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# Investigation of Action Potential Propagation in a Syncytium

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Certain excitable cells, such as those in cardiac and smooth muscle, are known to form electrical syncytia. Cells within a syncytium are coupled to adjacent cells by means of structures known as gap junctions, which provide electrical continuity between cells. This results in the spread and propagation of electrical activity, such as action potentials (APs), from the originating cell to other cells in its syncytium. We propose that this ability of APs to propagate through an electrical syncytium depends on various syncytial features, and also the AP profile. The current study attempts to investigate these various factors using a computational approach. Simulations were conducted on a model of a three-dimensional syncytium using the NEURON simulation platform. The results confirm that the capacity of action potentials to propagate in a syncytium is influenced by the features of the action potential, and also the arrangement of cells within the syncytium. The excitability of biophysically identical cells was found to differ based on the size of the syncytium, their location within it, and the extent of gap junctional coupling between neighboring cells. Only a window of gap junctional coupling levels allowed both the initiation and propagation of action potentials. The results clearly exhibit the role of AP diversity and syncytial features in determining the spread of action potentials. This has significant implications for understanding the functioning of syncytial tissues, such as the detrusor smooth muscle, both in physiology and in disease.

## INTRODUCTION

Cells in certain tissues, such as cardiac muscle, smooth muscle and liver, are known to form three-dimensional electrical syncytia (Eisenberg *et al*., 1979). In a syncytium, cells are electrically coupled to adjacent cells by means of protein structures known as gap junctions. These gap junctions provide intercellular pathways for the exchange of ions and other small molecules (Meşe *et al*., 2007). This allows electrical activity, such as action potentials (APs), to spread from one cell to another. Therefore, in a syncytium, the electrical

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activity that is recorded at any cell need not necessarily have originated in that cell, but could have been propagated from a neighboring cell. Also, the electrical response exhibited by a cell in a syncytium depends not only on the biophysical properties of that individual cell, but is also influenced by various syncytial features. These include the extent of electrical coupling between cells, the size of the syncytium, the arrangement of cells in the syncytium, and also the location of the cell within the syncytium. We propose that the ability of APs to propagate through a syncytium is affected by these syncytial features. In addition, the AP profile itself is also likely to determine its capacity to propagate, as was demonstrated in a preliminary study (Appukuttan *et al*., 2015b). The latter is particularly relevant to the detrusor smooth muscle (DSM) of the urinary bladder wall, as DSM cells are known to form electrical syncytia (Fry *et al*., 2004), and exhibit action potentials of varying profiles, i.e. varying in shape and size (Meng *et al*., 2008). Neither the origin nor the need for this diversity in AP profiles is presently understood. Though the present study is relevant to electrical syncytia in general, we direct our focus on the DSM of the urinary bladder wall in view of the added complexity of diversity exhibited in AP profiles.

The urinary bladder manages both the storage as well as voiding of urine. During the storage phase, the bladder wall undergoes localized contractions to maintain tone as the bladder increases in volume with the accumulation of urine (Drake *et al*., 2003; Andersson, 2010; 2011). In the voiding phase, coordinated contractions along the bladder wall result in emptying the bladder. Studies have attributed the localized contractions to spontaneously occurring APs, while the coordinated contractions are a result of nerve-evoked APs (Andersson, 2011). It is imperative to note the role of APs in both the phases – storage as well as voiding. The former warrants limited spread of the APs, whereas the latter requires a wider coordinated spread. Therefore, the regulation of AP propagation through a syncytium is crucial to the physiological functioning of the detrusor.

Experimental investigation of the electrophysiological properties of syncytial tissues, especially the detrusor, is inherently difficult owing to the small size of the cells and their complex innervation. It is further compounded by

the need for simultaneous impalements of multiple cells in the syncytium, in order to study syncytial features (Bramich and Brading, 1996; Hashitani *et al*., 2004). Under such circumstances, a computational approach holds much promise in obtaining a better understanding of the syncytial interactions, and their influence on the exhibited electrical properties. Here, we have extended an existing syncytial model of the detrusor (Appukuttan *et al*., 2015a), by incorporating mechanisms for generating APs in each of the cells. In a preliminary study we had demonstrated how a single AP mechanism can produce a variety of AP profiles owing to propagation in a syncytium (Appukuttan *et al*., 2015b). In the present work we analyze the initiation and propagation of APs having different profiles under different syncytial environments.

The detrusor, as stated earlier, is known to exhibit multiple AP profiles. The DSM cells possess an ensemble of nine or more different ion channels that contribute towards the generation of these AP profiles (Brading, 2006; Brading and Brain, 2011; Petkov, 2011; Steers and Tuttle, 2009), and a model for their AP generation mechanism has not been satisfactorily developed. As the objective of the current study is not the interpretation of DSM APs, but rather the investigation of syncytial features and AP profile in determining the propagation of APs through a syncytium, we have employed the classical Hodgkin-Huxley (HH) AP generation mechanism in our model. This offers a well understood paradigm for the analysis of syncytial features. The study undertaken here significantly extends our understanding of the physiology of syncytial tissues.

## METHODS

A three-dimensional (3-D) model of detrusor smooth muscle syncytium was developed on the NEURON simulation environment, a compartmental modeling platform (Hines and Carnevale, 2001), as described by Appukuttan *et al.* (2015a). This primarily involved three major tasks: (i) modeling of the individual cells, (ii) development of gap junctional coupling mechanism, and (iii) arrangement of cells in 3-D to form a syncytium. Cells in the original model were inherently passive, i.e. non-excitable. To enable the cells to produce action potentials, each cell in the syncytium was endowed with identical active mechanisms. In most of the simulations, these were in the form of

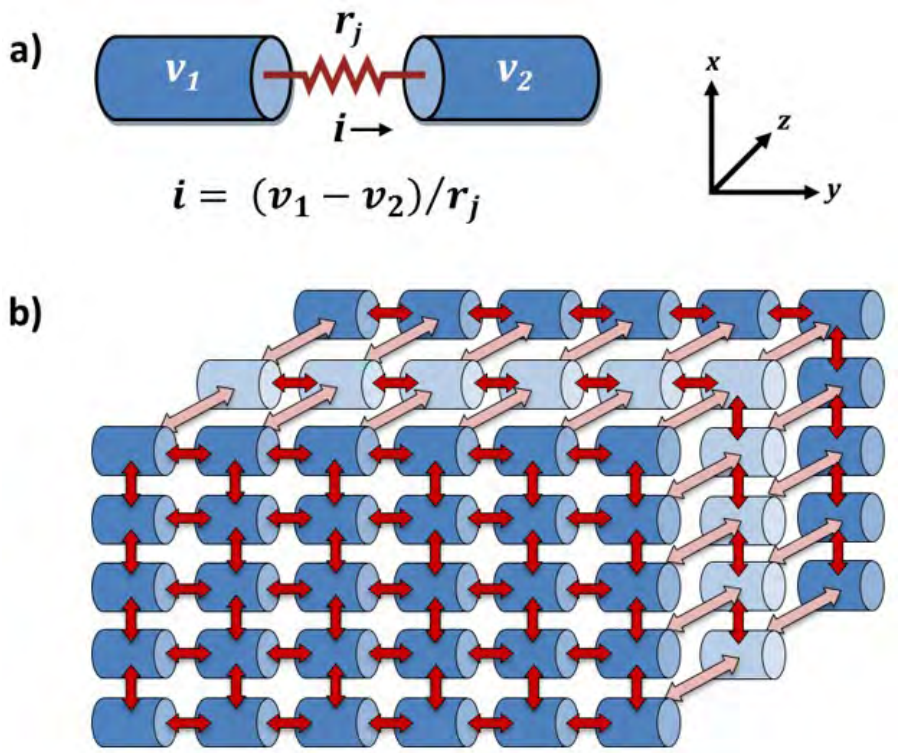


**Figure 1:** Conceptual representations of (a) gap junctional coupling between two cells modeled as a resistive pathway, (b) a 3-D syncytium with a cubic lattice arrangement of cells. Figure adapted from Appukuttan *et al*., 2015b.

Hodgkin-Huxley (HH) channels, unless otherwise specified. Figure 1 shows a simplified representation of the 3-D syncytium having a cubic lattice arrangement of cells, with adjacent cells being coupled by means of resistive pathways denoting gap junctions. Every cell in the syncytium, except the peripheral cells by virtue of their location, was coupled to six other cells – two along each axis. The size of the syncytium was 5-cube, i.e. 5 cells along each axis. This corresponds to experimental studies that have revealed functional syncytia containing up to 100 cells (Neuhaus *et al*., 2002). Simulations involving changes in the syncytial size have been stated wherever pertinent. APs were elicited by means of two types of stimuli: (i) intracellular current injection in the form of a rectangular current pulse, and (ii) synaptic activity simulated by means of an alpha function (Purves, 1976; Bennett *et al*., 1993).

## RESULTS

We first present the effect of variations in AP profiles on its capacity to propagate through a syncytium. This is followed by an investigation of various syncytial features, and their influence on AP propagation.

**Varying AP Shapes**

In a preliminary study (Appukuttan *et al*., 2015b), we had shown the successful propagation of APs, generated via the HH mechanism, through a syncytium. However, the detrusor APs were known to be different in shape and much wider in time course (30–50 ms) than the HH type (< 5 ms). We therefore scouted modelDB (Hines *et al*., 2004), a repository for computational models, for published models of action potentials that showed a good contrast to the HH type. The primary criteria were a much larger time course and variation in overall shape. The action potentials produced in the atrial cell model by Courtemanche *et al*. (1998) fitted our requirements. It was found that the atrial AP, when evoked at a cell in our syncytial model, was unable to propagate even to its immediately neighboring cells (Appukuttan *et al*., 2015b).

An attempt was made to evaluate the underlying factors determining the capability of APs to propagate. As the atrial AP shape was quite different from the HH AP, several potential factors could be listed, such as differences in RMP, threshold, width, shape, rate of depolarization and repolarization, kinetics of underlying current, and so on. It was deemed more suitable, if possible, to compare two similar AP mechanisms, producing APs similar in shape and size, but which differed in their capacity to propagate. This would simplify the evaluation of the underlying factors.

With this objective, we tweaked the HH model, as little as was required, such as to obtain an action potential that failed to propagate through the syncytium. It was found that a minor modification affecting the kinetics of the sodium conductance was sufficient. The following is the equation for sodium conductance in the classical HH model:

$$g_{Na} = \bar{g}_{Na} \times m^3 \times h \quad \text{.....(1)}$$

where $g_{Na}$ is the instantaneous sodium conductance, $\bar{g}_{Na}$ is the maximum sodium conductance, $m$ is the activation parameter and $h$ is the non-inactivation parameter ($0 \leq m,h \leq 1$). This equation was altered to:

$$g_{Na} = \bar{g}_{Na} \times m^4 \times h \quad \text{.....(2)}$$

thereby slowing the activation kinetics of sodium conductance. This results in a rise in the AP threshold owing to the need for increased inward current to become regenerative. We shall call this modified model henceforth as 'HH-mod'.

A comparison of the action potential shapes is illustrated in Figure 2a. The overall shape of the HH-mod AP bears

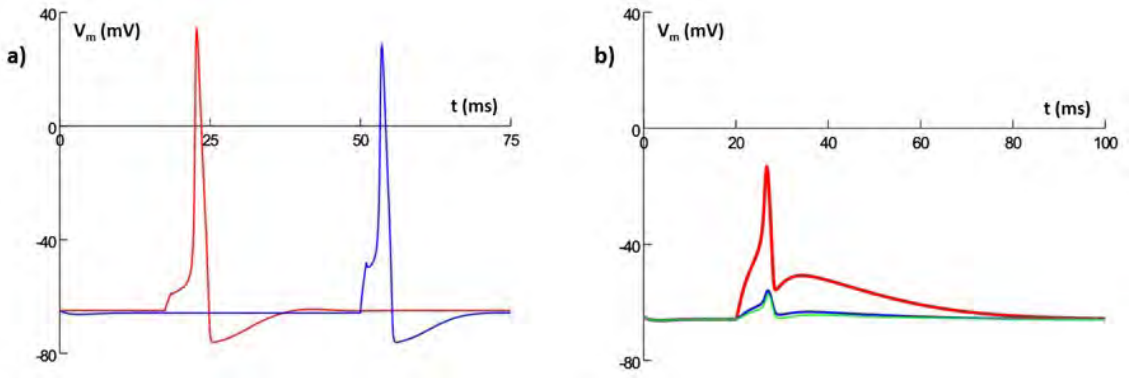


**Figure 2:** (a) Comparison of APs produced by HH (red) and HH-mod (blue) mechanisms in single cell models. Cells stimulated with minimal supra-threshold stimulus via current injection. (b) APs produced in a syncytium model using HH-mod AP mechanism via synaptic stimulus. Response of centroidal cell is shown (in red) along with two of its immediate neighboring cells.

similarities with the HH AP, and also in terms of parameters such as height, width and RMP. Despite these similarities, the HH-mod AP failed to propagate when initiated in a syncytium, as seen in Figure 2b. Cells with HH-mod were found to be less excitable and had a higher threshold for AP generation, requiring a stimulus three-fold higher in magnitude. Thus, the high value of threshold had potential to be a factor in preventing the AP from spreading to neighboring cells. To verify this, it would have been apt to investigate the effect of maintaining a more depolarized RMP, thereby reducing the additional depolarization required to attain threshold. But owing to the voltage dependence of $Na^+$ conductance, this would result in the inactivation of $Na^+$ channels, and thus reduction of the net inward current, leading to a failure in producing APs (a classical 'depolarization block').

As an alternative, to test the effect of threshold, we decided to hyperpolarize the RMP for cells with the HH mechanism and check for any change in its capacity to propagate. The RMP of the cells was hyperpolarized from -65 mV to -75 mV. It was verified that this did not significantly shift the absolute value of threshold, the change being a reduction by $\approx$ 1 mV. The larger depolarization now required to attain threshold also translated to reduced excitability. On applying a minimal supra-threshold synaptic stimulus to the centroidal cell in the syncytium, it was observed that an AP was produced in that cell, but it failed to propagate to any of its neighboring cells, the latter only undergoing a sub-threshold depolarization, as shown in Figure 3a. If the stimulus was increased, then the AP attained a greater height and

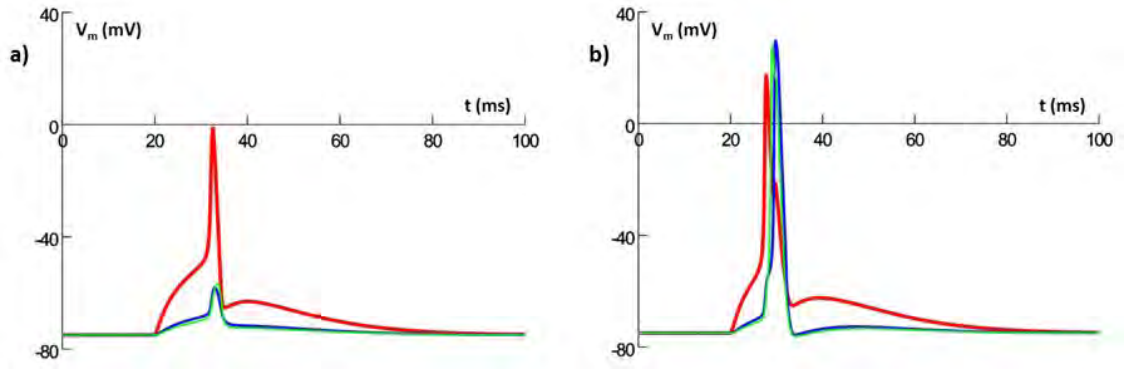


**Figure 3:** Effect of maintaining a hyperpolarized RMP on AP propagation in a syncytium, under application of (a) a minimal supra-threshold stimulus, (b) a higher supra-threshold stimulus. The cells were endowed with HH mechanism. Response of the centroidal cell is shown in red, along with two of its immediate neighboring cells.

now succeeded in spreading to its neighboring cells, and subsequently also through the rest of the syncytium, as illustrated in Figure 3b. Therefore, in conclusion, it has been shown that the AP threshold plays a crucial role in determining its capacity to propagate. The above findings also imply that in a syncytium consisting of identical cells, the ability of cells to generate propagating APs could depend upon the pattern of innervation. Densely innervated cells would be more likely to produce propagating APs as compared to cells with sparse innervation.

## Varying Topology

In the previous section, we investigated AP properties in a syncytium with a fixed topology – simple cubic lattice arrangement with each interior cell coupled to six other cells, two along each axis. Here, we altered the syncytium topology such that only 80% of the cells, picked from a uniform distribution, along each axis were functionally coupled to neighboring cells. This resulted in higher input resistances of the cells, and thereby greater excitability. It was verified that each cell in the syncytium continued to remain electrically interconnected, and that APs generated from HH mechanism continued to spread throughout the syncytium. Next, we replaced the HH with the HH-mod mechanism that had previously failed to produce propagating action potentials. On applying supra-threshold stimulus, it was found that these APs now propagated through the entire syncytium as shown in Figure 4a. Figure 4b shows that even the atrial action potential model was able to spread across the syncytium with the modified syncytial topology.

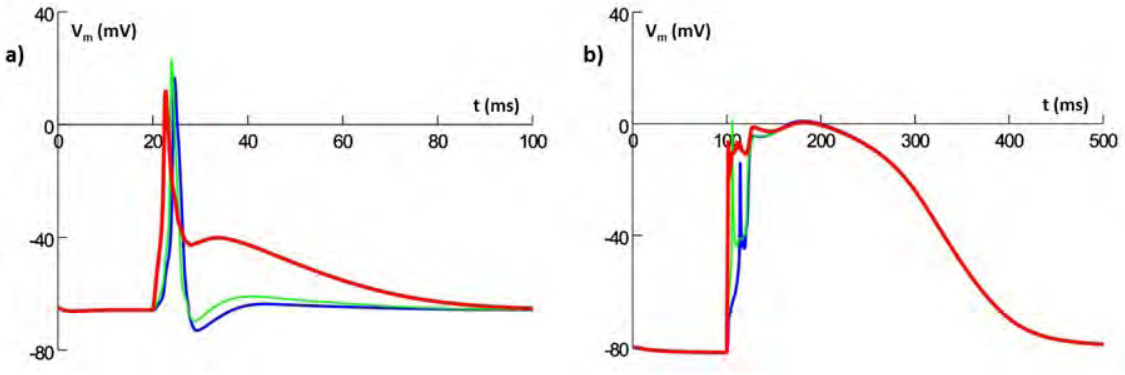


**Figure 4:** Propagation of APs produced from (a) HH-mod mechanism and (b) atrial cell model, under modified syncytial topology. Response of the centroidal cell is shown in red, along with two of its immediate neighboring cells.

## Differences in Excitability

In the previous section, we saw that differences in excitability could potentially impact AP propagation. As all the cells in the syncytium have been endowed with identical biophysical properties, it might be expected that they exhibit similar electrical properties. But in the case of a syncytium, syncytial parameters come into play and thereby influence the electrical properties of the cells, such as their excitability. These include the size of the syncytium, the location of the cell within the syncytium, the syncytial topology and the extent of coupling between cells. Strength-duration curves help characterize the excitability of cells and these were developed here under different syncytial environments.

Figure 5a shows the strength-duration relation for the centroidal cell in syncytia of varying sizes – viz., 3-, 5-, 7-, 15-cube, and also for a single isolated cell. It is seen that the excitability is not greatly affected by changes in the syncytial size, especially beyond 5- cube, with syncytia of smaller size showing marginally greater excitability. In comparison, a single isolated cell is markedly more excitable. A much greater variation in excitabilities is found when considering cells at different locations in a syncytium, as shown in Figure 5b. Cells located at the vertices exhibit highest excitability followed by cells on the edges, then surface cells, with the centroidal cell found to be least excitable. This trend corresponds to the number of directly coupled neighboring cells at these locations. We then analyzed the strength-duration curves for the same cell in a syncytium of fixed size, here the centroidal cell in a 5-cube syncytium,

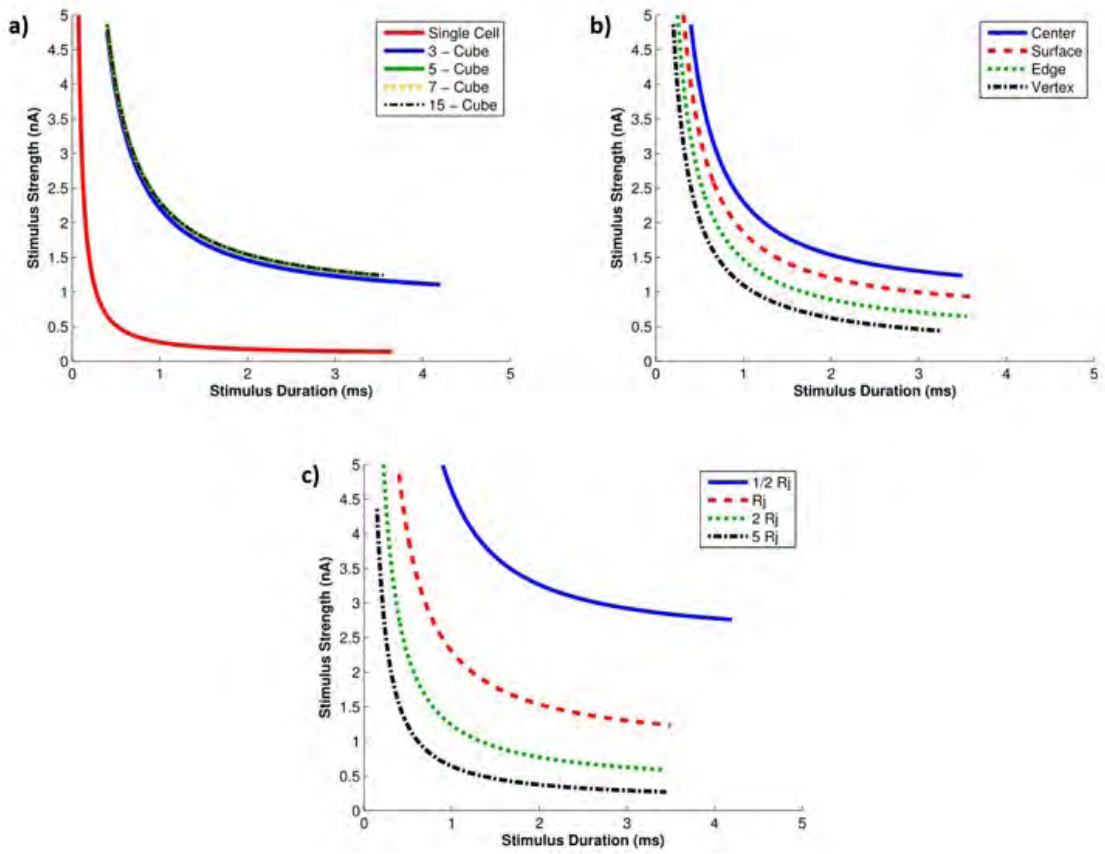


**Figure 5:** Strength-duration relations for (a) the centroidal cell in syncytia of varying sizes, (b) cells at different locations in a syncytium of size 5-cube, (c) the centroidal cell in a syncytium of size 5-cube under varying levels of coupling.

under varying levels of gap junctional coupling (Figure 5c). It was found that with increased coupling, *i.e.* reduced gap junctional resistance, the cell became less excitable and eventually ceased to elicit action potentials. Correspondingly, decrease in the coupling caused the cell to be progressively more excitable. The above observations, in totality, exemplify the strong influence of syncytial parameters on the behavior of otherwise identical cells.

## The Coupling Window for Action Potential Propagation

The above results demonstrated that changes in the strength of gap junctional coupling could have profound effects on AP generation. Here we take this further and explore its effect on AP propagation in a syncytium. Gap junctional resistance was varied over a wide range of values with minimal supra-threshold synaptic stimuli being provided at the centroidal cell of the syncytium. The response of the syncytium was noted in terms of its

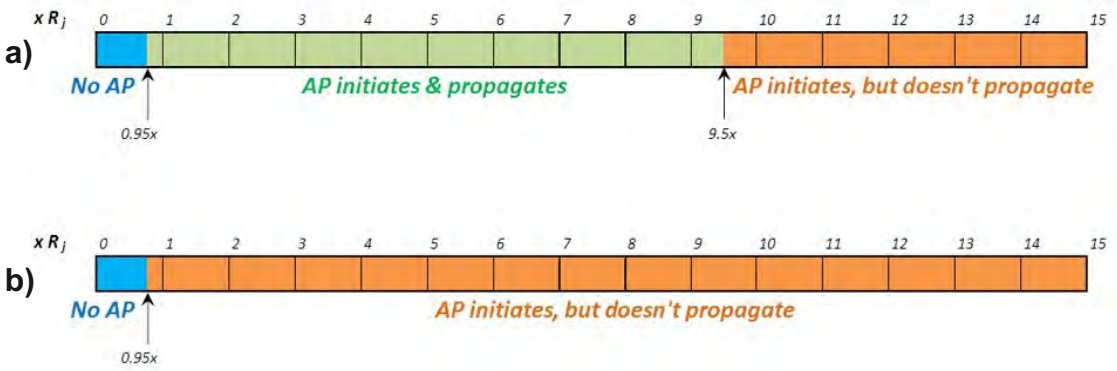


**Figure 6:** Effect of varying gap junctional resistance ($R_j$) on AP initiation and propagation for (a) HH mechanism, (b) HH-mod mechanism.

capacity to generate an AP at the centroidal cell, and its ability to propagate through the syncytium.

Figure 6a summarizes the behavior of the syncytium, when each cell is equipped with HH mechanism, under varying levels of coupling. As the synaptic stimuli is of minimal supra-threshold strength, any reduction in the gap junctional resistance (*e.g.* 0.95 $R_j$) results in a failure to generate an AP at the centroidal cell. For increased values of resistance, *i.e.* lower coupling, an AP is initiated at the centroidal cell and this propagates through the whole syncytium. Further increase in the resistance ($\geq$ 9.5 $R_j$) results in failure of AP propagation, with only the stimulated centroidal cell exhibiting an AP. Thus, there exists only a window of gap junctional coupling strengths for which the generated AP is capable of spreading through the syncytium.

Figure 6b shows a similar analysis for a syncytium having cells with HH-mod mechanism. Here, no such window exists for which the generated AP propagates to the rest of the cells. Reduction in the gap junctional resistance, as previously, leads to a failure in AP generation, while for higher values the generated AP lacks the capacity to propagate in a syncytium. The trend therefore depends upon the mechanism of AP generation, and thus also on the resultant AP profile.

## DISCUSSION

Cells with identical biophysical properties are expected to exhibit identical electrical responses. But this does not hold true in the case of syncytial tissues. In a syncytium, a cell's response is additionally influenced by a host of syncytial factors as discussed in the current study. It was seen that the ability

of APs to propagate through a syncytium is also influenced by the AP profile. Therefore, the propagation of an AP generated from a particular mechanism does not guarantee the successful propagation of an AP generated from a different mechanism. In the case of tissues such as the detrusor, this is of particular importance as APs of diverse shapes are recorded even from a single cell. This could suggest the presence of multiple AP generation mechanisms, or the presence of a single mechanism and its variable modulation due to cellular factors. Thus, certain APs produced in a cell could have the ability to propagate to other cells whereas other APs might not, leading to differences in their physiological roles.

The excitability of a cell was found to depend upon its location within the syncytium, as indicated by the strength-duration curves. Cells on the periphery were found to be more easily excited in comparison to those in the interior. As we move from the periphery to the interior, the number of directly coupled neighboring cells increases, *i.e.* more shunting pathways for charge to dissipate through, leading to lower excitability. This fits well with reports in experimental studies that spontaneous action potentials and calcium transients are found to originate at bundle boundaries (Hashitani *et al*., 2001, 2004).

Tomita (1967) reported that for the guinea-pig vas deferens, another syncytial smooth muscle organ, in 80% of the cells that were stimulated by intracellular current injection, no AP could be triggered. Stimulus strengths up to 4 nA were employed. These same cells were found to exhibit action potentials when stimulated via large external electrodes. Such observations can be explained using our model of smooth muscle syncytia. As opposed to the detrusor smooth muscle, the guinea-pig vas deferens is reported to be electrically well coupled (Tomita, 1967; Bywater and Taylor, 1980; Rahman *et al*., 2009), and hence would have much lower gap junctional resistances. From the strength-duration curves for varying degrees of coupling in our simulations, it can be seen that for increased levels of coupling action potentials are not elicited under such stimulus even with strength up to 5 nA and durations up to 50 ms. This is because in a well coupled syncytium, injected current will tend to dissipate heavily into neighboring cells, thereby limiting its capacity to accumulate charge within the cell to depolarize towards AP

threshold. When large external electrodes are used, several cells in the vicinity are simultaneously stimulated, thereby reducing the potential gradient between neighboring cells. This results in lower degree of dissipation from any given cell and therefore more charge build-up within the cell.

From the studies involving variations in the extent of coupling between cells, it is conceivable that myogenic changes at the syncytial level could lead to pathology. For example, the spread of spontaneously occurring action potentials could lead to aberrant contractions as characterized by unstable bladders. Healthy bladder cells exhibit spontaneous spiking, but these apparently lack the ability to propagate through the syncytium; possibly restricted to a single cell, or small bundles of cells. It has been hypothesized that during detrusor instability, an increase in the gap junctional coupling takes place (Brading, 1997), thereby allowing the spread of these spontaneous action potentials. This is supported by experimental studies, using electron microscopy and immunolabeling, which suggest an increase in gap junctional coupling under pathology (Elbadawi *et al*., 1993; Haferkamp *et al*., 2004; Neuhaus *et al*., 2005). It is interesting to note that, in the case of HH, there exists only a window of gap junctional resistances which allows both the occurrence of the APs and their spread. For values above this window the APs would fail to propagate, and at lower levels APs would not be produced owing to the difficulty in exciting cells. An implication of this is that, in an unstable bladder, the propagation of spontaneous action potentials could be therapeutically targeted by modulating the gap junctional coupling.

One of the limitations of the present work is that we employed AP mechanisms which are not physiologically accurate for the tissue under consideration. We employed these as they offered a well understood paradigm for the analysis of syncytial features. Once a physiologically relevant AP model is developed for the detrusor, it can easily be substituted into the model. An elaborate study of the various syncytial features, such as that undertaken here, would have been improbable with an experimental approach owing to the inherent difficulties and limitations. It is evident

that changes in one or more of the syncytial factors could lead to pathology, and consequently are targets for therapy. The results presented here provide considerable insight into the functioning of syncytial tissues, and help further our understanding of syncytial tissues both in physiology and in disease.

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