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# Determination of urine ionic composition with potentiometric multisensor system



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## ABSTRACT

The ionic composition of urine is a good indicator of patient's general condition and allows for diagnostics of certain medical problems such as e.g., urolithiasis. Due to environmental factors and malnutrition the number of registered urinary tract cases continuously increases. Most of the methods currently used for urine analysis are expensive, quite laborious and require skilled personnel. The present work deals with feasibility study of potentiometric multisensor system of 18 ion-selective and cross-sensitive sensors as an analytical tool for determination of urine ionic composition. In total 136 samples from patients of Urolithiasis Laboratory and healthy people were analyzed by the multisensor system as well as by capillary electrophoresis as a reference method. Various chemometric approaches were implemented to relate the data from electrochemical measurements with the reference data. Logistic regression (LR) was applied for classification of samples into healthy and unhealthy producing reasonable misclassification rates. Projection on Latent Structures (PLS) regression was applied for quantitative analysis of ionic composition from potentiometric data. Mean relative errors of simultaneous prediction of sodium, potassium, ammonium, calcium, magnesium, chloride, sulfate, phosphate, urate and creatinine from multisensor system response were in the range 3–13% for independent test sets. This shows a good promise for development of a fast and inexpensive alternative method for urine analysis.

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## 1. Introduction

Chemical analysis of biological liquids (blood, saliva, urine, etc.) plays a very significant role in medical diagnostics. Analysis of urine is one of the most informative for medical doctor since it reveals general condition of organism and nutrition character. Urine is an aqueous solution of various substances in different concentrations. It is a convenient object for analysis, components being easily extracted or analyzed right after plain dilution step. Any serious deviation from the normal composition of urine indicates certain metabolic disorder. One of the most widespread metabolic disorders is urolithiasis characterized by the formation of stones in the kidneys and urinary organs [1].

The stone formation begins if equilibrium between urine components is disturbed. The main markers of urolithiasis are separated

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into promoters and inhibitors. Increased concentrations of promoters (calcium, ammonium, oxalate, phosphate, urate) indicate a risk of possible stone formation. The presence of inhibitors (magnesium, citrate) reduces a possible stone formation since these components enter into competing interaction. The history of urolithiasis markers study is very long [2] and the interest to this issue is growing. The main problem of urolithiasis is that at early stages this disease proceeds asymptotically. The patient becomes aware of his illness only when the stone is already formed and starts obstructing normal organism activities [3]. Early diagnostics is a half of successful treatment, thus biochemical analysis of urine ionic composition is very important to fight against the urolithiasis. The adequate medical conclusion can be given in laboratory on the basis of biochemical analysis consisted of 14 parameters: contents of sodium, potassium, ammonium, calcium, magnesium, chloride, sulfate, phosphate, oxalate, citrate, urate, creatinine, pH level and density. Also a registration of sex, age and diuresis is required. The analysis of combination of these parameters can indicate a possible stone formation [4].

Various analytical methods are employed on routine basis for determination of urine composition in medical laboratories.

Capillary electrophoresis (CE) is considered to be one of the most accurate analytical techniques for urine analysis, offering a number of simple techniques for quantification of inorganic and organic cations and anions in urine. Direct and indirect UV-detection is used most often in CE [4–10]. Spectrophotometric techniques are applied for calcium, magnesium, phosphate, uric acid and creatinine quantification. In this case a preliminary derivatization reaction with specific agent is required to yield colored substance which can be analyzed [11]. Ion-selective electrodes are employed for determination of sodium, potassium and chloride [12].

There are also a number of approaches for urine analysis which were suggested in literature but were not massively introduced into a common laboratory practice so far. A very interesting diagnostic technology is so called “Lithos-system” [13]. The main principle of this system is in observation of crystals of the dried urine sample. The shape and arrangement of crystals is further compared with certain standard figures and this methodology allows to judge on the risk of stone formation [13].

Determination of urine components can be carried out using ion chromatography with piezoelectric or conductivity detectors [14,15]. Classical chromatography (liquid and gas) can be successfully applied for analysis of nonionic substances [16–18]. Creatinine and urate as uric acid can be quantified with liquid chromatography–tandem mass spectrometry in urine samples [16,17]. The derivatization with 2,3,4,5,6-pentafluorobenzyl bromide is used for creatinine determination in urine sample by gas chromatography–tandem mass spectrometry [18].

The application of electrochemical methods for urine components analysis is usually hindered by the presence of interfering signals. For example, limited selectivity towards different ions of PVC-plasticized potentiometric sensors in the presence of ammonium lead to attempts to create more selective electrodes for sodium [19] and calcium [20]. An important issue is adsorption of organic urine components on a membrane surface, which leads to reduced reproducibility and lifetime of the sensors. The authors of [21] proposed to use solvent–solvent extraction, membrane-immobilized solvent extraction and solid phase extraction to remove lipophilic compounds from urine samples. However, such kind of sample preparation significantly reduces the benefits of sensors ensuring fast and simple analysis.

There are many reports on application of different biosensors for urine analysis. The analytical signal of these devices is typically based on reactions of target analyte with a biomolecule immobilized on the surface of chemically modified electrode [22]. The content of urate or oxalate in urine can be determined by biosensors based on uricase [23] or oxidase [24] respectively. The main advantage of biosensors is their high selectivity due to specificity of biological reactions. However, it is often hard to obtain reproducible microstructure of a substrate layer to warrant good batch reproducibility.

The idea to use the sensor arrays (“electronic tongues”) for simultaneous determination of numerous chemical parameters seems to be quite obvious for urine analysis and there were several attempts reported in literature [25–27]. The authors of [25] have proposed the sensor array consisting of urea biosensor and ion-selective electrodes for ammonium, potassium, sodium, hydrogen and one sensor with generic response towards alkaline ions. The response of the array in 37 model solutions was processed with artificial neural network (ANN) and partial least squares (PLS) to construct regression models for simultaneous quantification of urea, ammonium, potassium and sodium. Validation was done with 21 samples (three real urine samples and 18 spiked samples were prepared by addition of different quantities of urea, ammonium, potassium and sodium). It was possible to quantify individual components with relative errors around 8% for ANN-models

and 13% for PLS-models. Later the same authors extended this sensor array with a creatinine biosensor [26]. TRIS buffer (tris (hydroxymethyl)aminomethane) pH=7.5 was used as a solvent since biosensors require this acidity level to support the catalytic activity of the enzymes. The training of this system was performed on 27 model solutions consisting of five analytes in various concentrations. Independent test-set (13 model solutions) was applied for validation and after that 11 samples (three real urine samples and eight spiked samples were prepared by addition of different quantities of urea, creatinine, ammonium, potassium and sodium) were analyzed. The maximum relative error was 9% in the determination of creatinine [26].

Another report [27] dealt with the sensor array of eight 8 metallic electrodes (Co, two component alloys – Sn/Pb, Cu/P, Cu/Zn, four alloys of silver – Ag/Cu/Zn/Cd, Ag/Cu/Sn, Ag/Cu/Zn/Sn – in two different ratios) and five polymeric membrane sensors. The purpose of the study was to detect urinary system dysfunctions and to analyze creatinine levels. 51 urine samples were classified in four classes according to the creatinine content by PLS-Discriminant Analysis (PLS-DA) and neural net. It was shown that this sensor system is able to distinguish between urine samples from healthy patients and those with malignant and non-malignant tumor diagnosis of bladder.

The idea of the present study was to construct the sensor array which would be capable of exhaustive analysis of urine ionic composition. These data are of ultimate importance for early medical diagnosis of several disorders, such as e.g., urolithiasis. Furthermore the intention was to validate this approach with sufficient number of real urine samples employed in independent test sets. The issue of proper validation of promising methods is, unfortunately, ignored in literature pretty often and far-reaching conclusions are being done just with cross-validation on model samples or only a small number of real ones. This is not enough for proper evaluation of such systems for urine analysis.

## 2. Materials and methods

### 2.1. Urine samples preparation

136 urine samples were collected for this study. 117 samples from patients were provided by Urolithiasis Laboratory (Medical Center of Laboratory Diagnostics, St. Petersburg). 19 samples from healthy people were collected from persons who did not express complaints. The accumulation of sufficient number of samples took about six months since only three to six urine samples per week are available from the Urolithiasis Laboratory. All urine samples (50 ml of each) were frozen in a biomedical fridge at  $-25^{\circ}\text{C}$ . The literature suggests that ionic composition of urine varies by less than 5 percent on freezing-thawing during 5 years [28].

The urine samples were prepared for analysis with potentiometric multisensor system by unfreezing on a water bath at room temperature ( $25^{\circ}\text{C}$ ) and then by thorough mixing. 10 ml of urine were diluted with 90 ml of distilled water and the resulted solution was employed for direct potentiometric measurements. Each sample was measured in 4 physically different replicas. Replicated measurements were randomized between the samples.

### 2.2. Potentiometric multisensor systems

The potentiometric multisensor system consisted of 19 chemical sensors. Ten ion-selective electrodes for  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{NH}_4^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+} + \text{Mg}^{2+}$ ,  $\text{NO}_3^-$ ,  $\text{Cl}^-$ ,  $\text{CO}_3^{2-}$ ,  $\text{SO}_4^{2-}$  were prepared based on standard Fluka® ionophores following the producer recommendations. Five poly (vinylchloride) (PVC)-plasticized anion-sensitive sensors were based on various anion-exchangers, three were PVC-plasticized cation-sensitive

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