Natural Variation and Neuromechanical Systems

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ABSTRACT

Natural variation plays an important but subtle and often ignored role in neuromechanical systems. This is especially important when designing for living or hybrid systems which involve a biological or self-assembling component. Accounting for natural variation can be accomplished by taking a population phenomics approach to modeling and analyzing such systems. I will advocate the position that noise in neuromechanical systems is partially represented by natural variation inherent in user physiology. Furthermore, this noise can be augmentative in systems that couple physiological systems with technology. There are several tools and approaches that can be borrowed from computational biology to characterize the populations of users as they interact with the technology. In addition to transplanted approaches, the potential of natural variation can be understood as having a range of effects on both the individual's physiology and function of the living/hybrid system over time. Finally, accounting for natural variation can be put to good use in human-machine system design, as three prescriptions for exploiting variation in design are proposed.

INTRODUCTION

Variation can be a good thing in engineered systems, especially when one or more component is a living entity. In neuromechanical systems and more generally in bioengineering applications, variation plays an important role in adaptive and maladaptive processes alike. Ultimately, the existence of variation allows for adaptation to new environments without the recurring need for specialization (for example, see Appendix 1, Number 1). This is a lesson the engineering community is currently learning by working with biomimetic materials and structures [1, 2]. Biologically-inspired designs often include materials or control strategies that are both compliant (e.g. adaptive) and specialized to a certain task [3, 4]. This broad survey and conceptual framework will focus on how this lesson can be transferred to the context of neuromechanical technology design by relating variation exhibited during performance and across individuals to the unique optimality criteria for such systems.

Standardization and its discontents

The role of standardization in modern engineering design has many advantages from a mass production standpoint [5]. In human-machine systems, however, mass customization plays more of a role in minimizing functional defects. Much as is the case with internet technologies [6], neuromechanical and bionic systems (for definitions, see Appendix 1, Numbers 2 and 3) rely on user characteristics to achieve this mass customization. However, the characteristics of interest in the latter type of system are biological and physiological in scope.

One interesting outcome that arises from this is a general research approach that distinguishes between fully synthetic technologies (e.g. automobiles or laptop computers) and living/hybrid technologies (e.g. domesticated animals or prosthetic limbs). A particular question can also be posed: why is standardization generally a good thing for fully synthetic machines (e.g. automobiles), but bad for living industrial systems (e.g. domesticated animals)? For additional discussion, see Appendix 1, Number 4. The short answer to this question involves recognizing that what generally holds true for synthetic technologies may not hold true for living/hybrid ones.

Variation and Noise

The relationship between variation and noise is also important in the design of both synthetic and living/hybrid systems. Noise arising from variation can serve a constructive role [9]. One example of this is stochastic resonance, which is based on a combination of a patterned signal generated from inside the system functionally coupled with environmental noise. Stochastic resonance can be defined as the alteration or enhancement of a signal through the addition of a stochastic, or noisy, component [10]. In more technical terms, Mitaim and Kosko [11] define stochastic resonance as noise that enhances an external forcing signal in a nonlinear dynamical system. This is particularly important in neuromechanical systems that involve vibrational or oscillatory components. This could improve the designs of a series of products ranging from motorcycles to heart pacemakers.

Another example of beneficial noise, which happens to be a particularly powerful force in shaping living/hybrid systems, is the intrinsic generation of randomness [12]. This type of noise involves randomness expressed as part of processes internal to the system. According to Wolfram [12], this type of noise allows highly complex systems to be constructed from rather simple rules, thus demonstrating the constructive role of noise and the need to consider living/hybrid systems apart from purely synthetic ones.

In living/hybrid systems, these forms of beneficial noise are closely tied to variation observed both in real-time and over the course of extended interaction. Specifically, variation in living/hybrid systems involves baseline genetic characteristics, physiological processes, and regulatory mechanisms. The expression of this variation over the course of interaction is triggered by these forms of beneficial noise.

The need for variation in living/hybrid engineered systems

In both living/hybrid and synthetic contexts, variation comes in two forms: behavioral and structural. In synthetic systems, behavioral and structural variation not accounted for in the original design often plays a deleterious role[1]. Likewise, structural and behavioral variation in living/hybrid systems can play a deleterious role. However, the inherent existence of this variation can also allow the entity to adapt given a range of environmental conditions. In systems with a living/bionic component, the ability to adapt allows for a diverse set of responses. Two of these that will be covered in this paper are 1) population-based, genome-wide variation that sets the baseline for performance in an individual, and 2) expression mechanisms that augment the differences characterized by these baselines over the course of interaction between living and non-living components.

INTRODUCTION TO NATURAL VARIATION FOR ENGINEERING

Natural variation can be defined as the genetic, hormonal, and morphological diversity found among what will be referred to herein as *in situ* populations. This is especially important for understanding the function of neuromechanical systems, which can be defined as the biologically-salient

[1] For examples from bridge structural mechanics, see [7, 8].

study of how neuromuscular, environmental, and movement variables are interrelated.

In situ populations

In situ populations can be defined in contrast to statistical populations. *In situ* populations represent groups belonged to by the individual (e.g. familial or ethnic) being sampled. While the full extent of variation in each population not known, several approaches based on existing techniques used in organismal biology may allow us to uncover the structure and relevance of this variation.

There are three approaches I will introduce in the next section that are, in the context of this paper, specially tailored for better understanding standing variation in living/hybrid systems applied to *in situ* populations. These are population genetics, artificial selection, and gene expression and transcriptional regulation models. However, before we delve into methodology, the specific role of natural variation on living/hybrid must be clarified.

Understanding the role of biological variation in hybrid/living systems involves taking into consideration existing variation, expression of variation across the lifespan, and the by-products of evolutionary and demographic processes. One aspect of this variation involves biological differences which may be amplified or repressed in particular environments [13]. For example, two individuals who carry unique genetic and performance profiles to the task may respond similarly in one environment but much differently in another environment. Furthermore, these differences may be further mitigated and/or augmented by the effects of aging or adaptation to the environment in question.

On the other hand, switching between two environments in a rapid and patterned manner may encourage the expression of previously hidden variation [14]. Such results have been found in animal and bacterial models in response to environmental fluctuations, and may also apply in a limited sense to human neuromuscular systems. In a general sense, environmental switching involves an internal response to an oscillation. When coupled with environmental settings where external forces are applied to the body in this fashion, complex physiological responses may result that may only be understood by looking at variation in the structure and expression of the genome.

Population phenomics: an approach for living/hybrid engineered systems.

In biology, phenomics [15] is the study of phenotypes as they relate to physiological, cellular, and genetic regulation. This is an important consideration for design in a number of technological systems. In this section, three means to understand this diversity will be covered: the use of population genetics techniques, artificial selection experiments, and gene expression and transcriptional regulation models.

Population genetics techniques. Population genetics tells us that traits are heritable [16]. Therefore, specific traits can be confined to familial or ethnic lineages, which make up varying proportions of any particular *in situ* population. The relevance of population-level variation to neuromechanical systems is that such variants set the baseline for response during performance. One promising technique that can be used to better understand how these types of variant are distributed among in situ populations is SNP genotypic [17]. Fortunately, emerging technologies such as the HapChip 550K [18] allow us to explore thousands of SNP markers from across the genome in parallel.

Artificial selection experiments. Artificial selection experiments with wearable devices have the potential to trigger both adaptive and maladaptive responses in cell populations. These include epigenetic and metabolic mechanisms which might be selected for by using specially-designed training regimens. This is in addition to the normal use of neuromechanical technologies.

One approach that might be developed further is the use of prosthetic devices which change the force and surface properties that the human user normally encounters during movement [19]. One such device is a wand with a large moment of inertia (I_o) and a forcing chamber at its end filled with different types of materials. These materials can be isotropic (such as water or sand), electrorheological, or a matrix of custom-made compliant, soft materials. When swung or used to reach for objects in virtual simulations, a degree of mismatch can occur that decouples forces normally produced during like movements under non-simulated conditions. Changing the surface properties in the forcing chamber and selectively using the forcing chamber over time might either mitigate or augment this effect in relation to an evaluatory function described in the next paragraph.

Artificial selection experiments are typically used in an across-generation context using model organisms [20]. However, artificial selection can also be used to understand how variation affects performance in behavioral contexts [21]. Artificial selection can be used to uncover advantageous traits in an *in situ* population. Given that all individuals in a given population have a specific function for evaluating performance[2], selection for performance can be applied by introducing novel forces built into the neuromechanical technological device.

Gene expression and transcriptional regulation models. Of particular interest is how the regulation of gene expression as a functional response to external stimuli plays a role in regulating performance. This regulation is characterized by the output of a physiological system. We can characterize this variation in a theoretical manner, using known information about the structure of the genome and how environmental pressures produce an adaptive response. The techniques that can be borrowed from this domain include gene regulatory networks [22] and metabolic engineering models [23]. The take-home message is that physiological regulation forced by a specific neuromechanical technology can yield differential results in different individuals. Overall, the interaction between transcriptional regulation, metabolic networks, and environmental stimuli can trigger the additional expression of variation *in situ* [14].

POTENTIAL OF NATURAL VARIATION FOR SYSTEM DESIGN

The potential of natural variation in system design can be characterized as the relationship between robustness and brittleness. Noise and variation are the most important concepts that define these variables. However, robustness and variation can also be defined in terms of numbers and relationships between real-world physics

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[2] a hypothetical specific function for evaluating performance is analogous to fitness as defined in an evolutionary context. Rather than being based on the ability to produce greater or fewer offspring, the goal of artificial selection in the context of this evaluatory function is to favor specific adaptations and/or maladaptations over a finite period of time.

(see Appendix 2, Sections 1 and 2, respectively).

One way noise and variation play a role in physiological responses and performance outputs for specific performance settings is by contributing to the nonlinear control mechanisms needed to control complex interacting systems. More specifically, the interaction between environmental force feedback and physiological response can lead to effects such as dampening and saturation, which result from the unfolding of physiological processes over time as they are selectively perturbed by variation inherent in environmental feedback.

Examples of adaptation and maladaptation

Another way in which noise and variation affect performance in neuromechanical systems is by mediating how individuals adapt to a particular interface or wearable device. When provided with an environmental challenge, biological mechanisms can rise to this challenge and adapt immediately, adapt with some training, or fail to adapt altogether. To better characterize this phenomena, two variables must be defined while specific examples of adaptation and maladaptation must be given.

Specific example of adaptation: feedback from interaction to physiology. During the course of interaction between humans and neuromechanical technologies, closed-loop control is established between the individual's physiology and control over the technology at any one point in time. This is why good ergonomic design usually requires technological design to conform to natural postures and do not introduce a lot of extreme stresses, strains, and torsional forces. This is hypothesized to lead to a normal physiological response to technology use.

Specific example of maladaptation: dystonia. Dystonia is one example of how mechanical technologies and individual variation interacts in a deleterious manner (see Figure 1). Dystonias of skeletal muscle can be defined as muscle contractions that cause twisting and repetitive movements and overall abnormal function [24]. Focal dystonia afflicts a specific set of muscles in the hand and fingers. One classic example of focal dystonia is the dysfunction of finger muscles after the extended use of a stringed instrument [25]. In this case, open-loop control is responsible for the mismatch between the mechanical system (in this case a musical instrument) and the biological system (in this case, muscles in a specific part of the body).

APPLICATION OF VARIATION TO NEUROMECHANICAL SYSTEM DESIGN

The variation found in a single individual or group of individuals can be the basis for nonlinear control strategies [26, 27]. It also allows us to better understand how short-term decrements in performance can lead to more substantial long-term gains. Examples might include the rate-limiting effects of pharmaceutical agents, the dampening effects of muscle and connective tissues, and the feedback effects of physical training on the regulation of gene expression. The following sections explore and propose ways in which this variation can be better characterized in the context of neuromechanical technology design.

Tool for design #1: variation and control strategy curve.

One tool that can be generated from the population phenomics approach to predict performance in specific systems is the variation and control strategy curve. This curve is based on understanding how control strategies employed during use of neuromehcanical technologies relates to expressed variation across a population.

We can use the Segway™ motor scooter and Figure 1 as an example of how this theoretical model works. For purposes of expediency, we can characterize the physiological metric as being the thigh-to-shank ratio of the human lower extremity. In the theoretical example, the thigh-to-shank ratio across the population yields a Gaussian probability density function (pdf). Within the area of this pdf, other control strategies are nested. It is of note that while other control strategies are predicted to be nested within the population-wide Gaussian, these sub-functions need not be Gaussian distributed themselves.

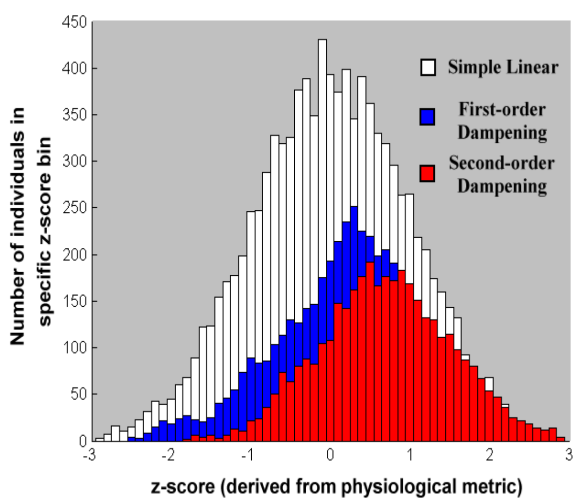

Figure 1. Graphical representation of the variation and control strategy model.

In Figure 1, a sample distribution derived from pseudodata is shown. As demonstrated in Figure 1, subsets of the population are representative of specific trait values. Of all individuals characterized by this trait value (a bin in standard histogram parlance), a certain proportion of them will exhibit a unique control strategy for a task give to the entire population. In Figure 1, for the bin characterizing a z-score of 0, 18% of individuals exhibit a second-order dampening strategy. Likewise, 24% of individuals exhibit a first-order dampening strategy, and 58% a simple linear strategy.

In the case of a gyroscopically-controlled, electric powered scooter, a plurality of individuals may use different physiological control strategies when challenged with a simple balance problem. Artificially and biologically-controlled physical models [28, 29] suggest that a simple linear control strategy is sufficient for solving this problem using a passive dynamic methods or a neural controller. However, the above model suggests that biologically-generated balancing using a range of morphological parameters that interface with a mechanical device can produce multistability. Adding in ability to produce muscle power might yield an even greater number of control strategies used across the population.

Tool for design #2: designing for fault-tolerance using natural variation.

A better understanding of variation and its functional consequences during interaction with neuromechanical technologies may open the door to fault-tolerant neuromechanical system design. The standard approach to fault-tolerant design in the field of computer networks includes designing interactive systems with several goals in mind [see 30, 31 for inspiration of approach taken here]. Natural variation can play a role in several of these goals for neuromechanical systems, which we will now review in a point-by-point manner.

Redundancy. An understanding of how physiological regulation responds to induced loads allows us to distribute loads to multiple anatomical points. This allows for multiple modes of use across different components of the population.

Isolation and containment of system malfunction. A detailed understanding of how genetic variants and biomechanical function are interrelated allows for a way to better contain maladaptive responses to neuromechanical system use. This is especially true over long periods of time during which metabolic and other physiological stresses induced by transitory features of the mechanical system can turn into deleterious conditions. Isolation and containment at an early enough stage can prevent these deleterious conditions. This can also be accomplished in part by building in safety mechanisms called reversion modes.

Existence of safety mechanisms or reversion modes. The ability to revert to safe modes of operation in cases of malfunction can be augmented by accounting for natural variation in the design of neuromechanical systems. One common example of a reversion mode is the Windows™ "safe mode". The safe mode can be deployed when the normal operating parameters become corrupted. Likewise, a neuromechanical system should allow for the emergency shut-down of all non-essential and potentially harmful components of the interface once maladaptation is considered probable by means of physiological indicators, functional genomic data, and predictive genomic markers.

EXPLOITING VARIATION IN DESIGN

There are three ways in which we might exploit variation in design contexts: genotyping individuals, designing for the mapped physiological substrate, and engaging specific traits with design. These are not potential variables and relationships. Rather, they are strategies for defining the connection between measured/observed physiological variation and the technological and physical environment.

Individual variation in time-frequency space. There is a need to redefine the standard Gaussian definition of variation in human physiology which will not be further discussed here. In anthropometry, the sizes of body segments and dimensions are distributed according to a "bell curve" model. While this is adequate for static traits, such a model may be inadequate for appreciating how these static traits contribute to performance over the course of technological interaction.

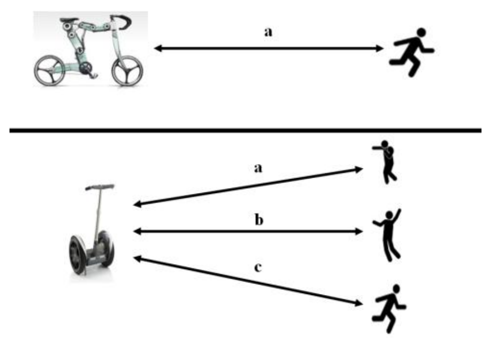

Figure 2. Top frame: relationship between human and machine according to traditional view (top frame) and proposed view (bottom frame)[3].

One example of this stems from a prediction of population genetics: polymorphisms which contribute to different

[3] in Figure 2, the letter a) represents dystonia, a specific maladaptive condition. Bottom frame: three different humans interacting with the same machine. Letter a) represents Human A being prone to maladaptation, letter b) represents Human B having a 'normal' response to interaction with the machine, and letter c) represents Human C having a dampened response to maladaptive stimuli. The hypothetical response observed in Human C is example of how a high degree of robustness translates into system design.

trait states are distributed according to a power-law. In cases where there is diversity at a particular locus, there tend to be a few predominant variants and potentially many variants at very low frequencies [32]. Rather than a percentile model of understanding variation, this new way of viewing variation might be based on time-frequency decomposition (for more information, see Appendix 2, Section 3).

Defining a "mapped physiological substrate". There is also a need to understand the relationship between genotype and phenotype [33]. In the context of the population phenomics approach, the mapped physiological substrate can be defined as what phenotypic precursors make an individual more or less susceptible to maladaptation. Getting at this question allows us to better understand what we are perturbing in the physiology with particular technological designs. A more detailed understanding of these new ergonomic considerations may lead to the modification of technology for specific components of the population.

Integrating specific biological traits with design. This point stems from defining a mapped physiological substrate. Phenotypic traits with complex regulatory underpinnings have greater opportunities for adaptation during interaction. The dynamics of a neuromechanical system in settings such as this introduces a level of complexity that goes well beyond the focal dystonia example provided earlier. In such cases, a nonlinear control system may be used to tease out the complex effects of interaction in various subsets of the *in situ* population being sampled. For points on how this could be applied to real-world systems, see Appendix 2, Section 4.

CONCLUSIONS

In this paper, a number of concepts were introduced that serve as a conceptual framework for better understanding how human variation plays a role in neuromechanical system function and ultimately effective design. These concepts can be grouped into three general categories: the role of noise and statistical distributions of variation, methods for discovering biological variation in so-called *in situ* populations, and the integration of mechanical and physiological function. Of the three, the last of these points holds the greatest potential for future development.

APPENDIX 1: EXAMPLES AND DEFINITIONS.

Number 1: Specialization.

A simple example of this can be found among bird's beaks. Among one group of birds (species A), there is a single morphology specialized to perform specific tasks such as fighting or feeding. Members of species A are said to be ecological specialists. Among birds of species B, single beak morphologies are also exhibited among its members. However, in this species, individual birds can exploit a wide range of resources and perform a multitude of tasks. Members of species B are said to be ecological generalists. In species C, a range of beak morphologies might exist. Members of species C all perform the same sets of tasks with divergent morphologies. It is this latter type of variation seen in human traits that might serve as an untapped resource rather than a hindrance for purposes of system design.

Number 2: Neuromechanics, Neuromechanical.

Neuromechanics can be defined as the study of anatomical mechanics as it relates to the nervous system. In many neuromechanical systems, there is a tight relationship between kinematics, biochemical and muscle kinetics, and neural control. Neuromechanical systems can be better understood by examining examples from humans, non-human animals, and robots.

Number 3: Bionic systems.

Bionic systems are technological systems that interface either closely or explicitly with physiological systems. Biomedical applications are the most high-profile examples of bionic systems. However, technologies that affect the nervous system in a transformative manner can also be considered to be bionic systems. Examples include wearable or manipulable interfaces that induce the effects of resistance exercise, or technologies that induce specific neuromuscular disorders such as dystonias.

Number 4: Differential standardization considerations in synthetic and living/hybrid systems.

This definition is closely related to specialization in that variation in different types of technological systems is proposed to have opposing effects. For example, variation in synthetic systems may have deleterious effects including production defects which lead to malfunction. On the other hand, variation in living systems introduces additional levels of complexity to product design.

In older products such as bicycles, the recognition of variation as an assistive component of the design process already exists, albeit in limited form. In emerging technologies such as brain-machine interfaces, individual variation may be both an aid to customization and a barrier to understanding uniform responses across human populations.

APPENDIX 2: PARAMETER AND ANALYTICAL DEFINITIONS

Section 1: Robustness definition

Robustness can be defined as the ability of the living/hybrid system to absorb environmental noise challenges. In neuromechanical systems, this absorption is a function of a technology designed to minimize the resistance forces encountered during movement. Robustness can be measured using the parameter *A*[4]. In the case of brittleness, *A* should be above 0.5 and in extreme cases near 1.0.

Section 2: Brittleness definition

Brittleness must be defined as the inability of the living/hybrid to respond to an environmental noise challenge. Brittleness is typically a function of technologies that create a large number of resistance forces against some set of muscles. Brittleness can also be measured using the parameter A. In the case of brittleness, however, the value of *A* should be above 0.5 and in extreme cases near 1.0.

Section 3: Time-frequency approach to variation

This provides inspiration for a new approach to understanding biological variation in the context of technological systems. Specifically, a time-frequency decomposition of combined physiological and performance data is necessary. Such an analysis is hypothetical at this point, but may inspire future applications to specific datasets. The proposed time-frequency approach might involve the analysis of genetic variants, the expression of genes over time, and other variables that

[4] the parameter *A* can be defined as the degree of adaptability, which is the ratio of external forces (measured in Newtons) against muscle power (measured in Joules / meter · meter and representative of internal forces).

characterize movement or muscle activity over time [34].

Section 4: Approach to nonlinear control and natural variation

One way this can be applied to design is by mapping A) specific physiological traits and B) suites of traits that define a population to 1) specific trait states and 2) their potential to be affected by feedback from environmental forces. These relationships can be combinatorial so that single and multiple trait relationships can be related to either specific trait states such as muscle hypertrophy or the robustness and brittleness parameters (which define the potential to be affected by feedback from environmental forces).

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