Simulating the Pupillary Light Reflex with Alcohol Intoxication

BME 355
Professor Richard Nuckols
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Victor Crisan
Michael Frew
Jaeyoung Kang
Joey Mitchell
Sean Rose
Kyle Scenna

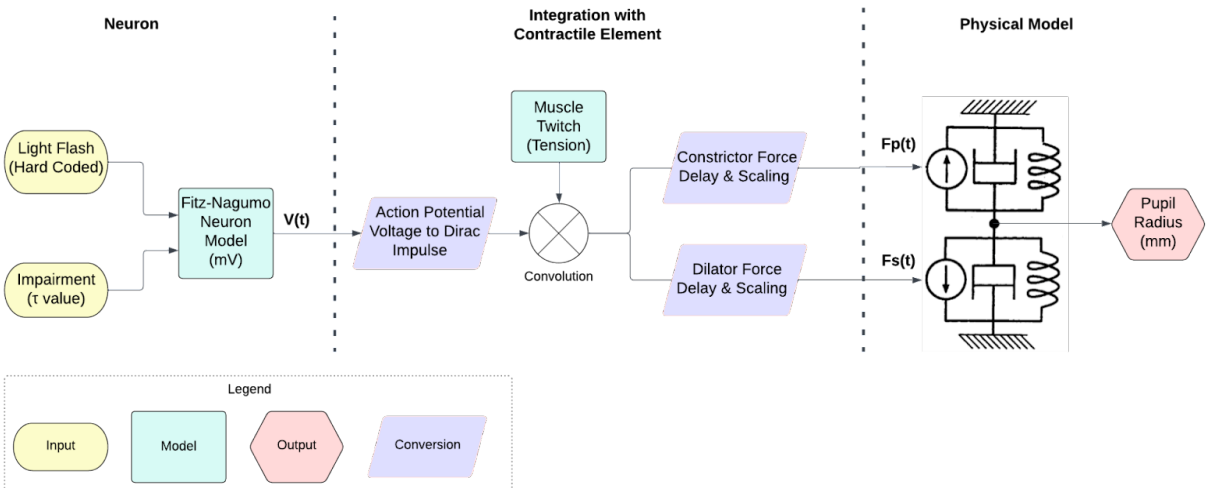

Figure 1. Overview of modelling approach

Our approach consists of integrating multiple models. A light stimulus is fed into the FN model along with impairment (τ). This outputs neuron action potentials over time (V(t)) which are subsequently converted to unit impulses. These Dirac delta functions are convolved with a muscle twitch to produce the profile of normalised muscle force. This profile is then delayed and scaled appropriately and used as the tension developed by the constrictor and dilator muscles in the pupil model ($F_p(t)$ and $F_s(t)$, respectively). The final output of the system is pupil radius over time.

Neuron

Simulating the effects of impairment on the human PLR required a mathematical model of neural activity. The literature review concluded that the optimal model for this task is the FN model due to its relative simplicity and use in previous literature surrounding the effects of alcohol on neuron dynamics [3]. The FN model is a simplification of the Hodgkin-Huxley (HH) model which is a system of four state-space equations, three that represent the sodium activation, potassium, and sodium inactivation gates open at a given time, and a fourth that represents the rate of change of a neuron's voltage during an action potential [8]. The FN model simplifies the HH model by combining the 3 equations related to ion gate activity into a single equation representing a neuron's ability to regain its resting potential [3, 8]. This reduces the number of equations and variables, while maintaining the essential features of neuronal dynamics related to the generation of action potentials and the refractory period. The two coupled differential equations of the FN model are seen below:

$$\frac{dv}{dt} = v - \frac{v^3}{3} - \omega + I \qquad (1)$$

$$\frac{d\omega}{dt} = \varepsilon(v + a - \Upsilon\omega) \qquad (2)$$

Where v is the membrane potential, ω is the recovery variable, I is the initial stimulus, and *a,* ϒ, ε are parameters whose values are determined from literature [3]. Franca et al. altered these equations to incorporate the effects of alcohol by adding a time delay to ω in the x_1 state space equation [3]. This alteration results in a longer repolarization, extending the absolute refractory period, and effectively stopping the neuron from firing in fast succession. Following these simplifications, the FN model equations can be transformed into the following form:

$$\frac{dv}{dt} = v(t)(a - v(t))(v(t) - 1) - \omega(t - \tau) + I \quad (3)$$

$$\frac{d\omega}{dt} = \varepsilon(v(t) - \Upsilon\omega(t)) \quad (4)$$

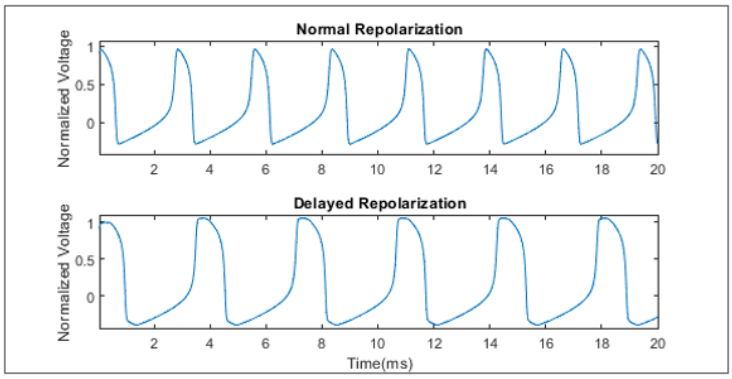

Figure 2. Comparison of neural activity with and without the addition of a time delay

There are 21 topologically unique regions in the FN model, however, only three are relevant due to the presence of a limit cycle, a necessary feature for generating action potentials [3]. Parameters *a,* ϒ, and ε determine which region the model is in and were obtained from Franca et al. [3]. The phase portraits for these regions were simulated as further validation which can be seen in appendix 12, and upon further work, region two was selected as the optimal limit cycle for this implementation.

The work of Franca et al. was an important resource for validation since their work focuses directly on modelling the impacts of alcohol with the FN model [3]. Values for parameters were obtained directly from this paper with the exception of τ, as the given value for τ was not reasonable. Appropriately time delaying the state variable was determined through a sweep of τ values in the results section, however, this is not optimal and should be explored in future work.

Integration

When a neuronal action potential reaches a motor unit a muscle twitch occurs [9]. This muscle twitch must be modelled in order to convolve it with the action potential and determine the overall amount of force generated within the muscle when it contracts. Initially, a simplified

triangular muscle twitch was developed as a proof of concept since it enabled quick testing of the feasibility of deriving muscle force by convolving the action potentials generated from the FN neuron model with the muscle twitch. The simplified muscle twitch was created by developing linear equations that approximated the latent, contraction and relaxation periods of a muscle twitch and graphing this data for a time span of 0 to 100 milliseconds as suggested by literature [9]. The convolution with the simplified muscle twitches produced a muscle force graph that was similar to literature (yet slightly more jagged) and hence validated the approach [10]. After this, a new iteration of the muscle twitch function was developed based on the Fuglevand et al. model [11]. It is important to note that a limitation of basing the muscle twitch off of the Fuglevand paper is the fact that the Fuglevand model assumes a skeletal muscle contraction whereas the pupillary muscles are smooth muscle. This simplification had to be made since a specific model of pupillary smooth muscle could not be found in literature. Smooth muscle twitches differ from skeletal muscle twitches and are highly variable [12]. The Fuglevand model uses an exponential function and contraction period in order to generate the muscle twitch graph resulting in the equation $\frac{Pt}{T} \cdot e^{1-(\frac{t}{T})}$ where P is the peak twitch force. T represents the contraction period and t is the corresponding time point in milliseconds. The function was normalized in order to allow for easy convolution with the action potentials and timeshifting was used in order to represent the latent period. This implementation was also validated against literature [11].

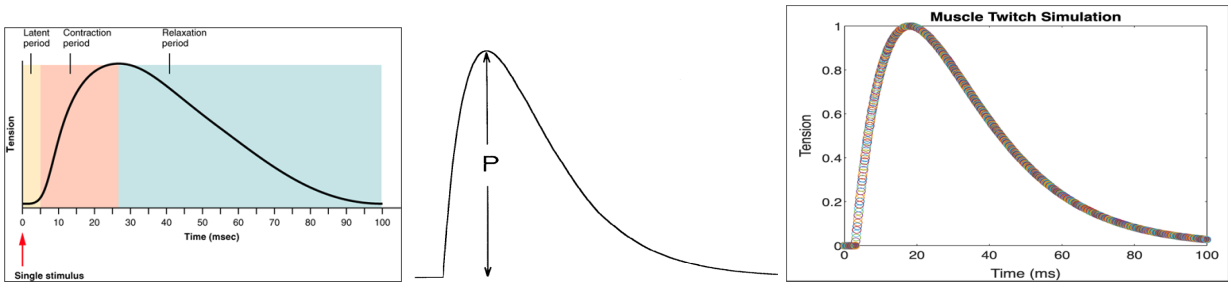

Figure 3. Example of muscle twitch tension output (left) and comparison of Fuglevand muscle twitch (middle) with our implementation where P [Peak Force] = 1 (right) [13, 11].

The action potentials generated by the FN model are simplified by the conversion to Dirac delta impulses for easier convolution with the muscle twitch. This was accomplished by placing an impulse at the rising edge of every action potential. This simplification is appropriate since the action potential is an all-or-nothing response. Consultation with literature indicates this is an acceptable technique for modelling action potentials providing further validation [14]. Since action potential duration is short, ~1ms, the area underneath the graph is quite small and as such it is relatively negligible when considering its impact on the convolution [15]. Using the Dirac delta functions impulses instead of action potentials still elucidates the impacts of alcohol intoxication since the location of the Dirac delta impulse will still be delayed relative to a non-intoxicated individual which means the effect of alcohol on muscle force is still captured in the convolution.

To achieve an overall muscle response of the pupillary muscles that can be inputted into the physical model of the PLR, convolution of the neuronal action potentials with the aforementioned muscle twitch function was performed. This method has been validated in literature which used convolution to model isometric contractions based on motor unit activation [14]. A simplification was made by time scaling the FN model to achieve a realistic physiological time span for the neuron action potentials. The implementation of the model from Franca et al. is unitless, requiring a conversion factor of 50000 units to achieve a period of about 1 ms per action potential in an undelayed state, which aligns with literature [16]. Convolving the time-scaled neuron function with the muscle twitch function was performed using MATLAB's *conv* function at each action potential spike. This yielded the overall muscle response through the temporal summation of the muscle response at each action potential. The resulting graph of muscle activation can be supported by literature in which muscle activation was simulated using the same muscle twitch function [10].

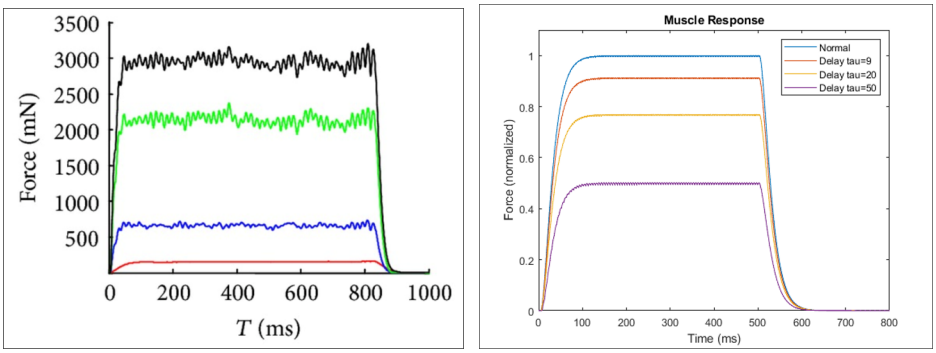

Figure 4. Comparison of muscle activation from literature (L, Raikova et al.) with delayed and non-delayed muscle response achieved through convolution (R) [10].

As can be seen in Figure 4, the simulated muscle response was comparable to muscle responses from literature in overall shape. Additionally, it can be seen that increasing the alcohol factor, τ, results in lower muscle force as well as a slight delay in activation, which aligns with the assumptions made in the implemented FN model. The resulting response was used in the physical model in $F_p(t)$ and $F_s(t)$. This is done by multiplying the normalised muscle force from the convolution with the implemented step functions in the implementation of the physical model.

Physical Model

In this work the modelling approach taken for the PLR was based on the model used by Fan & Yao [7]. This involved representing the pupil dilator and constrictor muscles both as a combination of a spring, damper, and contractile element (force-generating component).

The sphincter contractile element force is denoted by $F_p(t)$ because it is stimulated by the parasympathetic nervous system and the dilator $F_s(t)$ because it is controlled by the sympathetic

system. Simplified versions of the equations for the state-space model taken from Fan & Yao's work are shown:

$$x_1 = r \quad (5) \qquad x_2 = \frac{dr}{dt} \quad (6)$$

$$\frac{dx_1}{dt} = x_2 \quad (7) \qquad \frac{dx_2}{dt} = \frac{d^2r}{dt^2} = F_{elastic} - F_{damping} + F_p(t) + F_s(t) \quad (8)$$

Where 'r' represents pupil radius, $F_{elastic}$ is the force attributed to the elastic components, $F_{damping}$ is the force attributed to the dampers. The geometry and mass of the pupil is also taken into account in the calculations of these force values. Full equations with all parameters can be seen in the appendix.

The input to the model is a 100ms light flash at time 1 second. For this reason, it is not passed to the function but hard-coded into the simulation code that model muscle response. $F_p(t)$ and $F_s(t)$ are the force functions as a result from a 100ms light flash occurring at time = 1 second. Fan & Yao represent this as step functions with fitted amplitude and delays.

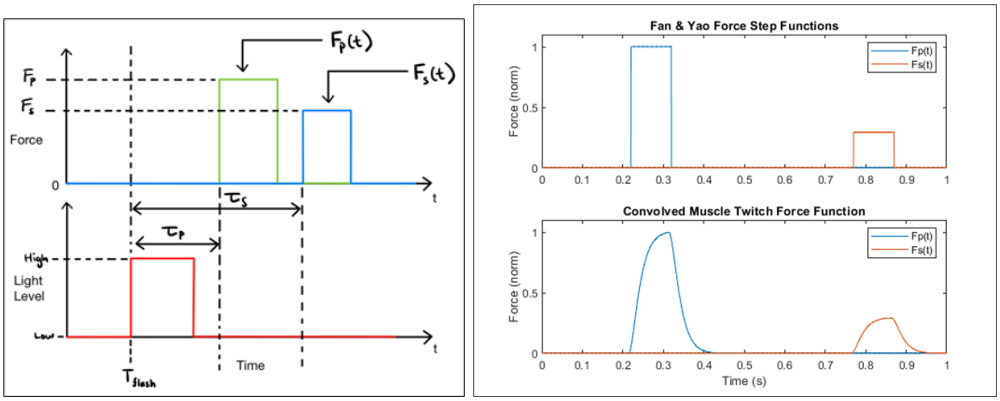

Figure 5. $F_p(t)$ and $F_s(t)$ as step functions with fitted delays (τ_p, τ_s) and amplitudes (F_p, F_s) as in Fan & Yao's work (Left, top right) and convolved muscle twitch force profile (bottom right).

The MATLAB implementation of the physical model uses ODE45 to solve the linear system. This was validated by comparing the output with the results from Fan & Yao at three different light intensities.

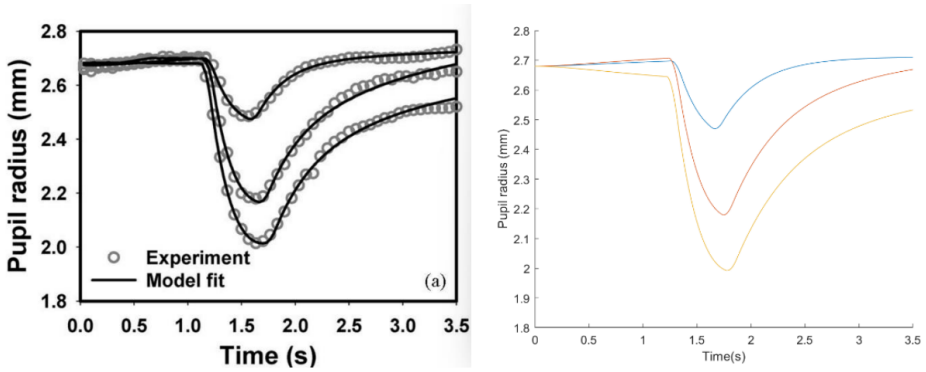

Figure 6. Literature model results (L) and our MATLAB implementation results (R).

Parameter Sweep

To determine the value of τ to best represent intoxication, a range of values were used to simulate the PLR. The output could then be compared with experimental PLR data. Ideally, raw PLR data would be compared to the output of our model. However, this data was not available so other derived statistics needed to be used. Typical statistics calculated include latency, acceleration, contraction velocity, quarter-dilation velocity, and half-dilation time of the pupil radius [17]. Refer to appendix Table 1 for further elaboration of the different variables. Code was written to effectively calculate these values from the raw pupil radius data. Latency was calculated by the time difference (in seconds) between the light stimulus and the onset of contraction (initial inflection point). The initial inflection point was identified as the first drastic drop of the radius. Appendix Figure 13 shows the pupil radius profile over time, and the acceleration of change of pupil radius over time. The radius graph shows that before the first inflection point, there is a steady drop. This is verified in the acceleration graph as acceleration is close to zero, until it hits the specific time value where the first drop occurs. With this knowledge, signal processing was conducted, and the inflection point was calculated. With the calculated points, the latency value was found.

Acceleration was calculated as the time to reach max acceleration during contraction; the units are therefore seconds rather than mm/s^2. Contraction velocity describes the mean velocity (mm/s) during contraction. This was calculated by the rate of change from the minimum radius point, and the initial inflection point with its respective time values. Quarter dilation velocity is the velocity of the pupil dilation reaching its quarter dilation point from the minimum radius. Lastly, the half-dilation time was calculated as the time it took to reach its half-dilation point. The visual aid of each variable can be shown in Figure 7.

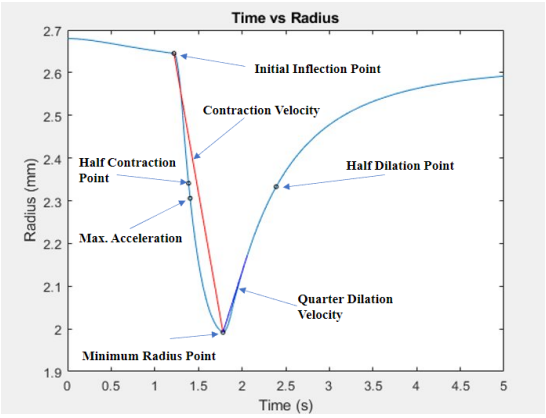

Figure 7. Radius profile with its respective variables calculated and plotted

Appendix Figure 14 shows the radius profile with its calculated variables from literature [17]. When comparing Figure 7 to Appendix Figure 14, in most situations, the calculated points show similarity. After validating that the steps taken led to similar results, the simulation was run for τ ranging from 0-50. The τ value of 0.001 was the 'baseline' to represent zero intoxication because the DDE23 requires a non-zero delay. Statistical analysis was then conducted with the calculated metrics for each respective τ value.

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