Intercellular Coupling Mediated by Potassium Accumulation in Peg-and-Socket Junctions

Edward J. Vigmond, Berj L. Bardakjian*, Lars Thuneberg, and Jan D. Huizinga

Abstract—Coupling of smooth muscle cells is important for coordination of gastrointestinal motility. Small structures called peg-and-socket junctions (PSJs) have been found between muscle cells and may play a role in electrical coupling due to extracellular potassium accumulation in the narrow cleft between the muscle cells. A model was developed in which an electrical boundary element model of the cell morphology is used in conjunction with a finite difference model which described ionic fluxes and diffusion of extracellular potassium in the PSJ. The boundary element model used a combination of triangular and cylindrical elements to reduce computational demand while ensuring accuracy. Barrier kinetics were used to model the underlying ionic transport mechanisms. Seven ionic transport mechanisms were used to create the transmembrane voltage waveform. Results indicate that PSJs may produce significant coupling between smooth muscle cells under appropriate conditions. Coupling increased exponentially with increasing length and with decreasing intercellular gap.

Index Terms—Boundary element method, coupling, morphology, peg-and-socket junctions, potassium accumulation, smooth muscle.

Electrical pacemaker activity in the gastrointestinal tract is manifested by electrical rhythmic activity, called electrical control activity (ECA), generated in the musculature. The ECA originates in an interconnected network of interstitial cells of Cajal (or ICC) and smooth muscle cells [1]–[3]. Dissection of tissues from the stomach and small intestine reveal different frequencies than those recorded in situ with proximal sites having higher intrinsic frequencies [4]–[6]. In situ, muscle cells are electrically coupled and the ECA is synchronized with the proximal slow waves leading and creating an apparent propagation in aboral direction. The rhythmic nature of the pacemaker activity and the entrainment of intrinsic frequencies has led to modeling of the ECA as a population of coupled relaxation oscillators [7], [8], [5], [9]. Indeed, normal functioning of the stomach and proximal small intestine relies on entrainment of intrinsic ECA activity. Apparent propagation in aboral direction governs propulsive contractile activity when the musculature is appropriately stimulated by distension and/or excitatory neural activity [10]–[12].

Coupling between ICC and smooth muscle cells and coupling between smooth muscle cells is essential for entrainment of ECA to obtain coordinated contraction of muscle cells. If only coupling is altered between such oscillators then the mode of the oscillation can change from periodic to chaotic [13]. Gap junctions play an important role in intercellular communication since they provide direct electrical and metabolic coupling between the cytoplasm of neighboring cells [14], [15] but cells are coupled also by a variety of other structures [16], [17]. Pacemaker cells may be coupled to smooth muscle cells by gap junctions as in the submucosal plexus of the canine colon [18], but at other sites, such as between ICC and the muscle layers of the mouse small intestine, gap junctions are not to be found and coupling appears to be mediated by an abundance of close apposition contacts [19]. Within certain muscle layers no gap junctions can be recognized by electron microscopic techniques such as in the longitudinal muscle of the intestine and colon of a variety of species [20], [21]. In these muscle layers, muscle cells are seen to communicate in different ways. In such tissues, close apposition contacts are always observed. Whether such contacts provide direct cytoplasmic communication is debated. Such contacts may contain small groups of connexons which would allow electrical and metabolic communication although it could not be identified as a gap junction; only a large aggregate of connexons can be recognized as a gap junction by electron microscopy. Evidence for direct cytoplasmic communication comes from the observation that tracer molecules can be found to diffuse from one cell to the other [21], [22]. Nevertheless, electrical communication other than purely resistive is likely to occur.

One type of conspicuous intimate contact is the peg-and-socket junction (PSJ), where an extrusion or short branch of one cell, forms a peg which penetrates a neighboring cell, and fits into an intrusion or socket with an intercellular gap of 20 nm. This extrusion can be up to 10 μm long, undergo a 90° bend upon entering a cell, and be up to 1.5 μm in diameter [23]. The abundance of these structures in areas of no demonstrable gap junctional coupling and their absence in areas shown to be well coupled by gap junctions [23], [24] suggest they may be important for indirect electrical coupling. These structures facilitate field coupling [25], but may also facilitate propagation of a depolarization pulse through accumulation of K⁺ in the extensive narrow gap between the cells created by the PSJs. Such a mechanism for cell to cell coupling has been proposed in other systems [26]–[30] and its study in smooth muscle is the subject of the present study.

This study modeled a PSJ to determine the conditions under which coupling becomes significant between the two cells comprising the PSJ. One cell was called a source cell and the voltage it induced in a second cell, called the receiving cell, was com-
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Fig. 1. Schematic of PSJ cross section showing pertinent dimensions. The intercellular region (shaded gray) was discretized into toroidal regions (shown) and the \( K^+ \) concentration was modeled using a finite difference scheme. The concentration at the open end was kept constant at 6 mM since it was assumed that the change in \( [K]_e \) in the PSJ would be much larger than that outside of the PSJ due to the larger membrane separation between source and receiving cells. Only the portion of the source cell comprising the intrusion (thick line) was modeled. The inset box on the right shows the source cell and the receiving cell with the PSJ (circled and not to scale).

The PSJ was modeled as a series of compartments, each with active membranes for both cells and extracellular potassium concentrations were computed using a finite difference scheme. The compartmental PSJ model was coupled to a boundary element model (BEM) of the receiving cell. The BEM model used a mixture of triangular and cylindrical elements to reduce computation while providing a realistic geometry [31].

I. METHODS

Two isolated cells in an infinite bath were considered, a source cell with an intrusion and a receiving cell with an extrusion (see Fig. 1). Together, the extrusion and intrusion and the gap between them comprised the PSJ. It was assumed an ECA waveform propagated over the source cell and, furthermore, that the transmembrane voltage was constant over the intrusion while the receiving cell was assumed to remain in a resting state. The only part of the source cell membrane that was modeled was the portion which constituted the intrusion. \( K^+ \) flux through the \( K^+ \) channels and pumps in the source and receiving cell membranes of the PSJ altered the \( K^+ \) concentration in the gap which, in turn, altered the \( K^+ \)-dependent current. The effect of these currents on the voltage of the receiving cell was computed.

The complete model was divided into two parts, a finite difference scheme which was coupled to a BEM model. The finite difference scheme was used to compute the transmembrane currents for the portions of source and receiving cells’ membranes which formed the PSJ as well as tracking the extracellular \( K^+ \) in the gap of the PSJ. The BEM model then used the transmembrane voltage and current information of the receiving cell to compute the derivatives of the receiving cell transmembrane voltages. The ionic currents of the cell body outside the PSJ were calculated using a passive network to reduce computation while the equations used for the membranes of the PSJ were much more detailed. Finally, a differential equation solver based on Gear’s method, LSODE [32], was used to integrate the system. The elements of the model are discussed in detail below.

A. Ionic Current Equations

The equations describing the ionic current are a modified form of the barrier kinetic (BK) model presented by Skinner and Bardakjian [33]. Seven ionic transport mechanisms were incorporated into the membrane to produce a waveform which resembled the ECA of canine smooth muscle. The total ionic current density, \( i_{\text{BK}} \), was composed of the following components:

\[
\mathbf{(1)}
\]

where the subscripts of the individual current densities refer to the transport mechanism as follows:

- \( Na^+ \) for the voltage-dependent \( Na^+ \) channel;
- \( Ca^2+ \) for the voltage-dependent \( Ca^2+ \) channel;
- \( K^+ \) for the voltage-dependent \( K^+ \) channel;
- \( K(Ca) \) for the \( Ca^2+ \)-dependent \( K^+ \) channel;
- \( NaK \) for the \( Na^+ -K^+ \) pump;
- \( NaCa \) for the \( Na^+ -Ca^2+ \) exchanger;
- \( Cap \) for the \( Ca^2+ \) pump.

Barrier kinetic equations (Eyring rate theory) [34] were used to describe the voltage-dependent channels which have the generic form for ion species \( X \)

\[
\mathbf{(2)}
\]

where

- \( \nu_m \) transmembrane voltage;
- \( z_X \) valence of \( X \);
- \( \tau \) membrane thickness;
- \( F' \) Faraday’s constant;
- \( k_B \) Boltzmann’s constant;
- \( T \) temperature (310.15K);
- \( \kappa_X \) transmission coefficient representing a periodic function of time which was used to describe the gating of the channel (see Fig. 3) while the other parameters describe the permeation through an open channel.

Changes in \( \nu_m \) were solely the result of the changing of the transmission coefficients with time; there was no current stimulation. Transmission coefficients were chosen to produce a physiological looking waveform, and, were further constrained to properly balance the voltage and ionic concentrations over one ECA cycle. For the source cell, the transmission coefficients changed with time since the cell was active, but, for the receiving cell, they remained at their basal values. The calcium pump was treated as a channel operating only in an outward direction with no transmission coefficient.

The equations for the remaining ionic transport mechanisms used are described in [33] and [35] were

\[
\mathbf{(3)}
\]
### Table I  
**MODEL PARAMETERS**

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<td>( D_K )</td>
<td>( 10^{-9} )</td>
<td>( m^2 s^{-1} )</td>
</tr>
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</table>

where \( \gamma \) is the volume/area of the source cell and \( f \) is a factor representing the effect of calcium buffering. Values used for the parameters are given in Table I. The intracellular concentrations were assumed spatially to be constant over the cell since the volume of the cell is much larger than the gap. Of the three concentrations, [Ca\(^{2+}\)]_e was by far the most important. Changing of \([K^+]_e\) had very little effect since it was much larger than \([K^+]_e\) so that the ratio of the two was relatively unaffected by a change of several mM in \([K^+]_e\). Na\(^+\) is only significant during the initial spike of the ECA and is less important than in neurons and myocytes for producing the upstroke.

### C. Diffusion in the PSJ

The PSJ was divided into toroidal compartments of rectangular cross section with each compartment containing a portion of source cell membrane, receiving cell membrane and the intercellular volume between the two portions of membrane. The rate of change of extracellular \( K^+ \) concentration within each compartment was given by a finite difference equation of the form

\[
\frac{\partial [K^n]^i}{\partial t} = -\frac{I^n_{K}}{FV} + \frac{D_K}{L^2} \left( [K^n]^i - [K^n]^j - 2 [K^n]^j \right)
\]

where

- \( i \) (superscript) denotes the compartment;
- \( D_K \) diffusion coefficient of \( K^+ \);
- \( L \) compartmental length;
- \( V \) compartmental volume;
- \( I^n_{K} \) total \( K^+ \) current introduced into the compartment of extracellular space

\[
I^n_{K} = A_s \left( \varphi^n_{K} + \varphi^n_{(KCa)} - 2 \varphi^n_{NaK} \right)
\]

where the superscript ‘‘\( s \)’’ denotes receiving cell quantities and \( A_s \) is the surface area of the source or receiving portion of membrane.

The concentrations of the \( Na^+ \) and \( Ca^{2+} \) were assumed to remain constant in the gap since the concentration of these two ionic species is much higher than that of \( K^+ \) and, a very large change in extracellular concentration of these ions must occur for there to be a significant effect because of the transmembrane ion concentration ratios.

### D. BEM Model of the Receiving Cell

The finite difference method considered both the source and receiving cells but only over the PSJ. To compute the induced voltage in the receiving cell, the entire cell had to be considered, so, a BEM representation was used for the receiving cell (see Fig. 2). The smooth muscle cell was modeled as a cylinder of length 100 \( \mu m \) with a radius of 5 \( \mu m \), an extrusion of radius 0.31 \( \mu m \) and extrusion length with a nominal value of 2 \( \mu m \). The surface of the extrusion was discretized into a set of cylinders.
Fig. 2. The figure on the left shows the BEM model of the receiving cell with the extrusion circled while the right figure shows the extrusion in detail. The extrusion membrane was modeled by a series of cylinders while the rest of the cell membrane was discretized into a set of triangles, necessitating a special interfacial element between the two regions: a triangle with a circle cut into it.

of length 0.2 μm while the rest of the cell body was discretized into a set of 204 triangles (see Fig. 2).

For the BEM, there must be no gaps in the surface and, hence, the cylindrically discretized extrusion had to interface exactly with the triangularly discretized body. A special element was used to join the two sections, a triangle with a hole formed by a negative disk element centered on the triangle (Fig. 2).

Had triangles been used for the entire surface, many more would have been required. This would be due to the small size of the triangles needed to discretize the extrusion. Although the body section does not require small triangles, it must merge with the extrusion and the transition zone between the two sizes of elements would have been appreciable.

Assuming equal intra- and extracellular conductivities, $\sigma_e$, to reduce computational requirements, and by transforming Laplace’s equation to an integral form and discretizing it, the vector of transmembrane current densities, $i_{m}$, can be related to the transmembrane voltage vector, $v_{m}$, as previously described [25]

$$Gc_{m} = \sigma_e \left( \frac{R^2}{4} - \frac{1}{4} \right) v_{m}$$

where $G$ and $H$ correspond to the monopole and dipole current sources on the membrane respectively.

Analytic formulae were available for the double layer calculations involving triangles [36] [37], and discs and cylinders [31]. For disc and cylinders, single layer calculations had to be performed with one-dimensional Gaussian quadrature [31] while analytic expressions were available for triangular elements [37].

Once $i_{m}$ was determined, the derivative of the transmembrane voltage could be found [38]

$$\frac{\partial v_{m}}{\partial t} = \frac{1}{c_{m}} (v_{m} - i_{\text{ionic}})$$

where $c_{m}$ is the membrane capacitance. Given the linear portion of the membrane had a static conductance, $g_{m}$, the individual entries of the ionic current density vector were computed from

$$i_{\text{ionic}} = \begin{cases} i_{m}^{\text{extrusion}} & \text{extrusion} \ 
\frac{V_{m}^r - V_{m}^f}{g_{m}} & \text{non-extrusion} \end{cases}$$

Thus, a system of first-order differential equations was constructed.

E. Resultant System of Equations

The final number of equations solved depended on the length of the interdigititation. Convergence in the $K^+$ concentration in the gap was obtained when the toroidal compartments of the PSJ were less than 0.3 μm long. Typically, compartments of length 0.2 μm were used. For the nominal case of a PSJ of length 2 μm, the BEM model solved a system of 214 equations (204 triangular elements and ten cylindrical elements) to determine the derivatives of the transmembrane voltages of the receiving cell. This meant that a system of 228 equations needed to be integrated which was broken down as follows: three equations to monitor the intacellular concentrations of the source cell, $[Ca]_{e}$, $[K]_{e}$, $[Na]_{e}$; the source transmembrane voltage, $V_{m}^r$, $[K]_{e}$, and $V_{m}^f$ of each of the ten compartments of the PSJ; and, the transmembrane voltages of the 204 triangular elements of the receiving cell body. The number of equations to solve was, thus, only dependent on the PSJ length. LU decomposition was used to solve for the derivatives and the integrator used was capable of handling stiff systems [32]. The initial conditions are given in Table II.

## II. Results

### A. ECA Cycle

Variation in several quantities during one cycle of the ECA are plotted in Fig. 3. There are two phases to the cycle: 1) the resting phase where the voltage in the source cell was constant, and 2) the active phase where the voltage in the source cell was a pulse of 30-mV amplitude with a small initial spike. Although the voltage was flat during the resting level portion of the ECA cycle, current flow through each transport mechanism as well as the ionic concentrations were changing. The system was in a steady state, i.e., currents cancelled out on the whole during the resting phase of the ECA.

During the active phase, 1) the intracellular concentration of $K^+$ decreased, the concentration of $Ca^{2+}$ increased and the $Na^+$ concentration decreased slightly, and 2) the outward flow of $K^+$

### Table II: Initial Conditions

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<td>$[K]_{e}$</td>
<td>6</td>
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<td>$[Na]_{e}^+$</td>
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<td>mM</td>
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<td>$[Ca]_{e}$</td>
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<td>$[K]_{e}^+$</td>
<td>107</td>
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</tr>
<tr>
<td>$v_{m}$</td>
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</table>
increased the extracellular $K^+$ concentration which decreased $i_K$ and $I_{K(Ca)}$, but increased the rate of the $Na^+-K^+$ pump. The net effect was to decrease the current, resulting in depolarization of the receiving cell. While the increase in $[K_e]$ reached its peak amplitude quickly, within approximately 150 ms, the voltage change occurred much slower, appearing to act with a time constant of 680 ms.

Note the gradient in $[K_e]$ and currents along the length of the PSJ in the bottom three graphs of Fig. 3. Even at low currents, the $K^+$ clearance from the PSJ is slow enough that accumulation results. Changing the location of the PSJ along the length of the receiving cell body did not affect results.

### B. Open End Concentration

The model as presented assumed that the concentration of $[K_e]$ at the open end of the PSJ was fixed at 6 mM. Due to the much larger separation between the source and receiving cells outside the PSJ, it was assumed the change in $[K_e]$ outside the PSJ would be much less than that inside. The distance between the cells is an order of magnitude larger, meaning that the surface area per unit volume, which determines the change in concentration, will be an order of magnitude lower. The extreme case of the concentration of $[K_e]$ outside the PSJ following the concentration of $[K_e]$ inside the PSJ, i.e., the no flux boundary condition, was simulated to determine the effect of this assumption.

As can be seen in Fig. 4, a no flux boundary condition increases the amplitude of the received voltage oscillation by a factor of three. The average of the voltage was slightly increased from 71.3 mV for the fixed concentration case to 70.0 mV for the no flux case meaning the minimum was reduced by 2.2 mV while the maximum was increased by 2.6 mV. These changes occurred because the coupling mechanism depends on an increase in $[K_e]$. The fixed concentration allows $K^+$ to escape from the PSJ during the resting phase, thereby lowering the maximum $[K_e]$ attained.

### C. Length of Junction

The effect of changing the length of the PSJ is shown in Fig. 5. As the length was increased, the peak voltage induced in the receiving cell increased and the voltage resting level decreased. The voltage resting level was tied to the resting level of $[K_e]$ which also decreased. During the resting phase, there was an influx of $K^+$ into the source cell which must be supplied by $K^+$ from the bulk medium, at the open end. Thus $[K_e]$ decreased along the PSJ. Since $[K_e]$ was fixed at the open end, the only way to achieve this gradient was to lower $[K_e]$ at the closed end.

As the length was increased, the resting level continued to decrease and the peak continued to increase, but the peak $[K_e]$, which occurred in the closed end compartment, did not increase much after a length of 1 $\mu$m. The extent of the peak $[K_e]$ (the length of the PSJ over which the peak $[K_e]$ exceeded a certain value) continued to increase with length, however, even though the peak level did not.

Both the increase of the peak $v_m$ and the decrease in the resting level of $v_m$ served to increase the amplitude of the $v_m$ oscillation. The oscillation started to become significant after
D. Receiving Cell Membrane Conductivity

The effects of changing the receiving cell conductivity, $g_{m_r}$, is shown in Fig. 6. Increasing the conductivity decreased $\tau_{m_r}$, showing the PSJ acted like a current source. Above 0.1 S/m² (or, equivalently, less than 10 kΩ cm²), the PSJ did not affect the receiving cell. There was no effect on the resting level of $[K]_e$ and only a small effect on the peak $[K]_e$.

E. Intercellular Gap

The gap between the cells was increased from the nominal value of 30 nm to 1000 nm (Fig. 7). Increasing the gap decreased the efficacy of the coupling. At smaller gaps, the resting level of $[K]_e$ decreased since the concentration gradient had to become stronger to overcome increased resistance to diffusion while maintaining the same membrane current flow. The peak $[K]_e$ was constant for gaps of less than 500 nm. The extent of the peak region was larger at smaller gaps. The induced voltage decreased with increasing gap as the resting level increased.

F. Cell Size

Two other cell sizes were simulated. Results are shown in Table III. As the cell size was increased, the voltage was affected more than $[K]_e$. The peak voltage decreased with cell size. The peak $[K]_e$ also decreased with cell size but to a smaller extent than the voltage reduction. The total peak current induced in the receiving cell normalized with respect to that induced at nominal conditions ($g_{m_r} = 0.01$ S/m², PSJ length = 2 μm, gap = 30 nm) is also shown in Table III. As the receiving cell increased in size, the induced current increased slightly but had a much larger surface to depolarize. The effect was only noticeable for the 200-μm-long cell.
III. DISCUSSION

Under certain conditions, extracellular $K^+$ accumulation in a PSJ due to an active source cell can induce significant changes in the transmembrane voltage of the receiving cell. Such coupling is in addition to any electric field coupling, i.e., coupling not through gap junctions, that may exist. The two mechanisms may be operating simultaneously. Although the simulations used the cell with the intrusion as the source cell, results would have been the same using the other cell as the source cell.

Coupling through $K^+$ accumulation acts to inject current through the membrane of the PSJ. One may think of the PSJ as a current source which is relatively independent of cell size. Current flowing out through the PSJ must flow in through the rest of the cell with the current spreading itself out evenly. Hence, smaller cells experience higher current densities which cause greater voltage changes. The position of the PSJ makes no difference. The current injected is slightly dependent on cell size since the current–voltage relation is nonlinear. Larger receiving cells experience a slightly larger current.

Electric field coupling, in contrast, induces a voltage that is highly spatially dependent, depends on the propagation velocity of the transmembrane voltage waveform over the membrane and increases with increasing cell size [25].

The peak voltage induced was increased at the same time that the resting level of the cell was reduced. Both these factors contributed to an increase in voltage oscillation amplitude. Of the two factors, the resting level was always affected as much, if not more, than the peak induced voltage. Decoupling two cells connected by a PSJ should result in a small depolarization in the resting levels of the cells.

During the active phase of the ECA, the peak $[K^+]_e$ reached a saturation level (10.4 mM) unlike the peak voltage in the receiving cell. After the peak $[K^+]_e$ saturated, the region of the peak $[K^+]_e$ would expand as the induced voltage increased. This is demonstrated in Fig. 8 where the $[K^+]_e$ normalized with respect to the peak $[K^+]_e$ is shown along the entire length of the PSJ for three different cases. The peak extracellular potassium concentrations for the three cases were not very different, about 10.3 mM, yet the peak induced voltages range from $-67$ to $-65$ mV. The model suggested that the peak induced voltage increased with the increase of the extent of the $[K^+]_e$ elevation. Furthermore, it was assumed that the interstitial volume outside the PSJ was large enough to buffer the $K^+$ efflux, resulting in a negligible change in $[K^+]_e$ outside the PSJ. If this assumption does not hold, possibly due to some pathological condition, and $[K^+]_e$ does increase outside the PSJ, diffusion of $K^+$ from the PSJ will be diminished, resulting in larger oscillations of $[K^+]_e$ and, subsequently, voltage.

The conductance of the cell body was not matched to the conductance of the PSJ since channel densities may change in different regions of the cell. The densities chosen for PSJ are based on those for a membrane with uniform properties. Differing channel densities may lead to greater coupling if a greater concentration of $K^+$ channels are present along the PSJ. This increased density would only have to be local for increased coupling.

The perpendicular bend observed in some PSJ [23], [24] may serve to increase the length of the PSJ which will greatly enhance any coupling effects. The cells are ellipsoidal and get narrower at the ends. A 2-μm-long PSJ without a bend might actually go completely though the cell if the PSJ were to occur near an end. Coupling may also be enhanced by the presence of more than one PSJ between cells. It has been observed that small intestinal smooth muscle cells of approximately 400 μm in length have about ten PSJ per cell [23].

In conclusion, coupling between smooth muscle cells via extracellular $K^+$ accumulation can reach significant levels with the presence of one or more PSJ between the cells. The coupling is increased with increased PSJ length, a decreased PSJ gap and a lower conductance in the receiving cell.

REFERENCES


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