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Integrative biology for integrative medicine: A complete approach

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ABSTRACT

Background: India's AYUSH systems of medicine, Ayurveda, Yoga and Naturopathy, Unani, Siddha and Sowa-Rigpa, and Homeopathy, use natural self-healing abilities of body and mind. Their ways to treat non-communicable diseases reduce use of modern drugs with their side-effects. Scientific acceptance requires them to be explained from a modern biological perspective. This paper indicates how to achieve such an integrative approach, using aspects of biology not yet taught in medical schools.

Methods: A new, 'Sandwich Model' of biology is introduced that includes holistic epigenetic regulation; also, complexity biology's concept of self-organized criticality; a systems treatment of organism function from Ayurveda; and Ayurveda's six stages of etiology, Shadkriyakala.

Results: Molecular biology is upgraded by the sandwich model's layer of epigenetics, leading to a new, scientific definition of health as optimized regulation. Fractal Physiology then expands this to explain self-healing, used in all AYUSH systems. Ayurveda contributes in two ways: its systems approach yields a holistic understanding of organism functioning, while Shadkriyakala improves our understanding of pathophysiology.

Discussion: These additions create an integrative biology; modern biology expands to include AYUSH systems' concepts. It provides a scientific basis for India's plan for integrative medical education, with AYUSH systems treated as equal to modern medicine.

1. Introduction

For the past half century, developed countries have suffered a pandemic of non-communicable diseases (NCDs) that include all the leading causes of mortality [1,2]. The problems they cause, combined with the limited ability of chemical drugs to treat them, are major contributors to misery and pain in the final decades of most people's lives. Drugs prescribed by modern medicine usually only palliate their symptoms, and almost always cause unwanted side-effects. As this article shows, modern medicine's failures in this regard are due to two factors: first its inadequate understanding of the physiology of health; and second, its idea that ill health and disease can be adequately understood in terms of shifts in the values of chemical biomarkers.

In contrast, India's complementary systems of medicine, Ayurveda, Yoga & Naturopathy, Unani, Siddha & Sowa-Rigpa, and Homeopathy, together known as AYUSH, all use self-healing abilities that are inherent in the physiology [3]. Their power to do so is based on different understandings of health and pathology; one where health is understood in terms of 'balance' between different physiological process, while pathology is seen in terms of corresponding 'imbalances' – as depicted in the Graphical Abstract. The aim of this article is to explain these differences in ways that can bridge the gap. It shows how the seemingly opposed understandings of the two systems are related. The resulting Integrative Biology provides every doctor with strategies to treat NCDs. It forms the basis for of a system of medicine that integrates modern medicine with the AYUSH systems, i.e. Integrative Medicine.

First, consider the failure of modern biomedicine to provide a clinically useful definition of health. The definition offered by the World Health Organization, WHO, Perfect Functioning on the Levels of Body, Mind and Society [4], does not suggest a fundamental strategy for G.P.s to employ when faced by a sick person. Second, consider its use of biomarkers, chemical or psychophysiological measures to make a diagnosis. Treatments aim to restore them to healthy ranges of function, but mostly by using chemicals to interfere with processes influencing their values. Even when trying to remedy underlying causes of biomarkers' shifts away from normal ranges, such treatments do not usually improve a patient's underlying condition. Such conditions are mostly caused by personal habits injurious to health, and, other than advising

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against tobacco and alcohol, little attempt is made to remedy them. The Graphical Abstract conveniently summarizes most of the above.

Practitioners of the AYUSH disciplines, on the other hand, are able to use natural self-healing abilities of body and mind. Stimulating and enhancing self-healing is the main strategy to treat any ailment in Naturopathy [5]. The discipline of Yoga Therapy [6] adds knowledge of the 'subtle energy', or Life Breath, Prana. It enhances it through breathing practices like Pranayama [7], Kapalabhati [8] and other well-known practices. Yoga further adds a deep understanding of the influence of mind on body, and how to prevent negative influences on health arising from emotional problems and intellectual understanding of life [9]. This is parallel to modern psychology's recognition that repressed emotions can lead to physical problems as well as mental ones [10,11].

For example, the Yoga Sutras of Patanjali state that Fear of Death (Abhinivesha) is the root cause of many diseases, see II.9 in Ref. [9] More profoundly, Yoga teaches that overcoming Avidya, and thereby achieving Vidya, deep understanding of reality, takes the body and mind beyond the reach of most diseases [12]. The aim of Yoga Therapy is to act on mind-body-spirit. That is inherently an integrated approach. Another example is Kapalabhati [9], where breathing at a rate of 60–120 breaths per minute increases oxygen levels sufficiently to reverse the bad effects of habitual repressed breathing [13]. Yoga's ultimate strategies of improving personal health also include its fifth and seventh limbs, Pratyahara and Dhyana, meditation, to achieve stable peace of mind in Samadhi [14].

To these more holistic considerations, Ayurveda adds detailed analysis of a person's inherent state of physiology, known as their 'Prakriti' [15,16]; balance of the three dynamic controllers of the physiology: Vata, Pitta and Kapha Dosha, together called Tridosha [17]. How doshas go out of balance, increasing tendencies to fall ill at different times of day, and during different seasons of the year are also aspects of Ayurveda's fundamental concepts [18].

Now consider further AYUSH medical disciplines: Unani, India's Islamic system of medicine; Siddha in Tamil Nadu, founded by Maharishi Agastya; and Sowa Rigpa, the Tibetan System of Medicine brought to India with the Dalai Lama. All include most Ayurveda fundamentals, with minor variations. Their relationships are well explored [19,20]. The final AYUSH system, Homeopathy, was brought from Europe in the 19th century, like Naturopathy; India has more Homeopaths successfully practising that discipline than any other country [21].

In the last few years, developments in modern medicine have been moving in the direction of the AYUSH systems, e.g. by using a functional medicine model employing a systems biology approach [22]. They are beginning to address the body's complex physiological systems, for which systems biology offers a global, holistic approach to wellness. Modern science has thus recognized the importance of complexity biology and the systems approach for personalized medicine [6,17]. As is well recognized [23], these approaches are deeply rooted in AYUSH systems. Both were inherent aspects of the holistic healing achieved by AYUSH treatments long before the birth of modern medicine [18]. Recently modern medicine has begun to recognize it, see e.g. Ref. [24].

This review proposes using Integrative Biology to train all professional doctors and nurses in an integrative system of medicine that includes both the AYUSH disciplines and modern medicine. It envisions making cures for chronic diseases available to all patients, reducing the incidence of drug side-effects and levels of iatrogenic disease [25]. It also addresses an important challenge in this program.

The current age being the age of science, all government-funded proposals require scientific acceptance. They need to be expressed in the language of science. The AYUSH systems should be explicable in terms of systems theory, physics, chemistry and biology. Not being taught in medical schools for modern medicine, the AYUSH systems are widely believed to lack a basis in biology. But that is not the case, the past 25 years have witnessed a steady increase in scientific understanding of AYUSH [17,26,27], much originating in early research on epigenetic regulation [28,29].

The advantages of the AYUSH systems can now be explained in terms of up-to-date biology; this review highlights several novel aspects of biology not yet in medical school curricula. Some were independently formulated, but others arose from study of the AYUSH systems [26]. The following are most important: complexity biology [30], fractal physiology [31] and self-organized criticality [32], for which brief explanations are now given.

Complexity Biology: The study of complexity in biology started with the founding of the Santa Fe Institute in 1984 to study complex (adaptive) systems, across a multiplicity of scientific domains ranging from physics, through biology and economics. Waldrop's book [30] describes how, in becoming more complex, complex systems develop successive layers of structure that become essential, fixed components of later iterations. In business, the concept of a limited company brought great advantages to nations that adopted it; in commerce, marine insurance played a similar role. Both are now the sine qua non of a thriving economy.

In biology, complexification works from Wholes to Parts. Starting with single cell organisms that complexified to eukaryotic cells; next developing layers; a digestive system in Cnidarians; a digestive tract in Nematodes; a circulatory system in Annelids; etc. In humans, the sequence cells, tissues, organs, organ systems, and whole organism seen in embryogenesis, exemplifies the principle of recapitulation, sometimes known as 'ontogeny recapitulates phylogeny'.

Fractal Physiology: the discipline of fractal physiology, much studied at the Santa Fe Institute, originated in unexpected observations made when a physiologic system receives a series of identical stimuli [31]. Instead of responses in the sequence being identical, as one would expect, a completely new, different statistical distribution of responses is observed, universally in all organisms: fractal (1/f) distributions of response [31].

Self-Organized Criticality is the principle proposed to understand why fractal physiology's fractal (1/f) distributions of response occur. Danish physicist Per Bak, and his colleagues Tang and Wiesenfeld pointed out [32] that similar distributions are found at critical points in the field of phase transitions and critical phenomena [33]. They then proposed that organism dynamics must keep them at critical points, by means of a principle, which they named 'self-organized criticality' [32]. The way that the principle works is outlined in the Discussion section.

Another concept introduced in this paper is the 'Sandwich Model' of biology [34], an extension of the current molecular biology model [35]. The molecular biology model concerns itself with macromolecules that enable cells to function, DNA, RNA and enzymes, depicted in the left side of Fig. 1. The sandwich model, on the right side, also includes epigenetic regulatory processes, and the fractal physiology enabling them to function optimally. Fig. 1 includes icon-symbols to explain the differences, parallel to those portrayed in the Graphical Abstract.

Finally, Vata, Pitta and Kapha doshas of Ayurveda [36]: These function as Input/Output, Turnover and Storage, respectively, at all levels of organism function: whole organism; organ subsystems; organs; tissues; and cells [37]. They present a holistic, systems perspective.

2. Methods

Four tools are used in this paper, aspects of modern biology and AYUSH systems of medicine that are either new or inadequately appreciated scientifically.

1. The new 'Sandwich Model' of life, extending the present 'molecular biology model'.
2. Differences between the two models portrayed by both the Graphical Abstract and Fig. 1.
3. Fractal Physiology's Self-Organized Criticality.
4. Ayurveda's Tridosha: organisms' three principal systems functions.

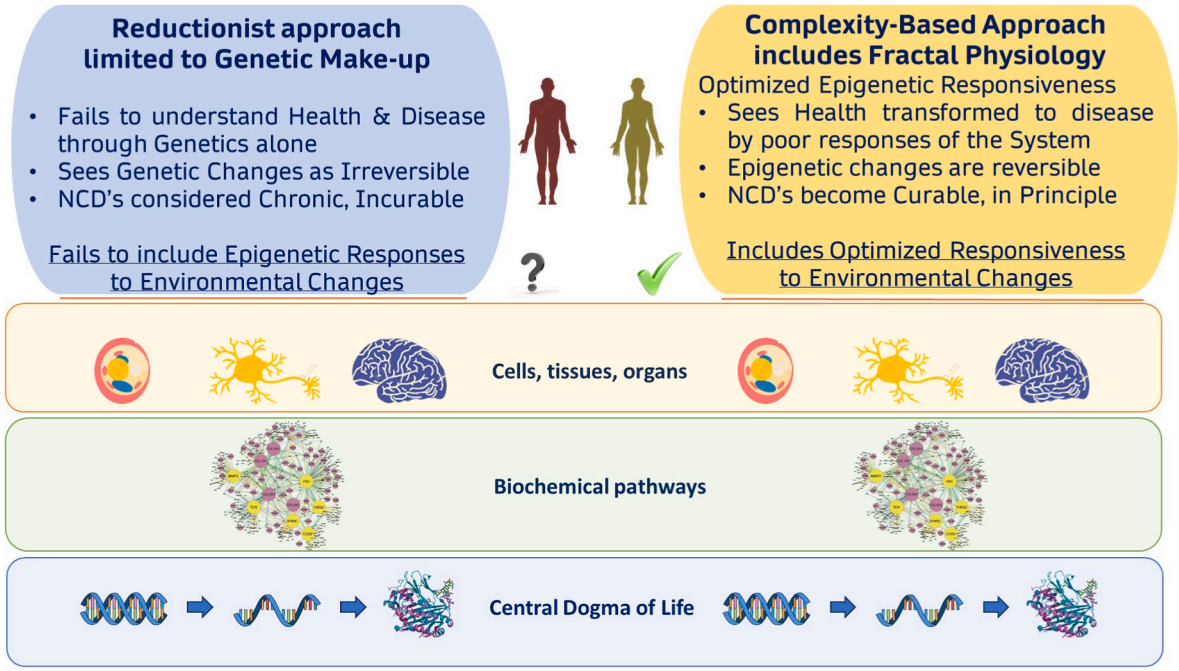

Fig. 1. Depicts the differences between the two models of biology.

Each of the four has been described in the introduction; the Discussion gives further comments.

3. Results

First: the epigenetics in the Sandwich Model's upper layer bolsters molecular biology by providing mechanisms for organism adaptability and competitiveness [37]. Adaptability results from its power to up- or down-regulate the expression of loops of genes; varying expression of specific enzymes then maintains balance in the biochemical pathways over a wider range of external conditions. Optimizing regulation (see next point) maximizes competitiveness.

Second: the Sandwich Model brings a new definition of organism health, Optimized Regulation and Optimized Function at all levels, Body, Mind and Social [37]. In contrast to WHO's definition as perfect function on those levels [4], optimal regulation can guide treatment strategies; it is clinically useful, as discussed later. Because optimization and regulation are scientific concepts, it is a scientific definition of health; derivation given in the Discussion section.

Optimizing adaptability makes an organism maximally competitive in its ecological niche [37,38], an idea also recognized in tumor growth [39]. In Fig. 1, adding the upper half of the right side's Sandwich Model of Life resolves problems in the left side's Molecular Biology of Life. These necessary, ecological properties of all organisms enable them to survive in real environments [37,38], rather than merely in test tubes/flasks in a microbiology laboratory.

Third, the property of self-organized criticality [32], introduced through fractal physiology [31], also explains Optimized Regulation, and Optimal Function, stated above [38].

Fourth, the critical instabilities involved in self-organized criticality [32] are sited at loci of control of regulatory functions [40], an ideal location for maintaining optimized regulation. When, under pressure from the environment, regulation departs from optimal, the physiology possesses dynamical means to restore it, as long as it has not gone too far (see point six below). Dynamically restoring regulation to optimal constitutes restoration of health; a process of self-healing, a physiological ability used in various forms by all the AYUSH systems. Indeed, in Naturopathy, promoting self-healing is the foremost strategy of curing disease [5,38,40].

Fifth, the systems function interpretation of Tridosha, Vata ⇔ Input/Output, Pitta ⇔ Thruput, Kapha ⇔ Storage [17,36,37]; the tridosha functions integrate all organism functions into a single unit. They bring a holistic value to the scientific understanding of organism functioning. When applied to each level of the physiology, every level is seen to function as a whole, to be holistic: Whole Organism, Organ Systems, Organs, Tissues and Cells [37].

Sixth, another principle for medicine: Ayurveda's account of etiology, its Shadkriya Kala, the Six Stages of Dosha Imbalance [42]. Ayurveda holds that, when the three doshas are in perfect balance, no disease is present, not even a tendency to disease. The six stages account for how states of disease develop; first in potential form (four stages); fifth in manifest form, Vyakta, recognized by all systems of medicine; and sixth, Bheda, when the state of one organ or other has become dysfunctional, with danger of morbidity. The context for stages of etiology in modern medicine is discussed later in the next section.

4. Discussion

First, Health as 'Optimal Regulation': this important concept arose from the realizations that, in AYUSH systems of medicine, poor health corresponds to poor regulation, so that improving regulation tends to improve health. Optimal regulation is then a state of optimal health. But 'optimal health' must be 'health', so Health equates with Optimal Regulation [34,38].

Second, optimizing regulation includes optimizing organisms' epigenetic responses to external stimuli, it is an aspect of Fractal Physiology. It is often assumed that genes are switched 'on', when up-regulated, and switched 'off', when down-regulated. This would make switching processes phase transitions. But phase transitions often get blocked, because phases can enter metastable states [33]. Physiological switching processes avoid this problem by having switching functions with vertical points of inflection in the middle, i.e. critical points [33]. That condition optimizes sensitivity of switching: the critical points optimize regulation [40,41].

Fractal physiology [31] can now be properly understood: the critical points in SoC are designed to optimize sensitivity of switching processes.

Table 1
Modern medicine versus the AYUSH systems of medicine.

System	Health Definition	Key Concepts	Reductive/Holistic
Modern Medicine	**WHO ⇔ NONE**	Central Dogma of Mol Biology Form & Function of Molecules	Reductive
Ayurveda (AV)	Dosha Balance	Dosha Prakriti, Shadkriya Kala	Holistic
Yoga Therapy	Balanced Prana	Panchakoshas, Panchapranas	Holistic
Naturopathy	Perfect Function	Self-Healing, Life Force, Toxicity	Holistic
Unani	Hippocrates/AV	Four Doshas (incl. Rakta Dhatu)	Holistic
Siddha Medicine	As Yoga **&** AV	Healing	Holistic
Sowa Rigpa	As Yoga **&** AV	Tridosha, Saptadhatu, Life Force	Holistic
Homeopathy	Perfect Function	Correct Epigenetic Regulation	Holistic
Integrative Medicine	Optimal Regulation	Sandwich Model, Molecular Biol + All AYUSH System Concepts	Holistic

Caption: Table 1 contrasts the Reductive picture of Modern Biomedicine with Holistic Principles of AYUSH systems of medicine, which can avert humanity from the Pandemic of Chronic NCD's.

Their self-organizing property enables them to restore regulation to optimal: to bring about self-healing [38,40,41] and restore health.

The four advances in biology named in the Methods section yield ways to provide scientific accounts of various treatments used in AYUSH: self-healing in Naturopathy, together with its vision of restoring the Life-Force [5], or Life-Breath, known as Prana in Yoga [7,9] and Ayurveda [42,43]; Yoga's methods of 'expanding the Life-Breath', Pranayama [7], together with certain practices, called Kriyas, like the well-known Kapalabhati [8]; lastly, Ayurveda's six stages of etiology, Shadkriya Kala [42]. Interestingly, these advances in biology also remedy severe deficiencies in molecular biology's model of biology [35]: poor adaptability and competitiveness, usually unacknowledged even in college level courses on biology [35].

Molecular biology [35] sees the cell as the fundamental unit of life, a factory of enzyme-driven biochemical pathways, as in Fig. 1, left side. Modern medicine aims to alleviate disease or ailments at the cellular level. In contrast, AYUSH systems extend the aim of treatment from alleviating symptoms to removing underlying causes, i.e. healing. (5, 6, 40.41) They are not restricted to cells, but extend to the whole organism, understanding its complexity at all levels: cells, tissues, organs, organ systems and organism [37]. AYUSH is holistic, Graphical Abstract.

The new model derived from complexity biology [30] and AYUSH specifically recognizes the importance of epigenetic regulation to maintain balance in biochemical pathways [38], using increased/decreased production of enzymes catalyzing biochemical reactions in each pathway.

Hormesis [44] is a phenomenon where nano quantities of a toxin result in *increased* rate of the reaction of the poisoned enzyme. Lowering levels of reaction products increases transcription of gene(s) encoding the enzyme. The same mechanism enables cells to adapt to changes in pH and temperature, essential for organisms to survive in changing environments; the failure of modern biology to teach it, is probably based on scientists' habit of growing cells and other organisms in ideal laboratory conditions that do not require adaptation. In the real world, organisms have to adapt to time of day, time of year etc.

In the Sandwich Model in Fig. 1 right side, the upper layer, epigenetics regulating expression of each gene, also includes the ability to optimize its level of expression. Such optimization permits an organism to function most efficiently, and so to maximize its prevalence in its ecological niche; to 'thrive and survive'. The ability to function optimally constitutes a fundamental property of all organisms. Regulation is the aspect of organism function that is optimized; achieving optimal regulation [37,40,41] is integral to dynamics in all organisms.

Using Optimal Regulation to guide treatment strategies: AYUSH systems recognize many factors in life that compromise system regulation, poor dietary habits, bad lifestyle, not allowing the physiology to adapt to changes of season. All the AYUSH systems incorporate strategies of treatment that aim to restore system regulation to optimal, i.e. to restore health. Typical is the approach of Yoga Therapy [6–9], described in the Introduction, where a major aim of treatment is to fortify Prana, the Life Breath, equivalent to Life Force in Naturopathy. Such systems also cure physical conditions resulting from mental trauma [10,45].

Naturopathy emphasizes the pathogenic effects of build-up of toxins; its treatments include good ways to remove them [5]. In contrast, drugs used in modern medicine are designed to occupy enzyme active sites, preventing them from working. They thus act just like toxins; a good reason why the system is also called 'Allopathy'. Now, an important corollary: the upper layer in Fig. 1's right side 'Sandwich Model' means that all toxins, including drugs, induce *integrated* responses. These will inevitably include unwanted secondary changes in enzyme levels. Side-effects of drug treatment are thus *unavoidable* disadvantages of that system.

Regarding Shadkriya Kala, its first three stages are those of the stress reaction: adaptation, maladaptation and malfunction [46]. In later stages, dysfunction becomes irreversible and the organism cannot survive, as in Claude Bernard's 'Pathophysiologie' [47]. Shadkriya Kala was conceptualized over thousands of years. Ayurveda's earliest text, Charaka Samhita [43] gives three stages, but Sushrutha Samhita, composed at the time of Lord Buddha, 2500 years BP, names six stages, a complete pathophysiology. (Sutrasthana in 42) Bernard, realizing that his work was a pathophysiology of death, speculated that a complete theory must exist, starting from health. Little did he know that Ayurveda had been teaching it for over 2500 years.

In Ayurveda, health is expressed either as 'Arogya' or 'Swasthya'. Arogya translates directly as 'free from disease (Rogya)', as in the WHO declaration [4]. Swasthya literally means, 'established (sthya) in self (swa)'. But 'self' implies feedback, the root of regulation, and connects to health as 'Optimal Regulation', the new scientific definition [38,40]. Concerning whether or not cure can be achieved, Ayurveda gives more detail. When one dosha is out-of-balance, restoring balance is easy; when two are out-of-balance, it may often be possible, but not always; when all three are out-of-balance, nothing can be done [42].

A 2005 paper [26] suggested that scientific understanding of complementary medicine would advance theoretical biology. Results given above confirm this idea: first, the systems theory of Tridosha [17,36,37], with its holistic implications for organism dynamics. Successive refinements then resolved limitations in the molecular biology model of life [35], explaining organism adaptability, competitiveness and health, which that model could not.

These advances in our understanding of biology integrate our understanding of properties of organisms derived from modern science with various aspects of their functioning proposed by AYUSH systems. The net result may be termed an Integrative Biology. The Indian Government recently appointed a high-powered committee through NITI Aayog to plan India's next generation of medical education. The plan aims to include all AYUSH systems of medicine, on a par with modern medicine. Medical colleges and universities will teach similar syllabuses [3]. Graduating students will understand all such systems of medicine,

and be able to specialise either in one of modern medicine's specialties or one of AYUSH's. Those wishing to pursue a medical discipline not from their own college will be able to do so.

5. Conclusion

This paper proposes an 'Integrative Biology', based on the expanded 'Sandwich Model' of biology, together with additions from AYUSH systems of medicine. Integrative Biology offers scientific explanations for many aspects of the AYUSH systems, thus forming the foundation for a system of Integrative Medicine that can cure chronic disease. The new system can also nip tendencies to NCDs in the bud, before they fully develop, acting as preventive medicine.

Declaration of competing interest

Neither Author has any Conflict of Interest to declare.

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