

Systems Thinking in Medicine and New Drug Discovery

Systems Thinking in Medicine and New Drug Discovery:

Volume One

By

Robert E. Smith

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This book is dedicated to my grandchildren. I hope they can work with others in their generation to end civilization's addiction to fossil fuels and reverse the damage that my generation has done to the environment.

CONTENTS

Preface	xi
Chapter One.....	1
Overview of Systems Thinking	
1.1 Introduction.....	1
1.2 Reductionist Thinking and DNA	7
1.3 Systems Thinking.....	15
1.3.1 Definition and the importance of change	15
1.3.2 Misconceptions that are clarified by systems thinking.....	16
1.3.3 Characteristics of systems thinking.....	21
1.3.4 The roots of systems thinking	42
1.3.5 Autopoiesis and Gaia.....	43
1.3.6 Systems view of autopoiesis and stem cells	50
1.3.7 The importance of networks in life	53
1.3.8 Genetics and systems thinking	66
1.3.9 Nonlinearity and rhythms in living systems	81
1.3.10 The –omics, from genomics to personal –omics	104
1.3.11 A multidimensional, non-linear view of diseases.....	109
1.3.12 Drugs that bind to multiple targets	110
1.3.13 Modularity of biological networks	111
1.3.14 Going beyond genomics and looking for hidden connections	112
1.3.15 Tools for understanding metabolism better	113
1.3.16 Evidence based medicine and the Critical Path Initiative....	115
1.3.17 Cancer Genome Characterization Initiative, CGCI.....	120
1.3.18 Systems-based thinking in education, in contrast with reductionist thinking in advertisements and propaganda.....	122
1.4 More systems thinking is needed	141
1.5 Reductionist thinking is still useful.....	147
Chapter Two	167
The Deep Ecology of the Human Biology	
2.1 The human ecosystem, holobionts, hologenome and viruses.....	167
2.2 The widespread existence of microbes in the human body.....	170
2.3 Gut microbiome and the enteric nervous system (ENS)	172
2.3.1 Composition of the gut microbiome.....	172

2.3.2 Interactions and communication between the ENS and the rest of the body	175
2.3.3 Communication between the gut microbiome, ENS, brain and immune system	180
2.3.4 The gut microbiota and ENS comprise an entero-endocrine organs	184
2.4 The role of the gut microbiome in preventing diseases.....	187
2.5 The role of gut microbiome dysbiosis in causing diseases	191
2.5.1 The importance of biodiversity	191
2.5.2 The gut microbiome and inflammation	193
2.5.3 The benefits of vegan and vegetarian diets	193
2.5.4 The gut microbiome and cardiovascular diseases	196
2.5.5 The role of the gut microbiome in stress, anxiety and neurodegenerative diseases	197
2.5.6 The importance of healthy microbiota in obtaining an effective response to Vaccines.....	201
2.5.7 The importance of oral health and preventing periodontal disease.....	203
2.6 Factors affecting the composition of the microbiome.....	206
2.7 Viruses are important, too	215
2.8 Eukarya in the human microbiome	219
2.8.1 Introduction to the microbial eukaryotic cells in the human microbiome.....	219
2.8.2 Fungi	220
2.8.3 Protozoa and intestinal worms (helminths)	223
Chapter Three	241
Systems Thinking in New Drug Development	
3.1 How new drugs are developed	241
3.1.1 Select a disease.....	245
3.1.2 Select a therapeutic target or phenotype.....	250
3.1.3 Find a lead compound	284
3.1.4 Improve the lead compound	336
3.1.5 Drug delivery.....	339
3.1.6 Manufacturing and cGMP	347
3.1.7 Clinical trials	356
3.1.8 Many drugs that were developed and approved had a single therapeutic target	358
3.1.9 Combinations of drugs are also used and are being developed.....	360

3.1.10 Some targets are now known to have formerly unexpected biological roles	365
3.1.11 Some drugs may be useful in treating other diseases	366
3.1.12 The Reemergence of Phenotypic Screening	369
3.1.13 Other new approaches to new drug discovery	373
3.2 The difference between how prescription drugs, dietary supplements and ‘super-foods’ are developed and used.....	380
3.2.1 ‘Superfoods’	387
3.2.2 Dietary supplements: from amphetamine to fish oil to vitamin D and folic acid	393
3.2.3 A complex, nonlinear dynamic systems perspective on Ayurveda and Ayurvedic research.....	415
3.2.4 Discovery and development of innovative drug from traditional medicine by integrated chinmedomics strategies in the post-genomic era.....	417
3.2.5 A complex systems science perspective for whole systems of complementary and alternative medicine research.....	417
3.2.6 A Pilot Feasibility Study of whole-systems Ayurvedic medicine and yoga therapy for weight loss.....	418
3.2.7 Prescription drugs and weight loss supplements for weight loss.....	419
3.2.8 Prescription drugs: strict protocols and quality management systems, take much longer to reach the market	422
3.3 Immunotherapy – using one’s own body to cure one’s self.....	424
3.4 Synthetic biology and CRISPR technology in new drug development	437
3.5 Rapid prototyping by 3D and 4D printing	447
3.5.1 Introduction	447
3.5.2 Biodegradable scaffolds	448
3.5.3 Other applications of 3D and 4D printing	448
3.5.4 Other personalized medical devises	451
Appendix	494
Primer on Physical and Analytical Chemistry	
A1.1 Introduction.....	494
A1.2 Ultraviolet-Visible (UV-Vis) Spectrophotometry and Fluorescence Spectroscopy.....	506
A1.3 HPLC and UPLC	511
A1.4 Gas Chromatography, GC.....	515
A1.5 Mass Spectrometry, GC-MS and LC-MS	518
A1.6 Quantitative Analysis.....	539

A1.7 IR and NMR.....	540
A1.8 Magnetic Resonance Imaging, MRI.....	555
Abbreviations and Acronyms Used.....	558
Index.....	576

PREFACE

Medicinal chemistry is undergoing an important paradigm shift (or way of thinking) from reductionist to systems thinking. This is based on a similar paradigm shift in medicine and the pharmaceutical industry. Network science is an integral part of this. It has led to the emergence of network medicine. It not only aims to develop safe and effective new prescription drugs for patients who become sick, but also to recommend diets, lifestyles and even some dietary supplements that can prevent diseases. Instead of focusing on just one aspect of health, network medicine uses systems thinking to predict peoples' susceptibilities to diseases and find ways to prevent them. In addition, patients who have specific cancer-causing oncogenes are being identified before clinical trials begin. That way, only the patients who are likely to benefit from the anticancer therapy will be recruited into clinical trials. This will increase the success rates of these trials and help to reduce the cost of new drug development and healthcare.

Network medicine also emphasizes precise, personalized treatments, in which patients and their caregivers can actively participate. It recognizes the important human need for patients and caregivers to be involved in preventing and curing their diseases. This is done with the types of extensive teamwork, open collaborations and continuous feedback which are hallmarks of Total Quality Management (TQM) and Total Quality Leadership (TQL) that are used in modern businesses. This leads to new insights. In business, it means that every employee is important because they all make crucial contributions to the organization. It also means listening to the voices of the customers, so their demands can be met. Similarly, TQM and TQL in systems medicine means listening to the voices of the patients and their caregivers, so their health needs can be met. It also means that the needs of every part of the human body are recognized by other parts of the body that interact synergistically and communicate with each other constantly. In addition, there is a deep ecology in the human body in which even the lowliest viruses and Bacteria make crucial contributions to the health of their human hosts and serve as essential parts of the neuroendocrine immune system. So, the human body operates under the principles of total quality, in which every component interacts, communicates and undergoes nonlinear feedback and feed

forward mechanisms. However, the human body is not a machine that is involved in manufacturing. Machines don't make themselves. Humans and other living creatures make themselves in the process called autopoiesis (self-making). So, TQM in the human body means total quality making, not total quality manufacturing, like it does in some industries.

The main goals of this two-volume set are to inform people with different backgrounds about the new ways that we are looking at human life and medicine, help healthcare professionals do their jobs better, provide background information and references for patients and their caregivers, as well as clarify some serious misconceptions that have emerged. For example, some people believe that the FDA and other governments' regulatory agencies are in a conspiracy with pharmaceutical companies and physicians to keep people sick, so they can maximize profits and continue to sell patients prescription drugs that don't cure any diseases. This thinking can lead some people to avoid seeing physicians, who prescribe 'chemicals'. Some people believe that all dietary supplements are always safe and effective – especially if they are labeled 'natural'. Many misconceptions like these can be exposed by using systems thinking.

The first volume provides an overview of systems thinking. The first chapter compares and contrasts reductionist and systems thinking in biochemistry and medicine. Some basic principles of systems thinking and network science are introduced. The new ways that diseases are prevented, treated and cured are described. This includes changing how new drugs and dietary supplements are being developed. Network science is crucial in this change, as is using one's own body and natural resources to prevent, treat and cure diseases. At the same time, a huge, interactive network supports healthcare. It starts with the smallest viruses and Bacteria. It includes patients, caregivers, nurses, physicians, hospitals, research institutes, universities, industry and many government agencies. It is based on a holistic view. Doctors no longer engage in a man-to-man struggle to cure the disease. Instead, they work with large interdisciplinary teams to focus on treating the whole patient and not just the disease. Moreover, pharmaceutical companies have realized that the former, secretive approach to developing new drugs was inadequate. Now, they collaborate with each other and with academia and even individual patients working at home. Part of this paradigm shift is the realization that there is a deep ecology.

So, the second chapter in the first volume also includes a description of how the human body is an ecosystem, consisting of not just human cells, but also viruses, Bacteria, Archaea, and Eukarya. At the same time, a type

of deep ecology has emerged in science and medicine. That is, biology and medicine are just as important as math, physics, chemistry, engineering and industry.

The third chapter in the first volume describes how systems thinking is used in every stage of new drug development. In this new paradigm, some of the best work is done by people who are educated in more than one field, so they can do interdisciplinary research using systems thinking. They are using 3D printing to produce plastic models based on CT and/or MRI images of patients, so they will know what to expect when they start surgical procedures. Such models are also quite useful in teaching surgical techniques to new residents. Interdisciplinary teams are also using 3D and 4D printing to make devices that are specific for each patient and can alter their shape as young patients grow and recover. In addition, interdisciplinary scientists are using 3D printing to make personalized organs on a chip to test the safety and efficacy of new drugs. This is eliminating the need for animal toxicity testing. Moreover, 3D printing may be able to provide personalized food and feed the world's growing population.

However, it's also important to look for hidden connections. For example, one substance used in 3D printing (UVR-6105) became popular decades ago because it's resistant to photobleaching by UV light. Also, it is less genotoxic than the substance it replaced (bisphenol A diglycidyl ether, or BADGE). However, UVR-6105 can undergo hydrolysis that can be catalyzed by either esterase enzymes or the acid in gastric fluid. The hydrolysis products are produced in an autopoietic system that resembles death more than life. The hydrolysis products are more bioavailable and more carcinogenic than BADGE. Instead, a silicone-based material is resistant to hydrolysis and has very low toxicity. It might be better for regenerative medicine and for making devices that will go into patients' bodies.

CRISPR technology is another important advance. It may be able to produce new cures for diseases as well as make new organisms. Sterile mosquitoes are being made that may eliminate malaria and the Zika virus. Genetically modified Bacteria and algae may be able to remediate pollution and make biofuels. However, there are many potential pitfalls. Just as many fear the uncontrolled dissemination of genetically modified foods into the environment, some fear the release of genetically modified Bacteria and plant seeds. Also, CRISPR could potentially make designer babies and people with super-human powers.

In the meantime, many people think that only natural remedies should be used and chemicals (prescription drugs) should be avoided. As a result, dietary supplements are widely consumed. Some are quite dangerous and

potentially deadly. So, a quick, easy way to see if your turmeric is adulterated with carcinogenic chromium (Cr^{6+} , hexavalent chrome) is presented. In addition, the different ways that prescription drugs and dietary supplements are developed, brought to market and sold are discussed.

Systems thinking is an interdisciplinary process requires scientists to learn other scientific disciplines. So, there is an Appendix in volume 1 that describes some basic chemistry to biologists. There is another Appendix in volume 2 that explains some basic principles of neurology, immunology and endocrinology to chemists and non-specialists.

Volume 2 starts by describing predictive, preventive, personalized and participatory P4 medicine. This includes the use of systems thinking in primary care medicine and an explanation of how our understanding of causality has changed. It also tells what P4 medicine does and how all the stakeholders are collaborating and using evidence based medicine. This includes the Advancing Regulatory Science Initiative and listening to the voices of the patients, in the spirit of TQM. There is also a description of how metabolomics shows what is happening within a patient's body and provides fundamental insight into the causes of diseases. Targeted radiation therapy is also described, along with precision systems medicine that targets cancer stem cells. The second chapter discusses the important role of inflammation. This includes dispelling some previous misconceptions on how dietary antioxidants work to prevent diseases, including cancer. Since nutrition and lifestyle are important in preventing diseases and maintaining good health, they are discussed in chapter 3. This includes an explanation of how the superfood cult is misleading many people – especially women. In fact, the only true superfood is mother's breast milk. The second volume finishes by describing the harmful effects of a toxic environment, with recommendations about trying to reverse the effects of global climate change through systems thinking. Then, there is an Appendix that describes the basic principles of the neuroendocrine immune system.

It's also important to be able to speak each other's languages. So, several examples are given of the same word, abbreviation or acronym being used in very different ways in different fields of science. Also, since many people who don't speak or write English as a native language can easily become confused by the way that numbers are written in English. The English language uses commas (like 10,000) where other languages use periods (like 10.000). So, in this book, the number ten thousand (and all larger numbers) are written using a space (like 10 000) instead of a

comma or period, except when directly quoting sources that were written in English.

This book also provides information that people can use in their work and their lives. For example, if a healthcare professional is ever challenged by someone who believes that he or she is part of a conspiracy to keep dietary supplements out of the hands of people who need them, he or she only needs to talk about folic acid. It's a dietary supplement that physicians and governmental regulatory agencies help people find and take to prevent birth defects and many types of cancer. It can be found in most breads and cereals, as well as vitamins for pregnant women. It tells how mother's breast milk is the only true superfood. Also, many databases, government websites and other internet sources are provided, along with over 1600 references to the scientific literature. There is also a list of hundreds of toxic substances that have been found in dietary supplements and information (m/z values that can be seen in a mass spectrometer) that chemists can use to detect them. Moreover, there have been cases where seemingly harmless supplements like vitamin D can be formulated wrong by manufacturers. So, educating physicians and patients on the adverse effects of high doses may be the most important way to prevent unnecessary or excess supplementation. Moreover, the FDA and other governments' regulatory agencies are not in a conspiracy to keep people sick. It is just the opposite. They and many other organizations and individuals are collaborating to make modern medicine predictive, preventive, personalized and participatory.

This work should not be taken as having an impact on the FDA or any other governmental regulatory agency.

CHAPTER ONE

OVERVIEW OF SYSTEMS THINKING

1.1 Introduction

Systems thinking has become an important paradigm in many areas of science. Fritjof Capra described how it is important in modern physics and biology [1, 2]. He and Pier Luigi Luisi further showed how it is important in mathematics, biology and medicine [3]. This includes a deep ecology, in which humans are viewed as just one of many equally important parts of the global ecosystem [2]. However, medicinal chemistry has been viewed as being conservative, since it only recently started emphasizing the need for systems thinking [4-6]. So, one of the primary goals of this book is to describe how the tools and methods of systems thinking are being used to improve medical science and accelerate new drug development. This contrasts with the ways that medicine and new drug development were done previously using reductionist thinking. That is, many prescription drugs were developed based on their abilities to either activate or inhibit a single therapeutic target, such as an enzyme or an ion pump [4]. This was based on reductionist thinking that preached that one should look for the single root cause of a disease. More recently, many new drug candidates and medical devices are being developed based on their ability to modify the activities of many therapeutic targets [4-6]. This is based on systems thinking, which recognizes that complex problems (like diseases) have many causes. Not all of them are obvious upon initial inspection. So, researchers and pharmaceutical companies are looking for hidden connections, which is another important feature of systems thinking [7]. This includes looking for ways to affect protein-protein and protein-DNA interactions and the development of allo-network drugs that don't bind to an enzyme's active site [6]. This contrasts with reductionist thinking, in which a drug should bind to the active site of an enzyme or the ligand-binding site on a protein receptor or ion pump. This is how medicinal chemistry was once taught.

However, there is a growing consensus that systems thinking is improving healthcare and new drug development dramatically [8]. In some

ways, this is a return to the way drugs were developed before the 1970s – before many therapeutic targets were known. Not until the 1980s was the paradigm shifted from observations of physiology to the studies on the molecular level. In the late 20th and now in the 21st Century, a Renaissance in systems thinking is occurring and it is being used to develop new, improved prescription drugs and medical devices. This was due, in part, to new advances in robust high-throughput platforms that produce much data, the construction and free public access to curated databases, and the emergence of interdisciplinary teams that conducted research that enabled us to understand the data better. This has led to a new code of behavior, in which data are shared, with an emphasis on quality rather the quantity of data. It also led to the development of predictive toxicology. Still, datasets are growing exponentially in size. The data describing the three billion nucleotides in the human genome grew to about one petabyte (2^{50} bytes, 1024 terabytes or about a million gigabytes) of data by 2008 and one Exabyte (billion times billion bytes) by 2012. This increase has inspired the creation of new computational tools that help us understand better the complexities of human health and disease. In this context, complexity has been defined as follows: “in a complex system the whole is more than the sum of its parts”. There are several properties of complex systems. They have many heterogeneous interacting parts. They operate on many different scales. There are many possible states, as well as relatively complicated laws governing their transitions. Complex systems have emergent properties and are sensitive to initial conditions. There are path-dependent dynamics and a networked hierarchical connectivity. Autonomous agents interact. There is self-organization, as well as collective shifts and non-equilibrium dynamics. Complex systems can adapt to changing environments. Finally, there are co-evolving subsystems, ill-defined boundaries and multilevel dynamics [8].

So, extreme reductionist thinking is seldom useful any more when developing new drugs [8]. However, the other extreme that tries to take into account all the possible variables and their interactions is not feasible. Still, complex systems can be understood well enough to make systems thinking very valuable. The structure of complex living systems is modular and has many redundant or expendable parts. So, it is important to identify the most important segments of the system. Moreover, the state space of complex living systems has a relatively low number of major attractors. So, there is some simplicity in complex systems. As a result, many of the emergent properties of complex living systems can tolerate some error in the data that are used to predict them or in the biochemical factors that determine them [8].

Systems thinking has led to a better understanding of diseases [8]. They are now understood to be perturbations in the complex networks in the human body. In addition, network analysis is becoming crucial in new drug development. Networks are usually visualized by graphs containing points (nodes) that are connected by line segments (edges) that may or may not have a direction (making them a vector). However, the nodes in complex, cellular systems are not points, but rather biopolymers (DNA, RNA, proteins) that have their own network structures. Moreover, a good understanding of network dynamics is crucial for understanding the complexities of diseases and the actions of drugs. So, edges can have a direction and a sign (activation or inhibition). They can also have conditionality, since some edges are active only if one of their nodes have another edge [8].

An excellent review article listed several tools that are available for visualizing networks as well as human disease-related networks [8]. It also provided data on networks, and made network-based predictions of disease-related genes that can serve as biomarkers. It described different methods that are available for comparing networks. There is also a list of chemical compound similarity networks, a list of resources for studying protein-protein interaction networks and signaling network resources, as well as lists of metabolic network resources and resources related to drug design. Finally, there is a list of system-level hallmarks of drug quality and trends of network-related drug design that are designed to help achieve the hallmarks [8].

It is also important to understand network theory when developing new drugs using systems thinking [8]. Networks exist throughout living systems [5]. The human brain contains a network of neurons that are connected by axons and supported by glial cells. Cells are networks of ions and molecules, connected by biochemical reactions. Some ions and molecules (such as H^+ , adenosine triphosphate or ATP and H_2O) are highly connected nodes in the biochemical network. On the other hand, some compounds (like 1,3-bisphosphoglycerate) are intermediates in just one metabolic pathway and are not hubs. At the same time, people, animals and plants cannot exist without networks of symbiotic relationships. The average adult human has about 10^{15} cells, only 10% of which are human. Almost all the rest are Bacteria. They help us digest our food while properly treating and excreting wastes. Moreover, societies are networks of people, connected by family, friends and work. Food webs and ecosystems consist of networks of organisms [5].

Properly organized networks are essential for life and help make us human [5]. We are complex, self-regenerating, autopoietic organisms,

whose bodies are ecosystems living in larger ecosystems. Life is sustained by a network of production processes, in which the function of almost every component is to participate in the production or transformation of itself and the other components in the network [2, 3, 9]. So, network theory and systems thinking have emerged as guiding principles in biology and medicine [9].

Information storage and processing in cells, along with the execution of cellular programs exist in distinct levels of organization. Our genes may contain essential information for life, but they are not sufficient. RNA, proteins, enzymes, hormones and proper organization are also needed. Genes interact with histones and protein transcription factors, as well as with RNA and with other genes. The activation and repression of the expression of genes depend on the environment. There is structural coupling [5].

There has also been a change in how 3D printing (rapid prototyping) is used. That is, rapid prototyping and reductionist thinking were once used to make models of proteins with a single ligand or inhibitor bound to it [10]. This was used to demonstrate the lock and key model of ligand binding in the Smithsonian Institute of American History's exhibit "Chemistry in American Life". Plastic models of proteins and DNA were used in the Brookhaven National Laboratory to show their three-dimensional crystalline structures, based on X-ray diffraction. It ignored the fact that proteins actually have many different structures when they are dissolved in an aqueous solution, such as the cytoplasm of cells. It also assumed that all proteins are the same in everybody. Reductionist thinking preceded personalized medicine. Rapid prototyping has now improved so that it can be used with systems thinking to make personalized devices such as a bioresorbable tracheal splint for an infant who was critically ill [11]. It is now called three- or four-dimensional (3D or 4D) printing. A social, medical and scientific network has emerged from systems thinking. It enables predictive, preventive, personalized and participatory (P4) medicine. The days when reductionist thinking taught that diseases can only be cured by a man-to-man struggle between the doctor and the disease are gone forever. We now treat the person and not just his or her disease. We also realize that we all need some personalized treatments, even though some preventive treatments (like vaccines) are useful to almost everybody. All people (including homozygotic twins) are unique. Medical science is becoming much better at predicting every individual's susceptibility to different diseases by analyzing his or her genetics, epigenetics and metabolism. In addition, proper diet, physical activity and positive thinking, as well as avoiding unhealthy habits can help prevent

diseases. When illnesses do emerge, patients and their caregivers can participate with healthcare professionals to come up with the best treatments and cures. All of this is compatible with the very natural process of total quality management (TQM), which has been adopted throughout modern industry and which has always been a hallmark of good health and wellness. It is an essential part of systems thinking. Moreover, systems thinking is needed for proper TQM. Note that the term total quality leadership (TQL) is often used synonymously with TQM.

Systems thinking has been integrated into TQM for many years [12]. It is essential for survival in an increasingly competitive environment that requires efficient use of modern technologies, such as 3D and 4D printing. The health and productivity of an organization requires using a holistic approach. Traditional operating methods must be continuously evaluated and replaced when they become dysfunctional or unnecessary, just like ancestors of cetaceans (whales and dolphins) did when they no longer needed legs as they evolved into creatures that spent their entire lives in water [12].

One of the most important tools of TQM in industry and living systems is system dynamics [11]. The process helps associates work together while leveraging their knowledge and skills by applying the tools of system dynamics. The acronym LEARN sprang from a similar term used in by educators when teaching in classrooms. LEARN is used with the PDSA (Plan, Do, Study and Analyze) quality model. The steps in LEARN are locate, employ, assess, reflect and nominate. First, locate a core interest for systemic evaluation. This step identifies key variables and uses both positive and negative feedback to establish a proper balance. Second, employ system dynamics tools for leveraging and increasing understanding. Connections between variables are identified to help recognize causal loops. Third, assess the adequacy of the current systems and repeat step two as often as necessary. Fourth, reflect on the process and the results and make important suggestions. Fifth, nominate or propose solutions and enter the PDSA cycle. In this step, a hybrid of many solutions may be produced [11]. So, like TQM in living systems, this is a cyclic process.

Even though it has not been recognized by most people, the same principles of TQM are used by our bodies to maintain good health and to prevent diseases. Just as businesses listen to the voices of customers and communicate with them, cells within our bodies communicate with each other. Many medicinal chemists now realize that the human body is an ecosystem with a deep ecology. Human eukaryotic cells are just one component of the ecosystem. This is similar to the concept in TQM in

which all associates are important to the organization. In modern biology, we are changing the way we think about what it is to be human. That is, the viruses, Bacteria, Archaea and other microorganisms in us help make us healthy humans. As in TQM, there is an extensive communication network among different microbes and between microbes and human (eukaryotic) cells. However, TQM in industry is often involved in manufacturing tools and machines. They don't make themselves. They are made by people. In contrast, living systems are not machines. We make ourselves in a process called autopoiesis (self-making). We make ourselves and we team with other people and organizations made by humans to improve all aspects of our healthcare. So, in biology, TQM means Total Quality Making, not Total Quality Manufacturing.

The principles of TQM are used by an extensive networking system in many governments. For example, the FDA's Center of Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) are developing a more systematic approach for incorporating the "Patient's Voice" into drug development. The goal is to build on the series of public workshops that occurred under the current patient-focused drug development program. This is being used to produce guidances to assess the burdens of diseases and the treatments that are most important to patients, as well as impact measures, clinical outcome assessments, and endpoints to inform drug development and regulatory decisions.

In addition, physicians are distinguishing between care that concentrates on the patient's disease and care that looks at the whole patient [13]. Healthcare that is centered on the patient's disease usually focuses on individual visits. It can be oriented towards a specific episode while managing diseases that emerge. It is primarily concerned with the progression of a patient's disease, while thinking of the many systems and organs in the human body as being distinct. It defines co-morbidity as the number of chronic diseases occurring simultaneously. In contrast, healthcare that is focused on the individual looks for changing interrelationships over time. It also views episodes in illness as being part of experiences with health that occur throughout the course on one's life. It considers diseases to be interrelated as well affecting the evolution of one's health problems. Moreover, organs and systems in the body are also thought to be interrelated, while morbidity is a combination of interacting illnesses. This is called multi-morbidity. One of the major limitations of primary care in the USA is the underestimation of the importance of long-term relationships with patients that is independent of the care that is given for each individual episode of an illness. Instead, it is important to

consider the patient's (or individual's) viewpoint of the relative importance of each illness and symptom. It is also important to pay attention to an individual's illnesses in the context of multi-morbidity. Finally, good primary care and an individual patient's health are not just the sum of the care that is given for each illness. It is the care of the whole person that is important [13].

1.2 Reductionist Thinking and DNA

To understand systems thinking better, it is important to compare it to its opposite - reductionist thinking. By doing so, we can see some of its strengths and weaknesses. It is an important part of a good childhood education. It is needed to learn how to add, subtract, multiply, divide and do quantitative analyses [4]. In our first science classes, we were taught to do controlled scientific studies. Only one independent variable should be changed at a time and only one dependent variable should be measured. We learned that the universe is made up of basic building blocks (protons, neutrons, electrons, atoms and molecules). It was thought that the best way to understand something was to break it down into its smallest components. Once the smallest building blocks of matter were understood completely, this could be combined with a thorough knowledge of math and physics to make predictions. All we needed to know was the position, mass and momentum of an object to be able to predict the future position and momentum of that object when it is affected by a force. For example, if you kick a ball with a force of 20 Newtons on a smooth, frictionless surface, you can calculate exactly how far it will go. If you kick it again, it will go the same distance. If there is no friction, no strong wind or any other interference from the environment, the calculations will be accurate. That is, reductionist thinking teaches that we are separate from the environment. Every individual proton, neutron, electron, atom and molecule is separate, and interactions are always additive. The whole is said to be equal to the sum of its parts. To determine the properties of a group of atoms, molecules, cells, tissues or organisms, all that is needed is to just add up their individual properties [4].

Sir Isaac Newton used reductionist thinking to describe the law of gravity and many aspects of classical mechanics [4]. These laws worked rather well in helping people understand many physical phenomena. This led 18th and 19th century societies to believe that the universe was predictable. Even now, many scientists think that it is possible to predict all the properties of matter and energy, if we could just learn more about the so-called fundamental particles and apply the 'hard' sciences of math

and physics [4]. Living organisms, including people, are made of matter and were thought to be like machines [2]. Metabolic pathways were studied independently and were described as a linear sequence of reactions such as in glycolysis, or a single cycle, such as the tricarboxylic acid cycle. In business, hard management skills such as technical knowledge and individual sales figures were of paramount importance. They can be taught in traditional business schools. They can also be quantified and shown on colorful graphs. Soft skills such as being able to communicate effectively and become genuinely interested and involved with one's employees were not so important.

Reductionist thinking accurately described many of the mechanics of the human heart. The vascular system of the body was thought of as pipes in plumbing in a house. If they became clogged with too much cholesterol, it could cause a heart attack. Also, specific functions were assigned to every organ in the body. For example, the alimentary tract and human gut were responsible for digestion and the production of solid waste. Bacteria were thought to be separate from the human body, most of which contained no Bacteria or viruses. Nobody had any idea that the human gut was an essential part of the nervous, immune and endocrine systems. The renin-angiotensin system (RAS) was thought to be responsible only for controlling water and electrolyte homeostasis as well as blood pressure. The brain was for thinking, even though a myth began that claimed that we only use 10% of our brain when we think. People who had psychosomatic illnesses were simply considered to lack proper self-discipline. Normal diseases were dealt with by a single physician in a kind of man-to-man struggle. Nurses were there simply to obey doctor's orders and were discouraged from ever questioning a doctor's decisions. Files on a patient's health history were kept in large manila folders. There was often important information in them, but it was very hard to find. The system worked like a poorly controlled machine or inanimate object that often broke down.

One of the properties of inanimate objects is a linear response. Toxicologists looked for a linear response when estimating the excess relative risk of mortality from solid cancer due to exposure to ionizing radiation. Despite the large amount of scatter in the data at each dose, the results were fit to a straight line that did not pass through the origin. That is, when the straight line was extrapolated to a very low dose (near zero), there was still some mortality. This led to the conclusion that there is no safe dose of radiation. Fortunately, it is widely accepted that the low dose of ionizing radiation that patients receive during diagnostic imaging by X-rays, computed tomography and other methods is safe and does save lives.

Similarly, reductionist thinking can lead some to think that linear dose-response curves also apply to nutrition. That is, if a nutrient or biochemical is healthy at the relatively low dose that exists in a food or beverage (like green tea), then higher doses must be better. This has led to the widespread sale and consumption of dietary supplements, such as vitamins, green tea extract and epigallocatechin-3-gallate or EGCG (the most abundant antioxidant in green tea). It also led to the idea that dietary antioxidants exert their health benefits by reacting directly with dangerous free radicals (also known as reactive oxygen species or ROS). So, foods like kale (*Brassica oleraceae*) and açai (*Euterpe edulis*) that have very high antioxidant activities *in vitro* were called superfoods. For several years, the U.S. Department of Agriculture listed the *in vitro* antioxidant activities of many foods, beverages and spices.

Reductionist thinking also teaches that you gain weight if the number of Calories that you consume exceeds the number of Calories that you burn up through metabolism and exercise. All Calories are thought to be the same – regardless of their source. It doesn't matter if they come from carbohydrates, fats or proteins. Also, endurance exercises were thought to be the best way to burn off Calories.

However, reductionist thinking does have its uses. It is important in current Good Manufacturing Practices (cGMP) and Good Laboratory Practices (GLP). That is, one of the first steps in new drug development is to synthesize the drug in accordance with cGMP and measure its toxicity and pharmacokinetics in accordance with GLP. When the U.S. National Toxicology Program determines the toxicity of industrial chemicals a toxicokinetic study is done under GLP. In both cGMP and GLP, a method is needed to quantify the new drug or potentially toxic chemical. The first step in validating the method is to analyze several different concentrations of the chemical that one wants to quantify. Analytical methods such as high performance liquid chromatography (HPLC) are used to separate the compounds being analyzed (the analytes) from other chemicals in the sample. Either ultraviolet (UV) absorption or mass spectrometry (MS) can be used to detect each separate analyte. Ideally, the detector response is linear. The results are used to construct what is called a calibration curve – even though there is no curvature, as shown in Figure 1.

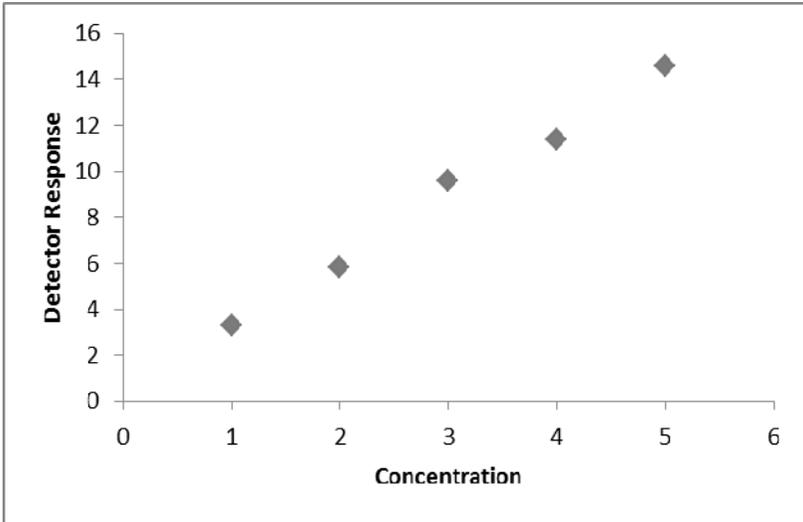


Figure 1. Simulated Calibration Curve for cGMP or GLP.

Next, the data are fit to a straight line using linear regression analysis, as shown in Figure 2.

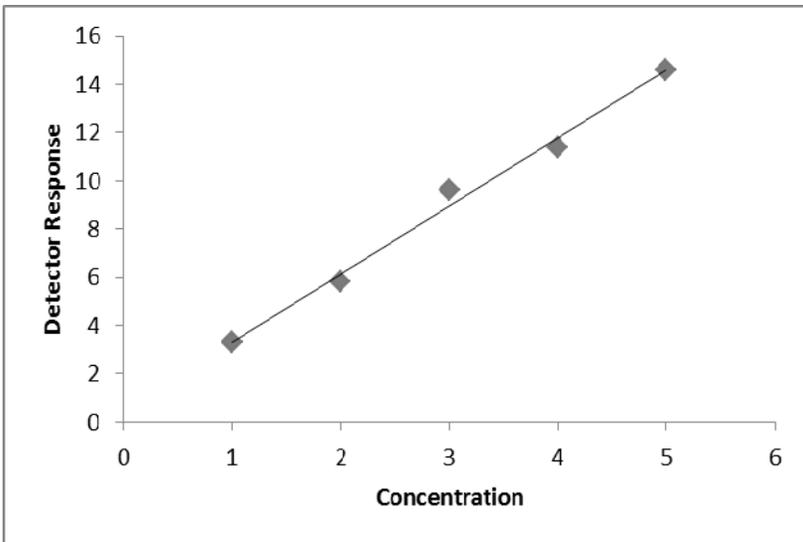


Figure 2. Simulated calibration curve fit to a straight line by linear regression analysis.

This illustrates an important point in reductionist thinking. It tends to separate different scientific disciplines from each other. Almost all areas of science have their own special vocabulary that often contradicts the vocabulary in other areas of science. This tends to reduce science into distinct disciplines that have trouble communicating with each other. For example, if one considers math to be the only true science, then the nomenclature of the analytical chemist is wrong. There is no curvature in the calibration ‘curve’ and the detector response is nonlinear. Still, the terminology is widely accepted and understood by analytical and medicinal chemists. Moreover, the use of ‘linear’ calibration ‘curves’ is required by the laws of the USA and many other countries when developing new drugs or testing potentially toxic substances.

The different uses of the same word and concepts in physics and biology can also be problematic. For example, the theory of evolution is the foundation of all of biology. No biology makes sense without evolution. Microbiologists and virologists can even show that Bacteria and viruses do evolve in real time. So, many biologists say that the theory of evolution states that all life on Earth evolved from the same single cell. A physicist may ask the biologist to define the word cell with mathematical equations, just like the terms force, mass, velocity, momentum and acceleration have exact mathematical definitions. The biologist may say that we are still learning more about cells. For example, some very large viruses that were once thought to be cells are now classified as viruses. The physicist would probably still want a mathematical definition of a cell. Without a set of mathematical equations, there is a significant gap in the definition of a cell. That is, how can a biologist say that we all evolved from something that we don’t know much about and can’t even define in terms that a mathematician or physicist would accept? So, widely differing vocabularies and definitions have historically made scientists specialize and reduced science into many distinct disciplines.

Reductionist thinking also implies that there is a hierarchy [4]. Mathematicians might feel that theirs is the only true science. Physicists might accept this as they use mathematics to prove many principles in physics. However, biologists might see a problem. I remember one of the first meetings of mathematicians and biologists in 1994. A mathematician gave a talk that only half of the audience understood. A biologist asked, “Does your work have any practical applications?” The speaker proudly answered no and about half the audience applauded. Many of them were skeptical of almost anything a biologist might claim. Then, a biologist talked about two different species of deer that looked almost identical, but one had twice as many protein-coding genes than the other. A

mathematician asked if the ratio was exactly two and the biologist answered no. The mathematician then said that the answer indicated that the difference in the number of genes meant nothing. She was right.

There can be good reasons for such skepticism. For example, the complete title of Charles Darwin's book describing evolution was "On the Origin of Species by Means of Natural Selection. Preservation of Favoured Races in the Struggle for Life" [14]. At that time, slavery and subjugation of 'inferior races' was rampant. The misuse of the term race helped lead to the Holocaust in World War II. Fortunately, the scientific process requires all hypotheses to be tested experimentally and be modified as new facts emerge. So, we now realize that there is only one race – the human race. However, new technologies may make it possible to produce designer babies and people with super-human powers.

Reductionist thinking led scientists into thinking that there is a hierarchy in biochemistry. It was thought that all the information needed to produce an organism was in its DNA. Supposedly, there was a one-way flow of information, producing a cause and effect. That is, genes make RNA, which makes proteins, which make cells, which make organs, which make tissues. Because of this hierarchy, RNA and proteins were not thought to influence the production of DNA. There was even an idea that our genes were selfish [15]. In the first 12 chapters of his book, *The Selfish Gene*, Richard Dawkins suggested that we are like machines, created to spread our selfish genes. We exist and perform acts of self-sacrifice so our genes can survive. We can be thought of as vessels that contain our genes. Much of human behavior was supposedly under the control of our selfish, human genes. Professor Dawkins wrote that "genes swarm in huge colonies, safe inside gigantic lumbering robots sealed off from the rest of the outside world ... They are in you and me; they created us, body and mind; and their preservation is the ultimate rationale for our existence" [15]. This book helped explain why some of our human genes might make us do things that are altruistic. This includes helping society at the expense of the individual, since the genes survive and are reproduced. However, in chapter 13, Professor Dawkins went on to write, "We, alone on earth, can rebel against the tyranny of the selfish replicators" [15]. In that chapter, he introduced many principals of evolutionary psychology. That is, we give our children not only our human genes, but also a society, complete with education, technology and civilization; all which help us survive and reproduce, regardless of our genetic differences. So, Professor Dawkins' idea of selfish genes was a metaphor, meant to stimulate debate and thinking and not a mathematical law [15].

Before the human genome was solved, it was thought that humans must have at least 100 000 genes that code for proteins because other simpler organisms that were already analyzed had as many as 20 000 genes. DNA was thought to be the book of life or the blueprint of life. Since humans were the most complex organisms, our book of life must be more complex and longer than that of other species. Bacterial and viral DNA was ignored. Even though it was known that Bacteria helped us digest our food, they were thought of as being more like digestive enzymes. Moreover, they were not considered to be human. They usually caused diseases and even death. There was even a time when nursing students were taught that when a doctor could not determine why a patient was sick, it must be due to a viral infection.

Diseases were thought to be caused by something becoming defective in the living machine. To cure the disease, all that was needed was to identify the single root cause of the problem and fix it by giving a medicine with a single active ingredient. So, many prescription drugs approved by the United States Food and Drug Agency (FDA) and other countries' medical regulatory agencies were thought to have a single molecular target. Doctors were also taught to act like machines. They were taught to avoid any emotional bond with the patient, just as a car mechanic should avoid becoming emotional when repairing a car [4]. Moreover, nurses were told that they were subordinate to doctors and should never question their authority, much like union workers before the advent of TQM.

In reductionist thinking, the whole is equal to the sum of its parts [2-4]. In this type of thinking, mathematics is always quantitative and is the foundation of all science [4]. Physics is thought to be the basis of all of chemistry and chemical principles can potentially describe all of biology. It may be possible eventually (with enough research) to describe all of biology, chemistry and physics with mathematical equations. If we can just learn all the mathematical and physical properties of all the chemicals in the human body, we will know everything about human biology and medicine. Reductionist thinking teaches that it is theoretically possible to find the smallest fundamental particles and fundamental laws of physics. This idea has been expressed as, "Nothing exists but atoms and space. Everything else is opinion" [16]. Even though chemists and physicists know that there are smaller particles than the atom, reductionist thinkers feel that there must be a small set of fundamental particles, and all of them should be governed by the same fundamental laws. Still, scientists are quite interested in learning more about subatomic particles, regardless of whether they mostly use systems thinking or reductionist thinking. So,

they noticed with interest when the search for smaller particles in the super collider in Geneva, Switzerland resulted in success in 2012. Scientists found the fundamental Higgs boson, which is believed to give all other particles their mass. Reductionist thinking and the search for the Higgs boson were explained more thoroughly by the Nobel Prize winner, Leon Lederman, in his book, *The God Particle* (not because he thought that the particles would tell us anything about God, but because the book editor didn't like his originally proposed title) [16].

Reductionist thinking is often very effective in selling products and is used during political debates. A clever salesman or politician knows that one of the most effective ways of lying is to over-simplify and tell just part of the truth. They can use simple expressions that evoke strong emotions. One of the best examples is when products are advertised as being "all natural", as if everything that is made by nature is good and things made by people are bad. Slavery was once called "the natural order". Other popular examples of over-simplifications include "this product contains no toxic chemicals", "it has been scientifically formulated and clinically tested" and "it has been clinically proven to be safe and effective". Two of the most misused terms are prove and proof, as in "We will prove that the defendant is guilty beyond a shadow of doubt" or "Where is the proof to support your claim?" Scientists would use the term 'evidence' instead of proof. In contrast, systems thinking teaches that science can't prove anything [3]. The main role of science is to learn how to ask the right questions. If done properly, almost every answer can generate ten or more questions and open new avenues of exploration.

Reductionist thinking can also produce arbitrary rules that are not supported by scientific evidence. For example, "All the living things on earth died - birds, domestic animals, wild animals, small animals that scurry along the ground, and all the people" [17]. Reductionist thinkers may also tend to label something as strong or weak. When asked to identify their greatest strength and greatest weakness, they will give two different answers. For example, they might say that their greatest strength is their extensive knowledge and their greatest weakness is not being able to put up with ignorant people. They may not realize that certainty is an enemy of wisdom. A specialist might be very certain about all that their discipline teaches but be quite ignorant of other disciplines. This can lead to serious mistakes and miscommunication when people from each discipline only know their own specific vocabulary. For example, the fact that we can be infected with pathogenic viruses and Bacteria could be one the greatest weaknesses of the human body, while many other Bacteria and