Global Linearizing Control of Calcium Dynamics in Cardiac Myocytes

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ABSTRACT The external control of a physiological system is a challenging task. In this paper, a nonlinear feedback control design is developed and demonstrated on a system that describes calcium (Ca) fluxes that control muscle contraction and relaxation in human cardiac myocytes or the calcium-induced calcium release mechanism. The particular control formulation uses a global feedback linearization method that is based on differential geometric control theory. The model that describes the calcium dynamics includes the kinetics of ryanodine-sensitive (RyR) calcium channels that are critical to signal conversion and cell function in cardiac myocytes and Ca balance among the sarcoplasmic reticulum, the cytosol, and the extracellular space (Tang and Othmer (1994)). Analysis of the full system is presented to show input multiplicities and the slow approach to the equilibrium (non-pathological) values. To achieve the controller formulation, the full system was divided into two subsytems - one for the RyR kinetics, the other for the Ca balance. The control formulation was then developed for the Ca balance subsystem, which in turn controlled the RyR kinetic subsystem. Without this novel division, the system did not lend itself to this type of advanced control. More than one variable may be used to regulate the Ca balance subsytem. Simulated results are presented to compare the closed-loop performance for two different, but natural, choices of the manipulated variables to regulate the total system in the presence of unmeasured disturbances and parameter uncertainty encountered by the system.

Keywords Ryanodine receptors, calcium-induced calcium-release, feedback control

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