captures the overall behavior reasonably well over a full order-of-magnitude change in the ratio r_s/r_f, at both volume fractions. We note that the data of Johnson et al. (1996) were actually obtained at $\phi = 0.055$ instead of $\phi = 0.05$. Also, the heterogeneous nature of the fiber radii in agarose is not taken into account in Fig. 4, nor is the nonspherical nature of $C_{12}E_6$ micelles (Johansson et al., 1993). These simplifications were needed to facilitate the comparison. In all cases, the solute and fiber radii used in conjunction with Eq. 8 are those given in Table 2. No adjustable parameters are needed to make the predictions.

The hydrodynamic model given by Eq. 8 is a simple result that is relatively easy to use and requires only basic geometric information about a particular gel-solute system. Comparisons with data taken in agarose gels, provided by Clague and Phillips (1996), Johnson et al. (1996), and Pluen et al. (1999), combined with the comparisons with polyacrylamide, alginate, and carrageenan gels given here, demonstrate that Eq. 8 captures much of the basic physics that affect hindered diffusion in gels. However, with the exception of agarose, there does appear to be a consistent tendency of the theory to underpredict the actual rate of diffusion. Because the theory is based on a physical model that consists of a monomodal, homogeneous distribution of immobile, rigid fibers, it is not surprising that it tends to yield a lower bound for D/D_0. A relaxation of these features, allowing consideration of microstructural heterogeneity, fiber flexibility and motion, and nonsteric fiber-solute interactions will likely lead to better predictions, albeit at the cost of greater complexity.

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Ronald J. Phillips

Department of Chemical Engineering and Materials Science
University of California at Davis
Davis, California

The Model of Snyder et al. Does Not Simulate Graded Ca^{2+} Release from the Cardiac Sarcoplasmic Reticulum in Intact Cells

The recent paper by Snyder et al. (2000) represents a commendable and carefully executed effort to marshal the currently understood mechanisms in cardiac excitation-contraction coupling into a simplified, qualitatively correct macroscopic model. However, one major deficiency of the model needs to be pointed out. Their paper leaves the impression that the feedback interaction between sarcoplasmic reticulum luminal calcium and kinetics of the ryanodine receptor is sufficient to give rise to graded release of sarcoplasmic reticulum calcium in response to the triggering L-type calcium current. This is not the case. The authors base their claim of gradedness on a simulation of the classic experiment of Fabiato, in which calcium is applied to a skinned muscle cell whose "fuzzy space" is not intact (Fig. 3 in Snyder et al., 2000). However, if one uses their model to simulate the experiment in which the L-type current is varied over a wide range in an intact cell (Wier et al., 1994; Cannell et al., 1995; Janczewski et al., 1995), the result is

Received for publication 28 July 2000 and in final form 13 September 2000.

Address reprint requests to Michael D. Stern, M.D., Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, 5600 Nathan Shock Drive, Baltimore, Maryland 21224. E-mail: sternm@grc.nia.nih.gov.

0006-3495/00/12/3353/02 $2.00

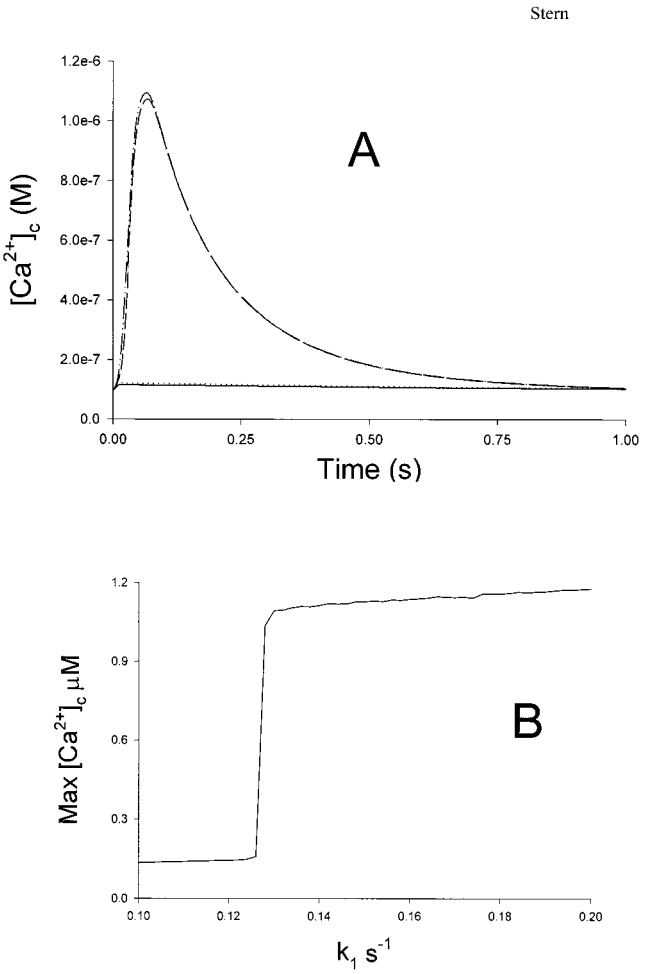

FIGURE 1 Cytosolic calcium transients generated by the model of Snyder et al. (2000) as the L-type current parameter, k_1, is varied. All parameters were the same as in their Fig. 5 and Table 3, for which $k_1 = 0.2$. (*A*) Stack plot of 4 transients corresponding to $k_1 = 0.1$, 0.125, 0.15, and 0.175. The transients fall into two sets of large and small, nearly all-or-none responses (sub- and supra-threshold responses). (*B*) Peak cytosolic $[Ca^{2+}]$ as a function of k_1 showing clear-cut threshold behavior. Simulations were carried out by transcribing the model equations from Snyder et al. (2000) into the modeling language MLAB (Civilized Software, Bethesda, MD), in consultation with the original authors in order to correct minor typographical errors and ambiguities.

entirely ungraded, in disagreement with the experimental findings. In this more physiological context, the model shows nearly all-or-none threshold response (Fig. 1). This is consistent with the idea that such a common-pool compartmental model cannot demonstrate high gain and also robust gradedness (Stern, 1992). Thus, although the sarcoplasmic reticulum luminal feedback mechanism can produce a stable quiescent state together with high gain, it cannot provide a macroscopic approximation of the graded response, which is produced robustly by microscopic stochastic local-control models (Stern et al., 1999).

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Michael D. Stern

Laboratory of Cardiovascular Science, National Institute on Aging
National Institutes of Health
Baltimore, Maryland