Translation of middle out rational approach (MORA) in an understanding of the therapeutic outcome of cancer: Experience from India.

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Introduction

After the Human Genome Project and to ensure the outcome of it, Systems Biology (SB) is the most desired approach for providing better health care to the mankind [1]. Along with the other branches of medicine, SB approach also influences oncology. It is expected that with this approach better care can be provided to the cancer patients. In the area of SB two approaches namely, Bottom-up and Top-down are widely discussed. Among the two, former approach is widely practised. India's initiative towards SB venture is discussed in some recent articles. Due to large population, increased economic growth in terms of GDP and unique geopolitical location in South East Asian countries, India is regarded as the representative country for the developing nations across the globe and hence, its importance in scientific endeavour cannot be denied [2,3].

Bottom-up approach fascinates the molecule centric scientific community, because hopefully it may predict the disease at an early stage. During the last decade numerous research initiatives has taken that delineate numerous unknown proteins; thereby numerous interactions and cross-talks have been predicted. The experimental basis of the approach mostly relies on *in vitro* cancer cell lines based observation followed by single shot data analysis with the dichotomy of states. Undoubtedly the efforts are appreciable intellectually due to uniformity of cellular characteristics at the experimental level and hence, reliability of the analysis of the obtained data exists [4,5]. However, it is undeniable fact that in clinical cancer cases there is cellular heterogeneity within the tumour mass. Hence the approach ignores the influence of mesocosmos [6,7]. The goal of the approach is to combine every molecular events to tissue level functionality. Recently, cardiac model developed model by Noble et al is approved by U.S. Food and Drug Administration for drug testing [8]. This is a successful indication towards the generalized pharmacological action of testing of a drug, but translation of the approach in individual patient is in question. In clinical scenario it is commonly noticed that the function of a particular drug differs widely among patients under the same patho-physiological state of cancer [9]. Moreover, its translation towards clinical arena may lead towards the indulgence of the initiation of unwanted and unnecessary treatment protocol. This is due to fact that so far there is no confirmatory method to distinguish between phenomenal and epiphenomenal factor; thereby, diagnostic/prognostic benefits in individual patients, as expected are also in question [10,11]. Another limiting factor is the cost of investigation, as already present day diagnostic cost is beyond the reach of the majority of patients in low income and developing countries. Hence newer type of technology, mostly the high-throughput technology would put an extra economic burden to them [3].

Top-down approach is basic tenant of the present day clinical practises, as patients appear with organ level dysfunction. Disease is diagnosed with some morphological and functional alteration at the tissue level and thus therapeutic intervention is initiated. However, therapy is effective at the molecular level; contrarily, effect of therapy is noted at the tissue level. Such differences in scale is not quantitatively connected and hence not assessed. In practice, understanding of the therapeutic outcome is predicted on a population based analysis and the individual patients are treated with the population mean. Hence, treatment and patient care are taken in an empirical manner. However, this gap is enough to allow the disease state out of control. Though some experimental correlation are exemplified with some metabolic changes, but logical and quantitative relationship still not established [12-16].

Hence both bottom-up and top-down has some limitation that makes SB inoperable specially, in the clinical cancer cases. To overcome the existing limitations of either the approaches towards the translation of SB view, another approach called middle out is suggested. This view admits the clinically detectable disease state as the starting point; hence focus is imparted towards the control and management [12,13]. It appreciates the removal of residual malignant cells through the same process, thus hesitates about any drastic steps. For its unique starting point, it negates the unnecessary panic regarding the pre-disease state. To reduce the cost of investigation together with the demand of handling of a disease situation in a patient specific manner, a sense of rationality is the pre-requisite. Hence, this outlook is termed as Middle-out Rational Approach (MORA).

MORA view mostly relies on the existing methodology, repurposing of drug and gives a special emphasis towards qualitative clinical information. This view like to impart more focus towards the development of a scientific framework by intermingling between the presently available technologies and patient specific qualitative (clinical) information. Hence, if this view is practised, it can be expected that poor patients of the developing nation including India would be most benefitted.

However, to translate such information into a meaningful quantitative statement requires rationality and a wide variety of scientific know-how along with different pros and cons. A strong domain knowledge and experience about clinical cancer cases are the essential pre-requisite for the rationality, while an exposure to wide variety of scientific knowledge is very much needed not only for seeking a meaningful solution but also to make a communication between different specialists across the disciplines [12,13,17]. However, this is a challenging task specially, under the present administrative structure in India. It is the fact that most of the Indian universities do not encompass all the disciplines and existence of distinct type of universities are there for the academic pursuits in the area of health care (medicine) and basic science. So for each of the courses separate administrative controls exist. In India, science academics is governed by Ministry of Human Resource and Development while medical is governed by Ministry of Health and Family Welfare. There is primary objective differences between the two as well, former is targeted to develop man-power for purely academic institutions like schools and colleges while later is targeted to develop man-power for primary health care. Due to physical and administrative separation, practice of biomedical research including translational aspect of SB specially, practice of MORA view is difficult.

Hence, in Indian context, bio-medical research problem is equated as a problem of basic biology and viewed with same approach as of other laboratory sciences like Physics. Contrarily medical research is mostly oriented as survey based research. Translational research is viewed as product development for industrial applications like enzyme production. Under this purview what sort of medical problem can be extended is only vaccine and/or monoclonal antibody research. Possibly this may be reason that in India a large emphasis is put to the infectious disease research. Undoubtedly, survey based research is being encouraged and conducted to align with the 'evidence based medicine', but longitudinal studies are out of focus and its importance is mostly overlooked even in medial fraternity [15]. There is almost no research how a specific patient reacted with any particular treatment protocol. Unfortunately, individual patient is lost under the purview of mass or majority counting.

Individual patient specific treatment which is one of the major pillar of Systems Biology/Medicine, have a very remote scope for its practise. There is almost no funding for patient specific research specially, in the area of biomedical field. To carry out the patient specific research by transcending the existing physical and administrative barrier is possible provided a good amount of grant is sanctioned. Undoubtedly there are numerous research funding available however, granting agencies generally fund small budgetary research grant which is most of the cases less than INR 50 lakhs. With this low budgetary fund it is difficult to transcendent the existing physical and administrative barrier, and as a result, research which is pursuable is confinded within test tube or laboratory based practices. Contrary to western world, in India, there is almost no public funding available for scientific research, though numerous public fundings are available for charity based work. Possibly this may be reason that in India public funding is synonymous with government based funding. Even there is almost no initiative to generate public based fund for scientific research. Generally scientific societies may take an initiative in this aspect; however, people are unaware and skeptic in this aspect and moreover, there is a general trend of suspiciousness regarding this aspect [3].

In several faculty recruitment interviews a SB researchers are frequently face several sub-standard questions like - “What about the practical aspects in your work?”, “What sorts of practical you may conduct?” These issues are due to training in test tube oriented science, cross-sectional data analysis and empirical research in the biological fraternity in most of the universities across the India. Ironically, most of the senior biologists who are trained as experimental biologists are ignorant about the quantitative facets of science, no exposure to patient oriented clinical research and unexposed to the hardship of the simulation work. Their exposure towards the use of computer is confined with some statistical software, typing works and internet accesses. Interestingly, majority of the people in science academic administration or in policy making bodies do not have any experience about the aspect of clinical implication. In faculty recruitment policy, even at the university sector such experience does not add any value; however undergraduate teaching is appreciated as experience. In majority of the universities there is no start up grant for faculties. In a number of cases faculties are recruited without having doctoral degree. Interestingly, with the academic administrative point, in corollary to the western world, it is expected that recruited faculties should bring some grant to that university, and, this is important to meet the expectation that the recruited faculty can conduct laboratory classes with the research grant money and hence, small budgetary fund is appreciated in the faculty recruitment policy even for higher position. It is quite ironic that research concerned with computer or mathematics is unappreciated within the biological faculty structure.

Due to existing separation and fund crunch, imparting of requisite training for capturing qualitative (clinical) data of dynamical nature is difficult in an academic environment. As such research is not appreciated by funding, so students do not find any interest for such type of research for their career development. Hence, finding of a suitable graduate student is also very difficult. India is a low income country; so there is a prevalent tendency among students to get a job of permanent nature at an early age as early as possible. Moreover, in Indian education system, astonishingly from early childhood we learn the definition of science as the experimental validation of facts that is being exercised in laboratory. So in the cognition there is always an imprint that scientific investigation can only be done within the four walls bounded space. Unfortunately in most of the biology courses, imparting of training with (laboratory) technical skills is more appreciated rather analytical skills. Though the concept of science within the four walls bounded space had shattered in both physical and biological sciences with the development of Chaos theory and Evolutionary theory; however, in the field of bio-medicine, techniques that are being used in both the fields are remotely applied and hence unappreciated.

The issue of addressing the biological system through mathematical/computational models has a long history [8]. However, in majority of the approaches, there is a superimposition or fitting of biological variables with the existing mathematical framework. Hence model validation is important. Very few models are available that is developed by following biological rationality. Several problems of biomedical sciences can be addressed with simple mathematical or computational approach provided if the intricacy of the biological system is clarified with rationality and intricacy. This is often termed as domain knowledge by the Information Technology personnel. There are very few personnel are available who have exposure to both clinical problem as well as the quantitative aspect of science. Academicians within physical sciences do appreciate mathematical or algorithmic jugglery but the relevance of the bio-medical problem is readily unappreciated. Contrarily experimental jugglery followed by empirical analysis is often appreciated in basic biological fraternity. As a result in either of the approaches of physical science or biomedical science provides no solve towards the suffering of the patients or in the up-lifting of the quality of life specially, for the poor patients.

With the availability of longitudinal and/or dynamical data it is possible to develop bio-medically meaningful analytical framework, often this can be represented by simple mathematical framework. But longitudinal and/or dynamical data is quite absent in public domain. There is almost no patient specific record system in Indian medical fraternity. Health care is provided on the basis of 'evidence based practises' and care of the individual patients are managed empirically.

As a result, such type of research are mostly neglected and ignored even by the academic administrators in both the fraternity. To circumvent the data problem computer and information technology could be the way-out. However, it still becomes difficult in translation due to proper academic and administrative support. Though in India, most of the people are well aware about information technology and its associated industry; but surprisingly, academic administrators in medical fraternity are unaware about these fields. Interestingly, a good number of administrators and policy making people in medical fraternity are interested with some sort of genome analysis – the reason may be that such approach can be carried out with low cost and does not affect the on-going practices. As a result, there is almost no growth of the field of Medical Informatics or Telemedicine, the issue of Medical Analytics is far away. Commonly SB venture is equated with bioinformatics, computational biology, mathematical biology, theoretical biology or other laboratory sciences. Though translation of SB to Systems Medicine require genome based personal information (termed as P4 Medicine); however, in contrary to that MORA view requires some qualitative clinical information (to provide treatment in low cost). Such information, if not provided, MORA view would be inoperative. Such information which are mostly verbose based patients may object to provide such information considering as personal information. In Indian context people appreciate in sharing costly high through-put technology driven personal data but many of them may object in sharing verbose based data and in that aspect make comparison SB with other disciplines. Due to restriction in sharing of clinical (personal) information, it is noticed in the global context that most of the available works concerned with the translation of SB in clinical arena are mostly available with the terminal cancer cases and children patients.

Under the present administrative control MORA view of the SB venture is difficult to pursue in India. To translate the benefit of the MORA view for the poor patients of the developing nations some form of immediate affirmative actions are required – from restructuring in the administrative control to the scientific thought process. To change in the scientific thought process, teaching curriculum is needed to be changed. A multitude dimension across the disciplines along with the faculty structures are needed to be incorporated in the teaching curriculum. Though at present time Choice based credit system is suggested to implement; however, it does not have any indication of the exposure across the faculty structure. Such exposures are needed for the future generations. Multitude dimensions are also needed for the faculty recruitment policy. Clinical and research experience are needed to be considered as experience. In western world several dedicated research institutes have already established for SB [3]. Though a very few interdisciplinary research institutes have established, however, in India no single institute is there which is dedicated for SB activity. Some dedicated research institutes for SB in association with health care are urgently needed and in the faculty recruitment emphasis should put on the patients oriented research experience in an interdisciplinary environment. If academic research is coupled with patients oriented service then MORA view can be successfully implemented by the properly trained personnel and we hope that with the practice of MORA view poor cancer patients of the developing countries would be most benefitted.

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