(Chiron Corp., Emeryville, CA, USA) described the Chemiluminescent Nitrogen Detector as a valuable complement to the UV detector. Although not of universal utility, this nitrogen detector has a potential in pharmaceutical development, because most drugs and biologically interesting molecules contain nitrogen atoms. The detector allows accurate quantification even with limited amounts of impure samples. The analytical system described combines UV and nitrogen detection with MS. A single analytical run thus provides information on sample purity, concentration and identity.

Liquid chromatography is one of the most powerful techniques for sample purification, but it is expensive and throughput is limited, even with highly automated systems. Liquid–liquid extraction, on the other hand, is a fast and simple purification technique. S. Hadida (University of Pittsburgh, PA, USA, currently at CombiChem) gave a talk about the 'fluorous' phase, which has unique properties in comparison with water and organic solvents. For example, a reaction carried out with a fluorous reagent such as the commercially available $(C_6F_{13}CH_2CH_2)_3SnH$ can be purified by extraction with water, an organic solvent like dichloromethane and perfluorinated hexanes. Inorganic salts will dissolve in the aqueous phase, the product can be isolated from the dichloromethane phase and the fluorous reagent ends up in the fluorous phase; the target compound is obtained in high purity in the organic phase. This liquid–liquid-extraction protocol has been further developed into a solid-phase-extraction method using fluorous silica gel.

Summary

The conference made it clear that combinatorial chemistry now has become an established subdivision of organic chemistry. The pharmaceutical industry has recognized the potential of combinatorial libraries in the search for lead compounds. In addition, it is now obvious that combinatorial methods have great potential in medicinal chemistry. As a consequence, large efforts are being made to adopt the large number of transformations employed in organic chemistry for combinatorial purposes. Several presentations also indicated that parallel synthesis of large numbers of discrete compounds is emerging as a complement to split-pool synthesis of compound mixtures. Furthermore, the nature of combinatorial chemistry has spurred the development of fully automated systems capable of carrying out a majority of the operations required in parallel or split-pool library synthesis. The advances made in high compound throughput have, in turn, driven the development of new strategies for compound characterization and purification. The post-conference workshop focused on several of these techniques for the analysis and purification of libraries. Automated systems for rapid characterization and purification are now available, and it is obvious that the recent developments have resulted in systems that can cope with the number of compounds prepared in high-throughput synthesis. In summary, the conference and workshop created an interactive forum to discuss current issues in depth. Furthermore, the speakers were generous in sharing their results and experiences in detail, which resulted in a creative and inspiring atmosphere.

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Dielectric estimation of microbial biomass using the Aber Instruments Biomass Monitor

Letter

The recent article by Olsson and Nielsen, *On-line and in situ monitoring of biomass in submerged cultivations*[1], contained a number of inaccuracies regarding both the dielectric method for measuring cellular biomass on-line and *in situ*, and its exploitation in the Aber Instruments Biomass Monitor that we would like to correct.

The glossary states that the 'dielectrical [sic] permittivity consists of the capacitance (the ability to store electrical charges) and conductance (the ability to conduct electrical charges) of the subject'. It does not. The dielectric permittivity is the capacitance normalized to take into account the geometry of the electrodes. Permittivity does not have a conductivity term, and conductivity is the conductance normalized to take into account the geometry of the electrodes. To understand the basis of the method, it is useful to recognize the relevant units, which are for capacitance Farads (usually pF), for conductance Siemens (usually mS) and for conductivity S m^{-1}. Permittivity is dimensionless. Many reviews and books describe this, including those aimed at biologists (e.g. Refs 2–4). This incorrect definition of the dielectric permittivity inevitably means that most of the basis of the dielectric method is simply misrepresented. In addition, Olsson and Nielsen refer readers to Matanguihan *et al.*[5], which is a poor choice for a discussion of biological dielectrics as its abstract, which is what most people will read, also conflates capacitance and permittivity.

Many groups[6–11] have published work on the use of the Aber Instruments Biomass Monitor, which exploits the dielectric/capacitance method via the β-dielectric dispersion for on-line and real-time measurement of biomass. It is not true that 'the effect of the medium conductance has to be calibrated before the cell concentration can be determined'. The effect of conductivity is entirely well understood (and

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note the difference: it is conductivity, not conductance, that affects the β dispersion). It is necessary to know only the actual conductivities and the cell size to be able to determine what the effects of changing the conductivity will be.

The statement is made that the 'Aber [Instruments] Biomass Monitor (previously called the Bug-meter)...is restricted to measuring cultivation media with conductivities below 20 mS'. In fact, the Aber Instruments machine currently measures up to 40 mS cm^{-1} (and note the units), whilst the electrochemical cleaning method used in the Biomass Monitor does not date from the cited reference in 1994, but was actually discussed by Harris *et al.* in 1987[6].

It is not just at frequencies of 0.1–10 MHz that cells act as capacitors; if they have a larger capacitance than the background then they are acting as capacitors at any frequency. What the authors presumably intended to state is that it is in this range that the cell-membrane capacitance dominates the frequency-dependent dielectric properties, which is the basis of the (patented) Aber Instruments Biomass Monitor approach. It is at lower frequencies that the flow of ions round the cells comes into play, so the comment concerning this is irrelevant to measurements based on the β-dispersion.

The comments on the Fehrenbach *et al.* paper[9] are inaccurate. Those authors correlated capacitance, not conductivity, with dry weight and found excellent correlations, the slope of which depended (according to the theory) on the size of the cells. The conclusion that 'the correlations... could be considered doubtful for scientific applications' is Olsson and Nielsen's, not Fehrenbach's. It is also worth pointing out that current software sensors have not yet produced good results, and have been criticized in this journal[12].

Regarding the concluding remarks, we would point out that multivariate methods have already been applied to the dielectric biomass-measurement problem[13]. Thus perhaps the authors' final conclusion, that 'probably the best available *in situ* sensor is the Biomass Monitor (Aber Instruments)' best reflects the fact that many companies routinely use it to control their bioprocesses.

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Letter

Directing the Directive

How can we bring biotechnology regulations down to earth? Genetically modified microorganisms (GMMs), once the bugbear of those who oppose biotechnology, are now everyday tools in companies and laboratories across the world. Obviously, biotechnology should be regulated according to the inherent risk, evaluated through criteria based upon existing scientific evidence, new rigorous information and/or records of safe applications and performances[1]. The regulatory framework of the contained use of GMMs in the European Union (EU) is given by Directive 90/219/EEC[2]. On the basis of the Commission's White Paper *Growth, Competitiveness and Employment*, necessary amendments to the Directive are currently being discussed in the Council and by the European Parliament[3].

Containment and other protective measures have to be adapted to technical progress. The old discrimination between small-scale operations used for teaching, research, development or nonindustrial, noncommercial purposes (type A) and any other operations (type B) will be abandoned. Instead, general principles of containment and protective measures for laboratory activities, for glasshouses and growth rooms, for animal units, and for other activities are listed. Containment and other protective measures will be classified according to four levels of containment, in correspondence with WHO and CDC/NIH recommendations for work involving nonrecombinant microorganisms. This harmonization should readily promote the exchange of scientific views on the safe handling of GMMs in relation to long-standing experiences with, for example, pathogenic microorganisms.

In the EU, standards are one of the means of ensuring compliance with Directives. Currently, the European Committee for Standardization (CEN) is developing biotechnology standards[4] relating *inter alia* to

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