Quantitative aspects of L-type Ca$^{2+}$ currents

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Abstract

Ca$^{2+}$ currents in neurons and muscle cells have been classified as being one of 5 types of which four, L, N, P/Q and R were said to be high threshold and one, T, was designated low threshold. This review focuses on quantitative aspects of L-type currents. L-type channels are now distinguished according to their structure as one of four main subtypes Ca$_V$1.1 - Ca$_V$1.4. L-type calcium currents play many fundamental roles in cellular dynamical processes including pacemaking in neurons and cardiac cells, the activation of transcription factors involved in synaptic plasticity and in immune cells. The half-activation potentials of L-type currents (I$_{Ca_L}$) have been ascribed values as low as -50 mV and as high as near 0 mV. The inactivation of I$_{Ca_L}$ has been found to be both voltage (VDI) and calcium-dependent (CDI) and the latter component may involve calcium-induced calcium release. CDI is often an important aspect of dynamical models of cell electrophysiology. We describe the basic components in modeling I$_{Ca_L}$ including activation and both voltage and calcium dependent inactivation and the two main approaches to determining the current. We review, by means of tables of values from over 65 representative studies, the various details of the dynamical properties associated with I$_{Ca_L}$.
that have been found experimentally or employed in the last 25 years in deterministic modeling in various nervous system and cardiac cells. Distributions and statistics of several parameters related to activation and inactivation are obtained. There are few reliable experimental data on L-type calcium current kinetics for cells at physiological calcium ion concentrations. Neurons are divided approximately into two groups with experimental half-activation potentials that are high, $\approx -18.3$ mV, or low, $\approx -36.4$ mV, which correspond closely with those for $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ channels in physiological solutions. There are very few experimental data on time constants of activation, those available suggesting values around 0.5 to 1 ms. In modeling, a wide range of time constants has been employed. A major problem for quantitative studies due to lack of experimental data has been the use of kinetic parameters from one cell type for others. Inactivation time constants for VDI have been found experimentally with average 65 ms. Examples of calculations of $I_{CaL}$ are made for linear and constant field methods and the effects of CDI are illustrated for single and double pulse protocols and the results compared with experiment. The review ends with a discussion and analysis of experimental subtype ($\text{Ca}_v1.1$ - $\text{Ca}_v1.4$) properties and their roles in normal, including pacemaker activity, and many pathological states.

**Keywords:** L-type calcium currents, neuronal modeling, calcium-dependent inactivation

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**Abbreviations:** AHC, auditory hair cells; AM, atrial myocyte; B, Brugada syndrome; BAPTA, 1,2-bis (2-aminophenoxy) ethane-$N, N, N', N'$-tetra-acetic acid; BK, big potassium channel; $\text{Ca}_i$, $[\text{Ca}^{2+}]_i$, internal calcium ion concentration; $\text{Ca}_o$, $[\text{Ca}^{2+}]_o$, external calcium ion concentration; CDI, calcium-dependent inactivation; CH, chromaffin; CICR, calcium-induced calcium release; CORT, cortical; DA, dopamine; DCN, dorsal cochlear nucleus; DRG, dorsal root ganglion; dors, dorsal; DRN, dorsal raphe nucleus; EGTA, ethylene glycol ($\beta$-amino-ethyl ether)-$N, N, N', N'$-tetra-acetic acid; GABA,
gamma-aminobutyric acid; HEK, human embryonic kidney; HVA, high-voltage activated; IC, inferior colliculus; KO, knockout; LD, laterodorsal; LVA, low-voltage activated; Mag, magnocellular; MR, medullary respiratory; med, medial; MID, midbrain; MN, motoneuron; N, neuron; NRT, nucleus reticularis thalami; PC, pituitary corticotroph; PF, Purkinje fiber; PM, pacemaker; RF, renal failure; SA, sino-atrial; SE, serotonergic; SH3-GK, src homology 3 - guanylate kinase; SK, small potassium channel; SM, skeletal muscle; SMM, smooth muscle; SN, substantia nigra; SNC; substantia nigra pars compacta; SON, supraoptic nucleus; SS, disulphide bond; SYMP, sympathetic; TR, thalamic relay; VDI, voltage-dependent inactivation; VM, ventricular myocyte; VWA, Von Willebrand Factor A; WT, wild-type.
1 Introduction

1.1 Perspective

The passage of ions across cell membranes, and within cells, is of fundamental importance in determining the electrophysiological responses of nerve and muscle cells. Such responses are manifested ultimately in the functioning of the nervous and muscular systems, including organs of crucial biological importance such as the heart and brain. In the late 19th and early 20th centuries, key discoveries were made and biophysical theories proposed concerning such ionic...
currents, for example by Nernst (1889), Planck (1890) and Bernstein (1902). With new electrophysiological recording techniques, many advances were made in the 1940’s and 1950’s by, amongst others, in alphabetical order, Eccles, Hodgkin, Huxley and Katz - see Huxley (1959) for a summary. In the 1970’s and 1980’s, much additional insight was obtained when recordings were made of currents through single ion channels, notably by Neher and Sakmann (Hamill et al., 1981). In the last 20 or so years there has been an enormous number of discoveries concerning the factors which determine ionic current flows in neurons and muscle cells. The present review concerns modeling aspects of the class of calcium currents called L-type, which, as will be seen below, have many consequences beyond electrophysiology.

For graphic but brief historical accounts of calcium current discoveries see Tsien and Barrett (2005) and Dolphin (2006). According to the former review, “...it is apparent that Ca$^{2+}$ channels have reached the forefront of the field of ion channel research...due to their vital role in cellular signaling, their diversity, and great susceptibility to modulation...”. Records of the first single channel recording of currents identified as being L-type were given in (Nowycky et al., 1985). More recent single channel recordings are in Cens et al. (2006), where a comparison of results for Ca$^{2+}$ and Ba$^{2+}$ as charge carrier is shown, and Schröder et al. (1998), where the much greater magnitude of L-type currents in failing heart are compared with those in normal heart.

The principal motivation for the analysis and quantitative modeling of L-type calcium currents is that they occur in most nerve and muscle cells. They often play basic roles in pacemaker activity (see Section 5.2) and more generally in regulating spike frequency by inducing afterhyperpolarization, as for example in the hippocampus by coupling to SK channels (Tanabe et al., 1998). Wu et al. (2008) showed that L-type Ca$^{2+}$ current in CA1 pyramidal cells, by coupling to delayed rectifier potassium channels (Kv7.x), can give rise to long-lasting changes in adaptation.

Comprehensive models of nerve cells may include spatial variations or not, but in either case the minimum number of current components is at least 10 and amongst these there should or will usually be included several Ca$^{2+}$ currents. If they are included in a
model, L-type currents require a careful treatment and our aim here is to attempt to summarize several details of their basic properties and modeling which have been employed for many kinds of nerve and muscle cell.

1.2 Ion channels and neurons

Many protein molecules are embedded in the cell membranes of neurons. Some of these molecules are receptors for the main central neurotransmitters glutamate (excitatory) and GABA (inhibitory), as well as transmitter/modulators such as noradrenaline, dopamine, and serotonin all of which are released from vesicles in response to signals arriving at synapses where neighboring cells make close contact. (See for example Cooper et al. (2003) for an introduction to basic neurochemistry and neuropharmacology.) Of particular importance in determining the way in which a neuron behaves in response to electrical and chemical stimuli are other protein molecules which serve as entrance and exit pathways for electrically charged ions. Such molecules are called ion channels.

If an ion channel is relatively more selective for a certain kind of ion, for example, sodium, Na\(^+\), then it is called a sodium channel. The most commonly occurring cation channels in neurons are sodium, potassium and calcium. Such ion channels may be open or closed, which means they may or may not permit the passage of ions through them. One of the chief consequences of the ionic currents which flow through such channels when they are open is the alteration of the electrical potential difference across the cell membrane. In the resting state, this potential difference is in the approximate range from -80 mV to -50 mV. An inward flux of positive ions such as Na\(^+\) or Ca\(^{2+}\) leads to a diminution of the potential difference, called depolarization or excitation, which, if sufficiently strong, may give rise to an action potential or spike. When the membrane is depolarized, ion channels such as those of Ca\(^{2+}\) undergo conformational changes which lead to their opening for certain time intervals. Hence they are called voltage-gated ion channels.
1.2.1 Activation and inactivation

The process of opening the channel is called activation. However, channels may be in several different states because often there is also a process of inactivation which is not simply the cessation of activation. For a channel to be conducting, the inactivation component must be switched off and the activation component switched on. If we denote the probability of activation being on by \( m \) (for example) and the probability of inactivation being off as \( h \), then Table 1 gives the various channel states and their probabilities. It will be seen that the sum of the probabilities in the third column of the table add to unity, as they must. For more details, see, for example, texts such as Levitan and Kaczmarek (1997) or Koch (1999).

| Activation process | Inactivation process | Probability | Conducting state |
|--------------------|----------------------|-------------|------------------|
| Off (deactivated)  | On (inactivated)     | \((1 - m)(1 - h)\) | Non-conducting   |
| On (activated)     | On (inactivated)     | \(m(1 - h)\)    | Non-conducting   |
| On (activated)     | Off (de-inactivated) | \(mh\)        | Conducting       |
| Off (deactivated)  | Off (de-inactivated) | \((1 - m)h\)    | Non-conducting   |

In the case of voltage-gated ion channels, the activation and inactivation probabilities usually depend on voltage and time. Hence if \( V \) denotes membrane potential and \( t \) denotes time, then \( m = m(V, t) \) and \( h = h(V, t) \). As in the pioneering work of Hodgkin and Huxley (1952) on squid axon, the activation and inactivation variables satisfy approximately differential equations whose solution enables one to predict reasonably accurately the ion currents flowing across nerve or other membrane. This is further elaborated on in Section 2.3.

1.3 Voltage-gated calcium channels

Calcium currents, which are found in all excitable cells, were divided into the two main groups of low-threshold or low-voltage activated
(LVA) and high-threshold or high-voltage activated (HVA). The former group contains the T-type (T for transient) and the latter group consists of the types L, N, P/Q and R (L for so called long-lasting, N, either for neither T nor L, or neuronal, P for Purkinje, and R for resistant). For interesting reviews of the history of the discoveries of these various types and the experiments that preceded them, back to 1953, see Tsien and Barrett (2005) and Dolphin (2006).

Although L-type currents, the main topic of the present article, were originally designated as belonging to the HVA group, their properties are diverse (Avery and Johnston, 1996; Lipscombe, 2002), varying greatly with cell-type and ionic environment - see the data below and in particular the review of Lipscombe et al. (2004). They have been implicated as playing an important role in pacemaker activity in some neurons and cardiac cells (see for example, Kamp and Hell, 2000; Mangoni et al., 2003; Brown and Piggins, 2007; Marcantoni et al., 2007; Putzier et al., 2009a, b; Vandael et al., 2010) and being involved in the amplification of certain synaptic inputs (Bui et al., 2006).

Calcium channel molecules have up to four subunits, $\alpha_1$, $\alpha_2-\delta$, $\beta$ and $\gamma$, which may exist in different forms, and which modulate the conductance and dynamical properties of the channel (Dolphin, 2006, 2009; Davies et al., 2010). The ten forms of the conducting pore subunit, $\alpha_1$, lead to an expansion of the above groups (Catterall et al., 2005; Dolphin, 2009) to 10 main subtypes. According to the accepted nomenclature, L-type channels consist of the subtypes $\text{Ca}_{v1.1} - \text{Ca}_{v1.4}$. The remaining “high-threshold” currents, P/Q, N and R are respectively $\text{Ca}_{v2.1} - \text{Ca}_{v2.3}$ and the T-current subtypes are $\text{Ca}_{v3.1} - \text{Ca}_{v3.3}$. Of the L-channel subtypes, sub-type $\text{Ca}_{v1.1}$ is mainly found in skeletal muscle and the subtype $\text{Ca}_{v1.4}$ is found mainly in retinal cells (Lipscombe et al., 2004; Baumann et al., 2004; Catterall et al. 2005; Lacinová, 2005; Dolphin, 2009; Weiergräber et al., 2010). In cardiac myocytes and most central nervous system cells the subtypes are mainly $\text{Ca}_{v1.2}$ or $\text{Ca}_{v1.3}$. See subsection 5.1 for further discussion.

In Figure 1 is shown a recent schematic representation of the molecular structure of a voltage-gated calcium channel, showing the subunits $\alpha_1$, $\beta$ and $\alpha_2-\delta$. Note that until recently the $\delta$ subunit had been thought to straddle the membrane rather than project into
Figure 1: Recent schematic of a voltage-gated calcium channel, taken with permission from Davies et al. (2010). The main pore containing subunit which straddles the membrane is $\alpha_1$ which has 4 juxtaposed components. The $\beta$ subunit is intracellular and the $\alpha_2 - \delta$ subunit projects into the extracellular compartment. In this example there is no $\gamma$ subunit.

the extracellular compartment (Bauer et al., 2010; Dolphin, 2010). Figure 2 schematically depicts some of the structures involved in the important phenomenon of calcium-dependent inactivation, which is elaborated upon in Section 2.

Since there are several different types of calcium current, and in particular high threshold ones, whose current-voltage relations are not completely distinguishing, in order to identify them, pharmacological methods are used. Each channel type/subtype, acts as a receptor for specific molecules, most often toxins, leading to reduced calcium current. In some cells, R-type currents, once thought not to have a specific blocker and which are borderline between HVA and LVA, have been more recently found to be blocked by the tarantula toxin SNX-482 (Li et al., 1997; Newcomb et al., 1998). Table 2, adapted from Striessnig and Koschak (2008) and Catterall et al. (2005), summarizes the main agents used for blocking or
Figure 2: Sketch representation of an L-type Ca\(^{2+}\) channel depicting the mechanism of CDI. Calcium ions are depicted as filled red circles. The calcium binding protein calmodulin is shown tethered to one of the intracellular motifs alongside the EF hand. For the role of calmodulin in inactivation, see Section 2.1. This figure has been composed from figures in Bodi et al. (2005), Dolphin (2009), Davies et al. (2010) and Doan (2010).

partially blocking the various types/subtypes. Note, however, that dihydropyridines, phenylalkylamines and benzothiazepines block all L-type channels to some degree.

It is noteworthy that one of the most important areas in which the quantitative study of L-type (and other) Ca\(^{2+}\) currents plays a fundamental role is in the electrophysiology of the heart. In medicine, L-type calcium currents are the prime target of important calcium channel blockers such the benzothiazapine diltiazem, the phenylalkylamine verapamil and the dihydropyridines such as nifedipine, which are used to treat, \textit{inter alia}, hypertension, angina and cardiac arrhythmias.

Within the above subtypes, various configurations of other sub-units lead to channels, with quite different properties (Dolphin, 2009; Catterall, 2010). Thus, L-type Ca\(_{\alpha1.3}\) variants may have differing current magnitudes and pharmacology (Andrade et al., 2009). One cannot therefore ascribe definite parameters in the dy-
Table 2: Summary of pharmacological agents used to identify various types/subtypes

| Type | Subtype by $\alpha_1$ subunit | Agent (Example)     |
|------|-------------------------------|---------------------|
| L    | Ca$_v$.1.1                    | Dihydropyridines (Nifedipine) |
|      | Ca$_v$.1.2                    | Phenylalkylamines (Verapamil) |
|      | Ca$_v$.1.3                    | Benzothiazepines (Diltiazem) |
|      | Ca$_v$.1.4                    |                      |
| P/Q  | Ca$_v$.2.1                    | $\omega$-Agatoxin IVA |
| N    | Ca$_v$.2.2                    | $\omega$-Conotoxin-GVIA |
| R    | Ca$_v$.2.3                    | SNX-482              |
| T    | Ca$_v$.3.1                    | Kurtoxin             |
|      | Ca$_v$.3.2                    |                      |
|      | Ca$_v$.3.3                    |                      |

namical description of L-type calcium currents based on the subtypes Ca$_v$.1.1 – Ca$_v$.1.4. For example, the $\beta$ subunit regulates current density (defined, for example, as current per unit area) and the properties of activation and inactivation. There are four forms of the $\beta$ subunit, $\beta_3$ and $\beta_4$ being highly expressed in the brain (Dolphin, 2003).

1.3.1 A brief background and useful references

It has become apparent that quantitative descriptions of L-type calcium currents are often a fundamental component in computational modeling of neuronal and muscle cell dynamics. The first descriptions of L-type current dynamics in such a context appear to be those of Belluzzi and Sacchi (1991) and McCormick and Huguenard (1992), although there had been many models containing calcium currents, prior to the division into the above types, for example for cardiac cells. In fact Belluzzi and Sacchi’s (1991) model for a sympathetic neuron in the rat superior cervical ganglion described a high-threshold current which had an inactivation similar to the L-type of Fox et al. (1987) but an activation similar to the N-type current.

For an introduction to fundamentals about ion channels see, for example, Levitan and Kaczmarek (1997). Additional reviews
on voltage-dependent Ca\textsuperscript{2+}-channels pertaining to their molecular structure, nomenclature and function, including modulation and regulation are contained in, for example, in chronological order, Tsien et al. (1988), Bean (1989), Tsien and Tsien (1990), Anwyl (1991), Catterall (1995), De Waard et al. (1996), Jones (1998), Hofmann et al. (1999), Catterall (2000), Ertel et al. (2000), Kamp and Hell (2000), Lacinová (2005), Zamponi (2005) and Catterall (2010). Reviews addressing specific related topics include those on synaptic transmission (Meir et al., 1999; Neher and Sakaba, 2008), T-type currents (Perez-Reyes, 2003; Cueni et al., 2009), calcium-dependent inactivation in neurons (Budde et al., 2002), dynamics of calcium signaling in neurons (Augustine et al., 2003), models of calcium sparks and waves (Coombes et al., 2004), L-type currents in the heart (Bodi et al., 2005), the role of calcium currents in circadian rhythms (Brown and Piggins, 2007), calcium release and the roles of ryanodine receptors in heart and skeletal muscle diseases (Zalk, 2007), Ca\textsuperscript{2+} channels in chromaffin cells (Marcantoni et al., 2008) and calcium dynamics in relation to absence epilepsy (Weiergräber et al. 2010). Calcium ion influx through L-type channels leads via various signaling pathways to the activation of transcription factors such as CREB and hence the expression of genes that are essential for synaptic plasticity and other important cellular processes (Dolmetsch et al., 2001; Hardingham et al., 2001; Mori et al., 2004; Power and Sah, 2005; Satin et al., 2011). The role of calcium ion influx through L-type channels in immune cells has also been recently reviewed (Suzuki et al. 2010). It was also recently demonstrated that calcium currents of L-type, together with R-type, are involved in the activation of SK channels, which attenuate excitatory synaptic transmission in pyramidal cells of the medial prefrontal cortex (Faber, 2010).

Mathematical modeling of the electrophysiology of cardiac cells has a history spanning nearly the last 50 years - see for example DiFrancesco and Noble (1985) - and reviews by Noble (1995), Wilders (2007), Fink et al. (2011) and Williams et al. (2010). Brette et al. (2006) reviews background physiology and biophysics of calcium currents in cardiac cells. The modeling has taken into account details of the dynamics of several ionic currents, particularly calcium currents (as for example in Luo and Rudy, 1994). For a
discussion of the dynamics underlying the large difference between the relatively short action potential duration in neurons and heart cells, see Boyett et al. (1997). In ventricular cardiomyocytes L-type calcium currents play a pivotal role (Benitah et al., 2010) although T-type currents, important in development and in some pathologies (Ono and Iijima, 2010) are also present (Bean, 1989) and play a role in pacemaker activity (Bers, 2008). L-type channels, located in the sarcolemma, are involved in arrhythmias, and are activated by depolarization and inactivated by both voltage-dependent and intracellular Ca$^{2+}$ mechanisms. The inactivation of L-channels, which is elaborated upon below, is complex, not only in cardiac cells, and not completely understood (Imredy and Yue, 1994; Findlay et al. 2008; Grandi et al., 2010). See also Lacinová and Hofmann (2005) and the review of mechanisms of calcium and voltage-dependent inactivation in Cens et al. (2006). The website of David Yue (Calcium signals lab) http://web1.johnshopkins.edu/csl/ contains a wealth of information about calcium dynamics.

In the electrophysiology of neurons and muscle cells, calcium currents usually have crucial roles. Hence there is the need to represent as accurately as possible, in mathematical or computational modeling, calcium entry into cells along with related processes, such as buffering and pumping. The latter two topics are not explored in depth here, but see for example Standen and Stanfield (1982), Blaustein (1988), Tsien and Tsien (1990), McCormick and Huguenard (1992), Tank et al. (1995), Lindblad et al. (1996), Blaustein and Lederer (1999), Stokes and Green (2003), Shiferaw et al. (2003), Rhodes and Llinás (2005), Roussel et al. (2006), Higgins et al. (2007), Friel and Chiel (2008) and Brasen et al. (2010).

2 Quantitative description of L-type Ca$^{2+}$ currents

We are here concerned with deterministic approaches that have been employed in the quantitative description of L-type Ca$^{2+}$ currents. Such descriptions are probably adequate in many preparations although it has not been found to be the case for high rates of action potentials in cardiac myocytes, where a many-state Markov chain
model, used in conjunction with the constant field method (Maha-
jan et al., 2008), was found to be more accurate. See also Jafri et
al. (1998), Sun et al. (2000), Fink et al. (2011), Grandi et al.
(2010) and Williams et al. (2010) for more details on the Markov
chain approach for determining L-type channel-open probabilities.
Destexhe and Sejnowski (2001) contains a brief introduction to such
models, especially for voltage-dependent sodium channels. As far
as can be discerned, until now there have been no Markov models
of L-type calcium channels in non-cardiac cells.

2.1 General description: VDI and CDI

Whereas activation kinetics of L-type channels are voltage-dependent
(Budde et al., 2002; Lacinová, 2005), inactivation has often been
found to have dependence on both voltage and the internal “con-
centration” of calcium ions, as discovered by Brehm and Eckert
(1978) in Paramecium and Tillotson (1979) in molluscan neurons.
The two components are called CDI (calcium-dependent inactiva-
tion) and VDI (voltage-dependent inactivation). A hallmark of CDI
is that it has a maximal effect where the relevant calcium currents
are themselves maximal. Other markers are the reduction in CDI
if Ba$^{2+}$ is the charge carrier or if the buffers EGTA or BAPTA are
present in the pipette (see Budde et al., 2002, for a discussion).

The relative contributions of CDI and VDI vary widely amongst
cell types and modeling these contributions is not always as straight-
forward as in the simplified scheme presented below. Sometimes
CDI may be absent, especially in the case of Ca_v1.4 channels (Koschak
et al., 2003; Baumann et al. 2004, Singh et al., 2006; Wahl-Scott
et al., 2006; Liu et al, 2010). Indeed, often CDI is not included
in modeling and often there is no inactivation at all, neither volt-
age nor calcium dependent, but it is not clear if this renders some
calculations inaccurate.

In Tables A1.1-A1.4 of the Appendix, there are given data for
about 65 studies, which involved L-type (or undefined high thresh-
old calcium) currents. This survey is not exhaustive but represen-
tative of works from 1987 to the present. About half of these are
experimental and about half concern mathematical modeling. Some
salient aspects of the experimental studies are discussed in Section
3. Here we note that for the 24 neuronal modeling studies, 16 included no inactivation, 3 included VDI only, 3 included CDI only and a further 2 included both VDI and CDI. It is not clear if inactivation was omitted in several cases simply because the models employed data extrapolated from other cell types or the inactivation was considered to be unimportant or extremely slow. For the 7 models for cardiac cell L-type calcium currents, 2 studies included VDI only and 5 included both CDI and VDI. It is claimed (De Waard et al., 1996) that inactivation of L-type currents is generally slow in neurons and secretory cells but more rapid in cardiac cells. The data in Table A3 indicate that this may not always be the case, but the definition of the term rapid is no doubt flexible.

Generally, CDI has been cited as being more rapid than VDI (Budde et al., 2002; Lacinová and Hoffman, 2005; Grandi et al., 2010). The molecular basis of the dynamics of CDI has been an active and fascinating research area in the last two decades (Imredy and Yue, 1992, 1994; Lee et al., 1999; Peterson et al., 1999; Qin et al., 1999; Zühlke et al., 1999; Erickson et al., 2003; Soldatov, 2003; Bazzazi et al., 2010). It was found that calmodulin, which is tethered to the channel, must bind Ca$^{2+}$, as depicted in Figure 2, whereupon a configurational change takes place resulting in inactivation. Crump et al. (2011) have reported that calmodulin and Ca$^{2+}$ can compete to limit CDI in Ca$\text{v}_{1.2}$. The roles of the $\beta$ and $\alpha_2\delta$ subunits in determining the properties of Ca$\text{v}_{1.2}$ channels have been discussed in Ravindran et al. (2008) and Ravindran et al. (2009).

There have been developed, since the original discovery of CDI, two main modeling ideas concerning the spatial distribution of calcium ions which participate in the inactivation process. One, called shell theory and posited originally by Standen and Stanfield (1982), is that there is a region of some 100 nm depth inside the cell membrane where calcium ions may accumulate, giving a concentration Ca$^*_i$ much higher than in the remaining cytoplasm and that it is Ca$^*_i$ which should be used to determine the rate of CDI. This approach is widely used in neuronal modeling, if indeed CDI is included. The second approach, called domain theory (Sherman et al., 1990), takes account of the calcium ions just inside the pore where they have entered the cell. In fact, according to Imredy and Yue (1994) and
Cens et al. (2006), inactivation (CDI) can be induced in a section of membrane which contains a single L-type channel. However, in some cells, in a region with many channels, averaging over all channels should make the often used and simpler shell approach a reasonable approximation.

Special consideration is made for some cardiac and other muscle cells where calcium entry, principally through L-type channels, leads to Ca\textsuperscript{2+}-induced calcium release (CICR) of stored calcium via ryanodine receptors and results in rapid CDI. Many articles have addressed the modeling of CICR and the geometrical details and the formation of localized increases in Ca\textsubscript{i}, called calcium sparks, and their triggering of a large local increase in Ca\textsubscript{i} (see for example and references therein, Shiferaw et al., 2003; Soeller and Cannell, 2004; Koh et al., 2006; Bers, 2008; and Groff and Smith, 2008). Many of these approaches employ Markov models (Hinch et al., 2004; Shannon et al., 2004; Greenstein et al. 2006; Faber et al., 2007). Scriven et al. (2010) have provided detailed information on the geometry and numbers of Ca\textsubscript{v}1.2 channels and ryanodine receptor clusters in rat VM which are useful in modeling Ca\textsuperscript{2+} dynamics.

Ryanodine receptors may also be coupled to L-type calcium channels in some neurons so that CICR plays a role. A comprehensive review containing many examples of CICR in neurons, including that involving L-type currents in the hippocampus, was compiled by Verkhratsky (2005). Coulon et al. (2009) report the occurrence of both low threshold and high threshold calcium currents in connection with CICR in the thalamus. In bullfrog sympathetic neurons, Albrecht et al. (2001) showed that small elevations of Ca\textsubscript{i} evoked by weak depolarization lead to Ca\textsubscript{i} accumulation by the endoplasmic reticulum, and that Ca\textsubscript{i} accumulation became stronger after inhibiting CICR with ryanodine. A mathematical model was presented in support of these results. In another interesting related study, Hoesch et al. (2001) concluded that caffeine is a reliable agonist for CICR in rabbit vagal sensory neurons, but that caffeine-activated rises in Ca\textsubscript{i} in nerve cells could not be attributed solely to release from intracellular stores. See Tsien and Tsien (1990), Friel and Tsien (1992), Chavis et al. (1996) and Ouyang et al. (2005) for further examples and discussions of neuronal CICR.
2.2 The basic model for L-type \( \text{Ca}^{2+} \) current

In the following, the membrane potential is \( V \), the internal calcium concentration is \( \text{Ca}_i \), the external calcium concentration is \( \text{Ca}_o \), and \( t \) is time. All the deterministic formulations of the L-type calcium current employed in modeling to date are included in the general form

\[
I_{\text{CaL}} = m^{p_1}(V, t)h^{p_2}(V, t)f(\text{Ca}_i, t)F(V, \text{Ca}_i, \text{Ca}_o),
\]

(1)

where \( m(V, t) \) is the voltage-dependent activation variable, \( h(V, t) \) is the voltage-dependent inactivation variable and \( f(\text{Ca}_i, t) \) is the (internal) calcium-dependent inactivation variable. The factor \( F \) contains membrane biophysical parameters and, as described below, is of the Ohmic (or linear) form (as in (15)) used in the original Hodgkin-Huxley model, or the constant-field form (as in (17) or (19)), often called the Goldman-Hodgkin-Katz form. The values of \( p_1 \) and \( p_2 \) are ideally dictated by best fits of current-voltage relations to experimental data. The power \( p_1 \) to which \( m \) is raised, is about equally frequently \( p_1 = 1 \) or \( p_1 = 2 \), with invariably \( p_1 = 1 \) for cardiac cells. For skeletal muscle, before the L-type was distinguished, the value \( p_1 = 3 \) was employed (Standen and Stanfield, 1982). Details are given in Tables A1.1- A1.4 in the Appendix. The value of \( p_2 \), if indeed VDI is included, is invariably \( p_2 = 1 \). (Putting \( p_2 = 0 \) implies no VDI.) The notation \( f_{\text{Ca}} \) is often used for \( f \) and \( f \) often used for \( h \), but the present notation avoids excessive subscripts in subsequent formulas. If other calcium currents were under consideration, the variables for L-type current might be usefully written as \( m_L, h_L \) and \( f_L \). In some reports, L-type \( \text{Ca}^{2+} \) channels are described as being also permeable to \( \text{Na}^+ \) and \( \text{K}^+ \), the relative permeabilities being given for ventricular myocytes as 2800:3.5:1 (Luo and Rudy, 1994; Faber et al., 2007) and 3600:18:1 (Shannon et al., 2004). The contributions from \( \text{Na}^+ \) and \( \text{K}^+ \) are evidently sufficient to bring the reversal potential for \( I_{\text{CaL}} \) from its value around the Nernst potential for \( \text{Ca}^{2+} \) (about 120-150 mV), which it would be close to if it was through a purely \( \text{Ca}^{2+} \)-conducting channel, to the observed values of about 70 mV. However, in what follows there is no focus on the \( \text{Na}^+ \) and \( \text{K}^+ \) components of the L-type current. In modeling neuronal or other cell-type dynamics, there of course many other components, one of which will be the intracellular calcium concentration \( \text{Ca}_i(t) \) whose value will directly influence \( I_{\text{CaL}}, \text{Ca}_o(t) \)
usually being regarded as constant.

Each of the variables $m$, $h$ and $f$ takes values between 0 and 1, inclusively, and the product $m^p_1 h^p_2 f$ is interpretable as the probability that the channel is open or conducting or equivalently gives the expected fraction of such channels in a large sample. As can also be seen from Tables A1.1-A1.4, there have been many forms other than what might be called the full description as in Equ. (1) in which there is both time-varying voltage-dependent inactivation and time-varying calcium-dependent inactivation. Thus, as mentioned in Section 2.1, in some computations, there is no inactivation whatsoever, or there may be just one or the other of voltage-dependent or calcium-dependent inactivation, either with or without time dependence. Sometimes, if a time constant for an activation or inactivation variable is very small, the steady state value of the variable is assumed to hold instantaneously with no time dependence. With a few exceptions, this has been the case in modeling calcium-dependent inactivation.

### 2.3 Activation and inactivation variables

Most of the material in this subsection is standard but is repeated here for notational purposes and to make the account self-contained. According to the above basic model there are three dynamical variables determining the magnitude of the current. These are the activation variable, always assumed to be purely voltage-dependent, the voltage-dependent inactivation variable, and the calcium-dependent inactivation variable.

#### 2.3.1 Activation variable $m$ and voltage-dependent inactivation variable $h$

The activation variable $m(V,t)$ is usually assumed to satisfy the differential equation

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m}, \quad (2)$$

where $m_\infty(V)$ is the steady state value $m(V, \infty)$ and $\tau_m$ is a time constant which may depend on $V$. Similarly for the voltage-dependent
inactivation variable

\[
\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}.
\]

(3)

In the classical approach, the voltage dependence of the steady state activation variable is written in the Boltzmann form

\[
m_\infty(V) = \frac{1}{1 + e^{-(V - V_{m,\frac{1}{2}})/k_m}}
\]

(4)

where \( V \) is the membrane potential. The half-activation potential is given by \( m_\infty(V_{m,\frac{1}{2}}) = 0.5 \), and if the derivative of \( m_\infty \) is denoted by \( m'_\infty \) then the slope factor is \( k_m = \frac{1}{4m'_\infty(V_{m,\frac{1}{2}})} \). Similarly, if a voltage-dependent inactivation is included then its steady state form may be written as

\[
h_\infty(V) = \frac{1}{1 + e^{(V - V_{h,\frac{1}{2}})/k_h}}
\]

(5)

where \( h_\infty(V_{h,\frac{1}{2}}) = 0.5 \) and the slope factor is \( k_h = -\frac{1}{4h'_\infty(V_{h,\frac{1}{2}})} \).

In many instances the Boltzmann forms are not used but rather forward and backward rate coefficients \( \alpha(V) \) and \( \beta(V) \) respectively, are introduced, so that

\[
\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m
\]

(6)

with a similar equation for \( h \). It is usually the case that \( m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)} \) and \( \tau_m(V) = \frac{1}{\alpha_m(V) + \beta_m(V)} \) and similarly for the inactivation variable, but as will be seen from Table A2, variations have been employed.

The Boltzmann forms for \( m_\infty \) and \( h_\infty \) have the advantage of making it immediately transparent at which voltages these functions have their half-maximal values and over what ranges of \( V \) they are significantly different from zero or one. If \( \alpha \) and \( \beta \) are given, and \( m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)} \), then one may determine an approximating Boltzmann curve by graphical inspection or calculation to ascertain the \( V_{\frac{1}{2}} \) and \( k \)-values.

### 2.3.2 Calcium-dependent inactivation variable \( f(Ca_i, t) \)

It will be seen in the summary of various models presented below that the inactivation variable \( f(Ca_i, t) \) has entered the modeling in
many different forms. The most general, which contains all those employed, can be written as

\[
\frac{df}{dt} = \frac{f_\infty - f}{\tau_f},
\]

where \( f_\infty (C_{a_i}) \) is the steady state \( f(C_{a_i}, \infty) \) and \( \tau_f \) is a time constant which may depend on \( C_{a_i} \). Here \( f_\infty \) and \( \tau_f \) are defined through

\[
f_\infty = \frac{1}{1 + \left( \frac{C_{a_i}}{K_f} \right)^n},
\]

(8)

\[
\tau_f = \frac{1}{\alpha_f \left[ 1 + \left( \frac{C_{a_i}}{K_f} \right)^n \right]},
\]

(9)

where \( \alpha_f \), with units time\(^{-1}\), is a constant and \( K_f \) in mM is the value of \( C_{a_i} \) at which the steady state inactivation has half-maximal value. The index \( n \) has been given the values 1 (Standen and Stanfield, 1982), 2 (Luo and Rudy, 1994) and 3 (Fox et al., 2002). It can be argued that \( n \), which is often referred to as a Hill coefficient, is the approximate number of calcium ions which bind to a channel or associated molecule to give inactivation. However this reasoning is open to considerable doubt (Weiss, 1997). Höfer et al. (1997) reported that the Hill coefficient for binding of \( Ca^{2+} \) to the site mediating CDI was close to 1 with an “inhibition constant ” of 4\( \mu \)M. In the original derivation of Standen and Stanfield (1982) it was assumed that the underlying reaction was in fact simply

\[
Ca + R \rightleftharpoons CaR,
\]

(10)

with \( K_f = \alpha_f/\beta_f \). Using standard reaction rate theory (e.g. McConigle and Molinoff, 1989) this scheme gives the ratio of inactivated to activated as

\[
1 - f = \frac{C_{a_i}}{C_{a_i} + K_f}.
\]

(11)

(Recall that \( f \) is the interpretable as the probability that a channel is not inactivated by a \( Ca^{2+} \)-dependent mechanism.) The alternative formulation of the time-dependent behaviour in the case of \( n \)
calcium ions binding to give an inactivated channel is through the
differential equation

\[ \frac{df}{dt} = \alpha f (1 - f) - \beta f Ca_{i}^{n} \]  

(12)

where \( \beta = \frac{\alpha f}{K_{n}f} \) which is consistent with (7)-(9). However, re-
finements of this basic model would be needed to incorporate other
findings such as the dependence of CDI on voltage in cardiac my-
ocytes (Faber et al., 2007).

2.4 Determining the current

Although they are well-known, we give here for completeness the
two most generally used methods for calculating membrane ion cur-
rents (see e.g., Tuckwell, 1988; Koch, 1999). These are the linear
and constant field methods, of which the former is simpler. In the 22
works on non-cardiac cells summarized in Table A1.1, which state
the method of determining the current, 15 use the linear method
and 7 use the constant field method. All cardiac cell studies in Ta-
ble A1.4 use the constant field method. Although the constant field
method is considered more appropriate, if the voltage doesn’t spend
much time above 0 then the linear method may be sufficiently accu-
rate, especially when there is voltage-dependent inactivation, which
is supported by the calculations in Section 4.1.

2.4.1 Linear method

This method, employed by Hodgkin and Huxley (1952) in their fun-
damental modeling of the action potential in squid giant axon, con-
stitutes of multiplying the membrane conductance \( G_{L} \) by the driving
potential \( V - V_{rev,L} \), where \( V_{rev,L} \) is a reversal potential, to give

\[ I_{Ca_{L},Lin} = G_{L}(V - V_{rev,L}) \]  

(13)

This method is called linear (or Ohmic), as the term \( V - V_{rev,L} \) is
linear in \( V \), but not of course the conductance. The conductance
\( G_{L} \) is the product of a maximal value \( G_{L,max} \) and one to three of
the factors \( m(V, t)^{p_{1}}, h(V, t)^{p_{2}} \) and \( f(Ca_{i}, t) \), all of which are dimen-
sionless and take values between 0 and 1 inclusively. That is,

\[ G_{L} = m(V, t)^{p_{1}} h(V, t)^{p_{2}} f(Ca_{i}, t) G_{L,max}. \]  

(14)
Assuming a membrane area $A$ sq cm, a channel density $\rho_L$ per sq cm and a single channel open conductance of $\overline{g}_L$, the maximal conductance is $G_{L,max} = A\rho_L\overline{g}_L$. Then in terms of fundamental quantities

$$I_{Cal,lin} = A\rho_L\overline{g}_L m(V, t)^{p_1} h(V, t)^{p_2} f(Ca_i, t)(V - V_{rev,L}).$$

(15)

As can be seen from Tables A1.1-1.4, $p_1$ and $p_2$ are usually small non-negative integers between 0 and 2 for L-type currents. If $\overline{g}_L$ is in mS and voltages are in mV, then $I_{Cal,lin}$ given by (15) is in $\mu$A.

The reversal potential for an ion type is often taken to be its Nernst potential which for Ca$^{2+}$ is

$$V_{Ca} = \frac{RT}{2F} \ln \left( \frac{Ca_o}{Ca_i} \right)$$

(16)

where $Ca_o$ and $Ca_i$ are external and internal concentrations, $R$, $T$ and $F$ have their usual meanings, $RT/F$ having units of volts. Although $V_{Ca}$ is sometimes taken as the value of $V_{rev,L}$, it is usually of magnitude about 120 mV, which is much higher than experimentally determined values of $V_{rev,L}$ which are around 60-70 mV. In modeling, using $V_{Ca}$ thus gives substantially larger calcium currents than expected.

### 2.4.2 Constant field method

From the basic expression for the current density under the constant field assumption (see for example Tuckwell, 1988, Chapter 2), the L-type calcium current, in $\mu$A, through a membranous area of $A$ square cm is given by the Goldman-Hodgkin-Katz flux equation

$$I_{Cal,CF} = AP_L m^{p_1}(V, t) h^{p_2}(V, t) f(Ca_i, t) \frac{4FV}{V_0} \frac{[Ca_i - Ca_o e^{-\frac{2V}{V_0}}]}{1 - e^{-\frac{2V}{V_0}}},$$

(17)

where for convenience of expression we have defined the temperature-dependent voltage

$$V_0 = \frac{RT}{F},$$

(18)

$F$ is Faraday’s constant (96500 coulombs/mole), $P_L$ is the membrane permeability coefficient in cm/sec, and $Ca_i$ and $Ca_o$ are the
intracellular and extracellular concentrations of Ca\(^{2+}\) in mM. Note that the partition coefficient, here assumed the same for the intracellular and extracellular boundaries, is absorbed into the permeability coefficient. However, if the intracellular and extracellular partition coefficients are different, then additional multiplicative factors will appear with ion concentrations, as in, for example, Sun et al. (2000) and Fink et al. (2011). In terms of single channel properties, the current in \(\mu\)A through an area of \(A\) cm\(^2\) is

\[
I_{CaL,CF} = A \rho_L P_L^* m^{\mu_1}(V,t) h^{\mu_2}(V,t) f(Ca_i, t) \frac{4FV}{V_0} \frac{[Ca_i - Ca_o e^{-\frac{2V}{V_0}}]}{1 - e^{-\frac{2V}{V_0}}} \tag{19}
\]

where \(\rho_L\) is the density of channels in cm\(^{-2}\) and \(P_L^*\) is the single channel permeability in cm\(^3\)/sec.

3 Data on L-type activation and inactivation

A large number of sources of data for L-type activation and inactivation, including both VDI and CDI, have been considered, back to the first uses of the term “L-type” (Nowycky et al., 1985; Fox et al., 1987). Data on the half activation potentials \(V_{m,1/2}\) and slopes \(k_m\) are given in Tables A1.1-A1.4. In these and all subsequent tables the authorship of articles is given only by first author and date to minimize column width. In the first column of Tables A1.1-1.4 are given carrier concentrations. M denotes a purely mathematical modeling study, the absence of M can denote either a purely experimental work, or experimental work in conjunction with modeling. The characterization of currents as L-type by various authors has been assumed to be correct. Voltage-dependent inactivation parameters \(V_{h,1/2}\) and \(k_h\) are also given if available. Table A1.1 contains data for neurons and secretory cells, whereas Table A1.2 is restricted to cardiac cells. In some cases, marked with asterisks (*), parameters have been estimated approximately from data presented graphically, but the original articles should be consulted for details. Table A1.3 has data for neurons and secretory cells with both VDI and CDI and Table A1.4 presents these data for cardiac cells. In Table A1.1 the
entry for Joux et al. (2001) for $V_{m,1/2}$ has two values as fits were
to a double Boltzmann function. Note that the concentrations $Ca_o$
may differ in the various preparations, (and occasionally be $Ba_o$) as
described in the first column of Tables A1.1-1.4. For example, the
value in the first entry (Fox et al., 1987) is $Ca_o=10\text{mM}$, which may
explain why the value of $V_{m,1/2}$ seems rather high. In general, much
of the variability in the data presented is attributable to various
ionic carrier concentrations and differing subunit isoforms. In order
to keep the Tables relatively simple, many such details are omitted,
but these can be obtained from the original sources in most cases.

3.1 Steady state activation $m_\infty(V)$ and inactivation $h_\infty(V)$

In the top part of Figure 3 the steady-state activation $m_\infty$ is plotted
against $V$ for the two lowest and two highest values of the half-
activation potential found in a comprehensive, but not exhaustive,
search of the literature, including all modeling and experimental
results in the Tables A1.1-1.4. The two lowest are for midbrain
dopamine neurons, with half-activation potentials of -50 mV (Amini
et al., 1999; Komendantov et al., 2004).

The two highest are +5 mV for ventricular myocytes (Shiferaw
et al., 2003) and +2 mV for chick dorsal root ganglion (Fox et al.
1987). Also shown in the top part of the figure are examples of the
$m_\infty$ curves found for the channel subtypes $Ca_{v1.1}$-$Ca_{v1.4}$. It can
be seen that the curves for the subtypes cover or span those for the
lowest and highest activation curves for cells except for the one for
midbrain dopamine neurons.

In the lower part of Figure 3 are shown the corresponding steady
state V-dependent inactivation $h_\infty$ curves for the two highest half-
activation potentials. For the other two cases with $V_{m,1/2}=-50$, there
was only CDI. Also shown in the lower part of Figure 3 are the
$h_\infty$ curves for each channel subtype. The curve for $Ca_{v1.2}$ seems
more extreme than that for any cell. In some cases Boltzmann
functions for $m_\infty(V)$ and $h_\infty(V)$ were not given but rather explicit
expressions for the forward and backward rate functions $\alpha_m(V),
\beta_m(V), \alpha_h(V)$ and $\beta_h(V)$. Such formulas when available are given
for all cell types in Table A3. The parameters of fitted Boltzmann
Figure 3: Steady state activation $m_\infty$ and inactivation $h_\infty$ versus membrane potential for L-type currents in neurons for extreme cases. Top panel. Activation curves $m_\infty(V)$ are given for L-type currents in midbrain DA neurons, (blue solid curve, Amini et al., 1999; red solid curve, Komendantov et al., 2004) chick DRG (green solid curve, Fox et al., 1987) and rabbit atrial myocytes (black solid curve, Lindblad et al., 1996). These are the cases with the two highest and two lowest half-activation potentials found in the literature. The two lowest (midbrain DA) have $V_{m,1/2}=-50$ mV, and the highest two are for rabbit atrial cell, with $V_{m,1/2}=-0.95$ mV and chick DRG with $V_{m,1/2}=2$ mV. Also given are examples of activation curves (dashed) for the four subtypes, Ca$_{v}$1.1 (green, from Catterall, 2005), Ca$_{v}$1.2 (blue, average from Lipscombe et al., 2004 and Catterall, 2005), Ca$_{v}$1.3 (red, average from Lipscombe et al., 2004 and Helton et al., 2005) and Ca$_{v}$1.4 (black, mean of lowest and highest, from Catterall, 2005). Bottom panel. Steady state inactivation $h_\infty(V)$ for cases shown in the top panel with the same color coding. For the two cells with the lowest two half-activation potentials, inactivation was given only as Ca$^{2+}$-dependent - see Tables A1.1-A1.4.
functions for the corresponding $m_{\infty}$ and $h_{\infty}$ were given in Tables A1.1-A1.4. When explicit expressions were given for the activation time constants $\tau_m(V)$, these are given in Table A4.

### 3.1.1 Distribution of half-activation potentials

It can be seen from Tables A1.1-A1.4 that there is great variability in the parameters for the activation and inactivation properties of L-type currents in various cells. The underlying reasons for variability include, (a) the occurrence of different subtypes of L-channels, some examples of whose properties are listed in Table A6; (b) the various locations of the channels over the soma-dendritic surface; (c) the interaction of L-type channels with other neighboring ionic channels; and (d) the ionic compositions of the intracellular and extracellular compartments of the cell under consideration. One other source of variability is that there are different methods, some more accurate than others, for calculating Boltzmann curves.

The majority of data in tables A1.1-A1.4 concerns modeling studies and it is useful to separate out the experimental values, and to subdivide these into those for neurons and cardiac cells. In particular, the experimental results considered here are only those for calcium concentrations in the physiological range because high concentrations of either barium or calcium ions can shift the half-activation potential in the depolarizing direction by 10 or more mV (Jaffe et al., 1994; Muinuddin et al., 2004). With these restrictions there are 13 half-activation potentials given for neurons and 5 for cardiac cells. Histograms for the $V_{m,1/2}$ values are shown in Figure 4. For neurons, the data are divided into a high ($>−30$ mV) and a low group, the topmost panel being for the low group. The mean for the neuron high group is $< V_{m,1/2} > = −18.3$ mV whereas that for the low group is $< V_{m,1/2} > = −36.4$ mV. The mean slope factors for these two groups of neurons are $< k_m > = 8.4$ mV for the high group and $< k_m > = 5.8$ mV for the low group. These average slope factors are obtained on omitting the outliers 2.45 in the high group and 20.0 in the low group. The mean value of $V_{m,1/2}$ for the experiments with cardiac cells is −13.6 mV with a standard deviation of 7.8 mV, and the corresponding average $k_{m}$ is 6.84 mV with standard deviation 1.61 mV. It is then of interest to note that the average values of the half activation potentials for Ca$_v$1.2 and Ca$_v$1.3, using
Figure 4: Histograms of the half-activation membrane potentials $V_{m,1/2}$ for L-type Ca$^{2+}$ currents from the data of Tables A1.1-A1.4. The data, which are based on selected experiments (see text) are divided into 3 groups. Top, low neuron group. Middle, high neuron group. Bottom, cardiac cells. Note that the mean values for Ca$_{a1.2}$ and Ca$_{a1.3}$, using Table A6 values with physiological calcium ion concentrations, are -18.7 mV and -38.9 mV, respectively.

Table A6 values with physiological calcium ion concentrations, are -18.7 mV and -38.9 mV, respectively. These values correspond well with the mean values of the high and low groups of neurons. The values for cardiac cells tend to be higher than those in even the high neuron group, but the sample sizes are too small to draw any statistically significant conclusions.

For all the 25 neuronal modeling studies the mean value of $V_{m,1/2}$ is -21.0 mV with a standard deviation of 12.21 mV, and for $k_m$ the mean is 7.26 with a standard deviation of 2.33. The mean modeling study parameters correspond roughly to the experimental values for the high neuron group. For the 7 cardiac cell (all kinds) modeling studies the mean half-activation potential $V_{m,1/2}$ is -8.8 mV with a standard deviation of 9.1 mV and the corresponding mean for $k_m$
is 6.4 mV with a standard deviation of 0.52.

For the parameters of the Boltzmann function for the steady state inactivation, $V_{h,\frac{1}{2}}$ and $k_h$, there are, unfortunately little appropriate experimental data, and none which could be considered reliable, though many modeling studies have employed estimates (see Tables A1.1-A1.4) and see below. In order to provide crude estimates based on experiment, one may use the results of Koschak et al. (2001) as given in Table A6 for the differences in voltage between $V_{m,\frac{1}{2}}$ and $V_{h,\frac{1}{2}}$ for $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ in high barium concentration. This procedure yields values which are summarized in Table 3 for the activation and inactivation parameters.

|                  | High neuron group (expt) | Low neuron group (expt) | All models |
|------------------|--------------------------|-------------------------|------------|
| $V_{m,\frac{1}{2}}$ | -18.7                    | -38.9                   | -21.0      |
| $k_m$            | 8.4                      | 5.8                     | 7.26       |
| $V_{h,\frac{1}{2}}$ | -42.0*                   | -61.9*                  | -38.95     |
| $k_h$            | 13.8*                    | 6.6*                    | 6.82       |

* Estimated - see text.

For cardiac cells, based on the few experimental studies available, the mean $V_{h,\frac{1}{2}}$ is -40.0 mV with standard deviation 12.8, the corresponding mean value of $k_h$ being 6.85 mV with a standard deviation of 2.04 mV.

Of the 25 neuronal modeling studies in the tables, only 6 included VDI and these yielded a mean value of -38.95 mV for $V_{h,\frac{1}{2}}$ with standard deviation 14.29. For the corresponding values of the slope factor $k_h$, the mean is 6.82 with a standard deviation of 2.16, where one value is omitted as an extreme outlier. For the cardiac modeling, the mean value of $V_{h,\frac{1}{2}}$ is -30.1 mV with a standard deviation of 10.9 mV and the corresponding mean for $k_h$ is 6.1 mV with a standard deviation of 2.00 mV.
3.2 Time constants $\tau_m(V)$ for activation

Some values of $\tau_m(V)$ for activation, with corresponding inactivation, if available, are reported in Table A3. This table has been divided into a part with experimental results and a part on values of which have been employed in modeling studies. As seen in Table A3-Experimental, there are not many explicit experimental results available for the time constants of activation (or inactivation) of L-type Ca$^{2+}$ currents. In neurons values of $\tau_m(V)$ range from about 0.5 ms in sympathetic neurons (Belluzzi and Sacchi, 1991) to 2.3 ms in hippocampal pyramidal cells (Avery and Johnston, 1996), a maximum value of 1.541 ms being reported for thalamic relay cells (McCormick and Huguenard, 1992). These values seem compatible with those given for the appropriate subtypes in Table 6. For skeletal muscle, a value of 19.82 ms (Standen and Stanfield, 1982; here assuming L-type) is also compatible with the relatively high value for the Ca$_v$1.1 subtype. The experimental values reported for smooth muscle are around 4.0 ms (Muinuddin et al., 2004). Some available data for $\tau_m$ for subtypes are given in Section 5.

In Table A3-Modeling, there are reported 23 values employed for $\tau_m$, with a large range of values, many of which are much larger than the values for subtypes reported in Table 6. Many of the values employed for a given neuron type are not based on experiments for that neuron type but adapted from those for other, sometimes quite different, neurons. Often quite disparate values appear for what are possibly the same kind of cell. Discrepancies may arise because it is difficult to categorize a specific channel type in a neuron without a detailed voltage-clamp and pharmacological analysis. We consider cells in the following categories.

Dopaminergic neurons. The value of about 0.134 ms was employed by (Li et al., 1996) which contrasts greatly with the value 19.5 ms used by both Amini et al. (1999) and Komendantov et al. (2004). The approach of Li et al. (1996) is critically discussed by Amini et al. (1999).

Cardiac cells. Concerning the listed values, in the three modeling studies on ventricular myocytes, two (Luo and Rudy, 1994; Shannon et al., 2004) have $\tau_m$-values with a maximum around 2.25 ms whereas a third puts the maximum value much higher at about 19.3
ms (Fox et al., 2002) and at a considerably more hyperpolarized level. In their analysis of the firing properties of rabbit sino-atrial node pacemakers, Zhang et al. (2000) chose a value of about 3.8 ms for the maximum activation time constant. Thus in most of these studies the magnitudes of \( \tau_m \) are comparable with or near the values for \( \text{Ca}_{1.2} \) and \( \text{Ca}_{1.3} \) channels (see Table 6) which are plentiful in the heart.

**Hippocampal cells.** The range of activation time constants for hippocampal pyramidal cell models is from 0.83 ms for CA1 (Poirazi et al., 2003) to 4.56 ms for CA3 (Migliore et al., 1995). For the latter cell-type, Jaffe et al. (1994) used a value with a maximum of 1.5 ms. According to Table 6 and Figure 12 all of these values are within the ranges of the ones given for \( \text{Ca}_{1.2} \) and \( \text{Ca}_{1.3} \) channels, both of which are prevalent in the hippocampus.

**Thalamic relay cells.** The experimental findings of McCormick and Huguenard (1992) for \( \tau_m \), with a maximum of 1.541 ms at \( V = -15 \) mV, were implemented in a model by the same authors. The same values were later employed by Hutcheon et al. (1994). Rhodes and Llinas (2005) put the maximum value of the time constant somewhat larger at 2.1 ms at -19 mV, but in the table of parameter values the current is referred to as a generic \( I_{\text{Ca}} \) rather than specifically as an L-type current. All of these values are compatible with the expected subtype values.

**Pituitary corticotrophs.** The two modeling studies of these cells listed in the table have fairly large values of \( \tau_m \). In the first study, LeBeau et al. (1997) set the value at 27 ms for all \( V \), whereas Shorten and Wall (2000) had a maximum for \( \tau_m \) of value 11.32 occurring at \( V = -12 \) mV. There seems to be a fairly large difference between these values and the sub-type values, but there are many sources of variability as discussed elsewhere in this review.

**Cortical pyramidal cells.** In the one parameter set available (Rhodes and Llinas, 2001), the maximal time constant for L-type activation was set at 2.1 ms, occurring at -19 mV. This value is well within the range of the available data for the appropriate subtypes as given in Table 6 and Figure 12.

**Spinal motoneurons.** The L-type activation listed in the 3 listed
modeling studies of these neurons (Booth et al, 1997; Carlin et al. 2000; Bui et al, 2006) is much slower than the values available for either of the subtypes Ca\textsubscript{v}1.2 Ca\textsubscript{v}1.3 which are candidates for being present in CNS neurons. The first of these studies set $\tau_m = 40$ ms, whereas the two subsequent ones put $\tau_m = 20$ ms whereas the largest value in Figure 12 is about 4 to 5 ms.

Smooth muscle. In modeling a rat mesenteric smooth muscle cell, Kapela et al. (2008) for $\tau_m(V)$ used a Gaussian-like function with a maximum value of 3.65 ms at $V = -40$ mV. Such a value is close to the experimentally reported time constant in (Muinuddin et al., 2004).

Figure 5 shows two plots of $\tau_m$ versus $V$ for two of the few available experimental data sets (but see Section 5 for results for L-subtypes). These are both for rat sympathetic neurons (A, Belluzzi and Sacchi, 1991; B, Sala, 1991) and are, in the absence of reliable L-type data in physiological or near physiological solutions,

![Figure 5: Activation time constants for high threshold Ca\textsuperscript{2+} currents. Two sets of experimental results for sympathetic neurons. In both cases the corresponding steady state activation function is shown, using the same scale. A. From Belluzzi and Sacchi (1991) with 5mM Ca\textsuperscript{2+}. B. From Sala (1991), with 4mM Ca\textsuperscript{2+}.](image_url)
Figure 6: Histogram of the maximum values of time constants $\tau_m$, in ms, for activation for L-type Ca$^{2+}$ currents using data from Table A3. Includes both experimental and modeling studies less than 10 ms.

taken from HVA studies which may contain L-type and other high threshold components. These data sets are very different in magnitude and form from those used in many modeling studies, where sometimes the time constant for activation is taken to be a large value, constant and independent of voltage. They are also considerably less than the values reported for Ca$v_{1.2}$ and Ca$v_{1.3}$ in 2mM Ca$^{2+}$ in Section 5. Molitor and Manis (1999) report experimental values of $\tau_m$ with a maximum of about 1.2 ms at about $V=-20\text{ mV}$ in guinea pig dorsal cochlear nucleus neurons. In Figure 5 are also drawn the steady state activation functions, also based on experiment, for comparison.

The data of Table A3 on maximum values of activation time constants are collected into a histogram in Figure 6, but this includes only values less than 10 ms. The mean for the experimental results on neurons is 1.34 ms. For all the data shown (n=17) the mean is 2.38 ms and the standard deviation is 1.51.

For time constants $\tau_h$ for voltage dependent inactivation in neurons there are very few data. The average of the two available ex-
experimental maximum values is 65 ms and the average of 5 modeling maximum values is 140.9 ms.

3.3 Magnitudes of $I_{\text{CaL}}$ or related quantities

Data on the magnitudes of $I_{\text{CaL}}$ in various cells is collected in Table A5. Such data are presented in several forms, viz, (a) the actual current density, usually in pA/pF, which may be for the whole cell or a part thereof (b) the permeability (c) the conductance per unit area $g_L$ (d) the whole cell conductance $G_L$ (d) the fraction of total calcium current that is $I_{\text{CaL}}$. It can be seen that the proportion of $I_{\text{CaL}}$ across cell types is extremely variable from nearly all of the calcium current in some muscle and cardiac cells (Kapela et al., 2008; Benitah et al., 2010) to just a few percent, for example in serotonergic (dissociated) cells of the dorsal raphe nucleus (Pentington et al., 1991). The roles of $I_{\text{CaL}}$ are presumably very different in these examples. From Table A5, the largest $I_{\text{CaL}}$ current density is 19.3 pA/pF in supraoptic nucleus (Joux et al., 2001), but almost as high magnitudes are found in rat CA1 pyramidal cells (Xiang et al., 2008) and ventricular cardiomyocytes in rats with renal failure (Donohoe et al., 2000). The highest reported conductance density is 7 mS per square cm in rat CA1 pyramidal cells (Xiang et al., 2008). Note that current densities can differ significantly in different preparations such as those with different ages, or with different times in culture.

4 Examples of calculations of $I_{\text{CaL}}$

In this Section we apply the basic model (1) to determine the L-type calcium current in three cases. In the first, only VDI is considered, whereas in the remaining two examples, VDI and CDI are both operative.
4.1 Steady state currents obtained by the linear and constant field methods with voltage dependence only

The activation and inactivation variables, which are dimensionless and take values in [0,1], may depend on membrane potential or ion concentrations, or both, but in this section only voltage dependence is considered. Here we wish to compare current-voltage relations obtained by the two methods outlined in Section 2.4. In order to compare the steady state currents $I_{CaL, Lin}$ and $I_{CaL, CF}$ calculated by the two methods, an average maximal conductance density $g_L$ (from the values given in Table A5) of 1.3925 mS/cm$^2$ was assumed for the determination of $I_{CaL, Lin}$, although this value varies greatly from cell to cell. For the steady state activation variable $m_\infty$ used in the calculation of $I_{CaL, Lin}$, two values of $V_{m, \frac{1}{2}}$ were employed, being a relatively low value, $V_{m, \frac{1}{2}} = -29.6$ mV, and an intermediate value $V_{m, \frac{1}{2}} = -14.4$ mV. The corresponding values of $k_m$ were 6.97 mV (low) and 7.78 (intermediate). When inactivation was included, the values for $V_{h, \frac{1}{2}}$ were $V_{h, \frac{1}{2}} = -43.5$ mV (low) and $V_{h, \frac{1}{2}} = -36.2$ mV (intermediate), with corresponding values for $k_h$ of 9.55 mV (low) and 6.18 (intermediate).

Four sets of values for $p_1$ and $p_2$ were employed, giving the forms $m$, $m^2$, $mh$ and $m^2h$. The calculated results are shown in the four panels of Figure 7. In each case the current $I_{CaL, Lin}$ (linear method) was calculated first, the temperature being set at 25° C, the internal calcium concentration $Ca_i$ fixed at 100 nM and the external concentration $Ca_o$ fixed at 2 mM, giving $V_{Ca} = 128.4$ mV which was used as the reversal potential. The constant field current $I_{CaL, CF}$ was then calculated and the permeability adjusted to make the peak (inward, negative) current the same as that in the linear case. This gave 8 values of the permeability which are listed in Table 4 which are close to those reported for L-type calcium currents (Hutcheon et al., 1994; Luo and Rudy, 1994).

The following can be seen from the results in Figure 7. Details of the values of $V$ at which minima in $I_{CaL}$ (maximal current amplitude) occur are given in Table 5. Firstly, *without inactivation* (top two panels), as expected, the constant field and linear calculations are similar in magnitude until a value of $V$ just greater than
that at which the minimum of $I_{\text{CaL}}$ (maximum amplitude) occurs. However, the minima in the constant field case occur at voltages about 11-13 mV more negative than for the linear case, both for open probabilities given by $m$ or $m^2$ and whether $V_{m,\frac{1}{2}}$ is ascribed the low or high value. For larger values of $V$ the two calculations

![Graph](image)

Figure 7: Calculated asymptotic steady state ($t = \infty$) currents for L-type Ca$^{2+}$ currents with average activation and inactivation properties for a relatively low voltage activation ($V_{m,\frac{1}{2}} = -29.7$ mV), blue curves, and an intermediate value ($V_{m,\frac{1}{2}} = -14.4$ mV), red curves. The solid curves are for the constant field current (formula (17)) and dashed lines are for the linear current case (formula (15)). The top two panels are for activation only ($m$ and $m^2$) and the bottom two panels are for activation with inactivation ($mh$ and $m^2h$). In each of the 8 sets of curves, the maximum amplitudes of the constant field and linear currents are scaled to be equal, for a conductance density of 1.3925 mS/cm$^2$ in the linear case. Temperature 25°C.
Table 4: Estimated $P_L$ from $I_{CaL\,CF}$ in $10^{-4}$ cm/sec

| $V_{m,\pm}$ | $m$ | $m^2$ | $mh$ | $m^2h$ |
|------------|-----|-------|------|--------|
| Low (-29.6 mV) | 3.01 | 3.40  | 2.08 | 2.41   |
| Intermediate (-14.39 mV) | 4.41 | 5.26  | 2.11 | 2.76   |

give strikingly different results, as the constant field currents are almost symmetric about their minima and return to almost zero at values of $V$ around 70 mV whereas the linear calculation has the current returning to zero very gently by comparison, and of course reaching zero at the reversal potential of Ca\(^{2+}\) (about 128 mV). Whether such differences are significant for any given cell depend on how long the voltage stays at values greater than those at the minima (maximum amplitude), which are given in Table 5.

Changing from an $m$ to an $m^2$ dependence for $I_{CaL}$ shifts the voltage at which the greatest current amplitude occurs by about 5 or 6 mV in the depolarizing direction. Furthermore, there is not a large difference in the magnitude of the current between the low and high $V_{m,\pm}$ cases. Secondly, with inactivation (bottom two panels)

Table 5: Membrane potentials in mV at maximal current amplitude

| $V_{m,\pm}$ | Linear | Const Field | Linear | Const Field |
|------------|--------|-------------|--------|-------------|
| $m$        | -9     | -20         | 6.5    | -7          |
| $m^2$      | -4     | -15         | 12     | -1          |
| $mh$       | -32    | -35         | -32    | -34         |
| $m^2h$     | -25    | -27         | -18    | -21         |

the current/voltage relations are practically symmetric for all combinations of $V_{m,\pm}$ and the factors $mh$ and $m^2h$. Thus, the constant field calculations are practically the same as the linear calculations for all values of $V$. Inactivation, either as $mh$ or $m^2h$ shifts the voltage of maximal current amplitude by very large amounts in the hyperpolarizing direction. The smallest shift is -12 mV with $m^2h$ and the constant field calculation and the largest is -30 mV with $m^2h$ and the linear calculation. The magnitudes of the currents are
reduced by an order of magnitude by the inactivation and the reductions are much greater for the higher value of $V_m$ (red curves). The difference for the linear and constant field results for the voltage of maximal current amplitude is only a few mV.

4.2 Time dependent $I_{CaL}$ for high and low group neurons with VDI: $m$ or $m^2$?

The question arises as to when the time-dependent results for an $mh$ form of current differ significantly from those for an $m^2h$ form. This was investigated using the parameters for steady state activation and inactivation for the two sets called high and low summarized in Table 3.

The time constant of activation was set at the average maximal experimental value of 1.34 ms for neurons and the time constant for inactivation was set at 29.9 ms as found in Belluzzi and Sacchi (1991), this being one of the only two experimental values available. Current flows were computed for voltage steps from an initial value $V_0 = -80$ mV to final values $V_1 = -30$ mV and $V_1 = 0$ mV. The following Hodgkin-Huxley (1952) formula may then be applied

$$I(t; V_0, V_1) = \overline{g}_L(V_1 - V_{rev,L})[m_1 - (m_1 - m_0)e^{-t/\tau_m}]p$$
$$\times [h_1 - (h_1 - h_0)e^{-t/\tau_h}],$$

where we have employed the abbreviations $m_0 = m_\infty(V_0), m_1 = m_\infty(V_1)$ for the activation, $h_0 = h_\infty(V_0), h_1 = h_\infty(V_1)$ for the inactivation, $\tau_m$ and $\tau_h$ being the time constants. For these calculations $\overline{g}_L$ was set at unity as only relative magnitudes are of interest.

The results are shown in Figure 8. It can be seen that in most of the examples shown, there are only minor differences in the currents computed by the $mh$ versus $m^2h$ form. The case where the difference is very significant (plot 8A) is for the high neuron group with a voltage step from -80 mV to -30 mV. However, only a detailed neuron model, which is beyond the scope of this article, could ascertain whether significant differences arise in the ongoing spiking activity when L-type currents are one of an array of current types. Nevertheless, it has been demonstrated that the choice of the form of the open probability contribution from voltage dependent terms, $m^{p_1}h^{p_2}$, can have significant consequences for the current/voltage
Figure 8: In all plots, current in arbitrary units versus time in ms. Blue curves are for \( p = 1 \) and red curves are for \( p = 2 \). A. High neuron group parameters (see Table 3) with a step from -80 mV to -30 mV. B. High neuron group parameters with a voltage step from -80 mV to 0 mV. C. Low neuron group parameters with a step from -80 mV to -30 mV. D. Low neuron group parameters with a voltage step from -80 mV to 0 mV.

relations or for current versus time. In the ideal situation voltage-clamp data for both activation and inactivation would be used to find the best fitting theoretical form for a component current, as in the original Hodgkin-Huxley (1952) analysis. Care is required in reporting parameters for activation and functions so that it is clear whether they are for \( m \) or \( m^2 \). It is also important that the experimental data have been analyzed correctly.
4.3 Two time constants in $I_{CaL}$ inactivation

For L-type calcium current inactivation, most reports indicate that there are two time constants, one fast and one slow (Luo and Rudy, 1994; Romanin et al., 2000; Meuth et al., 2001; Budde et al., 2002; Lacinova and Hoffman, 2005; Faber et al., 2007; Findlay et al., 2008). According to Lacinova and Hoffman (2005), such is the case for smooth muscle, ventricular myocytes, several neurons and the $Ca_{v1.2}$ channel. Furthermore, in cells, fast time constants range from 7 to 50 ms and slow ones from 65 to 400 ms whereas for the $Ca_{v1.2}$ channel, the ranges are 20 to 100 (fast) and 160 to 2000 (slow). See Table A3 for several data although no distinction is made between fast and slow inactivation time constants in the cited works. In an earlier study of calcium currents (not specifically stated as L-type) in CA1 pyramidal cells, Kay (1991) found, with 5mM $Ca^{2+}$, a fast time constant with a maximum value of about 240 ms at $V$=-10 mV, and a slow time constant with a maximum of about 2200 ms at $V$=-11 mV. It was pointed out that typically (in cells without CDI) the amount of inactivation increases with increasing $V$, and that the rate of inactivation tends to be Gaussian-like as a function of $V$, with a maximum around the voltage $V_{h,1/2}$ at which the steady state inactivation is half-maximal.

The relative contributions of CDI and VDI vary. Lacinova and Hoffman (2005) state that in general for a brief pulse, CDI is responsible for about 80% of inactivation and VDI responsible for the remaining 20%. The faster time constant is usually taken to be associated with CDI. However, in some cases there are taken to be two time constants for VDI of L-type Ca currents, such as in ventricular myocytes (Faber et al., 2007; Findlay et al., 2008) where the dichotomy is attributed to the existence of two voltage-dependent inactivation states. Two time constants were also demonstrated by Morad and Soldatov (2005) for barium currents with no CDI for $Ca_{v1.2}$.

To illustrate the occurrence of two time constants we show results obtained for $I_{CaL}$ for the basic model of Equation (1) using the constant field expression for the current. These are designed to be comparable to the experimental results on thalamic relay (LGN) neurons in Budde et al. (2002), where a step to a test voltage of 10 mV is made for 800 ms after holding at -60 mV. The parameters
Figure 9: Showing two time constants for calculated L-type Ca\(^{2+}\) currents evoked by a test pulse of duration 800 ms at 10 mV after a holding potential of -60 mV. The blue curves are for CDI and VDI, whereas the red curves are for no CDI. The figure on right shows clearly the change in time constant from early to late (blue curve) compared with the single time constant for VDI only (red curve).

used were as follows. For activation, \(V_{m,1}\) was set at -37.5 mV with slope factor 5 mV, and for voltage-dependent inactivation, \(V_{h,1}\) was set at -59.5 mV with a slope factor of 10 mV. The time constant for activation was given by

\[
\tau_m = 1 + 2e^{-[(V-V_{m,1})/15]^2}
\]  

(20)

and that for VDI was set at \(\tau_h = 300\) ms for all \(V\). In addition, a calcium pump term was added of the form

\[
f_{pump}(Ca_i) = K_c \frac{Ca_i}{Ca_i + K_p}
\]  

(21)
where $K_p = 0.0005$ mM (Rhodes and Llinás, 2005) and $K_c = 0.000002$. Initial internal calcium concentration was set at 70 nM and extracellular at 2 mM. The standard value of the multiplicative factor $A\rho_L P_{L}^*$ in (19) was chosen to make the maximum amplitude of $I_{CaL}$ about 0.2 nA as in Budde et al. Figure 2. For the CDI term we use the standard model (7) and (8) with $n = 1$, $\tau_f = 10$ ms (constant) and $K_f = 0.0002$ mM.

Results are shown for $I_{CaL}$ in Figure 9, the contribution from the pump being small and not included. During the pulse the internal calcium concentration rose to a maximum of about 300 nM. In the left panel, $I_{CaL}$ is plotted against time in the cases of CDI + VDI (blue curve) and for VDI only (red curve). With CDI the initial decline of current is very rapid and merges into a slower decay after about 100 ms; with VDI only, the decline in current is slow and relatively uniform as can be seen in the right hand panel where $\ln(-I_{CaL})$ is plotted against time to reveal changes in time constant. The curve for VDI is a straight line, indicating a single time constant. The early (fast) time constant for CDI + VDI was approximately 49 ms and the slow time constant about 264 ms. Both of these values are in the ranges given by Lacinova and Hoffman (2005) quoted above. They are also similar in magnitudes to the values reported in Budde et al. (2002).

4.3.1 Effects of varying parameters

The effects of varying several parameters on the inactivation of $I_{CaL}$ according to the above test pulse procedure are shown in Figure 10. Here both CDI and VDI are present, but the graphical results are given only for the first 200 ms. The parameters used here are as given by Rhodes and Llinás (2005) as in Table A1.3, using the same $f_\infty$, but with time dependent $f(Ca_i, t)$. The standard set of parameters is taken to be as for Figure 9, with the following variations. In the top left panel, the current is calculated for four values of the CDI time constant $\tau_f$, being 5, 10, 30 and 100 ms. Note that most modeling of L-type currents effectively takes $\tau_f = 0$ (see Table A1.3), as the steady state is assumed to be attained immediately. When $\tau_f$ is 5 or 10 ms (blue and red curves), the current has almost the same time course as it does when the immediate steady state assumption is made. For $\tau_f = 30$ ms (green curve), which is the
value used by Standen and Stanfield (1982), the decay of current is much slower for the first 100 ms, very different from that for the immediate steady state assumption. For \( \tau_f = 100 \) ms (black curve), the decline does not reach values comparable with the remaining three cases for at least 200 ms. In the top right panel are shown \( I_{CaL} \) for four values of the time constant \( \tau_h \) for voltage-dependent inactivation, no dependence on \( V \) being assumed. The value of \( \tau_f \) is set at 10 ms. Results are shown for time constants \( \tau_h \) (in ms) of 100 (blue), 200 (red), 300 (green) and 400 (black), which values encompass approximately the values employed (Table A3). As could be anticipated, increasing \( \tau_h \) from 100 to 400 has a negligible effect for the first 20 ms but quite noticeable effects on the late current.

In the bottom left panel are shown results of varying the parameter \( K_c \) which determines the rate of calcium pumping as in (21). The values employed are 1, 2, 3 and 10 times a base rate with blue, red, green and black curves respectively. When the pump rate is higher, \( Ca^{2+} \) is less available for CDI so the current has a larger magnitude. However, in the situation modeled here, it can be seen that a significant difference in \( I_{CaL} \) occurs when the pump rate is increased tenfold, but that increases of 100\% and 200\% have only a small effect. Finally, in the bottom right panel are shown the time courses of \( I_{CaL} \) for various channel densities, being 1 (blue), 4 (red), 8 (green) and 12 (black) times a base rate. The current amplitude is assumed proportional to the channel density so the higher channel densities result in more effective CDI. These results indicate that these four quantities have a significant influence on the amounts of CDI and VDI and thus the magnitude and time course of \( I_{CaL} \).

### 4.3.2 CICR

If there is a substantial amount of CICR, as occurs in cardiac and other muscle cells, then there may be two phases of CDI, consisting of an early rapid component due to release of \( Ca^{2+} \) from the sarcoplasmic reticulum and then a slower phase in response to calcium ion entry through L-type channels (or other calcium channels) (Budde et al., 2002; Bodi et al., 2005; Cueni et al., 2009; Empson et al., 2010). This raises the possibility of three time constants in the decay of \( I_{CaL} \), two for the two phases of CDI and one for VDI, or even four time constants if as mentioned above there are
Figure 10: The effects of changing 4 parameters on the time course of the L-type calcium current when there are both CDI and VDI.  
Top left: the time constant $\tau_f$ for CDI is varied. Values in ms are 5 (blue), 10 (red), 30 (green) and 100 (black).  
Top right: the time constant $\tau_h$ of VDI is varied. Values in ms are 100 (blue), 200 (red), 300 (green) and 400 (black).  
Bottom left: The effects of various calcium pump strengths $K_c$ on $I_{CaL}$ - see Equation (21). Values of $K_c$ are 1 (blue), 2 (red), 3 (green) and 10 (black) times a base rate of 0.000001.  
Bottom right: How the channel density $\rho_L$, through the magnitude of the current, affects $I_{CaL}$. The multiplicative factor $A\rho_L P^{*}_L$ has values 0.25 (blue), 1 (red), 2 (green) and 3 (black) times the base rate, where the base rate is the standard value described for the previous figure.

two for VDI. The effect of Ca$^{2+}$ released from sarcoplasmic reticulum is graphically illustrated in Hinch et al. (2004). The basic model (1) can incorporate the influence of CICR on CDI by taking account of the time-course of the Ca$^{2+}$ concentration, as stated
in Section 2.1. This quantity will usually be obtained from either ordinary (for $C_a(t)$) or partial differential equations (for $C_a(x,t)$, where $x$ is from 1 to 3 space variables) which incorporate calcium ion concentration changes due to pumping and buffering as well as fluxes through various channels. See Luo and Rudy (1994) for such a deterministic example. A detailed stochastic model for CICR in cardiac myocytes has been analyzed by Williams et al. (2007).

### 4.4 Calculations for double-pulse protocols

According to Budde et al. (2002), CDI tends to be rapid and results in a “U-shaped” inactivation curve when investigated using a double pulse protocol (Tillotson, 1979; Kay, 1991; Meuth et al., 2001). We show corresponding results for the standard model for L-type calcium currents as described in section 2. The voltage is held at a “conditioning” value, $V_{COND}$ followed by a pause and then a “test” pulse at $V_{TEST}$ is delivered. Of interest is the relationship between the first and second responses. As in Figure 1 of Budde et al. (2002), mathematically we have

$$V(t) = \begin{cases} 
V_1 & 0 \leq t < t_1, \\
V_{COND} & t_1 \leq t < t_2, \\
V_1 & t_2 \leq t < t_3, \\
V_{TEST} & t_3 \leq t < t_4, \\
V_1 & t \geq t_4.
\end{cases} \quad (22)$$

We use the constant field method and assume, as the results of Section 4.2 indicate a relative insensitivity to the power of $m$,

$$I_{CaL} = F(V, C_a, C_o)m^2(V, t)h(V, t)f(C_a, t) \quad (23)$$

where $F$ contains physical constants and the constant field factor as given by (17). For the CDI term we use (7) and (8) with $n = 1$, $\tau_f = 30 \text{ mS (constant)}$ and $K_f = 0.0005 \text{ mM}$.

For the voltage-dependent activation and inactivation parameters we use the two sets for thalamic relay cells as given by Pospischil et al. (2008) (see Table A1.1) and Rhodes and Llinás (2005) (see Table A1.3). The time constant for activation was chosen as in Equation (20), and the inactivation time constant was set at $\tau_h = 500 \text{ ms for all } V$. 

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Figure 11: Calculated L-type calcium currents in the two-pulse protocol described in the text using the standard model given by (1) with VDI and CDI. Time is in ms, voltages in mV and currents in nA. In the left column are results with data for activation and VDI of Pospischil et al. (2008), and in the right column of Rhodes and Llinás (2005). The voltage is held at $V_{COND}$ from $t = 20$ to $t = 220$ and at $V_{TEST}$ from $t = 225$ to $t = 445$. In the bottom graphs the amplitude (minimum) of $I_{CaL}$ is plotted against the conditioning pulse voltage for the first pulse (blue curves) and for the second pulse (red curves). $V_{TEST}$ is at the minimum of the blue curves which occur at -20 mV for the left set of results and -5 mV for the right set. In the top graphs, responses are shown for three particular values of $V_{COND}$. The red curves are for $V_{COND}$ at the value of $V_{TEST}$, which gives a large reduction in $I_{CaL}$ on the second pulse due to CDI. The blue curves are for $V_{COND} = 70$ where the current on the first pulse is very small. The green curves are for $V_{COND} = -35$ (left) and $V_{COND} = -25$ (right). The results may be compared with those of Figure 1 in Budde et al. (2002).
The conditioning pulse is on from 20 to 220 ms and the test pulse is on from 225 to 445 ms. The voltage at the test pulse is taken as that at which the response to the first pulse has the largest (negative) amplitude. Results of these calculations are shown in Figure 11. The curves in the bottom part of the figure show the magnitudes of the currents in response to the first (blue) and second (red) pulses. The reduction in the amplitude of in the second pulse is most prominent when the response to the first pulse is the greatest, because $C_{\text{a}}$ has increased the most, resulting in the greatest amount of CDI. In the top parts of the Figure are shown responses to two-pulse clamps for three particular values of $V_{\text{COND}}$, as explained in the Figure caption. Although such results indicate that the standard model for $I_{\text{CaL}}$ with the usual voltage-dependent activation, coupled with VDI and CDI may be adequate for describing certain experimental paradigms, it is uncertain whether this is the case in applications to single cell models, mainly due to the lack of concrete data. The relative contributions of CDI and VDI depend on the particular cell type, mainly through the various combinations of subtypes of L-channels as well as modulating factors such as sub-unit configurations and various ligands.

4.5 Difficulties in the accurate modeling of $I_{\text{CaL}}$

Mathematical modelers of nerve cell physiology are invariably faced with the dilemma of insufficient accurate data concerning the many ion channels influencing a neuron or muscle cell’s activity. It is hard to think of a single neuron for which such data is available for all known channel types. As an example, L-type current data, for a current denoted by $I_{\text{L}}$, were not available for thalamic relay neurons when they were first comprehensively modeled (McCormick and Huguenard, 1992). Instead, the parameters were obtained from the calcium current results of Kay and Wong (1987) for CA1 pyramidal cells, where in fact an L-type current had not been pharmacologically identified. Kay and Wong hypothesized that the channels they had analyzed were from a homogeneous population. The same or similar data were employed by Traub et al. (1991) for $I_{\text{Ca}}$ in CA1 pyramids, Hutcheon et al. (1994) for $I_{\text{L}}$ in thalamic relay cells, Traub et al. (1994) for for $I_{\text{Ca}}$ in CA3 pyramids, Wallen-
stein (1994) for $I_L$ in nucleus reticularis thalami neurons and Wang (1998) for $I_{Ca}$ in cortical pyramidal cells. In none of these models was calcium-dependent inactivation included.

It is hoped that in the future, experiments can be performed to remedy the paucity of accurate data required for L-type (and other) current modeling. There are other limitations apart from the use of data from one cell type for another. The fact that the majority of experiments are performed on dissociated cells means that existing data must be biased towards those for cell somas, so that guesses have to be made for dendrites. To make choice of parameters even more difficult is the use of various different concentrations of either calcium or barium ions which may give results for such quantities as activation potentials which are very different from those for physiological concentrations. Temperature is another key factor which may alter the dynamic properties considerably. Furthermore, results for heterologous ion channels may not be the same as for the corresponding channels in native cells.

Thus, given the many uncertainties in the parameters describing the kinetics of the various ion channels, it is hard to know whether model-based predictions are truly descriptive of cell electrophysiology even when they agree with experimental observations. The hope is then that the modeling results are robust enough with respect to relatively small changes in the parameters. To construct a model of a nerve cell is a very large undertaking, and fortunately many researchers have had the courage to proceed with such endeavours in the light of uncertainties concerning the underlying channel data.

5 L-channel subtype properties

L-type currents are not only important for neuronal and cardiac cell dynamics. Although L-type channels play a limited role in the process of synaptic transmission, they are crucial for activity-dependent gene expression and for regulating plasticity at certain synapses (Hardingham et al. 2001; Dolmetsch et al., 2001; Helton et al. 2005). Thus they have been found to play an essential role in long-term alterations in synaptic efficacy underlying learning and memory in the hippocampus (Kapur et al., 1998; Graef et al., 1999; Leitch et al., 2009) where both $Ca_{v}1.2$ and $Ca_{v}1.3$ channel subtypes
are predominantly located in postsynaptic dendritic processes and somata. Furthermore, current through Ca\textsubscript{v}1.3 channels has been demonstrated at the output synapses of mice AII amacrine cells (Habermann et al., 2003).

5.1 Distribution

The Ca\textsubscript{v}1.1 subtype is mainly found in skeletal muscle and Ca\textsubscript{v}1.4 is found in the retina, but also in human T lymphocytes (Kotturi and Jefferies, 2005). The remaining subtypes Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 constitute the main L-type channels in neurons, endocrine cells and heart cells. The Ca\textsubscript{v}1.2 subtype is widely expressed in heart, brain, smooth muscle and endocrine systems (Ertel et al., 2000). In the brain it is found in cortex, hippocampus, thalamus, hypothalamus, caudate putamen and amygdala (Splawski et al., 2004). In neuroendocrine cells, Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 channels are involved in action potential generation, bursting activity and hormone secretion (Lipscombe et al., 2004; Marcantoni et al., 2007). According to Vignali et al. (2006), 60% of calcium current in both mouse pancreatic A- and B-cells is L-type, with mainly Ca\textsubscript{v}1.2 in B-cells and both Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 in A-cells. The Ca\textsubscript{v}1.3 subtype is found in sinoatrial node, cochlear hair cells, and dendritic neuronal processes (Dolphin, 2009). Schlick et al. (2010) reported distributions of subtypes in many brain regions, including during development, and found that patterns tended to be intrinsic rather than dependent on neural activity. Using barium as charge carrier, Navedo et al. (2007) investigated isoform contributions in mouse arterial smooth muscle. Both Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 were involved in calcium sparklet formation but Ca\textsubscript{v}1.2 was primarily responsible (see Table A6).

Immunofluorescence studies have determined that both Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 have mainly proximal locations on neurons, particularly on the dendrites, and they may make a substantial contribution to the inward current and the action potential (Holmgaard et al., 2008). According to Martinez-Gomez and Lopez-Garcia (2007), in mouse and rat spinal neurons Ca\textsubscript{v}1.2 channels tend to localize in soma and proximal dendrites whereas Ca\textsubscript{v}1.3 channels are also found in distal dendrites. However, Zhang et al. (2006) found that
in the cat, Ca\textsubscript{v}.1.3 channels were dense in ventral horn motoneurons, occurring mainly on somata and proximal dendrites and being responsible for plateau potentials in these cells. Forti and Pietrobon (1993) found that functionally different L-type Ca\textsuperscript{2+} channels coexist in rat cerebellar granule cells. Although Ca\textsubscript{v}.1.2 and Ca\textsubscript{v}.1.3 are often found in the same neuronal processes, particularly dendrites, their subcellular distributions are sometimes distinct (Hell et al. 1993). An interesting graphical representation of the distribution of various calcium channels over the surface of hippocampal pyramidal cells was given in Magee and Johnston (1995).

Differential effects of corticosterone have been found for Ca\textsubscript{v}.1.2 and Ca\textsubscript{v}.1.3 in the CA1 region of hippocampus and the basolateral amygdala (Liebmann et al., 2008). In the former, corticosterone increases the amplitude of the slow afterhyperpolarization whereas in the latter no such effect is observed. The different responses are thought to reflect the expression of Ca\textsubscript{v}.1.3 in hippocampus and the absence of this subtype in the basolateral amygdala.

5.2 Role in pacemaking

In the heart, Ca\textsubscript{v}.1.3 is found in atrial tissue where it contributes to pacemaking but not in ventricular muscle that expresses Ca\textsubscript{v}.1.2 (Lipscombe et al. 2004). According to Torrente et al. (2011), SA node pacemaker activity controls heart rate and local Ca\textsuperscript{2+} release is tightly controlled by Ca\textsubscript{v}.1.3 channels. In Ca\textsubscript{v}.1.3 KO mice, the frequency of Ca\textsuperscript{2+} transients in pacemaker cells was reduced by 45% relative to WT. In another study with KO mice, Zhang et al. (2011) found that Ca\textsubscript{v}.1.3 channels are highly expressed in atrioventricular node cells and played a critical role in their firing. Mesirca et al. (2010) pointed out that atrioventricular node cells may contribute to pacemaker activity in the case of SA node failure.

The properties of Ca\textsubscript{v}.1.3 channels which make them more suitable for pacemaking activity than Ca\textsubscript{v}.1.2 channels were discussed in Vandael et al. (2010) with particular attention to dopaminergic neurons, cardiac pacemaker cells and adrenal chromaffin cells. Ca\textsubscript{v}.1.3 activates with steep voltage dependence at voltages considerably more negative than Ca\textsubscript{v}.1.2 and has faster activation but slower and less complete voltage-dependent inactivation. According
to Striessnig (2007), such activation at low voltages enables Ca\textsubscript{v}1.3 Ca\textsuperscript{2+} currents to support pacemaking activity in sinoatrial node and some neurons (for example Putzier et al., 2009a). For adrenal chromaffin cells, Marcantoni et al. (2010) found that although Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 occurred with about equal frequency in WT cells, most of which fired at about 1.5 Hz, Ca\textsubscript{v}1.3-deficient cells had significantly less firing. The essential role of Ca\textsubscript{v}1.3 and their coupling to BK channels in the pacemaker activity of these cells was established. Alternative splicing of the C terminus of the α\textsubscript{1} subunit of Ca\textsubscript{v}1.3 has been shown to give two forms, of which one (short, 42A) is expected to be more supportive of pacemaker activity (Singh et al., 2008) with 73.6% inactivation of $I_{Ca}$ in 30 ms. See also Table A6.

### 5.3 Biophysical properties: activation and VDI

In Table A6 are listed some of the available data on voltage-dependent activation and inactivation for examples of the four main subtypes. As pointed out in the Introduction, there are no definitive results for each subtype because of the modulatory effects of other subunits and varying experimental conditions such as the use of different hosts and different ionic concentrations. That is, one can expect considerable variability in channel properties for a given subtype from different preparations. As seen in the examples shown in Figure 3, Ca\textsubscript{v}1.3 channels can have quite low activation thresholds compared to the Ca\textsubscript{v}1.2 subtype and which are, in the data given here, similar to that of T-type. The latter have strong VDI whereas Ca\textsubscript{v}1.3 currents are reported to have have weak VDI and strong CDI (Lipscombe, 2002). Very few modeling studies have distinguished subtypes, an exception being Shapiro and Lee (2007). It is also apparent from the steady state inactivation function for Ca\textsubscript{v}1.2 shown in Figure 3, based on Hu and Marban (1998), that virtually no Ca\textsubscript{v}1.2 channels would be available to open around resting membrane potential (about -60 mV).

In a pioneering study using tsA201 cells, Koschak et al. (2001) determined electrophysiological properties for Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 (see Table A6) with current densities of 24.5 and 24.3 pA/pF, respectively, in 15 mM Ba\textsuperscript{2+}. Generally in the cases reported Ca\textsubscript{v}1.3
has faster kinetics than Ca_v.1.2 (Helton et al., 2005) which is seen in the data of Table 6 and Figure 12. Inspection of Table A6 reveals surprisingly that \( V_{m,1.2} \) is lower in the example for Ca_v.1.3 than for Ca_v.1.2, but that \( V_{h,1.3} \) is higher for Ca_v.1.3 than for Ca_v.1.2. Unfortunately the incompleteness of the data for all subtypes prevents a quantitative comparison of their relative current amplitudes, either singly or in combinations. Such a program will be useful for future work when more data are available.

Table 6: Examples of data on activation time constants for L-current subtypes

| Reference          | Ca_v.1.1 | Ca_v.1.2 | Ca_v.1.3 | Ca_v.1.4 |
|--------------------|----------|----------|----------|----------|
| Koschak (2001)     | 2.3 ms   | 1.2 ms   | 15 mM Ba++ | 15 mM Ba++ |
| Hildebrand (2004)  | Control  | 1.34 ms  |          |          |
| 2 mM Ba++          | 10 mM allethrin | 1.23 ms |          |          |
| Catterall (2005)   | > 50 ms  | 1 ms     | < 1 ms   | <1 ms    |
| 10 mV              | 10 mV    |          |          |          |
| Helton (2005)      |          | 2.43\(e^{-0.02V}\) | 1.26\(e^{-0.02V}\) |          |
|                   |          | \(V \in [-20, 20]\) | \(V \in [-55, 10]\) |          |
| Shapiro (2007)     | Model, MN| 30 ms    | 24 ms    |          |
| young 53.6*        |          |          |          |          |
| old 62.5*          |          |          |          |          |

There are only limited data on activation time constants for L-channel subtypes, some being given in Table 6. Those for Ca_v.1.2 and Ca_v.1.3 are graphed in Figure 12. Data from Koschak et al. (2001) are for tsA201 cells. The data of Helton et al. (2005) were given over the membrane potential ranges \(-55 \leq V_m \leq 10\) for Ca_v.1.3 and \(-20 \leq V_m \leq 20\) for Ca_v.1.2. The following expression was employed by Putzier et al. (2009a) for the activation time constant of Ca_v.1.3:

\[
\tau_m = \left( \frac{0.020876(V + 39.726)}{1 - e^{-(V+39.726)/4.711}} + 0.19444e^{-(V+15.338)/224.21} \right)^{-1}. \tag{24}
\]

This function is plotted in Figure 12 and can be seen to be approximately the same as the function \(1.26e^{-0.02V}\) given by Helton
Figure 12: Solid lines: time constants for activation, in ms, versus membrane potential in mV, found for examples of L-channel subtypes Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3. Red and blue curves from Helton et al. (2005) (see also Table 6), black curve from Putzier et al. (2009a) (see also Equation (24)). Dashed lines: corresponding activation functions \(m_\infty\), scaled upwards.
et al. (2005) over the range $[-55, 10]$. Also shown for comparison in Figure 12 are the steady state activations $m_\infty(V)$ corresponding to the three graphs of $\tau_m$ versus $V$.

5.4 Pathologies linked to Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 channels

Several pathologies have been linked to Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 channels. Examples include autism, bipolar disorder, and Parkinson’s disease (Andrade et al., 2009). On the other hand, Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 were shown to not be directly related to absence epileptogenesis (Weiergräber et al., 2010). Mutations of Ca\textsubscript{v}1.2 have been found to result in Timothy syndrome (Splawski et al., 2004), which is a multi-organ disease manifesting in cardiac arrhythmias, metabolic and immune system deficiencies and autism. It has been posited (Barrett and Tsien, 2008; Yarotskyy et al., 2009) that strongly decreased voltage-dependent inactivation, but not CDI, associated with the mutant channel subtype is a possible underlying cause. Alterations in L-channel density and activity have been found in aged rat hippocampal neurons with the possibility of a role in cognitive decline and the occurrence of Alzheimer’s disease (Thibault and Landfield, 1996; Thibault et al., 2001, 2007; Norris et al., 2010). The expression of amyloid precursor protein was shown to increase L-type Ca\textsuperscript{2+} currents, thus leading to the inhibition of calcium oscillations (Santos et al., 2009). Further, performance of rats in a maze task was found to be strikingly negatively correlated with L-channel density (Thibault and Landfield, 1996).

Altered properties of L-type calcium channels have also been implicated in muscular dystrophy (Collet et al., 2003) and epilepsy (Fuller-Bicer et al., 2009). N’Gouemo et al. (2009) found upregulation of various high threshold calcium currents including $I_{CaL}$ in rat models of epilepsy.

The role of Ca\textsubscript{v}1.3 in pacemaking in sino-atrial node and inner hair cells of the cochlea has been demonstrated in KO mice which exhibit significant sinus bradycardia and hearing loss (see Lipscombe et al., 2004). Striessnig et al. (2004) reviewed the role of L-type calcium channels in human disease caused by genetic channel defects (channelopathies) in $\alpha_1$ subunits. Recently it has been
demonstrated in humans that a mutation in a gene which encodes the α1-subunit of Ca\(_v\)1.3 channels is associated with deafness and sino-atrial node dysfunction (Baig et al., 2010). The possibility and usefulness of subtype-specific therapeutic drugs has been discussed in Striessnig et al. (2006) and more recently in Zuccotti et al. (2011). A comprehensive review of L-subtype properties (and other calcium currents) and associated channelopathies was compiled by Piedras-Rentería et al. (2007).

6 Concluding remarks

L-type Ca\(^{2+}\) currents have many fundamental roles, including providing basic depolarization in action potential generation, amplification of synaptic inputs (established in spinal motoneurons) and involvement in signaling pathways for activating transcription factors such as CREB and hence the expression of genes that are essential for synaptic plasticity and other important cellular processes. Ca\(_v\)1.4 L-type channels are also involved in Ca\(^{2+}\)-signaling in immune cells.

Quantitative descriptions of L-type Ca\(^{2+}\) currents thus play an important role in understanding the dynamics of many processes in neurons and other cells, particularly cardiac myocytes. We have here reviewed the basic deterministic methods for a mathematical description of these currents. Whereas activation is usually taken to be voltage dependent, inactivation has varying degrees of CDI and VDI and each cell type requires a separate analysis of their relative contributions, which requires experimental investigation in addition to fundamental current-voltage relations. Incorporating L-type Ca\(^{2+}\) currents in a neuronal model is often hampered by lack of knowledge as to the location of the corresponding ion channels, which is important to ascertain their contributions to cell dynamics. An additional complication is that some cells have more than 1 subtype of L-type channels with separate properties and locations.

The use of Markov chain theory, not described here, for transitions between various channel states has proven useful for cardiac cells but as far as can be discerned has not yet been applied to L-type channels in neurons. The deterministic, or averaging approach, outlined in this review has the advantage of simplicity and
is thus likely to continue to be employed in modeling L-type (and other) calcium currents in multi-component nerve cell models. It is nevertheless not capable of capturing the fine details of the gating schemes for the activation and inactivation processes (Peterson et al., 1999; Erickson et al., 2003; Tanskanen et al., 2005; Tadross and Yue, 2010; Williams et al., 2010) which are made complicated by the roles of subunits and the varying degrees of voltage-dependent and calcium-dependent dynamics. See also Section 4.4 for a discussion of some of the general difficulties encountered in constructing accurate mathematical models for neurons.

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8 Appendix: Tables of data on L-type currents

The following tables are representative of experimental and modeling studies involving L-type calcium currents or calcium currents with properties similar to (or claimed to be similar) to L-type. In the years following the introduction of the term L-type, the term was often taken to imply a high threshold current, although later some L-type currents were found to be activated at quite low membrane potentials. The pharmacological distinction between the various types is desirable but has not always been possible. Except in the case of experiments on subtypes which are clearly identified, usually in transfected cells, original sources may be consulted to determine the likelihood that the ion channels under consideration belong to the L-type category. Table A1.1 contains activation and
inactivation data and modeling studies as opposed to experimental
determinations have been marked M. Table A3 on time constants
has been divided into an experimental part and a modeling part.
Table A1.1
Parameters for L-type Ca\(^{2+}\) activation and, if included, VDI
Non cardiac cells *Denotes estimated  M denotes model

| Source, cell type | Form for current if given | \(V_{m,1}\) | \(k_m\) | \(V_{h,1}\) | \(k_h\) |
|-------------------|---------------------------|-------------|---------|-------------|---------|
| Fox (1987)        |                           | 2           | 4       | -40         | 8       |
| Chick DRG, 10mM Ca\(^{2+}\) |                           | m\(^2\)    | -19     | 7.73        |         |
| Kay (1987)        |                           |             |         |             |         |
| CA1 pyramidal, 2mM Ca\(^{2+}\) |                           |             |         |             |         |
| Fisher (1990)     |                           | 17          | 4.7     |             |         |
| CA3 pyramidal, 100mM Ba\(^{2+}\) |               |             |         |             |         |
| Belluzzi (1991)   |                           | m\(^3\)h, const. field | -8.1 | 9.85 | -19.91 | 4.5 |
| SYMP N, 5mM Ca\(^{2+}\) |                       |             |         |             |         |
| Sala (1991)       |                           | m\(^2\)    | -4      | 9.7         |         |
| SYMP N, 4mM Ca\(^{2+}\) |                        |             |         |             |         |
| Thompson (1991)   |                           |             |         |             |         |
| CA1 pyramidal, 3-10mM Ba\(^{2+}\) |                   |             |         |             |         |
| Traub (1991), M   |                           | m\(^2\)h(V - V_{Ca}) | -19 | 7.73 |         |         |
| CA3 pyramidal, \(V_{Ca}=140\) |                       |             |         |             |         |
| McCormick (1992), M |                         | m\(^2\), const. field | -14.1* | 8.7* |         |         |
| TR cell, 2mM Ca\(^{2+}\) |                       |             |         |             |         |
| Schild (1993), M† |                           | m\(^2\)h(V - V_{Ca}) | -2.8 | 9.85 | -14.61 | 4.5 |
| Rat med, 2.4mM Ca\(^{2+}\) |                       |             |         |             |         |
| Hutcheon (1994), M |                           | m\(^2\), const. field | -14 | 9.1  |         |         |
| TR med dors, 2mM Ca\(^{2+}\) |                      |             |         |             |         |
| Jaffe (1994), M   |                           | m\(^2\), const. field | 4   | 4.7  |         |         |
| CA3 pyramidal     |                           |             |         |             |         |
| Traub (1994), M   |                           | m\(^2\)h(V - V_{Ca}) | -19 | 7.73 |         |         |
| CA3 pyramidal, 2mM Ca\(^{2+}\) |                       |             |         |             |         |
| Wallenstein (1994), M |                         | m\(^2\), const. field | -14.1 | 8.7  |         |         |
| NRT N, 2mM Ca\(^{2+}\) |                       |             |         |             |         |
| Johnston (1995)   |                           | m\(^2\)h, const. field | -15 |       |         |         |
| General           |                           | -12.3       | 7.8     |             |         |
| Kuryshov (1995)   |                           |             |         |             |         |
| Rat corticotropes, 10mM Ba\(^{2+}\) |                       |             |         |             |         |
| Migliore (1995), M |                           | m\(^2\)h(V - V_{Ca}) | -11.3 | 5.7  |         |         |
| CA3 pyramidal, 2mM Ca\(^{2+}\) |                       |             |         |             |         |
| Source, cell type | Form for current if given | $V_{m, \frac{1}{2}}$ | $k_m$ | $V_{h, \frac{1}{2}}$ | $k_h$ |
|-------------------|---------------------------|----------------------|--------|---------------------|--------|
| Magee (1995)      |                           | 9                    | 6      |                     |        |
| CA1 pyramidal, 20mM Ba$^{2+}$ | $m^2(V - V_{Ca})$ | -20.0                | 5.3    |                     |        |
| Avery (1996)      |                           | -30                  | 6      |                     |        |
| CA3 pyramidal, 2 mM Ca$^{2+}$ | $m^2(V - V_{Ca})$ | -40                  | 7      |                     |        |
| Li (1996), M      |                           |                      |        |                     |        |
| DA SN, $V_{rev,L}=120$ | $m^2(V - V_{Ca})$ | -20.0                | 5.3    |                     |        |
| LeBeau (1997), M  |                           | -12                  | 12     |                     |        |
| PC                |                           |                      |        |                     |        |
| Booth (1997), M   |                           | -10                  | 8      |                     |        |
| Spinal, $V_{rev,L}=80$ | $m^2(V - V_{Ca})$ | -22.8                | 9.85   | -34.61              | 4.5    |
| Wang (1998), M    |                           | -15                  | 6      | -33.5               | 4.5    |
| CORT pyramid, $V_{Ca}=120$ | $m^2h(V - V_{Ca})$ | -27.3                |        |                     |        |
| Molitor (1999)    |                           |                      |        |                     |        |
| DCN N, 10mM Ba$^{2+}$ | $m^2(V - V_{Ca})$ | -43.4                | 5.0    | -78.2               | 11.5   |
| Athanasiades (2000), M | $m^2h(V - V_{Ca})$ |                      |        |                     |        |
| MR, 2.4 mM Ca$^{2+}$ | $m^2h(V - V_{Ca})$ |                      |        |                     |        |
| Guyot (2000)      |                           |                      |        |                     |        |
| Bovine adrenal, 20mM Ba$^{2+}$ | $m^2h(V - V_{Ca})$ |                      |        |                     |        |
| Shorten (2000), M |                           |                      |        |                     |        |
| PC, 20 mM Ca$^{2+}$ | $m^2(V - V_{Ca})$ | -10                  | 6      |                     |        |
| Carlin (2000), M (HVA) | $m(V - V_{Ca})$ | -6.4                 | 6.2    |                     | mdx    |
| Carlin (2000), M (LVA) | $m(V - V_{Ca})$ | -43                  | 4.2    |                     | low frequ |
| Spinal MN, $V_{rev,L}=60$ | $m(V - V_{Ca})$ | -1.1                 | 6.7    | control             |        |
| Joux (2001)       |                           |                      |        |                     |        |
| SON, 5mM Ca$^{2+}$ (Double Bolt) | $m(V - V_{Ca})$ |                      |        |                     |        |
| Zhuravleva (2001) |                           |                      |        |                     |        |
| LD thalamic N, 10mM Ba$^{2+}$ | $m(V - V_{Ca})$ |                      |        |                     |        |
| Collet (2003)     |                           |                      |        |                     |        |
| Mouse, SM, 2.5 mM Ca$^{2+}$ | $m(V - V_{Ca})$ |                      |        |                     |        |
| Schnee (2003)     |                           |                      |        |                     |        |
| Turtle AHC, 2.8 mM Ca$^{2+}$ | $m(V - V_{Ca})$ |                      |        |                     |        |
| Durante (2004)    |                           |                      |        |                     |        |
| Rat DA SNC, 2mM Ca$^{2+}$ | $m(V - V_{Ca})$ |                      |        |                     |        |
| Muinuddin (2004)  |                           |                      |        |                     |        |
| Cat SMM, 20mM Ba$^{2+}$ | $m(V - V_{Ca})$ |                      |        |                     |        |
| Jackson (2004)    |                           |                      |        |                     |        |
| Dorsomedial SCN, 1.2 mM Ca$^{2+}$ | $m(V - V_{Ca})$ |                      |        |                     |        |

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Table A1.1 continued

| Source, cell type | Form for current if given | $V_{m,\frac{1}{2}}$ | $k_m$ | $V_{h,\frac{1}{2}}$ | $k_h$ |
|-------------------|---------------------------|-------------------|--------|-------------------|--------|
| Liu (2005)        |                           | -16.6             | 2.45   | -16.8             | 5.95   |
| Rat IC, 2 mM Ca$^{2+}$ |                           |                   |        |                   |        |
| Bui (2006), M     | $m$                       | -33               | 6      |                   |        |
| Spinal MN, $V_{rev,L}=60$ |                   |                   |        |                   |        |
| Marcantoni (2007) |                           | -30*              | 9*     |                   |        |
| Adrenal CH cells, 2 mM Ca$^{2+}$ |                   |                   |        |                   |        |
| Kager (2007), M   | $m^2h(V-V_{Ca})$          | -11.3             | 5.7    |                   |        |
| CA3 pyramidal, 1.5 mM Ca$^{2+}$ |                   |                   |        |                   |        |
| Kapela (2008), M  | $mh$ const. field         | -40†              | 8.3    | -42               | 9.1    |
| Mesenteric SMM, 2.5 mM Ca$^{2+}$ |                   |                   |        | Printed as 0      |        |
| Luin (2008)       | young                     | 8.73              | 7.72   | -5.77             | 7.30   |
| Cultured human SM, 10 mM Ca$^{2+}$ | old                     | 14.47             | 7.74   | 2.38              | 10.1   |
| Pospischil (2008), M | $m^2h(V-V_{Ca})$          | -33.4             | 4.45   | -58.5             | 20.28  |
| TR, CORT, $V_{rev,L}=120$ |                   |                   |        |                   |        |
| Xiang (2008)      | -6                        | 16.7              | -30.5  | 11.2              |        |
| CA1 pyramidal, 5 mM Ca$^{2+}$ |                   |                   |        |                   |        |
| Marcantoni (2009) | -15                       | 11*               |        |                   |        |
| Adrenal CH cells, 2 mM Ca$^{2+}$ |                   |                   |        |                   |        |
| Marcantoni (2010) | -23 (WT)                  | 6.9               |        |                   |        |
| Adrenal CH cells, 2 mM Ca$^{2+}$ | -18.1(KO)               | 7.9               |        |                   |        |
| Adrenal CH cells, 2 mM Ca$^{2+}$ |                   |                   |        |                   |        |
Table A1.2
Parameters for L-type Ca\(^{2+}\) activation and, if included, VDI
Cardiac cells

| Source, cell type                  | Form for current if given | \(V_{m,\frac{1}{2}}\) | \(k_m\) | \(V_{h,\frac{1}{2}}\) | \(k_h\) |
|-----------------------------------|---------------------------|----------------------|--------|----------------------|--------|
| Lindblad (1996), M                | \((m_1 h + m_2)\times(V - V_{Ca})\) | -0.95(1)            | 6.6(1) | -28                  | 4.52   |
| Rabbit AM, 2.5 mM Ca\(^{2+}\)     |                           | -33 (2)             | 12(2)  |                      |        |
| Handrock (1998)                   |                           | -3.5                | 4.9    | -60                  | 7.5    |
| Failing human VM, 1 mM Ca\(^{2+}\)|                           | -14*                | 7.75*  | -31.7                | 4.6    |
| Van Wagoner (1999)                |                           |                      |        |                      |        |
| Human AM, 1 mM Ca\(^{2+}\)       |                           | -25.9               |        |                      |        |
| Donohoe (2000)                    |                           |                      |        |                      |        |
| Rat VM, 1 mM Ca\(^{2+}\)         |                           |                      |        |                      |        |
| Zhang (2000), M                   | \((m_1 h + m_2)\times(V - V_{Ca,L})\) | -23.1 (1)           | 6      | -45                  | 5      |
| Rabbit SA PM, 2 mM Ca\(^{2+}\)   |                           | -14.1 (2)           | 6      |                      |        |
| Arikawa (2002)                    |                           | -10.7               | 6.2    | -28.2                | 6.2    |
| Rat VM (Control)                  |                           | -11.5               | 6.0    | -27.2                | 6.4    |
| Rat VM (Diabetic)                 |                           | -25                 |        | -45                  | 10     |
| Mangoni (2003)                    |                           |                      |        |                      |        |
| Mouse SA PM, 4 mM Ca\(^{2+}\)    |                           |                      |        |                      |        |
| Mangoni (2003)                    |                           | -3                  |        | -36                  | 4.6    |
| Mouse SA PM 1.3KO                 |                           |                      |        |                      |        |
| Benitah (2010)                    |                           |                      |        |                      |        |
| VM, 1.5 mM Ca\(^{2+}\)           |                           |                      |        |                      |        |
Table A1.3
Parameters for L-type Ca\textsuperscript{2+} current activation, VDI and/or CDI.

| Source, cell type | Form for current | \( V_{m,1/2} \) | \( k_m \) | \( V_{h,1/2} \) and/or | \( k_h \) |
|------------------|------------------|----------------|---------|------------------|---------|
| Amini (1999), M  | \( m f_{\infty}(V - V_{Ca}) \) | -50            | 3       | \( f_{\infty} = \frac{0.00045}{0.00045 + C_{a_i}} \) |         |
| MID DA, 2.4 mM Ca\textsuperscript{2+} |                  |                |         |                  |         |
| Rhodes (2001), \textit{M} | \( m^2 h f_{\infty}(V - V_{Ca}) \) | -19.3 \textsuperscript{†} | 7.5 | -42              | 8       |
| CORT pyramidal   |                  |                |         |                  |         |
| Poirazi (2003), M | \( m f_{\infty} \) const. field | -30.1         | 4.8     | \( f_{\infty} = \frac{0.0005}{0.0005 + C_{a_i}} \) |         |
| CA1 pyramidal soma |                  |                |         |                  |         |
| Komendantov (2004) | \( m f_{\infty}(V - V_{Ca}) \) | -50            | 20      | \( f_{\infty} = \frac{0.00045}{0.00045 + C_{a_i}} \) |         |
| MID DA, 2.4 mM Ca\textsuperscript{2+} |                  |                |         |                  |         |
| Rhodes (2005), \textit{M} | \( m^2 h f_{\infty}(V - V_{Ca}) \) | -19\textsuperscript{†} | 8       | -42              | 8       |
| TR, \( V_{rev,L}=60 \) |                  |                |         |                  |         |
| Komendantov (2007), M | \( m(f_{1,\infty} + f_{2,\infty}) \)× | -27            | 4.5     | \( f_{1,\infty} = \frac{0.0001}{0.0001 + C_{a_i}} \) | \( f_{2,\infty} = \frac{0.8 \times 0.002}{0.8 \times 0.002 + C_{a_i}} \) |
| Mag Endocrine, 2.4mM Ca\textsuperscript{2+} | \( (V - V_{Ca}) \)× |                |         |                  |         |
| Source, cell type | Form for current | \( V_m \) | \( k_m \) | \( V_{h,\frac{1}{2}} \) and/or \( k_h \) | \( k_h \) |
|------------------|-----------------|--------|----------|------------------|--------|
| Standen (1982), M Insect SM, \( I_{Ca} \) | \( m^3 f \) const. field | -21.1 | 4.69 | \( df/dt = (f_\infty - f)/\tau_f \) | \( \approx -35^* \) |
|                   | \( f_\infty = \frac{1}{1+(Ca_0/K_f)} \) | \( \alpha_f = 0.1 \text{ms}^{-1} \) | \( K_f = 1.0 \mu M \) | \( \approx 8.6 \) |
| Luo (1994), M VM, 1.8 mM Ca\(^{2+} \) | \( mhf_{\infty} \) const. field | -10 | 6.24 | \( f_\infty = \frac{1}{1+(Ca_i/0.0006)^2} \) | \( \approx -35^* \) |
| Fox (2002), M VM, 2 mM Ca\(^{2+} \) | \( mf \) const. field | -10 | 6.24 | \( df/dt = (f_\infty - f)/\tau_f \) | \( \approx 35^* \) |
|                   | \( f_\infty = \frac{1}{1+(Ca_i/0.0006)^2} \) | \( \approx 8.6 \) | \( \tau_f = 30, K_f = 0.18 \mu M \) | \( \approx 5 \) |
| Shiferaw (2003), M VM, 1.8 mM Ca\(^{2+} \) | \( mhf_{\infty} \) const. field | 5 | 6.24 | \( f_\infty = \frac{0.0005}{0.0005+Ca_i} \) | \( \approx 8.6 \) |
| Shannon (2004), M VM, 1.8 mM Ca\(^{2+} \) | \( mhf \) const. field | -14.5 | 6 | \( df/dt = 11.9(1 - f) - 1.7Ca_i f \) | \( \approx 3.7 \) |
| Stewart (2009), M PF, 2 mM Ca\(^{2+} \) | \( mhf_1 h_2 f \) const. field | -8 | 7.5 | \( f_\infty = 0.4 + \frac{0.6}{1+(Ca_i/0.05)^2} \) | \( \approx 7 \) |
|                   | \( \tau_f = \frac{2 + \frac{80}{1+(Ca_i/0.05)^2}}{1+(Ca_i/0.05)^2} \) | \( \approx 7 \) | \( \approx 3.7 \) | \( \approx 5 \) |

See source for details
### Table A2
Forward and backward rate functions, $\alpha$ and $\beta$ for $m$, and, if given, $h$

**All cell types**

| Source, cell type | $\alpha_{m,h}(V)$, $\beta_{m,h}(V)$ | $\tau_m$ | $\tau_h$ |
|-------------------|-------------------------------------|----------|----------|
| Standen (1982)    | $\alpha_m = \frac{0.01(V+20)}{1-e^{-(V+20)/3}}$ | $1$     | $\alpha_m + \beta_m$ |
| Insect SM, $I_{Ca}$ | $\beta_m = 0.31e^{-(V+20)/25}$ |          |          |
| Kay (1987)        | $\alpha_m = \frac{1}{1-e^{-0.9(V-5)}}$ |          |          |
| CA1 pyramidal     | $\beta_m = \frac{0.02(V+8.69)}{e(V+8.69)^{1.36}}$ |          |          |
| Sala (1991)       | $\alpha_m = \frac{0.058(11.3-V)^{1.36}}{e^{(11.3-V)^{1.36}}}$ | $1$     | $\alpha_m + \beta_m$ |
| SYMP N, 4mM Ca$^{2+}$ | $\beta_m = \frac{0.085(V+15.4)}{e^{(V+15.4)/9.9-1}}$ |          |          |
| McCormick (1992)  | $\alpha_m = \frac{1}{1-e^{-0.9(V-5)}}$ |          |          |
| TR N              | $\beta_m = \frac{0.02(V-1.31)}{e(V-1.3)/3.36-1}$ | 0.33     | $\alpha_m + \beta_m$ |
| Hutcheon (1994)   |                                         |          |          |
| TR N med dors     |                                         |          |          |
| Rybak (1997)      |                                         |          |          |
| Respiratory N     |                                         |          |          |
| Lindblad (1996)   | $\alpha_m = \frac{16.720(V+35.0)}{e^{(V+35.0)/2.5}}$ $+ \frac{1}{e^{V/7.136}}$ | $1$     | $\alpha_m + \beta_m$ |
| Rabbit AM         | $\beta_m = \frac{4.480(V-5.0)}{e^{(V-5.0)/2.565-1}}$ |          |          |
|                   | $\alpha_h = \frac{8.490(V+28.0)}{e^{(V+28.0)/4.900-1}}$ |          |          |
|                   | $\beta_h = \frac{67.922}{e^{(V+28.0)/4.900}}$ |          |          |
| Athanasiades (2000) | $\alpha_m^* = 0.346e^{0.0925(V+20)}$ |          | $\alpha_m + \beta_m + \frac{1}{\alpha_m^* + \beta_m^*}$ |
| MR                | $\beta_m^* = 1.8818e^{-0.00732(V+20)}$ | 0.1      |          |
| Rhodes (2001)     | $\alpha_m = \frac{1600}{e^{(V+13.9)/5.1}}$ | $\alpha_m + \beta_m$ | $0.2$ |
| CORT pyramid      | $\beta_m = \frac{5.23(V-71.5)}{e^{(V+71.5)/2.8}}$ | 0.2      | $\alpha_m + \beta_m$ |
| Poirazi (2003)    | $\alpha_m = \frac{0.655(V+27.01)}{e^{(V+27.01)/3.8}}$ |          |          |
| CA1 pyramidal, soma | $\beta_m = \frac{0.94e^{-(V+63.01)/17}}{e^{(V+37.5)/3.8}}$ |          |          |
| Kager (2007)      | $\alpha_m = \frac{5.23(V-71.5)}{e^{(V+71.5)/10}}$ |          | $\alpha_m + \beta_m$ |
| CA3 pyramidal     | $\beta_m = \frac{0.097e^{-(V+10.86)}}{e^{(V+10.86)/17}}$ |          |          |
| Pospischil (2008) | $\alpha_m = \frac{0.055(V+27)}{e^{(V+27)/3.8}}$ |          | $\alpha_m + \beta_m$ |
| TR, CORT          | $\beta_m = \frac{0.94e^{-(V+75)/17}}{e^{(V+75)/3.8}}$ |          | $\alpha_m + \beta_m$ |
|                   | $\alpha_h = \frac{0.000457e^{-(V+13)/50}}{e^{(V+13)/28}}$ | $\alpha_h + \beta_h$ | $0.0065$ |

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Table A3 - Experimental

Time constants for L-type Ca^{2+} activation and, if included, VDI

| Source, cell type       | \( \tau_{m, \text{max}} \) | \( V_{\tau_{m, \text{max}}} \) | \( \tau_{h, \text{max}} \) | \( V_{\tau_{h, \text{max}}} \) |
|-------------------------|-----------------------------|-------------------------------|-----------------------------|-------------------------------|
| Standen (1982)          | 19.82                       | -28                           |                             |                               |
| Insect SM, I_{Ca}       |                             |                               |                             |                               |
| Kay (1987)              | 1.5-2.07                    | -18                           |                             |                               |
| Insect SM, I_{Ca}       |                             |                               |                             |                               |
| Belluzzi (1991)         | 0.564                       | -8.0                          | 29.90                       | -22                           |
| SYMP N                  |                             |                               |                             |                               |
| Sala (1991)             | 1.16                        | 1                             |                             |                               |
| SYMP N                  |                             |                               |                             |                               |
| Thompson (1991)         |                             |                               | 100                         |                               |
| CA1 pyramidal           |                             |                               |                             |                               |
| Avery (1996)            | 2.3                         |                               |                             |                               |
| CA3 pyramidal           |                             |                               |                             |                               |
| Molitor (1999)          | 1.5                         | -10                           |                             |                               |
| DCN N                   |                             |                               |                             |                               |
| Donohoe (2000)          |                             | \( \tau_{\text{fast}} = 17 \), \( \tau_{\text{slow}} = 57 \) at 0 mV |
| Rat VM                  |                             | \( \tau_{\text{fast}} = 15 \), \( \tau_{\text{slow}} = 46 \) RF |
| Muinuddin (2000)        | 4.0 ms distal               | \( \tau_1 = 4402 \), \( \tau_2 = 255 \) |
| Cat SMM, 20mM Ba^{2+}   | 4.2 ms proximal             | \( \tau_1 = 3905 \), \( \tau_2 = 222 \) |
| Schnee (2003)           | \( \approx 0.5 \)           |                               |                             |                               |
| Turtle AHC              | \( \approx 2 \)             |                               |                             |                               |
| Jackson (2004)          |                             |                               |                             |                               |
| Dorosmedial SCN         |                             |                               |                             |                               |
| Luin (2008)             | young 53.6*                 |                               |                             |                               |
| Cultured human SM       | old 62.5*                   |                               |                             |                               |
Table A3 - Modeling
Time constants for L-type Ca\(^{2+}\) activation and, if included, VDI

| Source, cell type        | \(\tau_{m,max}\) | \(V_{\tau_{m,max}}\) | \(\tau_{h,max}\) | \(V_{\tau_{h,max}}\) |
|--------------------------|------------------|----------------------|------------------|----------------------|
| Traub (1991, 1994)       | 2.11             | -18                  |                  |                      |
| CA3 pyramid              |                  |                      |                  |                      |
| McCormick (1992)         | 1.541            | -15                  |                  |                      |
| TR neuron                |                  |                      |                  |                      |
| Luo (1994)               | 2.23             | -10                  | 25.2             | -10                  |
| VM                       |                  |                      | Min not max      |                      |
| Hutcheon (1994)          | 1.541            | -15                  |                  |                      |
| TR med dors              | 1.5              |                      |                  |                      |
| Jaffe (1994)             |                  |                      |                  |                      |
| CA3 pyramidal            |                  |                      |                  |                      |
| Wallenstein (1994)       | 1.541            | -15                  |                  |                      |
| NRT N                    |                  |                      |                  |                      |
| Migliore (1995)          | 4.56             | -11                  |                  |                      |
| CA3 pyramidal            |                  |                      |                  |                      |
| Li (1996)                | 0.134            | 4                    |                  |                      |
| DA SN                    |                  |                      |                  |                      |
| Lindblad (1996)          | 4.7              | -39                  | 226              | -37.4                |
| Rabbit AM                | 27 (all V)       |                      |                  |                      |
| LeBeau (1997)            | 40 (all V)       |                      |                  |                      |
| PC                       |                  |                      |                  |                      |
| Booth (1997)             |                  |                      |                  |                      |
| Spinal MN                |                  |                      |                  |                      |
| Amini (1999)             | 19.5             | -45                  | CDI only         |                      |
| MID DA                   |                  |                      |                  |                      |
| Athanasiades (2000)      | 0.563            | -28                  | 29.9             | -42                  |
| MR                       |                  |                      |                  |                      |
| Zhang (2000)             | 3.8              | -37                  | 40               | -28                  |
| Rabbit SA PM             | 11.32            | -12                  |                  |                      |
| Shorten (2000)           |                  |                      |                  |                      |
| PC                       |                  |                      |                  |                      |
| Carlin (2000) (HVA)      | 20, all V        | -10                  |                  |                      |
| Carlin (2000) (LVA)      | 20, all V        | -30                  |                  |                      |
| Spinal MN                |                  |                      |                  |                      |
| Rhodes (2001)            | 2.1              | -18                  | 20.0             |                      |
| CORT pyramid             |                  |                      |                  |                      |
| Fox (2002)               | 19.3             | -33                  | 230              | \(\approx -60\)      |
| VM                       |                  |                      |                  |                      |
| Source, cell type                  | $\tau_{m,max}$ | $V_{\tau_{m,max}}$ | $\tau_{h,max}$ | $V_{\tau_{h,max}}$ |
|-----------------------------------|----------------|-------------------|----------------|-------------------|
| Poirazi (2003)                    | 0.826          | -35               | 4.8            |                   |
| CA1 pyramidal soma                |                |                   |                |                   |
| Komendantov (2004)                | 19.5           | -45               | CDI only       |                   |
| MID DA                            |                |                   |                |                   |
| Shannon (2004)                    | 2.38           | -15               | 25.2           | -15               |
| VM                               |                |                   | Min not max    |                   |
| Rhodes (2005)                     | 2.1            | -19               | 200, all V     |                   |
| TR N                              |                |                   |                |                   |
| Bui (2006)                        | 20             | all V             |                |                   |
| Spinal MN                         |                |                   |                |                   |
| Komendantov (2007)                | 0.9            | all V             |                |                   |
| Mag Endocrine                     |                |                   |                |                   |
| Pospischil (2008)                 | 7.04           | -38               | 449.8          | -67               |
| TR, CORT                          |                |                   |                |                   |
| Kapela (2008)                     | 3.65           | -40               | 110            | -35               |
| Mesenteric SMM                    |                |                   |                |                   |
Table A4
Time constants if given by explicit formulas
All cell types

| Source, cell type                  | $\tau_m$                                                                 | $\tau_h$                                                                 |
|------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Belluzzi (1991)                    | $0.1 + \left(0.343e^{0.925V} + 1.88e^{-0.00732V}\right)^{-1}$            | $1 + \frac{1}{a+be^{-(0.0337(V+10))^2}}$                                  |
| SYMP N, 5mM Ca$^{2+}$              |                                                                            |                                                                            |
| Luo (1994)†                        | $\frac{1-e^{-(V+10)/6.4}}{0.035(V+10)(1+e^{-(V+10)/6.4})}$                | $\frac{1}{a+be^{-(0.0337(V+10))^2}}$                                      |
| VM                                 |                                                                            |                                                                            |
| Li (1996)                          | $\frac{0.4}{5e^{\theta} + e^{-\theta}}$                                  | $a = 0.02, b = 0.0197$                                                    |
| DA SN                              | $\theta = -\frac{(V + 11)}{8.3}$                                         |                                                                            |
| Amini (1999)                       | $1.5 + 18e^{-\left(\frac{V+45}{20}\right)^2}$                           |                                                                            |
| Komendantov (2004)                 |                                                                            |                                                                            |
| MID DA                             |                                                                            |                                                                            |
| Shorten (2000), PC                 | $\frac{27}{e^{(V+60)/22} + 2e^{-2(V+60)/22}}$                             |                                                                            |
| Fox (2002), VM                     | $\frac{0.25e^{-0.01V}}{1 + e^{-0.01V}} + \frac{0.07e^{-0.05(V+40)}}{1 + e^{0.05(V+40)}}$ | $30 + \frac{200}{1+e^{(V+20)/9.5}}$                                       |
| Shannon (2004)                     | $\frac{0.035(V+14.5)(1+e^{-(V+14.5)/6})}{1-e^{-(V+14.5)/6}}$             | $a = 0.02, b = 0.0197$                                                    |
| VM                                 |                                                                            |                                                                            |
| Rhodes (2005)                      | $0.6 + \frac{6}{\cosh[(V+19)/24]}$                                       | $200$                                                                     |
| TR N                               |                                                                            |                                                                            |
| Kapela (2008)                      | $1.15 + e^{-\left(\frac{V+40}{30}\right)^2}$                            | $45 + 65e^{-\left(\frac{V+35}{25}\right)^2}$                            |
| Mesenteric SMM                     |                                                                            |                                                                            |
Table A5
Magnitude of L-type Ca\(^{2+}\) currents or related quantities
All cell types

| Source, cell type | L-type magnitude | Remarks |
|-------------------|------------------|---------|
| Penington (1991)  | ∼ 4\% of total I\(_{\text{Ca}}\) | Soma, dissociated cells |
| DRN SE            |                  |         |
| McCormick (1992)  | ∼ 1pA/pF \(\ast\), \(p_L = 80.10^{-6}\) cm\(^3\)/sec | Dissociated cells |
| TR N              | \(g_L = 1.44\) mS/cm\(^2\) | Cell, \(G_L = 0.075\) \(\mu\)S, \(C = 0.052\) nF |
| Schild (1993)     |                  |         |
| Hutcheon (1994)   | 1.3mS/cm\(^2\)   | \(p_L\) as in McCormick (1992) |
| TR med dors       |                  |         |
| Kuryshov (1995)   | 52\% of HVA is L-type | ∼ 70pA |
| Rat corticotropes |                  |         |
| Li (1996)         | 0.19 mS/cm\(^2\) | 10mM Ba\(^{2+}\) |
| DA SN             | (dendrites)      |         |
| Booth (1997)      | 0.33 mS/cm\(^2\) |         |
| Spinal MN         | (dendrites)      |         |
| Schröder (1998)   | 13.2 fA (control) | Ensemble averages |
| Human VM          | 38.2 fA (failing heart) | single channel (Ba\(^{2+}\)) |
| Amini (1999)      | \(G_L = 0.0005\) \(\mu\)S | ∼ 30pA; \(g_L = 0.018\) mS/cm\(^2\) |
| MID DA            |                  | (sphere, rad 15\(\mu\)) |
| Van Wagoner (1999)| 9.13 pA/pF       | 3.35 pA/pF |
| Human AM          | (control)        | (atrial fibrillators) |
| Athanasiades (2000)| \(G_L = 0.075\) \(\mu\)S | \(g_L = 1.44\) mS/cm\(^2\) |
| MR                |                  | cf Schild (1993) |
| Carlin (2000)     |                  |         |
| Spinal MN         |                  |         |
| LVA & HVA, soma   | 10mS/cm\(^2\)   |         |
| LVA & HVA, dend   | 0.3mS/cm\(^2\)  |         |
| Donohoe (2000)    | 16.8 pA/pF       | at -10 mV |
| Rat VM            | 18.3 pA/pF       | RF |
| Joux (2001)       | 19.3 pA/pF       |         |
| SON               |                  |         |
| Fox (2002)        | ∼ 1pA/pF, \(\overline{P}_{Ca} = 0.000026\) cm/ms |         |
| VM                |                  |         |
| Mangoni (2003)    | 3.32 pA/pF       | 1.05 pA/pF |
| Mouse SA PM       | (wild type)      | (1.3 knockout) |
| Poirazi (2003)    | 7 mS/cm\(^2\)   |         |
| CA1 pyramidal     | (soma)           |         |
### Table A5 continued

| Source, cell type | L-type magnitude | Remarks |
|-------------------|------------------|---------|
| Tipparaju (2004)  | 2.5 pA/pF        | 1.2 pA/pF, 2.6 pA/pF |
| Human AM          | Young adults     | Infants, Older Adults |
| Durante (2004)    | 27% of I\textsubscript{Ca} is L-type |
| Rat DA SNc        |                  |         |
| Komendantov (2004)| 0.216 mS / cm\textsuperscript{2} |
| MID DA            |                  |         |
| Rhodes (2005)     | 4 mS / cm\textsuperscript{2} |
| TR N soma         | 60% of I\textsubscript{Ca} is L-type |
| Vignali (2006)    |                  |         |
| Pancreatic A,B    |                  |         |
| Komendantov (2007)| 0.4 mS / cm\textsuperscript{2} | 0.22, 0.46 mS / cm\textsuperscript{2} |
| Mag Endocrine     | (soma)           | (prim., sec. dendrites) |
| Marcantoni (2007) | 10% of I\textsubscript{Ca} | ~ 15 pA |
| Adrenal CH cells  | -60 to -40 mV    |         |
| Kapela (2008)     | 100% of I\textsubscript{Ca} is I\textsubscript{CaL} |
| Mesenteric SMM    |                  |         |
| Xiang (2008)      | 18.7 pA/pF       | I\textsubscript{Ca} is mainly I\textsubscript{CaL} |
| CA1 pyramidal     | (control)        |         |
| Fuller-Bicer (2009)| 5.76 pA/pF  | 3.17 pA/pF |
| Mouse VM          | WT               | \(\alpha_2/\delta-1\) KO |
| Benitah (2010)    | I\textsubscript{Ca} is mainly I\textsubscript{CaL} |
| VM                |                  |         |
| Empson (2010)     | \(\leq 5\%\) of I\textsubscript{Ca} | Soma & dendrites |
| Purkinje neuron   |                  |         |
| Source                  | Subtype          | $V_{m,\downarrow}$ | Carrier          | $k_m$ | $V_{h,\downarrow}$ | $k_h$ |
|------------------------|------------------|---------------------|------------------|-------|---------------------|-------|
| Koschak (2001)         | $\text{Ca}_v.1.2$ | -3.9                | 15 mM Ba$^{2+}$  | 7.8   | -27.6               | 13.8  |
| tsA201                 | $\text{Ca}_v.1.3$ | -17.5               | 15 mM Ba$^{2+}$  | 8.9   | -42.7               | 6.6   |
| Xu (2001)              | $\text{Ca}_v.1.2\;\alpha_1$ | 3.3                | 5 mM Ca$^{2+}$   |       |                     |       |
| Xenopus oocytes        |                  |                     |                  |       |                     |       |
|                        | $\text{Ca}_v.1.2\;\alpha_1$ | -8.8               | 5 mM Ba$^{2+}$   |       |                     |       |
|                        | $\text{Ca}_v.1.3\;\alpha_1$ | -20                 | 5 mM Ca$^{2+}$   |       |                     |       |
|                        | $\text{Ca}_v.1.3\;\alpha_1$ | -36.8               | 5 mM Ba$^{2+}$   |       |                     |       |
| Schnee (2003)          | $\text{Ca}_v.1.3$ | -35                 | 2.8 mM Ca$^{2+}$ | 4.7   | high frequ          |       |
| Turtle AHC              |                  |                     |                  |       |                     |       |
|                        | $\text{Ca}_v.1.3$ | -43                 | 2.8 mM Ca$^{2+}$ | 4.2   | low frequ           |       |
| Hildebrand (2004)      | $\text{Ca}_v.1.2$ | -16.1               | 2.8 mM Ca$^{2+}$ | 6*    |                     |       |
| Helton (2005)          | $\text{Ca}_v.1.2$ | -17.6               | 2 mM Ca$^{2+}$   |       |                     |       |
| tsA201                 | $\text{Ca}_v.1.3$ | -39.4               | 2 mM Ca$^{2+}$   |       |                     |       |
| Catterall (2005)       | $\text{Ca}_v.1.1$ | 8 to 14             | 10 mM Ca$^{2+}$  | -8    |                     |       |
| HEK                    | $\text{Ca}_v.1.2$ | -17                 | 2mM Ca$^{2+}$    | -60 to -50 |                     |       |
| HEK                    | $\text{Ca}_v.1.3$ | -37                 | 2 mM Ca$^{2+}$   | -43 to -36 |                     |       |
| HEK                    | $\text{Ca}_v.1.4$ | -2.5 to -12         | 2 - 20 mM Ca$^{2+}$ | -27 to -9 |                     |       |
| Navedo (2007)          | $\text{Ca}_v.1.2$ | 31.9                | 110 mM Ba$^{2+}$ | 9.3   | -2.7                | 5.2   |
| tsA201                 | $\text{Ca}_v.1.3$ | 9.7                 | Arterial SMM     | 10.8  | -18.7               | 3.5   |
| Arterial SMM           |                  |                     | Shapiro (2007)   | 33.8  | 8.0                  | 5.4   |
| Shapiro (2007)         | $\text{Ca}_v.1.2$ | -20                 | Model, MN        | -41   | 6                    |       |
| Model, MN              | $\text{Ca}_v.1.3$ | -41                 |                  |       |                     |       |
Table A6 continued

| Source                  | Subtype            | $V_{m,\pm}$, Carrier | $k_m$ | $V_{h,\pm}$ | $k_h$ |
|-------------------------|--------------------|----------------------|-------|-------------|-------|
| Luin (2008)             | $\text{Ca}_{\text{v}}$ 1.1 | 8.73 young          | 7.72  | -5.77       | 7.30  |
| Cultured human SM       | (Assumed)          | $\text{Ca}_{\text{v}}$ 1.1 | 10 mM $\text{Ca}^{2+}$ | 14.47 old | 7.74  | 2.38  | 10.1 |
| Peloquin (2008)         | $\text{Ca}_{\text{v}}$ 1.4 | 5                    |       |             | 5.9   |
| tsA201                  |                    |                      |       |             |       |
| Singh (2008)            | $\text{Ca}_{\text{v}}$ 1.3 (42, long) | -2.2               | 9.1   |             |       |
|                         | $\text{Ca}_{\text{v}}$ 1.3 (42A, short) | -12.9              | 6.9   |             |       |
|                         |                    |                      |       |             |       |
|                         | $\text{Ca}_{\text{v}}$ 1.3 (42, long) | -11.8              | 8.1   |             |       |
|                         | $\text{Ca}_{\text{v}}$ 1.3 (42A, short) | -20.2              | 6.6   |             |       |
|                         |                    |                      |       |             |       |
| Fuller-Bicer (2009)     | WT                 | -3.5                 | 4.87  | -15.15      | 5.54  |
| Mouse VM                | $\alpha_2/\delta$-1 KO | 4.66                | 5.88  | -2.18       | 6.14  |
|                         |                    |                      |       |             |       |
| Putzier (2009a)         | $\text{Ca}_{\text{v}}$ 1.3 | -31.1               | 5.35  |             |       |
| Cordeiro (2009)         | $\text{Ca}_{\text{v}}$ 1.2 $\beta_2$ WT | 1.5                | -24.8 | 9.13        |       |
| tsA201                  | B mutant           | 3.5                 | -30.0 | 6.25        |       |
|                         |                    |                      |       |             |       |
| Gebhart (2010)          | $\text{Ca}_{\text{v}}$ 1.3 $\beta_3$ | -0.9               | 9     |             |       |
| tsA201                  |                    |                      |       |             |       |

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