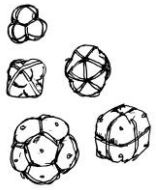
HOLISTIC PERSPECTIVES ON CANCER

Complexity, Coherence and Context

Laura Batson



When human life comes into form, during its period of organogenesis, tumours are not able to grow. Why is this? Dr. Pier Mario Biava explores this phenomenon and its implication for cancer treatment, in his groundbreaking book: *Cancer and the Search for Lost Meaning.*[1] Before Dr. Biava's eureka moment in cancer treatment, he journeyed through a professional and personal transformation in thought; his understanding of health and disease evolved from a molecular epistemology, to a holistic epistemology that *included* molecular biology but also refused to reduce living beings to genetic material. With the realization that less than 2% of all diseases could be traced back to the alteration of a single gene, Dr. Biava knew something more than the gene had to be considered in order to grapple the complexities of disease in general, and of cancer in particular. With this insight, Dr. Biava turned to the mathematics of complexity theory, and together with pulses of intuition, he came to the conclusion that cancer genesis is due to a loss of complexity, coherence and meaningful context.
This paper proposes a more-than-molecular understanding of health and disease as it relates to cancer. Concepts of biological coherence are presented, along with the science of complexity theory, and the role of context in the generation of meaningful relationships. It then highlights the work of Dr. Pier Biava as an example of how this holistic epistemology is leading to exciting outcomes cancer research.

A More-than-Molecular Understanding

The Somatic Mutation Theory has dominated cancer research for the last 50 years.[2] This is a molecular theory stating that tumours originate from genetic mutations in a single cell. According to some proponents of this theory, "…all the complexity of cancer on any level (e.g., tissue) can be explained on the molecular level."[3] The error in this way of thinking was pointed out by Dr. Paul Weiss, professor of biology who, in 1951, introduced the term 'molecular biology' to his curriculum. He was attempting to reorganize biological studies into genres indicating the scale of magnitude of biological investigation.[4] According to Weiss, however, scientists mistakenly took molecular biology to mean the most important level of investigation. He defends: *"Nothing in the nomenclature insinuated that [molecular biology] should assume the role of pars pro toto. As I once put it, there is no phenomenon in a living system that is not molecular, but there is none that is only molecular, either."*[4]

Cancer cannot be understood solely through molecular theory.[5,6] Knowledge of molecules alone is not sufficient to explain the properties that arise at higher levels of organization, let alone the complex dynamics of how these multiple levels of organization are coordinated in health and disease. Both the molecular and more-than-molecular levels of organization must be considered. The truth is: the *whole* of cancer is more than the sum of mutations. After all, genes mutate all the time and yet cancer does not develop. This makes sense considering the regulatory systems in place at higher levels of organization such as tumour suppressor proteins which repair gene mutations or immune cells which detect and destroy cancerous cells.
As stated by Dr. Paolo Bellavite, MD: "If the molecular disorder is not compensated for by supramolecular systems, it is the latter that are responsible for the disease, and not the molecule."[7]

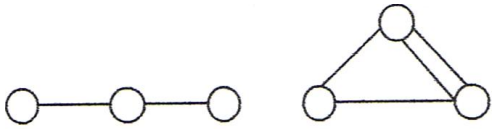
So which comes first: the genetic mutation or the cellular dysfunction? According to Tissue Organization Field Theory, the latter comes first. Carcinogenesis takes place at the level of tissue organization by disrupting the normal communication between cells and their surrounding matrix.[8] It is the disruption of normal cell function that then leads to alterations in gene expression. This is referred to as an epigenetic causation. While scientists debate over chickens and eggs, the relevant conclusion is that *both* events are occurring: 1) information is altered on a genetic level—in the form of gene mutation, and 2) communication is altered on an epigenetic level—by errors in the interpretation of information from gene-to-proteins and cell-to-cells. The result is a cancerous growth, in which malignant cells proliferate ceaselessly while losing coherence with the

whole organism.
To better understand this incoherence between the part (cell) and the whole (organism), it helps to understand how coherence emerges in states of health.

Coherence
In health, a living system is poised between maximum freedom of its parts and maximum coherence of its whole.[9] In similar thought, Paul Weiss wrote in his 1968 publication, *Dynamics of Development*: *"elements are subject to constraints of their degrees of freedom so as to yield a resultant in the direction of maintaining the optimum stability of the collective."*[10]
Weiss offers this equation to explain:
Vs < (va + vb + vc +…..vn)

The variance (V) of the whole system (s) is significantly less than the sum variance of its parts. "In short," he says, "the basic characteristic of a system is its essential invariance beyond the much more variant flux and fluctuations of its elements or constituents." The whole acquires coherence, maintains stability, while at the same time the parts retain their flexibility and variations. Maintaining maximum variation of the parts in context with maximum coherence of the whole means creative and adaptive changes can arise at the level of the parts while maintaining meaningful relation to the whole. In the organism, this means: 1) the cells are exploring possibilities while always relating back to what is appropriate and most meaningful for all other cells and the organism; and 2) The organism is actively interpreting the cells and engaging their potentials in a direction most appropriate for coherence and stability. It is a hermeneutic circle of sorts.
In cancer, the healthy part-whole relationship is altered. Cancer cells proliferate relentlessly, exploring maximum freedom without perceiving what is best for the whole organism. At the same time, the organism is not interpreting this sudden freedom as being detrimental to its health. This breakdown in part-whole relationship is a breakdown in communication. And it can be attributed to a loss of information complexity.

Complexity
Essentially, when a system gets its level of complexity right, communication takes care of itself. This is a key concept that will be elaborated in the section on Dr. Biava's discoveries in cancer treatment. For now, what is meant by complexity?
Complexity theory describes how order emerges from highly complex systems, where 'complex systems' are not defined as systems with a high *quantity of things* per se, but a high *quality of expressions.* It is not so much the number of components in a system, but the number of possible relationships between these components, that defines its complexity. The two images below provide a simple example.



The diagram on the left is less complex than the one on the right, not because it has fewer components (circles) but because it has fewer relationships between its components (lines).

Another example is the genome of humans compared to fruit-flies. Humans have nearly the same number of codifying genes as the fruit-fly, however humans are far more complex beings. Our complexity is not due to greater quantity of genes, but due to greater regulation capacity: we have more flexibility and possibilities of relationships between our genes. Through splicing and recombination, the same gene can code for multiple different proteins. As well, genes are turned on and off at different times and in a multiplicity of combinations, depending on when certain proteins are required. Moreover the same molecule can have different functions depending on its cellular environment. For example, lactate dehydrogenase is an enzyme found in muscle. This same molecule, under a different name: crystalline, is a structural component in the eye's lens. This redefinition ability is important for the robustness of a system.

Complexity ensures that multiple possibilities are available at any given moment, adaptive changes can readily be made, part-whole relationships are balanced between freedom and coherence, and order is never too still while disorder is never too rampant. Achieving optimal complexity means having just the right amount of

dynamic connections between the component parts and the whole, so that dynamic order emerges in the direction of health.

In cancer, this complexity between the part and the whole is lost on many levels: "The malignancy of cancer results from a breakdown of the fundamental rules that govern how cells organize within tissues, tissues within organs, and organs within the whole living organism."[11] The cancerous cell is no longer in meaningful communication with all other cells and the organism. For example, cells normally grow until they make contact with other cells, at which point they send signals back and forth to tell one another to stop growing. In cancer there is a significant loss of gap junctions – small pores in the cell membrane which allow signal to transfer between adjacent cells. As a result, signals that stop cell growth are no longer being perceived by cancer cells. It must be noted that the tumour itself is not disordered, otherwise it would not be able to survive and proliferate. Rather, the tumour has assumed a new order of complexity, one that is not in resonance with the complexities of all other cells and the whole organism. This new order of complexity is called a new "attractor state" in the mathematics of complexity theory. The gene networks are 'attracted' into a new and stable configuration of relationship, resulting in a transition in cell phenotype and function, from differentiation to proliferation.

The pathways of communication are many and tangled within the cancer attractor state. Molecular and cellular biologists have produced impressive amounts of work, mapping these multiple pathways (see figure below). The idea being, if specific genes or proteins or signal transduction pathways can be identified, then they can be targeted and disrupted by pharmaceutical therapies, causing cell death. In practice however, over 100 oncogenes and over 15 tumour suppressor genes have been identified and yet we are still far from a cure.[8] Many problems arise when specific genes and proteins are targeted in cancer therapy. Most notably, cancer adapts. Malignant cells are highly robust; they find ways around obstacles to growth. This is because, as mentioned earlier, carcinogenesis is a state of complexity, where flexibility and redefinition ability are in full swing. Cancer is too intelligent for our linear approaches.

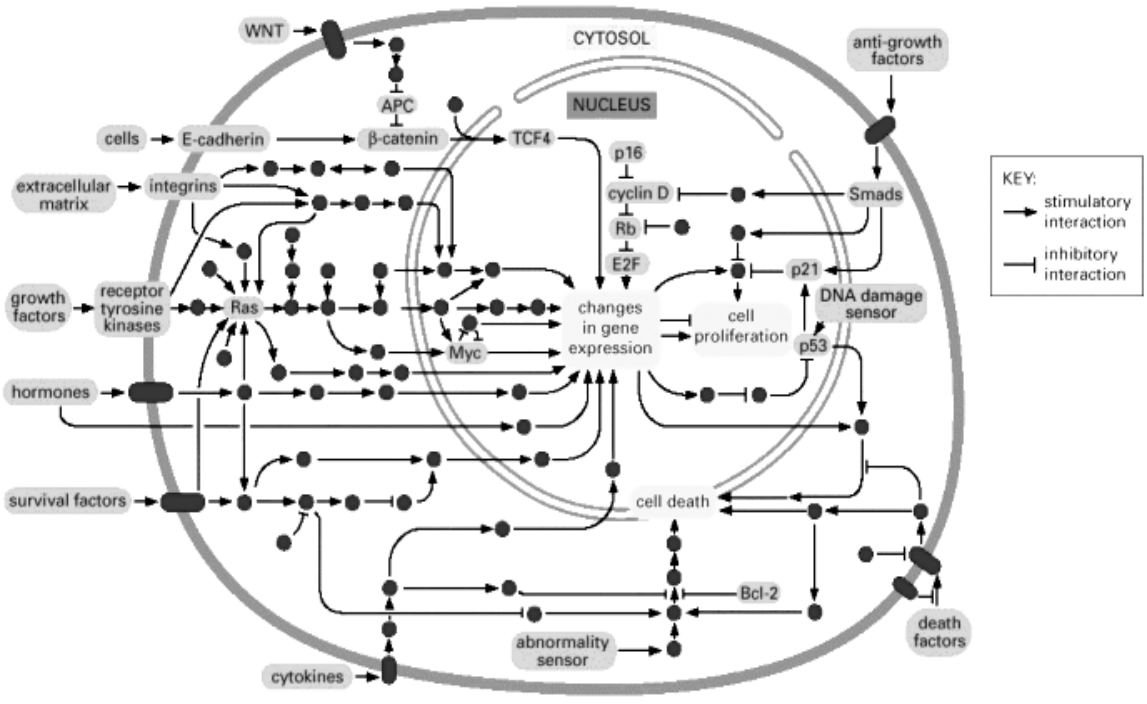


Fig. 2: Major signaling pathways relevant to cancer in human cells.[12]

As maps continue to be filled with more and more lines of causation, the dilemma continues to be: "The great increase in the *extent* of our knowledge is not enough to guarantee an *intensive* understanding of the deeper meaning which the abnormalities observed have in the dynamics of the onset and development of disease process."[7] The disease is deeper than the component parts and all their miscommunications. The underlying dynamics have been altered. And, as the cancer cell transforms from one order of complexity into another order of complexity, there is a break in the meaningful connection between cell and organism.

So, rather than intervening in individual communication pathways, what if we exposed malignant cells to a level of complexity that informed them how to re-connect with the whole again? This is exactly what Dr. Biava had in mind.

Restoring a Meaningful Context: the experiments of Dr. Biava

Rather than attempting to kill cancer by deleting single genes or targeting single pathways through the use of pharmaceuticals, we can teach cancerous cells how to re-differentiate by providing them with the information complexity necessary to re-relate to their environment in a coherent way. In other words, when a system gets its level of complexity right, communication takes care of itself.

Where will this information complexity come from? Dr. Biava did not turn to a cocktail of pharmaceuticals. Rather he looked within, literally. Our very own embryos hold answers. The greatest regulation capacity of our genes occurs during embryonic development, when the multiplication and specialization of over one quadrillion cells occurs at an extraordinary pace. An impressive level of coordination and coherency must balance the high amount of multiplicity and diversity occurring simultaneously. By the third week of gestation, rapidly dividing stem cells are beginning to commit themselves to specific organ systems. This stage of development is called organogenesis. Certain genes are turned on and others are turned off, shifting the cellular morphology from proliferation into differentiation - a process of specialization into tissues and organs of the foetus.

Remarkably, during this stage of organogenesis, tumours do not develop. In his research on toxicology and cancer, Dr. Biava discovered that embryos, exposed to toxins during organogenesis, did not develop tumours. Rather, the cells mutated and were either repaired completely, repaired partially and resulted in life-compatible malformations, or the mutations were too severe and the cells spontaneously aborted. Malignant transformations were never an option.

There must be something about the embryonic environment during this stage of development that is resistant to tumour growth. And if so, then perhaps the embryonic environment could resist growth of cancer cells *introduced* into the embryo. To test this hypothesis, Dr. Biava performed in vitro experiments implanting human cancer cells into cultures of zebrafish embryonic tissue. To his amazement, the cancerous cells reversed their malignant phenotype.

Dr. Biava is not alone in this paradigm of thought. Dr. Paul Kulesa and a team of researchers[13] transplanted melanoma cells into embryonic chick tissues. The cancerous cells incorporated themselves into the surrounding chick tissues, becoming *re-programmed* into neural-crest-like morphologies and distributing along host neural-crest pathways.

In similar experiments, Lee et al. [14] transplanted human metastatic melanoma cells into zebrafish embryos. The cells survived and divided without forming metastatic tumours, rather they became incorporated into the interstitial spaces of the embryo.

Intrigued by these findings, Dr. Biava wanted to know *how* this was possible.

First, he noted that embryonic cells are very similar to cancer cells. Characteristics of cancer cells include processes such as proliferation, migration, tissue invasion and stimulation of blood vessel growth; these are all characteristics of cells during embryonic development. Cancer and embryonic cells share similar metabolic pathways; rather than oxidative phosphorlyation, they use glycolytic energy production. Also, there is a convergence of signalling pathways with common molecular messengers and protein expressions such as alpha-fetoprotein and placental alkaline phosphatase. It is as though the cancerous cell has reverted back to the attractor state of an embryonic cell, and thus reactivating embryonic genes – genes that have long been turned off.

The difference between cancer and embryonic cells is that cancer cells are trapped in a state of proliferation, whereas embryonic cells eventually change their program of proliferation into a program of differentiation when the time and place is appropriate for organs to form. Embryonic cells have an extraordinary sense of spatial-temporal order, relating to one-another and the whole in a complex and coherent manner. The cancer cell does not have this context. The cancer cell is proliferating without coherent relation to all other cells and the whole. The difference is: context. The context of the embryo includes not only the part-whole relationships of the developing embryo but the entire microenvironment encasing the embryo, that of the mother's womb. The mother's womb creates a micro-environment with maternal factors responsible for guiding embryonic gene and protein networks. This 'embryonic milieu' [13] between embryo and womb is an information rich exchange.

The cancer attractor state is not appropriate in the context of a fully formed being; there is incoherence between the cancerous states and the whole organism. However, when a cancer attractor state is placed into an environment with a similar attractor state (in embryo), within a microenvironment that provides a relevant context (womb), then proper communication occurs. The cancerous cell is informed to differentiate and become integrated into the whole again. By providing the right level of information complexity, cancer cells become reprogrammed.

The hope is that this pool of embryonic and maternal regulation factors can be collected and compiled in a way that they can be administered to people with malignant tumours, to induce a reversal of malignant phenotype. In Dr. Biava's words, it is a "shift from therapies centered on synthesis molecules that do not repair the organism and have adverse effects, to therapy using networks of biological molecules that constitute a correct information therapy aimed at balancing the networks of which the organism is made." The dilemma we face now is: how can the embryonic and maternal *context* be extracted and preserved so that the information complexity is not lost? Dr. Biava is working to decipher this mystery as we speak.

Epilogue: The Larger Context

While Dr. Biava's experiments are of a molecular nature, they are founded upon a holistic understanding - a way of knowing that includes molecular biology but also refuses to reduce living beings to genetic material and deterministic fates. Old truths speak loud in his work: the whole is more than the sum of the parts; the wisdom to heal resides within, and; meaning is not held in the parts, but comes forth through their relationship.

Dr. Biava presents a story of cancer in which coherence, complexity and meaningful relationships are lost. As an extension of this understanding, we must note that this loss of meaning is not limited to the molecular and cellular level of organization. Cancer is a pathology of our modern society, psychology and relationship with our environment. Cancer will only be healed once we realize the healing that must occur on all levels of life, for which we are all connected. With this insight, Dr. Pier Biava brings his book, *Cancer and the Search for Lost Meaning, to a close:*

"Never before has society lacked so much meaning…cancer is one of the by products of this loss of meaning. Cancer, as I said earlier, is a pathology of significance: the codes needed to communicate in living beings are changed in tumour pathologies. These codes attempt to reorganize and re-establish life in instances where it has lost meaning. Healing caner also means finding meaning in our existence…We belong to the world and must reclaim our sense of belonging in order to widen our consciousness and give meaning to our existence…"

References

[1] Biava, P.M. (2009) *Cancer and the Search for Lost Meaning: The Discovery of a Revolutionary New Cancer Treatment,* North Atlantic Books, Berkeley California.
[2] Hahn, W.C., and Weinberg, R.A., (2002) Modelling the molecular circulatory of cancer, *Nat Rev Cancer*, 2, p331-342.
[3] Blagosklonny, M.V. (2005) Molecular Theory of Cancer, *Cancer Biology & Therapy*, 4:6, p 621-627.
[4] Weiss, P. (1969) 'The living System', in J.R. Smythies and A. Keostler (eds.), *Beyond Reductionism: New Perspectives in the Life sciences*, Hutchinson, London.
[5] Sadikovic B, et. al. (2008) Cause and consequences of genetic and epigenetic alterations in human cancer, *Curr Genomics*, 9, p394-408.
[6] Jones, P.A., and Laird, P.W. (1999) Cancer epigenetics comes of age. *Nat Genet*, 21, p163-167.
[7] Bellavite, P., and Signorini A (2002) Emerging Science of Homeopathy: Complexity, Biodynamics and Nanopharmacology, North Atlantic Books, Berkeley California, p.88.
[8] Soto, A.M., and Sonnenschein, C. (2005) Emergentism as a default: cancer as a problem of tissue organization, *J. Biosci.,* 30:1, p103-118.
[9] Goodwin, B. (2006) 'Science of Qualities', Lecture at Schumacher College, UK.
[10] Weiss, P.A. (1968) *Dynamics of Development: Experiments and Inferences,* Academic Press, New York.
[11] Huang, S., and Ingber, D.E. (2006, 2007) A non-genetic basis for cancer progression and metastasis: self-organizing attractors in cell regulatory networks, *Breast Disease*, 26, p27-54.
[12] Alberts B, Johnson A, Lewis J, et al. (2002) *Molecular Biology of the Cell*. 4th edition, Garland Science, New York.
[13] Kulesa, P.M., et. al. (2006) Reprogramming metastatic melanoma cells to assume a neural crest cell-like phenotype in an embryonic microenvironment. *Proc Natl Acad Sci USA*, 103, p3752-3757.
[14] Lee, L.M., et. al. (2005) The fate of human malignant melanoma cells transplanted into zebrafish embryos: assessment of migration and cell division in the absence of tumour formation. *Dev Dyn*, 233, p1560-1570.

Laura Batson *has completed a bachelors degree in Biology from the University of Western Ontario, CA (2004). In search of a more satisfying and encompassing understanding of living form, she pursued a Masters in Holistic Science from Schumacher College, UK (2007). Bringing it all together now, she is completing her 4th and final year of Naturopathic Medicine, at the Canadian College of Naturopathic Medicine.*