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Reverse Engineering of Biological Gravity-Sensing Organs: Neurocomputational and Biomedical Implications

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Introduction

"Before living man can penetrate the hazardous vastness of space, many complex problems of space biology must be solved."
J.S. Hanrahan & D. Bushnell
'Space Biology', 1960[1]

As humans began to project themselves into the environment of interplanetary space during the early 1960s, it was clear that the opening of this new frontier would require a comprehensive understanding of the effects of near-weightlessness (microgravity) on biological organisms. After all, life on planet Earth has evolved under the stable and pervasive influence of gravity. In terrestrial ecosystems, a force of one gravitational unit represents a continuous epigenetic agent that affects living systems at levels ranging from the morphogenetic to the behavioral[2]. However, an unexpected, beneficial outcome of research in gravitational biology and medicine is that it not only improves the conditions and prospects for space travelers, but it also results in enhanced knowledge that could contribute to the solution of physiological and biomedical problems for humans here on Earth[3].

Several Space Shuttle missions over the past decade have included experiments aimed at improving our understanding of the effect of microgravity on living organisms. For instance, the recent orbiter Columbia mission Neurolab (STS-90), proposed at the beginning of this "Decade of the Brain", focused on basic neuroscience questions which will not only expand our understanding of how the nervous system develops and functions in space, but also increase our knowledge about how it develops and functions on Earth, thus contributing to the study and treatment of neurological diseases and disorders.

One of the biological neural systems studied during Neurolab (and other Space Shuttle missions) is the inner ear's neurovestibular labyrinth[4]. The vestibular peripheral system contains the organs responsible for gravireception, which form part of our sense of balance. In addition to space life sciences applications (such as the etiology of space adaptation, motion sickness, developmental exobiology, etc.), molecular investigations of biological gravity-sensing organs under altered gravity conditions may generate insights of developmental, therapeutic, and prophylactic importance related to the vestibular system. This is significant considering that although 90 million Americans suffer from vestibular disorders, the sense of balance is much less studied than vision, hearing, or olfaction. Moreover, neurocomputational modeling approaches of biological gravity-sensing organs can also have cybernetic applications, such as the design of pattern recognition adaptive neural network systems.

We have participated in Space Shuttle experiments (such as CUE-GENEX in STS-87[5,6,55] and the L-7 experiment in Spacelab-J[7,8,9]) directed at understanding ontogenetic aspects of gravity-sensing mechanisms at the cellular and molecular levels. In order to gain insights into the development, structure, and function of vertebrate gravity receptors in microgravity and in terrestrial environments, we are designing a biomimetic artificial gravity-sensing organ (AGSO) based on the neural cytoarchitectonics of its biological counterpart (BGSO). Our basic purpose is two-fold:

1) To further understand the chronology and topology of BGSO ontogenetic network dynamics in relation to the spatiotemporal expression of several biological macromolecules (enzymes, cytoskeletal elements, RNAs) during development under various gravity conditions, mapped by means of analytical morphology; and

2) To produce a biologically inspired AGSO based on a functional architecture that resulted from the efficiency of biological evolution, with applications ranging from neurocomputational cybernetics to biomedical pathophysiology.

Biomimetic Computational Paradigms

The objective of creating artificial intelligence and artificial life[10,11] can be traced back to antiquity[12,13]. Greek mythology describes Daedalus' attempt to create artificial people, while in the "Iliad" Homer includes an account of Hephaistos' automata. Even the earliest computer scientists —Alan Turing[14], John Von Neumann[15], Norbert Wiener[16], and others— looked to natural systems as guiding metaphors to achieve their goals of intelligent machines. Turing became interested in biological pattern production by means of morphogenesis, while Von Neumann envisioned a nervous system language that superseded that of mathematics.

More recently, biologically inspired computer paradigms such as artificial neural net-works[17,18,19], genetic algorithms[20,21], cellular automata[22,23], and evolutionary programming[24] have appeared. These approaches have been useful in their application to a myriad of disciplines ranging from economics to the engineering of machines and proteins, and form part of a field that we call "biomimetic computation". Biomimetic computational paradigms seek to develop artificial intelligence by means of methodologies inspired by natural information processing mechanisms. However, there are other bioinformatics approaches that instead of simulating natural processes actually employ biological macromolecular substrata, as in the case of DNA Computing[56].

Biomimetic computation may yield significant contributions to several aspects of space missions. For instance, it is being used in the control, design, and engineering of evolvable hardware[52]. This emerging field is expected to have a major impact on systems in which adaptive information processing is required, such as deployable machines and other applications that need to perform optimally and survive in changing environments like space. The following overview summarizes the salient features of various biomimetic computational paradigms.

Genetic Algorithms and Genetic Programming

The concept of genetic algorithms was originally introduced and developed by John Holland[25] and his collaborators. His pioneering book "Adaptation in Natural and Artificial Systems"[26] provided a perspective for analyzing all adaptive systems (whether natural or artificial), and demonstrated how the biological evolutionary process can be applied to artificial systems by formulating any problem in adaptation in genetic terms, which may be solved by "genetic algorithms". These highly parallel mathematical algorithms transform a "population" of individual mathematical objects into a new population. The objects in the original set are patterned after "chromosomal" strings with associated "fitness" values, and are transformed into the next "generation" by means of operations based on Darwinian principles such as reproduction and survival of the fittest, as well as other naturally occurring genetic mechanisms like recombination.

By increasing the complexity of the structures undergoing adaptation, the genetic programming paradigm employs general hierarchical computer programs of dynamically varying size and shape. Thus, its search space includes all functions and terminals adequate to the problem domain. Recent applications of genetic programming include prediction of transmembrane domains and omega loops in proteins, obstacle-avoiding robots, and artificial ants[27].

Evolution Strategies and Evolutionary Programming

Other paradigms based on biological evolution were originally developed independently by several computer scientists who used them as optimization tools for engineering problems. Rechemberg's "Evolutionsstrategie" (evolution strategies[28]) and Fogel, Owens, and Walsh's evolutionary programming[24] involve selection of the "fittest" candidate (optimal) solution to a task. In the evolutionary programming paradigm, those candidate solutions are represented as finite-state machines, which are randomly evolved by mutating their state transition diagrams. Although both genetic algorithms and evolutionary programming represent stochastic optimization strategies, the latter places emphasis on the linkage between "parents" and their "offspring", rather than on the emulation of specific genetic operators. Moreover, in contrast to the genomic string encoding used by genetic algorithms, there are no representational constraints in evolutionary programming. Evolutionary programming has been applied to biomedical problems ranging from computer assisted mammography[29] to molecular recognition and HIV docking with drugs designed against AIDS[30].

Artificial Neural and Fuzzy-Neural Networks

Artificial neural network models are algorithms based on the structure of biological nervous systems which are used for cognitive tasks such as learning and optimization. McCulloch and Pitts[31] originally proposed a general theory of information processing based on binary switching networks of decision elements (highly simplified "neurons"), and demonstrated their computational capabilities. Later, Rosenblatt[32] and others studied the "perceptron", a specific type of neural network representing a simplified model of the biological mechanisms for processing of sensory information. Further development of these systems occurred when Hopfield[33] and others applied concepts from statistical mechanics to the representation of artificial neural networks, introducing the notion of energy function, and considering memories as dynamically stable attractors. In addition, the back-propagation algorithm was eventually widely introduced in this field. Recent applications of neural networks include the design of neural associative memories[34], and they have been used in combination with genetic algorithms as hybrid neural-genetic algorithms[35].

In the realm of logic, Heisenberg's uncertainty principle and logical paradoxes gave rise to multivalued logic, which was formalized as fuzzy set theory by Lofti Zadeh[36]. Since neural networks and fuzzy systems process inexact information inexactly, encode sampled information in a parallel distributed framework, and share the same state space, they can be applied in combination as artificial fuzzy-neural networks. Fuzzy-neural networks have been used in problems such as pattern recognition[37]. Further hybrid approaches result in various paradigm combinations including fuzzy genetic neural systems used for modeling[38].

Cellular Automata and Cellular Neural / Nonlinear Networks

Inspired by the geometrical organization of biological cells in tissues, cellular automata[22] are prototypical models for complex processes consisting of numerous identical, simple, locally connected elements with computational capabilities, which provide insights into the behavior of extended dynamical systems. A related paradigm is the cellular neural / nonlinear network[23], characterized by geometrical local connectedness and analog dynamics of its processing units. It provides a natural and universal model of multilayer analog processor arrays, and has been used in the field of biological sensory information processing[39], as in the case of artificial visual systems.

Epigenetic Operators and Ontogenetic Algorithms

The best studied computational paradigms based on evolutionary phenomenologies are genetic algorithms, evolution strategies, and evolutionary programming, which collectively form part of the field of evolutionary computation[24]. While genetic algorithms represent a "bottom-up" paradigm based on genotypic transformations, and evolutionary programming's "top-down" approach emphasizes phenotypic adaptation, our novel ontogenetic algorithms view the evolutionistic mapping of genomes to phenomes from the perspective of the developmental process, involving epigenetic factors.

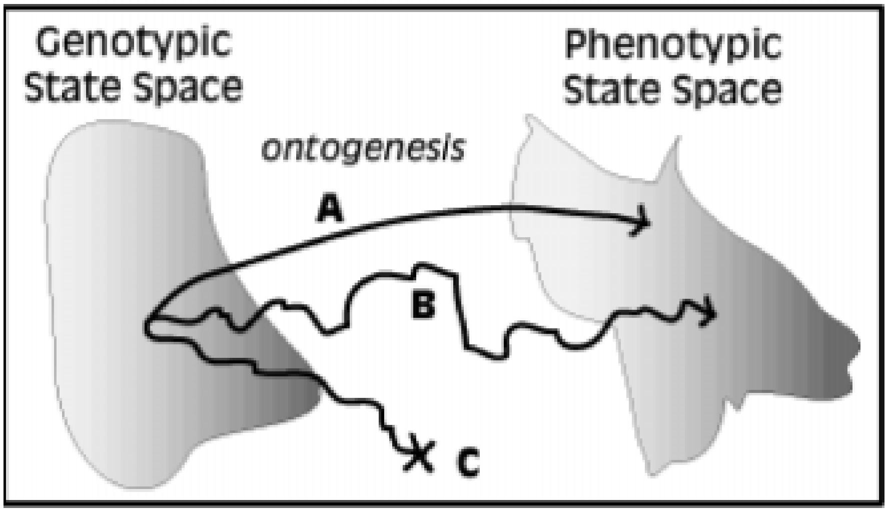

Figure 1
Lewontin-type diagram illustrating the mapping of genotypic state space to phenotypic state space. The ontogenetic process is not deterministic (A), but rather a sinuous trajectory (B) shaped by epigenetic factors, which can result in regressive developmental events such as somatic cell death (C).

In biological systems, the ontogenetic mapping of genotypic state space to phenotypic state space is not deterministic, exhibiting irregular trajectories that may even result in developmental events such as somatic cell death (Figure 1). This is because the process of ontogenesis is influenced by epigenetic factors, which act at the microenvironment (e.g. epistatic effects) and macroenvironment (e.g. gravitoinertial forces) levels. Hence, phenotype results from a combination of both genetic and epigenetic operators during ontogenesis. Nonetheless, although the genome and phenome levels are fundamental aspects of current evolutionary theory, developmental evolutionism requires further integration into the neoDarwinian framework, and epigenetic operators need to be included as part of evolutionary computational paradigms. In this context, a novel perspective for simulated evolution has been proposed: ontogenetic algorithms.

Ontogenetic algorithms[43] employ epigenetic operators which shape the trajectories of massively parallel cellular tensor manifolds (denoting differential gene expression in multi-dimensional space) on adaptive landscapes during somatic development (Figure 2). This paradigm is partly based on our investigations of epigenetic effects on morphogenesis and cellular differentiation, such as induction of topological DNA rearrangements by gene amplification[53], cellular tensegrity[42,54], and biological neural network histogenesis[8,9], within the topobiological context of neural evolutionism[40,41]. Ontogenetic algorithms are being developed as part of the biocognitronics[50] symbolic modeling approach, which has been applied to the study of the effect of altered gravity, an epigenetic factor, on embryonic sensory systems of plants[55] and vertebrates[51]. They are also involved in the engineering of adaptive evolvable hardware[52].

Computational Neuroscience and Sensory Systems Modeling

The subdiscipline of computational neuroscience represents an area of overlap between neuroscience and computer science defined by “difficult algorithmic or implementational questions that are intimately related to the data of the nervous system” (Schwartz[44]). Its dialectics include geometries ranging from Turing machines to computational anatomy, approaches ranging from the theoretical to the experimental, and scales ranging from the synaptic to the cortical map.

Several investigators in this field have used neuroanatomical data to reconstruct biological neural networks in sensory systems and simulate their electrophysiological behavior. For instance, Bower et al. have used the olfactory system as a model for biological associative memory[45,46], and have developed GENESIS (General Neuronal Simulation System) for biologically realistic simulations[47]. NASA Ames Research Center’s Biocomputation Laboratory has used computer generated imaging to produce compartmentally modeled three-dimensional reconstructions of serially sectioned vestibular maculas[48,49]. However, the latter approach emphasizes anatomical ultrastructural fidelity without addressing developmental or molecular issues, which have been a major focus of our research.

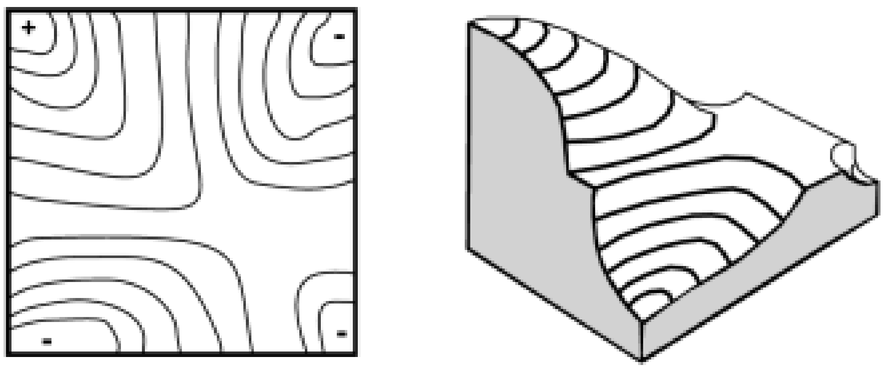

Figure 2
Statistical mechanics inspired rugged fitness landscape (top and side views). During the ontogenetic process, developing cells adapt to a varying topography shaped by epigenetic factors, following trajectories toward optimized phenotypes (attractors, denoted by landscape peaks).

Cellular Architecture of Vertebrate Gravity-Sensing Organs

Vertebrate gravity-sensing organs (VGSO) are linear bioaccelerometers that transform gravito-inertial information into neural space topology by means of biological networks. VGSOs together with the semicircular canals (angular acceleration detectors) form part of the peripheral vestibular apparatus located in the membranous labyrinth of the inner ear. As mechanoreceptors, VGSOs map gravitational and translational acceleration into electrochemical changes, transmitted to a biological neural network. Thus, in contrast to the complexity of the brain's neuronal architecture, these organs represent a relatively simple adaptive parallel distributed processing (PDP) neural control system. As a prototypic neuronal ensemble, VGSOs may reflect the fundamental organization of nervous tissue, and could form the basis for designing adaptive evolvable hardware modules to be used in artificial brains[52].

We have investigated morphogenesis of the avian (*Gallus domesticus*) VGSOs by means of several methodologies, including histochemical, immunocytochemical, enzyme cytochemical, electron microscopic, and energy dispersive X-ray microanalytic techniques. Our studies confirm a basic structural organization consisting of a sensory neuroepithelium (macula) superimposed by a mucopolysaccharide gel in which a 'test mass' of calcium carbonate compound crystallites (statoconia, otoconia) is embedded, the otolithic membrane (located within the fluid-filled lumenal area of the organ). Linear acceleration and gravitational fields can shift this gelatinous mass in relation to the sensory epithelium, which results in deflections of the directionally sensitive sensory hairs (stereociliary bundles, kinocilium) located on the apical surface of mechanoreceptors (hair cells). The hair cells transduce this mechanical information elicited by gravito-inertial forces into electrochemical changes, resulting in nervous impulses that reach the central nervous system by means of an afferent weighed PDP reentrant neural network with interconnected microcircuitry.

The Biocognitronics Reverse Engineering Hybrid Approach

In contrast to the compartmental modeling methodologies for sensory systems referenced above, our strategy toward an AGSO focuses on the ontogenetic dynamical geometry of biological information networks. This approach, called biocognitronics[50] (BCT), uses hybrid reverse engineering paradigms to produce biomimetic adaptive neurocomputational symbolic abstractions. BCT modeling combines fuzzy logic, cellular nonlinear automata, evolutionary computation, and artificial neural network elements in addition to the tools of statistical mechanics, tensor calculus, complexity, and dynamical systems theory. With BCT, spatiotemporal aspects of the nascent artificial network are evaluated within the framework of neoDarwinian topobiology[40,41] (involving ontogenetic algorithms[43]), and correlated with chronological and topographical aspects of the expression of biological macromolecules related to afferent and efferent neuronal differentiation, neurotypy, and synaptogenesis in the developing biological neural network of the sensory organ.

We are applying BCT approaches to VGSOs, which have resulted in a prototypical multi-layered AGSO,GRAVICOGNITOR[51] (GC). GC is based on the cellular geometry and dynamic connectivity of developing VGSOs, and in its preliminary version exhibits the following pattern recognition characteristics. The gravito-inertial tensor space input on the otoconial membrane (depicted as a matrix with viscoelastic and piezoelectric properties) is converted to an Ising-like fuzzy encoding lattice (representing the directional sensitivity of apical sensory hair cell bundles) by means of coordinate transformations. The resulting fuzzy electrotonic functional polarization patterns (hyperpolarization / depolarization) are then mapped to a manifold of hyper-cubical nonlinear fuzzy cytodes (representing the neuroepithelium), which are linked to a cellular non-linear network of multidimensional fuzzy neurodes (representing the canonical nerve cell bodies in the first order sensory ganglion) interconnected by means of reentrant pathways. In this manner, the computational mechanics of gravicognitive pattern recognition are described by means of sequential mapping functions that transform gravito-inertial state space into sensori-neural state space. Further development of GC with improved BCT methodologies may result in comparative applications of this modeling approach to other sensory and cortical organs, as well as pattern recognition systems in general, and will form the basis for related adaptive evolvable hardware.

Biomedical Implications

Improved understanding of vertebrate gravity sensing organ ontogenesis and physiology in microgravity, as well as under terrestrial conditions may contribute not only to space biomedicine and developmental exobiology, but also to the enhanced knowledge necessary for the treatment of vestibular disorders on Earth. In the field of space life sciences, vestibular-related phenomena such as space motion sickness and space adaptation have been well documented since the orbital flight of cosmonaut Gherman Titov in 1961. With the advent of the International Space Station era, the prospect of prolonged spaceflights for many space travelers will become a reality. However, the effects of microgravity on the structural and functional development of gravity-sensing organs remains an important open question that needs to be answered. In other sensory systems, studies of their developmental vulnerabilities under environmentally modified, sensory modality deprived, conditions have produced a better understanding of the morphogenesis and pathophysiology of those systems. For example, in the visual system, partial or total deprivation of stimulus at a critical period during development can result in irreversible abnormalities of the retina, the eyeball, and several of the neural elements involved in the processing of visual information. Similar deficits have been reported for the auditory system as well. In contrast, little is known about the effect of altered gravity on vestibular development.

Furthermore, some 90 million Americans suffer from balance disorders whose etiology, therapy, and prophylaxis could benefit from improved understanding of the vestibular system. For instance, in addition to the common neurological syndrome known as positional vertigo, other conditions such as Meniere's disease, as well as various infectious, metabolic, developmental, and neoplastic labyrinthine disorders could be better understood and treated with enhanced knowledge concerning vertebrate gravity-sensing organs. These benefits also apply to other more generalized neurological pathologies ranging from multiple sclerosis to Bell's palsy, conditions that exhibit vestibular dysfunction among their symptomatology.

In summary, increased understanding of the dynamical organization of vertebrate gravity-sensing organs by means of reverse engineering hybrid approaches may yield contributions to gravitational biology, biomedicine, computational neuroscience, and adaptive evolvable hardware.

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