or 75%, an impressive value that is given curiously little acclaim. There is, however, the embarrassment that Nature, perhaps following some celestial fair-trading agreement, evidently considers that 75% efficiency is excessive and carries out the reaction in the presence of inorganic phosphatase, a ne'er-do-well enzyme with an efficiency of zero. If this is taken into account the appropriate ATP hydrolysis to consider is the following:

$$\text{ATP} + 2H_2O \rightleftharpoons \text{AMP} + 2P_i \qquad \Delta G^{0\prime} = -61.0\,\text{kJ/mol}$$

and the overall efficiency is a respectable 31.4/61.0, or 52%.

The reaction catalysed in gluconeogenesis by 3-phosphoglycerate kinase provides a more extreme example:

$$\text{3-Phosphoglycerate} + \text{ATP} \rightleftharpoons \text{1,3-bisphosphoglycerate} + \text{ADP} \qquad \Delta G^{0\prime} = +18.8\,\text{kJ/mol}$$

The hydrolysis reactions to consider here are the following:

$$\text{1,3-Bisphosphoglycerate} + H_2O \rightleftharpoons \text{3-phosphoglycerate} + P_i \qquad \Delta G^{0\prime} = -49.3\,\text{kJ/mol}$$

$$\text{ATP} + H_2O \rightleftharpoons \text{ADP} + P_i \qquad \Delta G^{0\prime} = -30.5\,\text{kJ/mol}$$

and the efficiency is 49.3/30.5, or 162%. This result also tends not to be mentioned when the efficiency of metabolic processes is being discussed. Perhaps gluconeogenesis is regarded as in some obscure way less fundamental than glycolysis. In glycolysis the identical reaction occurs, but the phosphate group is transferred in the opposite direction, so the partitioning should be done as follows:

$$\text{ATP} + H_2O \rightleftharpoons \text{ADP} + P_i \qquad \Delta G^{0\prime} = -30.5\,\text{kJ/mol}$$

$$\text{1,3-Bisphosphoglycerate} + H_2O \rightleftharpoons \text{3-phosphoglycerate} + P_i \qquad \Delta G^{0\prime} = -49.3\,\text{kJ/mol}$$

The efficiency is now only 30.5/49.3, or 62%, even though the reaction being considered is unchanged.

A quite separate worry about calculating the efficiency of an enzyme-catalysed reaction is that it usually involves chemical species that do not participate in the reaction of interest, usually water and inorganic phosphate. This might not matter if the calculated efficiency were independent of the particular partitioning used, but it is not. For example, it is not obvious why we cannot study the efficiency of the hexokinase reaction in relation to the transfer of a phosphate group to fructose rather than to water. If we do this we have the following (equally legitimate) partitioning:

$$\text{Glucose 6-phosphate} + \text{fructose} \rightleftharpoons \text{glucose} + \text{fructose 6-phosphate} \qquad \Delta G^{0\prime} = +2.1\,\text{kJ/mol}$$

$$\text{ATP} + \text{fructose} \rightleftharpoons \text{ADP} + \text{fructose 6-phosphate} \qquad \Delta G^{0\prime} = -14.6\,\text{kJ/mol}$$

Thus replacing one pair of irrelevant species (water and inorganic phosphate) with another (fructose and fructose 6-phosphate) has changed an efficiency of 45% into one of $-2.1/14.6$, or -14%.

It might be argued that hydrolysis is in some way a more 'natural' basis for calculation than phosphorylation of fructose, though it is not clear to me that such an argument would have any objective validity. Even if we accept it, however, we have an element of arbitrariness resulting from the choice of 1 M as the standard state of a substance in solution. Our predecessors could just as legitimately have chosen 0.1 μM instead (as biochemists habitually do for the proton, though not for other species). If they had done so we should now have, for the hexokinase reaction:

$$\text{Glucose 6-phosphate} + H_2O \rightleftharpoons \text{glucose} + P_i \qquad \Delta G^{0\prime\prime} = -53.7\,\text{kJ/mol}$$

$$\text{ATP} + H_2O \rightleftharpoons \text{ADP} + P_i \qquad \Delta G^{0\prime\prime} = -70.4\,\text{kJ/mol}$$

where $\Delta G^{0\prime\prime}$ refers to a standard Gibbs energy calculated with the revised standard of 0.1 μM. The efficiency of the reaction would be 53.7/70.4, or 76%. It will be clear that the usual value does not have any fundamental chemical meaning, but is simply the result of the historical accident of choosing a particular, but completely arbitrary, concentration as standard.

Perhaps the most convincing way of demonstrating the absurdity of dividing one standard Gibbs energy by another is to consider, as Atkinson (1977) has done, what it means in terms

of equilibrium constants. If we define an efficiency E as the ratio $\Delta G_1^{0'}/\Delta G_2^{0'}$ of two standard Gibbs energies, and these are expressed in the ordinary way as $\Delta G_1^{0'} = -\boldsymbol{RT}\cdot\ln K_1$, $\Delta G_2^{0'} = \boldsymbol{RT}\cdot\ln K_2$, in terms of the corresponding equilibrium constants K_1 and K_2 we find that E is the powder to which K_2 has to be raised to give K_1, i.e.:

$$K_2^E = K_1$$

This would be a bizarre enough equation if K_1 and K_2 were dimensionless, but it is clearly a monstrosity if units have to be considered. For example, for the hexokinase reaction the equilibrium constants for hydrolysis of both ATP and glucose 6-phosphate are concentrations, and so this equation expresses the mathematically absurd notion that we can raise a concentration to a non-unit power to get another concentration. [How the usual definition of $\Delta G^{0'}$ in terms of the logarithm of a dimensioned quantity needs to be qualified to prevent it from being dimensional nonsense itself is a separate issue that I shall not discuss here, though I have done so elsewhere (Cornish-Bowden, 1981).]

Some authors (e.g., Hamori, 1975) calculate efficiencies from actual Gibbs energies (ΔG), rather than from standard Gibbs energies ($\Delta G^{0'}$), or they imply that $\Delta G^{0'}$ is a sort of approximation to ΔG that can be used when actual ΔG values are not known (e.g. Lehninger, 1975, pp. 432–433). Use of ΔG does avoid some of the difficulties I have discussed; for example, it gives a result that is independent of the units of measurement; but it does not avoid the need to introduce irrelevant species, such as water and inorganic phosphate, and indeed it makes this difficulty worse. If we put [ATP]/[ADP] = 10, and [glucose 6-phosphate]/[glucose] = 0.01, for example, we find that the Gibbs energy of the hexokinase reaction is as follows:

$$\Delta G = 16.7 + \boldsymbol{RT}\cdot\ln(0.001) = -34.5\,\text{kJ/mol}$$

This result is independent of the concentration of inorganic phosphate, which is as it should be because inorganic phosphate has nothing to do with it. But the Gibbs energy for the hydrolysis of glucose 6-phosphate is:

$$\Delta G = -13.8 + \boldsymbol{RT}\cdot\ln(100) + \boldsymbol{RT}\cdot\ln[\text{P}_\text{i}] = -1.9 + 5.9\log[\text{P}_\text{i}]\ \text{kJ/mol}$$

and that for the hydrolysis of ATP is:

$$\Delta G = -30.5 + \boldsymbol{RT}\cdot\ln\ (0.1) + \boldsymbol{RT}\cdot\ln[\text{P}_\text{i}] = -36.5 + 5.9\log[\text{P}_\text{i}]\ \text{kJ/mol}$$

So the efficiency is now $(1.9-5.9\log[\text{P}_\text{i}])/(36.5-5.9\log[\text{P}_\text{i}])$, and we see that the cell can increase the efficiency of the hexokinase reaction from a feeble 36% to a more acceptable 42% merely by decreasing the concentration of an irrelevant species, inorganic phosphate, from 1 mM to 0.1 mM. It is not clear to me that this sort of result makes any more sense than those given by standard Gibbs energies.

Although I have concentrated on the calculation of efficiencies of individual reactions, because these provide the clearest illustration of why the calculation is meaningless, the calculation is also often done for whole pathways. For example (Lehninger, 1975, p. 550), the oxidation of palmitate may be represented as the difference between two partial reactions:

$$129\text{ATP} + 129\text{H}_2\text{O} \rightleftharpoons 129\text{ADP} + 129\text{P}_\text{i} \quad \Delta G^{0'} = -3930\,\text{kJ/mol}$$

$$\text{Palmitic acid} + 23\text{O}_2 \rightleftharpoons 16\text{CO}_2 + 16\text{H}_2\text{O} \quad \Delta G^{0'} = -9780\,\text{kJ/mol}$$

and thus proceeds with an efficiency of 3930/9780, or 40%. This calculation again has a sort of superficial plausibility, and it at least avoids the introduction of irrelevant species (all of the molecules shown appear in the overall stoicheiometry), but it is subject to all of the other problems inherent in the division of one standard Gibbs energy by another. It also involves all of the artitrariness that derives from the use of different standard states for different species.

Can anything of value be salvaged from this quagmire? I suspect that any attempt to treat the Gibbs energy of a reaction as a commodity to be moved around from one metabolite to another, a sort of 20th-Century caloric, is doomed to failure. Yet the idea of metabolic efficiency does have an intuitive appeal, and it is difficult to accept that there is no way in which it can be defined meaningfully. Thermodynamic efficiency is certainly not an invention of biochemists, and was a major concern of Carnot, the father of thermodynamics (see, e.g., Cooper, 1968). However, Carnot was concerned with heat engines, and the living organism is not a heat engine. Not only does it contain no pistons, but it cannot possibly operate as a heat engine because it operates isothermally and there is no way in which an isothermal engine can convert heat into work. To proceed further, we need not classical thermodynamics but irreversible thermodynamics, which does appear to offer a meaningful way of talking about metabolic efficiency (Stucki, 1980). However, it is also mathematically a more complex approach and is beyond my present purpose, which has been to demonstrate in as simple a way as possible that naively defined metabolic efficiencies are meaningless.

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