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# Modelling the vascular response to sympathetic postganglionic nerve activity

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## HIGHLIGHTS

- We model the sympathetic-driven contraction of a vascular smooth muscle cell.
- The cell is unresponsive to tonic stimulation at typical sympathetic frequencies.
- We quantify the force produced by the cell in response to sympathetic bursting.
- The response of the cell is strongly dependent on burst amplitude and duration.
- Recordings from hypertensive animals produce significant contractile forces.

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## ABSTRACT

This paper explores the influence of burst properties of the sympathetic nervous system on arterial contractility. Specifically, a mathematical model is constructed of the pathway from action potential generation in a sympathetic postganglionic neurone to contraction of an arterial smooth muscle cell. The differential equation model is a synthesis of models of the individual physiological processes, and is shown to be consistent with physiological data.

The model is found to be unresponsive to tonic (regular) stimulation at typical frequencies recorded in sympathetic efferents. However, when stimulated at the same average frequency, but with repetitive respiratory-modulated burst patterns, it produces marked contractions. Moreover, the contractile force produced is found to be highly dependent on the number of spikes in each burst. In particular, when the model is driven by preganglionic spike trains recorded from wild-type and spontaneously hypertensive rats (which have increased spiking during each burst) the contractile force was found to be 10-fold greater in the hypertensive case. An explanation is provided in terms of the summative increased release of noradrenaline. Furthermore, the results suggest the marked effect that hypertensive spike trains had on smooth muscle cell tone can provide a significant contribution to the pathology of hypertension.



## 1. Introduction

The contractile behaviour of smooth muscle cells (SMCs) in resistance arteries is known to be controlled by the sympathetic nervous system, whose activity exhibits bursting rhythms. In particular, the activity of sympathetic postganglionic neurones innervating such cells comprises intermittent bursts of varying amplitude and frequency (Malpas, 1998). The bursting discharge drives arterial smooth muscle cell contractions, causing vasoconstriction and increases in arterial blood pressure. This activity, in both pre- and postganglionic neurones, is known to exhibit bursting that is entrained to the respiratory rhythm, due to central coupling with respiratory pattern generators (Habler et al., 1994). A quantification of how this bursting activity influences arterial smooth muscle cell contractility is important as changes to sympathetic bursting are characteristic of cardiovascular diseases, such as hypertension and heart failure. This sympathetic nerve activity is known to be elevated in the spontaneously hypertensive (SH) rat and to exhibit amplified sympathetic-respiratory coupling (Simms et al., 2009). Recently, intracellular studies in the SH rat have shown that preganglionic neurones exhibit amplified respiratory modulation in their discharge pattern (vs normotensive

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controls; Wistar–Kyoto rats, WKY), characterised by 2–3 more action potentials per respiratory burst (Briant et al., 2014). However, this amounts to a relatively small ($\approx 1$ Hz) increase in average firing frequency, which is still below the threshold for a mechanical response in many sympathetic effectors (Nilsson et al., 1985; Lacroix et al., 1988; Pernow et al., 1989). Because of this, the contribution of the amplified respiratory-sympathetic coupling to vasoconstriction and the pathology of hypertension is unclear. As we shall see in this paper though, it is not the average firing frequency alone that accounts for change in SMC contractility.

Specifically, to investigate and quantify the influence of sympathetic bursts on the degree of smooth muscle cell tone, we have built a mathematical model of sympathetic transmission to a single arterial smooth muscle cell (SMC). Several sets of differential equations are coupled to provide a pathway from action potential generation in a sympathetic postganglionic neurone (Briant et al., 2014) to noradrenaline release from a postganglionic terminal (Yamada and Zucker, 1992), intra-SMC signalling (Li and Rinzel, 1994; Fink et al., 1999; Lemon et al., 2003; Bennett et al., 2005) and the subsequent cross-bridge formation and contractile force produced by the SMC (Hai and Murphy, 1988). In particular, the latter stages of the model adopts the differential equation model described by Bennett and co-workers (Lemon et al., 2003; Bennett et al., 2005) for the behaviour of SMCs surrounding the rat tail artery. Our model begins with the neural signalling and the consequential release of noradrenaline, that drives this SMC model. We have also revised the assumptions and physiological parameters from Bennett et al. (2005) in the light of physiological data (Julien et al., 2001). This has enabled us to investigate the influence of the pattern of sympathetic postganglionic neurone activity on the contraction of arterial SMCs.

The rest of this paper is outlined as follows. Section 2 provides an overview of the model we have developed, highlighting the key assumptions made and giving reference to the appropriate literature where the individual components of the model were developed. Section 3 presents the simulation methodology and any adaptations to the models. Section 4 contains the simulation results, both those that were used to check the modelling parameters and assumptions against previously published data and also the simulation of the entire pathway. Care is taken to quantify the contractile force observed as a function of various input burst parameters. Finally, Section 5 discusses the results of our modelling in context of the literature and proposes novel hypotheses to be tested experimentally.

## 2. Model overview

Fig. 1 summarises the neurovascular pathway modelled—the transmission of information from a sympathetic postganglionic neurone (SPGN) to an arterial SMC. The model considers separately the mechanisms of action potential generation in a SPGN (Fig. 1A), its transmission to the distal end of the axon, causing release of noradrenaline (NA) from the axon terminal into the neuromuscular junction (Fig. 1B), the subsequent activation of the SMC triggering contraction (Fig. 1C).

This model is novel in that it investigates the of influence sympathetic output on SMC contraction at a cellular level, and can relate sympathetic discharge patterns to contractile response. The system includes a model of a sympathetic neurone (Briant et al., 2014) coupled to a model of neurotransmitter release (Destexhe et al., 1994). The released noradrenaline is used to drive a model of SMC contraction (Bennett et al., 2005). By modelling the vasoconstrictor processes at this level of detail, the influence of sympathetic patterning on arterial smooth muscle cell contractility can for the first time be fully quantified and add to our understanding of increased vascular tone in pathological conditions such as hypertension.

### 2.1. Postganglionic action potential generation and propagation

Action potentials are generated in the sympathetic postganglionic neurone. We use a Hodgkin–Huxley style partial differential equation model of a sympathetic neurone that was reported by Briant et al. (2014) and implemented in NEURON (Carnevale and Hines, 2006). The code for this model has been deposited on ModelDB (senselab.med.yale.edu/modeldb; accession number: 151482). The model is represented schematically in Fig. 1A, and described in brief as follows. A single un-branched axon emerges from the soma (length 500 μm and diameter of 0.5 μm, 20 segments), ending at the site of release of NA. The ion channel currents included in the model are depicted graphically in Fig. 1A. These currents are all present in the soma, with the exception of the leak ($I_{pas}$) that is present throughout the cell membrane. The axon has the Hodgkin–Huxley conductances $I_{Na}$, $I_{DR}$ required for spike generation and also includes N- and L-type calcium currents $I_N$ and $I_L$, because these channels are known to drive synaptic transmission at sympathetic nerve-endings (Rittenhouse and Zigmond, 1999). Spiking in the neurone model was driven by the injection of current pulses (2 nA × 2 ms) into the soma.

The calcium current at the distal end of the axon, generated in response to action potentials arriving from the soma of the neurone model, is used to drive release of NA at the neuromuscular junction. An action potential arriving at the axon terminal of the postganglionic model activates high-threshold voltage-sensitive calcium currents $I_N$ and $I_L$. This calcium influx locally elevates the intracellular concentration of calcium at the terminal/synapse of the axon, $[Ca^{2+}]_{syn}$. Here and in what follows, square brackets $[\cdot]$ are used to describe the concentration of a chemical species, with a subscript, in this case $_{syn}$, indicating a particular sub-concentration.

The kinetics of this sympathetic calcium is determined by the calcium fluxes across the membrane of the synapse ($I_{Ca} = I_N + I_L$ and the calcium pumps) and by calcium buffering:

$$\frac{d[Ca^{2+}]_{syn}}{dt} = -\frac{I_{Ca}}{2F_d d} - \frac{k_t[Ca^{2+}]_{syn}}{[Ca^{2+}]_{syn}+K} + \frac{[Ca^{2+}]_{\infty} - [Ca^{2+}]_{syn}}{\tau_r}. \quad (1)$$

Here, $F_d$ is Faraday's constant and $d$ is the depth of the hemispherical calcium domain. $I_{Ca}$ is the sum of all calcium currents across the membrane $I_N + I_L$, extracted from the distal end of the axon in the SPGN model. The pumping of calcium across the membrane occurs at a rate $k_t$ with Michaelis constant $K$. Calcium is buffered with time-constant $\tau_r$ to a concentration $[Ca^{2+}]_{\infty}$. The calcium concentration $[Ca^{2+}]_{syn}$ drives the release of NA.

### 2.2. Noradrenaline release kinetics

Yamada and Zucker (1992) constructed a differential equation model of transmitter release from a neurone terminal, based on a model by Parnas and Parnas (1988). These kinetics are summarised in Fig. 1B and given by the following equations:

$$\frac{d[F_A]}{dt} = k_b(F_{max} - [F_A] - [V_A])[Ca^{2+}]_{syn}^4 - k_u[F_A] - k_1[F_A][V] + k_2[V_A], \quad (2)$$

$$\frac{d[V_A]}{dt} = k_1[F_A][V] - (k_2 + k_3)[V_A], \quad (3)$$

$$\frac{d[NA]}{dt} = Nk_3[V_A] - k_h[NA]. \quad (4)$$

Here, calcium ions are assumed to reversibly bind to a fusion protein $F$. Four calcium ions bind to this protein at a rate $k_b$, changing it to its activated state $F_A$. The reverse process has an unbinding rate $k_u$. Destexhe et al. (1994) simplified this system by assuming that there exists an inexhaustible pool of pre-docked vesicles $V$, with concentration $[V]$, that are ready for activation. The