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WILL NANO-BUTLERS WORK FOR MICRO-PAYMENTS?
INNOVATION IN BUSINESS SERVICES MODEL MAY REDUCE COST OF DELIVERING GLOBAL HEALTHCARE SERVICES

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Will Nano-Butlers Work for Micro-Payments?

Innovation in Business Services Model may Reduce Cost of Delivering Global Healthcare Services

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ABSTRACT

This paper represents an emerging view of personalized care and patient-centric systems approach. It integrates biomedical informatics and business services. A potentially innovative model may evolve from this convergence and may serve as a global template to reduce cost of service. The future of global healthcare may increasingly rely on "sense and *then*, respond" systems but excluding the instances of exception management, necessary for accidents and emergencies. Solutions suggested in this paper are neither complete nor a panacea but are elements that deserve inclusion in the delivery of healthcare that may combine a portfolio of approaches to suit the needs of the community. As a potential future direction to improve analytics in healthcare, the concept of molecular semantics is proposed.

KEYWORDS

Decision Systems, Systems Engineering, Remote Monitoring, Nano-sensors, Nano-radio, Glucose Sensors, Field Effect Transistors, ICT, Semantics, Informatics, Business Services, Business Process Re-engineering, Analytics, Electronic Medical Records, EMRS, Interoperability, Mash-Up, Service Oriented Architecture, Agents, AI, Biomarkers, Cardiovascular Diseases, Peptides, Epitopes, Protein Structure, Early Detection, Cancer, Preventative Medicine, Medical Google, Social Networking, Linguistics, RFID, Supply Chain, RNAi, Nash Equilibrium, Information Asymmetry, GARCH, Reality Mining

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1.0 INTRODUCTION

Proclaiming health as a human right [1] is a platitude when healthcare still remains inaccessible to millions, even in affluent nations, or billions elsewhere, yet, few dispute the fact that more than 30,000 children, less than 5 years old, die every day, many suffering from preventable diseases. According to the Institute of Medicine [2] at the National Academy of Sciences, healthcare is substantially underperforming on several dimensions: effectiveness, appropriateness, safety, cost, efficiency, prevention, value. Increasing complexity in healthcare and regulatory steps are likely to accentuate current problems, unless reform efforts go beyond financing, to foster sustainable changes in the ethos, culture, practice and delivery of healthcare. If the effectiveness of healthcare is to keep pace with the opportunity of prognostic, diagnostic and treatment innovation, then, design based on systems thinking [3] and information technology must be structured to assure access and application of evidence at the right time, continuous learning and research insights, as a natural by-product of healthcare process. We need to re-engineer the development of a research-driven learning healthcare organization [4] integrating a systems engineering approach, to keep the individual in focus, while continuously improving, concepts, quality, safety, knowledge and value.

In particular, commitment to research may be emphasized by lessons from the past [5] to catalyse a future where creative cross-pollination of diverse concepts from unconventional [6] strategic thinkers are rewarded. It is equally essential to build multi-disciplinary collaborative global research teams, imbued with the true spirit of discovery [7] in basic and applied domains. These teams must be enabled to drive an entrepreneurial [8] enterprise approach to create proof of concepts. Translation of unconventional concepts into reality may be guided by innovators with horizontal global vision rather than gate-keepers who prefer to stay "in-the-box" and avoid risks that leadership demands. The caveat in this process is the impatience of "practical" people for unconventional concepts but the "nail on the coffin" is often driven by political polemicists who also get impatient with concepts, no matter how justified or pragmatic, because it gets in *their* way to sell *their* plans [9]. The latter may block funding or policy that may better enable the convergence of unconventional vision into reality, only limited by our imagination [10].

Yet, unconventional thinkers and business leaders [11] are largely credited for globalization [12]. Striking transformations have occurred through decision systems and process engineering, not only in established markets but also in creating new markets [13] despite omnipresent global uncertainty [14]. These changes have reshaped political economy [15], governments [16], the service industry and manufacturing sector,

including business process [17], software, hardware, banking, retail, airline safety, automobile industry, national security and the business of the military industrial complex [18].

Lessons from the failures and the fruits of success, enjoyed by the business world, may not be irrelevant for exploration and/or adaptation by healthcare organizations, despite the irreconcilable differences that exist in the dynamics of mechanical versus biological and social systems. The current challenges in healthcare compel a fresh view of the organization, structure and function of the delivery and monitoring processes in healthcare, not only for the industrial world that may afford the increasing cost (macro-payments) but for global healthcare services, in a manner accessible to, as well as feasible for, the billions (micro-payments). Financial sustainability of healthcare is a key issue in the design of innovative health services. The latter evokes the paradigm of services that may be deliverable for "micro-payments" rather than the current spending that claims a double digit share of the gross domestic product of rich nations.

One of many lessons from the business world is that to survive in business, businesses must exploit the power of "now" [19], perhaps best illustrated by the surge to use real-time data, almost for everything, through use of radio frequency identification (RFID) tools [20]. To remain profitable, in a RFID driven world, industry must "adapt or die" [21]. Real-time consumer-driven supply chain [22] dynamics also determine the speed at which the industry must change to remain competitive [23]. Hence, business models are continuously focused on data, new technologies [24], cost reduction and the quest for new growth without sacrificing quality of product and/or service. Systems that help to maintain "everyday low cost" at Wal-Mart and efficiencies at Dell that still allow "making boxes" a profitable pursuit, deserve strategic exploration and integration of germane ideas to improve sustainable healthcare delivery. Health care systems were not designed with scientific principles in mind [25] and the ethos of "innovate or die" [26] is not salient to healthcare providers.

While software systems, like enterprise resource planning (ERP), generate benefits for business and industry, through some degree of integration of data and automation of planning, there are few healthcare electronic medical records (EMR) systems (EMRS) which have autonomous decision making capability. Healthcare, even preventative or wellness, if available, is still dependent on expensive human resources for data acquisition, monitoring, analysis, reporting and follow-up. Re-engineering this cost structure and hospital-centric service model is necessary. Configuring a reliable business service model for health

services may meet with entrenched resistance to change but may catalyse extended healthcare for billions and may even improve healthcare quality of service.

2.1 PROBLEM SPACE: Background

The multitude of problems and issues in management of healthcare are beyond the scope of any paper or book. Here, I shall briefly touch upon only one issue: acquisition of medical data to improve healthcare. However, the fundamental nature of this issue shall force us to address a series of integrated problems, some of which may be text book cases in basic physiology [27] and biochemistry [28]. Therefore, it will be well nigh impossible to do sufficient and equal justice to all the inter-dependent processes and areas.

The naïve thrust of this issue is to *reduce healthcare cost but with concomitant expansion of improved healthcare services for billions*. Healthcare cost reduction is a hackneyed topic of discussion but the thrust of this paper is to suggest solutions where emerging ideas and innovation may help **expand** and **improve** healthcare service at a cost that may be soon sustainable even by the developing countries of the world. Hence, the solution space shall deal with the issue in focus: innovation in acquisition and analysis of medical data. It is obvious that one can remain oblivious of the fact that innovation in data collection calls for innovation in tools for data collection *as well as* analysis of data, to extract information and knowledge, that can add value to healthcare services. Due to the latter, the problem (and solution) space of this paper is bound to evolve in multiple directions, each indicating a further line of innovation.

One general problem in global healthcare is due to the mimicry of the Western model focused on acute-care hospital-centric view of what health "care" is supposed to deliver [29]. The aphorism that "better health is inherently less expensive than worse health" is equally applicable in the West and the East [30] yet seldom practised. In fact, the profitability of the acute-care hospital-centric Western model appears to be the preferred line of health service delivery (Figure 1). It reasons that the word "care" must be omitted from healthcare [31] because the hospital-centric revenue model is at odds with the "care" that health services are expected to deliver for an individual in a patient-centric view of personalized healthcare.

I hasten to add, that in general, the acute-care hospital-centric model still offers appreciable services when it concerns accidents and emergencies (A&E). It is vital to respond to the challenges of uncertainty

in healthcare stemming from A&E. But, the criticism surfaces when the A&E *modus operandi* is extended to other areas of non-A&E healthcare. The systemic efficiencies necessary to respond to A&E situations must continue to be supported. Suggestions in this paper or elsewhere about patient-centric personalized healthcare must not be viewed as a replacement, but as a realignment of the existing system that is necessary for economic transformation to keep healthcare sustainable. A&E and non-A&E approaches are not mutually exclusive and there is a need for elements of both systems to co-exist for mutual enrichment.
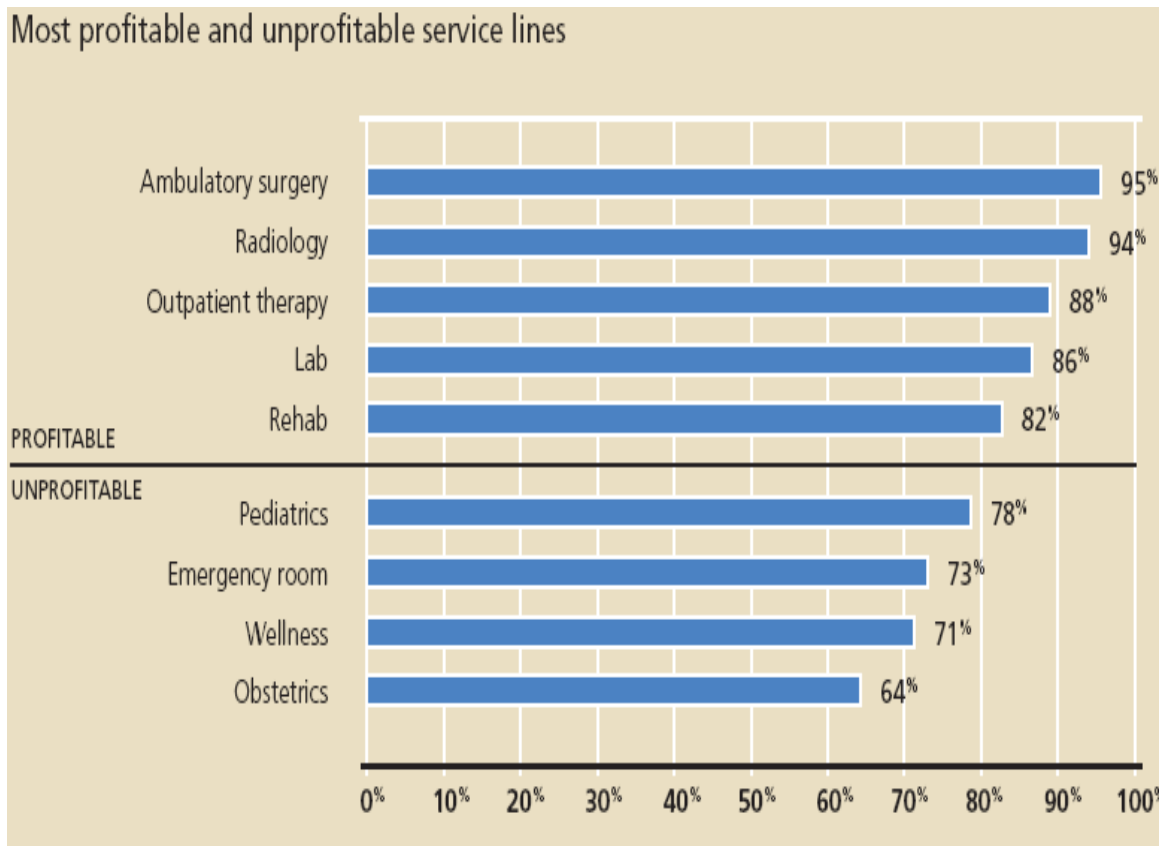
Figure 1: Percentage of hospitals reporting service lines as profitable or unprofitable [32]

Another problem that has evolved over the past few decades concerns an inability or incongruent response of the healthcare community to adopt advances in information technology in order to develop an integrated systems approach to services. The human-driven decision model practised by the medical community is adept in maintaining and/or sequestering data, information and knowledge, about cases and patients in paper-driven silos. It prevents the improvement and development of a *learning healthcare*

system based on insight and experience. Critics of information technology within the medical community will defend this *status quo* by pointing to issues of confidentiality of patient-doctor relationship, privacy of patient data, lack of standards for medical systems interoperability and quagmire of ethical guidelines for medical knowledge diffusion. The critics are justified in their claims. But they also remain refractive to extract and use the principles which have increased profitability in the services industry and catapulted businesses such as GE, P&G, Nokia and Wal-Mart to luminous heights of profitability. In addition, the chasm between medical education and engineering education creates a lack of awareness of the advanced tools and information technologies that exist and potential for innovation in intelligent decisions sciences that are possible, in order to provide data protection the critics demand and the patient-doctor deserves.

The business services approach to healthcare, admittedly, raises alarms if individuals or patients are to be viewed as cost-centers with the administration trying to function as a profit-center. This view assumes a literal translation of business services to health service, which is not what the proposal calls for. As an example of successful transformation of business service efficiencies, one may site education, a domain with distinctly different dynamics from business. The Open University in UK [33] and University of Phoenix in USA [34] has pioneered profitable business service type approaches, integrated with extensive use of information communication technologies (ICT), to deliver education of a reasonable standard for vast number of individuals, who were unable to access traditional higher education, for a variety of reasons.

Remote access to education had humble origins in "correspondence" courses but were transformed by the growth of the ICT sector and accelerated by the diffusion of the internet. This is a form of "personalized" education that is enabling individuals to move ahead in careers of their choice and contribute to economic growth. This educational-economic transformation may offer a paradigm for the healthcare industry. Of course, the academic level of OU and other similar outfits may not train an individual to be the next "big bang" theorist or lead research to garner a Nobel Prize. But, for those elite purposes the academic system is well prepared with its select institutions. The elite academic institutions may be analogous to the "elite" equivalent in healthcare, which may be, the acute-care and A&E. However, the "elite" model in healthcare system may exclude or restrict, based on grounds of profitability or cost, the accessibility of non-A&E type preventative or early diagnostic modes of healthcare (analogous to OU and similar outfits) for the masses.

2.2 PROBLEM SPACE: Focus

To reiterate, the focus of this paper relates to innovation in acquisition of medical data and analysis to improve healthcare by expanding coverage for the masses yet deliver greater value of healthcare services. Service orientation, systems architecture and use of software as infrastructure will depend on data sources and analytics needed from healthcare monitoring, sensing and responding to situations. The business services concept of data, information transparency between systems, as well as data exchange and/or interoperability issues, may be more complex in this context due to regulatory and security constraints. It may be quite useful if the business service type approach can also introduce some degree of automated decision making, even based on rules and workflow, for non-exceptional healthcare case management.

The next level of decision making based on acquired data with reference to standards (eg: pulse rate, blood pressure, normal range of blood glucose) may require some basic algorithms based on simple artificial intelligence (AI) principles that can induce a *learning* healthcare approach when evaluating data about a specific individual or patient. For example, if the individual is otherwise "normal" even under a higher systolic or diastolic blood pressure (BP) reading, then, the analytical algorithm can **learn** that the deviation from the medical standard reference model (120/80 mm Hg) is not readily a cause for alarm in this **specific** case since the individual is physiologically "normal" even under an elevated (or lower) than standard BP reference data. Hence, billions of learning instances will be necessary for a global model.

This very important decision, to conclude an individual or patient is "normal" despite a slightly aberrant standard data, must be made, under most current circumstances, by a trained medical professional. That translates to cost. Aggregated over numbers of in-patient and out-patient related data, these cumulative costs soon begin to destabilize the financial infrastructure. Equally and perhaps more important is the time spent by the trained medical professional to review the data and arrive at the decision. Time spent for non-exception management siphons away valuable time from exception management and patients who indeed need attention. Therefore, it is not difficult to comprehend that small changes in the healthcare process pose minimal risk (see reference 201) yet may improve quality of service and reduce cost.

Documenting the acquired data, for example the blood pressure reading mentioned above, is the next level that deserves exploration due to the cascade of events that this data may trigger. With a few exceptions, even in the most advanced industrialized nations, paper-based documentation is the norm [35]. Unless paper-based documentation is the exception, rather than the norm, healthcare systems may

continue to be crippled from displaying their true functional potential. Given human errors of data input, the transformation of pre-existing and accumulating data as well as notes and decisions, poses a major challenge. Without the available information on existing patients and cases, the ability of decision systems to arrive at non-exception management related decisions, on these existing patients and cases, may be seriously flawed and hence may be rendered unacceptable, to help deal with existing patient management.

Thus far we have referred to patients but what about individuals who are not patients, yet? Wellness or preventative medicine and early risk identification is critical to reduce the probability that an individual shall *become* a patient or need acute-care or emergency attention. The acute-care hospital-centric model is largely viewed as a failure to address this broader spectrum of personalized healthcare even though it may be well equipped to deal with A&E in nations big (for example, USA) and small (for example, Ireland).

3.1 SOLUTION SPACE: Existing Electronic Medical Records (EMR) Systems (EMRS)

Before embarking on the discussion of emerging trends and potential for innovation to address the problem focus outlined above (section 2.2), it may be pointed out that medical data captured in electronic format (electronic medical records system) exist in practice in some form or the other [36]. It may offer architectural clues or serve as a basic template (starting point) for nations beginning to grapple with the problem of creating EMR systems. However, expecting the current EMRS to serve as a "best practice" or benchmark may not be prudent. There is ample room for improvement of EMR which is essentially a generic data aggregation platform. The evolution of future versions or variations of generic EMR platform may not bear any resemblance to current systems that are generally command-driven, archival data stores, with little, if any, analytical capabilities, such as clinical decision support (see reference 63).

Since 1907, the Mayo Clinic (USA) claims to have kept unified medical records and exists in electronic format since 1993 [37] in a single database with 5 million records including patient files, x-rays, laboratory results and electrocardiogram (ECG) records. Since 2004, it includes data mining and pattern-recognition tools to discover relationships among specific proteins, genetic make-up and treatment responses (see section 3.2 and section 5.1). Information can be shared between the different geographic locations of the Mayo Clinic and physicians can conduct a virtual consultation on any patient because the electronic medical records are accessible from all three sites. This may represent the primordial role of data in personalized healthcare.

The **VistA** system in use by the Veterans Administration (USA) hospitals cover 150 medical centers and 1400 sites across the country [38]. 85% of 57 million out-patient visits and almost all in-patient notes are available online through VistA. In addition, 94% of out-patient prescriptions (equivalent to 200 million 30-day prescriptions) and almost all of in-patient prescriptions are entered in VistaA (EMR) directly by the prescribing clinician. A study in 2004 compared VA versus non-VA patients in 12 communities and found that VA patients scored higher on quality of care, chronic disease care and preventative healthcare.

The scope of benefits that can be derived from EMRS, as one component in the solution space, is only limited by our imagination but at present several thorny challenges remain. Unlike the Mayo Clinic records and their visibility across the three different geographic locations, the infrastructure of VA or Partners HealthCare [39] is more extensive. Patients can move between locations and their treatment can change over time. This introduces major systemic issues, as follows. Partial solutions are suggested, if applicable.

Of immediate concern is *unique* identification of data (see reference 39). How do we uniquely identify the patient, and patient records, that may be assigned different id numbers, in different locations, as well as different records of the same patient, that may be numbered according to the system in operation at a given location? The critical value of unique identification that unambiguously links the individual to his/her records, irrespective of the physical location of the hospital, does not need emphasis. The sheer number of individual records (laboratory tests, x-ray, CT scan, ultrasound, physician's notes, medication, response) multiply over time and may present a numbering scheme dilemma that requires a solution but without re-inventing the wheel or introducing yet another 'new' system.

Creating unique identification is not a competency of the healthcare industry. Hence, the health services may opt for an existing identification scheme that [1] can offer vast number of unique addresses [40] that can be organized in relationships or subclasses, [2] is truly portable, [3] internet-ready, [4] already in operation and [5] globally pre-agreed in a manner that can aid adoption by the healthcare industry.

A proposal that can address this issue of unique identification of octillions of items using the globally agreed IPv6 format is presented in a separate paper (see reference 40). Support for the potential use of IPv6-based identification may soon gain momentum [41] and the need for this approach in healthcare was highlighted in problems discussed elsewhere (see testimony that follows from reference 38).

Personalized unique identification in healthcare may offer a robust id solution, but its **value** for the patient, who may move between various healthcare units (for example: physiotherapy, stroke care, out-patient clinic) or hospitals, local and/or global, shall remain constrained without **interoperability** between systems of different healthcare providers, public and private, engaged with the patient. There is little value in deploying unique identification if an individual permanently resides in one location and receives healthcare from one medical professional, in one clinic or hospital, which is entirely self-contained in all its services and without any external interaction, can guarantee total quality healthcare, for the entire life cycle of the individual.

Interoperability segues to the issue of standards. The IPv6 standard governing the unique identification scheme mentioned above will make it possible to identify the unique number ("address") in any healthcare system anywhere in the world, because the standard has made provisions for assigning that number or address to that record, or patient, in a manner that shall remain unique over the life of an individual. It is logical to anticipate that a "number re-claiming scheme" that may be deployed to claim back and re-use dormant numbers (for example: a patient number may be claimed back and re-used every 150 years if it is assumed that a human being is unlikely to live for more than 150 years).

Standards shall prominently feature in EMRS solutions space when and if the healthcare system begins to experiment with rule-based or intelligent decision sciences to help evolve clinical decision support (see reference 63). Standards or "rules of operation" are immediately necessary for the granular and diverse quality of record-keeping that commences with **patient history** and physical examination. It is most often carried out by the local primary care physician or general practitioner (GP), in communities where Primary Care may be in operation and where EMRS may be available for record keeping. Of course, the same could commence for individuals who report to the A&E.

Standard "history" data in an EMRS that is also *interoperable* is a complex problem that must dig deep and wide for multi-disciplinary convergence to generate a working solution. It is complicated by the multitude of descriptive syntax that may be used by the patient and the written form in which the medical professional scripts the information. The natural language (mother tongue), cognitive abilities, culture, education, values and experience of both the patient and the physician or medical professional shall colour the content and context of this "history" document. It is apparent that existing ICT and computer systems may find it difficult, if not impossible, to extract with reasonable precision the "meaning" of the "history" written in words, and transform them to a standard (?) format that is medically relevant, for EMRS

interoperability. Even more crucial is the to "understand" the importance of the phenotypic information relative to the context of the patient and her genotype, which, to be of value, must refer to a reference model of the community, geography and environment where the patient lives or lived.

To the serendipitous reader, it may become obvious that the transformation from a paper-based localized healthcare system, with limited number of professionals from a homogeneous background to EMRS, may aid in dispensing global healthcare services by a myriad of diverse professionals, but, requires substantial research and innovation to develop standards [42]. The informed reader may have already concluded that the development of these standards requires deep integration with cognition and semantic theory. I will return to the issue of semantics when I discuss the proposal of molecular semantics (section 4.0).

Before "boiling the biomedical ocean" in cognition and semantics, it may be useful if the healthcare system may globally agree to partially address the gulf between syntax and semantics in a "quick and dirty" approach, as adopted by business processes in global organizations [43] or the efforts spawned by the semantic web movement [44] to create biomedical ontologies [45]. These solutions, albeit temporary, if deployed and implemented in EMR type systems, are likely to offer some benefits, if the questions and content are less descriptive and are already expressed in a manner that is medically relevant, irrespective of the "background and culture" of the involved medical professional.

Development of "quick and dirty" rules and partial standards may help with (1) exchange of clinical data, (2) defining categories or circumstances when a physician in one healthcare organization can change or amend the problem list entry of a physician in another organization, (3) conditions under which clinical staff from one organization may discontinue medication prescribed by another clinician in the same organization or from another organization, (4) types of data and information that must be secured by privacy policies and their enforcement, so that confidential data and patient information cannot be shared with, or released to, any external non-medical organization without due authorization from the patient.

Finally, EMR systems, even with its current healthcare service handicaps and restrictions, can still provide business value that may translate to cost savings. Because organization-specific EMR systems like VistA operated by the VA, covers a majority of its operations, the supply-demand profile of the operation can be deduced with a fair degree of precision. Using economies of scale, products and services may be bought at a bargain. VistA offers an indication of volume of patients that are likely to be served and that volume

information may be analysed to forecast [**46**] inventory of supplies necessary to meet the projected demand. For perishable products (drugs, IV fluids, food) the design and management of supply chain [**47**] of vendors and partners can partner with the business operations unit to ensure adequate inventory of perishables to meet 'peace' time and 'war' time [**48**] type volatilities, analogous in the healthcare supply chain if one compares normal course of events versus epidemics, pandemics, natural disasters or acts of terrorism. However, it is well nigh impossible to stress that the key performance indicators (KPI) for business operations and inventory management or purchasing decisions must be based on different operating principles and are significantly distinct between business [**49**] and healthcare (see section 5.1). Nevertheless, gaining business efficiencies in healthcare is not an automatic process simply because EMRS offers an aggregated view of potential consumption of products and services. It is for this reason, that some countries with national health service, whether servicing a large [**50**] or small [**51**] population, may still suffer from an inability to take full advantage of the economies of scale to drive business efficiencies.

3.2 SOLUTION SPACE: Changing the Dynamics of Medical Data and Information Flow

The thesis of this paper outlined in section 2.2 selects medical data as one conduit which may offer the potential to catalyse low-cost, high-quality healthcare services. An analysis of the nodes of origin of data in the context of their relationship to cost (to acquire data) and quality of service (decision based on data) may form the basis for suggesting how the current dynamics may benefit from a paradigm shift (Figure 2).
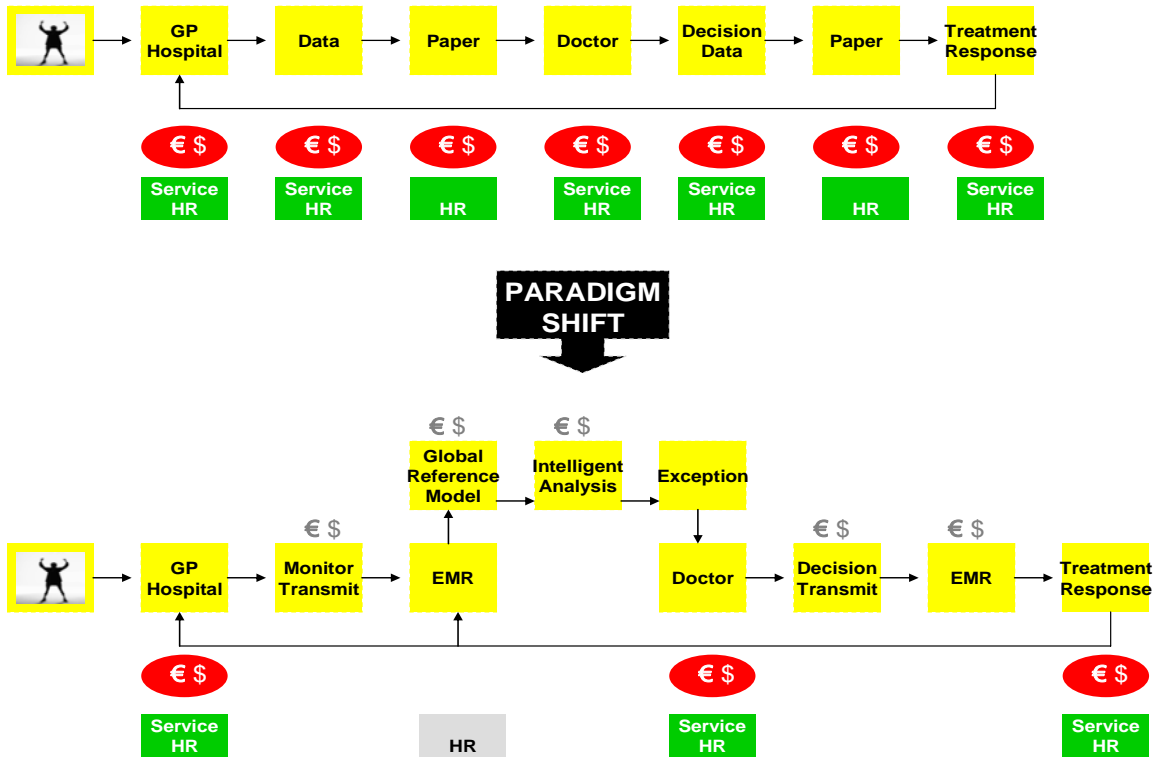
Figure 2: A generic model of data flow in healthcare and potential benefits of a paradigm shift

In some industrialized nations and in the developing world, the current healthcare practice may be loosely represented by the schematic outline shown in the top portion of Figure 2. In the current scenario, almost all points of interaction (yellow squares) incur cost (red oval) and each action consumes time from professionals (green rectangles). The latter, as a result, is a drain on the available working hours of medical personnel and is an improper use of valuable time, which could have been, otherwise, put to better use by offering health "care" service focused on the elements connected to the treatment of the patient.

The paradigm shift outlined in the lower portion of Figure 2 is neither new nor an innovative breakthrough. It is a strategic process engineering that is driven by common sense. It suggests how basic integration of some tools and technologies may lead to savings in cost and improvement in quality of care by focusing the time of medical professionals on the patient, rather than on standard tasks and chores. In this scheme the lack of the red oval under the points of interaction (yellow squares) indicates potential for cost savings.

Above the yellow squares the currency signs (€ $) in light grey imply that implementing and maintaining these changes are not free but the cost is lower (than the red ovals) and return on investment (ROI) is higher if the cost of installing the systems are amortized over their productive life cycle. Less time spent by medical personnel at various stages (lack of green rectangle) leaves more time to focus on patient care.

Three elements that drive the paradigm shift (Figure 2) are (1) data monitoring, addressed in sections 3.3 and 3.4, (2) electronic data capture or EMR, discussed in section 3.1 and (3) diversion in data flow. In the remainder of this current section (3.2), I will discuss the latter since it is perhaps the key in the proposed paradigm shift.

Diversion of data flow leads to an information loop that channels acquired data to flow through a global reference model and directs the outcome of analytics to medical personnel if it appears to be an exception. By concentrating on the patients that need attention (exceptions) the system is able to improve its quality of service.

Critics are eager to pose the thorny question: how reliable is the machine-based analytical process? Due to the experimental nature of the scientific process, I find it reasonable to conclude, that there may not be, ever, an unanimously acceptable, complete and absolute scientific certainty, with which anyone can predict that a machine learning process can be guaranteed to be fool proof. Error in medical diagnosis by medical experts should suffice to bring home the fact that neither man nor machine is entirely infallible. It follows, therefore, that the "thorny" question is the wrong question. Attempts to find the precise answer to the wrong question has, thus far, fractured the determination of, and seriously distracted the healthcare and decision sciences experts (see reference 63) effort, to focus on finding an approximately reasonable answer to the right question: how much and for what type of cases can we generally depend on the analytical tools in clinical decision support?

In the US, healthcare spending was in excess of $2.1 trillion in 2007 and projected to double to $4.2 trillion by 2016. Thus, reducing 10% of health services workload through monitoring and analytics may save US nearly half a trillion dollars [52] in a few years. A small country like Ireland may save a couple billion euro [53] per year. It may also translate to a 10% improvement in the quality of service (QoS). Financial savings may be re-invested in community primary care centers, home-help for independent living and early risk identification, for example, for diabetes.

Therefore, the information loop proposed in the paradigm shift must be created and implemented, soon, even if the construction occurs in steps or modules. Inevitable "growing pains" are expected to accompany any change of direction. The "loop" is a generic expression that involves critical sub-elements of great depth that require precision knowledge. This paper shall not provide a prescription for building the sub-elements but will strive to present examples that may convey the nature of these components. It goes without saying that the loop is not an "IT" job but demands collaboration between IT and medical experts.

Figure 2 alludes to a Global Reference Model (GRM) where the acquired data is fed via a database, such as an EMRS. The schema indicates that the data flows through the GRM into the intelligent analytics domain. What is unclear from the illustration and requires explanation is that the suggestion positions the GRM to represent an umbrella, or collection of, multiple modular databases, each embedded with some form of rule-based analytical engine that can evaluate the incoming data (streaming data) and use conventional workflow to query its database (specific to that module) to find relationships, homologies or discrepancies based on its own stored data, specifically with reference to and in the context of that module of the GRM.

For example, a patient with elevated temperature suffering from severe bouts of coughing undergoes exploration in an out-patient clinic. A nurse records the blood pressure, temperature, draws blood for total blood count and based on the ethnicity of the patient, she decides to take a sputum (saliva) sample in addition to administering a Manteaux Test. It is an immunological test designed to detect tuberculosis (TB), an infectious disease [54], caused mainly by the microorganism *Mycobacterium tuberculosis*.

What types of modules in the GRM can process and analyse the data from this patient? Medical experts can define the nature of the GRM sub-modules but for the non-medical reader it may be of interest to note the following. Reference for normal blood pressure, correlated to age, is common, as is temperature. Total blood count is a common standard and easily included in a GRM module. However, the GRM module that can deal with the results of the Manteaux Test will require medical details as well as environmental details that relate to the epidemiology of TB, length of habitat of the patient in geographies where TB is prevalent, immunological profile of individuals with confirmed infection by *Mycobacterium tuberculosis*. The Manteaux Test is an intracutaneous tuberculin skin test usually applied on the forearm and contains tuberculin purified protein derivative (PPD) to elicit the immune response that is visible on the epidermis within 2-3 days. For a patient who was born or lived in south-east Asia or resident of warm humid coastal areas in the US, a positive Manteaux Test, but measuring less than 10 mm in transverse diameter of induration, as detected by gentle palpation at 48 to 72 hours, is not indicative of TB but rather indicates tuberculin

hypersensitivity, resulting from contact with non-pathogenic environmental mycobacteria or childhood vaccination by Bacillus Calmette-Guerin (BCG), which is an attenuated strain of *Mycobacterium bovis* [55].

The above example illustrates the web of relationships that the GRM and analytics must be able to extract and transmit, to the point-of-care medical professional, using a visualization interface such as personal digital assistant or Blackberry type mobile phone. However, irrespective of the apparent complexity of the above example to the non-medical reader, most of the data and information mentioned above is already available in several databases and classified under variety of topics, including the obvious heading of infectious diseases. There is no need to create, *de novo*, any basic medical data or information database. For example, from the scenario above, the sputum sample from the patient may hold several clues for early detection and diagnosis, based on advances in saliva-based biomarkers [56]. The data from sputum analysis may be transmitted to the GRM and it can query the SKB or Salivaomics Knowledge Base [57] to extract the information for further analysis. Several such databases exist with specialized knowledge and information which are accessible via the World Wide Web. Unfortunately, the traditional web works as a directed graph of pages with undifferentiated links between pages. This is not conducive to the type of relationships necessary for healthcare analytics. Emerging principles from social networking may be quite helpful for healthcare service analytics (see section 5.1). Blogosphere (see reference 10) has a much richer network structure in that there are more *types* of nodes which have more *kinds* of relations between the nodes. Deploying the principles of blogosphere in healthcare analysis may be quite promising.

Thus, the challenge is to find new ways or tools to identify and relate the selected sources that may serve as components of GRM through a virtual amalgam. GRM requires a mechanism to search and detect the information database and then query the database depending on the case or patient under investigation. For every patient, these strands of data-dependent or symptom-dependent or test-dependent tasks must be created, in real-time, on demand, perhaps, as a higher layer integrated abstraction in the form of an application module (poor choice of word but hopefully, it conveys the concept). For example, continuing the TB scenario, the data from the Manteaux Test plus the symptom of cough and the eosinophil count from blood test may serve as three variables that may trigger an *ad hoc* application that asks, either as single queries or collectively, what is the potential diagnosis if the Manteaux Test reveals a 10mm transverse diameter, chesty coughs are persistent and eosinophil count is 8%? To execute this process, the system may create an *ad hoc* application specific interface (ASI), application specific query (ASQ) and an application specific relationship (ASR) that can act, either alone or as a bundled application, to probe

relevant knowledge repositories or databases, to extract the information. This information may be further refined by the intelligent analytics component in the information loop or transmitted to the point-of-care (POC) medical professional.

The scenario above may be loosely suggestive of a medical example of mash-up software [58] that is gaining popularity in business services utilizing SOA or service oriented architecture [59]. SOA is touted to help business services remain agile and adaptable to meet the competitive challenges due to volatility of consumer preferences and uncertainty stemming from globalization of the supply chain. To capture sales, these business services, on-demand, in real-time, creates a personalized web-service and displays a collage of objects, optimized for consumer choice. The collage is culled from different domains or databases that may nor may not belong to the business but secures content-on-demand through licensing. The mash-up appears seamless through the wizardry of visualization tools. The consumer views it as a web page on a computer screen or mobile phone. The view may include, for instance, a company logo (a software object), price of a product (database table format, stored as an object) aimed at a market segment (extracts clients preferences and matches with stored classes of objects, eg, sports) and ordering information (another standard shipping and handling object) with links to track and trace details provided by a third party logistics provider (for example, link to FedEx site).

The analogy in the above two paragraphs may fall short of the specifics or lack the precision that experts in respective domains (medicine and information technology) may demand but it may convey the essence of case-specific exploration, on-demand, integrated to knowledge discovery from databases, or other domains, necessary for delivering healthcare analytics. Each country may create their own GRM infrastructure to optimize how the GRM may be relevant to the nation and deliver value in medical analytics, at least in cases that are simple enough to be acted upon by machine intelligence, where reasonable confidence can be placed in the decision. Determining what is "simple" may vary, widely.

Triggered by patient data input, the search function of GRM may evoke the notion of Medical Google. One difference is that the search is not the end point of GRM but is for the Google search engine [60]. The granularity of the search process implicit in GRM also differs from that of Google in its quest for knowledge databases, followed by the extraction of relevant data and/or information and/or knowledge that must be first 'discovered' and then re-synthesized and presented to the intelligent analytical engine.

The "intelligent analysis" referred to in Figure 2 is a "place holder" for multiple analytical tools that are available and may be developed in future where the "learning" ability of the tools may be a key emphasis in addition to rule-based applications. The tools, for example, artificial neural networks (ANN), originate from the domain of artificial intelligence (AI) and new algorithms may continue to evolve. Since medicine is an intensely integrated science, the *network of inter-relationships* between medical parameters and physiological function is key to understanding health. The plethora of reasons that may offer generic symptoms, for example, fever, makes it imperative that the point-of-care (POC) physician is sufficiently aware of the spectrum of reasons why an individual may present the symptoms of fever. Presentation of a list of reasons may stem from the use of rule-based engines that may search and compile a list. However the value of the "list" is limited unless the **context** of the patient and history is taken into consideration.

Rules, to combine and select the best possible match between the list and context, may be created but the rigidity of rule-based selection may make it less reliable if compared to a set of algorithms based on AI principles that can "learn" and **forget** the subtle, or not so subtle, changes in the context of the patient, that may include parameters, such as, age, activity, profession, environment, habitat and nutrition. For this reason, GRM and the intelligent analysis cluster of the information loop may use data cubes [61] and components that may be country-specific, nation-specific or community-specific but may also draw on synergies between demographically related co-localized nations (eg: Scandinavia or Eurasian Steppes).

Let us consider an example where, Jane, 11, contracts a fever on Monday morning after a hot weekend which she spent on the beach and swimming in the ocean. On Monday, Patrick, 71, complains of fever, too. He also has chronic obstructive lung disease (COLD). The attending physician may focus on determining whether Jane may have an ear infection while gearing to treat Patrick for chest infection. But, can we approach this level of interaction and perhaps a treatment suggestion without incurring the cost and time of the physician? Use of acquired data (see section 3.3) and decision sciences may offer a route to savings. To execute this interaction and offer a reliable, low-risk decision or treatment suggestion, intelligent analytics views the GRM-evaluated raw data plus "list" of possibilities for the fever and integrates the context with patient history. It also checks the GRM pharmacology module. The system transmits the exploratory analytical sequence log, diagnosis and recommends age-appropriate antibiotics, in each case.

Although use of artificial neural networks (ANN) and artificial intelligence based algorithms (for example, ant-based algorithms) were mentioned only for business services applications (for example, mash-up), the use of AI-based Agent Systems [62] can provide a robust and granular system. Experimental use of AI in

clinical decision making [63] and productive implementation of AI in industry [64], business [65], business to business exchanges [66] and other applications [67] provide confidence that Agent-based systems may become the norm in healthcare, too. Due to the inter-related nature of medicine, numerous parameters must be concomitantly evaluated for any decision and each patient must be treated as an independent instance, that will be specific for that patient only. Data related to the patient will always remain patient-specific without sharing, aggregating or clustering data, in any form, whatsoever. For each patient, the classes of data and volume of data points are likely to be quite high. All data points must be stored and relationships evaluated for diagnosis and prognosis. Therefore, the use of data cubes and the ability of Agent systems to connect between all data points through the cube-on-cube organization of data cubes, may make this approach particularly essential and beneficial for the billions of instances necessary for healthcare services.

Re-visiting the earlier example where a Manteaux Test was administered, from an Agent perspective, the applications, in that discussion, may be dissociated into single Agents, each with its specific task in relation data and exploration of the web of relationships with respect to the data or task assigned to the Agent. In other words, the Agent that holds the results of the Manteaux Test (data = 10mm) for the observed induration, is charged with the task to find out, through the medium of the GRM, what are the implications of the observed data (10mm). Development of intelligent Agents systems [68] are within the grasp of current technology (see reference 182) and can be implemented in healthcare systems. The "bundled" higher layer abstraction of individual applications (ASI+ASQ+ASR) mentioned earlier in this section is analogous to multi-Agent systems [69] that work with Agents in a hierarchical fashion with higher level Agents tasked to integrate the information or data from lower level Agents. It is likely that multi-Agent systems (MAS) may become the workhorse of the AI-based intelligent analytics in healthcare.

AI-based Agents generally use programming languages from the open source domain. Hence, Agents are highly mobile and suited to query a variety of databases for knowledge discovery using open source tools, for example, RDF or resource description framework [70] and OWL or ontology working language [71]. Agents are likely to form an integral part of the emerging semantic web [72]. But, Agents need special interfaces if interacting with proprietary databases. Proprietary software vendors [73] deny RDF from accessing their data dictionaries through use of proprietary programming language, for example, the use of proprietary ABAP programming by the software behemoth SAP AG. These problems may spur novel approaches. One data transformation tool called Morpheus [74] may facilitate extraction of data from

various locations by transforming them into a common format which is then sent to "holding tank" or a repository of transformations. Morpheus, used as a browser tool, may help to find a repository transformation that GRM (Figure 2) may be seeking. The transformation tool may drag-and-drop data or information in a format used by GRM.

In another vein, the Open Source movement is catalysing the diffusion of software tools that may make it easier for Agents to access proprietary formats through standard application programming interfaces (API) that still preserves the proprietary nature of the system but through a "translational interface" or flat file type format exchanges data or information. If the data or information sought by the Agent is secured and in need of authorization for release, Agent systems are capable of exchanging proofs to provide such authorization and release the data. The mobility of Agents raises important questions about data security and its implications for healthcare. It is well documented that Agent-based models are more robust to ensure data security by virtue of the AI algorithms used in its construction. At present, generally most software architecture, for example, of the type used in EMRS, depends on equation-based models which are inherently far less secure.

Taken together, Agent-based architecture may soon become pervasive in emerging healthcare systems. Agent-based software may form part of the **infrastructure** of the healthcare system of systems (HSOS). HSOS not only consists of the components illustrated in Figure 2 but extends to include mobile Agents that [1] monitor the functional status of medical devices, [2] schedule human resources, [3] aid in the planning of meal services to match nutritional needs or restrictions of patients, [4] guide business functions to benefit from economies of scale and [5] oversee financial records to monitor the fiscal health of the healthcare service. Other forms of conventional non-AI software (Morpheus, mash-up, SOA, ERP, web services) may co-exist within the Agent-based software infrastructure for routine transactions.

Agent based "learning" systems may augment the depth and precision of data mining and pattern recognition (se sections 3.1 and 5.1). Rule based data mining and pattern recognition may be out-of-date soon after 'new' rules are updated. The latter may be particularly relevant to healthcare tools, data structures and analysis of parameters in diagnosis or early risk identification. Systems must continuously learn, adapt or improve to extract and use the subtle changes that may be indicative of future disease potential or can differentiate between closely related types of anomalies. Some of these parameters may differ or be altered sometimes, albeit slightly, between populations [75]. In the context of the patient, that can impact the outcome, considerably, to prevent false positives or wrong treatment. Agent systems can

continuously "learn" about changes and hence offers greater confidence in the outcome of Agent-based GRM integrated intelligent analytics (AGRMIA) compared to rule based tools. Algorithms for relation analysis are emerging from research on social networking [76] and reality mining [77] that may be adapted for use in AGRMIA (see section 5.1).

Application of pattern recognition, in one study, achieved perfect discrimination (100% sensitivity, 100% specificity) of patients with ovarian cancer, including early-stage disease [78]. The study identified subset of proteomic biomarkers using mass spectroscopy of proteomic analysis of serum from ovarian cancer patients and cancer-free individuals. Statistical algorithms analysed the mass spectral data and selected, using random field theory, all biomarkers that were significantly different in expression levels between affected and unaffected subjects. The best discriminating pattern was chosen among all significant biomarkers by using the best-subset discriminant analysis method (Linear Discriminant Analysis). Another study along the same lines, developed an algorithm employing Principal Component Analysis followed by Linear Discriminant Analysis on data from mass spectrometry and achieved sensitivity, specificity and positive predictive values above 97% on three ovarian cancer and one prostate cancer dataset [79]. Detection of ovarian cancer using sensitive molecular biomarkers is especially urgent in women who have a high risk of ovarian cancer due to family or personal history of cancer and for women with a genetic predisposition to breast cancer due to abnormalities in genes such as *BRCA1* and *BRCA2* [80].

Application of remote monitoring (see next section) of body fluids using protein microarray chips [81] that can transmit data, advanced mathematical tools for biomarker data analysis, AI-based intelligent pattern recognition and Agent-based GRM information flow (AGRMIA), if taken together, may hold promise for global healthcare. Tools, such as, mass spectroscopy (MS) provides clues about molecular identities of differentially-expressed proteins and peptides in body fluids or in breath [82] that may be critical for early diagnosis. Agent based systems, operating through the GRM (Figure 2), can extract these types of data as well as information catalogues of biomarkers from other fields [83] and apply the knowledge to patient data, to identify risk and improve diagnosis. Hence, mass spectroscopic (MS) analysis of protein or peptide biomarkers [84] in body fluids using micro-fabricated miniaturized MS device [85] operating as a low-cost wireless sensor may offer a general ***population-based assessment*** of proteomic pattern technology, as a screening tool for early risk identification for several diseases, to complement lab-on-a-chip type sensors for early detection of cardiovascular diseases [86] and carcinomas [87]. A proposed systems approach, by

which mass spectroscopic data (protein and peptide biomarkers) may be compared **between** systems, will be explored in section 4.0 on molecular semantics.

3.3 SOLUTION SPACE: Data Acquired through Remote Monitoring and Wireless Sensor Network

The paradigm shift in Figure 2 illustrates that data acquisition and transmission, even if partially assisted by use of medical devices for remote monitoring tools and information communication technologies, may reduce cost and free up time for medical professionals. In principle, few can argue about the value of this approach. In the preceding section (3.2), references were made to potential for remote monitoring and sensors to improve healthcare services. In this section, I shall focus on one remote monitoring device. The basic strategy, from a medical device perspective, may be similar for the majority of vital measurements (data) carried out by the primary care GP or at the hospital. Security of transmitted data and unauthorized access is preventable using Agents. To guarantee even more stringent data security, recent research on PUF or Physical Unclonable Functions [88] may generate unique "fingerprints" that can distinguish identical chips or IC from the same manufacturing batch, that are used in bio-sensors and other medical devices.

Remote sensing technologies are well developed [89] yet their application to non-invasive, wearable bio-instrumentation capable of wireless transmission of reliable data, has only emerged in the past few years. One innovative device, the Ring Sensor (Figure 3) has emerged from the convergence of robust self-organizing wireless radio frequency (RF) transmission and an improved photoplethymographic (PPG) wearable sensor to monitor vital signs [90]. The Ring Sensor minimizes motion artifacts when measuring arterial blood volume waveforms and blood oxygen saturation, non-invasively and unobtrusively, from the wearer's finger base. Figure 4 shows the results from Ring Sensor monitoring of heart rate (data transmitted through a wireless sensor network) and compares the results to conventional electrocardiogram and wired finger photoplethymograph. The latter is susceptible to motion artifacts.
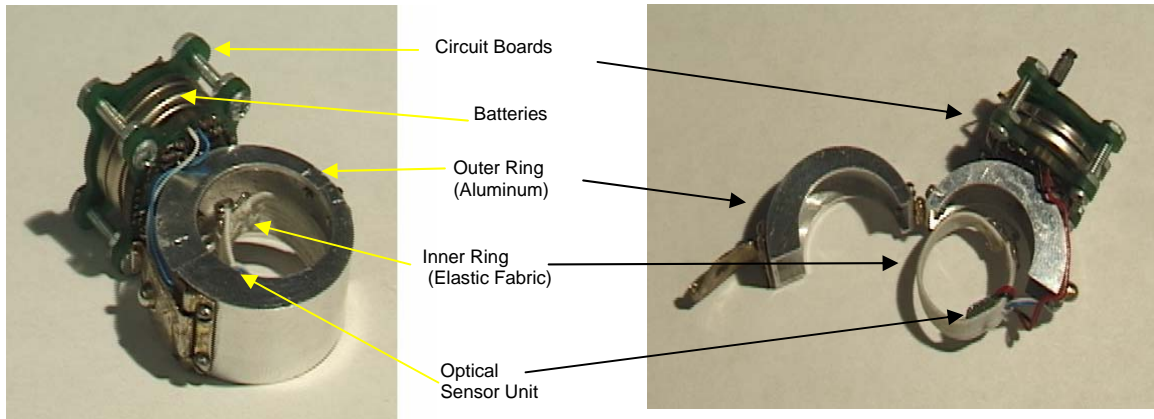
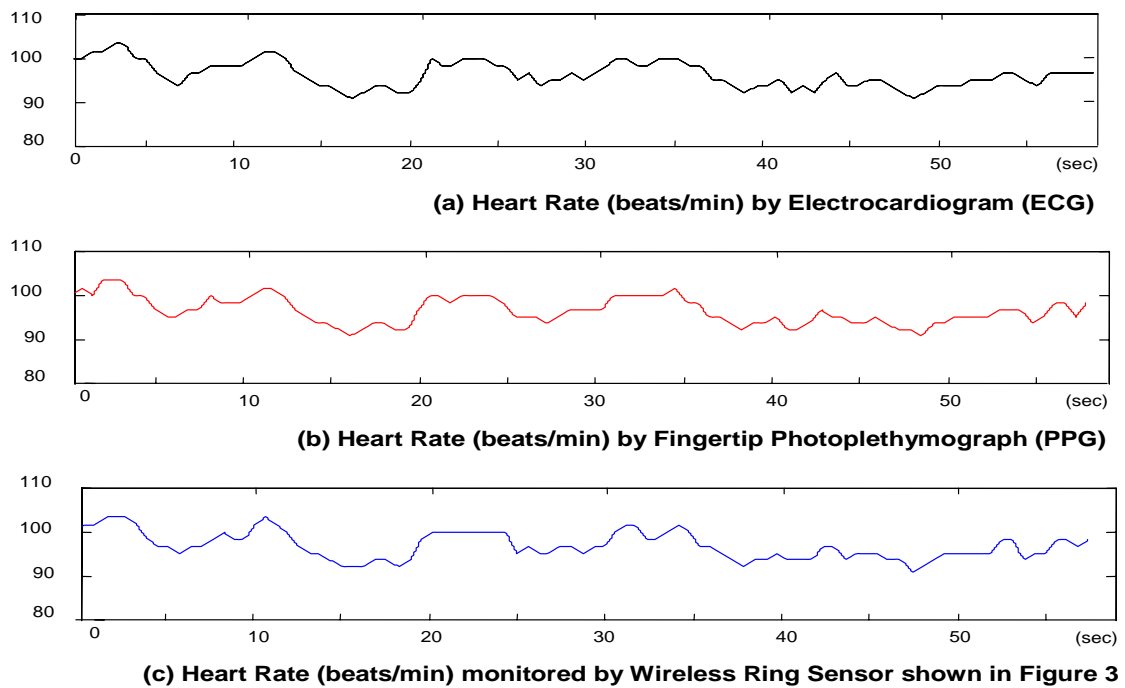**Figure 3: Non-invasive Ring Sensor for Wireless Monitoring of Heart Rate (Rhee & Liu, 2002)**

(a) Heart Rate (beats/min) by Electrocardiogram (ECG)

(b) Heart Rate (beats/min) by Fingertip Photoplethymograph (PPG)

(c) Heart Rate (beats/min) monitored by Wireless Ring Sensor shown in Figure 3

Figure 4: Heart rate monitoring by conventional, wired and wireless devices (Rhee & Liu, 2002)

It does not require any stretch of imagination to slip on the Ring Sensor (or a refined version of a similar device shown in Figure 3) on a patient's finger to monitor key vital signs, such as heart rate, continuously.

Real-time streaming data under the "watchful eye" of a dedicated AI-based Agent, embedded in the monitoring system or even in the Ring Sensor operating system (OS) monitors waveforms in real-time. It may be similar in principle to motes with TinyDB (database) and TinyOS [91]. If the Ring Sensor 'senses' reasonable deviation of the PQRST wave in the **context of the patient** (rather than the PQRST *standard* in GRM or global reference model) then it immediately 'responds' by sending an alert (code blue, code red) to the PDA or mobile phone of the medical professional, on duty. Reference to context is important for patients with chronic cardiovascular diseases in order to prevent false alarms. Patients diagnosed with myocardial infarction or angina pectoris may display a PQRST waveform that may be different from the standard GRM version but this altered PQRST waveform may be the "patient-specific normal" waveform. The data monitoring and analysis components of the system must be able to contextualize this difference.

This distinction in the **analysis** of monitored data highlights the need for caution to treat this suggestion as a medical device business bonanza. The challenge is to converge the sophistication of the waveform monitoring medical device (for example, the Ring Sensor) with patient-specific context and history under the 'supervision' of an Agent (intelligent analytical tools). Agents may optimize the 'sense, *then* respond' outcome, to be transmitted in a visual format comprehensible by a consultant cardiologist **as well as** a student nurse, to initiate the medical professional driven response, decision and treatment plan, if needed.

In practice, patients with cardiovascular problems are often required to wait. Intermittent monitoring of their vital signs is possible when the student nurse or trainee gets around to the patient. Physiological events that may happen *in between* the human resource dependent monitoring, may well determine the long-term morbidity (stroke victims) or mortality of the patient.

In the at-home scenario, Ring Sensor type applications offer greater value. Continuous monitoring is the key to preventative care, in this case, for people with chronic cardiovascular diseases or individuals at high risk of cardiovascular diseases, that may stem from other conditions, for example, increasing blood cholesterol or obstructive pulmonary diseases. Transmitted data from continuous real-time monitoring in the home, if subjected to real-time analysis (systems located in the community or primary care center or local hospital) are likely to (1) improve the quality of life for the patient, (2) reduce health service expenses by keeping the patient out of the hospital for longer periods, (3) optimize resource planning by creating a management plan and predicting when the patient may need to visit GP or out-patient clinic for non-acute follow-up or treatment, (4) reduce health service expenses and demand on service from A&E medical professionals by decreasing the probability for acute-care emergency services that may be

required by the patient, more often, without remote monitoring provisions, (5) improve the overall quality of healthcare by extending remote monitoring not only for patients but the at-risk group, as well, by using the Ring Sensor with an ultra-low power wireless device, the "i-Bean" which is an *ad hoc*, self-organizing network protocol that is as simple as plugging in a wireless WiFi router in home or office (Figure 5) or any location which can connect to the medical analytical system through the internet and (6) expand the reach of healthcare services (without mortgaging the treasury) by extending low cost remote monitoring to an otherwise healthy demographic who may volunteer to keep an eye on their cardiovascular wellness profile.
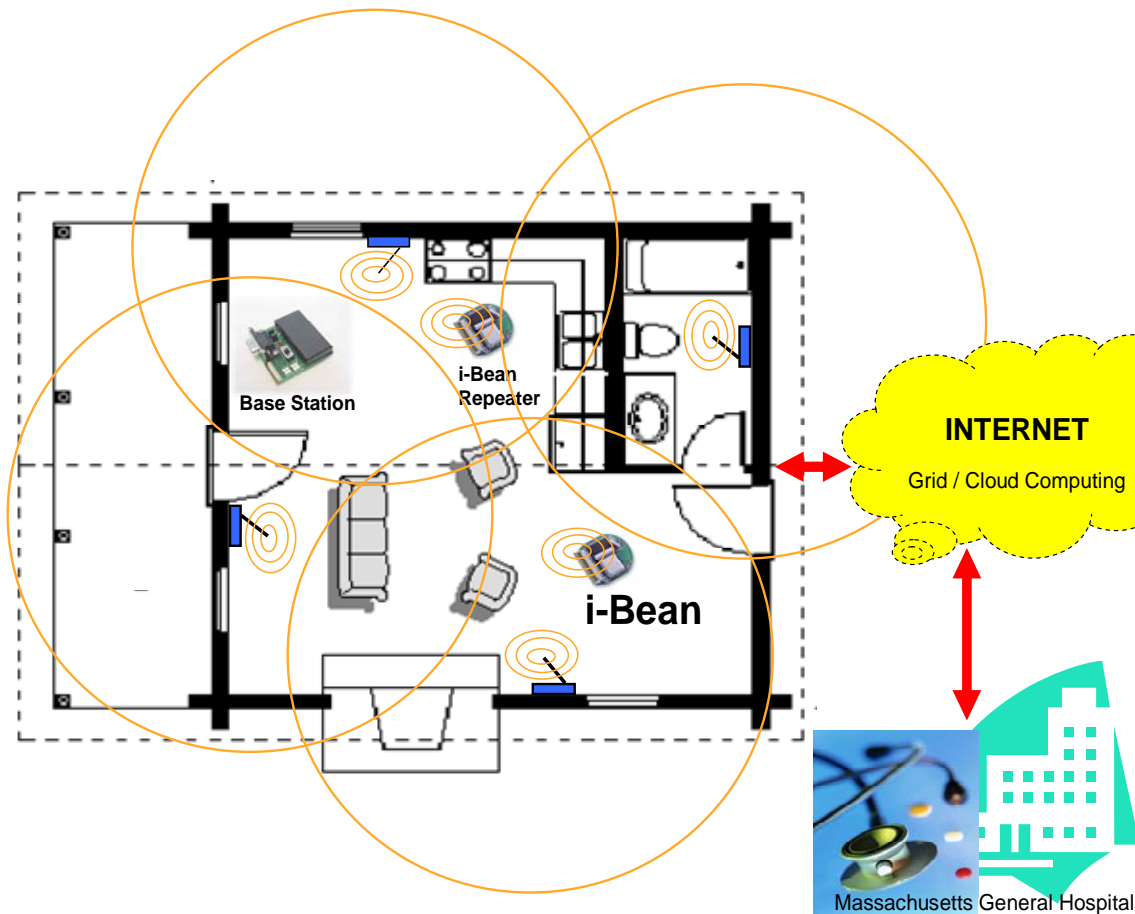
Figure 5: Wireless Cardiac Monitor uses Plug-n-Play i-Bean Sensor Network (Rhee & Liu, 2002)

The benefits from remote monitoring are undoubtedly robust but it is also necessary to remain cautious because, whether remote or on-site, wireless or wired, local or global, healthcare produces data that may be difficult to interpret and lack of proper interpretation may be fatal. The role of the medical professional

and human-driven decisions, even for apparently routine instances, such as blood pressure check, may, sometimes, cast a doubt if data or symptoms are too generic. Table 1 (in section 3.4) illustrates this point by highlighting that monitoring blood pressure and recording an elevated, lower or normal reading, in some cases, may not identify the reason or provide diagnosis based on that data, alone. Convergence of diagnostic tools are necessary to further any decision on such diagnosis. Current tools and tests may gradually undergo changes with the emergence of personalized healthcare, made possible by sequencing of the human genome [92] and development of genomics [93] based tools (see section 3.4).

The illustration is Figure 5 has yet another dimension that is particularly important in global healthcare, especially for emerging and developing economies where the number of and access to medical experts are limited. The goal is to support local data analysis either with information or connectivity that may enable access to experts, opinions and resources. Various efforts to deliver information [94] through ICT [95] have been pioneered by pioneers [96]. However, there is room for further advances with diffusion of broadband and other high speed networks to the far corners of the world. It may transform the vision where a patient in a remote village clinic in Malawi may have access to an electrocardiograph (ECG) or low-cost Ring Sensor **and** can transmit that data through a standard network or innovative 3G system [97] that offers mobile phone service even from airplanes, during flight [98]. In the village in Malawi, a nurse practitioner may be the only medical professional in the clinic and she may be unable to decipher the ECG and hence incapable to suggest medication. It is here that the value of the transmitted ECG data becomes obvious. Through a consultancy network, on the other end of the world, a cardiologist [99] may review the data and diagnose cardiac arrthymia due to repolarization abnormality (clinical effect) causing Long-QT syndrome [100].

This simple example and other types of analysis which, *in addition to connectivity*, may also *require computational power*, for example, analysis of brain activity data from magnetoencephalography (MEG), may immensely benefit from grid computing [101]. Advances in microfabrication of atomic magnetometers could enable the development of precision magnetic resonance imaging (MRI) systems for self-monitoring, in any location [102].

The **striking** benefits that may emerge from the trinity of grid infrastructure, remote MRI monitoring and intelligent or expert data analysis (AGRMIA) may be appreciated in view of the fact that mental health anomalies often display signs that may resist diagnosis due to lack of adequate expression of symptoms.

Individuals may even fail to recognize that something is amiss because the rate of increment in the expression of some mental health conditions may be infinitesimal and over several years or decades. It may not be uncommon that individuals may even adapt to these changes as 'age relevant' rather than differentiating them as potential symptoms of a disease and demanding medical exploration or treatment. Personal MRI devices coupled with microfabricated mass spectroscopy (MS) may create the remote ms-MRI personal monitoring device that could work as a non-invasive **wearable wireless sensor** that can be placed on the head to fit as a **swimming cap**. This development shall unleash a new horizon in "being digital" [103] in personalized medicine. In particular, remote monitoring using ms-MRI sensors may be instrumental for early detection of **biochemical changes** in the brain, either sporadic or due to aging.

The immeasurable value of ms-MRI remote sensors may be best illustrated by Alzheimer's disease. It is a condition where the activity of the choline acetyl transferase (CAT) enzyme, responsible for the synthesis of acetylcholine, shows a 60%-90% decrease [104]. Acetylcholine is a key neurotransmitter and a marker for cholinergic neurons. The ability of ms-MRI to detect and profile (using MS) biological and biochemical molecules, is the driving technology to determine the shape and **concentration** of acetylcholine molecules and hence by extrapolation, determine the activity of CAT. The biochemical identification of **molecules** (and in future identify differences in the *structure* or shape of the molecules) is critical in Alzheimer's disease and ms-MRI is one promising tool that is amenable to work as a wireless sensor for remote monitoring. The choice for ms-MRI over conventional MRI is based on the fact that conventional MRI only identifies physical structures. Recent developments in functional imaging using MRI have created the functional-MRI (fMRI) that can identify the rate of blood flow within a physical structure or area in the brain. Hence, fMRI may be useful to monitor learning disabilities where external stimuli may fail to activate certain regions of the brain, suggesting abnormalities. However, in Alzheimer's disease the biochemical loss of enzyme activity of choline acetyl transferase occurs in the cerebral cortex, hippocampus and related areas but cell counts of the neocortex and hippocampus of patients with Alzheimer's disease did not reveal major reductions in **numbers** of cholinergic neurons when compared with age-matched controls. Thus, for the purpose of early detection, individuals *developing* Alzheimer's Disease may appear 'normal' by conventional MRI analysis since the physical structure of the potentially affected areas of the brain remains unchanged as far as the *numbers* of neurons are concerned. The formation of plaques in the brain of patients affected by Alzheimer's disease may be detected by MRI. Remote monitoring using ms-MRI wireless sensors may be also applicable to other conditions related to changes in neurotransmitter related proteins and molecules in the brain, for example, Parkinson's disease, Huntington's disease and some forms of dementia.

The adoption of these developments in personal remote monitoring of mental health coupled with the ability of individuals to obtain an expert opinion by transmitting the data as well as learn about the implication, of the ***changes recorded over time***, may help determine a medical management plan that may improve the individual's quality of life. The analysis of data may require computational resources that may be unavailable in many locations, even in affluent nations. The ability of the transmitted data via the local network to access "medical grid" based expert services offers immense benefits. The access to these resources through the network and medical grid services, even from the developing nations [105], can reshape the fabric of global mental health.

In addition to magnetic resonance imaging (MRI), grid computing has the potential to add remarkable value to other forms of remote biomedical imaging systems as well as bio-telematics [106] since current operations [107] are limited to groups [108] that engage in stand-alone point-to-point systems [109] without the benefit of a platform to aggregate medical grid type services. Bringing together this platform may be similar in effort to creating the GRM and is expected to be a part of the GRM (Figure 2) that may run on a grid infrastructure. Several biomedical imaging databases are in existence and taken together they may form a biomedical imaging platform (BIP) tethered to a proposed "bMDs" services infrastructure [110] through an accessible open format where images (data) may be uploaded from anywhere in the world and viewed (analysed) by expert(s) who will share observations and/or deliver their interpretation or diagnosis directly to the patient or the healthcare service provider. Tools for simulation and visualization will be important and significant advances [111] can be resourced. Agents embedded in the architecture may monitor, device to device (D2D), machine to machine (M2M) and device to system (D2S) or vice versa (S2D), medical data to ensure data security and privacy issues.

Progress in the AI vision of autonomic computing, may gradually transform BIP, either independently or in combination with an AGRMIA type infrastructure. Inclusion of embedded intelligence may provide opinions or recommendations or diagnosis or referrals (exception management) *without* active human intervention. The latter should be welcome news to the aging population in Europe and Japan who wish to remain independent and live in their own homes rather than in long-term healthcare communities that can drain national healthcare resources. Nations may be prudent to explore ms-MRI type high technology medical practices and find new ways to think about diseases [112] with long term impact and challenge the medical *governance* [113] to reduce cost by investing in and accelerating the convergence of medical

knowledge and engineering technologies. The convergence proposed in bMDs shall include advances such as ms-MRI remote monitoring platforms and may be a part of future healthcare tapestry.

Thus, grid computing is an enabling technology for healthcare service connectivity in much the same way that grid can facilitate business services [114]. In healthcare, as in business, grid computing may provide access to on-demand computational resources (that are in a different location) for real-time data processing and analysis, through grid-based tools, such as Globus [115].

3.4 SOLUTION SPACE: Innovation in Wireless Remote Monitoring and the Emergence of Nano-Butlers

Nano-Butlers is a facetious term but is expected to convey an "image" to suggest that nano (small) tools and technologies act as 'small butlers' serving the demands of healthcare (and their 'fees' are also small, hence they work for 'micro' payments). The 'tongue-in-cheek' image is expected to create an awareness that detection of biological molecules including proteins or peptides, at the nano levels may be critical for identification of biomarkers that may associated with the risk of a disease. When the investment to develop nano-detection is recovered (return on investment) from the savings from reduced acute-care responses, if may be, that the actual cost of nano (small) detection will be small enough to enable global diffusion of the tools which can be sustained by micro (small) payments, mimicking the concept of micro-finance that has gained global acclaim [116] for alleviating poverty in some parts of the developing world. This approach, due to the inclusion of the term nano, may also draw some unfounded attention [117].

Early risk identification, prior to detectable symptoms, offers the potential to develop a management plan to contain the disease or even stop it from presenting any symptoms. This approach reduces the acute-care response that may be necessary if the condition was not detected and left unattended. A&E responses and acute-care is far more expensive and often increases morbidity and mortality if the response fails to be administered in near real-time. For example, from the time of onset of a cardiac attack, there is only a 30 minute window for successful administration of tissue plasminogen activator (TPA) to dissolve clot(s) if a patient with cardiovascular diseases or stroke is the victim of thrombosis (blood clot). It is likely that more than 30 minutes may elapse between recognizing that a person is *having* a "heart attack" and the arrival of A&E services at the location, assuming not only that the paramedics will correctly diagnose the reason (clot) but that they will also have an inventory of TPA-type

drugs in their mobile unit (ambulance). It is also assumed that the person is coordinated and coherent enough to call to A&E services if the individual is alone in the location.

Prevention through preventative healthcare may require, in the above scenario, the convergence of wireless sensors with remote monitoring technologies and data driven analytics based on biomedical research knowledge bases. Advances in understanding the basic physiological, biochemical and molecular relationships (Figure 6) that contributes to heart disease [118] offers hope for rigorous early detection mechanisms. There is ample evidence both from basic biological sciences [119] and clinical research [120] that early warning signs of cardiovascular diseases are amenable to identification from research on biomarkers. Several biomarkers for cardiovascular diseases (CVD) are already in the market [121] but the commercial "kit" approach is far from the innovative potential of next generation diagnostics [122].
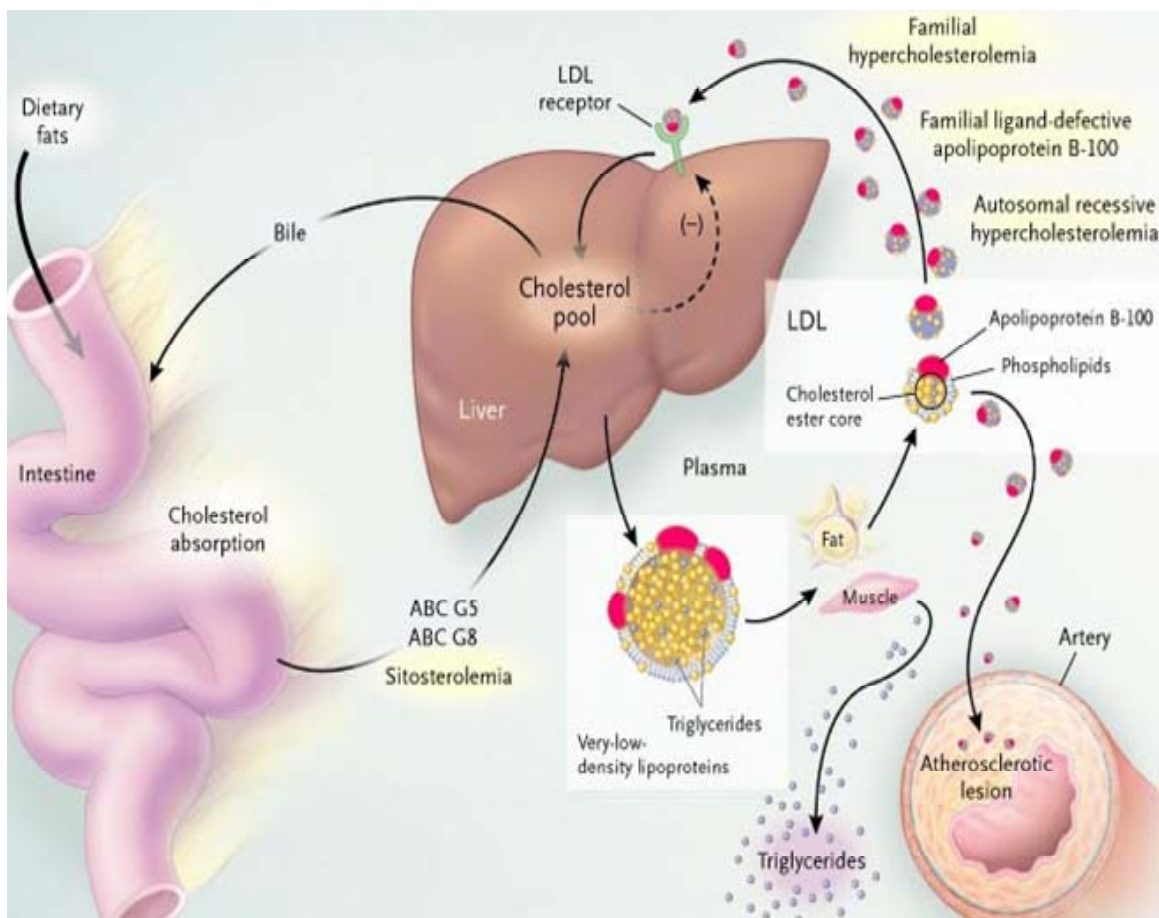
Figure 6: Components of Cholesterol Synthesis & Excretion (Goldstein & Brown, 2001; Nabel, 2003)

Innovation in detection is based on the generally applicable principle that physiological systems respond to thresholds. In other words, few, if any, reactions occur in the human body or fetus, without a critical mass or concentration of molecules. If allowed to reach the "threshold" only then the "rogue" molecules may trigger a cascade of events, which may, eventually, over time, present itself as a detectable symptom. Hence, molecular identification of the biomarkers and "rogue" molecules is vital for noninvasive detection. Tools for detection require convergence of the knowledge from identification of molecules from biomedical research with engineering based detection technologies to determine the number and concentration of the molecules, beginning at the single molecule [123] level or at the pico (10^{-12}) level, but most reliably at the nano level. A medical management plan or treatment must exist, to prevent the concentration of the molecules from reaching the threshold, where it may commence the cascade of events leading to a disease or symptom or precipitating a heart attack. In case of fetal diagnosis, the management issues may be complex but early detection of sporadic or genetic diseases of the unborn child may offer scope for medical intervention. Fool-proof identification of specific biomarkers for multi-factorial diseases such as cardiovascular disease (CVD) is complex. Without reliable specificity, the next generation nano-diagnostic tools may offer less value. Therefore, the healthcare industry must remain vigilant to combine advances in one field with another through parallel investments both in medicine and engineering.

To illustrate, let me re-visit the case of blood pressure (BP) measurement and what diagnostic information the BP data may provide if the BP is elevated, lower or normal, compared to the standard reference. In short, the BP data, alone, provides little diagnostic value unless it is analysed in conjunction with existing case history or other data. One reason for this is summarized in Table I. If a definitive diagnosis of the BP data is sought, in some patients, it will be necessary to identify which particular gene is affected.

Disease	Mutation	Molecular Mechanism	Effect on Blood Pressure
Glucocorticoid-remediable aldosteronism	Duplication of genes encoding aldosterone synthase and 11β-hydroxylase, caused by an unequal crossover	Ectopic expression of a protein with aldosterone synthase activity regulated by corticotropin; increased plasma volume	Increased
Aldosterone synthase deficiency	Mutations in the gene encoding aldosterone synthase	Defective aldosterone synthase activity; decreased plasma volume	Decreased
21-Hydroxylase deficiency	Mutations in the gene encoding 21-hydroxylase	Absence of circulating aldosterone; decreased plasma volume	Decreased
Apparent mineralocorticoid excess	Mutation in the gene encoding 11β-hydroxylase	Absence of circulating aldosterone; decreased plasma volume	Increased
Hypertension exacerbated by pregnancy	Mutation in the ligand-binding domain of the mineralocorticoid receptor	Activation of the mineralocorticoid receptor by steroids lacking 21-hydroxyl groups (probably due in part to the rise in progesterone levels during pregnancy)	Increased
Pseudohypoaldosteronism type I (autosomal dominant)	Loss-of-function mutations in mineralocorticoid receptor	Partial loss of function of the mineralocorticoid receptor, impairing salt reabsorption; improvement with age and a high-salt diet	Decreased
Liddle's syndrome	Mutations in the ENaC β or γ subunit	Deletion of the C-terminal domain of ENaC, resulting in increased ENaC activity	Increased
Pseudohypoaldosteronism type I (autosomal recessive)	Loss-of-function mutations in ENaC subunits	Impairment of ENaC subunits, which is not ameliorated by activation of the mineralocorticoid receptor by aldosterone; no improvement with age; massive salt supplementation required	Decreased
Gitelman's syndrome	Loss-of-function mutations in the sodium−chloride cotransporter of the distal convoluted tubule	Salt wasting from the distal convoluted tubule, leading to activation of the renin−angiotensin system; subsequent activation of the mineralocorticoid receptor increases ENaC activity, preserving salt homeostasis	Normal or decreased
Bartter's syndrome	Loss-of-function mutations in genes required for salt reabsorption in the thick ascending loop of Henle	Salt wasting in the thick ascending loop of Henle leads to activation of the renin−angiotensin system and the mineralocorticoid receptor, increased ENaC activity, and relative salt homeostasis	Normal or decreased

Table 1: Single Gene Diseases that Elevate or Lower Blood Pressure [124]

Sequencing of the human genome and advances in search tools and genomic technologies [125] makes it possible to extract the DNA sequence from the Human Genome Database [126] of the genes implicated in a disease (for example, genes that may elevate or lower blood pressure). Based on the DNA sequence, anti-sense RNA may be used to determine gene expression profile. By extrapolation from the DNA sequence, protein-based peptide fragments can be synthesized for use in non-invasive proteomics based microarrays, using the lab-on-a-chip wireless sensor, to detect expression levels of one or more proteins and/or their mutant variations, in body fluids, that may be involved in the etiology of the condition under investigation. Based on the gene and protein expression profile, in some cases and some diseases, the promise of gene therapy may be realized by "silencing" harmful candidate genes using RNAi [127] and

snRNA techniques, that are already under intense commercial exploration and have reported some degree of success [128] for future therapeutic applications.

This scenario, starting with a possible gene, followed by expression profiling data remotely monitored by a wireless sensor and potential for selective silencing therapy of the disease, is a part of the evolution likely to chart the future of individualized medicine and personalized healthcare. The value and impact of this approach may not qualify as a "disruptive innovation" [129] but may reflect the systemic lessons from the age of introduction of the electric dynamo, from the turn of the 20th century [130], the wisdom of which may have been ignored by other emerging technologies [131].

The pragmatic credibility of this vision garners support both from current practices, albeit in part, and information based on recent research that clearly points to the need for this vision. Current practices already use one or more of the steps outlined in this strategy, for example, the use of genomic [132] and proteomic biomarkers in diagnosis of cardiovascular diseases [133] and some forms of cancer [134]. But even more important support for this vision draws on seminal medical research [135] that has identified one single human gene, for low density lipoprotein (LDL) receptor-related protein 6 (*LRP6*), that is involved in the etiology of a specific type of cardiovascular disease, referred to as coronary artery disease (CAD). It is a leading cause of death worldwide and early detection is essential to save lives.

Coronary artery disease (CAD) is commonly caused by a constellation of risk factors called the Metabolic Syndrome, the symptoms of which include hyperlipidemia, hypertension, diabetes and in addition, causes osteoporosis. Analysis of *LRP6*, the gene identified as responsible for coronary artery disease, has uncovered a single nucleotide substitution that changes the wild-type (normal) Cytidine base to Thymidine. This single nucleotide missense mutation, located in the protein coding region (exon 9) of the human gene for low density lipoprotein (LDL) receptor-related protein 6 (LRP6), causes a single amino acid substitution, which inserts the amino acid Cysteine to replace the normal counterpart, Arginine, at codon 611 (R611C). The importance of this finding and the fundamental significance of the *LRP6* gene in human evolution is further highlighted by the extremely high degree of conservation of the protein sequence from humans to amphibians, such as frogs (*Xenopus laevis*). Among species surveyed, the amino acid Arginine (R) is conserved from frogs to humans (Table 2). Substitution of Arginine with Cysteine (R611C) creates havoc and results in coronary artery disease and accompanying diabetes, hyperlipidemia, hypertension and osteoporosis.

Human	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Chimp	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Monkey	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Mouse	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Rat	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Dog	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Cow	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Opposum	C	L	F	R	P	Q	G	L	R	C	A	C	P	I	G	F	E	L
Chicken	C	L	Y	R	P	Q	G	L	R	C	A	C	P	I	G	L	E	L
Frogs	C	L	F	R	P	Q	G	P	R	C	A	C	P	I	G	L	E	L

Table 2: Conserved amino acid Arginine (R) is substituted in *LRP6* gene & causes heart disease

Genomic technologies can help identify R611C mutation in at-risk populations even in the fetal state since this *LRP6* is transmitted as an autosomal dominant trait. Life long management plan for inherited genetic diseases, for example, phenylketonuria, is common. Early detection of individuals homozygous for R611C may follow a recommended life style and that may enable them to enjoy normal life expectancy. The evolutionary conservation of *LRP6* gene and its protein product indicates a fundamental role of this protein in physiology. Indeed, LRP6 is involved in cellular signaling pathways, disruption of which leads to a plethora of problems. Proteins and other molecules, referred to as transcription factors [136], are often conserved and fundamental to gene expression [137] from bacteria to humans. Transcription factors can alter gene expression positively and negatively [138] or may serve as secondary or tertiary targets [139]. Early detection of non-fatal mutations in transcription factors are warranted because they may also cause profound physiological disturbances and present multiple symptoms, related in scope to mutation in *LRP6*.

While the case for early detection of genetic diseases needs little emphasis, the need for early detection of the bulk of sporadic cases, such as, type II diabetes mellitus and several other disease states deserves emphasis. Globalization has also created a need for remote monitoring. To make globalization work better for the world economy [140] it is imperative to contain infectious diseases by determining the risk and at-risk factors at the *origin* rather than at an immigration check-point of a country. The lightning spread of SARS, from its origin in HongKong to Toronto, in a few days, highlights the need for remote monitoring tools and the vulnerability of current healthcare system (in most nations) that is ill-equipped for global challenges and may actually *aid* an epidemic or pandemic.

Epidemics, however, are no longer limited to only infectious diseases. Type II diabetes may reach nearly epidemic proportions in many nations. It is alarming in some countries, where, despite a small population [141] a high number of sporadic cases of diabetes are documented. In addition, an equally high number of projected at-risk population are acknowledged but the latter estimates exclude the segment of population projected to be defined as clinically obese. That can potentially increase the at-risk numbers for sporadic type II diabetes but remains unaccounted by the system. Individuals with other anomalies may also have diabetes, as pointed out in course of the discussion on *LRP6* where heart disease and diabetes can occur simultaneously. Recent evidence suggests that in individuals without any genetic predisposition, there may be a direct effect of elevated cholesterol level on reducing insulin production by the β (beta) cells in the pancreas [142]. This increases the risk of diabetes for obese as well as non-obese individuals who have elevated levels of cholesterol, without genetic predisposition.

Diagnosed diabetics often monitor their blood glucose levels using over the counter kits but its use in preventative healthcare remains dubious. For diabetics, the frequency of testing using kits is weekly or daily but expert interpretation and advice may be far in between. Let us assume that a weekly out-patient visit to the clinic for blood glucose test and insulin therapy costs the healthcare service an average of $25 in direct cost and costs the economy another $25 in indirect costs, such as, the cost of time spent by patient, cost of travel and decrease in productivity due to time taken off work by patient. If only 1% of the population require weekly attention (serious diabetics), then for a hypothetical nation with a population of 5 million, there will be 50,000 diabetics requiring this attention. For 50 visits a year at $50 a visit, the attention to 50,000 diabetics for simple monitoring of blood glucose and administration of insulin, will cost the nation $125 million per year. The focus on those who need it the most, aggravates the unattended conditions in other diabetics and at-risk population, driving them to seek acute-care services or catapults

them to the $50 category. However, a far greater concern is the need for ***in-patient*** services if some of the diabetic patients need hospitalization. Can the national healthcare system respond adequately [**143**] if only 1% of the 50,000 diabetics (that is, 1% of the 1% documented diabetics in the population) need hospital beds? For example, in Ireland, overall, there are 2.9 beds available per 1,000 people [**144**].

Preventative remote monitoring can alter this vicious cycle of crisis, reduce cost and improve actual care.

Apart from individuals who are obese or juvenile diabetics or those with history of genetic predisposition to early onset diabetes, the definition of "early stage" in monitoring is rather vague for sporadic diabetes. There is little scientific rationale either to include or to exclude young adults and individuals with dynamic vivacity in the prime of their life and in their 40's or even younger. Hence, effective monitoring of blood glucose that is not shunned by the otherwise healthy population may require a ***lifestyle approach*** that offers a product and service that is easy to use, low risk, low maintenance, socially acceptable, offers robust value, safe and medically effective. Since the adoption of this device may be voluntary, it may be less attractive if the monitor is a visible wearable [**145**] or a "thing" that an individual must "remember" to do. Thus, nanotechnology based [**146**] monitoring tools that may function as "always-on" wireless nano-sensors and may be hidden under the epidermis in locations that are not in plain sight even in course of intimate interactions, may make blood glucose monitoring of general population an attractive *modus operandi* for early risk identification and prevention of diabetes as well as associated morbidity, such as diabetic glaucoma, that can lead to partial or complete blindness in severe diabetics or juvenile diabetics, if left untreated.

Early detection of diabetes as a function of monitoring blood glucose concentration benefits from a plethora of glucose sensors developed over the past 25 years but challenges still exist. A key advantage in the development of a miniaturized or nanoscale device that can quickly and reliably monitor glucose *in vivo*, is based on the fact that the level of blood glucose detection does *not* require nano level detection. The benefit of a nano device or nano sensor is to make the monitoring tool virtually unobtrusive to the user. The normal clinical range for blood glucose is in the millimolar (mM) range between 3.5mM and 6.1mM but abnormal glucose levels may reach 20mM. This concentration range can be easily monitored using electrochemical reactions. What is critical for diabetes is a tool that does not deter early stage frequent vigilance about the changes in blood glucose levels, also measured in mg (milligrams) per dl (deciliter) of blood. Alterations may signal the ability or inability to maintain the standard equilibrium

concentration of glucose (120 mg / dl or 3.5 – 6.1 mM). For example, if the blood glucose concentration in an individual takes longer to return to normal after meals, then it may signal germinating problems with glucose clearance and/or tolerance in the individual.

The innovation required to develop a wireless blood glucose nano-sensor that is capable of subcutaneous monitoring of blood glucose and transmission of the data to a wireless node, may be simple and at hand. The core components are a nano-sensor [147] capable of detecting blood glucose concentration *in vivo* and a nano-radio [148] that can transmit (?) the data. The combination is illustrated in Figure 7.
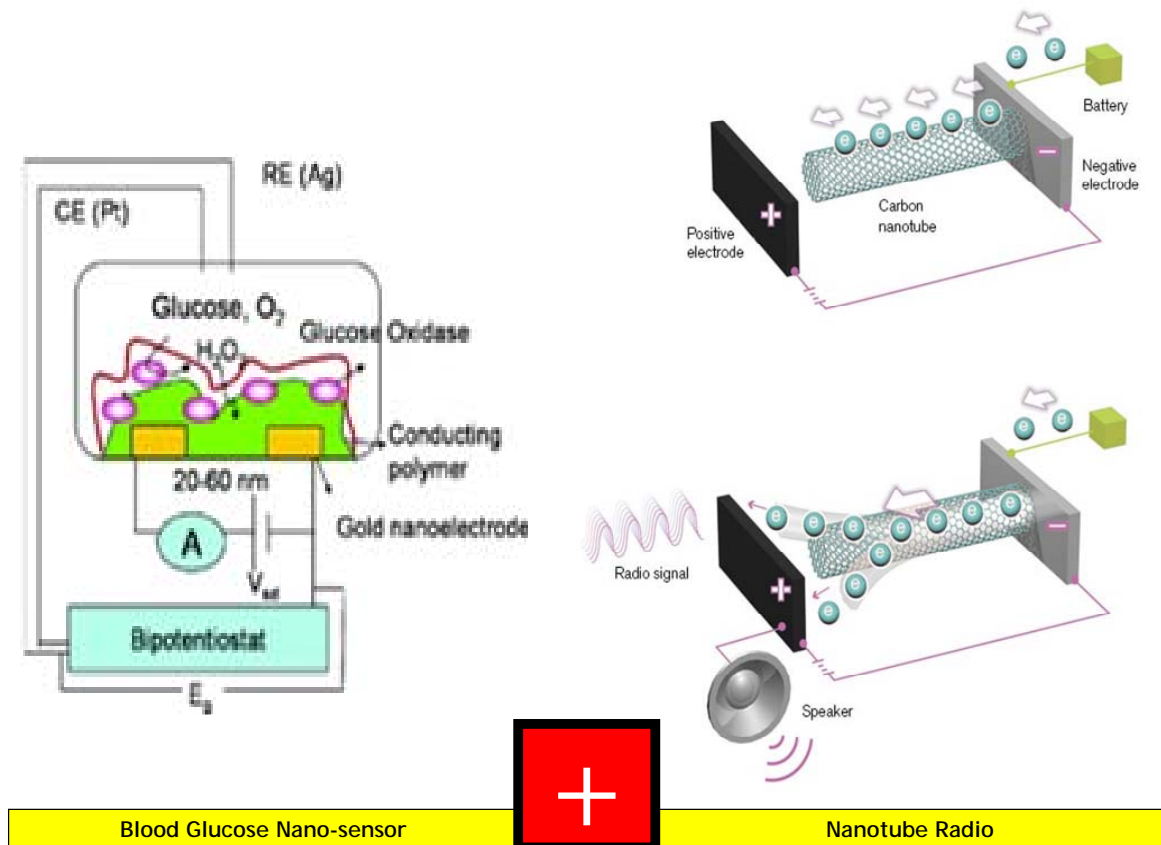
Figure 7: Blood glucose monitoring and wireless data transmission 24.7.365

The open questions presented by this innovative potential may be divided into two broad categories: data acquisition and data transmission. The issues are as follows:

(01) Glucose sensor data transmission by the nanotube radio illustrated in Figure 7 and other similar [149] devices is not proven because they are constructed as receivers, not data transmitters. But, in general, single wall nanotubes (SWNT) are like single-mode fiber for electrons (Figure 7) and hence have data properties that were made to act as a receiver (Figure 7) for the nano-radio but may be altered to transmit the acquired data from the glucose sensor.

(02) Functional co-fabrication or simply co-locating or 'housing' glucose nano-sensor and data transmitter on a non-allergenic matrix or platform suitable for use as a subcutaneous implant

(03) Optimizing signal to noise ratio

(04) Interference minimized nano communication link to wireless sensor node

(05) Physical locations for safe subcutaneous insertion per customer preference

(06) Procedure for safe extraction of sensor device with minimal discomfort

(07) Fool-proof immobilization of implant after implant

(08) Containing degradation or breakage of components within the 'housing' of the nano-device

(09) Customer's ability to 'forget' about sensor implant

(10) Customer control (Agent based web tool) over function of the device

(11) Customer control over data transmission or modulating the frequency of monitoring

(12) Low maintenance of sensor and transmitter

(13) Battery life of transmitter

(14) Explore use of electrolyte gradient of the body or energy from movement to power data transmission

The responses to the open questions are beyond the scope of this paper but the different mechanisms of detection by sensors are important to review, briefly, because wireless nano-communication must be an integral part of the sensor or sensor combination in order to reliably transmit the data outside the body.

The glucose sensor in Figure 7 detects glucose based on principles of electrochemistry. The assumption is that the sensor will perform *in vivo* as well as it has performed in body fluids tested *in vitro*. Specific detection of glucose is mediated by glucose oxidase, GOx, an enzyme (hollow circles with pink borders, Figure 7) that is immobilized onto PANI-PAA, a conducting polymer (green area, Figure 7) made up of polyaniline (PANI) polymerized with PAA (poly{acrylic acid}). Upon exposure to glucose, GOx, with the help of a natural co-enzyme, flavin adenine dinucleotide (FAD), catalyzes the oxidation of glucose to gluconolactone and becomes reduced, {GOx(FADH$_2$)}, Step 1. The reduced GOx form, {GOx(FADH$_2$)}, is regenerated via re-oxidization by oxygen (O$_2$) in solution to GOx(FAD) and produces hydrogen peroxide (H$_2$O$_2$), Step 2. Polyaniline, which exists in its reduced (red) state (PANI$_{red}$), is oxidized (ox) by H$_2$O$_2$ to PANI$_{ox}$ and triggers an increase in polyaniline conductivity (Step 3) due to the sensitive dependence of polyaniline conductivity on its redox state. This change of conductivity is data, indicating glucose detection.

Step 1: **Glucose + GOx(FAD) $\rightarrow$ gluconolactone + GOx(FADH$_2$)**

Step 2: **GOx(FADH$_2$) + O$_2$ $\rightarrow$ GOx(FAD) + H$_2$O$_2$**

Step 3: **H$_2$O$_2$ + PANI$_{red}$ $\rightarrow$ H$_2$O + PANI$_{ox}$ (increase in conductivity)**
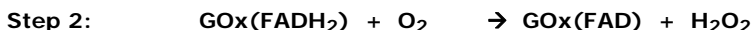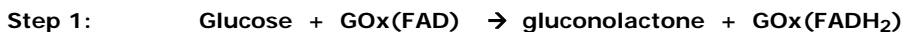
Other types of construction use carbon nanotubes (CNT) but may still use the electrochemical principles for detection of glucose on a CNT scaffold (instead of PANI-PAA, as shown in Figure 7). Nano-wires [150] represent one such type of construction. Nano-wire based glucose biosensors [151] use carbon nanotube (CNT) nanoelectrode ensembles (NEE) for selective detection of glucose based on the high electro-catalytic effect and fast electron-transfer rate of carbon nanotubes but employ the same electrochemical mechanism described above. GOx, glucose oxidase is immobilized on CNT-NEE, instead of PANI-PAA, via carbodiimide chemistry by forming amide linkages between the amine (NH$_2$) residues and carboxylic acid (COOH) groups of the enzyme, GOx, covalently linked to the exposed tips of single carbon nanotubes (CNT), illustrated as perpendicular black bars in Figure 8 (center). Numbers of CNT on a CNT-NEE are in the millions, with each nanoelectrode being less than 100 nm in diameter, thereby, increasing sensitivity

of the sensor (by analogy, the speed of a processor, for example, Intel Pentium, is a function of the number of micro-processor circuits etched on the chip). The catalytic reduction of hydrogen peroxide liberated from the enzymatic reaction of glucose oxidase covalently immobilized on the CNT-NEE, in the presence of glucose and oxygen, leads to the **selective** detection of glucose. CNT are excellent electrochemical transducers and each CNT serves as a nano-electrode that detects the change in current (conductivity) when glucose reacts with GOx linked CNT (the coupling drives the specificity of glucose detection) in a CNT-NEE sensor. The sensor effectively performs a selective electrochemical analysis of glucose in the presence of interference from common molecules, for example, acetaminophen {AA}, uric acid {UA} and ascorbic acid {AC}, shown in Figure 8 (top panel). But most important, the sensor is sensitive to increments of glucose. Detecting fluctuations in concentration of blood glucose is the key to early detection in diabetes (Figure 8, lower panel and inset).
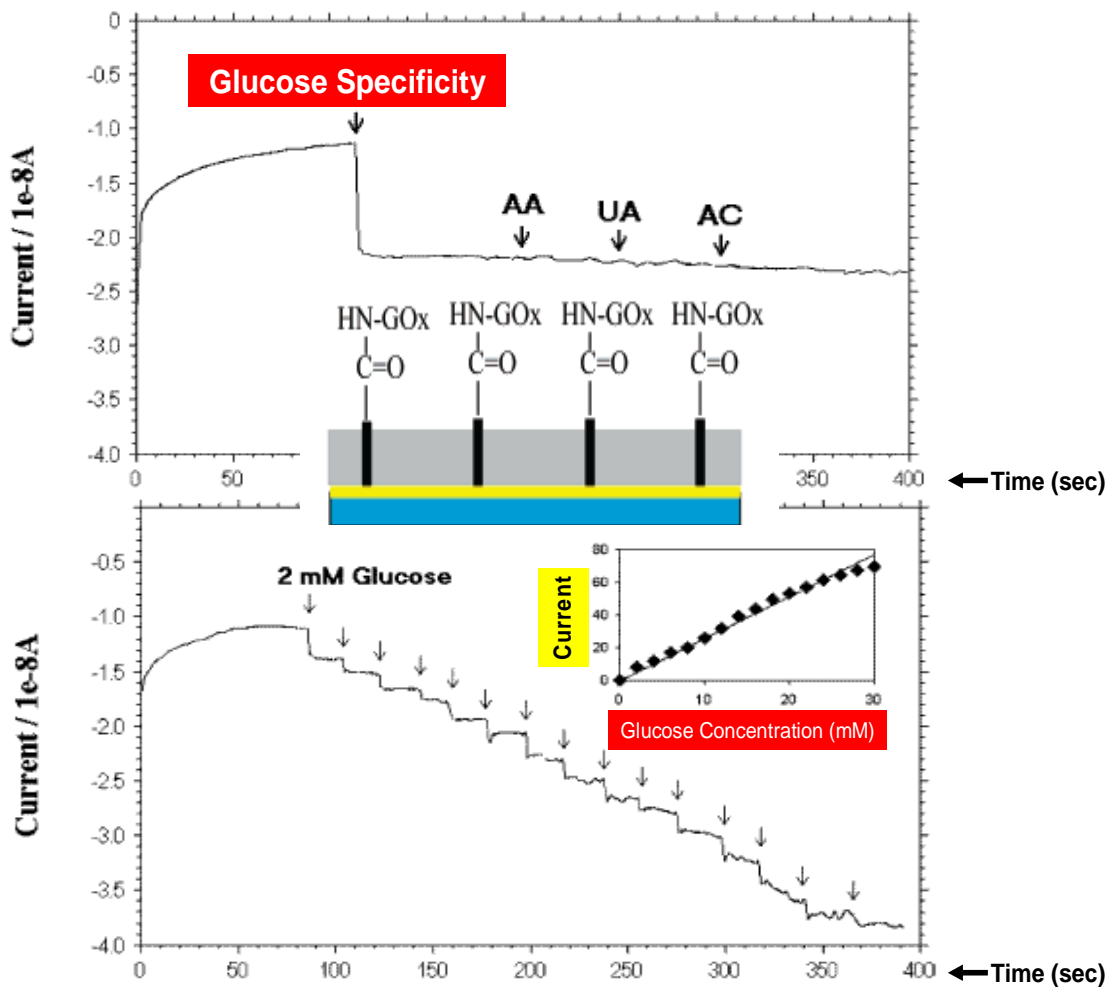
Figure 8: Nano-wire glucose sensor shows glucose specificity and sensitivity to concentration

It is relevant to note that nano-wire sensors that detect changes in chemical potential, accompanying a target or analyte binding event, such as DNA or RNA hybridization, peptide interactions or oxidation-reduction in electrochemical reactions, can act as a field effect gate upon the nano-wire, thereby changing its conductance. This is similar, in principle, to how a field-effect transistor (FET) works [152]. Today, FETs are low cost and in extensive use in environmental and agricultural monitoring. Advances in technology has made the expensive electronic marvel of a "transistor radio" of the 1950's only suitable for infant's toys mass manufactured in China and sold in discount chains. The transistor radio has evolved to dirt cheap FETs now used in animal farms to alert owners that the stench from the ammonia-rich waste from animal excreta in the holding tanks needs attention. The expensive transistor of yesterday is now a low cost (or no cost) component, today, that delivers significant value for environmental monitoring. It benefits the meat industry at such a negligible cost that it has only increased productivity of the meat industry and concomitant increase in global consumption. The evidence for the latter is gleaned from the beef and chicken consumption data from the US and EU that exceeded 120 kg per person per year (330 grams / day) compared to 16 kg per person per year (44 grams / day) in China and India, combined [153].

Knowledge from research and applications of FET are available from archives that may date back to the initial discovery of transistors [154], nearly 70 years ago. Development of nano-wire nano-sensors and nano-communication may benefit from the experience and wisdom of the FET pioneers.

The principle of FET indeed may be crucial for nano-communication for wireless transmission of data from the *in vivo* sensor to a senor communication link or node outside the body that can connect to the internet. The characteristic of a carbon nanotube to act as fiber that can transport electrons is under scrutiny in order to use the material for high speed data transmission in a variety of ways, that includes the emerging field of plasmonics [155] that studies interactions between light and nanoscale particles and structures. Remote monitoring *in vivo* that may take advantage of light-emitting luciferase [156] enzyme-linked sensors, by immobilizing luciferase (on PANI-PAA matrix or) **preferably** on CNT-NEE type scaffolds, may find it useful to exploit the potential of nanoscale antennae that converts light into broadband electrical signals capable of carrying approximately one million times more data than existing systems [157].

The illustration in Figure 7 is simple to understand and conveys the "image" of the components necessary to drive the convergence of *in vivo* detection and transmission of data. But, caution is necessary to extrapolate the application of the components illustrated in Figure 7. Although it may be ideal for visualizing the concept, the components illustrated are not proven or guaranteed to be the combination of

choice that could drive the development of an *in vivo* nano-device that is equally reliable as a detection tool and a nano-communication tool, for reasons that I shall explain in the next few paragraphs. But of course that argument holds for any innovation. We shall not know the outcome unless we attempt to create the device if there is even "just enough" reason that the innovation may bear fruit. Reasonably, one issue in the glucose *nano-junction* sensor is that it does not use *nano-materials*, that is, in this case, carbon nanotubes, in its construction. Nano-wire glucose biosensors use carbon nanotubes (CNT) as the nano-electrode, as shown in the CNT-NEE sensor illustrated in Figure 8 (center). This may be an issue in terms of the ability to transmit the data out of the body.

If the nanotube radio *receiver* illustrated in Figure 7 can be modified or designed as an *in vivo transmitter* and if it can successfully detect the data emerging as the change in conductivity between the two states of PANI (PANI reduced versus PANI oxidized, as shown in Step 3) from the non-CNT glucose *nano-junction* sensor illustrated in Figure 7, *then*, the nano-device that may be produced, by the combination illustrated in Figure 7, for wireless *in vivo* glucose monitoring.

The preference for carbon nanotube based sensors like CNT-NEE (Figure 8, center) is linked to the central need to transmit the data from the *in vivo* sensor and the potential for using individual nanotubes within CNT networks to carry information. Innovation in nano-communication using CNT communication network [158] is likely to become a core competency necessary for the future of nano-device use in healthcare, in general. It is in this context, that the principle of field effect transistors (FET) springs back into action. Current technology utilizes an entire CNT network as semiconducting material to construct a single FET. Several FET are required to build traditional or legacy network equipment. The result is that there are many nano-scale networks embedded within each device (FET) that might be otherwise more effectively utilized for communication. In other words, the CNT network *itself* is the communication media and individual carbon nanotubes (CNT) are the links. But, individual CNT and tube junctions (forming nodes) do not have the equivalent *processing capability* of a traditional network link and network node. To compensate for this, the system needs to leverage large numbers of carbon nanotubes. The illustration in Figure 8 (center) shows individual CNT linked to GOx (black bars) but *millions* of CNT (black bards) make up an ensemble (CNT-NEE). The latter is precisely what is necessary for the single wall carbon nanotube communication network (NanoCom) of the future. However, NanoCom may not function according to the traditional architecture of data communication layers [159]. Comparison of legacy communication and NanoCom highlights the changes necessary, as shown in Table 3.

Basic Network Components	Traditional Networking	Nano-scale Networking
Protocol	Processors	Gate Control
State	Node Memory	Semiconducting Tube Resistance
Network	Links	Nanotubes

**Table 3: NanoCom requires modification of current networking concepts (Bush & Li, 2006)**

At the bottom level (least sophisticated level), communication links may be between hosts and routers in a communication network or they may be carbon nanotubes (CNT) overlapping at points that will be identified as nodes. A network functions by changing state. Data must either flow or be switched or routed through nodes. State may be implemented as a routing table on a router or an electromagnet field controlling the resistance within a specific area of a carbon nanotube network. Finally, a mechanism needs to be in place to control state (ascending level of sophistication, Table 3), be it a routing algorithm or FET gate voltages applied to a carbon nanotube network. The traditional networking protocol stack is inverted in this approach because, rather than the network layer being logically positioned above the physical and link layers, as in the standard OSI model [160], the CNT network and routing of information is an integral part of the physical layer.

Data transmission in a CNT network occurs via modulated current flow (changes in conductance) through the CNT network guided towards specific nano-destination addresses. The addresses identify spatially distinct areas of the CNT network that may be made up of nanosensor arrays. Since gate control is used to induce routes through the CNT network, nano-addresses are directly mapped to combinations of gates to be turned on that induce a path from a source to a destination. Is the "combination of gates" in any way analogous to the network, subnet, host type of partitions that specify a 32-bit IPv4 address of the

type 151.193.204.72 or the 128-bit IPv6 format 21DA : 00D3 : 0000 : 2F3B : 02AA : 00FF : FE28 : 9C5A (or equivalent 21DA : D3 : 0 : 2F3B : 2AA : FF : FE28 : 9C5A with leading zero suppression)?

Does nano-addressing require an entirely new scheme for unique identification? Is unique identification necessary at the level of individual nano-addresses? If necessary, is a relativistic identification of information [161] necessary? Is "source" and "destination" comparable to client-server architecture?

These and several other open questions are likely to emerge. Figure 9 illustrates a conceptual network view of the CNT infrastructure. Superimposed on NanoCom are some of the medical benefits that makes carbon nanotube based sensors and data communication a powerful ally for healthcare improvements.
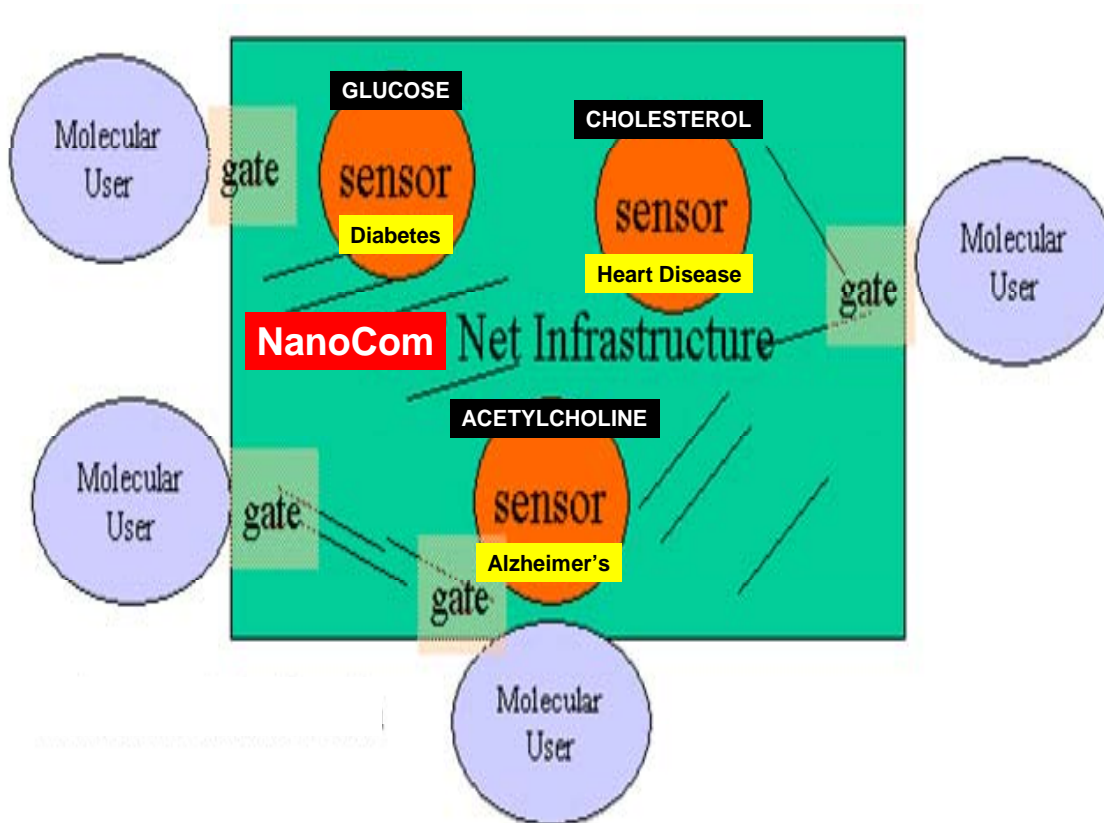
Figure 9: NanoCom transmits data for multiple biomarkers from *in vivo* sensor nano-array

Diabetes is not the only disease that merits prevention and monitoring. For early detection and monitoring, several other diseases qualify prominently. Sensor nano-arrays may be one answer for a multi-functional detector, as conceptualized in Figure 10. Sensors constructed from nanotubes change their resistance based on the amount and specificity of the material or biomarker detected (sensed). Thus, the act of sensing may change the routing through the NanoCom network. In other words, in a staggered approach the duty cycle and/or the sleep time [162] of the different CNT nanosensors can be regulated to allow any one sensor to function in a specified interval and detect or sense its specific analyte (glucose, cholesterol or acetylcholine, Figure 9). The change in the properties of the carbon nanotubes, when the act of sensing is in progress, opens the appropriate 'gate' and when a gate is turned on, the nanotubes within the gate area, become conducting. Then, the data acquired for that specific sensor is transmitted to an external node. For complex diseases, where multiple pieces of data and vital signs may be necessary to make an informed decision, either by humans or initially by an AI based intelligent analytical system (AGRMIA, Figure 2), properly choosing the sequence of sensor, hence gates, to turn on, changes the current flow to the edges of NanoCom, the CNT network. The latter effectively creates a controlled NanoCom, which may act as or provide weights in a neural network for AGRMIA type system requiring a collection of different biomarker data, to determine the **relative** impact or relationships or values of variables that may be co-integrated [163], which, if taken *together*, may better reflect the state of the patient and the status of the disease. The Metabolic Syndrome caused by the mutation in the *LRP6* gene, may be an example of a multi-factorial disease where multiple conditions are affected and may require simultaneous monitoring.

Although this paper, thus far, may have synthesized a number of promising practical ideas, far better and innovative ideas and concepts about products and services, than the ones mentioned here, have perished. Rarely acknowledged is the observation that no matter how good an idea may be, it may only shine in obscurity unless there is a strategic plan that charts an appropriate use and adoption path in context of other complementary technologies and social awareness of its value. A common example is the introduction of the first hand-held "Newton" the personal digital assistant (PDA) from Apple that few may recall. Apple only sold 140,000 Newton PDAs at its peak in 1993-1994 and soon discontinued production. A few years later, 3Com introduced the Palm Pilot PDA with features that were even primitive to Apple's Newton but with the option of internet access. Today, it may be hard find anyone in the industrial world and professionals in the developing world who do not have a PDA, of some form or the other. The "social awareness" of the value of PDA accelerated with the penetration of the internet. Newton, RIP, was slightly ahead of its time.

Calls to contain the unbridled cost of healthcare are demanding exploration of tools and technologies. The need for wireless remote monitoring and use of nano-bio sensors in healthcare is as vital as desalination projects, carbon sequestering, metabolic engineering, clean water and clean air. Hence, innovative tools and technologies must also outline a strategic path for their integration and potential for adoption by healthcare systems without expecting a complete overhaul of the existing system, anytime soon.

The overall strategy for use of wireless remote monitoring tools and the manner in which it may function in the landscape of healthcare cost reduction (Figure 2) is illustrated in Figure 10. The time saved by attending to the 2 individuals identified in Figure 10 instead of out-patient visits by 7 individuals (Figure 10) saves cost of service and supplies, and enables healthcare professionals to devote necessary time to those who need the attention, hence, improving the quality (QoS) of health *care*.
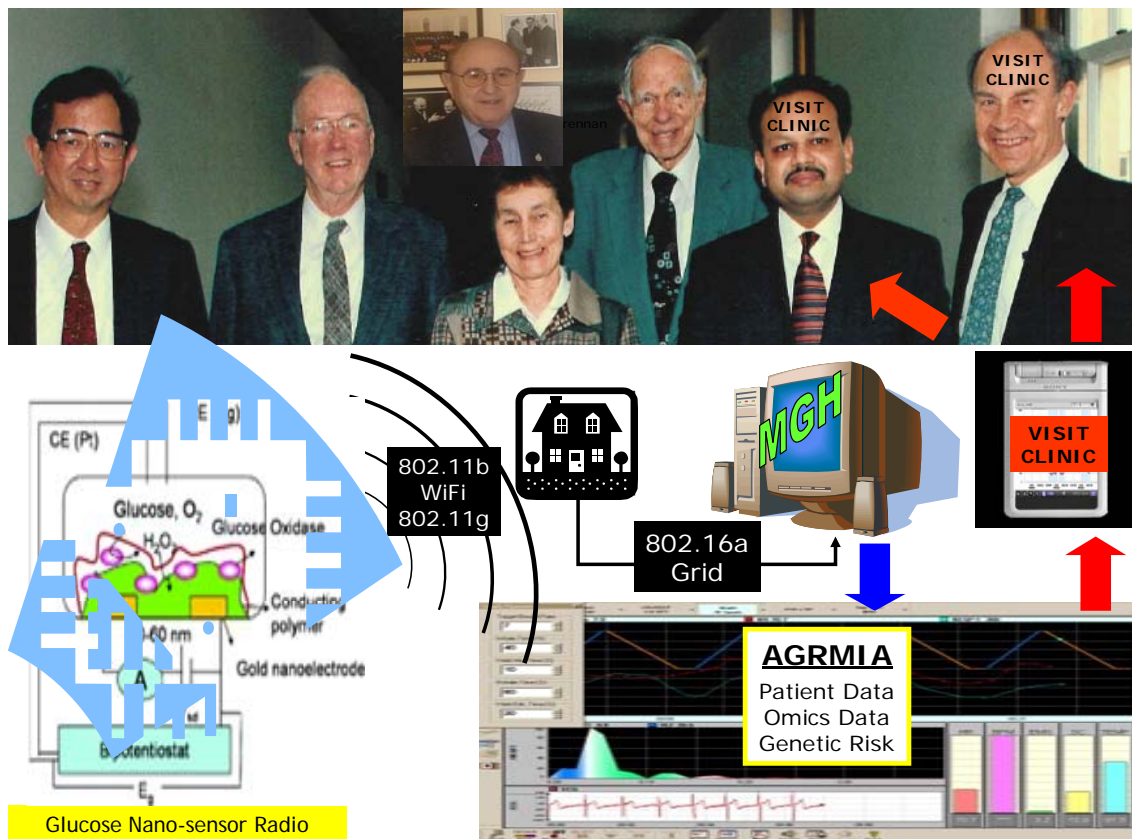
Figure 10: Improving Healthcare from the home to the hospital: "Sense, *then* Respond"

The normal clinical concentration of glucose in blood is in the millimolar range and that precludes the need for nano level detection. However, early detection of other diseases may indeed be far more effective if detection was possible at the nano level of proteins, peptides, molecules or **degraded** macromolecules that may hold clues to problems in their embryonic stages. The task of medical research is to identify these markers and the task of the technical experts is to find ways to identify these markers through remote sensing tools. Differential profiling of gene and protein expression between normal and disease states may be helpful to identify biomarkers that are only expressed in disease states. The amounts of such disease dependent biomarkers may benefit from pico or nano level detection and offer "true" early detection.

Data and detection as a component of the systems approach to future healthcare requires medical science and engineering technology to create tools linked to systems that may be purchased, as ubiquitous generic plug-n-play commodities, from the local pharmacy or convenience store in a gas station or corner grocery store. Consider the revolutionary discovery of transistors that produced field effect transistors (FET). The field has been shaped by evolutionary market forces over the years and FET are now used as **low-cost commodities** in the design of environmental and agricultural monitoring. It is **this** trend that Figure 7 illustrates, in concept. The value they will deliver through specificity and sensitivity is illustrated in Figure 8. The strategy for integration and adoption pathway is illustrated in Figure 10, which includes one of the key "behind the scene" drivers that may materialise as modular analytical engines of the AGRMIA type collection of resources, illustrated in Figure 2, connected on global grids. Taken together, remote monitoring by internal wireless nano-sensors or external sensors (as fashion rings, bracelets, wrist watches) will co-evolve and diffuse as a lifestyle approach in healthcare, not because individuals are sick but because they prefer to stay healthy. The healthcare industry may benefit from business advice in order to take advantage of **time compression**. In other words, the **time to market** from idea (Figure 7) to adoption (Figure 10) may be shorter than the decades between the discovery of transistors and the use of FET as a dirt cheap *commodity* for agricultural and environmental monitoring.

This is the "*writing on the wall*" for what is in store for remote monitoring by wireless nanosensors, the nano-butlers, that can deliver value at a reduced cost, for micro-payments, in local and global healthcare. Ignoring the suggestions in this and other reviews or the failure to accelerate the necessary convergence to create the suggested healthcare services as well as support research [164] may lead to chaos.

Healthcare imbalances will continue to proliferate in the US and severe consequences are also predicted for EU nations, particularly Ireland. Projected rise in age-related government spending as a share of GDP of Ireland, over the ext 40 years, is among the highest in the euro zone [165]. In the absence of reforms in Ireland and adequate investments, the advances in innovative convergence suggested here may be sluggish, at best. But, cost of healthcare in Ireland, which is approaching €3000 per capita, may continue to increase (see reference 53). Rising public debt in Ireland may force spending cuts with a concomitant decrease in the quality of life for those who need healthcare services. Cost containment in healthcare services may grossly reduce preventative measures, selective or elective procedures, palliative care and all non-emergency services. Individualized medicine and personalized healthcare will be a matter of fiction and A&E type acute-care services may be the healthcare skeleton. Enterprise, academia and government can prevent this state of affairs.

4.0 INNOVATION SPACE: Molecular Semantics

The proposal of molecular semantics, whether right or wrong, does not impact the implementation of nano-butlers. Introducing the concept of molecular semantics as an independent paper may have been prudent but the preliminary idea merits inclusion in this paper to indicate the importance of structure in medical science. Current systems, such as EMRS and AGRMIA may be, in general, incapable to deal with structures unless dedicated programs are used.

Molecular semantics is about structure recognition.

Classical semantics includes descriptive ontologies and extracting word relationships that form bulk of the thinking [166] prevalent presently to move from the syntactic to the semantic web. Molecular semantics may not be necessary for general usage but may aid special analytical applications in the future to uniquely identify molecular or chemical structures or units of structures or epitopes, in a manner that may have some similarity with the concept of digital semantics (see reference 40). Unique identification of structures may enable diverse systems to compare structures in a catalogue or database with those that may be identified in some disease states, or query, if an identified structure has any known homologies or close similarities to one or more parts of chemical or biological molecules. The significance of partial

structures and segments of structures or epitopes in healthcare diagnostics may be better appreciated from the discussion, later in this section, on autoimmune diseases and molecular mimicry [167].

To deliver value in healthcare, part of the solution calls for analytical tools to extract information from data. Healthcare presents three types of data that may need to work together, in some cases. They are:

(1) Numerical data in EMRS systems and AGRMIA platforms may be fed directly to the analytical engines.

(2) Syntax from patient history and physician "notes" still on paper are likely to create syntax versus semantics nightmare if transcription is necessary to create electronic medical records. The syntactic web of today also plagues the business world. The semantic web movement and organic growth of ontological frameworks contributed by experts from various disciplines are continuing their valiant efforts to enable computer systems to "understand" and extract meaning from syntax. In this context, I have proposed a parallel approach to explore semantic and ontological frameworks using an IPv6 type unique identification scheme to enumerate data, information and decision in a relativistic approach (see reference 40).

(3) Molecular patterns may be partially novel and especially relevant for healthcare diagnostics.

This section on molecular semantics is similar yet distinct from "digital semantics" proposed earlier (see reference 40) but both share the concept of unique identification to enable global systems interoperability without ambiguity of identification or errors due to ambiguity in ontological frameworks, that may be incomplete. Both proposals, however, are also likely to be incomplete.

The current proposal on molecular semantics addresses the third type of healthcare relevant data structure, that is, molecular patterns or molecular structures. Organic chemistry and biomedical sciences place a great deal of emphasis on patterns and structures. Hence, it may be worthwhile to dare to forward this new idea of how to enable computer systems to recognize patterns and structures through the use of agreed (?) units of molecular structure, that form parts of macromolecules. This proposal freely borrows ideas from seminal works of great scholars but with rudimentary understanding of their depth and without any guilt. In addition to a few building blocks of linguistic theory [168], I have also stretched the outlines of semantic theory and cognition [169], perhaps to an unnatural and unreasonable extent.

Cognition as relates to **structure** in natural language is mapped to the units of molecular **structure** in biological macromolecules. I have extrapolated the ideas and elements of the linguistic system to **fit** molecular semantics in a way that proposes the use of molecular units of structures (of macromolecules, such as, proteins) as "agreed lexicon" to catalyse recognition and understanding of these **structures** between diverse systems to aid systems interoperability. However, in my biased view, elements of the linguistic system (Figure 11) seem to resonate with the proposal of molecular semantics. But, I shall be the first to recognize that this convergence, however attractive, may not be right, in the form proposed, and admit that it may be in error, if it is.
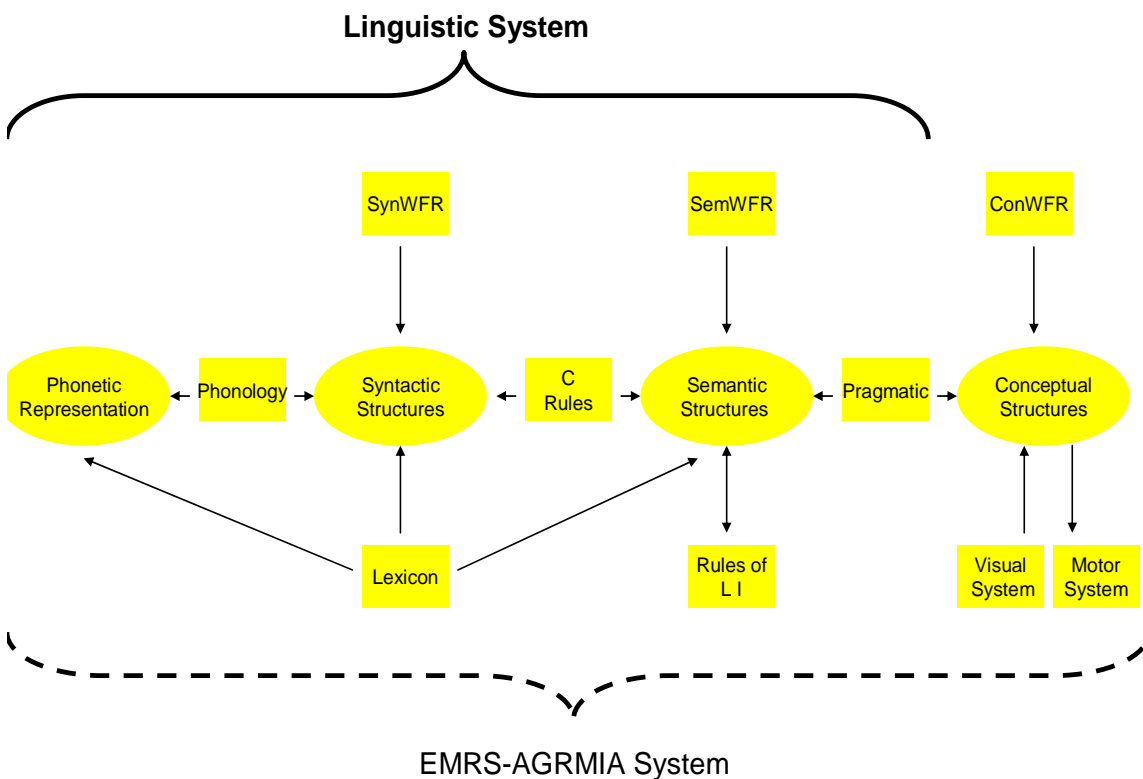
SynWFR	→	Syntactic Well Formedness Rules (WFRs)
SemWFR	→	Semantic Well Formedness Rules (WFRs)
ConWFR	→	Conceptual Well Formedness Rules (WFRs)
C Rules	→	Correspondence Rules
Rules of L I	→	Rules of Linguistic Inference

Figure 11: Proposed Molecular Semantics extrapolates concepts from the Linguistic System

There may be other ways but the concept of molecular semantics may be yet another tool to explore this scenario: mass spectroscopic (MS) analysis of serum from a patient with unidentified type of fever has identified a high concentration of a short peptide with some ambiguity about its sequence but it appears that the peptide may be part of a common protein, myelin. First, a general practitioner may rarely send a serum sample for mass spec (MS) analysis. Second, if the MS data was uploaded and an AGRMIA type system was available, is there a tool to compare the MS signature from this patient (MSpat) with other MS data in a database? The data (MSpat) entry point in the Linguistic System is the Conceptual Structure, the EMRS part of the EMRS-AGRMIA system, in this context. The computational resources that may be needed to perform the comparative search, one MS data at a time in the database, may make this approach untenable. If there was a catalogue of unusual MS signatures (MScat) in the form of a (data) dictionary, then, perhaps, it may be feasible to perform this search and determine if a match or close relationship exists between MSpat and a pattern in MScat.

In the Linguistic System the dictionary equivalent may be the Lexicon (Figure 11). Is it really necessary to bring the Lexicon into this discussion? The MS data and accompanying explanatory notes could also exist in a relational database and that may suffice for this exploration. The introduction of the Lexicon in this scheme may seem, initially, on shaky grounds but following the model of the Linguistic System, it reasons that if the MS data catalogue (MScat) did exist in a Lexicon equivalent, it may also have links to Syntactic Structure and Semantic Structure (Figure 11). The wide variation in syntax needs no extra justification. Hence, the difficulty to match Syntactic Structures with respect to the Lexicon even if it contained a match to MSpat may not be unexpected. But the data (MSpat) could point to descriptions that may be more specific in the Semantic Structures. It may identify MSpat as belonging to neural proteins (myelin **is a** neural protein). Once the MSpat data matched to data from the Lexicon (MScat) points to neural proteins in the Semantic Structure, the Correspondence Rules could point back to the Syntactic Structures and identify one or more descriptions of neural proteins that may offer matching segments to MSpat. The real finding is however the match between MSpat and the potential link to myelin that may happen if an extensive MScat was matched by protein sequence and classified in the Semantic Structure. It is quite possible that an equivalent set of rules may work in place of the Rules of Linguistic Inference to relate the MS data with MSpat and point out the class of neural proteins and the ontological relationship: myelin **is a** neural protein. The Lexicon (data) and Rules of Linguistic Inference (rules) may be working in concert to indicate the Semantic Structure and another set of rules, Correspondence Rules, could point to syntax or descriptions in the Syntactic Structure that builds on the identified Semantic Structure. The extent of the classification, precision, granularity and other factors of the Semantic and Syntactic Structures could be

determined by rules, the equivalent in the Linguistic System are the Semantic and Syntactic Well Formedness Rules (SemWFR and SynWFR, Figure 11), respectively. The presentation of the data may find some far fetched relatedness to the Phonetic Representation and Phonology domains in EMRS-AGRMIA, when visualization of the data is important.

Thus far, I have not addressed molecular semantics but attempted to explore how the Linguistic System seems may offer a parallel in data analysis. The latter is expected because linguistics and artificial intelligence share common elements such as cognition, semantics and ontology. The idea of molecular semantics was camouflaged in the discussion because the data (MSpat) attempted to find a match to an existing equivalence relationship to a description of relevance of the structure. Molecular semantics indeed performed its task in trying to find a match between MSpat and MScat. The location of the MScat in the Lexicon may not be an optimal explanation and the Lexicon may have a database equivalent where the incoming data through EMRS, equivalent to the Visual System that feeds the Conceptual Structures in Figure 11, is formatted by certain rules (equivalent to the Pragmatics in Figure 11) and channeled to MScat that operates under the AGRMIA umbrella, which could be a database with MS data, linked to the Lexicon (dictionary).

Molecular semantics, the definition and identification of structures, may contribute to the ability of the system to compare MSpat to MScat profiles. Although MS analysis does not deliver an actual structure, the spectral data offers a pattern and for this discussion this pattern or profile is referred to as structure. This comparison can be performed today only by special applications.

Current semantic web efforts are striving to stimulate global groups to contribute **descriptive ontologies** for chemical and biological systems that may be accessible by the software tools and standards promoted by the semantic web experts. That effort may not include the potential for considering ontological frameworks for chemical and biological **structures** or data **patterns**. Tools such as mass spectroscopy, echocardiogram, magnetoencephalography, etc., *do not generate syntax* and thus may be excluded from ontological frameworks. This deficiency in the current practice is addressed by this proposal on molecular semantics.
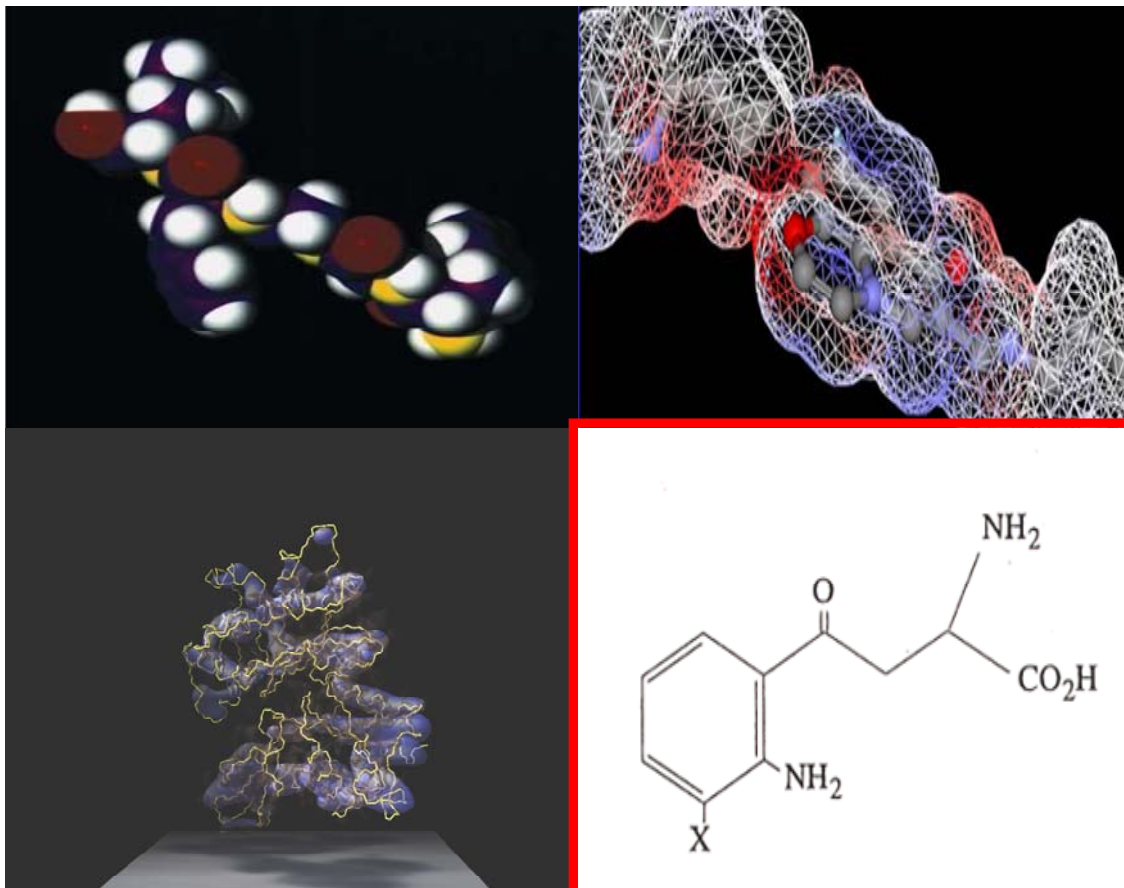
Figure 12: Molecular Semantics as a "Lexicon" for structures and their *relative* identification

Conservation of the amino acid Arginine in *LRP6* protein product from frogs to humans may help to make it less surprising to understand, following the logic of evolution, why viruses and bacteria may also share homologies with sections of human DNA or why viral proteins [170] and bacterial proteins [171] may have some homology to amino acid sequences found in normal and common human proteins, such as myosin. This apparently benign observation often produces some disastrous medical consequences. Because small segments of proteins are involved, these segments or epitopes may have structures that may be distinct. Understanding form (structure) is crucial to understanding function in biological systems. Hence the need for molecular structure in healthcare analysis, albeit only in special cases, and the potential importance of a mechanism that can enable analysis of structure, i.e., molecular semantics.

Disastrous medical consequences are observed due to the phenomenon commonly referred to as **molecular mimicry**. The situation is often caused by a foreign protein from a virus or bacteria that share a short stretch of amino acid sequence homology to a normal human protein. The immune system happens to target the foreign protein but for some reason specifically recognizes this homologous region which serves as the antigen. The body elicits an immune response and attacks the protein. Because this antigenic region (epitope) is also a part of a normal human protein, the antibodies produced by the body's immune system also recognizes the epitope that is present on normal "self" proteins. Unfortunately, the immune system begins to destroy the "self" protein (autoimmune) with severe consequences for the patient. Because the short amino acid sequence of the foreign protein, as short as only six amino acids [172], may mimic the corresponding sequence of the normal "self" protein, the phenomenon is referred to as molecular mimicry.

This autoimmune response is partly to blame in some cases where an individual in almost perfect health suddenly drops dead from cardiac arrest or succumbs to a heart attack. The etiology may be linked to common Streptococcal infection (strep throat) that most children and adults experience at some stage or the other. Segments of some proteins from *Streptococcus* share homology to proteins specifically found in heart tissue [173]. Various other cases of molecular mimicry are well known including T cell mediated autoimmunity [174] and ankylosing spondylitis caused by only 6 amino acids (QTDRED) found in *Klebsiella pneumoniae* nitrogenase enzyme (protein) that exactly matches the human leukocyte antigen (HLA) receptor protein (HLA-B27) antigenic epitope [175].

Do these very short stretches of amino acids create antigenic epitopes with certain **structures** that may form a class of "super antigens" responsible for eliciting the human immune response that leads to autoimmune diseases? Using basic rules of protein structure and conformation, these epitopes may reveal **structural patterns** that may influence "function" in biological systems, such as eliciting an immune response. The *structure* of a short sequence of amino acids may be almost identical to *another structure* of a short sequence of amino acid but the **structural** homology **may not** indicate that the two short stretches of amino acids share **sequence** homology. Computer systems of the syntactic web and of the semantic web may help in the data analysis that involves sequence (words, such as, QTDRED) homologies or differences but may be incapable to deal with structures that may be homologous whereas sequences are not. The likely analytical result of a system presented with QTDRED vs QTDREG may suggest, erroneously, that the structures are different. However, if the system, in future, could use the tools of

molecular semantics and refer to the Lexicon (Figure 11) of structures, it might reveal that the two stretches of 6 amino acids analysed are different in sequence but produces identical structures. Because antigen-antibody binding is structure dependent as long as the side chains and groups are similar, it is possible that two slightly different amino acid sequences may result in nearly identical structures that can still elicit the same autoimmune response. A relevant scenario often occurs in organic chemistry where the empirical formula of a chemical or compound is same but the properties of the resonant structures may be different. The current semantic web may be impotent to address these structural issues. In combination with the power of the semantic web, there may be a need to address structural issues in healthcare diagnostics. Hence, the value of the proposal of molecular semantics.

Why did I choose molecular mimicry and autoimmune diseases to make the case for the value of the structural approach in the proposal of molecular semantics? The partial answer is based on the fact that almost an infinite number of allergens and antigenic epitopes can share short homologies to "self" proteins. By exploiting molecular mimicry, it can lead to autoimmune diseases. Healthcare in general and clinical immunologists, in particular, may wish to understand at a greater depth the form and function relationship in biological systems and autoimmunity. It cannot be done without structure and structural comparison, for reasons already elaborated above. Globalization now provides wide access to food from all around the world. This window on world cuisine has the potential to spawn new and undocumented forms of allergies to various ingredients and antigens foreign to the body. The potential to cause some forms of autoimmune reaction may manifest as inflammatory bowel disease [176] or the generic irritable bowel syndrome [177].

Globalization and mobility will usher new domains of healthcare and seek knowledge about many more issues to diagnose complex diseases, for example, autoimmunity caused by antigens in food products. Early detection of antigens, that can pose the threat of molecular mimicry, may be of great significance. Research is needed to determine how to identify candidates for molecular mimicry and what type of assays, *in vivo* or *in vitro*, can detect these short segments? Only time can tell whether the growing demand for detection and need for analysis in healthcare may trigger an exploration to "productize" molecular semantics. In some cases, structural analysis may be necessary or even pivotal to complement numerical data and syntactic/semantic information for use in EMRS-AGRMIA (Figure 2) type systems that must be globally interoperable and locally responsible.

Molecular semantics or ideas that may originate from linguistics [178] may evolve when more people, on both sides of the aisle, medicine and engineering, can better appreciate the value, however subtle, of form

versus function in biology. This proposal in its current format may become irrelevant but it may provide some clues or may even serve as The Golden Key [179] to unlock creativity and innovative patterns in the mind [180] of young people to drive convergence of syntax, traditional semantics, numerical data and structure, to improve analysis and benefit healthcare.

5.1 AUXILIARY SPACE: Potential for Massive Growth of Service Industry in Healthcare

Adoption of this data driven model may increase the diffusion of a new class of **service industry**. Growth of health services may create new markets, trigger new business and revenue models (**pay-per-use**) even in sectors not directly involved in healthcare but offers products that may be used by health services, for example, (1) software vendors deploying cloud and grid computing platforms, (2) telecommunications companies billing for data transmitted in real-time, (3) data routing or IP connectivity architects to ensure privacy, data confidentiality and address verification using internet protocol version 6 (IPv6) and other security tools and (4) data mining outfits that may create intelligent differential decision engines (IDDE) running on grids, cloud computing environments, in-network processing, embedded browser applications or a host of other platforms yet to be determined or discovered.

The pivotal role of data mining in healthcare data analytics is expected to evolve in ways that are yet to be defined. Data mining as applied to so-called "business intelligence" applications may play a role but may be inadequate to address the *service* part of healthcare because the "service" of healthcare is about an individual or patient-centric data. On the other hand, the healthcare *industry* may have distinctive needs but in general it is about business and operational efficiencies. Data, information and knowledge holds the potential to improve both healthcare service and the healthcare industry, but the tools and applications are expected to differ, in their pursuit of different goals and functions. This is where the prevalent view of data mining is expected to diverge.

The tools of data mining were enriched with a sea of changes when principles associated with complexity theory and swarm intelligence [181] emerged to offer practical business solutions [182] for a wide variety of routing and scheduling needs. A similar wave (see reference 10) is imminent under the generic banner of data mining tools that may stem from reality mining (see reference 77) and its link with social networking relationships (see reference 76). Principles extracted from reality mining and social networking

paradigms may yield tools applicable to a variety of fields including business services and healthcare analytics.

Data mining in healthcare, service and industry perspectives taken together, also offers a fertile ground for exploring whether the convergence of economic principles, tools and techniques, in healthcare data analytics may lead to further innovation. The healthcare ecosystem offers the opportunity to test at least four different economic principles as analytical tools. For healthcare **service**, the focus is on patient data and this data is generated by the physiological system. Since human physiology is highly integrated, it may follow, naturally, that the physiological variables (for example, blood pressure, heart rate, pulse rate) are likely to be co-integrated (see reference 163). In other words, because physiological systems strive to maintain homeostasis, it follows, that the goal of physiology is to attain equilibrium. When one variable is affected, for example, pulse rate, its effect is "integrated" or reflected or related to another linked variable, for example, blood pressure. Physiological balancing mechanisms within the human body will attempt to rectify this situation and may try to restore the blood pressure of the individual to 120/80 mm Hg, the normal reading. Due to the innate physiological drive to restore equilibrium, data analysis in healthcare service may benefit from a potential exploration and application of the principles of Nash Equilibrium [183] to predict from a set of patient data what other parameters (co-integrated) are likely to change or may be influenced by the change documented (data at hand). It may provide clues to improve diagnosis.

Data mining tools for the healthcare **industry** may benefit from some traditional approaches coupled with a few emerging concepts. Like most businesses, healthcare industry suffers from systemic gaps of data and information in its complex supply chain. Consequently, the healthcare industry is prone to information asymmetry [184] and expected to benefit if information asymmetry could be reduced through appropriate acquisition of data including real-time data, for example, from RFID. Availability of high volume data from deployment of automatic identification technologies (see reference 131) may help improve forecasting to better manage human resources and inventory planning in the healthcare industry. High volume data may be instrumental in improving the accuracy of forecasting using time-series data in combination with a host of forecasting tools including the econometric technique of generalized autoregressive conditional heteroskedasticity (see reference 46).

Contrary to public opinion in business consulting, except in specifically designed business collaborations, the application of Nash Equilibrium in business (see reference 65) may be conceptually flawed. It is less useful for business decisions but better suited to healthcare analytics for healthcare **service**. In contrast,

the concept of information asymmetry is foreign to human physiology but is almost a second nature to the competitive dynamics of business, which makes it useful as an analytical tool in the healthcare **industry**.

The global growth of the health services industry through the model illustrated in Figure 5 will dwarf the current revenues of $748 billion [185] from business services. Three major global giants that currently offer business services (IBM, HP, Microsoft), taken together, command less than 10% of the $748 billion in revenues. Therefore, by extrapolation, it seems reasonable to suggest that small companies, start-ups and small and medium enterprises (SME) shall find the barrier to entry in the healthcare service industry to be low or nil. The healthcare service industry will be driven by innovation, which is best executed by small 'skunk' works of talented individuals. Due to multiple convergences necessary to produce a complete product and/or health service, core competencies will be a driving factor. The latter may stimulate the need for collaboration and partnerships between a number of small or medium enterprises with local and global research institutions and medical facilities. Each group or alliance or SME may contribute its own specific module or component but may find it essential to cooperate with multi-talented team made up of scientists, other companies, medical personnel, patient advocates and strategists to act as an interface to catalyse implementation.

Stringent requirement for a higher level world-class advising and supervision to guarantee credibility of the process, products and health services is necessary and essential. The non-commercial *ad hoc* supervisory team may begin their involvement from the conceptualization stage and continue through the cycle of planning, research, product development, service creation, testing and implementation. Critical evaluation by a team of academic and commercial experts [186] may help define performance indicators (KPI) and determine the strength of this emerging vision of healthcare by exploring (1) quality of care improvements, (2) impact on human resources in terms of time savings for medical professional, (3) reduction in cost and potential for savings, (4) length of time required for return on investment, (5) profitability of businesses (SME) and growth of high potential start-ups, (6) economic benefits for the nation's healthcare system, (7) reproducibility, portability and sustainability of the services model as a global template, (8) business opportunities to implement similar services in other communities or nations, (9) creating market alliances in emerging economies to implement healthcare services and (10) liaison with global organizations (World Health Organization, United Nations Development Fund, World Bank, Asian Development Bank, Bill & Melinda Gates Foundation) to help in the global diffusion and adoption of health services industry model.

5.2 AUXILIARY SPACE: Back to Basics Approach is Key to Stimulate Convergence

The discussion in this paper, in general, has continuously oscillated between medicine, engineering and information technology in an attempt to emphasize convergence and suggest fruitful analogies between the fields. This paper is about data, analytics and tools from research that may improve healthcare. Hence, the preceding sections seeks to harvest advances in systems engineering and information communication technologies (ICT) as well as translational medicine to improve healthcare through multi-disciplinary confluence. Therefore, I shall be ethically remiss if I do not digress and fail to highlight in this section why the need for convergence is accepted but in reality organizations are sluggish to address the challenges in the clinical enterprise [187]. The problem has deeper implications and unless reformed, the ramifications are bound to be increasingly disappointing.

In its simplest form, implementing convergence is often inhibited by the general biomedical illiteracy of technical experts and technical illiteracy of biomedical experts. Insightful degree programs in biological engineering [188] and health science technology [189] are key mechanisms to create the supply chain of talented individuals who have understanding of one field and depth in another, to act as a knowledge bridge, which is key for progress of convergence. The US physician-scientist programs [190] that produces graduates with a PhD and MD are equally valuable and other countries are beginning to implement related strategies [191]. However, these programs only attract the *crème de la crème* of the nation and in some countries the total number of these highly qualified individuals fails to reach a critical mass. Consequently, the few who succeed often move to other parts of the world where a critical mass of talent exists and where their multiple skills are valued, duly rewarded and challenged to guide the nation or global groups.

What is sorely needed and missing in most countries is the focus on training programs for "middle level" workforce executing the bulk of the work yet remain firmly sequestered in one job or domain without the scope or the desire to become multi-functional. Programs with financial incentives, paid leave of absence, structured academic training and practical internships are necessary to provide technical education for medical experts [192] and other healthcare professionals (consultants, general practitioners, nurses, physiotherapists, home-helpers, mental health workers) to understand (**not** necessarily gain expertise) the fundamentals of medical device engineering, sensors, remote monitoring, communication technologies, transmission protocols such as TCP/IP, software architecture, statistics, principles of artificial intelligence, basic principles of logic and programming. Similarly, experts in engineering and technology should be

offered the attractive opportunity to gain understanding of human physiology, pathology, pharmacology, anatomy, cellular and molecular biology, neurology and mental health, genetics, principles of internal medicine, nuclear medicine, medical imaging, biomedical data, in-patient and out-patient management in hospitals, hierarchy of decision making, nutrition, social and environmental factors in health, laboratory data reporting and epidemiology. Cross-pollination of ideas is key to innovation.

Implementing these parallel training programs may not pose an insurmountable barrier in most countries even if their vision of the future and commitment to financially invest in its people is modest, at best. What is likely to surface is the difficulty of attracting sustainable number of cohorts to the programs. The problem to attract mature mid-level working class for re-training or life-long learning, at the tertiary level, is partially rooted in the primary and secondary education of the nation. The emphasis or lack thereof on mathematics and science education either due to [1] archaic policies, [2] compromised rigour to feign inclusion, [3] misguided teacher education programs that chooses process and dilutes content to serve the lowest common denominator, [4] emphasis on test preparatory teaching without room for problem-based learning, [5] inability to stimulate increasing number of female students to take up advanced mathematics and science or catalyse young women to pursue career paths in the hard sciences, [6] shoddy and second grade teacher qualifications (especially in mathematics and science) masquerading as good enough [193].

In USA, a seminal report [194] revealed that 51% of mathematics teachers in US public K-12 (primary and secondary) schools never took mathematics as a part of their college curriculum. A third of the "education school certified" science teachers never took science as a major in college. A national survey [195] of high school physics found 25% of students took 'some' physics in high school and 1.2% of senior students [33,000 out of 2.8 million] enrolled in advanced physics. About 18% of certified teachers teaching high (secondary) school physics had degrees in physics while 11% certified teachers had "degree in physics education but not physics" and 27% certified teachers teaching physics had neither a degree nor any relevant experience in the subject.

In the 3rd International Mathematics and Science Study [TIMSS], US ranked 28th in mathematics and 17th in science, lower than countries like Slovakia, Slovenia, Bulgaria, not to mention nations in Asia [196]. In 1998, US high school students outperformed only two (Cyprus, S. Africa) of the participating countries. In addition, the TIMSS classroom study revealed 90% of US middle school mathematics lessons are of low

quality compared to Japan [10% low] and Germany [30% low]. The quality of mathematics teaching was reflected in the poor performance of US 8th graders (middle school) reported in the 1999 TIMSS analysis.

The declining effectiveness of mathematics and science education is reflected in the fact that US colleges and universities awarded 24,405 bachelor degrees in computer science in 1996, 50% *less* than 1986 (30,963 in 1989) and engineering graduates dropped from 66,947 in 1989 to 63,066 in 1996 [197].

Despite these disappointing trends, the US is still regarded as the 'cradle of innovation' by global experts and organizations [198]. The enigma clears if one considers the actual *number* of qualified graduates: in thousands. That generates a critical mass of talent to innovate and contribute to economic growth. Each qualified individual contributes several magnitudes more than the average per capita contribution to the US gross domestic product (GDP). As an example, by 1997, graduates of one US institution, alone, had founded 4,000 companies employing over 1.1 million people with annual sales close to $250 billion [199]. A recent analysis of the same institution indicates that innovation and inventions of this one institution, annually, creates new companies that add 150,000 jobs and $20 billion in revenue to the US economy, each year [200]. By extrapolation, this institution alone, therefore, thus far, has created companies that may directly employ over 2.5 million people and generate about *half a trillion dollars* in annual revenue. The dedication to research-based entrepreneurial spirit coupled with the freedom of some US institutions to think out-of-the-box as well as the strength of the US investors to assume substantial risks are factors that continue to ignite innovation and profit even though investments, both academic and financial, are not immune from failure.

Attempts by other industrialized nations, with far smaller population, to partially mimic the US strategy have produced mixed results. The striking visibility of the global success of the graduates and faculty from US research institutions in creating innovative companies, products and services are buoyed by investors willing to assume great risks. In addition to the favourable financial environment, the numbers or critical mass necessary for innovation is a major determinant to spawn success and that may not be available for countries with limited population. Equally, a public basic education system that lacks emphasis on rigorous mathematics and science education at the primary and secondary level will reduce the supply chain of talent for the future MD or PhD pool. It may be one reason why mature mid-level professionals in one field prefer to cast a 'blind eye' to convergence and stay in their comfort zone rather than acknowledge and take measures to improve their basic skills in mathematics and/or science. The latter prevents them from

exploring training options to acquire new dimensions or pursue life-long learning, as is necessary to create the type of multi-disciplinary convergences important for healthcare and help build a knowledge economy.

6.0 Temporary Conclusion: Abundance of Data Yet Starved for Knowledge?

Patients want answers, not numbers. Evidence-based medicine must have numbers to generate answers. Therefore, analysis of numbers to provide answers is the Holy Grail of healthcare professionals and its future systems. Lack of action due to paralysis from analysis of risk associated with the complexities [201] in healthcare is no longer acceptable in view of spiraling costs. Generating data without improving the quality of healthcare service and extracting its value for business benefits [202] will not provide the return on investment (ROI). Distributed data and their relationships are dispersed in multiple network of systems or system of systems (SOS). The role of data analysis is central. The comatose stage of the Information Age due to data overload and information overdose is predicting its demise unless new ideas [203] emerge as its savior. The imminent death of the Information Age makes its imperative to better understand the Systems Age. The single most important system that deserves our attention in the 21st Century is the Healthcare Eco-System. The convergence of characteristics such as enterprise, innovation, research and entrepreneurship (EIRE), often common in organizations with foresight, in parallel, with the vision to drive convergence of biomedical sciences, engineering and information communication technologies, may act as the purveyor to advance healthcare for the progress of civilization [204].

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