4bv Modeling, Analysis, and Design in Biological Systems Using Engineering Approaches

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In recent years, there have been significant advances in the integration of mathematical modeling and analysis techniques in the study of biological systems. Many of these techniques are inherent to the field of systems engineering. As such, systems engineers are playing an increasingly important role in this area. A key difference between the problems considered in the biological sciences and those often encountered in the consideration of engineering systems is that biological problems often have as their objectives issues of *modeling* and *analysis*, while engineering problems also address those issues but with an additional focus on *design*. In addition to the important results obtained from the research, the two problems discussed in this poster demonstrate the integration of systems engineering and biology that is necessary to achieve beneficial outcomes in the consideration of biological systems. The two projects are focused in the fields of neuroscience and diabetes research, respectively. Areas of future research that would benefit from similar advancements are also discussed. In what follows, the two projects are summarized.

A. Modeling and Analysis of the Mechanisms Leading to Calcium Concentration Spikes in Cerebellar Purkinje Cells

Long-term depression (LTD) of cerebellar Purkinje synapses is a form of synaptic plasticity that is a necessary component of the motor learning process [1]. It has been shown that induction of LTD requires coincident activation of both the parallel fiber (PF) and climbing fiber (CF) inputs of a Purkinje cell. Interestingly, coincident activation of these inputs results in an increase in dendritic spine cytoplasmic calcium concentration that is significantly more than the sum of the calcium responses obtained by exciting the PF and CF separately [2]. It is hypothesized that this supralinear calcium response is the mechanism by which the cell detects the coincident activation of the PF and CF and is the first step in the mechanism leading to LTD. It has been demonstrated experimentally that the PF-activated pathway, which results in the release of calcium from the endoplasmic reticulum due to activation of inositol-1,4,5-trisphosphate (IP_3) receptors, is necessary for the onset of LTD [3]. It is the objective of this work to develop and use models of a Purkinje spine to identify the precise mechanisms that lead to the onset of the supralinear calcium spike and to investigate the significance of certain unique physiological characteristics of the Purkinje cell to this process. The model reproduces the experimentally observed supralinear calcium response. Additionally, it demonstrates how the low sensitivity and high density of IP_3 receptors in these cells play important roles in the onset and localization of the supralinear calcium spikes. The modeling is performed using the Virtual Cell biological modeling framework and includes explicit consideration of the varying time scales in the system including those due to binding of calcium to a number of calcium buffering species and those due to species diffusion from the dendritic spine.

This work was performed as part of my post-doctoral research at the Center for Cell Analysis and Modeling at the University of Connecticut Health Center and was advised by Prof. Leslie M. Loew.

B. Control Design Using Nonlinearity Assessment Techniques for Glucose Regulation in Persons with Diabetes

There exists a vast body of research involving techniques for automating glucose regulation in diabetic patients through the use of glucose sensors and computer-controlled insulin delivery devices. With the onset of technological improvements in these sensors and delivery devices, the use in these systems of many of the available advanced process control techniques has become a realizable possibility. In this work, the nonlinear minimal diabetic patient model of Bergman et al. [4] is analyzed with the objective of determining the best control design choice for this biological problem. The model is characterized using a numerical nonlinearity measure to characterize the severity of the control-relevant system nonlinearity. Systems with high control-relevant nonlinearity are assumed to be effectively controlled only through use of nonlinear control algorithms (e.g., nonlinear model predictive control). Conversely, systems with low control-relevant nonlinearity are effectively controlled using simple techniques (e.g., PI control). Based on the determined degree of control-relevant nonlinearity, a statement can be made about the necessary level of complexity of the control algorithm that should be used in automated insulin delivery systems. Control-relevant nonlinearity is a strong function of the performance objective of the closed-loop system. As negative deviations in glucose levels (hypoglycemia) have more serious health ramifications than positive deviations (hyperglycemia), an asymmetric performance objective that places a higher weighting on negative deviations [5] may be appropriate. The results indicate that the key contribution to the control-relevant nonlinearity is then the asymmetric performance objective and that the system itself is only mildly nonlinear in typical regions of glucose deviation given a set of parameter values obtained from the literature. Further information can be found in Ref. 6.

This work was performed as part of my Ph.D. dissertation research at the University of Delaware and was advised by Prof. Francis J. Doyle III (University of California, Santa Barbara).

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