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A Simple Nonlinear Model of Electrical Activity in the Intestine

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We have simulated electrical activity of the intestine in a computer model that describes the coupled layers of longitudinal muscle (LM) and interstitial cells of Cajal (ICC). The model suggests that pacemaker activity is due to the ICC layer, while the pulse propagation involves the LM layer that is in the excitatory state. The model describes well the experimentally observed phenomena: frequency change along the intestine, synchronization along short distances and desynchronization for long distances, and the decrease of propagation distance and propagation time along the intestine. We have observed the occurrence of phase interruptions or breaks, which are responsible for the limited values of propagation distance and time.

1. Introduction

Modeling of slow-wave propagation in the gastrointestinal (GI) tract has been conducted since the late 1960s, when Nelson & Becker (1968) suggested that a chain of *relaxation oscillators* could simulate activity in the small intestine. Later, Sarna *et al.* used a modified set of Van der Pol oscillators to simulate different aspects of the GI tract activity (Sarna *et al.*, 1971, 1972a–c, 1976; Sarna & Daniel, 1973, 1975). The pioneering works by these authors had an essential impact on the terminology and approaches used in later studies. The basic concept was to simulate the electrical activity by a set of oscillators. The approach has shown qualitative agreement with the experimental observations. However, the parameters of the model and the coupling scheme used in those simulations could not be rationalized in terms of the electrical behavior of single cells. On the other hand, the recent progress achieved in simulations of nerve and cardiac tissue (Hodgkin & Huxley, 1952; Luo & Rudy, 1991, 1994a,b) resulted from the consideration of ionic mechanisms of membrane activity and on the symmetric electrical coupling of cells. Similar models for the GI tract were termed *core conduction* models and have been used to simulate the electrical dynamics as well. Arguments on the applicability of the two approaches can be found in various references (Sarna, 1975; Publicover & Sanders, 1989; Daniel *et al.*, 1994).

In this paper, we propose a model that combines the advantages of core conduction and relaxation oscillator models to simulate electrical activity in the intestine.

2. Model and Methods of Integration

The proposed model is close in structure to the FitzHugh–Nagumo (FHN) model (FitzHugh,

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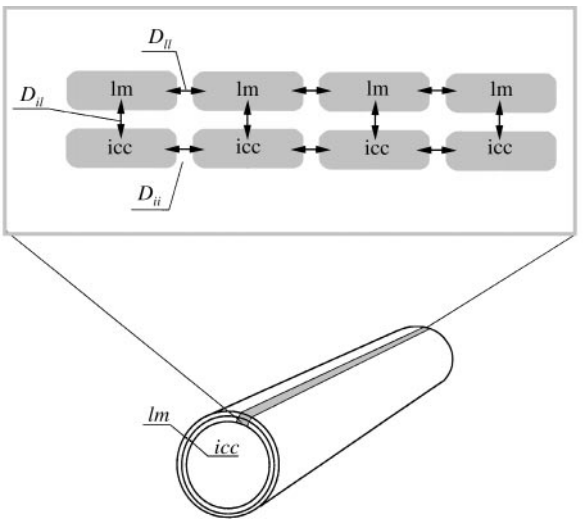

FIG. 1. A schematic presentation of the model. Two layers of intestine were simulated: longitudinal muscle (lm) and interstitial cells of Cajal (icc). The quantities D_{ll}, D_{ii} and D_{il} simulate the connectivity inside and between layers.

1961; Nagumo *et al.*, 1962), which was derived to mimic Hodgkin–Huxley membrane dynamics (Hodgkin & Huxley, 1952) while maintaining the simplicity and physical meaning of the famous Van der Pol oscillator model. The FHN model is widely used to simulate the dynamics of many biological systems, including microbial populations and heart; see Holden *et al.* (1991) and Winfree (1980) for additional references. We have simulated the two layers of the intestine: a longitudinal muscle (LM) layer and the interstitial cells of Cajal (ICC) layer (Fig. 1). The dynamics in each layer is described by a pair of differential equations

$$u_t = ku(u-a)(1-u) - v + D\nabla_u^2 + \alpha D_{il}(u_l - u_i), \qquad (1)$$

$$v_t = \varepsilon(\gamma(u-\beta) - v).$$

The parameters for the LM layer are

$$k = 10, \quad a = 0.06, \quad \beta = 0, \quad \gamma = 8, \quad \varepsilon = 0.15,$$

$$D = D_{ll} = 0.4, \quad D_{il} = 0.3, \quad \alpha = 1,$$

while those for the ICC layer are

$$k = 7, \quad a = 0.5, \quad \beta = 0.5, \quad \gamma = 8, \quad \varepsilon = \varepsilon(r),$$

$$D = D_{ii} = 0.04, \quad D_{il} = 0.3, \quad \alpha = -1.$$

The variables u and v stand for the transmembrane potential and slow currents, respectively, u_t and v_t are their first derivatives with respect to time. The two equations (1) describe the dynamics of the nonlinear membrane in the same spirit as do the FHN equations. Cells of each layer are described by a pair of differential equation. The first equation of each pair has a characteristic "N"-shaped nullcline, which is typical for excitable and oscillatory systems, and describes the dynamics of the transmembrane potential. The second equation describes slow transmembrane currents; the detailed discussion of the origin of these equations and the meaning of the parameters can be found in the original paper by FitzHugh (1961). The values of the parameters in the model (1) were chosen so that the LM layer is in the excitatory state, while the ICC layer is in the oscillatory state (Sanders, 1996). This was achieved by adjusting the parameter β, which was chosen to shift the equilibrium point from the stable branch of the nullcline (LM layer) to the unstable one (ICC layer). The parameter ε, which is proportional to the frequency of oscillations in the ICC layer, was adjusted [Fig. 2(b)] to mimic the experimental observation that the intrinsic frequencies of isolated segments vary along the intestine (Sarna *et al.*, 1971). The simulated dependence of intrinsic frequencies vs. distance is shown in Fig. 2(a) (thin line). The parameter α describes the symmetry of coupling between the two layers. Assuming the absolute value of α the same for LM and ICC layers we assume a symmetrical electrical coupling.* Actually, the last term of the first equation (1) describes current density between LM and ICC layers. The values of coupling coefficients D, which are inversely proportional to the resistivity of membrane

* Note that symmetrical electrical coupling does not result in a symmetrical "effect" of the ICC on the LM and the LM on the ICC layers. The two layers are affected differently by the current from the other layer due to different intrinsic dynamics of ICC and LM cells.

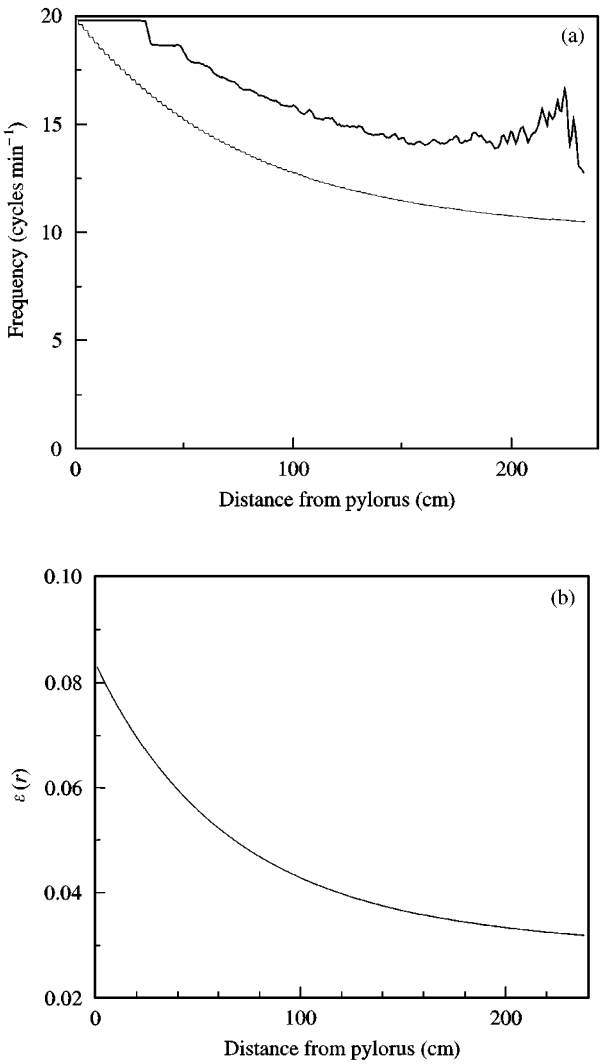

FIG. 2. (a) Frequencies along the intestine. The thin line shows the intrinsic frequencies of isolated oscillators in the ICC layer that were specified to match the experimental data (Sarna *et al.*, 1971). The bold line depicts the averaged frequencies measured in the fully connected model. Note that the measured frequencies are higher than the intrinsic ones at every point, there is a long plateau in the proximal part (left), and the frequencies distribution becomes chaotic toward the distal part (right). (b) dependence $\varepsilon(r)$ used in eqn (1). This dependence affects the distribution of intrinsic frequencies [Fig. 2(a), thin line].

contacts, were chosen to mimic a strong coupling inside the LM layer and weaker coupling between the two layers and inside the ICC layer.

We have simulated a one-dimensional array of 300 coupled cells (one cell roughly corresponds to an 8 mm long section of tissue in the case of human intestine) using the Euler method of integration with space and time steps $h_x = 1$ and $h_t = 0.05$. This method is described in detail in the literature (see e.g. Press *et al.*, 1998); in brief we approximate derivatives in eqn (1) by difference equations e.g. $u_t(x,t) = (u(x,t+h_t) - u(x,t))/h_t$ and the Laplacian $\nabla^2 u(x,t) = (u(x+h_x,t) + u(x-h_x,t) - 2u(x,t))/h_x^2$ (the last formula is valid for the one-dimensional case only). Substituting these estimated derivatives into eqn (1), we obtain a set of difference equations which is solved numerically. We use the Euler method because of its simplicity and effectiveness, we believe that this method is well suited for solutions of nonlinear parabolic equations like eqn (1). To verify the insensitivity of the solutions to the chosen time and space steps, we have found that a two-fold decrease of h_x and four-fold decrease of h_t did not affect the parameters measured more than a few percent. We also ran control simulations of 2400 coupled cells without observing any marked changes in the dynamics studied. We used dimensionless parameters to integrate eqn (1); for the sake of convenience the computed data were scaled to ordinary units as it is seen in the figures below.

3. Results

Our model accurately simulates the known experimental observations, such as the dependence of the frequency along the intestine [Fig. 2(a)]. It is seen that while we utilize the experimentally measured distribution of intrinsic frequencies in the intestine, which was measured by cutting the gut into segments (Sarna *et al.*, 1971), the calculated frequency does not coincide with that of the intrinsic frequency, but is higher at every point. However, there is a long plateau in the proximal part of the intestine; the frequency drops toward the distal part, where oscillations become chaotic. These simulations are in good agreement with experimental data reported by Sarna *et al.* (1971). Our observations show that in addition to a long plateau of synchronized oscillations in the proximal part (19.7 cycles min^{-1}, 0–38 cm) there exist a few shorter plateaus of synchronized oscillations with lower frequencies (18.6 cpm, 38–53 cm, and 17.8 cpm, 53–63 cm). The length of each subsequent plateau decreases until the plateaus become indistinguishable at

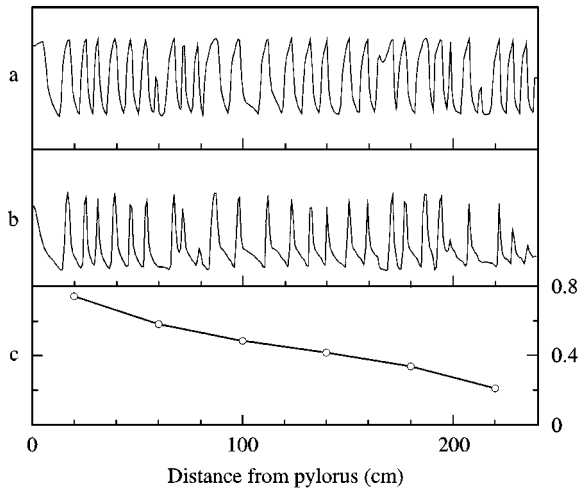

FIG. 3. Profile of excitation (transmembrane potential) along the intestine simulated in the longitudinal muscle (a) and interstitial cells of Cajal (b) layers. Cross correlation of the transmembrane potential distribution for the two layers (c) shows that there is a synchronized (correlated) activity in the proximal part, while the oscillations are desynchronized in the distal part.

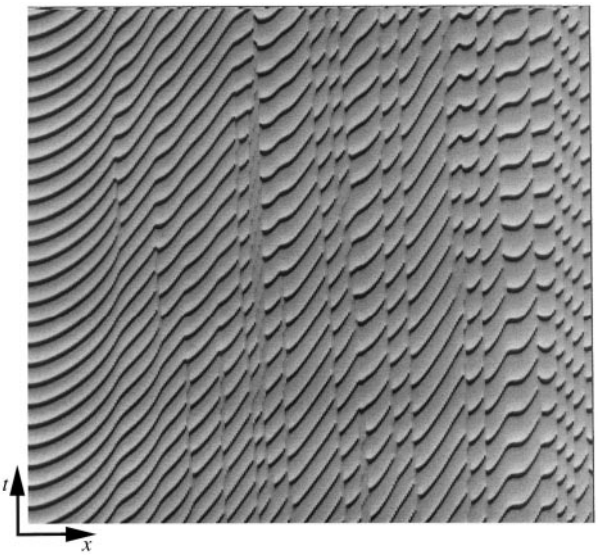

FIG. 4. Space–time plot of the trasmembrane potential distribution in the LM layer. Note that pulses are synchronized in the proximal part and propagate toward the distal part; pulses are desynchronized in the distal part and have a short propagation length. X-axis stands for distance from pylorus (0–240 cm), *y*-axis is time (0–75 s); dark areas correspond to higher transmembrane potential.

about 60 cm from the pylorus [Fig. 2(a)]. The existence of several adjacent plateaus of locked frequencies has not been reported in the literature to date; we propose a hypothesis on the origin of this phenomenon in the Discussion section.

A rise of frequencies in the distal part [Fig. 2(a)] is due to randomization of oscillations as described below.

Examples of the spatial distribution of transmembrane potential are shown in Fig. 3(a) and (b). Note that pulses in the two layers are synchronized in the proximal part as they propagate toward the distal part. This suggests that the oscillations initiated in the ICC layer excite the LM layer and an excitation propagates in the LM layer. However, excitation is desynchronized in the distal part; strictly speaking there still exist islands of synchronized excitations, or *wavelets*, with short propagating lengths (Fig. 5). The cross-correlation function [Fig. 3(c)], which was calculated for the potentials shown in Fig. 3(a) and (b), illustrates the loss of synchronization toward the distal part.

Figure 4 presents a space–time plot of excitation registered in the LM layer. Dark stripes, corresponding to the crest of pulses, are inclined with respect to *x*-axis (Fig. 4), meaning that pulses are propagating toward the distal part. Note that a pulse which originates near the pylorus never reaches the distal part, i.e. there is no continuous propagation along the intestine. In contrast, pulses propagate over a limited distance; a piecewise structure of such wavelets is clearly seen in Fig. 4. At some point, an excitation in the ICC layer initiates a new wavelet in the LM that propagates toward the distal part, which destroys the approaching wavelet from the proximal part. This process is seen as a phase interruption between wavelets in Fig. 4. Similar dynamics were termed *phase breaks* in Aliev & Vasiev (1995), where FHN equations were utilized.

Mean propagation length and time of the wavelets varies along the intestine (Fig. 5), decreasing toward the distal part by a factor of 3. This observation is in agreement with recent experimental observations (Golzarian & Richards, 2000).

4. Discussion

In this paper, we present a model that for the first time combines features of the two widely

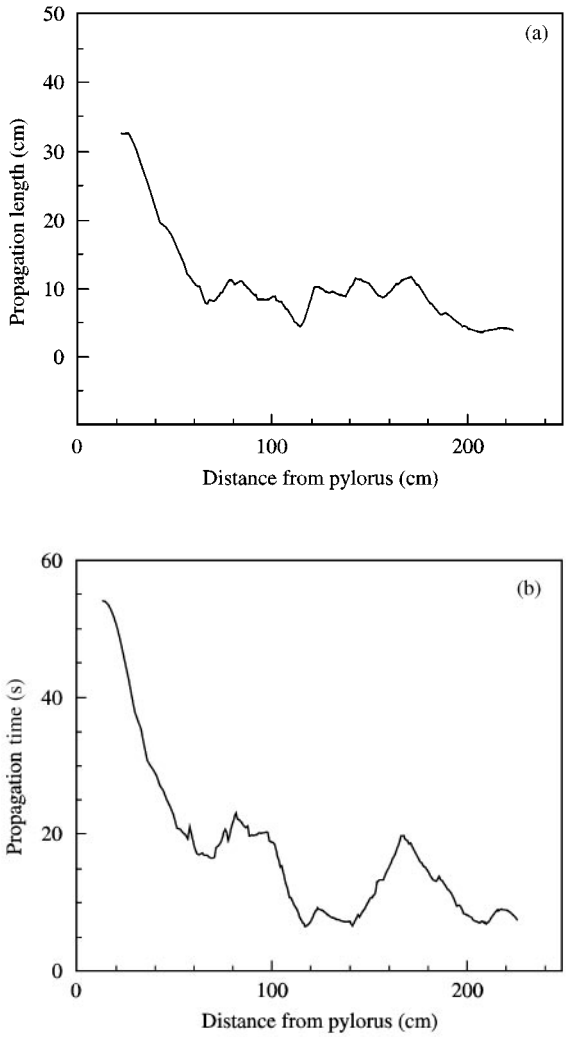

FIG. 5. Mean propagation length (a) and time (b) along the intestine. The data were averaged over a period of 10 min.

used "relaxation oscillator" and "core conductor" approaches to simulate the GI electrical activity. We describe the two tissues, the longitudinal muscle and interstitial cells of Cajal, as active layers electrically coupled to each other. The model allows us to simulate correctly such important characteristics of the intestine as the spatial variation of the frequency of oscillations along the gut, the fact that intrinsic frequencies are lower at each point with respect to those in isolated segments of tissue [Fig. 2(a)], limited propagation length and time, and a reduction in propagation length and time toward the distal part (Fig. 5).

It is interesting to note that in contrast to a network of coupled oscillators with nearly identical frequencies, such that oscillators can be entrained to a single common frequency, the frequency and phase gradients in the gut are sufficiently steep that frequency entrainment is impossible. The phase breaks (Fig. 4) are the direct result of the failure to entrain all oscillators. Figure 4 shows, for the first time, that these phase breaks are localized in time, appear at different locations along the gut, may drift along the gut, and the density of the breaks (or, in other words, the probability for breaks to occur) increases toward the distal part. It should be noted that similar phase breaks that occur as a result of large phase gradients have been found in a simpler FHN system (Aliev & Vasiev, 1995).

The model also allows us to predict new behavior, which has yet to be confirmed experimentally:

(1) The widely known variation of frequencies along the intestine, like that presented by Sarna *et al.* (1971), was interpreted as having a single long plateau in the proximal part where the oscillations are synchronized. Our simulations confirm the existence of such a plateau [Fig. 2(a)]. However, in addition to this plateau, there may exist a few more plateaus of shorter length where the oscillations are synchronized. Thus, the dependence of frequencies upon distance has a staircase structure in the proximal part. A detailed experimental measurment of the distribution of frequencies along the intestine is badly needed to clarify the point.

(2) A sharp three-fold drop of propagation length and time along the gut can be interpreted as a loss of spatial and temporal correlations for excitations in the distal part, as it is illustrated in Fig. 3, or, in other words, oscillations in distal part resemble chaotic oscillations.† This hypothesis can be verified experimentally by conducting specific tests (Fourier analysis, Poincare return

† Strictly speaking, the term *chaotic* is sometimes used in physics to describe the low-dimensional irregular dynamics. The problem if the dynamics studied is low-dimensional chaos or high-dimensional noise will be studied in a separate publication.

maps, analysis of fractal dimensions, number of turning points, etc.) for chaotic oscillations in the distal part; this will be the subject of future study. It should be noted that some level of randomness in the electrical activity of the GI tract has been recently observed (Mintchev *et al.*, 1998; Sanmiguel *et al.*, 1999), which emphasizes the importance of studying the irregular dynamics of the GI tract.

An interesting point, which is widely discussed in the recent literature, is the question of connectivity between and inside layers in smooth muscle of the GI tract. In a recent survey (Horowitz *et al.*, 1999) the importance of ICC cells as pacemaker cells and the importance of connection between ICC and LM layers for slow wave generation and conductance are emphasized. The authors suggest that propagation occurs along the network of ICC layer, while they state that connectivity inside LM layer can be neglected. At the same time there are references that point out the importance of conductance in the LM layer (Tomita, 1990; Bortoff *et al.*, 1981). Actually, the arguement occurs because unlike in cardiac myocytes, which are known to support the orderly propagation of pulses, only a relatively small number (if any) of gap junctions have been observed in cells of LM layer. It should be noted that in our model we do not include detailed, microscopic ionic mechanisms of conduction in the GI tract, and simply state that for our macroscopic model, the correct simulations should include coupling between the layers and propagation inside the layers, which in our model is accounted for by the parameters D_{ii}, D_{il} and D_{ll}. We have found that large values of D_{il} and D_{ll}, and relatively small value of D_{ii} result in the behavior which fits well to the experimental data. Although we used slightly higher values for D_{ll} than for *Dil*, these values are actually close in magnitude and it is not the point of the article to argue which of the two values, if measured experimentally, would be higher and if it remains high at all the circumstances. At no point do we claim that propagation exclusively occurs in the LM layer, vice versa, we claim that the both layers play important role in propagation. We believe that further experimental work is needed to clarify the mechanism of electrical conduction and to measure the actual values of connectivities inside and between layers.

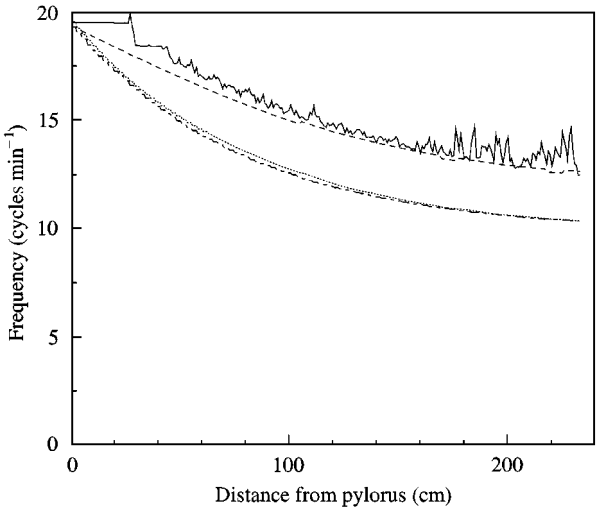

FIG. 6. Frequencies along intestine with different connectivities zero. Solid line: $D_{ii} = 0$; dashed line: and $D_{ll} = 0$; dotted line: $D_{il} = 0$; dot-dashed line: $D_{ii} = D_{il} = D_{ll} = 0$ (intrinsic frequency).

To determine the importance of coupling inside and between layers, we ran control simulations in which we assumed that either one of connectivity coefficients D equals zero, or all three are zero. The results presented in Fig. 6. It is seen, that the connection of ICC and LM layers (coefficient D_{il}) is important, because such a connection results in rise of frequency of oscillations. The zero coefficient D_{ll} (no connectivity inside LM layer) results in some change of measured frequency, however, more important, that stepwise structure of frequency dependence appears only in the case of non-zero D_{ll}.

An interesting question is whether the ICC network be modeled as a continuum, or, alternatively, considered as discrete sites along the continuum LM layer? We do not know the final answer to this question, and available experimental data are insufficient to answer this unambiguously. We have simulated the ICC as a continuous layer for the sake of simplicity. However, the results presented in Figs 2(a) and 6 suggest that were the connectivity inside the ICC layer absent ($D_{ii} = 0$), there would be only small changes of dynamics.

To construct the model, we used relatively simple FHN equations to facilitate simulations.

We assumed that LM layer is in excitatory state (i.e. an over-threshold excitation is required to produce a large amplitude response). We believe that this is the general case, even though under some abnormal conditions LM cells can spontaneously generate pulses. The situation is similar to those with myocytes, which are known to be in the excitatory state, although exceptions may occur during altered rhymes or abnormal physiology. In our simple model we considered a typical case and ignored rare events of spontaneous activity in the LM layer. A shortcoming of such a simple model is the deformed shape of excitation pulses (Fig. 3) in comparison to the experimentally measured ones. To simulate the shape of excitations with better precision, advanced ionic models of smooth muscle, such as presented in Miftakhov & Abdusheva (1996), Miftakhov *et al.* (1999) and Vigmond & Bardakjian (1998), would be required. An obstacle for the application of ionic models is the large number of equations involved, which makes it difficult to simulate on available computers distributed systems with hundreds or thousands cells linked together.

In conclusion we would like to emphasize that the simple model we have presented is useful for simulating the basic properties of electrical activity in the intestine. The model for the first time simulates the dynamics of coupled LM and ICC layers, yielding results that fit well available experimental data. The model contains the parameters, such as connectivity coefficients, that can be adjusted to account for future experimental measurements. However, the major advantage of this theoretical model, in our opinion, is that it is able to predict new behavior and hence presents a challenge for experimentalists.

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