

Towards Model-Based Control of Parkinson's Disease: A Perspective

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Abstract—Since the 1950s, we have developed mature theories of modern control theory and computational neuroscience with almost no interaction between these disciplines. With the advent of computationally efficient nonlinear Kalman filtering techniques, along with improved neuroscience models that provide increasingly accurate reconstruction of dynamics in a variety of important normal and disease states in the brain, the prospects for a synergistic interaction between these fields are now strong. I show recent examples of the use of nonlinear control theory for the assimilation and control of single neuron and network dynamics, as well as the modulation of oscillatory waves in the cortex, and the assimilation of epileptic seizures. A control framework for modulating Parkinsonian dynamics is presented, and a perspective offered. As the computational models of dynamical diseases such as Parkinson's disease improve, embedding those models within rigorous model-based control frameworks is now feasible.

I. INTRODUCTION

MODEL based predictor-controller systems employ a computational model to observe a dynamical system, assimilate data through sensors, reconstruct and estimate the remainder of the unmeasured variables and parameters using the model, and then calculate a control vector to generate a desired manipulation of the system. The result of the actual system dynamics is then compared with the predicted outcome, the expected errors within the model are updated and corrected, and the process repeats iteratively. This extremely powerful recursive control engineering framework has never been applied to the range of significant applications to bio-

medical applications that it warrants.

Model based predictor-controller algorithms were developed in parallel with the US space program in the 1960s. The most prominent of such strategies was the Kalman filter [1], which for linear systems is a maximum likelihood estimator that gives the optimal tracking of system state and calculation of control vectors to modulate such states. The dual theorems of observability and reachability for such systems have been considered one of the most important developments in mathematics of the 20th century [2]. Observability and reachability theorems essentially state that if you can observe a system's state variables, you can optimally control it (reach a given state). Incredibly, these theoretical concepts have been largely absent in the observation and control of complex biological systems.

Of course the linearized equations of motion of missile guidance are a far cry from more complex biological system applications. In the decades since Kalman's seminal work in the 1960s, the extended (linearized) Kalman filter approaches for nonlinear systems have met with mixed success. Even the simplest of nonlinear system dynamics, such as sine and cosine functions to convert bearings to common coordinates, are notorious for being terrible candidates for linearized Kalman approaches [3].

It was the advent of true nonlinear predictor-controller algorithms that has opened for us an entirely new set of possibilities for biological systems. These methods have been in large part driven by the meteorological use of nonlinear convection models of the

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atmosphere in data assimilation and weather prediction, termed ensemble Kalman filtering [4-5]. In parallel with this meteorological work, Julier and Uhlmann [3,6] published a nonlinear Kalman strategy termed the unscented Kalman filter (UKF). These strategies were based on using fundamental nonlinear models directly, while iterating the noise and error expectations through these nonlinear equations. The Bayesian framework for updating predictions with measurements remains the same as linear Kalman filtering. By employing an optimized sparse sampling of the possible dynamics, the UKF can be computationally efficient.

The UKF can be viewed as a very efficient and selective ‘particle filter’. Particle filtering creates a large number of initial conditions based upon the probability distribution function of the errors in a system, and iterates all of the ‘particles’ through the linear or nonlinear equations of the system. This brute force Monte Carlo scheme can be extremely powerful, but is computationally very inefficient. There have been a wide variety of schemes for selecting subsets of initial conditions (reviewed nicely in [7]). There are several computational neuroscience applications of particle filtering in recent years including [8] and [9], each nicely outlining the natural links with Bayesian state estimation. But as [7] exhaustively demonstrates, UKF is not only more efficient, but often more accurate, than particle approaches.

It is truly remarkable how well UKF methods can estimate state in highly nonlinear, even nondifferentiable systems. Although heavily used now in robotics [10], this nonlinear filtering work has been developed in almost complete isolation from biology and medicine. It was a groundbreaking study by [11] that demonstrated a clear strategy for applying UKF to a model single neuron. In their work, [11] were not at all optimistic that

spatiotemporal applications of cell-to-cell interactions would be tractable.

Simultaneous with the work of [11], we demonstrated that mammalian cortex can generate a wide variety of spatiotemporal structures to accompany typical oscillation frequencies observed in motor, sensory, and navigational cognitive phenomena [12]. In this work, we also demonstrated that a fundamental model of general cortical dynamics, the networked differential equations of Wilson and Cowan [13-14], can replicate all of the qualitative dynamics seen in these experiments: ring, plane, spiral, and irregular waves.

We have extended the work of [11] to cell-to-cell interactions in a spatiotemporal system [15]. Our control system was designed to speed up, slow down, or quench spatiotemporal oscillations in cortex. We performed this work using a model of the middle layers of cortex, reflecting cellular dynamics as well as cell-to-cell communications, and we incorporated an ‘observer’ model to track and filter the real system, as well as generate the control vector to modulate the system. We proved that the use of an observer system is a substantial improvement in the tracking and control of such systems when noise is sufficiently high [15]. It is now increasingly recognized that transient cortical oscillations, seen ubiquitously in sensory and motor cortices, reveal spatiotemporal wave patterns when modern multisite optical [16] or electrical [17] measurements are made. We are unaware of any previous nonlinear state estimation for such spatiotemporal neuronal data.

Nevertheless, incorporating the results of [15] directly into real-time experiments faces a variety of technical issues that must be addressed. In order to stabilize our algorithms, we needed to empirically adjust the covariance of the estimated state. This is a universal

problem in all nonlinear ensemble Kalman filters, and even the seminal work of [6] incorporated a multiplier to adjust estimated covariance. Later, in the meteorological literature, [18-19] termed this strategy covariance inflation, and we followed the formalism of [20] in adjusting our covariance estimate of state. There have been a variety of additional schemes suggested for adjusting covariance inflation, and an efficient method for handling real-time biological systems awaits development.

We have explored taking the foundational ionic dynamical equations of neuronal excitability, the Hodgkin-Huxley equations [21], and incorporated them into an ensemble Kalman framework [22]. We found that not only can we measure voltage alone and reconstruct the entire set of parameters and variables in the setting of significant noise, but we can deliberately damage this model (assuming for instance constant values of the sodium rate variable), and still achieve adequate reconstruction. Assigning trivial dynamics is what [11] did with neuronal threshold, and works because of the iterative nature of the UKF framework. For slow variables or parameter fitting this is reasonable. For fast variables, such as sodium, the instantaneous tracking abilities belie the decrement in prediction from the substitution of a non-predictive formulation for fast dynamics. In UKF constant parameters with trivial dynamics can be tracked if the iteration time constant is fast compared with the dynamical parameter being tracked. Obviously one can only carry this so far in a model, but again, the potential robustness of ensemble Kalman filters to neuronal model inadequacy is intriguing.

We have also done considerable work to explore the metabolic dynamics of potassium flow into and out of cells and compartments during neuronal activity [23-24]. We found

that combining such dynamics with biophysical neuron dynamics was possible, and showed how measuring voltage could permit reconstruction of potassium dynamics in the extracellular space, and vice versa [22].

Another finding is that such use of a Bayesian assimilation of data, combined with UKF, offers the prospect of an improvement in dynamic clamp approaches [22], where the typical data assimilation technique of direct insertion [25] has been shown to be non-optimal compared with an optimized ensemble Kalman strategy.

We can incorporate the metabolic model for the flow and diffusion of potassium from neuron, to extracellular space, into the buffering glial compartments, and to the distant reservoir such as the vascular system in vivo or the perfusion bath in vitro [23-24]. We have taken dual recordings from different types of neurons undergoing epileptic seizures, and shown that we can validate the ability to use a combined model of cellular dynamics along with potassium dynamics to record from one cell type, excitatory or inhibitory, and reconstruct the dynamics of the contrasting cell type [26]. Of importance in this work was the finding that without the incorporation of the potassium dynamics from [23-24], we were unable to track and reconstruct the cellular dynamics in the complex seizure patterns we were observing [26].

All neurons are different – we therefore need to account for significant parameter variations in our model systems. We need a method that treats heterogeneity in neurons formally, and our solution is what we term the ‘consensus set’ of parameters. It turns out that it is straightforward in ensemble Kalman filters to let the filters seek a local mean field for model parameter averaging. Surprisingly, such local mean fields frequently converge to values close to the true mean values, but it is not at all clear that such convergence to the true values

is necessary. I say this because we need to track dynamics, and not validate models in systems where we can never truly replicate the full underlying biophysics. We therefore developed a consensus set to optimize the mean field parameters for a region in space, and afford tracking of such noisy heterogeneous systems [27].

Parkinson's disease is an arena for these model-based control techniques that is very much unexplored. With the advent of solid fundamental models for the regions of the brain involved in generating Parkinsonian dynamics [28], and the control theoretic tools mentioned above, a fusion of such models with control strategies is now very timely.

One of the primary advantages of using a model-based control observer for Parkinson's disease is that one would like to be a surgical minimalist – implanting the smallest number of electrode shafts into deep targets in the brain as possible. One electrode with multiple contacts for sensing and stimulation, into one deep nucleus, would be the ideal. But the interconnected nuclei in the basal ganglia of the brain where the pathological dynamics of Parkinson's disease are generated would require several electrodes to adequately observe the system. So one can use a model of the network, and an ensemble Kalman filter, to perform such reconstruction. Driving such a model with the same control signals delivered to the brain would also enable us to achieve more sophisticated control of such deep brain circuitry.

We have explored these issues in some detail in [29]. One of the key questions in observing complex brains with complex models is to reduce the complexity of the models, preserving their dynamics, in order to increase the accuracy of tracking and reconstruction. A variety of strategies for such model reduction with preservation of dynamical fidelity have been explored in [23]

and [28]. In [29], we examine in some detail the use of reduced models of thalamic neurons to assimilate signals from the basal ganglia, as well as to estimate the reliability of the thalamus in control paradigms for Parkinson's disease.

Another rich area for exploration in Parkinson's disease is the area of control law design. Most controller designs in use are variations of proportional-integral-differential (PID) schemes. In collaboration with Patrick Gorzelic and Alok Sinha, we are completing a comprehensive analysis of several PID control law schemes for Parkinson's disease control. More sophisticated geometrical control schemes are very much worth exploring in the future.

This paper has reviewed some of the recent progress in the fusion of computational neuroscience with modern control theory. A more comprehensive treatment of this fusion can be found in [30]. It is the author's impression that we are just at the beginning of a very fruitful synergy between the computational modeling of dynamical disease and our ability to better control such conditions.

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