Tutorial: Lab on a Chip in vitro Diagnostics and Home-Care

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Abstract: **Although medical house-call a decade ago was declared a vanishing practice, statistics show an upwelling of home visits by physicians, in the developed countries, during the last ten years. A major reason for this is the radical alteration of the contents of the physicians' black bag that beyond the stethoscope includes also, a Personal Digital Assistant with embedded Cell-phone safekeeping detailed patient-records, sophisticated point-of-care diagnostic equipment and reagents, along with other technical means, that allow for providing care, comparable to that of an emergency room, at home. It is the purpose of this presentation to explore the more important issues concerning the specific employment of the vitro Diagnostics emerging Lab on Chip Technologies in contemporary Home-Care.**

I. Introduction

We define a medical house-call as an encounter between a patient and a physician in a private residence [Meyer, 1997]. Although house-calls by physicians traditionally formed the core of home health care, their number has declined dramatically after World War II. From 40% of all patient–physician encounters in 1930, house-calls made up only to 0.6% of such encounters by 1980, mainly reserved for the elderly.

However, during the last decade the house - call is gradually going through a revival in the USA and elsewhere and the demand for doctors examining patients in the bedroom will soar. Medicare data show a 37% surge to more than 2 million home visits by physicians from 1995 to 2005, partly because Medicare changed the rules for reimbursement in 1998. Comparable trends appear in various countries with high level health-care systems, as for example in Great Britain, where it seems that patients expect their family physician to make house-calls and the doctors agree that house calls are valuable for good patient care [Aylin, 1996], or in Greece, where just one private organization has performed about 100.000 house calls in Attica, an over 4.000.000 inhabitants area, over a 5 years period [Peppas, 2006].

We argue in this paper that the 21st Century already seems to provide for an altered professional activity environment, and a new physician-patient interaction modus. We experience presently the merging of Biomedical Technology, Information Technology Systems, and Medical Decision-Making Procedures in the specific professional and scientific context of the modern managed Health-care. Furthermore, the miniaturization of equipment and their falling prices, combined with a highly Computerized, Wireless, and a Hi-Tec social environment, will result in alternative diagnostic and treatment patterns.

The revival of house calls in Medical Practice is due, beyond the health-insurance adaptation to the altering social conditions, to the highly developed equipment made available to the General Physician of the emerging networked society. The Personal Digital Assistant, with embedded Cell-phone, safekeeping detailed patient-records, and permitting Electronic Order Entry, the sophisticated point-of-care diagnostic equipment and reagents, along with other technical means, allow for patient care, comparable to that of an emergency room, at home.

Adapting Medical Decision-making and Treatment methods to the emerging Hi-Tec homecare environment, and training and equipping the General Practitioner with appropriate equipment and software is an essential condition, in order to ensure, first, sustainable high-quality Health-care of the aging population, second, Rehabilitation and Assistance Services for impaired persons, and finally, the necessary Psychosomatic Support for the aging population.

It is the purpose of the presentation to synopsize our experience in the field, about some important issues, concerning the employment of mobile in vitro Diagnostics techniques, and more specific, the emerging Lab on Chip Technologies in the contemporary Home-Care and House-Call Medical Practice.

II. In vitro Diagnostics at point of Care

Concerning home-based in vitro Diagnostics, Clinical Chemistry offers today a variety of products, covering the whole range of important parameters, like metabolites, enzymes, electrolytes etc. Beyond Diabetes daily strip-based monitoring, which is a routine for the last 2-3 decades, a variety of Home Diagnostic Tests is offered over the counter in the USA, in Europe and elsewhere.

This fact virtually leads to a home-based in vitro diagnostics laboratory, that could be very useful, if combined with medical advice and supervision, before, during, and after a house call, or a call to facilities offering medical care supported housing, for elderly people. A lot of people are already using a test for cholesterol, blood glucose, or evidence of colon or rectal cancer, and in fact, a snippet of a child's hair can now confirm the use of illicit drugs [Lewis, 2001]. Home Diagnostic Tests are often seen as an inexpensive and convenient alternative to a visit to the doctor's office.

However, this trend could result in serious problems for those who rely on the tests instead of on the expertise of a physician, especially if the Diagnostic Test concerns serious or potentially fatal diseases. For years, pregnancy tests and ovulation predictors dominated the home test kit market, but health-care costs, increased interest in preventive health care, and a desire for privacy are opening the way to a variety of products, from cholesterol and triglyceride levels up to tests for the determination of drugs or abuse.

The U.S. Food and Drug Administration (FDA) displays on his Web-site numerous commercially available approved tests for the determination of 60 in vitro Diagnostics parameters for Home Use, presented in Table I. The development of the reagents from the Dry Chemistry Strips to the contemporary emerging Biochips has already changed the landscape of the Point of Care in vitro Diagnostics several times, during the last decades. Various miniaturized structures, composed of chemically sensitized beads that are populated into etched silicon wafers, with integrated fluid-handling and optical detection capabilities, have been used for the identification and quantification of electrolytes, sugars, proteins, antibodies, toxins, and biological cofactors, as well as, for the determination of pH [Lavigne, 1998].

Table 1. List of the FDA approved home- test kits sold over the counter (www.fda.gov/cdrh/ode/otclist.html).

FDA Code and Test Name	
486 Alcohol, Breath	027 Luteinizing Hormone (LH)
392 Allergen Specific IgE / Allergen Panel	090 Methadone
041 Amphetamines	92 Methamphetamine/Amphetamine
103 Barbiturates	100 Methamphetamines
101 Benzodiazepines	256 Methylenedioxymethamphetamine (MDMA)
409 Bilirubin, Urine	003 Microalbumin
084 Cannabinoids (THC)	143 Morphine
171 Chloride	087 Opiates
161 Cholesterol	030 Ovulation Test (LH) Visual Color Comparison
086 Cocaine Metabolites	285 Oxycodone
159 Creatinine	408 pH, Urine
494 Estrone-3 Glucuronide	085 Phencyclidine (PCP)
274 Fecal Occult Blood	245 Protein, Total (Urine)
249 Fern Test, Saliva	364 Semen
026 Follicle Stimulating Hormone (FSH)	246 Tricyclic Antidepressants
184 Fructosamine	021 Triglyceride
122 Glucose	188 Uric Acid
116 Glucose Monitoring Devices	448 Urinary Protein, Qualitative
072 Glucose, Fluid	186 Urine Dipstick Or Tablet Analytes
422 Glucose, Urine	125 Urine hCG By Visual Color Comparison Tests
208 Glycated Hemoglobin, Total	264 Urine Qualitative Dipstick Bilirubin
172 Glycosylated Hemoglobin (Hgb A1c)	265 Urine Qualitative Dipstick Blood
261 hCG, Serum, Qualitative	266 Urine Qualitative Dipstick Glucose
370 hCG, Urine	001 Urine Qualitative Dipstick Ketone
121 HDL Cholesterol	268 Urine Qualitative Dipstick Nitrite
016 Hemoglobin	269 Urine Qualitative Dipstick pH
460 Hemoglobin A1	270 Urine Qualitative Dipstick Protein
124 Ketone, Blood	271 Urine Qualitative Dipstick Urobilinogen
352 Ketone, Urine	410 Urobilinogen, Urine
024 Lactic Acid (Lactate)	042 Vaginal pH

Miniaturized micro fluidic systems that support cellular analysis applications have also been developed. These membrane-based Microsystems have been demonstrated as suitable for measurement of CD4 cell counts, for use in immune function monitoring of HIV-positive patients. Further, an integrated Lab-on-a-Chip (LOC) assay method has been developed, suitable for the concurrent measurement of C-reactive protein CRP concentrations and Leukocyte counts. This dual-function microchip system uses both bead- and membrane-based assay platforms, each of which is packaged within an integrated flow cell system [Goodey, 2001], [Wiskur 2003].

Further hematological tests could also be carried out, if needed, in a homecare setting. Small portable devices that generate a Prothrombin Time (PT) or an International Normalized Ratio (INR) [Hambleton, 2003], from finger stick capillary blood, simplify Home Monitoring of Anticoagulation, by allowing for selected patients, or their immediate care-takers, to monitor and manage their own doses. Early studies established that patients can be self-tested at home, with accurate results, and this Point-of-care testing of elderly patients, or children, resulted in tighter INR control, and a lower incidence of major hemorrhage, especially at the initiation of Anticoagulant Therapy [Marzinotto, 2000], [Mähönen, 2004].

These emerging technologies provide for the physician on house call, a powerful and miniaturized, and thus portable, in vitro Diagnostics Instrumentarium, supporting reliably, conveniently, and promptly, Medical Decision Making, either during an emergency house-call, to identify for example the on-set of an Acute Myocardial Infarction, or to evaluate, for instance, the Anticoagulant level of a post-operative or post-stroke patient, during a follow up visit at home.

III. The structure of the Lab-on-a-Chip

Lab-on-a-chip (LOC) is a term for devices that integrate multiple laboratory functions, on a single chip, of only millimeters to a few square centimeters in size, and that are capable of handling extremely small fluid volumes, down to less than picoliters. Lab-on-a-chip devices are a subset of Micro Electro Mechanical Systems (MEMS), and indicate generally the scaling of, single or multiple, lab-processes, down to chip-format, frequently combining also Microfluidics, that is mechanical flow control devices, like pumps and valves, or sensors, like Flow-meters and Visco-meters.

The first LOC analysis system was a Gas Chromatograph, developed in 1975 by S.C. Terry in Stanford University. However, only at the beginning of the 1990's, the LOC research started to seriously grow, as a few research groups in Europe developed micro-pumps and flow-sensors and, thus, the integrated fluid treatment and analysis systems concepts.

These concepts demonstrated that integration of pre-treatment steps, usually done at lab-scale, could extend the simple sensor functionality towards a complete laboratory analysis, including, for example, additional cleaning and separation steps.

A big boost in research and commercial interest came in the mid 1990's, when these technologies turned out to provide interesting tools for Genomics applications, like Capillary Electrophoresis and DNA Micro-Arrays. Research support also came from the Military, especially from DARPA (Defense Advanced Research Projects Agency), for their interest in portable Biochemical Warfare agent-detection systems. The added value was not only limited to the integration of lab processes for analysis, but included also the characteristic possibilities of individual components, and the application to other, non-analysis, lab processes. Hence the global term "Lab-on-a-Chip" was introduced.

Although the application of LOCs is still novel and modest, a growing interest of Companies and Applied Research groups is observed, in different fields, such as Chemical Analysis, Environmental Monitoring, Medical Diagnostics and Cell Therapy. Besides, further application Research and Developments in LOC systems, is expected to downscale fluid handling structures, towards sub-micrometer and nano-sized channels, DNA-labyrinths, and single-cell detection.

The basis for most LOC fabrication processes is Photolithography. Initially, most processes were in silicon, as these well-developed technologies, were already derived, from Semiconductor Fabrication.

Due to the demands for specific Optical characteristics, Biochemical Compatibility, lower Production Costs and faster Prototyping, new processes have been developed such as, first, Glass, Ceramics and Metal etching, second, deposition and bonding, third, PDMS processing, fourth, Thick-film and Stereo-lithography, as well as, fast replication methods via Electroplating, Injection molding and Embossing.

Furthermore, the LOC field more and more exceeds the borders between Lithography-based Micro-system Technology, Nano-technology and Precision Engineering.

Despite the remarkable advances in the development of miniaturized Sensing and Analytical components, for use in a variety of Biomedical and Clinical applications, the ability to assemble and interface individual components, in order to achieve a high level of integration in complete working systems, continues to pose daunting challenges, for the scientific community as a whole.

IV. Conclusions

Lessons learned from the Microelectronics and Computer Software Industries, provide inspiration for what may be gained from the merging of Microelectronics and in vitro Diagnostics areas. Indeed, there are some interesting parallels between the current state of Medical Devices, in particular, in vitro Diagnostics, and the evolution of Software and Microelectronics Industries. While medical tests have traditionally been completed in central laboratories with specialized equipment and trained technicians, there is currently a trend to complete more and more tests using portable Instrumentation [Price, 2001].

The point of care medical device area represents now the fastest growing sector of in vitro Diagnostics. At some level, this evolution of Medical Diagnostic testing follows the same pathway the Computer Industry took where initial Work-stations were dedicated to single tasks. Over time, the Computer became programmable and portable to the point where "personal computers" have evolved with high degree of task flexibility. Clearly, the availability of portable medical devices that could be tailored for "personal medical exams" using noninvasive Diagnostic Fluids, such as saliva, would have a profound influence on the way Medical testing is practiced.

Table I2 correlation of LOC techniques with established macroscopic "gold standard methods". Source: McDevitt Research Laboratories (http://www.tastechip.com/labchip/research_comparisons.html)

Analyte	Range or LOD	Gold Standard	Level of Agreement	Matrix	References
pH	2< pH < 12	Glass Electrode	+/- 0.02 pH units, R 2 = 0.99 correl.	Serum, buffer	Goodey et al., JACS, 2001;123:2559-2570.
Ca(II)	10^{-7}-10^{-3} M	ISE	R2 = 0.999 for dose dep. curve	Serum, buffer	Goodey et al., JACS, 2001;123:2559-2570.
CRP	10-100000 ng/mL	ELISA	0.987	Human serum	Christodoulides et al., Anal. Chem., 2002; 74:3030-3036.
CRP	10-10000 pg/mL	ELISA	N/A	Human saliva	Christodoulides et al., LOC, 2004; 5:261-269.
DNA-18 mer	10 -13 M	PCR	N/A	Buffer	Ali et al., Anal. Chem., 2003, 75:4732-4739.
CD4, CD3, CD8, CD45 cells	50-15,000 cells/μL	Flow Cytometry	R 2 = 0.9 8	Human serum	Rodriguez et al., PLOS Med. 2005, 2:663-672. Cohen J., Science 2004, 304:1936-1936
Bacillus Spores	500	Culture	N/A	Bioaerosol samples	Floriano et al., Biosens. and Bioelec., 2005; 20:2079-2088

The performance metrics of these miniaturized sensor systems have been shown to correlate nicely with established macroscopic "gold standard methods", making them suitable for use as subcomponents of highly integrated detection systems, for the analysis of complex fluid samples. These efforts remain unique worldwide, in terms of functional lab-on-a-chip methods, having a demonstrated capacity to meet or to exceed the analytical characteristics, such as, sensitivity, selectivity, precision, and limit of detection, of mature "macroscopic" Instrumentation, for a large variety of analyte systems (Table II).

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