Drug Metabolism and Analytical Chemistry

Short presentation of the group

Our work can be summarised as:
- Develoment of new instrumental techniques
- Drug metabolism. reactive drug metabolites and side effects
- Solving analytical chemical challenges

The Group

At present (November 2010) the group consists of:

2 full time and one part time (shared with the University of Oslo, Norway) Full Professors,

One Associate Professor,

Three Assistant Professors

Four technicians and a number of Ph.D. students.

The central focus of the group is on Drug oriented analytical chemistry with special focus on Drug metabolism and instrumental development.

The Group

Drug metabolism is an integrated part of drug discovery and drug development. In general, drugs are metabolized by a variety of enzymes, primarily located in the liver, to more polar metabolites that are rapidly excreted. Drug metabolites are less likely to exert a pharmacological or toxicological effect in humans and thus metabolism is an important factor in the evaluation of new drug candidates.

The Group

Although the metabolism of drugs is generally considered a detoxification process, a major concern in the development of new drug candidates is metabolite-mediated toxicity. Drugs may be metabolized to chemically reactive metabolites, which react with endogenous macromolecules such as proteins or DNA. Such covalent modification of macromolecules is thought to play an important role in the pathogenesis associated with the intake of some drugs.

The research on drug metabolism is focused on the identification and reactivity of drug metabolites.

The Group

In addition to the central focus of the group, the members are involved in numerous related projects including collaborations within as well as outside the department.

Steen Honoré Hansen. Full Professor. shh@farma.ku.dk

Separation mechanisms. Dynamic modification of the surface of silica using surfactants and macromolecules in order to obtain separation systems in high performance liquid chromatography (HPLC) and capillary electrophoresis (CE) systems with new and more reproducible selectivity .

Coupling of separation and spectroscopic techniques. Coupling of HPLC and CE to mass spectrometry (MS) and nuclear magnetic resonance spectrometry (NMR). Optimization of separation and detection systems in order to achieve lower limits of detection in bioanalytical methods.

Drug Metabolism. Studies on reactive drug metabolites. Development of new analytical techniques and methods to facilitate the determination of polar drug metabolites and conjugates in biological materials. Isolation and structure elucidation of unknown metabolites.

Natural medicine. Development of analytical chemical methods for the use in quality assessment of natural medicine and herbal remedies.

Food and environmental analysis.
Development of analytical techniques for the determination of xenobiotics and metabolites thereof for the assessment of exposure from the environment to living organisms

Frants R. Lauritsen. Full Professor. frl@farma.ku.dk

Portable mass spectrometry for real time analysis in the field. There are many situations, where it is important to get information in real time, and we develop miniaturized mass spectrometric equipment for on-site identification of chemicals and/or monitoring of chemical and biological processes.

On-site identification of drugs (forensic chemistry). A novel mass spectrometric interface makes it possible to analyze practically any sample without any pretreatment. We explore the possibilities of using the new interface together with miniaturized mass spectrometers for onsite identification of chemicals, for example drugs found beside or near poisoned humans.

Real-time monitoring of chemical and biological processes. Continuous monitoring of chemical processes, such as the creation of disinfection byproducts in swimming pools, can supply important information for use in toxicological exposure estimations. Whole cell reactors may also be setup for real-time studies of volatile metabolites.

Hand-held liquid chromatography mass spectrometry. Current miniaturized mass spectrometers are only able to analyze volatile organic compounds. To change this, we currently work with the development of miniaturized electrospray mass spectrometry to be used with miniature liquid chromatography.

Stig Pedersen-Bjergaard. Full Professor. sbp@farma.ku.dk
20 % Pharma, 80 % University of Oslo.

Sample concentration. Development of new micro extraction principles and technologies based on artificial liquid membranes. Application of the new technologies for extraction of drugs, drug metabolites, and peptides from biological fluids. Combination of the new technologies with electrophoresis, chromatography, and mass spectrometry. Implementation of the new technologies on Lab-on-a-chip systems.

Claus Cornett. Associate professor clco@farma.ku.dk.

NMR spectroscopy applied to structure elucidation and determination of physical chemical properties of small molecules. Structure elucidation of drug metabolites. Structureelucidation of drug metabolites and metabolites thereof. Use of other analytical methods necessary to support these objects. Small volume NMR. Metabolomics.

Data processing. Improvement of the processing of timeseries NMR data and chemometric methods applied to quantitative Analytical Chemistry.

Spectroscopy and imaging of drug formulations. Spectroscopy (NMR, NIR, IR, Raman) and multivariate data processing applied to drug formulation problems

Quantitative NMR spectrometry. Application of quantitative NMR spectrometry to small - primarily drug like - molecules such as metabolites and regulated compounds with tracing to primary standards.

Hyphenation of NMR with HPLC and CZE in combination with MS. Flow Injection NMR. Optimization of the strategy for obtaining hyphenated NMR data.

Christian Janfelt. Assistant Professor. cja@farma.ku.dk

Mass Spectrometry.
Mass spectrometry, instrumentation, direct MS-analysis, DESI-MS, mass spectrometry imaging and miniaturization of MS.

Christian Skonberg. Assistant Professor. cs@farma.ku.dk

Bioanalysis. Development of methods for analysis of endogenous compounds and xenobiotica in biological matrices, primarily using HPLC-MS. Special focus on optimization of detection limits and analysis of highly polar compounds and metabolites.

Drug Metabolism. The formation and toxicity of reactive drug metabolites. Subcellular fractions and whole cell culture models for prediction of drug metabolism and adverse drug reactions in hepatocytes and mitochondria.

Nickolaj J. Petersen Assistant Professor.
njp@farma.ku.dk

Minuaturized Analytical Chemistry. Miniaturized systems (µ-TAS), micro- and nanofluidics. Ionic transport during electrokinetically driven separations. Concentration techniques. Capillary electrochromatography (CEC).

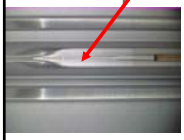
Bente Larsen
Senior Laboratory Technician

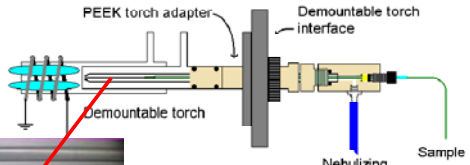
Monika Medved
Laboratory Technician

Kirsten Andersen
Senior Laboratory Technician

Marianne Reni Andersen
Laboratory Technician

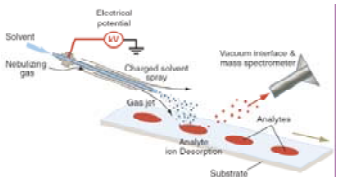
Efficient inexpensive CE-MS interface

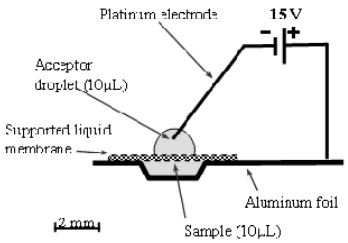




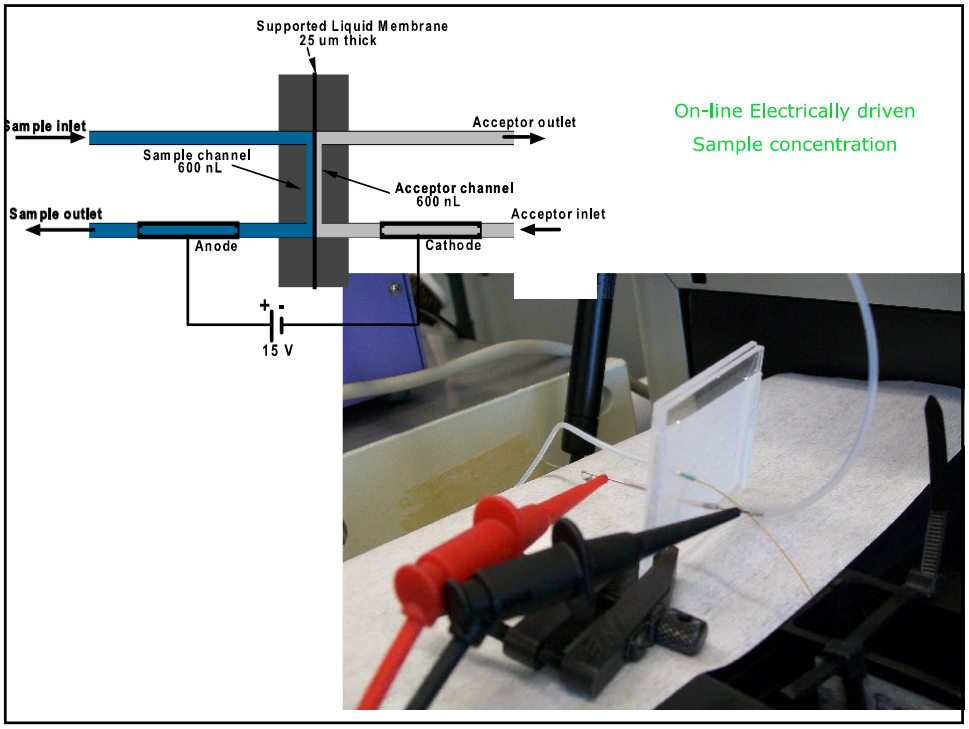
Improved inexpensive torch for ICP MS

Desorption Electrospray Ionisation (DESI). 1D and Imaging





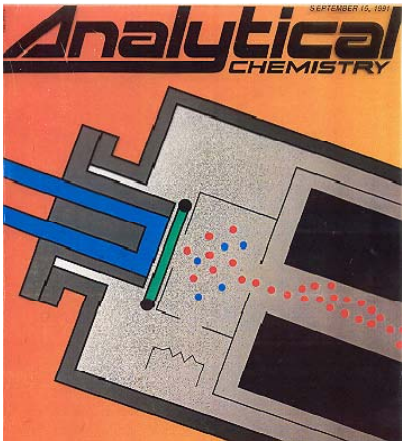
Static Electrically driven Sample concentration

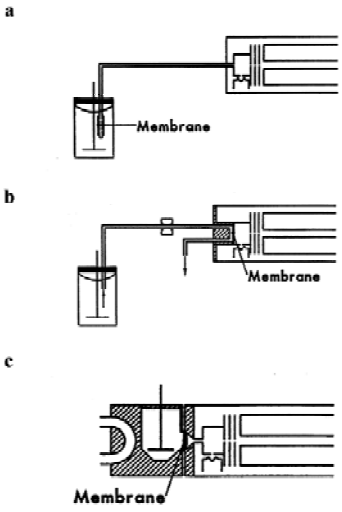


On-line Electrically driven
Sample concentration

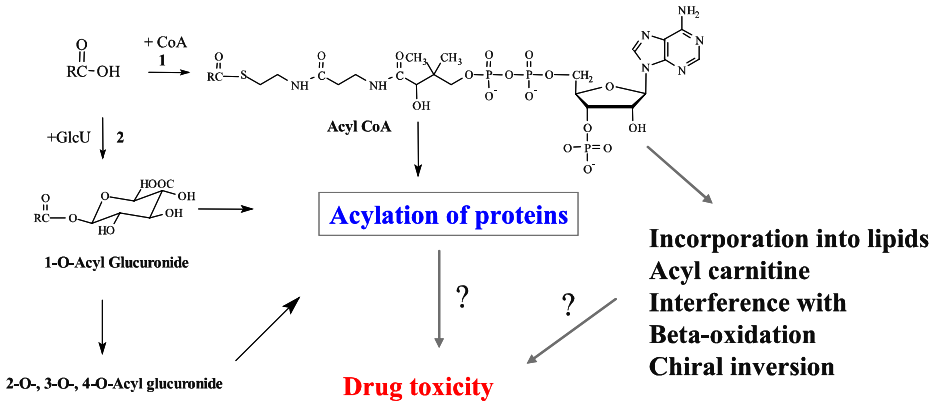
MS. Sample introduction by Membrane inlet

The MIMS principle

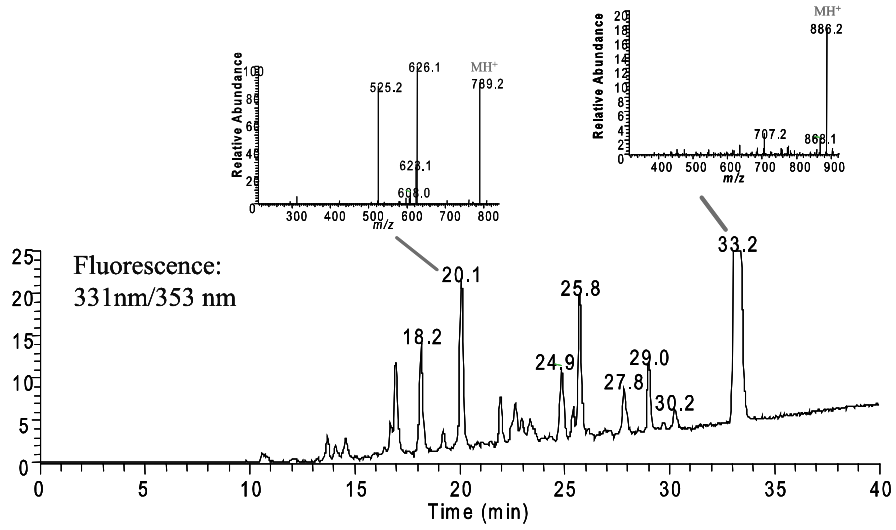




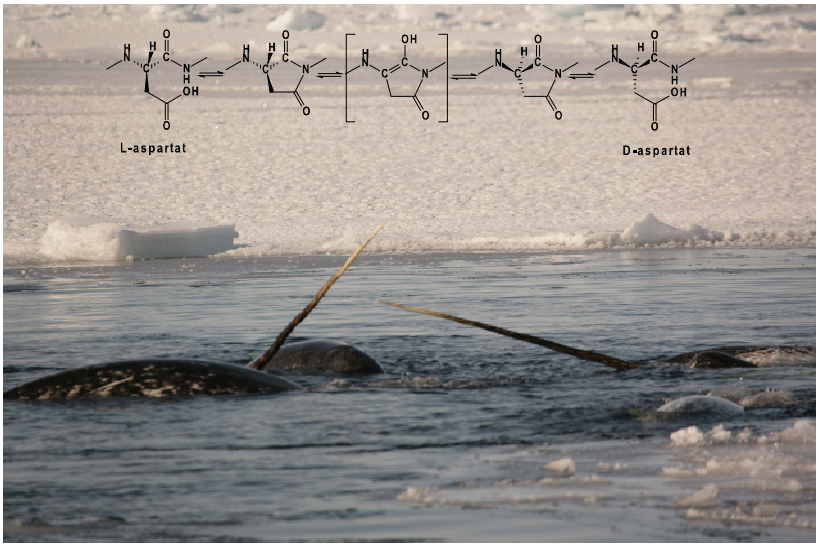
Drug Metabolism: Reactive drug metabolites



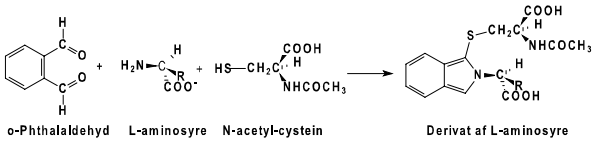
Drug Metabolism: Reactive drug metabolites
Tryptic digest of albumin after reaction with naproxenGlcU

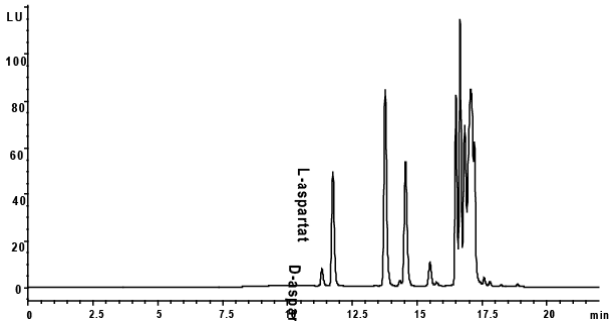


Age determination of arctic sea mammals

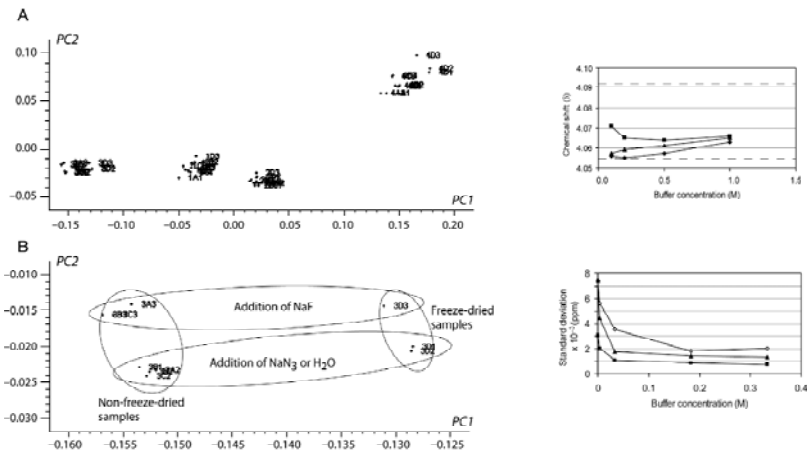


The Apartate method for age determination





Metabolomics



Effect of sample treatment on NMR based metabolomics data for urine

Analytical Chemical Challenges adressed in the near future:
Danish Wine and Spirits. Urea can be formed during fermentation of grapes, can react with ethanol froming ethyl urea which is carcinogenic. Challenge: Develop analytical method.
Simultaneous analysis of ethanol, methanol, organic and amino acids, pH, carbohydrate etc. using NMR. Challenge: Determine best experimental conditions for Metabolomics.
Ladybirds excrete the compound 2-isopropyl-3-methoxypyrazine that can ruin wine. Challenge: Develop analytical method.

Grasshoppers as animal models. Develop analytical methods to determine a series of compounds in the brain and metabolism studies.

Reactions between Drug Substances and Excipients. Citric Acid, sorbitol, glycerol etc. are common excipients but in some cases reatcs with the drug substance causing browning, unwanted impurities etc. Challenge: Develop appropriate analytical method s to identify and quantitate reaction products.