Global Linearization and Control of a Calcium Dynamics in Cardiac Myocytes

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Extend Abstract

The external control of a physiological system is a challenging task. In this work, a nonlinear feedback control design is proposed and demonstrated on a system that describes calcium fluxes that control muscle contraction and relaxation in cardiac myocytes. The particular control formulation uses a global feedback linearization method[1] that is based on differential geometric control theory.

This global linearization method is developed for a class of *affine* nonlinear systems. There are many reasons to motivate a global feedback linearization method. Here, two reasons, relevant to this work, are provided.

(1) If the nonlinear system can be made equivalent to a linear system under state feedback, a linear controller can be designed using the wealth of linear control theory that is available. Thus, the problem of designing a nonlinear controller is *reduced* to the problem of designing a linear control.

(2) The merit of a controller is based on achieving attractive closed-loop dynamics. It is clear that linear systems' dynamics is well understood. Once the closed-loop system (nonlinear system and controller) is equivalent to a linear system, linear system theory can be used to analyze the nonlinear system. Therefore, global state feedback linearization *extends* linear controller synthesis theory to the design and analysis of the nonlinear control problem.

In chemical engineering, the first application to a nonlinear chemical reactor was demonstrated by Hoo and Kantor[2]. This is the first time to use this nonlinear control method to a very fast nonlinear physiological system.

The model that describes the calcium dynamics includes the kinetics of ryanodine-sensitive calcium channels that are critical to signal transduction and cell function in cardiac myocytes. The calcium release in these channels is triggered by a rapid increase of calcium concentration at the outside of the sarcoplasmic reticulum. Several mechanisms have been proposed to explain this phenomenon[3][4]. In this work, the

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[1] A. Isidori. *Nonlinear Control Systems*. Springer, 3rd edition, 1995.
[2] K. A. Hoo and J. C. Kantor. An exothermic continuous stirred tank reactor is feedback equivalent to a linear system. *Chem. Eng. Commum.*, 37:1-10, 1995.
[3] A. Fabiato. Two kinds of calcium-induced release of calcium from the sarcoplasmic reticulum of skinned cardiac cells. In G.B.B. Frank, P.Bianchi, and H. Heurs, editors, *Excitation-Contraction Coupling in Skeletal, Cardica, and Smooth Muscle*, pages 245-263. Plenum Press, New York, 1992.
[4] J. Keizer and L. Levine. Ryanodine receptor adaptation and Ca^{2+}-induced Ca^{2+}-release dependent Ca^{2+}-oscillations. *Biophysical Journal*, 71:3477-3487, December 1996.

mechanism by Tang-Othmer[5] is adopted because the model predicts the adaptation of the channels to constant Ca stimulus, and non-constant Ca perturbations at certain pathological conditions. This model form is also suitable to develop a global feedback linearizing controller for physiological system control. A comprehensive system analysis is applied in this physiological system.

This work demonstrates that when the calcium influx or the maximal rate of the sarcolemma pump is varied, satisfactory closed-loop performance can be obtained with the feedback controller. Simulated results are presented to demonstrate the closed loop system for a wide region of the phase space.

To show the effectiveness of global linearizing and control strategy, a comparing PI controller is designed for this system, which shows that PI controller does not work for this very nonlinear system, even though the same set of control parameters are suitable to control the linear system that sterns from linearization of the nonlinear model at the nominal steady state.

[5] Y. Tang and H. G. Othmer. A model of calcium dynamics in cardiac myocytes based on the kinetics of ryanodine-sensitive calcium channels. Biophysical Journal, 67:2223-2235, December 1994.