Computational modeling of the neural circuit of rodent lower urinary tract

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071.09 / R19

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, a reduced order version of biophysically accurate model
- 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 biophysical computational model of the rodent LUT using the Brain Modeling Tool Kit (BMTK) Python library

LUT Biology

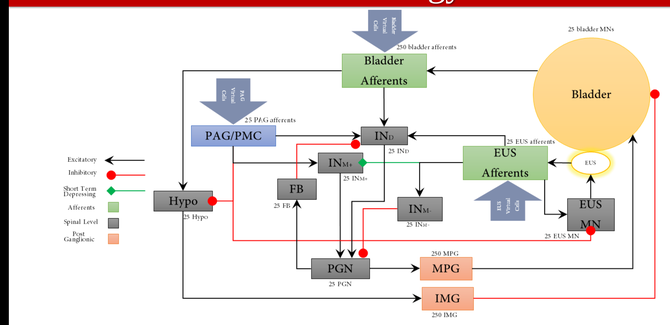

Figure 1: The neural circuit of the rodent lower urinary tract

Circuit Logic - Filling:

- **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+}

Circuit Logic - Voiding:

- **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

Biophysical Single Cell Models and Network

- Gaussian connectivity (with an adjustable percentage) for all neurons
- Firing rates (all in Hz) 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

Spinal Interneuron Model

- 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

Bladder Volume **v_t**

- 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]**

Bladder Pressure $\mathbf{P_B(t)}$

- 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

Spinal Interneuron Model:

- 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]**

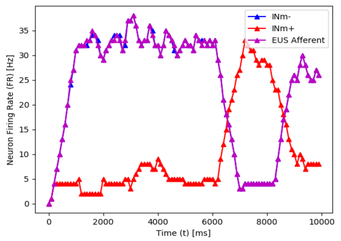

Figure 2: Firing rates of the spinal interneuron model

Bladder Feedback:

- 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]**

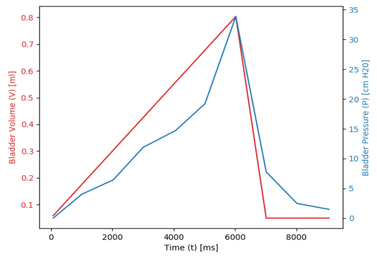

Figure 3: Bladder volume and pressure

Guarding Reflex:

- Within the existing bladder feedback loop, we have added a connection between the EUS afferent firing rate and bladder pressure based on reports in the literature **[8]**
- Currently using **Δpressure = pressure(t) – pressure(t-1) > 10 cm H_20** as the trigger that results in enhanced EUS afferent firing
- 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

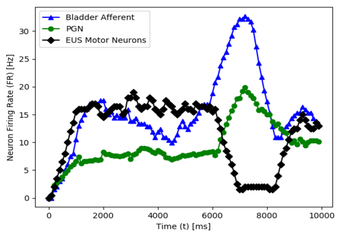

Figure 4: Firing rates of bladder feedback loop

Limitations & Future Work

- Model is continuing to be developed. Biological data related to single cell characteristics need to be tuned further, although such data are scare and from different species. Also, all firing rates need to be within the biological ranges, for all regions, including bladder efferents.
- MPG has cells that exhibit phasic and tonic characteristics
  - Present 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 a separate model of its own
  - A circuit has been reported 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 to reverse engineer LUT functioning in both normal and spinal cord injury cases

Conclusions

- A biophysically realistic LUT model framework has been developed that reproduces the fill/void cycle. For this, we used the BMTK library in Python
- We propose an improved spinal interneuron model that implements a low-pass filter using depressing synapses
- Incorporated closed feedback loop from PGN firing rate to bladder pressure using experimental curve fits in Grill et al. **[4]**
- Reproduced the guarding reflex that matches experimental data using proposed connection between bladder pressure and EUS motor neuron spiking
- On-going studies explore other reported reflexes
- By permitting study of normal and abnormal physiology of LUT networks, the model will provide hypotheses for both understanding as well as interventions such as electrical stimulation.
- Some of the hypotheses will be tested in rodents, and stimulation techniques will be designed to alleviate conditions resulted from SCIs. Insights from the model and planned experiments have potential application to humans.

References & Acknowledgements

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This project was supported in part is supported by grants NSF DBI-1659831 and NIH MH122023.