PEEK INSIDE THE FELINE SPINAL CORD WITH X-RAYS AND MACHINE LEARNING SUPERPOWERS

MARTA GARCIA MARTINEZ
Principal Project Specialist – Computational Science
Computational Science Division
Electrical stimulation of the spinal cord has become an accepted therapeutic tool. Its most successful approach is in pain management, where 30,000 patients per year have electrodes implanted epidurally. With respect to spinal cord injury, the approach has been much less successful and has remained at a research state. We believe that this is due to a lack of a detailed stimulation map able to predict the effect of spinal cord electrical stimulation on the underlying motor circuits. In order to construct this stimulation map, a model based on the 3D structure of the spinal cord internal network needs to be built.

In this talk I will present how we are using high powered X-Ray tomography at the Advanced Photon Source (APS) to image, at 1 µm resolution, sections of feline spinal cord and how we used deep learning techniques to train a convolutional neural network with the images obtained at the APS to detect somas (neural cell bodies) that will help us build this model.
“INGREDIENTS”

Hardware (HW)

- APS for imaging
- Supercomputers
  - Bebop (LCRC)
  - Cooley (ALCF)

Software (SW)

- Python
- Petrel
- Pytorch
- MATLAB
- tomopy
- Globus
- custom scripts

Funding

($ / node-hours / beamtime)

- NAISE
- NIH
- DOE
- APS beamtime
- LCRC allocations
- ALCF DD

People

- Matthieu
- Marta
- Nicole
- Tiberiu
- Rafael
- Josh
- Vincent
- Mike
- Jeff
- CJ
- Vandana
- Randy
- Bobby
- …
In this talk you will hear these words:

- imaging
- stimulation map
- experiments
- imaging
- Advanced Photon Source (APS)
- lumbar region L4-5-6
- spinal cord
- simulations
- feline
- X-ray
- microCT
- tomography
- Renshaw cells (RC)
- Ia
- motoneuron (MN)
- Canonical Motor Microcircuit (CMM)
THE ONE WITH THE INSTITUTIONS
COLLABORATIVE EFFORT – INSTITUTIONS
The Spinal Cord Song

“You can’t connect the dots looking forward; you can only connect them looking backwards. So you have to trust that the dots will somehow connect in your future.”

Steve Jobs
1955-2011

NAISE seed
Experiments
Staining
Imaging
Simulations
THE ONE WITH THE SPINAL CORD
THE SPINAL CORD

- The spinal cord is a cylindrical shaped bundle of nerve fibers that is connected to the **brain** at the **brain stem**.

- The spinal cord runs down the center of the protective spinal column extending from the neck to the lower back.

- The brain and spinal cord are the major components of the **central nervous system** (CNS).

- The CNS is the processing center for the nervous system, receiving information from and sending information to the **peripheral nervous system**.

Web: ThoughtCo.  
https://www.thoughtco.com/the-spinal-cord-373189


Types of Cells

There are **two types of cells** in the peripheral nervous system. These cells carry information to (**sensory nervous cells**) and from (**motor nervous cells**) the CNS.

- Cells of the **sensory nervous system** send information to the CNS from internal organs or from external stimuli.
- **Motor nervous system** cells carry information from the CNS to organs, muscles, and glands.
The basic element for motor control is the **motor unit**. A motor unit consists of a **motoneuron** in the ventral portion of the spinal cord, its **axon** that travels in the appropriate nerves, and the set of **muscle fibers** the axon innervates in its target muscle. The Heckman lab studies the motor unit and the spinal circuits that help generate motor unit firing patterns in both normal and pathological states. We are particularly interested in amplification of synaptic input by voltage-sensitive conductances in dendrites of spinal motoneurons and interneurons.

**THE HECKMAN LABORATORY & SPINAL CORD RESEARCH**

Motoneuron

Motor Control

Spinal Circuits


https://cnx.org/contents/cs_Pb-GW@5/How-Neurons-Communicate
WHAT EXPERIMENTAL PROTOCOL?

Map of the spinal cord motorpools

The idea
If you stimulate the spinal cord at a certain location you should be able to see that muscle turn on.

Objective
Build a map of how to stimulate the spinal cord to create functional motion.
Left image shows a typical spinal cord stimulator. These stimulators are therapeutically used to provide analgesic relief to patients.

Central image shows a finite element electromagnetic model of a feline spinal cord surrounded by a cerebral spinal fluid layer. A bipolar electrode is shown on top and the electric field they generated are shown in color. The ultimate goal of this proposal is to predict the neural activity of the spinal circuits within the spinal cord given the stimulation provided by the bipolar electrode.

Right image Human Spine Blueprint. This is a detailed blueprint of a human spine showing the side view with different regions and vertebrae labeled. (wetcake/Getty Image)
WOULD IT BE USEFUL?

- Well established market for pain
  - 30,000 implants/year
  - 1.8 Billion USD
  - 50% do not work
  - No placebo studies
  - Hard to measure

- SCI Autonomic system: bladder control, blood pressure, etc.

- SCI Motor system: believe to be best model as it is can be measured in animal models easily.

**SCI** = Spinal Cord Injury
THE ONE WITH THE NEURONS
1. Neural Encoding I: Firing Rates and Spike Statistics

1.1 Introduction

Neurons are remarkable among the cells of the body in their ability to propagate signals rapidly over large distances. They do this by generating characteristic electrical pulses called action potentials or, more simply, spikes that can travel down nerve fibers.

Neurons represent and transmit information by firing sequences of spikes in various temporal patterns.

The study of neural coding involves measuring and characterizing how stimulus attributes, such as light or sound intensity, or motor actions, such as the direction of an arm movement, are represented by action potentials.
Neuroscientists are interested in knowing what neurons are doing. More specifically, researchers want to understand how neurons represent stimuli from the outside world with changes in their firing properties.
Differentially synchronized spiking enables multiplexed neural coding
Milad Lankarany, Dhekra Al-Basha, Stéphanie Ratté, and Steven A. Prescott
PNAS May 14, 2019 116 (20) 10097-10102

Fig 1
Neurons in primary somatosensory (S1) cortex use spike timing and rate to encode different tactile stimulus features.

(A) Rasters from 17 neurons, four trials each, during tactile simulation (Top). FRH was calculated using a narrow ($\sigma = 5$ ms; black) or broad ($\sigma = 100$ ms; green) Gaussian kernel. Black FRH was thresholded to distinguish synchronous (red) from asynchronous (blue) spikes. Arrow highlights 10 g stimulus.
HOW MANY NEURONS ARE IN THE SPINAL CORD?

ABSTRACT: In the cynomolgus monkey spinal cord, the isotropic fractionator and stereology yielded 206–275 million cells, of which 13.3–25.1% were neurons (28–69 million). Stereological estimates yielded 21.1% endothelial cells and 65.5% glial cells (glia-neuron ratio of 4.9–5.6).

In human spinal cords, the isotropic fractionator and stereology generated estimates of 1.5–1.7 billion cells and 197–222 million neurons (13.4% neurons, 12.2% endothelial cells, 74.8% glial cells), and a glia-neuron ratio of 5.6–7.1, with estimates of neuron numbers in the human spinal cord based on morphological criteria.

Fig. 5.
Cellular composition of the spinal cord in cynomolgus monkey and human compared with the composition in an entire human brain, showing the relative percentage of neurons (blue), glial cells (red) and endothelial cells (green), based on the data obtained in the current study.

Approximate percentages are indicated on the columns. The bar for the entire human brain adds to 99%, not 100%, due to rounding.

The cellular composition in the spinal cord differed considerably from that in the entire brain, and was most similar to the composition found in the brainstem (“rest of brain”).

The Cellular Composition and Glia-Neuron Ratio in the Spinal Cord of a Human and a Nonhuman Primate: Comparison With Other Species and Brain Regions.
Jami Bahney & Christopher von Bartheld. November 2017 The Anatomical Record Advances in Integrative Anatomy and Evolutionary Biology 301(4) DOI: 10.1002/ar.23728
CANONICAL MOTOR MICROCIRCUIT (CMM)

Model choice

- **Fundamental**: Basis for locomotion (reciprocal inhibition),
- **Understandable**: Large background of its structure (motorpools location),
- **Accessible**: Highest sensitivity to activation by DES are almost certainly the Ia axons arising in muscle spindles (large diam fiber).
- **Generalizable**: Circuit is repeated throughout the spinal cord.
THE ONE WITH THE EXPERIMENTS
GENERAL MOTORPOOL MAP OF THE LUMBAR REGION
All post-mortem feline spinal cord tissues were collected at the Feinberg School of Medicine (NU) by collaborator Matthieu K. Chardon.

This study was conducted following NU protocols for experiments and tissue sample extraction.

COVID-19 → Labs closed
To use imaging and computational neuroscience to predict where we should stimulate and come up with paradigms to control the muscles in an effective way.
THE ONE WITH THE STAINING
SPINAL CORD TISSUE SAMPLES STAINED

The tissue samples are stained with heavy metals including multiple rounds of osmium tetroxide followed by uranyl acetate and lead.

OsO₄
UA
Pb

highly poisonous!

\{[\text{UO}_2(\text{CH}_3\text{CO}_2)_2\text{H}_2\text{O})\text{H}_2\text{O}]_n\}
SAMPLE CHANGES

Cut the sample to get a “carrot” or cylindrical shape
X-ray microtomography (µCT)

Technique provides mesoscale anatomy, of neurons, glial cells and vasculature, at an isometric resolution of \(\sim 1\mu m^3\) using large tissue samples (1-2 mm thickness)
APS-U in the news!!

Advanced Photon Source Upgrade

In the almost **25 years** since the Advanced Photon Source (APS), a U.S. Department of Energy (DOE) Office of Science User Facility

As the APS readies to undergo an **$815 million** upgrade that will, as early as late-2023, enable science at a completely new and unprecedented scale,

More than **5,000 researchers** from around the world conduct experiments at the APS **every year**

“The APS Upgrade will allow us to conduct new experiments that we can barely even imagine right now. It will be transformational.” — Jonathan Lang, the APS X-ray Science Division (XSD) director

“We want to ensure the APS is relevant **for another 25 years**,” Lang said.

https://www.aps.anl.gov/APS-Upgrade

APS/CELS Town Halls

The upgraded APS will be able to generate X-rays **up to 500 times brighter** than those created by the current APS.
## IMAGING “TOOLS”
### High Energy Synchrotrons

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<th>Name</th>
<th>Location</th>
<th>City / Country</th>
<th>Generation</th>
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<tr>
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<td>ANL</td>
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<tr>
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<td>ANL</td>
<td>Lemont (USA)</td>
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<td>BNL</td>
<td>Sayo (JAPAN)</td>
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<td>Diamond II</td>
<td>DLS</td>
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<td>SSRF</td>
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</table>

https://www.esrf.fr/home/UsersAndScience/Accelerators.html
ADVANCED PHOTON SOURCE (APS)

The APS is one of the most technologically complex machines in the world.

This premier national research facility provides ultra-bright, high-energy X-ray beams that enable the collection of data in unprecedented detail and in amazingly short time frames.

Electrons are accelerated to over 99 percent of the speed of light around its ring, which is the size of a baseball stadium.

More than 5,700 scientists come to the APS each year from academia, industry, medical schools, and other research institutions to conduct experiments that promise new discoveries in nearly every scientific discipline.
ADVANCED PHOTON SOURCE (APS)

Spectroscopy
Spectroscopy is used to study the energies of particles that are emitted or absorbed by samples that are exposed to the light-source beam and is commonly used to determine the characteristics of chemical bonding and electron motion.

Scattering
Scattering makes use of the patterns of light produced when x-rays are deflected by the closely spaced lattice of atoms in solids and is commonly used to determine the structures of crystals and large molecules such as proteins.

Imaging
Imaging techniques use the light-source beam to obtain pictures with fine spatial resolution of the samples under study and are used in diverse research areas such as cell biology, lithography, infrared microscopy, radiology, and x-ray tomography.

https://www.aps.anl.gov/Beamlines/Research-Techniques
## APS BEAMLINES

[https://www.aps.anl.gov/Beamlines](https://www.aps.anl.gov/Beamlines)

<table>
<thead>
<tr>
<th>Beamline</th>
<th>Disciplines</th>
<th>Techniques</th>
<th>Energy Range</th>
<th>Access</th>
<th>Operator</th>
<th>Status</th>
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<td>32-ID-B,C</td>
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<td>Tomography</td>
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</table>

2-BM-A,B • 2-ID-D • 2-ID-E (XSD) 32-ID-B,C (XSD)
TOMOGRAPHY

XSD-IMG: 2-BM-A,B

Welcome to 2-BM-A,B

The sector 2 bending magnet beamline is fully dedicated to microtomography with capability to perform large field of view (20x2 mm²) fast 2D phase contrast imaging for slow dynamic phenomena studies (0.1 m/s). The applications of this beamline range from life science [1], geoscience [2, 3], physics [4], material science and engineering [5, 6], and paleontology [7]. The flexibility of switching setups and capabilities of developing on-demand accessory experimental techniques make this beamline versatile in tomography applications.

Beaml ine Specs

<table>
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<tr>
<th>Source</th>
<th>Bending Magnet</th>
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<td>Energy Range</td>
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<td>Beam Size</td>
<td>25mm x 4mm</td>
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<td>Energy Resolution (ΔE/E)</td>
<td>1 x 1012 @17 keV</td>
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https://en.wikipedia.org/wiki/Tomography
32-ID-C SETUP
APS BEAMLINES
https://www.aps.anl.gov/Beamlines

Inside Argonne | TMS - Training Profile

<table>
<thead>
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<th>Course</th>
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<tr>
<td>APS232</td>
<td>Sector 32 Orientation</td>
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A PEEK INSIDE APS

Beamline station
APS BEAMLINES
https://www.aps.anl.gov/Beamlines
THE ONE WITH THE RECONSTRUCTION
Thanks to the collaboration with B. Kasthuri group at UChicago: Rafael Vescovi and Vandana Sampathkumar
THE ONE WITH THE DEEP LEARNING
Feline Spinal Cord

The Dataset
- Images of feline spinal cord obtained via X-ray microtomography
- Image corresponds to horizontal cross-section of spinal cord

Project Goals
- Aid in the 3D mapping of the feline spinal cord’s relevant structures via image segmentation
- Develop Neural Network based segmentation approach to avoid time-consuming manual alternative
- Move machine learning program from MATLAB to Python
- Optimize resulting network with respect to segmentation metrics as well as computational resources
We employ the SegNet NN architecture to perform image segmentation.

Semantic segmentation is the process of assigning a class label to each pixel of an image.

Given an input image, a trained NN will return a predicted segmentation whose pixels can be classified as true positive, true negative, false positive, or false negative.

Illustration of SegNet Architecture
IMAGE SEGMENTATION

Goals and Related Metrics

- **Step 1**: Train the network, manual annotation of somas.
- **Step 2**: Find metrics to track accuracy/correctness

Segmentation Metrics

\[
\text{Accuracy} = \frac{\text{Correctly Segmented Pixels}}{\text{Total Pixels}} = \frac{TP + TN}{TP + TN + FP + FN}
\]

\[
\text{IoU} = \frac{\text{Target } \cap \text{ Prediction}}{\text{Target } \cup \text{ Prediction}} = \frac{TP}{TP + FP + FN}
\]

\[
BF1 \sim \frac{1}{|B_{ps}|} \sum_{z \in B_{ps}} \left[ d(z, B_{gt}^z) < \theta \right]
\]
COMPUTATIONAL RESOURCES @ ANL

<table>
<thead>
<tr>
<th><strong>Bebop (LCRC)</strong></th>
<th><a href="http://www.lcrc.anl.gov/systems/resources/bebop/">www.lcrc.anl.gov/systems/resources/bebop/</a></th>
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<td><strong>Partition</strong></td>
<td>BDWALL (Intel Broadwell)</td>
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<td><strong>CPU Type</strong></td>
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<table>
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<td><strong>GPUs per Node</strong></td>
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<tr>
<td><strong>Memory per GPU</strong></td>
<td>12GB RAM</td>
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</table>

- Initial training runs focused on reducing computational time and tuning hyperparameters
- Despite CPU based architecture, Bebop offers an approximate two-fold decrease in training time per epoch
- Also used initial training to determine upper bound on epochs needed for convergence
### IMAGE SEGMENTATION CASES AND RESULTS

#### Training Hyperparameters and Image Datasets

**Number of images**

In choosing a number of images for our training set, we need balance whether or not enough data is present to affect meaningful training with oversampling of training data.

**Image size:** Smaller images, which are randomly cropped from our full-sized dataset, require a fewer number of trainable weights and biases, thus exhibiting quicker convergence. Yet, such images can neglect the global characteristics of certain classes, resulting in poorer performance on full-sized images.

- Initial training images: 2300 x 1920 pixels

<table>
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<tr>
<th>Images</th>
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<th>224 pixels</th>
<th>400 pixels</th>
<th>800 pixels</th>
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<table>
<thead>
<tr>
<th>Hyperparameter</th>
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<td>Platform</td>
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<td>Learning Rate</td>
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<td>Training Batch Size</td>
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<tr>
<td>Validation Batch Size</td>
<td>1</td>
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</table>
RANDOM IMAGE CROPS

Smaller training images are created by sampling

- NN assigns a node to each pixel of an incoming image
- Number of training weights and biases directly related to the size of training images
- Smaller images leads to faster training convergence and allows more data to be obtained from full-sized images
- May result in poorer performance on full-sized test images
IMAGE SEGMENTATION RESULTS

Global and Soma Accuracy
IMAGE SEGMENTATION RESULTS
BF1 Scores and Soma IoU

Oversampling occurs when network becomes over-adjusted to segment the training data and loses its transferability in the process (i.e. metrics go down with more images)
OUTPUT AND OVERLAYS
NN Trained Using Full-Sized Images

Test Metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<tbody>
<tr>
<td>Soma IoU</td>
<td>35.79 %</td>
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<tr>
<td>BF1 Score</td>
<td>13.51 %</td>
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</tbody>
</table>

Image (F0010)

Ground Truth

NN Prediction

Overlay

- True Positive (Soma)
- True Negative (Background)
- False Positive
- False Negative
OUTPUT AND OVERLAYS
Best NN Trained Using 1000 Images, Size 224 pixels

Test Metrics
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Soma IoU</td>
<td>58.12 %</td>
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<tr>
<td>BF1 Score</td>
<td>30.99 %</td>
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Image (F0010)  
Ground Truth  
NN Prediction  
Overlay

- True Positive (Soma)
- True Negative (Background)
- False Positive
- False Negative
3D RECONSTRUCTION

3D reconstruction from best NN results (T. Stan, NU)
ACKNOWLEDGEMENTS

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This research used resources of the Argonne Leadership Computing Facility, which is a DOE Office of Science User Facility supported under Contract DE-AC02-06CH11357.

We gratefully acknowledge the computing resources provided on Bebop (and/or Blues), a high-performance computing cluster operated by the Laboratory Computing Resource Center at Argonne National Laboratory.”

This research used resources of the Advanced Photon Source, a U.S. Department of Energy (DOE) Office of Science User Facility operated for the DOE Office of Science by Argonne National Laboratory under Contract No. DE-AC02-06CH11357.