



**Figure 10.11.** Primary measurements, shown on top, may be used to calculate many related process properties and parameters. (With permission, from L. P. Tannen and L. K. Nyiri, "Instrumentation of Fermentation Systems," p. 331, in *Microbial Technology*, 2d ed., Vol. II, H. J. Peppler and D. Perlman, eds., Academic Press, New York, 1979.)

in response to acetate accumulation. On-line measurement of acetate is not now routine, but improvements in sensors certainly make this a tenable approach. A strategy that is easier to implement with current sensors is based on measuring the rates of carbon dioxide evolution. Measurement of carbon dioxide in the off-gas, coupled with information on substrate concentration in the feed and nutrient flow rates, allows the glucose feed rate to be manipulated to maintain glucose concentrations at an optimal level. This indirect strategy depends on the use of mass balances and the gateway sensor concept. Another strategy is to control glucose concentration with a feedback control system, if a glucose sensing system is available. The easiest approach is to use a predetermined glucose feeding schedule, although this usually results in significant periods of sub- or superoptimal glucose concentrations. These strategies have been used successfully. High-density *E. coli* cultures (ca. 100 g dry wt/l) have greatly increased product concentration and productivities in *E. coli*-based fermentations to make proteins from recombinant DNA. At these high densities, special strategies for oxygen supply (e.g., O<sub>2</sub>-enriched gas) are often required. This example illustrates the important interaction between process-control strategies and cellular metabolism.

As we develop better sensors and a better understanding of metabolic pathways, it becomes more feasible to combine information from primary sensors with models of metabolism to develop better control strategies. Without direct measurement of the product, simple feedback control on the process itself is impossible. Without extremely good