Lab-on-valve: a useful tool in biochemical analysis

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Despite the short life-time of lab-on-valve (LOV) devices – the third generation of dynamic approaches invented by J. Ruzicka – they have proved to be of great interest in biochemical analysis. LOV works automatically with sequential injection to move micro or sub-micro volumes of liquids, gases and/or beads in a "digital" manner by stopping, reversing, and accelerating flow rates in a way that is of interest in sample preparation – especially modes such as bead-injection spectrometry, micro affinity chromatography or in-line LOV–bioreactor – and when LOV is coupled to high-resolution equipment, such as capillary electrophoresis and chromatography.

LOV-based equipment has proved to be useful in handing μl volumes (e.g., in cell-culture and antibody studies, to assess the metabolic regime of living cells; and, in DNA assays, to detect single-stranded nucleic acid sequences). LOV therefore offers a promising way ahead for in-valve biochemical steps, which can be expanded by coupling to separation units (e.g., dialyzers, gas diffusers, pervaporators, and novel liquid–liquid extractors), which facilitate automatic interference removal and preconcentration in complex samples with low concentrations of analytes.
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1. Introduction

Automation and miniaturization of solution-based analysis are essential to make them fast and efficient for routine and research tasks in biochemical laboratories. Ideally, analytical equipment should be versatile, capable of accommodating a wide variety of assays without the need for system reconfiguration, and compatible with a wide range of detectors [1].

Since the introduction of flow injection (FI) in 1975 [2], thousands of scientific publications [3] have demonstrated its feasibility for automation, which has evolved through two new generations [4–6]:

- sequential injection (SI) [7], introduced in the 1990s and referred to as the second-generation FI; and,
- laboratory-on-valve (lab-on-valve, LOV), a recent continuous methodology, referred to as third-generation FI

and also introduced by Ruzicka [8], which works in SI mode and has downscaled reagent-based analysis to ml and sub-ml levels.

During the past decade, miniaturization has gained increased interest in several analytical fields. Taking into account that the ultimate goal of miniaturization of reagent-based analysis is to decrease use of materials consumed and waste generated [8], its importance in the biochemical field is crucial, as both biochemical reagents and samples are usually scant and/or expensive. Thus, reducing consumption of expensive (or scant) sample and/or reagents through different approaches to miniaturization is obviously one of the most effective strategies to reduce analytical costs.
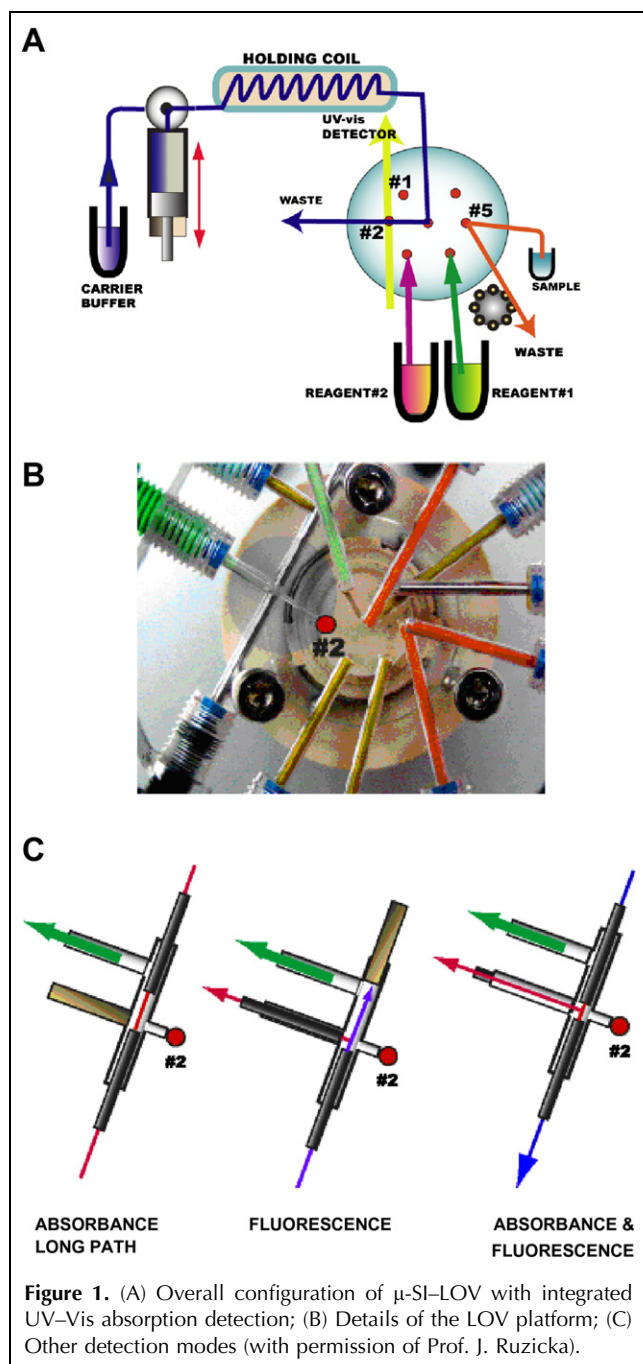
A key way to downscale is to replace continuous flow by programmable flow, which allows moving liquids, gases and/or beads in a "digital" fashion, by stopping, reversing, and accelerating flow rates [5]. This principle of SI [4] has been downscaled, integrated into the LOV platform and used for miniaturization of reagent-based analysis, immunoassays, bioligand-interaction analysis, and ion-exchange and affinity chromatography [9], among others.

A LOV platform consists of:
(1) a transparent, monolithic structure made of Perspex;
(2) a multiposition valve as the main component of the structure; and,
(3) a propulsion unit, usually a syringe pump, characteristic of SI, to circulate the required liquids through the system, which is overall referred to as μ-SI–LOV.

Fig. 1 shows a scheme of a LOV manifold, which also includes details of the valve itself and the ways the flow cell can

Figure 1. (A) Overall configuration of μ-SI–LOV with integrated UV–Vis absorption detection; (B) Details of the LOV platform; (C) Other detection modes (with permission of Prof. J. Ruzicka).

selection valve [11,16,17]; one or two holding coils [12,18]; an auxiliary peristaltic pump [5,8,19–21]; a mixing coil [5,22]; and, T connections [12,19]. These units confer on LOV the high versatility, which, together with other characteristics, makes it an attractive tool in the biochemical field.

LOV allows miniaturization of the flow channel; thus, sample and reagent volumes are downscaled to the 10–20-μl range, while waste production is typically 0.1–0.2 ml per assay [1]. These systems are therefore positioned between traditional flow techniques that operate at the ml scale and the more futuristic designs of the micro total analysis systems (μTAS) concept, which is supposed to work at the nl scale. (The SI–LOV manifold is also known as a meso-fluidic system – ''meso'' from its capability to manipulate fluid between ''micro'' and ''macro''. Despite of this, most authors refer to SI–LOV manifolds to as micro-fluidic systems).

Similarly to microchips, LOV must be assisted by external units for proper circulation of samples and reagents. By operating within the μl range with channel diameters about 0.5 mm, μ-SI–LOV systems are compatible with real-life samples that often contain particles that can clog the μm-sized channels of nl-scale devices. The choice of LOV channel dimensions has two significant advantages:

(1) a large volume-to-surface ratio, which minimizes the unwanted adsorption on channel walls that may result in carry-over; and,

(2) even more importantly, this channel geometry allows LOV devices to be used as platforms for the bead-injection (BI) technique [1,5].

The main goal of a LOV system is sample preparation, which can involve sample dilution, common analyte preconcentration and derivatization or steps such as those based on BI. We discuss below these goals, the coupling of LOV approaches to high-resolution equipment and very different detectors, and salient applications in biochemical analysis.

An approach quite similar to LOV that can sometimes be found in the literature and confused with it is the lab-at-valve (LAV), introduced as an alternative cost-effective μTAS device. In it, instead of replacing a stator plate of a multiposition selection valve by a perfectly machined piece, as in LOV, sample processing and detection unit(s) in LAV are attached or plugged onto port(s) of a commercial conventional multiposition selection valve without taking apart any component of such a valve [23].

2. Sample-preparation steps

The LOV manifold uses a universal hardware configuration to control the units that form part of the overall manifold (syringe pump, additional valves, detector) and

be integrated into the platform, depending on the detection technique. Integration of the multipurpose flow-cell, in which light measurements are carried out through optical fibers, means that the system is very versatile in measurements, although LOV can also be used with non-integrated cells for optical or electroanalytical measurements.

In addition, an adequate selection of auxiliary units is essential in order to achieve the required configuration. Auxiliary units more frequently used are: one [8,10,11] or two [12–15] syringe pumps; an auxiliary six-port