

#### **Presentation Outline**

#### Introduction

- Central pattern generators
- Spinal cord injury
- Proposed locomotion controller
- Experiments & results
  - Model systems
  - Gait controller: in vivo results
- Phase controller: in vitro results
- Ongoing and future research
  - Adaptation and Learning: in roboto
- Conclusion

#### Central Pattern Generator (CPG)

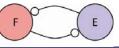
- Networks of neurons in the spinal cord of vertebrates
- Generate sequences of patterned outputs to activate muscles
- Control motor systems with regular, periodic activity (breathing, chewing, locomotion, etc.)
- Basic architecture is preserved across species [Cohen et al., 1988]
- Basis of locomotion in all vertebrates studied to-date, including primates and humans\*
- Convincing evidence in marmosets [Fedirchuk et al., 1998]
- Similar data in humans (without deafferentation) [Dimitrijevic et al., 1998]
- CPG is used for "periodic" not specialized, locomotion



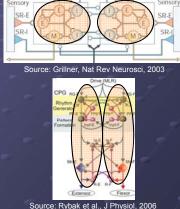
Source: J. M. Cleese, MPFC, 1970

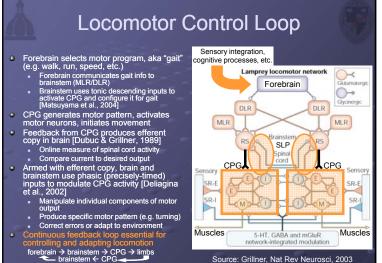
# CPG Architecture First conceptual "model"

in 1911 by T. G. Brown: half-center oscillator

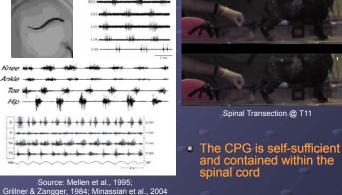


- HCO structure preserved in modern models
- Cellular models in primitive vertebrates
- Models in higher vertebrates are less detailed: designed to
  - detailed; designed to match behavioral data



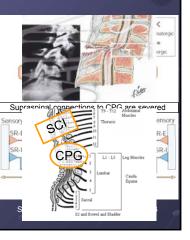


# CPGs in Action



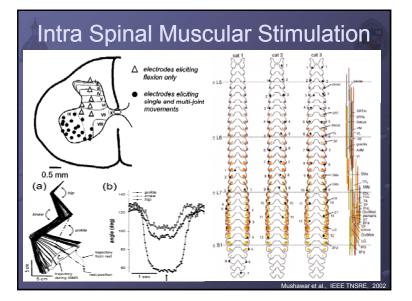
# Spinal Cord Injury (SCI)

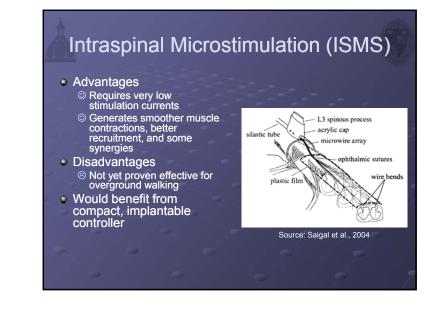
- SCI is usually a focal injury: vertebral body dislocation → spinal cord contusion
  - Kills spinal cord cells at lesion site
  - Severs connections
  - Leaves cells above/below
     lesion intact
- In most cases (~65%), lower limb CPG is intact after SCI
- Paralysis is caused by loss of descending control of the CPG, not by loss of CPG itsel
- Tonic & phasic inputs to CPG are disconnected
- Efferent inputs required to activate CPG and control locomotion
- → Paralysis



# How to Restore Locomotion

- Historically, locomotor prostheses have ignored the CPG after SCI and activated muscles directly through functional electrical stimulation (FES) of peripheral motor axons (PMA)
- Advantages
  - © Simple in concept: one electrode per muscle © It kinda works: elicits strong contractions
- Disadvantages
- Requires a lot of power (mA per contraction)
- Requires a lot of (distributed) electrodes
   PMA stimulation causes reverse muscle recruitment
  - Rapid fatigue (avg. range 300m [Klose et al., 1997])
  - Inelegant, jerky movements (poor synergies)
- Alternative: intraspinal microstimulation (ISMS)





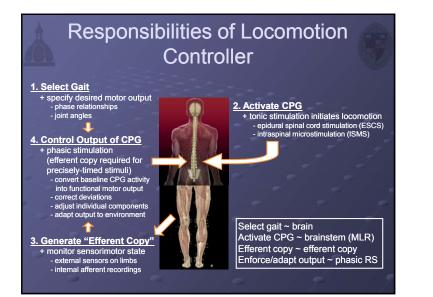
#### State of the Art: Commercial Locomotion Prostheses

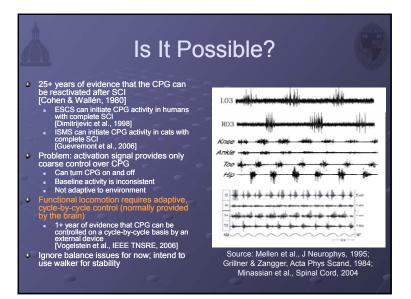
- Parastep system uses FES of PMA (FDA approved in 1994)
- Designed as external (nonimplanted) system
  - Surface FES electrodes
  - Hand-switches on walker control step timing
- Some work on automatic controllers, some neural nets [Strange & Hoffer, 1999; Fisekovic & Popovic, 2001; Abbas 2001; Guevremont et
- al., 2007]
- Little motivation for compact, implantable controller



Source: Sigmedics, Inc.

#### **Our Approach** Previous approaches ignore CPG and focus on controlling muscles to generate locomotion • We propose to directly control the CPG and use it to generate locomotion Basic idea is to recreate natural neural control loop in an external artificial device (i.e. replace tonic and phasic descending inputs to the CPG with electrical stimulation) RS Pattern generation Selection Initiation Muscles SLP Brainstem Spinal cord Forebrain Source: Grillner, Nat Rev Neurosci, 2003





#### Is It A Good Idea?

"The [spinal] cord contains a number of more or less complicated mechanisms capable of producing, as reflex results, coordinated movement altogether similar to those which are called forth by the will. Now it must be an economy to the body, that the will should make use of these mechanisms already present, by acting directly on their centres, rather than it should have recourse to a special apparatus of its own of a similar kind" - M. Foster, Textbook of Physiology (1879)

- Summary: why should the brain "reinvent the wheel" when the spinal cord already does so much?
- Relevance: our approach is to maximally utilize CPG and spinal cord functionality remaining after SCI to take advantage of existing spinal "intelligence" instead of recreating everything in an external device
  - Muscle synergies
  - Recruitment order
  - Coordinated actions

#### Components of the Proposed Locomotion Controller

Activation system

Implanted epidural (ESCS) or intraspinal (ISMS) electrodes Tonic stimulation to activate CPG "Outsourced" to other labs (i.e. already being addressed by independent researchers)

#### Components of the Proposed Locomotion Controller

Activation system

- Implanted epidural (ESCS) or intraspinal (ISMS) electrodes
- Tonic stimulation to activate CPG
- "Outsourced" to other labs (i.e.
- already being addressed by independent researchers)
- Control system
  - Specifies desired motor pattern (gait)
  - Generates efferent copy from current sensorimotor state
  - Enforces desired output:
     © Control activated CPG with precisely-timed (phasic) spinal cord stimulation (à la RS system)
     © Directly control the muscles with inactive CPG (à la FES)

Gait Controller (GC): Proof-of-concept in hardware

Phase Controller (PhC): Proof-of-concept in software

#### State of the Science

- Existing technologies for proposed neuroprosthesis
  - Epidural spinal cord stimulation (Dimitrijevic et al., 1998; Minassian et al., 2004)
  - Intraspinal microstimulation (Guevremont et al., 2006; Saigal et al., 2004)
- Alternative rehabilitation strategies
  - Spinal cord regeneration (Bradbury & McMahon, 2006)
  - Partial body-weight support training (Carhart et al., 2004; Dietz & Harkema, 2004; Reinkensmeyer et al., 2006; Abbas et al., 2006)

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#### Model Systems

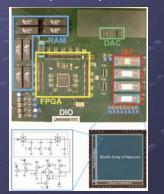
- Model system 1: Cat
  - Used to study locomotion for almost 100 years
  - Application: Gait controller
- Model system 2: Lamprey
  - Used to study CPG and spinal motor control for over 25 years
  - Application: Phase controller
- Model system 3: Legged Robots
  - Provides a reproducible platform to test out algorithms for real-time adaptation
  - Application: Gait shape, transition and controller

#### Hardware Development: Gait Controller

- Goal: develop a hardware system that can prescribe appropriate motor output based on pre-defined gait and current sensorimotor state
- Justification: need to know what the biological CPG is doing at all times and what we want it to do next in order to effectively control it
- Approach: build a silicon model of biological CPG, i.e. a neuromorphic silicon CPG chip (SiCPG)
- Why neuromorphic SiCPG?
   Biological system provides good model for functions we want to implement
  - Neuroprosthesis should be implantable
    - Alternative solution: robotics approach—compute gait by inverse dynamics (computation- and powerintensive)
    - Neuromorphic circuits can be compact and low-power
  - Compatible with both muscle (FES/ISMS) and spinal (phasic CPG) control schemes

#### Reconfigurable Integrate-and-Fire Array Transceiver (IFAT)

- Designed as a generalpurpose cortical array
  - Four custom mixed-signal VLSI chips with 2,400 neurons each
  - Up to 4,194,304 "virtual synapses" in RAM, each with programmable weight
- Microprocessor routes spikes between cells via AER
- Ideal for prototyping largescale neural networks with real-time operation
  - Combinatorial Attractor model of hippocampal place cells
  - Reisenhuber & Poggio model for object recognition network



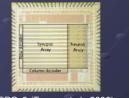
Silicon CPG Chip (SiCPG)

- Designed specifically for CPG networks
  - Intended to be standalone system after programming
  - 24 fully-interconnected (hardwired) silicon neurons
  - Continuous-time external inputs for sensory feedback
  - Early version of programmable synapses based uses an array of multiplying DACs
     New models uses programmable synapses
  - New models uses programmable synapses based on floating gate transistors (FGT)
     Based on 9-T OTA
    - Multiplies input by weight stored on FG diff pair (programmable gated conductance)
       Facilitates evaluation of different CPG network topologies
  - Programmable cell properties: refractory period, SFA, pulse-width
  - Uses direct synapses on the neurons and neurons act directly on motor system

Source: Tenore et al., Proc IEEE ISCAS, 2005; Tenore et al., Proc IEEE ISCAS, 2006



#### CPGv2 (Tenore et al., 2004)



CPGv3 (Tenore et al., 2006)

#### In Vivo Testing of SiCPG Gait Controller

Source: Vogelstein et al., IEEE TNN, 2006; Vogelstein et al., Neural Comput, 2007

- Goal: apply hardware to locomotion controller
  - Demonstrate that SiCPG can function as a Gait Controller in vivo (i.e. prescribe appropriate motor output in real-time based on pre-defined gait and current sensorimotor state: i.e. generate our "Efferent Copy")

#### Procedure:

- Design CPG network to produce forward walking; specify gait in terms of:
   Phase relationships between muscles
- Joint angles for swing, stance, etc.
- Program CPG network onto SiCPG chip
- Use external sensors on limbs to provide sensory feedback to SiCPG chip
- Use output of SiCPG chip to control locomotion
- → For testing purposes, use intramuscular (IM) electrodes to stimulate muscles directly (not phasic CPG control)
  - Causes rapid fatigue and has other problems, BUT...
  - Directly controlling all motor activity in closed-loop (by controlling the muscles) verifies that we can use the current state to prescribe appropriate motor output - Output of limbs - CPG activity (efferent copy)
  - Simplifies testing GC component (biological CPG inactive)
  - Can be extended to phasic control of activated CPG (next section)

#### In Vivo Testing of SiCPG Gait Controller

#### Animal model: cat

- Well-characterized locomotor system; studied for over 100 years
- Our collaborators have protocol to use deeply anesthetized cat as model of paralysis—convenient experimental preparation
- Details
  - Experiments were conducted at University of Alberta with Vivian Mushahwar
  - Three adult male cats were anesthetized and implanted for acute experiments
  - Hip angle and ground reaction force sensors provided sensory feedback to SiCPG chip
  - SiCPG chip's output controlled 12 IM electrodes implanted cat's hind limbs to generate locomotion

# Cat Walking 101

First task: design a CPG network to specify motor pattern for cat locomotion
 To design a CPG network, it is useful to first know the normal locomotor patterns observed during cat walking

# Cat Walking 101





First task: design a CPG network to specify motor pattern for cat locomotion
 To design a CPG network, it is useful to know the normal locomotor patterns during cat walking

#### Cat 101: Basics

- Cats are cute, furry, quadrupedal mammals
- Typically, they are found chasing mice, Tweety birds, Odies, and fish
- For reasons not entirely clear, their hair falls out after cryogenic freezing

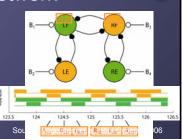






#### Designing the Gait Controller's **CPG** Network

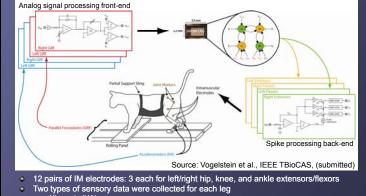
- Patterns in normal walking and IF-THEN formulation provides basis for CPG network
- Incremental design process, starting with the basics
  - Extensors and flexors are active in counterphase
  - Hindlimbs alternate between stance (extension) and swing (flexion) phases with roughly 70-30 duty cycle Transitions from stance to swing and
  - vice-versa are triggered by two main proprioceptive inputs
    - Hip angle: inputs indicate degree of left/right extension/flexion
       Ankle load: inputs indicate degree of left/right loading
- Extensible: replace flexor and extensor neurons with hip/knee/ankle subpopulations
- Structure similar to biology-based models [Pearson, personal comm.]



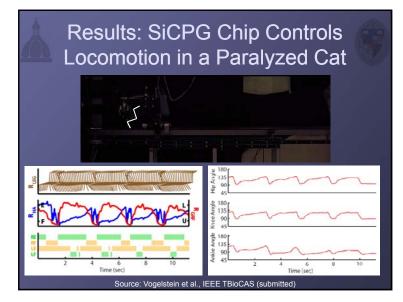
Source: Vogelstein et al., IEEE TBME (submitted)

- Synaptic weights on bias, sensory, and lateral inhibitory inputs, along with rate of SFA, determine whether swing/stance (extensor/flexor) transitions are timed or sensory-driven
  - For these experiments, cats were allowed to walk at self-driven pace





Hip angle (HA) Ground reaction force (GRF)



#### Summary of Results: In Vivo Testing of Gait Controller

- SiCPG is capable of implementing CPG networks for walking gaits and prescribing appropriate motor activity in real-time
  - First demonstration of a neuromorphic chip controlling functional behavior in an animal (i.e. it could replace its biological equivalent in a paralyzed cat)
  - Verified that SiCPG-based Gait Controller knows the current motor state (efferent copy) and what to do next; required for phasic control of an activated CPG
- Next set of experiments demonstrates how to use phasic spinal cord stimulation to control the CPG and motor output
  - Instead of having SiCPG chip control muscles directly, we want to:
     Activate the biological CPG
    - Have the SiCPG chip run in the "background" and tell us when to intervene with phasic spinal cord stimulation
      - Caveat: next experiments use a different (simpler) model system, so we used a software equivalent of the SiCPG chip to execute these functions

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3. Generate "Efferent Copy"

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+ monitor septorimotor state

ansors on limbs

afferent recordings

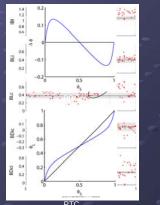
#### Nonlinear Oscillators 101 CPG can be characterized -SWAG effect of stimules ANCE as a high-dimensional nonlinear system in a limit cycle oscillation Each step represents one \_\_\_\_ - E revolution $\Phi = 0$ 0.25 0.50 0.75 1 Phase Φ in S<sup>1</sup>: [0, 1] CPG's state variables generally unknown (internal properties of neurons) We don't care about Ф=0.0, variables, just limit cycle Φ=0.75 Regardless of state space, effects of fixed perturbations to a nonlinear oscillator are likely to vary as a function of phase

#### 10

#### Nonlinear Oscillators 101

#### Standard techniques:

- Phase-response curve (PRC)
- Phase-transition curve (PTC) aka Poincaré map
- Our technique: phasedependent response (PDR) plots
  - Advantage: simultaneously illustrates effects of stimulation on any observable output of the nonlinear system (no state variables necessary)
  - Descriptive: illustrates how stimulation affects all relevant output dimensions
  - Prescriptive: specifies when to stimulate to achieve specific output



PTC Source: Vogelstein et al. (in preparation)

#### Nonlinear Oscillators 101

- CPG can be characterized as a high-dimensional nonlinear system in a limit cycle oscillation
  - Each step represents one revolution
  - Phase Φ in S<sup>1</sup>: [0, 1]
  - CPG's state variables generally unknown (internal properties of neurons)
  - We don't care about state variables, as long as there's a limit cycle in some space dless of state space
  - ikely to vary as a function of





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#### CPG as Nonlinear Oscillator

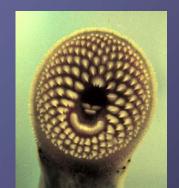
- Goal: show that phasic stimulation of the spinal cord can manipulate the output of the CPG
  - Use analytical techniques for nonlinear limit cycle oscillators and apply them to CPG
  - Standard techniques: phase-response curve (PRC) and phase-transition curve (PTC)
  - Our technique: phase-dependent response (PDR) plots
    - Advantage: simultaneously illustrates effects of stimulation on any observable output of the nonlinear system (no state variables necessary)
    - Descriptive: illustrates how stimulation affects all relevant output dimensions
    - Prescriptive: specifies when to stimulate to achieve specific output
- General experimental protocol
  - Activate CPG (i.e. initiate limit cycle oscillations)
  - Apply stimuli at all phases throughout locomotor cycle
  - Measure effects of stimulation on all parameters of locomotion as a
    - function of phase (PDR)
    - Cycle period
    - Burst length (duration of muscle activity)
    - Burst delay (duration between activity in different muscles)

#### **CPG as Nonlinear Oscillator**

#### Model system: Lamprey (primitive fish) — NOTE: Not a cat

- Why not a cat?
  - These experiments were the first attempt (ever?) to use phasic spinal stimulation to control CPG, so we wanted to start with a simple prep
  - Spinalized cats are expensive and hard to care for
- Benefits of lamprevs:
  - Cheap, plentiful, and convenient experimental preparation
  - Standard model for studying locomotion for over 30 years
  - Very well-characterized CPG and spinal cord
  - Simple motor output (good for initial testing)
- Working assumption: lamprey results can be translated to cats, humans
  - Basic elements of CPGs are conserved throughout vertebrate phylogeny
  - General principles of CPG-based control should apply to all vertebrates
  - We've selected the most convenient model system for these experiments
     Will translate species-specific details to cats and humans (electrode type, placement, gait, etc.) after proof-of-concept

# Lamprey 101





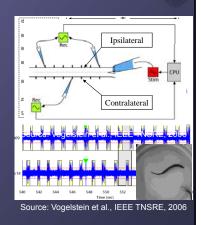
Business end of a lamprey

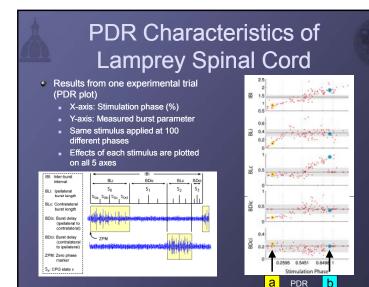
Lamprey-related casualty

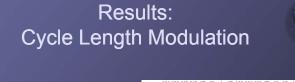
# CPG as Nonlinear Oscillator

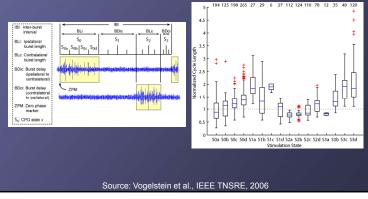
- Specific experimental protocol Excise spinal cord
  - Initiate CPG activity with bath application of D-glutamate: "fictive swimming"
  - Record motor outputs on ventral roots
  - Apply suction electrode for stimulation at rostral end
  - Stimulate at 100 phases throughout CPG cycle
- Measure effects of stimulation on all parameters of fictive locomotion as functions of phase (PDR)

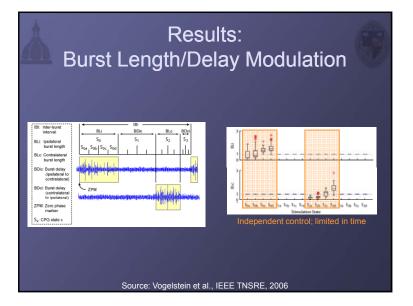
  - Cycle period (IBI)
    Burst length (BLi, BLc)
  - Burst delay (BDic, BDci)











#### Summary: Phase-Dependent Responses

- Results so far:
  - Spinal cord stimulation can alter CPG output
  - Effects of stimulation are functions of phase
  - PDR specifies when to stimulate to affect a specific parameter of locomotion

Examples:

- Increase burst length
- Decrease burst length

Short Burst

(contralateral)

#### Application: Control CPG via Phasic Spinal Stimulation

- Instead of merely observing effects of stimulation, *choose* a specific desired motor output and stimulate to achieve it
- Procedure
  - Determine desired motor pattern (e.g. BLi = 0.3 sec, BLc = 0.25 sec)
  - Measure PDR curves for specific stimulus
  - Use PDR curves to determine appropriate stimulation phase(s) to effect desired output
  - Monitor CPG activity and measure phase in real-time
  - Apply stimulation each cycle at appropriate phase(s)

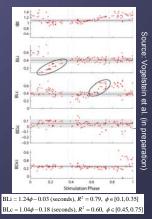
#### Experiment: Control CPG in Real-Time via Phasic Spinal Stimulation

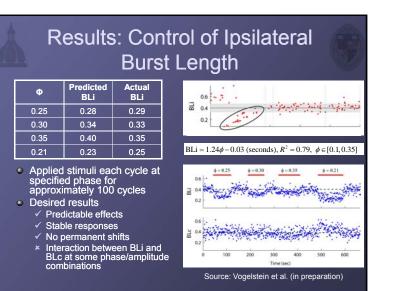
Long Burst

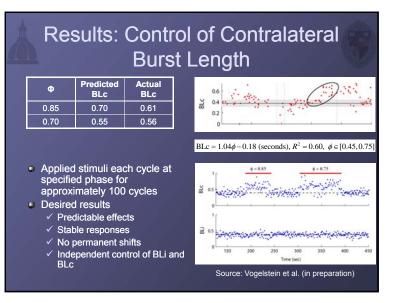
(ipsilateral)

- Goal: Control ipsilateral and contralateral burst length by phasic stimulation of lamprey spinal cord
- Observed PDR shows mostly independent control of BLi and BLc (some overlap)
- Can choose value for BLi or BLc by doing linear regression and solving for stimulation phase

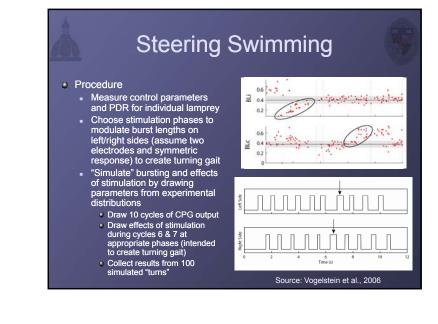
Example: For BLi = 0.3 sec,  $\Phi$  = 0.21

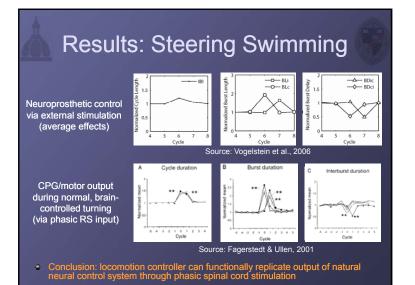






#### **Steering Swimming** Ideal: use phasic spinal stimulation to control CPG and motor output and steer lamprey swimming ("remotecontrol lamprey") Time (s) Source: Vogelstein et al., 2006 We want to show that precisely-timed external stimulation can functionally replace brain-controlled phasic RS input Cycle duration Burst duration Interburst duration CPG/motor output ..... during normal, braincontrolled turning (via phasic RS input) Ovcle Source: Fagerstedt & Ullen, 2001





#### Summary of Results: Phasic Control of Locomotion

- Spinal cord stimulation affects motor output
  - Effects of stimulation are functions of phase
  - Effects tend to be isolated in time
- CPG can be controlled by phasic stimuli
  - Independent control over individual parameters of locomotion
  - Reliable and predictable output based on PDR
  - Consistent effects over multiple cycles of stimulation (no short-term adaptation)
- Reconstructed data show that external phasic control of CPG is functionally similar to natural brain control; can effect specific motor pattern (e.g., turning gait)
   Proof-of-concept for Phase Controller
- Relevance to other experimental preparations:
  - Expect phasic spinal cord stimulation to modulate CPG output in cats, humans, etc.
  - Electrode design, placement, quantity, and stimulus will vary
  - Experimental design will be similar: apply stimuli, measure response of CPG as function of phase and use PDR curves to prescribe stimulation phase

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  - Gait controller: in vivo results
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#### **On-Going Work**

- Investigate effects of continuous control of CPG via phasic stimulation (in lamprey)
  - Cumulative effects when stimulation is applied for many consecutive cycles
  - Interaction terms when multiple stimuli applied within a cycle
- Investigate phase-dependent effects of spinal cord stimulation in cats
  - Find effective stimulation loci (same as location of ISMS synergies?)
  - Determine number of electrodes needed for independent control of motor parameters
  - Generate PDR curves to validate method
- Create convenient test platforms for technology development
  - Animal studies limit number of trials per day/week due to muscle fatigue, dosing limits, cost, etc.
  - Difficult to test real-time control loops in simulation (need a good model); don't want to waste animals perfecting technology
  - > Biomorphic robots & neuromorphic chips as test platform?

#### **Example Application for Bio/Neuromorphic Testbed**

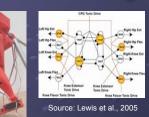
- for on-line (real-time) phase control
  - Condition signals
  - Detect bursts
  - Measure phase
  - Apply stimulation
- Motivation for using testbed: initial experiments had technical difficulties
  - Burst detection algorithm
  - Stimulation timing issues
  - Real-time operation

- Developing hardware/software Requires interactive model of CPĠ
  - Phase-dependent response to stimulation
  - Intrinsic noise sources and
  - variability Bonus features
  - Interaction between multiple
  - stimuli per cycle would allow for developing analytical tools and coping strategies Motor output would allow for
  - studying neuro-motor delays Could operate "faster than real-

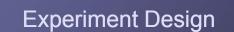
#### time"

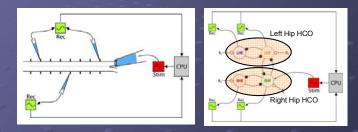
#### **Bipedal Robot + CPG Chip**

- <u>Goal</u>: Use artificial motor system to develop on-line phase control infrastructure (for future use in animal studies)
- Materials:
  - Partially-supported bipedal robot ("RedBot")
  - Servo motors actuate hips, knees, and ankles Reconfigurable silicon CPG chip
  - CPG controls hip movements, knee/ankles are passive
- Strategy: Use same experimental design as lamprey preparation to test
- Choose desired gait
- Measure PDR of CPG chip
- Apply stimuli at specific phases



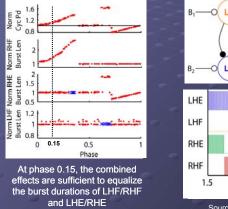


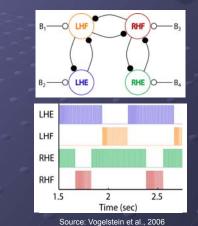




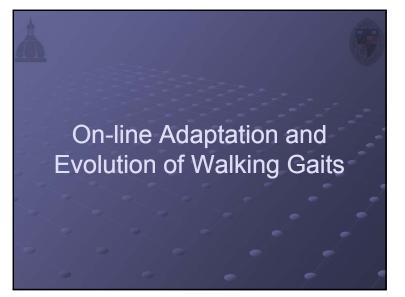
- Constraint: Use same hardware and software as used for lampreys
- purpose: Evaluate stimulation timing accuracy, check for correct tification of bursts, etc.
- Protocol:
  - Measure PDR by applying inhibitory stimulation to RHF at phases throughout CPG cycle
  - Observe effects on bursting of left/right extensor/flexor neurons
  - Apply stimulation each cycle to correct gait asymmetry (30/70)

#### **PDR Characteristics**



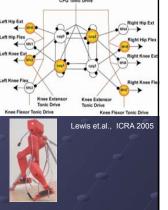


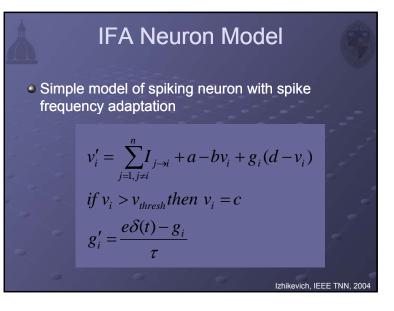
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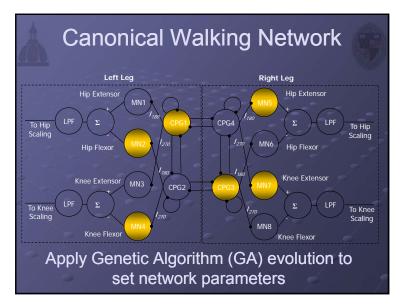


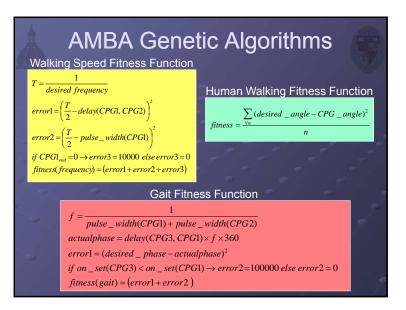
# Improvements Required to the Locomotion Controller

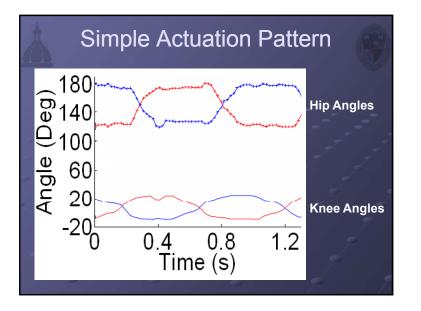
- Need for more complex waveforms that allow actuation of independent muscles
  - Produce smoother stepping
  - Implement more bio-realistic muscle actuation profiles
- Need to dynamically change gait characteristics
  - Respond to changes in the
  - environment and desire
- Automatic reconfiguration of CPG network
  - Increase in parameters with network complexity

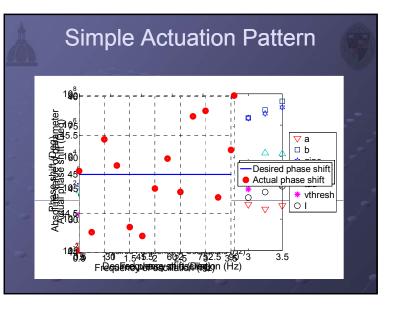




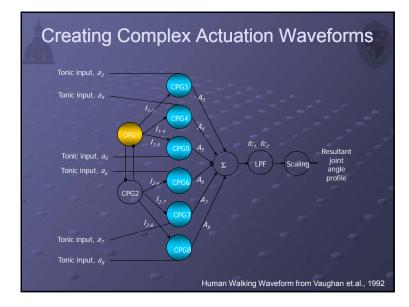


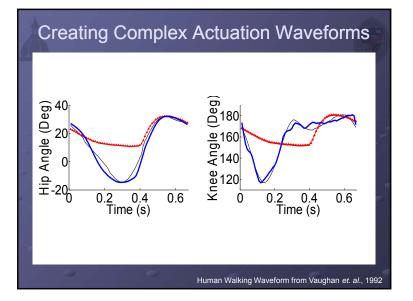


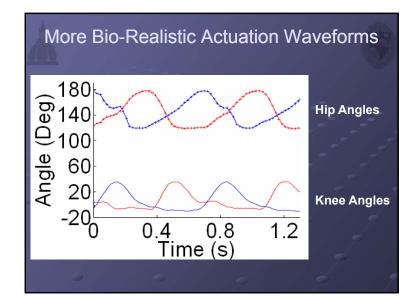


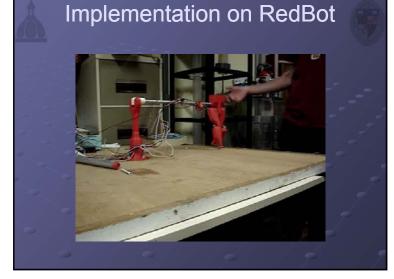












#### Summary of Results

- Implemented elaborated CPG networks for more bio-realistic locomotion control
  - Based on our canonical locomotion network
- Used Genetic Algorithms to configure the network
  - Adaptive Mutation Breeder Algorithm
- Networks converged with three generations
  - Allowed near real-time implementation of GA on a PIC
  - Execution of IFA neurons on PIC was rate limiting step

#### **Presentation Outline**

- Introduction
  - Central pattern generators
  - Spinal cord injury
  - Proposed neuroprosthetic system
- Experiments & results
  - Model systems
  - Phase controller: in vitro results
- Gait controller: in vivo results
- Ongoing and future research
  - Adaptation and Learning
- Conclusion

#### Conclusion

- We've proposed to use dynamic, cycle-by-cycle control of the CPG to restore locomotion after spinal cord injury
- Two components of a proposed locomotion controller were tested successfully
  - Neuromorphic CPG can generate desired motor output based on sensory input in real- time – The Efferent Copy
  - Stimulation of spinal locomotion circuits has repeatable phasedependent effects on CPG output – Brain Control
- We have demonstrated adaptation and learning with CPG networks to control a legged robot
- Future work focuses on testing cumulative effects of stimulation, translating lamprey results to cat preparation, and adaptive/learning hardware development

