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Flow Based Clinical Analysis Systems: Potential Applications for Telehealth

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Abstract

Telehealth and telemedicine are the approach to provide health care coverage to people in rural areas or patients who cannot conveniently travel to meet with doctors at a hospital. The telehealth system requires a multidisciplinary collaboration involving various sectors such as telecommunications, information technology, medical experts, hospitals, equipment suppliers and social workers. The advantages of automatic flow based systems in reducing the volume of sample, the analysis cost, the analysis time and the need of having highly trained personnel, make them suitable for use where the healthcare facility budget is inadequate. Therefore, flow based techniques have potential for applications in clinical analysis as part of the telehealth system in the developing countries.

Keywords telehealth, flow based techniques, clinical analysis**,** flow injection analysis, sequential injection analysis

1. Introduction

Telehealth

Definition of telehealth and telemedicine is a delivery of health-related services and medical information via telecommunication technologies for the purpose of consulting, examinations and remote medical processes. [1] This idea was introduced several years ago as a new approach to provide health care coverage for people who cannot visit doctors in person. It began to take place in the USA in the mid-90's. [2] Some activities that can be adapted for use in telehealth/telemedicine include health advisory by phone in emergency cases, live video conferencing, and transmission of medical images.

The possibility of having health service without actually seeing doctors will especially benefit people who are facing a natural disaster, soldiers that are patrolling in the remote areas and people who live far away from any hospital. Even people who live in urban areas but whose busy life style results in an unmatched schedule with their doctors will benefit from a telehealth system.

Although, the idea of telehealth has been around for a long time, the development of an effective telehealth system has not yet been reported. This might be due to the need of collaboration between various sectors such as doctors, social services, telecommunication technologies experts, health insurance companies and government.

Why do we need a telehealth system?

In highly advanced countries such as the USA and some European countries, although there is no limitation on technologies, people may still want to have a telehealth system for better choices of doctors that may not live in close by areas. It has also been proven that in many psychology treatment cases, telephone consulting is better than confrontation between patient and doctor. [3-4] People who live far from a hospital may also prefer not to travel such a great distance to the nearest city for a health check up.

The need of telehealth systems in Thailand and other developing countries may arise from different concerns. The lack of technologies, inadequate number of hospital facilities and medical personnel, and the lack of safe and effective transportation from rural area to the urban hospital are the main limitations in the health service system. Some statistics on the number of facilities and doctors in Thailand are shown in Table 1. Comparison of the number of doctors per 1000 people in different countries around the globe, reported by WHO, is also shown in Table 2. It is alarming that in most developing countries including Thailand, this number is less than 0.5 doctor per 1000 people. [5,6]

Thailand actually has become known for world class medical services. A recent report showed that each year there are as many as 1.2 million tourists from Japan, Europe and the Middle East have come to Thailand and scheduled to have their health checked while on vacation. [7] These services are conducted by highly skilled doctors and with advanced machineries located in hospitals in big cities. These services are available for people who have adequate financial support and accessibility. However, for people in the rural areas and low income group, the problem of ineffective healthcare coverage exists. An effective telehealth system should help to shrink down this gap and make healthcare available to more people.

Telehealth in Thailand

In Thailand some attempts have been made to support the development of telehealth. Some software companies have promoted specialized software for long distance data transfer.[8] Some scientific research works that gear toward development of instrumentation, robots and other devices for the purpose of medical care have been proposed. [9,10] In the southern area where there are situations that make

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traveling to the hospital unsafe, telephone consulting services have been set up for medical and health treatment.[11] The main project involves the set up of a satellite communication link for the remote villages near the Myanmar border to serve the telehealth program.[12] However, there has not been any concrete national telehealth project going on. They are in the trial period and it is still not clear how much it costs or who should pay for it. In the developing countries like Thailand, apart from collaboration of different sectors and people as previously mentioned, the effective telehealth system should be composed of simple and cost effective screening/diagnosis systems. If these systems are set up and operated at health centers near where people live, they will help cut down the analysis and transportation costs and make traveling to crowded urban hospitals unnecessary. Results can be transferred via telecommunication technologies and the decisions on further treatment can be made by doctors in town.

Table 1 Statistics on medical facilities in Thailand (Reported by Thailand Ministry of Public Health in 2004) [5]

Region	No. of hospital with overnight beds	No. of bed	Bed:Patients	No. of doctors	Doctor:Population
Bangkok	111	25,596	1:4	6,526	1:879
Central	360	38,211	1:8	4,752	1:3,134
Northeast	345	28,736	1:10	2,875	1:7,466
North	259	23,807	1:9	2,639	1:4,534
South	203	16,895	1:8	2,126	1:3,982
TOTAL	**1,278**	**133,245**	**1:7**	**18,918**	**1:3,305**

Table 2 Number of doctors per 1000 people in different selected countries (Reported by WHO) [6]

Countries	No. of doctors	No. of doctors : 1000 people
Europe		
Belgium	46,268	4.49
Denmark	15,653	2.93
France	203,487	3.37
Germany	277,885	3.37
Spain	135,300	3.30
Sweden	29,122	3.28
UK	133,641	2.30
North America		
Canada	66,583	2.14
USA	730,801	2.56
Asia/ Oceania-Asia Pacific		
Australia	47,875	2.47
Cambodia	2,047	0.16
China	1,364,000	1.06
Indonesia	29,499	0.13
Japan	251,889	1.98
Malaysia	16,146	0.7
Singapore	5,747	1.4
South Korea	75,045	1.57
Thailand	22,435	0.37
Vietnam	42,327	0.53
Africa		
Uganda	2,209	0.08
Zambia	1,264	0.12

2. Possibilities of flow based techniques for telehealth in Thailand

Flow based techniques have many features that are suitable for bioassay in clinical samples. Being closed systems helps to reduce the chance of sample contamination as well as decrease the risk of the operator having direct contact with body fluid samples. Reactions are at a small scale which require only a minute amount of sample and produce little waste. Capability of detection for chemical product at non-equilibrium state helps to shorten the analysis time. The whole analysis process can be made automatic which can reduce personal error and has less requirement for well trained medical personnel to operate the test. Parts of flow based systems can be built and adapted separately as needed, resulting in lower cost systems as compared to most instrumental based chemical analysis techniques. Data are normally collected by a computer which enables them to be easily transferred online. All these benefits make flow based systems have high potential to be put to use in a telehealth system.

Many groups around the world have reported flow based analysis systems for various biochemical substances in clinical samples. In Thailand, the Flow Based Analysis (FBA) Group at Chiang Mai University has pioneered the flow based screening/diagnosis system for some diseases based on different biomarkers. These systems are developed based on the interest of medical doctors in Thailand which can also be adapted for the international use. The following are examples of flow based disease screening systems that have been developed by the FBA Group with the aim of improving the performance of the existing batch technologies in terms of automation, analysis time, sample volume and cost. The comparison of features and performances of the flow based systems and batch systems are summarized in Table 3. All these systems were evaluated with real blood samples which indicates their potential for the future use in a telehealth system.

Table 3 Comparison of features and performances of some flow based systems and batch systems for disease screening/diagnosis

Flow based systems	Conventional techniques	Disease (Analyte/Sample)	Comparison of performances Flow based system vs Batch	Ref. No.
FI-reduced volume anion exchange chromatography	Batch micro-column	β-thalassemia (HbE/packed red cells)	35 min /run vs 4 h 80 μL of 50 fold dilution packed red cells (1.6 μL of undiluted sample) vs 2 mL undiluted sample	13
FI-immunoaffinity micro-chromatographic column	Well plate ELISA	Ovarian cancer (chondroitin-6-sulphate/serum)	30 min/run vs 5-8 h 200 μL of 2 fold dilution serum vs 300-400 μL Reusability of column for 90 runs	14
FI-bead injection	Well plate ELISA	Osteoporosis (Bone ALP/serum)	30 min/run vs 4 h 200 μL vs 300-400 μL Better differentiation of bone diseases from healthy cases as compared to commercial ELISA kit	18
SI-bead based immunoassay	Well plate ELISA	Cancer, Liver and Bone diseases (hyaluronan/serum)	30 min/run vs 5-8 h 30 μL vs 300-400 μL	19

2.1 Flow injection (FI) based system

Some simple first generation flow injection systems have been coupled with various standard analytical techniques to scale down the amount of time and reagents while improving precision, the ease of operation and interpretation of results.

FI- reduced volume anion exchange chromatographic system for hemoglobin typing

One of the screening techniques for HbE thalassemia commonly used in Thai hospitals is micro-column anion exchange chromatography. A plastic syringe with the plunger removed is used as a column for packing DEAE sephadex resin. Packed red cells are passed through the column and each type of hemoglobin, with different degree of net negative charge, can be eluted by pH gradient buffers. Fractions of eluate are collected to measure for absorbances with a spectrophotometer. When plotting absorbances with elution time or volume, a chromatogram of peak separation can be obtained. Order of hemoglobin eluted are in the order of HbA2, followed by HbA and HbF. HbE will co-elute with HbA2, causing an abnormally large HbA2 peak as compared to a normal blood sample. By coupling a smaller plastic column of 3 mm i.d. x 2 cm length with the flow injection-spectrophotometric detection system, this hemoglobin typing technique can be done more automatically with much smaller blood sample volume and much less analysis time. [13]

FI-immunoaffinity micro-chromatographic column system for chondroitin sulphate proteoglycans (CSPGs)

The flow injection system was also successfully coupled to a mini-immunoaffinity column made of a 3 mm i.d x 5 cm length persplex glass packed with WF6 coupled beads. WF6 is specific antibody against chondroitin 6 sulphate. This separation technique can be used as an alternative method for determination of CSPGs by ELISA. The system is based on selective retention of CSPGs before elution with different buffers. Quantitative analysis was done indirectly from the assay of protein contents of proteoglycans by Bradford reagent. Relative amount of CSPGs in total amount of proteoglycans was compared for serum samples of patients with various cancers. The results show the same trends as the previous preliminary study using ELISA which is that CSPGs seem to more specifically indicate ovarian cancers. This flow based immunoaffinity chromatographic system involves easier operational steps as compared to standard (well) ELISA and it is more economical because of the reusability of the column. [14]

FI-bead injection (FI-BI) system for bone alkaline phosphatase (BALP)

Bead injection (BI) technique utilizes beads as solid surfaces to selectively retain analyte of interest and accommodate chemical reaction. The first generation flow injection system is successfully coupled to the bead injection technique for various uses.[15] The early reported FI-BI systems used Fe as a model analyte.[16,17] The flow injection-bead injection system was developed for the assay of bone specific alkaline phosphatase as an alternative to other more complicated techniques such as HPLC and ELISA. The system utilized wheat germ coated beads to specifically capture BALP. The subsequent introduction of substrate PNPP into the bead retention cell yielded yellow product PNP that flowed into and was detected by a spectrophotometer. The used beads were discarded to eliminate the memory effect. Interpretation of the results is based on peak height or peak area which is more precise and easier as compared to observation of the degree of precipitation which is normally observed with bare eyes in the conventional wheat germ agglutination technique. The system is also superior to a commercial ELISA kit in that it can better differentiate bone osteoporosis patients from healthy people which is probably due to the higher surface area of beads as compared to a micro-well.[18]

2.2 Sequential injection (SI) based system

Sequential injection system with advanced small volume manipulation capability and precise timing is very suitable for automation of an analytical technique with multi-steps operation such as immunoassay. An example is described here.

SI-bead based immunoassay for hyaluronic acid (HA)

An automatic immunoassay system was developed to determine the amount of HA in serum of patients with cancer and liver diseases. The system was designed to 1) reduce back pressure from beads that act as solid surfaces for immobilization of the target substance by using opened end cell, 2) reduce dispersion and dilution of the reagent during incubation by separation the reagents zone with air segment, and 3) maximize signal while minimizing incubation time by employing a sensitive detector. Competitive ELISA was performed with HA coupled bead, biotinylated HABPs and anti-biotin-HRP. Product from substrate TMB was electrochemically detected with an amperometer. Sample volume and analysis time per sample were dramatically reduced as compared to the standard well ELISA. The automatic immunoassay system clearly demonstrates the benefit of SI system on reducing the need of having highly experienced personnel to operate a complicated multi-steps analytical technique. [19]

3. Conclusion remarks

Having presented some examples, there are many steps yet to be done on further development of the flow based clinical analysis systems to enable them to be put to use for telehealth system. These steps include miniaturization and standardization of equipment parts, stabilization of reagents for long storage duration, and collaboration of doctors for study and evaluation of the system in real medical situation. However, we hope that our on going attempts on the development of simple and cost effective flow based clinical analysis systems will help in completing the picture of an effective telehealth system in Thailand and elsewhere in the future.

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