

TABLE 10.6 (continued)

Approach	Possible measuring devices and compounds monitored	Comments
3. Measurements from liquid slip stream	Semiconductor gas sensors; flammable or reducing gases or organic vapors	Has been used in bioreactors primarily for ethanol measurements
	HPLC (high-performance liquid chromatography); dissolved organics; particularly useful for proteins; auto analyzer	Highly specific; compound need not be volatile; response time is long (min); solids must be removed by filtration; membrane fouling can be a problem; guard columns must remove compounds that may foul columns; expensive; main value is to differentiate among closely related proteins or variants of a particular protein
	Mass spectrometers; dissolved compounds that can be volatilized	Same instrument can be used also for exit gas analysis; rapid, specific, but expensive; complex molecules present problems
	Enzymatic methods; potentially wide range, but glucose has received most attention	Slow response (min), not highly flexible, but very discriminating; potential for contamination; has limited acceptance

On-line HPLC (high-performance, or high-pressure, liquid chromatography) is potentially very powerful for measuring the levels of dissolved solutes, particularly proteins made from genetically engineered cells. Although this assay is not routine, many vendors are actively developing systems for this application. However, this method, as well as most others using a liquid slip stream, requires sample preparation and has a significant time delay associated with sampling. Typically, a small side stream is pumped from the reactor, and microfiltration or an ultrafilter is used to remove cells and particulates. The filtrate usually requires further processing (e.g., the removal of compounds that could foul the analytical-grade columns). After injection of the sample, there can be a significant time (min) before a response is obtained. One other problem with slip streams is the potential for contamination; the membrane filtration step is of particular concern. Nonetheless, the use of liquid slip streams allows the relatively rapid determination of important product information.

Other methods not listed in Table 10.6 have the potential to significantly affect the on-line measurement of fermentation parameters. Nuclear magnetic resonance (NMR) has given important information on intracellular metabolism for off-line or small-scale growth experiments. *In situ* NMR has the potential for use with at least bench-scale systems, although significant technical advances must first be made. Selective fluorescence in combination with flow cytometry has given important information, off line, on the distribution of intracellular parameters (e.g., plasmid content) in a population. The adaptation of such techniques to on-line measurement is conceivable, but again a number of technical prob-