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What is Systems Biology?

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This reading is a Chapter from Dr. VA Shiva Ayyadurai's Text Book *Systems Health: The Revolution in Medicine.*

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Introduction

What is *Systems Biology*? A *system* is any set of connecting things, working together with a specific goal or purpose. We are all familiar with mechanical systems: Your car is a system; so is your cell phone. Some systems are relatively simple; others are more complicated, containing within them a variety of still other systems. The house or apartment in which you live is one such example; think about the systems it holds such as electrical, plumbing, and heating. Look around and what do you see? Do you have a washing machine, a dishwasher, a computer, a CD player, a clock, a pencil sharpener, or iPhone? These are all systems.

Biology is the study of all living things. In modern biology, we study life by conducting simple and complex experiments. In biology, as yet there are no mathematical laws, and there may never be. There are no equations available to predict how tall someone will become under various circumstances based on how much food this person eats or what kind of sports he plays. This is different from physics where observations and many experiments have created mathematical laws that always hold true. Biology, therefore, is fundamentally an experimental science and experiments are the key to the knowledge we have thus far acquired.

Systems Biology is a way of applying the science of systems to the study of life, in all its forms. The mission of systems biology is to give us a new way to grasp the complexity of life—a way to look at all parts of Alex or the elephant, as it were, and to see and understand the *interconnection* of the parts. Interconnection is the operative word here. Thus, systems biology attempts to create a total understanding of human existence from the smallest quanta of energy all the way to the cosmos. It aims to link together, and *interconnect*, the patterns of molecular mechanistic interactions from the small to the massive, across all spatial and temporal scales, from the atom to protein to cell to tissue to organism to ecosystem to the cosmos.

Systems biology is a relatively new field that requires integration of multiple disciplines. Nearly every university has formed new departments called Systems Biology. These are interdisciplinary departments bringing together scientists, engineers, and designers across the disciplines of engineering, science and the arts. The complexity of Systems Biology requires this level of cooperative research.

One of the most far-reaching applications of systems biology is Personalized Medicine. This means that one day, you will be able to go to your doctor's office (or possibly simply get on the internet) to access your DNA, which has already been stored in a secure information repository, and submit a sample of that day's blood or saliva. Within moments you will get a read out telling you exactly what to eat for that day and what activities you should do to optimize your day's health.

This is revolutionary since most medicine is currently based on a "one size fits all." Pharmaceutical companies spend years finding one drug to cure a particular disease across all people. And, results are showing, year after year, that one drug does not work for everyone. In fact, most drugs work effectively for no more than 10% of the population. Some patients have an immediate positive response; others have a variety of side effects. A specific drug may not work for certain people, who are subject to certain conditions. Systems biology hopes to cure this fundamental problem. By molecularly understanding each one of us as individual and unique beings, it will help deliver the right medicine, personalized to each of us. Systems biology owes its beginning to end of the Human Genome Project.

Beyond the Genome

In 2002, after more than a decade of research, the Human Genome Project completed sequencing of the human genome or DNA. By now, anyone who has ever watched a police based drama on television has some idea of what DNA is. Our personal DNA, which is unique to each of us, stores information and instructions on our physical characteristic. The genes in our DNA determine our eye color, how many teeth we have, the color of our hair, as well as a tendency to develop certain illnesses. The Human Genome Project's goal was to identify all the genes in the human DNA, their location and their function. It was a massive undertaking.

When the Human Genome Project got under way, there were two key assumptions:

1.) The difference between us and other animals was the complexity and number of genes in our DNA.
2.) If we could map the entire human genome, then any aspect of life could be manipulated.

The irony of the Human Genome Project was that it revealed that not only were the two key assumptions wrong, but also that DNA may be relatively less important to our current and future state of existence. It revealed that we are more than our genes and, as humans, we have power over our destiny, beyond the DNA we were given from our parents and ancestors.

The scientists involved with the Human Genome Project originally believed that humans possessed a larger number of genes than other life forms. It was an understandable assumption: we have preeminence over other life forms; therefore we must have more genes. During the early stages of the Project, most expected that humans would have at least 500,000 to 1,000,000 genes. As time went on during the sequencing phase, the estimates changed to 100,000, then 50,000 then 30,000. Eventually it was revealed that we have the about the same number of genes as the lowly earthworm—somewhere in the neighborhood of 25,000.

The scientific community reeled from this discovery. How was it possible that a worm, which looks so different from a human being, could have the same number of genes? To help understand that question, we have to think about the function of our genes and, consequently, our DNA. People are often confused about the difference between DNA and genes. DNA, which is stored in the nucleus all of our cells, is often likened to a set of blueprints or codes that contains the instructions necessary to construct other components of cells. The co-discoverers of DNA, Watson and Crick, stated that DNA was completely in charge—the central controller of who we are and what we become. Genes are an essential part of our DNA. Genes hold the secret of the most basic traits you are going to inherit from your familial ancestors. Do you, for example, have a gene that makes you susceptible to a specific illness?

Genes provide instructions to create different proteins. These proteins are created outside of the cell nucleus, in what is known as the cytoplasm of the cell. In the cytoplasm, instructions from the genes are carried via a molecule called messenger RNA (often shortened to mRNA) to the cytoplasm, where the proteins are synthesized. Each protein has a particular function. The protein Insulin, for example, is critical in metabolizing or breaking down sugars. If you don't have enough insulin, you have a high likelihood of getting diabetes. This tendency to diabetes is something we inherit through our genes.

The "central dogma" (as it is called in most biology books) of Watson and Crick concerning DNA went like this in a step-by-step dictatorial manner:

1. DNA, within the nucleus of each cell, stores the genetic information of who we are.
2. The genes in our DNA provide instructions through a molecule called messenger RNA (mRNA) to create proteins.
3. Proteins are created outside of the nucleus of our cells.
4. Proteins, the molecular machines of our body, interact or "dance" with each other in order to orchestrate different types of molecular pathways, such as metabolism, synthesis, etc.

Looking at this, we can see how DNA was believed to be the "mastermind" of the entire operation of life, giving rise to the successive effects of mRNA, proteins, and molecular pathways. It was a one-way street with DNA as the source; other elements were its effects.

The Human Genome Project revealed that the complexity of us as humans cannot be explained by looking at our DNA alone. We especially need to consider the dance of proteins and molecules, known as *molecular pathways* that take place in the cytoplasm, in the stuff outside of the nucleus. These molecular pathways are the interaction of a set of proteins, each at particular concentration levels, working together to elicit a particular *cellular function* such as cell signaling, metabolism and transcription. These cellular functions may even turn on and off genes, and have a *feedback* effect to control gene expression. So, it's not just the genes in our DNA, located in the nucleus, that determines who we are, but the molecular pathways that are in constant activity across the nucleus and cytoplasm. For example, insulin interacts with multiple molecules to provide a complex set of molecular pathways to elicit the cellular function of metabolism.

Recent discoveries are now emerging in a field called *epigenetics* that substantiate that we are not merely our genes. Epigenetics has demonstrated some remarkable events. For example, prior to the Human Genome Project, it was thought, and taught in biology class, that because identical twins have the same DNA, they must both look the same. Consider eye color, where both identical twins have genes for blue eyes. The thinking was that, by definition, both twins would have blue eyes. However epigenetics has shown that identical twins, having the exact same DNA to code for blue eyes, don't necessarily have to share the same blue eye color. How is this possible? Research in epigenetics shows that molecular pathways may serve as the *epigenome* to turn on and off the genes in the DNA that codes for eye color through a feedback mechanism, not yet fully understood. This means that while DNA is important, the molecular pathways that occur across the nucleus (where the DNA is stored) and the cytoplasm of the cell may be more important in determining who we are than the DNA itself.

What does this mean on a larger, more personal scale? This means that while you may have the gene for diabetes or certain types of cancer, other factors are capable of suppressing the expression of that gene. What are these factors? Some examples include diet, environment, lifestyle choices, what we think, and ultimately our state of consciousness, a theme of many ancient and traditional systems of medicine. These factors affect the molecular pathways, which in turn affect gene expression.

While the Human Genome Project gave us invaluable information on the genetic map of the human genome, including the location of various genes and their functions, it also provided us with knowledge that is even more far-reaching: We are more complicated than our genes. We are the interconnection of our genes in the nucleus and the molecular pathways outside of the nucleus. These molecular pathways are influenced by multiple factors, which each of us can control with our mind, body and spirit.

A Systems Approach

A systems approach aims to go beyond the DNA so that we can understand the entire organism and our relation to the environment and the cosmos. Systems Biology, based on the foundational history of molecular genetics, attempts to link the dance of proteins and create a total understanding of human existence from DNA to mRNA to Proteins, to single Protein-Protein Interactions, to Molecular Pathways to Cells, to Tissues, to Organs, to Organism, to Ecosystem all the way to the Cosmos.

How It All Works

Cosmos

Ecosystem

Organism

Organ

Tissues

Cells

Molecular Pathways

Protein-Protein Interactions (dance of proteins)

Proteins

mRNA

DNA

Look at the ladder leading us from DNA up to the cosmos, and let's do a quick recap: DNA gives rise to proteins through mRNA. Proteins, through protein-protein interactions, give rise to molecular pathways. A molecular pathway can be likened to choreography of multiple dancers, e.g. multiple proteins. These molecular pathways give rise to particular cellular functions e.g. metabolism, for example, which is a molecular pathway that provides the cellular function to breakdown of sugars; this requires the interaction of many molecules from glucose to insulin, as well as hundreds of others. The interconnection of multiple proteins defines particular molecular pathways. In turn, this interconnection of molecular pathways defines specific cellular functions. There are a hundred different types of cells in the human body, each performing a different cellular function using an interconnection of molecular pathways. Different cell types make up different tissues, and cell types are unique to the tissue in which they reside. Liver cells, to use one example, are different from cardiac cells. Organs such as kidney, heart, spleen, lung, etc are made up of different tissue types and hence different types of cells.

As organisms, we all have a variety of different organs. This is also true of all other organisms whether they are worms, frogs, dogs, cats, or giraffes. As organisms, we are part of an ecosystem or biological environment that includes animals, plants, rocks, lakes or rivers. Finally, ecosystems are part of the cosmos including the earth, sun, moon, and stars.

Systems Biology aims to link all of the individual molecular reactions in each of these systems, enabling us one day to understand all of life and how it interacts and interconnects. Starting with the genetic system of DNA, we progress to the system of messenger (mRNA), which converts genes to proteins, and then on upward until we model the system of the entire Cosmos. Systems Biology hopes to build the interconnected knowledge from the small to the massive, spanning all spatial and temporal scales.

Most importantly, Systems Biology will provide the foundations of a new Systems Medicine. It will be personalized, dynamic, and interconnected. Personalized to your unique chemistry and state of existence, dynamic in recognizing that the environment around you and within is under constant change, and interconnected in recognizing that the interconnections among the parts of you and the world around you yields something that is bigger and different than the sum of your parts, bigger than your 25,000 genes.