Computational modeling of the neural circuit of rodent lower urinary tract

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Introduction

- The lower urinary tract (LUT) is involved in the involuntary storage of urine and voluntary expulsion of urine at a determined time and place (micturition)
- Spinal cord injury (SCI) causes dysfunction in the lower urinary tract (i.e. detrusor sphincter dyssynergia (DSD), urinary incontinence, etc.)
- Existing models of the LUT tend to focus on the mechanical properties of the LUT [1][2]
  - Current neuron models are based on integrate and fire neurons, which are not biophysically accurate
- There are physiological differences between human and animal models [3]
  - Directly measuring neural responses in human systems is difficult
  - Bladder pressure and filling characteristics have been well reproduced with appropriate, although reduced, neural infrastructure [2]
  - Computational modeling is a powerful tool that can complement experimental investigations in such cases
- We have developed a computational model of the rodent LUT using the Brain Modeling Tool Kit (BMTK) Python library

LUT Biology

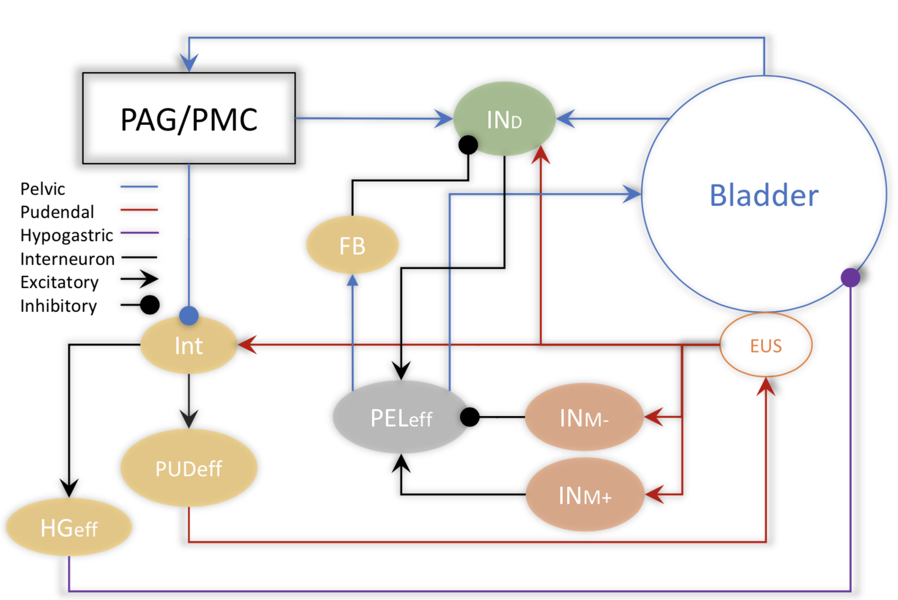

Figure 1: The neural circuit of the rodent lower urinary tract

<u>Circuit Logic - Filling</u>:
- **Parasympathetic: Pelvic/bladder afferent -> MPG pathway**: OFF – bladder muscles are relaxed so there is no excitation from this pathway to the bladder motor neurons
- **Sympathetic: Pelvic/bladder afferent -> IMG pathway**: ON – bladder muscles are relaxed by IMG -> bladder motor neuron inhibiting synapses
- **Somatic: Pudendal/EUS pathway**: ON – EUS muscles are contracted by excitation from this pathway to the EUS motor neurons
- **PAG/PMC pathway**: OFF – higher-level control has not turned on to begin the voiding process so the EUS motor neurons are not inhibited
- **Assumptions**: synaptic connection between PAG afferent and IN_{M+}

<u>Circuit Logic - Voiding</u>:
- **Parasympathetic: Pelvic/bladder afferent -> MPG pathway**: ON – bladder muscles are contracted by excitation from this pathway to the bladder motor neurons
- **Sympathetic: Pelvic/bladder afferent -> IMG pathway**: OFF – bladder muscles are contracted so there is no inhibition from this pathway to the bladder motor neurons
- **Somatic: Pudendal/EUS pathway**: OFF – EUS muscles are relaxed so there is no excitation from this pathway to the EUS motor neurons
- **PAG/PMC pathway**: ON – higher-level control has turned on to begin the voiding process and the EUS motor neurons are inhibited

Methods

<u>Biophysical Single Cell Models and Network</u>
- Gaussian connectivity (with an adjustable percentage) for all neurons
- Firing rates (<u>all in Hz</u>) from biological data; interpolating for IN_{M+} and IN_{M-}

Bladder-A: low = 4 ± 1, high = 21 ± 2   **IN_D**: low = 4 ± 1, high = 14 ± 2   **PAG-A** : low = 4 ± 1, high = 15 – 21
FB: low = 4 ± 1 Hz, high = 14 ± 2 Hz   **Bladder motor neurons**: low = 2.5 ± 2, high = 14 ± 2

<u>Spinal Interneuron Model</u>
- Idea: Model EUS afferent -> IN_{M+} synapse **[4]** using a depressing synapse. Assumed an excitatory connection from PAG afferent to IN_{M+}. This implements a **low-pass filter** for the EUS afferent
- IN_{M-} is modeled as a **high-pass filter** for the EUS afferent, so we implemented it using an excitatory synapse with the EUS afferent

<u>Bladder Volume</u> **<u>v_t</u>**
- Fill: **v_t = v_0 + fill_rate*t** ; fill rate = 0.05 ml/min **[5]** ,v_max = 0.76 **[6]**
- Void: **v_t = v_t[t – 1] – void_rate*t**; void rate = 4.6 ml/min **[7]**

<u>Bladder Pressure</u> $\mathbf{P_B(t)}$
- Bladder pressure: $\mathbf{P_B(t) = f(FR_{SPN}) + f(Vol_B(t-1))}$ where
  - $f(FR_{SPN}) = 2 * 10^{-3} FR_{SPN}^3 - 3.3 * 10^{-2} FR_{SPN}^2 + 1.8 FR_{SPN} - 0.5$; **and** $f(Vol_B) = 1.5 Vol_B - 10$
- Pelvic (bladder) afferent firing rate equation: $\mathbf{FR_{blad\_aff}(t) = -3 * 10^{-8} P_B^5 + 1 * 10^{-5} P_B^4 - 1.5 * 10^{-3} P_B^3 + 7.9 * 10^{-2} P_B^2 - 0.6 P_B}$

Results & Discussion

<u>Overview</u>:
- We have reproduced the Grill, et al. model **[4]** using biophysical models

<u>Spinal Interneuron Model:</u>
- Our spinal interneuron network uses a depressing synapse with the EUS afferent and an assumed excitatory synapse with the PAG afferent to model IN_{M+} as a low-pass filter for the EUS afferent
- An excitatory synapse with the EUS afferent was used to model IN_{M-} as a high-pass filter for the EUS afferent
- Resulting firing rate trends match those achieved in previous models **[4]**

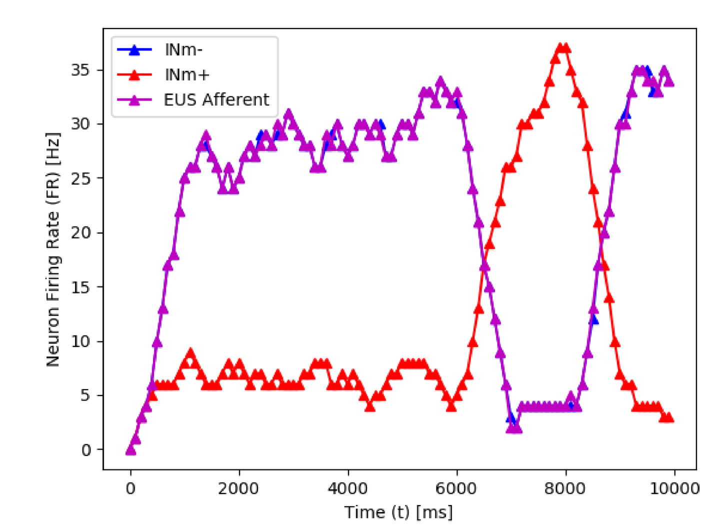

Figure 2: Firing rates of the spinal interneuron model

<u>Bladder Feedback</u>:
- Our feedback network uses BMTK's simulation modification capabilities to collect the PGN firing rate, use it to calculate bladder pressure, and use bladder pressure and bladder volume to calculate bladder afferent firing rate at user-specified intervals during the simulation
- This implementation allows for a closed-loop feedback given initial trends of bladder afferent firing rate
- Resulting firing rate trends match those achieved in previous models **[4]**

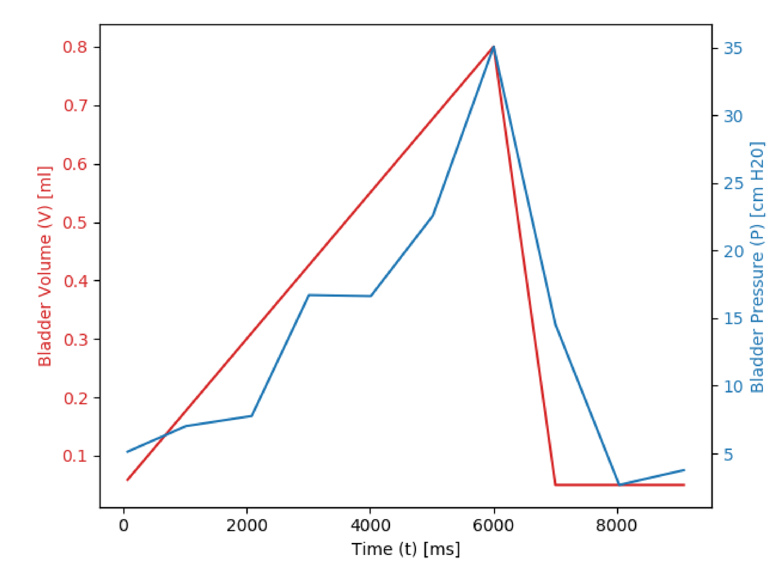

Figure 3: Bladder volume and pressure

<u>Guarding Reflex</u>:
- Within the existing bladder feedback loop, we have added a connection between the EUS afferent firing rate and bladder pressure assumed to exist based on literature **[8]**
- Currently using **Δpressure = pressure(t) – pressure(t-1) > 10 cm $\mathbf{H_20}$** to determine if a spike is occurring
- At each detected spike, the code sets the EUS afferent neurons to fire at a rate given by the following equation: **eus_fr = constant1*pressure(t) + constant2*Δpressure**
- Small peaks in EUS motor neuron firing rate that result from our code represent "guarding" contractions of the EUS in response to sudden increases in bladder pressure

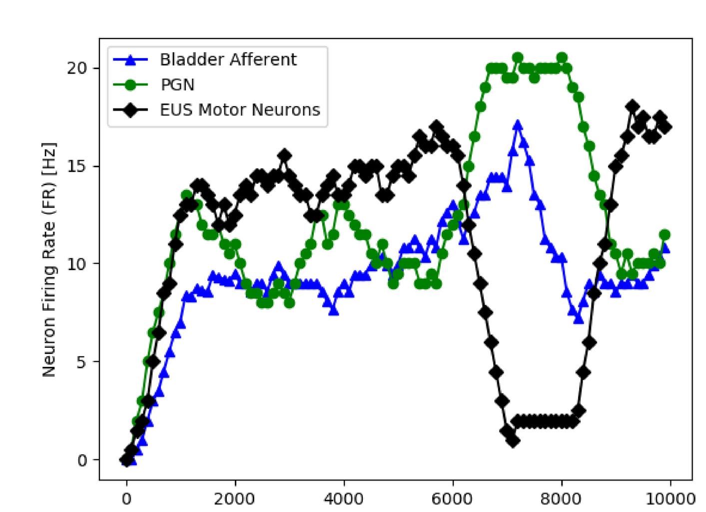

Figure 4: Firing rates of bladder feedback loop

Limitations + Future Work

- Model needs to be scaled up to include more cells in each region
- More biophysical values and firing rates need to be added to other neurons in model as they are published
- MPG has both phasic and tonic types of cells
  - Current model includes only tonic cells with phasic cells being planned to be incorporated in next iteration of the model
- PAG afferent may be expanded into its own model
  - There exists a circuit that more accurately models the higher-level control of micturition in the PAG and PMC **[9]**
- Need to incorporate a log-normal distribution for synaptic weights
- After adding further realism, a goal is to use the model for reverse engineer functioning in normal and spinal cord injury cases

Conclusions

- A biophysically realistic LUT model framework that reproduces fill/void cycle has been created using the BMTK library in Python
- Improved spinal interneuron model including the idea of low-pass filter using depressing synapses
- Incorporated the closed feedback loop from PGN firing rate to bladder pressure using experimental curve fits in Grill et al. studies **[4]**
- Reproduced the guarding reflex that matches experimental data using assumed connection between bladder pressure and EUS motor neuron spiking
- We would like to move to the extended model to study various other reported reflexes
- This model will permit study of normal and abnormal physiology of LUT networks, improving our understanding of such networks in both cases
  - The model will then provide better hypotheses for animal and potentially human studies

References + Acknowledgements

1. Bastiaanssen, E. H., van Leeuwen, J. L., Vanderschoot, J. & Redert, P. A. A myocybernetic model of the lower urinary tract. *Journal of theoretical biology* 178, 113–33 (1996).
2. Van Duin, F. *et al.* A Computer model of the neural control of the lower urinary tract. *Neurourol. Urodyn.* 17, 175–196 (1998).
3. Birder, de Groat, *et al.* Neural Control of the Lower Urinary Tract: Peripheral and Spinal Mechanisms. *Neurourol Urodyn* 29, 128–139 (2010).
4. McGee, M. J. and W. M. Grill (2016). "Modeling the spinal pudendo-vesical reflex for bladder control by pudendal afferent stimulation." *J Comput Neurosci* 40(3): 283-296.
5. van Asselt E, le Feber J, van Mastrigt R. Threshold for efferent bladder nerve firing in the rat. *Am J Physiol Integr Comp Physiol*. 2017;276(6):R1819-R1824. doi:10.1152/ajpregu.1999.276.6.r1819
6. Gonzalez EJ, Grill WM. Sensory pudendal nerve stimulation increases bladder capacity through sympathetic mechanisms in cyclophosphamide-induced cystitis rats. *Neurourol Urodyn*. 2019;38(1):135-143. doi:10.1002/nau.23860
7. Streng T, Santti R, Talo A. Similarities and differences in female and male rat voiding. *Neurourol Urodyn*. 2002;21(2):136-141. doi:10.1002/nau.10004
8. Livingston BP. Anatomy and neural control of the lower urinary tract and pelvic floor. *Top Geriatr Rehabil*. 2016;32(4):280-294. doi:10.1097/TGR.0000000000000123
9. Zare A, Jahanshahi A, Rahnama'i MS, Schipper S, van Koeveringe GA. The Role of the Periaqueductal Gray Matter in Lower Urinary Tract Function. *Mol Neurobiol*. 2019;56(2):920-934. doi:10.1007/s12035-018-1131-8

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