New Directions in Computation, Biology, and Behavior: harnessing emerging perspectives

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Part I: Introduction to Performance Augmentation
Introduction to Performance Augmentation (1.8)

Performance augmentation definition:

How can we uncover and harness the “physiological reserve” of an organism (e.g. human) for purposes of improving performance (e.g. optimizing the function of complex behavioral, phenotypic traits)?

How can we better understand the variation and genetic background that constitutes expression of an adaptive range for these traits? Applications to basic and applied (e.g. medical and Human Factors) research.

Means of uncovering these phenomena/effects:

* selectively perturb a particular phenotypic or behavior system during its expression (in humans, sensorimotor system = nervous system, phenotype).

* target adaptive features of this behavior (in this case, proprioceptive feedback).

* measure the result of this outcome using several indicators (muscle activity, gene expression assays, neuroimaging, simulation, & computation).
Introduction to Performance Augmentation (2.8)

Why choose sensorimotor systems?

#1: Mechanism both highly-conserved and derived in humans, other species:

* locomotory specializations, tool use, etc.

#2: Has been successfully replicated in robots:

* interlimb coordination, force production modeling of internal mechanisms (e.g. sensorimotor integration).

#3: characterizes a model of homeostasis vs. allostatic drive:

**Homeostasis:** a single regulatory mechanism modulated by multiple feedback pathways.

**Allostatic Drive:** multiple, distributed regulatory mechanisms modulated by only a few feedback pathways.
Introduction to Performance Augmentation (3.8)

Why do we need to know about this?

* development of information technologies that interface closely with human physiology, what is their effect over time?

* better understanding of human variation (adaptability) and how to apply computational methods to novel physiological questions.

What has been done?

* behavioral experiments in virtual environments using a measure of muscle activity (surface Electromyography – EMG *instrumentation work was necessary).

* characterizing the morphometric parameters of augmented performance (phenotypic measurements, capturing force production in a virtual environment *instrumentation work was necessary).

* modeling and parameterization: what occurs at various biological scales? How might augmentation be measured better (genes, imaging)?
**Introduction to Performance Augmentation (4.8)**

**Augmented Cognition (AC) Model:**

- Example: Yerkes-Dodson curve (arousal level)

Constrain behavior within the black bars on performance curve (Gaussian).

What happens when performance is not Gaussian? What if it is like a complex fitness landscape?

**Example of a contemporary model:** (see Schmorrow, *Foundations of Augmented Cognition*, 2005)

- Characterize mathematical function of physiological response for characteristic of interest.

- Determine suboptimal and optimal range of performance.

- Generalized mathematical function (no accounting for hysteresis over time).

- For all suboptimal behaviors, implement filter or “mitigation”.

- In theory, keeps behavior within the optimal range (e.g. augmented).
Introduction to Performance Augmentation (5.8)

Consequences of AC model (lessons from evolutionary physiology):

* basically a model of artificial selection across a single generation (selects against pathways – effects of learning, adaptation - to even more optimal behaviors).

* selecting against a range of potential behaviors (would be expressed under different environmental circumstances).

* how does the physiological reserve of an organism deal with this restriction? Loss of robustness, adaptability?

Principles from phylogenetically distant systems??

* genes that are expressed more tend to evolve less (yeast model - Pal et.al, Genetics, 2001).

* medium switching examples in bacteria: Kashtan et.al (PNAS USA, 2007) in silico of accelerated mutation rate, Balaban et.al (Science, 2004) of robustness mechanism.
Introduction to Performance Augmentation (6.8)

Instead of augmenting through enforcing a large selection coefficient on an individual, use the strategic perturbation approach:

* introduce one set of environmental parameters, switch those parameters after a short period of time, then return to the original environment.

* for human and animal models, approach used in motor learning and preconditioning (induces long-term adaptation, affects neurotransmitter production/release).

* environment recognized as previously experienced = potential robustness to switching,

* environment not recognized as previously experienced = can interact with past memory consolidation and other adaptations.

Sensorimotor adaptation ultimately a genomic problem:

* activates early-immediate genes, inhibits apoptotic pathways, contributes to hypertrophy of tissues (IGF-1) and learning and memory (CREB, cAMP regulation).

* adaptive response (positive, negative aspects) is poorly understood, but this method has potential to uncover adaptive variants in population/understand system better.
Introduction to Performance Augmentation (7.8)

Two examples of results for strategic perturbation method: A) prosthetic device switching experiment, B) tactile surface resistance experiment.
Workloop trace analysis of selected muscle in forearm (x-axis) vs. selected muscle in humerus (y-axis) for prosthetic device switching experiment (left), and tactile surface resistance experiment (right).
Part II: Virtual Environments
Approach: Virtual Environments (1.9)

**Basic Computational Features**

* every object, interaction, and physics in environment can be controlled and quantified.

* mapping scheme (virtual representation of physical systems).

* sensor networks, scanning technologies can be deployed to quantify environments (ecological settings, physiological systems).

* dynamics of system can be simulated.

* kinematics & kinetics can be “captured” using visualization techniques, force feedback, motion tracking, positional sensors, and EMG electrodes.

http://www.pennhealth.com/breakthroughs/images/neuro_imaging.jpg
Approach: Virtual Environments (2.9)

Use #1: Innovative Experimental Design:

Transgenic organisms (e.g. inducible genetic knockdowns):

* add, subtract a gene and observe loss/gain of function.

Transenvironmental organisms (e.g. environmental knockdowns):

* add, subtract environmental stimuli, observe loss & gain of function.

Environmental enrichment: has effects on development, sustained neuronal effects in rats.

Prosthetic manipulation: has effects on typical biomechanics of the phenotype.

http://www.untu.cas.cz/pics/sindbis.jpg
Approach: Virtual Environments (3.9)

Most (if not all) physiological traits related to behavior are:

* polygenic (multiple genes required to explain variance)
* pleiotropic (single gene = multiple effects; alternative splicings, multiple transcripts)
* GxG (epistasis; additive gene-gene interactions)
* GxE (multiplicative gene-environmental interactions)

Experimental design allows for the teasing out of these complexities:

* virtual environment manipulations allow us to fix E, solve for G
* existing mutants (clinical populations and animal models, solve part of G by knowing functional effect of one term in G)
* rTMS (repetitive transcranial magnetic stimulation) knockdown, stimulate entire circuits in brain, constrain number of terms in G
* Cre/loxP system (controlled knockdown of genes – animal models only, really reduce number of terms in G).
Use #2: Scientific Instrumentation:

Capturing muscle force output in virtual environment (mapped physiological output):

* capture physiological output (muscle force production).

* activate muscles in upper extremity, produce force.

* force moves virtual object a certain distance (compared to goal distance).

* mismatch should differ during, after perturbation.

* can also compare with muscle activity (unmatched muscle power).
Approach: Virtual Environments (5.9)

Sensorimotor learning: a closed-loop adaptive behavior.


Uncovering the adaptive range of sensorimotor behaviors in virtual environments:

1) Physiology-environmental “decoupling”

* *Drosophila* flight arena, movement and perception physiology are altered by controlling sensory and motor variables.

2) Environmental switching

* real vs. virtual, virtual A vs. virtual B (perturbation).

* switching expands range of responses required by physiology.

* switching has both molecular-scale and “higher-order” effects (e.g. behavior and cognition).

* force stimuli = activation of molecular pathways in muscle, synaptic modification and learning in brain.
Approach: Virtual Environments (6.9)

Physiology-Computational Coupling:

* subjects performed reaching activity, motion of hand mapped to a virtual environment.

* add (hard distortion), remove (weak distortion) weights and force fields.

Force contributed to movement of a virtual object / force required for movement of virtual object (referred to as mapped physiological output, related to muscle power).

* muscle activity in arm segments (measured using electromyography, muscle biopsy).

* spikiness of data series (also used to determine “fitness” of mapped physiological output): 

  \[ z = \frac{\min_i - \max_i}{\text{mean}_i} \text{ where } i \text{ is a set of trials over time (set of trials, block of trials)} \]
**Approach: Virtual Environments (7.9)**

*In silico* demonstration of effects on phenotype by prosthetic manipulation and genotypic factors.

Simple (binary) representation of:

* genotype of physiology ($G_t$)

* phenotype of computational device ($G_p$)

$G_t + G_p = \text{augmented phenotype}$

Frame #1: isometric mapping ($G_p$ dominant)

Frame #2: mixed mapping (some effect from both $G_t$, $G_p$)

Frame #3: robust augmented phenotype (protected from effects of $G_p$ on phenotype).

Combinations of binary states $G_t$, $G_p = \text{logic gates (i.e. AND, OR, NAN)}$
Approach: Virtual Environments (8.9)

Simulation provides link between virtual representation and system dynamics:


Use #3: Scientific Simulation

Agent-based models:

* population of agents, interact according to a series of rules.

* interactions produce a series of emergent phenomena (B-Z reaction, human settlement patterns, wasp’s nests).

Cellular Automata (CA):

* grid of cells, each cell is either on or off (finite state automata). Current state depends on state of neighbors.

* leads us to “evolutionary” or “adaptive” outcomes via simple rules.
Large-scale predictive models can also be built using these tools, such as those that deal with climate or weather prediction:

* similar types of environments already exist (SimCity).

* each cell in the environment has a series of attributes, cells interact.

* secondary purpose is to model systems in virtual world, compare with real world (perhaps even allow them to interact).
Part III: A Need for Systems Physiology
A Need for Systems Physiology (1.7)

#1: Why advocate a systems approach?

* many interacting elements in physiological systems driven by behavior & environmental stimuli.

* captures “emergent“ features of phenotype and behavior (e.g. IPUI Physiome project).

* goal should be to capture emergent features of these systems.

Allows for a “vertical” approach to regulatory mechanisms (genes to phenotype to behavior).

*current approaches to sensorimotor behavior in Human Factors engineering, rehabilitation, and even basic research do not approach problem this way.

* focus should not be on the vertical approach per se, but on processes manifest at each scale of analysis.
**A Need for Systems Physiology (2.7)**

Force learning (adaptive sensorimotor behavior based on proprioception).

* network centered on cerebellum, site of motor learning and VOR conditioning (“internal model” proposed by several groups).

Muscles, spinal cord also involved. (neuromuscular system is regulatory, has control system quality).

**Homeostasis**: system is able to maintain current state through a single regulatory mechanism (brain region, gene regulation).

**Allostasis**: system moves to a new state via multiple regulatory mechanisms (cognition, molecular memory).

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Figure 2. Motor learning in the VOR. Before learning, eyes move with the same speed, but in the opposite direction, as the head, keeping the eyes stationary in world coordinates. Foveal points of the eyes are indicated by an x. An increase in VOR gain is produced by training with image motion in the direction opposite that of the head (gain-up stimulus). A decrease in VOR gain is produced by training with image motion in the same direction as the head (gain-down stimulus). After each training session, the VOR is retested in the dark with the same head movement stimulus used in the pretraining measurements. The data shown are representative traces acquired from monkeys after 2 h of training.
# A Need for Systems Physiology (3.7)

Considering problem from a systems-level perspective:

* concepts of homeostasis/allostasis provide unified framework.

* various aspects of function exhibit either robustness or brittleness

* closely tied to homeostasis and allostasis (or allostatic drive).

* robustness and brittleness relate to a control-system characteristics

* “robust” mechanisms are responsive to both positive & negative feedbacks.

* less so for “brittle” systems.

<table>
<thead>
<tr>
<th></th>
<th>Homeostasis</th>
<th>Allostatic Drive</th>
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</thead>
<tbody>
<tr>
<td><strong>Systemic response</strong></td>
<td>Robustness</td>
<td>Britleness</td>
</tr>
<tr>
<td>Potential for compensation, regulatory response</td>
<td>One compensatory mechanism (responds to challenge of perturbation – learning-related adaptation in nervous system)</td>
<td>Many compensatory mechanism (may force peripheral tissues to adapt, initial response to perturbation unstable)</td>
</tr>
<tr>
<td>Effects of standing variation</td>
<td>Allelic factors, gene expression pathways allow for compensatory mechanism, limits further adaptability</td>
<td>Allelic factors, gene expression pathways may exist for multiple stable states, no immediate limit on further adaptability.</td>
</tr>
<tr>
<td>Extent of learning-related changes (physiological)</td>
<td>Extensive, long-term changes in synaptic efficacy (more global consolidation)</td>
<td>Limited changes in synaptic efficacy (lack of global consolidation)</td>
</tr>
<tr>
<td>Cause of systemic response (perturbatory stimulus)</td>
<td>Device with familiar shape, operating kinematics</td>
<td>Device with novel shape, requires novel operating kinematics</td>
</tr>
<tr>
<td>Performance scaling</td>
<td>“Core” variation exhibited</td>
<td>“Extreme” variation exhibited</td>
</tr>
<tr>
<td>Adaptive potential of system</td>
<td>Overall adaptability low, adaptability of specific compensatory mechanism high</td>
<td>Overall adaptability high, adaptability of specific compensatory mechanism high</td>
</tr>
</tbody>
</table>
A Need for Systems Physiology (4.7)

#2: How do we get at gene networks and the epistatic relationships behind behavior and phenotype?

* uncover latent variation that might only be expressed during times of “stress”.

* introduce stress (e.g. alternate simulated stimuli), results in an adaptive response.

* activity-dependent, reactive plasticity parallels developmental plasticity, but in a more limited way.

* robustness vs. fragility to perturbation, can be described in terms of homeostasis.

* some individuals have larger physiological reserve (capacity for robustness) than others (allelic basis).
A Need for Systems Physiology (5.7)

# 3: allows us to build a better “internal model”.

In robotics and neuroscience, there is a need to characterize “internal” (messy biological) processes using computational means.

* solution: build a representation of what is going on internally (based on indirect observation).

* computational (series of boxes with some functional significance).

* can be multi-scalar (deal with molecular-scale, phenotypic/behavioral effects).

* parallel in this example with functional aspects of genome, genotype (from phrenology to Allen Atlas of genotypic function).

Turn of the 20th century: Speculation about what “brain” was, fixed level of empirical validation.


20th century: “neuron doctrine”, computational models of neuronal systems.

21rst century, Allen Atlas: anatomy, genomics, computation; better idea of internal model function.
A Need for Systems Physiology (6.7)

Internal model in practice:
Biological performs some computation in response to a stimulus.

* “computation” is really the functioning of some process we want to know more about (data structure).

* approximate this using computational, experimental means.

Physiological control system:
* distinct input and output (from & to environment, phenotype).

* boxes = process, computational center (regulatory element, transcription factor, specific set of cells).

* feedback and direct connections between boxes allow us to approximate complex processes.
A Need for Systems Physiology (7.7)

Internal components of “simple” phenotypic mechanisms not well described using reductionist approaches.

Models of low-order feedback in sensorimotor integration, incomplete description of complexity:

Pole balancing model:

* 1-D model, keep the pole balanced using a series of corrections (positive and negative feedbacks).

* crudely approximates simple neural integrator (internal processes).

PDW models:

* one way to quantify optimal energy requirements for maintaining balance.

* does not work well when legs exert lots of muscle power, no regulation from brain, tissues.
Part IV: Data and Modeling Results
Data and Modeling Results (1.9)

#1: Robustness Analysis

Measurement of “fitness” for mapped physiological output for alternate methods of delivering force perturbations:

Condition 1: hard distortion = black, red functions, interleaved with weak distortion.

Condition 2: weak distortion = black, red functions, interleaved with hard distortion.

Condition 3: weak distortion = black, red functions, with hard distortion delivered before compared blocks.

Condition 4: hard distortion = black, red functions, with weak distortion delivered before compared blocks.

Conditions 1 and 2: robustness with positive and negative feedbacks.

Condition 3: weak correlation and regression coefficients.

Condition 4: big drop-off in fitness for secondary learning (third) set of trials.
#2: Performance Scaling Analysis

**Allometry:** scaling characteristics of different anatomical segments are “linked” due to genomic and developmental factors. Consequences for function:

\[ Y = ax + b, \quad Y = ax^b, \quad Y = -Ax^2 + Bx - c \]

**Functional effects of allometry:**
Herr et.al, *J. Experimental Biology*, 205, 2005:

* static allometry may affect movement performance (differences seen within and between species) in a systematic fashion.

* provides mechanism for determining functional effects of scaling.

* Collins et.al, *Science*, 307, 1996 have found that there is an optimal ratio of 1.06 between the length of the shank and thigh in human bipedalism.
Data and Modeling Results (3.9)

Performance scaling relationships not immediately apparent:

* sensitivity algorithm used to uncover datapoints that fit the predicted function (nonlinear regression).

Sensitivity analysis = take key data points out, changed regression coefficient improves fit of theoretically-defined curve.

* many different scalings, comparisons of different body dimensions can be used.

* in some cases, removing a few individual datapoints will improve these features greatly.

Predicts an “optimum” point: performance falls off as morphology gets too large, small.
Parameters tell you how good scaling fits the theoretical function:

* fewer steps = this particular scaling predicts performance for a broader range of individuals, perhaps this is critically organized somehow.

* larger regression coefficient value given smaller regression coefficient value = greater improvement of taking out single individuals.

Algorithm converges when removing another datapoint (i.e. taking another step) will not improve the regression coefficient value.
Data and Modeling Results (5.9)

Results of various performance scalings for muscle in humerus (left) and forearm (right).

Pseudocode for sensitivity analysis.

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Calculate regression coefficient for a performance measurement versus a morphological scaling.  
Search for the largest outlier in the dataset.  
Recalculate the regression coefficient on n-1 samples.  
Search for the next largest outlier in dataset.  
Recalculate the regression coefficient on n-1 samples.  
Continue until regression coefficient for n samples ≥ regression coefficient for n-1 samples.
How does scaling relate to performance alone?

* when a perturbation is introduced in the first (A-C) or second (B-D) block of trials, the homeostatic (blue) vs. the allostatic (red) response demonstrate differences.

* in Frame A, allostasis results in a higher overall performance measurement value, but trend mimics homeostatic function.

* in Frame B, allostasis results in a steady decrease in performance.

* Frame C vs. Frame D for performance scaling (hyper-allometry for C, neutral for D).

* regression coefficient for C much higher (.746) than for D (.351).
#3: Simulating the range of variation (artificial scaling experiment)

Dataset can be manipulated to examine “theoretical” performance and morphological parameters:

* body dimensions and performance indicators can be reduced, enlarged to simulate evolution and adaptation.

* extrapolate, interpolate changes in function that reflect potential changes in phenotypic growth

* infer subtleties in genomic linkage across within-species variation, evolution, and development.

* artificial scaling factors meant to uncover the effects of “hidden” variation or environmental conditions not previously encountered.

\[\alpha = \text{range along x-axis (morphological scaling)}\]
\[\beta = \text{range along y-axis (performance measure)}\]
\[\Omega = \text{artificial scaling factor (1.0, .75, .50, .25)}\]
In a linear context, changes in the size of one trait relative to another are referred to as hyper- and hypo-allometry:

* when slope of a scaling/performance relationship is > 1, = similar to hyper-allometry.
* when slope is <1, = similar to hypo-allometry.
* when slope is = 1, neutral.

In a nonlinear context, the polynomial function also changes. Relationship still exists, but more complex:

\[ RBC = \left( \alpha \right) / \left( \beta \right) - 1 \]

* the range of each axis weighted by artificial scaling factor -1 (0 = “neutral” linear relationship).
Data and Modeling Results (9.9)

Observations regarding data:

* $b_1$ and $b_2$ are variable in the nonlinear regression equation:
  * as polynomial function becomes more cane-shape and vertical, $b_1$ gets very large and $b_2$ approaches zero).

* size and shape are variables derived from:
  * size (internal volume) and shape (degree of elongation vs. girth) of the humerus and forearm
  * scaling of humerus against forearm.

* size variable for both muscles and mapped physiological output always yields slope $>> 1$.

* shape variable for mapped physiological output consistently yields slope $< 1$. 

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Part V: Conclusions and Projects Past
Conclusions (1.4)

#1: Special Case of Phenotypic Capacitance?

**Capacitance:** “hidden” polymorphism selectively exposed in phenotype (normally developmental).

* “stored” in the genotype, and released during times of stress (e.g. heat shock protein produces “extreme” phenotypes in *Drosophila*.

* in rats, sensorimotor ability (not adaptation per se) = divergent artificial selection peripherally associated with evolutionary fitness, demonstrates less pressure of natural selection (Koch and Britten (2003). *Physiological Genomics*, 13, 241-247).

Consider “standing variation” (set of allelic variants present via previous evolutionary processes that do not normally experience selection for expression):

* once a trigger is presented (environmental mutation/selection), what new/extreme phenotypes will be revealed?

* how do these relate to specific genes, expression of specific regulatory networks?
Conclusions (2.4)

#2: Potential Effects of Environmental Mutation/Selection

Mutation/Selection model (population genetics):

\[
\text{Freq}(\text{allele}_n) = \frac{1}{2N}, \text{ where } N = \text{population size}
\]

* in general, many alleles with low frequencies in the overall population (recessive deleterious alleles never entirely removed, new variants rare unless population undergoes extreme drift).

* relatively few “freaks”, with lots of variation, regardless of the population size (although more in larger populations).

* medical resequencing (Nature Genetics, 39(4), 407) shows that rare phenotypes (5\(^{\text{th}}\), 95\(^{\text{th}}\) percentile) show high degree of variation at less than 5% of loci involved in trait. Promising approach.......

Differences in response to environmental training across individuals (expression of “freak” variation). Presence of underutilized alleles might provide advantage to certain individuals in context.

* comes down to a difference in how robust or brittle the physiological system will be to variation in environmental stimuli.
Conclusions (3.4)

#3: Differential responses to same amount of training with same initial condition

Differences in morphological size, shape, internal mechanisms all provide a different response to the same set of stimuli.

* previous performance levels, hereditary factors can determine level of adaptation attained.

Robustness in training -- see Coyle, *Journal of Applied Physiology*, 98, 2191-2196 (2005):

Lance Armstrong’s muscle power:

**Gross**- production of muscle power.

**Net(Δ)**- production of muscle power not related to metabolic processes.

Rises over several years, regardless of detraining (chemotherapy), intense training (before W.C., Tour de France) intervals.
Conclusions (4.4)

Wheel Plot of Physiological States:

* arcs = transitions between states (allostasis).

* nodes = homeostasis (state maintained, some flexibility in measurements, but not a true state transition).

* structure of network – allostasis and robustness are not random.

* adjacent nodes = small changes in metabolic, gene expression pathways.

* distant nodes = large-scale changes in metabolic, gene expression pathways.

Wiring of network (exclusively local, random, scale-free) may provide insights into gene expression networks, complex effects of physiology on behavior.
Quick review of projects past (1.3)

#1: *Intraspecific variation & interspecific diversity in humans and non-humans:*

Used phylogenetic methods to uncover structure of human variation.

* mitochondrial DNA sequences used (HVR = high rate in human lineage, available for modern humans, Neanderthals, chimps, other species).

* mtDNA also used to resolve human, Neanderthal intraspecific datasets (non-recombining).

Rooting and in-group experiments: root trees with different outgroups (e.g. Neanderthal, chimp, non-Primate), record tree statistics and phyletic groups.

* mixed results (no consistent alteration of how human variation was partitioned), but done before large-scale genome data was available.
Quick review of projects past (2.3)

#2: Activity in the HFES community and interest in Chronobiology:

* reviewer for *Human Factors* Journal and conference.

* paper on biological (circadian) rhythms and behavior in “real-time” settings.

* computational representations (logistic map) of biological rhythmicity in relation to complex behaviors.

* in paper, theme of VEs, other human-machine systems.

* interest in human performance modeling (building models of real-time behavior and adaptation).

http://www.biocarta.com/pathfiles/h_circadianPathway.asp
Quick review of projects past (3.3)

#3: Fundamental elements of muscle-derived movement: towards a genomic model.

Model muscle at genomic scale:

* “cubes” of tissue (produce force output).

* model genotype-phenotype as a hybrid genetic algorithm/neural network.

Adaptive Motion of Animals and Machines (AMAM)

* focus on epistatic properties of genome (simple and complex).

* cubes of tissue can then be attached to anatomical structures such as limbs, x-bridges.