SYSTEMS BIOLOGY MEETS TRADITIONAL KNOWLEDGE SYSTEMS IN MEDICINE AND PHARMACOLOGY: POTENTIALS AND PITFALLS

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There is a revolution occurring in medicine. Until now, the prevailing Western paradigm based in reductionist science was situated in an approach that focused primarily on disease, and that looked for a singular target that was acted upon by a singular bioactive compound to treat it. The problem with this is that biological systems are complex, and elucidating the individual components is insufficient to understand the emergent properties that occur from the interactions within a dynamic system. In the last decade, systems biology has developed as a way to handle this complexity.

It has its genesis in general systems theory, and using the computational power of new technologies combined with massive amounts of data now generated, to model systems and make predictions based on these models. It aims to understand how the phenotypic behaviour of a system emerges from the individual components and their interactions. This is causing a paradigm shift in medicine referred to as "P4 Medicine" - Personalised, Preventative, Predictive and Participatory. It is a person-centric rather than disease-centric approach that focuses on health as opposed to disease, and the understanding that the disease state is unique to the individual and requires a personalised treatment protocol (Galas *et al*).

Each unique genome interacts in various ways with the environment, which is always a dynamic, open system, to maintain a state of health in the individual - or develop disease. In the study of a complex disease such as cancer it is being realised that tumours of the same tissue type have different sets of defects in dozens of different genes (Wood *et al*), and the expression or silencing of these genes depends on numerous factors that are just beginning to be understood. For instance, malfunctions in certain pathways such as fatty acid synthesis has implicated the role of diet in the development of cancer (Crou-Bou *et al*). The onset of Type 2 Diabetes has recently been linked to the exposure to a virus by a genetically susceptible individual (Conger), and gluten consumption has been associated with schizophrenia, Type 1 Diabetes and Huntington's Disease (Wei) among others. Even when a particular gene is determined to be important in the manifestation of a pathology this does not mean there is a clear cut treatment, as proteins have complex interactions at the transcriptional, translational and post-translational level (Turnbull). Pharmaceuticals are also metabolised differently depending on an individual's genetic makeup. There are many different paths that can lead to what appears physically as the same illness, and correspondingly different ways to return to a healthy state.

It is interesting to note that this "new" approach to medicine has similarities to traditional knowledge systems. Turnbull defines traditional knowledge (TK) as a "cumulative body of knowledge and beliefs, evolving by adaptive process and handed down through generations by cultural transmission." The traditional healing systems of Asia are related to each other and are based on theories of constitution, which identify unique characteristics of an individual and group them into similar phenotypes. For example, in Traditional Chinese Medicine, disease susceptibility and drug response is thought to depend on an individual's constitution type and the way it interacts with its environment. A system of personalised medicine is used in order to obtain optimal response to the treatment.

It's the very complexity of these alternate medical systems that has made them impossible to study with a reductionist methodology. It is proposed that systems biology can finally provide a platform to evaluate them in an evidence-based way. Studies are already indicating connections between phenotypic categorisation, metabolism and gene expression in both TCM (Ma *et al*) and Ayurvedic medicine (Joshi *et al*). Freeman, cited by Mazzocchi, suggests that systems biology is an approach that has much in common with TK systems in that both do not rely on a "*linear conception of cause and effect, but rather as a world made up of constantly forming multi-dimensional cycles, in which all elements are part of an entangled and complex web of interactions*."

Both Western science and TK systems make use of a plant-based pharmacopeia. We share many biological pathways and genes with plants due to our more than 400 million year-long coevolution. There are many

examples of human cells recognizing plant metabolites, such as plant sterols forming structural analogs of hormones and alkaloids that affect central nervous system activity (Kennedy). It is thought this is related to a direct symbiotic relationship that has developed between plants and vertebrates over time.

The World Health Organization reports that countries in Asia and Latin America primarily depend on traditional medicine, and in Africa up to 80% of the population uses traditional medicine for primary health care. In the West in areas such as cancer, pain and parasites, natural products have provided our core treatment options. In cancer treatment, from the 1940s-2012, 74.8 percent of drugs used were classed "other than S (synthetic)" (Newman *et al*). It is estimated only 1% of the 250,000 species of flowering plants have ever been scientifically researched for medicinal value. Despite this unexplored potential, in general the pharmaceutical industry has moved away from using plants as lead compounds over the last few decades, preferring to concentrate on testing high volumes of synthetic, small molecules that have been assembled in a laboratory. This has generally been considered a failure, as the average number of new molecular entities released on the market has remained constant since the 1950s, despite research and development costs increasing exponentially. It is now estimated that the development of a new drug can cost up to five billion dollars. Pharmaceutical industry leaders are calling this crisis an unsustainable situation.

The move away from natural products towards synthetics is attributed to practicalities that make working with plants difficult from a Western approach. The reductionist methodology attempts to isolate molecules without regard for the complex environmental systems in which they are embedded. Fluctuations that occur naturally in systems can mean that different samples of collected materials may contain differing amounts of active compounds due to age, season or time of day collected. Without knowing what other factors influence the system, reproducible results become problematic.

TK systems (specifically indigenous systems) utilise thousands of years of empirical and intergenerational observation of the interactions between the components of the environment that inform their relationship to the land, fauna and flora which inhabit it. Indigenous world-views can be characterized as holistic and ecologically based, with spiritually framed, contextualized and inclusive knowledge used to maintain society. Indigenous knowledge emphasizes the collective sense of belongingness with a people and the land they share, in contrast to Western epistemologies which are individualized and disconnected into an universal abstract.

Epistemological conflicts become apparent when considering a typical ethnobotanical research scenario. Information (i.e. plant material and its use) is extracted from a TK system, then scientists prepare the plant to perform a bioassay which looks for biological activity. If found, the material is then fractionated to determine which compound is contributing to the biological effects. It is then isolated and synthesized in the laboratory (if possible), usually with changes to the molecular structure. Ostensibly this is to improve the efficacy of the compound, but with complex patent laws surrounding natural products, it also ensures that a patent can be issued for a novel product.

The difficulties with this approach are manifold. Attempting to evaluate one system of knowledge through the methodology of another is problematic. Extracting information that seems to measure up to scientific criteria and ignoring the rest can threaten TK systems with dispossession, whilst useful information may be lost.

Also, TK systems often have completely different descriptions of disease aetiology. In identifying plants, a biologist will observe which plants are collected and identify them with a Western scientific taxonomy. There are cases where TK holders may identify different "types" of species of plants that are not differentiable to a Western-trained biologist. Preparation of the plant may not follow the traditional protocol, such as using water-based extractions whereas ethnopharmacologists may use solvents.

Furthermore, bioassays give indications of bioactivity, but are extremely simple in comparison to how a plant compound is metabolized in the human body, as secondary metabolites may be contributing to the clinical effects as well. The presumption that there is one compound in a plant that is responsible for the bioactivity is extremely limiting, as plants can contain up to 30,000 constituents. TK holders suggest synergy between the compounds is responsible for the clinical effects. Studies using systems biology protocols are now validating this. It has been demonstrated that gene expression profiles are different when herbal components or mixtures

are given in isolation or are administered together (Panossian *et al*). In a Cochrane study St. John's Wort was determined to be as effective as contemporary pharmaceutical anti-depressants (Linde *et al*), but without side effects, yet it has been documented that no single compound in the herb is responsible for its clinical efficacy, and it is accepted that various bio-actives work synergistically (Butterwerk *et al*). It has also been suggested that some of the synergy that occurs between compounds in a plant may contribute to lessening the side effects of the active constituent (Russo).

Finally, synthesis and manipulation of the compound in the laboratory may be done to improve the clinical efficacy, but this manipulation could also conceivably contribute to side effects. It has been reported that one in five new molecular entities (novel drugs), and one in three biologics, are so toxic they have the most severe warning labels, or are withdrawn from sale shortly after release (Lexchin).

With an emphasis on complexity and relationships, systems biology could appear to be a way to bridge these two opposing methodologies. Using metabolomics (the study of the interactions between all of the metabolites within a cell), complex phytopreparations can be studied without isolating active components. This has been suggested by numerous ethnopharmacologists as a possible way to re-evaluate the use of plants as medicine, and their role in pharmaceutical development (Yuliana et al).

Systems biology is a tool that allows better modeling and prediction of complex systems, but it does not remove the inherent power imbalance that permeated colonial interactions with TK systems. This new technology should not simply operate as a new "meta" system of knowledge that continues to attempt to simply validate/exploit other epistemologies extracted from their original context, practice and belief systems. The legacy of biopiracy from earlier interactions between scientists and TK holders looms large in the field of ethnopharmacology.

The Indigenous scholar Willie Ermine proposes a framework for interaction between epistemologies through communicating in what he terms “ethical space". Ermine suggests that when two human communities are disconnected through their vastly different knowledge tradition, philosophy and political realities, then two solitudes are created, each claiming their own distinct an autonomous view of the world, which opens a theoretical space between them. Ermine suggests it is possible that within this space, an ethical space can be created to dialogue:

"*The idea of an ethical space, produced by contrasting perspectives of the world, entertains the notion of ‘engagement.’ Engagement at the ethical space triggers a dialogue that begins to set the parameters for an agreement to interact modeled on appropriate, ethical and human principles. […] It is a way of observing, collectively, how hidden values and intentions can control our behaviour, and how unnoticed cultural differences can clash without our realizing what is occurring. Attentive work on these issues has not occurred in Indigenous-West relations, nor has there been a framework that enables this discussion to happen. […] The new partnership model of the ethical space, in a cooperative spirit between Indigenous peoples and Western institutions, will create new currents of thought that flow in different directions and overrun the old ways of thinking*.” (Ermine)

Furthermore, in creating an ethical space in which to dialogue with other knowledge systems, aspects of those systems which have historically been dismissed as "superstitious" may be seen from another perspective, and found to be useful even though they were initially unable to be perceived through the primary knowledge system. In the example of the Ashaninka tribes from the Amazon, shamans are reported as being able to detect the difference between two botanically identical chemotypes of the plant *Uncaria Tomentosa*. One contains a pentacyclic ring which is useful medicinally, whilst the other does not. The shamans do this at a distance and the knowledge is gained through secret ceremonies (Keplinger *et al*). Clinical studies have since confirmed that the pentacyclic oxindole alkaloid chemotype is demonstrated to be clinically useful in the treatment of HIV, cancer and rheumatoid arthritis (Williams). The other chemotype can actually counteract these effects. Initially, when this herb was used in the West the chemotypes were not differentiated, which obviously affected the efficacy of the treatments. It was only through learning from the Ashaninka shamans and their methodology, which is inexplicable within a Western framework, that this knowledge was discovered.

It has been suggested by some ethnobiologists, that certain plant mixtures used by tribes such as poisons, or hallucinogenic mixtures, are too chemically complex to have developed from empirical knowledge alone. Indeed shamans, when asked, describe their knowledge about the healing properties of plants as coming from the plants themselves, often through elaborate rituals. This type of knowledge, which can be called "revealed knowledge", provided through dreams, visions and intuitions, is not recognized in Western science. As we exclude this component we may lose knowledge that is valuable and useful to society, and contribute to its eradication as traditional communities are increasingly threatened with cultural as well as environmental destruction.

If Western science can find a way to enter an "ethical space", recognizing its own constructed nature as being but one of many systems of knowledge that has no claim to precedence, it would not only benefit from technological progress but also from the exposure to new ethical and community-based models, and different ways of accessing knowledge that have their basis in other knowledge systems. For example, due to complex patent laws and the exorbitant costs of human trials in pharmaceutical development, there is no economic incentive for pharmaceutical companies to progress promising in-vitro studies of crude plant extracts through to human trials, until a patentable molecule is synthesized. This filtering of knowledge through the ownership of patents should be contrasted with research-supported TK systems, where information about the medicinal value of crude plants is held by, and for, the community as a collective.

Current shifts in medicine and pharmacology are demonstrating a move away from reductionism and towards a more holistic systems-based approach which is beginning to validate knowledge that has existed for millennia in TK systems. Rather than continuing to presuppose a universal claim to the path to knowledge, hopefully it will encourage participation in ethical dialogues with other epistemologies. Indeed, until this occurs we can only wonder at what other knowledge is yet to be shared that could be mutually beneficial to all, irrespective of which world-view they look from.

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