Visualizing the Spinal Neuronal Dynamics of Locomotion

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ABSTRACT

Modern imaging and simulation techniques have enhanced system-level understanding of neural function. In this article, we present an application of interactive visualization to understanding neuronal dynamics causing locomotion of a single hip joint, based on pattern generator output of the spinal cord. Our earlier work visualized cell-level responses of multiple neuronal populations. However, the spatial relationships were abstract, making communication with colleagues difficult. We propose two approaches to overcome this: (1) building a 3D anatomical model of the spinal cord with neurons distributed inside, animated by the simulation and (2) adding limb movements predicted by neuronal activity. The new system was tested using a cat walking central pattern generator driving a pair of opposed spinal motoneuron pools. Output of opposing motoneuron pools was combined into a single metric, called *Net Neural Drive*, which generated angular limb movement in proportion to its magnitude. Net neural drive constitutes a new description of limb movement control. The combination of spatial and temporal information in the visualizations elegantly conveys the neural activity of the output elements (motoneurons), as well as the resulting movement. The new system encompasses five biological levels of organization from ion channels to observed behavior. The system is easily scalable, and provides an efficient interactive platform for rapid hypothesis testing.

INTRODUCTION

Our understanding of neural functions at the system level have been greatly advanced by modern imaging and simulation techniques.[14] An understanding of how the nervous system produces movement requires the spatial resolution of functional MR imaging and the temporal resolution of EEG. Simulation can be used to satisfy these competing demands, and when combined with interactive visualization tools, provides an efficient platform for hypotheses testing and rapid experimentation.

Our current software system, *NVIZ*[14] permits the creation of physiologically realistic and spatially organized neural models composed of multiple interacting populations. Each population is spatially organized as a 2D matrix of neurons, and dynamic height fields are used to visualize various system variables as a function of time. Simulation, visualization and statistical analysis are all integrated within *NVIZ*. We have found that visualizations in $NVIZ$ are abstract, as they lack realistic spatial information. This makes communication with colleagues difficult. In addition, we made no attempt to display the movement resulting from the neuronal activity. In this work, we focus on overcoming both of these deficiencies, by (1) constructing a realistic spinal cord model from published drawings,[15] and locating populations of neurons within the cord at their known locations, and (2) adding limb movements as part of the visualization. We illustrate the application of our system to a single joint walking application.

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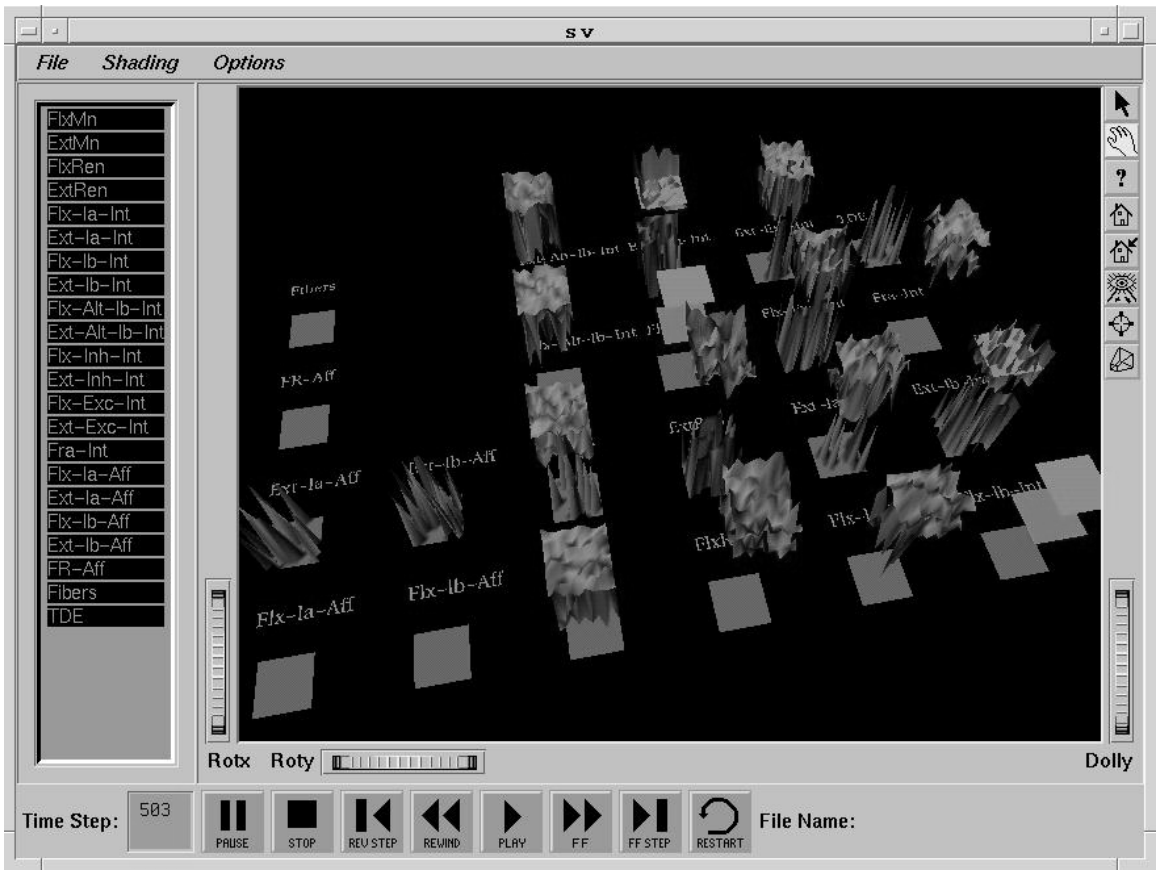

Figure 1. Neuron Activity in a 22 Population Spinal Circuit.*

BACKGROUND

The building blocks for movement are those circuits that are closest to the *motoneurons* that activate skeletal muscles. While the neural circuitry driving the motoneurons is complex, it is widely recognized that basic reflexes are reconfigured during specific behaviors, such as walking.[12]

The variety of behaviors the system may produce, coupled with the interneuronal complexity of the spinal cord makes it difficult to conceptualize the relationship between circuit and dynamics. Both theoretical and experimental studies[6,8] suggest that movement is *not* represented in a simple way in the activity of neurons. Therefore, to understand how the nervous system produces behavior, we must take a population approach. The population view leads us in the direction of seeing how individual neurons interact to form collective units of function. Simulation helps us understand how the spinal cord produces movement by bridging the gap between neurophysiological data collected one cell at a time and the population view, which shows how individual neurons interact to form collective units.

We created a general purpose neural population simulator, now integrated into *NVIZ*, an outgrowth of our earlier work.[14] Briefly, the simulation environment is optimized for creating interacting populations consisting of large numbers of neurons.[1] Cell, synapse and connection algorithms are part of this simulator. A two compartment model with a number of ionic currents forms the basis of the cell algorithm.[3,11] Details of the synaptic and connection algorithms can be found in the work of Bashor.[1] A sample visualization from our previous system is illustrated in Figure 1 *. Here we see 15 cell populations and 7 fiber (sensory, or other, input) populations. Each

*Color images can be found under http://www.cs.uncc.edu/~krs/research.html

square represents a 10×10 population matrix of neurons. Three system variables for cells are shown as height fields whose texture varies as a function of time, E (membrane potential, middle height field), TH (threshold, upper height field) and S (spike, lowest height field). When E equals or exceeds TH for any cell, the corresponding neuron fires ($S = 1$). Six of the seven fiber populations are on the left side of the visualization window; the seventh is in the upper right. Fibers are either "off" or "on" at each time step, so a single height field was used to represent them. The display is a very efficient representation of data, showing three variables for each of 1500 cells and 700 fibers at each time step. The current system permits neural circuits to be specified from a data file, and allows the simulation to be performed and recorded into a data structure over the specified interval. The visualization system provides VCR style controls to view the neuronal activity. A number of statistical operations can be performed on the simulation data.

While this environment is useful for rapid experimentation and hypotheses testing, the visualizations themselves are too abstract and are missing several important components:

1. The neurons lack spatial context with respect to the spinal cord.
2. Movement output as a result of the neuronal activity is not displayed.

In this work, we have constructed an anatomical model of a cat spinal cord based on published data, and have placed two populations of neurons within the cord at known locations, to illustrate rhythmic walking. We have used a simulation of the locomotor pattern generator (Figure 5) to animate the cells in the model, to visualize cellular activity. Furthermore, we developed a new representation of movement from this cellular activity, namely, the difference between the flexor and extensor halves of the circuit, called *Net Neural Drive* (Eq. 1-3). Net neural drive animates the hip joint, as an additional visual cue to the phase of activity being viewed.

We are aware of only one other dynamic spatio-temporal visualization of spinal motor activity, the recent elegant work of Yakovenko et al.[16] In that work, locations of 27 populations of hindlimb motoneurons were digitized from the same data set used here (36 sections of Figure 28 in[15]). Activity of cells during locomotion was animated using an extensive library of electromyographic recordings (muscle activation patterns) they generated from the literature of normal cat locomotion. Thus, cells in their visualization were animated from "output data" of cats walking on a treadmill, rather than from a model of the pattern generator, as in the present case. A single step (i.e., flexion-extension cycle) was divided into 100 piecewise-constant segments, each corresponding to about 7 ms of real time. Their visualization generated two main findings, (1) greater extensor activity than flexor, a reasonable result, given that there are a greater total number of extensor motoneurons than flexor motoneurons, and (2) the visualization of a front-to-back wave of neural activity in flexion and extension of a single step was not necessarily expected, since some motoneuron pools are distributed throughout the entire visualized region.

The visualization of a specific three-dimensional anatomy as implemented here is not a feature of either GENESIS[4] or NEURON[9] simulators, although both of those systems include two and three-dimensional representation of cells and networks.

Our implementation of the anatomical spinal cord differed from Yakovenko et al. in the following ways: (1) we used the 36 outlines with zero thickness to create a 3D structure with splines, (2) we only visualized a pair of populations acting at the hip joint, and placed cells randomly within bounding boxes in the spinal cord model, based on the reported location of the population. (3) Our animation of motoneuronal activity was based on a hypothesized central pattern generator, with a time resolution of one millisecond.

Our primary goal was to simulate dynamic interactions among spinal populations generating locomotor movement, and the present work adds the ability to display the spatial as well as temporal aspects of neural activity.

METHODS

Cat Spinal Cord Model Construction

The cat spinal cord reconstruction was derived by digitizing the drawings of spinal grey matter from Figure 28 of Vanderhorst and Holstege.[15] There are a total of 36 half-slices. Figure 2 (left frame) shows slice 16. Mirror

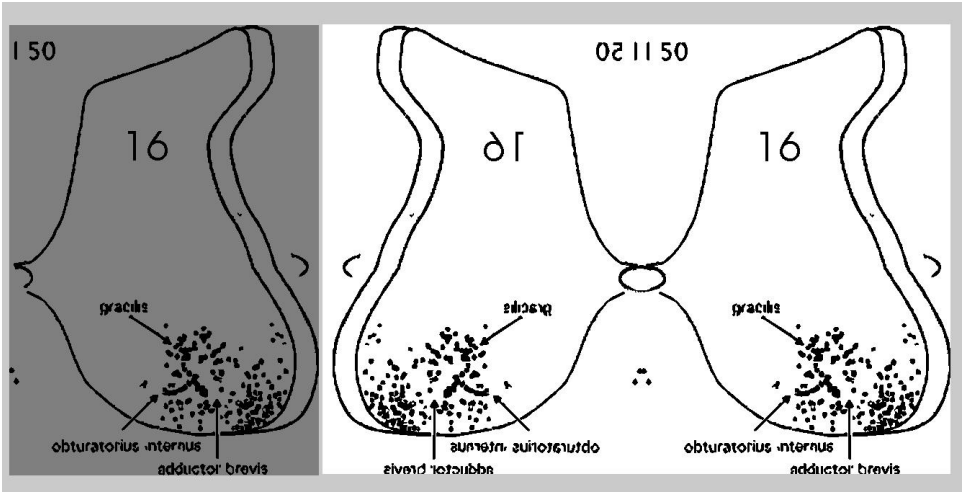

Figure 2. Cat Spinal Cord Reconstruction. (left) Original slice 16 from.[15] (right) Modeling tools used to combine a mirror reflection of original slice, to form a "complete" slice.

images of these half-slices were then appended to the original slices to form full slices, as seen in the right frame of Figure 2. Using the AC3D[5] modeling tool, these "full" image slices were imported as 2D textures and their outlines extracted. Polyline segments were used as the initial representation; each outline had 80 line segments.

In order to construct a smooth model, Kochanek-Bartels interpolating splines[10] were used to resample the polylines, as well as create additional slices between the original slices. In this manner the original model of 81×36 voxels (first dimension forms a closed loop in 2D) was resampled to a size of 243×360 voxels. The model is then scaled to the known physical dimensions, roughly 3 mm wide, 2.24 mm high and 35.1 mm deep.

Figure 3 shows several views of the constructed cat spinal cord. The top left panel is a dorsal anatomic view (from the "back" of the animal), with the front of the lumbar enlargement toward the top of the panel. The bottom panel is a view from above and to the right of the cord; front of the enlargement is to the right. It can be seen that there are bumps in the longitudinal views, which are likely registration artifacts of the acquisition process. The butterfly shaped cross-sectional view in the top right panel shows two neuron populations in the interior.

In this work, we illustrate a single hip joint walking application.[2] As an example for the anatomical visualization, we focus on two particular motoneuron populations, sartorius and semimembranosus. Sartorius neurons extend from slice 4 through 12 (in red, Figure 4), and, when active, cause flexion of the hip. Semimembranosus neurons extend from slice 17 through 22 (in green, Figure 4), and when active, cause extension of the hip. The approximate spatial extents of these two populations were estimated from the work of Vanderhorst and Holstege.[15] Two bounding boxes were created within the cord, and 100 small colored cubes, representing neurons, were placed randomly within the box. Each neuron has two states, active or inactive. In the visualizations, the neurons are either fully opaque (active) or transparent (inactive).

Spinal Cord Network Simulator

The simulation engine was developed from work described by Bashor.[1] The present system is implemented in C++, and the only other material change from the work of Bashor[1] is the addition of a more realistic neuronal algorithm containing two compartments.[11] Description of the two compartment algorithm and cell types in the model is in manuscript.[3]

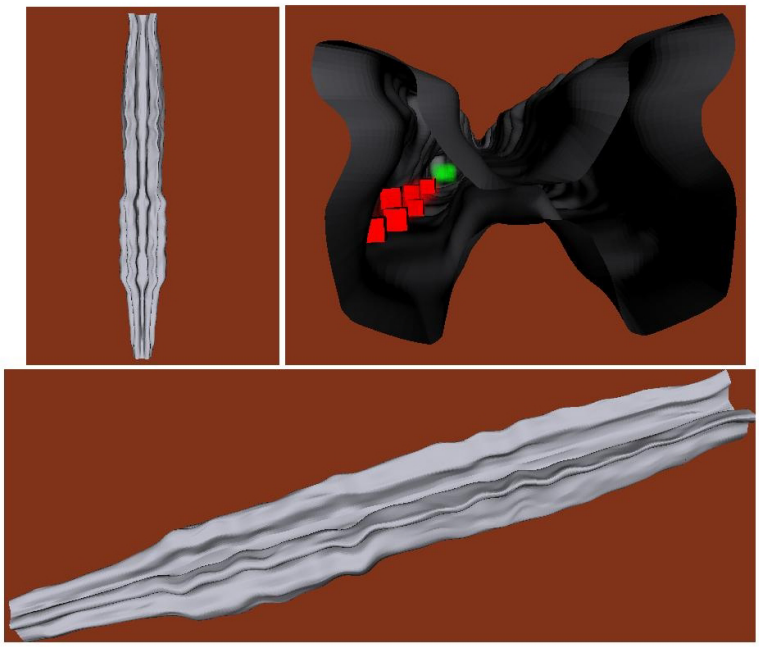

Figure 3. 3D Spinal Cord Model. Example views of reconstructed cat spinal cord model and neurons (colored cubes) located within.

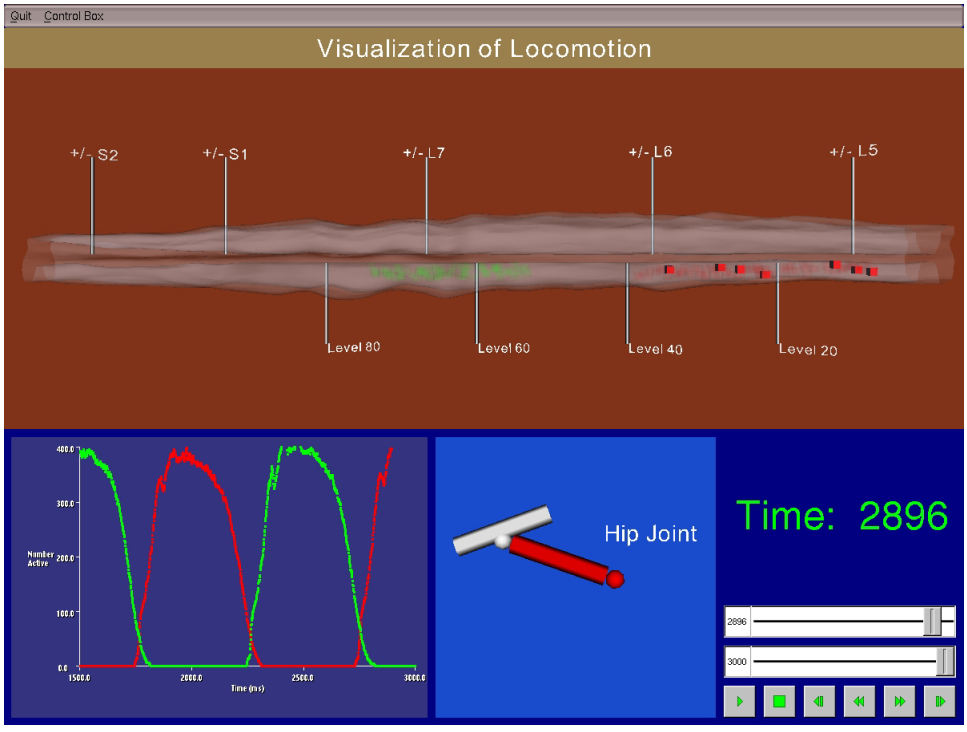

Figure 4. Locomotion Visualization Interface. (top) Anatomical model with two populations of motoneurons in place. (lower left) Smoothed curves of flexors(red) and extensors(green) active at each ms of the simulation. (lower middle) In plane limb movement. (lower right) VCR controls that permit interactive analysis of simulation sequences.

Joint Motion

The neural output from the simulator is used to illustrate the motion of a hip joint using a simple ball and stick (limb) display. To animate this, we keep track of the identity of the cells that spike at each time step (ms), for each population.

Over an interval (say 100ms) the mean frequency of the active cells, F_{af}, F_{ae}, was calculated for both flexors and extensors; similarly, the number of active cells, N_{af}, N_{ae}, for both flexors and extensors, was tabulated. From this we compute an $ActivityIndex(AI)$ for the flexor and extensor motoneuron populations, at each time interval t,

$$AI_f(t) = F_{af}(t).N_{af}(t) \tag{1}$$

$$AI_e(t) = F_{ae}(t).N_{ae}(t) \tag{2}$$

The *Net Neural Drive* NND is given by

$$NND(t) = AI_e(t) - AI_f(t) \tag{3}$$

Net Neural Drive is a new way to specify joint position from neuronal signal. In this case, the joint position depends on the difference in output between the flexor and extensor motoneuron populations.

We then linearly map NND into a limb angle, ensuring that the starting and ending angles correspond to the rhythmic cycle that is generated by the walking circuit (described below). Here again, the computed "raw" angles tend to be fairly noisy, and it is thus necessary to smooth them using a second moving window average. In a "real" musculoskeletal system, the muscle activation process and inertia of the limb act to convert the noisy neural output into a smooth motion. The smoothing we applied mimics these actions. In this work, the limb segment simply rotates in a plane between minimum and maximum chosen angles, representing the maximum flexion and extension, respectively, of the cat hip joint in normal locomotion.

IMPLEMENTATION

Our implementation is on Unix workstations (SGI/Linux). All visualizations were generated using the Visualization Toolkit[13] and embedded within the FLTK graphical interface.[7]

Figure 4 illustrates the various components of our anatomical visualization system. The top panel is the anatomical spinal cord with the two populations of motoneurons in place. Lines labeled L5, L6, L7, and L8 point to the approximate centers of the spinal roots having those names (Figure 28[15]); lines labeled Levels 20, 40, 60 and 80 are "percentage" markers of the length of the lumbar enlargement of the cat spinal cord (Figure 28[15]). Note that the anatomical visualization extends to about 120% of the lumbar enlargement length. For purposes of this paper, the labels only serve as anatomical reference points. Motoneurons active at the sampled time step are shown as bright cubes; inactive neurons are shown as muted (transparent) cubes.

The lower left panel shows smoothed curves of the number of flexors and extensors active at each millisecond in the simulation. The smoothing (a 100 ms box filter, or moving average) produces a record equivalent to the electrical activity recorded by standard methods from motor nerves near their muscle of termination in animal experiments.

The lower middle panel is a ball and stick figure of the pelvis, hip joint and femur (thigh bone) of a cat, animated by the motoneuronal activity as described above. The lower right panel contains VCR-style controls to view and analyze the neural activity. All three views are updated by the the same clock, illustrated by the time stamp of the visualized step. The integration interval used in the simulator is one ms.

By providing spatial (3D view), temporal (dynamic graph view) and a physical output (ball and stick view) of neural activity, the visualizations provide an effective means to communicate the neural output at multiple levels. The views are thus *linked*, as they are updated simultaneously, at the same time the VCR controls permit review and analysis of simulation sequences at a user-defined pace. The 3D view permits direct interaction (arbitrary pan, zoom and rotate).

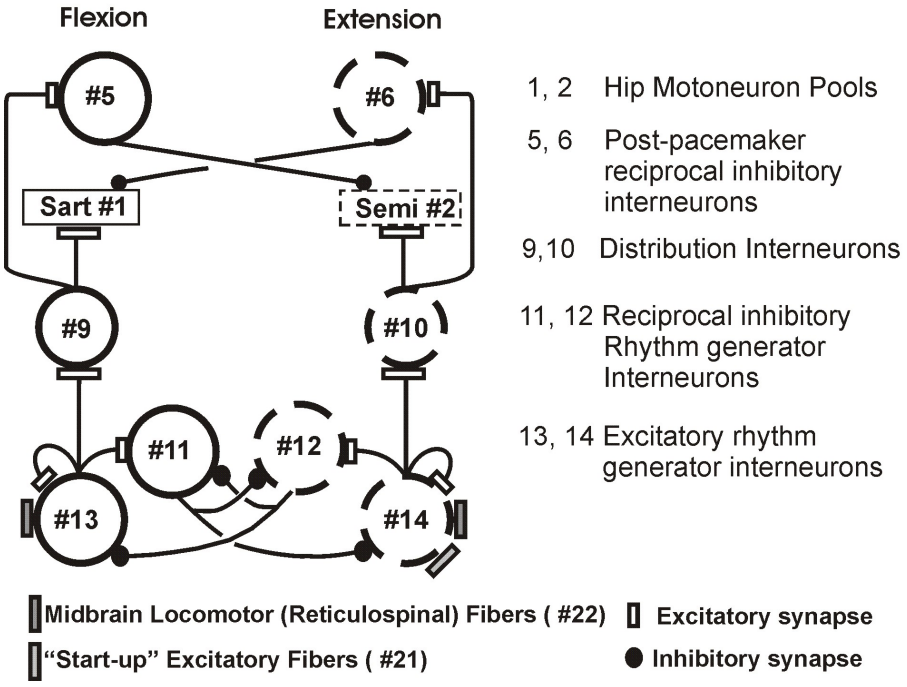

Figure 5. Walking Circuit for Hip Movement

RESULTS

Walking Circuit for Hip Movement.

The circuit diagram shown in Figure 5 is a candidate explanation for spinal control of the hip joint in walking.[2] Each circle represents a population of 100 model spinal interneurons. Circles with interrupted outlines (on the right) are responsible for generating the extension (lowering, or stance) phase, while solid circles (on the left) produce the flexion (lifting, or swing) phase. Motoneuron populations are represented by rectangles; population 1 represents the hip flexor motoneurons activating (in the "real" animal) sartorius muscle; while population 2 represents the hip extensor motoneurons activating the semimembranosus muscle, a hip extensor. Populations 13 and 14 contain excitatory pacemaker neurons which generate rhythmic bursts of activity followed by a silent period. Inhibitory neurons in populations 11 and 12 synchronize the circuit and create alternation between flexion and extension, i.e., prevent opposite phases from acting at the same time. Populations 9 and 10 distribute the output of the pacemaker populations to the motoneurons (1 and 2, respectively), and to inhibitory populations (5 and 6, respectively). Populations 5 and 6 provide direct inhibition to motoneurons during their off time, and are present to generate motoneuronal electrical responses seen in animal experiments.

Two inputs bring the circuit to "life": one is a continuous excitatory drive to cells of populations 13 and 14, shown by a black box labeled "midbrain locomotor fibers". Another input is a brief (25 ms) excitatory input to cells of population 14 at the beginning of the simulation, forcing the simulation to begin with extension, shown as a grey box labeled "start-up fibers".

Example Simulation

Motoneuronal outputs were recorded in a representative simulation on the walking circuit of Figure 5. The simulation was run for 3000 ms. Figure 6 shows motoneuronal outputs at 4 different time steps, corresponding to a cycle of extension and flexion.

At time step 1539 (panel A, Figure 6), we see the peak of the extension phase. The graph view (lower left part of the panel) shows about 6 cells active per ms, the limb visualization (lower middle part of the panel) is in an

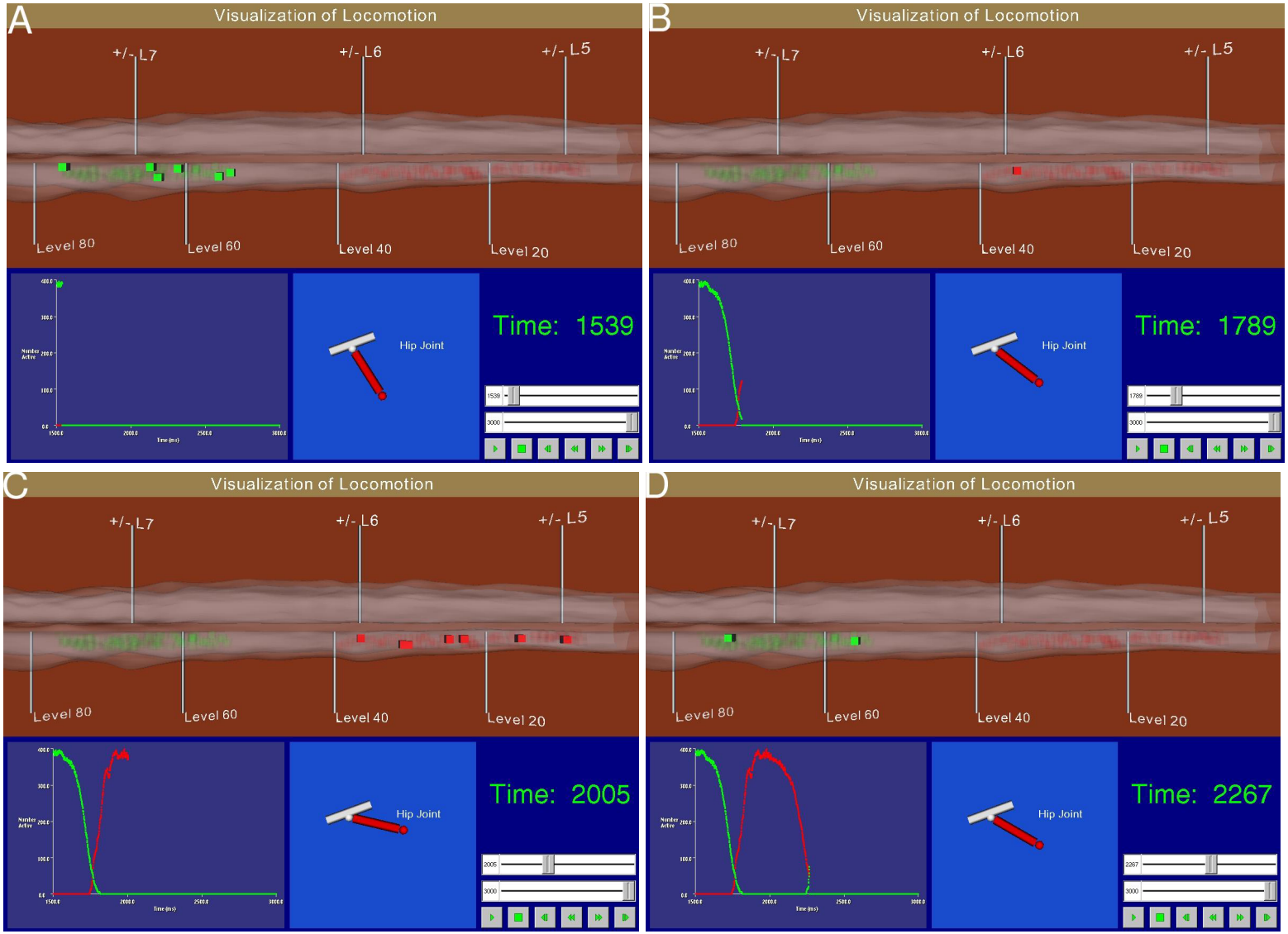

Figure 6. Hip Movement Cycle. (A) Peak of extension phase, limb is extended, about 6 cells active per ms. (B) Transition from extension to flexion, flexor output (red curve) is increasing, thigh elevated. (C) Maximum flexion achieved, thigh lifted, flexor output maximum. (D) Transition from flexion to extension, extensor motoneuron output (green curve) increasing.

extended (standing) position. The top part of the panel shows the anatomical location of active motoneurons at this time in the simulation. Six cells in the extensor population are opaque. At time step 1789 (panel B), we see the transition from extension to flexion. The graph view indicates that the output of the flexor population (red curve) is increasing; the limb visualization shows the thigh elevated. Cells active at this time step are shown in the upper part of the panel. One cell in the flexor population is opaque. At time step 2005 (panel C), maximum flexion (lifting) of the thigh has been reached. The graph view indicates the point of maximum activity of the flexor population, and the limb view indicates maximum flexion. Finally, time step 2267 (panel D) shows the transition from flexion to extension. The graph view (lower left part of panel D) shows the number of extensor motoneurons (green curve) increasing.

CONCLUSIONS

We have presented new visualization tools for our spinal cord simulator; in particular, we have added an anatomical representation to the spinal cord and a physical representation of limb movement generated by neural activity. The new system encompasses five biological levels of organization: ion channels, neurons, spinal network, musculoskeletal activation, and observed behavior.

The traditional view of movement at a joint is that there are opposing muscles crossing the joint on the front and back which cause the limb segment to flex (decrease the angle between limb segments) or extend (increase the angle between limb segments). The motoneurons are grouped into anatomical units which may be identified with the flexor and extensor movements, as illustrated in Figures 4 and 6. Thus we may think of joint movement as depending on two neural control signals, one for flexion and one for extension. Downstream from the neural control signals are the force-producing muscle cells, and biomechanical linkages providing the lever arms through which force is applied to bone. Net neural drive collapses all of these steps into a single metric, representing the force generation vector. Then we assume a linear mapping of force to deviation of the limb segment from a reference position. Here we chose to represent the neural output to the muscles as the net neural drive defined as the number of motoneurons active over a time interval (say 100 ms) multiplied by their mean frequency of firing over that interval. The net neural drive in the context of this paper is all the biomechanical steps up to the point where movement is actually generated.

The advantage of using the net neural drive algorithm to position the limb segment is that it is a computationally simple and efficient way of estimating limb position from neural output. If biomechanical activation were the main focus of our research, this method of estimating limb position would be too crude. Future work will add more biomechanical realism to the $NVIZ$ software system.

The visualization design reflects our motivation; the 3D spinal cord model and the neurons represented as colored cubes provide spatial structure and context. The time varying graph view (graph grows as the sequence is played) of the neuron activity provides more precise temporal information than was previously available online. The limb visualization gives a more physical (coarse) representation of the output of the neural circuit.

To the best of our knowledge, this interactive visualization system is the first to include anatomically realistic representation of simulated neural activity in combination with movement representation. In the future, our development path will be targeted towards adding more motoneuronal and interneuronal populations, as we study the neural basis of movement at other joints of the leg.

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