A general mathematical model of transduction events in mechano-sensory stretch receptors

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Abstract

Crayfish (\textit{Astacus astacus}) muscle stretch receptors show strong homology to mammalian muscle spindles and bipolar neurons in \textit{D. melanogaster}. All are typical, non-ciliated, stretch-sensitive, afferent neurons. Such receptors are observed in many species and perform an important sensory role. However, they are poorly characterised. A previous study reported a bio-mechanical and behavioural model of \textit{A. astacus} stretch receptors, which used the principles of elasticity and tension in a spring to describe the adaptation of a mechano-sensory ending. This model described the changing mechano-sensitive currents in the receptor when subjected to a stretch protocol. Here, we re-implement and extend this model. Notably, we introduce additional descriptions of voltage-gated channels that are suggested to contribute to stretch receptor mechano-transduction. Our model presents a more complete picture of the initiation of the mechano-receptor potential in response to a stretching stimulus. The inclusion of voltage-dependent sodium and potassium currents in addition to the initial mechano-sensitive sodium current allowed the model to account for most of the initial stretch response of the receptor. This preliminary model has potential for extension to describe fully the behaviour of non-ciliated mechano-sensors across species and predict the molecular mediators of mechano-transduction.

Keywords: ion channel, mechanosensation, muscle spindle, stretch receptor, modelling

Introduction

Mechano-sensation plays a key role in the ability of organisms to sense and interact with each other and their environment. Mechano-receptors detect mechanical stimuli such as tension, stretch and pressure. They have obvious roles in many
forms of touch sensation, as well as proprioception and internal regulation (Hunt et al. 1978; Carr et al. 2001; Calabrese et al. 2002). Mechanoreceptors are also involved in hearing, and they form an integral part of vertebrate auditory hair cells (Corey et al. 2004; Farris et al. 2004). Not only are mechano-sensory endings central to sensory modalities, but they also show a large degree of conservation between diverse animals.

Here we consider the non-ciliated stretch receptors, represented by type II sensory neurons in arthropods and muscle spindle cells in vertebrates. Such mechano-sensory endings have been studied in Caenorhabditis elegans, Drosophila melanogaster, Astacus astacus, Trachemys scripta elegans and Rattus norvegicus, amongst others (Rydgqvist and Swerup 1991; Goodman and Schwarz 2003; Farris et al. 2004; Goodman et al. 2004; Simon et al. 2010). In all of these species, whilst individual stretch receptors are specialised for specific functions, there are underlying anatomical commonalities. These anatomical similarities suggest an evolutionary relationship between them, which in turn underpins the hypothesis that these endings share a common physiological mechanism (Bewick et al. 2005; Hamill, 2006). Nonetheless, beyond a couple of candidates for a primary mechano-transducer, little is currently known about the underlying physiology of stretch-sensitive endings.

An alternative approach to understanding stretch receptor function involves computational modelling. Predictions from modelling can be compared with experimental data recorded from stretch receptors. This approach has produced a model of the electrical behaviour of the mechano-sensitive response of type-II, non-ciliated stretch receptors of the crayfish A. astacus and Pacifastacus leniusculus (Swerup and Rydgqvist 1996). This model was a significant step in understanding mechano-transduction.

Whilst an important first step, the model for crayfish stretch receptors was limited to describing the initial processes of mechano-transduction. The model described the contribution of a mechano-sensory sodium channel (MSC) in relation to the electrical adaptation of the afferent ending. It did not have the ability to describe any further components of this complex system, such as other ion channels known to be essential in mammalian spindle cells. As a result, the model had limited application in stretch receptors more generally.

In order to explore the utility of a mathematical model in describing the full response of a mechano-sensory ending, the mathematical relationships used in the original model were used to build a new model of a stretch-sensitive ending. Subsequently, extensions to the model were implemented to encode voltage-activated channels, which are also present in mechano-sensory endings.

**Methods**

*Modelling stretch*

The principle relationships used to model a stretch receptor are based on the model of Swerup and Rydgqvist (1996). The equations below are numbered to correspond to the stages detailed in the accompanying diagram (Figure 1). The crayfish stretch receptor was mathematically described as an adapting spring, with a linear
component in series with a Kelvin-Voigt element (Swerup and Rydqvist 1996). These were mathematically linked to the open probability of a mechanically-gated sodium channel (MSC). Principally, the tension in the receptor ($\sigma_m$) varies with the extension ($e$), given by:

$$\sigma_m = k \cdot e_2 = k_2 \cdot e_2^{n+1} = k_1 \cdot e_1 + B \cdot \frac{de_1}{dt}$$  \hspace{1cm} (1)$$

where $e_1$ is the linear component of the extension, representative of the tension in the inelastic, tendinous capsule of the receptor, $e_2$ is non-linear, representing the elastic components of the receptor, such as the membrane and muscle [$e = e_{linear} + e_{non-linear}$], $k$ is a non-linear parameter relating tension and extension, $k_2$ is a non-linear spring constant (2,200 kPa), $k_1$ is a linear spring constant (400 kPa), $B$ is the Dashpot constant of the Kelvin-Voigt element (12kPas) and $n$ is a power constant for the non-linear spring (1.5).

**Modelling the MSC adaptation**

Within the ending, the open probability ($P_o$) of the MSCs is dependent on the tension in the muscle according to the following:

$$P_o = \frac{1}{(1 + k_b \cdot \exp[-s \cdot (\frac{\sigma_m}{m})^q])}$$  \hspace{1cm} (2)$$

where $k_b$ is a Boltzmann constant of the MSC (106), $s$ is the MSC sensitivity constant (0.00277 Pa-1) and $m$ is a tension conversion factor (25).

This relationship
describes the likelihood of MSCs being open for a given extension of the receptor. The current flowing through these channels is therefore:

\[ I_s = P_O \cdot g \cdot (E_{rest} - E_{rev}) \]  

(3)

where \( g \) is the maximum channel conductance (2.5mS), \( E_{rest} \) is the resting membrane potential (−65 mV), and \( E_{rev} \) is the MSC reversal potential (10 mV). Finally, the membrane potential can be calculated as:

\[ E_m = E_{rest} - \left[ \frac{1}{C_m} \left\{ \left( 1 + k_b \cdot \exp[-s \cdot (\sigma - \sigma_0)^q] \right) \cdot I_s + g_{leak} \cdot (E_{rest} - E_{rev}) \right\} \right] \]  

(4)

where \( q \) is a power constant (1) and \( C_m \) is the membrane capacitance (4.3nF).

**Modelling voltage-gated channels**

All the above equations and constants are as stated by Swerup & Rydqvist (1996). In order to determine whether voltage-gated channels could be incorporated into this model, mathematical descriptions of neuronal, voltage-gated sodium channels (\( VNaCs \)) and potassium channels (\( VKs \)) (Angelino and Brenner 2007; Platkiewicz and Brette 2010) were incorporated. Specifically:

\[ g_{Na} = \frac{P_V \cdot (Na_{rev} - E_m) + g_{leak} \cdot (E_{leak} - E_m)}{C_m \cdot E_m} \]  

(5)

where \( Na_{rev} \) is the \( VNaC \) reversal potential (50 mV), \( g_{leak} \) is the \( VNaC \) leak conductance (8pS), \( E_{leak} \) is the membrane leak potential (−75 mV) and \( P_V \) is the \( VNaC \) open probability, i.e., the likelihood of a voltage-gated channel opening at a particular membrane potential, which is:

\[ P_V = \frac{1}{1 + \exp \left( \frac{(E_m - E_{act}) - \sigma_{Na}}{k_{Na}} \right)} \]  

(6)

where \( E_{act} \) is the \( VNaC \) activation potential (−50 mV), \( k_{Na} \) is a \( VNaC \) activation constant (6) and \( \sigma_{Na} \) is a function of the \( VNaC \) time constant, expressed as:

\[ \sigma_{Na} = 1 - \exp \left( \frac{-t}{\tau_{Na}} \right) \]  

(7)

where \( \tau_{Na} \) is the \( VNaC \) time constant (10) and \( t \) is time. The \( VK \) channels were modelled similarly with corresponding constants (\( KE_{rev} = -100 \text{ mV} \), \( K_{leak} = 2 \text{nS} \), \( K_{act} = 5 \text{ mV} \), \( k_K = 5 \), \( \tau_K = 10 \)).

**Implementation of the model**

Mathematical descriptions of the crayfish stretch receptor were encoded in Matlab®. All constants required for the simulation were established at the start of the programme. The stretch protocol was simulated as an incremental increase in receptor length (extension) over 100 iterations. The extension-dependent relationships were encoded within a for loop that updated the extension and all of the dependent relationships, at every iteration. Conditional statements added within
this loop encoded the voltage-dependent components, with these items becoming activated if the model should enter a pre-defined condition. These conditions may be set by the experimenter within the model. The hold and relaxation phases are similarly modelled over 100 iterations and contain identical instructions with the exception of the commands pertaining to the extension of the receptor. All variables, including time, extension rate and the value of all other parameters, are fully modifiable using a standard text editor.

Results

Initially, we reproduced the model of Swerup and Rydqvist (1996) using Matlab®, although we incorporated a modified representation of the stretch stimulus (see below). This model demonstrated the key features of the original model (Figure 2). It exhibited the stretch-induced depolarisation in the receptor, the post-stretch repolarisation observed in the hold phase, and the full repolarisation consistent with the relaxation response, restoring the receptor to its resting potential. However, we also observed closer correspondence with the original, physiological recordings with our model than the previous model. For the stretch rates simulated \(a = 0.01:0.03\) depolarisation of the modelled ending is observed from rest in accordance with that seen in the original model (our model: 0–45 mV; original model: 0–60 mV; recordings: 0–40 mV). Upon entering the hold phase, the dynamic component of the stretch is removed and the potential declines with the tension until it reaches the hold potential (new model: consistent −2 mV to −3 mV; old model: scaled between −15 mV at long stretch, −2 mV to −3 mV at short stretch; recordings: consistently c.−5 mV). This may be due to our modified method used to simulate the stretch length. Whilst the original model used a percentage increase in receptor length to simulate stretch, we modelled the stretch as a constant rate of length increase. Therefore, unlike the original, the absolute stretch is the same for all initial receptor lengths. This method may be more readily applicable to different receptors in different-sized organisms, allowing a single stretch value to be applied to data from a variety of receptors.

The experimental data used to characterise the original model was obtained from crayfish stretch receptors in the presence of TTX and TEA to abolish voltage-gated currents (Rydqvist and Swerup 1991). This allowed MSC-dependent depolarisation to be targeted for analysis and modelling. However, under normal conditions (in the absence of TTX and TEA), a voltage-gated component of receptor adaptation can be observed (Ottoson and Swerup 1984). This component presents itself as a sharp, rapid depolarisation (20 mV) in addition to the initial MSC-dependent depolarisation (30–40 mV). This inward current then rapidly inactivates and the membrane potential returns to the level mediated by MSC-dependent depolarisation alone (Figure 3, left). Therefore, we extended the model to include terms describing neuronal VNACs and VKs, based on known physiological characteristics (Angelino and Brenner 2007; Platkiewicz and Brettle 2010). This augmentation of the model enabled it to mimic previously recorded electrophysiological data from the crayfish receptor, determined in the absence of TTX and TEA (Figure 3, right). In addition to the mechano-sensory depolarisation (for \(a = 0.025\)), the augmented model suggests that voltage-gated channels can be activated by the MSC-mediated
Figure 2. The model accurately reflects *in vivo* recordings. Experimental recordings from the same receptor cell (a and c) were originally modelled (b and d), accurately reproducing the behaviour observed *in vivo* (Swerup and Rydqvist 1996). These traces were mimicked in the re-implementation (e – current data not shown). The re-implementation was achieved in Matlab® through the use of the original equations and the same empirically derived constants used to produce the original model (Swerup and Rydqvist 1996). Stretches are between 10 and 30 μm/ms.

Figure 3. The bio-mechanical model of stretch receptors was expanded to include voltage-gated channels. Experimental recordings from crayfish stretch receptors, in the absence of voltage-gated channels (a) demonstrate the electrically dependent response of the receptor following stretching (stretches of 25 μm/ms) (Ottoson and Swerup 1985). This is mimicked in the implementation of voltage-gated channel components in addition to the initial bio-mechanical model (b).
depolarisation. This results in an initial overshoot with a depolarisation of 25 mV, which subsequently falls off, following VNaC inactivation, to the level of the sustained MSC potential (−40 mV) for the duration of the hold phase (Figure 3).

We then explored whether this model could be expanded to address the mammalian muscle spindle system. This receptor expresses certain differences in its physiology compared to its crustacean counterpart. In particular, mammalian muscle spindle cells operate under different environmental conditions. This was addressed by employing a longer stretch protocol (0.1 mm/ms) to resemble more closely the mammalian system. Previous studies in the electrical behaviour of mammalian muscle spindles have demonstrated that the ending initially depolarises, as with the crayfish, but this is not then followed immediately by a return to the hold potential. Instead, the initial depolarisation is followed by a subsequent after-repolarisation and after-depolarisation (Hunt et al. 1978). Using the modified stretch protocol, we were able to model the initial depolarisation, as expected. In addition, the model exhibited subsequent, smaller depolarisations from the hold potential occur (+15 mV from hold), resulting in a potentiated supra-hold potential (Figure 4).

**Discussion**

Previously, it was shown that the bio-mechanical properties of crayfish stretch receptor mechano-transduction could be modelled with respect to the MSCs within these afferent endings (Swerup and Rydqvist 1996). This was the first attempt to simulate the actual events of transduction as opposed to using a simple input-output approach (Borsellino et al. 1965). We recreated the bio-mechanical model of the crayfish stretch receptor in a new format and extended it. The original model had

![Figure 4. Adapting the model with mammalian-like parameters accurately reflects mammalian recordings.](image)

Recording of a mammalian muscle spindle preparation shows a characteristic depolarisation (2), after-repolarisation and after-depolarisation (3) (grey, adapted from Hunt et al. 1978). The model (black) reproduces this. However, the model currently lacks accurate characterisation of the hold and release phases (4–7) and so these phases of the trace differ (for example, the higher-than-normal plateau in the hold phase).
been shown to be an accurate model of the initial transduction events within the crayfish stretch receptor. By including terms describing neuronal voltage-gated channels, it has been possible to reproduce further events in the primary mechano-transduction process. Nevertheless, electrophysiological studies suggest that mechano-transduction is a complex process involving many more mediators in addition to those modelled here. We anticipate that our model will be suitable for adaptation in the future to accommodate these. By utilising the empirically derived constants that were originally used to parameterize a similar model and incorporating them appropriately into the relationships given, it is possible to produce accurate representations of the mechano-sensitive stretch response observed in the crayfish stretch receptor. Future work will also be aimed at exploring these parameters further to determine their effect on the model’s performance.

There are two key differences in the output of our extended model compared with the original, MSC-centred model. First, we note that the new model focuses primarily on the initiation of the stretch response and hence there is a sharp drop in the potential at the beginning of the hold phase, as approximations are used to frame the rest of the model. Nonetheless, the new model reports a similar hold potential to the original for equivalent stretches. Therefore it is reasonable to maintain that, with additional tuning of this phase of the model, it would behave as the original in this regard. However, the new model appears to represent the original physiological data better in terms of the depolarisation values and the drop-off in potential following the end of the first dynamic phase. We suggest that this is due to new means of implementing the simulated stretch. Secondly, the original model effectively employs an instantaneous stretch stimulus, whereas we used a stimulus that operates over a period of time steps. Consequently, there is a delay in depolarisation apparent in the new model (cf. Figure 2d) that is not present in the original. However, the potential reported at the end of the dynamic phase is similar in both the new model and the original recordings.

Likewise, when a VNaC component is added to the model, the results mimic the observed physiological data. From the model, the post-stretch voltage-dependent depolarisation can be seen as an initial sharp voltage increase, and this is clearly also present in vivo.

With a small modification, the model was also able to produce key qualitative features of electrophysiological recordings in mammalian muscle spindles. The model demonstrates the presence of the initial stretch- and voltage-mediated depolarisation of comparable amplitude with the in vivo recordings of Hunt et al. (1978). Additionally, the model shows other characteristic features of the muscle spindle electrical profile, namely the after-repolarisation and after depolarisation (Figure 4, points 2–3).

Of note in all of the model predictions is the higher-than-expected plateau potential during the hold phase of the simulation. We postulate that this is due to the presence of additional ion channels in the afferent ending that our model does not currently include. In particular, we anticipate a mechano-sensory potassium channel or other voltage-gated potassium channel that is active during the hold phase, which results in this reduced hold potential. This high hold potential is also present in the mammalian simulation. The results here indicate a holding potential approximately 20 mV higher than is recorded in the muscle spindle and 10 mV higher than the crayfish recordings (immediately after cessation of dynamic stretching).
Compared with our current model, stretch receptors therefore exhibit an increase in potassium conductance approaching an additional 50%. However, it is also clear from further simulations that this phenomenon is a separate entity to the existing potassium components of this model (data not shown). We also note that crayfish and muscle spindle recordings both show a decay in the hold potential with time, which our model does not yet account for.

Therefore our model currently suggests that it is likely that further potassium components are present in vivo, mediating the lower hold potential as well as a post-release hyper-polarisation. In addition, experimental studies suggest a role for calcium in the stretch response (Hunt et al. 1978 Ottoson and Swerup 1984; Bewick et al. 2005; Simon et al. 2010). These processes are yet to be modelled. In summary, our model, although preliminary and requiring more extensive validation especially against other species, demonstrates the potential ability to describe a general class of model for mechano-transduction events in non-ciliated, primary, stretch-sensitive afferent neurons across different species. Moreover, it supports the hypothesis that these receptors may indeed share a common physiological mechanism.

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References


